International Study of Comparative Health Effectiveness with Medical and Invasive Approaches - Chronic Kidney Disease

Primary Report of Clinical Outcomes

Funded by the National Heart, Lung, and Blood Institute

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On behalf of the ISCHEMIA-CKD Research Group

ISCHEMIA-CKD Research Question

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

CKD Patients are Under-Represented in Contemporary Revascularization vs. Medicine SIHD Trials

2007

COURAGE

eGFR <30: 16 Subjects

2009

BARI 2D

A WINDOW OF OPPORTUNITY FOR COORDINATED CARE

Subjects with serum Cr >2 mg/dl excluded

2012

FAME 2 Trial

Serum Cr >2 mg/dl: 20 subjects

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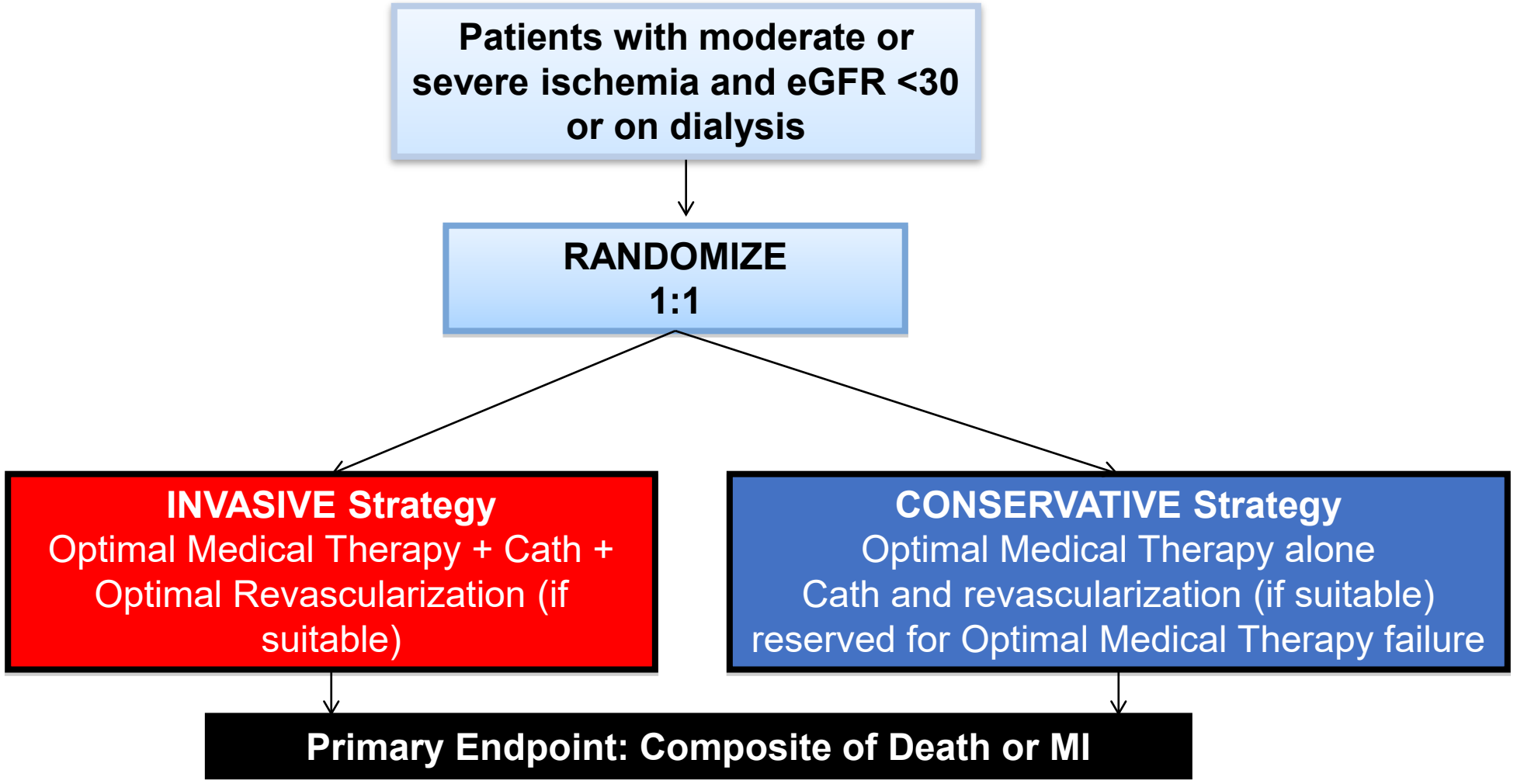
Study Design



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Eligibility Criteria

Key Inclusion Criteria

- At least moderate ischemia on an exercise or pharmacologic stress test (site determined)
- End-stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2

Key Exclusion Criteria

- Left ventricular ejection fraction <35%
- NYHA class III-IV heart failure
- Unacceptable level of angina despite maximal medical therapy
- ACS within the previous 2 months
- PCI or CABG within the previous 12 months

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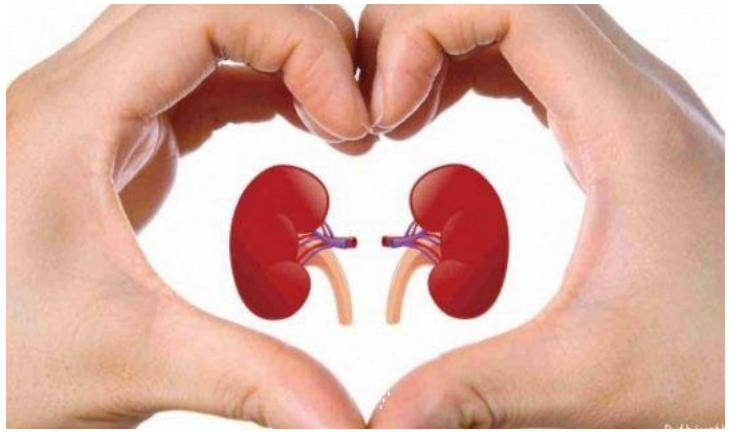
Optimizing Revascularization

Customized Hydration

LVEDP based (POSEIDON trial)

Heart/Kidney Team



Cardiology/Nephrology/CV surgery

Ultra low/Zero Contrast PCI

Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study

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Aims The feasibility, safety, and clinical utility of percutaneous coronary intervention (PCI) without radio-contrast medium in patients with advanced chronic kidney disease (CKD) are unknown. In this series, we investigated a specific strategy for 'zero contrast' PCI with the aims of preserving renal function and preventing the need for renal replacement therapy (RRT) in patients with advanced CKD.

Methods and results A total of 31 patients with advanced CKD [creatinine = 4.2 mg/dL, inter-quartile range (IQR) 3.1–4.8, estimated glomerular filtration rate = 16 ± 8 mL/min/1.73 m^2] who had clinical indication for PCI based on a prior minimal contrast coronary angiogram were included. Zero contrast PCI was performed at least 1 week after diagnostic angiography using real-time intravascular ultrasound (IVUS) guidance, with pre- and post-PCI measurements of fractional flow reserve and coronary flow reserve to confirm physiological improvement. This approach resulted in successful PCI, no major adverse cardiovascular events and preservation of renal function without the need for RRT within a follow-up time of 79 days (IQR 33–207) in all patients.

Conclusion In patients with advanced CKD who require revascularization, PCI may safely be performed without contrast using IVUS and physiological guidance with high procedural success and without complications.

Keywords Percutaneous coronary intervention • Chronic kidney disease • Contrast-induced nephropathy • Intravascular ultrasonography • Coronary physiology

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Endpoints

Primary Endpoint

- Time to death or MI

Major Secondary Endpoints

- Time to Death, MI, Hospitalization for Unstable Angina, Heart Failure or Resuscitated Cardiac Arrest
- Quality of Life (separate presentation)

Safety Outcomes

- Composite of initiation of maintenance dialysis or death
- Initiation of maintenance dialysis

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Statistical Considerations

Power Calculation (N = 777)

- >80% power to detect 22% to 24% relative reduction in primary endpoint assuming an aggregate 4-year cumulative rate of approximately 41% to 48%

Pre-Specified Statistical Analysis

- Intention-to-treat
- Nonparametric cumulative event rates accounting for competing risks
- Cox regression, covariate-adjusted
  - Emphasize nonparametric event rates if proportional hazards assumption is violated
- Bayesian analysis
  - Evaluate the probability of possible hypotheses/conclusions in light of a set of minimally informative prior probabilities and the current study data

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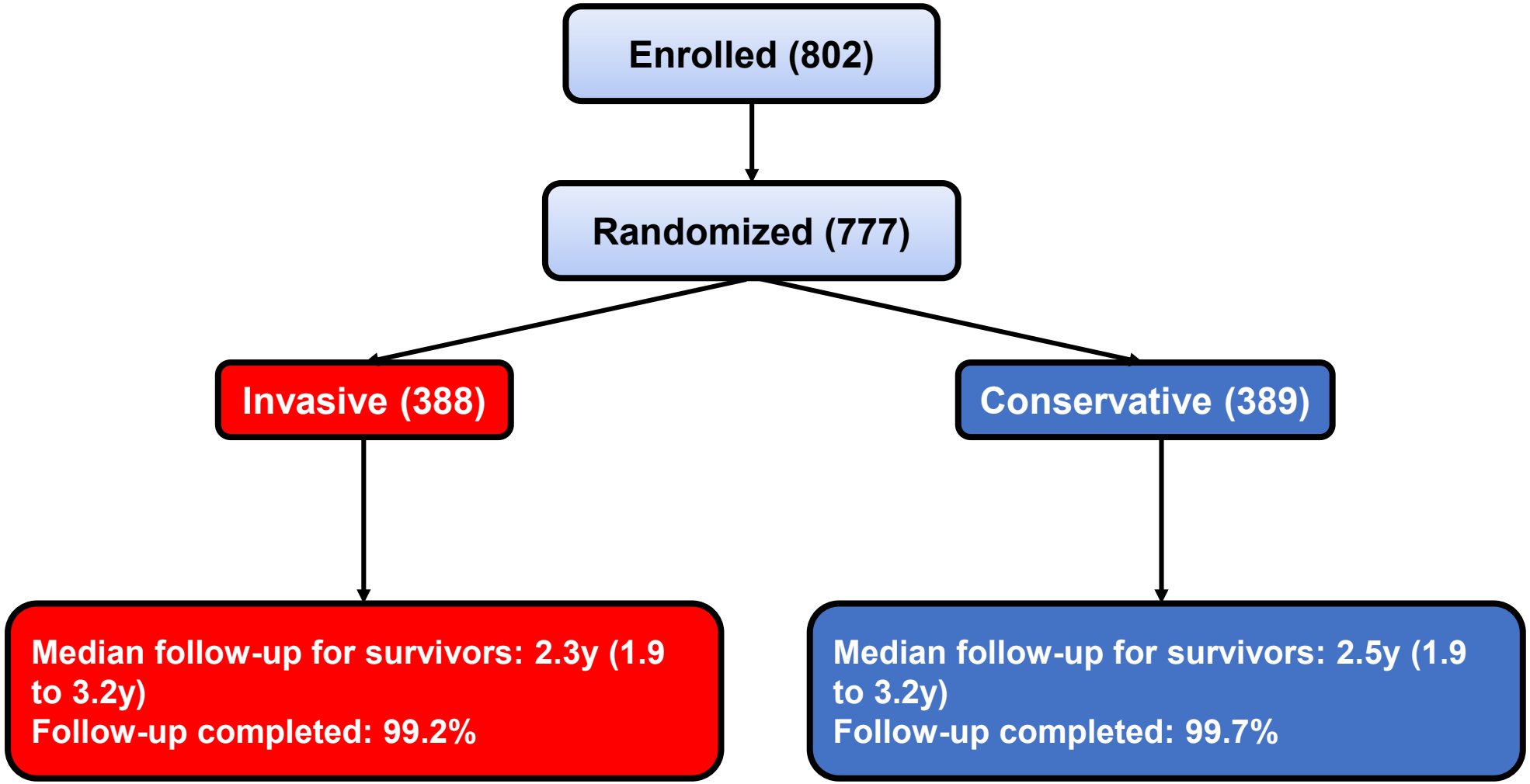
Patient Flow



