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MEETING HIGHLIGHTS

Highlights of the 2008 Scientific Sessions of the European Society of Cardiology

Munich, Germany, August 30 to September 3, 2008

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Aarhus, Denmark; Munster, Hannover, and Luebeck, Germany; Oxford, Edinburgh, and London, United Kingdom; Lausanne, Switzerland; Athens and Crete, Greece; Oskarshamm, Sweden; Liege, Belgium; and Rotterdam and Leiden, the Netherlands

The Annual Congress of the European Society of Cardiology (ESC) was held in Munich, Germany from August 29 to September 3, 2008. The total attendance was 30,500 participants from 137 different countries. Excellent congress facilities hosted 218 pre-arranged sessions in 29 meeting rooms (running in parallel) including several joint sessions in collaboration with other societies (e.g., the American College of Cardiology and the American Heart Association). A total of 9,669 abstracts from 96 different countries were submitted, and 3,532 (36%) were selected for presentation, including 392 dedicated to cardiovascular imaging.

The theme of the meeting was "cardiovascular imaging." This topic was addressed in 56 pre-arranged sessions and 17 scientific abstracts sessions. In this document, a summary of the most important contributions presented at the different sessions is provided.

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Imaging

Echocardiography. A large amount of studies used strain imaging in heart disease. Myocardial strain can be quantified separately in endocardial and epicardial layers using speckle tracking 2-dimensional (2D) strain imaging. In a pig model with different severities of ischemia, circumferential strain was obtained in areas at risk and control areas, both at rest and during dobutamine infusion. Sonomicrometry served as the reference method. Endocardial strain was more severely affected by ischemia as compared with epicardial strain (1). Strain can also be used to reflect the extent of left ventricular (LV) scar formation. In a rat model, speckle tracking 2D radial strain imaging was performed 24 h after reperfusion. The area at risk and the area of scar were quantified; contrast-enhanced magnetic resonance imaging (MRI) served as the gold standard. Segmental radial strain correlated with the transmural extent of scar on MRI ($r = 0.61$, $p < 0.0001$) (2). Mignot et al. (3) evaluated 147 heart failure patients and demonstrated that global longitudinal strain (measured by 2D speckle tracking) had superior prognostic value as compared with conventional parameters such as cardiac dimensions, LV ejection fraction, LV filling pressures, and mitral regurgitation. Ramshorst et al. (4) evaluated patients undergoing alcohol septal ablation for hypertrophic obstructive cardiomyopathy. The authors

showed that the immediate reduction in septal strain (assessed directly after ablation) correlated well with the decrease in LV outflow tract gradient at 6 months follow-up ($r = 0.70$, $p < 0.01$) (4).

Various studies evaluated echocardiography in valvular heart disease. Exercise testing may be useful in asymptomatic patients with significant mitral stenosis. Mean pressure gradient, estimated systolic pulmonary artery pressure, and a relative increase of pressure from rest to peak exercise were measured. Peak pressure was frequently ≥60 mm Hg without a difference between patients with dyspnea during the test or asymptomatic individuals, indicating that symptoms during exercise testing do not predict hemodynamic changes (5).

In asymptomatic patients with severe aortic stenosis, global longitudinal LV strain was measured by Lancellotti et al. (6) at rest and at peak exercise in 174 patients and 32 normal, age-matched control subjects. Patients had lower strain at rest and peak exercise. Moreover, exercise-induced depression of global strain was more prominent in patients who developed symptoms during the exercise test as compared with that seen in patients who remained asymptomatic.

Another topic of interest was paravalvular aortic regurgitation after percutaneous aortic valve replacement. The main determinant of paravalvular aortic regurgitation was the aortic annular size. Detaint et al. (7) demonstrated that correct prosthesis sizing and accurate measurement of annular dimensions are needed to minimize regurgitation; transthoracic echocardiography underestimated annular size as compared with that seen with (real-time) transesophageal echocardiography (8,9).

Nuclear imaging, MRI, and multislice computed tomography (MSCT). Various studies with nuclear imaging addressed long-term outcome in patients with coronary artery disease (CAD). Schepis et al. (10) evaluated the prognostic value of stress technetium-99m sestamibi single-photon emission computed tomography (SPECT) in 415 patients with 3-vessel disease and previous revascularization. The annual cardiac event rate was 3.8% in patients with an abnormal SPECT as compared with 0.3% in patients with normal SPECT ($p = 0.008$), indicating the ability of SPECT to risk stratify patients with previous revascularization. Galassi et al. (11) evaluated the prognostic value of technetium-99m tetrofosmin SPECT 4 to 6 weeks after incomplete revascularization of 126 patients with multivessel CAD who underwent incomplete revascularization by percutaneous coronary intervention (PCI). Absence of ischemia was associated with excellent outcome. Tio et al. (12) evaluated 480 patients with chronic CAD using stress-rest perfusion imaging with positron emission tomography and N13-ammonia; a reduced flow reserve was associated with an increased event rate.

