



HOT TOPICS IN CARDIOLOGIA 2023

13 e 14 Novembre 2023

Villa Doria D'Angri - Via F. Petrarca 80,
Napoli

Cardiopatia Ischemica Cronica: Terapia medica vs Angioplastica alla luce dello studio ISCHEMIA

Dr. Gaetano Quaranta

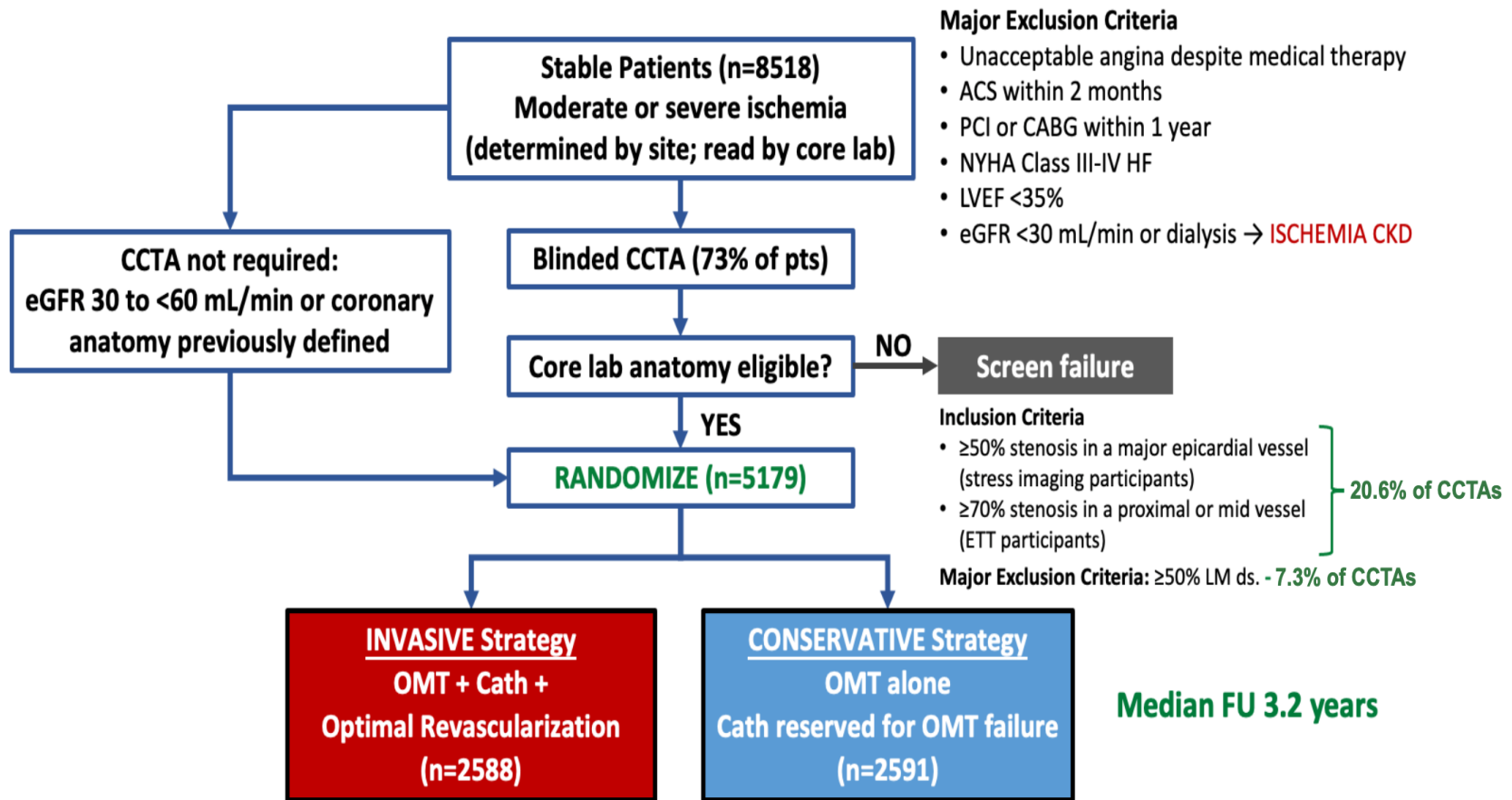
U.O.S. EMODINAMICA
U.O.C. CARDIOLOGIA-UTIC
Osp. "Umberto I" – Nocera Inferiore (SA)
ASL Salerno

ISCHEMIA Trial: Background

- In pazienti con Malattia Coronarica Stabile una serie di Trials precedenti (come il COURAGE) non hanno dimostrato un beneficio dell'approccio invasivo con rivascolarizzazione precoce nel prevenire eventi come Morte Cardiovascolare o Infarto Miocardico
- Il FAME 2 ha mostrato, in un follow-up a 5 aa, un effetto marginale della rivascolarizzazione funzionalmente guidata sulla riduzione dell'Infarto Miocardico ma nessun effetto significativo sulla Mortalità
- Limitazioni:
 - - pz arruolati dopo angiografia → Basso rischio
 - - esclusi quelli anatomicamente ad Alto Rischio
 - - molti avevano ischemia di lieve o moderata entità



ISCHEMIA Trial: patient flow



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



ISCHEMIA Trial: baseline characteristics

Characteristic	INV (n=2588)	CON (n=2591)
Clinical		
Age (yrs), median	64 (58, 70)	64 (58, 70)
Female (%)	23	22
Hypertension (%)	73	73
Diabetes (%)	41	42
Prior MI (%)	19	19
LVEF (%), median (n=4637)	60 (55, 65)	60 (55, 65)
History of angina	90%	89%
Angina began or became more frequent over the past 3 mos	29%	29%
SAQ Angina Frequency Score	80.8±20	82.1±19
- Daily/Weekly Angina	21.6%	19.0%
- Several Times per Month	44.1%	44.5%
- No Angina	34.3%	36.6%

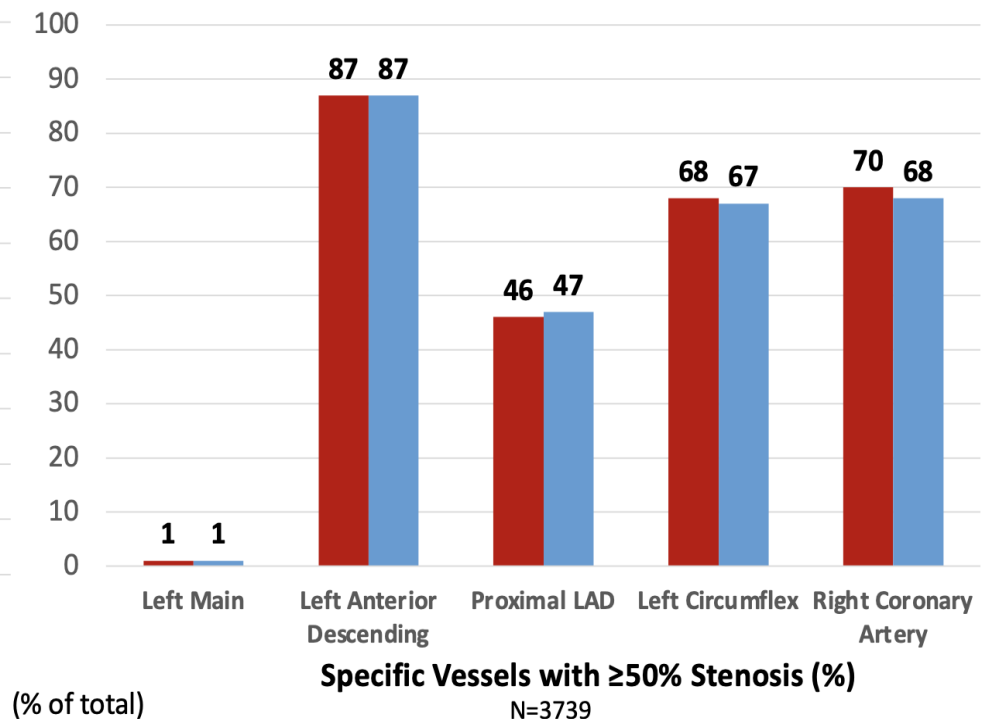
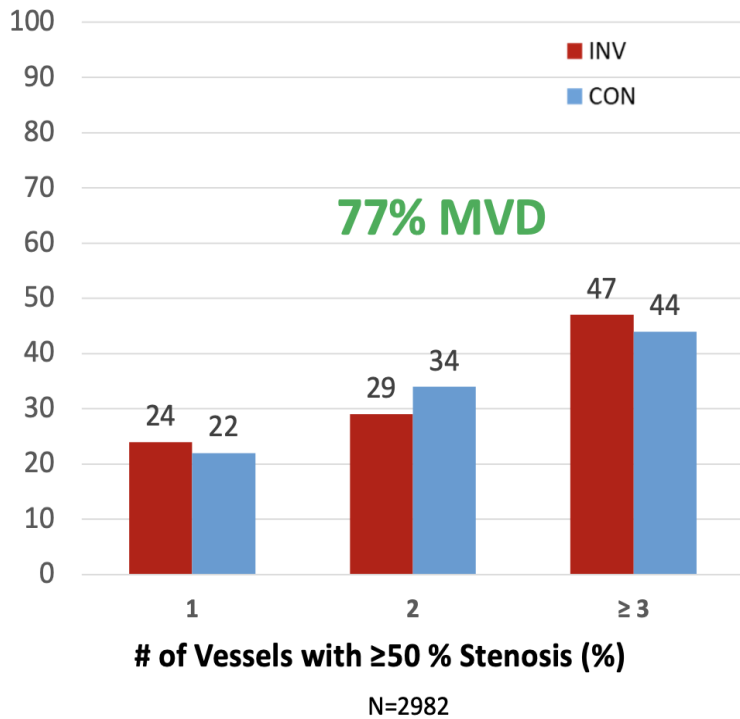


ISCHEMIA Trial: Qualifying stress test

	INV (n=2588)	CON (n=2591)
Stress Test Modality		
Stress imaging (%)	75	76
Exercise tolerance test (ETT) (%)	25	24
Baseline Inducible Ischemia*		
Severe	53%	55%
Moderate	34%	32%
Mild/None	12%	12%
Uninterpretable	1%	1%

