The Heartbreaking Killer: Women and Heart Disease

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Objectives

1. Describe why the American Heart Association (AHA) released a scientific statement on women and treatment of acute myocardial infarction (AMI).
2. Apply knowledge of sex-based differences in physiology and pathophysiology to identify how presentation for AMI differs between women and men.
3. Develop a patient-centered plan that facilitates treatment of cardiovascular risk factors for adult female patients.
4. Recommend treatments and therapies for AMI in women in a timely and appropriate fashion.
5. Design a roadmap to assess gaps in patient care for women with acute myocardial infarction and congestive heart failure.

MI in Women

- Leading cause of morbidity and mortality for women in the United States and globally
  - Afflicts 6.6 million women annually in the US
- Remains understudied, underdiagnosed, and undertreated in women.
- Multiple studies have demonstrated that women with acute coronary syndromes (ACS) are less likely to:
  - Be treated with guideline-directed medical therapies
  - Undergo cardiac catheterization or to receive timely reperfusion
  - Be enrolled in a cardiac rehabilitation course
- In 2016, the AHA published its first scientific statement on MI in women

Mehta LS, et al. Circulation. 2016;133.

Cardiovascular Disease
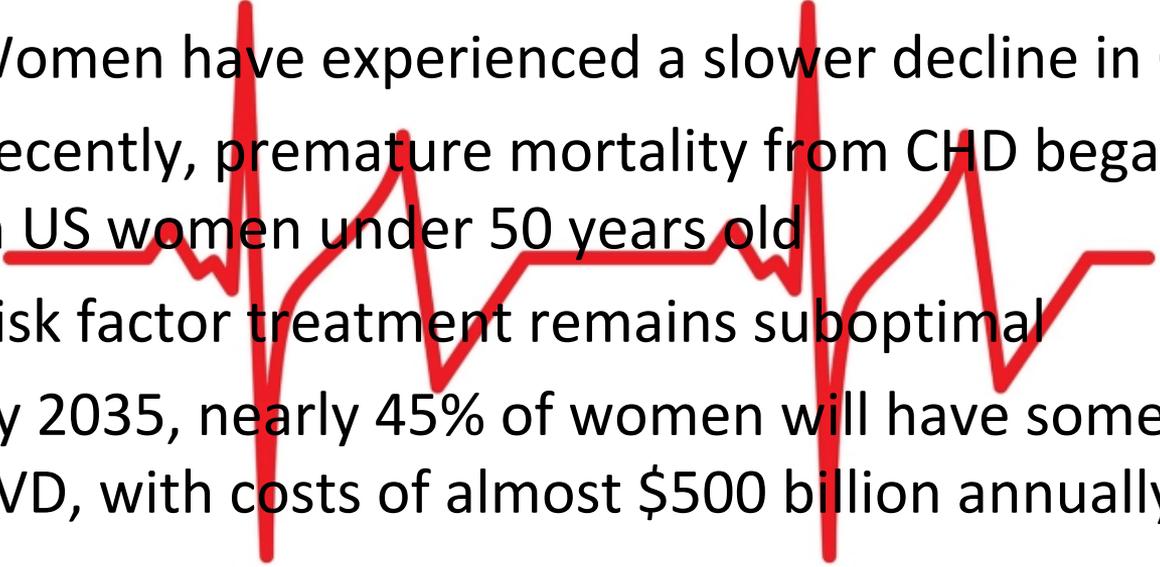
- Women have experienced a slower decline in CVD

- Recently, premature mortality from CHD began **increasing** in US women under 50 years old

- Risk factor treatment remains suboptimal

- By 2035, nearly 45% of women will have some form of CVD, with costs of almost $500 billion annually

Robinson JG, J Am Coll Cardiol 2017, ePub ahead of print

Why Such a Disparity?

