Cardiac mortality after revascularization in light of the ISCHEMIA trial

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Disclosures

Research grants from Abbott, Amgen, outside the submitted work.

- Lecture fees/honoraria from Amgen, Astra-Zeneca, Bayer, Pfizer and Sanofi-Regeneron, KYE Pharmaceuticals.
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>
<thead>
<tr>
<th>Table 1</th>
<th>Examples of evidence–based cardiovascular medicine trials not using total mortality as the primary endpoint</th>
</tr>
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<tr>
<td>Trial</td>
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</tr>
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<td>ISIS 2</td>
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<td>ISCHEMIA</td>
<td>Revascularization vs. conservative strategy</td>
</tr>
</tbody>
</table>

White. Eur Heart J. 2021 Dec 1;42(45):4697-4698.
Trends in cause of death following PCI

Cumulative incidence (%)

Years after PCI

Cardiac

- 1991-1996 (n=5115)
- 1997-2000 (n=7326)
- 2003-2008 (n=6636)

Non-Cardiac

Years after PCI

Spoon et al. Circ 2014;129:1286-1294
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 1. Examples of evidence–based cardiovascular medicine trials not using total mortality as the primary endpoint

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

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

Adjusted Hazard Ratio = 0.93 (0.80, 1.08)

Median FU= 3.2 yrs

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

Adequate power for mortality as individual endpoint


- 15,000 pts required to address cardiac mortality on Trial Sequential Analysis

Favours revascularisation

Favours medical therapy (MT)


