Disclosures: Research Grant and Salary Support, Speaker/Consulting Honorarium

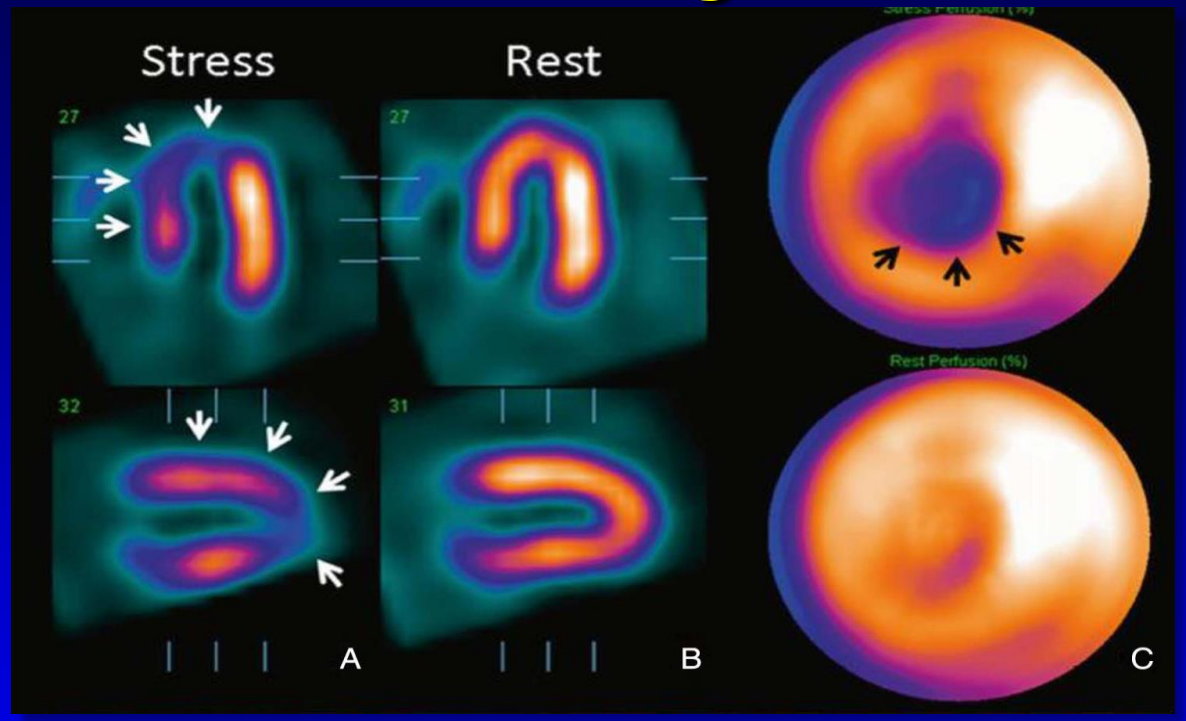
- Research grant support (e.g., steering committee or data and safety monitoring committee) and/or speaker/consulting honoraria (e.g., advisory boards) from:
  - Amgen
  - AstraZeneca
  - Bayer
  - Boehringer Ingelheim
  - Bristol Myers Squibb
  - CSL Behring
  - Daiichi-Sankyo/ American Regent
  - Eli Lilly
  - Esperion
  - Ferring Pharmaceuticals
  - GlaxoSmithKline
  - HLS Therapeutics
  - Janssen/ Johnson & Johnson
  - Merck
  - Novartis
  - Novo Nordisk A/C
  - Pfizer
  - Regeneron
  - Sanofi
  - Servier
- Honoraria and/or Salary support from:
  - Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair
  - Canadian Heart Research Centre and MD Primer
  - Canadian VIGOUR Centre
  - Duke Clinical Research Institute
  - New York University Clinical Coordinating Centre
  - PERFUSE Research Institute

Case

- 54 year old male
- Typical CCS Class I symptoms (slight limitation, with angina only during vigorous physical activity) over the past 3 months
- Prior smoker (quit 5 years ago)
- Hypertension on hydrochlorothiazide and amlodipine
- LDL 4.0 mmol/L, Triglycerides 2.1 mmol/L
- Examination normal apart from BP 152/88 mm Hg
- CBC, Electrolytes, Creatinine and eGFR normal
- Resting 12-lead ECG – non-specific ST-T wave changes
- Primary care physician started ASA, Nitroglycerin spray PRN

Exercise Perfusion Study

- Exercises for 8:30 (Bruce protocol) to a maximal heart rate of 164 beats/min
- Stops due to exertional dyspnea and mild central chest discomfort radiating to the jaw and left arm
- Exercise ECG demonstrates additional 1 mm horizontal ST segment depression in leads II, III, and aVF



- Stress and rest tomographic sestamibi images: moderate-to-large size, moderate-intensity, reversible defect involving the mid- and distal-anterior wall, extending into the apex and distal septum (LAD ischemia ~11% of left ventricle)
- Gated wall motion at rest: very mild apical and distal septal hypokinesis (post-stress) with estimated EF 54%; normal at rest with estimated EF 60%

- 54 year old male with typical CCS Class I symptoms x 3 months
- Multiple risk factors for CAD, including hypertension (not optimally treated) and dyslipidemia (untreated)
- Stress Perfusion study demonstrates moderate (~11% of LV) LAD territory ischemia

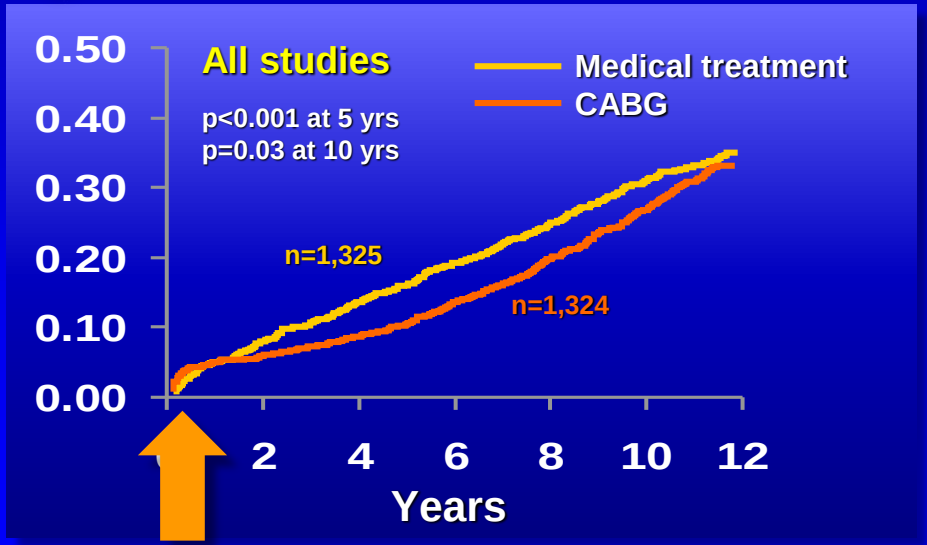
What management strategy would you undertake?

