Cardiovascular Health in Women

Matthew J. Budoff, MD

Professor of Medicine

Division of Cardiology

UCLA School of Medicine

Harbor-UCLA Medical Center, Torrance C.

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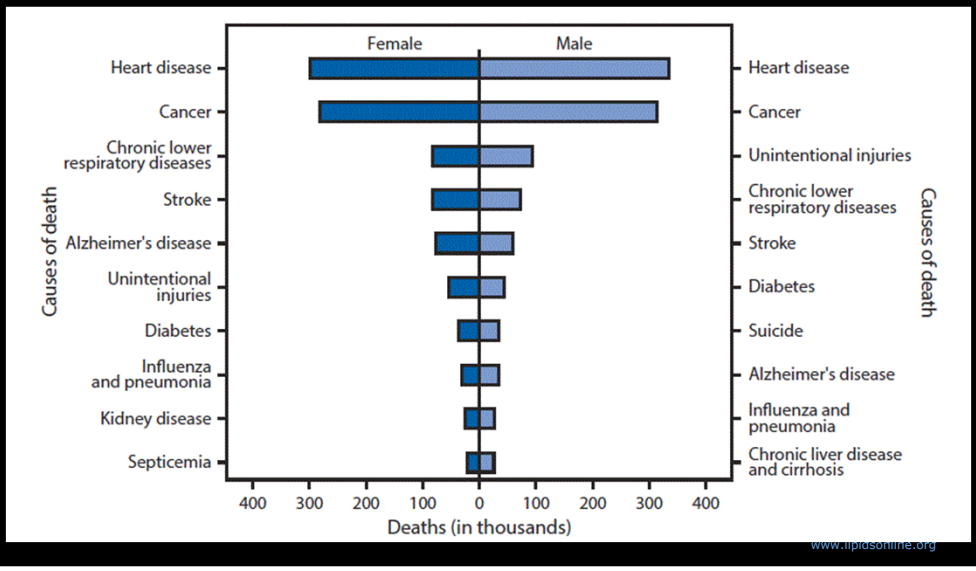
Heart Disease Still #1 Cause of Death Among Men and Women



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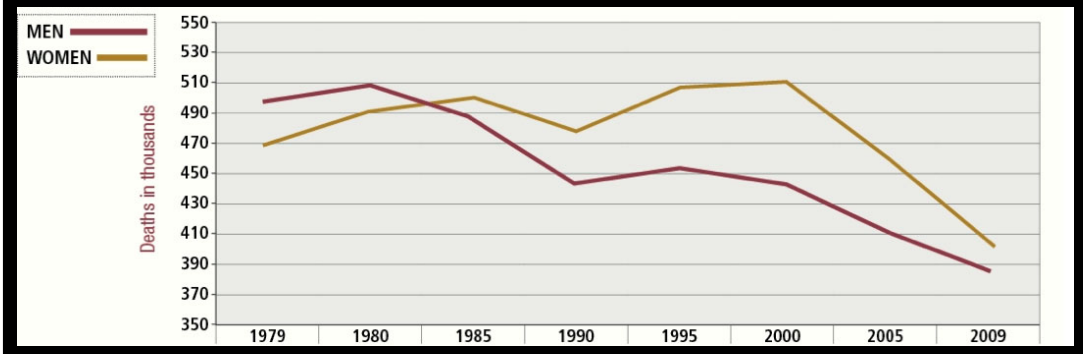
Cardiovascular Disease Deaths: *United States 1979–2009*



Years

American Heart Association. *2012 Heart and Stroke Statistical Update*. Dallas, Texas: AHA, 2012.

Slide Source:
Lipids Online
www.lipidsonline.org

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2018 STATS FROM AHA/ ASA

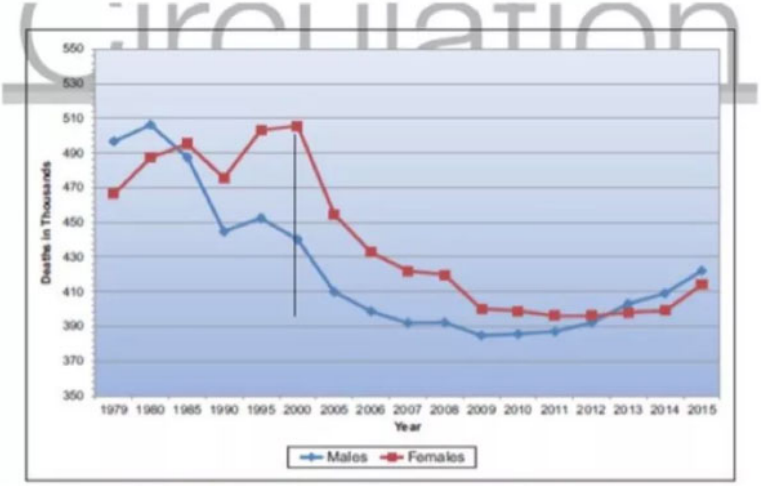

Chart 12-16. Cardiovascular disease (CVD) mortality trends for males and females (United States: 1979–2015).
CVD excludes congenital cardiovascular defects (*International Classification of Diseases, 10th Revision* [*ICD-10*] codes I00–I9
The overall comparability for cardiovascular disease between the *International Classification of Diseases, 9th Revision* (1979–1998) and *ICD-10* (1999–2015) is 0.9962. No comparability ratios were applied.
Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

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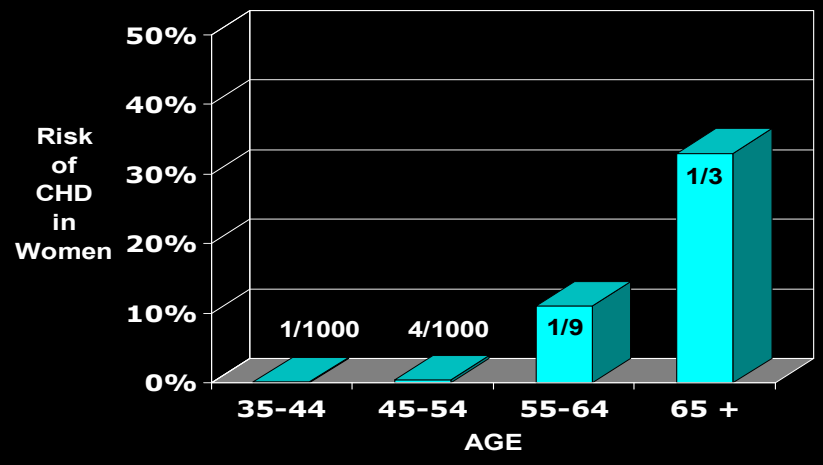
RISK OF CHD Death



