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ESC Paris

2019

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EDITORIAL

This year we had an excellent European Society of Cardiology (ESC) 2019 annual meeting. Location and timing could not have been better: Paris at the end of August!

The venue was not the usual one near the Charles De Gaulle airport, but right in the center, at Paris Expo Port de Versailles, very easy to access. The congress building was easy to “navigate,” located on three floors with exhibitions and the various villages on the second and third floors with business as usual (registration, audio-visual, plenary rooms, ESC village) on the first floor. In addition... what can we say about the Fellow’s room on the top floor, with a huge glass window overlooking the city and with the Eiffel Tower in front of you?

The congress was held jointly with the World Heart Federation (WHF) with a total of 33 510 participants. Yes, almost 23 000 health care professionals came from more than 150 countries enjoying over 600 sessions running in several parallel rooms! The organization was such that one could hardly see a queue or hear a complaint.

But...the best of the ESC/WHF was the science presented and this is what this issue of Dialogues in Cardiovascular Medicine is about: a very concise summary of what is new (in Cardiology) in the first part of 2019 presented in the usual, user-friendly format with the Snapshot in Cardiology section and a section on guidelines, registries, and trials presented by leaders on the topic.

Crowded with unexpected novelties was the field of heart failure. Diabetes is one of the most common comorbidities of heart failure and, likely enough, the novel sodium glucose cotransporter (SGLT2) inhibitors, which, when tested for their antidiabetic action, were constantly found to reduce cardiovascular mortality and hospitalization for heart failure.

In Paris, the DAPA-HF trial, conducted on a specific heart failure population, was presented and the results showed a significant reduction in heart failure outcomes. This effect was also found in nondiabetic patients. These results are important not only for the treatment of heart failure, but also for the better understanding of the pathophysiology of the disease. The SGLT2 inhibitors were created to treat diabetes, not heart failure. The mechanism of action is not known; however, several hypotheses have been raised, such as increasing ketones, affecting the Na/H pump, unloading the ventricles, etc. And...when there are hypotheses, the game is to discover the correct one.

Another long-time expected trial presented in Paris was PARAGON-HF for the treatment of patients with preserved ejection fraction with sacubitril/valsartan.

Unfortunately, PARAGON-HF joins a series of neutral trials with, literally, all the drugs that produced benefits in patients with heart failure with reduced ejection fraction. Even for PARAGON-HF, there are several explanations, but it seems that heart failure with preserved ejection fraction is more a “wording or a definition” than a real disease with a clear phenotype.

Several updates were also presented in the field of coronary artery disease or, as suggested in the 2019 guidelines presented in Paris, chronic coronary syndromes to distinguish it from the acute ones. The news relates more to diagnosis and risk assessment based on contemporary data on the prevalence of chronic coronary syndromes, which is likely decreasing as a result of a changes in lifestyle and a better control of risk factors. For diagnosis, it seems that the classic exercise ECG test is outdated by the more accurate noninvasive functional imaging tests (to detect ischemia) or coronary computed angiography (to detect coronary anatomy). In terms of treatment, the 2019 guidelines remain surprisingly very traditional and, actually, a corrigendum was published (European Heart Journal. <http://doi.org/10.1093/eurheartj/ehz825>) on November 14, 2019, as there were some inaccuracies. It is a pity that the newly proposed strategy called the “Diamond Approach” mentioned in the 2017 ESC issue of Dialogues in Cardiovascular Medicine was not followed.

In terms of risk reduction, there are also new suggestions according to the ESC/EAS guidelines and the most striking news is the further reduction in low-density lipoprotein levels to less than 1.4 mmol/L or <55 mg/dL in very-high-risk patients. Easy to say, more difficult to achieve! A more reasonable and reachable target has been emphasized for hypertension between 120/130 mm Hg with strong recommendations to use a fixed-drug combinations, renin-angiotensin system inhibitors (and especially ACE inhibitors) with calcium channel blockers or a diuretic being the preferred ones.

Finally, after 16 years from the previous one, the guidelines on supraventricular tachycardia were presented. In general, there is less confidence in pharmacological treatment and more enthusiasm in the efficacy of ablation, which should be offered as an initial choice in all reentrant and most focal arrhythmias. But summarizing 16 years in two or three lines is hard, even for us! So please, read the main messages from Professor Boriani and Professor Vardas.

We hope you will appreciate reading these highlights.

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

Snapshot in Cardiology



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, 2019 and August 31, 2019. All research articles on cardiology were included; reviews and guidelines were excluded.

January 2019

Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380(1):11-22.

Icosapent ethyl, a purified eicosapentaenoic acid ethyl ester, given at 2 g twice daily significantly lowered the risk of ischemic events in patients with cardiovascular disease or diabetes and other risk factors who have elevated triglyceride levels despite the use of statins vs those who received placebo.

.....

Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA.* 2019;321(4):364-373.

Patients with triglyceride-lowering lipoprotein lipase gene variants and low-density lipoprotein (LDL) cholesterol-lowering LDL receptor gene variants were associated with a similar lower risk of coronary heart disease per unit difference in apolipoprotein B.

.....

Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet.* 2019;393(10166):61-73.

The TRED-HF trials showed that, in patients with previous dilated cardiomyopathy who were now asymptomatic, phased withdrawal of heart failure medications will experience a relapse following treatment withdrawal.

.....

Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med.* 2019;380(1):23-32.

Among men aged 50 years or older and women aged 55 years or older in the US, n-3 fatty acid supplementation did not lower the incidence of major cardiovascular events or cancer vs placebo.

.....

Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* 2019;380(1):33-44.

Vitamin D supplementation did not lower the incidence of invasive cancer or cardiovascu-

lar events among men aged 50 years or older and women aged 55 years or older in the US vs placebo.

McCartney PJ, Eteiba H, Maznyczka AM, et al; T-TIME Group. Effect of low-dose intracoronary alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: a randomized clinical trial. *JAMA*. 2019;321(1):56-68.

Adjunctive use of low-dose intracoronary alteplase during a primary percutaneous intervention did not reduce the incidence of microvascular obstruction in patients presenting within 6 hours of an acute ST-segment elevation myocardial infarction due to a proximal-mid-vessel occlusion of a major coronary artery.

.....

Rosenstock J, Perkovic V, Johansen OE, et al; CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69-79.

In adults with type 2 diabetes, hemoglobin A1c levels between 6.5% and 10.0%, high cardiovascular risk, and high renal risk, linagliptin, a selective dipeptidyl peptidase 4 inhibitor, added to usual care resulted in a noninferior risk of a composite cardiovascular outcome over a median 2.2 years vs placebo added to usual care.

.....

Taggart DP, Benedetto U, Gerry S, et al; Arterial Revascularization Trial Investigators. Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med*. 2019;380(5):437-446.

No significant between-group differences were observed in the rate of all-cause death at 10 years among patients who were scheduled for coronary artery bypass grafting undergoing bilateral internal thoracic artery grafting or those undergoing single internal thoracic artery grafting.

.....

Wiviott SD, Raz I, Bonaca MP, et al; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.

The DECLARE-TIMI 58 trial showed that, in patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not affect the rate of major adverse cardiovascular events when compared with placebo; however, dapagliflozin lowered the rate of cardiovascular death or hospitalization for heart failure.

.....

Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31-39.

This systematic review and meta-analysis of randomized, placebo-controlled, cardiovascular outcome trials showed that sodium-glucose cotransporter-2 inhibitors moderately reduced major adverse cardiovascular events in patients with type 2 diabetes, but only in the subgroup with atherosclerotic cardiovascular disease. In addition, sodium-glucose cotrans-

porter-2 inhibitors robustly reduced hospitalizations for heart failure and progression of renal disease regardless of whether the patients had existing atherosclerotic cardiovascular disease or a history of heart failure.

Zenati MA, Bhatt DL, Bakaeen FG, et al; REGROUP Trial Investigators. Randomized trial of endoscopic or open vein-graft harvesting for coronary-artery bypass. *N Engl J Med.* 2019;380(2):132-141.

Among patients undergoing coronary artery bypass grafting, no significant differences were observed in the risk of major adverse cardiac events between those randomized to open vein-graft harvesting and those randomized to endoscopic vein-graft harvesting.

.....

Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA.* 2019;321(3):277-287.

In this systematic review and meta-analysis, the authors showed that, based on data from randomized clinical trials enrolling at least 1000 participants with no known cardiovascular disease and a follow-up of at least 12 months, aspirin use was associated with a lower risk of cardiovascular events and an increased risk of major bleeding.

February 2019

Carrier M, Abou-Nassar K, Mallick R, et al; AVERT Investigators. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med.* 2019;380(8):711-719.

Using apixaban 2.5 mg twice daily for thromboprophylaxis in ambulatory patients with cancer just starting chemotherapy who were at intermediate-to-high risk for venous thromboembolism significantly lowered the rate of venous thromboembolism vs placebo; however, apixaban increased the rate of major bleeding episodes compared with placebo.

Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet.* 2019;393(10170):407-415.

This meta-analysis analyzed 28 randomized trials on statin therapy, showing that statin therapy significantly reduces major vascular events over all ages, with the exception of patients aged 75 years or older where there is fewer direct evidence.

Khorana AA, Soff GA, Kakkar AK, et al; CASSINI Investigators. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med.* 2019;380(8):720-728.

In high-risk ambulatory patients with cancer, rivaroxaban 10 mg daily did not result in a significantly lower incidence of venous thromboembolism or venous thromboembolism-related deaths in the 180-day trial period; however, during the intervention period, rivaroxaban substantially lowered the incidence of such events, with a low incidence of major bleeding.

Lerman BJ, Popat RA, Assimes TL, Heidenreich PA, Wren SM. Association of left ventricular ejection fraction and symptoms with mortality after elective noncardiac surgery among patients with heart failure. *JAMA.* 2019;321(6):572-579.

Among patients undergoing elective noncardiac surgery, those with heart failure (with or without symptoms) had a significantly higher risk of mortality 90 days postoperation compared with those without heart failure.

Van Spall HGC, Lee SF, Xie F, et al. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure: the PACT-HF randomized clinical trial. *JAMA.* 2019;321(8):753-761.

The PACT-HF trial showed that, in patients hospitalized for heart failure in Ontario, Canada, implementation of a patient-centered transitional care model compared with usual care did not improve a composite of clinical outcomes.

Velazquez EJ, Morrow DA, DeVore AD, et al; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380(6):539-548.

In patients with heart failure with reduced ejection fraction, sacubitril-valsartan therapy led to a greater reduction in the concentration of NT-proBNP than did enalapril therapy; however, there were no significant between-group differences concerning the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema.

.....

Williamson JD, Pajewski NM, Auchus AP, et al; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321(6):553-561.

