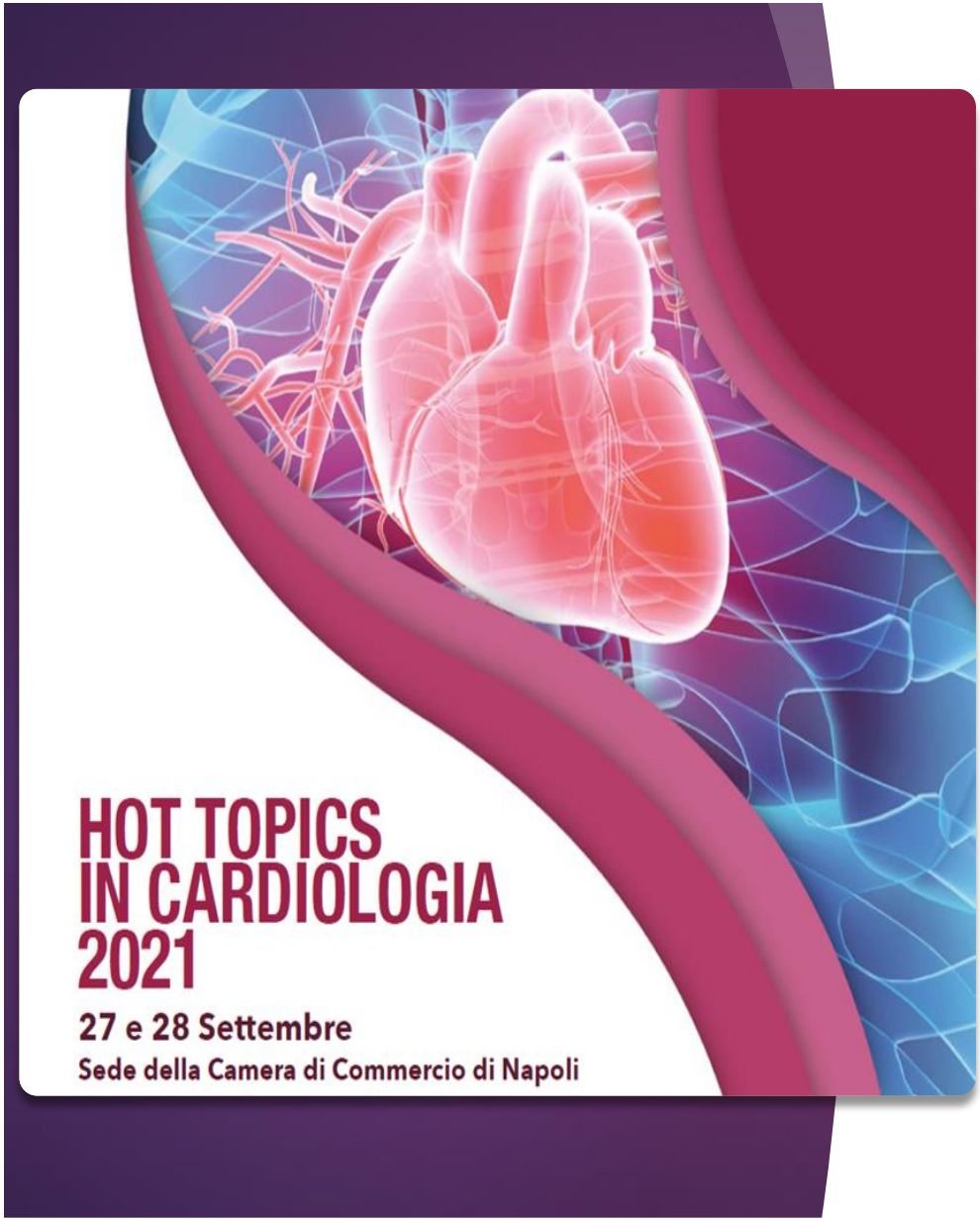

Medicina di genere: il rischio emorragico nelle donne e le evidenze del GLOBAL LEADERS

Cinzia Perrino
Università Federico II
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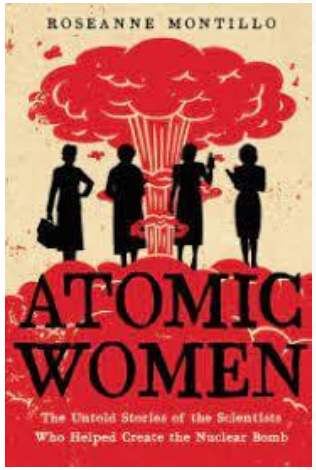
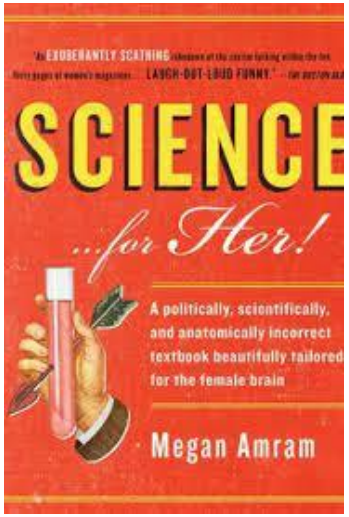
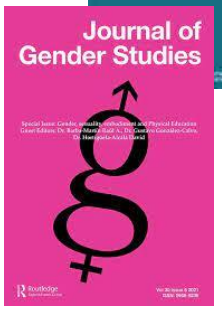
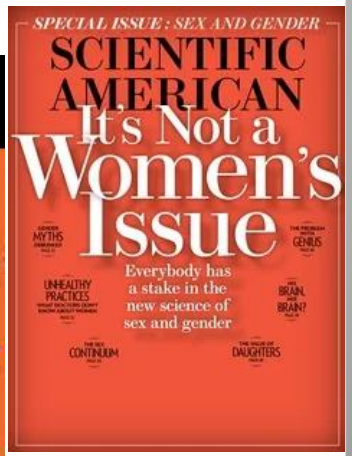
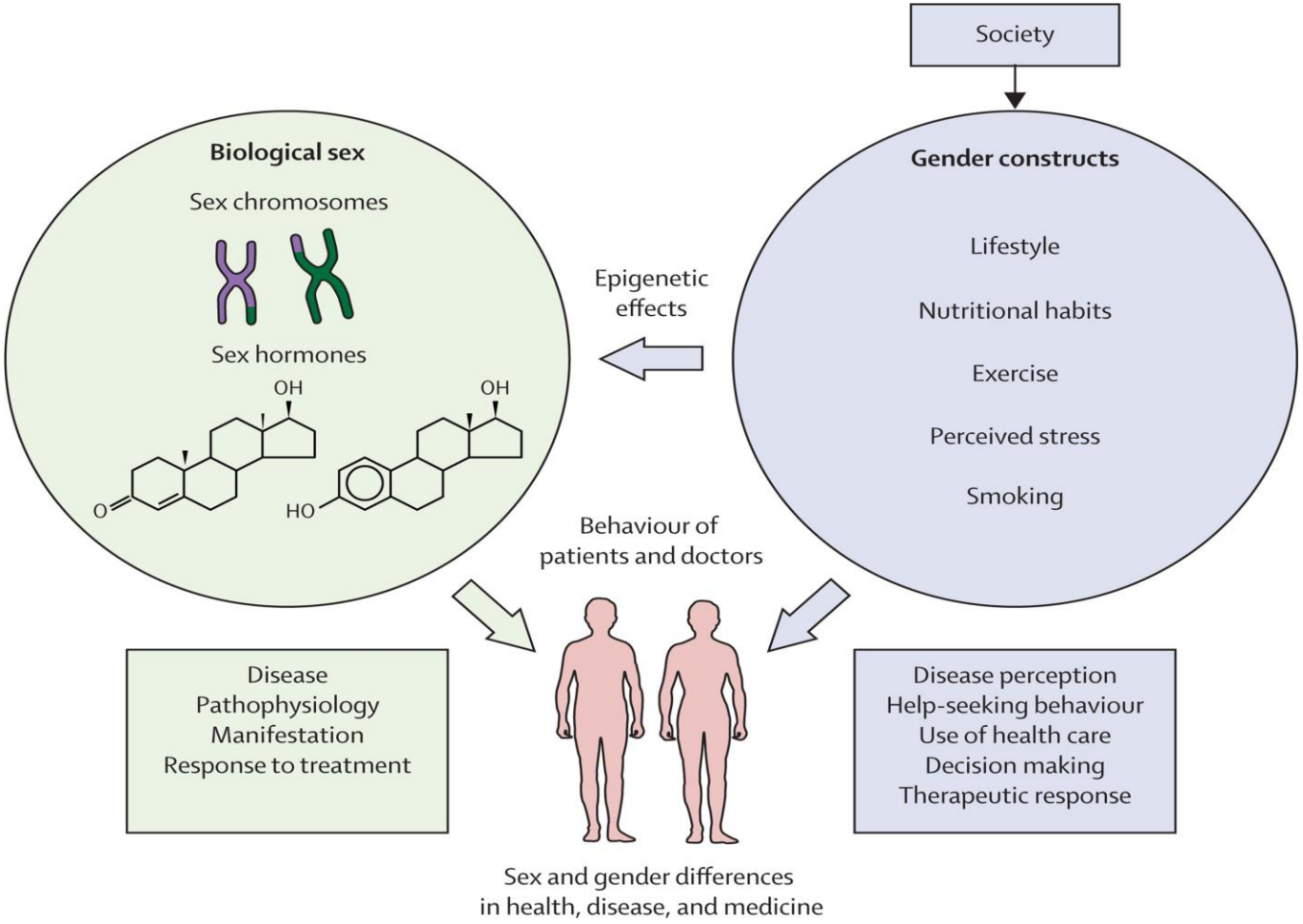






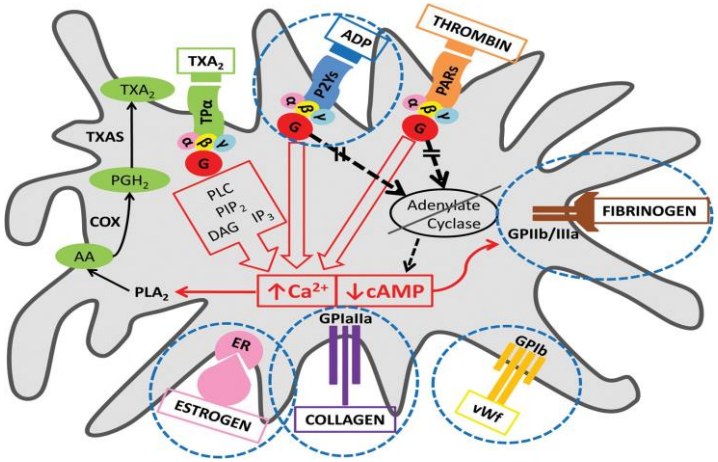


Sex and gender: modifiers of health, disease, and medicine



The Lancet, Volume 396 Issue 10250 Pages 565-582 (August 2020)

