Gender differences in drug responses to cardiovascular and heart failure medication

Chim Lang

Professor of Cardiology

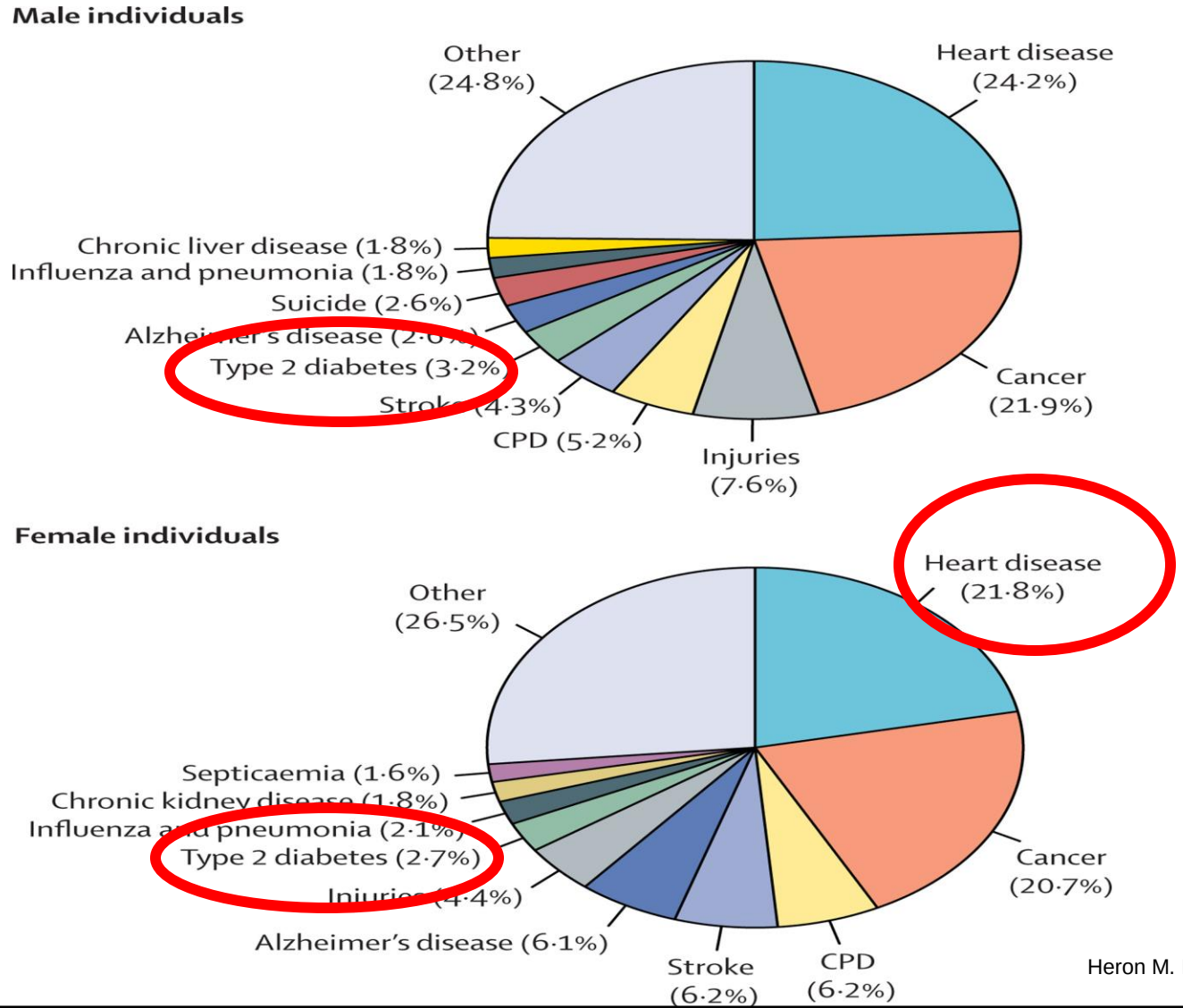
University of Dundee

Conflicts of interest

- I have received consultancy fees and/or research grants from Amgen, AstraZeneca, Boehringher Ingelheim, MSD, Novartis, Novo Nordisk and Servier;
- I have grant funding from European Union FP-7 and Horizon 2020 IMI2 Program, MRC, UKRI-Newton Ungku fund, NIHR, British Heart Foundation, EFSD, Tenovus, Chief Scientist Office

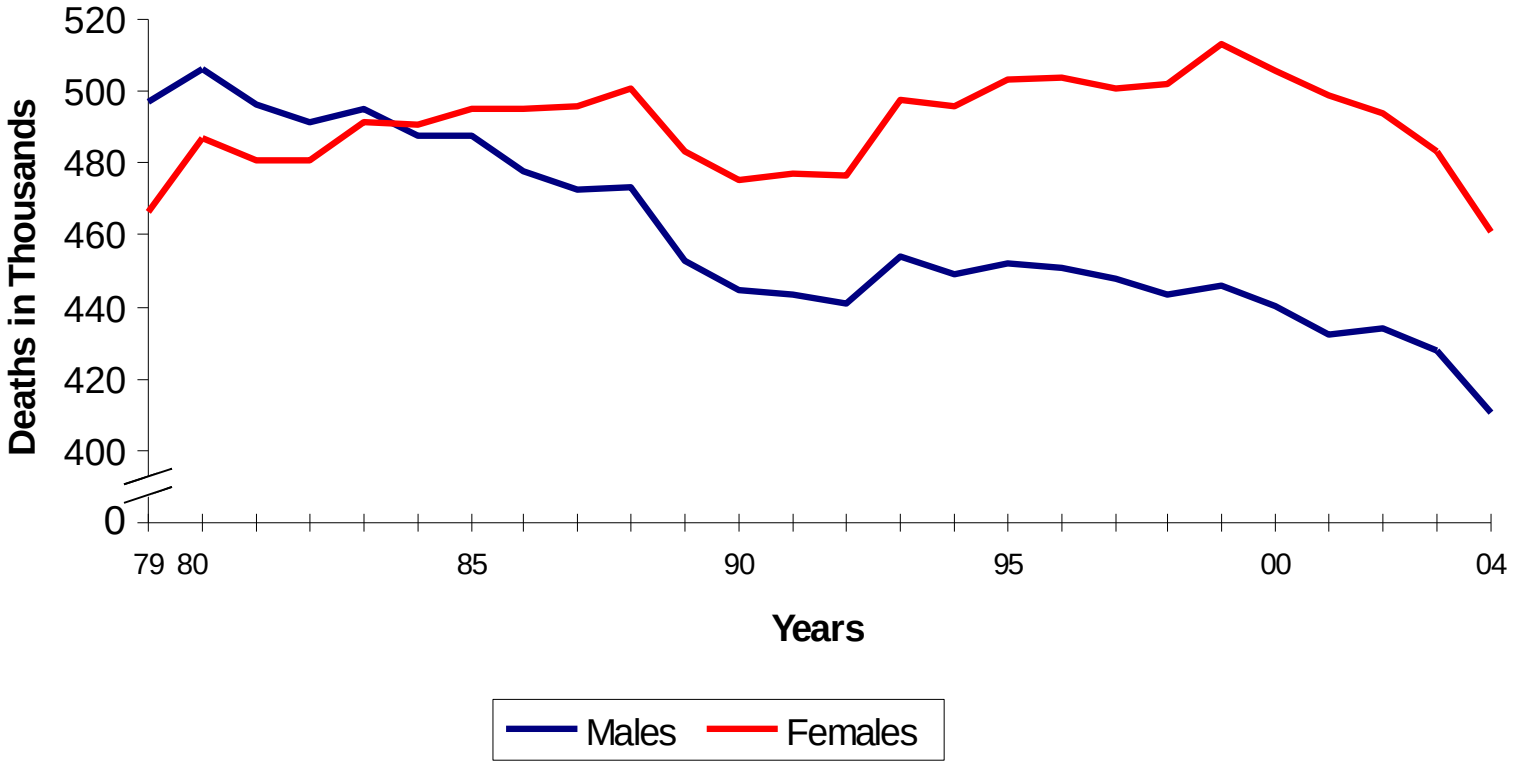
University of Dundee

CVD is a leading cause of death in both Men and Women



Heron M. Natl Vital Stat 2019

Cardiovascular Disease Mortality Trends for Women and Men United States: 1979-2004



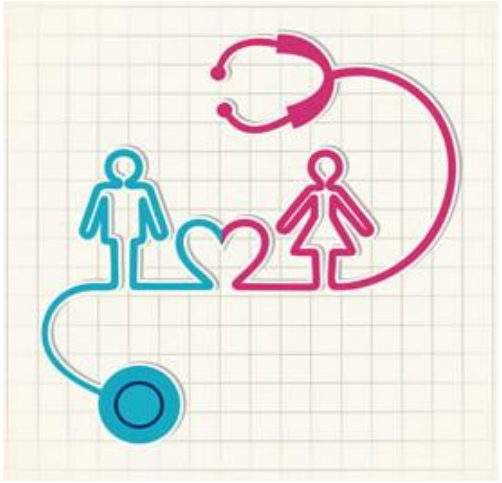
Rosamond et al. *Circulation* 2007;115;e69-e171, Source: NCHS and NHLBI

Striking sex and gender disparities in CVD

Epidemiology

Pathophysiology
- Risk factor profile

Clinical Manifestation
- Presentation
- Testing



Disease Progression and Outcome

Treatment
- Efficacy
- Side effects

Sex versus Gender

Sex

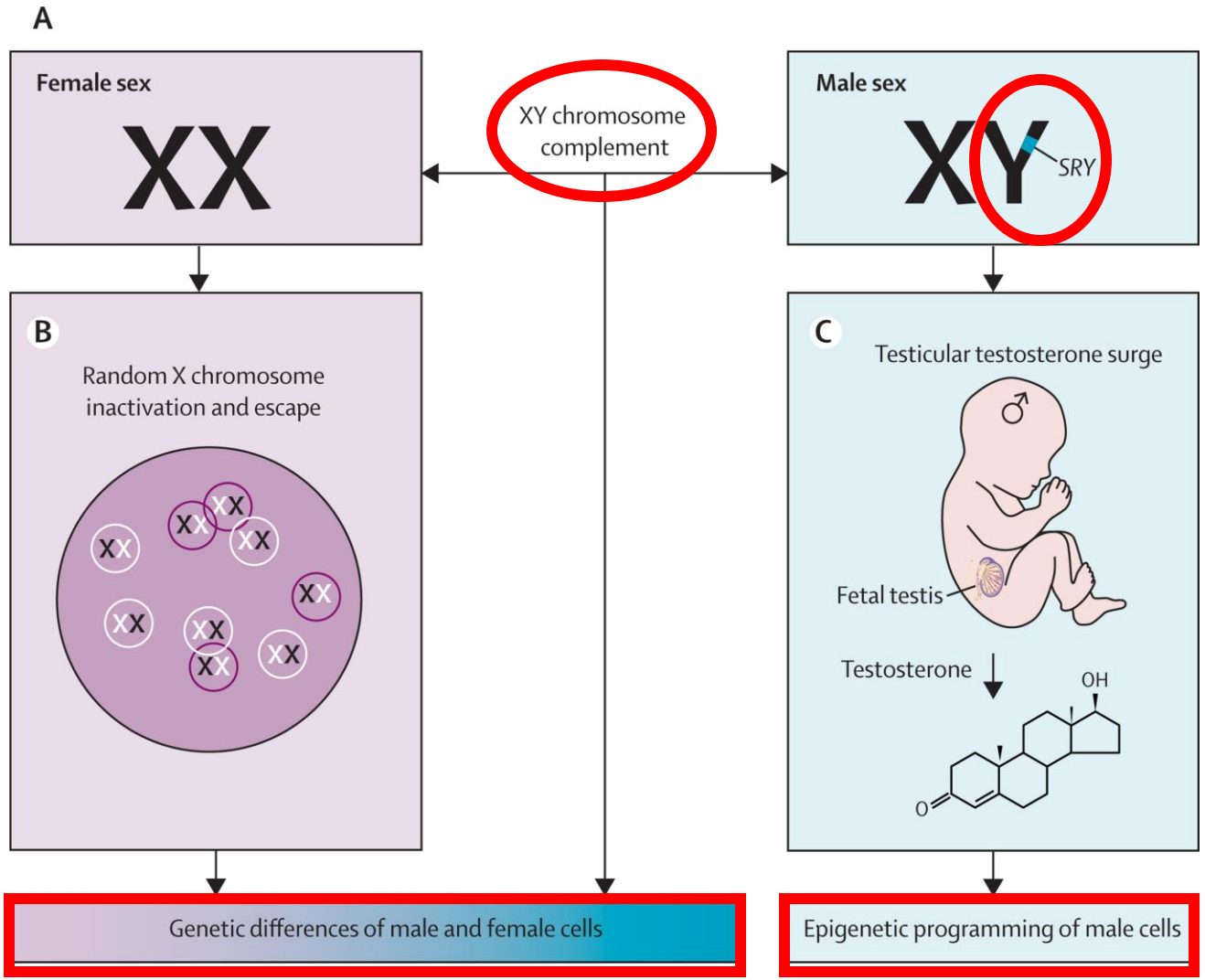
- Biological
- Given by Birth
- Therefore, CANNOT BE CHANGED

Gender

- Behavioural, psychological, emotional and cultural traits associated with one's sex
- Learned through socialization
- Therefore, CAN BE CHANGED

Sex differences, rooted in genetic differences, modifies disease via genetic, hormonal and epigenetics

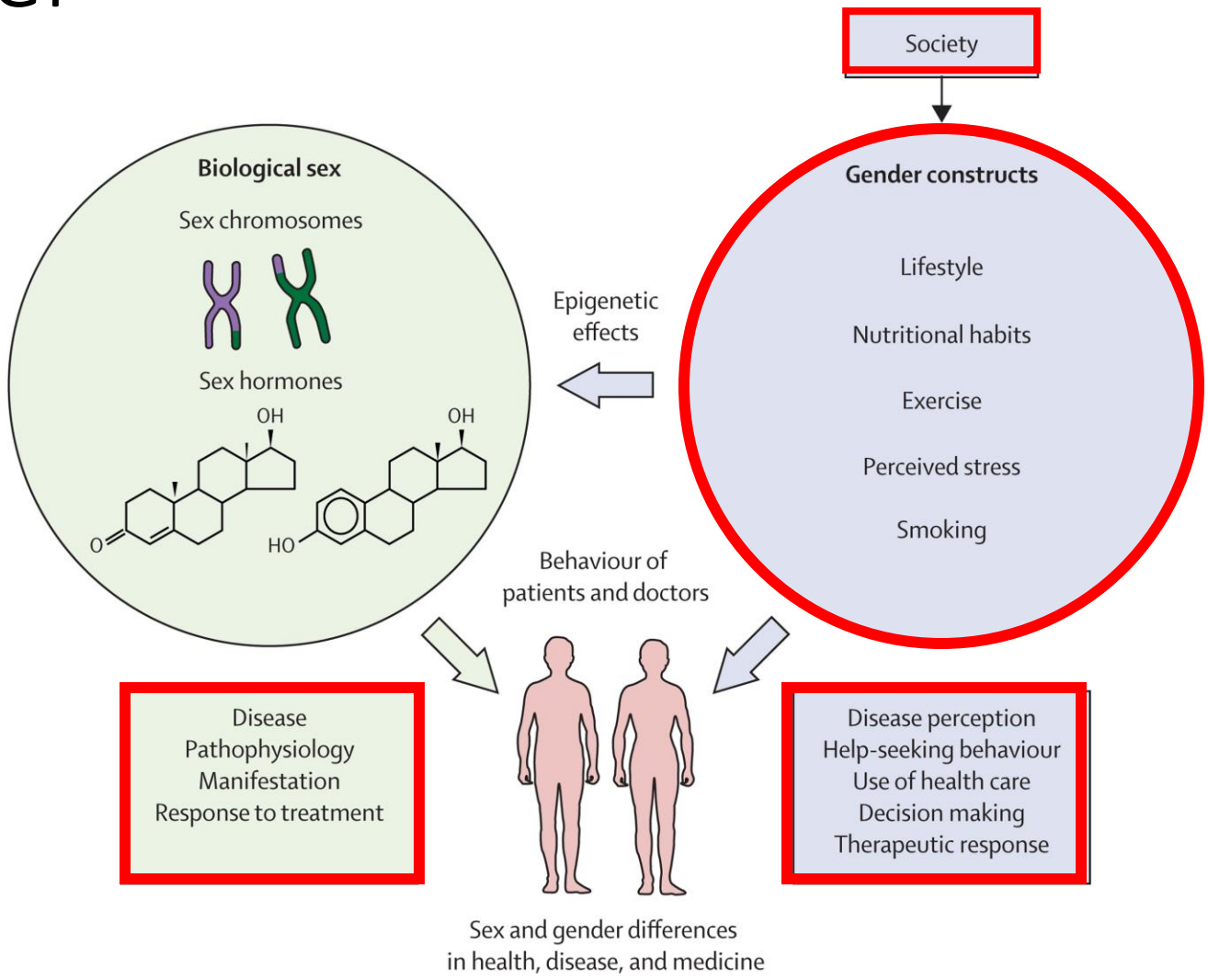
In women, X chromosomes carry both maternal and paternal imprint



In men, X chromosome carries only the maternal imprint

Mauvais-Jarvis F et al. Lancet 2020

Inter-relation between sex and gender



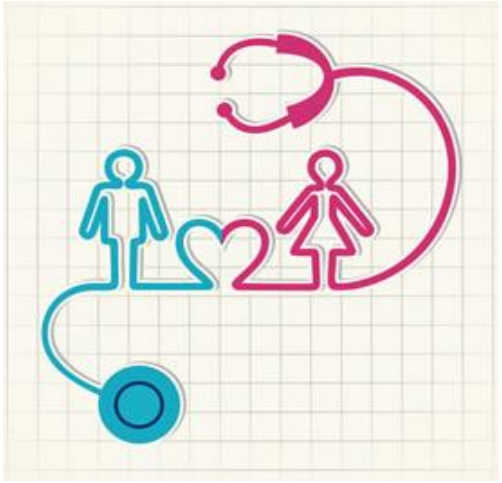
Mauvais-Jarvis F et al. Lancet 2020

Striking sex and gender disparities in CVD

Epidemiology

Pathophysiology
- Risk factor profile

Clinical Manifestation
- Presentation
- Testing



Disease Progression and Outcome

Treatment
- Efficacy
- Side effects

Sex and Gender differences in CVD and DM

	Male Sex	Female Sex	Gender Differences, women
Heart Disease	Younger age; more obstructive CAD, more HFrEF	Older age, more coronary micro-vascular dysfunction, more HFpEF	Less evidence based treatment, higher MI mortality
Ischaemic Strokes	Younger age of onset	Older age onset, aspirin greater benefit	Untreated, poorer outcome
Type 2 DM	More frequent Impaired fasting glycaemia	More frequent IGTT, **greater clustering of CV risk factors**, **higher prevalence of CV complications**	Under-treatment of T2DM in women

