Comparative Tolerability and Harms of Individual Statins

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Disclosure of conflict of interest

- none

HMG CoA Reductase inhibitors (statins)

- Inhibits cholesterol production
- Effective lowering of LDL cholesterol
- Potency of LDL lowering differs slightly between statins
- Proven efficacy in reduction of CV risk in primary and secondary prevention
- ESC guidelines: LDL target based on CV risk (SCORE)
  - Very high risk: LDL <1.8 or 50% reduction
  - Statin first choice, at highest tolerable dose

HMG CoA Reductase inhibitors (statins)

- Potential harmful side effects:
  - myalgia,
  - transaminase elevations
  - CK elevations
  - debated risk of diabetes and cancer.
- No direct head-to-head comparisons between statins
  - class effect?
  - individual differences between statins? doses?

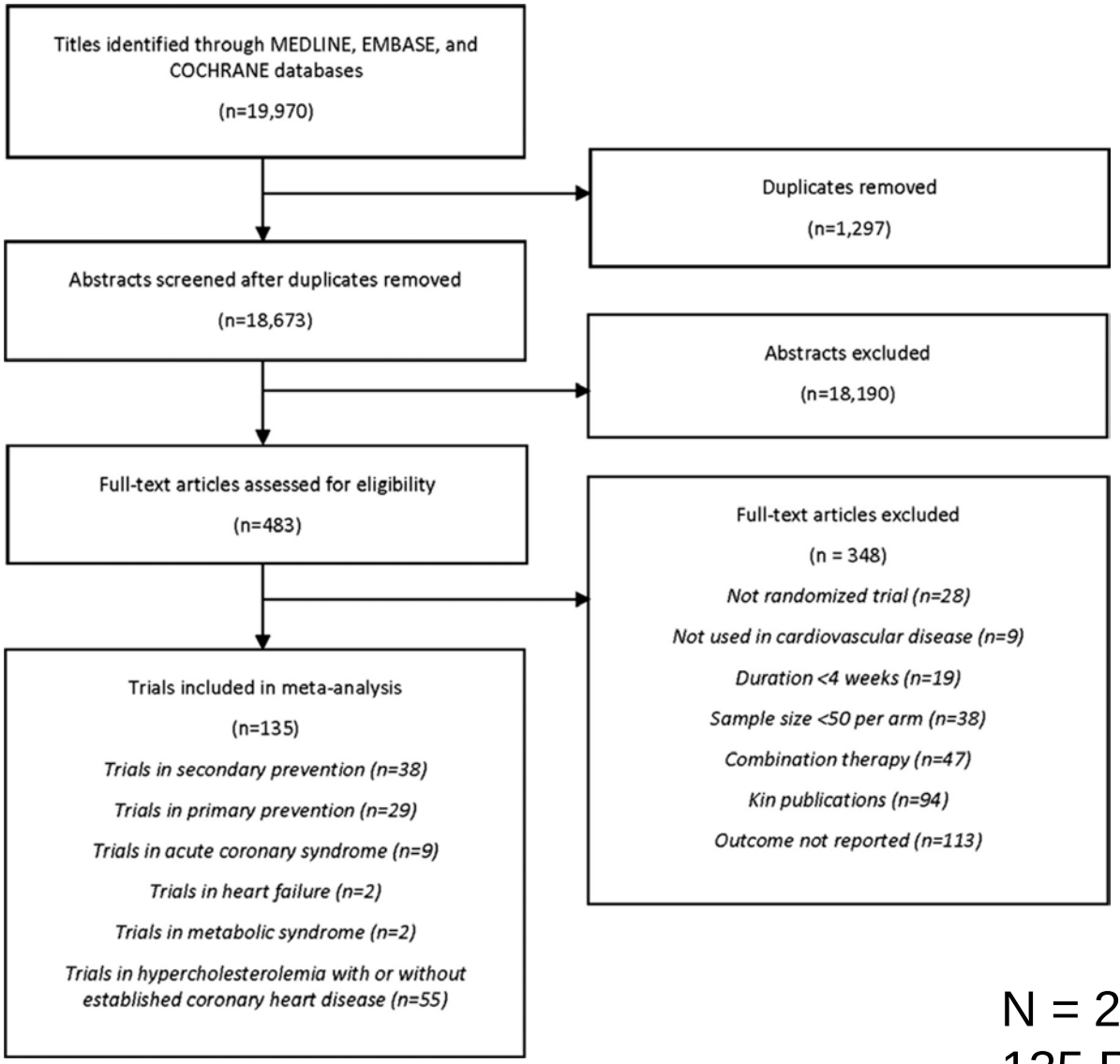
Head-to-head comparisons

- New analyses and methods needed to study the comparability of individuals statins in tolerability

- We performed a new state of the art network meta-analysis to compare all individual statins (7).

- We included 55 two-armed placebo-controlled and 80 two- or multi-armed active-comparator trials including 246.955 individuals treated with statins.

Flow diagram of trial identification and selection.



