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MEETING HIGHLIGHTS

Highlights of the 2006 Scientific Sessions of the European Society of Cardiology

Barcelona, Spain, September 2–5, 2006

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Leiden and Rotterdam, the Netherlands; Aalst and Leuven, Belgium; Ludwigshafen, Germany; Paris, France; Manchester, United Kingdom; Brescia, Italy; Aarhus, Denmark; Stockholm, Sweden; Lisbon, Portugal; Wroclaw and Katowice, Poland; and Chapel Hill, North Carolina

The World Congress of Cardiology (WCC) held in Barcelona (4 days, September 2006) was a joint meeting of the annual congress of the European Society of Cardiology (ESC) and the World Heart Federation (WHF), with more 25,500 active participants attending from 135 different countries. In particular, 25% of the total attendance was from Africa, North and South America, and Asia.

A record number of 229 prearranged sessions (30 meeting rooms running in parallel) were organized, including 12 with other societies including the American College of Cardiology and the American Heart Association. A total of 10,594 abstracts from 94 different countries were submitted, and 3,917 (37%) were selected for presentation, including 34% dedicated to basic science.

The theme of the meeting was "cardiovascular disease and ageing." The clinical profile and the management of elderly patients with cardiovascular diseases (CVDs) were addressed in 18 pre-arranged sessions and 125 scientific abstracts. In this document, the Global Health Agenda (a summary of special reports from the WHF plenary sessions) is discussed first, followed by the Euro Heart Survey program and Hotline sessions. Thereafter, a summary of the most important contributions presented at the different sessions is provided.

THE GLOBAL HEALTH AGENDA

Cardiovascular diseases are now the leading cause of death worldwide claiming more than 17.5 million lives in 2005. The greatest numbers of CVD deaths (80%) occur in low- and middle-income countries where the prevalence of CVD is increasing at an alarming rate and health care resources are limited. For inexplicable reasons, the United Nations has not included CVD and chronic diseases among the Millennium development goals, designed to reduce poverty and promote health in developing countries by the year 2015. Limited funds mean limited action directed at prevention and control. This situation must be corrected if progress is to be recognized in preventing the early morbidity and mortality from CVD worldwide.

In an adult population, poor health due to CVD threatens sustainable economic growth and has an especially crippling effect on countries with developing economies. In 2000, the productive years of life lost due to CVD occurring in the workforce of 5 selected countries included 1.1 million in Brazil, 0.3 million in South Africa, 3.3 million in Russia, 6.7 million in China, and 9.2 million in India for a total of 20.1 million. It is estimated that, between 2005 and 2015, CVD and its risk factors such as hypertension and diabetes will impose huge costs through lost productivity and reduce the gross domestic product in most low- and middle-income countries that are now experiencing rapid economic growth. Obesity and diabetes are 2 risk factors for CVD that are growing in prevalence worldwide. Their incidence among children is of particular concern as childhood obesity generally predicts adult obesity. Childhood obesity is increasing across all continents such that 10% of the world's childhood population is now overweight or obese. In many Westernized countries, the prevalence of children who are overweight is as high as 20% and increasing prevalence is

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ACS	= acute coronary syndrome
CRT	= cardiac resynchronization therapy
CVD	= cardiovascular disease
ESC	= European Society of Cardiology
MRI	= magnetic resonance imaging
MSCT	= multislice computed tomography
NYHA	= New York Heart Association
PCI	= percutaneous coronary intervention
SPECT	= single-photon emission computed tomography
STEMI	= ST-segment elevation myocardial infarction
VHD	= valvular heart disease
WCC	= World Congress of Cardiology
WHF	= World Heart Federation

now occurring in many developing countries. Type 2 diabetes in childhood, secondary to obesity, is increasingly common in many countries, and its complications, especially the increased risk of CVD, greatly shorten the life expectancy for many in the obese childhood population.

Africa faces now a double burden, the combined epidemics of communicable diseases and emerging chronic diseases. In Africa, CVD is major component of chronic diseases and includes hypertension, stroke, cardiomyopathy, rheumatic heart disease, and the increasing prevalence of ischemic heart disease. Prevention must be the cornerstone of effective clinical and public health intervention. For example, only 60 children need to be treated with penicillin to prevent 1 case of rheumatic heart disease. Hypertension prevention and control can eliminate most stroke morbidity and mortality. In Africa, increased emphasis must be made on CVD risk factor awareness, surveillance, advocacy, and adherence to best practices.

Worldwide, more than 15 million people have rheumatic heart disease and at least 350,000 related deaths occur yearly. The WHF sponsors demonstration sites and training workshops in the South Pacific and is and is developing sites in Africa to assist with the development of critically needed register-based programs. Portable echocardiography is increasingly available in countries with developing economies and is the only reliable method for the detection of subclinical rheumatic heart disease. Vaccines for the prevention of rheumatic heart disease are now in early clinical trials and hold great potential if effective, safe, and affordable.

