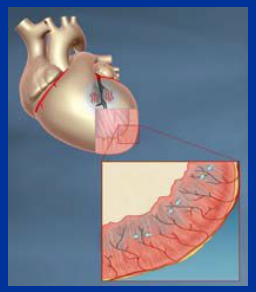
Heart disease in women: sex-specific risk factors and non-obstructive coronary artery syndromes

Tara L Sedlak, MD, FRCPC, MBA
Medical Director, Leslie Diamond Women's Heart Health Clinic

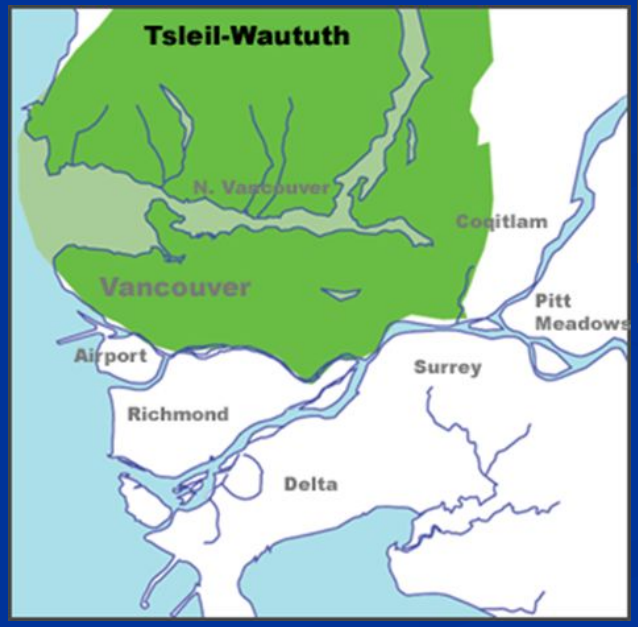
Oct 18th, 2023

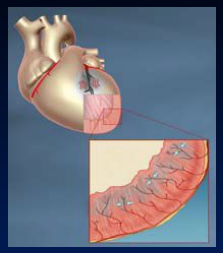


HER HEART MATTERS
WEAR RED CANADA • FEB 13

I would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

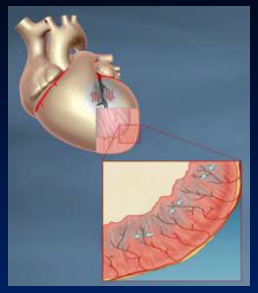
Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html





Faculty/Presenter Disclosures

- Tara Sedlak
- Speakers Bureau/Advisory Boards/Honoraria: Amgen, Novo Nordisk, Bayer, BI Lilly, KYE Pharmaceuticals, Novartis, HLS, Pendopharm, Pfizer



Objectives

HER HEART MATTERS
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- Review risk stratification in women
  - Sex-specific risk factors
- Review data on lipid lowering in women
- Review non-obstructive CAD
  - Microvascular angina

HER HEART MATTERS
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Case 1

- 62 year old female, BMI 28
- Previously asymptomatic, limited by knee/hip pain
- PMHx:
  - Dyslipidemia
    - LDL 4.4, total chol 6.2, HDL 1.0, TG 2.2
    - IFG
    - FBG 6.1, HbA1c 6.2
  - Borderline BP: 138/80, pre-eclampsia in 2 pregnancies
  - FMHx: mom had an MI at 58
  - SLE: managed on hydroxychloroquine 200mg

Case 1

- Framingham risk
  - 12%
- Reynold's risk
  - 9% (hsCRP 2.0)
- ASCVD risk
  - 6.5%

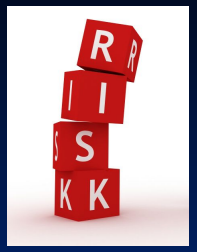
- Felt to be at least moderate risk (SLE, FMHx)
- tried rosuvastatin 5mg
- myalgias discontinued

 In whom should we continue to try other lipid lowering options?

Case 1

- One year later:
  - NSTEMI (trop 4.5, ST depression on ECG)
  - Cath: 80% pLAD, 70% pLCx, 90% mid RCA
  - EF 60%
- CABG:
  - LIMA to LAD
  - SVG to OM1
  - SVG to PDA
- Lp(a) ~1700
- Discharged home on atorvastatin 10mg
  - Cannot tolerate due to myalgias

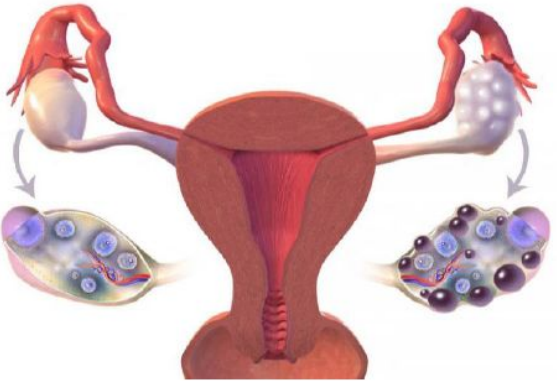
 What other options do we have ?



Primary Prevention Scores

- RRS
- FRS
- SCORE
- ASCVD
- QRISK
- ASSIGN

Sex-Specific Risk Factors



Polycystic ovarian syndrome: Increased risk of CV disease

Gestational diabetes: HR 1.70-2.0 for future CVD

Placental abruption: ↑odds of CVD by 82%

Premature delivery: CVD risk ↑ by 63% and ↑ odds of CV mortality by 95%

Stillbirth: CVD risk ↑ by 42% and ↑ odds of CV mortality by 64%

Menopause: Risk of CVD increases markedly after menopause.

Early menopause (≤ age 40): 95% higher risk of future MI

Grandi SM et al. Circulation 2019. Kramer CK et al. Diabetologia 2019

CANADIAN WOMEN'S HEART HEALTH ALLIANCE ATLAS

Epidemiology, Diagnosis, and Management of Cardiovascular Disease in Women

CHAPTER 4 | SEX- AND GENDER-UNIQUE DISPARITIES: CVD ACROSS THE LIFESPAN OF A WOMAN

MENARCHE, MENSTRUATION, CONTRACEPTION

Assessments of women's risks of CVD may need to consider experiences of menstruation, menarche, and contraception use.

POLYCYSTIC OVARY SYNDROME (PCOS)

Affects women of reproductive age, resulting in increased risk of obesity, insulin resistance and other metabolic risk factors (increased blood sugars, dyslipidemia, and hypertension). These complications increase the risk for CVD and stroke and should be assessed in women with PCOS.

PREGNANCY-RELATED RISKS

Cardiac disease is a leading cause of maternal morbidity and mortality both during pregnancy and in the postpartum period. Several common adverse pregnancy outcomes (eg: hypertensive disorders of pregnancy, gestational diabetes, preterm birth) are associated with increased lifetime CVD risk.

MENOPAUSE

Menopause is a risk factor for CVD, particularly premature spontaneous or surgical menopause. Endogenous estrogen is cardioprotective; the effects of exogenous estrogens (and progesterone) are complex and less clear. Time and type of menopause should be considered when assessing CV risk and when recommending menopausal hormone therapies.

DEPRESSION

Depression is more prevalent in women than men, both before and following cardiac diagnosis. Younger women are particularly vulnerable to depression following cardiac diagnosis. Depressed individuals should be monitored for CVD in primary care. Upon CVD diagnosis, all individuals should be screened and treated early for depression.

SEX-BASED PHARMACOLOGY OF CV DRUGS

Sex differences in pharmacokinetics underly adverse drug reactions.

CHRONIC KIDNEY DISEASE (CKD)

Sex- and gender-related differences in kidney disease presentation, diagnosis, treatment, and prognosis impact CKD-associated CVD risk in women.

DISPROPORTIONATE IMPACT OF TRADITIONAL RISK FACTORS

Traditional CVD risk factors and gendered psychosocial stressors contribute to increased risk of CVD in women.

AUTOIMMUNE RHEUMATIC DISORDERS (ARDs)

ARDs are more prevalent in women. Cardiac symptoms can be misinterpreted as being related to an ARD or even be clinically silent; therefore, careful cardiac and ARD assessment, reporting and attention to traditional CV risk factors with early specialist referral is essential.

CANADIAN WOMEN'S HEART HEALTH CENTRE
CENTRE CANADIEN DE SANTÉ CARDIAQUE POUR LES FEMMES
NATIONAL ALLIANCE NATIONALE

CWHHA.CA

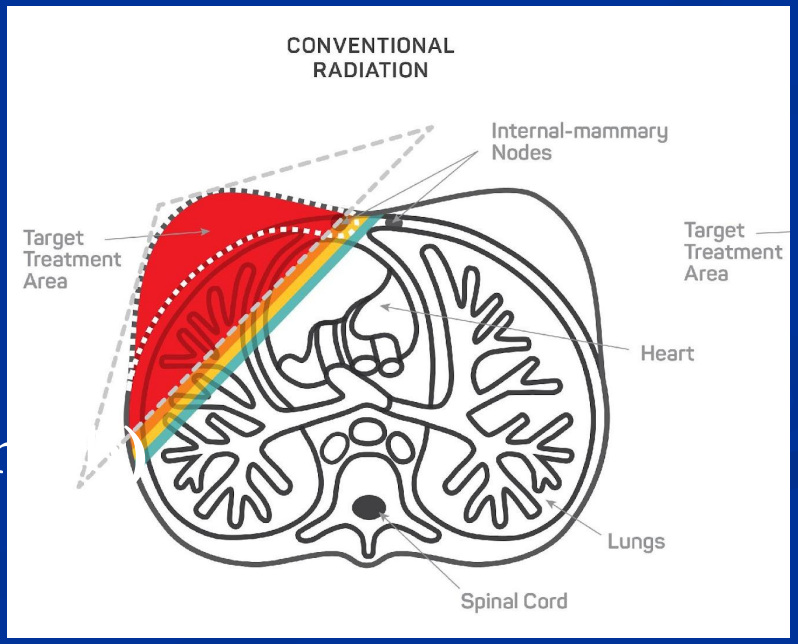
Mulvagh et al. Can J Cardiology Open 2022; 4: 115-132

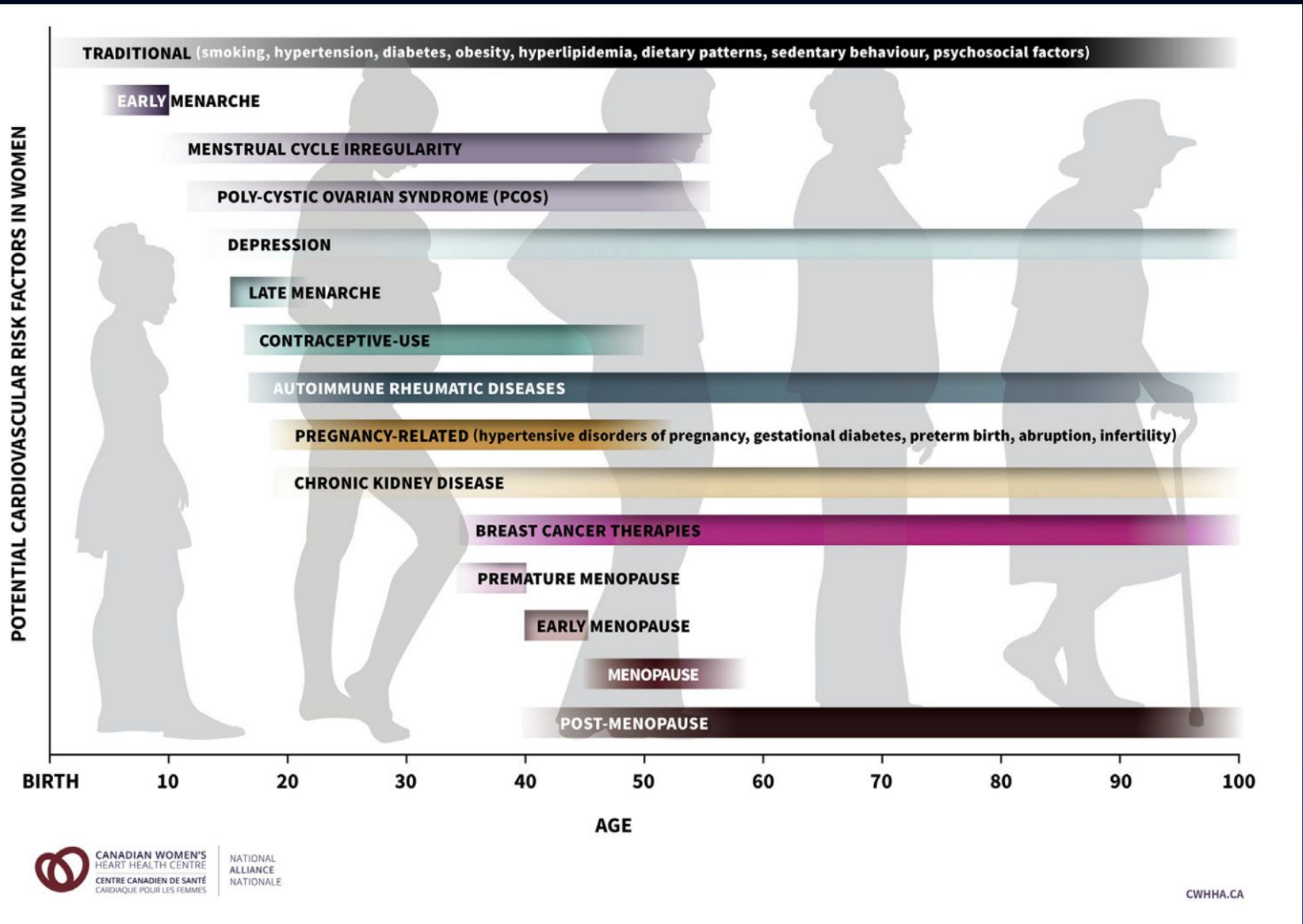
Inflammatory Risk Factors

- Double CVD risk

Breast Cancer Survivors

Chemotherapy
(anthracycline-based, trastuzur
Radiation Therapy





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Sex-Specific Risk Factors

Table 1. Who to screen for dyslipidemia in adults at risk

Who to screen
Men 40 years of age or older; women 40 years of age or older (or postmenopausal)
• Consider earlier in ethnic groups at increased risk such as South Asian or indigenous individuals
All patients with any of the following conditions, regardless of age
• Clinical evidence of atherosclerosis
• Abdominal aortic aneurysm
• Diabetes mellitus
• Arterial hypertension
• Current cigarette smoking
• Stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma)
• Family history of premature CVD*
• Family history of dyslipidemia
• Chronic kidney disease (eGFR $\leq$ 60 mL/min/1.73 m^2 or ACR $\geq$ 3 mg/mmol)
• Obesity (BMI $\geq$ 30)
• Inflammatory diseases (RA, SLE, PsA, AS, IBD)
• HIV infection
• Erectile dysfunction
• COPD
• History of hypertensive disorder of pregnancy