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Key Baseline Characteristics

Characteristic	Total (N=777)	INV (N=388)	CON (N=389)
Age at Enrollment (yrs.)			
Median (25th, 75th)	63 (55, 70)	62 (55, 69)	64 (56, 70)
Female Sex (%)	31	31	31
Hypertension (%)	92	90	93
Diabetes (%)	57	58	56
Prior heart failure (%)	17	17	18
Ejection Fraction			
Median (25th, 75th)	58 (50, 64)	58 (50, 63)	58 (50, 64)
ESRD on Dialysis (%)	53	51	56
Duration of Dialysis (years)	2.0 (1.0, 5.0)	3.0 (1.0, 6.0)	2.0 (1.0, 4.0)
Type of Dialysis			
Hemodialysis (%)	84	83	85
Peritoneal dialysis (%)	15	16	13
eGFR among those not on dialysis			
<15 ml/min/1.73m^2 (%)	14	15	13
15 to <30 ml/min/1.73m^2 (%)	86	85	87

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Key Stress Test and Angiographic Characteristics

Characteristic	Total (N=777)	INV (N=388)	CON (N=389)
Stress Test Modality			
Stress Imaging (%)	82	81	82
Non-imaging ETT (%)	18	19	18
Stress Test Severity (site determined)			
Severe (%)	38	36	39
Moderate (%)	62	64	61
Number of Native Vessels With ≥ 50% Stenosis (QCA)			
0 (%)		26	
1 (%)		22	
2 (%)		28	
3 (%)		23	
Specific Native Vessels With ≥ 50% Stenosis (QCA)			
Left Main		2	
Left Anterior Descending (LAD)		57	
Proximal LAD		21	
Left Circumflex		44	
Right Coronary artery		45	

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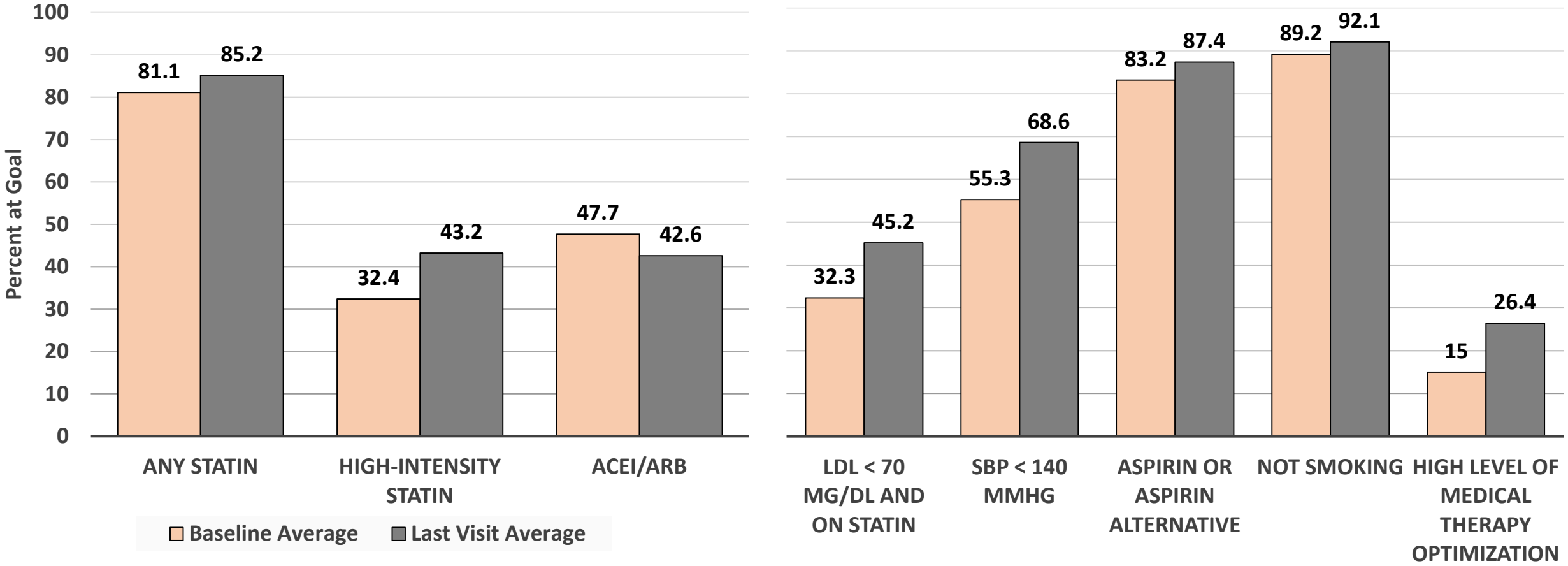
Risk Factor Management

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, 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.

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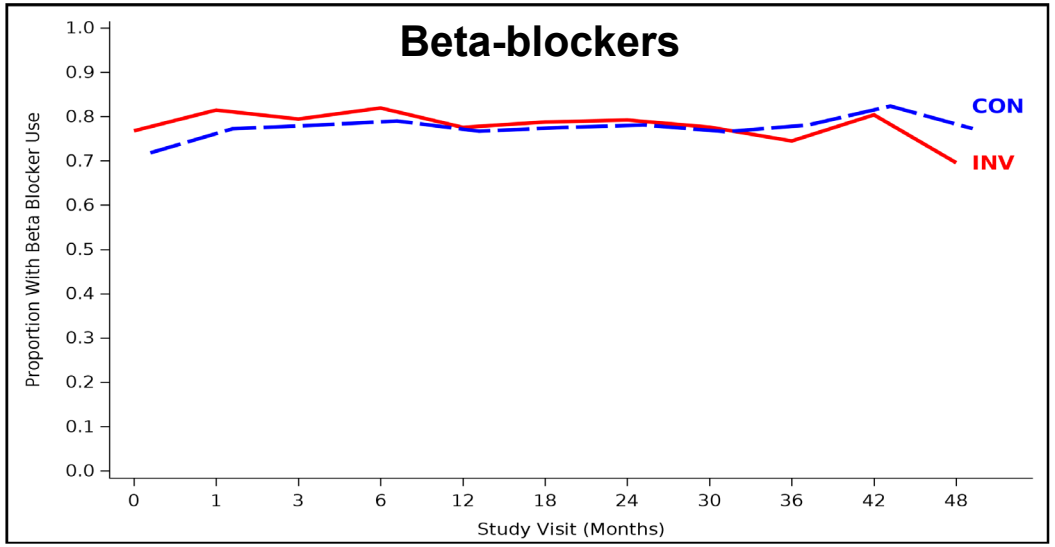
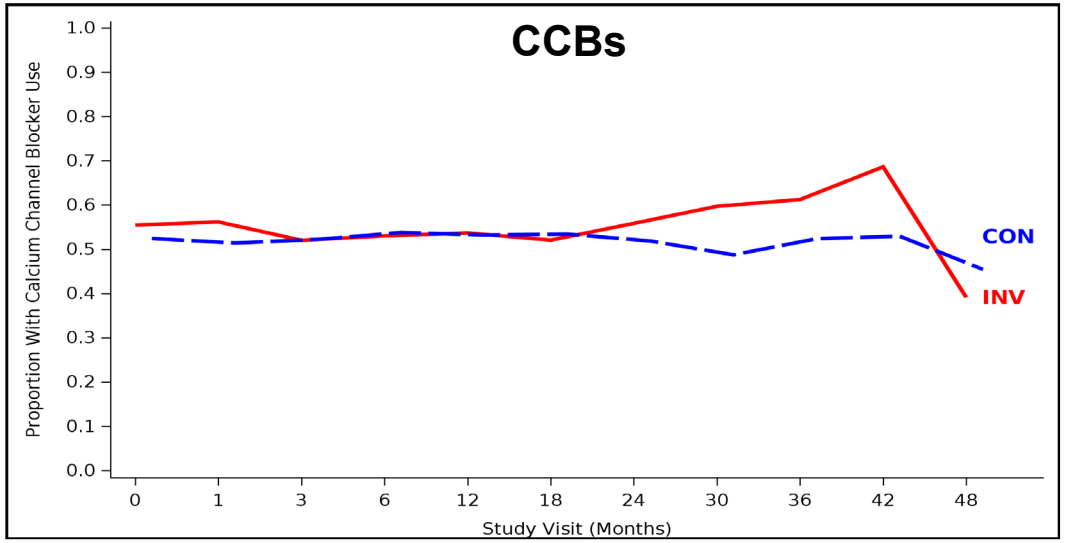
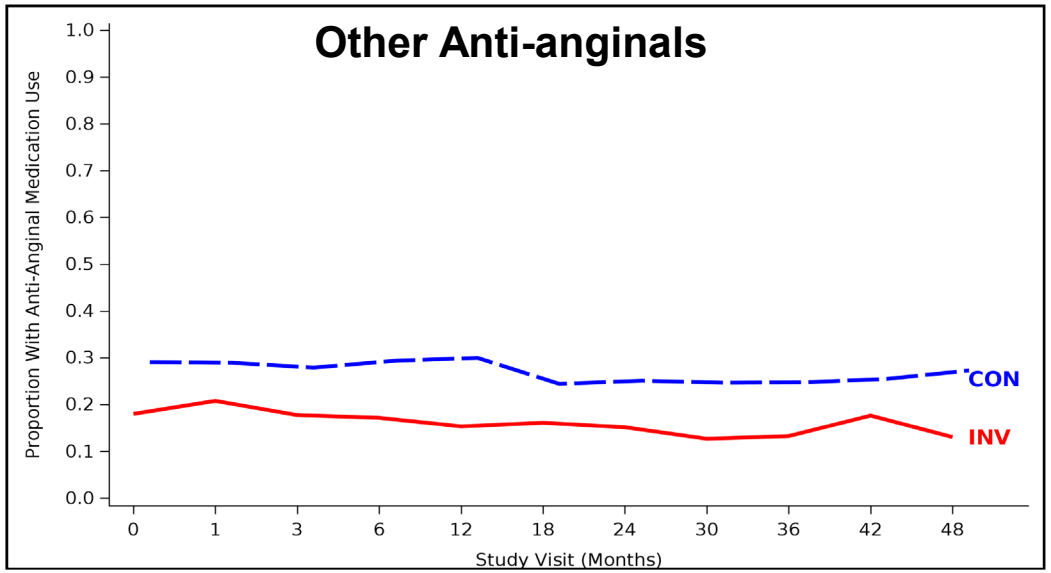
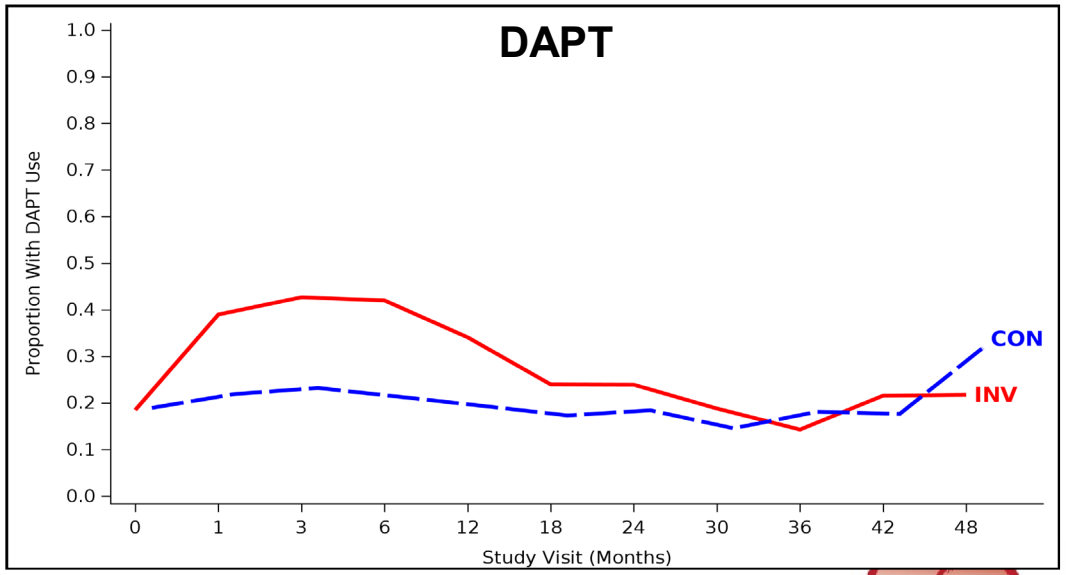
Medications









