

## MEETING HIGHLIGHTS

# Highlights of the 2009 Scientific Sessions of the European Society of Cardiology

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The annual congress of the European Society of Cardiology (ESC) was held in Barcelona, Spain, August 29 to September 2, 2009. The total attendance was 31,323 participants from 136 different countries. Excellent congress facilities hosted 237 pre-arranged sessions in 30 meeting rooms running in parallel, including several joint sessions in collaboration with other societies (e.g., the American College of Cardiology, the American Heart Association, and the World Heart Federation). A total of 9,848 abstracts from 96 different countries was submitted, and 4,085 (42%) abstracts were selected for presentation.

## Prevention

Prevention was the theme of this year's meeting, and interesting novelties were presented. From the Copenhagen

City Heart Study, Jensen et al. (1) reported that the resting heart rate was linearly related to fibrinogen and high-sensitivity C-reactive protein plasma levels. After adjustment for inflammatory markers, heart rate remained an independent risk factor for both cardiovascular (CV) and all-cause mortality: the relative risk (RR) for CV mortality was 1.2 ( $p < 0.001$ ) for each 10 beats/min increase of heart rate.

Among >300,000 French adults, Plichart et al. (2) found increments of 7 beats/min and 5 beats/min in resting heart rates in women and men, respectively, in the decade 1990 to 2000; no further change was noted in the last decade. This puzzling finding could not be explained by conventional risk factors, medication, or physical activity, and prognostic implications remain to be demonstrated.

The outcome of the French law on a smoke-free environment in public places inspired Bura et al. (3) to study the effect of this law on employees in bars and restaurants. Comparison of 23 nonactive smokers exposed to passive smoking in the workplace (but not exposed at home) and 23 controls (exposed neither at work nor at home) showed a significant reduction in flow-mediated dilation (5.8% vs. 9.1%) before application of the law. This was almost normalized 4 months after the law was imposed: 8.3% versus 9.5%, illustrating the impact of smoking restriction on vascular function.

Pereg et al. (4) evaluated the role of stress in patients with acute myocardial infarction (MI) and compared hair samples from 45 patients admitted for acute MI with samples from 45 patients admitted for noncardiac causes. The authors reported a significant increase in hair cortisol levels: 320 ng/g (range 102 to 937 ng/g) versus 231 ng/g (range 82 to 1,123 ng/g;  $p < 0.001$ ), respectively. This observation suggests that infarct patients may have experienced chronic stress during the 3 months preceding the acute event.

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The winners of the featured research award session were Erbs et al. (5) from Leipzig, who studied 80 obese children (body mass index  $28 \text{ kg/m}^2$ ) and 60 lean children (body mass index  $18 \text{ kg/m}^2$ ). Peak serum insulin levels after an oral glucose tolerance test were considerably higher among the obese children:  $1,079 \pm 80 \text{ pmol/l}$  versus  $598 \pm 23 \text{ pmol/l}$  ( $p < 0.001$ ). Flow-mediated dilation was impaired in the obese children, and the intima media thickness in the carotid artery was increased. The endogenous regenerative capacity, expressed as the number of circulating endothelial progenitor cells, was impaired. Thus, childhood obesity appears to be associated with early stages of atherosclerosis.

Children are recommended to engage in 1 h per day of physical activity. Walther et al. (6) showed that 12-year-old children with a higher level of physical activity ( $>15$  h weekly) had a significant beneficial impact on a range of markers of vascular function when compared with less active age-matched controls participating only in school exercise lessons (2 to 3 h weekly).

The role of regular physical activity on surrogate markers of vascular aging (telomere length in leukocytes) was investigated by Werner et al. (7). They compared young athletes and nonsmoking healthy volunteers (mean age 21 years) and found no difference in telomere length at this age level. Telomeres do shorten with increasing age. However, when older athletes were compared with age-matched less active controls (mean age 51 years), the athletes had a significant inhibition of the telomere erosion, indicating a potent “anti-aging” effect of regular physical activity.

Earlier surveys, namely, EuroAspire III, have shown a large gap between recommendations and clinical practice in cardiovascular disease (CVD) prevention. In England, Jones et al. (8) have started novel family-centered community-based programs in which multidisciplinary teams of health workers provide preventive care for CVD patients, for persons at high CVD risk, and for their families. A first evaluation suggested that this model is effective and should be extended beyond the already 15 existing centers in the country.

Garzia et al. (9) studied the effect of acute, moderate red wine consumption ( $5 \text{ ml/kg}$ ) in 40 young volunteers as compared with consumption of nonalcoholic beverages: acute intake of red wine appeared to be associated with an increase in various electrocardiography (ECG) time intervals, which may indicate a potential arrhythmogenic risk of red wine consumption.

Barone Adesi et al. (10) evaluated the possibility of increased risk for acute coronary syndromes (ACS) in the Piedmont area in Italy in relation to watching soccer matches. Studying the relative risk of hospital admissions for ACS during the Soccer World Championships in 2002 and 2006 and the European Championship in 2004 revealed no increase in admissions, in contrast to earlier findings.

## Hypertension

In the Malmö Prevention Project, a cohort of 33,346 subjects (ages  $45.7 \pm 7.4$  years) was followed up for  $22.7 \pm 6.0$  years (11). Orthostatic hypotension, defined as systolic blood pressure (BP) fall  $\geq 20$  mm Hg and/or diastolic BP fall  $\geq 10$  mm Hg within 3 min of standing, was present in 6% of the participants. After adjustment for traditional risk factors, orthostatic hypotension moderately increased mortality (hazard ratio [HR]: 1.19,  $p < 0.001$ ) and coronary events (HR: 1.18,  $p < 0.01$ ), but not stroke. The authors also assessed the prognostic significance when orthostatic hypotension was defined as systolic BP fall  $\geq 30$  mm Hg and diastolic BP fall  $\geq 15$  mm Hg, which distinctly increased mortality and coronary event risks, with HRs of 1.40 to 1.65. In the PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) study on ambulatory BP monitoring, a cohort of 2,011 subjects (ages 25 to 74 years) representative of the general population of Monza was followed up for an average of 12.3 years (12). Morning BP surge was defined as the average systolic BP 2 h after awakening minus the lowest night-time systolic BP. In univariable analysis, the morning BP surge predicted all-cause mortality and CV events, but the relationships disappeared after adjustment for potential confounders, such as age and other 24-h BP variables. The authors concluded that morning BP surge reflects overall BP variability but does not independently predict mortality. However, one has to consider that there is no generally accepted definition of morning BP surge, and definitions usually lack the concept of “morning surge.”

