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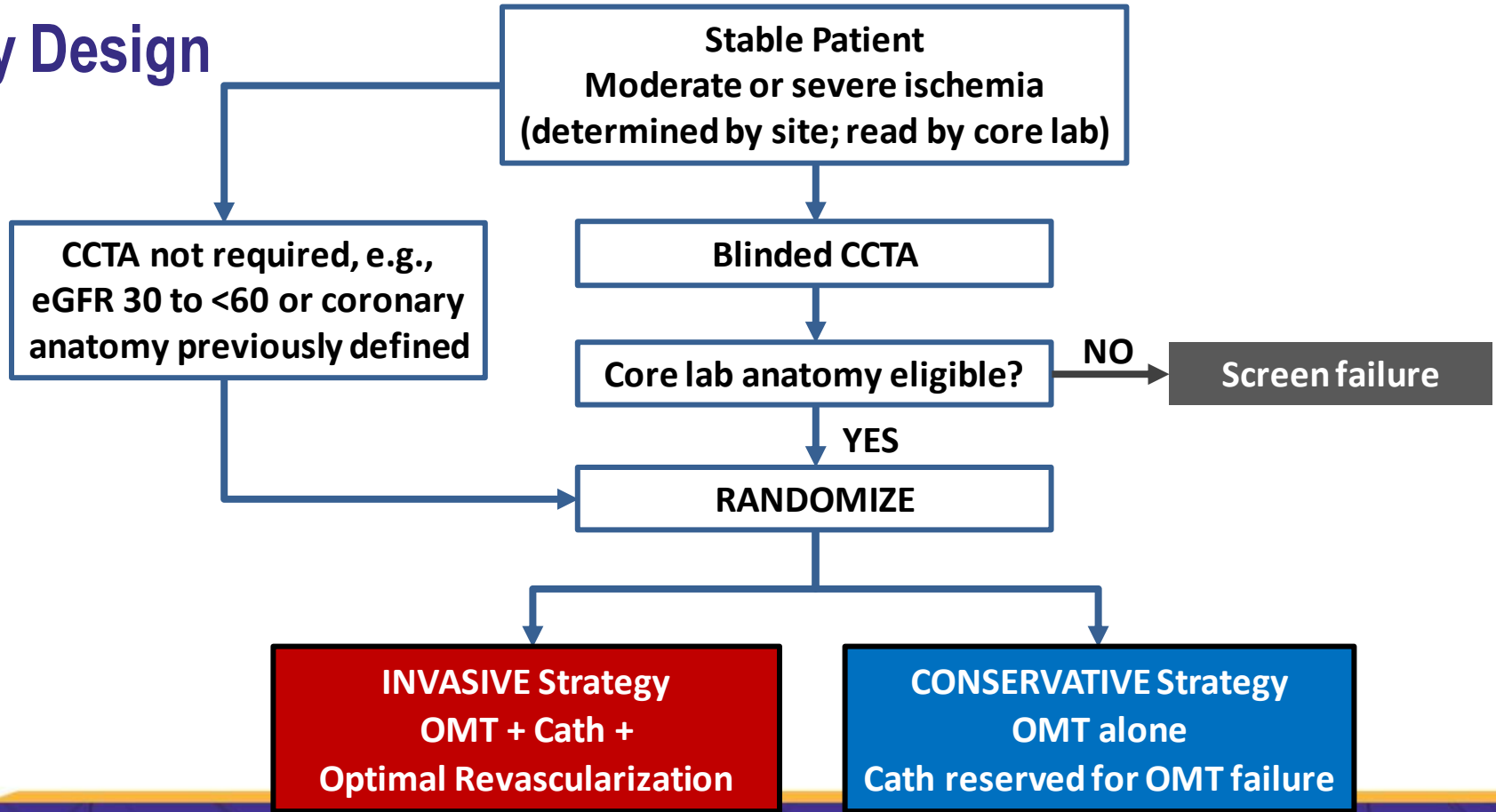


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**Relationships of Ischemia
Severity and Coronary Artery
Disease Extent with
Clinical Outcomes in the
ISCHEMIA Trial**

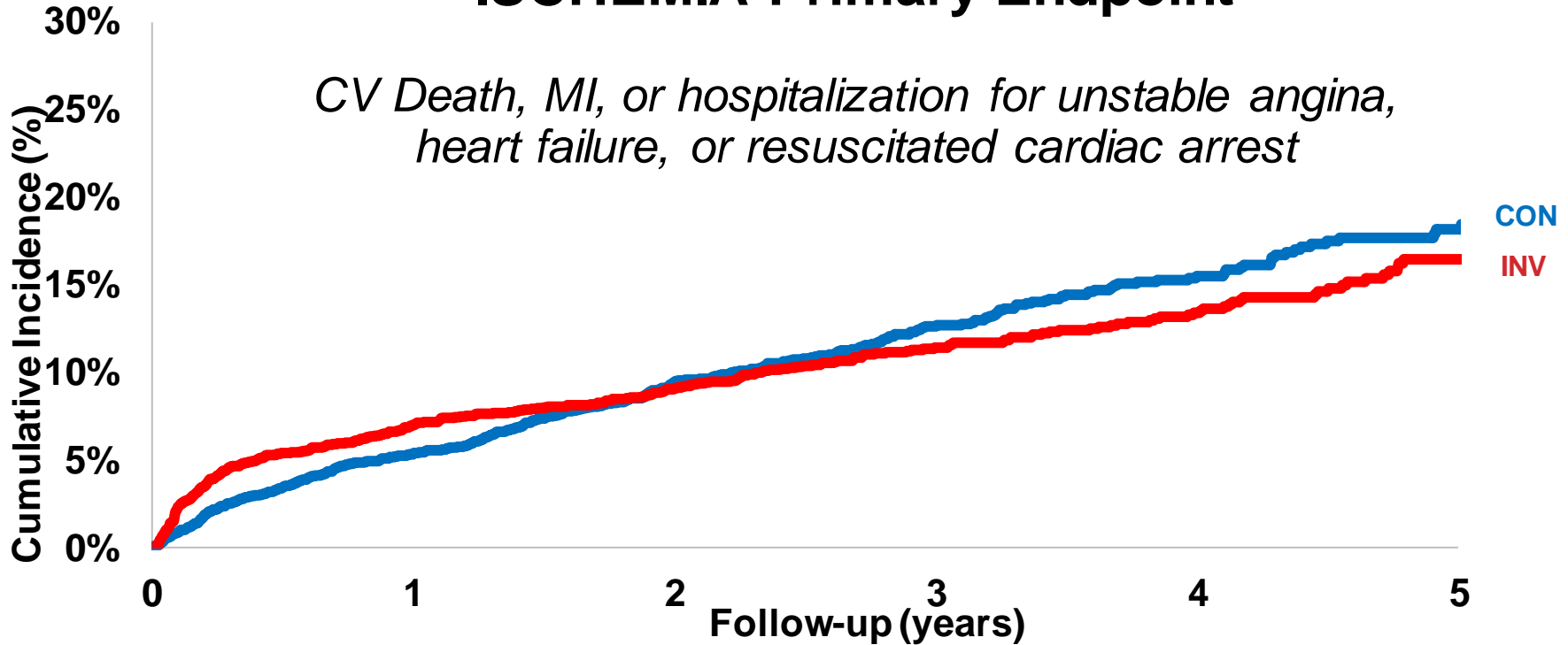
**David Maron, MD on behalf of
Harmony Reynolds, MD
and the ISCHEMIA Investigators**

