EXPERT EXCHANGE®

A CME Lecture Series for **Stable Ischemic Heart Disease**

# Women and Stable Ischemic Heart Disease

University of Nebraska Medical Center
BREAKTHROUGHS FOR LIFE®

This activity is jointly provided by the University of Nebraska Medical Center, the University of Florida College of Pharmacy, and Practice Point Communications®

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**Gilead Sciences Medical Affairs**

# Sign-In Process

- Please clearly print all information on the sign-in sheet
- You must indicate your NAME, DEGREE, MAILING ADDRESS, EMAIL, and SIGNATURE in order to attend this lecture
- You must indicate a unique identification number to attend this lecture:

  MD/DO/PA: NPI Number

  NP/RN: State License Number

  PharmD/RPh: NABP & Date of Birth

  Other: NPI or State License Number (if available)

- Completion is required for all healthcare providers
- Failure to provide complete information may disqualify you from participating in future lectures

# Accreditation and Disclosure Information

- Please refer to your program handouts to review the following:
  - Accreditation statements
  - Disclosure policy
  - Disclosures of content faculty, reviewers, and planners

# Evaluation and Outcomes Measurement Process

- You will receive an electronic initial evaluation to the email address provided within 1 business day
- Reminder email communications will be sent up to 5 days post lecture until the evaluation is completed
- Incomplete evaluations may preclude attendees from receiving their CME/CNE/CPE certificate & future communications about lectures in your area
- In addition, you will receive a long-term evaluation via email 8 to 12 weeks after completing this course to measure competence, performance and/or patient outcomes achieved as a result of your participation in this CME/CNE/CPE sponsored educational activity

***(Please note: If you attended multiple Expert Exchange® lectures throughout the year, a separate initial and long-term evaluation will be sent to you for each lecture.)***

# Learning Objectives (CME/CNE/CPE)

- Upon completion of this educational activity, participants should be able to:
  - Describe the gender-based epidemiologic trends and the health and economic burden of stable ischemic heart disease (SIHD), in particular chronic stable angina
  - Discuss approaches to risk stratification for women with SIHD, specifically chronic stable angina, and their probability of a coronary event
  - Discuss the important pathophysiologic factors in chronic stable angina in women
  - Review current thinking on use of optimal medical therapy versus surgical and interventional approaches plus optimal therapy in the management of women with chronic stable angina

# Program Overview

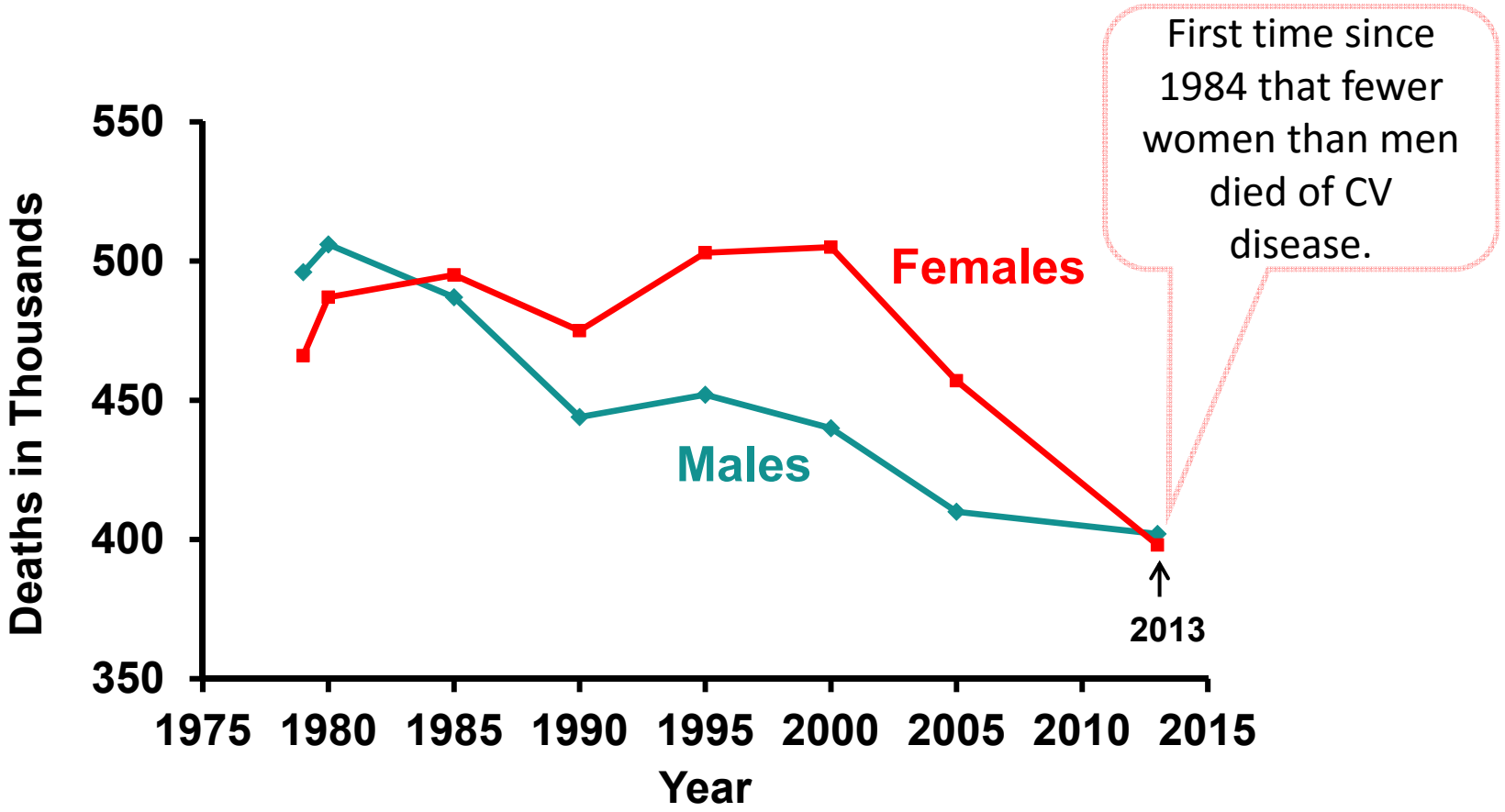
| | |
|---|---|
| **1** | **Gender-related epidemiologic patterns in SIHD** |
| 2 | Risk and symptom assessment in women |
| 3 | Pathophysiologic and pathoanatomic gender differences |
| 4 | Prognosis in women with SIHD |
| 5 | Clinical considerations in the management of SIHD in women |

# The Magnitude and Impact of Ischemic Heart Disease in Women

- Cardiovascular disease—especially ischemic heart disease and stroke—is the leading cause of death in women
- Initial presentation of coronary heart disease as angina more common in women than men
- Ischemic heart disease in women
  - Presents at older age on average than in men
  - Less likely to be diagnosed and treated than in men
  - Higher disease-specific mortality rate for women than men
- Estimated annual cost for cardiovascular disease in men and women (2011): $320.1 billion

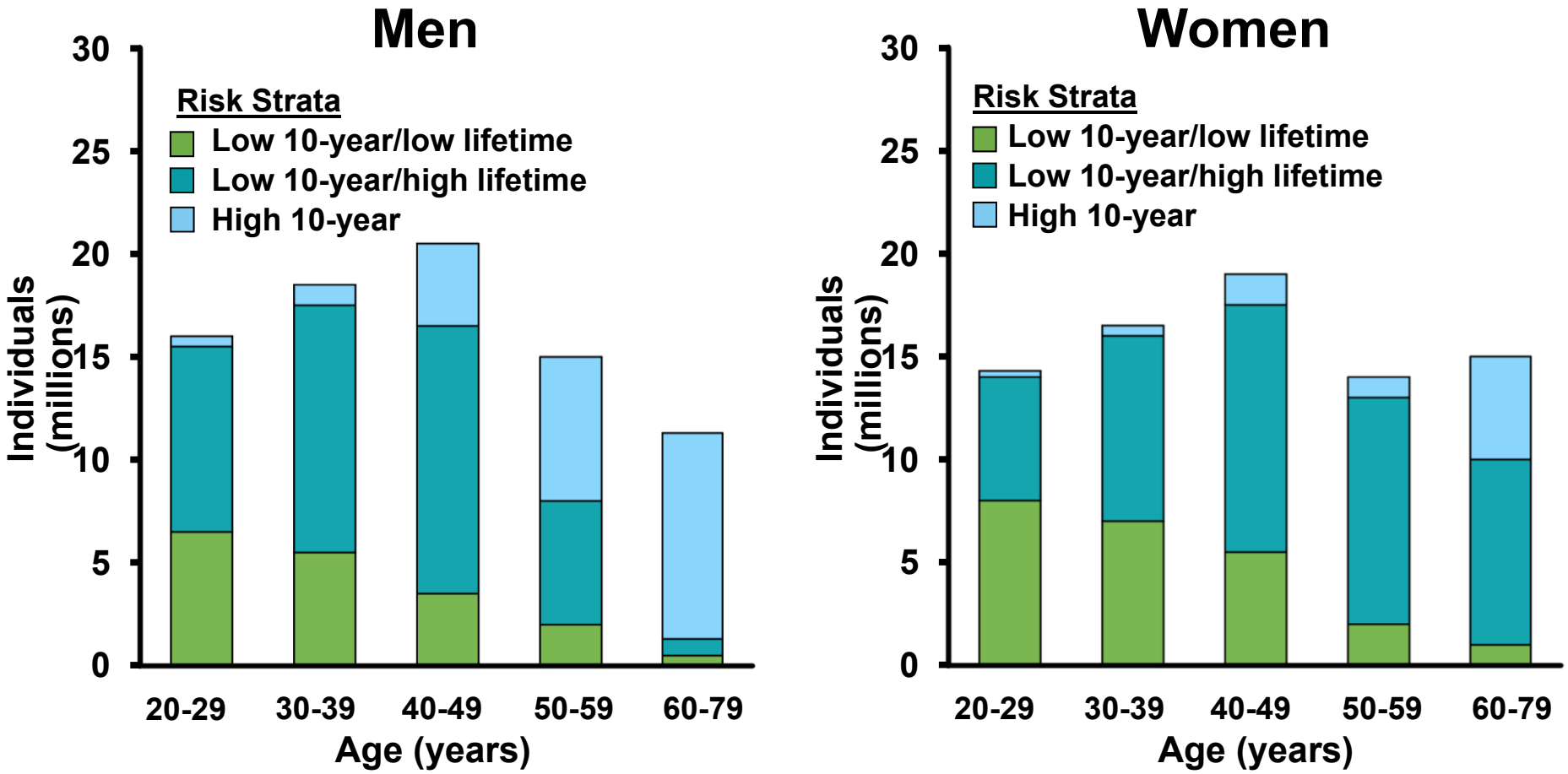
Mozzafarian D, et al. *Circulation.* 2015;131:e29-e322.
Wenger NK. *Prog Cardiovasc Dis.* 2003;46:199-229.
Hemingway H, et al. *JAMA.* 2006;295:1404-1411.
Daly C, et al. *Circulation.* 2006;113:490-498.

# Cardiovascular Disease Mortality Trends for Males and Females (United States: 1979–2013)




Mozaffarian D, et al. *Circulation*. 2016;133:e38-e360

# NHANES (2003-2006): 10-Year and Lifetime Risk for CVD



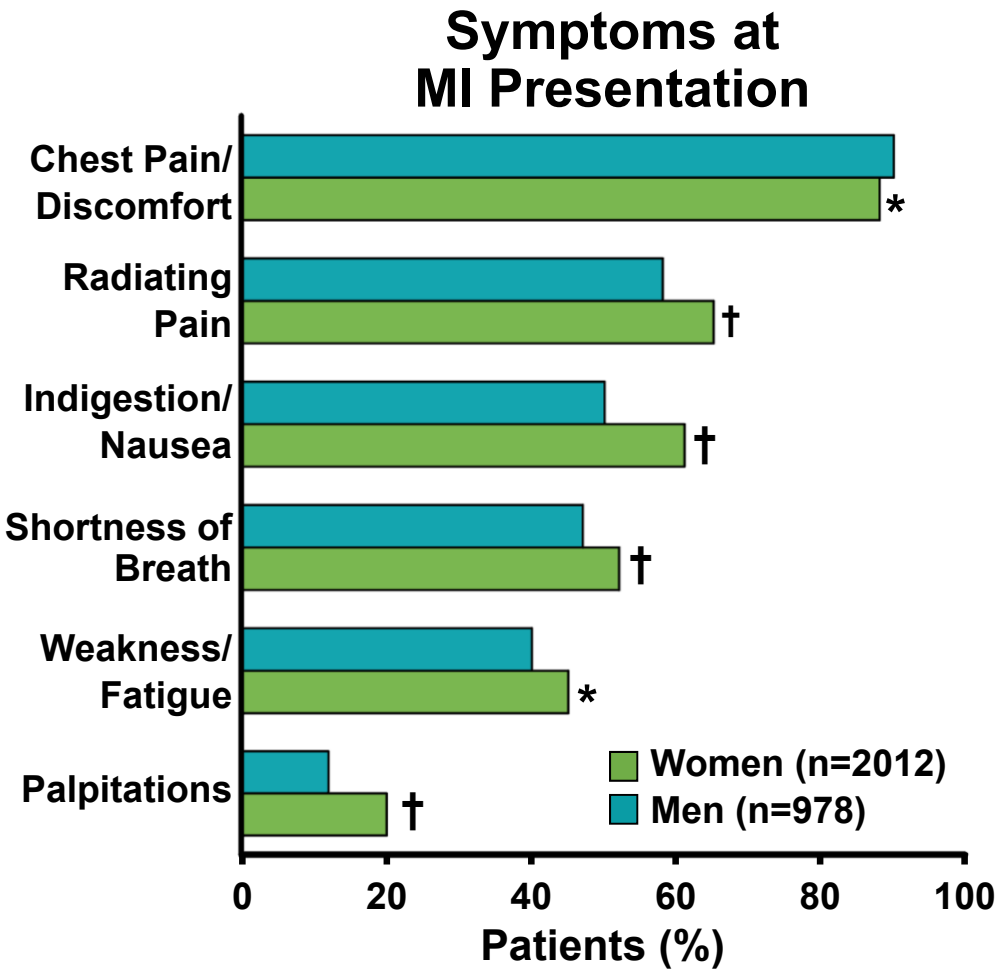

- **Many middle-aged women have low 10-year risk but high lifetime risk**

n=6329 nonpregnant NHANES participants (20-79 years of age) free of CVD representing 156 million US adults.
Low risk (<10%), low lifetime (<39%), high 10-year (≥10%), high lifetime (≥39%).

Marma AK, et al. *Circ Cardiovasc Qual Outcomes*. 2010;3:8-14.

# VIRGO Study: Gender Differences in Symptom Presentation and Perception in Younger MI Patients

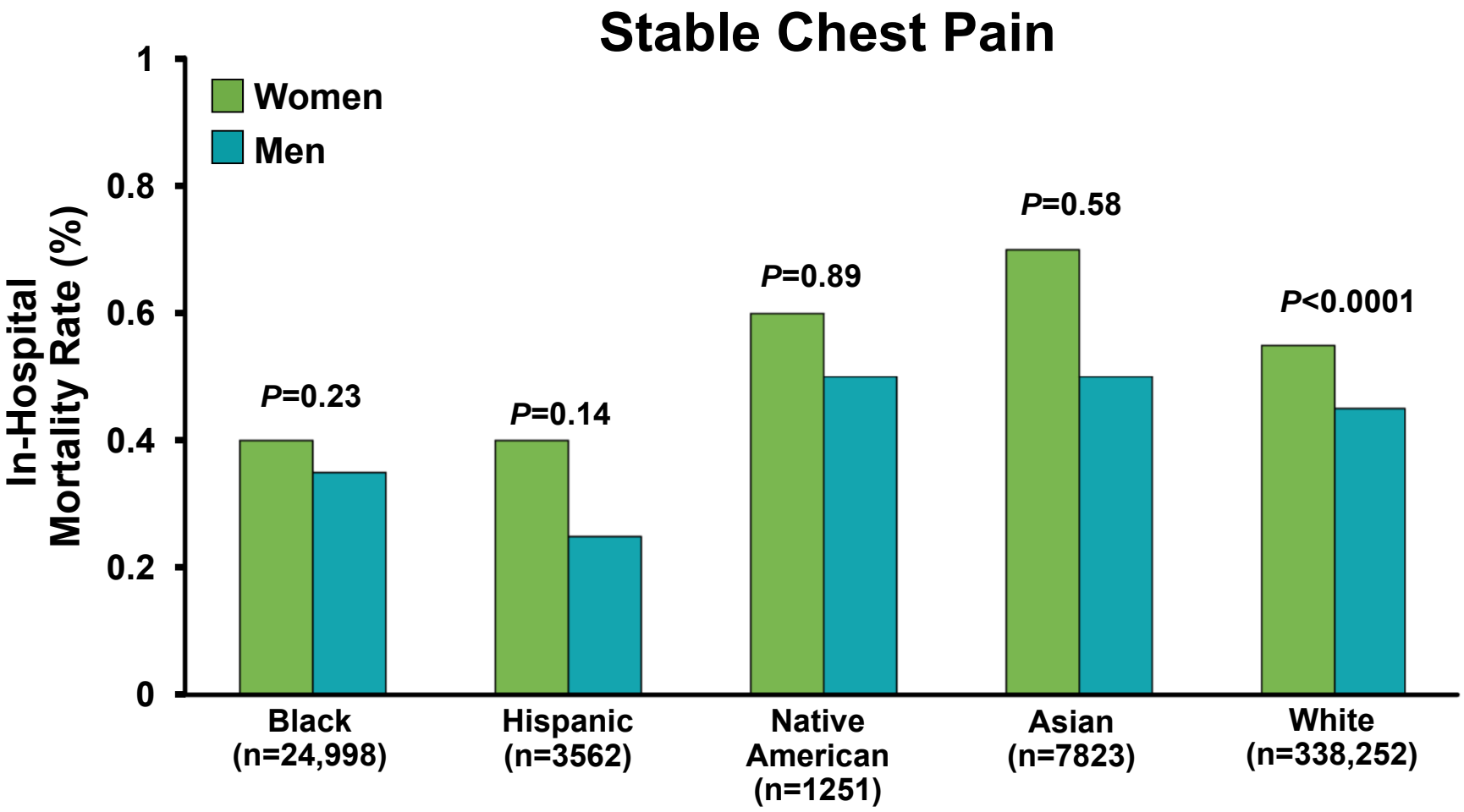
- Younger patients with MI from 104 US hospitals, 2008-2012 (n=2990)
  - Age: 18 to 55 years
  - 2:1 female to male enrolment
- 90% of men and 87% of women presented with chest pain, pressure, tightness, or discomfort
  - Women presented more additional symptoms
  - More women waited >1 day to seek care than men (55% versus 49%; *P*<0.05)
- At time of hospitalization
  - 24% of women said health care provider did not think symptoms were heart related compared with 12% of men (*P*<0.001)




*P<0.05 and †P<0.01 versus men.

Lichtman JH, et al. *Circulation.* 2012;126(suppl). Abstract 17831.

# ACC National Cardiovascular Data Registry: Gender/Ethnicities and In-Hospital Mortality




In-hospital mortality after coronary angiography.
Among patients with stable chest pain, white women with 1- to 3-vessel CAD had 1.67- to 2.02-fold higher in-hospital mortality than white men (*P*=0.013).

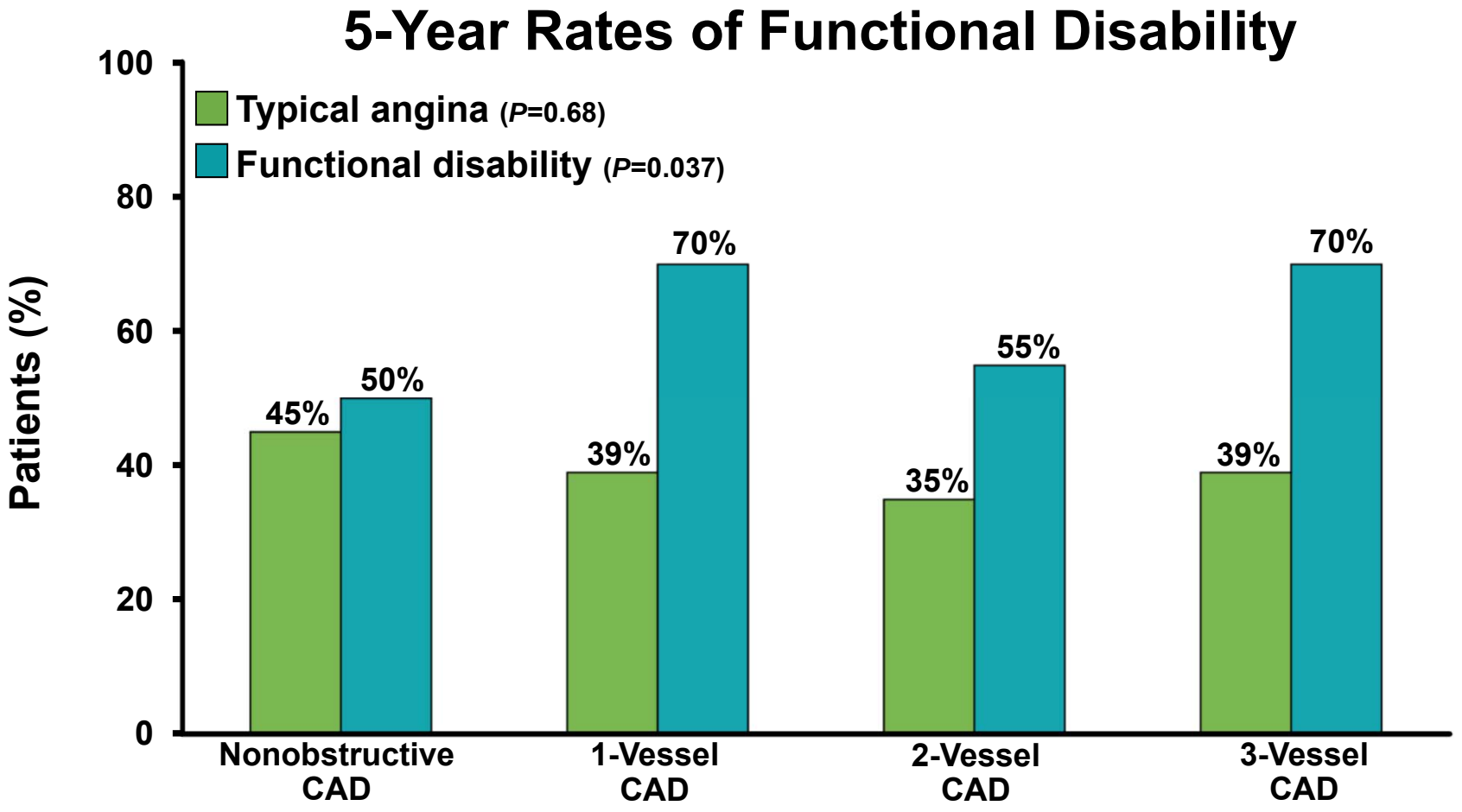
Shaw LJ, et al. *Circulation.* 2008;117:1787-1801.

# Women's Ischemia Syndrome Evaluation (WISE) Study

- NHLBI-sponsored 4-center study
  - Women (>18 years of age) undergoing clinically ordered coronary angiography for suspected myocardial ischemia (n=936)
    - Myocardial ischemia at non-invasive testing
  - Exclusion criteria
    - Emergency referral, pregnancy, cardiomyopathy, NYHA class IV CHF, recent acute MI or unstable angina, recent coronary revascularization, significant valvular or congenital heart disease, any contraindication to provocative myocardial stress testing, and any condition likely to affect study retention
- Objectives
  - Optimize symptom evaluation and diagnostic testing for ischemic heart disease in women
  - Explore mechanisms for symptoms and myocardial ischemia in the absence of epicardial coronary artery stenoses
  - Evaluate the influence of reproductive hormones on symptoms and diagnostic test response

Merz CN, et al. *J Am Coll Cardiol.* 1999;33:1453-1461.

# WISE Study: Typical Angina and Functional Disability in Women




Functional disability: Duke Activity Status Index score in metabolic equivalents ≤4.74.
n=883 women presenting for evaluation of chest pain or other equivalent symptoms.
All women had ischemia at noninvasive testing.

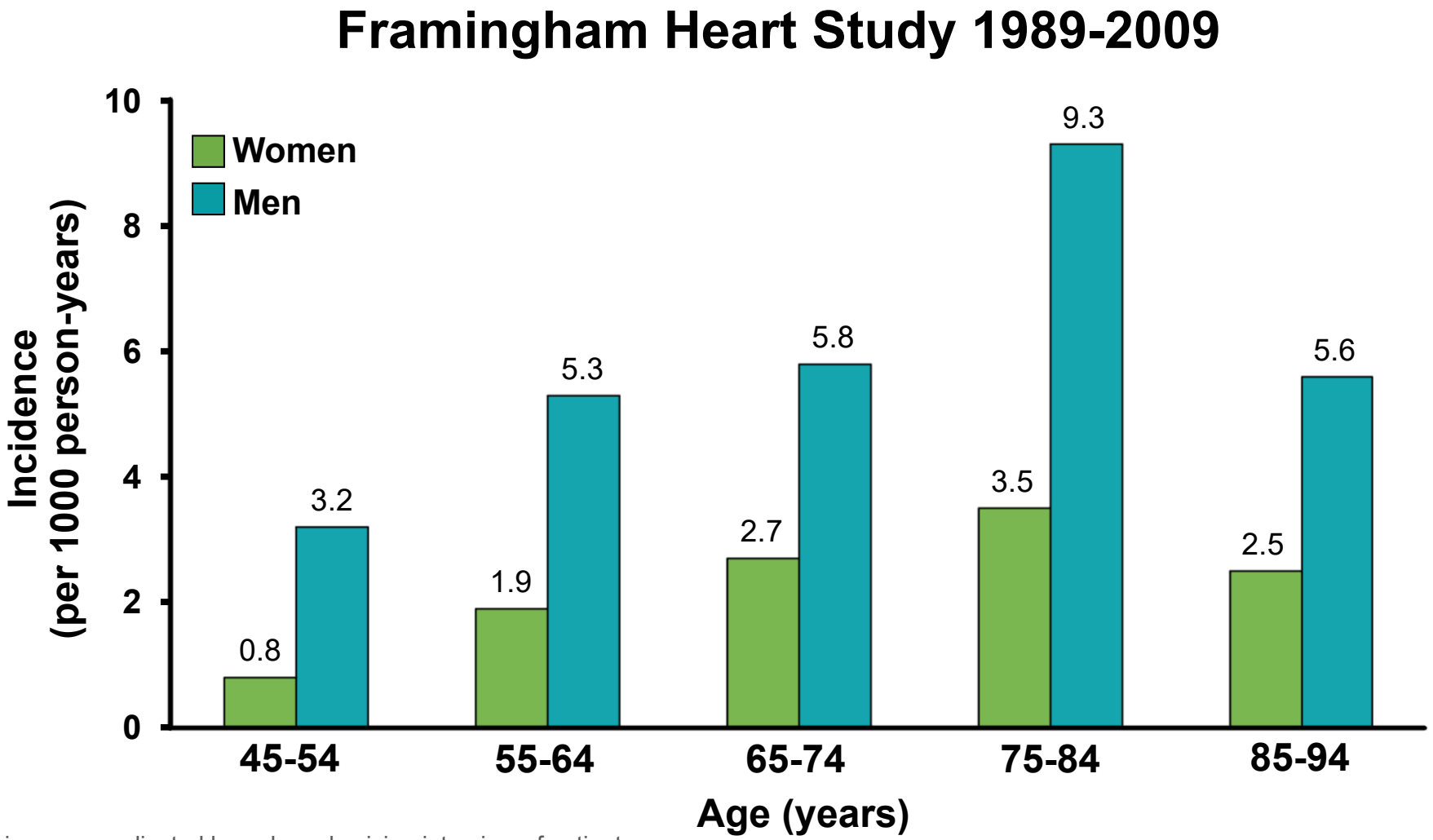
Shaw LJ, et al. *Circulation.* 2006;114:894-904.

# Gender Differences in Sudden Cardiac Death, Symptoms, and Quality of Life

- Sudden cardiac death before arrival at a hospital
  - Women: 42%
  - Men: 25%
- Symptomatic women versus men
  - More often have recurrent symptoms requiring repeat hospitalizations
  - Lower ratings of general well-being and limitations in ability to perform activities of daily living

Shaw LJ, et al. *J Am Coll Cardiol.* 2009;54:1561-1571.

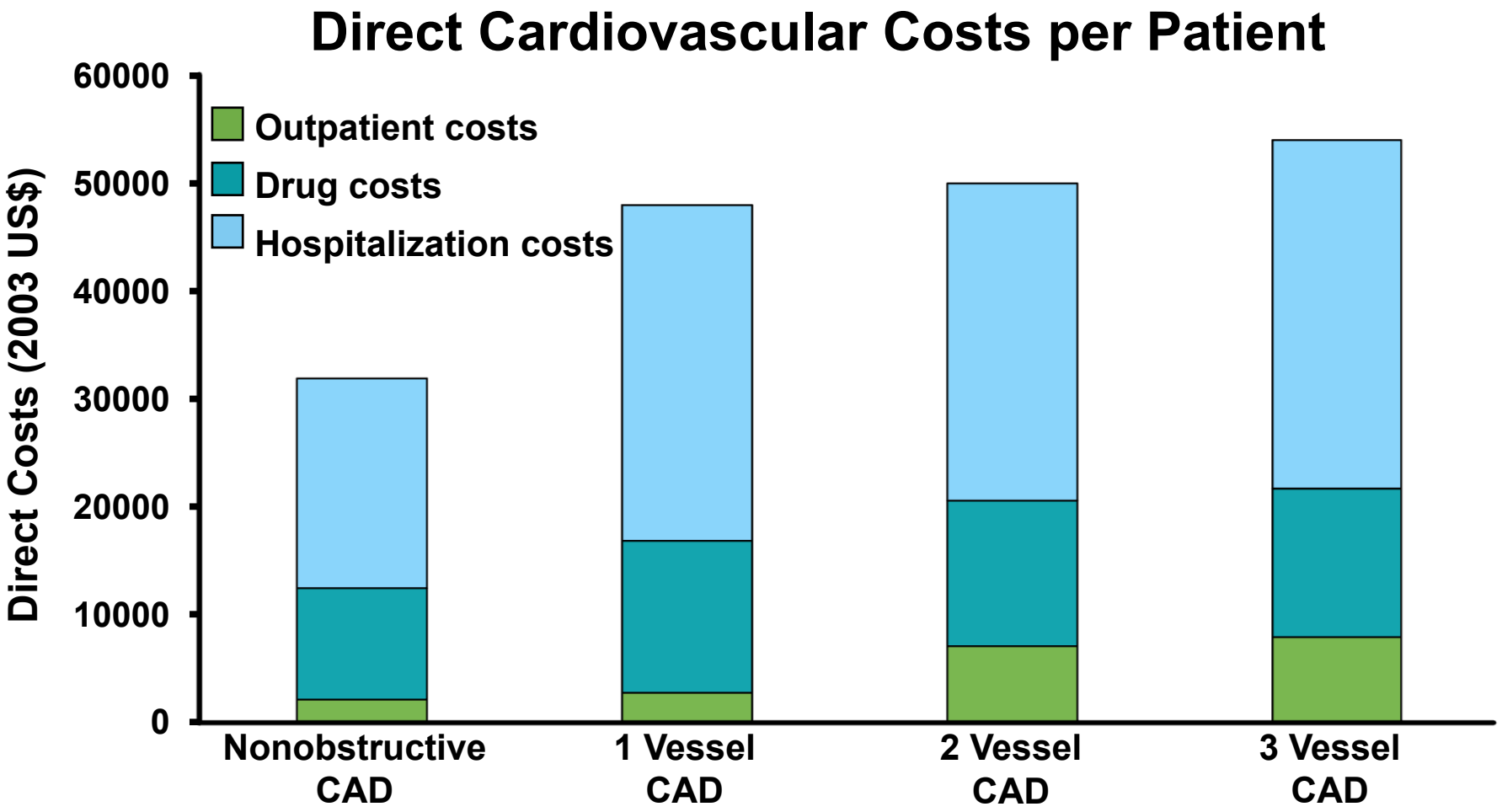
# Incidence of Angina (NHLBI)




Angina: uncomplicated based on physician interview of patient.
Rate for women 45-54 years of age considered unreliable.

