Impact of **Completeness of Revascularization** on Clinical Outcomes in Patients With Stable Ischemic Heart Disease Treated With an Invasive Versus Conservative Strategy:

The ISCHEMIA Trial

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On behalf of the ISCHEMIA Research Group

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Disclosures

The ISCHEMIA trial and my role as co-principal investigator were supported by NHLBI grants

General Disclosures

Consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Miracor, Neovasc, Abiomed, Ancora, Vectorious, Elucid Bio, Occlutech, CorFlow, Cardiomech, Gore; Equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix

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Background

- From a systematic review of >50 prior observational studies of pts with chronic coronary disease (CCD), the achievement of anatomic or ischemic (functional) complete revascularization (CR) after PCI and CABG has been associated with improved survival and freedom from MI
  - However, not all studies have shown this association
  - Few studies have adjusted for imbalances in baseline clinical and anatomic covariates
  - No studies have used a comprehensive QCA core laboratory analysis to assess CR after both PCI and CABG
- The impact of CR in pts with CCD undergoing an invasive (INV) compared with a conservative (CON) management strategy has not been reported

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Gaba P et al. Nat Rev Cardiol. 2021;18:155-68

Objectives

Among patients with CCD and at least moderate ischemia enrolled in the ISCHEMIA trial, we therefore sought to:

- **Objective 1:** Assess the frequency and outcomes of anatomic CR (ACR) and ischemic/functional CR (FCR) compared with incomplete revascularization (ICR) in pts treated with an INV management strategy
- **Objective 2:** Assess the impact that achieving CR in all pts randomized to an INV strategy might have had compared with CON management

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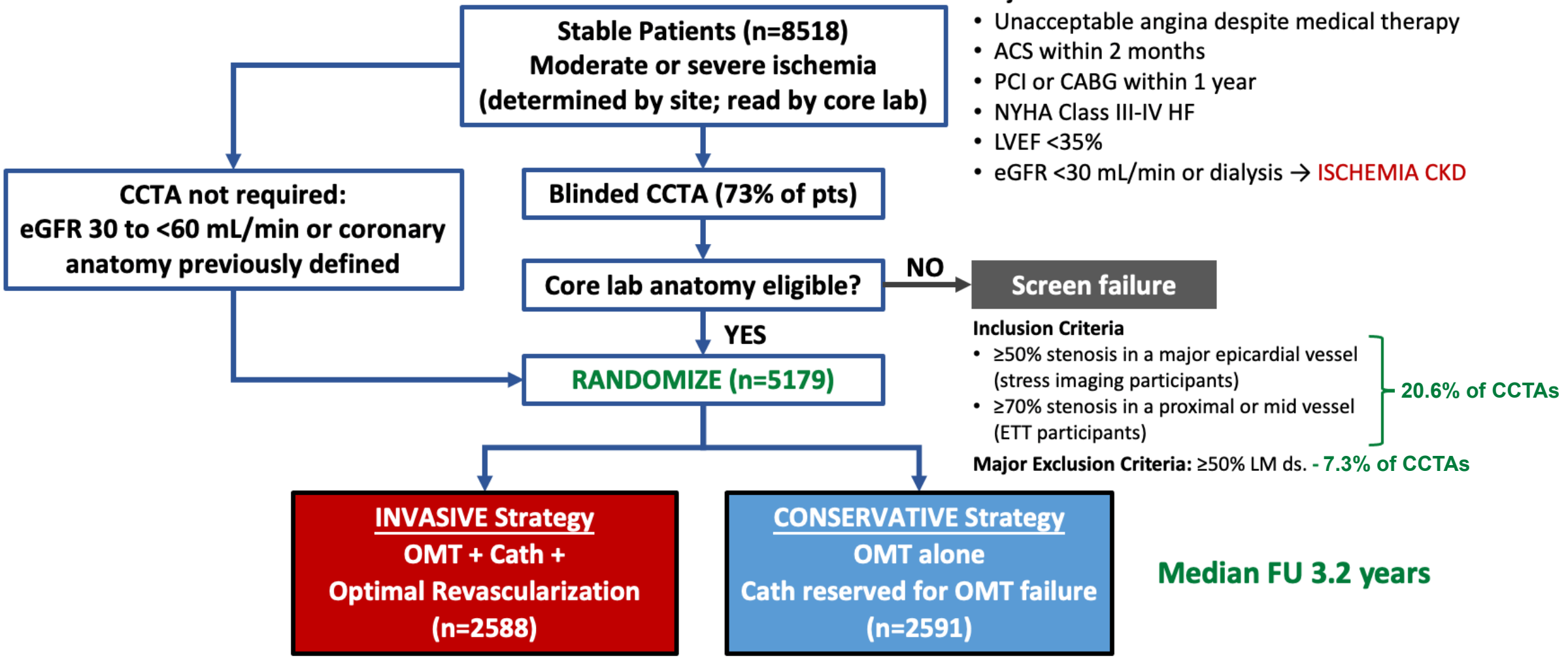
The ISCHEMIA Trial



Primary endpoint: CV death, MI or hospitalization for cardiac arrest, HF or UA

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Maron DJ et al. N Engl J Med. 2020;382:1395-1407

Angiographic Core Laboratory* Assessment of Anatomic and Functional Completeness of Revascularization After PCI and CABG

- **PCI:** CR assessed by review of pre- and post-procedure angiograms (includes planned staged procedures)
- **CABG:** CR assessed by review of pre-procedure angiograms and CABG procedure reports; accounts for diseased vessel segments and side branches

- **Anatomic CR:** Revasc of all lesions with QCA RVD ≥2.0 mm and QCA DS ≥50%
- **Functional CR:** Revasc of all lesions with QCA RVD ≥2.0 mm and:
  - Localizing FFR/iFR ≤0.80/0.89 plus QCA DS ≥30%, or
  - Localizing non-invasive ischemia in the vessel distribution plus QCA DS ≥50%, or
  - Non-localizing severe ischemia by ETT plus QCA DS ≥60%, or
  - QCA DS ≥70%

*Cardiovascular Research Foundation, NY

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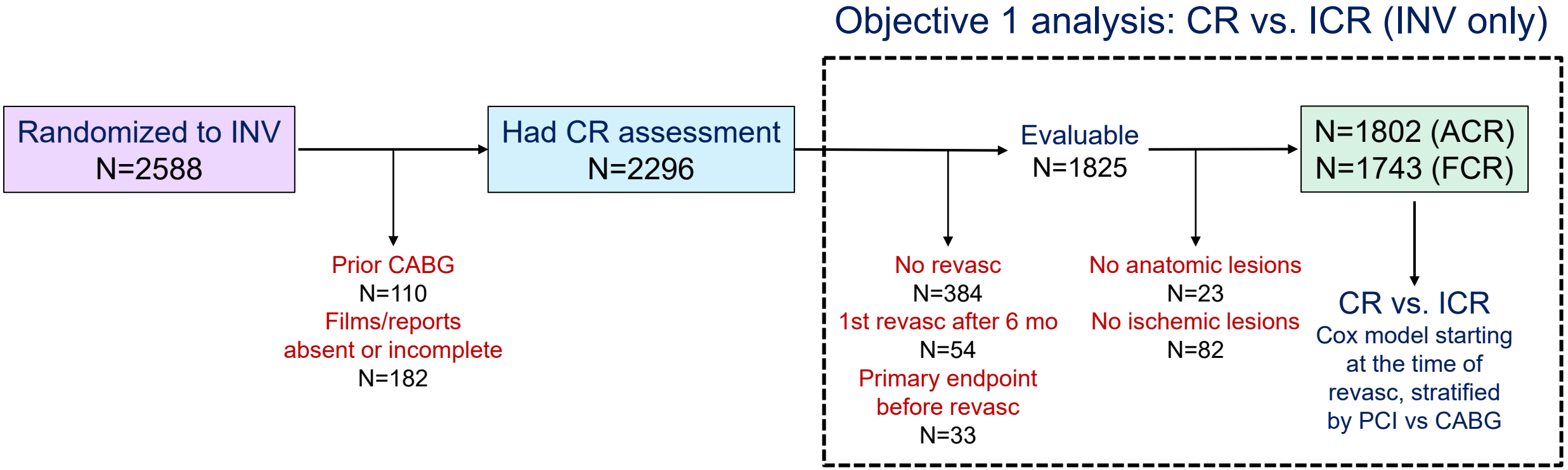
Modified from Ali Z et al. J Am Heart Assoc. 2021:e020110. doi: 10.1161/JAHA.120.020110

Objective 1: Patient Flow and Methods



- **Methods Objective 1 - INV arm only, CR vs. ICR:**
  Outcomes were compared in Cox multivariable models stratified by PCI vs. CABG, with follow-up beginning at the time of first revascularization
  - Anatomic complete revascularization (ACR) versus anatomic ICR (n=1802)
  - Functional complete revascularization (FCR) versus functional ICR (n=1743)

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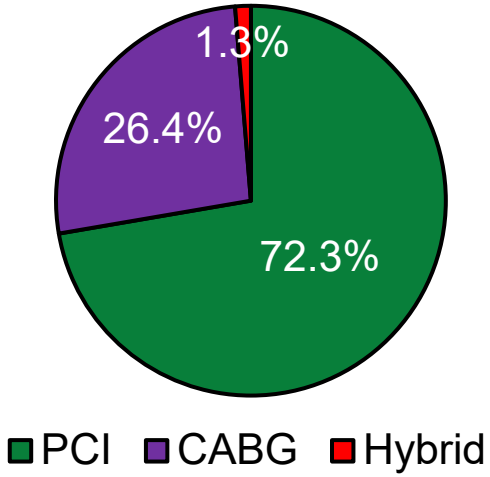
Objective 1: Completeness of Revascularization (INV)

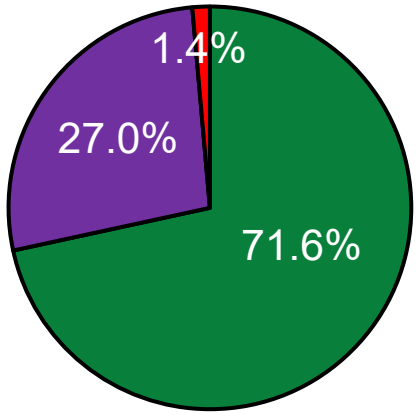
Among 1825 pts randomized to INV in whom a revasc procedure was performed within 6 months, prior to a primary endpoint event

