



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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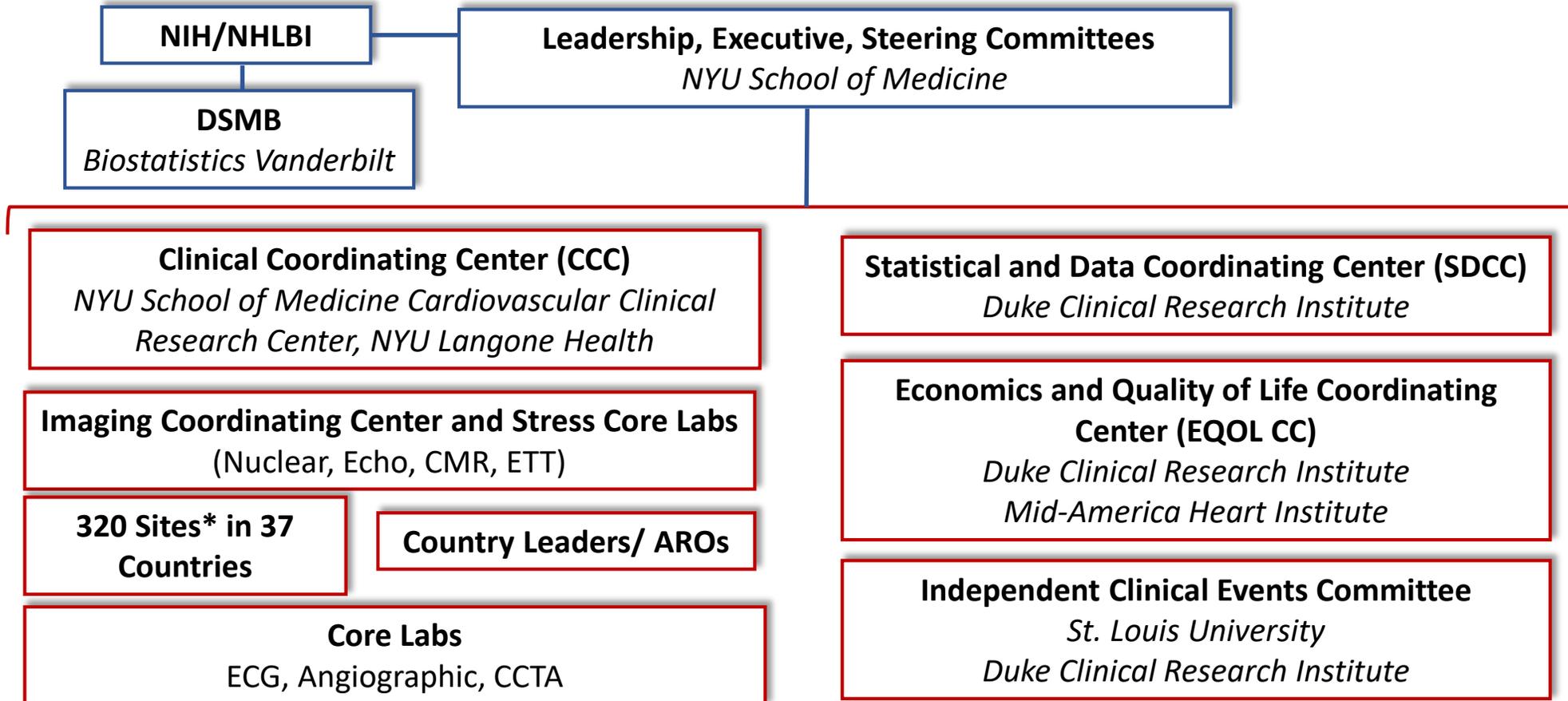
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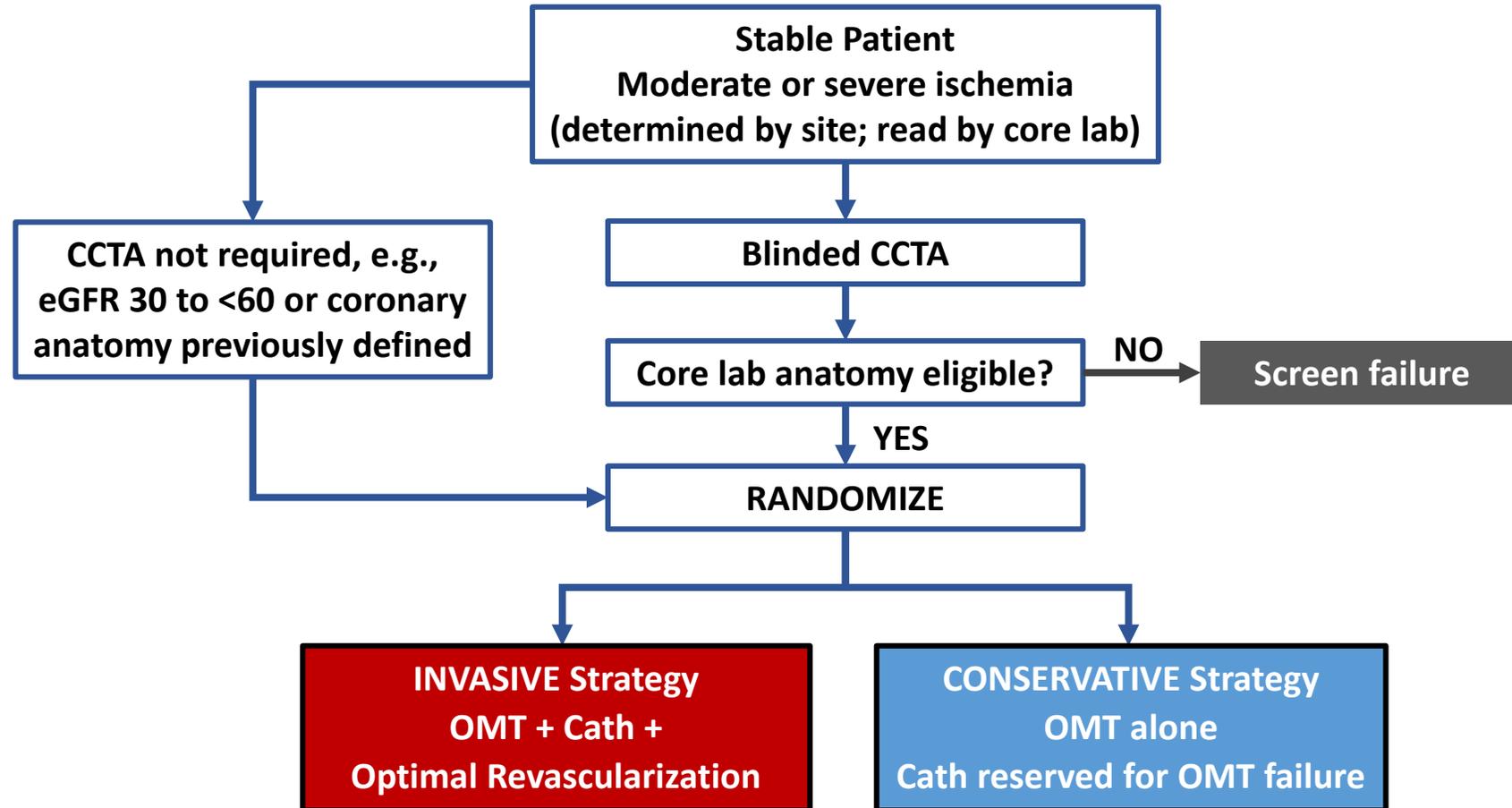


*Specific PCI and CABG volume and quality criteria were required for site participation.

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

Statistical Considerations

Power and Precision (N = 5,179)

- Power: >80% power to detect 18.5% relative reduction in primary endpoint assuming an aggregate 4-year cumulative rate of approximately 14%
- Precision: 95% confidence interval around primary endpoint treatment effect hazard ratio will extend from 15% lower to 17% higher than point estimate

Pre-Specified Statistical Analysis

- Intention-to-treat
- Model-free: Cumulative event rates accounting for competing risks
- Model-based: Cox regression (covariate adjusted)
 - Emphasize nonparametric event rates if proportional hazards assumption is violated
- Bayesian analysis of Cox model
 - Evaluate the probability of a small or large hazard ratio in light of minimally informative prior probabilities and the current study data

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.*

MI Endpoint Definitions

Event Collection and Adjudication Process

- Many methods were used to assure complete ascertainment and reporting of events
- All 5 primary endpoint events and stroke were adjudicated by an independent CEC comprised of senior experts from around the world

Cardiovascular
Death

**Myocardial
Infarction**

Unstable
Angina

Heart
Failure

Resuscitated
Cardiac Arrest

Universal Definition of MI *except*

- **Spontaneous MIs (types 1, 2, 4b, 4c)**
 - site-reported MI decision limits for troponin (upper limit of normal [ULN], not 99th percentile URL)
- **Procedural MI**
 - more **stringent** biomarker and supporting criteria for procedural MI

Procedural Myocardial Infarction Definitions

PCI-related MI (Type 4a)

Markers: CK-MB preferred over troponin

- CK-MB >5X ULN
- Troponin >35X ULN when CK-MB is unavailable

PLUS at least one of the following:

New ECG changes

- ST segment elevation or depression >0.1 mV in 2 contiguous leads
- New pathologic Q-waves in ≥ 2 contiguous leads or
- New persistent LBBB

Angio

- Reduced flow in major coronary
- Type C or greater dissection

Or stand-alone biomarker definition

- **CK-MB to >10-fold** the ULN (or when CK-MB is unavailable, a rise in troponin to **>70 fold** the MI Decision Limit/ULN)

CABG-Related MI (Type 5)

Markers: CK-MB preferred over troponin

- CK-MB to >10X ULN
- Troponin to >70X ULN when CK-MB is unavailable

PLUS at least one of the following:

Imaging

- A new substantial wall motion abnormality by (CEC assessed), except new septal and apical abnormalities

