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Cardiac mortality after revascularization in light of the ISCHEMIA trial

Prof. Eliano P. Navarese
MD, PhD, FESC, FACC

Associate professor,
Head Clinical and Experimental Cardiology
Department of Clinical Interventional Cardiology,
University of Sassari, Sardinia island, Italy

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Disclosures

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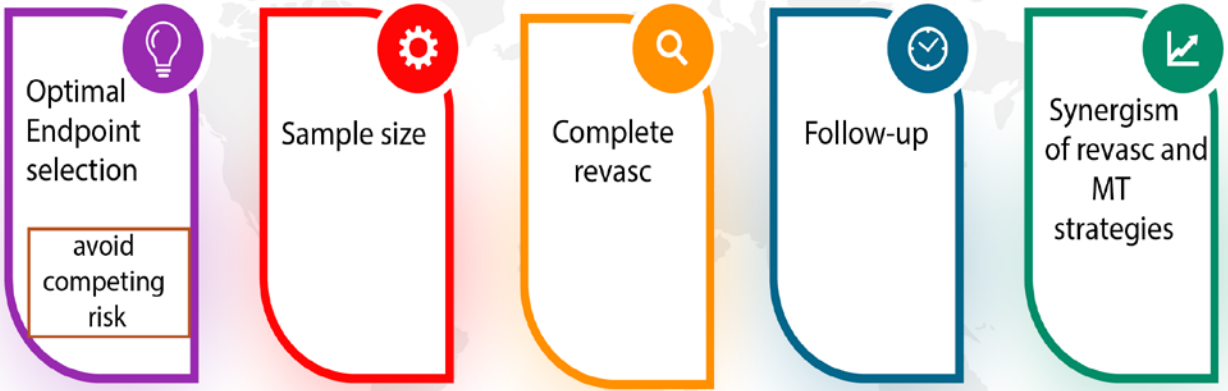
Determinants of the clinical effect with revascularization on a global scale



Risk multipliers: anatomic ischemic burden and degree of ischemia

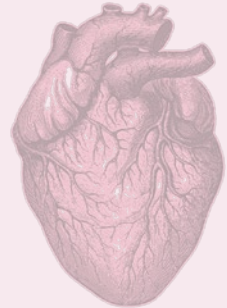
Breakdown of Mortality as trial endpoint

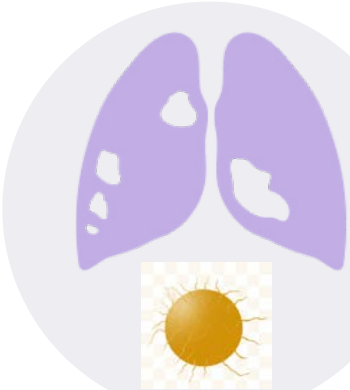
All-cause mortality

CV mortality

Non cardiac mortality

CV + non cardiac





Competing risk on CV death

Cancer
Sepsis
Other

Cardiac mortality endpoint in CV revasc trials and meta-analyses

- More specifically related to disease
- Avoids competing risks of non cardiac modes of death
- Greater power required for all-cause death: trends over the decades for proportional increases of noncardiac vs cardiac deaths

Navarese. Eur Heart J. 2021 Dec 1;42(45):4699-4700

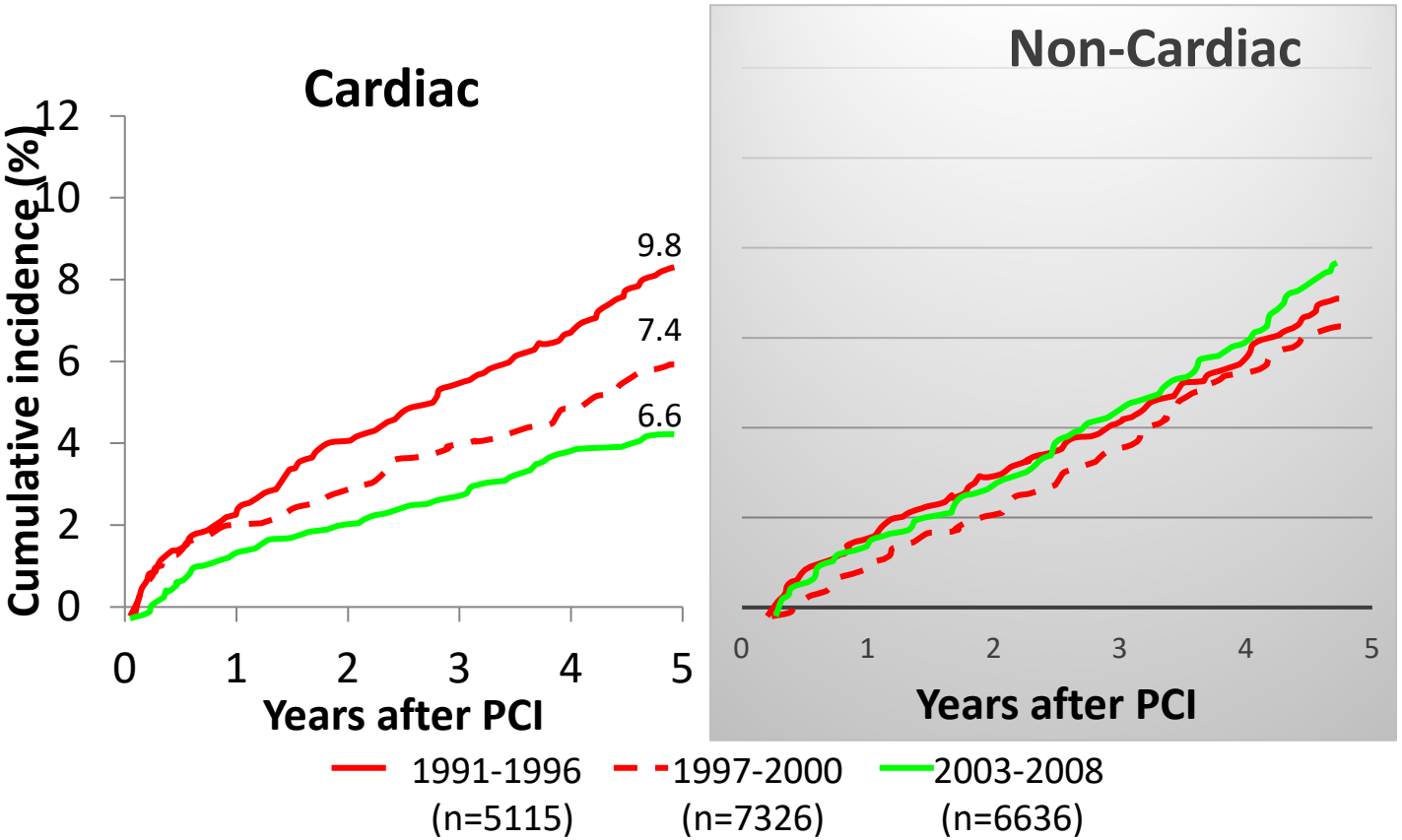
Table I Examples of evidence–based cardiovascular medicine trials not using total mortality as the primary endpoint

Trial	Treatment	Endpoint
ISIS 2	Aspirin/streptokinase vs. placebo	Vascular death
CURE	Clopidogrel vs. placebo	Cardiovascular death, nonfatal MI, or stroke
PLATO	Ticagrelor vs. clopidogrel	Death from vascular causes, MI, or stroke
ISCHEMIA	Revascularization vs. conservative strategy	Cardiovascular death, MI, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest

MI, Myocardial infarction.

White. Eur Heart J. 2021 Dec 1;42(45):4697-4698.

Trends in cause of death following PCI



Spoon et al. Circ 2014;129:1286-1294

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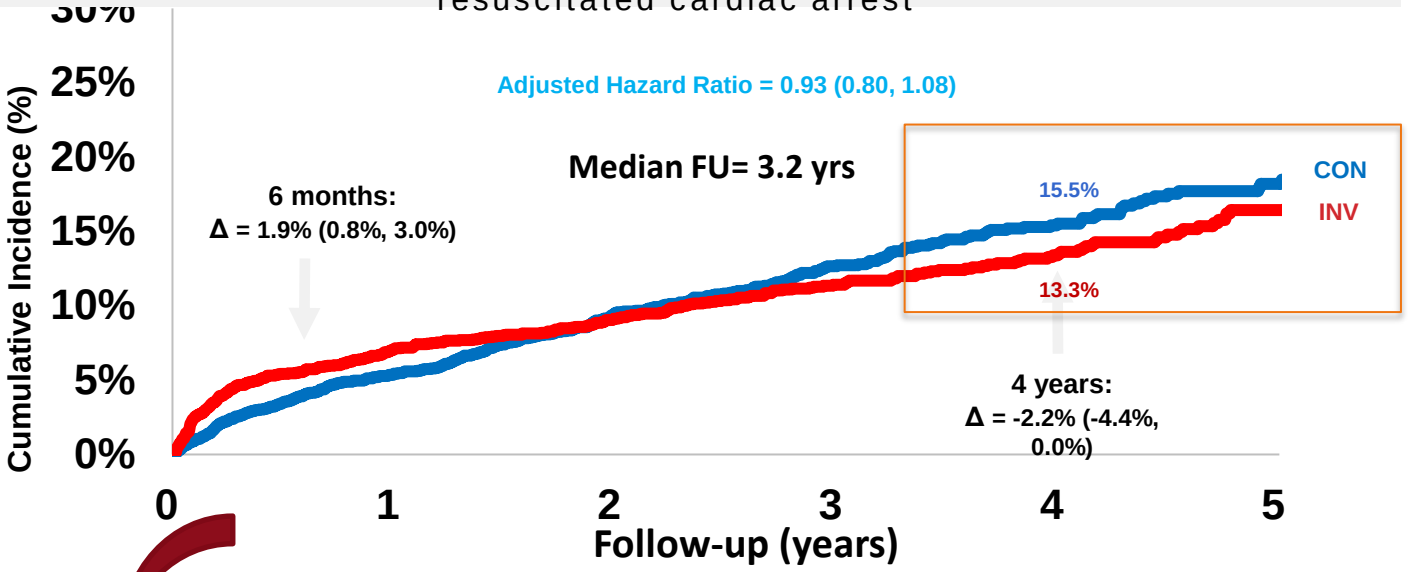
White. Eur Heart J. 2021 Dec 1;42(45):4697-4698.