1. Guideline-directed optimal medial therapy (OMT; i.e., ASA, beta-blocker, ACE inhibitor, statin)
2. Cardiac catheterization + OMT → ± coronary revascularization

Impact of Coronary Artery Bypass Graft Surgery (CABG) vs. Initial Medical Therapy in Stable CAD

Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration*

Salim Yusuf, David Zucker, Peter Peduzzi, Lloyd D Fisher, Timothy Takaro, J Ward Kennedy, Kathryn Davis, Thomas Killip, Eugene Passamani, Robin Norris, Cynthia Morris, Virendra Mathur, Ed Varnauskas, Thomas C Chalmers



40 deaths (32%) within 30 days

- 7 trials (1972-84) with 2,649 patients comparing initial CABG with medical therapy in stable CAD
- 94% assigned to surgery underwent CABG vs. 41% in medical group at 10 yrs
- Significantly lower mortality with CABG at 5, 7, and 10 years
  - Greater risk reduction in Left Main vs. 3, 2, or 1 vessel disease
  - Survival extension of 5 months in moderate-risk and 8.8 months in high-risk groups
  - In low-risk patients: non-significant trend towards greater mortality with CABG

Yusuf et al *Lancet* 1994;344:563-70

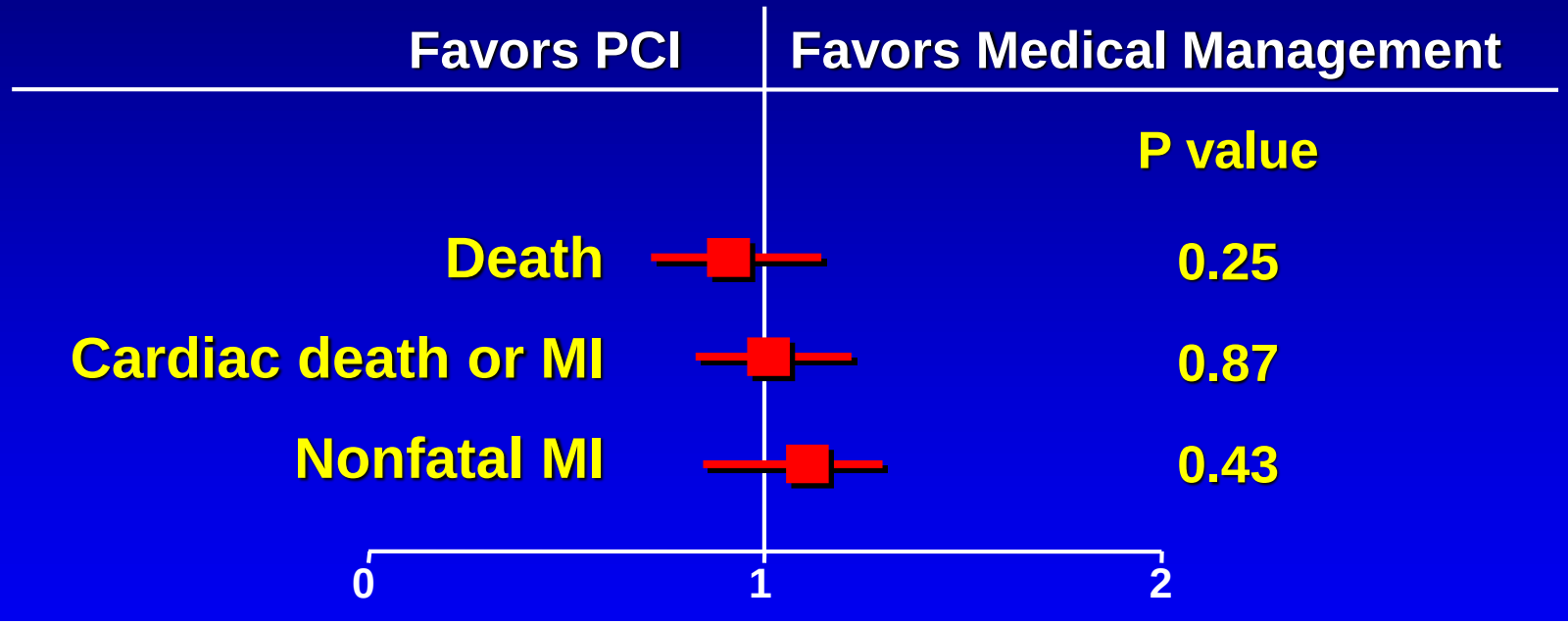
CABG vs. Medical Therapy: Limitations

- Very few patients enrolled in the randomized trials
- Medical therapy did not often include antiplatelet agents (ASA 3.2%), angiotensin-converting-enzyme (ACE) inhibitors or receptor blockers (ARBs), beta-blockers (47.4%), statins, or

Thus, the relevance of historic CABG vs. medical therapy trials today is uncertain

Stable CAD: PCI vs. Conservative Medical Management

Revised Meta-analysis of 13 randomized trials (n=5,442)



In patients with chronic stable CAD (in the absence of a recent MI), PCI does NOT offer any benefit in terms of death, MI, or the need for subsequent revascularization vs. conservative medical treatment

Katritsis & Ioannidis *N Engl J Med* 2007;357:414-15

ISCHEMIA Trial

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

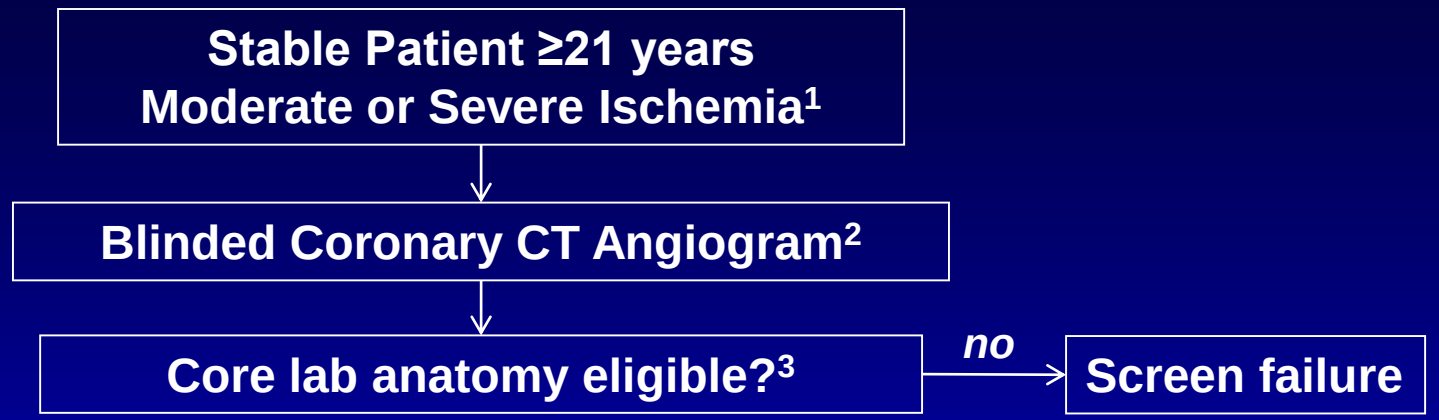
National Heart Lung and Blood Institute

NIH National Heart, Lung, and Blood Institute

ISCHEMIA Trial Research Question

- In stable patients with at least moderate ischemia on a stress test, is there a benefit to adding cardiac catheterization and, if feasible, revascularization to optimal medical therapy?