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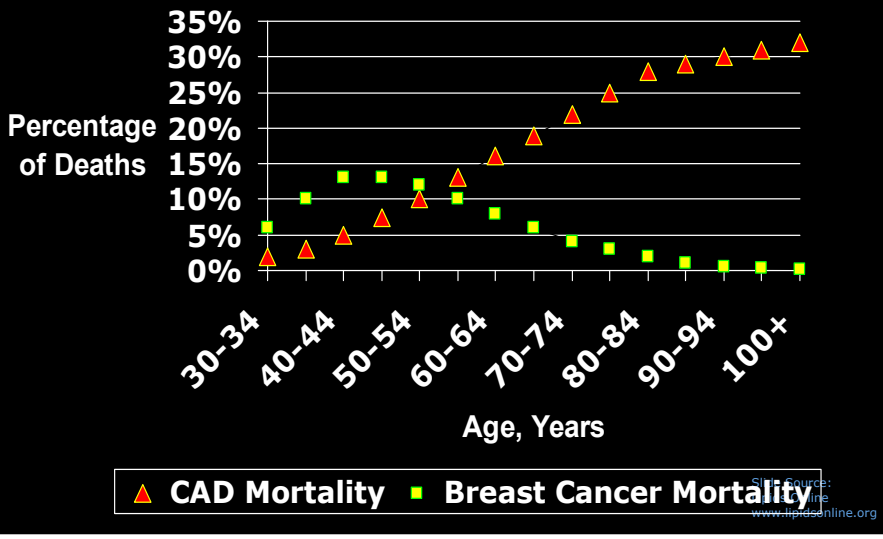
CHD - Breast Mortality



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RISK REDUCTION - III

- Traditional Cardiac Medications

A = Antiplatelet Therapy (Aspirin)

- 30% reduction (primary prevention) in men & women

B = Blood Pressure Reduction

- 25-30% reduction in MI and cardiovascular death (primary and secondary prevention)

C = Cholesterol therapy (statins)

- 32% reduction in mortality (prim & sec prev)

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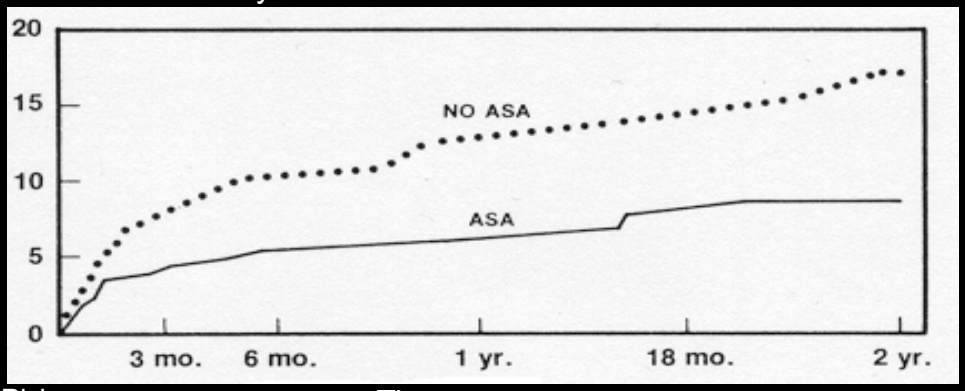
UA: CV Death or MI - ASA vs Placebo

Efficacy: Cardiac Death or Non-Fatal MI



At Risk					
ASA (263)	(174)	(137)	(107)	(73)
No ASA (274)	(180)	(144)	(115)	(80)

Cairns et al *NEJM* 1985;313:1369-1375

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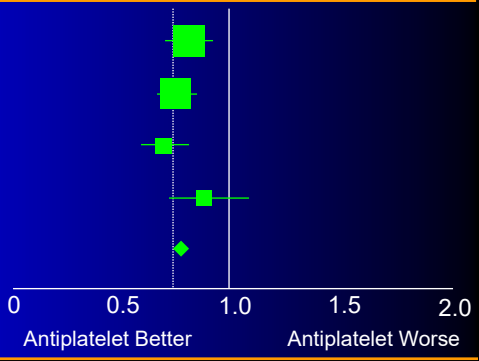
Efficacy of Aspirin Doses on Vascular Events in High Risk Patients

Aspirin Dose	# Trials	OR* (%)
500–1500 mg	34	19
160–325 mg	19	26
75–150 mg	12	32
<75 mg	3	13
Any aspirin	65	23



*Odds reduction.
Treatment effect *P* < 0.0001.

Adapted with permission from the BMJ Publishing Group. Antithrombotic Trialists' Collaboration. 6.

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Aspirin Evidence: Primary Prevention

Physician's Health Study (PHS)

22,071 male participants randomized to aspirin (325 mg every other day) followed for an average of 5 years

End point	Relative Risk (95% CI)	P value
CV Mortality	0.96 (0.60-1.54)	0.87
Myocardial infarction		
Fatal	0.34 (0.15-0.75)	0.007
Nonfatal	0.59 (0.47-0.74)	<0.00001
Total	0.56 (0.45-0.70)	<0.00001

There was a 44 percent reduction in the risk of myocardial infarction (relative risk, 0.56; 95 percent confidence interval, 0.45 to 0.70; P<0.00001) in the aspirin group (325 qOD). NEJM 1989

Slide Source:
Lipids Online
www.lipidsonline.org

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Women's Health Study: Low-Dose Aspirin in Primary Prevention Trial

39,876 initially healthy† women age ≥ 45
Randomized, blinded, factorial

Low-dose Aspirin
100mg on alternate days
n=19,934

Placebo
n=19,942

Endpoints (mean 10.1 years):
- Combined endpoint of nonfatal MI, nonfatal stroke, and total cardiovascular death.
- Incidence of total malignant neoplasms of epithelial cell origin.

†: No history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illness; no history of side effects to any of the study medications; not taking aspirin or nonsteroidal antiinflammatory medications (NSAIDs) more than once a week (or were willing to forego their use during the trial); not taking anticoagulants or corticosteroids; and not taking individual supplements of vitamin A, E, or beta carotene more than once a week.

Presented at ACC Scier

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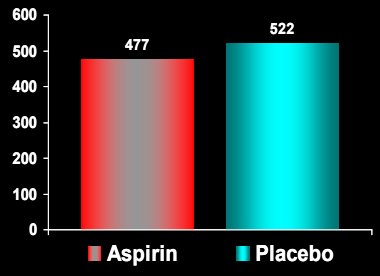
Women's Health Study: Low-Dose Aspirin in Primary Prevention Trial

Primary Composite Endpoint:
Major Cardiovascular Events
Relative Risk [RR] 0.91
95% CI 0.80-1.03
p=0.13

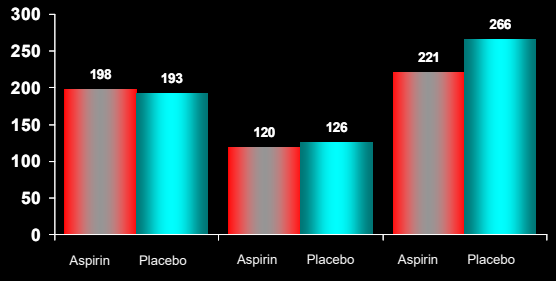


Composite Components:

MI
p=0.83

Death from CV Causes
p=0.68

Stroke
p=0.04



- Baseline characteristics were well matched between the two treatment groups.
- Among the individual components of the composite endpoint, there was no difference in MI or death from cardiovascular causes, but total stroke was lower in the aspirin group.

Presented at ACC Scientific

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CURE

Major Bleeding by ASA Dose

ASA Dose	ASPIRIN
<100 mg	**2.0%**
100–200 mg	**2.3%**
>200 mg	**4.0%**

* Other standard therapies were used as appropriate.

