

#AHA22



ISCHEMIA-EXTEND

ISCHEMIA Extended

Follow-Up Interim Report

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**American
Heart
Association.**

Disclosure Page

Judith S. Hochman is PI for ISCHEMIA-EXTEND

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BACKGROUND

Primary Goals of Treatment in Chronic Coronary Disease (CCD)

- To Improve Survival
- To Improve Quality of Life (QOL)

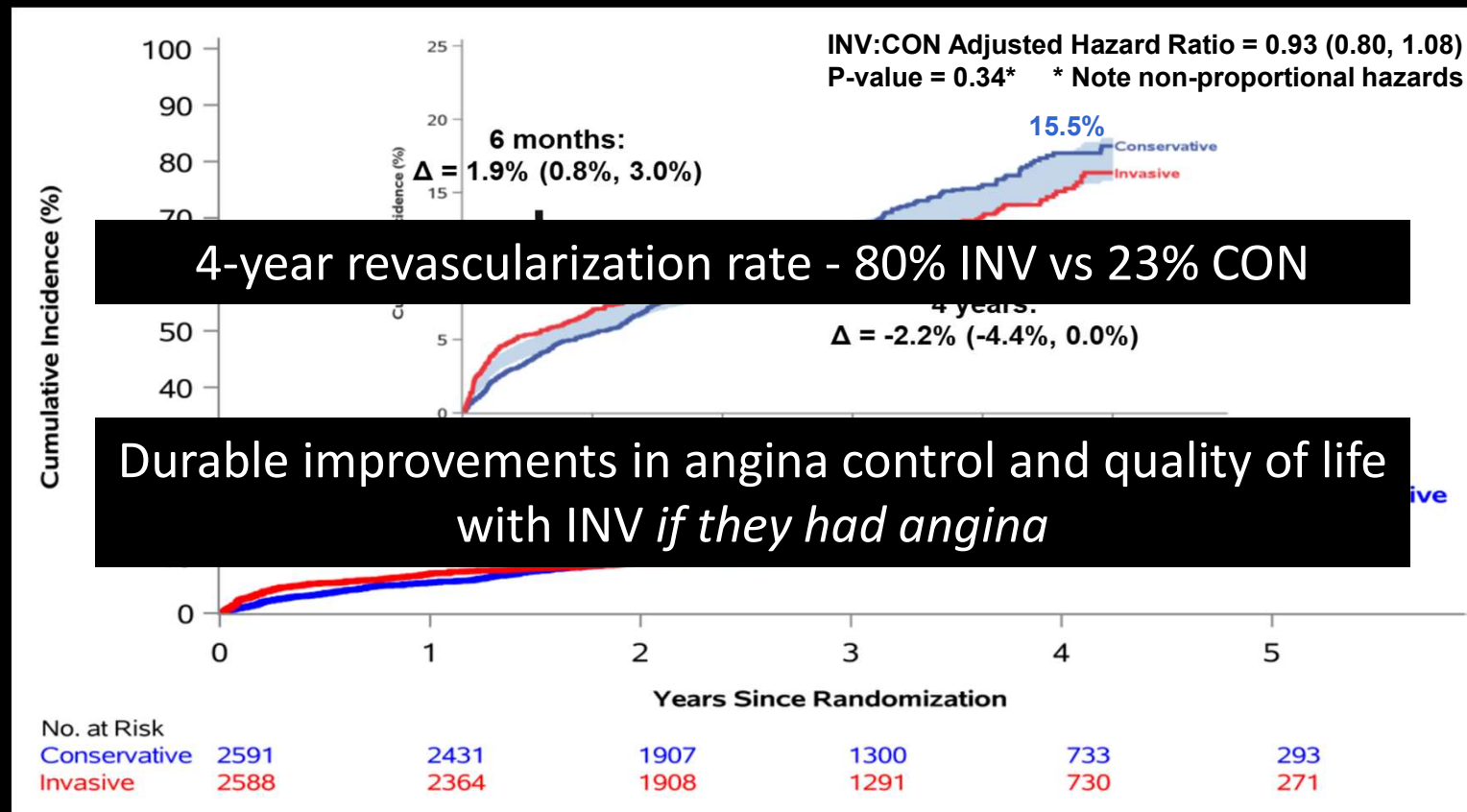
The ISCHEMIA trial tested an initial invasive vs conservative strategy for CCD pts with moderate or severe ischemia

- primary outcome: major adverse clinical events (5 components)
- secondary outcome: angina-related quality of life

Extended follow-up is comparing survival between the two strategies

Original Follow-Up, 3.2 Years (median)

Similar mean event-free time for primary outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

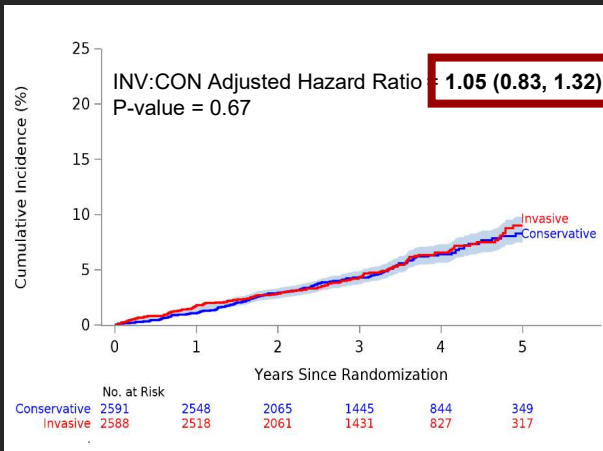


Maron, Hochman, Reynolds et al. N Engl J Med 2020

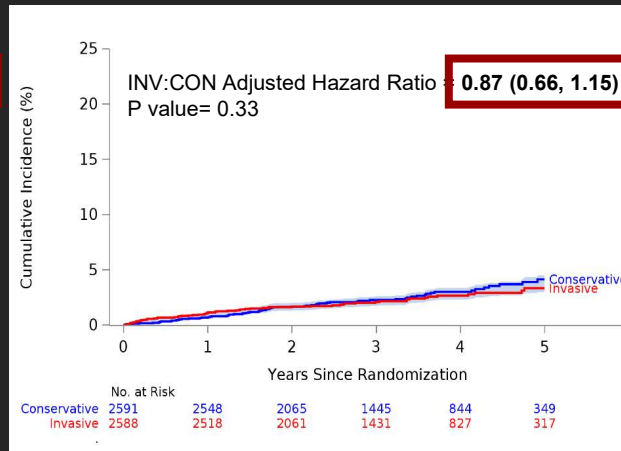
Original Follow-Up, 3.2 Years (median)