Mode of revasc

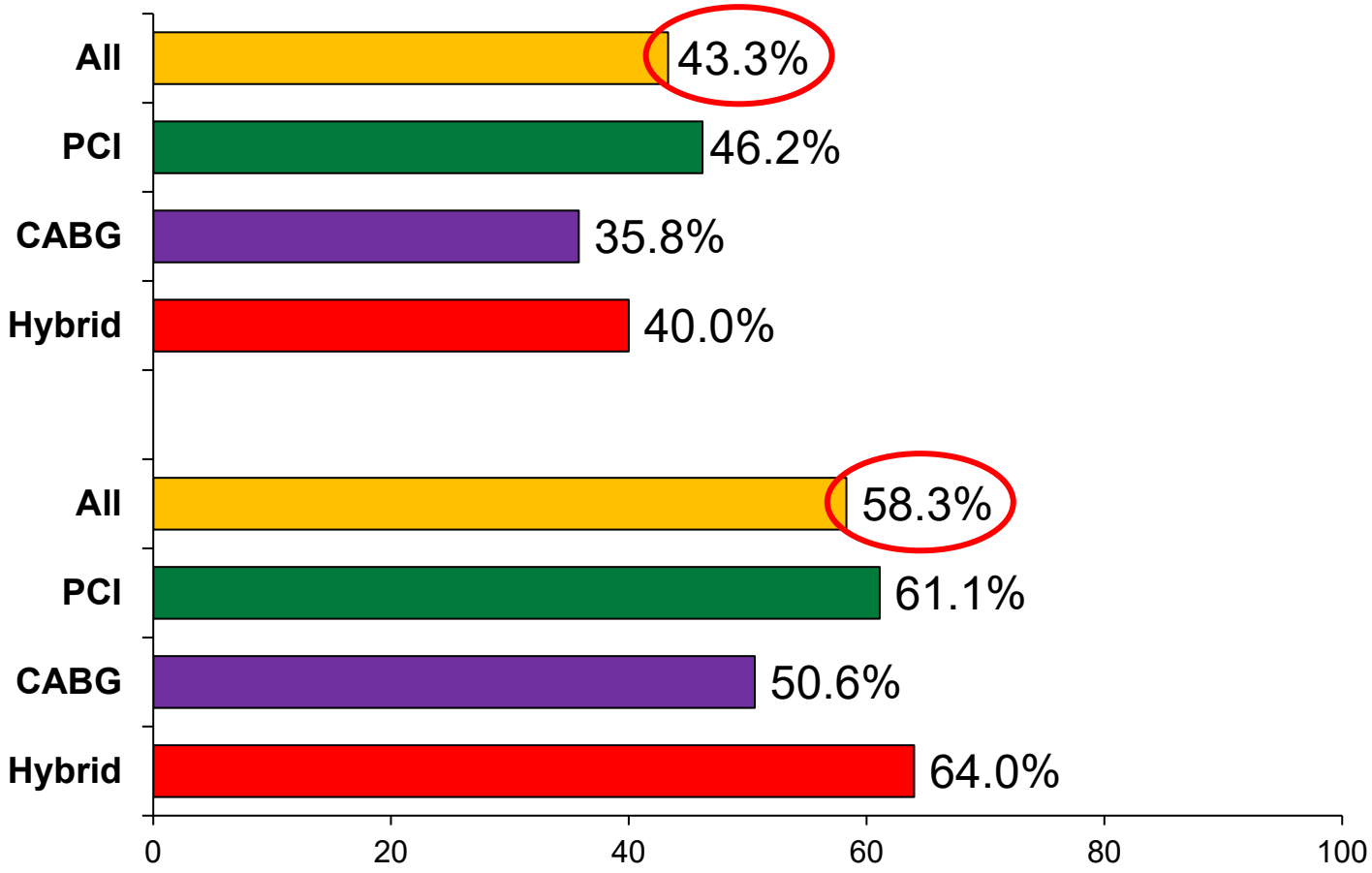
ACR assessment (n=1802)



FCR assessment (n=1743)



Complete revascularization rate (%)



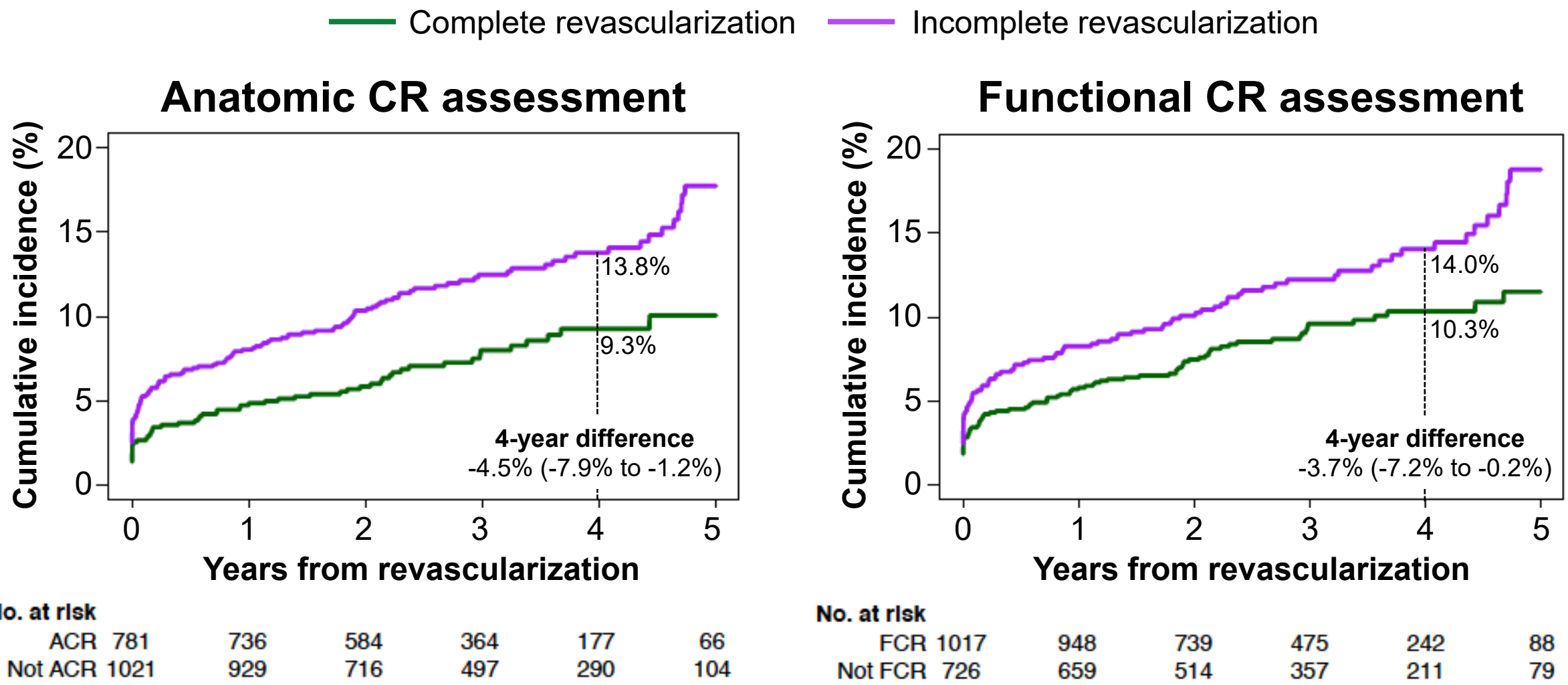
Multivariable Predictors of CR

	Anatomic CR		Functional CR	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Clinical covariates				
Diabetes	1.42 (1.10 - 1.84)	0.006	1.35 (1.06 - 1.72)	0.02
BMI (per 5 kg/m^2)	0.85 (0.74 - 0.98)	0.02	0.80 (0.70 - 0.92)	0.001
Angiographic covariates (ACL)				
Diseased vessels (2 vs 1)	0.41 (0.29 - 0.57)	<0.0001	0.55 (0.40 - 0.77)	0.0003
Diseased vessels (3 vs 1)	0.37 (0.22 - 0.62)	0.0002	0.55 (0.36 - 0.83)	0.005
# lesions (anatomic for ACR, ischemic for FCR)	0.37 (0.31 - 0.44)	<0.0001	0.41 (0.35 - 0.48)	<0.0001
CTOs (1 vs 0)	0.53 (0.39 - 0.71)	<0.0001	0.46 (0.35 - 0.60)	<0.0001
CTOs (≥2 vs 0)	-	-	0.54 (0.32 - 0.91)	0.02
# lesions with mod/sev calcification	1.16 (1.05 - 1.29)	0.005	-	-
Left main disease	2.60 (1.23 - 5.48)	0.01	-	-
Proximal LAD disease	1.41 (1.06 - 1.88)	0.02	1.47 (1.13 - 1.93)	0.005
SYNTAX score (per 5 units)	0.89 (0.79 - 1.00)	0.05		
Duke Jeopardy score (per 1 unit)	1.20 (1.07 - 1.34)	0.001	-	-
Revascularization modality				
First procedure CABG (vs PCI)	2.30 (1.64 - 3.21)	<0.0001	1.90 (1.39 - 2.59)	<0.0001

Logistic regression model. OR >1→CR more likely. Other covariates that were not significantly associated with CR included region of enrollment (NA, EU, Asia, LA/other), age, sex, HTN, smoking, prior MI, h/o HF, h/o stroke or cerebrovascular ds, PAD, prior PCI, LVEF, eGFR, SAQ-AF, NYHA class, stress test type (imaging vs other), ischemia severity (core lab), SYNTAX score, tortuosity, use of FFR or IVUS.