Agonists, receptors, and effector systems participating in platelet activation



Sex-related differences

Table I Gender differences in platelet function

Reference	Experimental setting	Platelet assay	Main findings
O'Brien[8]	Male and female volunteers standardized skin incision	Bleeding time	Longer bleeding time in women
Stevens and Alexander[9]	Male and female blood donors citrated blood	Platelet count	Higher platelet count in women
Bain and Forster[6]	Male and female volunteers Standardised skin incision	Bleeding time	Longer bleeding time in women
Lawrence *et al.*[18]	Male and female donors Citrated blood	Platelet spreading, adherence and aggregability	Greater spreading and adherence in men Greater ADP-aggregability in women
Faraday *et al.*[11]	Male and female volunteers Washed platelets	Platelet binding of fibrinogen or PAC-1 in response to ADP or TRAP	More activatable glycoprotein IIb/IIIa in women independently of platelet count
Caulin-Glaser *et al.*[21]	Female human umbilical vein endothelial cells (HUVEC)	Release of the platelet inhibitor nitric oxide by HUVEC	Endothelial nitric oxide synthase activity induced by 17 beta-estradiol
Haque *et al.*[13]	Male and female volunteers platelet-rich plasma	Platelet aggregability by light transmission/scatter	Greater ADP-induced aggregability in women
Leng *et al.*[22]	Male and female littermate mice—washed platelets	Agonist-induced fibrinogen binding and aggregation	Greater fibrinogen binding and aggregability of female mouse platelets
Becker *et al.*[20]	Healthy men and women Citrated blood and plasma	Aggregability in response to collagen, arachidonic acid, ADP and epinephrine	Greater ADP and collagen-induced aggregability in women
Eshel-Green[19]	Male and female inbred littermate mouse platelets	Platelet responses to fibrinogen, thrombin, or collagen	No gender differences in platelet adhesion, spreading or aggregation under flow

ADP, adenosine diphosphate; PAC-1, antibody against glycoprotein IIb/IIIa; TRAP, thrombin receptor activating peptide.

«Available data seem overall to suggest increased activity of primary haemostasis (i.e. enhanced platelet adhesion and shorter bleeding times) in males, but more re- active platelets in response to ex vivo agonists in females».

Eur Heart J, Volume 35, Issue 33, 1 September 2014, Pages 2213–2223.

ACC/AHA FOCUSED UPDATE

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

TABLE 4 Clinical and Procedural Factors Associated With Increased Ischemic Risk (Including Stent Thrombosis) or Increased Bleeding Risk (62-70)

Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT)	Increased Bleeding Risk (may favor shorter-duration DAPT)
Increased ischemic risk	History of prior bleeding
Advanced age	Oral anticoagulant therapy
ACS presentation	Female sex
Multiple prior MIs	Advanced age
Extensive CAD	Low body weight
Diabetes mellitus	CKD
CKD	Diabetes mellitus
Increased risk of stent thrombosis	Anemia
ACS presentation	Chronic steroid or NSAID therapy
Diabetes mellitus	
Left ventricular ejection fraction <40%	
First-generation drug-eluting stent	
Stent undersizing	
Stent underdeployment	
Small stent diameter	
Greater stent length	
Bifurcation stents	
In-stent restenosis	

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; MI, myocardial infarction; and NSAID, nonsteroidal anti-inflammatory drug.

ESC European Society of Cardiology
European Heart Journal (2018) 39, 213–254
doi:10.1093/eurheartj/ehx419

ESC GUIDELINES

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Marco Valgimigli* (Chairperson) (Switzerland), Héctor Bueno (Spain), Robert A. Byrne (Germany), Jean-Philippe Collet (France), Francesco Costa (Italy), Anders Jeppsson[1] (Sweden), Peter Jüni (Canada), Adnan Kastrati (Germany), Philippe Kolh (Belgium), Laura Mauri (USA), Gilles Montalescot (France), Franz-Josef Neumann (Germany), Mate Petricevic[1] (Croatia), Marco Roffi (Switzerland), Philippe Gabriel Steg (France), Stephan Windecker (Switzerland), and Jose Luis Zamorano (Spain)

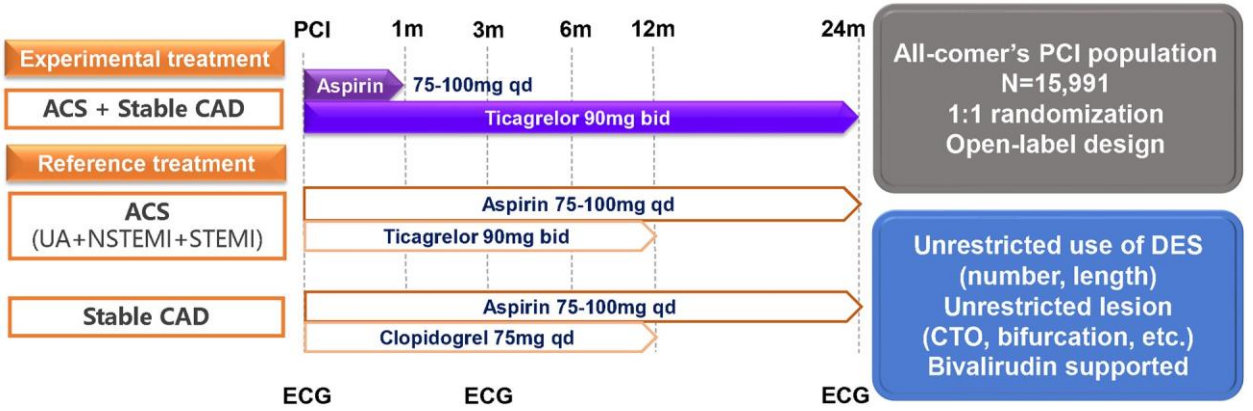
Gender considerations and special populations

Recommendations	Class[a]	Level[b]
Similar type and duration of DAPT are recommended in male and female patients.[26,240]	I	A
It is recommended to reassess the type, dose, and duration of DAPT in patients with actionable bleeding complications while on treatment.	I	C
Similar type and duration of DAPT should be considered in patients with and without diabetes mellitus.[145,242]	IIa	B
Prolonged (i.e. >12 months[c]) DAPT duration should be considered in patients with prior stent thrombosis, especially in the absence of correctable causes (e.g. lack of adherence or correctable mechanical stent-related issues).	IIa	C
Prolonged (i.e. >12 months) DAPT duration may be considered in CAD patients with LEAD.[140,246]	IIb	B
Prolonged (i.e. >6 months) DAPT duration[d] may be considered in patients who underwent complex PCI.[247]	IIb	B

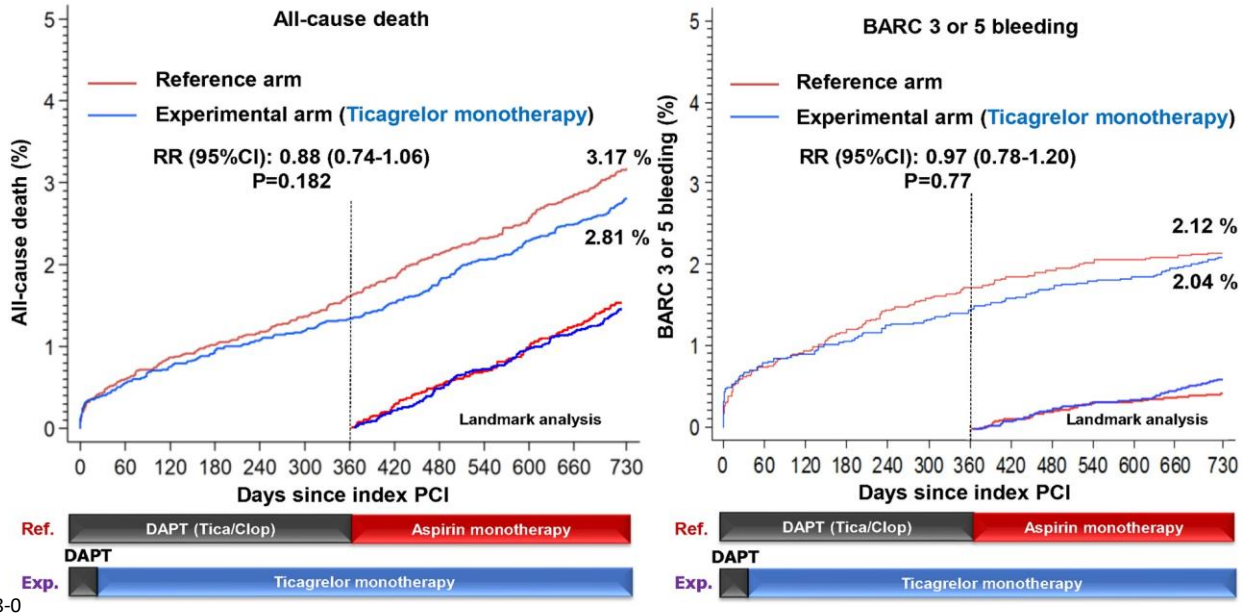
CAD = coronary artery disease; DAPT = dual antiplatelet therapy; LEAD = lower-extremities artery disease; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]Possibly for as long as can be tolerated.
[d]Complex PCI defined as the composite of at least three stents implanted, at least three lesions treated, bifurcation with two stents implanted, total stent length >60 mm, and chronic total occlusion as target lesion.

