Gender differences in ACS and CAD

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Ph Gabriel Steg – Disclosures

- **Research grants (to INSERM U-698):** NYU School of Medicine, Sanofi, Servier
- **Speaker/consultant:** Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Daiichi/sankyo, GSK, Lilly, Medtronic, MSD, Novartis, Otsuka, Pfizer, Roche, Sanofi, Servier, The Medicines Company, Vivus
Causes of death in women < 75 years in Europe

- CV-CHD: 18%
- CV-Stroke: 14%
- CV-Other: 10%
- Cancer: 27%
- Other: 31%

Adapted from www.ehnheart.org/cdv-statistics.html,

Prevalence of CAD among US adults by age and sex

NHANES 1999-2004
Gender differences

• In AMI
Excess hospital mortality after AMI in women

Odds Ratios for Death during Hospitalization for Myocardial Infarction in Women as Compared with Men, According to Age in NRMI-2

Unadjusted ORs were derived from the model that included sex, age, the interaction between sex and age, and the year of discharge.

Hypothetical mechanisms of higher AMI mortality in women than men

- Biological differences
  - Women are older with more comorbidities

- Behavioural differences
Comorbidities are more frequent in women than men with AMI

74,038 hospital AMI admissions – 1999 - France

P<0.001 for all comparisons

Hypothetical mechanisms of higher AMI mortality in women than men

**Biological differences**

- Women are older with more comorbidities
- More frequent atypical symptoms

**Behavioural differences**
In-hospital mortality in ACS according to presenting symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Atypical</th>
<th>Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ant STEMI</td>
<td>23.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Inf/lat STEMI</td>
<td>15.4</td>
<td>5.4</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>11.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Brieger et al. *Chest* 2004;126:461-9
Hypothetical mechanisms of higher AMI mortality in women than men

**Biological differences**

- Women are older with more comorbidities
- More frequent atypical symptoms
- Frequent non obstructive CAD

**Behavioural differences**
Prevalence of normal or nonobstructive coronary arteries by gender on early angiography in recent ACS trials

Anderson RD. and Pepine CJ. *Circulation* 2007;115:823-826
Hypothetical mechanisms of higher AMI mortality in women than men

**Biological differences**

- Women are older with more comorbidities
- More frequent atypical symptoms
- Frequent non obstructive CAD
- Smaller arteries
- Lower rates of PCI success

**Behavioural differences**
Hypothetical mechanisms of higher AMI mortality in women than men

**Biological differences**

- Women are older with more comorbidities
- More frequent atypical symptoms
- Frequent non obstructive CAD
- Smaller arteries
- Lower rates of PCI success
- A different disease process?

**Behavioural differences**
Hormonal Alterations coupled with:

Sex-specific precursors
- PCOS
- Hypoestrogenemia
- Menopause

Pro-atherogenic factors
- Hyperlipidemia
- HTN
- Smoking
- Metabolic dysfunction
- Inflammation

Pro-vasculopathy

Nonobstructive atheroma

Microvascular dysfunction

Accelerating factors
- Early menopause
- Risk factor clustering

Subendocardial or epicardial ischemia

Vascular dysfunction symptoms
- Atypical symptoms, including prolonged symptoms at rest, shortness of breath, unusual fatigue, and more frequent pattern
Hypothetical mechanisms of higher AMI mortality in women than men

**Biological differences**
- Women are older with more comorbidities
- More frequent atypical symptoms
- Frequent non obstructive CAD
- Smaller arteries
- Lower rates of PCI success
- A different disease process?

**Behavioural differences**
- By the patient
  - Longer delay to call
  - Lower adherence to Rx
- By the physician
  - Higher threshold for diagnosis
  - Less invasive approach
  - Less intensive treatment
Excess hospital mortality after AMI in women may be explained by undertreatment

Information abstracted from the charts of 138,956 Medicare beneficiaries (49% of them women) who had an AMI in 1994 or 1995

30-Day Mortality and Hazard Ratio for Death among Women and Men with Acute Myocardial Infarction. The CCP project

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>WOMEN (N=68,108)</th>
<th>MEN (N=70,848)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day mortality — % (n.o.)</td>
<td>21.0 (14,274)</td>
<td>17.2 (12,211)</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1.24 (1.21–1.28)</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted HR (95% CI) in model not including treatments†</td>
<td>1.04 (1.01–1.07)</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted HR (95% CI) in model including early treatments‡</td>
<td>1.02 (0.99–1.04)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Impact of differences in CAD severity on use of revascularization in ACS

Data from 2579 pts with coronary angiography in the GRACE registry

Dey S et al. *Heart* 2009;95:20-6
Sex differences in cardiac catheterization within 60 days after AMI: the role of procedure appropriateness

143,444 Medicare patients hospitalized for AMI between 1994 and 1996
The Yentl Syndrome
Lower use of invasive strategy in ACS accounts for higher mortality in women