ISCHEMIA trial: n= 5,179

Adjusted Hazard Ratio = 0.87 (0.66, 1.15)
P-value = 0.33
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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Revascularisation+MT Events</th>
<th>Revascularisation+MT P-Y</th>
<th>MT alone Events</th>
<th>MT alone P-Y</th>
<th>Cardiac mortality</th>
<th>RR</th>
<th>95%−CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathur (1979)</td>
<td>8</td>
<td>308.00</td>
<td>12</td>
<td>330.00</td>
<td></td>
<td>0.71</td>
<td>[0.29; 1.75]</td>
<td>3.0%</td>
</tr>
<tr>
<td>ECSS (1988)</td>
<td>46</td>
<td>4728.00</td>
<td>76</td>
<td>4476.00</td>
<td></td>
<td>0.57</td>
<td>[0.40; 0.83]</td>
<td>11.7%</td>
</tr>
<tr>
<td>AVERT (1999)</td>
<td>1</td>
<td>265.50</td>
<td>1</td>
<td>246.00</td>
<td></td>
<td>0.93</td>
<td>[0.06; 14.81]</td>
<td>0.3%</td>
</tr>
<tr>
<td>MASS-1 (1999)</td>
<td>6</td>
<td>710.00</td>
<td>2</td>
<td>360.00</td>
<td></td>
<td>1.52</td>
<td>[0.31; 7.54]</td>
<td>1.0%</td>
</tr>
<tr>
<td>RITA-2 (2003)</td>
<td>13</td>
<td>3528.00</td>
<td>22</td>
<td>3598.00</td>
<td></td>
<td>0.60</td>
<td>[0.30; 1.12]</td>
<td>4.8%</td>
</tr>
<tr>
<td>TIME (2004)</td>
<td>32</td>
<td>612.00</td>
<td>34</td>
<td>592.00</td>
<td></td>
<td>0.91</td>
<td>[0.56; 1.48]</td>
<td>8.2%</td>
</tr>
<tr>
<td>INSPIRE (2006)</td>
<td>1</td>
<td>104.00</td>
<td>2</td>
<td>101.00</td>
<td></td>
<td>0.49</td>
<td>[0.04; 5.36]</td>
<td>0.5%</td>
</tr>
<tr>
<td>COURAGE (2007)</td>
<td>23</td>
<td>5285.40</td>
<td>25</td>
<td>5234.80</td>
<td></td>
<td>0.91</td>
<td>[0.52; 1.61]</td>
<td>6.5%</td>
</tr>
<tr>
<td>SWISSI-2 (2007)</td>
<td>3</td>
<td>979.20</td>
<td>22</td>
<td>1071.00</td>
<td></td>
<td>0.15</td>
<td>[0.04; 0.50]</td>
<td>1.7%</td>
</tr>
<tr>
<td>JSAP (2009)</td>
<td>2</td>
<td>633.60</td>
<td>3</td>
<td>633.60</td>
<td></td>
<td>0.67</td>
<td>[0.11; 3.99]</td>
<td>0.8%</td>
</tr>
<tr>
<td>BARI 2D (2009)</td>
<td>72</td>
<td>5880.00</td>
<td>64</td>
<td>5960.00</td>
<td></td>
<td>1.14</td>
<td>[0.81; 1.60]</td>
<td>12.9%</td>
</tr>
<tr>
<td>MASS-2 (2010)</td>
<td>51</td>
<td>4080.00</td>
<td>42</td>
<td>2030.00</td>
<td></td>
<td>0.60</td>
<td>[0.40; 0.91]</td>
<td>10.2%</td>
</tr>
<tr>
<td>DEFER (2015)</td>
<td>4</td>
<td>1350.00</td>
<td>5</td>
<td>1365.00</td>
<td></td>
<td>0.81</td>
<td>[0.22; 3.01]</td>
<td>1.5%</td>
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<tr>
<td>ORBITA (2017)</td>
<td>0</td>
<td>11.55</td>
<td>0</td>
<td>10.45</td>
<td></td>
<td>0.90</td>
<td>[0.02; 45.60]</td>
<td>0.2%</td>
</tr>
<tr>
<td>REVASC (2018)</td>
<td>0</td>
<td>101.00</td>
<td>2</td>
<td>104.00</td>
<td></td>
<td>0.21</td>
<td>[0.01; 4.29]</td>
<td>0.3%</td>
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<tr>
<td>EURO-CTO (2018)</td>
<td>7</td>
<td>777.00</td>
<td>2</td>
<td>411.00</td>
<td></td>
<td>1.85</td>
<td>[0.38; 8.91]</td>
<td>1.1%</td>
</tr>
<tr>
<td>FAME-2 (2018)</td>
<td>11</td>
<td>2252.88</td>
<td>7</td>
<td>2222.64</td>
<td></td>
<td>1.55</td>
<td>[0.60; 4.00]</td>
<td>2.7%</td>
</tr>
<tr>
<td>DECISION-CTO (2019)</td>
<td>8</td>
<td>1668.00</td>
<td>14</td>
<td>1592.00</td>
<td></td>
<td>0.55</td>
<td>[0.23; 1.30]</td>
<td>3.2%</td>
</tr>
<tr>
<td>ISCHEMIA (2020)</td>
<td>92</td>
<td>8281.60</td>
<td>111</td>
<td>8291.20</td>
<td></td>
<td>0.83</td>
<td>[0.63; 1.09]</td>
<td>15.6%</td>
</tr>
<tr>
<td>ISCHEMIA-CKD (2020)</td>
<td>76</td>
<td>853.60</td>
<td>82</td>
<td>855.80</td>
<td></td>
<td>0.93</td>
<td>[0.68; 1.27]</td>
<td>13.9%</td>
</tr>
</tbody>
</table>

Random-effects model 456 42409.33 528 39484.49
Heterogeneity: $I^2 = 21\%$, $\tau^2 = 0.0251$, $p = 0.19$
Test for overall effect: $z = -2.76$ ($p < 0.01$)
Favours Revascularisation+MT Favours MT alone

