6th International Symposium on Taiwan Nuclear Cardiology

CAD IN WOMEN: THE VALUE OF MYOCARDIAL PERFUSION IMAGING

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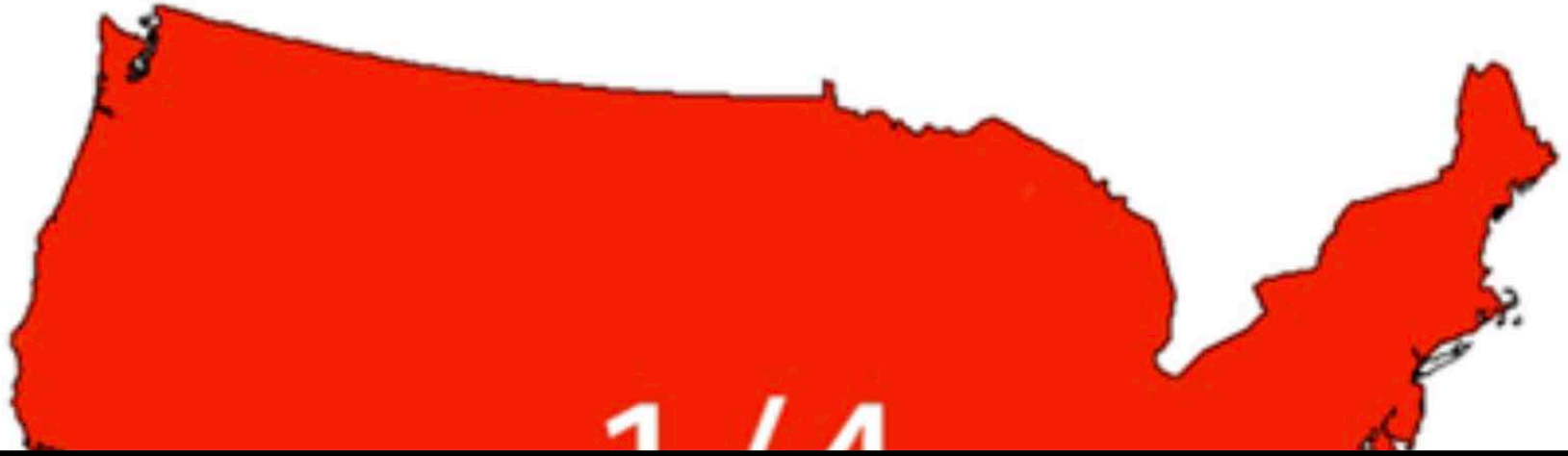
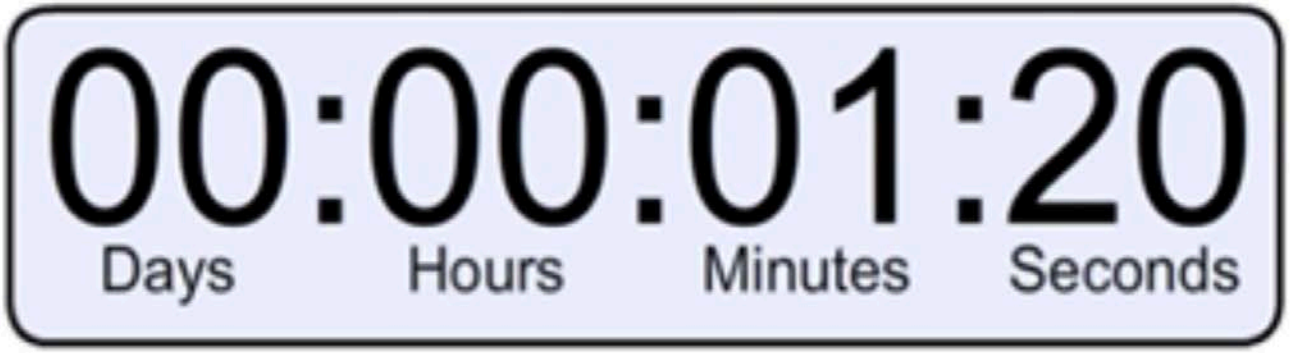
In 2013, roughly one in four deaths in women are from heart disease