The risk of probable dementia was not significantly reduced in ambulatory adults aged 50 years or older with hypertension, but without diabetes or a history of stroke whose blood pressure was being treated to obtain a systolic blood pressure less than 120 mm Hg vs less than 140 mm Hg.

March 2019

Anderson CS, Huang Y, Lindley RI, et al; ENCHANTED Investigators and Coordinators. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet*. 2019;393(10174):877-888.

The ENCHANTED trial showed that, in patients ≥ 18 years old with acute ischemic stroke and a systolic blood pressure ≥ 150 mm Hg, intensive blood pressure lowering (target systolic blood pressure 130 to 140 mm Hg within 1 hour) is safe; however, the observed reduction in intracranial hemorrhage did not improve clinical outcomes compared with guideline-recommended treatment.

Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA*. 2019;321(11):1059-1068.

The CAPTAF trial showed that, in patients in Sweden and Finland aged 30 to 70 years who have been receiving treatment for atrial fibrillation for more than 6 months and have experienced treatment failure with 1 antiarrhythmic drug or β -blocker, those treated with catheter ablation had an improvement in their quality of life at 12 months vs those on antiarrhythmic medication alone.

Ference BA, Ray KK, Catapano AL, et al. Mendelian randomization study of ACLY and cardiovascular disease. *N Engl J Med*. 2019;380(11):1033-1042.

This analysis of inherited variants in the genes encoding ATP citrate lyase (ACLY) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR) showed that genetic variants that mimic the effect of ATP citrate lyase inhibitors and statins appeared to lower plasma low-density lipoprotein cholesterol using the same mechanism of action and they had similar effects on the risk of cardiovascular disease per unit decrease in the low-density lipoprotein cholesterol.

Landoni G, Lomivorotov VV, Nigro Neto C, et al; MYRIAD Study Group. Volatile anesthetics versus total intravenous anesthesia for cardiac surgery. *N Engl J Med*. 2019;380(13):1214-1225.

While volatile (inhaled) anesthetic agents have cardioprotective effects, there was no difference in death from any cause 1 year after patients underwent coronary-artery bypass grafting between volatile or total intravenous anesthesia.

Ray KK, Bays HE, Catapano AL, et al; CLEAR Harmony Trial. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019;380(11):1022-1032.

In patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both, bempedoic acid added to maximally tolerated statin therapy did not

increase the incidence of overall adverse events vs placebo and it significantly lowered low-density lipoprotein cholesterol levels.

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Yau TM, Pagani FD, Mancini DM, et al; Cardiothoracic Surgical Trials Network. Intramyocardial injection of mesenchymal precursor cells and successful temporary weaning from left ventricular assist device support in patients with advanced heart failure: a randomized clinical trial. *JAMA*. 2019;321(12):1176-1186.

In patients with advanced heart failure who are undergoing a left ventricular assist device implant, intramyocardial injections of mesenchymal precursor cells, did not improve successful temporary weaning from left ventricular assist device support at 6 months vs injections of a cryoprotective medium as sham treatment.

.....

Zaman A, de Winter RJ, Kogame N, et al; TALENT trial investigators. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial. *Lancet*. 2019;393(10175):987-997.

The TALENT trial showed that, in an all-comer population, a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts (Supraflex) was noninferior to an everolimus-eluting stent with a durable polymer coating (Xience) for a device-oriented composite clinical end point (ie, cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularization) at 12 months.

.....

Zhong VW, Van Horn L, Cornelis MC, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA*. 2019;321(11):1081-1095.

In an analysis 29 615 participants in the US (median follow-up of 17.5 years), those with a higher consumption of dietary cholesterol or eggs had a significantly higher risk of incident cardiovascular disease and all-cause mortality, which occurred in a dose-response manner.

April 2019

Hamada H, Suzuki H, Onouchi Y, et al; KAICA Trial Investigators. Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. *Lancet*. 2019;393(10176):1128-1137.

The KAICA trial showed that intravenous immunoglobulin plus ciclosporin was safe and effective as the primary treatment to prevent coronary artery abnormalities in Japanese patients with refractory Kawasaki disease.

.....

Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. *N Engl J Med*. 2019;380(15):1397-1407.

Concerning overall survival at 90 days, there was no difference between performing an immediate coronary angiography and a percutaneous coronary intervention (if needed) and performing a coronary angiography after neurologic recovery in patients who were successfully resuscitated after out-of-hospital cardiac arrest, but who had no signs of ST-segment elevation myocardial infarction.

.....

Lopes RD, Heizer G, Aronson R, et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380(16):1509-1524.

The AUGUSTUS trial showed that, in patients with atrial fibrillation who had an acute coronary syndrome or had undergone a percutaneous coronary intervention, using the combination of a P2Y12 inhibitor and apixaban (without aspirin), compared with the use of a vitamin K antagonist, aspirin, or both, led to less bleeding, fewer hospitalizations, and no significant differences in the incidence of ischemic events.

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Mark DB, Anstrom KJ, Sheng S, et al; CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321(13):1275-1285.

The CABANA trial showed that, among patients with symptomatic atrial fibrillation, catheter ablation resulted in clinically significant improvements in quality of life at 12 months vs medical therapy.

.....

Mehra MR, Uriel N, Naka Y, et al; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device -final report. *N Engl J Med*. 2019;380(17):1618-1627.

The final analysis of the MOMENTUM trial showed that, among patients with advanced heart failure, a left ventricular assist device with a centrifugal-flow pump was superior to a device with an axial-flow pump in terms of survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.

Packer DL, Mark DB, Robb RA, et al; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321(13):1261-1274.

While catheter ablation is effective in restoring sinus rhythm in patients with atrial fibrillation, it did not significantly reduce the composite end point of death, disabling stroke, serious bleeding, or cardiac arrest compared with conventional medical therapy.

.....

Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, et al; RACE 7 ACWAS Investigators. Early or delayed cardioversion in recent-onset atrial fibrillation. *N Engl J Med*. 2019;380(16):1499-1508.

In patients with hemodynamically stable, recent-onset (<36 hours), symptomatic atrial fibrillation, delayed cardioversion was shown to be noninferior to early cardioversion at 4 weeks regarding the restoration of sinus rhythm.

.....

Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2019;393(10181):1597-1608.

In patients with compensated cirrhosis and clinically significant portal hypertension (ie, a hepatic venous pressure gradient ≥ 10 mm Hg) without high-risk varices, treatment with β -blockers reduced the incidence of ascites.

May 2019

Bhatt DL, Pollack CV, Weitz JI, et al. Antibody-based ticagrelor reversal agent in healthy volunteers. *N Engl J Med.* 2019;380(19):1825-1833.

This phase 1 trial showed that treatment with intravenous PB2452, a monoclonal antibody fragment that binds ticagrelor with high affinity, led to an immediate and sustained reversal of the antiplatelet effects of ticagrelor.

Chan MTV, Wang CY, Seet E, et al; POSA Study Investigators. Association of unrecognized obstructive sleep apnea with postoperative cardiovascular events in patients undergoing major noncardiac surgery. *JAMA.* 2019;321(18):1788-1798.

The POSA study showed that unrecognized severe obstructive sleep apnea in at-risk patients who were undergoing major noncardiac surgery had a significantly higher risk of 30-day postoperative cardiovascular complications.

Diener HC, Sacco RL, Easton JD, et al; RE-SPECT ESUS Steering Committee and Investigators. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med.* 2019;380(20):1906-1917.

In patients with a recent embolic stroke of an undetermined source, dabigatran was not superior to aspirin for the prevention of a recurrent stroke, and, while dabigatran did not increase the incidence of major bleeding, it increased the incidence of clinically relevant nonmajor bleeding events.

Lederle FA, Kyriakides TC, Stroupe KT, et al; OVER Veterans Affairs Cooperative Study Group. Open versus endovascular repair of abdominal aortic aneurysm. *N Engl J Med.* 2019;380(22):2126-2135.

When comparing endovascular repaired with open repair of asymptomatic abdominal aortic aneurysms, the long-term overall survival rates were similar, but more patients with endovascular repair underwent more secondary therapeutic procedures.

Ma H, Campbell BCV, Parsons MW, et al; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med.* 2019;380(19):1795-1803.

The EXTEND trial showed that, in patients who had an ischemic stroke, but with salvageable brain tissue detected on automated perfusion imaging, alteplase treatment given within 9 hours after the onset of a stroke increased the percentage of patients with no or minor neurologic deficits compared with placebo.

Mack MJ, Leon MB, Thourani VH, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* 2019;380(18):1695-1705.

In patients with severe aortic stenosis and low surgical risk, transcatheter aortic valve replacement with transfemoral placement of a balloon-expandable valve significantly lowered the rate of the composite of death, stroke, or rehospitalization at 1 year compared with surgery.

.....

Popma JJ, Deeb GM, Yakubov SJ, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* 2019;380(18):1706-1715.

Transcatheter aortic-valve replacement with a self-expanding supra-annular bioprosthesis was noninferior to surgical aortic valve replacement with respect to the composite end point of death or disabling stroke at 24 months in patients with severe aortic stenosis who were at a low surgical risk.

.....

Tarakji KG, Mittal S, Kennergren C, et al; WRAP-IT Investigators. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med.* 2019;380(20):1895-1905.

The use of an absorbable, antibiotic-eluting envelope with cardiac implantable electronic devices significantly lowered the incidence of major infections vs the standard-of-care infection prevention strategies alone.

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Wise RA, Chapman KR, Scirica BM, et al. Effect of acclidinium bromide on major cardiovascular events and exacerbations in high-risk patients with chronic obstructive pulmonary disease: the ASCENT-COPD randomized clinical trial. *JAMA.* 2019;321(17):1693-1701.

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June 2019

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August 2019

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*Guidelines,
Registries, & Trials*



HEART FAILURE HIGHLIGHTS FROM THE 2019 ESC CONGRESS IN PARIS

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Hear failure is one of the most prevalent health care problems affecting high-risk patients, particularly elderly individuals not only in high-income, but also in middle- and low-income countries. Of these patients, 50% have a reduced ejection fraction (HFREF), while the other 50% have a preserved (HFPEF, EF \geq 50%) or mildly reduced EF (mid-range EF, 40% to 49%) as defined by the European Society of Cardiology (ESC). At the ESC congress, two landmark studies in either of the two conditions were presented.

