SPECIAL ARTICLE

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (New Orleans, United States, November 8-12, 2008)

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In the Scientific Sessions of the American Heart Association 2008, certain clinical studies were chosen to be presented in special sessions. These studies were selected for their particular importance and their findings were reported in oral presentations, whose summaries have been published in electronic format. The following is a brief summary of the objectives, methods, and results of these studies, as presented in the congress. Given that for the most part the results have not been published in the form of an original article, the information offered in this article should be interpreted as preliminary.

SUMMARY BY TOPICS

Primary Prevention

FIT heart study: study of intervention in family members to improve cardiovascular health.

J-PAD Study: low dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes mellitus.

JUPITER study: rosuvastatin for the prevention of vascular events in subjects with elevated C-reactive protein.

PHS study: vitamin E and C in the prevention of cardiovascular disease in men.

SEARCH study: effectiveness of additional reductions in cholesterol and homocysteine. Comparison of folic acid plus vitamin B_{12} versus placebo for 7 years in infarction survivors. Effectiveness of additional reductions in cholesterol and homocysteine. Comparison of simvastatin 80 mg versus 20 mg daily for 7 years in infarction survivors.

Ischemic Heart Disease

Results of the MASS-DAC registry: drug-eluting stents or bare-metal stents in patients with diabetes mellitus.

ATLAS ACS-TIMI 46 trial: study of rivaroxaban versus placebo in patients with acute coronary syndrome.

TIMACS trial: study of early or late invasive strategy in high-risk patients with nSTE-ACS.

Loading-Dose titration of clopidogrel according to monitoring of platelet reactivity in order to prevent stent thrombosis

Heart Failure

I-Preserve study: irbesartan in patients with heart failure and preserved ejection fraction.

The BACH Study: midregional proadrenomedullin (MRproADM) versus BNP and NT-proBNP as a prognostic marker in patients with heart failure.

The BICC study: effects of subcutaneous treatment with interferon beta-1b in patients with chronic viral myocarditis.

HF-ACTION: morbidity and mortality after an exercise training program in patients with heart failure.

HF-ACTION substudy: effect of an aerobic training program on the quality of life of patients with heart failure.

Arrhythmias

THINRS study: study of the prognostic impact of home-testing of INR.

PRIMARY PREVENTION

The FIT Heart Study: A Novel Study Based on Intervention in Family Members to Improve Cardiovascular Health

Presented by L. Mosca, United States.

Background. Family members of patients with cardiovascular disease (CVD) may be at

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higher risk because they share genes and lifestyle. The hypothesis of the FIT-Heart study was that hospitalization for CVD may be a "motivational moment" for family members to take their own preventative measures. The aim of this 1-year, controlled, randomized study, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), was to assess the efficacy of a new approach for screening for risk factors and educating the family members about lifestyle. For this, the moment when a family member was hospitalized was used in order to improve compliance with the goals of prevention.

Methods. The participants were adult family members (n=501; 66% women; mean age, 48 years) of patients admitted with atherosclerotic CVD. The participants were eligible for primary prevention of CVD and diabetic patients and pregnant women were excluded. The participants were randomized to: *a)* a special interventional group (SI), who underwent personalized screening to determine their level of risk and who received counseling on diet and therapeutic exercise for lifestyle change (LSC) from paramedic health educators at regular intervals throughout the year; or *b)* control intervention group, who received the first part of the general message on cardiovascular health and were informed of the cut-off values recommended for each of the risk factors. Research assistants who were blinded to group assignment recorded standard CVD risk factors for all participants at baseline and after 1 year. Follow-up was available for 94% of the sample. Lipids were measured in the CTSA Biomarker Laboratory of the University of Columbia. Diet was assessed using Block98 and MEDFICTS validated questionnaires.

Results. There was a significant improvement in the SI group compared to the control group in the mean percentage change in the MEDIFCTS diet score between baseline and 1 year later (*P*=.04; difference, 13.4%) and both groups showed significant improvements in saturated fats, dietary cholesterol, trans fat intake, low-density lipoprotein cholesterol (LDL-C), and physical activity. High-density lipoprotein cholesterol (HDL-C) significantly decreased in the control intervention group but not the SI group. The mean percentage change in baseline HDL-C at 1 year was significantly greater in the SI group than in the control intervention group (*P*=.01; difference, 3.5%). The SI group were more likely to exercise more than 3 days a week in comparison with the control group at 1 year (*P*=.04).

Conclusions. A timely, specific, and inexpensive educational intervention was more successful at improving lifestyle and HDL-C than the control intervention. Admission to hospital of a family member with CVD is a clear opportunity, both motivational and educational, for reducing the individual risk of CVD.

