Efficacy and Safety of Ximelagatran Compared With ACE-Inhibitors

**Background:** Nonvalvular atrial fibrillation (AF) affects women less often than men, but the risk of stroke is greater among women. Warfarin protects against stroke, but it is associated with bleeding, which occurs more often in women than in men. The oral direct thrombin inhibitor, ximelagatran (ExantaTM, AstraZeneca), is a potential alternative anti-coagulant to warfarin.

**Methods:** The SPORTIF III (open-label, n = 3410) and V (double-blind, n = 3922) noninferiority trials included 2257 women with AF and at least 1 stroke risk factor randomized to fixed-dose ximelagatran (36 mg twice daily). Adjusted-dose warfarin (target INR 2.0–3.0) or fixed-dose ximelagatran (36 mg twice daily) were randomized to target INR 2.0–3.0 or fixed-dose ximelagatran (36 mg twice daily). The primary endpoint was stroke (ischemic or hemorrhagic) and systemic embolism based on blinded assessment and intention-to-treat.

**Results:** During 11,233 patient-years (mean 19 months) exposure (3468 in women and 7765 in men) 72 primary events occurred in women and 112 in men. The mean INR with warfarin (2.5±0.7) was within target range for 67% of follow-up for both genders. In women, the primary event rate was 2.0%/year with warfarin and 2.2%/year with ximelagatran, relative risk reduction (RRR) 10% (95% CI: −33%, 31%; p = NS); in men, warfarin rates were 1.5%/year and 1.4%/year in the warfarin and ximelagatran groups (RRR 16%, 95% CI: −46%, 52%; p = NS). Compared to 1.5%/year and 1.4%/year among women (RRR 5%, 95% CI: −40%, 36%; p = NS). Combined rates of minor and major hemorrhages were greater among women (42.6%/year vs 36.9%/year on warfarin and 33.8%/year and 30.8%/year on ximelagatran; treatment difference in women p = 0.0001).

**Conclusion:** In both women and men with AF, oral ximelagatran without coagulation monitoring or dose adjustment was at least as effective as well-controlled warfarin for prevention of thromboembolism, and was associated with less bleeding.

Efficacy and Safety of Ximelagatran Compared With Well-Controlled Warfarin in Women and Men With Nonvalvular Atrial Fibrillation in the SPORTIF Trials

Jonathan L. Halperin, for the Executive Steering Committee on Behalf of the SPORTIF Investigators, Mount Sinai Medical Center, New York, NY, City Hospital, Lund, Sweden

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Effect of Fosinopril and Pravastatin on Carotid Intima-Media-Thickness in Microalbuminuric Subjects Without Hypertension or Hypercholesterolemia


**Background:** ACE-inhibitors and HMG-CoA reductase inhibitors have shown to reduce the progression of intima-media-thickness (IMT) in patient populations with hypertension or hypercholesterolemia. PREVEND-IT investigated the effect of fosinopril and pravastatin on IMT in non-hypertensive, non-hypercholesterolemic microalbuminuric subjects.

**Methods:** Prevention of REnal and Vascular ENdStage Disease Intervention Trial is a double-blind, randomized, placebo-controlled trial with a 2×2 factorial design (n = 864). Subjects were randomized to pravastatin 40 mg or matching placebo and to fosinopril 20 mg or matching placebo. Key entry criteria were persistent microalbuminuria (15–300 mg/24h), no hypertension (<160/100 mmHg) and no hypercholesterolemia (<308 mg/dl). Microalbuminuria was measured in 24-hour urine collection. The IMT was measured at the posterior wall of the common carotid artery using radiofrequency signal analysis obtained by M-mode ultra-sonography.

**Results:** Mean age was 50.8 ± 11.4 years and 65% was male. The table below shows the median IMT values found in this population suggests that microalbuminuria is an early risk indicator already present before detectable vascular changes.

**Conclusion:** Neither fosinopril nor pravastatin showed an effect on the carotid IMT after 4 years of follow-up. The normal IMT values found in this population suggests that microalbuminuria is an early risk indicator already present before detectable vascular changes.