DIABETES: A COMORBIDITY FOR HEART FAILURE

Comorbidities affect the heart failure syndrome, thus strongly impairing outcomes and increasing health care costs. One comorbidity, among others, is diabetes mellitus. Diabetes is one of the most important and growing health care problems in middle-income countries, as well as in low-income countries. When diabetes is diagnosed between the ages of 40 and 50 years, about 6.2 lifetime years are lost due to diabetes in men and 6.8 lifetime years are lost in women. This not only relates to cardiovascular death, but also to cancer-related death and all-cause death.¹ Cardiovascular events are increased in diabetic patients compared with nondiabetic patients by about 30% to 60%. Controlling cardiovascular risk factors completely eliminates the effects of diabetes on acute myocardial infarction and stroke, but not on heart failure where, despite controlling the risk factors, a residual risk (hazard ratio [HR], 2.4; 95% CI, 1.63-3.54) remains in diabetic patients.²

All oral antidiabetic drugs have been the mainstay of diabetes mellitus therapy for many years. However, several antidiabetic drugs, such as those in the glitazone class, exhibited an increase in hospitalizations for heart failure (PROACTIVE [PROspective pioglitAzone Clinical Trial In macroVascular Events] and RECORD trial [Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes] trials). This led the FDA to mandate safety studies for all novel antidiabetic drugs. In 2015, the EMPA-REG-OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) was published as a designed safety study for the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin. There

was a reduction in the primary end point of cardiovascular death, myocardial infarction, and stroke, which was primarily carried by a reduction in cardiovascular death. However, as an exploratory end point, EMPA-REG OUTCOME showed a 35% reduction in hospitalizations for heart failure worsening, which was a very rapid effect that was stable over 48 months.³ This data was then later supported by data from the CANVAS study (CANagliflozin cardioVascular Assessment Study), as well as data from the DECLARE study (Dapagliflozin Effect on CardiovascuLAR Events). It is notable that these data were generated in a diabetes population with only a few heart failure patients, which were not characterized in detail. The information on heart failure was only provided by the investigators from their medical history. However, recently, many potential mechanisms beneficially affecting myocardial function and myocardial outcomes have been identified, such as an increase in ketones, unloading of the heart by sodium and glucose excretion, weight loss, reduction in blood pressure, and protective effects on the kidney by inhibiting the tubuloglomerular reflex.

DAPA-HF TRIAL

The positive effects on heart failure hospitalization led to the hypothesis that SGLT2 inhibitors might be efficient in treating heart failure. Since the pharmacological effects, such as glucose and sodium excretion, also apply for nondiabetic patients, the hypothesis in the recently published DAPA-HF study (DAPAgliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic Heart Failure) and other ongoing heart failure studies is testing whether the beneficial effects of SGLT2 inhibition on heart failure outcomes in heart failure patients also apply to patients without diabetes.

At the ESC-congress in Paris, data from the DAPA-HF study were presented. Dapagliflozin is an SGLT2 inhibitor that has shown beneficial effects in the DECLARE study for cardiovascular death and heart failure hospitalization, while the effects on vascular end points were neutral in a diabetes population with cardiovascular risk factors. In this placebo-controlled trial, 4744 patients were assigned either to dapagliflozin or to placebo on top of optimal medical treatment. The hypothesis of this trial was whether dapagliflozin reduces cardiovascular and heart failure-related outcomes in patients with or without diabetes and HFREF. Patients were screened and randomized to placebo or 10 mg of dapagliflozin. Individuals were evaluated 14 and 16 days after randomization, with follow-up visits at 4-month intervals thereafter. The primary outcome was the composite of worsening of heart failure or death from cardiovascular causes. Heart failure worsening was either an unplanned hospitalization for heart failure or an urgent visit resulting in intravenous therapy for heart failure. Secondary outcomes involved hospitalization for heart failure and cardiovascular death (the classic heart failure end point), as well as other outcomes, such as the total number of hospitalizations, recurrent

heart failure hospitalizations, and cardiovascular death, as well as improvements in the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores.⁴ The trial was of high quality because only 2 patients out of 4744 randomized patients had an unknown vital status at the end of the study. A total of 386 patients (16.3%) in the dapagliflozin group and 502 patients (21.2%) in the placebo group reached the primary end point (HR, 0.74; 95% CI, 0.65-0.85; $P < 0.001$). Components of the composite end point all favored the treatment effect of dapagliflozin with risk reductions of 22% to 25% for all secondary outcomes. In the nonadjusted forest plot, there was no interaction between any of the subgroups, particularly not between sex, age, previous heart failure hospitalization, etc. In DAPA-HF, patients were excellently pretreated with a majority of patients on optimal background, guideline-directed therapy. The results have been recently published.⁵

This trial showed that, in a specific heart failure population with reduced ejection fraction, dapagliflozin added on top of guideline-recommended therapies at high-intensity treatment, resulted in a significant reduction in heart failure outcomes. Interestingly, this effect was also similar in patients without diabetes. This study extends the armamentarium of heart failure treatment to a drug, which was initially developed to treat diabetes.

DAPA-HF showed add-on effects to guideline-directed therapies of dapagliflozin in patients with and without diabetes, showing that the myocardium in heart failure and in diabetes might exhibit similar metabolic problems, which can be addressed by SGLT2 inhibitors. Many attractive mechanisms have been discovered, which could potentially explain the effect of dapagliflozin. However, the role and importance of each individual mechanism, such as increasing ketones, affecting sodium/hydrogen cotransporters, or unloading the heart, remains to be elucidated. Nevertheless, the study extends not only the armamentarium of heart failure treatments, but also the physiological insights into heart failure. Many secondary analyses will elucidate specific effects, such as those on quality of life and renal outcomes. In the comments to the Paris congress, DAPA-HF was commented as one of the most influential studies that might affect clinical practice in the future. It gained great visibility and provided great hope in patients with heart failure.

TREATMENT OF HFPEF

Studies on HFPEF with renin-angiotensin system (RAS) inhibitors (I-PRESERVE [Irbesartan in heart failure with PRESERVED systolic function], CHARM-Preserved [Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-patients with Preserved LV function], PEP-CHF [Perindopril in Elderly People with Chronic Heart Failure]), ivabradine (EDIFY), spironolactone (TOPCAT [Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist], mixed results!), as well as β -blockers (subanalysis from SENIORS [Study

of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure]) have obtained more or less neutral results. The sacubitril/valsartan combination blocks maladaptive remodeling by valsartan and accentuates adaptive responses by augmenting the effects of natriuretic peptides. In HFREF, the PARADIGM-HF study (Prospective comparison of Angiotensin Receptor–neprilysin inhibitor with an Angiotensin-converting enzyme inhibitor to Determine Impact on Global mortality and Morbidity in Heart Failure trial) demonstrated a 20% reduction in the composite end point of cardiovascular death and heart failure hospitalization, an effect that was homogeneous through all secondary exploratory end points as well throughout all subgroups.

PARAGON-HF TRIAL

Given the fact that there are no available treatments improving cardiovascular outcomes in patients with HFPEF and that the antihypertrophic effect of valsartan together with maladaptive and antihypertrophic effects of natriuretic peptides have been convincingly shown in experimental and observational studies, this background provides solid hypotheses to test the sacubitril/valsartan combination on clinical outcomes in patients with HFPEF.

The PARAGON-HF trial (Prospective comparison of ARNi with Arb Global Outcomes in heart failure with preserved ejection fraction) randomly assigned 4822 patients with ejection fractions of 45% or higher to either placebo or sacubitril/valsartan. The study aimed to investigate 894 primary events. The primary outcome was cardiovascular death and all heart failure hospitalizations. The active comparator was valsartan. The quality of the study was high because only 9 patients (4 on valsartan and 5 on sacubitril/valsartan) had an unknown vital status at the end of the trial.

Overall, the results were neutral. On sacubitril/valsartan, 894 primary events occurred in 526 patients and, on valsartan, 1009 primary events occurred in 557 patients (HF, 0.87; 95% CI, 0.75 to 1.01; $P=0.06$). Both drugs were well tolerated. For the secondary end points, there were no significant differences in KCCQ score changes, no differences in renal outcomes (low incidence), and no differences in all-cause-death (HR, 0.97; 95% CI, 0.84-1.13). The nonadjusted analysis of prespecified subgroups was a significant interaction between sexes with females having a benefit (HR, 0.73; 95% CI, 0.59-0.90), while there was no effect in males (HR, 1.03; 95% CI, 0.85-1.25). Furthermore, patients with a mildly reduced ejection fraction (eg, below the median $\leq 57\%$) showed a benefit, while at higher ejection fractions, sacubitril/valsartan (vs valsartan) had no effect (HR, 1.00). The data have been recently published.⁶

Overall, the results of PARAGON, comparing sacubitril/valsartan with valsartan, showed neutral results. However, the results were very tight. Evidence in prespec-

ified special populations, such as in females and in patients with mildly reduced ejection fraction, might provide information that a benefit might exist from neprilysin inhibition add-on to angiotensin antagonism, which could be prospectively studied. Although, in the discussions after the presentation of the PARAGON results, there was a trend by presenters, investigators, and sponsors to interpret PARAGON as a positive trial (only about 6 events were lacking on valsartan to receive a significant result), PARAGON should be considered as neutral. Similar trial results with nonsignificant trends have also been reported for PEP-CHF, which was underpowered and was prematurely interrupted due to problems in recruitment. However, PARAGON is important in showing subgroups and providing information to inform investigators and the medical community on special subgroups, in whom these drug interventions should be specifically investigated.

It is difficult to explain the differences in the results between PARADIGM-HF and PARAGON-HF.

1. In patients with HFREF, neprilysin activity (above and below the median) was associated with poor or favorable outcomes (cardiovascular death or heart failure hospitalization or cardiovascular death).⁷ In contrast, in patients with HFPEF, circulating neprilysin activity does not correlate with outcomes in patients with HFPEF.⁸ Therefore, there may be principal differences in the role of neprilysin in the pathophysiology of outcomes in HFPEF and HFREF.
2. PEP-CHF and potentially other studies, such as CHARM-Preserved, showed trends for a beneficial effect of RAS inhibition in patients with HFPEF. Notably, the comparator was not placebo, but valsartan. If valsartan has a slight, but nonsignificant, effect on outcomes, it could have diluted the effect of the outcome of sacubitril/valsartan.
3. PARAGON did not use the ESC classification of HFPEF ($\geq 50\%$), but included patients with an ejection fraction $>45\%$. Patients with mildly reduced EF ($<50\%$) might benefit from the combination, which could explain the trends in the overall population. Here, further secondary analyses must be awaited.
4. Specific causes of HFPEF, such as amyloidosis, sarcoidosis, hemochromatosis, etc, were not excluded. Therefore, the treatment effect could also have been diluted by specific cardiac pathologies, which cannot be addressed by RAS inhibition combined with neprilysin inhibition.

Sacubitril/valsartan did not improve outcomes in an overall population with HFPEF. However, PARAGON showed subgroups that might benefit from this treatment. Prospective randomized trials in more specific populations are needed to scrutinize potential benefits in dedicated heart failure subgroups. There are many controversial discussions expected from this trial.