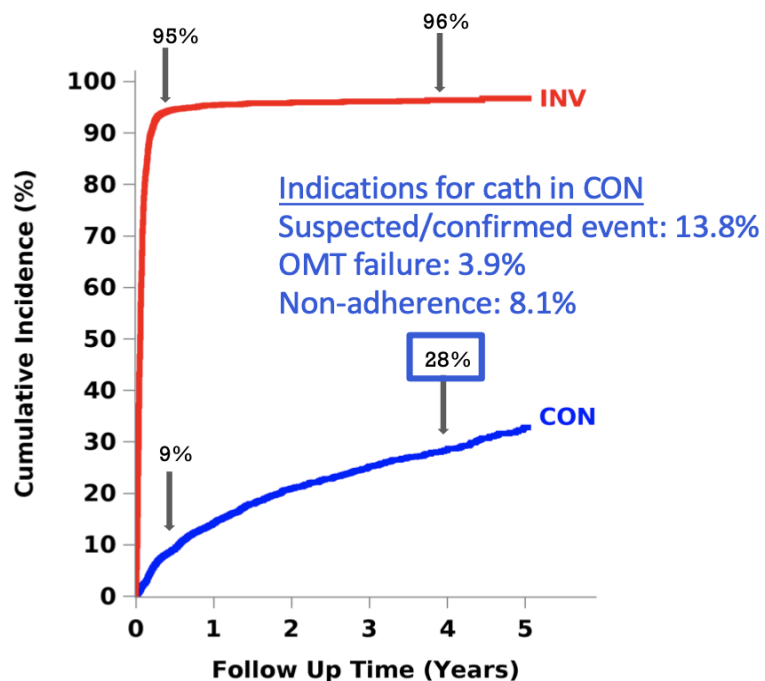


ISCHEMIA Trial: Baseline Coronary Artery anatomy by CCTA



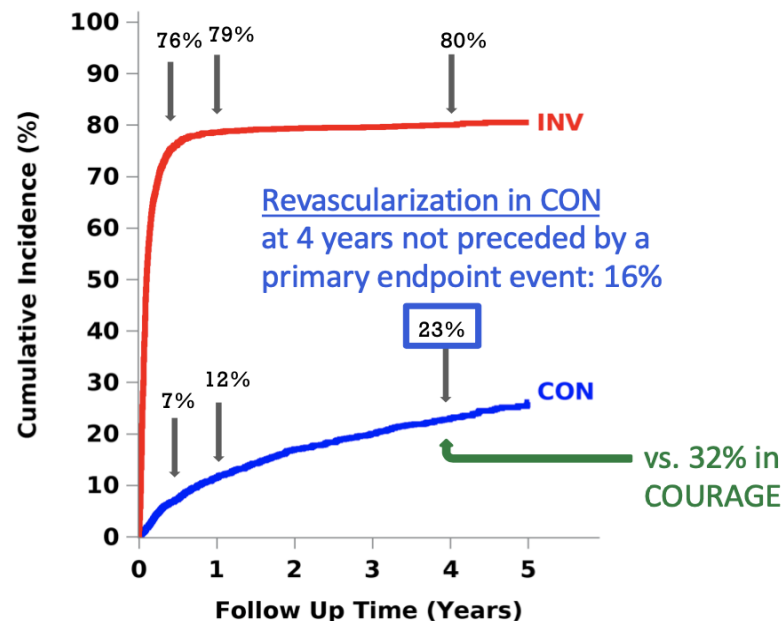
ISCHEMIA Trial: Cardiac Catheterization and Revascularization

Cardiac Catheterization



CON	2591	2186	1646	1087	601	232
INV	2588	111	79	50	20	4

Revascularization



CON	2591	2250	1721	1157	642	254
INV	2588	523	410	289	155	54



ISCHEMIA Trial: mode of revascularization

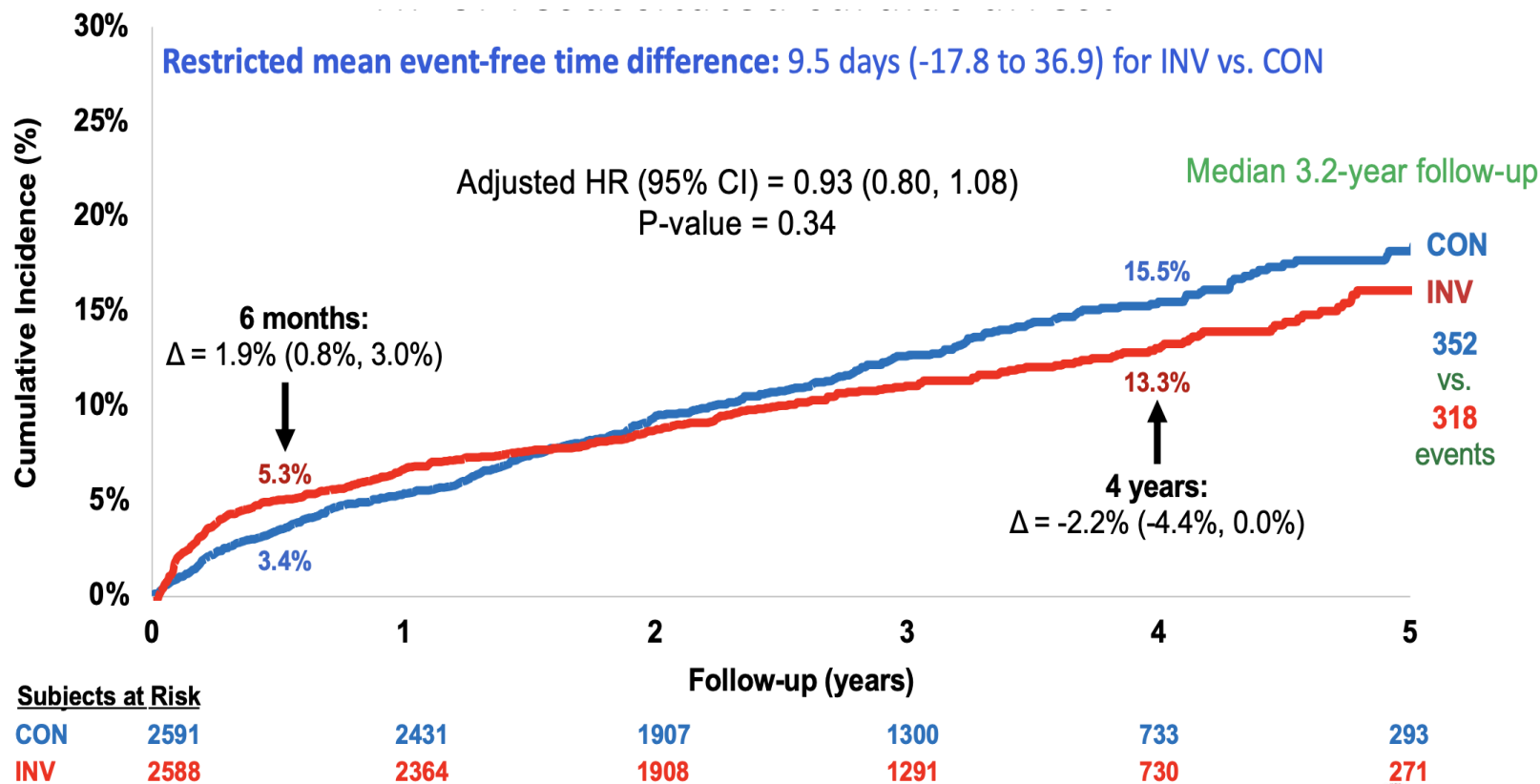
First Procedure for Those Revascularized in Invasive Group (~80% of INV)

Of the ~ 20% with no revascularization:
~ 2/3 had insignificant disease on coronary angiogram
~1/3 had extensive disease unsuitable for any mode of revascularization

First Procedure	Total	First Procedure	Total
PCI	74%	CABG	26%
• Successful, stent implanted	93%	• Arterial Grafts	93%
• Of stents placed, drug-eluting	98%	• IMA	92%

**ISCHEMIA**

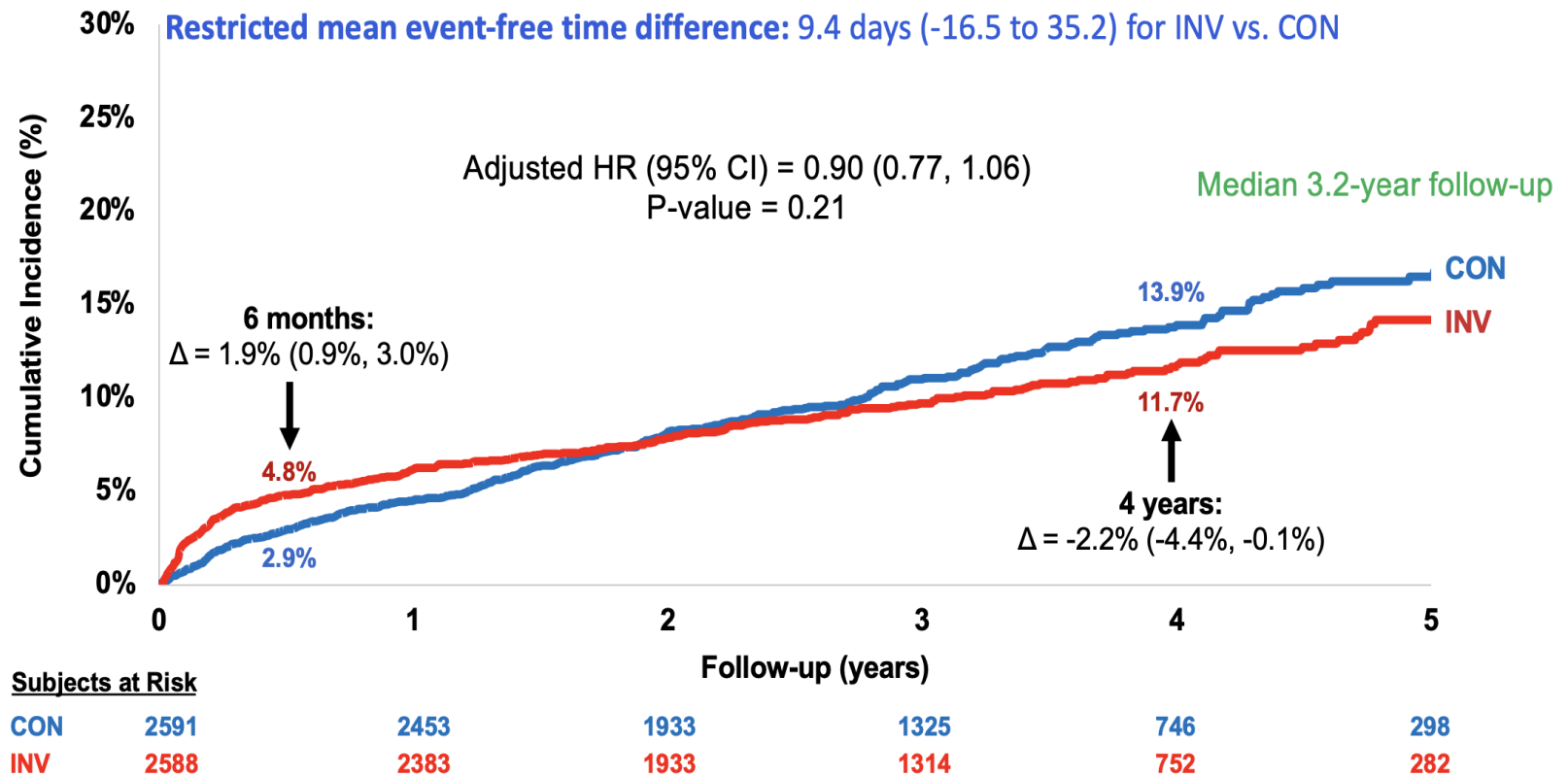
ISCHEMIA STUDY Primary Outcome: CV Death, MI, Hospitalization for UA, HF or resuscitated cardiac arrest