Many studies with MRI were related to the use of contrast-enhanced imaging to detect scar tissue. One study addressed the relation between scar tissue on MRI and the occurrence of nonsustained ventricular tachycardia in 88 patients with hypertrophic cardiomyopathy (13). Patients (17%) with ventricular tachycardia on Holter monitoring had more extensive scar formation than those without ventricular arrhythmias (21.0 ± 11.1% vs. 7.5 ± 8.7% of the LV, $p < 0.0001$). Chan et al. (14) studied the prognostic value of scar tissue on MRI in 269 patients with CAD, and demonstrated that scar tissue was predominantly related to outcome in patients with relatively preserved LV ejection fraction (≥40%).

MSCT is increasingly used for noninvasive angiography, and recent studies focus on its prognostic value. Aldrovandri et al. (15) obtained 2-year follow-up data in 310 patients with suspected CAD who underwent MSCT calcium scoring and noninvasive angiography. A completely normal MSCT examination (zero calcium score and normal angiogram) had a 0% event rate; of note, the MSCT findings were superior for outcome over clinical risk factors. Hadamitzky et al. (16) reported similar findings with a negative predictive value of 99.2% for MSCT angiography in 645 patients who were followed-up for almost 4 years. This high negative predictive value makes MSCT extremely useful for ruling out CAD, and screening of asymptomatic patients has been suggested. Chang et al. (17) demonstrated, in a large population ($n = 1,043$), that screening of asymptomatic individuals was useful to rule out CAD, but resulted in a significant increase of additional diagnostic procedures and even revascularizations in asymptomatic patients with atherosclerosis on MSCT. According to this observation, and several other studies, the presence of atherosclerosis does not necessarily imply ischemia. This has increased interest in so-called hybrid imaging: integration of MSCT for atherosclerosis assessment and SPECT or positron emission tomography imaging for ischemia assessment. Fujitaka et al. (18) evaluated 126 patients with suspected CAD and demonstrated an improvement in specificity (97% vs. 60%, $p < 0.001$) and positive predictive value (96% vs. 66%, $p < 0.001$) without significant changes in sensitivity (93% vs. 98%, p = NS) and negative predictive value (94% vs. 98%, p = NS) compared with that seen with MSCT alone. Another study used the combination of MSCT angiography and perfusion imaging with MRI (19), showing similar results.

The major limitation of MSCT is the radiation burden, and a snapshot pulse protocol was proposed (20); a significant reduction in radiation exposure with this protocol was shown as compared with that seen with the conventional approach.

Valvular Heart Disease

The effect of statins on the progression of aortic stenosis was presented in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial (21). A total of 1,873 patients with mild-to-moderate aortic stenosis were randomized to the combination of simvastatin (40 mg) and ezetimibe (10 mg)

versus placebo. The primary study end point was major cardiovascular events, which was the composite of events associated with aortic sclerosis and atherosclerotic disease. The combination treatment resulted in a 61% low-density lipoprotein (LDL) cholesterol lowering that was sustained during the 4-year study period. However, no effect was noted on the incidence of the study end point (hazard ratio [HR]: 0.96, 95% confidence interval [CI]: 0.83 to 1.12). Besides the failure of reduction in progression of aortic sclerosis, serious concern was raised because of the increased incidence of cancer in the treatment group (11.1% vs. 7.5%, $p = 0.01$). This unexpected finding could, however, not be confirmed in reanalysis of data from 2 larger trials ($n = 20,617$ patients) using the same medication (22).

Interestingly, Antonini-Canterin et al. (23) performed a retrospective analysis of 1,046 patients with aortic sclerosis/stenosis with a mean follow-up of 5.6 ± 3.2 years. The authors showed that 309 patients treated with statins had significantly slower progression rates as compared with nontreated patients when aortic sclerosis or mild stenosis was present. In patients with moderate aortic stenosis, statin therapy did not make a difference on progression of stenosis severity.

In an interesting animal study of hyperlipidemic apoE-knockout mice, uremia was shown to induce aortic stenosis (24). This uremia-induced aortic valve thickening could be inhibited by the use of angiotensin-converting enzyme (ACE) inhibition. Herrmann et al. (25) studied 58 patients with aortic stenosis who underwent surgical valve replacement and also myocardial biopsy. Performing echocardiography and MRI before, 2 weeks, and 9 months after surgery, the authors demonstrated that scar tissue on MRI as well as longitudinal systolic LV function correlated with the histological degree of fibrosis. Significant fibrosis was closely related to an unfavorable post-operative outcome.

The outcome of transfemoral aortic valve implantation was shown to improve with further increase in experience. Comparing 112 patients in their "18-F Safety and Efficacy Trial" with 282 registry patients, the Corevalve Investigators (26) reported a significant reduction in intervention time and lower mortality rates. The first-in-man experience with a new transfemoral implantable stentless aortic valve that can be repositioned and also is fully retrievable was reported by Schofer et al. (27). A permanent implant was achieved in 13 of 17 (76%) high-risk patients with 1 death, 1 stroke, and 1 surgical conversion; hemodynamic and symptomatic results were adequate. Weisenberg et al. (28) followed 262 patients with moderate aortic regurgitation for 42 ± 32 months. Progression to severe disease was observed in 6.9% (1.9% per year) with a need for surgery in 0.3% per year. Progression rate was slower in patients with valve pathology (3.7% per year) compared with that seen in patients with aortic root pathology (1.4% per year) suggesting that valve replacement for moderate regurgitation caused by valve pathology may not be required at the time of other cardiac surgery.