N = 246.955 pts.
135 RCT's

Brugts et al. Circ Cardiovasc Qual Outcomes 2013;6:390-399

Methods

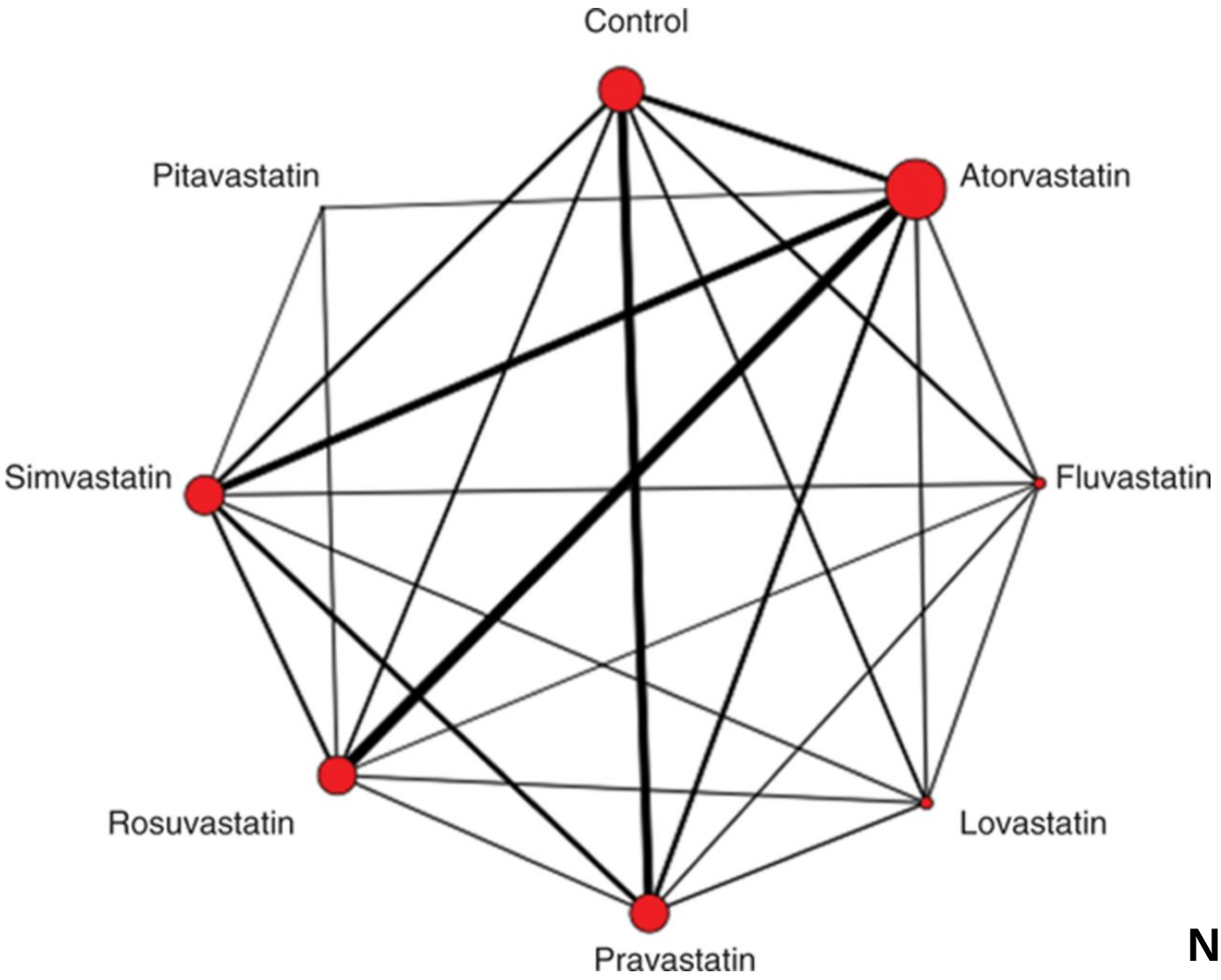
- Network meta-analysis with direct / indirect comparisons
- Facilitates the comparison of multiple treatments even when they are not directly compared to each other in clinical trials.

Main assumption:

- Balanced distribution of relative treatment effect modifiers across comparisons.
- Carefully checked for this assumption using meta-regressions, subgroup analyses, and inconsistency checks

Ades T et al. Network comparison of multiple treatments. *BMJ* 2011;331:897–900.
Ades T et al. Network meta-analysis for treatment comparisons. *Stat Med*. 2012;21:2313–2324.

Network of available comparisons for the drug-level analysis.



