#AHA22

NYU Langone Health

ISCHEMIA–EXTEND
ISCHEMIA Extended Follow–Up Interim Report

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BACKGROUND

Primary Goals of Treatment in Chronic Coronary Disease (CCD)

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

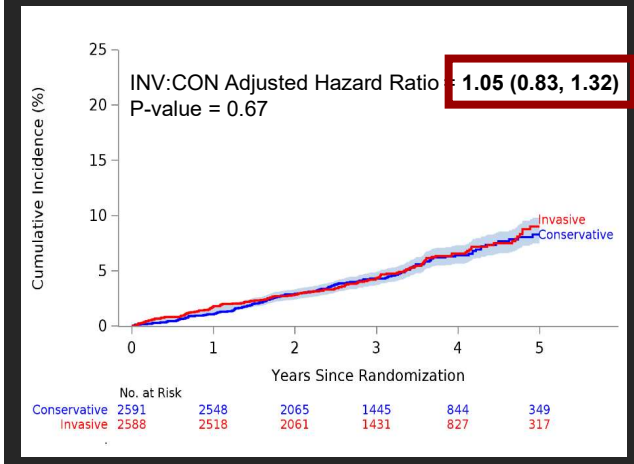
The ISCHEMIA trial tested an initial invasive vs conservative strategy for CCD pts with moderate or severe ischemia

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

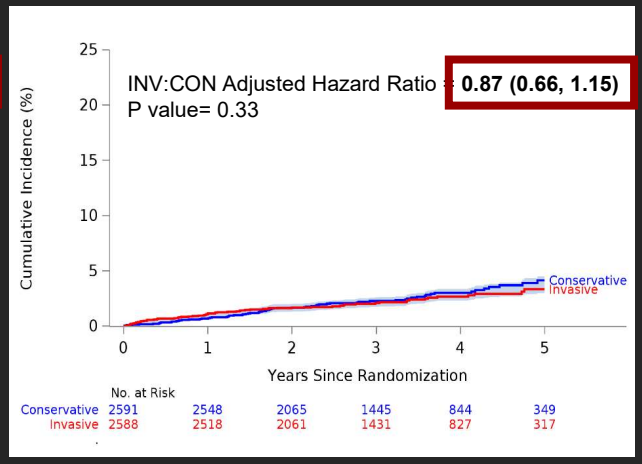
Extended follow-up is comparing survival between the two strategies

Original Follow-Up, 3.2 Years (median)

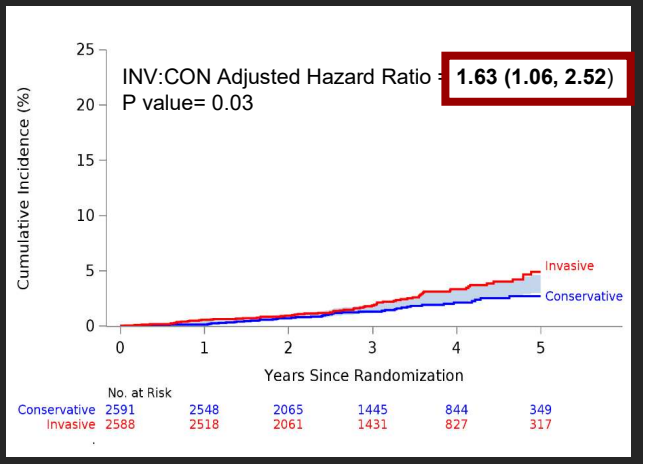
All-Cause Death



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.

