Women & Atrial Fibrillation

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SCRIPPS CLINIC
3.27.2021

Faculty Disclosure

Commercial Interest	Nature of Relevant Financial Relationship	
	What Was Received	For What Role
• None	• N/A	• N/A

Historical Perspective…why we need more conferences emphasizing women

- 1950s: Heart disease linked to diet, exercise, and physical factors rather than psychological causes (anger, ambition)
- 1982 Multiple Risk Factor Intervention Trial: 12,866 men, 0 women
- 1995 Physician's Health Study: 22,071 men, 0 women
- 1999 NEJM physicians survey: women less likely to recommend cardiac catheterization, bypass, balloon valvuloplasty
- 2021: women are less likely to be referred for afib ablation….
  - YET THEY ARE MORE SYMPTOMATIC…

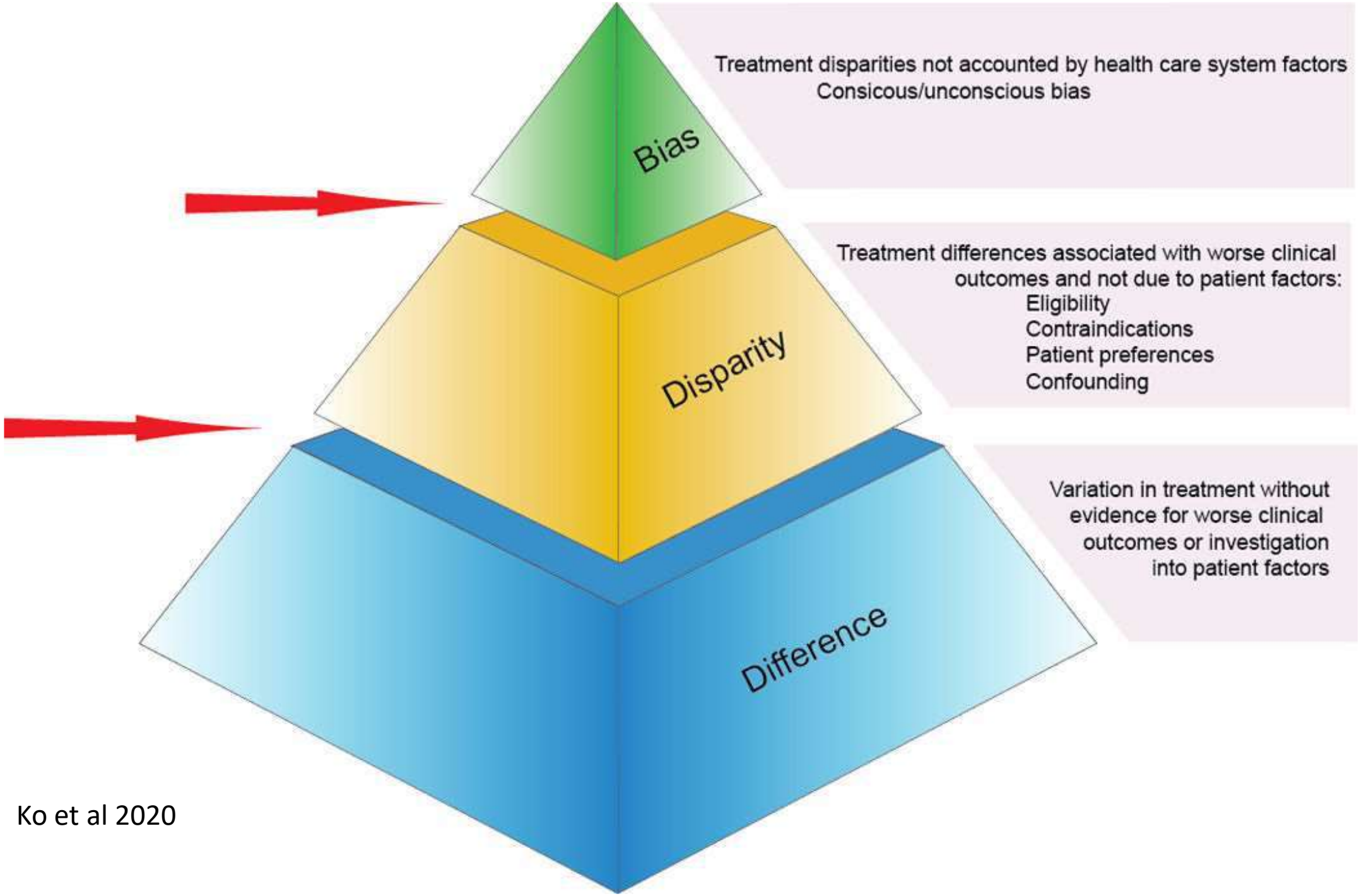
Historical Reference

- American Heart Association: first evidence-based guidelines for CVD prevention in women in **1999**
  - Ongoing perceived lower risk in women by MDs
- NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research **2001**
- Women constitute, on average, 20% of population of RCTs; few trials having women as a pre-specified subgroup
- **2012** Effective-based guidelines for prevention of women and heart disease is released by AHA and ESC

- **Sex-specific reporting of cardiovascular clinical trial results is limited, rarely pre-specified, precludes rigorous statistical analysis of sex differences**

Gender disparities in health care

- Women historically account for only 20-30% of research subjects in cardiac RTC
- Increasing awareness in the multitude of sex-specific differences
- **Gender differences in arrhythmias has received less attention than CAD**
- Sex differences in cardiac electrophysiology effects epidemiology, management, and prognosis
- Women typically have a later onset of CVD, Afib than men, increasing potential risks, comorbidities, and prognostic outcomes
- Complex reasons: Sex differences in treatment strategy: patient preferences or treatment bias?


