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Sex Difference in Inflammation marker & Myocardial Infarction

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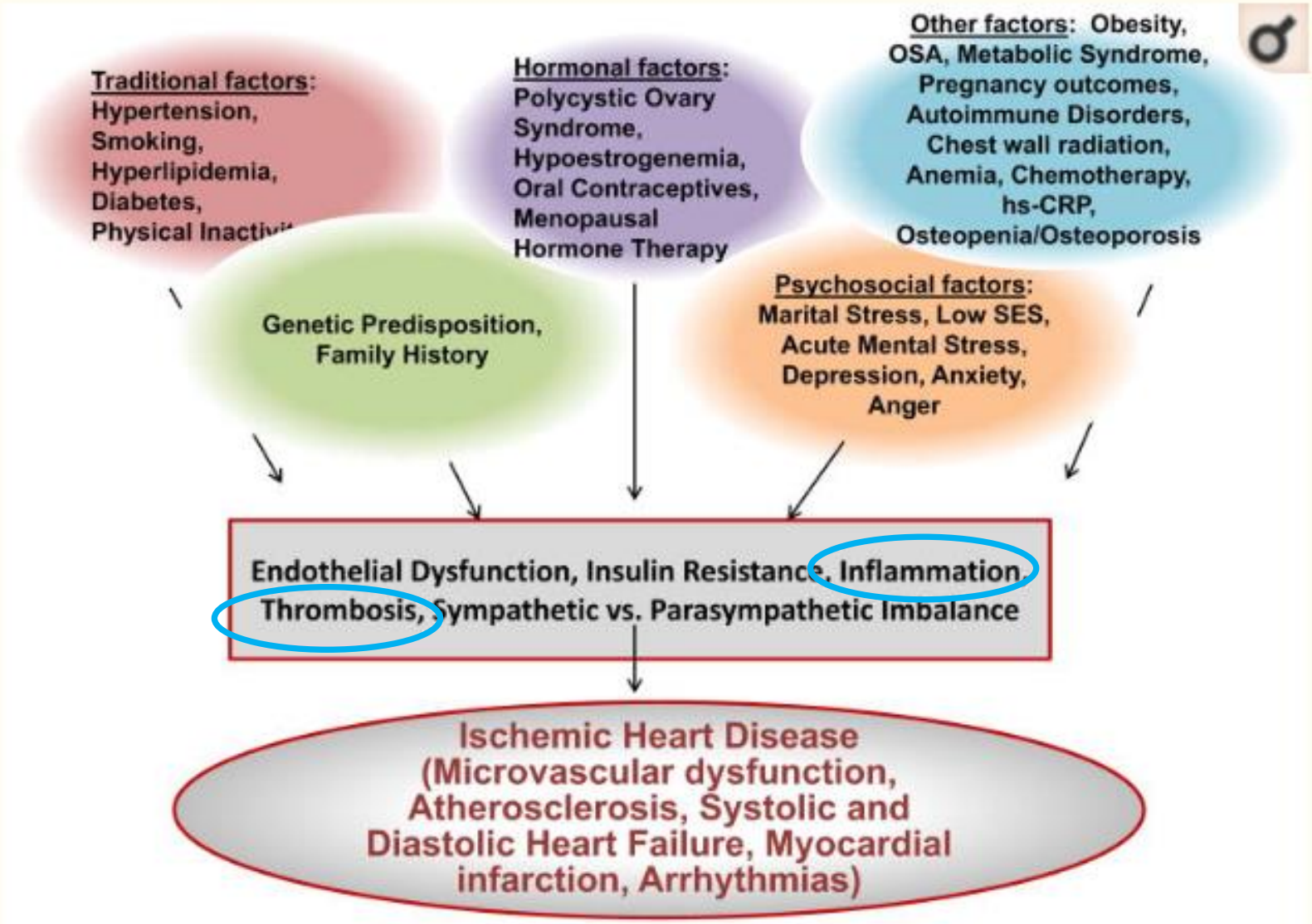
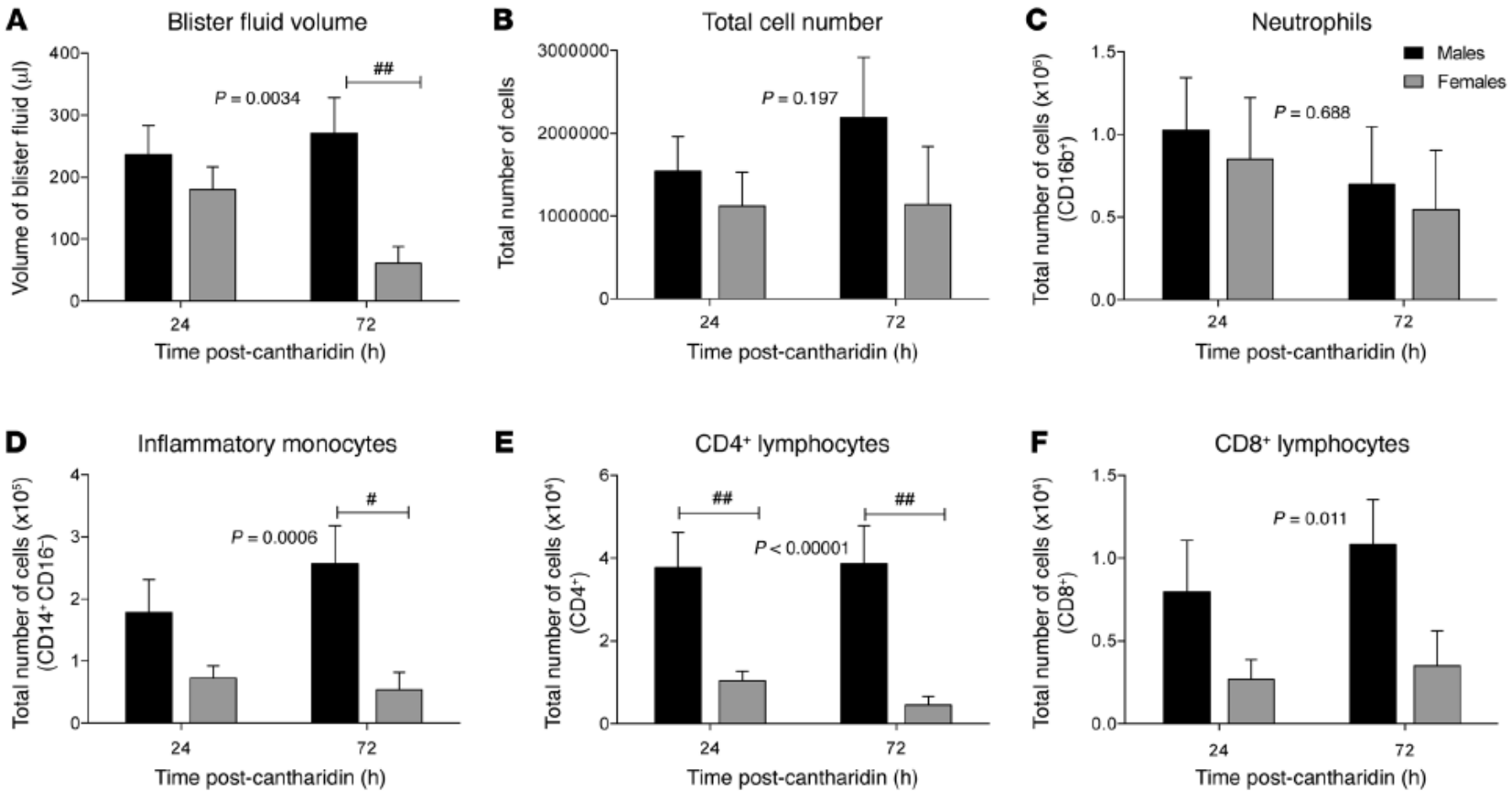
Woman and Ischemic Heart Disease