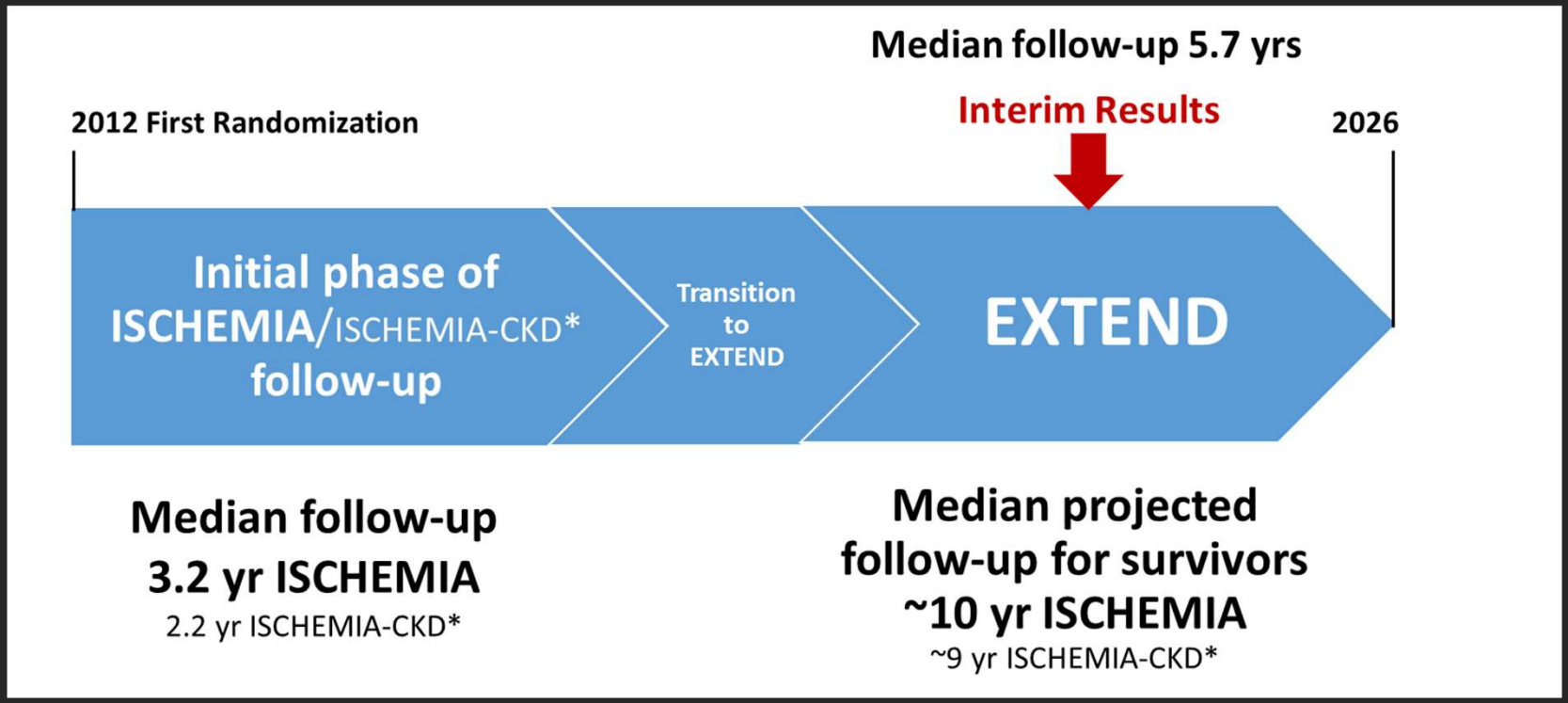
OBJECTIVE

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

Anthopolos R et al. Am Heart J 2022;254:228-233

METHODS

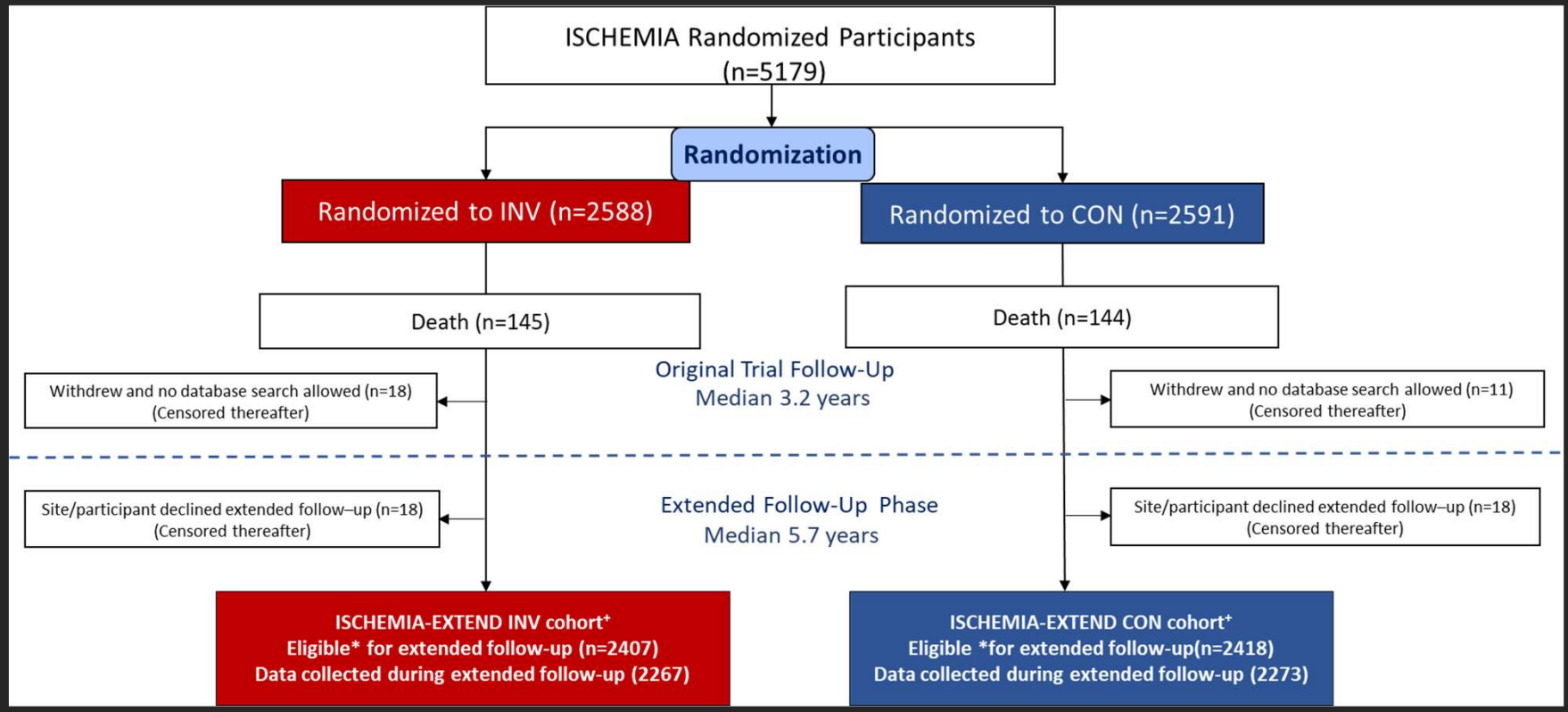
- Original trial eligibility:
  - Inclusion: moderate or severe ischemia,
  - Exclusion: ejection fraction <35%, recent acute coronary syndromes, unacceptable angina, left main ≥50% stenosis
- Data obtained through December 2021
- Vital status ascertainment
  - 33 countries with direct **participant 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