ISCHEMIA trial Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest



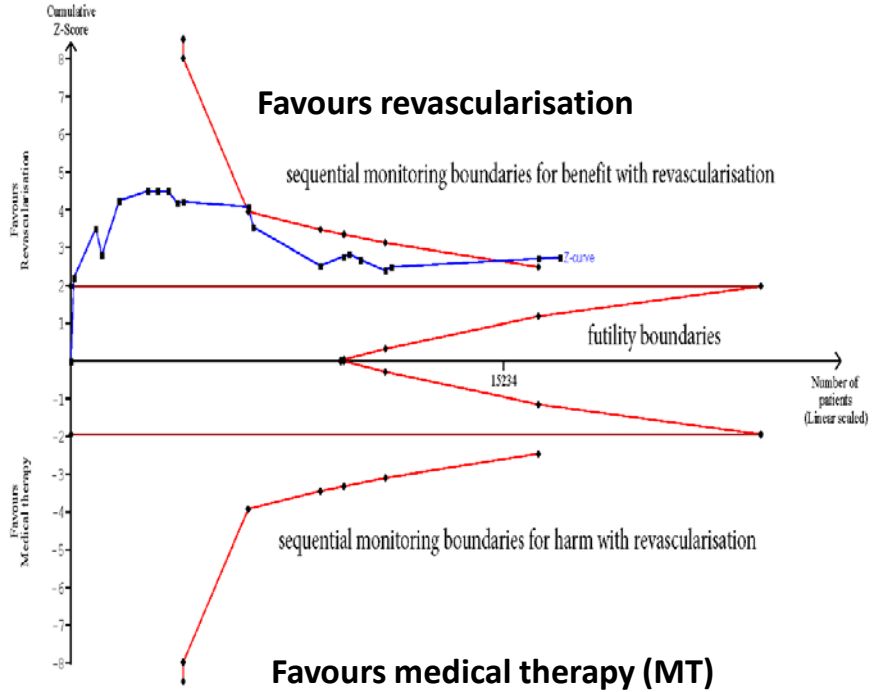
Cardiovascular Death	Cumulative difference
2-year	-0.3%
3-year	-0.6%
4-year	-1.0
5-year	-1.3%

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

Adequate power for mortality as individual endpoint

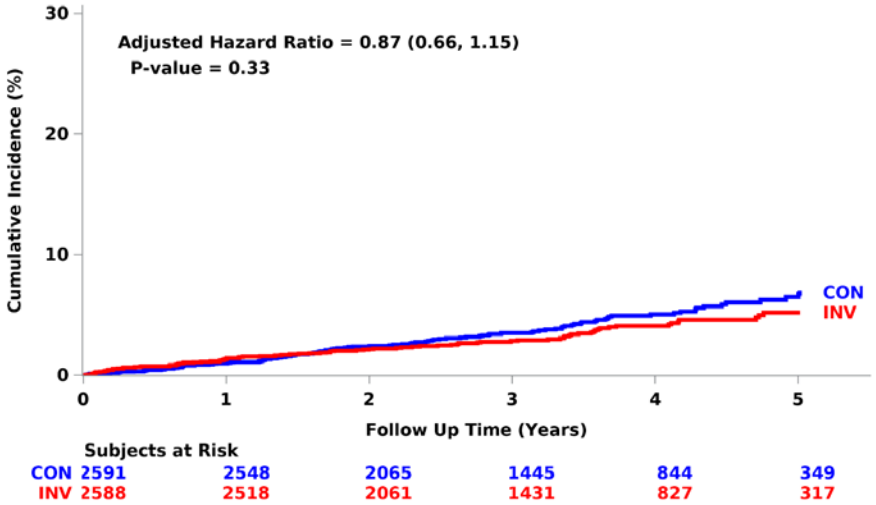
Navarese. Eur Heart J. 2021;42:4699-4700.

- **15.000 pts required to address cardiac mortality on Trial Sequential Analysis**



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

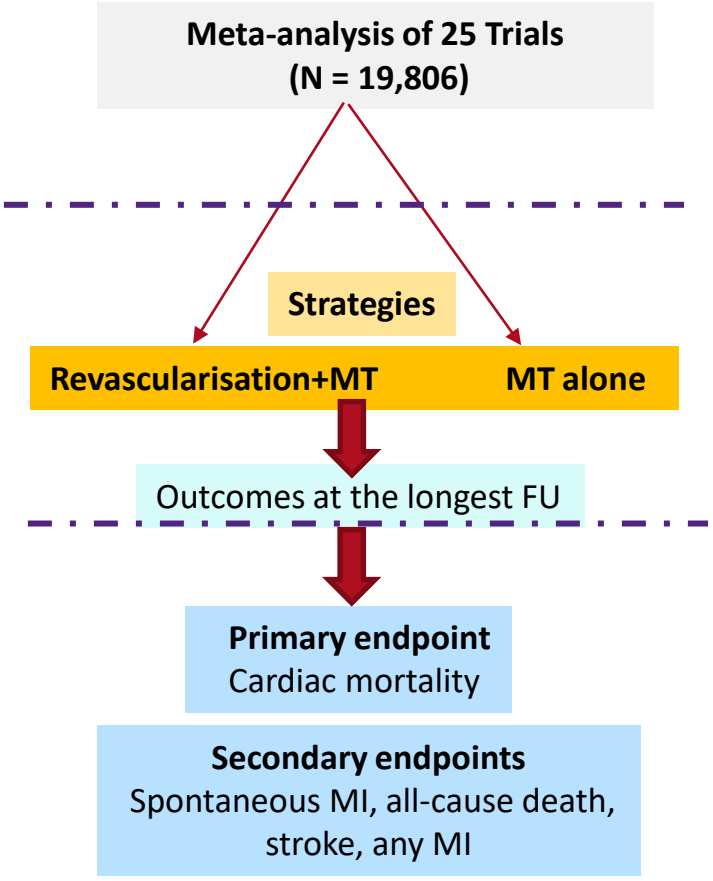
ISCHEMIA trial: n= 5.179



Revasc+MT vs MT in clinically stable patients: Study design

Methods

- Rates rather than crude number of events because they incorporate trial duration
- Heterogeneity assessed by I^2 statistic
- Random-effects model (primary model)
  - Trial sequential analysis with sequential monitoring boundaries (benefit/futility)
- Sensitivity analysis without ACS, CTO, CABG
- Meta-regressions for the impact of follow-up duration, trial medications, absolute differences for MI on cardiac death

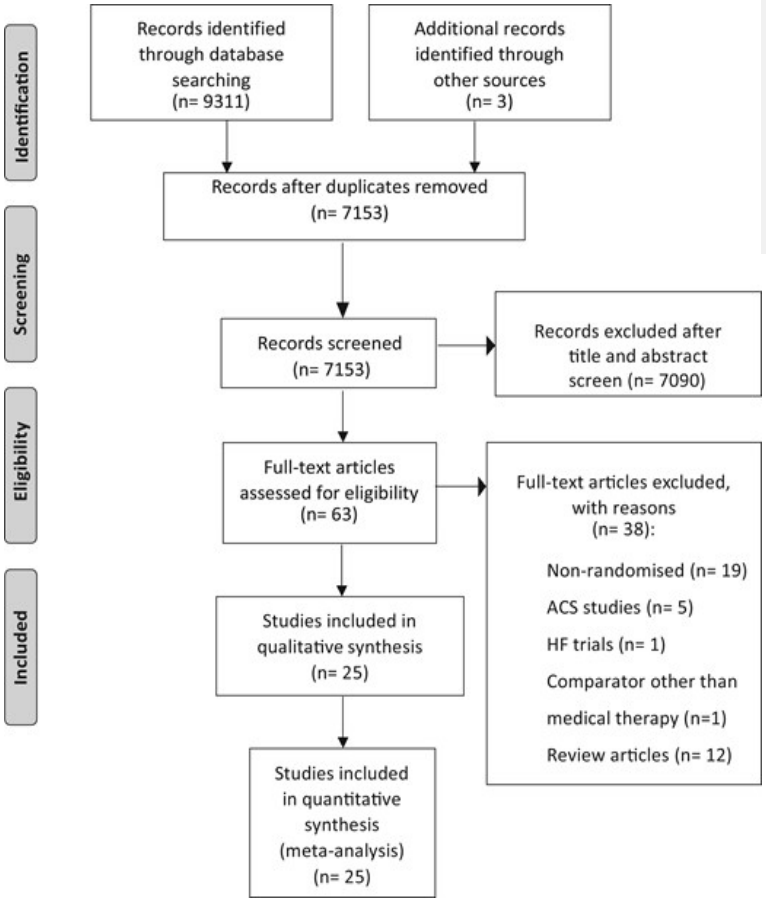


Inclusion Criteria

- Clinically stable CAD pts undergoing elective revascularization (planned, deferrable, non urgent/non emergent) *plus medical therapy (MT)* or *medical therapy alone*
- Clinical stability defined by absence of symptoms or signs of ischaemia at rest

Navarese. Eur Heart J. 2021;42:4699-4700.

Updated Systematic search

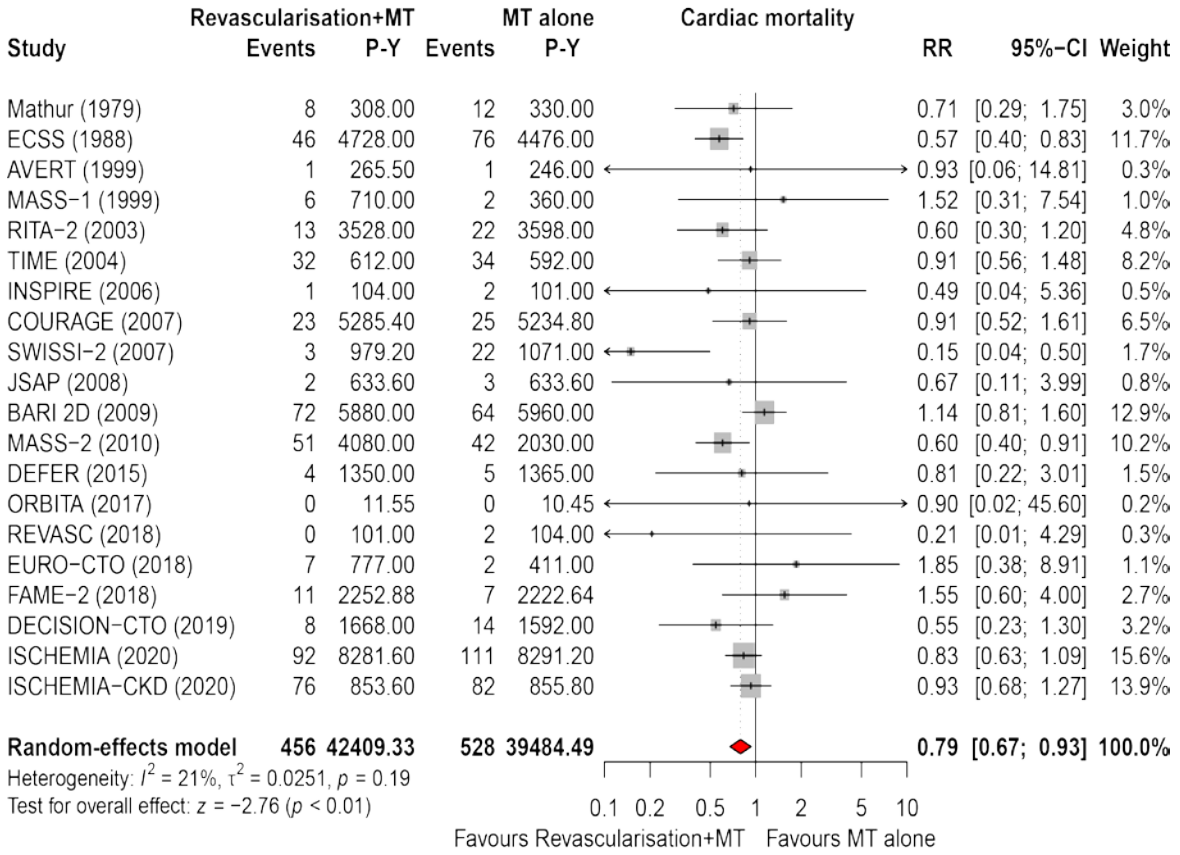


Post-ACS studies additional criteria:

1) absence of symptoms or signs of ischaemia at rest.

