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OLV Hospital  
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Zamorano JL, MD  
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Hospital Ramón y Cajal  
Madrid, Spain
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From the 25th to 29th of August 2018, the European Society of Cardiology hosted the annual ESC congress in Munich again. This year, a total of 33,000 health care professionals attended the 4.5-day event, one the most successful cardiology meetings ever. The attendees came from more than 150 countries and enjoyed almost 600 sessions running in parallel in 30 rooms. Importantly, more than 10,000 scientific abstracts were submitted and 4,461 were selected for oral or poster presentation. Among the top 10 abstract-submitting countries were Germany, the United Kingdom, France, Italy, Japan, the United States, and China. These facts underscore the transition of a European congress into a worldwide, global meeting!

More than 1,500 faculty members from over 80 different countries had active roles at the ESC congress 2018 in Munich. Importantly, a further increase to 25% of all faculty was noted in the number of women involved in the program.

The opening ceremony on the 26th of August highlighted the progress that has been made over the last decades in cardiovascular medicine. Eugene Braunwald elegantly summarized the enormous progress in lipid-lowering therapy, which was only possible through the intensive collaboration between physicians, researchers, and the pharmaceutical industry. Another highlight was Barbra Streisand’s welcome address to our delegates. The ESC gold medals were awarded to Ottavio Alfieri, Evgeny Shlyakhto, and Marc Pfeffer for their enormous contributions to academic medicine and science. A significant number of travel grants were given to young researchers and clinicians to spend time in a center of excellence in Europe.

The facilities of the congress center in Munich were excellent, and 9 villages covered all the important topics in the entire spectrum of cardiology: electrophysiology, heart failure, valvular heart disease, coronary artery disease, coronary intervention, hypertension, prevention, basic science, and cardiac imaging. Excellent state-of-the-art overviews were provided by luminary speakers from all over the world. In the oral abstract presentations, a new interactive app was introduced enabling the audience during the sessions to submit their questions, which could then be addressed in the subsequent discussion.

More discussions took place in the popular “hubs” (open areas in the congress center, where the audience is seated around the speaker and interactive discussions take place), a concept introduced several years ago by Keith Fox.

A specific forum for new developments in digital health was created, where technology meets cardiology and where attendees could learn about the increasing
possibilities and opportunities in this field, including telemedicine, telemonitoring, mobile apps, and many more applications.

Much attention was paid to the area where the poster presentations took place: open, spacious areas with colorful lighting and soft music, inviting participants to enter into lively discussions.

An overwhelming exhibition area was created, where delegates could learn about the latest developments in the pharmaceutical and medical device industry, as well the rapidly evolving possibilities in (noninvasive and invasive) imaging technology.

The spotlight of the ESC congress 2018 was “heart valve disease” and many sessions were dedicated to the diagnosis and treatment of valvular heart disease (specifically aortic stenosis and mitral regurgitation, but also endocarditis and rheumatic heart disease). With the increasing interest in transcatheter heart valve therapy, a significant part of the program involved the innovations in this field, with a focus on expanding indications for transcatheter aortic valve replacement and MitraClip. A highlight was the Andreas Gruentzig Lecture given by Martin Leon on the past, present, and future of transcatheter heart valve therapy.

Innovations in cardiology were discussed extensively in the “innovation corner,” and a special moment was the first Paul Hugenholtz Lecture, given by Francesco Maisano.

Furthermore, four new guidelines were presented at this year’s congress on highly relevant clinical topics, including myocardial revascularization, hypertension, syncope, as well as pregnancy and heart disease. In addition, the fourth edition of the universal definition of myocardial infarction was released.

Finally, the most important, exciting new science was presented in the traditional Hotline sessions, with specific sessions on the latest new trials in pharmacotherapy, coronary interventions, electrophysiology and devices, heart failure, heart valves, and imaging. Several of these trials will have an impact on the practice of cardiology. Here is a short summary of some of the leading trials:

- The GLOBAL LEADERS trial (16,000 patients) failed to show any benefit of 23 months of ticagrelor after 1 month of DAPT following PCI over standard treatment to prevent adverse outcome during 2-year follow-up.

- The ATTR-ACT trial (almost 450 patients, follow-up 30 months) illustrated the benefit (event-free survival) of tafamidis in patients with transthyretin amyloid cardiomyopathy.
The CAMELLIA-TIMI 61 trial (12,000 patients, follow-up 3.3 years) demonstrated the cardiovascular safety of lorcaserin in obese patients.

The MARINER trial (more than 12,000 patients, follow-up 45 days after hospitalization) did not show any benefit of rivaroxaban in preventing (venous) thromboembolic events after hospitalization.

The COMMANDER HF trial (more than 5,000 patients) did not show any benefit of rivaroxaban in patients hospitalized with heart failure during 21 months of follow-up.

The SCOT-HEART trial showed that CT coronary angiography is an alternative to standard care in patients with chest pain and low-intermediate pre-test likelihood of coronary artery disease.

The ARRIVE study (>12,500 patients, follow-up 60 months) did not show any benefit of aspirin in patients with intermediate risk (based on traditional risk factors), but a trend towards lower prevalence of infarction in patients taking aspirin was noted.

Finally, much was also done for the physicians who could not attend the 2018 ESC congress in person: every day, the highlights were broadcast from the ESC TV studio and all sessions were recorded and can be reviewed at any time during the coming year in our ESC congress 365 program.

In the current issue of *Dialogues in Cardiovascular Medicine*, various experts in different fields of cardiology share their experiences at the 2018 ESC congress. They provide summaries of the different subspecialties in cardiology. Specifically, Martin Cowie reports on advances in (digital) technology, whereas Michel Komajda and others address novelties in prevention and treatment, and Filippo Crea summarizes the new ESC guidelines, the different ESC registries, and new important clinical trials presented at the 2018 ESC congress. In addition, Kim Fox and Roberto Ferrari provide an excellent comprehensive overview of studies in heart disease published in the major journals during the last year.

We hope you will appreciate these highlights of the 2018 ESC congress in the current issue of *Dialogues in Cardiovascular Medicine*!

JEROEN J. BAX, FESC

Leiden University Medical Center, The Netherlands
SNAPSHOT IN CARDIOLOGY

ROBERTO FERRARI, MD, PhD & KIM FOX, MD, FRCP

These articles were taken from the New England Journal of Medicine, The Lancet, and JAMA between January 1, 2018 and June 30, 2018. All research articles on cardiology were included; reviews and guidelines were excluded.

JANUARY


The multicenter randomized ORBITA trial showed that, in patients with angina and severe coronary stenosis, percutaneous coronary intervention did not increase exercise time compared with placebo.


The COMPASS trial showed that, in patients with peripheral artery disease, low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events vs aspirin alone. Although major bleeding was increased, fatal or critical organ bleeding was not.


The COMPASS trial showed that, in patients with stable coronary artery disease, the addition of rivaroxaban to aspirin lowered major vascular events, but increased major bleeding. Overall, there was also a significant net benefit in favor of rivaroxaban plus aspirin, including a 23% reduction in death.


The REPRISE III trial showed that, in high-risk patients with severe, symptomatic aortic stenosis, the use of a mechanically expanded valve was not inferior to a self-expanding valve for the primary safety end point or the primary effectiveness end point.


In older patients (≥65 years old) with atrial fibrillation undergoing cardiac surgery (ie, coronary artery bypass grafting, mitral valve surgery with or without coronary artery bypass grafting, or aortic valve surgery with or without coronary artery bypass grafting), surgical left atrial appendage occlusion was associated with a lower risk of readmission for thromboembolism over 3 years.
compared with no surgical left atrial appendage occlusion.


This self-controlled case-series study showed that, in patients hospitalized for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test for influenza, there was a significant association between respiratory infections, especially influenza, and acute myocardial infarction.


In patients with severe aortic stenosis and preserved left ventricular ejection fraction, perioperative myocardial injury was significantly lower in those who underwent isolated aortic valve replacement surgery in the afternoon. An ex-vivo analysis of human myocardium showed transcriptional alterations in circadian gene expression with the nuclear receptor Rev-Erbα being highest in the morning, suggesting that Rev-Erbα antagonism may be a pharmacological strategy for cardioprotection.


Thrombectomy plus standard care resulted in better 90-day disability outcomes post-treatment in patients with acute stroke who had been well 6 to 24 hours prior to the stroke and who had a mismatch between clinical deficit and infarct vs standard care alone.


The CANTOS showed that, in patients with a history of myocardial infarction, reaching a high-sensitivity C-reactive protein concentration <2 mg/L with canakinumab resulted in a 25% reduction in major adverse cardiovascular events and a 31% reduction in both cardiovascular mortality and all-cause mortality, whereas no significant benefit was observed with high-sensitivity C-reactive protein concentrations ≥2 mg/L.


The SENIOR trial showed that, among elderly patients (≥75 years old) who underwent primary coronary intervention, the combination of a drug-eluting stent and a short duration of dual antiplatelet therapy is better than the combination of a bare-metal stent and a similar duration of dual antiplatelet therapy regarding the occurrence of all-cause mortality, myocardial infarction, stroke, and ischemia-driven target lesion revascularization.

This population-based study showed that, from 2002 to 2014, despite seeing a decrease in the incidence of heart failure, the estimated absolute number of individuals with newly diagnosed heart failure in the UK increased, as did the estimated absolute number of prevalent heart failure cases. In addition, socioeconomic disparities were observed for heart failure incidence and age at onset.


The DESSOLVE III trial showed that MiStent, a sirolimus-eluting bioabsorbable polymer stent, was noninferior to the everolimus-eluting durable polymer stent for a device-oriented composite clinical end point at 12 months in an all-comer population.


The ACS QUIK trial showed that, in patients with acute myocardial infarction in Kerala, India, the use of a quality improvement intervention, which included audit and feedback, checklists, patient education materials, and links to emergency cardiovascular care and quality improvement training, did not decrease the major adverse cardiovascular events at 30 days compared with usual care.


The CASTLE-AF trial showed that treating atrial fibrillation in patients with heart failure using catheter ablation resulted in a significantly lower rate of the composite end point of death from any cause or hospitalization for worsening heart failure than in those receiving medical therapy.


The PRESERVE trial showed that, among patients at high risk for renal complications who were undergoing angiography, there was no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, the need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury.
MARCH


The TARDIS trial showed that, among patients with recent cerebral ischemia, the incidence and severity of recurrent stroke or transient ischemic attack did not differ between intensive antiplatelet therapy with three agents and guideline-recommended therapy (ie, aspirin plus dipyridamole or clopidogrel alone). In addition, the intensive therapy resulted in a significantly higher risk of major bleeding.


This community cohort study showed that, despite the poor outcomes associated with isolated mitral regurgitation, only a minority of affected patients undergo mitral (or any type of cardiac) surgery, even when all means to diagnose and treat the disease are available and accessible.


The SMART-DATE trial showed that a 6-month duration of dual antiplatelet therapy in patients with acute coronary syndrome who underwent percutaneous coronary interven-

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SNAPSHOT IN CARDIOLOGY


This systematic review showed that coronary artery bypass grafting resulted in a mortality benefit compared with percutaneous coronary intervention in patients with multivessel disease, particularly those with diabetes and higher coronary complexity, but not in patients with left main disease.


The TASMINH4 trial showed that, in patients with poorly controlled hypertension, the use of self-monitoring, with or without telemonitoring, to titrate antihypertensive medication results in significantly lower blood pressure than titration guided by clinic readings.

An analysis of a registry-based, multicenter, national cohort that included 63910 adults recruited from 2004 through 2014 in Spain showed that ambulatory blood pressure measurements were a stronger predictor of all-cause and cardiovascular mortality than clinic blood pressure measurements.


The SECURE-PCI trial showed that periprocedural loading doses of atorvastatin did not reduce the rate of 30-day major adverse cardiovascular events in patients with acute coronary syndrome and a planned invasive management with percutaneous coronary intervention.


The HONOR trial showed that a home-based exercise program, which involved using wearable activity monitoring and telephone coaching for patients with peripheral artery disease, did not improve walking performance at the 9-month follow-up appointment vs usual care.


The MOMENTUM 3 trial showed that, in patients with advanced heart failure, a fully magnetically levitated centrifugal-flow pump was superior to a mechanical-bearing axial-flow pump with regard to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.


This meta-analysis showed that patients with a high baseline level of low-density lipoprotein cholesterol (>100 mg/dL) had a greater reduction in the risk of total and cardiovascular mortality when receiving a more intensive therapy to lower low-density lipoprotein cholesterol vs those who received a less intensive therapy.


Among non–Hispanic black male barbershop patrons with uncontrolled hypertension, health promotion by barbers resulted in larger reductions in blood pressure when coupled with medication management in barbershops by specialty-trained pharmacists.

In rural areas of China, higher risks of cardiovascular and all-cause mortality was associated with the use of solid fuels for cooking and heating; however, this risk may be reduced by switching to clean fuels and using ventilation.


In patients undergoing elective coronary artery bypass grafting, graft patency after 1 year significantly increased in those receiving ticagrelor plus aspirin vs those receiving aspirin alone.


This meta-analysis showed that, in patients with type 2 diabetes, the use of sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide 1 agonists was associated with lower mortality that the use of dipeptidyl peptidase 4 inhibitors.

MAY


During a 12-month follow-up of patients undergoing stenting of de-novo saphenous vein bypass graft lesions, no significant differences in outcomes were found between patients receiving drug-eluting stents and those receiving bare-metal stents.


The RADIAL investigators showed that radial-artery grafts for coronary artery bypass grafting procedures resulted in lower rates of adverse cardiac events and a higher rate of patency after a 5-year follow-up period than did saphenous vein grafts.


This meta-analysis showed that, in patients with distributive shock, the combination of vasopressin and catecholamine vasopressors was associated with a lower risk of atrial fibrillation compared with catecholamines alone.

Pooled cohort equations, which are based mainly on old patient cohorts, overestimate the risk of cardiovascular disease in New Zealand, as evidenced by a large prospective cohort study. This study was representative of typical patients in primary care in New Zealand who were recommended for cardiovascular disease risk assessment, showing that most patients are now at a low risk of cardiovascular disease.


Performing surgical occlusion of the left atrial appendage in patients during cardiac surgery (eg, coronary artery bypass graft or valve surgery) reduced the risk of subsequent stroke and all-cause mortality vs patients not undergoing surgical left atrial appendage occlusion during surgery.


The RADIANCE-HTN SOLO trial showed that, compared with a sham procedure, endovascular ultrasound renal denervation reduced ambulatory blood pressure at 2 months in patients with combined systolic-diastolic hypertension in the absence of medications.


The MANAGE trial showed that, in patients who had myocardial injury after non-cardiac surgery (MINS), dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding.


The multicenter trial PREDIMED showed that, in people at high cardiovascular risk in Spain, the incidence of major cardiovascular events was lower among those assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet.

The SPYRAL HTN-ON MED trial showed that, compared with a sham control, renal denervation in the main renal arteries and branches significantly reduced blood pressure, with no major safety events.


This prospective cohort study determined a baseline bleeding risk estimate in people without cardiovascular disease who were not taking antiplatelet therapy, which could be useful in the decision-making process for the primary prevention of cardiovascular disease.
THE UNDERUTILIZATION OF CARDIAC REHABILITATION: HIGHLIGHTS FROM THE 2018 ESC CONGRESS

MARCO AMBROSETTI, MD

Author affiliations: Istituti Clinici Scientifici Maugeri, Care and Research Institute, Department of Cardiac Rehabilitation, Pavia, Italy
Address for correspondence: Marco Ambrosetti, MD, Istituti Clinici Scientifici Maugeri, Care and Research Institute, Department of Cardiac Rehabilitation, Via S. Maugeri, 4, 27100 Pavia, Italy (email: marco.ambrosetti@icsmaugeri.it)

Keywords: adherence; cardiac rehabilitation; referral

In August 2018, an accompanying editorial in the current issue of the European Journal of Preventive Cardiology, affiliated with the ESC, evoked the figure of a “bottleneck” to describe a phenomenon that is very familiar to the cardiac rehabilitation community: after a myocardial infarction, all patients have an indication for cardiac rehabilitation, but only very few benefit from an adequate program. Together with reduced patient adherence and the eventuality of suboptimal cardiac rehabilitation protocols, lack of systematic referral represents the main reason for the “cardiac rehabilitation bottleneck,” and similar consideration might be applied to other target groups for cardiac rehabilitation as well (ie, chronic heart failure or peripheral arterial disease). In the same month, more than 30,000 cardiologists attended the 2018 ESC congress in Munich, and the problem about underutilization of cardiac rehabilitation has been extensively discussed, with further support provided by growing evidence.