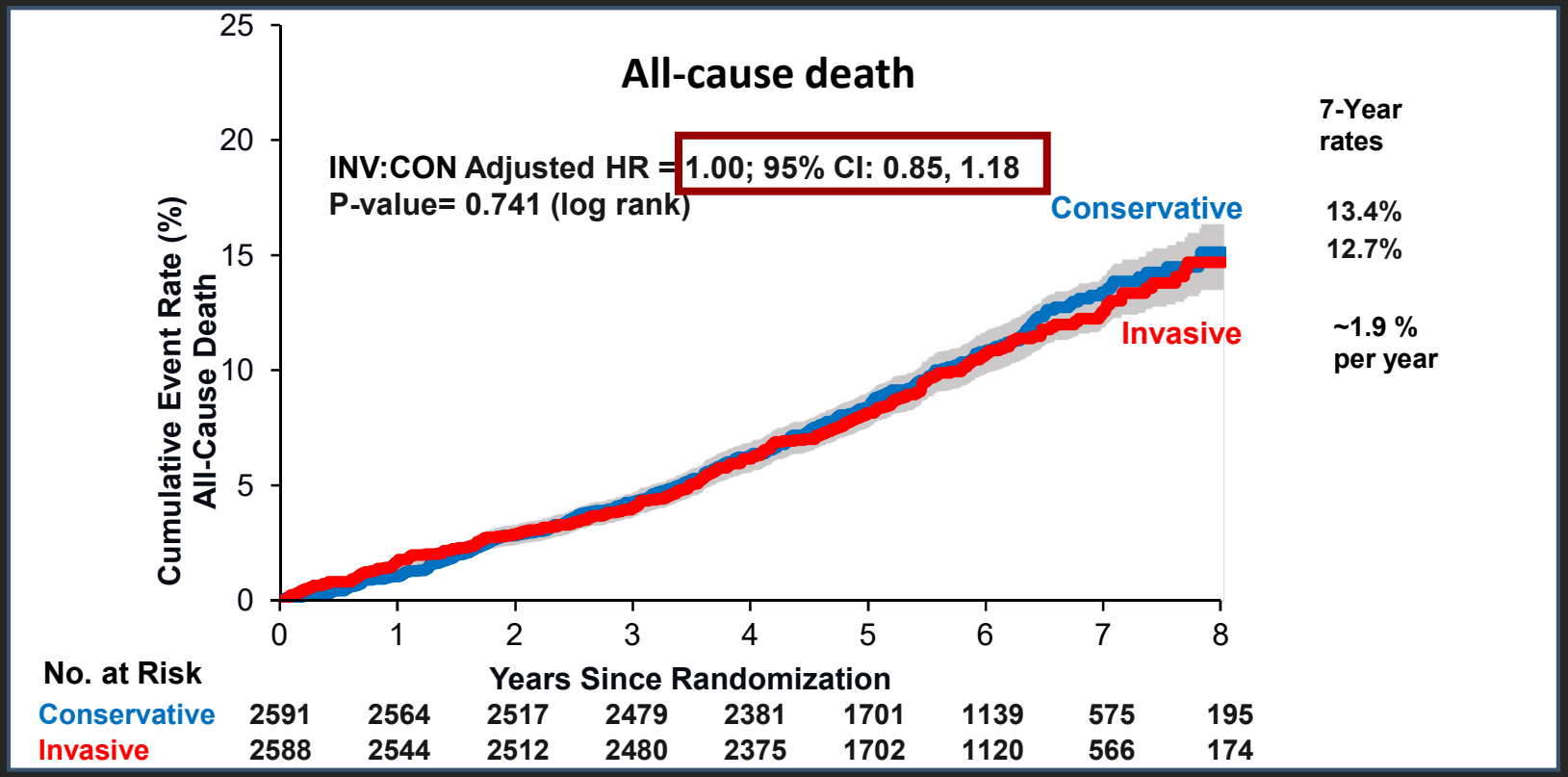
Baseline Data

	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%	2%
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%