New ECG changes

- New pathologic Q-waves in ≥ 2 contiguous leads or
- New persistent LBBB present on day 3 post CABG or hospital discharge

Or stand-alone biomarker definition

- **CK-MB to >15-fold** the ULN (or when CK-MB is unavailable a rise in troponin to **>100 fold** the MI Decision Limit/ULN)

Elements in common with SCAI definition of clinically relevant MI

Endpoint Definitions

Unstable Angina

Prolonged ischemic symptoms at rest or accelerating pattern resulting in hospitalization

AND at least 1 of the following (core laboratory assessed):

- New or worsening ST or T wave changes
- Angiographic evidence of a ruptured/ulcerated plaque, or thrombus

Heart Failure

- ≥ 24 hour hospitalization for HF

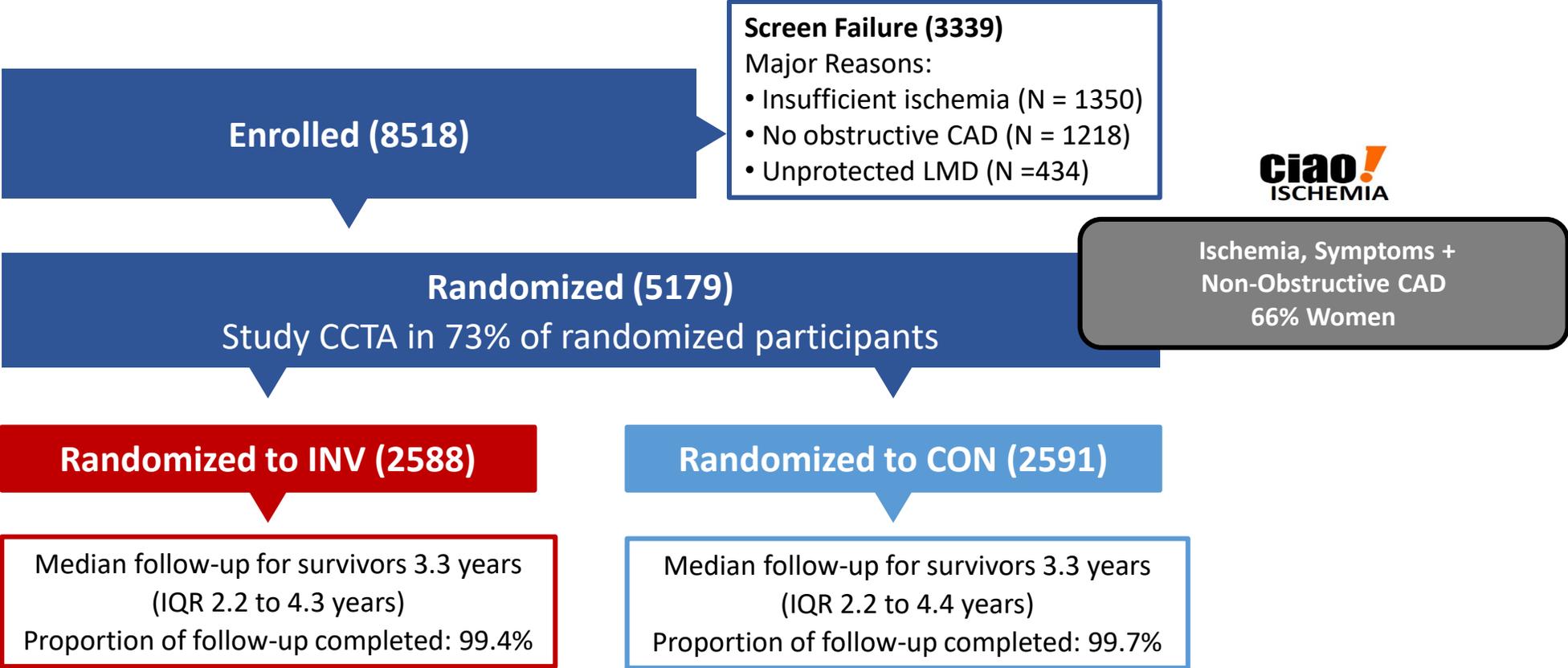
AND all of the following:

- **Symptoms** New/worsening dyspnea, orthopnea, PND, fatigue, reduced exercise tolerance AND
- **Signs** of HF AND
- **Increased pharmacologic** Rx or initiation of **mechanical** or surgical intervention AND
- No other cause identified

Resuscitated Cardiac Arrest

- Successful resuscitation for documented cardiac arrest **out-of-hospital** (or ER), discharged from hospital alive

Study Flow



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

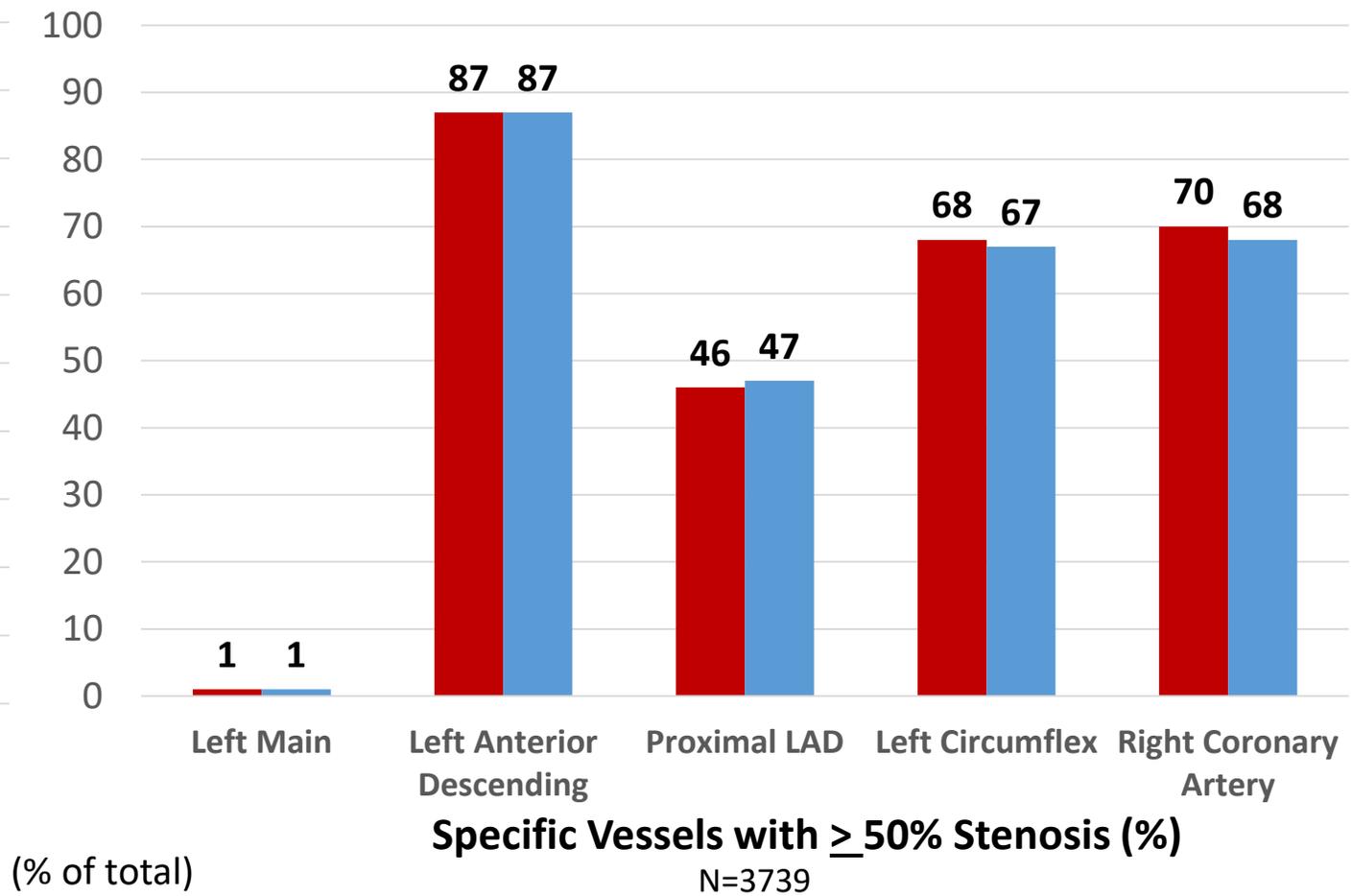
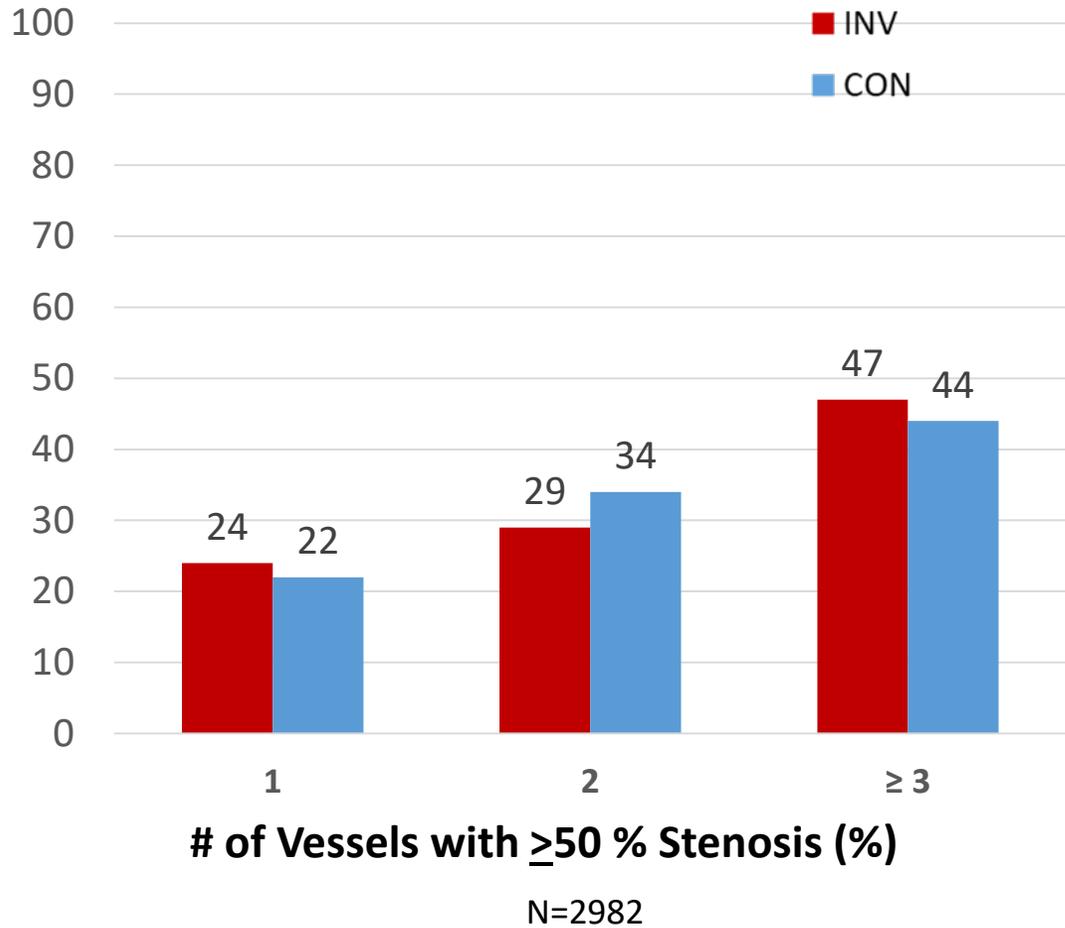
Median values reported with 25th and 75th percentiles