Mehta PK, et al. Trends Cardiovasc Med. 2015;25:140-151

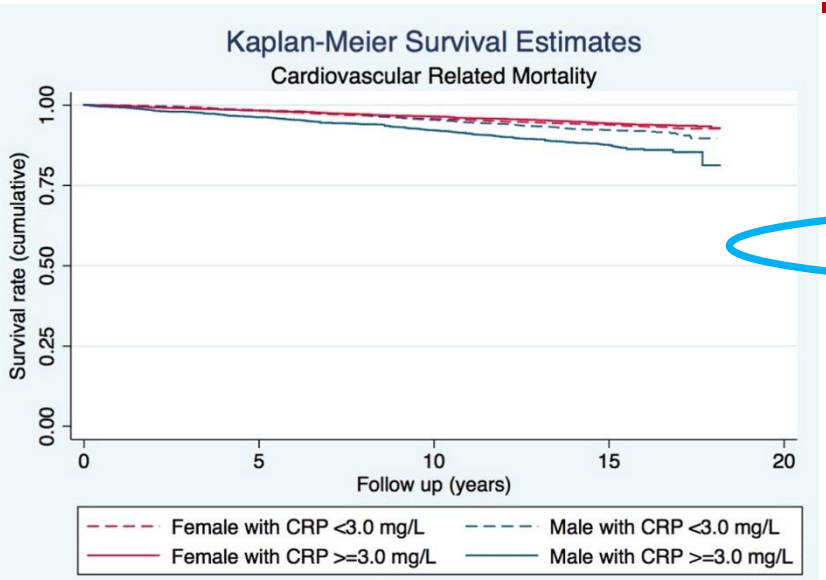
the sex difference in Inflammation, True or not?

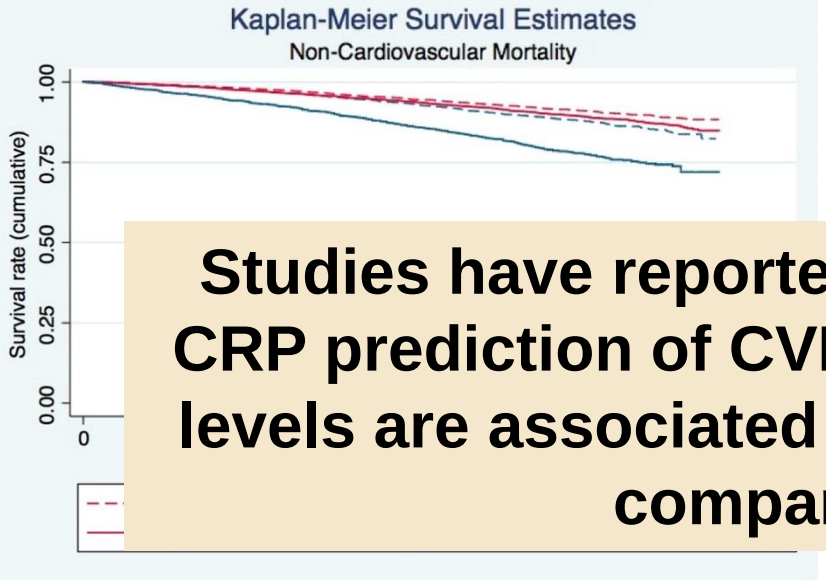
Accelerated resolution of inflammation underlies