REFERRAL TO AND PARTICIPATION IN CARDIAC REHABILITATION PROGRAMS

First, data from the EUROASPIRE IV survey confirmed the problematic situation of cardiac rehabilitation across Europe, where only about half of the patients with coronary artery disease are currently advised to participate in a cardiac rehabilitation program, and, among those advised, about 20% do not attend. This picture has not significantly improved during the last 10 years, since similar rates were found in the previous EUROASPIRE III survey published in 2009. The fourth EUROASPIRE study included 7,998 patients in 78 hospital centers in 24 European countries, who underwent either elective or emergency coronary artery bypass graft surgery or percutaneous coronary intervention, and were interviewed after 6 months to 3 years. The main results of the survey concerning the achievement of therapeutic and lifestyle targets were published in 2016, but only recently was information about referral to cardiac rehabilitation programs and related adherence made available. Indeed, now we know a little more than the crude (unsatisfactory)
referral rate to cardiac rehabilitation programs. For example, we know that older patients, women, those with a low educational level, and those with heart failure, hypertension, or diabetes are at the highest risk to not be advised about the importance of a cardiac rehabilitation program.

Furthermore, we know that entering in a cardiac rehabilitation program does not provide a guarantee of success per se, as about one-fifth of patients usually miss at least half of the sessions, with wide heterogeneity among different European countries. Smokers and patients with a low education level represent a particularly vulnerable cluster in terms of nonadherence, and, consequently, they may be considered for targeted interventions. These results give more emphasis to the recently described socio-ecological health model that identifies 63 factors associated with nonparticipation in and/or dropouts of cardiac rehabilitation programs that are divided into six categories: intrapersonal factors, clinical factors, interpersonal factors, logistical factors, cardiac rehabilitation program factors, and health system factors. Focusing on how to achieve systematic referral of all eligible patients and how to decrease the nonparticipation and dropout rates, there is probably a need for taking greater account of the geographical access: more availability of cardiac rehabilitation sites closer to home, the delivery of home-based or community-based programs, the consideration of economic incentives or transport facilitations for those participants with low socioeconomic status, may represent examples of concrete actions, which would be better if coupled to an automatic referral process and supported by digital health tools.

However, EUROASPIRE IV was not the only source of evidence presented at the 2018 ESC congress to help identify “who is” the patient who generally does not attend cardiac rehabilitation programs. The SWEDHEART registry included 31 297 patients with myocardial infarction, mean age 62.4±4 years, during the time period between 2010 and 2016. Nonattenders of cardiac rehabilitation programs were older, more often retired, had more previous disease (diabetes, heart failure, stroke), higher body mass index, reduced left ventricular function, and were more often smokers at baseline than attenders. Interestingly, sex was not associated with nonattendance, and the strongest predictors of nonattendance were smoking, type of hospital (country hospital vs university hospital), occupational status (sick leave vs employed), and previous disease in terms of surgical or percutaneous revascularization. The latter point particularly reflects the importance of the patient’s diagnosis on physician recommendation: in the current scenario, patients who have received coronary artery bypass graft intervention (or other types of cardiac surgery) have higher probabilities of participating in cardiac rehabilitation programs, but there is a need to increase the awareness of the benefits derived from cardiac rehabilitation in other cardiac conditions.
ADHERENCE TO CARDIAC REHABILITATION PROGRAMS

Moving from referral to adherence, an Australian administrative database of 3350 patients enrolled in outpatient cardiac rehabilitation programs between 2007 and 2017 found that dropouts occurred more frequently among younger subjects, people with higher depression/anxiety/stress levels, lower overall quality of life, and in case of delayed tracks to the cardiac rehabilitation facility. Adults who were divorced, diabetic, current smokers, heavy drinkers, or who had a sedentary lifestyle were also significantly more likely to drop out of cardiac rehabilitation programs. On the other hand, almost like a “loyalty bonus,” those who did not drop out of cardiac rehabilitation had a significant reduction in depression and anxiety scores on completion, and this could represent a way to promote adherence to the whole program.

Then, a reappraisal of “referral to cardiac rehabilitation programs” as a strong predictor of prognosis in cardiovascular patients was also supported by several studies presented at the 2018 ESC congress. As an example, the AMIS Plus Registry from Switzerland analyzed the impact of direct cardiac rehabilitation referral at hospital discharge on 1-year outcomes after a myocardial infarction. Data was collected between 2005 and 2016 in 10,141 patients referred to home cardiac rehabilitation or to cardiac rehabilitation centers: the main result was that the cardiac rehabilitation group received more immediate treatment and more secondary prevention medication, as shown by a lower 1-year mortality (OR, 0.65; 95% CI, 0.48-0.88), even after adjusting for confounders, without differences for outpatients vs inpatients. Further evidence, in the field of chronic heart failure, came from a population study on incident cases observed from 2005 to 2012 in the Lombardy region of Italy. This study analyzed the impact of residential cardiac rehabilitation programs on all-cause mortality and readmissions, and data was collected by the regional health care system administrative database: interestingly, patients experienced a mean of 3.26±1.78 admissions in acute wards before they were referred to a cardiac rehabilitation facility, thus suggesting a delayed referral process even in more complicated cases. Above all, patients actively referred to cardiac rehabilitation programs showed a 43% decrease in mortality after adjusting for different covariates and a 31% reduction in the risk of readmission. As a remark, the importance of this study not only refers to the proven beneficial relationship between the use of cardiac rehabilitation and patient survival, but also to the identification of potential savings for health care organizations, since readmissions constitute major expenditures during the care process of patients with heart failure.

“STATE OF THE ART” OF THE UNDERUTILIZATION OF CARDIAC REHABILITATION

Apart from conventional studies and registries, the 2018 ESC congress offered several occasions to speculate about the “state of the art” of the underutilization of
cardiac rehabilitation. This was opportunely the title of a lecture given by Heinz Voeller (DE), Chairman of the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology, who emphasized how cardiac rehabilitation is able to maintain efficacy in terms of improved functional capacity, increased use of cardioprotective medications, and better prognosis even now in the modern era of revascularization strategies. Nevertheless, this depends on mechanisms by which cardiac rehabilitation may work, and the following three are not negligible: cardiac rehabilitation referral from an inpatient setting, cardiac rehabilitation referral from an outpatient setting, and cardiac rehabilitation adherence. If appropriately considered and managed by general cardiologists and the whole cardiac rehabilitation community, these measures seem reasonable to overcome the cardiac rehabilitation bottleneck, which may contribute to a reduction in the impact of cardiovascular diseases.

REFERENCES


CARDIO-ONCOLOGY AT THE 2018 ESC CONGRESS: FROM OBSERVATION TO TREATMENT

ALESSIA LENA; MARKUS S. ANKER, MD

Author affiliations: 1Division of Cardiology and Metabolism, Heart Failure, Cachexia & Sarcopenia; Department of Internal Medicine & Cardiology; and Berlin-Brandenburg Center for Regenerative Therapies (German Center for Cardiovascular Research partner site Berlin), at Charité University Medicine, Berlin, Germany; 2Charité Campus Benjamin Franklin, Department of Cardiology, Berlin, Germany

Address for correspondence: Markus S. Anker, MD, Department of Cardiology, Campus Benjamin Franklin (CBF), Charité University Medicine, Berlin, Germany (email: markus.anker@charite.de)

Keywords: cancer, cardiotoxicity, 2018 ESC congress

Cardio-oncology has gained growing consideration among clinicians in the last years. In parallel, anticancer strategies are constantly improving and many new antineoplastic drugs are being developed. However, these therapies do not exclusively target malignant cancer cells, but also nontumor cells. Depending on cancer diagnosis and treatment strategies, cardiotoxicity is observed in up to 48% of patients with tumors. A lot of research worldwide is focusing on understanding the underlying mechanisms and related negative effects on the myocardium better.

To promote research and understanding of this field, a joint session on cardio-oncology was implemented between the ESC and the American Heart Association during the 2018 ESC congress in Munich, Germany. This session looked at clinical and instrumental possibilities to recognize cardiovascular toxicity in patients with cancer and different treatment options. The congress itself was attended by more than 30,000 participants from >150 countries.

CARDIOVASCULAR TOXICITY

Dr Nicola Maurea (Naples, IT) illustrated possible cardiovascular side effects, such as heart failure, arterial hypertension, acute coronary syndromes, and venous thromboembolism, with respect to the most frequently used target agents. He presented a classification of cardiotoxic events based on the currently existent 9 classes of anticancer drugs (anthracyclines, HER2 inhibitors, vascular endothelial growth factor inhibitors, Bcr-Abl inhibitors, 5-fluoruracil, checkpoints inhibitors, proteasome inhibitors, histone deacetylase inhibitors, tyrosine kinase inhibitors).

In accordance with this model, heart failure associated with targeted cancer therapies is most commonly reported in patients treated with trastuzumab (2% to 28%). In particular, trastuzumab alone and together with anthracyclines were demonstrated to be strongly associated with the development of left ventricular dysfunction in 45,537 elderly female patients with breast cancer. After 3 years of...
follow-up, the occurrence of heart failure or cardiomyopathy differed depending on the treatment received: 32% in patients treated with trastuzumab, 42% with trastuzumab and anthracyclines, and 18% in patients without adjuvant therapy (P<0.001).

Other anticancer drugs that are frequently associated with the development of heart failure are proteasome inhibitors. In particular, after carfilzomib treatment, patients develop heart failure in up to 25% of cases. Furthermore, we have recently learned that immune checkpoint inhibitors (eg, nivolumab, ipilimumab) can be associated with the sudden onset of fulminant myocarditis, but we still do not know how to identify patients at high risk before the commencement of treatment. A recent report looked at 101 case reports of severe myocarditis following immune checkpoint inhibitor treatment. The authors found that this adverse event occurred in all ages, was mostly seen in patients with lung cancer or melanoma, and two-thirds developed myocarditis after only one or two doses of the medication. Death occurred in 46% of patients and each year more cases are described in the literature, which might be due to a more frequent use of this new therapy in recent years and greater awareness for such severe complications.

VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER

Professor Farouk Mookadam (US) focused on venous thromboembolism in patients with cancer, which is considered a frequent cause of morbidity and mortality and may affect as many as 20% of hospitalized patients. Venous thromboembolism is observed with different anticancer therapies, such as histone deacetylase and tyrosine kinase inhibitors. With respect to the treatment of venous thromboembolism in patients with cancer, the CLOT trial, in 672 patients, showed significantly reduced venous thromboembolism recurrence with dalteparin (9%) compared with warfarin (17%) in the 6-month follow-up (HR, 0.48; 95% CI, 0.30–0.77; P=0.002). At the same time, the CATCH trial, in 900 patients, did not show reduced mortality or recurrence of venous thromboembolism with tinzaparin vs warfarin, but tinzaparin was associated with less frequent clinically relevant nonmajor bleeding (HR, 0.58; 95% CI, 0.40–0.84; P=0.004).

Until recently, few data was available about the management of venous thromboembolism with novel anticoagulants, since patients with cancer are often excluded from trials testing novel anticoagulants. The Hokusai VTE Cancer study recently reported noninferiority of edoxaban vs dalteparin in 1050 patients with cancer in reducing the composite of major bleeding or recurrent venous thromboembolism. Further analysis revealed that edoxaban treatment, compared with dalteparin, was associated with a higher rate of major bleeding, but a lower risk of recurrent venous thromboembolism.
DIAGNOSIS OF CARDIOVASCULAR SIDE EFFECTS

Dr Ana Barac (US) discussed the current challenges in the early detection of antineoplastic treatment-related cardiovascular complications. Macroscopic alterations can be detected through different diagnostic tools, such as cardiac biomarkers, echocardiography, cardiac magnetic resonance, or nuclear cardiac imaging. Dr Barac stated that patients with cancer treated with anthracyclines and HER2-target agents frequently receive routine cardiac imaging before, during, and after anticancer therapy, whereas patients treated with other agents, such as tyrosine kinase inhibitors, vascular endothelial growth factor antagonists, and immune checkpoint inhibitors, are infrequently referred to a cardiologist in the clinical routine. She recommended, particularly in high-risk patients, to perform echocardiography before treatment and then reassess left ventricular ejection fraction at least every 3 months. If abnormalities are detected, an interdisciplinary team, including oncologists and cardiologists, should discuss a joint treatment plan.

A rather new tool, which is considered more sensitive than the assessment of left ventricular ejection fraction, is the determination of global longitudinal strain. It has been discussed as a good predictor of subsequent deterioration of left ventricular function; therefore, it may help identify patients who need additional attention. Cardiac magnetic resonance is another option, which is particularly useful in suspected cardiac injuries, not detectable by standard echocardiograms. Its accuracy and characterization of myocardial fibrosis helps in the definition of different phenotypes of myocardial injuries. However, this diagnostic procedure is supplementary to the echocardiogram and only accessible in specialized centers.

ESC REGISTRY ON CARDIO-ONCOLOGY

Professor Maurizio Galderisi (IT) showed the first results obtained from the ESC Cardio-Oncology Toxicity Registry, which involves 132 participating centers in 26 different countries and is aiming to include 3000 patients. At the congress, the baseline characteristics of the first 1972 female patients with breast cancer were shown and discussed: 2% of patients presented with atrial fibrillation, 9% had a diagnosis of diabetes mellitus before or during enrollment, 29% had arterial hypertension (15% not pharmacologically controlled), 21% suffered from dyslipidemia, 23% presented with obesity, and 12% had thyroid disturbances. Concerning the prevalence of metabolic syndrome, 19% of the patients had at least two cardiovascular risk factors and 10% of the patients were in NYHA classes II-IV. Regarding prior anticancer drug treatment, 30% of patients had completed therapy at the time of the recruitment and 32% were currently undergoing chemotherapy treatment (39% anthracycline-based therapy), with 15% of patients having already received radiotherapy before. At the time of enrollment, an echocardio-
gram was performed in 96% of participants, whereas a resting electrocardiogram was conducted in 73%. Moreover, the percentage of patients who presented with any signs of anticancer drug cardiotoxicity was 15%. After 3 months of follow-up, uncontrolled hypertension had decreased from 15% to 10%, while no significant differences were reported concerning change in NYHA class.

CONCLUSION
This session dealt with new possibilities in terms of clinical interventions and diagnostic instruments to contrast cardiovascular complications that frequently occur during and after antineoplastic treatment in patients with cancer. Improvements in the early detection of cardiovascular dysfunctions are promising and research interest in this field is steadily growing. To continue advancing treatments in cardio-oncology, cardiologists and oncologists have to work together in a multidisciplinary team.
REFERENCES


At the European Society of Cardiology Annual Scientific Meeting in Munich in August 2018, there was a digital area, where the full range of digital technologies were discussed. The area was extremely popular, with standing room only for nearly all sessions.

It is impossible to cover all of the excellent presentations on digital health, but the ones that caught my eye are mentioned below. Please go to the ESC website for more detail regarding the presentations (see callout box).

**mHEALTH, INCLUDING APPS**

Mobile health (mHealth) includes many technologies, including “applications” (apps) that can be downloaded onto a smartphone. These are very popular and many of us use these to manage our bank accounts, book and check-in to flights, watch films, and catch up on the news. There are more than 300,000 medical or health and lifestyle apps, and it is impossible to keep up to date with all that is available.