= 398,086 deaths

The disease burden of CAD in women

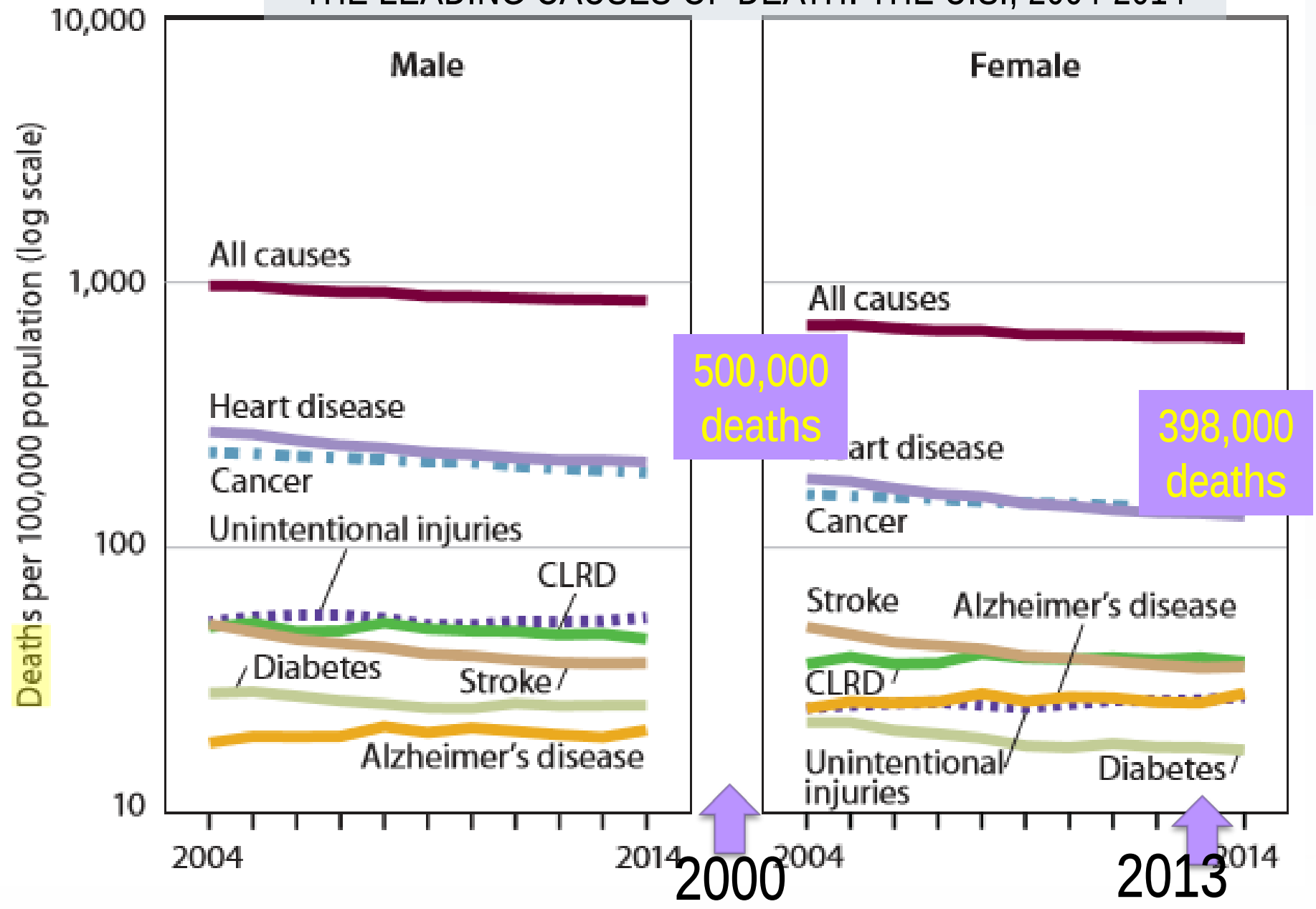
J Nucl Cardiol 2016;23:973–



One women died every 1'20",
in the US, from
cardiovascular diseases

J Nucl Cardiol 2016;23:973-

THE LEADING CAUSES OF DEATH: THE U.S., 2004-2014



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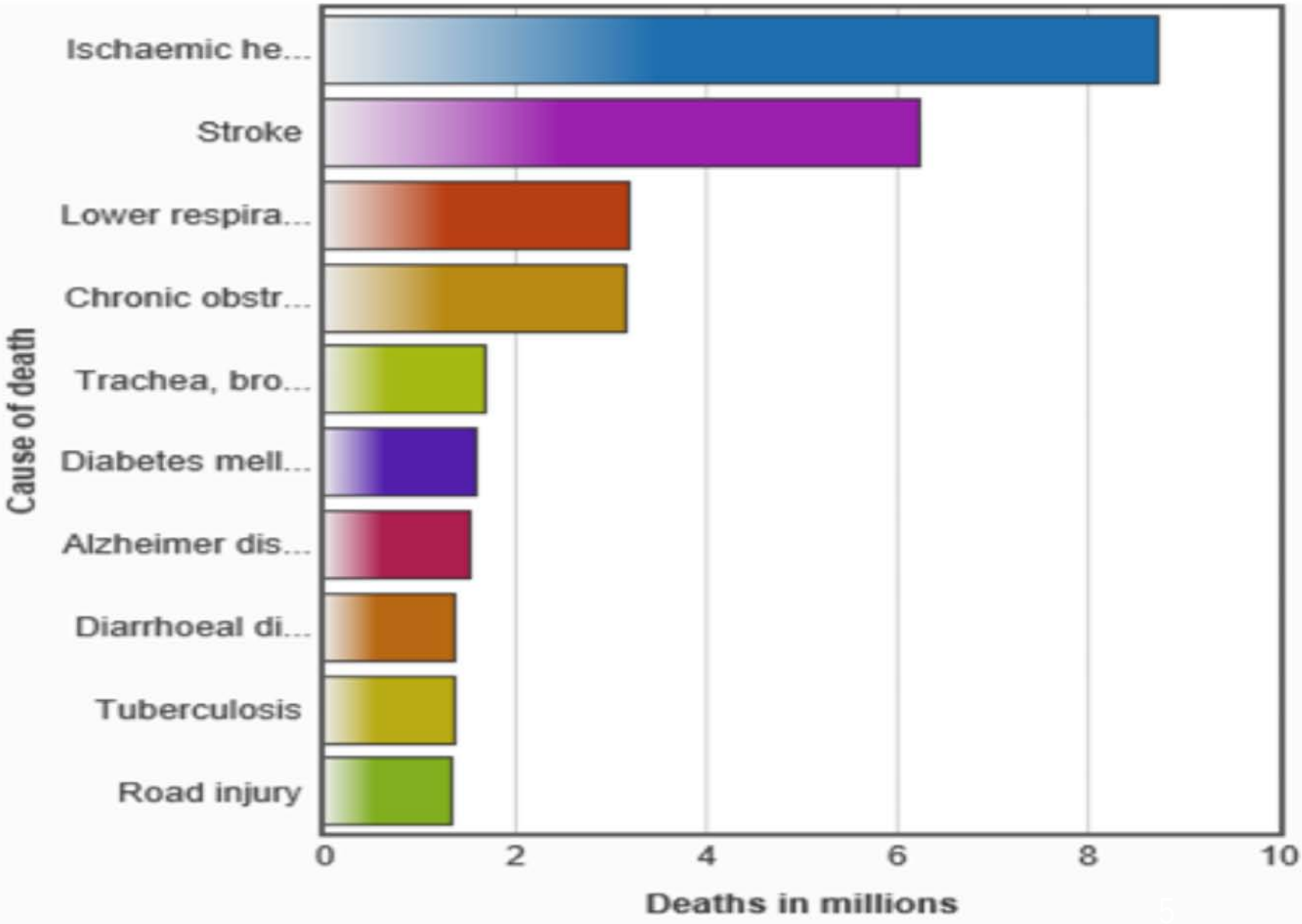
Health, United States, 2015, Chartbook p.11

World Health Organization

THE TOP 10 CAUSES OF DEATH GLOBALLY 2015

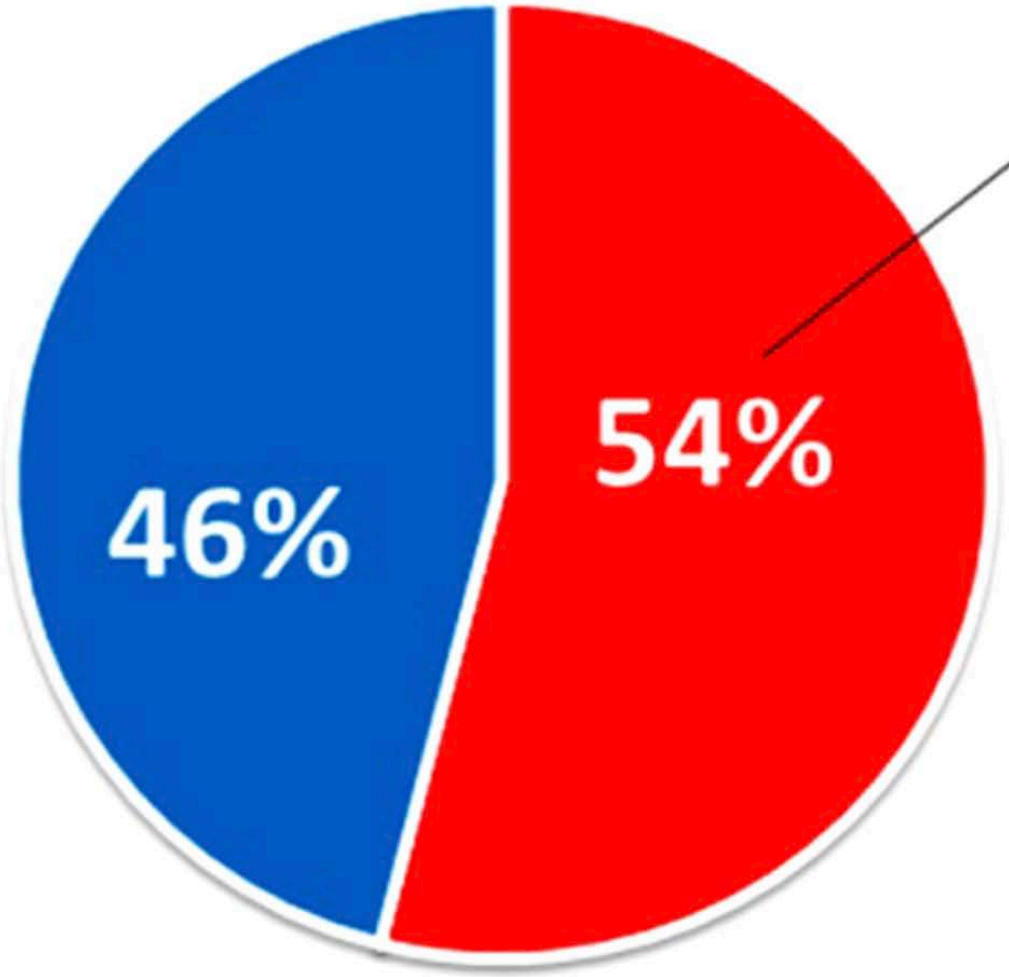


Number of female deaths attributable to breast cancer 1 in 31.6

Number of female deaths attributable to cardiovascular diseases 1 in 8

J Nucl Cardiol 2016;23:973–5

Awareness of CAD Among Women



Women who recognize that heart disease is their number 1 killer

J Nucl Cardiol 2016;23:973–5

THE DIFFERENCES BETWEEN WOMEN AND MEN: THE PATHOPHYSIOLOGY

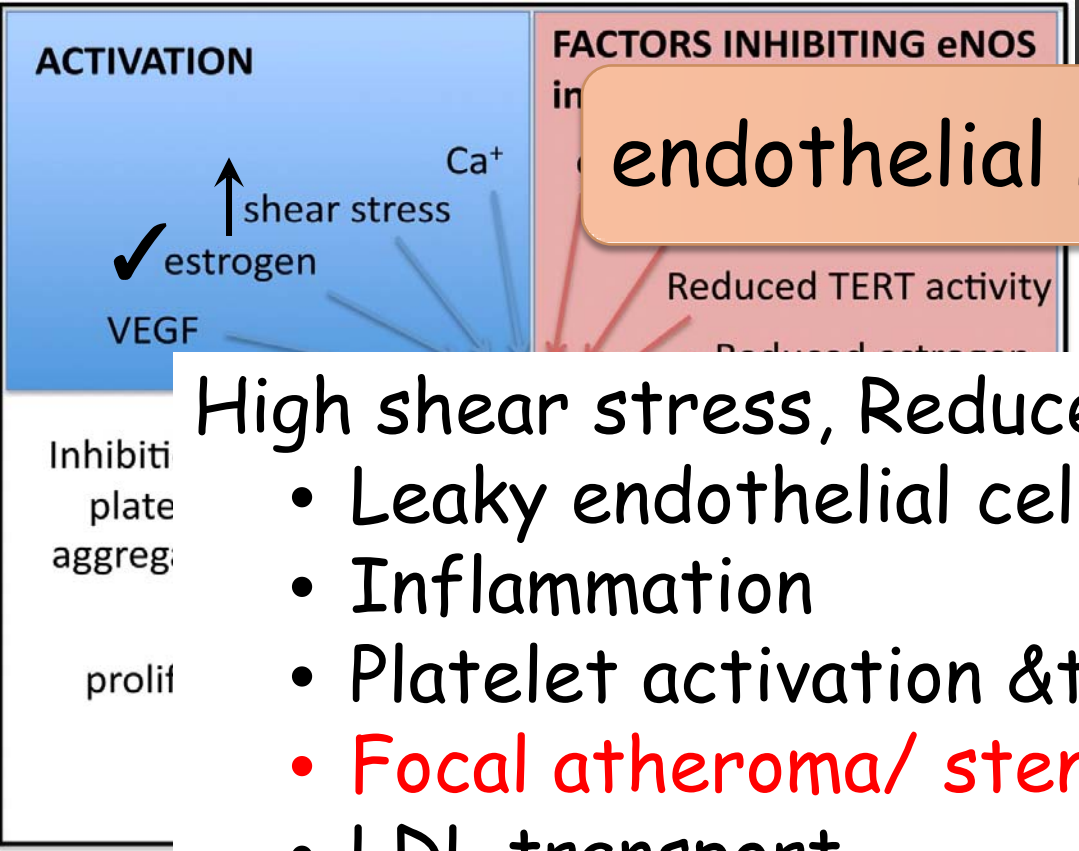
TABLE 1 Arterial Diameter, Myocardial Perfusion, LV Bed Size, and Shear

