Gender and Cardiovascular Research: the EuroHeart Project

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EUGenMed Kick-off Conference
Bruxelles
April 7th, 2013
Gender and Cardiovascular Diseases

Gender differences in the clinical presentation of cardiovascular diseases have been demonstrated and some therapeutic options may not be equally effective and safe in men and women.

Furthermore, sex differences in pharmacokinetics, pharmacodynamics and physiology may contribute to a different response to cardiovascular drugs in women when compared with men.

Accordingly, preventive and therapeutical interventions should be tested in populations that fairly represent the gender distribution for each specific clinical condition or group at risk.
Women, for many years, have been under-represented in randomized clinical trials.

The majority of therapeutic interventions were tested for safety and efficacy in male populations.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Enr. pts</th>
<th>Females %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-1</td>
<td>11 711</td>
<td>25</td>
<td>Lancet 1986;1:397-402</td>
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<td>GISSI-2</td>
<td>12 490</td>
<td>20</td>
<td>Lancet 1990;336:65-71</td>
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<td>18 023</td>
<td>22</td>
<td>Lancet 1994;343:1115-22</td>
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<td>4S</td>
<td>4 444</td>
<td>19</td>
<td>Lancet 1994;334:1383-89</td>
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<td>ISIS-4</td>
<td>58 050</td>
<td>26</td>
<td>Lancet 1995;345:669-685</td>
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<td>SMILE</td>
<td>1 556</td>
<td>27</td>
<td>NEJM 1995;332:80-85</td>
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<td>EMIAT</td>
<td>1 486</td>
<td>16</td>
<td>Lancet 1997;349:667-674</td>
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<tr>
<td>GISSI-P</td>
<td>11 324</td>
<td>15</td>
<td>Lancet 1999;354:447-52</td>
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<td>CIBIS-2</td>
<td>2 647</td>
<td>19</td>
<td>Lancet 1999;353:9-13</td>
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</tbody>
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Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology

Marco Stramba-Badiale* (Chairperson of the Policy Conference), Kim M. Fox (Chairperson of the Policy Conference), Silvia G. Priori (Chairperson of Women at Heart), Peter Collins, Caroline Daly, Ian Graham, Benct Jonsson, Karin Schenck-Gustafsson, and Michal Tendera
ICH
GENDER CONSIDERATIONS IN THE CONDUCT OF CLINICAL TRIALS
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

DRAFT

REFLECTION PAPER ON GENDER DIFFERENCES IN CARDIOVASCULAR DISEASES
Objectives:

♀ To address the issue of gender representation in cardiovascular research by collecting information on clinical trials and registries in Europe.

♀ To identify possible gender differences in the primary outcomes of clinical trials, in the current clinical practice and in the Guidelines of European Scientific Societies.
Electronic literature search of PubMed and International Controlled Trials website has been performed.

Time period covered: from 2006 (to follow up from ESC 2006 conference on women and cardiovascular disease) to June 2009.
Red Alert for Women’s Hearts

Women and Cardiovascular Research in Europe

November 2009

European Heart Health Strategy
EuroHeart Project, Work Package 6
Women and Cardiovascular Diseases

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www.ehnheart.org
Women and research on cardiovascular diseases in Europe: a report from the European Heart Health Strategy (EuroHeart) project

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62 randomized clinical trials

380 891 participants

127 716 women
Participants in Clinical Trials by Gender

<table>
<thead>
<tr>
<th>Condition</th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>BP</td>
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<tr>
<td>DM</td>
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<td>HF</td>
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<tr>
<td>Afib</td>
<td></td>
<td></td>
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<tr>
<td>Stroke</td>
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</tbody>
</table>