Relationship Between CR and Outcomes (INV) - Unadjusted

Primary endpoint: CV death, MI or hospitalization for arrest, HF or UA



Relationship Between CR and Long-term Outcomes (INV)

Anatomic CR Assessment						
	CR	ICR	Unadjusted		Adjusted	
Endpoint			HR (95% CI)	P value	HR (95% CI)	P value
Primary endpoint	**9.3%**	**13.8%**	**0.61 (0.45 - 0.82)**	**0.001**	**0.79 (0.55 - 1.15)**	**0.22**
CV death or MI	8.1%	12.6%	0.60 (0.44 - 0.83)	0.002	0.76 (0.52 - 1.13)	0.18
- CV death	2.5%	4.3%	0.41 (0.22 - 0.79)	0.007	0.56 (0.27 - 1.15)	0.11
- MI	6.2%	9.8%	0.64 (0.45 - 0.92)	0.02	0.80 (0.51 - 1.25)	0.32
All-cause death	5.7%	6.8%	0.65 (0.42 - 1.02)	0.06	0.66 (0.39 - 1.14)	0.13

Relationship Between CR and Long-term Outcomes (INV)

Anatomic CR Assessment						
	CR	ICR	Unadjusted		Adjusted	
Endpoint			HR (95% CI)	P value	HR (95% CI)	P value
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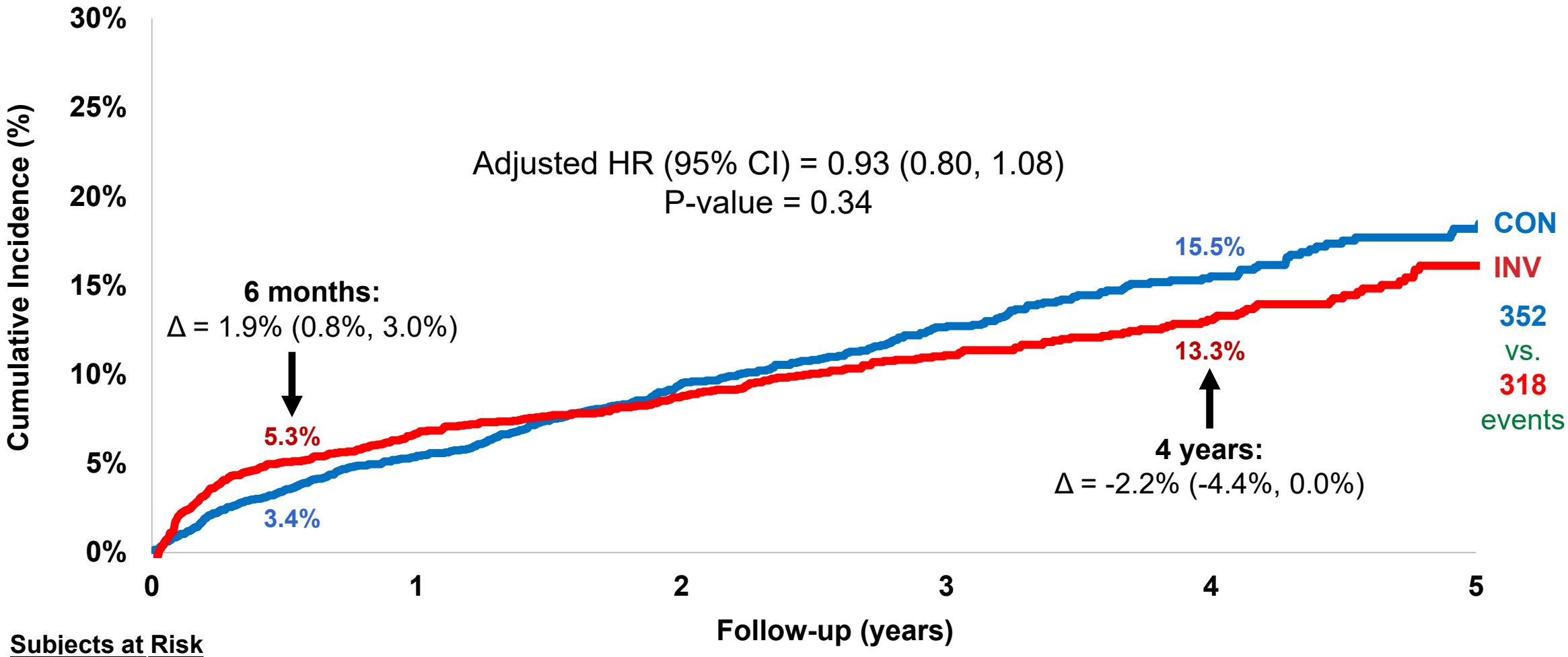
- MI	6.2%	9.8%	0.64 (0.45 - 0.92)	0.02	0.80 (0.51 - 1.25)	0.32
All-cause death	5.7%	6.8%	0.65 (0.42 - 1.02)	0.06	0.66 (0.39 - 1.14)	0.13
Functional CR Assessment						
	CR	ICR	Unadjusted		Adjusted	
Endpoint			HR (95% CI)	P value	HR (95% CI)	P value
Primary endpoint	**10.3%**	**14.0%**	**0.71 (0.54 - 0.95)**	**0.02**	**0.96 (0.68 - 1.34)**	**0.80**
CV death or MI	9.0%	13.2%	0.67 (0.50 - 0.91)	0.01	0.85 (0.60 - 1.22)	0.38
- CV death	2.8%	4.6%	0.57 (0.33 - 0.99)	0.05	0.83 (0.44 - 1.56)	0.55
- MI	6.9%	10.5%	0.67 (0.48 - 0.94)	0.02	0.83 (0.55 - 1.25)	0.37
All-cause death	6.0%	7.0%	0.80 (0.53 - 1.22)	0.30	0.90 (0.55 - 1.47)	0.68

Principal ISCHEMIA Trial Results

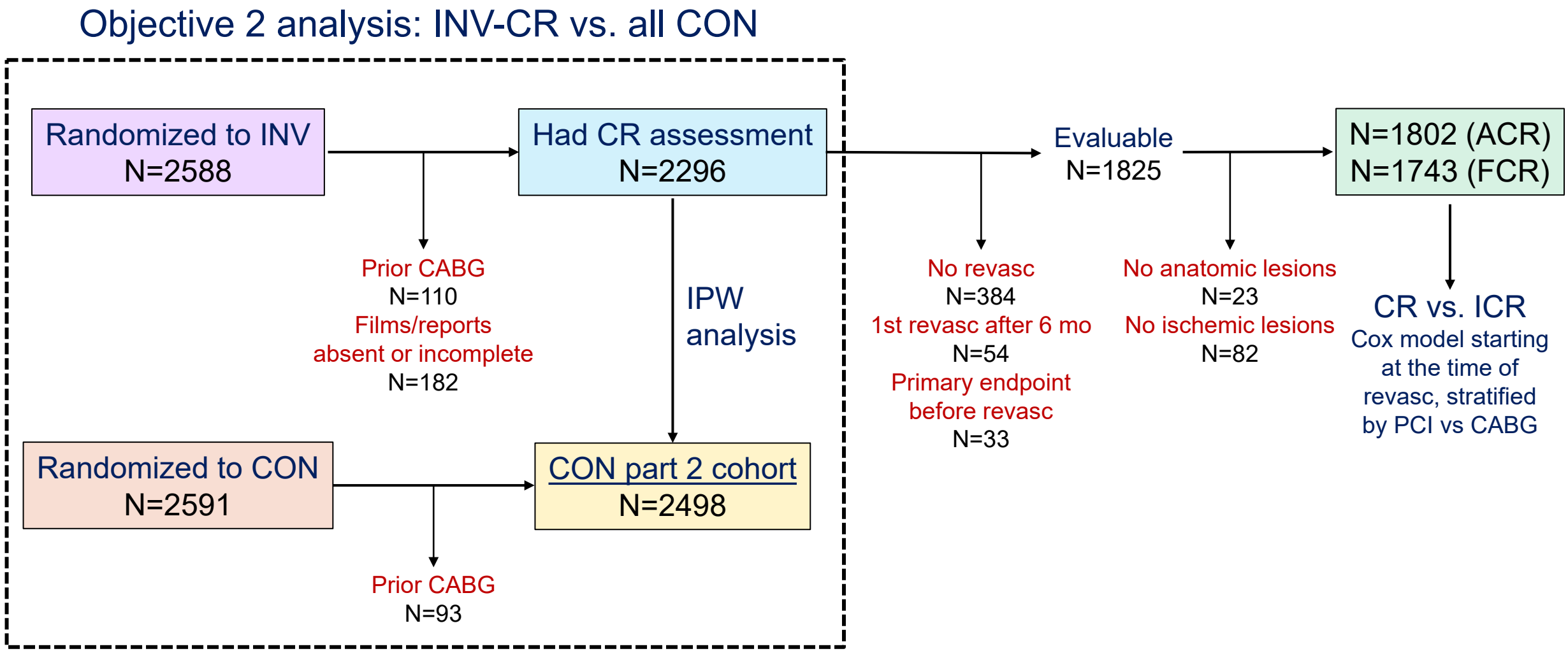
Primary endpoint: CV death, MI or hospitalization for arrest, HF or UA