This findings suggest that female sex protects against systemic inflammation-induced endothelial dysfunction. This effect is likely due to accelerated resolution of inflammation compared with males

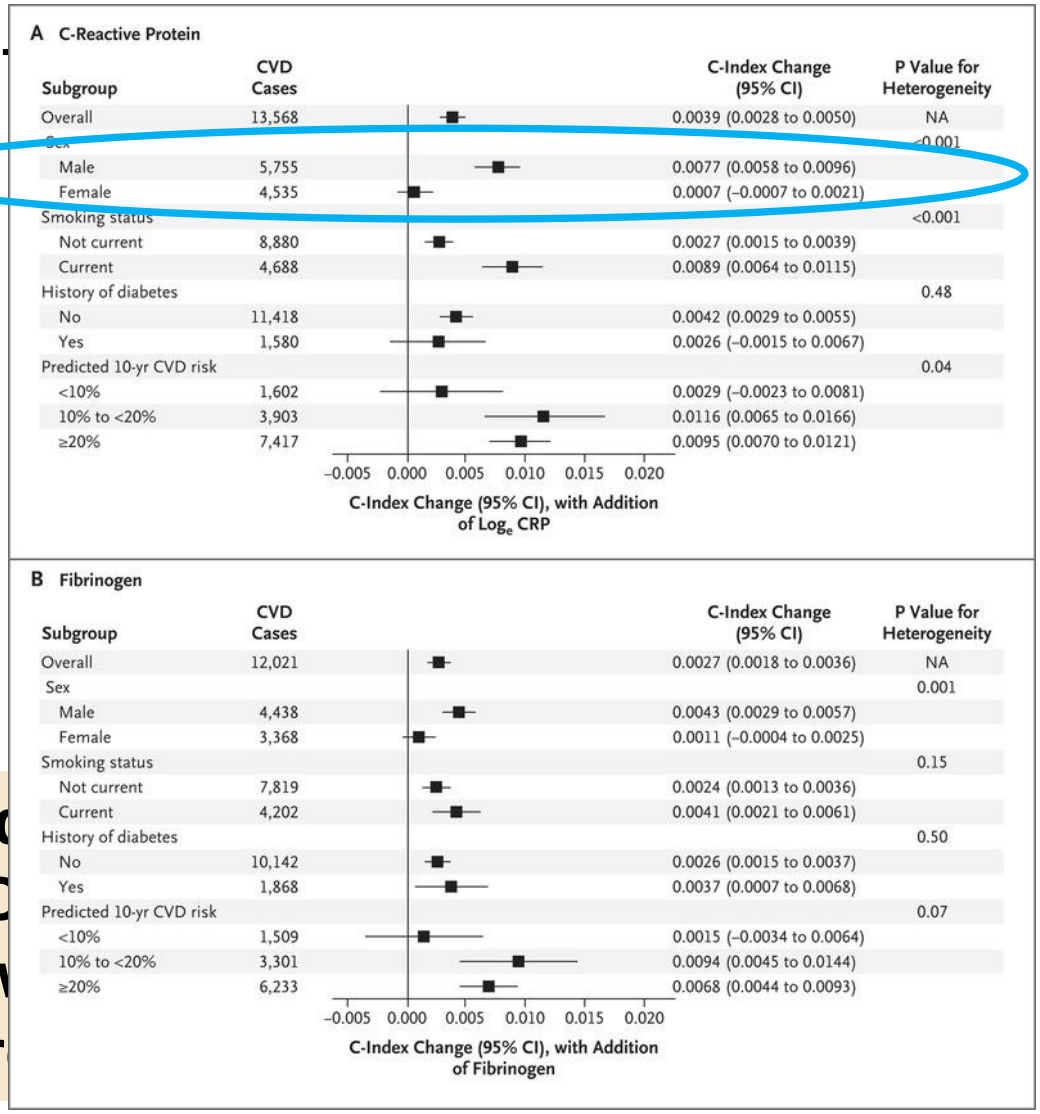
Gender differences in cardiovascular mortality by C-RP level in the United States: Evidence from the NHNESurvey III





