Session 1.1.: Clinical research and pharmacology

In which fields does reliable knowledge in gender medicine exist? – Suggestions from discussants

- Cardiovascular: Coronary artery disease, Coronary Surgery, Hypertension, Heart failure, Atrial fibrillation, Normal values!
- Diabetes
- Nephrology,
- Organ transplantation, kidney and heart TX
- Gastrointestinal disease, heptalogy, pulmonology
- Autoimmune diseases,
- Osteoporosis
- Mental health, Alcohol Use Disorder (AUD)

Pregnancy associated diseases

(not suggested: cancer, musculoskeletal),

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Treatment acute coronary syndrome (ACS): clinical differences in women and men expected


Focus on female specific risk factors (pregnancy disorders, early menopause) and future CVD risk
Non-obstructive coronary artery disease in women and men

More frequent in men: localized stenosis

More frequent in women: non-obstructive CAD, increased wall thickness, microangiopathy

Adequate guidelines for diagnosis and therapy

No guidelines for diagnostics and therapy

Mering G, Circ 2004; Bugiardini R, Merz NB JAMA 2005
Higher Early mortality of young women after coronary artery bypass surgery

Mortality of women versus men

Sex specific risk predictors

N=17528

VRZ, JACC, Clin Res Card 2012
Hypertension and normal values

MG Modena, Modena, Italy

Hypertension, LV morphology and hypertrophy regression may differ in hypertensive women and men (matched by age and BP level) under treatment on drugs with evidence of LVH regression property (ACE-I, AT blockers)

The standard values of blood tests and the limits of normality are not always distinguished by gender; the referral values that are used to define CV risk factors are those mainly standardized in the male population.
10-20% of European population above 70 years have diastolic heart failure (HFpEF). Despite large studies in HFpEF, pathophysiology and treatment remains unclear.

HFpEF is particularly common among elderly women and associated with hypertension, atrial fibrillation and obesity.

Several factors may predispose female heart to development of HFpEF.

A gender specific approach is needed to advance pathophysiological understanding, prevention and treatment of HFpEF.
Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association


on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research

Results—We provide current evidence, research gaps, and recommendations on risk of stroke related to preeclampsia, oral contraceptives, menopause, and hormone replacement, as well as those risk factors more common in women, such as obesity/metabolic syndrome, atrial fibrillation, and migraine with aura.

Conclusions—To more accurately reflect the risk of stroke in women across the lifespan, as well as the clear gaps in current risk scores, we believe a female-specific stroke risk score is warranted. (Stroke. 2014;45:000-000.)
Diabetes

Alexandra Kautzky-Willer, Wien, AT;

- Overweight/obesity, the metabolic syndrome and type 2 diabetes are increasing as well as related micro- and macrovascular complications.
- Environment and maternal and paternal factors can affect health of offspring in a sex-specific way (sex-specific fetal programming- session 1.3.).

Cecilia POLITI, Isernia; IT:

- FADOI-DIAMOND Study
- in the Southern Italy, the regular Human Insulin is prescribed only in the 4.1% of women vs 9.7% of men (p=0.006). Male patients are more satisfied with their management of the disease.
Maurizio Gallieni, Milano, It:

Chronic kidney disease (CKD) with GFR < 60 ml min has a high prevalence (8 to 13 %) and it is a major clinical issue

- Many clinical issues are affected by gender:
  - Chronic kidney disease and progression to end stage renal disease
  - Glomerular diseases (e.g. Lupus)
  - Genetic diseases (APKD, Alport, Fabry, …)

- A deeper understanding of gender differences in renal diseases and their impact on diagnosis, prevention and management of CKD is clinically and socially important.
Organ transplantation, kidney and heart

Gender imbalance in living donor kidney transplants:

- Donors
- Married donors

% of patients

Kayler et al. Transplantation 2002; 73:248-52
Males receive 82% of organs, even though women presenting at the TX center had more severe disease.
Gastrointestinal diseases

- Maria G Modena

Gastrointestinal diseases: the most common disorders for which women seek medical attention

- Peptic ulcer: > in women than in men: extensive use od non-steroidal antiinflammatory drugs

- Irritable bowel syndrome: at least twice as many women as men; sex difference: gastrointestinal transit times. Sex specific treatment based on the different response to %-HT3R antagonists (alosetron)

- Inflammatory bowel disease: female preponderance of Crohn’s disease

- Colorectal cancer: after age 70, colon cancer is more of a risk to women than breast cancer; ratial differences

- Gallstones
Autoimmune diseases

- **MG Modena**
- **Autoimmune diseases**
  - Women generate robust proinflammatory environment after challenge with an infectious agent or antigen
  - > antibody production and > cell-mediated immunity after immunisation
  - Sex hormones modulate the immune response
- **Thyroid diseases** (Hashimoto's thyroiditis and Graves disease)
  - Autoimmune hypothyroidism
  - Thyroid nodules
  - > risk of IFNα-induced thyroid dysfunction
- **Rheumatologic diseases**
  - Rheumatoid arthritis (75% women): Aggressive in women, worse long term prognosis
  - 20%: RA + Sjogren syndrome + high risk of lymphoma
  - Systemic LES (F:M=9:1)
Diseases that are more prevalent or manifest differently in women