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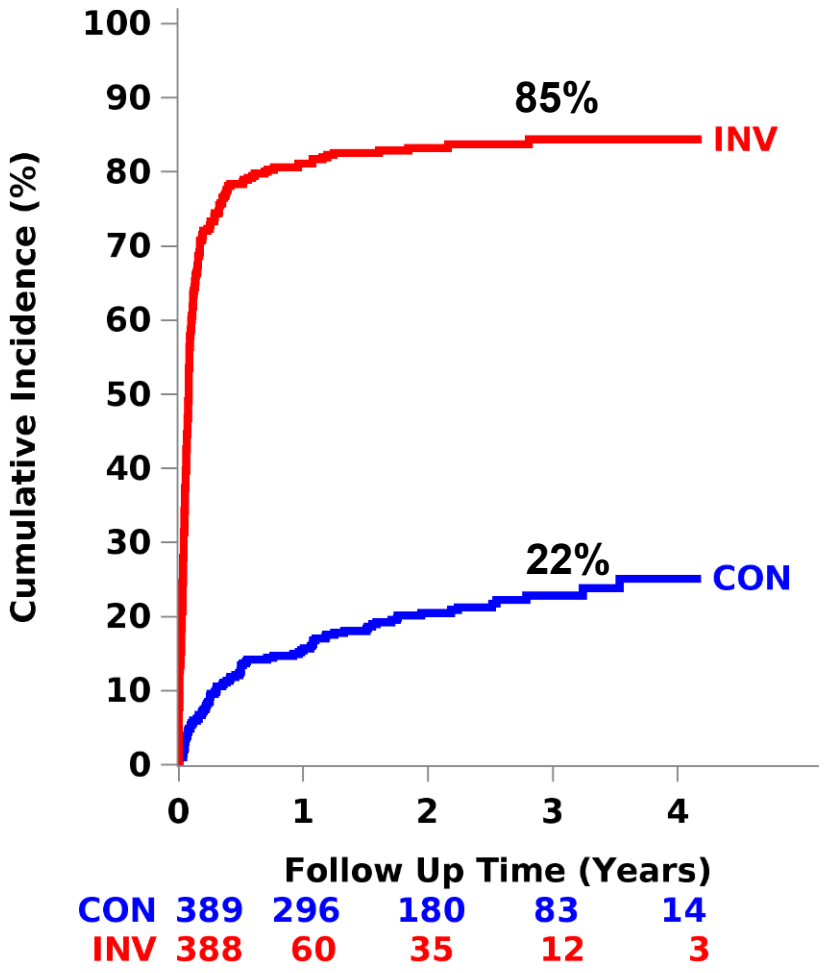
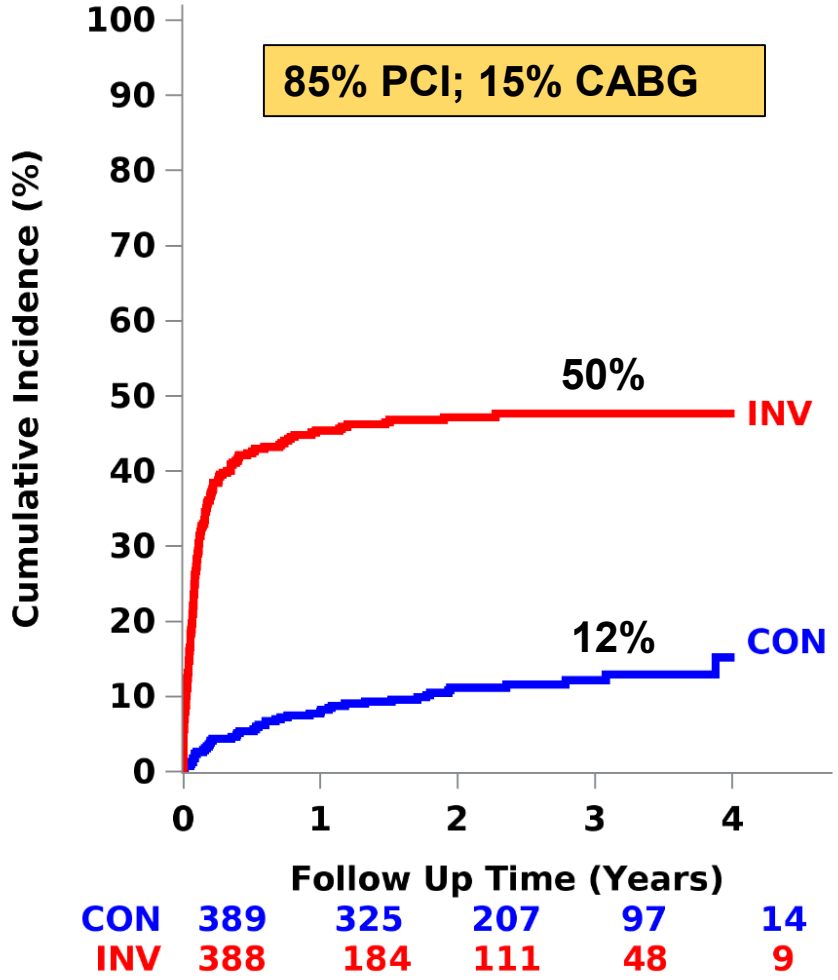
Coronary Angiography and Revascularization*

Coronary Angiography



Revascularization



*Not preceded by endpoint event

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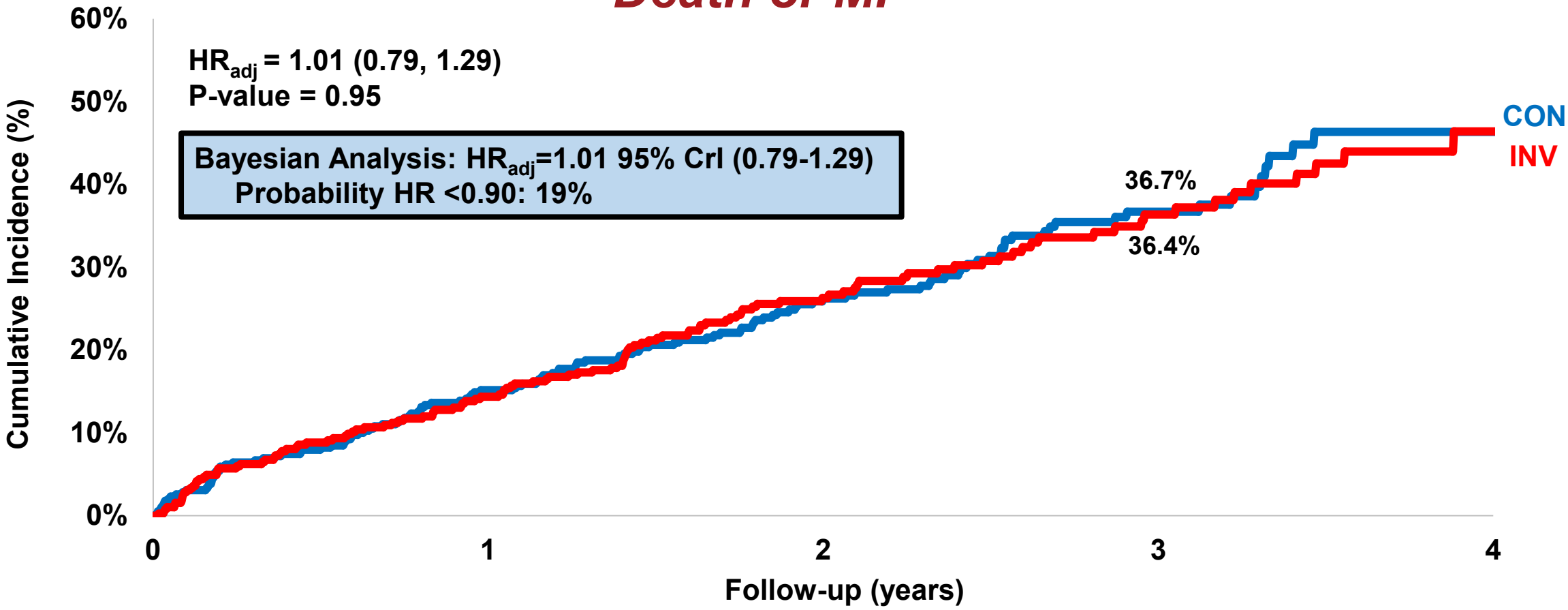
Primary End Point

Death or MI

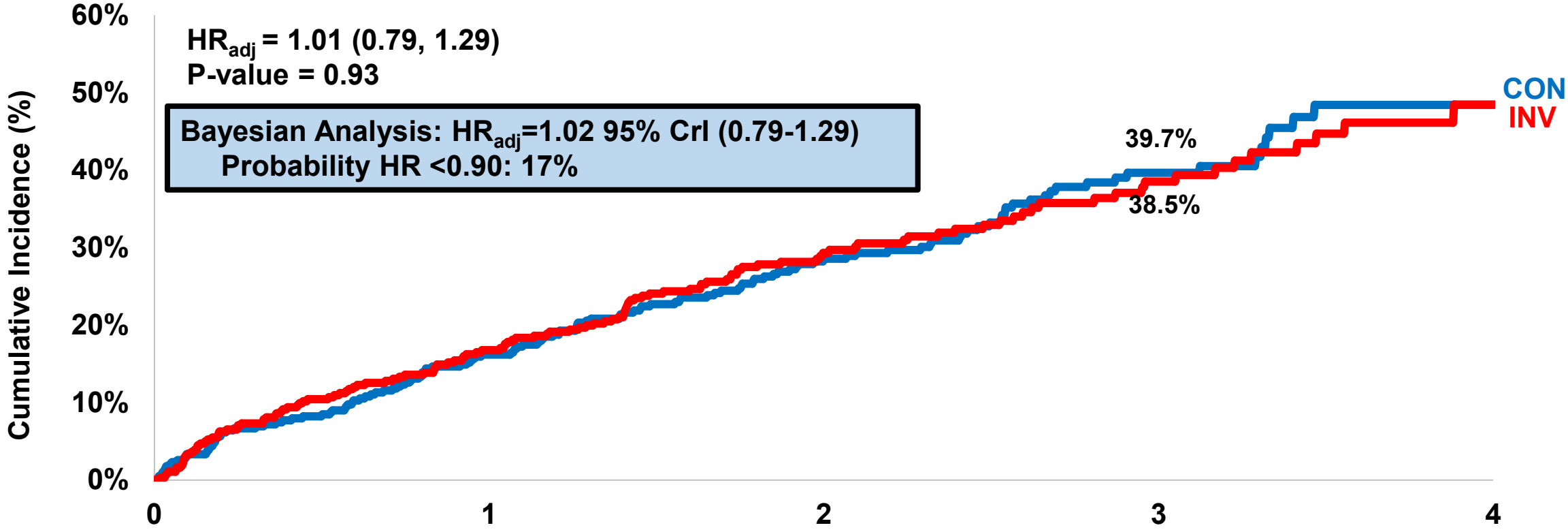


Subjects at Risk

CON	389	330	213	91	13
INV	388	323	190	80	18

Major Secondary End Point

Death, MI, Hospitalization for Unstable Angina or Heart Failure or Resuscitated Cardiac Arrest