The mortality from CVD in China has more than doubled during the last 20 years. The WHF sponsors a large secondary prevention program involving hospitals in all 31 provinces and regions of China. The goal is to improve utilization of secondary prevention therapies known to improve outcomes for patients hospitalized with CVD. Current utilization of these therapies is being determined for hospitals in each region, after which strategies designed to operate under limited resources will be initiated to improve their implementation. It is anticipated that this program will provide important information to assist in improving the outcome for patients with CVD in China and serve as a model for other low- and middle-income countries.

EURO HEART SURVEY

The Euro Heart Survey program of the ESC provides systematic information on the management of patients with CVD in clinical practice in Europe. During the WCC 2006, data of current surveys were presented in 5 symposia covering the following topics: ageing and CVD, acute coronary syndromes (ACS), heart failure, percutaneous coronary intervention (PCI), and atrial fibrillation.

Aging and CVDs. The population is ageing rapidly, with 13.7% of the European population aged 65 years or older, which is twice the world level. With age, the prevalence of death due to CVD increases steeply up to about 40% in the elderly. In the second Euro Heart Survey on ACS, 40% of consecutive patients were older than 70 years. The elderly less often received reperfusion and acute adjunctive treatment and had 3 times higher 30-day and 1-year mortality than patients younger than 70 years. In the PCI survey, 19% of all patients undergoing PCI were older than 75 years (mean age 79 years), with 75% having multivessel disease. Although the rate of complications was low, the elderly suffered from bleeding and renal failure requiring dialysis twice as often as younger patients. In the survey on valvular heart disease (VHD), the most common valve diseases were aortic stenosis and mitral regurgitation. In patients older than 75 years, surgery was denied in 33% with severe aortic stenosis and in 64% with severe mitral regurgitation.

ACS. The comparison of the 2 Euro Heart Surveys on ACS-I in 2000 and ACS-II in 2004 demonstrated a significant improvement in adherence to current treatment guidelines with an increase of primary reperfusion for ST-segment elevation myocardial infarction from 56% to 64% and a shift from thrombolysis to primary PCI. Adjunctive medical treatment with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, clopidogrel, and statins improved over the years. This improvement in adherence to guidelines was associated with a trend towards lower 30-day and 1-year mortality in clinical practice.

PCI. The Euro Heart Survey on PCI enrolled 13,152 consecutive patients in 134 centers of 39 ESC member countries between June 2005 and January 2006. The indications for the intervention were ACS in 57% of all patients. Two-thirds of the patients undergoing PCI had multivessel disease. However, in 69% of all cases, 1 lesion was treated, probably reflecting incomplete revascularization. Stenting rate in clinical practice was 93%; a total of 41% of patients received drug-eluting stents with great variation between countries from below 10% up to 80%. The use of diagnostic devices like intravascular ultrasound or pressure/flow wires and therapeutic devices like distal protection devices,

thrombectomy devices, or rotablation was below 2% in the overall population.

Heart failure. The Euro Heart Survey on Heart Failure-II enrolled patients with acute heart failure. Patients with acute de novo as compared with acute decompensated chronic heart failure had higher in-hospital mortality but lower 1-year mortality. In these subgroups, chronic treatment with beta-blockers and ACE inhibitors was associated with a significant reduction in 1-year mortality in unselected patients in clinical practice. The medical treatment with ACE inhibitors, beta-blockers, and spironolactone in patients with heart failure significantly improved between the 2 Euro Heart Surveys on heart failure in 2000 and 2004. However, the used dosages of particularly beta-blockers and ACE inhibitors remained unchanged over the years at a mean of only 50% of the recommended dosages derived from randomized controlled trials.

Atrial fibrillation. The Euro Heart Survey on atrial fibrillation revealed an under-treatment with long-term oral anticoagulation in 26% of patients with atrial fibrillation. This under-treatment was associated with a 2-fold increase of thromboembolic events during 1-year follow-up. Especially in paroxysmal atrial fibrillation, the rate of stroke within 1 year after pharmacologic or electrical cardioversion was 3-fold higher than in persistent atrial fibrillation. This higher incidence in stroke may have been related to a lower rate of effective oral anticoagulation and a higher rate of repeated cardioversions in this patient subgroup.

HOTLINES, NON-INTERVENTIONAL

The 2-year follow-up results of the international REACH (REduction of Atherothrombosis for Continued Health) registry were presented, and international differences were addressed. The study included more than 68,000 patients enrolled from 5,592 sites of 44 countries. This worldwide registry provides detailed information on risk factors, medical treatment, achievement of therapeutic goals, and long-term outcome among different health care systems. Results showed that, during 2-year follow-up, 20% of patients suffered a major event or were hospitalized. The incidence of cardiovascular death was 2.6% as compared with 6.2% for the combined end point of cardiovascular death, stroke, or myocardial infarction. Patients from Eastern Europe or the Middle East had the highest incidence of events, with 33% of the enrolled patients suffering a major event.