CONCLUSIONS

Two recent landmark trials have again provided positive trial results in patients with HFREF, but neutral data in patients with HFPEF. Nevertheless, DAPA-HF extends the treatment armamentarium in HFREF, but PARAGON, as a well-conducted large investigation, might provide clues to do the next trial in more specific HFPEF populations. ■

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THE 2019 ESC GUIDELINES ON SUPRAVENTRICULAR TACHYCARDIA: WHAT ARE THE MESSAGES?

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At the 2019 European Society of Cardiology (ESC) congress held in Paris, France (August 31–September 4), the new guidelines on the management of supraventricular tachycardia (SVT) were presented, which were authored by a group of experts from Europe and North America.¹ It is noteworthy that the delay between these European guidelines and the previous guidelines was 16 years, which probably indicated a relatively modest attitude from the scientific community about providing new evidence in this field, even if a consensus document was quite recently delivered by the European Heart Rhythm Association.²

In fact, the epidemiological impact of SVT in clinical practice is important, with an estimated prevalence in the general population of 2.25 per 1000 people and an incidence of 35 per 100 000 person-years. Women have a 2-fold higher risk, as compared with men, of developing SVT. In addition, SVT should not be considered a disease affecting only young people, as is the common belief, since the elderly (age 65 years or older) have more than a 5-fold risk of developing SVT than younger individuals. In an epidemiological view, it should also be stressed that SVT may occur in pediatric individuals, which may imply a risk of sudden cardiac death (eg, Wolff-Parkinson-White syndrome) that needs to be properly evaluated considering the possibility of a curative approach with ablation.

The occurrence of SVT episodes in the community induces a burden of acute admission to emergency departments for acute treatment, as well as to the cardiology wards for diagnostic and therapeutic clinical evaluations, which strongly suggests the need for an updated and authoritative re-evaluation of the best diagnostic and therapeutic resources currently indicated for the treatment of SVT in both acute and long-term cases, as provided in these guidelines.¹

An analysis, even at first look, of the main changes in the level of evidence and in the strength of recommendations that characterize the 2019 SVT guidelines,

as compared with the previous 2003 guidelines, leads to the consideration that pharmacological treatments have clearly lost confidence, mainly for safety precautions, since a detailed reassessment of available evidence resulted (*Table I*) in a constant downgrading of the class of recommendations in these guidelines, either for acute and long-term pharmacological treatment, with currently only one class I recommendation for a pharmacological agent among the 51 class I recommendations delivered (41% of the overall 123 recommendations). In detail, this single class I recommendation for a pharmacological agent is for intravenous ibutilide for acute termination of atrial flutter.

In a general view of the distribution of the grading of recommendations for these 2019 guidelines, it emerges:

For the level of evidence (graded as A, B, or C):

- **Level A** (availability of multiple randomized control trials or methodology supporting the recommendation) was obtained for <2% of the recommendations (2/123).
- **Level B** (availability of a single randomized clinical trial or large nonrandomized studies) was obtained for 54% of the recommendations (66/123).
- **Level C** (result of a consensus of experts and/or small retrospective studies or registries) was obtained for 45% of the recommendations (55/123).

For the strength of recommendations (traditionally reported as class I, IIa, IIb, and III):

- **Class I** (evidence/agreement that a treatment is beneficial, useful, and effective) was obtained for 41% of the recommendations (51/123).
- **Class IIa** (evidence/opinion in favor of usefulness/effectiveness) was obtained for 37% of the recommendations (46/123).
- **Class IIb** (less established usefulness/effectiveness) was obtained for 15% of the recommendations (19/123).
- **Class III** (evidence/agreement that an intervention is not useful or effective or may even cause harm) was obtained for 6% of the recommendations (7/123).

In a more general view, taking into account guidelines delivered for other diseases, such as atrial fibrillation or acute coronary syndrome, it is noteworthy to stress that the proportion of recommendations with a level of evidence A is usually around 11% to 15%,³⁻⁶ much higher than the 1.6% corresponding to only 2 recommendations with a level of evidence A found in these SVT guidelines.

Table 1. Comparison of the 2019 ESC guidelines for the management of supraventricular tachycardia with the 2003 ESC guidelines. Modified with permission from reference 1: Brugada J et al. Eur Heart J. 2019 Aug 31.

	Recommendation in the 2003 ESC guidelines	Recommendation in the 2019 ESC guidelines
Acute management of narrow QRS tachycardias		
β-Blockers	IIb	IIa
Verapamil/diltiazem	I	IIa
No longer mentioned in 2019		Amiodarone, digoxin
Acute management of wide QRS tachycardias		
Adenosine	IIb	IIa
Amiodarone	I	IIb
Procainamide	I	IIa
No longer mentioned in 2019		Sotalol, lidocaine
Therapy of inappropriate sinus tachycardia		
β-Blockers	I	IIa
No longer mentioned in 2019		Verapamil/ diltiazem, catheter ablation
Therapy of focal atrial tachycardia		
Acute treatment		
Amiodarone	IIa	IIb
β-Blockers	I	IIa
Flecainide/propafenone	IIa	IIb
No longer mentioned in 2019		Digoxin, procainamide, sotalol
Chronic treatment		
β-Blockers	I	IIa
Verapamil/ diltiazem	I	IIa
No longer mentioned in 2019		Amiodarone, disopyramide, sotalol

Table I. *Continued*

	Recommendation in the 2003 ESC guidelines	Recommendation in the 2019 ESC guidelines
Therapy of atrial flutter		
Acute treatment		
Atrial or transesophageal pacing	I	IIb
β-Blockers	I	IIa
Ibutilide	IIa	I
Flecainide/propafenone	IIb	III
Verapamil/diltiazem	I	IIa
No longer mentioned in 2019		Digoxin
Chronic treatment		
No longer mentioned in 2019		Disopyramide, dofetilide, flecainide, procainamide, propafenone, quinidine, sotalol
Therapy of atrioventricular nodal reentrant tachycardia		
Acute treatment		
No longer mentioned in 2019		Amiodarone, flecainide, propafenone, sotalol
Chronic treatment		
β-Blockers	I	IIa
Verapamil/ diltiazem	I	IIa
No longer mentioned in 2019		Amiodarone, flecainide, propafenone, sotalol, and the “pill in the pocket” approach
Therapy of atrioventricular reentrant tachycardia		
β-Blockers	IIb	IIa
Flecainide/propafenone	IIa	IIb
No longer mentioned in 2019		Amiodarone, sotalol, and the “pill in the pocket” approach

The limited innovation in the development of antiarrhythmic drugs is highlighted by the fact that only one new drug is currently in the premarket phase for the treatment of SVT, namely etipamil, a short-acting L-type calcium channel blocker with a rapid onset of action after intranasal administration, with conversion rates from SVT to sinus rhythm in the first clinical study ranging from 65% to 95%.⁷ The SVT guidelines mention this treatment, which is interesting, novel, and promising, but cautiously do not provide any recommendation in view of the need for additional studies following the first phase 2 evaluation.

The guidelines stress the importance of the differential diagnosis of SVT with an appropriate recognition of the type of SVT and of the related mechanisms (focal, multifocal, macro-reentry, macro-reentry involving an accessory pathway, reentry within the atrioventricular node) as a crucial step for acute and long-term management of these arrhythmias, also with the perspective of a curative treatment with ablation. Even if the step-by-step analysis of a 12-lead ECG is of primary value in defining the type of SVT in case of either narrow QRS tachycardia (QRS \leq 120 ms) or wide QRS tachycardia, the 2019 guidelines include a very practical approach for acute management, with specific recommendations also in cases where these arrhythmias still do not have an established diagnosis. Apart from the use of DC shock in case of hemodynamic instability, it is interesting and very practical to use intravenous adenosine for diagnostic purposes both in case of narrow and wide QRS tachycardia, provided that, in the latter case, an anterograde preexcitation is not present at the 12-lead ECG.

One of the most harmful settings among SVT is the occurrence of atrial fibrillation with overt preexcitation and these guidelines propose an important change compared with the previous guidelines by stressing that, in preexcited atrial fibrillation, intravenous amiodarone may not be as safe as previously thought because enhanced pathway conduction and degeneration in ventricular fibrillation has been reported in several cases, and therefore use of amiodarone in this setting should not be considered (recommendation of class III with a level of evidence B for intravenous amiodarone in the setting of preexcited atrial fibrillation).⁸

The recent SVT guidelines stress the efficacy of ablation and indicate that, in all reentrant and most focal arrhythmias, catheter ablation should be offered as an initial choice. The efficacy of ablation techniques, which the literature reports to be \approx 97% for atrioventricular nodal reentrant tachycardia, \approx 92% for atrioventricular reentry tachycardia, \approx 95% for cavotricuspid dependent atrial flutter, and \approx 85% for focal atrial tachycardia,¹ strongly support the predominant role that the interventional treatments gained in recent years. However, the guideline recommendations do not cover technical aspects, such as the type of energy⁹ or the type of ablation catheters to be preferred in specific settings.

With regard to the delicate issue of the risk of thromboembolism and stroke associated with atrial flutter, the 2019 ESC guidelines clearly stress that “anticoagulation as in atrial fibrillation is recommended for patients with atrial flutter and concomitant atrial fibrillation” (class I recommendation, level of evidence B). In patients with atrial flutter without atrial fibrillation, the guidelines indicate that anticoagulation should be considered, but the threshold for the initiation of anticoagulation has not been established (class IIa recommendation, level of evidence C), thus implying that, if the risk of bleeding is not substantial, the same criteria for atrial fibrillation could be considered, in the absence of other suggestions.