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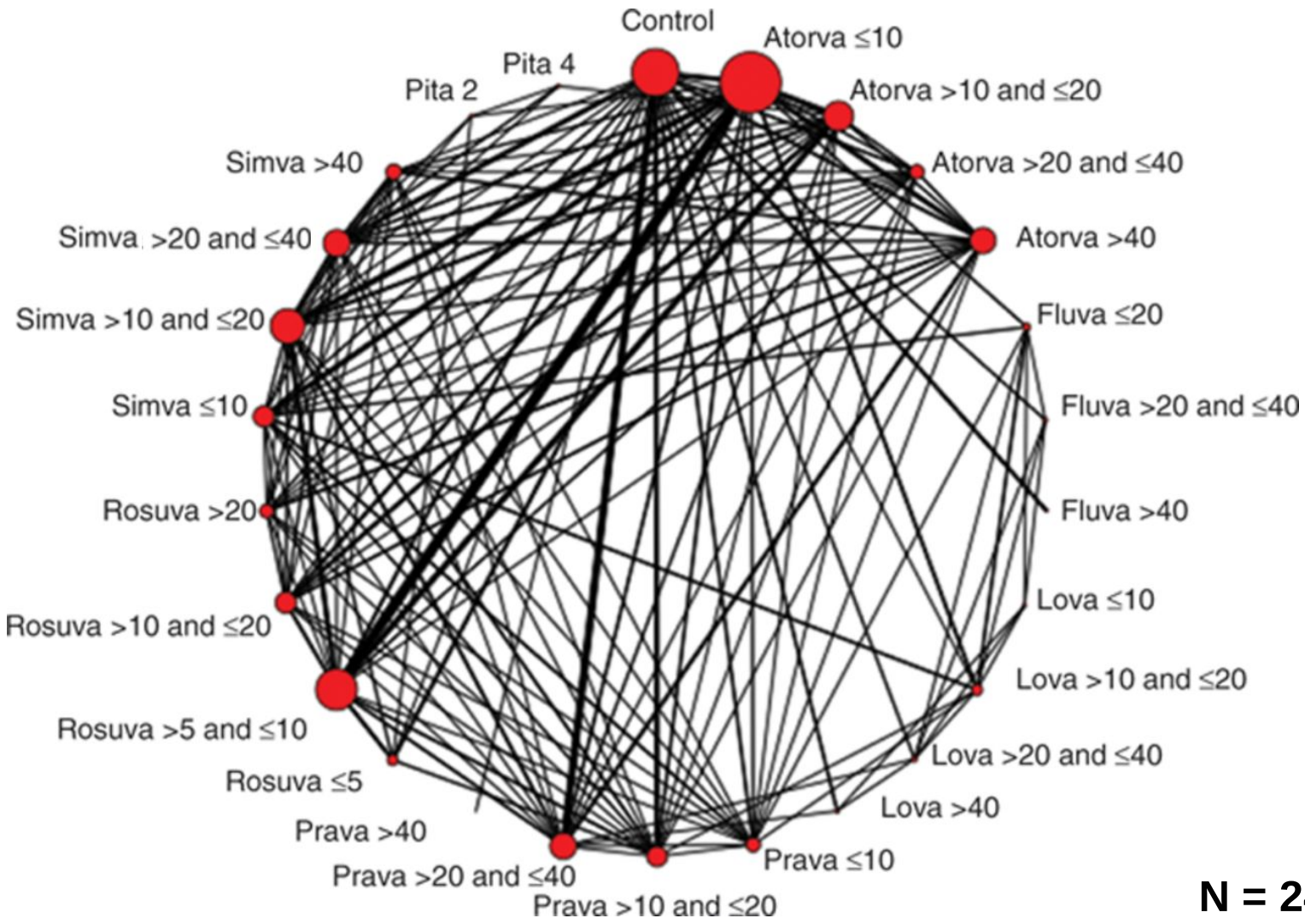
Network of available comparisons for dose-specific analysis.



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METHODS

Meta-regression analyses

- Random effects model, all analyses are adjusted for publication year, mean age and baseline LDL cholesterol

Definitions of endpoints:

A. Discontinuation of statin due to serious adverse events

B. Myalgia reported

C. Significant elevation of hepatic transaminases (3x norm)

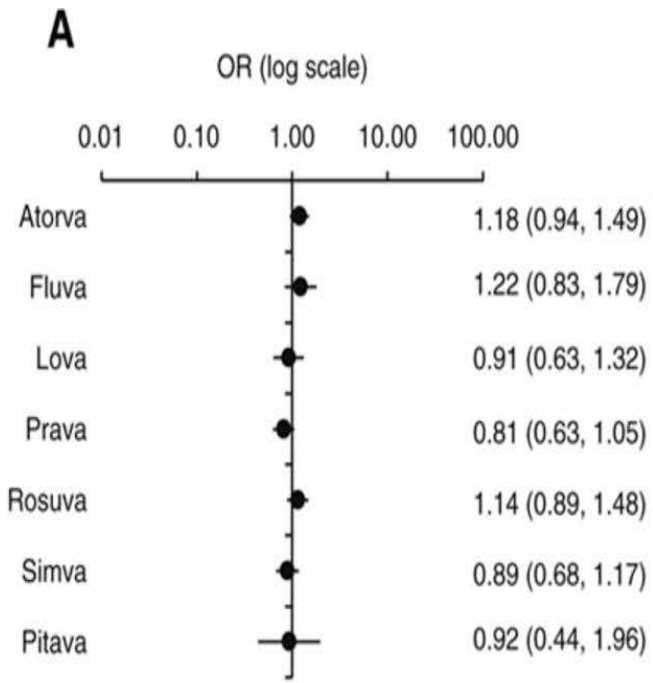
D. Significant elevation of CK (5x norm)