Low Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes Mellitus: The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (J-PAD Study)

Presented by H. Ogawa, Japan

Background. Previous studies have investigated the effects of low-dose aspirin in the primary prevention of cardiovascular events, but not in patients with type 2 diabetes mellitus (DM2). The objective of the present study was to examine the efficacy of low doses of aspirin in the primary prevention of atherosclerosis in these patients.

Methods. Multicenter, prospective, randomized, open-label, blinded, study, whose size was determined according to the rate of events, and that was conducted between December 2002 and April 2008 in 163 institutions throughout Japan. In total, 2539 patients with DM2 and no history of atherosclerotic disease were included. The median follow-up period was 4.37 years. The patients were assigned to receive either low-dose aspirin (81 mg or 100 mg per day) or no aspirin. The primary outcome measure was defined as atherosclerotic events (fatal and nonfatal ischemic heart disease, fatal and nonfatal stroke) and peripheral artery disease. The secondary outcome measures were each individual primary outcome measure and combinations between them, as well as all-cause mortality.

Results. A total of 154 atherosclerotic events were reported: 68 in the aspirin group (13.6/1000 person-years) and 86 in the group without aspirin (17/1000 person-years) (hazard ratio [HR] = 0.80; 95% confidence interval [CI], 0.58-1.10; log-rank test, *P*=.16). The composite endpoint of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the group without aspirin (HR=0.10; 95% CI, 0.01-0.79; *P*=.0037). A total of 34 patients in the aspirin group and 38 patients in the group without aspirin died (all causes) (HR=0.90; 95% CI, 0.57-1.14; log-rank test, *P*=.67). The composite endpoint of hemorrhagic stroke and severe gastrointestinal bleeding showed no significant differences between the aspirin-treated group and the group without aspirin.

Conclusions. In this study of patients with DM2, a low dose of aspirin in primary prevention did not reduce the risk of cardiovascular events.

The study has already been published in the form of a full text article.[1]

Rosuvastatin for Preventing Vascular Events in Subjects With Elevated C-Reactive Protein: Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (The Jupiter Study)

Presented by P. Ridker, United States

Background. It is known that the increase in concentrations of C-reactive protein, a highly sensitive biomarker of inflammation, predicts cardiovascular events. Given that the statins reduce both highly sensitive C-reactive protein and cholesterol, our hypothesis was that individuals with high C-reactive protein levels but no hyperlipidemia might benefit from statin therapy.

Methods. A total of 17 802 nominally healthy men and women with LDL-C <130 mg/dL (3.4 mmol/L) and highly sensitive C-reactive protein ≥2 mg/L were randomized to receive rosuvastatin 20 mg/d or placebo. The primary outcome measure of the study was the appearance of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death.

Results. The study was terminated after a median follow-up of 1.9 (maximum 5) years. Rosuvastatin decreased LDL-C levels by 50% and C-reactive protein levels by 37%. The rates of the primary outcome measure were 0.77 and 1.36/100 person-years of follow-up in the rosuvastatin and placebo arms, respectively (rosuvastatin, HR=0.56; 95% CI, 0.46-0.69; *P*<.00001), with the corresponding rates of 0.17 and 0.37 for myocardial infarction (HR=0.46; 95% CI, 0.3-0.7; *P*=.0002), 0.18 and 0:34 for stroke (HR=0.52; 95% CI, 0.34-0.79; *P*=.002), 0.41 and 0.77 for revascularization or unstable angina (HR=0.53; 95% CI, 0.4-0.7; *P*<.00001), 0.45 and 0.85 for the composite outcome measure of myocardial infarction, cerebrovascular accident, or cardiovascular death (HR=0.53; 95% CI, 0.4-0.69; *P*<.00001), and 1 and 1.25 for all-cause mortality (HR=0.80; 95% CI, 0.67-0.97; *P*=.02). Consistent effects were observed in all subgroups assessed. There was no significant increase in myopathy or cancer in the rosuvastatin group, but the investigators did report a greater incidence of DM.

Conclusions. In this study of apparently healthy people, with no hyperlipidemia but high highly reactive C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

The study has already been published in the form of a full text article.[2]

Vitamin E and C in the Prevention of Cardiovascular Disease in Men: The Physicians' Health Study II (PHS)

Presented by M. Gaziano, United States

The present study was designed to assess whether long-term administration of vitamin C or vitamin E supplements reduces the risk of major cardiovascular events in men. The Physicians' Health Study II is a double-blind, placebo-controlled, randomized clinical trial of vitamins E and C that started in 1997 and continued until the programmed termination on August 31, 2007. It included 14 641 male physicians in the United States aged 50 years old or more, of whom 754 (5.1%) had already been diagnosed with cardiovascular disease at the time of randomization. The participants received individual supplements of 400 IU of vitamin E every other day and 500 mg of vitamin C per day. The primary outcome measure was defined as the composite of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, cardiovascular disease, and death).