Bias
Treatment disparities not accounted by health care system factors
Consicous/unconscious bias
Disparity
Treatment differences associated with worse clinical outcomes and not due to patient factors:
Eligibility
Contraindications
Patient preferences
Confounding
Difference
Variation in treatment without evidence for worse clinical outcomes or investigation into patient factors

Ko et al 2020

Sex Differences in Basic Electrophysiology

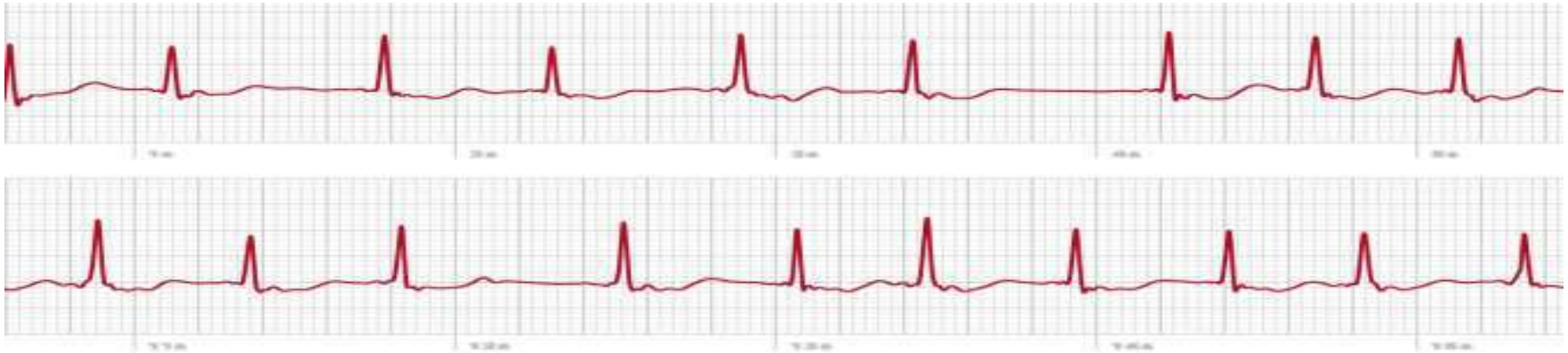
Parameter	Females vs Males
Basal heart rate	Higher
SNRT	Shorter
AERP	Shorter
AH interval	Shorter
AVN ERP	Shorter
HV interval	Shorter
QRS duration	Shorter
QTc	Longer
VERP	Longer
Ventricular APD	Longer
I_{Kr}	Decreased
I_{Ks}	Decreased
I_{K1}	Decreased
I_{to}	Decreased

AERP indicates atrial effective refractory period; APD, action potential duration; AVN, atrial ventricular node; I_{Kr}, rapid delayed rectifies K^+ current; I_{Ks}, slow delayed rectifier K^+ current; I_{K1}, inward rectifier current; I_{to}, transient outward current; QTc, rate corrected QT interval; SNRT, sinus note recovery time; and VERP, ventricular effective refractory period.

Gillis, Circulation 2017

Importance of Atrial Fibrillation

- Most common type of sustained arrhythmia
- Associated with increased morbidity, mortality, hospital admission: health care expenditure
- Accounts for approximately 20% of all strokes*
- Prevalence and incidence has been increasing



Afib & Women: EPIDEMIOLOGY

- ARIC DATA: age related incidence, race differences exist
- MEDICARE DATA, Framingham Data
- Older AF patients tend to be female
- Incidence and prevalence of AF is lower in women than men; however, because AF incidence increases with age **the absolute number of women with AF exceeds men**
- Framingham Heart Study: cumulative lifetime risk 1:4 after 40 years
- **Women have worse, atypical symptoms, higher risk for adverse events (stoke and death)**

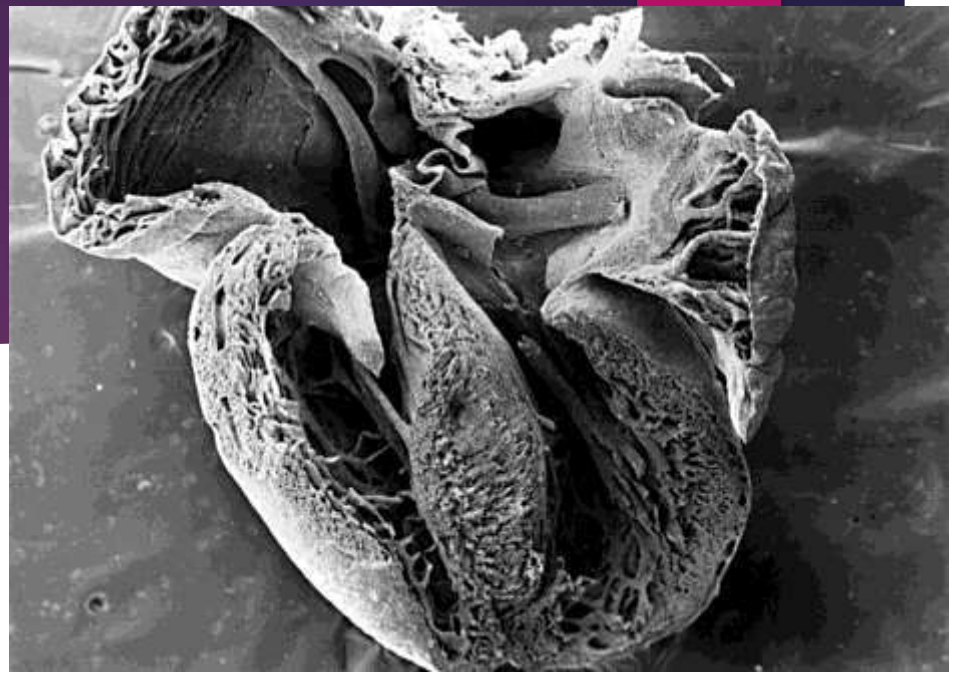
Afib & Women: RISKS

- Hypertension
- Obesity
- Age
- Genetics
- Sedentary behavior
- High ETOH intake
- Sleep Apnea
- Thyroid issues

"I'm seeing an EPIC Order Set in my future."