Subjects at Risk

CON	389	326	206	87	13
INV	388	315	183	77	18

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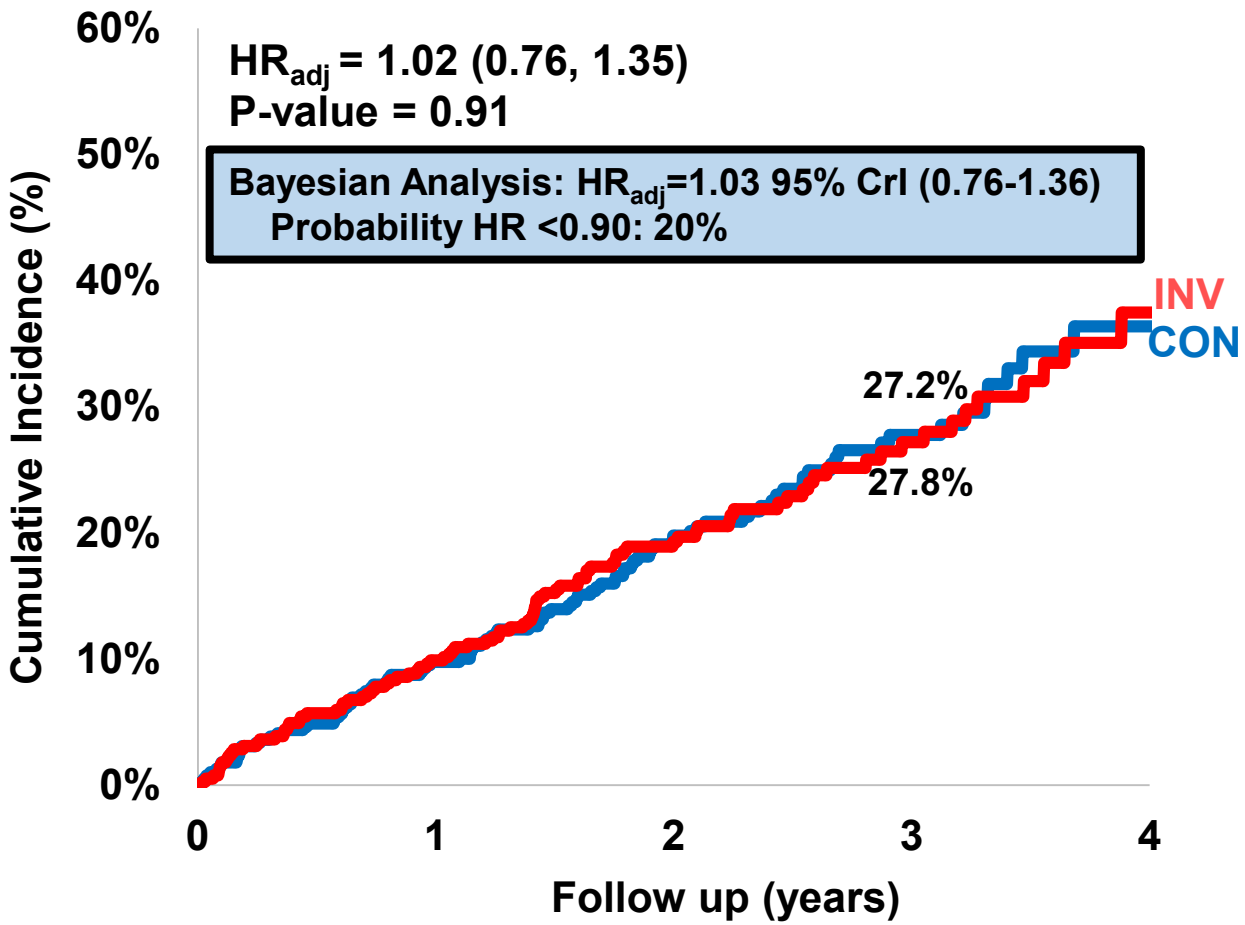
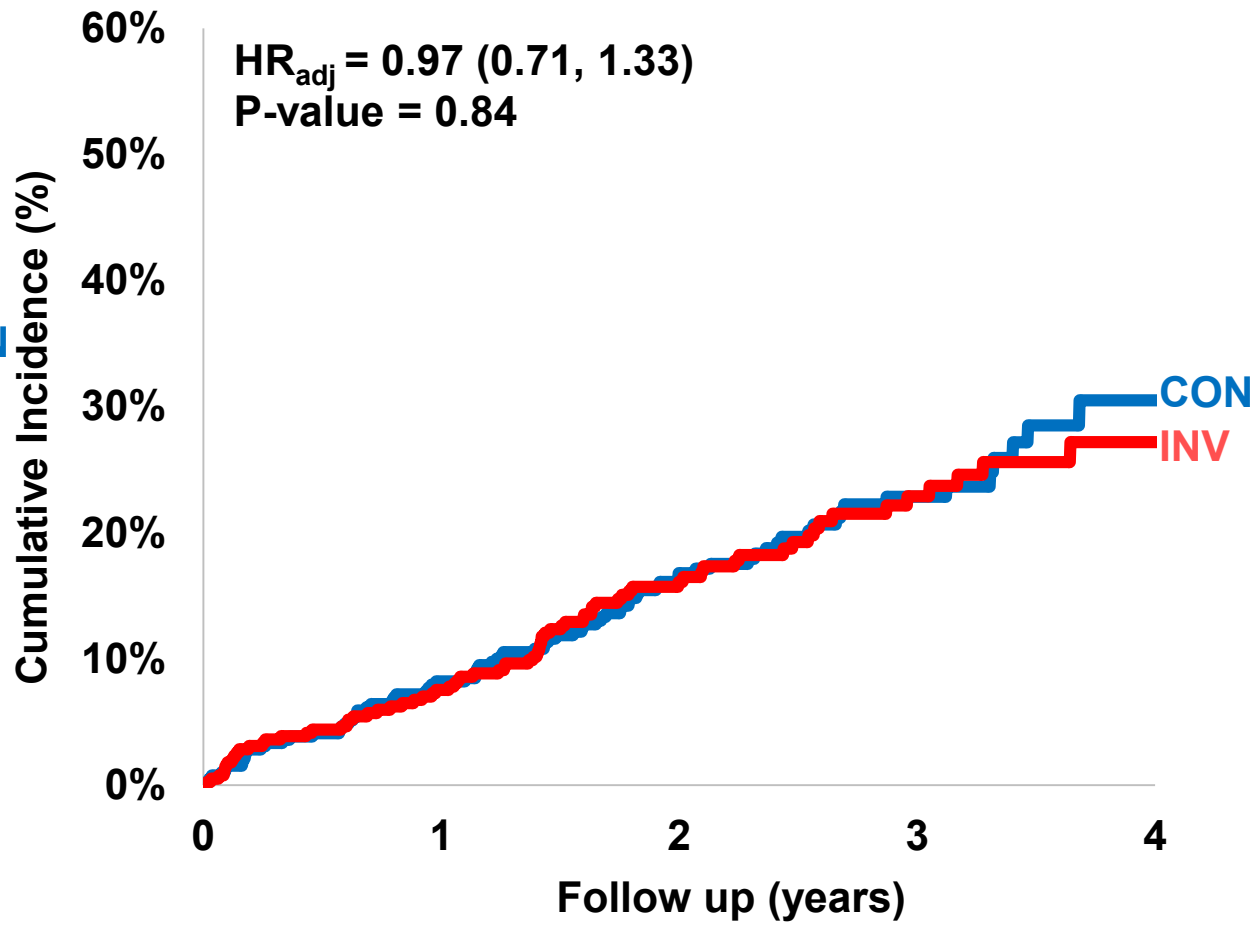
Secondary End Points

Death



CV Death



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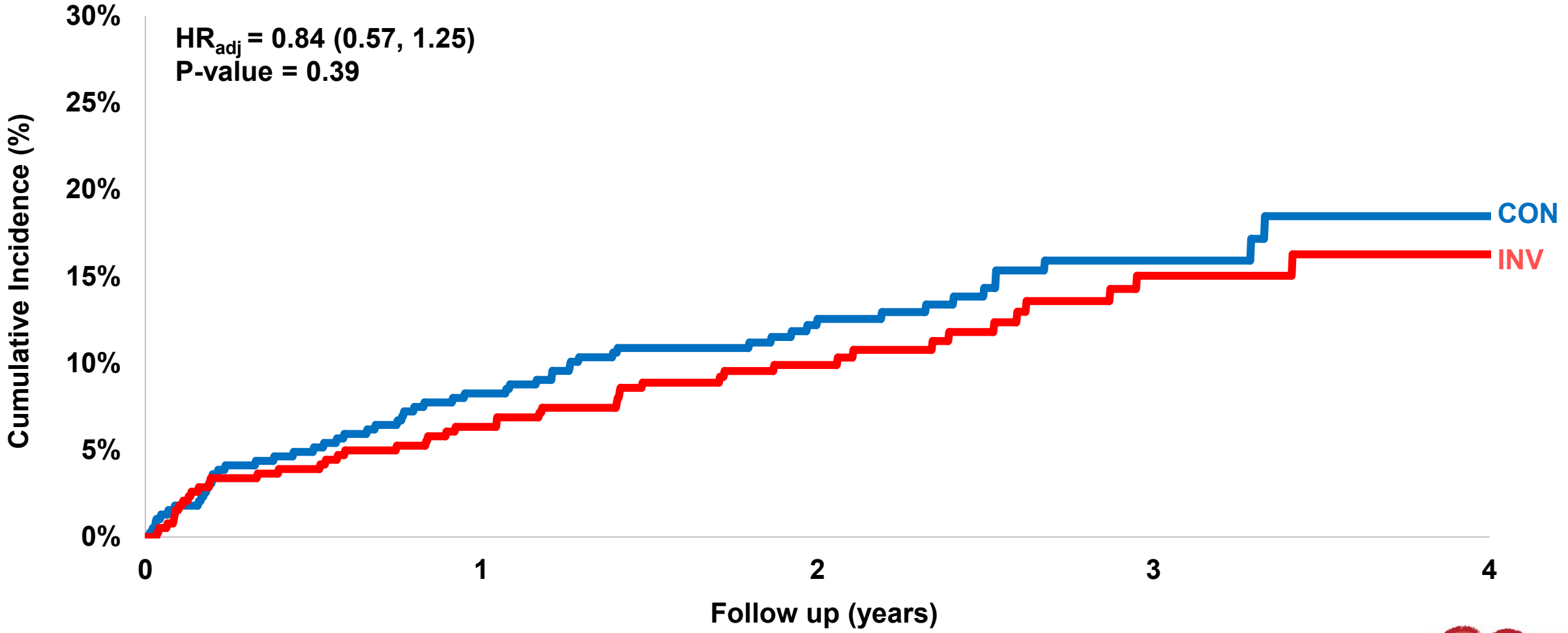
Secondary End Points

