



ISCHEMIA

**International Study Of Comparative Health Effectiveness
With Medical And Invasive Approaches (ISCHEMIA):**

Primary Report of Clinical Outcomes

Funded by the National Heart, Lung, and Blood Institute

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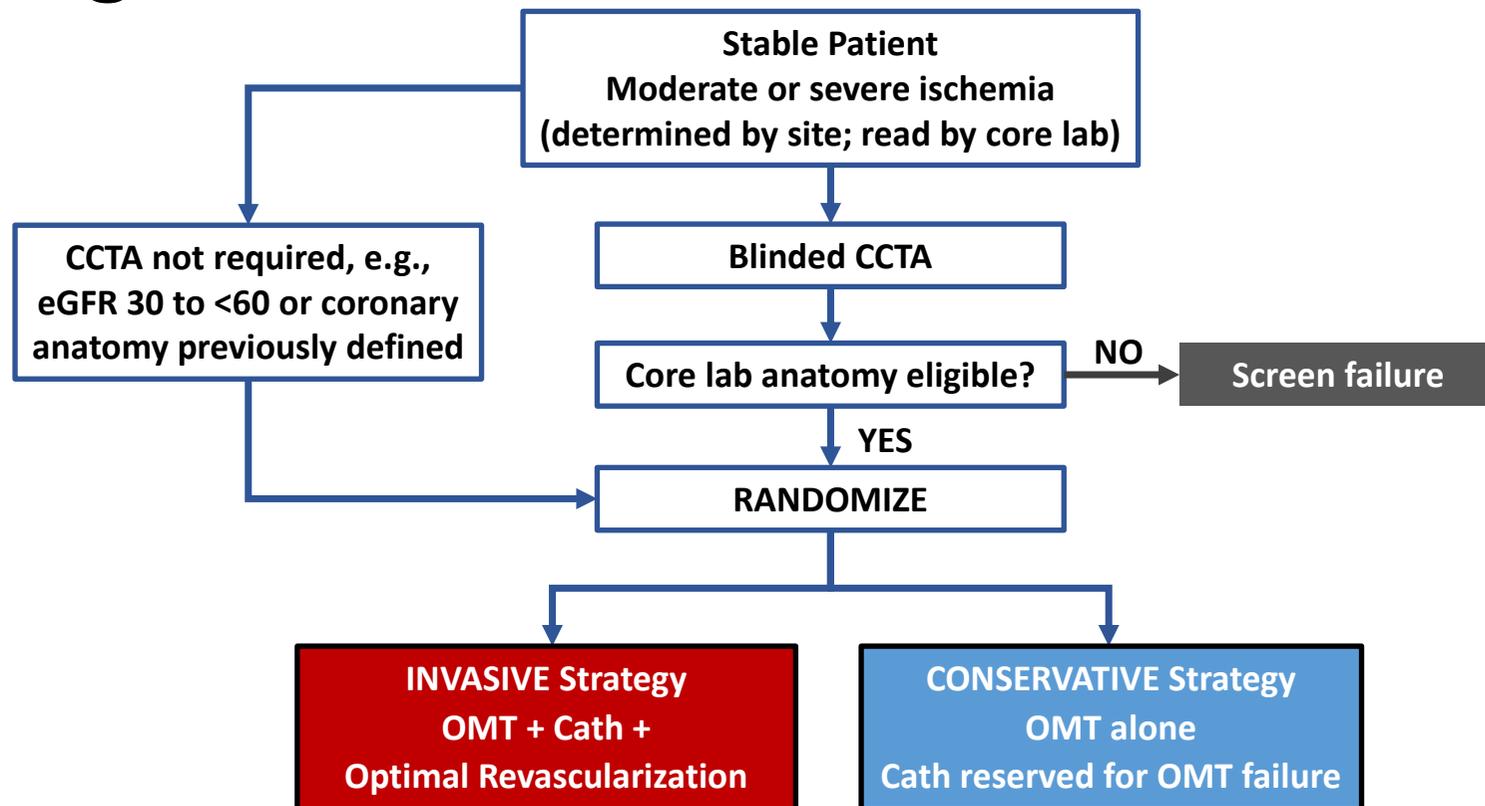
NYU School of Medicine

On behalf of the ISCHEMIA Research Group

ISCHEMIA 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?

Study Design



Endpoints

Primary Endpoint:

- Time to CV death, MI, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest

Major Secondary Endpoints:

- Time to CV death or MI
- Quality of Life (separate presentation)

Other Endpoints include:

- All-Cause Death
- Net clinical benefit (stroke added to primary endpoint)
- Components of primary endpoint

Eligibility Criteria

Clinical and Stress Test Eligibility Criteria

Inclusion Criteria

- Age ≥ 21 years
- Moderate or severe ischemia*
 - Nuclear $\geq 10\%$ LV ischemia (summed difference score ≥ 7)
 - Echo ≥ 3 segments stress-induced moderate or severe hypokinesis, or akinesis
 - CMR
 - Perfusion: $\geq 12\%$ myocardium ischemic, and/or
 - Wall motion: $\geq 3/16$ segments with stress-induced severe hypokinesis or akinesis
 - Exercise Tolerance Testing (ETT) ≥ 1.5 mm ST depression in ≥ 2 leads or ≥ 2 mm ST depression in single lead at < 7 METS, with angina

Major Exclusion Criteria

- NYHA Class III-IV HF
- Unacceptable angina despite medical therapy
- EF $< 35\%$
- ACS within 2 months
- PCI or CABG within 1 year
- eGFR < 30 mL/min or on dialysis



CCTA Eligibility Criteria

Inclusion Criteria

- $\geq 50\%$ stenosis in a major epicardial vessel (stress imaging participants)
- $\geq 70\%$ stenosis in a proximal or mid vessel (ETT participants)