Study Design



ISCHEMIA Primary Endpoint

CV Death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest



Subjects at Risk

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

ACC/AHA Guidelines for Revascularization to Improve Survival

Adapted from ACCF/AHA Guidelines
for PCI and CABG JACC 2011

Revascularization Method*	COR	LOE
3-vessel disease with or without proximal LAD artery disease*		
CABG	I	B
	IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score >22) who are good candidates for CABG	B
PCI	IIb—Of uncertain benefit	B
2-vessel disease with proximal LAD artery disease*		
CABG	I	B
PCI	IIb—Of uncertain benefit	B
2-vessel disease without proximal LAD artery disease*		
CABG	IIa—With extensive ischemia	B
	IIb—Of uncertain benefit without extensive ischemia	C
PCI	IIb—Of uncertain benefit	B
1-vessel proximal LAD artery disease		
CABG	IIa—With LIMA for long-term benefit	B
PCI	IIb—Of uncertain benefit	B

Analysis of Outcomes by Severity of Ischemia and Anatomy

- Assess relationship of ischemia and anatomy to death and MI
 - Ischemia severity (core lab interpretation)
 - Modified Duke prognostic index (integrates extent and severity of CAD on CCTA, core lab interpretation)
- Test for heterogeneity of treatment effect using these measures

Definitions

Ischemia Severity

- **Severe:** nuclear $\geq 15\%$ LV; echo ≥ 4 segments; CMR $\geq 25\%$ LV; ETT ST depression 1.5 mm in 2 leads or 2 mm in 1 lead at ≤ 7 METs with angina
- **Moderate:** nuclear 10-14% LV; echo 3 segments; CMR 12.5% LV; ETT either ECG or functional capacity criteria above
- **Mild:** nuclear 5-9% LV; echo 1-2 segments; CMR 1-12.4% LV; ETT 1 mm ST depression
- **None:** normal

Anatomic Severity of CAD*

- **6:** 3-vessel severe stenosis ($\geq 70\%$) or 2-vessel severe stenosis with proximal LAD
 - **5:** 2-vessel severe stenosis, 1-vessel severe proximal LAD, or 3-vessel moderate stenosis ($\geq 50\%$)
 - **4:** 2-vessel moderate stenosis or 1-vessel severe stenosis other than proximal LAD
 - **3:** 1-vessel moderate stenosis ($\geq 50\%$)
- (left main and no obstructive CAD were excluded)*