E. Risk of cancer

F. Risk of new onset diabetes mellitus

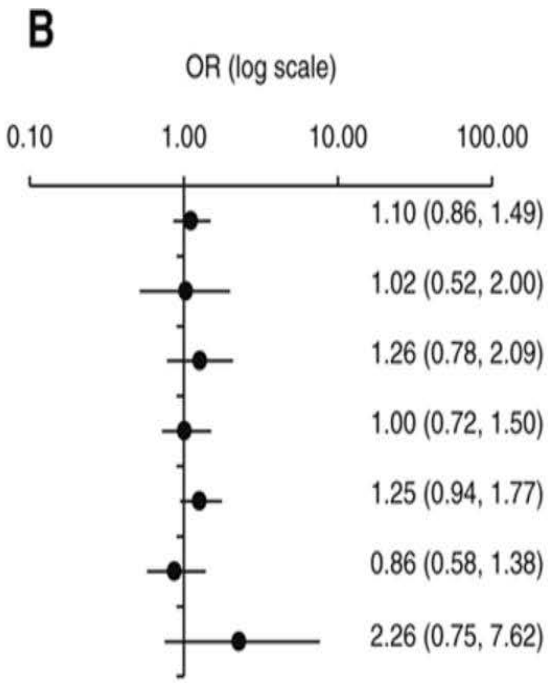
Network meta-analyses: effect of statins compared

(A) discontinuation due to serious adverse events



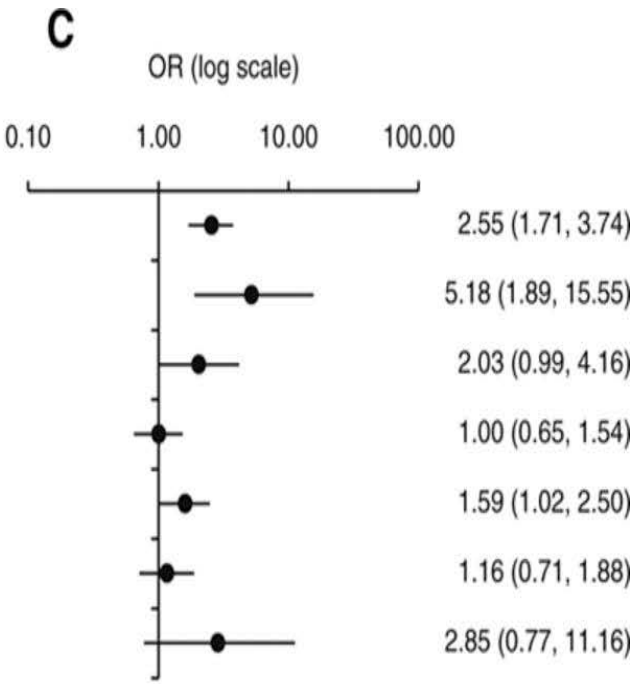
OR 0.95 (95% CI 0.83-1.08)
I^2 16.0%

(B) occurrence of myalgia



OR 1.07 (95% CI 0.89-1.29)
I^2 17.1%

(C) clinically significant elevation transaminases



OR 1.51 (95% CI 1.24-1.84)
I^2 18.0%

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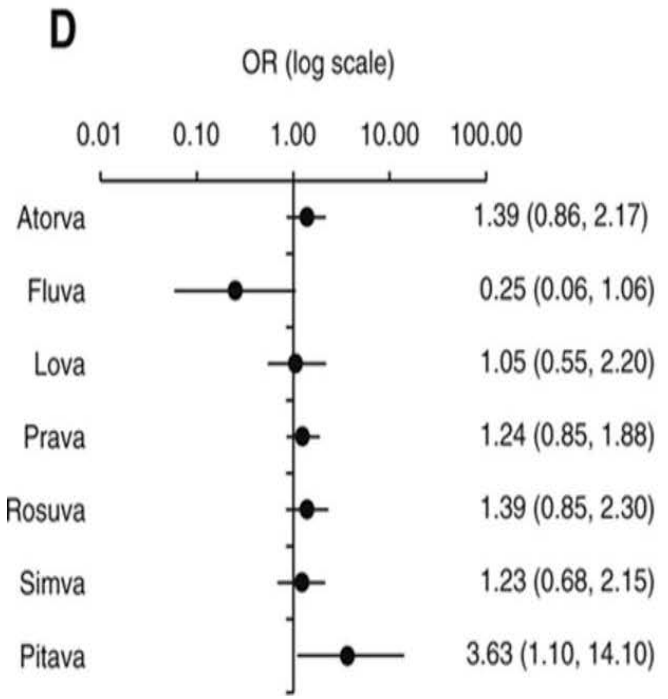
Network *meta-analyses: effect of statins compared*

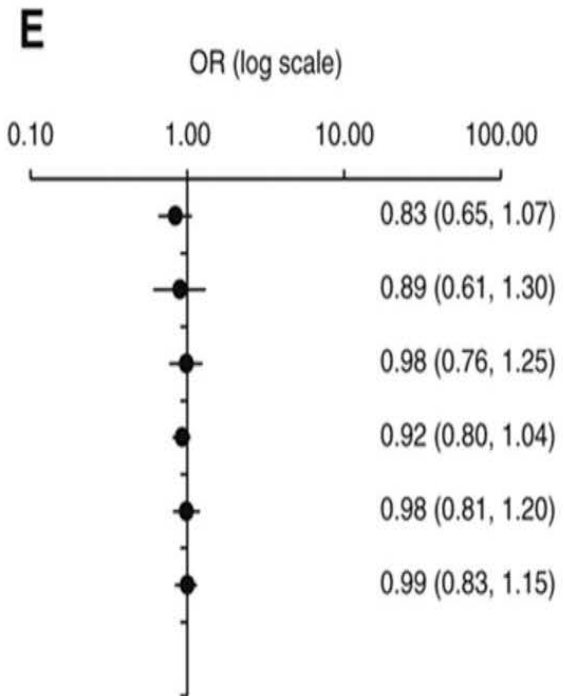
(D) clinical significant elevation in CK levels



