

Traitement Antithrombotique des SCA chez la femme

Farzin Beygui

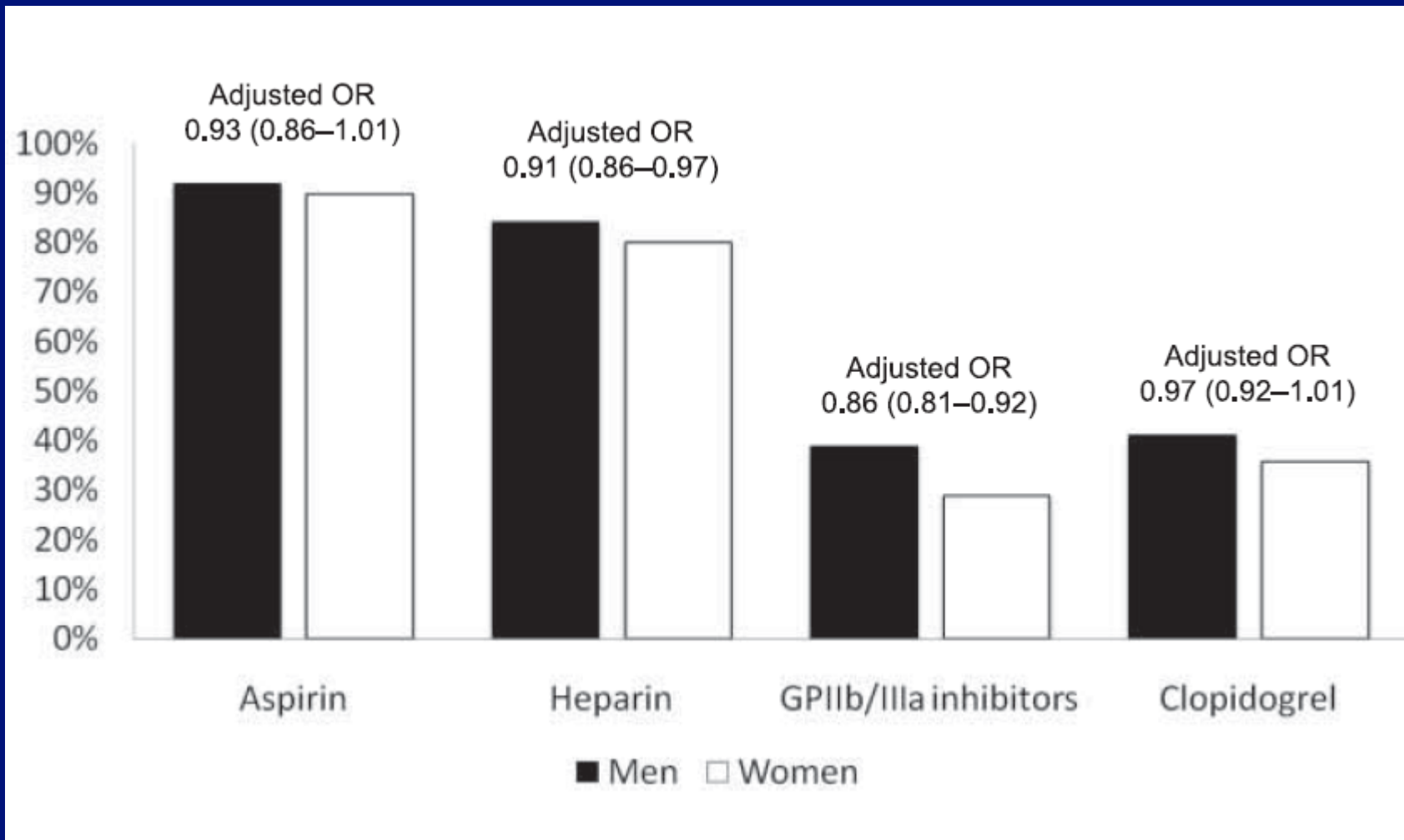


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Disclosures

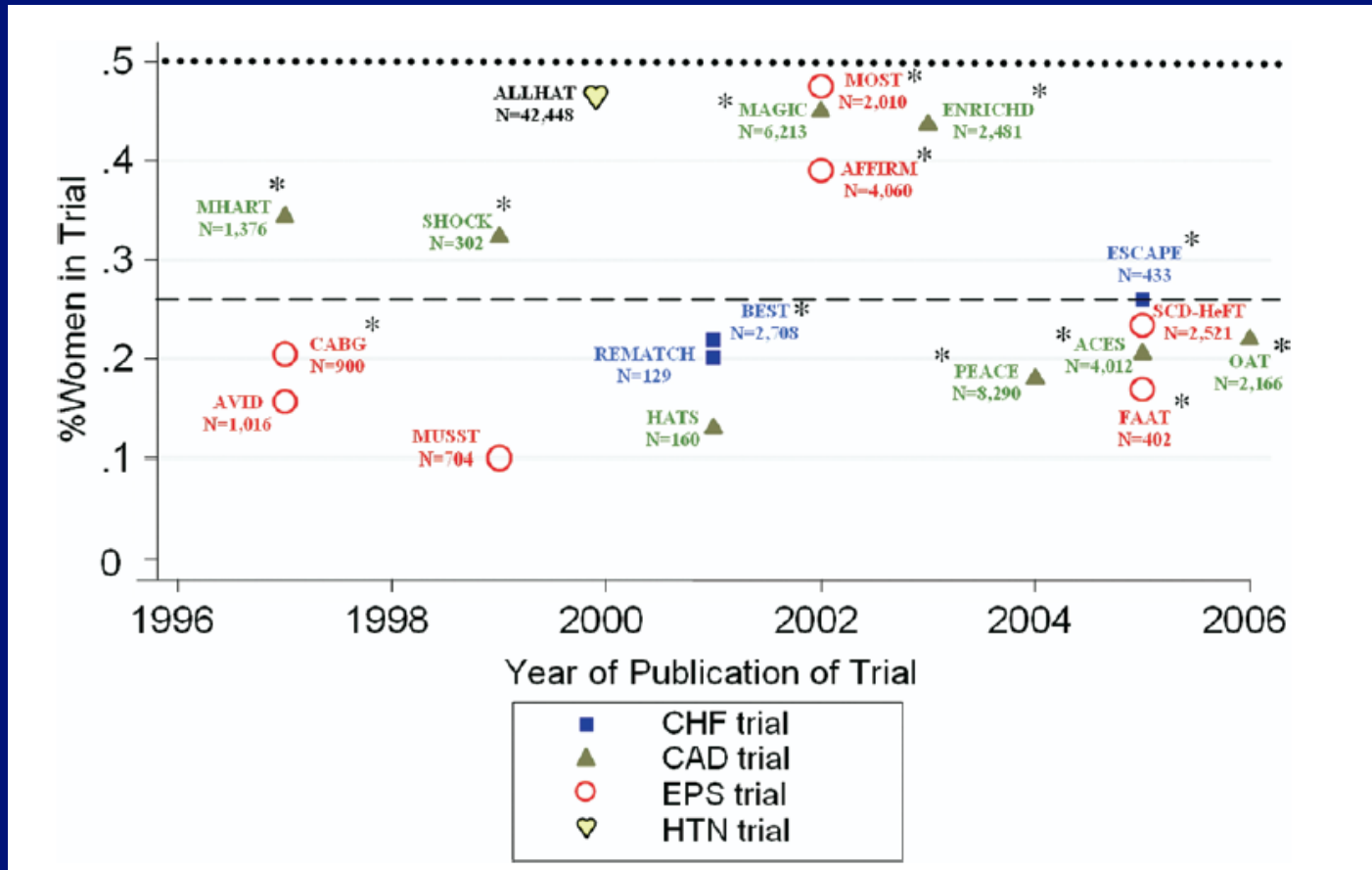
- Research grant
 - Fédération Française de Cardiologie
 - Fondation pour la Recherche Médicale
 - BRAHMS medical
 - Pfizer
- Lecture or consultancy honoraria
 - Pfizer
 - Lilly
 - AstraZeneca
 - Servier
 - HAC pharma

Use of antithrombotics in ACS



CRUSADE registry, JACC 2005

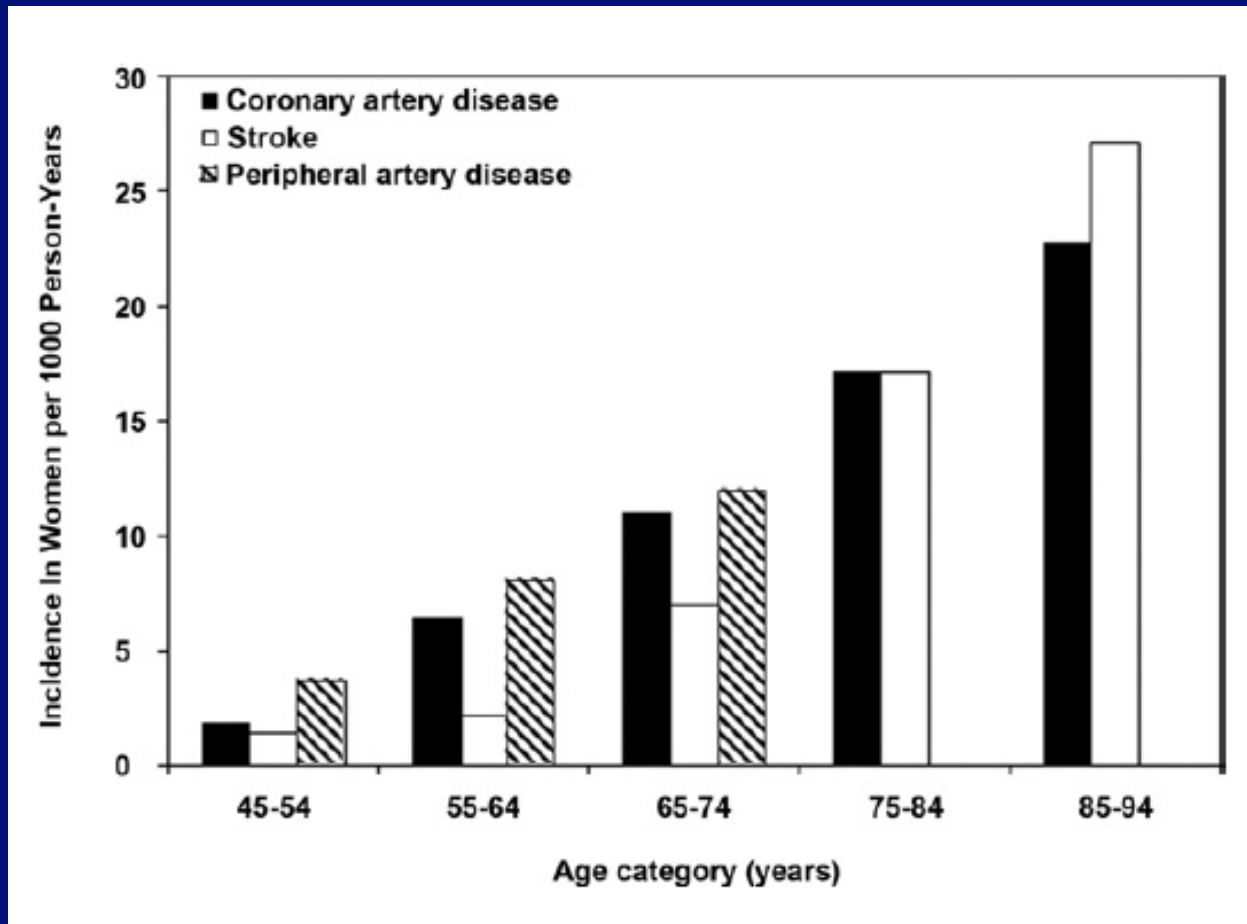
Women in clinical trials



Average % of women: 27% [10-47%]

Womens subgroups represented : 30% of studies

Atherothrombosis in women



Framingham Heart Study and ARIC cohorts

Différences entre hommes et femmes pouvant modifier la réponse aux antithrombotiques

- Génétiques
- Morphologique
 - Poids/taille/BMI/S²
 - Masse musculaire/graisseuse
 - Volume de distribution des médicaments
- Hormonales
- Métaboliques

