Microvascular Angina: Where are We?

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VA Greater Los Angeles Healthcare System

What is your background in medicine?

- ❑ A. Cardiologist
- ❑ B. Internal medicine
- ❑ C. Other primary care
- ❑ D. Other subspecialty
- ❑ E. Research only

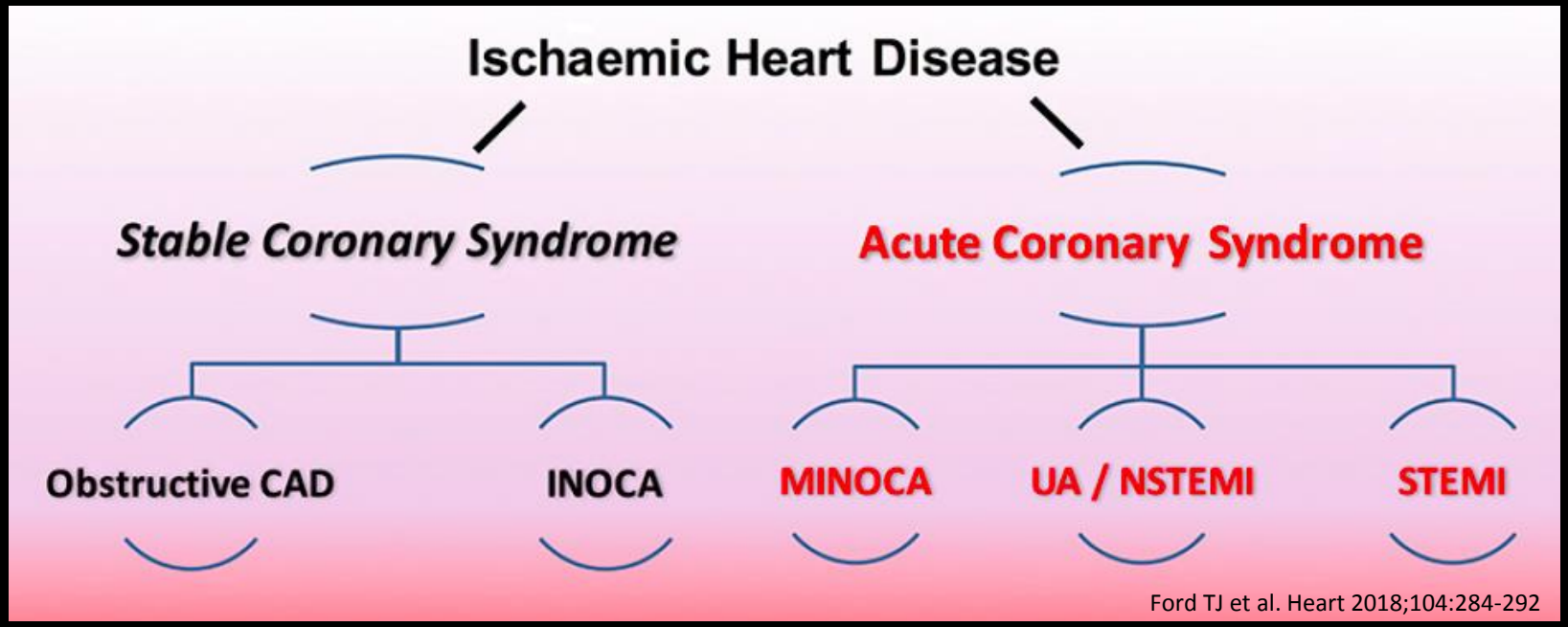
Microvascular disease

- New classification
- Diagnostics
  - Invasive
  - Non-invasive (established)
  - Non-invasive (novel)
- Therapeutics
  - Existing
  - Future needs

Ischemic Heart Disease: Remains the global leading cause of death

- Angina
  - Most common presentation
  - Problem of supply:demand mismatch, typically provoked by exercise or stress
  - Invasive coronary angiography is the reference test
- In U.S. and Europe, up to 4 million angiograms are performed
  - Only half have evidence of obstructive CAD

Taxonomy



Ford TJ et al. Heart 2018;104:284-292

CAD=coronary artery disease
INOCA=ischemia and no obstructive coronary disease
MINOCA=myocardial infarction and no obstructive coronary disease
UA=unstable angina
NSTEMI=non ST elevation myocardial infarction
STEMI=ST elevation myocardial infarction

Ford TJ et al. Heart 2018;104:284 292

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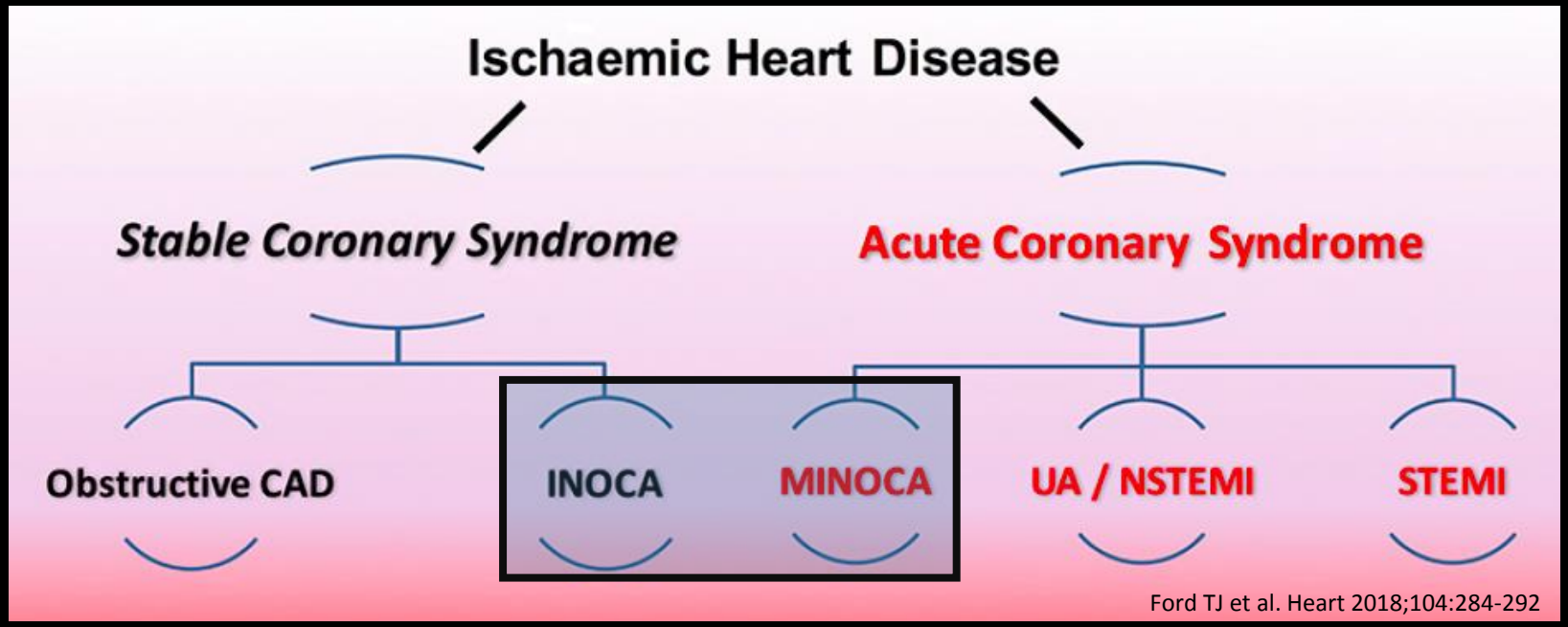

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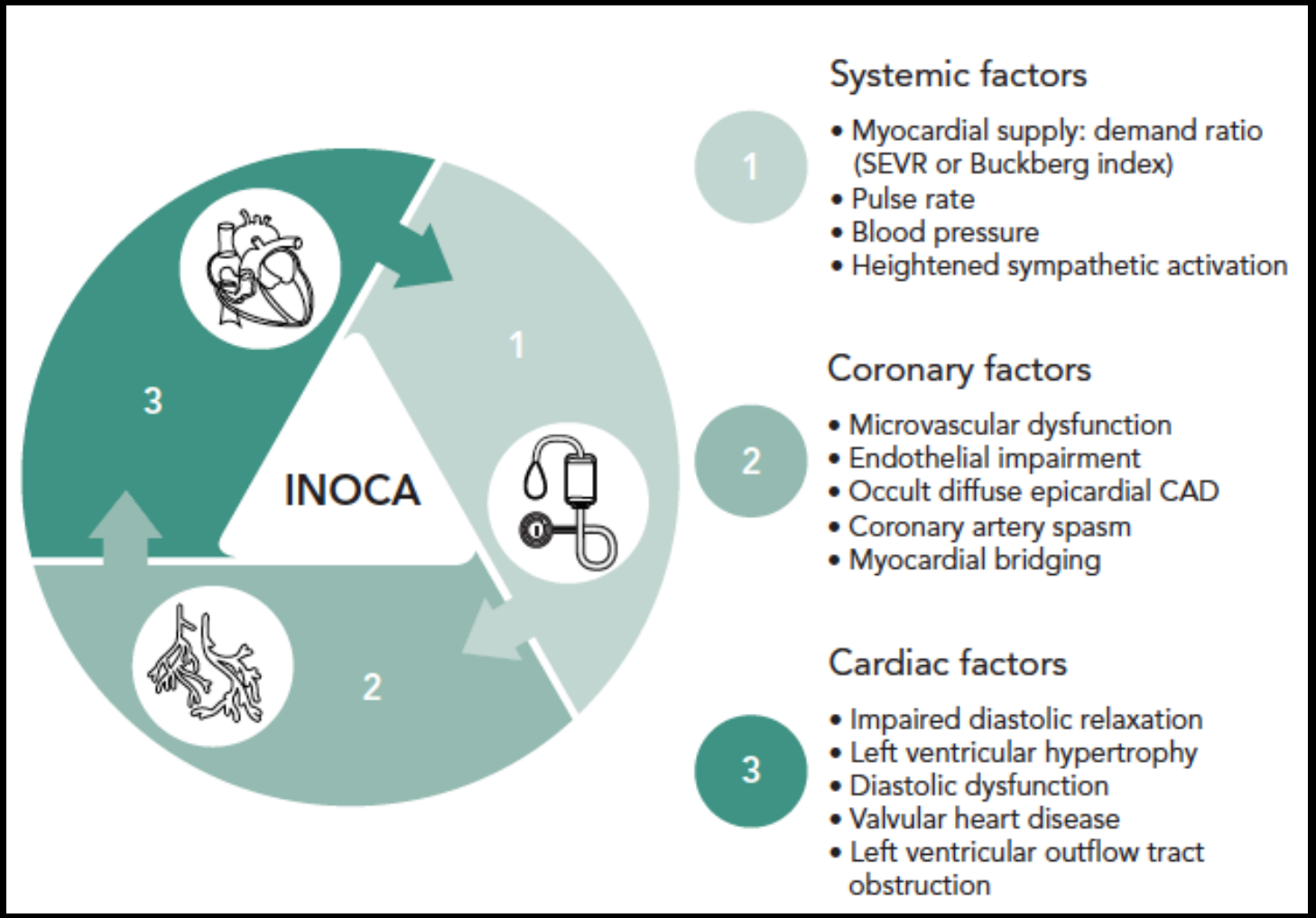
Traditional paradigm of IHD focuses on obstructive CAD, but overlooks other factors



Systemic factors

1

- Myocardial supply: demand ratio (SEVR or Buckberg index)
- Pulse rate
- Blood pressure
- Heightened sympathetic activation

Coronary factors

2

- Microvascular dysfunction
- Endothelial impairment
- Occult diffuse epicardial CAD
- Coronary artery spasm
- Myocardial bridging

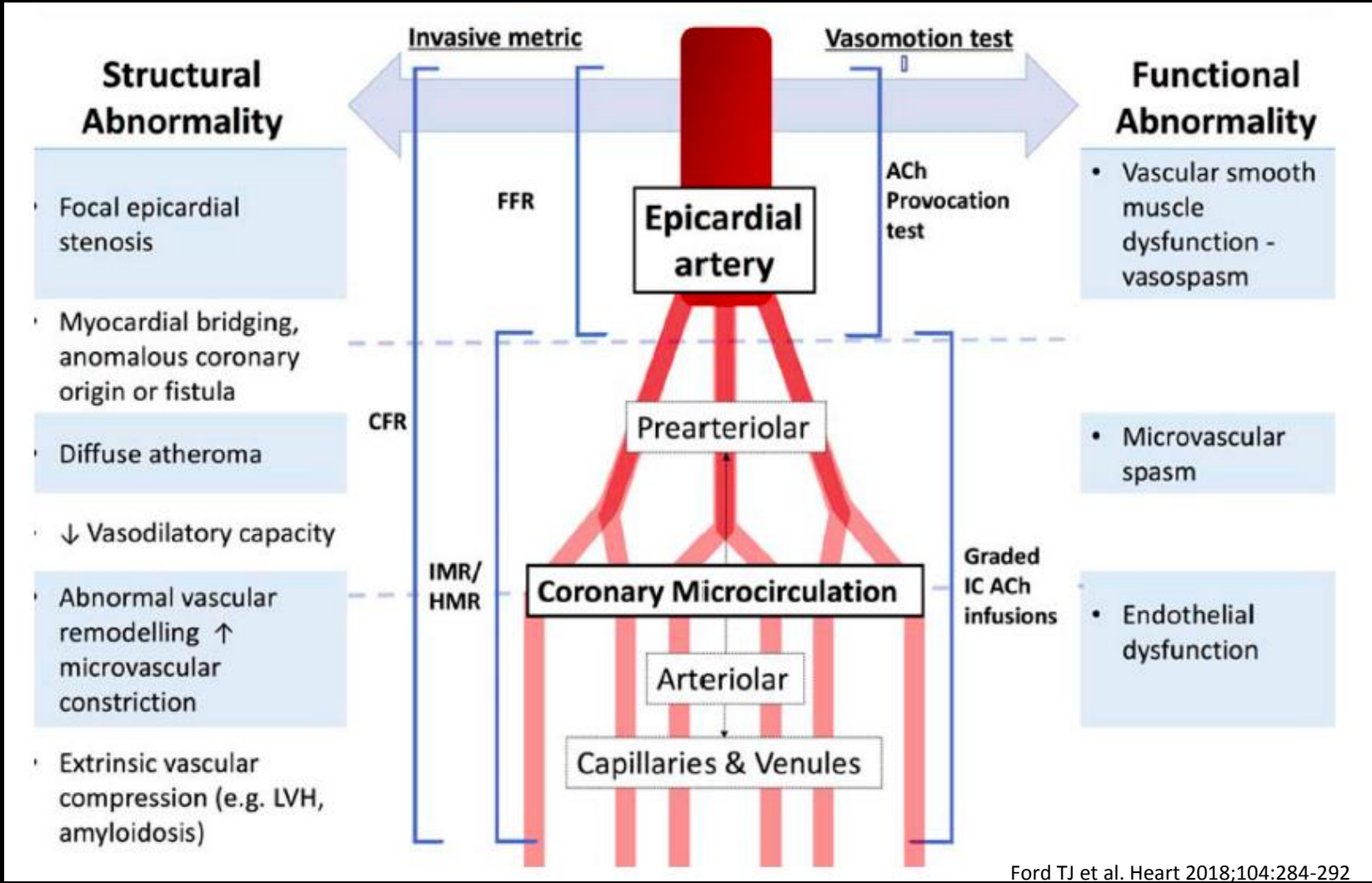
Cardiac factors

3

- Impaired diastolic relaxation
- Left ventricular hypertrophy
- Diastolic dysfunction
- Valvular heart disease
- Left ventricular outflow tract obstruction

Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76 82

Structural and functional disorders of the coronary circulation



Ford TJ et al. Heart 2018;104:284-292

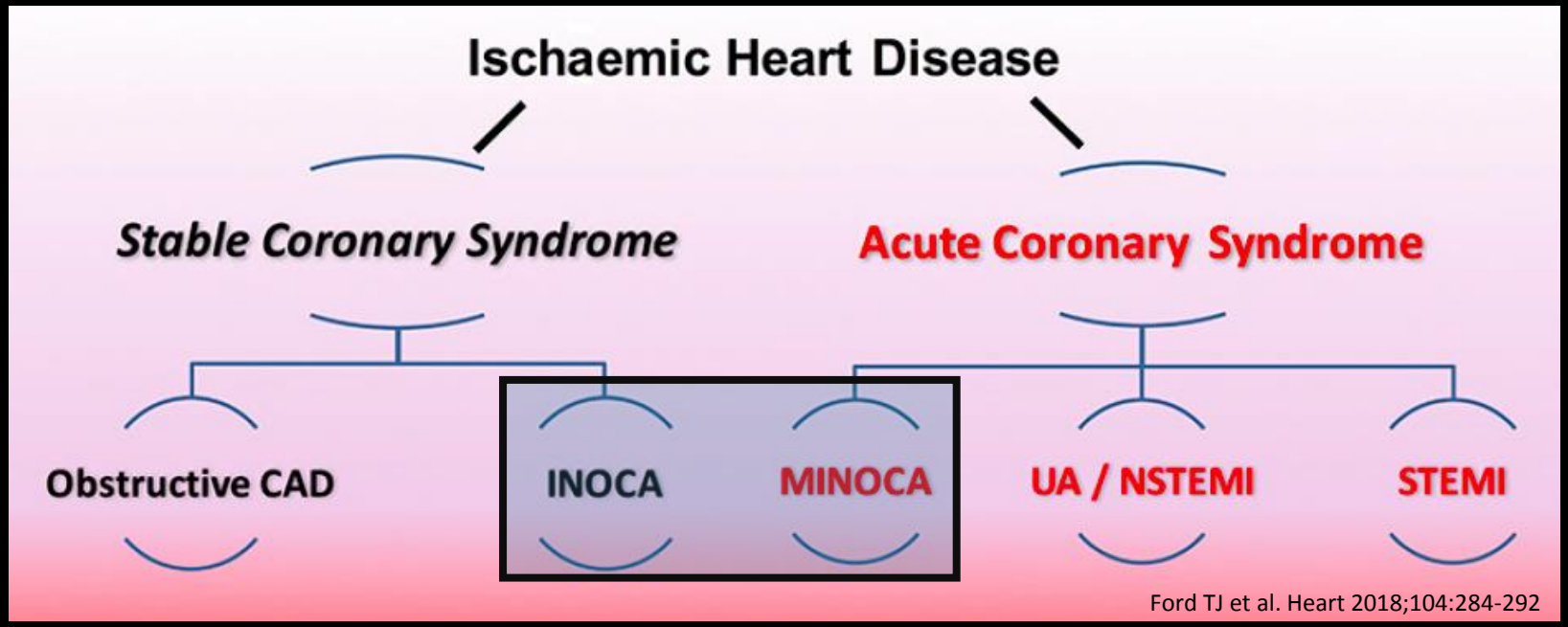
Taxonomy

Table 1 Classification of coronary microvascular dysfunction

Coronary microvascular dysfunction (CMD)	
Type 1	Primary CMD in the absence of underlying myocardial disease or obstructive epicardial CAD
Type 2	CMD in the presence of myocardial disease (eg, hypertrophic cardiomyopathy, hypertensive heart disease)
Type 3	CMD in the presence of obstructive CAD (either stable CAD or acute coronary syndrome)
Type 4	Iatrogenic CMD secondary to myocardial revascularisation
Type 5	CMD following cardiac transplantation

Ford TJ et al. Heart 2018;104:284 292

Taxonomy



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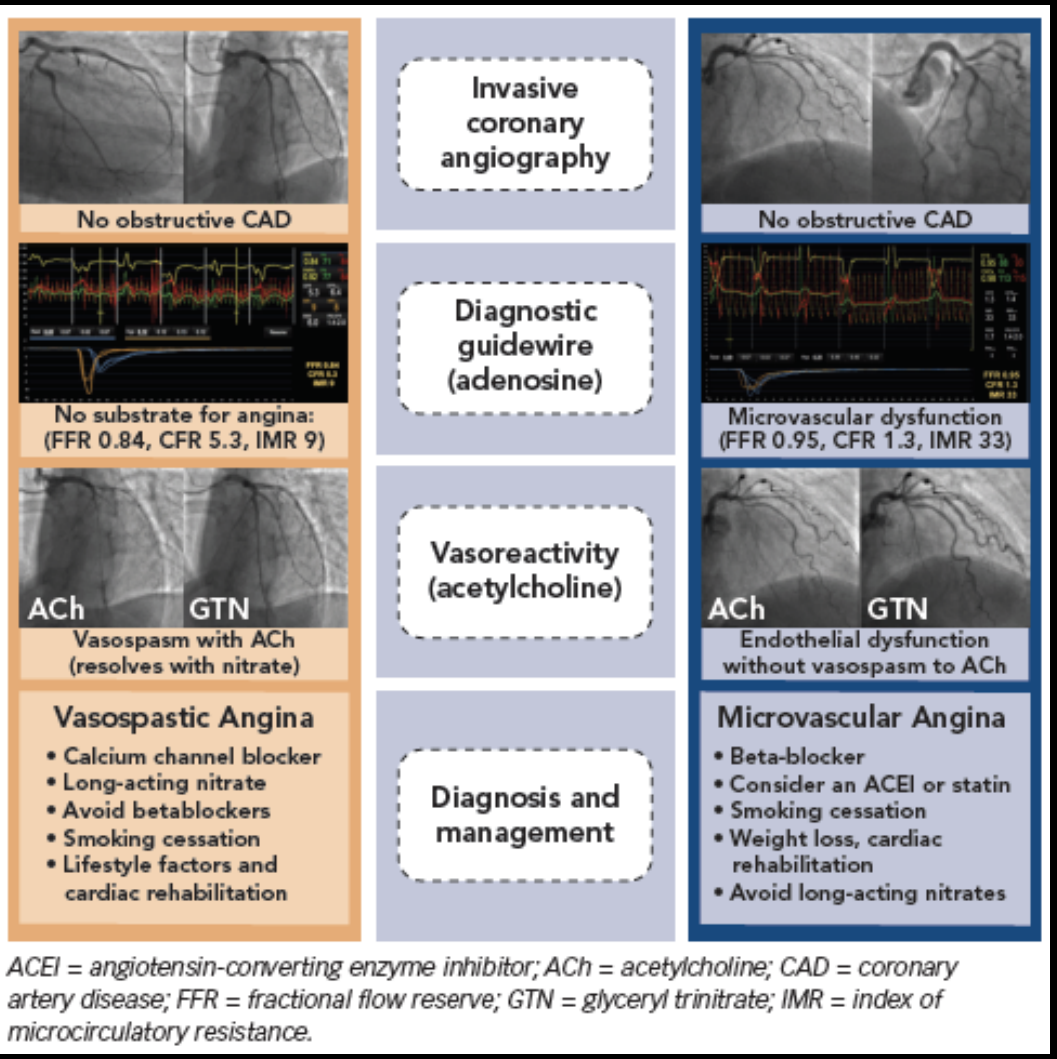
Invasive diagnostic testing



ACEI = angiotensin-converting enzyme inhibitor; ACh = acetylcholine; CAD = coronary artery disease; FFR = fractional flow reserve; GTN = glyceryl trinitrate; IMR = index of microcirculatory resistance.

Diagnostic criteria

Flow-limiting epicardial stenosis:
- FFR ≤0.80
- Contrast FFR ≤0.83
- iFR ≤0.89

Impaired epicardial and microvascular vasodilatation:
- CFR <2.0

Increased microvascular resistance:
- IMR ≥25
- HMR >2.4

Endothelial dysfunction:
- >20% angiographic reduction in coronary luminal diameter during acetylcholine infusion

Diagnostic criteria

Epicardial vasospasm:
- chest pain
- ischaemic ECG changes
- >90% vasoconstriction

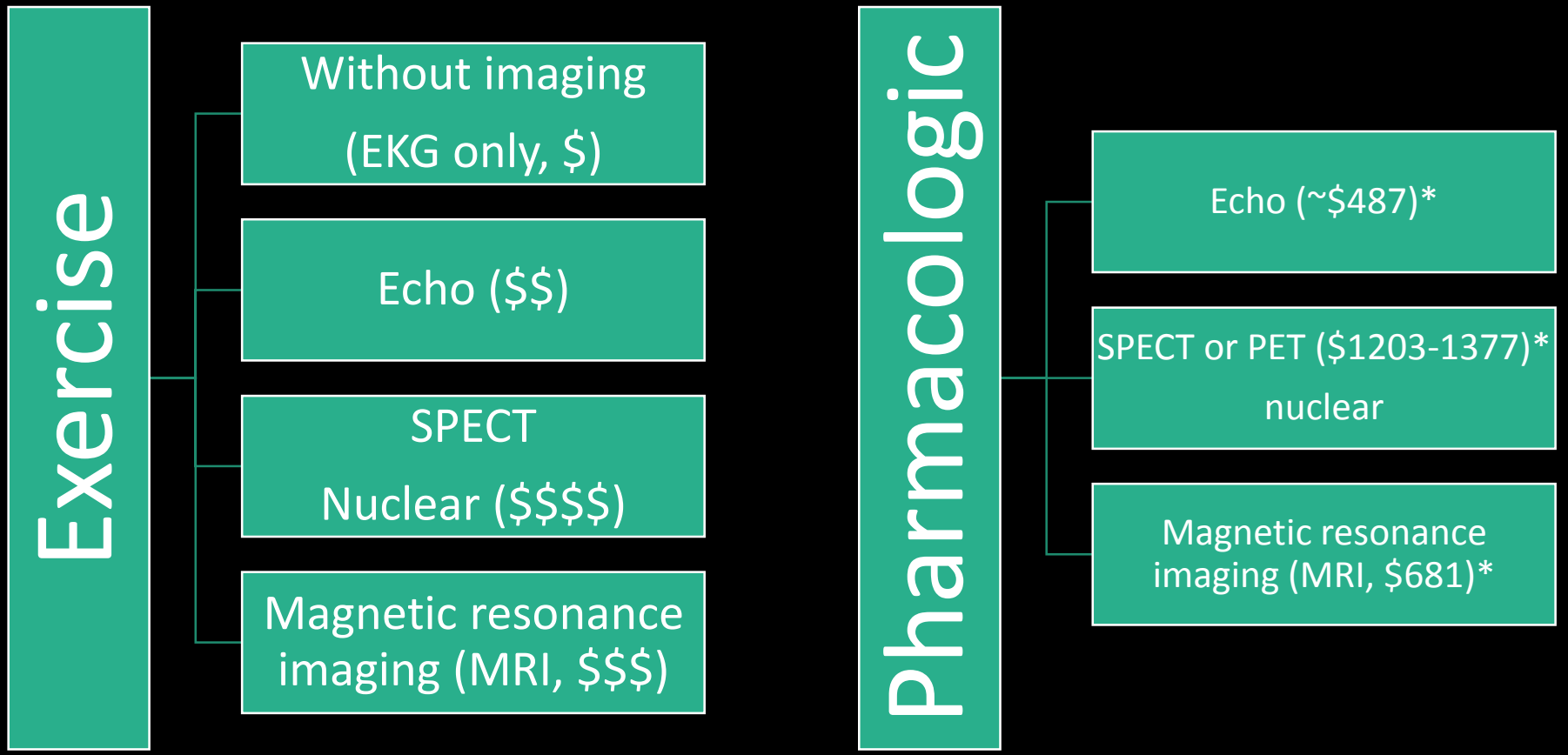
Microvascular vasospasm:
- chest pain
- ischaemic ECG changes
- ≤90% vasoconstriction

CFR=coronary flow reserve
iFR=instantaneous flow reserve
HMR=hyperemic microvascular resistance

Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76 82

Cardiac Stress Testing Algorithm

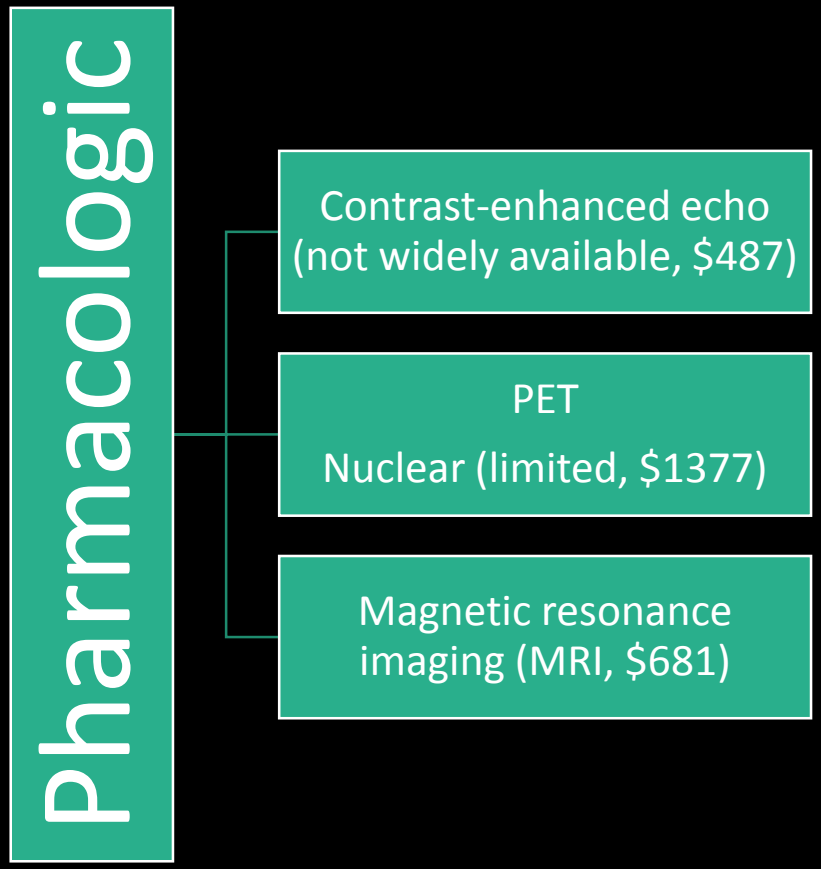
Exclude obstructive epicardial CAD



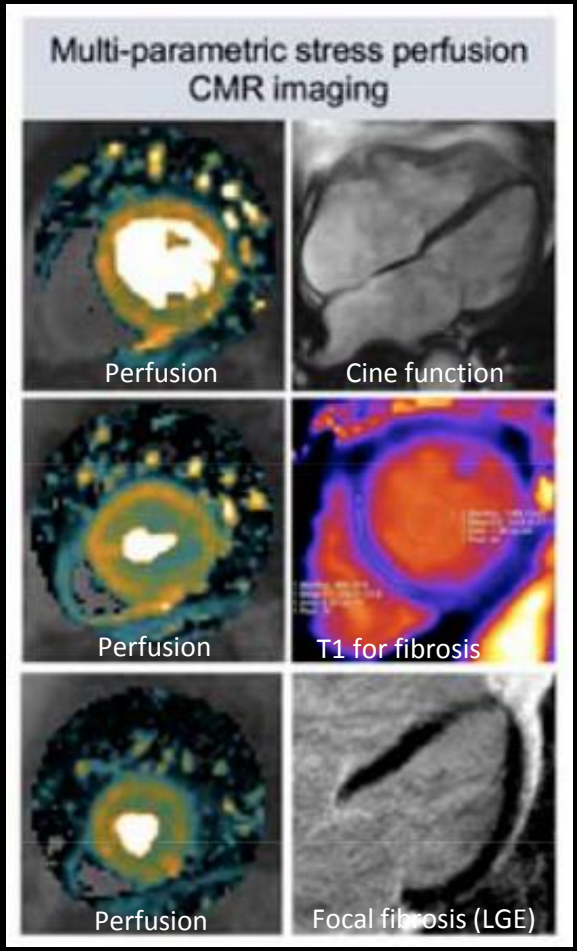
*2018 CMS rates. American Association of Nuclear Cardiology.

