Looking into the crystal ball…

Tailored Medicine in Coronary Artery Disease in Women

Cardiofemme 2018

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Disclosures

- **Consultant- Daiichi Sankyo, Bayer**
- **Honoraria for lectures- AstraZeneca, Daiichi Sankyo, Pfizer, Sanofi, Bayer**
- **Grant- Bayer**

In 20 years…

Looking at the past and present…

- **“ Historically, women with ACS have had worse outcomes compared with men….”**
- **“ This differences were recognized to be secondary to a higher incidence of atypical symptoms, late presentations, and consequently lower rates of optimal medical therapy and cardiac catheterization..”**
- **” With advances…, outcomes have improved and findings from recent trials indicate similar incidence of short- and long-term mortality in men and women…”**

Mehran R, JACC 2016; 9: 451-464.

AHA Scientific Statement

American Heart Association

Acute Myocardial Infarction in Women

A Scientific Statement From the American Heart Association

EUROPEAN SOCIETY OF CARDIOLOGY

Recommendations for gender

Recommendations	Class [a]	Level [b]	Ref [c]
Both genders should be evaluated and treated in the same way.	I	B	246

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference.
NSTE-ACS = non-ST-elevation acute coronary syndrome.

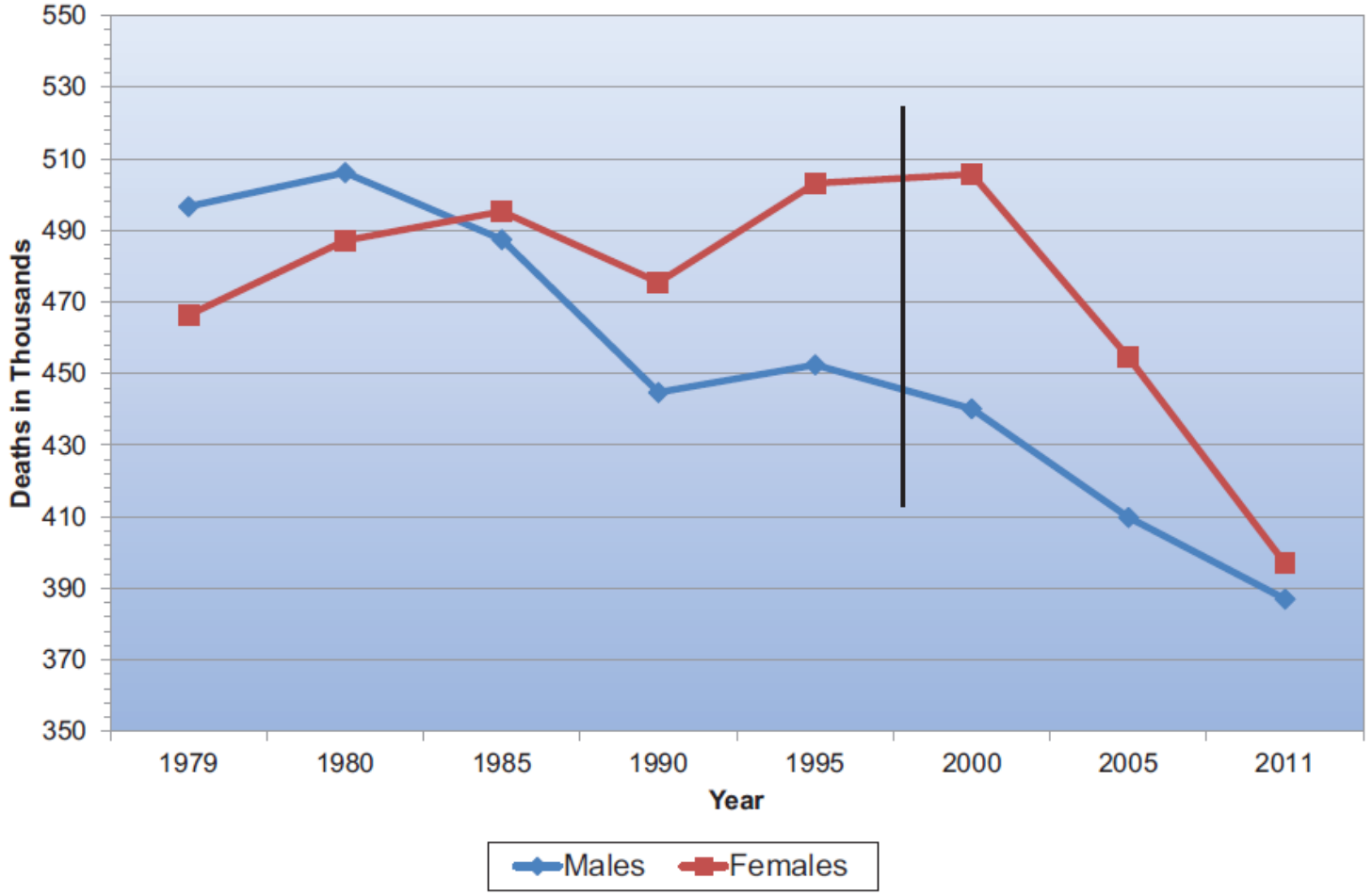
Table 17 Special subsets

Recommendations	Class [a]	Level [b]	Ref [c]
Both genders must be managed in a similar fashion.	I	C	-
A high index of suspicion for myocardial infarction must be maintained in women, diabetics, and elderly patients with atypical symptoms.	I	B	189
Special attention must be given to proper dosing of antithrombotics in elderly and renal failure patients.	I	B	190

AHA Scientific Statement

Acute Myocardial Infarction in Women

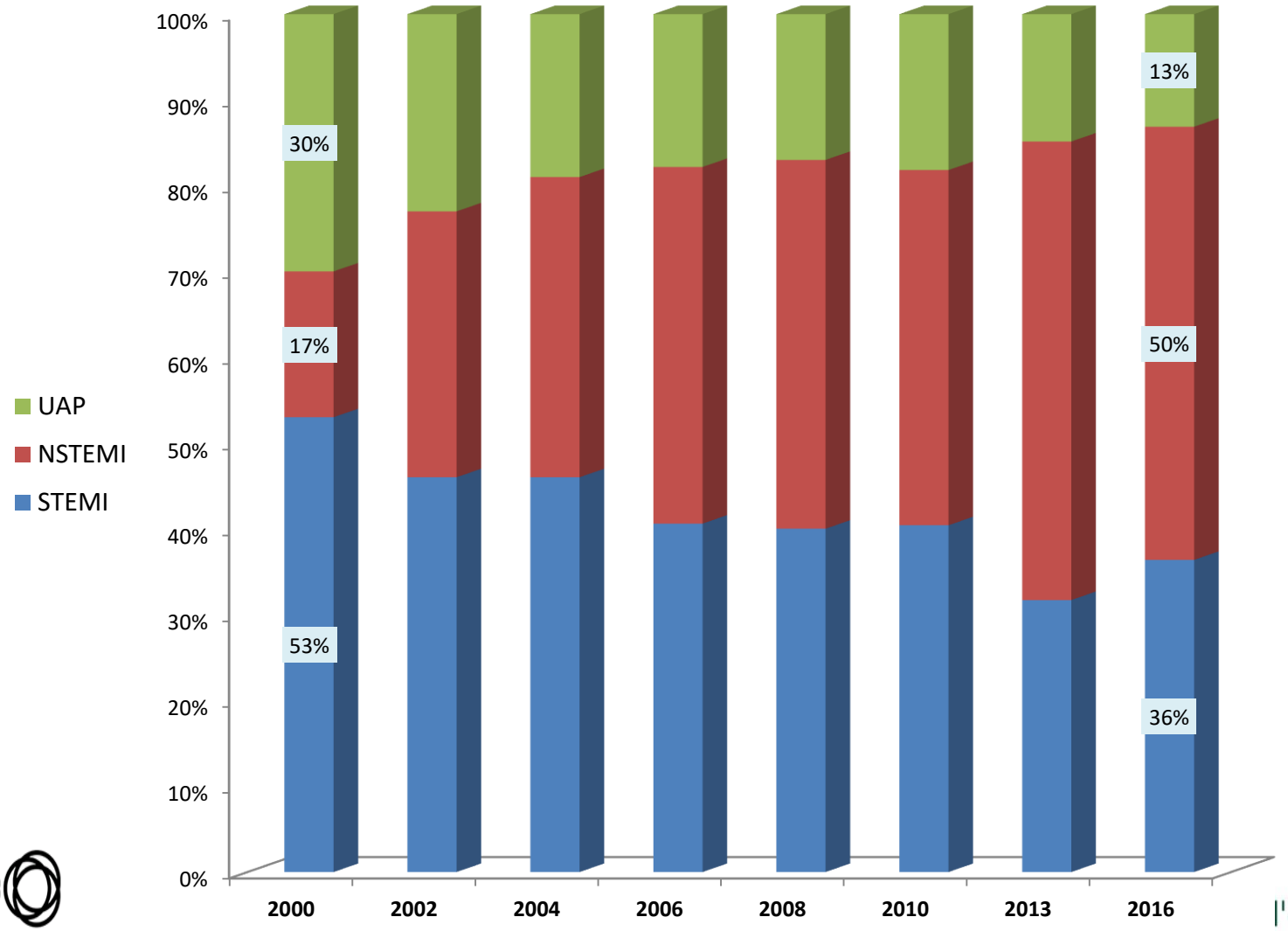
A Scientific Statement From the American Heart Association



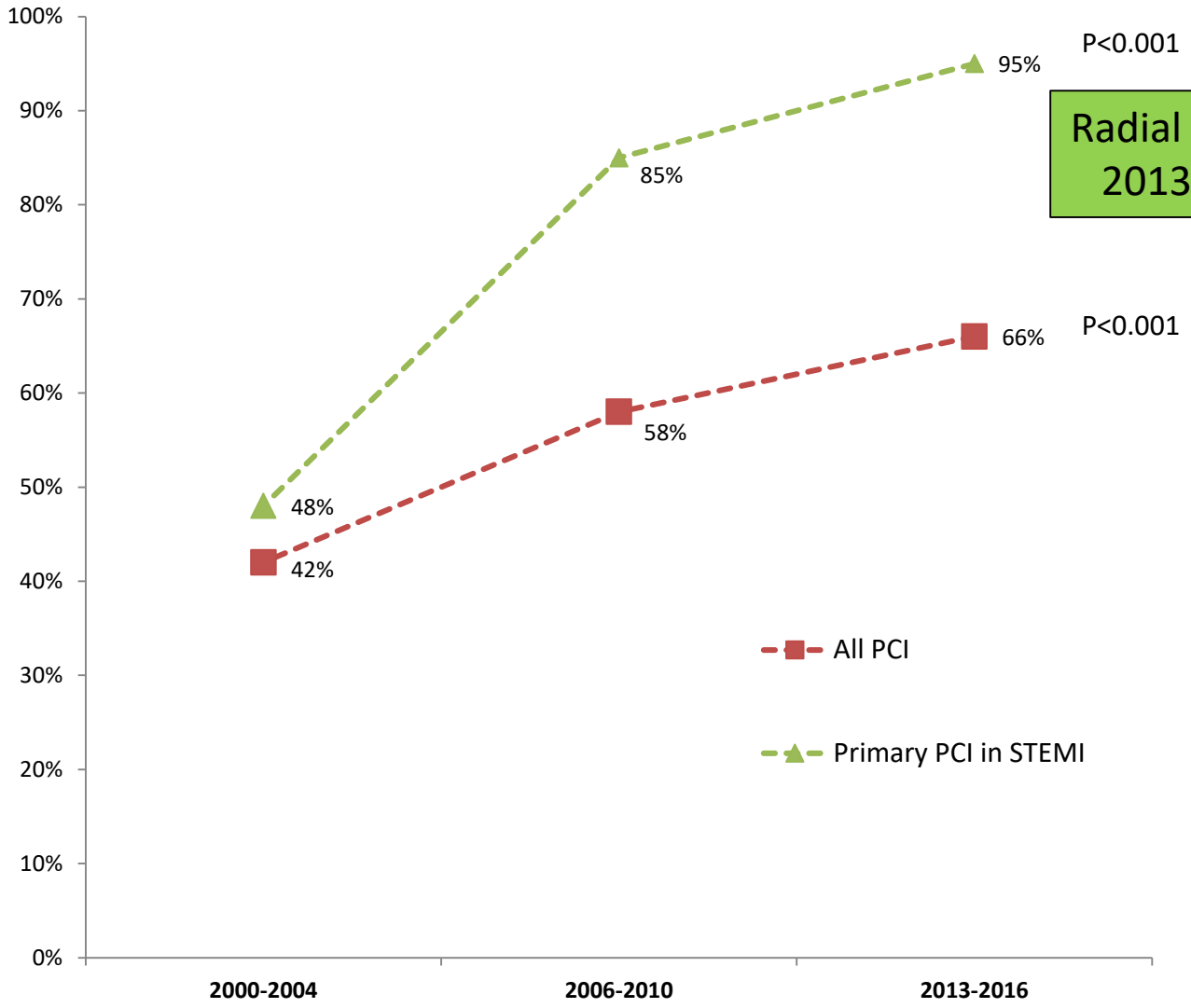
Baseline characteristics of Women

Characteristic (%)	2000-2004 (n=1480)	2006-2010 (n=1229)	2013-2016 (n=809)	P-value
Age, y- mean (SD)	70 (12)	70 (13)	70 (12)	NS
Dislipidemia	56	75	77	<0.001
Diabetes mellitus	42	44	44	NS
Current smoker	16	19	22	0.01
BMI, kg/m^2- mean (SD)	27 (5)	28 (5)	29 (15)	0.002
Prior PCI	16	24	23	<0.001
PVD	8	8	6	NS
Prior CVA/TIA	11	11	10	0.9
Prior HF	11	10	9	NS