Studies have reported CRP prediction of CVD levels are associated with compar

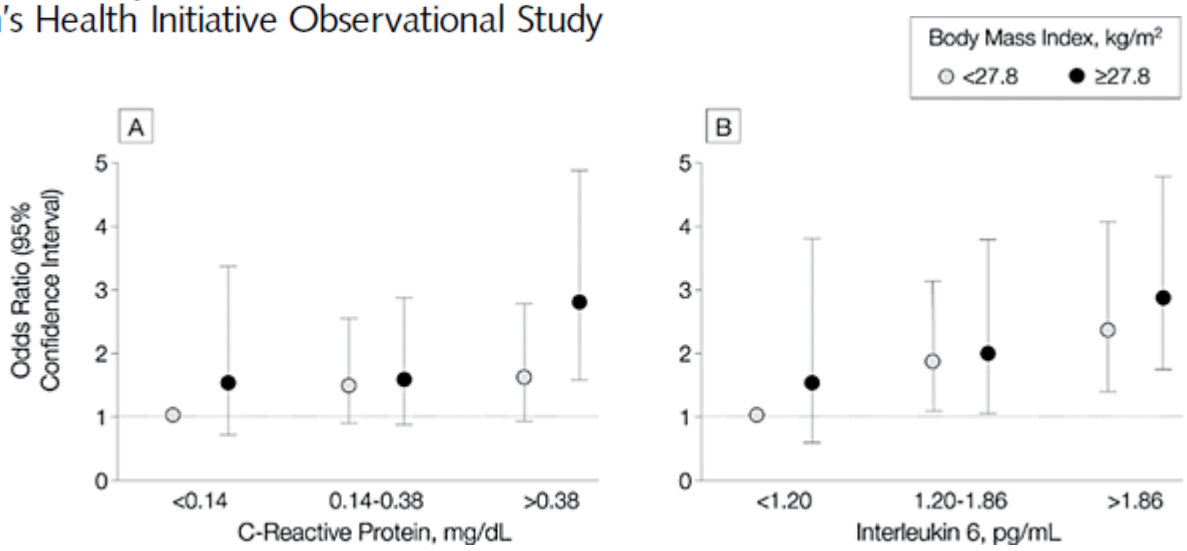
Am Heart J 2013;166:45-51



N Engl J Med 2012;367:1310-20.

Inflammatory Biomarkers, Hormone Replacement Therapy, and Incident Coronary Heart Disease

Prospective Analysis From the Women's Health Initiative Observational Study



These prospective findings indicate that CRP and IL-6 independently predict vascular events among apparently healthy postmenopausal women and that HRT increases CRP.

However, use or nonuse of HRT had less importance as a predictor of cardiovascular risk than did baseline levels of either CRP or IL-6.

The NEW ENGLAND JOURNAL of MEDICINE

Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women

Table 4. Relative Risks of Coronary Heart Disease during Follow-up According to the Baseline Level of C-Reactive Protein.*

Variable†	CRP <1.0 mg/liter	CRP 1.0–2.9 mg/liter	CRP ≥3.0 mg/liter	P for Trend‡
	relative risk (95 percent confidence interval)			
Women				
No				
No				
Mo				
Mo				
Mo				
Mo				
Mo				
Me				
No				
No				
Mo				
Mo				
Mo				
Mo				
Mo				
Me				
Mo				
Mo				
Mo				
Mo				
Mo				

Conclusion:

1. **After adjustment for matching factors, high levels of interleukin-6 and CRP were significantly related to an increased risk of CHD in both sexes, whereas high levels of sTNFa receptors were significant only among women.**
2. **Although plasma lipid levels were more strongly associated with an increased risk than were inflammatory markers,**
3. **CRP remained a significant contributor to the prediction of CHD.**

Level of C-Reactive Protein (CRP) and the Quintile of the Ratio of Total to HDL Cholesterol.

N Engl J Med 2004;351:2599-610

Atherosclerosis 233 (2014) 579–583

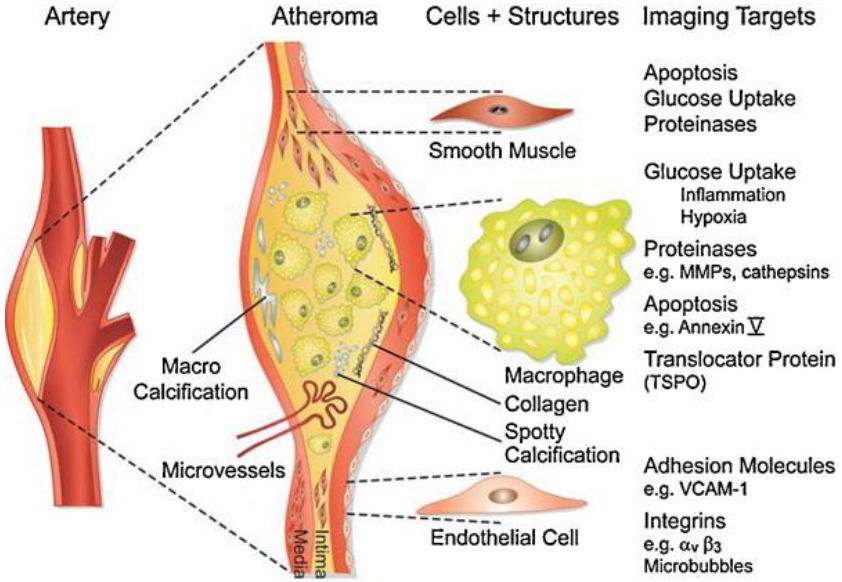
Contents lists available at ScienceDirect