Heart Failure

The BEAUTIFUL (Morbidity-Mortality Evaluation of the If Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction) trial evaluated the prognostic value of baseline heart rate and intervention using a pure heart rate modulator, ivabradine, in patients with CAD and LV dysfunction (29,30). Ivabradine is a selective heart-rate–lowering agent, acting on the sinus node without affecting other cardiac functions. Baseline heart rate is known to be a prognostic marker for cardiac events in patients with CAD. There is a continuous increase in risk with heart rates above 60 beats/min, though no specified heart rate threshold is defined, nor is it known at which heart rate intervention may improve long-term outcome. A total of 10,917 individuals with CAD and reduced LV function were randomized for ivabradine, 5 mg twice daily, followed by an up-titration to 7.5 mg twice daily if heart rate remained above 60 beats/min after 2 weeks versus placebo. Patients received treatment in addition to medical therapy including beta-blockers in 87% and ACE inhibitors in 90%. The primary study end point was the composite of cardiovascular mortality and hospitalization for myocardial infarction (MI) or heart failure. The median duration of follow-up was 19 months. Ivabradine failed to reduce the incidence of the primary study end point (HR: 1.0, 95% CI: 0.91 to 1.1, $p = 0.94$). Baseline heart rate, analyzed as a continuous variable, showed to be an important prognostic marker; patients with a heart rate over 70 beats/min had a significantly higher risk of cardiovascular mortality (34%, $p = 0.004$). Analysis of a pre-specified subgroup of patients with a baseline heart rate over 70 beats/min showed a significant reduction of the coronary end points acute MI and coronary revascularization (36%, $p = 0.001$ and 30%, $p = 0.016$, respectively). Importantly, the frequency of serious side effects was similar between the treatment groups, 22.5% versus 22.8%.

The results of rosuvastatin therapy in patients with chronic heart failure were reported within the GISSI-HF (Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico–Heart Failure) trial (31). A total of 4,574 patients with New York Heart Association (NYHA) functional class II to IV heart failure from any cause were randomized to rosuvastatin 10 mg daily or placebo. Study end points were mortality and hospitalization for cardiovascular reasons during a median follow-up of 3.9 years. Treatment was prescribed in addition to current therapy: beta-blockers in 62% and ACE inhibitors in 77%. No difference was observed in the study end point between the 2 treatment groups (HR: 1.01, 95% CI: 0.91 to 1.1, $p = 0.90$). In contrast to the failure of rosuvastatin to improve outcome in heart failure patients were the results of fish oil supplementation in these patients (32). Within the

GISSI-HF trial, 7,046 patients were randomized to 1.0 g n-3 polyunsaturated fatty acids or placebo in addition to optimal medical therapy; similar study end points and duration of follow-up were applied as described in the preceding text. Fish oil supplementation resulted in a significant reduction of the study end point (HR: 0.92, 95% CI: 0.85 to 0.99, p = 0.009).

The issue of how to manage inflammatory cardiomyopathy (virus negative myocarditis with evidence of inflammation on biopsy) was investigated in a trial by Frustraci et al. (33) comparing prednisone/azathioprine with placebo. A total of 85 patients (mean age 42 ± 15 years) were included with myocarditis, LV ejection fraction <45%, and negative myocardial polymerase chain reaction for viruses. Surprisingly, 6 months of prednisone/azathioprine treatment resulted in a dramatic improvement in LV ejection fraction, which was not observed in the placebo arm. Thus, immunosuppression in patients with virus-negative inflammatory cardiomyopathy appears to be effective and should be strongly considered.

Can a disease-managing program (telephone-based monitoring and education by specialized heart failure nurses) improve outcome and hospitalizations in chronic heart failure patients? A large trial addressed this issue and used the end points of time to first event (all-cause mortality, hospitalization), days alive and out of hospital, NYHA functional class, quality of life, and ESC guideline adherence (34). This study with more than 700 patients and 6 months follow-up revealed that this specific nurse-based management of disease program has the potential to reduce mortality by 43%, with also a significant improvement in morbidity.

Cardiac resynchronization therapy (CRT) is now established and indicated in patients with symptomatic heart failure (NYHA functional class III to IV), depressed LV ejection fraction, and wide QRS complex despite optimized medical therapy. The REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial conducted by Linde (35) addressed whether CRT is also beneficial in less symptomatic patients (NYHA functional class I to II), in whom the main goal would be prevention of heart failure progression. Patients with NYHA functional class I to II, wide QRS complex (≥120 ms), and depressed LV ejection fraction (≤40%) on optimized medical therapy were enrolled. The primary end point was a clinical composite score including all-cause mortality, heart failure hospitalization, and progression of heart failure/NYHA functional class. The interim 18-month follow-up data of the European arm indicate that benefits from CRT in NYHA functional class I to II patients are sustained over time, and CRT may help prevent heart failure progression.