At the 2018 ESC conference, we highlighted some of the most interesting and potentially relevant apps for the prevention, diagnosis, and treatment of cardiovascular conditions. My personal favorites were related to helping people manage their own condition better.

SMASH™ is an app that helps patients remember to take their medication, but many others exist. It was interesting to see the results of a randomized trial in Australia in 163 patients with coronary heart disease, with an average age of 58, who were taking an average of 4.2 medications each. Patients were randomized to usual care, a basic medication-reminder app, or a more interactive app that could be customized to the patient. Even the basic app improved medication adherence significantly at 3 months (as measured by the Morisky Medication Adherence
Scale-8), reducing the low adherence group from 29% of patients to 19%. The basic app seemed to be as effective as the more interactive and customizable app. Longer-term data, including the effect on blood pressure and lipid control would be good, but even these early results are likely to encourage cardiologists to recommend this (or similar apps) to their patients.

The BNK CardioCoach™ is an app that has modules for patient medical records, vital sign monitoring collected from, eg, home blood pressure devices, medication record and reminders, activity data and reminders, and a summary screen that provides the doctor with all of the key information from recent months on one screen. The patient controls who can access the data. Other similar apps were also presented, all with the underlying concept that the data being collected belongs to the patient, it can be collected and summarized, and used to enhance adherence to lifestyle and medication prescriptions, and facilitate efficient communication between the patient and the doctor or nurse at a clinic visit. We all know how frustrating it is for both patients and health care professionals if information is missing or only available after minutes of activity trying to get into different databases! It is likely that the use of such apps will increase as patients and health care professionals become more familiar with the technology. Perhaps, in the future, patients will no longer need to take sheets of paper out of their pockets with lists of blood pressure or weight details, but just email or Bluetooth to us a summary screen of all of the relevant information.

The ESC is increasingly using apps to support implementation of its guidelines and to support and educate patients. A good example is the ESC CATCH-Me apps, including AF Manager™ and MyAF™, the first helps health care professionals manage atrial fibrillation better and the second helps patients in terms of education, an atrial fibrillation diary, and collection of quality of life data. For both apps, UK, Japan, and Germany were the countries where the most downloads have taken place.

Dr Enrico Caiani, Associate Professor of Biomechanical Engineering and e-health and the past Chair of the e-cardiology working group of the ESC, presented a lecture on the evaluation of apps. He pointed out that it is difficult to navigate through the hundreds of thousands of apps in the health and lifestyle or medical categories. Most apps are downloaded from Google Play, with the Apple Store being the next most popular site. It is important to realize that the availability of an app does not mean that its content has been fully and independently validated. When you search for an app, they are generally listed in order of popularity, not necessarily the ease of use or the strength of evidence for any benefit for the user. Approximately 75% of apps are produced by individuals, with no connection to scientific or academic organizations, health care, or industry. Only 0.5% are considered “medical devices” by regulators, and those apps undergo intense
scrutiny and are usually related to a technology that is considered medical, such as an implantable device or a diagnostic platform. All other apps are likely to be only minimally assessed from a medical perspective.

The European Commission undertook a public consultation on mHealth in 2014, and set up a working group of key stakeholders, including patients, health care professionals, payers, and social insurance companies, industry, public authorities, and academics. Sadly, even a minimal level of consensus was not reached and it was impossible to provide and endorse any guidelines. Several national initiatives are underway, including “AppSalud” in Andalucia and “AppSalut” in Catalonia, and assessment by NHS Digital and the National Institute for Health and Social Care (NICE) in the UK. Only a handful of apps have been endorsed and even fewer subjected to more formal and robust assessment of their health care impact and cost-effectiveness. Some professional organizations have started to endorse apps, but the ESC has yet to embark on such a process.

**REMOTE MONITORING**

Remote monitoring has been a hot topic in heart failure for some years. It has been technically feasible to collect data remotely, either from stand-alone systems or from implantable devices, for more than a decade, but the challenge is to demonstrate the benefit that this brings, particularly when producing such data streams requires redesigning the health care pathway, and identifying new responsibilities within the health care professional team.

At the 2018 ESC conference, Dr Friedrich Koehler from Berlin Charité presented the long-awaited results from the TIM-HF2 trial (NCT01878630). A total of 1538 patients with a hospital admission for heart failure within at least the past 12 months, currently in NYHA class II or III, and without depression were randomized to usual care or remote monitoring for 12 months with a daily review of symptoms, blood pressure, weight, and ECG by a centralized telemonitoring center that was working 24/7. This monitoring center was in direct contact with the patient, the general practitioner, and the local cardiologist in 14 metropolitan and 11 rural areas, covering virtually the whole of Germany. The average age of the patients was 70, 70% were male, with an average ejection fraction of 41%, and patients were recruited on average 3 months after the last hospital admission.

The primary end point (percentage of days lost to unplanned cardiovascular hospitalizations or all-cause death) was reduced from 6.6% to 4.9% (P=0.046). The days lost to either an event during the year averaged 24.2 in the usual care arm and 18 in the remote monitoring arm. It is important to note that patients were well treated at baseline (90%+ on a RAS inhibitor and β-blocker, 55% on an aldosterone antagonist, 30% had an implantable cardioverter defibrillator, and 15%
had cardiac resynchronization therapy). The secondary end point of all-cause mortality was reduced by 30% (95% CI, 4%-50%; \(P=0.03\)), driven by a slightly larger, but notionally nonsignificant reduction in cardiovascular mortality (relative risk reduction, 33%; \(P=0.056\)). There was no change in overall quality of life or in plasma NT-proBNP concentrations, but the days lost to an unplanned heart failure hospitalization were reduced from 5.6 to 3.8 (\(P=0.007\)). The investigators argued that a remote monitoring program with a well-structured telemedical center providing 24/7 services is an effective approach to overcoming regional differences in heart failure management. In other words, the expertise comes to the patient, rather than the other way round, and patients gain the benefit of more standardized care across the whole country. In an accompanying editorial to the simultaneously published paper in *The Lancet*, Cleland and Clark suggest that the evidence for the mortality benefit of remote monitoring in heart failure is accumulating and that guideline writers should now be supportive and consider the totality of evidence available.

**WEARABLE TECHNOLOGIES**

An example of a wearable technology that caught my attention was Cardioskin™, which is a 15-lead ECG recording system embedded in a T-shirt that is washable and can be worn for days to weeks. The ECG can be transmitted continuously or stored in a memory card that is easily clipped to the T-shirt. It has been given FDA Class II 510(k) clearance, and it may well become a replacement for the traditional Holter-recording, as the electrodes embedded in the T-shirt are more comfortable to wear than conventional electrodes, and this approach can provide the more prolonged monitoring that is needed to confidently exclude paroxysmal arrhythmia. The ECG interpretation software is of high quality, and, with the good-quality signal identification of a clinically important arrhythmia, without numerous false positives, appears promising.

**REMOTE MONITORING OF HEART FAILURE USING IMPLANTABLE TECHNOLOGY**

A prize was awarded for the best presentation in the “Heart Failure and Digital Health” session to Dr Darshan Brahmbhatt, from the Royal Brompton Hospital, London. He presented the results to date from the HeartLogic™ multiparametric monitoring algorithm, which uses data from CRT and ICD devices to determine whether the heart failure syndrome is deteriorating. The algorithm integrates information from the intensity of the heart sounds (reflecting intraventricular pressure), respiratory rate and volume, transthoracic impedance, patient activity, and nocturnal heart rate. An alert is triggered by the algorithm if these parameters head in the wrong direction, and the health care team typically would telephone the patient and advise an increase in diuretic therapy until the alert re-
sets. Learning from previous approaches to remote monitoring with implantable devices, data from a large number of patients was used to develop and validate the algorithm, and currently a randomized outcome study is underway in the USA to determine if this approach can be used in routine practice to reduce the mortality and heart failure hospitalization rate in patients with heart failure and an implanted device (MANAGE-HF; NCT03237858). Early experience suggests that it is vital to integrate the data flow into the decision-making pathway at each institution and that monitoring staff act on the information quickly.

Interestingly, the chief investigator for the development and validation of the HeartLogic™ algorithm, Dr John Boehmer from Penn State Milton S. Hershey Medical Center in the USA, has taken the same multiparametric monitoring concept and applied it to a wearable undergarment using nanosensors. FDA Class II 510(k) clearance has been given, and the team is undertaking pilot work before starting a randomized validation trial called NanoSENSE using this undergarment.

**ARTIFICIAL INTELLIGENCE**

Artificial intelligence and machine learning are always topics of great interest to cardiologists, as well as to the general public. It has been interesting to see the evolution of the terminology used to describe this, moving from “disruptive” to “supportive,” with the increasing realization that, for most tasks, such an approach supplements human decision-making and interaction, rather than replacing it.

Obvious areas of application include pattern recognition of images, using echocardiographic or CT- or MRI-based images. In theory, a patient’s data can be analyzed more accurately by these algorithms than they can be by humans, using learning informed by hundreds of thousands of scans rather than merely thousands. How such approaches fit into the current image interpretation approach in cardiology remains to be seen, but undoubtedly, change is on the way.

More generally, computer-aided decision support is increasingly used in medical care to reduce the risk of mistakes and to ensure that management decisions are informed by the best current evidence. IBM-Watson has often been showcased in the media regarding decision support in the world of oncology, but, at the 2018 ESC conference, other approaches were also discussed. CardioNexion™ presented data on the use of artificial intelligence to supplement human intelligence when it came to long-term monitoring of the ECG in patients living their daily lives. The problem with many technologies is the false positive alert, requiring the cardiologist to view the ECG; the CardioNexion™ system appears to reduce the false positive rates to a low level, thereby allowing the cardiologist to concentrate on the (occasional) ECG that might influence clinical decision-making.
Another look toward the future was given by CardioCube®, where an “intelligent voice assistant,” such as some 70 million households now have in their homes, can interact with patients and their physician to capture information for the electronic health record automatically, take a history, monitor symptom control, and use machine learning to identify key information that might influence medical decision-making.

SOCIAL MEDIA

There were several sessions on social media, helping to educate and inform cardiologists about the opportunities of these platforms for education and case-based learning, but also to show how the clinical community (or at least a broad section of this) is reacting to new trial results or updates to the guidelines. Some of the potential problems were also highlighted, including public access to tweets or other material. My own experience with social media around the conference was that #ESC2018 and #ESCDigital were good hashtags to “follow”; they certainly showed me what had caught people’s attention and linked me in to other material that was useful.

The ESC Annual Scientific Meeting in Paris in 2019 will be bigger and better when it comes to digital health. Stay tuned for updates on the Escardio.org website (bookmark https://www.escardio.org/Education/Digital-Health-and-Cardiology) or follow @Escardio or search with #ESCDigital on Twitter.

Full resources from ESC 2018 in Munich are available at:
https://www.escardio.org/congresses-&-events/esc-congress/congress-resources
Also includes ESC 365 and ESC TV

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ATRIAL FIBRILLATION 2018: AN UPDATE ON RECENT DEVELOPMENTS IN DIAGNOSIS AND MANAGEMENT

PANOS E. VARDAS, MD, PhD

Author affiliations: Heart Sector, Hygeia Group Hospitals, Athens, Greece
Address for correspondence: Professor Panos E. Vardas, Heart Sector, Hygeia Group Hospitals, 5 Erythrou Stavrou Str, 151 23, Marousi, Athens, Greece (email: pvardas@hygeia.gr).

Keywords: anticoagulation; atrial fibrillation; catheter ablation; heart failure; left atrial appendage occlusion; prevention

At the annual conference of the European Society of Cardiology (August 25-29, 2018), a wide range of papers related to the diagnosis and treatment of atrial fibrillation were presented (esc365.escardio.org). I have chosen to focus on a small number of these papers, which, in my opinion, represent topics of major importance as relates to the epidemiology, pathophysiology, and the management of this persistent and very common arrhythmia.

DO ALL CASES OF ATRIAL FIBRILLATION QUALIFY FOR ANTICOAGULATION?

Pieter Vandervoort (BE) presented the paper “Results from a real-life digital population screening for atrial fibrillation using only a smartphone. Device-detected and subclinical atrial tachyarrhythmias.” This talk focused on an important and common question: do all cases of atrial fibrillation qualify for anticoagulation? The following conclusions were made during the talk:

- Atrial high-rate episodes and subclinical atrial fibrillation (nonsustained atrial tachycardia) occur often. If they persist for more than 24 hours, they are associated with an increased thromboembolic risk. Shorter episodes are less consistent as a predictor of stroke, while very short episodes only require monitoring.

- There is no consensus regarding a minimum or optimum threshold that could be used as an indication for anticoagulation; this may vary from patient to patient.

- Though the results of further studies are still awaited, there is so far no good clinical evidence to confirm the efficacy of anticoagulation for atrial high-rate episodes and subclinical atrial fibrillation. Therefore, these patients require an individual approach to the evaluation of their thromboembolic risk.

- We do not yet know whether atrial high-rate episodes and subclinical atrial fibrillation may serve as risk factors or markers. Further refinement of these criteria may be necessary in order to derive useful parameters for risk
stratification (eg, atrial high-rate episodes burden and density, markers of atrial myopathy or hypercoagulability, etc).

**LEFT ATRIAL APPENDAGE OCCLUSION**

In his presentation, Dariusz Dudek (PL) asked the question “Who is an LAA occlusion candidate?” and presented the selection criteria and current data. According to the author, the clinical and technical challenges involved in left atrial appendage closure include the following: (i) device-related thrombosis; (ii) postprocedural leaks; and (iii) device embolization. More specifically, we could focus on the following items:

- **Device-related thrombosis:**
  - The incidence with endocardial devices ranges from 3% to 7.2%.¹
  - For epicardial left atrial appendage exclusion, the risk of a thrombus appears to be comparable.
  - Independent predictors of thrombosis include a history of transient ischemic attack or stroke, permanent atrial fibrillation, large left atrial appendage diameter, and a low left ventricular ejection fraction.²

- **Postprocedural leaks**
  - Leaks are reported for both endocardial and percutaneous endo-epicardial closure, as well as exclusion system closure. The incidence ranges from 0% to 63%, depending on the type of left atrial appendage device and the modality of monitoring.
  - The consequences of postprocedural leaks remain unclear, with studies reporting conflicting results regarding the risk of stroke.
  - The contradictions in reported data expose the limitations of imaging modalities and device selection.
  - Continued surveillance with transesophageal echocardiography and temporary initiation of anticoagulation are recommended if a leak occurs.

Dariusz Dudek made the following conclusions:

- Stroke prevention remains a major goal in patients with atrial fibrillation. Although anticoagulation remains the first choice, the low compliance is alarming.

- Left atrial appendage closure devices will continue to evolve as an alternative strategy, as new technologies are developed, appropriate patient populations are identified, and operator skills and periprocedural techniques are improved.

- Catheter ablation with left atrial appendage closure offers a new clinical perspective. More studies are needed to address patients who are ineligible for
(new) oral anticoagulants—(N)OAC, ie, those patients with a high risk of a cardioembolic event, but who have exhibited major bleeding, and those patients with very high CHA\textsubscript{2}DS\textsubscript{2}-VASc scores who are at risk of stroke despite (N)OAC therapy.

**ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION**

Renato D. Lopes (US), in his lecture on “Anticoagulation in atrial fibrillation: what the trials tell us and gaps in current knowledge,” recognized the following data gaps in atrial fibrillation/NOAC trials: (i) patients with atrial fibrillation and renal impairment (including end-stage renal disease); (ii) subclinical (device-detected) atrial fibrillation; (iii) patients undergoing atrial fibrillation ablation; (iv) new-onset atrial fibrillation and acute cardioversion; and (v) patients with atrial fibrillation and ACS (on DAPT plus OAC).