[7]Mauvais-Jarvis F et al. Lancet 2020

Diabetes confers a greater risk for CVD events in women than men

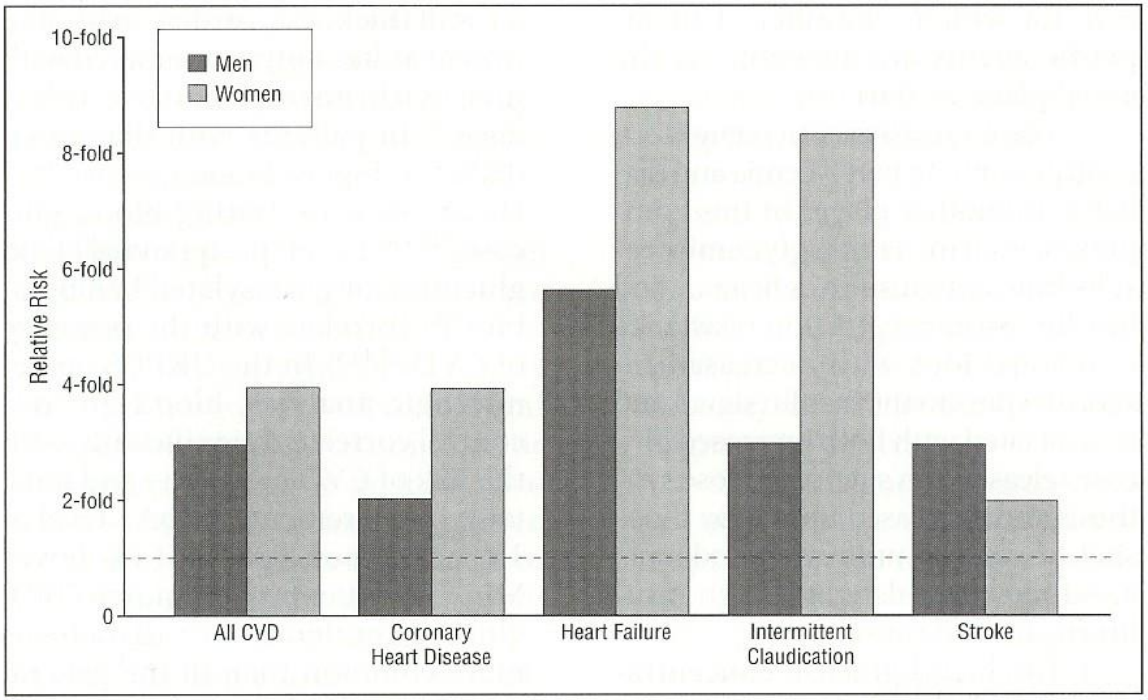


Figure 2. Relative risk of cardiovascular events in people with diabetes. Except for stroke, the relative risk of cardiovascular disease (CVD) associated with diabetes is greater for women than for men. The dashed line represents a relative risk of 1 (ie, the relative risk expected of a control group). Adapted from Wilson and Kannel[6] (1992), with permission.

Barrett-Connor et al. *Arch Int Med*. 2004;164:934-942

AHA Scientific Statement

Sex Differences in the Cardiovascular Consequences of Diabetes Mellitus

A Scientific Statement From the American Heart Association

Judith G. Regensteiner, PhD, FAHA, Co-Chair; Sherita Golden, MD, MHS, FAHA, Co-Chair; Amy G. Huebschmann, MD, MSc; Elizabeth Barrett-Connor, MD, FAHA; Alice Y. Chang, MD, MSc; Deborah Chyun, PhD, RN, FAHA; Caroline S. Fox,* MD, FAHA; Catherine Kim, MD, MPH; Nehal Mehta, MD, MSCE; Jane F. Reckelhoff, PhD, FAHA; Jane E.B. Reusch, MD; Kathryn M. Rexrode, MD, MPH; Anne E. Sumner, MD, FAHA; Francine K. Welty, MD, FAHA; Nanette K. Wenger, MD, FAHA; Blair Anton, MLIS, MS, AHIP; on behalf of the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Epidemiology and Prevention, Council on Functional Genomics and Translational Biology, and Council on Hypertension

Regensteiner JG et al. Circulation 2015; 132: 2424-2447

Striking sex and gender disparities in CV Consequences of Diabetes Mellitus

Diabetes Mellitus → CV Complications

Sex differences

- Impact of sex hormones
- CV risk factors
  - Gestational diabetes, PCOS
- Lifestyle
- Treatment

Although non-T2DM women have fewer MI events than non-T2DM men of the same age, this advantage is lost in the context of T2DM

Previous meta-analysis have shown sex specific association with MI risk but needed adjustment for confounders

RESEARCH

Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants

Elizabeth R C Millett,[1] Sanne A E Peters,[1,2] Mark Woodward[1,3,4]

[1]The George Institute for Global Health, University of Oxford, Oxford OX1 2BQ, UK
[2]Julius Center for Health Sciences and Primary Care, University Medical Center

ABSTRACT

OBJECTIVES

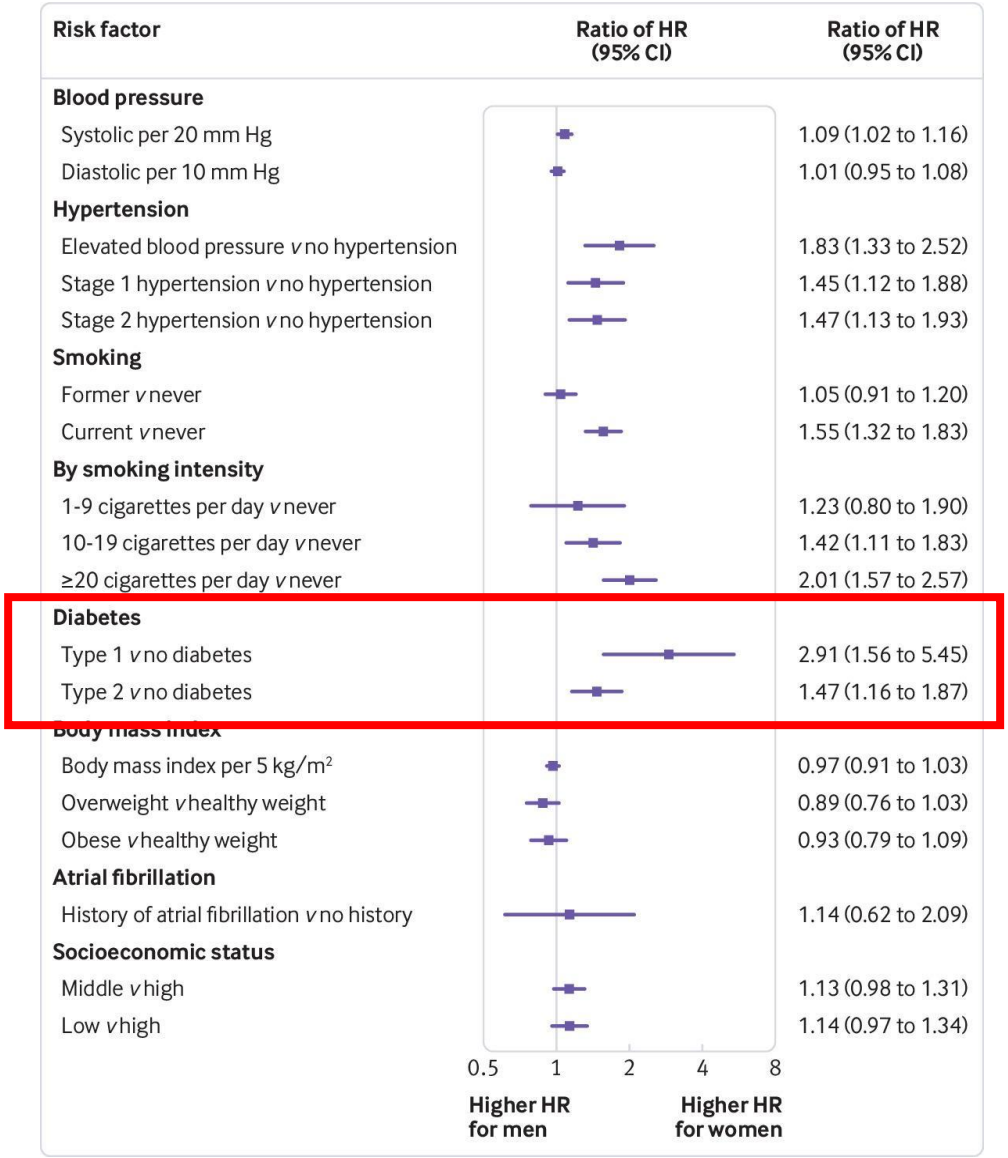
To investigate sex differences in risk factors for incident myocardial infarction (MI) and whether they vary with age.

CONCLUSIONS

Although the incidence of MI was higher in men than in women, several risk factors were more strongly associated with MI in women compared with men. Sex specific associations between risk factors and MI

Millet ER et al. BMJ 2018

Diabetes mellitus was associated with greater risk for incident MI in Women



HR 2.91 (T1DM)
HR 1.47 (T2DM)

Elizabeth R C Millett et al. BMJ 2018;363:bmj.k4247

thebmj

Ritter et al. Biology of Sex Differences (2020) 11:1
https://doi.org/10.1186/s13293-019-0277-z

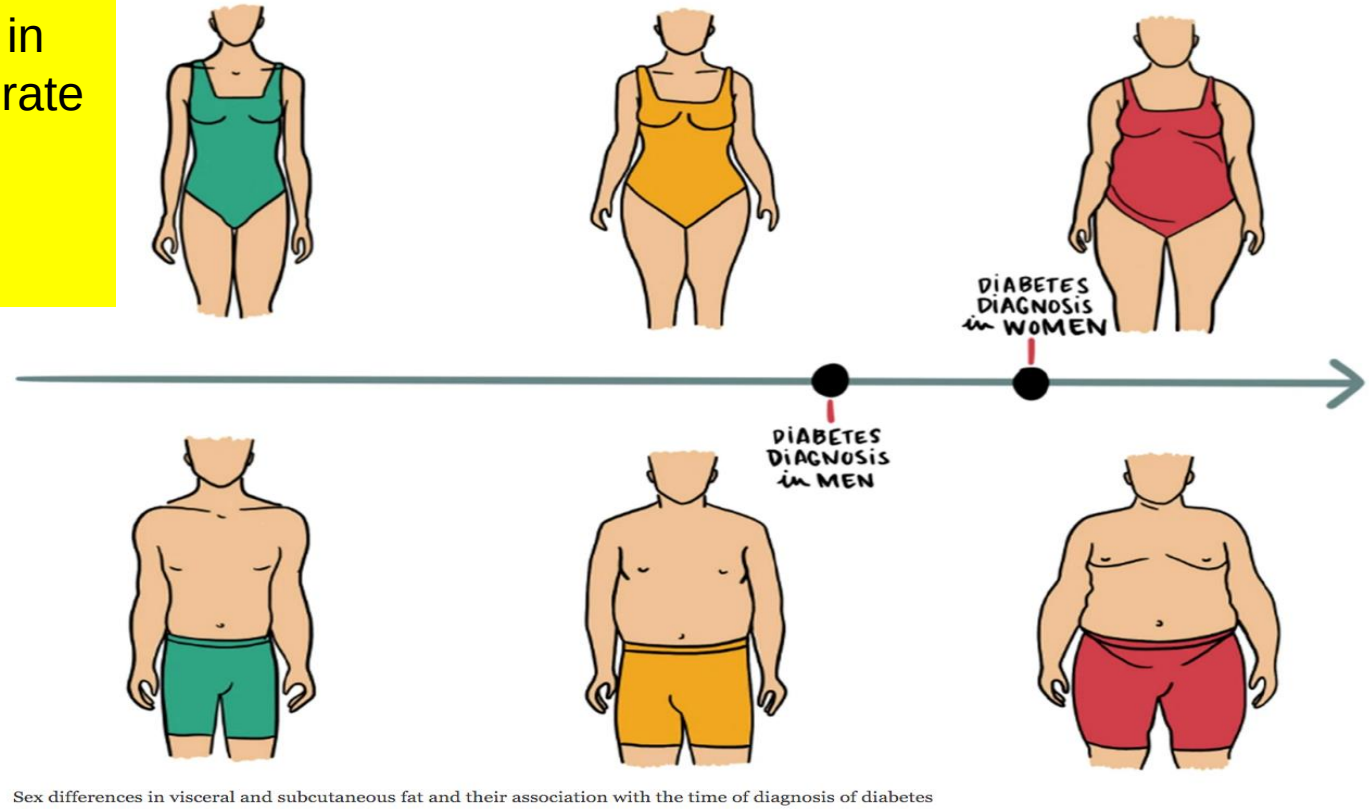
Biology of Sex Differences

REVIEW Open Access

Sex differences in the risk of vascular disease associated with diabetes

Rianneke de Ritter[1,2†], Marit de Jong[3†], Rimke C. Vos[3,4], Carla J. H. van der Kallen[1,2], Simone J. S. Sep[1,2], Mark Woodward[5,6,7], Coen D. A. Stehouwer[1,2], Michiel L. Bots[3] and Sanne A. E. Peters[3,5*]

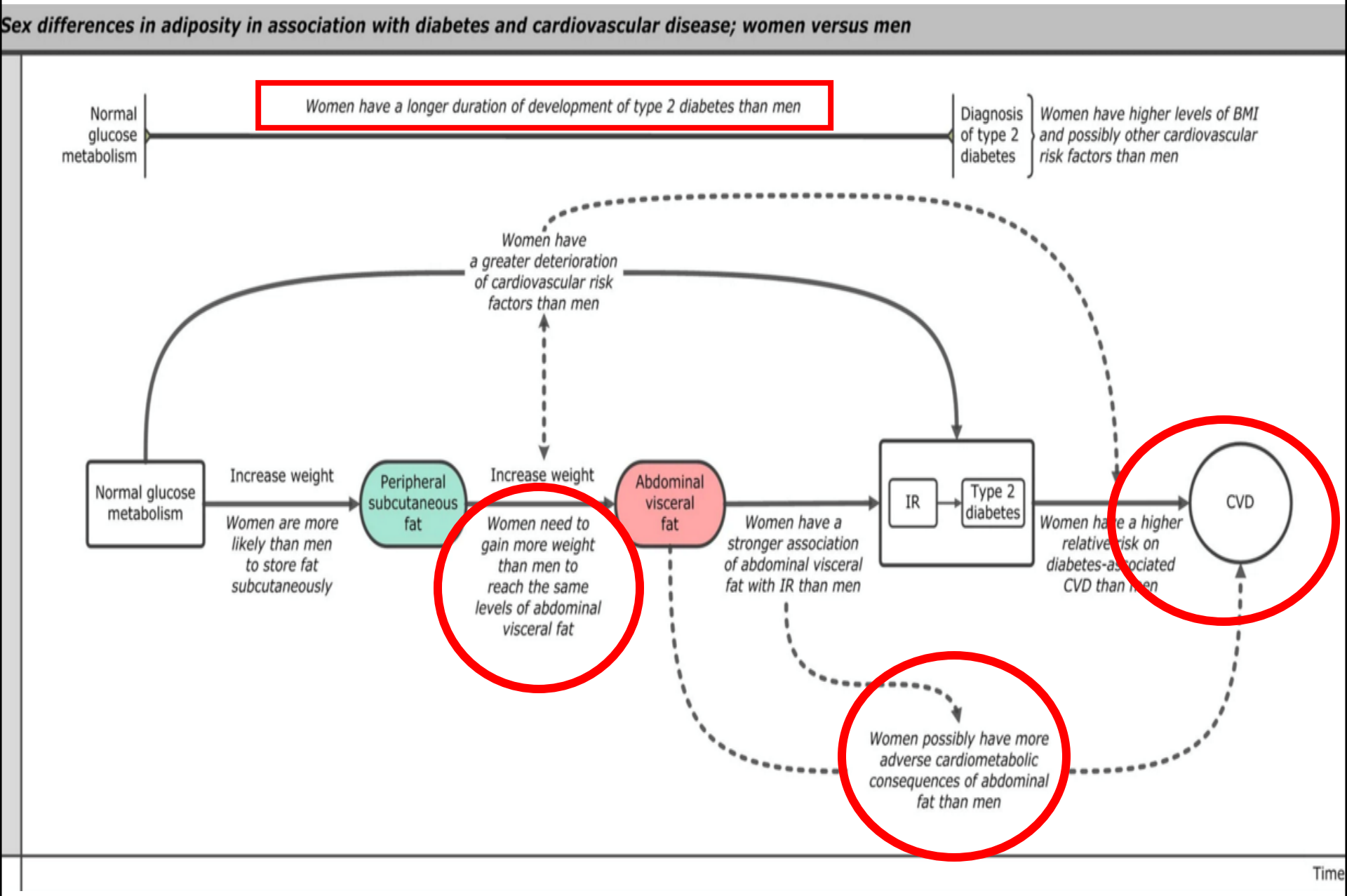
Metabolic risk factors in women has to deteriorate to a GREATER magnitude to develop diabetes



Sex differences in visceral and subcutaneous fat and their association with the time of diagnosis of diabetes

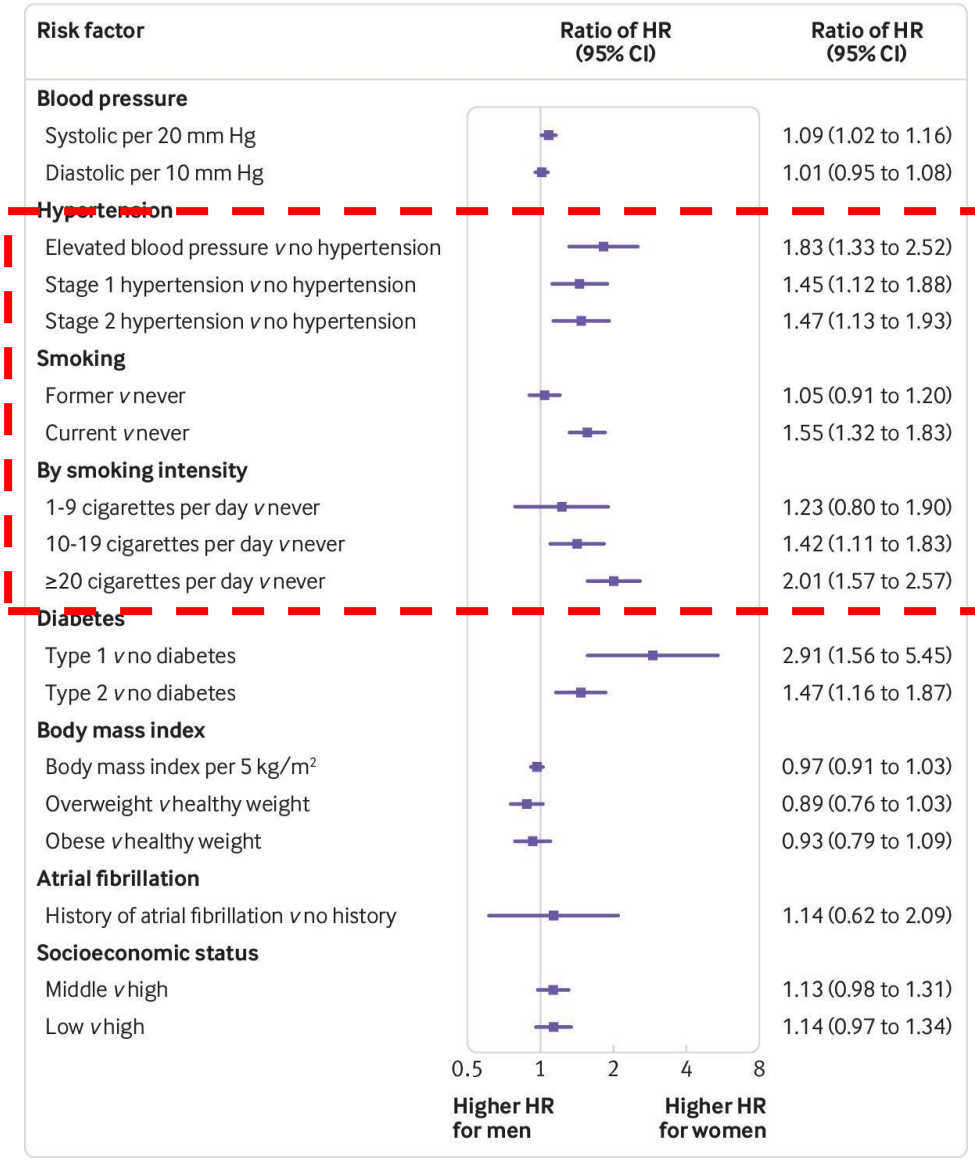
Pre-diabetes period: 8.5 yrs in Men and 10.3 years in women