Major Exclusion Criteria

- $\geq 50\%$ stenosis in unprotected left main

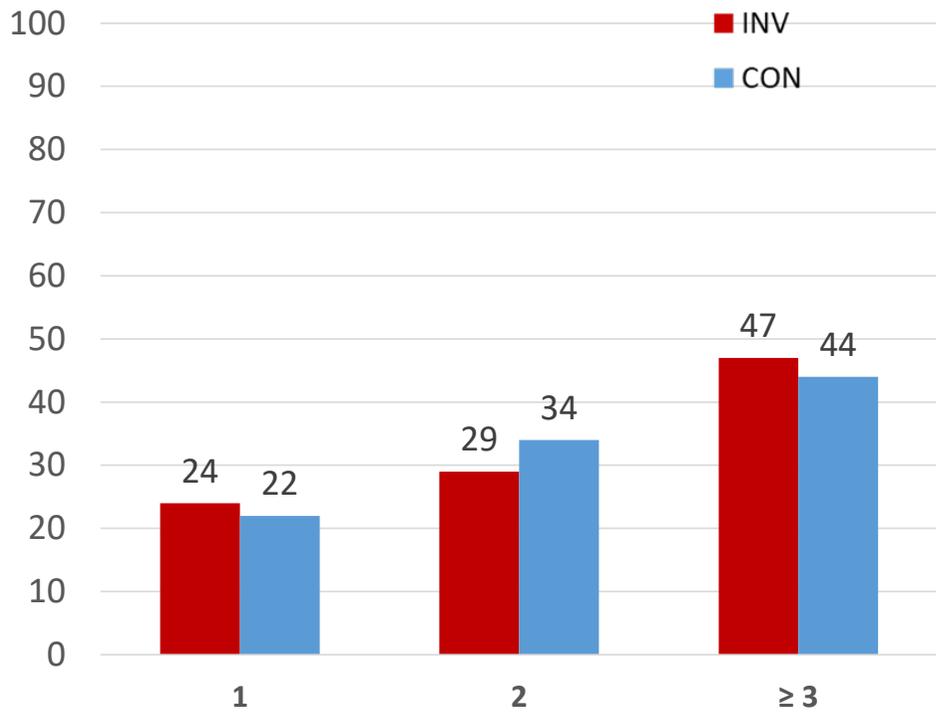
**Ischemia eligibility determined by sites. All stress tests interpreted at core labs.*

Baseline Characteristics

Characteristic	Total	INV	CON
Clinical			
Age at Enrollment (yrs.)			
Median	64 (58, 70)	64 (58, 70)	64 (58, 70)
Female Sex (%)	23	23	22
Hypertension (%)	73	73	73
Diabetes (%)	42	41	42
Prior Myocardial Infarction (%)	19	19	19
Ejection Fraction, Median (%) (n=4637)	60 (55, 65)	60 (55, 65)	60 (55, 65)
Systolic Blood Pressure, Median (mmHg)	130 (120, 142)	130 (120, 142)	130 (120, 142)
Diastolic Blood Pressure, Median (mmHg)	77 (70, 81)	77 (70, 81)	77 (70, 81)
LDL Cholesterol, Median (mg/dL)	83 (63, 111)	83 (63, 111)	83 (63, 109.5)
History of Angina	90%	90%	89%
Angina Began or Became More Frequent Over the Past 3 Months	29%	29%	29%
Stress Test Modality			
Stress Imaging (%)	75	75	76
Exercise Tolerance Test (ETT) (%)	25	25	24

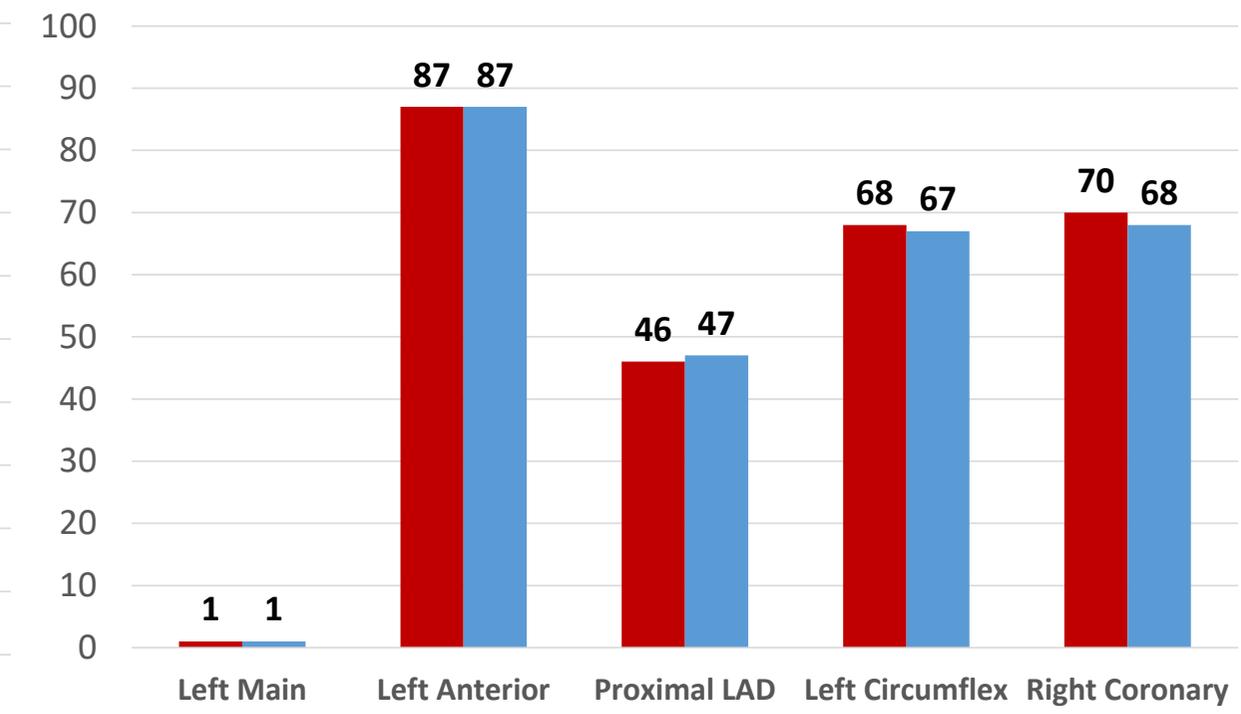
Median values reported with 25th and 75th percentiles

Baseline Coronary Artery Anatomy by CCTA



of Vessels with $\geq 50\%$ Stenosis (%)

N=2982



(% of total)

