



# Representation of Women in Cardiovascular Clinical Trials

**ACC Rockies 2020**



UNIVERSITY OF  
CALGARY

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# Disclosures:

- None

# Objectives:

- To understand the scope of contemporary and historical enrollment of women in cardiovascular clinical trials
- To appreciate the importance of adequate representation of women in cardiovascular clinical trials
- To discuss potential barriers to enrollment of women in cardiovascular clinical trials
- To explore potential approaches to encourage equitable representation of women in cardiovascular clinical trials

# Historical Insights:

- Historically, women been under-represented in cardiovascular clinical trials
- Cardiovascular disease has previously been perceived as a disease of men
- Cardiovascular disease is the leading cause of premature death in Canadian women
  - Equal prevalence of CVD between men and women by age 40
  - Increased prevalence of CVD in women after age 60

*Women's Health*

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**Report of the  
Public Health Service  
Task Force on  
Women's Health Issues**

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*Volume I*

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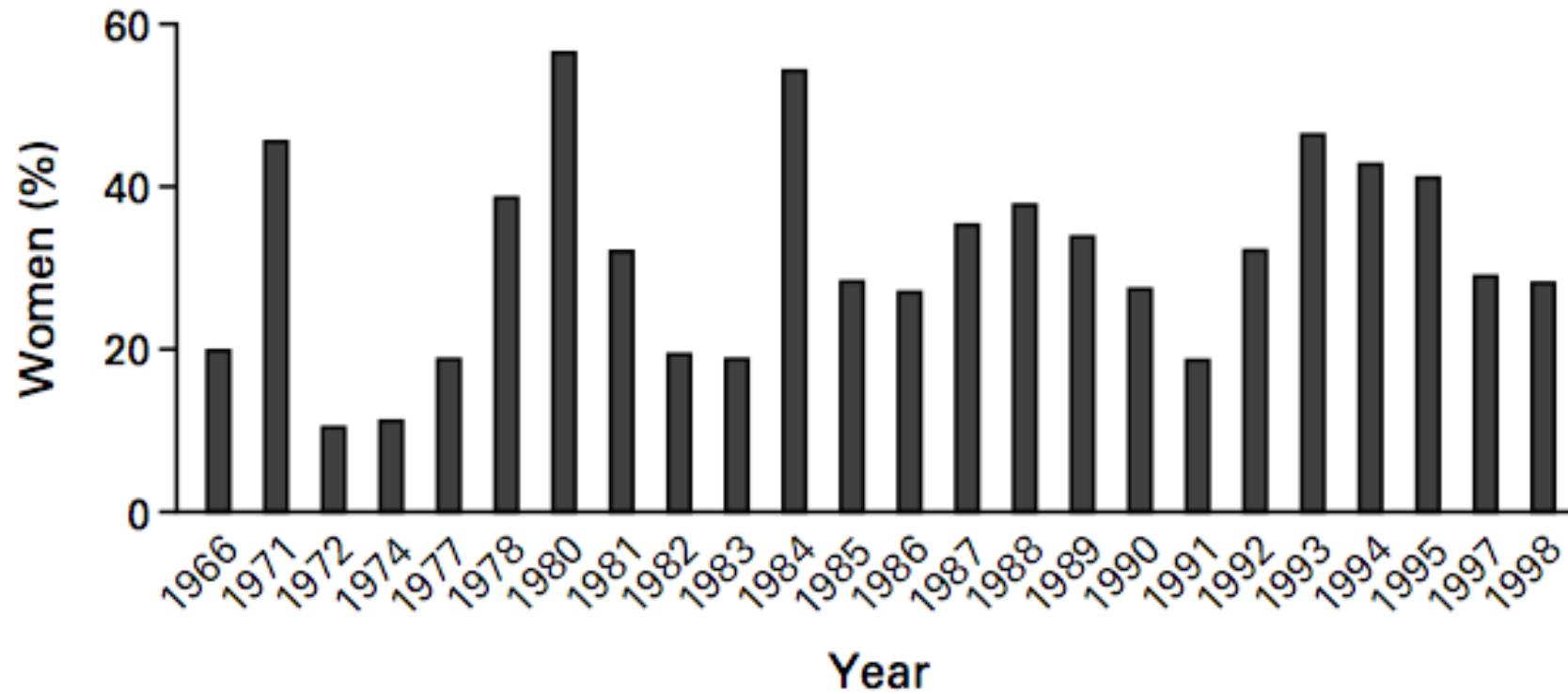


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## **Inclusion of Women in Clinical Trials During Drug Development**