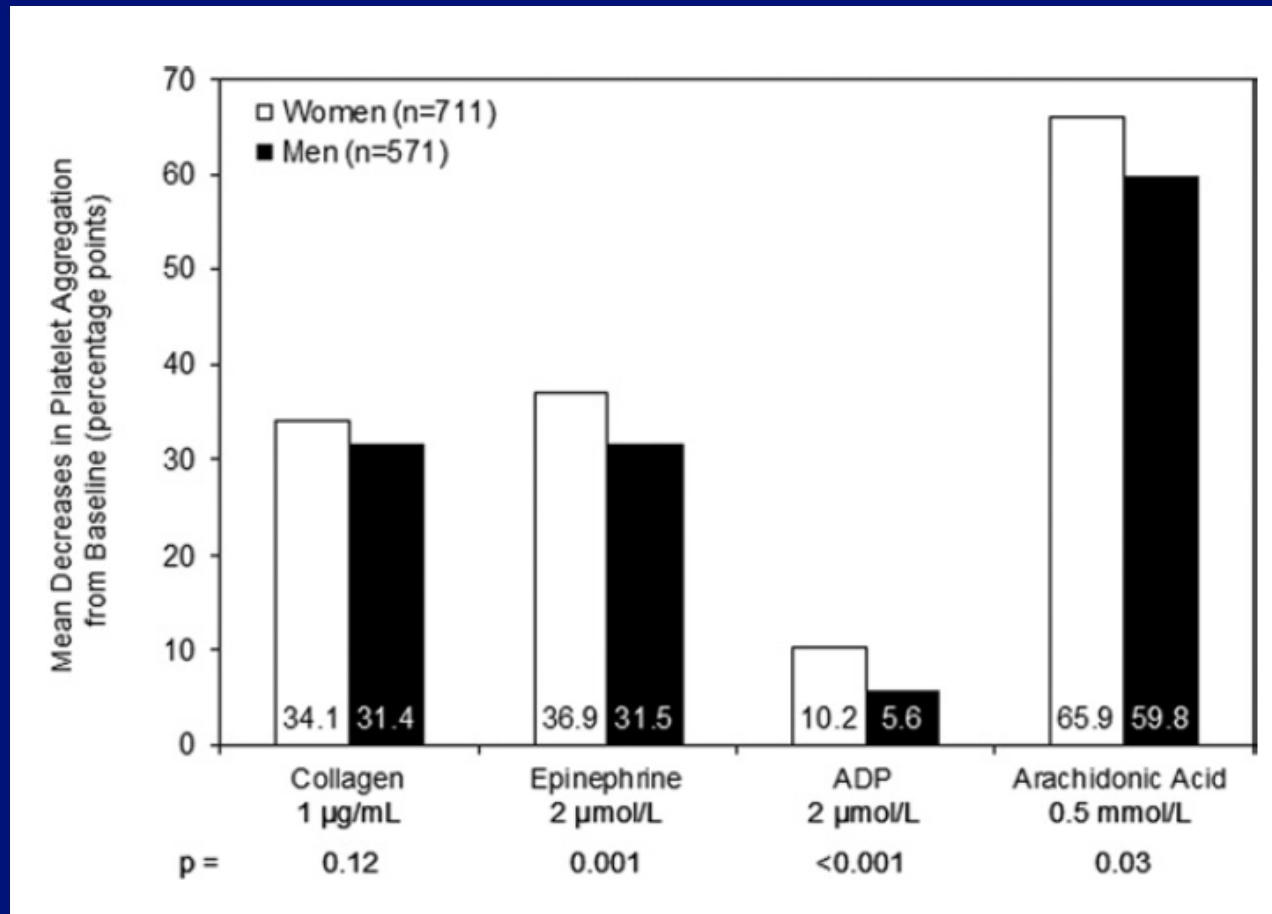
Platelet biology in women

- Platelets & megacaryocytes express estrogen receptors
- NOs and TxA₂ are modulated by estrogens and androgens
- Platelet and coagulation status change
 - menstrual cycle
 - pre-post menopause
 - oral contraceptive or substitutive hormone therapy

Platelet biology in women

- Baseline differences vs men
 - Higher baseline platelet reactivity to ADP and thrombin
 - 50-80% Higher concentration of GP2B3A receptors
 - Higher fibrinogen binding platelets
 - Higher rates of spontaneous platelet aggregation
 - Lower platelet signaling cascades
 - Prothrombotic clot (increased speed and strength of clot on elastography)
- Aspirin
 - More rapid absorption of aspirin, distributed in a larger apparent volume, more quick hydrolysis
 - Similar platelet inhibition
 - higher reactivity after ADP, Epinephrin, AA
- P2Y12 inhibitors
 - Similar levels of clopidogrel active metabolite
 - Similar platelet inhibition magnitude

Platelet aggregation after aspirin therapy in healthy adults



Platelet biology in women

- Inflammatory profile
 - Lower « effect » of CRP on CV events in women
 - Higher leukocyte counts
 - Higher P-selectin expression
 - Similar effects of aspirin and statins on CRP levels
 - Similar effects of clopidogrel on CRP levels
 - Higher CRP levels in postmenopausal women on estrogen
 - Different response to hormone therapy based on polymorphisms of GPI α -5C

Coagulation and fibrinolysis in women

- Association of estrogen with lower levels of
 - Fibrinogen
 - ATIII
 - Protein S
 - PAI-1
- Association of testosterone with higher levels of
 - Factor VII
 - α 2-antiplasmin
 - Plasminogen
- Global coagulation tests
 - Similar coagulation & fibrinolysis status
 - longer bleeding times in women

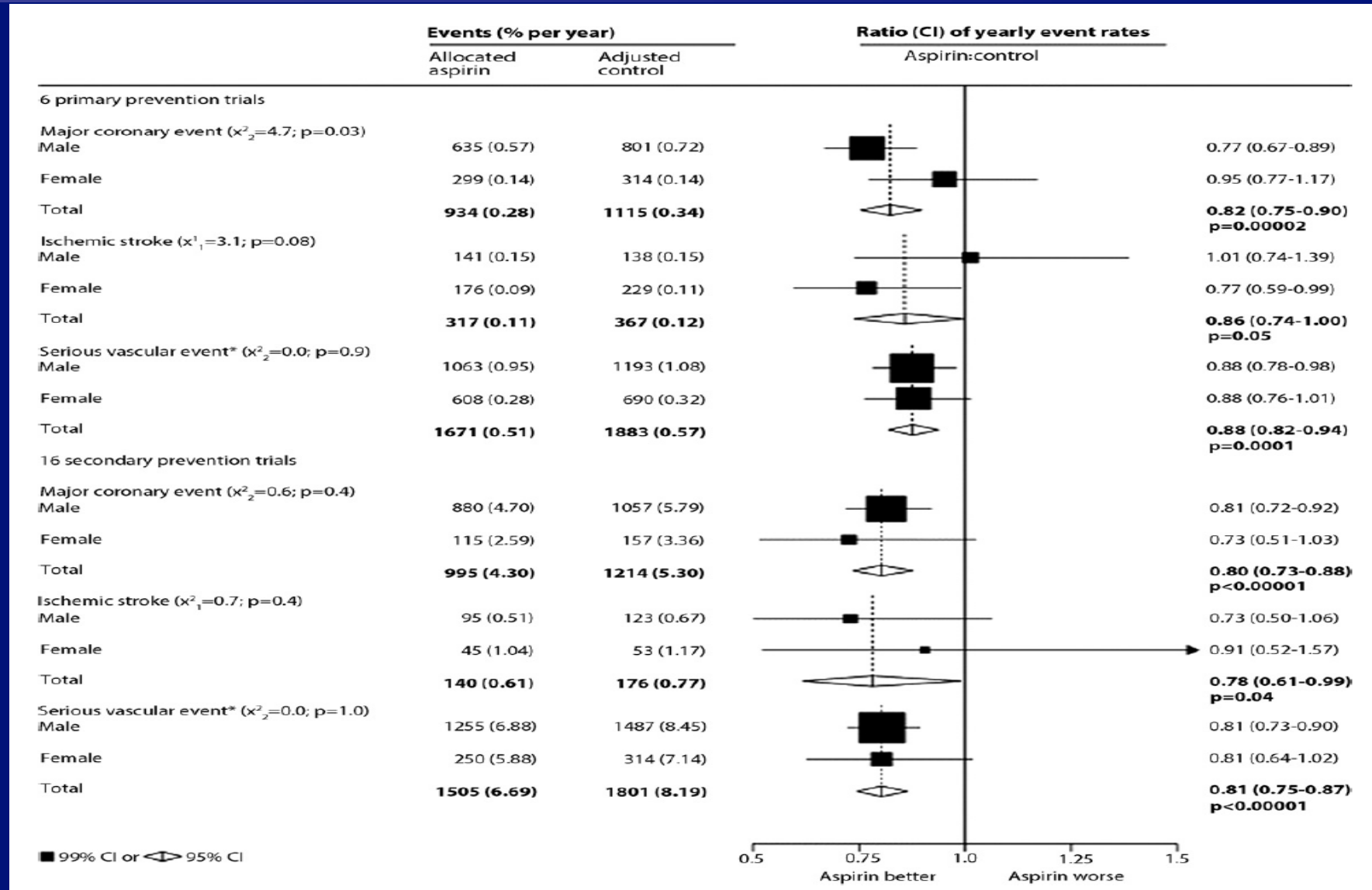
Coagulation and fibrinolysis in women

- More sensitive to UFH: higher aPTT times
- Similar response to enoxaparin
- Similar response to direct thrombin inhibitors
- Similar response to AntiXa