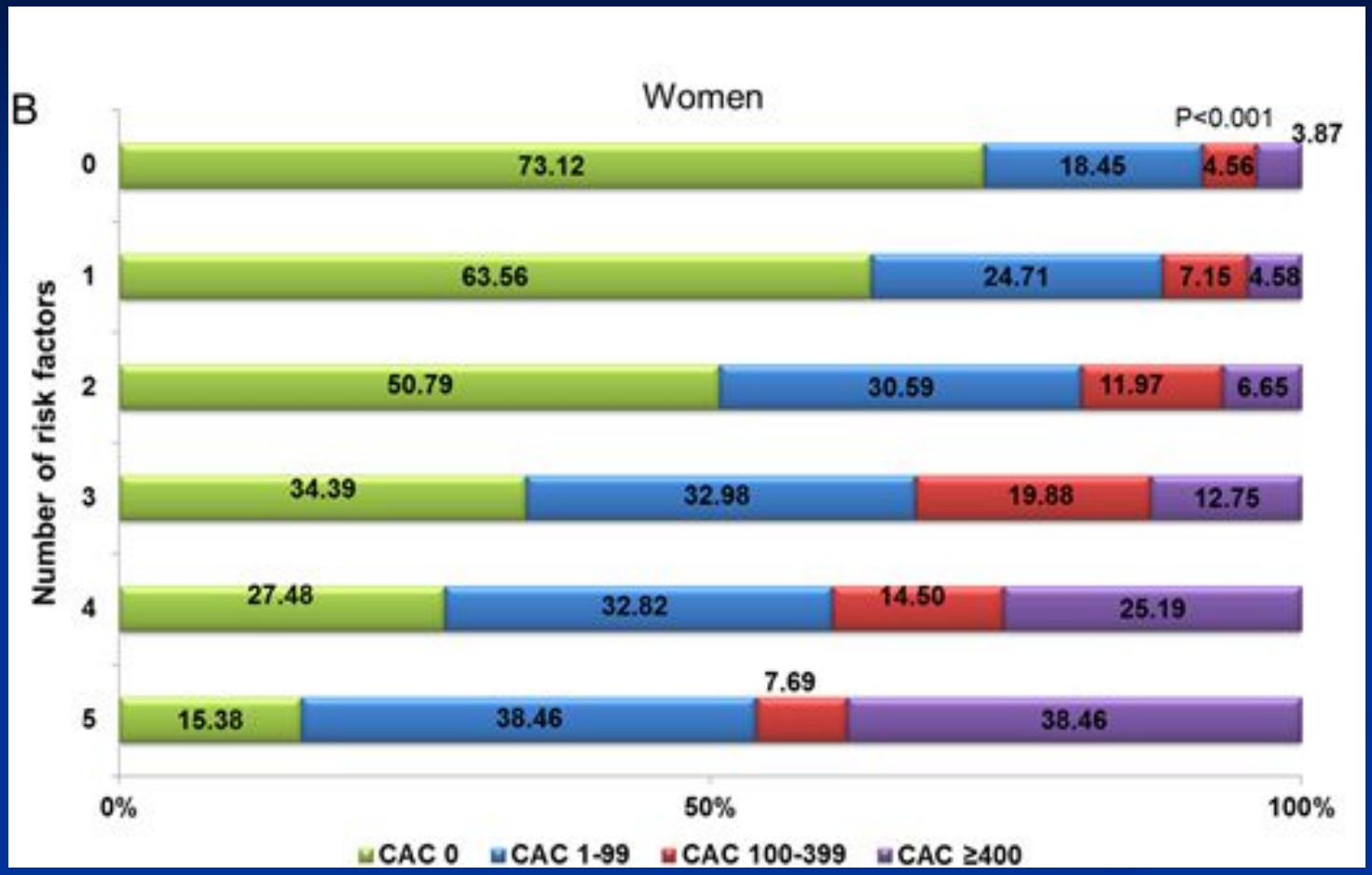
ACR, albumin-to-creatinine ratio; AS, ankylosing spondylitis; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematous.

*Men younger than 55 years of age and women younger than 65 years of age in first-degree relatives.Data from Anderson et al.[1]

Pearson et al., CJC 2021

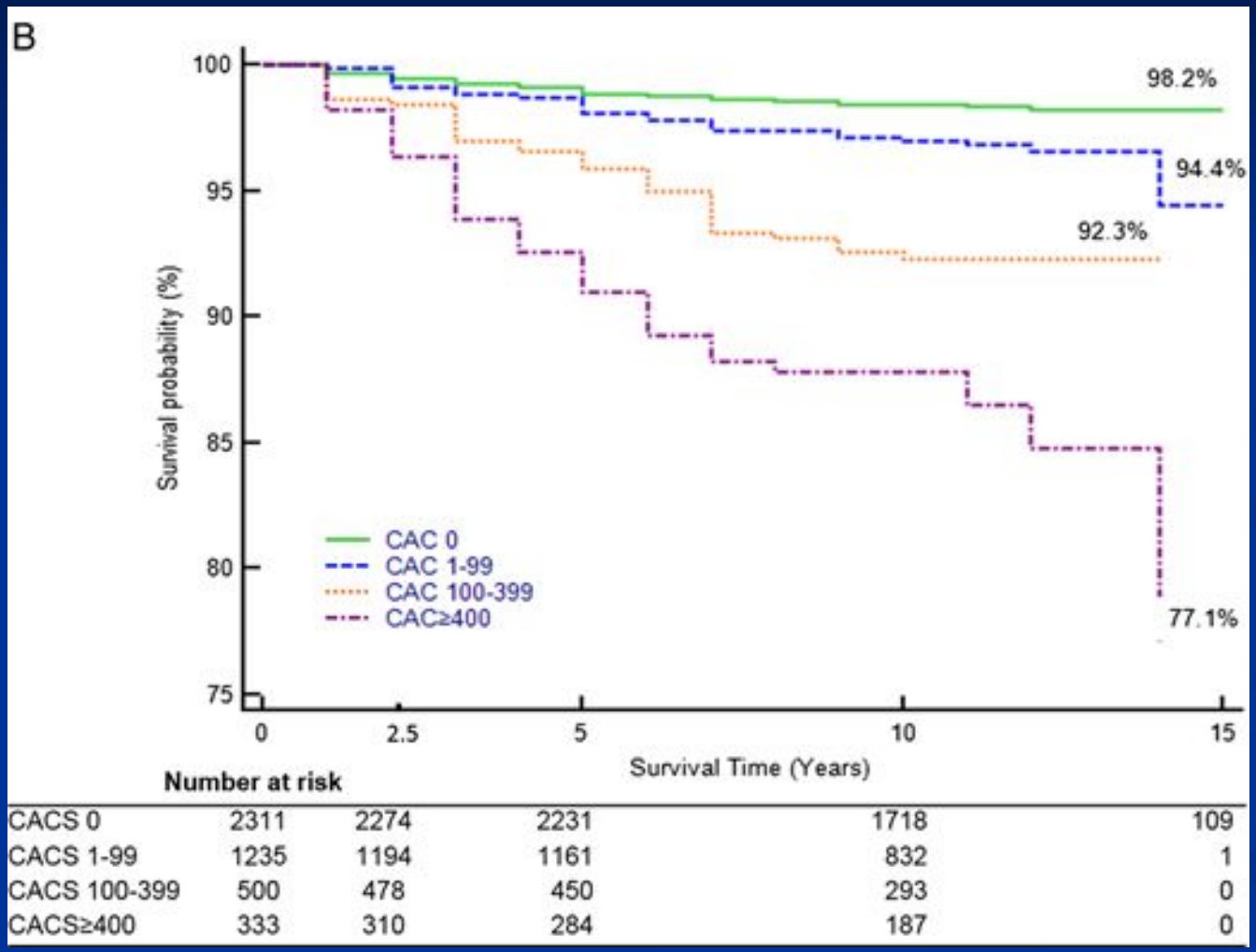
What other tools are available to help risk stratify?

CT calcium score



Nakanishi EHJ 2015;17:1305-1314

CT calcium score in women



Number at risk

CACS 0	2311	2274	2231	1718	109
CACS 1-99	1235	1194	1161	832	1
CACS 100-399	500	478	450	293	0
CACS≥400	333	310	284	187	0

- Risk of mortality increases 3 fold, 4 fold and 13 fold for each category

Nakanishi EHJ 2015;17:1305-1314

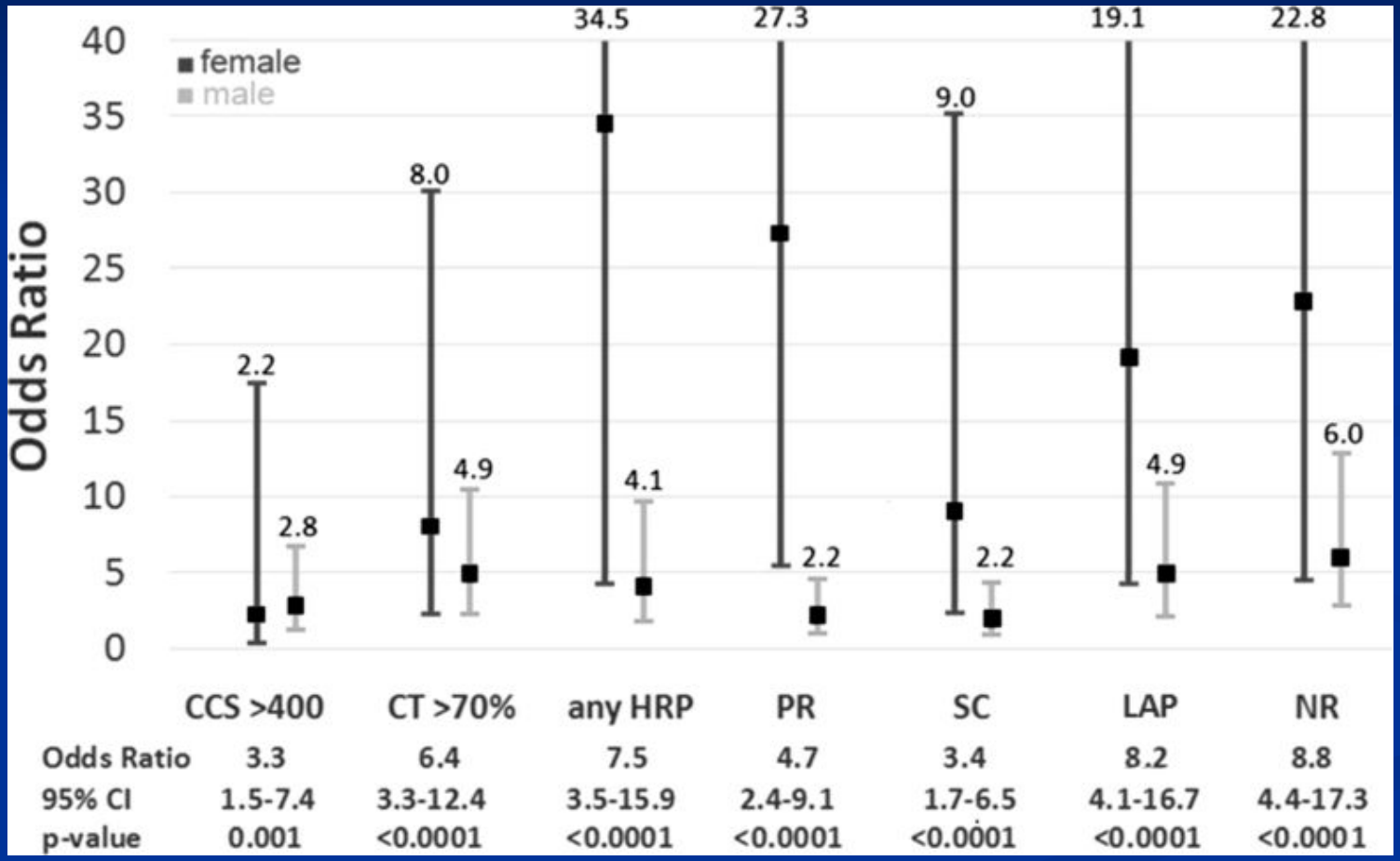
CT calcium score in women

RECOMMENDATION

7. We suggest that CAC screening using computed tomography imaging might be considered for asymptomatic adults 40 years of age or older and at intermediate risk (FRS 10%-20%) for whom treatment decisions are uncertain (Strong Recommendation; Moderate-Quality Evidence).
8. We recommend that CAC screening using computed tomography imaging not be undertaken for: (1) high-risk individuals; (2) patients receiving statin treatment; or (3) most asymptomatic, low-risk adults (Strong Recommendation; Moderate-Quality Evidence).
9. We suggest that CAC screening might be considered for a subset of low-risk individuals 40 years of age or older with a family history of premature ASCVD (men 55 years or younger; women 65 years or younger) in addition to identifying known genetic causes of ASCVD such as elevated Lp(a) level or FH (Weak Recommendation; Low-Quality Evidence).