- Heart disease traditionally considered a man's disease
- In 2014, a nationwide survey was conducted by the Women's Heart Alliance to determine barriers and opportunities for women and physicians with regard to CVD
  - Over 1,000 US women (ages 25 to 60 years) were interviewed
  - 100 cardiologists and 200 primary care physicians were interviewed

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Women's Health Alliance Survey

- Results: Women
  - Mean 45% of women were unaware that CVD is the #1 killer of women
    - Stratified by age, income, education and race/ethnicity
      - Least aware:
        » Patients under 30 years, making <$50,000 annually, no college degree and either Hispanic (73%) or African American (55%)
      - Most aware:
        » Patients 50 years or older, making >$100,000 annually, with college degree and Caucasian (34%)

What Women Don't Know CAN Hurt Them

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Women's Health Alliance Survey

- Results: Women
  - Only 27% knew a woman with heart disease
  - Only 11% knew a woman who died from heart disease
  - Over 70% almost never discussed heart disease with their physician
  - 74% of women reported having 1 more risk factor
    - Counseled more often to lose weight than address other CVD risk factors → caused 45% of women to cancel appointments until losing weight
  - 38% perceived something may be wrong with their heart
    - 1 in 2 told someone
    - Fewer than 1 in 3 called for medical attention

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Heart Disease Stigma

- Most (76%) rarely or never discussed heart health with family and friends
- 26% agreed that heart disease was embarrassing:
  - "people just assume you are not eating right or exercising"
- 57% said they knew they should be doing more to keep their heart healthy, but it could be overwhelming at times
- Among the 37% that were instructed to improve their heart health, the top reasons for making only some or none of the physician-recommended changes
  - Difficulties with getting time for regular exercise (41%)
  - Difficulties with losing weight (40%)

Women's Health Alliance Survey

- Results: Women
  - While over 80% knew that chest pain is a symptom of an MI, less than 50% knew that symptoms that are often specific to women
    - cold sweats
    - nausea or vomiting
    - anxiety
  - 82% agree the medical community needs to **do more** to educate women
  - 75% agree that women's heart disease needs **more attention** in medical training

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Women's Health Alliance Survey

Physician Survey Question	Primary Care Physicians	Cardiologists
List CVD as a top concern for women*	39%	--
Extremely well prepared to assess women's CVD risk	22%	42%
Implemented all 8 CVD risk assessments	16%	22%
Implement <5 CVD risk assessments	23%	20%
Currently using ASCVD Risk Calculator	44%	53%

*After weight loss and breast health

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Women's Health Alliance Survey

- Results: Physicians
  - Medical school prepared you to assess a woman's risk factors
    - Extremely or very well: PCP 49%, Cardiologist 59%
  - Receptive to awareness and education campaigns and supports **more research focusing on women**
    - **PCP 87%, Cardiology 82%**

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What Can Be Done?

1. Know the differences between men and women
2. Assess her with CVD in mind
3. Address her risk factors
4. If she presents, know the signs and symptoms unique to women
5. Treat her as aggressively as you would a man

What are some key differences between men and women in regards to heart disease?

1. Pathology of MIs
2. Pathology of MIs, risk factor response
3. Pathology of MIs, risk factor response, MI presentation
4. Pathology of MIs, risk factor response, MI presentation, response to treatment
5. Pathology of MIs, risk factor response, MI presentation, response to treatment, outcomes post MI

What are the Differences?

- Gender specific difference exist in
  - Pathophysiological mechanisms for MI
  - Response to risk factors
  - MI presentation
  - Responses to treatment
  - Outcomes post-MI

Mehta LS, et al. Circulation. 2016;133.

Pathophysiological Mechanisms

- The scientific evidence supports pathophysiological differences between women and men with AMI
  - Plaque rupture most responsible for fatal AMI events worldwide
    - 76% of men
    - 55% of women, rare in premenopausal women
  - Increased prevalence of plaque erosion (creates thrombus) in women compared with men
  - MI without obstructive CAD more common in women
    - 7 to 35% of women do not have not obstruction seen on angiography
      - Results in: plaque rupture and ulceration, plaque erosion, vasospasm, embolism

Mehta LS, et al. Circulation. 2016;133.