OR 1.13 (95% CI 0.85-1.51)

I^2 11.3%

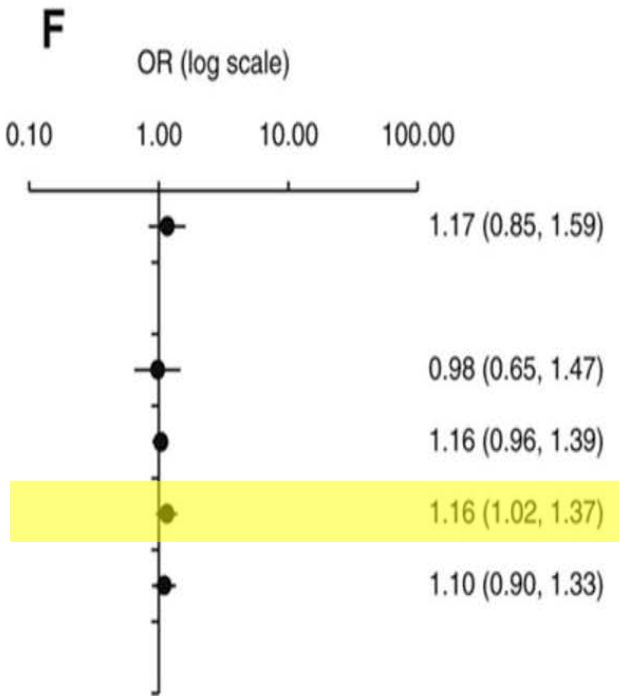
(E) incidence of cancer



OR 0.96 (95% CI 0.91-1.03)

I^2 0.1%

(F) incidence of new-onset diabetes mellitus



OR 1.09 (95% CI 1.02-1.16)