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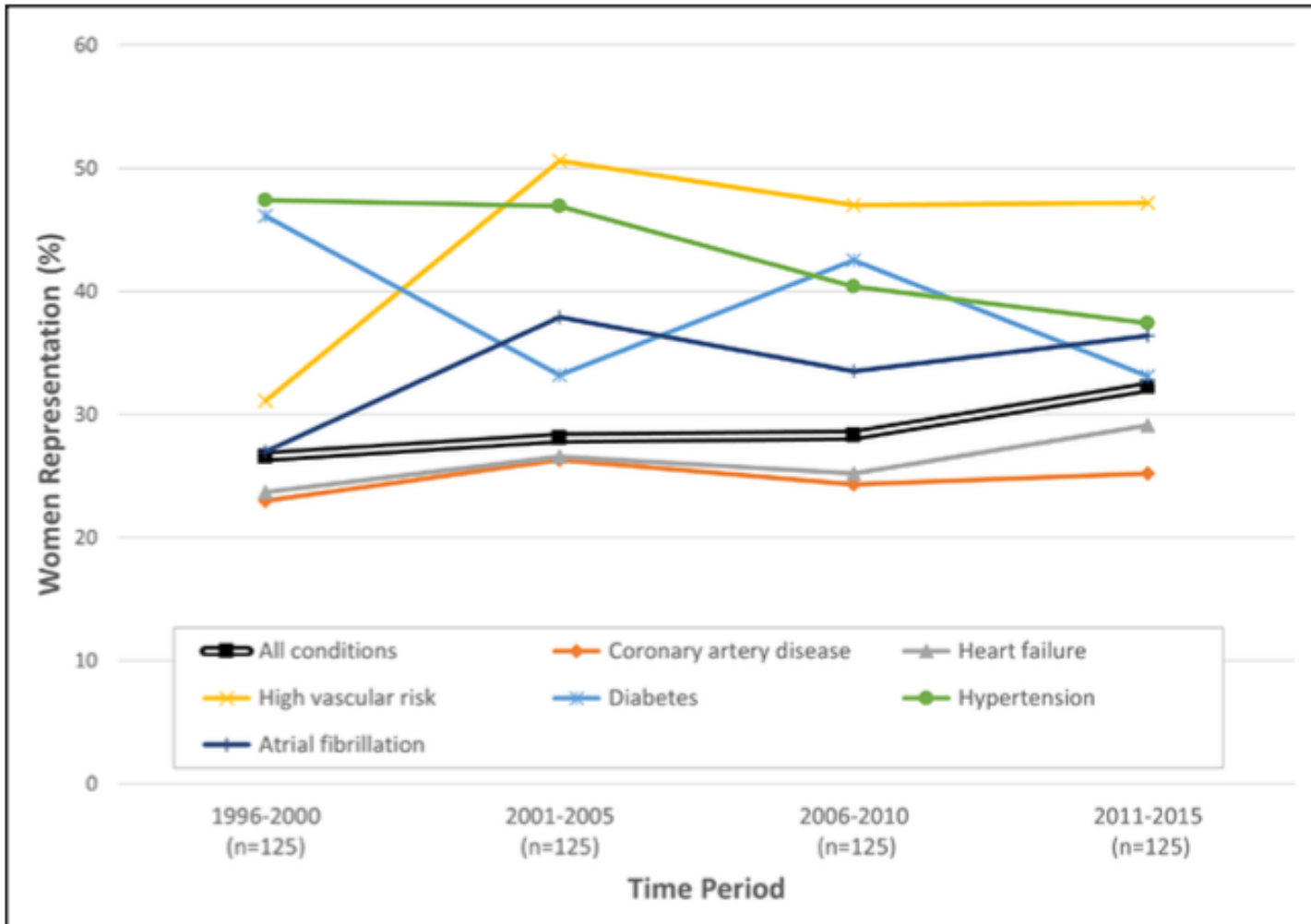


**Figure 2.** Percentage of Women among Enrollees in Cardiovascular Trials Involving Men and Women, According to the Year the Trial Was Started.

Years are shown for trials for which data on sex were available. Single-sex trials are not included.

## Evolution of Age and Female Representation in the Most-Cited Randomized Controlled Trials of Cardiology of the Last 20 Years

Quoc Dinh Nguyen, MD,  
MA, MPH  
c Peters, MD  
drene Wassef, MD  
lippe Desmarais, MD  
lphine Rémillard-  
abrosse, MD  
ixime Tremblay-Gravel,  
MD, MSc



**Figure 1. Female representation in cardiology trials over time.**

Shown are the percentage of women included in the 500 most-cited cardiology trials of the last 20 years, sorted by the cardiovascular condition studied and time period.