	♀	♂	p Value
Arterial diameter (mm)*			
LM	3.91 ± 0.67	4.35 ± 0.82	<0.001
LAD	3.24 ± 0.58	3.54 ± 0.67	<0.001
LCx	2.75 ± 0.64	3.18 ± 0.71	<0.001
RCA	3.26 ± 0.65	3.7 ± 0.70	<0.001
Mean size of all arteries	3.29	< 3.7	
Myocardial perfusion† (ml/min/g) for women (n = 1,150) and men (n = 3,178)			
Rest	0.97 ± 0.09	0.73 ± 0.04	<0.00001
Stress	2.36 ± 0.42	> 1.94 ± 0.4	<0.00001
CFR	2.57 ± 0.59	2.74 ± 0.71	<0.00001
LM	16.3	11.4	
LAD	19.2	14.1	
LCx	15.5	9.6	
RCA	9.4	6.2	
Mean size, all arteries	15.1	> 10.4	

Smaller arterial size, with high flow

→ endothelial HIGH shear stress

J Am Coll Cardiol Img 2016;9:465–82



endothelial HIGH shear stress

High shear stress, Reduces:

- Leaky endothelial cell junctions
- Inflammation
- Platelet activation &thrombosis
- Focal atheroma/ stenosis
- LDL transport
- Plaque instability

And, promotes:

- Mild stable uniform remodeling

J Am Coll Cardiol Img 2016;9:465–82
Pictures modified from Circ Res. 2012 Apr 27;110(9):1252-64
& Am J Physiol Endocrinol Metab. 2012;302:E481-95

Smooth muscle relaxation
Vasodilation
Inhibition of platelet aggregation

In women, the net effects of arterial size and high shear and their associated effects lead to stable diffuse CAD in women until late in life, after withdrawal of estrogens that interact with shear stress

"THE GENERAL RULE"

J Am Coll Cardiol Img 2016;9:465–82

However, endothelial shear stress and its effects are a complex, heterogeneously varying regional-, time-, and age-related continuum

"GREAT INDIVIDUAL DIFFERENCES"

J Am Coll Cardiol Img 2016;9:465–82

Consequently, with given risk factors,

Some women never develop CAD

Others develop focal disease prematurely (as men do)

And others have delayed focal disease

Whereas in many women,

coronary atherosclerosis is modified by these shear- dependent mechanisms into diffuse disease without focal stenosis

J Am Coll Cardiol Img 2016;9:465–82

Microvascular disease (MVD) is most commonly associated with diffuse epicardial coronary atherosclerosis

HIGH INCIDENCE OF MVD IN WOMEN

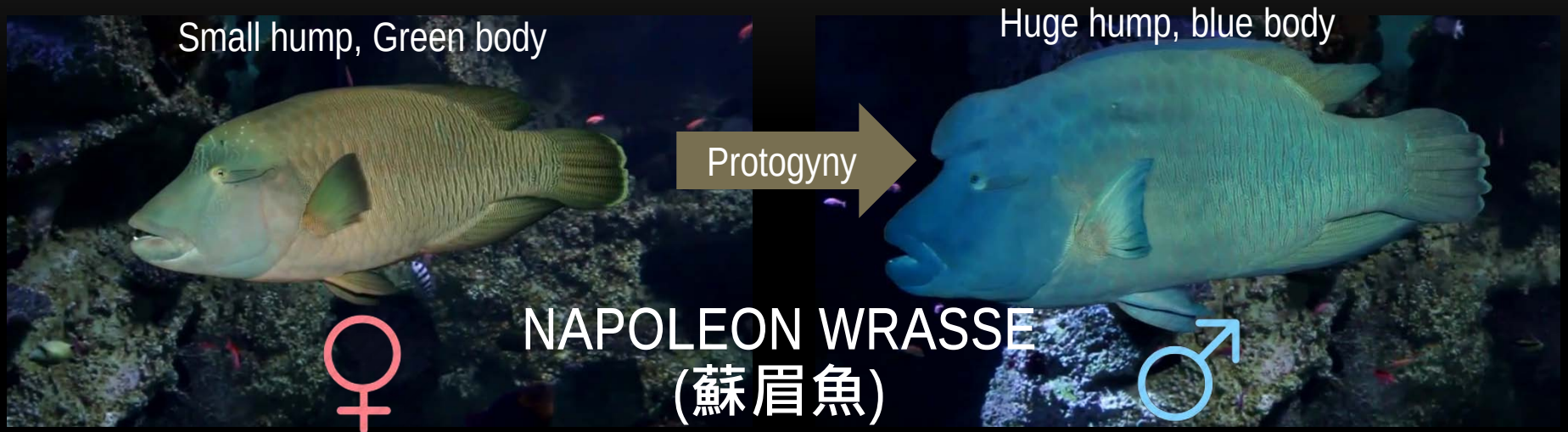
J Am Coll Cardiol Img 2016;9:465–82

TWO DISTINCT CHARACTERS OF CAD IN WOMEN

- Atypical nonexertional angina, related to diffuse coronary narrowing
- High mortality in post-menopausal women late in life when they do develop focal stenosis

J Am Coll Cardiol Img 2016;9:465–82

THE DESTINY OF WOMEN



In Men: Focal disease keeps going with age

In Women: Diffuse disease and MVD → superimposed with focal disease

from: Sydney Aquarium

PRETEST RISK STRATIFICATION FOR CAD IN WOMEN

NONTRADITIONAL WOMEN RISK FACTORS FOR CAD

Table 1. Risk factors for coronary artery disease in women

Major risk factors	Nontraditional risk factors
Hypertension	Chronic inflammatory autoimmune disease (SLE, RA, psoriasis)
Age	Menopause
Diabetes mellitus	Pregnancy-induced HTN, eclampsia, pre-eclampsia
Smoking	Gestational diabetes
Family history of premature CVD (men <age 55 or women <age 65)	Polycystic ovarian syndrome
Dyslipidemia (HDL-C <40 in men or <50 in women)	Mental stress/depression
Physical inactivity/obesity	

SLE Systemic lupus erythematosus, *HTN* hypertension, *HDL-C* high-density lipoprotein cholesterol

↑ MI 50X

↑ CAD 10 yrs after menopause

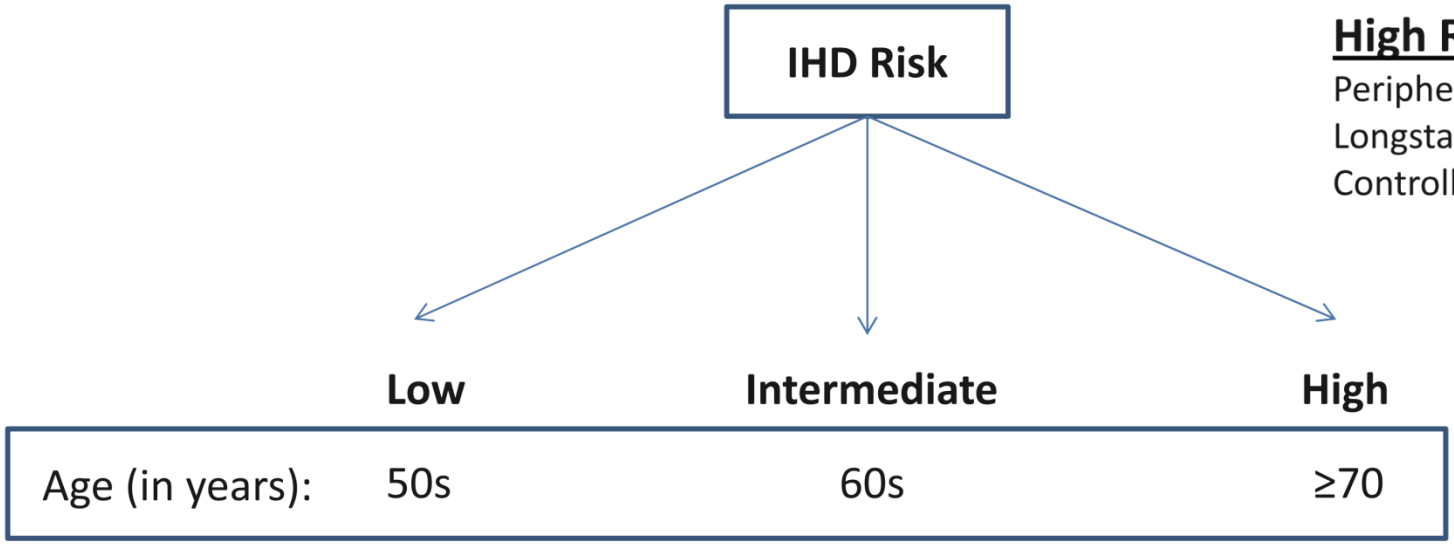
↑ HTN 3.7X; ↑ CAD 2X

↑ DM 4-7X→ ↑ CAD

→Traditional risk factors and the Framingham risk score (FRS) underestimate IHD risk in women