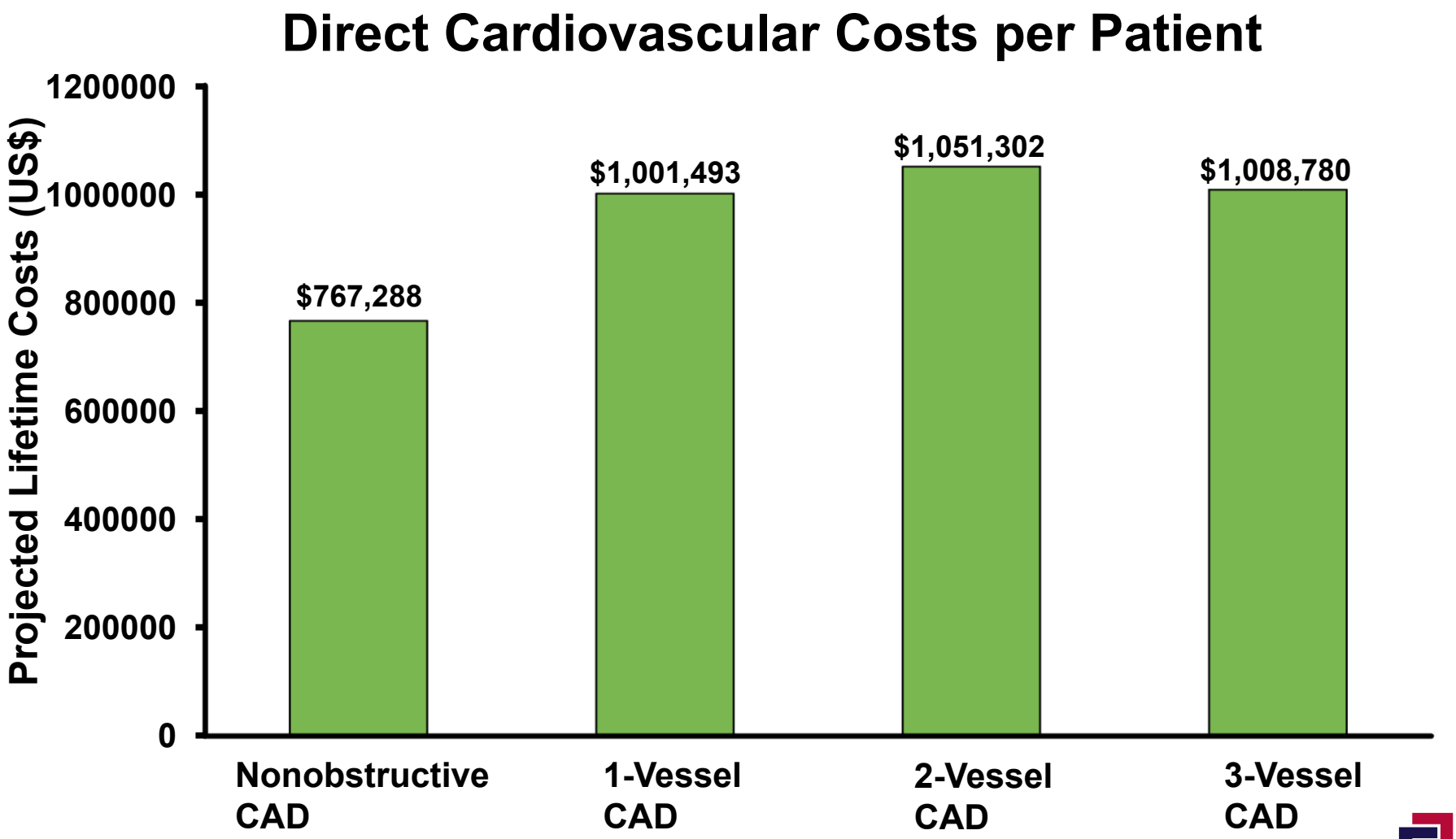
Mozaffarian D, et al. *Circulation*. 2016;133:e38-e360

# WISE Study: 5-Year Direct Costs for Women With Angina



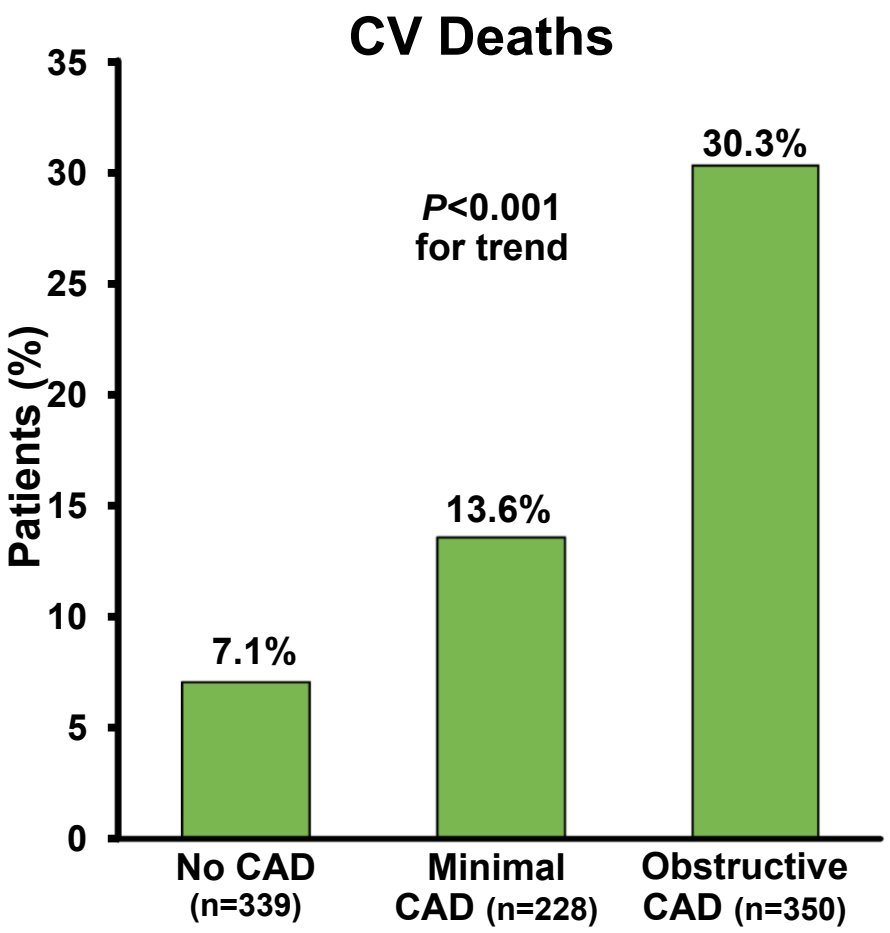

Shaw LJ, et al. *Circulation.* 2006;114:894-904.

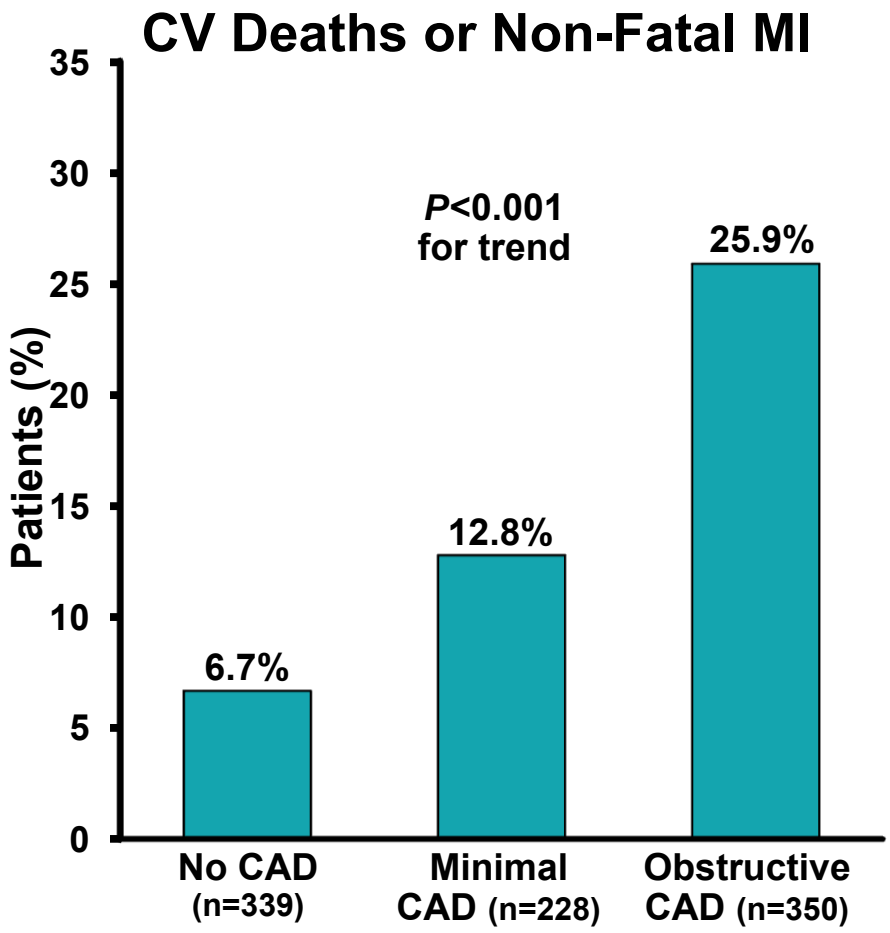
# WISE Study: Estimated Lifetime Costs for Women With Angina




Shaw LJ, et al. *Circulation.* 2006;114:894-904.

# WISE Study: Mortality at 10 Years Increases With Increasing CAD Severity




No (≤20% stenosis), minimal (20-49% stenosis), and obstructive (≥50% stenosis).
n=917 women referred for coronary angiography for symptoms of myocardial ischemia.
There were 161 (18%) deaths over median 9.3 years of follow-up.

Johnson BD, et al. *Am Heart J.* 2013;166:134-141.

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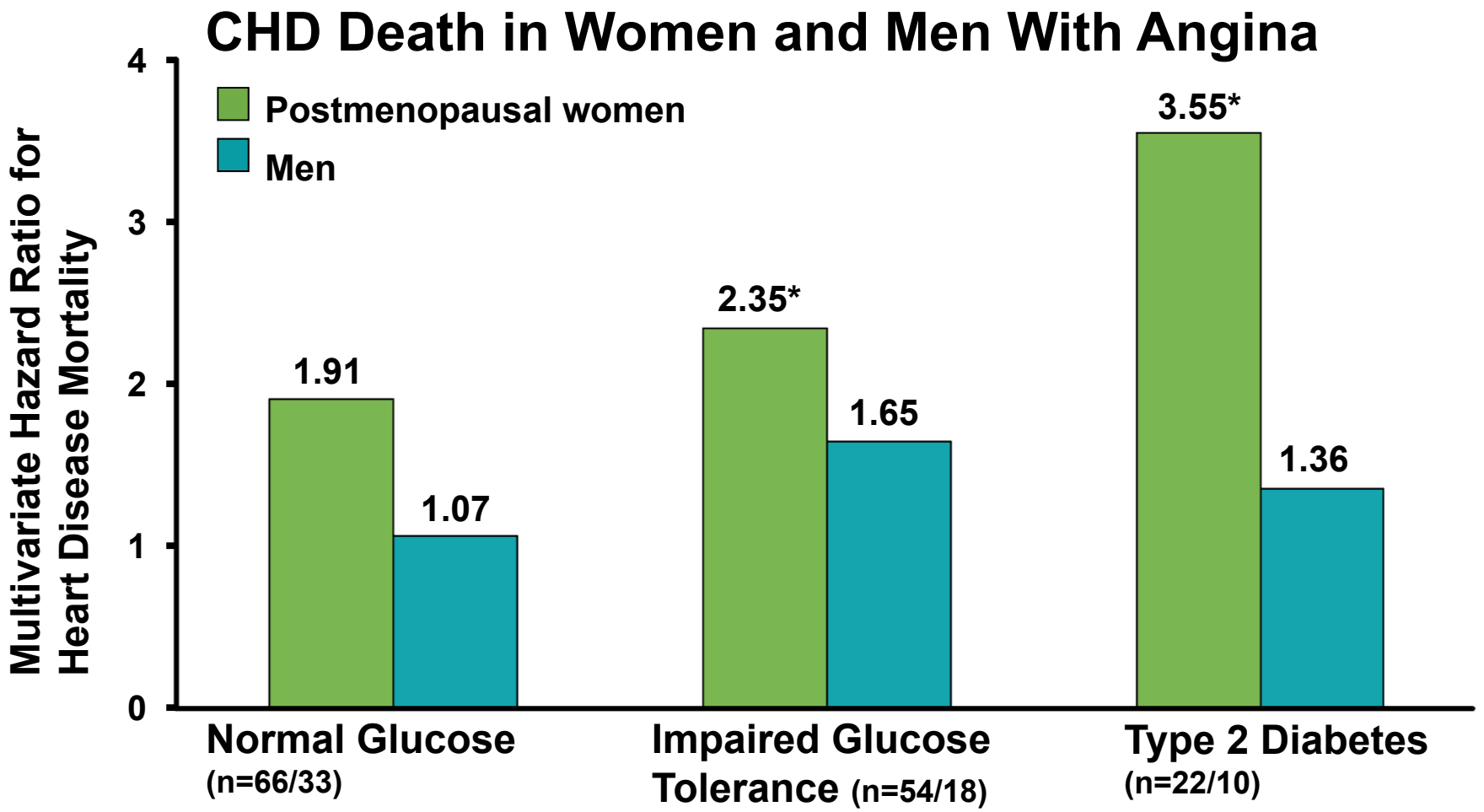
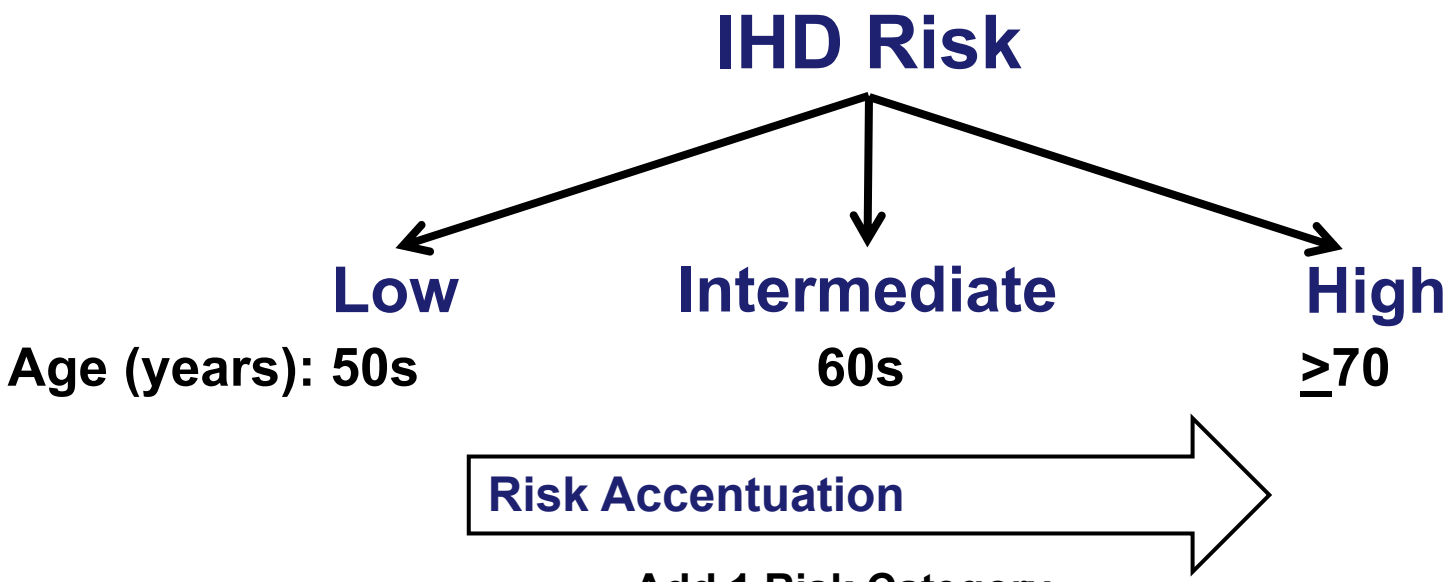
# Rancho Bernardo Study: Angina and Mortality by Diabetes Status




Men (n=822) and women (n=1184) 50-59 years of age at study entry. Average follow-up 13.2 years.
*$P$<0.05.

Carpiuc KT, et al. *J Womens Health.* 2010;19:1433-1439.

# Categorization of IHD Risk in Symptomatic Women




**Add 1 Risk Category**

- **Multiple cardiac risk factors**
- **Functional disability**
- **Extensive comorbidity**

**High Risk Equivalents**

- **Peripheral arterial disease**
- **Longstanding, poorly controlled diabetes**

Applies solely to women who present for evaluation of suspected IHD who have chest pain symptoms or some ischemic equivalent, including excessive dyspnea, with other cardiopulmonary comorbidities excluded.

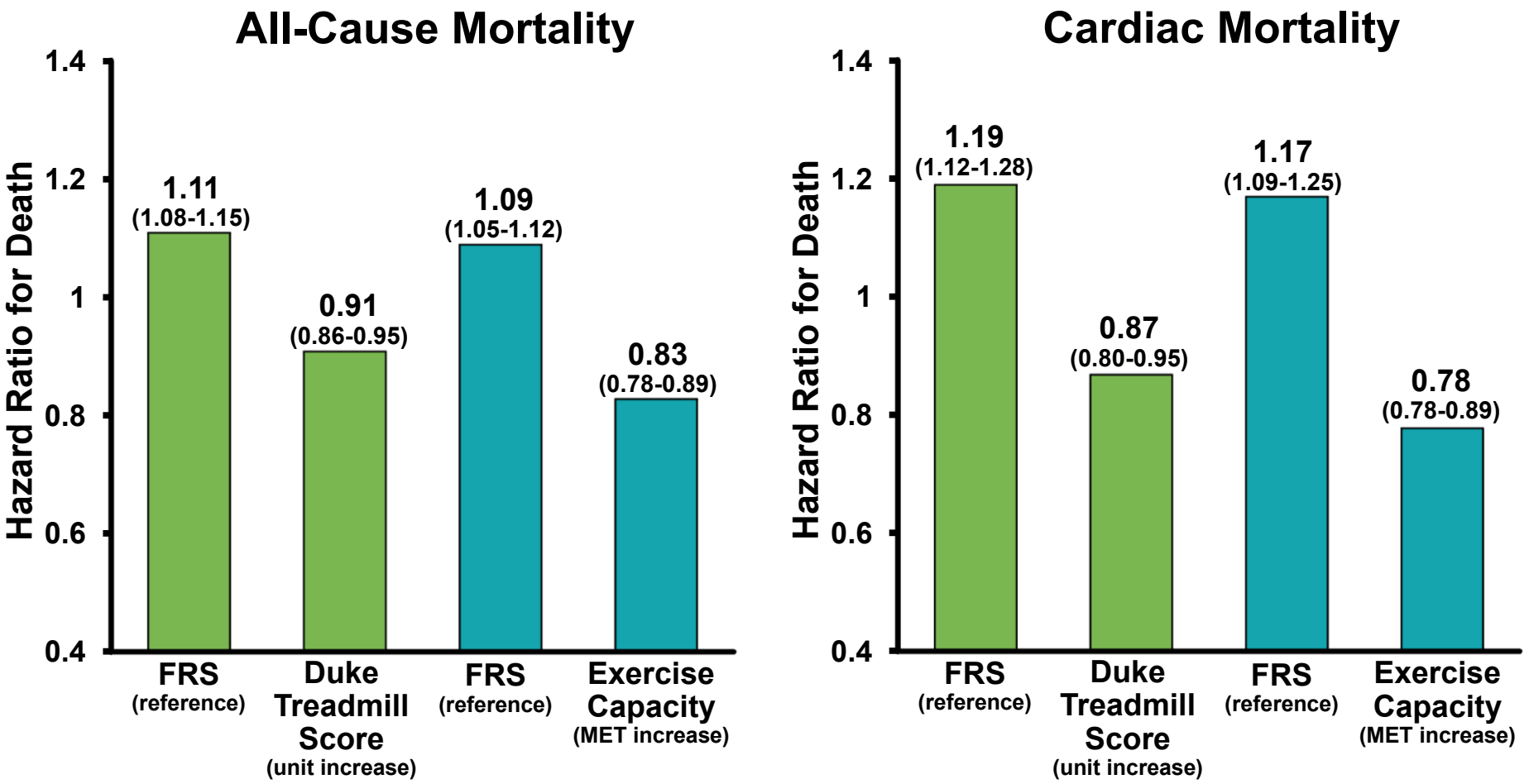
Mieres JH, et al. *Circulation.* 2014;130:350-379.

# Clinical Markers for High IHD Risk in Symptomatic Women

- Peripheral arterial disease
- Diabetes mellitus
  - 10-year history or poorly controlled in women >40 years of age
- Chronic obstructive lung disease
- Transient ischemic attack or cerebrovascular accident
- Chronic kidney disease
- Functional disability
  - Inability to perform activities of daily living or <5 estimated DASI METs

DASI METs: Duke Activity Status Index metabolic equivalents.
Applies solely to women who present for evaluation of suspected IHD who have chest pain symptoms or some ischemic equivalent, including excessive dyspnea, with other cardiopulmonary comorbidities excluded.
Mieres JH, et al. *Circulation.* 2014;130:350-379.

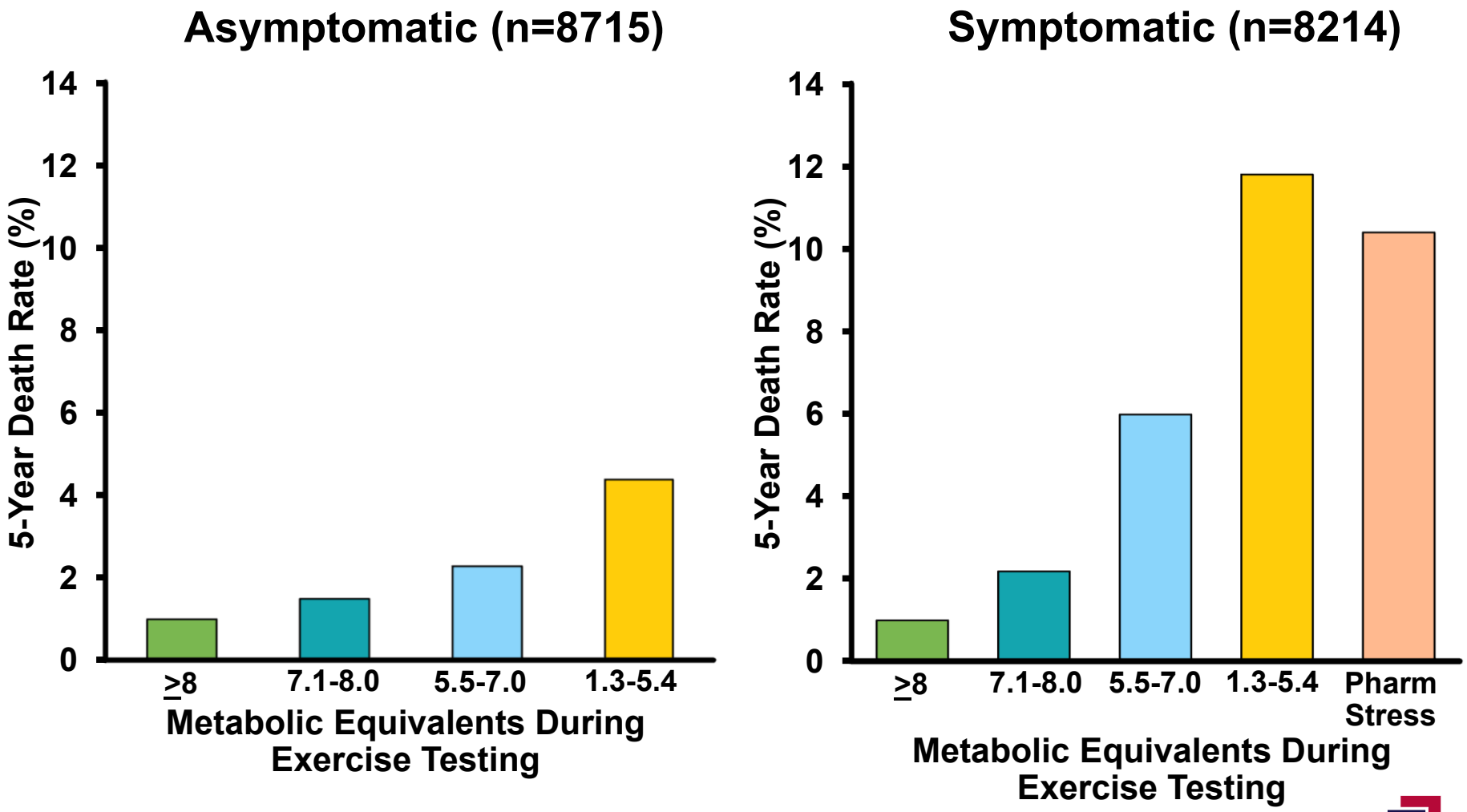
# St. James Women Take Heart Study: Exercise Capacity and Mortality in Asymptomatic Women




n=5636 asymptomatic women prospectively followed (1992-2000) for 9 years (171 deaths [3%]).
ST-segment changes and symptoms did not provide additional prognostic information.

Gulati M, et al. *Am J Cardiol.* 2005;96:369-375.

# Prognostic Value of Functional Capacity in Women: 5-Year Death Rates




Shaw LJ, et al. *J Am Coll Cardiol.* 2006;47(suppl):4S-20S.

# WISE Study and St. James Women Take Heart Project

- WISE Study
  - Symptomatic women referred for clinically indicated coronary angiography
  - Follow-up 5.2 years
- St. James Women Take Heart Project (WTH)
  - Asymptomatic, community-based women with no history of heart disease
  - Follow-up 10 years
- Compared cardiovascular events (MI, stroke, hospitalization for heart failure)

## Baseline Characteristics

| | | WISE | |
|---|---|---|---|
| | **WTH (n=1000)** | **Normal Coronary Arteries (n=318)** | **Non-obstructive CAD (n=222)** |
| BMI (kg/m$^2$) | 26.0 | 29.1* | 28.8* |
| History of CAD (%) | 43.6 | 66.2* | 64.5* |
| Hypertension (%) | 17.6 | 50.2* | 60.8* |
| Diabetes (%) | 5.0 | 14.2* | 19.8* |
| Metabolic syndrome (%) | 35.5 | 49.8 | 59.5* |
| Smoking history (%) | 17.2 | 45.6* | 57.7* |
| Postmenopausal (%) | 68.1 | 73.2* | 85.9* |
| Use of medications (%) | | | |
| Lipid lowering | 2.7 | 11.7* | 36.5* |
| Antihypertensives | 12.3 | 40.7* | 47.8* |
| Aspirin | 23.9 | 44.3* | 62.0* |

*$P$<0.001 versus WTH.
Normal coronary arteries (0% stenosis).
Nonobstructive CAD (1% to 49% stenosis).

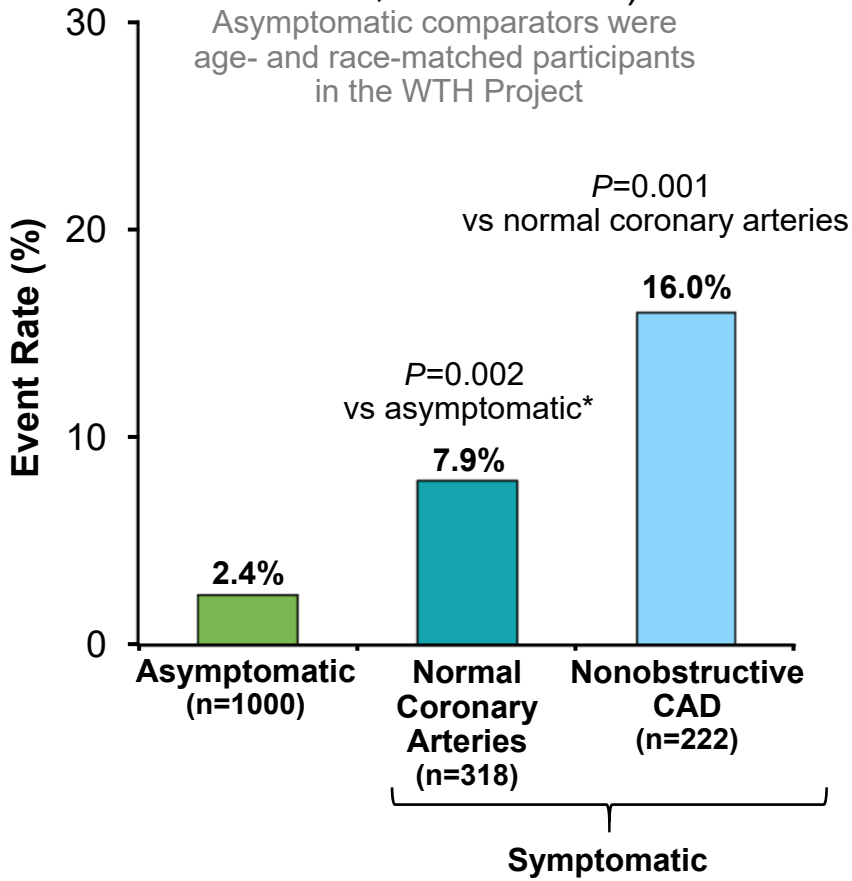
Gulati M, et al. *Arch Intern Med.* 2009;169:843-850.

# 5- and 10-Year CV Event Rates in Women With Symptomatic Ischemia and No Obstructive CAD Vs Asymptomatic Women

WISE – Women Take Heart (WTH) Collaboration

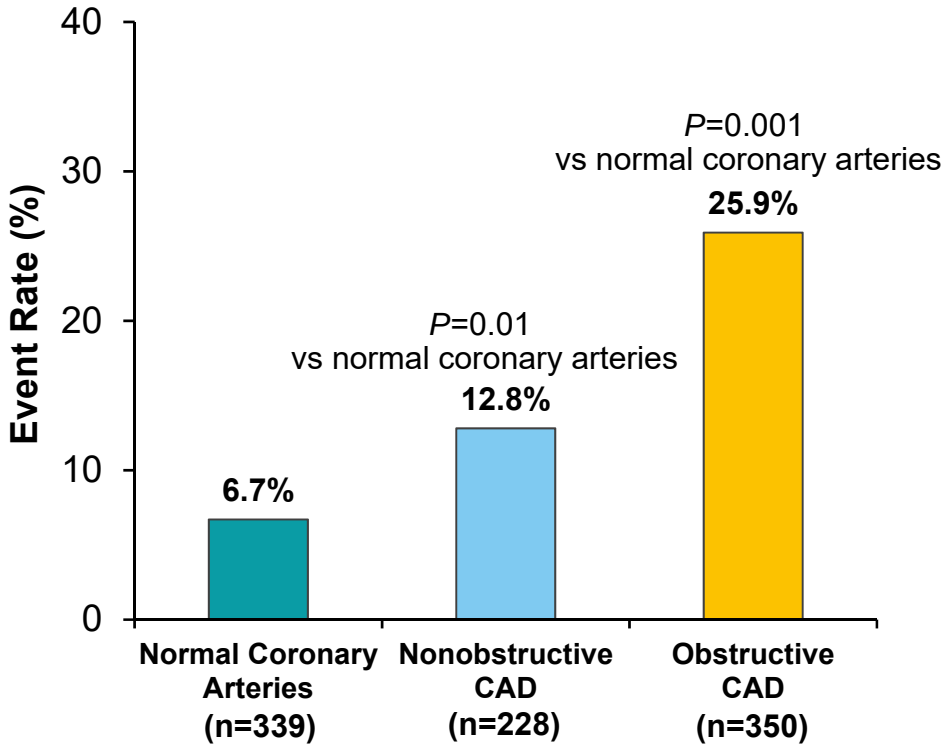
## 5-Year Event Rates vs Asymptomatic

(MI, hospitalization for heart failure, stroke, or CV death)




## 10-Year Event Rates

(MI or CV death)




* Driven mostly by hospitalization for heart failure and stroke.


Gulati M, et al. *Arch Intern Med.* 2009;169(9):843-850.

Sharaf B, et al. *Am Heart J.* 2013;166(1):134-141.

# Hamilton Health Sciences Angiography Registry: Class IV Angina and Severe CAD

- Prospective cohort (2000-2006)
  - Consecutive patients referred for coronary angiography (n=23,771)
    - Excluded: prior diagnosis of CAD
- Women versus men
  - More likely to have CCS class IV angina (56.9% versus 37.9%)
  - Less likely to have severe CAD (22.3% versus 36.5%)
- Conventional risk factors and CAD
  - Similar between women and men
- CCS class IV angina
  - Stronger predictor of severe CAD among older women than older men
    - Odds ratio: 1.82 (95% CI 1.61-2.04) versus 1.28 (95% CI 1.18-1.39); *P*<0.001

CCS: Canadian Cardiovascular Society.

Kreatsoulas C, et al. *J Intern Med.* 2010;268:66-74.

# Diagnostic Evaluation for Symptomatic Women Presenting With Suspected IHD

- Initial categorization of IHD risk should be used to define the index diagnostic procedure
  - Low IHD risk
    - Generally not candidates for further diagnostic testing
  - Low-intermediate or intermediate IHD risk
    - Exercise ECG (if functionally capable and normal or interpretable ECG)
  - Intermediate-high IHD risk with abnormal 12-lead rest ECG
    - May refer for stress imaging or CCTA
  - High IHD risk with stable symptoms
    - May refer for stress imaging for functional assessment of ischemic burden and guide to post-test, anti-ischemic therapeutic decision making

Mieres JH, et al. *Circulation.* 2014;130:350-379.