I^2 2.8%

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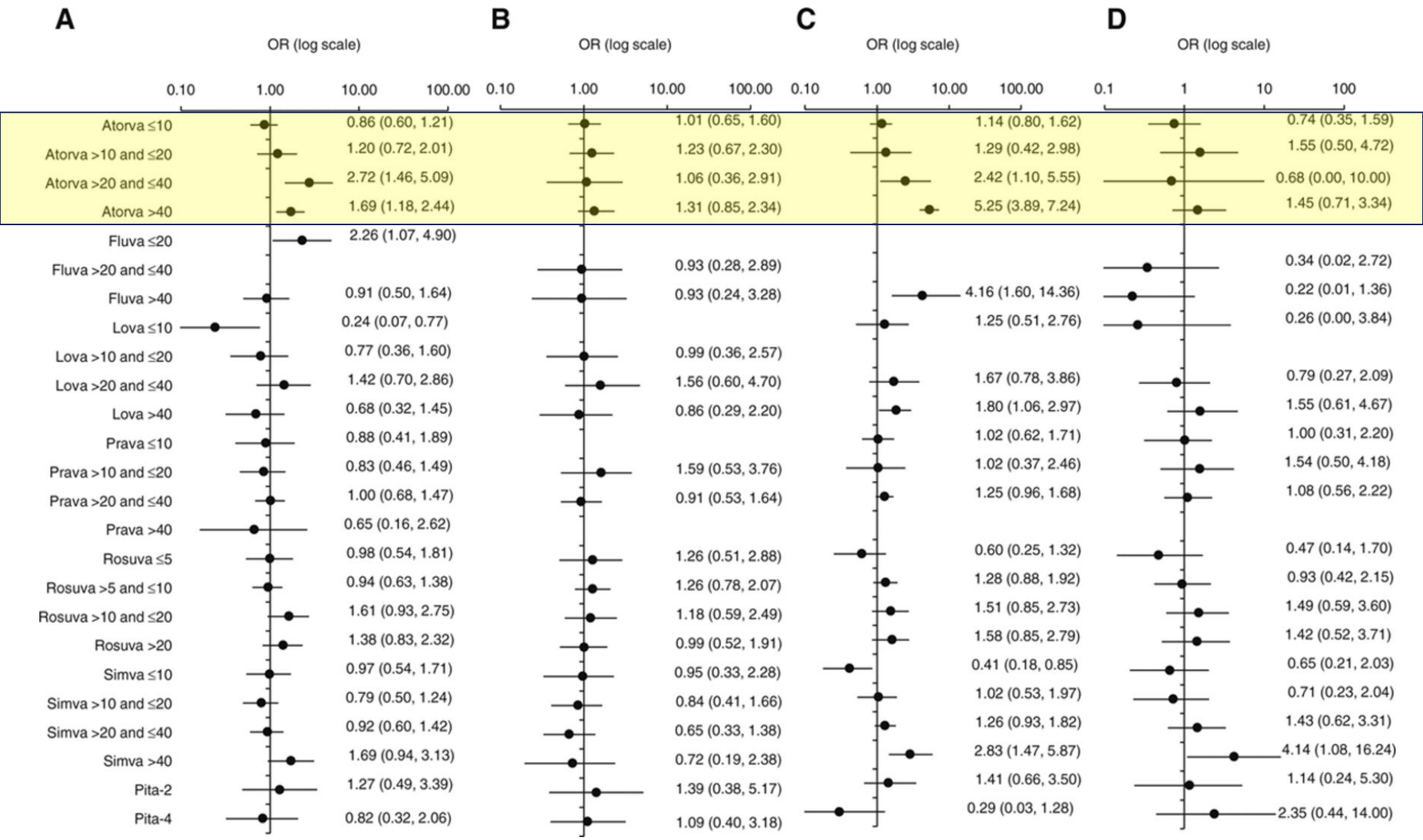
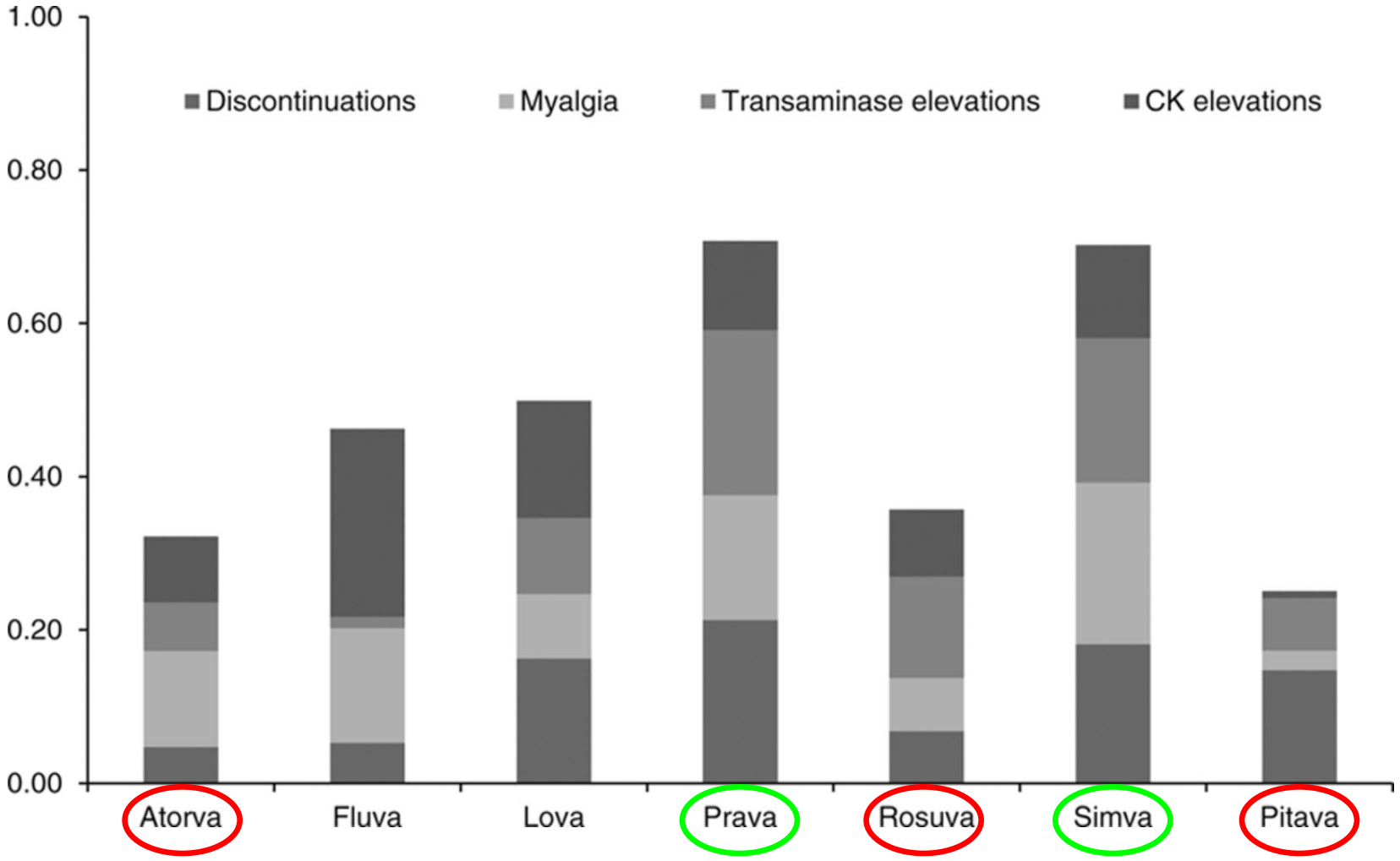
Effects of statin–dose combinations vs control



Tolerability of different statins (new)

- Combined score based on discontinuations, myalgia, transaminase elevations, and CK elevations
- Ranking analysis of statins using meta-regression
- For each endpoint, an individual statin could score 0.25 points when having the lowest number of events of all
- With 4 endpoints maximum score 1.00 (best tolerable statin)
  - score 1.00 = **best tolerable** statin
  - score 0.00 = worst tolerable statin