Type of ACS in Women



Invasive management in Women



Radial Access in PPCI
2013-2016: **62%**

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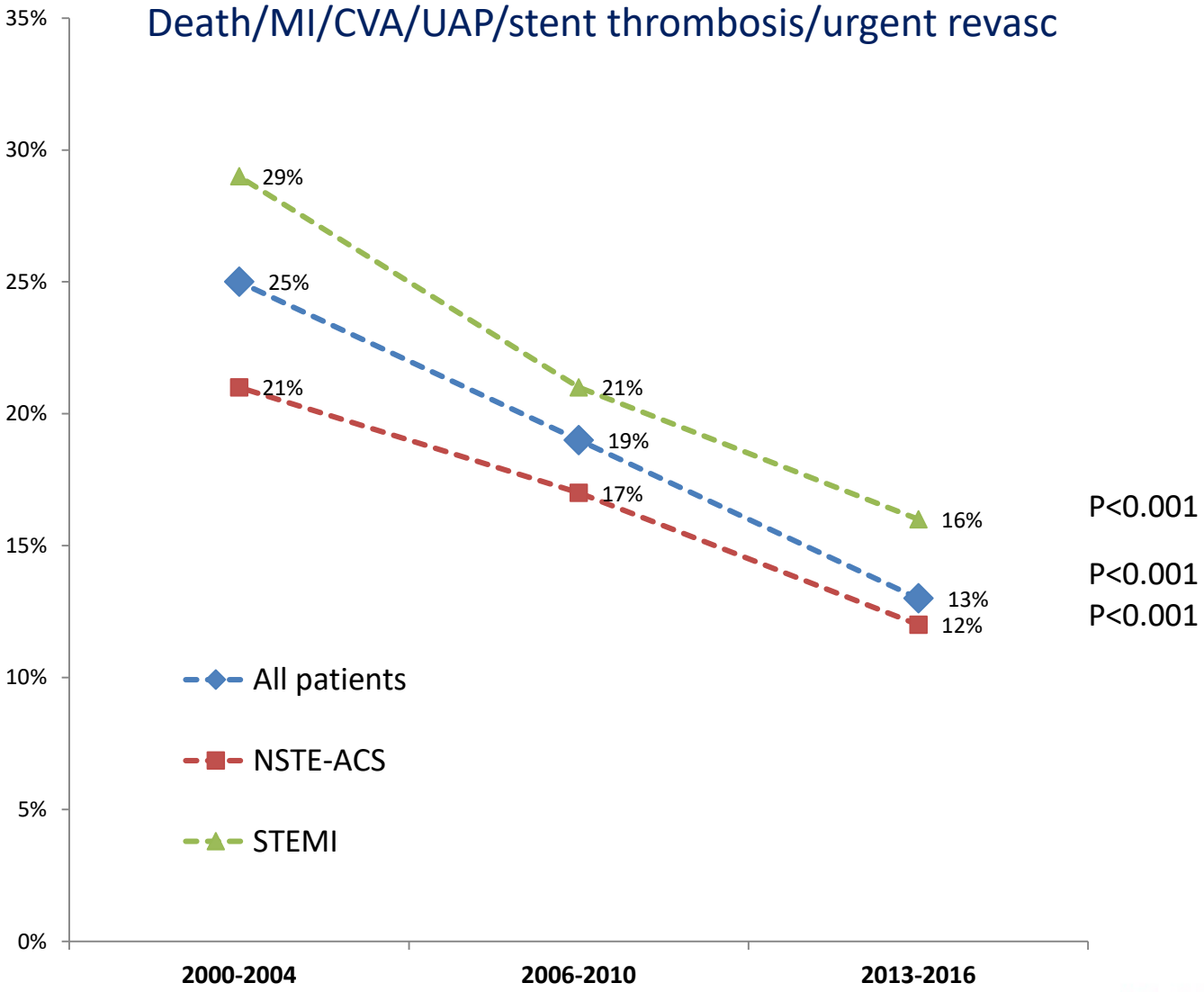
Discharge treatment in Women

Variable- %	2000-2004	2006-2010	2013-2016	P-value
Aspirin	88	94	91	<0.001
P2Y12 inhibitor	43	73	84	<0.001
Statins	66	91	93	<0.001
Ace inh/ ARBs	65	74	74	<0.001
Beta blockers	74	80	77	0.001
Cardiac rehabilitation (ref)	NA	35	46	<0.001

30d MACE



P<0.001

P<0.001

P<0.001

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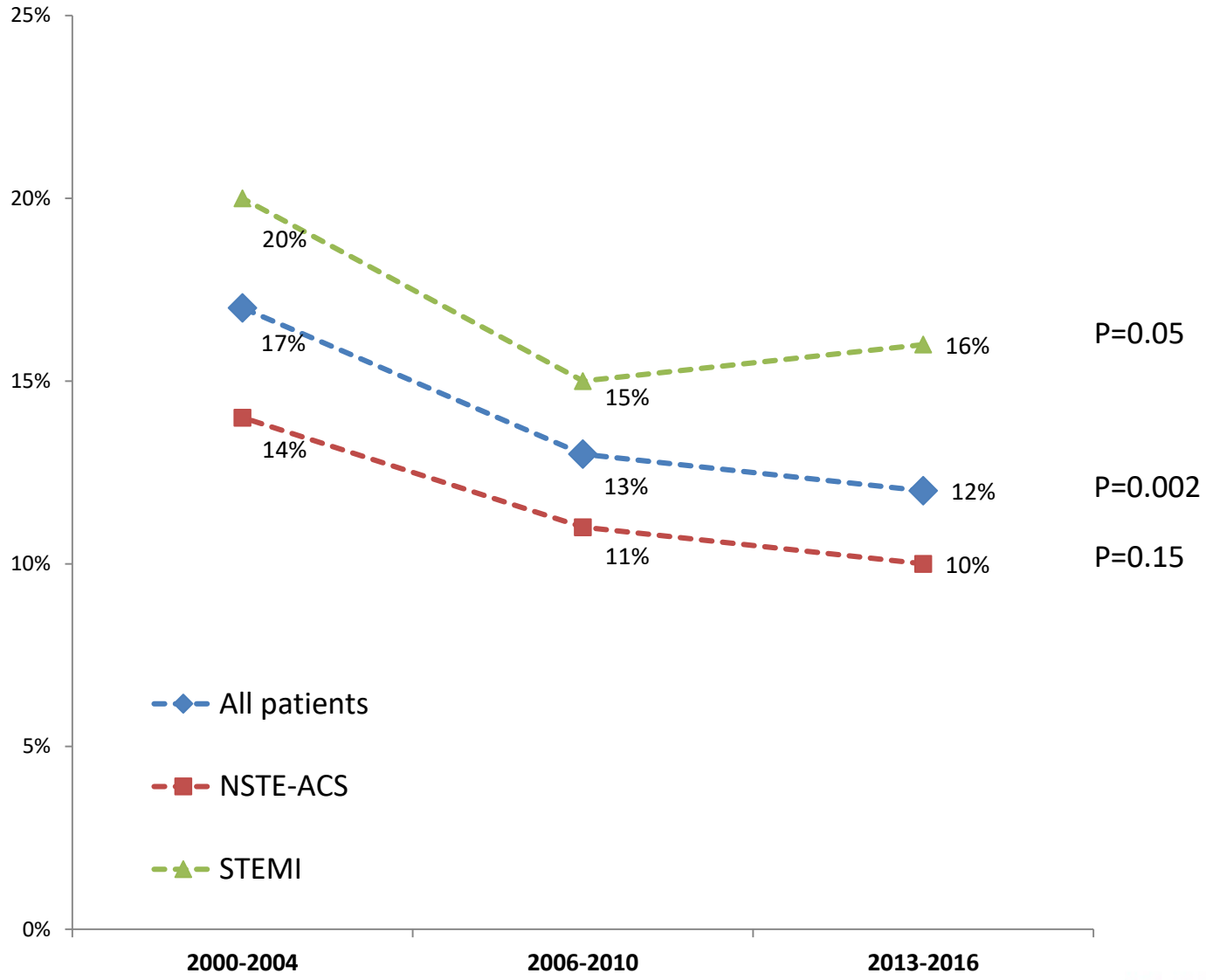
מרכז רפואי רבין בילינסון · השרון

1-year mortality



Looking into the crystal ball….

(or identifying gaps in knowledge…)

Looking into the crystal ball….

Common risk factors

Age
- Sex-specific differences in baseline risk factors vary by age[12]
- Among patients with ACS, women generally are older than men[5]

Depression
- More common in women with MI than in men[20]
- This sex-specific difference is particularly pronounced at young ages (<55 years)[21]

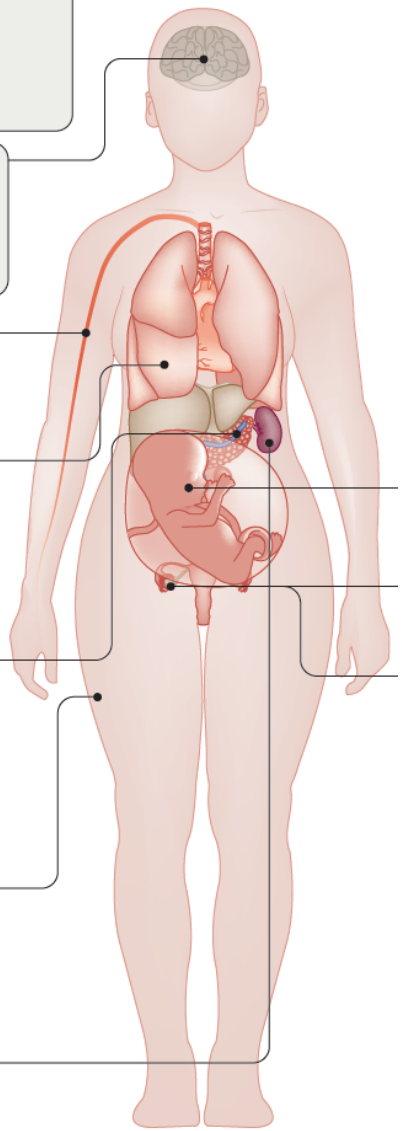
Hypertension
Women with ACS are more likely to have hypertension than men with ACS[5]

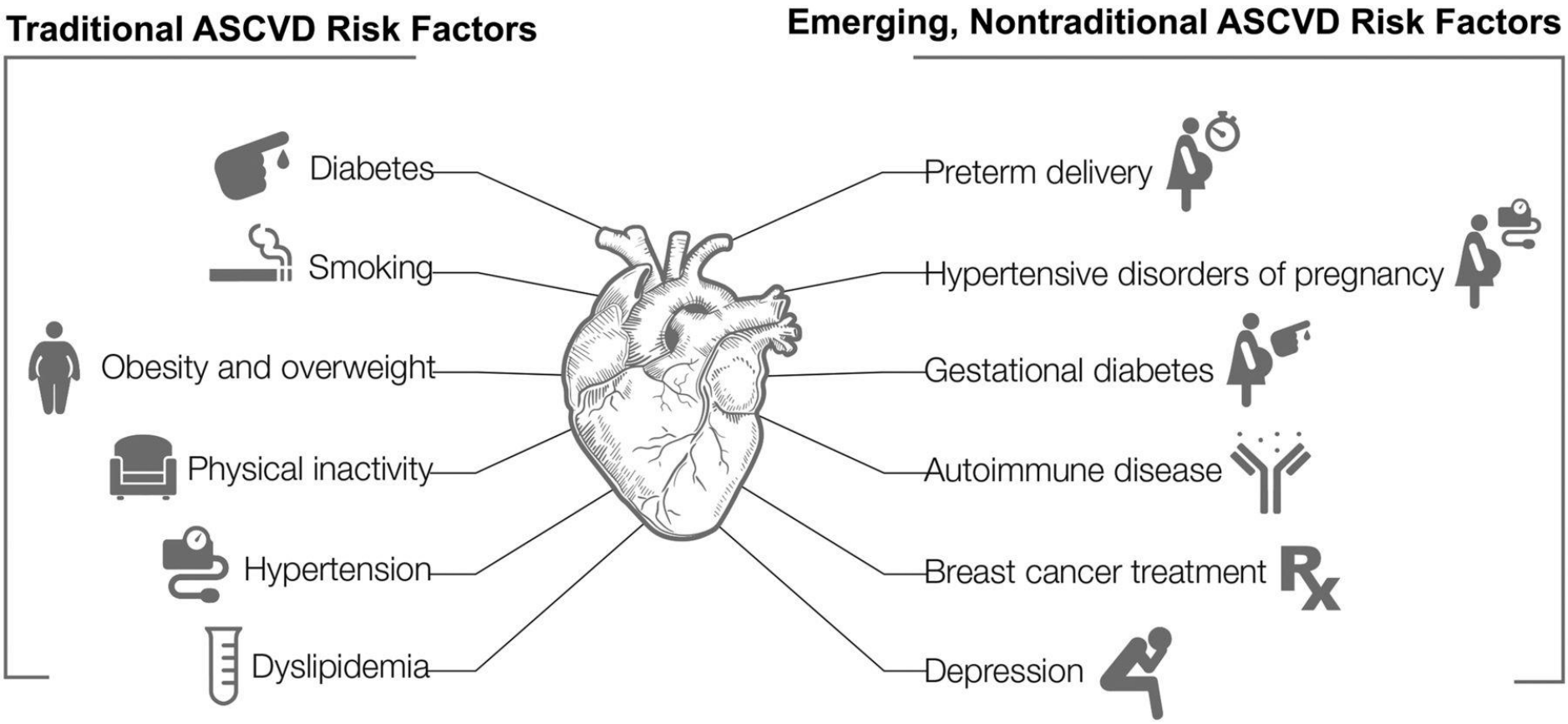
Smoking
- Stronger risk factor for MI in women than in men[18]
- The risk difference is even greater in women aged <45 years[18]

