Effects of early treatment withzofenoprilin male and female patients with acute myocardial infarction: gender analysis of the SMILE OVERALL project

C. Borghi[1], F. Franconi[2], E. Ambrosioni[1], S. Omboni[3], G. Reggiardo[4], S. Bacchelli[1], D. Degli Esposti[1], D. Zava[5], A. Casini[6] on behalf of the SMILE Working project

[1]Unit of Internal Medicine, Policlinico S. Orsola, University of Bologna, Bologna; [2]Farmacologia Cellulare e Molecolare, Facoltà di Farmacia dell'Università di Sassari; [3]Clinical Research Unit, Italian Institute of Telemedicine, Varese, Italy; [4]Mediservice, Agrate Brianza, Milano; [5]Istituto Lusofarmaco d'Italia, Peschiera Borromeo, Milano, Italy; [6]Menarini Industrie Farmaceutiche Riunite, Firenze, Italy.

Background: the renin angiotensin aldosterone system exhibits a sexual dimorphism, which can explain at least some of the gender differences in the prevalence of cardiovascular and kidney diseases and in the response to ACE-inhibitors (ACEIs) (Maric-Bilkan C et al. Gend Med 2012). However, clinical trials with ACEIs only occasionally and never systematically analyzed the results under such a perspective. The SMILE studies individually proved the prognostic benefit of zofenopril vs. placebo or other ACEIs in patients with acute myocardial infarction (AMI). In order to study whether the zofenopril effect is influenced by gender, a retrospective pooled analysis of the four SMILE studies was done separately for males and females.

Methods: the four phase IIIb, double-blind, parallel-group SMILE studies, compared the safety and efficacy of early administration of zofenopril 30-60 mg/day with that of placebo (SMILE-1 and 3), lisinopril 5-10 mg/day (SMILE-2) or ramipril 10 mg/day (SMILE-4) in 3,630 patients with AMI. Treatment was continued for 6 to 48 weeks. This pooled analysis separately compared treatment efficacy in 2,733 males and 897 females. The primary study endpoint of this retrospective analysis was the 1-year combined occurrence of death or hospitalization for CV causes.

Results: women were older than men (66±10 vs. 60±11 years), had a higher prevalence of diabetes (30% vs. 26%) and were less frequently submitted to a reperfusion therapy (thrombolysis: 40% vs. 47% men; percutaneous transluminal coronary angioplasty: 3% vs. 7%). The risk of a major CV event was significantly larger for women than for men (26% vs. 19%, $p<0.0001$). However, in either males or females zofenopril treatment was associated with a significantly ($p<0.001$) lower rate of 1-year cardiovascular morbidity and mortality (13% and 21%) as compared to placebo (27% and 36%) or other ACEIs (23% and 25%). The rate of drug related adverse events expressed as the number of adverse events divided by the person-time-at-risk throughout the observation period was significantly lower under zofenopril than under the other ACEIs for both males (34% vs. 43%, $p=0.084$) and females (24% vs. 60%, $p<0.001$).

Conclusions: zofenopril is equally effective and safe in men and women following an AMI. As compared to placebo and other ACEIs, zofenopril shows a more favorable long-term cardioprotective effect and is associated with a lower risk of drug-related adverse events.