Subjects at Risk

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

Objective 2: Patient Flow



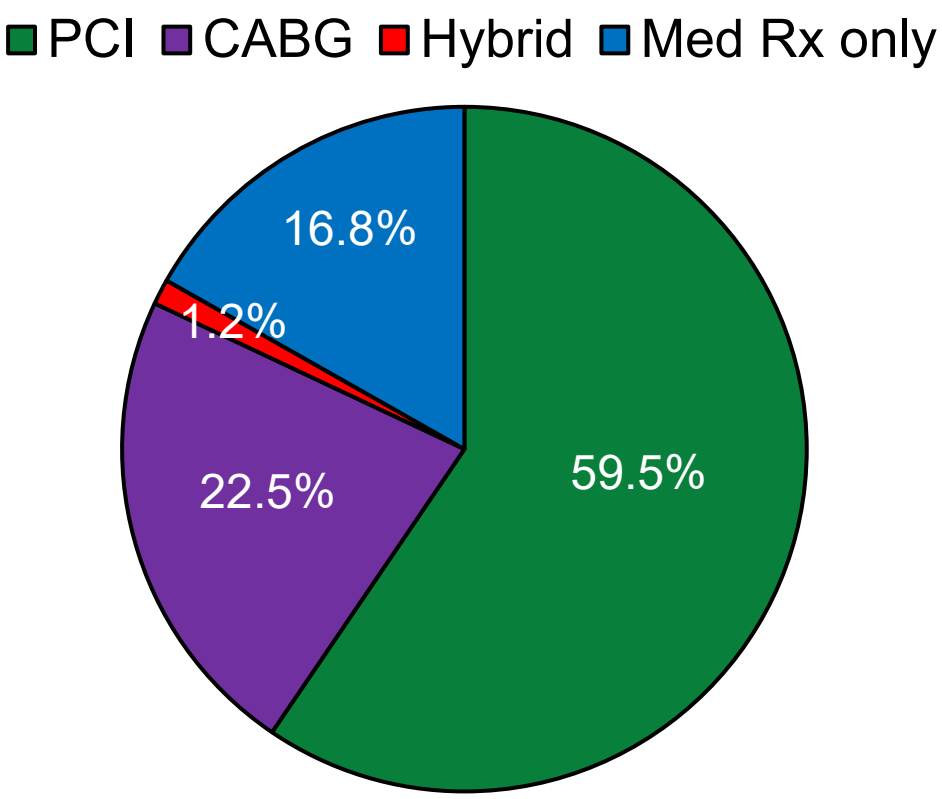
Methods Part 2

- **Part 2 - INV vs. CON:** Marginal structural modeling with CR as a time-dependent variable was used to estimate the hypothetical ideal treatment effect had all INV pts received CR at the time of randomization, compared with CON management
  - INV group: All INV pts without prior CABG were included; If med Rx only with no significant lesions → count as CR, if with significant lesions → count as ICR
    - Inverse probability weighting (IPW) was used to construct a propensity weighted CR group, adjusted so the prevalence of measured risk factors among the weighted CR pts was similar to the overall INV group, and by randomization to the CON group
  - CON group: Nonparametric Kaplan-Meier analysis of all CON pts without prior CABG, weighted for chance covariate imbalances between INV and CON
  - Sensitivity analysis: Multivariable Cox model adjusted for baseline covariates

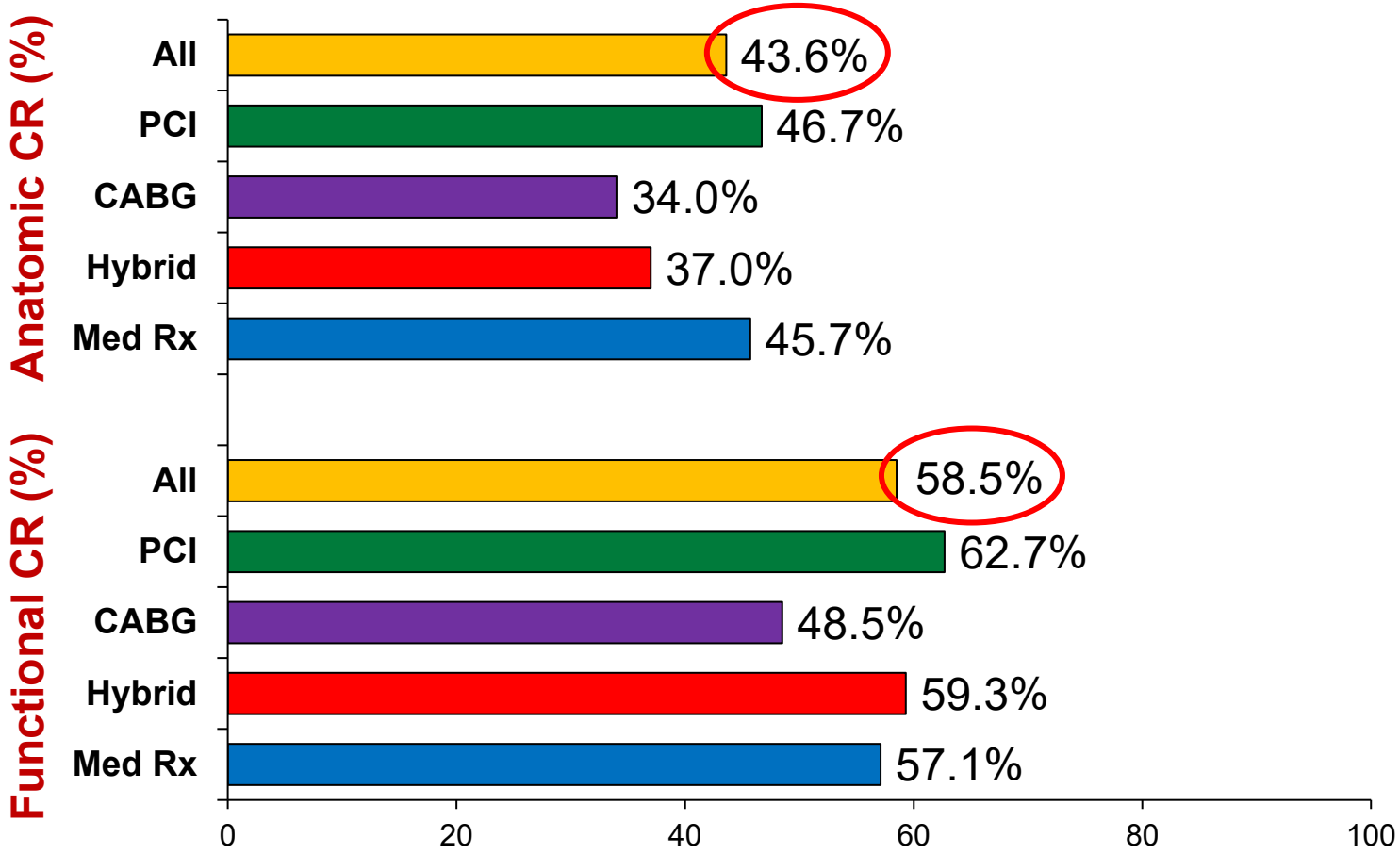
Objective 2: Completeness of Revascularization (INV)

Among 2296 pts randomized to INV

Mode of revascularization



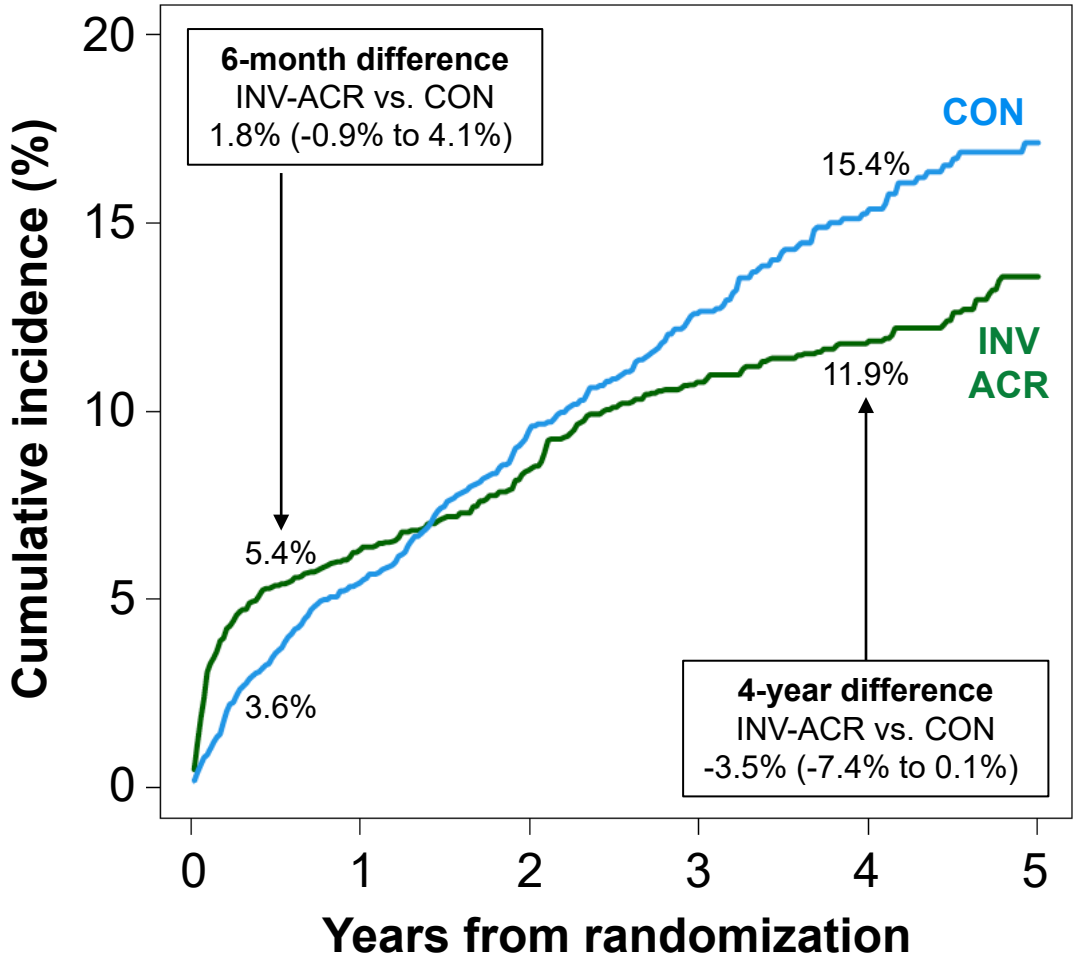
Complete revascularization rate (%)