Pearson et al., CJC 2021

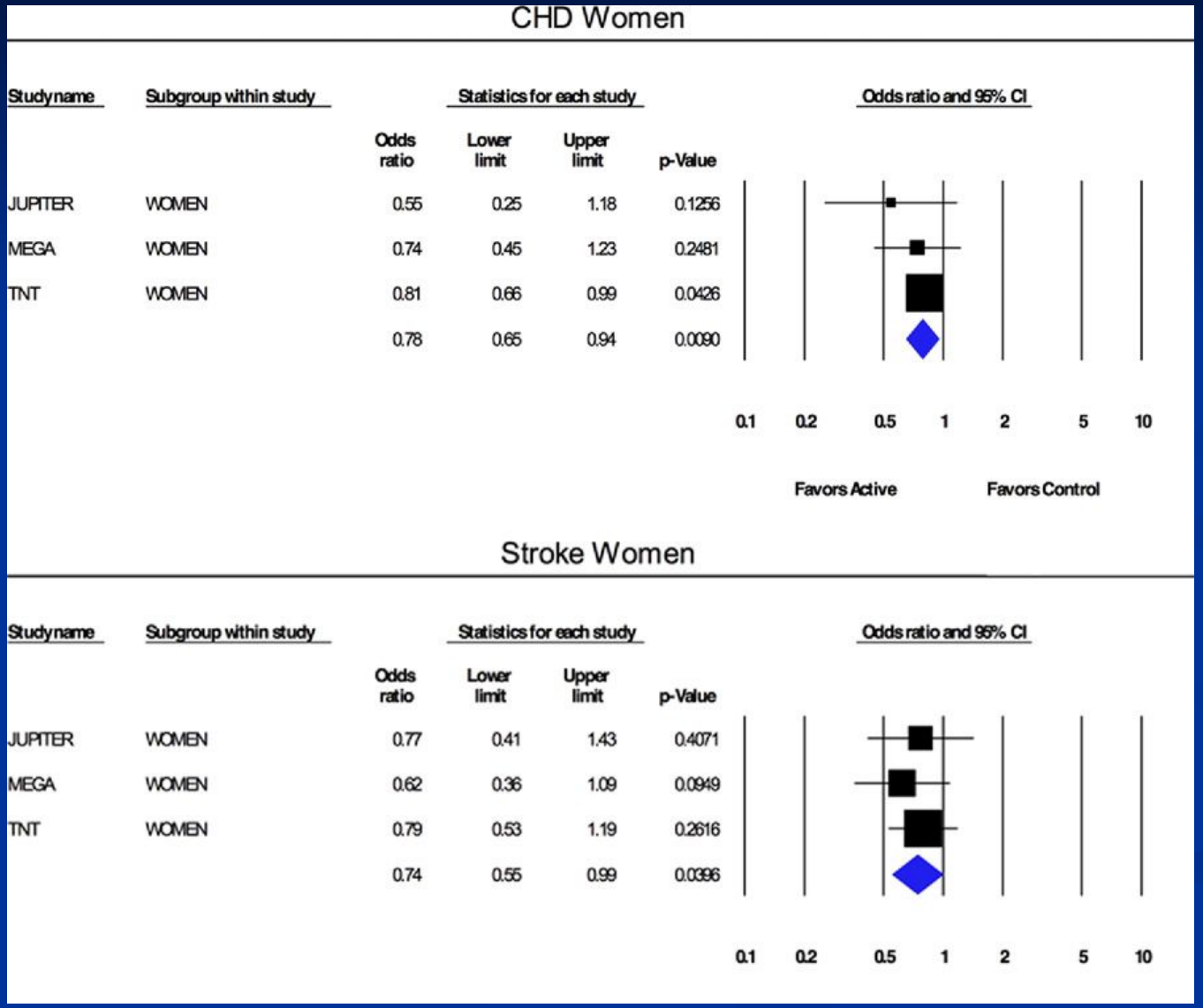
High Risk Plaque Features (CTA)



	CCS >400	CT >70%	any HRP	PR	SC	LAP	NR
Odds Ratio	3.3	6.4	7.5	4.7	3.4	8.2	8.8
95% CI	1.5-7.4	3.3-12.4	3.5-15.9	2.4-9.1	1.7-6.5	4.1-16.7	4.4-17.3
p-value	0.001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Plank *et al.* Netherlands Heart J 2019;27:272-1280

Statins in Women



Kostis *et al.* NEJM 2012;59:572-82

Statins in Women

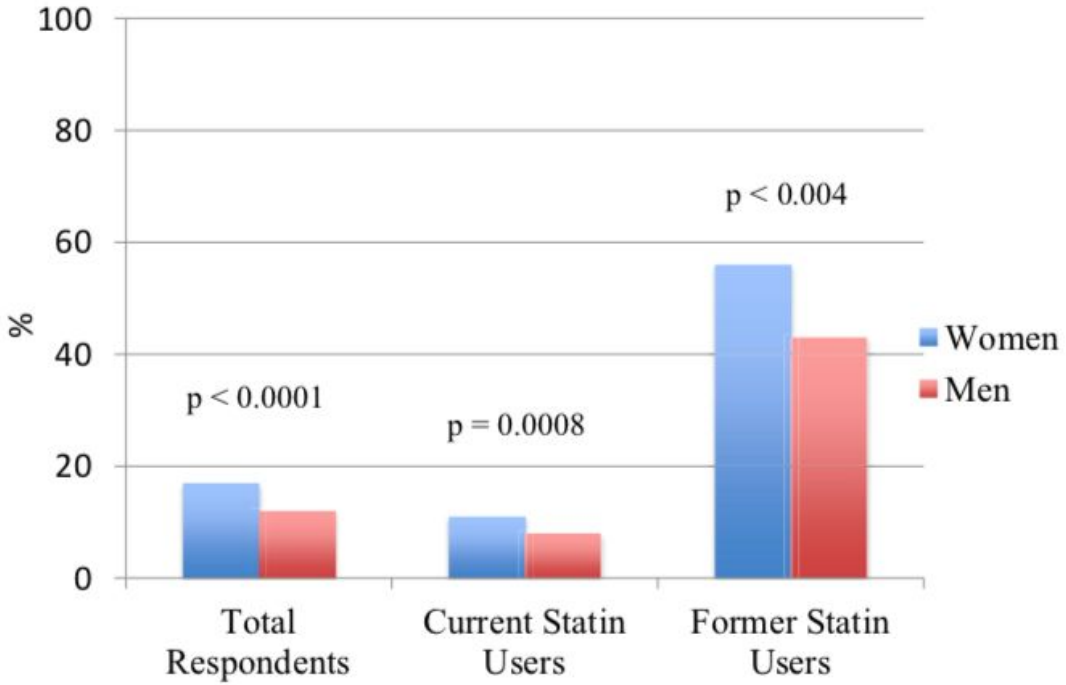
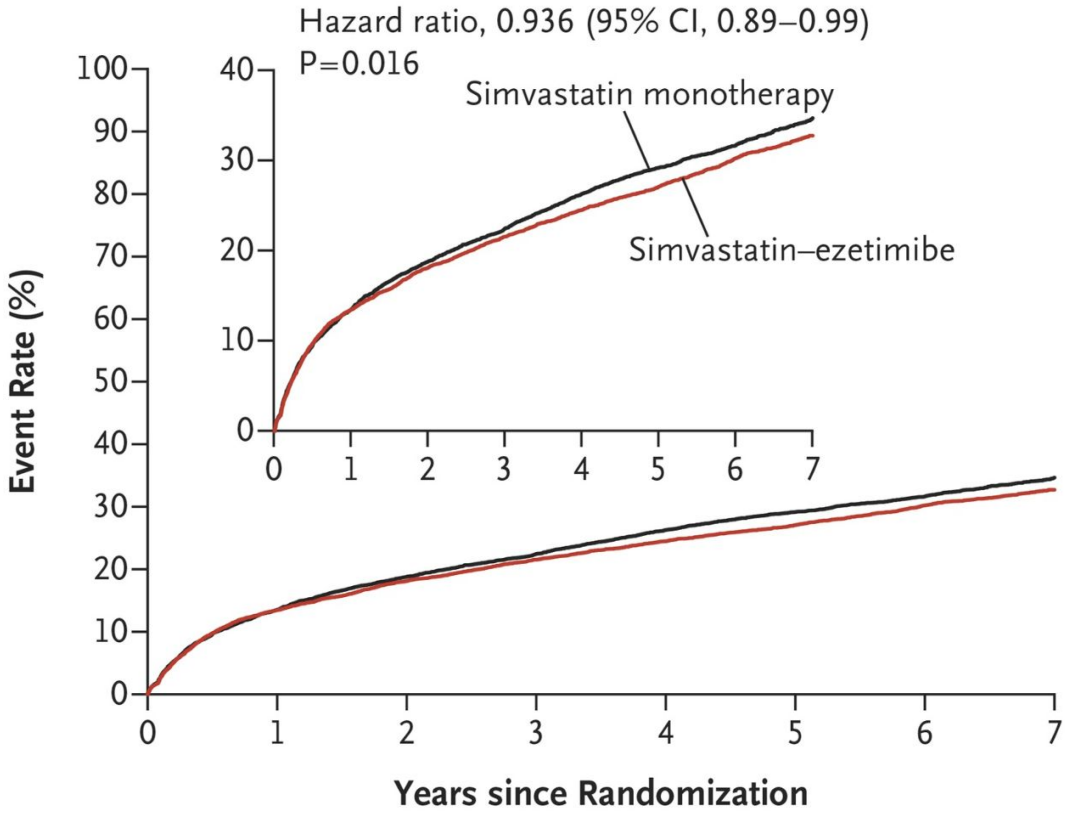


Figure 2 Prevalence of reporting of having stopped a statin due to muscle symptoms.

Karalis *et al.* J Clin Lipidology 2016;10:833-841

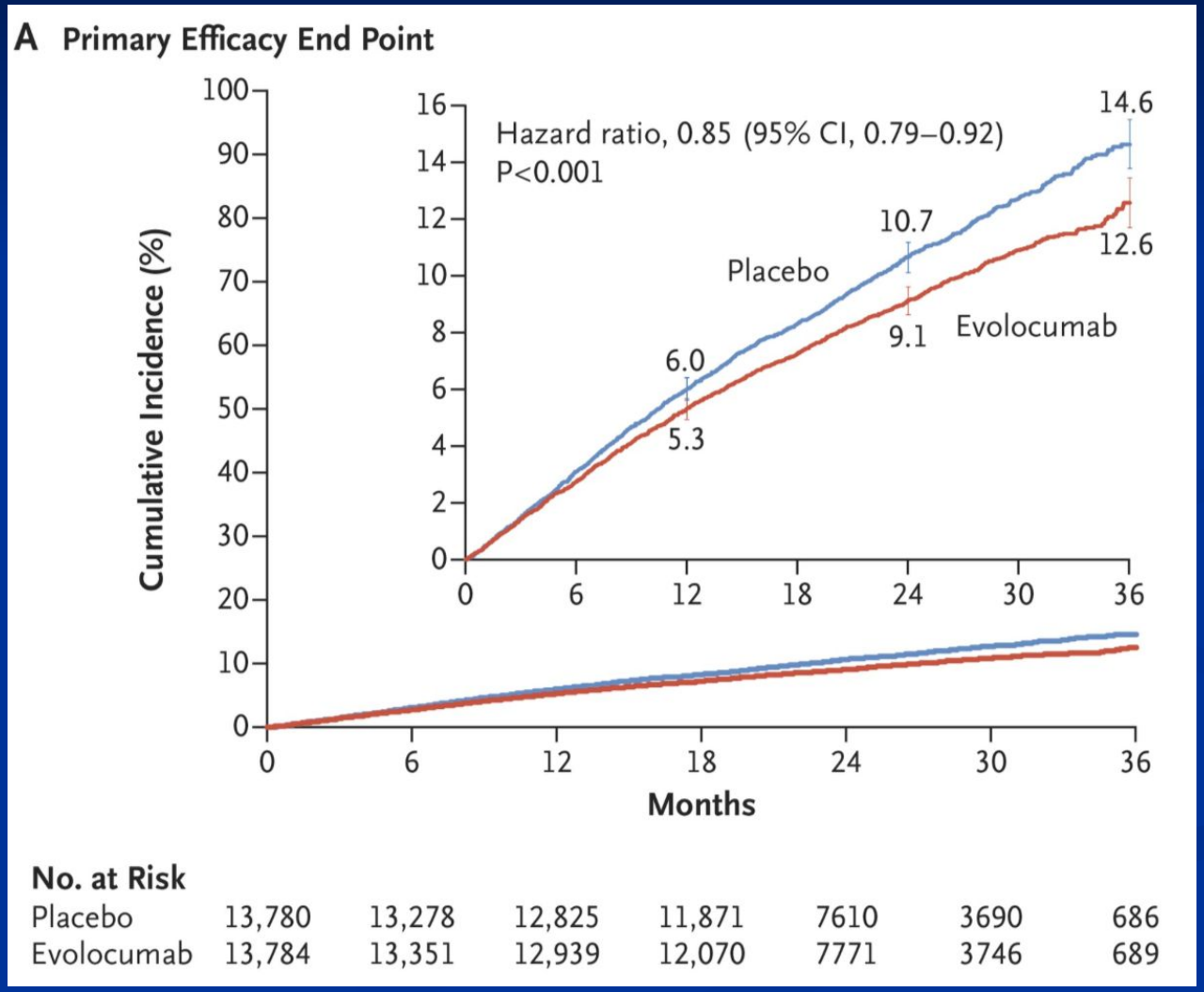
Ezetimide



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Cannon *et al.* NEJM 2015;372:2387-2397