2) by protocol a myocardial stress test as an additional criterion of clinical stability.

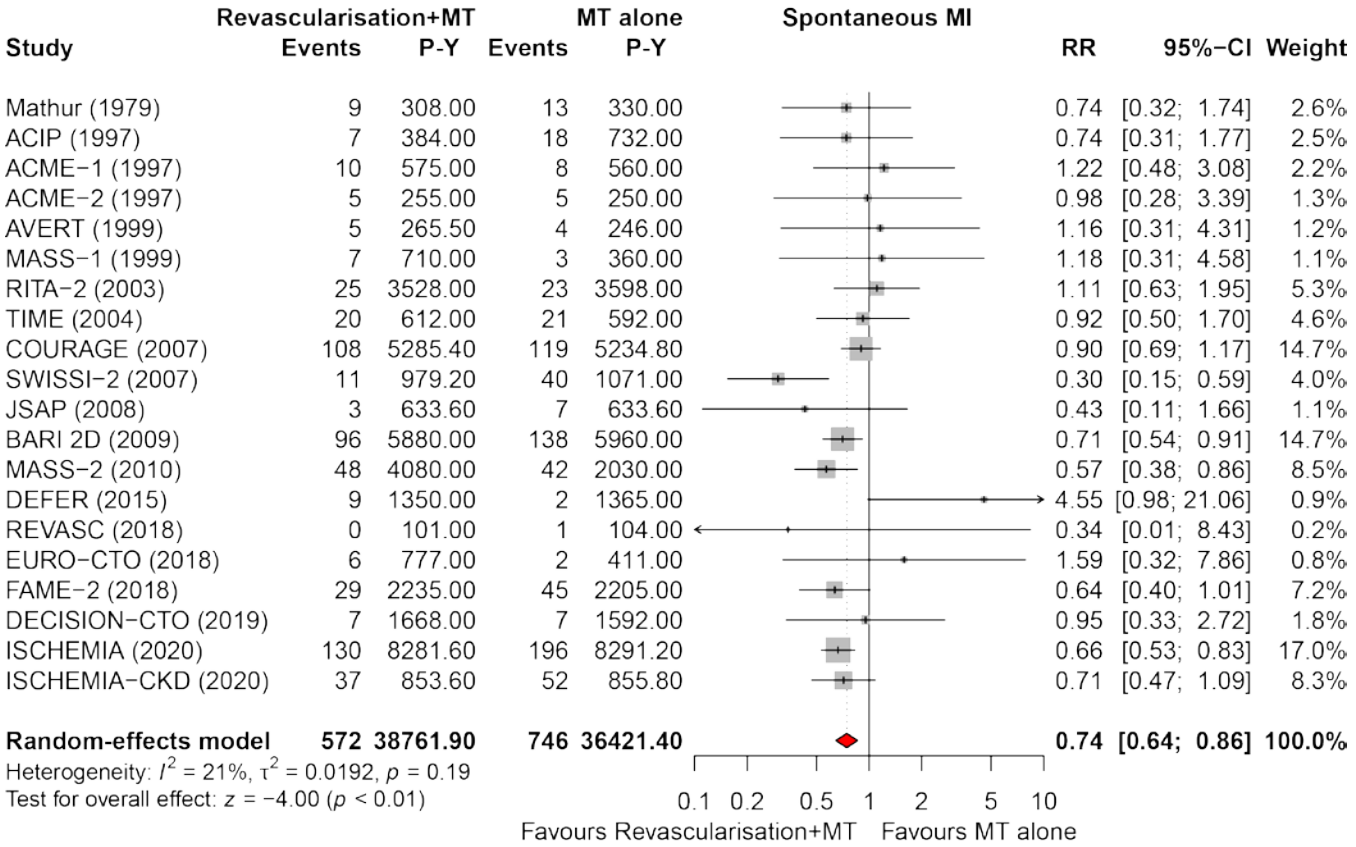
Revasc+MT vs MT alone in stable patients: Primary endpoint



21% cardiac death risk reduction with revasc + MT vs MT alone at 5.7 yrs

Navarese. Eur Heart J. 2021;42:4699-4700.

Secondary endpoint: Spontaneous MI



26% spontaneous MI risk reduction with revasc + MT vs MT alone

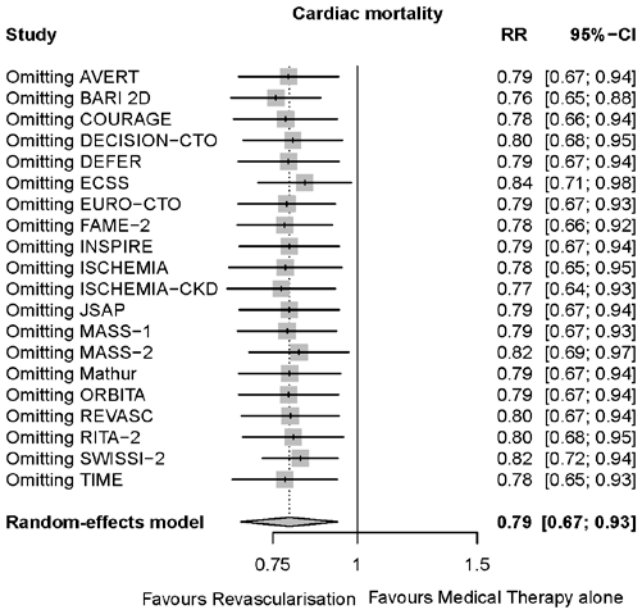
Navarese. Eur Heart J. 2021;42:4699-4700.

Benefits of revascularisation: overall and in prespecified subgroups

Navarese. Eur Heart J. 2021;42:4699-4700.

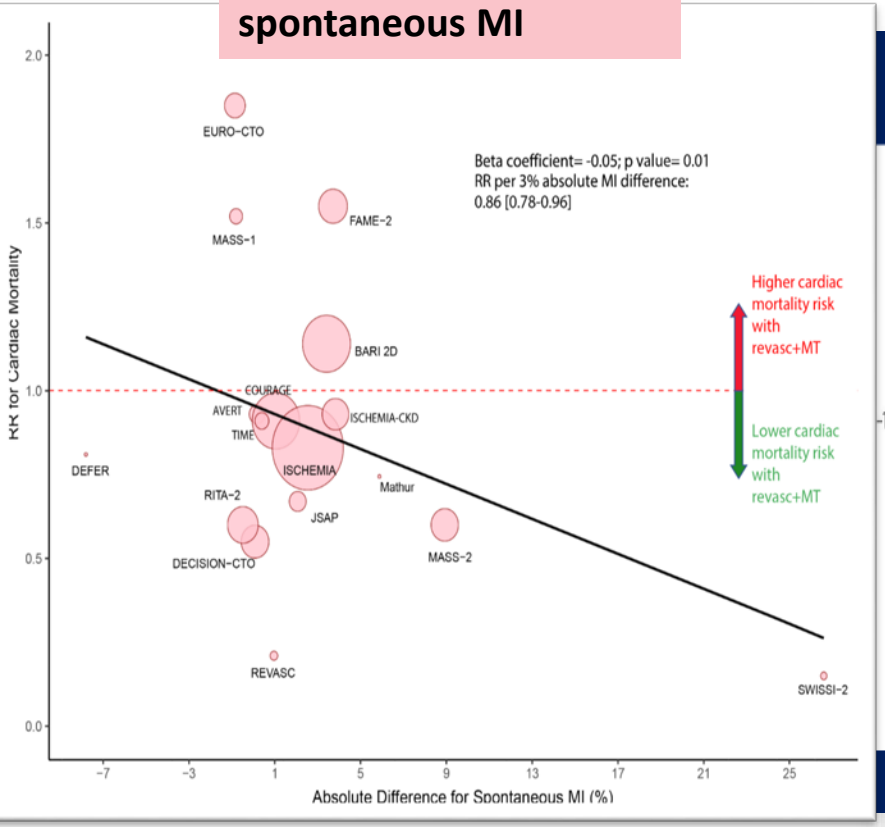
Sensitivity analyses excluding studies

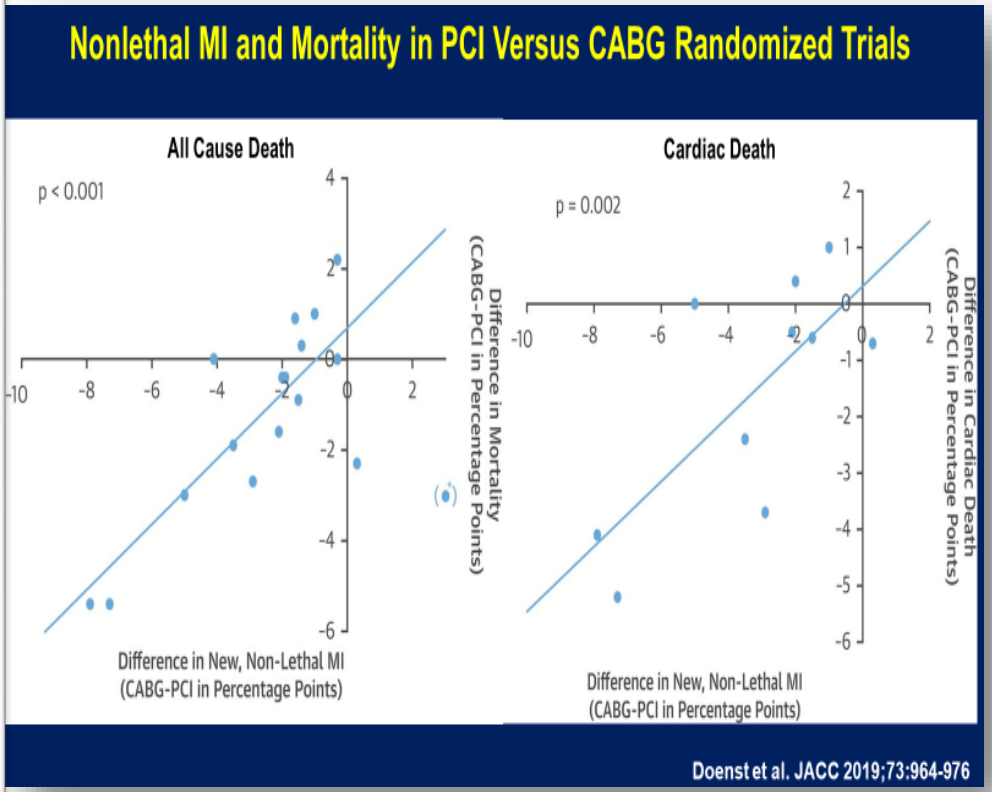
- After ISCHEMIA exclusion (~ 1.3 ARD at 5 yrs): RR 0.78 [0.65; 0.95]