Bénéfice clinique des antithrombotiques chez la femme

Outcomes with aspirin Gender-based analysis

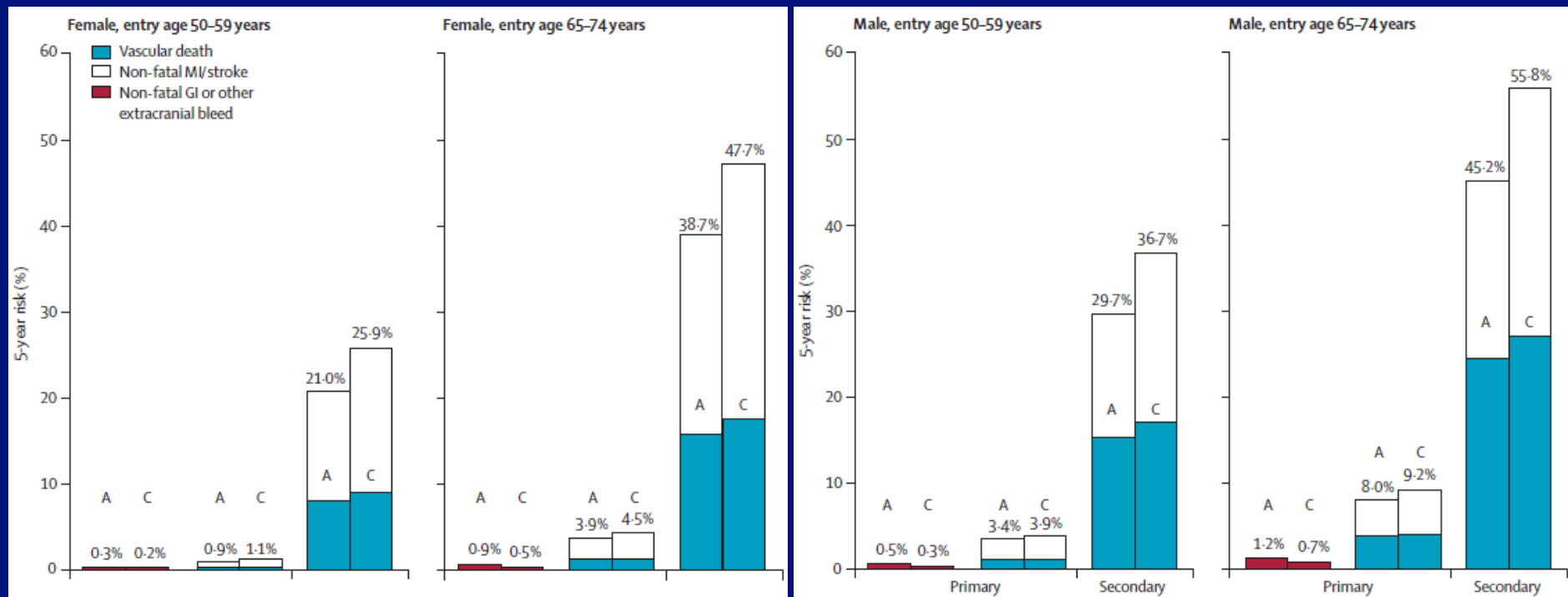
ATT collaboration. Lancet 2009



Outcomes with aspirin

Gender-based analysis

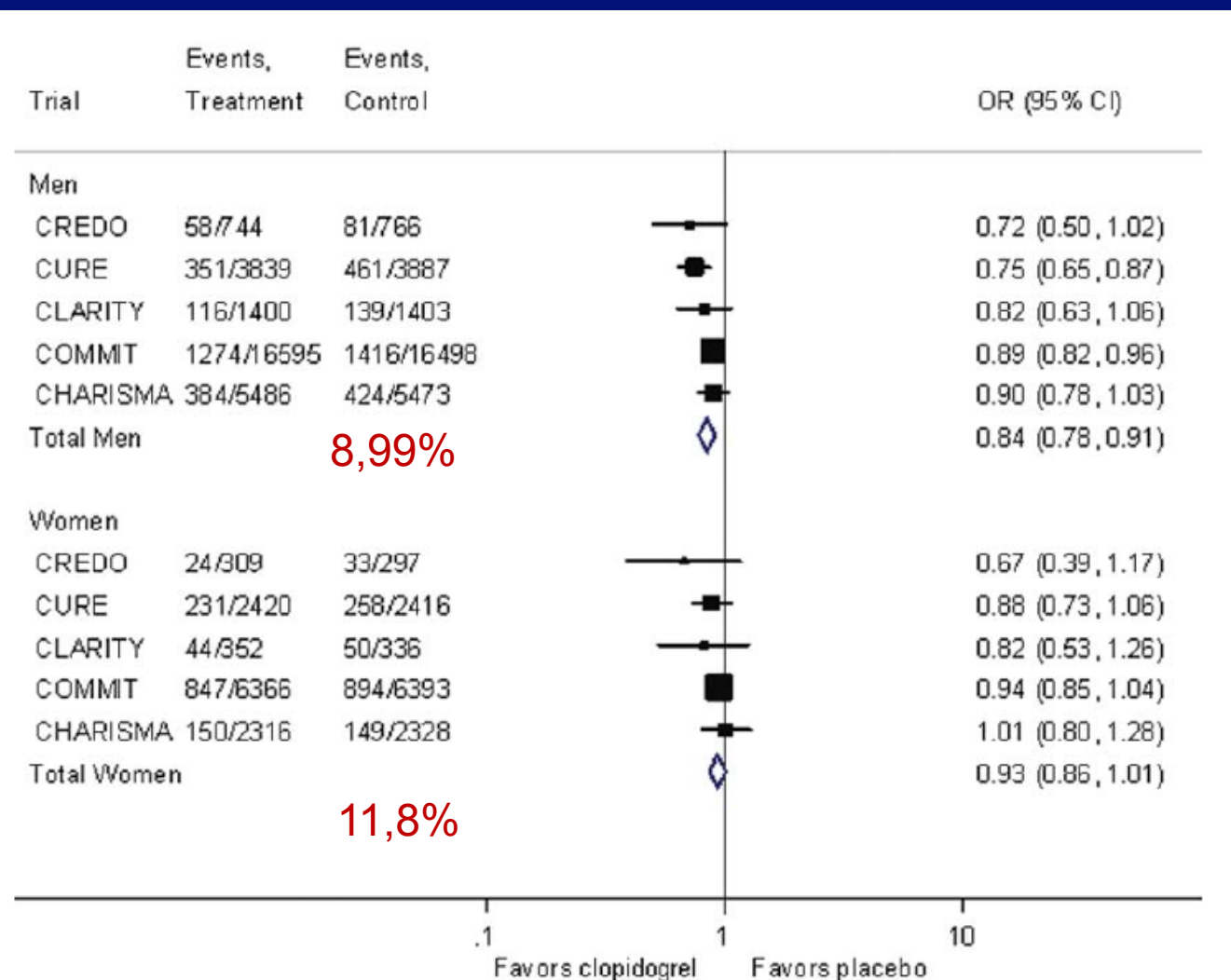
ATT collaboration. Lancet 2009



Outcomes with clopidogrel

Death/MI/Stroke

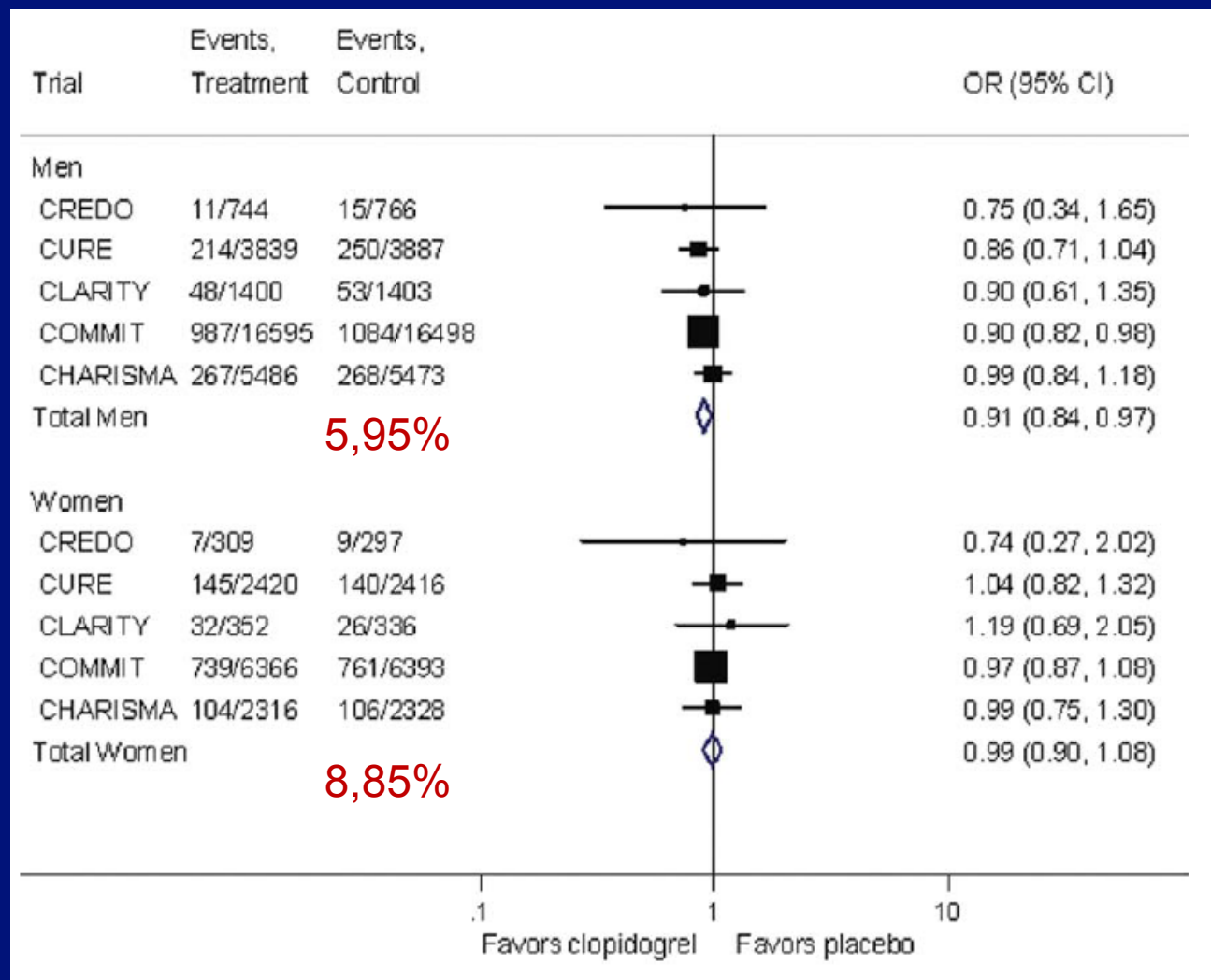
Berger et al. JACC 2009



Outcomes with clopidogrel

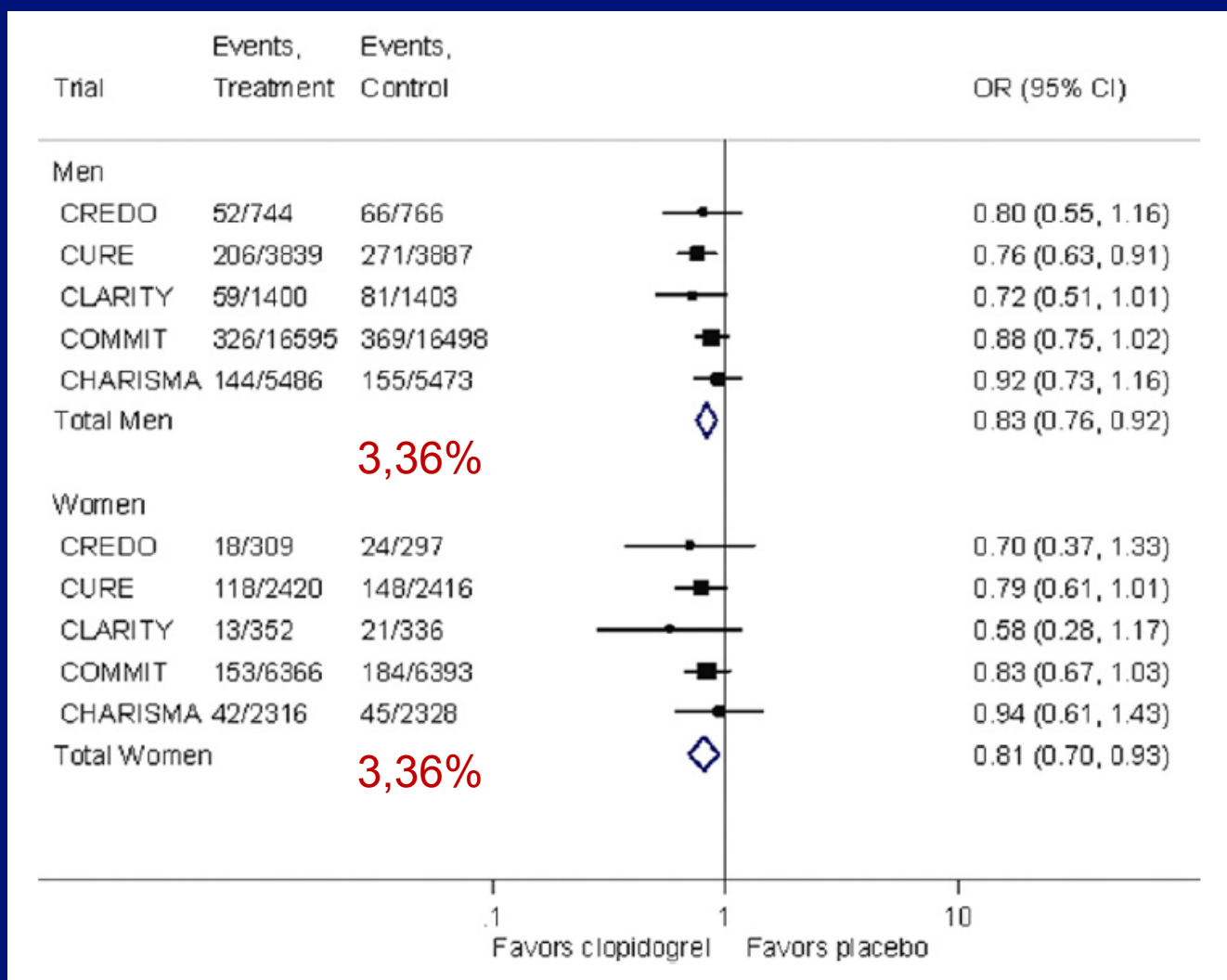
Total Mortality

Berger et al. JACC 2009



Outcomes with clopidogrel MI

Berger et al. JACC 2009



Antiplatelet therapy

Male	1854		112 (11.9%)	72 (7.9%)	0.65 (0.48-0.87)
Female	804		57 (14.1%)	44 (11.0%)	0.77 (0.52-1.15)

PCI CURE

Male sex	7726	11.9	9.1	
Female sex	4836	10.7	9.5	

CURE

Sex					
Female	6871	4.5	5.4	0.83	0.09
Male	18,213	4.1	4.1	1.00	0.95

CURRENT

Sex					
Male	10,085	9.5	11.9	21	
Female	3,523	11.0	12.6	12	

Triton

Sex					
Male	13336	9.2	11.1	0.85 (0.76, 0.95)	
Female	5288	11.2	13.2	0.83 (0.71, 0.97)	

Plato

Sex					
Female	30/107	47/113		0.67 (0.46-0.98)	0.035
Male	142/344	158/342		0.89 (0.75-1.06)	0.194

On-Time2

Sex					
Female	207 (17.0)	219 (13.3)		0.76 (0.47-1.25)	
Male	599 (8.6)	609 (8.6)		1.00 (0.68-1.48)	

Finesse

Benefit of GPI in men vs women in NST-ACS without early invasive strategy



	Women			Men			p Value†
	GPI	Control	OR (95% CI)*	GPI	Control	OR (95% CI)	
Overall	n = 6,410	n = 4,603		n = 11,886	n = 8,502		
Death	3.9%	3.6%	1.08 (0.89-1.33)	3.2%	3.8%	0.83 (0.71-0.96)	0.030
Death or MI	11.5%	10.4%	1.15 (1.01-1.30)	10.4%	12.6%	0.81 (0.75-0.89)	<0.001
Baseline cardiac troponin I or T <0.1 µg/l	n = 1,548	n = 1,003		n = 2,095	n = 1,449		
Death	2.3%	2.0%	1.20 (0.69-2.10)	2.3%	2.1%	1.07 (0.67-1.71)	0.84
Death or MI	6.2%	5.3%	1.29 (0.91-1.83)	7.6%	6.9%	1.10 (0.84-1.43)	0.65
Baseline cardiac troponin I or T ≥0.1 µg/l	n = 939	n = 567		n = 2,174	n = 1,284		
Death	6.2%	7.6%	0.80 (0.53-1.21)	4.1%	5.2%	0.75 (0.54-1.04)	0.88
Death or MI	12.7%	13.6%	0.93 (0.68-1.28)	9.3%	11.3%	0.82 (0.65-1.03)	0.48