# PROMISE Trial:
## **Pro**spective **M**ulticenter **I**maging **S**tudy for **E**valuation of Chest Pain

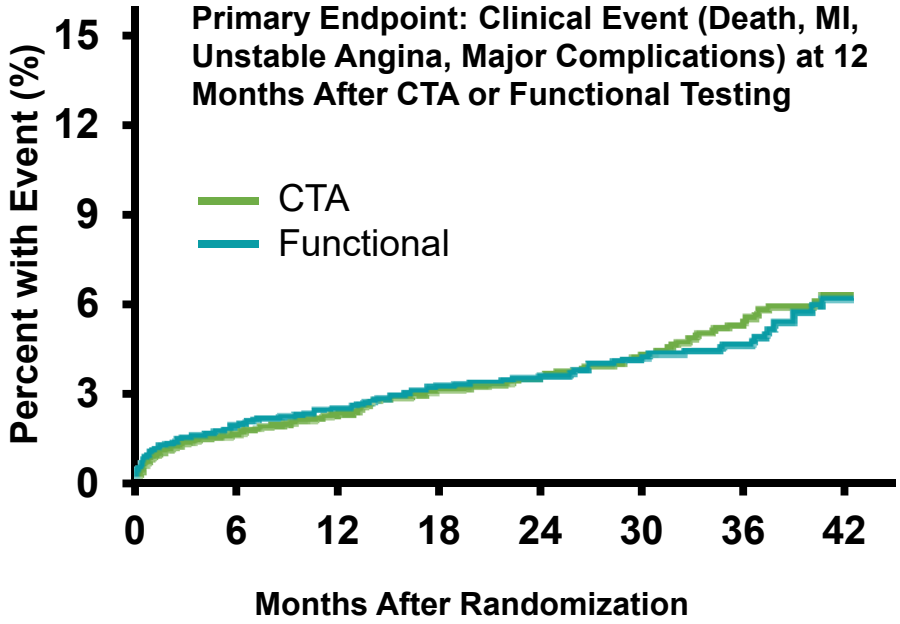
### Minimum 12-Month Study

**Patients (n=10,003)**
**Symptoms suspicious for CAD**
**(low- to intermediate-risk)**

→ **CTA Anatomic Testing (n=4,996)**

→ **Functional Testing (n=5,007)**

- Initial anatomic (CTA) and functional testing strategies showed similar clinical outcomes.
- Primary endpoint: HR, 1.04 (P=0.75)
- The CTA group had significantly fewer patients who had no obstructive CAD on catheterization (P=0.022)
- Cumulative cost differences were not significant at 90 days or 2 years





Douglas PS, et al. *New England Journal of Medicine*. 2015; 10.1056/NEJMoa1415516
Mark DB, et al. ACC Scientific Session, 2015 , San Diego, CA. Abstract 402-16

# WOMEN Study: ETT ± Myocardial Perfusion Imaging in Women With Suspected CAD

- Prospective study
  - Women with intermediate pre-test likelihood of CAD (n=772)
  - Interpretable ECG
  - ≥5 metabolic equivalents (Duke Activity Index)
- Randomized arms
  - Standard ECG ETT
  - Exercise myocardial perfusion imaging (MPI)
- Primary endpoint
  - Composite of cardiac death, nonfatal MI, or hospital admission for an acute coronary syndrome or heart failure

## Baseline Characteristics

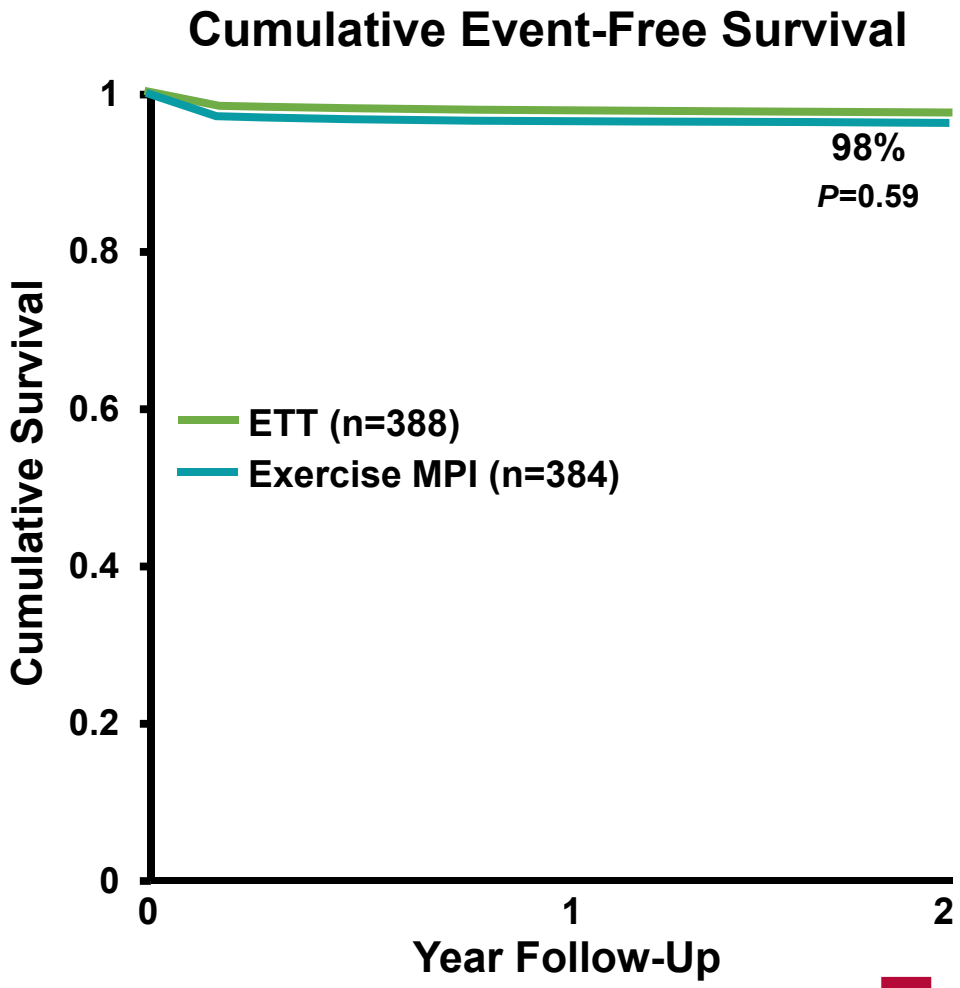
| | ETT (n=388) | Exercise MPI (n=384) |
|---|---|---|
| Age (years) | 63 | 62 |
| Postmenopausal (%) | 78.2 | 76.8 |
| BMI (kg/m$^2$) | 27.4 | 27.4 |
| Cardiac risk factors (%) | | |
| Family history | 47.3 | 45.8 |
| Current/past smoker | 48.8 | 42.4 |
| Hypertension | 55.2 | 52.0 |
| Hyperlipidemia | 50.0 | 53.7 |
| Diabetes mellitus | 12.6 | 14.2 |
| Presenting symptoms (%) | | |
| Chest pain | 89.4 | 90.0 |
| Typical angina | 61.2 | 59.8 |
| Atypical angina | 9.1 | 9.3 |
| Non-specific chest pain | 27.0 | 27.8 |
| Dyspnea | 53.5 | 48.3 |
| Depression (%) | 18.8 | 18.7 |

ETT: exercise treadmill test.
WOMEN: What is the Optimal Method for Ischemic Evaluation in Women.

Shaw LJ, et al. *Circulation.* 2011;124;11239-11249.

# WOMEN Study 2-Year MACE Rate: ETT Versus Exercise MPI

- No incremental benefit of an initial diagnostic strategy of exercise MPI versus ETT
  - Relative hazard for MACE
    - 1.3 (95% CI 0.5-3.5) for the exercise MPI versus ETT (*P*=0.59)
  - Index testing costs were higher for exercise MPI versus ETT (*P*<0.001)
  - Overall cumulative diagnostic cost savings
    - 48% with ETT versus exercise MPI (*P*<0.001)

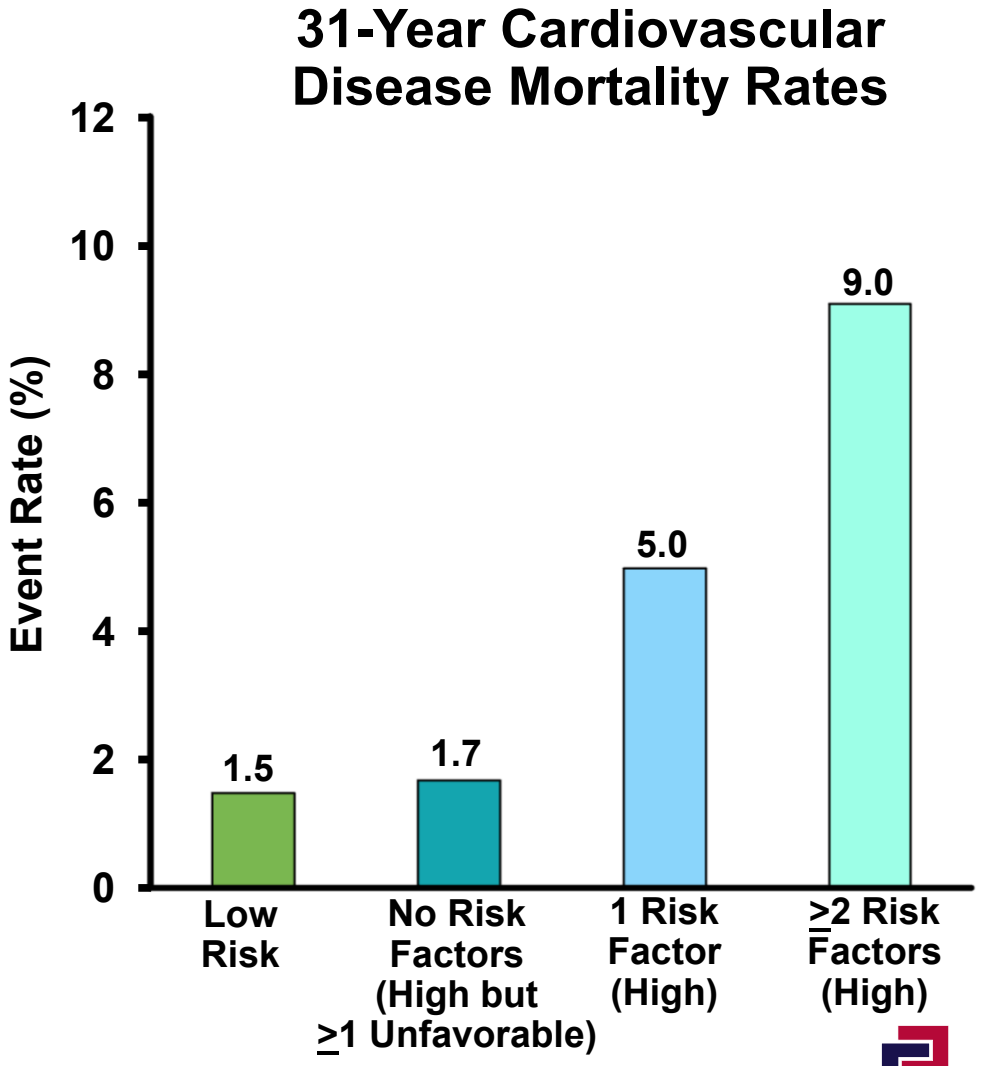



ETT: exercise treadmill test.
MPI: myocardial perfusion imaging.

Shaw LJ, et al. *Circulation.* 2011;124;11239-11249.

# SIHD Mortality and Traditional Cardiovascular Risk Factors

- Chicago Heart Association Detection Project in Industry
  - Prospective cohort study
- Women 18-39 years of age (n=7302)
  - No prior CHD or ECG abnormalities
- Mortality rates increased with increasing number of traditional risk factors




Mortality rates adjusted for age, race, minor ECG abnormalities, and education.

Daviglus ML, et al. *JAMA.* 2004;292:1588-1592.

# Coronary Calcium Scoring in Women

- Framingham risk score (FRE) and the NCEP ATP III guidelines
  - Fail to identify a sizable portion of asymptomatic women with low-risk FRE scores but with detectable and significant subclinical atherosclerosis
- MESA substudy
  - 84% of women with significant coronary artery calcium (>75$^{th}$ percentile) were classified as low risk by FRE
- Coronary artery calcium score may provide incremental value to FRE in identifying which asymptomatic women may benefit from targeted preventive measures

| CAC Score | Intermediate Risk FRE (%) | Low Risk FRE (%) |
|---|---|---|
| ≥100 (n=247) | 28 | 72 |
| ≥75$^{th}$ percentile for age and gender (n=489) | 16 | 84 |

Greenland P, et al. *J Am Coll Cardiol.* 2010;56:e50-e103.
Michos ED, et al. *Atherosclerosis.* 2006;184:201-206.

# Clinical Presentation of Angina

- Sensation of chest discomfort over or near sternum
  - Usually described as heaviness, pressure, squeezing, smothering, or choking, and only rarely as frank pain (Levine's sign)
  - Crescendo-decrescendo in nature, typically lasts 2 to 5 minutes
  - Can radiate to either shoulder and to both arms
    - May also arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium
  - Rarely localized below the umbilicus or above the mandible
- Precipitating factors
  - Exercise, cold environment, walking after a meal, emotional upset, fright, anger, coitus
- Relief with rest, nitroglycerin

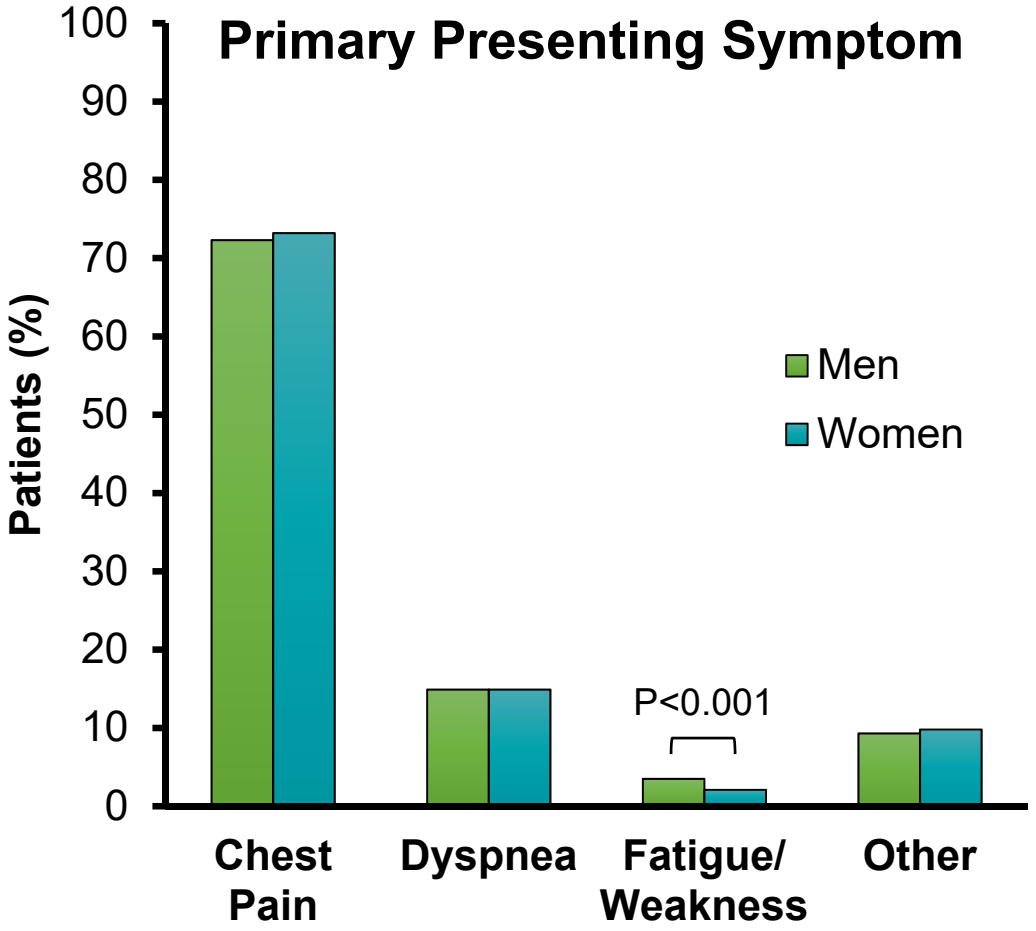
# Clinical Presentation of Angina

- Angina pectoris may be atypical in location and not strictly related to provoking factors, especially in women and diabetic patients
- Anginal “equivalents”
  - Symptoms of myocardial ischemia other than angina
    - Dyspnea, nausea, fatigue, and faintness
    - More common in the elderly and in diabetic patients

# Presenting Symptoms in Patients With Suspected CAD: Women and Men

## PROMISE Substudy

- PROMISE substudy
  - Randomized trial, entry criteria includes patients with stable chest pain
    - 5,270 women (age >65)
    - 4,733 men (age >55)
- Primary presenting symptom
  - Chest pain was equally common in men and women
  - Women were more likely to characterize their chest pain as "crushing/pressure/squeezing/tightness"
  - Men were more likely to characterize their chest pain as "aching/dull" and "burning/pins and needles"

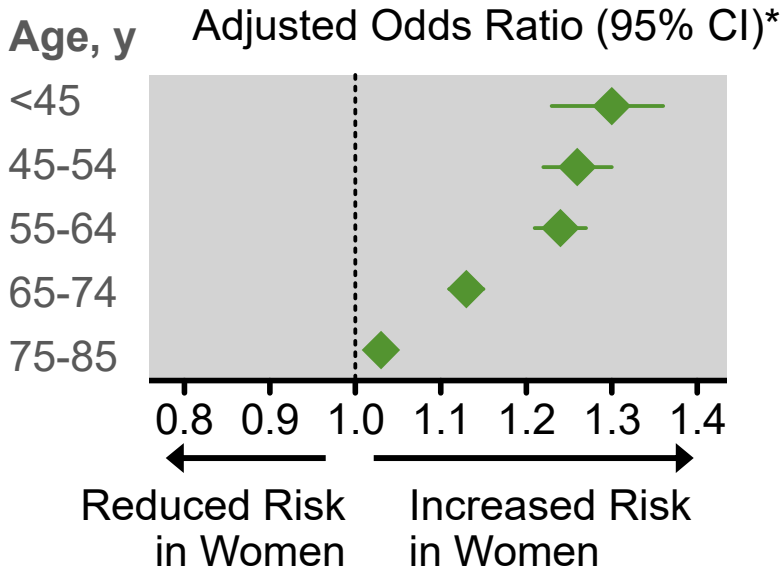



Hemal K, et al. Sex. *JACC Cardiovasc Imaging*. 2016; doi: 10.1016/j.jcmg.2016.02.001.

# Gender Differences by Age in Symptom Presentation in Patients with Acute MI

- NRMI (National Registry of Myocardial Infarction), observational study
  - Entry criterion: Diagnosis of MI by local health care providers
    - 481,581 women
    - 661,932 men
- Primary presenting symptom
  - Chest pain/discomfort was the most common symptom of MI for both women (58%) and men (69%)
  - However, women (especially younger women) were less likely to report chest pain/discomfort than men
    - This difference declined with increasing age

**Sex Differences in MI Presentation without Chest Pain/Discomfort**




*P<0.001 for all comparisons

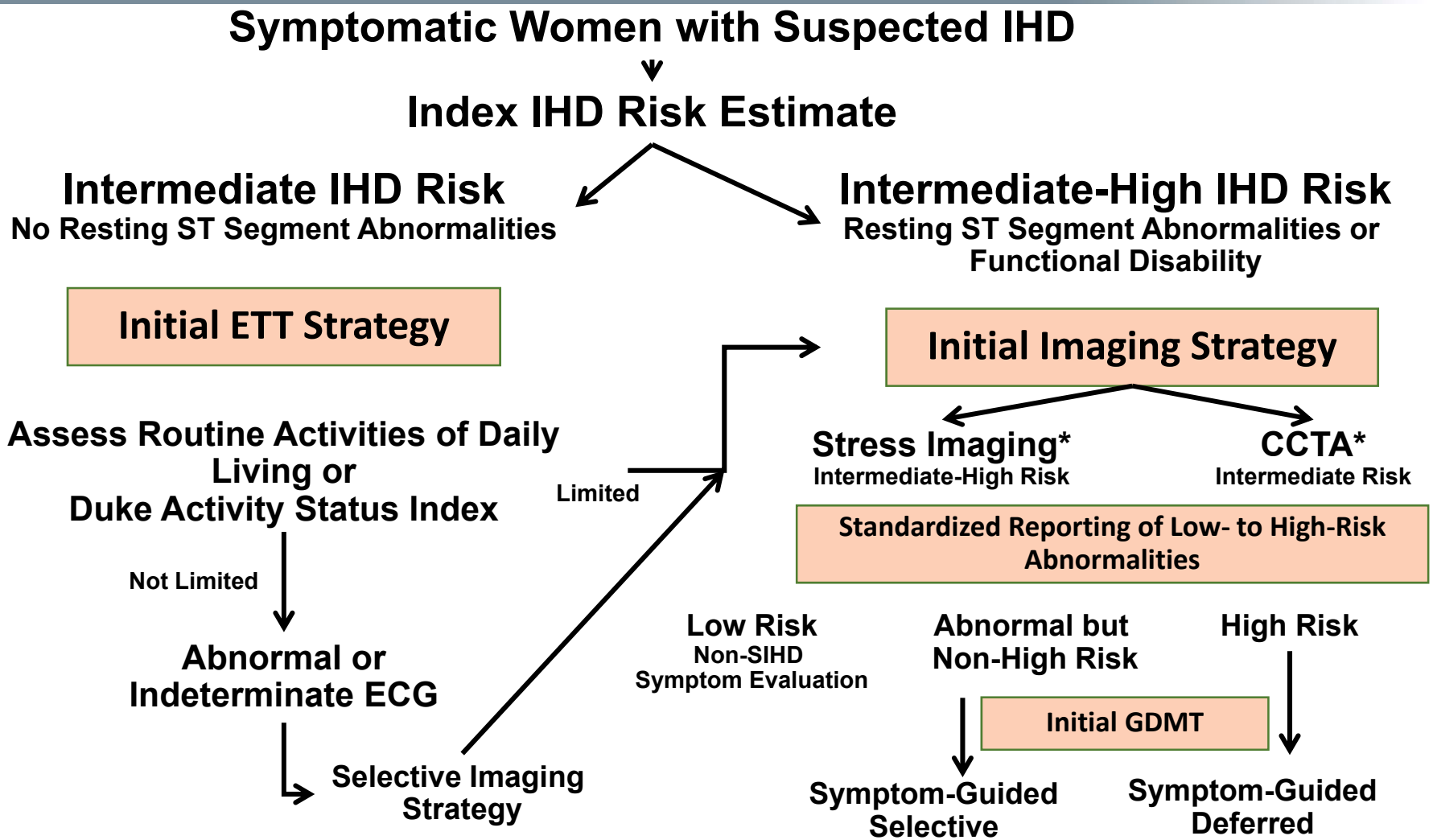
Canto JG, et al. *JAMA*. 2012; 307:813-22.

# Available Methods for Risk Stratification in Patients With Coronary Heart Disease

- Clinical parameters
  - Including laboratory data
- ECG
- Chest x-ray
- Noninvasive testing
  - Resting left ventricular function
  - Exercise test
  - Stress imaging
- Anatomic imaging
  - Coronary calcium scoring
  - Coronary CT angiography
  - Coronary angiography

# Diagnostic Evaluation of Women Presenting with Suspected IHD and Intermediate to High IHD Risk

AHA Consensus Statement




CCTA: coronary CT angiography; ETT, exercise treadmill testing; GDMT, guideline-directed medical therapy.

Mieres JH, et al. Circulation 2014;130:350-379.

***In younger women, the choice of a test should be based on concerns about radiation exposure and increased projected cancer risk and not higher reported accuracy *(I-C)*.**

# Typical Radiation Exposure From Rest-Stress MPI, CCTA, and Angiography in Women

| | Effective Dose (mSv) |
|---|---|
| Annual background exposure | ~3 |
| Invasive coronary angiography | ~7 |
| Rest-stress MPI SPECT | |
| Technetium Tc 99m | ~11 |
| Stress-only MPI SPECT | ~3 |
| Dual-isotope MPI SPECT | 22 |
| Rest-stress MPI PET | |
| Rubidium Rb 82 | ~3 |
| Nitrogen N 13 | ~2 |
| CCTA | |
| Overall | ~10 |
| With dose-reduction techniques | <2-5 |
| Coronary artery calcium scoring | 2 |

Mieres JH, et al. *Circulation.* 2014;130:350-379.

# ECG and Non-ECG Variables During Exercise Testing Associated With an Elevated IHD Risk in Women

| Stress Testing Variables | Method of Assessment | High-Risk Value |
|---|---|---|
| Exercise capacity | Estimated by ETT protocol (speed and grade) | <5 METs<br><100% age-predicted<br>METs = 14.7−(0.13 × age) |
| Heart rate recovery | Difference between peak heart rate and heat rate at 1 minute of recovery | ≤12 bpm after 1-minute recovery (upright cool-down period) |
| ST-segment changes | Difference in ST segment Δs (at 60 ms after the J point) between peak exercise (or recovery) and rest ECG | ST-segment depression ≥2 mm, ≥1 mm at <5 METs, or >5 min into recovery<br>ST-segment elevation ≥2 mm (not in q-wave lead or aVR) |
| Duke treadmill score | Exercise time−(5×STΔ)−(4×angina index) | High-risk score: ≤ −11 |
| BP response | Assessment of BP response to exercise, change in SBP from rest to peak exercise | Decrease in SBP >10 mm Hg from rest |
| Ventricular arrhythmias | | Persistent ventricular tachycardia/fibrillation |

BP: blood pressure; ETT: exercise treadmill testing; METs: metabolic equivalents; SBP: systolic blood pressure.

Mieres JH, et al. *Circulation.* 2014;130:350-379.

# Markers of High IHD Risk From Stress Imaging in Women

| | High-Risk Value |
|---|---|
| Stress echocardiography | Rest left ventricular ejection fraction: ≤40%<br>Extensive rest wall-motion abnormalities or extensive ischemia (≥4 to 5 left ventricle segments)<br>Right ventricular ischemia<br>Increase in end-systolic size with stress<br>Right ventricular ischemia<br>Left ventricular ejection fraction decrease with stress |
| Stress MPI | Summed stress score >8<br>≥10% of the abnormal myocardium at stress<br>≥10% of the ischemic myocardium<br>Left ventricular dilation<br>Peak stress or poststress left ventricular ejection fraction ≤45% |
| Stress CMR | Rest or stress left ventricular ejection fraction ≤40%<br>≥3 abnormal or ischemic CMR MPI segments<br>≥3 abnormal or ischemic CMR wall-motion segments |

MPI: myocardial perfusion imaging; CMR: cardiac magnetic resonance.

Mieres JH, et al. *Circulation.* 2014;130:350-379.

# Markers of High IHD Risk in Women for CCTA

| | High-Risk Value |
|---|---|
| CCTA | Coronary artery calcium ≥400<br>Proximal LAD stenosis ≥70%<br>2- or 3-vessel coronary artery disease<br>Left main stenosis ≥50%<br>3-vessel nonobstructive coronary artery disease |

CCTA: coronary computed tomography angiography; LAD: left anterior descending coronary artery.

Mieres JH, et al. *Circulation.* 2014;130:350-379.

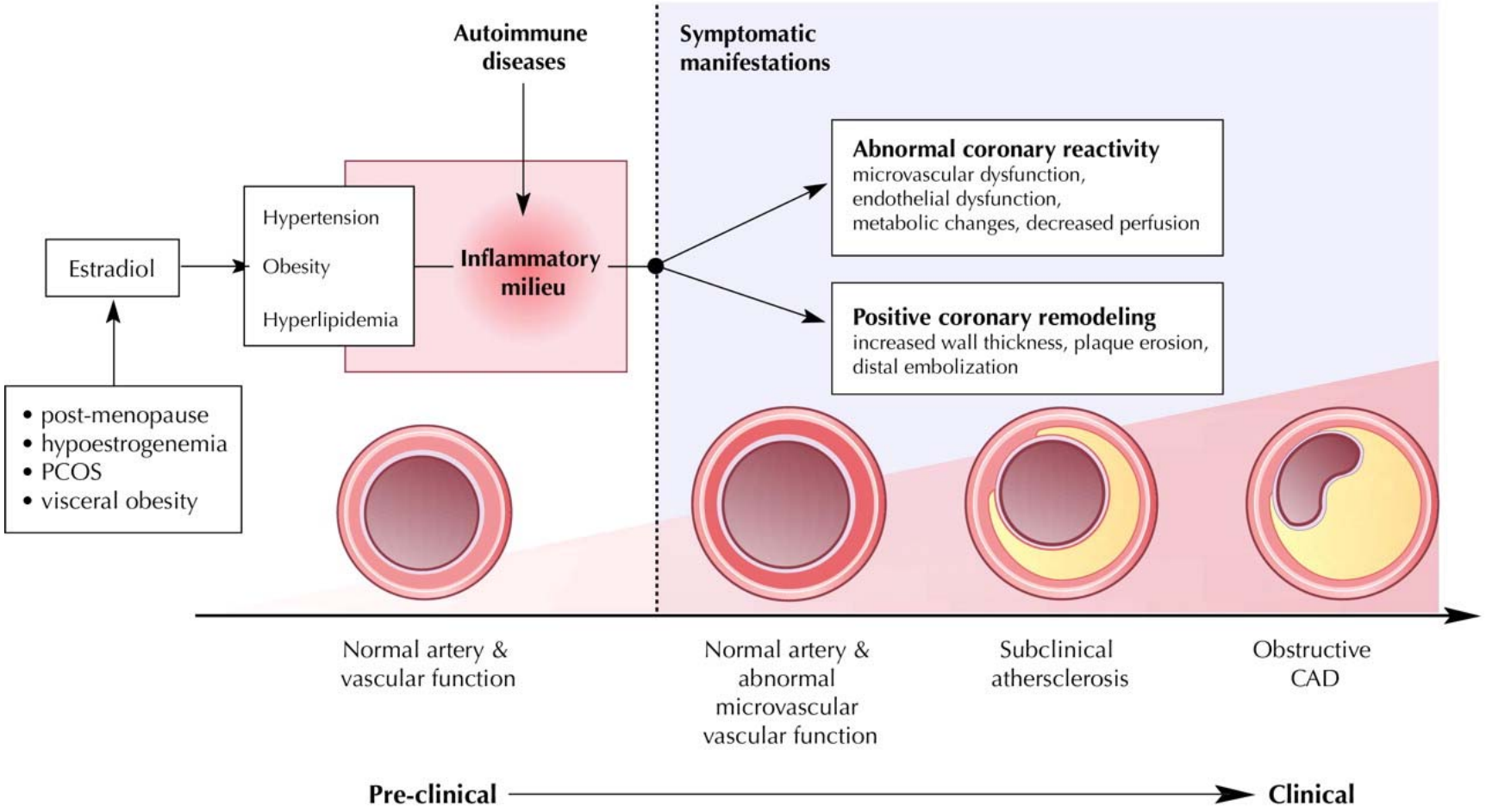
# Summary: Indications for Stress Testing/Imaging or CCTA in Women With Ischemic Symptoms

| | Exercise Status | | ECG Interpretable | | Pretest Probability Of IHD | | |
|---|---|---|---|---|---|---|---|
| | Able | Unable | Yes | No | Low | Intermediate | High |
| Exercise | | | | | | | |
| ECG | ✓ | | ✓ | | | ✓ | |
| MPI | ✓ | | | ✓ | | ✓ | ✓ |
| ECHO | ✓ | | | ✓ | | ✓ | ✓ |
| CCTA | ✓ | | | ✓ | | ✓ | |
| Pharmacologic | | | | | | | |
| Stress MPI | | ✓ | Any | | | ✓ | ✓ |
| Stress ECHO | | ✓ | Any | | | ✓ | ✓ |
| Stress CMR | | ✓ | Any | | | ✓ | ✓ |
| CCTA | | ✓ | | ✓ | | ✓ | |

MPI: myocardial perfusion imaging; ECHO: echocardiography; CCTA: coronary computed tomography angiography; CMR: cardiac magnetic resonance.

Mieres JH, et al. *Circulation.* 2014;130:350-379.

# Overarching Working Model of Ischemic Heart Disease Pathophysiology in Women




**Progressive manifestations of ischemic heart disease**

Shaw LJ, et al. *J Am Coll Cardiol.* 2009;54:1561-1571.