Overall ranking of tolerability of individual statins



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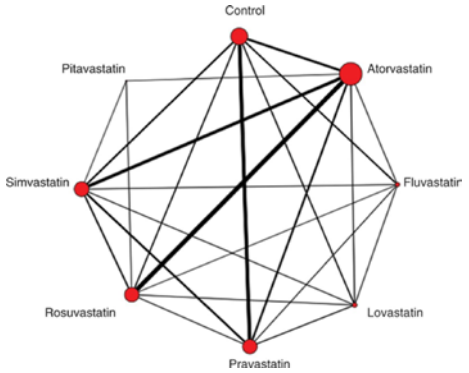
Conclusions

- First network meta-analysis comparing head-to-head all individual 7 statins in 246.955 patients using 135 RCT's
- Statins as a drug class are relatively safe and side effects are uncommon
- We found **no statistical increase in myalgia** or cancer not even at highest dose

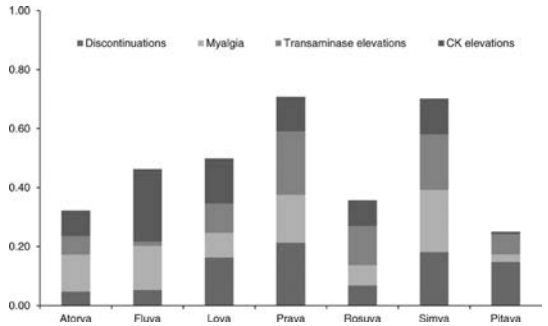


Conclusions

- Statins have a significant increased risk of hepatic transaminases elevations and CK, especially at higher dose

- Statins are also associated wit a 9% increase in relative risk of **new-onset diabetes**, with highest incidence rosuvastatine.

- **Simvastatine and pravastatine have the best tolerability** profile among 7 individual statins.



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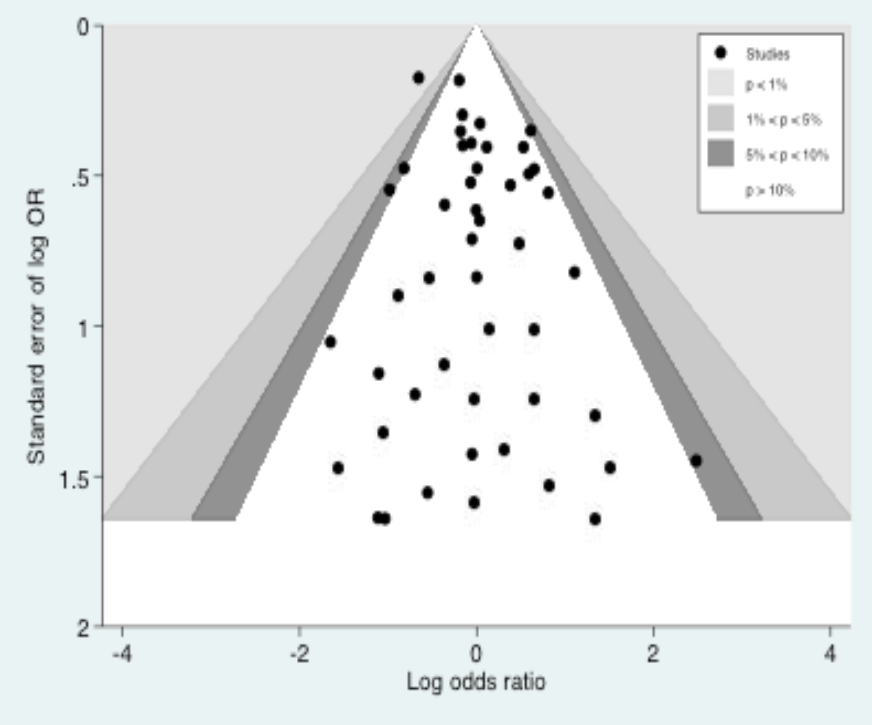
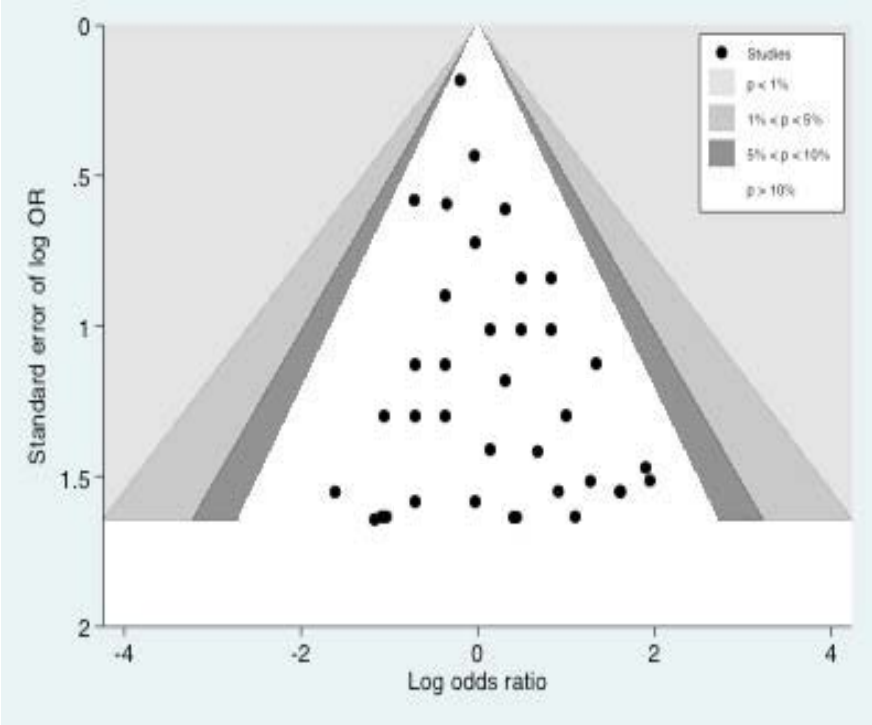
Assessment of publication bias by funnel plots for (A) myalgia, (B) CK elevations