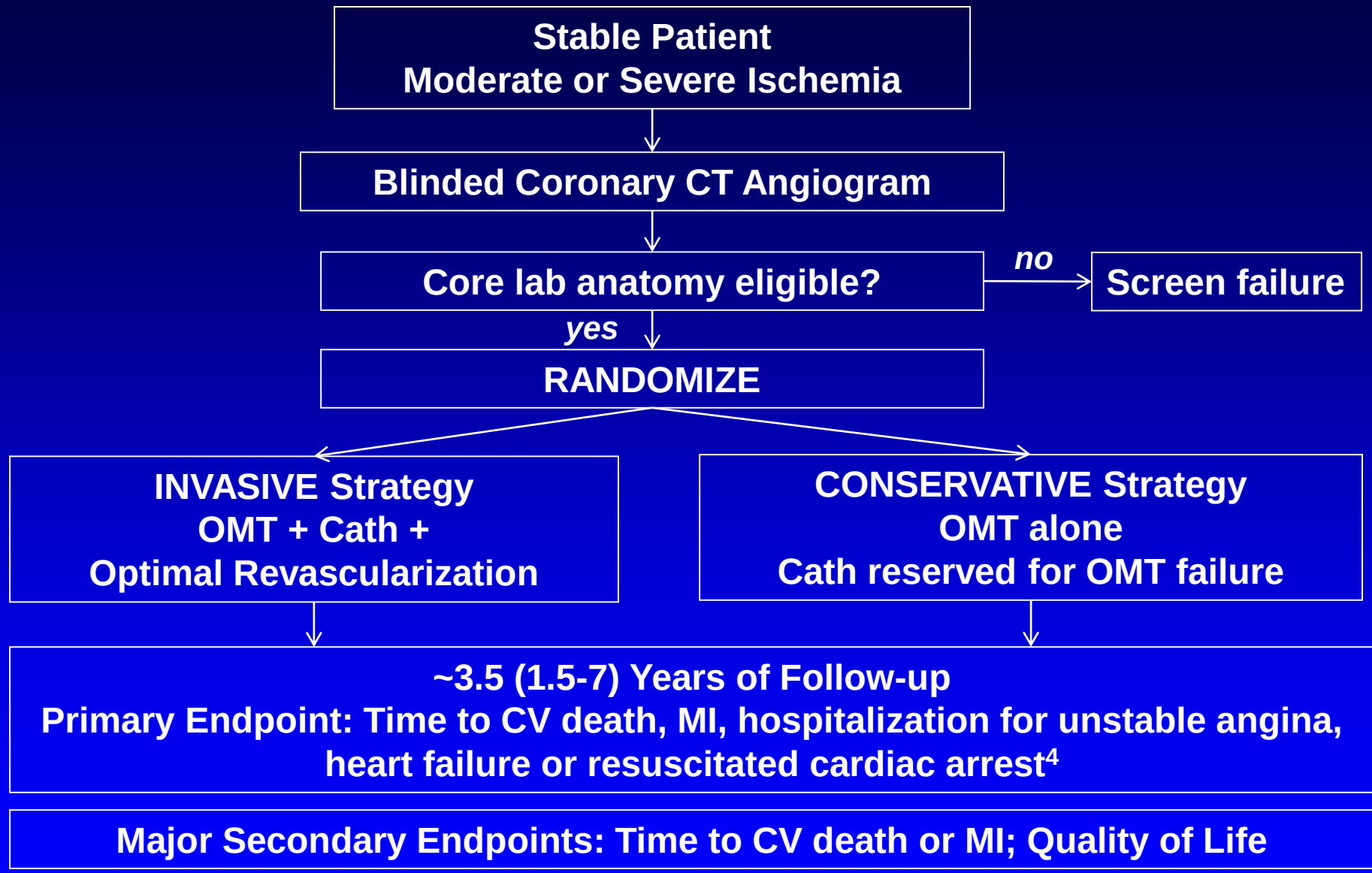
Maron et al *Am Heart J* 2018;201:124-135



[1] Nuclear Perfusion, Stress Echocardiography, Stress Cardiac MRI, or Exercise Treadmill Testing (without imaging)

[2] Coronary CT Angiogram performed in all patients with eGFR ≥60 mL/min to [3]exclude patients with Left Main disease or no obstructive disease

Maron et al *Am Heart J* 2018;201:124-135



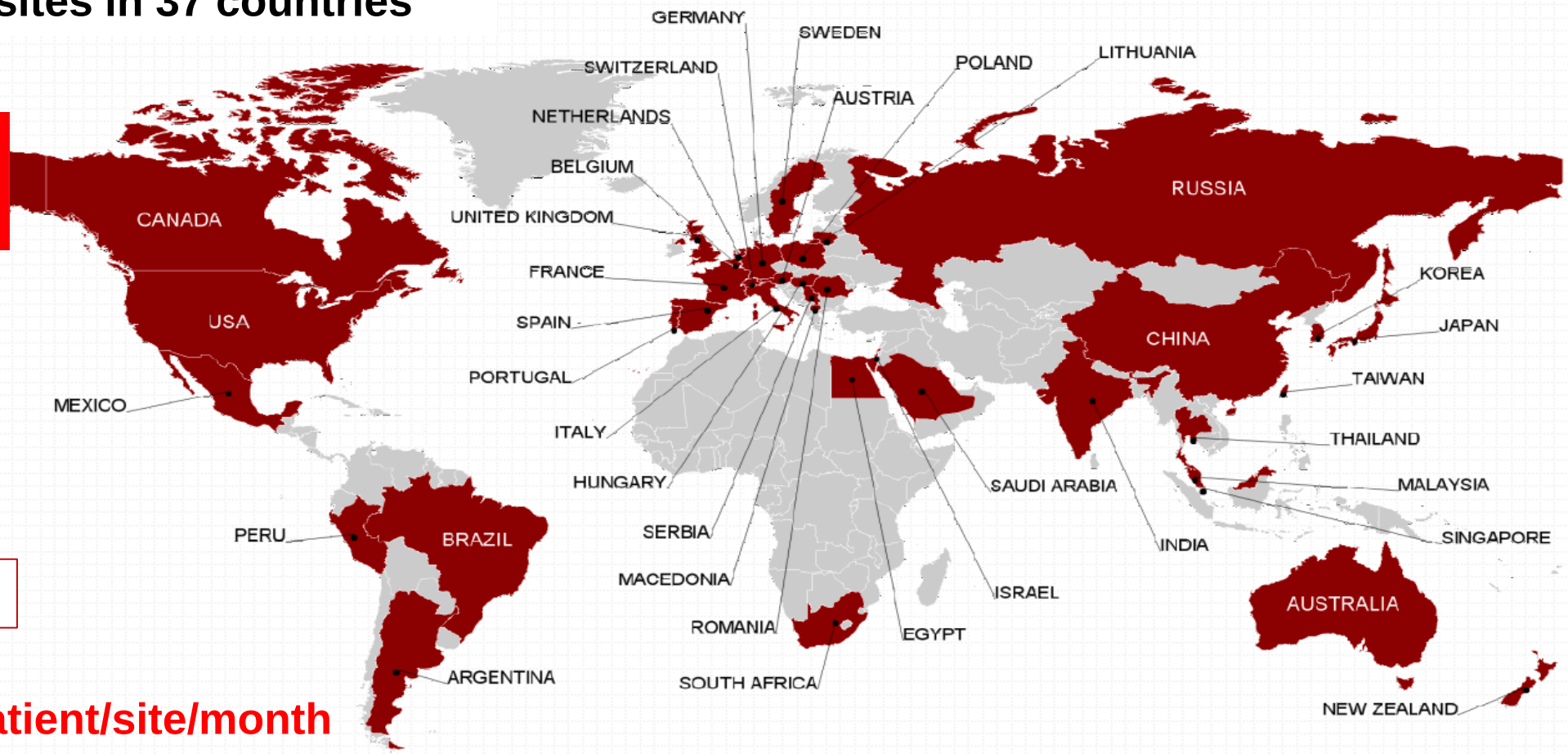
[4]Sample size estimation: Conservative vs. Invasive (16% vs. 13% at 4 years); 18.5% RRR; two-sided alpha=0.05; >80% power)

Maron et al *Am Heart J* 2018;201:124-135

320 sites in 37 countries

CANADIAN HEART RESEARCH CENTRE

19 sites



~1 patient/site/month

Final Country Leaderboard										
India:	941	Poland:	333	Singapore:	61	Mexico:	46	Portugal:	33
United States:	853	Russia:	303	Germany:	54	Australia:	45	Argentina:	29
United Kingdom:	539	Spain:	286	Austria:	50	France:	42	New Zealand:	28
Canada:	447	China:	246	Hungary:	49	Lithuania:	39	Macedonia:	28
Brazil:	399	Italy:	139	Serbia:	47	Netherlands:	37	Sweden:	23

ISCHEMIA

ISCHEMIA* Canada

Country Leaders: Vladimir Dzavik, Gilbert Gosselin, and Shaun Goodman
***CKD Country Leaders: Akshay Bagai, Kevin Bainey, and Ron Wald**

Gilbert Gosselin - Montreal Heart Institute
Ariel Diaz – Centre Hospitalier de Regional Trois-Rivieres*
Denis Carl Phaneuf – Höpital Pierre-Le Gardeur
Pallav Garg – London Health Sciences Centre*
Benjamin Chow – University of Ottawa Heart Institute
Kevin Bainey – University of Alberta Hospital*
Asim Cheema – St. Michael's Hospital*
Asim Cheema - Dixie Medical Group
James Cha – Oshawa
Andrew Howarth – U. of Calgary Foothills Medical Centre
Graham Wong – Vancouver General Hospital*
Amar Uxa – University Health Network*
Paul Galiwango – Scarborough Cardiology Research
Andy Lam – West Lincoln Memorial Hospital
Shamir Mehta – Hamilton General Hospital
Jacob Udell – Women's College Hospital
Philippe Généreux – Höpital du Sacré-Coeur de Montréal*
Adnan Hameed – St. Catharines General Hospital
Lejalem Daba – Northwest GTA CV & Heart Rhythm Program