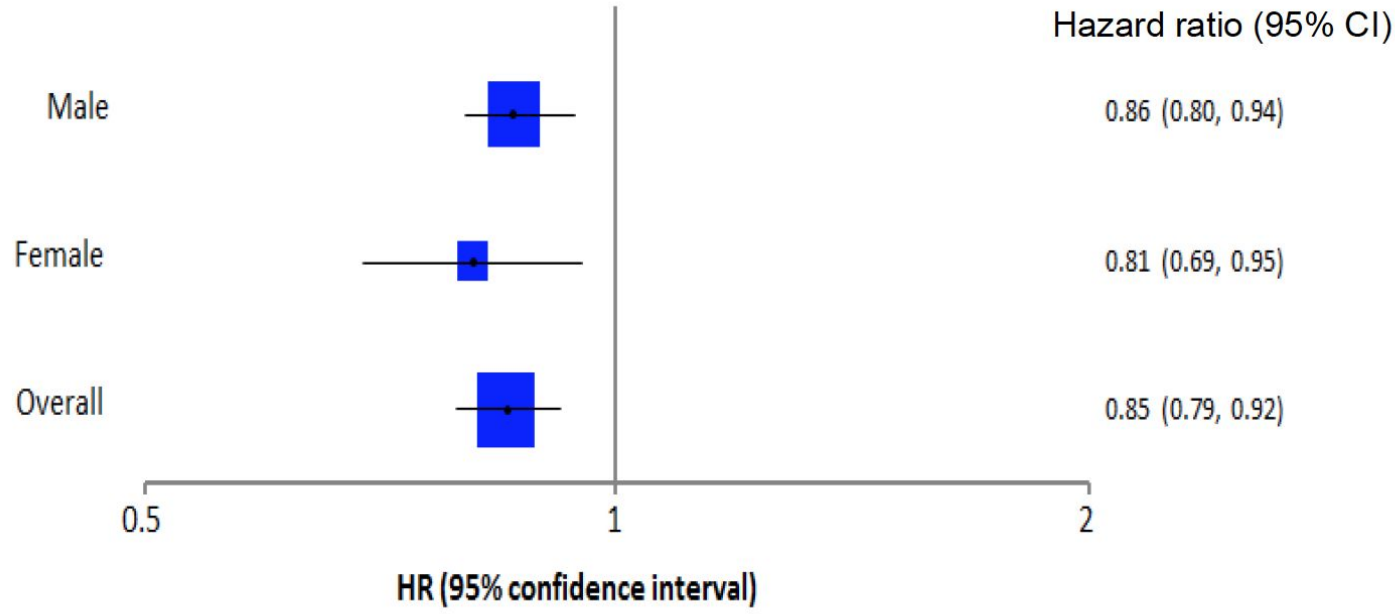
PCSK-9 inhibitors



Sabine *et al.* NEJM 2017;376:1713-1722

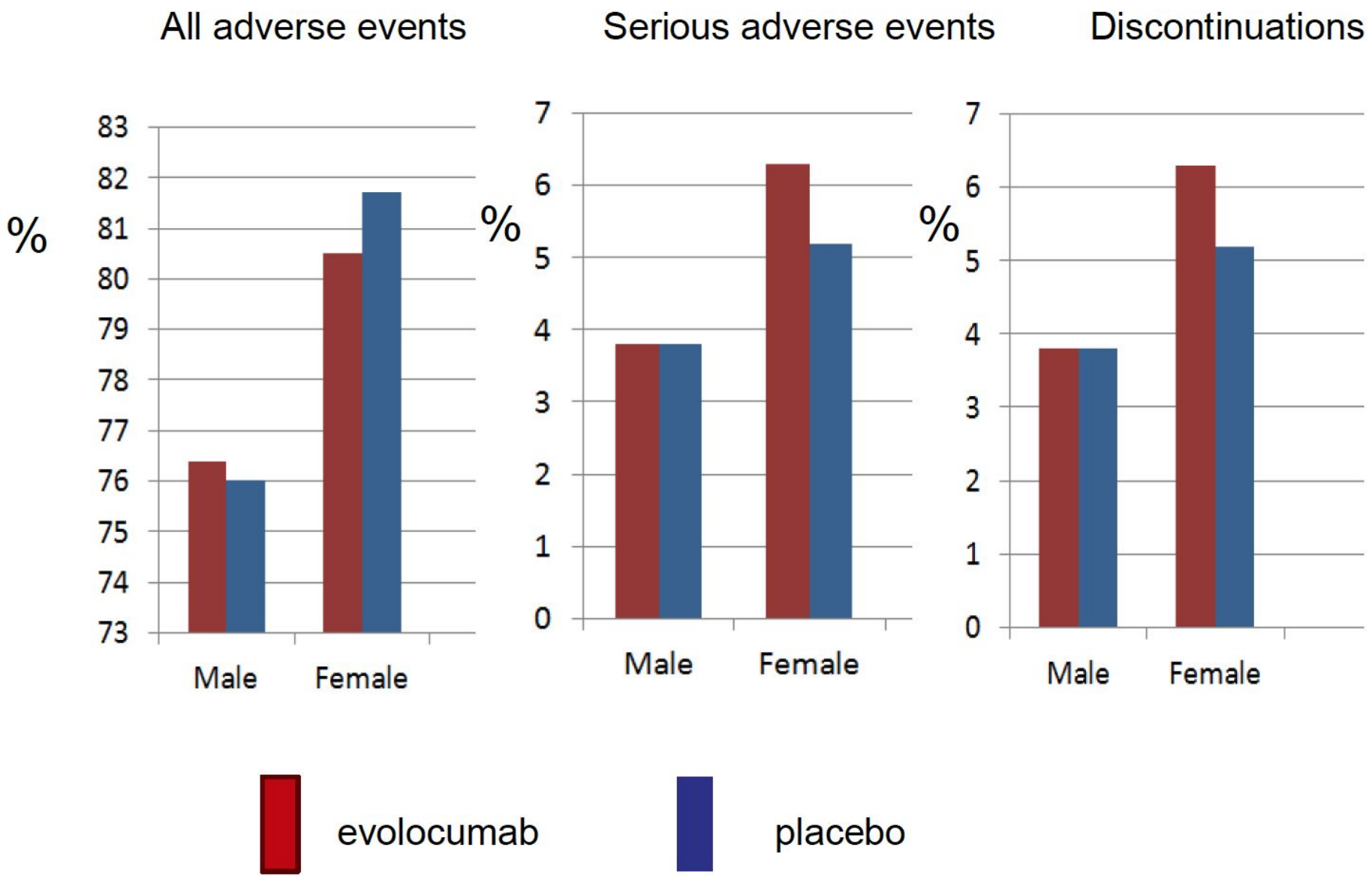
PCSK-9 inhibitors

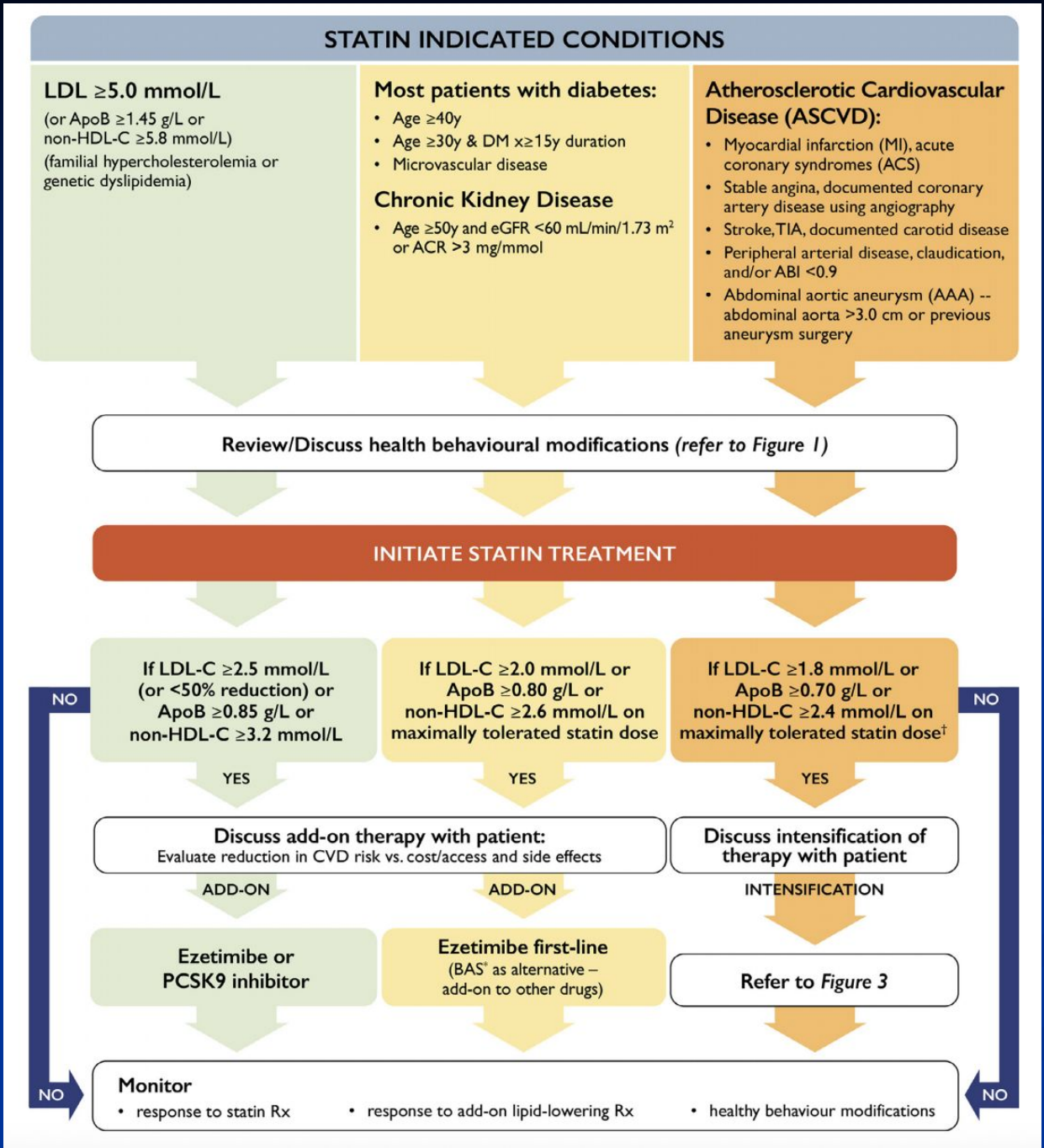
The efficacy of evolocumab stratified by sex