J Nucl Cardiol 2016;23:986–9

Categorization of IHD risk in symptomatic women



High Risk Equivalents

Peripheral Arterial Disease
Longstanding, Poorly-Controlled Diabetes

Risk Accentuation

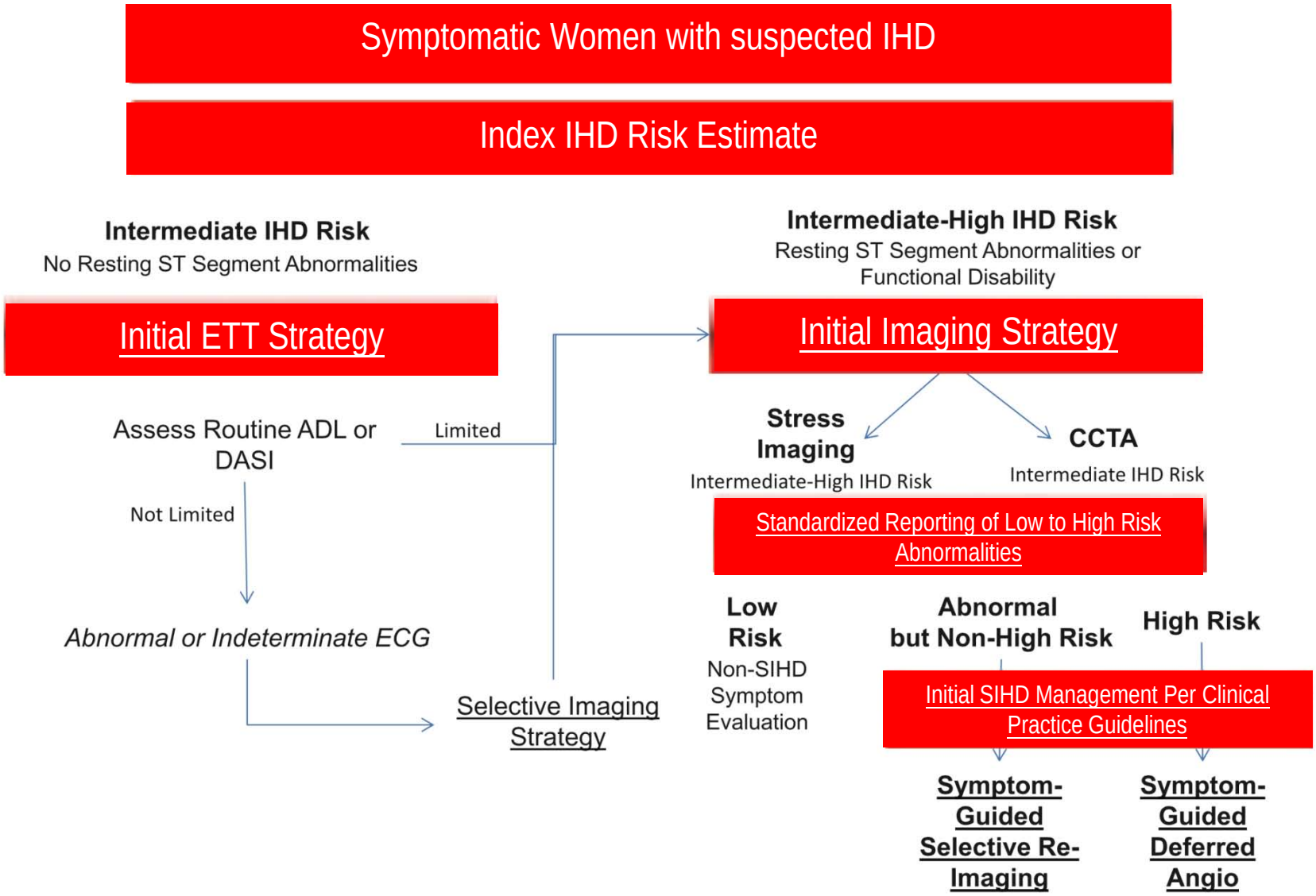
Add 1 Risk Category

Multiple Cardiac Risk Factors
Functional Disability
Extensive Comorbidity

PAOD
10-y history DM
>40F with poorly controlled DM
CKD
TIA or CVA
Functional disability

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

ROLE OF NONINVASIVE TESTING IN WOMEN WITH SUSPECTED IHD: AHA CONSENSUS



Circulation. 2014;130:350-

EXERCISE TREADMILL TEST (ETT)

	Overall	Women	Men
Sensitivity, %	60 (2)	61 (1)	68 (1)
Specificity, %	75 (2)	70 (1)	77 (1)
PPV, %	-	Lower (1) ⇔	Higher (1)
NPV, %	-	Similar (1) ⇔	Similar (1)

- Lower performance to exercise in women
- Autonomic and hormonal influences, inappropriate catecholamine release during exercise
- Estrogen, with molecular similarities to digitalis, can cause a digitalis-like false-positive response

(1) J Nucl Cardiol 2016;23:991–6
(2) The Massachusetts General Hospital Handbook of Internal Medicine_3rd ed.

STRESS SPECT

	Overall	Women	Men
Sensitivity, %	E: 85-90 (2)	S: 81 (4, 5) P Higher than E (3)	E: Higher (1) P: Higher (1)
Specificity, %	E: 70-75 (2)	S: 78 (4, 5)	S: Higher (3)

- Stress SPECT: Higher sen. & spe. than ETT
- Women: lower sen. & spe. than men
- Lower sen. in women: Exercise performance & small heart size
- Lower specificity in women: soft tissue attenuation & obesity

(1) J Nucl Cardiol 1997;4:329-35
(2) J Nucl Cardiol 2016;23:991–6
(3) J Nucl Cardiol 2016;23:997–1007
(4) JACC: Cardiovascular imaging 2016;9: 421-35
(5) AHRQ, Comparative effectiveness review, No. 58: Noninvasive technologies for the diagnosis of CAD in women

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

STRESS PET

	Overall	Women	Men
Sensitivity, %	90 (2)		
Specificity, %	89 (2)		
PPV, %	94 (2)		
NPV, %	73 (2)		
Accuracy, %	90 (2)	87 (1)	87 (1)

SIMILAR

- Excellent diagnostic performance:
  1. Routine attenuation correction→ High specificity
  2. High spatial & contrast resolution→ High sensitivity
- Short-lived radiopharmaceuticals→ High lab. efficiency
- High temporal resolution→ absolute quantification

(1) J Nucl Cardiol 2016;23:997–1007
(2) J Nucl Cardiol 2016;23:1008–15

CORONARY CT ANGIOGRAPHY (CCTA)

	Overall	Women	Men
Sensitivity, %	90 (3)	100 (2)	99 (2)
Specificity, %	90 (3)	75 (2)	90 (2)
PPV, %	-	81 (2)	95 (2)
NPV, %	99 (4)	100 (2)	98 (2)
Accuracy, %	-	Similar or 88 (1, 2)	Similar or 96 (1, 2)

A significant impact as an effective gatekeeper to ICA

Table 1 – Findings among patients without history of CAD who had a noninvasive stress test before elective coronary angiography.

Noninvasive test	Patients, N = 387,633, n (%)	Obstructive CAD, N = 173,448, n (%)	Nonobstructive CAD, N = 214,185, n (%)	*P*
Standard exercise stress test	37,969 (100)	17,016 (44.8)	20,953 (55.2)	<.0001
Stress echocardiogram	44,829 (100)	19,651 (43.8)	25,178 (56.2)	<.0001
Stress testing with SPECT MPI	302,651 (100)	134,670 (44.5)	167,981 (55.5)	<.0001
Stress testing with CMR	2926 (100)	1331 (45.5)	1595 (54.5)	<.0001
Coronary CTA	8323 (100)	5791 (69.6)	2532 (30.4)	<.0001

CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CTA, CT angiography; SPECT, single photon emission CT.
Table modified and adapted from Patel et al.[2]

(1) J Nucl Cardiol 2016;23:1016–22
(2) Am J Cardiol 2007;100:1532–1537
(3) JACC: Cardiovascular imaging 2016;9: 421-435
(4) J Cardiovasc Comput Tomogr 2014 8(6):480-2

STRESS ECHO (SE)

	Overall	Women	Men
Sensitivity, %	85 (1, 3)	Similar (2, 3) ⟺	Similar (2, 3)
Specificity, %	77 (1, 3)	Similar (2, 3) ⟺	Similar (2, 3)

- Accuracy: similar with stress SPECT
- Higher specificity
- Similar performance in women & men
- NO RADIATION!!!