* Using the Modified Duke Prognostic Index Categories

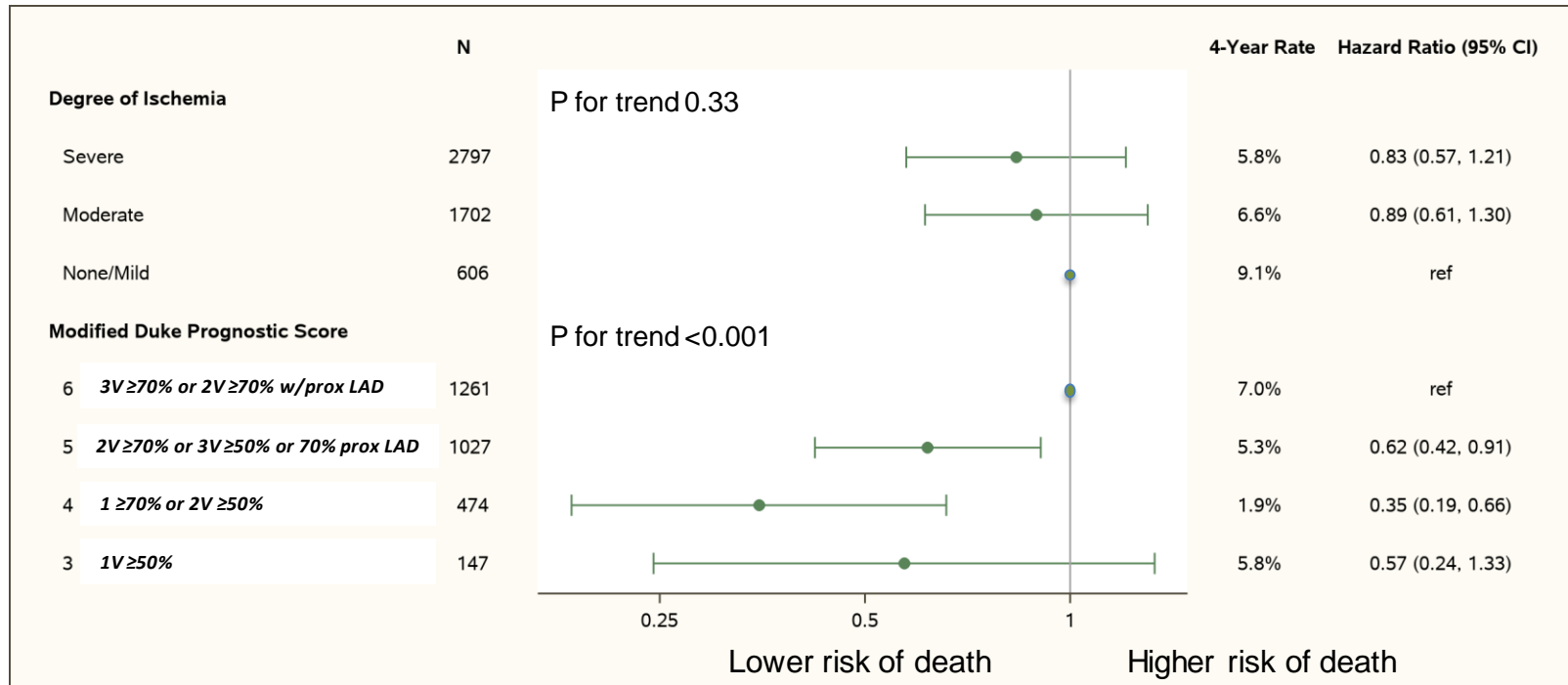
Statistical Analysis

- Outcomes assessed:
 - All-Cause Death
 - Myocardial Infarction
 - Primary Trial Outcome (CV Death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest)
- Adjusted for age, sex, geographical region, diabetes, hypertension, smoking, eGFR, BMI, LVEF, prior MI, heart failure or NYHA class II, prior revascularization, SAQ angina frequency at randomization, new or increasing angina

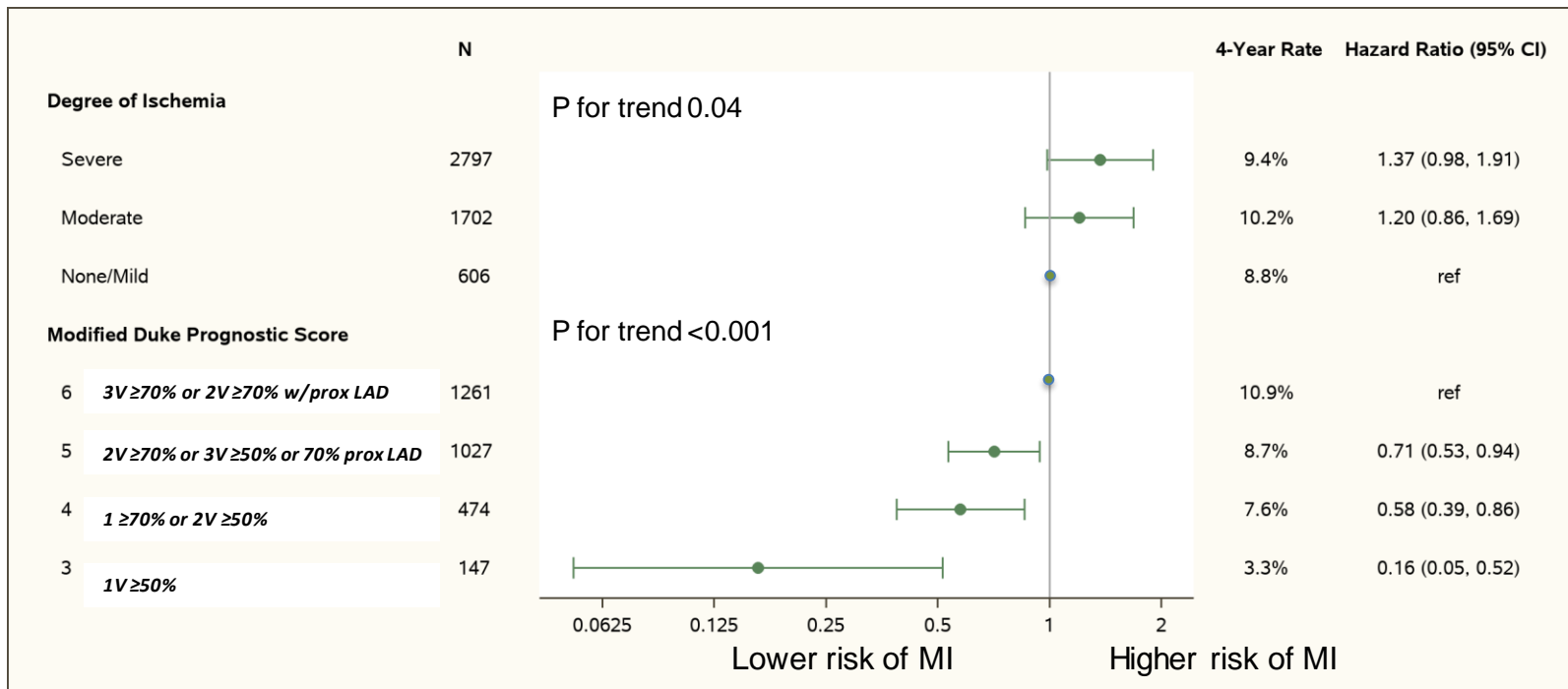
Statistical Analysis

- The association between ischemia or anatomy and outcomes was assessed using a Cox proportional hazards model adjusted for randomized treatment and baseline characteristics
- Heterogeneity of treatment effect was assessed by comparing 4-year cumulative rates of the study endpoints for INV vs. CON across levels of ischemia and anatomy severity

Association Between Ischemia, Anatomy, and All-Cause Mortality



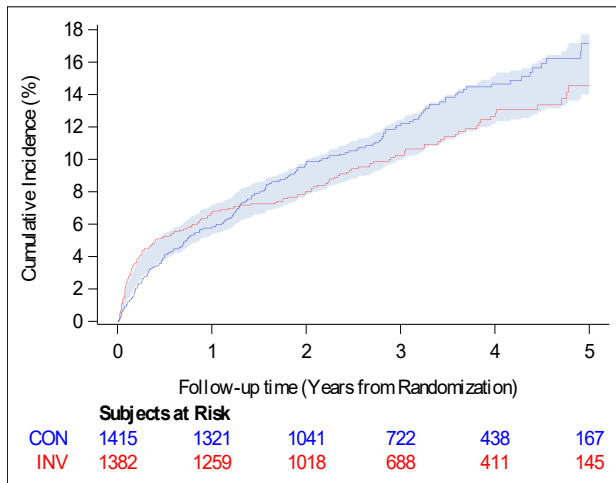
Association Between Ischemia, Anatomy, and MI