Finally, current generations of CRT devices provide continuous measurement of intrathoracic impedance to monitor changes in lung fluid status, which permits for early detection of heart failure either by device alarm or by transferring alert to physicians via the internet. A large study involving more than 500 patients has assessed the accuracy of this system as well as the practicality of internet-based alert transfer to the caring physician. The observations are encouraging, even though false positive alerts and technical issues are still to be overcome (36,37).

Acute Cardiac Care

The European Resuscitation Council guidelines recommend mild hypothermia for 24 h after cardiopulmonary resuscitation to improve survival and neurological outcome. However, intravascular cooling devices are expensive and not available in all hospitals. A retrospective analysis from 52 resuscitated patients showed that infusion of large volume, ice-cold saline is effective, safe, and inexpensive for the induction of neuroprotective hypothermia (38). In the same guidelines, administration of atropine is recommended. In a prospective, multicenter, observational trial, the effects of atropine have been assessed in 7,443 adults patients with asystole or pulseless electrical activity (39). The primary end point was a favorable neurological outcome at 30 days after cardiac arrest. Administration of atropine improved rate of return of spontaneous circulation, but did not increase the frequency of favorable neurological outcome. Moreover, in the group with pulseless electrical activity, atropine was associated with a trend toward worse survival.

It has been recommended that patients with ST-segment elevation myocardial infarction (STEMI) should stay in the intensive cardiac care unit for 48 h (40). However, in some centers, low-risk STEMI patients who have undergone successful primary PCI are admitted to a step-down care unit. This is supported by a study in 227 STEMI patients in Killip class I, treated with primary PCI. This low-risk group did not benefit from intensive cardiac care unit stay (41). Moreover, in another study, 45.5% of 471 STEMI patients treated with primary PCI were discharged after a 48-h hospitalization. Early discharge in these selected low-risk patients (Thrombolysis In Myocardial Infarction flow grade 3 with resolution of ST-segment elevation and good or moderately depressed LV function without arrhythmias after successful reperfusion) was associated with 0% mortality at 30 days and 0.9% during follow-up (283 ± 148 days) (42).

Interventional Cardiology and Peripheral Vascular Disease

During the main session on drug-eluting stents (DES) safety "2 years after Barcelona," the importance of large scale registries was stressed. Well-conducted registries reflect real life practice, which is often excluded from randomized trials. Mendiz et al. (43) presented the OLYMPIA registry, including 22,345 PCI patients treated with the TAXUS Liberté stent. Expanded use (beyond simple stenting) was performed in 74.9% of cases. At 1-year follow-up, the stent thrombosis rate was 0.8% while the total adverse events rate

(including the need for reintervention) was 3.8%. The German Cypher registry (44) reported on 11,070 PCI cases at 6 months follow-up. The registry population presented with more complex pathology (42% acute coronary syndromes [ACS], 70% multivessel disease), and the overall adverse events rate was, therefore, 10.9%. Both strategies reflect the current opinion, that DES provides sustained safety in a broad range of indications. Efficacy, however, depends on anatomy as the need for reintervention increases with lesion complexity.

Sirbu et al. (45) used different intravascular imaging modalities and thrombus aspiration analysis to demonstrate mechanisms of late stent thrombosis in patients: positive remodeling up to aneurysm formation, uncovered stent struts, aggressive restenosis, and hypersensitivity reactions were reported to be important. In line with this, Manterola et al. (46) documented 1.25% of coronary aneurysms during systemic angiographic follow-up in 1,197 patients treated with DES. There were significantly more adverse events in these patients, indicating a need for careful follow-up.

The SYNTAX (Synergy Between PCI and CABG) trial was one of the major studies presented by Mohr and Serruys (47). A heart team (cardiologist and surgeon) evaluated patients with multivessel disease for the amenability of both revascularization strategies. Eligible patients were randomized to coronary artery bypass grafting (CABG) or multivessel PCI with the TAXUS stent; uneligible patients were followed in a CABG or PCI registry. This multicenter trial involving 85 European and U.S. sites was characterized by very few exclusion criteria, consisting of previous or planned cardiac interventions and/or acute infarction. In addition to the classical surgical Euroscore, the investigators had developed a PCI risk score called the SYNTAX score. The role of this purely anatomical score needs further investigation in the future. The primary end point (adverse events being a composite of all-cause death, infarction, cerebrovascular accident [CVA], and repeat intervention at 1 year) as well as the registry results were presented. At 1 year, adverse events were 12.1% for CABG as compared with 17.8% for PCI ($p = 0.0015$). In terms of overall safety (death, CVA, MI), there was no difference between CABG and PCI (7.7% vs. 7.6%, $p = 0.98$). Therefore, the difference in the primary end point was mainly driven by a higher need for reintervention in the PCI group: 5.9% in the CABG group versus 13.7% in the PCI group ($p < 0.0001$). Further analysis indicated a higher incidence of CVA in the CABG group (5.9% with CABG vs. 13.7% with PCI, $p < 0.0001$). Symptomatic graft occlusion (3.4%) and stent thrombosis (3.3%) were similar. Interestingly, a subgroup analysis in 138 patients with left main disease and additional single-vessel involvement showed no difference in primary end point at 1-year follow-up. Finally, the CABG registry showed comparable adverse event rates at 1 year (8.8%) despite the presence of a much higher SYNTAX score (37.8 ± 13.3 vs. 29.1 ± 1.4 for the randomized CABG patients). The key messages from the SYNTAX trial are as follows: 1) equal safety of both revascularization procedures; 2) significant difference in the primary end point driven by a higher need for reintervention in the PCI group; and 3) lesion complexity, as assessed by the SYNTAX score, should guide the physicians in terms of the optimal revascularization strategy since this score has no impact on adverse outcome after CABG.