**Table 5. Comparison of Age and Female Representation in Randomized Clinical Trials and Population Prevalence**

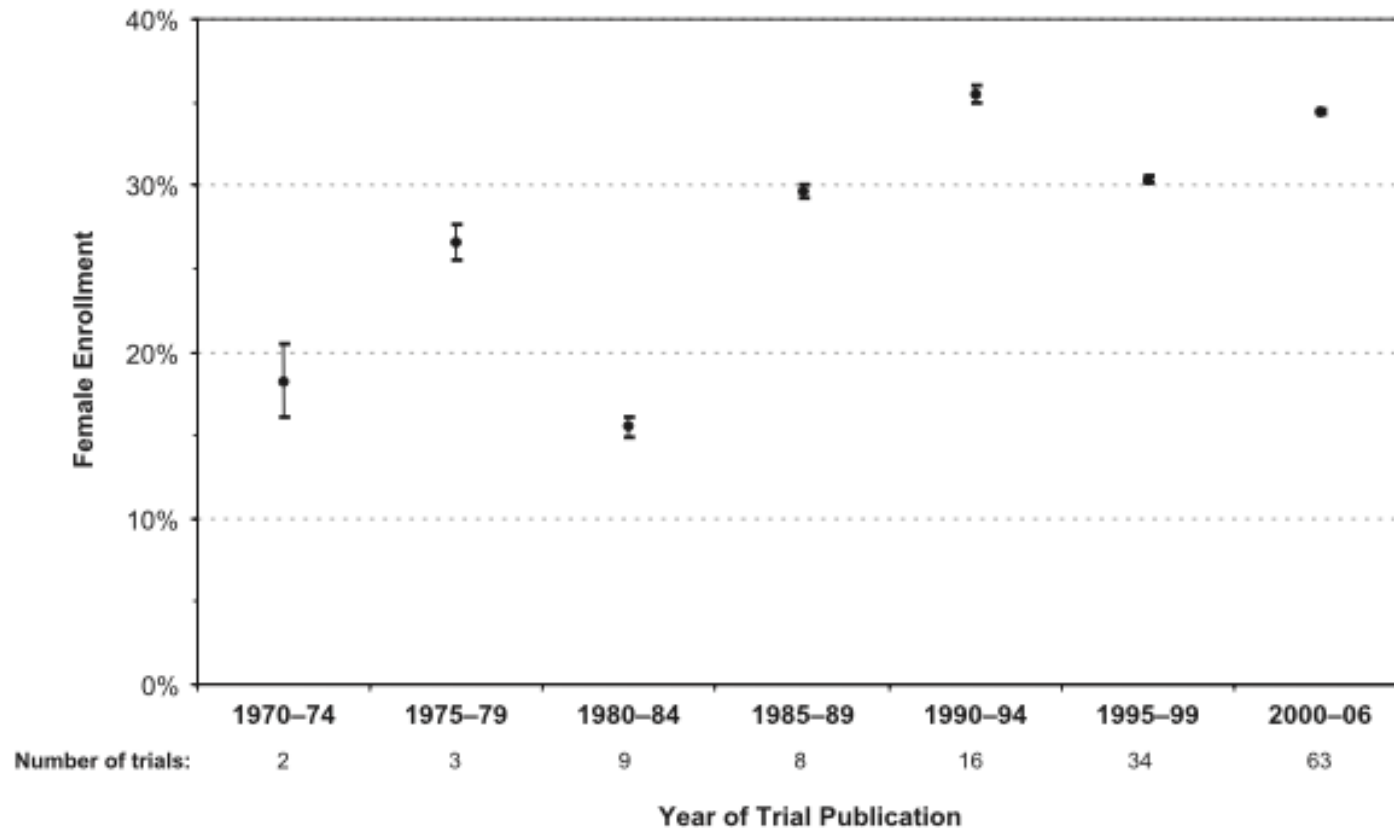
	Median Age in Trials, y	Median Age in NHANES and GBD, y	Gap, y	Women in Trials (Mean %)	Female Prevalence in NHANES and GBD, %	Gap, %
All conditions	63.0	...		33.0	...	
Coronary artery disease	62.0	67.0	-5.0	27.4	54.6	-27.2
Heart failure	64.0	70.0	-6.0	27.4	52.8	-25.4
High vascular risk	60.2	...		49.1	...	
Diabetes mellitus	60.0	61.0	-1.0	37.2	55.0	-17.8
Hypertension	63.0	60.0	3.0	46.2	48.0	-1.8
Atrial fibrillation	68.9	70.5*	-1.6	33.3	42.1	-8.8
Other	66.0	...		35.0	...	

GBD indicates Global Burden of Disease; and NHANES, National Health and Nutrition Examination Survey 2015–2016.

\*Estimates from the 2010 GBD standardized to the 2010 US population.