Pathophysiological Mechanisms

- Spontaneous coronary artery dissection is a rare cause of AMI that occurs more frequently in women

  – Should be suspected in any young woman who presents with an ACS without typical atherosclerotic risk factors

  – Occurs in 10.8% of women <50 years of age presenting with ACS or AMI

  – Associated with peripartum/postpartum status, oral contraceptive use, exercise, connective tissue disorders, and vasculitides (including fibromuscular dysplasia)

Mehta LS, et al. Circulation. 2016;133.

Cardiovascular Risk Factors

- Although men and women share similar risk factors for CHD, certain risk factors are more potent in women
  - Tobacco abuse
  - Type 2 DM
  - Depression
  - Other psychosocial risk factors
- For young women with favorable levels of all 5 major traditional risk factors (smoking, HTN, DM, cholesterol, and BMI), CHD is a rare.
- Unfortunately, only ~20% of US women <40 years of age meet the low-risk criteria
- Almost 50% of women have a clustering of ≥3 metabolic risk factors for ischemic heart disease.

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AHA's 8 CVD Risk Assessments

1. Personal (including pregnancy complications) and family medical history
2. Inquire about any heart disease symptoms
3. Inquire about smoking, diet, physical activity
4. Screen for depression and other psychological factors (anxiety, stress)
5. Physical exam, including BP, BMI, waist circumference
6. Measure cholesterol, TG and glucose levels
7. Calculate 10-year and lifetime CVD risk
8. Discuss what each of the above means for her heart health

Lifestyle

	Healthy Diet	Regular Physical Activity	Avoid Weight Gain	Modest Weight Loss in Some
Primary Prevention Age 20 to 75 years	✔	✔	✔	✔
Primary Prevention Over age 75 years	✔	✔		
High Risk Populations*	✔	✔	✔	✔

*Clinical ASCVD, diabetes (age 40 to 75 years), LDL-C ≥ 190 mg/dL

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Smoking

- **Smoking** is the most important preventable cause of MI in women
  - Leading cause of MI in women <55 years of age, increasing risk 7-fold
  - Smoking has a stronger correlation to MI in women than men
  - Risk of MI is substantially reduced within 1-2 years of cessation and falls to level of nonsmokers within 10-15 years
  - Decline in tobacco has been less pronounced in the US in women than in men

Mehta LS, et al. Circulation. 2016;133.

Depression/Stress/Anxiety

- Psychological factors and emotional stress influence ischemic heart disease, especially in women
- INTERHEART study: aggregate exposure to depression, home/work stress, low levels of control and major life events increase risk of AMI in women (OR 3.5)
- VIRGO study: Women presenting with MI have higher perceived stress scores
- Depression is ~2x more prevalent in women than men
  - Increases a woman risk of MI or cardiac death by at least 50%
  - Powerful predictor of early-onset MI, especially for women

Mehta LS, et al. Circulation. 2016;133.

Hypertension

- More strongly associated with MI in women
  - Risk of MI could be reduced by 36% if hypertension is eliminated
- In older women, isolated systolic BP most common
- Women have a low rate of HTN awareness, treatment and control
- Goal <140/90 mm Hg for most unless
  - HF <130/80 mm Hg
  - Albuminuria <130/80 mm Hg

Mehta LS, et al. Circulation. 2016;133.