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New USPSTF 2021

- The USPSTF concludes with moderate certainty that aspirin use for the primary prevention of CVD events in adults ages 40 to 59 years who have a 10% or greater 10-year CVD risk has a small net benefit,"
- "The USPSTF concludes with moderate certainty that initiating aspirin use for the primary prevention of CVD events in adults age 60 years or older has no net benefit"

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ASPIRIN USE TODAY

"Heads, you get a quadruple bypass.
Tails, you take a baby aspirin."

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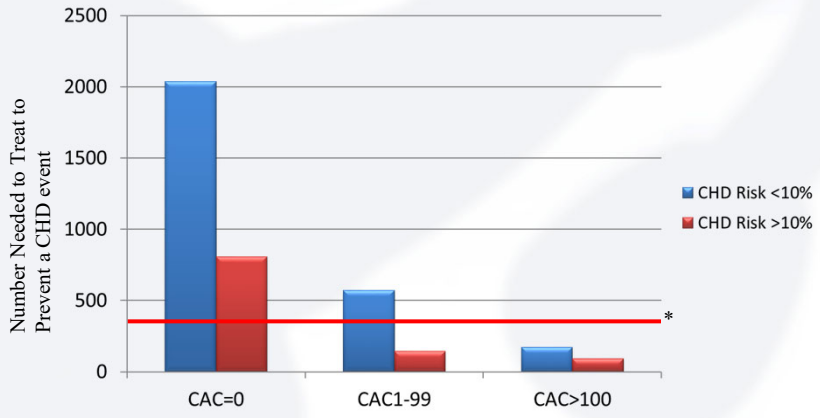
Risk/Benefits of ASA According to CAC



* Represents number needed to harm for a major bleeding event

Miedema et al. ASA and CAC – Circ Quality 2014

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Primary Prevention- AHA GUIDELINES

Preventive drug interventions

Aspirin—high risk*
Aspirin therapy (75 to 162 mg), or clopidogrel if patient is intolerant to aspirin, should be used in high-risk women unless contraindicated. (Class I, Level A)$_{GI=1}$

Aspirin—intermediate risk†
Consider aspirin therapy (75 to 162 mg) in intermediate-risk women as long as blood pressure is controlled and benefit is likely to outweigh risk of gastrointestinal side effects. (Class IIa, Level B)$_{GI=2}$

β-Blockers
β-Blockers should be used indefinitely in all women who have had a myocardial infarction or who have chronic ischemic syndromes unless contraindicated. (Class I, Level A)$_{GI=1}$

ACE inhibitors
ACE inhibitors should be used (unless contraindicated) in high-risk* women. (Class I, Level A)$_{GI=1}$

ARBs
ARBs should be used in high-risk* women with clinical evidence of heart failure or an ejection fraction <40% who are intolerant to ACE inhibitors. (Class I, Level B)$_{GI=1}$

Atrial fibrillation/stroke prevention

Warfarin—atrial fibrillation
Among women with chronic or paroxysmal atrial fibrillation, warfarin should be used to maintain the INR at 2.0 to 3.0 unless they are considered to be at low risk for stroke (<1%/y) or high risk of bleeding. (Class I, Level A)$_{GI=1}$

Aspirin—atrial fibrillation
Aspirin (325 mg) should be used in women with chronic or paroxysmal atrial fibrillation with a contraindication to warfarin or at low risk for stroke (<1%/y). (Class I, Level A)$_{GI=1}$

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2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

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Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

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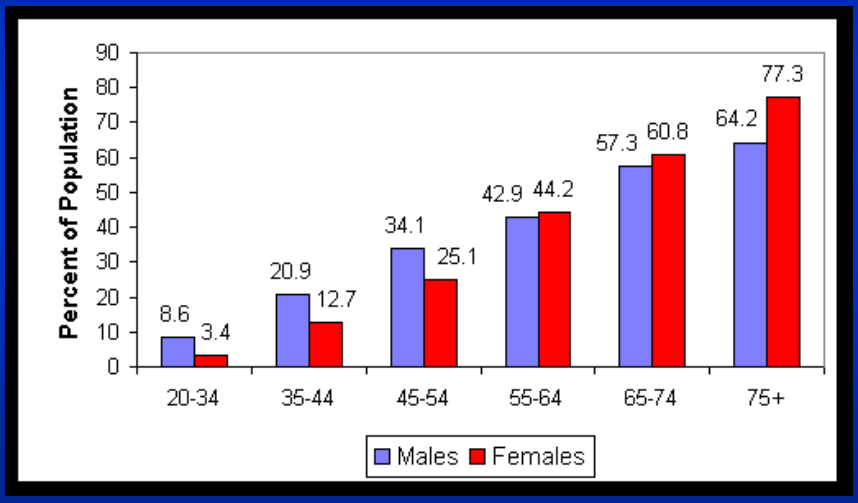
Estimated % of Americans With High Blood Pressure



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Nonpharmacological Interventions

COR	LOE	Recommendations for Nonpharmacological Interventions
I	A	Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese.
I	A	A heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension.
I	A	Sodium reduction is recommended for adults with elevated BP or hypertension.
I	A	Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion.

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SPRINT – NEJM 2015

SPRINT Research Question

Examine effect of more intensive high blood pressure treatment than is currently recommended

Randomized Controlled Trial
Target Systolic BP

Intensive Treatment
Goal SBP < 120 mm Hg

Standard Treatment
Goal SBP < 140 mm Hg

SPRINT design details available at:

- *ClinicalTrials.gov (NCT01206062)*
- *Ambrosius WT et al. Clin. Trials. 2014;11:532-546.*

SPRINT

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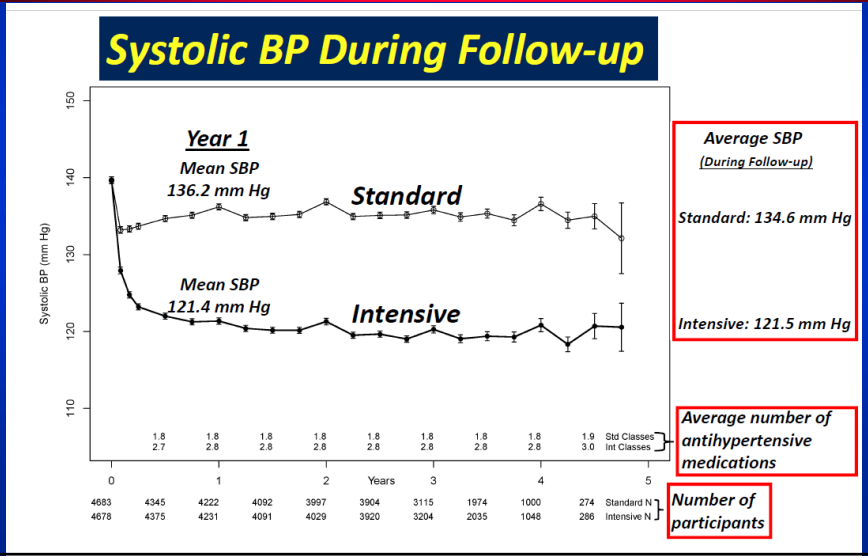
SPRINT NEJM 2015