Qualifying Stress Test: Core Lab Interpretation

Characteristic	Total	INV	CON
Baseline Inducible Ischemia*			
Severe	54%	53%	55%
Moderate	33%	34%	32%
Mild/None	12%	12%	12%
Uninterpretable	1%	1%	1%

*Only severe qualified by ETT

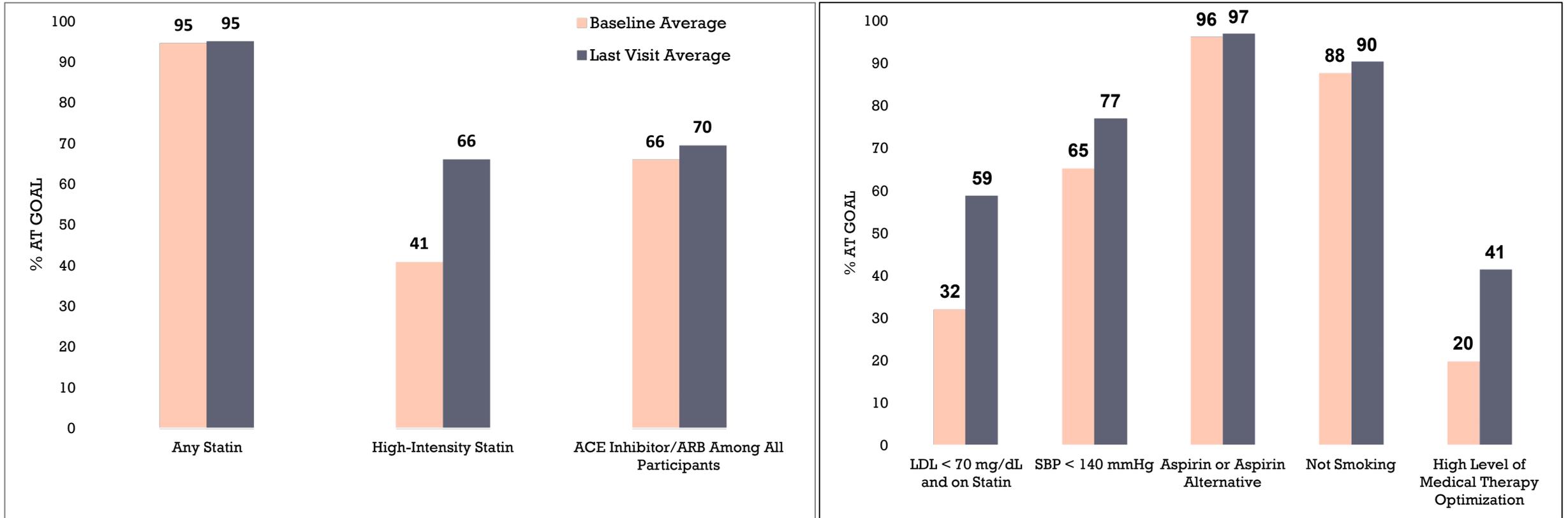
Baseline Coronary Artery Anatomy by CCTA



Risk Factor Management

Baseline vs last visit

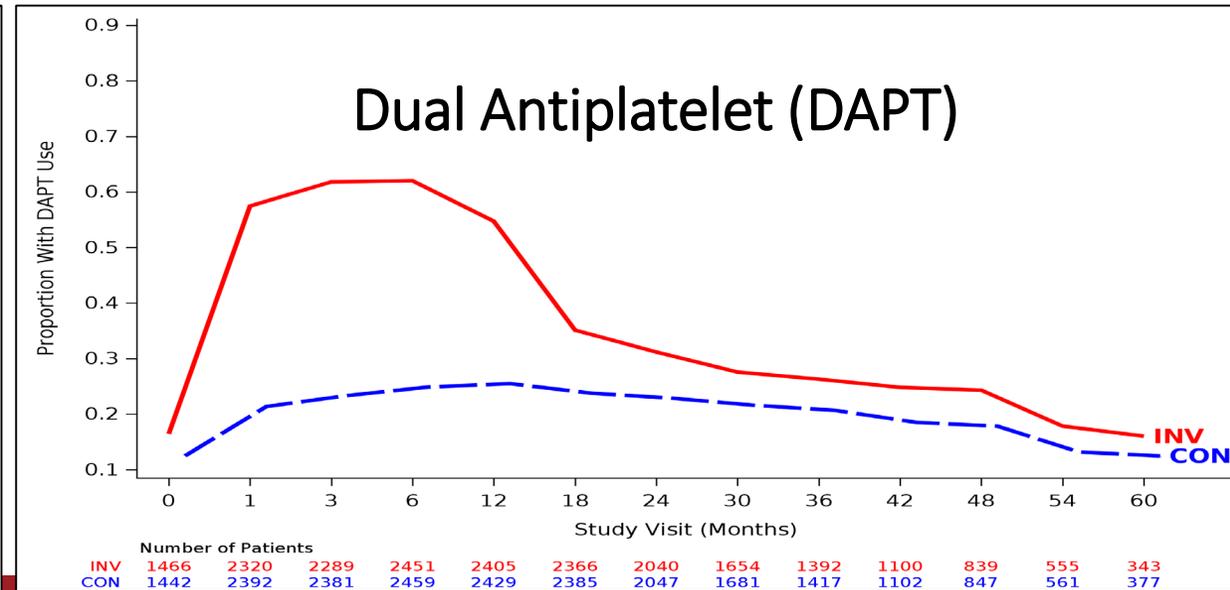
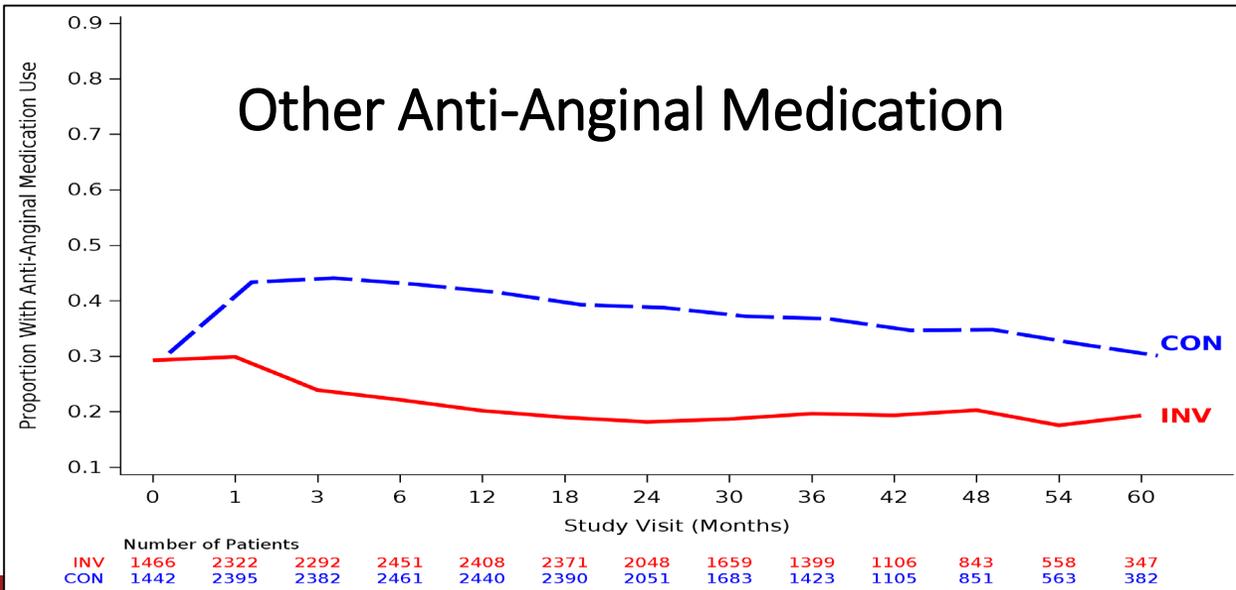
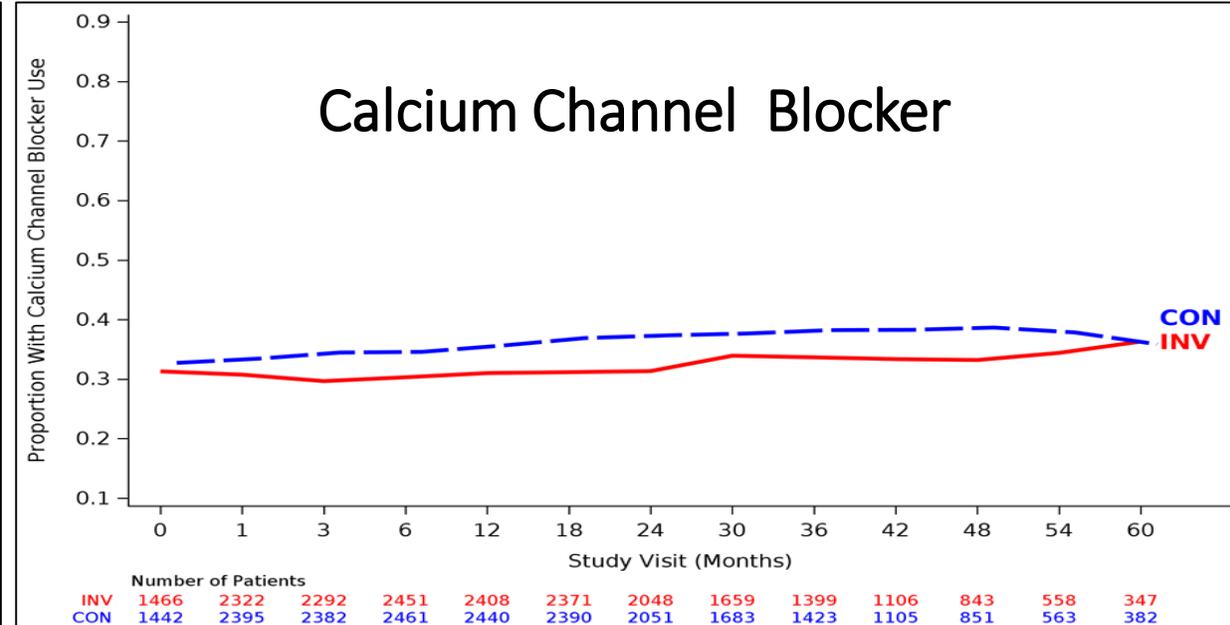
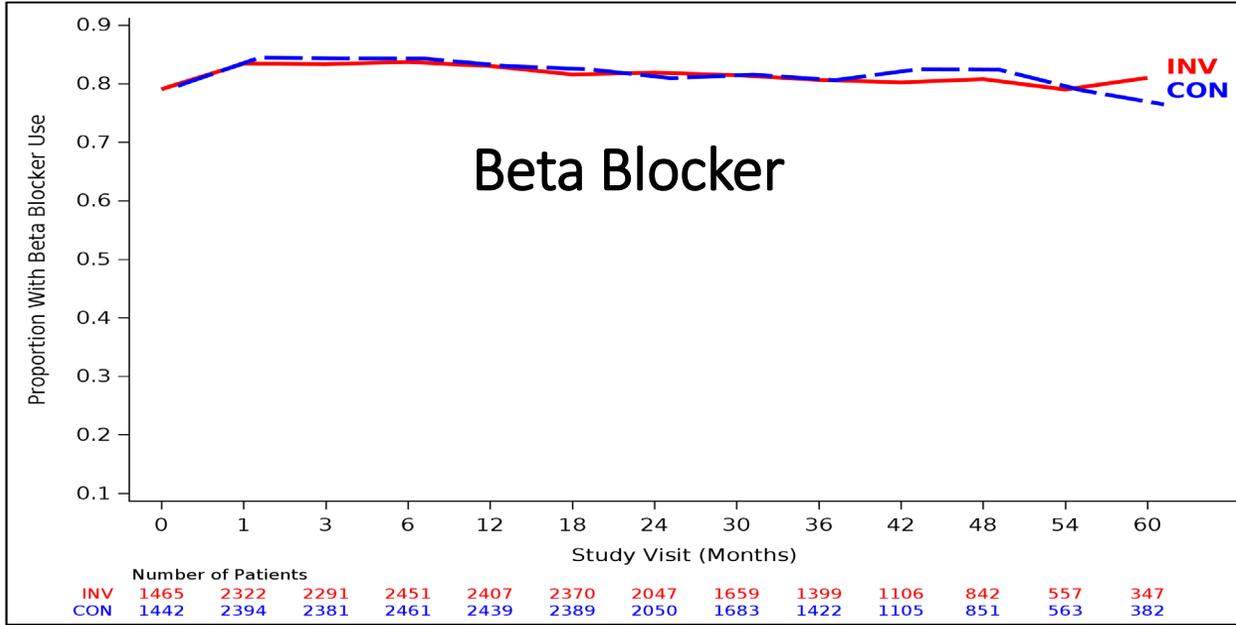
No between group differences INV vs CON