*ISCHEMIA CKD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 9, 2020 VOL. 382 NO. 15

Published online March 30, 2020

Initial Invasive or Conservative Strategy for Stable Coronary Disease

D.J. Maron, J.S. Hochman, H.R. Reynolds, S. Bangalore, S.M. O'Brien, W.E. Boden, B.R. Chaitman, R. Senior, J. López-Sendón, K.P. Alexander, R.D. Lopes, L.J. Shaw, J.S. Berger, J.D. Newman, M.S. Sidhu, S.G. Goodman, W. Ruzyllo, G. Gosselin, A.P. Maggioni, H.D. White, B. Bhargava, J.K. Min, G.B.J. Mancini, D.S. Berman, M.H. Picard, R.Y. Kwong, Z.A. Ali, D.B. Mark, J.A. Spertus, M.N. Krishnan, A. Elghamaz, N. Moorthy, W.A. Hueb, M. Demkow, K. Mavromatis, O. Bockeria, J. Peteiro, T.D. Miller, H. Szwed, R. Doerr, M. Keltai, J.B. Selvanayagam, P.G. Steg, C. Held, S. Kohsaka, S. Mavromichalis, R. Kirby, N.O. Jeffries, F.E. Harrell, Jr., F.W. Rockhold, S. Broderick, T.B. Ferguson, Jr., D.O. Williams, R.A. Harrington, G.W. Stone, and Y. Rosenberg, for the ISCHEMIA Research Group*

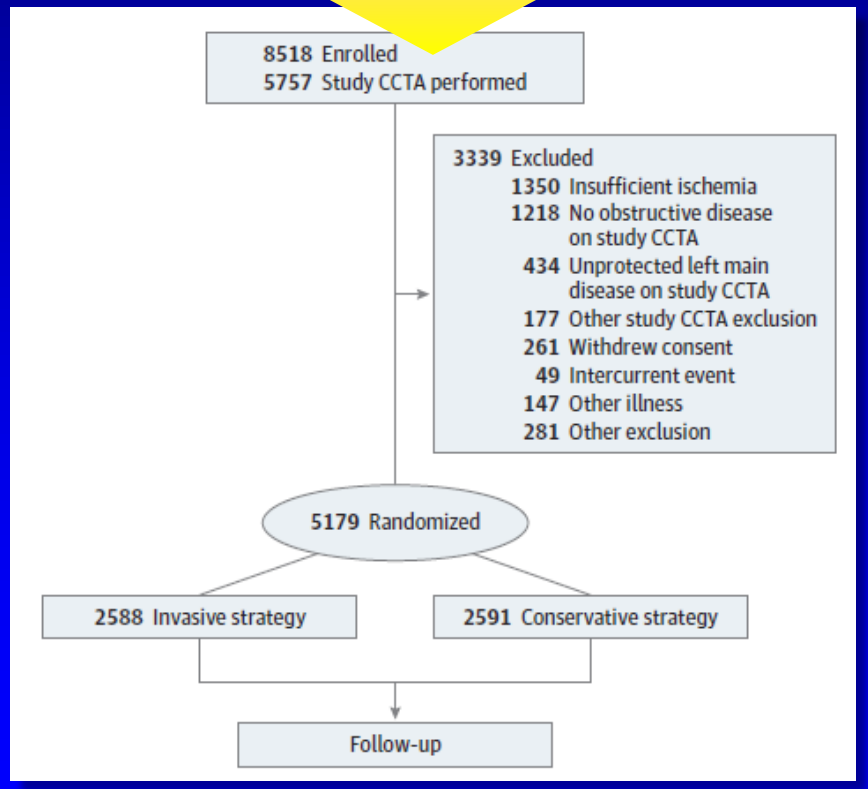
Maron et al *N Engl J Med* 2020;382:1395-407

Participant Flow From Enrollment to Randomization

n~26,000 stress test reports screened*

Stable CAD with moderate-to-severe ischemia

* All enrolling sites reported screening data for time-limited periods of variable duration



Selected Exclusion Criteria:

- LV Ejection Fraction <35%
- Unacceptable level of angina despite maximal medical therapy
- Very dissatisfied with medical management of angina
- Significant Left Main Disease (≥50%)
- ACS within the previous 2 months
- PCI within the previous 12 months
- Prior CABG
- Coronary anatomy unsuitable for revascularization
- eGFR < 30 ml/min

Hochman et al *JAMA Cardiol* 2019;4:273-86

Selected Baseline Characteristics

	Randomized (n=5,179)
Age, years*	64 (58, 70)
Female, %	23
White/Asian, %	66/29
Hypertension, %	73
Diabetes, %	41
Previous MI, %	19
Previous PCI, %	20
History/hospital. HF, %	4/1
Ejection Fraction, %*	60 (55, 65)
History of CeVD, %	7
History of PAD, %	4
eGFR, ml/min*	81 (67, 97)
History of angina/>prior 3 months, %	90/26
Stress imaging, %	75
Exercise tolerance test, %	25

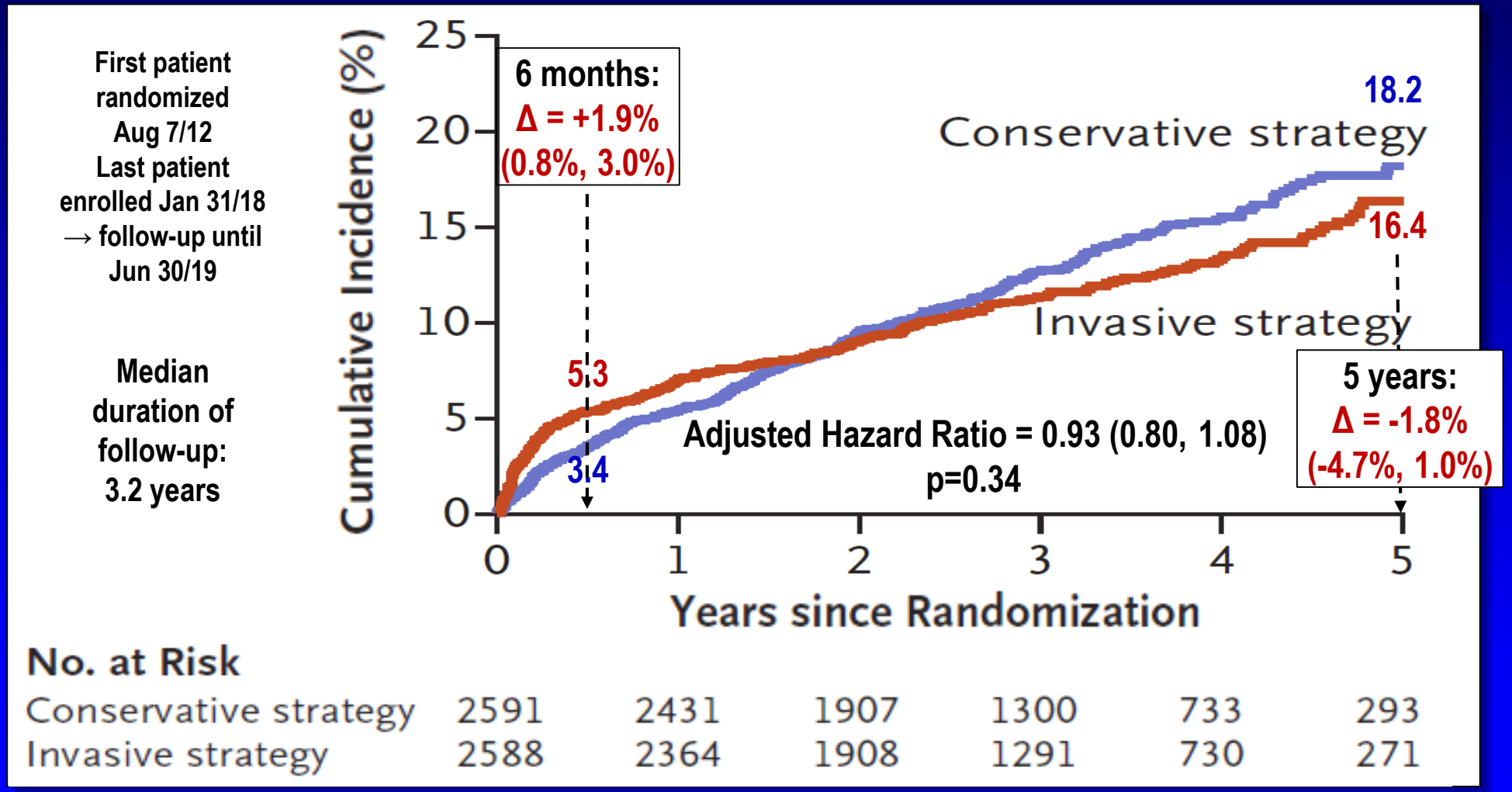
*Median (25, 75th percentiles)