In the WAVE (Warfarin Antiplatelet Vascular Event) study, patients with peripheral atherosclerotic disease from 80 centers in 7 countries were randomized to receive either antiplatelet therapy only (n = 1,081) or antiplatelet therapy combined with oral anticoagulants (n = 1,080). Patients with peripheral atherosclerotic disease are at increased risk of late cardiovascular events, and the combined strategy has been shown to be effective in patients with CVD. The aspirin dose varied between 81 and 325 mg. The oral anticoagulant therapy was of moderate intensity aiming at an international normalized ratio of 2 to 3. Results after 42 months follow-up showed that 12.2% of patients with combined therapy suffered cardiovascular death, infarction, or stroke compared with 13.3% of patients receiving aspirin only ($p = 0.49$). In addition, 4% of the patients with combined therapy experienced life-threatening bleeds compared with 1.2% in the aspirin only group ($p < 0.001$). It was concluded that the combined therapy offered no beneficial effect (with higher bleeding risk) in patients with peripheral atherosclerotic disease.

The effect of homocysteine lowering in patients with chronic vascular disease was studied in the HOPE-2 (Heart Outcomes Prevention Evaluation) trial. A total of 5,522 patients were randomized to treatment with folic acid (2.5 mg), vitamin B_6 (50 mg), and vitamin B_{12} (1 mg), or placebo. During 5-year follow-up, no difference was observed in cardiovascular death, infarction, or stroke in treated patients (18.8%) or the placebo group (19.8%), indicating no beneficial effect of vitamin supplementation.

The CIBIS (Cardiac Insufficiency Bisoprolol Study)-III evaluated the optimum sequence of initiating treatment of heart failure patients: starting with bisoprolol or enalapril. In a subanalysis, the incidence of sudden death was compared. A total of 1,010 patients with moderate heart failure were randomized to either starting with bisoprolol or enalapril for 6 months, followed by their combination up to 24 months. During the first year, the sudden death rate was marginally lower (3.1% vs. 5.7%, $p = 0.049$) in the patients receiving bisoprolol first. However, during the entire study period, no differences in the incidence of sudden death were observed. The results of initiating therapy with bisoprolol are promising, but need confirmation in a larger population.

The effect of patent foramen ovale closure in patients with invalidating migraine has been investigated in the MIST (Migraine Intervention with STARFlex Technology [NMT Medical, Inc., Boston, Massachusetts]) trial. Patients were randomly assigned to a closure device or sham intervention. The study confirmed for the first time the high rate of right-to-left shunt in patients with migraine (37%). The primary end point, complete cessation of migraine, was not reached. A significant decrease in the total disease burden was shown: 42% of patients with closure device reported a decrease of at least 50% of the number of headache days, as compared with 23% with sham operation. These results triggered the launch of the MIST-II trial that will aim at using a resorbable closure device in 600 patients.

HOTLINES, INTERVENTIONAL

The effect of age on the 1-year mortality after revascularization in patients with multivessel coronary artery disease was analyzed in the ARTS (Arterial Revascularization Therapy Studies) trials. Among the patients who underwent bypass surgery, a trend towards an increased mortality with age was observed whereas this trend was not seen after PCI with bare-metal or drug-eluting stents.

The antiproliferative effects of a new everolimus-eluting stent (Xience V stent; Abbott, Abbott Park, Illinois) was tested against the paclitaxel-eluting stent (Taxus, Boston Scientific, Natick, Massachusetts) in patients with 1 or 2 stenoses. At 6 months, the everolimus stent was associated with a significantly smaller neointimal hyperplasia than the paclitaxel-eluting stent. In 30% of lesions, the everolimus-eluting stent was associated with a negative angiographic late loss. The study was not powered to draw conclusions on clinical outcome.

Paralleling the development of new drug-eluting stents, several recent bare-metal stents have good track records in terms of clinical outcome. This was illustrated by a prospective randomized trial in which the rate of major adverse cardiac events was equally low after implantation of a biolimus A9 eluting stent (5.4%) or bare-metal stent (5.0%).

The 18-month clinical outcome data of the Basket (Basel Stent Cost-Effectiveness Trial) study were reported. The trial consists of a randomized comparison between drug-eluting stents (sirolimus- and paclitaxel-eluting stents) and bare-metal stents in 826 consecutive patients. The data suggest that the benefit (in terms of total major adverse cardiac events, and survival free of death or infarction) is significantly larger with drug-eluting stents as compared with after bare-metal stents in small vessels (<3 mm) or bypass grafts. This advantage was no longer present or even reversed in larger native vessels (≥3 mm). A detailed cost-effectiveness study performed on the same cohort of patients indicates that, if drug-eluting stents are used in all patients, incremental cost-effectiveness ratio to avoid 1 major adverse cardiac event is high (>€50,000). In contrast, the incremental cost-effectiveness ratio to avoid 1 major adverse cardiac event is favorable if drug-eluting stents are used only in patients with small stents or bypass graft stenting.

The 5-year clinical outcome data of the patients included in the RAVEL (Randomized Study with Sirolimus-Coated Bx Velocity Balloon-Eexpandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesion) study have been presented. The study, which was powered for an angiographic end point had shown that sirolimus-eluting stents virtually abolish neointimal hyperplasia: after 6 months, the angiographic late loss was −0.01 mm after sirolimus-eluting stenting versus 0.80 after bare-metal stenting. After 5 years, the number of target vessel revascularizations remains significantly lower in the sirolimus-eluting stent group than in the bare-metal stent group. In contrast, a trend towards a higher rate of death or infarction was reported.