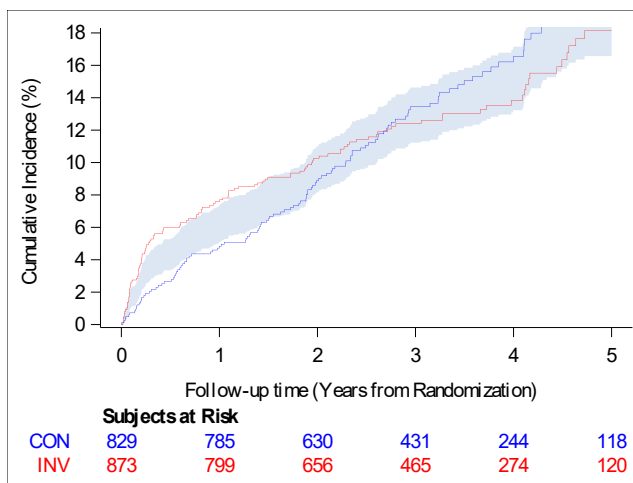
Ischemia Severity and Primary Outcome by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any ischemia subgroup

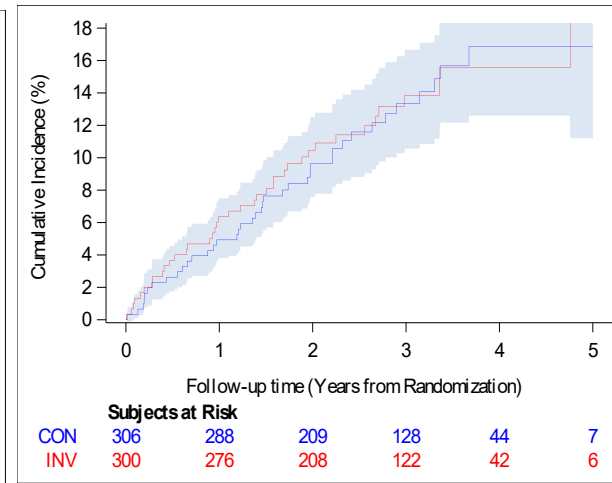
Severe Ischemia (N=2797)



Moderate Ischemia (N=1702)



Mild/No Ischemia (N=606)



4-year event rate interaction P = 0.28

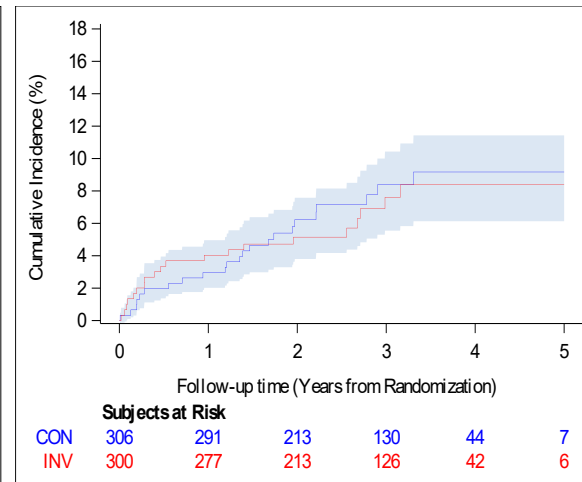
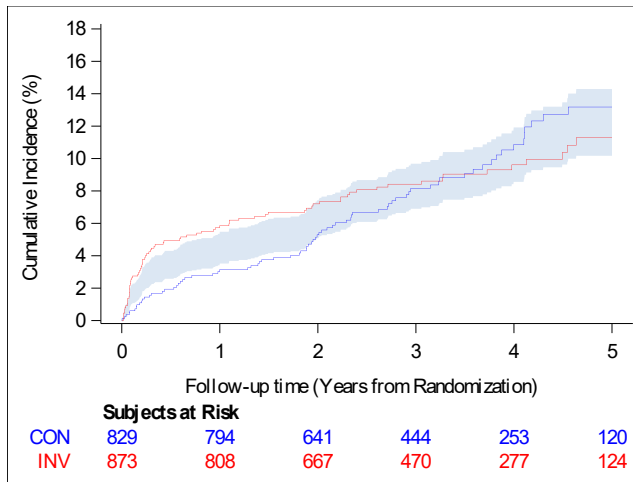
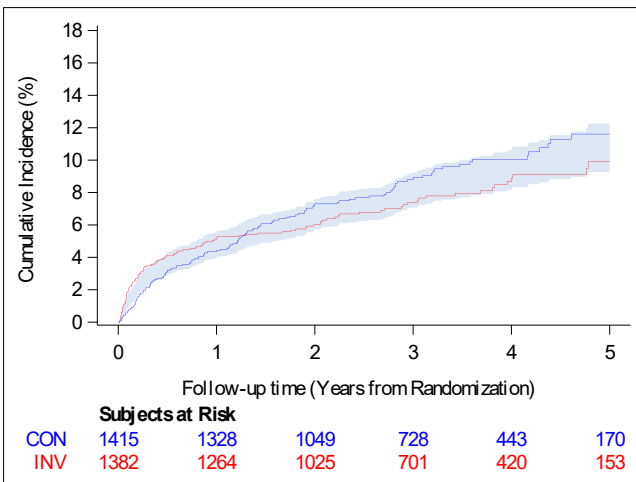
Ischemia Severity and Risk of MI by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any ischemia subgroup

Severe Ischemia (N=2797)

Moderate Ischemia (N=1702)

Mild/No Ischemia (N=606)