The author concluded by saying that:

- NOACs should be recommended in preference to warfarin for stroke prevention in atrial fibrillation; however, this transition from warfarin to NOACs has been slow.
- We need more data concerning various subgroups of patients with atrial fibrillation.
- Ongoing research hopes to deliver optimal management to all patients.

**STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION**

In addition to the foregoing, still focusing on stroke prevention in atrial fibrillation, Stuart J. Connolly (CA) summarized, in his lecture “ANNEXA-4 - andexanet alfa for reversal of Factor Xa inhibitors in patients with acute major bleeding,” some of the central findings that have emerged from the relevant studies so far, as follows:

- Antiplatelet therapy works.
- Anticoagulation works better.
- NOACs are even better, especially regarding safety.
- Bleeding matters a lot, perhaps a bit less than ischemic stroke prevention.
- The dose of NOAC matters too.

**ATRIAL FIBRILLATION AND HEART FAILURE**

Sidney C. Smith (US), in his very comprehensive lecture, focused on the important feedback relationship between atrial fibrillation and heart failure. The author identified certain factors that contribute to this dangerous association, including
more atrial and ventricular remodeling, greater neurohormonal activation, more advanced heart failure, more frequent hospital admissions and stroke, smaller reverse remodeling response to cardiac resynchronization therapy, more frequent cognitive dysfunction in atrial fibrillation.

The author concluded that:

- Atrial fibrillation and heart failure frequently coexist, which can lead to a vicious cycle.
- Atrial fibrillation affects heart failure outcomes via hemodynamic effects, risk of thromboembolic events, and exposure to adverse effects of therapy (anticoagulants, antiarrhythmics, and ablation).
- Growing evidence shows that rhythm control of atrial fibrillation in patients with heart failure, via catheter ablation, is of particular benefit.
- Patient selection is vital.

**RADIOFREQUENCY CATHETER ABLATION FOR ATRIAL FIBRILLATION**

Klaus Kettering (DE) and Felix Gramley (DE) focused on another very important issue: long-term outcomes of radiofrequency catheter ablation for atrial fibrillation, with a specific focus on the long-term outcomes of redo procedures after pulmonary vein isolation with the cryoballoon technique (first- vs second-generation cryoballoon). This very important study included 80 patients (59 with paroxysmal atrial fibrillation and 21 with persistent atrial fibrillation) who had to undergo a redo procedure after an initially successful circumferential pulmonary vein isolation with the cryoballoon technique. In 40 patients (group A), the Medtronic Arctic Front Balloon was used, while, in another 40 (group B), the Arctic Front Advance cryoballoon was employed. The redo ablation procedures were performed using a segmental approach or a circumferential ablation strategy (CARTO; Biosense Webster) depending on the intraprocedural findings.

During the redo procedure, reconducting pulmonary veins were detected (mean, 1.8) using a circular mapping catheter (group A, 2.3; group B, 1.3). There was a slightly higher incidence of chronic pulmonary vein reconnections related to the left-sided pulmonary vein ostia than to the right-sided pulmonary veins in both groups. In addition, more sites of chronic pulmonary vein reconnection were found in the inferior parts of the pulmonary vein ostia than in the superior parts. In 35 patients in group A, a segmental approach was sufficient to eliminate the residual pulmonary vein conduction because only a few pulmonary vein fibers had recovered (1 to 3 reconnected pulmonary veins; group A1). In the remaining 5 patients in group A, a circumferential ablation strategy was used to treat complete recovery of the pulmonary vein to left atrium conduction of all four pulmonary
veins (group A2). In group B, a segmental approach was sufficient in all patients because there was only a minor reconnection of 1 to 2 pulmonary veins. All recovered pulmonary veins were again isolated successfully. At the 24-month follow-up, 76.3% of all patients (61/80) were free from arrhythmia recurrence (group A, 29/40 [72.5%]; group B, 32/40 [80%]). No major complications were seen in either group.

The investigators concluded that, for patients who underwent initial circumferential pulmonary vein isolation using the cryoballoon technique, a repeat ablation procedure could be performed safely and effectively using radiofrequency catheter ablation. Since only a few reconducting pulmonary vein fibers were found in the majority of patients (especially those treated with the second-generation cryoballoon), a segmental re-ablation approach appeared to be sufficient.

CABANA TRIAL

Another extremely important study, the CABANA trial, examined the recurrence of atrial arrhythmias after catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation. The CABANA investigators randomized 2204 symptomatic patients with paroxysmal or persistent atrial fibrillation 1:1 to either percutaneous left atrial catheter or medical therapy. More specifically, the patients were classified according to age ≥65 or <65 years with ≥1 risk factor for stroke) and to those who were eligible for ablation and ≥2 drugs for rhythm or rate control.

The primary end point was a composite of death, disabling stroke, serious bleeding, or cardiac arrest. After a median 48.5-month follow-up, there was a nonsignificant 14% difference in favor of ablation, as assessed by an intention-to-treat (ITT) analysis (HR, 0.86; 95% CI, 0.65-1.15; P=0.30). The secondary end point was all-cause mortality. A nonsignificant 15% difference was observed in favor of ablation (ITT; HR, 0.85; 95% CI, 0.60-1.21; P=0.377). Analyses by treatment received and per protocol showed significant benefits of ablation for both the primary end points for mortality.

The following conclusions were made:

- Catheter ablation was associated with a significant reduction (≈50%) in the relative risk for the recurrence of atrial arrhythmias.
- The Holter-determined atrial fibrillation burden was significantly lower in patients randomized to catheter ablation compared with those who received drug therapy across the 5-year follow-up.
- Atrial fibrillation was the dominant first recurrent rhythm after the 90-day blanking period.
- No treatment-related difference was observed in recurrent atrial flutter/atrial tachycardia.
TOP TEN MESSAGES FROM THE 2016 ESC GUIDELINES

John Camm (UK), in his striking lecture on “Atrial fibrillation, the big picture,” focused on the top ten messages from the 2016 ESC guidelines. Specifically, he advised:

1. Using ECG screening in populations at risk for atrial fibrillation, especially stroke survivors and the elderly.
2. Proposing lifestyle changes to all suitable patients with atrial fibrillation to make their management more effective.
3. Using oral anticoagulation in all patients with atrial fibrillation unless they are at a low risk for stroke based on the CHA₂DS₂-VASc score or have true contraindications for anticoagulant therapy.
4. Reducing all modifiable bleeding risk factors in all patients with atrial fibrillation on oral anticoagulation, eg, by treating hypertension, minimizing the duration and intensity of concomitant antiplatelet and NSAID therapy, treating anemia, and eliminating causes of blood loss, maintaining stable INR values in patients on vitamin K antagonists, and moderating alcohol intake.
5. Checking the ventricular rate in all patients with atrial fibrillation and using rate-control medications to achieve lenient heart rate control (initially <110 bpm at rest).
6. Selecting antiarrhythmic drugs based on their safety profile and considering catheter or surgical ablation when antiarrhythmic drugs fail.
8. Not permanently discontinuing oral anticoagulation in patients with atrial fibrillation at an increased risk of stroke unless such a decision is taken by a multidisciplinary team.
10. Not performing cardioversion or ablation without anticoagulation unless an atrial thrombus has been ruled out by a transesophageal echo.

THE FUTURE FOR ATRIAL FIBRILLATION MANAGEMENT

Finally, Nassir F. Marrouche (US), in a futuristic lecture, focused on a very important issue: “The next 10 years in atrial fibrillation – my crystal ball.” In particular, he stressed that the outline of management is:

- Early detection of the substrate.
- A personalized path.
● Standardization of ablation lesions.
● Real-time MRI.
● Robotics.

Starting with genetics, metabolism, and risk factors, we progress to advanced imaging, aiming at the outcomes of early detection and prevention, treatment, and monitoring of progression. The futuristic approach begins with the patient’s risk profile (MRI image analysis, fibrosis, shape, and function). The findings will be processed by machine learning until the algorithms become sufficiently sophisticated for these outcomes to be attained.

The more futuristic VytronUS robotics system will allow the automatic detection of endocardial and epicardial borders, 3D evaluation of tissue thickness, automated or manually defined dosing and automated therapy delivery. Using the VytronUS system, in combination with machine learning, we will be able to perform preablation tissue characterization and intraoperative ultrasound tissue analysis. The big data from these measurements will be sent to a machine learning system, which may eventually yield a methodology for lesion prediction.

CONCLUSIONS

In conclusion, at the annual conference of the European Society of Cardiology, the topic of atrial fibrillation certainly had a leading role because of its epidemiology and its major complications. The particular scientific community that deals with this topic, namely arrhythmologists, specialists in heart failure, and stroke specialists, are continuing to uncover unknown and obscure features of this arrhythmia associated with the theory of chaos, but the same experts also acknowledge the enormous difficulties that remain in clarifying important aspects of this problem.

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Prevention & Treatment
**UPDATES ON DIABETES FROM THE 2018 ESC CONGRESS**

**GIANLUIGI SAVARESE, MD, PhD, FHFA, FESC; FRANCESCO COSENTINO, MD, PhD, FESC**

**Author affiliations:** Unit of Cardiology, Department of Medicine, Karolinska Institute and Heart and Vascular Theme, Karolinska University Hospital Solna, Stockholm, Sweden

**Address for correspondence:** Francesco Cosentino, MD, PhD, FESC, Unit of Cardiology, Department of Medicine, Karolinska Institute and Heart and Vascular Theme, Karolinska University Hospital Solna, S1:02, Stockholm, Sweden (email: francesco.cosentino@ki.se)

**Keywords:** diabetes; ESC congress; prevention

Diabetes was a key player at the 2018 ESC congress (Munich, Germany – August 25-29, 2018). Several sessions highlighted the importance of diabetes in the overall field of cardiovascular disease and discussed its interaction with other comorbidities and aging, current treatments, and future perspectives.

**ASCEND TRIAL**

A major study presented during the late-breaking trial session by Jane Armitage and Louise Bowman (UK) was the ASCEND trial, which was simultaneously published in two articles in the *New England Journal of Medicine.*[^1] The aim of this study was to test aspirin and n-3 fatty acid supplements in patients with diabetes mellitus without a previous cardiovascular event. Thus, between 2005 and 2011, the ASCEND investigators randomized 7740 patients to aspirin 100 mg once daily and 7740 to placebo. Participants were also randomized 1:1 to receive 1-g capsules of n-3 fatty acid (840 mg of marine n-3 fatty acids [460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid]) once daily or matching placebo.

Every 6 months after randomization, patients received, by mail, tablets and questionnaires assessing the occurrence of outcomes, adverse events, adherence to trial treatments, use of concomitant antiplatelet or anticoagulant therapy. Blood and urine samples and data on blood pressure and weight were collected from 1800 randomly selected participants after a mean follow-up of 2.5 years. Major inclusion criteria of the trial were a previous diagnosis of diabetes mellitus (any type) and the lack of known cardiovascular disease. During a mean follow-up of 7.4 years, 8.5% of patients randomized to aspirin vs 9.6% of those randomized to placebo experienced the occurrence of a cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or transient ischemic attack, or death from any cause). Thus, the risk of the primary efficacy outcomes was significantly reduced by 12% in patients taking aspirin vs placebo (absolute risk reduction, 1.1%).
In exploratory analyses, the difference in risk was seen mainly in the first 5 years. Aspirin was also shown to reduce the risk of the secondary outcomes (nonfatal myocardial infarction, nonfatal stroke, or transient ischemic attack, or death from any vascular cause or revascularization) by 12% (absolute risk reduction, 1.3%). However, patients receiving aspirin showed a 29% higher risk of major bleeding vs those randomized to placebo (4.1% vs 3.2%; absolute risk reduction, 0.9%), without any signal for attenuation of the effect over time and with an increasing incidence of major bleeding events and an increasing baseline vascular risk. Notably, there was no difference in the occurrence of fatal bleeding (0.2% vs 0.2%) and of fatal/nonfatal cancer across the study groups. A substantial proportion of the major bleeding events was in the upper GI tract, which might have been pharmacologically avoidable/preventable with a proton-pump inhibitor. In this regard, it should be emphasized that only one out of four ASCEND patients were being treated with a proton-pump inhibitor at the end of the study. Analyses on n–3 fatty acids reported neutral results.

In summary, the findings of the ASCEND trial provided direct evidence for the balance of the benefits and hazards of using aspirin for prevention purposes (and thus on top of other cardioprotective treatments, such as statins and blood pressure–lowering therapy) in contemporary patients with diabetes, but without a history of cardiovascular disease.

ADVANCES FROM PREVENTION TO INTERVENTION

In the European Heart Journal’s advances from prevention to intervention scientific session, the most important studies published on diabetes were reported. A systematic review of randomized controlled trials and genetic studies by Mach F et al focused on the perception vs the evidence of statin-related adverse effects. The main results were as follows:

1. Statin therapy is associated with a modest increase in the risk of new-onset diabetes (1/1000 patient-years), particularly in patients with metabolic syndrome or prediabetes.

2. Statins do not adversely affect cognitive function and are not associated with clinically significant deterioration of renal function or development of cataracts.

3. Of the patients treated with statins, 0.5% to 2.0% reported a nonclinically relevant transient increase in liver enzymes.

4. There is no evidence of an increased risk of hemorrhagic stroke in patients without cerebrovascular disease, whereas the small increase in risk suggested by the Stroke Prevention by Aggressive Reduction of Cholesterol Levels study in subjects with a prior stroke has not been confirmed in randomized controlled trials and observational studies.
In the same session, the findings of a post-hoc analysis of the EMPA-REG OUTCOME trial that focused on the effects of empagliflozin on the risk of cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk were discussed. This study considered diabetic patients without heart failure at baseline (90% of the overall EMPA-REG OUTCOME population) and reported that 67% of them had a low-to-average (<10%), 24% a high (10% to 20%) and 5% a very high (>20%) 5-year risk of heart failure. Empagliflozin was effective regardless of the risk of heart failure in terms of reducing cardiovascular death and heart failure hospitalization.

Another topic of discussion was an analysis of the Get With The Guidelines-Stroke registry investigating the impact of diabetes on outcomes in patients with a history of ischemic stroke. The results of this study that enrolled 409,060 patients with a previous stroke were that concomitant diabetes was associated with a higher risk of all-cause death, all-cause readmission, risk of the composite of mortality and all-cause readmission, risk of readmission for ischemic stroke/transient ischemic attack, heart failure readmission, noncardiovascular readmission, and nonischemic stroke/transient ischemic attack readmission.

Another study published in the European Heart Journal and discussed during the same session was a post hoc analysis of the SAVOR-TIMI 53 trial that assessed the optimal blood pressure for prevention of cardiovascular outcomes in high-risk patients with diabetes. The main result was the evidence of a U-shaped relationship between the risk of the composite of cardiovascular death, myocardial infarction, or ischemic stroke and baseline systolic and diastolic blood pressure, with nadirs at a systolic blood pressure of 130 to 140 mm Hg or a diastolic blood pressure of 80 to 90 mm Hg. Diastolic blood pressure <60 mm Hg was associated with an increased risk of myocardial infarction compared with diastolic blood pressure between 80 and 90 mm Hg.

Two lectures, one from Petar Seferovic (Serbia) and one from John McMurray (UK), focused on the tight relationship between diabetes and heart failure. Indeed, since patients with type 2 diabetes are at a high risk of developing heart failure, the prevention of heart failure has become a major emerging treatment goal in this setting. Previous studies showed an increased risk of heart failure in diabetic patients receiving peroxisome proliferator-activated receptor agonists, whereas metformin appears to have a favorable effect on outcomes in patients with diabetes mellitus and concomitant heart failure, and thus it is currently the first-line treatment option. Major attention has been dedicated to SGLT2 inhibitors, which are particularly promising for preventing heart failure in patients with diabetes mellitus (EMPA-REG and CANVAS trials). The mechanisms for SGLT2 inhibitor–related cardiovascular protection may be hemodynamic (diuretic/natriuretic effect, blood pressure reduction, arterial stiffness reduction) and metabolic
(improved myocardial metabolism, direct myocardial action, improved renal function) actions. Currently, SGLT2 inhibitors have been demonstrated to be beneficial for the prevention of heart failure in patients with type 2 diabetes, but there is a paradigm shift toward the use of these treatments in patients without diabetes. The DAPA-HF and EMPEROR-Reduced trials are currently testing the hypothesis of whether SGLT2 inhibitors will demonstrate an improvement in outcomes in these patients.