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

Secondary endpoint: Spontaneous MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Revascularisation + MT Events</th>
<th>P-Y</th>
<th>MT alone Events</th>
<th>P-Y</th>
<th>Spontaneous MI</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathur (1979)</td>
<td>9</td>
<td>308.00</td>
<td>13</td>
<td>330.00</td>
<td></td>
<td>0.74</td>
<td>[0.32; 1.74]</td>
<td>2.6%</td>
</tr>
<tr>
<td>ACIP (1997)</td>
<td>7</td>
<td>384.00</td>
<td>18</td>
<td>732.00</td>
<td></td>
<td>0.74</td>
<td>[0.31; 1.77]</td>
<td>2.5%</td>
</tr>
<tr>
<td>ACME-1 (1997)</td>
<td>10</td>
<td>575.00</td>
<td>8</td>
<td>560.00</td>
<td></td>
<td>1.22</td>
<td>[0.48; 3.08]</td>
<td>2.2%</td>
</tr>
<tr>
<td>ACME-2 (1997)</td>
<td>5</td>
<td>255.00</td>
<td>5</td>
<td>250.00</td>
<td></td>
<td>0.98</td>
<td>[0.28; 3.39]</td>
<td>1.3%</td>
</tr>
<tr>
<td>AVER (1999)</td>
<td>5</td>
<td>265.50</td>
<td>4</td>
<td>246.00</td>
<td></td>
<td>1.16</td>
<td>[0.31; 4.31]</td>
<td>1.2%</td>
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<td>MASS-1 (1999)</td>
<td>7</td>
<td>710.00</td>
<td>3</td>
<td>360.00</td>
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<td>1.18</td>
<td>[0.31; 4.58]</td>
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<td>3598.00</td>
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<td>1.11</td>
<td>[0.63; 1.95]</td>
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<tr>
<td>TIME (2004)</td>
<td>20</td>
<td>612.00</td>
<td>21</td>
<td>592.00</td>
<td></td>
<td>0.92</td>
<td>[0.50; 1.70]</td>
<td>4.6%</td>
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<td>5285.40</td>
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<td>0.30</td>
<td>[0.15; 0.59]</td>
<td>4.0%</td>
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<tr>
<td>JSAP (2008)</td>
<td>3</td>
<td>633.60</td>
<td>7</td>
<td>633.60</td>
<td></td>
<td>0.43</td>
<td>[0.11; 1.66]</td>
<td>1.1%</td>
</tr>
<tr>
<td>BARI 2D (2009)</td>
<td>96</td>
<td>5880.00</td>
<td>138</td>
<td>5960.00</td>
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<td>0.71</td>
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<td>42</td>
<td>2030.00</td>
<td></td>
<td>0.57</td>
<td>[0.38; 0.86]</td>
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<td>1350.00</td>
<td>2</td>
<td>1365.00</td>
<td></td>
<td>4.55</td>
<td>[0.98; 21.06]</td>
<td>0.9%</td>
</tr>
<tr>
<td>REVASC (2018)</td>
<td>0</td>
<td>101.00</td>
<td>1</td>
<td>104.00</td>
<td></td>
<td>0.34</td>
<td>[0.01; 8.43]</td>
<td>0.2%</td>
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<td>2</td>
<td>411.00</td>
<td></td>
<td>1.59</td>
<td>[0.32; 7.86]</td>
<td>0.8%</td>
</tr>
<tr>
<td>FAME-2 (2018)</td>
<td>29</td>
<td>2235.00</td>
<td>45</td>
<td>2205.00</td>
<td></td>
<td>0.64</td>
<td>[0.40; 1.01]</td>
<td>7.2%</td>
</tr>
<tr>
<td>DECISION-CTO (2019)</td>
<td>7</td>
<td>1668.00</td>
<td>7</td>
<td>1592.00</td>
<td></td>
<td>0.95</td>
<td>[0.33; 2.72]</td>
<td>1.8%</td>
</tr>
<tr>
<td>ISCHEMIA (2020)</td>
<td>130</td>
<td>8281.60</td>
<td>196</td>
<td>8291.20</td>
<td></td>
<td>0.66</td>
<td>[0.53; 0.83]</td>
<td>17.0%</td>
</tr>
<tr>
<td>ISCHEMIA-CKD (2020)</td>
<td>37</td>
<td>853.60</td>
<td>52</td>
<td>855.60</td>
<td></td>
<td>0.71</td>
<td>[0.47; 1.09]</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

Random-effects model: $I^2 = 21\%$, $\tau^2 = 0.0192$, $p = 0.19$

Test for overall effect: $z = -4.00$ ($p < 0.01$)

Favours Revascularisation + MT Favours MT alone

0.1 0.2 0.5 1 2 5 10


26% spontaneous MI risk reduction with revasc + MT vs MT alone
Benefits of revascularisation: overall and in prespecified subgroups

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


Adjusted Hazard Ratio = 2.98 (1.87, 4.74)
P-value = <0.01

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

Adjusted Hazard Ratio = 0.67 (0.53, 0.83)
P-value = <0.01

CV Death
Procedural MI: 245(13)
Procedural Type 4a or 5 MI: 115(8)
Procedural MI (INV Only): 204(12)
Type 4a/5 MI: 35(5)
Type 1 MI: 223(21)