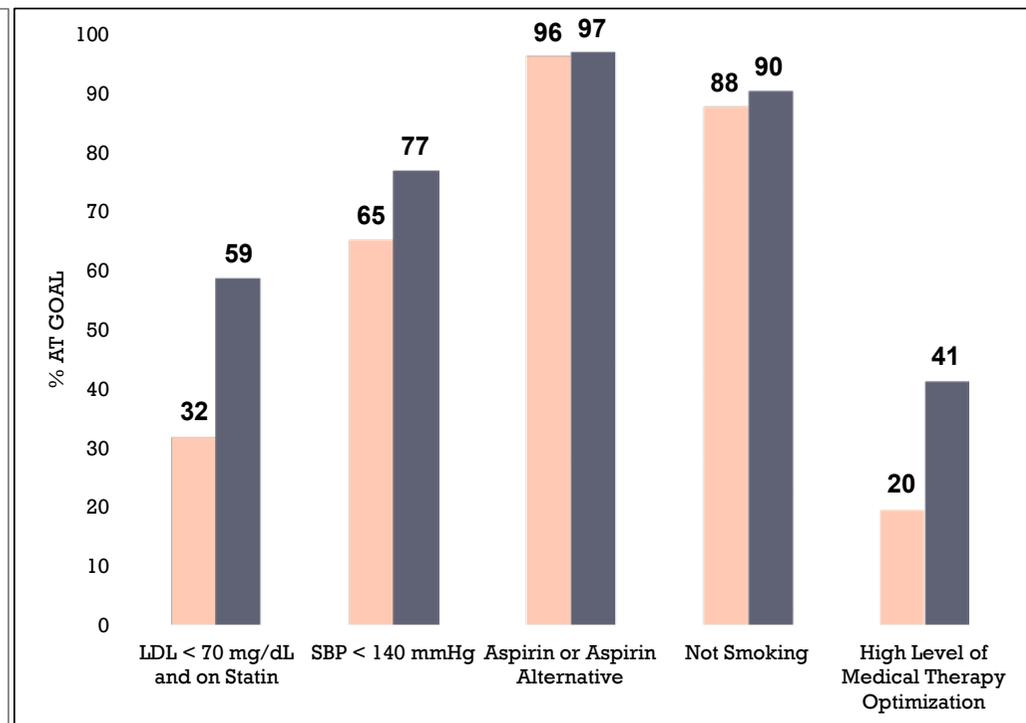
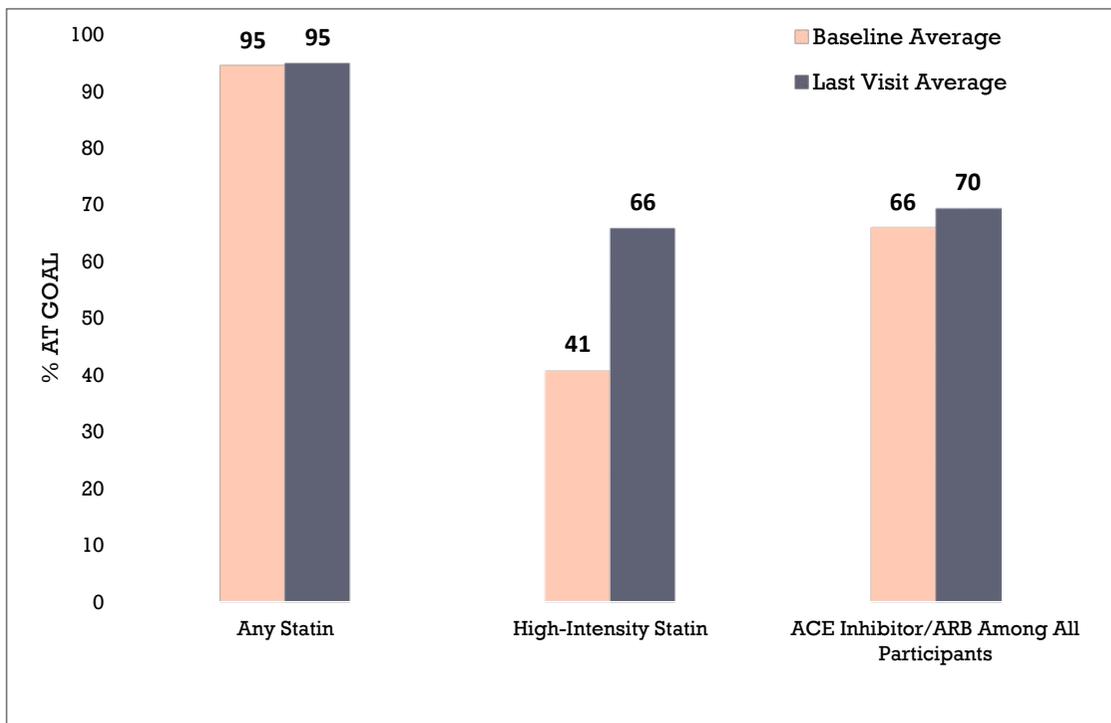
Specific Vessels with $\geq 50\%$ Stenosis (%)