Anticoagulation

Oasis 5 (NSTACS): fondaparinux vs enoxaparin

Sex					
Male	12,379	6.0	5.8		
Female	7,699	5.3	5.7		

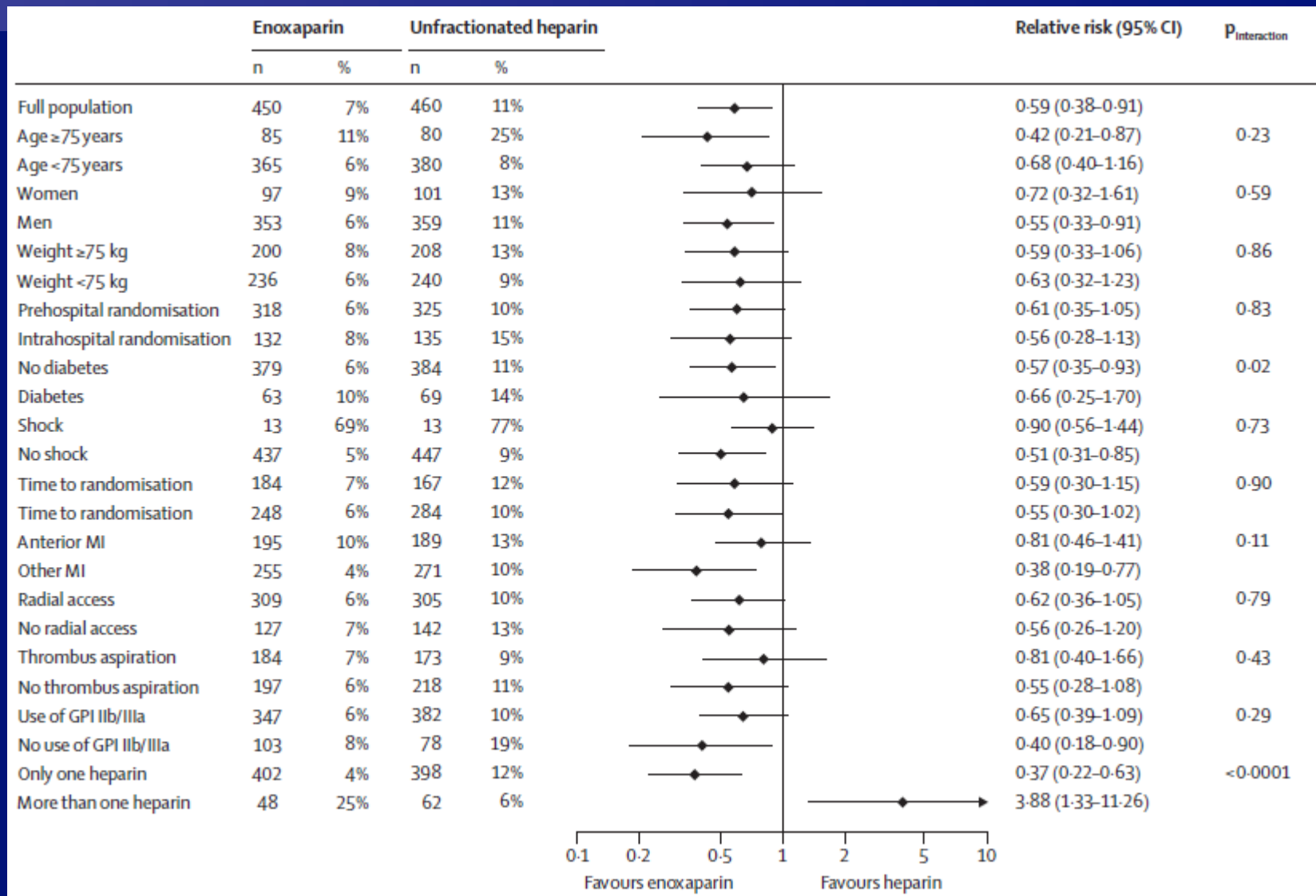
ATLAS (ACS) rivaroxaban on top of standard therapy

Sex					
Male	464/7627	270/3831			0.87 (0.75–1.01)
Female	162/2602	106/1282			0.77 (0.60–0.99)

Atoll (STEMI): enoxaparin vs UFH

Women	97	9%	101	13%		0.72 (0.32–1.61)
Men	353	6%	359	11%		0.55 (0.33–0.91)

ATOLL study main secondary EP



Risque hémorragique chez la femme

Bleeding risk in Acuity and Horizons AMI

Table 2

Independent Predictors of Non-CABG-Related Major Bleeding Within 30 Days, With Multiple Logistic Regression

Risk Factor	Odds Ratio	95% CI	Coefficient*	z Value†
Sex				
Male	1.00	—	—	
Female	2.32	1.98–2.72	0.84	10.36
Age, per 5 yrs	1.17	1.13–1.21	0.157	8.79
Serum creatinine, per 0.1 mg/dl	1.09	1.07–1.12	0.088	7.91
White blood cell count, g/lga/l	1.10	1.07–1.12	0.094	7.83
Anemia				
No	1.00	—	—	
Yes	1.98	1.65–2.37	0.68	7.47
Presentation				
Biomarker-negative ACS	1.00	—	—	
NSTEMI-raised biomarkers	1.26	1.04–1.54	0.23	2.30
STEMI	1.92	1.52–2.44	0.65	5.38
Randomized treatment				
UFH/Enox + GPI	1.00	—	—	
Bivalirudin monotherapy	0.56	0.47–0.67	–0.58	–6.38
Bivalirudin + GPI	0.89	0.73–1.08	–0.12	–1.21

The REPLACE-2 Trial (N=6,010):

Predictors of Major Bleeding in PCI

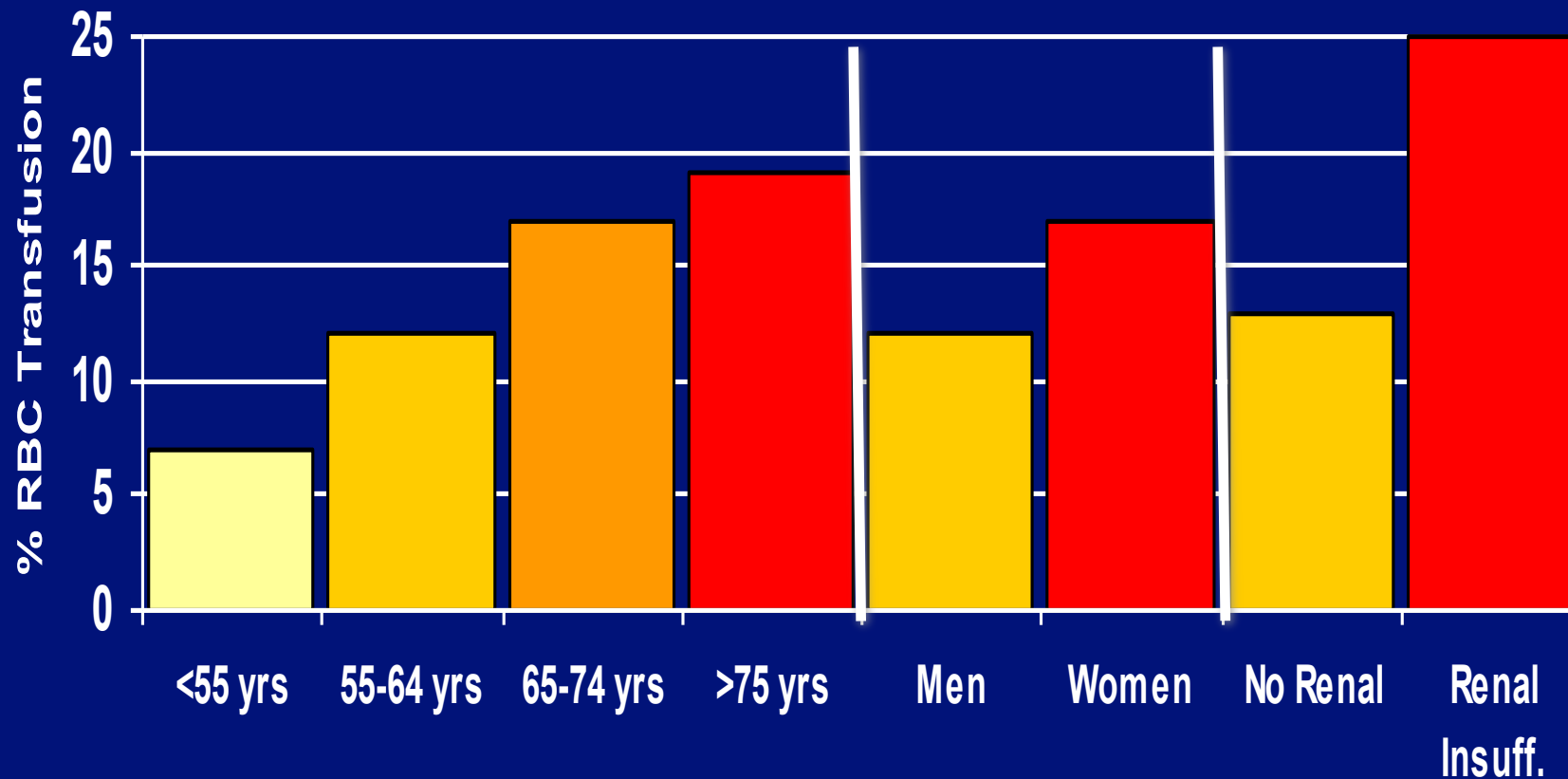
Variable	OR	95% CI	p-value
Baseline risk factors			
Age ≥ 75	1.482	1.01, 2.18	0.045
Gender (Female)	1.535	1.12, 1.10	0.007
Creatinine Clearance	1.008	1.00, 1.01	0.006
Anemia	1.403	1.02, 1.94	0.040
Prior Angina	1.589	1.08, 2.35	0.02
Prior PCI	0.629	0.45, 0.88	0.007
Prior Thienopyridine	0.601	0.39, 0.93	0.023
Peri-procedural risk factors			
Treatment Group (Heparin + GPI vs. bivalirudin)	1.969	1.37, 2.84	0.0003
Provisional GPI received	2.679	1.59, 4.51	0.0002
Procedure Duration >1h	2.049	1.22, 3.45	0.007
Time to Sheath Removal >6h	1.614	1.06, 2.45	0.024
Intensive Care Unit stay (days)	1.25	1.18, 1.32	<0.0001
Intra-aortic Balloon Pump	8.705	3.43, 22.07	<0.0001

Bleeding and ACS

- Older Age
- **Female Gender**
- Renal Failure
- History of Bleeding
- Right Heart Catheterization
- GPIIb/IIIa antagonists

Independent
Predictors of Major
Bleeding in Marker
Positive Acute
Coronary Syndromes

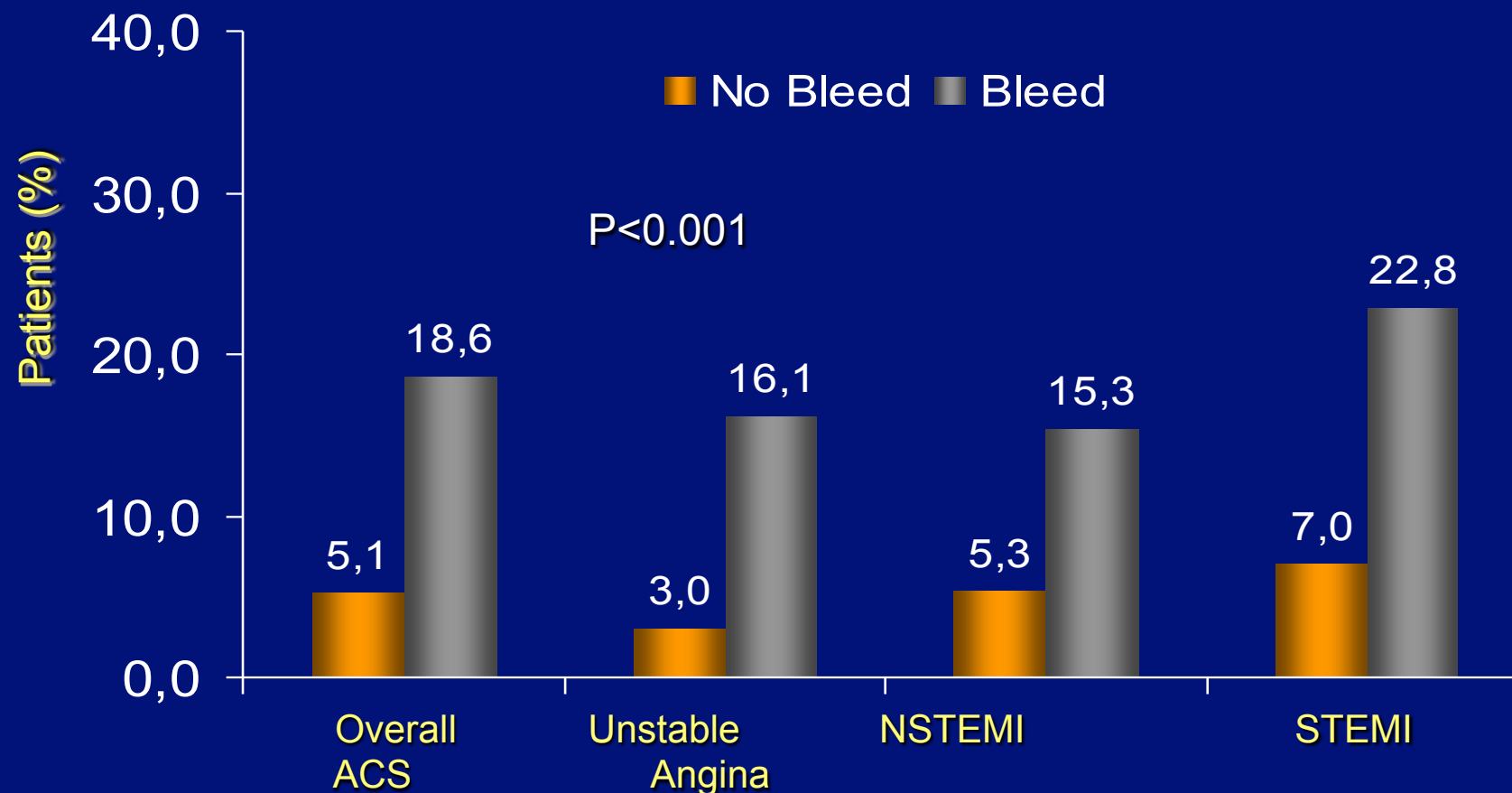
Safety Concerns in ACS Care: Need for Blood Transfusions



CRUSADE registry Yang X, JACC 2005;46:1490-5.