Ritter et al 2020; Bertram MY et al 2010



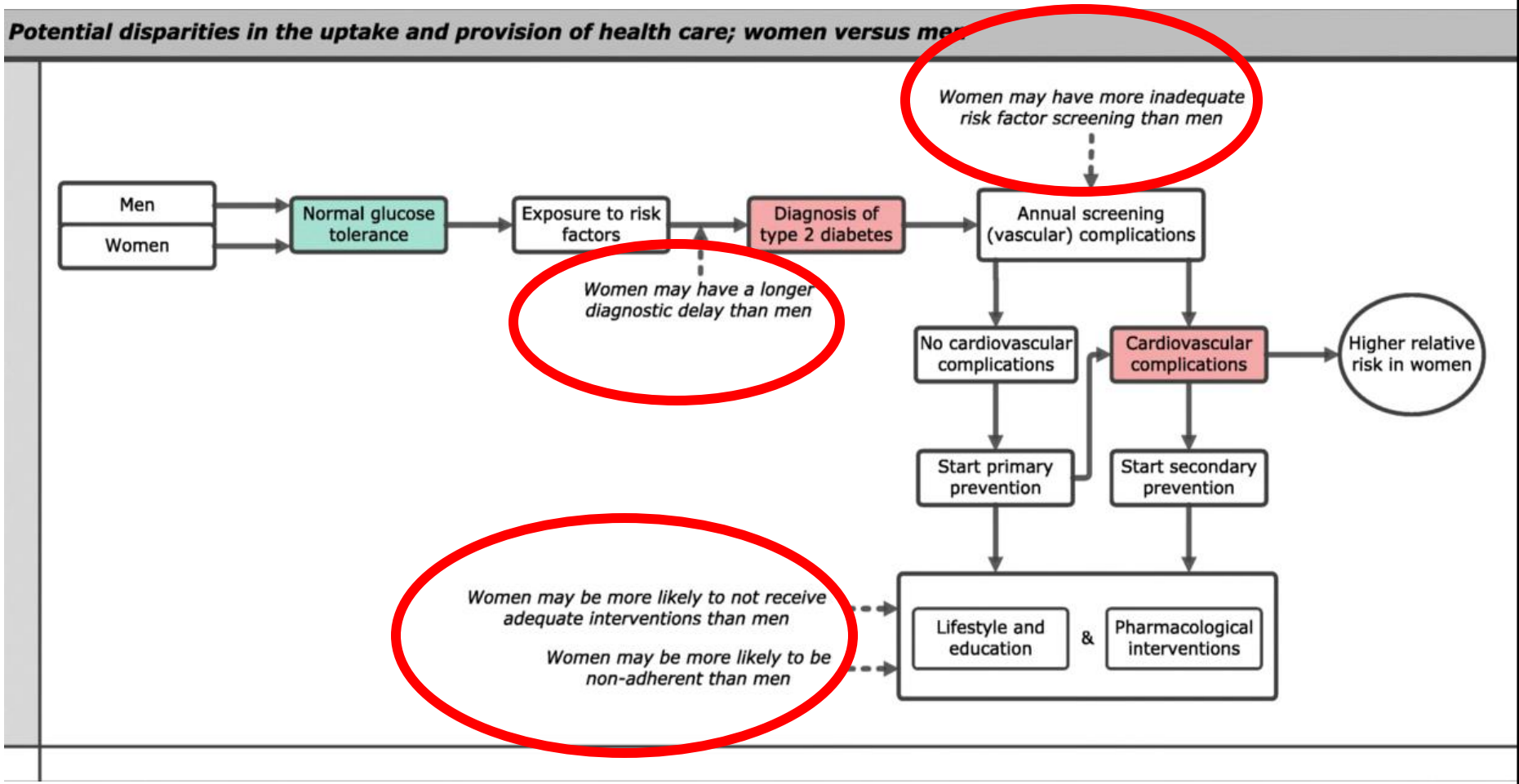
Ritter et al 2020

CV risk factors (BP, smoking) was associated with greater MI risk in Women



Elizabeth R C Millett et al. BMJ 2018;363:bmj.k4247

CV complication of T2DM in Women: Disparities in uptake and provision of healthcare



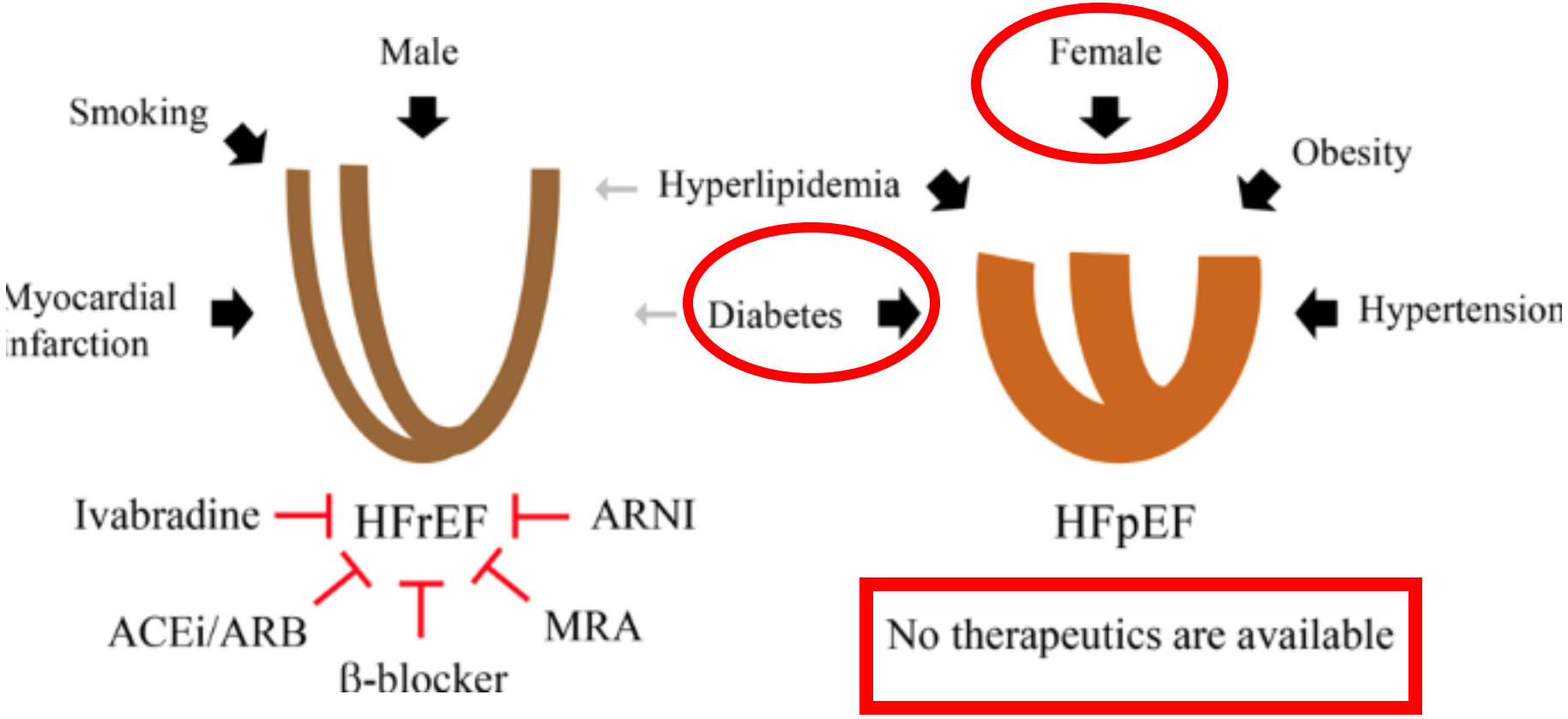
Ritter et al 2020

Sex and Gender differences in CVD and DM

	Male Sex	Female Sex	Gender Differences, women
Heart Disease	Younger age; more obstructive CAD, more HFrEF	Older age, more coronary micro-vascular dysfunction, **more HFpEF**	Less evidence based treatment, higher MI mortality
Ischaemic Strokes	Younger age of onset	Older age onset, aspirin greater benefit	Untreated, poorer outcome
Type 2 DM	More frequent Impaired fasting glycaemia	More frequent IGTT, **greater clustering of CV risk factors, higher prevalence of CV complications**	Under-treatment of T2DM in women

Mauvais-Jarvis F et al. Lancet 2020

HFreduced EF versus HFpreserved EF



Influence of co-morbidities in women on HFpEF

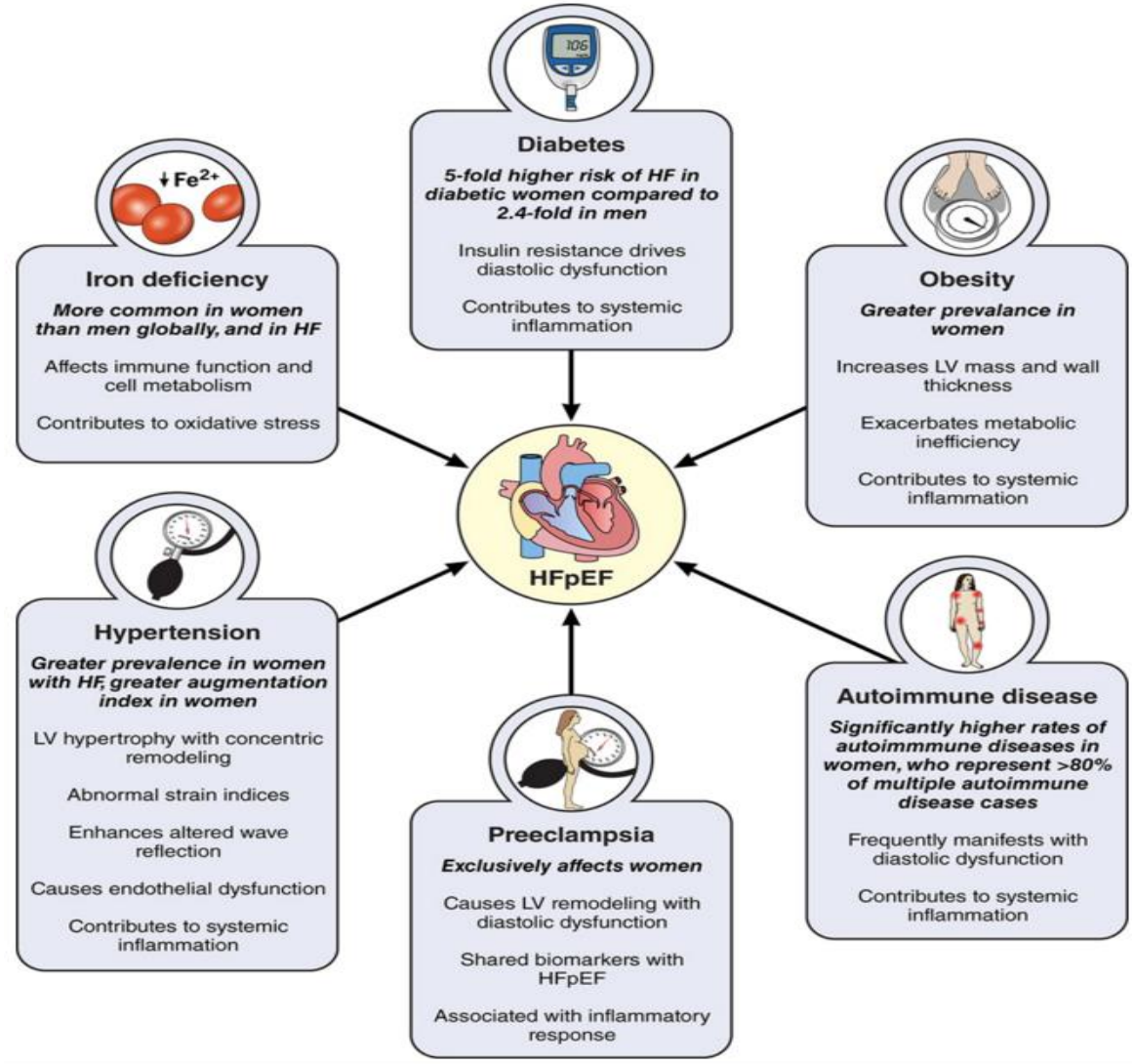
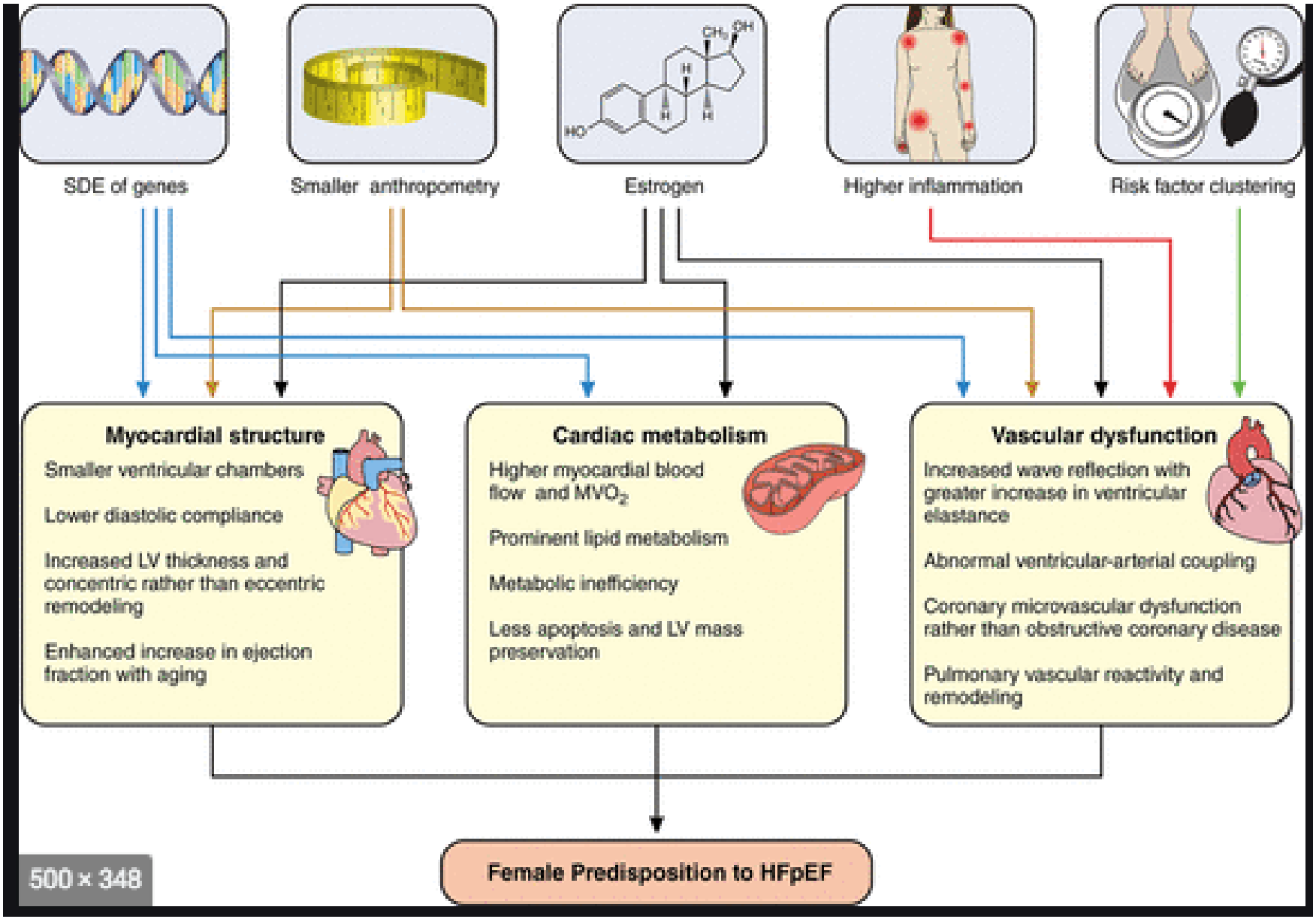


Figure 2. The influence of comorbidities on the development of HFpEF in women. Comorbidities including iror