Hypertension

- Treat HTN according to concomitant diseases, if applicable
  - Patients with essential HTN or diabetes:
    - Start with ACE inhibitor or ARB, thiazide diuretic, nondihydropyridine CCB
    - African Americans: Start with thiazide diuretic or nondihydropyridine CCB
  - Albuminuria (with or without diabetes)
    - Start with ACE inhibitor or ARB
  - Heart disease
    - Start with ACE inhibitor or ARB and beta blocker
  - Heart failure
    - Start with ACE inhibitor or ARB, HF beta blocker, and aldosterone antagonist (if indicated)

Dyslipidemia

- Reduced HDL-C and high triglycerides are powerful risk factors for CHD in women
- Statin Therapy: Benefits regardless of sex for primary prevention
  - Select statin intensity based on risk, if indicated:
    - Age 40 to 75 years:
      - If 10 year ASCVD risk ≥7.5%
    - Age over 75 years
      - Individualize
  - High risk populations – Moderate to high intensity statin, based on risk
    - Everyone if no contraindications
  - Women have a higher discontinuation rate from ADRs
  - All statins are pregnancy category X

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Obesity

- Obesity is a major risk factor for AMI in women and increases risk ~3-fold
  - Women in the heaviest category have a 4-fold increase in CV events
- 1/3 of US women are obese and 7% are extremely obese (BMI ≥40 kg/m^2)
  - More prevalent in black women: 54% obese and 15% extremely obese
- Risk of AMI associated with the metabolic syndrome is higher in younger women than any of the other groups, increasing their odds almost 5-fold
- Focusing too much on this RF can be discouraging for women

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Diabetes

- Powerful risk factor in young women, increasing their risk of CHD, by 4- to 5-fold.
  - Women with diabetes have a higher relative risk of coronary events when compared to men with diabetes
    - Higher rate of coexisting risk factors in women with DM
- For both men and women with DM, mortality after STEMI or UA/NSTEMI is significantly increased compared to patients without diabetes at 30 days and 1 year

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Estimate ASCVD Risk

- ASCVD Risk Assessment – primary prevention
  - Assess adults 20–79 years of age at least once every 4–6 years.
    - Age 20–39 – Assess risk factors.
    - Age 40–79 – Use Pooled Cohort Equations.
  - Pool cohort equation available at
    - http://tools.acc.org/ascvd-risk-estimator/

Risk Factor	Units	Value	Acceptable range of values	Optimal values
Sex	M (for males) or F (for females)	F	M or F	
Age	years	40	20-79	
Race	AA (for African Americans) or WH (for whites or others)	AA	AA or WH	
Total Cholesterol	mg/dL	255	130-320	170
HDL-Cholesterol	mg/dL	35	20-100	50
Systolic Blood Pressure	mm Hg	150	90-200	110
Treatment for High Blood Pressure (if SBP >120)	Y (for yes) or N (for no)	N	Y or N	N
Diabetes	Y (for yes) or N (for no)	Y	Y or N	N
Smoker	Y (for yes) or N (for no)	Y	Y or N	N

Your 10-Year ASCVD Risk (%)	21.0%
10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels	0.3%
Your Lifetime ASCVD Risk* (%)	50.0%
Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)	8.0%

*This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches.

ASCVD Risk Estimator*

10-Year ASCVD Risk

21.0% calculated risk

0.3% risk with optimal risk factors**

Lifetime ASCVD Risk

50% calculated risk

8% risk with optimal risk factors

Recommendation Based On Calculation ❯

Gender
Male | **Female**

Age
40

Race
○ White
● African American
○ Other

HDL - Cholesterol (mg/dL)
35

Total Cholesterol (mg/dL)
255

Diabetes
Yes | No

Treatment for Hypertension
Yes | **No**

Systolic Blood Pressure
150

Smoker
Yes | No

ashp 75
CELEBRATING YEARS

Consider High-Intensity Statin

Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. (I A)

High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. (IIa B)

It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. (IIa C)

Lifestyle Recommendations

AHA/ACC guidelines stress the importance of lifestyle modifications to lower cardiovascular disease risk. This includes eating a heart-healthy diet, regular aerobic exercises, maintenance of desirable body weight and avoidance of tobacco products.

