EURHOBOP

Work package n 6: sex inequalities assessment

Effect modification by gender in outcome studies

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BACKGROUND

- Controversial evidence of gender differences in outcome of acute coronary syndromes
- Some studies demonstrate increased rates of mortality among women, some indicate no difference and others show lower mortality among women
- Some studies found that higher mortality among women might be explained by different age and risk factors distribution
- Most of the evidence comes from pooled analysis of RCTs
- More evidence is needed from effectiveness studies (in real practice)and in different temporal and geografical settings

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CRITICAL ISSUES

- To investigate effect modification by gender in outcome studies several issues should be considered
- Confounding or effect modification by
  - Severity of ACS
  - Comorbidities
  - Access to treatment
  - Treatment effectiveness

SEVERITY

- Evidence of gender differences in outcome of acute coronary syndromes (Berger J et al 2009)
  - By type of ACS (higher among female STEMI and lower among nSTEMI)
  - Potential role of angiographic disease severity (no differences)

COMORBIDITIES

Sex Differences in Mortality Following Acute Coronary Syndromes

Jeffrey S. Berger; Laine Elliott; Dianne Gallup; et al.

JAMA. 2009;302(8):874-882 (doi:10.1001/jama.2009.1227)

Characteristics	STEMI		NSTEMI	
	Women (n = 26 032)	Men (n = 75 972)	Women (n = 4159)	Men (n = 10 307)
Demographics				
Age, median (IQR), y	68 (60-75)	60 (50-68)	69 (61-76)	63 (54-71)
White race	19 162 (93)	56 644 (92)	3819 (92)	9557 (93)
BMI, median (IQR)	26.5 (24-30)	26.5 (24-29)	27.0 (24-30)	26.9 (25-30)
Smoker	7728 (30)	31 523 (42)	870 (21)	3647 (36)
Geographic region				
North America	11 128 (44)	29 811 (41)	1510 (36)	3568 (35)
Western Europe	6938 (27)	23 438 (32)	1635 (39)	4631 (45)
Eastern Europe	4192 (17)	9516 (13)	643 (16)	1040 (10)
Other[a]	3062 (12)	10 710 (14)	371 (9)	1068 (10)
Clinical history				
Hypertension	14 167 (55)	27 323 (36)	2632 (63)	4618 (45)
Diabetes	5442 (21)	10 052 (13)	1107 (27)	1923 (19)
Hyperlipidemia	7095 (36)	17 356 (31)	1780 (43)	3944 (39)
Prior MI	3625 (14)	12 936 (17)	1042 (25)	3302 (32)
Prior CABG surgery	564 (2)	3025 (4)	260 (6)	1220 (12)
Heart failure	997 (4)	1455 (2)	533 (13)	759 (7)
Clinical presentation				
Heart rate, median (IQR), beats/min	75.0 (64-88)	74.0 (62-85)	76.0 (68-88)	72.0 (64-84)
Systolic BP, median (IQR), mm Hg	130.0 (115-150)	130.0 (116-148)	138.0 (120-152)	130.0 (120-150)
Killip class score[b]				
I	20 771 (81)	65 199 (87)	2864 (82)	7569 (88)
II	4126 (16)	8677 (12)	521 (15)	892 (10)
III-IV	880 (2)	1399 (1)	99 (3)	144 (2)

IN-ACS (Italian Network on Acute Coronary Syndromes) Outcome study

	STEMI (n=2452)				NSTEMI (n=2632)			
	Male (n=1746)		Female (n=706)		Male (n=1765)		Female (n=867)	
	mean	SD	mean	SD	mean	SD	mean	SD
Age (mean)	62.9	12.3	71.5	12.5	66.9	12.4	73.6	11.4
BMI (mean)	28.0	17.9	25.7	4.5	27.4	10.8	26.1	4.5
	N	%	N	%	N	%	N	%
Smoking	744	42.61	149	21.1	543	30.76	118	13.61
Killip class								
1	1494	85.57	541	76.63	1480	83.85	656	75.66
2	151	8.65	96	13.6	195	11.05	133	15.34
3-4	101	5.78	69	9.77	90	5.1	78	9
Dyslipaemia	661	37.86	261	36.97	769	43.57	382	44.06
Diabetes	366	20.96	165	23.37	489	27.71	289	33.33
Hypertension	864	49.48	473	67	1167	66.12	662	76.36
Previous myocardial infarction	234	13.4	66	9.35	483	27.37	191	22.03
Previous CABG	44	2.52	10	1.42	170	9.63	56	6.46
Previous PTCA	164	9.39	32	4.53	246	13.94	81	9.34
Previous stroke/TIA	74	4.24	55	7.79	127	7.2	76	8.77
Peripheral artery disease	134	7.67	42	5.95	288	16.32	123	14.19
Chronic renal failure	81	4.64	29	4.11	187	10.59	98	11.3
COPD	130	7.45	35	4.96	223	12.63	84	9.69
Family history of CHD	424	24.28	166	23.51	391	22.15	159	18.34
Previous chronic angina	196	11.23	61	8.64	376	21.3	182	20.99
Coronary artery stenosis diagnosed by angiography	202	11.57	44	6.23	421	23.85	135	15.57
Family history of heart failure	14	0.8	16	2.27	75	4.25	61	7.04