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.

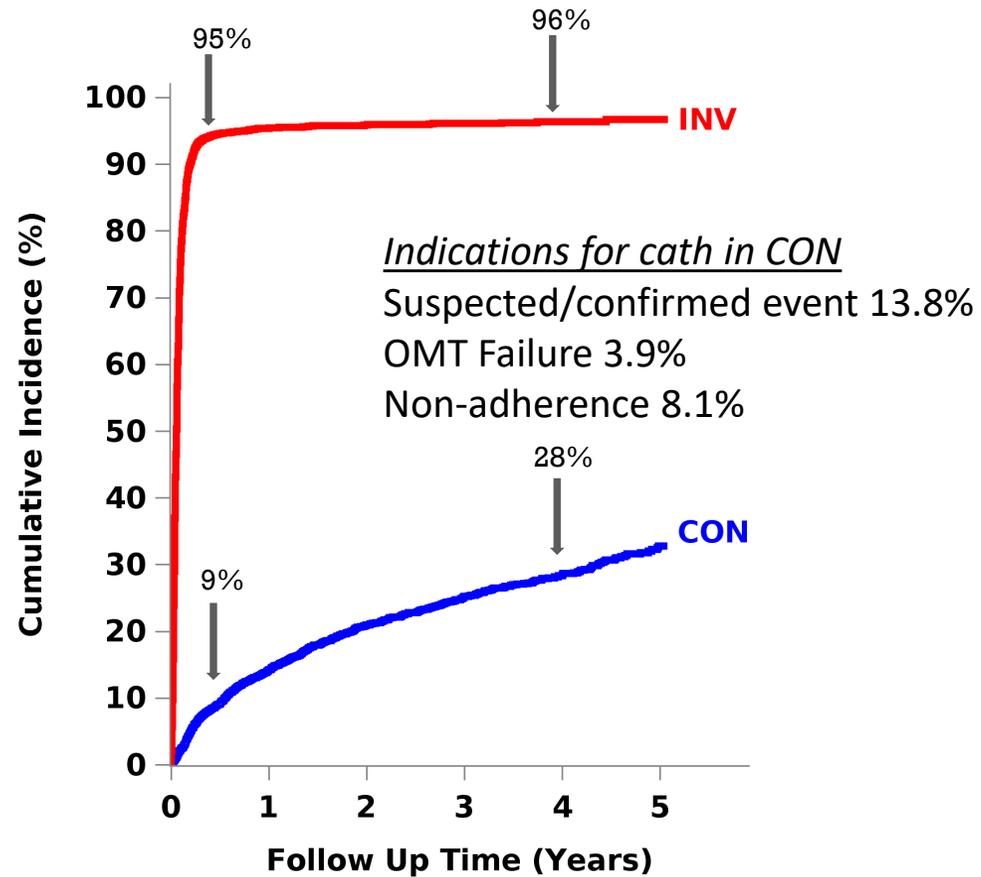


Medication Use Over Time



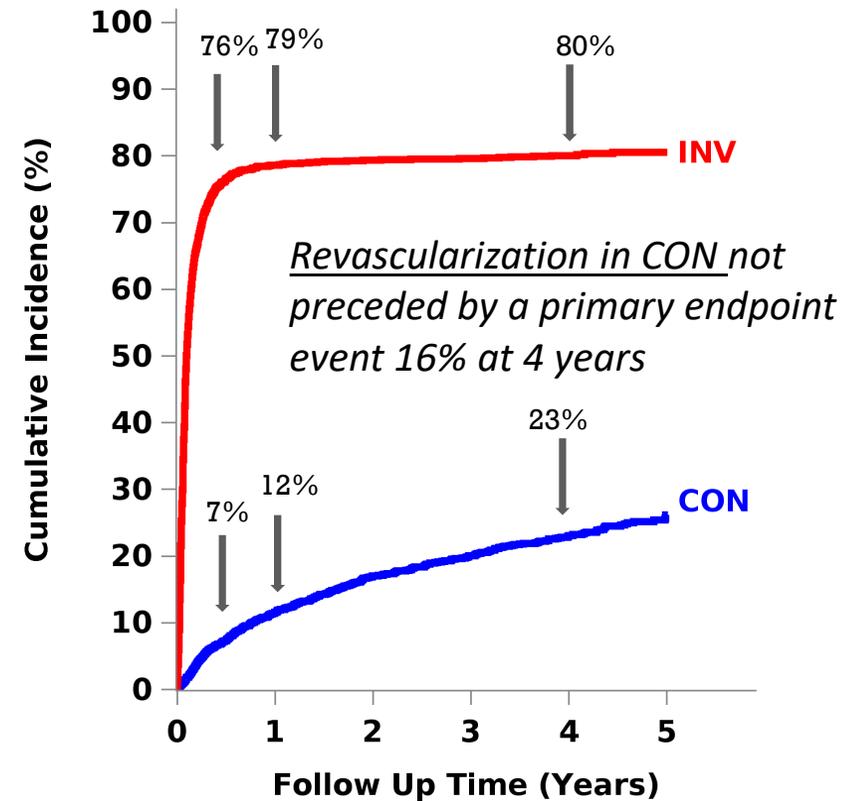
Cardiac Catheterization and Revascularization