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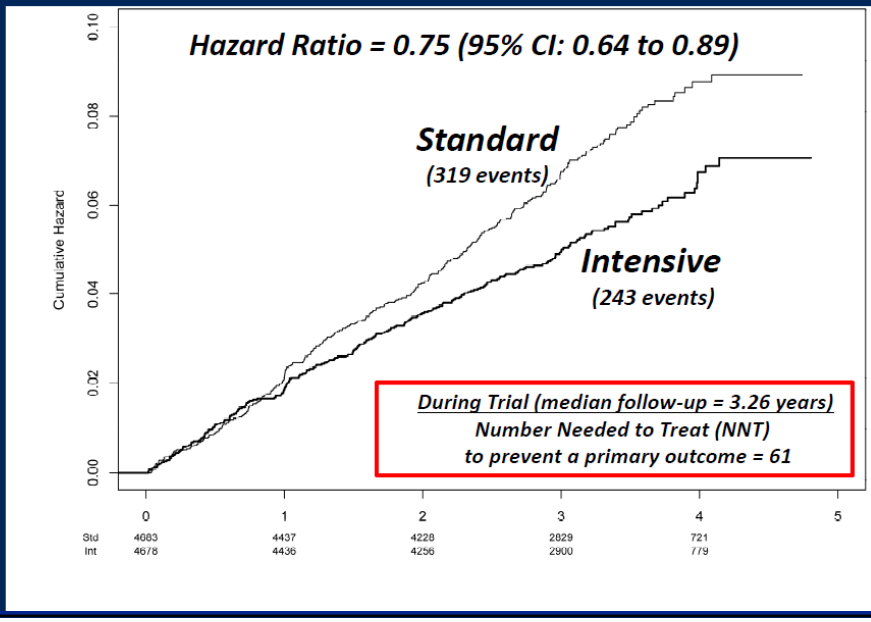
SPRINT Primary Outcome
Cumulative Hazard



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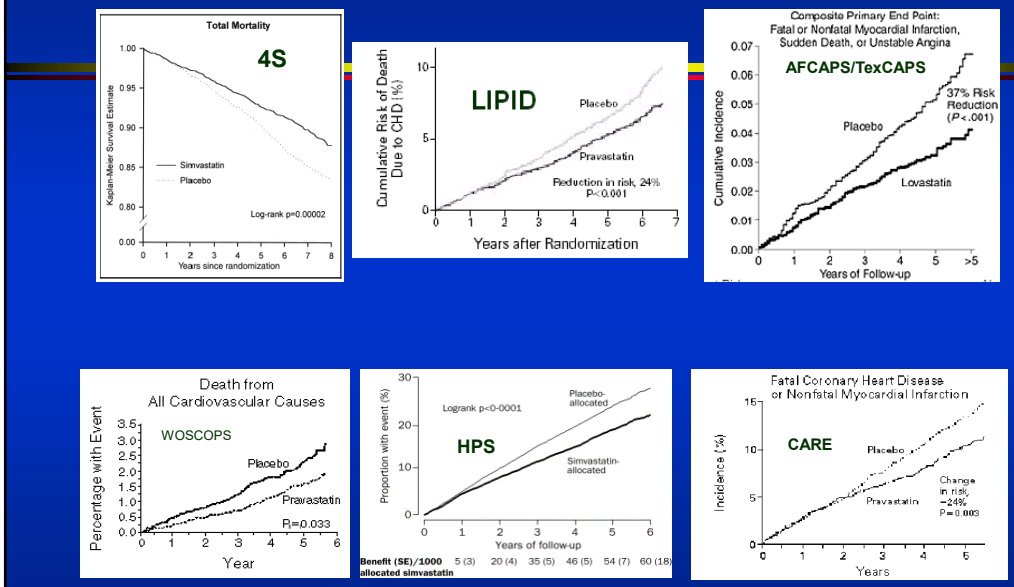

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Women In Clinical Trials

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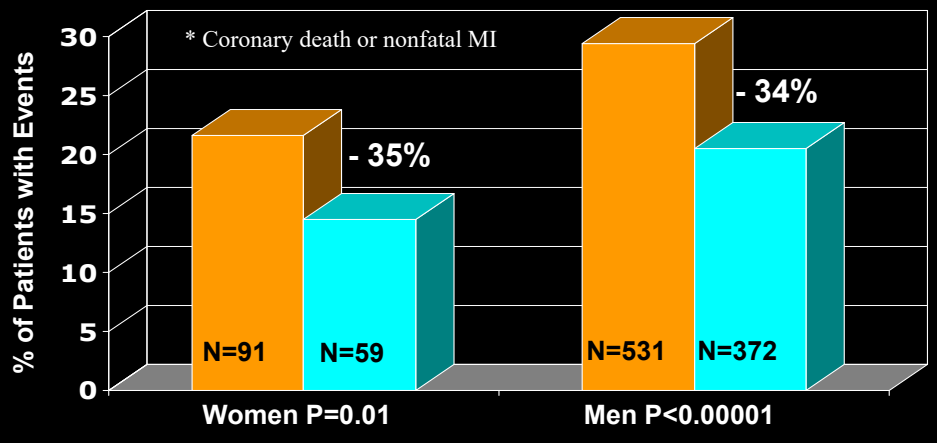
Simvastatin Survival Study

Subgroup Analysis: Gender - Women vs Men
Major Coronary Events *



Circulation 1977; 96: 4211-18

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Postmenopausal Women with CHD

Both 4S (827 women) and CARE (567 women) studies showed siginificant reduction in recurrent CHD events with LDL-C lowering therapy.

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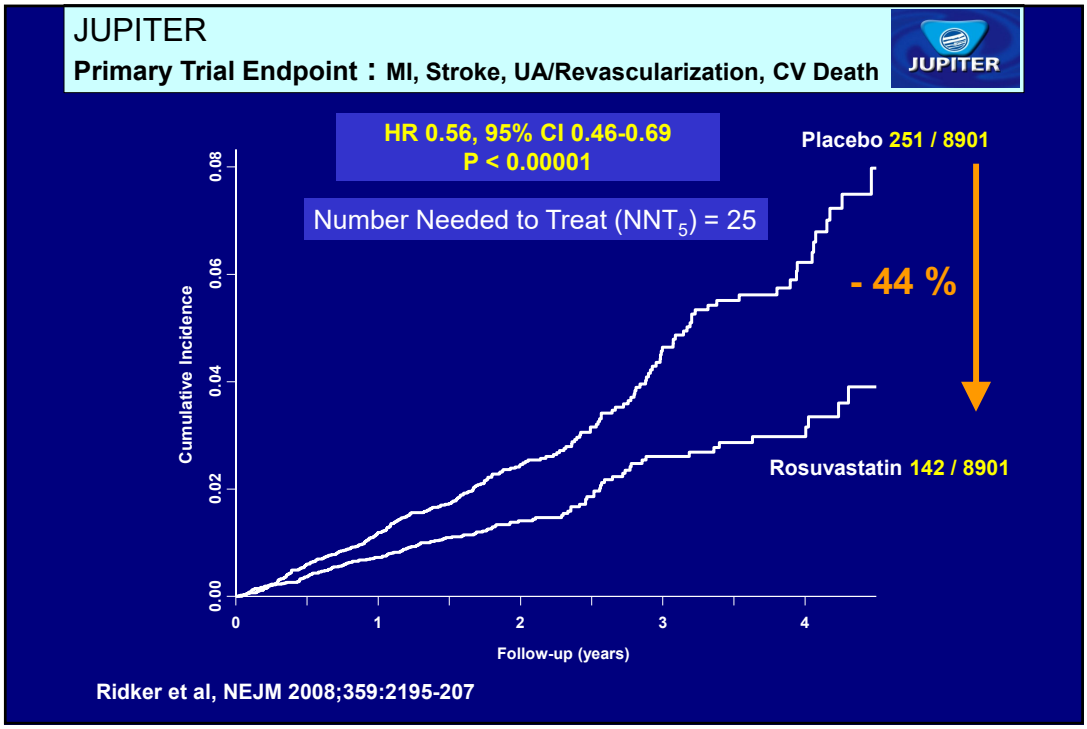
JUPITER
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death
JUPITER
HR 0.56, 95% CI 0.46-0.69
P < 0.00001
Number Needed to Treat (NNT5) = 25
Placebo 251 / 8901
- 44 %
Rosuvastatin 142 / 8901
Cumulative Incidence
0.00
0.02
0.04
0.06
0.08
0
1
2
3
4
Follow-up (years)
Ridker et al, NEJM 2008;359:2195-207