Moderate aerobic exercise is a generally accepted non-pharmacological measure in the management of hypertension. In a study from Norway, 89 patients (49 men) with grades I to II essential hypertension (age  $52 \pm 8$  years) were randomly divided into 3 groups: aerobic interval training at 95% of peak heart rate; isocaloric moderate continuous training at 70% of peak heart rate; and a control group (13). After 12 weeks, BP decreased by  $13/7$  mm Hg in the interval training group, by  $4/4$  mm Hg in the continuous training group, and remained unchanged in the control group. The authors concluded that both training modalities significantly reduce BP, but that interval training appears to be more effective than continuous training.

The double-blind placebo-controlled HYVET (Hypertension in the Very Elderly Trial) has shown benefit from antihypertensive treatment in octogenarians. The investigators presented the results from the study extension, in which 1,712 patients were actively treated (14). Comparing patients previously treated with active medication to patients previously on placebo, significant benefit was found for total and CV mortality, and no differences were seen for stroke or heart failure (HF). Therefore, octogenarians gained immediate benefit from treatment in the prevention of stroke and HF, but sustained differences with regard to reductions in total and CV mortality reinforce the need for early treatment.

In the joint session of the ESC and the European Society of Hypertension (ESH), the question was asked: what is new, what can be reinforced, and what may have to be changed in 2009 with regard to the 2007 ESC/ESH hypertension guidelines? The importance of global CV risk on the basis of risk factors, subclinical organ damage, and CV renal disease was re-emphasized. With regard to first-choice drugs, the position that all drugs have pros and cons and that no drug should be generally prescribed or proscribed was maintained. The role of combination treatment was reinforced by the evidence that initiation with combination treatment is associated with earlier BP control and better tolerability and compliance, and that adding a drug from another class is more effective than doubling the dose of the same drug. On the basis of the pronounced antihypertensive effect, evidence of CV protection, and optimal tolerability in recent trials, some combinations of drugs can be promoted to most-preferred combinations, namely, diuretics or calcium antagonists with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. Blood pressure thresholds and goals for drug treatment may need critical reappraisal, because in several instances they are not based on results from prospective outcome trials. Data from other sources may justify current recommendations, but further hard evidence is needed. In addition, the BP level below which vital organ perfusion is impaired is likely to differ according to patient characteristics; for example, post-hoc analyses of trials suggest that there is some reason for concern when high-risk patients' on-treatment BP is <120/75 mm Hg. Finally, new evidence for treatment in specific conditions includes the HYVET trial, which showed that even octogenarians benefit from antihypertensive therapy.

## HF

The prognosis of the patients with HF remains poor. Accurate prognostic stratification is, therefore, still important, and biomarkers represent a major objective of research. The independent prognostic values of increased serum urea levels during hospitalization (15), as well as of cystatin C (16), red cell distribution width (17), troponin I (measured by a highly sensitive assay) (18), and arginine-vasopressin and adrenomedullin plasma levels (19) were shown.

In HF patients with preserved left ventricular ejection fraction (LVEF), independent prognostic factors, as assessed in the I-PRESERVE (Irbesartan in HF With Preserved Ejection Fraction) study, were N-terminal pro-B-type natriuretic peptide (NT-proBNP), age, diabetes mellitus, and previous HF hospitalization (20). In 60% of deaths, the cause was CV, mostly due to sudden death or worsening HF (21).

Diabetes is a known risk factor for HF, and antidiabetic treatment may affect outcome. In the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) study,

CV outcomes were prospectively assessed after addition of rosiglitazone to either metformin or sulfonylurea, compared with the combination of the 2 alone in 4,447 patients with type 2 diabetes (22). The incidence of CV hospitalization or death (primary end point), as well as CV death, stroke, and MI, were similar between the 2 study groups. However, the incidence of deaths or hospitalizations caused by HF was greater among the patients treated with rosiglitazone (61 subjects vs. 29 subjects in the control group; HR: 2.1, 95% CI: 1.35 to 3.27).

Tachycardia may have a role as a determinant of HF. However, in the BEAUTIFUL (Morbidity-Mortality Evaluation of the I<sub>f</sub> Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction) trial, pure heart rate reduction with ivabradine had no effect on the primary composite end point of CV death or readmission due to HF or MI. In a subgroup analysis concentrating on the patients with limiting angina at baseline, ivabradine did not affect the rate of HF hospitalizations but did reduce admissions for MI, particularly among patients with heart rate at baseline >70 beats/min (23).

Rosuvastatin did not change major outcomes in the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure) trial (24). There are some data that statins may reduce the incidence of atrial fibrillation (AF). Among the 3,690 patients without AF at baseline in the GISSI-HF trial, AF developed in 15.0% during a median follow-up of 3.7 years (13.9% with rosuvastatin vs. 16.0% with placebo). Although the difference was not significant at unadjusted analysis ( $p = 0.097$ ), it was significant after adjustment for other clinical and laboratory variables ( $p = 0.039$ ). These data suggest that rosuvastatin may have beneficial effects on AF occurrence in patients with HF.