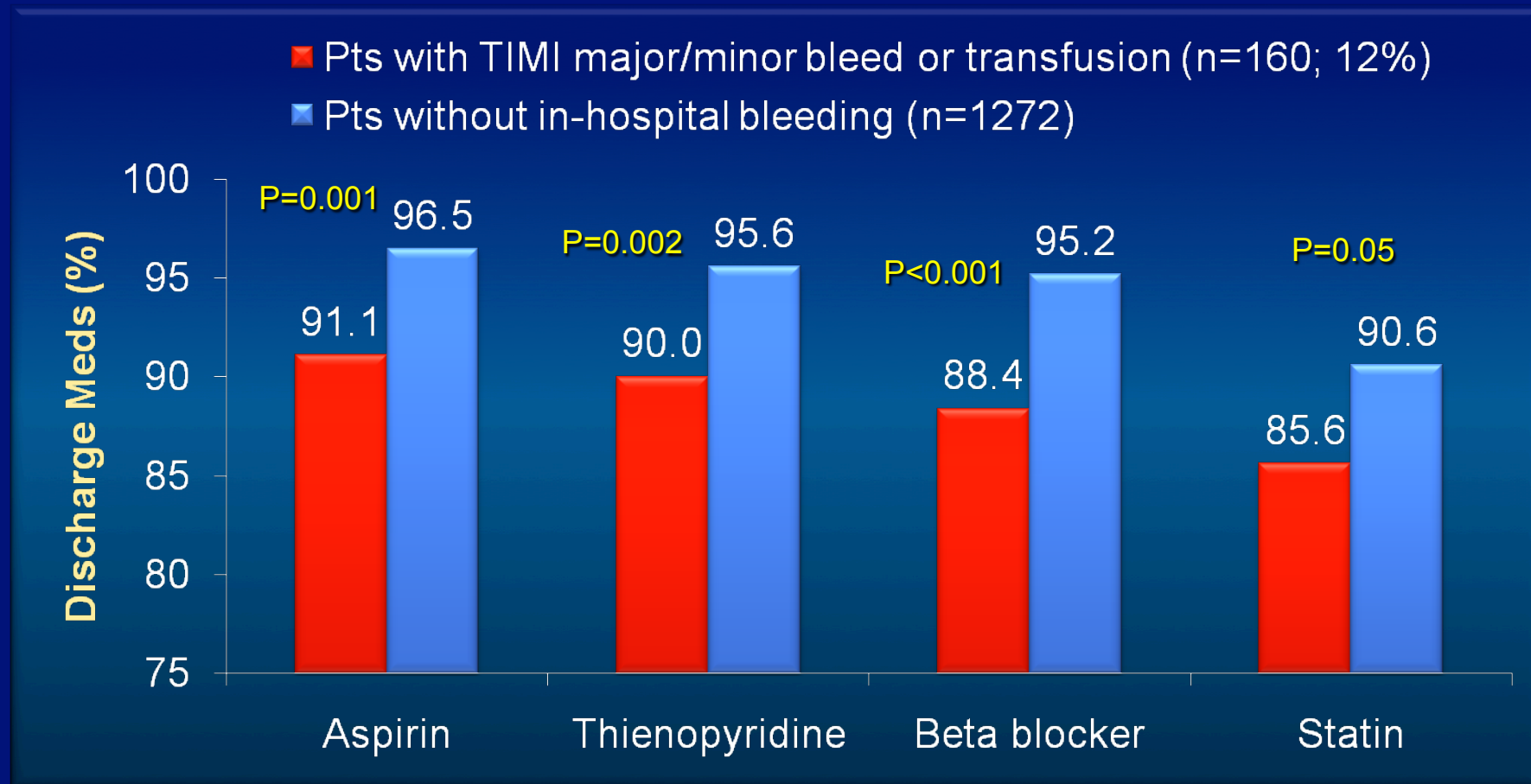
Major Bleeding Predicts Mortality in ACS

24,045 ACS patients in the GRACE registry, in-hospital death

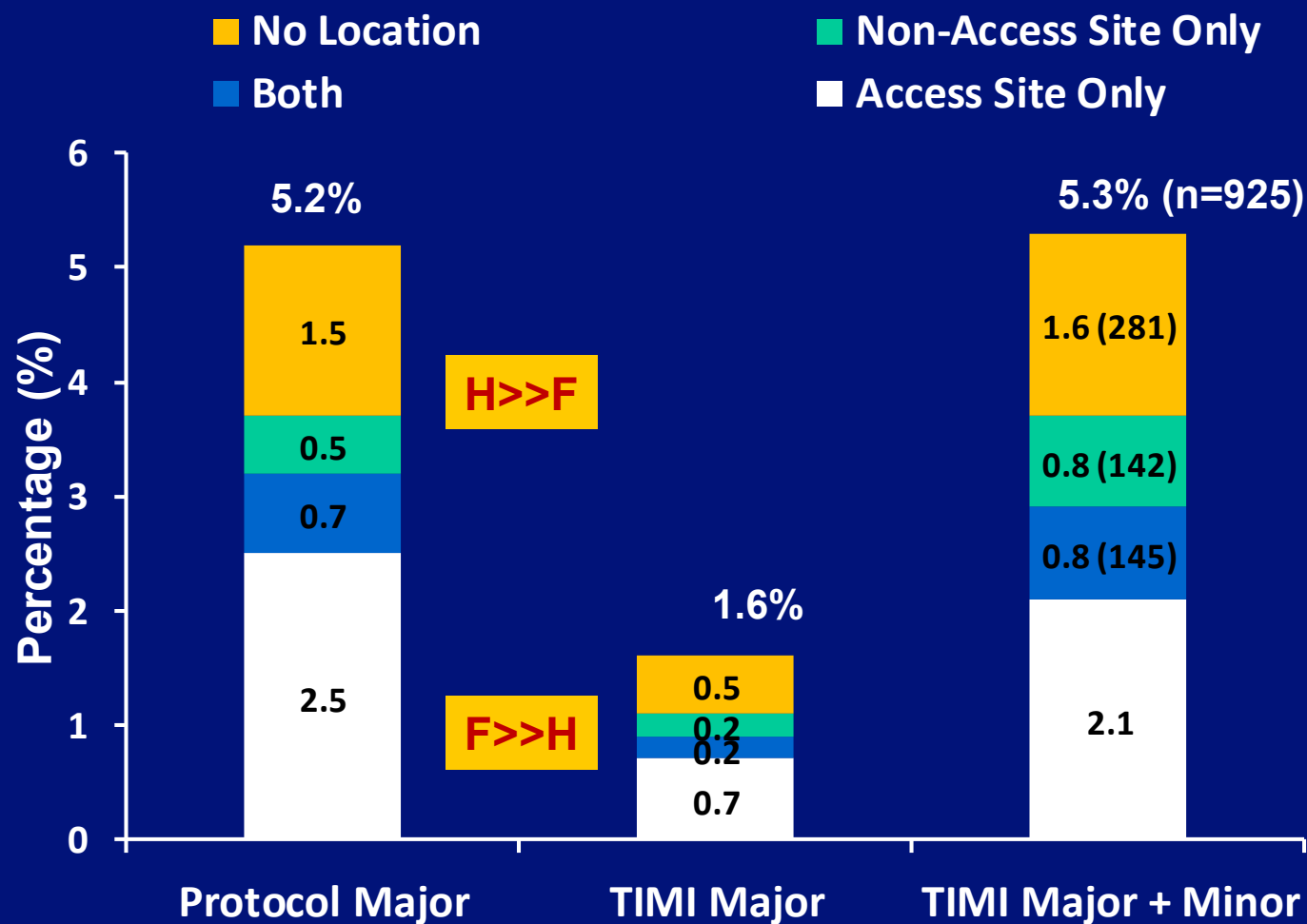


Discharge Medication Use in Patients who Bleed: PREMIER Registry (STEMI)