Results. During a mean follow-up of 8 years, 1245 major cardiovascular events occurred. Compared to placebo, vitamin E did not have any impact on the incidence of major cardiovascular events (10.9 events/1000 person-years in both the active-treatment group and placebo; HR=1.01; 95% CI, 0.9-1.13; *P*=.86), or total cases of myocardial infarction (HR=0.90; 95% CI, 0.75-1.07; *P*=.22), total cases of stroke (HR=1.07; 95% CI, 0.89-1.29; *P*=.45), or cardiovascular death (HR=1.07; 95% CI, 0.9-1.28; *P*=.43). Likewise, there was no significant effect of vitamin C on major cardiovascular events (active-treatment group and placebo for vitamin E, 10.8 and 10.9 events/1000 person-years, respectively; HR=0.99; 95% CI, 0.89-1.11; P=.91) or total cases of myocardial infarction (HR=1.04; 95% CI, 0.87-1.24, *P*=.65), total cases of stroke (HR=0.89; 95% CI, 0.74-1.07; P=.21), or cardiovascular mortality (HR=1.02; 95% CI, 0.85-1.21; *P*=.86). Neither vitamin E (HR=1.07; 95% CI, 0.97-1.18; *P*=.15) nor vitamin C (HR=1.07; 95% CI, 0.97-1.18; *P*=.16) had a significant effect on mortality, but vitamin E was associated with increased risk of hemorrhagic stroke (HR=1.74; 95% CI, 1.04-2.91; *P*=.04).

Conclusions. In this large long-term study in male physicians, neither vitamin E nor vitamin C supplements reduced the risk of major cardiovascular events. These findings do not support the use of these supplements for prevention of cardiovascular disease

in middle-aged and elderly men.

The study has already been published in the form of a full text article.[3]

Randomized Comparison of Folic Acid Plus Vitamin B_{12} Versus Placebo for 7 Years in Survivors of Infarction: Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)

Presented by J.M. Armitage, United States

Background. In observational studies, levels of homocysteine in blood of 3-4 µmol/L are associated with decreases of 10% and 20% in the risk of coronary artery disease and stroke, respectively. Until now, no randomized study has provided convincing evidence that reducing homocysteine in blood with folic acid reduces the risk of cardiovascular events. Long-term randomized studies with folic acid are necessary to assess the risk-benefit ratio.

Methods. Between September 1998 and October 2001, 12 064 survivors of myocardial infarction from 88 hospitals in the United Kingdom were randomized to receive 2 mg of folic acid and 1 mg of vitamins daily or placebo.

Follow-up visits were at 2, 4, 8, and 12 months, and then every 6 months for a mean of 6.7 (1.5) years. In the group assigned to folic acid and vitamin B_{12}, homocysteine levels decreased by 3.9 µmol/L in 1 year and 3.6 µmol/L during the rest of the study period. The prespecified primary outcome measure was a composite of nonfatal myocardial infarction, coronary death, or coronary revascularization (major coronary event), any type of stroke, or any noncoronary revascularization.

Results. Events of the primary outcome measure occurred in 1537 (25.5%) of the patients assigned to folic acid and vitamin B_{12} versus 1492 (24.7%) assigned to placebo (HR=1.04; 95% CI, 0.97-1.12). Major cardiac events were reported in 20.4% versus 19.6% in each group; stroke in 4.5% versus 4.4%; and noncoronary revascularization in 3% versus 2.5%. No significant differences were observed in vascular mortality (9.5% vs 9%) or nonvascular mortality (6.8% vs 6.7%), or the overall incidence of cancer (11.2% vs 10.5%), or any specific cancer.

Conclusions. SEARCH is the largest trial to investigate the effects of treatment to reduce homocysteine. Although low levels of homocysteine of between 3 and 4 µmol/L were obtained for 6.7 years, there were no significant effects on the incidence vascular events of any type, cancer, or any other events. The results agree with those obtained previously in shorter studies with fewer patients. Widespread use of folic acid supplements (to avoid neural tube defects) by fortifying flour is safe, but it does not have any effect on vascular disease or cancer.

Randomized Comparison of Simvastatin 80 mg versus 20 mg Daily for 7 Years in Survivors of Infarction: Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)

Presented by R.E. Collins, United Kingdom

The second part of the same study aimed to analyze the effects of a more aggressive reduction in cholesterol in the same population. Previous studies have shown that statin therapy reduces the incidence of major vascular events by about one-fifth per 40 mg/dL decrease in LDL-C. Higher doses of statins produce larger decreases in vascular events, but large randomized comparisons with long-term follow-up of different doses are needed to reliably assess the risk-benefit ratio.