Cardiac Stress Testing Algorithm

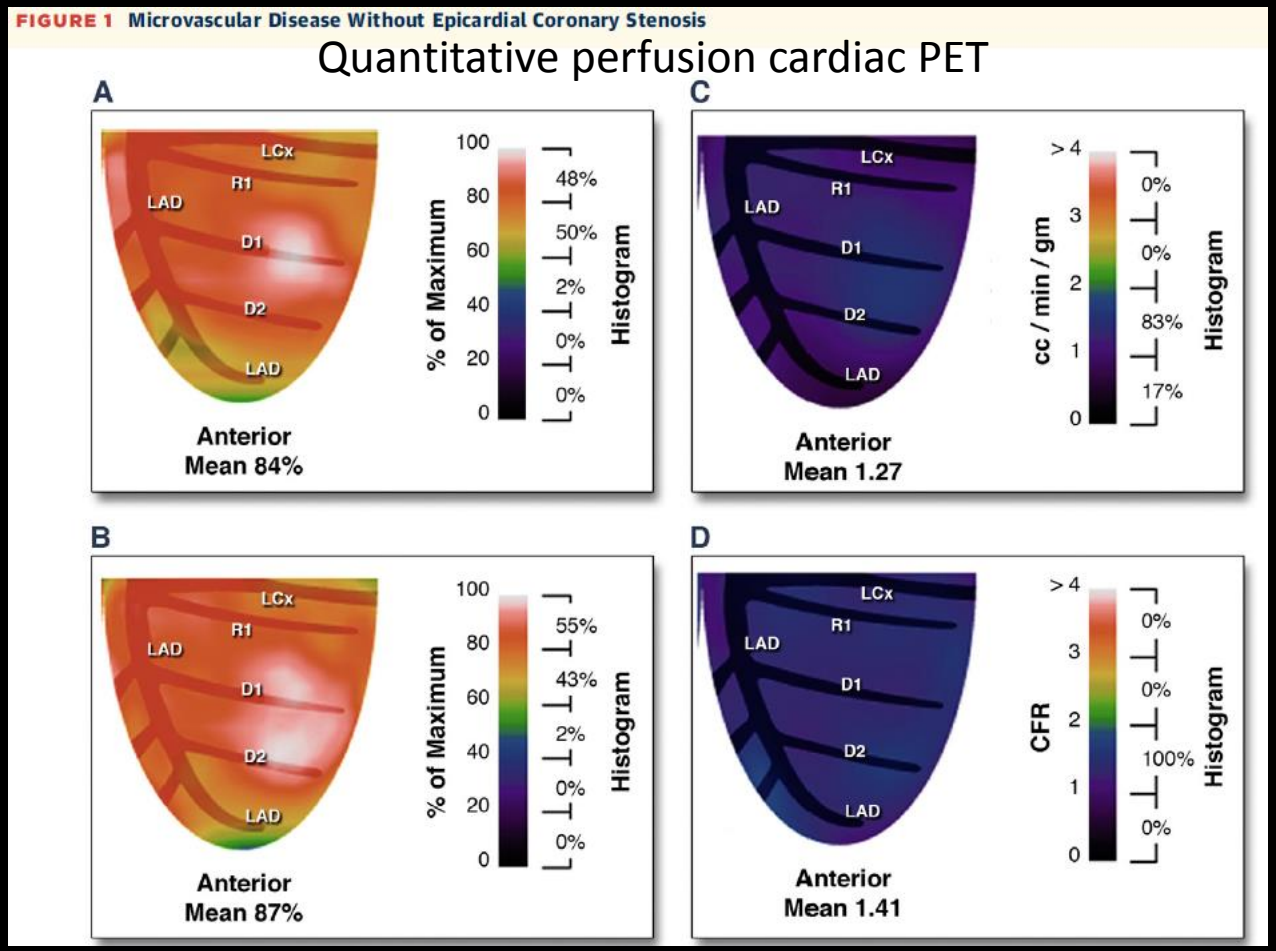
Evaluate for microvascular disease



Non-invasive diagnostic testing



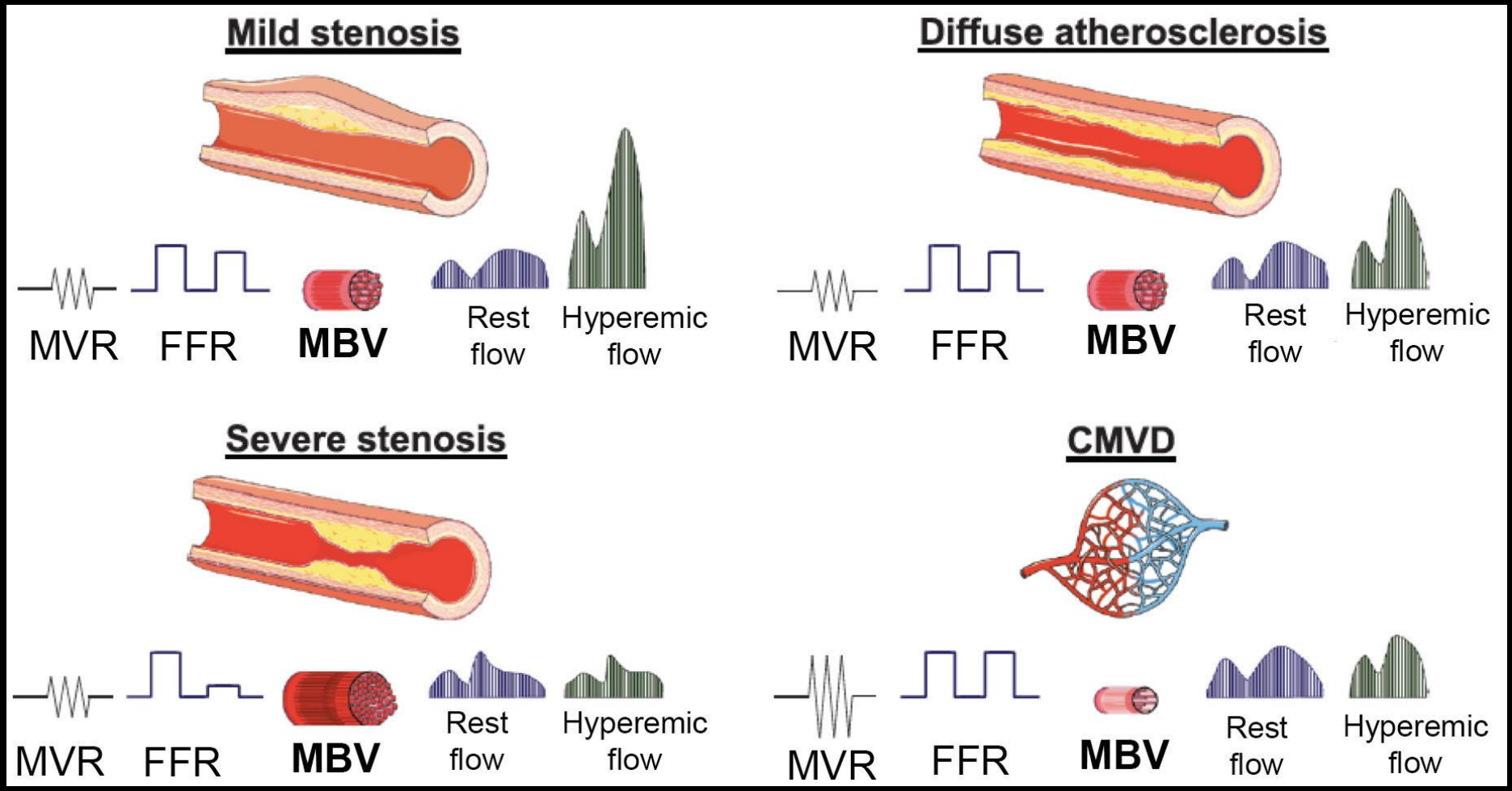
Ford TJ et al. Heart 2018;104:284 292



Gould et al. JACC Cardiovascular imaging 2016;9:465 82


Stress
Rest
Base
Mid
Apex

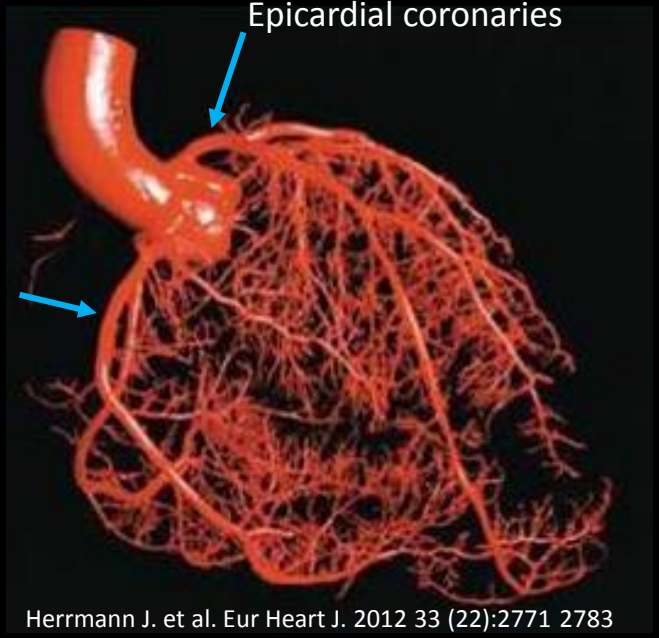
Spectrum of ischemic heart disease



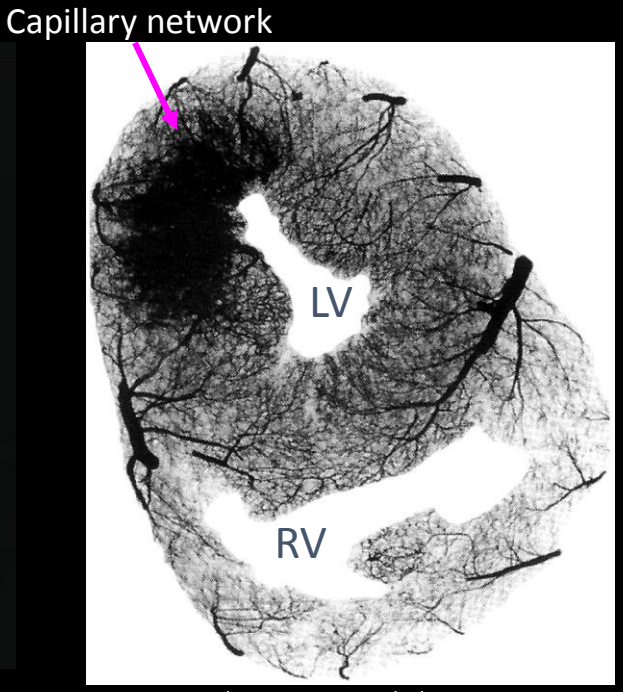
MVR=microvascular resistance; FFR=fractional flow reserve
MBV=myocardial blood volume

Circ Cardiovasc Imaging. 2017;10:e006427

VA-MERIT Project: Ferumoxytol-enhanced MRI Mapping of the Intramyocardial Vascular Compartment



Herrmann J. et al. Eur Heart J. 2012 33 (22):2771 2783



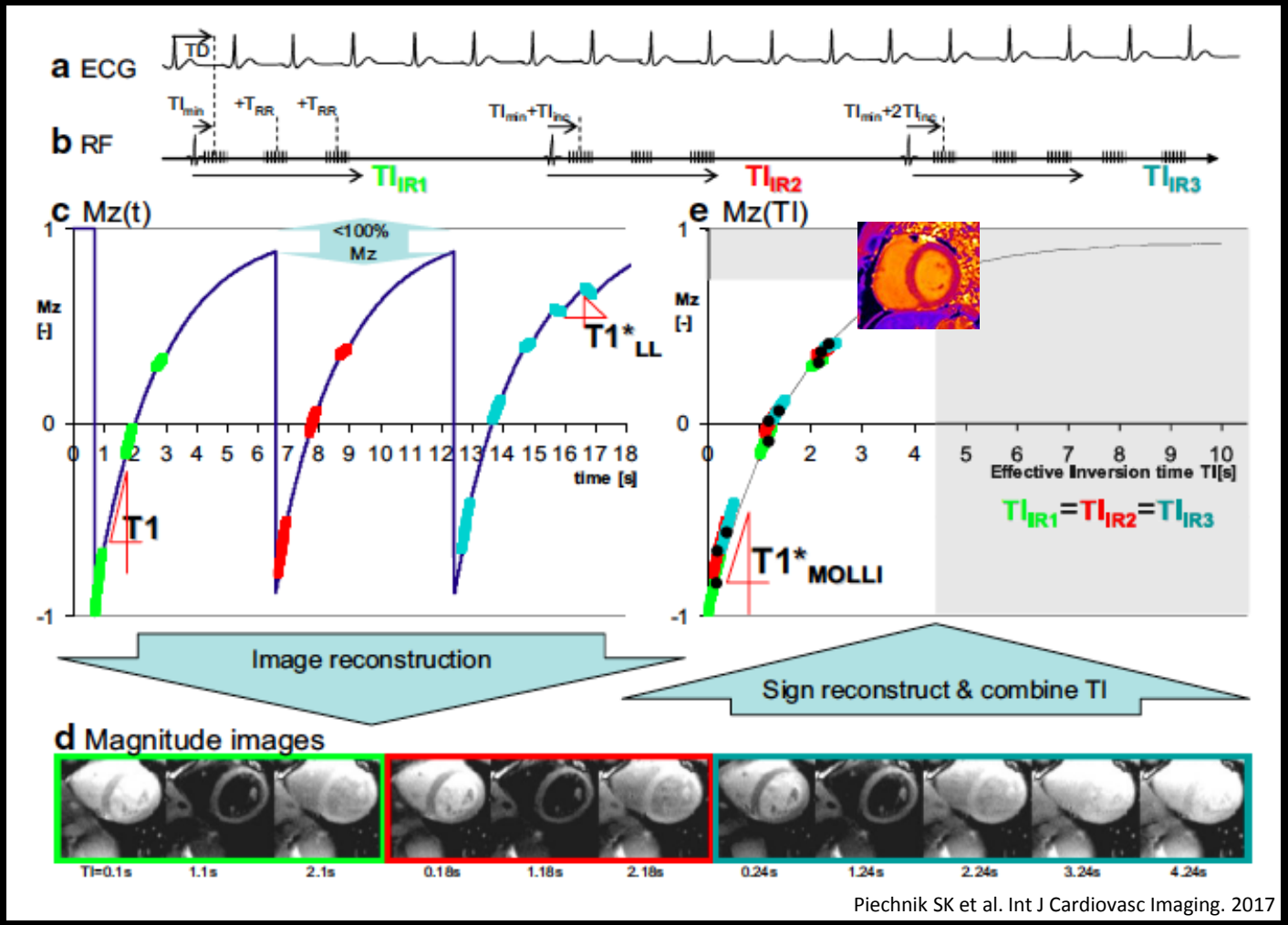
Gorge G et al. Basic Res Cardiol. 1989;84:524 535