Two meta-analyses sparked a lot of discussion. Both are based on earlier randomized studies comparing sirolimus- or paclitaxel-eluting stents to their bare-metal counterpart (more than 7,000 patients). The first meta-analysis showed a relative excess in combined death or Q-wave myocardial infarction in patients who received a first generation drug-eluting stent. The second meta-analysis focused on the rate of non-cardiac death, which tended to be higher with first generation drug-eluting stents (particularly sirolimus-eluting stents) than bare-metal stents. However, before drawing definitive conclusions, more details on the exact methodology used for these meta-analyses should be awaited. Nonetheless, the data presented during the meeting points towards a more tailored use of bare-metal and drug-eluting stents.

ACS

Diagnosis. Early diagnosis and triage are essential in treatment of ST-segment elevation myocardial infarction (STEMI). A British registry revealed that delay of thrombolysis was a predictor of increased mortality in STEMI patients (1). Time-to-reperfusion treatment can be reduced, when the patients can be directed to primary PCI based on pre-hospital diagnosis on-site or by wireless electrocardiogram transmission to the PCI center (2,3). Applying telecardiology to a large region also shortened diagnostic delay and diminished the number of improper hospitalizations (4).

Therapy. A French registry showed that guideline-recommended therapy was underutilized in acute infarction patients older than 80 years (5).

New data from the OASIS (Organization to Assess Strategies for Ischemic Syndromes)-5 study revealed that the 50% decrease in early bleeding with fondaparinux compared with enoxaparin was consistent regardless the use of unfractionated heparin, and that this lower risk of bleeding was associated with reduced long-term mortality (6). A randomized trial in 393 patients with non-STEMI treated with aspirin, clopidogrel, and invasive therapy revealed no benefit of eptifibatide (7).

In the recent publications, neither distal protection nor thrombectomy improved outcome during primary PCI. Accordingly, a meta-analysis showed no benefit of thrombectomy and distal protection (8). However, in a randomized trial including 368 STEMI patients, thrombus aspiration before primary PCI improved myocardial microcirculation as evaluated by myocardial blush rate (9).

Registries suggested that clopidogrel is beneficial in the treatment of STEMI (10,11). In a randomized study in patients undergoing PCI, a maintenance dose of 150 mg daily was shown to inhibit adenosine-diphosphate-induced platelet aggregation more efficiently than the usual dose of 75 mg daily (12).

Prognosis. Electrocardiogram data from the ASSENT (ASsessment of Safety and Efficacy of New Thrombolytic)-4 PCI study, where facilitated primary PCI with tenecteplase was found to be associated with a worse outcome than primary PCI without thrombolysis, revealed that resolution of ST-segment elevation at 60 min after randomization occurred more often in patients treated with facilitated PCI (13). However, at the time interval from 60 to 180 min, tenecteplase-treated patients had less ST-segment resolution, and this was associated with an in-

creased incidence of reinfarction and may explain the rather unexpected poor outcome in patients treated with facilitated PCI (13).

Reperfusion arrhythmias after primary PCI were associated with a favorable prognosis (14). Acute coronary syndrome patients presenting with left bundle branch block have a higher mortality than patients presenting with ST-segment elevation (15).

Analysis of the combined data from the OASIS-5 and -6 trials showed that low baseline hemoglobin levels were related to a poor outcome and risk of bleeding, which was significantly lower with fondaparinux than with enoxaparin/unfractionated heparin/placebo (16). Also, in STEMI patients undergoing primary PCI (17,18), anemia at presentation was associated with poor outcome. An increased white cell count at baseline was also associated with poor outcome in patients undergoing primary PCI (19).

HEART FAILURE

A substantial number of registries on heart failure were presented, with a focus on the elderly patients (see the preceding text Euro Heart Survey). The main conclusions of these trials were that heart failure is frequent among the elderly and that these patients are still poorly treated although they would equally benefit from life-saving therapies as compared with younger patients. In 1 registry, consisting of 1,054 heart failure patients most of which were older than 70 years, adherence to pharmacotherapy as recommended by the ESC guidelines was a strong and independent predictor of superior survival, and this benefit was irrespective of age, gender, and left ventricular function (20).

Next, more pathophysiological studies were presented. It is known that both the immune system and autonomic imbalance are key elements of the complex pathophysiology of heart failure. These factors are traditionally considered in isolation, but new evidence was presented supporting that immune dysfunction (as evidenced by elevated levels of proinflammatory cytokines) correlated with depleted vagal tone (21). In addition, an increase in cholinergic signaling with pirydostigmine (reversible acetylcholinesterase inhibitor) improved autonomic balance with concomitant attenuation of immune activation of circulating immunocompetent cells (21). Whether restoration of parasympathetic systems will ultimately lead to restoration of autonomic and immune control needs further study.