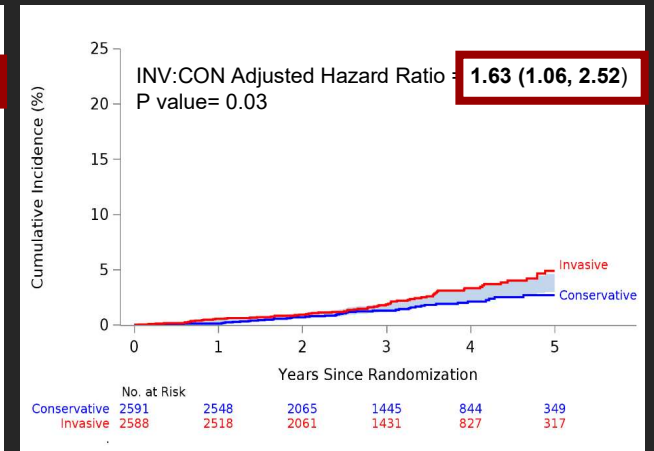
All-Cause Death



Cardiovascular Death



Non-Cardiovascular Death*



*Predominantly excess malignancy

Shading indicates the half width of the confidence interval for the difference. Overlap of the lines and shading indicates that the 95% CI for the difference includes zero.

OBJECTIVE

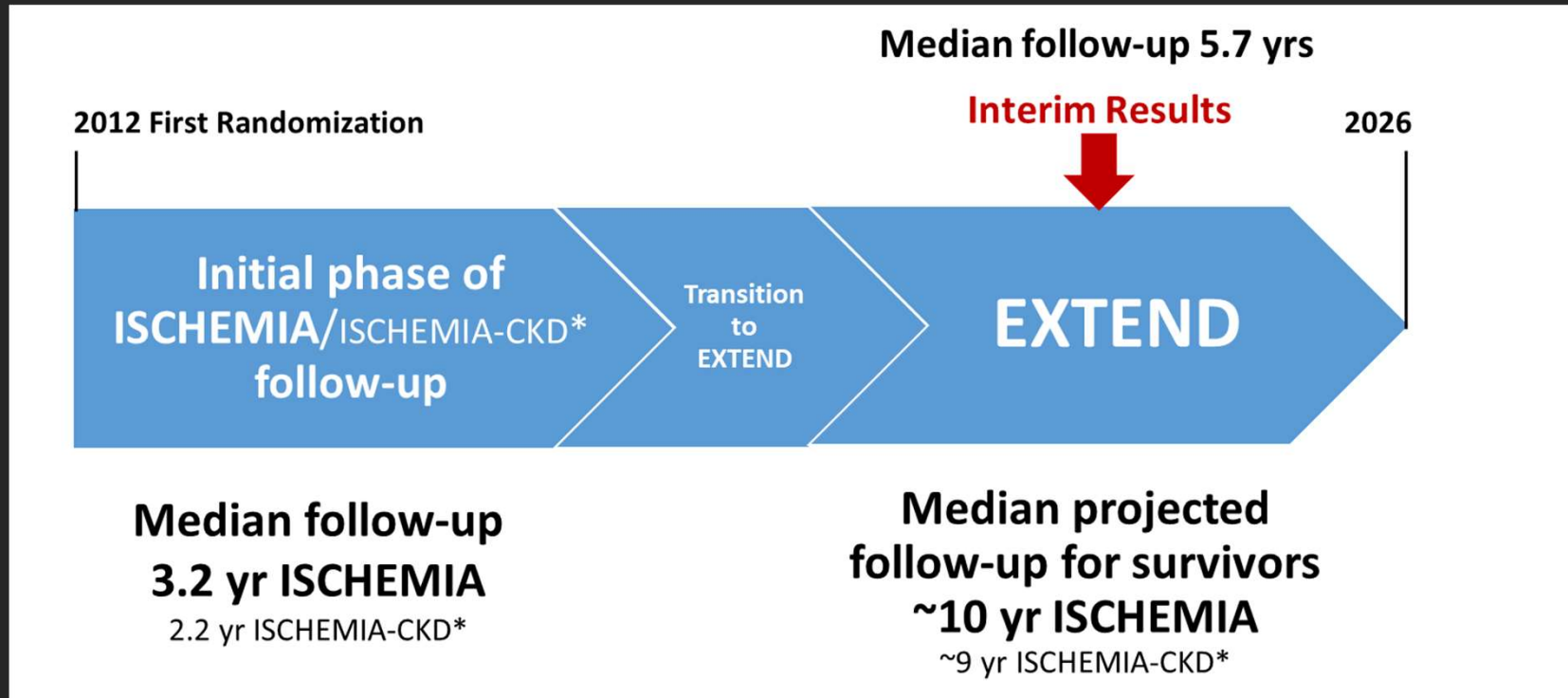
The overarching objective of long-term follow-up is to assess whether there are **between-group differences** and **increase precision** around the treatment effect estimates for:

- All-cause mortality
- Cardiovascular mortality
- Non-cardiovascular mortality

METHODS



Long-term follow-up in ISCHEMIA-EXTEND



*ISCHEMIA-CKD EXTEND was reported separately at ESC 2022

METHODS



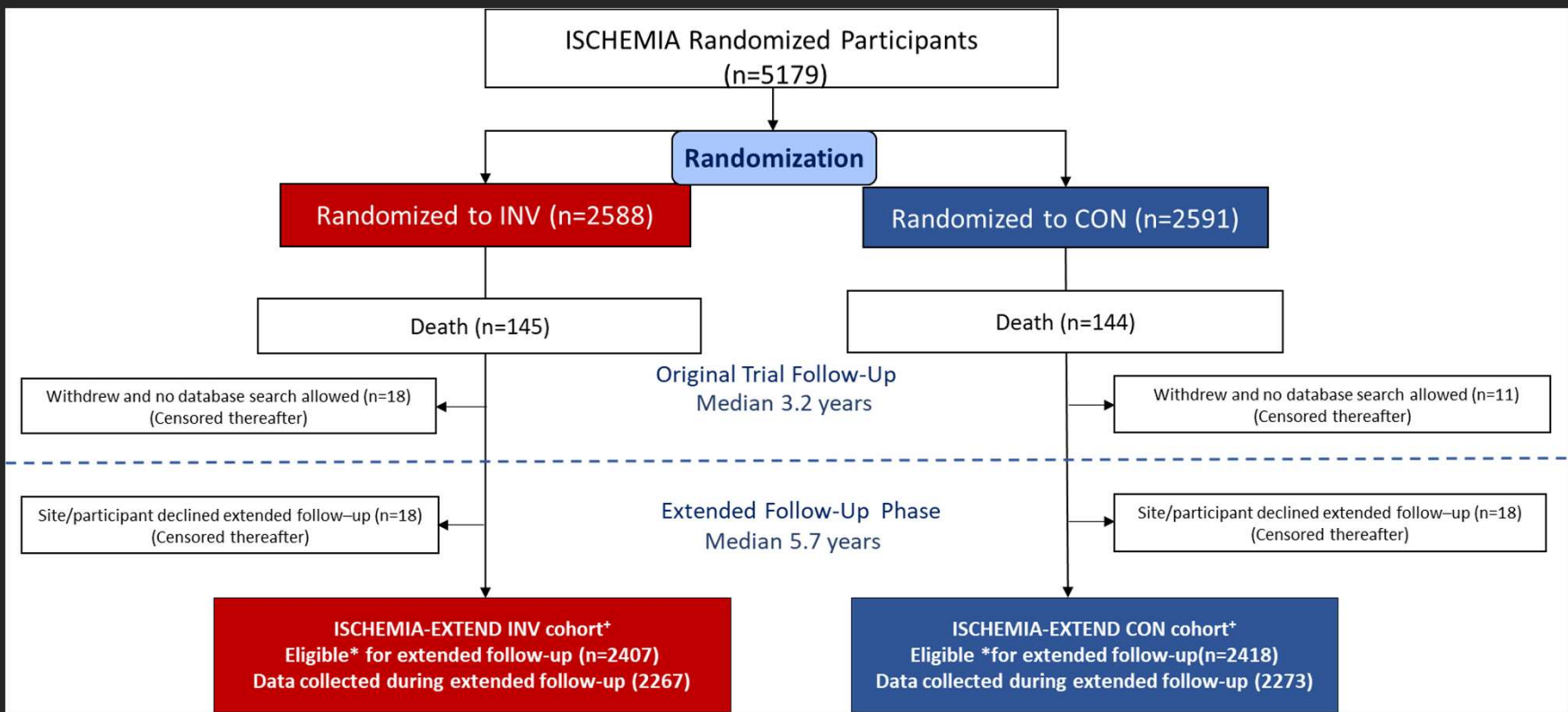
- Original trial eligibility:
 - Inclusion: moderate or severe ischemia,
 - Exclusion: ejection fraction <35%, recent acute coronary syndromes, unacceptable angina, left main \geq 50% stenosis
- Data obtained through December 2021
- Vital status ascertainment
 - 33 countries with direct participant contact by sites (67%) plus central methods
 - 3 countries with central death index search (33% of participants)
- Trial definition of CV mortality was broad and included undetermined cause of death
- During original trial phase, sensitivity of site-determined CV death was 91% and the positive predictive value was 96% based on CEC event adjudication

METHODS

Statistical Analysis

- Intent to treat analysis of 5179 pts based on original randomization
- Analysis of all-cause, cardiovascular, and non-cardiovascular mortality by randomized strategy, using nonparametric cumulative incidence estimators, cause-specific Cox regression models
- One country could not provide cause of death (N=22 deaths)
- Bayesian survival modeling to use the posterior distribution of the treatment effect
 - 100's of thousands of simulations using study data to determine post-study probabilities of between group differences in light of study data

Participant Flow for Long-Term Follow-Up in ISCHEMIA-EXTEND



+ Data on all 2588 (INV) and 2591 (CON) are included with varying lengths of follow-up

*Eligible= survived the original trial phase, did not withdraw consent, and did not decline long-term follow-up

Baseline Data

	Original ISCHEMIA Trial Cohort	Surviving, not withdrawn (eligible); in Extended Follow-Up Cohort*	Withdrew during Trial Phase/Declined Extended Follow-Up
	(N=5179)	(N=4825)	(N=65)
Treatment			
INV	50%	50%	55%
CON	50%	50%	45%
Sex, Male	77%	78%	78%
Age, years Median (Q1, Q3)	64 (58, 70)	64 (57, 70)	67 (61, 72)
Race			
White	66%	66%	54%
Black	4%	4%	7%
Asian	29%	29%	43%
Other or multiple race groups	1%	1%	2%
Ethnicity (Hispanic or Latino)	16%	16%	5%
Hypertension	73%	73%	69%
Diabetes	42%	41%	43%
Prior MI	19%	19%	23%
EF Median (Q1, Q3)	60 (55, 65)	60 (56, 65)	62 (58, 65)
History of angina	90%	90%	88%