1433 STEMI pts treated with primary stenting

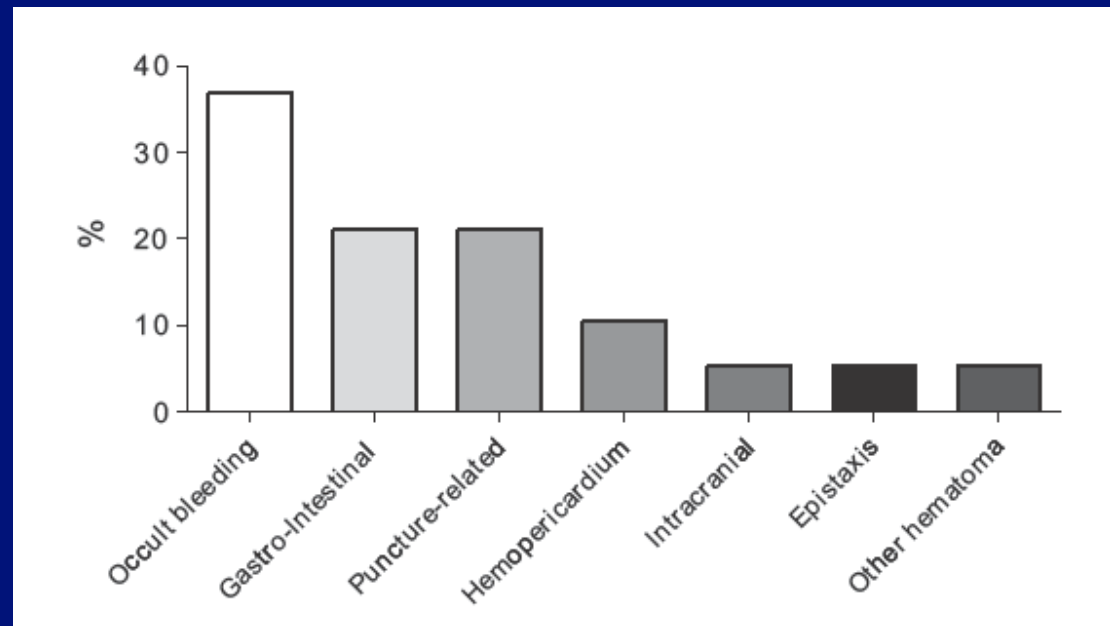


Sources and Incidence of Bleeding Among 17,393 PCI (93% Femoral) Patients

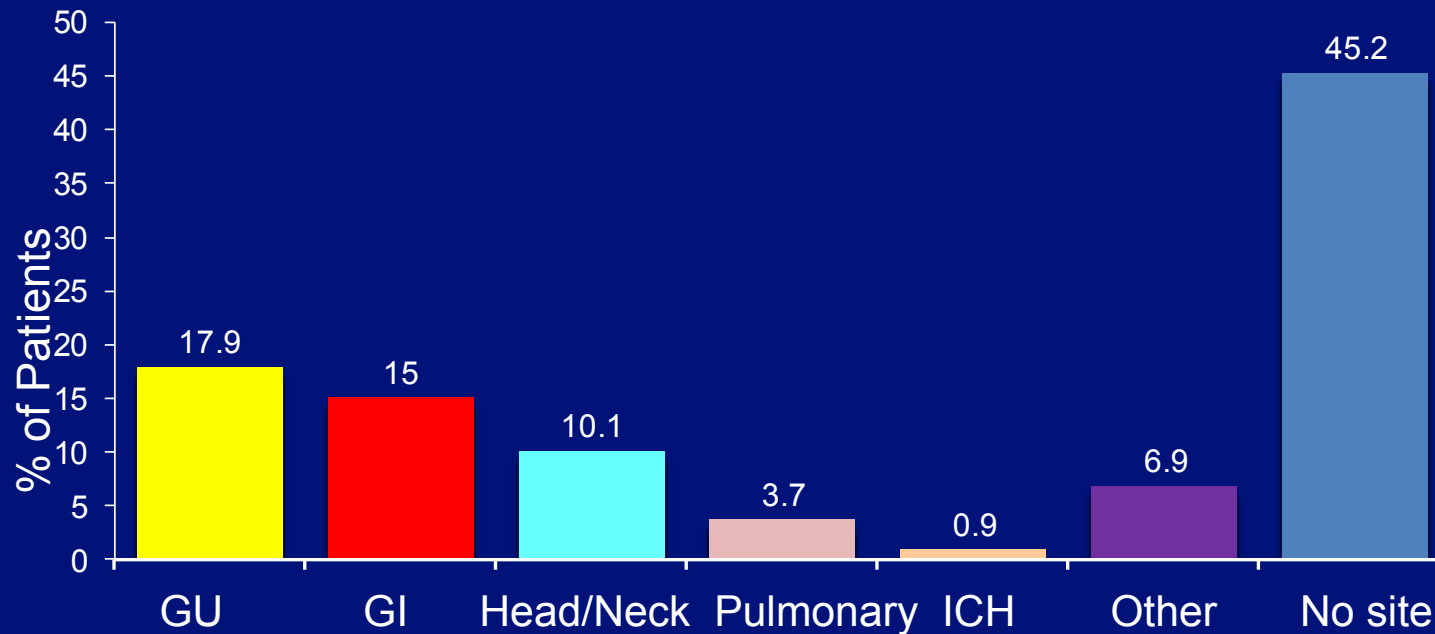


ABOARD trial

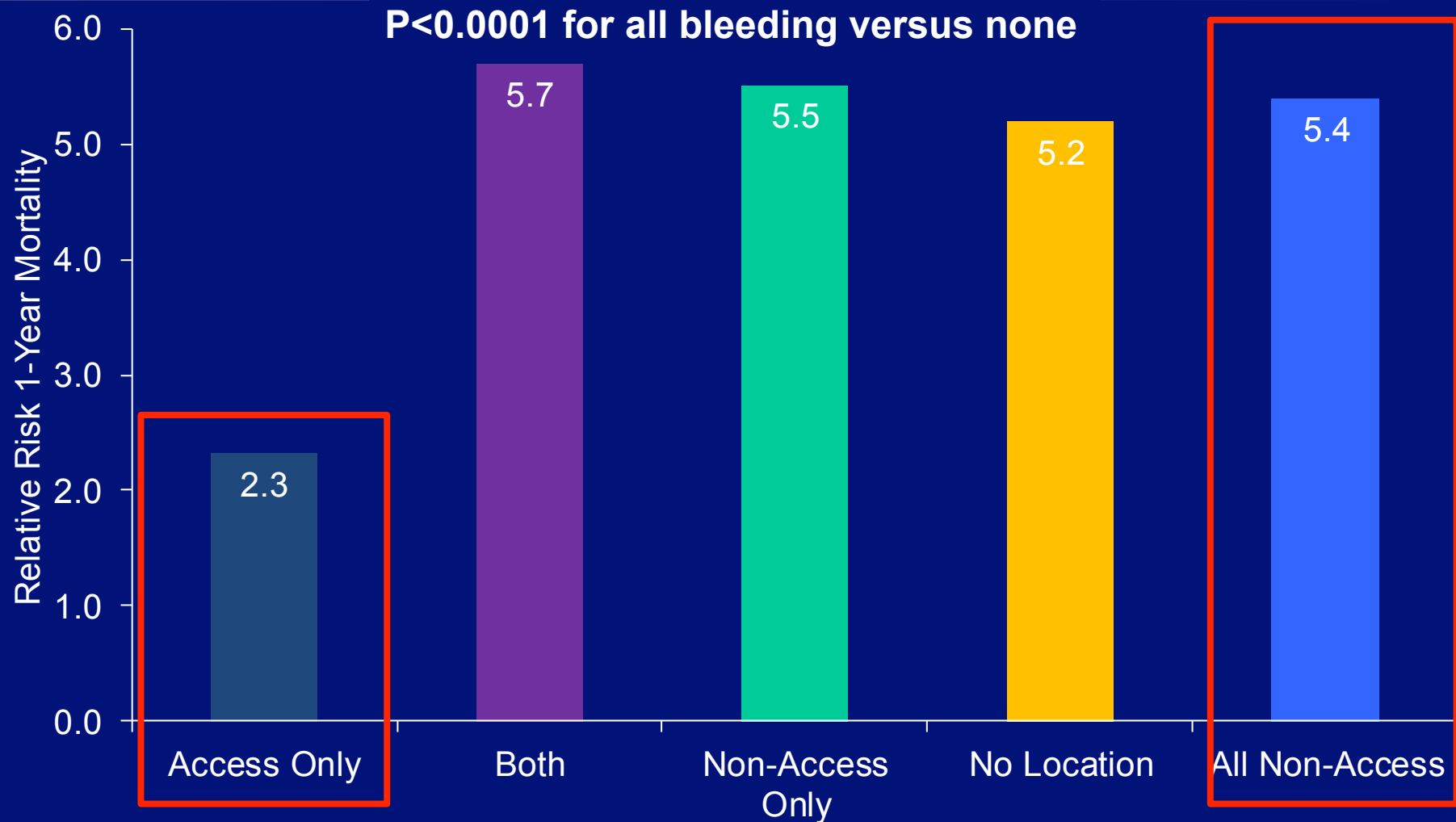
84% TRA
99% Abciximab
Major Bleeding 5.4%
Access site bleeding only in TFA



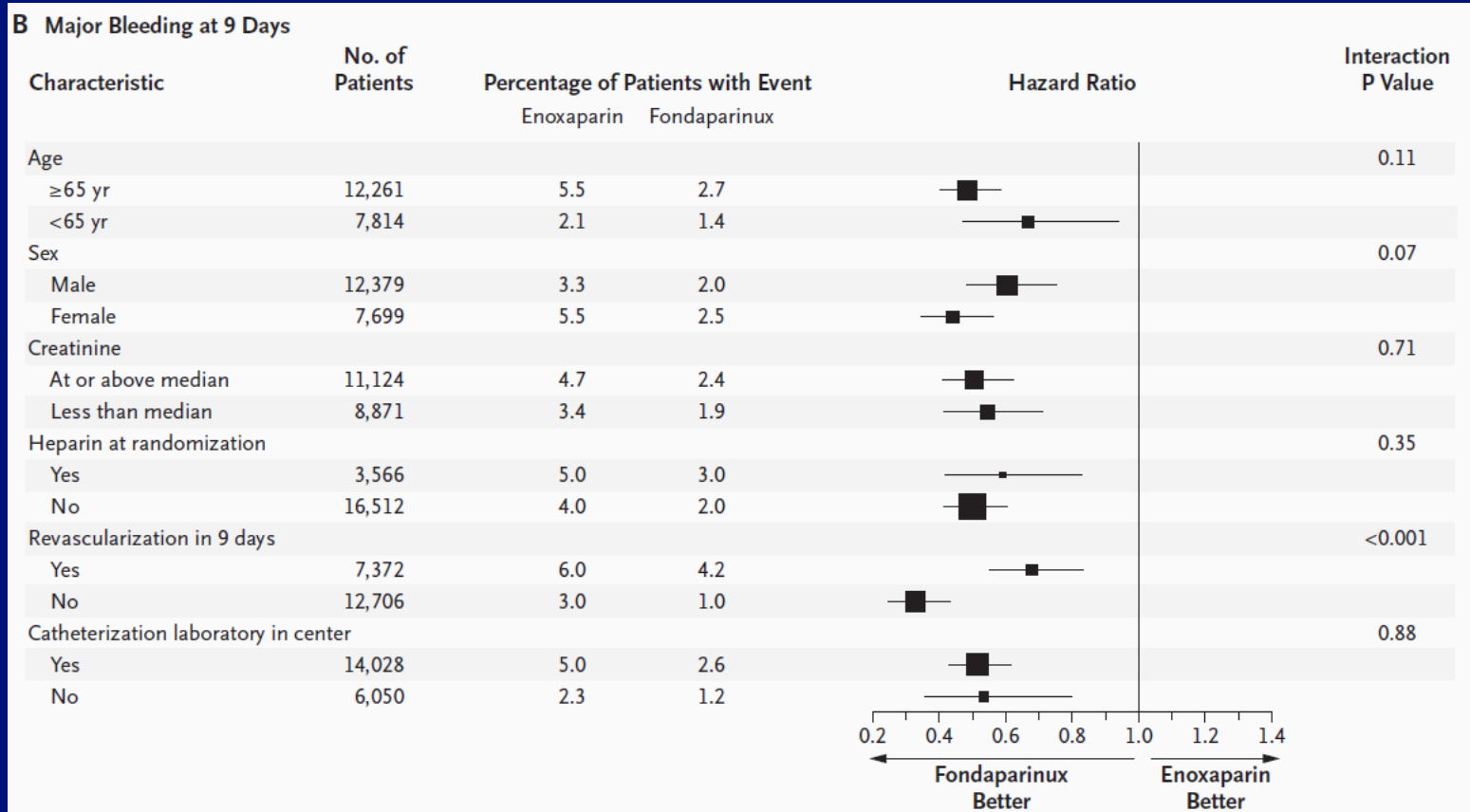
Incidence and source of bleeding excluding access site



Relative Risk of 1-year Mortality Associated with Bleeding and Source (unadjusted)



Major bleeding in OASIS 5



No adjustment for age or creatinine clearance in the enoxaparin arm

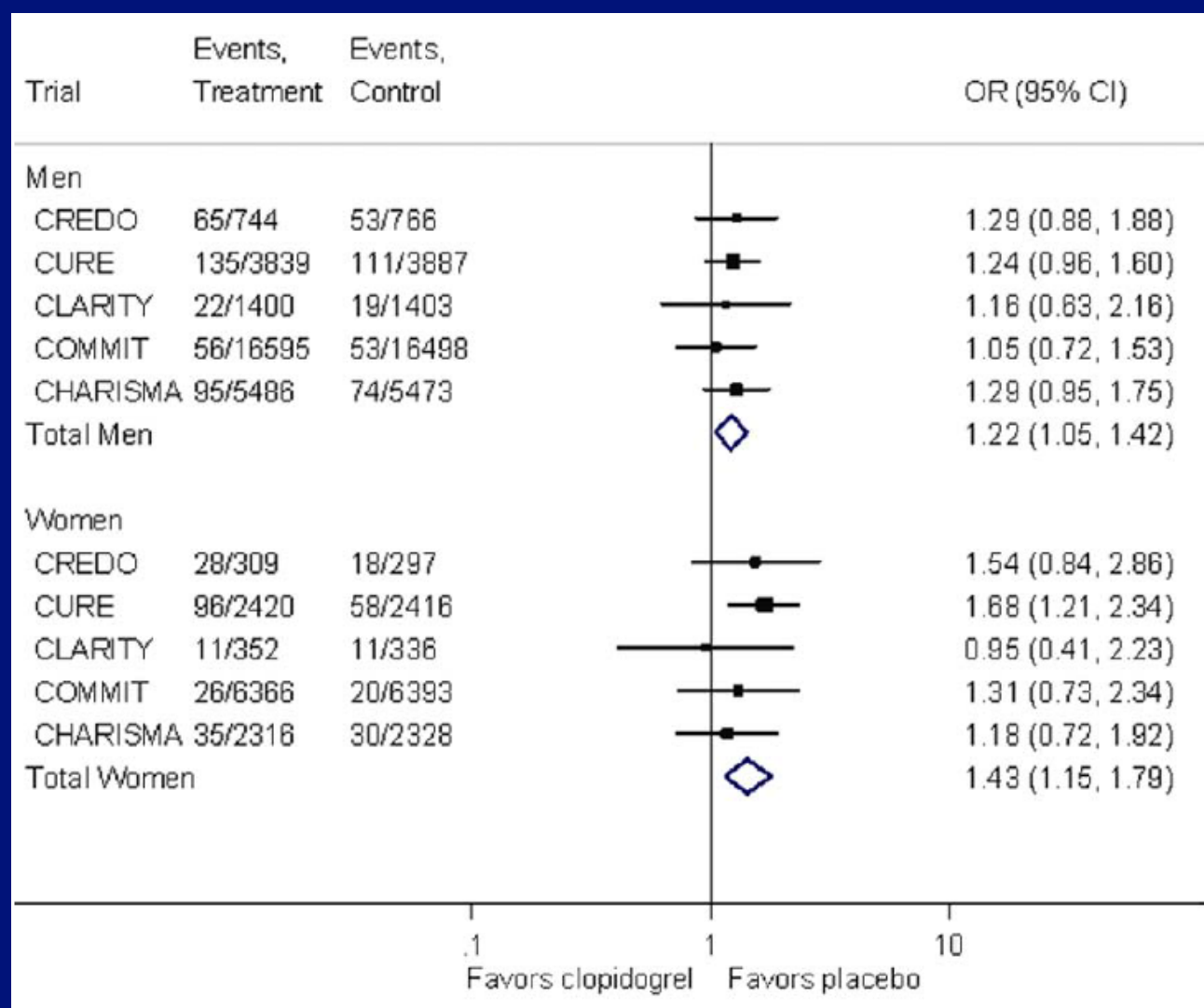
Pas de sur-risque hémorragique sous aspirine chez la femme

	Major coronary event	Probably ischaemic stroke	Haemorrhagic stroke	Major extracranial bleed
Age (per decade)	1.84 (1.74-1.95)	2.46 (2.27-2.65)	1.59 (1.33-1.90)	2.15 (1.93-2.39)
Male sex*	2.43 (1.94-3.04)	1.44 (1.14-1.82)	1.11 (0.52-2.34)	1.99 (1.45-2.73)
Diabetes mellitus	2.66 (2.28-3.12)	2.06 (1.67-2.54)	1.74 (0.95-3.17)	1.55 (1.13-2.14)
Current smoker	2.05 (1.85-2.28)	2.00 (1.72-2.31)	2.18 (1.57-3.02)	1.56 (1.25-1.94)
Mean blood pressure (per 20 mm Hg)†	1.73 (1.59-1.89)	2.00 (1.77-2.26)	2.18 (1.65-2.87)	1.32 (1.09-1.58)
Cholesterol (per 1 mmol/L)	1.18 (1.12-1.24)	1.02 (0.95-1.09)	0.90 (0.77-1.07)	0.99 (0.90-1.08)
Body-mass index (per 5 kg/m ²)	1.09 (1.03-1.15)	1.06 (0.98-1.14)	0.85 (0.71-1.02)	1.24 (1.13-1.35)