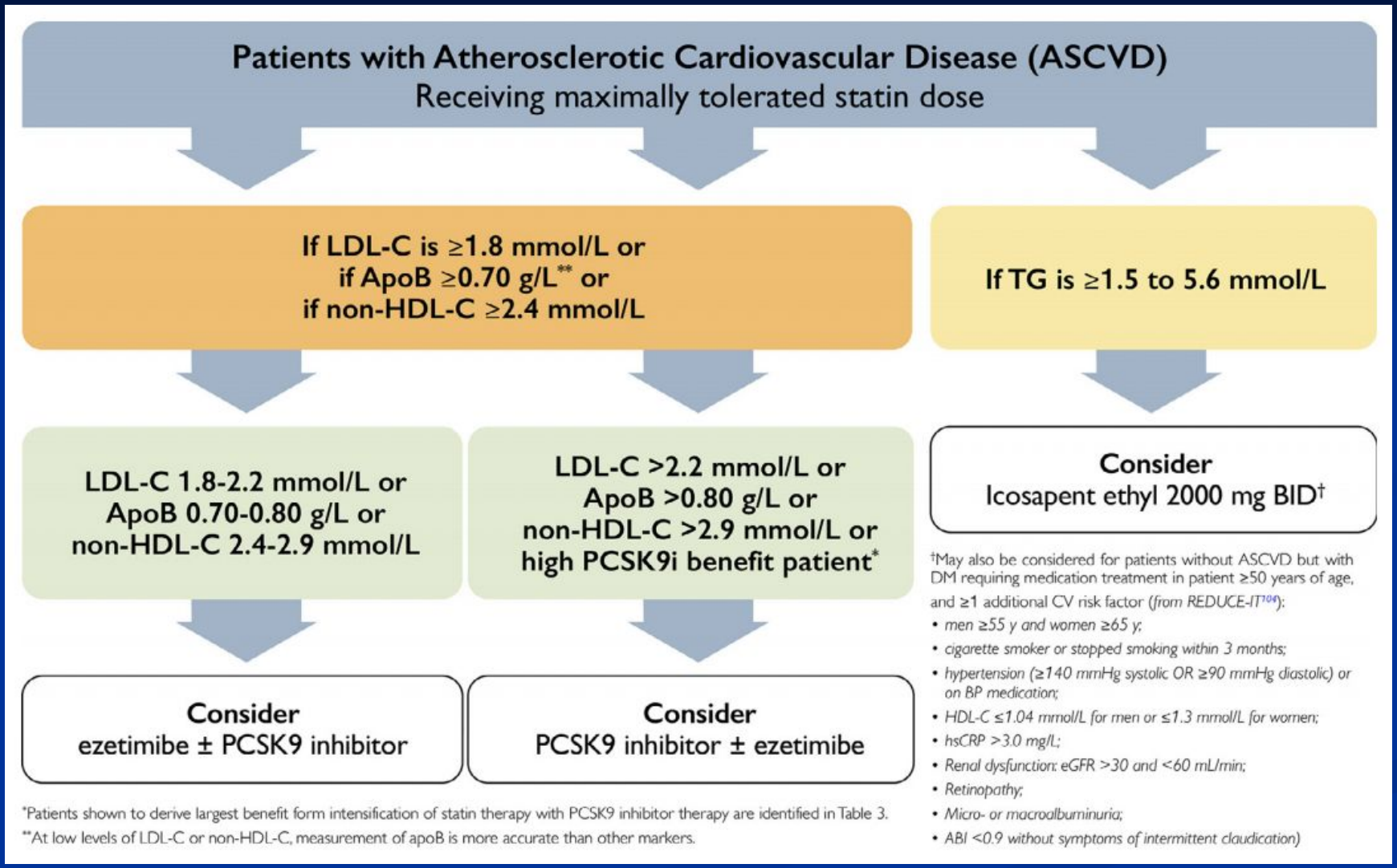
Sabine *et al*. NEJM 2017;376:1713-1722

Adverse events by sex and treatment allocation

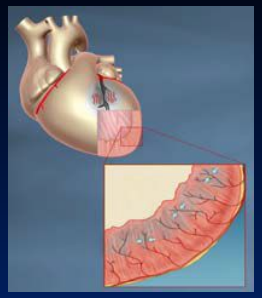




Pearson et al., CJC 2021



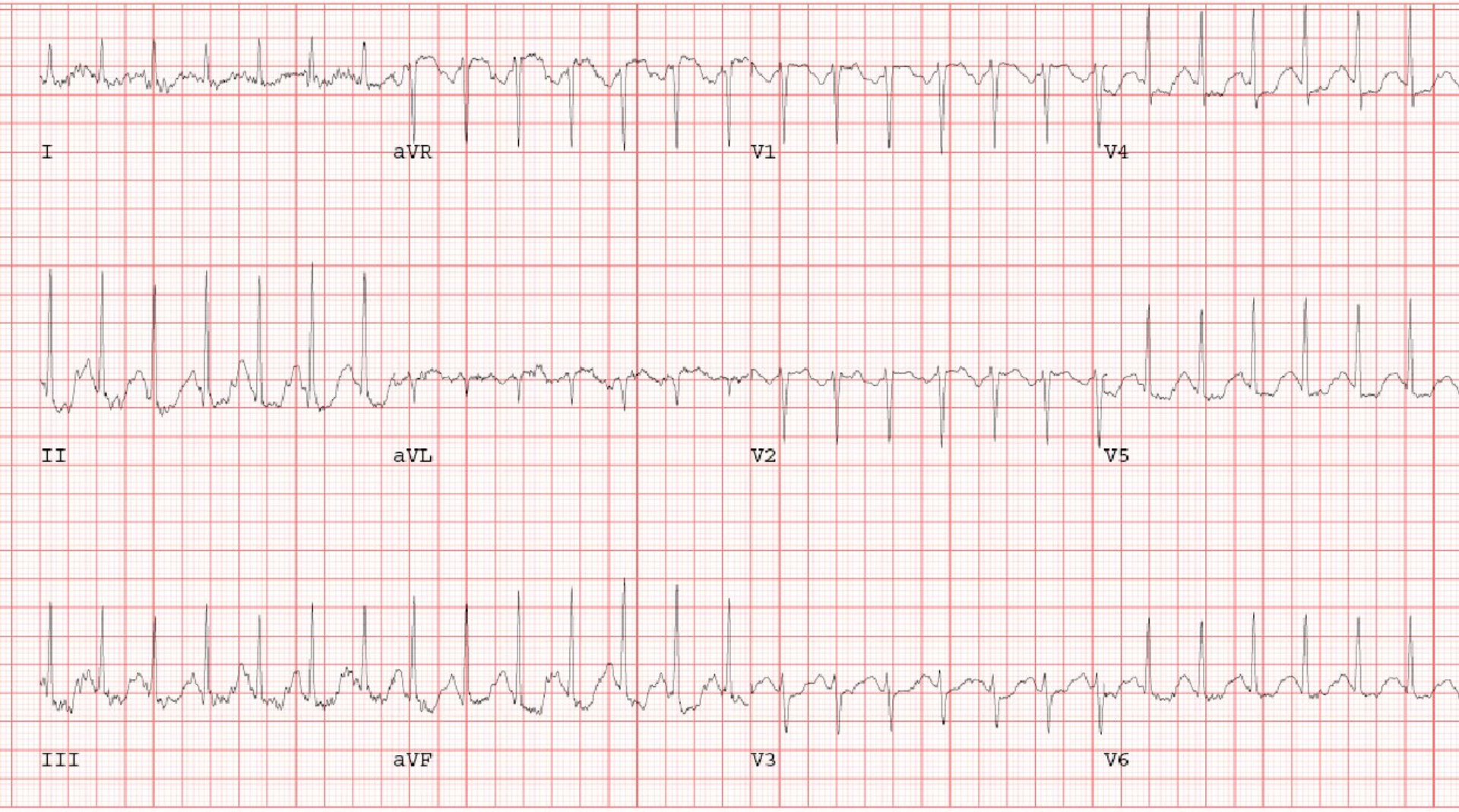
Pearson et al., CJC 2021



Case 2

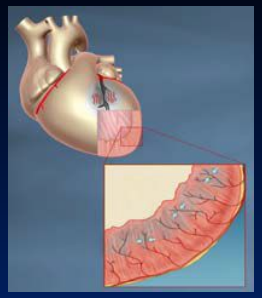
- 50 year old female
- PMHx: HTN and dyslipidemia
- Meds: ramipril 10mg
- HPI:
  - Well up until TAH & BSO for severe menorrhagia
  - Three weeks later, she began experiencing left sided chest pressure with exertion, relieved by rest

EST at 8 minutes (7/10 CP)



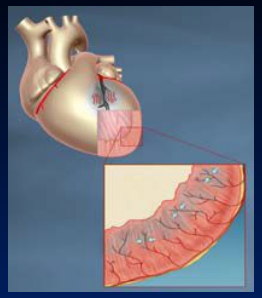
Cardiac CTA

- 1-24% mid RCA
- 1-24% PDA
- 25-49% prox LAD
- 1-25% mid LAD

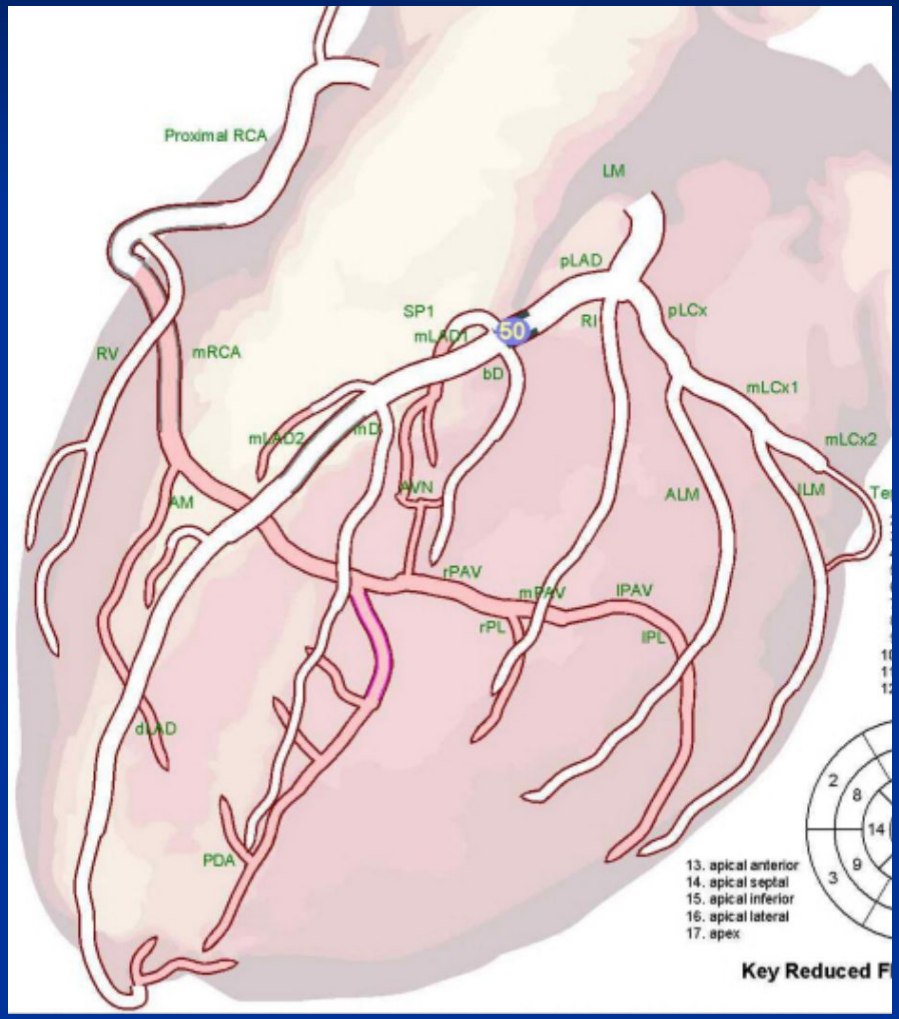


Case 2

- 2 more visits to ED with ongoing severe chest pain
- Gastroenterology work-up: normal
- 5 visits to the GP
- Referred to the Leslie Diamond Women's Heart Health Clinic



Case 2



- Invasive coronary reactivity testing
  - FFR LAD 0.92
  - CFR with adenosine: 1.8 in LAD, 1.4 in LCx
- Started on ASA, rosuvastatin 10mg, ramipril 2.5mg and a CCB
- Ongoing angina

CHAPTER 6 | SEX- AND GENDER-SPECIFIC DIAGNOSIS AND TREATMENT

CORONARY ARTERY DISEASE (CAD)

A higher prevalence of non-obstructive CAD in women results in lower diagnostic accuracy with conventional testing. Coronary angiography remains the gold standard test for diagnosis of CAD in women.

Women should be managed with the same guideline-directed pharmacologic therapies as men in the acute setting, recognizing that there are sex-unique and life-course precautions regarding dosing.

Women presenting with ST elevation myocardial infarction (STEMI) or non-STEMI with high-risk features should have early invasive stratification by coronary angiography with an intention to perform revascularization.

CEREBROVASCULAR DISEASE

Stroke affects women across their life course, although the risks are higher during pregnancy, menopause, and in later years. Symptoms (e.g., tingling, numbness, short duration visual or speech disturbances) may present as less serious in women, potentially leading to a missed diagnosis.

Sex differences in stroke symptoms and door-to-imaging times result in inappropriate treatments and/or missed opportunities for treatment within the recommended therapeutic time window for women.

VALVULAR HEART DISEASE

Current guidelines for the diagnosis and management of patients with valvular heart disease (VHD) have limited sex-specific recommendations, despite numerous sex-specific evaluations and outcomes having been reported.

HEART FAILURE

Women are less likely than men to receive certain heart failure medications, such as angiotensin-converting enzyme inhibitors.

Treatment of heart failure with preserved ejection fraction (HFpEF) includes treatment of comorbid conditions, with a need for more clinical trials stratified by sex.

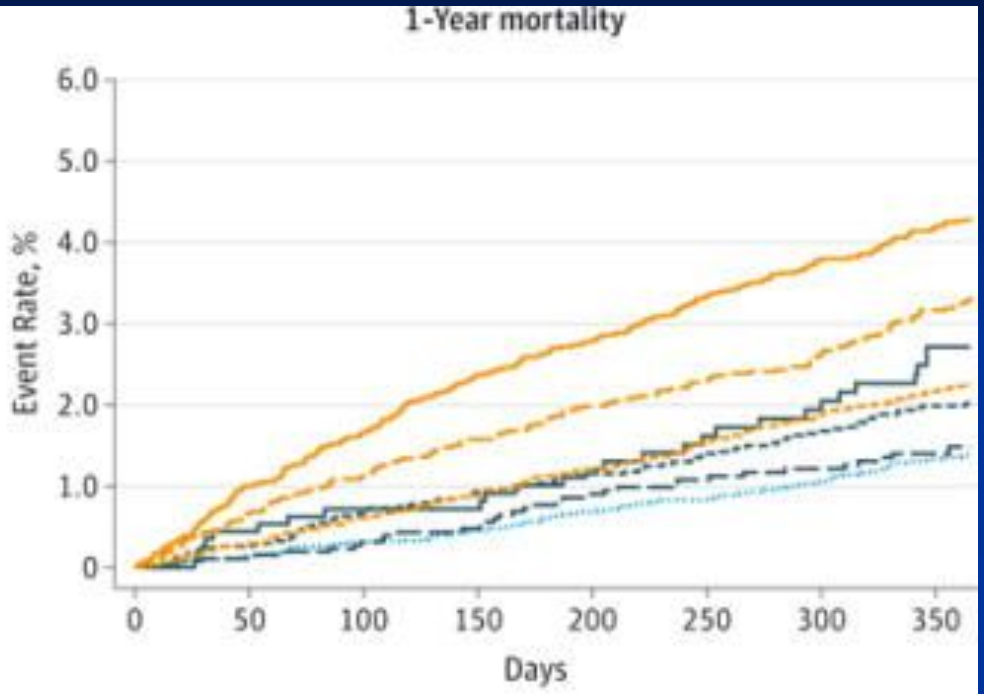
CARDIOVASCULAR REHABILITATION

All women should be referred for cardiovascular rehabilitation/ secondary prevention (CR/SP) after an acute cardiovascular event. However, women are less likely than men to be referred to or participate in CR/SP programs.

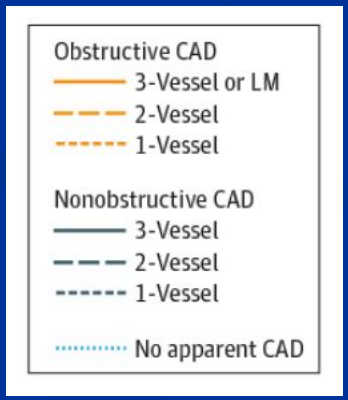
Women's reduced participation in CR/SP programs is due to an array of demographic, socioeconomic, medical, and societal challenges faced by women.

Mulvagh et al. Can J Cardiology Open 2022; 4: 115-132

Non-obstructive CAD

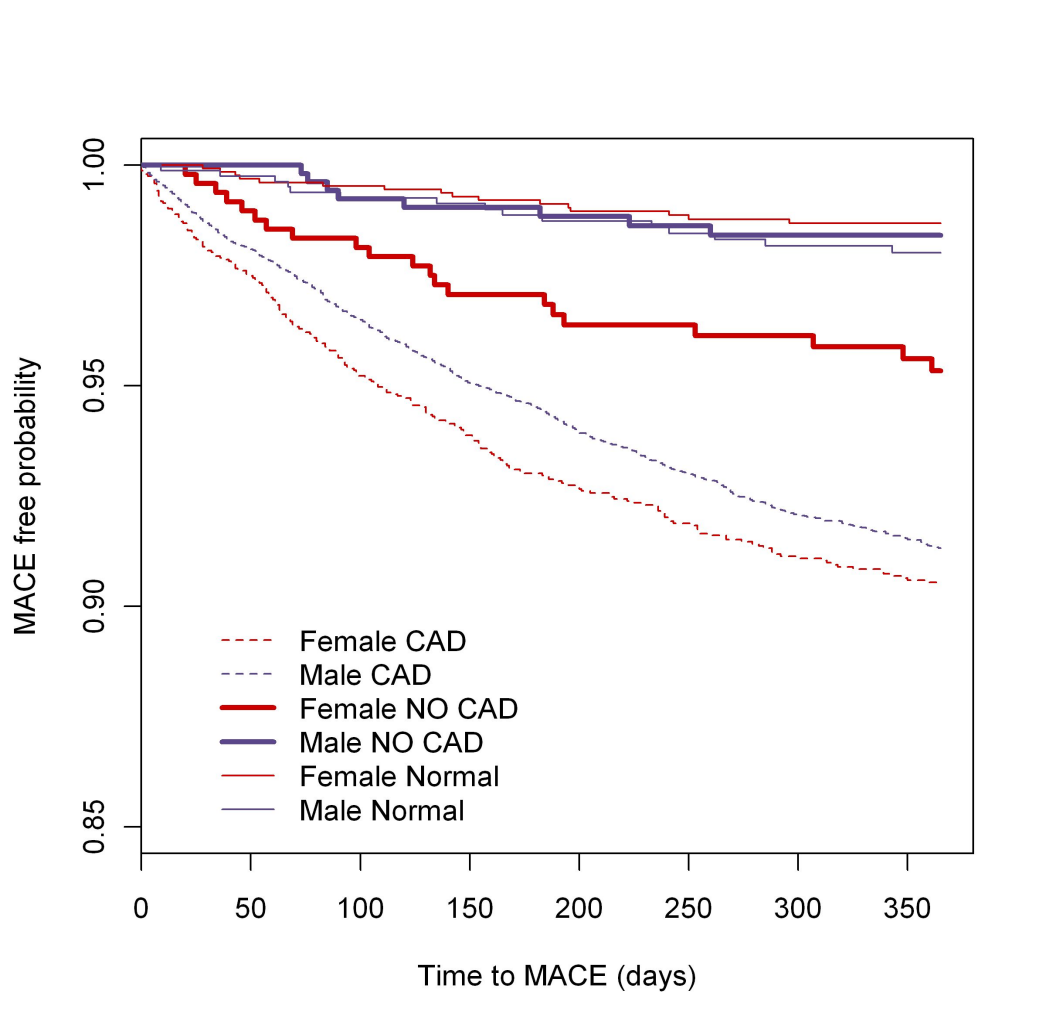


Obstructive CAD								
3-Vessel or LM	6036	5823	5630	5442	5247	5081	4897	4728
2-Vessel	5452	5266	5096	4916	4745	4572	4414	4240
1-Vessel	9411	9133	8887	8577	8273	7962	7662	7391
Nonobstructive CAD								
3-Vessel	1133	1099	1070	1033	985	942	901	871
2-Vessel	2605	2536	2465	2379	2291	2213	2145	2057
1-Vessel	4646	4515	4380	4247	4098	3947	3838	3679
No apparent CAD	8391	8148	7923	7665	7384	7115	6894	6664