Lower spontaneous MI with revasc ≈ lower cardiac death

Significant association btw cardiac death and spontaneous MI

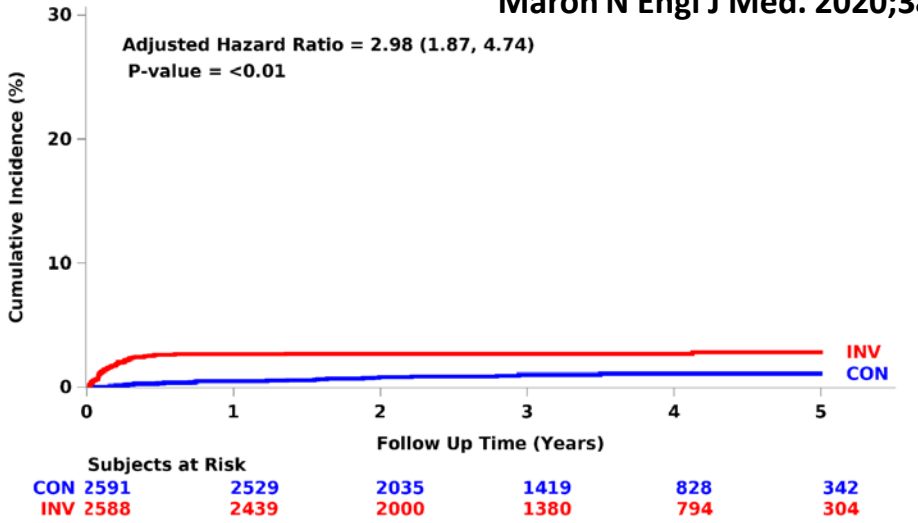


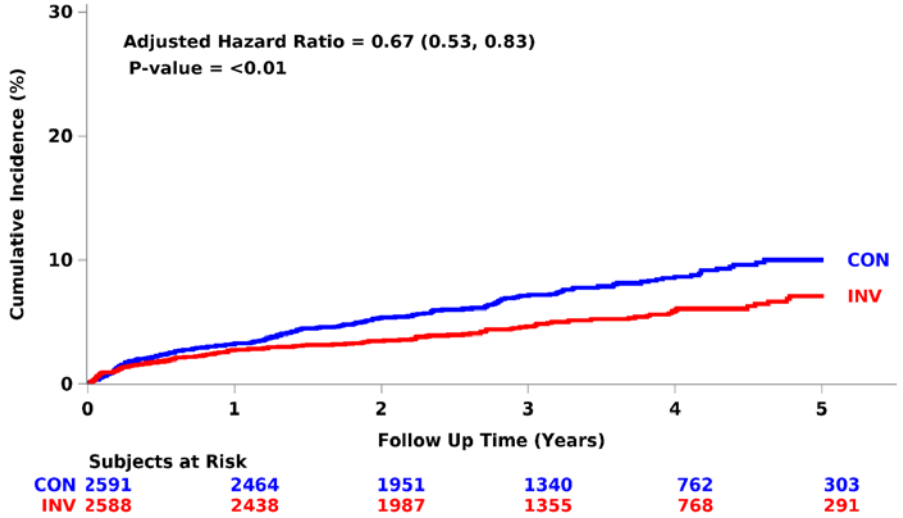


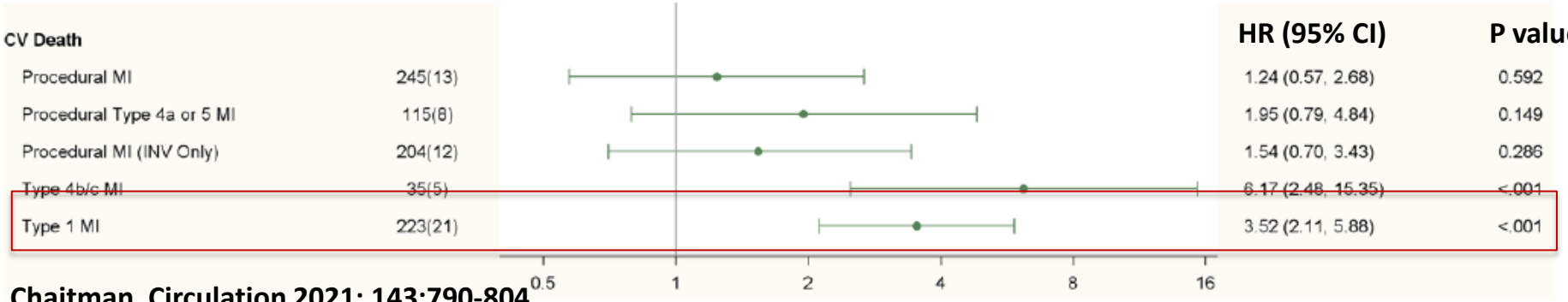
Procedural MI
Type 4a or 5 MI

Spontaneous MI: types 1, 2, 4b, or 4c

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

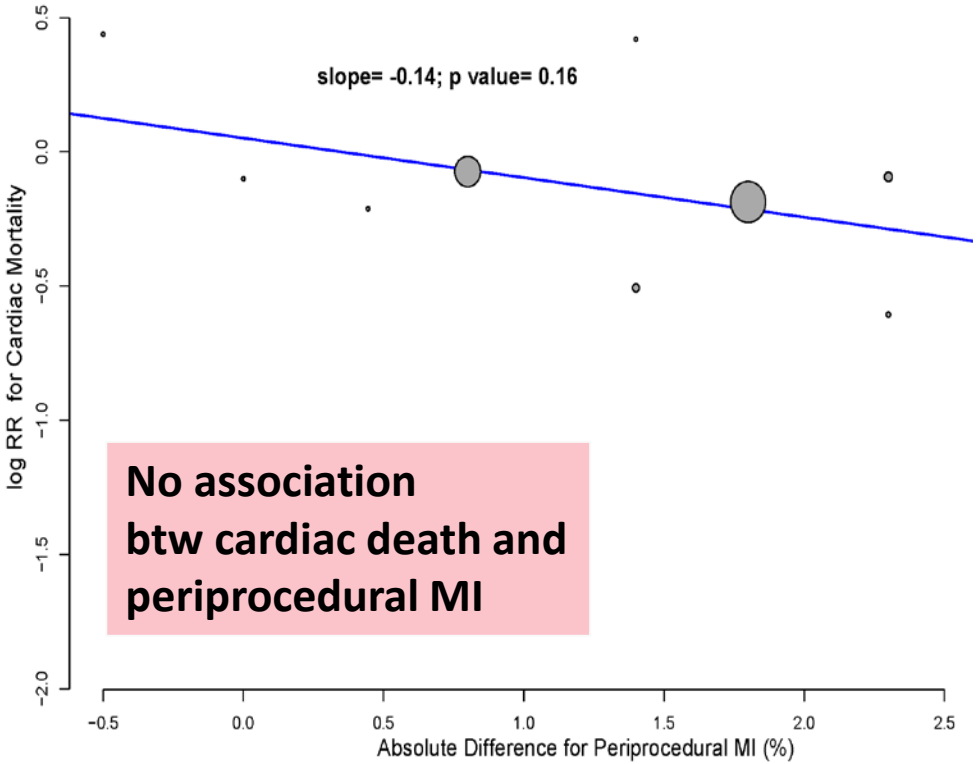






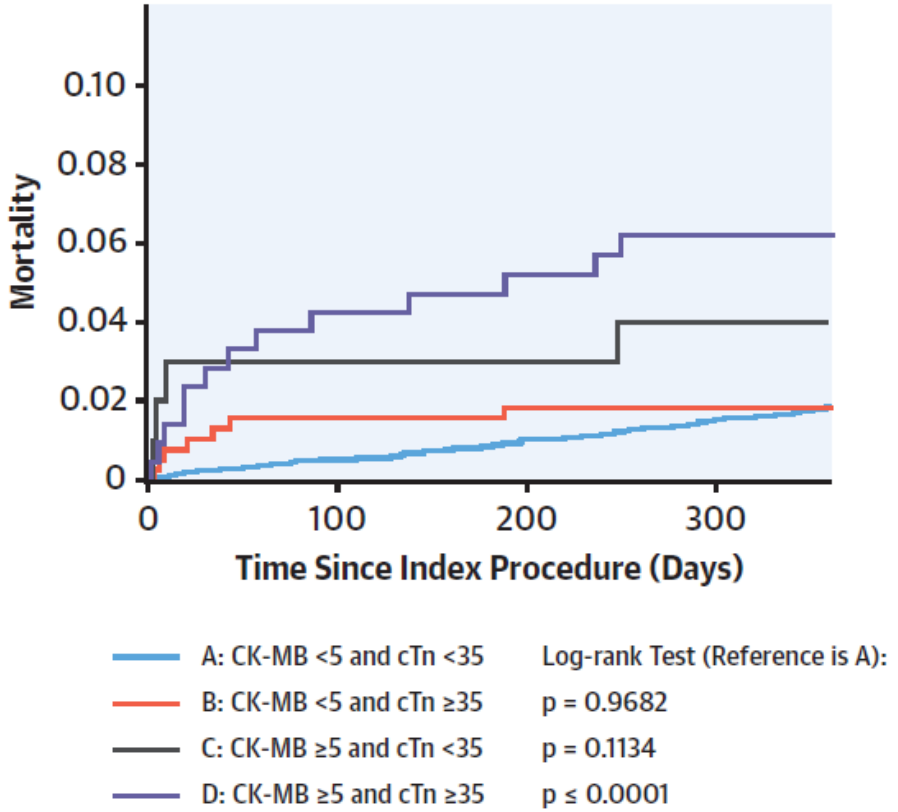
Chaitman. Circulation 2021; 143:790-804

Impact of periprocedural MI on mortality



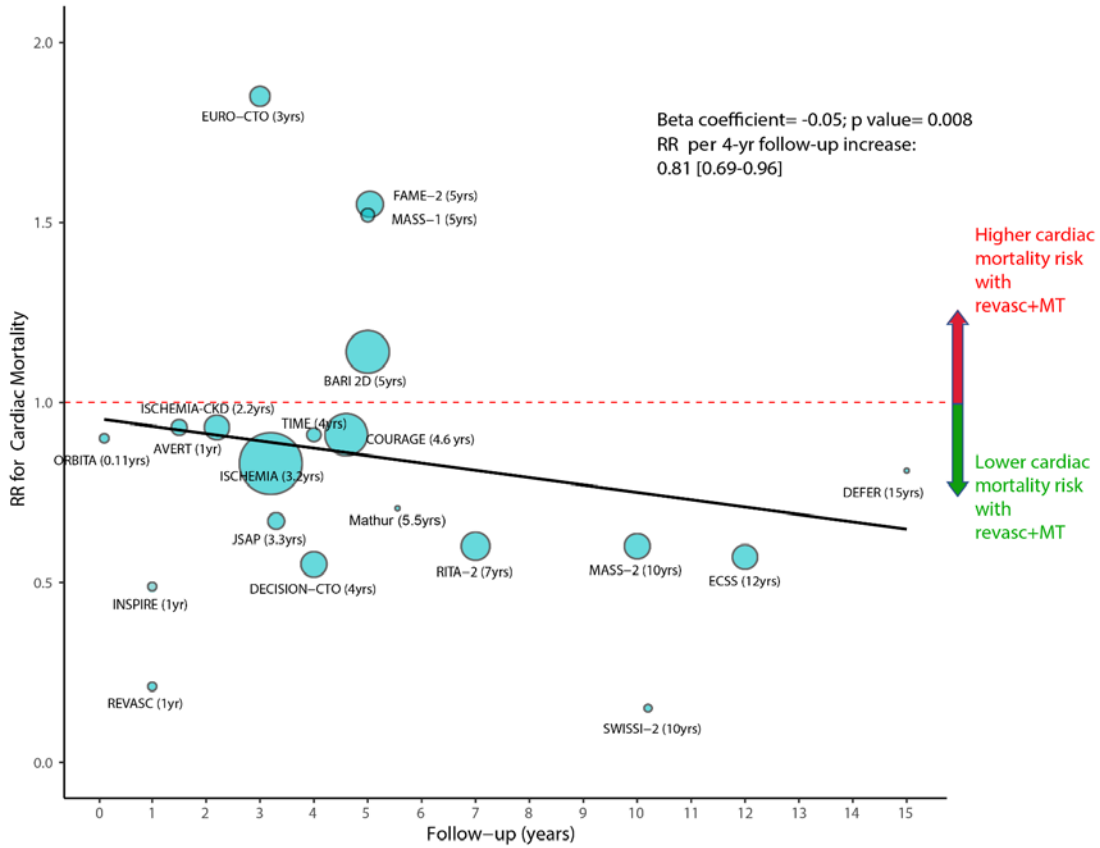
No association btw cardiac death and periprocedural MI

Navarese et al. Eur Heart J. 2021 May



Garcia-Garcia J Am Coll Cardiol Intv 2019;12:1954–62

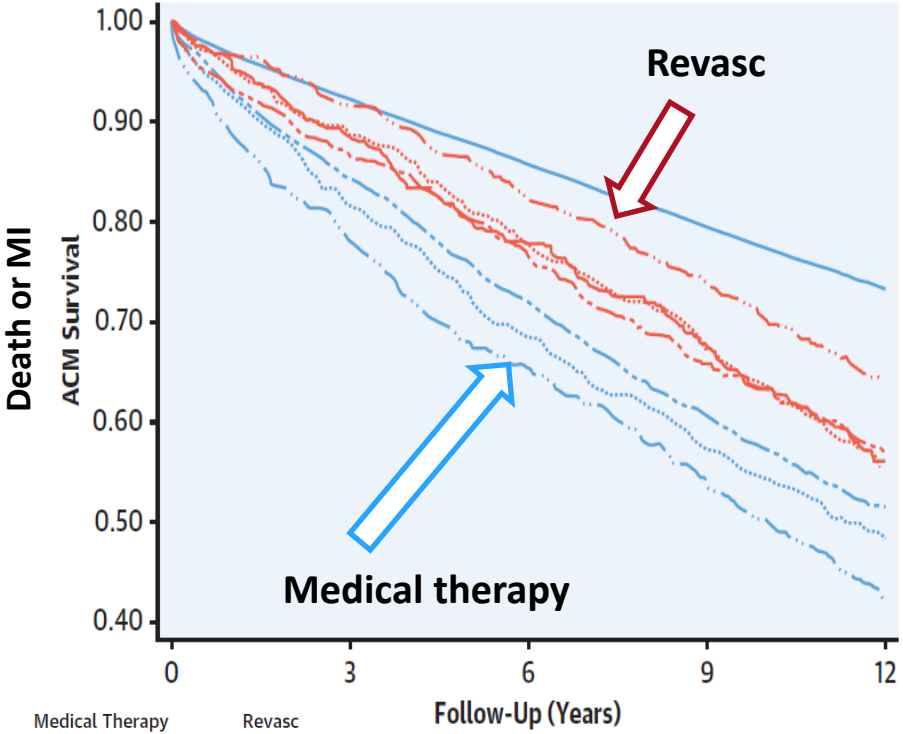
