Summary of the Clinical Studies Reported in the European Society of Cardiology Congress 2009 (August 29-September 2, 2009, Barcelona, Spain)

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The European Society of Cardiology held its 2009 annual congress in Barcelona. The results of some recently concluded clinical trials of outstanding importance were presented in special sections (Hot Lines).

Following the publishing policy established in recent years,[1-5] *Revista Española de Cardiología* offers for the first time a summary of these studies which briefly outlines their aims, methods and results in line with the oral presentations. In view of the fact that many have yed to be published in their final version, the information offered here should be considered preliminary. Where available, citations are provided at the end of the summary to facilitate reference.

SUMMARY BY SUBJECT

Acute Coronary Syndrome

PLATO study: comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndrome: results of platelet inhibition and patient outcome.

SEPIA-ACS1 TIMI 42 study: clinical efficacy and safety of otamixaban, an intravenous selective factor Xa inhibitor for the treatment of non-ST-segment elevation acute coronary syndrome.

NORDISTEMI study: immediate angioplasty versus ischemia-guided management after thrombolysis for ST-segment elevation myocardial infarction in areas with very long transfer distances.

GRACE study: unprotected left main revascularization in patients with acute coronary syndrome.

TRIANA study: primary angioplasty versus fibrinolysis in the very elderly.

PRAGUE-7 study: previous routine treatment with abciximab versus standard periprocedural therapy in patients undergoing primary percutaneous coronary intervention for cardiogenic shock.

ISAR-TEST-4 study: randomized noninferiority study of 3 limus agent-eluting stents with different polymer coatings.

Heart Failure

PROTECT study: effects of rolofylline on patients with heart failure syndrome and kidney failure.

European CRT study: European Study of Cardiac Resynchronization Therapy.

MADIT-CRT study: reduction in the risk of heart failure with preventive cardiac resynchronization therapy.

Atrial Fibrillation

RE-LY study: randomized trial of dabigatran, an oral direct thrombin inhibitor versus warfarin in 18 113 patients with atrial fibrillation at high risk of stroke.

ACTIVE program factorial design: randomized evaluation of irbesartan versus placebo in patients with atrial fibrillation.

Primary and Secondary Prevention

AAA study: randomized controlled trial of low-dose aspirin in the prevention of cardiovascular events and death in patients with asymptomatic atherosclerosis.

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KYOTO HEART study: effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients at high risk of cardiovascular events.

German PreSCD II registry: prevention of sudden cardiac death in post-myocardial infarction patients. Risk stratification, ICD therapy penetration and associated long-term outcomes.

ACUTE CORONARY SYNDROME

Ticagrelor versus clopidogrel in patients with acute coronary syndromes: platelet inhibition and clinical results (PLATO trial)[6]

Presented by L. Wallentin (Uppsala, Sweden)

Background and aims. Current clinical practice guidelines for patients with acute coronary syndrome (ACS) recommend dual platelet aggregation inhibition with aspirin and clopidogrel. The efficacy of clopidogrel is hindered by the slow and variable transformation of the prodrug into the active metabolite, modest and variable platelet inhibition, increased risk of bleeding and greater risk of stent thrombosis and myocardial infarction in patients with poor response. Ticagrelor is an oral reversible direct P2Y12 inhibitor that provides faster and greater platelet inhibition than clopidogrel.

Methods. PLATO was a multicenter randomized double-blind trial that compared treatment with ticagrelor (180 mg loading dose followed by 90 mg twice a day) to treatment with clopidogrel (300-600 mg loading dose followed by 75 mg once a day) for the prevention of cardiovascular events. A total of 18 624 patients were included who had been admitted for ST-segment elevation acute coronary syndrome (STEACS) referred to primary PCI (38%) or with non-ST-segment elevation acute coronary syndrome (NSTEACS) referred to an invasive or medical strategy (62%). Before randomization, 94% were treated with aspirin and 46% with clopidogrel. Patients were treated for an average of 278 days (6 months minimum and 12 months maximum). A total of 99.97% completed follow-up and only 5 patients were lost to follow-up.

Results. The primary endpoint of death from vascular causes (CV death), myocardial infarction (MI), and stroke was reduced from 11.7% to 9.8% (hazard ratio [HR] =0.84; 95% confidence interval [CI], 0.77-0.92; $P<.001$). In the predefined hierarchical testing of secondary endpoints, reductions were observed in the composite endpoint of death, MI, and stroke from 12.3% to 10.2% ($P=.0001$) and in CV, MI, stroke, severe recurrent ischemia, transient ischemic accident (TIA) and other arterial thrombotic events from 16.7% to 14.6% ($P<.001$); death from MI alone was reduced from 6.9% to 5.8% ($P=.005$), and CV death was reduced from 5.1% to 4% ($P=.001$). Total mortality was reduced from 5.9% to 4.5% ($P<.001$). There was no difference in total severe bleeding (11.6% vs 11.2% [$P=.434$]), but there was a greater incidence of severe bleeding unrelated to coronary artery bypass surgery (CABG) (4.5% vs 3.8% [$P=.026$]). Dyspnea episodes were more frequent with ticagrelor (14.2%) than with clopidogrel (9.2%), which led to the treatment being interrupted in 1% and 0.3% of patients, respectively. There were no differences in other relevant side effects.