The use of cardiac resynchronization therapy (CRT) for HF is increasing, and has been evaluated in a survey organized by ESC associations on heart failure and heart rhythm (25). This survey included 2,438 patients from 141 centers in 12 European countries and Israel who underwent successful CRT implantation. Approximately 80% of patients who underwent CRT implantation were in New York Heart Association (NYHA) functional class III or IV, but 2% were in NYHA class I and 20% were in NYHA class II. Approximately 80% of patients had QRS duration >130 ms, but 9% had QRS duration <120 ms, and 10% had durations between 120 ms and 130 ms. The vast majority had sinus rhythm, but 23% had AF, and 26% concerned upgrades from permanent right ventricular pacing or implantable cardioverter-defibrillator (ICD). Peri-procedural complications occurred during 11% of the procedures.

The hypothesis that an adenosine-blocking agent, rolofylline, could induce diuresis, prevent deterioration of renal function, and improve 60-day outcomes of patients with acute HF was tested in the PROTECT (Placebo-Controlled Randomized Study of Rolofylline for Patients Hospitalized With Acute HF and Volume Overload to

Assess Treatment Effect on Congestion and Renal Function) study (presented at ESC Hotlines). The study involved 2,033 patients hospitalized within 24 h of acute HF, with high BNP or NT-proBNP and an estimated creatinine clearance of 20 to 80 ml/min. The results failed to show the superiority of rolofylline on the composite primary end point, renal function and outcomes. Rolofoylline was associated with more improvement in dyspnea at 24 to 48 h (51.2% vs. 44.5% with placebo). Regarding safety, there was no difference in serious adverse events, but rolofylline was associated with seizures (0.8% vs. 0%) and a tendency to an increase in the number of strokes, either ischemic or hemorrhagic (1.2% vs. 0.5%), versus placebo.

For patients presenting with acute HF, predictors of a greater response of dyspnea to the new vasodilator relaxin, compared with placebo, were higher systolic BP at baseline (26), and a shorter time to treatment (27). Inotropic agents with novel mechanisms of action are currently studied. The direct cardiac myosin activator CK-1827452 has been shown to cause a dose-dependent increase in systolic ejection time, stroke volume, and LVEF. As excessive prolongation of systolic ejection time can limit diastolic coronary flow and ventricular filling, the effects of CK-1827452 on exercise tolerance have been studied in 94 patients with ischemic cardiomyopathy and angina using a double-blind, randomized, placebo-controlled study design. The myosin activator did not adversely affect exercise capacity and showed a good safety profile in these patients (28).

Beta-blockers have improved outcomes even when therapy is maintained in patients with acute HF, in retrospective analyses. The effects of maintenance of ongoing beta-blocker therapy, versus its withdrawal, was prospectively tested in 169 patients hospitalized for acute HF. Maintenance of ongoing beta-blocker therapy had no effect on dyspnea relief nor on other end points, including plasma BNP, length of hospital stay, rehospitalization rate, and death rate after 3 months (29).

### Acute Cardiac Care

The majority of successfully resuscitated out-of-hospital cardiac arrest patients will die during hospital stay. Giovannetti et al. (30) have shown, for 983 patients with out-of-hospital arrest, that the mortality among patients with a primary cardiac cause was lower (58%) than among patients with an extracardiac cause (80%;  $p < 0.001$ ). Current guidelines recommend coronary angiography and percutaneous coronary intervention (PCI) for patients resuscitated from cardiac arrest due to ACS. However, it usually is difficult to identify the cause of arrest, and the value of the ECG is controversial. Dumas et al. (31) performed coronary angiography in all arrest survivors ( $n = 372$ ) who did not have an obvious cause of arrest. After the return of spontaneous circulation, ST-segment elevation was noted in 30% of patients, ST-segment depression or negative T waves in 49%, and nonspecific changes or normal ECG in 21%. PCI

was more frequently performed in patients with ST-segment elevation (80%) than in the other groups (28% and 18%, respectively;  $p < 0.0001$ ). Overall, 41% of patients survived during their hospital stay. The survival was higher (51%) among patients with ST-segment elevation compared with the other 2 groups (41% and 27%, respectively;  $p < 0.005$ ).

Mild induced hypothermia lowers mortality and reduces neurologic damage after cardiac arrest. Current techniques involving total body cooling have many limitations and side effects. Salinas Sanguino et al. (32) have shown that ECG changes during mild induced hypothermia are similar to changes that occur with deep accidental hypothermia. Sinus bradycardia was the most common arrhythmia. Durations of PR, QTc, and QRS are prolonged, and changes revert with rewarming.

A new catheter that selectively cools the brain while maintaining normal systemic temperature has been evaluated in an animal model and may improve neuroprotection during cardiac arrest without adverse events (33). Moreover, Tuseth et al. (34) have shown in an experimental model that a percutaneous LV assist device can achieve hemodynamic support comparable to that of open chest cardiac massage during cardiac arrest.

### ACS

An updated analysis of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) study examined whether there was an interaction between the use of proton-pump inhibitors and thienopyridines (35). In contrast to the reports from observational studies, the data from this trial did not show evidence of a difference in outcomes for either clopidogrel or for prasugrel, with or without proton-pump inhibitors (but lower event rates with prasugrel compared with clopidogrel).

Similarly, in the CURRENT-OASIS 7 (Clopidogrel Optimal Dose to Reduce Recurrent Events-Organization to Assess Strategies for Ischemic Syndromes 7) trial (presented at the ESC Hotlines), no difference in outcomes was observed for patients taking or not taking proton-pump inhibitors. The findings suggest that unmeasured baseline variables may have contributed to the excess risk seen in some observational reports of concomitant administration of proton-pump inhibitors and thienopyridines.