SAME RISK FACTORS FOR MEN AND WOMEN WITH SOME SLIGHT VARIANCY

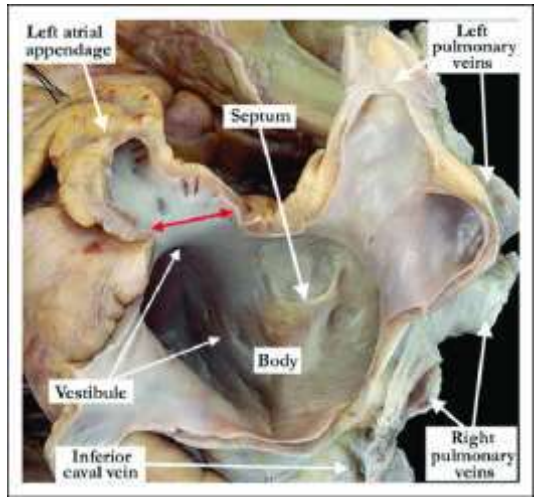
Afib & Women: RISKS



- Increased age at diagnosis
- Incidence increases after menopause
- Higher prevalence of **hypertension**
- Higher prevalence of **HFpEF**
- Higher risk of associated **valvular heart disease**
- Men develop post-op afib at higher rates after CABG
- Increase risk of afib with **increasing parity**
  - Increased exposure to physiological and hormonal stresses of pregnancy on LA
  - During pregnancy however afib prevalence is low 0.05%, usu valve disease, PPCM
- Unclear if GD and preeclampsia are associated with increased risk
- **Hypertension during pregnancy** increases lifetime risk

Sex Differences in Afib Predisposition

- **Women**
  - Heart failure, particularly HFpEF
  - Hypertension and LVH
  - Valvular Heart Disease
  - High BMI/metabolic dz/epicardial fat
  - High ETOH intake



- **Men**
  - Coronary heart disease, post of CABG
  - Vigorous exercise
  - High BMI, epicardial fat
  - Detrimental testosterone effects on CAD, Framingham data
  - Pro-arrhythmic effects shorter APD facilitating re-entry on afib
  - More pronounced fibrotic remodeling (animal model)
  - Moderate and high ETOH intake

What about types of afib: is there a gender difference?

- Idiopathic atrial fibrillation: **controversial** data on sex differences
- Genetic atrial fibrillation
  - Early onset, no data on sex-specific differences, X-linked variant KCNE5 gene, EMD deletion
- Exercise Associated Atrial Fibrillation: **definite** sex differences
  - More marked concentric ventricular and atrial remodeling
  - Vagal tone triggers vs sympathetic tone triggers
- Autonomic Atrial Fibrillation
  - Increased incidence in rest, sleep, postprandial states
- **Co-Morbidity Associated Afib: the usual risk factors" HTN, age, BMI, ETOH**
  - **Women are older at time of diagnosis**
  - **BMI is strongest predictor of afib, MEN>WOMEN**
- Hormonally related afib: peripartum and post-partum

Comorbid Afib: sex differences

Women with **heart failure** have a 14-fold increased risk (men 8.5)

AF is an independent risk factor for **new onset HFpEF** in women but not in men

- More HFpEF , more afib
- Estrogen deficiency increases diastolic dysfunction; treatment may improve DD

Higher prevalence of valvular heart disease and AF in women

Higher prevalence of hypertension in women and AF

Lower prevalence of CAD in women compared to men with afib

Microvascular disease: high in women: increased prevalence of afib, improvement with ranolazine?

Exercise associated Atrial fibrillation

- **Moderate and vigorous exercises LOWERS risk in women**
  - **Intense exercise is able to reduce afib risk >30%**
- Vigorous exercise in men is associated with increased risk: U shaped model
  - Atrial remodeling appears to be less marked in female athletes than male athletes
  - Men have more marked ventricular remodeling, higher SBP during exercise, higher sympathetic tone
  - **Athletes** have more PAF during high vagal tone situations: rest, sleep, postprandial than non athletes
  - Excessive endurance sports>1500h sports/year increases risk 3x in men
  - Higher recurrence rates after PVI

Mechanisms of sex differences in afib

Mechanisms of Afib: sex differences

Hormones

Differences in Atrial anatomy, structure and function

- In normal women, smaller atrial volumes and lower stroke volumes

Hormone function on atrial function and remodeling

- Women may have increased fibrotic remodeling
- Which leads to greater deterioration in LAA function