Conclusions. Treatment with ticagrelor instead of clopidogrel in a wide spectrum of patients with ACS provides a clinically important reduction in mortality and myocardial infarction without an increase in total severe bleeding, but does involve an increase in bleeding unrelated to the procedure.

Clinical efficacy and safety of otamixaban, an intravenous selective factor Xa inhibitor for the treatment of non-ST-segment elevation acute coronary syndrome: Results of the SEPIA-ACS1 TIMI 42 trial[7]

Presented by M. Sabatine (Boston, United States)

Background and aims. For many years, unfractionated heparin (UFH) has been the foundation of anticoagulant therapy in patients with non-ST-segment elevation acute coronary syndrome (NSTEACS). However, UFH has many drawbacks, such as being an indirect and non-selective inhibitor of the coagulation factors, and has unpredictable pharmacodynamic activity. In contrast, otamixaban is a new, selective, synthetic, direct, factor Xa inhibitor which is administered intravenously, having an initial half-life of 30 min and predictable pharmacodynamic activity.

Methods. A total of 3241 patients were randomized within 24 h after presenting NSTEACS (with elevated biomarkers of necrosis or ST-segment deviation and referred to an invasive strategy) to receive double-blind treatment with one of 5 doses of otamixaban (0.08 mg/kg bolus followed by infusion, range 0.035 mg/kg/h to 0.175 mg/kg/h) or UFH plus the glycoprotein IIb/IIIa inhibitor (GPI) eptifibatide (ClinicalTrials.gov unique identifier: NCT00317395). The primary efficacy endpoint was the composite of death from any cause, new myocardial infarction, severe recurrent ischemia requiring urgent revascularization, or rescue GPI until day 7. The primary safety endpoint was major
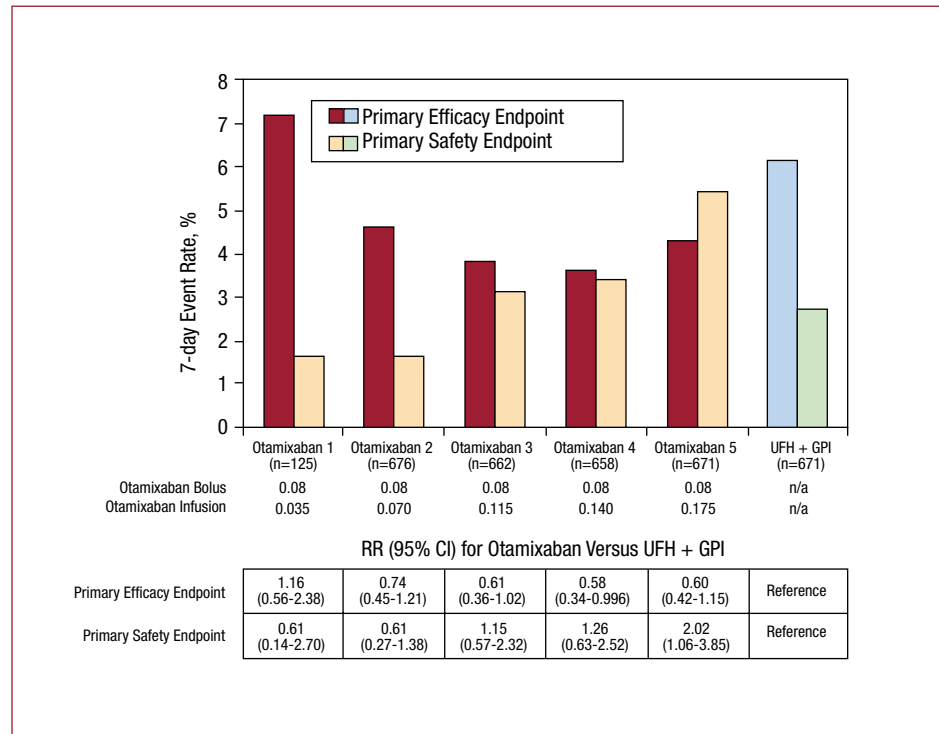
Figure 1. UFH indicates unfractionated heparin; CI, confidence interval; GPI, glycoprotein IIb/IIIa inhibitor; RR, relative risk.

or minor bleeding (according to TIMI criteria) unrelated to CABG. The dose 1 arm (lowest dose) was stopped very quickly, following the recommendation of the Data Safety Monitoring Committee, due to poor anticoagulation; the remaining arms completed as expected.

Results. The mean age of the patients was 61 years and 31% were women. A total of 99% underwent angiography, 63% underwent PCI and 4% underwent CABG; 98% were treated with aspirin and 98% with clopidogrel. The primary efficacy and safety endpoint rates are shown in Figure 1. There was no statistically significant difference in the primary efficacy endpoint rate between the otamixaban arms. However, in all the otamixaban groups except for the dose 1 arm, the point estimate for primary efficacy variable favored otamixaban over UFH + GPI. Specifically, at intermediate doses (dose arm 3, 0.105 mg/kg/h, and dose arm 4, 0.140 mg/kg/h), otamixaban treatment led to an approximately 40% reduction in the primary efficacy endpoint (relative risk [RR] =0.61 [95% CI, 0.36-1.02] and RR=0.58 [95% CI, 0.34-0.996], respectively) and an approximately 45% reduction in death or MI (RR=0.52 [95% CI, 0.28-0.98] and RR=0.56 [95% CI, 0.30-1.03], respectively) versus UFH + GPI. There was a significant dose-response relationship in the primary safety objective between the five groups of otamixaban (*P*=.0003), but the rate in

otamixaban dose groups 3 and 4 (3.1%-3.4%) was not significantly higher than the rate with UFH + GPI (2.7%).