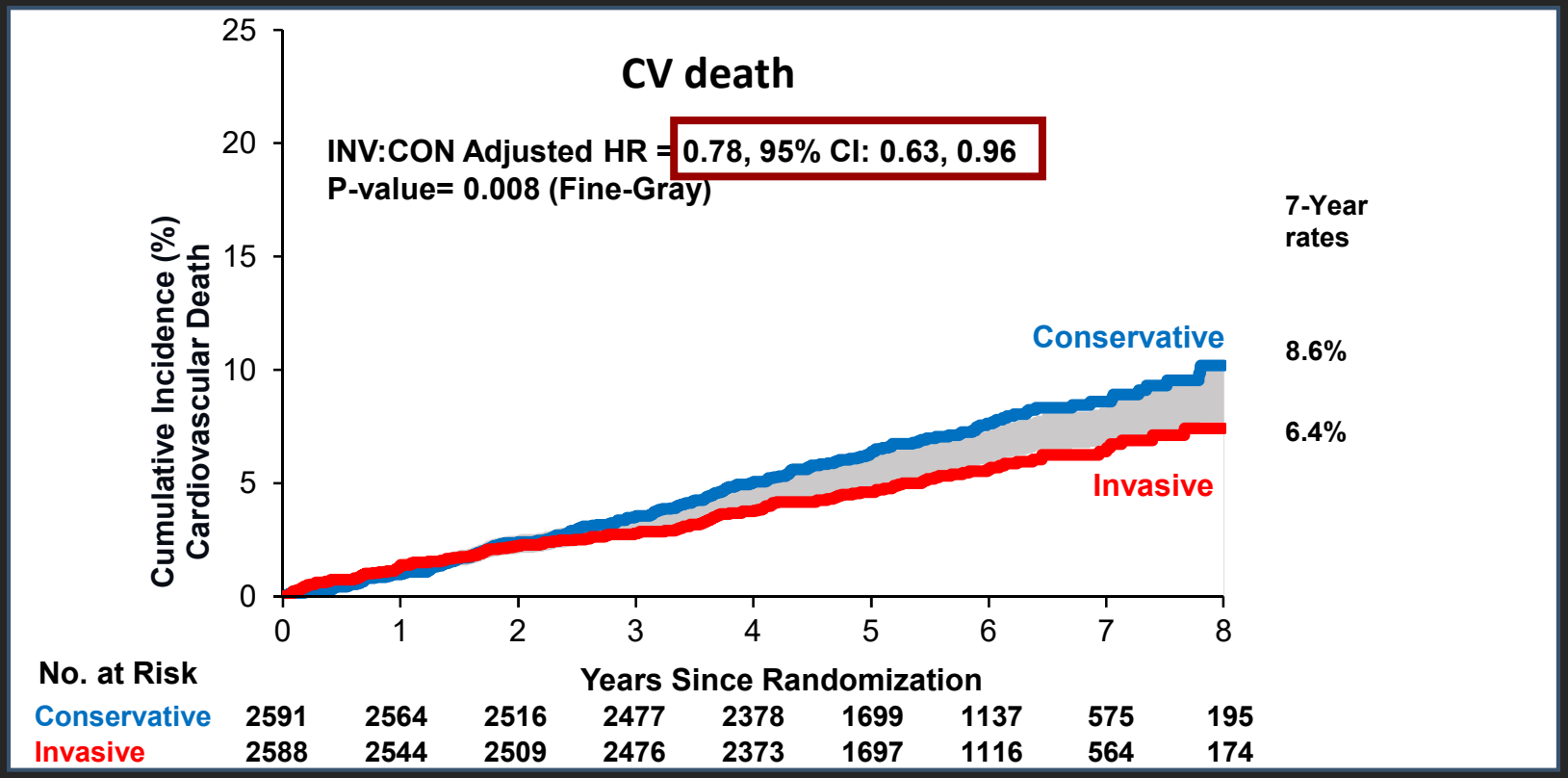
RESULTS

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