Table 3. Diagnostic value of various noninvasive stress testing modalities compared with coronary angiography for diagnosing CAD in women without prior history of IHD

Modality	Number of studies	Number of women	Strength of evidence*	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%)	NPV (%)
ECG	29	3392	High	62% (55%–68%)	68% (63%–73%)	57	72
Echo	14	1286	High	79% (74%–83%)	83% (74%–89%)	78	83
MPI	14	1000	High	81% (76%–86%)	78% (69%–84%)	75	83
CMR	5	501	Low	72% (55%–85%)	84% (69%–93%)	62	89
CCTA	5	474	Low	93% (69%–99%)	77% (54%–91%)	63	96

Tables adapted from Agency for Healthcare Research and Quality June 2012 report[5]
PPV, positive predictive value; *NPV*, negative-predictive value; *ECG*, electrocardiography; Echo, stress echocardiography, either with exercise or pharmacological stress; *MPI*, myocardial perfusion imaging, using single-proton emission computed tomography (SPECT); *CMR*, cardiac magnetic resonance imaging; *CCTA*, coronary computed tomography angiography
*Strength of evidence is lower for CMR and CCTA as documented by the wide 95% confidence interval (CI)

(1) JAMA 1998;280:913-920, (2) Am J Cardiol 2007;99:714 –717, (3) J Nucl Cardiol 2016;23:1023–35

CARDIAC MR (CMR)

	Women	Men
Sensitivity, %	89 (1, 2, 3)	86 (1, 2, 3)
Specificity, %	84 (1, 2, 3)	83 (1, 2, 3)
Accuracy, %	AUC 0.9 (1, 2, 3)	AUC 0.89 (1, 2, 3)

- Excellent diagnostic performance
- Comparable results in both genders
- Multidirectional and comprehensive information: cine image, stress/rest perfusion imaging, MR angiography and scar imaging
- No Radiation!!!

(1) J Nucl Cardiol 2016;23:1036–40
(2) Circulation. 2014;129:1129-1138
(3) JACC: Cardiovascular imaging 2016;9: 421-35

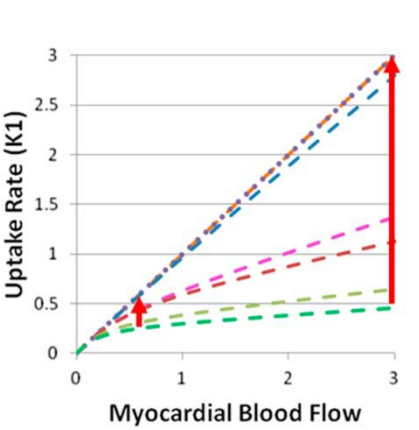
A PICTURE KEPT COMING INTO MY MIND, WHEN I WAS SUMMARIZING THE ABOVE INFORMATION...

A popular Quiz TV program years ago in Taiwan…

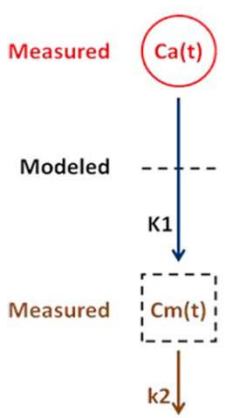
The MPIs (both SPECT & PET) face a FIERCE COMPETITION from many other excellent modalities

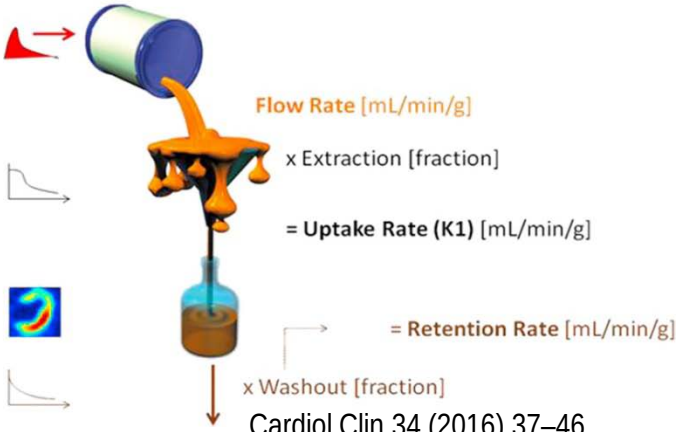
IS THERE A WAY OUT FOR MPI ?

QUANTIFICATION OF CORONARY BLOOD FLOW (CBF) & CORONARY FLOW RESERVE (CFR)

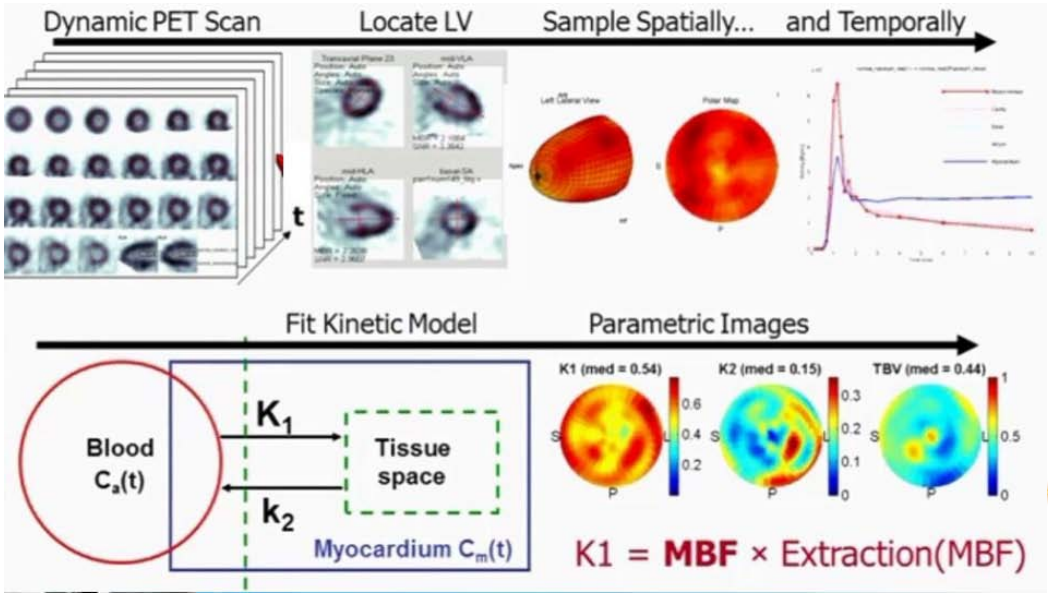


MBF Correction Factors	(rest - stress)
O-15 Water	1.0
Ideal	
N-13 Ammonia	1.0 – 1.1
Tl-201 Thallium	1.5 – 2.2
Rb-82 Rubidium	1.5 – 2.5
Tc-99m Sestamibi	2.0 – 4.5
Tc-99m Tetrofosmin	2.5 – 6.5





Cardiol Clin 34 (2016) 37–46



Lortie et al. EJNMMI 2007

$$CFR = \frac{MBF_{Stress}}{MBF_{Rest}}$$

CFR<1.9 ml/min/g, for high-risk angiographic CAD	
Sensitivity, %	86 [5, 11]
NPV, %	97 [5, 11]

J Nucl Cardiol 2016;23:1023–35

ABSOLUTE MYOCARDIAL PERFUSION BY PET

Table 1 Graded Absolute Flow and Coronary Flow Reserve Across Spectrum of Disease (N = 14,962)

Population	n	Rest Flow (cc/min/g)	Stress Flow (cc/min/g)	CFR
Normal controls	3,484	0.82 ± 0.06	2.86 ± 1.29	3.55 ± 1.36
Risk factors only	3,592	0.85 ± 0.08	2.25 ± 1.07	2.80 ± 1.39
Established coronary artery disease	1,650	0.83 ± 0.10	1.71 ± 0.71	2.02 ± 0.70
Mixed (risk factors and/or known coronary artery disease)	4,765	0.97 ± 0.10	1.86 ± 0.58	1.93 ± 0.48
Cardiomyopathy	594	0.73 ± 0.07	1.47 ± 0.56	2.02 ± 0.67
Hypertrophic cardiomyopathy	345	0.90 ± 0.10	1.57 ± 0.33	1.84 ± 0.36
Syndrome X	348	1.06 ± 0.11	2.65 ± 1.31	2.54 ± 1.31
After cardiac transplant	184	1.14 ± 0.18	2.44 ± 1.34	2.29 ± 0.86

N = 14,962 from 252 unique publications. N-13 ammonia = 5,541; 0-15 water = 3,161; Rb-82 = 6,175.