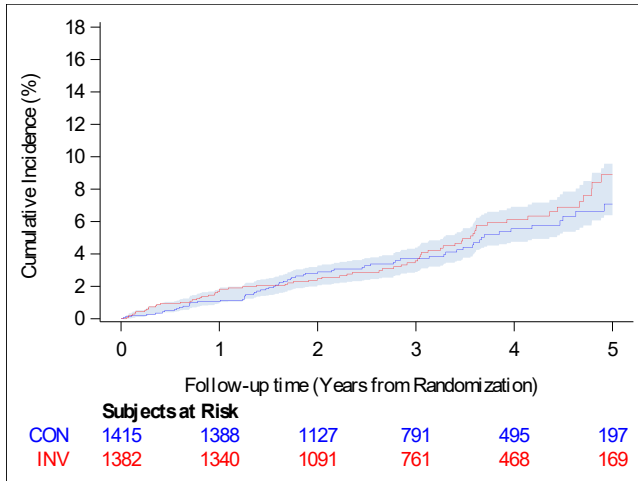


4-year event rate interaction P = 0.15

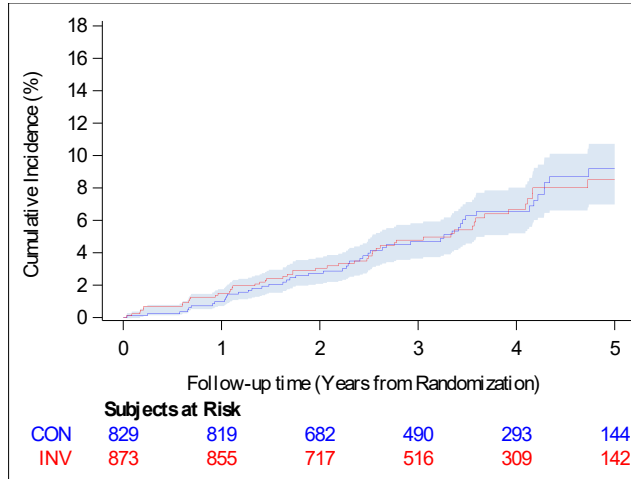
Ischemia Severity and All Cause Mortality by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any ischemia subgroup

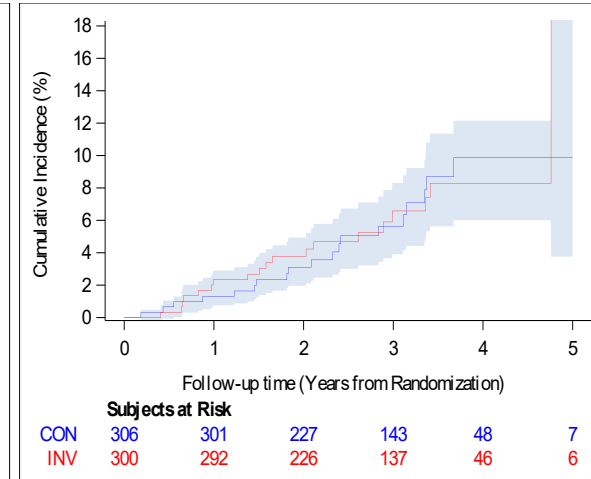
Severe Ischemia (N=2797)



Moderate Ischemia (N=1702)



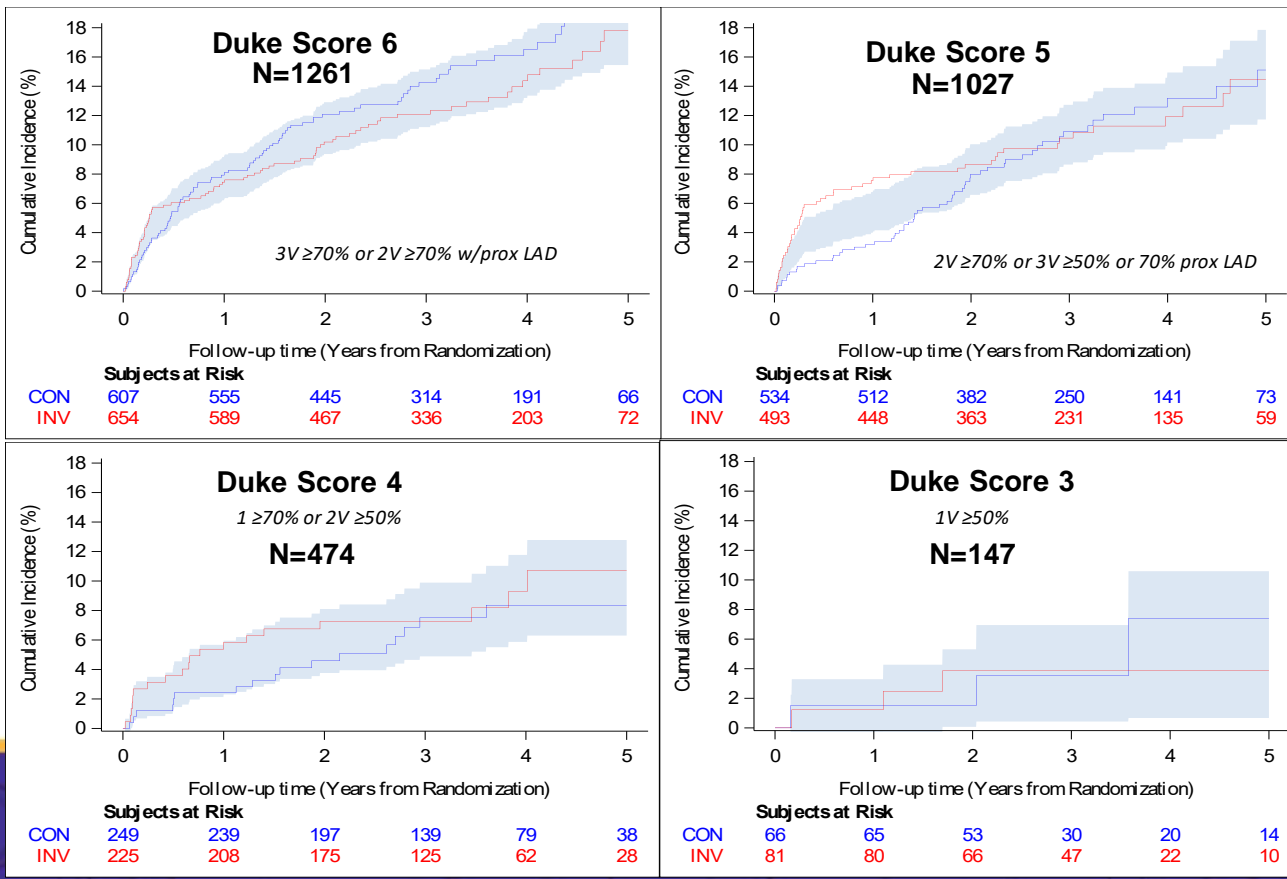
Mild/No Ischemia (N=606)



