ISCHEMIA Trial: Stents or Meds?

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ISCHEMIA Trial: Summary

- 5179 patients randomized to INV vs. CON
  - *Largest treatment strategy trial of SIHD*
- Enrolled high-risk subset
  - *54% severe ischemia; 76% with multivessel CAD; 47% with proximal LAD disease (CCTA)*
- Cath and Revascularization
  - *Invasive strategy: 80% revascularized (74% PCI/26% CABG)*
  - *Conservative strategy: 28% cath; 23% revasc at 4-years*
- Medication Therapy
  - *95% statins; 66% high intensity statin; LDL 64 mg/dl; SBP 129 mm Hg*

Which Patients were Not Enrolled in ISCHEMIA?

- ACS within 2 months
- EF < 35%
- NYHA Class III-IV HF
- Unacceptable angina despite medical therapy
- PCI or CABG within 1 year
- Severe left main disease

Potential Reasons for Revascularization in SIHD

- To improve survival
- To prevent other cardiovascular events
- To improve quality of life

Revascularization to Improve Survival in SIHD

- Overall cohort
- High risk subgroups
  - Left main disease
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

Contemporary Revascularization vs. Medicine SIHD Trials

No difference in mortality

2007

COURAGE

No difference in death

2009

BARI 2D

A WINDOW OF OPPORTUNITY FOR COORDINATED CARE

No difference in death

2012

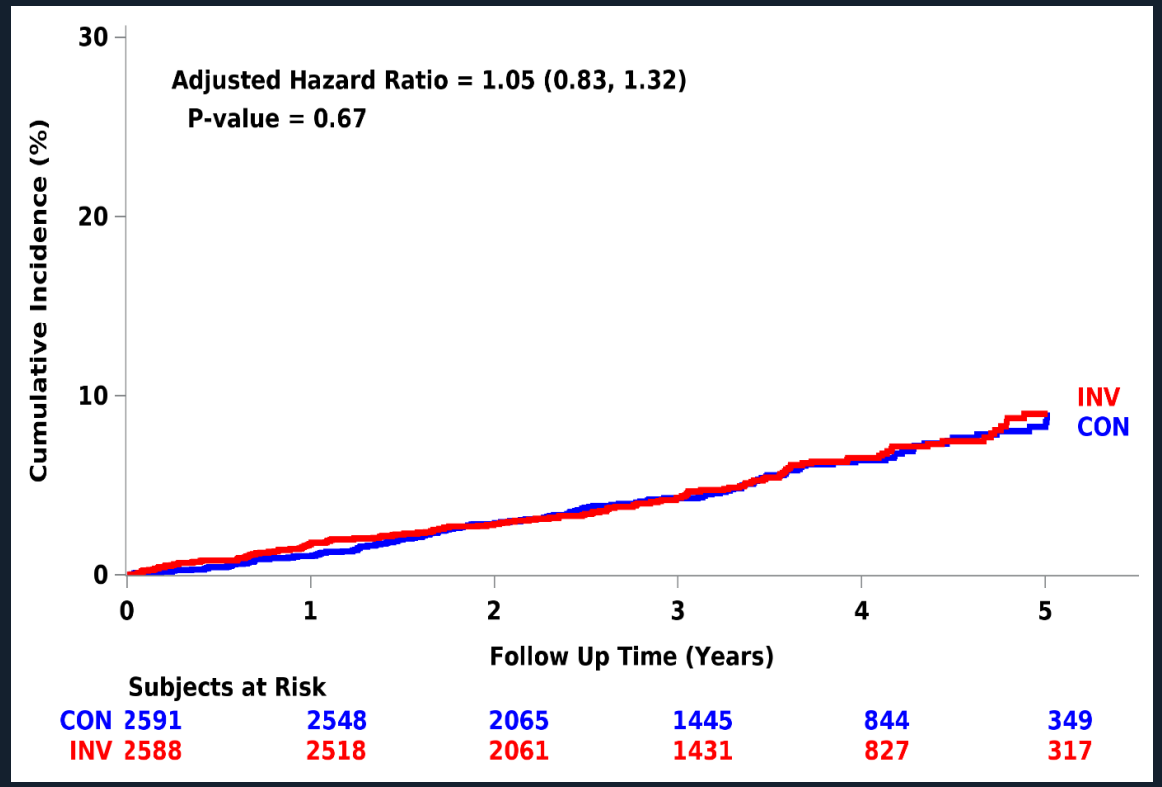
FAME 2 Trial

No difference in death

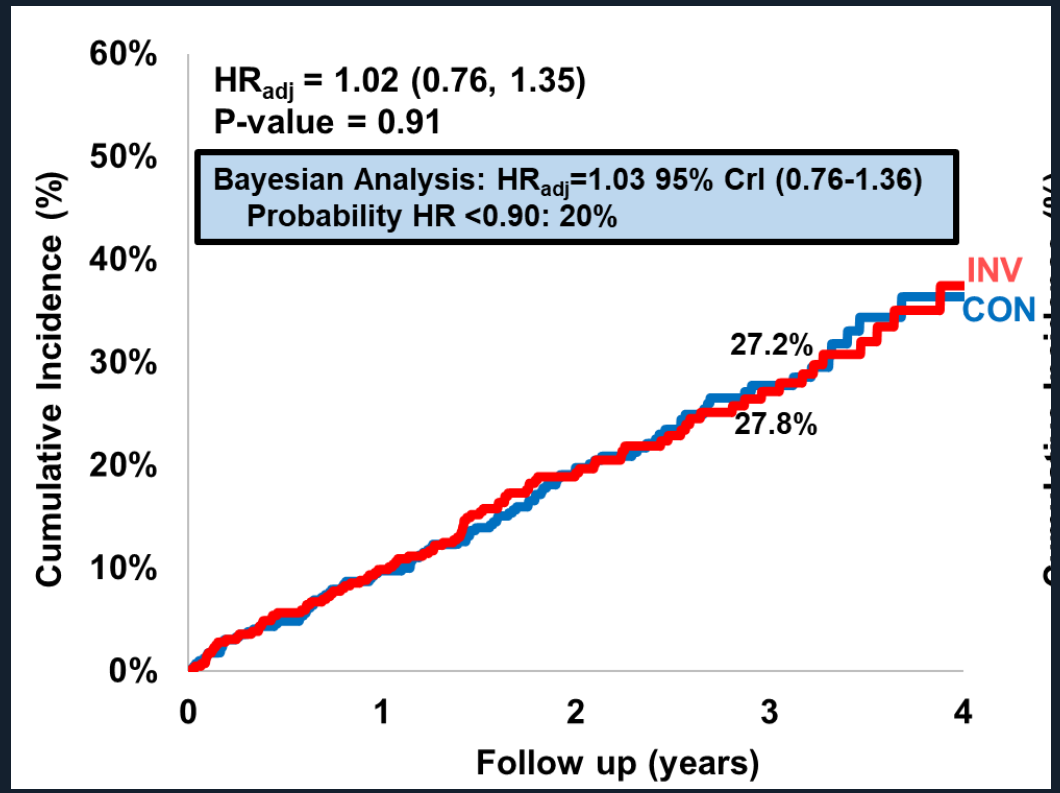
ISCHEMIA and ISCHEMIA-CKD trials

No difference in mortality

ISCHEMIA



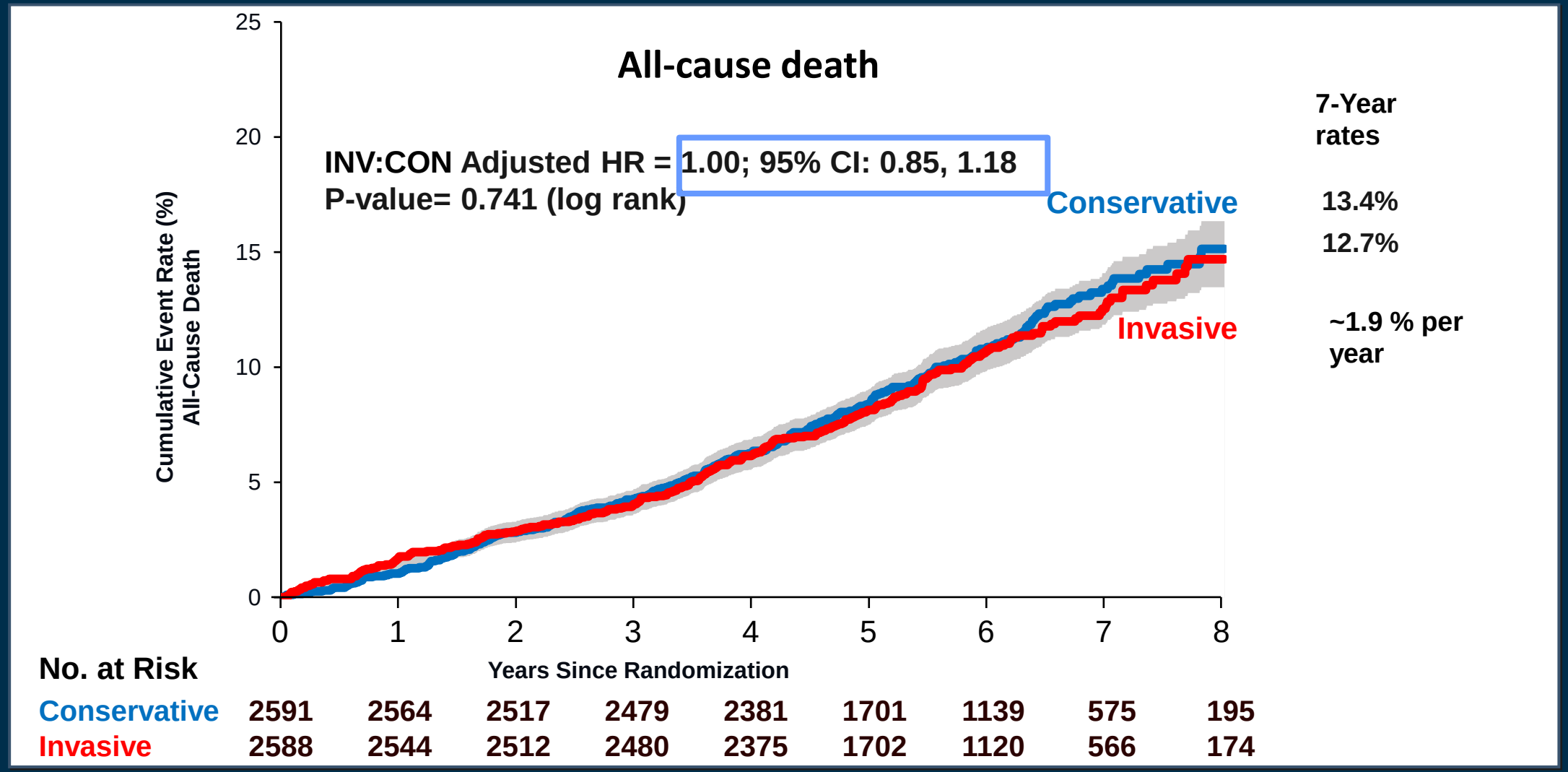
ISCHEMIA-CKD



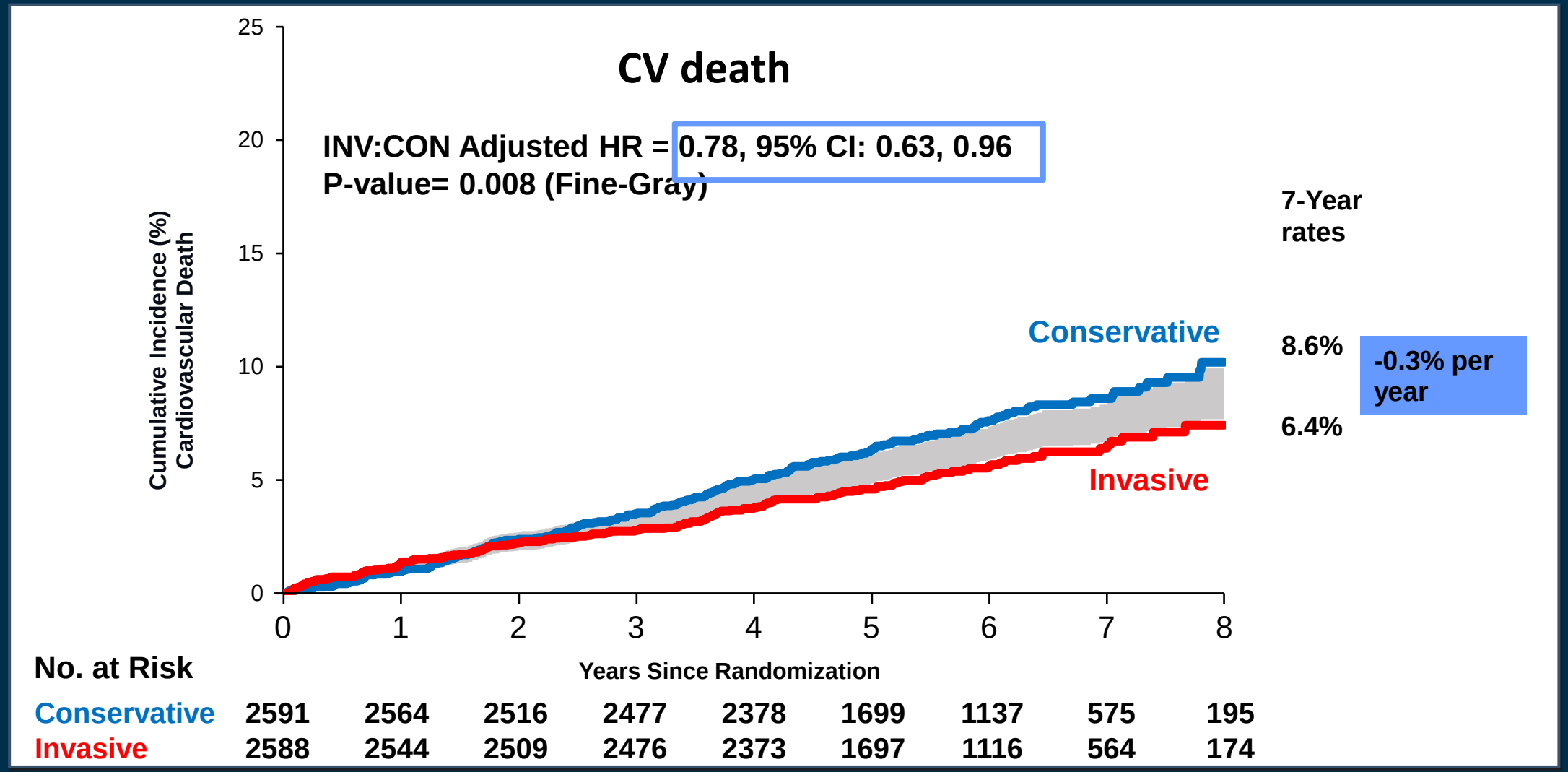
Maron et al. N Engl J Med. 2020 Apr 9;382(15):1395-1407