Cardiac death and length of follow-up



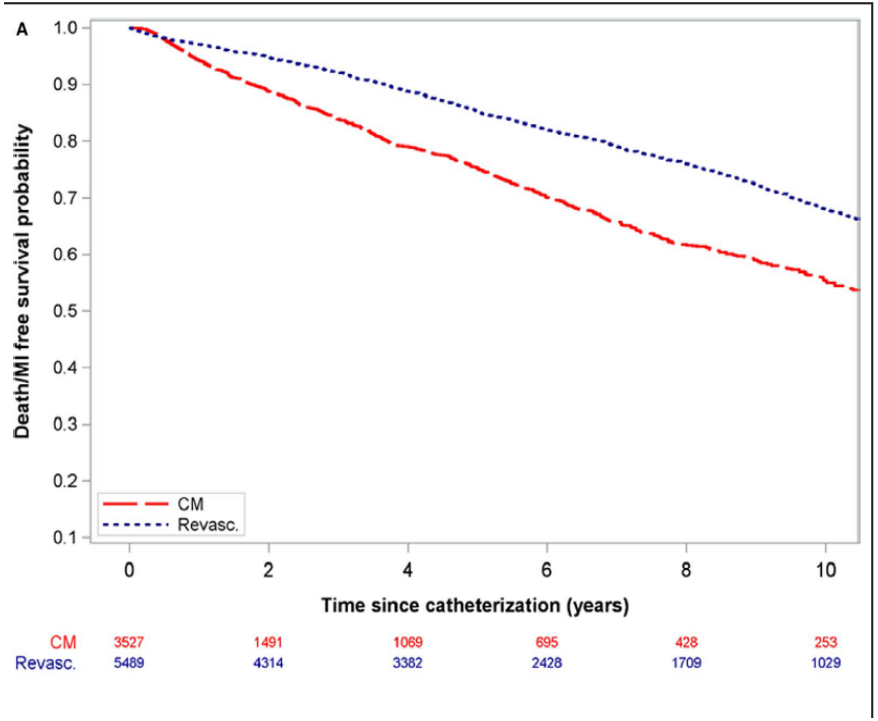
19% cardiac death relative risk reduction per 4-yr follow-up increase: 0.81 [0.69-0.96]

Navarese et al. EHJ 2021;42:4638-51

Consistent lower mortality or MI at long term (10 yrs) in large-scale observational studies

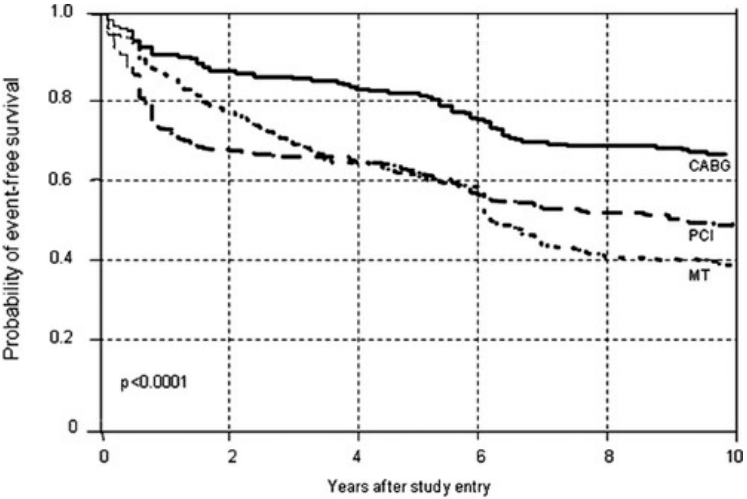


Rozanski JACC 2022



Bainey JAHA 2021

Outcomes at 10 year F/U in the MASS-2 RCT



Patients at risk

Treatment Group	Initial	3 Year	6 Year	10 Year
CABG	203	175	155	150
PCI	205	147	130	108
MT	203	140	121	93

	PCI	CABG	MT	P
Primary endpoint	42.4	33	59.1	<0.001
All-cause death	24.1	51.1	31	0.08
Cardiac death	14.3	10.8	20.7	0.01

Question 2:

Does the suboptimal therapy in older studies favor revasc?