HR (95% CI)  P value
1.24 (0.57, 2.68)  0.592
1.95 (0.79, 4.84)  0.149
1.54 (0.70, 3.43)  0.286
6.17 (2.48, 15.35)  <.001
3.52 (2.11, 5.88)  <.001

Chaitman. Circulation 2021; 143:790-804
No association between cardiac death and periprocedural MI
Cardiac death and length of follow-up

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

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

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
<th>MT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>42.4</td>
<td>33</td>
<td>59.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>24.1</td>
<td>51.1</td>
<td>31</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>14.3</td>
<td>10.8</td>
<td>20.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Question 2:

Does the suboptimal therapy in older studies favor revasc?

Hueb. Circulation. 2010 Sep 7;122(10):949-57
### Answer to question 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic agents</td>
<td>-0.01</td>
<td>0.27</td>
</tr>
<tr>
<td>Statins</td>
<td>0.001</td>
<td>0.71</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>-0.001</td>
<td>0.91</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>0.005</td>
<td>0.11</td>
</tr>
<tr>
<td>Study year</td>
<td>0.01</td>
<td>0.16</td>
</tr>
</tbody>
</table>

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

Balanced Randomization

Invasive strategy + MT vs MT alone

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
Annual mortality risk as a function of the severity of coronary artery disease (CAD)
Risk multiplier
Meta-regression of cardiac death in relation to % of MV disease

Outcomes for INV-CR versus CON: Primary endpoint

Anatomic CR achieved

<table>
<thead>
<tr>
<th>Cumulative incidence (%)</th>
<th>CV death or MI</th>
<th>Difference INV-CON [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month difference INV-ACR vs. CON</td>
<td>1.8% (-0.9% 4.1%)</td>
<td>Two-vessel CAD ≥70% or three-vessel ≥50% or 70% proximal LAD</td>
</tr>
<tr>
<td>4-year difference INV-ACR vs. CON</td>
<td>-3.5% (-7.4% to 0.1%)</td>
<td>Three vessel CAD ≥70% or two-vessel ≥70% including proximal LAD</td>
</tr>
</tbody>
</table>

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.

ISECHMIA-EXTEND was designed as a pragmatic long-term follow-up study of mortality.
Participant Flow for Long-Term Follow-Up in ISCHEMIA-EXTEND

ISCHEMIA Randomized Participants (n=5179)

- Randomized to INV (n=2588)
  - Death (n=145)
    - Withdrew and no database search allowed (n=18)
      (Censored thereafter)
    - Site/participant declined extended follow-up (n=18)
      (Censored thereafter)
  - Eligible* for extended follow-up (n=2407)
    Data collected during extended follow-up (2267)

- Randomized to CON (n=2591)
  - Death (n=144)
    - Withdrew and no database search allowed (n=11)
      (Censored thereafter)
    - Site/participant declined extended follow-up (n=18)
      (Censored thereafter)
  - Eligible* for extended follow-up (n=2418)
    Data collected during extended follow-up (2273)

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

Hochman, Circulation 2023 Jan 3;147(1):8-19
Extended follow-up - 5.7 years median

Cumulative incidence of cardiovascular death

Conservative vs Invasive

INV:CON Adjusted HR = 0.78, 95% CI: 0.63, 0.96
P-value= 0.008 (Fine-Gray)

No. at Risk

Conservative: 2591 2564 2516 2477 2378 1699 1137 575 195
Invasive: 2588 2544 2509 2476 2373 1697 1116 564 174

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.

<table>
<thead>
<tr>
<th>Cardiac Death</th>
<th>META-ANALYSIS</th>
<th>RR [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.79 [0.67:0.93]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>without post-ACS</td>
<td>0.82 [0.73:0.94]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>without CTO</td>
<td>0.80 [0.67:0.95]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>without CABG</td>
<td>0.83 [0.71:0.98]</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

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

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

![Graph showing cumulative incidence of myocardial infarction or cardiovascular death over time since angiography.](image)


![Graph showing log RRR for cardiac mortality vs multivessel disease.](image)

Navarese. EHJ 2021;42:4638-51
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

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!

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