The ESC non-ST-segment elevation ACS guidelines suggested that a 600 mg bolus of clopidogrel could be given to patients with planned PCI, in addition to aspirin and an anticoagulant, but the guideline highlighted that a definitive study was needed. The CURRENT-OASIS 7 trial randomly assigned 25,087 patients with non-ST-segment elevation ACS to a strategy of higher (600 mg bolus followed by 150 mg for 1 week, followed by 75 mg daily) or standard regimen of clopidogrel (300 mg bolus followed by 75 mg

daily). In this double-blind comparison, the primary outcome was CV death, MI, or stroke at 30 days, and the intent was to study these dosing regimens of clopidogrel in the context of PCI. The study also included an open factorial design of the first large-scale randomized comparison of aspirin dose (75 to 100 mg vs. 300 to 325 mg over 30 days). In the overall population, the primary end point was similar for the 2 clopidogrel strategies, but in the pre-specified analysis of the 17,232 patients undergoing PCI, there were significantly fewer combined end points of CV death, MI, or stroke with the higher-dose regimen (4.5% standard dose, 3.9% double dose, HR: 0.85, 95% CI: 0.74 to 0.99;  $p = 0.036$ ). The higher-dose regimen also demonstrated a reduced rate of stent thrombosis (HR: 0.58, 95% CI: 0.42 to 0.79;  $p = 0.001$ ). In contrast, for the 7,855 patients without PCI, there was no benefit in this short-term study (30-day outcomes). In the entire study, the rates of TIMI major bleeding were not different for the higher versus lower clopidogrel regimens (0.5% vs. 0.5%), but there were more transfusions of 2 or more units with the higher clopidogrel strategy. In the randomized comparison of aspirin dose, there was neither overall benefit nor greater bleeding risk for the higher-dose regimen. However, the factorial analysis suggests that most benefit may be seen for the high-dose aspirin, high-dose clopidogrel regimen.

The PLATO (Platelet Inhibition and Patient Outcomes) trial tested ticagrelor, an orally active and reversible non-thienopyridine P2Y<sub>12</sub> antagonist, against clopidogrel (300 mg bolus and 75 mg daily) in 18,624 patients with non-ST-segment elevation ACS or ST-segment elevation ACS with planned primary PCI (36). An additional 300 mg bolus of clopidogrel was allowed for PCI and was given to  $\approx 19\%$  of all patients. The double-blind regimen was administered for a median of 9 months, and the primary outcome of CV death, MI, or stroke occurred in 9.8% of patients receiving ticagrelor compared with 11.7% of patients receiving clopidogrel (HR: 0.84, 95% CI: 0.77 to 0.92;  $p < 0.001$ ). The authors pre-defined a system of hierarchical testing of secondary end points. This revealed significant differences in the rates of MI alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group,  $p = 0.005$ ), and deaths from CV causes (4.0% with ticagrelor vs. 5.1% with clopidogrel,  $p = 0.001$ ) but not stroke alone (1.5% vs. 1.3%,  $p = 0.22$ ). Death from any cause was also reduced with ticagrelor (4.5%, vs. 5.9% with clopidogrel,  $p < 0.001$ ). There was no significant difference in the rate of major bleeding between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively), but ticagrelor was associated with a higher rate of major bleeding unrelated to coronary artery bypass graft surgery (CABG) (4.5% vs. 3.8% with clopidogrel,  $p = 0.03$ ), and more cases of fatal intracranial bleeding (11 vs. 1, respectively,  $p = 0.02$ ) but fewer cases of fatal nonintracranial bleeding. Thus, compared with the currently published guidelines for the standard of care for patients with ACS, treatment with ticagrelor compared with clopidogrel significantly reduced the composite of death from CV causes, MI,

or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.

These recent PLATO study results need to be evaluated in the light of the earlier findings from the TRITON-TIMI 38 study in which superior efficacy was demonstrated for prasugrel over clopidogrel, but at the expense of higher rates of major bleeding, especially in certain high-risk groups (35). In contrast to the TRITON-TIMI 38 study, in which the study drugs were administered after diagnostic angiography, the PLATO study randomized patients with ST-segment and non-ST-segment elevation ACS after first presentation. Whether prasugrel offers advantages over ticagrelor among unselected patients with the full spectrum of ACS remains to be determined.

### Interventional Cardiology

In a session entitled "Three years after Barcelona 2006," James presented for the first time the 6-year follow-up of 60,937 patients enrolled in the SCAAR (Swedish Coronary Angiography Angioplasty Registry) study, equally divided between patients treated with bare-metal stents or drug-eluting stents (DES). The Kaplan-Meier curves for adjusted mortality and MI reported for single stents, for the overall population, and for on- or off-label indications were superimposable.

The ESTROFA-2 (Estudio Español Sobre Trombosis de Stents Farmacoactivos-2) registry closely followed 4,768 patients treated with second-generation DES (the zotarolimus-eluting stent Endeavor and the everolimus-eluting stent Xience/Promus) enrolled in 34 Spanish centers between 2006 and April 2008 (37). Definite thrombosis rate at 2 years was low (1.0% for zotarolimus-eluting and 0.9% for everolimus-eluting stents), with a particularly low incidence in the interval between 12 and 24 months (0.2% and 0.1%, respectively). The largest randomized comparison of DES with biodegradable and biostable polymers was reported by the ISAR (Intracoronary Stenting and Angiographic Results) study investigators (38). The stent studied was developed in Munich, Germany, and elutes sirolimus for 4 to 6 weeks after implant through a polymer expected to be fully absorbed by the surrounding tissue after 6 to 9 months. The 1,299 patients treated with this stent were compared with 1,304 patients receiving conventional commercially available sirolimus- and everolimus-eluting stents (Cypher [Cypher Corp., Bridgewater, New Jersey] and Xience [Abbott Laboratories, Abbott Park, Illinois]). At the 6- to 8-month angiographic follow-up, late lumen loss was 0.24 and 0.26 mm for the stents with biodegradable and biostable polymers, respectively. The similar restenosis rate explained the nearly identical rate of repeat revascularization at 12 months (13.7% and 13.9%). Death and MI were also similar in the 2 groups, with a definite stent thrombosis at 1 year of 1.5% for the biostable stent and 1.0% for the biodegradable polymer stent platforms ( $p = 0.29$ ). Nasu et

al. (39) assessed with optical coherence tomography 60 sirolimus-eluting (Cypher) and 60 paclitaxel-eluting (Taxus, Boston Scientific, Natick, Massachusetts) stents. Six months after implantation, there was absent or incomplete tissue coverage in 18% of Taxus stents versus 33% of Cypher stents ( $p = 0.03$ ). More than 20% of struts remained uncovered in 5% and 37%, respectively, of the paclitaxel- and sirolimus-eluting stents ( $p = 0.03$ ). In a separate study, 24 patients received a Cypher stent and a Taxus stent in the same artery. Six months after implantation, 4.6% and 11.1% of the apposed struts were uncovered in the respective groups, and they also differed in the average neointimal thickness, which was greater in Taxus stents ( $150 \pm 163 \mu\text{m}$  vs.  $94 \pm 103 \mu\text{m}$  for Cypher stents,  $p < 0.01$ ) (40).