The CARDIA (Coronary Artery Revascularization in Diabetes) trial randomized 510 diabetic individuals with multivessel disease (excluding left main disease) to PCI or CABG and was presented by Kapur (48). The primary end point was a composite similar to the SYNTAX study but excluding the need for reintervention. At 1 year, there was no difference in terms of death, MI, and stroke (CABG 10.2% vs. PCI 11.6%, p = NS). However, there was again a higher need for reintervention with PCI (CABG 2.0% vs. PCI 9.9%, $p = 0.001$). The CARDIA study refined the previous conclusions of the SYNTAX study on the safety of both PCI and CABG to diabetic patients specifically, but further follow-up is needed.

Finally, the LEADERS (Limus Eluted From a Durable Versus Erodable Stent) trial, investigating the role of new stent technology (biodegradable polymer [within 6 to 9 months] with biolimus on top), was presented by Windecker et al. (49). A total of 1,707 "all comer" patients were randomized to this stent versus a classical sirolimus-eluting stent. At 9 months, there was no difference in the primary end point of death, MI, and need for reintervention (biolimus: 9.2% vs. sirolimus: 10.5%, $p = 0.88$). This study demonstrates efficacy at 9 months as well as safety expected to be maintained because of the principle of a DES turning into "bare metal" after 6 to 9 months. However, long-term follow-up will be crucial to confirm this hypothesis.

The influence of statin use on the incidence of perioperative myocardial ischemia, myocardial ischemia, and cardiac death was evaluated in patients undergoing high-risk major vascular surgery. Cardiac events are the major cause of perioperative morbidity and mortality, and a titrated low-dosage bisoprolol regimen has been shown to effectively reduce post-operative cardiac events in these patients. However, up to 50% of all fatalities are related to coronary plaque rupture due to the stress of surgery. Poldermans et al. (50) randomized 497 statin-naïve patients to fluvastatin extended release 80 mg daily or placebo beginning 37 days before surgery on top of optimal medical therapy including bisoprolol in all patients. The primary study end point was the incidence of electrocardiographic-assessed ischemia and troponin release during the first 30 days after surgery. Fluvastatin extended release was chosen to bridge the early period after surgery in which patients can frequently not take oral medication, the only prescription form of statins. Fluvastatin use resulted in a significant reduction of the primary study end point (odds ratio: 0.53, 95% CI: 0.32 to 0.88, $p = 0.02$). Patients on fluvastatin therapy showed a significant reduction of LDL cholesterol, high sensitive C-reactive protein, and interleukin-6 levels. This systemic

anti-inflammatory effect of fluvastatin might have been associated with the improved post-operative outcome in this high-risk population, with an estimated number of patients needed to treat of 13 to prevent myocardial ischemia in the first 30 days after surgery.

ACS

New information from studies presented at ESC 2008 added to the evidence for the timing of interventional treatment and adjunctive antiplatelet and antithrombin therapy in conjunction with primary PCI. These complement the recommendations of the new guidelines for the management of STEMI presented at the meeting by Van de Werf (51).

The On-Time 2 (Ongoing Tirofiban in Myocardial Infarction Evaluation) study presented by van't Hof (52) tested the impact of pre-hospital administration of a glycoprotein IIb/IIIa inhibitor (tirofiban) or placebo in patients treated with aspirin and 600 mg clopidogrel. Survival free of major adverse clinical events (combination of death, re-MI, urgent target vessel revascularization, stroke, and major bleeding) was improved by pre-hospital tirofiban treatment ($p = 0.04$). There was improved resolution of ST-segment elevation, and the frequency of aborted infarction was increased (odds ratio: 1.38, $p = 0.04$). Interestingly, the benefits were especially marked in those presenting within 75 min of symptom onset. Although the study is not definitive, it raises important questions about the timing of adjunctive antithrombotic therapy in STEMI.