Beale et al Circulation 2018



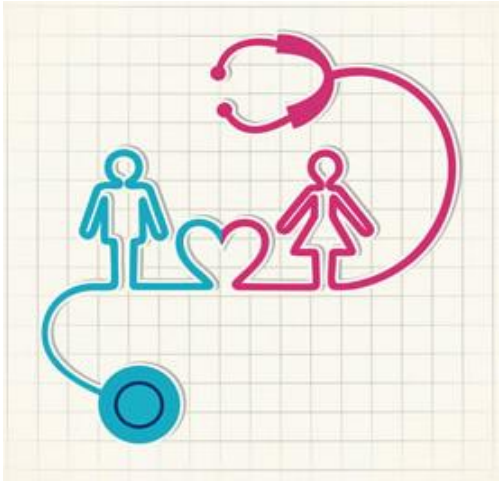
Beale et al Circulation 2018

Striking sex and gender disparities in CVD

Epidemiology

Pathophysiology
- Risk factor profile

Clinical Manifestation
- Presentation
- Testing



Disease Progression and Outcome

Treatment
- Efficacy
- Side effects

European Heart Journal (2015) **36**, 2677–2680
doi:10.1093/eurheartj/ehv161

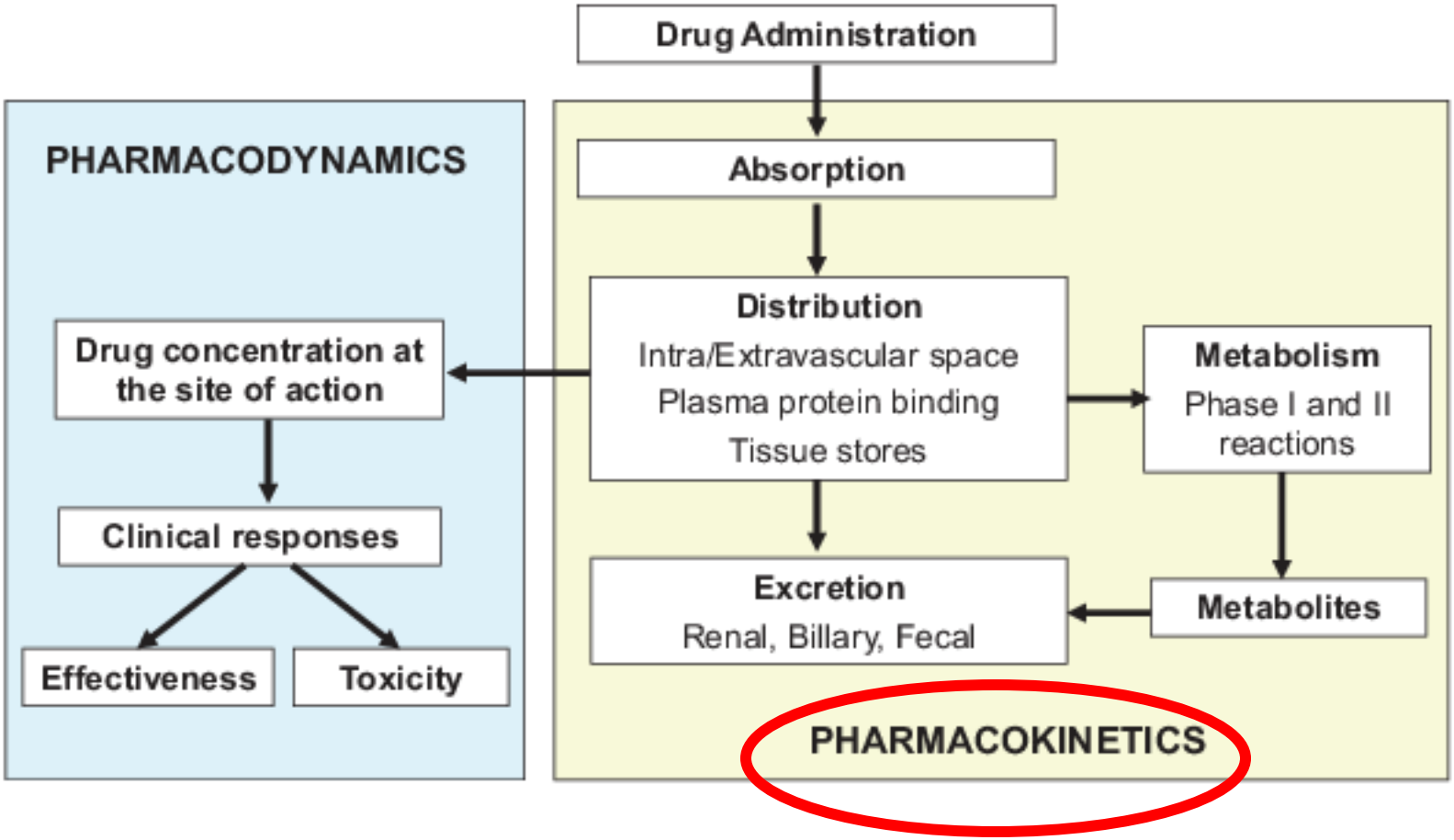
CURRENT OPINION

Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

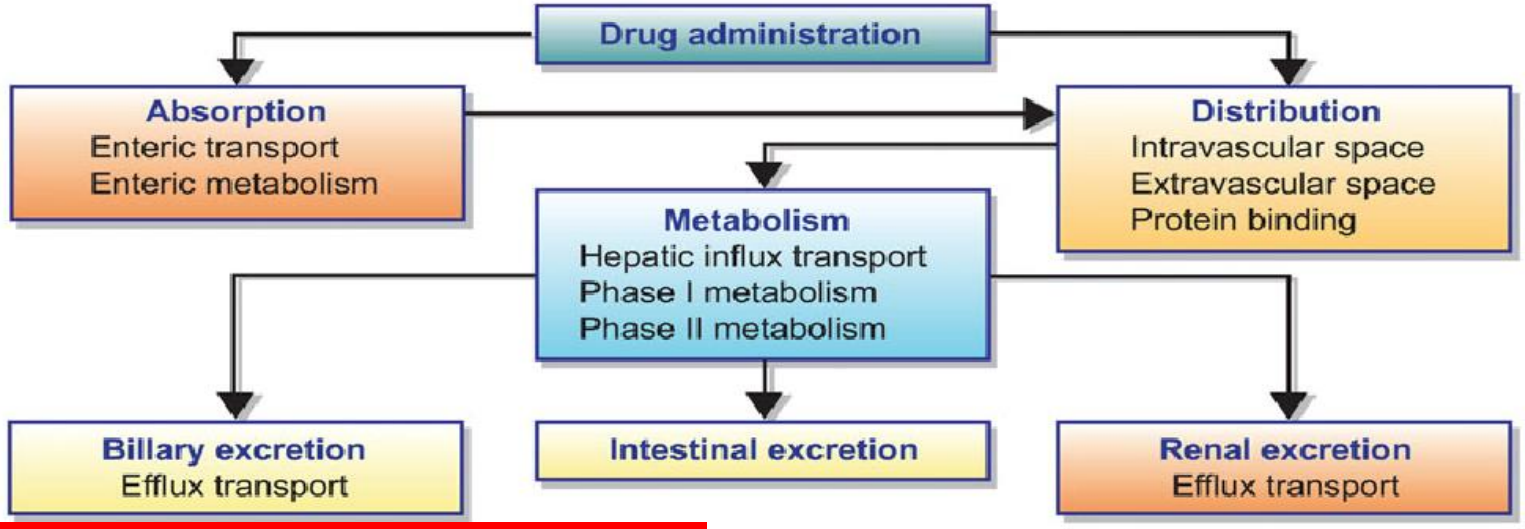
Giuseppe M.C. Rosano[1,2*], Basil Lewis[3], Stefan Agewall[4], Sven Wassmann[5], Cristiana Vitale[1], Harald Schmidt[6], Heinz Drexel[7], Atul Patak[8], Christian Torp-Pedersen[9], Keld Per Kjeldsen[10], and Juan Tamargo[11]

[1]Centre for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy; [2]Cardiovascular and Cell Sciences Research Institute, St George's University of London, UK; [3]Lady Davis Carmel Medical Center, Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Tel Aviv, Israel; [4]Oslo University Hospital Ullevål, and Institute of Clinical Sciences, University of Oslo, Oslo, Norway; [5]Department of Cardiology, Isar Heart Center, Isar Kliniken, Munich, Germany; [6]Pharmacology, Universiteit Maastricht, 6200 MD Maastricht, Limburg, Netherlands; [7]Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria; [8]Department of Pharmacology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [9]Department of Cardiology, Copenhagen University Hospital, Hellerup, Denmark; [10]Copenhagen University Hospital (Rigshospitalet) and Aalborg University, The Heart Centre, 2100 Copenhagen, Denmark; and [11]Department of Pharmacology, School of Medicine, Universidad Complutense, 28040 Madrid, Spain

Received 21 March 2014; revised 13 April 2015; accepted 21 April 2015; online publish-ahead-of-print 6 May 2015


Drug Administration
PHARMACODYNAMICS
Absorption
Distribution
Intra/Extravascular space
Plasma protein binding
Tissue stores
Drug concentration at the site of action
Metabolism
Phase I and II reactions
Clinical responses
Excretion
Renal, Billary, Fecal
Metabolites
Effectiveness
Toxicity
PHARMACOKINETICS

Gender differences in Pharmacokinetics



Absorption:
- Slower GI motility and transit time
- Lower gastric acid secretion
- Less drug enzymes and transporters
- Lower absorption rates

Body composition:
- Lower BW, organ size and blood flow

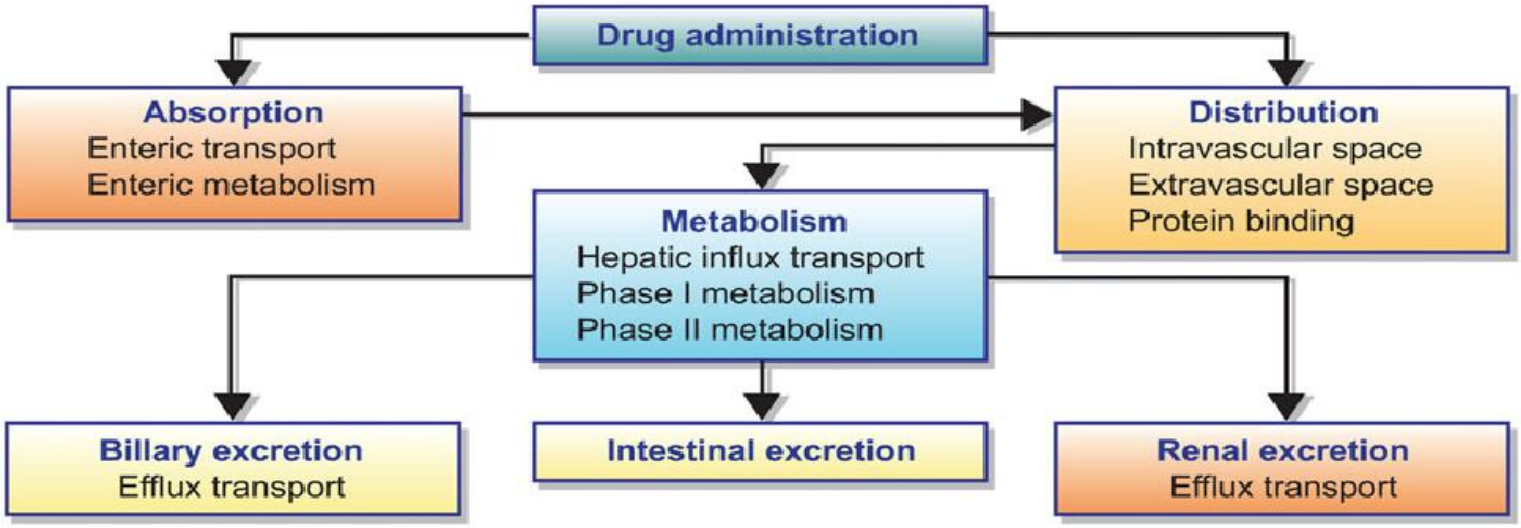
Distribution:
- Greater body fat and lower body water content (Higher Vd for lipophilic drugs, Lower Vd for water-soluble drugs)
- Less α1-acid glycoprotein
- Lower cardiac output

Excretion:
- Lower renal blood flow, glomerular filtration rate (GFR), tubular secretion and reabsorption
- Slower clearance of renally excreted drugs
- Longer elimination half-life

Other Factors:
- Differences in BW, cardiac output, plasma volume and

CYP Enzyme	Enzyme Activity
1A2	M > W
2A6	W > M
2B6	W > M
2C9	M = W
2C19	M = W
2D6	Mostly W > M
3A4	Mostly W > M
UDP-glucuronosyltransferases (UGTs)	M > W
Sulfotransferases	M > W
N-acetyltransferases	M < W
Methyltransferases	M > W

Gender differences in Pharmacokinetics



Absorption:
- Slower GI motility and transit time
- Lower gastric acid secretion
- Less drug enzymes and transporters
- Lower absorption rates

Body composition:
- Lower BW, organ size and blood flow

Distribution:
- Greater body fat and lower body water content (Higher Vd for lipophilic drugs, Lower Vd for water-soluble drugs)
- Less α1-acid glycoprotein
- Lower cardiac output

Excretion:
- Lower renal blood flow, glomerular filtration rate (GFR), tubular secretion and reabsorption
- Slower clearance of renally excreted drugs
- Longer elimination half-life

Other Factors:
- Differences in BW, cardiac output, plasma volume and regional blood flow

CYP Enzyme	Enzyme Activity
1A2	M > W
2A6	W > M
2B6	W > M
2C9	M = W
2C19	M = W
2D6	Mostly W > M
3A4	Mostly W > M
UDP-glucuronosyltransferases (UGTs)	M > W
Sulfotransferases	M > W
N-acetyltransferases	M < W
Methyltransferases	M > W

medical sciences

MDPI

Article

Metoprolol Dose Equivalence in Adult Men and Women Based on Gender Differences: Pharmacokinetic Modeling and Simulations

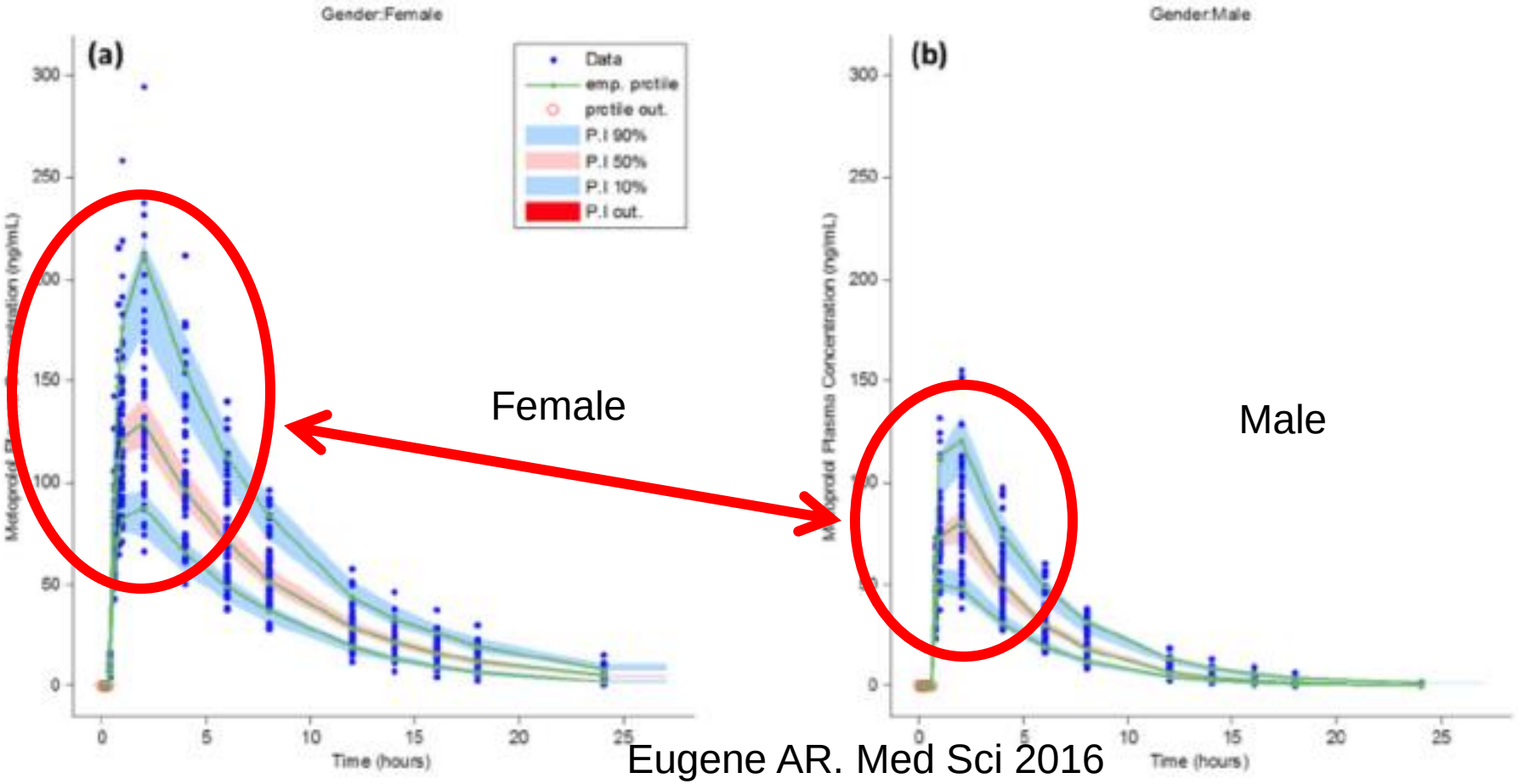
Andy R. Eugene

Division of Clinical Pharmacology, Department of Molecular Pharmacology and Experimental Therapeutics, Gonda 19, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; eugene.andy@mayo.edu; Tel.: +1-507-284-2790

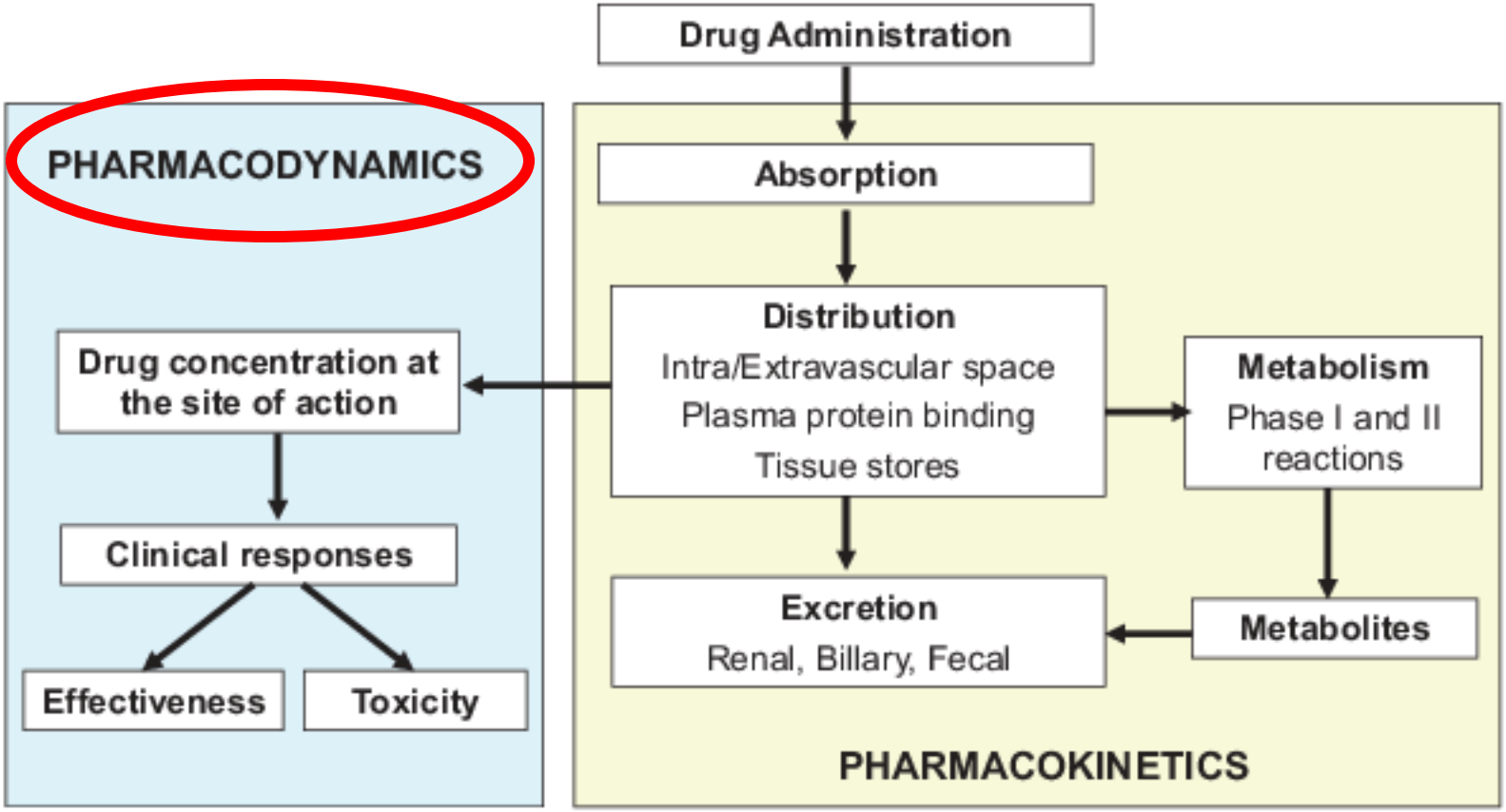
Eugene AR. Med Sci 2016

Table 1. One-compartment pharmacokinetic parameters for *R*- and *S*-metoprolol for young men and women.