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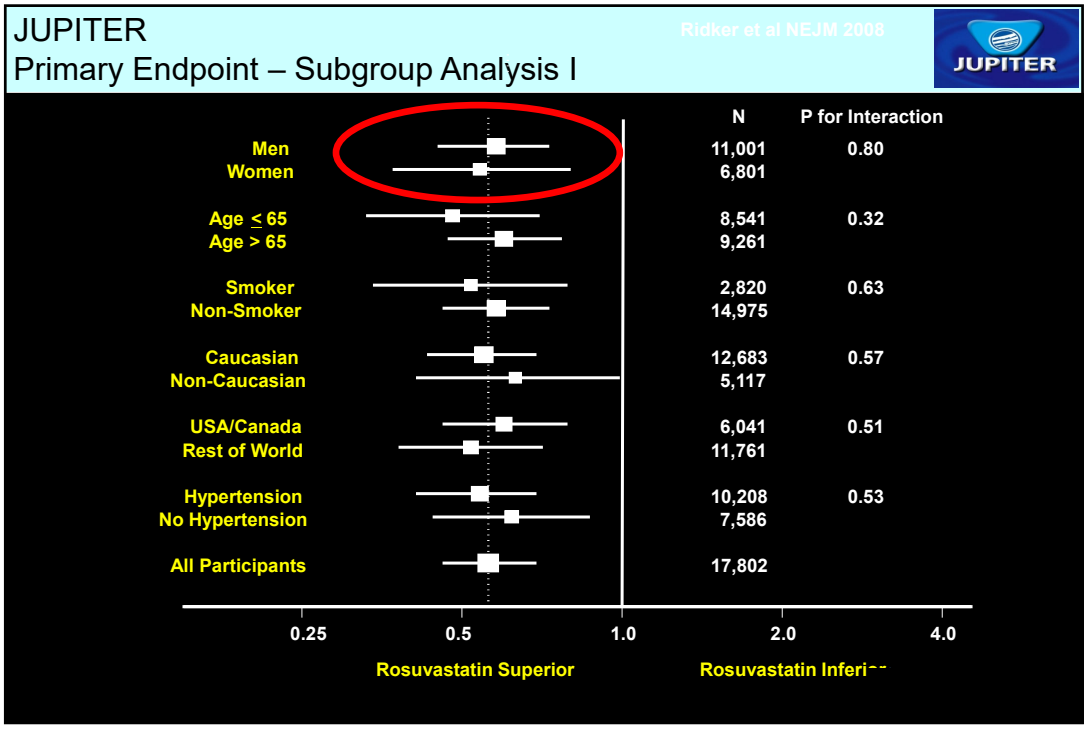
JUPITER
Primary Endpoint – Subgroup Analysis I
Ridker et al NEJM 2008
JUPITER
N
P for Interaction
Men
Women
11,001
6,801
0.80
Age ≤ 65
Age > 65
8,541
9,261
0.32
Smoker
Non-Smoker
2,820
14,975
0.63
Caucasian
Non-Caucasian
12,683
5,117
0.57
USA/Canada
Rest of World
6,041
11,761
0.51
Hypertension
No Hypertension
10,208
7,586
0.53
All Participants
17,802
0.25
0.5
1.0
2.0
4.0
Rosuvastatin Superior
Rosuvastatin Inferi--

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"Haven't We Met Somewhere Before?"
"Yes, I Think We Were All In The same Placebo Group"

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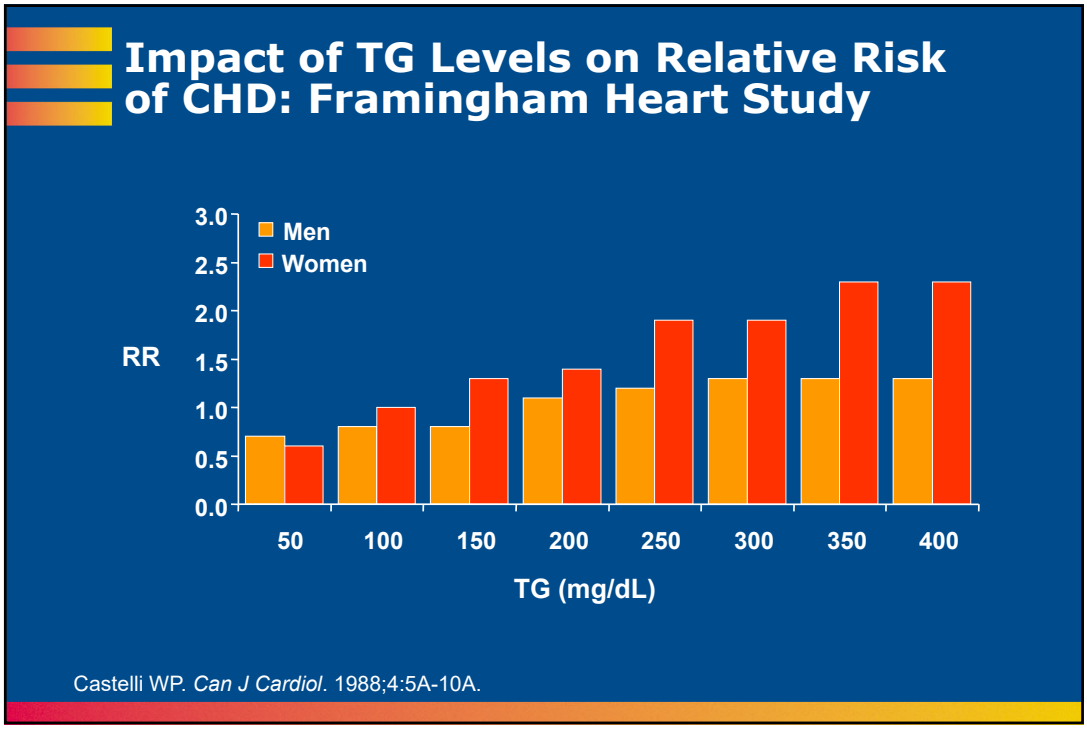
Impact of TG Levels on Relative Risk of CHD: Framingham Heart Study
Men
Women
RR
3.0
2.5
2.0
1.5
1.0
0.5
0.0
50
100
150
200
250
300
350
400
TG (mg/dL)
Castelli WP. Can J Cardiol. 1988;4:5A-10A.