**LATE-BREAKING SCIENCE**

At the late-breaking science session, Peter Ueda (SE) presented the results of propensity-score matched analysis comparing the occurrence of adverse events in 17,213 patients with diabetes receiving SGLT2 inhibitors vs 17,213 treated with GLP-1 receptor agonists enrolled in Swedish and Danish registers. This study showed that GLP-1 receptor agonist use was associated with a higher incidence of lower limb amputation and diabetic ketoacidosis vs SGLT2 inhibitors, whereas there were no differences between the treatments regarding the occurrence of bone fracture, acute kidney injury, serious urinary tract infection, venous thromboembolism, and acute pancreatitis.

**ADVANCES IN SCIENCE**

At the advances in science session, Rasmus Roerth (DK) discussed a post-hoc analysis of the DANISH trial that assessed the association between implantable cardioverter defibrillator treatment and outcomes in heart failure patients with vs without diabetes. Overall, this study showed that, compared with patients without diabetes, patients with diabetes had a higher risk of all-cause mortality, primarily driven by increased cardiovascular mortality, including sudden cardiac death. Implantable cardioverter defibrillator treatment was associated with a reduced risk of sudden cardiac death in patients without diabetes, but not in those with diabetes, although there was no statistically significant interaction between diabetes and treatment. Patients with diabetes did not have a significantly increased risk of device complications.

**SUMMARY**

Overall, the presentation of the important trials’ findings and lectures from key opinion leaders in cardiovascular medicine made the 2018 ESC congress a unique opportunity to widen the most recent knowledge on the burdensome relationship between type 2 diabetes and cardiovascular disease.
REFERENCES


The time after the ESC congress is always full of information about updates to the guidelines and many discussions around new trials and their results, which are sometimes very challenging ones.

**PREVENTION OF ATHEROTHROMBOTIC EVENTS**

Before the congress, the European Medicines Agency approved the new regimen of rivaroxaban 2.5 mg twice daily in combination with low-dose acetylsalicylic acid 75 to 100 mg once daily for the prevention of atherothrombotic events in adults with coronary artery disease or symptomatic peripheral artery disease at high risk for ischemic events.\(^1\) Within this context, it was very interesting to hear the results from other rivaroxaban trials.

**COMPASS trial secondary analysis**

First, in the late-breaking science session, the secondary analysis of the COMPASS trial was presented; the primary results became a scientific background for the new indication of rivaroxaban.\(^1\) In the COMPASS trial, successful treatment with low-dose rivaroxaban and acetylsalicylic acid was associated with an increased risk of bleeding events, mainly gastrointestinal. Thus, a secondary analysis was conducted to test whether gastrointestinal or genitourinary bleeding was associated with increased rates of gastrointestinal and genitourinary cancer diagnosis in patients with vascular diseases (coronary artery disease or peripheral artery disease) on long-term antithrombotic therapy. A total of 27395 patients with stable coronary artery disease or peripheral artery disease were randomized to rivaroxaban 2.5 mg twice daily plus acetylsalicylic acid, rivaroxaban 5 mg twice daily, or acetylsalicylic acid once daily only. Bleeding was defined using modified ISTH criteria.

A very strong association was revealed between gastrointestinal or genitourinary bleeding and gastrointestinal or genitourinary cancers; 1082 patients were
diagnosed with cancer during the COMPASS trial. About 1 new cancer diagnosis in 5 was predicted by a prior bleeding event. A Cox proportional study of association between gastrointestinal bleeding and gastrointestinal cancer demonstrated a 12-fold increase in the risk of diagnosed gastrointestinal cancer after bleeding (HR, 12.9; 95% CI, 9.77-17.0; P<0.0001). In addition, a Cox proportional study of association between genitourinary bleeding and genitourinary cancer demonstrated an 80-fold increase in the risk of diagnosed genitourinary cancer after bleeding (HR, 83.4; 95% CI, 58.6-118.6; P<0.0001). John Eikelboom (CA) concluded that any gastrointestinal or genitourinary bleeding should be investigated urgently to determine the underlying cause regardless of antithrombotic treatment, which could provide earlier and more effective treatment for gastrointestinal and genitourinary cancers. Of course, this data should be confirmed further in an extended follow-up of the COMPASS trial participants.

THROMBOPROPHYLAXIS

In the Hotline sessions, two studies, which investigated thromboprophylaxis in patients with sinus rhythm, were presented: COMMANDER-HF and MARINER. These two studies were conducted due to knowledge available on disease progression by inducing inflammation, endothelial dysfunction, and arterial and venous thrombosis with the activation of thrombin-related pathways, especially in medically ill patients in MARINER and only patients with heart failure in COMMANDER-HF.

COMMANDER-HF trial

Faiez Zannad (FR) presented the results from COMMANDER-HF, which investigated whether low-dose rivaroxaban reduces the morbidity and mortality associated with vascular and hemostatic dysfunction in patients with heart failure. COMMANDER-HF was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial that tested the hypothesis that rivaroxaban, at a dose of 2.5 mg twice daily, added to background antiplatelet therapy, would be associated with lower rates of death and cardiovascular events than placebo among patients with recent worsening of chronic heart failure, reduced ejection fraction, coronary artery disease, and no atrial fibrillation. A total of 5022 patients from 628 cities in 32 countries were randomly assigned to receive low-dose rivaroxaban or matching placebo. The primary efficacy end point was a composite of all-cause mortality, myocardial infarction, or stroke. The primary safety outcome was a composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. The results did not show a beneficial effect of low-dose rivaroxaban in patients with heart failure compared with placebo. Thus, the primary efficacy outcome occurred in 25% of patients in the rivaroxaban group and 26.2% in the placebo group (HR, 0.94; 95% CI, 0.84-1.05; P=0.27). A similar nonsuperiority effect of rivaroxaban was observed for the principal safety
outcome, which occurred in 0.7% patients in the rivaroxaban group and 0.9% in the placebo group (HR, 0.80; 95% CI, 0.43-1.49; \( P=0.48 \)). The investigators suggested that the most likely reason for these results is that heart failure, rather than death, mediated by atherothrombotic events contributed to a substantial proportion of all deaths.

**MARINER trial**

The aim of another thromboprophylaxis trial, MARINER, was to investigate whether rivaroxaban would reduce the risk of symptomatic or fatal events when initiated at discharge for 45 days to medically ill patients who were at risk for a venous thromboembolism.\(^3\) The primary safety outcome was major bleeding. Apparently, these results were eagerly awaited due to current guidelines that do not recommended the routine use of prophylaxis, with an exception of an acute hospital stay. MARINER included more than 12,000 medically ill patients who were ≥40 years old and who had been hospitalized for at least 3 to 10 days with additional risk factors for a venous thromboembolism, as indicated by an IMPROVE risk score of 4 or higher or a risk score of 2 or 3 plus a D-dimer level of more than twice the upper limit of the normal range. The patients were randomized to either placebo or rivaroxaban 10 mg/day or 7.5 mg/day depending on creatinine clearance for 45 days. The primary efficacy outcome in the rivaroxaban group occurred in 50 (0.83%) patients vs 66 (1.10%) in the placebo group (HR, 0.76; 95% CI, 0.52-1.09; \( P=0.14 \)). The same tendency was observed in the principal safety outcome: major bleeding occurred in 17 (0.28%) patients in the rivaroxaban group and 9 (0.15%) in the placebo group (HR, 1.88; 95% CI, 0.84-4.23). Certainly, this study did not show significant benefit with rivaroxaban vs placebo. The investigators suggest that this result is possibly due to the study’s limitations, including difficulty in defining venous thromboembolism–related death and the possible underdosing of patients with moderate renal impairment.

**CONCLUSIONS**

Thus, it remains unclear whether we should coagulate or not... Two trials investigated oral anticoagulants in patients with sinus rhythm in medically ill patients. Despite the nonbeneficial results, it does not reduce the significance of the studied hypothesis. The statement made by Marple in 1950 that “patients with congestive heart failure are prone to develop thromboembolic complications which increase the morbidity and mortality of the disease” reflects the rationale for the first attempts to introduce oral anticoagulants into the treatment of patients with heart failure.\(^5,6\) Moreover, there is limited evidence on thromboembolic risk in patients with HFPEF based on post hoc analyses of large clinical trials focused on HFPEF. Although oral anticoagulants might have been a reasonable therapeutic option in individual patients with heart failure, the routine use...
of anticoagulation therapy in patients with heart failure in sinus rhythm is not supported by the currently available data. ■

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WHAT WILL CHANGE IN MY PRACTICE AFTER THE 2018 ESC CONGRESS?

ANNA KLIMENKO, MD, PhD; AMINA RAKISHEVA, MD, PhD

Author affiliations: 1RUDN University, Medical institute, Moscow, Russian Federation; 2Department of cardiology, Scientific and research institute of cardiology and internal diseases, Almaty, Kazakhstan

Address for correspondence: 1Anna Klimenko, RUDN University, Clinical Diagnostic Center at RUDN University, Miklukho-Maklaya street 10, 117198 Moscow, Russian Federation (email: klimenko_as@rudn.university); 2Amina Rakisheva, Scientific and Research Institute of Cardiology and Internal Diseases; Ayteke be 120, 050000 Almaty, Kazakhstan (email: aminag.rakisheva@gmail.com)

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The ESC congress provides us with the most interesting and controversial data that may possibly change our daily practice. Primary prevention is one of the significant topics that needs lots of attention. During the 2018 ESC congress, in Hotline sessions, the anticipated data from the ARRIVE and ASCEND trials on primary prevention were presented.

ARRIVE TRIAL

The ARRIVE trial was a randomized, double-blind, placebo-controlled, multicenter clinical trial that was conducted to assess the efficacy and safety of aspirin in primary prevention in patients at a moderate risk of cardiovascular disease. The study included more than 12,000 patients without established cardiovascular disease or diabetes, but with multiple cardiovascular risk factors (men ≥55 years old with 2 or more cardiovascular risk factors or women ≥60 years old with 3 or more cardiovascular risk factors). Patients were randomized in a 1:1 ratio to receive either 100 mg aspirin or placebo. The primary efficacy end point was time to the first occurrence of the composite end point, which consisted of cardiovascular death, myocardial infarction, unstable angina, stroke, and transient ischemic attack. There was no overall reduction in major cardiovascular events between groups, even the event rates were lower than expected in both groups (4.29% in the aspirin group vs 4.48% in the placebo group; HR, 0.96; 95% CI, 0.81-1.13; \( P=0.60 \)). In the aspirin group, higher rates of gastrointestinal bleeding were observed; however, the rate of bleeding was also lower than expected (0.97% vs 0.46% in the placebo group; HR, 2.11; 95% CI, 1.36-3.28; \( P=0.0007 \)).

In the per-protocol analysis, there was a significant decrease in the first nonfatal myocardial infarction in the aspirin group (37% vs 72% in the placebo group; HR, 0.53; 95% CI, 0.36-0.79; \( P=0.0014 \)). A subgroup analysis revealed that aspirin may be better in patients with a lower BMI (≤25 kg/m²) (HR, 0.75; 95% CI, 0.52-1.09; \( P=0.0920 \)). The totality of the study was negative; one of the main reasons
contributing to treatment failure was a dramatically high level of treatment non-adherence (≈40%). Finally, J. Michael Gaziano (US) concluded that “the use of aspirin remains a decision that should involve a thoughtful discussion between a clinician and a patient given the need to weigh the cardiovascular and cancer benefits against the bleeding risks, patient preferences, cost, and other factors.”

**ASCEND TRIAL**

The ASCEND trial was the largest and longest trial that was conducted to assess the efficacy and safety of aspirin and omega-3 fatty acids in primary prevention in patients with diabetes. More than 15,000 patients underwent 2x2 factorial randomization to receive aspirin 100 mg daily or placebo and to receive omega-3 fatty acid supplements (1-g capsules) daily or placebo. The primary efficacy outcome was the incidence of serious vascular events (nonfatal myocardial infarction, non-hemorrhagic stroke, transient ischemic attack, or cardiovascular death, excluding any confirmed intracranial hemorrhage). The mean follow-up was 7.4 years.

Jane Armitage (UK) presented the results from the aspirin arm. A significant reduction in serious vascular events was demonstrated in the aspirin group compared with the placebo group (8.5% vs 9.6%; rate ratio, 0.88; 95% CI, 0.79-0.97; \(P=0.01\)). Unfortunately, this benefit was accompanied by a significant increase in major bleeding risk (4.1% in the aspirin group vs 3.2% in the placebo group; rate ratio, 1.29; 95% CI, 1.09-1.52; \(P=0.003\)) with no reduction in the incidence of gastrointestinal cancer (2.0% vs 2.0%, rate ratio, 0.99; 95% CI, 0.80-1.24). She concluded that “the absolute benefits from avoiding serious vascular events were largely counterbalanced by the increased risk of bleeding,” so once-daily aspirin should not be routinely prescribed in patients with diabetes for primary prevention.

Louise Bowman (UK) presented the results from the omega-3 fatty acid arm. Daily supplements of omega-3 fatty acid did not result in a reduction in serious vascular events (8.9% vs 9.2%; rate ratio, 0.97; 95% CI, 0.87-1.08; \(P=0.55\)) or in a reduction in the composite outcome of serious vascular events or revascularization (11.4% vs 11.5%; rate ratio, 1.00; 95% CI, 0.91-1.09). There was no effect on total or cause-specific mortality. Death from any cause occurred in 9.7% of patients in the omega-3 fatty acid group compared with 10.2% in the placebo group (rate ratio, 0.95; 95% CI, 0.86-1.05). There was also a nonsignificant between-group difference in the incidence of cancer (both overall and site-specific cancer) (11.6% in omega-3 fatty acid group vs 11.5% in placebo group; rate ratio, 1.00; 95% CI, 0.99-1.10). Although taking a daily supplement of omega-3 fatty acid remains safe, there was no difference in the rates of nonfatal serious adverse events. Thus, the investigators suggested reconsidering the guideline recommendations.

Once-daily aspirin failed in primary prevention in patients without established cardiovascular diseases and moderate cardiovascular risk, either in patients with
diabetes. A similar conclusion can be drawn about omega-3 fatty acid in primary prevention of cardiovascular events in patients with diabetes.

**OPTIMIZE HF PROGRAM**

Despite the negative results from the primary prevention trials, Yuri Lopatin (RU) presented substantial data from the international multicenter OPTIMIZE HF program about secondary prevention and the increase in physician and patient adherence. The main aim of this study was to evaluate the impact of physician and patient adherence to guideline-recommended therapy on all-cause mortality, death, and rehospitalization rates in patients with heart failure. All included patients (n=635; mean age, 62; 72% male; 75.6% in sinus rhythm) were hospitalized with decompensated heart failure, NYHA class II-IV, and an LVEF less than 40% (mean EF, 33.6%). The follow-up time was 12 months and, at every visit, a five-class guideline adherence score was collected. Adherence was classified as good, moderate, or poor. According to physician adherence, all patients were divided into three groups: good physician adherence (n=224), moderate (n=396), or poor (n=15). In the good and moderate groups of physician adherence, all patients were also divided into three groups depending on their adherence (good, moderate, or poor). In the poor physician adherence group (n=15), all patients also had poor adherence. The rate of all-cause mortality was significantly lower in the group with good physician and patient adherence (2.2%, P<0.0001) compared with the groups of moderate or poor physician adherence and poor patient adherence (19% and 21%, respectively). In addition, after the 12-month follow-up, the rates of all-cause mortality and heart failure rehospitalization were significantly higher in all three groups of physician adherence when patient adherence was poor (HR, 2.7; 95% CI, 1.8-3.4; P=0.0001). Today, physician and patient adherence remains a cornerstone in the prognosis of patients with heart failure, so it is time to continue the current optimize program and establish new initiatives to optimize the management of patients with heart failure.