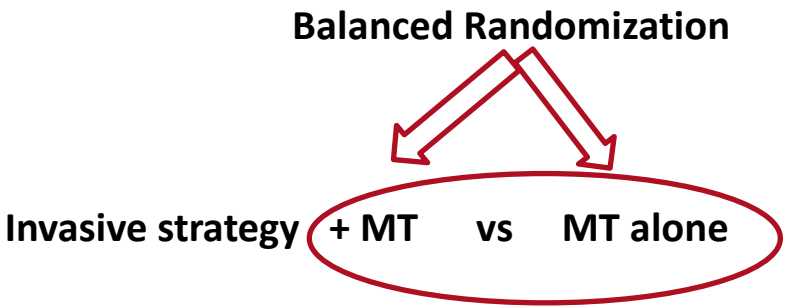
Hueb. Circulation. 2010 Sep 7;122(10):949-57

Answer to question 2

Variable	Beta	P value
Antithrombotic agents	- 0.01	0.27
Statins	0.001	0.71
Beta-blockers	- 0.001	0.91
ACE inhibitors/ARBs	0.005	0.11
Study year	0.01	0.16

No significant association btw effects of strategy on cardiac death and
- medical therapy
- study year

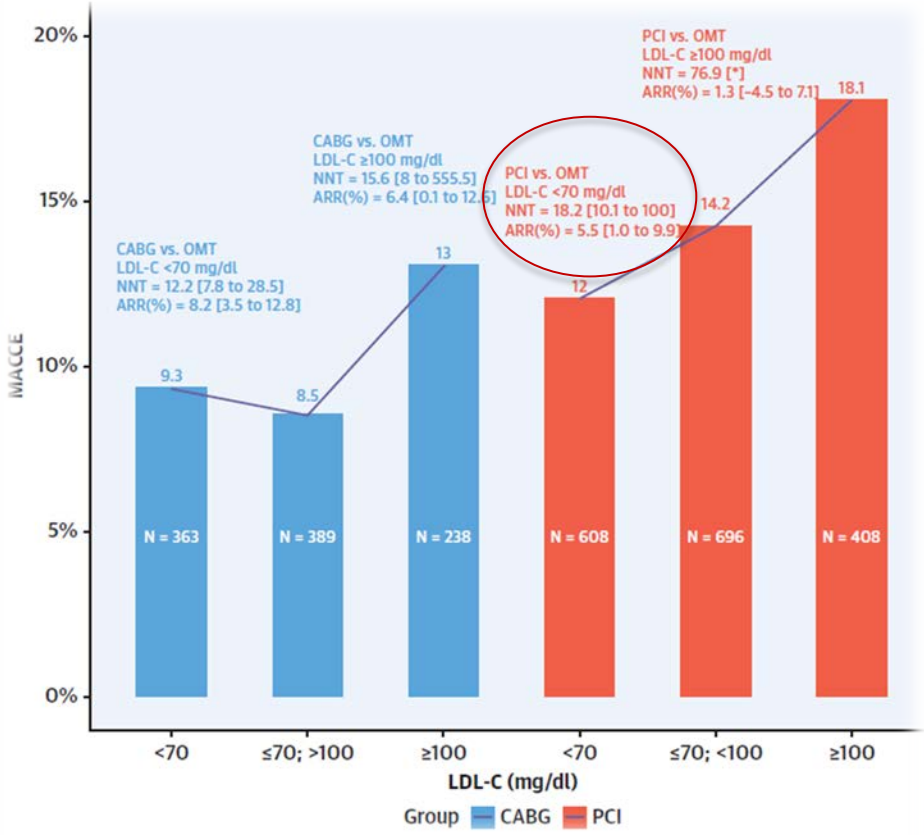
- **Balanced MT in both arms in each RCT (strength of RCTs)**
- **No effect of trial chronology**



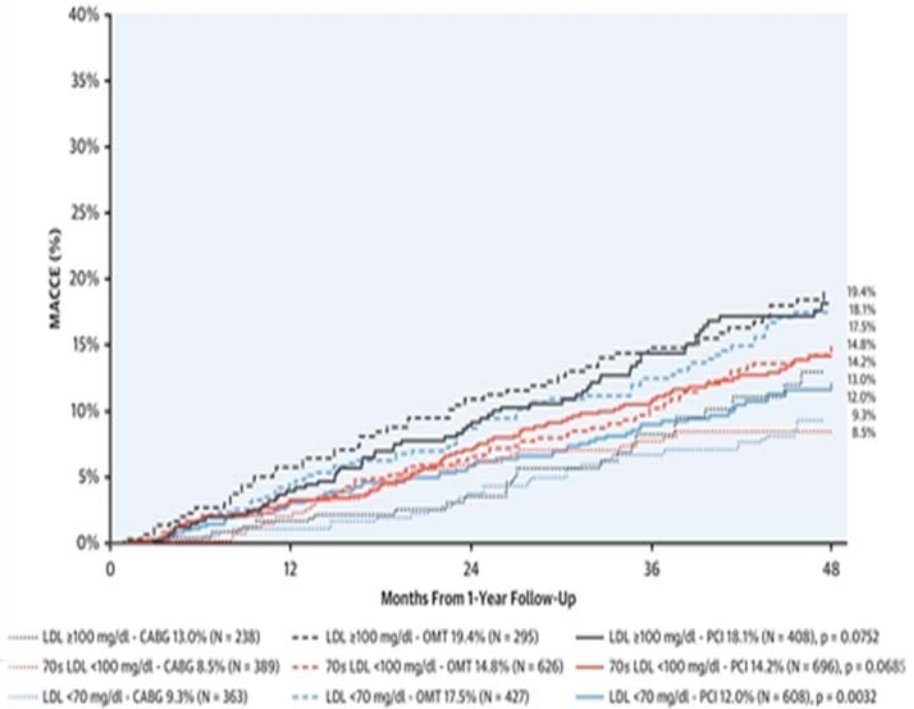
Navarese. Eur Heart J. 2021;42:4699-4700.

Sinergy between revascularisation+MT

MACCE with PCI and CABG based on LDL-C thresholds in DM: pooled analysis

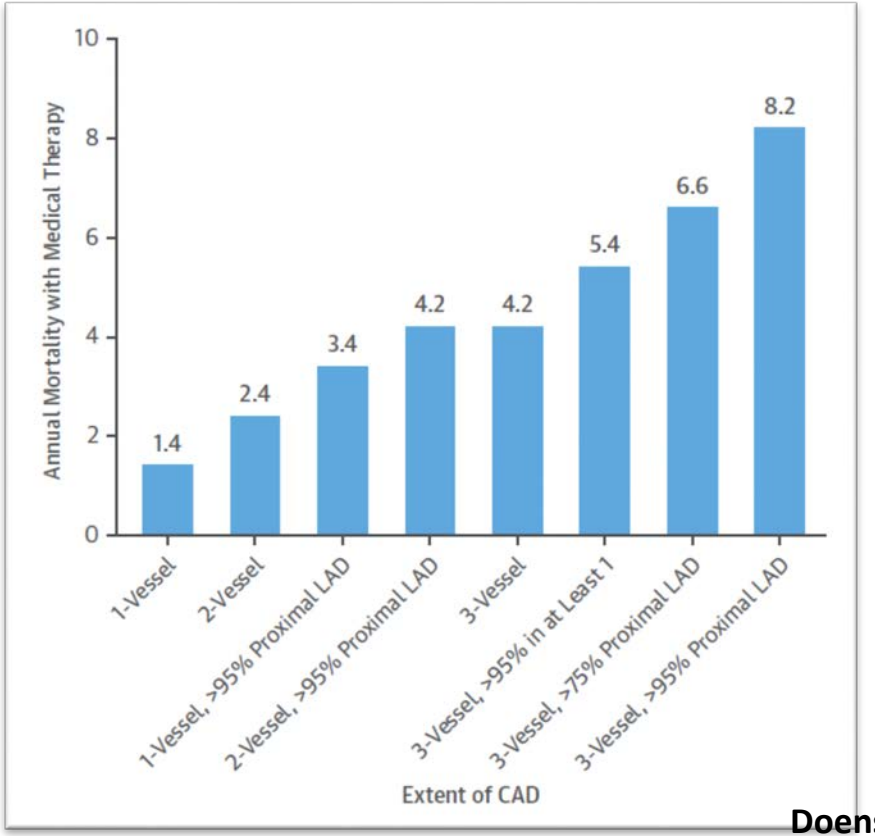


Navarese et al. J Am Coll Cardiol 2020;76:2208–11



Farkouh, M.E. et al. J Am Coll Cardiol. 2020;76(19):2197-207.

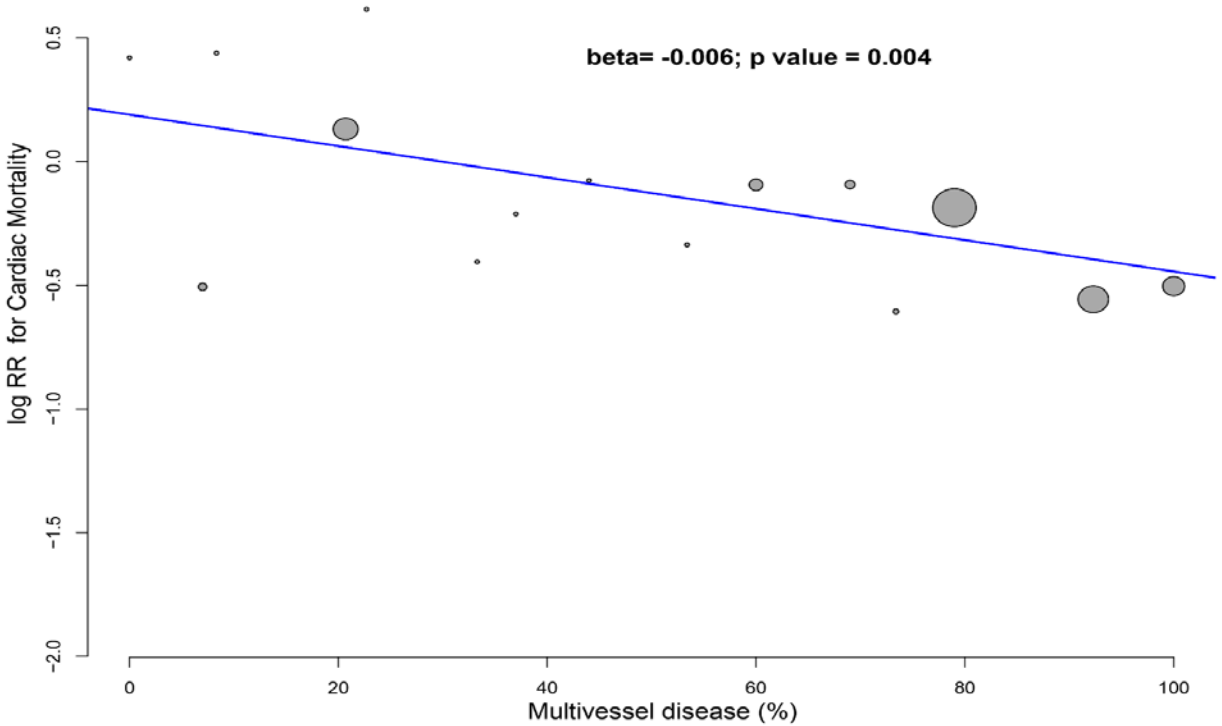
Annual mortality risk as a function of the severity of coronary artery disease (CAD)



Doenst. J Am Coll Cardiol. 2019;73:964–76.