Outcomes with clopidogrel

Major Bleeding

Berger et al. JACC 2009

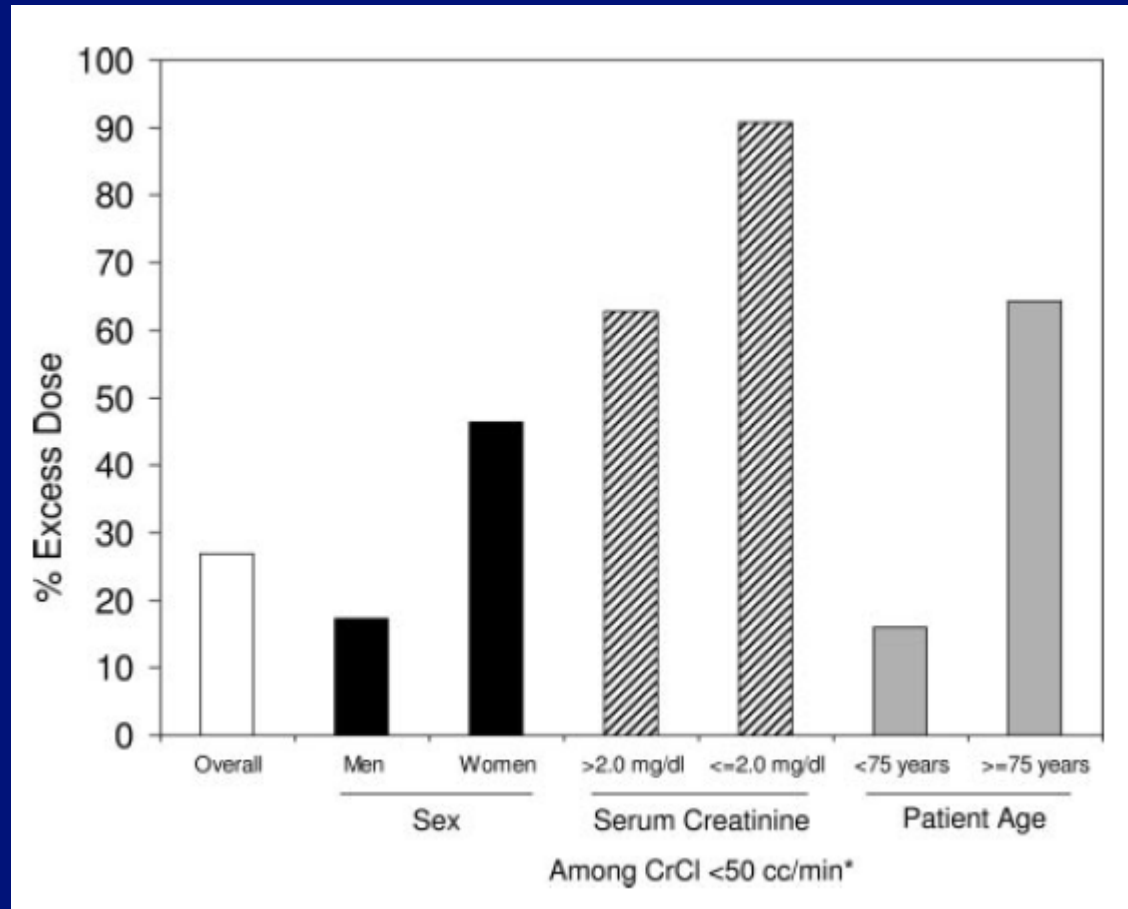


NN to treat or to harm

Berger et al. JACC 2009

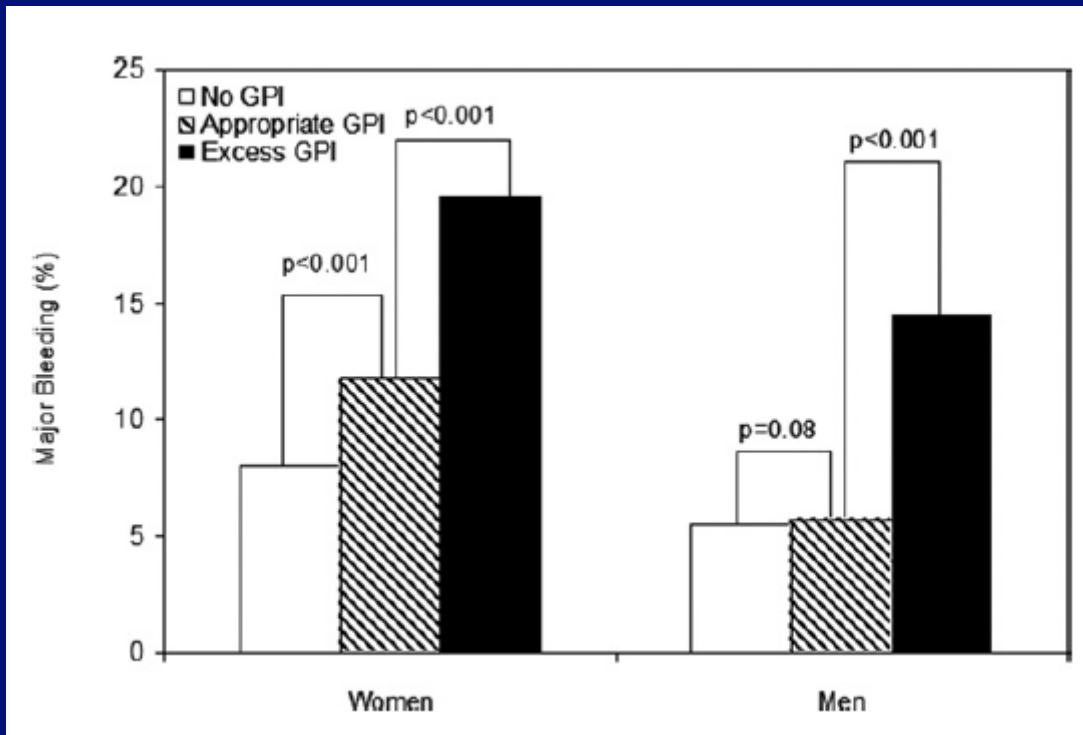
	Clopidogrel (%)	Placebo (%)	Change in Absolute Risk (%)	NNT or NNH
MACE				
Men	7.78	8.99	1.21	83
Women	11.02	11.76	0.74	135
All-cause mortality				
Men	5.44	5.996	0.52	192
Women	8.74	8.85	0.11	909
Myocardial Infarction				
Men	2.80	3.36	0.56	179
Women	2.92	3.59	0.67	149
Stroke				
Men	1.19	1.44	0.25	400
Women	1.61	1.95	0.34	294
Major bleeding				
Men	1.33	1.11	0.22	455
Women	1.67	1.16	0.51	196
MACE + major bleeding				
Men	9.11	10.1	0.99	101
Women	12.69	12.92	0.23	435

Excessive dosing of GPI (Ept. Tir.)



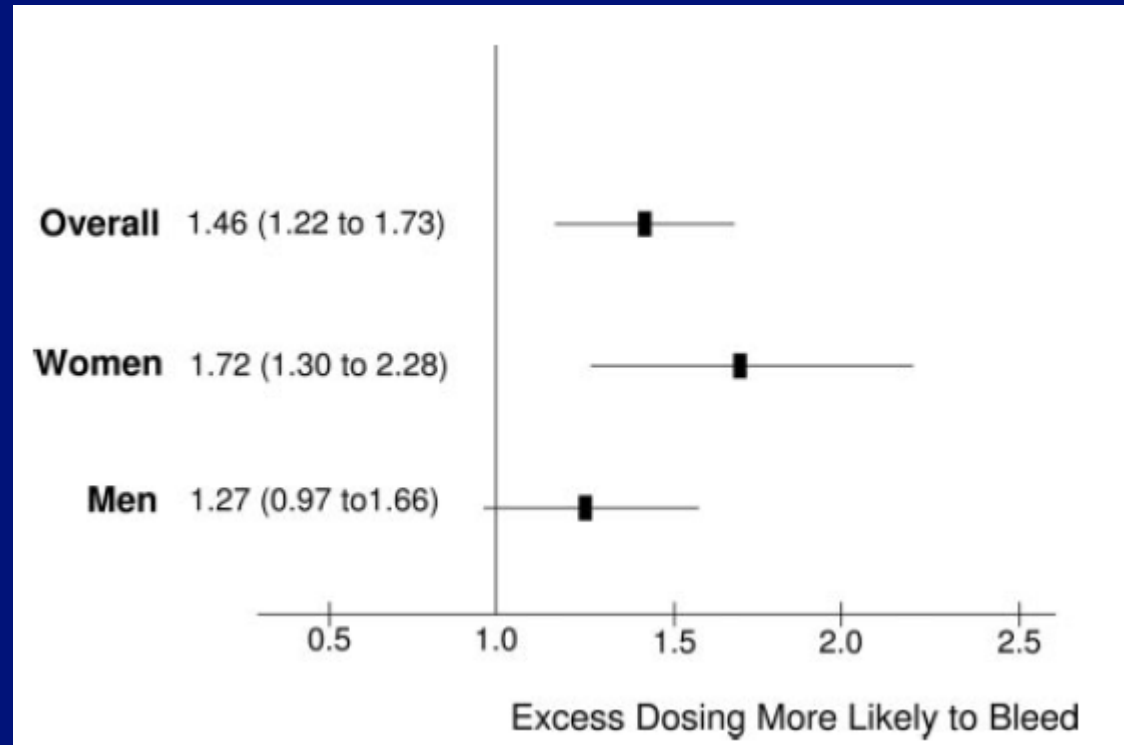
Alexander et al. Circulation 2006

Major bleeding with GPI



- Men: Gastrointestinal
- Women: Access site bleeding

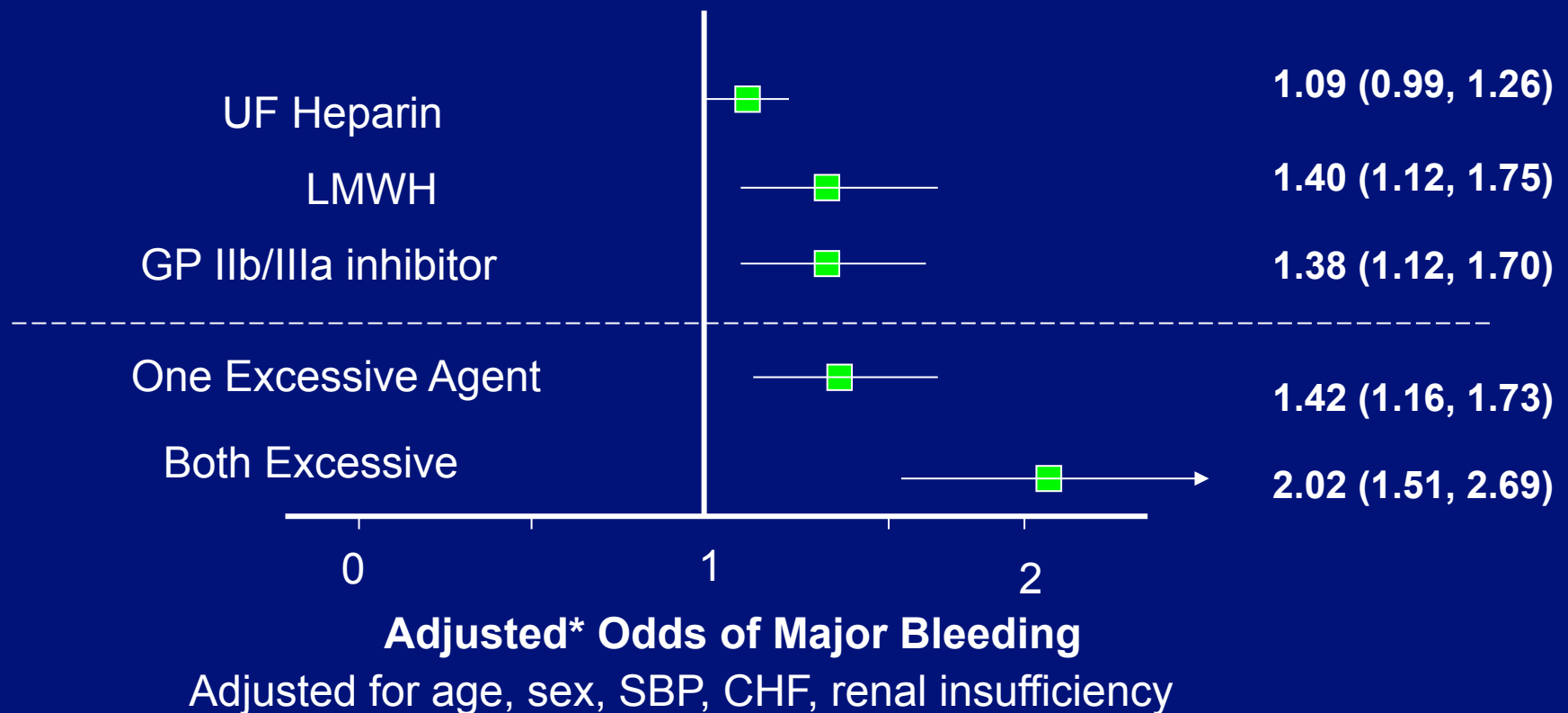
Excessive dosing and likelihood of bleeding with GPI