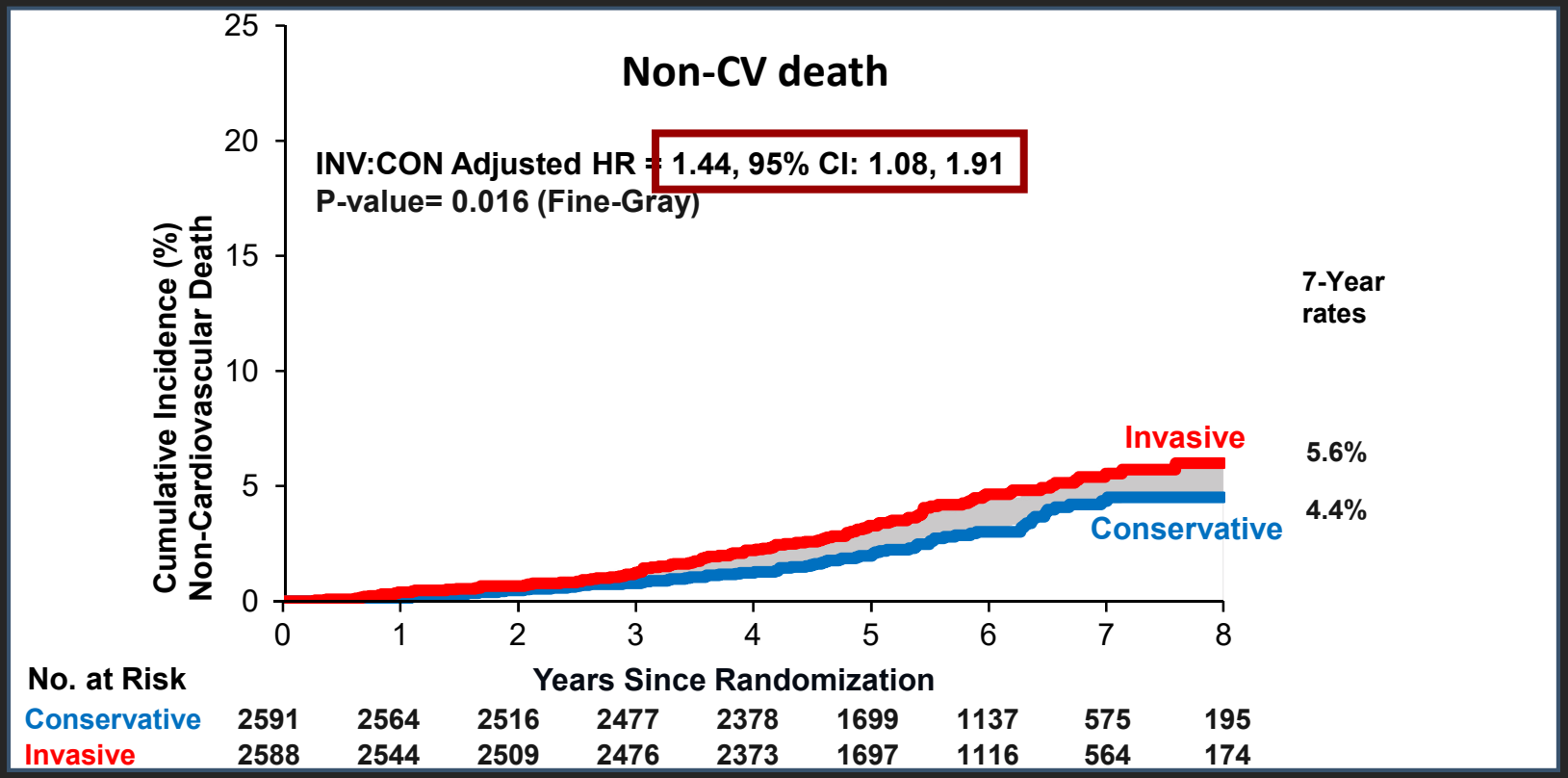


Extended follow-up – 5.7 years median
Cumulative incidence of cardiovascular death