Myocardial Infarction



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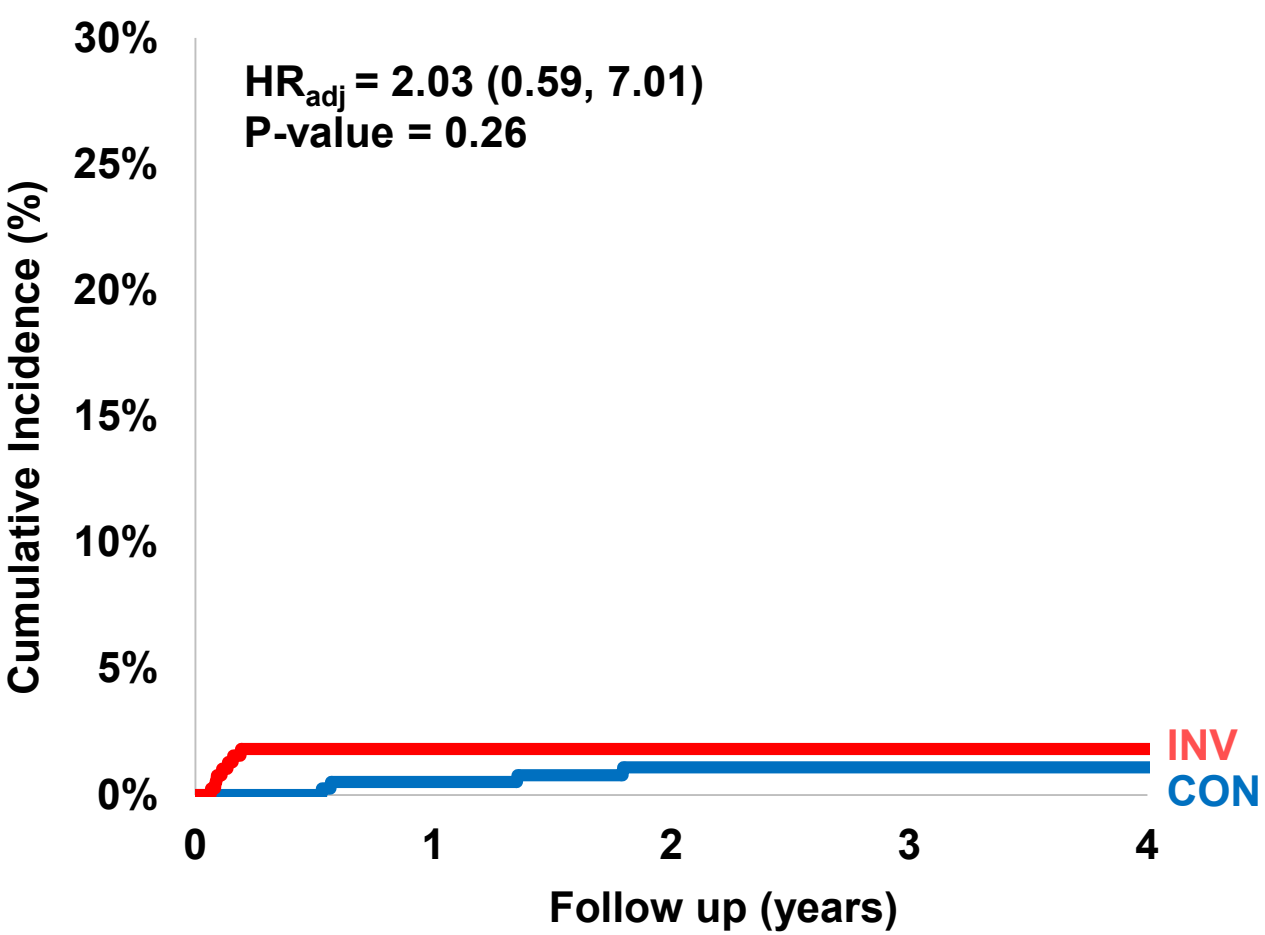
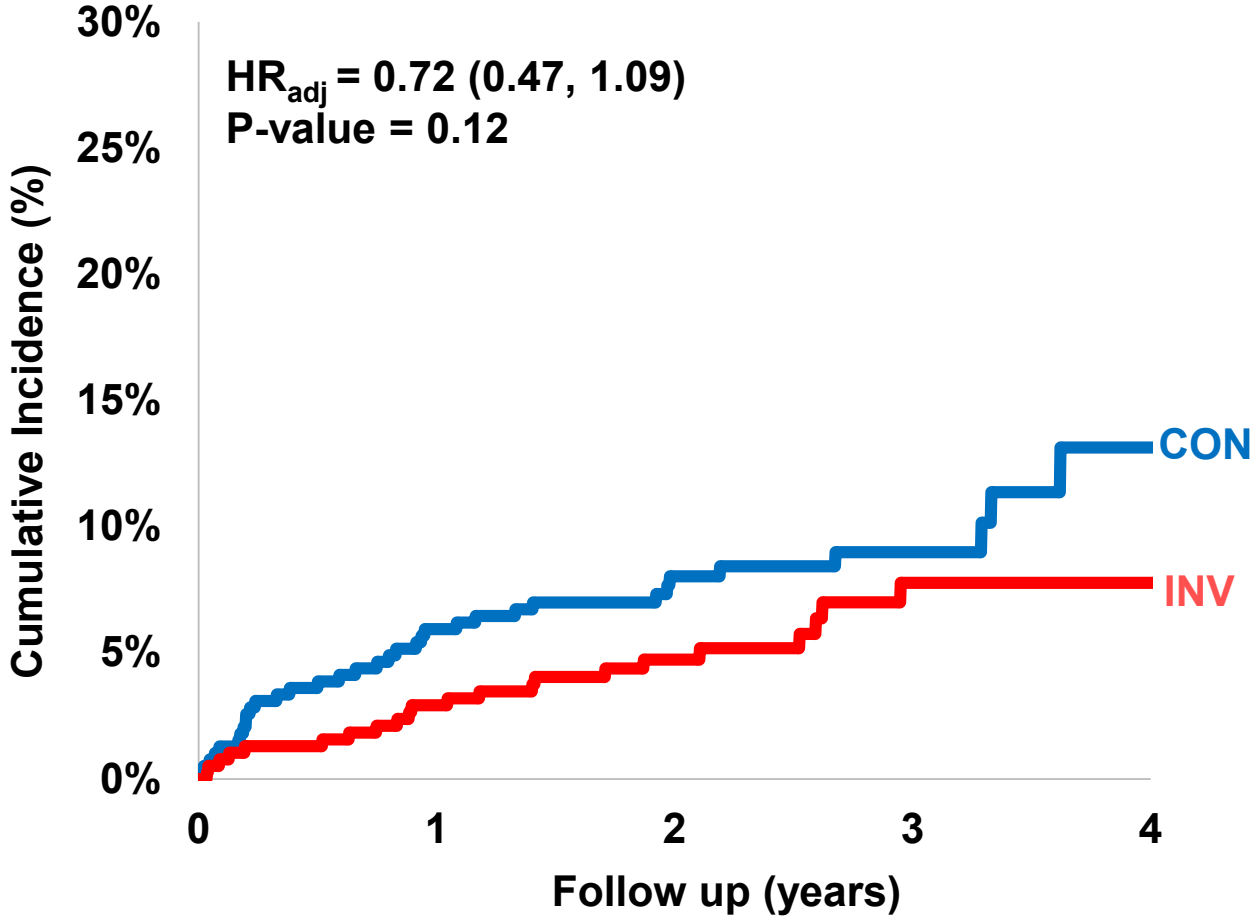
Secondary End Points

Procedural MI



Spontaneous MI



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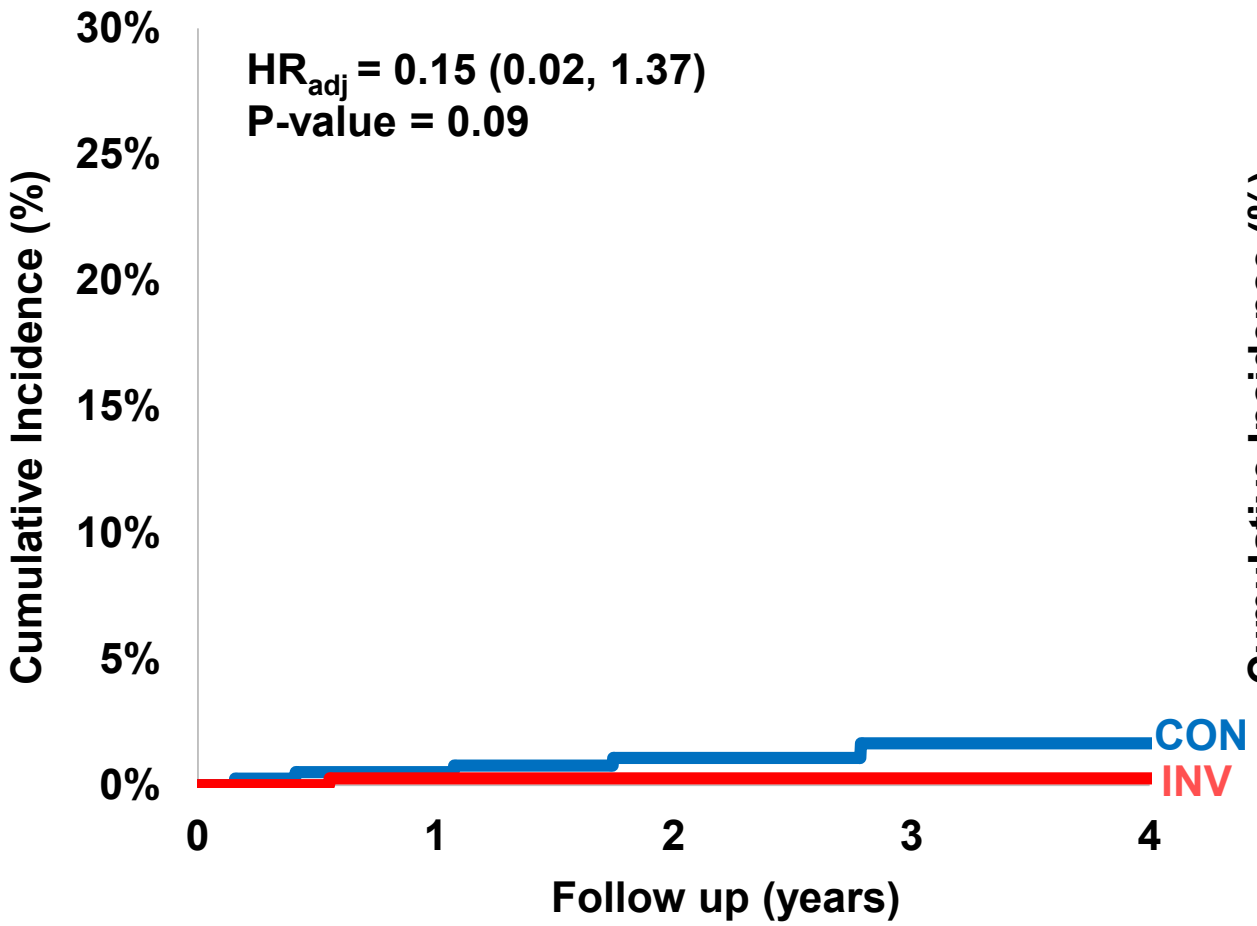
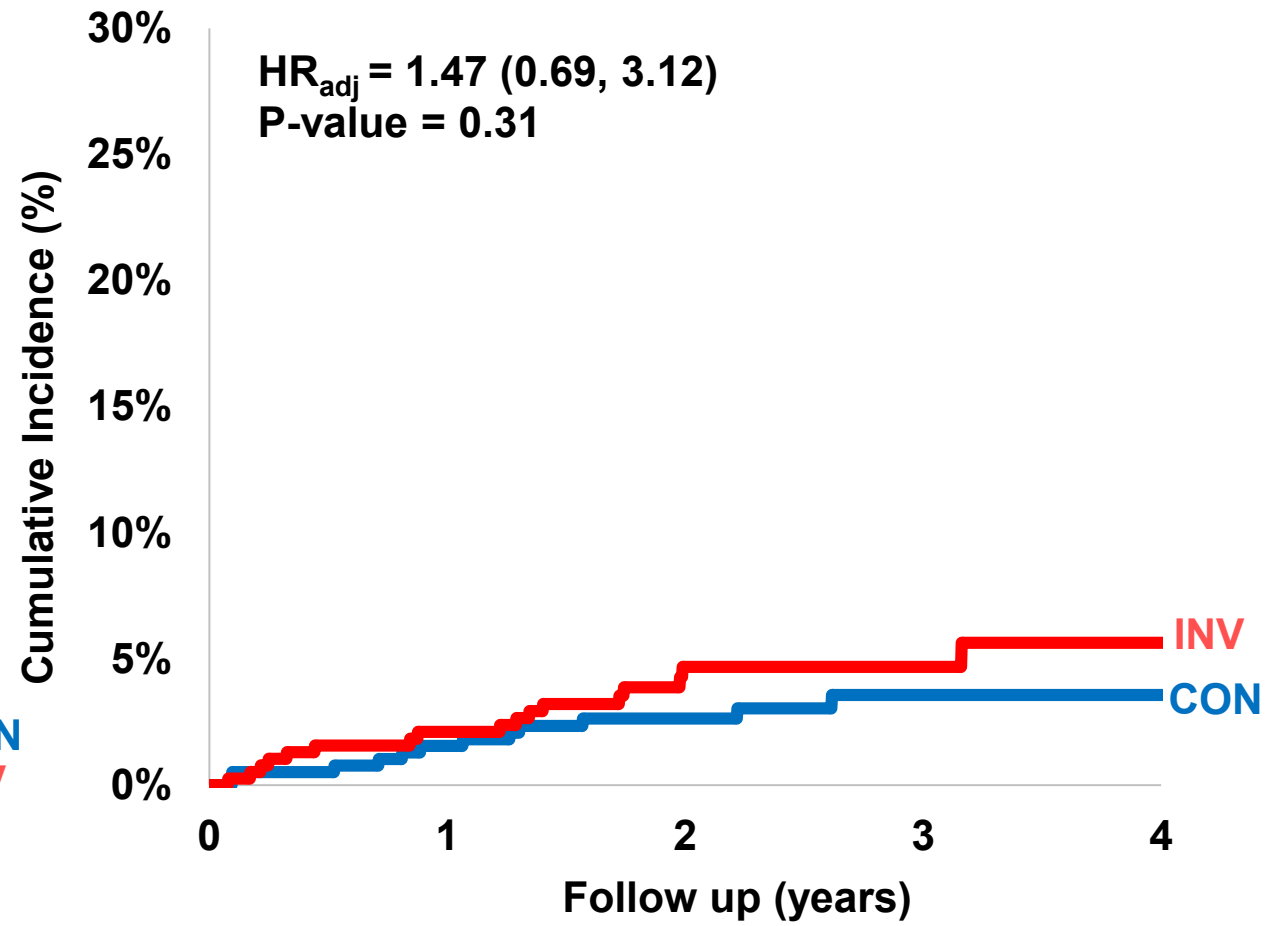
Secondary End Points