Effect of treatment on IMT (mm), expressed as median (interquartile range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IMT before</th>
<th>IMT after</th>
<th>Delta IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.75 (0.64-0.86)</td>
<td>0.70 (0.65-0.84)</td>
<td>0.05 (-0.05 to 0.13)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>0.81 (0.68-0.93)</td>
<td>0.78 (0.68-0.89)</td>
<td>-0.03 (-0.05 to 0.11)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0.05 (-0.05 to 0.16)</td>
<td>0.05 (-0.04 to 0.13)</td>
<td>0.05 (-0.04 to 0.13)</td>
</tr>
</tbody>
</table>

Long-Term Bosentan Improves the Quality of Life of Patients With Pulmonary Arterial Hypertension

Adam J. Frost, The BREATHE-1 Study Group, Baylor College of Medicine and the Methodist Hospital, Houston, TX

**Background:** Bosentan is an oral endothelin receptor antagonist that improves hemodynamics and delays the time to clinical worsening in patients with pulmonary arterial hypertension (PAH). In the BREATHE-1 study, the effect of long-term bosentan treatment on the well being of PAH patients was investigated.

**Methods:** 213 patients with PAH (primary or associated with scleroderma) in WHO functional class III or IV were enrolled in a double-blind, placebo-controlled study for 16 weeks (2:1 bosentan:placebo). Of these patients, 48 (35 bosentan: 13 placebo) continued double-blind study medication for up to 28 weeks (median exposure 26.9 weeks for bosentan, 26.3 weeks for placebo). Patients received bosentan (62.5 mg bid for 4 weeks then 125 or 250 mg bid) or placebo. Efficacy endpoints included the 6-minute walk distance, Borg dyspnea index and WHO functional class.

**Results:** Bosentan significantly improved the 6-minute walk-distance at Week 16 (+36 ± 6 m, mean ± sem) compared to placebo (+8 ± 12 m), (p < 0.001, n = 213) and the improvement was maintained for up to 28 weeks (bosentan: +43 ± 14 m; placebo: +6 ± 21 m, n = 48). In parallel, the Borg dyspnea index was decreased with bosentan and increased with placebo resulting in a mean treatment effect of -0.6 (CI: [−1.2−0.1]) at week 16 (p = 0.05, n = 213) which was maintained (−0.8; CI: [−2.0−0.3]; n = 48) for up to 28 weeks. At Week 16, more patients on bosentan than on placebo showed an improvement in WHO functional class (42.4% versus 30.4%, p = 0.04, n = 213). In the 48 patients studied up to week 28, there was no significant difference in percentage of patients with improvement over baseline in WHO class between the bosentan and placebo groups.

**Conclusion:** Bosentan reduces cardiovascular events to a greater extent in patients with albumin excretion above 50 mg/24h.
Long-Term Secondary Prevention With Folic Acid: No Effects on Clinical Outcomes (the GOES Extension Study)

A. Liang, G. H. Reynierse-Buitenwerf, A. H. Zwijnderman, J. W. Jukema, D. J. van Veldhuijzen, Oosterschelde Hospital, Goes, The Netherlands

Purpose: Folic acid has favourable effects on vascular endothelium and lowers plasma homocysteine levels. In addition, homocysteine appears to be an independent risk factor for atherosclerotic disease. However, the value of folic acid in secondary prevention had seldom been tested. Two yr folic acid treatment in the randomized GOES study showed no reduction in clinical endpoints despite a 18% homocysteine reduction in patients on folic acid. Suggested was that the follow up could have been too short, therefore the study was extended with another 18 months Tx. Here we report results of the extended Goes trial, an open-label trial with folic acid 0.5 mg per day in a patient population with stable coronary artery disease (CAD).

Methods: 593 Patients were included in this study; 300 were randomized to folic acid and 293 served as controls. Mean follow-up time was 42 months. At baseline all patients had been on statin therapy for a mean of 3.2 years.

Results: In patients treated with folic acid plasma homocysteine levels decreased with 18% from 12.0 ± 4.8 to 9.4 ± 3.5 µmol/L, while these levels remained unaffected in the control group (p <0.001 between groups). The primary endpoint (all-cause mortality and a composite of vascular events) was encountered in 75 (25.0%) patients in the folic acid control group (p <0.001 between groups). The primary endpoint (all-cause mortality and a composite of vascular events) was encountered in 75 (25.0%) patients in the folic acid control group (p <0.001 between groups). The primary endpoint (all-cause mortality and a composite of vascular events) was encountered in 75 (25.0%) patients in the folic acid control group (p <0.001 between groups). The primary endpoint (all-cause mortality and a composite of vascular events) was encountered in 75 (25.0%) patients in the folic acid control group (p <0.001 between groups).