Extended follow-up – 5.7 years median

Cumulative incidence of non-cardiovascular death



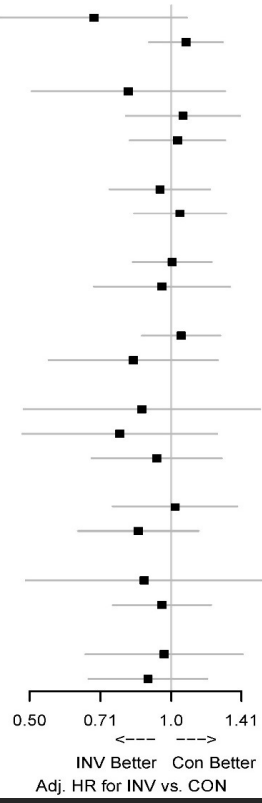
Subgroup Analyses

All-Cause Death

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

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

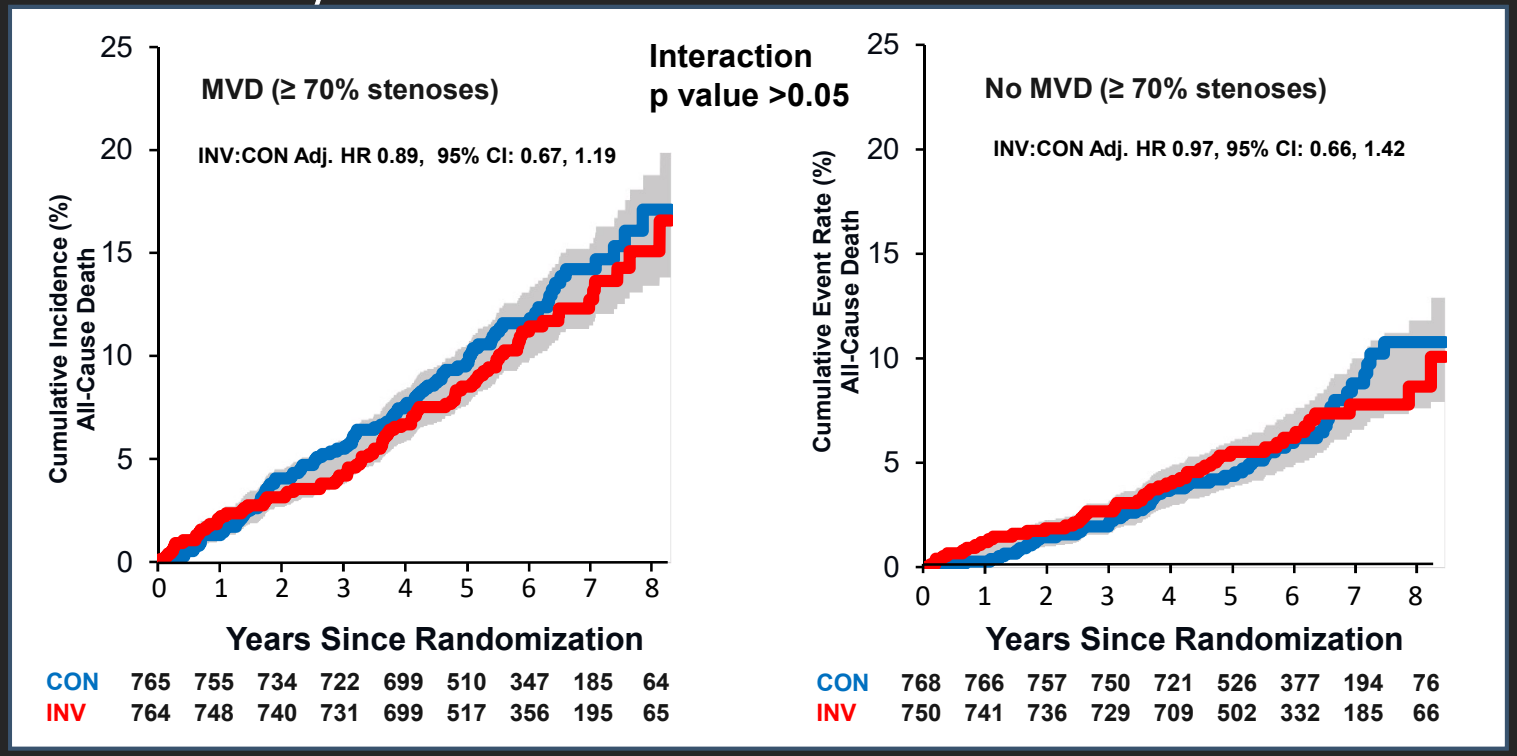
Subgroup	No. Participants (%)	Adj. HR (95% CI)	Interaction P-value
Met ischemia eligibility criteria, according to core laboratory			0.071
No	707 (14)	0.68 (0.43, 1.08)	
Yes	4398 (86)	1.08 (0.90, 1.29)	
Degree of baseline ischemia			0.616
None or mild	606 (12)	0.81 (0.50, 1.30)	
Moderate	1702 (33)	1.06 (0.80, 1.40)	
Severe	2797 (55)	1.03 (0.82, 1.30)	
Diabetes			0.563
No	3015 (58)	0.95 (0.74, 1.21)	
Yes	2164 (42)	1.04 (0.83, 1.31)	
New or more frequent angina within the past 3 months			0.797
No	3812 (74)	1.01 (0.83, 1.22)	
Yes	1355 (26)	0.96 (0.69, 1.33)	
Guideline-directed medical therapy at baseline			0.314
No	3944 (80)	1.05 (0.87, 1.27)	
Yes	968 (20)	0.83 (0.55, 1.26)	
CAD severity based on 50% stenosis			0.825
One vessel	697 (23)	0.87 (0.49, 1.54)	
Two vessel	938 (31)	0.78 (0.48, 1.25)	
Three or more vessels	1347 (45)	0.93 (0.68, 1.28)	
Stenosis of the proximal LAD coronary artery (50%)			0.406
No	1990 (53)	1.02 (0.75, 1.38)	
Yes	1749 (47)	0.85 (0.63, 1.14)	
Multivessel disease (50%)			0.784
No	711 (21)	0.88 (0.49, 1.56)	
Yes	2679 (79)	0.96 (0.75, 1.22)	
Multivessel disease (70%)			0.747
No	1518 (50)	0.97 (0.66, 1.42)	
Yes	1529 (50)	0.89 (0.67, 1.19)	



