Impact of Statin Dose on Major Cardiovascular Events: a Mixed Treatment Comparison Meta-analysis Involving more than 174,000 Patients

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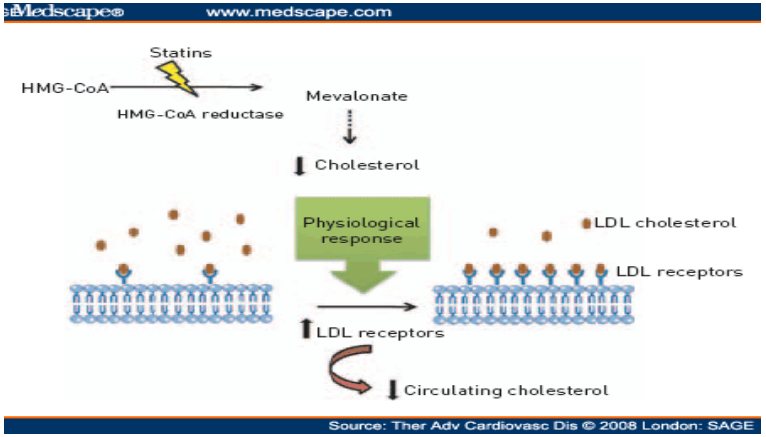
June 2011

Background

- Statins are a group of medications used in CV prevention, which have been studied in several clinical trials since 1994. One of its main mechanisms of action is the reduction of LDL-cholesterol:



Relationship between dose and LDL↓

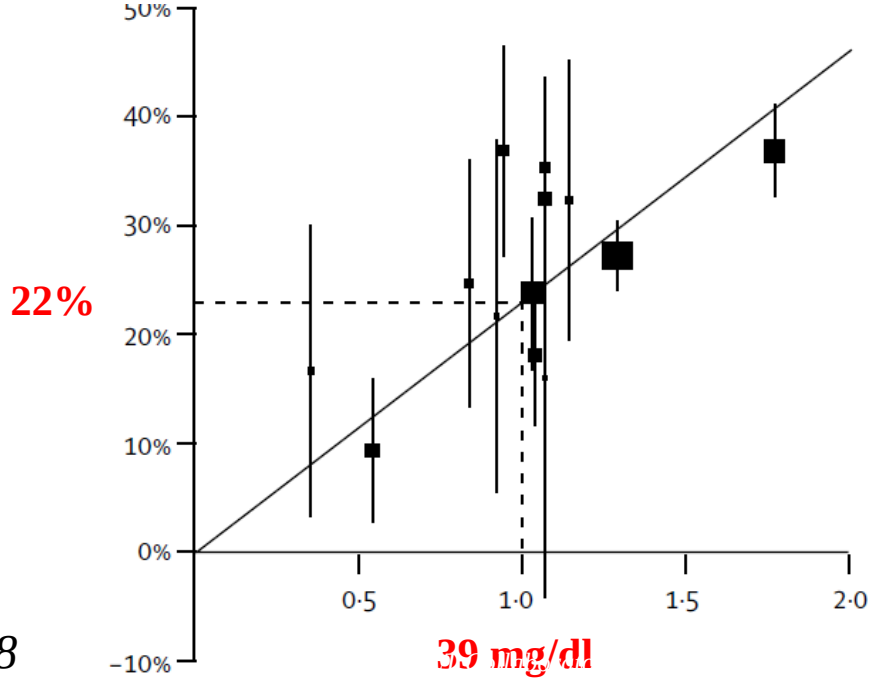
BMJ Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis

Statin/Dose	5mg	10mg	20mg	40mg	80mg
Atorvastatin	31%	37%	43%	49%	55%
Fluvastatin	10%	15%	21%	27%	33%
Lovastatin		21%	29%	37%	45%
Pravastatin	15%	20%	24%	29%	33%
Rosuvastatin	38%	43%	48%	53%	58%
Simvastatin	23%	27%	32%	37%	42%

Law et al. BMJ. 2003 Jun 28;326(7404):1423

Relationship between LDL↓ and CV events↓

Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins



CCT Collaborators, Lancet 2005; 366: 1267–78

Relationship between dose and events

Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients

European Heart Journal
doi:10.1093/eurheartj/ehr035

- RR non-fatal MI = 0.82 (0.76 – 0.89)
- RR AVC total = 0.86 (0.77 – 0.96)
- RR morte total = 0.92 (0.83 – 1.03)
- RR morte CV = 0.89 (0.78 – 1.01)
- RR IAM + morte DAC = 0.90 (0.84 – 0.96)

Mills EJ et al. Eur Heart J 2011 Mar 8

Objetive

To evaluate different regimens of statins (high, intermediate and low dose) using all the evidence available (direct and Indirect).