Testosterone deficiency is a component of impaired anabolic function in men with heart failure and predicts exercise intolerance and poor quality of life. A double-blind, placebo-controlled parallel study of testosterone replacement therapy (up to 12 months) at physiological doses was undertaken in 76 men with symptomatic heart failure (New York Heart Association [NYHA] functional class II to IV, left ventricular ejection fraction 32%) (22). The therapy was safe and significantly improved heart failure symptoms, functional capacity, and increased handgrip strength. The mechanisms underlying these findings merit further study.

Anemia is frequently observed in heart failure and is associated with increased morbidity and mortality. Preliminary studies have suggested that correction of anemia with erythropoiesis-stimulating proteins may improve exercise capacity, symptoms, and quality of life. Combined analysis of 2 randomized, double-blind, placebo-controlled studies was presented, in which 266 anemic patients (hemoglobin level $\geq$9.0 g/dl and $\leq$12.5 g/dl) with symptomatic heart failure were treated with darbepoetin alfa (long-acting erythropoiesis-stimulating protein) and 209 received placebo (23). Therapy with darbepoetin alfa was well-tolerated, increased and maintained hemoglobin level within the target range, but did not significantly improve quality of life or symptoms. Interestingly, however, there was strong trend towards improvement in composite outcome of morbidity and mortality. In another study, 35 symptomatic heart failure patients with iron deficiency were randomly assigned to a 16-week therapy with intravenous iron sucrose versus no treatment (24). Iron repletion with iron sucrose was safe, well tolerated, and associated with improvements in exercise capacity and symptoms. Of note, the benefits were particularly evident in anemic patients, showing a mean increase in peak V_{O_2} of 4.0 ml/kg/min.

Whether targeting inflammation with a novel, broad spectrum immune modulating therapy would reduce mortality and hospitalization rate in heart failure patients was evaluated in the ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy) trial. Immune modulating therapy was based on the novel device—Celacade System (Vasogen Inc., Mississauga, Ontario, Canada)—that delivers controlled oxidative stress to a patients' blood sample ex vivo, and results in apoptosis of autologous cells; the blood sample is then administered intramuscularly, which subsequently triggers an anti-inflammatory response. The ACCLAIM trial randomized more than 2,400 heart failure patients (70% in NYHA functional class III to IV, left ventricular ejection fraction 23%, all with optimized medical therapy with 94% receiving ACE inhibitors and/or angiotensin receptor blockers and 87% receiving beta-blockers) to treatment with either immune modulating therapy or placebo. Immune modulating therapy appeared safe and well-tolerated, but the primary end point (mortality and cardiovascular hospitalization) was not met. However, immune modulating therapy was effective in 2 pre-specified subgroups: patients with NYHA functional class II and patients without history of previous infarction.

HYPERTENSION

Epidemiologic studies focused on the prevalence and control of risk factors. A large annual survey (Cardiomonitor) in patients with CVD was presented, with data obtained by general practitioners and cardiologists from all over the

world (25). Results in 25,000 diabetic patients indicated that only 1 of 5 patients in Europe and 2 of 5 in the U.S. had well-regulated systolic blood pressure (≤130 mm Hg), indicating that, with the rising incidence of diabetes worldwide, there is also urgent need for better blood pressure control.

Hypertension is in large part determined by genetic factors. In 215 young patients with type 1 diabetes, it was shown that blood pressure progression was related to angiotensinogen gene polymorphism (26). Another study revealed that the atrial natriuretic peptide promoter gene variant was associated with higher blood pressure at young age (27). These individuals also showed a predisposition to develop cerebrovascular events.

Pathophysiological mechanisms in hypertension were also investigated. High adrenergic tone was associated with a neuroplastic reduction in sympathetic nerve density, with suppression of nerve growth factor being the possible mediating mechanism (28). In another study, an altered structure of subcutaneous small resistance arteries (i.e., increased wall thickness to lumen diameter ratio) was shown to be associated with increased morning rise of blood pressure, a factor of enhanced risk, possibly because of amplification of hypertensive stimuli in the early morning (29).

Among indicators of preclinical organ damage in hypertension, the importance of left ventricular hypertrophy as an independent risk factor is well recognized. The results of the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study confirmed that left ventricular geometry during treatment adds information on risk of major cardiovascular events (with concentric geometry associated with the highest risk) (30).

In general, prevention or regression of organ damage should be considered a specific goal of antihypertensive treatment. New therapeutic approaches were proposed. An inhibitor of rho-kinase was shown effective for preventing renal and cardiac damage in a rat-model of malignant hypertension (31). In man, the efficacy and safety of aliskiren (the first of a new class of orally effective renin inhibitors) were assessed in a pooled analysis from large randomized, double-blind, clinical studies, involving more than 700 patients. It was shown that doses of 150 to 300 mg daily effectively reduced blood pressure without significant side effects (32).

Hypertension is often associated to metabolic risk factors and abdominal obesity. Pooled data from trials with rimonabant (the first selective cannabinoid CB1 receptor blocker) confirmed its efficacy in improving glucose and lipid metabolism and in reducing body weight over 1 year of treatment (33). The ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) study confirmed that treatment with diuretics and beta-blockers is mostly associated with a greater incidence of new-onset diabetes, particularly in those at higher risk. Finally, the results of the EUROACTION program have shown that involving multidisciplinary teams in delivering the prevention message leads to a significant reduction in cardiovascular risk factors as compared with the usual preventive approach. This is a strong message, indicating that it is achievable to improve significantly the control of risk factors and, hence, the burden of CVD in clinical practice.