Aspirin

- Clinical ASCVD: everyone unless contraindicated

- Primary prevention
    - Consider for ages 50–59 years
        - With ≥10% 10-yr ASCVD risk
        - Without bleeding risk factors
        - Life expectancy ≥ 10 years
        - Willingness to take aspirin for 10 years

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Unique Opportunities

- Pregnancy as a stress test can identify women at high risk
- Evaluate CVD health during regular gynecologic exams
  - OBGYN docs should feel comfortable with assessment and treatment or referral as needed
- Coincide CVD risk evaluation with mammograms at minimum

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Patient Case

- Carrie is a 60 year old white woman new to your clinic.
- She had a NSTE-MI 2 years ago and she smokes 1 PPD. She has depression but has not been treated for it in the last year.
- Today, her BP 160/92 mm Hg with similar repeat; HR 90 bpm. She's been told in the past her BP high. Her BMI is 31.
- Fasting labs: TC 240, LDL-C 150, HDL-C 40, TG 250, Scr 1.2, glucose 95
- She is currently not taking any medications the past year because she did not feel well on them. Previously taking: aspirin 81 mg/day, simvastatin 40 mg/day, metoprolol 50 mg twice daily, venlafaxine 225 mg/day
- What medications should be started for her?

Patient Case

- Careful medication history is warranted to try to figure out what caused her ADRs and what they were
- Her high risk of a recurrent MI must be conveyed
- She needs smoking cessation counseling and therapies
- She needs treatment for her BP. Consider starting lower dose metoprolol, perhaps succinate (has not been statistically associated with depression). She needs an ACE inhibitor as well.
- Restart aspirin 81 mg/day.
- Consider a different statin, perhaps atorvastatin. Start low and attempt to titrate to high intensity.
- Trial a different antidepressant
- Counsel on healthy lifestyle

Differences in Presentation

- Sex differences remain in presentation of MI
- Differences create challenges for timely identification, diagnostic testing, and treatment initiation
  - AMI symptoms
  - Sudden cardiac death
  - Delays in presentation to emergency care

Clinical Presentation

- Women present with
  - Typical chest pain (pressure, tightness, squeezing)
  - Atypical chest pain (sharp, pleuritic, aching, reproducible)
  - Angina equivalent symptoms: dyspnea, weakness, fatigue, and indigestion
- Differences have consequences
  - Timely identification of ischemic symptoms
  - Appropriate triage
  - Judicious diagnostic testing and management
- Detrimental consequences for women are
  - Misdiagnosis
  - Delayed revascularization
  - Higher AMI mortality rates

Circulation. 2016;133:(ahead of print)

Treatment of AMI

- Women are referred for fewer appropriate treatments compared to men

- Multiple confounders and risk factors yield worse outcomes in women than men

- Will review key findings regarding treatments for AMI

STEMI: Thrombolytic Therapy

- Associated with higher risk of mortality and bleeding compared to PCI

- Appropriate for non-PCI capable facilities and when door-to-balloon time is greater than 120 min from first medical contact (Class I/LOE A)

- Women have greater rates of morbidity and mortality
  - More complex baseline illnesses
  - Greater rates of non-fatal complications from use

Mehta LS, et al. Circulation. 2016;133

STEMI: Thrombolytic Complications

- Increased frequency of bleeding complications in women
  - Moderate or severe bleeding at rate of 1.43 times that of men
  - Female sex is an independent predictor for ICH in women
- Less likely to receive thrombolytic therapy overall
  - Multiple relative contraindications
  - Greater physician hesitation

Weaver et al. JAMA 1996;275: 777-782.