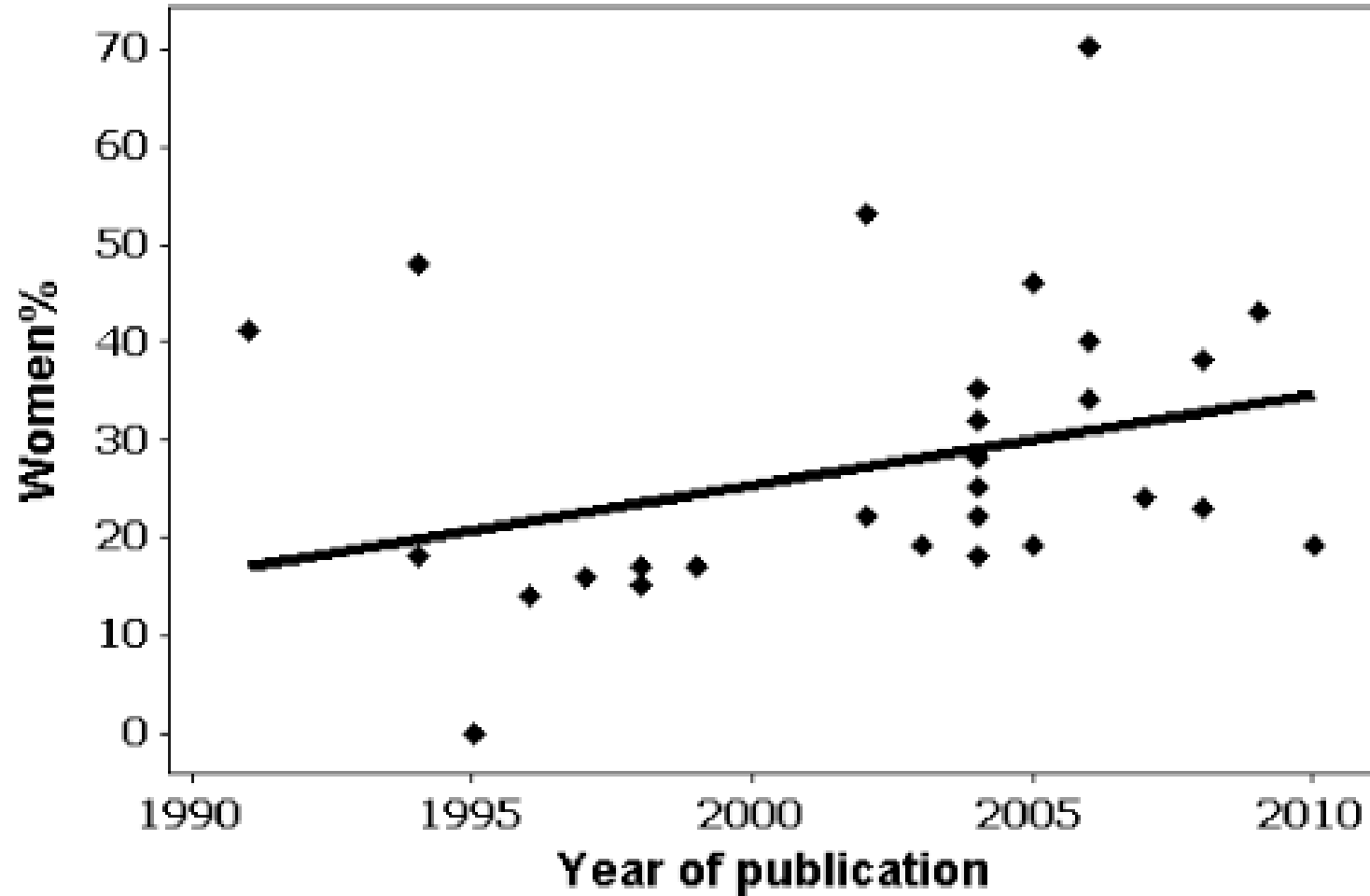
# Clinical Trials for Cardiovascular Disease Prevention:



**Figure 1.** Unadjusted rates of female enrollment in randomized clinical trials by year of publication of trial results. Trials that enrolled only men or only women are excluded.