Maddox *et al JAMA* 2014;312:1754-1763

Women with non-obstructive CAD

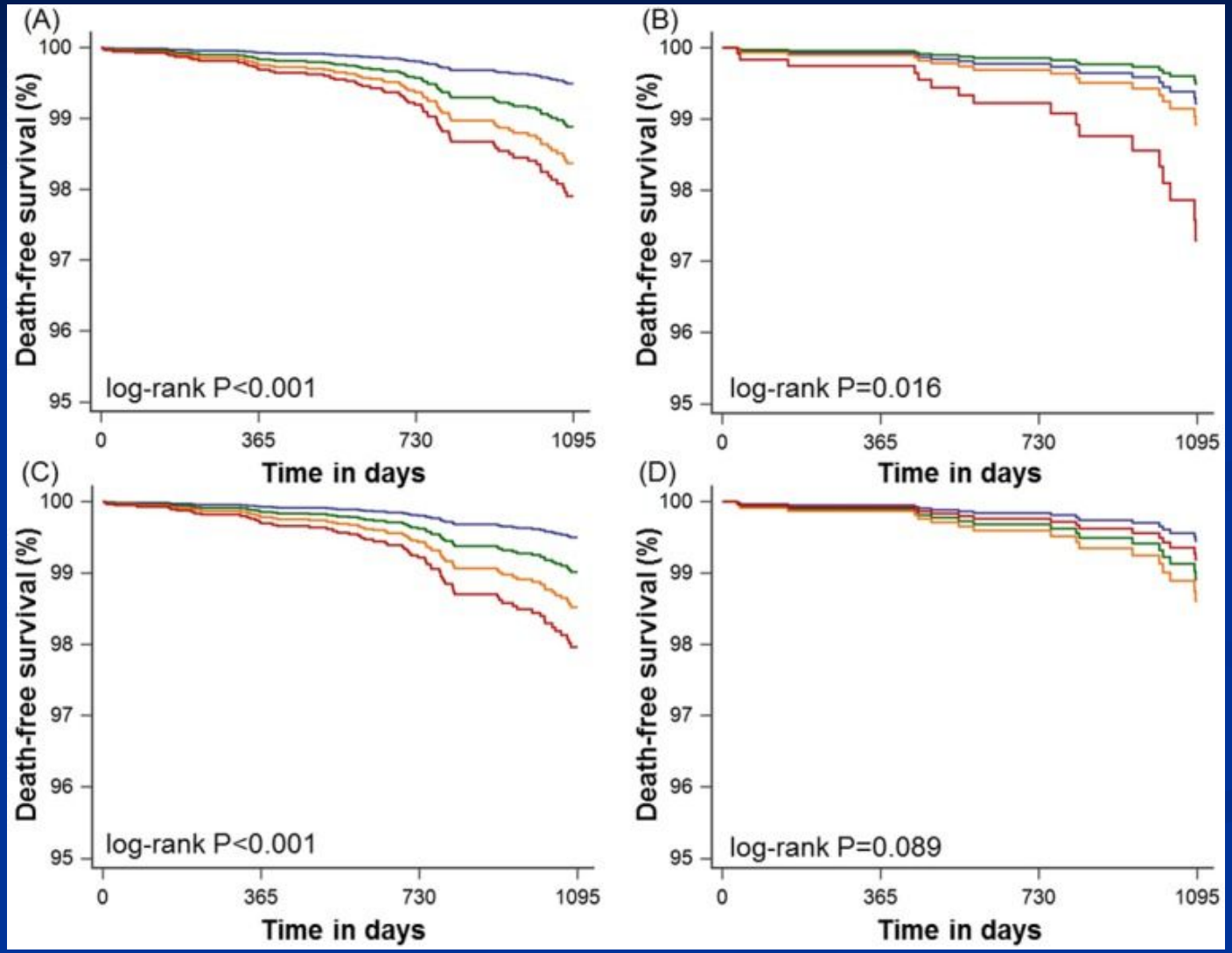


Sedlak *et al American Heart J* 2013;166: 38-44.

Risk is attenuated by statins

CACS

CTA



Min JK et al. *PLoSOne.2018*;13:e0207-194.

GLAGOV: Sex differences

Interventional Cardiology

SEX-RELATED DIFFERENCE IN THE REGRESSION OF CORONARY ATHEROSCLEROSIS WITH THE PCSK9 INHIBITOR, EVOLOCUMAB: INSIGHTS FROM GLAGOV

Conclusion: Female patients treated with the PCSK9 inhibitor, evolocumab, demonstrated greater regression of coronary atherosclerosis, despite the presence of less plaque burden at baseline. This may reflect potential gender related differences in the modifiability of coronary atherosclerosis.

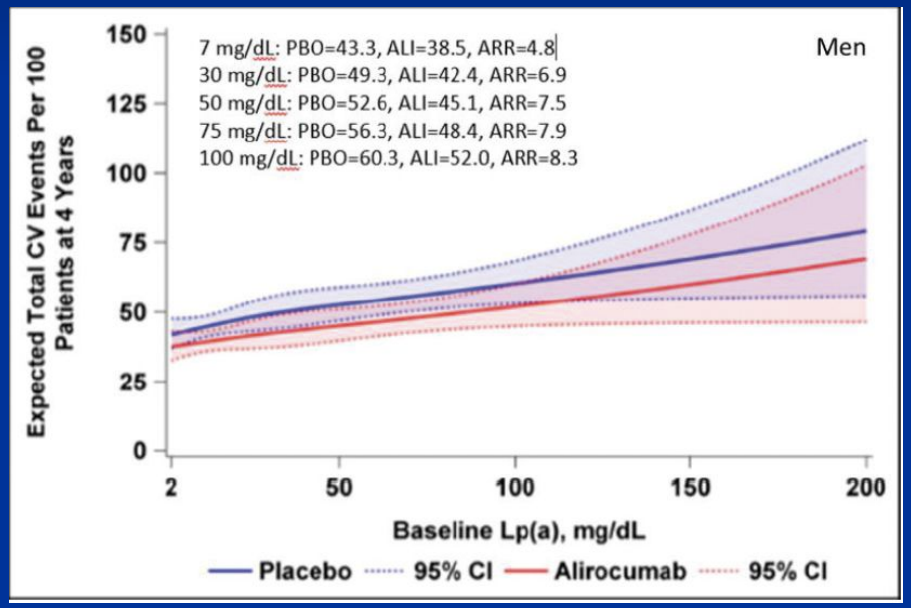
King et al *JACC 2018*;71

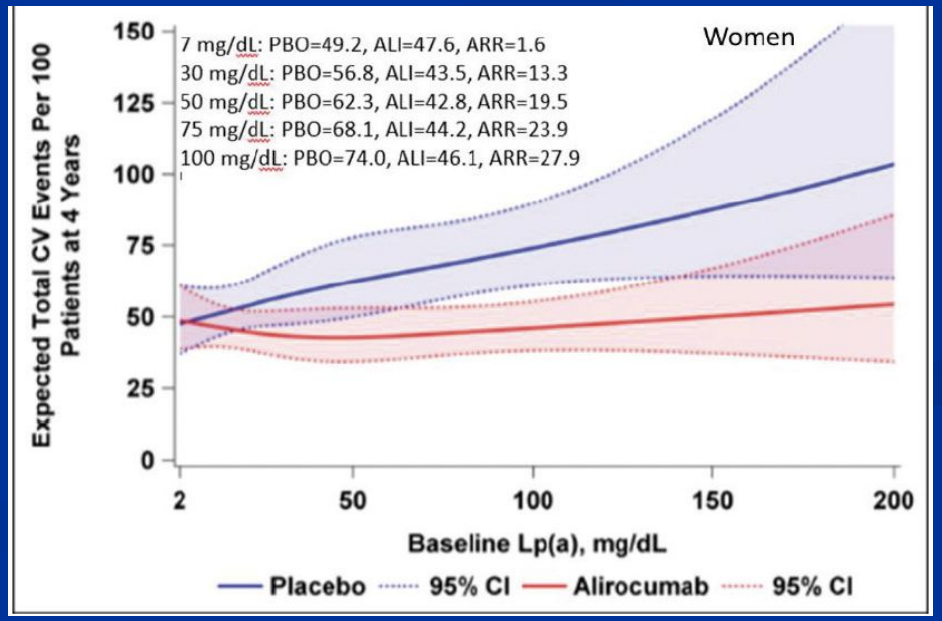
ACC.23 TOGETHER WITH WCC

1625
JACC March 7, 2023
Volume 81, Issue 8, suppl A

Prevention and Health Promotion

LIPOPROTEIN(A) AND CARDIOVASCULAR OUTCOMES IN WOMEN AND MEN AFTER AN ACUTE CORONARY SYNDROME: A POST HOC ODYSSEY OUTCOMES TRIAL ANALYSIS





Medication use in CAD in BC

TABLE 3. MEDICATIONS 3 MONTHS POSTCATHETERIZATION BY CORONARY ARTERY DISEASE STATUS AND SEX IN STABLE ANGINA PATIENTS

	No CAD			*Nonobstructive CAD*			*Obstructive CAD*		
Medications	*Female (N=901),* n *(%)*	*Male (N=653),* n *(%)*	p	*Female (N=480),* n *(%)*	*Male (N=608),* n *(%)*	p	*Female (N=1,142),* n *(%)*	*Male (N=3,751),* n *(%)*	p
Combination therapy	86 (9.5)	57 (8.7)	0.58	95 (19.8)	116 (19.1)	0.77	464 (40.6)	1,586 (42.3)	0.32
ACEI/ARBs	378 (42.0)	286 (43.8)	0.47	262 (54.6)	324 (53.3)	0.67	764 (66.9)	2,416 (64.4)	0.12
Beta-blockers	296 (32.9)	193 (29.6)	0.17	201 (41.9)	245 (40.3)	0.60	771 (67.5)	2,550 (68.0)	0.77
Statins	303 (33.6)	226 (34.6)	0.69	284 (59.2)	357 (58.7)	0.88	928 (81.3)	3,118 (83.1)	0.15
CCBs	204 (22.6)	115 (17.6)	0.02	149 (31.0)	146 (24.0)	0.01	437 (38.3)	1,039 (27.7)	<0.001
Clopidogrel	26 (2.9)	19 (2.9)	0.98	37 (7.7)	28 (4.6)	0.03	613 (53.7)	1,825 (48.7)	0.003

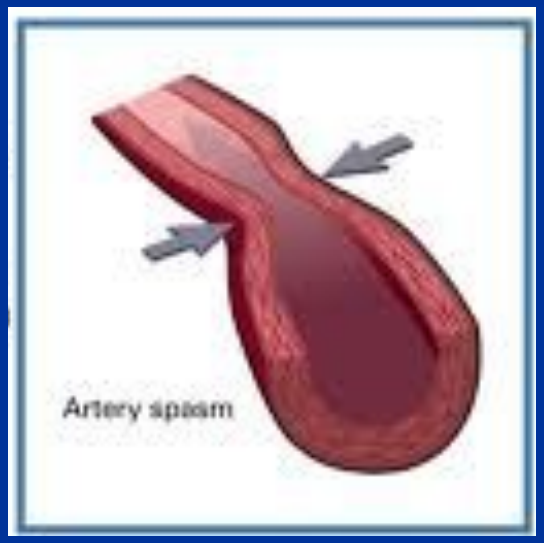
~60% statins
~55% ACEI/ARB

~80% statins
~65% ACEI/ARB

Sedlak *et al.* J of Women's Health 2017;26:976-983

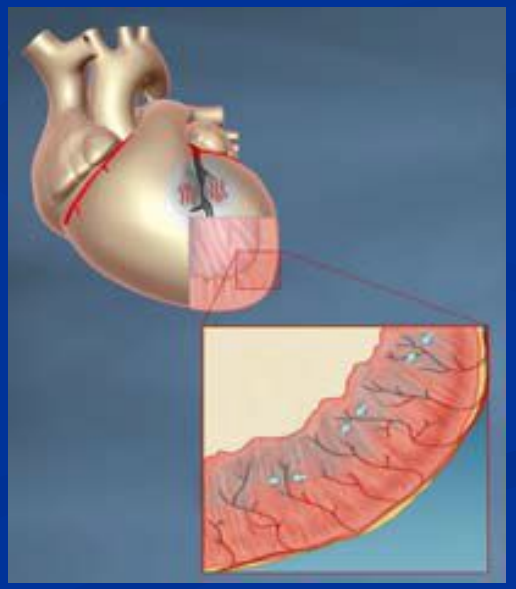
What are the causes of angina in women with normal coronary arteries?