The HORIZONS AMI (Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial Infarction) trial (n = 3,602 patients) tested bivalirudin monotherapy (with provisional glycoprotein IIb/IIIa usage) against unfractionated heparin and systematic glycoprotein IIb/IIIa blockers (all underwent primary PCI). Stone et al. (53) reported that net adverse clinical events (all-cause death, reinfarction, ischemic target vessel revascularization, stroke, and major bleeding) were reduced with bivalirudin (from 12.2% to 9.3%), and the largest component was the reduction in major bleeding (from 8.4% to 5.0%). Thirty-day mortality was lower with bivalirudin (3.1% vs. 2.1%).

A time-dependent covariate-adjusted Cox model (C statistic 0.87) was used to relate the impact of adverse events to 30-day mortality. Although the frequency of reinfarction was higher than major bleeding, the latter was more common, and hence the number of deaths attributable was higher for major bleeding than for MI (20.4 vs. 9.0). Definite stent thrombosis had approximately 4.5 attributable deaths.

In the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition–Thrombolysis In Myocardial Infarction 38) study, prasugrel versus clopidogrel was tested in patients with ACS with the study drug administered at the time or shortly after PCI. At ESC 2008, Montalescot presented the results for STEMI patients (n = 3,534). Approximately two-thirds of patients (69%) were treated with primary PCI, and the remainder had subsequent PCI. Adjunctive glycoprotein IIb/IIIa treatment was given in 60% to 64% of all cases. The primary end point (death, MI, stroke at 15 months) was reduced with prasugrel (10.0% vs. 12.4%, HR: 0.79) with no excess in major bleeding. The absolute difference was 3% during the very early phase of the trial and 2.4% at 15-month follow-up. Considering individual end points, significant differences were seen for MI and stent thrombosis. For the first time in a large trial (TRITON–TIMI 38), Morrow et al. (54) presented the MI outcomes using the newly introduced Global Definition of Myocardial Infarction and showed highly significant differences in favor of prasugrel for spontaneous and procedure-related MIs.

A coagulation substudy of the OASIS 5 (Organisation to Assess Strategies for Ischaemic Syndromes-5) trial showed new insights into the difference in efficacy and bleeding between fondaparinux and enoxaparin (lower anti-Xa activity with fondaparinux), and raised the question: "is less better?" (55).

In contrast to pre-clinical studies, human trials to limit reperfusion injury have been largely unsuccessful. The F.I.R.E. (FX06 in Ischemia Reperfusion) study presented by Atar et al. (56) tested a novel small peptide derived from the human fibrin sequence (FX06) in patients undergoing primary PCI for STEMI. Outcomes were assessed with contrast-enhanced MRI. The primary outcome was not different (total scar tissue), but the necrotic core was significantly reduced. This observation may encourage the development of a larger trial.

The APPRAISE-1 (APixaban for the Prevention of Acute Ischemic and Safety Events) trial presented by Alexander et al. was the first presentation of a phase 2 study examining an oral anti-Xa inhibitor for secondary prevention after ACS. There were efficacy trends in favor of apixaban (2.5 mg twice daily or 10 mg once daily) and a dose relationship with bleeding (higher bleeding with apixaban 10 mg vs. 2.5 mg vs. placebo), especially in patients who also received clopidogrel. This finding may have important implications for ongoing trials involving anti-Xa inhibitors, both in ACS and in atrial fibrillation (AF).

Hypertension and Risk Factors for CAD

The importance of life-style modification for risk reduction was emphasized by Erbs et al. (57). These investigators demonstrated that obesity in children was associated with a decrease in circulating endothelial progenitor cells. In contrast, physical exercise as demonstrated in children visiting a high school with intensive physical activity programs or others who underwent a training program displayed a marked rise in these vascular protective cells.

Hitherto unknown risk factors may modulate the probability of recurrence of vascular events. Pasterkamp et al. (58) studied the composition of carotid plaque material obtained during endarterectomy. Depending on the osteopontin

levels as well as other predictive markers expressed in the plaque, future cardiovascular events varied between 10% and 60% as analyzed in more than 600 patients prospectively followed for 3 years. At present, it is unclear whether osteopontin is causally involved in triggering further vascular events or, to the contrary, osteopontin is rather a marker that signals unstable plaques in various vascular territories.

A much discussed novel risk factor is the lipoprotein-associated phospholipase A2. Previous genetic research suggested that DNA variants associated with higher enzymatic activity also associate with an increased risk for MI. Now a placebo-controlled study in patients with CAD presented by Wijns et al. (59) suggests that a lipoprotein-associated phospholipase A2 inhibitor, darapladib, administered for 1 year stops the progression of the necrotic core in coronary plaques. This secondary end point of the IBIS-II (Integrated Biomarker and Imaging Study II) study encourages further development of this anti-inflammatory agent in patients with atherosclerosis.

Some disappointment came from the TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease) study, which studied 6,000 patients intolerant to an ACE inhibitor on either telmisartan or placebo (60). Surprisingly, the primary end point (i.e., the combination of cardiovascular death, infarction, stroke, and/or heart failure hospitalization) was not significantly different in the 2 groups. In contrast, the end point used in the recently published HOPE (Heart Outcomes Prevention Evaluation) study (cardiovascular death, infarction, and stroke) displayed a significant, 13% decrease in the telmisartan group (61). Given the profound effect of ramipril in the same group of patients as studied in the HOPE trial group, equivalence of ramipril and telmisartan in the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) study (62), it is puzzling to see the, at best, modest effect of telmisartan as compared with placebo in the TRANSCEND study. This certainly applies to hospitalization for heart failure since this end point was not prevented at all by telmisartan in the TRANSCEND study.