N=3739

Risk Factor Management

Baseline vs last visit

No between group differences INV vs CON

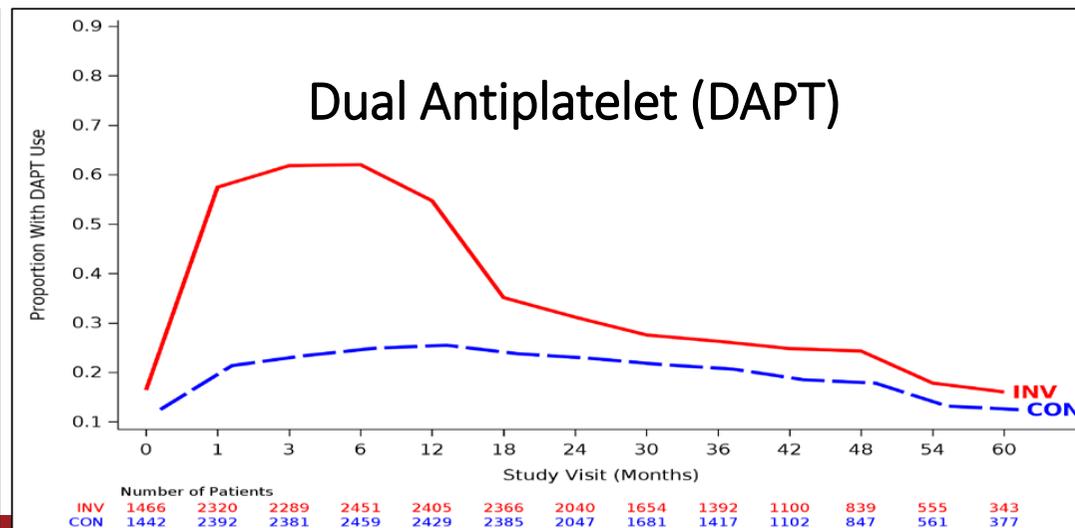
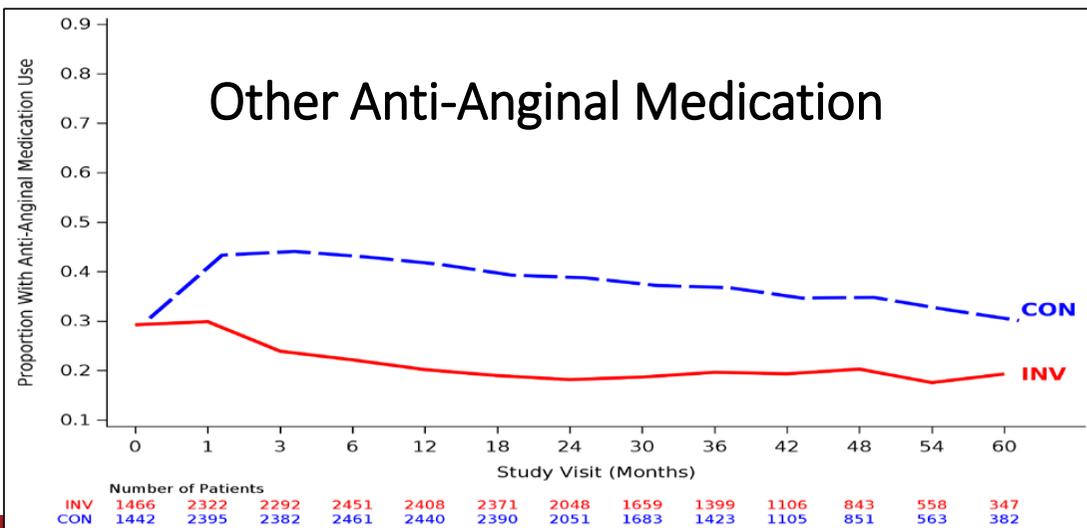
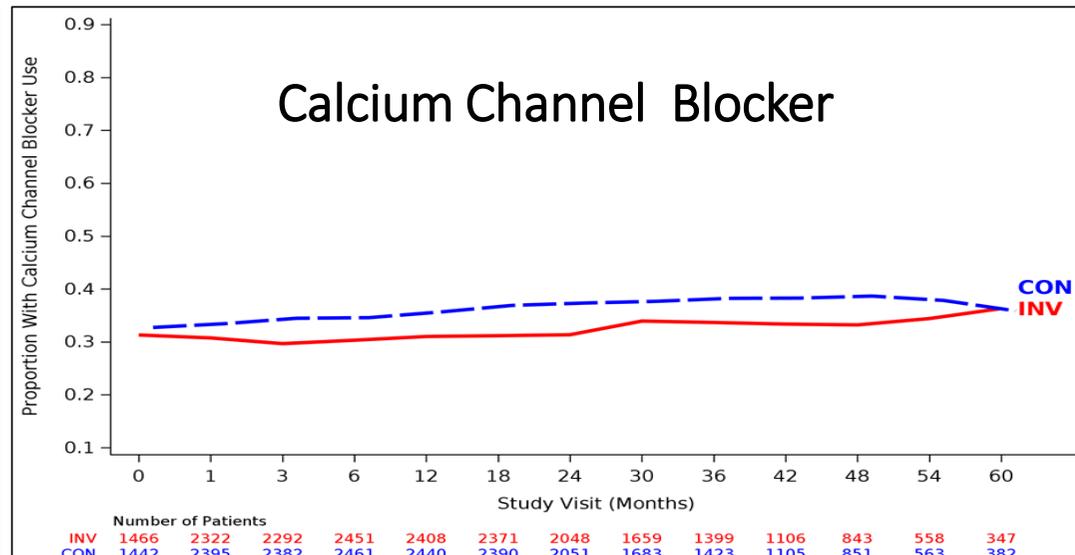
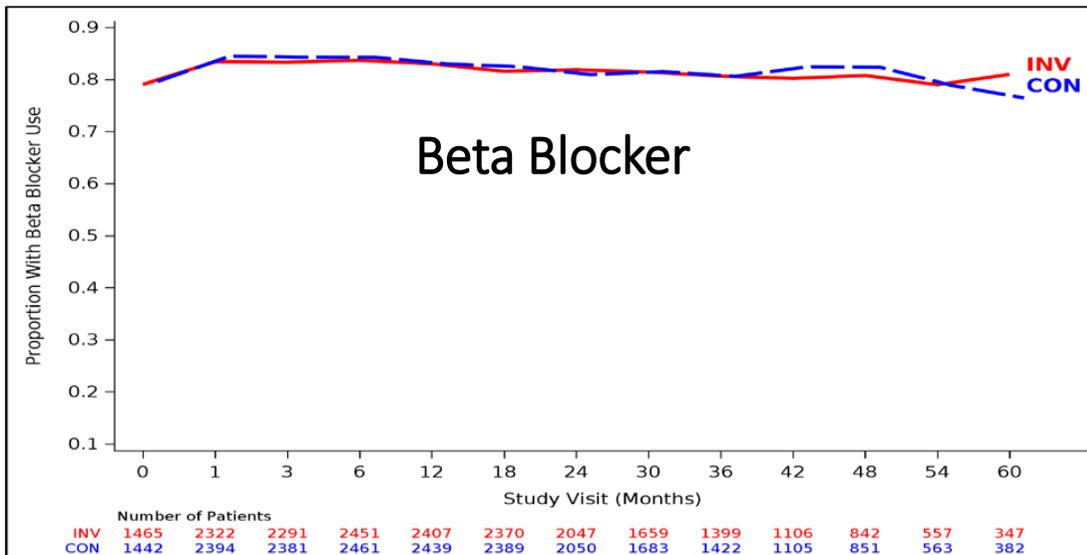


High Level of Medical Therapy Optimization is defined as a participant meeting all of the following goals: LDL < 70 mg/dL and on any statin, systolic blood pressure < 140 mm/Hg, on aspirin or other antiplatelet or anticoagulant, and not smoking. High level of medical therapy optimization is missing if any of the individual goals are missing.

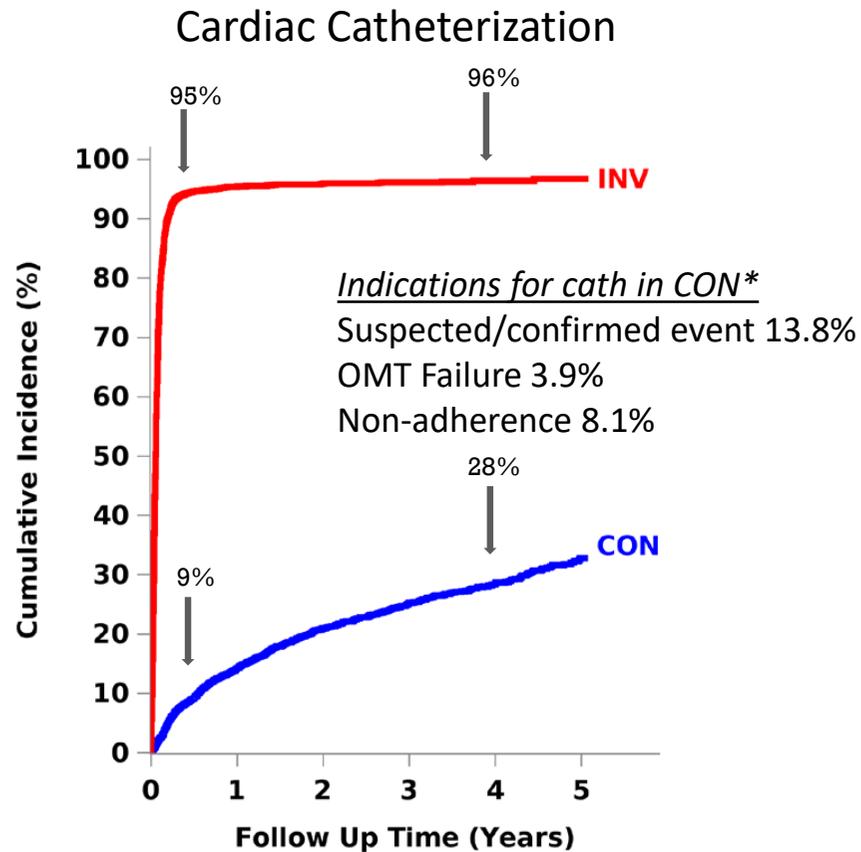
Baseline LDL = 83 mg/dL. Last visit LDL = 65 mg/dL.