Conclusions. Otamixaban is a new, synthetic, direct, selective, factor Xa inhibitor that, at intermediate doses in patients with NSTEACS, can be associated with up to 40% lower risk of ischemic events and a similar risk of bleeding as that with UFH + GPI. These data provide support for additional studies of otamixaban in NSTEACS patients.

Immediate angioplasty versus ischemia-guided management after thrombolysis for ST-segment elevation myocardial infarction in areas with very long transfers: the NORDISTEMI study[8]

Presented by S. Halvorsen (Oslo, Norway)

Background and aims. Thrombolysis is still the treatment of choice in ST-segment elevation myocardial infarction (STEMI) when primary percutaneous intervention (PCI) cannot be performed within 90-120 min. The efficacy and safety of early PCI after thrombolysis remain unresolved. The aim of this study was to compare an immediate transfer strategy for PCI after thrombolysis with ischemia-guided management in patients with very long transfer distances.

Methods. A total of 266 patients with acute STEMI of <6 h duration—who were living in rural areas in Norway with transfer distances for PCI of 100 km to 400 km—were administered full doses of tenecteplase, aspirin, enoxaparin, and clopidogrel. They were randomly distributed to immediate transfer for PCI or conservative treatment in local hospitals, or to urgent transfer only if there was indication for rescue or in case of clinical deterioration. The primary outcome was the composite of death, reinfarction, stroke, or new ischemia in the previous 12 months, and the analysis was by intention to treat.

Results. The primary outcome at 12 months was attained in 28 patients (21%) in the early intervention group versus 36 (27%) in the conservative treatment group (HR=0.72; 95% CI, 0.44-1.18; P=.19). The composite of death, reinfarction, or stroke at 12 months was significantly lower in the early intervention group than in the conservative treatment group (6% vs 16%; HR=0.36; 95% CI, 0.16-0.81; P=.01). No significant differences in bleeding or magnitude of the infarction were observed and few complications occurred during transportation.

Conclusions. Immediate transfer for PCI after thrombolysis did not significantly improve the primary outcome, but did reduce the death, reinfarction and stroke rates at 12 months compared to conservative treatment.

Unprotected left main revascularization in patients with acute coronary syndrome[9]

Presented by G. Montalescot (Paris, France)

Background and aims. In acute coronary syndrome (ACS), the optimal revascularization strategy for unprotected left main coronary disease (ULMCD) has undergone little study. The aim of the present study was to describe revascularization in ULMCD in patients with ACS and its course over 8 years, analyze prognosis within this population, and determine the effect of revascularization according to outcome.

Methods and results. Of 43 018 patients included in the Global Registry of Acute Coronary Events (GRACE) between 2000 and 2007, 1799 had significant ULMCD. The patients with ULMCD underwent revascularization with PCI (n=514), revascularization with CABG (n=612) or were not revascularized (n=673). Mortality was 7.7% during admission and 14% at 6 months. During the 8-year study period, the GRACE risk score stayed constant, but there was a steady changeover from CABG to PCI. The patients who underwent PCI more frequently presented with ST-segment elevation myocardial infarction (STEMI) after cardiac arrest or cardiogenic shock. A total of 48% of the patients in the PCI group underwent revascularization on the day they were admitted versus 5.1% in the CABG group. After adjustment, revascularization was associated with an early risk of hospital death versus no revascularization, and was significant for PCI (HR=2.60; 95% CI, 1.62-4.18), but not for CABG (HR=1.26; 95% CI, 0.72-2.22). Between the time of discharge and 6 months, the PCI approach (HR=0.45; 95% CI, 0.23-0.85) and the CABG approach (HR=0.11; 95% CI, 0.04-0.28) were significantly associated with better survival compared to the initial strategy of no revascularization. CABG revascularization was associated with a five-fold increase in stroke compared to the other two groups.

Conclusions. Revascularization of the unprotected left main artery in patients with ACS is associated with high mortality, particularly in patients with STEMI, hemodynamic instability, or arrhythmias. PCI is currently the most frequent revascularization strategy and is preferred in patients at high risk. Coronary artery bypass surgery is frequently delayed and performed in patients at low risk, which leads to good survival at 6 months. Thus, the approaches seem to complement each other.

Primary angioplasty versus fibrinolysis in very elderly patients. The TRIANA study[10]

Presented by H. Bueno (Madrid, Spain)

Background and aims. Currently, primary angioplasty (PCI) is considered the reperfusion therapy of choice for ST-segment elevation myocardial infarction (STEMI). However, there is little data on clinical outcomes comparing primary PCI with fibrinolysis in very elderly patients.

Methods. The TRIANA study (clinicaltrials. gov: NCT00257309) was a Spanish multicenter randomized study that compared primary PCI with a conservative strategy of fibrinolysis (weight-adjusted tenecteplase (TNK) plus unfractionated heparin (UFH) [TNK + UFH]) and rescue PCI. The study patients were 75 years of age or more and presented within 6 h after STEMI. Patients were excluded if they had accepted contraindications for fibrinolysis, or any previous cerebrovascular event, cardiogenic shock, or blood pressure >180/110 mm Hg at any time during the event. The primary endpoint was the composite of death from any cause, recurrent MI, or disabling stroke at 30 days. The secondary endpoints were recurrent ischemia requiring revascularization and major bleeding. The events were assessed by an adhoc committee blinded to the study treatments.