# Ancillary Substudy of WISE: Coronary Micro- and Macrovascular Measures in Women (1)

- Women with suspected ischemia without obstructive CAD (n=100)
  - Age: 55.1 years
  - <50% angiographic stenosis
  - BMI: 32.2 kg/m$^2$
- Coronary flow reserve measurements (adenosine)
- IVUS of left coronary segment

**Baseline Characteristics of Substudy Participants**

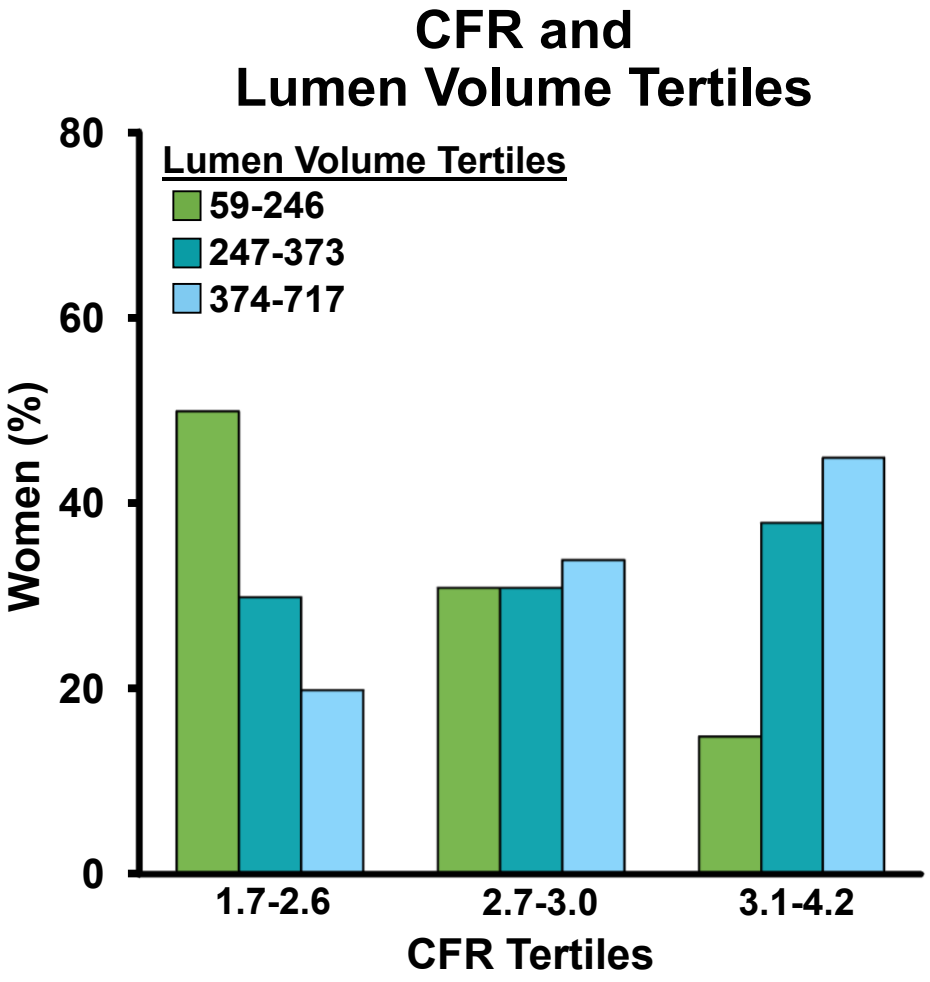
| | Women (n=100) |
|---|---|
| History of (%) | |
| Hypertension | 35.2 |
| Diabetes | 16.3 |
| Dyslipidemia | 42.4 |
| Family history with CAD | 44.6 |
| Menopause | 81.8 |
| Oral contraceptive use | 53.3 |
| Hormone replacement | 48.4 |
| Statin use | 33.0 |
| Smoking | |
| Never | 56.0 |
| Former | 29.7 |
| Current | 14.3 |

IVUS: intravascular ultrasound.

Anderson RD, et al. *J Am Coll Cardiol.* 2011;57(suppl A):e1150. Abstract 323.

# Ancillary Substudy of WISE: Coronary Micro- and Macrovascular Measures in Women (2)

- IVUS measures correlating with CFR
  - Lumen volume (*P*=0.004)
  - % atheroma volume (*P*=0.049)
  - Maximal luminal CSA (*P*=0.02)
  - Plaque CSA (*P*=0.008)
- Associations
  - Lower CFR: less lumen volume
  - Higher CFR: greater lumen volume
- IVUS predicts microvascular bed size in women without obstructive CAD




CFR: coronary flow reserve; CSA: cross-sectional area; IVUS: intravascular ultrasound.

Anderson RD, et al. *J Am Coll Cardiol.* 2011;57(suppl A):e1150. Abstract 323.

# Gender Effects on Coronary Microvascular Dysfunction

- Men and women referred for rest/stress Rb-82 PET testing (no overt CAD) (n=1218)
  - Normal MPI (summed stress score <3)
  - No coronary artery calcification
- Rest/stress myocardial blood flow was used to calculate coronary flow reserve
  - Microvascular dysfunction defined as coronary flow reserve <2.0
- Similar baseline medication use except diuretics: women 33%, men 24%; P=0.001

**Baseline Characteristics**

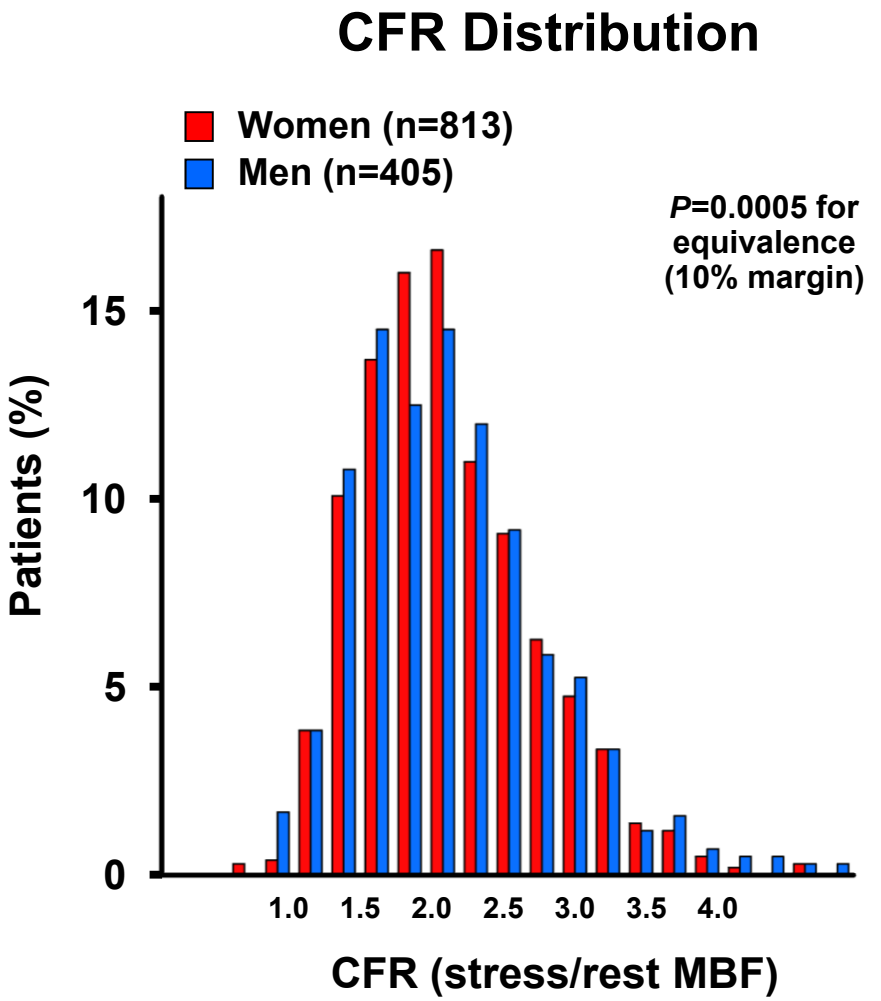
| | Women (n=813) | Men (n=405) | P value |
|---|---|---|---|
| Mean Age (years) | 62.3 | 61.2 | |
| Hispanic (%) | 18.7 | 10.4 | 0.0002 |
| Tobacco use (%) | 8.4† | 13.1 | 0.01 |
| Hypertension (%) | 75.6 | 68.9 | 0.01 |
| BMI ≥30 kg/m$^2$ (%) | 51.7 | 42.5 | 0.003 |
| Dyslipidemia (%) | 55.5 | 52.3 | |
| Diabetes mellitus (%) | 29.4 | 30 | |
| Family history of CAD (%) | 28 | 23.2 | |
| Chest pain (%) | 60.0 | 41.0 | <0.0001 |
| Dyspnea (%) | 30.1 | 24 | 0.03 |
| Rest LVEF (%) | 65 (59-70) | 59 (53-63) | <0.0001 |

LVEF: left ventricular ejection fraction.

Murthy VL, et al. Circulation 2014;129:2518-2527.

# Gender Effects on Coronary Microvascular Dysfunction:
## Coronary Flow Reserve in Men and Women

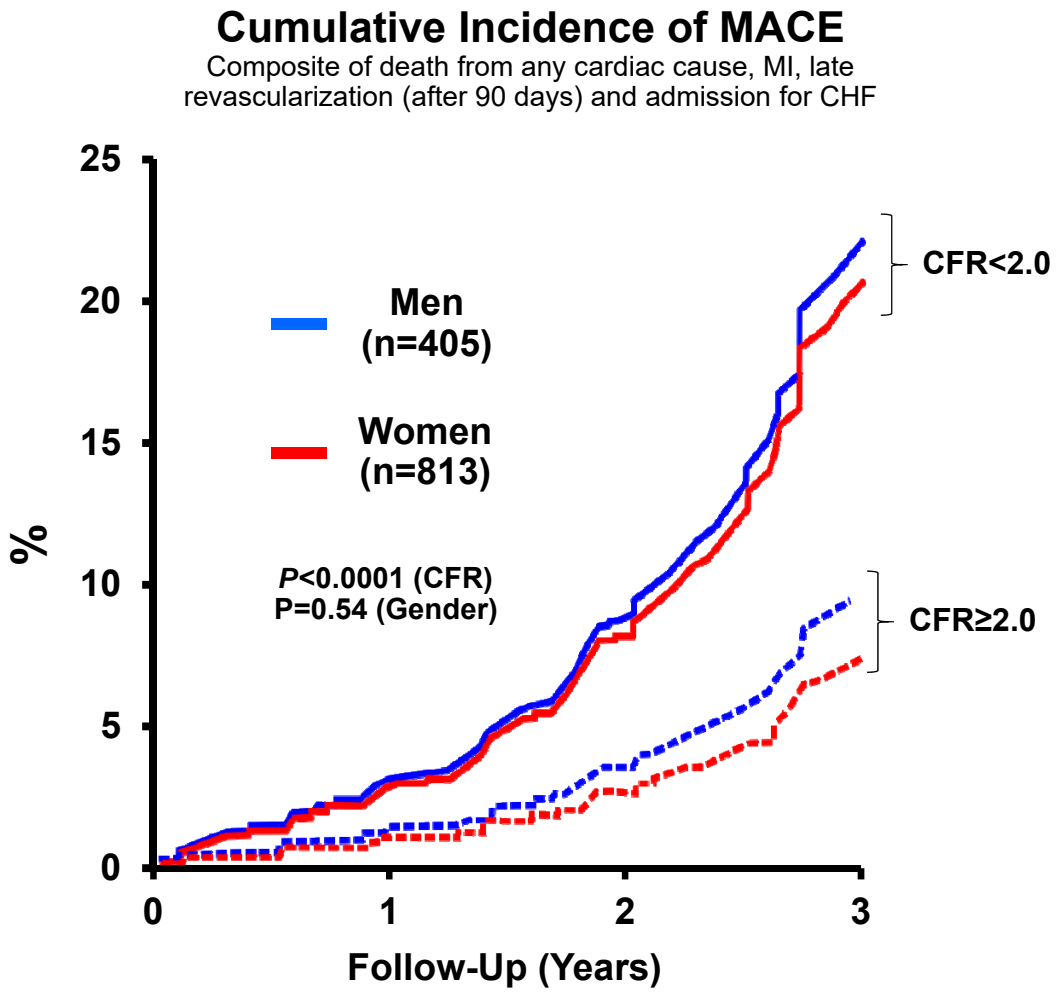
- Impaired CFR (<2.0) common in women and men regardless of symptoms (53.5% versus 50.9%; *P*=0.0002 for equivalence)
- Independent predictors of corrected CFR:
  - Age, body-mass index, hypertension, diabetes mellitus, dialysis, evaluation for preoperative risk stratification, and LVEF
  - Sex and race were not significant predictors of CFR

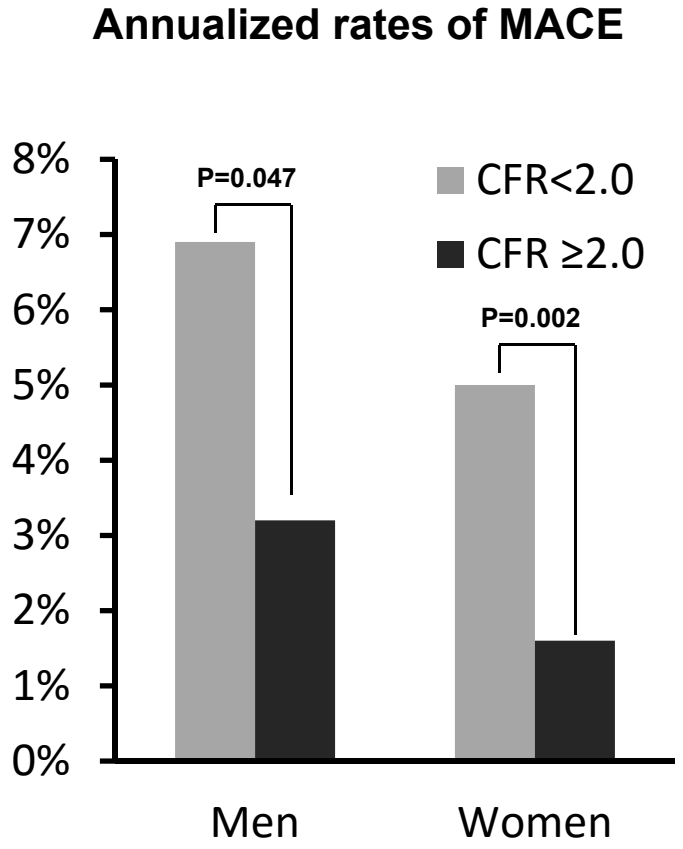



CFR: coronary flow reserve; MBF: myocardial blood flow.

Murthy VL, et al. Circulation 2014;129:2518-2527.

# Gender Effects on Coronary Microvascular Dysfunction:
## Adjusted Rates of MACE According to CFR and Gender




**Adjusted for modified Duke risk score and rest LVEF**

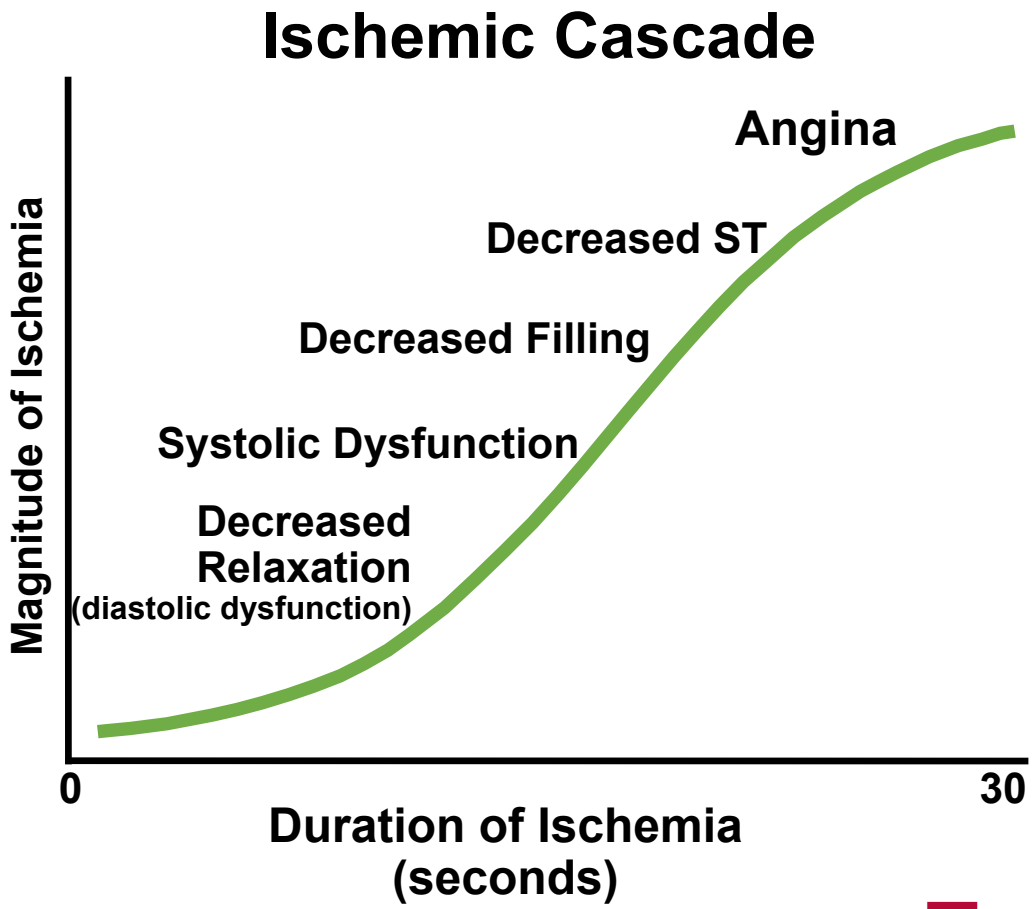
Murthy VL, et al. Circulation 2014;129:2518-2527.

# Program Overview

| | |
|---|---|
| 1 | Gender-related epidemiologic patterns in SIHD |
| 2 | Risk and symptom assessment in women |
| **3** | **Pathophysiologic and pathoanatomic gender differences** |
| 4 | Prognosis in women with SIHD |
| 5 | Clinical considerations in the management of SIHD in women |

# Abnormalities Evolving During Myocardial Ischemia

- Symptoms occur at end of ischemic cascade
- Approximately 50% of patients with angina also experience episodes of asymptomatic (silent) ischemia
- Many episodes of ischemia never become painful




Morrow DA, et al. In: *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th Edition.* 2012.

# Ischemic Heart Disease in Women: Differences From Men

## Structural Features (macro- and microvessels)

- Smaller size vessels
- Increased stiffness (fibrosis, remodeling, etc)
- More diffuse disease
- More plaque erosion versus rupture
- Microemboli, rarefaction (drop out), disarray, etc

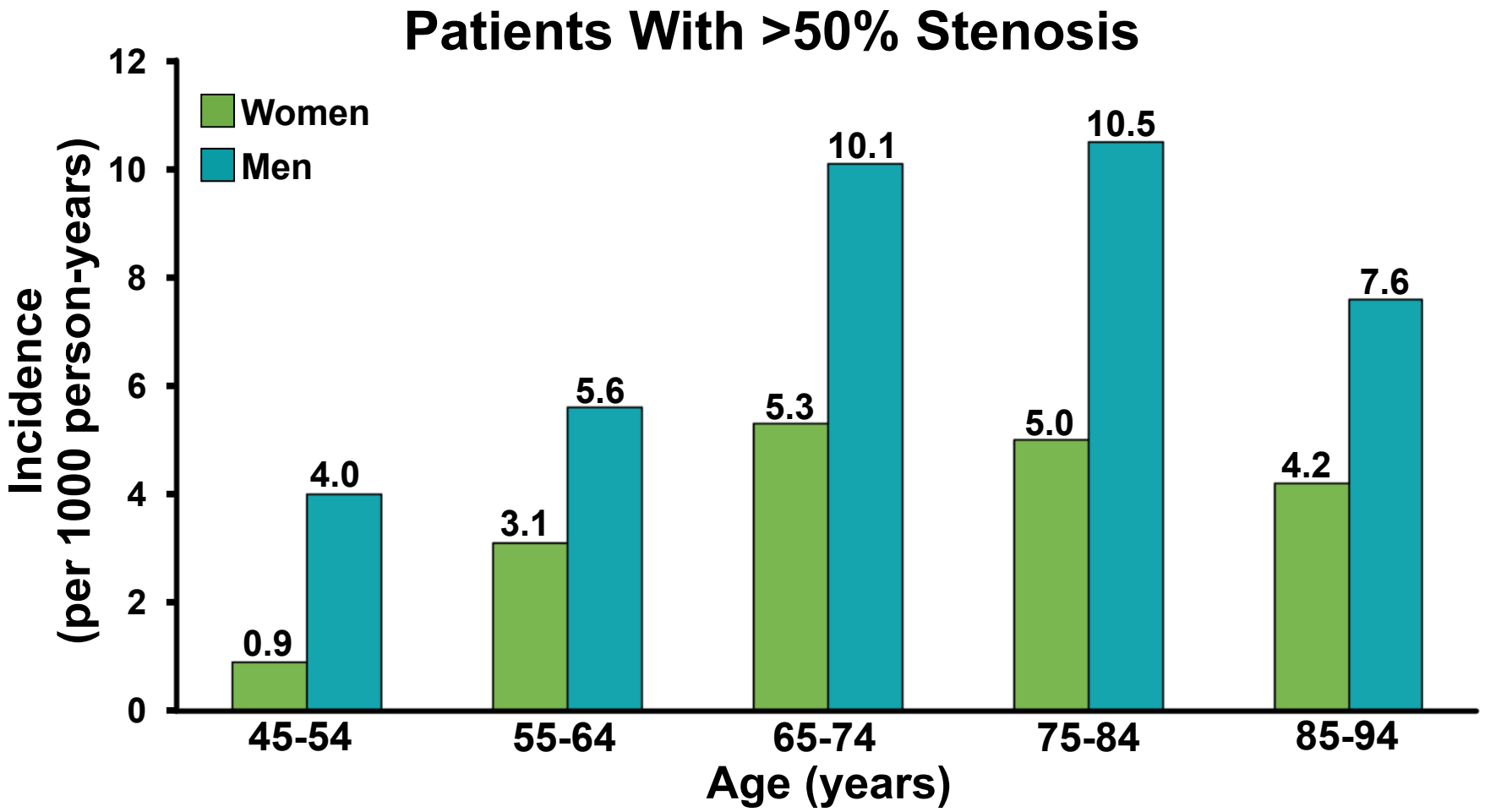
## Functional Features (macro- and microvessels)

- Endothelial dysfunction
- Smooth muscle dysfunction (Raynaud's, migraine, coronary artery spasm)
- Inflammation
  - Plasma markers
  - Vasculitis (Takayasu's, rheumatoid, SLE, CNSV, giant cell, etc)

CNSV, central nervous system vasculitis; SLE, systemic lupus erythematosus

Wenger NK. *Curr Cardiol Rep.* 2010;12:307:314.
Kramer MC, et al. *J Am Coll Cardiol.* 2010;55:122-132.
Shaw LJ, et al. *J Am Coll Cardiol.* 2009;54:1561-1575.

# Gender Differences in Obstructive CAD on Elective Diagnostic Angiography

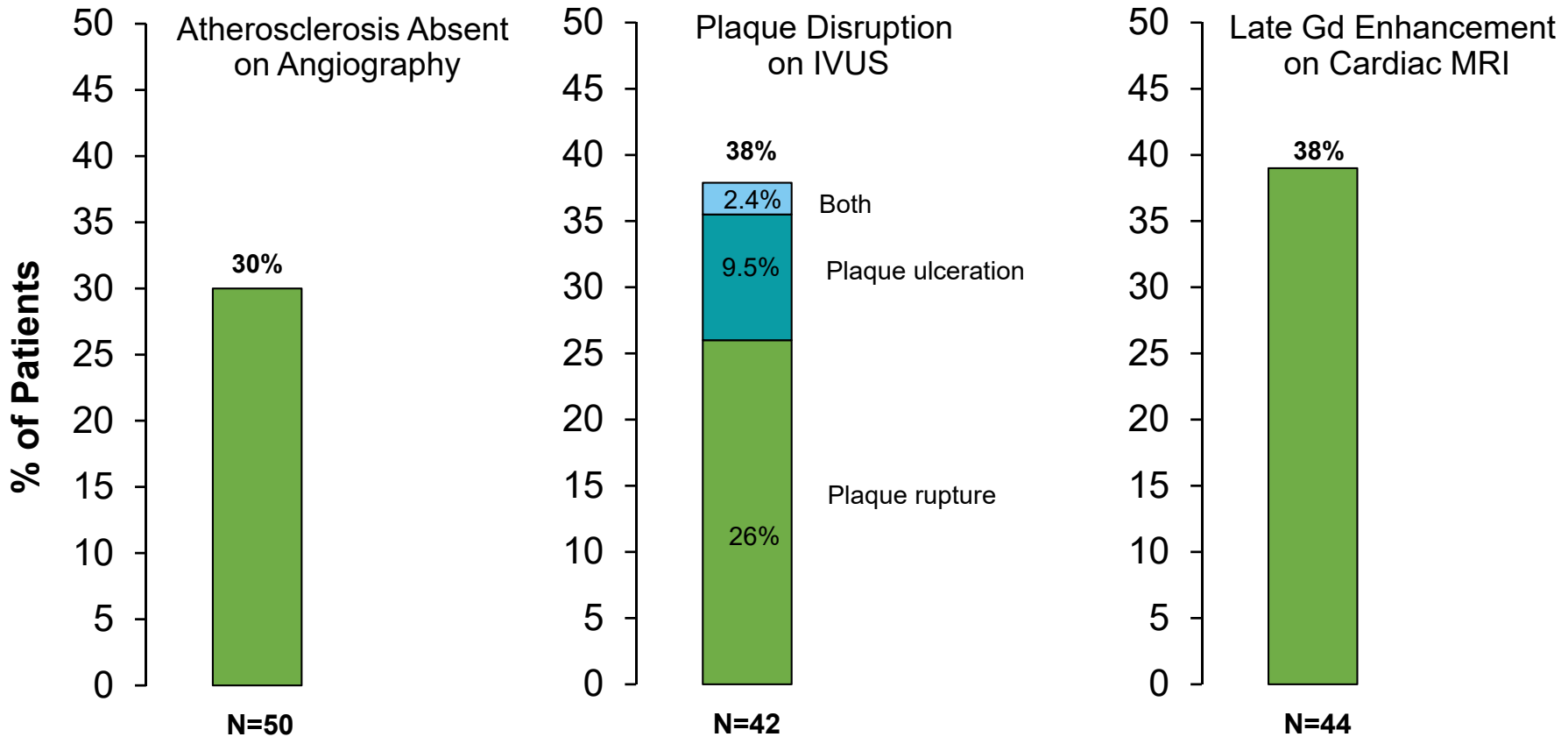



Angina: uncomplicated based on physician interview of patient.
Rate for women 45-54 years of age considered unreliable.

Go AS, et al. *Circulation.* 2014;129:e28-e292.

# Plaque Rupture and Ulceration Are Common Mechanisms of MI in Women Without Obstructive CAD

**Evaluation of Women (N=50) With MI but <50% Stenosis on Angiography**




Gd, gadolinium; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging.

Reynolds HR, et al. *Circulation.* 2011;124(13):1414-1425.

# Evolving Understanding of Angina

- Typical versus atypical angina diagnosis by gender
  - 3225 patients referred to Duke University for evaluation of chest pain with median of 5 episodes of chest pain weekly

| | Male (n=2249) | Female (n=967) |
|---|---|---|
| Typical angina (%) | 55 | 28 |
| Atypical angina (%) | 34* | 53 |

- Angina equivalents
  - Fatigue
  - Lightheadedness
  - Weakness
  - Diaphoresis
  - Shortness of breath
  - Nausea
  - Indigestion
- Coronary patients with angina rate their quality of life lower than those without angina

*$P$<0.05 for comparison across gender. No angina: males (11%) and females (19%).

Abrams J. *N Engl J Med.* 2005;352:2524-2533; Alexander KP, et al. *J Am Coll Cardiol.* 1998;32:1657-1664; Fang JC. *Braunwald's Heart Disease. 9th Edition*. 2012. Bandu I, et al. *Chest.* 1994;105:1009-1012; Stern S. *Circulation.* 2002;106:1906-1908; Marquis P, et al. *Eur Heart J*. 1995;16:1554-1560.

# Angina Symptoms in Men and Women With Stable CAD

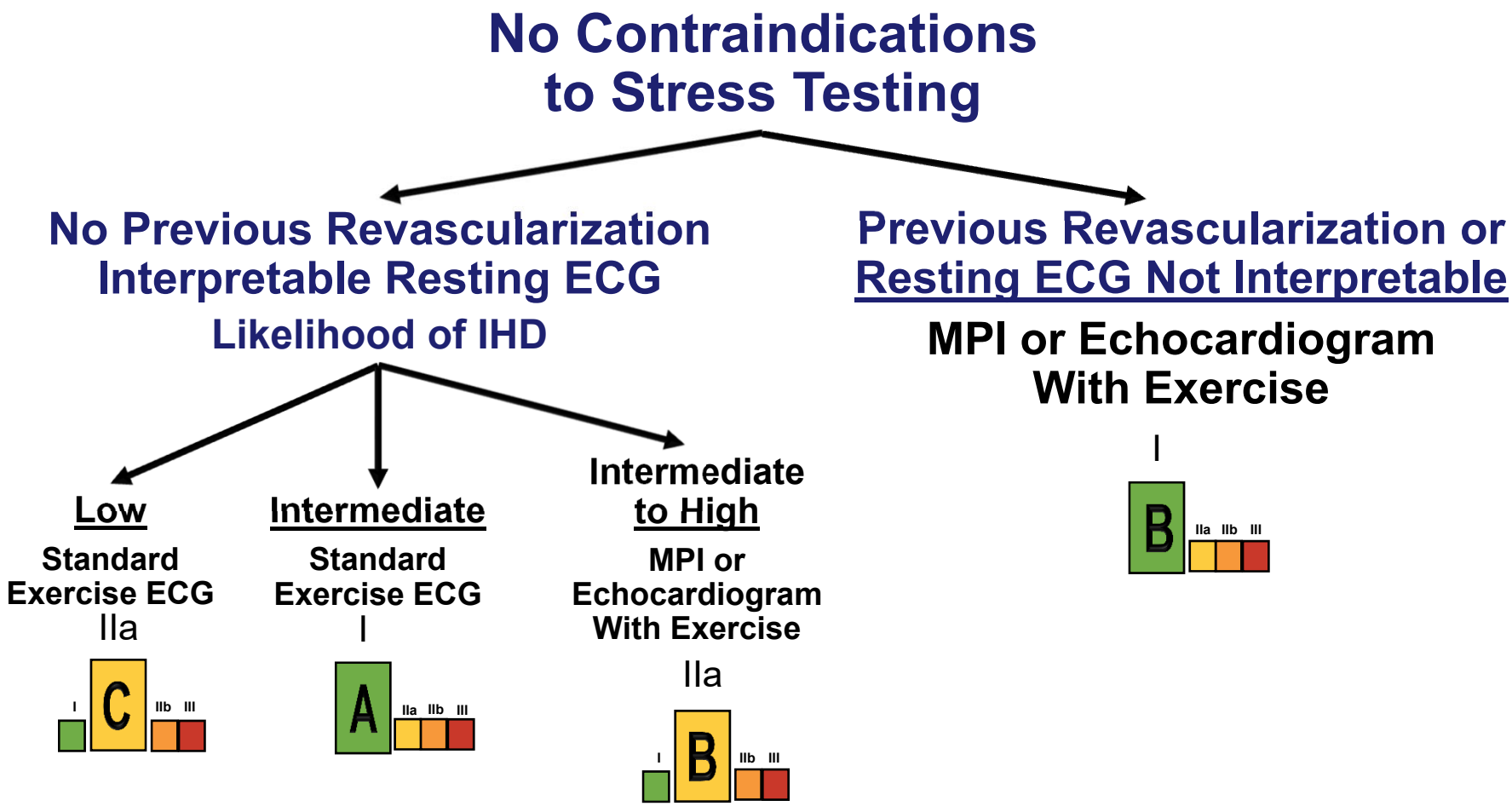
- Prospective study
  - Men and women with angina and evidence of ischemia during exercise on myocardial perfusion imaging (n=132)
- Pain intensity
  - Women rated angina pain as more intense
- Pain description
  - Women more often described pain as throbbing, sharp, hot-burning, fearful, pressing
- Pain location
  - Women more often reported pain/discomfort in the neck area

| | Women (n=94) | Men (n=38) |
|---|---|---|
| Pain intensity (MPQ-SF scales) | | |
| Sensory | 9.49 | 6.16 |
| Affective | 2.63 | 1.54 |
| Present pain intensity | 2.29 | 1.85 |
| Number of descriptors | 5.90 | 4.30 |
| Words describing pain (%) | | |
| Throbbing | 50 | 30.4 |
| Sharp | 34.2* | 13 |
| Hot-burning | 47.4* | 26.1 |
| Fearful | 28.9 | 14.1 |
| Pressing | 57.9 | 39.1 |
| Pain location (%) | | |
| Neck/throat area | 47* | 25 |
| Right upper chest/ shoulder area | 13 | 29 |
| Right middle chest | 10 | 25 |

*$P<0.05$ versus men (adjusted).

D'Antono B, et al. *Am Heart J.* 2006;151:813-819.