Methods

- Study design: systematic review
- Search strategy: initially, search for previous systematic reviews with broad search → Ward et al (2007, search until 2004, evaluation all statins except lovastatin)
- Search strategy adopted by us was similar to the one by Ward et al.

Ward S et al. Health Technol Assess 2007 Apr;11(14):1-160, iii-iv.

Methods

MEDLINE

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])

*

+

Cochrane CENTRAL

hydroxymethylglutaryl-coa reductase inhibitors, statins, atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin

Methods

- Inclusion: RCTs of statin vs statin (direct evidence) and statins vs control (indirect evidence), in primary and secondary prevention of CV events.
- Exclusion: < 6 months of follow-up, < 100 patients, lack of outcomes of interest, heart/kidney failure patients, oriental population.
- Outcomes of interest: non-fatal MI, fatal+non-fatal stroke, revascularization, death (coronary, CV and all-cause).

Methods

- Categorization of doses according to expected LDL reduction:

Estatina/Dose	10mg	20mg	40mg	80mg
Fluvastatina	15%	21%	27%	33%
Pravastatina	20%	24%	29%	33%
Lovastatina	21%	29%	37%	45%
Simvastatina	27%	32%	37%	42%
Atorvastatina	37%	43%	49%	55%
Rosuvastatina	43%	48%	53%	58%

Methods

- Direct: conventional random-effects meta-analysis.

  (statin vs statin)

- Indirect comparisons: Bucher method.

  (statin vs placebo)

- Combining Direct and Indirect: MTC model.