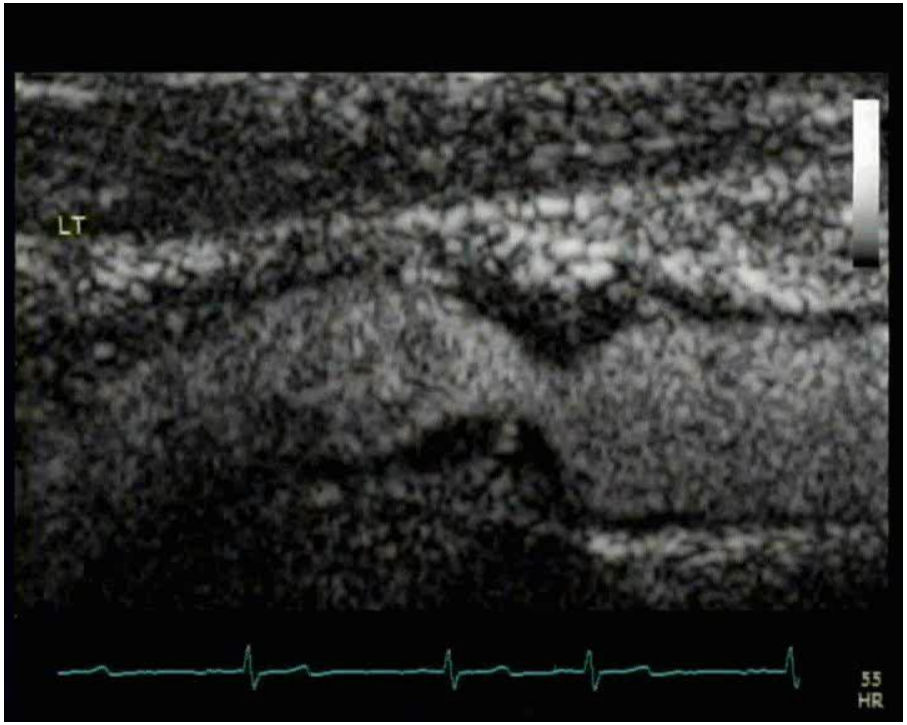
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Biochemical and clinical correlation of intraplaque neovascularization using contrast-enhanced ultrasound of the carotid artery

Hyun Soo Kim [a], Jong Shin Woo [a], Bu Yong Kim [a], Hyun Hee Jang [a], Seung Joon Hwang [a], Sung Jin Kwon [a], Eun Young Choi [a], Jin Bae Kim [a], Xianwu Cheng [b], Enze Jin [c], Woo Shik Kim [a,*], Kwon Sam Kim [a], Weon Kim [a,*,1]





P.G. Camici, Eur Heart J, (2012), 1309–1317

Gencer difference - Baseline characteristics

	Group 1 (N=30)	Group 2 (N=59)	P-value
Age (years)	62.9±10.1	68.4±9.65	0.015
BMI (kg/m2)	26.1±2.98	25.2±2.84	0.150
Gender (Male)	22(73.3%)	46(78.0%)	0.627

- There was no statistical difference between the gender and Biomarker levels

Multivariate logistic regression analysis for IPN on CECU

	P value	95% CI
Age	0.017	1.075(1.013-1.141)
Gender	0.876	1.110(0.300-4.110)
Cathepsin L	0.301	1.174(0.866-1.593)
MMP-2	0.781	1.009(0.946-1.071)
MMP-9	0.021	1.014(1.002-1.027)

the sex difference in Inflammation, True or not?

Yes,

- It's only true in premenopausal young woman

- high levels of CRP were significantly related to an increased risk of CHD in woman, but more weak than man. (fibrinogen, IL-6)

- But, some studies showed no significant difference in between sex. And, there is not woman-specific inflammatory biomarker.

Clinical impact by sex difference in Inflammation, especillay ACS, True or not?

Current Trend of KAMIR

Variables	STEMI (n=22,514)	NSTEMI (n=17,464)	*p* value
	n(%) or mean±SD		
Age (years)	64.1±13.2	66.5±12.5	<0.001
Male	16,823 (74.8)	11,715 (67.2)	<0.001
Body mass index (kg/m^2)	24.0±3.4	23.9±3.4	0.831
Overweight (BMI≥23)	7,541 (37.5)	5,773 (36.4)	0.029
Risk factors			
Hypertension	10,390 (48.9)	9,596 (58.4)	<0.001
Diabetes mellitus	5,548 (26.2)	5,546 (33.8)	<0.001
Dyslipidemia	2,221 (10.5)	2,227 (13.6)	<0.001
Smoking history	11,324 (51.2)	6,828 (39.8)	<0.001
Previous angina	7,278 (32.9)	7,512 (43.8)	<0.001

KAMIR data. Unpublished

Age ≤ 50

	6 Months		12 Months	
	Male (n=1971)	Female (n=141)	Male (n=1936)	Female (n=141)
Cardiac death	28 (1.4%)	1 (0.7%)	29 (1.5%)	2 (1.5%)
Noncardiac death	2 (0.1%)	0 (0%)	2 (0.1%)	0 (0%)
MI	15 (0.8%)	2 (1.4%)	25 (1.3%)	5 (3.5%)
Stroke	1 (0.1%)	0 (0%)	1 (0.1%)	1 (0.1%)
3P MACE	46 (2.3%)	3 (2.1%)	60 (3.1%)	8 (5.7%)
Repeated PCI	38 (1.9%)	2 (1.4%)	85 (4.4%)	9 (6.4%)
Repeated admission	6 (0.3%)	1 (0.7%)	9 (0.5%)	1 (0.7%)
Stent thrombosis	6 (0.3%)	0 (0%)	8 (0.4%)	1 (0.7%)
CABG	3 (0.2%)	0 (0%)	?	?
Overall MACE	78 (4.0%)	4 (2.8%)	129 (6.7%)	13 (9.2%)