Diabetes mellitus
- Among patients with ACS, diabetes is more common in women than in men[5]
- The risk of MI and coronary heart disease is higher in women with diabetes than in men with diabetes[13-15]

Obesity
In patients with ACS, the prevalence of obesity is higher in young women (aged <55 years) than in men in the same age group[16]

Chronic kidney disease
Approximately twofold more frequent in women than in men among patients with STEMI[22,23]





(*Circ Res*. 2016;118:1273-1293. DOI: 10.1161/CIRCRESAHA.116.307547.)

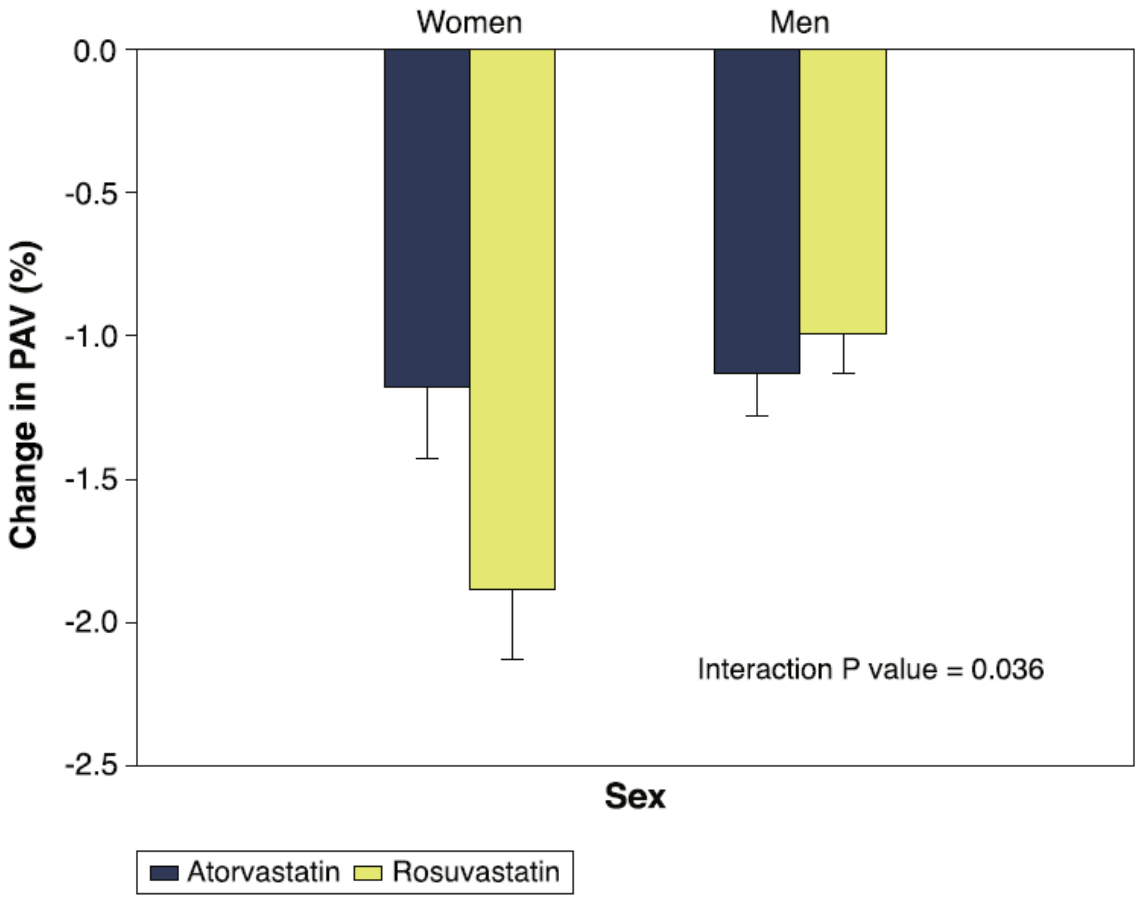


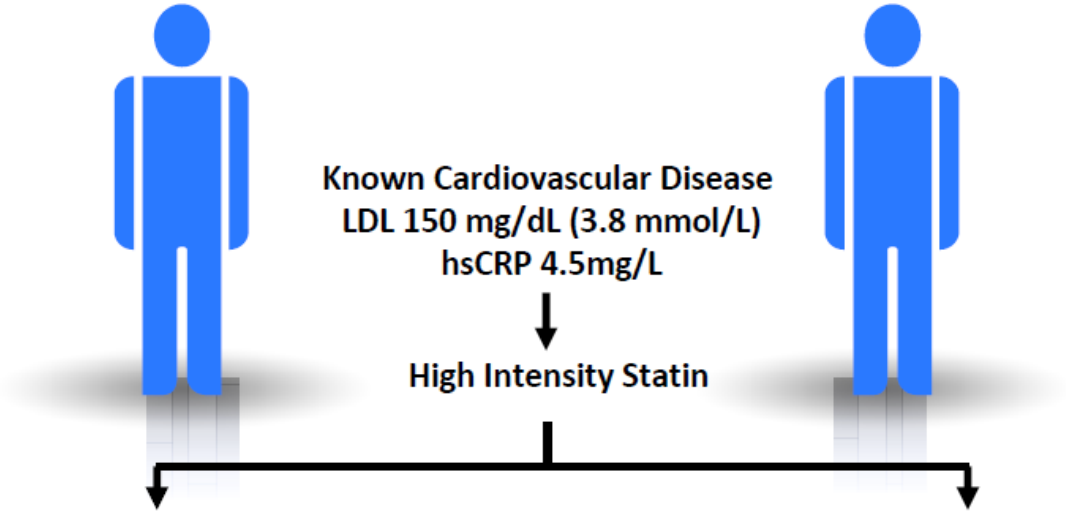
FIGURE 1 Interaction Between Sex and Treatment Upon Change in PAV

The interaction between sex and treatment specification upon change in coronary atheroma volume. PAV = percent atheroma volume.

ISSN 1936-878X/$36.00

Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22



"Residual Cholesterol Risk"

LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

"Residual Inflammatory Risk"

LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

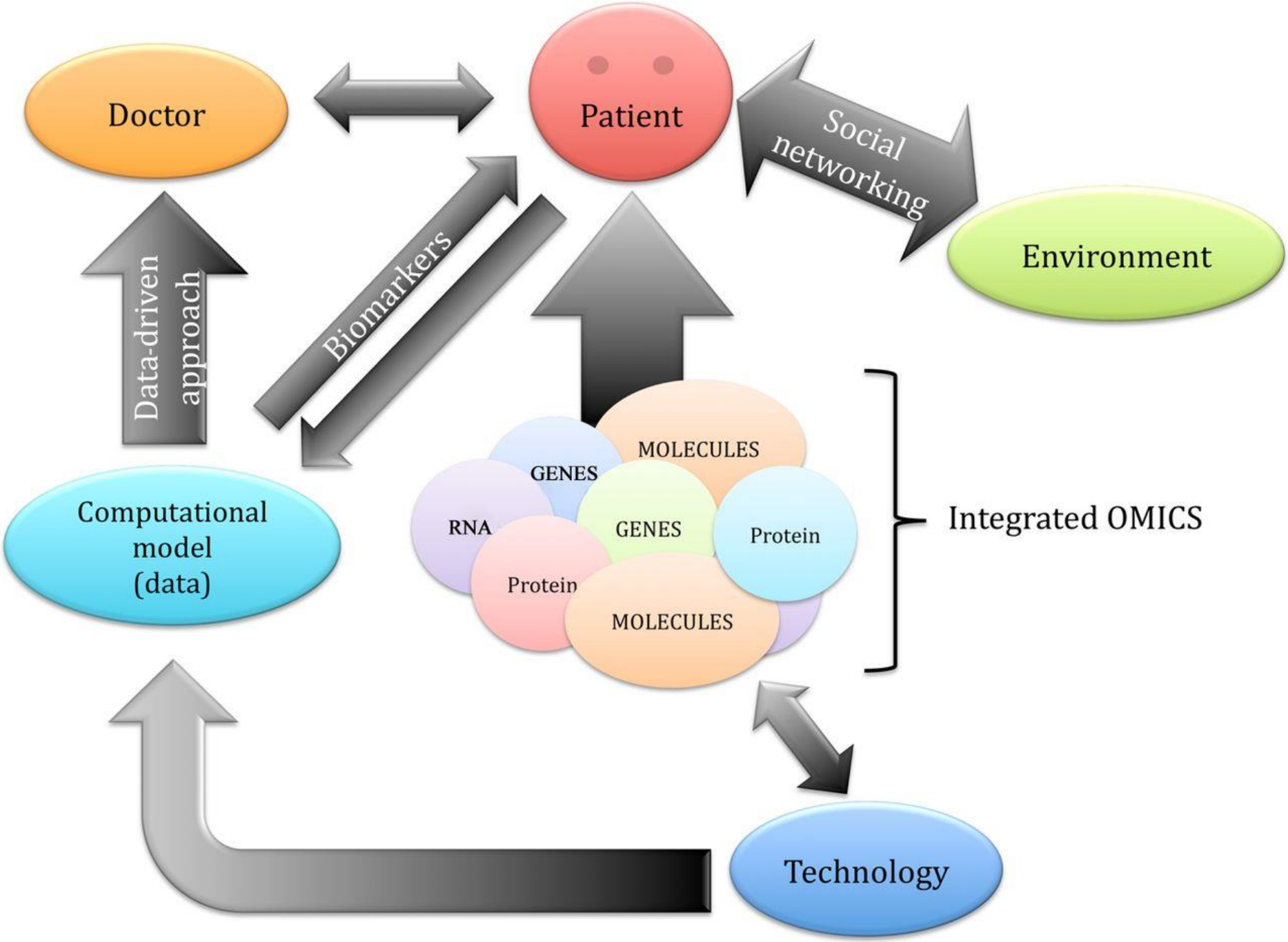
Additional
Inflammation Reduction

No Prior Proof of Concept

CANTOS has helped move the inflammatory hypothesis of coronary artery disease forward scientifically. However, the modest absolute clinical benefit of canakinumab cannot justify its routine use in patients with previous myocardial infarction until we understand more about the efficacy and safety trade-offs and identify the patients who might benefit the most.