Methods. Between September 1998 and October 2001, 12 064 survivors of myocardial infarction (MI) from 88 hospitals in the United Kingdom were randomized to simvastatin 80 mg or 20 mg daily. There were 10 012 men and 2052 woman with a mean age of 64 (9) years. At randomization, 33% had undergone coronary revascularization, 7% had cerebrovascular disease, 11% had DM, and 42% were receiving treatment for hypertension. Assignment to the 80 mg daily group of simvastatin led to a decrease in LDL-C of 0.5 mmol/L at 2 months and 0.3 mmol/L at 5 years. The primary outcome measure was a major vascular event (MVE), defined as nonfatal myocardial infarction or coronary death, any type of stroke, or arterial revascularization of any type. During a median follow-up of 7 years, almost 3000 participants suffered a MVE (1500 nonfatal myocardial infarctions or coronary death; 500 strokes; 1000 revascularizations); 1300 developed cancer; and 2000 died (1000 of vascular causes and 1000 of nonvascular causes).

Results. There were no differences between groups in the incidence of MVEs on comparison of the high and low doses of simvastatin or on comparison of the folic acid + vitamin B_{12} group with placebo (P>.005 in both cases). Neither the high dose of simvastatin (compared to the low dose) nor folic acid + vitamin B_{12} (compared to placebo) were effective at reducing MVEs in patients who had suffered a recent myocardial infarction.

Likewise, there were no significant differences

between the individual outcome measures studied. The risk of myopathy in the high-dose simvastatin group was higher than in the lower-dose group (0.88% vs 0.05%; *P*<.05).

Conclusions. Unlike other studies with similar objectives, no additional value was found for high doses of simvastatin compared to lower doses.

ISCHEMIC HEART DISEASE

Drug-Eluting Stents or Bare-Metal Stents in Patients With Diabetes Mellitus: Results of the Massachusetts Data Analysis Registry (MASS-DAC)

Presented by L. Mauri, United States

Patients with DM are at high risk of restenosis, myocardial infarction, and cardiovascular death after placement of coronary stents. In addition, the long-term safety of drug-eluting stents (DES) compared to bare-metal stents (BMS) has not been extensively studied in diabetic patients. The present registry analyzes the results of a large series of consecutive patients with DM followed for 3 years after receiving DES and BMS with follow-up of 3 years from all the hospitals practicing interventional cardiology in the state of Massachusetts (United States).

Methods. From a state database to which hospitals are legally obliged to submit data, all adults with DM who underwent percutaneous coronary intervention with stenting between April 1, 2003 and September 30, 2004 in all the acute coronary units of nonfederal hospitals in Massachusetts were identified. According to the type of stent, the patients were classified as DES treated if all the stents were drug-eluting and treated with BMS if all the stents were of the conventional type. Patients treated with both types of stent were excluded from the primary analysis. The mortality rates were obtained from the statistical registries, and the rates of myocardial infarction and revascularization were taken from the state database, with the full 3-years of follow-up available for the entire cohort. The adjusted risk of death, myocardial infarction, and differences in revascularization (DES-BMS) were calculated first with a propensity score based on clinical information and information on the procedure, hospital stay, and insurance gathered on admission. In total 5051 patients had DM (29% of the population) treated with DES or BMS during the study. Patients with DM were more likely to receive DES than BMS (66.1% vs 33.9%; *P*<.001). The raw 3-year mortality was 14.4% with DES versus 22.2% with BMS (P<.001). Once adjusted 1:1 using the propensity score (1.476 DES:1.476 BMS), the adjusted risk of mortality, myocardial infarction, and revascularization of the target vessel at 3 years was 17.5% versus 20.7% (difference in risk, –3.2%; 95% CI, –6 to –0.4; *P*=.02), 13.8% versus 16.9% (–3%; 95% CI, –5.6 to 0.5; *P*=.02), and 18.4% versus 23.7% (–5.4%; 95% CI, –8.3 to –2.4; *P*<.001), respectively.

Conclusions. In a real-word population of diabetic patients with mandatory reporting and medium-term follow-up, DES were associated with a decrease in mortality, myocardial infarction, and rates of revascularization at long-term follow-up compared to BMS.

The study has already been published in the form of a full text article.[4]

Randomized Trial of Rivaroxaban, a Direct Oral Inhibitor of Factor Xa Versus Placebo in Patients With Acute Coronary Syndrome: The Anti-Xatherapy to Lower cardiovascular Events in Addition to Aspirin With or Without Thienopyridine in Subjects With Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 46 Trial (ATLAS ACS-TIMI 46 Trial)

Presented by M.C. Gibson, United States.

Rivaroxaban is a new direct oral inhibitor of factor Xa and has proved effective at preventing venous thromboembolism after major orthopedic surgery. The efficacy and safety of rivaroxaban after acute coronary syndromes (ACS) has yet to be assessed.