Conclusions: Within 3.5 years folic acid does not seem to reduce clinical endpoints in patients with stable CAD while on statin treatment. Homocysteine might therefore merely be a marker of disease than a causal risk factor. Thus, until more trials will become available, levels of creatinine clearance, and homocysteine.

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Coronary Lumen Change is Determined Primarily by Adventitial Remodeling Rather Than Plaque Change During Therapy

David T. Linker, G. Greg Brown, University of Washington, Seattle, WA

Background: Remodeling of coronary arteries has been demonstrated during plaque regression, but the contribution to lumen change is unclear.

Methods: Intracoronary ultrasound automated pull-backs were recorded on S-VHS tape both before and after twelve months of lipid-lowering therapy in a target coronary artery in 18 subjects with known coronary artery disease. The pullbacks were digitized and calibrated, and identical segments with plaque in the target artery were identified on the pre- and post-therapy images. The lumen and adventitia-media borders were manually traced on all images in the segment that allowed image interpretation, with the longitudinal position noted. The plaque and adventitial volumes were calculated by a numerical integration of the area of the over the longitudinal length. The mean plaque adventitial, and lumen areas in sq. mm were calculated based on plaque and adventitial volume and segment length.

Results: The change in mean lumen area was poorly correlated with the change in mean plaque area (R = 0.903, p <0.001, see figure below). The relationship was Change in mean lumen area = 0.712 x Change in mean adventitial area + 0.347 mm². The changes in lumen area after one year of lipid-lowering therapy are better correlated with adventitial change than with plaque change, indicating that arterial remodeling is an important determinant of lumen change.

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ORAL CONTRIBUTIONS
Atherosclerotic Plaque, Inflammation, and Oxidative Stress: Clinical Studies

Tuesday, March 09, 2004, 8:30 a.m.-10:00 a.m.
Morial Convention Center, Room 265

Ruptured Diabetic Atherosclerotic Plaques Have More Inflammation and Neovascularization Than Ruptured Plaques From Patients Without Diabetes

K. Raman Purushothaman, William N. O’Connor, Dario Echeverri, Chikezie Amadi, Juan J. Badimon, Valentin Fuster, Pedro R. Moreno, Mount Sinai Medical Center, New York, NY, University of Kentucky, Lexington, KY

Background: Plaque rupture may be asymptomatic or precipitate acute thrombotic events, and patients with diabetes mellitus (DM) are at higher risk for acute events than patients without DM. To evaluate if this difference is related to plaque composition, we quantified inflammation and neovascularization in ruptured aortic plaques from patients with/without DM.

Methods: Neovessels and macrophages/T cells were identified by CD34 (blue) and CD68/CD3 (red) bicolor immunohistochemistry (Figure) in 41 DM ruptured and compared to 34 non-DM ruptured plaques.

Results: See table.

Conclusion: Ruptured plaques from DM have increased inflammation and neovascularization supporting plaque composition as a contributor for the increased incidence of atherothrombotic complications among DM population.

Circulating Endothelial Progenitor Cells Predict Coronary Artery Disease Severity

Geoffrey A. Kuzn, Grace Liang, Florim Cuculoski, David Gregg, Korkut Vata, Linda Shaw, Pascal Goldschmidt-Clermont, Chunming Dong, Doris Taylor, Eric Peterson, Duke University, Durham, NC

Background: Circulating endothelial progenitor cell (EPC) counts are hypothesized to play an important role in preventing atherosclerosis. EPC counts have been found to be inversely related to traditional coronary artery disease (CAD) risk factors, yet their association to CAD severity remains unknown.

Methods: We measured EPC counts by quantitative cell culture in 122 patients undergoing diagnostic cardiac catheterization. The association between patients’ EPC count and the presence of multi-vessel CAD and of traditional cardiac risk factors was assessed using logistic regression analysis.

Results: The median age of the study population was 50 years old; 70% were male, and the median NYHA class was II. The study population had a mean of 14 ± 11 cardiovascular risk factors. The mean EPC count was 108 ± 42 per ml. EPC count was inversely related to traditional CAD risk factors (p <0.05 for each risk factor). In a logistic regression analysis, EPC count inversely predicted the presence of multi-vessel CAD (Odds Ratio 0.94, 95% CI 0.89-1.00, p = 0.02) and of traditional CAD risk factors (Odds Ratio 0.94, 95% CI 0.89-1.00, p = 0.02).