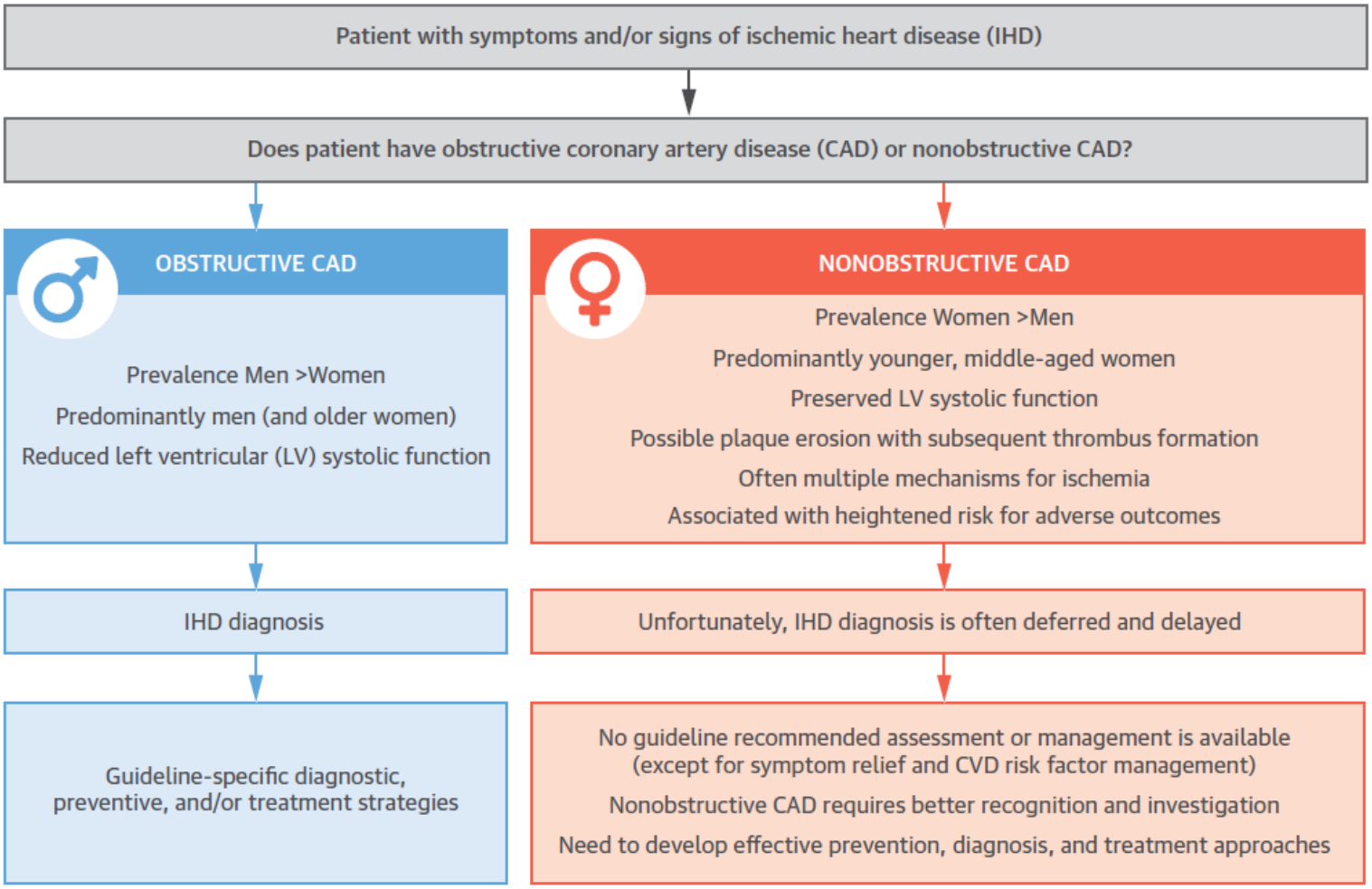
One Brave Idea Project

“ One Brave Idea will produce a way to detect coronary disease decades before symptoms arise. That would unlock a world of opportunities – insights into mechanisms, new treatments and therapies that could prevent patients from making the leap from disease-carrier to disease-sufferer…”


Doctor
Patient
Social networking
Environment
Data-driven approach
Biomarkers
MOLECULES
GENES
RNA
GENES
Protein
Protein
MOLECULES
Integrated OMICS
Computational model (data)
Technology

Looking into the crystal ball….

CENTRAL ILLUSTRATION **Nonobstructive CAD in Women: Sex-Specific CAD and Need for Ischemic Cardiac Disease Definition Changes**

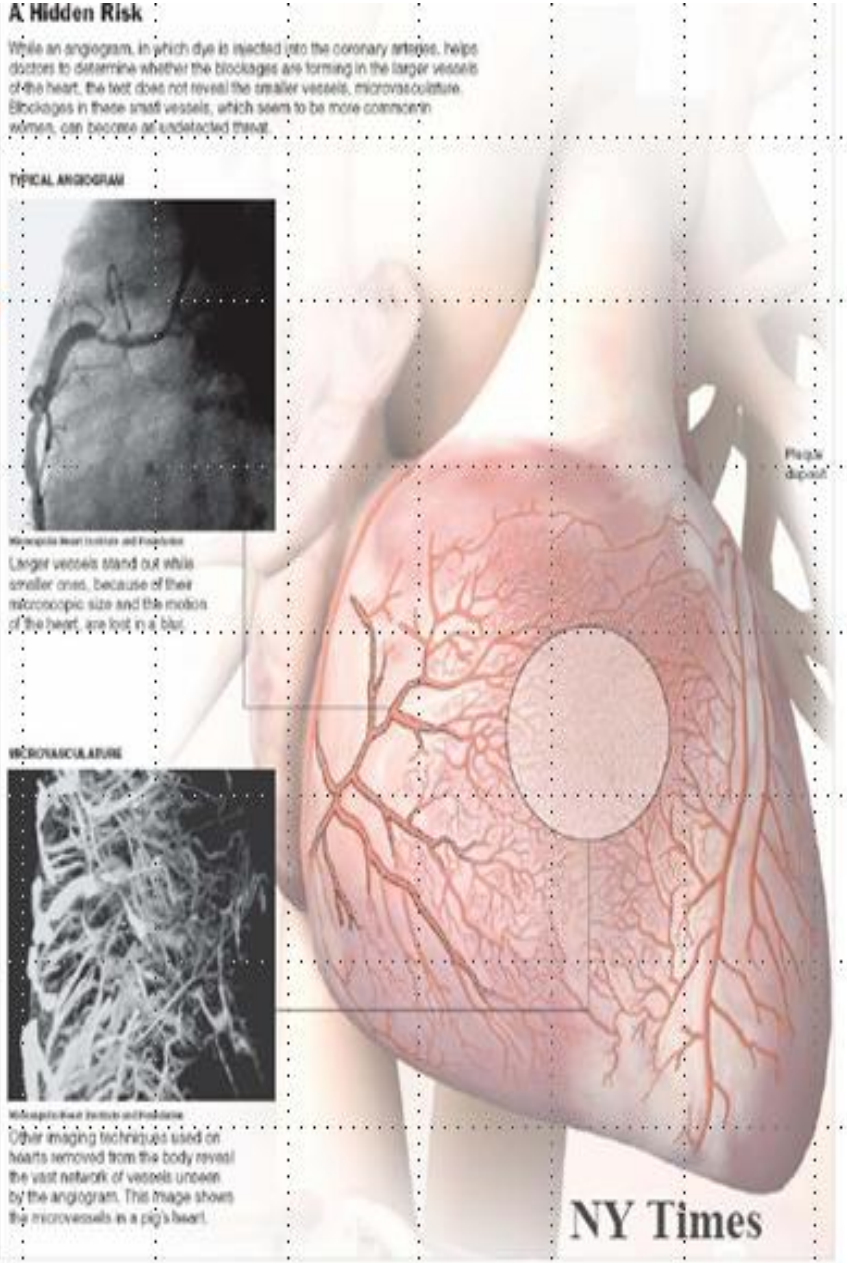


Pepine, C.J. et al. J Am Coll Cardiol. 2015; 66(17):1918–33.