CHD:Coronary Heart Disease

COPD: Chronic obstructive pulmonary disease

Effect modification by gender and clinical presentation: IN-ACS

Caratteristiche	STEMI						NSTEMI					
	Female n= 706			Male n= 1746			Female n= 867			Male n= 1765		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Hypertension	0.95	0.46 1.96	0.892	0.77	0.41 1.42	0.399	1.22	0.32 4.56	0.772	1.36	0.59 3.13	0.468
Diabetes	1.20	0.58 2.46	0.626	1.42	0.74 2.73	0.286	1.13	0.40 3.17	0.822	1.01	0.48 2.13	0.972
Dyslipaemia	0.80	0.38 1.68	0.554	0.46	0.21 1.04	0.063	2.45	0.88 6.81	0.087	0.67	0.31 1.46	0.316
Previous myocardial infarction	0.77	0.26 2.28	0.642	0.52	0.19 1.42	0.199	1.44	0.49 4.25	0.511	1.87	0.89 3.96	0.100
Previous CABG	1.96	0.28 13.98	0.501	0.89	0.09 9.14	0.923	2.50	0.50 12.52	0.264	0.70	0.22 2.18	0.536

ACCESS TO TREATMENT

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Differences in access to coronary care unit among patients with acute myocardial infarction in Rome: old, ill, and poor people hold the burden of inefficiency. *Ancona C et al BMC Health Services Research 2004*

Table 3: Effect of patients personal characteristics on risk of non admission to Coronary Care Unit (CCU)

	Patients	% directly admitted to CCU	OR	95% C.I.	OR*	95% C.I.
Gender						
Male	6243	56.7	1.00		1.00	
Female	2884	47.9	0.70	0.64 – 0.77	0.73	0.64 – 0.84
Age (years)						
<50	673	67.9	1.00		1.00	
50–64	2665	62.7	0.79	0.67 – 0.95	0.79	0.60 – 1.04
65–74	2606	55.1	0.58	0.48 – 0.69	0.72	0.55 – 0.95
75–84	2234	44.8	0.35	0.32 – 0.46	0.49	0.37 – 0.65
85+	949	37.7	0.29	0.23 – 0.35	0.35	0.25 – 0.48
Charlson's comorbidity index						
0	4516	60.2	1.00		1.00	
1	2807	53.1	0.75	0.68 – 0.82	0.69	0.60 – 0.80
2	1117	41.4	0.47	0.41 – 0.53	0.45	0.36 – 0.55
3+	687	36.8	0.38	0.33 – 0.45	0.48	0.37 – 0.61
SES level						
I	1523	52.6	1.00		1.00	
II	2840	53.5	1.04	0.91 – 1.17	0.90	0.75 – 1.09
III	2603	54.8	1.09	0.96 – 1.24	0.79	0.65 – 0.95
IV	1883	54.7	1.09	0.95 – 1.25	0.81	0.66 – 0.99

OR: Crude Odds Ratio
OR: Odds Ratio adjusted for age, gender, severity of illness, and SES. Random effect model with admitting hospital as clustering variable*

Use of evidence based treatment after ACS

Tuppin et al, 2009 France	Significant underuse of evidence based combination treatment medication 6 months after hospitalization for IMA in women OR = 1.2 (1.1-1.3) for males vs females
Vermeer et al, 2008 Australia	Men more likely discharged after ACS on a statin OR = 3.36 (1.11-10.15)
Lee et al, 2008 USA	During 3 months after ACS hospitalization women were less likey to receive statins OR = 0.65 (0.48-0.87)
Yan et al, 2007 Canada	Female sex was a negative independent predictor of optimal medical therapy after ACS OR = 0.71 (0.60-0.83)
Crilly et al, 2007 Liverpool, UK	Men with angina were significantly more likely to receive triple secondary prevention OR = 1.47 (1.07-2.02)
Van der Elst et al, 2005 Netherlands	Men were significantly more likely to receive a combination that included a statin at discharge and during 12 months after hospitalization for AMI P = 0.03

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Evidence-based drug therapy after acute myocardial infarction: a population-based cohort study in Rome, Italy 2006-2007