TABLE 1. TRIANA Study. 30-day Outcome

	Primary PCI (n=132)	Fibrinolysis (n=134)	OR (95% CI)	P
Primary endpoint	25 (18.9%)	34 (25.4%)	1.46 (0.81-2.61)	.21
Death	18 (13.6%)	23 (17.2%)	1.31 (0.67-2.56)	.43
Reinfarction	7 (5.3%)	11 (8.2%)	1.60 (0.60-4.25)	.35
Disabling stroke	1 (0.8%)	4 (3%)	4.03 (0.44-36.5)	.18
Recurrent ischemia	1 (0.8%)	13 (9.7%)	14.1 (1.8-109)	<.001
Severe bleeding	5 (3.8%)	5 (3.7%)	0.98 (0.28-3.48)	.98

Results. The trial was stopped prematurely due to slow recruitment, after enrolling 266 patients of the 560 planned. The mean age was 81 years, and 56% were men. The two treatment groups were balanced in relation to demographic characteristics and risk factors. Table 1 shows the 30-day outcomes. At 1-year follow-up the outcomes were fairly similar.

Conclusions. Despite the limited sample size, this study indicated a trend toward reductions in mortality, reinfarction and disabling stroke in very elderly patients undergoing primary PCI versus fibrinolysis. Furthermore, recurrent ischemia is drastically reduced by primary PCI. Thus, this approach could also be recommended in older patients with STEMI.

Previous routine treatment with abciximab versus standard periprocedural administration in patients undergoing primary percutaneous coronary intervention for cardiogenic shock. The PRAGUE-7 study[11]

Presented by P. Widimsky (Prague, Czech Republic)

Background and aims. The prognosis of AMI complicated by cardiogenic shock is poor. Early mechanical revascularization is superior to medical treatment, but mortality is still high. Registries have demonstrated the benefit of GP IIb/IIIa inhibitors during primary PCI in patients in cardiogenic shock. The aim of this study was to determine previous administration of abciximab (vs standard therapy) improved the outcomes of cardiogenic shock.

Methods. This multicenter open study randomized 80 patients (mean age 66 years) with AMI complicated by cardiogenic shock (25% after cardiopulmonary resuscitation, 46% undergoing mechanical ventilation) referred to primary PCI to group A (preprocedural abciximab bolus followed by abciximab infusion over 12 h) and to group B (standard therapy with optional abciximab according to the interventional cardiologist). The primary outcome was a composite of death, reinfarction, stroke and new kidney failure at 30 days. The secondary outcomes were as follows: left ventricular ejection fraction evaluated by echocardiography at 30 days, major bleeding complications, myocardial blush grade (MBG) after PCI, TIMI-flow after PCI.

Results. PCI was technically successful in 90% of patients (group A) vs 87.5% (group B). Abciximab was used in all the patients in group A vs 35% in group B. The primary endpoint was achieved in 17 patients in group A (42.5%) and in 11 patients in group B (27.5%; *P*=.24). Fifteen patients (37.5%) died in hospital in group A vs 13 patients (32.5%) in group B (*P*=.82). The ejection fraction in surviving patients at 30 days was 44% (11%) (group A) vs 41% (12%) (group B) (*P*=.205). There were major bleeding events in 17.5% (group A) vs 7.5% (group B) (*P*=.310) and stroke in 2.5% (group A) vs 5% (group B). No differences between group A and group were observed in TIMI-flow or MBG following PCI.

Conclusions. This study did not demonstrate any benefit from preprocedural treatment with abciximab versus the selective use of the abciximab during PCI.

Randomized noninferiority study of three limus agent-eluting stents coated with different polymers: the ISAR-TEST-4 study[12]

Presented by J. Mehili (Munich, Germany)

Background and aims. Although drug-eluting stents (DES) with biodegradable polymers have the potential to improve long-term clinical outcomes, to date there is little data available on their efficacy. We previously demonstrated efficacy in reducing angiographic restenosis with a microporous

biodegradable polymer DES. In this study, we hypothesized that, its clinical safety and efficacy would not be inferior at 12 months to that of a permanent polymer DES.

Methods and results. This prospective, randomized, open-label, active and placebo-controlled trial took place at two tertiary referral cardiology centers in Munich, Germany. Patients who presented stable coronary disease or acute coronary syndrome (ACS) undergoing DES implantation in de novo lesions in native coronary arteries were randomly assigned to treatment with biodegradable polymer DES (rapamycin-eluting, n=1299) or permanent polymer DES (n=1304: Cypher, rapamycin-eluting, n=652; or Xience, everolimus-eluting, n=652) and underwent clinical follow-up at 1 year. The primary endpoint was a composite of cardiac death, target vessel-associated myocardial infarction (MI) or target lesion-associated revascularization (TLR). The biodegradable polymer DES was not inferior to the permanent polymer DES in relation to the primary endpoint (13.8% vs 14.4%, respectively; non-inferiority, P=.005; RR=0.96 [95% CI, 0.78-1.17]; superiority, P=.66). The biodegradable polymer DES, when compared to the permanent polymer DES, demonstrated similar rates of cardiac death or target vessel-associated MI (6.3% vs 6.2%, P=.94), TLR (8.8% vs 9.4%, P=.58), and stent thrombosis (definite/probable, 1.0% vs 1.5%, P=.29). Analysis of the biodegradable polymer DES subgroups versus the Cypher and Xience stent groups demonstrated no differences in performance.