- At baseline, 8% of LV mass constitutes blood in the microcirculation
- 90% is in the capillaries, and reflects the myocardial blood volume (MBV), which represents "myocardial reserve"

Ischemia = imbalance between metabolic demand & blood supply

Blood supply = myocardial blood flow (MBF) and myocardial blood volume (MBV)

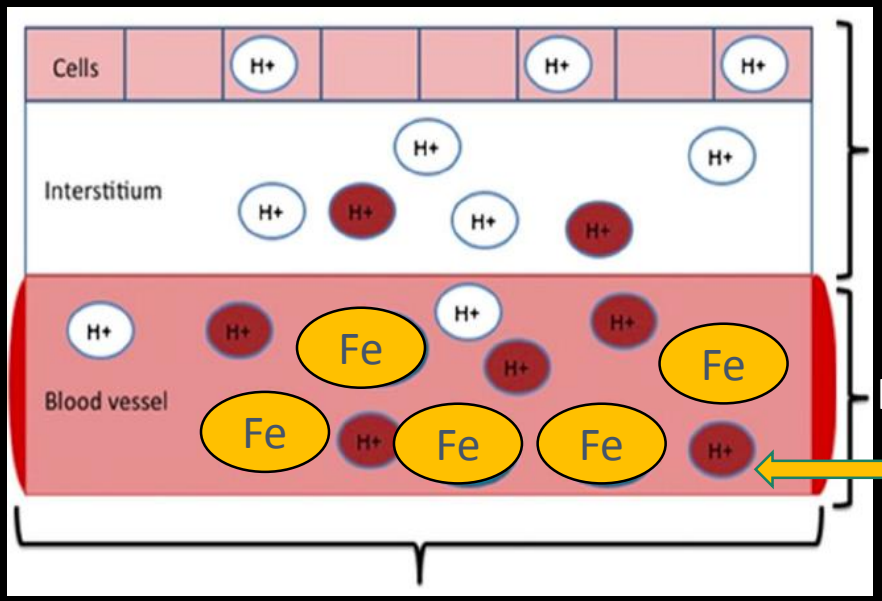
T1 myocardial mapping



Piechnik SK et al. Int J Cardiovasc Imaging. 2017

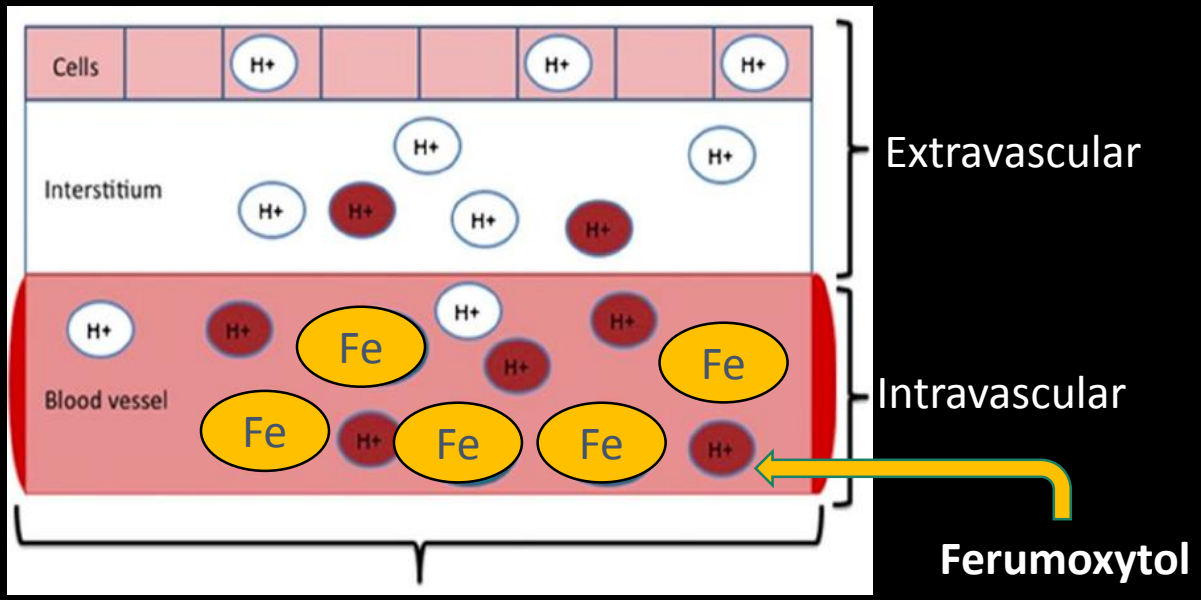
- T1 mapping = a color-encoded map of the myocardium whereby each pixel represents the T1 value in a voxel (rather than arbitrary signal intensity units)
- T1 values reflect normal physiology or in some cases pathophysiology

FE-MRI T1 reactivity as a surrogate for MBV



FE-MRI T1 reactivity as a surrogate for MBV

HYPOTHESIS: The percent change in FE myocardial T1 relaxation time at rest and peak stress, which we refer to as the FE T1 reactivity, reflects a dynamic change in the fractional myocardial blood volume (MBV)



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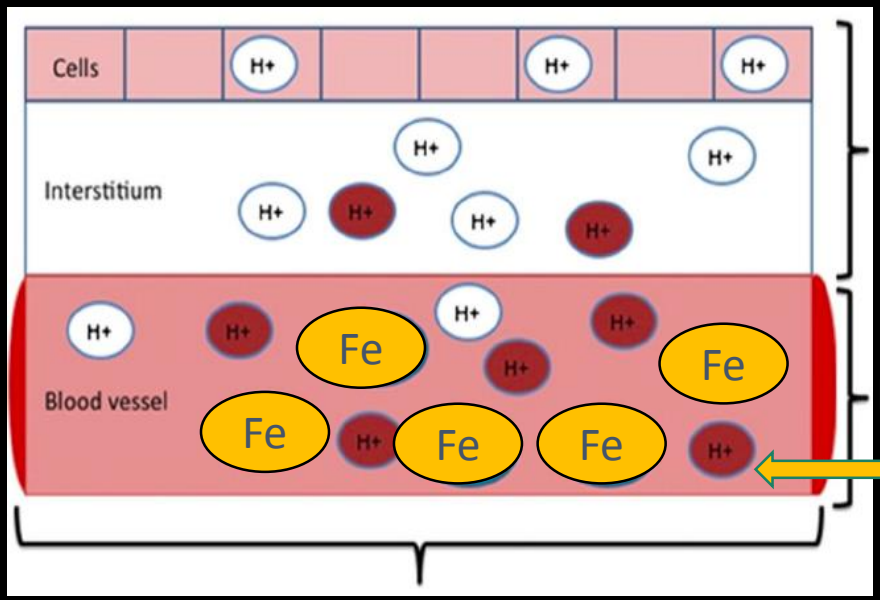


Using a vasodilator (such as adenosine), we may be able to

- map the dynamic nature of epicardial coronary stenoses and myocardial capillary network =ischemic burden
- quantify the fractional MBV

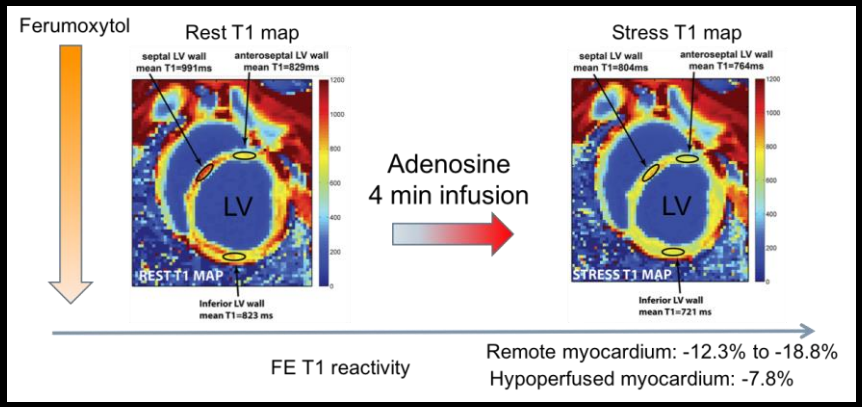
VA-MERIT funded project

Inclusion

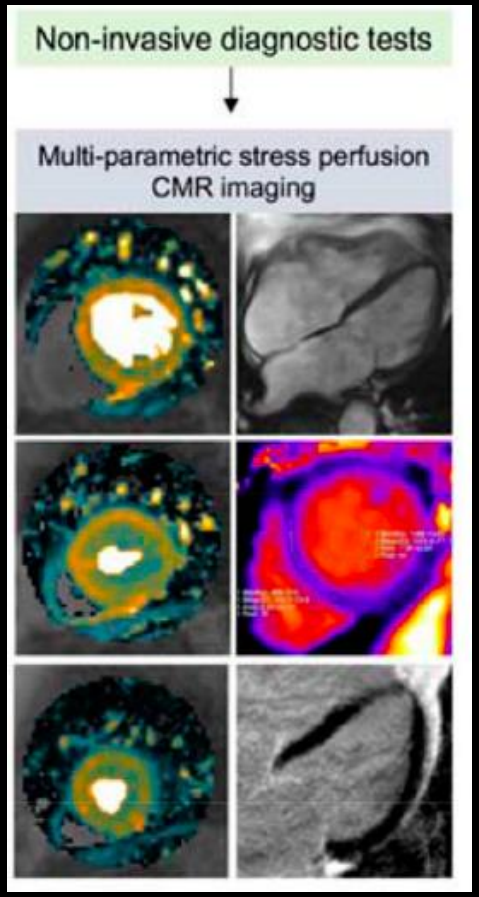
- Women (>18 years)
- Angina
- Positive stress cardiac PET or gadolinium enhanced stress cardiac MRI
- Agree to allow banking of blood specimen and enrollment in study registry

Exclusion

- Contraindications to MRI
- Arrhythmias
- History of intravenous iron intolerance or history of iron overload

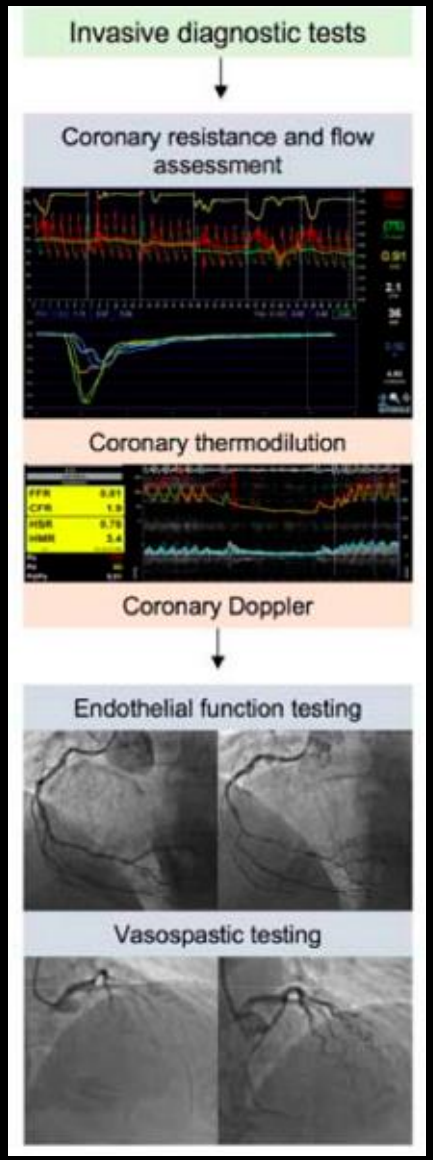


Proposed FE MRI steady state cardiac stress testing



Ford TJ et al. Heart 2018;104:284 292

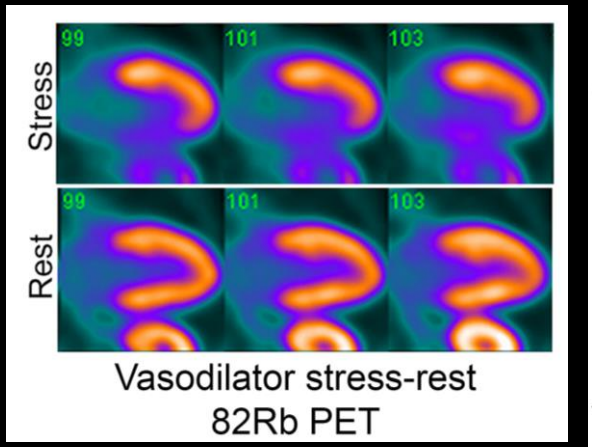
Reference standard



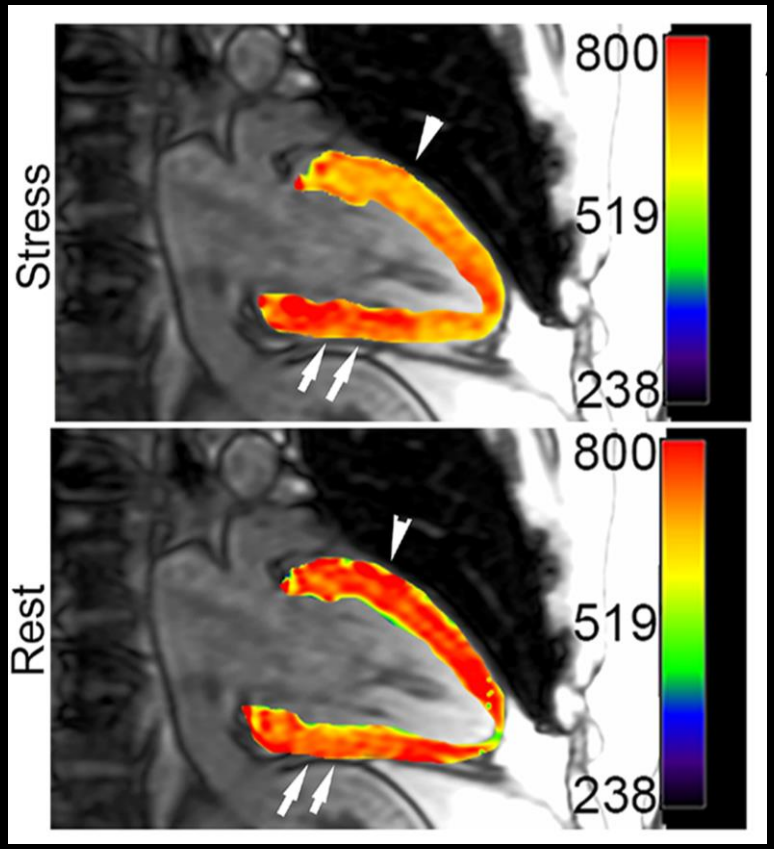
Ford TJ et al. Heart 2018;104:284 292

Reference standard

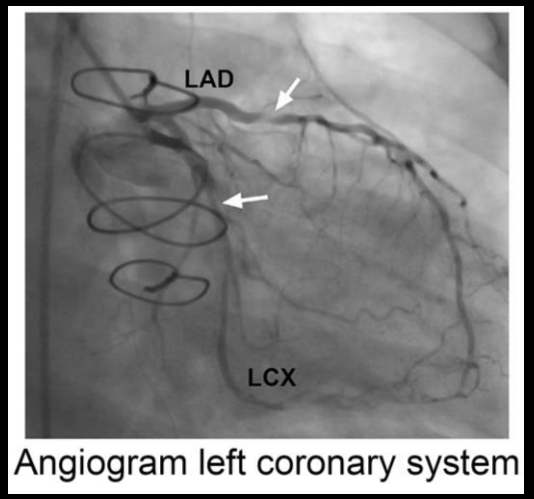
FE T1 reactivity as surrogate for MBV in stress testing



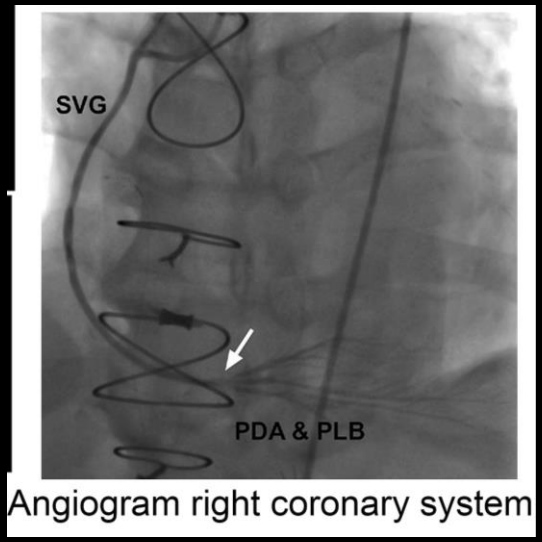
Vasodilator stress-rest
82Rb PET



Vasodilator stress-rest
FE T1 maps in a patient with IHD



Angiogram left coronary system



Angiogram right coronary system

Nguyen KL et al. JACC Imaging. 2019 Mar.

- Multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) evaluating IMT vs. Usual Care in 4,422 symptomatic women with ischemia but no obstructive CAD

- HYPOTHESIS: IMT (intensive medical therapy) will reduce MACE 20% vs UC.
  - primary outcomes: occurrence of death, MI, Stroke/TIA, Hospitalization for chest pain or heart failure
  - secondary outcomes: QOL, health resource consumption, angina, CV death and primary outcome components
  - Follow-up will be 3-years using 50 sites: primarily VA, Active Duty Military Hospitals/Clinics, PCORnet practice sites, and interested practice groups in the state of Florida.

Rationale and design of the Coronary Microvascular Angina Cardiac Magnetic Resonance Imaging (CorCMR) diagnostic study: the CorMicA CMR sub-study

David Corcoran,[1,2] Thomas J Ford,[1,2] Li-Yueh Hsu,[3] Amedeo Chiribiri,[4] Vanessa Orchard,[2] Kenneth Mangion,[1,2] Margaret McEntegart,[2] Paul Rocchiccioli,[2] Stuart Watkins,[2] Richard Good,[2] Katriona Brooksbank,[1] Sandosh Padmanabhan,[1] Naveed Sattar,[1] Alex McConnachie,[5] Keith G Oldroyd,[2] Rhian M Touyz,[1] Andrew Arai,[3] Colin Berry[1,2]

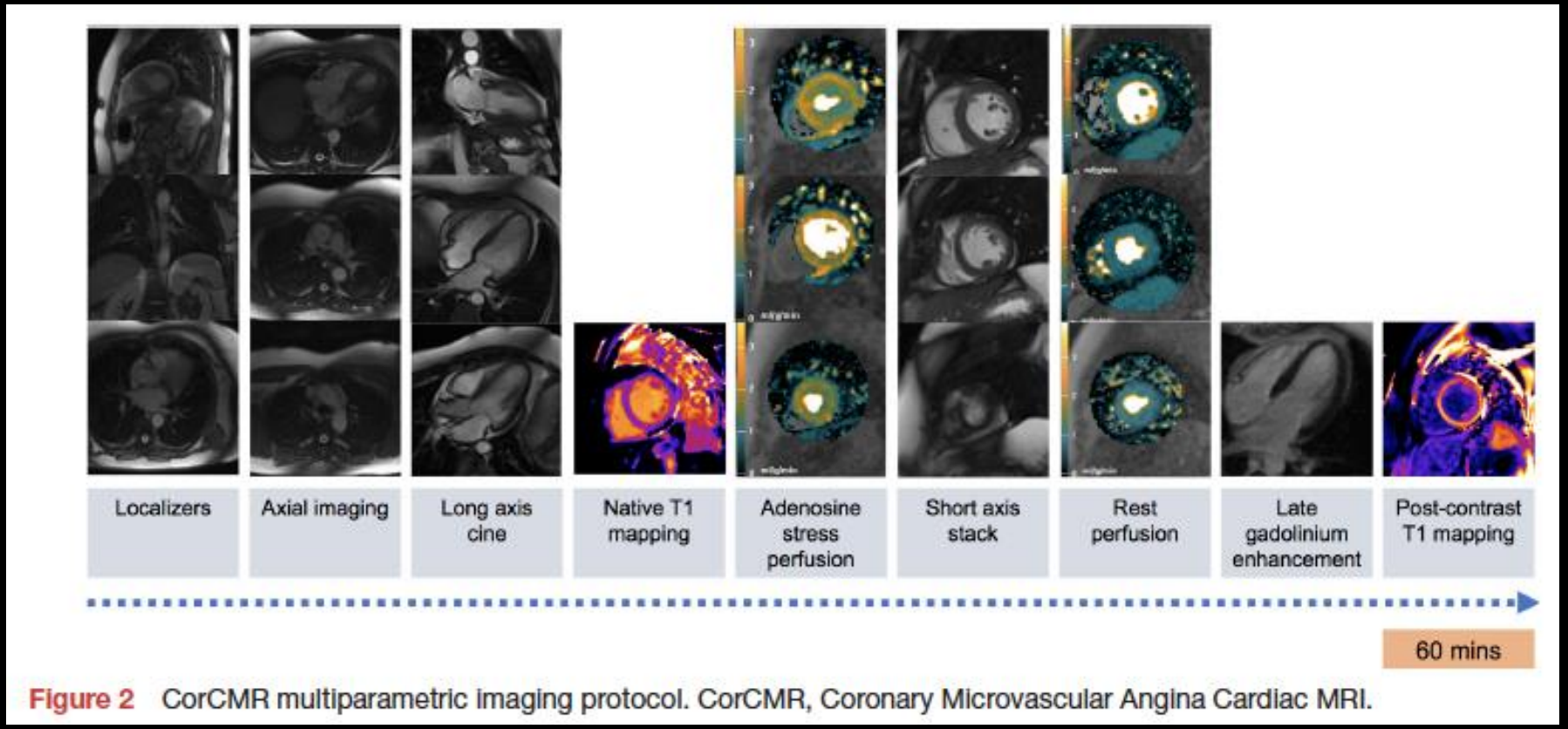
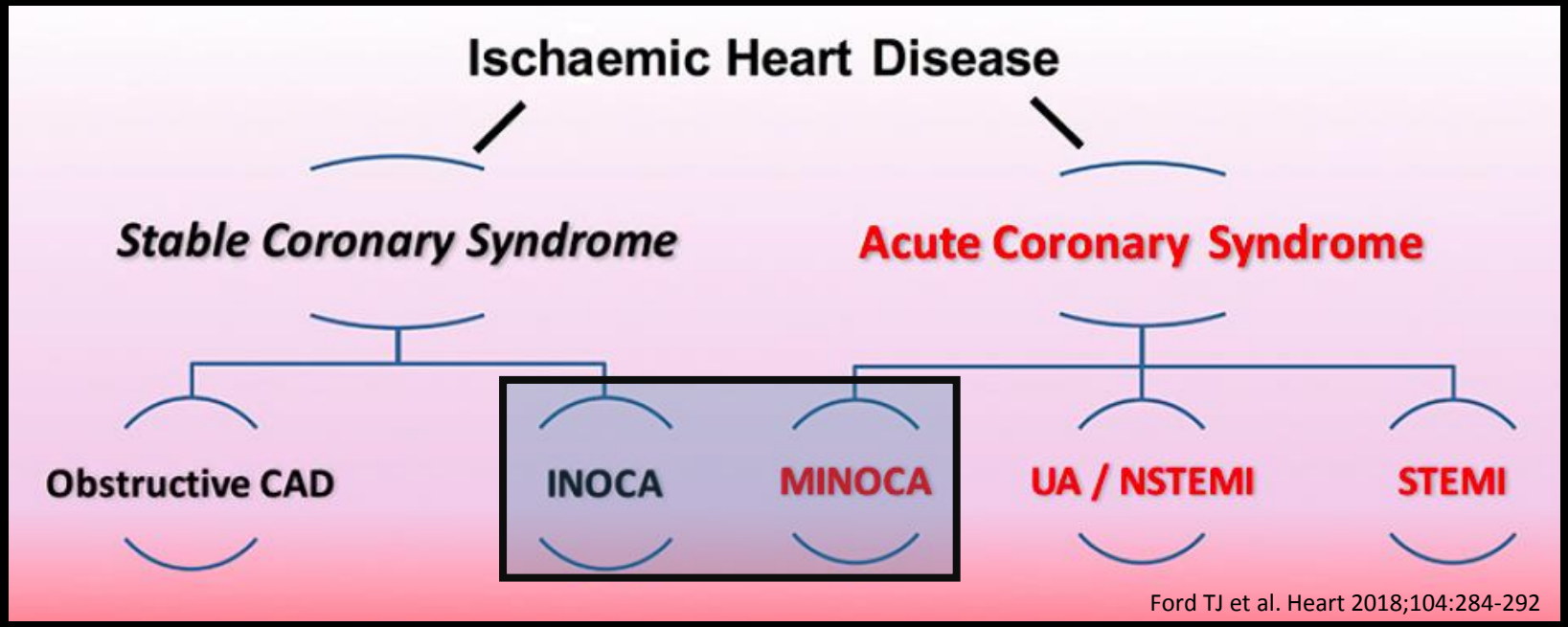


Figure 2 CorCMR multiparametric imaging protocol. CorCMR, Coronary Microvascular Angina Cardiac MRI.

Taxonomy



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Ford TJ et al. Heart 2018;104:284 292

MINOCA

- 5-10% of all patients with acute MI
- Younger, female
- Mechanisms
  - Plaque disruption
  - Spasm
  - Thromboembolism
  - Dissection
  - Microvascular dysfunction
  - Myocarditis or Takotsubo cardiomyopathy

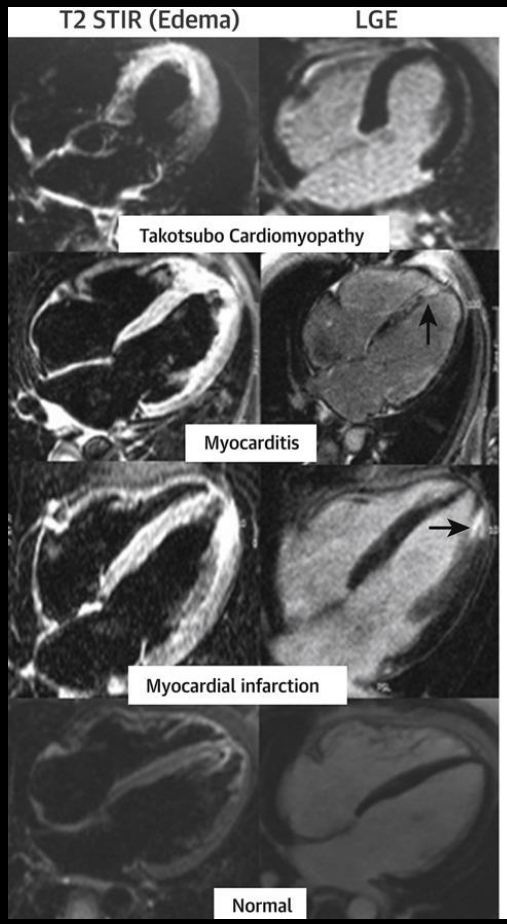
Prognostic Role of Cardiac MRI and Conventional Risk Factors in Myocardial Infarction With Nonobstructed Coronary Arteries

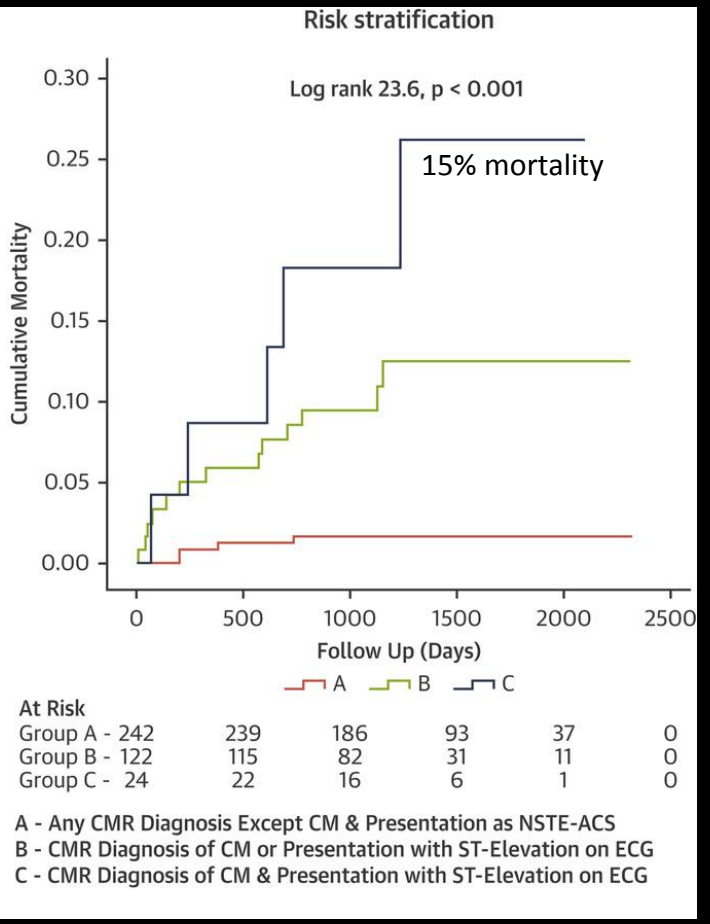
388 consecutive patients with MINOCA

Underwent CMR ➔ prognosis (all cause mortality within 3.5 years)

Using STE on presentation, ECG and CMR diagnosis of CM as risk factors, the presence of 0, 1, and 2 factors were associated with a mortality risk rate of 2%, 11%, and 21%

*Prior work showed CMR in MINOCA led to a change in diagnosis of 54% and change in management in 41% of patients.





Dastidar et al. JACC: Cardiovasc Imaging 2019 Feb (in press).
Dastidar et al. JACC Cardiovasc Imaging 2017;10:1204 6.