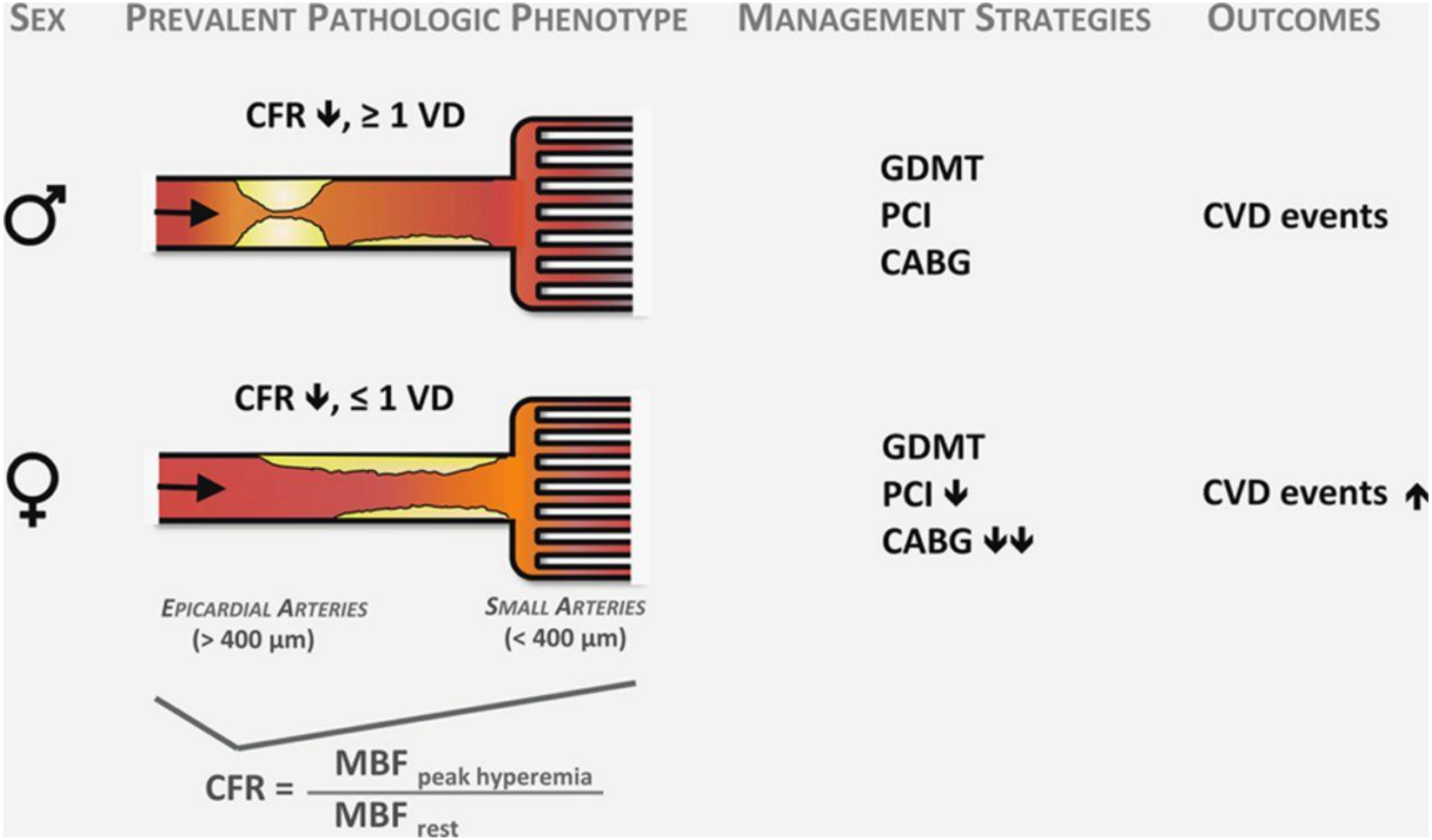
Obstructive CAD:
More prevalent In men

Microvascular Coronary Disease:
More prevalent in women

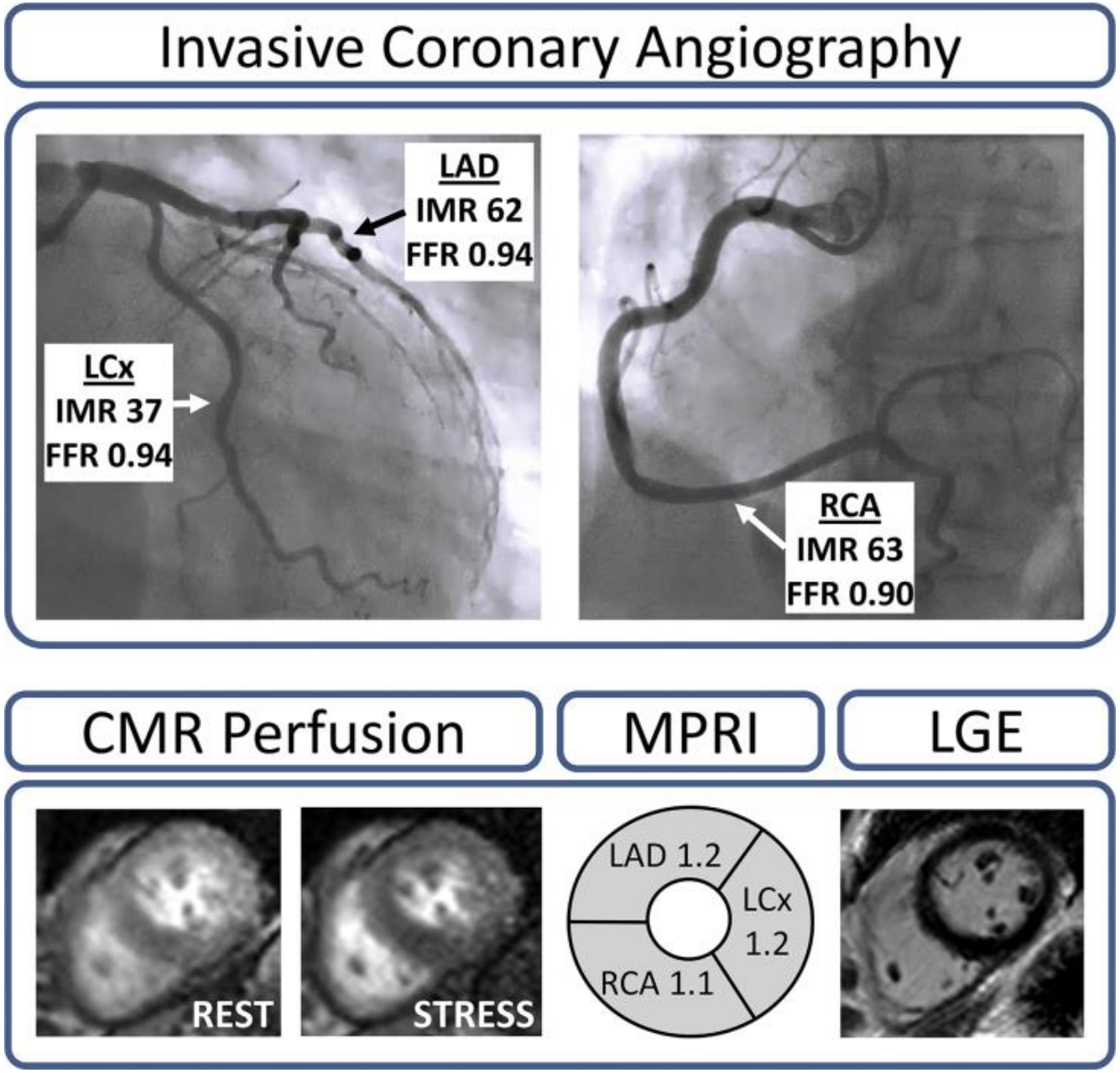
Female and male patients can have both



Conceptual model of prevalent pathological phenotypes in women and men with ischemic heart disease and possible impact on cardiovascular management strategies and outcomes.



Viviany R. Taqueti et al. Circulation. 2017;135:566-577



Liu A et al. JACC 2018

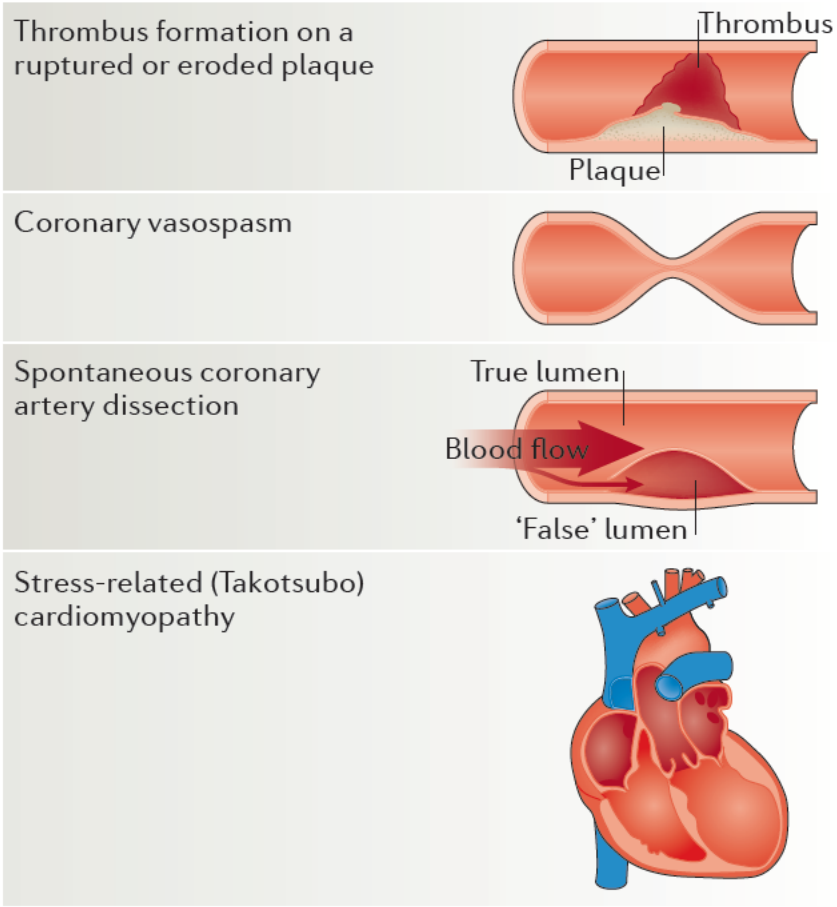


Figure 2 | **Sex-specific differences in the pathophysiology of acute coronary syndrome.** A substantial proportion of acute coronary syndrome cases, especially in women, are caused by mechanisms other than plaque rupture and thrombus formation[45]. Plaque erosion, coronary vasospasm, spontaneous coronary artery dissection, and stress-related (Takotsubo) cardiomyopathy are more prevalent in women than in men.

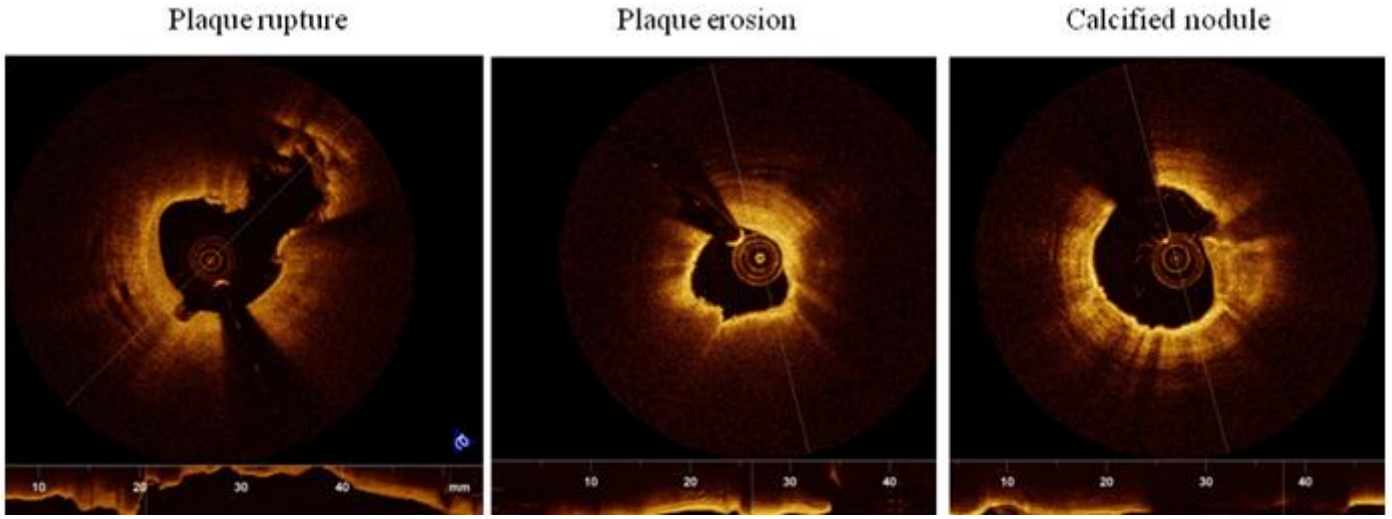
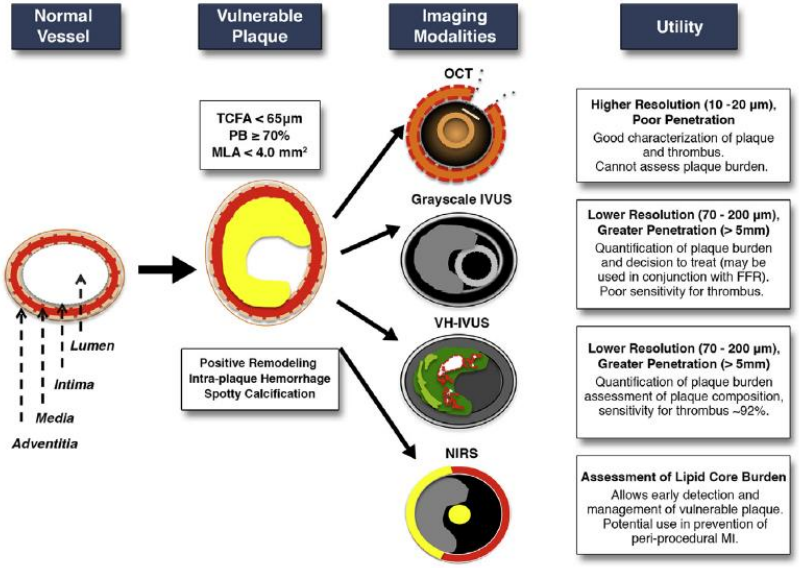
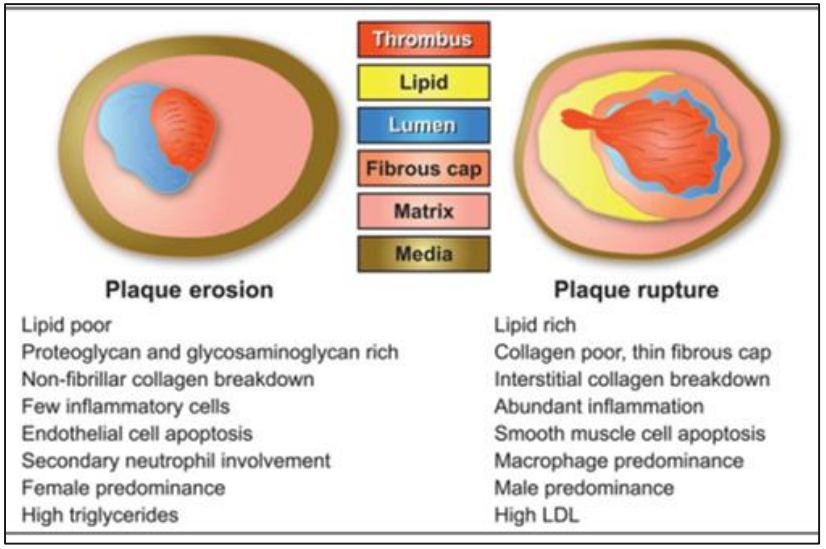
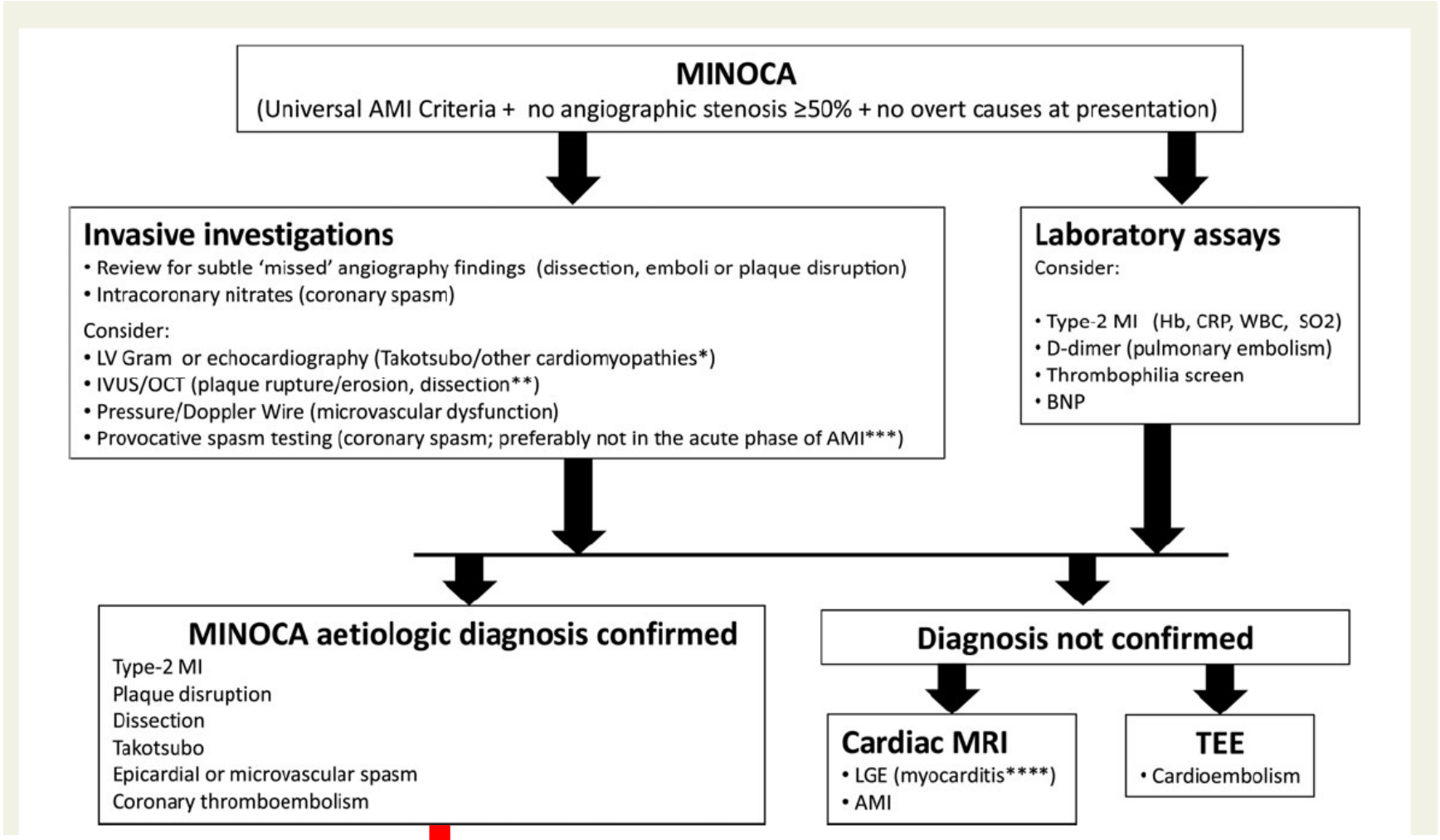