Conclusions. A biodegradable polymer rapamycin-eluting stent is not inferior to a permanent polymer DES in clinical efficacy during 1-year follow-up. These results provide a framework for assessing the potential clinical advantage of biodegradable polymer DES in the medium to long term.

HEART FAILURE

Effects of rolofylline in patients with heart failure syndrome and kidney failure: results of the PROTECT study[13]

Presented by M. Metra (Brescia, Italy)

Background and aims. Patients hospitalized with acute decompensated heart failure (ADHF) often undergo worsening renal function (WRF) and reduced diuretic response during treatment. This clinical problem is associated with prolonged hospital stay and worse in-hospital and post-discharge clinical outcomes. Recent studies have demonstrated that treatment with selective adenosine A1 receptor antagonists (A1RA) can enhance diuresis and prevent WRF. Our hypothesis was that early treatment with the A1RA, rolofylline, would facilitate early clinical improvement and reduce the risk of WRF as well as reduce the rates of post-discharge death and readmission caused by cardiovascular and renal events.

Methods: PROTECT was a multicenter, randomized, double-blind, placebo-controlled trial (rolofylline vs placebo at a 2:1 ratio) conducted in patients hospitalized for ADHF, indicated by resting dyspnea and signs of volume overload requiring intravenous loop diuretic therapy. It was predicted that patients would require furosemide at ≥40 mg/d for at least 24 h after recruitment. Included patients had impaired kidney function (estimated creatinine clearance of 20-80 mL/min) and B-type natriuretic peptide concentrations of ≥500 pg/mL or N-terminal fragment of the prohormone B-type natriuretic peptide concentrations of ≥2000 pg/mL. Key exclusions included current or planned intravenous vasoactive therapy (except for nitrates), mechanical or circulatory support, ultrafiltration, dialysis, acute coronary syndrome within 2 weeks, severe cardiac valve stenosis or a high risk of seizures (a known adverse effect of A1RA). Randomization occurred within 24 h and intravenous rolofylline was administered at 30 mg/d or placebo shortly afterwards at 4 h/d for 3 days. The primary endpoint had three categories, assessed until day 7 or discharge treatment success, no change, and treatment failure. Treatment success was defined as moderate to strong improvement in dyspnea at 24 h and 48 hours after randomization if treatment had not failed. Treatment failure included any of the following: death or readmission due to heart failure (HF) until day 7, worsening symptoms or signs of HF requiring rescue therapy between day 2 and day 7 or discharge, persistent kidney failure (increase in serum Cr ≥0.3 mg/dL at day 7 and confirmed at day 14, or the initiation of hemofiltration or dialysis at day 7). The secondary endpoints included time until death, rehospitalization caused by cardiovascular or kidney events at day 60 and the proportion of patients with persistent kidney failure (increase in serum Cr ≥0.3 mg/dL from randomization to day 7, confirmed at day 14, initiation of hemofiltration or dialysis, or death at 7 days).

Results. Between May 2, 2007 and January 23, 2009, in 173 centers in North America, Argentina, Israel, Europe, and Russia, participating patients (n=2033) were randomized to rolofylline (n=1356) or placebo (n=677). For the primary endpoint

TABLE 2. **PROTECT Study. Improvement in Dyspnea and Failure Criteria**

	Rolofylline (n=1356)	Placebo (n=677)
Moderate to strong improvement in dyspnea at 24 h and 48 h, % (n)	51.2 (694)	44.5 (301)
Components of treatment failure, % (n)		
Death, day 7	1.7 (23)	2.1 (14)
Readmission for heart failure, day 7	0.4 (5)	0.6 (4)
Worsening of heart failure, day 7 or discharge	9.1 (123)	9.7 (66)
Persistent kidney failure	12.7 (172)	11.1 (75)
↑ Serum creatinine (day 7 and day 14)	12.3 (167)	10.6 (72)
Initiation of hemofiltration	0.4 (6)	0.9 (6)

(Table 2), rolofylline was associated with better success than placebo, but also more failures (odds ratio [OR] = 0.92 vs placebo; 95% CI, 0.78-1.09; P=.348). The secondary composite endpoint of death or hospitalization caused by cardiovascular or kidney events occurred in 30.7% of patients in the rolofylline group (25.7% were hospitalized and 8.9% died) and in 31.9% of patients in the placebo group (25.6% were hospitalized and 9.5% died), with no differences in time to the first event (HR=0.98; 95% CI, 0.83-1.17; P=.86). Rolofylline did not reduce the incidence of kidney failure compared to placebo (15.0% vs 13.7%, respectively; OR=1.11; 95% CI, 0.85-1.46; P=.44). The number of patients who underwent one or more adverse events was similar (62.9% with rolofylline and 61.4% with placebo) (Table 3). However, more patients in the rolofylline group had nervous system disorders: 11 patients (0.8%) underwent convulsions and 16 (1.2%) had a stroke. In the placebo group, no patient underwent convulsions and 3 patients (0.5%) had a stroke.