SVT mainly occurs in patients with no or minimal heart disease, but may result in an important worsening of quality of life and may have a negative impact on recreational activities and sports activities and, in more severe cases, may be associated with syncope, also when driving. For these reasons, the principle that clearly inspired these guidelines is the “safety first” principle, to be applied from the time of acute treatment in the emergency department, thus avoiding drugs or interventions with potential risk, and to be subsequently applied for diagnostic as well as therapeutic interventions. The challenge now is to determine to what extent this principle, which should always inspire all fields of clinical medicine (“*primum non nocere*” is a well-known Hippocratic axiom), may be constantly applied in daily practice, where a gap in application and implementation of consensus guideline recommendations is frequently observed. In fact, it has been reported that 30% to 45% of patients may not actually be receiving evidence-based care with a proven benefit, and, on the contrary, 20% to 25% of care provided overall may not be justified or may even be potentially harmful.¹⁰

It is important to stress that, for any consensus guideline, the process of delivery of recommendations is just the first step of a virtuous circle that should include specific initiatives for guideline implementation, either for acute or chronic management, in all of the settings where SVT is managed (emergency departments, cardiology wards, outpatient clinics, internal medicine wards, and medical clinics where general practitioners visit outpatients). Monitoring of guideline implementation should include audits providing some feedback on potential barriers in the full application of the guidelines into real-world practice. This is, indeed, the right approach for instituting a “virtuous circle” connecting the field of clinical research with the field of clinical practice, thus leading to important suggestions on how to improve the organization of clinical care delivery.¹⁰ In other words, the guidelines should be a bridge between clinical research and daily practice, but also with some reverse feedback on how to direct future clinical research on SVT, which, in view of the characteristics of this arrhythmia is frequently physician-initiated and not strictly industry-promoted. ■

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NEW 2019 ESC/EAS GUIDELINES FOR THE MANAGEMENT OF DYSLIPIDEMIAS

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Keywords: cholesterol; dyslipidemia; guidelines; total cardiovascular risk; treatment

During the 2019 European Society of Cardiology (ESC) congress, on August 31, the new guidelines for the management of dyslipidemias were released, which were simultaneously published online in the *European Heart Journal*.¹

Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.² Professional guidelines are important because they provide a practical and ethical framework for decision-making and because they instill a sense of responsibility and accountability. The Members of the Task Force for the management of dyslipidemias of the ESC and European Atherosclerosis Society (EAS), including professionals involved with different aspects of the medical care of patients with dyslipidemias, undertook a comprehensive review of the published evidence in this field, with the aim of updating the previous ESC/EAS lipid guidelines published in 2016.³

A recently published EAS consensus statement,⁴ based on evidence from genetic studies, epidemiological studies, Mendelian randomization studies, and randomized clinical trials, clearly showed the causal role for low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apolipoprotein B-containing lipoproteins in atherogenesis. This implies that targeting elevated LDL-C, and doing it as soon as possible, will have greater benefit in terms of cardiovascular prevention.

Another crucial point is the focus on total cardiovascular risk, as explained in the title of the guidelines “lipid modification to reduce cardiovascular risk.”¹ The new guidelines recommend a lifetime approach to cardiovascular risk, implying that people of all ages should be encouraged to adopt or sustain a healthy lifestyle, and the customization of the lipid management approach, stratifying the patients into risk categories, each with a specific therapeutic goal:

- **For patients at very-high risk** (people with documented atherosclerotic cardiovascular disease [ASCVD], diabetes mellitus with target organ damage or at

least three major risk factors, severe chronic kidney disease, familial hypercholesterolemia with ASCVD or with another major risk factor, or a 10-year risk of cardiovascular death >10%), an LDL-C reduction of at least 50% from baseline and an LDL-C goal of less than 1.4 mmol/L (<55 mg/dL) are recommended. For very high-risk patients who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of less than 1.0 mmol/L (<40 mg/dL) is recommended.

- **For patients at high risk** (people with markedly elevated single risk factors, familial hypercholesterolemia without other major risk factors, diabetes mellitus without target organ damage, moderate chronic kidney disease, or 10-year risk for cardiovascular death of 5% to 10%), an LDL-C reduction of 50% or greater from baseline and an LDL-C goal of less than 1.8 mmol/L (<70 mg/dL) are recommended.
- **For individuals at moderate risk** (diabetic patients with a duration of diabetes mellitus <10 years and no others risk factors, 10-year risk for cardiovascular death of 1% to 5%), an LDL-C goal of less than 2.6 mmol/L (<100 mg/dL) should be considered.
- **For individuals at low risk** (10-year risk for cardiovascular death <1%), an LDL-C goal of less than 3.0 mmol/L (<116 mg/dL) may be considered.

The guidelines also introduce the recommendation of using new tests to stratify risk among moderate-risk patients. These tests include both coronary artery calcium imaging and biomarker tests. Coronary artery calcium score assessment may be helpful in people who are at moderate risk of ASCVD, informing discussions about treatment strategies in untreated patients not at their LDL-C goal. Likewise, assessment of arterial (carotid or femoral) plaque burden on ultrasonography may be informative. As concerns biomarkers, the use of apolipoprotein B may help in risk stratification in people where the measurement of LDL-C underestimates atherosclerotic burden (eg, in case of high triglycerides, diabetes mellitus, obesity, or very low LDL-C), as it recapitulates individual exposure to proatherogenic lipoproteins. Moreover, a measurement of Lp(a) (once in life) may be helpful for further risk stratification of patients at high risk of ASCVD or in patients with a family history of premature cardiovascular disease, besides the identification of people with very high inherited Lp(a) levels and so potentially at a higher ASCVD risk.

The key message of these guidelines, which has been carried forward from the previous edition and emphasized in this new version, is “the lower the better” in terms of reducing LDL-C. This emerges as two main novelties. First, these guidelines proposed more ambitious LDL-C goals, especially for high- and very-

high-risk patients. Second, for patients at high or very-high risk, a 50% reduction in the basal LDL-C is recommended, as has been derived from the previous guidelines, which has significant implications. For example, patients at very-high risk now have a recommended LDL-C goal of 1.4 mmol/L and at least a 50% reduction from baseline levels. If a patient at very-high risk has an untreated LDL-C level of 1.5 mmol/L, which is just above the goal, then the recommendation of needing a 50% reduction would require LDL to be further lowered to 0.75 mmol/L. At the same time, a patient with very high LDL-C levels (such as familial hypercholesterolemia) will also have, in addition to reaching the 50% reduction, to attempt to reach the goal level. The rationale for this approach is the increasingly confirmed evidence that the risk reduction is directly proportional to the magnitude of LDL-C lowering. Therefore, an optimal reduction in risk is secondary to a maximized LDL-C reduction.

The new guidelines recommend that patients be treated aggressively with high-dose statins and with the option of adding ezetimibe, and as third-line, a proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor, to achieve these goals. These changes from the 2016 document are based on several recent placebo-controlled clinical studies, which have shown that the addition of either ezetimibe or anti-PCSK-9 monoclonal antibodies to statin therapy provides a further reduction in ASCVD risk, proportional to the absolute LDL-C reduction. These studies have clearly indicated that the lower the achieved LDL-C values, the lower the risk of future cardiovascular events, with no lower limit for LDL-C values. In addition, studies to date have shown that reaching very low LDL-C values has no significant safety implications.

As stated in the preamble of the 2019 document, the “guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition.”¹ However, it is important to remember that the final decisions concerning an individual patient must be made by the responsible health professional(s), sharing the approach with patients (and their relatives, when appropriate) and taking into account their expectations and preferences, if feasible. Statins are very well tolerated, and true “statin intolerance” is uncommon, although patients often reported discomfort or muscle pains, and practitioners might find this difficult to manage. Several studies have shown a considerable LDL-C-lowering effect of alternative dosing, such as every other day or twice a week. When it is necessary to reduce the dose or discontinue statin therapy, ezetimibe and PCSK-9 inhibitors are effective treatment options to achieve the lipid goals. Notably, the guidelines clearly state that statins are not recommended in premenopausal women considering pregnancy or not using adequate contraception. In addition, the evidence for statin therapy is more limited in patients over 75, though it is still consistent

with a benefit. The guidelines advise taking the level of risk, baseline LDL-C levels, health status, and the risk of drug interactions into account before starting statin therapy in elderly people.

Finally, the patient's perspective should also be taken into account, trying to promote the adoption of healthy lifestyle changes and to maximize adherence to therapy. Practitioners should adequately motivate the patients, providing them with all the information necessary to understand the importance of cardiovascular prevention and the possible need for lifestyle and pharmacological interventions. When necessary, self-care by the patient should be facilitated, using written instructions (or electronic tools, where appropriate), simplifying the drug regimen, and possibly actively involving family members. ■

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HIGHLIGHTS OF THE 2019 ESC CONGRESS IN ARTERIAL HYPERTENSION

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Keywords: arterial hypertension; blood pressure; dyslipidemia; guidelines

This article summarizes the highlights of the 2019 ESC congress in the field of arterial hypertension; it does not include research protocols or abstracts.

INTRODUCTION

Arterial hypertension represents the leading risk factor for cardiovascular death worldwide,¹ and the burden of hypertension is expected to increase by up to 60% by 2025.² Thus, treatment and control of arterial hypertension is imperative, but also a challenge. Worldwide, 46.5% of adults with arterial hypertension are aware of their condition and 36.9% are treated with antihypertensive drugs, while only 13.8% have their blood pressure levels controlled.³ Thus, despite the availability of effective therapies, blood pressure is poorly controlled. Low adherence to treatment represents one of the main factors contributing to this phenomenon. It is estimated that 30% of patients with arterial hypertension will discontinue their antihypertensive drug treatment within the first 6 months, while this percentage grows up to 50% within the first year.⁴ In addition, 10% of the remaining patients who affirm to be adherent to treatment are not taking their medications every day.⁴ Moreover, the vast majority of hypertensive patients also present with other risk factors and comorbidities, classifying them into a higher cardiovascular risk categories.⁵ In these patients, the blood pressure target should be achieved in the shortest possible period since rapid blood pressure control translates into a prognostic benefit for these patients.⁶ Simplifying the drug regimen by administering fixed-dose combinations has the potential to break the barrier of low adherence to treatment and to improve blood pressure reduction, while also decreasing drug-related side effects.⁶ Current ESC/ESH guidelines for the management of arterial hypertension recommend starting with a dual combination in all hypertensive patients with blood pressure levels >150 mm Hg and <80 years of age in order to better control blood pressure levels and to improve adherence to treatment since the use of fixed-dose combinations can reduce the number of pills administered.⁶

ACHIEVING THE BLOOD PRESSURE TARGETS

Today, fixed-dose combinations are used broadly, especially in patients with arterial hypertension in order to achieve blood pressure targets since they promptly and significantly decrease blood pressure levels. Unfortunately, monotherapy decreases blood pressure levels to a lesser degree, and patients on monotherapy have lower adherence to treatment and higher drop-out rates than those on combination therapy.⁷⁻⁹ Patients usually require at least two drugs to control their blood pressure levels and patients on monotherapy are often discouraged for not achieving blood pressure targets, thus leading to treatment discontinuation.⁷⁻⁹ In addition, side effects or adverse events are often dose dependent and patients on monotherapy are under the maximal recommended dose in an attempt to control their blood pressure levels, increasing their risk for a subsequent adverse event or side effect.