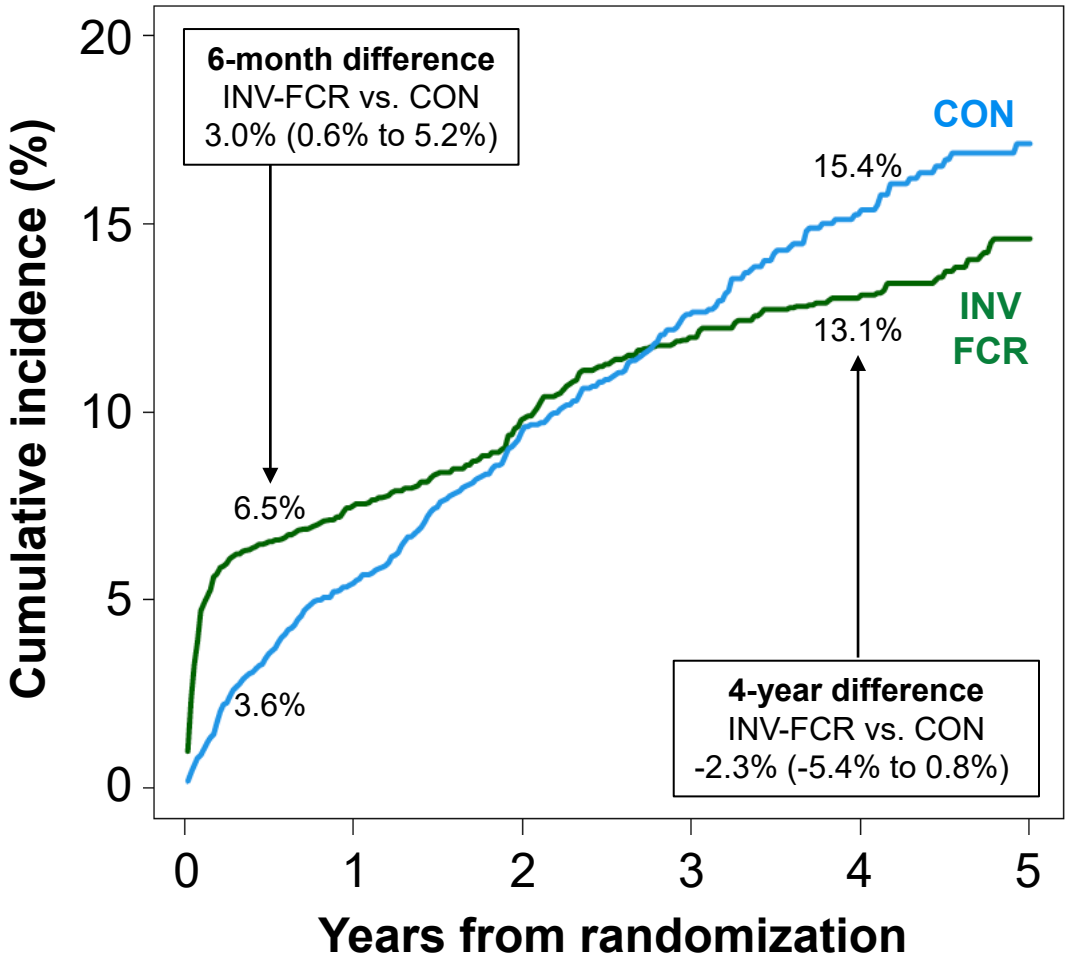
Outcomes for INV-CR versus CON: Primary endpoint

INV IPW-adjusted, marginal structural model using natural splines

Anatomic CR achieved



Functional CR achieved



Adjusted 4-Year Outcomes for INV-ACR versus CON

Anatomic CR Assessment - Marginal structural model using natural splines			
Endpoint	**INV-ACR**	**CON**	**Adj Difference (95% CI)**
Primary endpoint	**11.9%**	**15.4%**	**-3.5% (-7.4% to 0.1%)**
CV death or MI	10.3%	13.8%	-3.5% (-7.4% to -0.2%) *
- CV death	3.2%	5.0%	-1.8% (-4.3% to 0.3%)
- MI	7.9%	10.1%	-2.3% (-5.4% to 0.8%)
All-cause death	6.3%	6.4%	-0.1% (-4.2% to 3.2%)
Anatomic CR Assessment - Covariate-adjusted Cox model			
Endpoint	**INV-ACR**	**CON**	**Adj Difference (95% CI)**
Primary endpoint	**11.8%**	**15.4%**	**-3.6% (-6.9% to -0.7%)** *
CV death or MI	10.8%	13.8%	-3.0% (-6.5% to -0.1%) *
- CV death	2.8%	5.0%	-2.2% (-4.5% to -0.5%) *
- MI	9.1%	10.1%	-1.0% (-4.2% to 1.7%)
All-cause death	5.6%	6.4%	-0.8% (-3.9% to 1.5%)

Adjusted 4-Year Outcomes for INV-FCR versus CON

Functional CR Assessment - Marginal structural model using natural splines			
Endpoint	**INV-FCR**	**CON**	**Adj Difference (95% CI)**
Primary endpoint	**13.1%**	**15.4%**	**-2.3% (-5.4% to 0.8%)**
CV death or MI	10.9%	13.8%	-2.9% (-6.1% to 0.2%)
- CV death	3.4%	5.0%	-1.6% (-3.6% to 0.3%)
- MI	8.2%	10.1%	-1.9% (-4.5% to 0.7%)
All-cause death	6.3%	6.4%	-0.1% (-2.7% to 2.3%)
Functional CR Assessment - Covariate-adjusted Cox model			
Endpoint	**INV-FCR**	**CON**	**Adj Difference (95% CI)**
Primary endpoint	**12.9%**	**15.4%**	**-2.5% (-5.7% to 0.3%)**
CV death or MI	11.2%	13.8%	-2.6% (-5.7% to 0.1%)
- CV death	3.4%	5.0%	-1.6% (-3.7% to 0.0%) *
- MI	9.0%	10.1%	-1.2% (-4.1% to 1.3%)
All-cause death	6.3%	6.4%	-0.0% (-2.6% to 2.0%)

Randomized ISCHEMIA 4-Year Outcomes vs. CR Analysis

	ISCHEMIA Trial*	ISCHEMIA Anatomic CR Substudy Analysis	
4-year events	**INV vs CON Adj Difference (95% CI)**	**INV-ACR vs CON (model 1)† Adj Difference (95% CI)**	**INV-ACR vs CON (model 2)† Adj Difference (95% CI)**
Primary endpoint	**-2.5% (-4.6% to -0.2%)**	**-3.5% (-7.4% to 0.1%)**	**-3.6% (-6.9% to -0.7%)**
CV death or MI	-2.4% (-4.4% to -0.1%)	-3.5% (-7.4% to -0.2%)	-3.0% (-6.5% to -0.1%)
- CV death	-0.9% (-2.2% to 0.5%)	-1.8% (-4.3% to 0.3%)	-2.2% (-4.5% to -0.5%)
- MI	-1.3% (-3.2% to 0.6%)	-2.3% (-5.4% to 0.8%)	-1.0% (-4.2% to 1.7%)
All-cause death	0.0% (-1.6% to 1.7%)	-0.1% (-4.2% to 3.2%)	-0.8% (-3.9% to 1.5%)

*Excluding prior CABG pts from both groups (INV: n=2478, CON: n=2498), adjusted for differences in baseline covariates.
†Model 1 = Marginal structural model; Model 2 = Covariate-adjusted Cox model

Randomized ISCHEMIA 4-Year Outcomes vs. CR Analysis

	ISCHEMIA Trial*	ISCHEMIA Functional CR Substudy Analysis	
4-year events	**INV vs CON Adj Difference (95% CI)**	**INV-FCR vs CON (model 1)† Adj Difference (95% CI)**	**INV-RCR vs CON (model 2)† Adj Difference (95% CI)**
Primary endpoint	**-2.5% (-4.6% to -0.2%)**	**-2.3% (-5.4% to 0.8%)**	**-2.5% (-5.7% to 0.3%)**
CV death or MI	-2.4% (-4.4% to -0.1%)	-2.9% (-6.1% to 0.2%)	-2.6% (-5.7% to 0.1%)
- CV death	-0.9% (-2.2% to 0.5%)	-1.6% (-3.6% to 0.3%)	-1.6% (-3.7% to 0.0%)
- MI	-1.3% (-3.2% to 0.6%)	-1.9% (-4.5% to 0.7%)	-1.2% (-4.1% to 1.3%)
All-cause death	0.0% (-1.6% to 1.7%)	-0.1% (-2.7% to 2.3%)	-0.0% (-2.6% to 2.0%)

*Excluding prior CABG pts from both groups (INV: n=2478, CON: n=2498), adjusted for differences in baseline covariates.
†Model 1 = Marginal structural model; Model 2 = Covariate-adjusted Cox model

Limitations

- The 95% CIs around the point estimates for CR were wide; a larger sample size or higher CR rates would have afforded greater precision
- The present findings represent associations and not causality; the ability to achieve CR is not always predictable, and whether striving for CR in all cases of PCI and CABG would safely improve outcomes is unknown; the present results are therefore hypothesis-generating
- Given the ISCHEMIA trial entry criteria and baseline characteristics of enrolled pts, the trial results do not apply to:
  - Highly symptomatic pts
  - Acute coronary syndromes within 2 months
  - Left main disease
  - Heart failure or reduced LVEF

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Conclusions and Implications

- The present results suggest that among selected pts with CCD and at least moderate ischemia, the outcomes of an INV strategy may be improved if anatomic CR is achieved
- The likelihood of safely achieving anatomic CR should therefore be considered when selecting between an INV and CON approach in pts with CCD