Prevention

Within the field of cardiovascular prevention interesting new findings were presented. Grundtvig et al. (63) reported gender-based differences in the effect of smoking: a first acute MI occurs 14.4 years more prematurely in women than in men when compared with that seen in nonsmokers. Normal weight obesity, defined as normal weight and high body fat content, is found in 1 of 5 persons. It contributes to a 3.6-fold increased risk for cardiac death in women but not in men (64).

The winning abstract of the Young Investigator Award for population sciences was presented by Fosboel et al. (65), showing increased HRs for MI and death associated with the use of nonsteroid anti-inflammatory drugs among healthy individuals. Based upon this finding, the authors questioned the free over-the-counter sale of these drugs.

The metabolic syndrome is associated with a reduction of the anti-inflammatory properties of high-density lipoprotein cholesterol. German researchers showed that 8 weeks of exercise training restored the vasoprotective properties of high-density lipoprotein although the effect was lost after 8 weeks of nonactivity (66). Four weeks of training restored the catabolic-anabolic imbalance in the skeletal muscle of heart failure patients, thus providing a further rationale for exercise training (67).

Olsen et al. (68) showed that markers of subclinical vascular damage (urine albumin/creatinine ratio, carotid artery ultrasound, and pulse wave velocity) may improve the HeartScore risk stratification and thereby reduce the number of candidates for primary prevention up to 45%.

Daily physical activity by using the stairs instead of elevators at work contributes to cardiovascular prevention: at the Geneva University Hospital, sedentary healthy employees used the stairs during a 12-week period (69). Positive effects were noted on VO_2max, waist circumference, fat mass, blood pressure, and LDL cholesterol. However, after returning to the sedentary life-style, most of these beneficial results were lost within 3 months.

Arrhythmias and Pacing

Genetics in arrhythmias is a continually developing field, in which new discoveries, mainly of mutations, are associated with poorly understood clinical entities. In a 3-generation family with long QT syndrome and familial AF, a mutation in SCN5A, identified for the first time, showed the genetic association between these 2 clinical entities (70). Another novel mutation in KCNE3 was shown to reduce the repolarizing potassium current and cause long QT syndrome (71). Further genetic analysis showed that CRT not only corrects mechanical dyssynchrony, but also causes changes in regional gene expression (72).

Various studies were presented on new technology in management of AF; 2 centers presented their first experience on the use of irrigated tip catheters for magnetically navigated remote pulmonary vein isolation. Both concluded that the technique, in combination with electroanatomical mapping, is safe, effective, and has a high success rate. Completeness and continuation of mitral isthmus conduction block was easily achieved and rarely required crossover to manual or solid magnetic catheters (73,74). In addition, Badger et al. (75) showed that imaging scar tissue with MRI may be useful in detection of gap lesions after failed pulmonary vein isolation.

With regard to preventing esophageal injuries during AF ablation, 20 consecutive patients received circumferential ablation using irrigated tip catheters, while continuous intraesophageal temperature monitoring was performed with the use of a multisensor probe covering most of the length of the posterior left atrium. With an intraesophageal

temperature threshold of 40°C, no damage to the esophageal mucosa was observed (76). Finally, for patients with paroxysmal AF, anatomical ganglionate plexi ablation appears to be highly effective and safe, as well as satisfactory in terms of the long-term outcome (77).

Various clinical trials and registries on AF were also presented. In the AF-CHF (Atrial Fibrillation–Congestive Heart Failure) trial, 2 treatment options were compared: maintenance of sinus rhythm (rhythm control) versus control of the ventricular heart rate (rate control) in patients with AF and LV dysfunction (78). The primary study end point was cardiovascular death during a mean follow-up of 37 months. A total of 1,376 patients were randomized to cardioversion or medical therapy. There was no difference in outcome; HR in the rhythm-control group: 1.06, 95% CI: 0.86 to 1.30, $p = 0.59$. The effect of the treatment option might have biased outcome; in the rhythm control group, 58% of the patients had a reoccurrence of AF during follow-up, while in the rate control group the treatment targets were achieved in more than 80%. This underscores the need for effective new drugs and ablation techniques to restore sinus rhythm in patients with AF. It was concluded that in patients with heart failure, rate control is the preferred strategy, while rhythm control should be only considered in those with worsening of heart failure symptoms.

The significance of very early and early recurrences of AF after pulmonary vein isolation was investigated by Neumann et al. (79); the authors noted that 45% of patients with very early AF recurrences had no further relapses during long-term follow-up. The researchers suggested that repeat ablation procedures should be deferred for at least 3.5 months after pulmonary vein isolation.