Hochman et al *JAMA Cardiol* 2019;4:273-86 and Maron et al *N Engl J Med* 2020;382:1395-407

Primary Outcome: CV Death, MI, Hospitalization for Unstable Angina, HF, or Resuscitated Cardiac Arrest

First patient randomized Aug 7/12
Last patient enrolled Jan 31/18
→ follow-up until Jun 30/19

Median duration of follow-up: 3.2 years



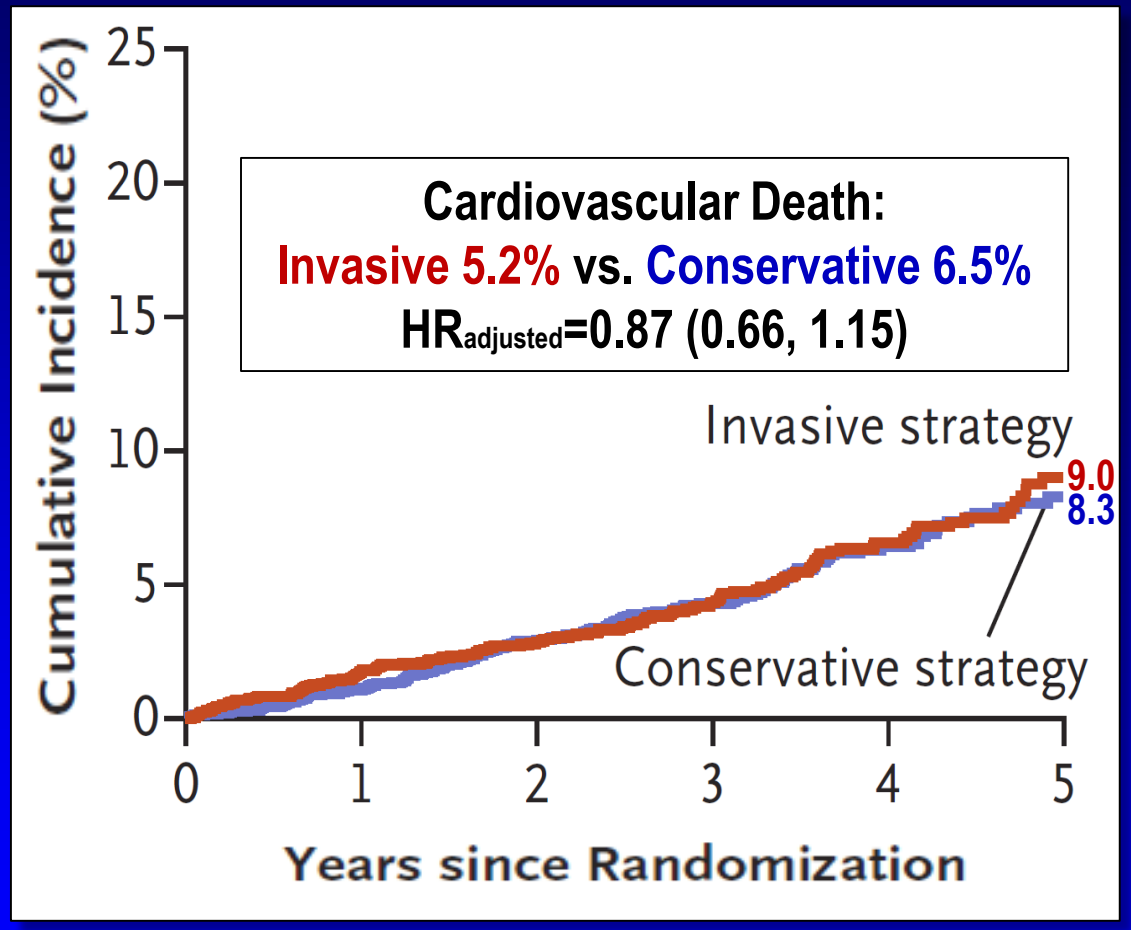
No. at Risk

Conservative strategy	2591	2431	1907	1300	733	293
Invasive strategy	2588	2364	1908	1291	730	271

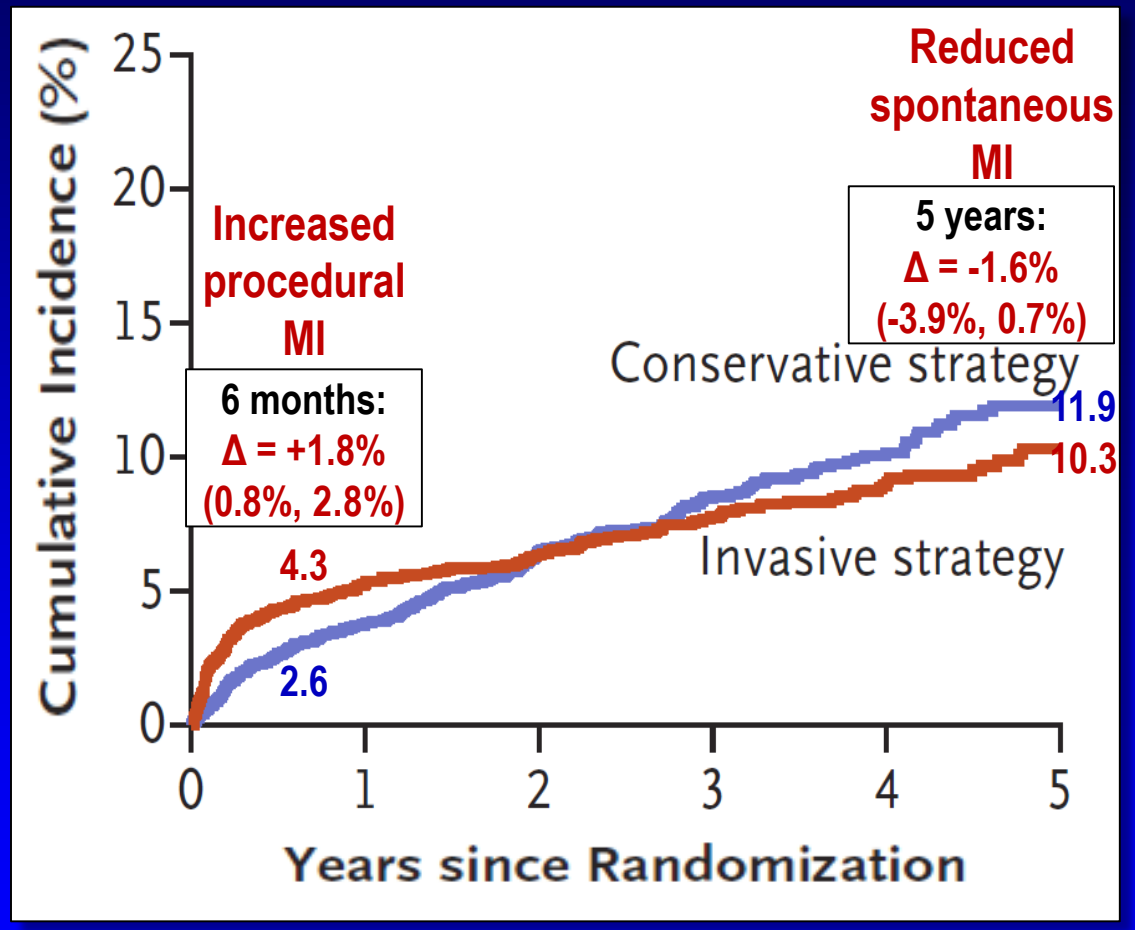
Maron et al *N Engl J Med* 2020;382:1395-407