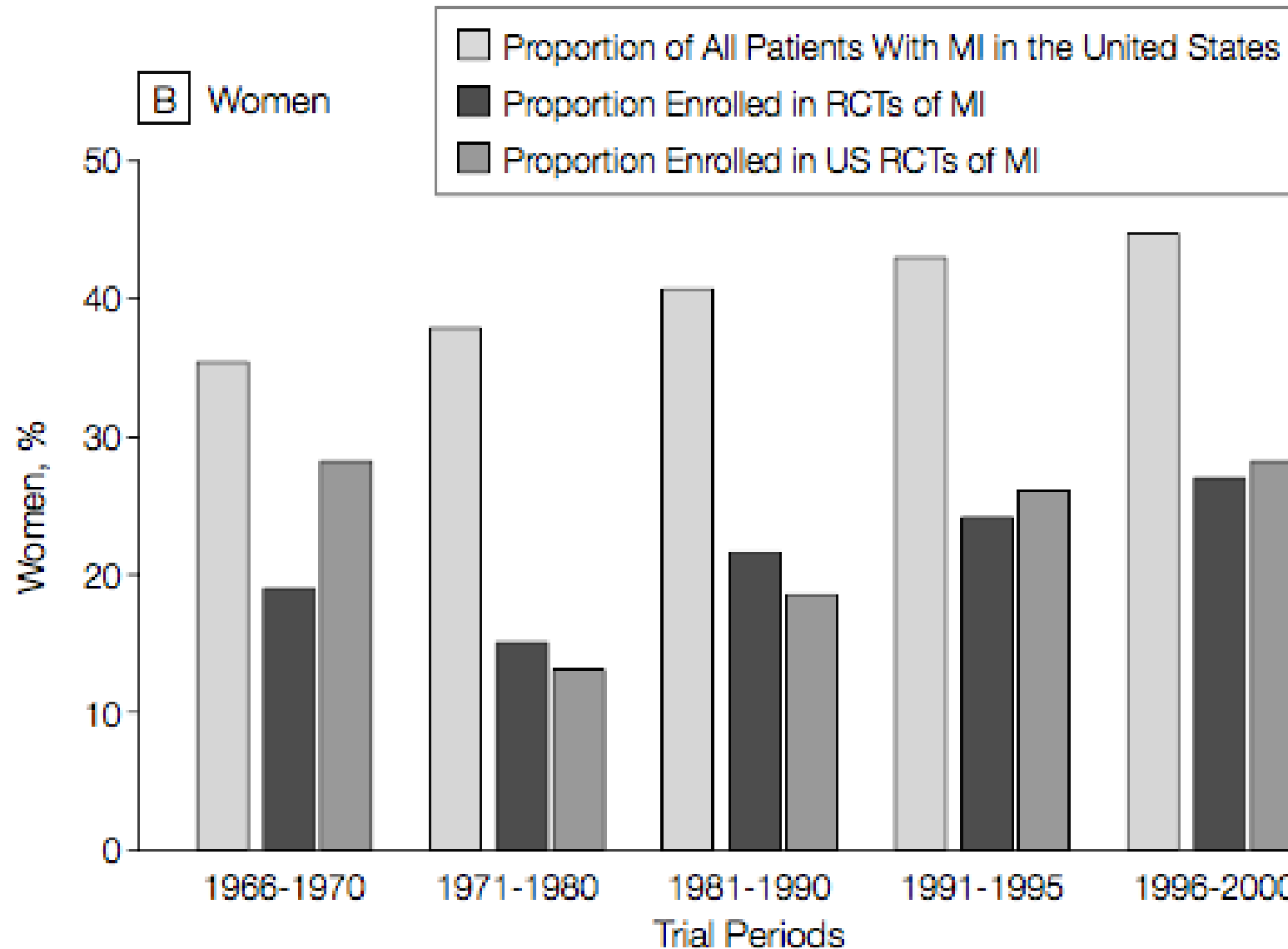
**Proportion of female enrollment increased from 18% to 34%**