Bangalore et al. N Engl J Med. 2020;382(17):1608-1618

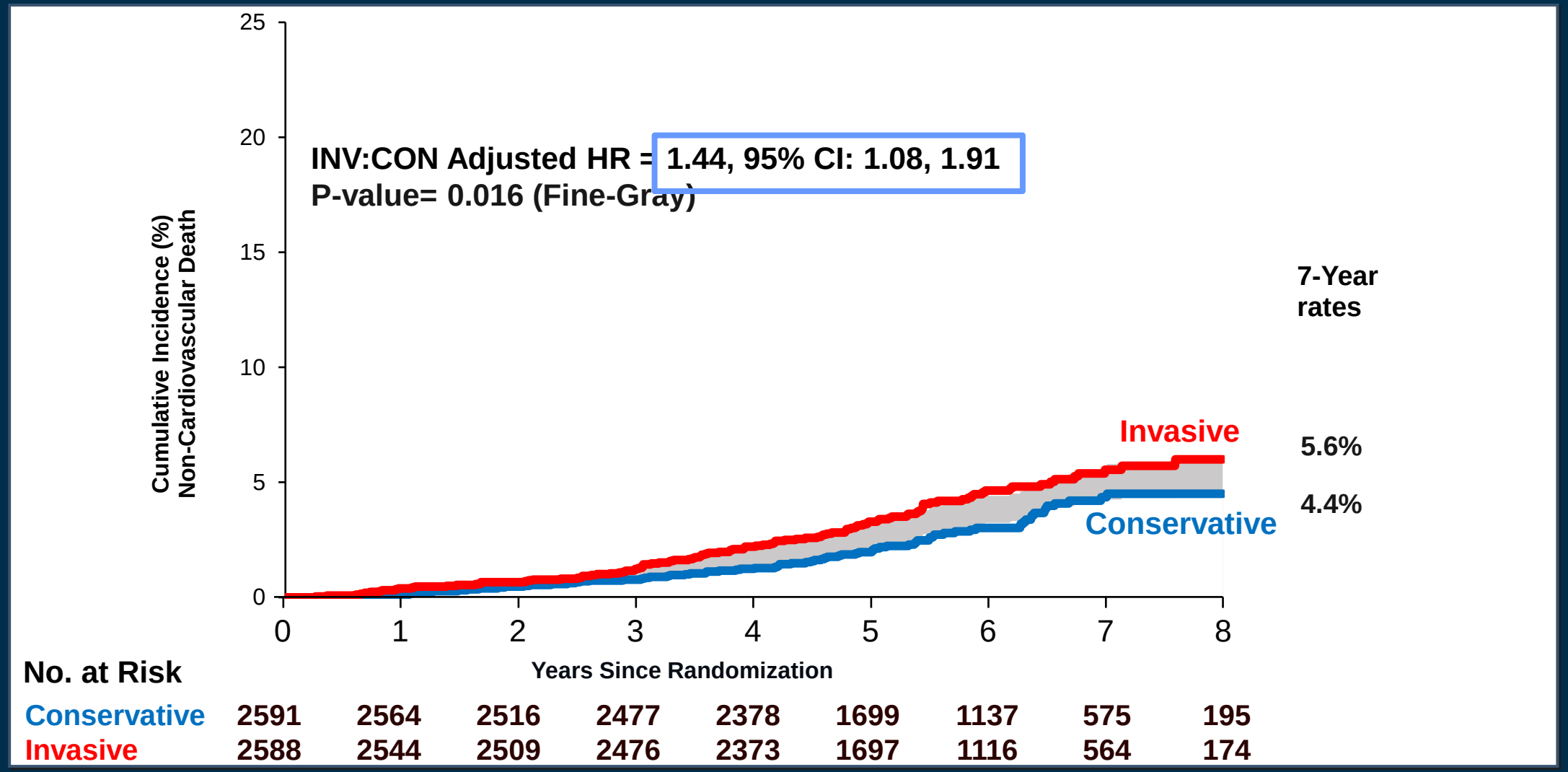
ISCHEMIA EXTEND: All-cause death



ISCHEMIA EXTEND: CV death



ISCHEMIA EXTEND: Non CV death



Revascularization to Improve Survival in SIHD

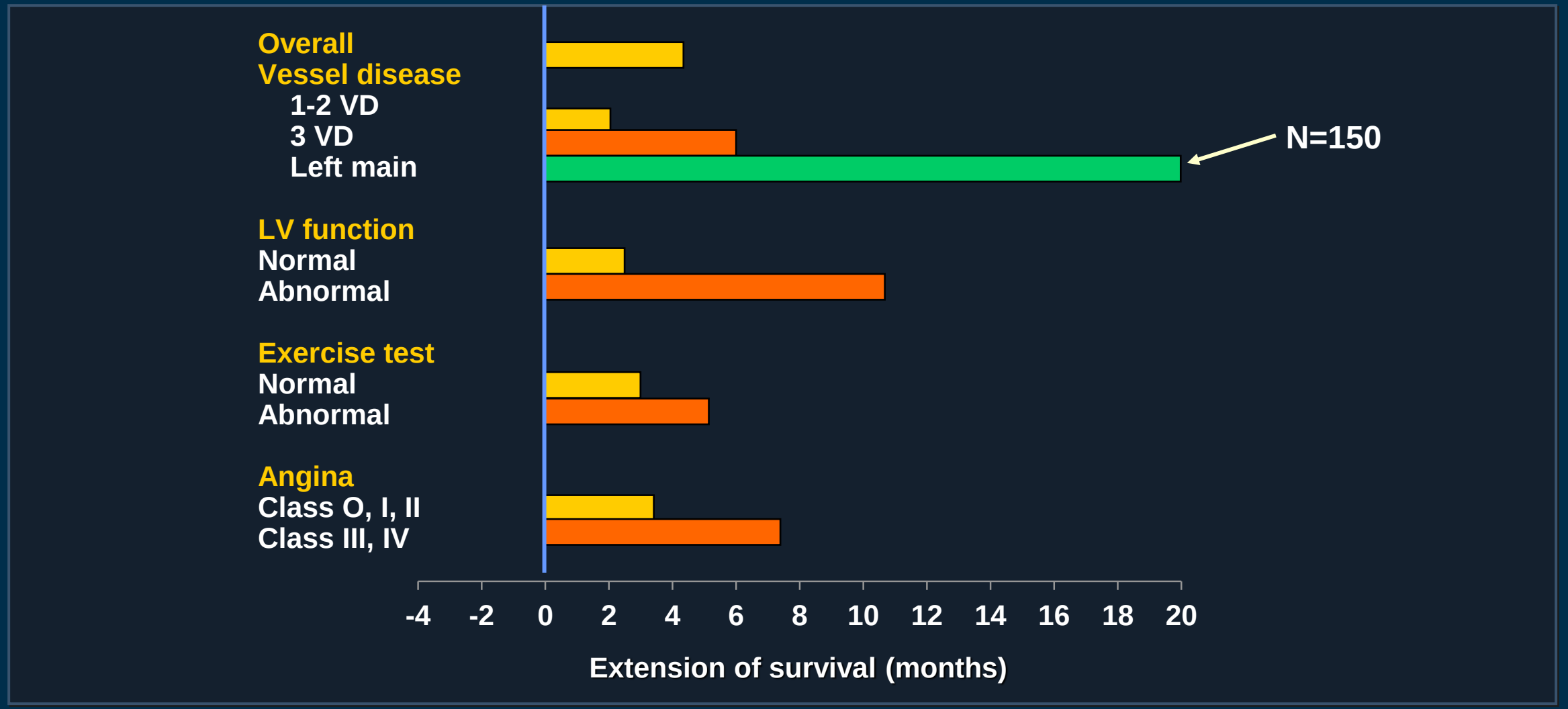
- Overall cohort
  - *Similar survival compared with MT*
  - *Small reduction (0.3%/year) in cardiac death*
- High risk subgroups
  - Left main disease
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

Revascularization to Improve Survival in SIHD

- Overall cohort
- High risk subgroups
  - Left main disease
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

Extension of Survival in Left Main Disease with Revascularization

CABG vs. No CABG trials-1980s



Yusuf et al. Lancet 1994;344:563-570.

Revascularization to Improve Survival in High Risk Subgroups

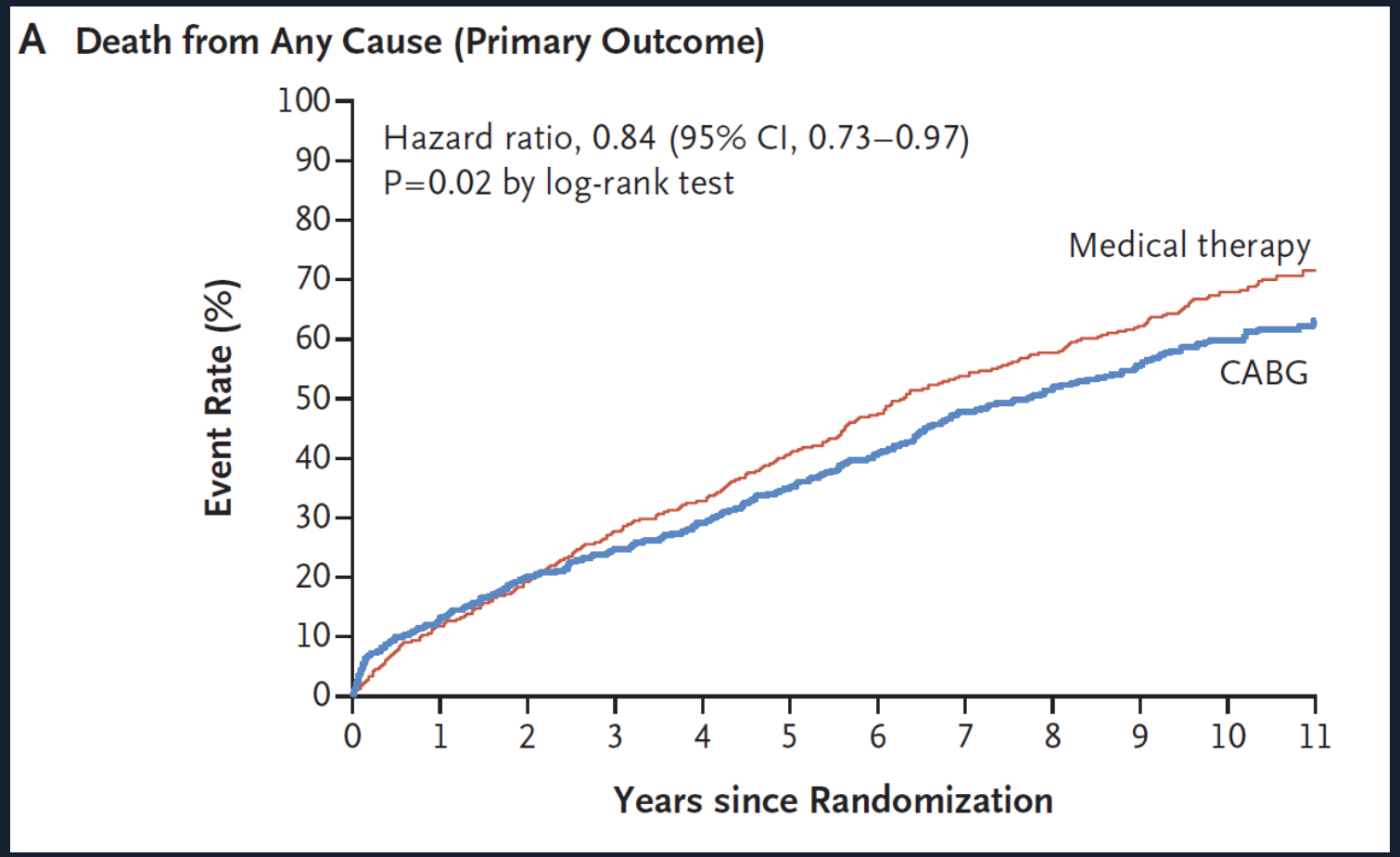
- Overall cohort
- High risk subgroups
  - Left main disease. *Revasc vs. Med: Survival benefit of CABG (older trials-150 patients)*
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