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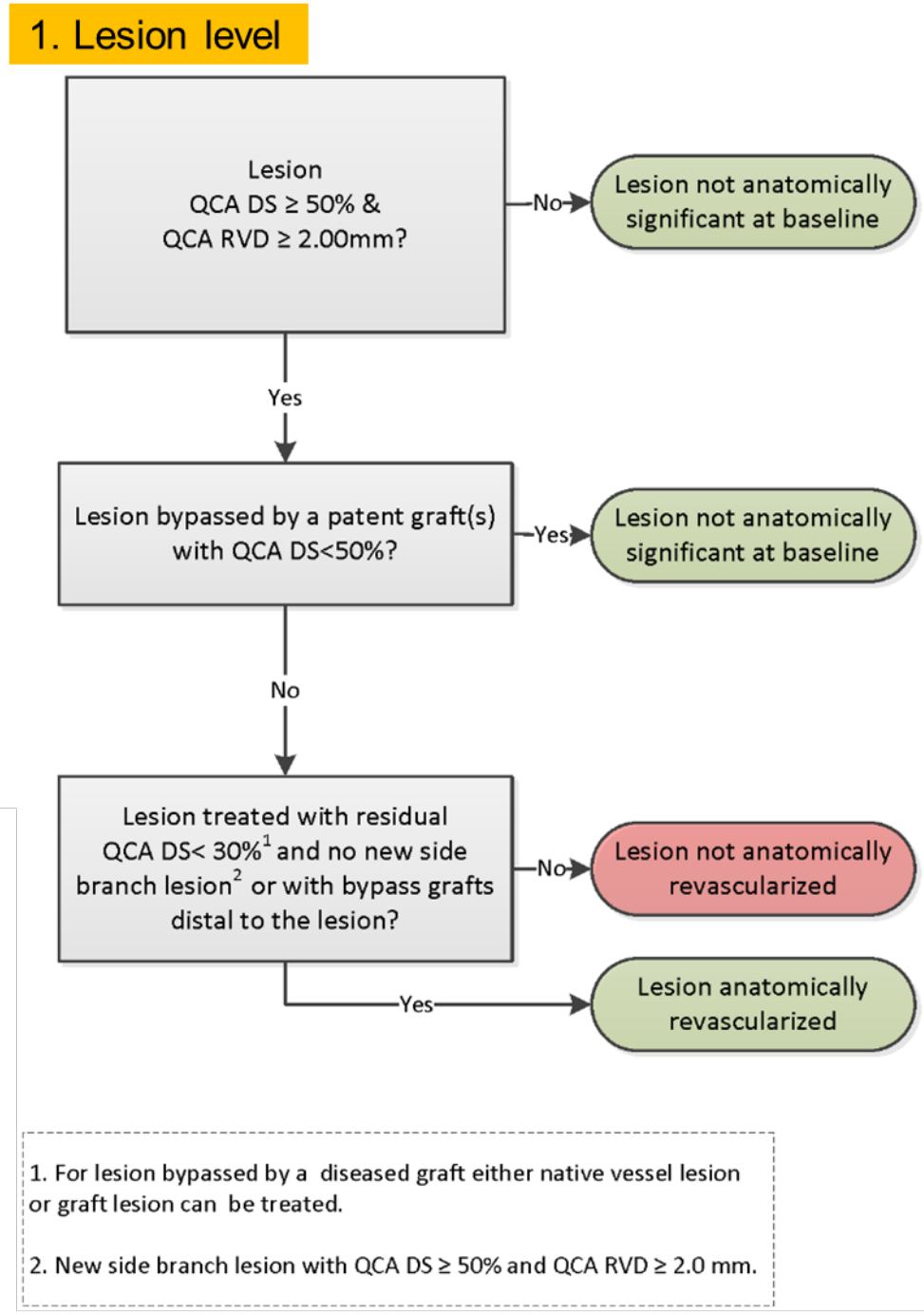
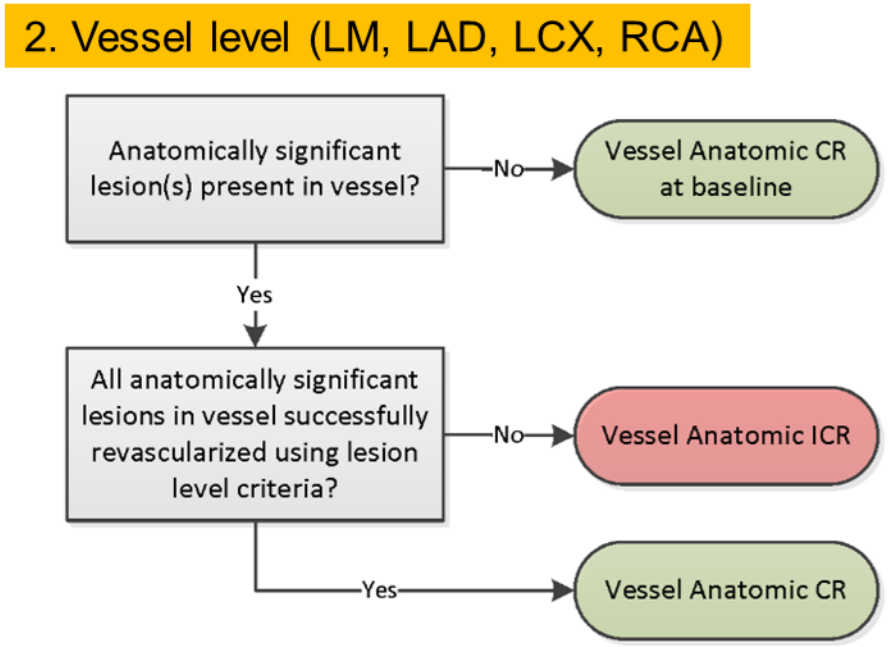
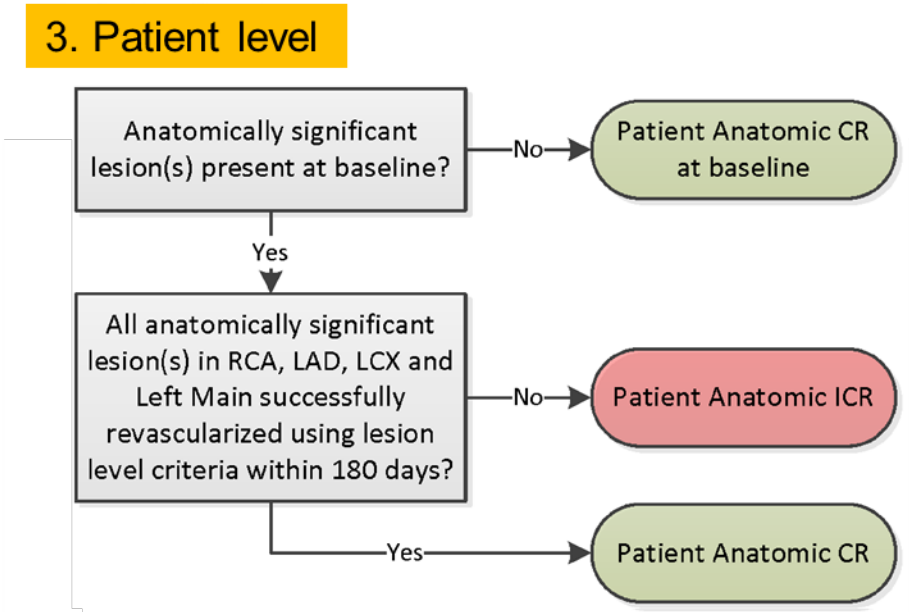
Back-up Slides

Angiographic Core Laboratory* Assessment of Anatomic Completeness of Revascularization After PCI and CABG







1. For lesion bypassed by a diseased graft either native vessel lesion or graft lesion can be treated.

2. New side branch lesion with QCA DS ≥ 50% and QCA RVD ≥ 2.0 mm.

*Cardiovascular Research Foundation, NY

Modified from Ali Z et al. J Am Heart Assoc. 2021:e020110. doi: 10.1161/JAHA.120.020110

Angiographic Core Laboratory* Assessment of Ischemic/Functional Completeness of Revascularization After PCI and CABG