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Triglycerides Are a Risk Factor for Coronary Disease

	Number Of Studies	Sample Size	Univariate RR	Independent RR
Men	12	33,214	1.30	1.17
Women	4	5,836	1.91	1.47

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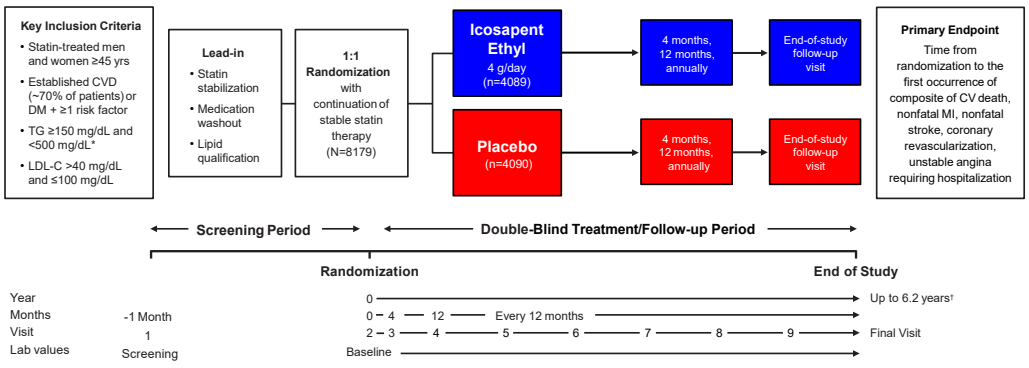
REDUCE-IT Design



*Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

†Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Participants agreed to follow and maintain a physician-recommended diet and refrain from excessive alcohol consumption.

Among the exclusions were HbA1c>10.0% and known lipoprotein lipase deficiency/apolipoprotein C-II deficiency/Frederickson Type I

Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. *Clin Cardiol.* 2017;40:138-148.
REDUCE-IT ClinicalTrials.gov number, NCT01492361.

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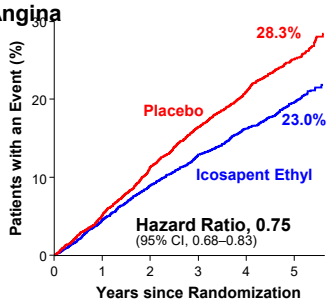
REDUCE-IT Primary and Secondary Endpoints

Primary End Point: CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina

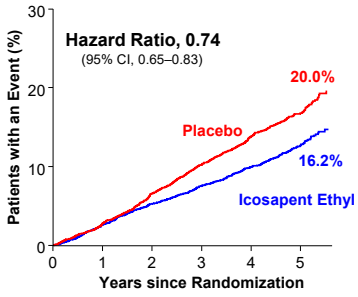


Key Inclusion Criteria

- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥ 1 risk factor
- TG ≥ 150 mg/dL and <500 mg/dL
- LDL-C >40 mg/dL and ≤100 mg/dL

RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

Key Secondary End Point: CV Death, MI, Stroke



RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

Bhatt DL et al. *N Engl J Med.* 2019;380:11-22.

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Myocardial infarction in the young women and NCEP Guidelines

- Young women<65 years presenting with MI (n=56)
- None had a calculated risk of >20%.
- 82% of women not eligible for pharmacotherapy as by NCEP ATP III guidelines.

Slide Source:
Lipids Online
www.lipidsonline.org

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Should we be Screening women for CAD?

Is resistance to screening for heart disease rational ?

42,690 deaths attributed to breast cancer

53,200 deaths attributed to colorectal cancer

360,000 deaths attributed to ischemic heart disease
(of the 655,00 deaths attributed to heart disease)

Slide Source:
Lipids Online
www.lipidsonline.org

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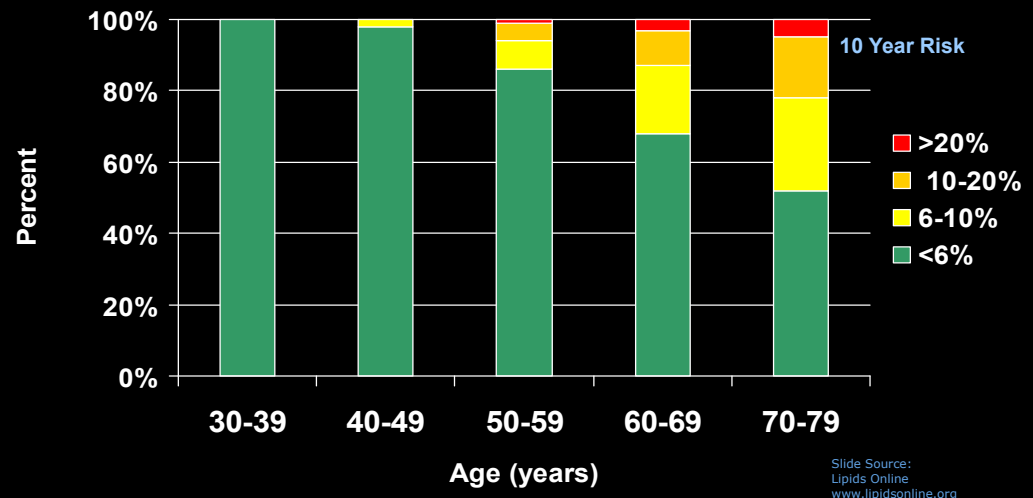
Estimated 10 Hard CHD Risk Framingham Offspring and Cohort Women



Slide Source:
Lipids Online
www.lipidsonline.org

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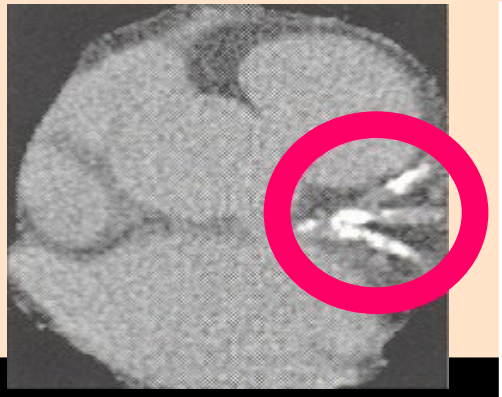
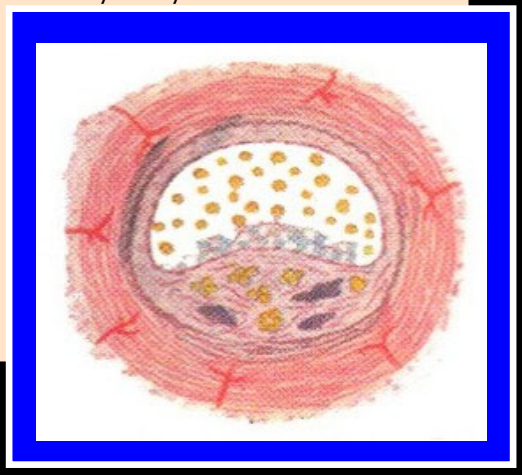
Scan



Coronary Artery



Heart with extensive calcification and plaque build-up.