A further advantage of antihypertensive combination therapy is the potential for pharmacological synergy between different classes of agents, which may lead to a reduction in the incidence of side effects and provide a wider range of positive clinical effects than a single agent.¹⁰ Current ESC/ESH guidelines for the management of arterial hypertension recommend starting with a dual combination in all hypertensive patients with blood pressure levels >150 mm Hg. This threshold was established in order to avoid significant hypotensive events resulting from dual combination therapy. We have to keep in mind, however, that the magnitude of blood pressure reduction with an antihypertensive drug usually depends on baseline blood pressure levels. The higher the blood pressure levels, the higher the decrease in blood pressure with antihypertensive drugs and vice versa. Thus, the incidence of hypotension is very low in the majority of studies with dual or triple antihypertensive drug combinations.⁷⁻⁹ In addition, there are low-dose combinations with rapid antihypertensive effects that permit prompt achievement of the recommended blood pressure target, with good safety profiles when administered in patients with stage I arterial hypertension.⁶

Current ESC/ESH guidelines⁶ recommend using the combination of a renin-angiotensin system inhibitor with a calcium channel blocker or a diuretic as a first-line treatment for the management of arterial hypertension. The combination of a renin-angiotensin system inhibitor with a calcium channel blocker represents one of the standard combinations that are used in everyday clinical practice. Several studies assessed the effect of the combination of low-dose perindopril and amlodipine, affirming that it is more effective in reducing blood pressure and, at the same time, safe, but with fewer adverse events than in monotherapy.¹¹ This prompt reduction is not only beneficial for high-risk patients with stage I arterial hypertension, but also for patients with lower cardiovascular risk.¹¹ Reducing blood pressure levels within a month of treatment would also help improve patient ad-

herence, possibly leading to additional long-term benefits, including a reduced risk of cardiovascular events.¹¹

A COMBINED APPROACH TO TACKLING BOTH HYPERTENSION AND DYSLIPIDEMIA

The vast majority of hypertensive patients also present with other risk factors and comorbidities, classifying them into a higher cardiovascular risk categories.⁵ Hence, the assessment of the risk factors in a hypertensive patient is imperative in order to assess the total cardiovascular risk and to treat these risk factors, since, in this way, physicians may improve prognosis in these patients.⁶ It is estimated that 55% of hypertensive patients also present with dyslipidemia and thus the addition of lipid-lowering drugs is often necessary.⁵ The beneficial effect of statin administration in patients with or without previous cardiovascular events is well established. In the HOPE-3 trial, the addition of a statin in patients without cardiovascular disease reduced the incidence of cardiovascular events by up to 24%.¹² Of course, there is overwhelming evidence regarding the beneficial effect of statins in patients with higher cardiovascular risk.⁶ Hence, often in addition to the antihypertensive drugs, physicians should also administer lipid-lowering drugs, such as statins. The beneficial effect of a combination treatment with an angiotensin-converting enzyme inhibitor, a calcium channel blocker, and atorvastatin was evaluated in the lipid-lowering arm of the ASCOT study.¹³ In this study, there was a significant reduction in cardiovascular events, even with the addition of the lowest dosage (10 mg) of atorvastatin. The relative risk of fatal coronary heart disease and nonfatal myocardial infarction was decreased by 53% in the group receiving perindopril, amlodipine, and atorvastatin. In contrast, in the group receiving atenolol and/or bendroflumethiazide, the addition of atorvastatin failed to achieve a significant reduction in any of these end points.

As mentioned above, the combination of a renin-angiotensin system with a calcium channel blocker represents one of the standard combinations that are used in every day clinical practice and the presence of a fixed combination of perindopril, amlodipine, and atorvastatin is based on this concept. The use of this fixed combination improves blood pressure and lipid control not only because of the efficacy of its components, but also because it improves adherence to treatment. This triple combination simplifies the drug regimen allowing a once daily administration of the drug instead of two or three. In particular, hypertensive patients with dyslipidemia usually present with the poorest adherence to treatment, as a patient with poor adherence to antihypertensive therapy is also usually not adherent to the lipid-lowering therapy.^{14,15}

CONCLUSIONS

Despite the availability of effective therapies, both blood pressure and lipid profiles are poorly controlled. Low adherence to treatment represents one of the main factors contributing to this phenomenon. The administration of fixed-dose combinations that may also include lipid-lowering drugs has the potential to break the barrier of low adherence to treatment and to improve blood pressure and lipid reduction. ■

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2019 ESC GUIDELINES ON CHRONIC CORONARY SYNDROMES: ONE STEP FORWARD, TWO STEPS BACK

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Keywords: angina; coronary artery disease; coronary atherosclerotic obstruction; guidelines; myocardial ischemia

For decades, it was assumed that a close link existed between coronary atherosclerotic obstructions and myocardial ischemia.¹ However, a large body of evidence has strongly challenged this assumption, suggesting that myocardial ischemia has a multifactorial nature where coronary artery obstructions are only one factor in the development of ischemic heart disease.² The 2013 ESC guidelines³ partially acknowledged that multiple mechanisms may precipitate myocardial ischemia, warning that these mechanisms are not mutually exclusive and that they may change in time within the same patient. Consequently, these guidelines strongly downgraded the diagnostic role of both invasive and noninvasive coronary angiography.

The 2019 ESC guidelines⁴ included the word “syndrome” in the title, which refers to a cluster of symptoms that may be associated with multiple mechanisms. Unfortunately, these guidelines do not appear consistent with their initial definition.

GUIDELINE INCONSISTENCIES

Lack of a diagnostic pathway and distinct therapeutic approach

No specific diagnostic pathway is presented to identify the mechanism(s) responsible for myocardial ischemia in individual patients and, after identifying the responsible mechanism(s), no distinct therapeutic approach is suggested. In addition, throughout the guidelines, no clear distinction is made between the diagnosis of myocardial ischemia and the identification of the responsible mechanism(s). Clinically detectable manifestations of myocardial ischemia include typical angina, typical ECG changes, regional wall dysfunction at echocardiography, perfusion defect at myocardial scan, and transc coronary lactate extraction at invasive assessment. The presence or absence of coronary atherosclerotic obstructions can no longer be considered as a surrogate for myocardial ischemia, as suggested by the high prevalence of absent or minor coronary artery disease in patients with proven myocardial ischemia (FAME 2⁵ and CorMicA⁶).

The diagnostic algorithms are stubbornly focused on the identification of atherosclerotic obstructions and/or the estimation of their probability. Even after a marked reduction in the so-called pretest probability in both men and women, these guidelines fail to realize that, compared with men, women have about half the prevalence of coronary atherosclerosis, but a similar level of severe myocardial ischemia, with an even worse prognosis.

Considering angina and chest pain equivalent

In the guidelines, angina and chest pain are considered equivalent. Furthermore, the addition of dyspnea, without objective evidence of ischemia, all contribute to an unjustified enlargement of the “patient population,” predisposing patients to an unjustified increase in investigations and procedures. Currently, 25.7% of patients undergoing percutaneous coronary intervention for stable coronary artery disease have no symptoms, and, moreover, many patients have minimal symptoms.⁷ The recent trend in trials and registries to consider “chest pain” as an inclusion criteria instead of “angina” (only 22% of patients in the SCOT-HEART trial⁸ had symptoms suggestive of real angina and only 5% in the CLARIFY registry⁹ had angina and proven ischemia) dilutes the events, limits the chance to prove the efficacy of any treatment, and makes it difficult to appreciate the real prognostic impact of angina/ischemia. In practice, it makes it impossible to understand to whom the conclusions apply, ie, to the general population or to the patients with real angina.

Clinical scenarios based on coronary artery disease with or without confirmation of myocardial ischemia

An arbitrary and wide-ranging list of clinical scenarios was proposed, including (i) patients with suspected coronary artery disease and “stable” angina symptoms and/or dyspnea; (ii) patients with new-onset heart failure or left ventricular dysfunction and suspected coronary artery disease; (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an acute coronary syndrome or patients with a recent revascularization; (iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization; (v) patients with angina and suspected vasospastic or microvascular disease; and (vi) asymptomatic subjects in whom coronary artery disease is detected at screening. Each case is again based on the presence of coronary artery disease, independently from the presence or absence of symptoms or proven/unproven myocardial ischemia, taking it to the point that the simple fact of having undergone a revascularization procedure makes the patient ischemic for life. The authors do not consider that a large fraction of revascularizations are performed in the absence of angina, in the absence of proven ischemia, and in patients who are under no medical therapy.¹⁰⁻¹²

Screening for coronary artery disease in asymptomatic patients

An entire section is dedicated to the screening of coronary artery disease in asymptomatic patients, which could be justified in an asymptomatic patient with proven myocardial ischemia. Otherwise, given the much larger prevalence of coronary atherosclerosis as compared with myocardial ischemia (10 to 1 in pathology reports), this recommendation may result in an incredible number of false-positive patients (no ischemia–coronary atherosclerosis) undergoing investigations and procedures. This approach looks even less understandable given the lack of any prognostic benefit of elective revascularization procedures and the growing awareness of the adverse effect of percutaneous coronary interventions (12.5% of periprocedural myocardial infarction,¹³ a concerning rate of intraprocedural cardiac arrest and death,¹⁴ a high rate of early unplanned hospital readmissions,¹⁵ and 30% to 40% recurrence or persistence of angina.¹⁶

Therapeutic recommendations appear largely unsupported by conclusive evidence

The shift from a “first-to-second line” approach to a “step-wise” approach does not address the need for selecting a drug based on the pathogenesis of ischemia. This algorithm is even more surprising because the manuscript acknowledges the absence of any evidence of the superiority of one drug versus another, and it does not consider adverse effects and patients’ tolerability in a life-long treatment.

The indication for β -blockers or calcium channel blockers as a “first-line” treatment is based on a paper¹⁷ that concludes by saying that “beta blockers are no more effective than other anti-anginal agents on prophylaxis of myocardial ischemia in stable angina patients” and on a paper dating back more than 20 years.¹⁸ Even more surprising is the maintenance of β -blockers as a first-step option, alternatively to calcium channel blockers, after the acknowledgement of coronary vasospasm as a possible pathogenetic mechanism of angina.

The upgrade of long-acting nitrates, recommended even before ivabradine, ranolazine, trimetazidine and nicorandil, does not appear to be supported by scientific evidence, as one of the meta-analyses,¹⁹ on which it is based, reports that “too few trials compared nitrates with calcium antagonists or β -blockers to draw firm conclusions about relative efficacy,” and the second meta-analysis²⁰ is based on studies with very small patient numbers, with open-label designs, and with almost no other background therapy that are comparing long-acting nitrates with placebo, showing nonconclusive results (nonsignificant *P* values) on the efficacy of long-acting nitrates vs placebo after 24 hours. Additionally, the new guidelines did not consider the recent reports suggesting an increase in major adverse cardiac events with the long-term use of these agents.^{21,22}

Even more surprising is the recommendation to combine ivabradine with nondihydropyridine calcium channel blockers, which has been shown to be detrimental and therefore clearly contraindicated.

Similarly, the recommendation to consider revascularization in asymptomatic patients with no proven ischemia is not based on evidence, given that 61 randomized controlled trials and 15 meta-analyses have failed to prove any prognostic benefits of elective revascularization versus optimal medical therapy. ■

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NEW TRENDS AND PROGRESS IN ARRHYTHMIAS, ELECTROPHYSIOLOGY, AND CARDIAC RHYTHM MANAGEMENT DEVICES

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At the recent annual congress of the European Society of Cardiology in Paris, a number of important topics related to arrhythmias, electrophysiology, and cardiac rhythm management devices were presented. This article attempts to give a brief overview of the main issues, judged in terms of clinical relevance, scientific perspectives, and technological innovation. Undoubtedly, the announcement of guidelines for the management of patients with supraventricular tachycardia (SVT) was of great importance for clinical practice in the field of arrhythmias.