Gender differences in cardiac autonomic /neurohormonal modulation

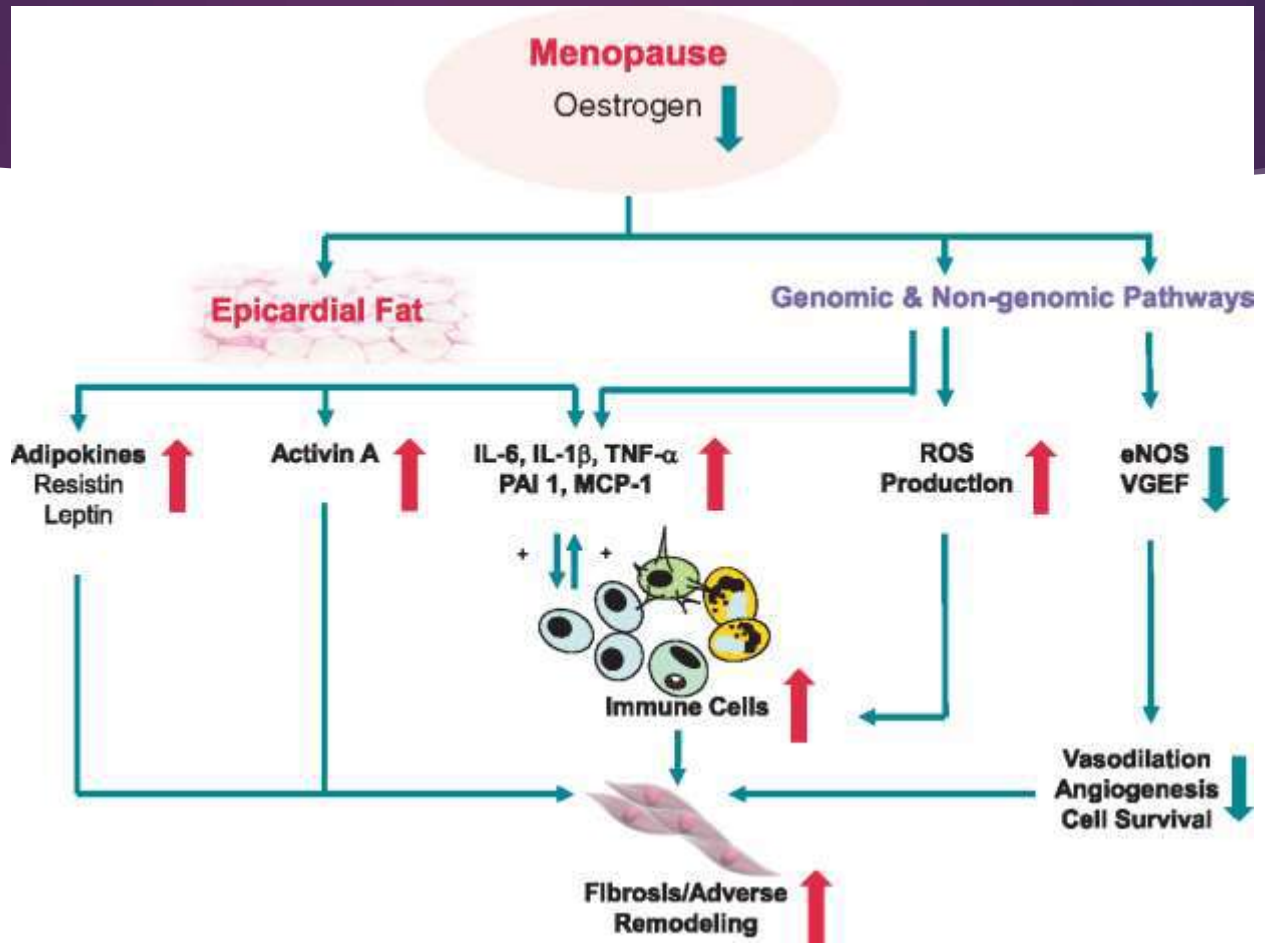
Hormones matter….

ITS COMPLICATED, WELL YOU KNEW THIS, WE'RE WOMEN….

Schematic figure indicating effects of menopause-associated reduction in oestrogen on epicardial fat and afib

Incidence of afib in premenopausal women is low, increases after menopause

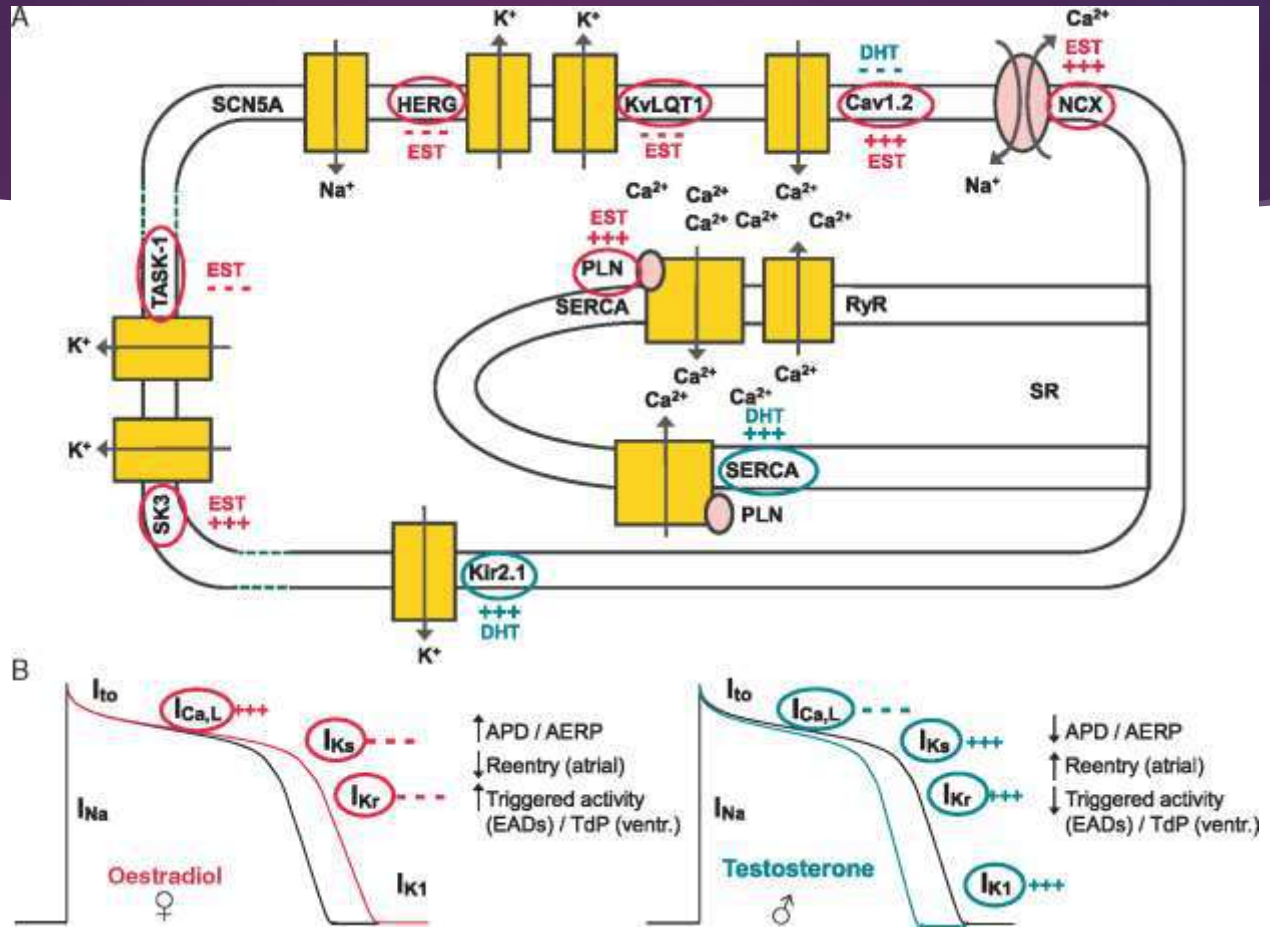
Is this a beneficial effect of estrogen or a harmful effect of post-menopausal changes?