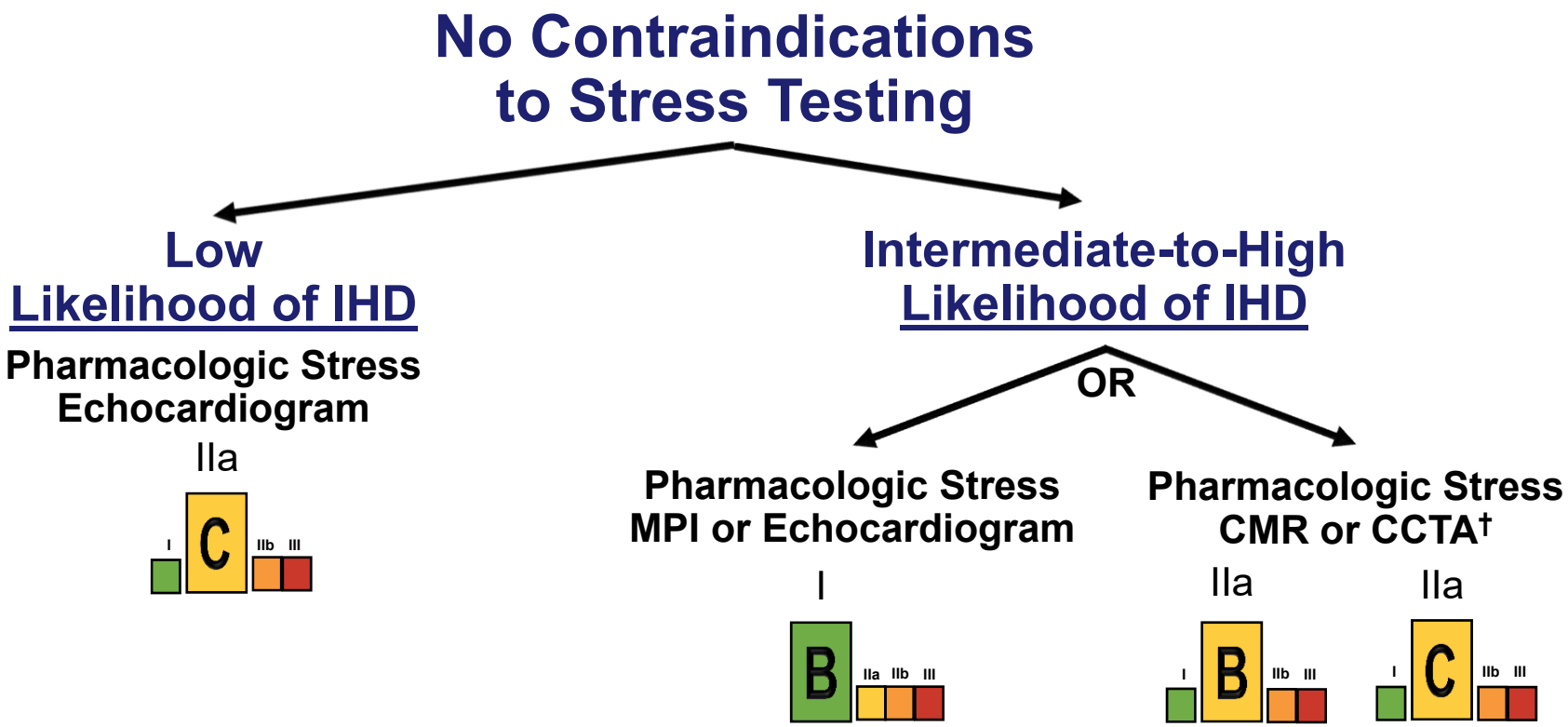
# Initial Cardiac Test for Diagnosis: Able to Exercise*




*Suspected IHD or change in clinical status in known IHD patients.
MPI: myocardial perfusion imaging.

Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.
Qaseem A, et al. *Ann Intern Med.* 2012;157:729-734.

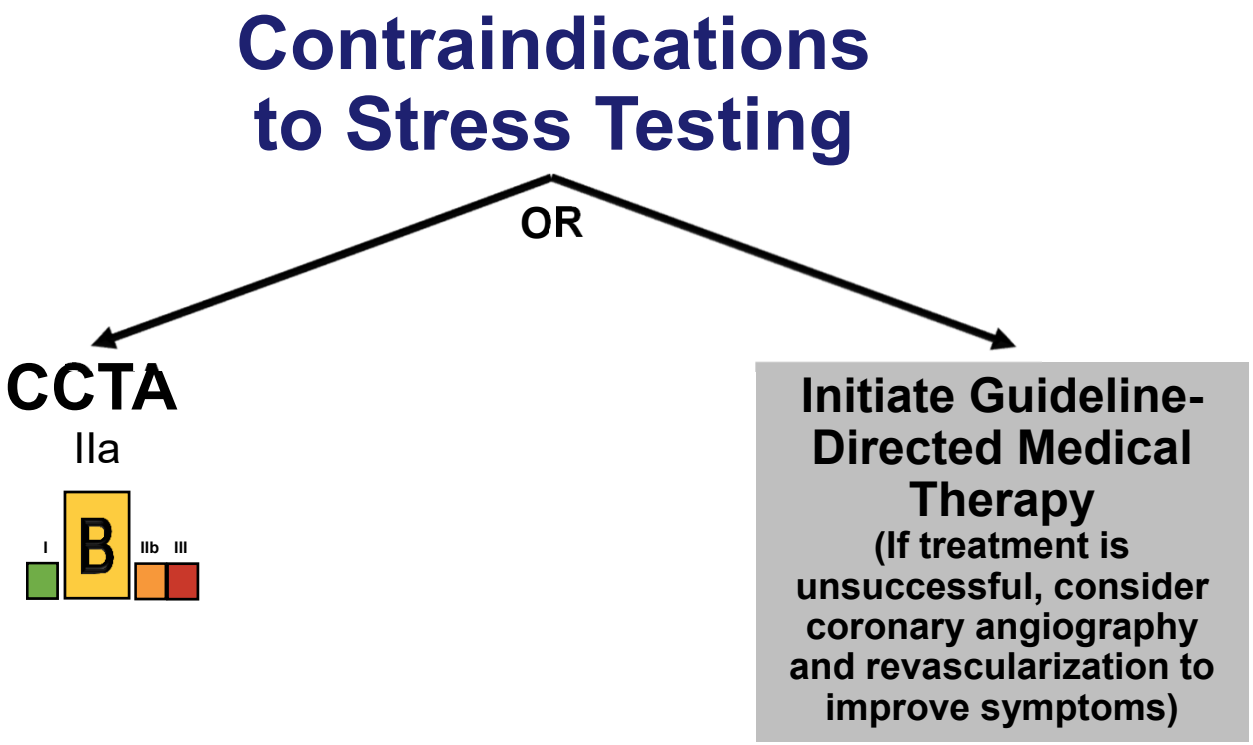
# Initial Cardiac Test for Diagnosis: Not Able to Exercise*




*Suspected IHD or change in clinical status in known IHD patients.
†CMR (recommendation: intermediate-to-high probability); CCTA (recommendation: intermediate probability).
MPI: myocardial perfusion imaging; CMR: cardiac magnetic resonance; CCTA: coronary CT angiography.

Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.
Qaseem A, et al. *Ann Intern Med.* 2012;157:729-734.

# Initial Cardiac Test for Diagnosis: Contraindications to Stress Testing*




*Suspected IHD or change in clinical status in known IHD patients.
CCTA: coronary CT angiography.

Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.
Qaseem A, et al. *Ann Intern Med.* 2012;157:729-734.

# WISE Study: Endothelial and Microvascular Dysfunction in Women

- Contemporary WISE cohort (2009-2011) (n=94)
  - Women with symptoms/signs of ischemia without obstructive coronary artery disease
    - <50% epicardial stenosis in any coronary artery
- Coronary reactivity testing
  - Intracoronary: adenosine, followed sequentially by acetylcholine and nitroglycerin with quantitative angiography and Doppler flow measurement
- Comparison arms (WISE cohorts)
  - 2009-2011 (n=94)
  - 1997-2001 (n=210)

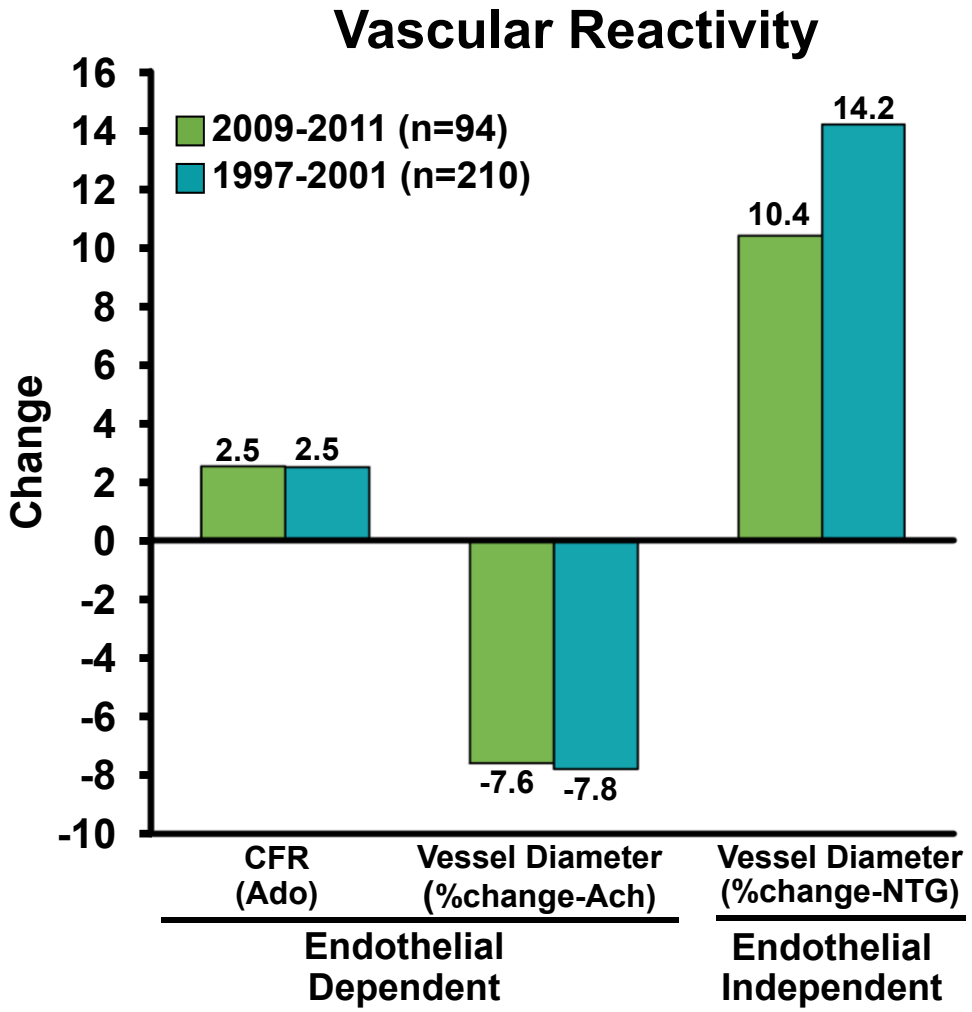
## Baseline Characteristics

| | 2009-2011 (n=94) | 1997-2001 (n=210) |
|---|---|---|
| Age (years) | 53.7 | 54.5 |
| White (%) | 63 | 83 |
| History (%) | | |
| Diabetes mellitus | 6 | 25 |
| Hyperlipidemia | 41 | 54 |
| Smoking | 49 | 55 |
| Hypertension | 33 | 55 |
| Hormone replacement therapy | 18 | 58 |

Anderson RD, et al. *Circulation.* 2011;124(suppl): Abstract 17055.

# WISE Study: Endothelial and Microvascular Dysfunction in Women

- Endothelial and microvascular dysfunction similar between the 2009-2011 and 1997-2001 WISE cohorts
  - Despite a reduction in CAD risk factors
- These abnormalities are associated with long-term adverse events
  - Emphasize need for clinical trials to address these disease pathways




CFR: coronary flow reserve.
Ado: adenosine.
Ach: acetylcholine.
NTG: nitroglycerin.

Anderson RD, et al. *J Am Coll Cardiol.* 2011;57(suppl A):e1150. Abstract 323.

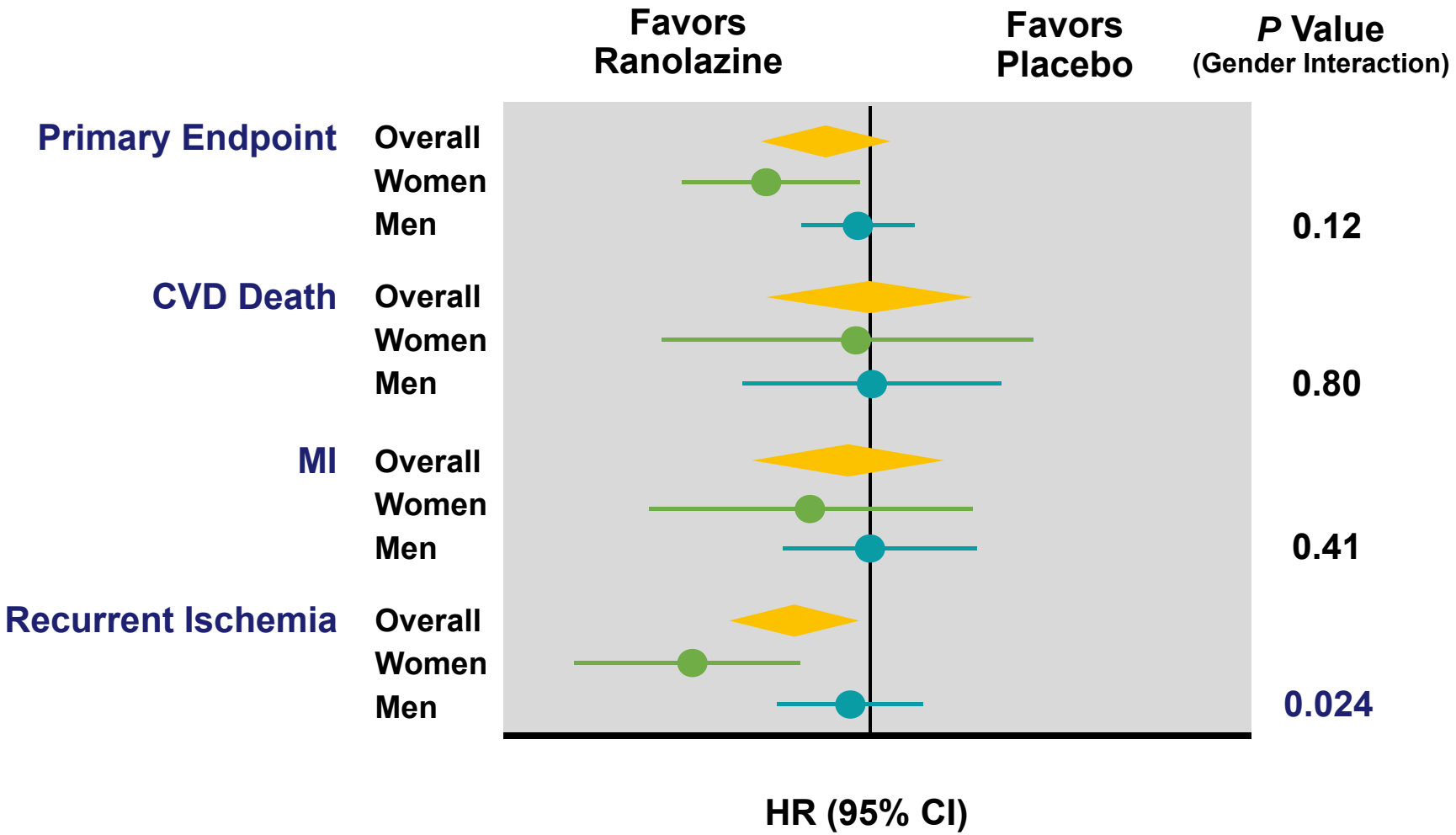
# Chest Pain in Women With "Angiographically Normal" Coronary Arteries

- Endothelial dysfunction
  - Endothelial function testing with acetylcholine
  - 28% had vasospasm in ACOVA study (1/2 enrollees women)
  - Vasospasm, macrovascular or microvascular → adverse prognosis
- Plaque rupture by intravascular ultrasound
  - Common with acute MI
  - Optical coherence tomography can distinguish plaque erosion from plaque rupture

ACOVA: abnormal coronary vasomotion.

Ong P, et al. *J Am Coll Cardiol.* 2012;59:655-662.
Reynolds HR, et al. *Circulation.* 2011;124:1414-1425.

# MERLIN-TIMI 36 Trial (NSTE ACS): Efficacy Outcomes by Gender




NSTE ACS: non-ST-elevation acute coronary syndromes.

Mega JL, et al. *Circulation.* 2010;121:1809-1817.

# CONFIRM Registry (2005-2009): Gender Differences in CAD

- Patients without prior known CAD undergoing CCTA (n=24,546)
  - CAD-matched men and women
- Women versus men
  - Older
  - Greater CAD risk factors
  - Higher rates of typical angina and dyspnea
  - Framingham risk score is lower
  - No difference in mortality
    - Hazard ratio: 1.19 (95% CI 0.95, 1.48)
- Framingham risk score underestimates risk in women

## Baseline Characteristics

| | Women (n=9783) | Men (n=9783) |
|---|---|---|
| Age (years) | 59.4* | 54.5 |
| Hypertension (%) | 44.1* | 54.6 |
| Diabetes (%) | 12.5* | 16.0 |
| Past smoking (%) | 41.1* | 47.0 |
| Dyslipidemia (%) | 55.8* | 51.9 |
| Framingham risk (%) | 9.7* | 14.3 |
| Symptoms (%) | | |
| Typical chest pain | 17.9* | 46.3 |
| Atypical chest pain | 43.1* | 33.2 |
| Noncardiac chest pain | 12.5* | 12.8 |
| Dyspnea only | 7.5* | 5.2 |
| Asymptomatic | 19.0* | 2.5 |

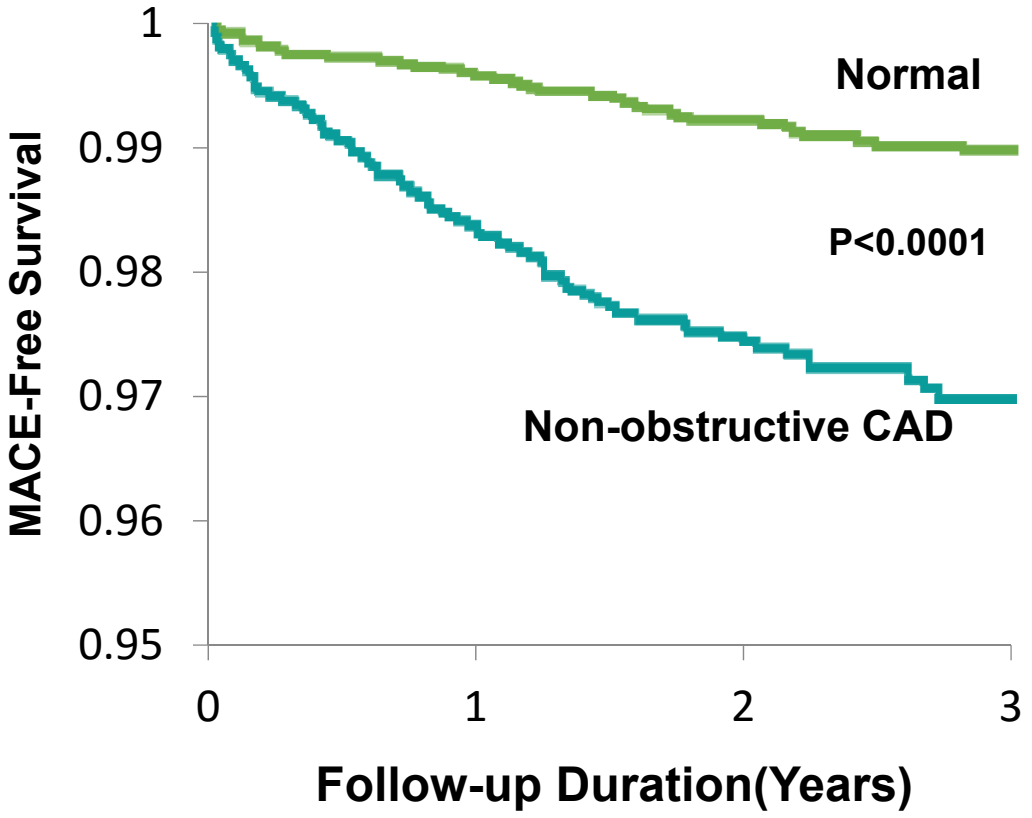
*$P$<0.001 versus men.

CCTA: cardiac computed tomography angiography.

Lin F, et al. *J Am Coll Cardiol.* 2011;57(suppl A):e773. Abstract 201.

# CONFIRM Registry: MACE-Free Survival In Propensity-Matched Cohort According to Presence of Non-obstructive CAD

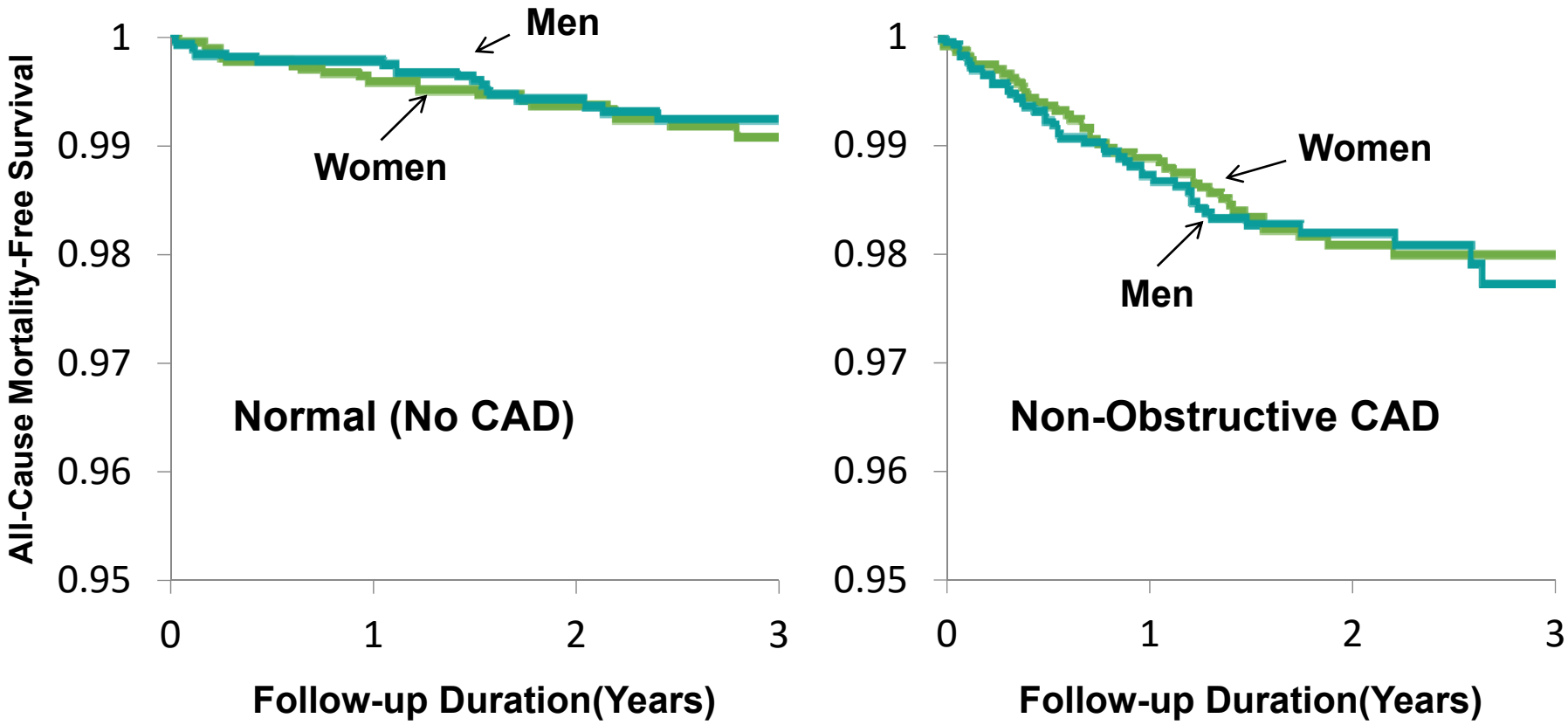
- Cohort of 11,462 patients
- **Men and women propensity matched** for:
  - Age
  - CAD risk factors
  - Angina typicality
  - CAD extent and distribution
- Major adverse cardiac events (MACE):
  - Death and MI




- **Patients with non-obstructive CAD had significantly higher event rates than patients without CAD**

Leipsic J, et al. *Radiology* 2014;273:393-400

# CONFIRM Registry: MACE-Free Survival In Propensity-Matched Cohort According to Sex




- When matched for age, CAD risk factors, angina typicality, and extent of non-obstructive CAD, men and women had comparable rates of mortality and MI
  - This finding was consistent in patients with no CAD (left panel) or with non-obstructive CAD (right panel)

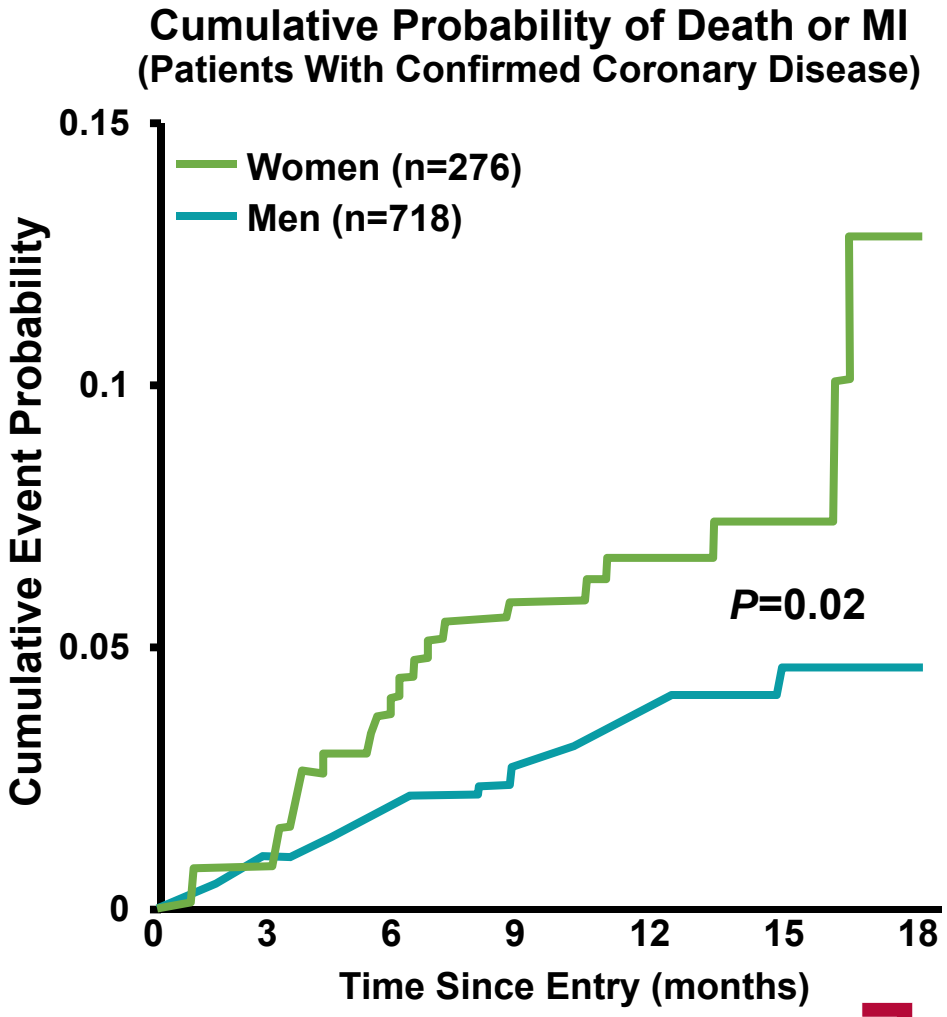
Leipsic J, et al. *Radiology* 2014;273:393-400

# Program Overview

| | |
|---|---|
| 1 | Gender-related epidemiologic patterns in SIHD |
| 2 | Risk and symptom assessment in women |
| 3 | Pathophysiologic and pathoanatomic gender differences |
| **4** | **Prognosis in women with SIHD** |
| 5 | Clinical considerations in the management of SIHD in women |

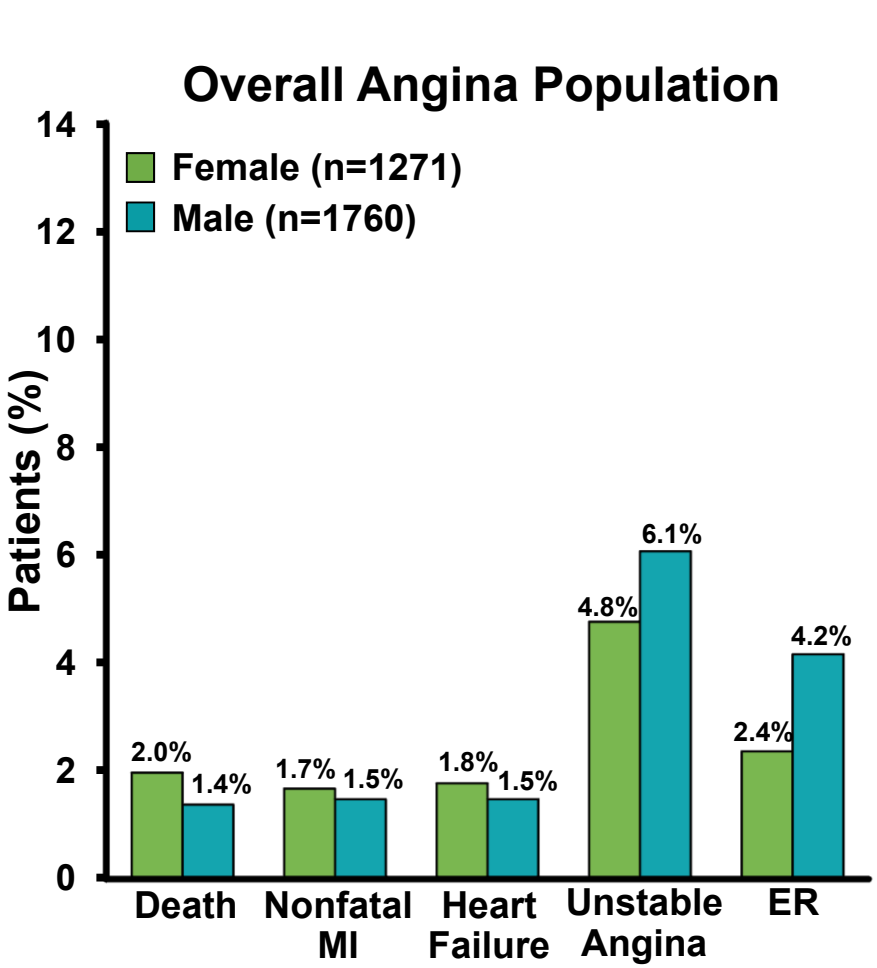
# Euro Heart Survey of Stable Angina: Increased Risk of Death in Women

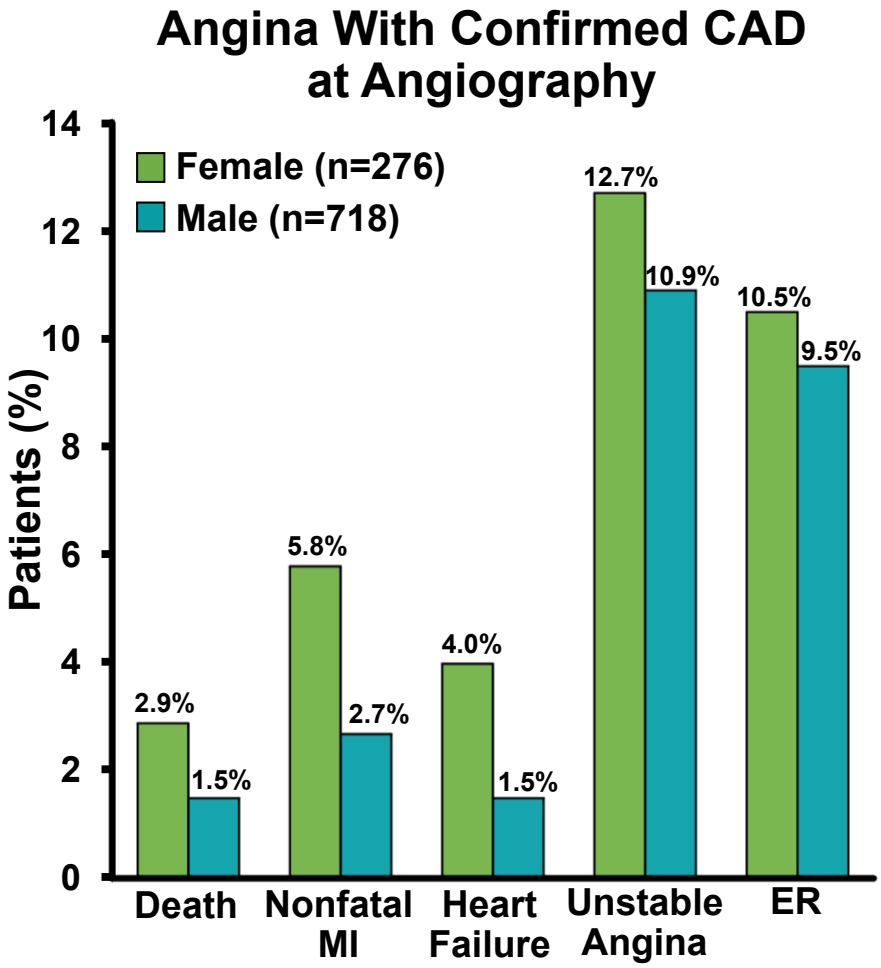
- Patients with clinical diagnosis of angina on initial assessment by a cardiologist (n=3779)
- Hazard ratio for death or MI (females versus males)
  - Overall: 2.07 (1.16-3.72; *P*=0.01)
  - Similar significant results when adjusted for
    - Age, diabetes, LV function, severity of coronary disease
    - Age and use of statin and antiplatelet therapy
    - Age and revascularization
- These results may reflect diagnosis in women at a later stage of the disease




Daly C, et al. *Circulation.* 2006;113:490-498.