STEMI: PCI

- Associated with lower mortality rate at 1 month compared to thrombolysis

- Reduced risk of ICH compared with thrombolytic use

- Stent placement:
    - Lower rates of major adverse clinical events
    - Target vessel revascularization

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STEMI: CABG

- Use of CABG during AMI remains rare

- Systematic reviews of literature demonstrate:
  - Women are older than men at presentation for CABG
  - Women have more comorbidities at time of CABG
  - Demonstrate increased in-hospital mortality than men

- More frequent post-op complications

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NSTEMI: PCI

- Women demonstrate higher complication rates:
  - Bleeding
  - Heart failure
  - Renal failure
  - Reinfarction
  - CVA
  - Readmission
- Early invasive strategy remains Class I/LOE A recommendation

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NSTEMI: PCI / CABG

- Myocardial revascularization may be considered in pregnant women if medical management ineffective (Class IIa/ LOE C)

- No notable differences in outcomes with DES

- CABG yields greater complication rates in women, though similar rates for death, MI or stroke

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Medical Management: Therapy Goals

- Reduce morbidity and mortality

- Prevent complications

- Improve quality of life

2014 ACC/AHA NSTEMI Recommendations

- ACC/AHA NSTEMI guidelines recommend treatment with same treatments as men both acute and after (Class I/LOE B)
  - Employ weight-based dosing
  - Renally adjust antiplatelet and anticoagulants to lessen ADRs.
- Evidence-based pharmacotherapy remains underutilized in women with nonobstructive disease

Amsterdam et al. Circulation 2014;130:2354-94.

Role of Medication Review

- Limit exposure to drugs that are not helpful or harmful
  - Estrogen and combination products should be avoided or discontinued
  - Antioxidants are not beneficial in secondary prevention
    - Vitamin E
    - Vitamin C
    - Beta-carotene
    - Folic acid

Medical therapy after AMI

- Antiplatelets and anticoagulants
- Beta-blocker therapy
- ACE-Inhibitors / ARBs
- Statins
- Non-pharmacological interventions
  - Cardiac rehabilitation

Antiplatelet Therapies

- Aspirin:
  - Used in secondary prevention to lessen recurrent ischemia
  - No efficacy difference in women and men
  - Start immediately
- Clopidogrel:
  - Meta-analysis finding: reduced MI rate in women
  - Meta-analysis finding: reduced MI/CVA/all-cause mortality
  - May be associated with chance
- Higher potency $P2Y_{12}$ inhibitors
- Continue antiplatelet therapy lifelong

Mehta LS, et al. Circulation. 2016;133.

Anticoagulants

- Class I recommendation for NSTEMI and STEMI
- No sex differences noted between men and women
  - Unfractionated heparin
  - LMWH
  - Bivalirudin
  - Fondaparinux
  - Glycoprotein Iib/IIIa inhibitors

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Beta-blocker therapy

- No significant differences in outcomes between sexes
  - 21% mortality reduction
  - 30% sudden cardiac death reduction
  - 25% lower reinfarction rate
- Therapies remain underused in women
- Avoid use in patients with coronary artery vasospasm

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Patient Scenario

- SN is a 53-year old female patient who had NSTEMI in 2013 with successful PCI with stenting.

- She returns for regular follow-up for secondary risk-factor management with complaints of extreme fatigue.

- Chart review demonstrates this concern is a consistent, and persistent issue for this patient.

Patient Scenario

- SN's current medications include aspirin 81 mg daily, metoprolol XL 25 mg daily, lisinopril 20 mg daily, atorvastatin 40 mg daily, metformin 500mg twice daily.

- Vital signs today reveal: weight 135 pounds, height 70 inches, BP 128/74, HR 62, RR 17.

- Lab values: A1c 6.7%, Mial 31, SCr 1.2 mg/dL, K 4.2.

- Ejection fraction is 50%.

- What medication changes should be undertaken for SN?

How should we adjust meds?