GLOBAL LEADERS trial

GLOBAL LEADERS Trial design



Kaplan–Meier estimate of mortality and safety outcome at 2 years of GLOBAL LEADERS trial



Lancet 2018; 392: 940–49 ;
DOI: http://dx.doi.org/10.1016/ S0140-6736(18)31858-0

JAMA Cardiology | Original Investigation

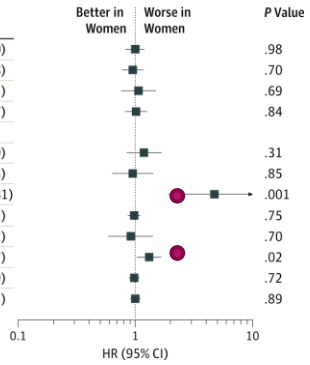
Association of Sex With Outcomes in Patients Undergoing Percutaneous Coronary Intervention

A Subgroup Analysis of the GLOBAL LEADERS Randomized Clinical Trial

Ply Chichareon, MD; Rodrigo Modolo, MD; Laura Kerkmeijer, MD; Mariusz Tomaniak, MD; Norihiro Kogame, MD; Kumiaki Takahashi, MD; Chun-Chin Chang, MD; Hidenori Komiyama, MD; Tiziano Moccetti, MD; Sunjeet Talwar, MD; Antonio Colombo, MD; Luc Maillard, MD, PhD; Peter Barlis, MD; Joanna Wykrzykowska, MD, PhD; Jan J. Piek, MD, PhD; Scot Garg, MBChB, PhD; Christian Hamm, MD; Philippe Gabriel Steg, MD; Peter Jüni, MD; Marco Valgimigli, MD, PhD; Stephan Windecker, MD; Yoshinobu Onuma, MD, PhD; Roxana Mehran, MD; Patrick W. Serruys, MD, PhD

Association of Sex With Clinical Outcomes at 1 Year After Percutaneous Coronary Intervention

Outcomes at 2 y	Men, No. (%)[a] (n = 12 254)	Women, No. (%)[a] (n = 3714)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[b] (95% CI)
All-cause mortality or new Q-wave MI	477 (3.90)	176 (4.75)	1.23 (1.03-1.46)	.02	1.00 (0.83-1.20)
All-cause mortality	346 (2.83)	131 (3.53)	1.26 (1.03-1.54)	.03	0.96 (0.78-1.18)
New Q-wave MI	139 (1.15)	47 (1.29)	1.12 (0.81-1.56)	.49	1.07 (0.76-1.51)
MI	380 (3.16)	118 (3.25)	1.03 (0.84-1.27)	.75	1.02 (0.82-1.27)
Stroke					
Overall	113 (0.94)	49 (1.35)	1.45 (1.03-2.02)	.03	1.19 (0.85-1.69)
Ischemic	97 (0.81)	34 (0.94)	1.17 (0.79-1.73)	.44	0.96 (0.64-1.43)
Hemorrhagic	9 (0.08)	13 (0.36)	4.81 (2.05-11.25)	<.001	4.76 (1.92-11.81)
Any revascularization	1188 (9.89)	344 (9.53)	0.96 (0.85-1.09)	.53	0.98 (0.87-1.11)
Definite stent thrombosis	102 (0.84)	26 (0.71)	0.85 (0.55-1.30)	.45	0.92 (0.59-1.42)
BARC 3 or 5 bleeding	223 (1.85)	109 (2.99)	1.63 (1.30-2.05)	<.001	1.32 (1.04-1.67)
Patient-oriented composite end points	1665 (13.72)	516 (14.08)	1.03 (0.94-1.14)	.53	0.98 (0.89-1.09)
Net adverse clinical events	1802 (14.84)	580 (15.82)	1.08 (0.98-1.18)	.12	1.01 (0.91-1.11)

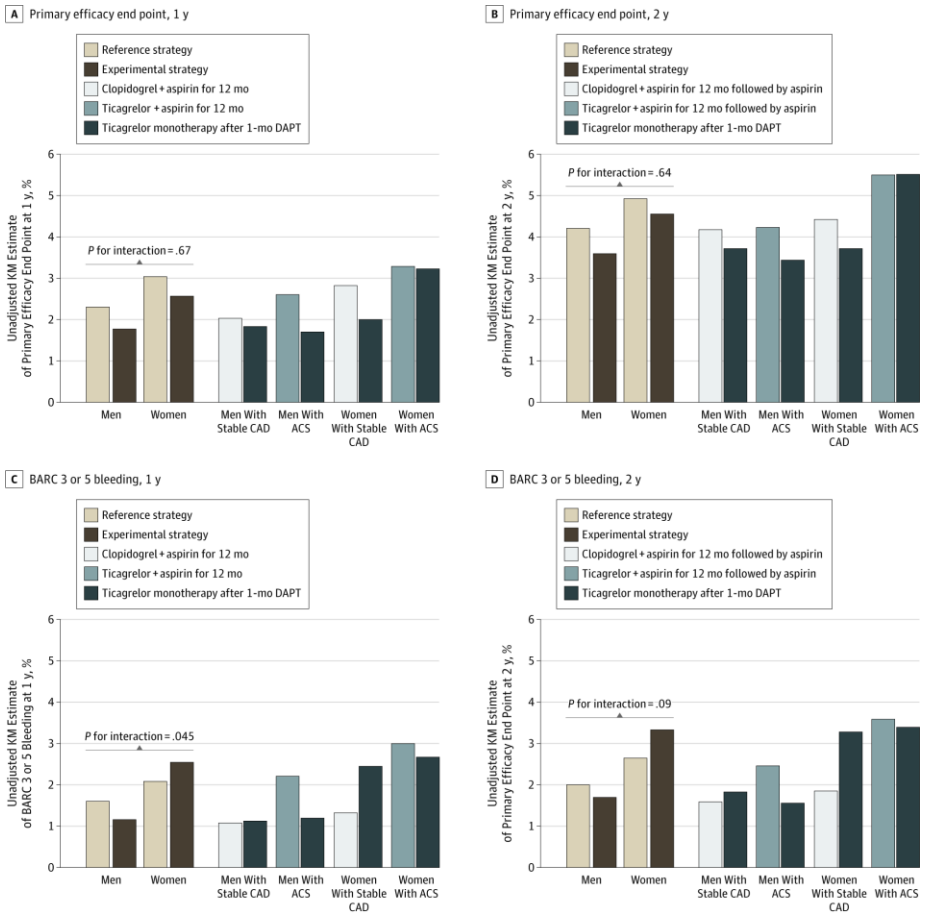


JAMA Cardiol. 2020;5(1):21-29. doi:10.1001/jamacardio.2019.4296

Baseline Clinical and Angiographic Characteristics According to Sex

Characteristic	No./Total No. (%) Men (n = 12 254)	Women (n = 3714)	*P* Value
Baseline clinical characteristics			
Age, mean (SD), y	63.69 (10.22)	67.35 (10.09)	<.001
BMI, mean (SD)	28.17 (4.30)	28.25 (5.44)	.34
Type 2 diabetes	2972/12 247 (24.27)	1066/3710 (28.73)	<.001
Insulin-dependent diabetes	828/12 220 (6.78)	395/3701 (10.67)	<.001
Hypertension	8791/12 212 (71.99)	2924/3702 (78.98)	<.001
Hypercholesterolemia	8241/11 876 (69.39)	2527/3589 (70.41)	.25
Current smoker	3338/12 254 (27.24)	831/3714 (22.37)	<.001
Peripheral vascular disease	799/12 144 (6.58)	206/3678 (5.60)	.04
Chronic obstructive pulmonary disease	618/12 198 (5.07)	203/3698 (5.49)	.33
Previous major bleeding	70/12 241 (0.57)	28/3706 (0.76)	.26
Impaired renal function[a]	1348/12 187 (11.06)	823/3696 (22.27)	<.001
Previous stroke	306/12 235 (2.50)	115/3710 (3.10)	.05
Previous myocardial infarction	3009/12 216 (24.63)	701/3706 (18.92)	<.001
Previous percutaneous coronary intervention	4196/12 243 (34.27)	1025/3711 (27.62)	<.001
Previous coronary artery bypass grafting	781/12 246 (6.38)	162/3709 (4.37)	<.001
Clinical presentation			
Stable coronary artery disease	6491/12 254 (52.97)	1990/3714 (53.58)	.53
Unstable angina	1493/12 254 (12.18)	529/3714 (14.24)	.001
Non–ST-elevation myocardial infarction	2637/12 254 (21.52)	736/3714 (19.82)	.03
ST-elevation myocardial infarction	1633/12 254 (13.33)	459/3714 (12.36)	.13
Baseline angiographic characteristics			
Index PCI attempted, No.	12 187	3696	NA
No. of lesions treated at index PCI per patient, mean (SD)	1.33 (0.62)	1.28 (0.57)	<.001
Lesion treated at index PCI			
1 lesion	8952/12 136 (73.76)	2853/3682 (77.49)	
2 lesions	2518/12 136 (20.75)	669/3682 (18.17)	<.001
3 or more lesions	666/12 136 (5.49)	160/3682 (4.35)	
Lesion level[b]			
No. of lesion	16 140	4701	NA
Vessel treated			
Left main coronary artery	306/16 140 (1.90)	81/4701 (1.72)	
Left anterior descending artery	6599/16 140 (40.89)	2067/4701 (43.97)	
Left circumflex artery	4051/16 140 (25.10)	1026/4701 (21.83)	.44
Right coronary artery	5005/16 140 (31.01)	1485/4701 (31.59)	
Bypass graft	179/16 140 (1.11)	42/4701 (0.89)	
No. of stent per lesion, mean (SD)	1.19 (0.53)	1.19 (0.54)	.70
Biomatrix stent used	15 038/15 896 (94.60)	4377/4628 (94.58)	.99
Mean stent length, mean (SD), mm	24.99 (14.01)	24.20 (13.80)	.001
Mean stent diameter, mean (SD), mm	3.01 (0.47)	2.93 (0.45)	<.001
Direct stenting	5076/15 896 (31.93)	1608/4628 (34.75)	<.001
Bifurcation PCI	1960/16 140 (12.14)	556/4701 (11.83)	.94

Interaction Between Sex and Antiplatelet Strategy on Primary Efficacy and Secondary Safety End Point (15968 pts)



Primary efficacy end point (all-cause mortality or new Q-wave myocardial infarction)

Secondary Safety End Point (Bleeding Academic Research Consortium [BARC] 3 or 5 Bleeding) at 1 and 2 Year

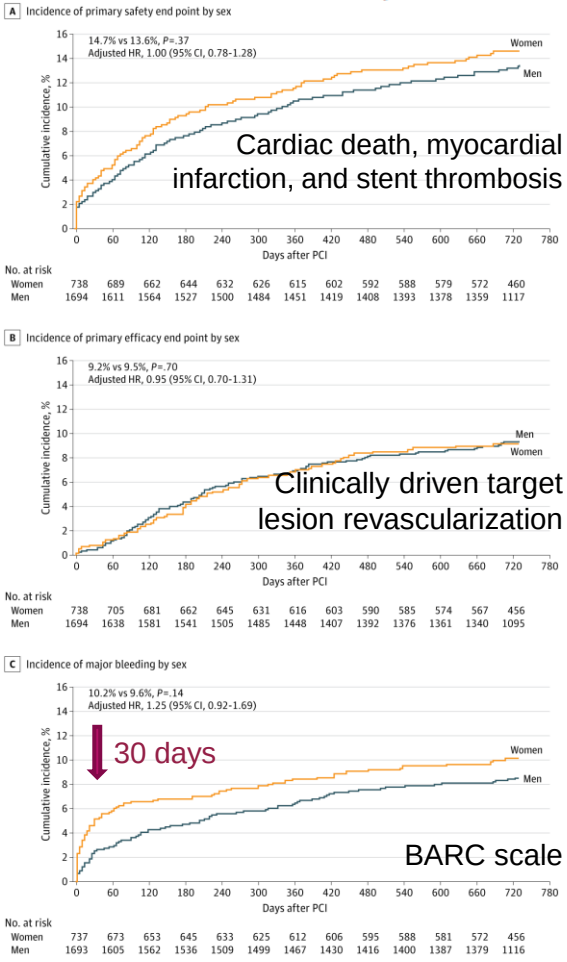
JAMA Cardiol. 2020;5(1):21-29. doi:10.1001/jamacardio.2019.4296