	N	% Poly-therapy*	OR crude	95% CI	OR 1**	95%CI	OR 2 ***	95% CI
Gender								
males	3642	51,3	1,00		1,00		1,00	
females	1876	37,7	0,57	0,51-0,64	0,73	0,64-0,83	0,82	0,72-0,94
Age class (yrs)								
35-64	1923	57,0	1,00		1,00		1,00	
65-74	1444	51,2	0,79	0,69-0,91	0,83	0,72-0,96	0,79	0,68-0,92
75-84	1531	40,5	0,51	0,45-0,59	0,62	0,53-0,72	0,67	0,57-0,78
85+	620	19,4	0,18	0,15-0,23	0,24	0,19-0,30	0,33	0,26-0,43

* Poly-therapy (overall 46,7%): at least one of the 4 ATC groups (platelet aggregation inhibitors, beta blocking agents, agents acting on renin-angiotensin system, statins)
**OR 1: adjusted for gender, age class and comorbidities
***OR 2: adjusted for gender, age, comorbidities, SES, revasc.procedures, previous AMI, specialistic ward at discharge

Evidence-based drug therapy after acute myocardial infarction: a population-based cohort study in Rome, Italy 2006-2007

	N	Platelet aggregation inhibitors		Beta-blocking agents		Agents acting on the renin-angiotensin		Statins	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Gender									
males	3642	1		1		1		1	
females	1876	0,84	0,70-1,00	0,87	0,76-1,00	0,85	0,73-0,98	0,83	0,71-0,96
Age class (yrs)									
35-64	1923	1		1		1		1	
65-74	1444	0,78	0,62-0,99	0,74	0,63-0,87	0,98	0,82-1,17	0,81	0,66-0,98
75-84	1531	0,57	0,45-0,71	0,63	0,53-0,74	0,96	0,80-1,16	0,55	0,46-0,67
85+	620	0,49	0,37-0,65	0,41	0,33-0,52	0,86	0,67-1,10	0,25	0,19-0,32

Note: Adjusted OR (full models)

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Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials

Mark A Hlatky, Derek B Boothroyd, Dena M Bravata, Eric Boersma, Jean Booth, Maria M Brooks, Didier Carrié, Tim C Clayton, Nicolas Danchi Marcus Flather, Christian W Hamm, Whady A Hueb, Jan Kähler, Sheryl F Kelsey, Spencer B King, Andrzej S Kosinski, Neuza Lopes, Kathryn M McDonald, Alfredo Rodriguez, Patrick Serruys, Ulrich Sigwart, Rodney H Stables, Douglas K Owens, Stuart J Pocock

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Summary

Background Coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) are alter treatments for multivessel coronary disease. Although the procedures have been compared in several rando trials, their long-term effects on mortality in key clinical subgroups are uncertain. We undertook a collabo analysis of data from randomised trials to assess whether the effects of the procedures on mortality are modifi patient characteristics.

Methods We pooled individual patient data from ten randomised trials to compare the effectiveness of CABG PCI according to patients' baseline clinical characteristics. We used stratified, random effects Cox proportional ha models to test the effect on all-cause mortality of randomised treatment assignment and its interaction with cl