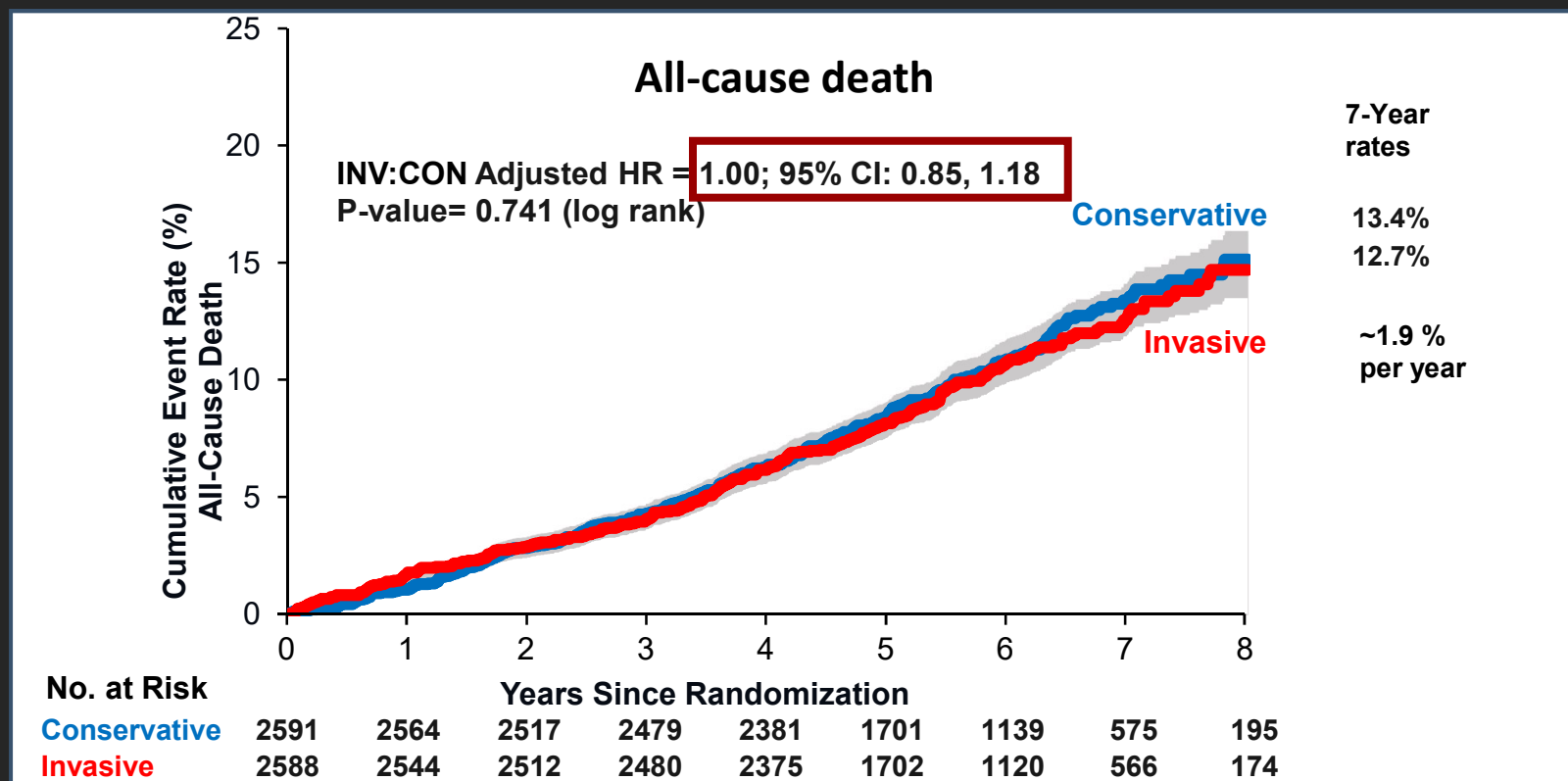
RESULTS



Time Point	Deaths
After 3.2 years median follow-up	289
Additional deaths during extended follow-up at 5.7 years median	268
Total deaths at 5.7 years median follow-up	557