# Clinical Trials of Statins:



**Significant increase in enrollment of women from 19% to 32%.**

# ACS Clinical Trials:

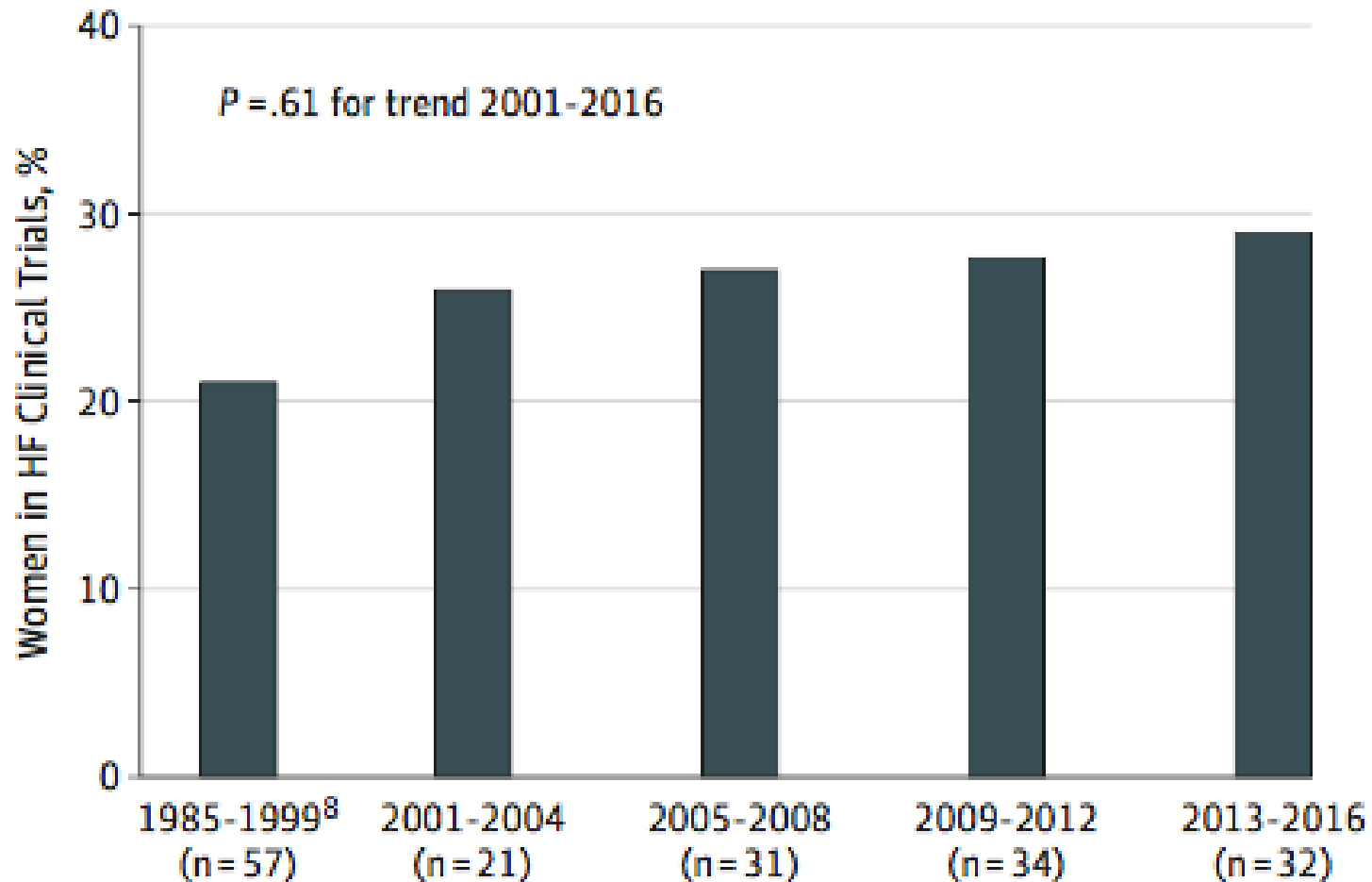


**Increased representation of women, from 20% to 25% (but still well below female disease prevalence rates)**

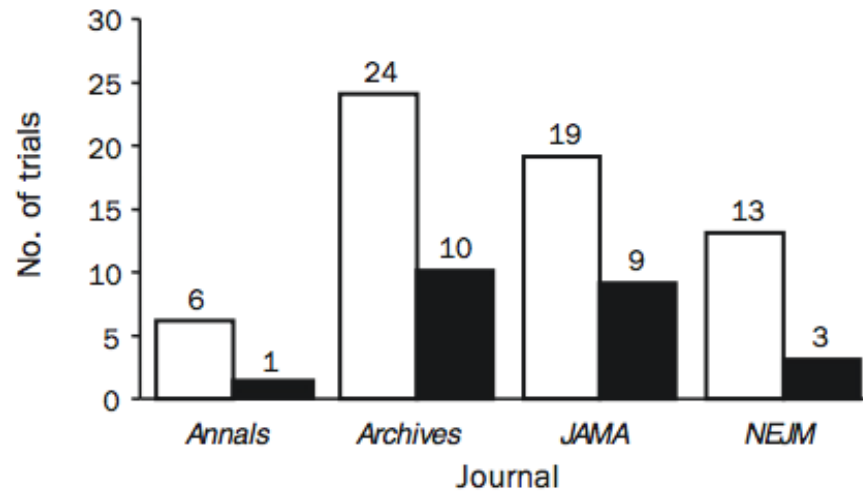
# HF Clinical Trials:

**No significant change in proportion of women enrolled (27%). Improved representation of women in: HFpEF (vs HFrEF) and non-drug, non-invasive trials (vs. drug therapy, invasive).**