Cardiac Catheterization



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

Revascularization



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



Mode of Revascularization

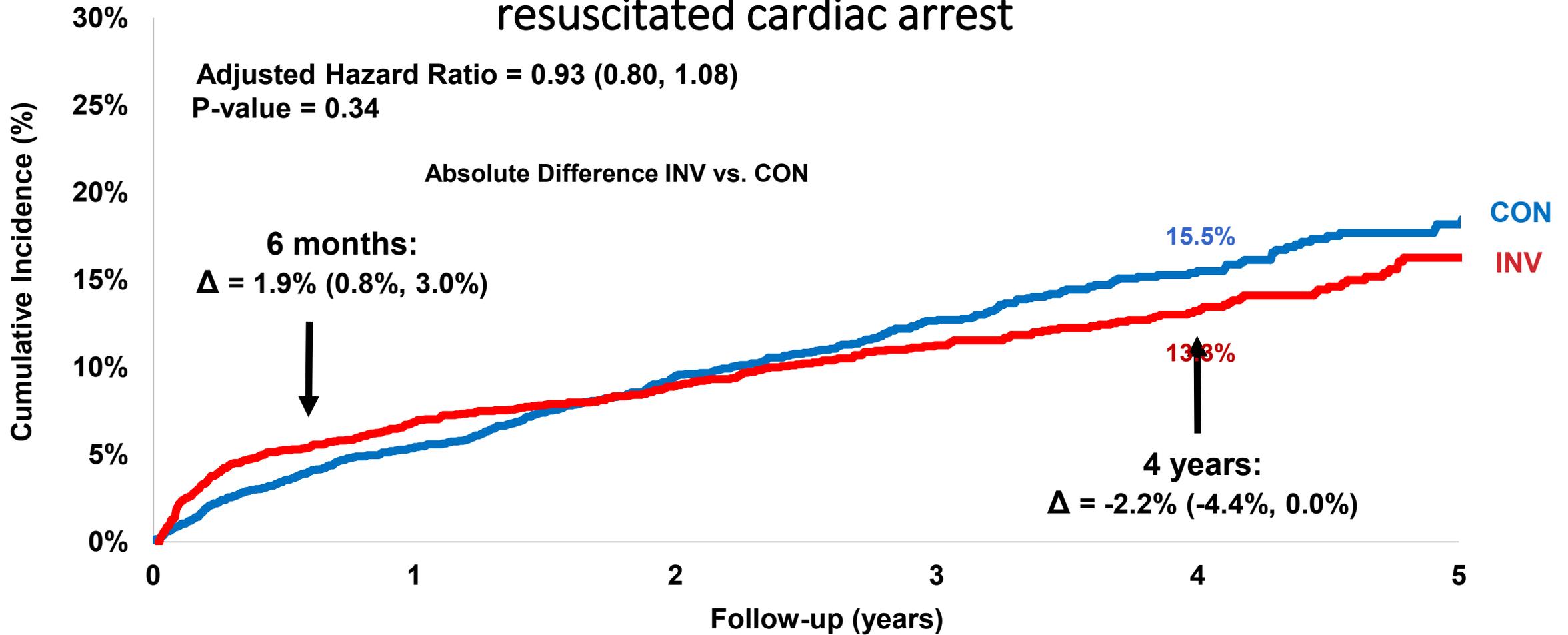
First Procedure for Those Revascularized in Invasive Group (~80% of INV)