N= 14,962 from 252 unique publications.

N-13 ammonia= 5,541; O-15 water= 3,161; Rb-82=6,175.

The earliest one: Japan, Iida et al., normal controls, N=13. Circulation 1988

Gould et al. in: J Am Coll Cardiol 2013;62:1639 – 53

ABSOLUTE MYOCARDIAL PERFUSION BY SPECT

Conventional SPECT

- Sugihara H, et al. J Nucl Cardiol. 2001;8:575– 9
- Di Bella EV, et al., Invest Radiol. 2001;36:178– 85
- Storto G, et al., J Nucl Cardiol. 2004;11(6):651– 5
- Iida et al., Eur J Nucl Med Mol Imaging 2008;35:896–905
- Christian et al., Int J Cardiovasc Imaging 2008;24: 269–76
- Hsu et al. Eur J Nucl Med Mol Imaging. 2014. Dec;41(12):2294-306

New heart-centered NaI camera/ CZT camera

- Ben-Haim et al. J Nucl Med. 2013;54:873–9
- Nkoulou et al. J Nucl Med. 2016;57(12):1887-1892
- Shrestha et al. J Nucl Cardiol. 2017;24(1):268-277

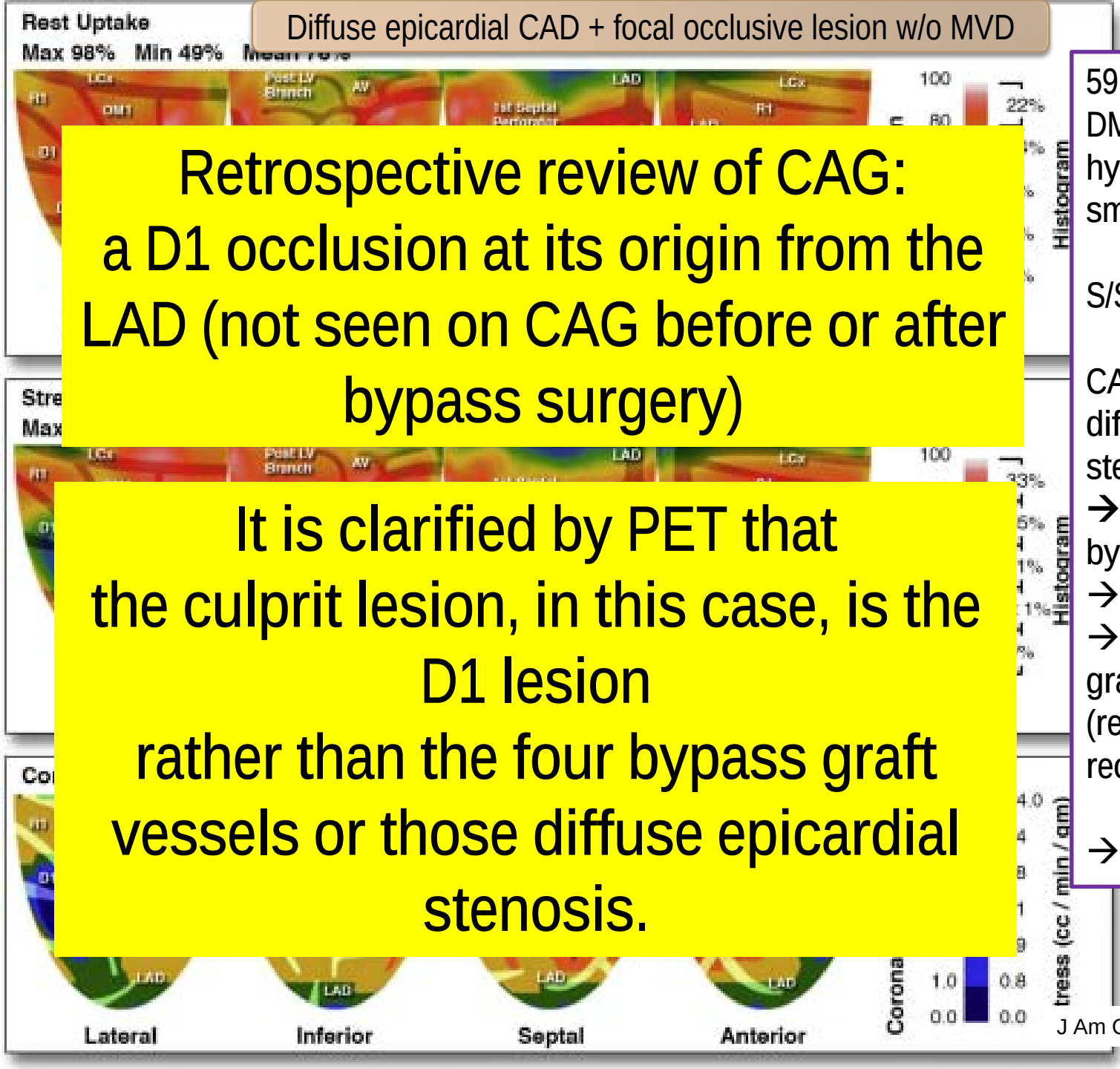
Small patient population or in animal experiments

Measuring MBF with SPECT is Feasible

Garcia. Eur J Nucl Med Mol Imaging. 2014, editorial page
J Nucl Cardiol. 2017; 24(1): 278–281

APPLICATION OF FLOW QUANTIFICATION IN CLINICAL CASES

Diffuse epicardial CAD + focal occlusive lesion w/o MVD



Retrospective review of CAG:
a D1 occlusion at its origin from the LAD (not seen on CAG before or after bypass surgery)

It is clarified by PET that
the culprit lesion, in this case, is the D1 lesion
rather than the four bypass graft vessels or those diffuse epicardial stenosis.

59F
DM, HTN, hyperlipidemia, smoking, FH(+)

S/S: atypical angina

CAG: CAD(+) with diffuse epicardial stenosis
→4-vessel coronary bypass
→No S/S improvement
→CAG: all 4 bypass grafts occluded (repeated bypass recommended)

→PET

usually angina and STΔ with dipyridamole stress (largest single contiguous region: 7%).

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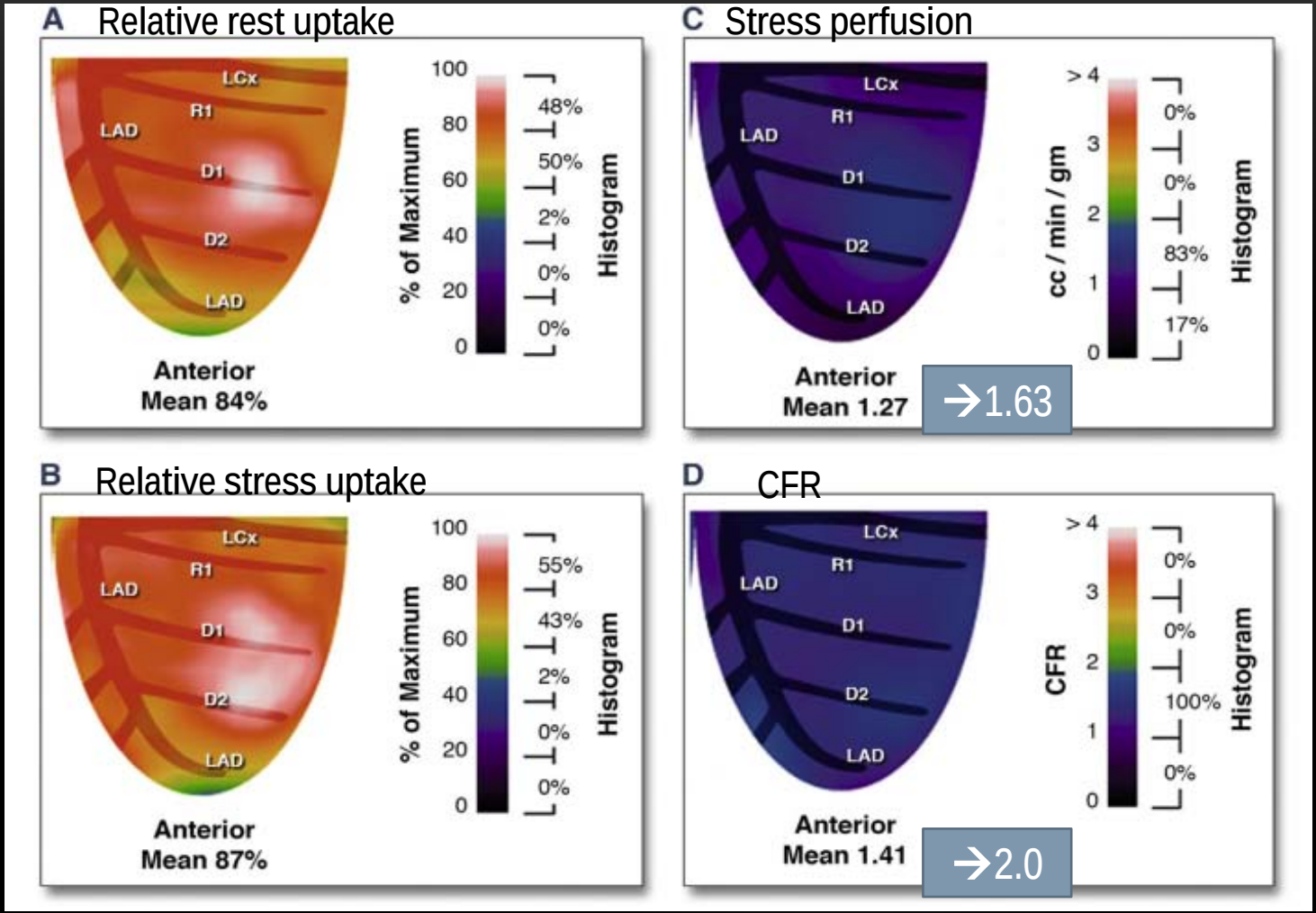
MVD w/o Epicardial stenosis