3P MACE = Death, MI, Stroke

Overall MACE = Death, MI, Stroke, repeated PCI, ST, CABG

Age ≥ 51

	6 Months		12 Months	
	Male (n=7575)	Female (n=3211)	Male (n=7468)	Female (n=3175)
Cardiac death	413 (5.5%)	256 (8.0%)	477 (6.4%)	307 (9.7%)
Noncardiac death	69 (0.9%)	48 (1.5%)	121 (1.6%)	78 (2.5%)
MI	88 (1.2%)	51 (1.6%)	135 (1.8%)	79 (2.5%)
Stroke	53 (0.7%)	30 (0.9%)	100 (1.3%)	62 (2.0%)
3P MACE	579 (7.9%)	367 (11.4%)	831 (11.1%)	513 (16.3%)
Repeated PCI	161 (2.2%)	75 (2.3%)	374 (5.0%)	142 (4.5%)
Repeated admission	129 (1.7%)	124 (3.9%)	177 (2.4%)	157 (5.0%)
Stent thrombosis	17 (0.2%)	9 (0.3%)	27 (0.4%)	11 (0.3%)
CABG	21 (0.3%)	7 (0.2%)	?	?
Overall MACE	759 (10.2%)	443 (13.8%)	1126 (15.1%)	612 (19.4%)

Age ≥ 71

	6 Months		12 Months	
	Male (n=2395)	Female (n=2121)	Male (n=7468)	Female (n=3175)
Cardiac death	245 (10.2%)	210 (9.9%)	284 (12.0%)	256 (12.3%)
Noncardiac death	47 (1.9%)	41 (1.9%)	78 (3.3%)	66 (3.2%)
MI	39 (1.6%)	38 (1.8%)	58 (2.5%)	55 (2.6%)
Stroke	21 (0.9%)	22 (1.0%)	37 (1.6%)	40 (1.9%)
3P MACE	342 (14.3%)	300 (14.1%)	469 (19.9%)	411 (19.8%)
Repeated PCI	54 (2.3%)	44 (2.1%)	113 (4.8%)	81 (3.9%)
Repeated admission	79 (3.3%)	102 (4.8%)	107 (4.5%)	126 (6.1%)
Stent thrombosis	8 (0.3%)	6 (0.3%)	11 (0.5%)	8 (0.4%)
CABG	5 (0.2%)	3 (0.1%)	?	?
Overall MACE	405 (16.9%)	343 (16.2%)	543 (23.1%)	463 (12.3%)

5186 young adults with both STEMI (64%) and NSTEMI (36%). youngest 5% of women (age 18–49, 4.6% of all AMI in woman) and men (age 18–44, 4.6% of all AMI in men).

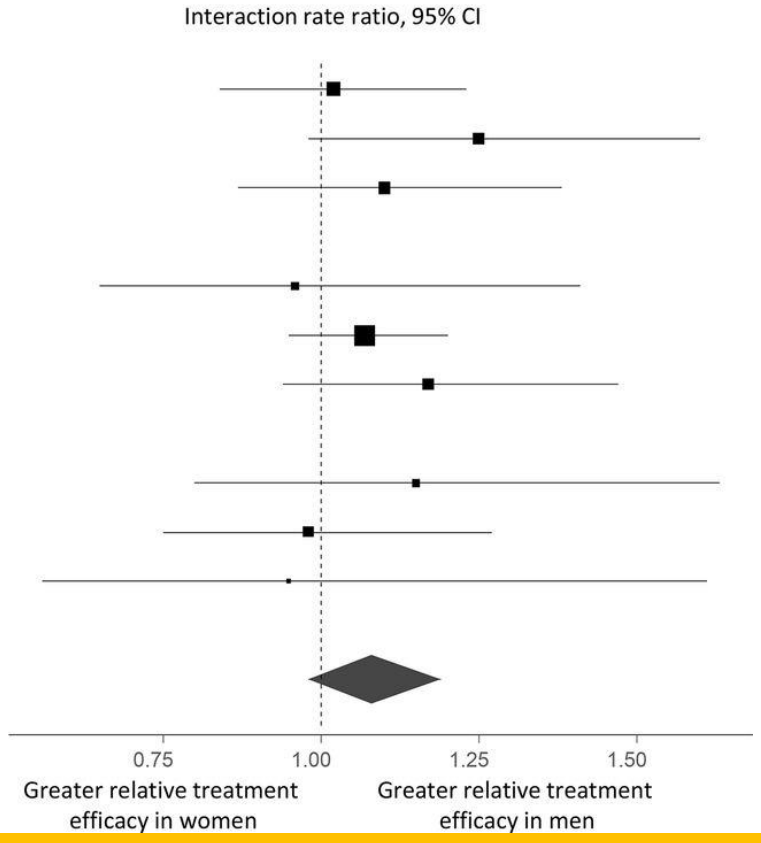
	Young women N=1870 (36%)	Young men N=3316 (64%)	P value
STEMI	59.4%	67.1%	<0.0001
Hypercholesterolemia	39.4%	38.6%	0.58
Hypertension	53.2%	47.4%	<0.0001
Obesity	21.2%	20.5%	0.50
Diabetes mellitus	12.9%	7.7%	<0.0001
Current smoking	55.4%	63.2%	<0.0001
History of stroke	1.7%	0.5%	<0.0001
Prior MI	8.8%	8.9%	0.85
Prior PCI or CABG	7.3%	8.1%	0.34
Killip 4 on admission	2.1%	2.4%	0.53
Coronary angiography	88.0%	88.6%	0.53
PCI	72.9%	73.9%	0.43
CABG	3.8%	4.6%	0.16
Major bleeding	1.8%	0.9%	0.0066
Stroke	0.3%	0.1%	0.12
Death	1.1%	1.5%	0.29
30-day mortality	2.3%	1.9%	0.44
12-month mortality	4.1%	3.3%	0.12

Coronary artery disease
Original research article

Differences in relative and absolute effectiveness of oral P2Y12 inhibition in men and women: a meta-analysis and modelling study

Relative treatment efficacy for cardiovascular events.