Estradiol vs conjugated estrogens vs combined estrogen-progesterone effects and afib: Conflicting data

Europace, Volume 21, Issue 3, March 2019, Pages 366–376, https://doi.org/10.1093/europace/euy215

Figure 1 (A) Schematic figure indicating sex hormone effects on cardiac ion channels/currents and calcium handling ...



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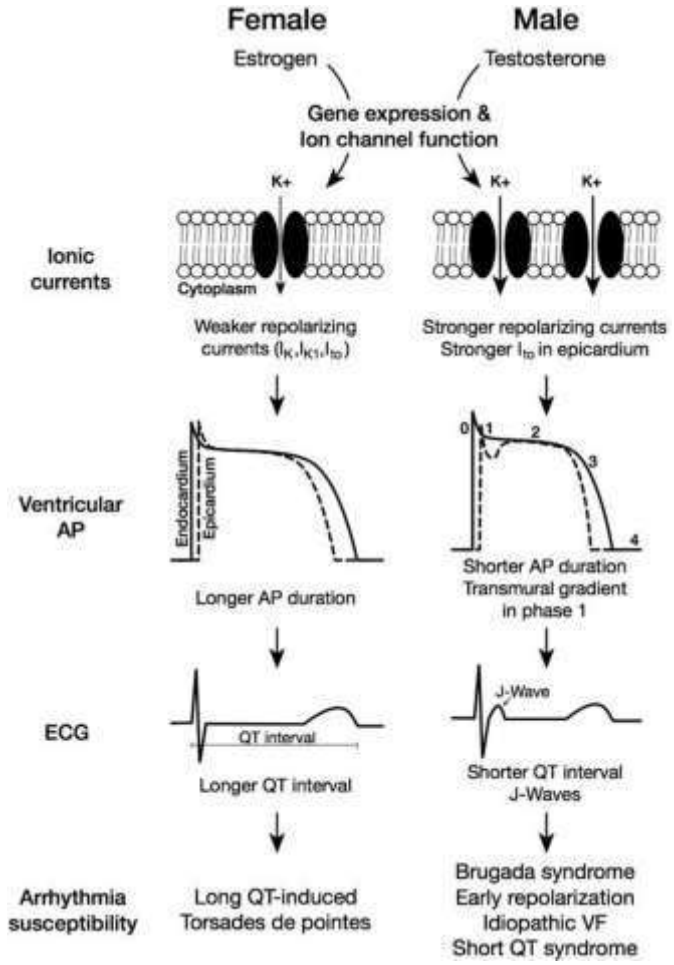
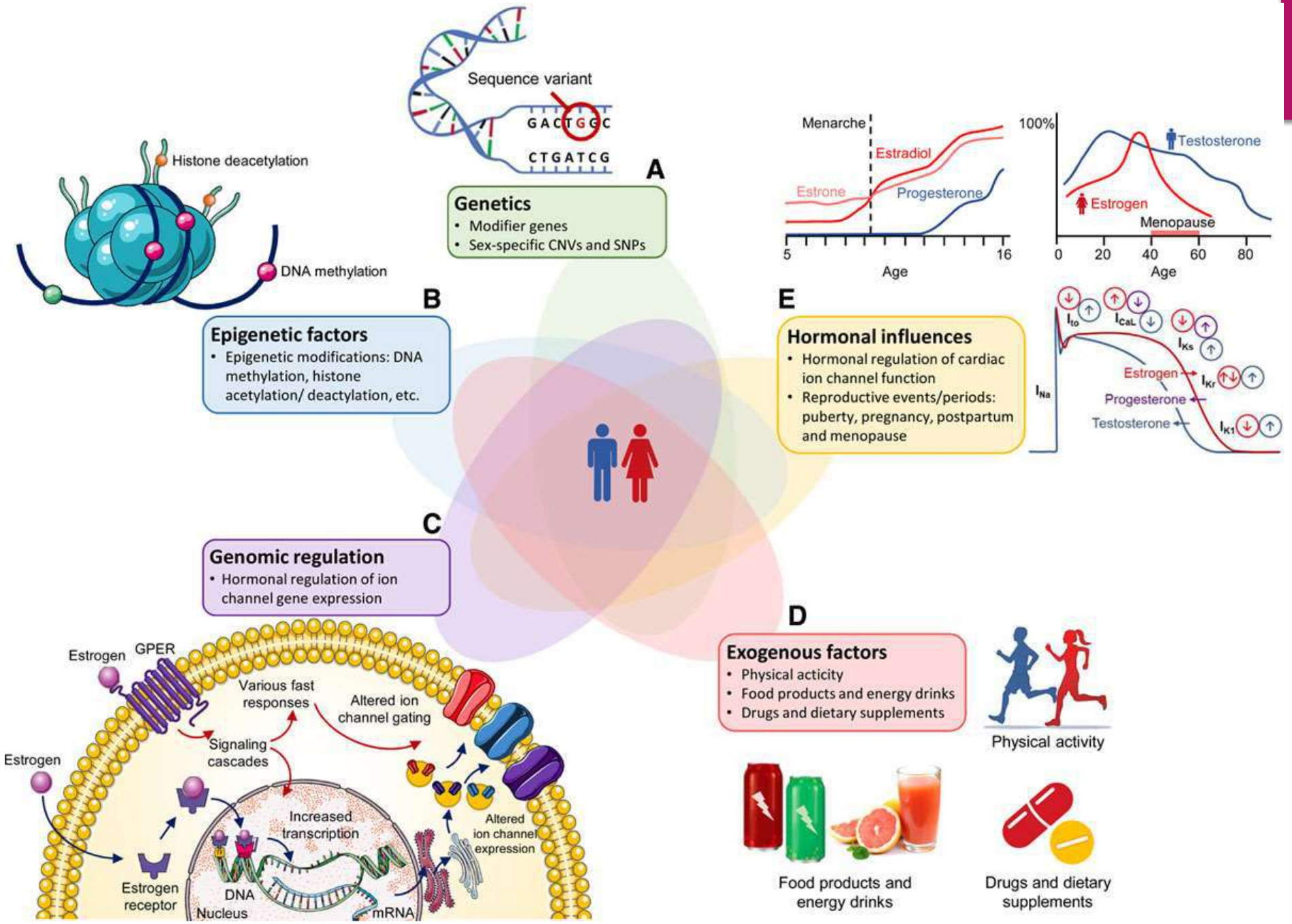
While the mechanism for prolonged QTs is understood, the exact mechanism for afib remains to be elucidated