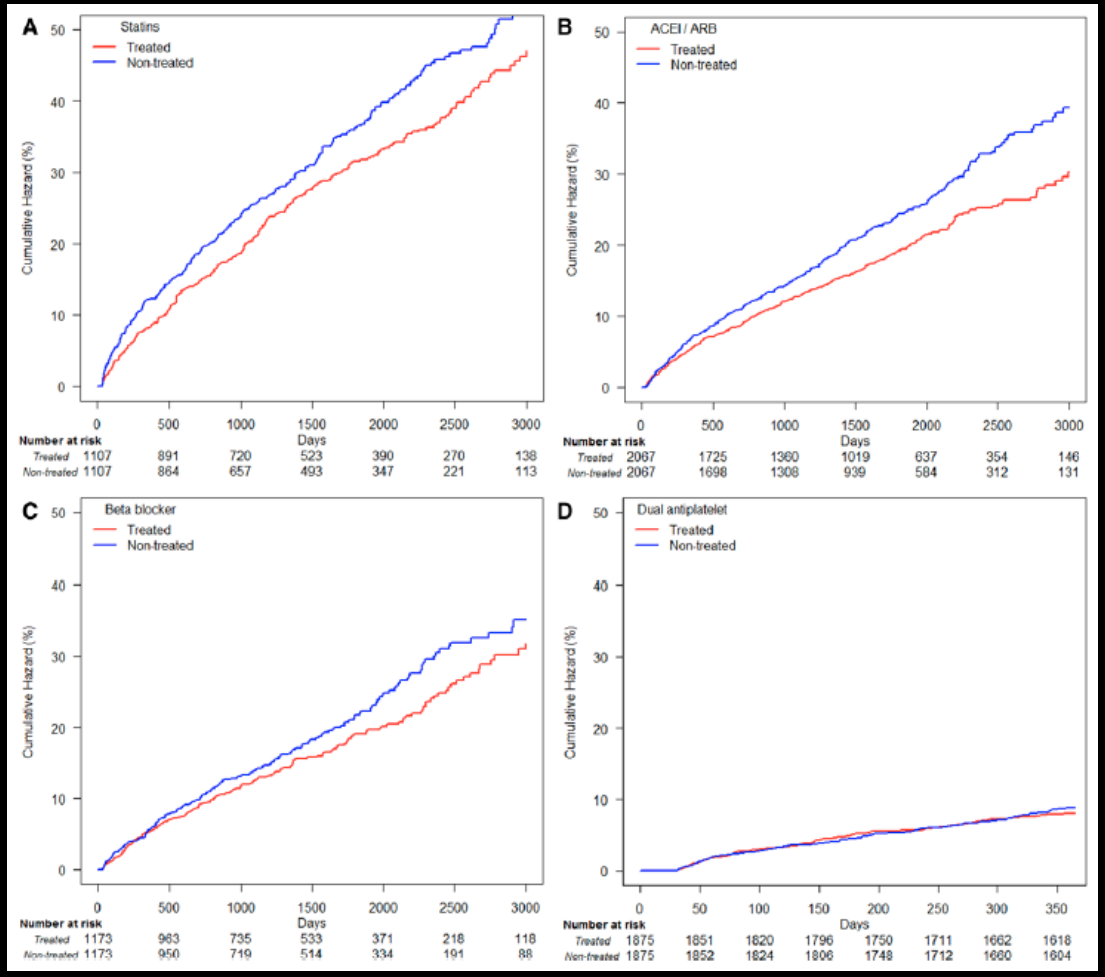
Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease

MINOCA patients from **SWEDEHEART** (Swedish Web-based system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy)

- 199162 patients with MI ➔ **9466** with MINOCA (LHC <50% stenoses, 7/2003-6/2013, followed until 12/2013 for MACE –all cause mortality, hospitalization for MI/ischemic stroke/heart failure)
- Stratified propensity analysis to **match treated vs untreated**
- Cox proportional hazards models for association between **treatment and outcomes**
- **Exposures were:** treatment with statins, ACEI/ARB, b-blockers, dual antiplatelet

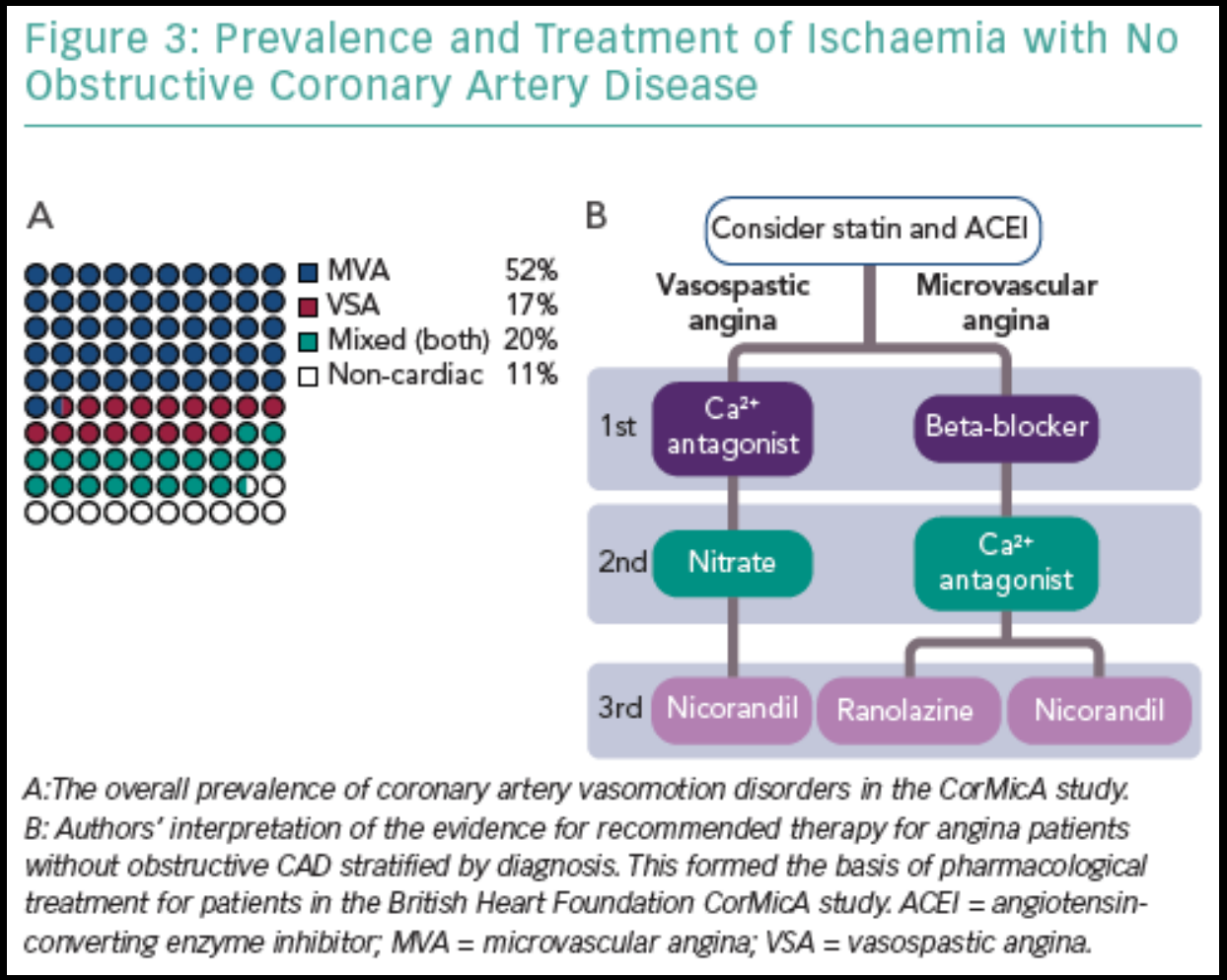
Lindahl et al. Circulation . 2017;135:1481 1489.

Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease



Lindahl et al. Circulation . 2017;135:1481 1489.

Treatment options



CORMiCA Study:
sponsored by British Heart Foundation

- N=391 with probable angina
- No obstructive CAD in 185 patients

Ford TJ et al. J Am Coll Cardiol 2018;72:2841 55
Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76 82

Treatment options

Diagnosis	Investigation	Pathophysiology	Treatment	Effects
Microvascular angina ↓ vasorelaxation	↓ CFR and/or ↑ microvascular resistance	Anatomical remodelling, vascular rarefaction, disturbed coronary regulation	Beta-blockers (e.g. nebivolol 2.5–10mg)	↓ myocardial oxygen consumption
			ACE inhibitors (e.g. ramipril 2.5 mg)	Improve CFR, ↓ workload, may improve small vessel remodelling
			Ranolazine (e.g. 375 mg twice daily)	Improves microvascular perfusion reserve index in patients with MVA and reduced CFR
Microvascular angina ↑ vasoconstriction	Hyper-reactivity to stimuli (e.g. acetylcholine, exercise, stress)	Endothelial dysfunction, inappropriate pre-arteriolar vasoconstriction	Calcium antagonists (e.g. amlodipine 10 mg)	Vascular smooth muscle relaxation, ↓ myocardial oxygen consumption
			ACE inhibitors (e.g. ramipril 2.5 mg)	Improves endothelial vasomotor dysfunction
			Nicorandil (e.g. 5–10mg twice daily)	Potassium-channel activator with coronary microvascular dilatory effect
			Statins (e.g. rosuvastatin 10–20 mg)	Improve coronary endothelial function, pleiotropic effects including reduced vascular inflammation
			Hormone replacement therapy	Oestrogen therapy improves symptoms but not proven to improve ischaemia or endothelial function

CORMiCA Study: sponsored by British Heart Foundation
N=391 with probable angina
No obstructive CAD in 185 patients

Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76–82

Treatment options

Diagnosis	Investigation	Pathophysiology	Treatment	Effects
Microvascular angina Abnormal pain processing	↑ nociception	Dysfunctional cortical pain processing	Tricyclic antidepressants (e.g. imipramine up to 25 mg)	Improved symptom burden potentially through ↓ visceral pain
			Xanthine derivatives (e.g. aminophylline 225 mg twice daily)	Anti-algogenic effect (due to the direct involvement of adenosine in cardiac pain generation)
Vasospastic angina	Propensity to coronary vasospasm	Vascular smooth muscle hyper-reactivity	Calcium channel blockers (e.g. amlodipine 10 mg or verapamil 240 mg SR)	↓ spontaneous and inducible coronary spasm via vascular smooth muscle relaxation and ↓ oxygen demand
			Nitrates (e.g. isosorbide mononitrate XL 30 mg)	↓ spontaneous and inducible coronary spasm via large epicardial vasodilation, ↓ oxygen demand, lack of efficacy in microvascular angina with potential deleterious effect
Adjunctive non-pharmacological interventions	May be useful in all endotypes	Metabolic syndrome, endothelial dysfunction, cardiovascular risk factors, anxiety/depression	Smoking cessation, exercise, cardiac rehabilitation, Mediterranean diet, cognitive behavioural therapy[93]	

ACE = angiotensin converting enzyme; CFR = coronary flow reserve; MVA = microvascular angina; SR = sustained-release preparation.

Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76 82

Future Directions & Take Away Points

- Development of non-diagnostic testing
  - Non-ionizing radiation
  - CMR is most promising with high spatial resolution
- New therapeutics to tailored to the specific mechanism
  - Medications
  - Exercise
  - Cognitive behavioral therapy and stress management

Acknowledgements

Our work is supported by

- UCLA Radiological Sciences Exploratory Research Program
- UCLA Department of Medicine Pilot Funding
- American Heart Association Transformational Award 18TPA34170049
- NIH (NHLBI) R01HL127153
- VA MERIT 1I01CX001901

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- Tzung K. Hsiai, MD/PhD
- Andrew E. Arai, MD (NHLBI)
- UCLA DLAM and TRIC Lab
- UCLA 3D Lab
- VA GLA Women's CV Health Group (Bevanne B. Upperman, MD/MHS)

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Primary Prevention of Cardiovascular Disease

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VA GREATER LOS ANGELES HEALTHCARE SYSTEM

DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

VA | U.S. Department of Veterans Affairs

UCLA Health | David Geffen School of Medicine

2017: Leading Causes of Death for U.S. Women

Rank	Cause of Death	Age-adjusted Death Rate
1	**Diseases of the heart**	**181.2**
2	Malignant neoplasms	171.8
3	Chronic lower respiratory diseases	51.5
4	**Cerebrovascular disease**	**38.4**
5	Accidents (unintentional)	36.4
6	Alzheimer's	50.9
7	Diabetes mellitus	22.5
8	Influenza and pneumonia	17.6
9	Nephritis, nephrotic syndrome, and nephrosis	15.1
10	Septicemia	12.9
11	**Essential hypertension and hypertensive renal disease**	**11.8**

2019 National Vital Statistics Reports – U.S. Death and Disease Burden - 2017

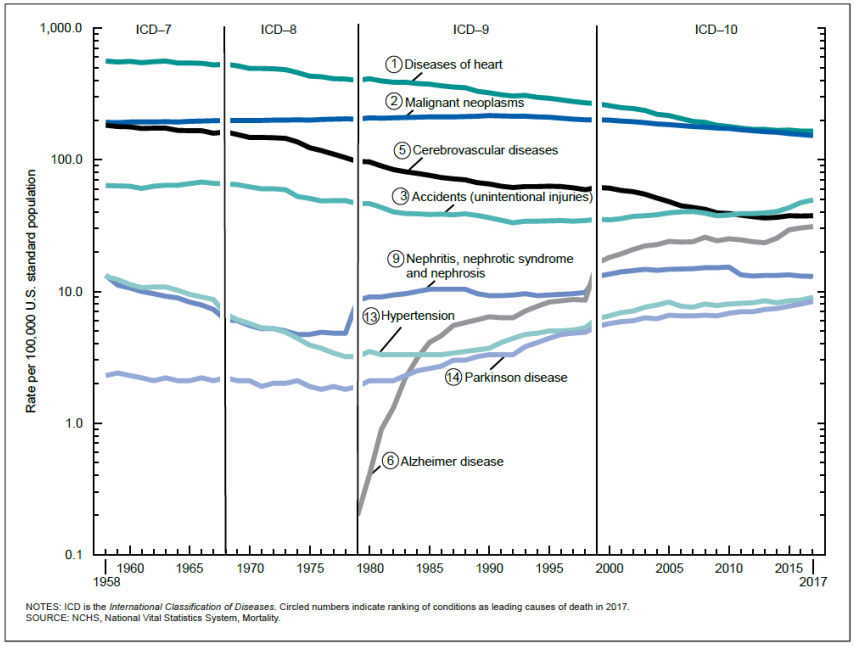

Figure 6. Age-adjusted death rates for selected leading causes of death: United States, 1958–2017

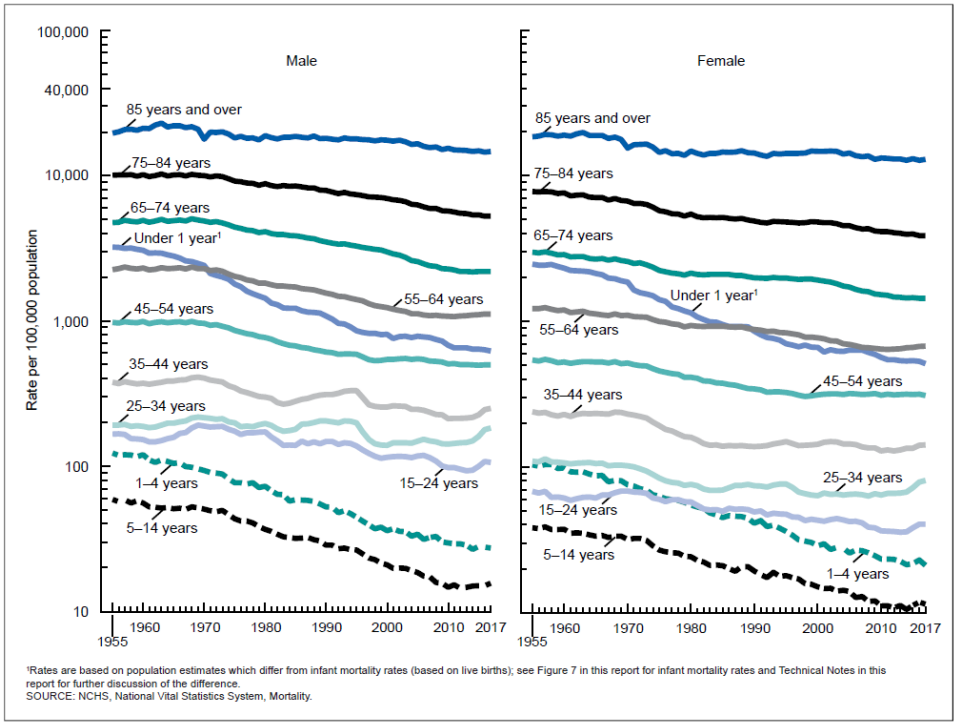

Figure 3. Death rates, by age and sex: United States, 1955–2017

2019 Primary Prevention Writing Committee

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*ACC/AHA Representative, †Lay Representative, § Task Force Performance Measures Representative

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

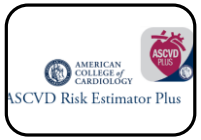
COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Patient centered approach

Shared-decision making

Social determinants of health

Team-based approach



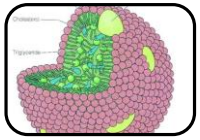
Assessment of risk


Nutrition and diet


Exercise and physical activity


Overweight and obesity


Type 2 diabetes


High blood cholesterol


High blood pressure and hypertension

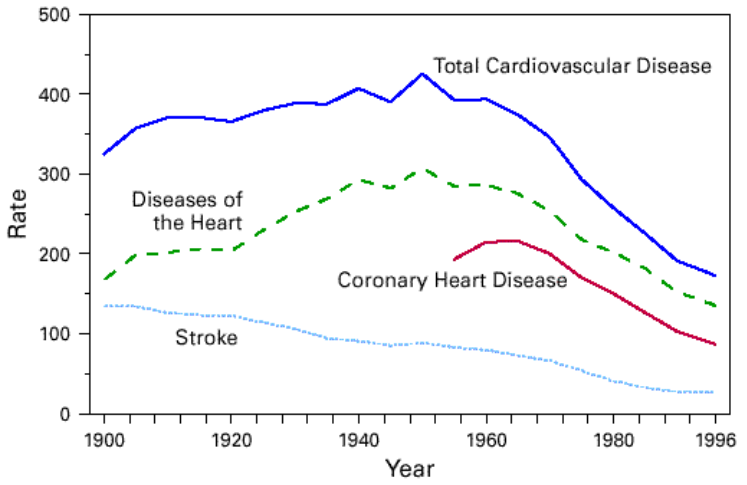

Tobacco use


Aspirin use

Top 10 Take Home Messages

1. Prevention by promoting a **healthy lifestyle** is the key to reducing the burden of atherosclerotic vascular disease, heart failure, and atrial fibrillation.