	S-Metoprolol		*R*-Metoprolol	
	Female	Male	Female	Male
V (L): Volume of distribution	34.9	55.3	38.1	63.9
CL (L/h): Clearance Rate	101	253	120	316
Ka (h^{-1}): Absorption rate constant	0.161	0.241	0.165	0.234
Tlag (h): Absorption lag time	0.38	0.67	0.39	0.59



Eugene AR. Med Sci 2016



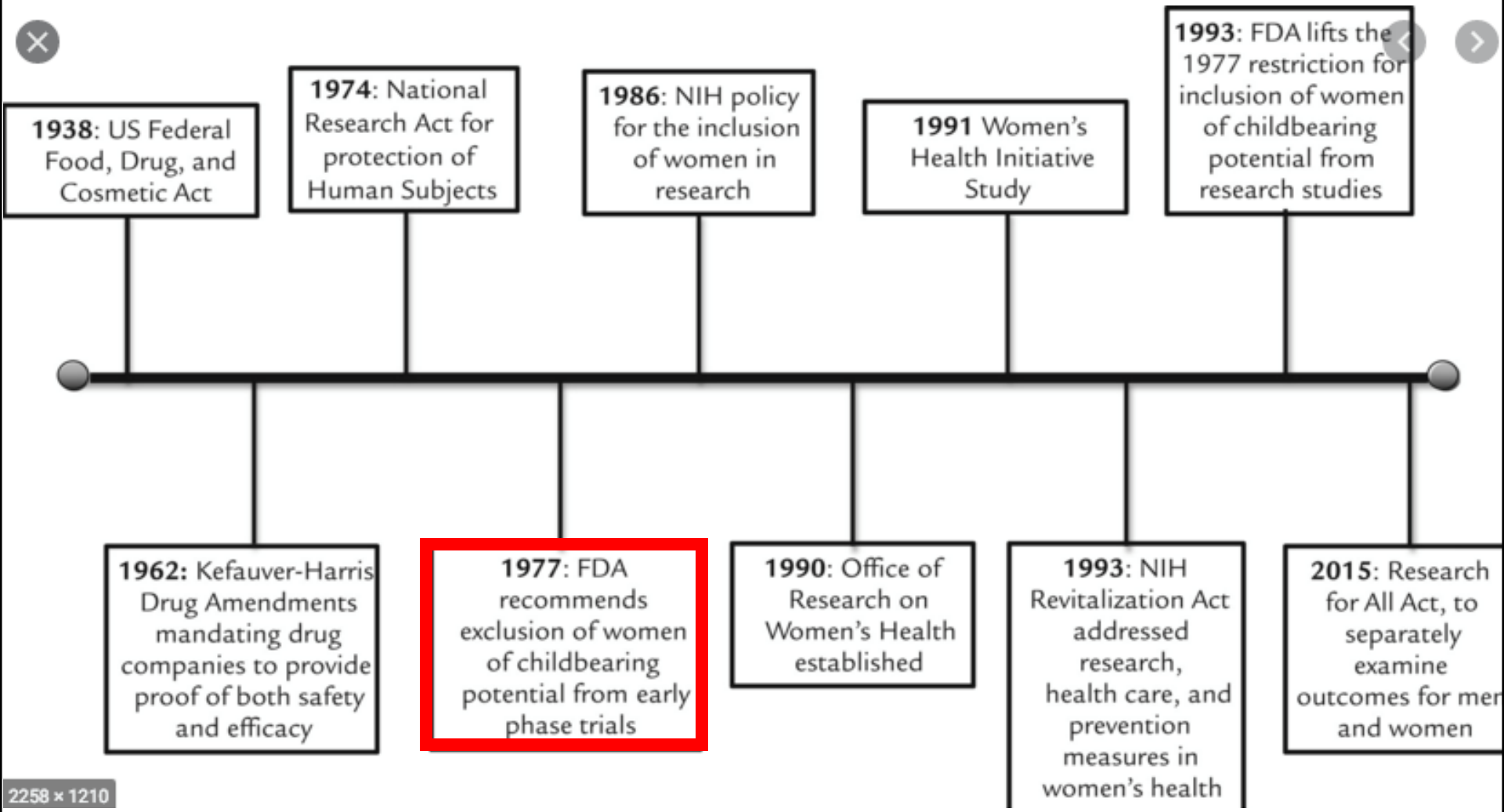
PD Differences less studied and difficult to quantify

Mainly retrospective analysis of clinical trials that have revealed gender differences

Gender differences un pharmacodynamics

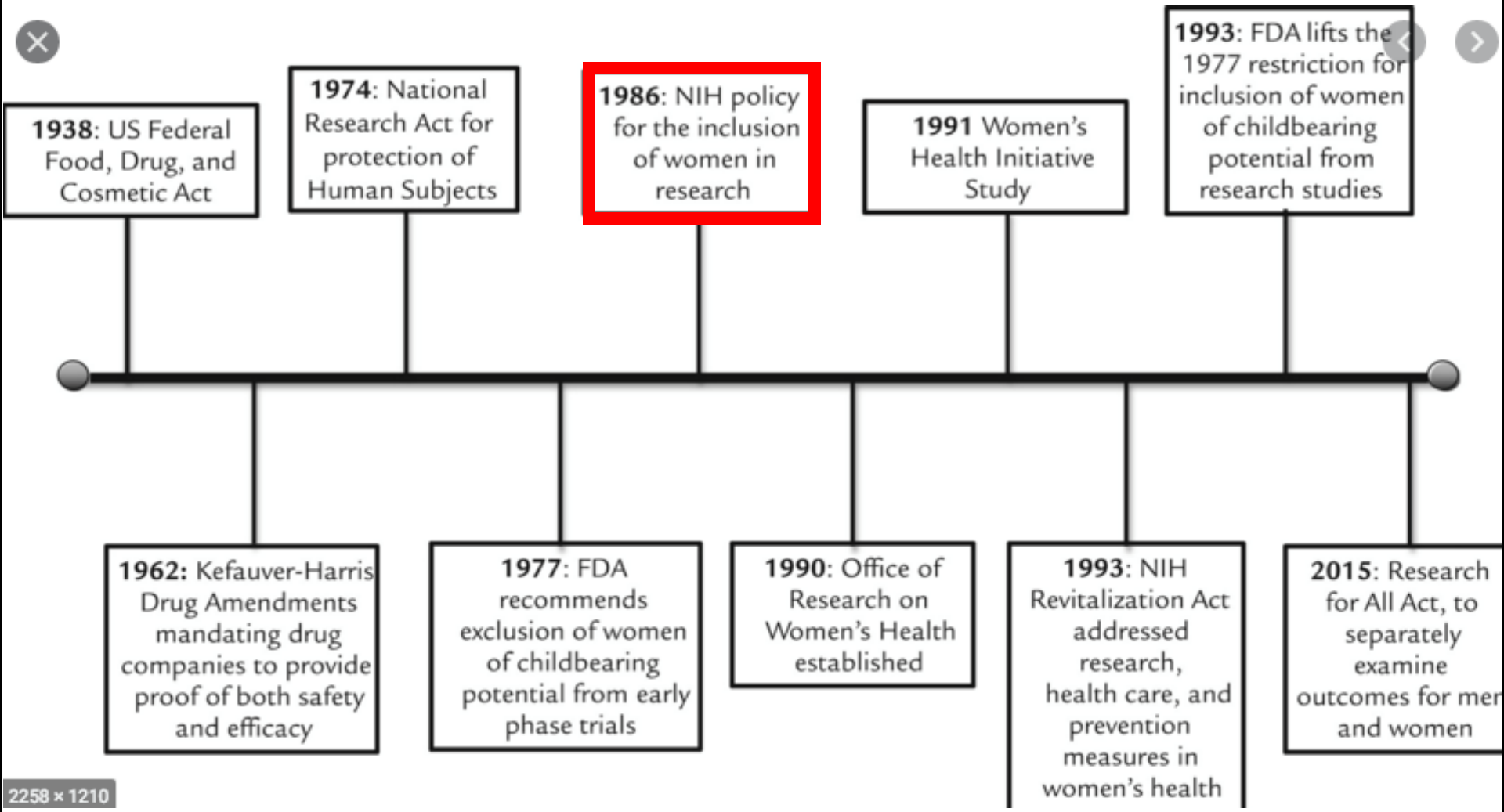
- Difficult to quantify as it is little studied
- Sex-based biology and medical research has not been a priority
- Pre-clinical research and drug development studies have predominantly used male animal models and cells
- Historically, women of child bearing had been excluded from trials

Recommendations and legislation of inclusion of women in clinical research



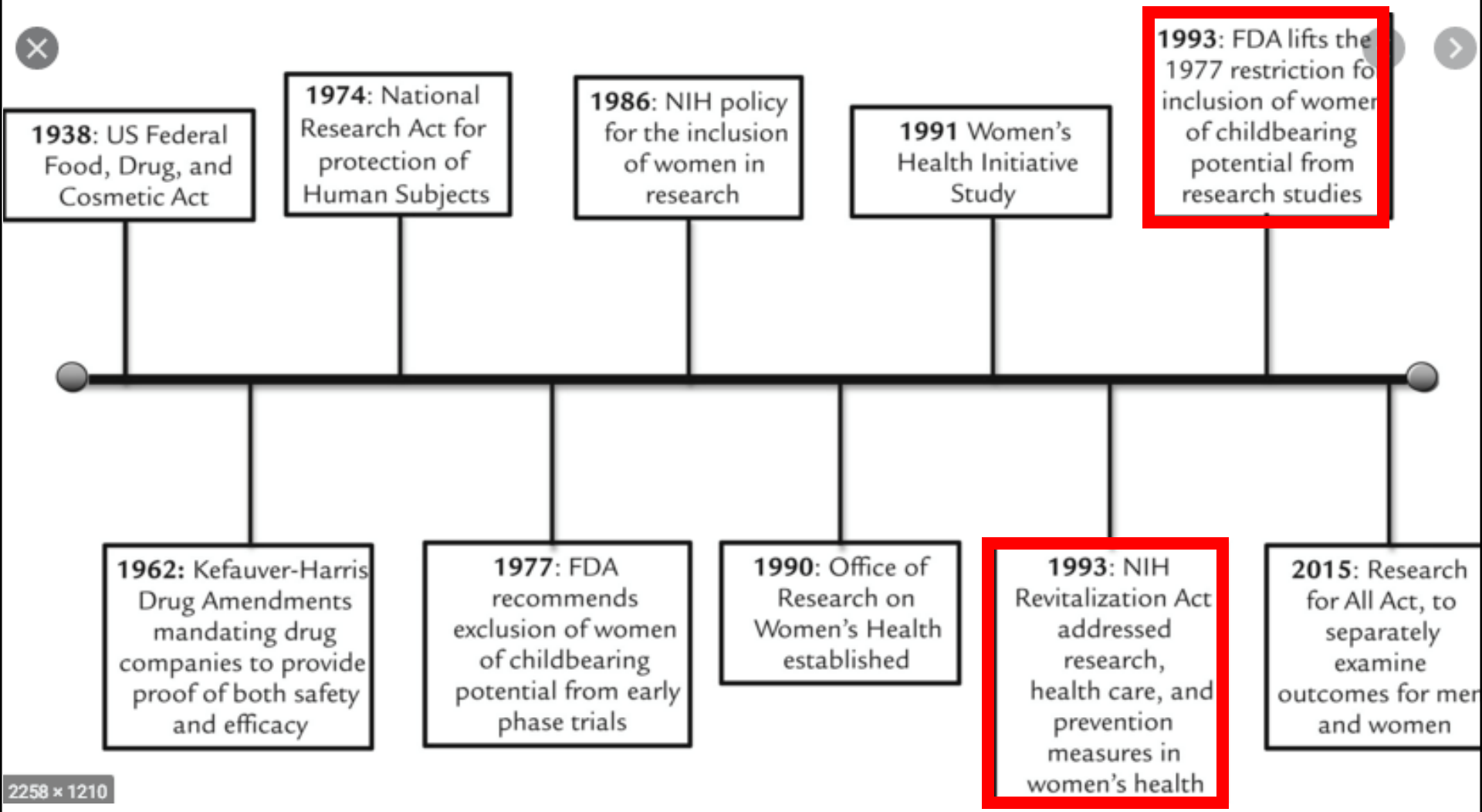
2258 × 1210

Recommendations and legislation of inclusion of women in clinical research



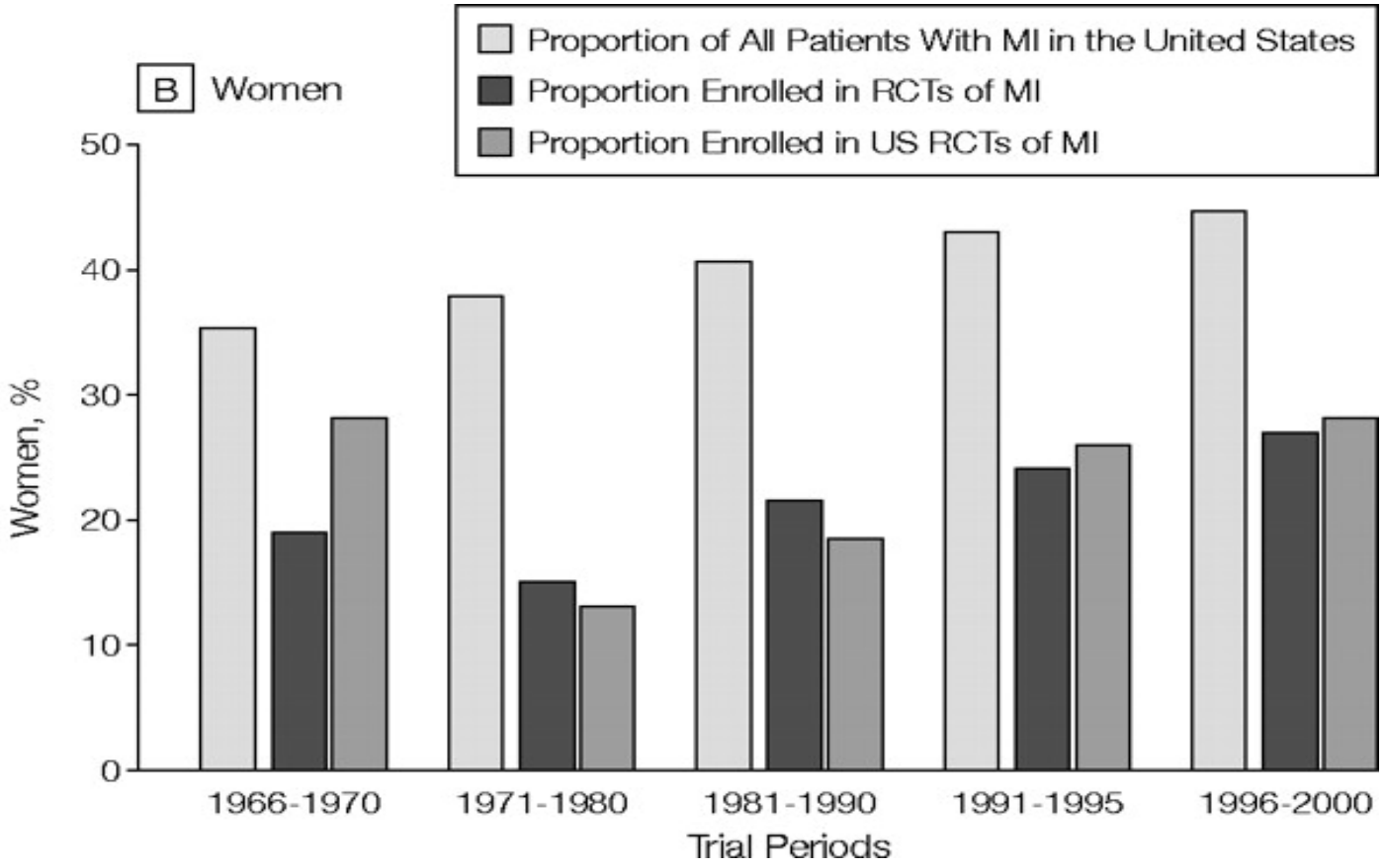
2258 × 1210

Recommendations and legislation of inclusion of women in clinical research



2258 × 1210

Under-representation of women in clinical trials



Lee et al. *JAMA*. 2001;286:708-713

Drug safety's Blind Spot: Gender Differences

US General Accounting Office 2001 Report..'
Most drugs withdrawn had greater health risks in Women'

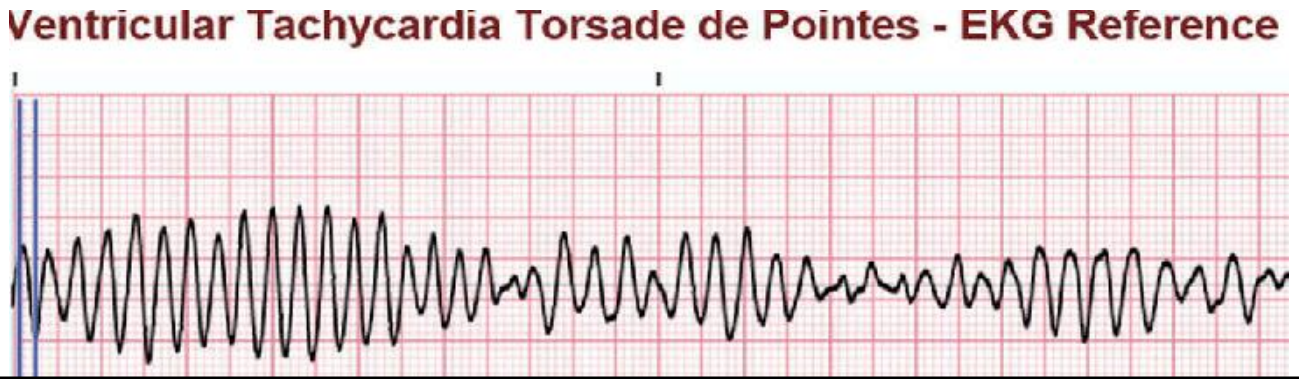
G.A.O. Report Finds Women Are Hurt by Withdrawn Drugs