Revascularization to Improve Survival in SIHD

- Overall cohort
- High risk subgroups
  - Left main disease
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

Extension of Survival in LV Dysfunction with Revascularization

STICHES trial



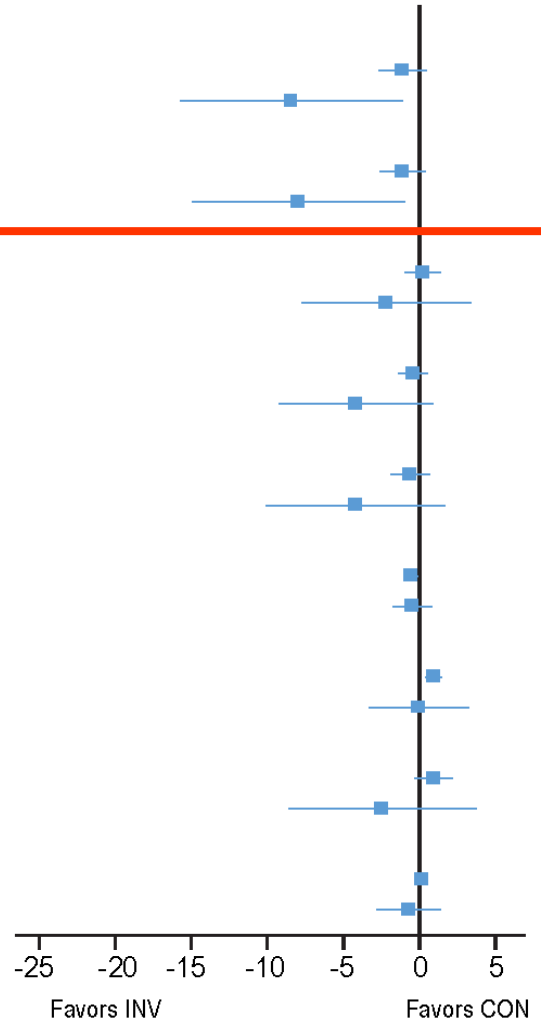
NNT = 14

Velazquez et al. N Engl J Med 2016;374:1511-20

ISCHEMIA: Heart failure/LVSD

398 (7.7%) participants with HF/LVD

Event	4-year Cumulative Incidence (95% CI)		Difference in Event Rate, INV - CON (95% CI)	Interaction P-value
	INV	CON		
Primary endpoint				0.055
No history of HF/LVD	13.0% (11.5%, 14.6%)	14.6% (13.0%, 16.2%)	-1.6% (-3.8%, 0.7%)	
History of HF/LVD	17.2% (11.6%, 23.8%)	29.3% (21.2%, 38.0%)	-12.1% (-22.6%, -1.6%)	
CV death or MI				0.061
No history of HF/LVD	11.4% (10.0%, 12.9%)	13.1% (11.5%, 14.7%)	-1.6% (-3.8%, 0.5%)	
History of HF/LVD	14.6% (9.4%, 20.9%)	25.9% (18.2%, 34.3%)	-11.4% (-21.4%, -1.4%)	
All-cause death				0.406
No history of HF/LVD	6.2% (5.1%, 7.5%)	5.9% (4.8%, 7.1%)	0.3% (-1.3%, 2.0%)	
History of HF/LVD	10.2% (5.8%, 15.9%)	13.3% (7.9%, 20.0%)	-3.1% (-11.1%, 4.8%)	
CV death				0.154
No history of HF/LVD	3.8% (3.0%, 4.9%)	4.5% (3.5%, 5.5%)	-0.6% (-2.0%, 0.8%)	
History of HF/LVD	6.7% (3.4%, 11.6%)	12.7% (7.5%, 19.5%)	-6.0% (-13.3%, 1.3%	
MI (Primary Definition)				0.244
No history of HF/LVD	8.8% (7.6%, 10.2%)	9.7% (8.4%, 11.1%)	-0.9% (-2.8%, 1.0%))	
History of HF/LVD	10.5% (6.2%, 16.2%)	16.5% (10.5%, 23.8%)	-6.0% (-14.4%, 2.4%)	
UA hospitalization				0.864
No history of HF/LVD	0.6% (0.4%, 1.1%)	1.5% (1.0%, 2.1%)	-0.8% (-1.5%, -0.2%)	
History of HF/LVD	0.5% (0.0%, 2.4%)	1.1% (0.2%, 3.7%)	-0.7% (-2.5%, 1.2%)	
Hospitalization for HF				0.550
No history of HF/LVD	2.0% (1.4%, 2.8%)	0.6% (0.3%, 1.1%)	1.4% (0.6%, 2.1%)	
History of HF/LVD	4.4% (1.9%, 8.6%)	4.5% (1.9%, 8.7%)	-0.1% (-4.8%, 4.6%)	
Death or HF hospitalization				0.293
No history of HF/LVD	7.5% (6.3%, 8.9%)	6.2% (5.1%, 7.5%)	1.3% (-0.4%, 3.1%)	
History of HF/LVD	13.3% (8.3%, 19.6%)	16.8% (10.7%, 24.1%)	-3.5% (-12.3%, 5.3%)	
HF death				0.401
No history of HF/LVD	0.3% (0.1%, 0.7%)	0.0% (0.0%, 0.3%)	0.3% (-0.0%, 0.6%)	
History of HF/LVD	0.7% (0.1%, 3.8%)	1.8% (0.3%, 6.2%)	-1.0% (-4.1%, 2.0%)	



Lopes R et al. *Circulation. 2020;142:1725–1735*

Revascularization to Improve Survival in SIHD

- Overall cohort
- High risk subgroups
  - Left main disease
  - LV dysfunction
    - *CABG vs. Med: Mortality benefit of CABG (STICHES)*
    - *CABG vs. PCI: Need RCT*
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