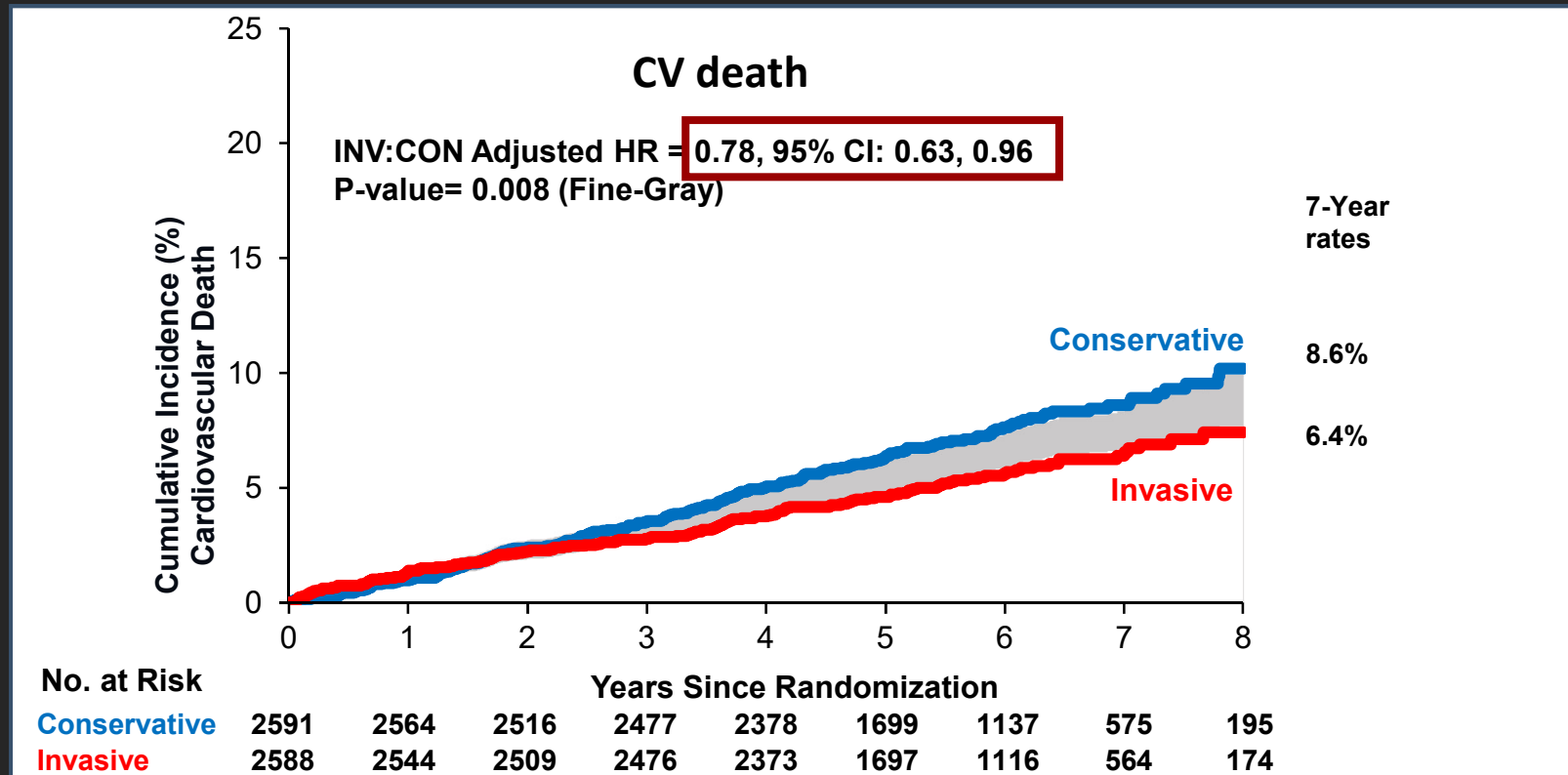
Extended follow-up – 5.7 years median

Cumulative event rate of all-cause death



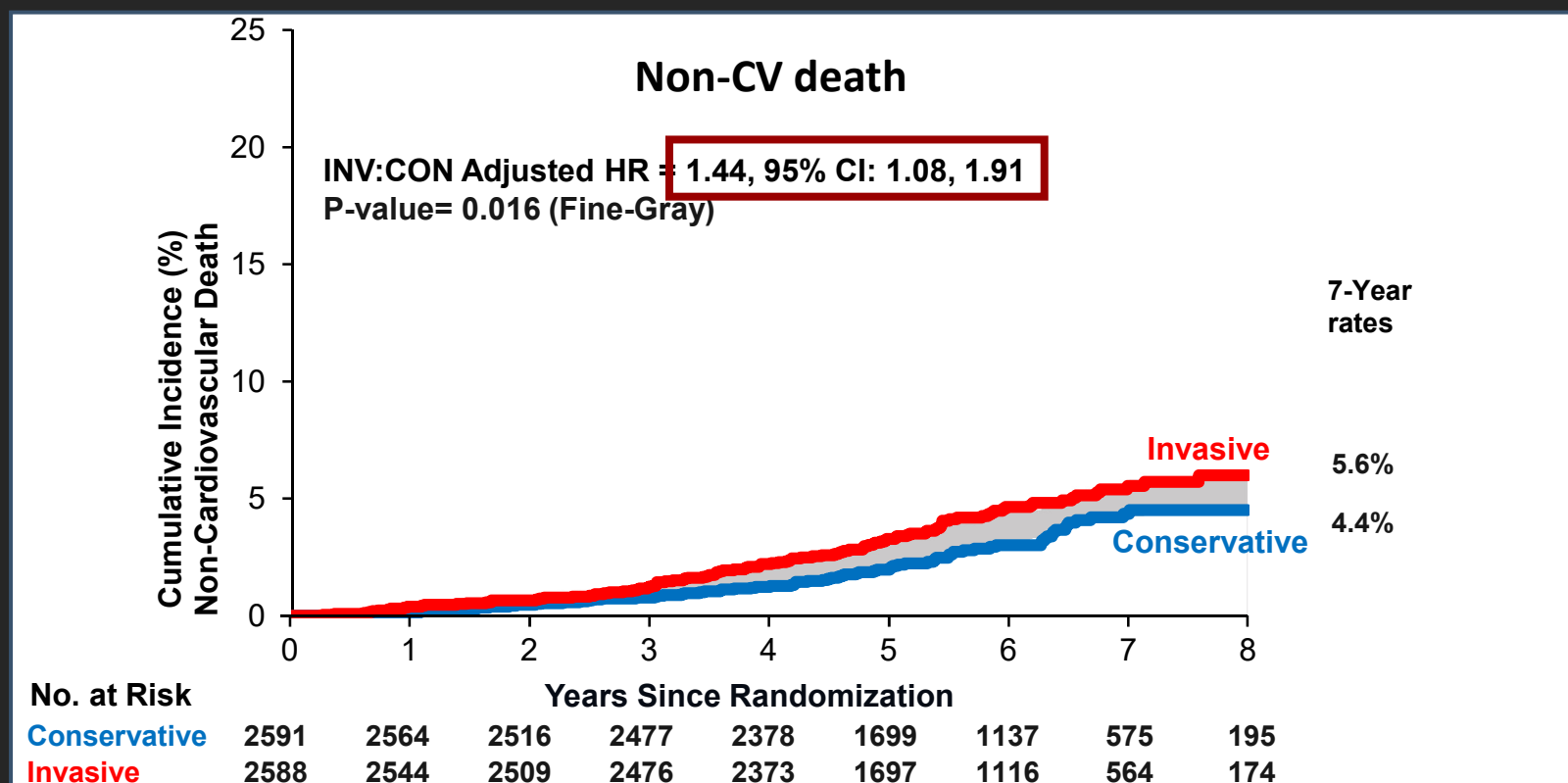
Extended follow-up – 5.7 years median

Cumulative incidence of cardiovascular death



Extended follow-up – 5.7 years median

Cumulative incidence of non-cardiovascular death



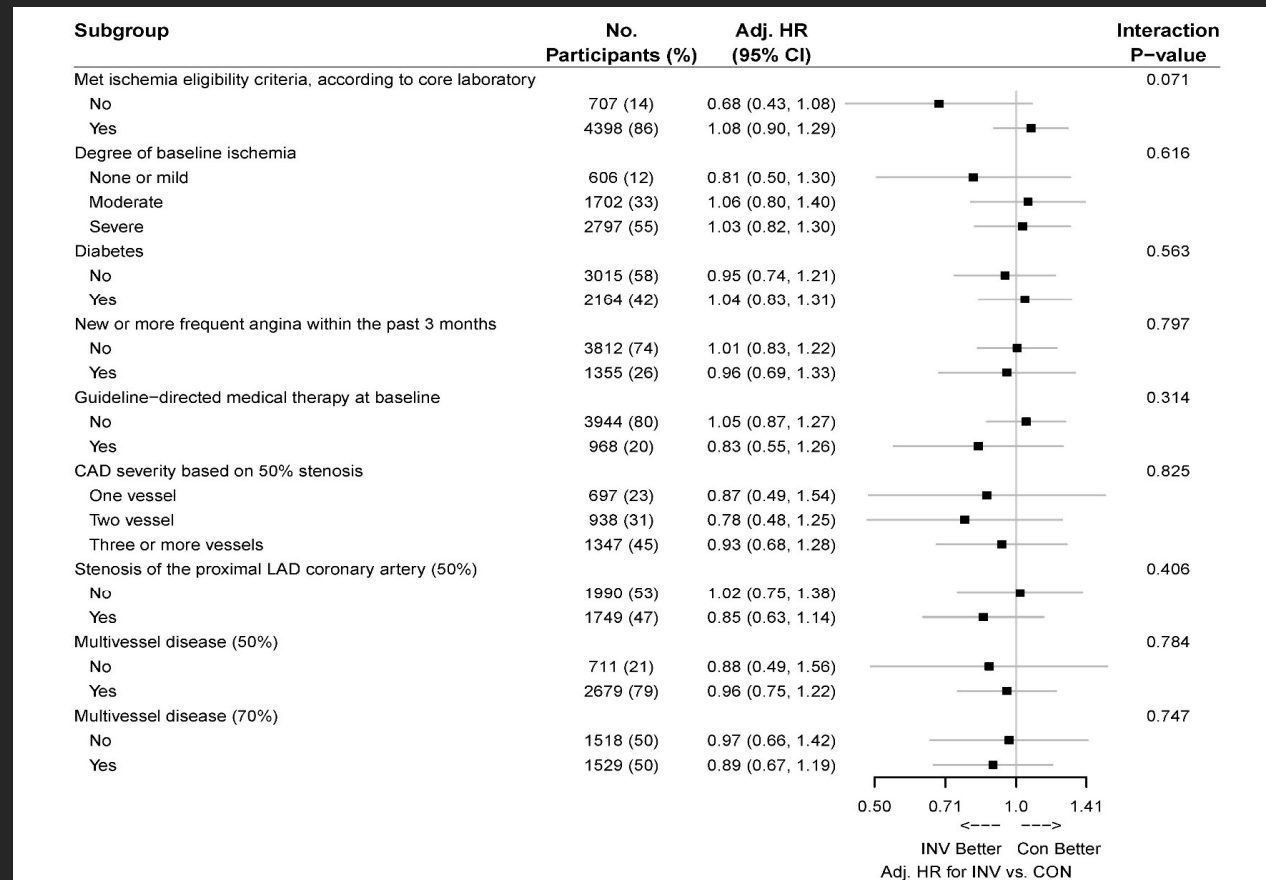
Subgroup Analyses