4-year event rate interaction P= 0.23

Anatomic Severity and Primary Outcome by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any anatomic subgroup

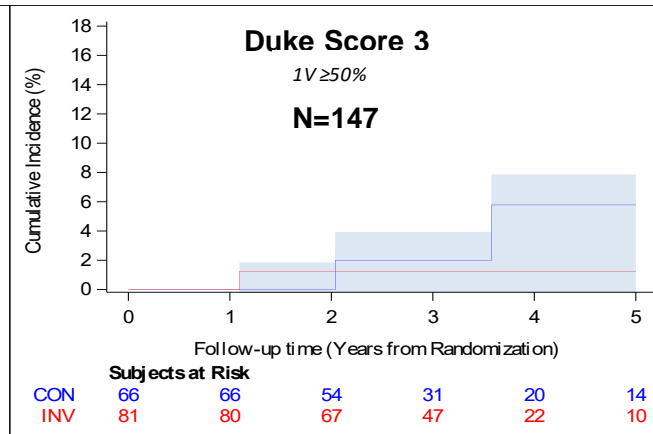
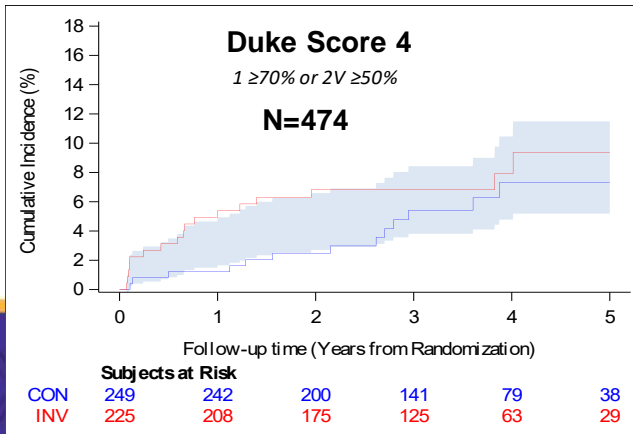
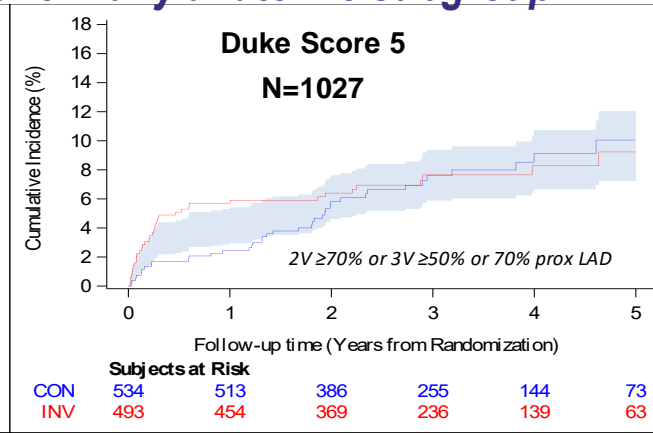
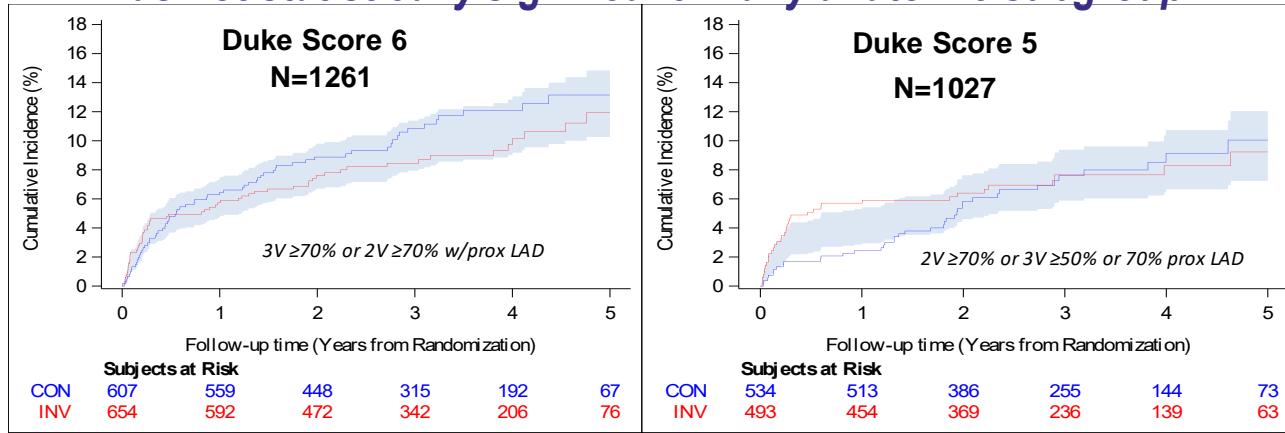


4-year event rate interaction
p = 0.17

Shading indicates half width of confidence bands for INV vs. CON difference

Anatomic Severity and MI by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any anatomic subgroup