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Lipids Online
www.lipidsonline.org

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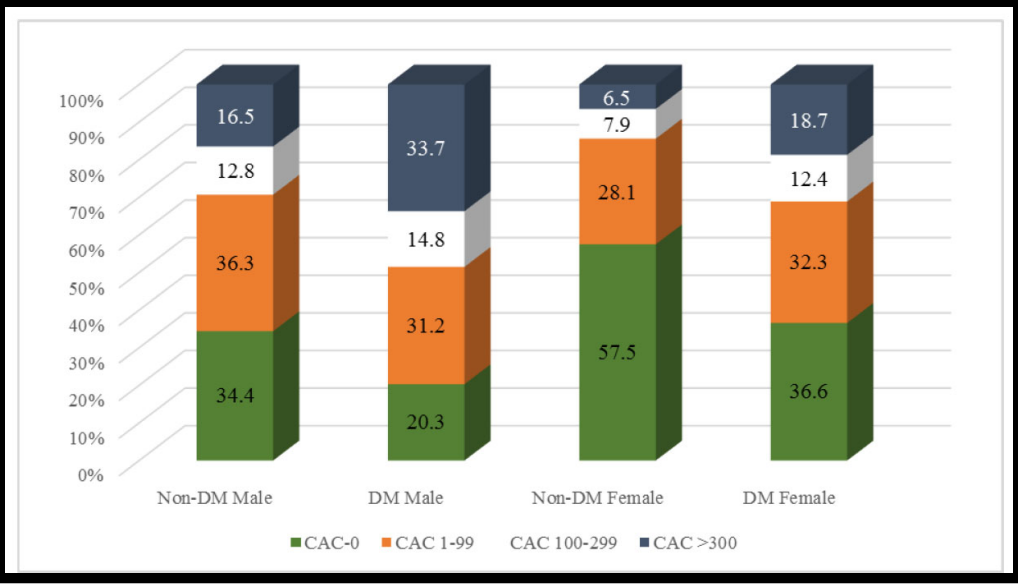
Coronary Artery Calcification (CAC)



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Diagnosis and Management of Coronary Artery Disease in Women

- Gender differences: presentation, manifestation and diagnosis of CAD
- Gender differences in mortality
  - 63% of women who die suddenly from CAD had no prior warning symptoms
  - 42% of women vs 24 % of men will die within one year after myocardial infarction (MI)
- Thus, early recognition of symptoms and accurate diagnosis of CAD is of great importance

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Heart Disease in Women: Lessons From the Past Decade

- The importance of studying gender-specific aspects of CAD have helped in the following clinical dilemmas:
  - Presentation of CAD: women are older than men
  - Less specific clinical manifestations of CAD in women
  - Greater difficulty in diagnosis: women > men
  - More severe consequences on MI when it occurs in women

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Gender Differences in Exercise ECG Testing

- ⇓ sensitivity in women >65 years
- ⇓ specificity in women on hormone replacement therapy
- ⇑ false-positive results due to autonomic/hormonal influences
- Digoxin like effect of estrogen
- Adequacy of flow reserve (smaller coronaries)

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Nuclear Imaging in Women

- Myocardial perfusion imaging (MPI)
- Large body of evidence in women
    - Less Accurate in women as compared to men due to: initial development done in men, breast attenuation artifacts, ECG changes at baseline due to hormonal effects and lower exercise capacity

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METHODS - CTA

- 0.5-0.625 mm slices
- Single Breath-hold Imaging
- 40-50 cc Non-ionic (IODINATED) contrast
- 20 minute procedure
- 15 minute interpretation

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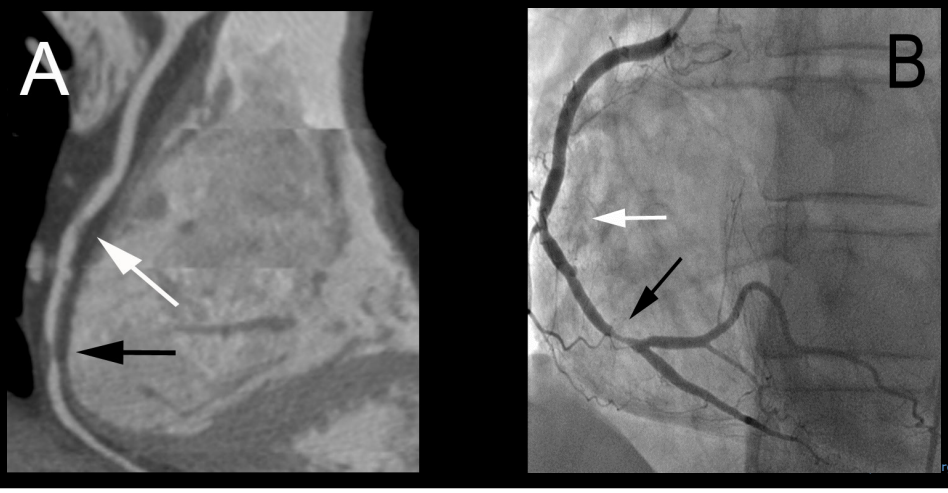
CT Angiography – Cath Correlation



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CTA by Gender – Jug B, JNC 2012

	≥70% Coronary stenosis		
	Women	Men	*P*
Sensitivity	95.8 (90.1-98.6)	94.1 (89.5-96.8)	.554
Specificity	83.0 (79.6-84.7)	91.1 (86.1-94.5)	.104
PPV	77.3 (72.7-79.6)	90.9 (85.7-94.3)	.007
NPV	97.1 (93.0-99.0)	94.3 (89.8-96.9)	.229
LR+	5.644 (3.993-7.978)	10.943 (6.653-17.024)	-
LR–	0.050 (0.019-0.131)	0.064 (0.035-0.118)	-

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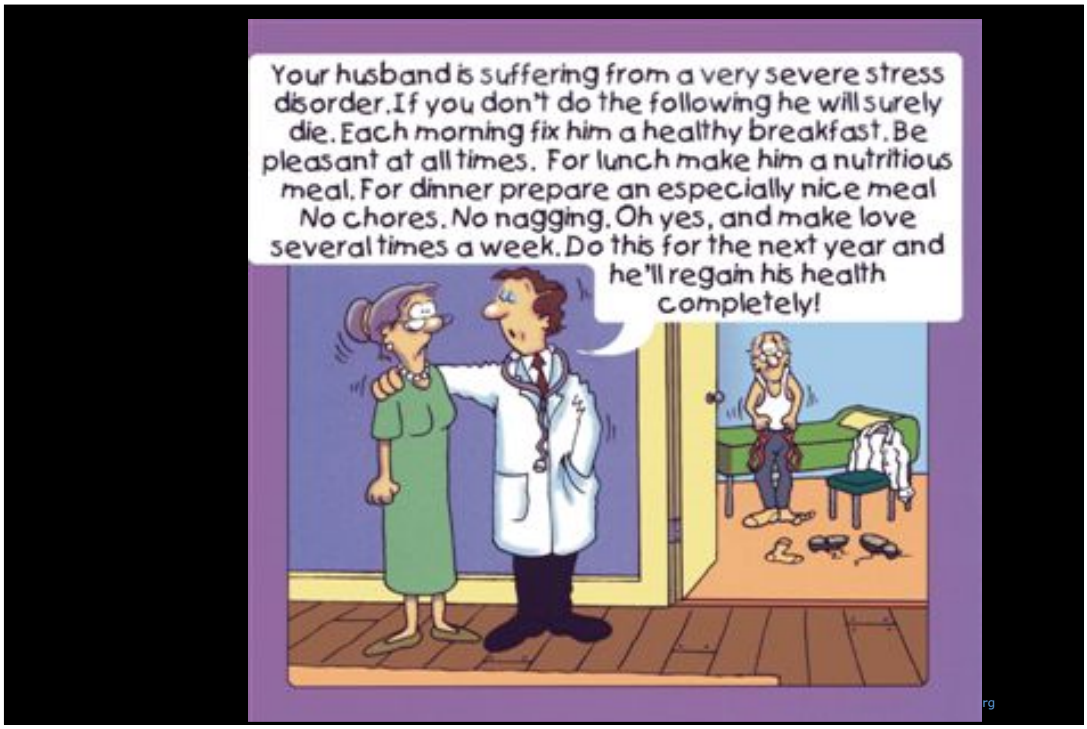
ISSUES THAT NEED ADDRESSING