ELECTROPHYSIOLOGY AND PACING

Cardiac resynchronization therapy (CRT). Many original scientific contributions were dedicated to CRT. Further analysis of the CARE-HF (Cardiac REsynchronization-Heart Failure trial) data aimed at prediction of sudden cardiac death (34). Severe mitral regurgitation at 3 months follow-up appeared a significant predictor of sudden death whereas CRT was protective against sudden death.

In another subanalysis of the CARE-HF study, it was shown that diabetic patients had similar benefit from CRT as compared with non-diabetic patients (35).

Randomized studies on CRT in atrial fibrillation are sparse, but observational studies suggest similar benefit to patients in sinus rhythm. An unresolved issue is whether patients with atrial fibrillation should undergo atrioventricular node ablation to ensure capture. In a 4-year open study with 243 heart failure patients, superior survival was demonstrated in patients who underwent atrioventricular node ablation (annual mortality 4.3% vs. 15.2% in non-ablated patients, $p < 0.001$) (36).

Atrial fibrillation. The new American College of Cardiology/American Heart Association/ESC guidelines on management of atrial fibrillation indicate that high-risk factors for thromboembolism are previous stroke, transient ischemic attack or embolism, mitral stenosis, and prosthetic valves. Moderate risk factors are age ≥75 years, hypertension, heart failure, left ventricular ejection fraction ≤35%, and diabetes. Oral anticoagulation is recommended (class I indication) in the presence of any high-risk factor or more than 1 moderate-risk factor. The risk/benefit of oral anticoagulation in relation to these risk factors was addressed in 290 elderly patients (median age 82 years) (37). For elderly patients with only 1 moderate risk factor, the number needed to treat (n = 58) and harm (n = 51) was relatively low, and the indication for oral anticoagulation may be questionable. For patients with 4 moderate- and 1 high-risk factor, the number needed to treat (n = 16) and to harm (n = 29) was relatively low indicating that oral anticoagulation should be individualized in these elderly patients. For the remaining patients with 2 to 3 moderate risk factors, oral anticoagulation should be provided.

The ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-Warfarin) substudy reported on the risk of stroke or thromboembolism in paroxysmal versus persistent/permanent atrial fibrillation (38). These patients had on the average 1.7 to 2 moderate-risk factors for thromboembolism. The risk of stroke or thromboembolism was compa-

rable in both groups (2.0 in paroxysmal vs. 2.2 in persistent/permanent/100 person-years), and oral anticoagulation in both groups was clearly superior to the combination of clopidogrel and aspirin in reducing the risk.

Polyunsaturated fatty acids reduced the risk for ventricular arrhythmias and sudden death in post-myocardial infarction patients. The properties of these fatty acids in reducing the risk of atrial fibrillation relapse after cardioversion was evaluated (39); the 1-year relapse risk after cardioversion was 23% in patients who received 1 g fatty acids in addition to conventional therapy, as compared with 66% in a control group ($p < 0.001$).

Devices and ablation therapy. The PEOPLE (Prospective Evaluation Of Pacemaker Lead Endocarditis) study (44 centers, 6,134 device implantations) focused on the need for antibiotic prophylaxis during device implantation (40). It was shown that the risk of infection was significantly lower in patients receiving antibiotic prophylaxis (1.3% vs. 0.6%, $p = 0.03$) (40).

In ablation therapy, recurrence after radiofrequency catheter ablation of accessory pathways occurs and generally a time window of 30 min is used to ensure absence of recurrence. This was evaluated in 439 ablations (419 patients), and the risk of recurrence after 10 min was 0.4% and 1.4% for left- and right-sided accessory pathways, respectively, and 3.8% for superior, peri-His and medioseptal locations (41).

VHD

The prevalence of VHD is rising, particularly in the ageing population. This group is characterized by under-referral for appropriate intervention associated with excess morbidity and mortality.

Calcification underlies degenerative VHD, and numerous groups seek underlying mechanisms. Human valve cells exposed to osteogenic media demonstrated increased activity of alkaline phosphatase, suggesting differentiation to an osteoblastic phenotype. These effects are abolished by atorvastatin, which decreased cytokines and increased adenosine triphosphate breakdown and adenosine formation (42). Similarly, in patients with aortic stenosis, levels of fetuin A (an inhibitor of vascular/soft-tissue calcification already implicated in vascular disease in dialysis recipients) were shown to inversely correlate with valve calcification and predicted disease progression (43,44). While clinical data are conflicting and randomized trials awaited, increased understanding of these pathways may demonstrate novel therapeutic targets.

Difficult clinical situations are commonplace in regurgitant VHD where a long symptom-free period often accompanies irreversible decline in left ventricular function. Although international guidelines provide criteria for early surgery, additional information can be obtained by indexing left ventricular end-systolic diameter to body surface area (45).