FIGURE 1. Age-adjusted death rates* for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke,† by year — United States, 1900–1996



*Per 100,000 population, standardized to the 1940 U.S. population.
†Diseases are classified according to *International Classification of Diseases* (ICD) codes in use when the deaths were reported. ICD classification revisions occurred in 1910, 1921, 1930, 1939, 1949, 1958, 1968, and 1979. Death rates before 1933 do not include all states. Comparability ratios were applied to rates for 1970 and 1975.

Source: Adapted from reference 1; data provided by the National Heart, Lung and Blood Institute, National Institutes of Health.

Top 10 Take Home Messages

2. Team-based care is an effective strategy for delivering evidence-based care and management.

I	A	**1. A team-based care approach is recommended for the control of risk factors associated with ASCVD.**

Top 10 Take Home Messages

3. Adults who are 40-75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation. Shared-decision making before starting pharmacological therapy.

I	**B-NR**	**1. For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using the pooled cohort equations (PCE).**

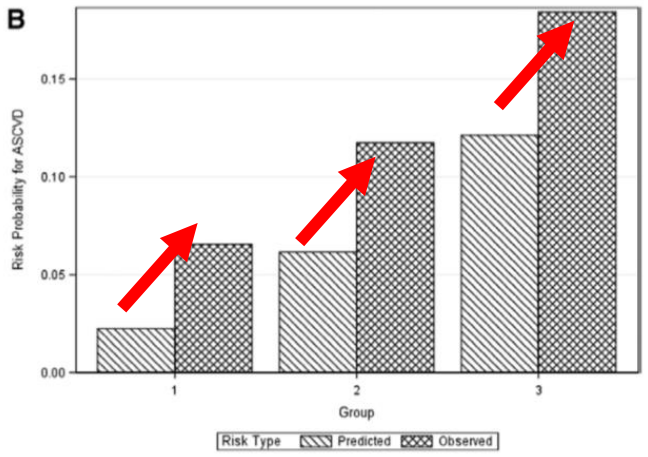
PCE and risk estimation

IIa	B-NR	3. In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions (e.g., statin therapy).

Not all factors are included in PCE:

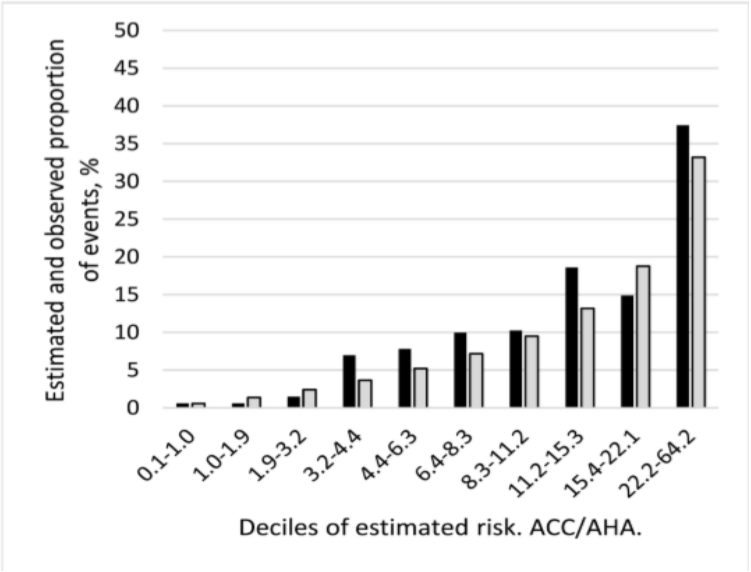
Age	**Aspirin therapy**	Elevated triglycerides
Sex	Family history	hsCRP
Race	Obesity	Lp(a)
Blood pressure	Physical inactivity	ApoB level
Total cholesterol	Socioeconomic factors	Ankle-brachial index
HDL cholesterol	Pregnancy related CVD	Coronary artery calcium
LDL cholesterol	Inflammatory conditions	
Diabetes	Mental stress/ depression	
Smoking	Chronic kidney disease	
Hypertension	Metabolic syndrome	
Statin therapy	South Asian ethnicity	

PCE may underestimate risk



HIV patients
(Group 1:<5%, Group 2: 5%–7.5%, Group 3: >7.5%)

Circulation. 2018 May 22;137(21):2203-2214.



Rheumatoid Arthritis patients
(Black: observed events, Gray: predicted events)

Rheumatology (Oxford). 2017;56:1102-10.

Risk-Enhancing Factors

- Whom to use in?
  - **Borderline** (5% to <7.5%) or
  - **Intermediate** (≥7.5% to <20%) 10-year ASCVD risk
- When to use?
  - If patient would value information in making treatment recommendation.
- What to do if risk still uncertain?
  - CAC strong factor, but probably not an effective population strategy.

Table 1. ASCVD risk enhancers
• Family history of premature ASCVD
• Primary hypercholesterolemia
• Chronic kidney disease
• Metabolic syndrome
• Conditions specific to women (e.g. preeclampsia, premature menopause)
• Chronic inflammatory conditions (especially rheumatoid arthritis, psoriasis, HIV)
• High risk race/ethnicity (e.g. South Asian ancestry)
Lipid/Biomarkers:
• Persistently elevated triglycerides (≥175 mg/dL)
In selected individuals if measured:
• hsCRP ≥2 mg/L
• Lp(a) levels ≥50 mg/dL or ≥125 nmol/L
• ApoB levels ≥130 mg/dL
• Ankle-brachial index <0.9

Top 10 Take Home Messages

4. A healthy diet emphasizes vegetables, fruits, legumes, nuts, whole grains, and fish. Minimize intake of *trans* fats, red meat and processed meats, refined carbohydrates, and sweetened beverages. For overweight and obese adults, recommend and caloric restriction and physical activity for achieving and maintaining weight loss.

I	B-R	1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors (S3.1-1–S3.1-11).

VIEWPOINT

The Challenge of Reforming Nutritional Epidemiologic Research

John P. A. Ioannidis, MD, DSc
Stanford Prevention Research Center and Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, California.

Some nutrition scientists and much of the public often consider epidemiologic associations of nutritional factors to represent causal effects that can inform public health policy and guidelines. However, the emerging picture of nutritional epidemiology is difficult to reconcile with good scientific principles. The field needs radical reform.

In recent updated meta-analyses of prospective cohort studies, almost all foods revealed statistically

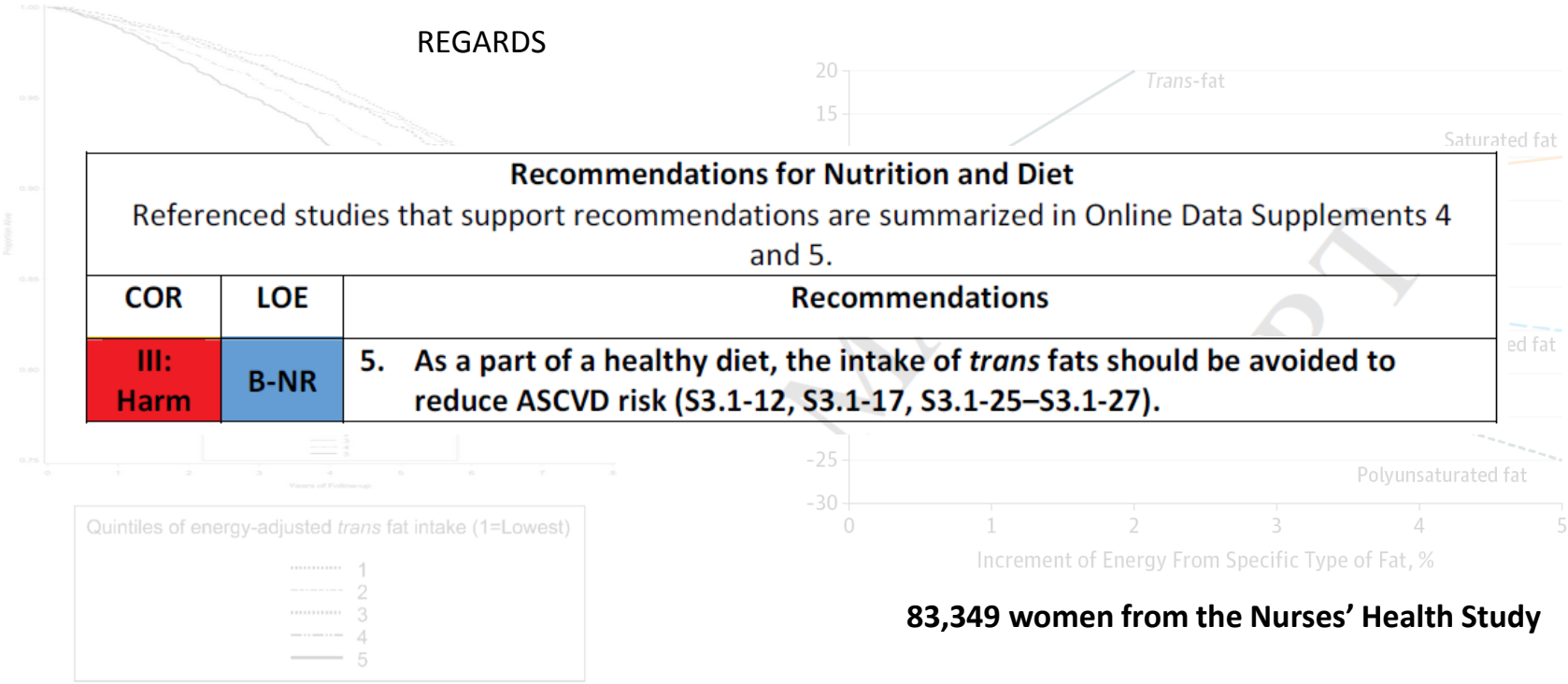
lyze in very different ways.[4] Consequ
become weighted averages of expert
sequence, instead of carefully condu
informing guidelines, expert-driven
advocates dictate what primary stud
surprisingly, an independent assessi
Academies of Sciences, Engineering
national dietary guidelines suggested

Assuming the meta-analyzed evidence from cohort studies represents life span–long causal associations, for a baseline life expectancy of 80 years, nonexperts presented with only relative risks may falsely infer that eating 12 hazelnuts daily (1 oz) would prolong life by 12 years (i.e. 1 year per hazelnut), drinking 3 cups of coffee daily would achieve a similar gain of 12 extra years, and eating a single mandarin orange daily (80 g) would add 5 years of life.

The harm of Trans fat

REGARDS

Recommendations for Nutrition and Diet Referenced studies that support recommendations are summarized in Online Data Supplements 4 and 5.		
COR	**LOE**	**Recommendations**
III: Harm	**B-NR**	**5. As a part of a healthy diet, the intake of *trans* fats should be avoided to reduce ASCVD risk (S3.1-12, S3.1-17, S3.1-25–S3.1-27).**



83,349 women from the Nurses' Health Study

Kiage JN, et.al. Am J Clin Nutr. 2013;97:1121-8.

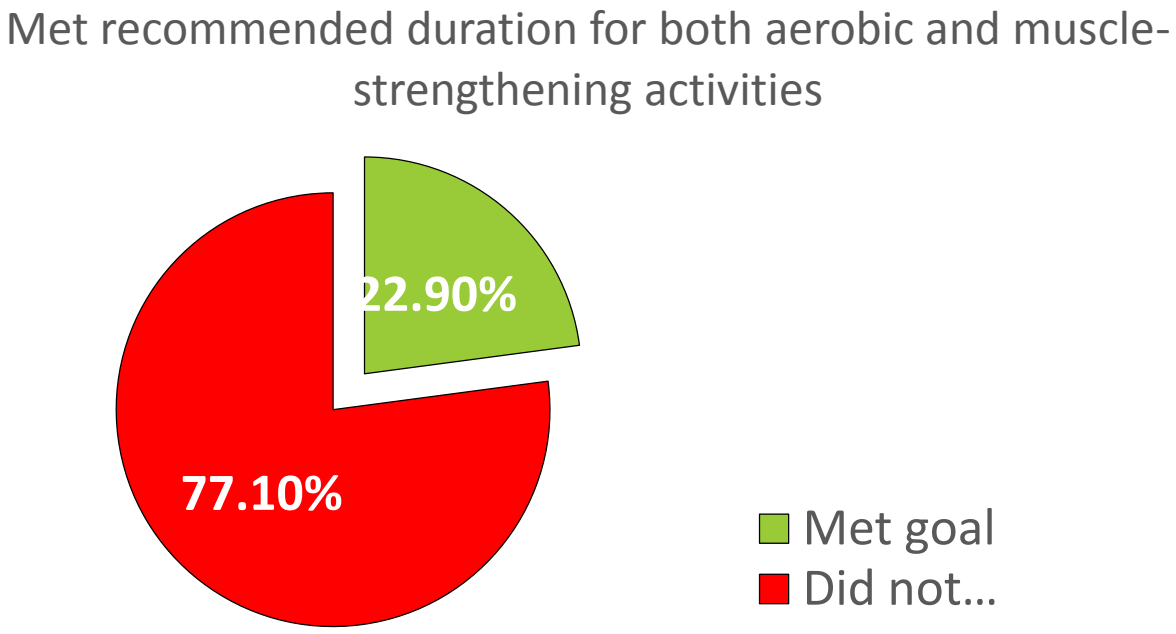
Wang et al., JAMA Intern Med. 2016;176:1134-45

Top 10 Take Home Messages

5. Adults should engage in **at least 150 minutes per week of accumulated moderate-intensity** physical activity or **75 minutes per week of vigorous-intensity** physical activity.