ISCHEMIA

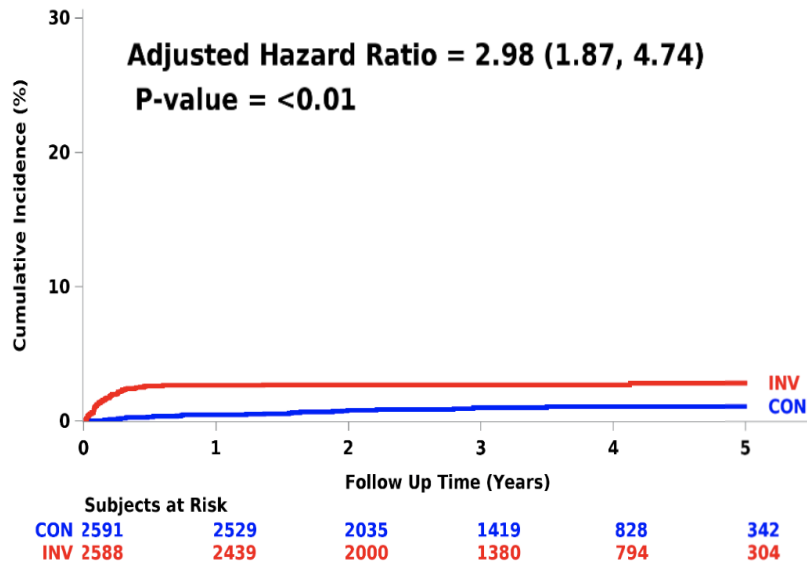
ISCHEMIA STUDY

Major secondary Outcome: CV Death or MI

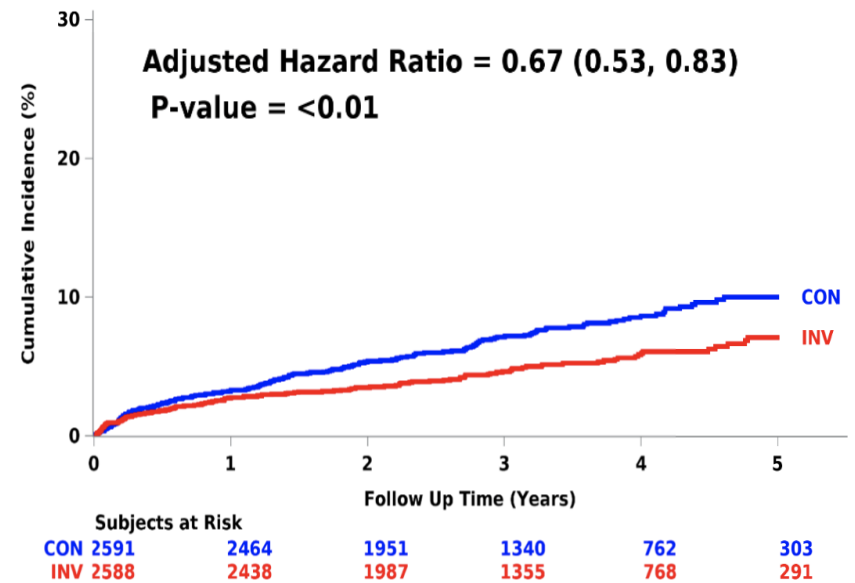


ISCHEMIA Trial: Myocardial Infarction

Procedural MI Types 4a or 5 MI

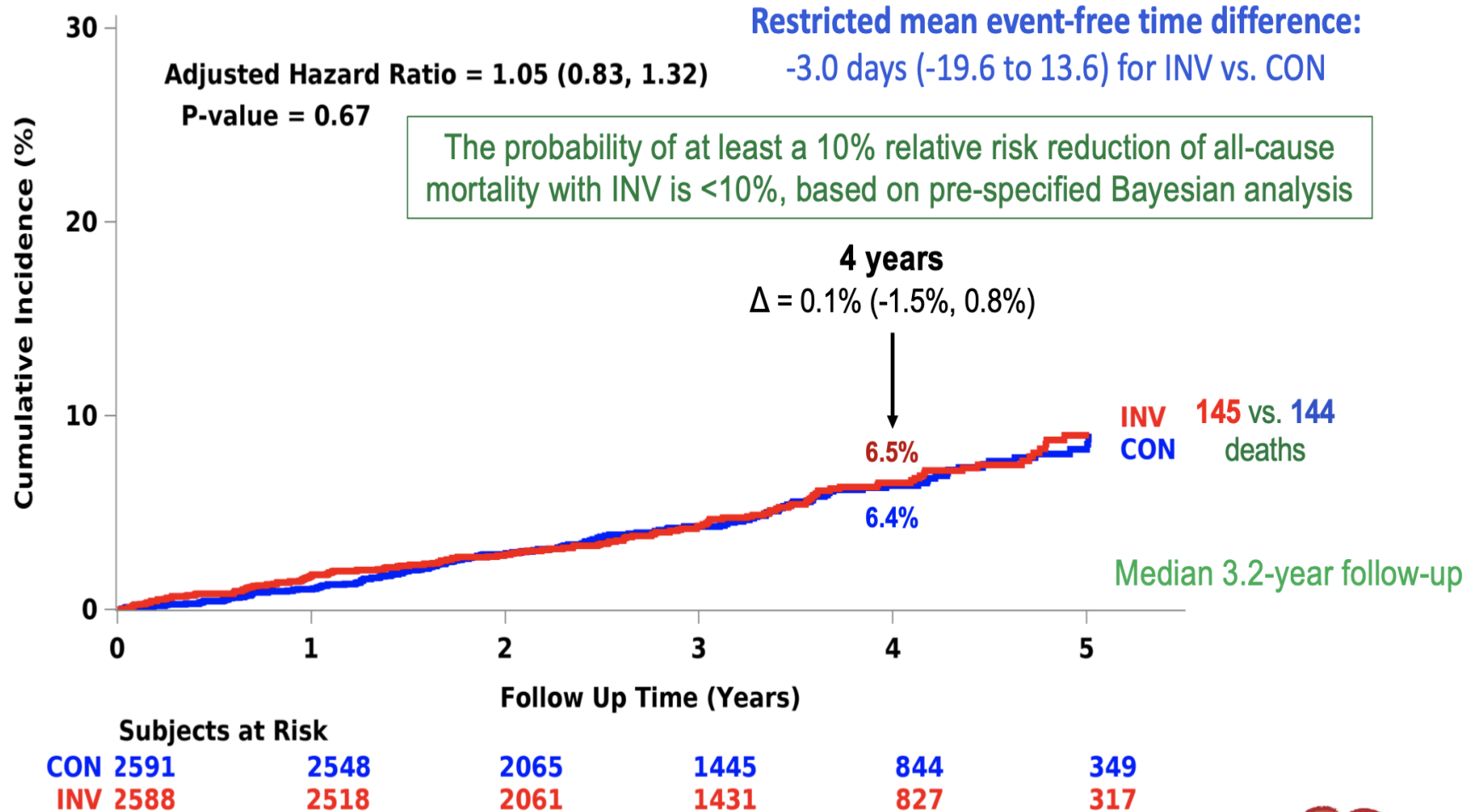


Non-procedural MI Types 1, 2, 4b, or 4c MI



ISCHEMIA

ISCHEMIA Trial: all cause Death



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



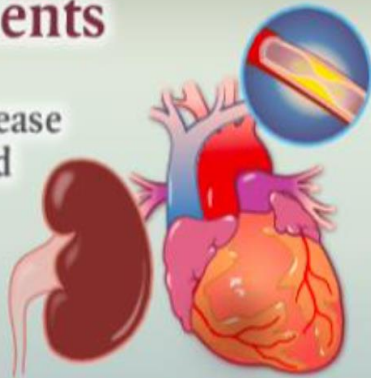
International Study of Comparative Health Effectiveness with Medical and Invasive Approaches - Chronic Kidney Disease

Primary Report of Clinical Outcomes



777 Patients

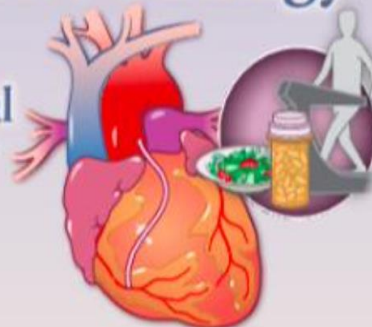
with stable coronary disease and advanced CKD



Invasive Strategy

+ Medical therapy

(N=388)



Conservative Care

Medical therapy

(N=389)



Death or nonfatal MI

123

129

Adjusted HR 1.01; 95% CI, 0.79–1.29; P=0.95

Angina-related health status

No difference in Seattle Angina Questionnaire summary score

Invasive treatment did not reduce the rate of death or nonfatal MI or improve angina-related health status

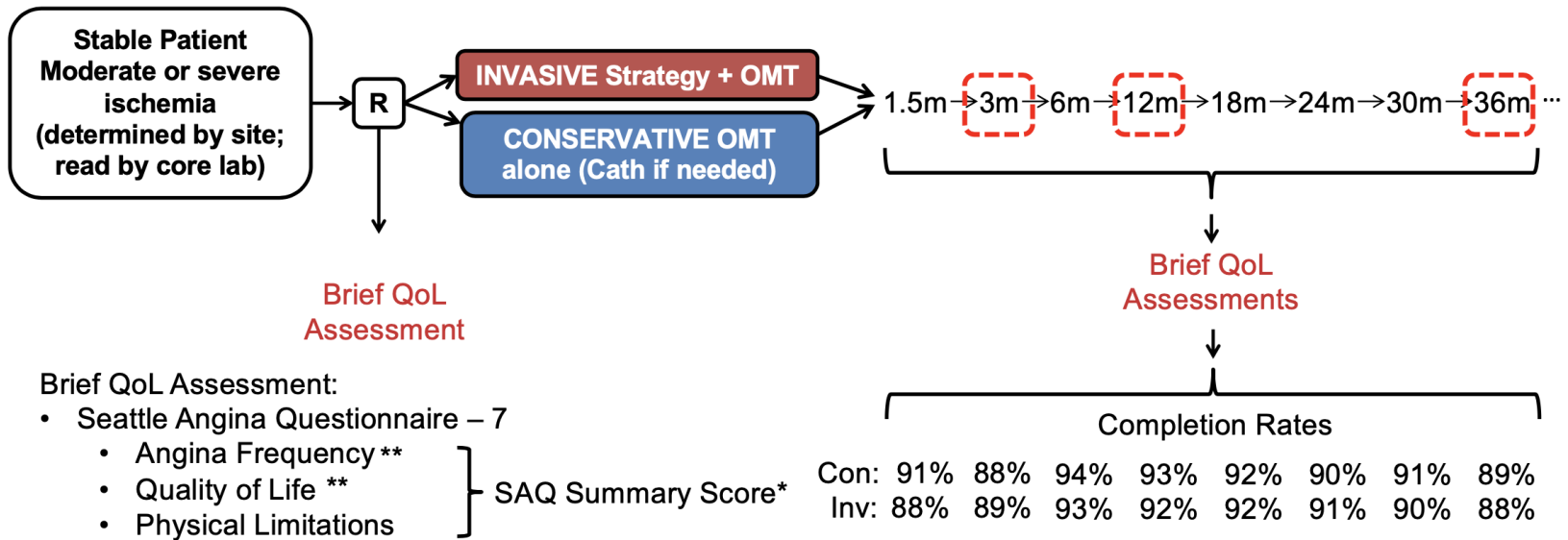
ISCHEMIA

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches Primary Report of Quality of Life Outcomes