There was great expectation for the update of the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial. The main criticism, particularly from cardiac surgeons, was that the equivalence in major hard end points (death, MI, stroke) at 1 year was not going to hold with time and that the difference in new revascularizations, which already drew at 1 year the major adverse cardiac and cerebrovascular events rate in favor of surgery (12.1% vs. 17.8%,  $p < 0.002$ ), was due to progressive increase over time. The 2-year results showed no difference in the incidence of additional deaths and strokes (presented at ESC Clinical Trial Updates). Myocardial infarction after the first year, on the contrary, occurred more frequently among the 903 patients treated with Taxus stents (1.2% vs. 0.1% in the surgery group,  $p = 0.008$ ), leading to an overall greater frequency 2 years after treatment in the Taxus group (5.9% vs. 3.3% in the surgical group,  $p < 0.01$ ). Still, there was no overall difference in the combined end point of death, MI, or stroke at 2 years (10.8% in the Taxus group and 9.4% in the CABG group,  $p = 0.44$ ). Unexpectedly, revascularization between 1 and 2 years was not significantly different in the 2 groups (3.4% for CABG, 4.7% for Taxus,  $p = 0.06$ ), with most of the absolute difference at 2 years (8.6% vs. 17.4%,  $p < 0.001$ ) occurring between 6 and 12 months and relatively flat, nearly parallel curves between 18 and 24 months. The overall event rate at 2 years remained significantly lower with CABG (16.3% vs. 23.4% with Taxus,  $p < 0.001$ ), but groups with a low and intermediate SYNTAX score ( $<33$ ) and the 707 patients with left main disease showed no significant difference. An update in results (from 12 to 18 months) was also shown by the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study investigators (presented at ESC Clinical Trial Updates). The study randomly allocated 1,005 patients with multivessel disease to angioplasty of all angiographically significant stenoses or to selective angioplasty only of lesions with a fractional flow reserve  $<0.80$ . The significant difference in major adverse cardiac events observed at 1 year in the group with a flow reserve guided approach ( $-5.1\%$ ) had a further increase in the subsequent

6 months ( $-5.3\%$ ), dispelling criticisms that leaving intermediate lesions untreated creates greater risks of late events.

Two studies on acute ST-segment elevation myocardial infarction (STEMI) were presented at the ESC Hotlines. The TRIANA (Tratamiento del Infarto Agudo de Miocardio en Ancianos [primary angioplasty vs. fibrinolysis in the very elderly]) trial was expected to randomly allocate 570 patients  $>75$  years of age to primary angioplasty or thrombolysis. The study had to be terminated prematurely with only 266 patients enrolled and did not meet the end point of showing significant reduction of the combined end point of death, reinfarction, and disabling stroke with primary PCI (odds ratio [OR]: 1.46, 95% CI: 0.81 to 2.61,  $p = 0.21$  in favor of primary PCI). Still, all components of the primary end point as well as major bleeding were lower in the primary PCI group, for example, a 3.0% incidence of disabling stroke after thrombolysis versus 0.8% after PCI.

The NORDISTEMI (Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction) trial randomized patients with acute ( $<6$  h) STEMI admitted to district general hospitals in an area of central-eastern Norway, remote from primary angioplasty centers (41). Consequently, tenecteplase was administered to all patients, with one-half ( $n = 132$ ) treated conservatively in the center of initial admission and the remaining 134 immediately transported for an average of 158 km to the nearest angioplasty center. The primary end point of death, reinfarction, recurrent ischemia, and stroke at 12 months was not met (20.9% vs. 27.3%,  $p = 0.18$ ), but the secondary end point of death, reinfarction, and stroke was in favor of an immediate transfer.

## Arrhythmias and Pacing

A significant number of studies focused on the mechanisms of arrhythmogenesis. Jadidi et al. (42) used left atrial high-density mapping during sinus rhythm, coronary sinus pacing, and AF and found evidence of rhythm-dependent functional fractionation, which possibly reflects critical sites for AF maintenance. Sossalla et al. (43) for the first time showed that AF leads to electrical remodeling of sodium currents (INa), whereas INa inhibition by ranolazine proved antiarrhythmic.

In genetics, Benito et al. (44) established that in Brugada syndrome, the presence of a mutation leading to a truncated protein is associated with a more than 3-fold increase in the risk of sudden cardiac death or ventricular fibrillation in Brugada SCN5A mutation carriers, highlighting the need for and efficacy of genetic testing in risk stratification.

Focusing on new diagnostic techniques and therapies of arrhythmias, a number of studies reported novel findings. The diagnostic value and cost effectiveness of implantable loop recorders (ILRs) for syncope evaluation were indicated in a study by Bajpai et al. (45), which recommends the early use of these devices in the assessment of patients

presenting with syncope or severe palpitations and presyncopal symptoms.

In the REVISE (Reveal in the Investigation of Syncope and Epilepsy) study, Petkar et al. (46) used ILRs and demonstrated that a high incidence of asystole in patients misdiagnosed with epilepsy was present. An ECG-symptom correlation by ILR was shown in 59% of patients, and specifically demonstrated asystole in 26% of patients.