Unstable Angina



Heart Failure



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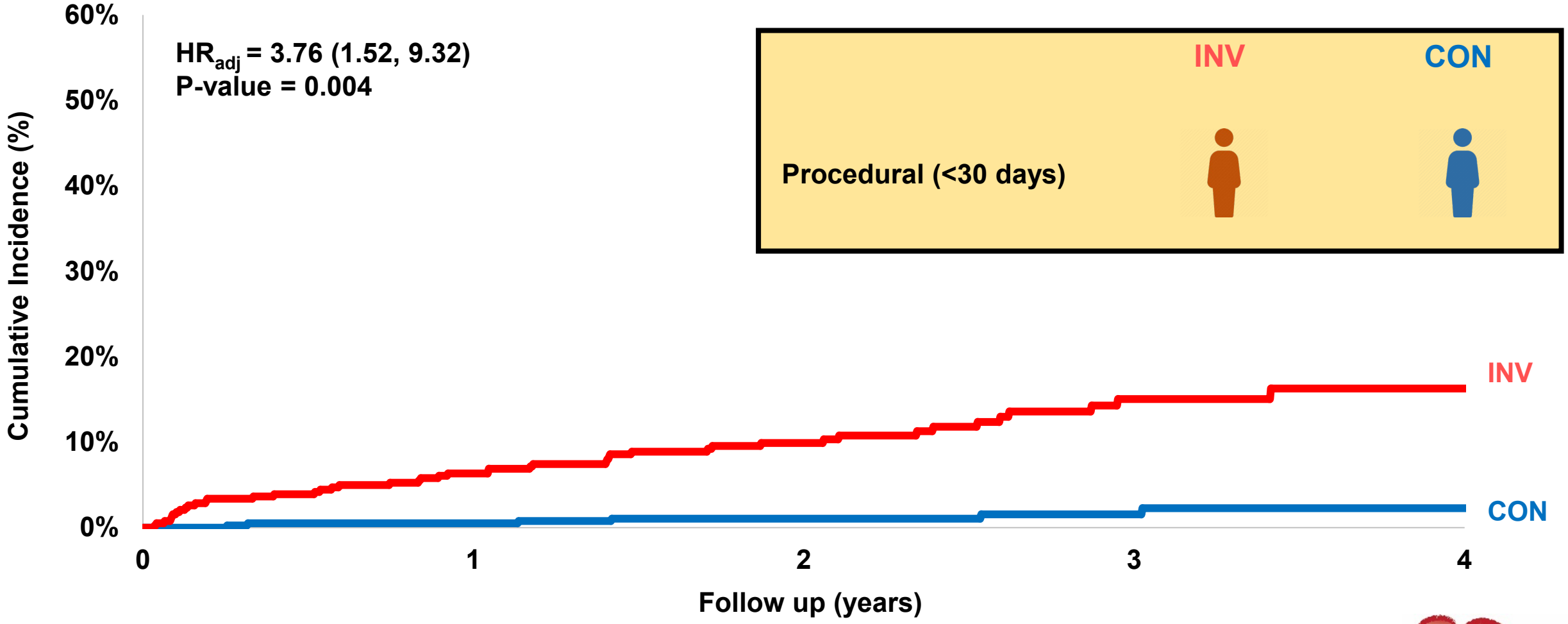
Secondary End Point

Stroke



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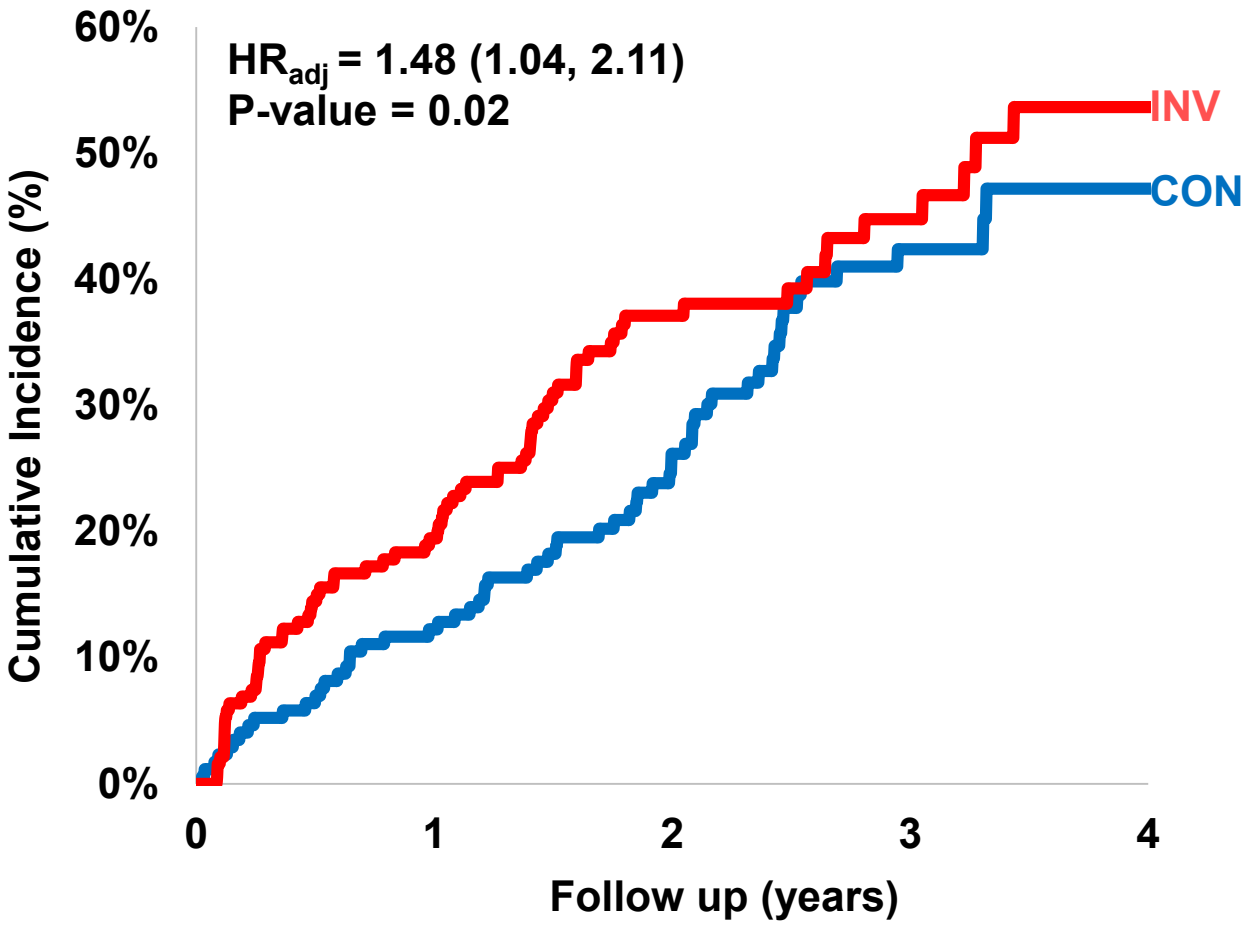
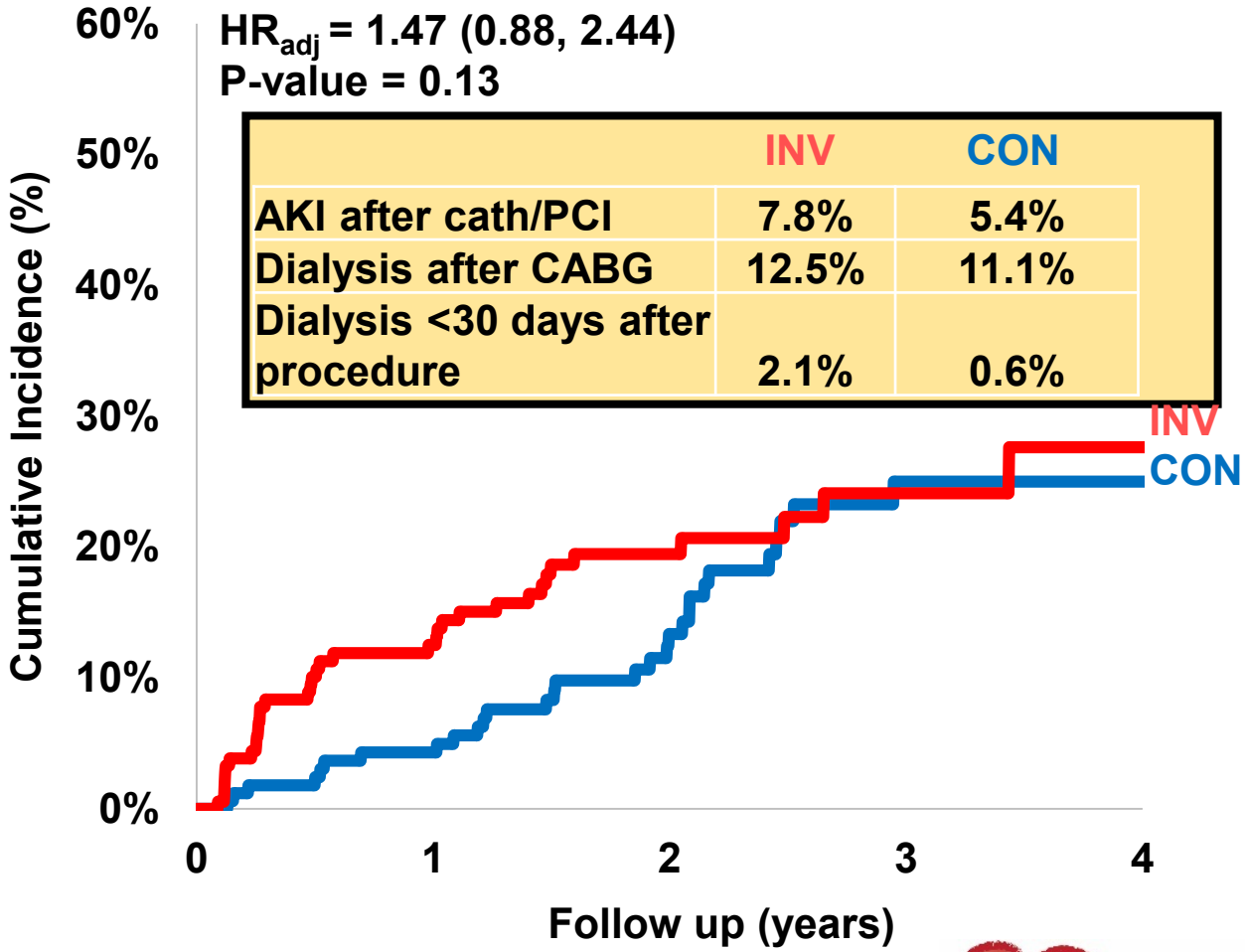
Safety End Points*