Percutaneous mitral commissurotomy is the treatment of choice for patients with mitral stenosis suitable for the procedure. Single-center data concerning 3,709 patients demonstrated good immediate results in 89% of patients with low mortality (0.4%), technical failure (1.1%), or severe mitral regurgitation (4.4%) (46). These excellent results were applicable worldwide despite varying patient characteristics (47), and long-term follow-up was similar to closed commissurotomy, the surgical alternative (48).

In addition, 1 study reported on the successful application of percutaneous mitral valve repair in 12 subjects with severe regurgitation and preserved left ventricular function (49). Another study was presented on 36 patients with severe aortic stenosis and advanced comorbidity who underwent successful percutaneous valve implantation; the adverse event rates were 19% at 1 month and 28% at 6 months follow-up, without valve migration (50). The percutaneous valve techniques are promising, but more data are needed.

Numerous factors predict adverse outcome in infective endocarditis. It was shown that diabetic patients had an increased incidence of staphylococcal and enterococcal infections with a higher mortality and incidence of heart failure and multi-organ failure (51). In another registry, an incidence of cerebrovascular complications of 22% in infective endocarditis was demonstrated using computed tomography of the brain (52). The benefits of early surgery in these high-risk patients were confirmed in summative data from the international collaboration on endocarditis (53).

IMAGING: ECHOCARDIOGRAPHY

Different studies on new technical developments and new clinical applications were presented. A contrast echocardiographic study evaluated the value of myocardial viability to predict outcome in patients with acute infarction. A total of 76 patients underwent vasodilator low power myocardial contrast echocardiography at 7 ± 2 days after thrombolysis (54). It was shown that the extent of residual myocardial viability was the only independent predictor of mortality and reinfarction.

Strain rate imaging was used to discriminate different degrees of myocardial necrosis and to identify segments with potential functional recovery in 18 patients with acute anterior infarction; the results were compared with contrast-enhanced magnetic resonance imaging (MRI) (55). Strain rate imaging could differentiate between non-transmural and transmural necrosis. The sensitivity, specificity, and area under the receiver operator characteristic curve to identify those segments with potential functional recovery (defined as <50% of scar tissue on contrast-enhanced MRI) were 74%, 71%, and 0.76, respectively. Strain rate imaging appears promising to evaluate the transmurality of necrosis and detect non-viable myocardium after acute infarction.

Real-time 3-dimensional echocardiography was used to assess the effects of CRT (56). Twenty patients were studied before and 6 months after CRT implantation. The dyssyn-

chrony index, defined as the standard deviation of the time it takes for each of the 16 left ventricular segments to reach their minimum volume, as well as the left ventricular ejection fraction were calculated. From the analysis of the regional volumes, an evaluation of the total volume change of the left ventricular segments that present with delayed contraction ("total delayed volume") was also feasible. In the responders (n = 14), significant reductions were observed in the left ventricular volumes and the dyssynchrony index with an increase in left ventricular ejection fraction (9 ± 2%) after CRT. A significant reduction in the total delayed volume was also observed, and a strong correlation was demonstrated between the dyssynchrony index and the total delayed volume. It was concluded that CRT has a significant impact on several functional and anatomical echocardiographic left ventricular parameters. Novel variables, such as the total delayed volume, could potentially offer a more extensive evaluation of the effects of CRT in the future.

Speckle-tracking echocardiography, which is a new strain-based method to assess left ventricular function, was used to evaluate left ventricular rotation and untwisting in 44 asymptomatic obese subjects (57); results were compared with standard tissue Doppler imaging. Obese subjects demonstrated reduced systolic left ventricular torsion and basal rotation, but preserved systolic apical velocities. The untwisting rotational velocities in diastole were similarly reduced. Systolic longitudinal tissue velocity on tissue Doppler imaging correlated significantly with left ventricular basal rotation and overall torsion. Left ventricular torsion also correlated with waist. Basal rotation and left ventricular torsion were significantly reduced even in patients without left ventricular dysfunction on tissue Doppler imaging. The novel speckle-tracking technique may be more sensitive to assess subclinical myocardial disease in obese patients as compared with standard tissue Doppler imaging.

IMAGING: NUCLEAR CARDIOLOGY, MRI, AND COMPUTED TOMOGRAPHY

The strength of nuclear cardiology remains risk stratification. The prevalence of perfusion abnormalities on single-photon emission computed tomography (SPECT) imaging in patients with diabetes was addressed in a European multicenter registry (58). Diabetic patients were prospectively recruited from 17 centers in 6 European countries; 539 patients underwent a rest-stress perfusion-gated SPECT examination. A history of CVD, male gender, body mass index >25 kg/m^2, alcohol consumption were independent predictors of abnormal SPECT studies. It was concluded that gated SPECT imaging permits further risk stratification in addition to the traditional risk factors in patients with diabetes.

Two studies used nuclear imaging to evaluate novel therapies. Metabolic imaging with F18-fluorodeoxyglucose was used to detect viability and scar tissue to better predict response to CRT (59). Sixty-one consecutive patients with advanced heart failure, left ventricular ejection fraction <35%, QRS duration >120 ms, and chronic CVD were included. The presence of myocardial viability was directly related to an increase in left ventricular ejection fraction after 6 months of CRT. The optimal cutoff value to predict clinical response to CRT was identified at an extent of 11 viable segments or more (in a 17-segment model), yielding a sensitivity of 74% and a specificity of 87%.