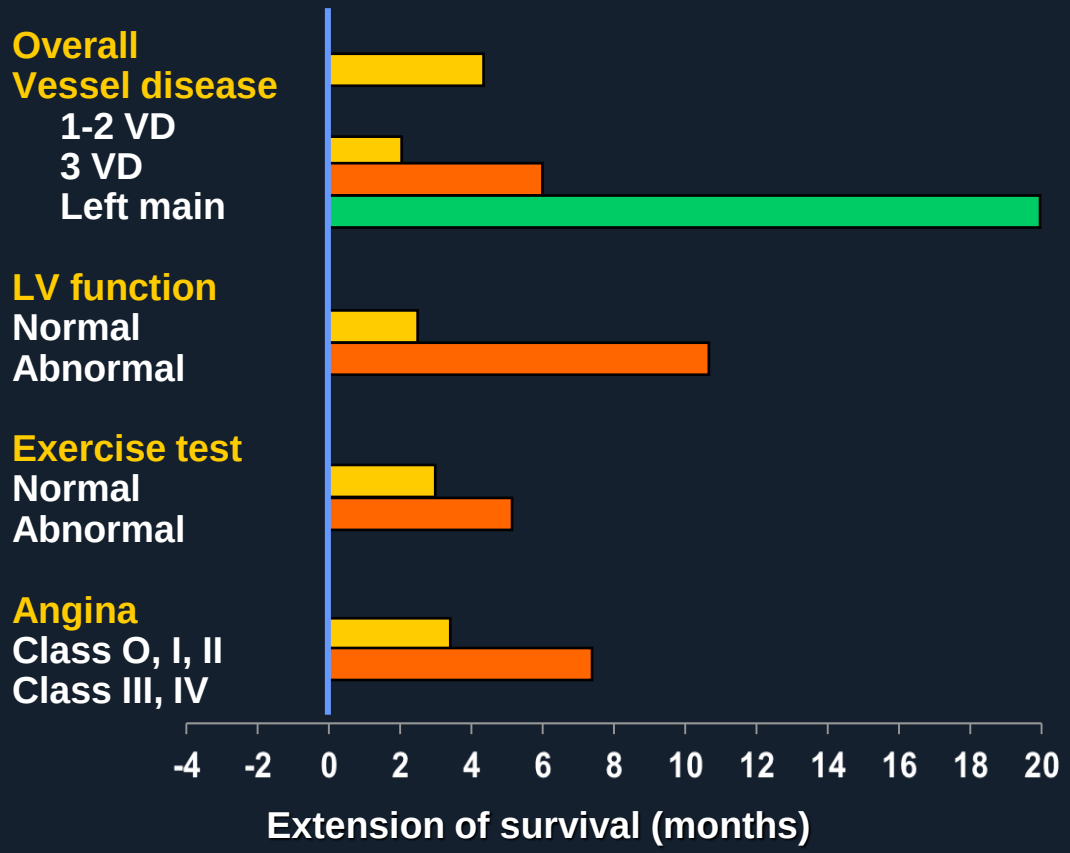
Revascularization to Improve Survival in SIHD

- Overall cohort
- High risk subgroups
  - Left main disease
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

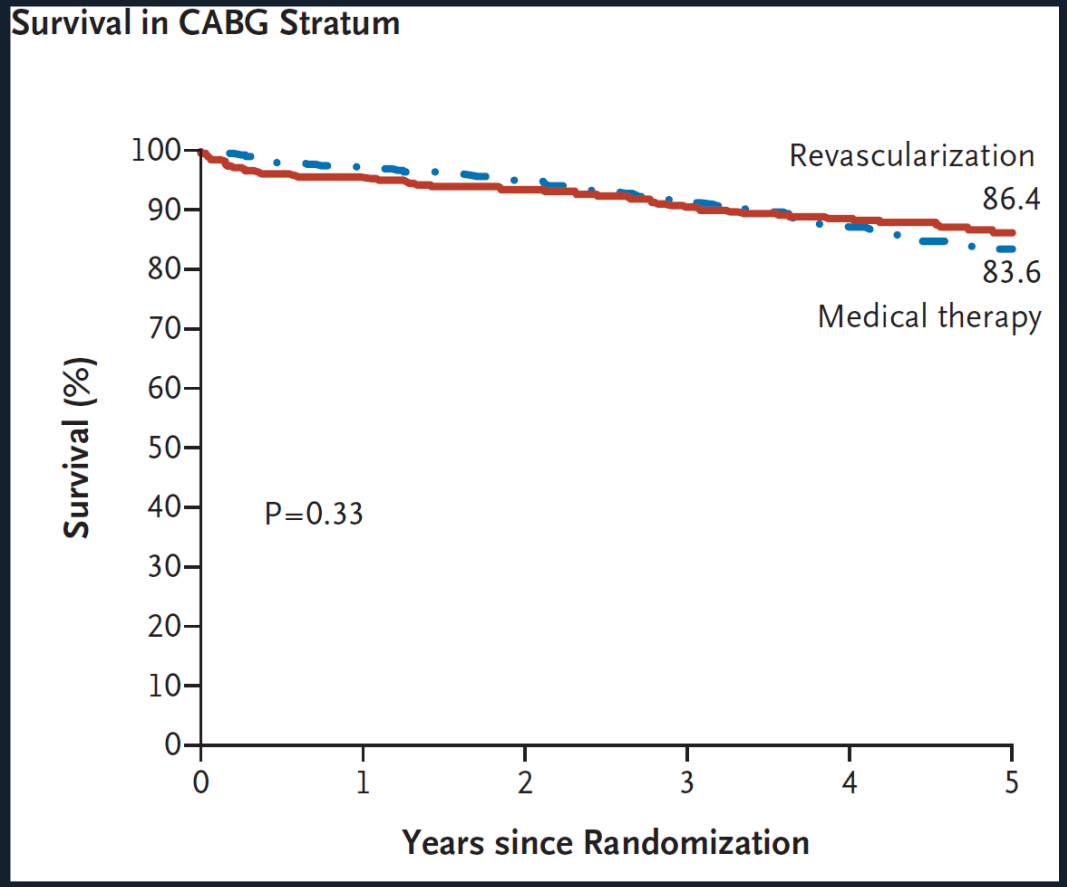
Extension of Survival with 3-vessel disease with Revascularization

1980s to Present

1980s (CABG vs. No CABG)



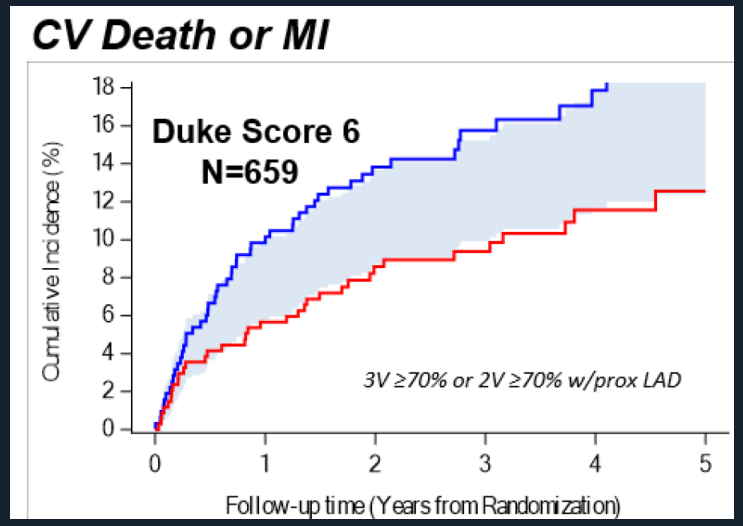
2009 (BARI-2 D: CABG vs. Med)

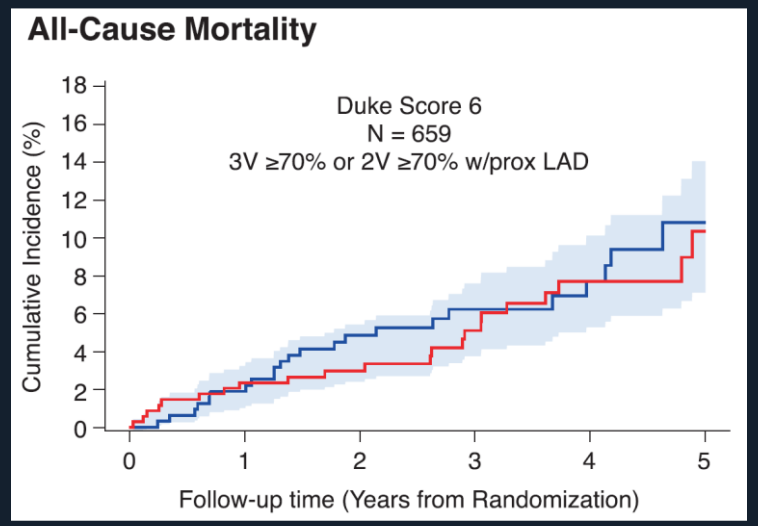


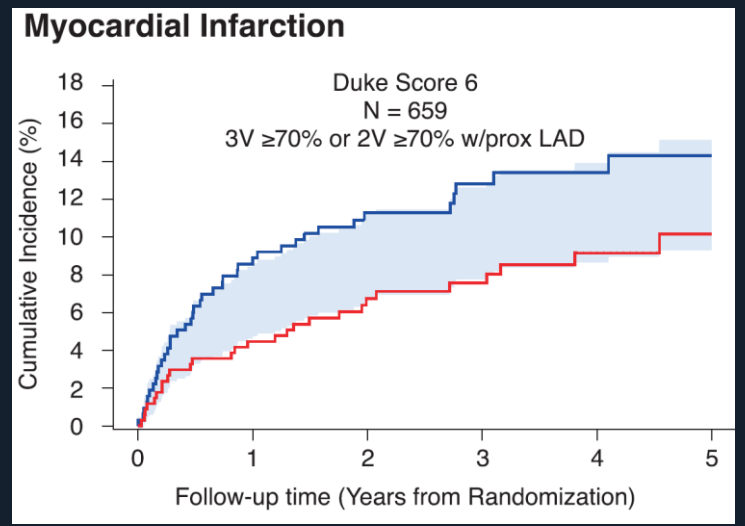
Velazquez et al. N Engl J Med 2016;374:1511-20

