Session report to Session 1.1: Gender in Clinical Research and Pharmacology

### Chairs
Vera Regitz-Zagrosek (Germany) and Flavia Franconi (Italy)

### Active participants
Robert Agabio (Italy), Renata Borotlus (Italy), Jaan Eha (Estonia), Maurizio Gallieni (Italy), Eva Gerdts (Norway), Alexandra Kautzky-Willer (Austria), Angela Maas (The Netherlands), Maria Grazia Modena (Italy), Karen Nieber (Germany), Nadia Carolina Oprandi (Italy), Cecilia Politi (Italy), Alessandra Protti (Italy), Karin Schenck-Gustafsson (Sweden), Giuseppe Seghieri (Italy)

Rapporteur: Sabine Oertelt-Prigione (Germany)

### Contribution of partners - fields where reliable knowledge on gender medicine already exists.

First, cardiovascular diseases were discussed. Angela Maas (Radboud University Medical Center, The Netherlands) and Jaan Eha (Tartu University Hospital, Estonia) described the relevance of acute coronary syndromes in women and men and its treatment. Maas pointed out the relevance of cardi-oncology and of female specific risk factors, mentioning the recently released guidelines for the prevention of stroke in women, which also reinforce the role of female-specific risk factors. Eha mentioned compliance differences in women and men, the lack of individualized therapy and less aggressive prescription patterns in women. Vera Regitz-Zagrosek included a comment on the relevant role of non-obstructive coronary artery disease in women and on the significant early mortality of young women after coronary artery bypass surgery. Maria Grazia Modena (University of Modena, Italy) focused on hypertension, which represents a greater risk factor for women than men, and the fact that regression of myocardial hypertrophy under treatment may differ in women and men. She also pointed out that the standard values for blood tests and limits of normality in echocardiography studies are not always appropriately defined for the female gender. Robert Agabio (University of Cagliari, Italy) gave details on Alcohol Use Disorder, which is more prevalent in men than in women, although women suffer serious negative consequences of alcohol consumption earlier and to a greater degree than men and feature specific alcohol-related problems. However, the majority of medications for Alcohol Use Disorder have been tested in an insufficient number of women to establish effectiveness and safety of these medications. Eva Gerdts (University of Bergen, Norway) focused on diastolic hearth failure, which is prominent in 10 % to 20 % of the European population above 70 years. There are large gender differences in pathophysiology, outcomes and treatment which are still unexplained. Risk factor association also depends on gender. Gender specific approaches are needed for the adequate treatment of this condition. Cecilia Politi (Ospedale F. Veneziaile, Italy) commented on the female specific risk factors in atrial fibrillation and also mentioned the recent guidelines for the prevention of stroke in women as a best practice example. Alexandra Kautzky-Willer (Medical University of Vienna, Austria) and Cecilia Politi (Ospedale F. Veneziaile, Italy) focused on the role of diabetes in women and men. They pointed out pointed out that the condition is particularly harmful for women increasing their risk of cardiovascular diseases and nephropathy more dramatically than in men. Treatment may differ in women and men and thereby patient satisfaction. Regional differences are also relevant; in southern Italy, for example, regular insulin is prescribed only in 4.1 % of women vs. 9.7 % of men with diabetes. It is also now being accepted that environment, maternal and paternal factors can affect diabetes in the offspring in a sex specific way. Following, nephrology was discussed. Maurizio Gallieni (Ospedale San Carlo Borromeo, Italy) discussed chronic kidney disease which has higher prevalence in women than in men. Chronic kidney disease progression to end stage renal disease, glomerular diseases and genetic kidney diseases differ in women and men. Most relevantly, he pointed out how many other diseases that display gender-dependent specificities, such as osteoporosis.
or cancer or autoimmune diseases interact with the kidney and urged for co-operations among these specialties. Organ transplantation and allocation of living kidney donations is different between the sexes with a preference towards men. The same is true in heart transplantation (VRZ): males receive 82% of organs, even though women coming to transplant centers may be in a more advanced stage. Unbalanced organ allocation occurs although the causing cardiovascular diseases have the same age dependent prevalence in women and men.