# Euro Heart Survey of Stable Angina: 1-Year Outcomes by Gender

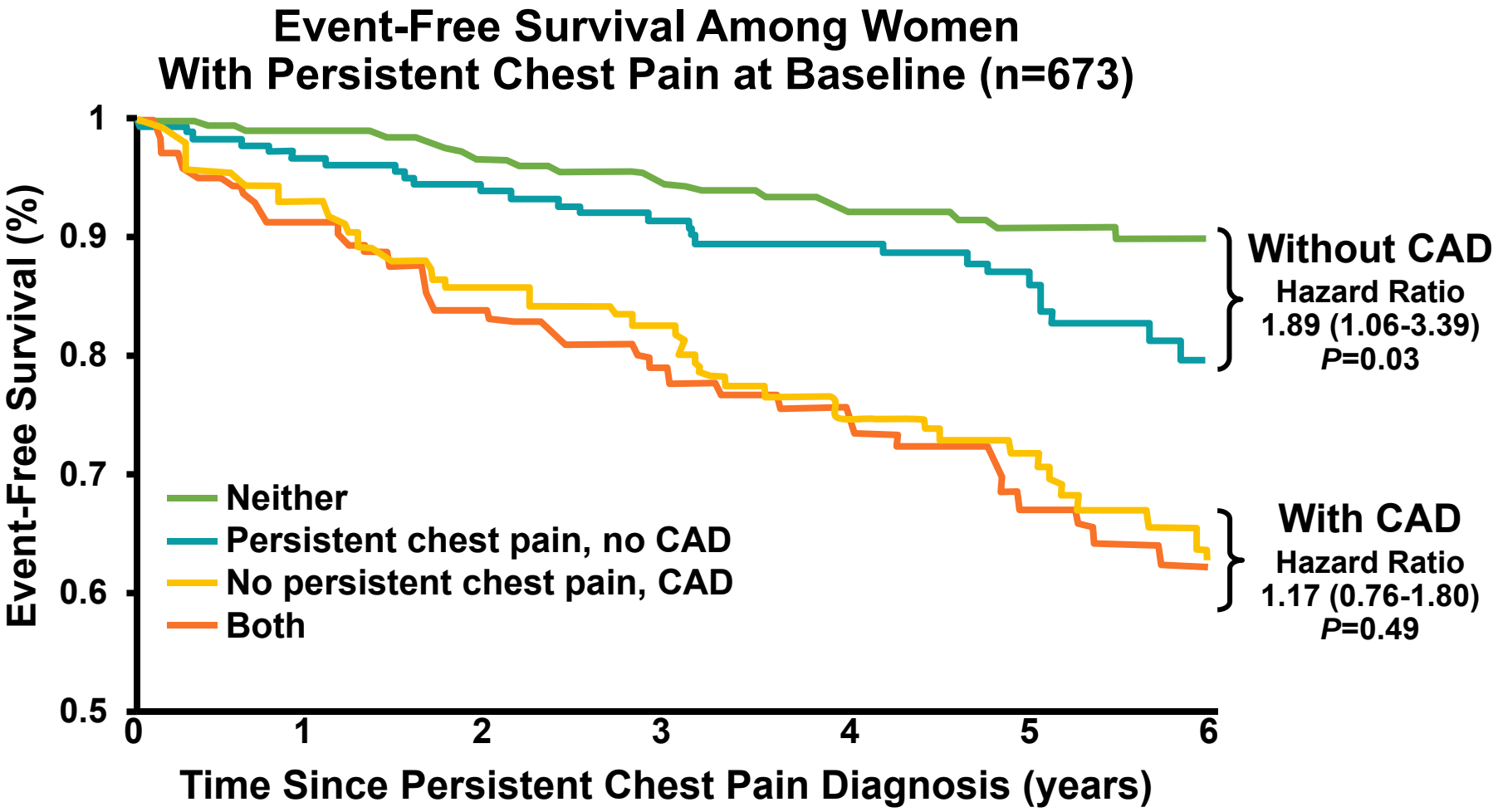



ER: emergency revascularization.
Heart failure and unstable angina: refer to admission to hospital for these conditions.

Daly C, et al. *Circulation.* 2006;113:490-498.

# WISE Study: Persistent Chest Pain Is Predictive of Future Cardiovascular Events




Johnson BD, et al. *Eur Heart J.* 2006;27:1408-1415.

# Meta-Analysis: Beta-Blockers, Calcium Channel Blockers, and Nitrates for Stable Angina

Meta-analysis of randomized crossover trials comparing therapies for stable angina*

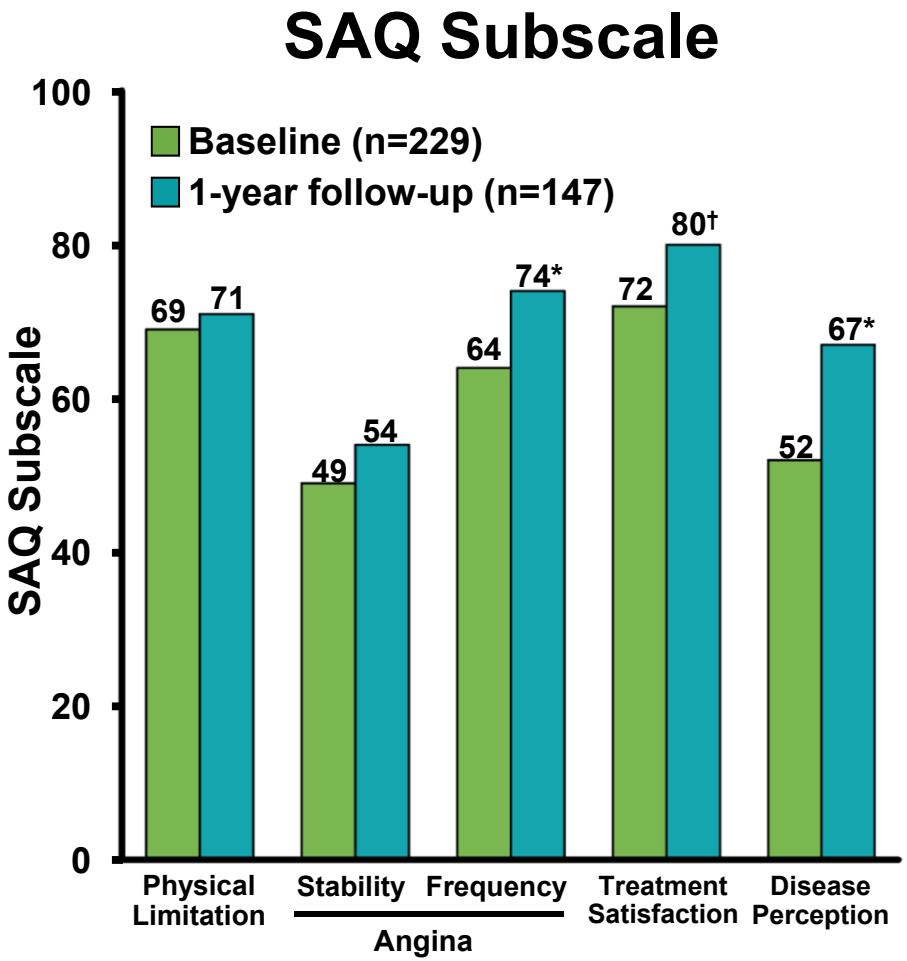
- Beta-blockers versus calcium channel blockers (72 trials)
  - Cardiac death: no significant difference (OR, 0.97; 95% CI, 0.67-1.38)
  - Angina episodes per week
    - Patients on beta-blockers had an average of 0.31 (95% CI, 0.62 to 0.00; *P*=0.05) fewer angina episodes per week than patients on calcium channel blockers

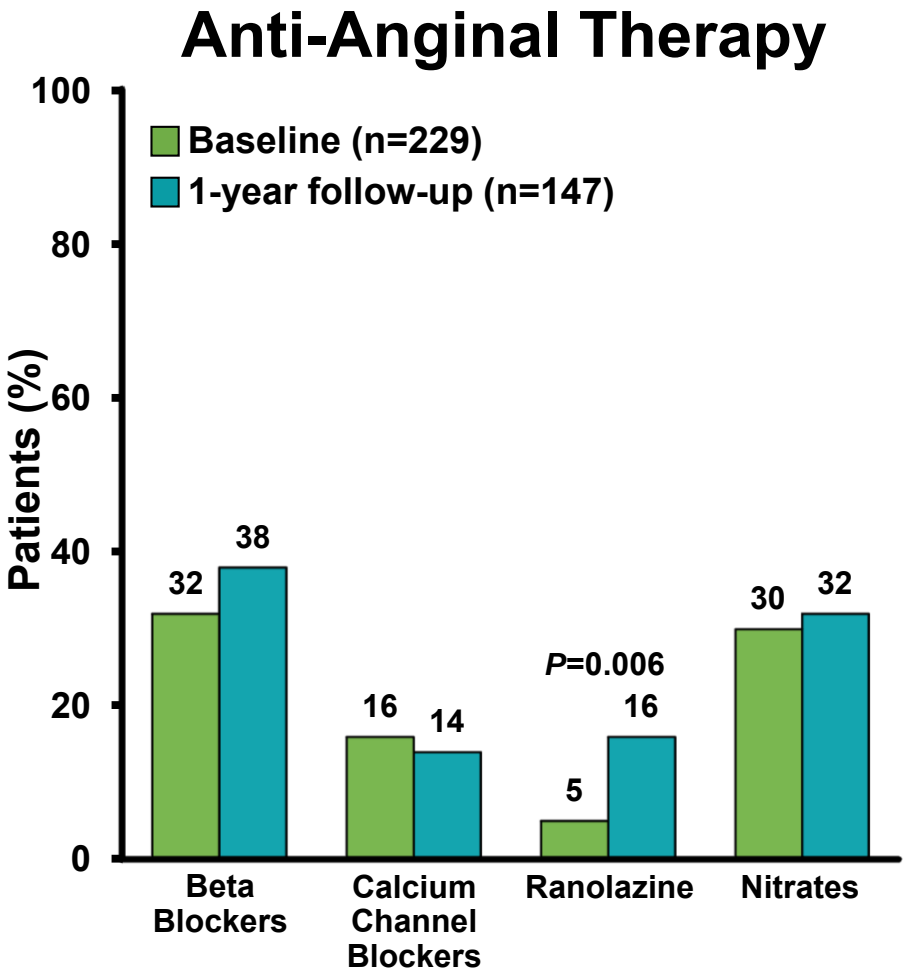

  - Beta-blockers associated with lower risk of discontinuation due to AEs
- Too few trials comparing nitrates with calcium channel blockers or beta-blockers to draw firm conclusions about relative efficacy

*Some trials excluded patients with heart failure (n=46), recent MI (n=45), bradyarrhythmia or heart block (n=31), significant lung disease (n=26), or diabetes mellitus (n=13).

Heidenreich PA, et al. *JAMA.* 1999;281:1927-1936.

# WISE Study: SAQ and Anti-Anginal Therapy Use After 1 Year

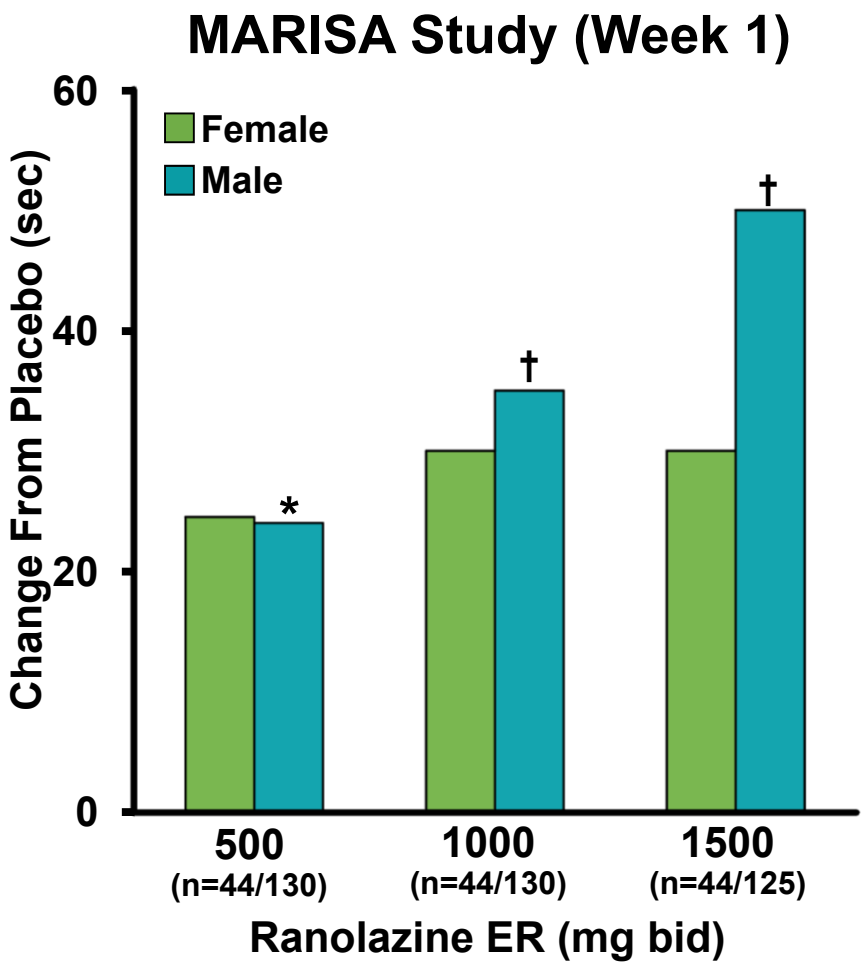


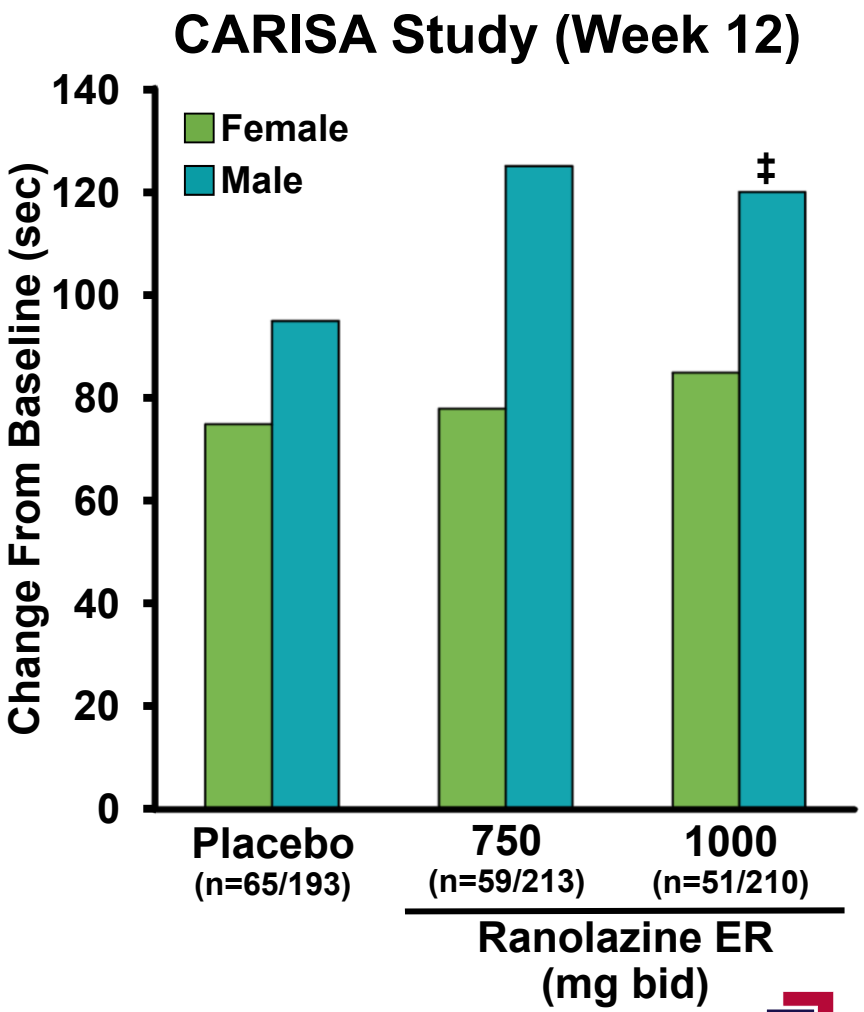




SAQ subscale range (0: worse; 100: best).
*$P$<0.001 and †$P$=0.03 versus baseline.

Mehta PK, et al. *J Am Coll Cardiol.* 2013;61(suppl A):A366. Abstract 1115-98.

# Impact of Ranolazine on Exercise Duration by Gender

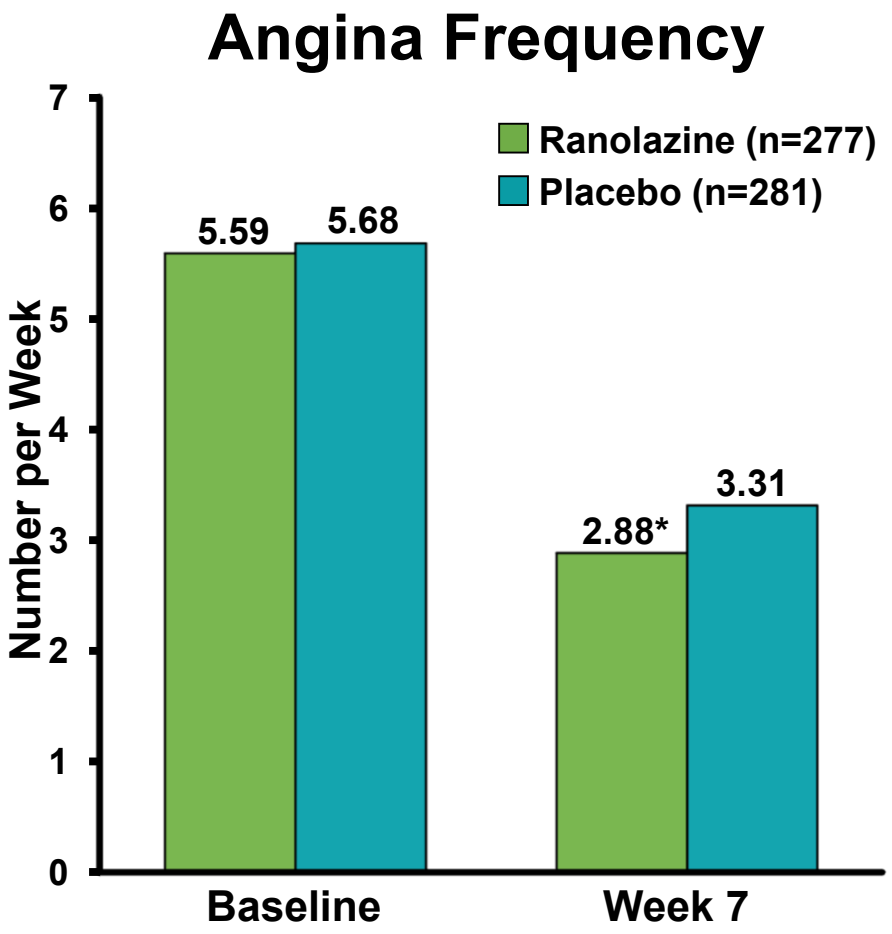


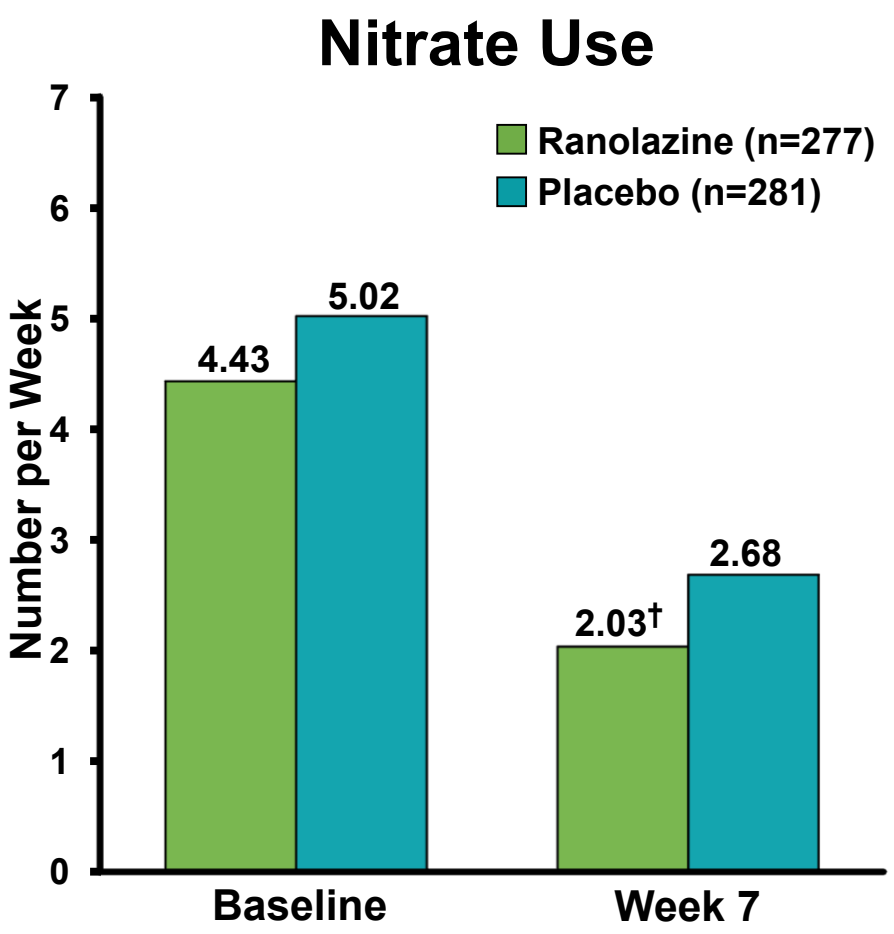




*$P$=0.014; †$P$<0.001, and ‡$P$=0.037 versus placebo.

Wenger NK, et al. *Am J Cardiol.* 2007;99:11-18.

# ERICA Study: Angina Frequency and Nitrate Consumption

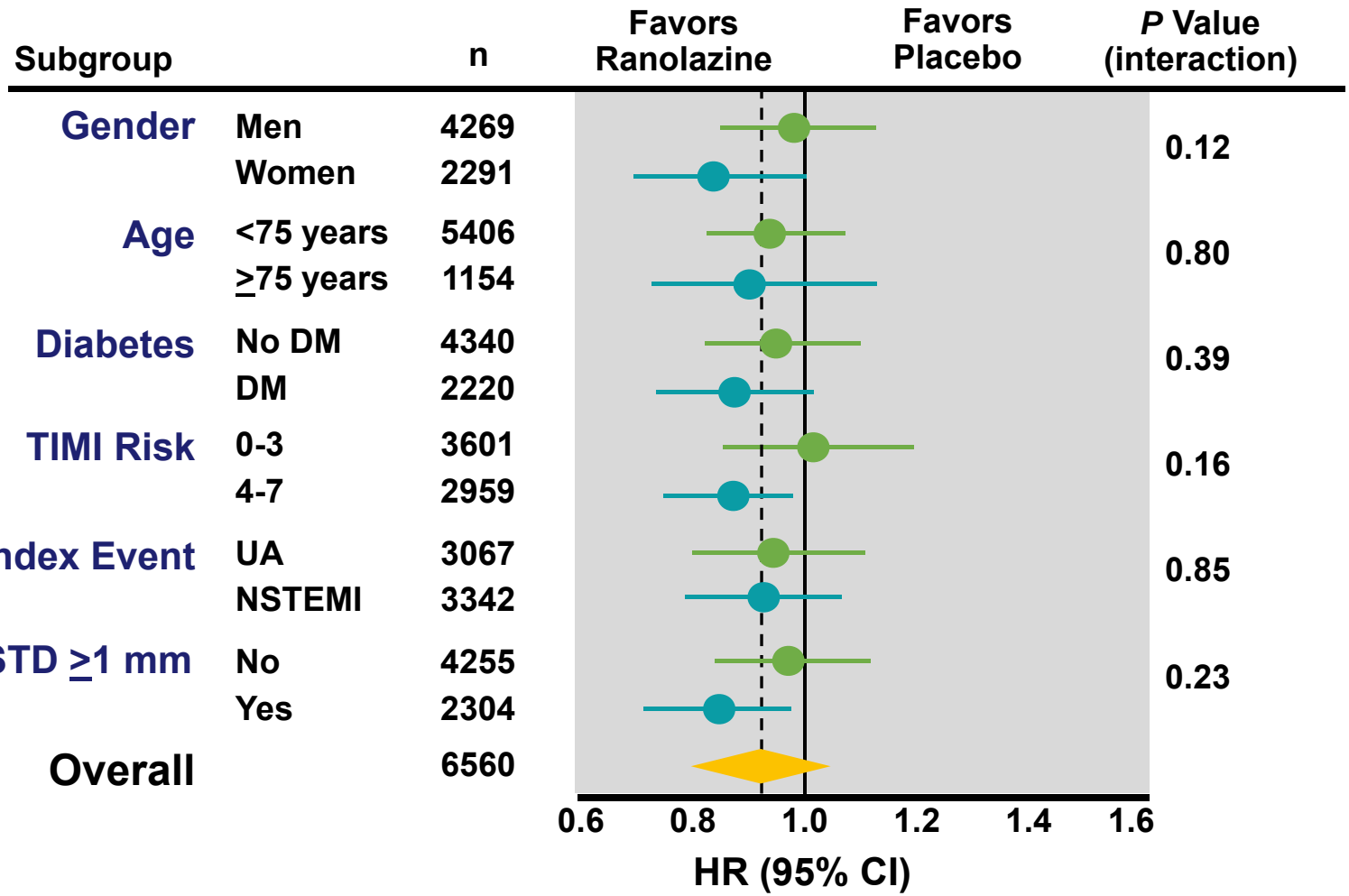



Both groups received amlodipine 10 mg/day bid.
*$P$=0.028 and †$P$=0.014 versus placebo.

Stone PH, et al. *J Am Coll Cardiol.* 2006;48:566-575.

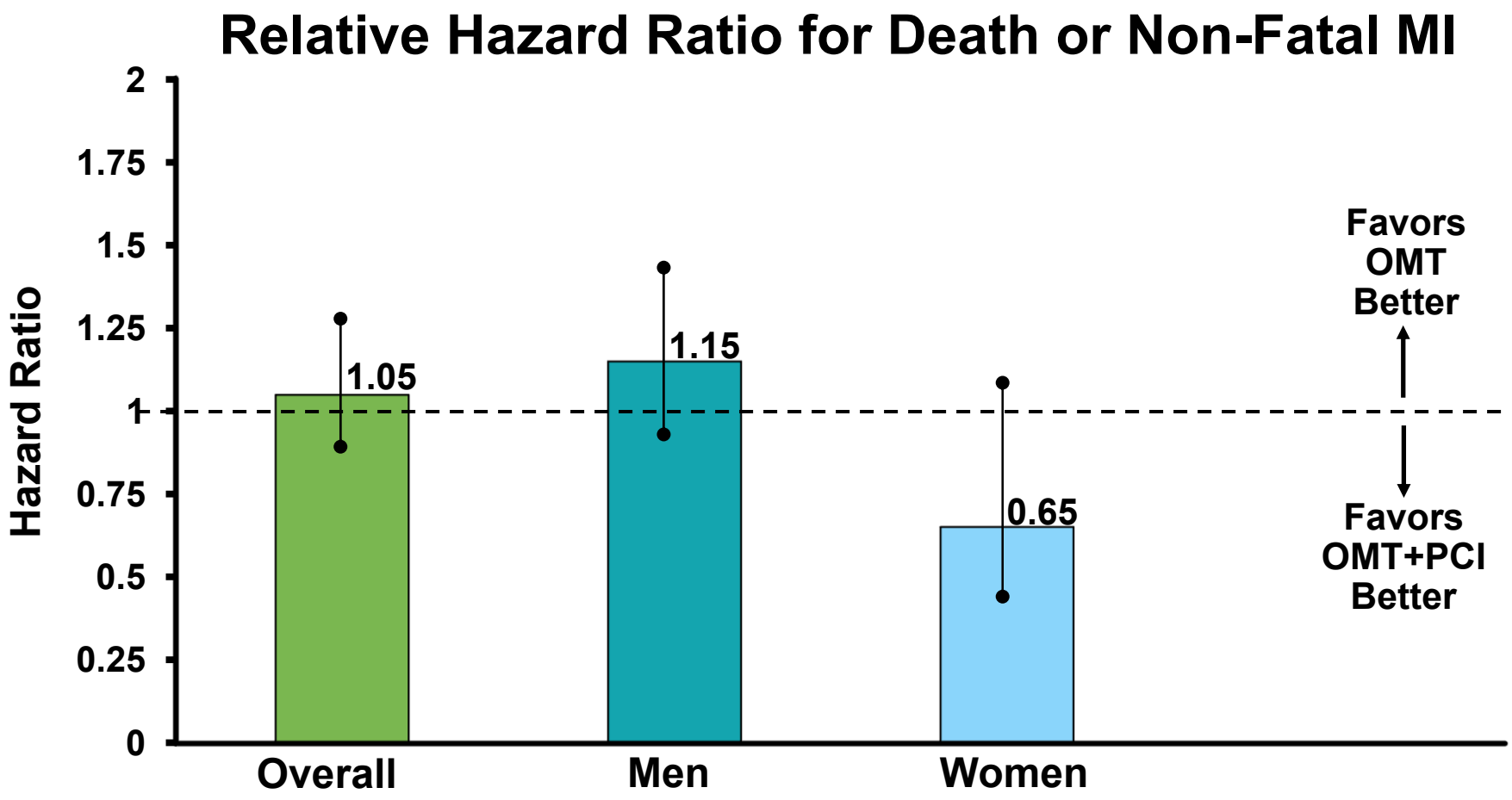
# MERLIN-TIMI 36 Trial (NSTE ACS): Efficacy Outcomes by Subgroups




NSTE ACS: non-ST-elevation acute coronary syndromes.

Morrow DA, et al. *JAMA.* 2007;297:1775-1783.

# COURAGE Study: Gender-Based Risk of Death or MI




OMT: optimal medical therapy.

Boden WE, et al. *N Engl J Med.* 2007;356:1503-1516.