By The Associated Press

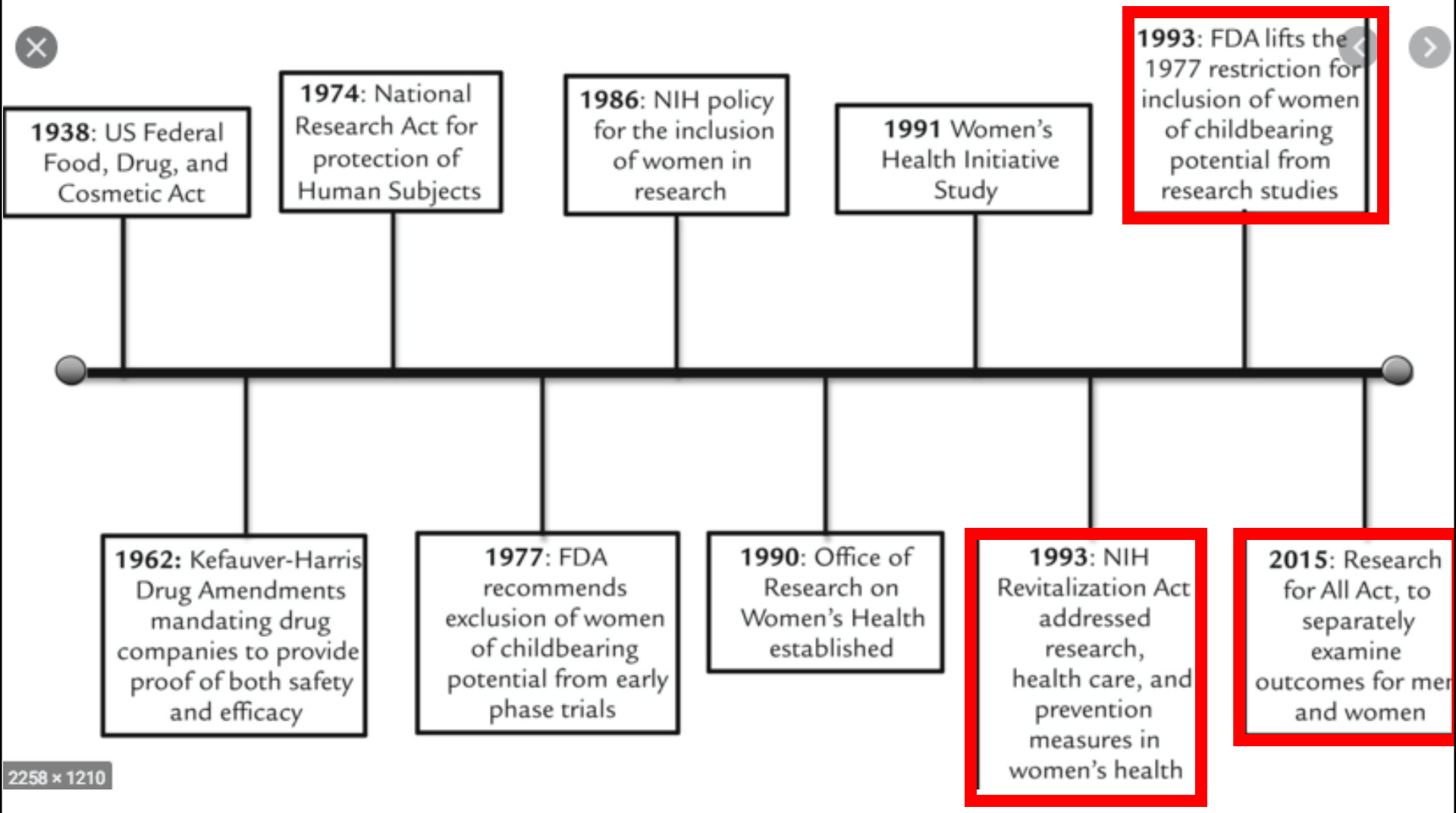
Feb. 9, 2001

Gender differences in Adverse drug reactions

- ADRs tends to more common and more severe (requiring hospitalizations) in women
- Causes
  - Greater use of drugs (polypharmacy)
  - Gender differences in pharmacokinetics
  - Risk of drug-induced torsade des despointes
    - Women have longer QTc and are an independent risk factor for TdP
    - Sex-related differences in drug-induced QT prolongation hormones



Recommendations and legislation of inclusion of women in clinical research



2258 × 1210

Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs

Pamela E. Scott, PhD, MA,[a] Ellis F. Unger, MD,[b] Marjorie R. Jenkins, MD, MEdHP,[a] Mary Ross Southworth, PharmD,[b] Tzu-Yun McDowell, PhD,[b] Ruth J. Geller, MHS,[a] Merina Elahi, BS,[a] Robert J. Temple, MD,[b] Janet Woodcock, MD[b]

ABSTRACT

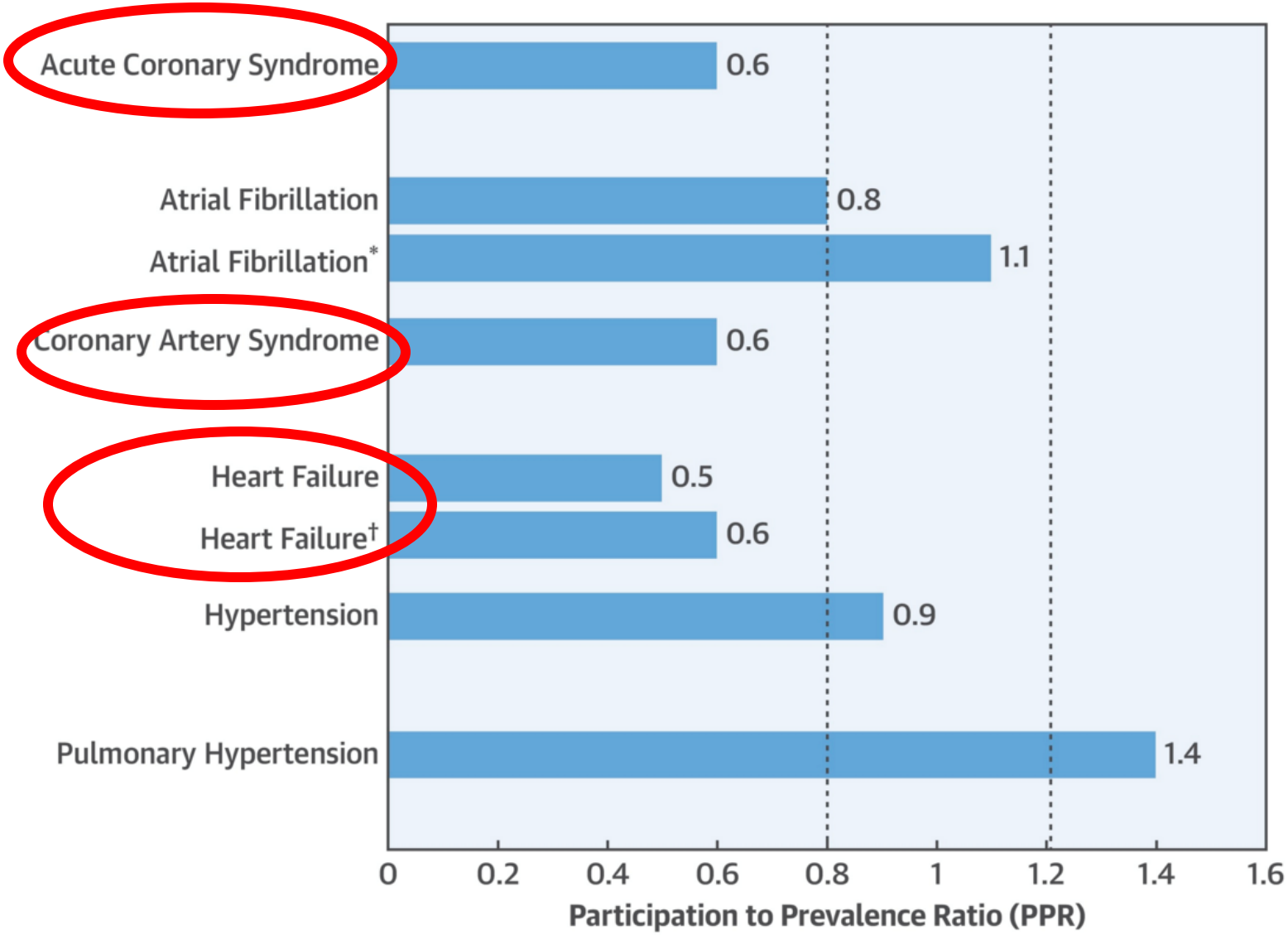
$$\text{PPR} = \frac{\text{Percentage of women among trial participants (\%)}}{\text{Percentage of women among disease population}}$$

PPR =1; gender composition approximates disease population

PPR <0.8, women under-represented

PPR > 1.2, women over-represented

CENTRAL ILLUSTRATION: Participation of Women of CVD Clinical Trial: Prevalence-Corrected Estimate



Scott, P.E. et al. J Am Coll Cardiol. 2018;71(18):1960-9.

Gender differences in common CV drugs

- Aspirin
- Digoxin
- Beta-blockers
- RAAS blockers
  - ARNIs

DIFFERENT RESPONSE TO ASPIRIN

Efficacy

Aspirin for the Primary Prevention of Cardiovascular Events in Women and Men

A Sex-Specific Meta-analysis of Randomized Controlled Trials

Jeffrey S. Berger, MD, MS
Marta C. Roncaglioni, MD
Fausto Avanzini, MD
Ilerta Pangrazzi, MD
Gianni Tognoni, MD
David L. Brown, MD

Context Aspirin therapy reduces the risk of cardiovascular disease in adults who are at increased risk. However, it is unclear if women derive the same benefit as men.

Objective To determine if the benefits and risks of aspirin treatment in the primary prevention of cardiovascular disease vary by sex.

Data Sources and Study Selection MEDLINE and the Cochrane Central Register of Controlled Trials databases (1966 to March 2005), bibliographies of retrieved trials, and reports presented at major scientific meetings. Eligible studies were prospective, randomized controlled trials of aspirin therapy in participants without cardiovascular disease that reported data on myocardial infarction (MI), stroke, and cardiovascular mortality. Six trials with a total of 95 456 individuals were identified; 3 trials included only men, 1 included only women, and 2 included both sexes.

Data Extraction Studies were reviewed to determine the number of patients randomized, mean duration of follow-up, and end points (a composite of cardiovascular events [nonfatal MI, nonfatal stroke, and cardiovascular mortality], each of these in-

Berger JS, et al. *JAMA*. 2006;295(3):306–313.

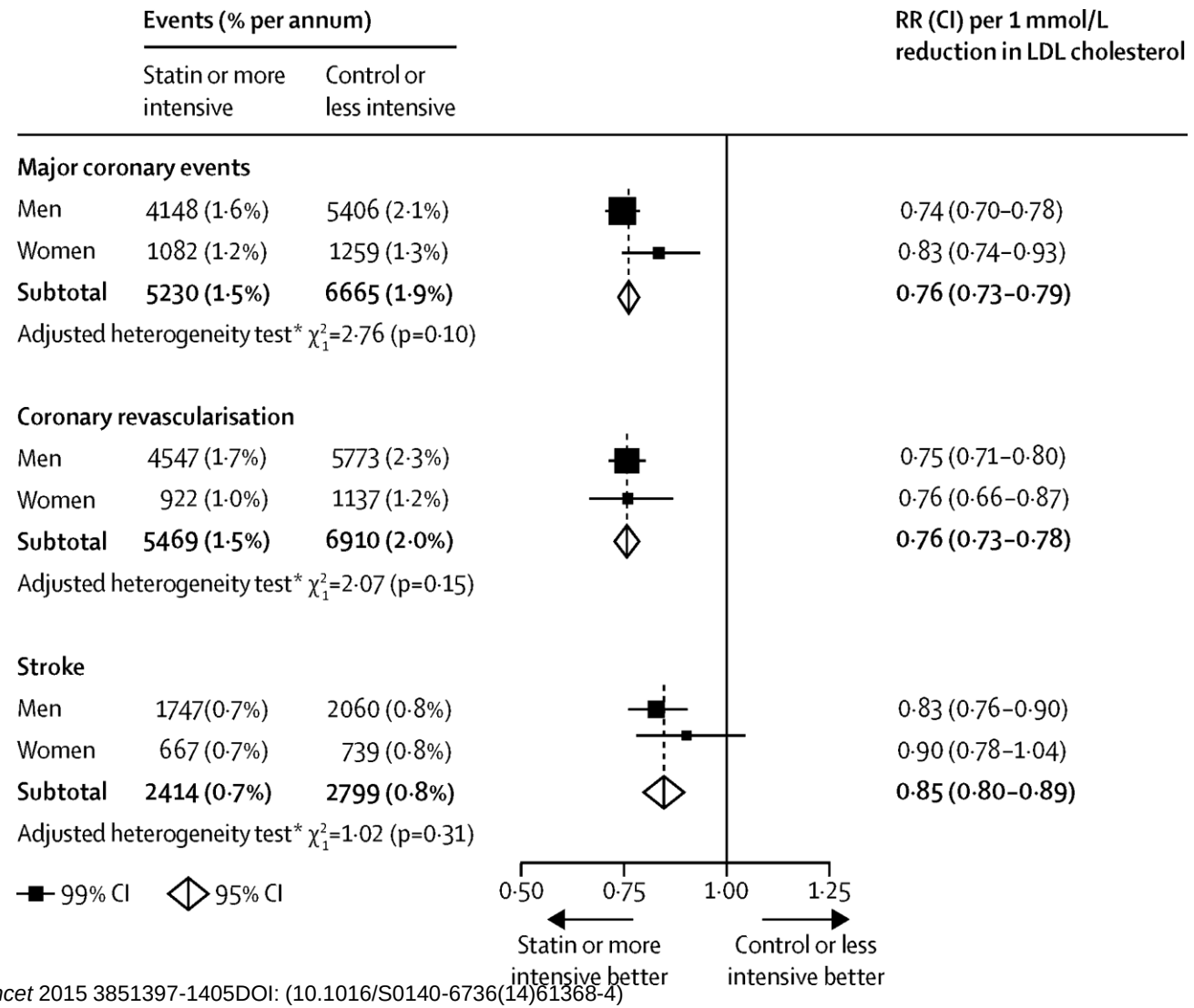
JS Berger et al *JAMA*. 2006;295:306-313

	MEN	WOMEN
Ischemic Stroke		↓
MI	↓	
Bleeding	↑	↑

Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaboration*

In secondary prevention trials, statins reduce risk of CV events similarly in men and women

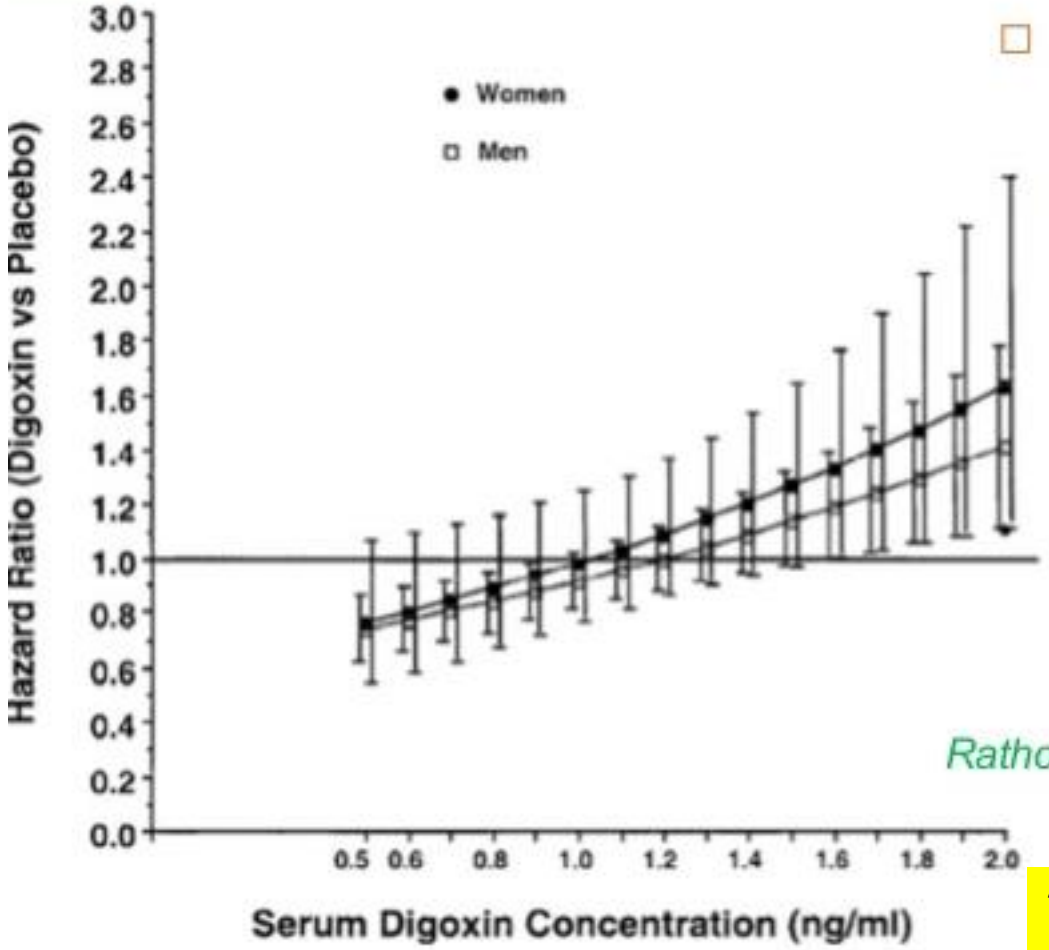


CTT et al. Lancet 2015 3851397-1405DOI: (10.1016/S0140-6736(14)61368-4)

Women have more statin associated ADRs

- Possible explanations
  - Lower metabolism
  - lower BMI
  - Lower plasma volume
  - reduced muscle mass