**Declaration of interest:** The authors have nothing to declare.
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Guidelines, Registries, & Trials
Among the several exciting late-breaking clinical trials on prevention presented at the 2018 ESC congress, I will focus on ARRIVE, ASCEND, and CAMELLIA.

ARRIVE

The benefit of low-dose aspirin in patients with acute coronary syndromes or a previous myocardial infarction, stroke, or transient ischemic attack is supported by more than 200 studies involving more than 200,000 patients. In contrast, the role of aspirin in the primary prevention of myocardial infarction and stroke in groups with a moderate estimated risk of a first cardiovascular event has been controversial, despite 30 years of randomized trials. A major issue complicating the interpretation of these studies is a low, but well-described, risk of bleeding, ranging from more common episodes of easy bruising and epistaxis to less frequent, but life-endangering, gastrointestinal hemorrhage and hemorrhagic stroke.

ARRIVE was a randomized, double-blind, placebo-controlled, multicenter study conducted in seven countries. Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate based on the number of specific risk factors. The primary efficacy end point was a composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack. Safety end points were hemorrhagic events and incidence of other adverse events. The trial enrolled 12,546 patients who were randomly assigned to receive aspirin (n=6,270) or placebo (n=6,276), with a median follow-up was 60 months. In the intention-to-treat analysis, the primary end point occurred in 269 (4.29%) patients in the aspirin group vs 281 (4.48%) patients in the placebo group (HR, 0.96; 95% CI, 0.81-1.13; P=0.6038). Gastrointestinal bleeding events (mostly mild) occurred in 61 (0.97%) patients in the aspirin group vs 29 (0.46%) in the placebo group (HR, 2.11; 95% CI, 1.36-3.28; P=0.0007). The overall incidence rate of serious adverse events was similar in both treatment groups (n=1,266 [20.19%] in the aspirin group vs n=1,311 [20.89%] in the placebo group).
Findings from ARRIVE are generally consistent with many other studies that tended to show aspirin’s ability to lower the risk of a first nonfatal myocardial infarction without affecting the risk of total stroke. With respect to safety, as expected, the rates of gastrointestinal bleeding events and some other minor bleeding events were higher in the aspirin treatment group.

**ASCEND AND ASPIRIN**

Another controversial area is the role of aspirin in the primary prevention of cardiovascular events in patients with diabetes. ASCEND was a two by two factorial study that randomly assigned adults who had diabetes, but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo and to receive 1-g capsules containing either n-3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. This section summarizes the effects of the randomization to aspirin or matching placebo. The primary efficacy outcome was the first serious vascular event (ie, myocardial infarction, stroke, or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (ie, intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer. A total of 15480 participants underwent randomization. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs 743 [9.6%]; rate ratio, 0.88; 95% CI, 0.79-0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group vs 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09-1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] vs 158 [2.0%], respectively) or all cancers (897 [11.6%] vs 887 [11.5%]). Thus, the absolute benefits were largely counterbalanced by the bleeding hazard. Indeed, aspirin use prevented serious vascular events in people who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.

Taken together, ARRIVE and ASCEND clearly indicate that the main goal in primary prevention remains optimization of lifestyle and control of traditional risk factors, including diabetes, hypertension, and dyslipidemia. They also probably put an end to the controversial issue of aspirin in primary prevention.
ASCEND AND n−3 FATTY ACID SUPPLEMENTS

This section summarizes the effects of the randomization to n−3 (also known as omega-3) fatty acid supplements or matching placebo.³ The primary outcome was a first serious vascular event (ie, nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization. The trial randomly assigned 15,480 patients with diabetes, but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules either containing n−3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% CI, 0.87-1.08; P=0.55). The composite outcome of a serious vascular event or revascularization occurred in patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91-1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86-1.05). In subgroup analyses of serious vascular events or revascularization, there was no evidence that the proportional effects of n−3 fatty acids varied according to aspirin or placebo assignment.

Observational studies in different populations have suggested that fish consumption once or twice a week is associated with a reduced risk of heart disease; these observations were confirmed in a meta-analysis. However, randomized trials of supplementation with n−3 fatty acids have shown conflicting results regarding the effects on fatal or nonfatal outcomes; meta-analyses of these trials have generally not identified significant beneficial effects of n−3 fatty acid supplementation on major vascular events.

These findings, together with results from earlier randomized trials involving patients with and without diabetes, do not support the current recommendations for routine dietary supplementation with n−3 fatty acids to prevent vascular events. Taken together, the totality of evidence suggests again that, in primary prevention, the main goal remains traditional risk factor control, while no room is left for anti-thrombotic drugs or dietary supplements.

CAMELLIA

The prevalence of obesity has nearly tripled during the past 40 years worldwide. As of 2016, 13% of adults globally were obese, with rates as high as 40% in several countries, including the United States. An additional 39% of adults worldwide are overweight. Obesity is associated with the development and progression of multiple coexisting complications, including hypertension, dyslipidemia, type 2
diabetes, coronary artery disease, stroke, and heart failure, as well as a risk of death from any cause. Yet, no pharmacologic strategy has shown cardiovascular safety or benefit. Indeed, several agents have precipitated various cardiovascular or neuropsychiatric complications, which has led to their removal from the markets by regulatory agencies and left clinicians without a pharmacologic weight-loss agent with proven cardiovascular safety.

Lorcaserin is a selective serotonin 2C receptor agonist that modulates appetite that has proven efficacy for weight management in overweight or obese patients. In CAMELLIA, 12,000 overweight or obese patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors were randomly assigned to receive either lorcaserin (10 mg twice daily) or placebo. The primary safety outcome of major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke) was assessed at an interim analysis to exclude a noninferiority boundary of 1.4. If noninferiority was met, the primary cardiovascular efficacy outcome (a composite of major cardiovascular events, heart failure, hospitalization for unstable angina, or coronary revascularization [extended major cardiovascular events]) was assessed for superiority at the end of the trial. At 1 year, weight loss of at least 5% had occurred in 1986 of the 5135 patients (38.7%) in the lorcaserin group and in 883 of the 5083 patients (17.4%) in the placebo group (odds ratio, 3.01; 95% CI, 2.74-3.30; P<0.001). During a median follow-up of 3.3 years, the rate of the primary safety outcome was 2.0% per year in the lorcaserin group and 2.1% per year in the placebo group (HR, 0.99; 95% CI, 0.85-1.14; P<0.001 for noninferiority); the rate of extended major cardiovascular events was 4.1% per year and 4.2% per year, respectively (HR, 0.97; 95% CI, 0.87-1.07; P=0.55).

Thus, the results of this trial are encouraging because they show that this new drug is safe and that it can reduce weight. On the other hand, at the end of the follow-up period, the difference in weight was about 2 kg and therefore probably inadequate to translate into a reduction in clinical end points, as confirmed by lack of efficacy in this trial, suggesting that the mainstay of treatment for obesity remains counseling and bariatric surgery in patients with morbid obesity.
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REMOTE MONITORING

Use of telemonitoring in patients with a cardiac implantable device failed to improve patient-reported outcome and device acceptance

The REMOTE-CIED trial is the first trial to investigate the role of telemonitoring in patients with cardiac implantable devices and heart failure, with respect to patient-reported outcomes and device acceptance. This prospective, multicenter, randomized controlled trial enrolled 600 patients from 5 countries. The patients were equally randomized to either remote patient monitoring or routine care by in-clinic follow-up. The primary outcome was the impact on patient-reported health status and implantable cardioverter defibrillator acceptance determined by the Kansas City Cardiomyopathy Questionnaire and the Florida Patients Acceptance Survey. Follow-up was 24 months and included in-office visits as well as telemonitoring in the remote patient monitoring group. The analysis of the primary outcome revealed identical values for all assessed patient-reported outcomes by the Kansas City Cardiomyopathy Questionnaire and device acceptance outcomes by the Florida Patients Acceptance Survey. Analyses of secondary outcomes, including mortality and implantable cardioverter defibrillator therapy, also did not show any between-group differences, only a trend toward a potential benefit with respect to less implantable cardioverter defibrillator therapies (P=0.1) could be observed in the remote patient monitoring group. Estimated cost calculations in both groups revealed lower costs in the remote patient monitoring group (-22%; P=0.02 vs routine care). In summary, the REMOTE-CIED trial failed to provide any evidence for a potential benefit by remote patient monitoring regarding patient-reported outcomes in patients with heart failure and cardiovascular implantable electronic devices. The results showing lower cost estimation in remote patient monitoring vs routine care are promising, but only hypothesis-generating that needs direct validation in future trials.
Benefit on mortality by use of telemonitoring-guided care in patients with heart failure

The TIM-HF 2, a prospective randomized open-label national trial, was conducted in Germany at 113 sites. The aim of the study was to evaluate the effect of the utilization of a telemonitoring system including pre-specified diagnostic and therapeutic algorithms in patients with heart failure. The primary end point was a composite of all-cause mortality and percentage of lost days due to hospitalization based on cardiovascular reasons. Inclusion criteria comprised symptomatic heart failure with a recent heart failure–associated hospitalization within the last 12 months. The main difference from previous telemonitoring trials was based on the prespecified algorithms including 24/7 surveillance by a telemedical center and immediate initiation of actions based on the telemonitoring findings (eg, occurrence of arrhythmias). In total, 1,538 patients were enrolled and randomized in a 1:1 fashion to the groups of remote patient monitoring or routine care. The follow-up was 12 months. The primary end point was a significant reduction in the remote patient monitoring group compared with the standard care group (HR, 0.8; \( P=0.046 \)). In addition, the single secondary end point of all-cause mortality was also reduced in the remote patient monitoring group (HR, 0.7; \( P=0.028 \)). Analysis of quality of life (QOL) was unaffected by the use of remote patient monitoring. Further prespecified subgroup analysis also failed to show an interaction for subgroups benefitting more from remote patient monitoring than others. In contrast to previous trials, the TIM-HF2 trial provides evidence for a potential benefit of remote patient monitoring use with respect to clinical outcomes in a setting with an around-the-clock telemonitoring center and predefined workflows for initiation of diagnostic and therapeutic work-ups based on the telemonitoring findings.1

ATRIAL FIBRILLATION

First trial on smartphone-based arrhythmia detection using a pulse plethysmogram application

The DIGITAL-AF trial presented by Pieter M. Vandervoort (BE) was one highlight of the ESC meeting from an electrophysiological point of view, since it is the first trial showing that the world’s first medically approved smartphone application using pulse plethysmography can detect AF in a broad real-life population. The objective of this trial was to compare the detection of AF based on the pulse plethysmography smartphone algorithm to an established 1-lead ECG device and to determine the prevalence of AF in a voluntary real-life population.

Within 48 hours, 12,328 volunteers were enrolled, resulting in 120,447 pulse plethysmography recordings (60 seconds each) over a 1-week recording period. The mean age was 49±14 years, with 58% of all participants being male. The primary automated heart rhythm analysis showed 98,586 regular recordings without
rhythm abnormalities, while 12,127 pulse plethysmography recordings suggested a potential arrhythmia; 9,733 recordings were insufficient in quality for a further analysis. The final analysis revealed 615 real AF episodes in 136 patients, confirmed by independent and trained technicians. Patients with AF were older (62±11 years), predominantly male (74%), and had a higher BMI. Overall, 76% of all AF episodes were asymptomatic and 72% were paroxysmal in nature. The total prevalence was 1.1% in the studied cohort. While the results of the prevalence are interesting, the main highlight of this trial was the feasibility of using a regular smartphone without an additional ECG device for AF detection in the broad population. In view of this first trial, further upcoming studies using digital devices implicated in the daily routine for arrhythmia screening will clearly follow. The impact of these digital devices on preventive approaches is still unclear and requires delineation in subsequent studies.

Ablation therapy improves QOL in patients with AF
This subanalysis of the CABANA trial, presented by Daniel Mark (US) during the ESC meeting, sought to evaluate the effect of ablation therapy compared with routine drug therapy in patients with AF with respect to QOL outcomes. The main CABANA trial randomized 2,204 patients 1:1 to either ablation therapy or drug therapy to evaluate a composite clinical end point of death, disabling stroke, serious bleeding, or cardiac arrest. The primary analysis revealed a neutral result of both treatment strategies regarding the primary end point. This predefined subanalysis aimed to investigate the effect of the two distinct treatment strategies on QOL as a secondary end point. The median follow-up was 48.5 months. QOL was assessed by SF-36, DASI, and EQ5D questionnaires. QOL data were collected for 92% of eligible patients at 12 months and 81% at 60 months. The QOL questionnaire analyses showed a consistent benefit with ablation vs drug therapy regarding a QOL change represented in significantly increased Mayo AF-Specific Symptom Inventory (MAFSI) and Atrial Fibrillation Effect on QualiTy of life (AFEQT) scores over the 60-month follow-up period. In summary, the secondary analysis of this large, prospective, randomized, open-label controlled ablation trial clearly suggests and confirms a substantial improvement in QOL when using an ablation strategy in patients with symptomatic AF, which was sustained for up to 5 years.

UPDATE ON ANTICOAGULATION

Comparative effectiveness of oral anticoagulation in everyday practice
The aim of the GARFIELD Prospective Registry was to (i) compare baseline characteristics and comparative safety and effectiveness of OAC with no OAC and (ii) compare the use of VKA vs non–VKA agents (NOACs) in a real-life AF cohort of the worldwide GARFIELD registry. End points included all-cause mortality,
stroke and/or systemic thromboembolism, and major bleeding episodes during a 2-year follow-up period. Analysis was performed using Cox proportional hazard models with propensity score weighting for treatment. In total, 34854 patients from 35 countries were screened for eligibility and finally 26742 patients with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score $\geq$2 were included for the analysis. Out of this cohort, 19134 were on OAC treatment (10234/53.3% on NOACs and 8900/46.5% on VKA), while 7608 received no OAC treatment (60% on antiplatelet agents). Primary analysis revealed a clear benefit of OAC vs no OAC with respect to all-cause mortality (HR, 0.83; 95% CI, 0.75-0.93; $P<0.001$), stroke/systemic thromboembolism (HR, 0.73; 95% CI, 0.59-0.90; $P=0.003$), while major bleeding rates strongly tended to be higher in the OAC group compared with patients not receiving OAC (HR, 1.36; 95% CI, 1.00-1.85; $P=0.053$). The analysis of NOAC vs VKA revealed a clear benefit for NOAC use with respect to all-cause mortality (HR, 0.81; 95% CI, 0.71-0.92; $P=0.001$), while stroke/systemic thromboembolism (HR, 0.85; 95% CI, 0.65-1.11; $P=0.237$) and major bleeding rates (HR, 0.81; 95% CI, 0.59-1.11; $P=0.192$) were unchanged compared with VKA-treated patients. This study provides further evidence for a beneficial use of a preventive OAC treatment in patients with AF. In addition, these results suggest and further highlight a preference for the use of NOACs instead of VKA in patients with AF and an indication for OAC in line with the current guideline recommendation.

REFERENCES

A number of interesting studies were presented in this very large international congress, which hosted more than 33 000 delegates from five continents.

HEART FAILURE

Low-dose rivaroxaban does not improve outcomes in patients with HFREF in sinus rhythm

The COMMANDER HF trial\(^1\) addressed the issue of anticoagulation in patients with chronic heart failure with reduced ejection fraction (<40%) and in sinus rhythm. It is well established that heart failure is associated with a prothrombotic state through inflammation and endothelial dysfunction, and it is a key component of the CHA\(_2\)DS\(_2\)-VASc score in patients with atrial fibrillation in order to define the risk of stroke and embolic events. However, the benefit of anticoagulation in patients with heart failure and in sinus rhythm is not well established and several trials have failed to demonstrate any benefit with warfarin, with an increased risk of bleeding compared with antiplatelet agents or no therapy.