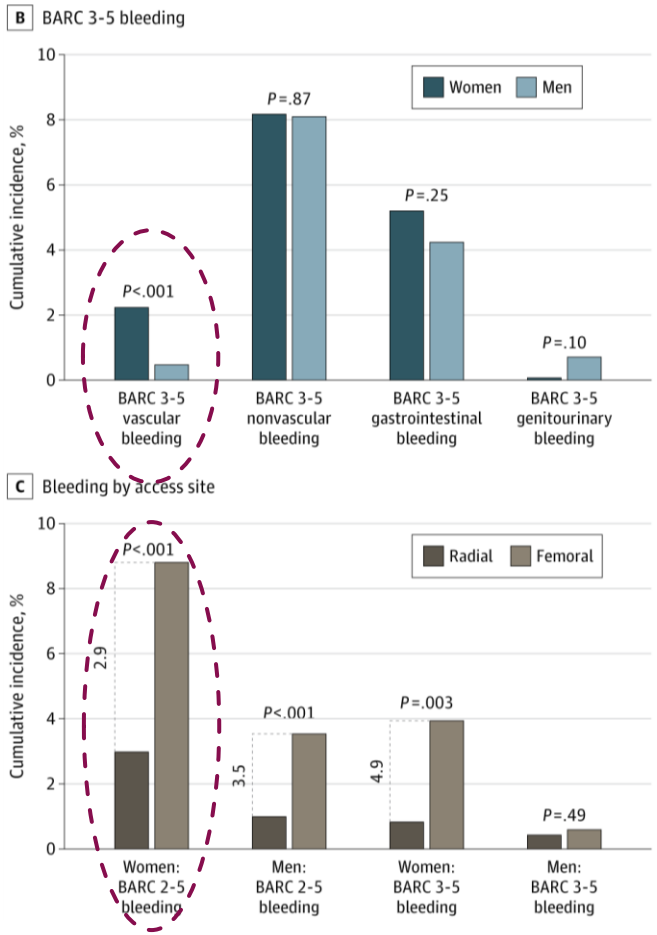
JAMA Cardiology | Original Investigation

Sex-Based Outcomes in Patients With a High Bleeding Risk After Percutaneous Coronary Intervention and 1-Month Dual Antiplatelet Therapy

A Secondary Analysis of the LEADERS FREE Randomized Clinical Trial

Roxana Mehran, MD; Jaya Chandrasekhar, MBBS, MS; Philip Urban, MD; Irene M. Lang, MD; Ute Windhoevel, PhD; Christian Spaulding, MD, PhD; Samuel Copt, PhD; Hans-Peter Stoll, MD; Marie-Claude Morice, MD; for the LEADERS FREE Investigators



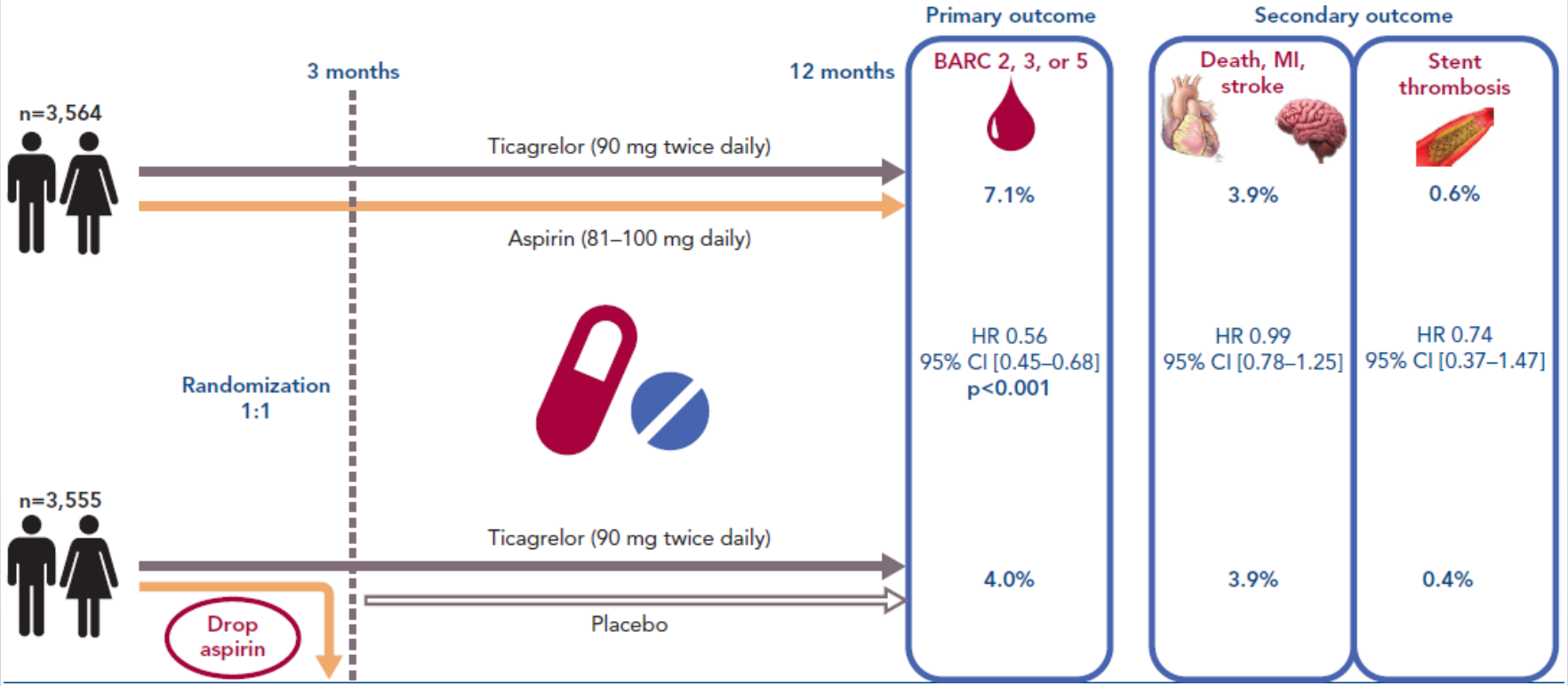


JAMA Cardiol. 2020;5(8):939-947. doi:10.1001/jamacardio.2020.0285

ORIGINAL ARTICLE

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

R. Mehran, U. Baber, S.K. Sharma, D.J. Cohen, D.J. Angiolillo, C. Briguori, J.Y. Cha, T. Collier, G. Dangas, D. Dudek, V. Džavík, J. Escaned, R. Gil, P. Gurbel, C.W. Hamm, T. Henry, K. Huber, A. Kastrati, U. Kaul, R. Kornowski, M. Krucoff, V. Kunadian, S.O. Marx, S.R. Mehta, D. Moliterno, E.M. Ohman, K. Oldroyd, G. Sardella, S. Sartori, R. Shlofmitz, P.G. Steg, G. Weisz, B. Witzenbichler, Y. Han, S. Pocock, and C.M. Gibson



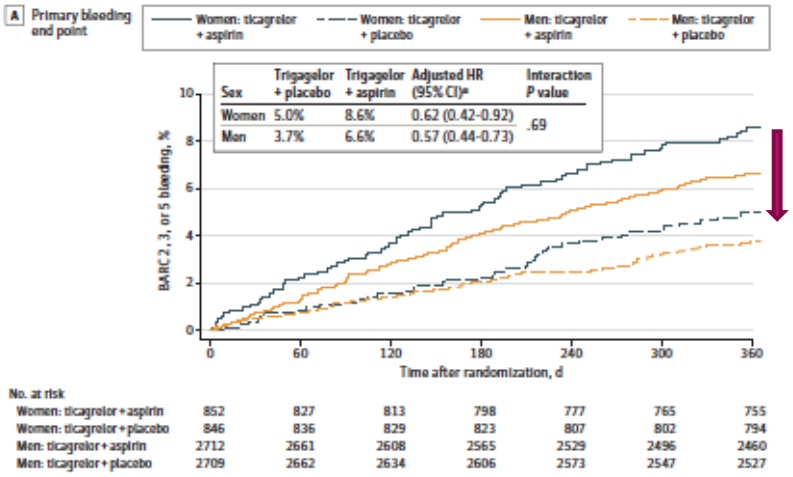
N Engl J Med 2019;381:2032-42.DOI: 10.1056/NEJMoa1908419

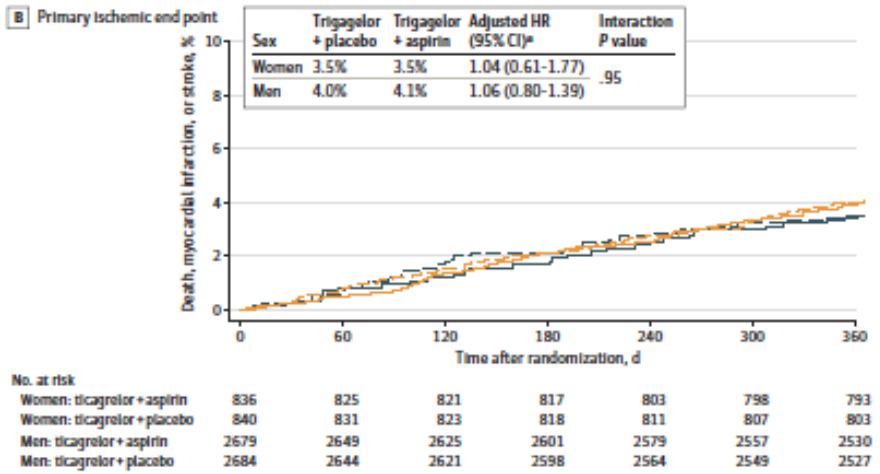
JAMA Cardiology | Original Investigation

Sex Differences Among Patients With High Risk Receiving Ticagrelor With or Without Aspirin After Percutaneous Coronary Intervention
A Subgroup Analysis of the TWILIGHT Randomized Clinical Trial