DIG Post-hoc: Sex Differences



- adjusted HR for death of
  - 1.23 for women vs pbo
  - 0.93 for men vs pbo

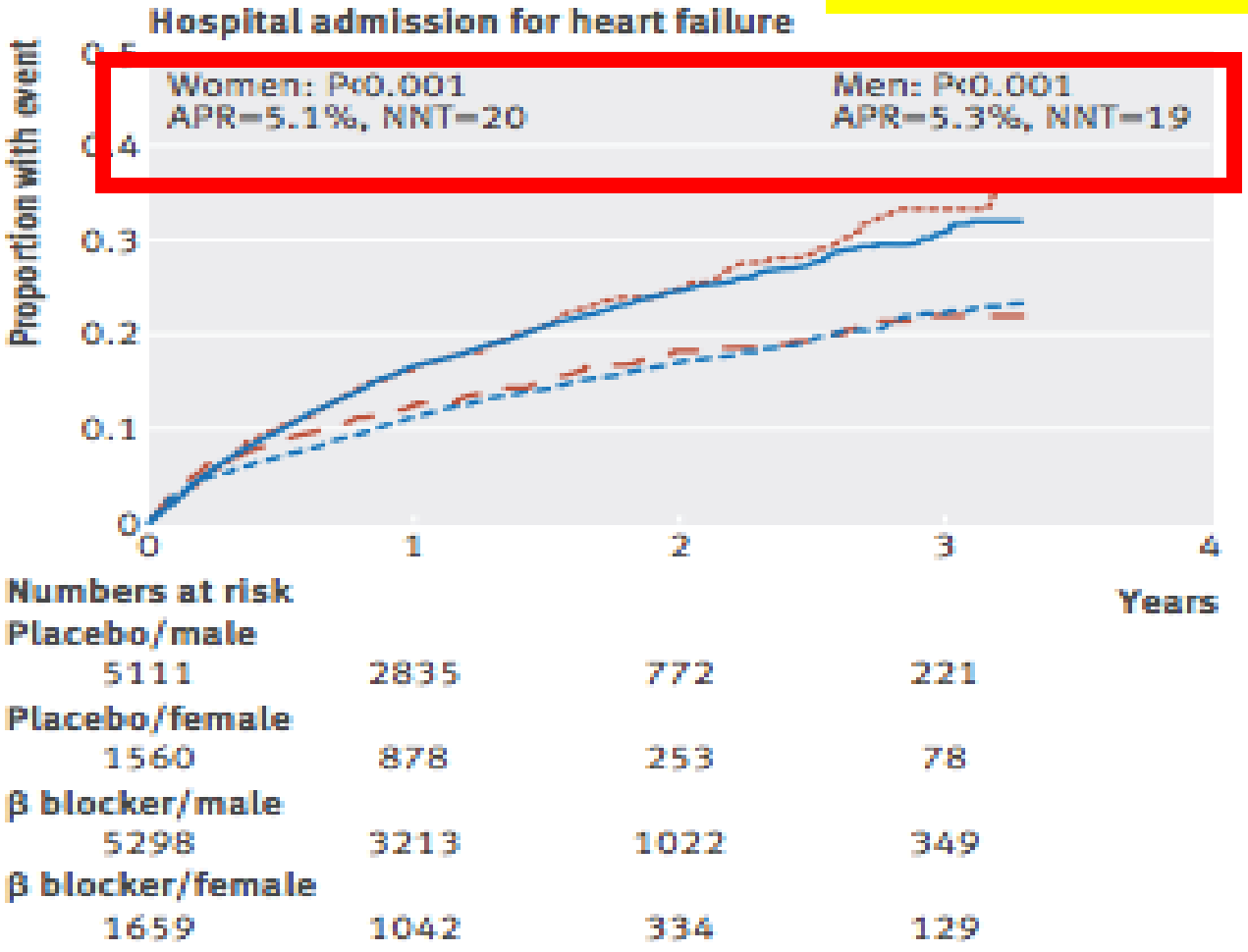
Rathore S et al., New Engl J Med 2002

? Supra-therapeutic plasma levels due
- Reduced Vd
- Slower renal clearance

Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis

Dipak Kotecha,[1,2] Luis Manzano,[3] Henry Krum,[2] Giuseppe Rosano,[4,5] Jane Holmes,[6]

No Gender Differences



Dipak Kotecha et al. BMJ 2016;353:bmj.i1855

Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients

Marcus D Flather, Salim Yusuf, Lars Køber, Marc Pfeffer, Alistair Hall, Gordon Murray, Christian Torp-Pedersen, Stephen Ball, Janice Pogue, Lemuel Moyé, Eugene Braunwald, for the ACE-Inhibitor Myocardial Infarction Collaborative Group

No Gender Differences

Subgroup	Number of patients	Deaths	Odds ratio (95% CI)	p	Death/CHF/MI	Odds ratio (95% CI)	p
Sex							
Men	10 367	2506	0·79 (0·72–0·87)	0·54	3759	0·71 (0·65–0·77)	0·34
Women	2396	671	0·85 (0·71–1·02)		1012	0·79 (0·67–0·93)	

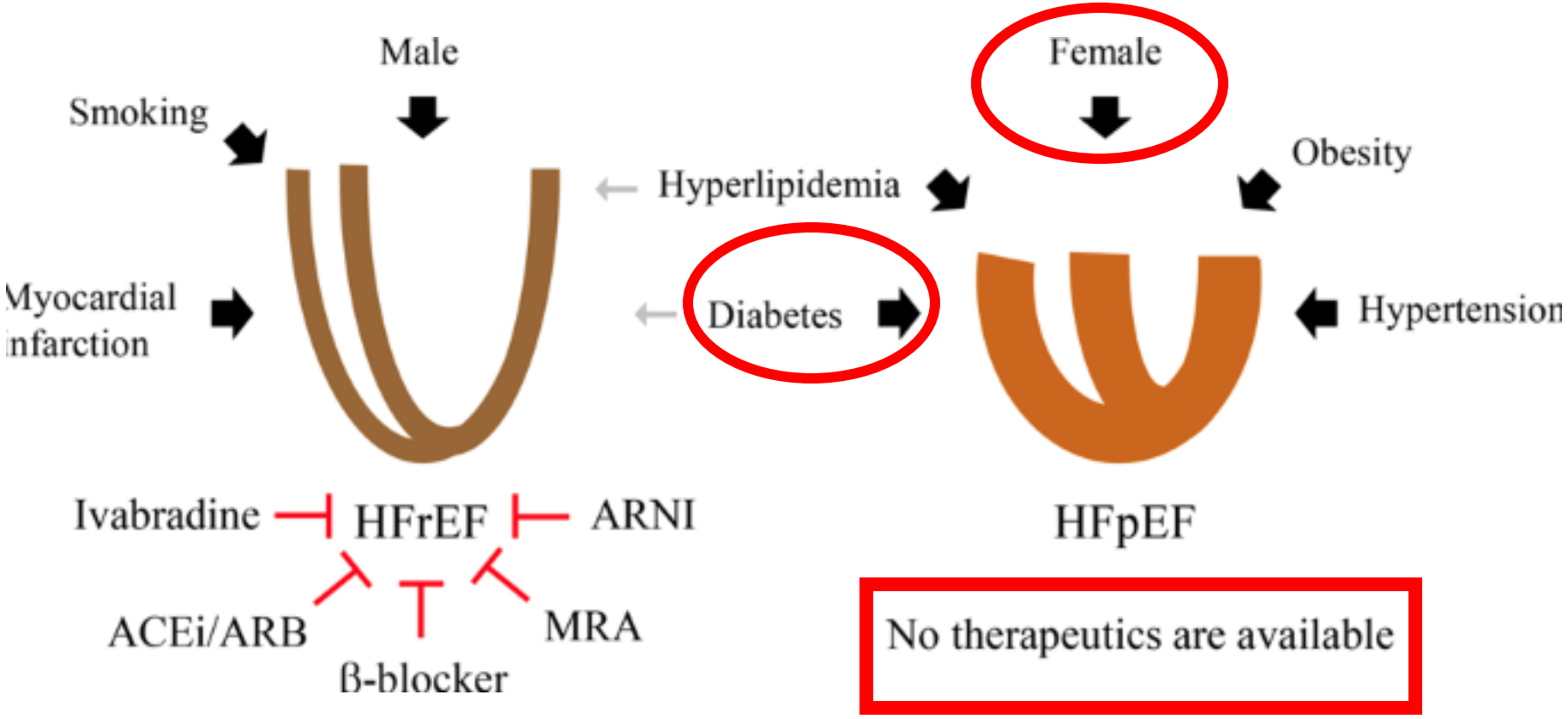
? Optimal dosing of ACEi and BBs

Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study

Bernadet T Santema, Wouter Ouwerkerk, Jasper Tromp, Iziah E Sama, Alice Ravera, Vera Regitz-Zagrosek, Hans Hillege, Nilesh J Samani, Faiez Zannad, Kenneth Dickstein, Chim C Lang, John G Cleland, Jozine M Ter Maaten, Marco Metra, Stefan D Anker, Pim van der Harst, Leong L Ng, Peter van der Meer, Dirk J van Veldhuisen, Sven Meyer, Carolyn S P Lam on behalf of the ASIAN-HF investigators, Adriaan A Voors*

The Lancet 2019 3941254 1263DOI: (10.1016/S0140-6736(19)31792-1)

HFreduced EF versus HFpreserved EF



PARAGONHF

Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction

Inclusion Criteria
- Age>50 years
- Symptomatic HF, NYHA class II-IV
- LVEF≥45%
- Elevated natriuretic peptides
- Structural heart disease on echocardiogram

n=4,822

Sequential Single-Blind Run-In Periods

Sacubitril/Valsartan at Target Dose

Valsartan at Target Dose

Median Follow-up 35 months

Primary Endpoint

- Modest 13% ↓ in CV Death or Total HF Hospitalizations
- Non-Significant P=0.058
- Driven by Effects on HF Hospitalization
- Consistent Sensitivity Analyses

Secondary Endpoints*

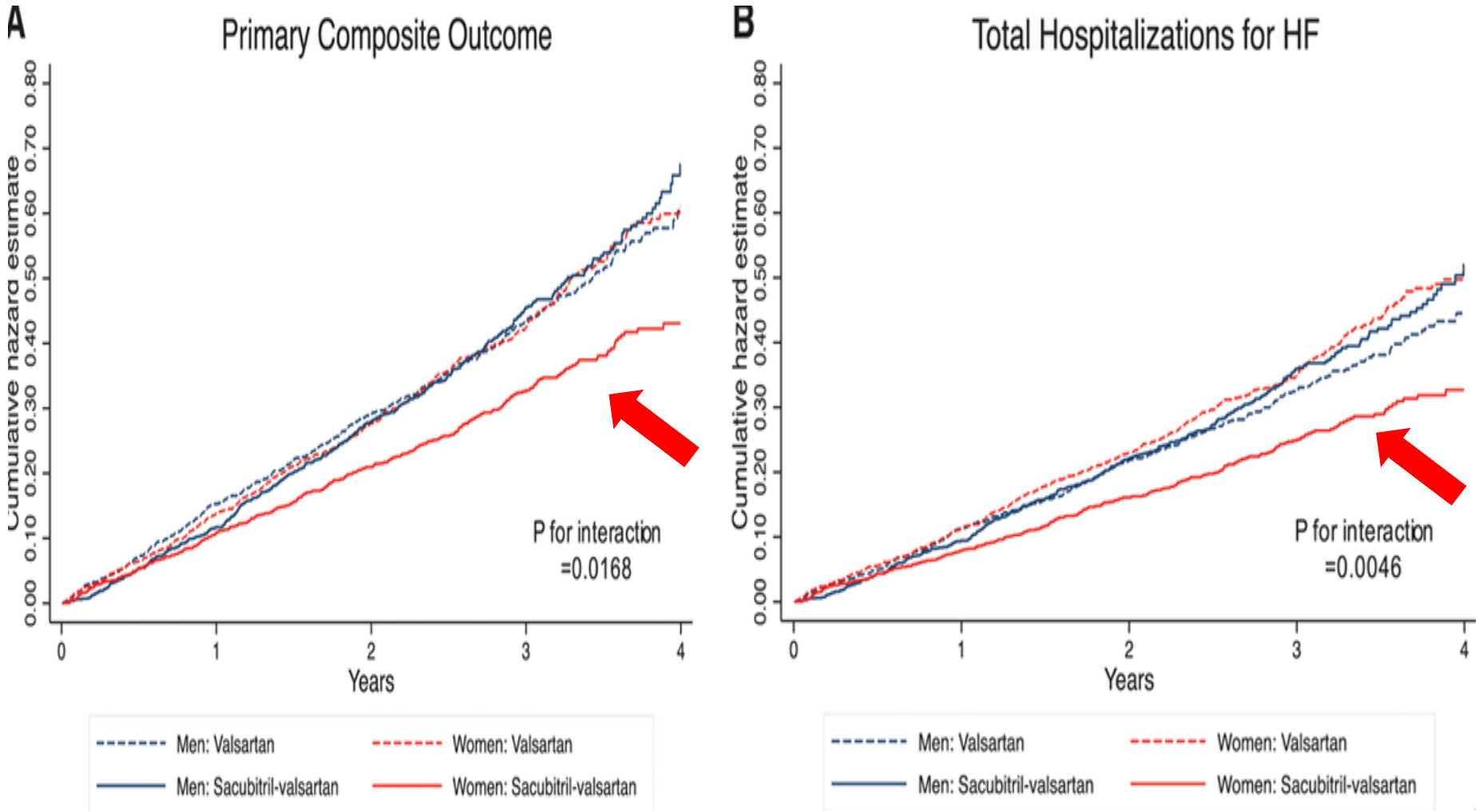
- Improved Health-Related Quality of Life
- Improved NYHA Class
- 50% ↓ Renal Events
- No Effect on Death

Potential Subgroups with Benefit

- Women
- Lower Range of LVEF

1421 × 1454

PARAGON HFpEF: Women versus Men pre-specified sub-group analysis



McMurray J et al. Circulation 2020

JACC: HEART FAILURE VOL. 7, NO. 3, 2019

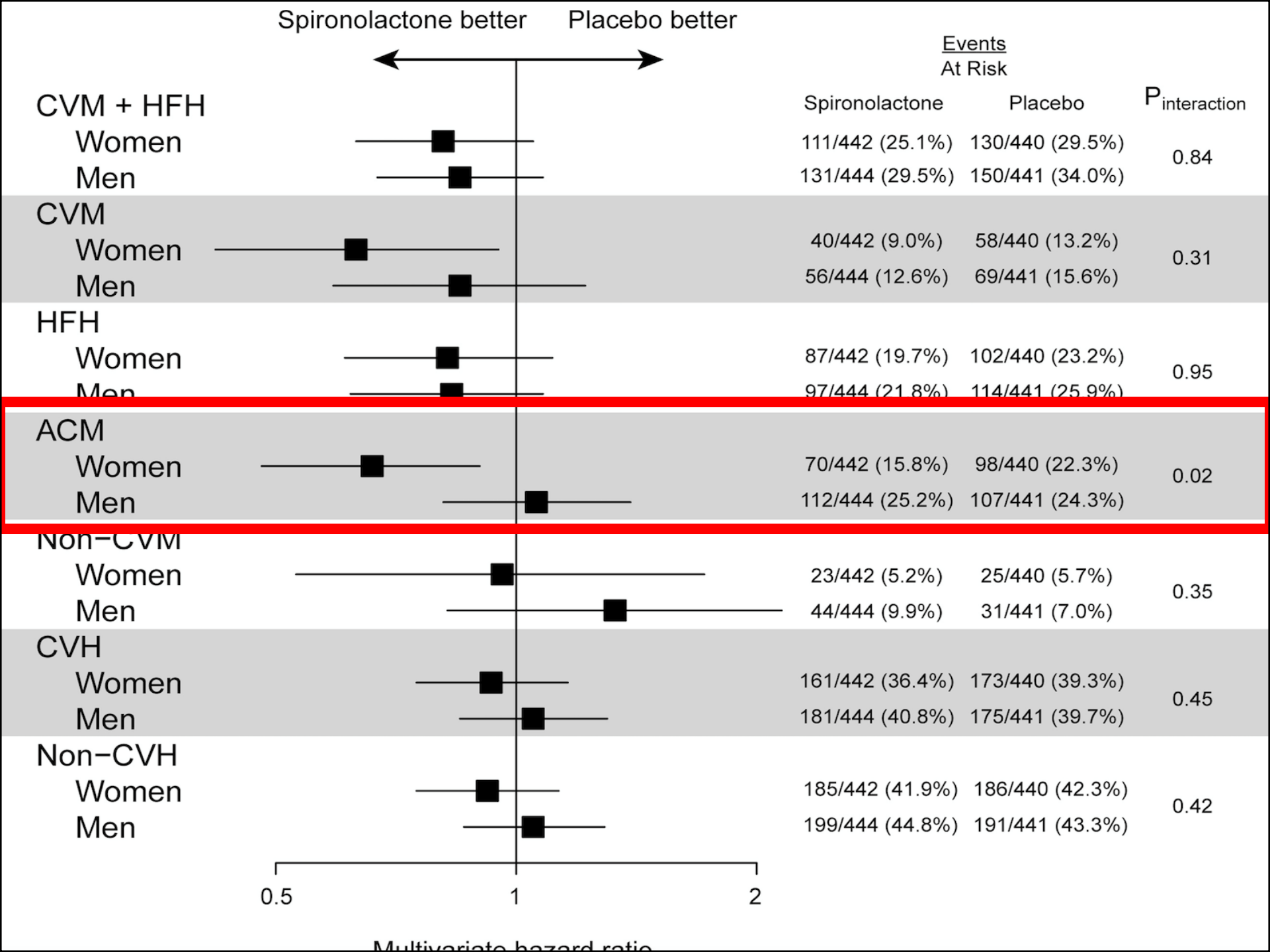
PUBLISHED BY ELSEVIER

Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction

A Secondary Analysis of TOPCAT Trial

Miranda Merrill, MD,[a] Nancy K. Sweitzer, MD,[b] JoAnn Lindenfeld, MD,[c] David P. Kao, MD[d]