FIGURE 1 Utility of Contemporary Coronary Imaging Technologies in ACS



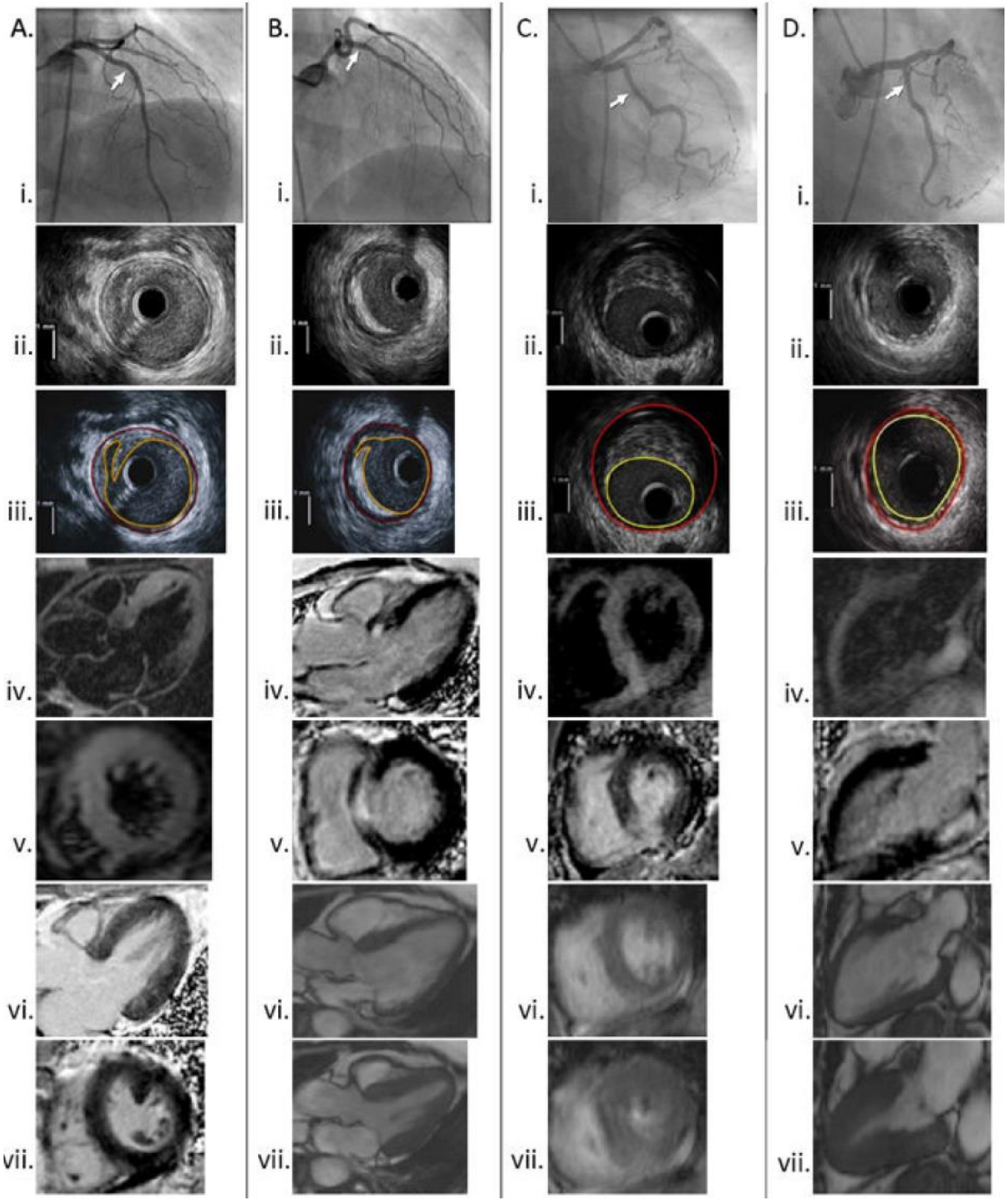
IVUS = intravascular ultrasound; NIRS = near-infrared spectroscopy; OCT = optical coherence tomography; MLA = minimal lumen area; PB = plaque burden; TCFA = thin-cap fibroatheroma; VH = virtual histology.





What is the specific treatment for each pathophysiology/aetiology?

EUROPEAN SOCIETY OF CARDIOLOGY®
European Heart Journal (2017) **38**, 143–153
doi:10.1093/eurheartj/ehw149
CURRENT OPINION


A.
B.
C.
D.
i.
ii.
iii.
iv.
v.
vi.
vii.

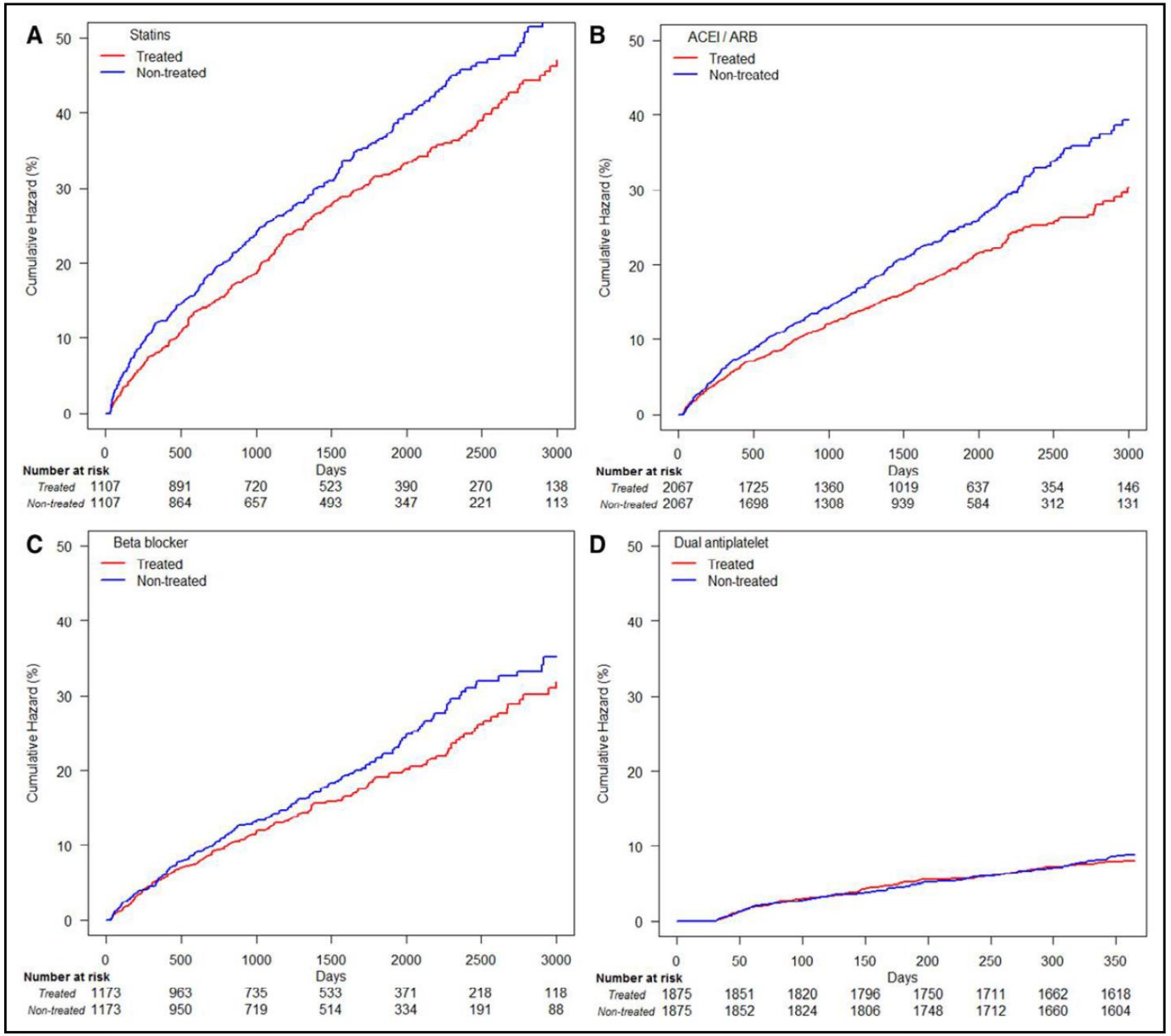


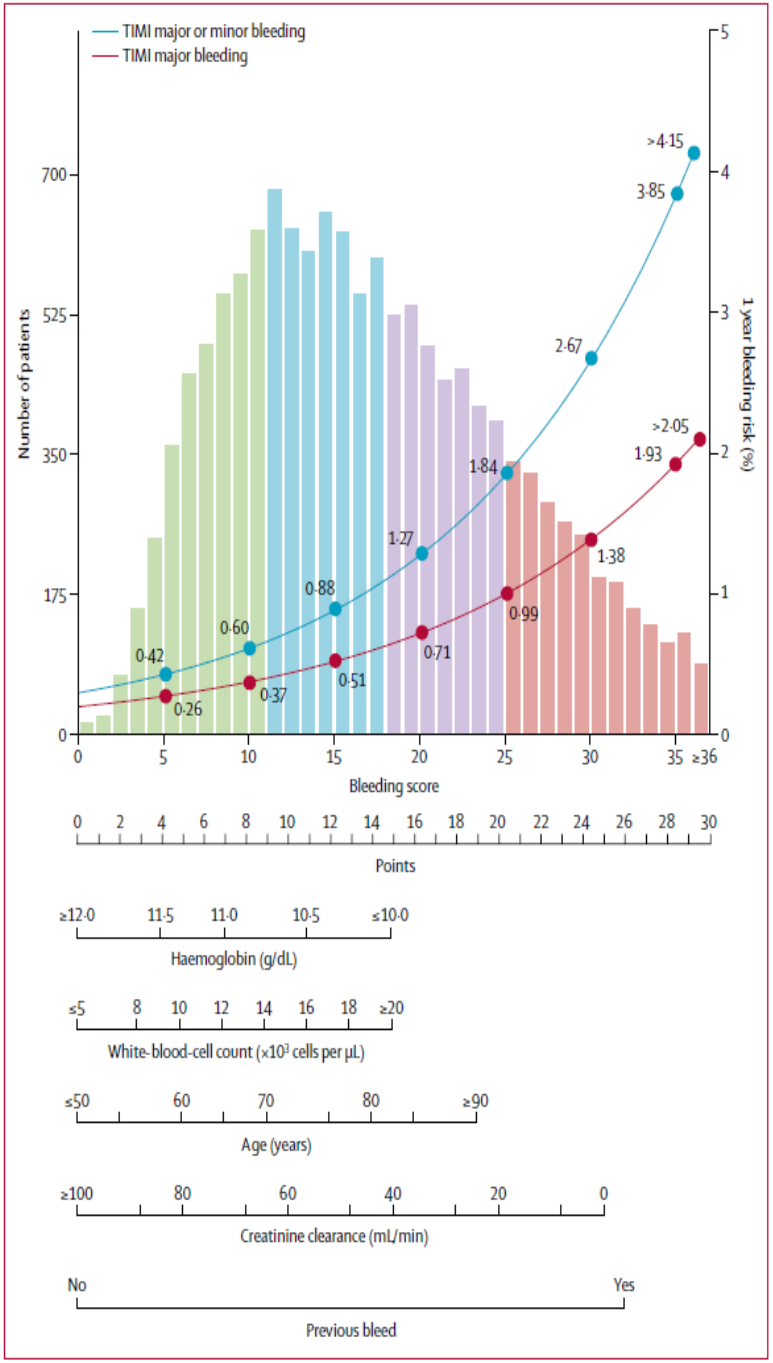
Figure 2. Survival curves for treated and untreated in the 1:1 propensity score–matched populations.
A, Statins. **B,** angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). **C,** β-blockers. **D,** Dual antiplatelet treatment.