The following are some of the most intriguing topics from the conference, grouped into three different categories.

2019 ESC GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH SUPRAVENTRICULAR TACHYCARDIA

This year, for the first time since 2003, the European Society of Cardiology revealed new guidelines for the management of SVT. It is evident that, in the 16 years since the previous guidelines, both arrhythmologists in general and electrophysiologists in particular have become fully aware of the effectiveness of using invasive techniques, such as ablation for the treatment of this type of arrhythmia. Based on existing developments, the new guidelines, following evidence-based medicine, algorithmically indicate the priorities and preferred methodologies for the use of antiarrhythmic drugs and ablation techniques for the treatment of symptomatic patients. It is also of interest to see that the new guidelines have imported the recommendations for pregnant women with a history of SVT.

The main content of the new guidelines could be summarized as follows:

- Vagal maneuvers and adenosine are the treatments of choice for the acute therapy of SVT, which may also provide important diagnostic information.
- In all reentrant arrhythmias and most focal arrhythmias, catheter ablation

should be offered as an initial choice to patients, once the potential risks and benefits have been explained in detail.

- Patients with macro reentrant tachycardias following atrial surgery should be referred to specialized centers for ablation.
- Atrioventricular nodal reentry tachycardia, typical or atypical, can now be ablated with almost no risk of atrioventricular block.
- If a patient undergoes assessment with an electrophysiology study and is found to have an accessory pathway with high-risk characteristics, catheter ablation should be performed.
- Do not use sotalol in patients with SVT.
- Do not use amiodarone in preexcited atrial fibrillation.
- Verapamil is not recommended in wide QRS-complex tachycardia of unknown etiology.
- Consider using ivabradine, when indicated, together with a β -blocker for inappropriate sinus tachycardia.
- Verapamil, diltiazem, and β -blockers remain options for the chronic management of atrioventricular nodal reentry tachycardia, but have been downgraded from class I to class IIa.
- Do not use flecainide or propafenone in patients with left bundle branch block or ischemic or structural heart disease.
- If possible, avoid all antiarrhythmic drugs during the first trimester of pregnancy. If β -blockers are necessary, use only β_1 -selective agents (but not atenolol). Flecainide or propafenone should be considered for the prevention of SVT in patients with Wolff–Parkinson–White syndrome and without ischemic or structural heart disease (class IIa).
- Amiodarone and digoxin have been dropped as the treatment of choice for the acute management of narrow-complex tachycardia.
- Consider tachycardiomyopathy in patients with reduced left ventricular function and SVT.
- Ablation is the treatment of choice for tachycardiomyopathy due to SVT.
- Atrioventricular nodal ablation with subsequent biventricular or His-bundle pacing (“ablate and pace”) should be considered if the SVT cannot be ablated.

We can see that, based on the previous key messages described in a recent paper,¹ a clear and up-to-date policy has been devised to address the common problem of SVTs, which are known to frequently affect children, adolescents, and/or young adults.

CLINICAL TRIALS AND REGISTRIES

Long-term outcomes of the DAPA trial

DAPA (Defibrillator After Primary Angioplasty) was a prospective, randomized, multicenter controlled study designed to evaluate the survival benefit of early prophylactic use of implantable cardioverter-defibrillators in high-risk patients with ST-segment myocardial infarction (STEMI) after primary percutaneous coronary intervention. The primary end point of the trial was to estimate the all-cause mortality within 3 years of STEMI treated with primary percutaneous coronary intervention in patients with at least one high-risk factor: (i) left ventricular ejection fraction <30% within 4 days; or (ii) thrombolysis in myocardial infarction flow <3 after primary percutaneous coronary intervention.

The trial enrolled 266 patients. During a median follow-up period of 9 years, 24.4% of the patients in the implantable cardioverter-defibrillator group died vs 35.6% in the control group ($P=0.02$). Sudden cardiac death was numerically lower in the implantable cardioverter-defibrillator group (3.1% vs 5.9%; $P=0.521$). This mortality difference has been mainly attributed to cardiac deaths, which were significantly higher in the medical group (18.5%) than in the implantable cardioverter-defibrillator group (11.5%). Another interesting finding of the study was that, after 18 months, half of the patients in both groups demonstrated improvement in their left ventricular ejection fraction. The benefit of implantable cardioverter-defibrillators was still preserved vs the group on medical therapy.

Although this trial offers great insight into the potential benefit of early use of implantable cardioverter-defibrillators in high-risk patients after a myocardial infarction, it cannot be considered conclusive because of its premature termination and the results need to be confirmed by larger randomized trials.²

Association between implantable cardioverter-defibrillator use for primary prevention and mortality

This study was based on the Swedish Heart Failure Registry (SWEDE-HF), involving patients who fulfilled the European Society of Cardiology criteria for primary prevention implantable cardioverter-defibrillator use. It is worth mentioning that the calculation of propensity scores was based on 31 clinically relevant variables. The aim of this trial was to evaluate the association between primary prevention implantable cardioverter-defibrillators and all-cause mortality in a large, contemporary cohort of patients with heart failure with reduced ejection fraction (HFrEF)

with a focus on prespecified subgroups (eg, ischemic heart disease, age, time of enrollment, and sex).

Of 16702 eligible patients in SwedeHF, 1599 (9.6%) had an implantable cardioverter-defibrillator. The unusually low number of implantable cardioverter defibrillator implantations in Sweden was cause for comment. The study population consisted of 1305 patients who were treated with an implantable cardioverter-defibrillator compared with 1305 patients who were not. The researchers found that implantable cardioverter-defibrillator use was associated with a 4.2% absolute reduction in the risk of all-cause mortality at 1 year (HR, 0.73; 95% CI, 0.60-0.90) and a 2.1% absolute reduction in the risk of all-cause mortality at 5 years (HR, 0.88; 95% CI, 0.78-0.99). It is important to mention that the reduction in both short- and long-term mortality associated with primary prevention implantable cardioverter-defibrillators was consistent in all subgroups evaluated.

This study supports the current guideline recommendations for use of implantable cardioverter-defibrillators in primary prevention in patients with HFREF and is a reminder of the need to expand the use of implantable cardioverter-defibrillators in clinical practice.³

AFIRE study

The AFIRE study (Atrial Fibrillation and Ischemic events with Rivaroxaban in patients with stable coronary artery disease) is a multicenter, prospective, randomized, open-label, parallel-group study conducted in patients aged ≥ 20 years with nonvalvular atrial fibrillation and coronary artery disease. At this point, it is worth mentioning that it is common practice to use anticoagulants in combination with antiplatelet agents in patients with atrial fibrillation and coronary artery disease. The current guidelines support monotherapy with oral anticoagulants after 12 months of combination therapy. However, this approach had not been supported by evidence from randomized controlled trials. The AFIRE study aimed to investigate whether rivaroxaban monotherapy is noninferior to combination therapy (rivaroxaban plus an antiplatelet agent) in patients with atrial fibrillation and stable coronary artery disease more than 1 year after revascularization or in those with angiographically confirmed coronary artery disease not requiring revascularization.

Two primary end points were set. The primary efficacy end point was stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause. As the primary safety end point, the investigators intended to assess the major bleeding events, as defined according to the criteria of the International Society on Thrombosis and Haemostasis. A total of 2236 patients from 294 centers in Japan were randomly assigned to two groups. The incident rate of the primary efficacy end point was of 4.14% per year for patients

in the monotherapy group and 5.75% per year for the patients in the combination therapy group ($P < 0.001$ for noninferiority). The incident rate of the primary safety end point was significantly lower for monotherapy compared with combination therapy (1.62% vs 2.76% per year; HR, 0.59; 95% CI, 0.39-0.89; $P = 0.0115$). In addition, both all-cause mortality (1.85% vs 3.37%; HR, 0.55; 95% CI; 0.38-0.81) and the rate of adverse clinical events (3.90% vs 6.28% per year) were significantly lower for patients on rivaroxaban monotherapy than for those on combination therapy. The results confirm the noninferiority of the oral anticoagulation monotherapy with rivaroxaban over the combination therapy of an anticoagulant plus a P2Y12 inhibitor, as regards both efficacy and safety. The above data could support a review of the current guideline recommendation for antithrombotic treatment of patients with atrial fibrillation and coronary artery disease.⁴

ENTRUST-AF PCI trial

The current guidelines for patients with atrial fibrillation undergoing percutaneous coronary intervention with stent placement recommend the use of oral anticoagulation with a vitamin K antagonist combined with dual antiplatelet therapy with acetylsalicylic acid (aspirin) and P2Y12 inhibitors (triple therapy).

ENTRUST-AF-PCI (Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen following successful coronary stenting in atrial fibrillation patients) was a randomized, open-label, phase 3b trial whose primary objective was to assess the incidence of major or clinically relevant nonmajor bleeding (ISTH) over a 12-month period in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent placement, who were receiving treatment with edoxaban in combination with a P2Y12 inhibitor vs the triple therapy currently recommended by the guidelines. A total population of 1506 patients from 18 different countries participated in this trial. Patients were randomly assigned either to edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or to a vitamin K antagonist in combination with a P2Y12 inhibitor and aspirin (100 mg once daily for 1 to 12 months).