A second study evaluated the effect of intracoronary infusion of autologous bone marrow stem cells in patients with acute infarction (60). Patients were randomized either to cell therapy or a control group. The patients who received cell therapy showed superior left ventricular function and perfusion as compared with control subjects at 12 months follow-up.

Magnetic resonance imaging has become the gold standard for assessment of cardiac function and myocardial scar by contrast-enhanced imaging. Despite excellent diagnostic accuracy of contrast-enhanced MRI, the prognostic significance is unknown. This was addressed in a multicenter trial (61). In 1,493 patients, the prognostic value of MRI assessment of left ventricular ejection fraction and scar tissue was evaluated. The median follow-up time was 2.4 years, and the primary end point was all-cause mortality. On univariate analysis, the only clinical predictors were older age and history of CVD. Magnetic resonance imaging predictors were left ventricular ejection fraction and the presence/extent of scar tissue. On multivariate analysis, age, left ventricular ejection fraction, and extent of scar tissue were independent predictors of all-cause mortality.

Similarly, the prognostic value of contrast-enhanced MRI was assessed in 101 patients with dilated cardiomyopathy (62). Mid-wall fibrosis was present in 35% of patients, was the single significant predictor of death/hospitalization, but also predicted sudden cardiac death/ventricular tachycardia. Both of these studies (61,62) suggest a potential role for MRI in risk stratification of patients with ischemic or dilated cardiomyopathy.

Multislice computed tomography (MSCT) permits noninvasive assessment of the coronary arteries. This concept was applied in patients referred for valve surgery (63). In these patients, MSCT was used to exclude or detect CVD, to decide whether valve surgery should be combined with bypass surgery or not. In 70 patients, the sensitivity and specificity of MSCT to detect significant stenoses were excellent, indicating that MSCT may replace invasive angiography in these patients.

In another study, the accuracy of 64-slice MSCT for assessment of plaque composition was compared with intravascular ultrasound (64). Multislice computed tomography correctly detected 83% of non-calcified plaques, 97% of mixed plaques, 95% of calcified plaques. Multislice computed tomography may, thus, be helpful in assessment of plaque composition.

In addition to evaluation of coronary arteries, MSCT also permits detection of potential aortic valve stenosis (65). In 30 patients with aortic stenosis, the valve area on MSCT was closely related to echocardiography.

BASIC SCIENCE

In the area of stem cell therapy, several experimental studies reported on potential new sources of multipotent cells for cardiac repair, such as cells from amniotic fluid (66), adipose tissue (67), or testis (68). The spermatogonial cells seem to have a similar potential as embryonic stem cells for differentiation into functional cardiac myocytes, a desired end point not as easily reached by cells from other sources. Pre-differentiation may facilitate the incorporation of embryonic cells into the myocardium (69), but for xenogeneic transplant several immunological hurdles still need to be taken (70), not counting the ethical issues to be addressed. Adult human cardiac tissue as obtained during atrial biopsies can also be a source of multipotent stem cells (71), or could contain cells that drive vasculogenesis as during embryonic development. Injection of such epicardium-derived cells improved post-myocardial infarction remodeling as shown in a murine model of myocardial infarction (72). The postulated paracrine effects of stem cell therapy after myocardial infarction were elegantly confirmed by the improved calcium handling of the native cardiac myocytes in a rat model (73). Targeting the matrix to prevent cardiac dilation was proposed as an alternative to cellular replacement therapy; alginate injection could significantly reduce infarct expansion and improve function (74).

Several studies also examined the signaling pathways for cardiac hypertrophy as targets to prevent maladaptive remodeling. An interesting report described the protective effects of celecoxib, inhibiting Akt, on the development of heart failure after aortic banding (75). In the area of vascular biology, insights into the mechanisms of atherosclerosis have provided the basis for novel therapeutic approaches such as the testing of immunization against ox-low-density-lipoprotein. Novel potential strategies could include the up-regulation of "beneficial" immune cells. Gene therapy has long aimed for increased or novel protein expression, but gene silencing through interference with RNA translation has in recent years opened new approaches. CC-chemokine receptor 2 and monocyte chemoattractant protein-1 play a central role in monocyte recruitment to sites of inflammation. Local application of lentiviral short hairpin RNA against CC-chemokine receptor 2 could prevent vein graft thickening in vivo (76). In the area of "classic" pharmacology, HMR1766, a drug that activates the nitric-oxide-resistant oxidized soluble guanylate cyclase, could significantly reduce atherosclerotic plaque formation in the ApoE−/− mouse (77).

Identifying essential pathways promoting arteriogenesis could advance treatment of peripheral ischemic disease. Using a genetic print of a model for enhanced collateral flow, the actin-binding Rho activator was postulated to be a key regulator. Gene transfer in a hind-limb model of ischemia indeed enhanced arterial collateral perfusion by more than 70% (78).

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