- **Lung diseases**
  - Less cancer, more death; higher susceptibility to tobacco carcinogenesis and COPD
  - Asthma: throughout childhood, girls are more affected than boys
  - Late onset asthma is largely confined to women, usually starting around menopause, and > risk by HRT

- **Osteoporosis**
  - 75-80% of affected individuals are women
  - Preventable: ERT/HRT

- **Urologic and kidney diseases**
  - Urinary tract infections
  - Interstitial cystitis
  - Urinary incontinence
Alcohol Use Disorder (AUD) and mental health

Roberta Agabio, Cagliari, It:

AUD:
More prevalent in men than in women (2:1).
Women develop consequences earlier and to a greater degree than men.
Women feature specific alcohol-related problems (e.g. fetal alcohol syndrome)

Mental health:
major depression, seasonal affective disorder, suicide attempts, eating disorders, phobias, generalized anxiety and panic disorder, and somatization are more prevalent in women
Pregnancy associated problems

- Guidelines: VRZ: European GL on CVD in pregnancy
- Existing registries: Heart Failure Association of ESC, EORP, Dutch registries,
- Ongoing studies, Renata Bortolus, IT

“Randomized clinical trial to evaluate the efficacy of higher dose of folic acid to prevent the occurrence of congenital malformations”
ITALY
Pharmacology - where do we need gendered approaches?

Pharmakokinetics
With regard to pharmakokinetics, differences in absorption rate and duration have been reported for several drugs, but generally lack to have major clinical relevance. Differences in oral bioavailability, however, seem to be more important and are usually caused by sex differences in the activity of major intestinal and hepatic metabolic enzymes.

Consequence:
FDA guideline recommends that sponsors conduct pharmakokinetic studies in both men and women to ensure accurate dosing in the clinical trials.
Example: Men metabolized the sleeping pill zolpidem (Intermezzo®) faster than women. Ultimately the FDA approved a 3.5 milligram pill for men, and a 1.75 milligram pill for women.
Pharmacology - where do we need gendered approaches?

**Pharmakodynamics**

Females have a 1.5–1.7-fold greater risk of developing an adverse drug reaction than male patients. There are a few examples in the literature of sex-dependent differences in pharmacodynamics:

- The gender difference in torsades de pointes and QT prolongation is the most dramatic example of a gender-based pharmacodynamic difference.
- Premenopausal females responded better to the SSRI, and males responded better to the tricyclic antidepressiva (TCA). Postmenopausal females had similar rates of responses to both the SSRI and TCA.
- The role of sex differences in receptors and transporters has been largely uncharacterized. Virtually nothing is known about sex differences in the organic anion, transporters, and the research on P-glycoprotein is contradictory.
Pharmacology - where do we need gendered approaches?

**Sex differences in the effects of digitalis**

1997: Digitalis-Study – Improvement of morbidity in HF by digitalis, no effect on mortality.

2002: First sex-specific analysis shows over-mortality in women with digitalis

Rathore et al, NEJM 347:1403, 2002

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Cost and prescription of daily drug doses in women and men
"Sex and gender differences in drug utilization"
Knowledge bank (also text in English)

www.janusinfo/genus

1. Systematic analyses of all data bases linked to...
   300 drugs (recommended in guidelines)

2. "Gender button"
   A support for electronic prescriptions direct in the patients electronic charts for support of MD’s prescription

Initiative from Centre for Gender Medicine, Karolinska Institutet, Stockholm
Stockholm County Council
Swedish Government (via SALAR)
Collaboration with FDA and Swedish MPA
1.1 Best practice

- Use of administrative datasets to study gender differences in stroke and diabetes. Data from Regional Health Agency (2006-2012), Tuscany, Italy
- Analysing gender effects in large epidemiological cohorts
- Studies in women, or focussed on gender (BEFRI)
- Institutes for Gender medicine at Berlin, Charite, Karolinska at Maastricht, Nimwegen, Radboud University
- **Guidelines**: prevention of stroke in women
- Prevention of CVD in women (Mosca)
- Management of CVD in pregnancy (VRZ; ESC)
- **Grants calls** with a gender focus: Information, communication and gender medicine (considering gender in device construction, Germany)
- FADOI (Italian scientific Society of hospital internal medicine, has a section of gender in the journal (Italian Journal of Internal Medicine)
1.1. Additional approaches

- Which additional approaches should be discussed?
  - More studies, lectures, networking, patient organisations, implementation in medical education
  - Involvement of scientific societies at the European and National levels
Whom to invite to WS, where and when

- Active researchers (50 %)
- Journal editors
- Funding organization representatives
  - Insurance companies?
  - Medical society representatives?
  - Guideline groups?
- Berlin
- December 2014 – February 2015

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Session 1.1.: How to achieve needs

Whom should we convince in your country? Which medical societies to discuss with? What is the position of industry and funding agencies?

- Suggestions for persons and societies: ……
- ….political representatives of ministry of Health or Pair Opportunities of European countries as well as Industry and Funding Agencies. …it is effectless to discuss to main Medical Societies
- The Dutch alliance Gender & Healthcare, the Hague, Netherlands
- Radboud Reshape innovationcenter radboudreshapecenter.com, Nijmegen the Netherlands

- Suggestions for workshop co-chairs: Flavia Franconi

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