A. Continue meds, and refer for further workup of fatigue.

B. Stop metoprolol, continue other medications to see if fatigue lessens.

C. Stop lisinopril, continue other medications to see if fatigue lessens.

D. Hold all meds, and refer for further workup of fatigue

ACE-Inhibitors / ARBs

- Women underrepresented in clinical trials overall
- Trend towards improved survival and less frequent death and hospitalization
- Avoid during pregnancy (category C – 1st trimester / category D – 2nd and 3rd trimester)

Statins

- Beneficial in patients with CHD patients of both sexes
- Effective for secondary prevention of re-infarction
- No stroke or all-cause mortality benefit in women vs. men
- Pregnancy category X

Non-pharmacologic treatment

- Cardiac rehabilitation:
  - Class I recommendation
  - More than 80% of eligible women have not received since 1980s
  - Depressed women are at 2x increased risk of not completing
  - RCT of women only demonstrated increased QoL and symptoms
- Sex counseling

Complications after AMI in women

- Bleeding
- Cardiogenic shock
- Heart failure
- Mechanical complications
- Arrhythmias

Mehta LS, et al. Circulation. 2016;133.

Bleeding

- GRACE registry
  - women have 43% higher risk of bleeding over men
  - STEMI bleeding: women have greater risk over men (odds ratio 1.71)
- Causes of inappropriate bleeding
  - Access-related complications
  - Inappropriate dosing of antithrombotic therapies

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Indicators for Adverse Outcomes

- Disease severity

- Presentation characteristics

- Traditional risk factors

- Psychosocial risk factors

Disease Severity Markers

- Risk prediction models in use were developed with 2/3 majority male population

- TIMI risk score performs well in both men and women

- LVEF and ECG parameters predicted 5-year mortality

- Absence of sinus rhythm

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Characteristics of Presentation

"Better" outcomes	"Worse" outcomes
Chest pain	No chest pain
NSTEMI	STEMI
	DM
	"early" age (greater than 60 years)

Mehta LS, et al. Circulation. 2016;133.

Gaps in Knowledge of AMI in Women

- Effective interventions to reduce treatment delays

- Mechanisms for complications that occur

- How do psychological factors affect occurrence and recovery from MI

- Most effective interventions for diagnosis and treatment

- Modifiable factors contributing to sex disparities in applying EBM

Mehta LS, et al. Circulation. 2016;133.

Priorities to Improve Outcomes

- Increase awareness
- Examine role of genetic-environment interactions
- Determine how psychosocial risk factors influence CVD development
- Improve diagnostic and treatment methods
- Offer sexual counseling to women and partners prior to hospital discharge
- Increase pharmacotherapy treatment rates for secondary prevention
- Implement psychological treatments to increase adherence
- Develop and implement patient-specific strategies in place of cardiac rehab completion
- Identify and evaluate primary and secondary prevention interventions
- Develop strategies to increase female patient participation in CV research

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Roadmap for Primary Prevention

Indicated therapy	When to start	Duration of Treatment
Education on MI	Immediately	Continuously
Mitigation of risk factors - Hypertension - Lipids - Diabetes	Immediately	Continuously
Exercise therapy	Immediately	Continuously
Smoking Cessation	Immediately	Continuously
Medication adherence counseling	Immediately	Continuously

Roadmap for Secondary Prevention

Indicated therapy:	When to start:	Duration of treatment:
Aspirin	Immediately	Indefinitely
Antiplatelet		Situation-based
Anticoagulant	Immediately*	Situation-based
Beta-blocker	Upon presentation	Indefinitely vs. 3 years
ACE-Inhibitor	As soon as possible	Indefinitely
Statin	ASAP	Indefinitely
Cardiac rehab referral	At time of discharge	6-12 weeks

Key Takeaways

- Key Takeaway #1
  - Misperception continues that heart disease is a "man's disease" and that heart disease isn't as big of a risk in women
- Key Takeaway #2
  - Heart disease remains understudied, under-diagnosed, and under-treated in women
- Key Takeaway #3
  - There are unique pathological mechanisms for heart disease in men and women that should be identified and treated
- Key Takeaway #4
  - Risk factor management is key to lowering a woman's risk of a first or subsequent CHD event