Birgit Vogel, MD; Usman Baber, MD, MS; David J. Cohen, MD, MSc; Samantha Sartori, PhD; Samin K. Sharma, MD; Dominick J. Angiolillo, MD, PhD; Serdar Farhan, MD; Ridhima Goel, MD; Zhongjie Zhang, MPH; Carlo Briguori, MD, PhD; Timothy Collier, MSc; George Dangas, MD, PhD; Dariusz Dudek, MD, PhD; Javier Escaned, MD, PhD; Robert Gil, MD, PhD; Ya-ling Han, MD, PhD; Upendra Kaul, MD; Ran Kornowski, MD; Mitchell W. Krucoff, MD; Vijay Kunadian, MBBS, MD; Shamir R. Mehta, MD, MSc; David Moliterno, MD; E. Magnus Ohman, MD; Gennaro Sardella, MD; Bernhard Witzenbichler, MD; C. Michael Gibson, MD, MS; Stuart Pocock, PhD; Kurt Huber, MD; Roxana Mehran, MD

Primary Bleeding and Ischemic End Points by Sex and Randomized Treatment Assignment





JAMA Cardiol. 2021;6(9):1032-1041. doi:10.1001/jamacardio.2021.1720

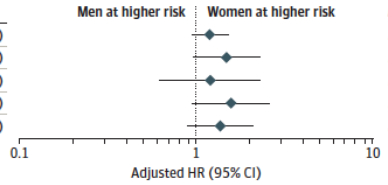
Bleeding Events and Ischemic Events by Sex at 12 Months After Randomization

Table 1. Baseline Clinical and Procedural Characteristics by Sex

Parameters	No. (%) Women (n = 1698)	Men (n = 5421)	P value
Age, mean (SD), y	65.5 (9.6)	63.4 (10.3)	<.001
Non-White race[a]	572 (33.7)	1624 (30.0)	.004
BMI, mean (SD)	28.8 (6.4)	28.5 (5.3)	.12
Enrolling region			
North America	725 (42.7)	2247 (41.4)	
Europe	545 (32.1)	1964 (36.2)	.003
Asia	428 (25.2)	1210 (22.3)	
Diabetes	618 (36.4)	2002 (36.9)	.69
Treated with insulin	207 (33.5)	502 (25.1)	<.001
Chronic kidney disease	347 (21.2)	764 (14.7)	<.001
Anemia	379 (23.2)	950 (18.3)	<.001
Current smoker	288 (17.0)	1260 (23.3)	<.001
Hypercholesterolemia	1000 (58.9)	3303 (60.9)	.13
Hypertension	1299 (76.5)	3855 (71.1)	<.001
Peripheral arterial disease	112 (6.6)	377 (7.0)	.61
Previous MI	355 (20.9)	1685 (31.1)	<.001
Previous PCI	552 (32.5)	2446 (45.1)	<.001
Previous CABG	108 (6.4)	602 (11.1)	<.001
Previous major bleed	19 (1.1)	44 (0.8)	.24
Indication for PCI			
ACS	1160 (68.4)	3454 (63.7)	<.001
Stable CAD	537 (31.6)	1966 (36.3)	
Radial artery access	1196 (70.4)	3990 (73.6)	.01
Multivessel CAD	941 (55.4)	3525 (65.0)	<.001
Target vessel			
Left main	75 (4.4)	278 (5.1)	.24
LAD	1031 (60.7)	2972 (54.8)	<.001
LCX	445 (26.2)	1852 (34.2)	<.001
RCA	593 (34.9)	1907 (35.2)	.85
Vessels treated, mean (SD), No.	1.26 (0.50)	1.29 (0.53)	.04
Lesions treated, mean (SD), No.	1.47 (0.71)	1.54 (0.76)	<.001
Lesion morphology[b]			
Moderate/severe calcification	250 (14.7)	737 (13.6)	.24
Bifurcation	200 (11.8)	666 (12.3)	.58
Total occlusion	92 (5.4)	354 (6.5)	.10
Thrombotic	178 (10.5)	571 (10.5)	.95
Total stent length, mean (SD), mm[c]	37.6 (22.1)	40.6 (24.9)	<.001
Minimum stent diameter, mean (SD), mm	2.8 (0.5)	2.9 (0.5)	<.001

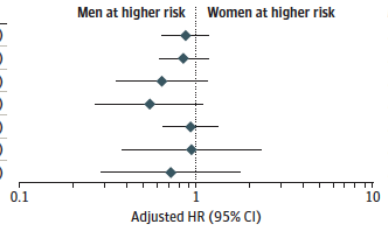
A Bleeding events

Outcome	Women, No. (%)	Men, No. (%)	HR (95% CI)	P value	Adjusted HR (95% CI)	Adjusted P value
BARC type 2, 3, or 5	114 (6.8)	277 (5.2)	1.32 (1.06-1.64)	.01	1.20 (0.95-1.52)	.12
BARC type 3 or 5	34 (2.0)	69 (1.3)	1.57 (1.04-2.37)	.03	1.49 (0.96-2.32)	.08
TIMI (major)	13 (0.8)	38 (0.7)	1.09 (0.58-2.04)	.79	1.20 (0.62-2.31)	.59
GUSTO (moderate or severe)	25 (1.5)	50 (0.9)	1.60 (0.99-2.58)	.06	1.57 (0.95-2.61)	.08
ISTH (major)	35 (2.1)	76 (1.4)	1.47 (0.99-2.20)	.06	1.37 (0.89-2.11)	.16



B Ischemic events

Outcome	Women, No. (%)	Men, No. (%)	HR (95% CI)	P value	Adjusted HR (95% CI)	Adjusted P value
Death, MI, or stroke	58 (3.5)	214 (4.0)	0.86 (0.65-1.15)	.32	0.87 (0.64-1.18)	.36
CV death, MI, or ischemic stroke	54 (3.2)	202 (3.8)	0.85 (0.63-1.15)	.30	0.85 (0.62-1.17)	.32
All-cause death	15 (0.9)	64 (1.2)	0.75 (0.43-1.31)	.31	0.64 (0.35-1.15)	.14
CV death	11 (0.7)	52 (1.0)	0.67 (0.35-1.29)	.23	0.55 (0.27-1.09)	.09
MI	41 (2.5)	149 (2.8)	0.88 (0.62-1.24)	.45	0.93 (0.64-1.33)	.68
Ischemic stroke	7 (0.4)	17 (0.3)	1.31 (0.54-3.17)	.55	0.94 (0.38-2.35)	.90
Stent thrombosis (definite or probable)	6 (0.4)	27 (0.5)	0.71 (0.29-1.71)	.44	0.72 (0.29-1.78)	.47



JAMA Cardiol. 2021;6(9):1032-1041. doi:10.1001/jamacardio.2021.1720

Conclusions

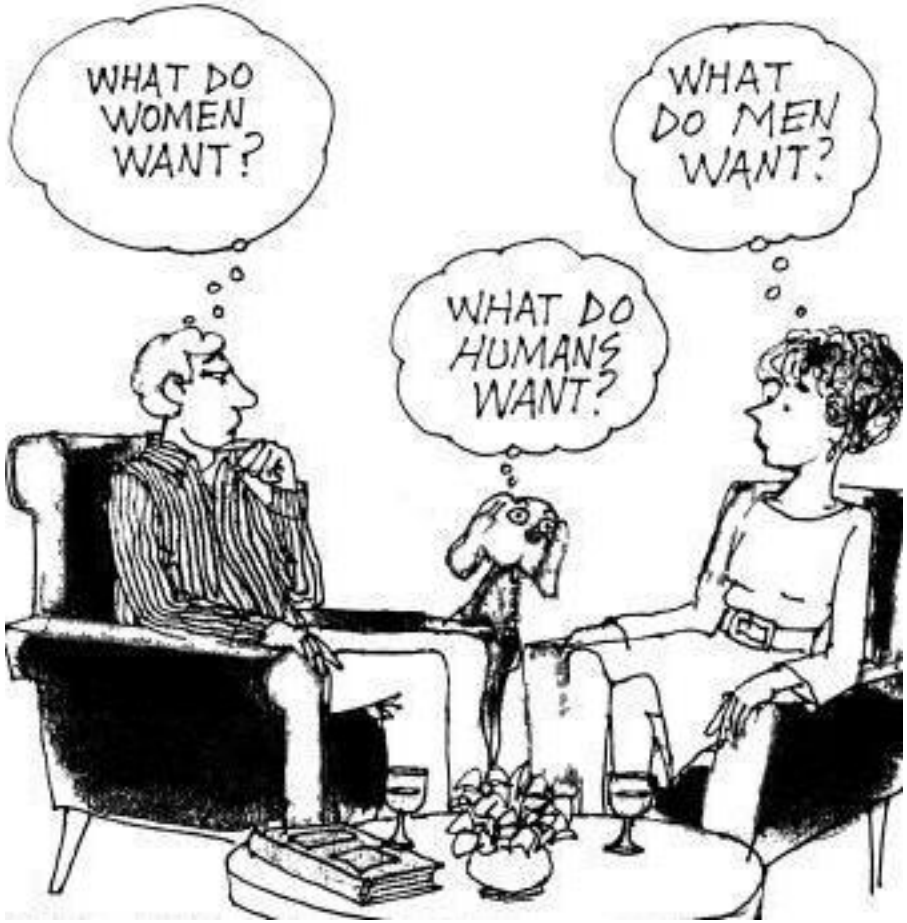
Women have similar ischemic outcomes to men after PCI, even in patients with high bleeding risk undergoing drug-coated stent implantation.

Women have increased bleeding risk after PCI, with higher incidence of vascular bleeding compared to men.

Higher bleeding risk in women could be attributable to baseline differences.

However…

…these findings should be cautiously interpreted and motivate dedicated studies.


WHAT DO WOMEN WANT?
WHAT DO HUMANS WANT?
WHAT DO MEN WANT?

What is missing?