78F
FH(+), strong

S/S: angina with jaw & arm radiation, at both rest and exertion for 11 yrs
NTG response (+)

CT: no coronary calcium
→CAG (-) years ago
→PET

Caffeine inhibition(?):
24hr = 5.7 ug/ml
48hr = 1.8 ug/ml
72hr = 0 ug/ml
→Repeat PET when no caffeine detectable

Other views (right septal, lateral, and inferior topographic views) were all similar

J Am Coll Cardiol Img 2016;9:465–82

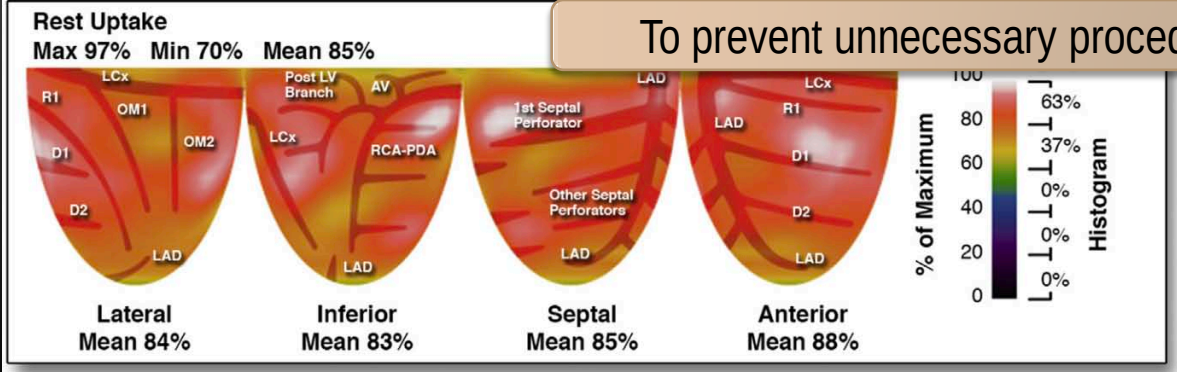
To prevent unnecessary procedures

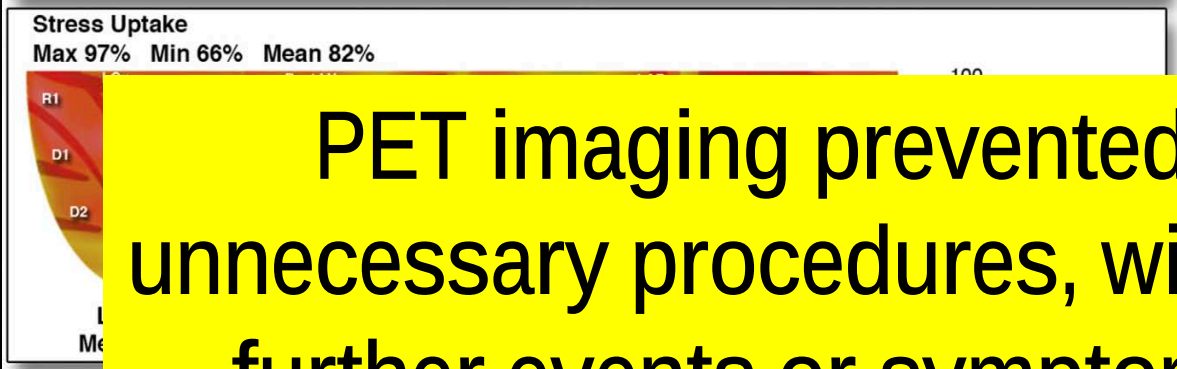
63F
FH(+), dyslipidemia

Presented with NSTEMI

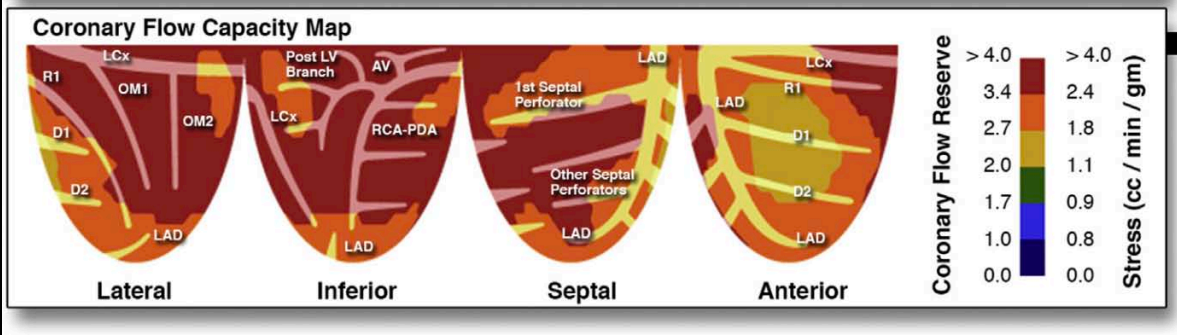
CAG: occluded D1; moderate to severe stenosis at LAD, EF 60%
Elective PCI recommended despite no symptoms after the acute episode

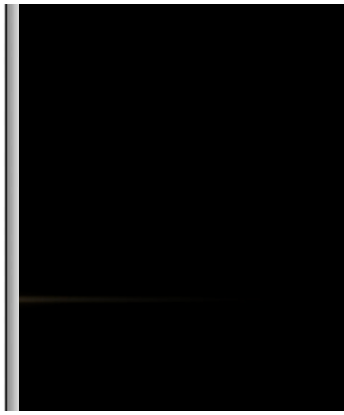
→PET as a second opinion





PET imaging prevented unnecessary procedures, with no further events or symptoms through 7-year follow-up on atorvastatin





J Am Coll Cardiol Img 2016;9:465–82

WHAT A HIGH-QUALITY QUANTITATIVE PERFUSION IMAGING CAN TELL US

- To facilitate diagnosis/ DDx of the following conditions:
  - Epicardial focal disease
  - Diffuse disease
  - Microvascular disease (MVD)
  - Any combination of the above
  - MVD v.s. Anterior wall attenuation artifact
- To prevent unnecessary procedures
- To quantitatively evaluate risk factors control

IN SUMMARY, CAD IN WOMEN IS…

- Prevalent, but Less aware
- Pathophysiologically different
- Atypical symptoms
- Integration of nontraditional risk factors needed
- Heterogeneous, with component of more diffuse disease/ MVD
- Poorer diagnostic performance
- Higher mortality rate
- SPECT: still the modality of choice in S/S(+) intermediate risk women
- Blood flow quantification may help a lot in:

Further diagnosis/ DDx, and prevent unnecessary procedures

WE HAVE COME A LONG WAY BUT STILL HAVE A WAYS TO GO

…. The " long way " that we have come is the enormous amount of data already presented, and for that we should all rejoice in this progress on women ' s health issues.

Leslee J. Shaw, PhD. et al, iJACC 2016;9:502-503

WE HAVE COME A LONG WAY BUT STILL HAVE A WAYS TO GO

The “ ways to go ” is whether we can commit to a strategic plan encompassing women ’ s health as a primary goal for cardiovascular imaging research.

WE HAVE COME A LONG WAY BUT STILL HAVE A WAYS TO GO

We need to know where we stand and only then will we know where to go.

WHY?

BECAUSE OF THEM?










BUT ALL OF THEM!