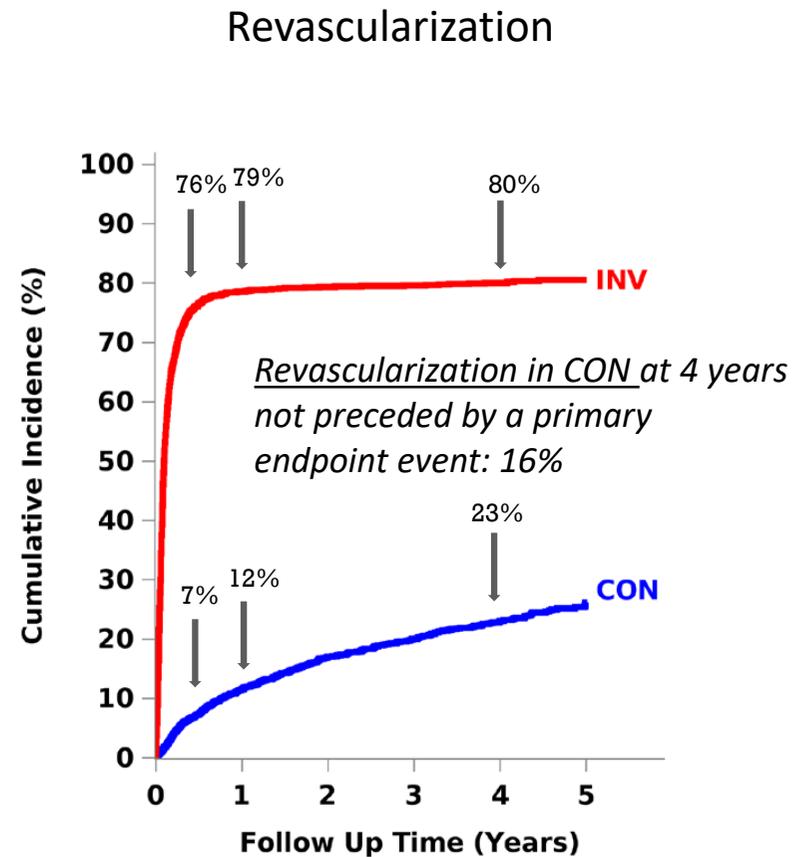
Medication Use Over Time



Cardiac Catheterization and Revascularization



CON	2591	2186	1646	1087	601	232
INV	2588	111	79	50	20	4



CON	2591	2250	1721	1157	642	254
INV	2588	523	410	289	155	54

*Indications for Cath are percentages of CON patients whereas cumulative event rate shown at 4 years reflects censoring and the rate at that time point.

Mode of Revascularization

First Procedure for Those Revascularized in Invasive Group (80% of INV)

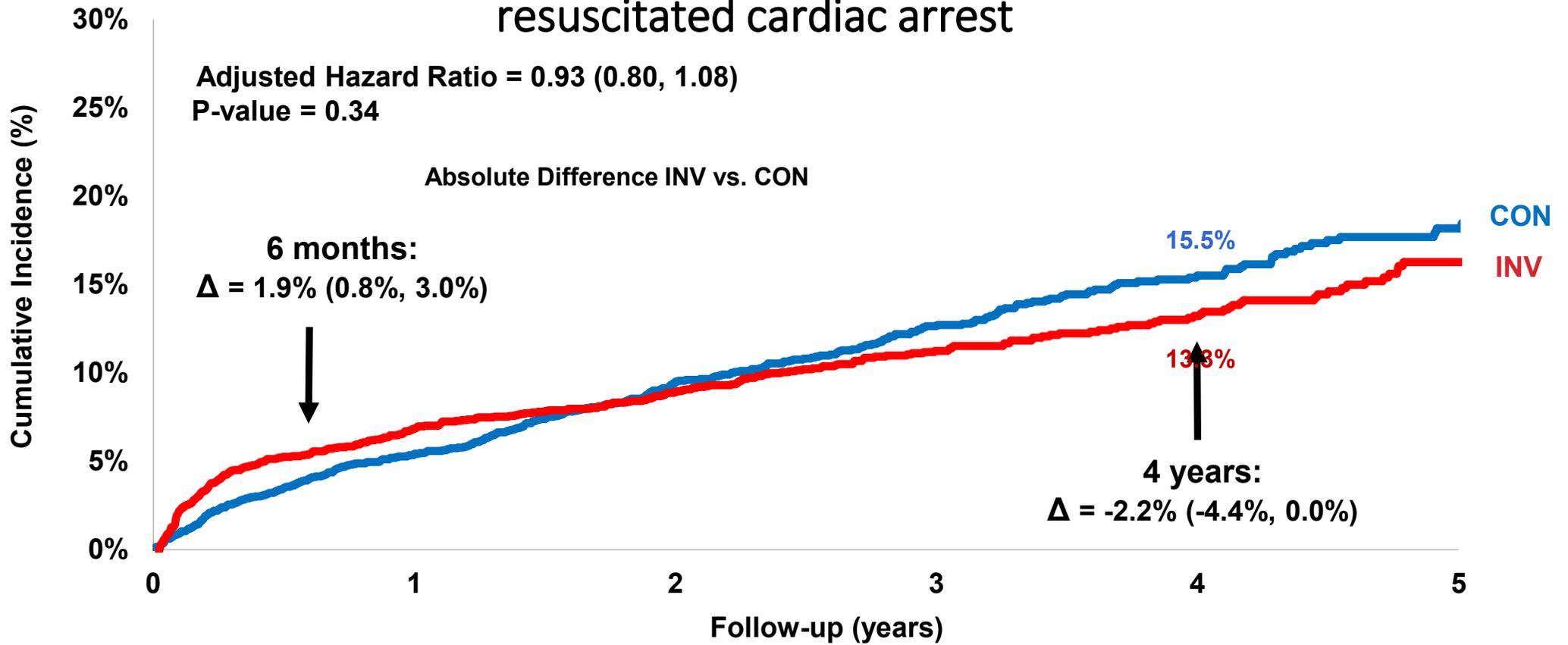
Of the 20% with no revascularization
~2/3 had insignificant disease on coronary angiogram
~1/3 had extensive disease unsuitable for any mode of revascularization

First Procedure	Total
PCI	74%
• Successful, stent able to be placed	93%
• Of stents placed, drug eluting	98%