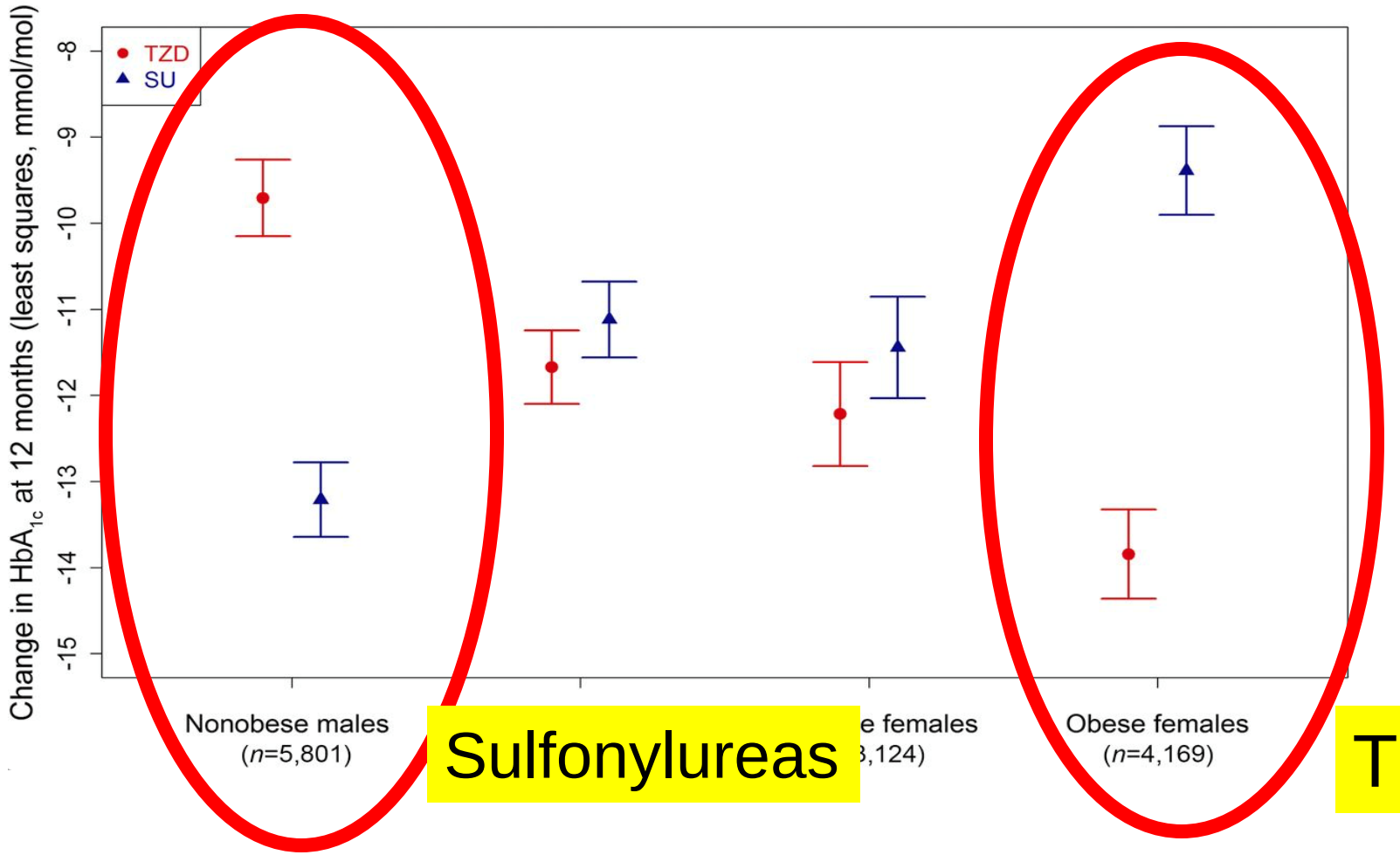
Exploratory, post-hoc and non-pre-specified


Spironolactone better
Placebo better
Events
At Risk
Spironolactone
Placebo
P interaction
CVM + HFH
Women
111/442 (25.1%)
130/440 (29.5%)
Men
131/444 (29.5%)
150/441 (34.0%)
0.84
CVM
Women
40/442 (9.0%)
58/440 (13.2%)
Men
56/444 (12.6%)
69/441 (15.6%)
0.31
HFH
Women
87/442 (19.7%)
102/440 (23.2%)
0.95
ACM
Women
70/442 (15.8%)
98/440 (22.3%)
Men
112/444 (25.2%)
107/441 (24.3%)
0.02
Non−CVM
Women
23/442 (5.2%)
25/440 (5.7%)
Men
44/444 (9.9%)
31/441 (7.0%)
0.35
CVH
Women
161/442 (36.4%)
173/440 (39.3%)
Men
181/444 (40.8%)
175/441 (39.7%)
0.45
Non−CVH
Women
185/442 (41.9%)
186/440 (42.3%)
Men
199/444 (44.8%)
191/441 (43.3%)
0.42
0.5
1
2
Multivariate hazard ratio

Sex and BMI Alter the Benefits and Risks of Sulfonylureas and Thiazolidinediones in Type 2 Diabetes: A Framework for Evaluating Stratification Using Routine Clinical and Individual Trial Data

John M. Dennis,[1] William E. Henley,[1] Michael N. Weedon,[2] Mike Lonergan,[3] Lauren R. Rodgers,[1] Angus G. Jones,[4,5] William T. Hamilton,[2] Naveed Sattar,[6] Salim Janmohamed,[7] Rury R. Holman,[8,9] Ewan R. Pearson,[3] Beverley M. Shields,[4] and Andrew T. Hattersley,[4,5] on behalf of the MASTERMIND Consortium*

Diabetes Care 2018;41:1844–1853 | https://doi.org/10.2337/dc18-0344

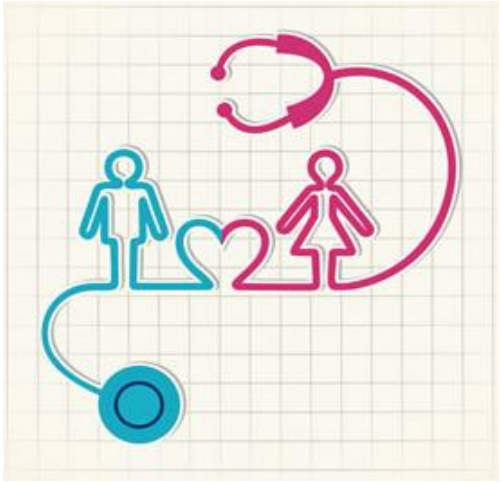


Striking sex and gender disparities in CVD

Epidemiology

Pathophysiology
- Risk factor profile

Clinical Manifestation
- Presentation
- Testing



Disease Progression and Outcome

Treatment
- Efficacy
- Side effects


we need
to do
more
THE
DOERS.

Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs

Pamela E. Scott, PhD, MA,[a] Ellis F. Unger, MD,[b] Marjorie R. Jenkins, MD, MEdHP,[a] Mary Ross Southworth, PharmD,[b] Tzu-Yun McDowell, PhD,[b] Ruth J. Geller, MHS,[a] Merina Elahi, BS,[a] Robert J. Temple, MD,[b] Janet Woodcock, MD[b]

ABSTRACT

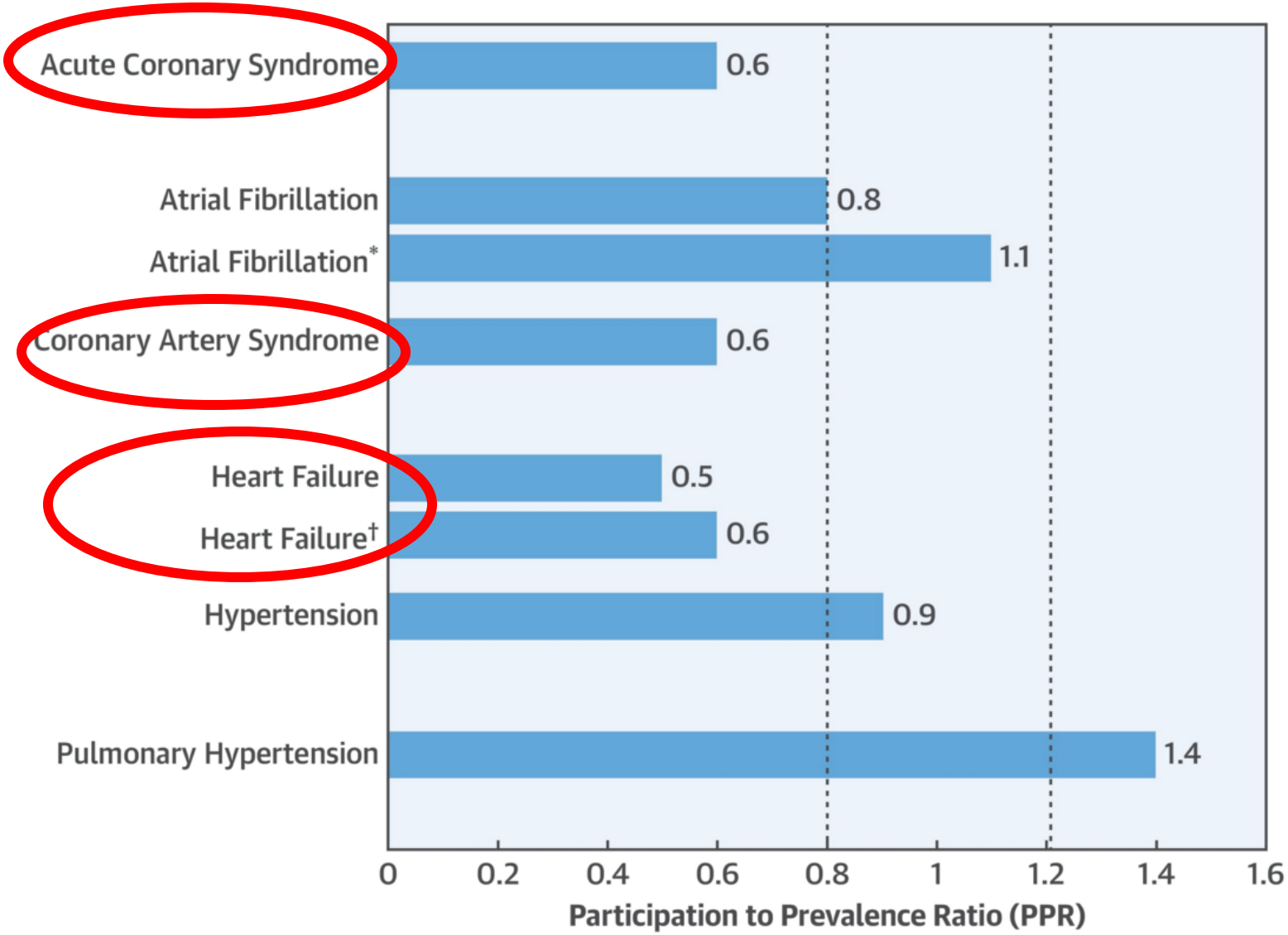
$$\text{PPR} = \frac{\text{Percentage of women among trial participants (\%)}}{\text{Percentage of women among disease population}}$$

PPR =1; gender composition approximates disease population

PPR <0.8, women under-represented

PPR > 1.2, women over-represented

CENTRAL ILLUSTRATION: Participation of Women of CVD Clinical Trial: Prevalence-Corrected Estimate



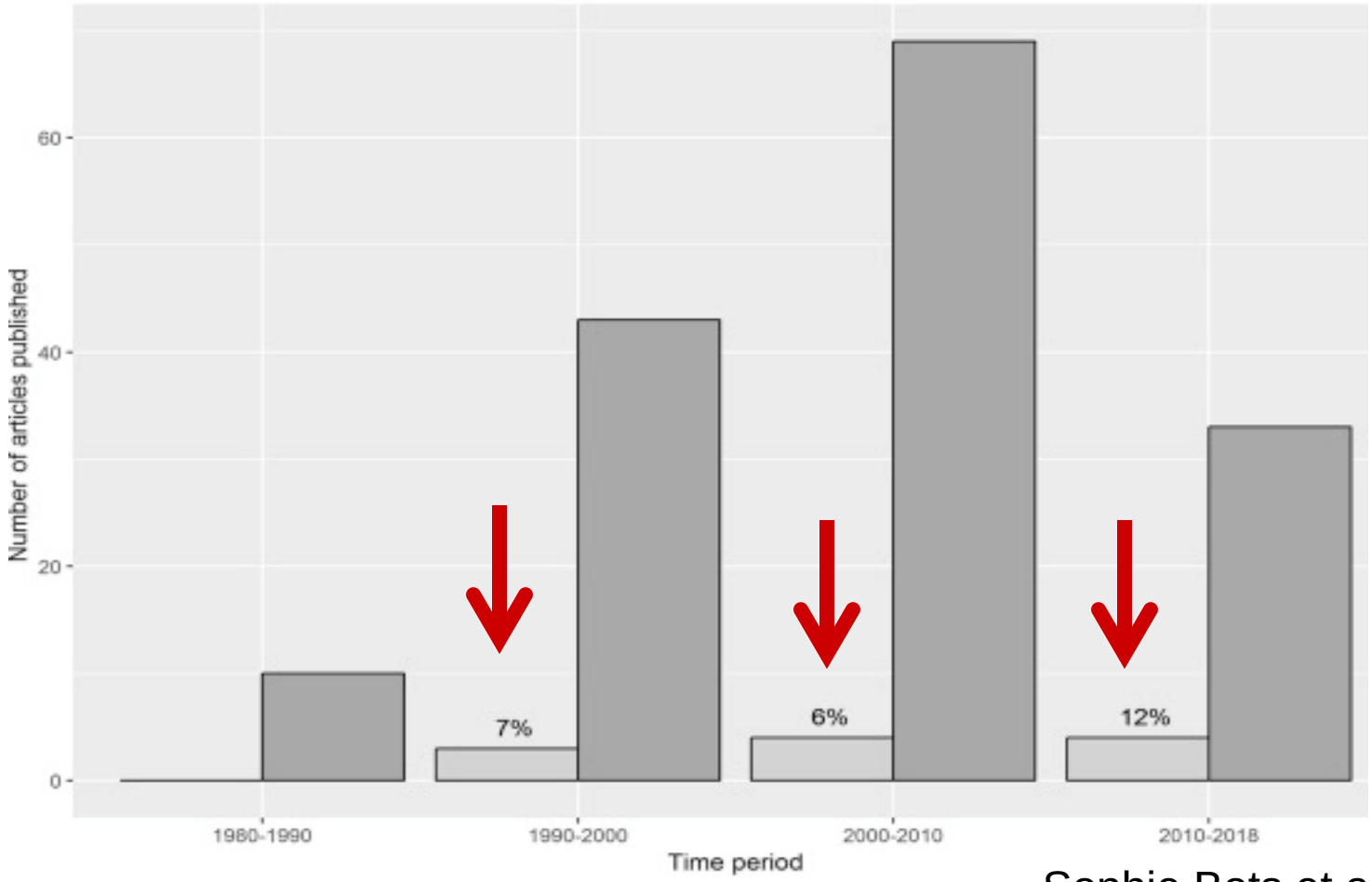
Scott, P.E. et al. J Am Coll Cardiol. 2018;71(18):1960-9.

Adverse Drug Reactions to Guideline-Recommended Heart Failure Drugs in Women

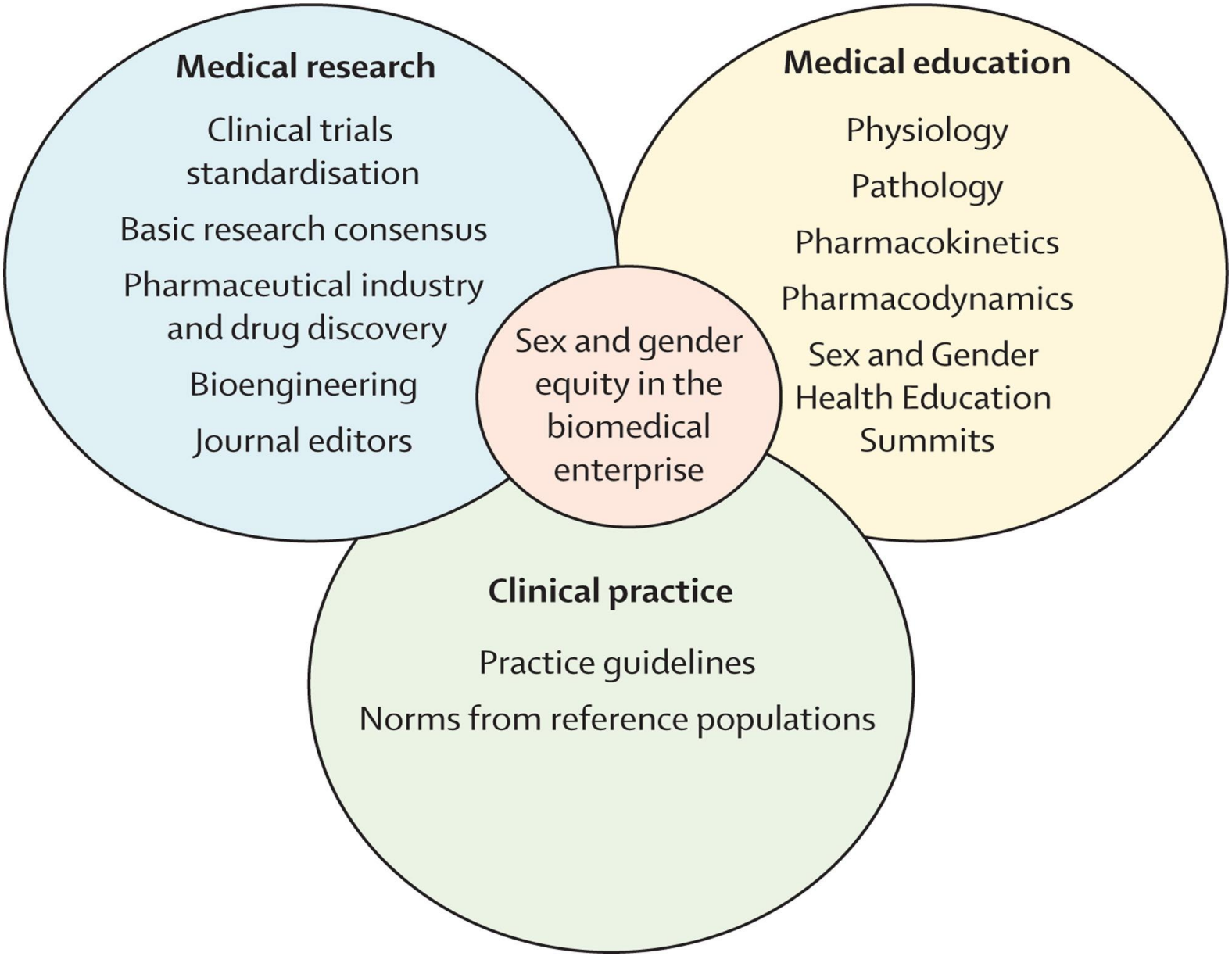
A Systematic Review of the Literature

Sophie H. Bots, MSc,[a] Floor Groepenhoff, MD,[b] Anouk L.M. Eikendal, MD, PhD,[a] Cara Tannenbaum, MD, MSc,[c] Paula A. Rochon, MD, MPH,[d,e] Vera Regitz-Zagrosek, PhD,[f,g] Virginia M. Miller, PhD,[h] Danielle Day, PhD,[i] Folkert W. Asselbergs, MD, PhD,[j,k,l] Hester M. den Ruijter, PhD[a]

Persistent Lack of sex-specific ADR data



Sophie Bots et al JACC HF 2019



Mauvais-Jarvis F et al. Lancet 2020

More work to be done

- Medical Education
  - Sex and Gender Health Education Summit [Chin et al 2016]
- Research
  - Inclusion in International guidelines
    - International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human use
  - All phases of drug development
    - Discovery phase/ Pre-clinical
    - Proof principle studies: Block randomisation by gender
    - If warranted, then to inform Phase 3 trials that adequately powered studies to address sex-specific endpoints
- Clinical Practice
  - Sex-based clinical practice recommendations

Thank you


British Heart
Foundation


SEVENTH FRAMEWORK
PROGRAMME


HORIZON 2020


TENOVUS SCOTLAND


100 YEARS OF CARING
CHEST, HEART
& STROKE
SCOTLAND


NHS
Tayside


UNIVERSITY OF
DUNDEE


EFSD
European Foundation for the Study of Diabetes


MRC
Medical
Research
Council


esros
EXTERNALLY SPONSORED
SCIENTIFIC RESEARCH
OPERATIONS SYSTEM