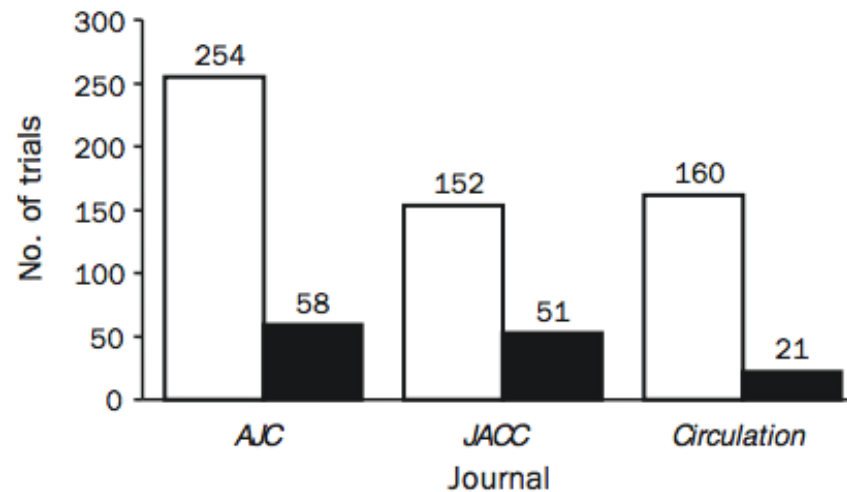
**B** Proportion of women



# Rates of Sex Specific Outcome Reporting:



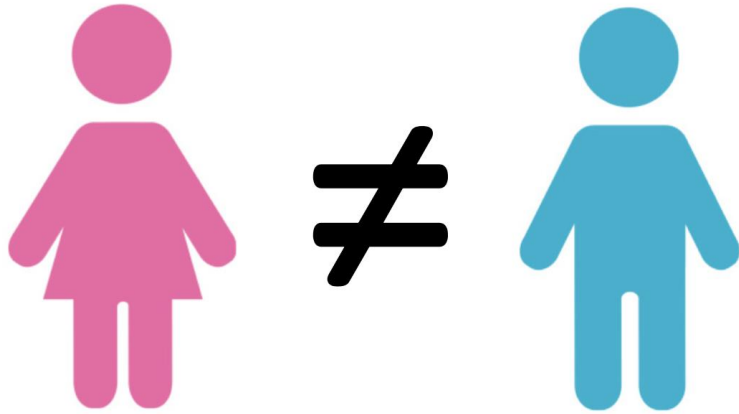
**37%**



**24%**

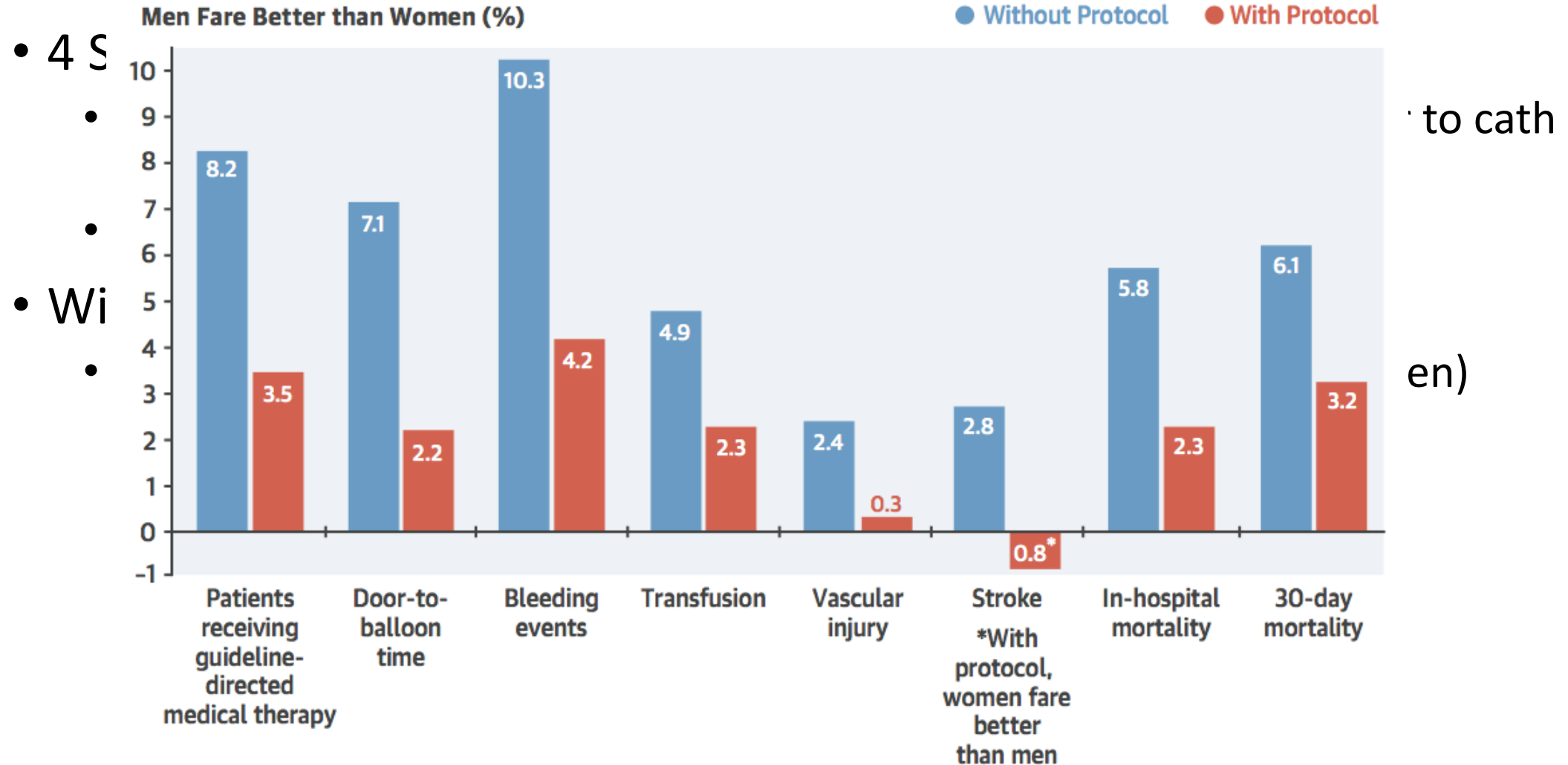
**23%**

# Is under-representation of women in cardiovascular clinical trials really a problem?



- There are significant differences between men and women's CVD in terms of:
  - Risk factors
  - Pathophysiology
  - Presentation
  - Pharmacodynamics and pharmacokinetics
  - Response to invasive therapy
  - Complications of therapy
  - Prognosis
- Relevant issues to diagnosis and treatment of CVD
- Trial translation is only effective in adequately represented populations
- Disparate outcomes
  - CVD mortality declining  $M > F$

# When sex disparities are reduced, mortality decreases!



# Women: Barriers to Participation in Clinical Trials and Future Approaches

## 1) Implicit Bias

- Perceived CVD burden is lower in women compared to men
  - Perceived CVD risk is more heavily attributed to body weight vs other validated risk factors
- Leads to inaccurate risk assessment and reduced opportunity to be screened for CV trial participation
  - Reduced CVD testing
  - Reduced/delayed CVD diagnosis
  - Reduced referral to cardiology

## How can we reduce the effects of implicit bias?

- **Protocolized approaches to CVD care to reduce sex disparities**
- **Marketing campaigns that aim to increase awareness of prevalence, presentation and outcomes of CVD in women**





# Women: Barriers to Participation in Clinical Trials and Future Approaches

## 2) Inclusion/Exclusion Criteria that disproportionately exclude women

- Age
  - Women diagnosed with CVD at older age, age criteria could reduce eligibility
- Male-standard thresholds
  - Women may not meet study thresholds for biomarkers, QTc, medication doses etc, therefore reduced eligibility
- Rates of interventions and devices