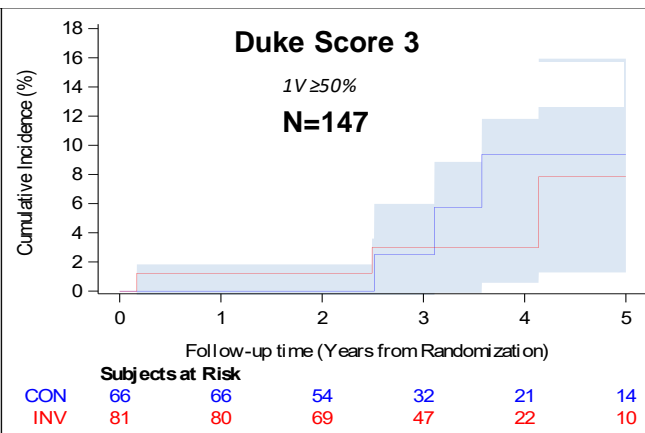
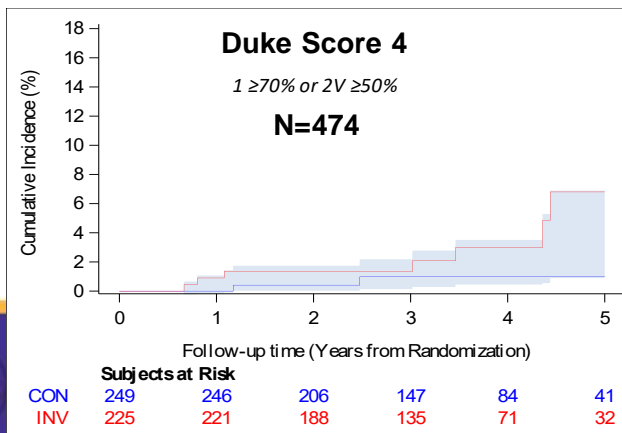
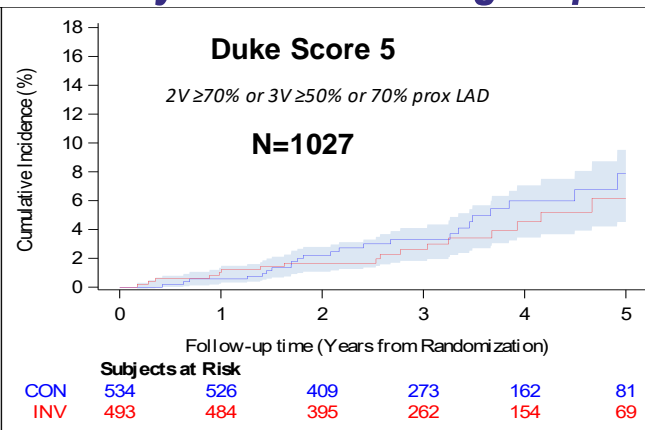
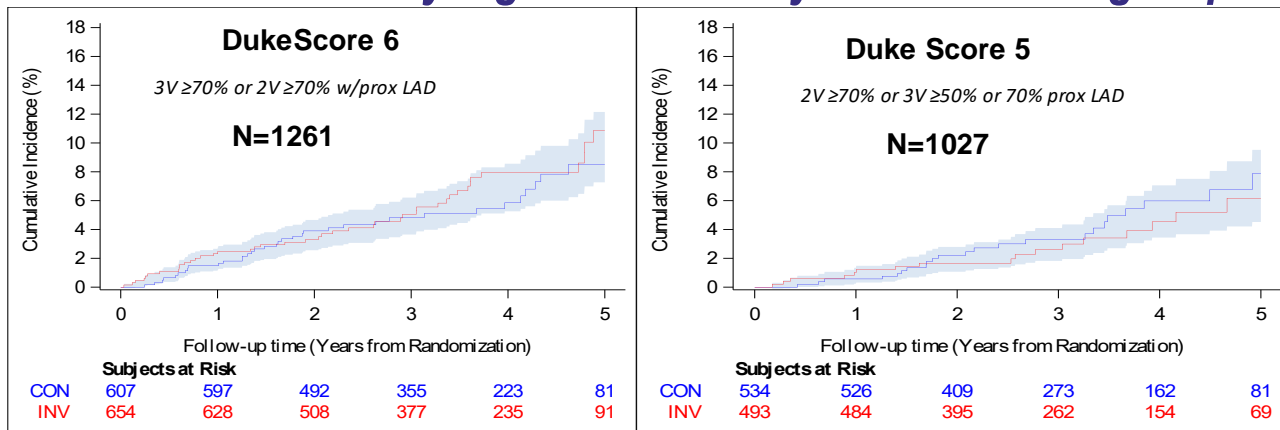


4-year event rate interaction
P= 0.26

Shading indicates half width of confidence bands for INV vs. CON difference

Anatomic Severity and All Cause Mortality by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any anatomic subgroup



4-year event rate interaction
P= 0.83

Shading indicates half width of confidence bands for INV vs. CON difference

Limitations

- Limited duration of follow up, median 3.2 years
- Anatomy was defined by CCTA, not conventional invasive angiography
- Patients with very severe ischemia (e.g., fall in BP with exercise, very limited functional capacity) were not likely enrolled by sites
- Patients with an unacceptable degree of angina were excluded, as were patients with left main disease, recent ACS, HF, EF <35%
- No adjustment for multiple comparisons

Anatomy was More Predictive of Outcomes than Ischemia

- In these patients with site-determined moderate or severe ischemia, there was no association between core laboratory-determined ischemia severity and death, but there was a marginal association between ischemia severity and risk of MI
- There was a strong association between extent and severity of CAD and risk of death and MI

ISCHEMIA Main Trial Results Apply to All Ischemia and Anatomic Subgroups

- There was no statistically significant evidence of a benefit from the invasive strategy on 4-year event rates for any level of ischemia
- More severe and extensive coronary disease increased risk for death and MI, but an invasive approach did not significantly lower that risk at 4 years
- This includes the subgroup with severe 3-vessel disease or 2-vessel disease with proximal LAD