First Procedure	Total
CABG	26%
• Arterial Grafts	93%
• IMA	92%



Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

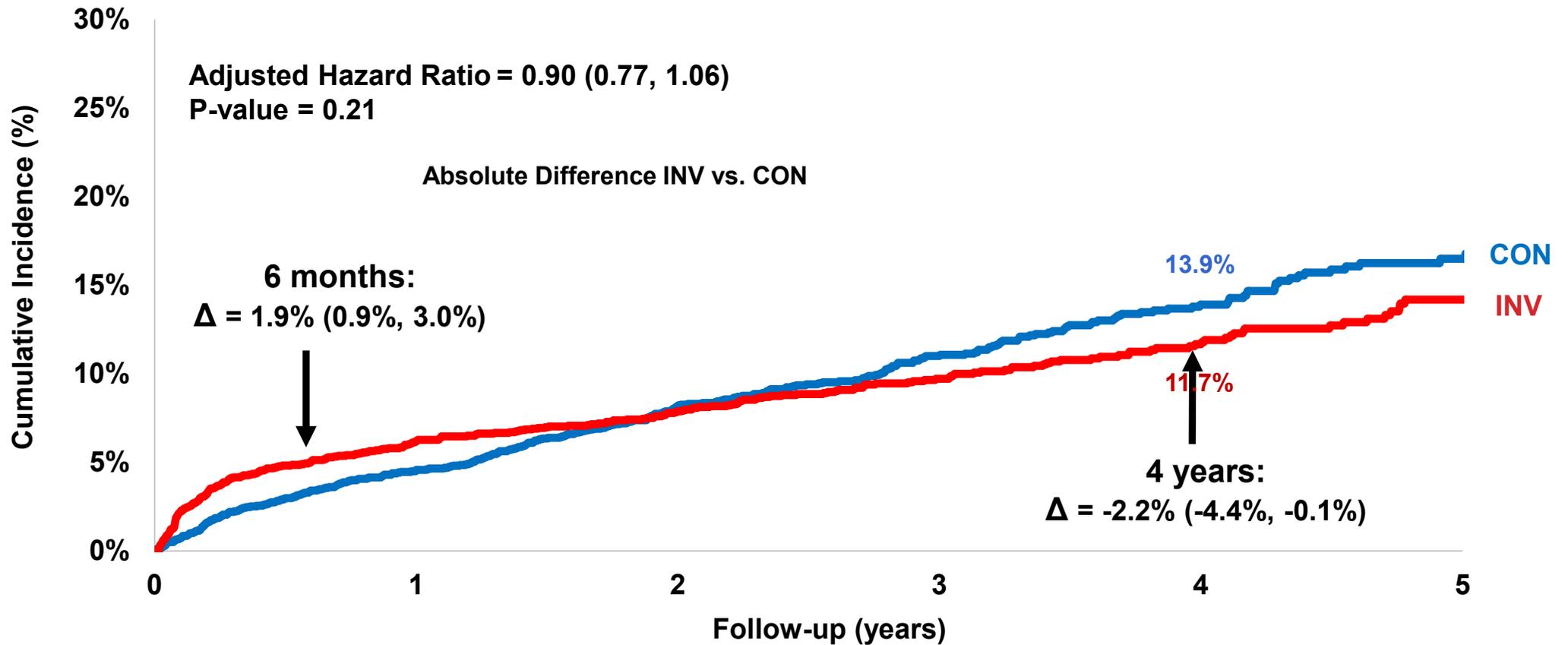


Subjects at Risk

	0	1	2	3	4	5
CON	2591	2431	1907	1300	733	293
INV	2588	2364	1908	1291	730	271



Major Secondary: CV Death or MI

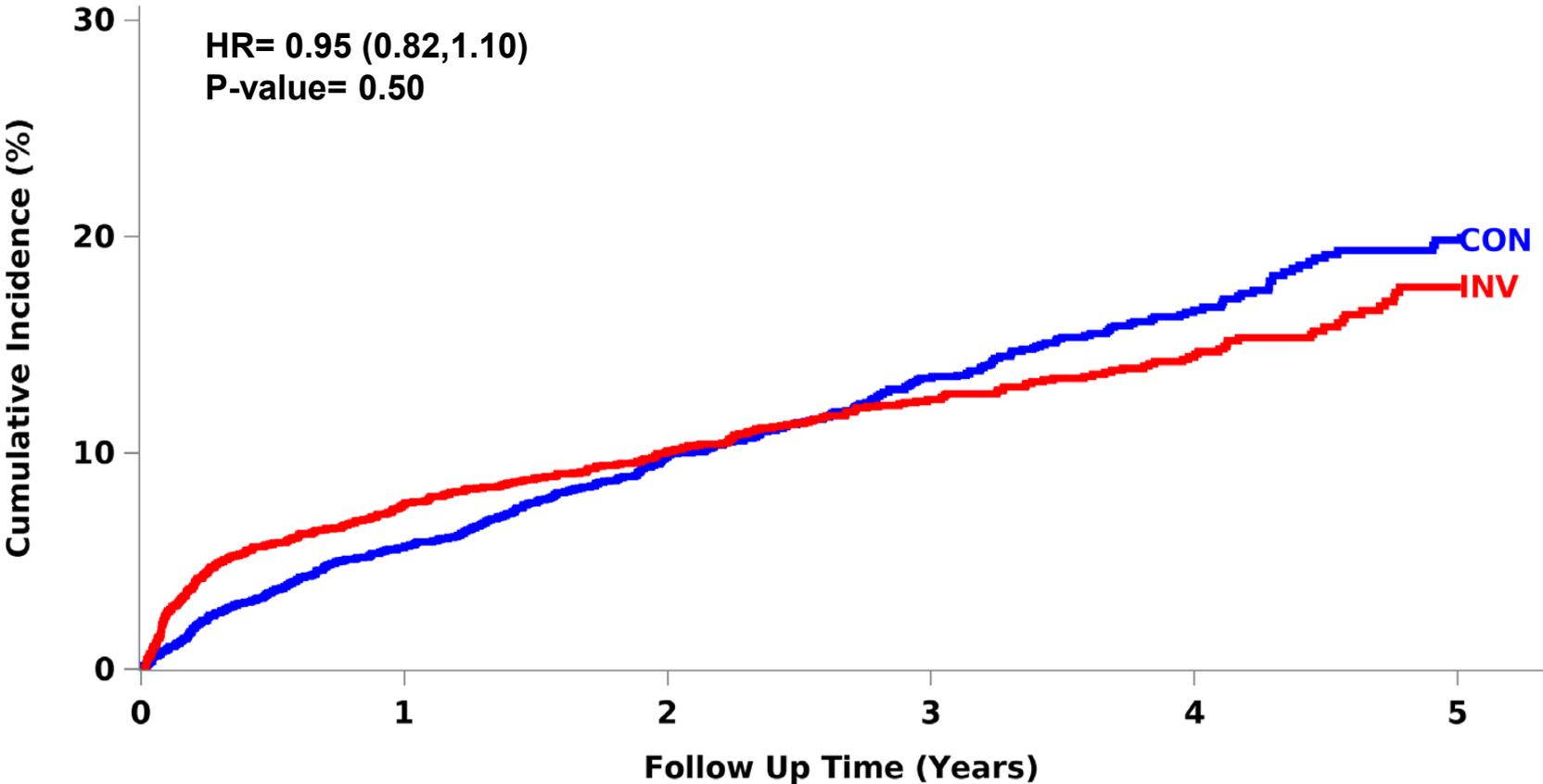