Key Secondary Outcomes

Death from Any Cause



Myocardial Infarction



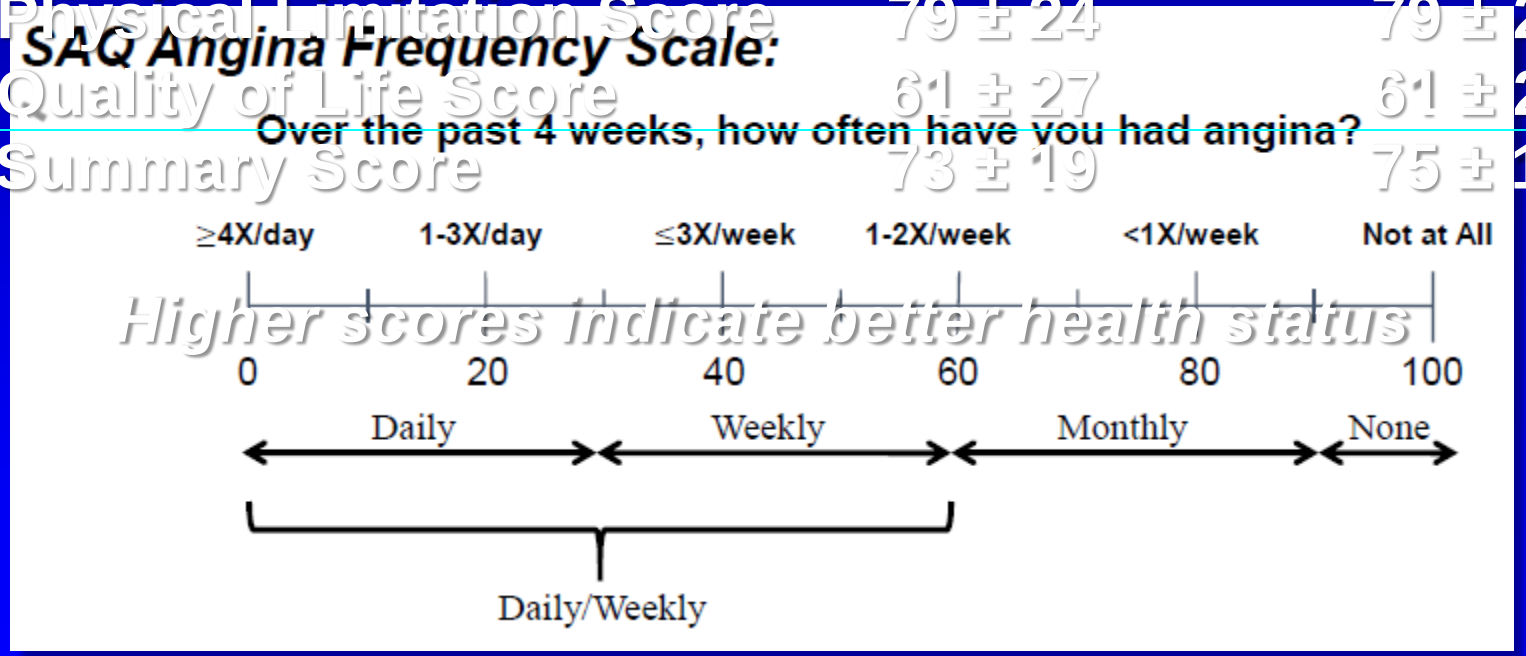
Maron et al *N Engl J Med* 2020;382:1395-407

Goals of Treatment

- Reduce morbidity and mortality
  - Help people have fewer heart attacks and live longer
- Relief of symptoms
  - Make people feel better

Angina Frequency and Seattle Angina Questionnaire (SAQ)

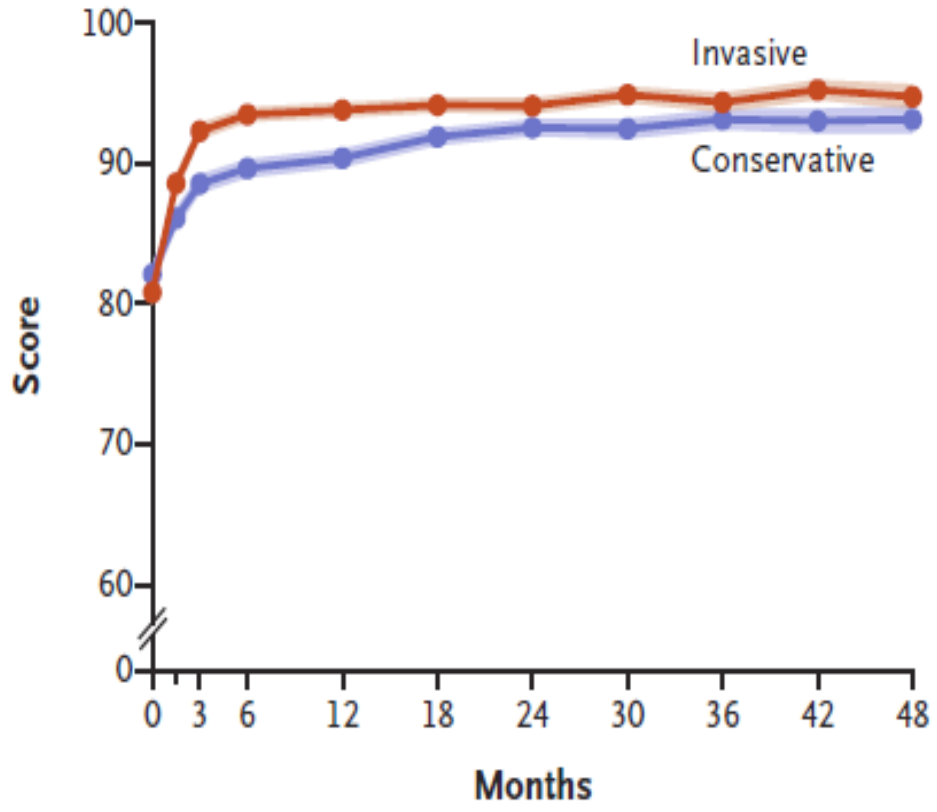
	Invasive	Conservative
Daily/Weekly Angina	22%	19%
Several times per month	44%	46%
No Angina	34%	37%
SAQ Angina Frequency Score	81 ± 20	82 ± 19
SAQ Physical Limitation Score	79 ± 24	79 ± 24
SAQ Quality of Life Score	61 ± 27	61 ± 27
SAQ Summary Score	73 ± 19	75 ± 19