All-Cause Death



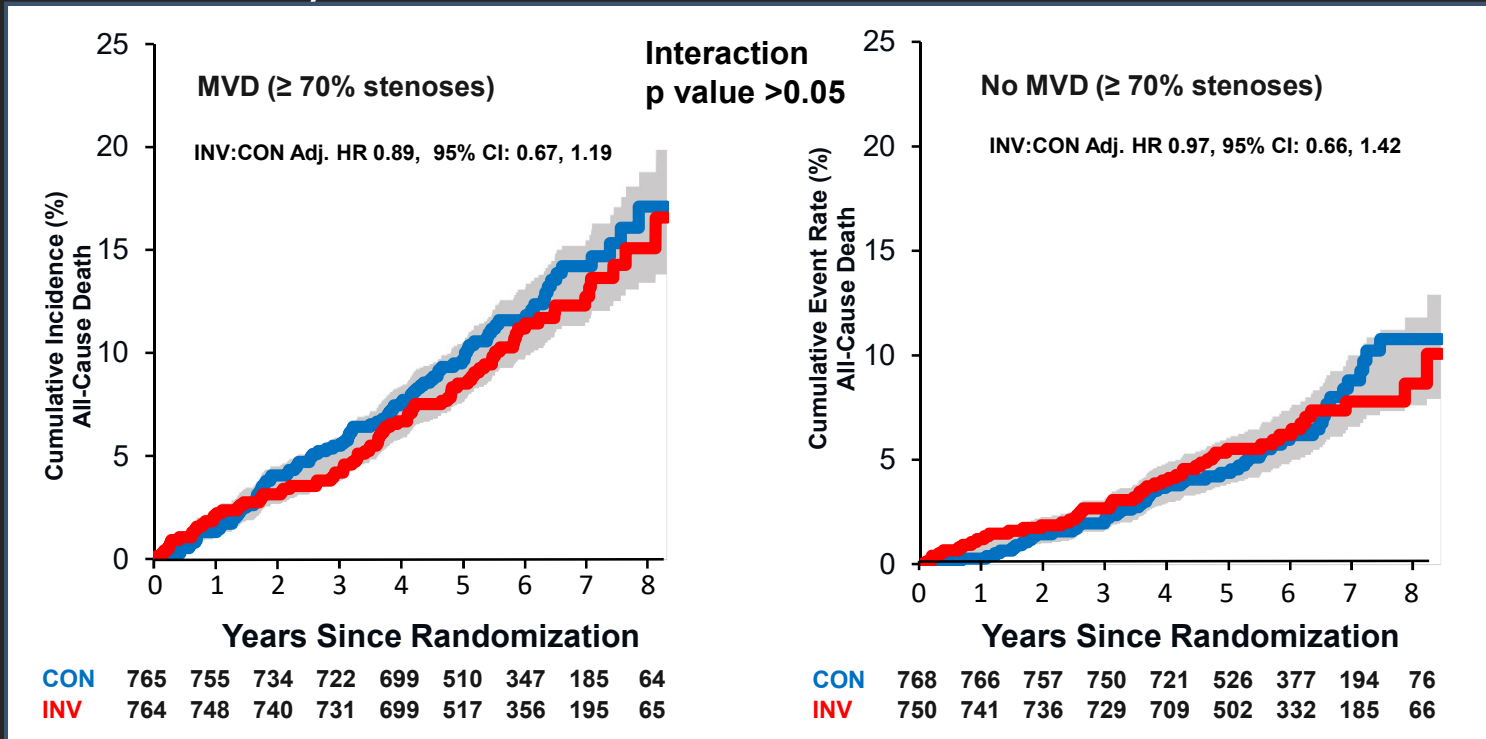
No interaction between initial strategy assignment and pre-specified subgroups for:

- All-cause death
- CV death
- Non-CV death



Extended follow-up – 5.7 years median – All-Cause Death

Subset with CCTA evaluable for multivessel (≥ 2 vessels) disease defined by stenoses $\geq 70\%$
CCTA subset excludes pts with low eGFR