Methods. The ATLAS ACS-TIMI 46 trial is a phase II, international, randomized, double-blind, placebo-controlled dose-ranging study performed in post-ACS patients to assess the efficacy and safety of rivaroxaban in combination with aspirin (stratum 1) or aspirin-thienopyridine (stratum 2). Patients received rivaroxaban (total daily dose, 5, 10, 15, or 20 mg once or twice a day) or placebo, with 6 months follow-up.

Results. A total of 3491 patients (760 in stratum 1; 2731 in stratum 2) at 297 sites in 27 countries were randomized. The mean age was 57 years (range, 24-88 years); 77% were men, 19% had diabetes, and 21% had suffered previous MI. At the time of inclusion, 52% had suffered ST-elevation myocardial infarction and 63% had undergone percutaneous coronary intervention.

There were no differences in the primary outcome

measure (death, MI, stroke, severe ischemia) between the rivaroxaban group and placebo (HR=0.79; 95% CI, 0.60-1.05; *P*=.10). There was a lower incidence of death, MI, and stroke in the rivaroxaban group.

Conclusions. Rivaroxaban shows a reasonable efficacy compared to placebo in patients with ACS who are at greater risk of hemorrhage. The ATLAS TIMI 46 trial is the phase II study of a clinical trial aimed at identifying the effective and safe doses of rivaroxaban that will be used in the phase III trial.

Comparative and Randomized Study of Early or Late Invasive Approach in High-Risk Patients With nSTE-ACS: Main Results of the TIMing of intervention in Acute Coronary Syndrome Trial (TIMACS Trial)

Presented by S.R. Mehta, Canada

Randomized clinical trials have shown the benefit of an invasive management strategy in patients with nSTE-ACS. However, the optimum timing of the intervention in these patients has not been determined. This was a prospective, multicenter, international, randomized trial that compared early and late invasive strategies in high-risk patients with nSTE-ACS. The hypothesis is that an early invasive strategy would be superior to a late invasive strategy in reducing deaths, MI, or stroke.

Methods. Patients were included with signs and symptoms consistent with acute infarction or nSTEMI and 24 hours from the onset of these symptoms and with at least 2 of the following criteria: age ≥60 years, elevated troponin T or I or creatine kinase MB (CK-MB) isoenzyme, or ischemic changes in the ECG. An early invasive strategy was defined as coronary angiography as early as possible (and no later than 24 hours), followed by the revascularization intervention (PCI or surgery). A late invasive strategy was defined as coronary angiography after 36 hours, followed by revascularization, PCI, or surgery. The primary outcome measure was a composite of death, MI, or stroke at 6 months.

Results. There were no significant differences in the primary outcome measure (death, MI, stroke) between the 2 groups (HR=0.85; 95% CI, 0.68-1.06; *P*=.15), although differences were observed in the patients with highest risk (HR=0.65; 95% CI, 0.48-0.88; *P*=.005). There was a lower incidence of death, MI, or refractory ischemia in the group of early invasive strategy (*P*=.0002), due to a similar decrease in refractory ischemia (*P*<.0001), death (*P*=.81), and stroke (*P*=.74). The incidence of major hemorrhage was similar (*P*=.53).

Conclusions. No benefits were observed in the form of reduction of the primary outcome measure of the study in the strategy of early coronary revascularization in patients with high-risk nSTE-ACS. However, there was a potential benefit in patients with highest risk regarding a reduction in ischemia refractory to treatment.

Loading-Dose Titration of Clopidogrel According to Measurement of Platelet Reactivity in Order to Prevent Stent Thrombosis

Presented by F. Paganelli, France

Stent thrombosis is an important obstacle in percutaneous coronary revascularization. Inhibition of platelet reactivity has been associated with a decrease in thrombotic events in patients undergoing PCI. The objective of the study was to investigate the impact of an individualized loading dose of clopidogrel—set by monitoring platelet reactivity using the VASP index—on the rate of confirmed stent thrombosis (CST) in patients undergoing PCI.

Methods. Prospective and randomized multicenter study that included all patients undergoing PCI who had low response to clopidogrel after a 600 mg loading dose of clopidogrel. The control group included 214 patients and the VASP-guided group included 215 patients who received up to 3 additional loading doses of 600 mg clopidogrel to obtain a VASP index (50% before PCI). The primary outcome measure was rate of CTS at 1 month. The secondary outcome measures were the rate of major cardiovascular events (MACE) and bleeding.