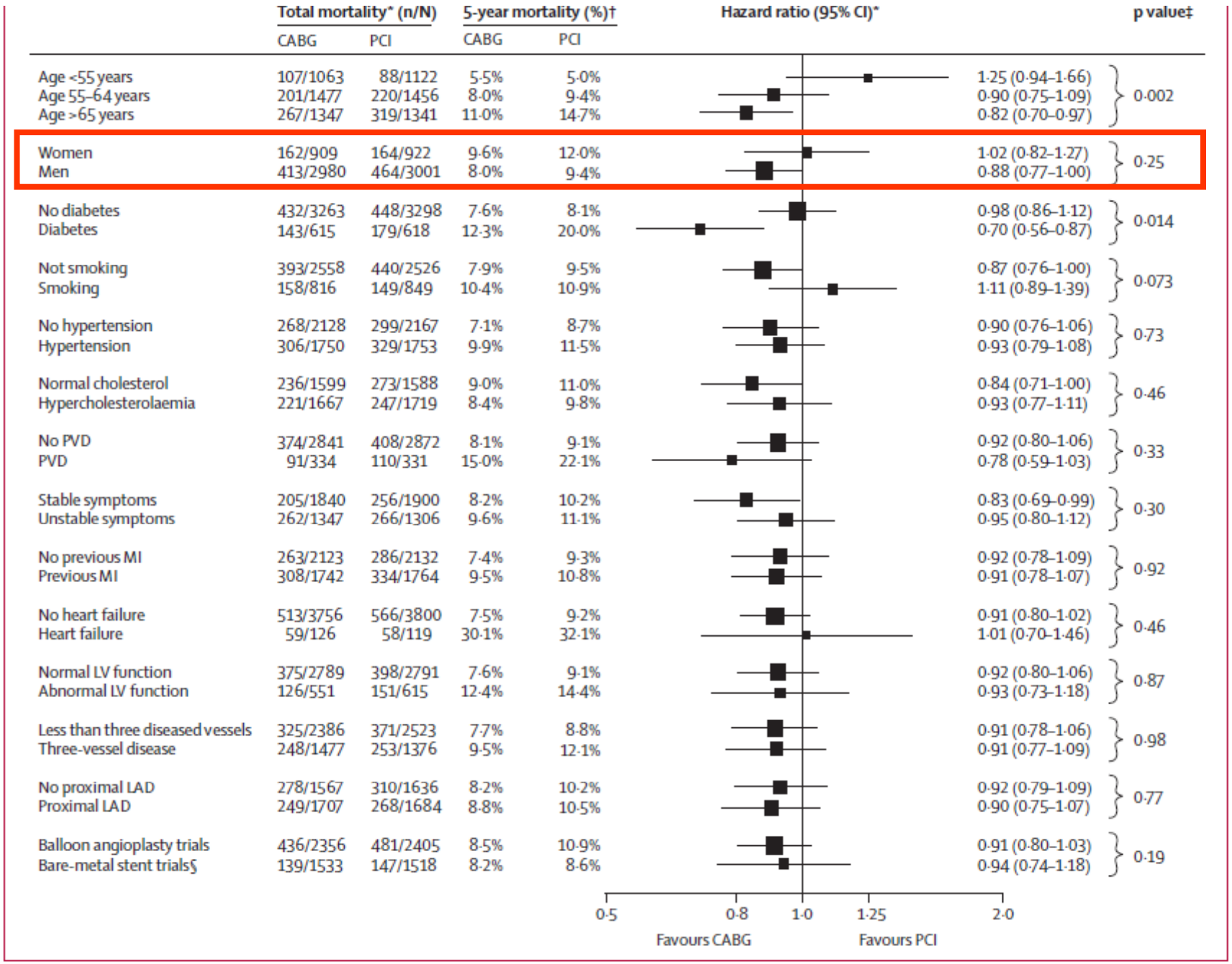

Figure 2: **Subgroup analyses for mortality after treatment with coronary artery bypass graft or percutaneous coronary intervention**

CABG=coronary artery bypass graft. LAD=left anterior descending artery. LV=left ventricular. MI=myocardial infarction. PCI=percutaneous coronary intervention. PVD=peripheral vascular disease. The vertical line indicates a hazard ratio of 1·0, equivalent to no difference between treatment groups. *Based on on the full duration

Wp 6: OBJECTIVES

- To determine whether gender is an effect modifier of MI's outcomes by different exposures

  - Hospital of care
  - Socio demographic characteristics
  - Severity
  - Comorbidities
  - Access to specialist care
  - Access to treatment
    - PTCA
    - Trombolysis
    - Pharmacological therapies

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Wp 6: ACTIVITIES

- Literature review
- Study protocol definition
  - Case definition
  - Outcome
    - In-hospital case fatality
      - 30 day in-hospital case fatality
    - MACCE (mortality, cardio and cerebrovascular events)
  - Exposure (see previous slide)
  - Confounding and selected effect modifiers
- Data availability from different particpants
- Data analysis

- Delivery date M28

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AMI mortality. Adjusted ORs calculated by using HIS and RAD-Esito, by hospital of treatment

	Males		Females	
admission hospital	crude OR	adjusted OR	crude OR	adjusted OR
019	1,72	2,58 *	3,39	1,52
026	1,32	1,60	2,60	1,27
043	1,29	1,59	2,55	1,44
044	1,76	2,17 *	3,48	2,37 *
045	2,34	1,77	4,61	4,44 *
061	1,32	0,90	2,61	2,15 *
066	1,76	1,89	3,48	2,25 *
071	2,91	3,76 *	5,74	3,04 *
076	1,28	1,82	2,52	1,29
134	2,06	3,17 *	4,07	3,61 *
165	1,10	0,97	2,18	1,82
180	1,55	1,86	3,07	2,38 *
200	1,85	2,30 *	3,65	2,83 *
206	1,53	2,85 *	3,02	1,54
215	1,80	3,46 *	3,55	1,43
267	1,58	1,98	3,12	2,62 *
271	1,63	1,33	3,22	3,46 *
901	1,62	2,09 *	3,20	1,82
903	1,57	1,58	3,09	2,85 *
906	1,58	2,34 *	3,11	1,88
920	0,64	1,10	1,26	1,43
ref group	1,00	1,00	1,00	1,00

*** p<0.05**

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