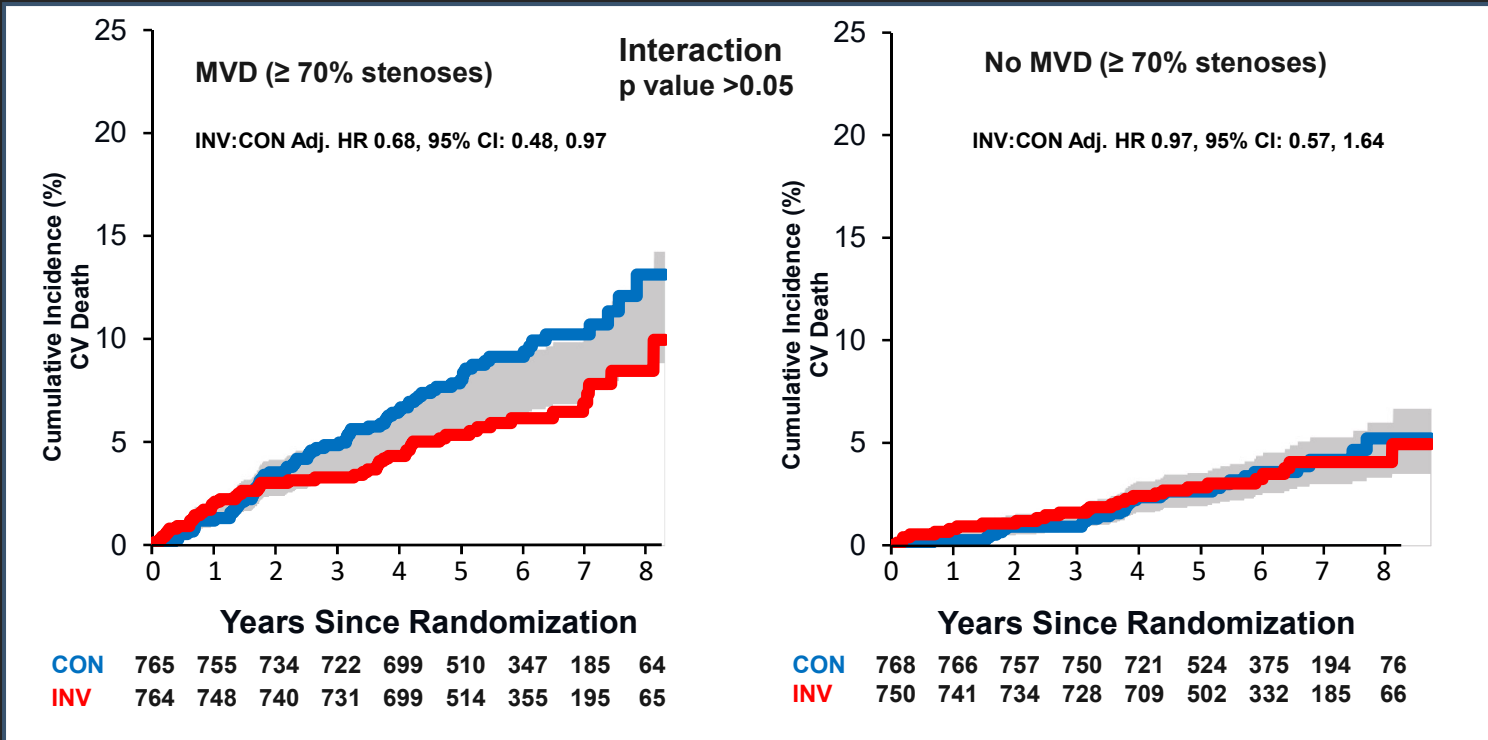


Cox models - the HR for the treatment effect did not differ by presence or absence of MVD

Extended follow-up – 5.7 years median – CV Death



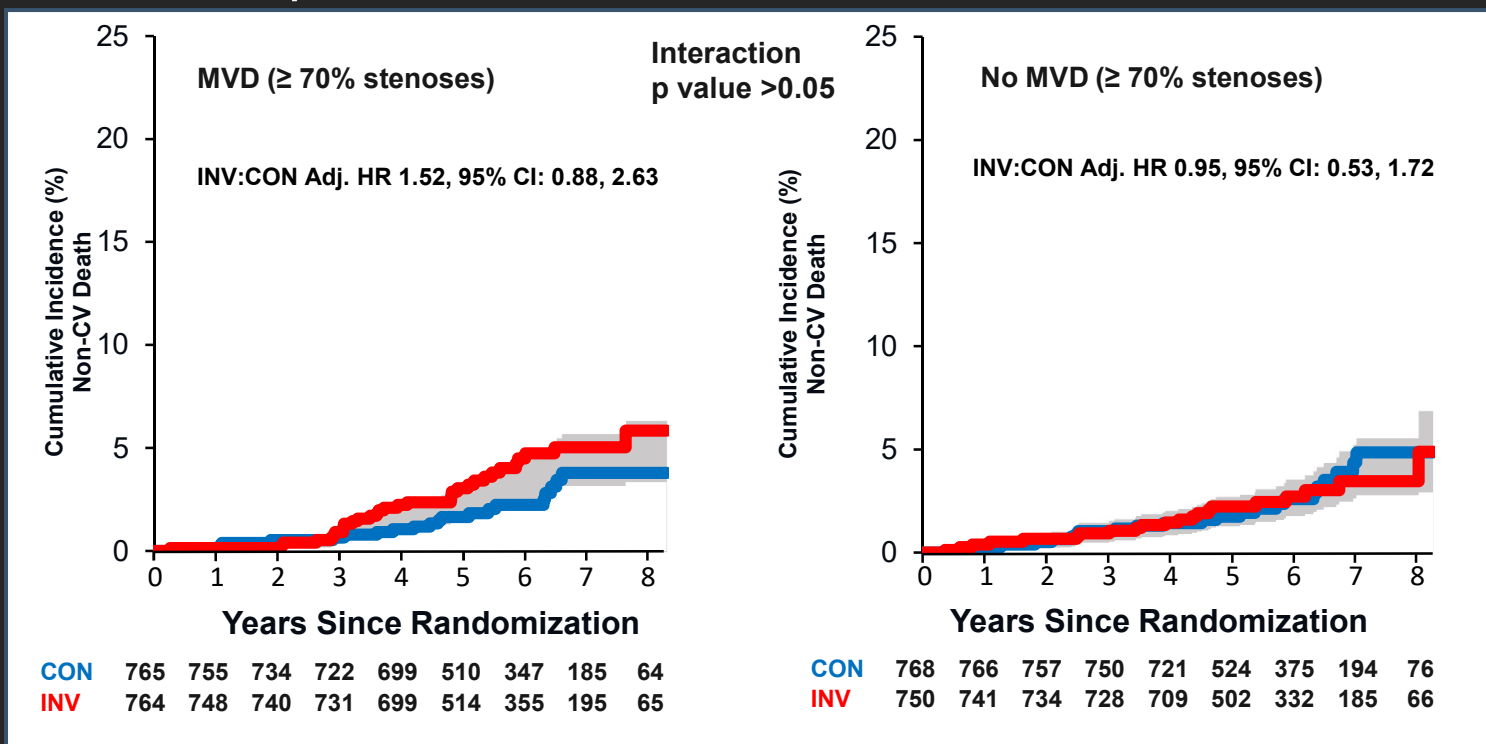
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 CCTA subset excludes pts with low eGFR



Cox models - the HR for the treatment effect did not differ by presence or absence of MVD

Extended follow-up – 5.7 years median – non-CV Death

Subset with CCTA evaluable for multivessel (≥ 2 vessels) disease defined by stenoses $\geq 70\%$
CCTA subset excludes pts with low eGFR