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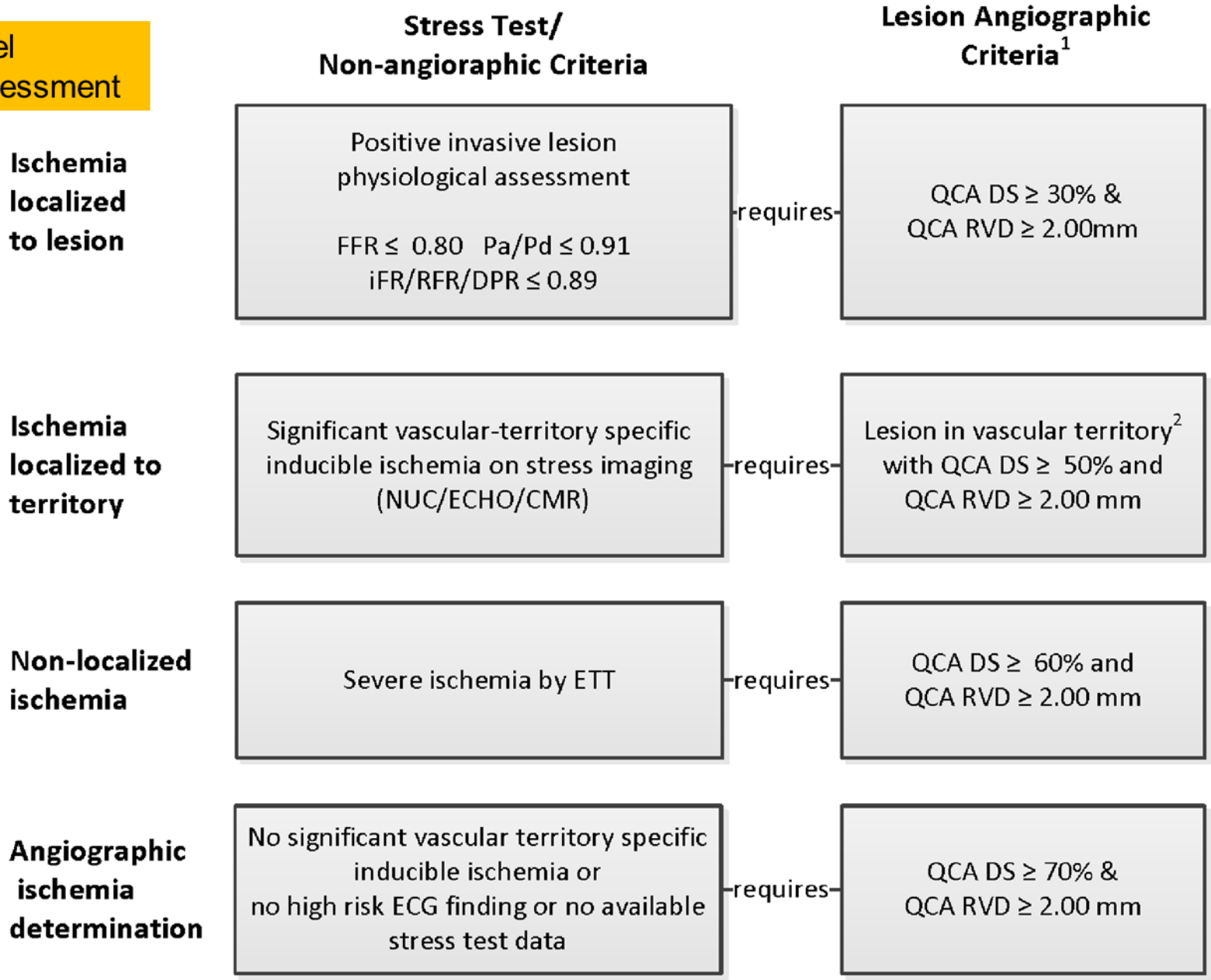
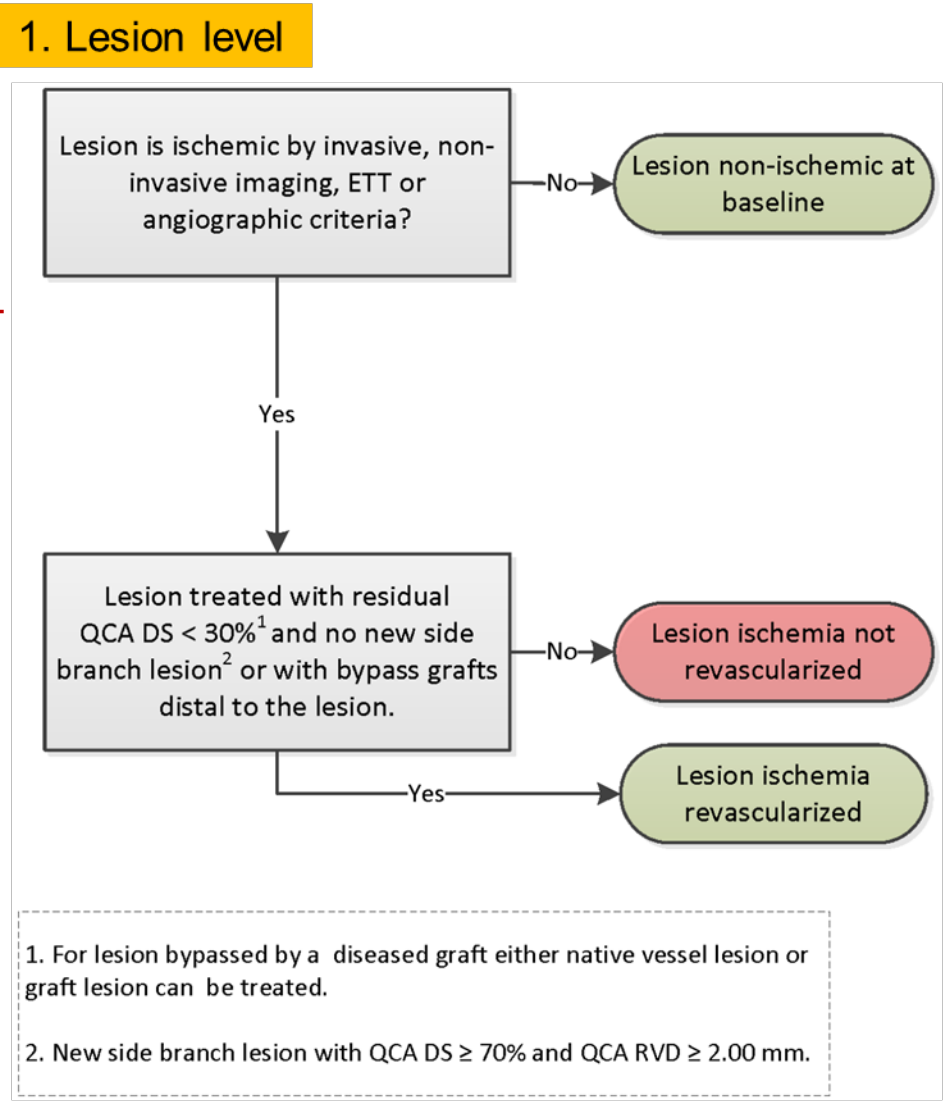
1. Lesion level ischemia assessment

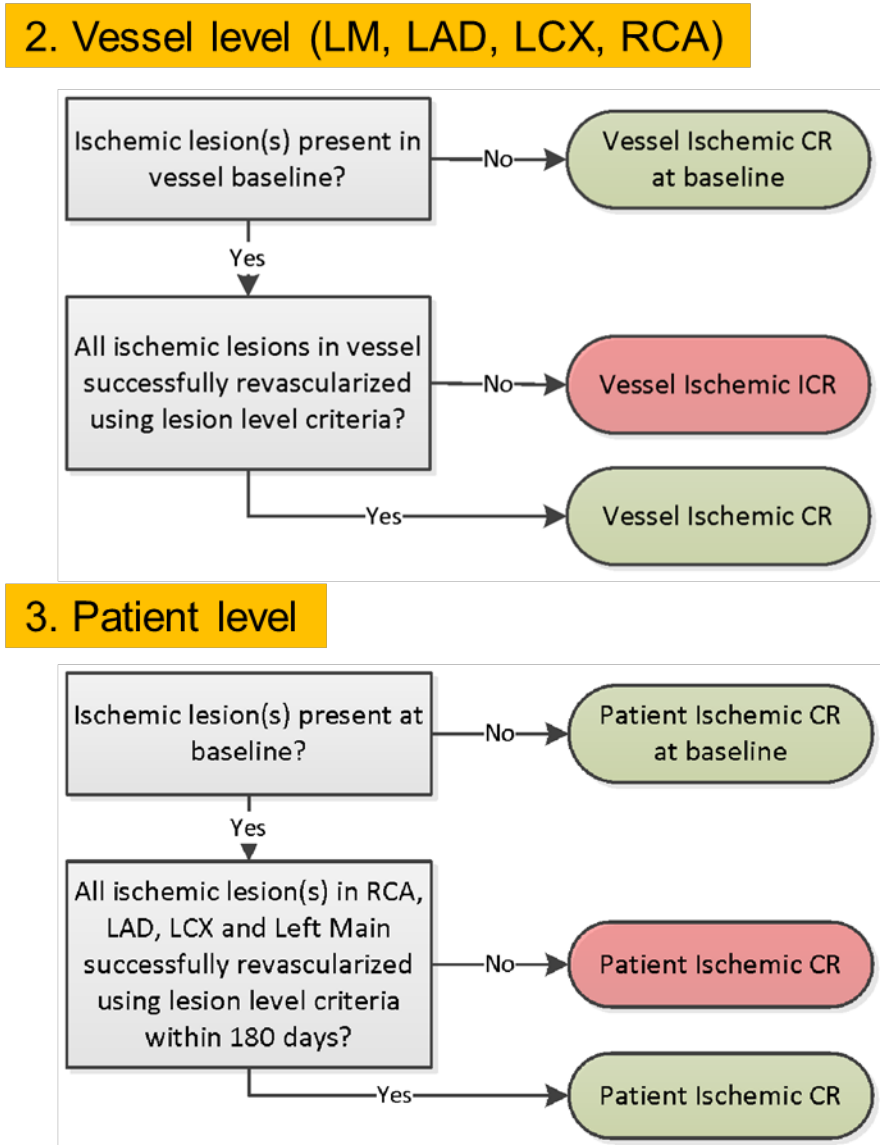


1. Lesion not considered ischemic if patent graft supplying antegrade or retrograde vascularization to territory.
2. Lesion in native vessel or in graft to vascular territory

Modified from Ali Z et al. J Am Heart Assoc. 2021:e020110. doi: 10.1161/JAHA.120.020110

Angiographic Core Laboratory* Assessment of Ischemic/Functional Completeness of Revascularization After PCI and CABG