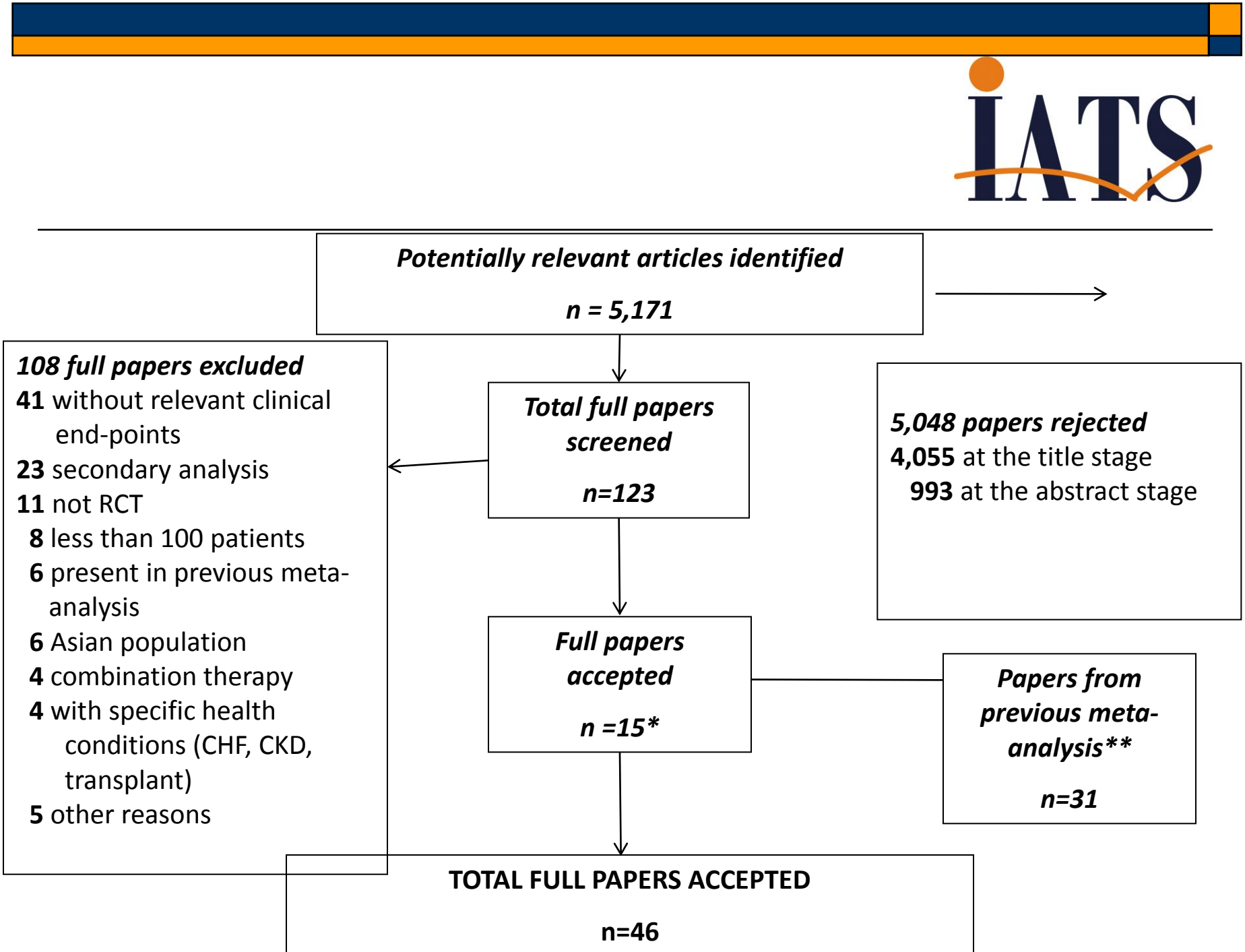
Methods

MTC (Mixed Treatment Comparison): Bayesian model that evaluates a single consistent summary for each pairwise comparison.

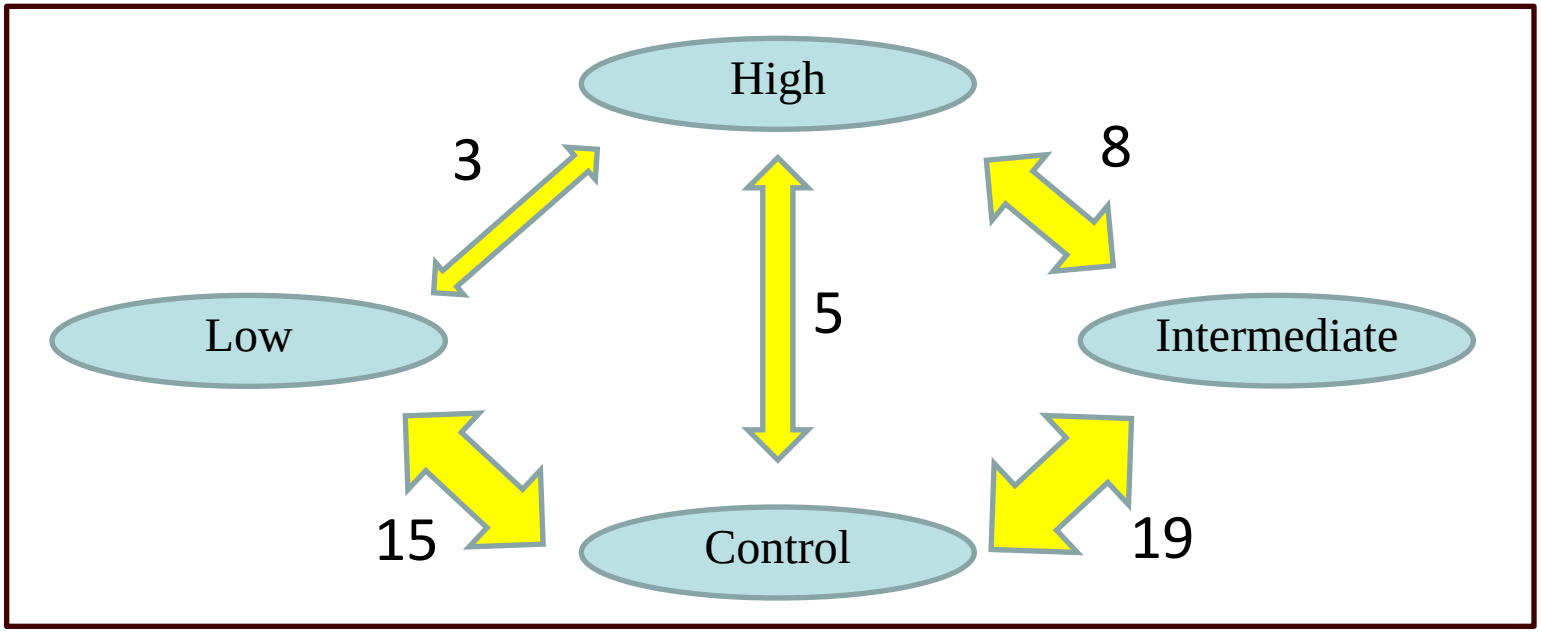
The MTC point estimate is a weighted average between the direct and the indirect estimates.