Funded by National Heart, Lung, and Blood Institute

John A. Spertus, MD, MPH
Saint Luke's Mid America Heart Institute/UMKC
On behalf of the ISCHEMIA Research Group

**In a stable patient with at least moderate ischemia, does an invasive strategy...
*improve patients' health status (their symptoms, function and quality of life)?***



Brief QoL Assessment:

- Seattle Angina Questionnaire – 7
 - Angina Frequency **
 - Quality of Life **
 - Physical Limitations

SAQ Summary Score*

Con:	91%	88%	94%	93%	92%	90%	91%	89%
Inv:	88%	89%	93%	92%	92%	91%	90%	88%

*Primary QoL Outcome
**Secondary QoL Outcome

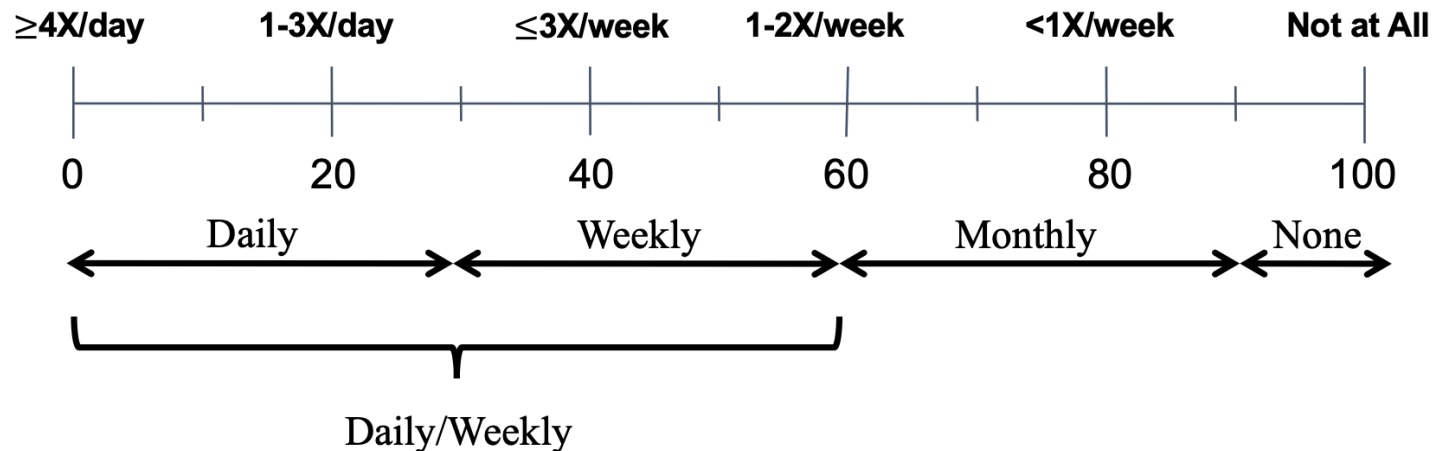


International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches
Primary Report of Quality of Life Outcomes

Interpreting and stratifying SAQ Scores

SAQ Angina Frequency Scale:

Over the past 4 weeks, how often have you had angina?



Spertus JA et al. *N Engl J Med.* 2020;382:1408-1419



International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches
Primary Report of Quality of Life Outcomes

Baseline Health Status

Scale	Invasive	Conservative
SAQ Summary Score	73.3±19	74.8±19
SAQ Quality of Life Score	60.9±27	62.7±26
SAQ Angina Frequency Score	80.8±20	82.1±19
Daily/Weekly Angina	21.6%	19.0%
Several Times per Month	44.1%	44.5%
No Angina	34.3%	36.6%

Spertus JA et al. *N Engl J Med.* 2020;382:1408-1419

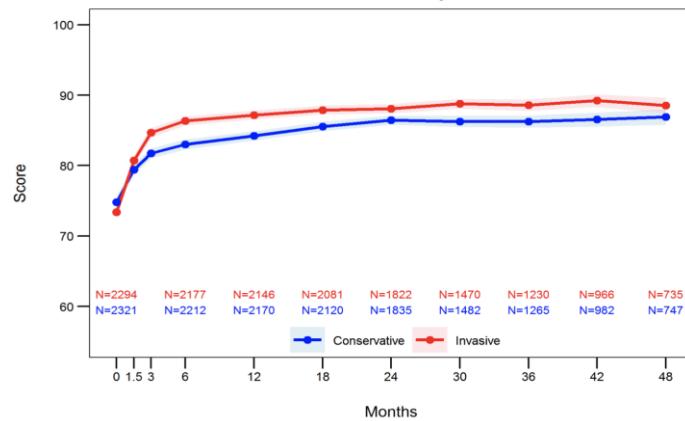


International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches

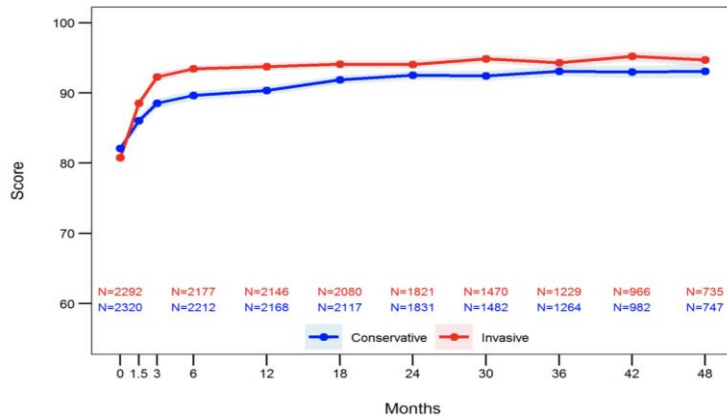
Observed Data

Primary Report of Quality of Life Outcomes

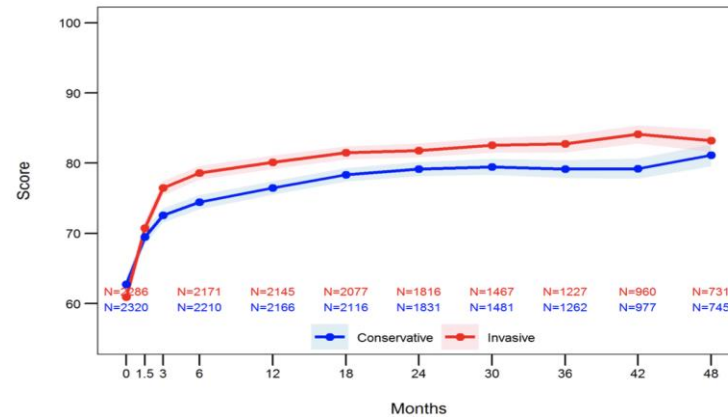
SAQ Summary Score



SAQ Angina Frequency



SAQ Quality of Life

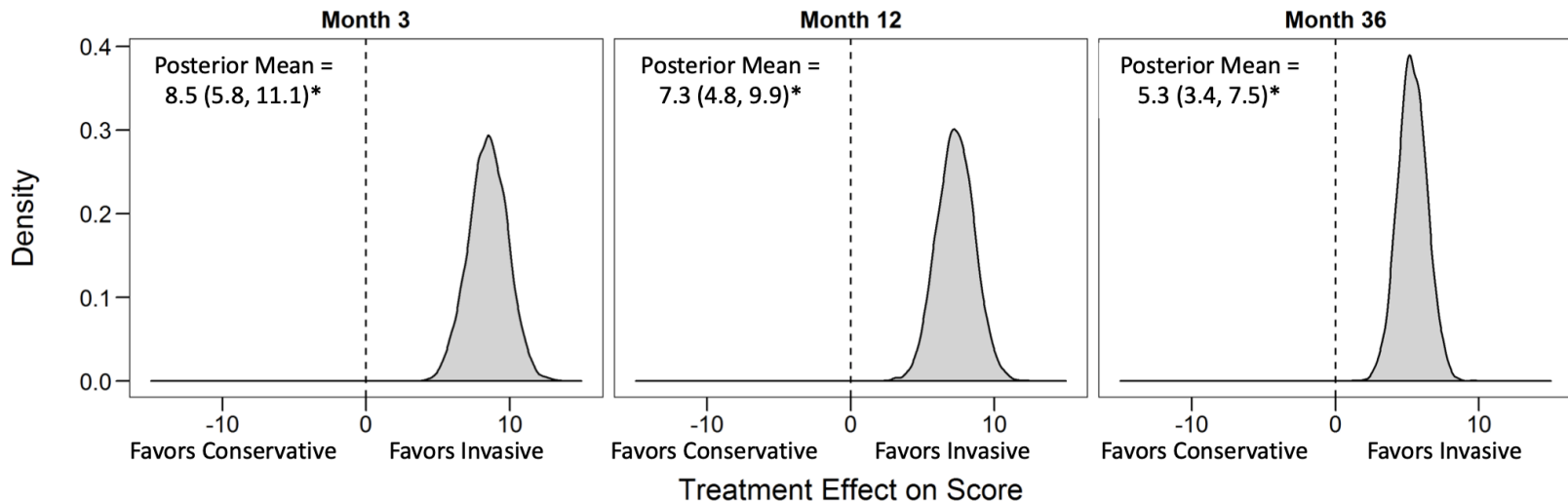




International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches
Primary Report of Quality of Life Outcomes

Primary Outcome: Benefit of Invasive Rx on SAQ Summary Score

Typical Patient with Daily to Weekly Angina



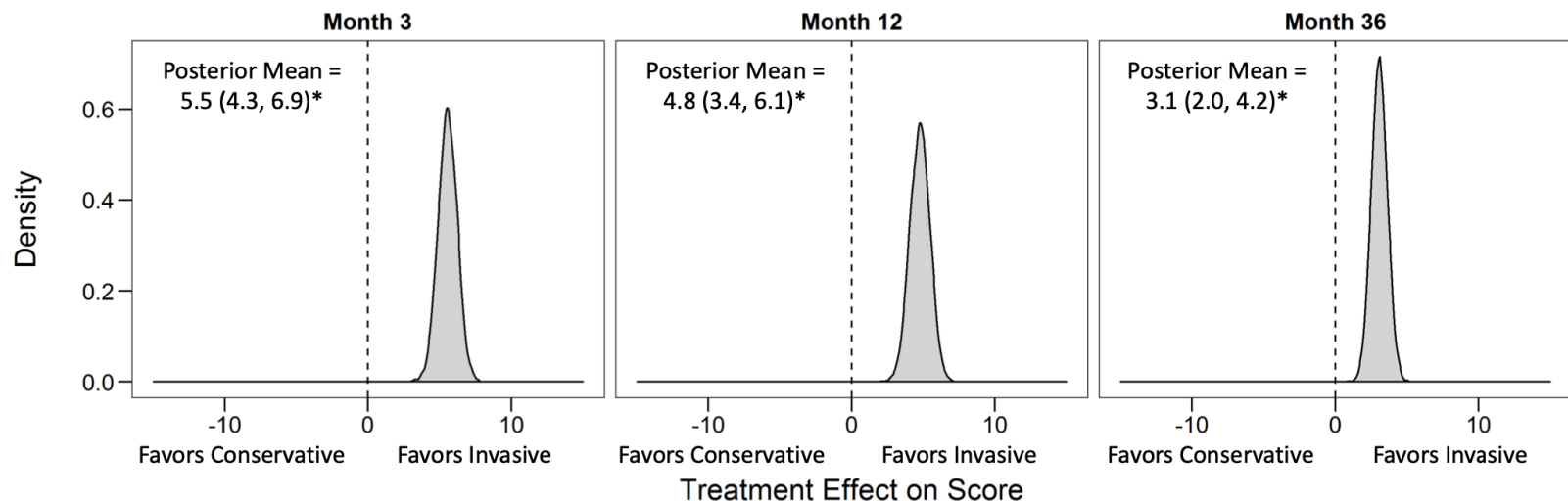
Spertus JA et al. *N Engl J Med.* 2020;382:1408-1419