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

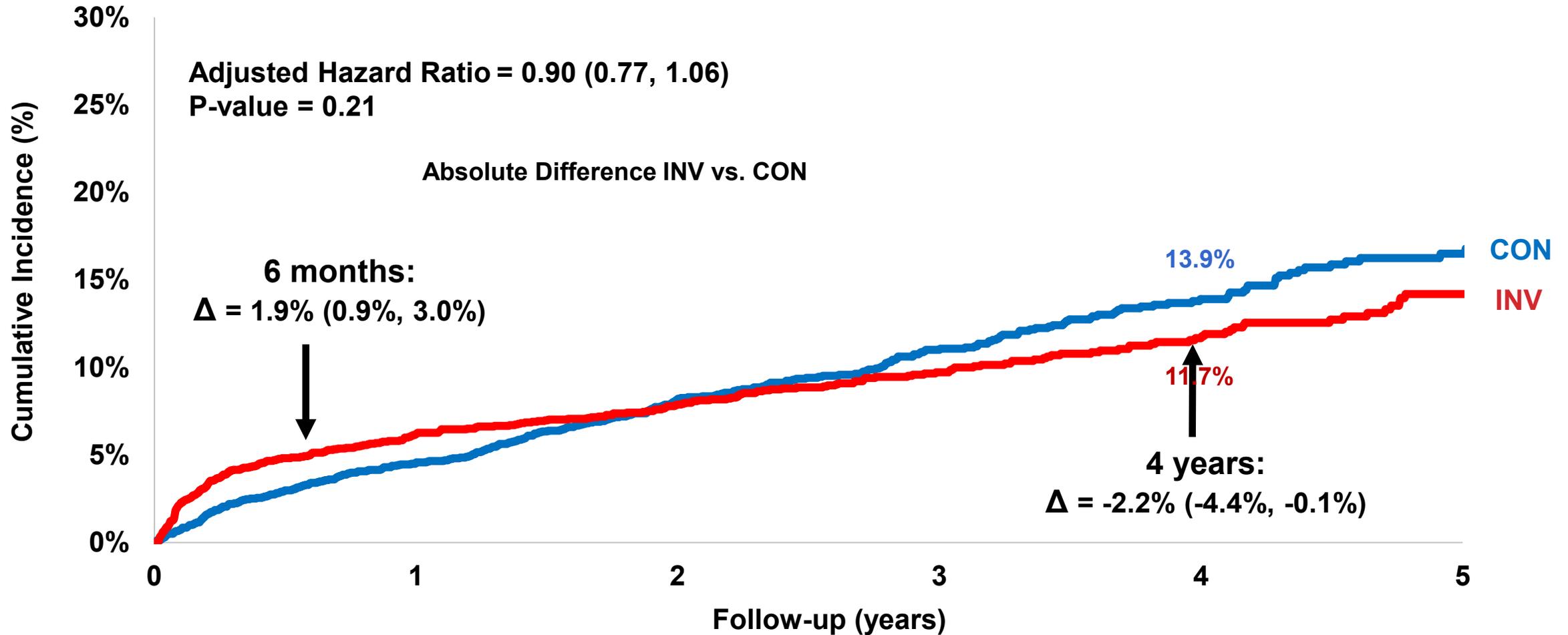


Subjects at Risk

CON	2591	2431	1907	1300	733	293
INV	2588	2364	1908	1291	730	271



Major Secondary: CV Death or MI

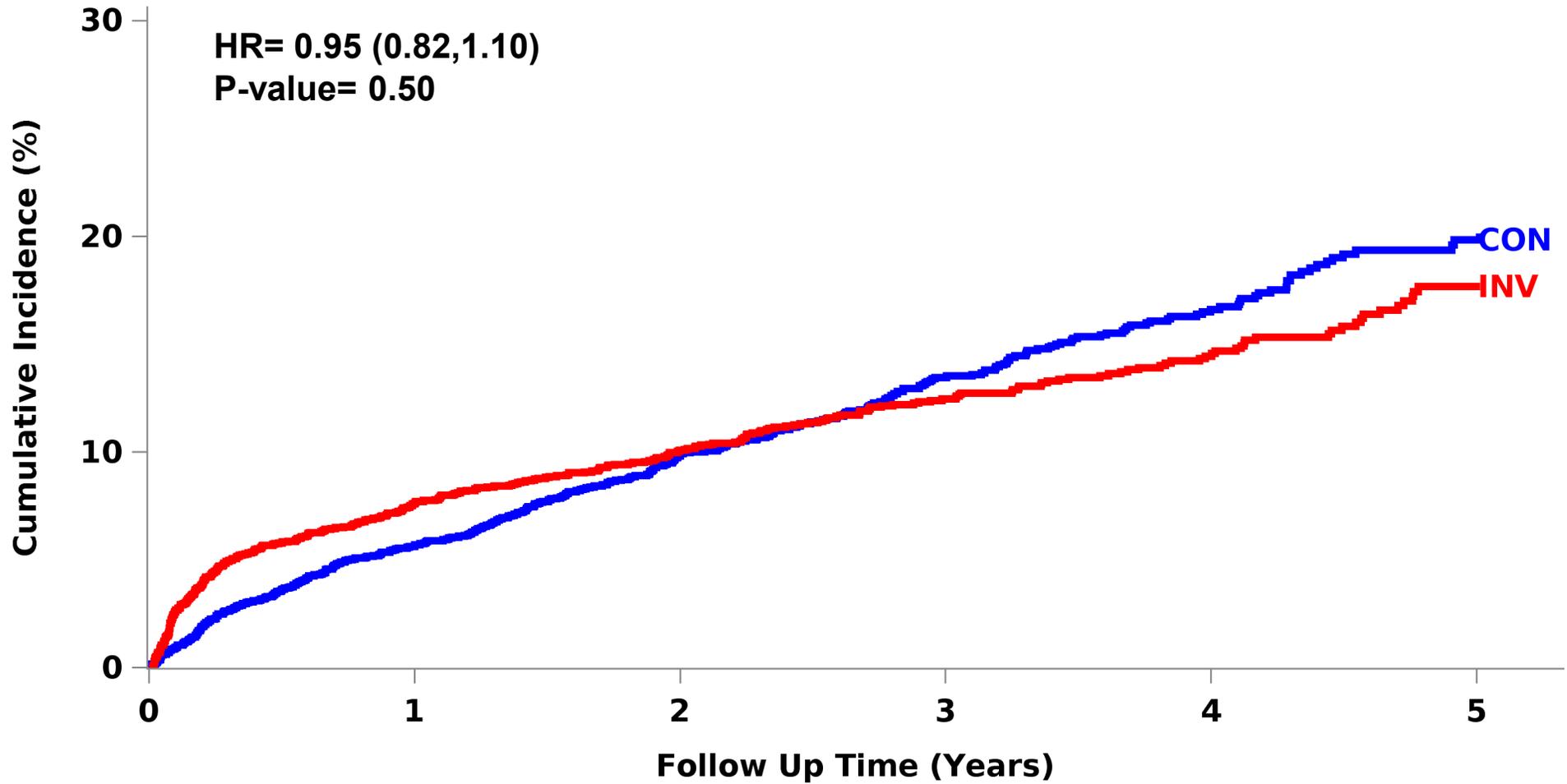


Subjects at Risk

CON	2591	2453	1933	1325	746	298
INV	2588	2383	1933	1314	752	282



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

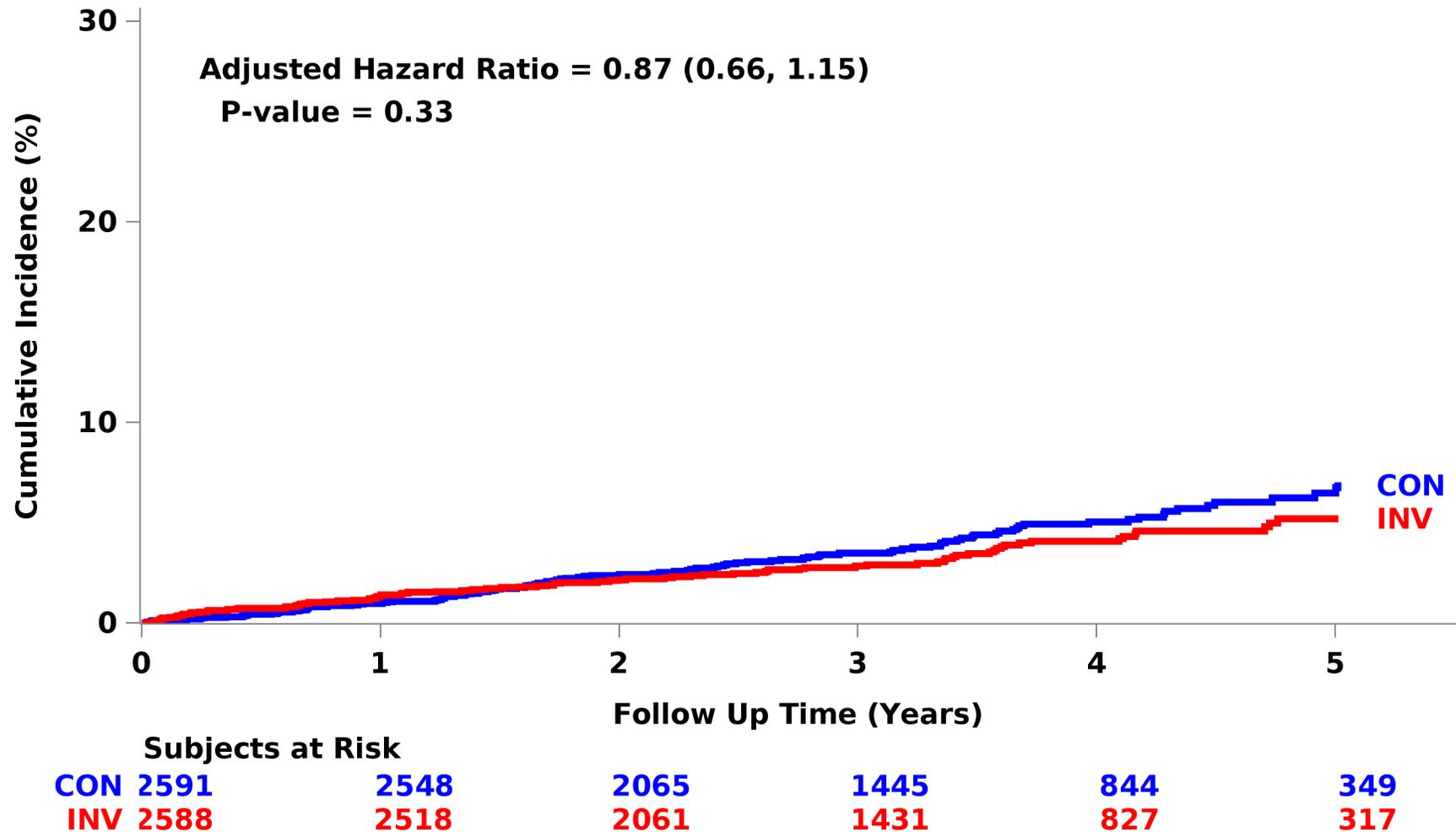


Subjects at Risk

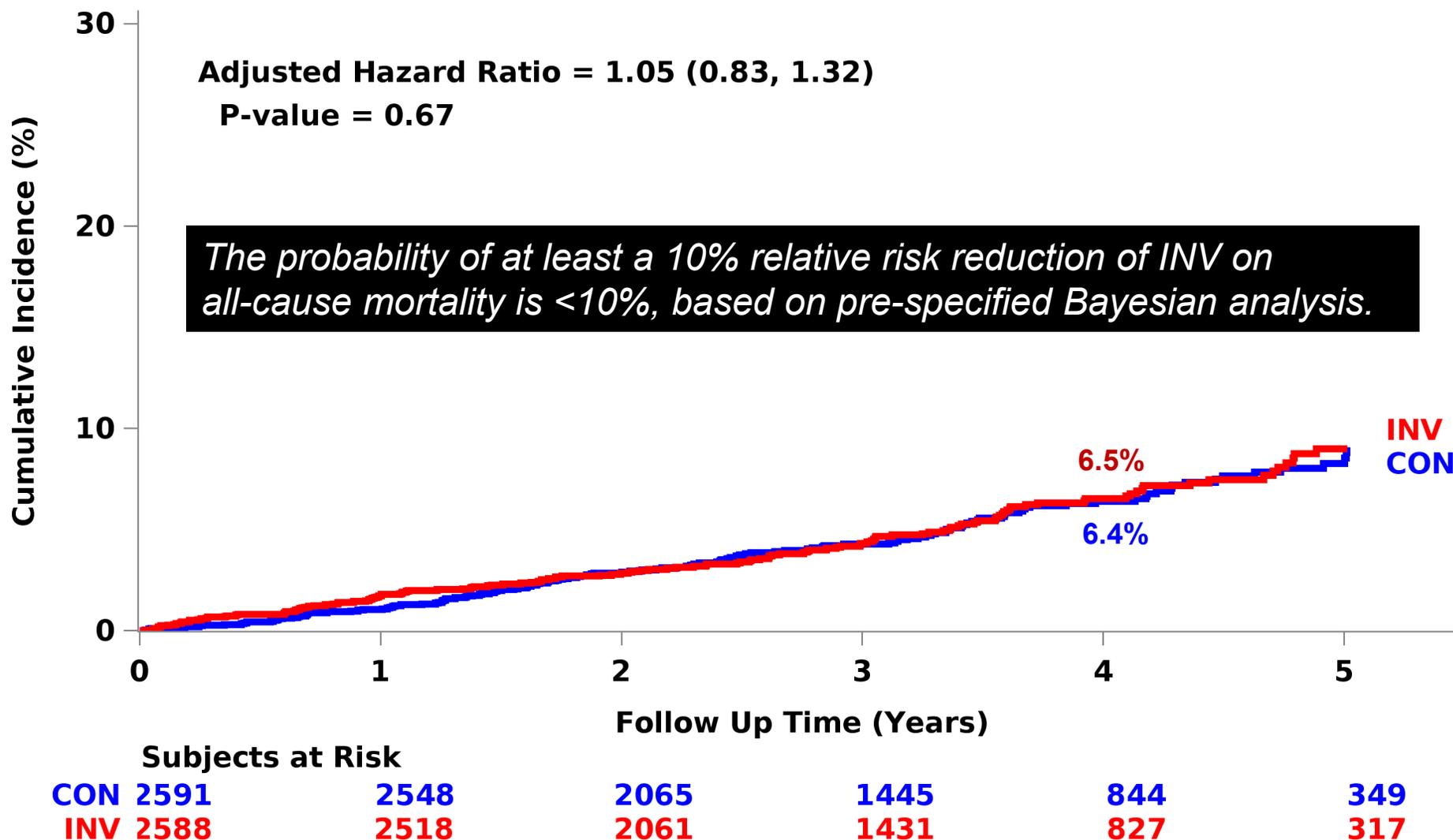
	0	1	2	3	4	5
CON	2591	2424	1898	1287	727	287
INV	2588	2347	1888	1271	721	268