Data from the FAST MI 2005 nationwide french registry

Three-year survival in the whole population

Adjusted Hazard Ratio (reference: men, invasive):
- Women, invasive: 1.01 [0.81-1.26]
- Men, conservative: 1.96 [1.57-2.44]
- Women, conservative: 1.63 [1.28-2.08]

<table>
<thead>
<tr>
<th>Months</th>
<th>Men, invasive</th>
<th>Men, conservative</th>
<th>Women, invasive</th>
<th>Women, conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2243</td>
<td>272</td>
<td>859</td>
<td>296</td>
</tr>
<tr>
<td>6</td>
<td>2057</td>
<td>139</td>
<td>770</td>
<td>168</td>
</tr>
<tr>
<td>12</td>
<td>1976</td>
<td>104</td>
<td>732</td>
<td>129</td>
</tr>
<tr>
<td>18</td>
<td>1453</td>
<td>65</td>
<td>530</td>
<td>79</td>
</tr>
<tr>
<td>24</td>
<td>1397</td>
<td>88</td>
<td>470</td>
<td>53</td>
</tr>
<tr>
<td>30</td>
<td>1249</td>
<td>61</td>
<td>369</td>
<td>40</td>
</tr>
<tr>
<td>36</td>
<td>1110</td>
<td>44</td>
<td>273</td>
<td>34</td>
</tr>
</tbody>
</table>
AMI mortality is higher in younger women compared to younger men, even after accounting for comorbidities and interventions.


Age group, y (reference = men)  OR (95% CI)

≤55  1.50 (1.06–2.13)

56–65  1.46 (1.15–1.87)

66–75  1.47 (1.31–1.66)

76–85  1.33 (1.21–1.46)

>85  1.11 (0.99–1.25)
Excess mortality in women is not observed when AMI is Treated Predominantly With PCI

One-Year Cumulative Incidence of Death

1937 patients (502 women and 1435 men) admitted with a diagnosis of AMI to a tertiary referral institution between January 1995 and December 2000

Increased proportion of younger women among French patients with AMI

The French AMI registries 1995-2005

Puymirat et al. *JAMA* 2012

The French AMI registries 1995-2005
Current smoking

Obesity

Puymirat et al JAMA 2012
Ongoing reduction in incidence and lethality of AMI in both men and women

Standardised 30 day and 31–365 day mortality after first time hospitalisation for myocardial infarction among men and women between 1984 and 2008

Schmidt 2012 BMJ
Gender differences

• In AMI

• In stable CAD
Higher risk of death/MI in women vs men with stable angina

Data from the Euro Heart Survey on stable angina

Cumulative probability of death or MI in pts with confirmed CAD and stable angina

Daly C et al. *Circulation* 2006;113:490-498
Impact of female gender on outcomes in the EHS on stable angina

Hazard of Death or MI Associated With Female Gender in Individuals With Proven Coronary Disease From the Euro Heart Survey of Stable Angina

<table>
<thead>
<tr>
<th>Event Description</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI</td>
<td>2.07</td>
<td>1.16–3.72</td>
<td>0.01</td>
</tr>
<tr>
<td>Death or MI,</td>
<td>2.09</td>
<td>1.14–3.85</td>
<td>0.02</td>
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<tr>
<td>adjusted for age,</td>
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<tr>
<td>diabetes, LV</td>
<td></td>
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<td></td>
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<tr>
<td>function, and</td>
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<td></td>
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<tr>
<td>severity of CAD</td>
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<tr>
<td>Death or MI,</td>
<td>2.07</td>
<td>1.14–3.74</td>
<td>0.02</td>
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<tr>
<td>adjusted for age</td>
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<td>and use of</td>
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<td>antiplatelet</td>
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<tr>
<td>therapy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Death or MI,</td>
<td>2.20</td>
<td>1.22–3.98</td>
<td>0.009</td>
</tr>
<tr>
<td>adjusted for age</td>
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<td>and revasculariza-</td>
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<td>tion</td>
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</tbody>
</table>

Daly C et al. *Circulation* 2006;113:490-498
The CLARIFY registry

Data on 30977 stable CAD Pts (23% women)

Western Europe
- Austria: 425
- Belg/Luxem: 577
- Denmark: 133
- France: 2428
- Germany: 2250
- Greece: 559
- Ireland: 190
- Italy: 2114
- Netherlands: 206
- Portugal: 949
- Spain: 2257
- Switzerland: 291
- UK: 2351

Central/Eastern Europe
- Bulgaria: 172
- Czech Rep: 393
- Hungary: 344
- Poland: 1004
- Romania: 502
- Slovakia: 183
- Latvia: 120
- Slovenia: 81
- Lithuania: 214