Remote monitoring of ICD patients is a new and evolving technique that offers a number of benefits in more personalized health care for patients with devices. De Ruvo et al. (47) found that patients with ST-segment elevation combined with an ICD (CRT-D) not remotely controlled (using a home monitoring system) had a 78% higher risk of delayed detection of clinical adverse events within the first 6 months from implantation, despite a follow-up program of quarterly in-office visits. Varma et al. (48) reported on the TRUST (Lumos-T Safely Reduces Routine Office Device Follow-Up) study, involving 1,312 patients implanted with ICDs with remote monitoring technology who were randomly allocated 2:1 to remote monitoring or conventional office visits. The results showed that event notification with automatic daily surveillance occurs infrequently, without overburdening clinical resources, and provides rapid detection and notification of implant events.

The relatively innovative technique of remote magnetic navigation for AF ablation was addressed in a number of studies. Chen et al. (49) evaluated 98 patients, (42% with persistent/permanent AF) who underwent radiofrequency ablation using a remote magnetic navigation system. Complete pulmonary vein isolation was achieved in 96% of patients, without major complications. At  $12 \pm 2$  months of follow-up, 73% of patients were free of AF. The second study (50) concluded that AF ablation with remote magnetic navigation had similar procedure times but significantly decreased fluoroscopy times as compared with conventional ablation.

In another study, by Sommer et al. (51), it was determined that AF ablation in patients with HF significantly improved LV function (LVEF increased from 23% to 53%).

The results of various registries and clinical trials were also announced. Among the registries, the FINGER Brugada registry stood out, presented by Probst et al. (52), in which 1,029 consecutive patients (745 males [72%]) were followed up for  $37 \pm 28$  months. At initial enrollment, 64% of the subjects were asymptomatic. During follow-up, it was noted that the cardiac event rate per year was 7.7% for patients with a history of aborted sudden death, 1.9% for patients with syncope, and only 0.5% for asymptomatic patients. It was also observed that the inducibility of ventricular tachyarrhythmias and a family history of sudden death were not predictive of cardiac events

Moss et al. (53), in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) examined whether CRT-D in minimally symptomatic cardiac patients with ischemic heart

disease (NYHA functional class I or II) or nonischemic heart disease (NYHA functional class II),  $QRS > 130$  ms, and  $LVEF < 30\%$  would reduce the combined end point of all-cause mortality or HF, when compared with ICD-only therapy. With CRT-D, 34% reduction in death or HF was observed, with 41% reduction in HF events and improvement in LVEF. Moreover, significant reverse LV remodeling was observed on echocardiography.

Two substudies of the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial with a follow-up of 24 months were also important. Linde et al. (54) showed that CRT for mild HF improved clinical outcome, ventricular structure and function, and modified disease progression with a more pronounced effect in NYHA functional class II patients. Gold et al. (55) showed that QRS duration at baseline was a strong predictor of reverse LV remodeling.

Adequate selection of patients who may benefit most from CRT remains an intriguing topic. To further characterize the patients who benefit, a substudy from the PROSPECT (Predictors of Response to CRT) trial, presented by Van Bommel et al. (56), compared patients with substantial LV reverse remodeling after 6 months of CRT with patients who did not show LV remodeling. Patients with extensive remodeling after CRT were more often female, had nonischemic HF, longer QRS duration, no history of ventricular tachycardia, and extensive LV dyssynchrony on echocardiography.

The RELY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial presented by Connolly et al. (57) compared dabigatran, a thrombin inhibitor, with warfarin. In that trial, 18,113 patients with AF at risk for stroke were randomly assigned to blinded fixed doses of dabigatran 110 mg or 150 mg twice daily versus unblinded adjusted warfarin. Median follow-up was 2.0 years, and the primary outcome was stroke or systemic embolism. Rates of the primary outcome were 1.69% per year on warfarin versus 1.53% per year on dabigatran 110 mg (RR: 0.91, 95% CI: 0.74 to 1.11,  $p < 0.001$ ) and 1.11% per year on dabigatran 150 mg (RR: 0.66, 95% CI: 0.53 to 0.82,  $p < 0.001$ ). Mortality rates were 4.13% per year on warfarin versus 3.74% per year on dabigatran 110 mg ( $p = 0.13$ ) and 3.64% per year on dabigatran 150 mg ( $p = 0.05$ ). The study concluded that a dose of 150 mg of dabigatran twice daily significantly reduced stroke compared with warfarin and had a similar risk of major bleeding. Dabigatran 110 mg twice daily had a stroke rate similar to that of warfarin, with significantly reduced major bleeding. Dabigatran had no major toxicity, but did increase dyspepsia and gastrointestinal bleeding.

Finally, the new guidelines on the diagnosis and therapy of syncope (58) emphasized that a new diagnostic approach is necessary, focusing on risk stratification for SCD, for the patient with an uncertain diagnosis on initial evaluation of a syncopal episode. Furthermore, the guidelines stressed the importance of a diagnostic strategy based on prolonged

ECG monitoring (i.e., wearable/ILRs) in contrast to the conventional strategy based on laboratory testing (i.e., tilt testing and electrophysiological studies).

## Imaging

A clear shift to applications of imaging techniques to address clinical dilemmas was noted. In the field of cardiovascular magnetic resonance (CMR), data from the EuroCMR (European Cardiovascular Magnetic Resonance) registry (59) were presented on 11,040 patients. The results demonstrated that patient management was altered in 62% of cases based on CMR data, with a change of final diagnosis in 16% of patients. In 82% of the examinations, CMR was able to satisfy all imaging needs. Similar data are needed from other modalities to get a better understanding of imaging utilization and to base prospective randomized trials on this experience.

Yilmaz et al. (60) used CMR to look into a group of false positive results of perfusion imaging (22 of 42 patients tested in this selected population) and compared results with invasive coronary angiography. The authors concluded that the majority of these patients either showed microvascular dysfunction (13 patients) or epicardial coronary spasm (7 patients) during intracoronary acetylcholine. A significant correlation was found between a perfusion defect and hypertension ( $r = 0.61$ ,  $p < 0.01$ ) and symptoms on exertion ( $r = 0.68$ ,  $p < 0.01$ ). Although these patients require a treatment other than revascularization, they do have abnormalities and may thus not be considered real false positives.