Death or New Dialysis



New Dialysis



	INV	CON
AKI after cath/PCI	7.8%	5.4%
Dialysis after CABG	12.5%	11.1%
Dialysis <30 days after procedure	2.1%	0.6%

* In those not on dialysis at baseline

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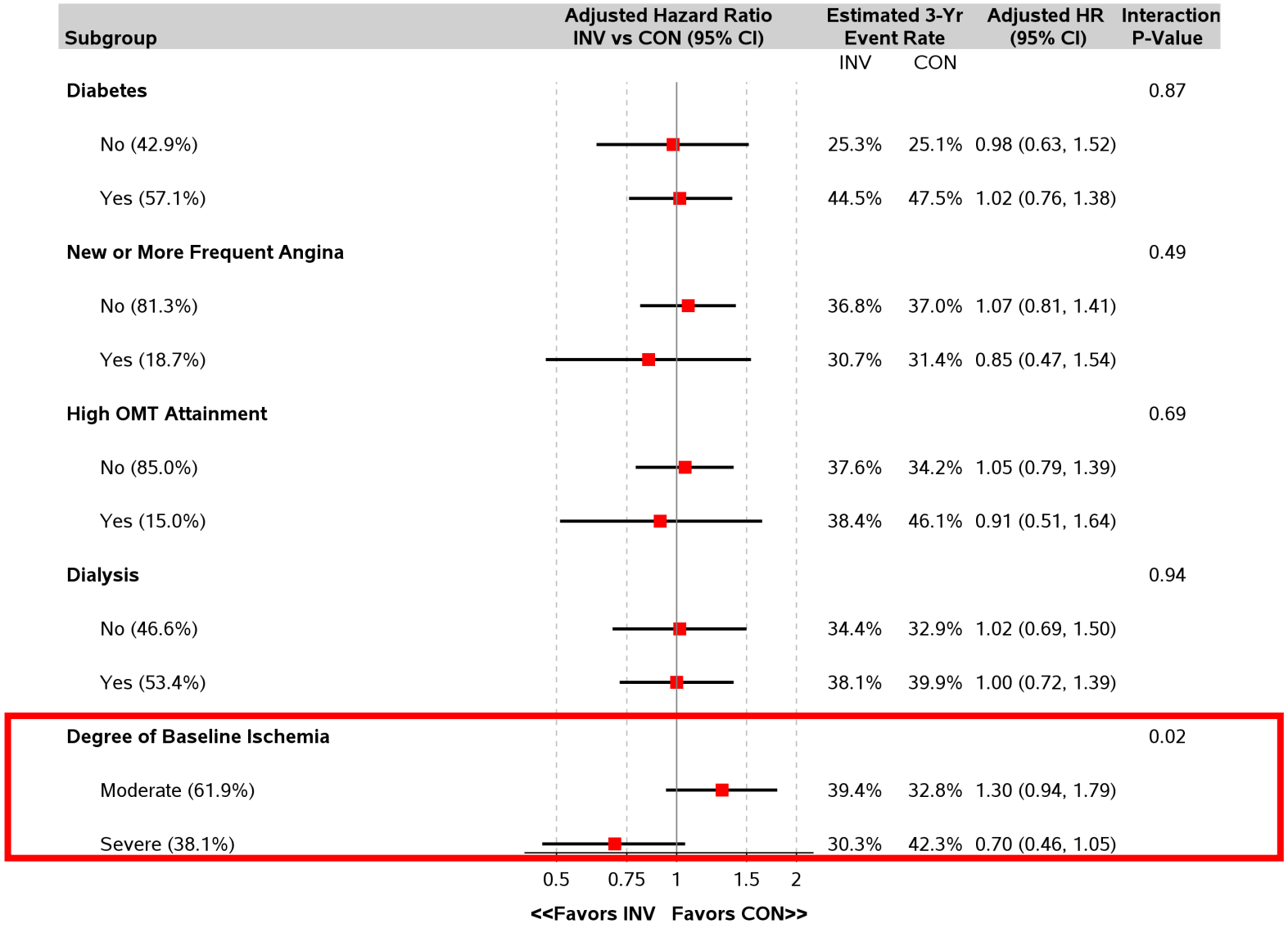
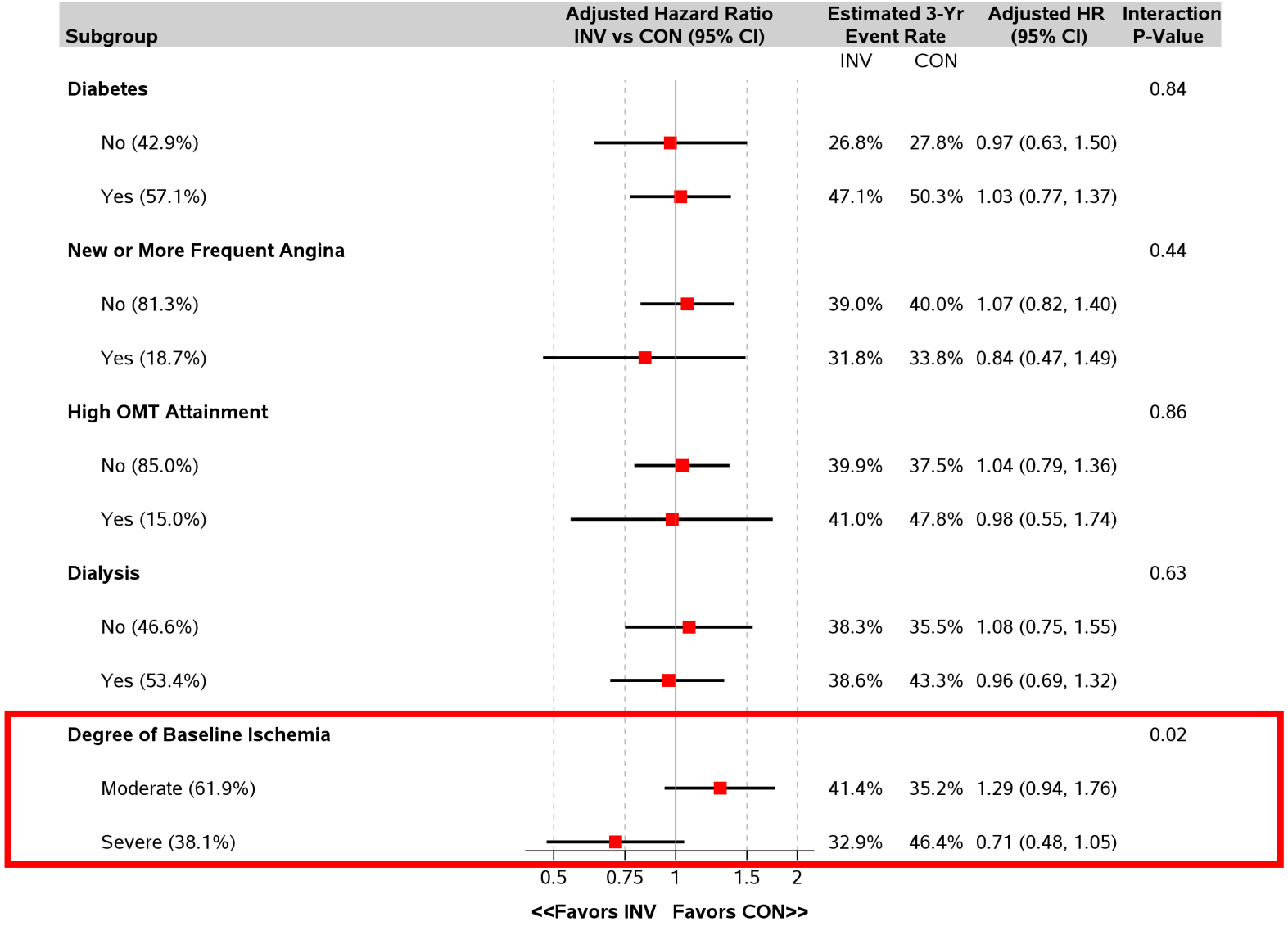
Heterogeneity of Treatment Effect

Death or MI



Heterogeneity of Treatment Effect

Death, MI, Hospitalization for Unstable Angina or Heart Failure or Resuscitated Cardiac Arrest



Study Limitations

- Low rates of revascularization in the invasive arm
  - Sensitivity and specificity of stress testing in CKD cohort is poor
  - No requirement for CCTA in the trial
- Based on exclusion criteria, the trial results do not apply to patients with:
  - Acute coronary syndromes within 2 months
  - Highly symptomatic patients
  - LVEF <35%
- Sites were specifically trained to minimize risk of AKI after cardiac catheterization and revascularization.
  - Trial findings not generalizable to centers with higher complication rates

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Conclusions

- Largest trial of invasive vs. conservative strategy in patients with advanced CKD and SIHD
- Low rates of procedural complications (stroke, AKI)
- Overall, an initial invasive strategy did not demonstrate a reduced risk of clinical outcomes as compared with an initial conservative strategy

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We thank the investigators, the study coordinators and especially the participants in the trial