The trial showed that the antithrombotic regimen with a full dose (60 mg once daily) of edoxaban in combination with a P2Y12 inhibitor was noninferior to triple therapy with a vitamin K antagonist as regards the risk of major or clinically relevant nonmajor bleeding events over 12 months. In addition, the two different regimens demonstrated similar rates with respect to the main efficacy outcome—a composite of death from cardiovascular causes, stroke or systemic embolic events, myocardial infarction, or definite stent thrombosis.⁵

NEW RESEARCH STUDIES AND SUBANALYSES OF KNOWN TRIALS

AliveCor ECG recording and a deep learning model to predict atrial fibrillation

The AliveCor product KardiaMobile represents an FDA-cleared, smartphone-enabled device with a capability for single-lead ECG recording. Researchers used a deep learning model where the objective was to predict atrial fibrillation from normal sinus rhythm ambulatory ECG data. They trained a deep convolutional neural network on 1984581 normal ECGs from 19267 patients with (i) only normal ECG recordings or (ii) at least 30% of the ECGs with atrial fibrillation. Using an operating point with equal sensitivity and specificity, the model's sensitivity and specificity was 73.1%. Using an operating point with high specificity (90.0%), the model's sensitivity was 48.0%. Although these are early findings that still need validation, they suggest that artificial intelligence might be a potential new tool for the early diagnosis and appropriate treatment of atrial fibrillation.^{6,7}

Sudden cardiac death in endurance racing

The main objective of this study was to investigate preventable factors for sudden cardiac death in endurance races. The study included 1 073 722 runners who participated in 46 long-distance Parisian races during 2006 and 2016. Researchers collected all incidents of sudden cardiac death that occurred over the 10-year period and attempted to correlate them with race characteristics, such as temperature and air pollution, as well as the age and sex of the participants. The results showed that 36 sudden cardiac deaths occurred during this time, with 7 of them being related to high temperature (heat stroke) and 25 due to myocardial ischemia. Researchers found that, of the 25 patients who died of myocardial ischemia, one-third of them demonstrated symptoms during the race that did not prevent them from continuing. Another very interesting finding is a correlation between the air pollution index and the occurrence of events. Elevated levels of microparticles and sulfur derivatives were present in the majority of the events. It is obvious that sudden cardiac death in long-distance endurance races could be, to some extent, preventable. For this to happen, it is necessary for participants to be adequately educated; organizing committees also need to be more concerned and strict about the external factors that prevail during the different races.⁸

Arrhythmia services in 22 African countries

Morbidity and mortality due to arrhythmias in African countries are still a distressing topic, as high rates persist. It was this fact that motivated the Pan-African Society of Cardiology to address the matter by conducting this study. The investigators collected data from 22 countries in the period between 2011 and 2018 regarding the availability of human resources (pacemaker operators, electro-

physiologists), use of drugs, cardiac implantable electronic devices, ablation techniques, and the availability of facilities to perform these invasive procedures.

The results showed a direct correlation between the cost of cardiac implantable electronic devices compared with the GDP per capita and the device implantation rate, highlighting the need to reduce the cost of these procedures. Another interesting finding is the availability of antiarrhythmic and antithrombotic drugs, with some countries completely lacking this possibility (Tunisia: non-vitamin K-dependent oral anticoagulants) and most of the drugs being unequally available over the African market, with only 17% of the countries using all of the non-vitamin K-dependent oral anticoagulants. It is of course worth mentioning that 20% of the countries did not implant pacemakers, while none of the sub-Saharan countries, apart from South Africa, was able to perform complex ablation with 3D mapping. The survey confirms all previous reports about the inadequate confrontation of arrhythmias in most African countries, especially in the sub-Saharan area, and calls for immediate restructuring of the public health policies.⁹

CABANA: atrial fibrillation type substudy

A subanalysis of the CABANA trial (Catheter Ablation vs ANti-arrhythmic drug therapy for Atrial fibrillation) found that radiofrequency catheter ablation was not superior to antiarrhythmic therapy in terms of efficacy and safety over a 5-year period in patients with new-onset or untreated atrial fibrillation, although it could provide better quality of life. In this study, researchers investigated the impact of atrial fibrillation type on the outcome of ablative or drug therapy. Researchers discovered a gap in the data concerning patients with persistent and long-standing persistent atrial fibrillation, as most previous trials had demonstrated the effectiveness of catheter ablation only in patients with paroxysmal atrial fibrillation. Another main objective of the trial was to assess the correlation between atrial fibrillation type and the progression or regression of the arrhythmia over time. Of the 2204 subjects who participated in the CABANA trial, 42% had paroxysmal atrial fibrillation, 48% persistent atrial fibrillation, and 10% long-standing persistent atrial fibrillation.

The results of this subanalysis showed that the primary composite end point of death, disabling stroke, severe bleeding, and cardiac arrest was similar for the different categories of atrial fibrillation patients. Interestingly, however, results related to all-cause mortality or cardiovascular hospitalization showed that patients with paroxysmal and persistent atrial fibrillation had a better outcome when treated with catheter ablation, while patients with long-standing persistent atrial fibrillation had a higher event rate when treated with catheter ablation compared with drug therapy. It is important to mention that ablation demonstrated

superiority over drug therapy in decreasing atrial fibrillation recurrence, regardless of the atrial fibrillation type. Furthermore, it was more effective in decreasing the rates of all three types of atrial fibrillation and increasing the proportion of patients in normal sinus rhythm.^{10,11}

Real-life scenarios for catheter ablation in patients with heart failure and atrial fibrillation

The recent CASTLE-AF trial (Catheter Ablation vS convenTional thErApY for patients with Atrial Fibrillation and left ventricular dysfunction) indicated the superiority of catheter ablation over drug therapy for atrial fibrillation patients with heart failure in terms of all-cause mortality and hospitalization for worsening atrial fibrillation. Researchers looked into the French Nationwide Heart Failure database and investigated how the CASTLE-AF trial reflected real-life scenarios. They identified 252 395 atrial fibrillation patients with heart failure, of whom almost 99.5% were treated with conservative therapy, while the remaining 0.5% underwent catheter ablation, mostly in less experienced centers. French investigators carried out 1:1 propensity score matching, which confirmed the CASTLE-AF findings of lower all-cause mortality and heart failure–related hospitalization in unselected atrial fibrillation patients undergoing catheter ablation.^{12,13}

ATTEST trial

The ATTEST trial (Atrial Fibrillation Progression Trial) was a controlled, randomized trial whose main object was to investigate how radiofrequency catheter ablation compares with antiarrhythmic therapy in relation to the progression of paroxysmal atrial fibrillation to persistent atrial fibrillation or atrial tachycardia. The results demonstrated the superiority of catheter ablation over antiarrhythmic therapy, with 17.5% of patients treated with antiarrhythmic drugs over a 3-year period developing persistent atrial fibrillation, in contrast to patients undergoing radiofrequency catheter ablation, of whom only 2.4% saw their disease progress. The authors suggested that paroxysmal atrial fibrillation ablation could be up to 10 times more effective than conservative therapy in preventing the progression of the disease. This trial reinforces recent findings suggesting that early radiofrequency ablation in patients with paroxysmal atrial fibrillation could prevent the progression of the disease, drastically increasing the patients' quality of life.¹⁴

Stereotactic body radiotherapy for resistant ventricular tachycardia

Researchers from the Czech Republic proposed an upgrade to stereotactic body radiotherapy, a new technique in the field of electrophysiology for the treatment of resistant ventricular tachycardia. The authors of the trial integrated electro-anatomical voltage mapping with cardiac CT, enabling the precise stereotactic body radiotherapy of the substrate to be identified in the electrophysiology study.

This is an innovative method for treating patients who have undergone unsuccessful catheter ventricular tachycardia ablation (≥ 2), both endo- and epicardial. Researchers merged CARTO-derived 3D models with CT-derived 3D models and proceeded to the noninvasive, gamma-knife-driven ablation of the ventricular tachycardia. Undoubtedly, this advancement in treating ventricular tachycardia resistant to catheter ablation could be of great importance in the future in the field of electrophysiology.^{15,16}

CONCLUSIONS

Summarizing the evaluation of the issues presented at the annual European Society of Cardiology congress in Paris this year, we could argue that, in the field of arrhythmias and electrophysiology, there is very limited development in pharmacology and antiarrhythmics for the management of arrhythmias, whereas, in contrast, therapeutic techniques related to biotechnology applications are gaining ground. ■

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Abbreviations &
Acronyms



ACLY	ATP citrate lyase
AFIRE	Atrial Fibrillation and Ischemic events with Rivaroxaban in patients with stable coronary artery disease
ASCENT-COPD	effect of Acridinium bromide on major cardiovascular events and Exacerbations in high-risk patients with Chronic Obstructive Pulmonary Disease
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCVD	atherosclerotic cardiovascular disease
ATTEST	Atrial Fibrillation Progression Trial
AVERT	Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients
CABANA	Catheter Ablation vs Anti-arrhythmic drug therapy for Atrial fibrillation
CAPTAF	Catheter Ablation compared with optimized Pharmacological Therapy for Atrial Fibrillation
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin
CASTLE-AF	Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation
CLARIFY	prospective observational Longitudinal Registry of patients with stable coronary artery disease
CorMicA	CORonary MICROvascular Angina
CREOLE	Comparison of three combination therapies in Lowering blood pressure in black Africans
DEBUT	Drug-Eluting Balloon in stable and Unstable angina: a randomized controlled non-inferiority Trial
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
EAS	European Atherosclerosis Society
ECASS-4	European Cooperative Acute Stroke Study-4

ENCHANTED	Enhanced Control of Hypertension and Thrombolysis Stroke Study
ENTRUST-AF-PCI	Edoxaban-based versus vitamin K antagonist-based anti-thrombotic regimen following successful coronary stenting in atrial fibrillation patients
EPITHET	EchoPlanar Imaging THrombolytic Evaluation Trial
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EXTEND	Extending the Time for Thrombolysis in Emergency Neurological Deficits
FAME	Fractional flow reserve versus Angiography for Multivessel Evaluation
FDA	Food and Drug Administration
HFREF	heart failure with reduced ejection fraction
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HOPE-3	Heart Outcomes Prevention Evaluation
ImpACT-24B	IMPlant Augmenting Cerebral blood flow Trial-24B
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein a
LPL	lipoprotein lipase
MOMENTUM	Multicenter study Of MagLev tEchNology in paTients Undergoing Mechanical circulatory support therapy with HeartMate 3
MR-INFORM	Myocardial perfusion CMR versus angiography and FFR to guide the management of patients with stable coronary artery disease
PACT-HF	Patient-Centered Care Transitions in HF
PARTNER 3	Placement of aortic Transcatheter valves
PCSK-9	proprotein convertase subtilisin/kexin type 9

PIONEER-HF	Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode
POSA	Postoperative vascular complications in unrecognized Obstructive Sleep Apnea
PREDESCI	β-blockers to PREvent DEcompensation of Cirrhosis with portal hypertension
REGROUP	Randomized Endovascular Graft Prospective
RELAX-AHF	RELAXin in Acute Heart Failure
RE-SPECT ESUS	Randomized, double-blind, Evaluation in Secondary stroke Prevention comparing the Efficacy and safety of the oral thrombin inhibitor dabigatran etexilate versus acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source
SCOT-HEART	Scottish Computed Tomography of the HEART
SGLT2	sodium glucose cotransporter 2
SHINE	Stroke Hyperglycemia Insulin Network Effort
SMART-CHOICE	SMART angioplasty research team: Comparison between P2Y12 antagonist monotherapy vs dual antiplatelet therapy in patients undergoing Implantation of Coronary drug-Eluting stents
STEMI	ST-segment elevation myocardial infarction
STOPDAPT-2	Short and Optimal duration of Dual Antiplatelet Therapy after everolimus-eluting cobalt-chromium stent
SVT	supraventricular tachycardia
WRAP-IT	Worldwide Randomized Antibiotic envelope infection Prevention Trial

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INSTRUCTIONS FOR AUTHORS

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- Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689-2696.

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● Web-based material

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