The purpose of COMMANDER HF was to evaluate the potential benefit of the new oral anticoagulant rivaroxaban administered at a low dose (2.5 mg twice daily) compared with placebo on top of the standard of care in a population of 5022 patients who had chronic heart failure, coronary artery disease, a reduced ejection fraction, and evidence of elevated plasma natriuretic peptides after an episode of decompensated heart failure within 21 days. After a median 21-month follow-up, there was no between-group difference in either the occurrence of the primary composite end point of death of any cause, myocardial infarction, or stroke (HR, 0.94; 95% CI, 0.84-1.05; \(P=0.27\)) or in all-cause mortality. There was a numeric trend for reducing stroke events. There was also no difference in the major safety end point of fatal or serious bleeding with potential permanent disability.

This trial has limitations, including the absence of a central adjudication of events so that one cannot exclude misclassification of events and of electrocardiographic monitoring with possible underdiagnosis of asymptomatic atrial fibrillation.
However, these negative results have important clinical implications:

- They confirm the fact that nonfatal thrombotic events, particularly deep venous thrombosis and pulmonary embolism, are rather uncommon during the course of heart failure.

- They lead to the conclusion that new oral anticoagulants are not routinely indicated in patients with heart failure of ischemic origin with low ejection fraction in sinus rhythm.

**Remote patient monitoring is associated with improved clinical outcomes**

Inconsistent results have been reported with remote distance monitoring of patients with heart failure: a few studies are positive, whereas others negative. The TIM-HF2 trial\(^2\) was a randomized, prospective trial conducted in 1538 patients with heart failure in NYHA class II or III with an ejection fraction <45% or >45% provided that they were treated with diuretics. Patients were recruited in German cardiology centers and among general practitioners; they were assessed by a specific score in order to rule out significant depression. The rationale for excluding depression derived from a post hoc analysis from a previous telemonitoring study, TIM-HF1, which suggested that patients without depression might benefit from this approach. A previous heart failure hospitalization within 12 months was also required as an inclusion criterion. The median time from the index hospitalization was approximately 3 months and patients were well treated by modern standards.

Several biomarkers and vital signs or urgent calls were transferred online 24/7 to a telemonitoring center, allowing, if needed, immediate action by contact of the general practitioner, the cardiologist, or of an emergency unit. All data were reviewed on a daily basis. The primary end point was a composite of all-cause mortality and percentage of days lost due to unplanned cardiovascular hospitalization. There was a significant reduction in favor of the patients receiving telemonitoring vs patients receiving usual care with a 20% relative risk reduction (\(P=0.046\)). All-cause mortality was also significantly reduced by 30% (\(P=0.028\)) and there was a nonsignificant trend for a reduction in cardiovascular mortality. The number of days lost due to unplanned heart failure hospitalization was also significantly reduced by 20% (3.8 vs 5.6 days/year; \(P=0.007\)).

This positive study highlights the fact that, in order to be successful, remote monitoring in patients with heart failure must include transmission of data, patient education, and a good cooperation between the monitoring center and the downstream professionals. One key for the success of TIM-HF2 is undoubtedly the fact that the monitoring center was active 24/7 in order to manage the flow of information.
Tafamidis: first medication to show benefit in cardiac amyloidosis

Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils, composed of misfolded transthyretin proteins, in the myocardium. These deposits result in abnormally stiff ventricles, restrictive cardiomyopathy, and conduction defects, but no treatment so far has shown any benefit in this disabling, late-onset condition that is associated with a very poor prognosis. The condition can be an autosomal dominant trait caused by mutations in the transthyretin gene or by the wild-type transthyretin protein. Although the prevalence of the disease is not well known, some studies suggest that it could account for 10% to 15% of the cases of heart failure with preserved ejection, particularly in older patients.

Tafamidis is a drug that binds to the thyroxine binding sites of transthyretin, thus inhibiting the dissociation of tetramers into monomers, limiting intramyocardial deposits. The ATTR-ACT trial assessed the efficacy and safety of tafamidis in 441 patients with transthyretin amyloid cardiomyopathy in a double-blind, placebo-controlled design. Two doses of tafamidis, 20 and 80 mg, were tested against placebo for 30 months. In the primary analysis, all-cause mortality followed by cardiovascular hospitalizations was hierarchically assessed. Secondary analyses included 6-minute walking distance and quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

There was a significant reduction in the primary end point (P<0.001) in the pooled tafamidis arms related to a reduction in all-cause mortality (HR, 0.70; 95% CI, 0.51-0.96) and in cardiovascular hospitalizations, which were reduced by 32%. Tafamidis treatment was also associated with a lower rate of decline in exercise capacity and quality of life. The effect on functional capacity was observed at 6 months, whereas the effect on mortality was only apparent at 18 months. The benefit was similarly observed in inherited and wild-type transthyretin amyloidosis. There was no differential effect across prespecified subgroups except the rate of cardiovascular hospitalizations, which was higher in tafamidis-treated patients in NYHA class III. Finally, there were no specific safety concerns and the rate of adverse events was similar in the intervention and the placebo groups, as well as with the two doses of tafamidis.

This trial, which enrolled a growing proportion of elderly patients with heart failure, has important clinical implications, as it shows, for the first time, benefit of an intervention in a deadly condition, where only palliative treatments have been provided so far.
PREVENTION

Secondary prevention

The EUROASPIRE program is a survey that has been conducted across European countries since 1996. The survey assesses, at regular intervals, the quality of secondary prevention measures in patients with documented coronary artery disease. The results of EUROASPIRE V, which was conducted in 2016–2018 in 21 European countries, were presented in Munich. The results from this survey are appalling: if medical therapy in general is in line with the recommendations, lifestyle and preventive measures do not show any progress compared with EUROASPIRE IV, which was conducted in 2012–2015.

Patients included in the latest survey had a history of acute coronary syndrome or myocardial revascularization 6 months to 3 years before enrollment. The rate of smoking increased from 48% to 53%, patients exercising regularly declined from 44% to 34%, the rate of patients who were overweight remained stable and concerned 81%, and increased blood pressure was reported in 46% vs 45%. The proportion of patients having a diet based on a sufficient proportion of fruits and vegetables declined from 80% to 68%. The only matter of satisfaction was the decline in patients with raised LDL cholesterol, which dropped from 43% to 36%.

Overall, these results highlight the need for a better cooperation between professionals and a better education of patients regarding lifestyle and prevention measures in the large population of European citizens with coronary artery disease.

Primary prevention in patients with diabetes mellitus

Low-dose aspirin is not beneficial

Patients with diabetes mellitus have an increased risk of cardiovascular events compared with patients without diabetes mellitus. Aspirin is beneficial in secondary prevention, but the benefits in primary prevention have not been well established in the general population or in patients with diabetes mellitus. Moreover, excess bleeding has been reported, thus counterbalancing the potential benefit observed in patients treated in primary prevention.

The ASCEND trial[^4] was a randomized trial that compared the efficacy and safety of enteric-coated aspirin 100 mg/day with placebo in patients with diabetes and without manifest cardiovascular disorder. A factorial design was used to assign patients to a regimen of n-3-fatty acid or placebo. A total of 15 480 patients with diabetes of any type were randomized and followed-up for an average of 7.4 years. The primary efficacy end point was the first serious vascular event, ie, myocardial infarction, stroke, transient ischemic attack, or cardiovascular death, and the primary safety end point was the first major bleeding event, ie, intracranial hem-
orrhage, a sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleedings.

Aspirin was associated with a significant reduction in the occurrence of the primary end point (HR, 0.88; 95% CI, 0.79-0.97; \( P = 0.01 \)), but the benefit was offset by a significant increase in serious bleeding events (HR, 1.29; 95% CI, 1.09-1.52; \( P = 0.003 \)), with most of the excess being gastrointestinal bleeding. There was no difference in the incidence of gastrointestinal tract cancers or in any cancer between groups. The randomization to the n-3-fatty acid arm did not yield any benefit in this population.

The ASCEND trial confirms that low-dose aspirin in patients with diabetes without documented cardiovascular disease confers a mild benefit on cardiovascular events, but that this benefit is counterbalanced by an excess in major bleeding events. Therefore, these results should lead the guidelines on prevention not to recommend aspirin in primary prevention in patients with diabetes in the absence of manifest cardiovascular disease.

**Primary prevention in moderate-risk patients**

*Low-dose aspirin fails*

The absence of benefit of low-dose aspirin in primary prevention has been confirmed by another study, ARRIVE\(^5\), which was conducted in 7 countries in patients without known cardiovascular disease or diabetes and with an estimated moderate risk of cardiovascular events (20% to 30% at 10 years). Male patients had to be at least 55 years old with at least 2 risk factors and female patients had to be at least 60 years old with 3 risk factors. A total of 12,546 patients were randomized to either enteric-coated aspirin 100 mg or to placebo. Due to a low event rate, the study moved from an event-driven design to a fixed-termination date.

The primary composite end point was cardiovascular death, myocardial infarction, stroke/unstable angina, or transient ischemic attack. Aspirin did not confer benefit (HR, 0.96; 95% CI, 0.81-1.10; \( P = 0.60 \)) and the only positive effect was observed in a per-protocol analysis in patients who were at least 60% treatment compliant, where a significant reduction in fatal or nonfatal myocardial infarction was observed (HR, 0.53; 95% CI, 0.36-0.79; \( P = 0.0014 \)). Prespecified subgroup analyses did not show any difference between the different subgroups. There was a significant 2-fold increase in the risk of gastrointestinal bleeding (HR, 2.11; 95% CI, 1.36-3.28; \( P = 0.0007 \)), with most of these events being mild or moderate.

This second primary prevention study in patients at moderate cardiovascular risk without diabetes mellitus suggests that aspirin should not be given routinely in the absence of documented cardiovascular disease and that it is associated with a substantial increase in the risk of bleeding.
REFERENCES


The 2018 ESC and ESH guidelines for the treatment of hypertension were presented at the ESH meeting in Barcelona in June 2018 and the final presentation with the publication of the full paper made at the ESC congress in Munich in August 2018.1

PREVALENCE AND DEFINITION OF HYPERTENSION

Based on office BP, the global prevalence of hypertension was estimated to be 1.13 billion in 2015 (30% to 45% of adults worldwide), affecting over 150 million people in Central and Eastern Europe. The definition of hypertension was unchanged as compared with the version available in the 2013 guidelines, with office SBP ≥140 mm Hg and/or DBP ≥90 mm Hg. The 2018 guidelines still categorize patients with an SBP/DBP of 130-139/85-89 mm Hg as having high-normal blood pressure, and then grade 1, 2, and 3 hypertension and isolated systolic hypertension (SBP >140 mm Hg). Definitions are still based on office blood pressure measurements, which is in contrast with the ACC/AHA guidelines that classify patients with an SBP/DBP of 130-139/85-89 mm Hg as having grade 1 hypertension and then all the other patients as grade 2.

Regarding the diagnosis, in addition to office BP, out-of-office BP measurements (home and/or ambulatory BP measurements) should be used. There is now more evidence to suggest that doctors can diagnose hypertension based on home blood pressure measurements, which reduces the number of people with the diagnosis of white-coat hypertension who then receive unnecessary treatment.

TOTAL CARDIOVASCULAR RISK

There is an emphasis on the importance of total CV risk, as in the previous ESC/ESH guidelines, and not just on blood pressure level, because hypertension rarely occurs in isolation and often clusters with other CV risk factors, such as dyslipidemia and...
glucose intolerance. In addition, it is now recommended to measure serum uric acid as part of the screening process of patients with hypertension. A unique and important aspect of CV risk estimation in patients with hypertension is the need to consider the impact of hypertension-mediated organ damage. This was previously termed “target-organ damage,” but hypertension-mediated organ damage more accurately describes hypertension-induced structural and/or functional changes in major organs (ie, the heart, brain, retina, kidney, and vasculature). Finally, quantification of total CV risk is an important part of the risk stratification process for patients with hypertension.

**DRUG TREATMENT INITIATION AND BLOOD PRESSURE TARGETS**

All guidelines recommend that patients with grade 2 or 3 hypertension receive antihypertensive drug treatment in addition to lifestyle interventions. The guidelines also recommend that patients with grade 1 hypertension and high CV risk or hypertension-mediated organ damage should be treated with BP–lowering drugs. However, is not clear whether BP–lowering drugs should be offered to patients with grade 1 hypertension and low to moderate CV risk or older patients (>60 years) with grade 1 hypertension, nor is it clear whether patients with high-normal BP levels need BP–lowering drug treatment. However, based on the new data, the Task Force recommends that, in patients with grade 1 hypertension and a low to moderate CV risk, lifestyle advice should be accompanied by BP–lowering drug treatment.

Other new messages include recommendations for BP–lowering drug treatment in those with high-normal BP (ie, 130-139/85-89 mm Hg) when CV risk is very high and in those with grade I hypertension (ie, 140-159/90-99 mm Hg), including older patients (between 65 and 80 years old), in addition to lifestyle advice.

Treatment targets in all patients are recommended at or below 130/80 mm Hg, and, in patients <65 years old, a BP range of 120 to <130 mm Hg is advised. These guidelines pay more attention to hypertension in the elderly. Frailty and biological age rather than chronological age determine the tolerability and benefit of BP–lowering drugs. For patients >65 years old, the treatment target is ≥130 to <140 mm Hg. Targets should never be <120 mm Hg, as this could result in adverse effects.

**Lifestyle recommendations**

Healthy lifestyle choices can prevent or delay the onset of hypertension and can reduce CV risk. Effective lifestyle changes may be sufficient to delay or prevent the need for drug therapy in patients with grade 1 hypertension. The recommended lifestyle measures that have been shown to reduce blood pressure include:
• Restricting salt intake to less than 5 g/day.
• Limiting alcohol consumption to less than 14 units/week for men and less than 8 units/week for women.
• Increasing the consumption of vegetables.
• Controlling body weight.
• Performing regular aerobic exercise at least 30 min/day.
• Quitting smoking.

**Drugs for the treatment of hypertension**

Most patients will require drug therapy in addition to lifestyle measures to achieve optimal BP control. Since the release of the previous guidelines, different meta-analyses have been published. These meta-analyses have reported cause-specific differences on outcomes between some drugs (e.g., less stroke prevention with β-blockers and less heart failure prevention with CCBs); however, overall, major CV outcomes and mortality were similar with treatment based on initial therapy, with all five major classes of treatment. Therefore, these guidelines recommend that the same five major classes of drugs should form the basis of antihypertensive therapy. However, as in previous guidelines, there are preferred and less preferred drugs based on BP level, risk factors, and subclinical and clinical organ damage.

Previous guidelines have generated a variety of different strategies to initiate and escalate BP-lowering medication to improve BP control rates. In previous guidelines, the emphasis was on the initial use of different monotherapies, increasing their dose, or substituting for another monotherapy. Despite this, BP control rates worldwide have remained poor, close to 35%. This failure to achieve BP control in most hypertensive patients, despite numerous interactions of previous guidelines, suggests that these treatment strategies are not working and that a different approach is needed. The Task Force believes that one of the most important issues is how to improve BP control in patients receiving treatment, which has become an even more pressing matter because, based on new evidence, current guidelines are recommending more stringent BP targets (on-treatment values of ≤130/80 mm Hg in the general population and ≤140/90 mm Hg in older hypertensive patients), which will make the achievement of BP control even more challenging.

The new guidelines recommend starting with a two-drug combination in most patients (high BP levels and/or high CV risk) as initial therapy to rapidly and effectively reduce BP, this is in contrast to the stepwise treatment in the previous
recommendations. As nonadherence plays a major role in poor BP control and increases with the number of pills, drug combinations of two or even three drugs in a single tablet “could transform blood pressure control rates.”