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Device donations:
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Medtronic, Inc.
St. Jude Medical, Inc.
Phillips Co.
Omron Healthcare, Inc

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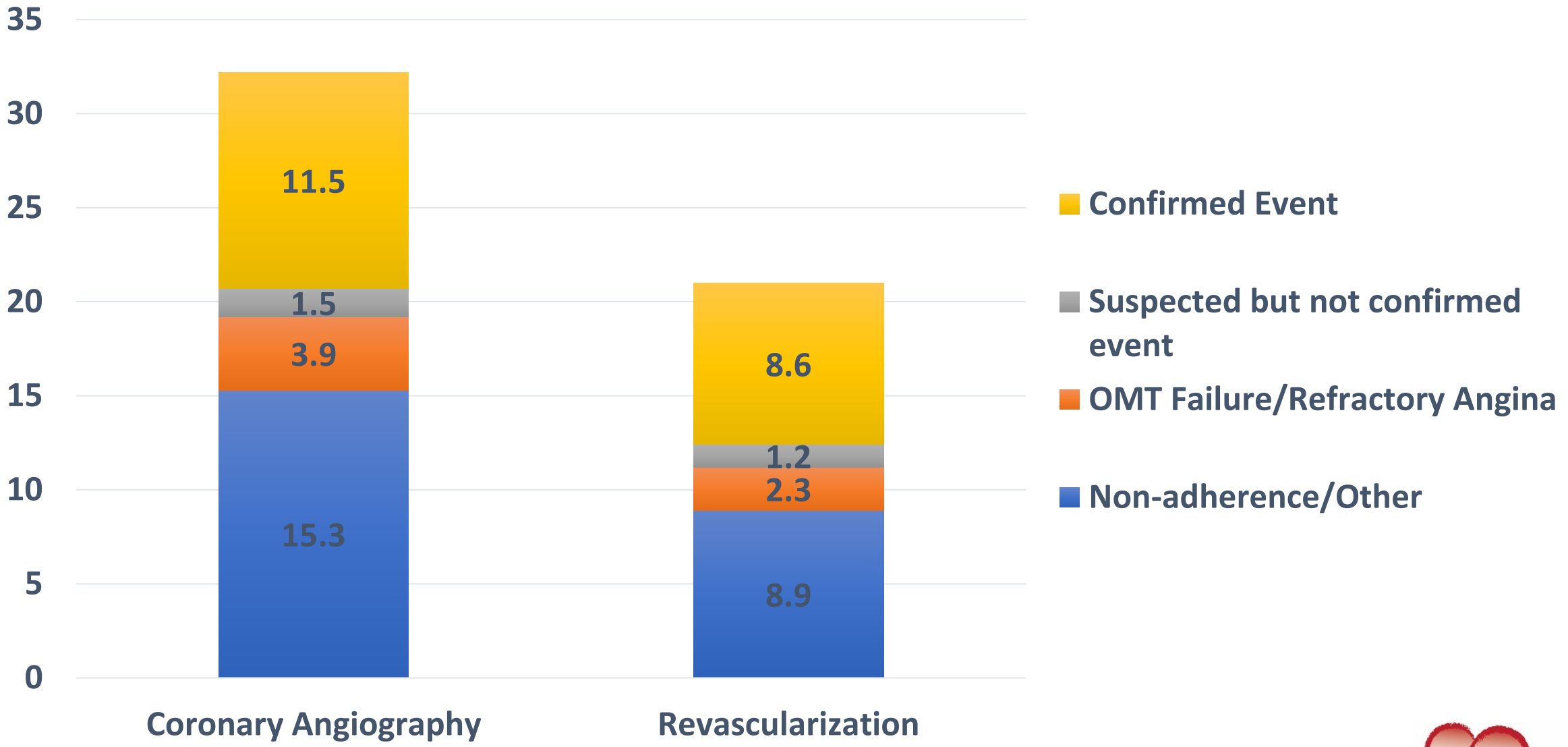
Coronary Angiography and Revascularization in CON



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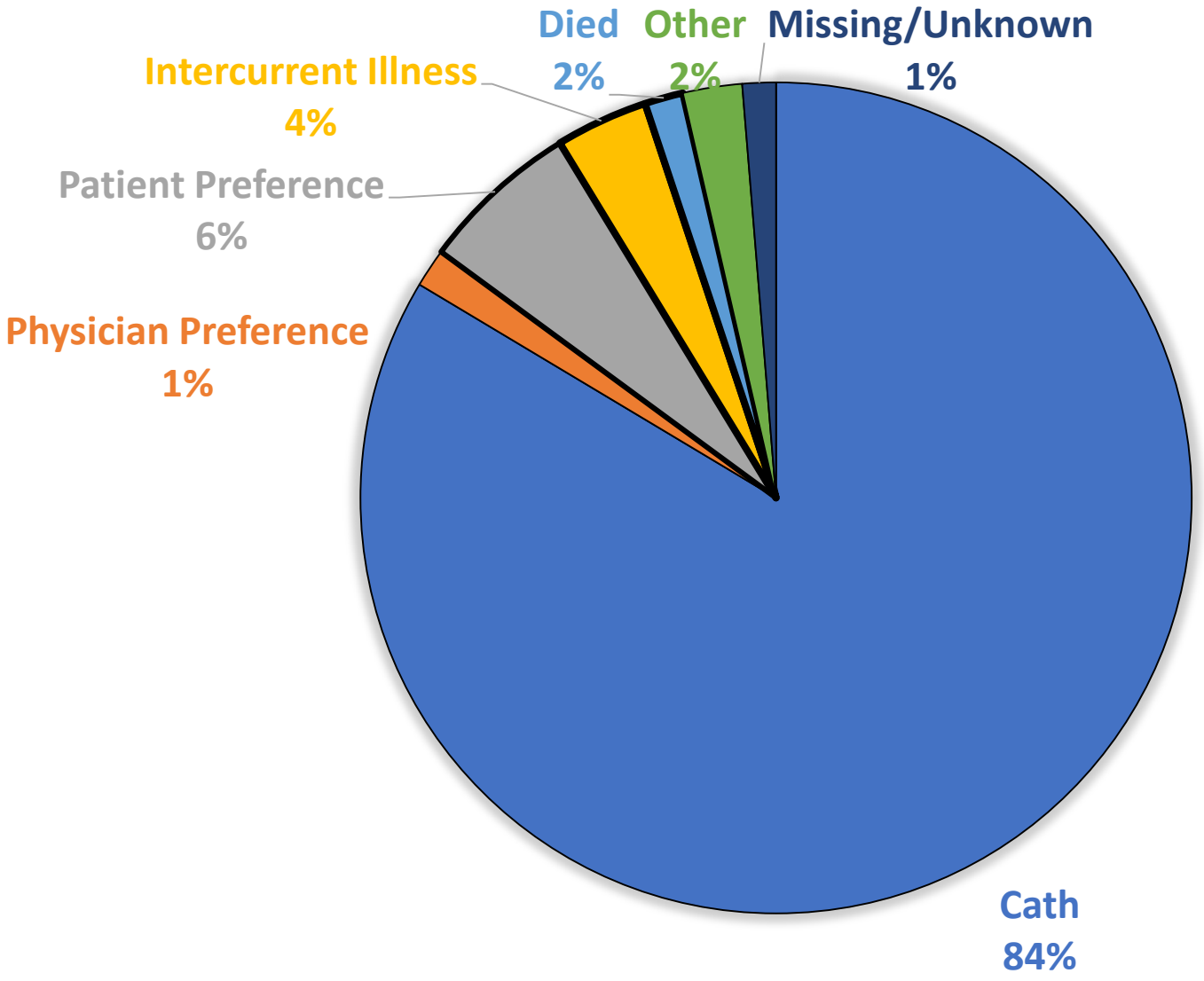
Reasons for No Cardiac Catheterization in Invasive



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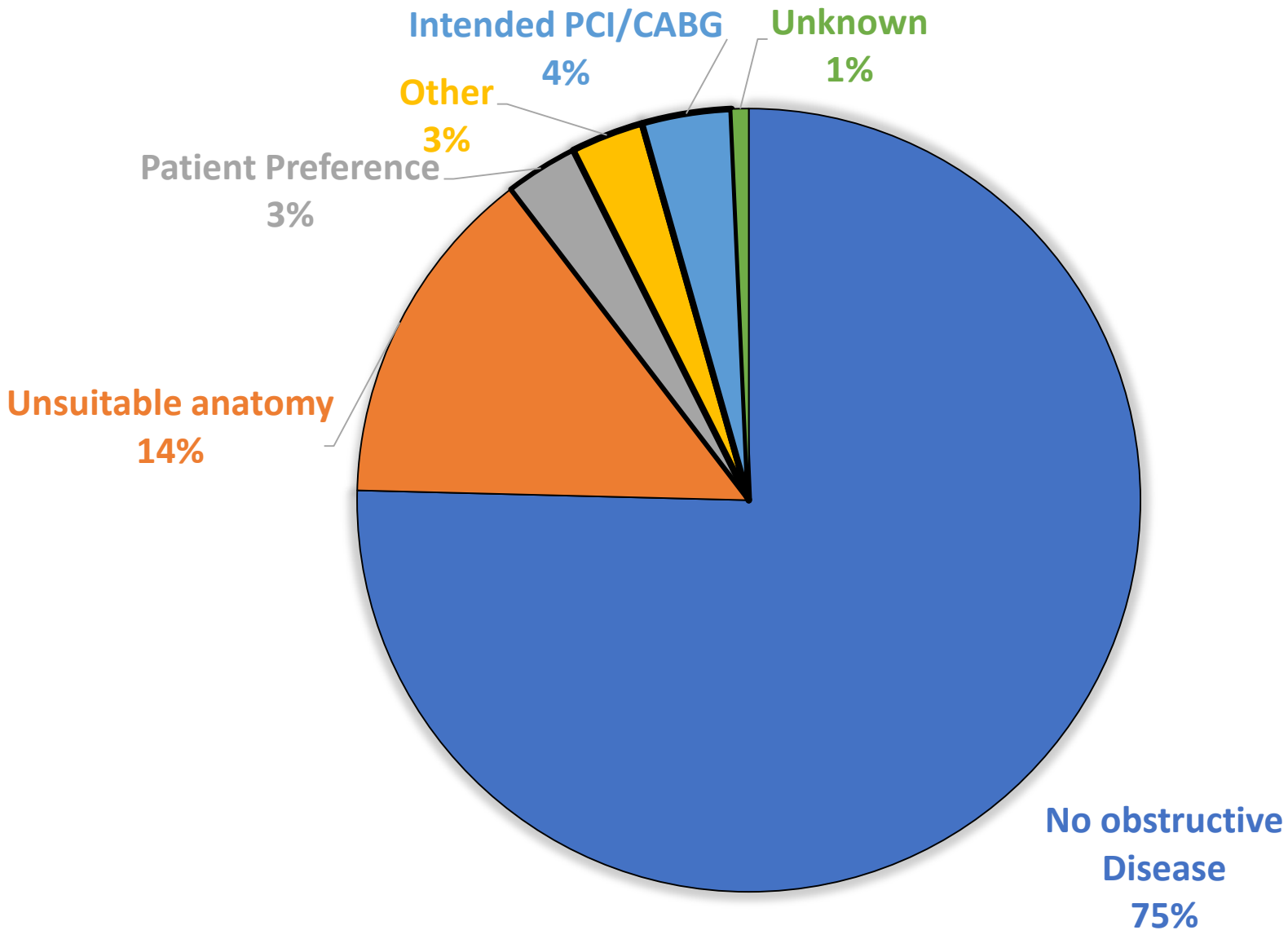
Reasons for No Revascularization after Cath in INV



N=134

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