Results. Despite receiving a 2400 mg loading dose of clopidogrel, 8% of the patients randomized to the VASP-guided group had a low response. The rate of CTS was significantly lower in the VASP-guided group than in the control group (0.5% vs 4.2%; *P*<.01). In total, 50% of the patients who had suffered stent thrombosis had received glycoprotein IIb/IIIa inhibitors at the time of the initial procedure. The rate of MACE was also significantly lower in the VASP-guided group than in the control group (0.5% vs 8.9%; *P*<.001). There were no differences in the hemorrhage rates (control group vs VASP-guided group, 2.8% vs 3.7%; *P*<.8).

Conclusions. The tailored loading doses of clopidogrel guided by monitoring of platelet reactivity decreased the rate of early CTS after PCI without increasing the risk of bleeding.

HEART FAILURE

Irbesartan in Patients With Heart Failure and Preserved Ejection Fraction: I-Preserve Study

Presented by B.M. Massie, United States

Approximately 50% of patients with heart failure have a left ventricular ejection fraction ≥45%, but it has not be shown that therapy improves the outcomes in these patients. In the present study, the effects of irbesartan were studied in patients with heart failure and preserved ejection fraction.

Methods. The study included 4128 patients aged at least 60 years old, with class II, III, or IV heart failure (according to the New York Heart Association classification) and an ejection fraction ≥45%. They were randomized to receive 300 mg of irbesartan per day or placebo. The primary outcome measure was a composite of all-cause mortality or hospitalization for cardiovascular causes (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke). The secondary objectives were the composite of death due to heart failure or hospitalization for heart failure, all-cause mortality and mortality due to cardiovascular causes, and quality of life.

Results. During a mean follow-up of 49.5 months, the primary outcome measure occurred in 742 patients in the irbesartan group and 763 patients in the placebo group. The rates of primary outcome measure events in the irbesartan group compared to placebo were 100.4 and 105.4/1000 patient years, respectively (HR=0.95; 95% CI, 0.86-1.05; *P*=.35). In general, the mortality rates were 52.6 and 52.3/1000 patient-years, respectively (HR=1.00; 95% CI, 0.88-1.14; *P*=.98). Hospitalization rates for cardiovascular causes that contributed to the primary outcome measure were 70.6 and 74.3/1000 patient-years, respectively (HR=0.95; 95% CI, 0.85-1.08; P=.44). There were no significant differences in the remaining prespecified outcome measures.

Conclusions. Irbesartan does not improve the outcomes of patients with heart failure and preserved left ventricular ejection fraction.

The study has already been published in the form of a full text article.[5]

Mid-Regional pro-Adrenomedullin (MRproADM) Versus BNP and NT-proBNP as a Prognostic Marker in Patients With Heart Failure: The BACH Study

Presented by S.D. Anker, Germany

Natriuretic peptides have a well-established prognostic value in acute heart failure (AHF). MRproADM is a marker of endothelial function and previous studies indicate that it is a clear prognostic factor in patients with AHF.

Methods. The international BACH study is a prospective international study of multiple serum biomarkers conducted in 15 centers and 1641 patients who presented to the emergency department with the primary symptom of dyspnea. The primary outcome measure was to test the superiority of MRproADM vs BNP for predicting mortality at 90 days in patients with heart failure. The secondary outcome measures included investigating the superiority of this marker compared to NT-proBNP and its prognostic value in patients with dyspnea. The physicians were blinded to the MRproADM levels. Two or 3 cardiologists established the reference diagnosis of AHF. The levels of the troponin (TnI or TnT) in the clinical laboratory were considered elevated if they were above the normal range.

Results. Of the 1641 patients, 568 (34.6%) were diagnosed with heart failure. Of these, 65 (11.4%) died in the first 90 days. The prognostic yield of MRproADM (73.1% correct) was greater than that of BNP (60.6%; *P*<.001) and NT-proBNP (63%; *P*<.001). These findings were confirmed in the overall study population of 1641 patients (130 deaths) and for the 477 patients with AHF who were admitted (all, *P*<.001), satisfying the primary and secondary prognostic outcome measures of the study. The HR comparing the second, third, and forth quartile of MRproADM with the first in the 1641 patients of the population with dyspnea were 7.4 (95% CI, 2.2-24.8; *P*=.001), 10.7 (3.3-35; *P*<.001) y 26.8 (9.5-85.1; *P*<.001), respectively. Troponin levels were available in 511 of the 568 patients with heart failure, and these were elevated in 107 (20.9%) of the patients. MRproADM significantly predicted 90-day mortality in the Cox analysis, independently of both BNP and NT-proBNP in the models with and without troponin.

Conclusions. MRproADM is superior to BNP and NT-proBNP, regardless of the troponin concentrations, for predicting 90-day mortality in patients with acute heart failure.