Conclusions. The primary endpoint of this study—that rolofylline 30 mg compared to placebo would provide a favorable change in the distribution of the primary variable (success, no change, failure)—was not fulfilled. Neither were the two secondary efficacy variables fulfilled.

TABLE 3. **PROTECT Study. Effects on the three primary outcome categories**

	Rolofylline (n=1356)	Placebo (n=677)
Success, % (n)	40.6 (551)	36 (244)
No change, % (n)	37.5 (509)	44.2 (299)
Failure, % (n)	21.8 (296)	19.8 (134)

In general, the safety profiles of the placebo and rolofylline groups were similar. No increase in adverse cardiac events was observed. However, treatment with rolofylline 30 mg was associated with a greater incidence of convulsions and a trend toward increased stroke.

European Cardiac Resynchronization Therapy Study (European CRT Survey)[14]

Presented by N. Bogale (Stavanger, Norway)

Background and aims. The European CRT Survey is a joint initiative conducted by the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the European Society of Cardiology. The main aim of this study is to describe current European practice in relation to cardiac resynchronization therapy implantations.

Methods and results. Between November 2008 and June 2009, 141 centers in 13 European countries contributed study data from 2438 consecutive patients who had undergone successful implantation with a cardiac resynchronization therapy (CRT) device, with or without an implantable cardioverter-defibrillator (ICD). A total of 2438 patients were enrolled. The median age was 70 [interquartile range, 62-76] years and 31% were 75 years of age or more. A total of 78% were in NYHA functional class III or IV and 22% were in classes I or II. The mean ejection fraction was 27 (8%) and the mean QRS duration was 157 (32 ms. The QRS duration was <120 ms in 9%. A total of 23% presented atrial fibrillation. A permanent pacemaker or ICD had been implanted in 26% of the patients. An electrophysiologist performed 76% of the procedures. A total of 82% were admitted for elective implantation, and the median duration of hospital stay was 3 [2-7] days. A CRT-D device was implanted in 73% of patients, who were more often young and male with ischemic etiology.

The mean QRS duration was reduced to 133 (27) ms (*P*<.0001) at discharge. The periprocedural complication rates were similar to those reported in randomized trials.

Conclusions. This registry-survey provides important information by describing current European practice in relation to patient demographics, selection criteria, procedural routines and status at discharge. These data should prove useful for assessing individual patient management and national practice against wider experience.

Reduction of the risk of heart failure with preventive cardiac resynchronization therapy: the MADIT-CRT trial[15]

Presented by A.J. Moss (Rochester, United States)

Background and aims. This trial was designed to determine if cardiac resynchronization therapy would reduce mortality and heart failure events in patients with mild cardiac symptoms, reduced ejection fraction and wide QRS.

Methods. Over 4.5 years, 1820 patients with ischemic or nonischemic cardiomyopathy, an ejection fraction ≤0.30, QRS ≥130 ms and New York Heart functional class I or II symptoms were enrolled and followed up. The patients were assigned randomly in a 3:2 ratio to receive cardiac resynchronization therapy with a defibrillator (1089 patients) or implantation with a defibrillator (731 patients). The primary endpoint was mortality from any cause or a heart failure event, whichever was the first to occur.

Results. During a mean follow-up of 2.4 years, 17.2% of the patients in the resynchronization group and 25.3% of those in the defibrillator group underwent a primary endpoint event. There was a demonstrated benefit in favor of resynchronization therapy: HR=0.66 (95% CI, 0.52-0.84; *P*=.001), with similar benefits in patients with ischemic and non-ischemic myocardiopathy. The superiority of cardiac resynchronization therapy was indicted by a 41% reduction in the risk of a first heart failure event, a finding that was evident mainly in patients with a QRS ≥150 ms. Resynchronization therapy was associated with significant reduction in left ventricular volumes and improved ejection fraction. Severe adverse events were rare.

Conclusions. Cardiac resynchronization therapy decreases the risk of heart failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex. This therapy is effective in the prevention of heart failure in patients at a high risk of cardiac events.

ATRIAL FIBRILLATION

RE-LY: randomized trial of dabigatran, an oral direct thrombin inhibitor, compared to warfarin in 18 113 patients with atrial fibrillation at high risk of stroke[16]

Presented by S.J. Connolly (Hamilton, California, United States)

Background and aims. Warfarin reduces stroke in atrial fibrillation, but increases bleeding and is difficult to use. Dabigatran is a novel oral direct thrombin inhibitor.

Methods. In a noninferiority trial, 18 113 patients with atrial fibrillation and risk of stroke were randomized to blinded fixed doses of dabigatran (110 mg or 150 mg twice a day) or to nonblinded adjusted doses of warfarin. The median duration of follow-up was 2 years. The primary endpoint was stroke or systemic embolism.

Results. The outcomes of the primary endpoint were 1.69% per year with warfarin versus 1.53% per year with dabigatran 110 mg (RR=0.91; 95% CI, 0.74-1.11; *P* [noninferiority] <.001) and 1.11% per year with dabigatran 150 mg (RR=risk 0.66; 95% CI, 0.53-0.82; *P* [superiority] <.001). The major bleeding rates were 3.36% per year with warfarin versus 2.71% per year with dabigatran 110 mg (*P*=.003) and 3.36% per year with dabigatran 150 mg (*P*=.31). The hemorrhagic stroke rates were 0.38% per year with warfarin versus 0.12% per year with dabigatran 110 mg (*P*<.001) and 0.10% per year with dabigatran 150 mg (*P*<.001). The mortality rates were 4.13% per year with warfarin vs 3.74% per year with dabigatran 110 mg (*P*=0.13) and 3.64% per year on dabigatran 150 mg (*P*=0.05).