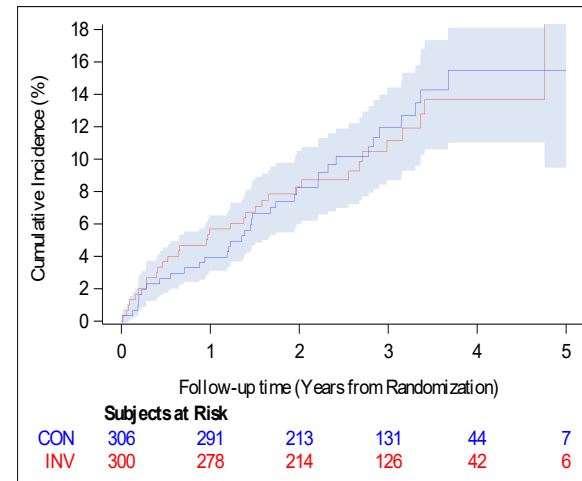
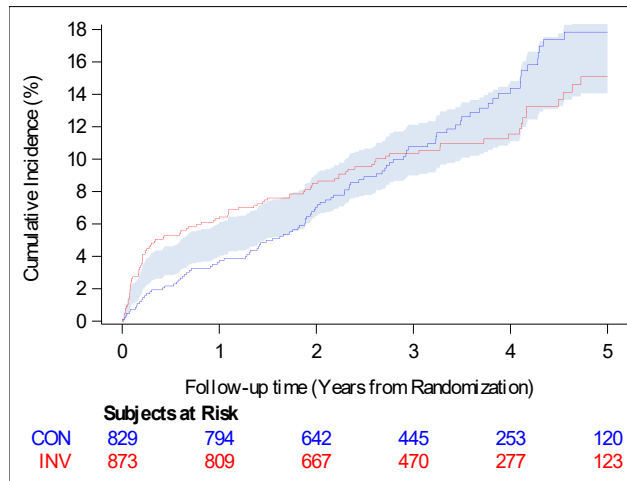
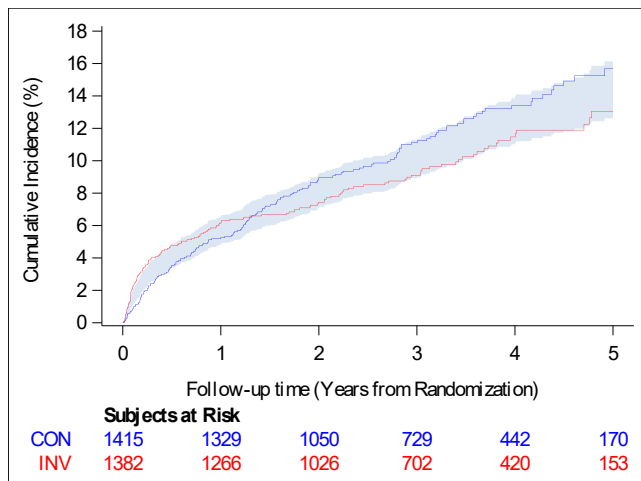
Thank you

CVD/MI by Treatment Group – Ischemia Severity

Severe Ischemia

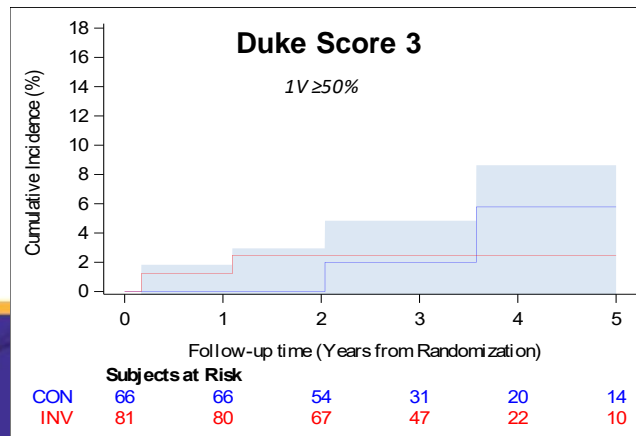
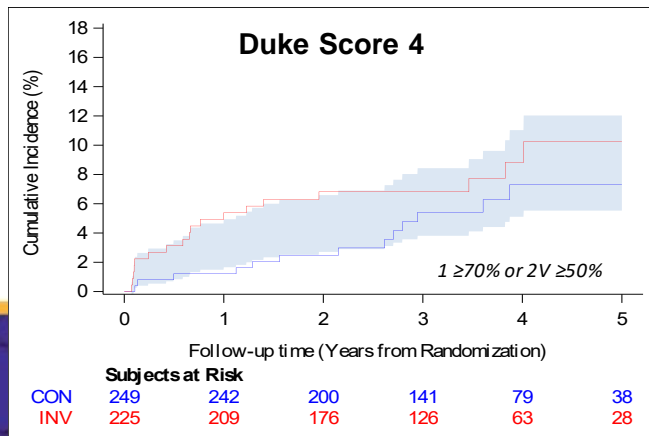
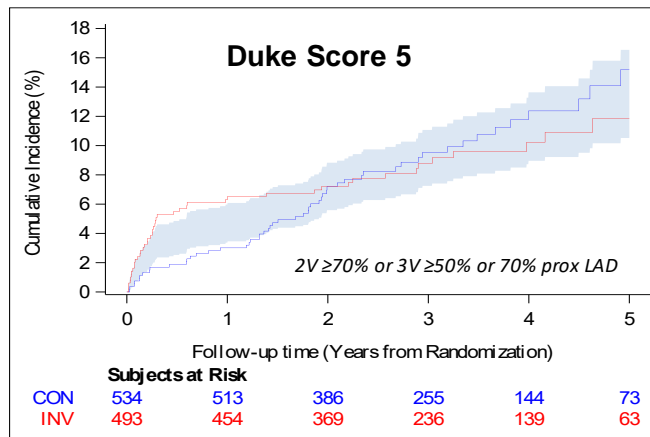
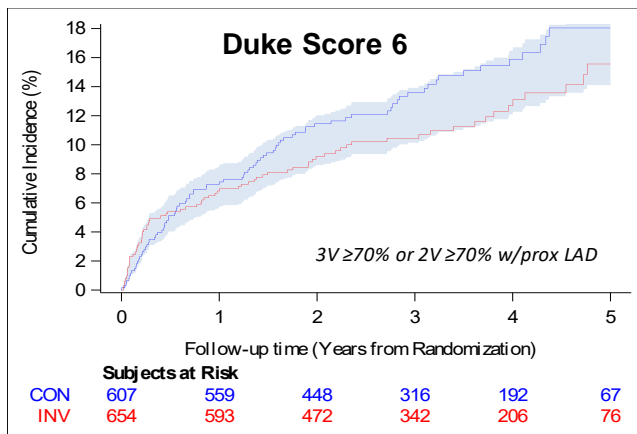
Moderate Ischemia

Mild/No Ischemia



Interaction P= 0.25

CVD/MI by Treatment Group – Coronary Artery Disease



**Interaction
P= 0.43**

Shading indicates half width of confidence bands for INV vs. CON difference