Spertus et al *N Engl J Med* 2020;382:1408-19

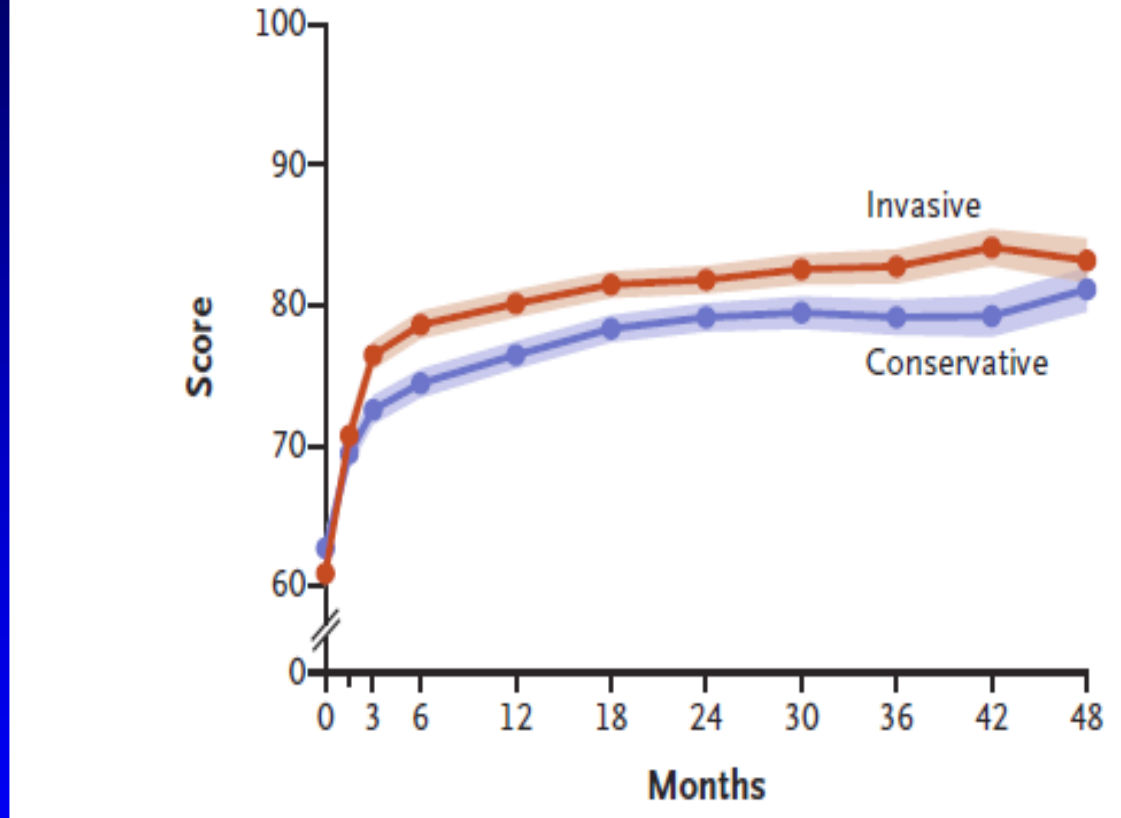
Crude Mean Health-Status Scores

SAQ Angina Frequency Score



No. at Risk									
Invasive	2292	2177	2146	2080	1821	1470	1229	966	735
Conservative	2320	2212	2168	2117	1831	1482	1264	982	747

SAQ Quality of Life Score

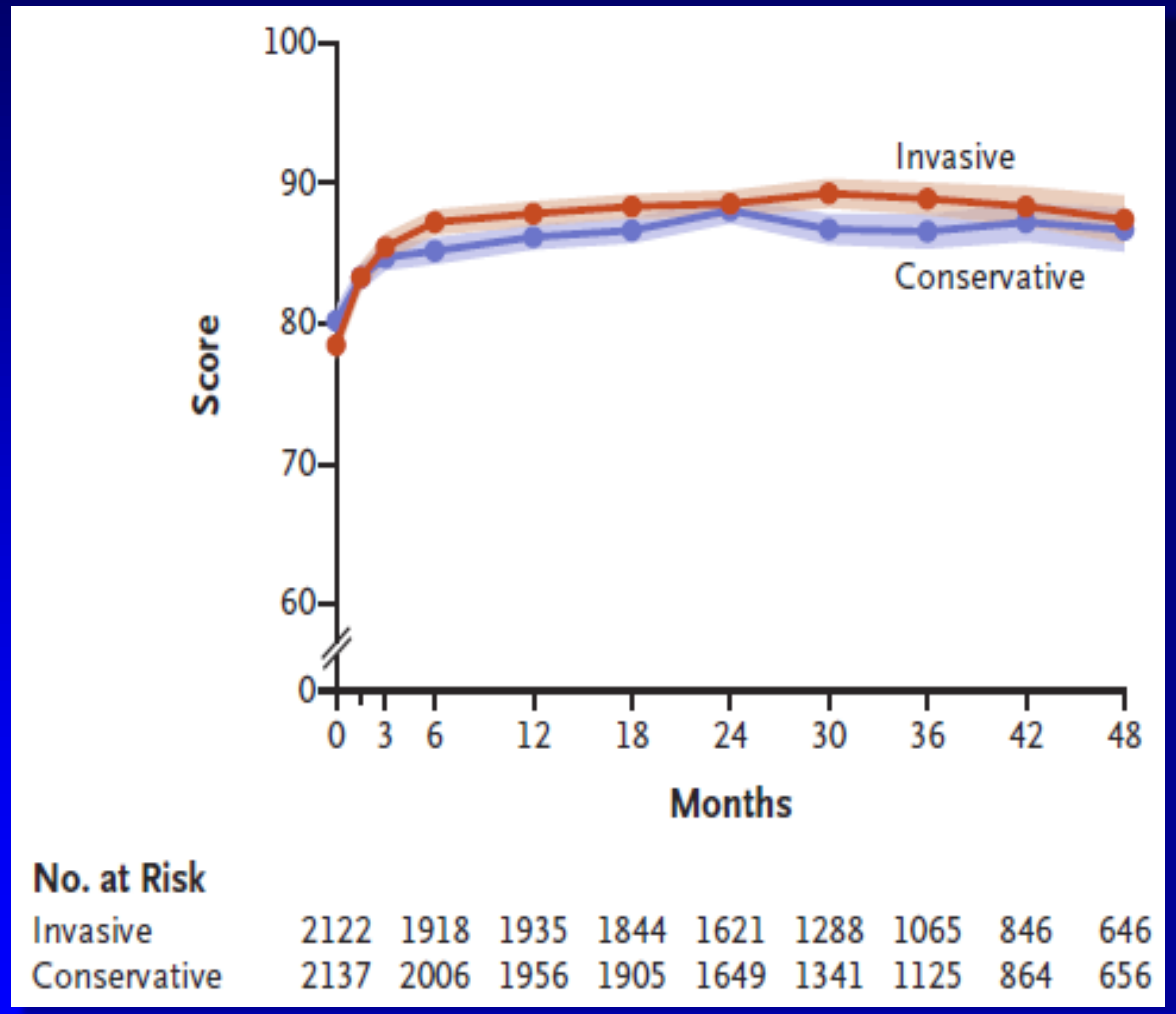


No. at Risk									
Invasive	2286	2171	2145	2077	1816	1467	1227	960	731
Conservative	2320	2210	2166	2116	1831	1481	1262	977	745