Effects of Subcutaneous Treatment With Interferon Beta-1b for 24 Weeks on Safety, Viral Clearance, and Clinical Prognosis in Patients With Chronic Viral Myocarditis: Beta-Interferon in Chronic Viral Cardiomyopathy (BICC Study)

Presented by H.P. Schultheiss, Germany

Thirty-one sites in 7 European countries participated in this randomized, double-blind, placebo-controlled,

multicenter, parallel group, phase II study that assessed the efficacy and safety of 2 doses of interferon beta-1b (IFNβ-1b) versus placebo in patients with biopsy-proven chronic viral cardiomyopathy (CVC).

Methods. Diagnosis of CVC for the target population was based on the presence of chronic heart failure and adenovirus, enterovirus, or parvovirus in the endomyocardial biopsy samples. In the 3 treatment groups, the patients received 2 different doses of IFNβ-1b or placebo, administered subcutaneously every 2 days for 24 weeks. The primary outcome measure was the presence of adenovirus, enterovirus, or decrease in parvovirus in endomyocardial biopsies taken 12 weeks (14 days) after ending treatment. For the parvovirus group, viral clearance or decrease in viral load was assessed by a quantitative method that defined a preset threshold. The secondary efficacy outcome measures were change in NYHA functional class, 6-minute walk distance, individual clinical symptoms, quality of life, left ventricular ejection fraction (LVEF) at rest and during exercise, echocardiographic findings, the inflammatory status in the endomyocardial biopsy, combined clinical outcome, pulmonary capillary pressure, and mean pulmonary artery pressure.

Results. In total, 368 patients were screened during selection and 143 were randomized to treatment; 131 patients completed the study. In comparison with placebo, elimination of the virus or reduction of the viral load was significantly greater in the IFNβ-1b groups compared to placebo (odds ratio [OR] = 2.33; *P*=-049), with no significant differences between the 2 interferon doses. Treatment with IFNβ-1b was associated with beneficial effects on the NYHA functional class (*P*=.013 at week 12 of follow-up), improvement in quality of life (total Minnesota score) (*P*=.032 at week 24 of follow-up) and the general assessment of the patient (at week 12 and week 24 of follow-up) (*P*=.039). There were no safety conerns in the group receiving active treatment.

Conclusions. The results show that treatment with IFNβ-1b leads to an effective viral clearance or decrease in viral load with favorable effects on quality of life, NYHA functional class, and the general assessment of the patient in patients with CVC.

Morbidity and Mortality After an Aerobic Training Program in Patients With Heart Failure: Results of the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION)

Presented by D Whellan, United States

Aerobic exercise in patients with heart failure improves symptoms, exercise tolerance, and quality of life. Guidelines for heart failure recommend exercise for stable outpatients. No studies have assessed the prognostic impact of standard practice of exercise on patients with heart failure. HF-ACTION investigated the hypothesis that aerobic exercise in patients with heart failure improves clinical outcomes.

Methods. HF-ACTION is a randomized, controlled, multicenter trial (1:1) that compared the usual care plus exercise with usual care alone in stable patients with LVEF ≤35% and NYHA functional class II-IV heart failure. The main exclusion criteria were regular exercise, use of cardiac devices that might interfere with the measurement of heart rate, and exercise testing results that indicated that exercise might not be safe. The intervention included 36 sessions of structured training (goal, 3 times per week). The intensity of the exercise was increased according to reserve heart rate and perceived rate of effort. Patients were provided with equipment to train at home and they were recommended to perform 5 sessions per week. The usual care group received the CAC/AHA recommendation of performing 30 minutes of moderate exercise most days a week, but they were given no additional instructions about exercise. Compliance was measured in both groups, and physical activity in the usual care group was recorded. The patients in the study were followed for at least 1 year. The primary outcome measure was the composite of all-cause mortality or hospitalization. The study was designed with 90% power for detecting an 11% reduction in the rate of events of the primary outcome measure at 2 years, taking into account loss to follow-up and treatment cross-overs. The secondary outcome measures included each of the components of the primary outcome measure, morbidity and mortality due to specific causes, measures of cardiopulmonary efficiency, quality of life, and costs.

Results. In total, 2331 patients were included between April 2003 and February 2007. The median age was 59 years, 28% were women, and 40% belonged to ethnic minorities. The mean LVEF was 25% and 51% of the patients had ischemic disease. Baseline treatments included angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (94%), beta-blockers (95%), and ICD or dual-chamber pacemakers in 45% of all patients and 53% of those with ischemic disease. The median follow-up period was 2.5 years. There were no differences in the incidence of mortality/hospitalization between the 2 groups (HR=0.93; 95% CI, 0.84-1.02; *P*=.13). Adjusting for other prognostic factors, there was a decrease in the exercise group (*P*=.03). Cardiovascular mortality and hospitalizations (*P*=.14) and the 6-minute walk

distance (*P*=.26) were similar, but peak oxygen uptake VO_2 was higher in the exercise group. Side effects were similar in the 2 groups.