Conclusions. In patients with atrial fibrillation, dabigatran 110 mg was associated with stroke and systemic embolism rates similar to those of warfarin, and lower rates of major bleeding. Dabigatran 150 mg was associated with lower stroke and systemic embolism rates than those of warfarin, and similar major bleeding rates.

Randomized evaluation of irbesartan versus placebo in patients with atrial fibrillation (factor design of the ACTIVE program)[17]

Presented by S. Yusuf (Hamilton, Canada)

Background and aims. One of the most relevant risk factors for atrial fibrillation (AF) is arterial hypertension. Stroke and heart failure are frequent complications of AF and are also associated with

hypertension. A series of small studies have indicated that renin-angiotensin-aldosterone system (RAAS) blockade may be beneficial in AF. However, blood pressure (BP) reduction and RAAS blockade have not been studied in large trials of patients with AF.

Methods. Evaluation of the comparative effects of irbesartan, an angiotensin receptor blocker, (target dose 300 mg/d) or placebo over a mean of 4.1 years in reducing severe vascular events (CV death, MI or stroke: first coprimary endpoint) and heart failure (CV death, MI, stroke: second coprimary endpoint) in 9016 patients with AF receiving standard treatment. These patients were taken from two parallel trials (ACTIVE-A and ACTIVE-W) which included more than 14 000 patients using a partial factorial design.

Results. Blood pressure at admission was 138/75 mm Hg; mean age was 69.5 years. Reductions in BP were modest (–2.6/–1.9 mm Hg) with irbesartan versus placebo. Irbesartan did not reduce the risk of the first coprimary endpoint of CV death, MI or stroke (5.4% per year in each group), but there was a lower rate of the second co-primary of CV death, MI, stroke and hospitalizations due to heart failure (7.3% vs 7.7%; P=.12) with irbesartan. This was mainly due to a significant reduction in the risk of hospitalization due to heart failure (3.2% per year in the placebo group vs 2.7% with irbesartan) in 14% (P=.018). The analysis of recurrent events of the second co-primary endpoint (39.6% with irbesartan vs 44.3% with placebo) showed clearer differences (RR=0.89; 95% CI, 0.82-0.98; P=.06). Post-hoc analysis demonstrated a significant reduction in the risk of the composite of stroke, non-central nervous system embolism and transient ischemic attacks (3.4% per year in the placebo group vs 2.9% with irbesartan) in 13% (P=.02), with consistently lower rates in each component of the composite endpoint. The number of admissions (4055 with placebo vs 3816 with irbesartan; P=.004) and days patients were hospitalized for CV events were significantly reduced (39 941 with placebo vs 36 480 with irbesartan; P=.0001). Irbesartan was well-tolerated, with treatment interruption rates similar to those of placebo.

Conclusions. The discreet reduction in BP with irbesartan in this "normotensive" population with AF was associated with a reduction in hospitalizations due to heart failure and thromboembolic events, but not in death or MI. These findings indicate that it is worth investigating the impact of larger reductions in BP and that this could potentially lead to greater reductions in thromboembolic events and heart failure.

PRIMARY AND SECONDARY PREVENTION

Randomized controlled trial of low-dose aspirin in the prevention of cardiovascular events and death in patients with asymptomatic atherosclerosis (AAA)[18]

Presented by G. Fowles (Edinburgh, United Kingdom)

Background and aims. The effectiveness of antiplatelet therapy in the prevention of severe vascular events in patients with known cardiovascular disease is well established, but the value of platelet aggregation inhibitors in primary prevention is still unclear. The ankle-brachial index (ABI), that is, the ratio between systolic pressure at the ankle and that at the arm, is an indicator of subclinical atherosclerosis. In many cohort studies of healthy populations, it has been clearly demonstrated as a predictor of risk of vascular events, independently of established cardiovascular risk factors. Therefore, individuals who are free from clinical cardiovascular disease, but have a low ABI, may form a high-risk group that could benefit from antiplatelet therapy in a similar manner to those with established clinical disease. Given that the ABI is a simple, cheap and noninvasive test, it has the potential to be used in cardiovascular screening programs, although it remains unknown whether platelet aggregation inhibitors, such as aspirin, should be administered to patients with a low ABI.

Methods. From April 1998 to December 2001, 28 980 men and women aged between 50 and 80 years who were free from cardiovascular disease were recruited from the general practitioner age and sex registers in Lanarkshire, Glasgow and Edinburgh in Scotland and underwent an ABI screening test. A total of 3350 participants with a low ABI (≤0.95) were included in the trial and randomized to 100 mg of enteric-coated aspirin or placebo. The size of the sample provided 80% power at the 5% significance level (2-tailed) to detect a statistically significant reduction in the proportion of patients with at least one component of the primary endpoint from 12% with placebo to 9% with aspirin.