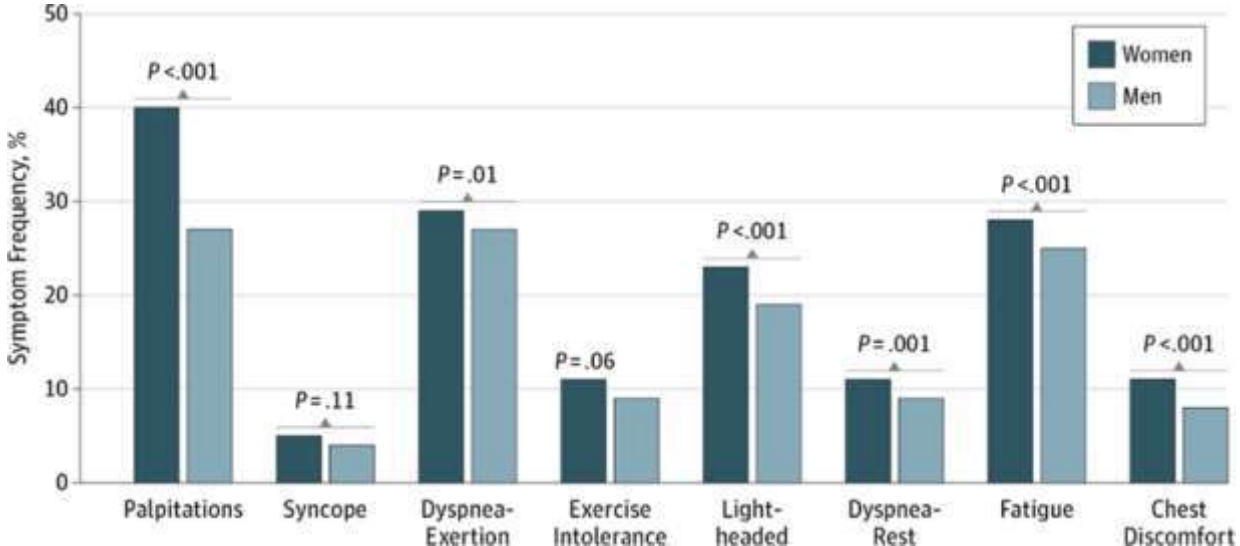
Potential Anti-arrhythmic mechanisms effecting AF prevalence

- Estrogen effects on atrial electrical feature: longer atrial APD
- Testosterone effects on atrial electrical activity: shortening atrial APD
  - Conflicting data: Framingham, MESA
  - What about testosterone replacement?
- Effects of estrogen and testosterone on atrial remodeling and fibrosis: attenuation vs worsening


Sequence variant
GACTGGC
CTGATCG
A
Genetics
• Modifier genes
• Sex-specific CNVs and SNPs
Histone deacetylation
DNA methylation
B
Epigenetic factors
• Epigenetic modifications: DNA methylation, histone acetylation/ deactylation, etc.
Menarche
Estradiol
Estrone
Progesterone
5
16
Age
100%
Testosterone
Estrogen
Menopause
0
20
40
60
80
Age
E
Hormonal influences
• Hormonal regulation of cardiac ion channel function
• Reproductive events/periods: puberty, pregnancy, postpartum and menopause
Estrogen
Progesterone
Testosterone
C
Genomic regulation
• Hormonal regulation of ion channel gene expression
Estrogen
GPER
Various fast responses
Altered ion channel gating
Signaling cascades
Estrogen
Increased transcription
Altered ion channel expression
Estrogen receptor
DNA
Nucleus
mRNA
D
Exogenous factors
• Physical acticity
• Food products and energy drinks
• Drugs and dietary supplements
Physical activity
Food products and energy drinks
Drugs and dietary supplements

Afib & Women: PRESENTATION

- **Symptomatic and ATYPICAL**
  - Palpitations, exertional dyspnea, effort intolerance, lightheadedness, dyspnea at rest, fatigue, weakness and chest discomfort
  - Vague symptoms such as fatigue and weakness may lead to **delayed diagnosis**
  - Which leads to women presenting with **persistent afib**
- Functional impairment
- Worse quality of life
- Later presentation
- More likely hospitalized
- More prone to AF recurrences