**Renata Bortolus** (Verona University Hospital, Italy) focused on the risk of women being undertreated during pregnancy and on the need to implement available best practices especially in pregnancy associated problems. An experience of a large trial in this area was presented.

The discussion on significant sex and gender differences in pharmacology was led by **Flavia Franconi**. It was explained how differences in drug absorption and duration have been reported for a number of drugs. Differences in oral bioavailability are most important and caused by sex differences in the activity of major gastric and hepatic enzymes. A very good example on the relevance of sex in pharmacogenetics is the recent recommendation by the FDA to reduce the dosage of the sleeping pill zolpidem for women but not for men. There are a number of sex differences in pharmacodynamics. Gender differences in torsades-de-pointes and QT prolongation incidence is the most dramatic example of a gender-based pharmacodynamic difference. The role of sex differences in receptors and transporters has, however, been largely un-characterized. Virtually nothing is known about sex differences in the organic anion transporters and the research on P-glycoprotein is inconclusive.

**Karin Schenck-Gustafsson** (Karolinska Institute, Sweden) reported on a new Swedish database that gives physicians an indication when they need to modify the dose of a drug according to sex or pregnancy state ([www.janusinfo.se/genus](http://www.janusinfo.se/genus)).

### Best practice examples

- The use of administrative data sets to study gender differences on stroke and diabetes, as explained by **Giuseppe Seghieri** (Agenzia Regionale Sanità Toscana, Italy) using data from the regional health agency in Tiscali, Italy (2006-2012). Health surveys of the total Austrian population (PNAS 2013, BMC Public Health 2012).
- Analyzing gender in large epidemiologic cohort studies and Hamburg City Health also belong to this group (**Renate Schnabel**)
- The Institute for Gender Medicine at Berlin Charité, Karolinska Institute, Nijmegen, Radboud University, the Medical University of Vienna and the University of Innsbruck belong to the examples of institutionalization of the area to offer outlets for targeted research.
- Re-analysis the old clinical studies with a gender approach has been done for tryptans by **Flavia Franconi (University of Sassari)** (in press on Neurol Sci)
- Systematic reviews about the efficacy and the safety profiles of drugs in both sexes
- Use of available drug registers at regional, national or international levels to collect information with a gender perspective
- The program “Early treatment for Women with Alcohol Addiction (EWA)” of the Karolinska Hospital (Sweden), a woman-only program specifically developed to meet a broad spectrum of problems affecting women, constitutes an example of the best practice in the field of medical treatment of women with Alcohol Use Disorder.
- Gender aspects have been introduced in some **Guidelines**: the prevention of CVD and stroke (AHA) and the management of CVD in pregnancy (ESC).
- **Calls for grant proposals** with a gender focus are of major importance for the development field. A very good example is to call on information communication in gender medicine from North Rhine Westphalia.
- Also **scientific journals** play a role. For example, the Italian scientific society of hospital internal medicine has section on gender in their journal.
Additional approaches

More studies, lectures, network involvement of scientific societies. During the planning of the workshop it is very important to include, among others, active researchers and journal editors, funding agencies, insurance companies, medical societies, guidelines committees. A number of relevant addresses for stakeholders to involve in the workshop have also been mentioned, such as, for example, representatives of ministry of Health or Pair Opportunities of European countries as well as Industry and Funding Agencies, The Dutch alliance Gender & Healthcare, the Hague, Netherlands, Radboud Reshape Innovation Center (radboudreshapecenter.com), Nijmegen or the Netherlands Scientific institute for quality of healthcare (http://www.iqhealthcare.nl/en).

Implications for WS planning

- **Topics**: see contribution of partners
- **Special audiences to be invited**: journalists and journal editors. A representative list for Europe will be drafted
- **Specific strategies for communication**: write position paper, reviews in scientific journals, suggestions for guidelines.
- **Satisfy specific needs of roadmap (discussion ongoing)**
- **Date and location**: Berlin, early December 2014
- **Chairs**: Vera Regitz-Zagrosek, Flavia Franconi