Circulation. 2017;135:1481–1489. DOI: 10.1161/CIRCULATIONAHA.116.026336

TABLE 4 Clinical and Procedural Factors Associated With Increased Ischemic Risk (Including Stent Thrombosis) or Increased Bleeding Risk (62-70)

Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT)	Increased Bleeding Risk (may favor shorter-duration DAPT)
Increased ischemic risk	History of prior bleeding
Advanced age	Oral anticoagulant therapy
ACS presentation	Female sex
Multiple prior MIs	Advanced age
Extensive CAD	Low body weight
Diabetes mellitus	CKD
CKD	Diabetes mellitus
Increased risk of stent thrombosis	Anemia
ACS presentation	Chronic steroid or NSAID therapy
Diabetes mellitus	
Left ventricular ejection fraction <40%	
First-generation drug-eluting stent	
Stent undersizing	
Stent underdeployment	
Small stent diameter	
Greater stent length	
Bifurcation stents	
In-stent restenosis	

doi: 10.1016/j.jacc.2016.03.513



European Heart Journal (2016) **37**, 2816–2820
doi:10.1093/eurheartj/ehw057

Is takotsubo syndrome a microvascular acute coronary syndrome? Towards a new definition

Thomas F. Lüscher* and Christian Templin

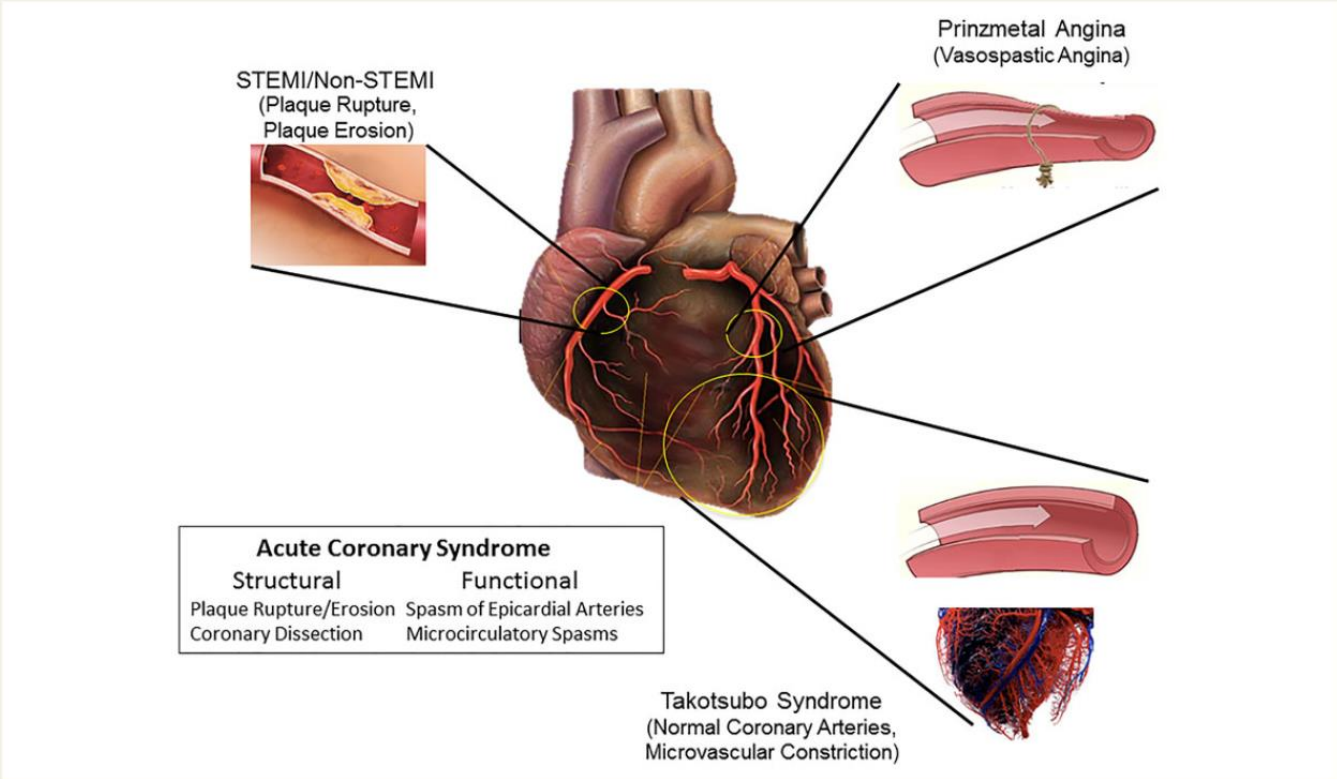


Figure 3 Macrovascular and microvascular ischaemia in patients with ST-segment elevation myocardial infarction (STEMI), non-STEMI, Takotsubo syndrome and Prinzmetal angina, respectively.

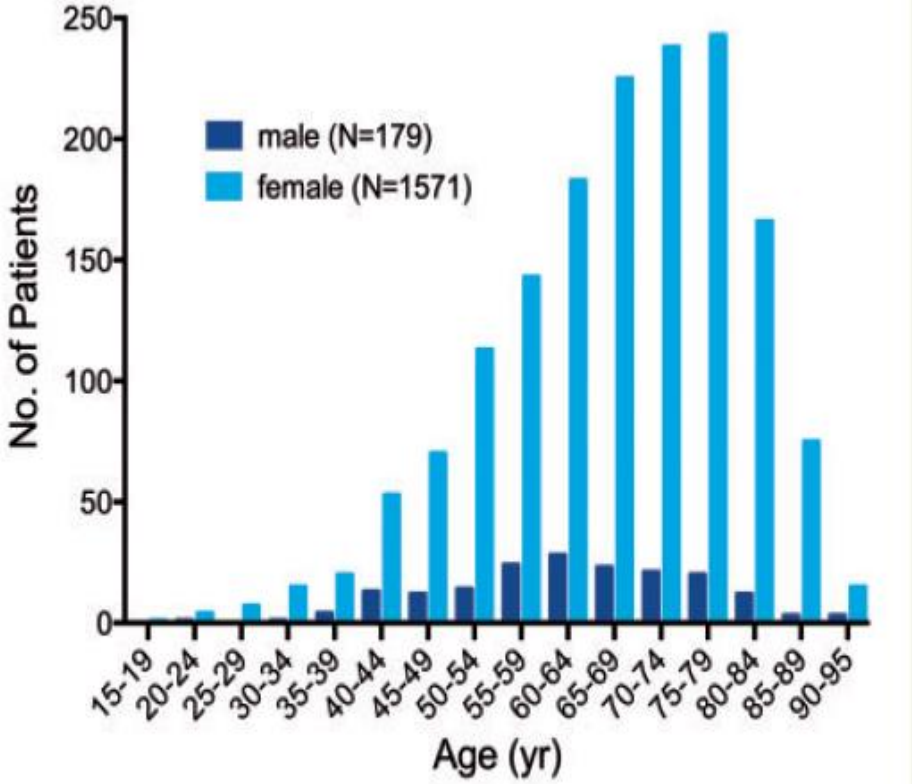
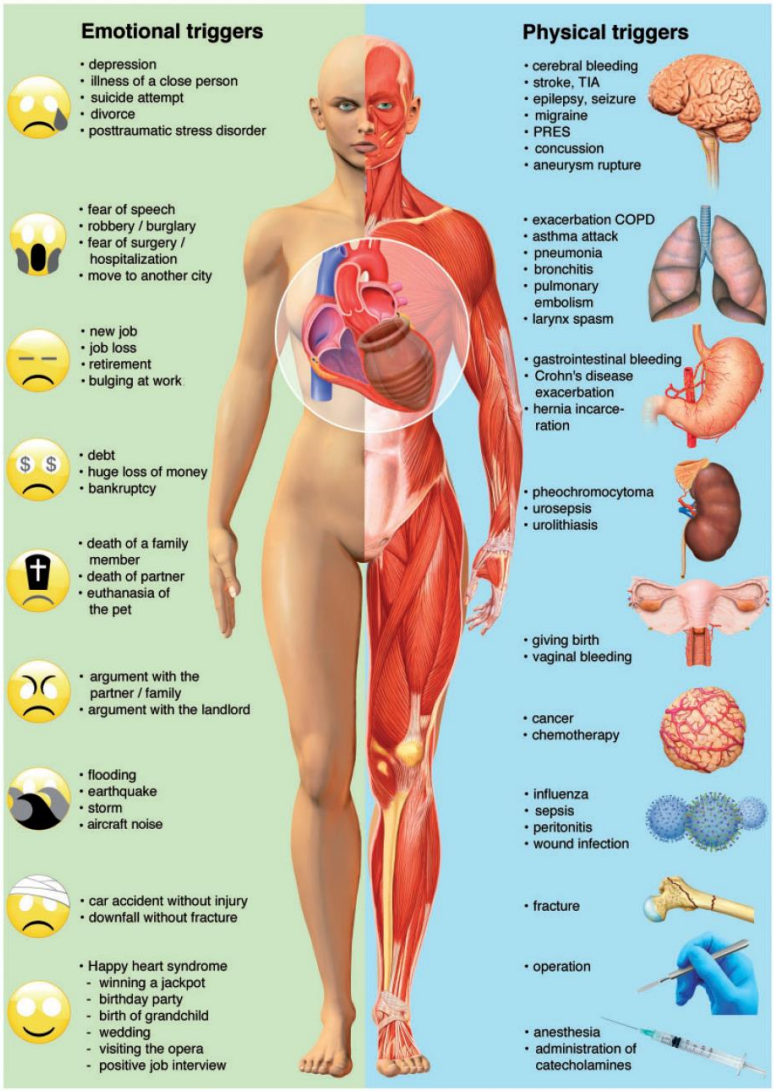
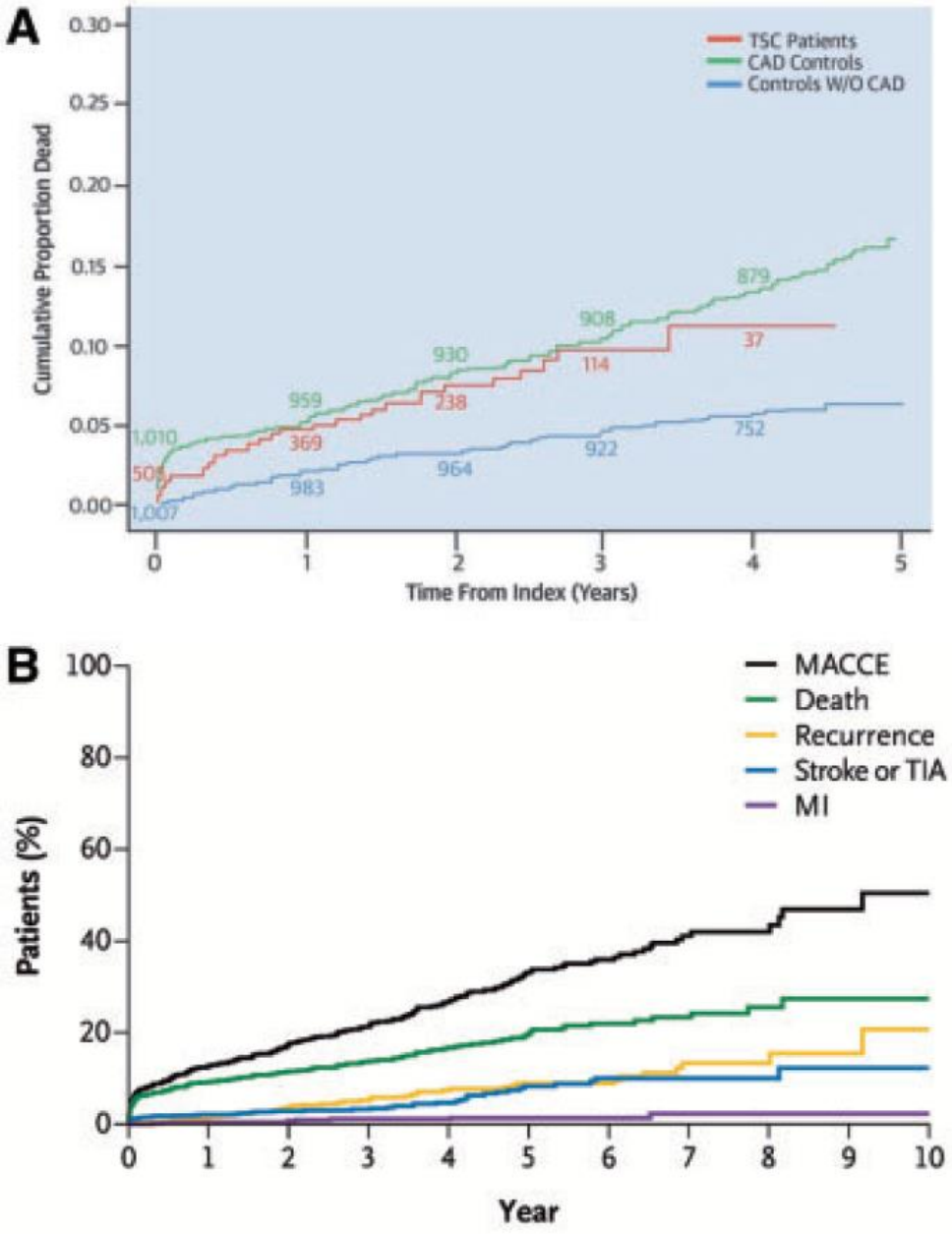