ISCHEMIA: Potential Reduction in CV death/MI in High Anatomic Risk

	Events, n		4-y event rate, %			
	Invasive strategy	Conservative strategy	Invasive strategy	Conservative strategy	Difference (95% CI), %	Interaction *P* value
Cardiovascular death or myocardial infarction						0.33
1-Vessel CAD ≥50%	3	4	3.3 (0.9 to 8.6)	8.7 (2.5 to 19.9)	−5.4 (−14.9 to 4.2)	
1-Vessel CAD ≥70% or 2-vessel ≥50%	26	25	8.8 (5.7 to 12.8)	8.7 (5.6 to 12.5)	0.2 (−4.7 to 5.1)	
2-Vessel CAD ≥70% or 3-vessel ≥50% or 70% proximal LAD	38	48	10.2 (7.2 to 13.9)	12.8 (9.5 to 16.7)	−2.6 (−7.5 to 2.3)	
3-Vessel CAD ≥70% or 2-vessel ≥70% including proximal LAD	34	50	11.6 (8.1 to 15.7)	17.9 (13.4 to 22.8)	−6.3 (−12.4 to −0.2)	







Reynolds et al. Circulation. 2021;144:1024–1038

Revascularization to Improve Survival in SIHD

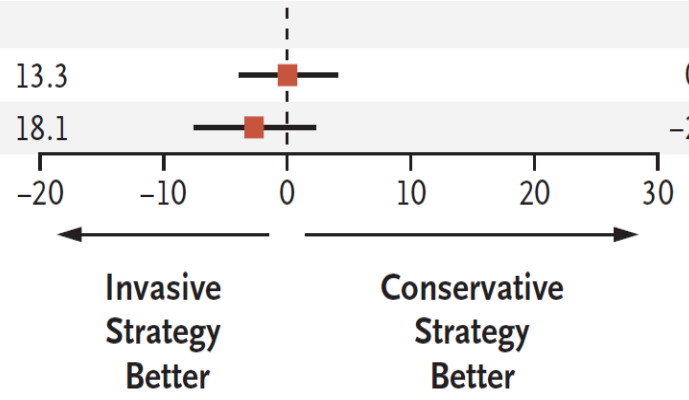
- Overall cohort
- High risk subgroups
  - Left main disease
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

Extension of Survival with Proximal LAD with Revascularization

ISCHEMIA: Invasive vs. Conservative

No heterogeneity of treatment effect based on proximal LAD stenosis status for the primary endpoint

Subgroup	Percent of Patients	Estimated 5-Yr Event Rate (%)		Difference in Event Rate, Invasive Strategy Minus Conservative Strategy (95% CI)
		Invasive Strategy	Conservative Strategy	
Stenosis of the proximal LAD coronary artery (≥50%)				
No	53.2	13.4	13.3	0.1 (–3.9 to 4.1)
Yes	46.8	15.5	18.1	–2.6 (–7.5 to 2.3)



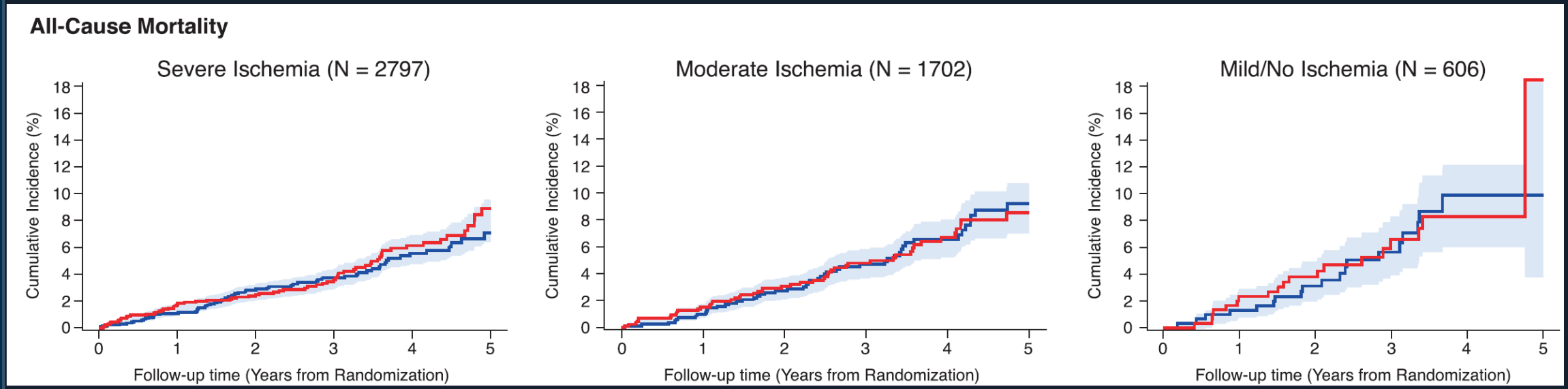
Maron et al. N Engl J Med. 2020 Apr 9;382(15):1395-1407

Revascularization to Improve Survival in SIHD

- Overall cohort
- High risk subgroups
  - Left main disease
  - LV dysfunction
  - 3-vessel disease
  - Proximal LAD disease
  - Extensive ischemia

Extension of Survival with Revascularization Based on Ischemia Severity

ISCHEMIA: Invasive vs. Conservative



Reynolds et al. Circulation. 2021;144:1024–1038

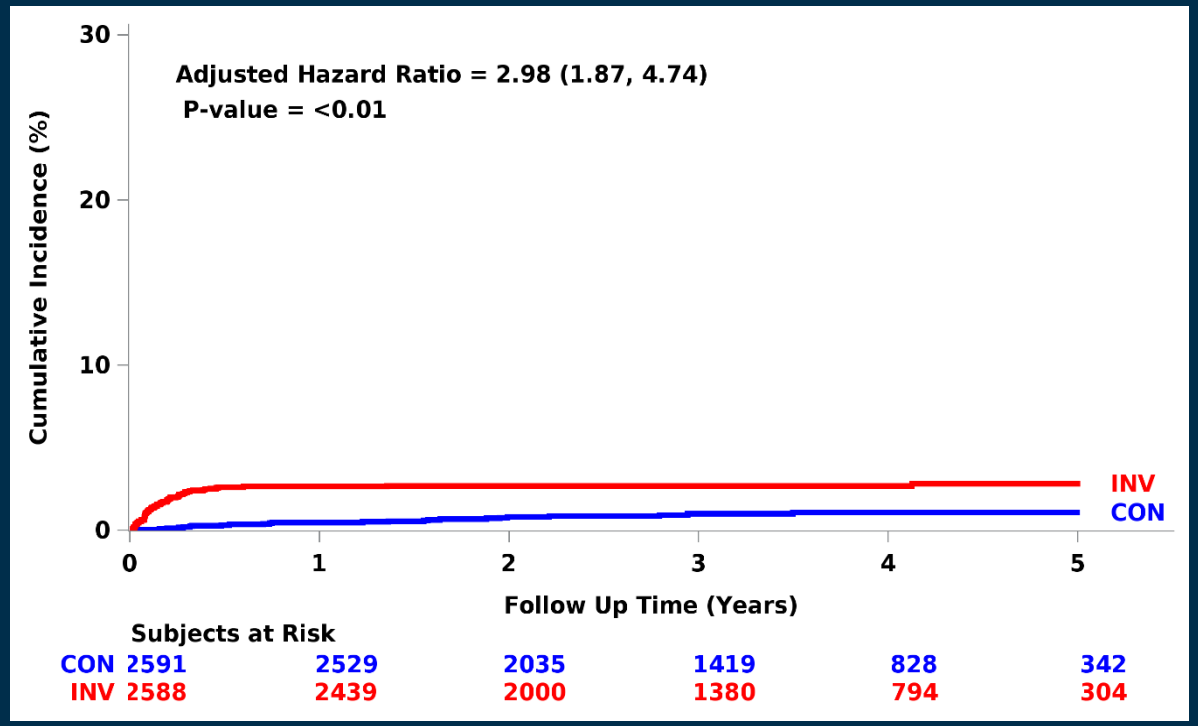
Potential Reasons for Revascularization in SIHD