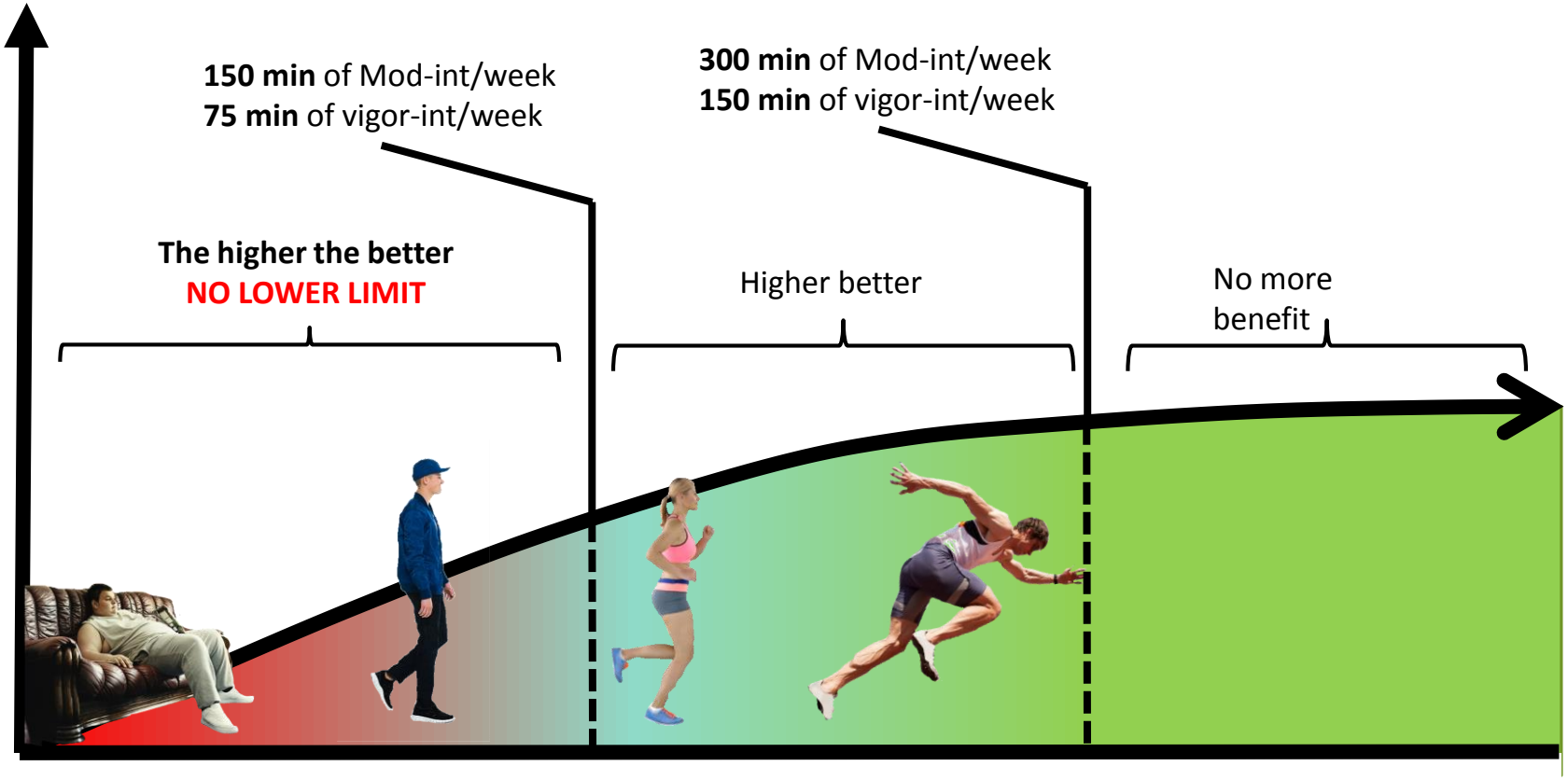
I	B-R	**1. Adults should be routinely counseled in healthcare visits to optimize a physically active lifestyle.**
I	B-NR	**2. Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk.**

22.9% of Americans met minimum physical activity recommendations 2010-2015



National Health Statistics Reports ■ Number 112 ■ June 28, 2018

The spectrum of physical activity



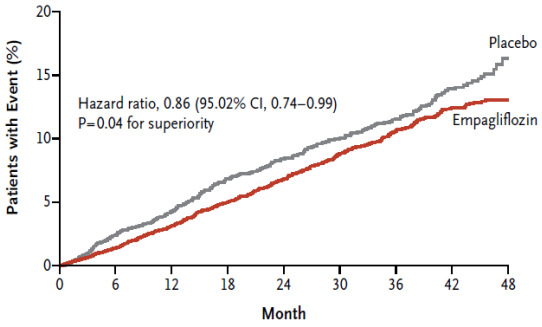
Top 10 Take Home Messages

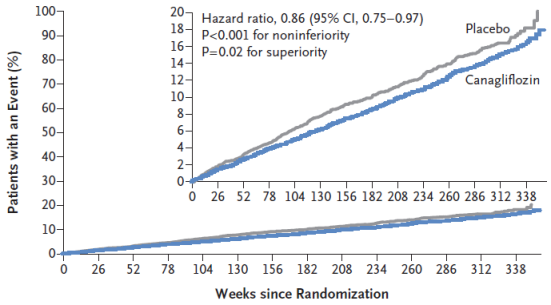
6. For adults with DMII, lifestyle changes (**diet and exercise**) are initial recommendations. If Rx are indicated, **metformin** is 1st-line therapy (IIa, B-R), followed by consideration of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a glucagon-like peptide-1 (GLP-1) receptor agonist (IIb,B-R).

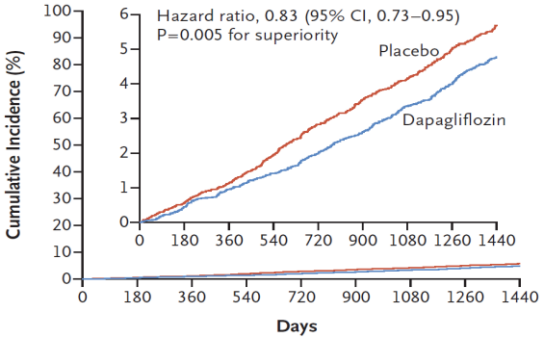
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).
I	A	2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).

Recommendations for Adults With Type 2 Diabetes Mellitus Referenced studies that support recommendations are summarized in Online Data Supplement 10.		
COR	**LOE**	**Recommendations**
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).
I	A	2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).
IIa	B-R	3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk (S4.2-5–S4.2-8).
IIb	B-R	4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk (S4.2-9–S4.2-14).

Type 2 Diabetes: SGLT-2 inhibitors

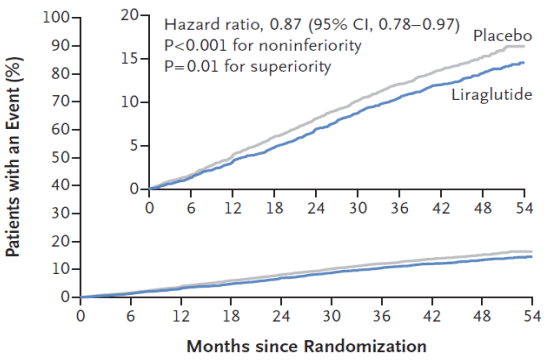


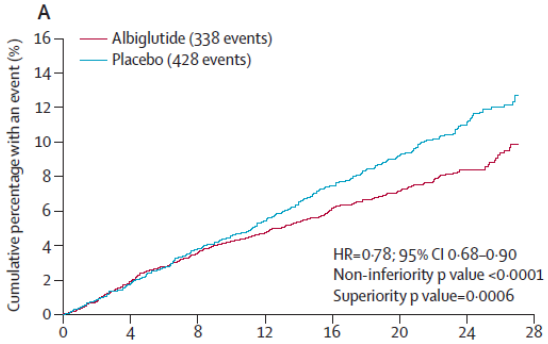


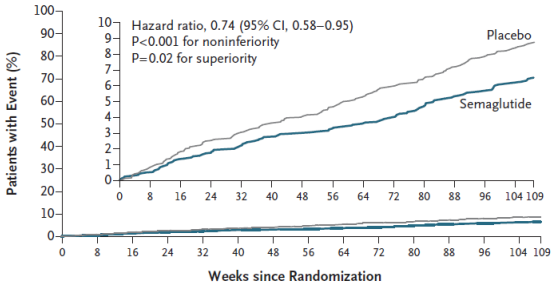


EMPA-REG OUTCOME	CANVAS	DECLARE–TIMI 58
7028 patients with type 2 DM	10,142 patient with type 2 diabetes and high CVD risk	17160 T2DM who had or were at risk (**10,186**) for ASCVD
Empagliflozin vs. placebo	Canagliflozin or placebo	Dapagliflozin vs placebo
14% reduction in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. **Reduction in HF**	**14% reduction** in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. **Reduction in HF**	Did not reduce MACE. **17% reduction in** CVD death or HF hospitalization. Reduced CKD progression.
NEJM. 2015 Nov 26;373(22):2117-28.	NEJM. 2017;377:644-57	NEJM. 2019 Jan 24;380(4):347-357.

Type 2 Diabetes: GLP1 agonists







LEADER	Harmony Outcomes	SUSTAIN-6
9340 patient with T3DM and high CVD risk	9463 patient with T2DM and CVD	3297 patients with T2DM
Liraglutide vs. placebo	Albiglutide vs. placebo	Semaglutide vs. placebo
13% reduction in first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	**22% reduction** in occurrence of cardiovascular death, myocardial infarction, or stroke	**26% reduction** in first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke

NEJM. 2016 Jul 28;375(4):311-22.

Lancet. 2018 Oct 27;392(10157):1519-1529

NEJM. 2016 Nov 10;375(19):1834-1844

Top 10 Take Home Messages

7. All adults should be assessed at every healthcare visit for tobacco use. Those who use tobacco should be assisted and strongly advised to quit.

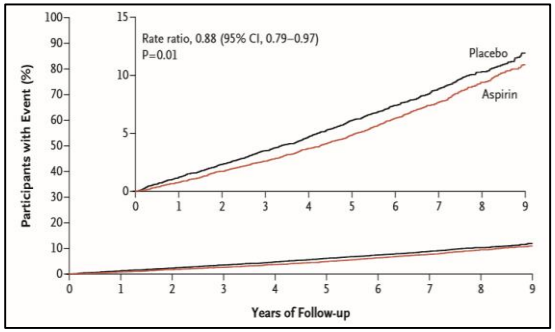
Top 10 Take Home Messages

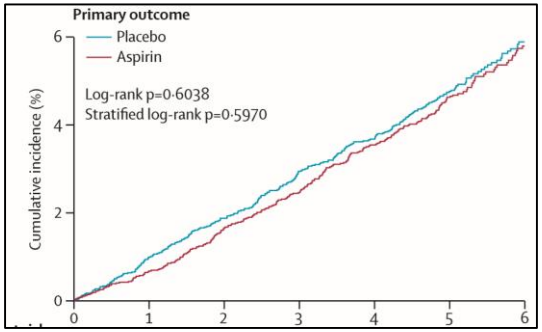
8. Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit.

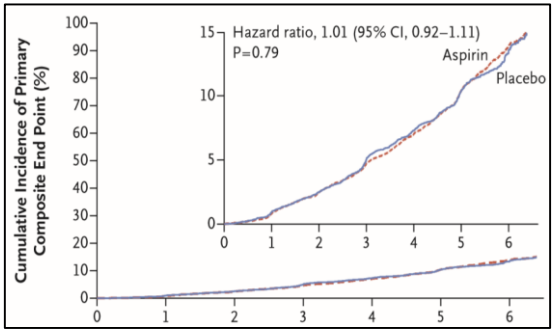
Aspirin Use

Recommendations for Aspirin Use		
COR	**LOE**	**Recommendations**
IIb	**A**	**1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.**
III: Harm	**B-R**	**2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.**
III: Harm	**C-LD**	**3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.**

Trials of aspirin for primary prevention







ASCEND	ARRIVE	ASPREE, 2018
15,480 **with diabetes** and no evident CVD.	12,546 with Moderate CVD risk **w/o DM** or high risk of GI bleeding	19,114 adults > 70 yr with no cardiovascular disease.
100 mg of aspirin vs. placebo	100 mg aspirin vs. placebo	100 mg aspirin vs. placebo
Reduction in vascular events was counterbalanced by bleeding	No difference in a composite of CV death, MI, UA, CVA, or TIA. With increased risk of bleeding	Aspirin did not prolong disability free survival but **increased major** hemorrhage

N Engl J Med. 2018;379:1529-39

Lancet. 2018;392:1036-46

N Engl J Med 2018; 379:1509-1518

Prescribing based on totality of evidence

Elevated PCE
+ CAC
+ risk enhancing factors
Inability to achieve lipid or BP targets

Previous GIB or PUD
Bleeding from other sites
Age >70 years
Thrombocytopenia
Coagulopathy
CKD
Use of NSAIDs, steroids, DOAC, and warfarin

Patient-clinician preference
Shared-decision making

Low dose ASA
(Class IIb)

Avoid ASA (Class III)
Focus on other risk factors

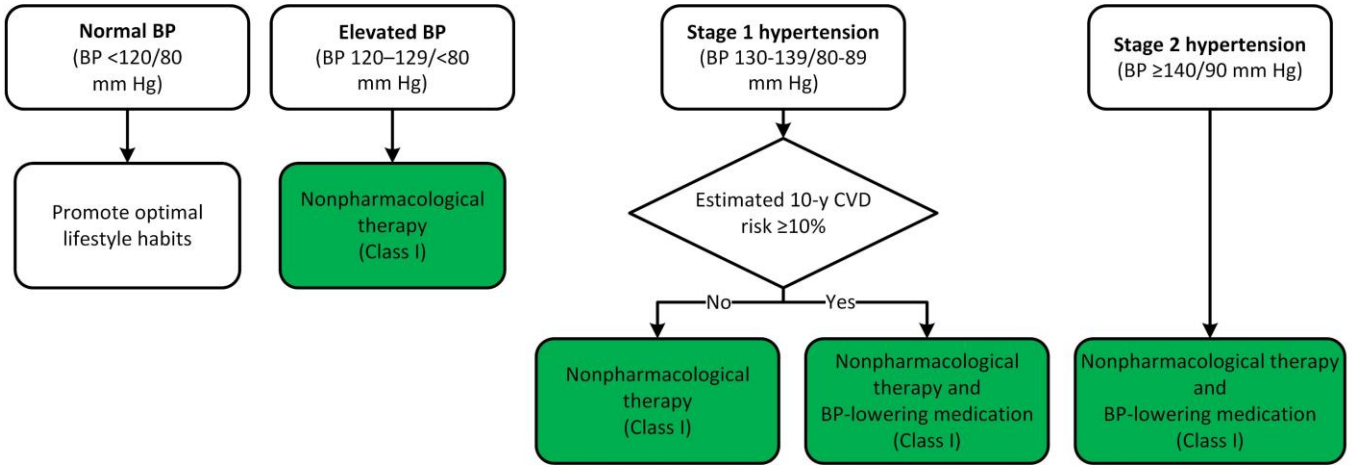
Top 10 Take Home Messages

9. Statin therapy is 1st-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (**≥190 mg/dL**), those with **diabetes mellitus**, who are 40 to 75 years of age, and at sufficient ASCVD risk (PCE) after a clinician–patient risk discussion.

Top 10 Take Home Messages

10. Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg.

Figure 4. BP Thresholds and Recommendations for Treatment



BP indicates blood pressure; and CVD, cardiovascular disease.

Figure 1. ABCDE of Primary Prevention: Lifestyle Changes and Team-Based Care