In another registry, very late relapses of paroxysmal AF were studied after pulmonary vein isolation (80). A database of 827 patients treated with pulmonary vein isolation for paroxysmal AF was screened for 7 years. Overall, 10 patients (1.2%) were identified with AF relapse >12 months after the initially successful ablation. Late AF relapse occurred 2.05 ± 0.73 years after the initial ablation. In these patients repeat isolation appeared to be only moderately effective.

In a post hoc analysis of the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization of Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter) trial presented by Connolly et al., the antiarrhythmic agent dronedarone was associated with a 34% drop ($p = 0.027$) in adjusted risk of stroke compared with that seen with placebo over a follow-up period of 21 ± 5 months.

This reduction occurred in patients who were already receiving appropriate antithrombotic therapy. The ATHENA trial had already shown a 24% decline ($p < 0.001$) in the time to first cardiovascular hospitalization or any-cause death, which was its primary end point, as well as reductions in risk of cardiovascular mortality (29%, $p = 0.034$), cardiovascular hospitalizations (25%, $p < 0.001$), and arrhythmic death (45%, $p < 0.01$).

In the field of CRT, new technology also offers a wider range of possibilities, both in placement of the LV lead and in the long-term follow-up of patients. Taborsky et al. (81) presented a magnetically guided approach for LV lead implantation, based on image integration of angiography and 3D computed tomographic reconstruction of the coronary sinus. Remote device monitoring and heart failure management in CRT-implantable cardioverter-defibrillator patients, with the use of new devices produced by advanced technology that can be reviewed by clinicians on an internet-accessible website, has proved to be an evolving new methodology (82).

Two substudies from the CARE-HF (CArdiac REsynchronication in Heart Failure) trial were presented. The first, a secondary analysis of 302 patients with mean age of 75 years, showed that in elderly patients with moderate or severe heart failure and markers of cardiac dyssynchrony, CRT has a substantial effect on morbidity and mortality (83). The second substudy analyzed the effects of CRT on long-term quality of life, length of hospital stay, and survival and confirmed that the initial, short-term improvement in quality of life with CRT was sustained at long-term follow-up (84).

A PROSPECT (PRedictor Of reSPonsE to Cardiac resynchronization Therapy) substudy presented interesting, though preliminary, results of CRT in patients with a narrow QRS complex and LV dyssynchrony. The majority of patients improved in terms of clinical criteria, together with a significant reduction in LV end-diastolic dimension (85).

Finally, an interesting registry, Credit Heart Failure, showed that in a total of 3,148 patients there was a clear discrepancy between the number eligible for CRT or implantable cardioverter-defibrillator therapy and the actual frequency of device implantations (86). The authors noted that only 4.3% of the patients who met the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study criteria received a device during the recording period.

Basic Science

Genetic modifiers and environmental factors influencing gene expression and expressivity are increasingly called into play when attempting to explain the variable relationship between a gene mutation and the associated clinical phenotype. For example, auxiliary β-subunits of the cardiac sodium channel are known to modulate the channel expression at the cell surface as well as the channel's gating properties and voltage dependence; through these mechanisms, mutations in the gene encoding $\beta 1$ transcripts appear to be sufficient to produce an arrhythmogenic phenotype in humans. By the same token, strain-dependent differences in the expression of the $\beta 4$ ancillary subunit markedly influence the arrhythmogenic/conduction phenotype in mice carrying a loss of function mutation in the sodium channel

subunit that is associated with Brugada syndrome in humans (87). These studies suggest that variability in the expression of genetic modifiers may be as important as the identification of the culprit gene mutation in guiding the management and risk stratification of these patients.

More on the theme of "regulation" was provided by a number of studies on the burgeoning roles of micro-RNAs. These short, noncoding segments of RNA are now widely recognized as key post-transcriptional regulators of gene expression, participating in the control of almost every cellular process. In the cardiovascular system, Condorelli (88) reported that micro-RNAs regulate cardiac development, myocardial excitability, and post-natal growth, and Abdellatif (89) reported that micro-RNA also mimics the myocardial response to hypoxia and ischemic preconditioning. Importantly, inhibition of specific micro-RNAs can be exploited for therapeutic purposes, as illustrated by the beneficial effect of antagonizing micro-RNA 21 in an animal model of pressure overload-induced LV hypertrophy and failure (90). It is now clear that what is "lost in translation" is not "lost in transcription," and discovery of the multivarious wonders of noncoding DNA and its transcribed products will dominate basic and translational research for many years to come.

The genome-wide hunt for variants associated with premature CAD continues to yield exciting and provocative findings (91,92). The now vastly replicated association between variants on chromosome 9p21.3 and premature CAD (93) remains mechanistically elusive in its ability to predict coronary events and angiographic severity of CAD independent of known risk factors (94–96). The possibility of unearthing new targets for the treatment and prevention of CAD seems now tantalizingly close. An excellent example of interdisciplinary research generating true innovation was provided by studies pioneering applications of nanomedicine and molecular imaging in animal models of atherosclerosis (97–100). The application of these techniques in clinical practice will open a new dimension in the diagnosis and staging of disease processes as well as deliver unprecedented insights into the effect of therapeutic interventions in individual patients.

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