  - Women have lower rates of referral for interventions and devices therefore less eligible for device/interventional trials
- Differences in CV function
  - ie Women excluded from HF studies as less reduction in EF (HfpEF > HFrEF)

## How can we reduce the effects of disproportionate exclusion of women?

- **Integration of female-specific age inclusion criteria**
- **Introduction of female-standard thresholds for inclusion**
  - **ie maximum tolerated dose vs maximum dose**
  - **ie female-specific QTc criteria**
- **Protocolization of cardiovascular care to reduce sex disparities in referral for device/interventional care**
  - **Female-sized devices**

# Women: Barriers to Participation in Clinical Trials and Future Approaches

## 3) Non-enrollment after screening

- Limited female leadership in study design
  - Female PIs enroll greater % female participants
- Reduced female representation on recruitment teams
- Fear-distrust of system
  - Women have increased perception of study risk
- Practical barriers
  - Transportation, child care, financial constraints, interference with work/family obligations

## How can we reduce non-enrollment of women after screening?

- **Increased female leadership in study design & implementation**
  - **Gender gap in cardiologists & cardiovascular researchers**
- **Diversification of research staff**
- **Alteration of traditional study limitations:**
  - **Childcare**
  - **Transportation**
  - **Home visits**
  - **Meal provision**
  - **Evening/weekend participation**
  - **Mobile research units**

# Summary:

- Significant under-representation of women in cardiovascular clinical trials
  - Modest improvement over time
- Adequate representation of women in cardiovascular clinical trials has the potential to reduce the significant knowledge gap and improve cardiovascular outcomes in women
- Women have specific barriers to participation in cardiovascular clinical trials
  - Novel strategies are necessary to improve representation of women



**Questions?**