# Revascularization in Women

## Gender-Related Differences in Referral and Outcomes

| | Cleveland Clinic Study (1971-2011)[1] | NIS Study (2009-2011)[2] |
|---|---|---|
| **Women had different baseline risks at time of referral for coronary angiography to evaluate CAD.** | • On average, women were older and had higher rates of hypertension, peripheral artery disease, stroke, diabetes, and heart failure than men. | • On average women were older and had higher rates of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, obesity, peripheral vascular disease, and congestive heart failure. |
| **Revascularization was different in men and women.** | • Revascularization procedure was different in men (BITA/ SITA; complete/ incomplete.<br>• BITA benefited women less. | • Men were more likely to receive revascularization. |
| **Women had worse outcomes following coronary revascularization.** | • Men survived longer, on average after revascularization.<br>• Women had higher rates of death, myocardial infarction, stroke, wound infection, and prolonged ventilation. | • In gender risk-matched groups, women had increased rates of in-hospital death, hematoma, and vascular complication. |

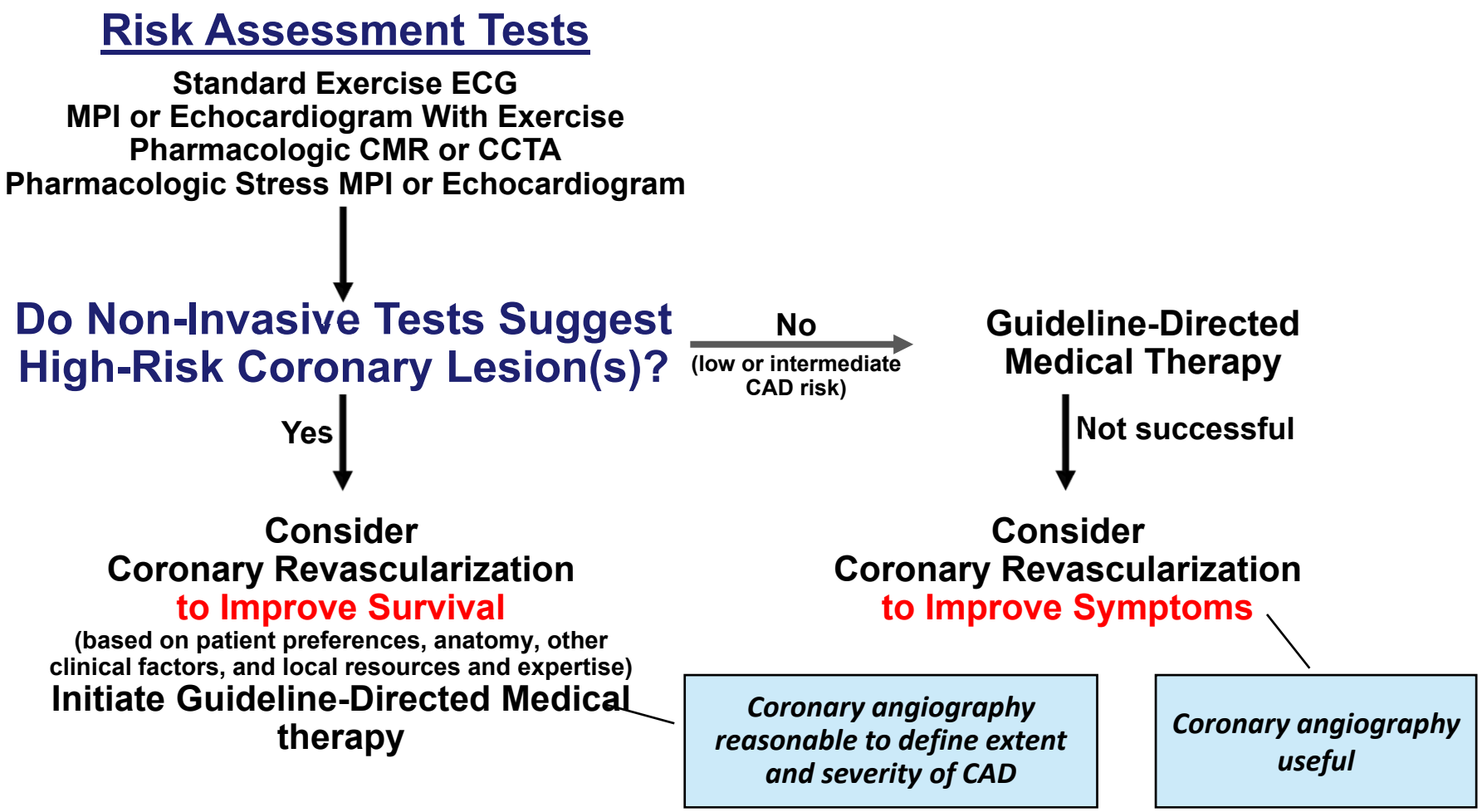
BITA,, bilateral internal thoracic artery revascularization;
NIS, Nationwide Inpatient Sample database;
SITA, single internal thoracic artery revascularization


1. Attia, T, et al. *ACC Scientific Session, 2015* , San Diego, CA. Abstract 905-06.
2. Oliveros E, et al. *ACC Scientific Session, 2015* , San Diego, CA. Abstract 1263-361.

# Program Overview

| | |
|---|---|
| 1 | Gender-related epidemiologic patterns in SIHD |
| 2 | Risk and symptom assessment in women |
| 3 | Pathophysiologic and pathoanatomic gender differences |
| 4 | Prognosis in women with SIHD |
| **5** | **Clinical considerations in the management of SIHD in women** |

# General Approach to Therapy in SIHD




MPI: myocardial perfusion imaging; CMR: cardiac magnetic resonance; CCTA: coronary CT angiography.


Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.
Qaseem A, et al. *Ann Intern Med.* 2012;157:729-743.
Fihn SD, et al. *J Am Coll Cardiol*. 2014;64:1929-1949.

# Guideline-Directed Medical Therapy: Relief of Symptoms

## Therapy for Angina

**Beta blocker**
**(especially if prior MI, heart failure, or other indication)**

I


***OR***

**Long-acting non-dihydropyridine CCB**

IIa


**Contraindication**

**Unacceptable side effects**

**Add/Substitute**
**CCB and/or long-acting nitrate**

I


***OR***

**Add (IIaA)/ Substitute (IIaB) Ranolazine**

IIa


IIa


**Persistent Symptoms Despite Adequate Trial of Guideline-Directed Medical Therapy**

**Consider Revascularization to Improve Symptoms**

Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.

# Foundations for First-Line Pharmacologic Agents

- Aspirin
- β-blockers
  - Prior MI
- ACE inhibitors/ARBs
  - Especially in patients with diabetes or LV systolic dysfunction
- Lipid-lowering therapy
  - High- or moderate-intensity statin therapy for secondary and primary prevention
- Short-acting nitroglycerin (sublingual or spray)
  - Immediate angina relief

Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.
Stone NJ, et al. *J Am Coll Cardiol.* 2013;63(25 Pt B):2889-2934.

# Dosing for Anti-Anginal Agents Approved for Angina in the United States

| | Dosage Range |
|---|---|
| Nitrates | |
| Isosorbide dinitrate | Short acting (5-40 mg bid or tid); sustained release (60-120 mg qd) |
| Isosorbide mononitrate | Short acting (20 mg bid); sustained release (60-120 mg qd) |
| Nitroglycerin patch | 0.2-0.8 mg/hour |
| Beta blockers | |
| Propranolol | Long acting (80-240 mg qd) |
| Metoprolol | Short acting (50-150 mg bid)<br>Sustained release (100-300 mg qd) |
| Atenolol | 25-100 mg qd |
| Nadolol | 40-240 mg qd |
| Calcium-channel blockers | |
| Nifedipine | Sustained release (30-90 mg qd) |
| Amlodipine | 2.5-10 mg qd |
| Verapamil | Short acting (40-120 mg bid or tid)<br>Sustained release (180-240 mg qd or bid) |
| Diltiazem | Short-acting (30-120 mg qid)<br>Sustained release (120-480 mg qd) |
| Late Na+ current inhibitor | |
| Ranolazine | 500 mg bid and increase to 1000 mg bid, as needed, based on clinical symptoms |

Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.

# Traditional Anti-Anginal Therapy: Conditions That May Limit Their Uses

| Beta-Blockers | Nitrates | Calcium Channel Blockers† |
|---|---|---|
| • Hypotension<br>• Asthma<br>• Severe bradycardia<br>• AV block<br>• Severe depression<br>• Raynaud's syndrome<br>• Sick sinus syndrome | • Hypotension<br>• Severe aortic stenosis<br>• Hypertrophic obstructive cardiomyopathy<br>• Erectile dysfunction* | • Hypotension<br>• AV block<br>• Bradycardia<br>• Heart failure<br>• LV dysfunction<br>• Sinus node dysfunction |

*Treated with PDE5 inhibitors.
†Non-dihydropyridine.

Fihn SD, et al. *J Am Coll Cardiol.* 2012;60:e44-e164.

# Other Mechanisms for Anti-Anginal Agents

## Approved in the US

- Late $Na^+$ inhibition
  - Ranolazine

## Not Approved for Angina in the US

- Metabolic modulation
  - Trimetazidine (approved outside the US)
- Sinus node inhibitor
  - Ivabradine (approved only for heart failure in the US)
- Preconditioning
  - Nicorandil (approved outside the US)
- Vasopeptidase inhibition
  - Omapatrilat (denied approval in the US)

# Ranolazine Pilot Study: Women With Angina

- Double-blind, cross-over trial in women with angina (n=20)
  - No obstructive CAD by angiography
  - Myocardial ischemia (>10% SDS on adenosine stress perfusion with CMRI
- Randomized groups (4 weeks treatment; 2-week washout)
  - Ranolazine
  - Placebo
- Outcomes
  - Seattle Angina Questionnaire
  - CMRI

**Baseline Characteristics**

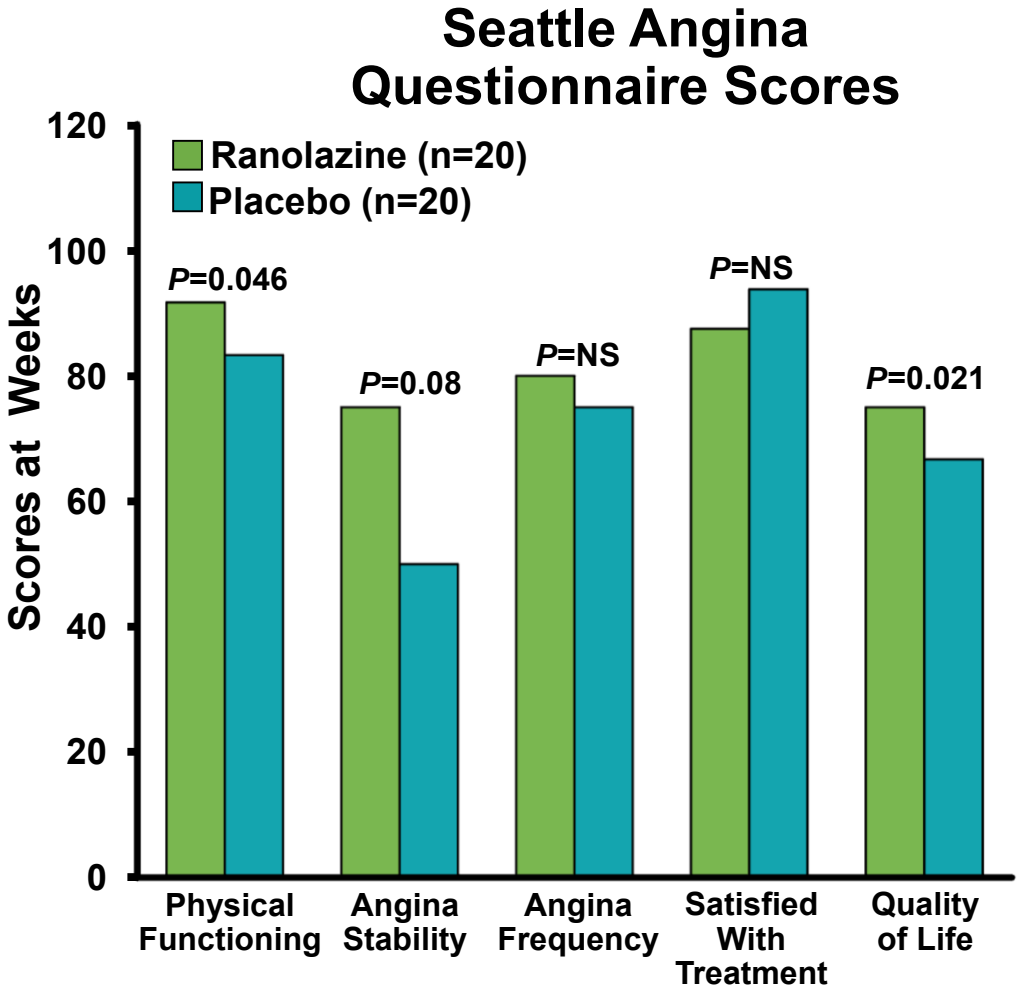
| | Women (n=20) |
|---|---|
| Age (years) | 57 |
| BMI (kg/m$^2$) | 25.6 |
| Caucasian (%) | 80 |
| Symptoms (%) | 95 |
| Typical angina | 45 |
| Shortness of breath | 30 |
| Palpitations | 15 |
| Premature CAD (%) | 70 |
| Medications (%) | |
| Beta-blockers | 70 |
| CCBs | 20 |
| ACE inhibitors | 45 |
| ARBs | 15 |
| Nitrates | 45 |

CMRI: cardiac magnetic resonance images.

Mehta PK, et al. *JACC Cardiovasc Imaging*. 2011;4:514-522.

# Ranolazine Pilot Study: Women With Angina

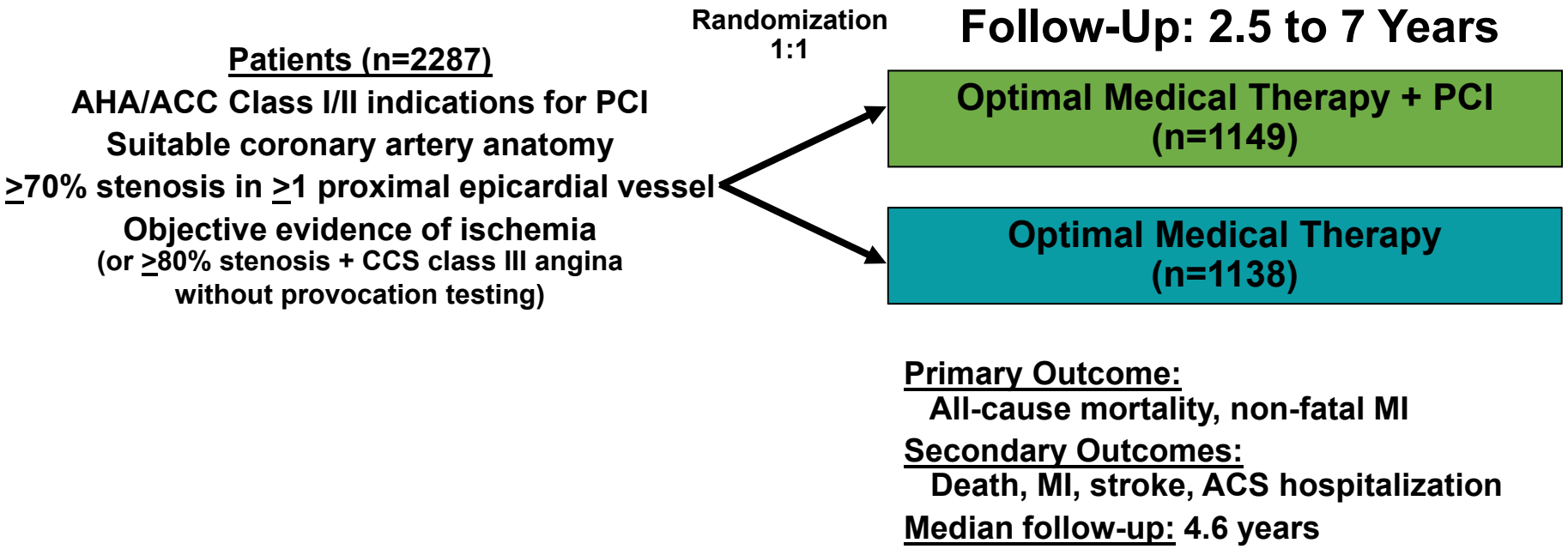
- Ranolazine improved SAQ subscales
  - Physical functioning
  - Angina stability
  - Quality of life
- Among women with invasive coronary flow reserve (n=13)
  - Improvement in MPRI on ranolazine among those with CFR ≤3.0 versus >3.0 (*P*=0.04)
- Results document feasibility for a large-scale study of the impact of ranolazine in women with microvascular coronary dysfunction




SAQ: Seattle Angina Questionnaire.
MPRI: myocardial perfusion reserve index.

Mehta PK, et al. *JACC Cardiovasc Imaging*. 2011;4:514-522.

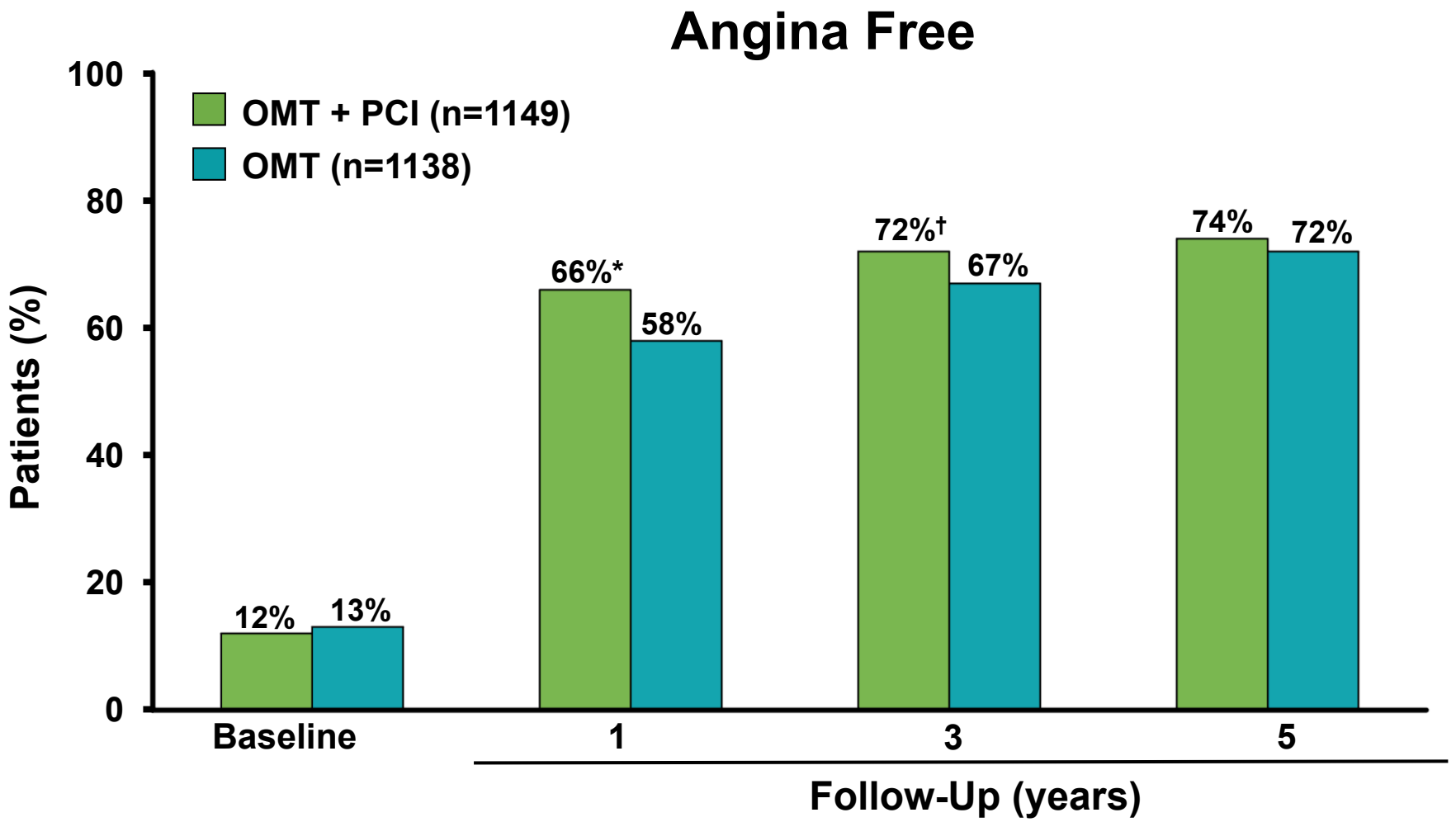
# COURAGE Trial: Optimal Medical Therapy ± PCI for Stable Coronary Disease




CCS: Canadian Cardiovascular Society; ACS: acute coronary syndrome.

Boden WE, et al. *Am Heart J.* 2006;151:1173-1179.
Boden WE, et al. *N Engl J Med.* 2007;356:1503-1516.

# COURAGE Study: Impact of Treatment on Angina




*$P$<0.001 and †$P$=0.02 versus OMT (optimal medical therapy).

Boden WE, et al. *N Engl J Med.* 2007;356:1503-1516.

# COURAGE Study: Gender Differences in Angina Severity, Ischemia, and Angiographic CAD (1)

- Post-hoc analysis
  - Suitable coronary artery anatomy
  - >70% stenosis in >1 proximal epicardial vessel
  - CCS class I-III or objective evidence of ischemia
- Men and women with baseline
  - Angiography (n=2279)
  - Stress MPI (n=625)

| | Unadjusted Analysis | |
|---|---|---|
| | **Women** | **Men** |
| Any angina (%) | 86.4 | 87.8 |
| CCS II or III (%) | 64.5* | 56.5 |
| Mean Jeopardy score | 2.3 | 2.5 |
| Mean ischemic myocardium (%) | 7.9 | 7.7 |
| 3-vessel disease (%) | 14.5† | 24.5 |

*$P$=0.006 and †$P$<0.001 versus men.

CCS: Canadian Cardiovascular Society.

Acharjee S, et al. *Circulation.* 2013;128(suppl 22): Abstract 18129.

# COURAGE Study: Gender Differences in Angina Severity, Ischemia, and Angiographic CAD (2)

- Women had less extensive angiographic CAD compared with men, but had a larger proportion of moderate-to-severe angina
- Female sex was independently associated with a greater risk of moderate-to-severe angina
- For any given severity of angiographic CAD or extent of myocardial ischemia, women had greater moderate-to-severe angina compared with men

**Adjusted Odds Ratio of Angina Severity More Common in Women Versus Men**

| | Odds Ratio (95% CI) |
|---|---|
| CCS class | |
| 0 (n=283) | 0.99 (0.66, 1.48) |
| I (n=681) | 0.56 (0.41, 0.77) |
| II (n=834) | 1.25 (0.95, 1.64) |
| III (n=482) | 1.43 (1.04, 1.96) |
| II/III (n=1316) | 1.62 (1.23, 2.15) |

CCS: Canadian Cardiovascular Society.
Odds ratio adjusted for age, family history, prior MI, prior PCI, left ventricular ejection fraction, LDL-C, HDL-C, total cholesterol, number of diseased vessels.

Acharjee S, et al. *Circulation.* 2013;128(suppl 22): Abstract 18129.

# COURAGE Substudy: Relation Between Burden of Coronary Atherosclerosis and Cardiovascular Events

- Patients with baseline coronary angiography (n=2279) or baseline stress myocardial perfusion imaging (n=625) were stratified into 3 subgroups according to
  - Number of diseased epicardial vessels
  - An unspecified myocardial jeopardy score
- Correlations calculated between CAD severity and rates of death or MI during 4.6 years of follow-up

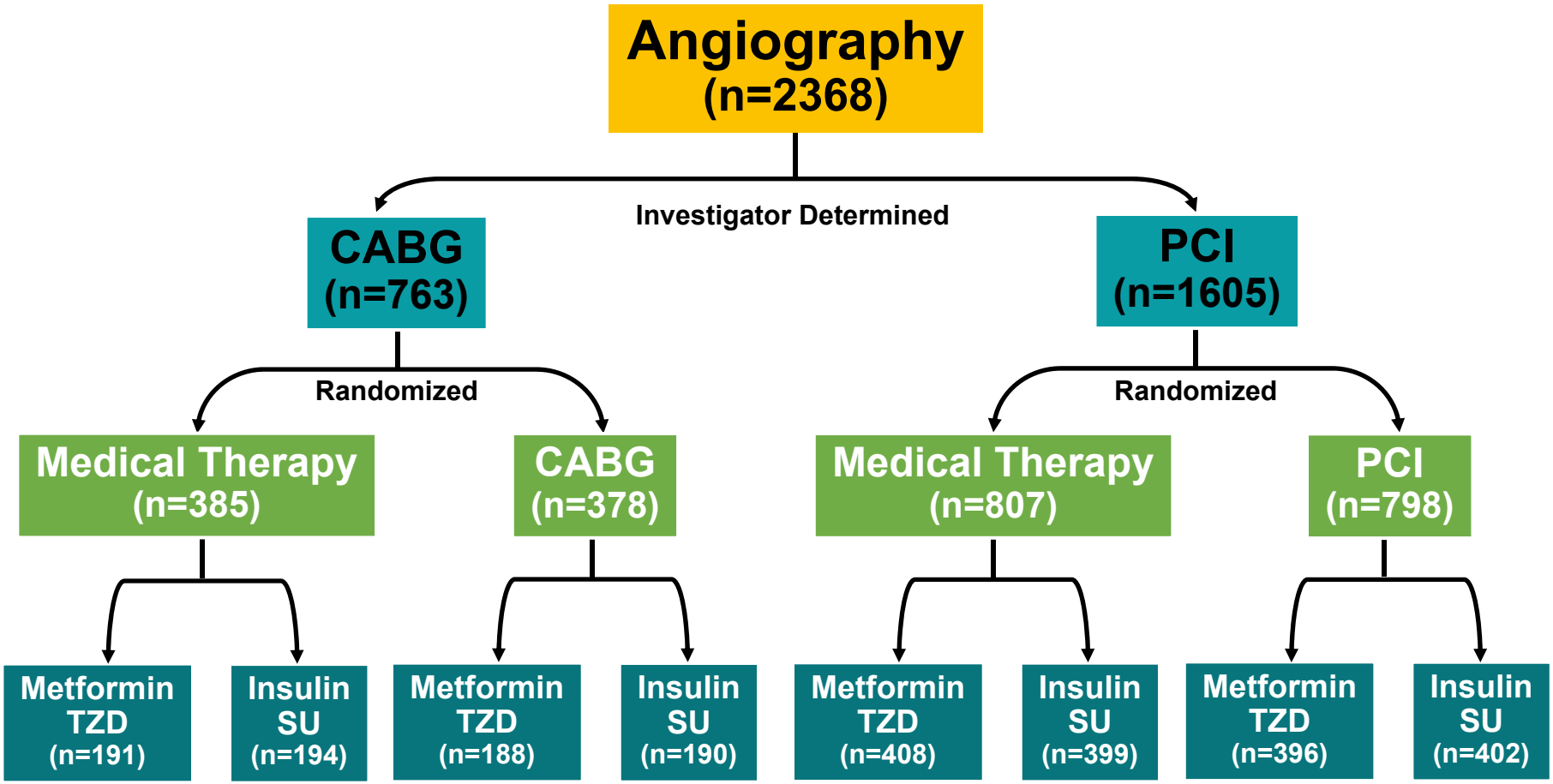
Correlation Between Events and Measures of CAD by Sex

| Outcome | % Ischemia | | | | No. Diseased Vessels | | | | Jeopardy Score | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | | Men | | Women | |
| | r | P | r | P | r | P | r | P | r | P | r | P |
| Death | -0.04 | 0.30 | -0.001 | 1.00 | 0.08 | <0.001 | 0.16 | 0.003 | 0.05 | 0.003 | 0.14 | 0.01 |
| MI | 0.03 | 0.47 | 0.05 | 0.64 | 0.11 | <0.001 | 0.24 | <0.001 | 0.05 | 0.04 | 0.18 | 0.001 |
| Death/MI | 0.005 | 0.89 | -0.001 | 0.99 | 0.112 | <0.001 | 0.24 | <0.001 | 0.07 | 0.005 | 0.19 | <0.001 |

- In both men and women, number of diseased vessels and jeopardy score were significantly correlated with events, but severity of ischemia was not

Acharjee S, et al. *Circulation* 2014;130 (suppl 2): Abstract 19993

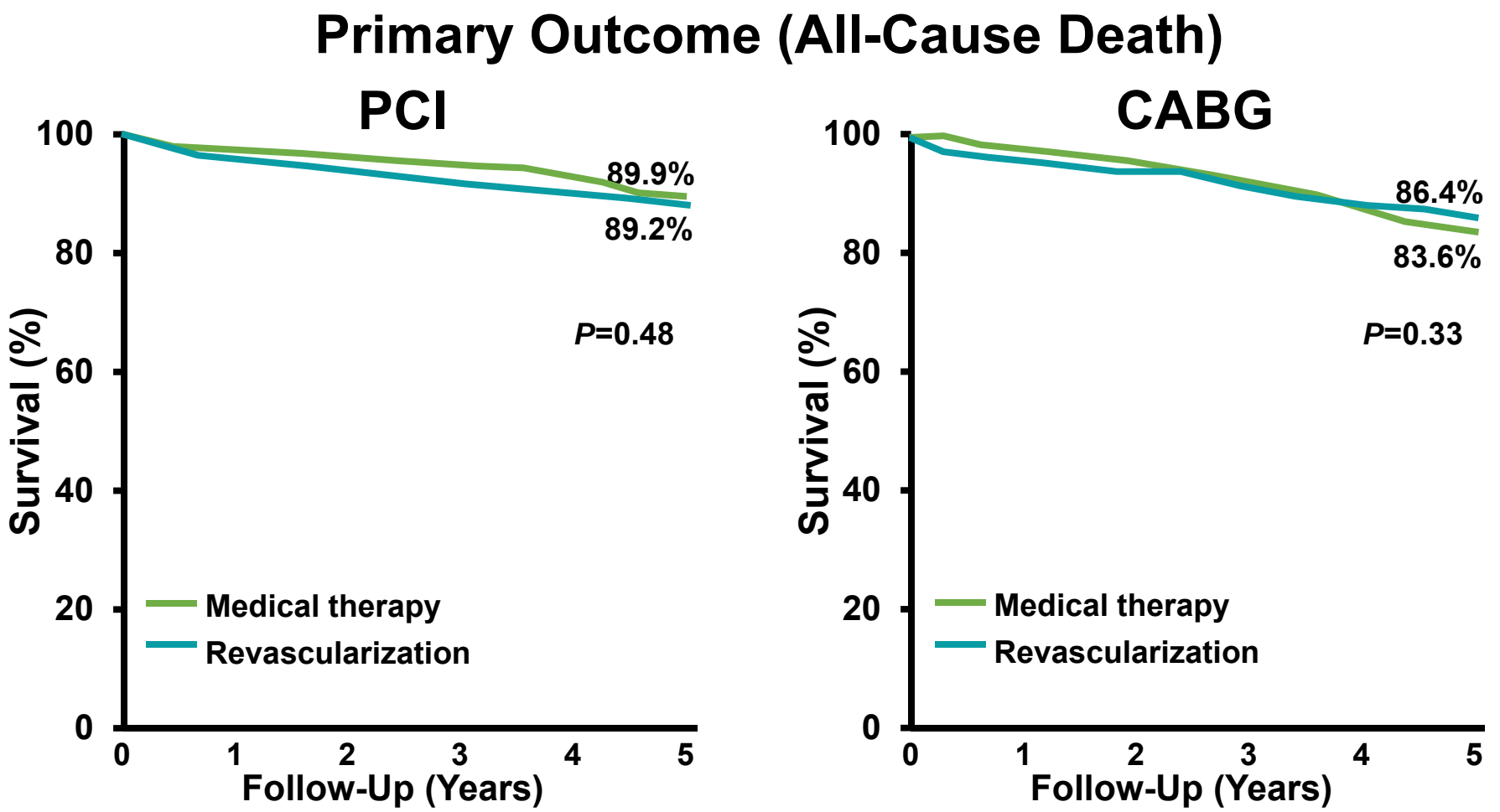
# BARI 2D Study: Revascularization in Type 2 Diabetes Mellitus and Angiographic CAD




TZD: thiazolidinedione; SU: sulfonylurea.

BARI 2D Study Group. *N Engl J Med.* 2009;360:2503-2515.

# BARI 2D Study: Medical Therapy Versus Revascularization




BARI 2D Study Group. *N Engl J Med.* 2009;360:2503-2512.

# BARI 2D Study: Type 2 Diabetes and CAD by Gender

- Women had a higher risk profile at baseline compared with men
- Women tended to have less severe or less extensive disease on coronary angiography despite a longer duration of diabetes

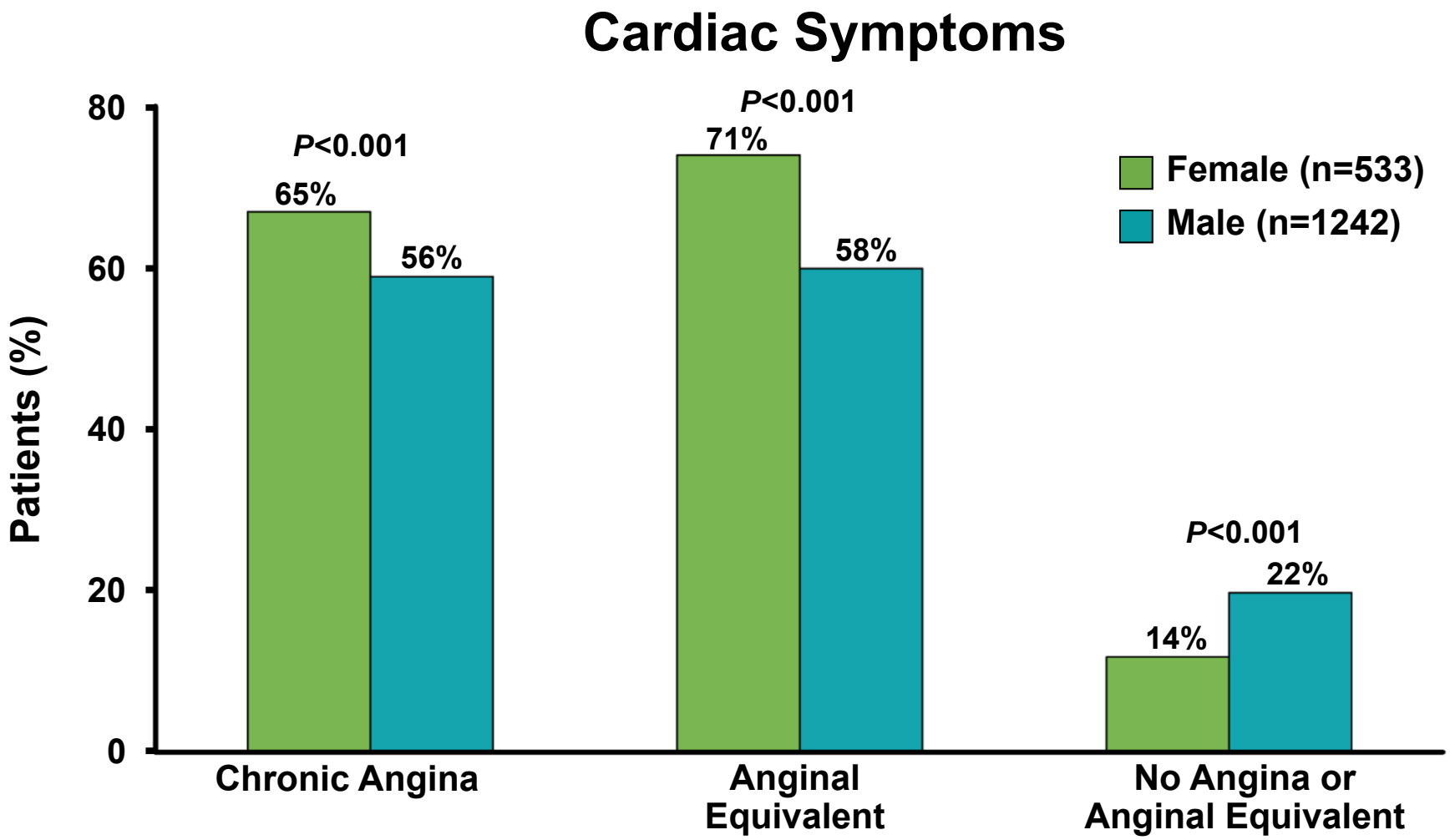
## Baseline Characteristics

| | Female (n=702) | Male (n=1666) |
|---|---|---|
| BMI (kg/m$^2$) | 32.6* | 31.2 |
| Duration of diabetes (years) | 12.0* | 9.5 |
| Hypertension (%) | 87† | 79 |
| Current insulin use (%) | 35* | 23 |
| $HbA_{1c} \geq 7$ (%) | 68* | 58 |
| History of (%) | | |
| MI | 22‡ | 33 |
| CHF | 6 | 6.2 |
| Current smoker (%) | 10‡ | 13 |
| Proximal LAD disease (%) | 11 | 13 |
| Totally occluded vessel (%) | 29* | 42 |
| 3 diseased regions (%) | 25* | 35 |

*$P$<0.0001; †$P$=0.0002; ‡$P$=0.04 versus males.