Statistical power to address sex-specific differences

Summary of some relevant contemporary antiplatelet trials

YEAR OF PUBLICATION	2010	2011	2015/2020	2019
STUDY	OASIS-7	GRAVITAS	LEADERS FREE	SMART CHOICE
POPULATION	25,086 Unstable Angina NSTEMI STEMI	2,214 High platelet reactivity 12-24hrs post PCI with DES	2432 HBR undergoing PCI with DCS vs. BMS	2993 ACS or stable angina undergoing PCI with DES
FEMALE	6,773 27.4%	775 35%	738 30.3%	808 27%
METHODS	2*2 Factorial trial	Double blind, active control RCT	Double blind RCT	Open label, non-inferiority RCT
ANTI-PLATELET REGIMEN	High vs. standard dose aspirin clopidogrel	High vs. standard dose clopidogrel	1-month DAPT (aspirin/ clopidogrel)	3 months DAPT followed by P2Y12 inhibitor monotherapy or DAPT
RESULTS	No differences in the overall population In the PCI group double dose clopidogrel associated with decreased ischaemic events	No differences in 6-month incidence of death from cardiovascular causes, nonfatal MI or ST. No differences in bleeding	DCS Superior to BMS. No differences in ischaemic or bleeding out comes between women and men at 2 years	P2Y12 monotherapy, non inferior to DAPT for MACCE Lower BARC 2-5 bleeding with P2Y12 monotherapy
FOLLOW UP DURATION	30 days	6 months	2 years	1 year

YEAR OF PUBLICATION	2019	2019/2021	2021	2021
STUDY	STOP-DAPT 2	TWILIGHT	HOST EXAM	TALOS AMI
POPULATION	3,045 ACS or stable angina post PCI with CoCr-EES	7119 HBR or high ischaemic risk post PCI	5,438 ACS or stable angina undergoing PCI with DES	2,697 Acute MI undergoing PCI with DES
FEMALE	3,045 21%	1,698 23%	1,384 25.5%	485 17%
METHODS	Multicentre open label, non-inferiority RCT	Double blind, RCT	Multicentre open label, RCT	Multicentre open label, RCT
ANTI-PLATELET REGIMEN	1-month DAPT followed by clopidogrel monotherapy or DAPT (aspirin/ clopidogrel)	3 months DAPT aspirin/ticagrelor) followed by DAPT or ticagrelor & placebo	DAPT 6-18 months post PCI followed by monotherapy with clopidogrel or aspirin	1 month aspirin & ticagrelor followed by aspirin & clopidogrel or aspirin & ticagrelor
RESULTS	1-month DAPT followed by clopidogrel monotherapy superior for both ischaemic and bleeding events	Lower BARC 2,3 or 5 bleeding at 12 moths with ticagrelor monotherapy. Higher unadjusted but similar adjusted bleeding in women	Lower incidence of primary endpoint all-cause mortality, MI, stroke, ACS, major bleeding with clopidogrel	Clopidogrel & aspirin superior for primary endpoint of cardiovascular death, MI, stroke & BARC 2,3 or 5 bleeding
FOLLOW UP DURATION	1 year	1 year	1 year	1 year

Mirvat Alasnag et al. Open Heart 2021;8:e001761

What is missing?

Statistical power to address sex-specific differences

Stratification of risk in women

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 213–254
doi:10.1093/eurheartj/ehx419

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

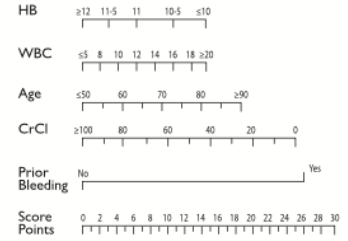
The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

Use of risk scores as guidance for the duration of dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations[c] may be considered.[15,18]	IIb	A

DAPT = dual antiplatelet therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]The DAPT and PRECISE-DAPT scores are those currently fulfilling these requirements.

Table 3 Risk scores validated for dual antiplatelet therapy duration decision-making

	PRECISE-DAPT score[18]	DAPT score[15]	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 –2 pt –1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	–2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

CHF = congestive heart failure; CrCl = creatinine clearance; DAPT = dual antiplatelet therapy; Hb = haemoglobin; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; WBC = white blood cell count.
[a]For the PRECISE-DAPT score use the score nomogram: mark patient's value for each of the five clinical variables of the score and draw a vertical line to the 'Point' axis to determine the number of points obtained for each clinical variable. Then summate the points obtained for each clinical variable to the total score. A practical case example for score calculation is provided in Web Figure 1 of the Web Addenda.
For the DAPT score summate positive points for each value and subtract values for age to the total score.

Circulation

WHITE PAPER

Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention

A Consensus Document From the Academic Research Consortium for High Bleeding Risk

Table 3. Major and Minor Criteria for HBR at the Time of PCI

Major	Minor
	Age ≥75 y
Anticipated use of long-term oral anticoagulation*	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count $<100\times10^9$/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 mo	
Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 mo Presence of a bAVM Moderate or severe ischemic stroke§ within the past 6 mo	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 d before PCI	

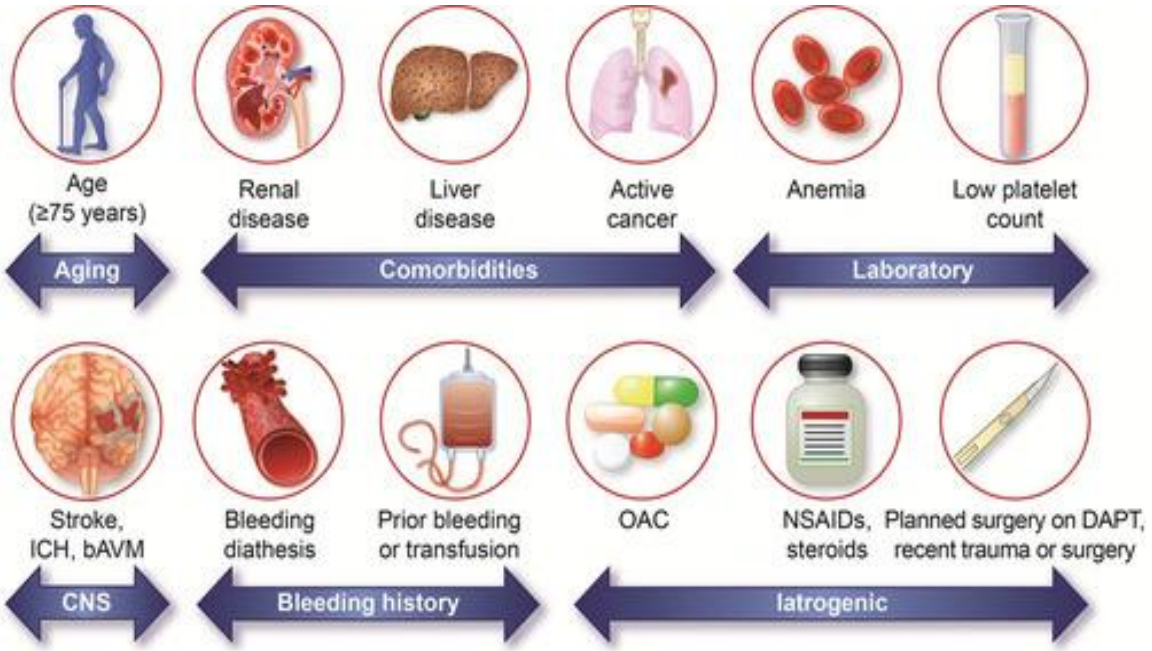
bAVM indicates brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and PCI, percutaneous coronary intervention.

*This excludes vascular protection doses.[42]

†Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

‡Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

§National Institutes of Health Stroke Scale score ≥5.



Philip Urban. Circulation. Volume: 140, Issue: 3, Pages: 240-261, DOI: (10.1161/CIRCULATIONAHA.119.040167)

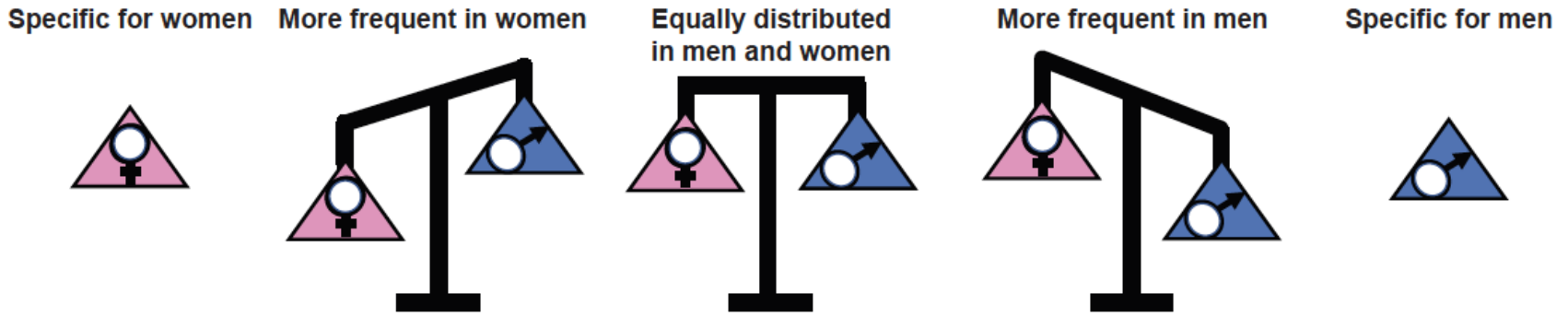
What is missing?

Statistical power to address sex-specific differences

Evaluation of comorbidities

Stratification of risk in women

Special conditions, risk factors and comorbidities in men and women with ischemic heart disease



Specific for women	More frequent in women	Equally distributed in men and women	More frequent in men	Specific for men
Pregnancy and lactation	Aging	Stress	Arterial hypertension	Erectile dysfunction
Pregnancy-related disorders	Physical inactivity	Hyperlipidemia	Smoking	Androgenetic alopecia
Polycystic ovary syndrome	LVH	Atrial fibrillation	PAD	
Menopause	Depression and anxiety	Heart valve disease	COPD	
	Metabolic syndrome	OSA	Stroke	
	Obesity	Degenerative brain disease		
	Diabetes	Clock disruption		
	Thyroid disease	Kidney and urinary tract diseases		
	Osteoporosis	Infections		
	Pulmonary hypertension	Anemia		
	Rheumatic diseases	Cancer		
	Irritable bowel disease			

Perrino C, Cardiovasc Res. 2021 Jan 21;117(2):367-385. doi: 10.1093/cvr/cvaa155.

ESC European Society of Cardiology
Cardiovascular Research (2021) 117, 367–385
doi:10.1093/cvr/cvaa155

REVIEW

Improving translational research in sex-specific effects of comorbidities and risk factors in ischaemic heart disease and cardioprotection: position paper and recommendations of the ESC Working Group on Cellular Biology of the Heart

Cinzia Perrino [1*†], Péter Ferdinandy[2,3†], Hans E Bøtker[4], Bianca J J M Brundel [5], Peter Collins[6,7], Sean M Davidson[8], Hester M den Ruijter[9], Felix B Engel [10], Eva Gerdts[11], Henrique Girao [12,13], Mariann Gyöngyösi[14], Derek J Hausenloy[15,16,17,18,19], Sandrine Lecour [20], Rosalinda Madonna [21,22], Michael Marber [23], Elizabeth Murphy[24], Maurizio Pesce [25], Vera Regitz-Zagrosek [26,27], Joost P G Sluijter [28,29], Sabine Steffens [30], Can Gollmann-Tepeköylü[31], Linda W Van Laake[32], Sophie Van Linthout[33,34,35], Rainer Schulz[36†] and Kirsti Ytrehus [37†]

Table 1 Effects of general risk factors or comorbidities on IHD risk in women

Increasing risk	Decreasing risk	Unknown or unclear
Ageing	Physical activity	Thyroid diseases
Smoking		Osteoporosis
Stress		LVH
Obesity		Pulmonary hypertension
Hyperlipidaemia		Atrial fibrillation
Hypertension		Heart valve diseases
Diabetes		PAD
Depression		COPD
HIV		OSA
Inflammatory diseases		Brain diseases
		Clock disruption
		Gastro-intestinal diseases
		Kidney diseases
		Anaemia
		Cancer

LVH, left ventricular hypertrophy; OSA, obstructive sleep apnoea; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease, HIV, human immunodeficiency virus.