Spertus et al *N Engl J Med* 2020;382:1408-19

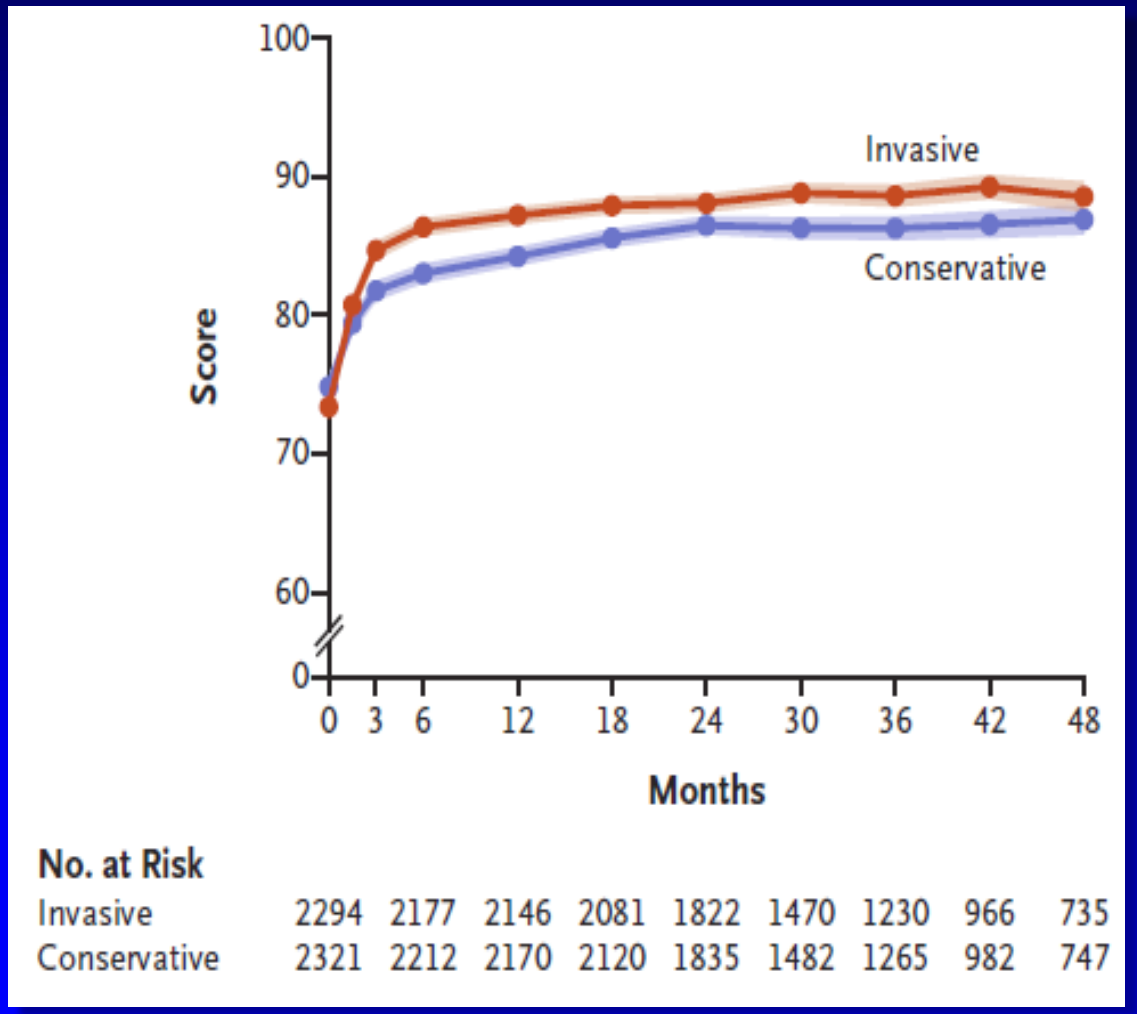
Crude Mean Health-Status Scores

SAQ Physical Limitation Score



No. at Risk									
Invasive	2122	1918	1935	1844	1621	1288	1065	846	646
Conservative	2137	2006	1956	1905	1649	1341	1125	864	656

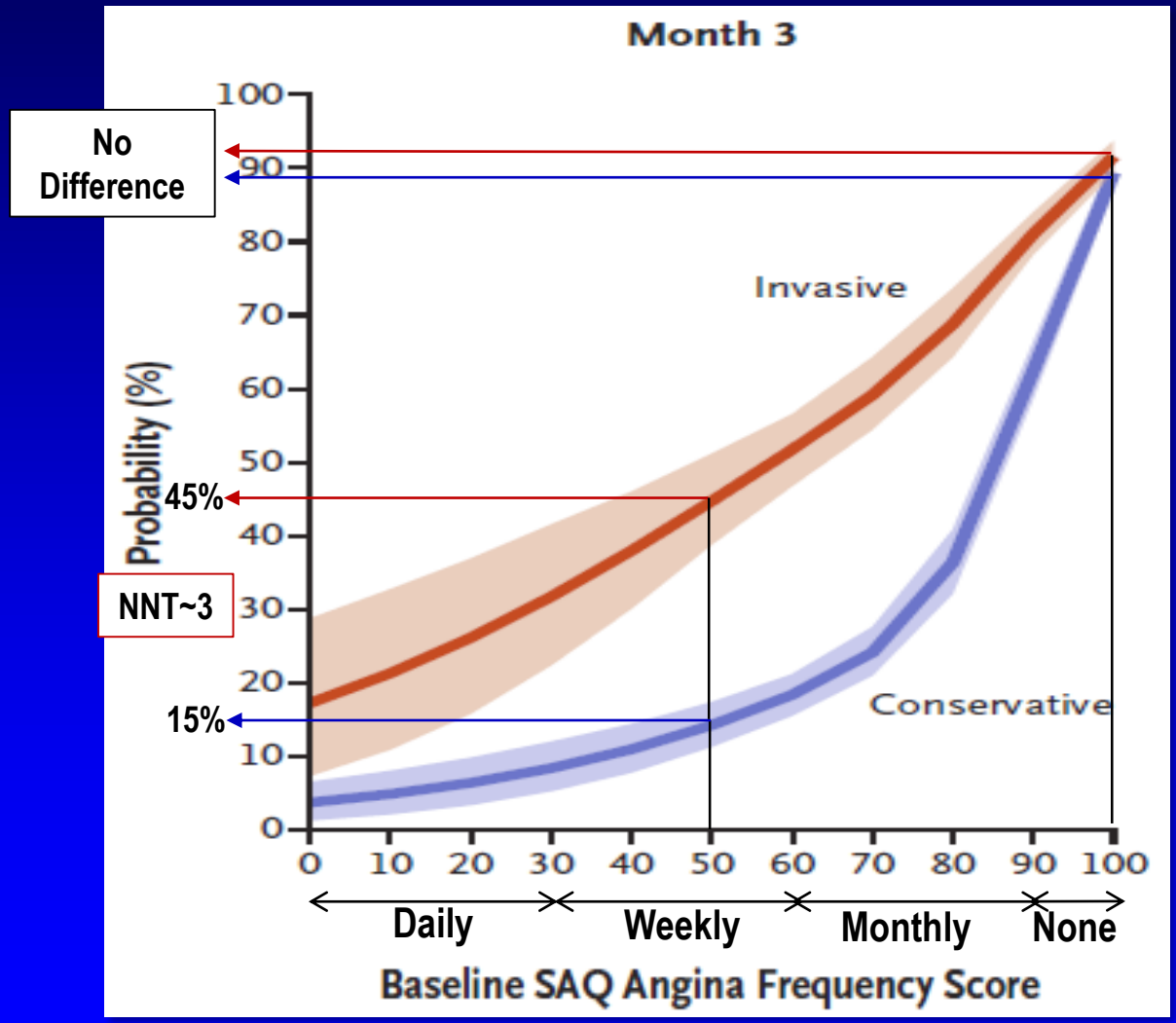
SAQ Summary Score



No. at Risk									
Invasive	2294	2177	2146	2081	1822	1470	1230	966	735
Conservative	2321	2212	2170	2120	1835	1482	1265	982	747

Spertus et al *N Engl J Med* 2020;382:1408-19

Probability of Being Angina-Free as a Function of Baseline Angina Frequency



Spertus et al *N Engl J Med* 2020;382:1408-19

Conclusions

- ISCHEMIA is the largest trial of an invasive vs. conservative strategy for patients with stable ischemic heart disease
- Overall, an initial Invasive as compared with an initial Conservative strategy did not demonstrate a reduced risk over median 3.2 years for
  - Primary endpoint - CV death, MI, hospitalization for UA, HF, resuscitated cardiac arrest
  - Major Secondary endpoint - CV death or MI
- Significant, durable improvements in angina control and quality of life with an invasive strategy if patients had angina (daily/weekly or monthly)
  - In patients without angina (35%), an invasive strategy led to minimal symptom or QoL benefits, as compared with a conservative strategy
- In patients with angina, shared decision-making should occur to align treatment with patients' goals and preferences

Maron et al *N Engl J Med* 2020;382:1395-407 and Spertus et al *N Engl J Med* 2020;382:1408-19

- 54 year old male with typical CCS Class I symptoms x 3 months
- Multiple risk factors for CAD, including hypertension (not optimally treated) and dyslipidemia (untreated)
- Stress Perfusion study demonstrates moderate (~11% of LV) LAD territory ischemia

What management strategy would you undertake?

1. Guideline-directed optimal medial therapy (OMT; i.e., ASA, beta-blocker, ACE inhibitor, statin)
2. Cardiac catheterization + OMT → ± coronary revascularization

Canadian Cardiovascular Society

Tips, pitfalls and red flags for family physicians caring for patients with cardiovascular disease during the COVID-19 pandemic

Chronic Chest Pain Syndromes

- Patients with stable chest pain with a moderate to high probability of obstructive coronary disease may benefit from a functional or anatomic test for diagnosis and prognosis (~~exercise treadmill test~~, nuclear stress test, or coronary CT angiography)

  Dipyridamole (Persantine)

- Consider referral to Cardiology prior to initiating testing to determine the highest yield test and to minimize unnecessary testing

Guidance from the CCS COVID-19 Rapid Response Task Force (April 15, 2020)