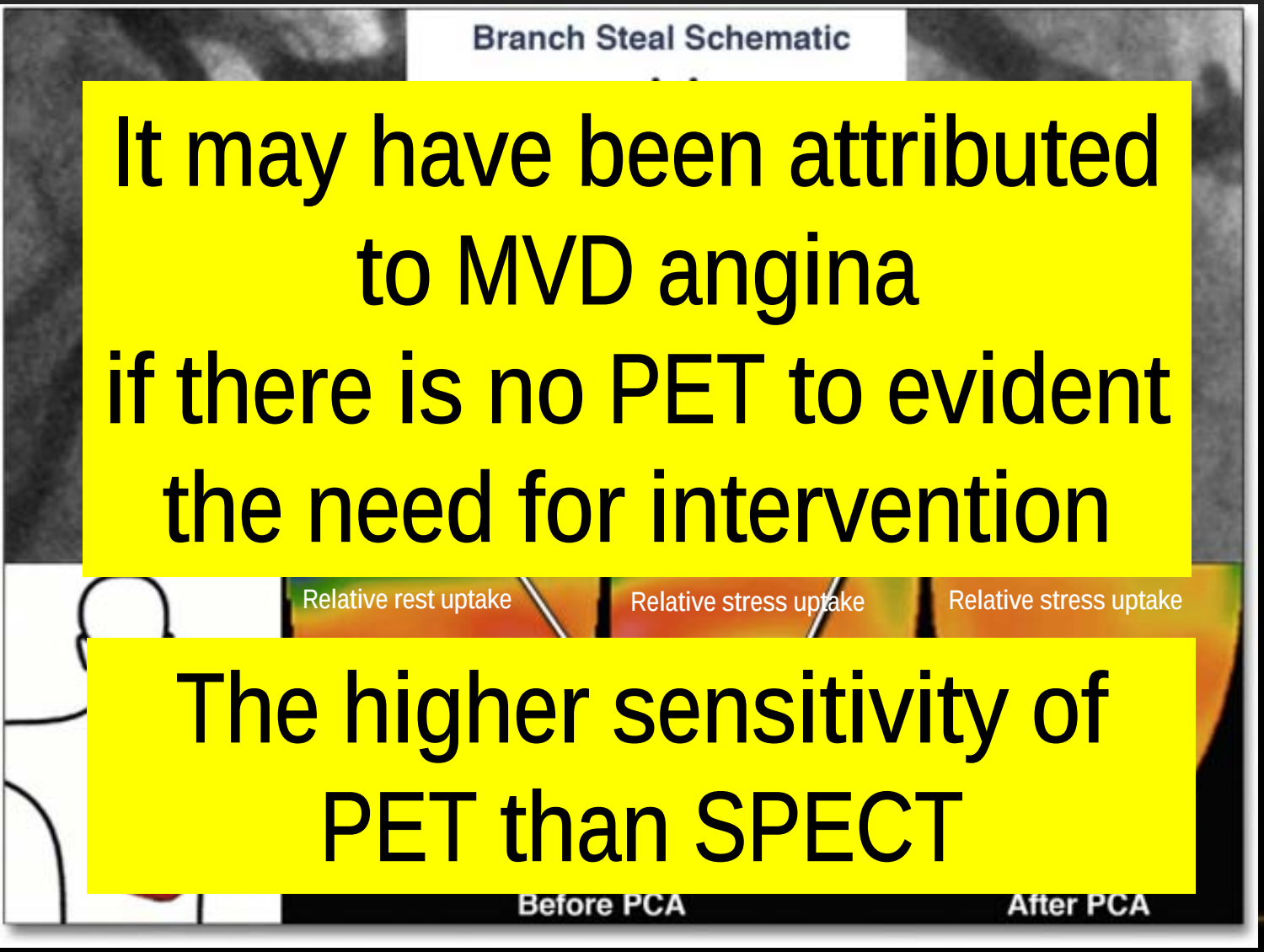


Should we not owe our best when it comes to taking care of one-half of the population of the planet.

Leslee J. Shaw, PhD. et al, iJACC 2016;9:502-503

THANKS FOR YOUR ATTENTION

Epicardial focal CAD or MVD ✓



58F
MVP, HTN
smoking (+), quited
FH (+), strong,
dyslipidemia

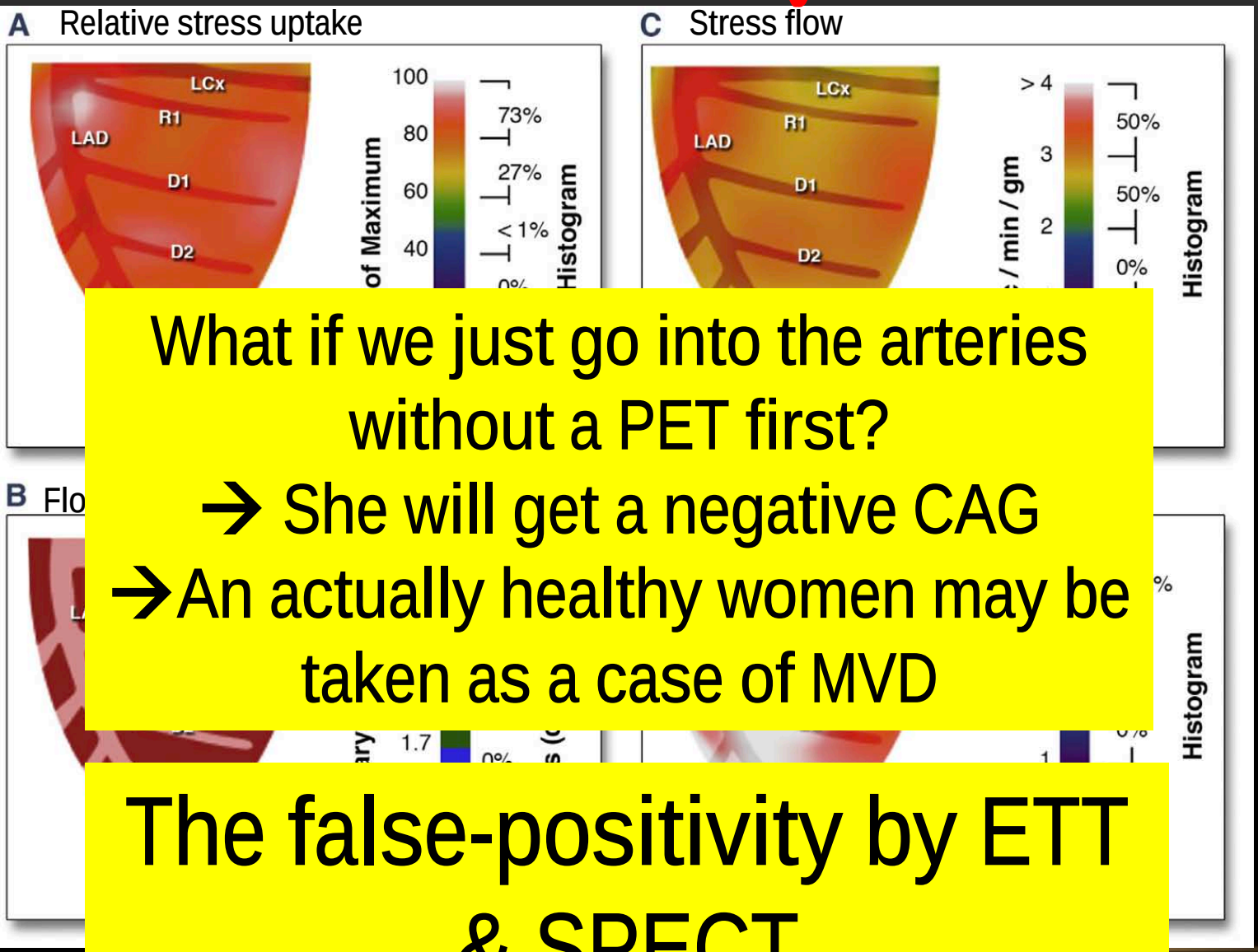
S/S: exertional angina for 3 weeks

Stress EKG (-),
SPECT (-)
CT calcium score 118 in LAD, 1 yr ago "no CAD" by her cardiologist (MVD?)

→PET
→CAG: severe diagnal stenosis (80%) and mild LAD stenosis (57%)
→PCI: open LAD and diagnal lesion
→S/S relived

J Am Coll Cardiol Img 2016;9:465–82

MVD or Anterior wall attenuation artifact



What if we just go into the arteries without a PET first?

→ She will get a negative CAG

→An actually healthy women may be taken as a case of MVD

The false-positivity by ETT & SPECT

43F

S/S(-)

ETT(+) (check-up)
SPECT(+): anterior ischemia

CAG recommended

→PET as a second opinion

J Am Coll Cardiol Img 2016;9:465–

PROGNOSTIC VALUE OF NIT

- Stress SPECT: Graded increased event rate with extensiveness & severity of defect.
- Stress PET: the percentage of abnormal stress myocardium was independently predictive of CAD mortality in women and men.
- CCTA: obstructive coronary artery disease revealed by CCTA in women, as in men, has significant predictive value for future cardiovascular events
- Stress ECHO: The prognostic utility has also been demonstrated in numerous studies and appears similar in both genders. Workload and exercise wall motion score index in exercise ECHO; negative and positive in pharmacological ECHO→ Increased event risk.
- CMR: high prognostic performance, studies revealed that the presence of inducible perfusion defects or WMA as independent predictors of hard cardiac events.

J Nucl Cardiol 2016;23:1008–15
J Nucl Cardiol 2016;23:1016–22
J Nucl Cardiol 2016;23:1036–40
J Am Coll Cardiol 2016;67:1158–69

CONFIRM STUDY