International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches
Primary Report of Quality of Life Outcomes

Primary Outcome: Benefit of Invasive Rx on SAQ Summary Score

Typical Patient with at least Monthly Angina



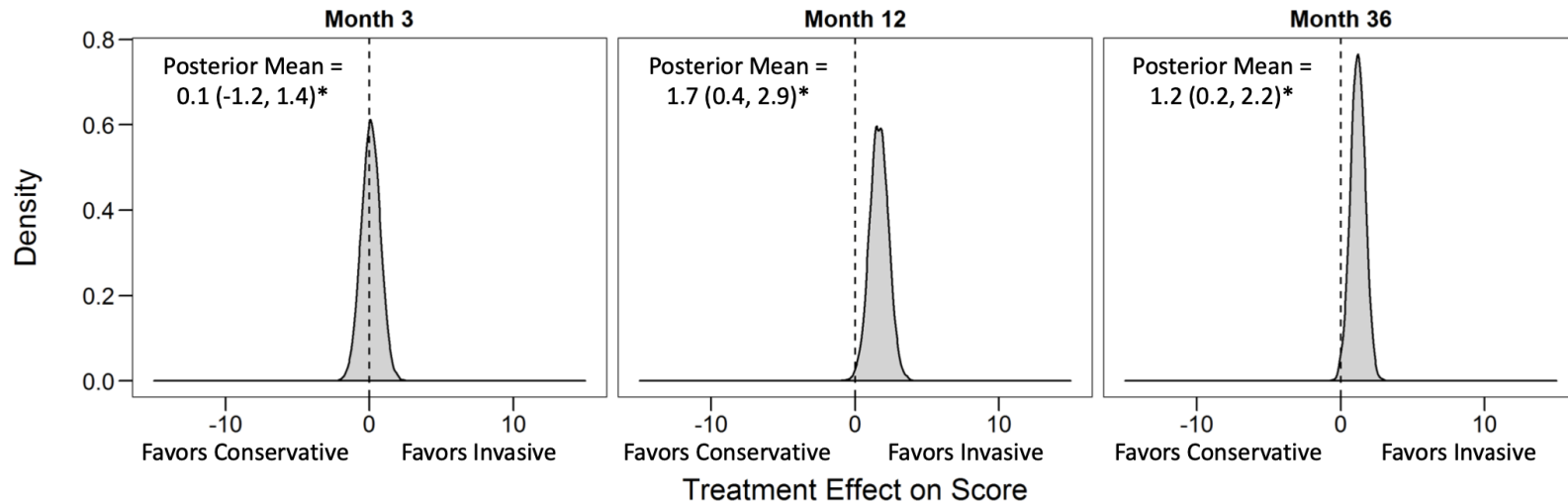
Spertus JA et al. *N Engl J Med.* 2020;382:1408-1419



International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches
Primary Report of Quality of Life Outcomes

Primary Outcome: Benefit of Invasive Rx on SAQ Summary Score

Typical Patient with No Angina

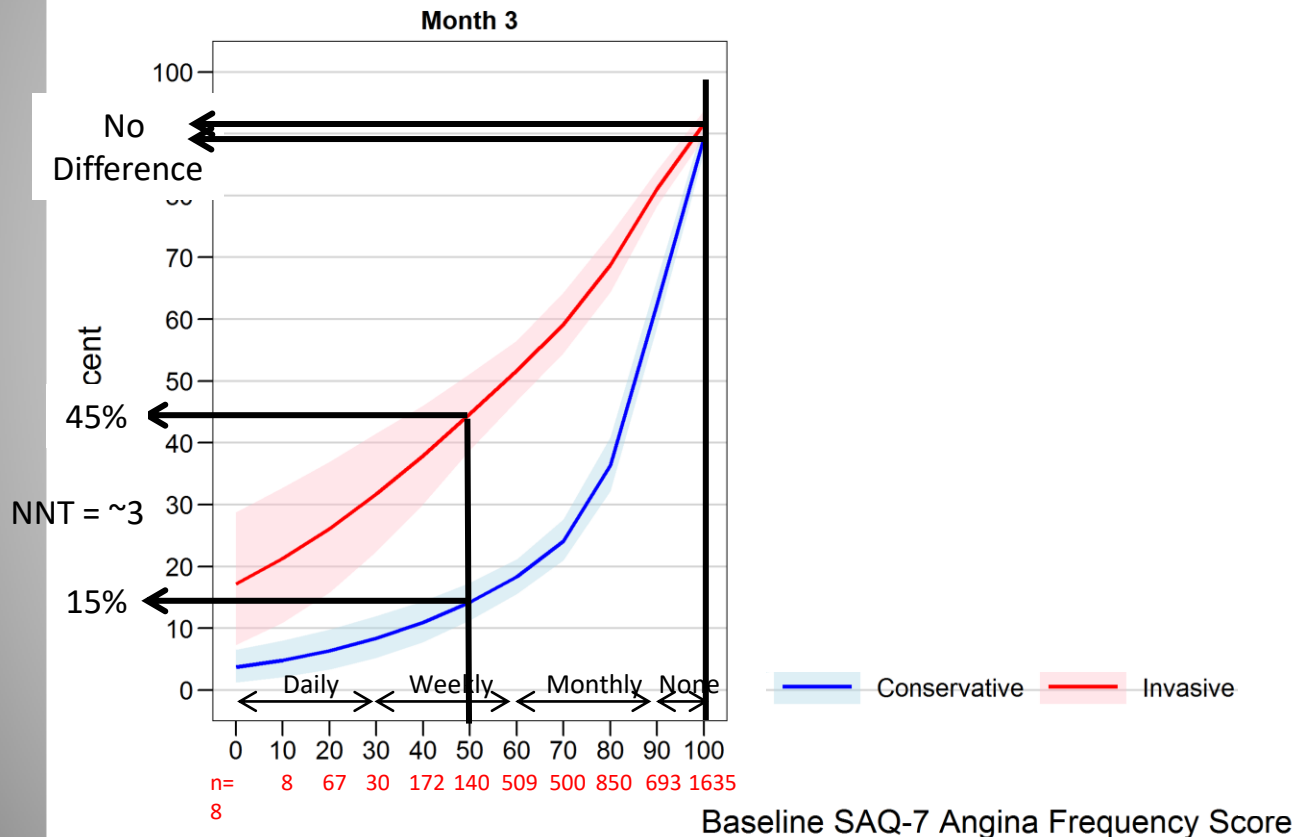


Spertus JA et al. *N Engl J Med.* 2020;382:1408-1419



International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches
Primary Report of Quality of Life Outcomes

Probability of No Angina by Baseline Angina Frequency





International Study of Comparative Health Effectiveness with
Medical and Invasive Approaches
Primary Report of Quality of Life Outcomes

Conclusions

- ❑ Patients with stable CAD and moderate to severe ischemia had significant, durable improvements in angina control and quality of life with an invasive strategy *if they had angina* (daily/weekly or monthly)
- ❑ In patients without angina, an invasive strategy led to minimal symptom or quality of life benefits, as compared with a conservative strategy
- ❑ In patients with angina, shared decision-making should occur to align treatment with patients' goals and preferences

Spertus JA et al. *N Engl J Med.* 2020;382:1408-1419

Impact of Complete Revascularization in the ISCHEMIA Trial

Original Investigation

Gregg W. Stone, Ziad A. Ali, Sean M. O'Brien, Grace Rhodes, Philippe Genereux, Sripal Bangalore, Kreton Mavromatis, Jennifer Horst, Ovidiu Dressler, Kian Keong Poh, Ranjit K. Nath, Nagaraja Moorthy, Adam Witkowski, Sudhanshu K. Dwivedi, Olga Bockeria, Jiyan Chen, Paola E.P. Smanio, Michael H. Picard, Bernard R. Chaitman, Daniel S. Berman, Leslee J. Shaw, William E. Boden, Harvey D. White, Stephen E. Femes, Yves Rosenberg, Harmony R. Reynolds, John A. Spertus, Judith S. Hochman, David J. Maron, and

J Am Coll Cardiol. 2023 Sep, 82 (12) 1175–1188

Background

Anatomic complete revascularization (ACR) and functional complete revascularization (FCR) have been associated with reduced death and myocardial infarction (MI) in some prior studies.

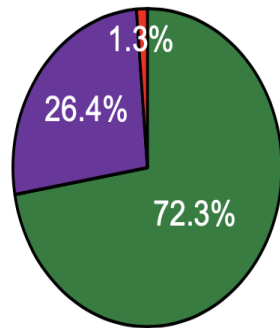
The impact of complete revascularization (CR) in patients undergoing an invasive (INV) compared with a conservative (CON) management strategy has not been reported.

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

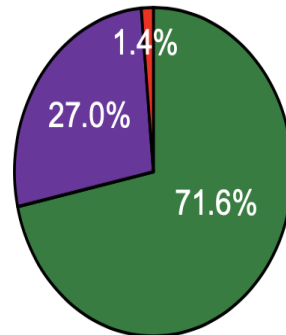
Mode of revasc

ACR assessment
(n=1802)

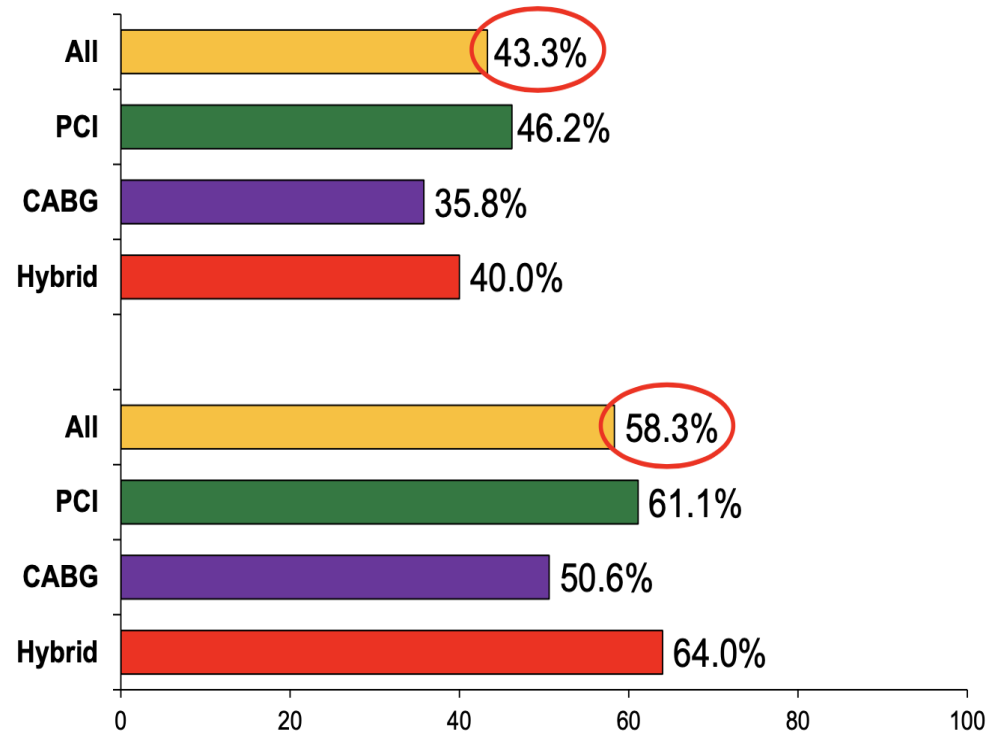


■ PCI ■ CABG ■ Hybrid

FCR assessment
(n=1743)