Alexander et al. Circulation 2006

Excessive Anti-thrombotic Dose

Excess v. Recommended



Procedural factors

Femoral arterial access

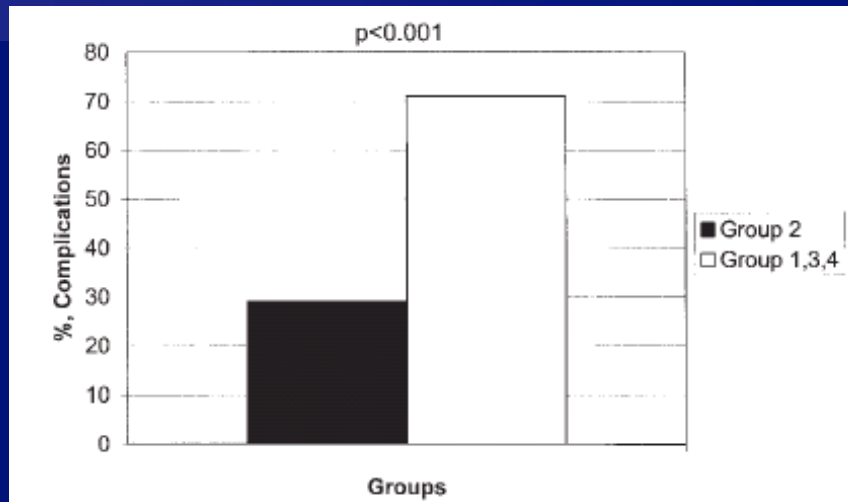
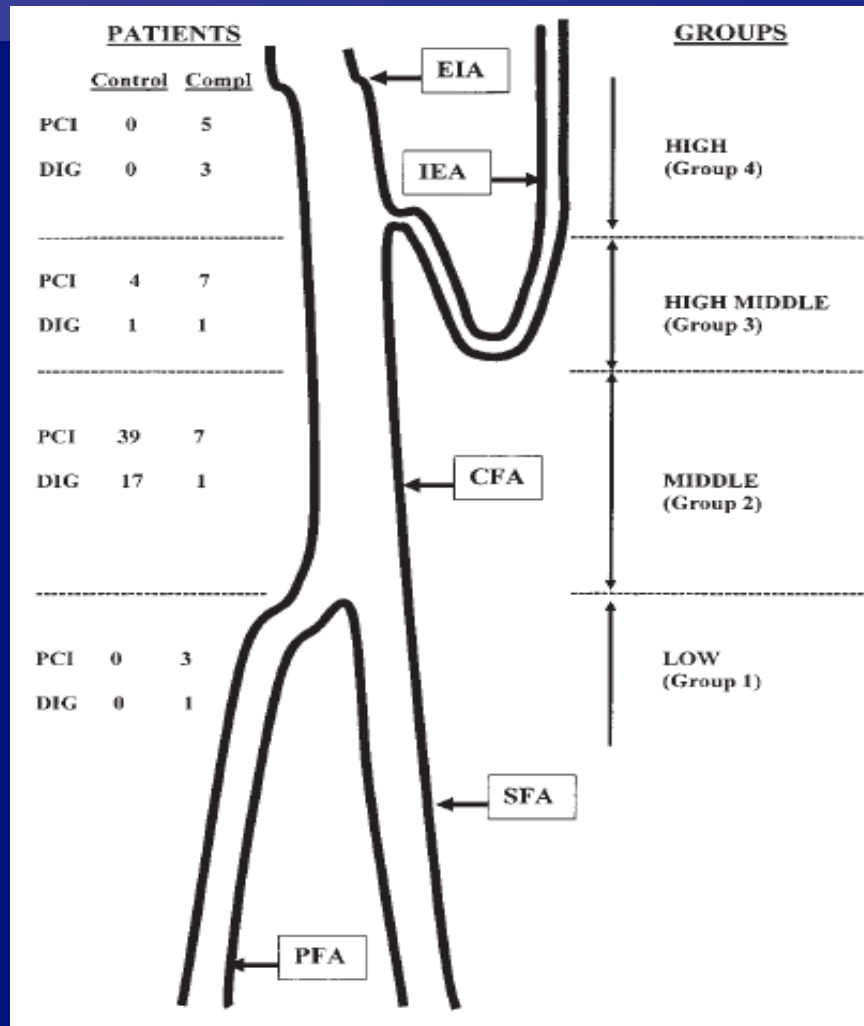
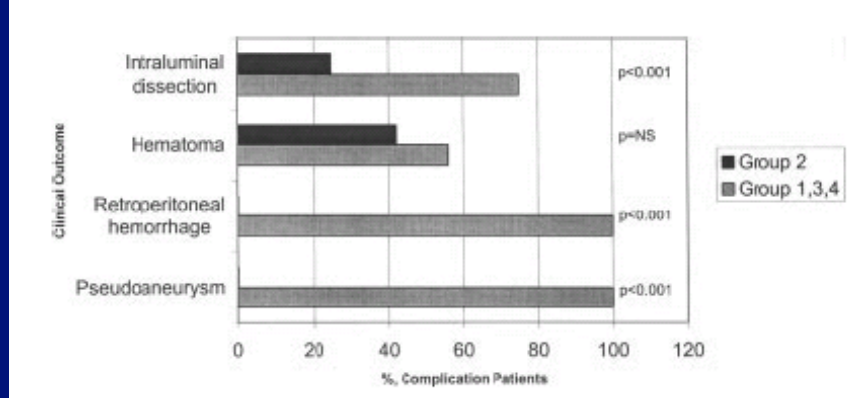


Fig. 2. Prevalence of complications based on the arteriotomy site location (groups 1, 3, and 4 vs. group 2).



Conclusions

- Le bénéfice clinique des antithrombotiques est globalement comparable entre femmes et hommes malgré des différences physiologiques et biologiques entre les 2 sexes
- Les femmes sont pris en charge de façon plus tardive et moins optimale
- Les femmes sont à plus haut risque de saignement sous traitement antithrombotique (P2Y12, GP2B3A)
 - Une meilleure adaptation des doses permet de réduire les risques hémorragiques chez la femmes, même si le sur-risque persiste

Le sur-risque hémorragique explique en partie le traitement sub-optimale des SCA chez la femme mais ne la justifie pas

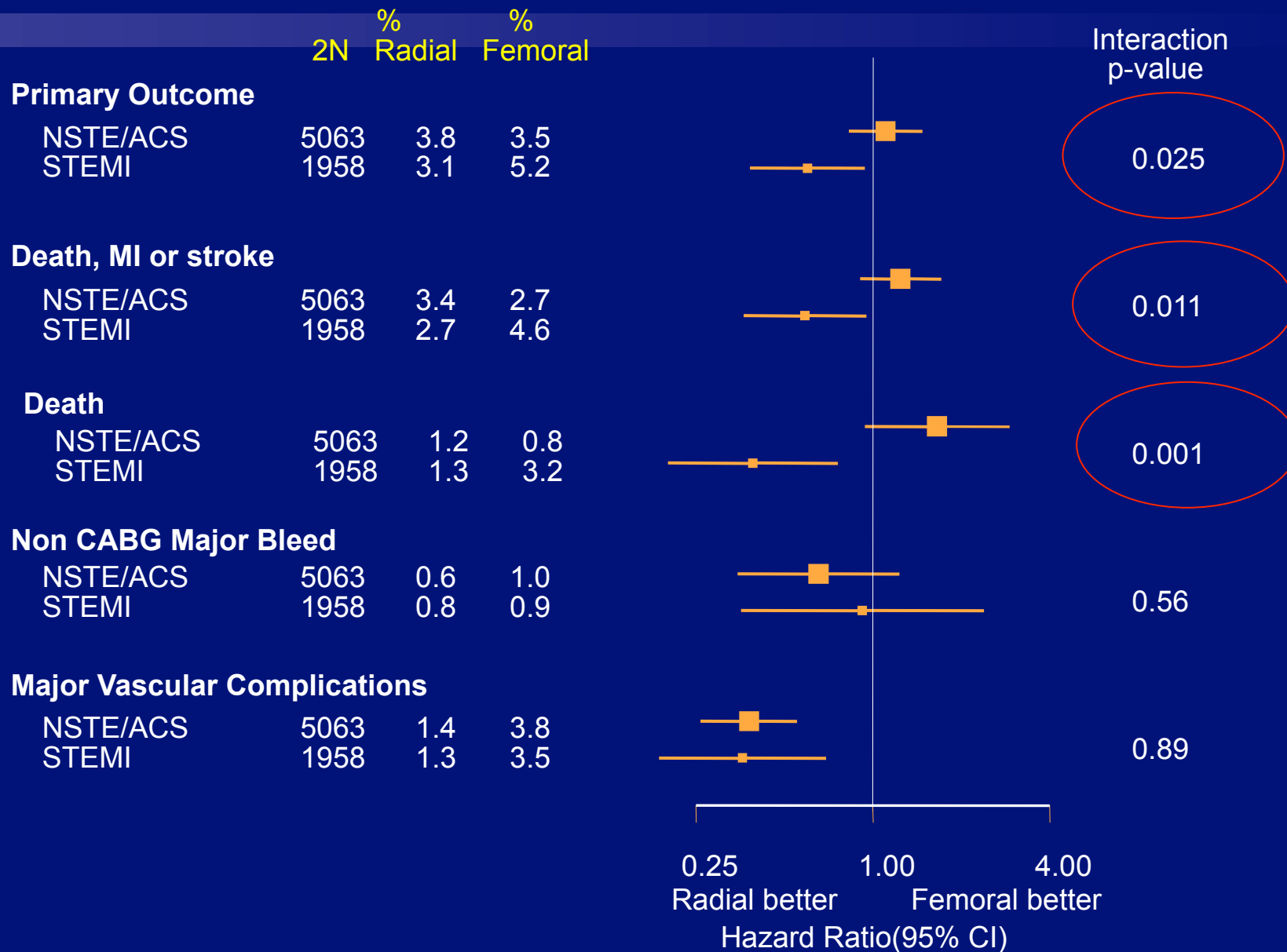
Conclusions

- Evaluation du risque hémorragique et thrombotique
 - **Caractéristiques des patients**
 - Poids
 - CI créatinine
 - ATCD hémorragiques ou AVC
 - **Intensité du traitement antithrombotique**
 - Adapter les doses +++++
 - Faible risque thrombotique: pas de nouveaux AA
 - Surveiller effets biologiques (AntiXa, TCA, Plaquettes)
 - Favoriser les antithrombine directe quand le risque élevé
 - **Durée du traitement antithrombotique**
 - Minimum nécessaire: après revascularisation: pas d'indication à l'anticoagulation efficace
 - La durée optimale de la bithérapie AA baisse avec les DES 4G
 - **Interactions médicamenteuses**
 - Attention aux surdosages multiples
 - Patientes sous AVK/NACO

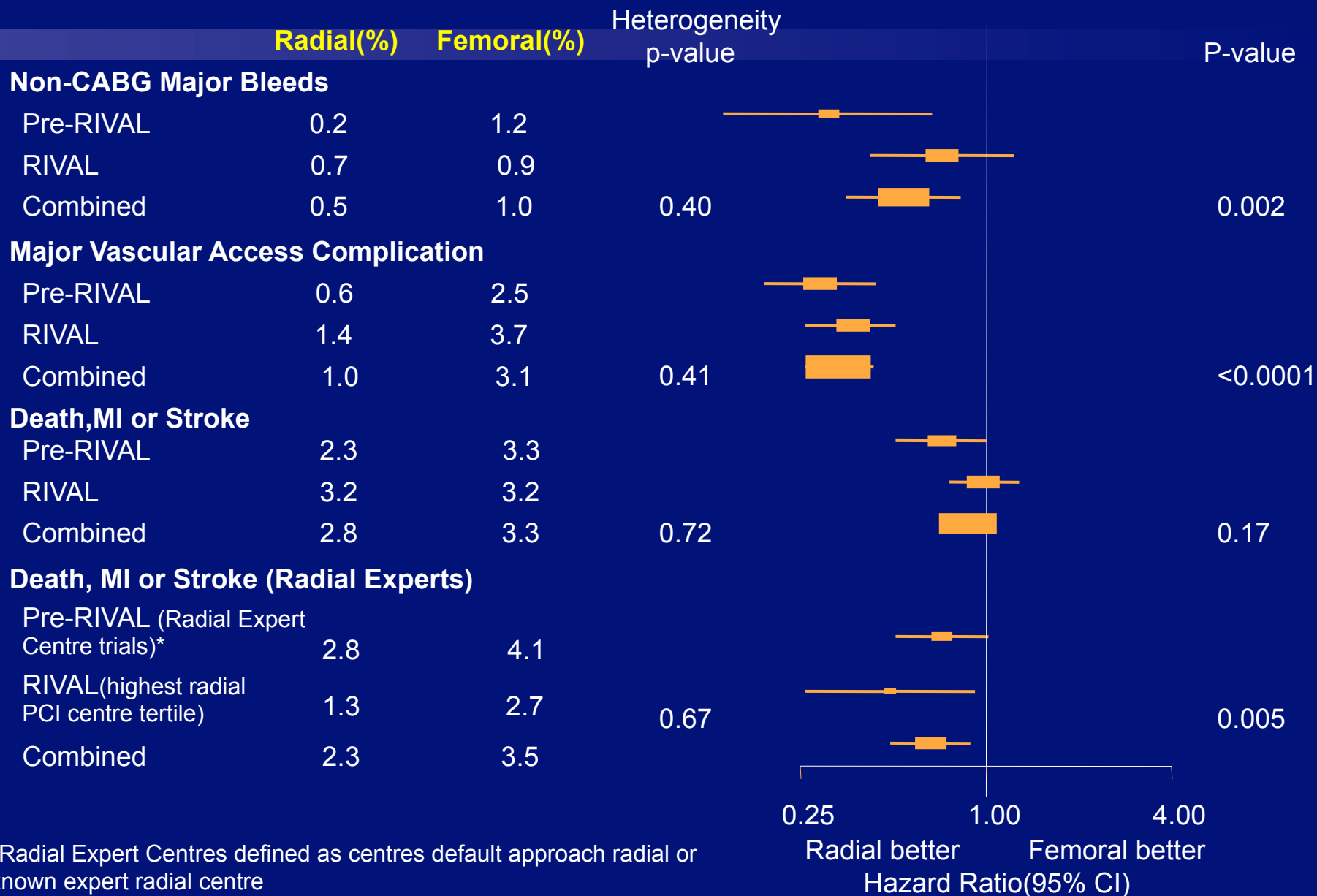
Conclusions

- **Gestes invasifs: voie radiale++++**
 - STEMI: réduction parallèle des complications vasculaires majeurs et de la mortalité de 60%
- **Prévenir et détecter précocement les complications hémorragiques**
 - IPP, surveillance NFS, complications locales
- **Tests fonctionnels ou génotypage?**
 - Hypo-répondeurs
 - Hyper-répondeurs
- **Cibler d'autres voies d'activation plaquettaires ou de coagulation**
 - Cilostazol en plus de la bithérapie
 - AntiXa à long terme (rivaroxaban)

Outcomes stratified by STEMI vs. NSTEMI/ACS



Updated Meta-analysis of RCTs



*Radial Expert Centres defined as centres default approach radial or known expert radial centre