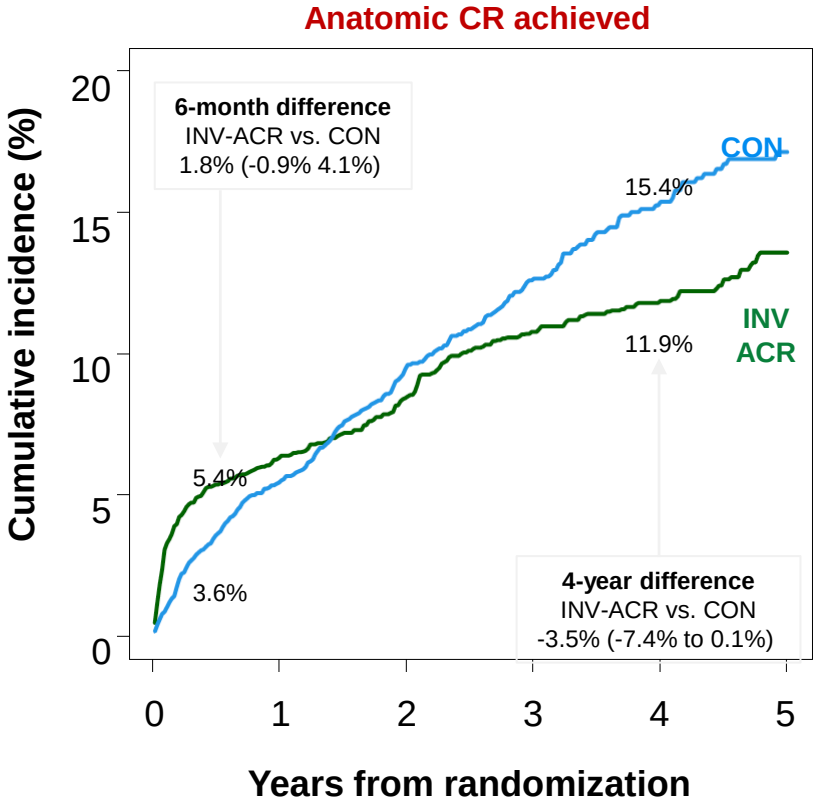
Risk multiplier

Meta-regression of cardiac death in relation to % of MV disease



Navarese. Eur Heart J. 2021;42:4699-4700.

Outcomes for INV-CR versus CON: Primary endpoint



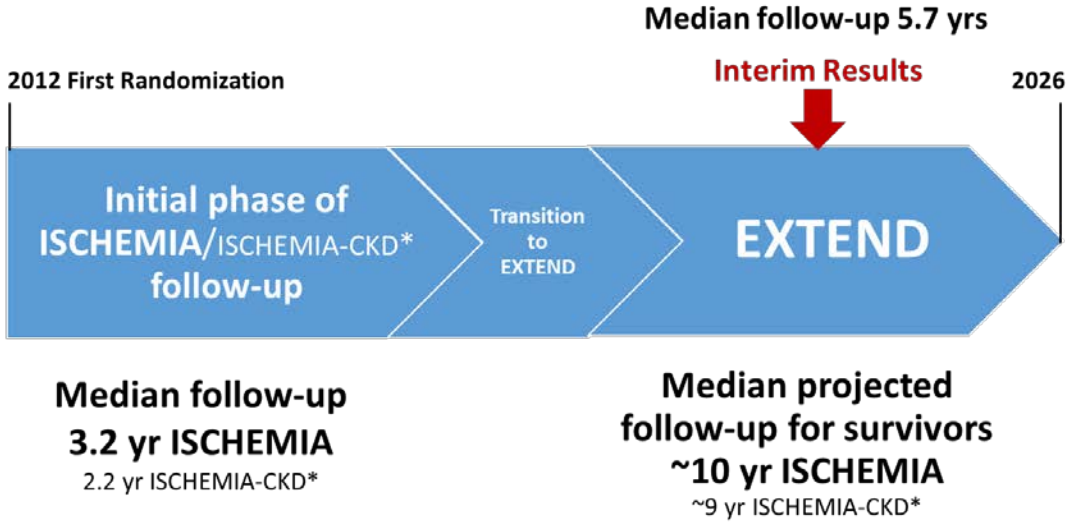
CV death or MI	Difference INV-CON [95% CI]
Two-vessel CAD ≥70% or three-vessel ≥50% or 70% proximal LAD	-5.4% (-14.9%;-4.2%)
Three vessel CAD ≥70% or two-vessel ≥70% including proximal LAD	-6.3% (-12.4%;-0.2%)

Stone GW - ACC 2021

Reynolds . Circulation. 2022 Jun 7;145(23):e1072. doi:

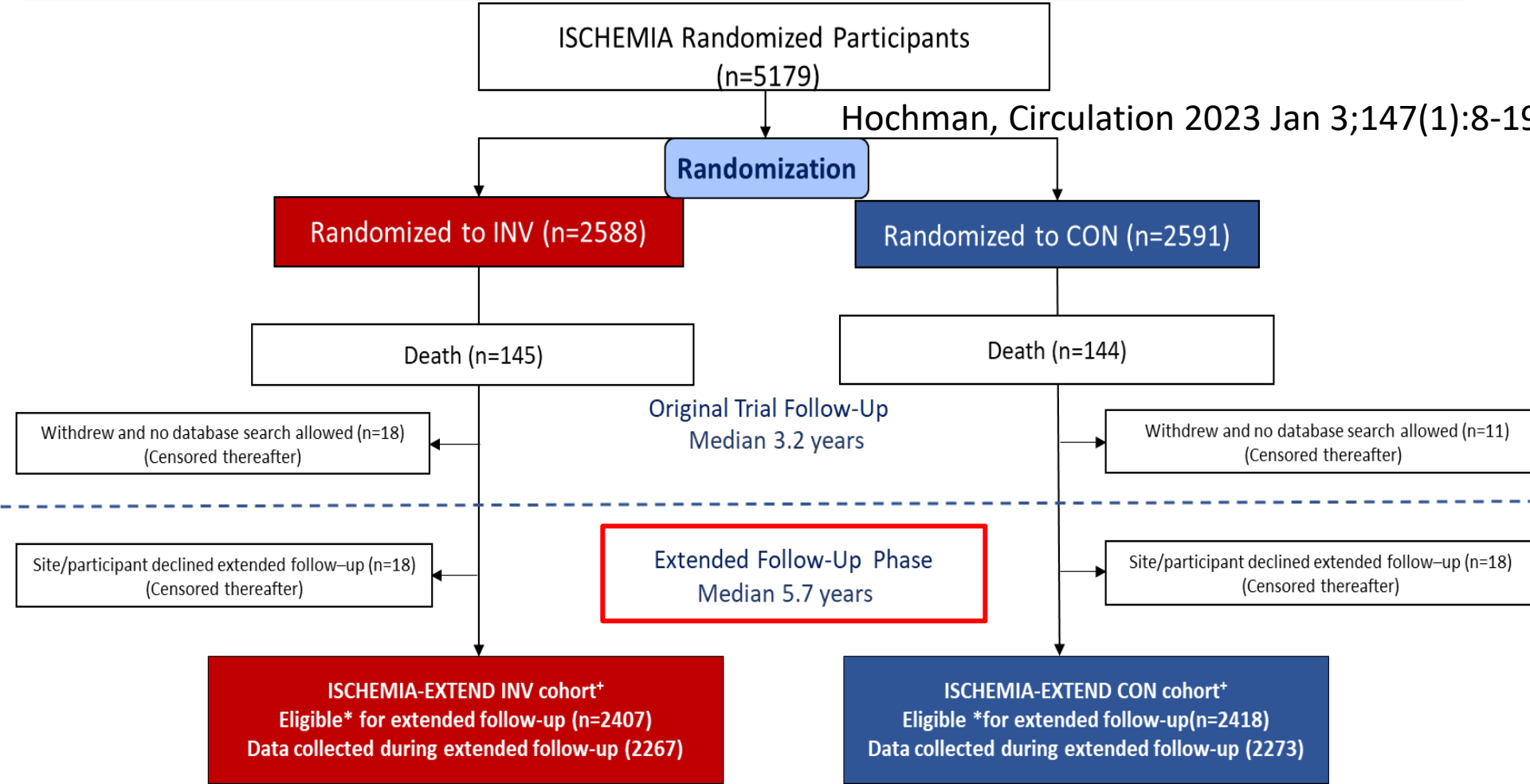
Long-term follow-up in ISCHEMIA-EXTEND

Hochman, Circulation 2023 Jan 3;147(1):8-19.



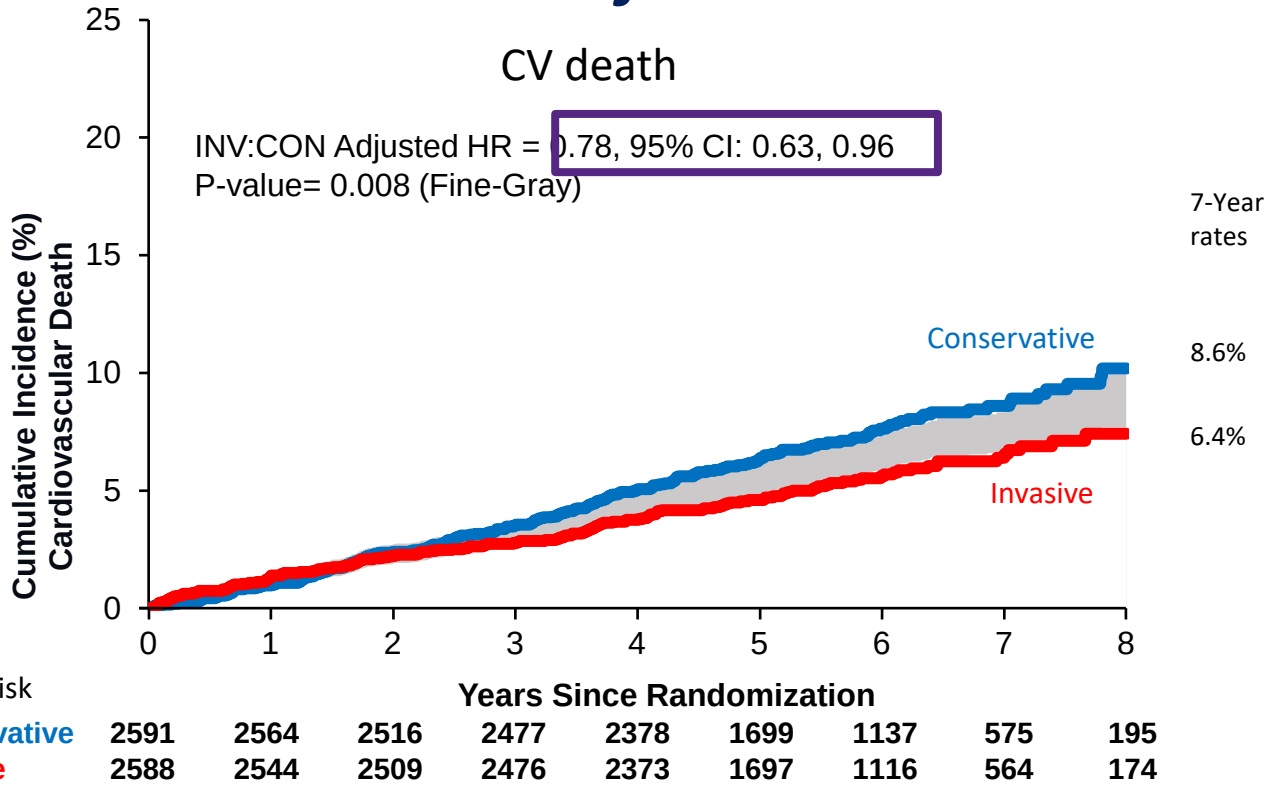
ISCHEMIA-EXTEND was designed as a pragmatic long-term follow-up study of mortality