Conclusions. Undertaking an exercise program is safe and effective for patients with systolic heart failure when added to optimal medical therapy.

Effect of an Aerobic Training Program on the Quality of Life of Patients With Heart Failure: Results of a Substudy of the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION)

Presented by K.E. Flynn, United States

Patients with heart failure have a lower exercise tolerance, resulting in a worse health-related quality of life. Performing exercise can improve physical performance, reduce symptoms, and improve health-related quality of life; but in previous studies, the effects of taking exercise on health-related quality of life have been inconsistent. The HF-ACTION study was designed to test the hypothesis that outcomes in patients with heart failure who take exercise are improved. One of the secondary objectives was to assess the effects of exercise on health-related quality of life.

Methods. HF-ACTION is a large, multicenter, randomized, controlled (1:1) trial conducted in clinically stable patients with LVEF ≤35% and NYHA class II-IV heart failure. Patients were randomized to normal care plus aerobic exercise (consisting of 3 months of supervised aerobic exercise followed by home exercise under instruction) or to the group of usual care alone. The main health-related quality of life outcome measure was the patient's state of health assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) completed by the patients themselves. The KCCQ was administered at baseline, and then at 3 month intervals during clinical visits for the first year and then every year for up to a maximum of 4 years. Group treatment effects were examined and the differences measured on the Global Summary Scale of the KCCQ and the main subscales (physical limitation, symptoms, social limitations, and health-related quality of life) were estimated using mixed linear models based on the intention-to-treat population.

Results. In total, 2331 patients were included. The median age was 59 years, and 28% were women. The mean LVEF was 25% and 51% of the patients had ischemic disease. The median follow-up period was approximately 2.5 years. The results of the KCCQ during follow-up were +5 points in the exercise group versus +2 points in the normal care group (P=.001). Clinical improvement was 53% in the exercise group vs 33% in the usual care group (*P*<.001).

Conclusions. In patients with heart failure caused by left ventricular systolic dysfunction, participation in an exercise program slightly improved their health status compared with the normal care group, and the improvement was apparent at an early stage, after 3 months.

ARRHYTHMIAS

Prospective, Randomized, Controlled Study of the Prognostic Impact of Home Measurement of INR: The Home INR Study (THINRS)

Presented by A.K. Jacobson, United States

Background. Anticoagulation with coumarin agents reduces thromboembolic complications in patients with atrial fibrillation and mechanical heart vales, but effective management is difficult and patients are often above or below the target range of INR. Currently, patients can use INR devices in their homes. As patients can check their levels more often, these devices may potentially improve clinical outcomes. The investigators assessed whether weekly measurement at home reduces the risk of stroke, major bleeding, or death compared with monthly measurements.

Methods. Patients treated with warfarin because they were carriers of mechanical heart valves or had atrial fibrillation were shown how to use the ITC ProTime® POC-INR measuring device, and their competence in recording these measurements was assessed after 2 to 4 weeks. Patients who were competent in using the device were randomized to a weekly test at home or a monthly measurement in the clinic. In a substudy, approximately 100 patients did 2 weekly tests at home, and a further 100 did monthly tests at home. The primary outcome measure was time to first event: stroke, major bleeding, or death. The sample size calculation was based on the assumption that the composite endpoint would be met in 5.5% in the clinical test group and 3.75% in the home-testing group. Secondary outcome measures included time in target range, myocardial infarction, thromboembolism not related to stroke, minor hemorrhages, patient satisfaction, competence and compliance with patient-self testing, quality of life related to anticoagulation, and cost-effectiveness.

Results. Of the 3745 individuals included in 28 medical centers in Virginia, 2922 (78%) were randomized. The indications for use of warfarin

were mechanical heart valves in 23% and atrial fibrillation in 83%. Follow-up lasted between 2 and 4.75 years, with 8730 patient-years of follow-up: 4495 patient-years in the home-testing group and 4235 patient-years in the clinic-testing group. The time to first event did not show any significant differences in the home-testing group (HR=0.875; 95% CI, 0.741-1.033; *P*=.11 in the log-rank test) for the primary outcome measure or for any of its components (stroke, major bleeding, and death). The time in target range was greater in the self-testing group (65.9% vs 62.2%; *P*<.001), as was patient satisfaction (47.7% vs 49.1%; *P*<.02; lower score indicates greater satisfaction).

Conclusions. Compared with monthly INR testing in the clinic, weekly testing of INR at home did not improve the composite outcome of stroke, major bleeding, or death as expected. However, this self testing does seem to improve the time in the target range and patient satisfaction with anticoagulant therapy. The results support the idea that patient self testing is an acceptable alternative to normal care, and may be preferable when patient access to the site is difficult.

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