- Spasm of artery



- Microvascular disease

(small vessel disease)



Coronary Microvascular Dysfunction

- Pathophysiologic Definition:
  - Disordered function of the smaller (<100-200 um) coronary resistance vessels
- Functional Definition:
  - Increase in coronary blood flow to maximal hyperemic stimuli (eg, adenosine) < 2.5 fold from baseline
  - ***Abnormal coronary microvascular resistance (either arteriolar or pre-arteriolar) that is clinically evident as inappropriate coronary blood flow response***

Vasculopathy (Men vs Women)

Table 2. The Vasculopathy of Women With IHD: Coronary Structure and Function Versus Men

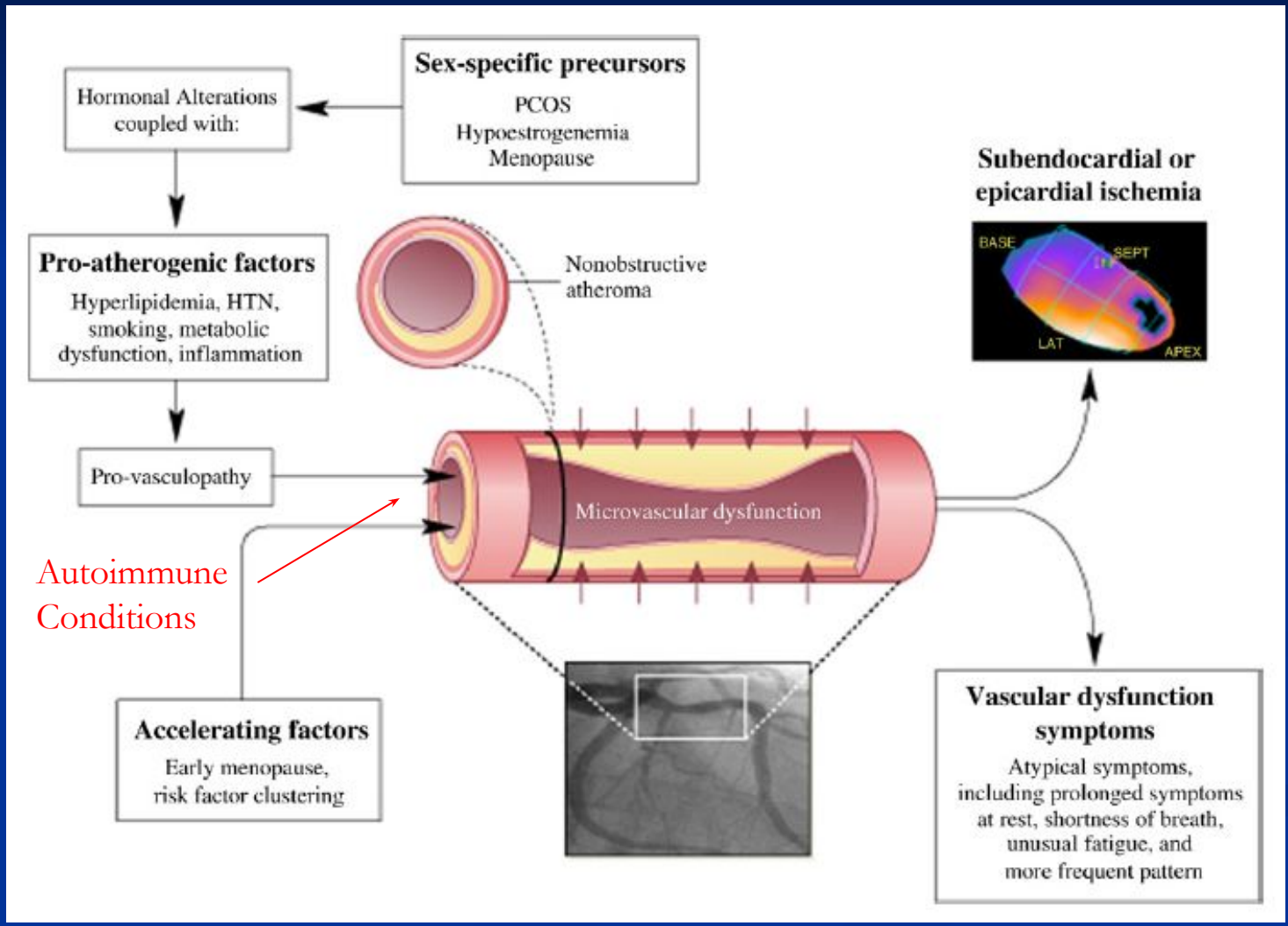
Structural findings
Macrovessels and microvessels
Smaller size
Increased stiffness (fibrosis, remodeling, and so on)
More diffuse disease, erosion >rupture
Microemboli, rarefaction (drop out), disarray, and so on
Functional findings
Macro- and microvessels
Endothelial dysfunction
Smooth muscle dysfunction (Raynaud's, migraine, CAS)
Inflammation
Plasma markers
Vasculitis (Takayasu's, rheumatoid, SLE, CNSV, giant cell, and so on)

More CAD in men

More MCD in women

Pepine *et al.*, JACC 2006;47:30S-35S

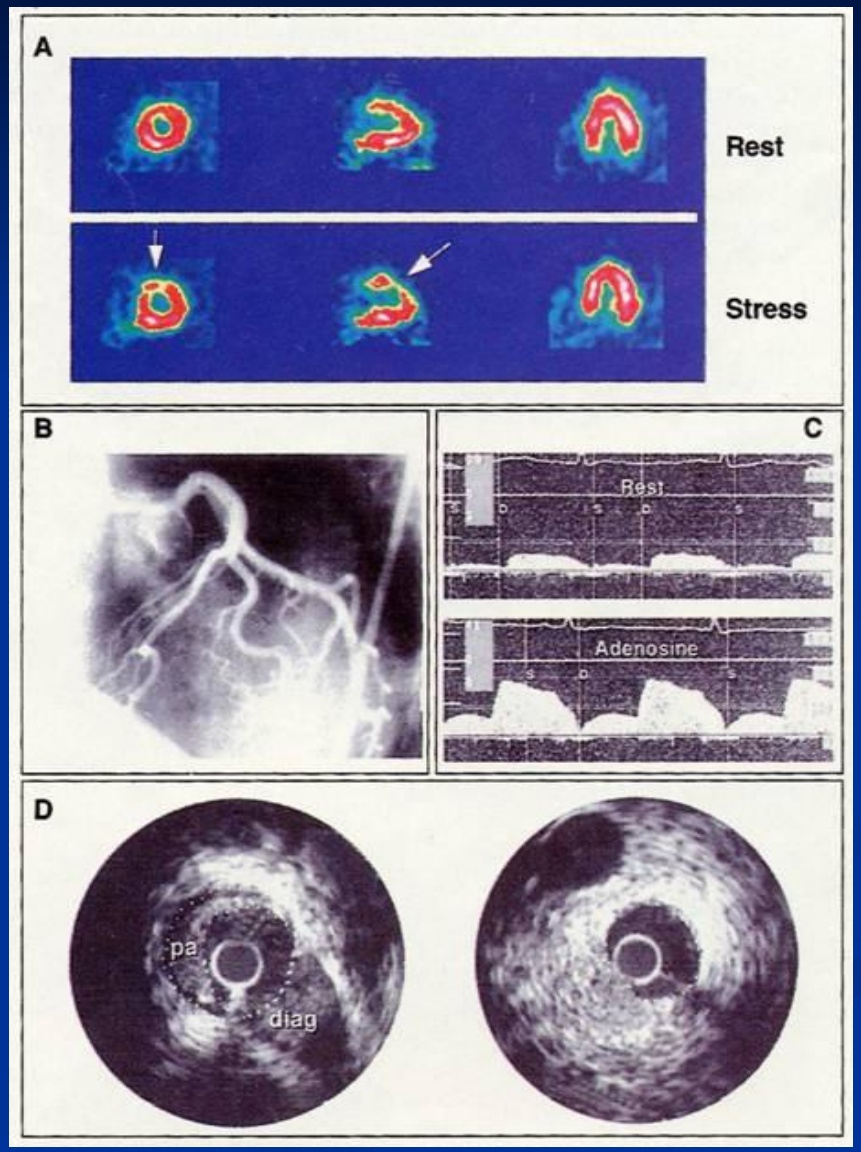
Etiology of Primary CMD



Shaw *et al.*, JACC 2009;54:1561-75

Diagnosis of CMD

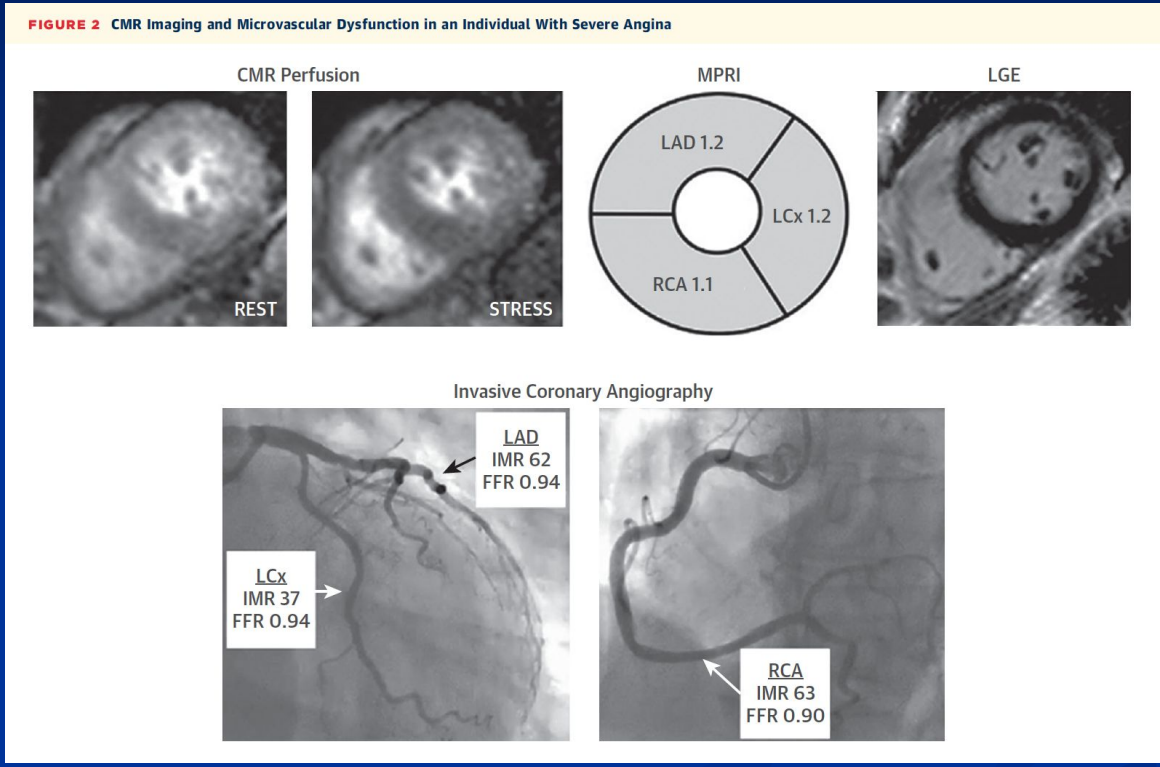
- Exertional angina or ACS presentation
- Abnormal stress testing
- No obstructive CAD
- Abnormal coronary flow reserve
- Diffuse atherosclerosis by IVUS



Circulation 1999;99:1774

Cardiac Perfusion MRI

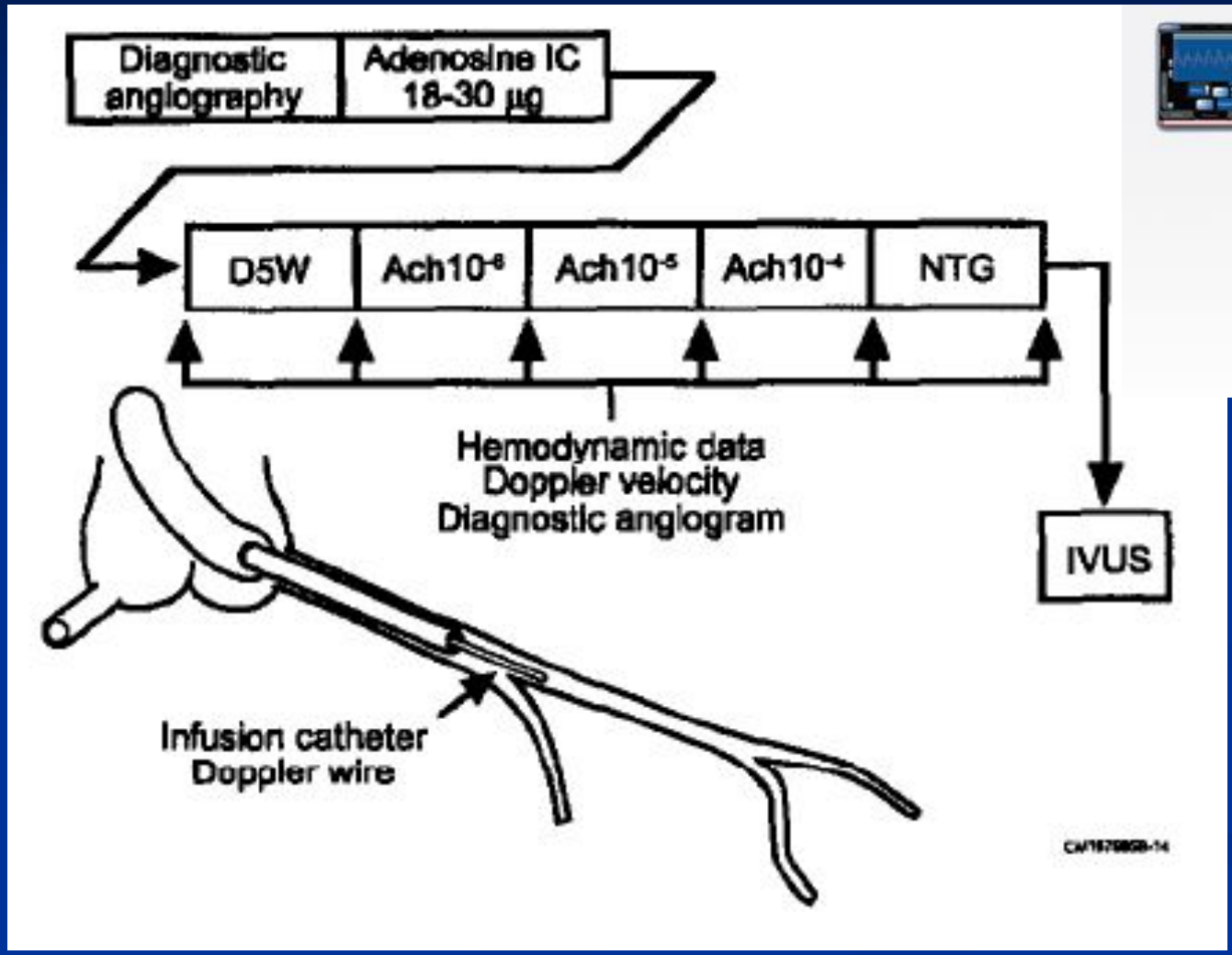
- CMRI allows evaluation of:
  - subendocardial perfusion
  - myocardial flow reserve
  - fibrosis and microinfarction
  - assessment of left ventricular function and mass
  - calculation of MPRI