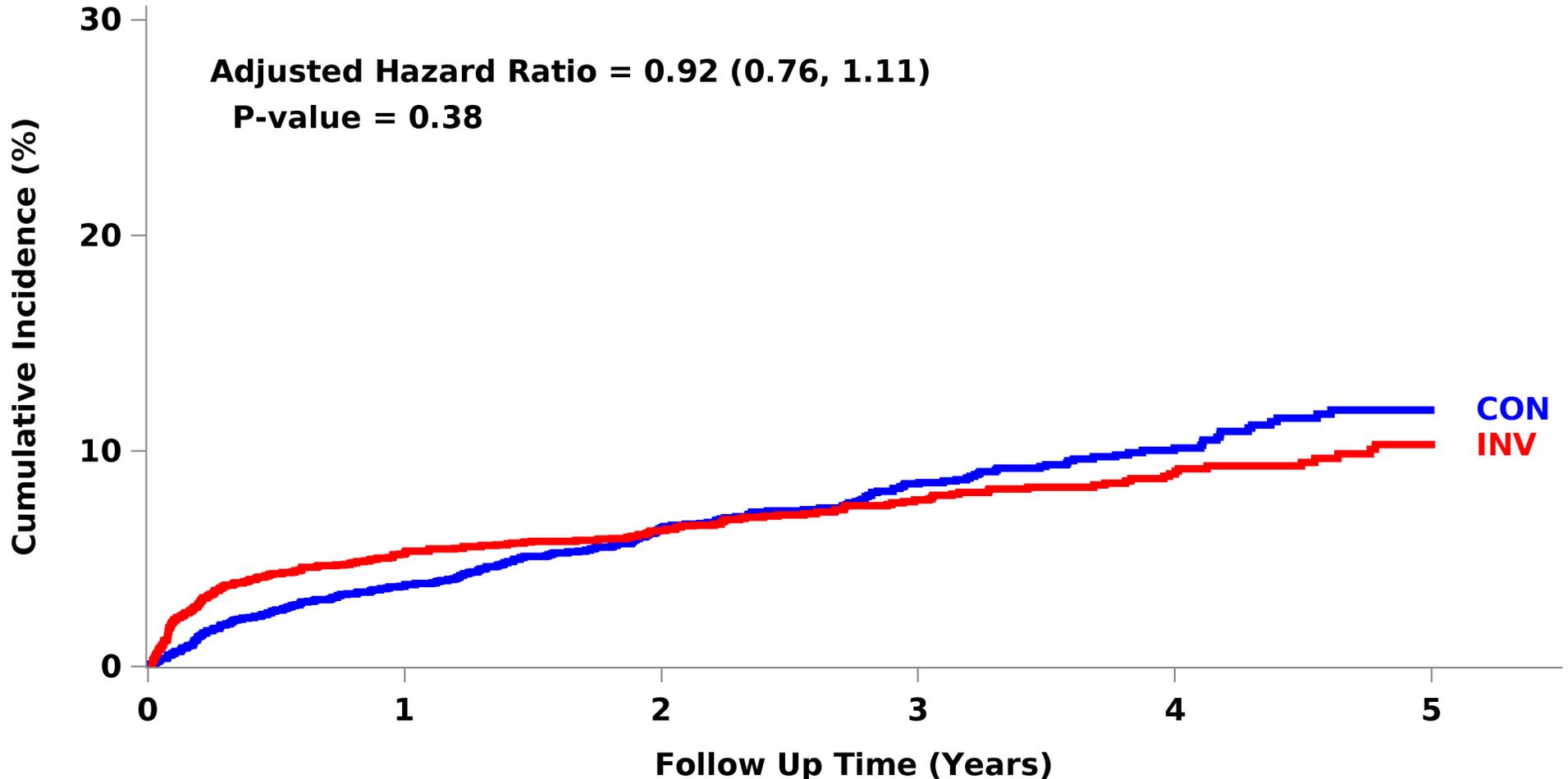
Cardiovascular Death



All-Cause Death



Myocardial Infarction

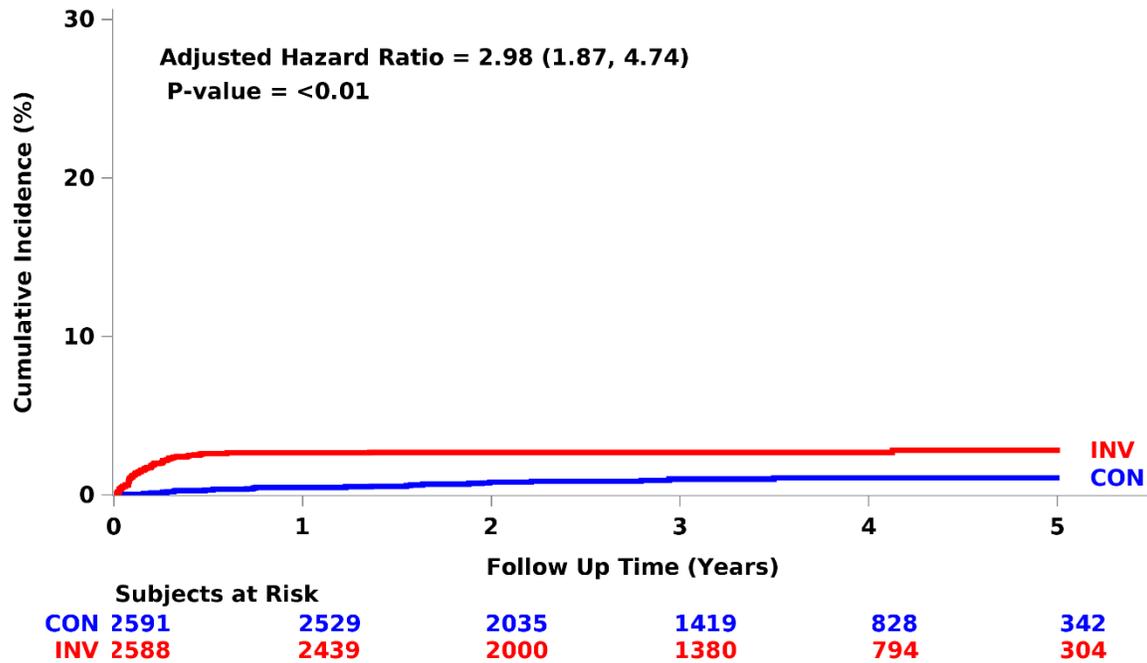


Subjects at Risk

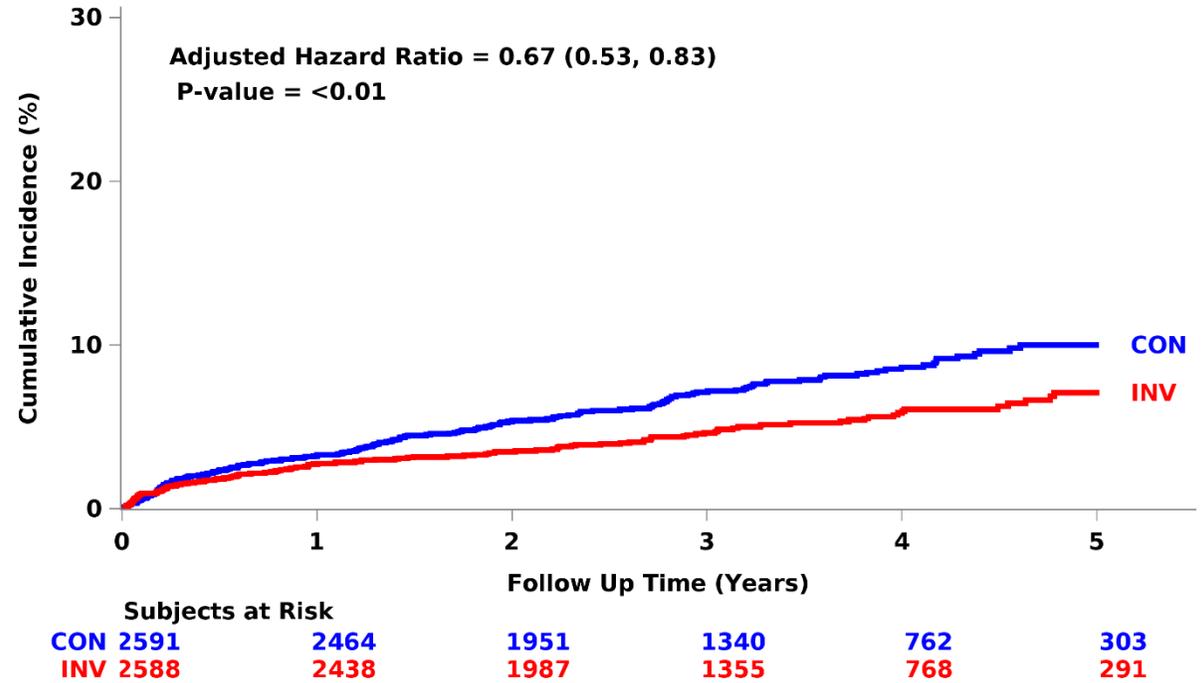
	0	1	2	3	4	5
CON	2591	2452	1931	1321	747	298
INV	2588	2379	1931	1313	742	283



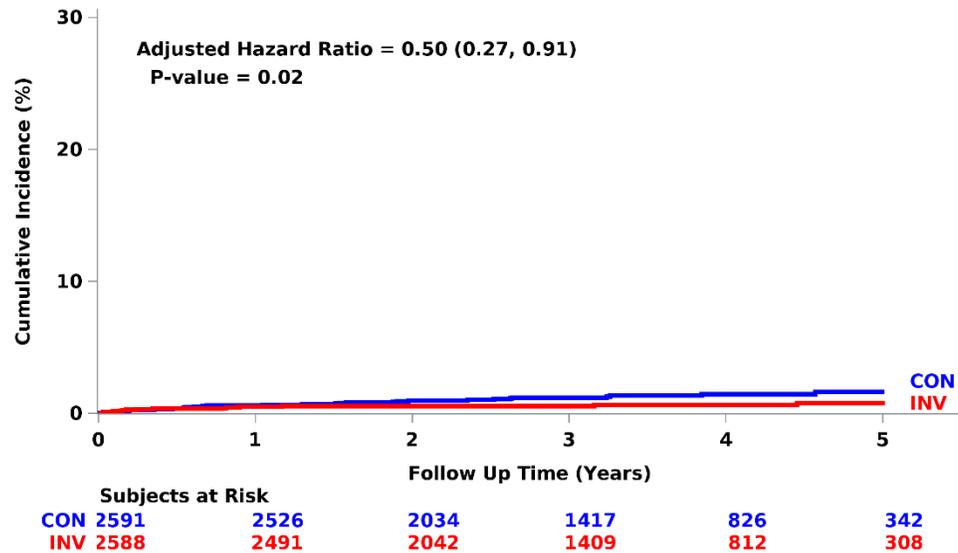
Procedural MI *Type 4a or 5 MI*



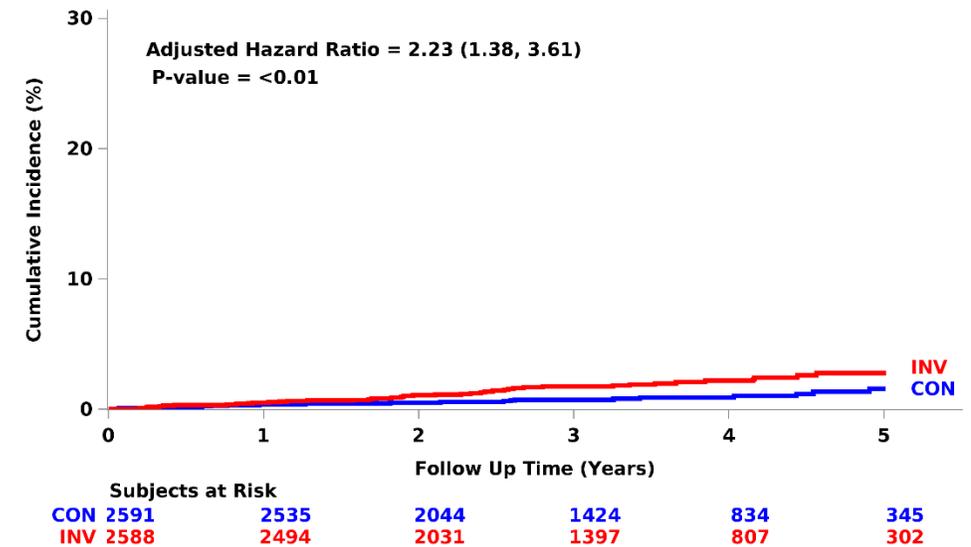
Spontaneous MI *Types 1, 2, 4b, or 4c MI*