Subjects at Risk

	0	1	2	3	4	5
CON	2591	2453	1933	1325	746	298
INV	2588	2383	1933	1314	752	282



Net Clinical Benefit: CV Death, MI, UA, HF, RCA, Stroke

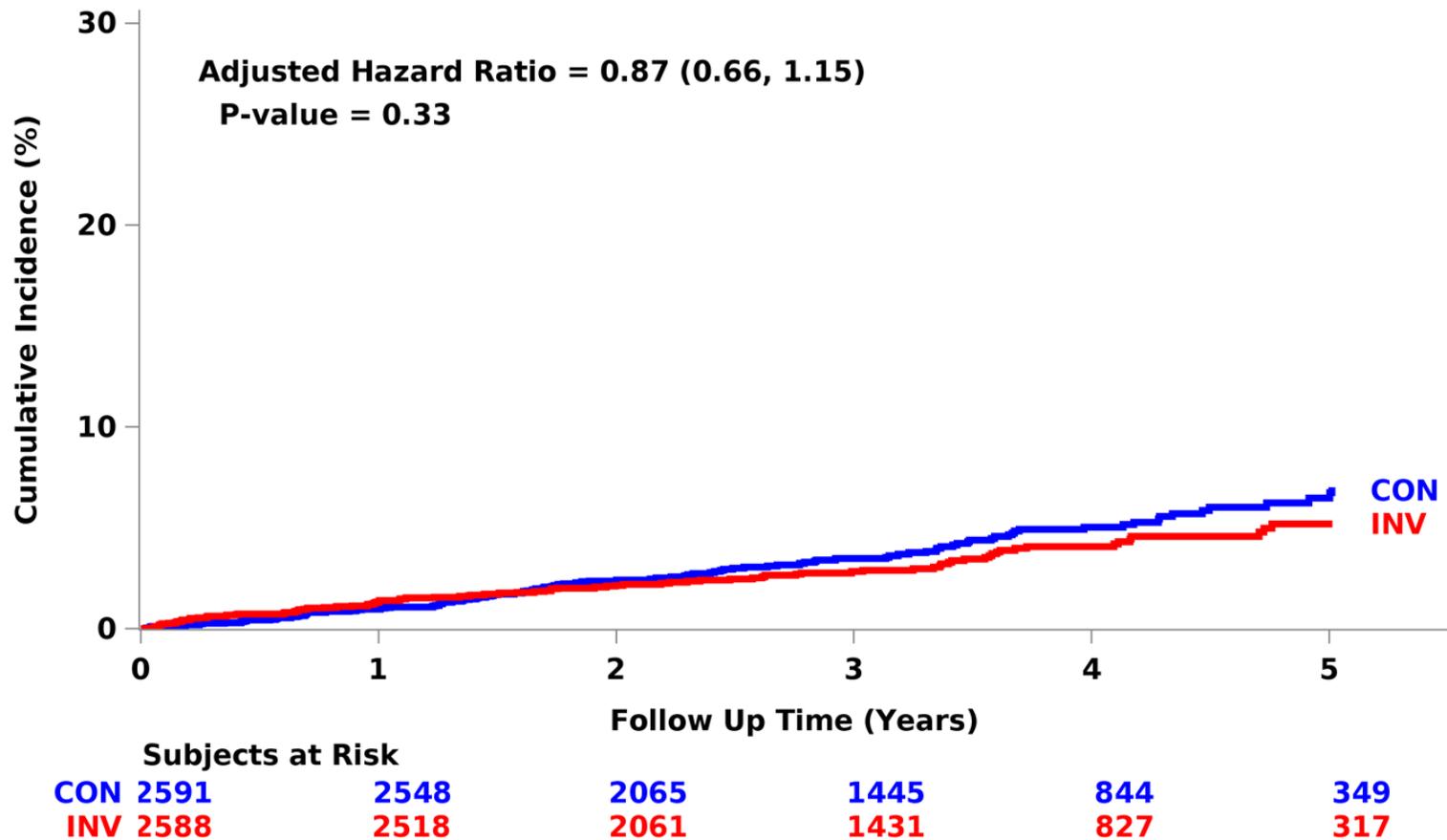


Subjects at Risk

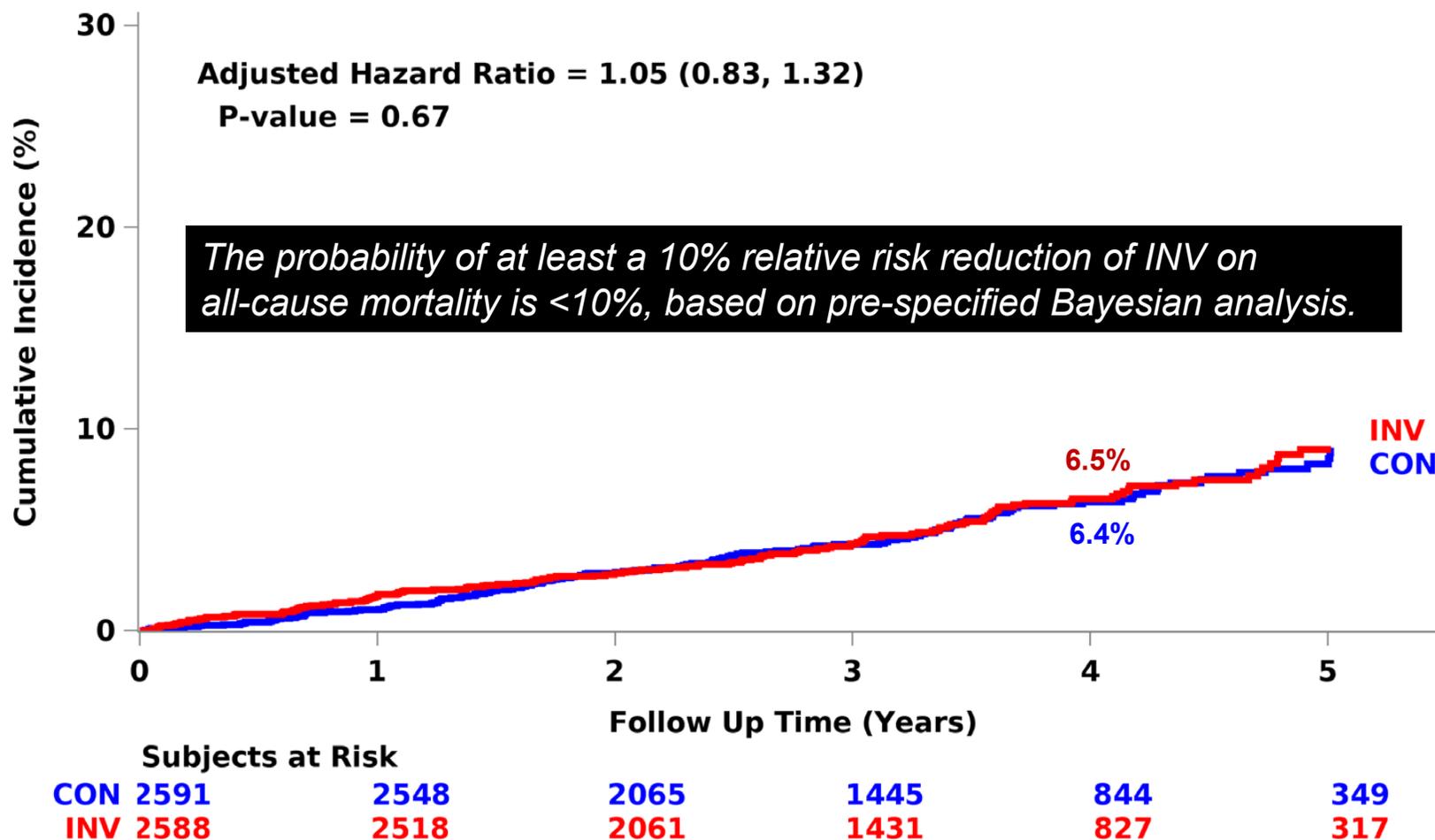
	0	1	2	3	4	5
CON	2591	2424	1898	1287	727	287
INV	2588	2347	1888	1271	721	268