Figure 2 Age and sex distribution of patients with takotsubo syndrome. Reprinted with permission from Templin *et al.*[16]

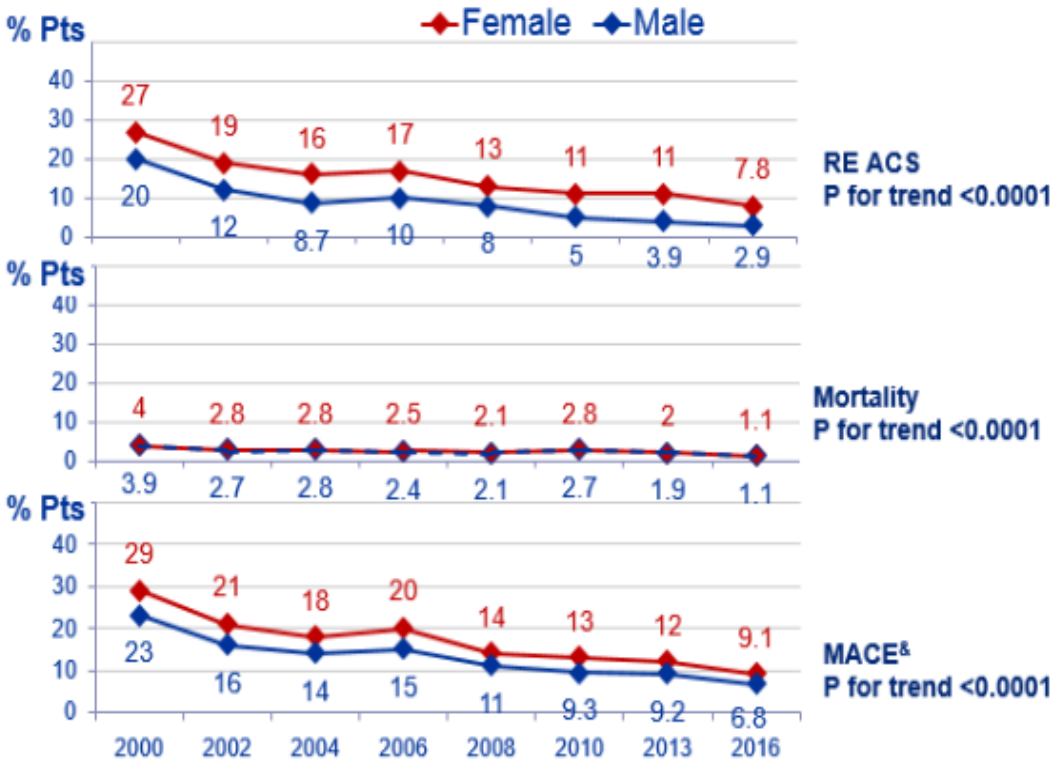



A
TSC Patients
CAD Controls
Controls W/O CAD
Cumulative Proportion Dead
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1,010
506
1,007
959
369
983
930
238
964
908
114
922
879
37
752
0
1
2
3
4
5
Time From Index (Years)
B
MACCE
Death
Recurrence
Stroke or TIA
MI
Patients (%)
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
10
Year

Looking into the crystal ball….

30 Days Adjusted* Outcomes

ACSIS 2000 - 2016



&MACE 30D : DIED/UAP/MIISCH/CVA/ST.THRMB/FU URG.REVASC

*outcomes are adjusted for: mean age at 65.5

Sex Differences in the Management and 5-Year Outcome of Young Patients (<55 Years) with Acute Coronary Syndromes

THE AMERICAN JOURNAL of MEDICINE®

Avi Sabbag, MD,[a] Shlomi Matetzky, MD,[a] Avital Porter, MD,[b] Zaza Iakobishvili, MD,[b] Mady Moriel, MD,[c] Donna Zwas, MD,[d] Paul Fefer, MD,[a] Elad Asher, MD,[a] Roy Beigel, MD,[a] Shmuel Gottlieb, MD,[c] Ilan Goldenberg, MD,[a] Amit Segev, MD[a]

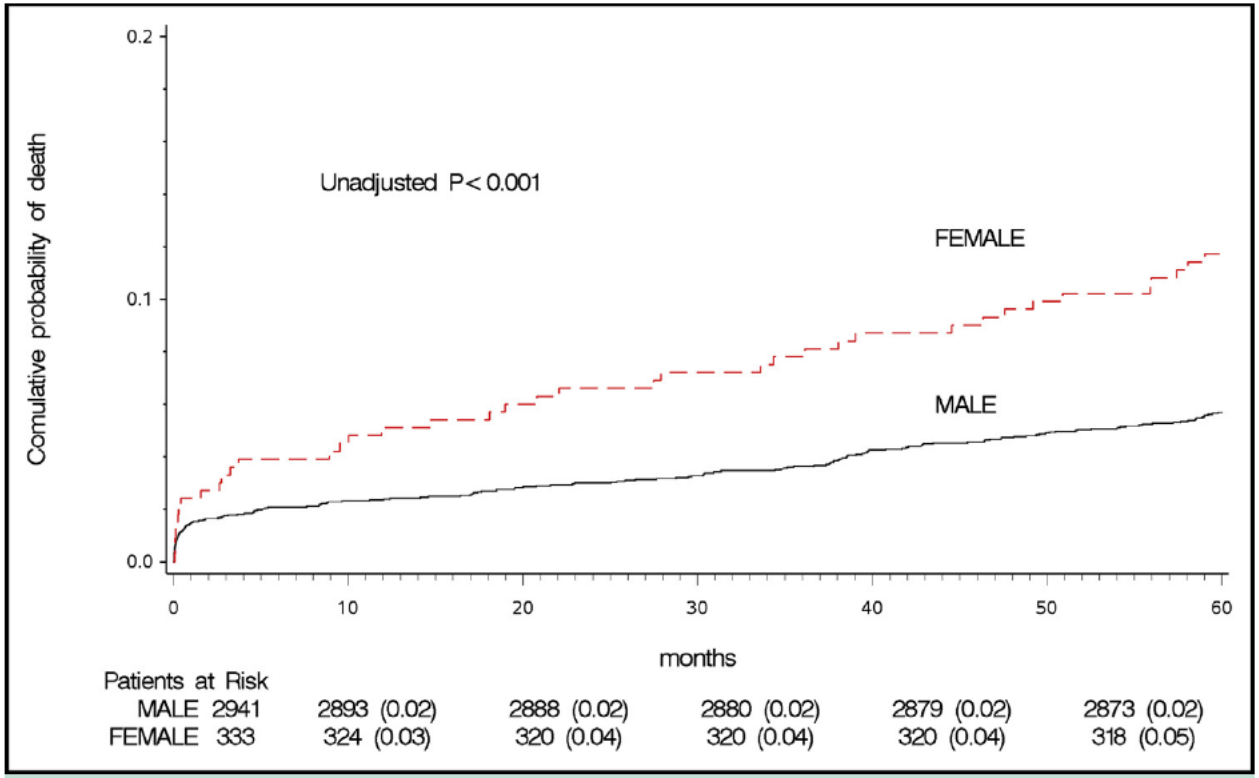
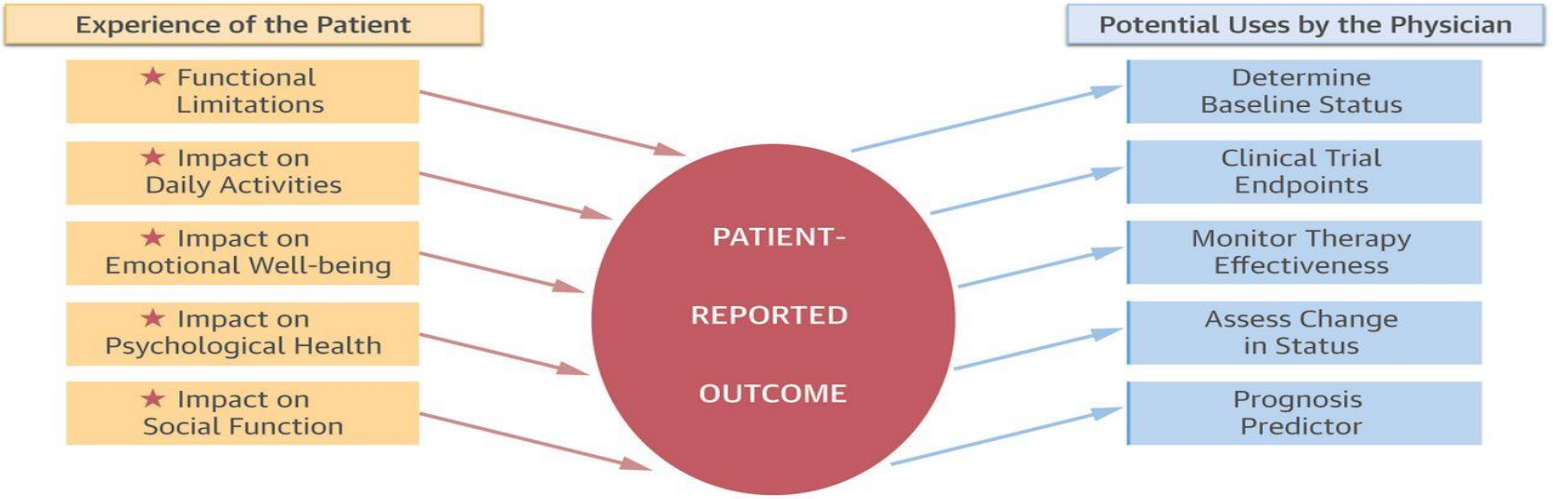
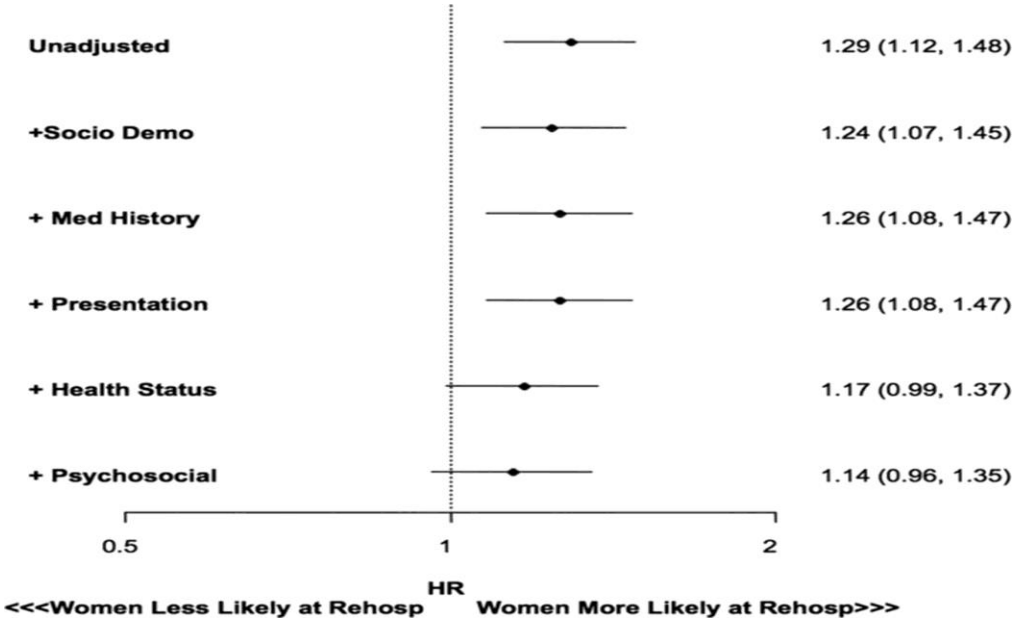


Figure 1 Cumulative probability of 5-year all-cause mortality by sex.



Kelkar, A.A. et al. J Am Coll Cardiol HF. 2016; 4(3):165–75.



Circulation. 2017;135:521-531

Personalized Tailored Medicine in acute coronary syndrome

“The most important change in the management of patients with ACS is likely to come from changing our current “population based” approach to these heterogeneous disorders to a more precise (personalized) approach.

“In this effort, cardiologists will likely take a page from the oncologists’ notebook…”

Eisen A, Braunwald E. JAMA Cardiology 2017