Perrino C, Cardiovasc Res. 2021 Jan 21;117(2):367-385. doi: 10.1093/cvr/cvaa155.

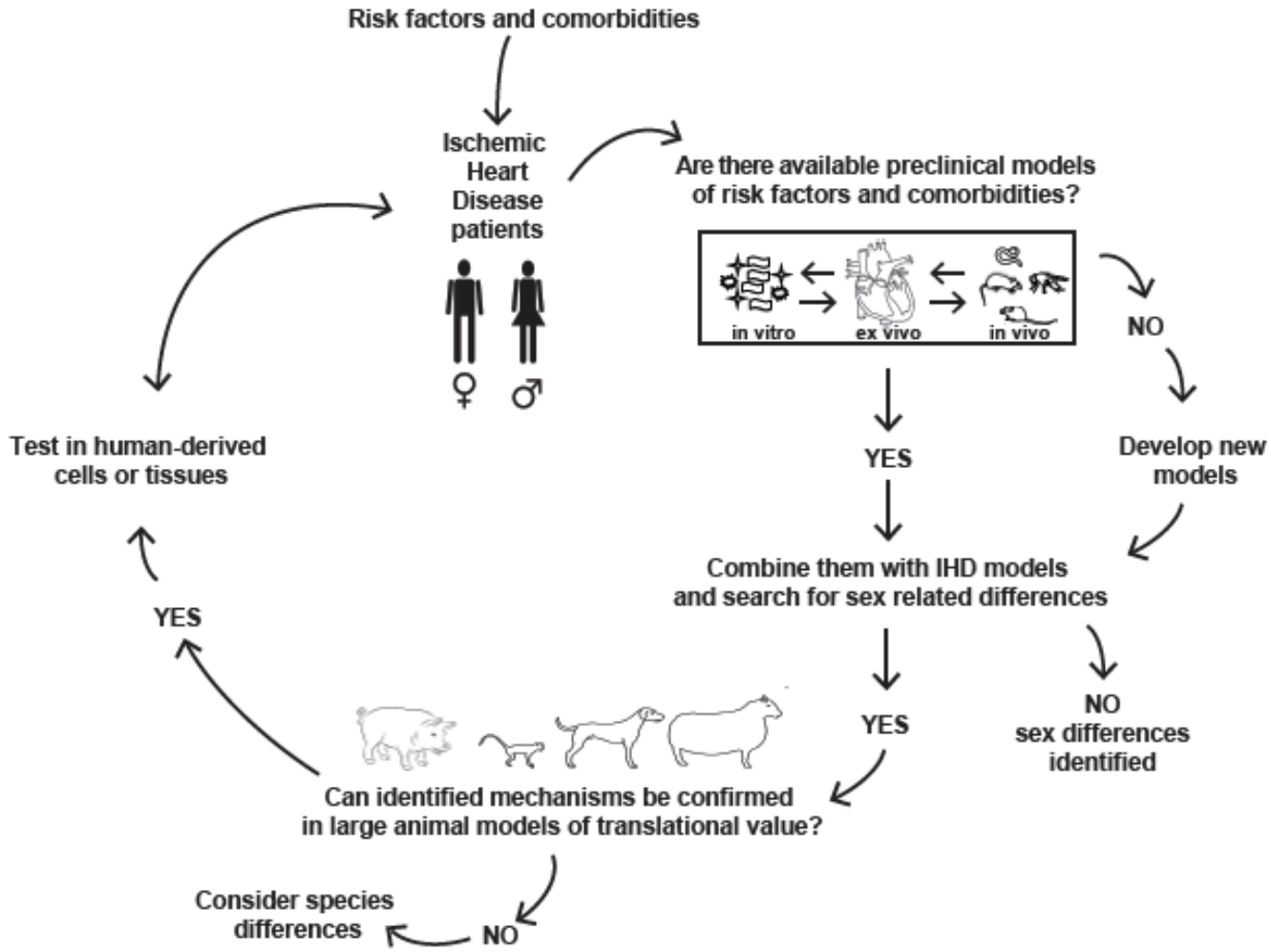
What is missing?

Statistical power to address sex-specific differences

Evaluation of comorbidities

Stratification of risk in women

Biological mechanisms responsible for sex-specific increased hemorragic risk



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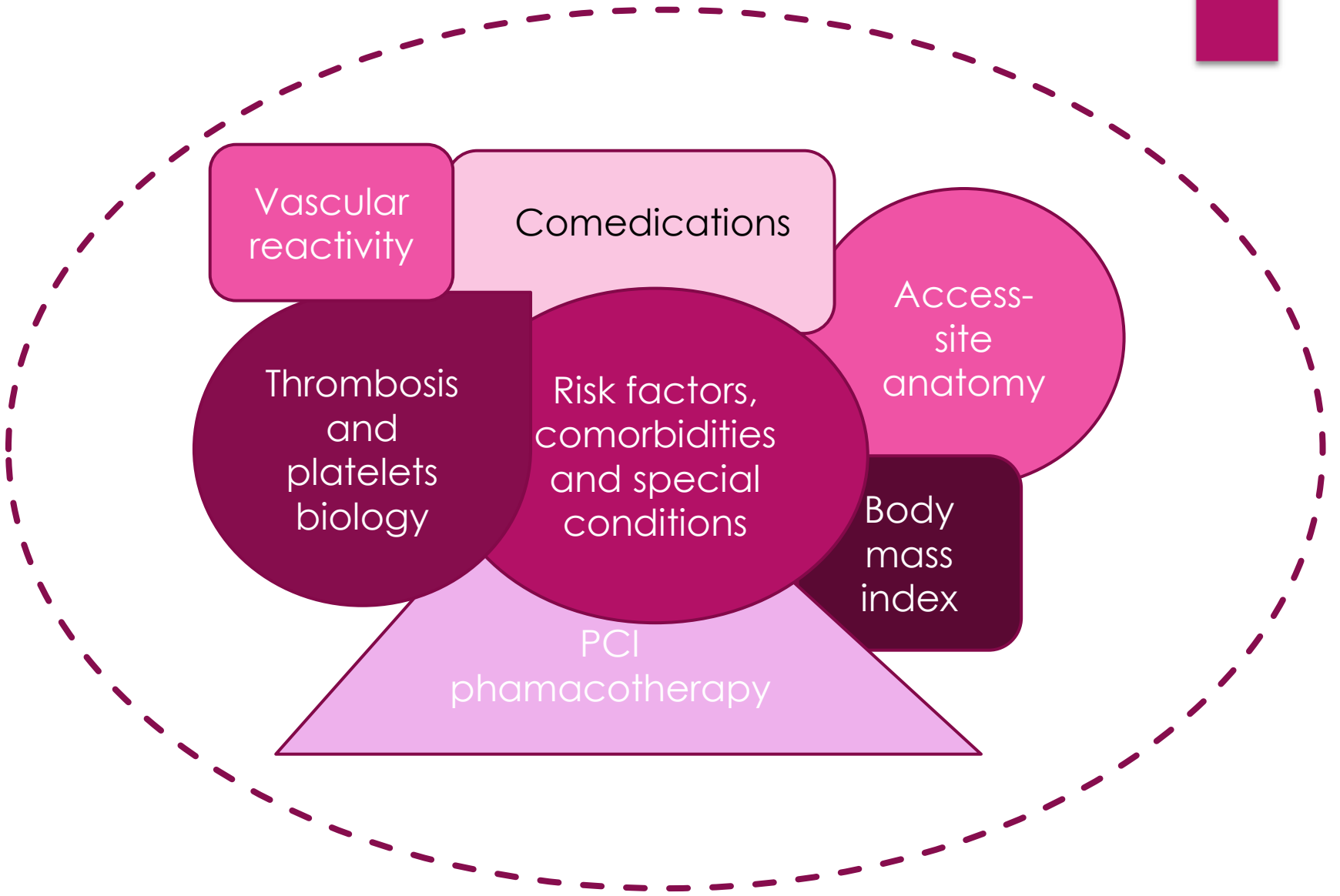
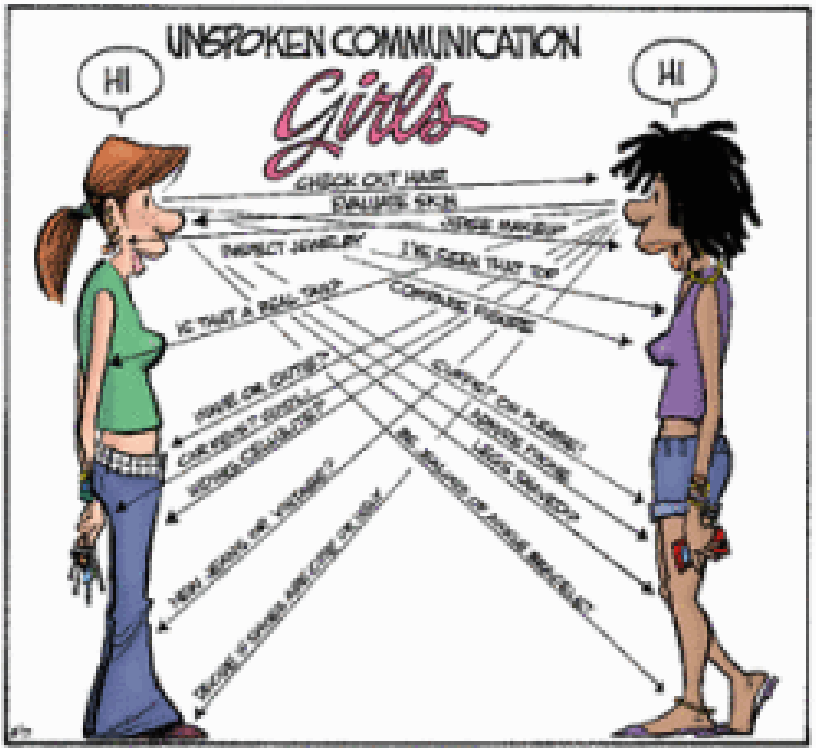
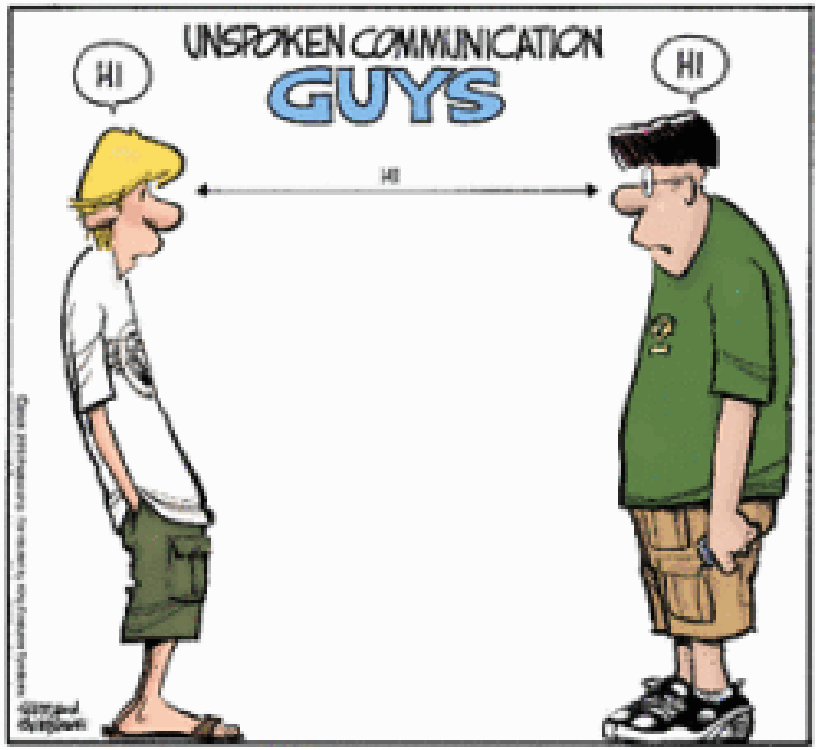