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

Subset with CCTA evaluable for multivessel (≥2 vessels) disease defined by stenoses ≥70%

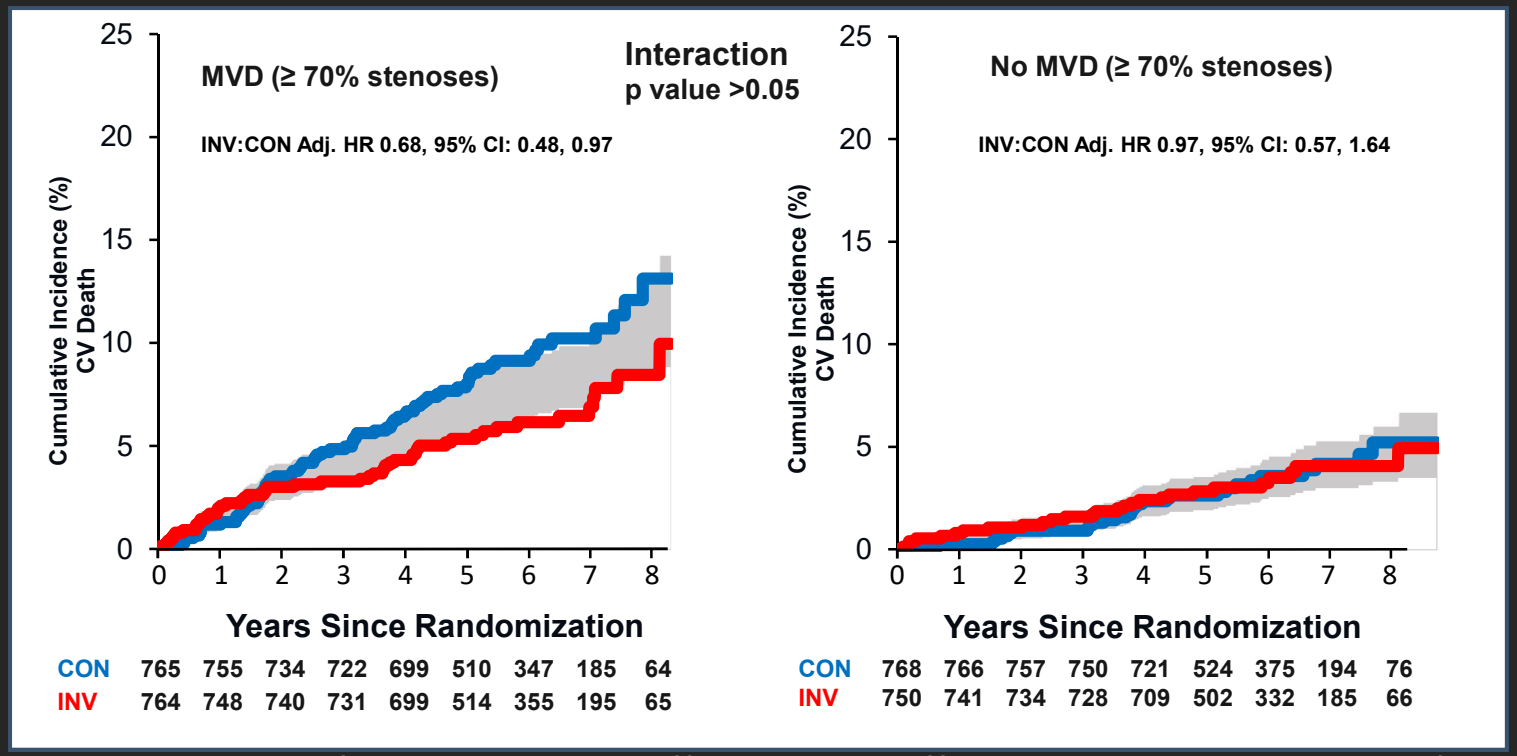
CCTA subset excludes pts with low eGFR



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

Subset with CCTA evaluable for multivessel disease defined by stenoses ≥70%
CCTA subset excludes pts with low eGFR