Complete revascularization rate (%)

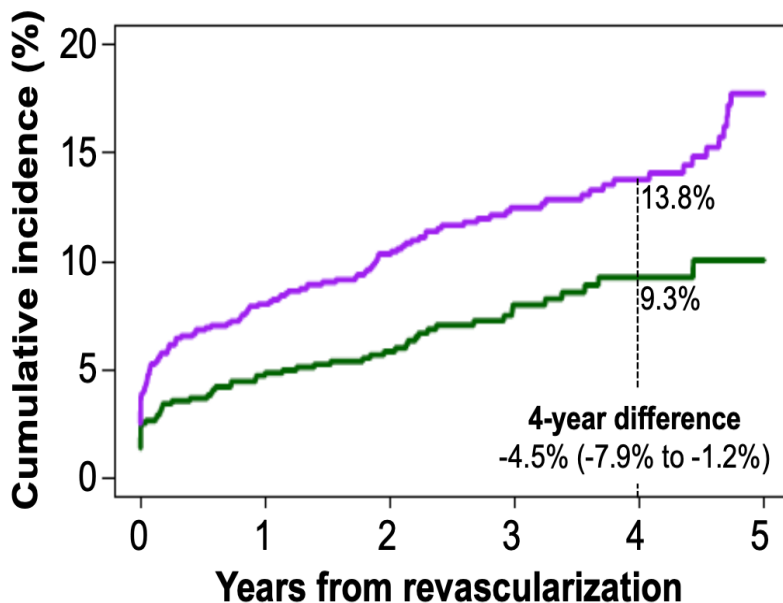


Relationship Between CR and Outcomes (INV)

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

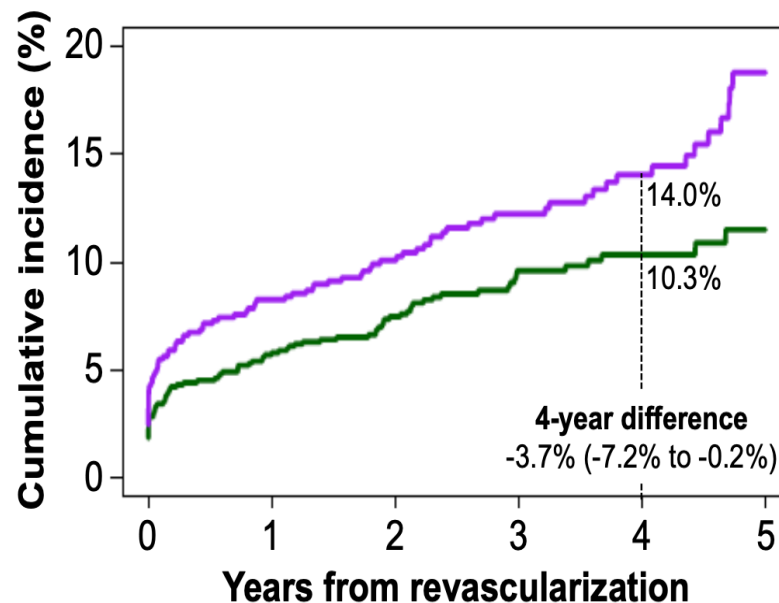
— Complete revascularization — Incomplete revascularization

Anatomic CR assessment



No. at risk						
ACR	781	736	584	364	177	66
Not ACR	1021	929	716	497	290	104

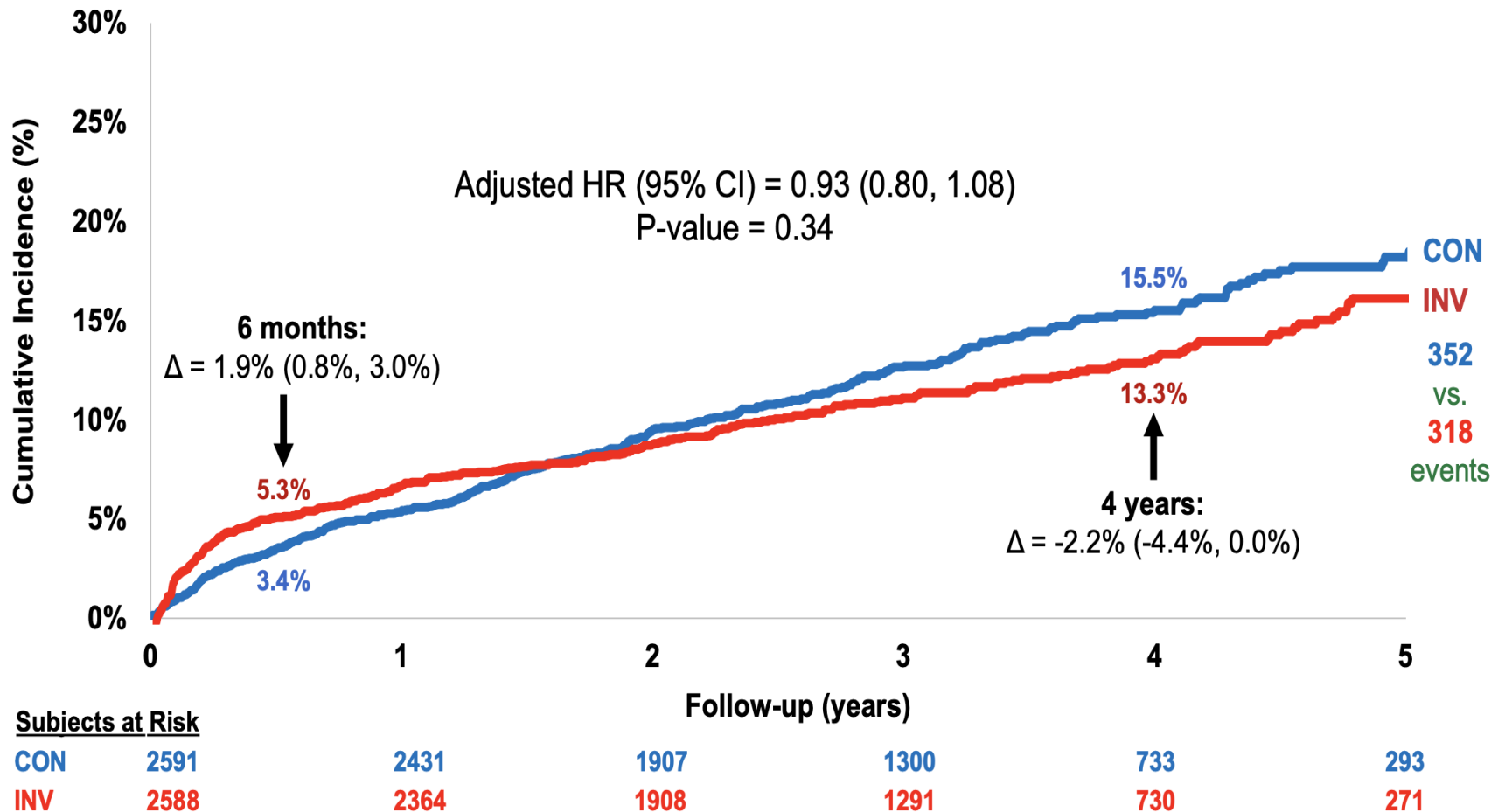
Functional CR assessment



No. at risk						
FCR	1017	948	739	475	242	88
Not FCR	726	659	514	357	211	79

Principal ISCHEMIA Trial Results

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



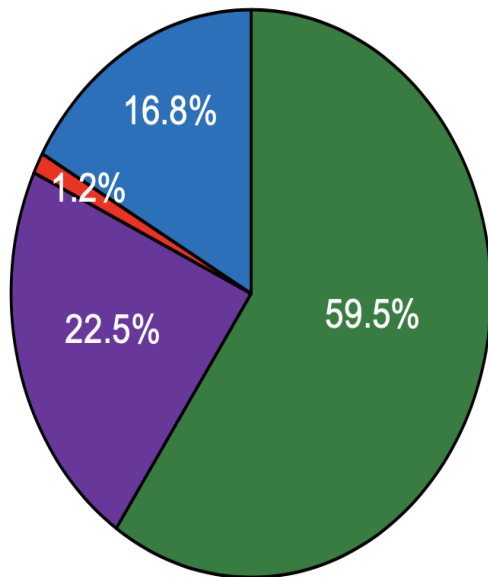
Maron DJ et al. N Engl J Med. 2020;382:1395-1407

Completeness of Revascularization (INV)

Among 2296 pts randomized to INV

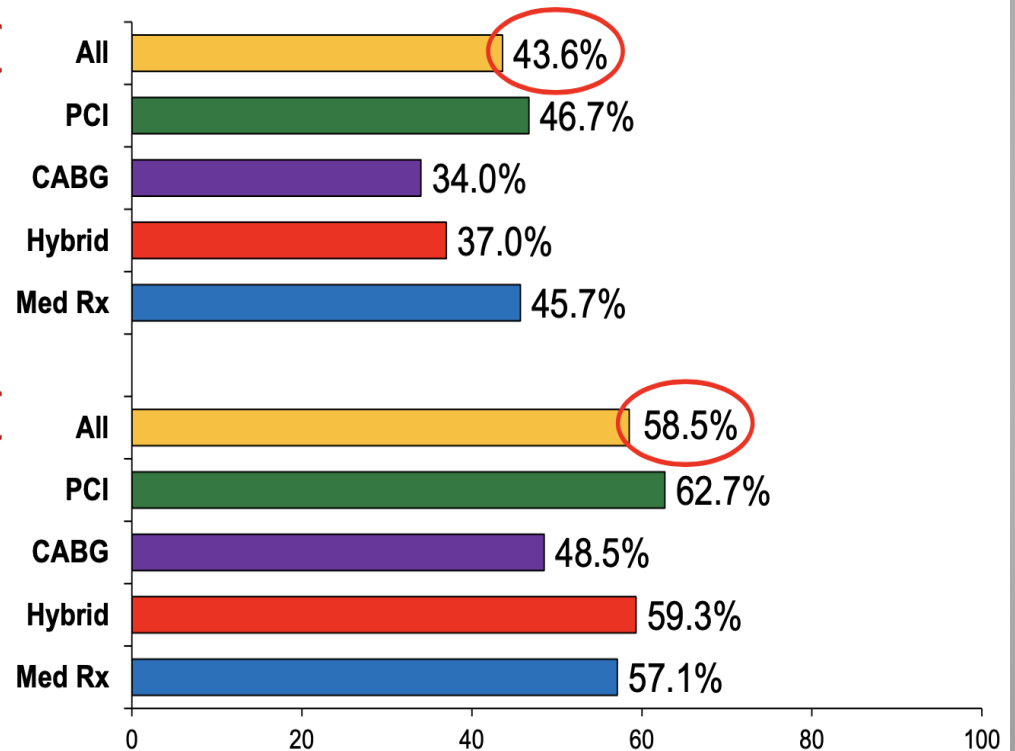
Mode of revascularization

■ PCI ■ CABG ■ Hybrid ■ Med Rx only



Complete revascularization rate (%)