Trial	Interaction rate ratio
ACS, novel P2Y12	
PLATO	1.02 (0.84 to 1.23)
TRILOGY ACS	1.25 (0.98 to 1.60)
TRITON-TIMI 38	1.10 (0.87 to 1.38)
ACS, clopidogrel	
CLARITY-TIMI 28	0.96 (0.65 to 1.41)
COMMIT	1.07 (0.95 to 1.2)
CURE	1.17 (0.94 to 1.47)
Stroke	
CHANCE	1.15 (0.80 to 1.63)
SOCRATES	0.98 (0.75 to 1.27)
SPS3	0.95 (0.56 to 1.61)
Meta-estimate	1.08 (0.98 to 1.19)
Between trial standard deviation	1.07 (1.02 to 1.19)



Newer P2Y12 inhibitors may be slightly less efficacious in women than men, but the absolute risk reduction is similar in both sexes

Heart

Table 1-8. Sex-Specific Outcomes from Major Cardiovascular Trials

Study	Study Drugs	n (% Women)	End Points and Sex-Specific Findings	Findings Similar Between Sexes
Acute Coronary Syndrome				
ISIS-1	Atenolol vs. placebo	16,027 (23)	↓ Mortality	Y
ISIS-2	ASA vs. placebo; streptokinase vs. placebo; ASA + streptokinase vs. placebo	17,187 (23)	↓ Mortality	Y
GUSTO V	Retaplase vs. abciximab + half-dose retaplase	16,588 (25)	↑ Mortality (nonsignificant in overall population)	Y
GUSTO V substudy (Impact of Female Sex on Death and Bleeding)	Retaplase vs. abciximab + half-dose retaplase	16,588 (25)	Significant ↑ mortality in women; ↑ moderate and severe bleeding in women	
ExTRACT-TIMI 25	Planned fibrinolytic therapy with enoxaparin vs. UFH	20,479 (23)	↓ Death or nonfatal MI at 30 days	Y
ExTRACT-TIMI 25 substudy (Outcomes in Women with STEMI)	Planned fibrinolytic therapy with enoxaparin vs. UFH	20,479 (23)	Similar bleeding among men and women receiving enoxaparin but in women receiving enoxaparin compared with UFH Greater absolute risk reduction of enoxaparin on death, nonfatal MI, or nonfatal major bleeding in women	
OASIS-6	Fondaparinux vs. UFH	12,092 (28)	↓ Composite of death or reinfarction at 30 days	Y
COMMIT	75 mg of clopidogrel + 162 mg of ASA	45,852 (28)	↓ Composite of death, reinfarction, or stroke; ↓ death from any cause	Y
COMMIT/CCS-2	Early metoprolol vs. placebo	45,852 (28)	No benefit from early intravenous metoprolol therapy with composite of death, reinfarction, or cardiac arrest	Y
CLARITY-TIMI 28	Fibrinolytic + clopidogrel (300-mg load + 75 mg daily) vs. placebo	3491 (20)	↑ Patency rate of the infarct-related artery; ↓ ischemic complications with clopidogrel	Y
ACUITY	Heparin + GPI, bivalirudin + GPI, or bivalirudin alone	13,819 (30)	Bivalirudin alone was noninferior to heparin + GPI in the primary composite ischemia end point with significantly ↓ bleeding Bivalirudin + GPI was noninferior to heparin + GPI in rates of composite ischemia or bleeding	Not reported
ACUITY substudy (Impact of Gender on Antithrombin Strategy)	Heparin + GPI, bivalirudin + GPI, or bivalirudin alone	13,819 (30)	Similar ↓ 30-day mortality and composite ischemia end point but ↑ bleeding in women vs. men	
PROVE IT-TIMI 22	Atorvastatin 80 mg vs. pravastatin 40 mg	4162 (22)	↓ Death, MI, unstable angina, revascularization, and stroke	Y
Dyslipidemia				
4S	Simvastatin	4444 (29)	↓ Mortality	Y

Clinical impact by sex difference in Inflammation, especillay ACS, True or not?