Legend: Women, Men
Percentage of Women in Clinical Trials

- BP
- DM
- Chol
- Asp
- IHD
- HF
- Afib
- Stroke
- Total

%
Clinical Trials with Analysis by Gender

- BP
- DM
- Chol
- Asp
- IHD
- HF
- Afib
- Stroke
- Total

%
Mean Age of Participants in Clinical Trials

years

BP  DM  Chol  Asp  IHD  HF  Afib  Stroke  Total

0  10  20  30  40  50  60  70  80
Mean Follow-up of Clinical Trials

years

BP  DM  Chol  Asp  IHD  HF  Afib  Stroke  Total

0  1  2  3  4  5
Summary

♀ Despite an increase in the number and proportion of women enrolled in cardiovascular clinical trials, there is still an under-representation of women, particularly in the field of cholesterol-lowering therapy, ischemic heart disease and heart failure, which may have affected the reliability of subgroup analysis.

♀ Clinical trials and meta-analyses on cardiovascular diseases did not show a significantly lower efficacy of interventions in women when compared with men, although 50% of the studies did not report an analysis of the results by gender. For some therapies there is a suggestion for greater efficacy in women than in men, as in the case of cardiac resynchronization therapy in heart failure or thrombolysis after ischemic stroke.

♀ Women may have more frequently adverse effects, such as for newer glucose-lowering agents, or in the treatment of acute coronary syndromes, where they appear to be more prone to bleedings.
Reasons for the Under-representation of Women in Clinical Trials

👩‍❤️‍👨 Lower occurrence of outcomes in females, which may affect the costs of the study.

👩‍❤️‍👨 Lower willingness of women to be enrolled, due to their misperception of risk of cardiovascular diseases.

👩‍❤️‍👨 Difficulties in terms of transportation or support for the follow-up visits.
Clinical trials enrolling a significant proportion of women to allow for pre-specified gender analysis should be conducted, especially in the fields of ischemic heart disease, cholesterol-lowering therapy and heart failure.

Enrollment criteria and follow-up duration should allow the inclusion of women at risk of developing cardiac events.

A minimum enrollment for women should be ensured (e.g., maintain open enrollment for women until pre-specified proportion is reached).

External barriers to the enrolment of women in clinical trials need to be addressed, and in particular transportation difficulties for follow-up visits.

Regulatory agencies are urged to adopt strict rules on the inclusion of women in clinical trials and a systematic gender analysis.
HEART for Women Act – US Senate 2009

111th Congress
1st Session

S. 422

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the prevention, diagnosis, and treatment of heart disease, stroke, and other cardiovascular diseases in women.
Directs the Secretary to:

(1) require that a new drug application include any clinical data possessed by the applicant that relates to the safety and effectiveness of the drug involved by gender, age, and racial subgroup;

(2) develop guidance for the staff of the Food and Drug Administration (FDA) to ensure that new drug applications are adequately reviewed to determine whether they include the required clinical data.
Red alert for women’s heart: the urgent need for more research and knowledge on cardiovascular disease in women

Proceedings of the Workshop held in Brussels on Gender Differences in Cardiovascular disease, 29 September 2010

Angela H.E.M. Maas¹*, Yvonne T. van der Schouw², Vera Regitz-Zagrosek³, Eva Swahn⁴, Yolande E. Appelman⁵, Gerard Pasterkamp⁶, Hugo ten Cate⁷, Peter M. Nilsson⁸, Menno V. Huisman⁹, Hans C.G. Stam¹⁰, Karin Eizema¹⁰, and Marco Stramba-Badiale¹¹
CHAMBER OF DEPUTIES OF THE ITALIAN PARLIAMENT

A bill of Law
Proposed by the following deputies:

Vargiu, Capua, Oliari, Vezzali, Cusin, Cimmino, Librandi, Materrese, Peipoli, Quintarelli, Vecchio

Legislation concerning Gender Medicine

Submitted to the Chamber on 5th August 2013
Conclusions

Scientific societies, patients’ associations and foundations should cooperate with European institutions, national health care authorities and regulatory agencies to promote scientific research on gender issues in cardiovascular medicine and a larger representation of women in clinical trials.