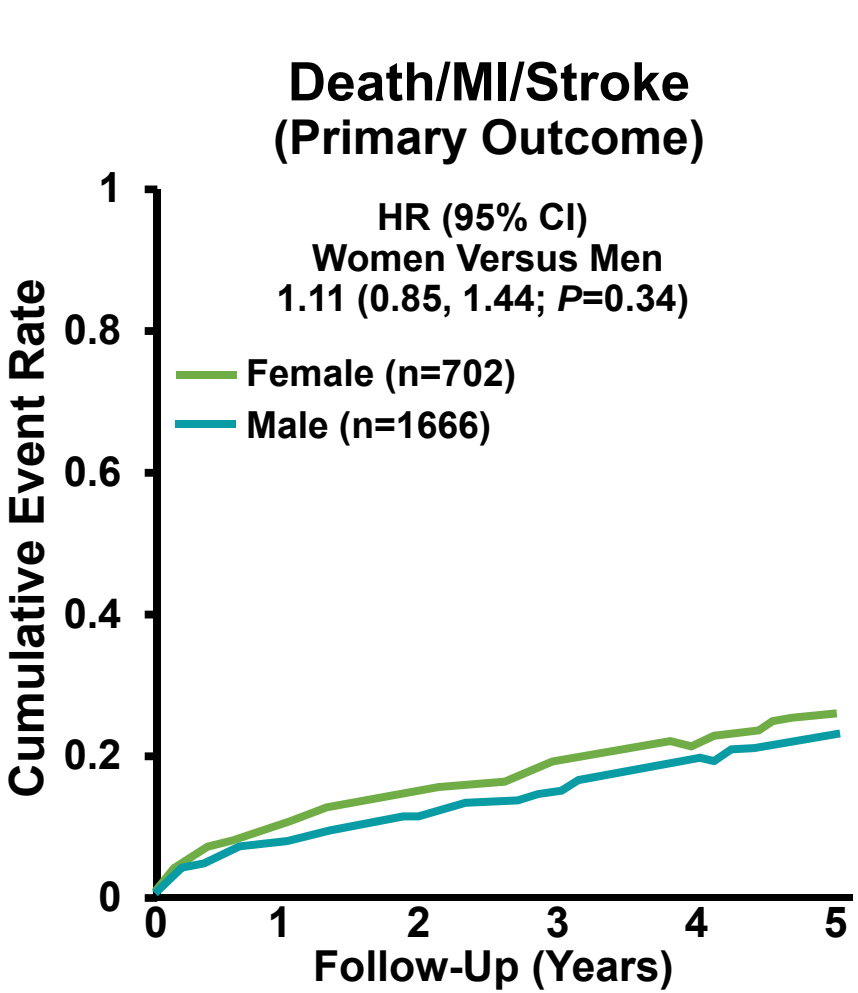
Tamis-Holland JE, et al. *Am J Cardiol.* 2011;107:980-985.

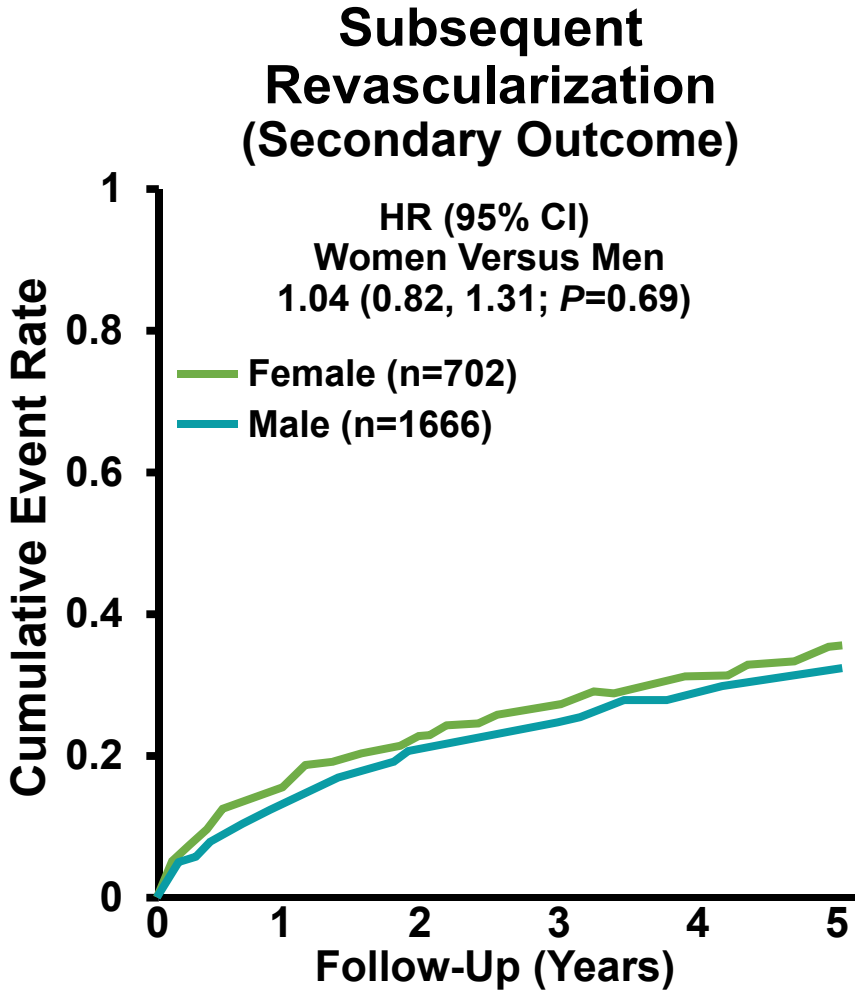
# BARI 2D Study: Baseline Cardiac Symptoms by Gender




Tamis-Holland JE, et al. *Am J Cardiol.* 2011;107:980-985.

# BARI 2D Study: Gender-Based Outcomes




Tamis-Holland JE, et al. *J Am Coll Cardiol.* 2013;61:1767-1776.

# BARI 2D Study: Clinical Variables Associated With Typical Angina

- Baseline BARI 2D data (n=2319)
  - Typical angina: 19%
  - Anginal equivalent: 21%
  - Both: 42%
  - No angina: 18%
- Multivariate regression analysis of patients with typical angina
  - More likely
    - Hypertension, beta-blocker use
  - Less likely
    - Male, >60 years of age, current exercisers, thiazolidinedione use

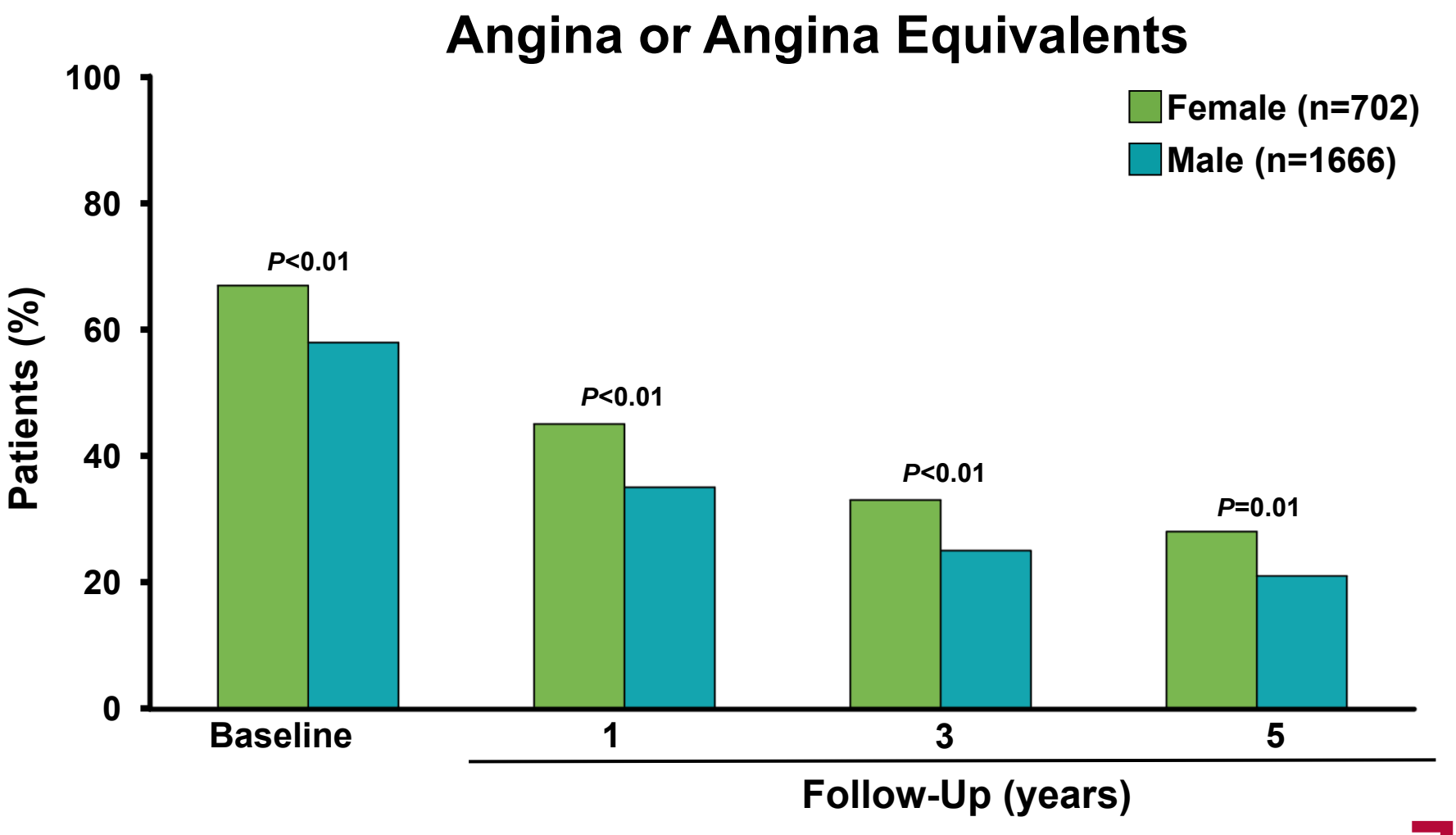
**Odds of Typical Angina Versus Anginal Equivalent or No Symptoms**

| | Odds Ratio (95% CI) |
|---|---|
| Male | 0.70* (0.57-0.87) |
| Age >60 years | 0.68† (0.55-0.83) |
| Exercisers | 0.77‡ (0.61-0.96) |
| Hypertension | 1.43† (1.11-1.83) |
| Use of thiazolidinedione | 0.65† (0.51-0.84) |
| Beta blocker use | 1.56† (1.26-1.93) |

*$P<0.001$; †$P\leq0.0001$; ‡$P=0.005$.

Krishnaswami A, et al. *Am J Cardiol.* 2012;109:36-41.

# BARI 2D Study: Gender-Based Angina Outcomes




Tamis-Holland JE, et al. *J Am Coll Cardiol.* 2013;61:1767-1776.

# MERLIN-TIMI 36 Trial: Ranolazine For Prevention of Recurrent Events After Non-ST-Elevation ACS

**Eligibility**

**Symptoms consistent with myocardial ischemia at rest**

- **Lasting at least 10 minutes**
- **Within last 48 hours**

**And at least one of the following:**

- **Elevated biomarker of necrosis**
- **ST depression of at least 0.1 mV**
- **Diabetes mellitus**
- **TIMI risk score for unstable angina/non-ST-elevation MI ≥3**

**All patients received standard treatment for non-ST-elevation ACS and secondary prevention**

**12 Weeks**
**Double-Blind**

**Ranolazine (n=3279)**
**200 mg IV over 1 hr,**
**followed by 80 mg/hr for 12-96 hours,**
**followed by 1000 mg orally once daily**

**Placebo (n=3281)**

**Primary Endpoint (composite):**
**First occurrence of CV death, MI, or recurrent ischemia**

Morrow DA, et al. *JAMA.* 2007;297:1775-1783.

# MERLIN-TIMI 36 Trial (NSTE ACS): Overall Major Safety Outcomes

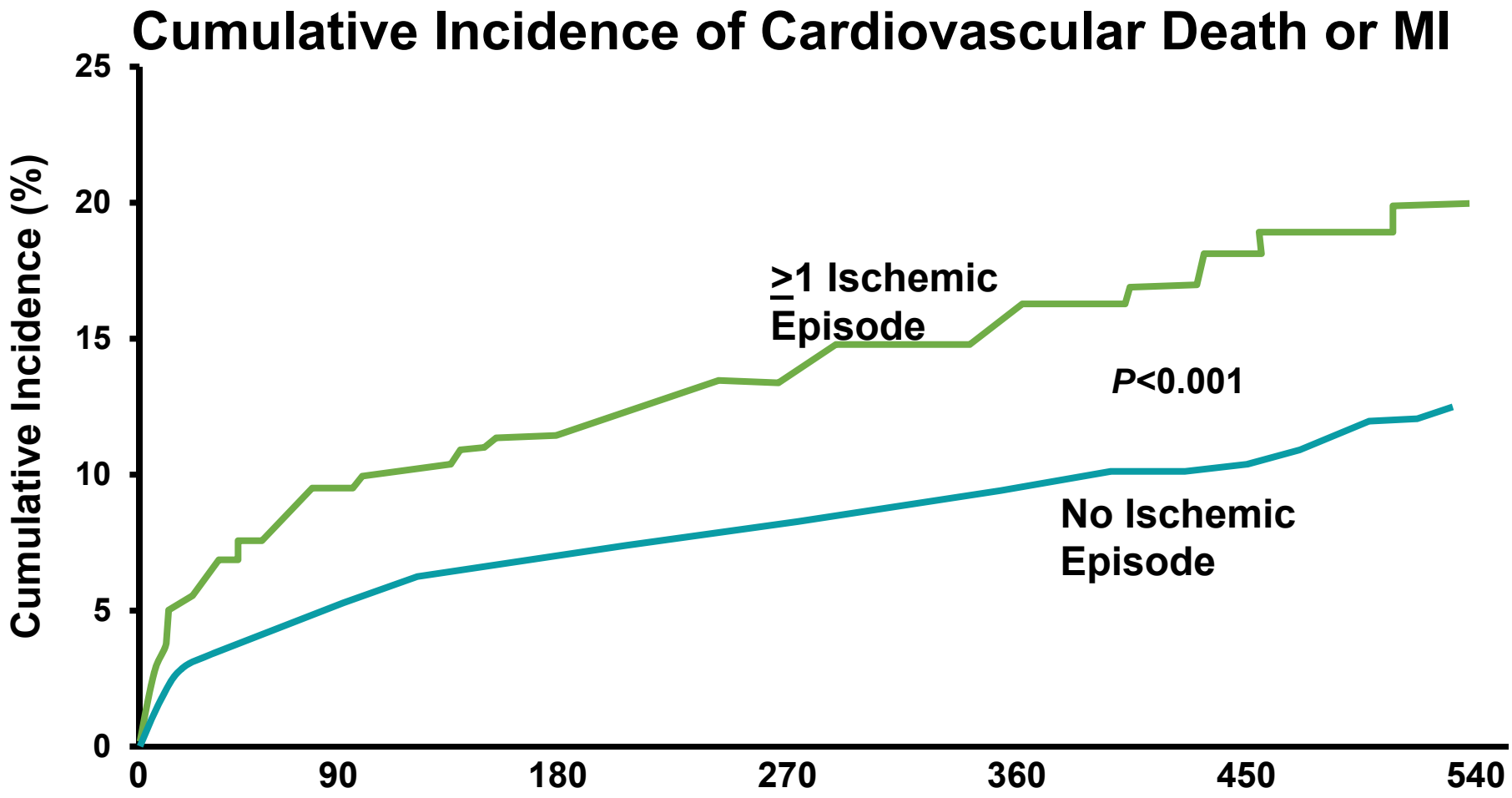
| | Event Rate (%) | | |
|---|---|---|---|
| | **Ranolazine (n=3268)** | **Placebo (n=3273)** | ***P* Value** |
| All-cause death | 5.3 | 5.4 | 0.91 |
| Sudden cardiac death | 1.7 | 1.8 | 0.43 |
| All-cause death or CV hospitalization | 33.2 | 33.4 | 0.53 |
| Symptomatic documented arrhythmia | 3.0 | 3.1 | 0.84 |
| Clinically significant arrhythmia on Holter* | 73.7 | 83.1 | <0.001 |

NSTE ACS: non-ST-elevation acute coronary syndromes.

*Ventricular tachycardia ≥100/min for ≥3 beats, supraventricular tachycardia ≥120/min for ≥4 beats, bradycardia ≤45/min, pauses >2.5 seconds, or third-degree heart block.

Morrow DA, et al. *JAMA.* 2007;297:1775-1783.

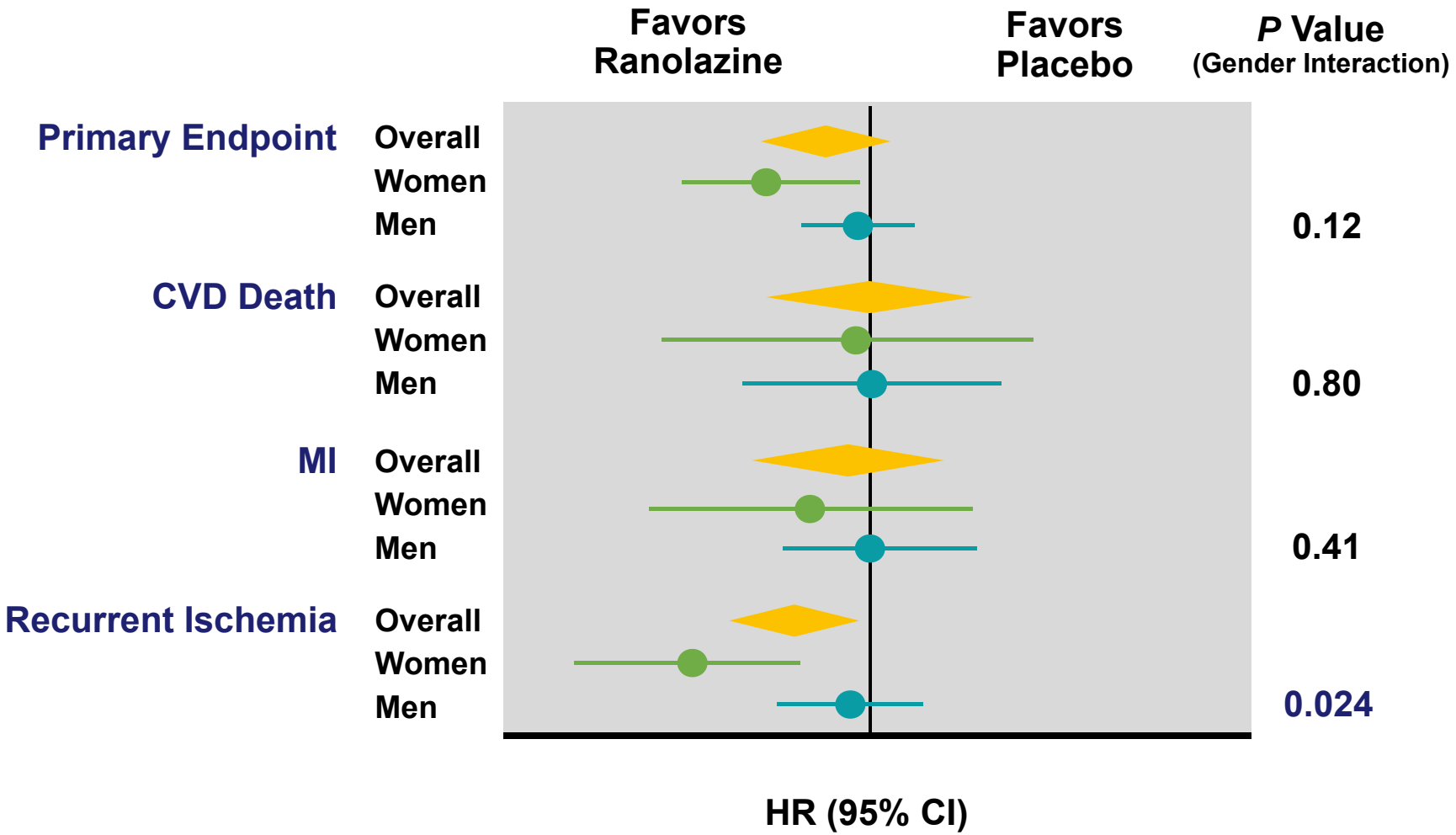
# MERLIN-TIMI 36 (NSTE ACS): Women With Ischemia Detected on cECG Monitoring




NSTE ACS: non-ST-elevation acute coronary syndromes.

Mega JL, et al. *Circulation.* 2010;121:1809-1817.

# MERLIN-TIMI 36 Trial (NSTE ACS): Efficacy Outcomes by Gender

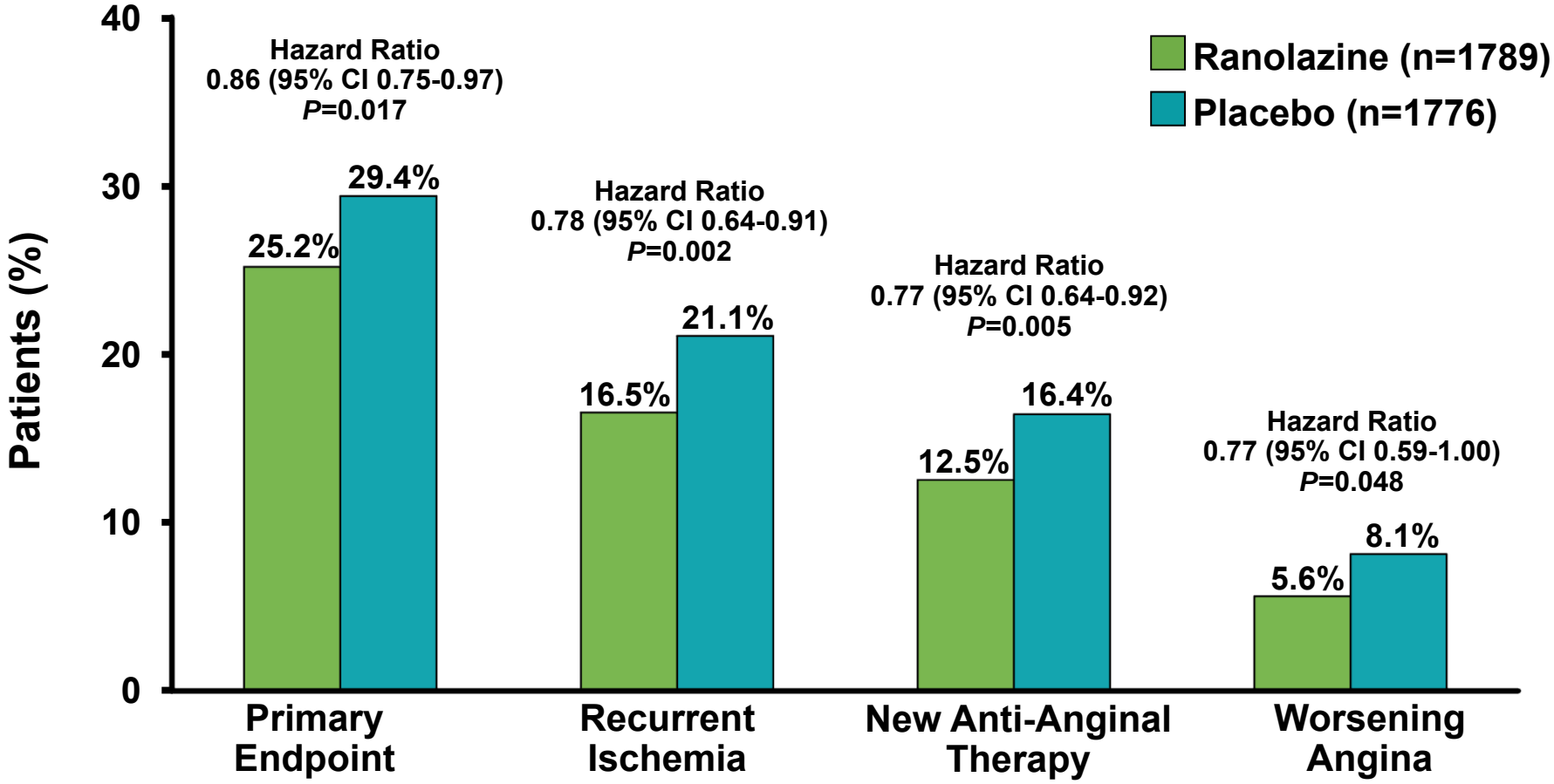



NSTE ACS: non-ST-elevation acute coronary syndromes.

Mega JL, et al. *Circulation.* 2010;121:1809-1817.

# MERLIN-TIMI 36 (NSTE ACS): Chronic Angina Subanalysis

## Patients With Chronic Angina Presenting With ACS




NSTE ACS: non-ST-elevation acute coronary syndromes.
Primary outcome: cardiovascular death, MI, or recurrent ischemia.

Wilson SR, et al. *J Am Coll Cardiol.* 2009;53:1510-1516.

# Potential Therapies for Endothelial Dysfunction

## Pharmacologic

- Nitrates
- Calcium-channel blockers
- Statins
- ACE inhibitors
- Tricyclic antidepressants
- Estrogen

## Non-Pharmacologic

- L-arginine
- Exercise
- Cognitive behavioral therapy
- Transcendental meditation
- Transcutaneous electrical nerve stimulation

# WISE Substudy: ACE Inhibition and Microvascular Dysfunction

- Double-blind substudy (n=78)
  - Women with microvascular dysfunction with signs and symptoms of ischemia without obstructive CAD
  - CFR <3.0 (adenosine)
- Randomized arms
  - ACE inhibitor
  - Placebo
- Outcome variables
  - Primary: CFR at week 16
  - Secondary: angina frequency subscore (SAQ)

**Baseline Characteristics**

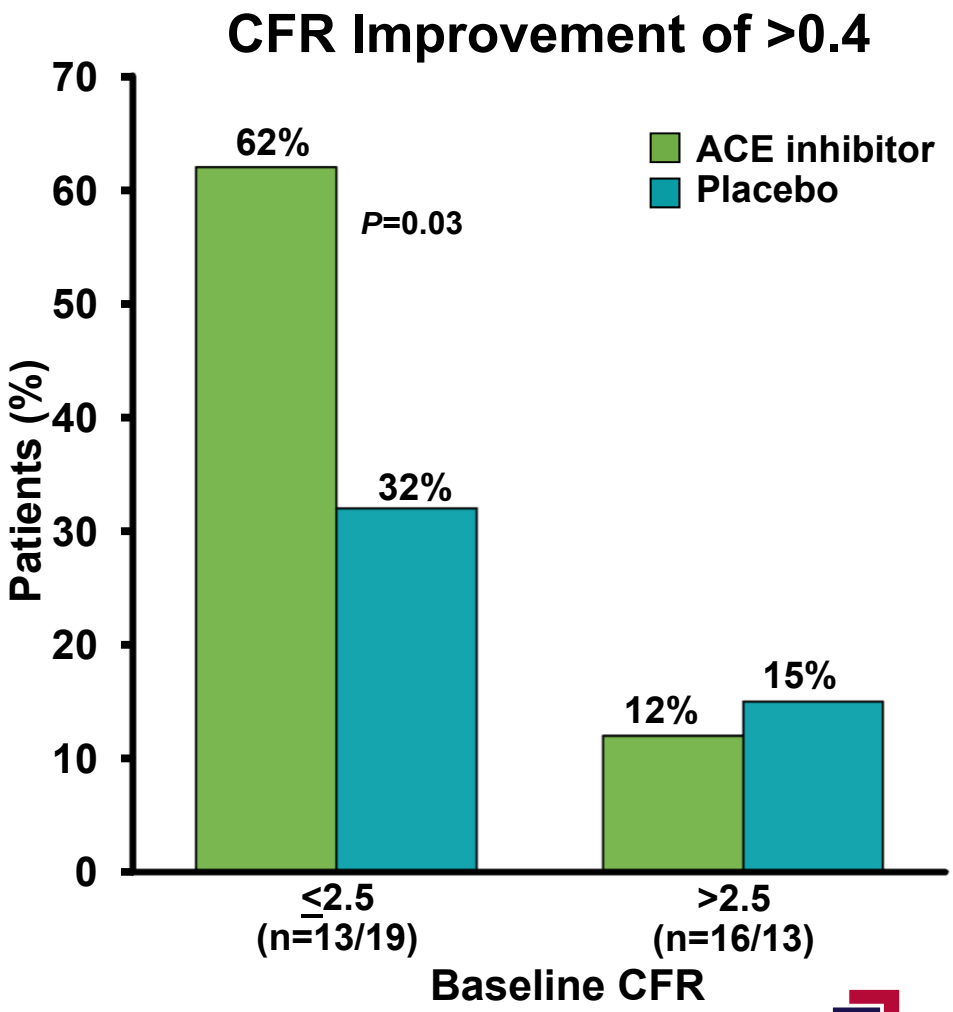
| | ACE-I (n=29) | Placebo (n=32) |
|---|---|---|
| Age (years) | 56 | 51 |
| Racial minority (%) | 7 | 9 |
| Mean CFR | 2.52 | 2.44 |
| Angiographic findings | | |
| CAD severity score | 5.9 | 6.6 |
| Stenosis ≥20% (%) | 35 | 41 |
| LVEF | 69 | 68 |
| BMI (kg/m$^2$) | 29.4 | 32.9 |
| History (%) | | |
| Diabetes | 17 | 6 |
| Hypertension | 34 | 44 |
| Dyslipidemia | 61 | 45 |

CFR: coronary flow reserve.

Pauly DF, et al. *Am Heart J.* 2011;162:678-684.

# WISE Substudy: Effect of ACE Inhibition on Coronary Flow Reserve

- At 16 weeks, CFR significantly improved with ACE inhibition versus placebo (*P*=0.019; adjusted for baseline CFR, diabetes history, and clinical site)
  - Improvement limited to women with lower baseline CFR values
- Improvement in CFR associated with reduction in angina
  - ACE inhibition arm had higher (indicating improvement) SAQ scores at week 4 (*P*=0.0003) and 16 (*P*=0.02) versus placebo




CFR: coronary flow reserve.

Pauly DF, et al. *Am Heart J.* 2011;162:678-684.

# Summary

- Cardiovascular disease is the leading cause of death in women
  - Mostly due to ischemic heart disease and stroke
  - Angina is a more common manifestation
- Diagnostic tests can be used to accurately risk stratify women
  - Exercise capacity and markers of ischemia particularly important
- Microvascular angina: angina and ischemia without epicardial CAD in women
- Treatments effective for symptom and ischemia management in symptomatic women with evidence of ischemia and no obstructive CAD
- Future studies needed to tailor diagnostic and therapeutic strategies to optimize outcomes

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- Reminder email communications will be sent up to 5 days post lecture until the evaluation is completed
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- In addition, you will receive a long-term evaluation via email 8 to 12 weeks after completing this course to measure competence, performance and/or patient outcomes achieved as a result of your participation in this CME/CNE/CPE sponsored educational activity

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