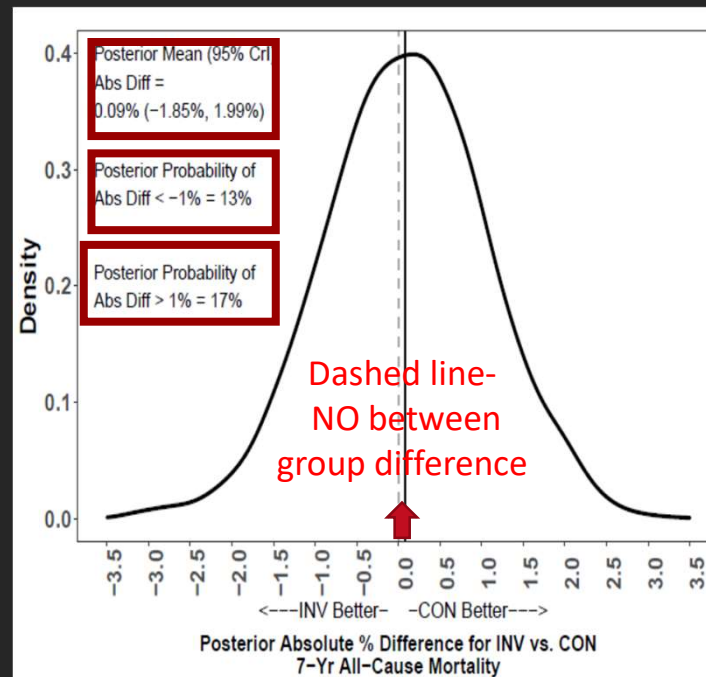


Cox models - the HR for the treatment effect did not differ by presence or absence of MVD

Probability that one strategy is better than another for 7-year all-cause death

Absolute difference in 7-year rates: INV rate - CON rate

All-Cause Death



CONTEXT AND LIMITATIONS

- ISCHEMIA-EXTEND was designed as a pragmatic long-term follow-up study of mortality, with limited data collection
- No data were collected on non-fatal events, use of medications, revascularization procedures, or quality of life after the initial median 3.2-year follow-up
- The cause of death (cardiovascular vs. non-cardiovascular) was adjudicated during the original trial phase but not during the extended phase
- The strategy did not test routine revascularization for those with angiographic findings suitable for revascularization
- We tested routine cardiac catheterization and revascularization compared with selective use of catheterization and revascularization based on clinical need, e.g., acute coronary syndrome or refractory angina

CONCLUSIONS

Extended follow-up of the ISCHEMIA randomized trial over a median 5.7 years demonstrated that an initial invasive strategy compared with an initial conservative strategy resulted in:

- No difference in all-cause mortality with nearly twice the number of deaths (557)
- Lower risk of cardiovascular mortality
- Higher risk of non-cardiovascular mortality

IMPLICATIONS

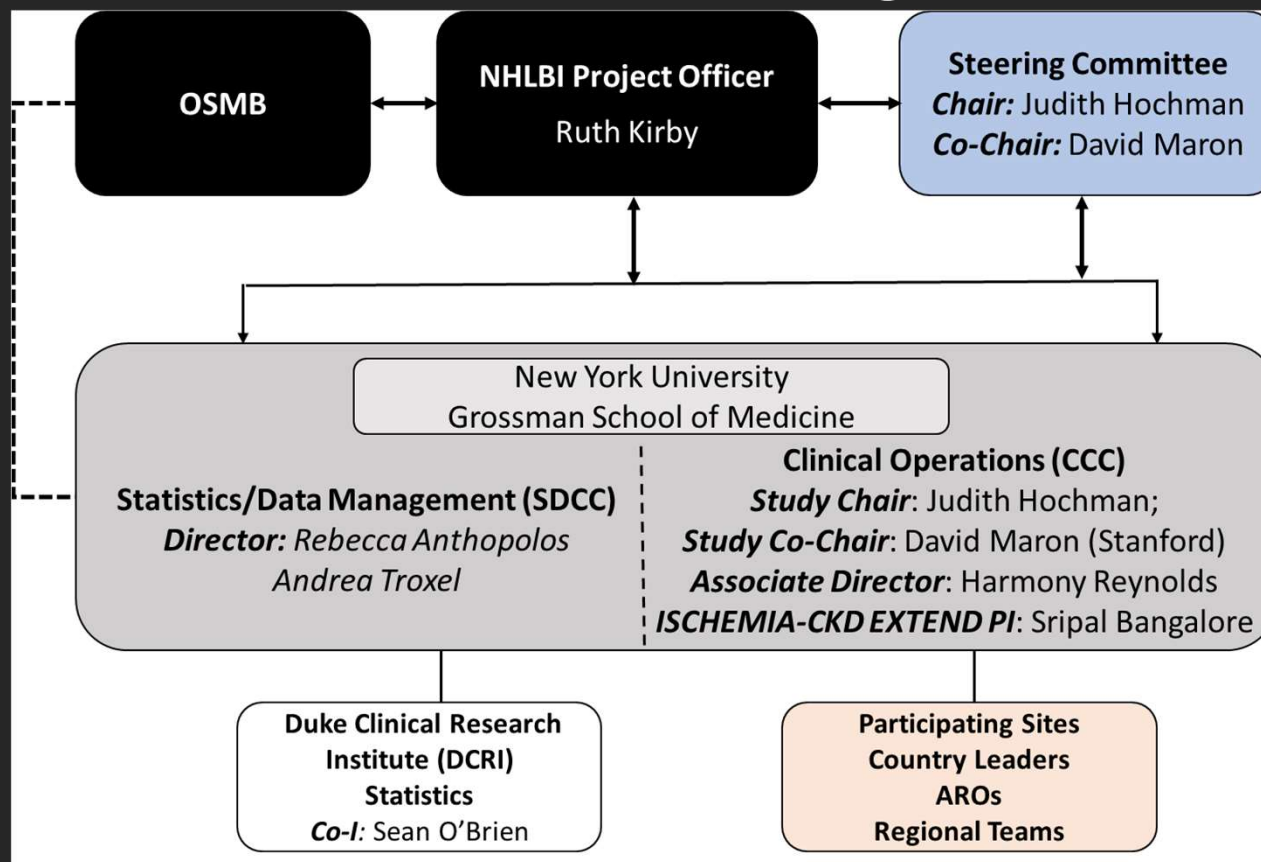
- These findings provide evidence for patients with chronic coronary disease and their physicians as they decide whether to add invasive management to guideline-directed medical therapy
- Follow-up is ongoing

Circulation

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Hochman et al. Survival After Invasive or Conservative Management of Stable Coronary Disease
CIRCULATIONAHA/2022 On line today

ISCHEMIA-EXTEND Study Organization



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