- MPRI < 1.84 correlated with a sensitivity of 73% and specificity of 74% compared to invasive testing

Schindler, *et al. J Am Coll Cardiol Img*

Coronary Reactivity Testing (CRT)



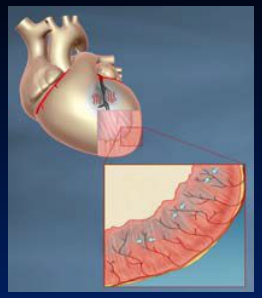
Hasdai *et al.*, Int J Cardiology 1996;53:203-208

International standardization of diagnostic criteria for microvascular angina☆

Peter Ong [a,*,1], Paolo G. Camici [b,1], John F. Beltrame [c], Filippo Crea [d], Hiroaki Shimokawa [e], Udo Sechtem [a], Juan Carlos Kaski [f,2], C. Noel Bairey Merz [g,2],
On behalf of the Coronary Vasomotion Disorders International Study Group (COVADIS)

- 1. Symptoms of myocardial ischemia
- 2. Absence of obstructive CAD (<50%)
- 3. Objective evidence of ischemia
  - ECG changes
  - Reversible perfusion defect
  - Reversible wall motion abnormality
- 4. Evidence of impaired microvascular function
  - CFR<2.5 (or 2.0)
  - Microvascular spasm with Ach
  - IMR >25
  - Slow flow (TIMI frame count >25)

Ong *et al.* Int J Cardiol 2018;250:18-20



Therapy for CMD

- Coronary Endothelial Dysfunction
  - ACEI, statins, aspirin, exercise, EECP
- Angina
  - B-blockers, CCB, ranolazine
- Coronary smooth muscle dysfunction (vasospasm)
  - CCB
- Abnormal cardiac nociception
  - Low dose TCAs (imipramine), Spinal Cord Stimulation (TENS unit), Cognitive Behavioral Therapy
- Other
  - Aminophylline, PDE5 inhibitors, L-arginine

CorMicA Trial

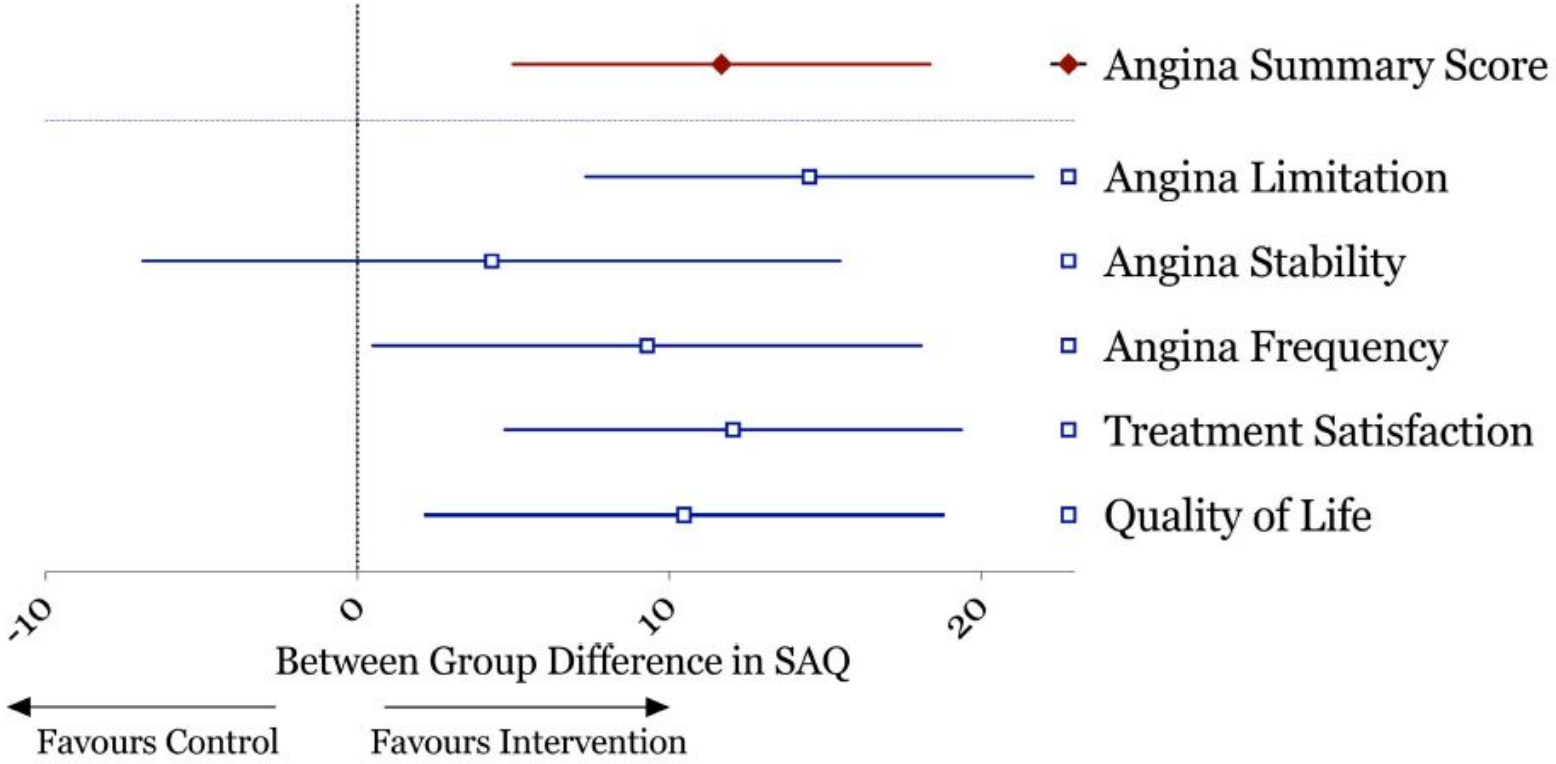
Stratified Medical Therapy Using Invasive Coronary Function Testing In Angina: CorMicA Trial

Thomas J. Ford [1,2,3] MBChB (Hons), FRACP, Bethany Stanley[5] MSc, Richard Good[1] MD, Paul Rocchiccioli [1,2] PhD, Margaret McEntegart [1,2] PhD, Stuart Watkins[1] MD, Hany Eteiba[1] MD, Aadil Shaukat[1] FRCP, Mitchell Lindsay[1] MD, Keith Robertson[1] MD, Stuart Hood[1] MD, Ross McGeoch MD[4], Robert McDade[1], Eric Yii[2], Novalia Sidik[2] MBChB, Peter McCartney[2] MBChB, David Corcoran[2] MBChB, Damien Collison[1,2] MB BCh, Christopher Rush[2] MBChB, Alex McConnachie[5] PhD, Rhian M. Touyz[2] PhD, Keith G. Oldroyd[1,2] MD(Hons), Colin Berry[1,2] PhD

[1]West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, UK; [2]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK; [3] University of New South Wales, Sydney, Australia; [4] University Hospital Hairmyres, East Kilbride, UK. [5] Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow

Ford *et al.*, JACC 2018; epub ahead of print

Results



- Anti-anginal medication and statin/ACEI doubled (85%) in the intervention arm

Ford *et al.*, JACC 2018; epub ahead of print

Women's ischemiA tRial to Reduce events In non-ObstRuctive CAD

- Statin/ACEI versus placebo
- 5 year MACE

INOCA in a Dedicated Women's Heart Center

ELSEVIER

Canadian Journal of Cardiology ■ (2022) 1–11

Clinical Research

One-Year Prospective Follow-up of Women With INOCA and MINOCA at a Canadian Women's Heart Centre

Mahraz Parvand, MSc,[a,b] Lily Cai, BA,[a] Siavash Ghadiri, MD,[a,b] Karin H. Humphries, DSc,[b] Andrew Starovoytov, MD,[a,b] Patrick Daniele, MSc,[b] Natasha Prodan-Bhalla, DNP,[c] and Tara L. Sedlak, MD[a,b,c]

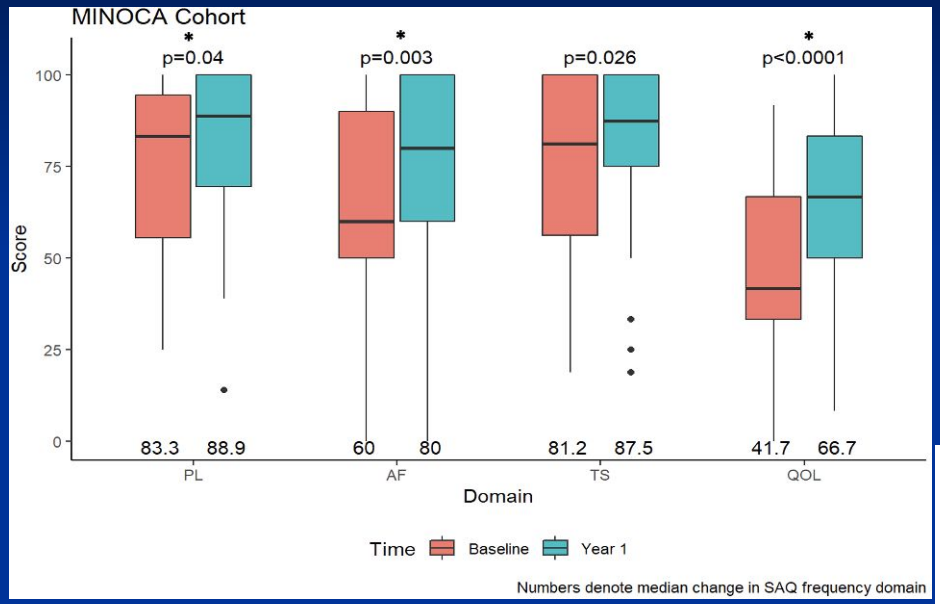
[a] *Vancouver General Hospital Department of Cardiology, Vancouver, British Columbia, Canada*

[b] *University of British Columbia Faculty of Medicine, Vancouver, British Columbia, Canada*

[c] *British Columbia Women's Hospital, Vancouver, British Columbia, Canada*

Parvand, Sedlak *et al.* CJC 2022; 38: 1600-10.

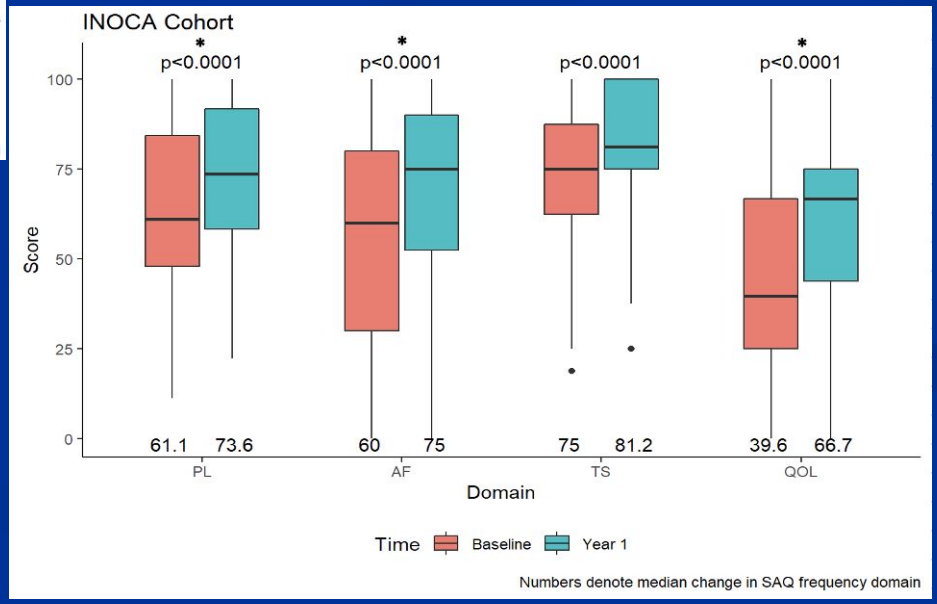
Angina and QoL
Pre- and Post- WHC Entry



MINOCA

- Attendance at a WHC significantly improved most angina categories and quality of life

INOCA



ED visits and angina hospitalizations

- Decrease in ED visits from 46 (41.1%) to 32 (28.6%)

- Decrease in angina hospitalizations from 12 (10.7%) to 2 (1.8%)

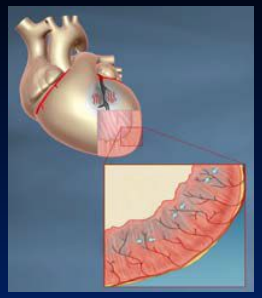
Case 1

- 62 F with multiple risk factors
- Obstructive CAD CABG
- Lp(a) 1700

- Statin myalgias (rosuvastatin 5mg; atorvastatin 10mg)
  - Statin every other day
  - ezetimide 10mg
  - PCSK-9 inhibitor (third party coverage)

Case 2

- Angina with non-obstructive CAD
- Coronary Microvascular Dysfunction (CMD)
- On ASA, statin, ACEI (LDL 1.5)
- Ongoing angina:
  - B-blocker
  - Amlodipine
  - NTG patch
  - Ranolazine



HER HEART MATTERS
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Questions?