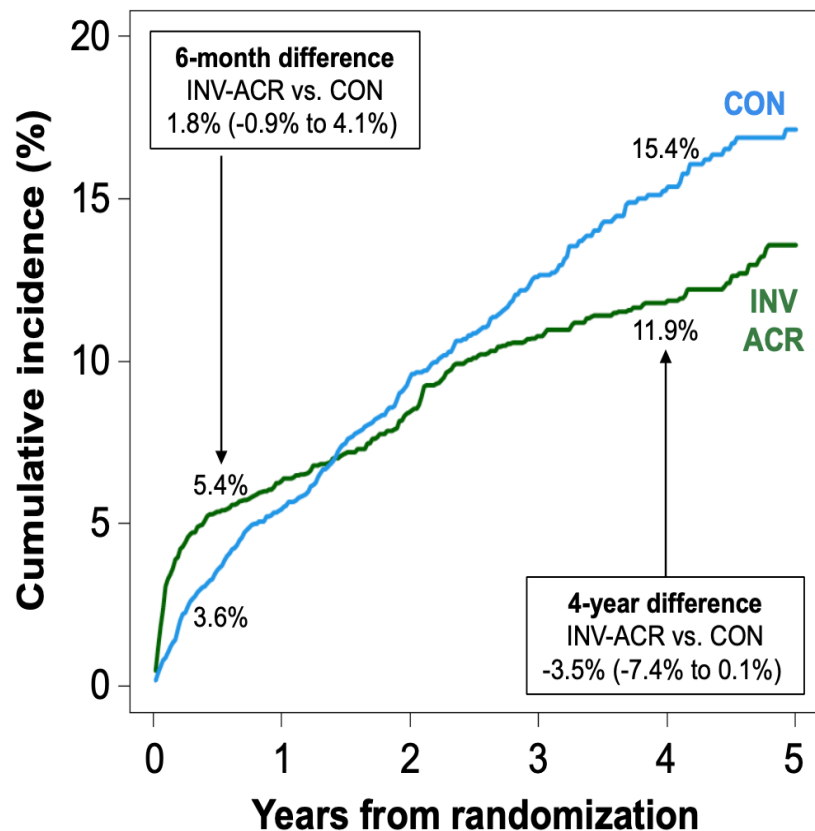
Functional CR (%) Anatomic CR (%)



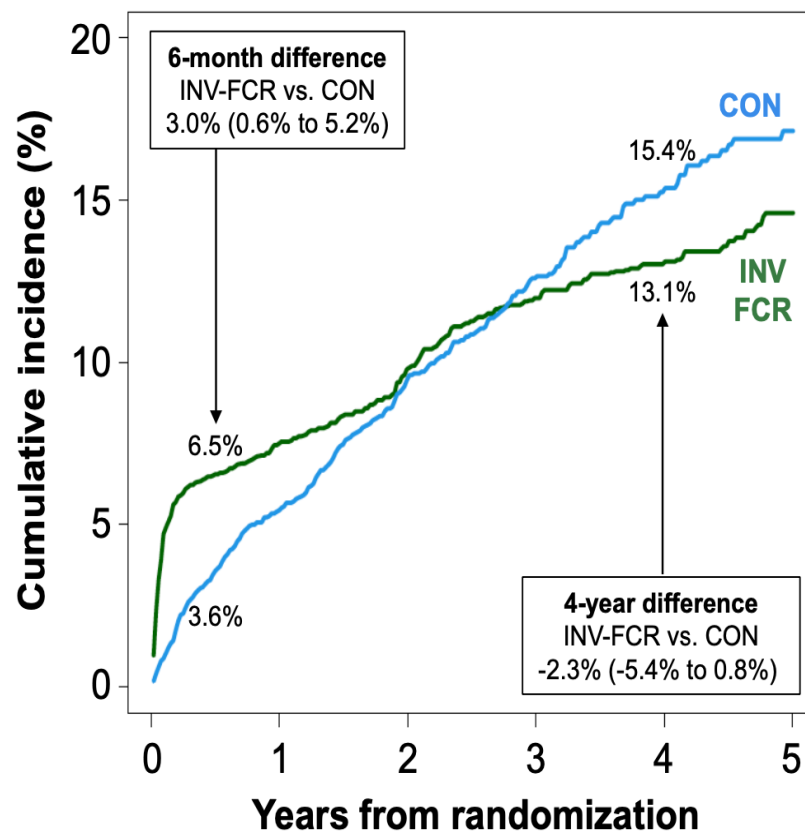
Outcomes for INV-CR versus CON: Primary endpoint

INV IPW-adjusted, marginal structural model using natural splines

Anatomic CR achieved



Functional CR achieved



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



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

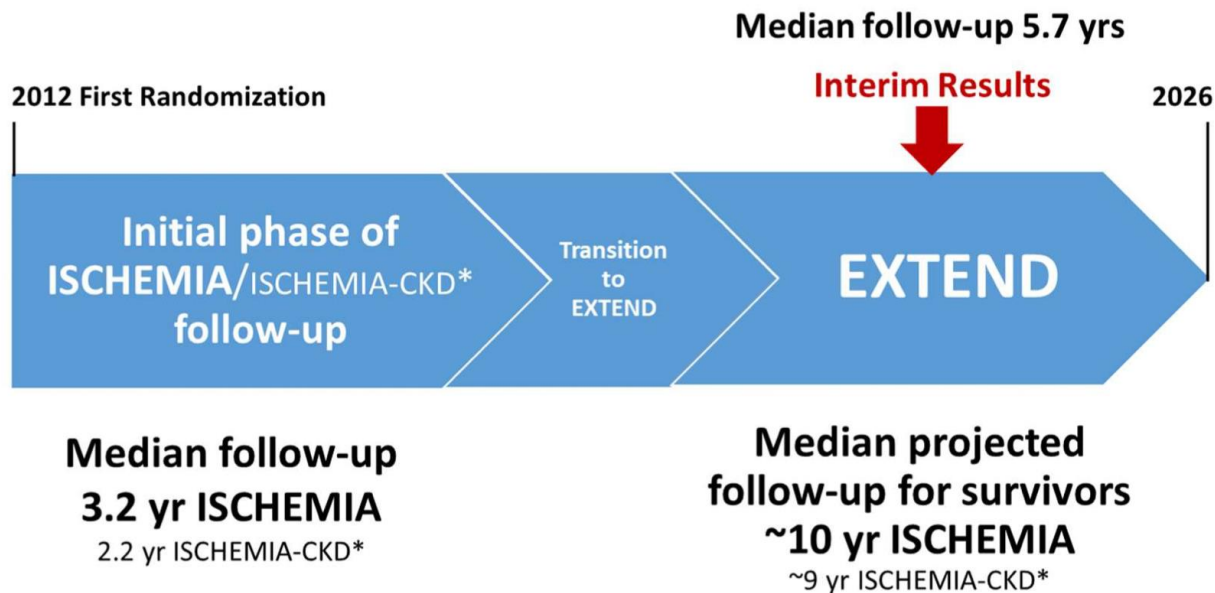


#AHA22

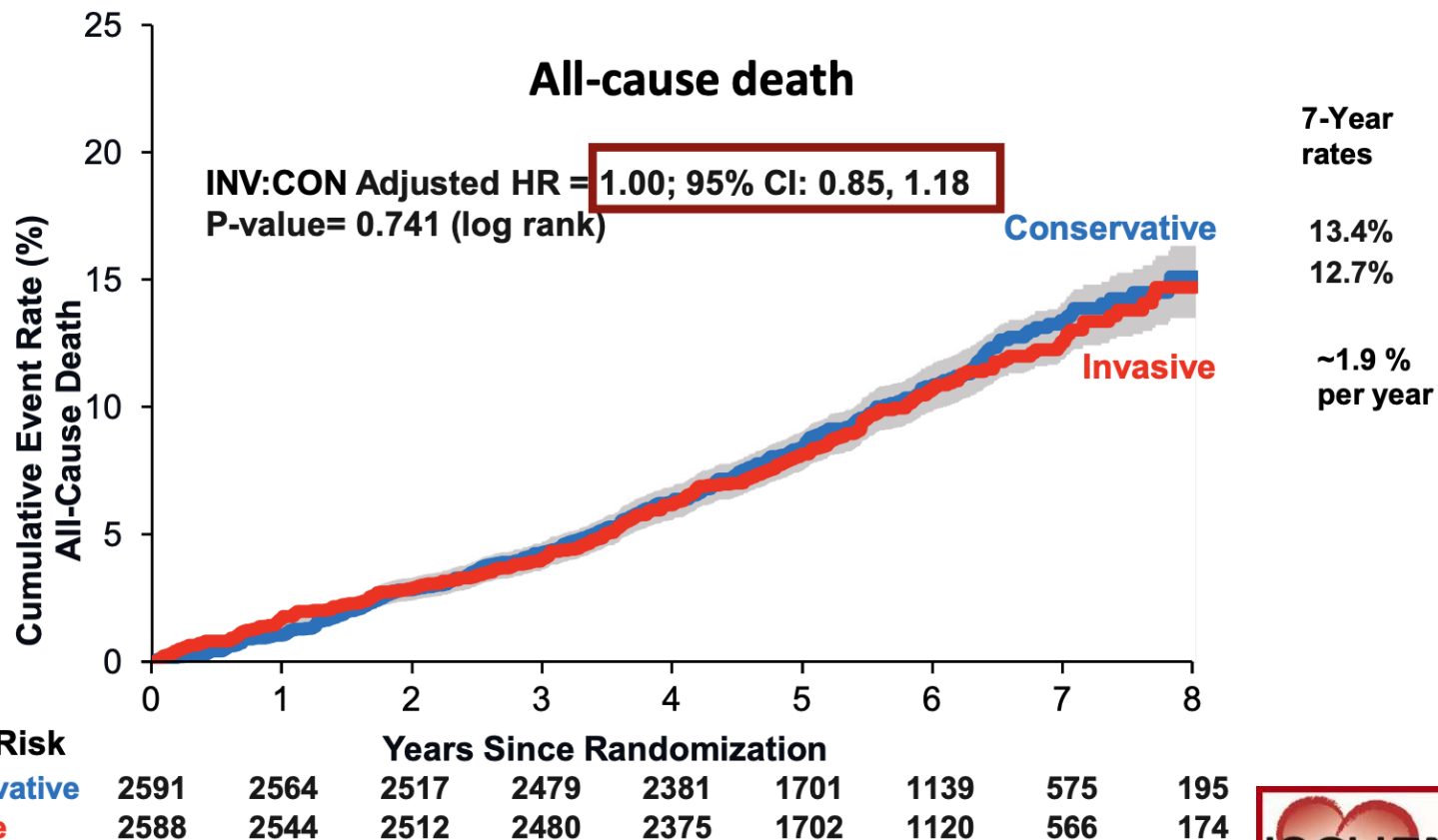


ISCHEMIA-EXTEND *ISCHEMIA Extended Follow-Up Interim Report*

Judith S. Hochman, MD
on behalf of the ISCHEMIA-EXTEND Research Group
Senior Associate Dean For Clinical Sciences
Co-director, Clinical And Translational Science Institute
Harold Snyder Family Professor and Associate Director of Cardiology
Director, Cardiovascular Clinical Research Center
NYU Grossman School of Medicine