ORBIT-AF Data, EORP-AF

Afib & Women

Increased Age at Diagnosis

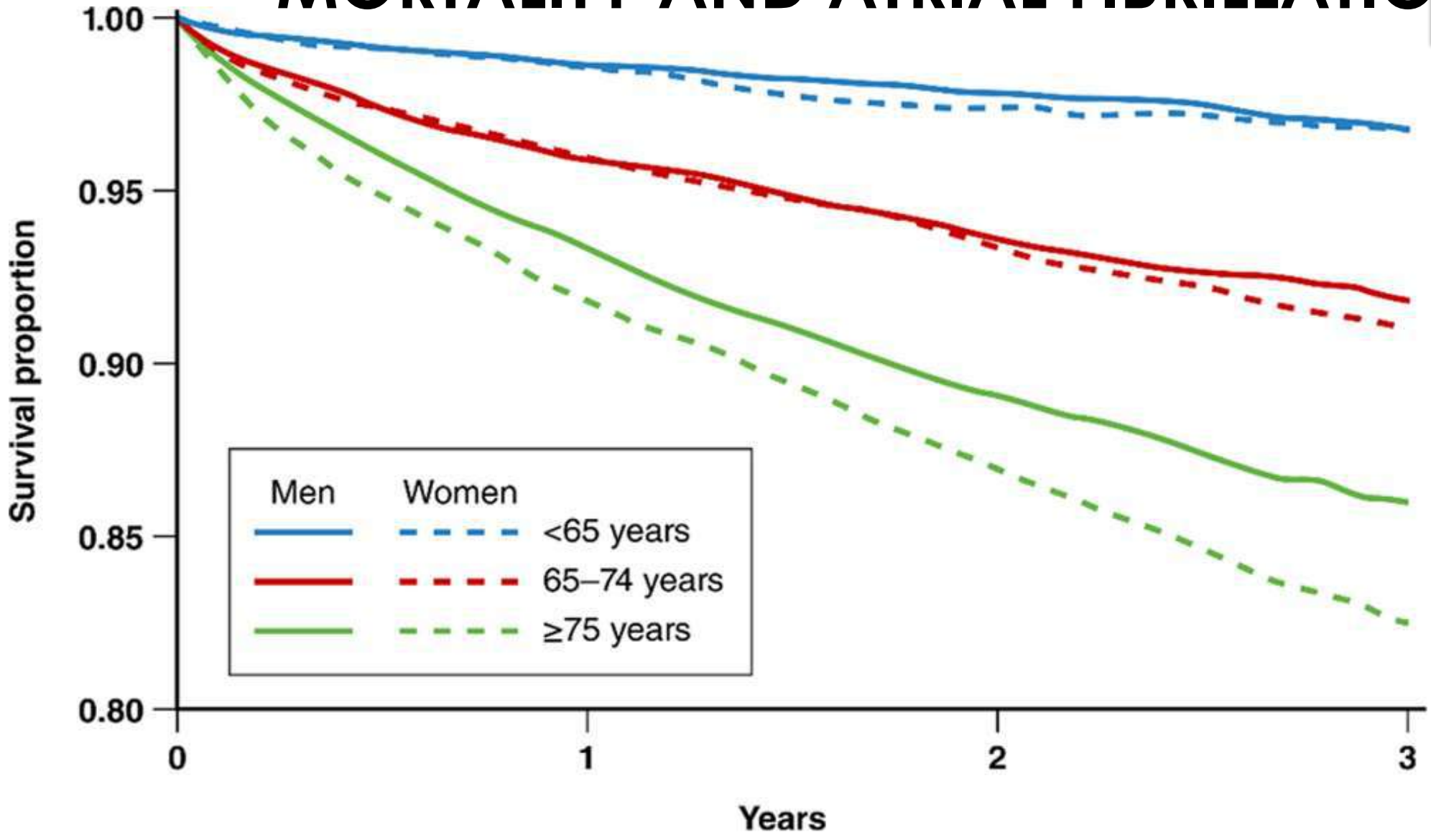
Increased comorbidities
-hypertension
-obesity
-sleep apnea
-sedentary behavior

Increased risk of stroke

Worse outcomes,
Poor quality of life
More prone to afib recurrences

Should we be more proactive in following a rhythm control strategy and referring for ablation?

MORTALITY AND ATRIAL FIBRILLATION



Afib & Women: MANAGEMENT

- Interplay between social and pathophysiological factors
- **Women less likely to receive rhythm control antiarrhythmic Rx therapy, electrical cardioversion, or catheter ablation**
- ORBIT-AF: no difference in use of antiarrhythmic therapy however less likely to undergo cardioversion
- More likely to undergo AV node ablation
- Women with symptomatic AF more likely to received rate control strategy alone
- **Less likely to be referred for ablation: old age at presentation? More concern for risk of complications?**

Afib & Women: MANAGEMENT

- AFFIRM data
- DIAMOND-CHF
  - 25% women
  - Dofetilide in afib CHF patients:
  - More **TdP 3.3%, OR 3.2 female**
- Link between adverse effects: QT prolongation
- 2017 Dofetilide Tx: 22% women, **all TdP occurred in women**; similar efficacy in pharmacological conversion rates

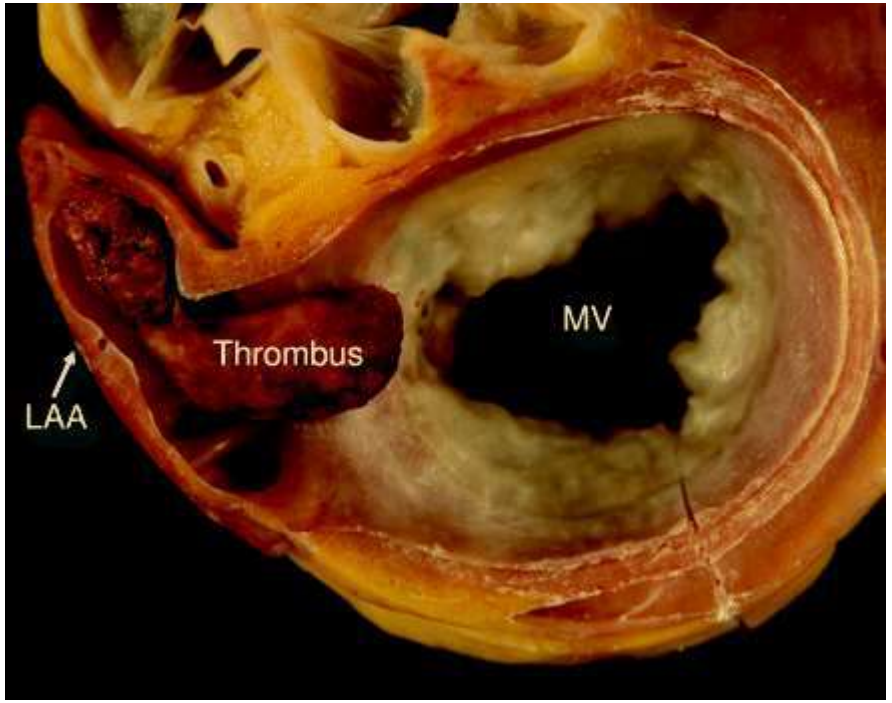
"Choose your anti-arrhythmic wisely"