Russia/Ukraine
- Russia: 2248
- Ukraine: 777

South America
- Argentina: 234
- Brazil: 291

North America
- Canada: 1232

Central America
- Mexico: 1342
- West Indies: 368

West Indies
- 368

Africa
- South Africa: 543

Asia
- Brunei (Incl. in Mal): 761
- China: 2622
- India: 809
- Korea: 1020
- Malaysia: 380
- Singapore: 113
- Thailand: 693
- Vietnam: 506

Middle East
- Bahrain: 750
- Kuwait: 361
- Oman: 831
- Qatar: 221
- Saudi Arabia: 761
- UAE: 761

Australasia
- Australia: 833
Primary Outcome

CV death, MI and stroke

- 407 events in men (1.7%)
- 122 events in women (1.8%)

Odds ratios & 95% CI:

- Crude: 1.03 (0.84-1.26)  p = 0.78
- Adjusted*: 0.93 (0.75-1.15)  p = 0.5

* Adjusted on age, presence and severity of angina, diabetes, hypertension, MI, PAD, HR, and SBP
| Event                                      | Men  | Women | OR  | Odds Ratio | P     
|--------------------------------------------|------|-------|-----|------------|-------
| All cause death                            | 1.5% | 1.6%  | 1.07| 0.91       | 0.52  
|                                            | Unadjusted |    |     |            |       
|                                            | Adjusted   |    |     |            | 0.39  
| Fatal or non-fatal MI                      | 1.0% | 0.9%  | 0.88| 0.81       | 0.36  
|                                            | Unadjusted |    |     |            |       
|                                            | Adjusted   |    |     |            | 0.15  
| CV death or non-fatal MI                   | 1.4% | 1.4%  | 0.98| 0.89       | 0.87  
|                                            | Unadjusted |    |     |            |       
|                                            | Adjusted   |    |     |            | 0.33  
| CV death, non-fatal MI or non-fatal stroke | 1.7% | 1.8%  | 1.03| 0.93       | 0.78  
|                                            | Unadjusted |    |     |            |       
|                                            | Adjusted   |    |     |            | 0.5   
| All coronary events*                       | 5.8% | 6.2%  | 1.09| 0.98       | 0.14  
|                                            | Unadjusted |    |     |            |       
|                                            | Adjusted   |    |     |            | 0.67  
| Unstable angina                            | 3.8% | 4.7%  | 1.24| 1.09       | 0.001 
|                                            | Unadjusted |    |     |            |       
|                                            | Adjusted   |    |     |            | 0.23  
| Revascularization (PCI or CABG)            | 2.6% | 2.1%  | 0.83| 0.77       | 0.04  
|                                            | Unadjusted |    |     |            |       
|                                            | Adjusted   |    |     |            | 0.007 

*: MI, revascularization or unstable angina
### Special subsets

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both genders must be managed in a similar fashion.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>A high index of suspicion for myocardial infarction must be maintained in</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>women, diabetics, and elderly patients with atypical symptoms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special attention must be given to proper dosing of antithrombotics in</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>elderly and renal failure patients.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• There are important differences between men and women, in AMI, ACS and stable CAD presentation and management.

• Women tend to receive less intensive therapy and be referred less frequently and later for invasive management.

• With increasing use of revascularization, and improved outcomes sex differences in lethality tend to vanish.

• But the proportion of younger women with AMI increases, presumably because of the increased prevalence of smoking and obesity in women.

• Future research should address
  – Behavioral differences in management of AMI and CAD (patients and physicians).
  – Exploration of biological differences.

• In the interim, women should not be deprived of the same management as men (particularly interventions) and we must close the “gender gap”
Gender and probability of death after primary PCI for STEMI

Coronary Artery Disease/Age and Gender Interaction in STEMI

Juliard JM et al. *Am J Cardiol* 2013
- clustered risk factors/metabolic syndrome
- elevated inflammatory markers
- reproductive hormonal variability/change
- subclinical atherosclerosis
- angina (or equivalent) frequency & stability
- microvascular and endothelial dysfunction
- myocardial ischemia (subendocardial or segmental)
- diastolic & systolic dysfunction
- reduced functional capacity
- lower rates of guideline therapies
- knowledge gap of sex-specific IHD therapeutic strategies

High-risk

Vascular dysfunction

Subclinical atherosclerosis

Obstructive CAD

Multivessel CAD/
heart failure

Low-risk
Atypical presentation: impact on hospital mortality

All ACS (referent typical ACS)

STEMI (referent typical STEMI)

NSTEMI (referent typical NSTEMI)

Unstable angina (referent typical unstable angina)

Dyspnea (referent typical presentation)

Diaphoresis (referent typical presentation)

Nausea/vomiting (referent typical presentation)

Syncope/presyncope (referent typical presentation)

0 1 2

Reduced risk of mortality

Increased risk of mortality

Brieger et al Chest 2004;126:461-9