The indirect estimate is a result from all network of evidences.

Consistency evaluated through the split-node methodology.

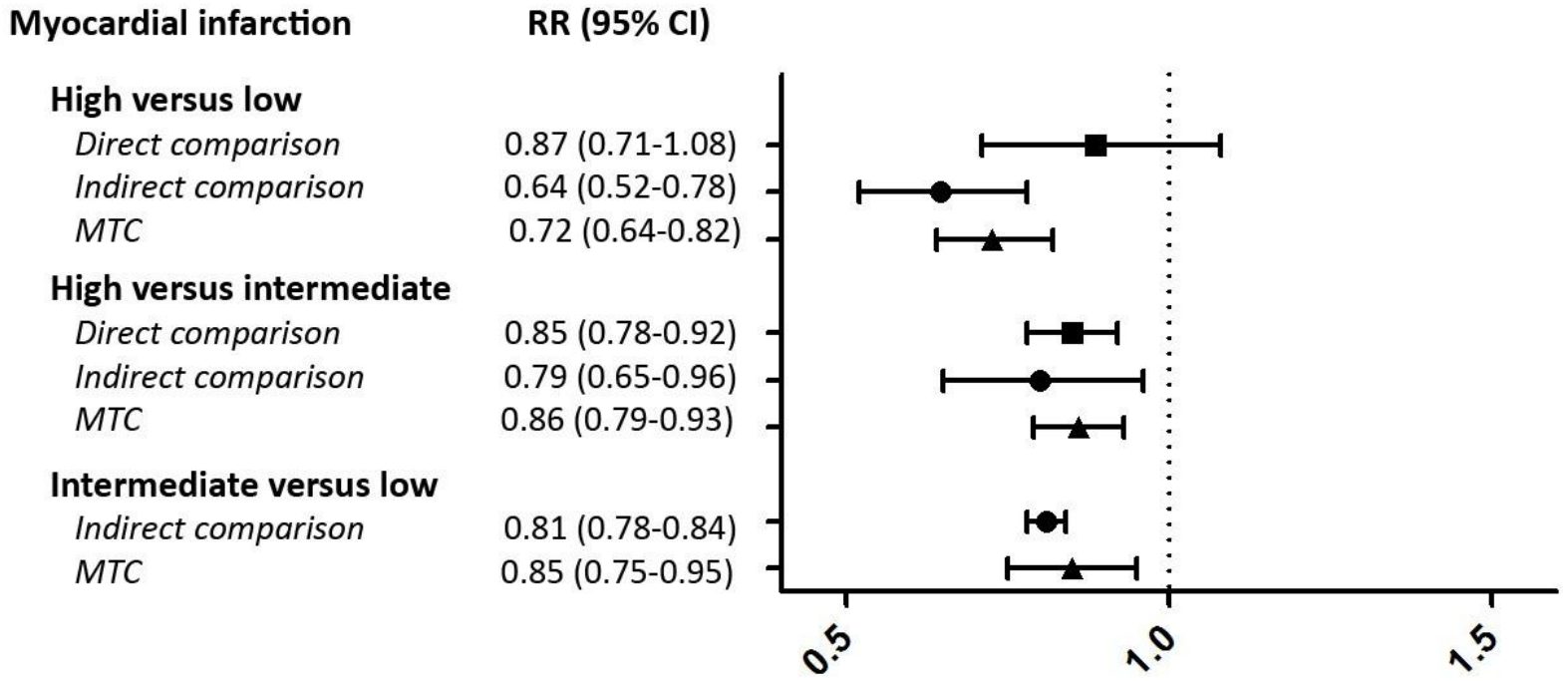

Potentially relevant articles identified
n = 5,171
108 full papers excluded
41 without relevant clinical end-points
23 secondary analysis
11 not RCT
8 less than 100 patients
6 present in previous meta-analysis
6 Asian population
4 combination therapy
4 with specific health conditions (CHF, CKD, transplant)
5 other reasons
Total full papers screened
n=123
5,048 papers rejected
4,055 at the title stage
993 at the abstract stage
Full papers accepted
n =15*
Papers from previous meta-analysis**
n=31
TOTAL FULL PAPERS ACCEPTED
n=46