Two studies looked into the use of myocardial salvage, in other words, the difference between the ultimate infarct size (assessed by contrast-enhanced CMR) and the area at risk (edema imaging) in the setting of ACS. One study (61) involving 230 consecutive STEMI patients with early PCI (<12 h) showed that the percent myocardium that can be salvaged decreased in time after the onset of ischemia, but more slowly than was expected (73% within 2 h, 53% after 2 to 4 h, 38% after 6 to 8 h, 26% after 10 to 12 h), leaving a longer timeframe for opening the culprit vessel. The salvage index was also a strong predictor of mortality (10% above median vs. 1% below median,  $p = 0.003$ ) and remodeling (B coefficient 0.61,  $p < 0.0001$ ) (62); finally, this salvage concept can be used as an outcome parameter in early intervention studies, aiming at myocardial protection.

In the field of positron emission tomography (PET), a large prognostic study on the use of flow reserve in addition to perfusion was presented. Herzog et al. (63) applied  $N^{13}$ -ammonia PET to evaluate perfusion and coronary flow reserve in 256 patients. During a follow-up of 5.4 years, the authors demonstrated that flow reserve provided incremental prognostic information over the perfusion data. Particularly, patients who had normal perfusion but abnormal coronary flow reserve had higher major CV event rate (4.9%) as compared with patients who had normal perfusion

and normal flow reserve (1.3%,  $p < 0.05$ ); cardiac death rates were 2.9% and 0.3% ( $p < 0.05$ ), respectively.

Mazurek et al. (64) investigated the potential role of inflammation in the pericardial adipose tissue on progression and stability of coronary plaques. Standardized uptake value (as a measure of macrophage activity) on integrated PET-computed tomography (CT) imaging was assessed in the fat surrounding the coronary arteries and compared with that in the heart and other regions in 12 patients with coronary artery disease and controls; standardized uptake value was significantly higher in the coronary fat of coronary artery disease patients (right coronary artery 0.86, left circumflex artery 1.34, left anterior descending artery 1.23) versus controls (right coronary artery 0.50, left circumflex artery 0.58, left anterior descending artery 0.59) or any other fat location (subcutaneous 0.21, visceral 0.40, right ventricular epicardial 0.39). This finding could provide some pathophysiologic insight in this difficult area, but could also turn out to be a good proxy to study interventions on plaque inflammation.

Recurrence of AF after cardioversion remains a common clinical problem. De Vos et al. (65) evaluated the mechanical properties of the atrial wall during AF using echocardiography with tissue Doppler imaging in 104 patients referred for electrical cardioversion; the derived AF-velocity score was a strong predictor of AF recurrence (AF recurrence 78% in patients with AF-velocity score 2, as compared with AF recurrence 6% in patients with velocity score 0,  $p < 0.01$ ).

Various echocardiographic studies addressed long-term outcome in patients with known or suspected coronary artery disease. In a large study involving 10,054 subjects (66), stress echocardiography provided useful prognostic information (ischemia HR: 2.67,  $p < 0.0001$ ; resting wall motion abnormalities HR: 1.41,  $p < 0.0001$ ), but an ischemic test on top of existing resting wall motion abnormalities or not had very different implications in normal subjects versus hypertensive subjects (hypertensive event rates 42% and 40%, respectively,  $p = 0.67$ ; normotensive event rates 32% and 18%, respectively,  $p = 0.02$ ), illustrating that interpretation of test results needs to take into account the clinical background of the patient.

In 2 studies from Australia, patient outcome in terms of survival after 5 years was evaluated on the basis of clinical indicators (535 and 546 patients); when LVEF or LV end-systolic volume was added to the model, derivation from 3-dimensional data (chi-square = 7.5,  $p = 0.006$ ) rather than 2-dimensional (chi-square = 5.9,  $p = 0.015$ ) proved to be superior (67). Similarly, the use of global longitudinal strain obtained with speckle tracking (HR: 1.5,  $p < 0.001$ ) was superior to LVEF (HR: 1.2,  $p < 0.05$ ) or wall motion scoring (HR: 1.3,  $p < 0.01$ ) (68). These results indicate that the mode of derivation and the method, in addition to the choice of physiologic parameter, are relevant for the prognostic strength.



## Valvular Heart Disease

Understanding the pathophysiological mechanisms of valvular heart disease is important for potential therapeutic approaches. Lommi et al. (69) found that high-density lipoprotein was decreased in aortic stenosis and that it induced osteoprotegerin secretion and decreased tumor necrosis factor- $\alpha$  expression in cultured valvular cells. Thus, high-density lipoprotein may have a protective role inhibiting valve calcification. Rajamannan et al. (70) demonstrated in a rabbit model that a hypercholesterolemic diet could lead to mitral valve thickening and induction of mitral regurgitation. This effect was mediated through an Lrp5-induced cartilage phenotype that could be attenuated by atorvastatin. Herrmann et al. (71) showed that in severe aortic stenosis, a low mean gradient was associated with a lower longitudinal myocardial function assessed by strain rate, a higher degree of fibrosis assessed by biopsy during valve replacement, and worse long-term outcome.

Aortic stenosis quantification can be challenging when ventricular function is impaired. Cuff et al. (72) showed that aortic valve calcification score assessed by CT correlates with aortic valve area ( $r = 0.66$ ,  $p < 0.0001$ ). In a testing set of 31 patients with reduced LVEF, it was confirmed that a threshold of 1651 Agatston Units confers a high sensitivity (92%) and specificity (86%), with a positive predictive value of 96% for identification of severe aortic stenosis.

With regard to risk stratification, a score integrating information of aortic jet velocity, brain natriuretic peptide (BNP), and sex was developed by Monin et al. (73) (score =  $[AV - Vel \times 2] + [\text{nat Log BNP} \times 1.5] + 1.5$  [if female]) and shown to predict event-free survival among patients with moderate and severe aortic stenosis. Rosenhek et al. (74) observed a high event rate (indication for aortic valve replacement in 90 patients; 6 cardiac deaths in previously asymptomatic patients) among 116 asymptomatic patients with very severe aortic stenosis defined by a peak aortic jet-velocity  $\geq 5.0$  m/s. Event-free survival was 36% and 12% at 2 and 4 years, respectively, raising the question of performing early elective surgery in these patients.