Vascular reactivity
Comedications
Access-site anatomy
Thrombosis and platelets biology
Risk factors, comorbidities and special conditions
Body mass index
PCI phamacotherapy

What is missing?


UNSPOKEN COMMUNICATION
Girls
HI
HI


UNSPOKEN COMMUNICATION
GUYS
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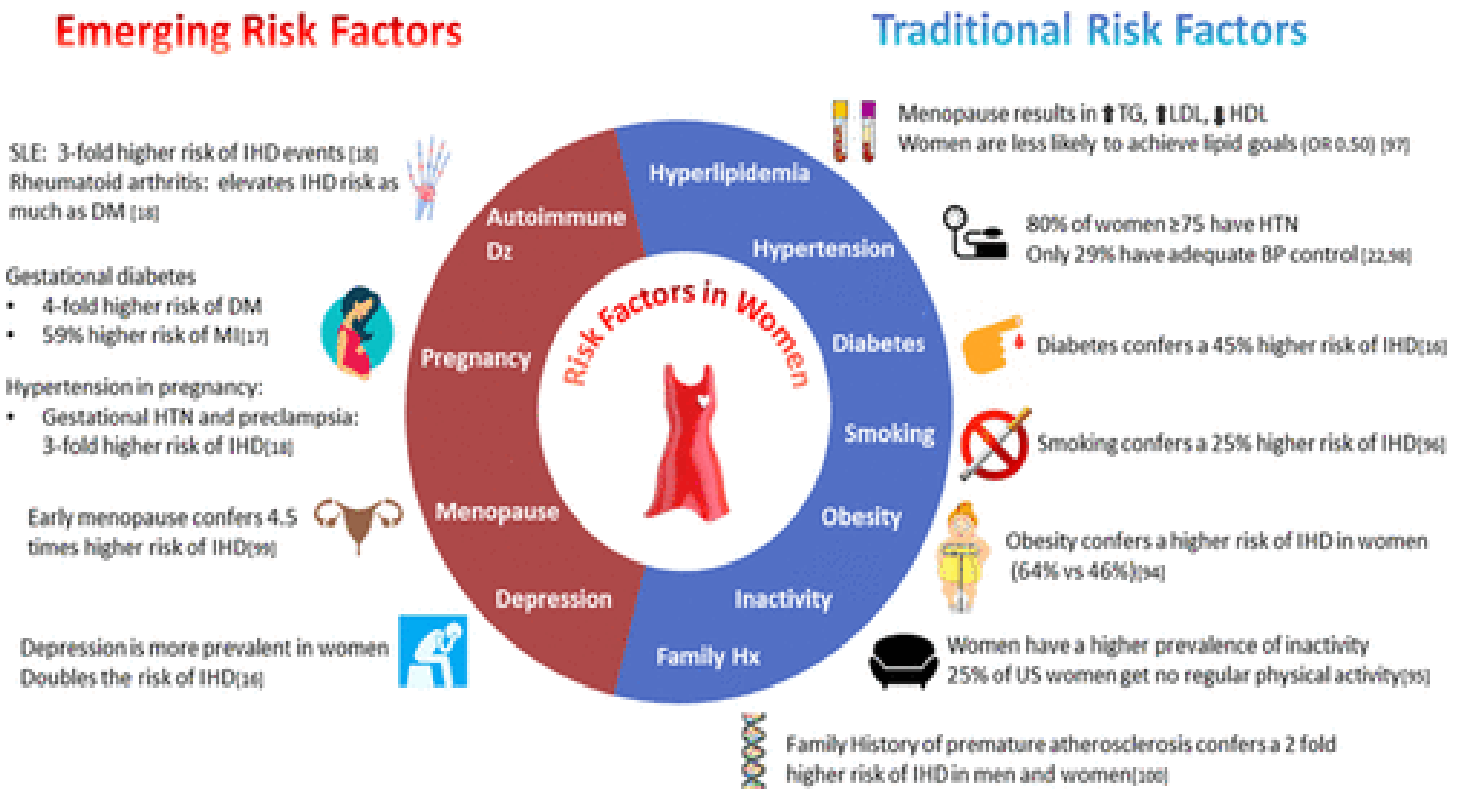
Acknowledgements

ESC Working Group Cellular Biology of the Heart

Péter Ferdinandy, Hans E Bøtker , Bianca J J M Brundel, Peter Collins , Sean M Davidson, Hester M den Ruijter, Felix B Engel, Eva Gerdts, Henrique Girao, Mariann Gyöngyösi, Derek J Hausenloy, Sandrine Lecour, Rosalinda Madonna, Michael Marber, Elizabeth Murphy, Maurizio Pesce, Vera Regitz-Zagrosek, Joost P G Sluijter, Sabine Steffens, Can Gollmann-Tepeköylü, Linda W Van Laake, Sophie Van Linthout, Rainer Schulz, Kirsti Ytrehus

Traditional and emerging risk factors for ischemic heart disease in women



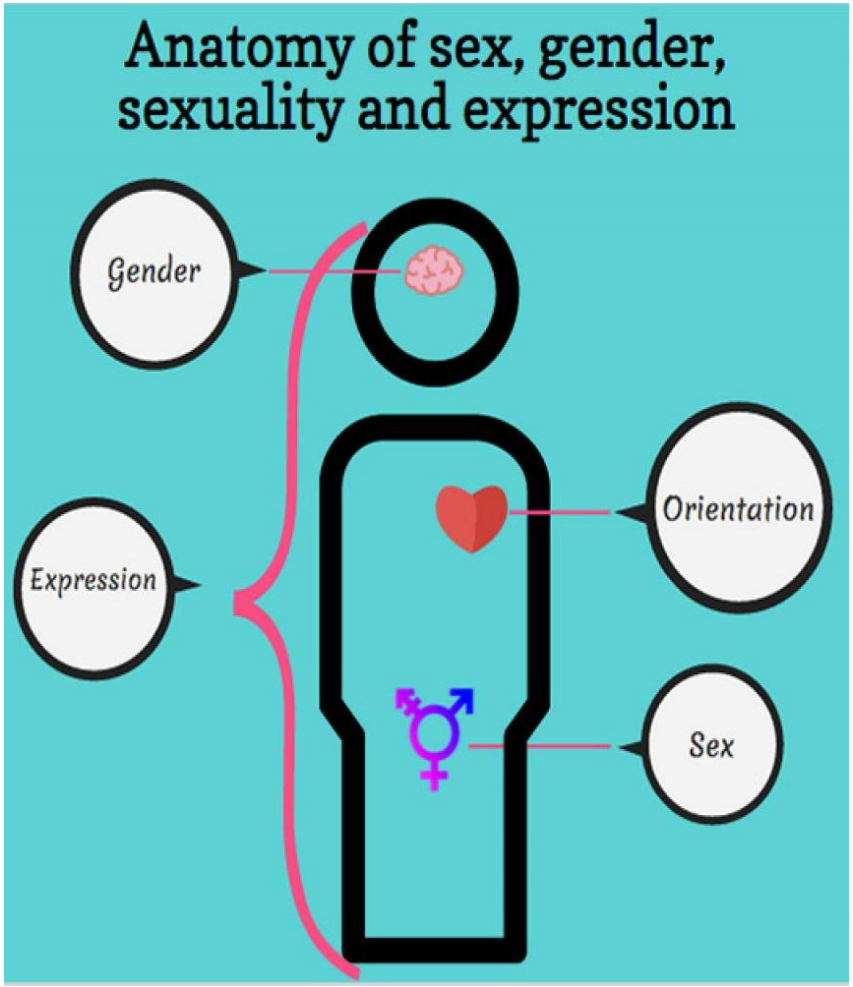
Niti R. Aggarwal. Circulation: Cardiovascular Quality and Outcomes. Sex Differences in Ischemic Heart Disease
DOI: (10.1161/CIRCOUTCOMES.117.004437)

Sex

- Biological and physiological differences due to chromosomes and sexual hormones.
- Remains the same regardless of time or culture.

Gender

- Cultural and social differences between men and women.
- May change over time and culture.
- Distinctions created by social norms.



BARC (Bleeding Academic Research Consortium)

Type 1*:* bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional.

Type 2*:* any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation.

Type 3a*:* overt bleeding plus a hemoglobin drop of 3 to 5 g/dL* (provided the hemoglobin drop is related to bleed); any transfusion with overt bleeding.

Type 3b*:* overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents.

Type 3c*:* intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision.

Type 4*:* coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period.

Type 5a*:* probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.

Type 5b*:* definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation.

Female Sex As A VARIABLE in a SCORE ?

OR

A Score For Female Sex?

What is missing?

- Statistical power to address sex-specific differences
- Evaluation of comorbidities
- Stratification of risk in women
- **Biological mechanisms responsible for increased hemorragic risk**

Bleeding Academic Research Consortium (BARC) definitions

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	CABG-related bleeding within 48 hours
Type 5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)