- To improve survival
- To prevent other cardiovascular events
- To improve quality of life

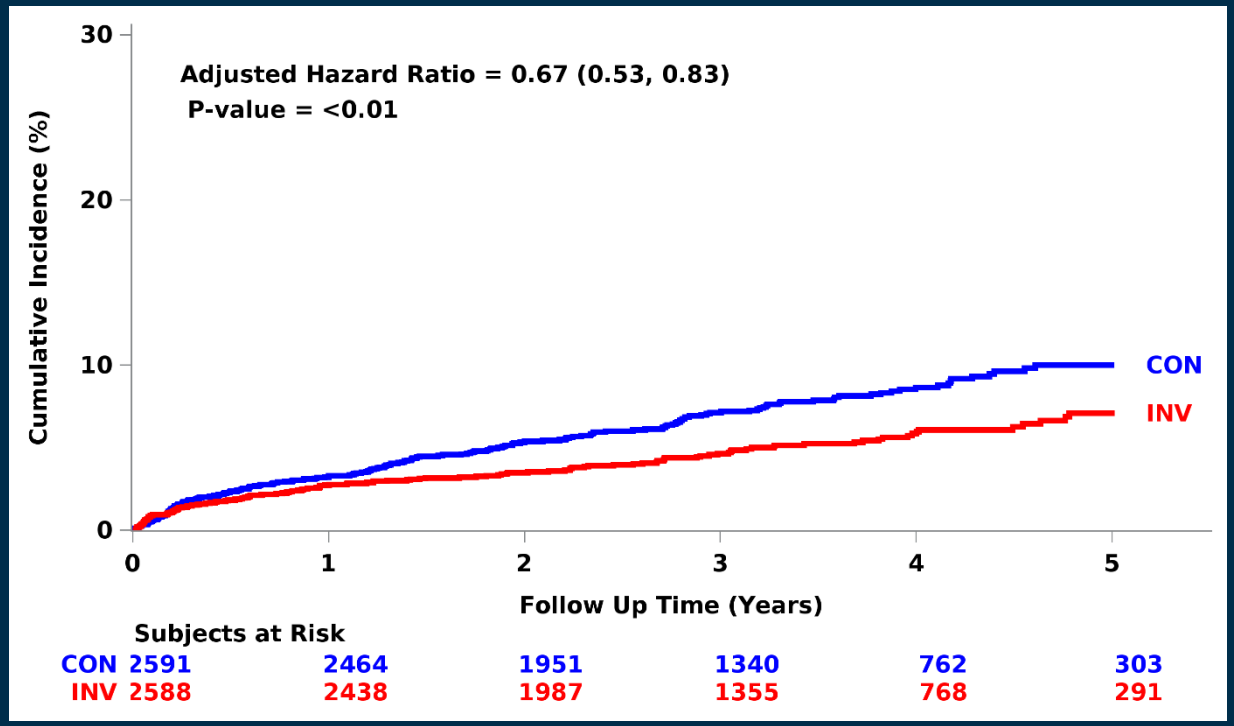
Revascularization Reduces Spontaneous MI

ISCHEMIA: Invasive vs. Conservative

Procedural MI
Type 4a or 5 MI



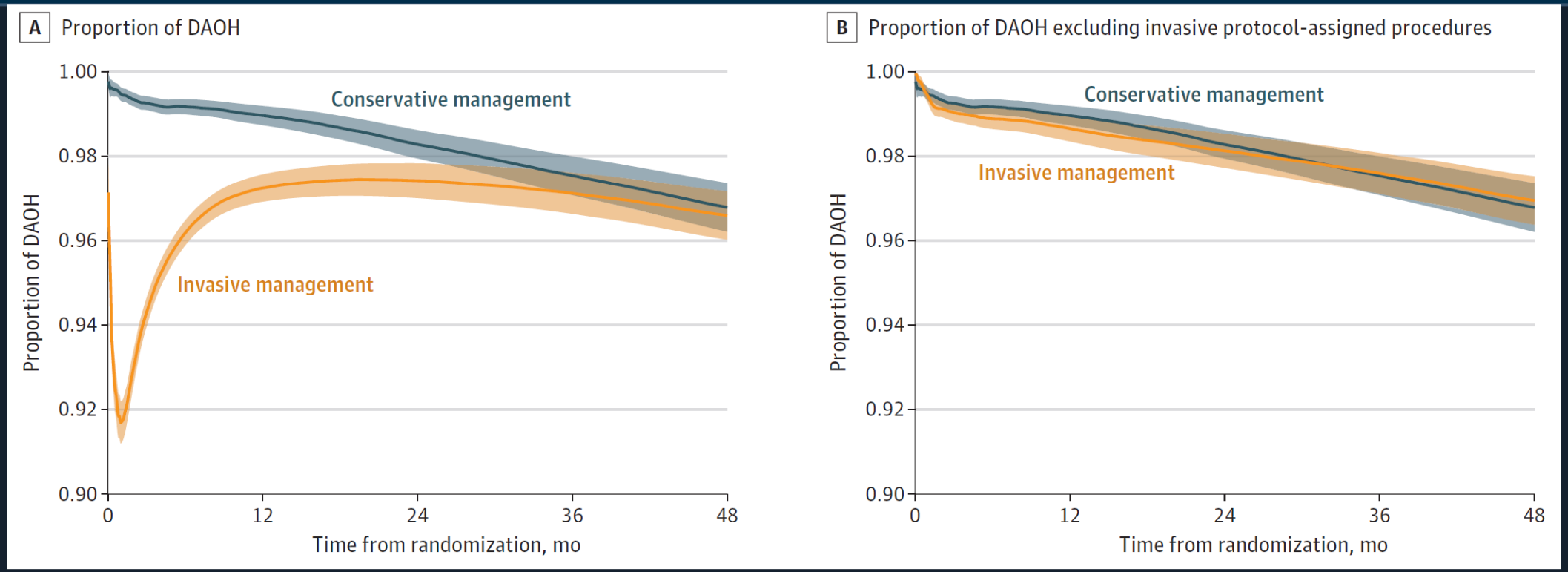
Spontaneous MI
Types 1, 2, 4b, or 4c MI



Maron et al. N Engl J Med. 2020 Apr 9;382(15):1395-1407

Revascularization: Beyond Symptoms

Lower CV Hospital Stays (ISCHEMIA)



- Lower CV stays (685 vs. 1095; P<0.001)
  - Lower stay for spontaneous MI (65 vs. 123; P<0.001)
  - Lower stay for unstable angina (119 vs. 216; P<0.001)

White, O'Brien, Alexander, Boden, Bangalore S et al. JAMA Cardiol. 2021;6(9):1023-1031

Potential Reasons for Revascularization in SIHD

- To improve survival
- To prevent other cardiovascular events
  - *Reduces spontaneous MI, unstable angina and lowers CV stays*
- To improve quality of life