- "A heart attack is more likely to kill a woman than a man, perhaps because women are more likely to delay seeking treatment for myocardial infarction symptoms,"
- "Compared with men, women had a significantly higher rate of intra-hospital mortality from MI (P<0.0001),"
- women "had significantly longer median delay between onset of MI symptoms and calling for medical assistance (60 versus 44 minutes, P<0.0001)
- Women were less likely to be discharged on aspirin, clopidogrel, beta-blockers, ACE I, Statins and Rehabilitation

48


Your husband is suffering from a very severe stress disorder. If you don't do the following he will surely die. Each morning fix him a healthy breakfast. Be pleasant at all times. For lunch make him a nutritious meal. For dinner prepare an especially nice meal No chores. No nagging. Oh yes, and make love several times a week. Do this for the next year and he'll regain his health completely!

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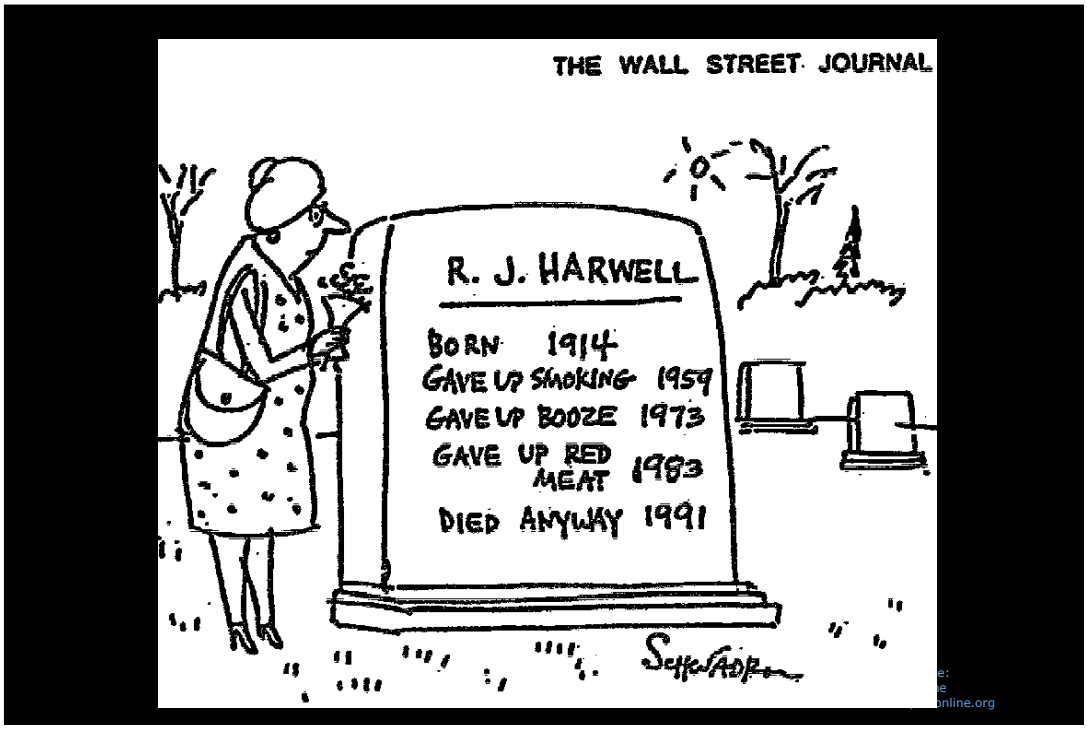
What did the doctor say ?
You're going to die!

50


THE WALL STREET JOURNAL
R. J. HARWELL
BORN 1914
GAVE UP SMOKING 1959
GAVE UP BOOZE 1973
GAVE UP RED MEAT 1983
DIED ANYWAY 1991

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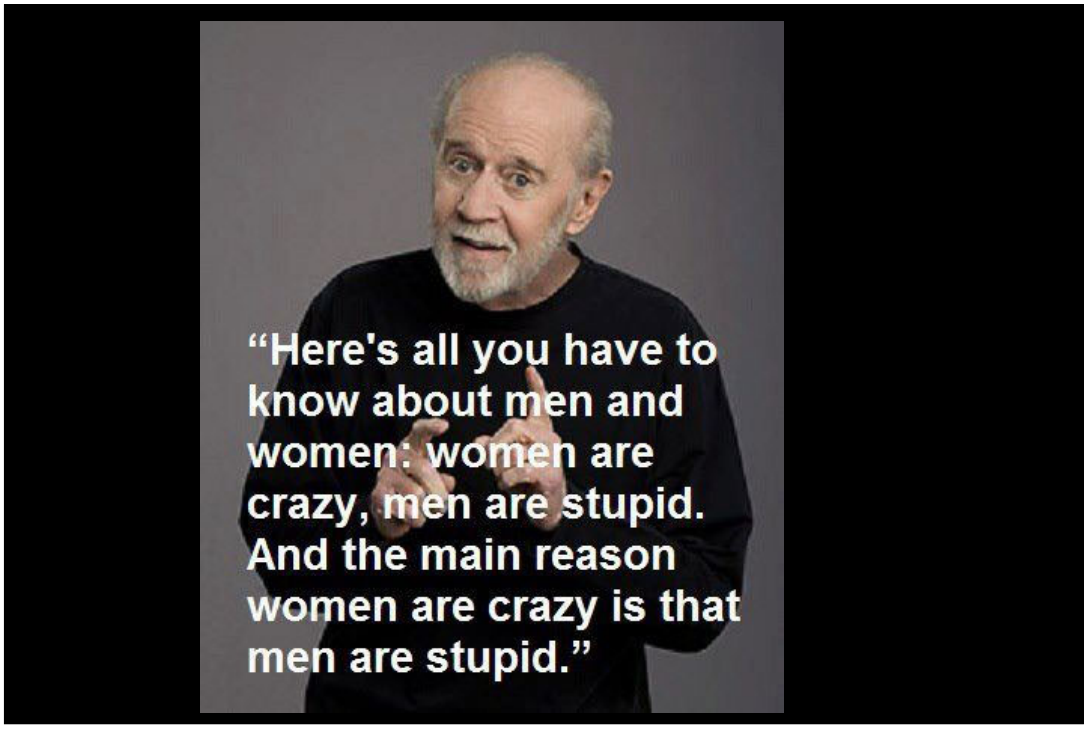
"Here's all you have to know about men and women: women are crazy, men are stupid. And the main reason women are crazy is that men are stupid."

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