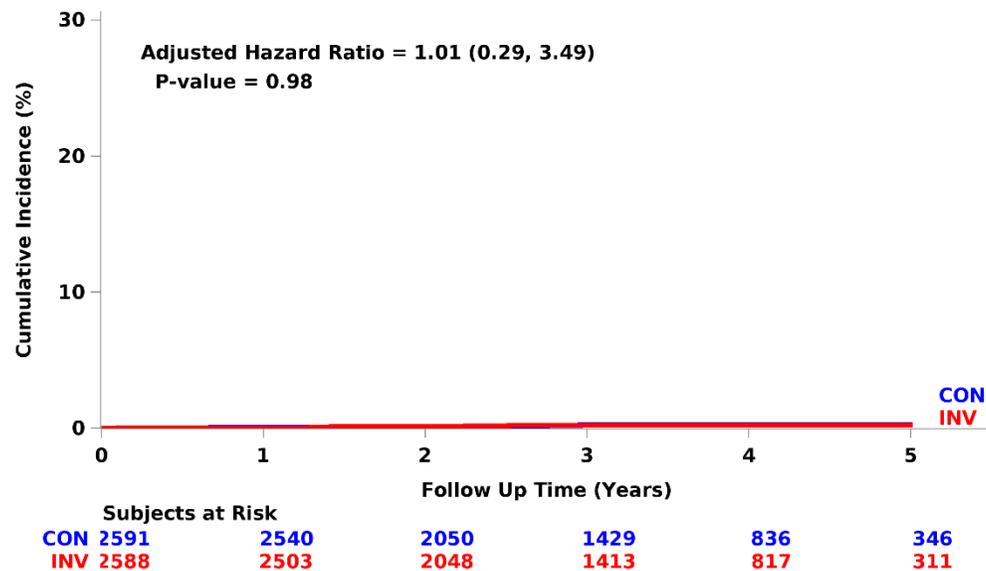
Hospitalization for Unstable Angina



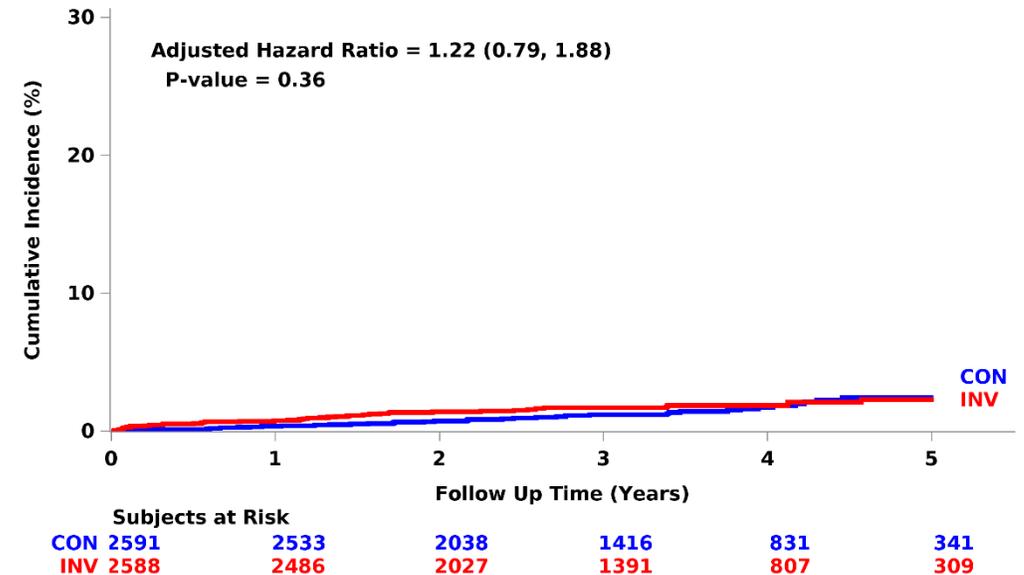
Hospitalization for Heart Failure



Resuscitated Cardiac Arrest



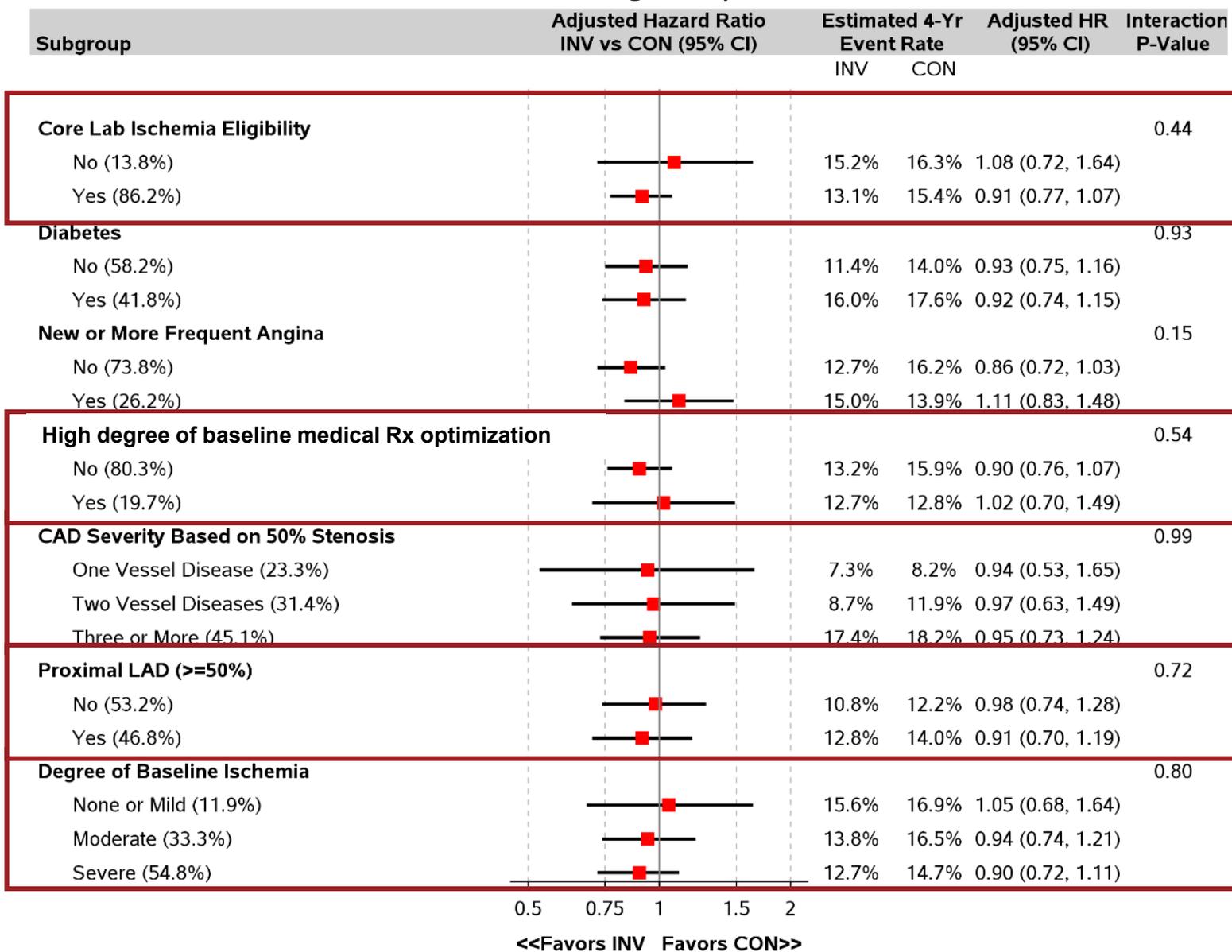
Stroke



Primary endpoint

Pre-specified Important Subgroups

There was no heterogeneity of treatment effect



N=3739 for Prox LAD Y/N
 N=2982 for # diseased vessels



Primary endpoint and major secondary endpoint (CV death or MI)

*No heterogeneity of treatment effect
based on any characteristic*

- Age
- Sex
- Ethnicity
- Race
- Geographic region
- Stress test, imaging vs no imaging
- Stress imaging modality
- Moderate or severe anterior ischemia
- Prior MI
- Prior cardiac cath
- Prior PCI
- Prior CABG
- Ejection Fraction
- eGFR



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



Thank you

- To the thousands of investigators and coordinators
- The dedication of thousands of participants
- The NHLBI
- We are extremely grateful for their contribution to advance our understanding of the relative risks and benefits of two commonly used management strategies for stable ischemic heart disease

Slides at ischemiatrial.org

Simultaneous publication precluded by short time from last patient, last visit to database lock to AHA



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Merck Sharp & Dohme Corp.

Financial donations

Arbor Pharmaceuticals LLC
AstraZeneca Pharmaceuticals LP

*in memoriam