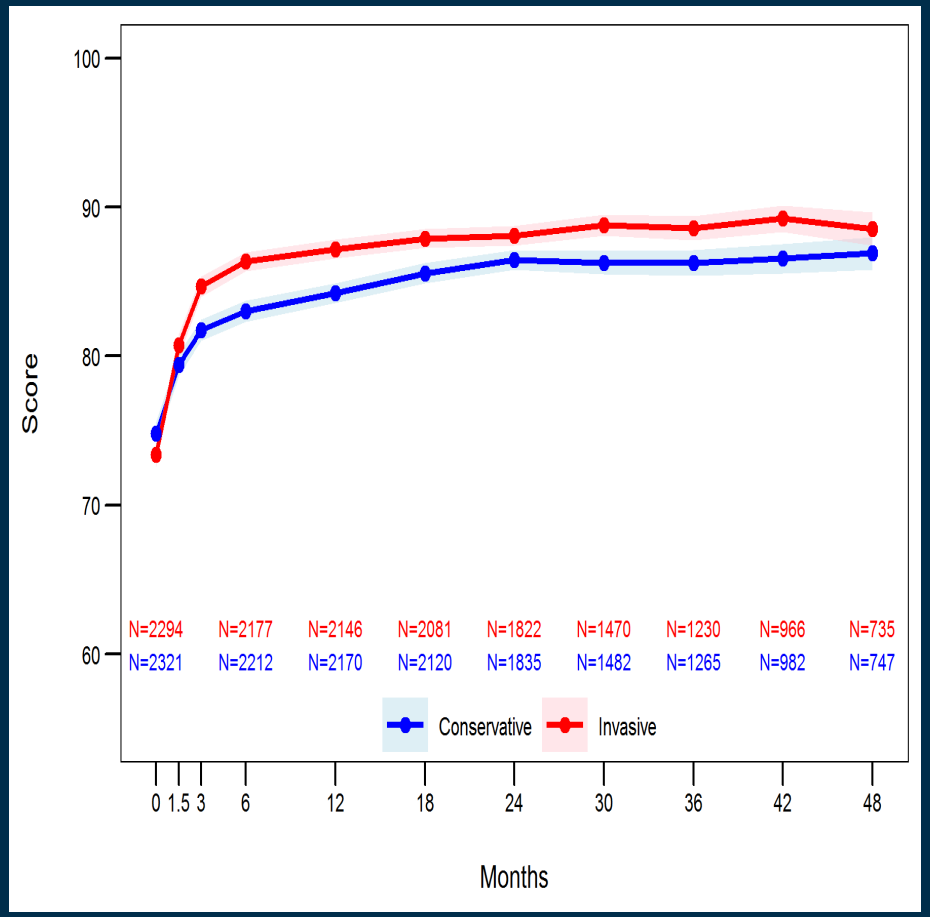
Potential Reasons for Revascularization in SIHD

- To improve survival
- To prevent other cardiovascular events
- To improve quality of life

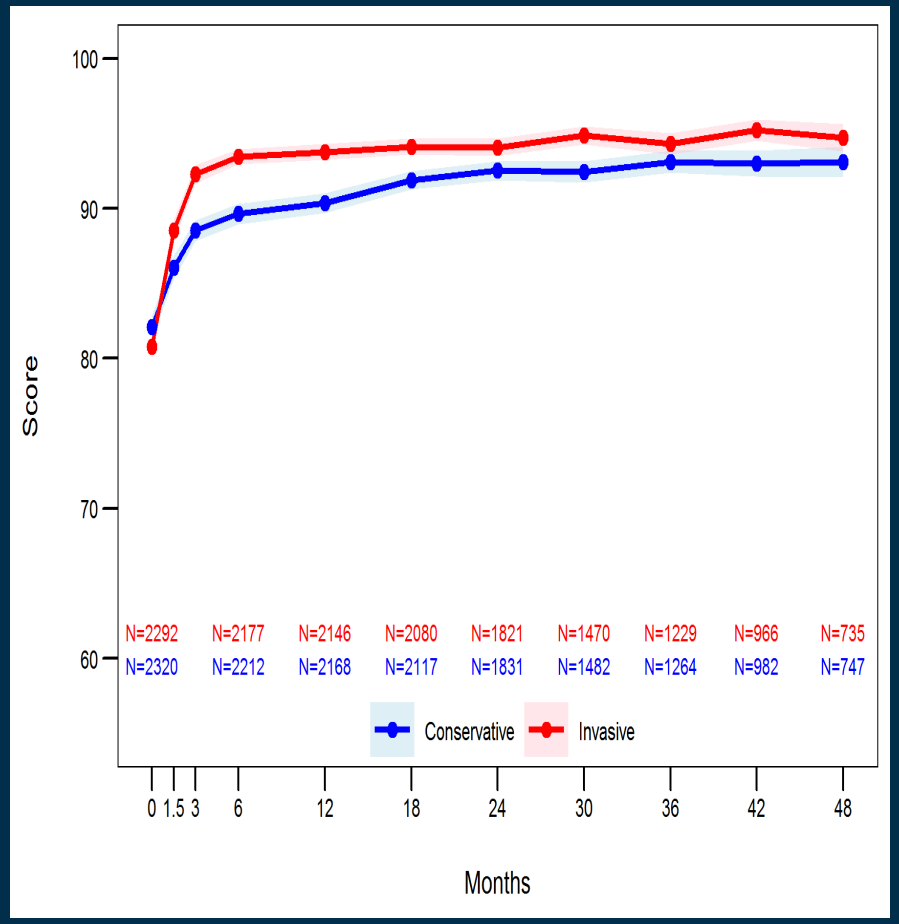
Durable Improvement in Angina Related QoL

ISCHEMIA

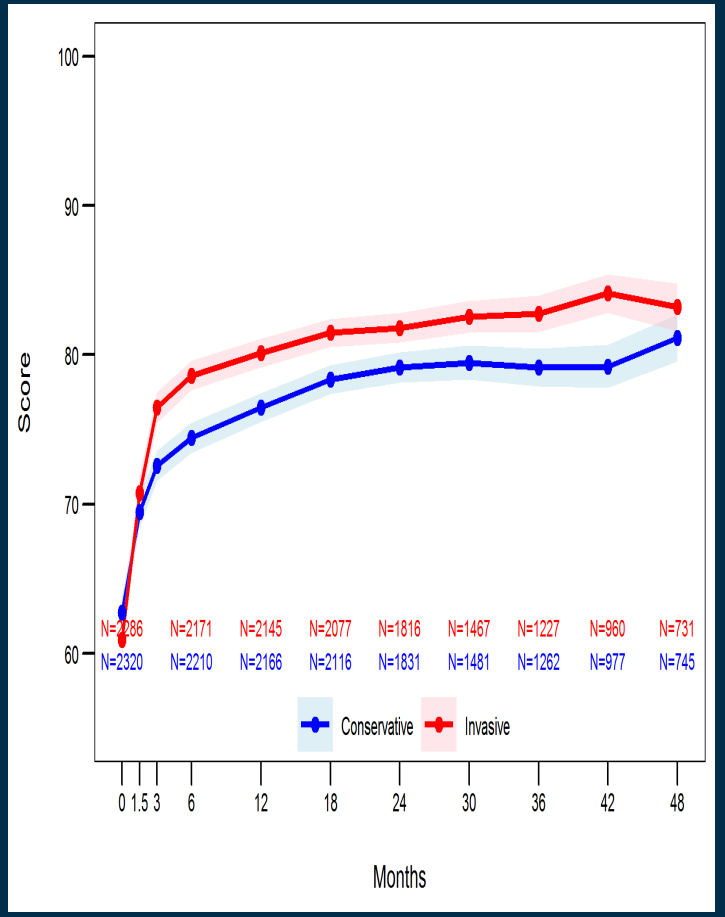
SAQ Summary Score



SAQ Angina Frequency



SAQ Quality of Life



Potential Reasons for Revascularization in SIHD

- To improve survival
- To prevent other cardiovascular events
- To improve quality of life
  - *Yes, but not in the asymptomatic patients*

Potential Reasons for Revascularization in SIHD

Summary

- To improve survival
  - *No improvement in survival compared with MT, except in those with LM disease and LV systolic dysfunction*
  - *Small reduction (0.3%/year) in cardiac death*
- To prevent other cardiovascular events
  - *Reduces spontaneous MI, unstable angina and lowers CV stays*
- To improve quality of life
  - *Faster and more durable relief of angina in symptomatic patients*

2021 ACC/AHA Revascularization Guidelines

SIHD and Normal EF

LM: CABG is recommended to improve survival	1 B-R
3V-CAD: CABG maybe reasonable to improve survival	2b B-R
3V-CAD: Usefulness of PCI to improve survival is uncertain	2b B-R
Prox LAD: Usefulness of revasc to improve survival is uncertain	2b B-R
1 or 2VD and no Prox LAD: Revasc is not recommended to improve survival	3: No Benefit B-R

Lawton JS, Tamis-Holland JE, Bangalore S, et al. J Am Coll Cardiol. 2021

2021 ACC/AHA Revascularization Guidelines

SIHD and Normal EF

Multivessel-CAD: revascularization is reasonable to lower the risk of cardiovascular events such as spontaneous MI, unplanned urgent revascularizations, or cardiac death

Lawton JS, Tamis-Holland JE, Bangalore S, et al. J Am Coll Cardiol. 2021