Results

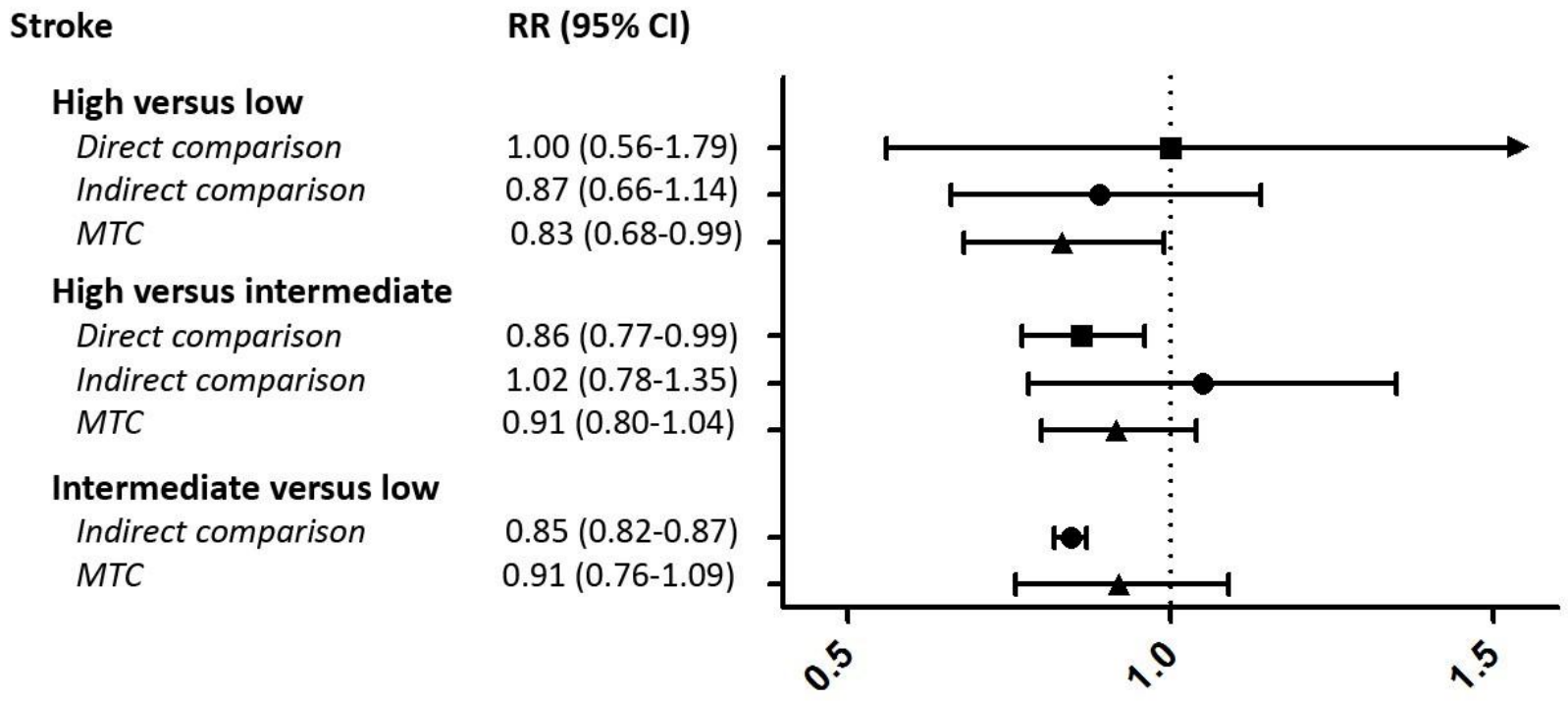


- Methodological quality usually good;
- 27 studies including secondary prevention patients;