Now, based on the results of outcome RCTs and recent meta-analyses, all five major drug classes can be combined, except for ACE inhibitors and ARBs, whose concomitant use may lead to further BP reduction, but increased adverse effects and is thus discouraged. The guidelines recommend that the treatment of hypertension should be preferentially based on combinations of an ACE inhibitor or ARB with a CCB and/or a thiazide or a thiazide-like diuretic. These combinations are now widely available in a single pill and in a range of doses, facilitating treatment simplification from lower to higher doses, and they will limit potential adverse effects associated with diuretic or CCB monotherapy, reducing the risk of hypokalemia due to diuretics, and reducing the prevalence of peripheral edema due to CCBs. In addition, these combinations also ensure that the RAS is inhibited as part of the treatment strategy, which is an important consideration for many patient groups (eg, diabetes, metabolic syndrome, LVH, proteinuria, CHD, CHF).

Other combinations, such as a CCB and a diuretic, also have evidence from RCTs supporting their use. However, they are much less widely available and do not include RAS blockade, which may be desirable in many patient groups. β-Blockers in monotherapy or combination should be preferentially used when there is a specific clinical indication for their use (eg, CHD, angina, postmyocardial infarction, high heart rate, CHF along with ACE inhibitors or ARBs, etc). Previous studies have shown that some low- or moderate-risk patients with grade 1 hypertension may achieve their BP target with monotherapy, but this is unlikely in patients with an initial SBP >150 mm Hg who would require a BP reduction of ≥20 mm Hg. The new guidelines also suggest starting with a low-dose combination of two antihypertensive drugs, even in patients with grade 1 hypertension and a low to moderate CV risk.

For patients with resistant hypertension, they suggest reinforcement of lifestyle measures, especially sodium restriction, addition of low-dose spironolactone to existing triple treatment, or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, a higher dose of the thiazide or thiazide-like diuretic, or a loop diuretic, or the addition of bisoprolol or doxazosin.

In patients with white-coat hypertension, it is recommended to implement lifestyle changes aimed at reducing CV risk. Drug treatment may be considered in people with evidence of hypertension-mediated organ damage or in whom the CV risk is high or very high.
Routine drug treatment is not indicated. In masked hypertension, lifestyle changes are recommended to reduce CV risk, with regular follow-ups, including periodic out-of-office BP monitoring. Antihypertensive drug treatment should be considered in masked hypertension to normalize the out-of-office BP, based on the prognostic importance of out-of-office BP elevation.

Finally, in contrast with the 2013 guidelines, device-based therapy for hypertension is no longer recommended, until further evidence regarding safety and efficacy becomes available.

REFERENCES
Traditionally, the studies presented in Munich will influence practice and may lead to guideline updates in the future. However, if the “bright side” of the trials is highlighted during the ESC congress, it is now time to identify the “take-home messages”!

**HIGH-STEACS TRIAL**

The High-STEACS trial, a cluster-randomized controlled trial that compared the high-sensitivity troponin assay with the contemporary assay, enrolled consecutive patients with suspected acute coronary syndrome. The trial included 2 phases: (i) a 6-month validation phase during which the contemporary cardiac troponin assay was used to guide clinical decisions; and (ii) a 6- to 24-month implementation phase during which only the results from the high-sensitivity assays were disclosed. Both assays were measured throughout the trial, and hs-TnI sex-specific cutoffs were used to reclassify patients with troponin levels below the diagnostic threshold as having myocardial injury.

A total of 48,282 consecutive patients were enrolled with 1771 (17%) patients being reclassified as having a myocardial injury or infarction by hs-TnI who were not identified with the contemporary assay. Reclassified patients had a hospital stay that was twice as long and they were more likely to undergo coronary angiography (11% vs 4%). However, 1-year outcomes showed no differences between the two groups (adjusted odds ratio for implementation vs validation phase, 1.10; 95% CI, 0.75-1.61; \( P=0.620 \)). These results were surprising and disappointing, suggesting that the selection of an appropriate population needs to be rethought in order to give the best possible care.

**ASCEND TRIAL**

With the ASCEND trial, another established concept has been challenged. The ASCEND trial included 15,480 participants, with no previous cardiovascular disease, who were randomized to aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (ie,
myocardial infarction, stroke, or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (ie, intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs 743 [9.6%]). Major bleeding events occurred in 314 participants (4.1%) in the aspirin group vs 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09-1.52; \( P=0.003 \)).

Again, there was no net benefit in taking aspirin since the reduction in vascular events was counterbalanced by an increase in bleeding. The ASCEND trial was also a good test of the overall hypothesis of aspirin for total cancer prevention, and, in this setting, the results were disappointing since no suggestion of benefit was noted.

**GLOBAL LEADERS TRIAL**

GLOBAL LEADERS\(^3\) was an open-label superiority trial that randomized patients undergoing percutaneous coronary intervention for stable coronary artery disease or acute coronary syndrome to receive (1:1) either 75–100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, which was followed by 23 months of ticagrelor monotherapy, or standard dual antiplatelet therapy with 75–100 mg aspirin daily plus either 75 mg clopidogrel daily (for patients with stable coronary artery disease) or 90 mg ticagrelor twice daily (for patients with acute coronary syndromes) for 12 months, which was followed by aspirin monotherapy for 12 months. A total of 15968 participants were randomized (7980 to the experimental group and 7988 to the control group). After the 2-year follow-up, 304 (3.81%) participants in the experimental group died or had a nonfatal MI vs 349 (4.37%) participants in the control group (rate ratio, 0.87; 95% CI, 0.75-1.01; \( P=0.073 \)). Again, the results [the overall results] did not show that ticagrelor alone was better than the traditional approach.

**VERDICT TRIAL**

In the VERDICT trial,\(^4\) 2147 patients with clinical suspicion of NSTE-ACS were randomized to receive (1:1) very early invasive coronary angiography (within 12 hours) or standard invasive care (within 48 to 72 hours). The primary end point was a combination of all-cause death, nonfatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia or hospital admission for heart failure. Of the patients randomized to the very early invasive care arm, 1075 had invasive coronary angiography performed at a median of 4.7 hours after
randomization, whereas 1072 patients assigned to standard invasive care had invasive coronary angiography performed 61.6 hours after randomization. The primary end point occurred in 296 (27.5%) of the participants in the very early invasive coronary angiography group vs 316 (29.5%) in the standard care group (HR, 0.92; 95% CI, 0.78-1.08). In conclusion, a very early invasive strategy did not improve clinical outcomes vs an invasive strategy conducted within 2 to 3 days in patients with NSTE-ACS. Of note, one-third of patients enrolled with a diagnosis of NSTE-ACS had no significant coronary stenosis.

**SCOT HEART TRIAL**

Now we come to the only trial, the SCOT HEART trial, that was presented at the 2018 ESC congress as clearly positive. According to the authors, CT coronary angiography in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years. Please consider that, in the previously published shorter follow-up, only 25% of the patients in the SCOT HEART trial had obstructive coronary artery disease, and, at 6 weeks, only 12% had a diagnosis of angina due to coronary artery disease, and CT coronary angiography use was associated with more invasive procedures. These differences seem to disappear at the 5-year follow-up in favor of CT coronary angiography.

Several points challenge the credibility of the conclusions of this study. Patients were included because of “chest pain,” which is not a diagnosis of angina and even less of myocardial ischemia. Actually, only 35% of included patients had possible angina and 61% atypical chest pain. Moreover, half of the trial population presented with normal or near-normal coronary arteries. At the 5-year follow up, the event rate was higher in patients with possible angina and, in this subgroup, there was no difference between CT coronary angiography and standard care, suggesting that clinical presentation and risk assessment should drive the therapeutic approach.

Given that the number of invasive procedures was similar in the two groups, the authors attributed the advantage of the CT coronary angiography arm to more preventive measures. However, the reduction in events in the CT coronary angiography group exceeds even the most optimistic expectations from aspirin/statin therapy. Relative to the observed reduction of 33 fewer events in 97 patients, only 3 could be attributed to aspirin/statin, assuming a NNT of 50. The effect size is much lower than expected: 3.1% vs a predicted 13.1%. The small number of events makes the trial susceptible to the play of chance. In addition, bias is always a major concern in open-label trials.
Once again, an implausible conclusion reached the highest level of medical communication, along with the results of the previously published PROMISE trial, namely:

1. Almost 50% more invasive coronary angiographies were performed in the CT coronary angiography group, without any benefit in clinical outcome.

2. Most revascularizations in the CT coronary angiography group were performed in patients who had no objective evidence of myocardial ischemia.

3. Most importantly, in the CT coronary angiography group, about 400 patients had no obstructive coronary artery disease despite overt symptoms.

They all hold true!

**THE DIAMOND APPROACH**

An encouraging signal from the Munich ESC congress comes from the high interest and active participation in events proposing a new approach to diagnose and treat ischemic heart disease. This major cultural change began several years ago, when a “Copernican Revolution” proposing a multifactorial nature of myocardial ischemia was launched. No longer was it a one-to-one association with obstructive coronary atherosclerosis, but a complex array of precipitating mechanisms, including severe stenosis, microvascular dysfunction, coronary vasospasm, etc. The notion was also popularized that these mechanisms may act in combination or alternate in time, leading to a much more complex and dynamic pathogenesis of myocardial ischemia.

A direct implication of this new understanding of ischemic heart disease is that both diagnostic and therapeutic algorithms must consider the complexity of the pathogenesis of myocardial ischemia. Moreover, drug selection for the optimal treatment of ischemic heart disease must also consider associated cardiac conditions and systemic comorbidities.

So, the diamond approach suggests abandoning the traditional distinction between first-line and second-line agents, which is not supported by any evidence, and making an effort to match the agent with the precipitating mechanism(s) of ischemia in the individual patient and with the associated cardiac and systemic conditions (eg, heart rate, left ventricular function, blood pressure, diabetes, CKD, COPD, etc, etc).

**TAKE-HOME MESSAGES**

- High-STEACS: hs-TnI does not identify the correct patients to deliver the best possible care in the setting of ACS.
VERDICT: In patients with NSTE-ACS, an early invasive strategy does not improve outcomes.

ASCEND: There is no net benefit in taking aspirin in primary prevention.

GLOBAL LEADERS: Ticagrelor alone is not better than the traditional approach.

SCOT HEART: CT coronary angiography does not add any benefit in terms of outcomes in patients with angina.

REFERENCES


Abbreviations & Acronyms
ACC  American College of Cardiology
ACE  angiotensin-converting enzyme
ACS  acute coronary syndrome
ACS QUIK  Acute Coronary Syndrome QUality Improvement in Kerala
AF  atrial fibrillation
AHA  American Heart Association
ANNEXA-4  Andexanet alfa, a Novel aNtidote to the anticoagulation Effects of FXA inhibitors
ARB  angiotensin receptor blocker
ARRIVE  Aspirin to Reduce Risk of Initial Vascular Events
ASCEND  A Study of Cardiovascular EveNts in Diabetes
ATTRACT  Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis
BMI  body mass index
BP  blood pressure
CABANA  Catheter ABlation vs ANti-arrhythmic drug therapy for Atrial fibrillation
CAMELLIA-TIMI 61  Cardiovascular And MEtaboLic effects of Lorcaserin In overweight And obese patients–Thrombolysis In Myocardial Infarction 61
CANTOS  Canakinumab Antiinflammatory Thrombosis Outcome Study
CASTLE-AF  Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation
CATCH  Comparison of Acute Treatments in Cancer Hemostasis
CCB  calcium channel blocker
CHA₂DS²-VASc  Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack–VAscular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma) and Sex category
CHD  coronary heart disease
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CHF</td>
<td>chronic heart failure</td>
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<td>CKD</td>
<td>chronic kidney disease</td>
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<td>CLOT</td>
<td>Comparison of Low-molecular-weight heparin versus Oral anticoagulant Therapy for the prevention of recurrent venous thromboembolism in patients with cancer</td>
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<td>COMMANDER HF</td>
<td>COMparison of the efficacy and safety of rivaroxaban with placebo for reducing the risk of death, Myocardial infArctioN or stroke in subjects with heart failure and significant coronary artery Disease following an episode of decompensated Heart Failure</td>
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<td>COMPASS</td>
<td>Cardiovascular Outcomes for People Using Anticoagulation StrategieS</td>
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<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>CRT</td>
<td>cardiac resynchronization therapy</td>
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<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CV</td>
<td>cardiovascular</td>
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<td>DANISH</td>
<td>DANISH study to assess the efficacy of ICDs in patients with nonischemic systolic heart failure on mortality</td>
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<td>DAPA-HF</td>
<td>DAPAgliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic Heart Failure</td>
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<td>DAPT</td>
<td>dual antiplatelet therapy</td>
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<td>DASI</td>
<td>Duke Activity Status Index</td>
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<td>DAWN</td>
<td>DWI or CTP Assessment with clinical mismatch in the triage of Wake-up and late presenting strokes undergoing Neurointervention with Trevo</td>
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<td>DBP</td>
<td>diastolic blood pressure</td>
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<td>DESSOLVE III</td>
<td>DES with Sirolimus and a bioabsorbable pOLymer for the treatment of patients with de noVo lEsion in the native coronary arteries</td>
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<tr>
<td>DIGITAL-AF</td>
<td>DIGITAL noninterventional Atrial Fibrillation</td>
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<td>EMPA-REG OUTCOME</td>
<td>Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>EMPEROR-Reduced</td>
<td>EMPagliflozin outcome trial in Patients With chronic heart failure with reduced ejection fraction</td>
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<td>EQ-5D</td>
<td>EuroQol-5 dimension</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>ESH</td>
<td>European Society of Hypertension</td>
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<td>EUROASPIRE</td>
<td>EUROpean Action on Secondary and Primary prevention by Intervention to Reduce Events</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GARFIELD</td>
<td>Global Anticoagulant Registry in the FIELD-Atrial Fibrillation</td>
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<td>GLP-1</td>
<td>glucagon-like peptide 1</td>
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<td>High-STEACS</td>
<td>High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome</td>
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<td>HFMEF</td>
<td>heart failure with midrange ejection fraction</td>
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<td>HFPEF</td>
<td>heart failure with preserved ejection fraction</td>
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<tr>
<td>HFREF</td>
<td>heart failure with reduced ejection fraction</td>
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<tr>
<td>hs-TnI</td>
<td>high-sensitivity troponin I</td>
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<td>ICD</td>
<td>implantable cardioverter-defibrillator</td>
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<td>IMPROVE</td>
<td>International Medical Prevention Registry on Venous Thromboembolism</td>
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<td>LAA</td>
<td>left atrial appendate</td>
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<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<td>MANAGE</td>
<td>MANAGEment of myocardial injury after noncardiac surgery</td>
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<td>MANAGE-HF</td>
<td>Multiple cardiac sensors for mAnAGEment of Heart Failure</td>
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<td>MOMENTUM</td>
<td>Multicenter study Of MagLev tEchNology in paTients Undergoing Mechanical circulatory support therapy with HeartMate 3</td>
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<td>Abbreviation</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NOAC</td>
<td>non-vitamin K oral anticoagulants</td>
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<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
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<td>NSTE-ACE</td>
<td>non–ST-segment elevation acute coronary syndrome</td>
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<td>NT-proBNP</td>
<td>N-terminal pro-brain natriuretic peptide</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>OPTIMIZE-HF</td>
<td>Organized Program To Initiate lifesaving treatment In hospitalized patients with Heart Failure</td>
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<td>PREDIMED</td>
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<td>RAS</td>
<td>renin-angiotensin system</td>
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<td>RADIAL</td>
<td>Radial Artery Database International Alliance</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>REMOTE-CIED</td>
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<td>systolic blood pressure</td>
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<td>short-form 36</td>
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<td><strong>SGLT2</strong></td>
<td>sodium glucose cotransporter 2</td>
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<td><strong>SMART-DATE</strong></td>
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<td><strong>VKA</strong></td>
<td>vitamin K antagonist</td>
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INSTRUCTIONS FOR AUTHORS

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