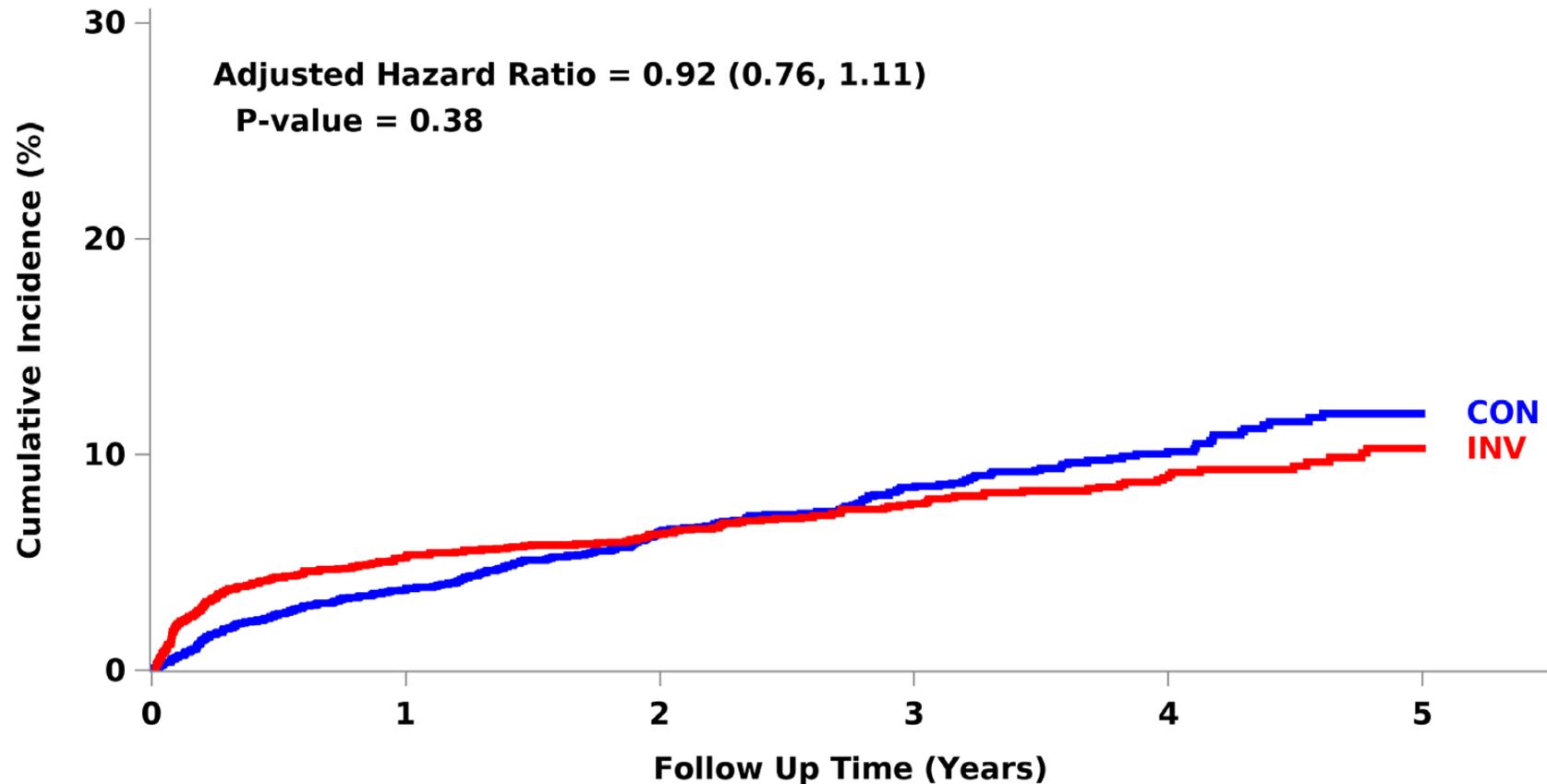
Cardiovascular Death



All-Cause Death



Myocardial Infarction



Subjects at Risk

	0	1	2	3	4	5
CON	2591	2452	1931	1321	747	298
INV	2588	2379	1931	1313	742	283



Limitations

- Unblinded trial – no sham procedure
- Based on exclusion criteria, the trial results do not apply to patients with:
 - Acute coronary syndromes within 2 months
 - Highly symptomatic patients
 - Left main stenosis
 - LVEF <35%
- Trial findings may not be generalizable to centers with higher procedural complication rates
- Completeness of revascularization has not yet been assessed
- Women were enrolled in the trial but more often excluded from randomization compared to men due to less ischemia and more non-obstructive CAD

Summary

- The curves cross for the primary endpoint and the major secondary endpoint at approximately 2 years from randomization
 - ~2 in 100 *higher* estimated rate with INV at 6 months
 - ~2 in 100 *lower* estimated rate with INV at 4 years
- Procedural MIs were increased with an invasive strategy
- Spontaneous MIs were reduced with an invasive strategy
- Low all-cause mortality in both groups despite high-risk clinical characteristics, high-risk ischemia and extensive CAD
- No heterogeneity of treatment effect, including by type of stress test, severity of ischemia or extent of CAD
- Very low rates of procedure-related stroke and death



Conclusions

- ISCHEMIA is the largest trial of an invasive vs conservative strategy for patients with SIHD
- Overall, an initial INV strategy as compared with an initial CON strategy did not demonstrate a reduced risk over median 3.3 years for
 - Primary endpoint - CV death, MI, hospitalization for UA, HF, RCA
 - Major Secondary endpoint - CV death or MI
- The probability of at least a 10% benefit of INV on all-cause mortality was <10%, based on pre-specified Bayesian analysis