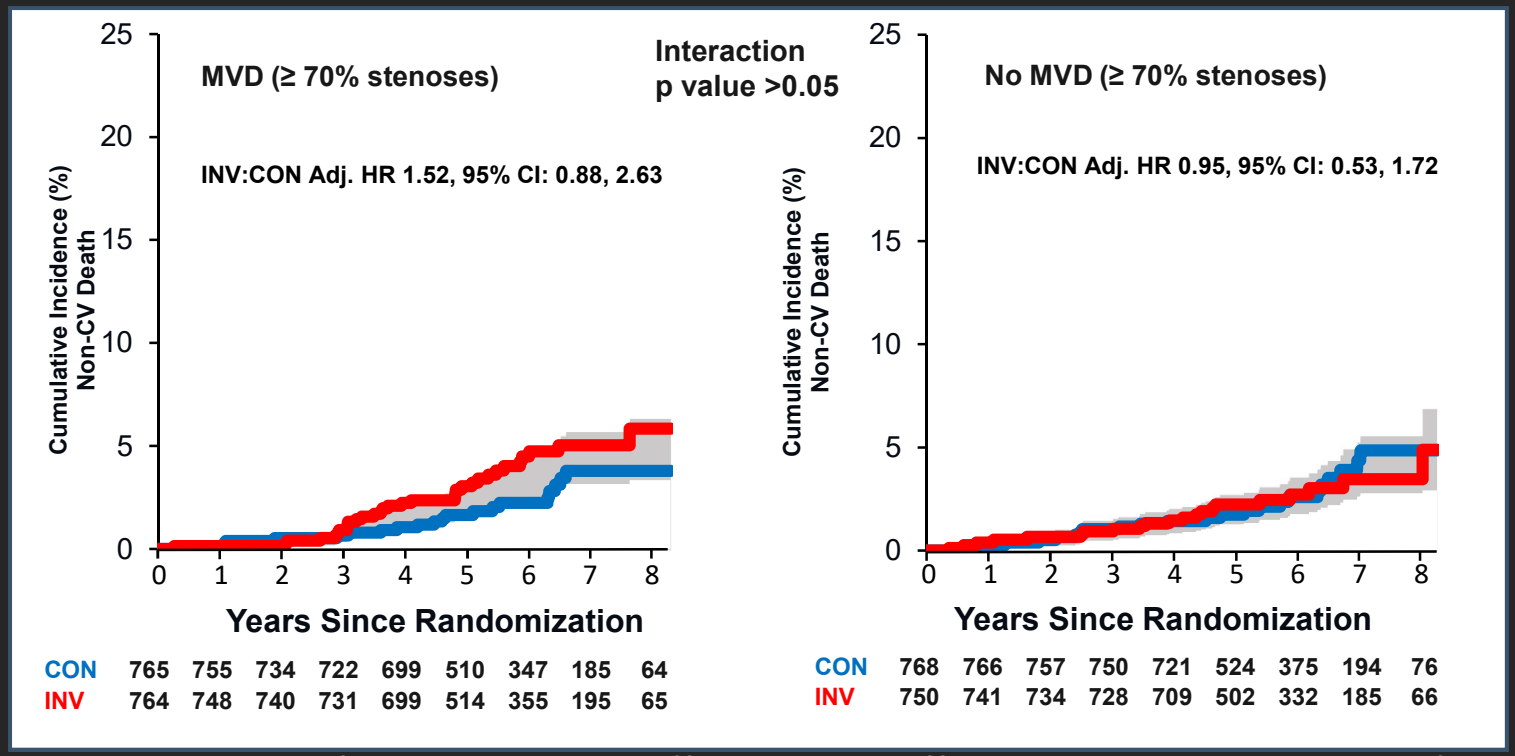


Cox models - the HR for the treatment effect did not differ by presence or absence of MVD

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

Subset with CCTA evaluable for multivessel (≥2 vessels) disease defined by stenoses ≥70%

CCTA subset excludes pts with low eGFR

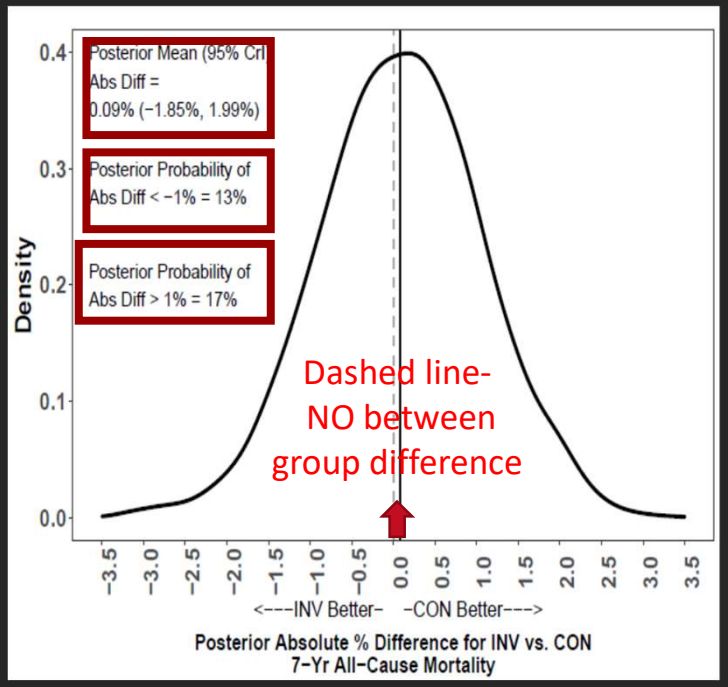


Cox models - the HR for the treatment effect did not differ by presence or absence of MVD

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

Absolute difference in 7- years 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