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



Extended follow-up - 5.7 years median

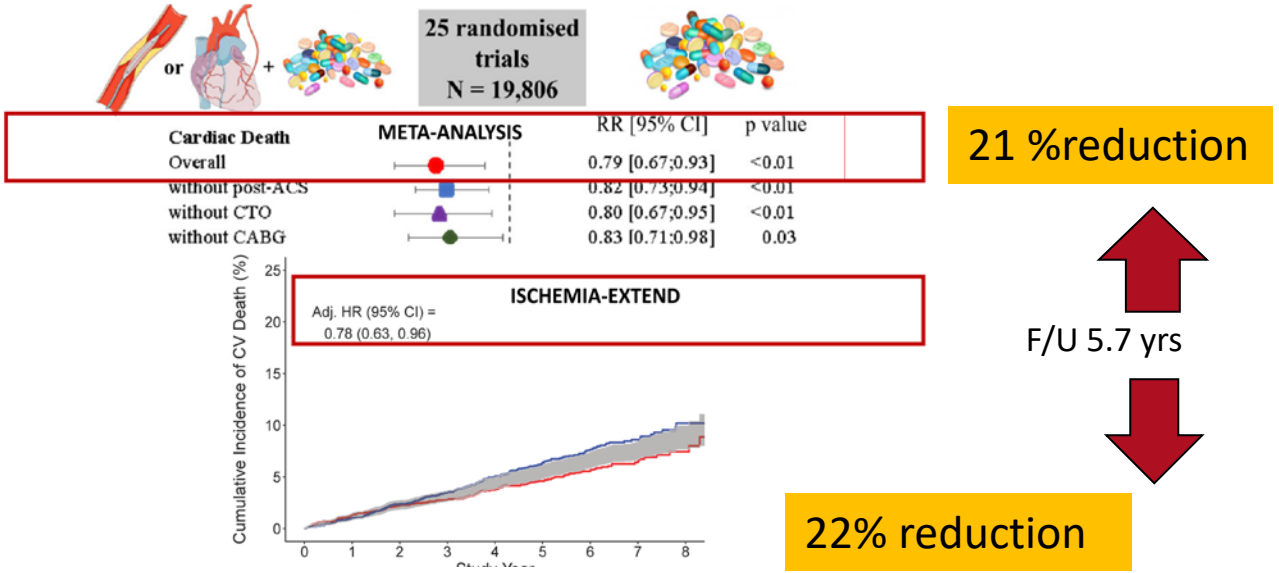
Cumulative incidence of cardiovascular death



Hochman, Circulation 2023 Jan 3;147(1):8-19.

A meta-analysis showed a significant cardiac mortality reduction in CCS with revascularization+ medical therapy (MT) vs MT alone. These findings have been confirmed in the ISCHEMIA-EXTEND study.

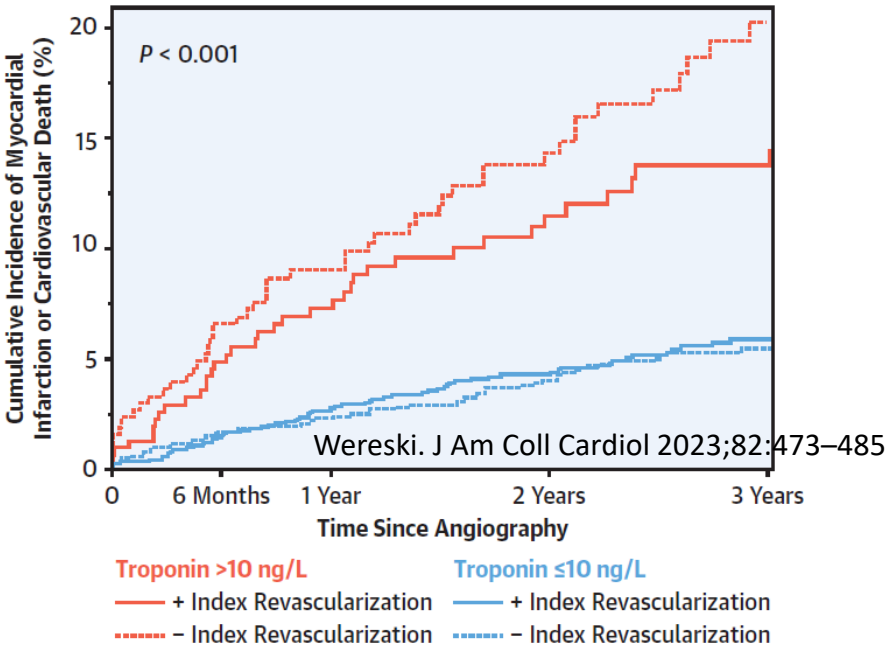
Navarese, Eur Heart J. 2021 ;42(45):4638-4651.



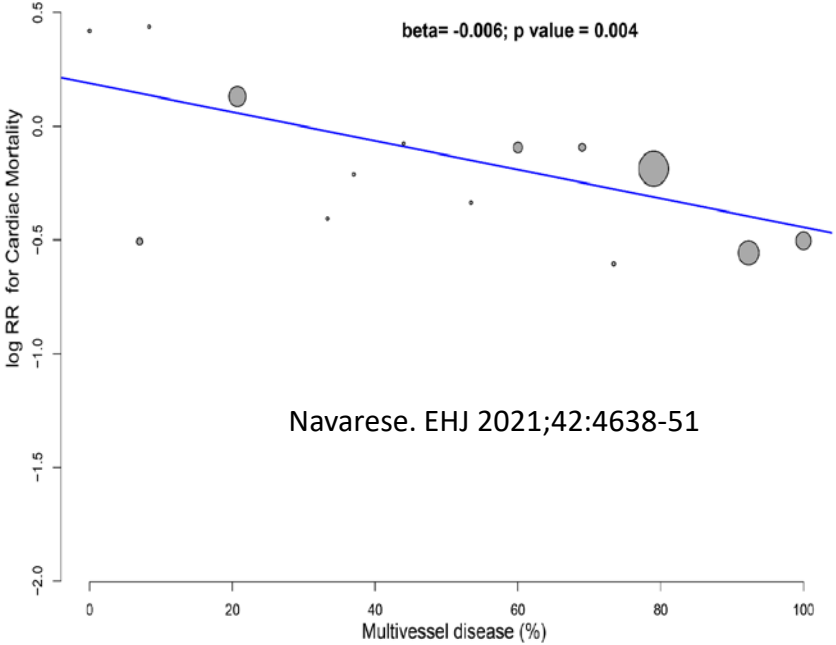
Hochman, Circulation 2023 Jan 3;147(1):8-19.

Cardiac mortality reduction multipliers

cardiac mortality with revasc+MT vs MT alone and MV disease



Wereski. J Am Coll Cardiol 2023;82:473–485



Navarese. EHJ 2021;42:4638-51

Final remarks

Clear benefits of revascularization vs. OMT alone are a function of:

- The synergy of revasc and optimal MT strategies that ↓ *patient vulnerability*
- Appropriate endpoint selection: ↓ *cardiac mortality*-more specific than all-cause death- to avoid *competing risks* that dilute benefits, driven by ↓ spontaneous MI vs no impact of small procedural MIs.
- Length of follow-up(>4.5 yrs) to allow *for* event ↓ over time and event accrual in the untreated group. Every 4 years, a 19% reduction of cardiac death events may be expected with revasc.
- Significantly ↓ CV mortality and spontaneous MI events expected on a global scale with large numbers (N > 15000 for CV mortality) of individuals treated
- Extent, severity and ischemic impact of CAD, and the likelihood of achieving complete revascularisation increase the chance of improved outcomes.

Contact: **elianonavarese@gmail.com**; Twitter: **@ElianoNavarese**

E(*expected CV death reduction from revasc*) =M(*MV disease*)C(*cycle of life-FU*)^2

Contacts:
elianonavarese@gmail.com
Twitter:
@ElianoNavarese

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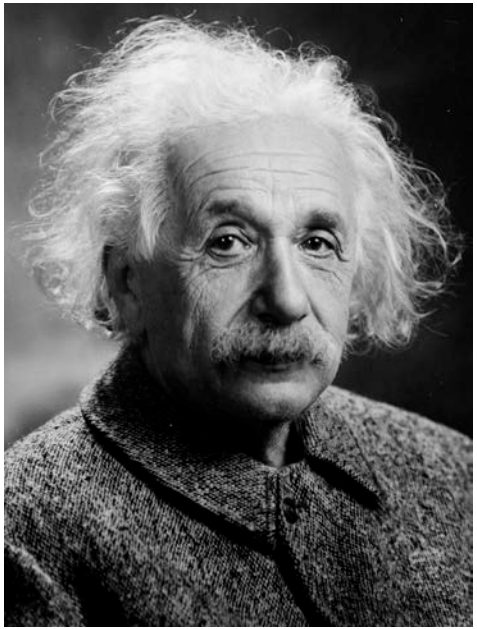

If your patient has longer life expectation, risk multipliers such as multivessel disease, revascularization will likely reduce cardiac mortality at FU. Be patient and you will observe the effect.

Thank you!