*Cardiovascular Research Foundation, NY

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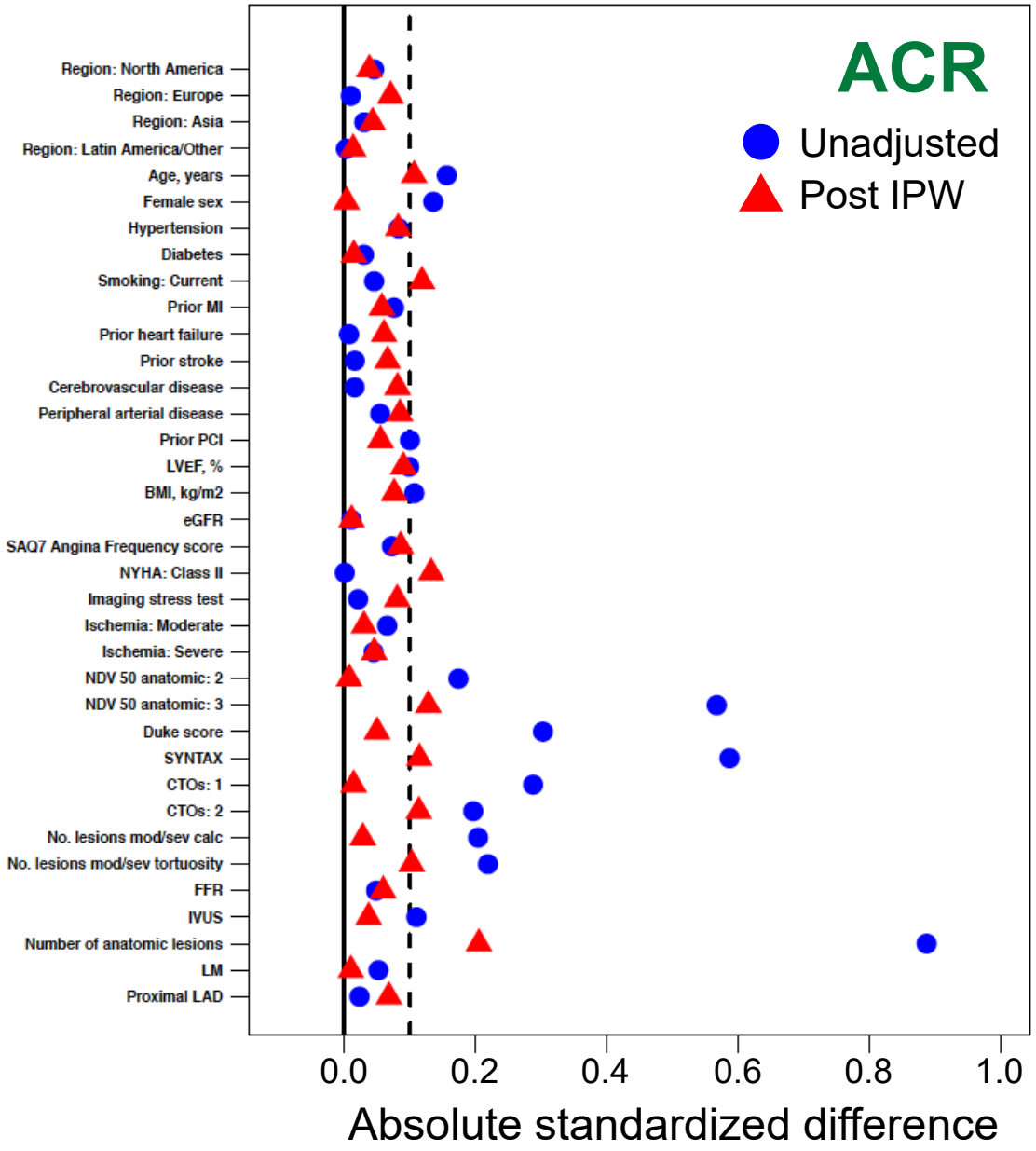
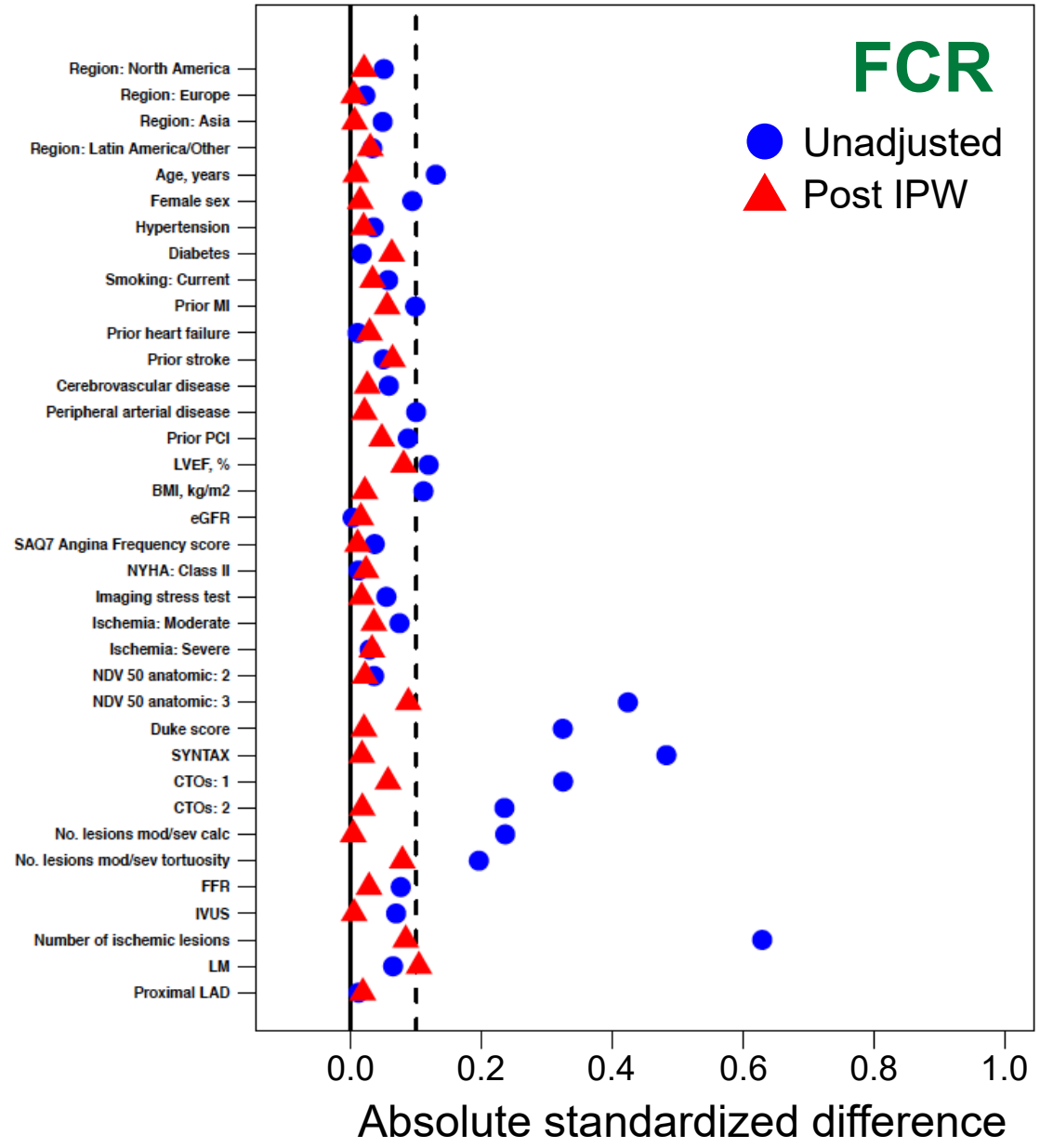
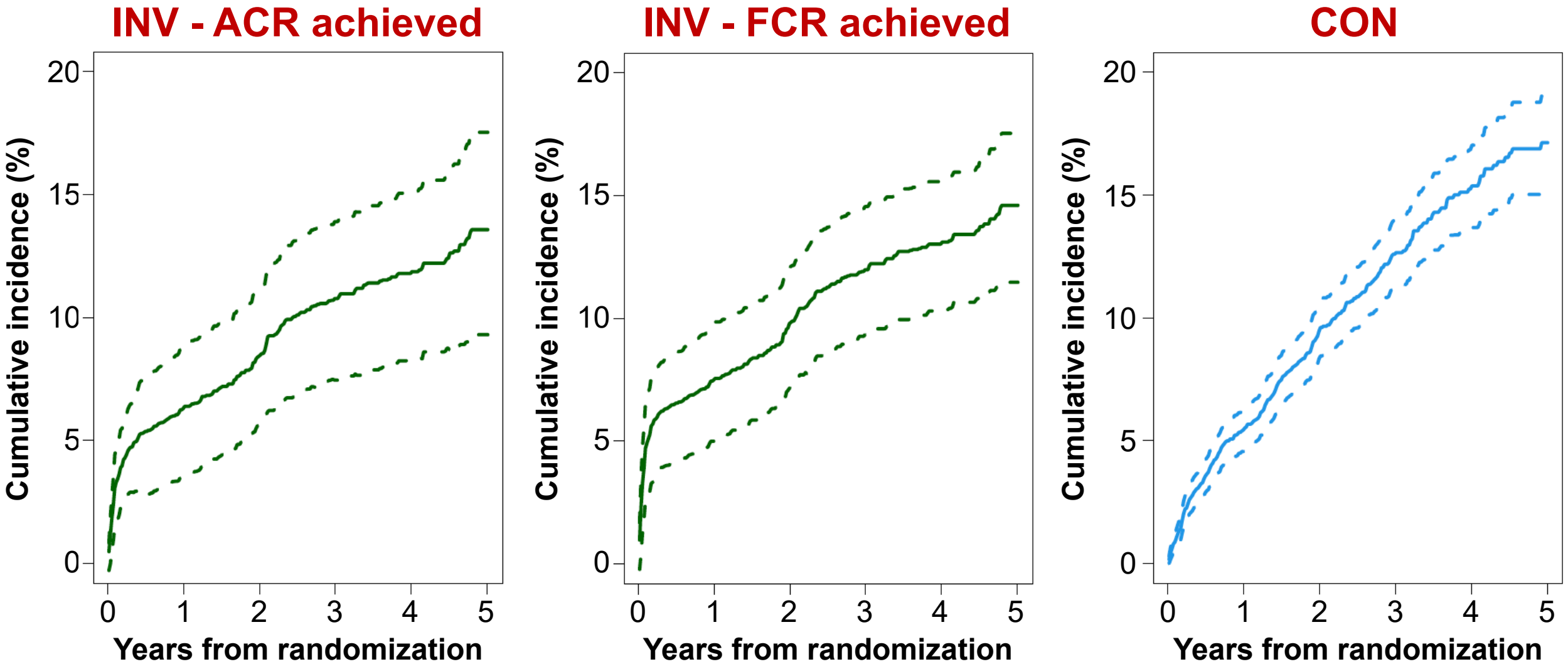
Covariate Balance Before and After Inverse Probability Weighting (INV)





Outcomes for INV-CR versus CON: Primary endpoint

INV IPW-adjusted, marginal structural model using natural splines



Summary and Conclusions

- In the ISCHEMIA trial, among pts assigned to an INV strategy in whom revascularization was performed, anatomic and functional CR were achieved in 43.3% and 58.3% of pts respectively; CR rates were similar in the entire INV population by ITT (43.6% and 58.5% respectively)
- CR was associated with improved 4-year clinical outcomes compared with ICR, although the differences were attenuated after adjustment for baseline covariates
  - ACR was more strongly associated with improved outcomes than was FCR
- After IPW, the 4-year difference in the primary endpoint was 3.5% lower among INV pts achieving ACR compared with pts treated with a CON approach
  - In contrast, this difference was 2.5% at 4 years among all randomized ISCHEMIA pts*
  - The improved outcomes in pts achieving ACR was driven by lower rates of CV death and MI; all-cause mortality remained similar between the INV and CON groups even if CR was achieved

*excluding pts with prior CABG

ISCHEMIA