The participants included in the trial had a clinic follow-up visit at 3 months and 1 year. Over a mean of 8.2 years, follow-up was subsequently conducted annually by telephone and included a letter every 6 months. Contact was maintained with 95% of the survivors. At 5 years, 2557 subjects (85% of the survivors) underwent a detailed clinical follow-up examination. Any cardiovascular events and deaths were also checked by comparing general practitioner notes, reviewing hospital discharges in Scotland using record linkage, and identifying deaths in the NHS Central Registry. The Outcome Events

Committee confirmed the events by reviewing the medical records and death certificates.

The primary endpoint was a composite of an initial fatal or nonfatal coronary even, stroke or revascularization. The 2 secondary endpoints were as follows: *a)* all initial vascular events defined as a composite of a primary endpoint event or angina, intermittent claudication or transient ischemic attack, and *b)* all-cause death.

Results. A total of 357 participants underwent a primary event (13.5/1000 person/y, 95% CI, 12.2-15.0). There were no statistically significant differences between those assigned to aspirin or placebo (181 vs 176 events) (HR=1.03; 95% CI, 0.84-1.27); 578 participants (22.8/1000 people/y; 95% CI, 21-24.8) suffered a vascular event included in the secondary endpoint; no statistically significant difference was observed between the aspirin group and the placebo group (288 events vs 290 events; HR=1; 95% CI, 0.85-1.17). All-cause death was similar in both groups (176 deaths vs 186 deaths; HR=0.95; 95% CI, 0.77-1.16). An initial severe bleeding event requiring hospital admission occurred in 34 (2%) of participants in the aspirin group and in 20 (1.2%) in the placebo group (HR=1.71; 95% CI, 0.99-2.97).

Conclusions. These results do not support the routine use of aspirin for preventing vascular events in the context of ABI screening in the general population.

Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients at a high risk of cardiovascular events (KYOTO HEART study)[19]

Presented by H. Matsubara (Kyoto, Japan)

Background and aims. The best therapeutic strategy in patients with uncontrolled hypertension has not been established. The aim of this study was to evaluate the effect of adding valsartan to conventional treatment on morbidity and mortality in high-risk hypertensive patients.

Methods and results. KYOTO HEART is a study with a multicenter, prospective, randomized, open and blinded (PROBE) design, whose primary endpoint was a composite of fatal and nonfatal cardiovascular events (clintrials.gov NCT00149227). A total of 3031 Japanese patients (43% women; mean age, 66 years) with uncontrolled hypertension were randomized to added-valsartan or treatment without angiotensin II receptor antagonists (ARA-II). The median follow-up time was 3.27 years. In both groups, baseline blood pressure (BP) was 157/88 mmHg, and 133/76 mmHg at the end of the study. Compared to the non-ARA-II group, the valsartan group underwent fewer primary endpoints (83 vs 155; HR=0.55; 95% CI, 0.42-0.72, *P*=.00001).

Conclusions. The addition of valsartan to conventional treatment to improve BP control prevented more cardiovascular events than conventional treatment without ARA-II in high-risk hypertensive patients in Japan. These benefits cannot be completely explained by the difference in BP control.

Prevention of sudden cardiac death in patients after myocardial infarction: risk stratification, ICD therapy penetration, and related long-term outcomes. Final results of the German preSCD II registry[20]

Presented by H. Voeller (Rudersdorf, Germany)

Background and aims. The current guidelines recommend implantable cardioverter-defibrillator (ICD) therapy for the primary prevention of sudden cardiac death (SCD) in patients with reduced left ventricular ejection function (LVEF ≤30%-35%) for more than 40 days after myocardial infarction (MI). The aim of the PreSCD II registry was to investigate the daily practice of ICD therapy in patients after MI and assess their long-term survival.

Methods. Between December 2002 and May 2005, 10 612 patients were enrolled after consecutive MI (61 [12]years; 76% men) in 19 cardiac rehabilitation (CR) centers in Germany. All patients with LVEF ≤40% were followed up for 36 months as well as a random subsample with preserved LVEF (LVEF >40%). Logistic regression modeling was performed to characterize patients with ICD therapy. To study overall survival, Cox proportional hazard models were used with ICD therapy as a time-dependent covariable.

Results. Of the 10 612 study participants, 77.4% were included within 60 days or MI and 10.71% more than 1 year after MI; all were assigned to LVEF study groups: Group 1 ≤30% (269, 2.5%), Group 2 31-40%. (727, 6.9%), Group 3 >40% (all others). Follow-up was performed in 2058 patients: 259 in group 1, 693 in group 2 and 1106 in group 3 (LVEF >40%); 75 patients received an ICD within 4 months after risk stratification, 57 (22%) in group 1 and 15 (2.2%) in group 2. After 36 months, 142 (6.9%) patients had received an ICD, 47% of them within 1 year after index MI. An LVEF ≤30% was the main reason for ICD implantation, and to a lesser extent, unsustained ventricular tachycardia, previous syncope, NYHA II-IV, wide QRS, kidney failure or MI prior to index. The patients with an ICD had an adjusted 44% lower mortality (HR=0.56; 95% CI,

0.32-1.01; *P*=.053) than comparable patients without ICD therapy. There was a significant trend toward lower mortality among the patients who received ICD if the device was implanted in the phase prior to the MI index (*P*<.001).

The PreSCD II registry demonstrated a low prevalence of patients with reduced LVEF after MI. Few patients with an indication for ICD based on the guidelines received ICD therapy. Mortality was reduced if an ICD was implemented late after MI.

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