Aortic valve disease is frequently associated with a dilated ascending aorta. Llibre Palares et al. (75) found a good correlation between transthoracic echocardiography and CT for measurement of aortic diameters. Echocardiography appeared very accurate for the diagnosis of significant aortic enlargement ( $\geq 50$  mm) and may help to reduce radiation exposure for such patients.

A systematic management strategy for the use of transcatheter aortic valve implantation was proposed by Himbert et al. (76). Among 230 high-risk patients, the first step was to rule out general contraindications to a transcatheter procedure. In 83 patients, a transfemoral approach was feasible, whereas 37 patients were candidates for only a transapical approach. A total of 41 patients had specific contraindications to both methods—of whom 31 were then scheduled for surgery. The strategy resulted in good out-

come, and a learning curve was observed. It has to be recognized that some patients cannot be treated by a transcatheter approach. Contraindications to conventional surgery are mostly related to comorbidity but can be due to specific technical/anatomical reasons; Taramasso et al. (77) reported an excellent outcome for transcatheter aortic valve implantation in 31 such patients (15 with porcelain aorta, 4 with previous thoracotomy and open grafts).

Importantly, the new guidelines on the prevention, diagnosis, and treatment of infective endocarditis were presented by the task force led by Habib (78). While the principle of antibiotic prophylaxis in patients with predisposing cardiac conditions is maintained, it is now limited to patients with the highest risk of endocarditis undergoing high-risk dental procedures. Particularly novel are the recommendations for the timing of surgery based on 3 main indication categories: HF, uncontrolled infection, and prevention of embolism.

## Basic Science

The last few years have witnessed a great deal of progress in identifying genetic variants associated with common CVDs but have also highlighted the complexity and problems that are associated with the interpretation of such a plethora of new and often unexpected findings. There are many genetic variants associated with coronary artery disease or MI; most of them are common, and all of them appear to have a relatively small effect on the risk of CVD. To date, it seems unlikely that this newly acquired knowledge will add significantly to the predictive value of known risk factors of coronary artery disease in individual patients; nevertheless, these findings have great potential for informing us of new mechanisms that underlie coronary artery disease and, by doing so, for uncovering new therapeutic targets.

It should be noted that, when taken together, these variants still explain only a fraction of the genetic contribution to coronary artery disease, suggesting that epidemiology might have overestimated heritability, that the effect size of some variants might be underestimated by imperfect DNA tagging, or that epigenetic/environmental factors may interfere with the penetrance of the associated disease in the population.

The increased incidence of birth defects among obese mothers may be explained by epigenetics, but how can we demonstrate that this association is causal? This is a case when murine models can be very useful. For example, CITED2 gene deletion is known to be associated with a variety of congenital malformations of the central nervous and CV system in a proportion of mice. To understand whether the incomplete penetrance of CITED2 gene deletion were susceptible to epigenetics, pregnant mice were fed with a high-fat diet inducing moderate obesity, and it was found that this intervention was sufficient to increase the penetrance of cardiopulmonary laterality defects in the embryos of CITED2 deficient mothers. By analyzing the

embryos' transcriptome, it was demonstrated that diet had a profound impact on the molecular phenotype; in particular, among >40 transcripts affected by diet, they showed a profound reduction in *Pitx2*—a transcription factor that involved determination of left-right asymmetry during development. An interesting property of *Pitx2* is to influence the formation of the pulmonary myocardium, a structure that is known to have a crucial role in the pathogenesis of AF. Holm et al. (79) reported an association between AF and a variant in the *ZFHX3* gene (encoding for a putative regulator of *Pitx2* expression) on chromosome 16q22 (OR: 1.21,  $p = 1.4 \times 10^{-10}$ ). This variant was also associated with ischemic stroke (OR: 1.11,  $p = 0.00054$ ) and cardioembolic stroke (OR: 1.22,  $p = 0.00021$ ). These intriguing findings suggest that AF might account for a greater percentage of strokes than it had previously been envisaged, or that genetic variations in the *ZFHX3* gene may contribute a common pathway to the pathogenesis of both cerebrovascular disease and AF.

The proinflammatory and adverse paracrine actions of perivascular adipose tissue have been highlighted by a number of investigators (80–82), providing yet another mechanism by which increased oxidative stress can lead to the progression of atherosclerotic and CVD (83–86). In particular, the expression and activity of the small G protein, *Rac1*, was found to be increased in the atrial myocardium of patients with AF (87) in association with an increase in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived superoxide production. Treatment with rosuvastatin prevented AF in mice with myocardial overexpression of *Rac1*, suggesting that putative antioxidant effects of statins may contribute a much needed “upstream” tool in the prevention of this common arrhythmia. All the same, it seems unlikely that this approach would benefit all patients at risk of AF development, as indicated by a meta-analysis of 15 trials on statins versus placebo that collected data on AF (68,504 randomized patients and 1,514 events) (88); in this large cohort of patients, statin therapy did not reduce the risk of AF (RR: 0.96, 95% CI: 0.87 to 1.07,  $p = 0.49$ ), suggesting that previously reported benefits of statin therapy on AF may be limited to specific groups of patients (e.g., patients undergoing cardiac surgery, in which inflammation and atrial NADPH oxidase activity have been implicated in the new onset of AF in the post-operative period).

But are reactive oxygen species always “bad?” Maybe not, as suggested by direct activation of protein kinase G (the downstream effector of nitric oxide) by hydrogen peroxide, leading to vasodilation. Similarly, protein kinase A can be directly activated by reactive oxygen species, causing positive inotropy in the myocardium. These findings indicate that signaling that has been canonically associated with endothelial shear stress or beta-adrenergic receptor stimulation can be activated independently by the redox state of the cell.

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