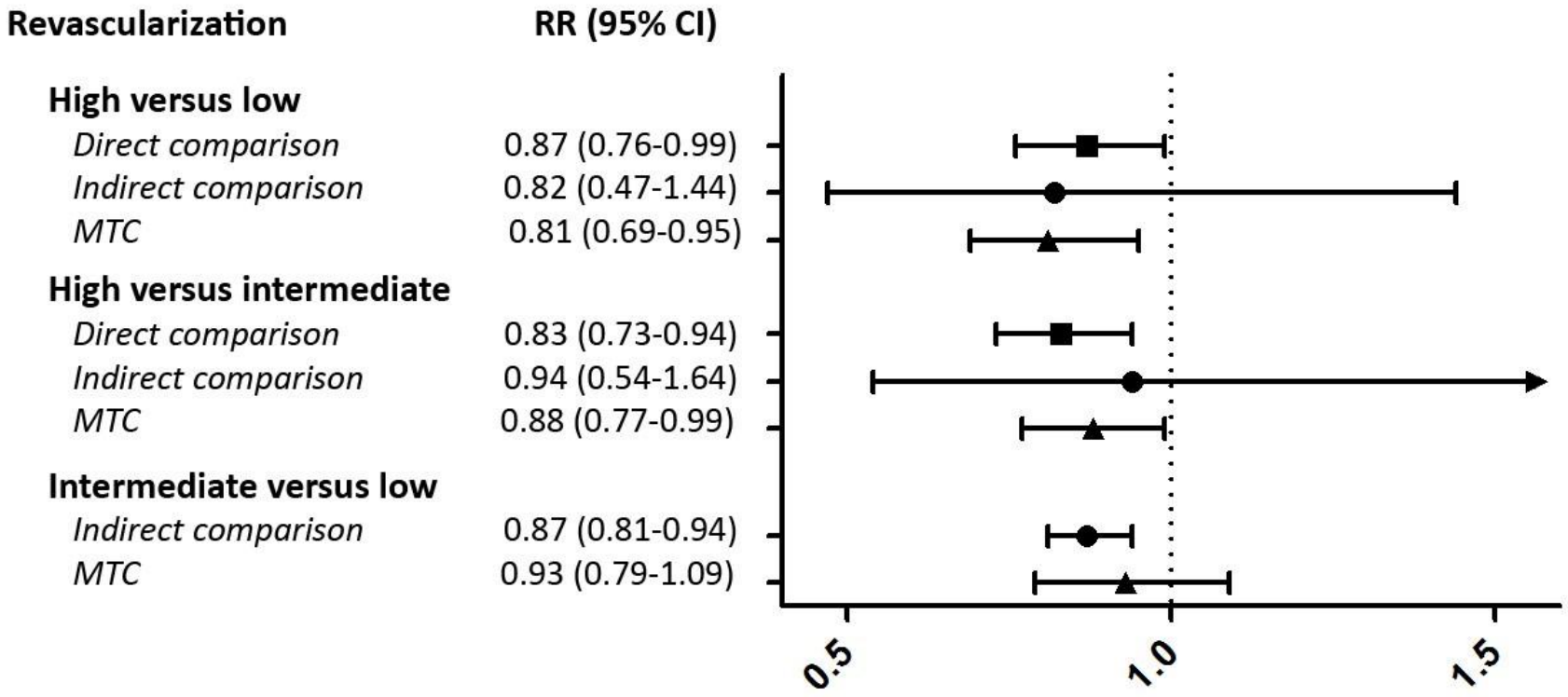
Results: Non-fatal MI



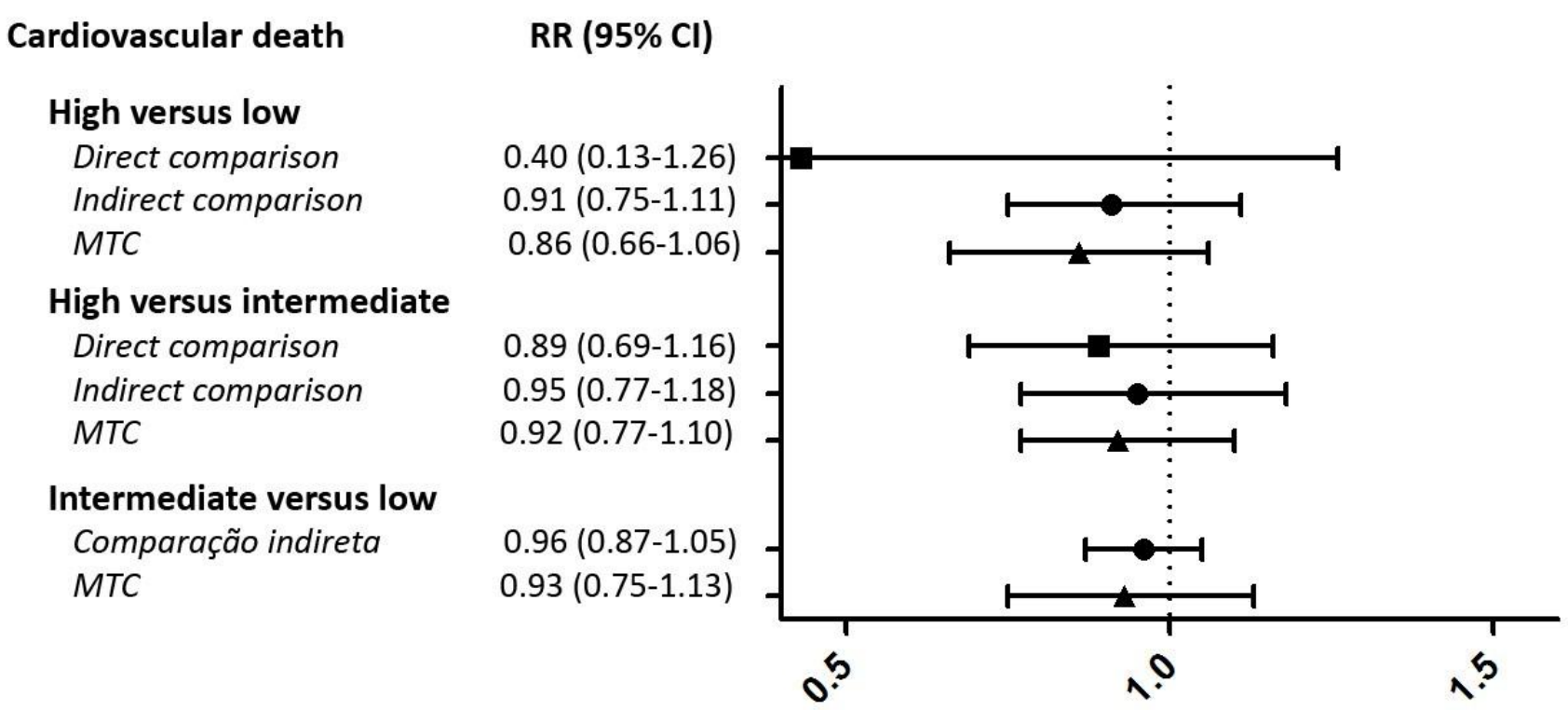
Results: Stroke



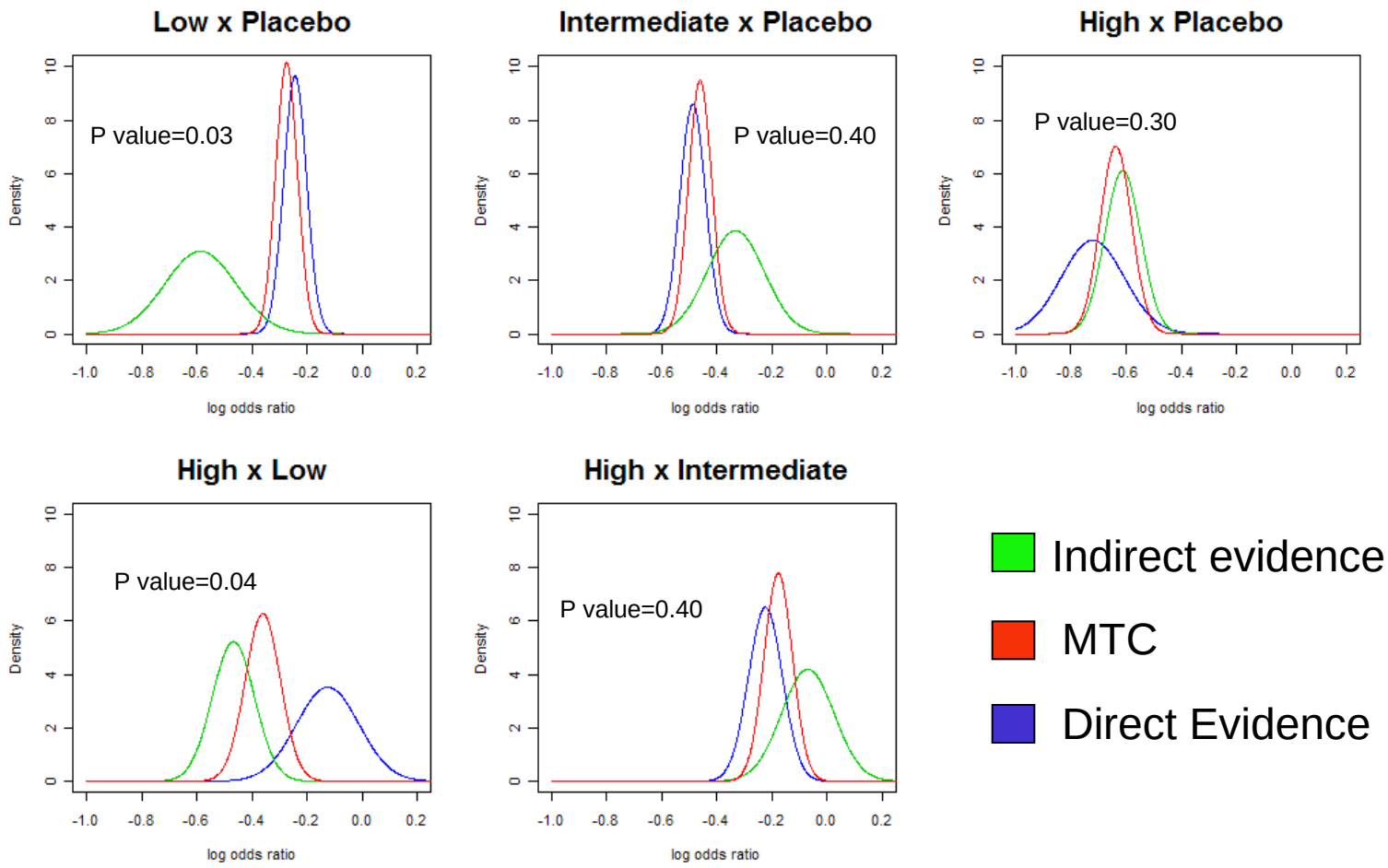
Results: Revascularization



Results: Mortality



Consistency - MI



Split node method: proposed by Dias et all (Statistics in Medicine 2010).

Conclusions

- The only outcome with a dose-response effect was non-fatal MI (in all three analysis).
- An impact on stroke was observed only in the high vs low comparison.
- An impact on revascularization was observed between high and both low and intermediate dose.

Conclusions

- In the outcomes mortality: no difference between statins;

- The MTC model did not show consistency problems, therefore being an adequate model to combine all evidence available (some results were more precise).

Thanks

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