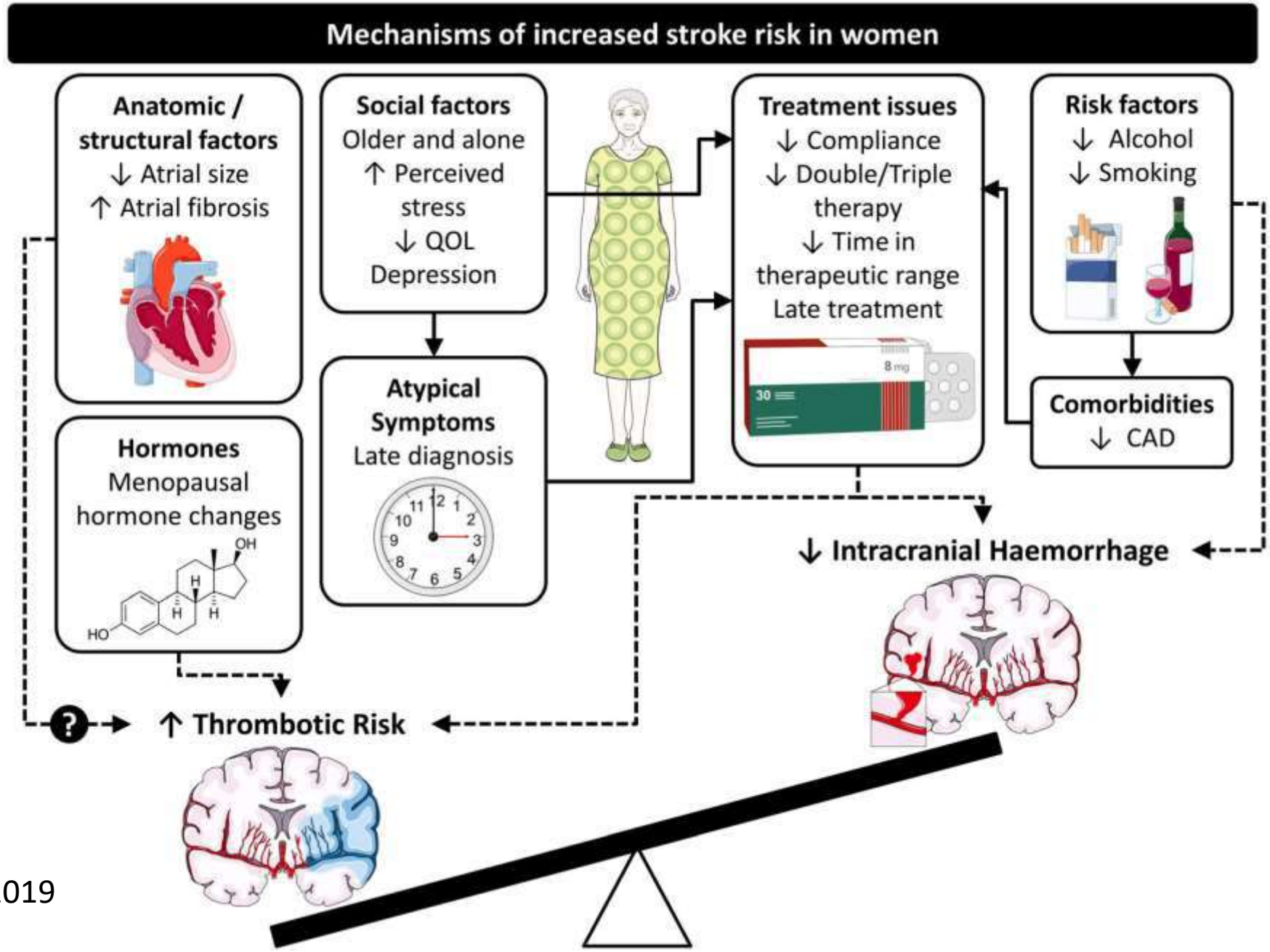
Afib & Women: CATHETER ABLATION

- Increased venous access and vascular complication
- German Ablation Registry:
  - Women older at time of procedure, higher prevalence of PAF,
  - More bleeding complications
  - More tamponade
- CABANA Trial concluded that ablation was as effective for women as for men
  - 37% women
  - Older
  - Symptomatic
  - Heart Failure
  - Similar complication rate
  - Less likely to received ancillary ablation procedures

Afib & Women: STROKE RISK

- CHA2DS2-VASc
- GARFIELD-AF registry
- Etiology of increased risk:
  - Smaller atrial volumes
  - Lower left atrial mechanics and velocities
  - HFpEF: atrial strain, remodeling,
  - Systemic inflammation and prothrombotic state
  - Older women have higher blood pressures





Kostopoulou et al 2019

Afib TREATMENT: For clinicians on the front lines of afib

- **Proactive and aggressive risk factor management**
  - Hypertension
  - Obesity
  - Sleep Apnea
  - Sedentary Behavior

Consider an order set for first diagnosis of afib:
-nocturnal oximetry
-exercise Rx
-weight loss referral
-blood pressure follow up

- Care with anti-arrhythmic therapy, specifically QT prolongation anti arrhythmics
- **Consider** early treatment for cardioversion, rhythm control, or ablation before significant remodeling begins

Women and Atrial Fibrillation: Conclusions and future directions

- More and often atypical symptoms
- Worse quality of life
- Higher risk for adverse events such as stroke and death
- Less likely to be referred for catheter ablation
- Better understanding regarding sex differences is important for prognostic purposes and optimization of therapeutic approaches
- More studies on gender specific outcomes and therapies