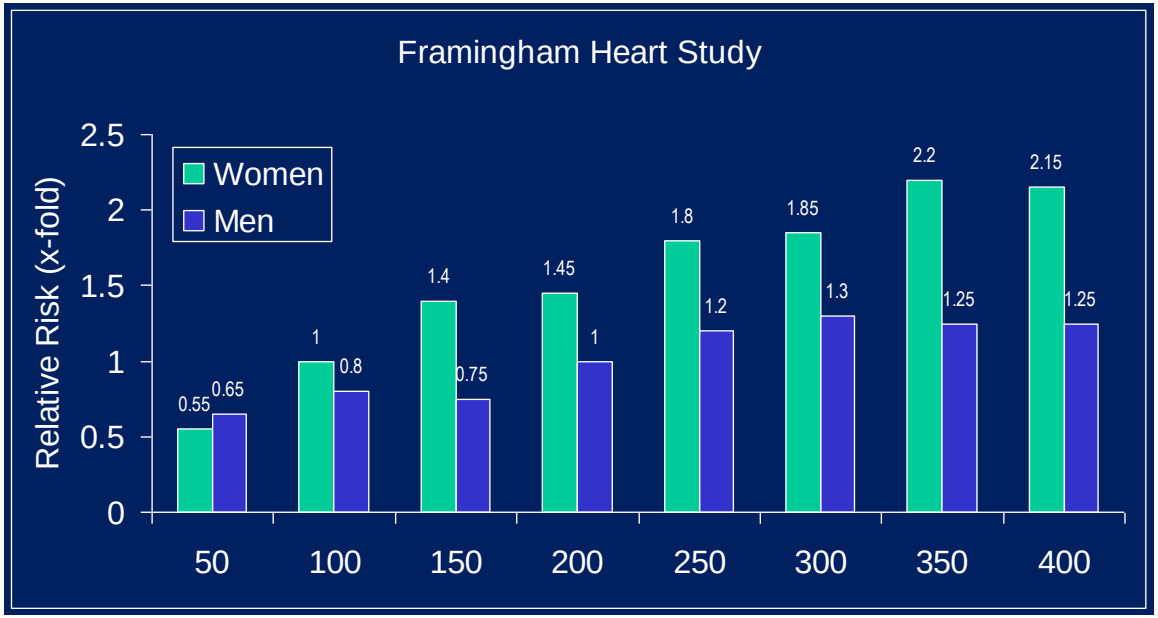
Unclear,

- **Sex is not only single factor but combined factor, especillay postmenopausal woman**

Women and CAD Risk Factors

- **Higher prevalence of avoidable risk factors**
  - **↑ blood cholesterol, ↑ TG**
  - **↑ physical inactivity**
  - **↑ overweight (body mass index, 25.0-29.9)**
- **Diabetes is a more powerful risk factor for CAD**
  - **3- to 7-fold in women vs 2- to 3-fold in men**
- **↓ HDL cholesterol levels more predictive of CAD**

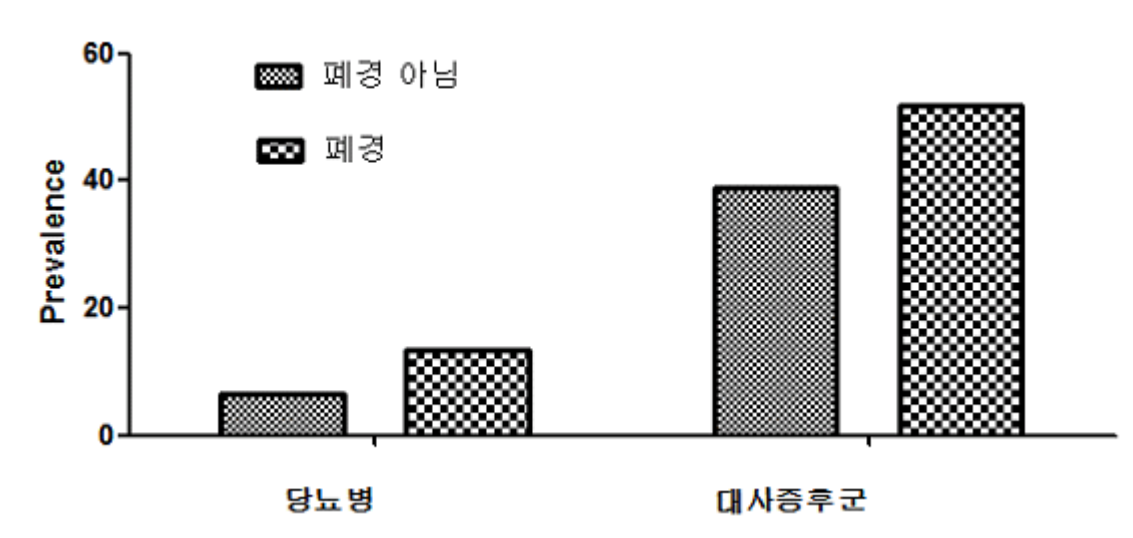
Impact of TG Levels on RR of CAD



1. American Heart Association. *1999 Heart and Stroke Statistical Update.* 1998
2. Mosca L, et al. *Circulation.* 1999

Castelli WP. *Can J Cardiol.* 1988

High prevalence of Metabolic syndrome in postmenopause population



- DM (6.5% vs. 13.3%) and Metabolic syn (38.9% vs. 51.7%) are elevated in postmenopause.
- Hypertension by postmenopause should mediatd by elevated metabolic syndrome, not postmenopause itself.

Prevalence of Dyslipidemia

Four among 10 adults aged 30 years or older have dyslipidemia.
"About 5 out of every 10 men and 3 out of every 10 women are dyslipidemic."

30-39 yr	40-49 yr	50-59 yr	60-69 yr	≥70 yr
26.1 %	32.8 %	46.3 %	55.8 %	50.1 %
38.9 %	48.0 %	52.0 %	55.0 %	46.4 %
14.9 %	19.8 %	41.4 %	56.4 %	52.9 %

Dyslipidemia	All	30-39 yr	40-49 yr	50-59 yr	60-69 yr	≥70 yr
Total	40.5 %	26.1 %	32.8 %	46.3 %	55.8 %	50.1 %
Men	47.9 %	38.9 %	48.0 %	52.0 %	55.0 %	46.4 %
Women	34.3 %	14.9 %	19.8 %	41.4 %	56.4 %	52.9 %

Dyslipidemia Fact Sheet in Korea 2018

Summary and Conclusion

- **There are sex difference in Inflammation and Thrombogenicity.**
- **But, do not poor prognosis factors for female only.**
- **When the Aging process meet postmenopause, The CV risk factors were amplified through a metabolic abnormality (Metabolic syndrome).**
- **We need new approach for Age-Gender-Medicine.**

Thank You for Your Attention !