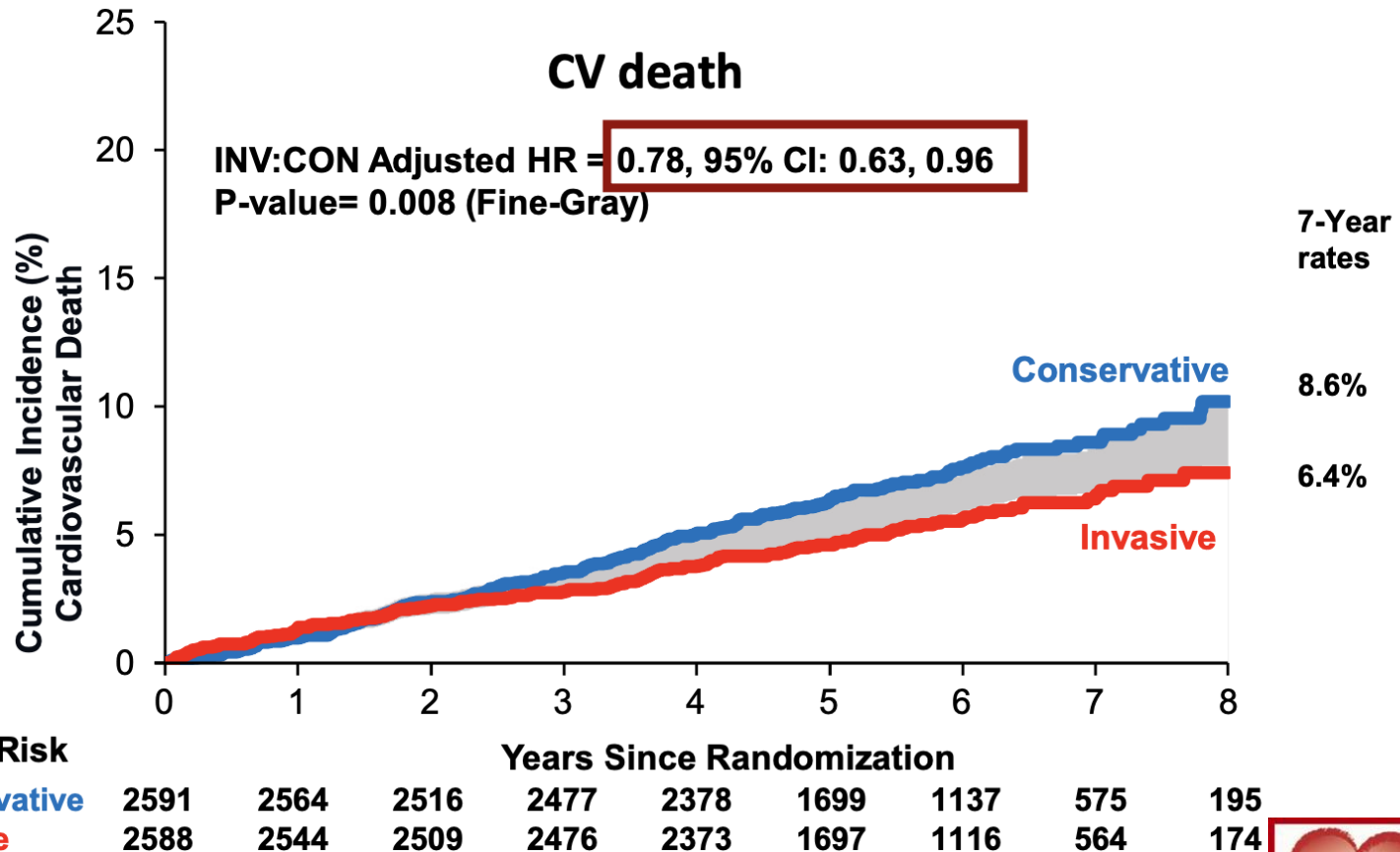


Extended follow-up: 5.7 years median Cumulative event rate of all cause Death



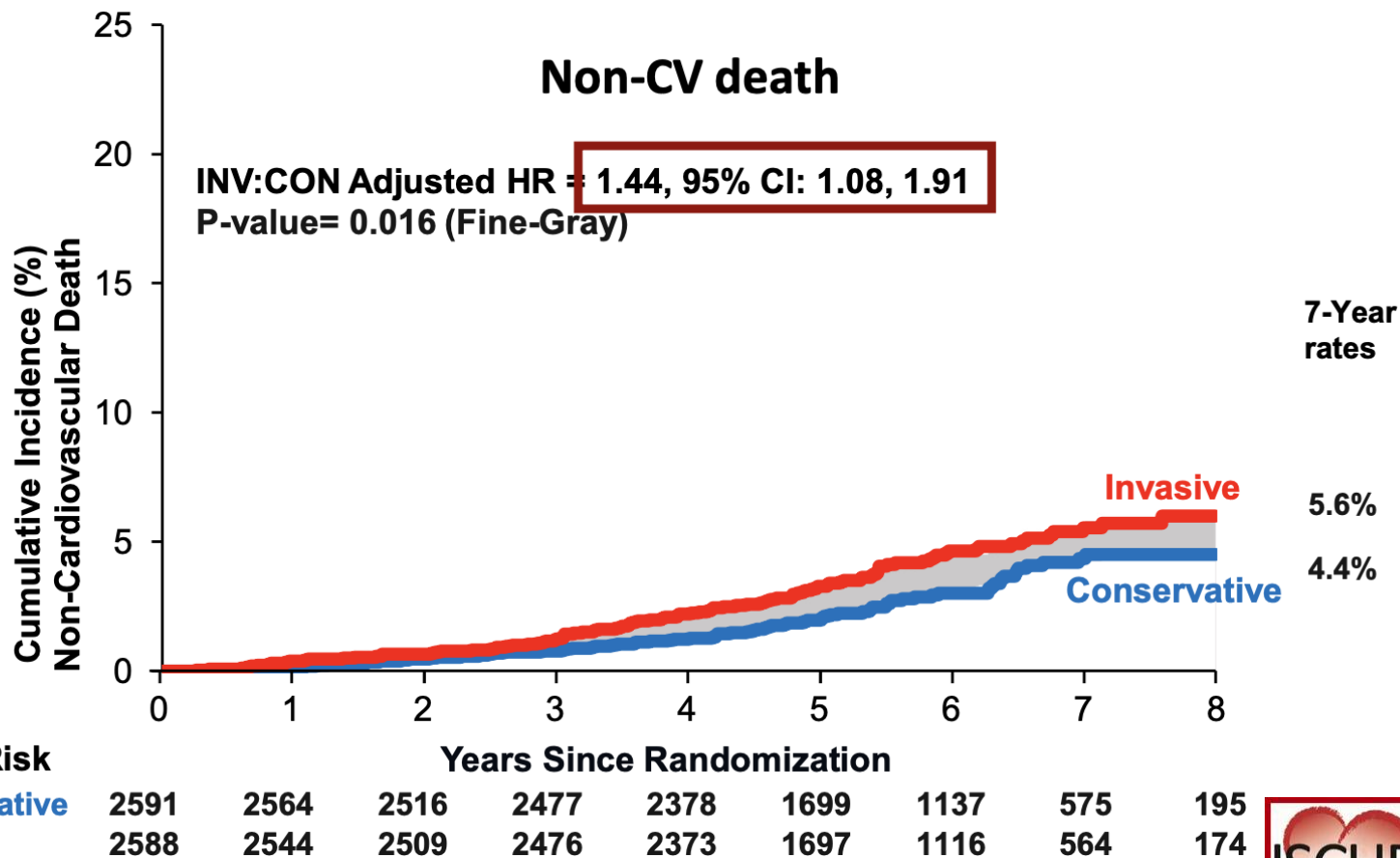
Extended follow-up: 5.7 years median

Cumulative incidence of Cardiovascular Death



Extended follow-up: 5.7 years median

Cumulative incidence of non Cardiovascular Death



Extended follow-up: 5.7 years median

Conclusions

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



.....dopo lo studio ISCHEMIA?

- ❑ I risultati dello studio Ischemia si applicano a pazienti con Sindrome Coronarica Cronica, documentazione di ischemia moderata-severa e FE conservata in cui una **strategia invasiva precoce** di routine **non riduce** gli eventi maggiori, in particolare la Mortalità, rispetto ad un **approccio inizialmente conservativo**
- ❑ Una strategia invasiva routinaria riduce il tasso di **MI** tardivo (spontaneo), sebbene a costo di un numero di **MI** procedurali. Pertanto non c'è impatto a lungo termine sul tasso di **MI, CV Death or MI, MACE** come da protocollo (**CV death, MI, hospitalization for UA, HF or resuscitated cardiac arrest**)
- ❑ Proseguendo il follow-up (Ischemia-Extended) nel tempo si osserva una **riduzione di Mortalità Cardiovascolare** che fa sperare in una ulteriore riduzione a distanza, anche se accompagnata ad una inspiegato **aumento della Mortalità non Cardiovascolare**

.....dopo lo studio ISCHEMIA?

- ❑ Pazienti con Sindrome Coronarica Cronica, documentazione di ischemia moderata-severa trattati con una **strategia invasiva precoce** ottengono un **miglioramento del controllo dell'angina e della qualità di vita** tanto più significativo e duraturo quanto più sono **sintomatici per angina** (quotidiana, settimanale o mensile)
- ❑ Nell'attuare una **strategia invasiva precoce**, per migliorarne il beneficio, occorre ottenere una **Rivascolarizzazione Completa** soprattutto in termini anatomici. Nel programmare il trattamento invasivo di un paziente va considerata quindi anche la fattibilità di una rivascolarizzazione anatomicamente completa.

.....dopo lo studio ISCHEMIA?

- ❑ **Pazienti con recente Sindrome Coronarica Acuta, malattia severa del Tronco Comune della CSn, FE < 35% rappresentano una quota di pazienti a rischio più alto, esclusi dallo studio ISCHEMIA**
- ❑ **Anamnesi accurata e valutazione anatomica e/o funzionale devono aiutare ad identificare tali pazienti che possono beneficiare assolutamente di una strategia invasiva precoce con rivascularizzazione**

...quali pazienti rivascularizzare subito?

- ❑ **Pazienti con Sindrome Coronarica Cronica ad alto rischio:**
 - ✓ recente Sindrome Coronarica Acuta,
 - ✓ malattia trivasale severa o del TC CSn,
 - ✓ Bassa frazione di eiezione (FE < 35%)

- ❑ **Pazienti sintomatici per angina e con una ampia area ischemica (cercando di ottenere una rivascularizzazione possibilmente completa)**