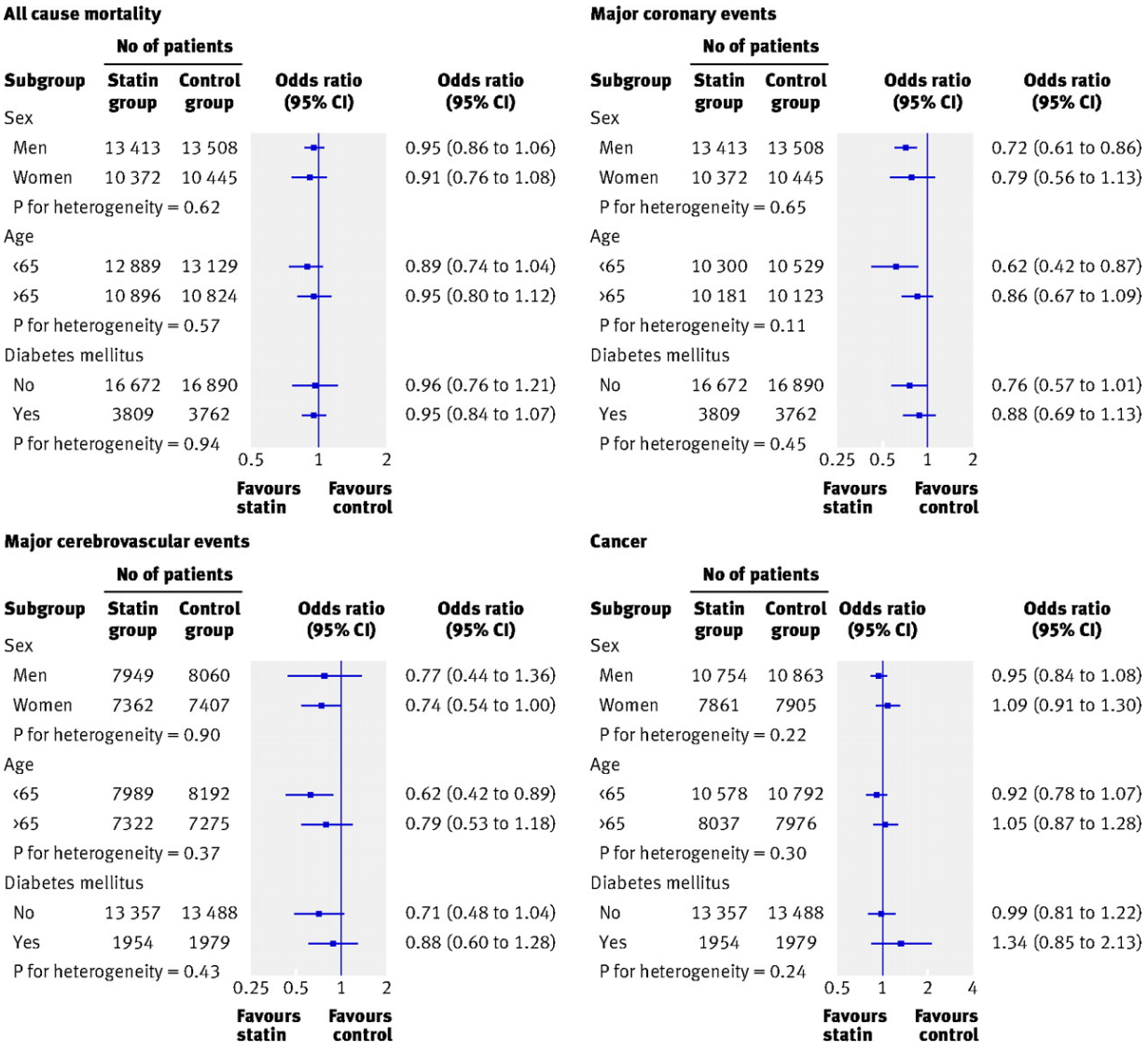




- *similar plots for other endpoints*
- *Egger regression test P-values ns.*

Odds ratios (95% CI) for subgroups of sex, age, and diabetes in 70.388 patients without established CV disease

Primary prevention
10 RCT's



All cause mortality

Subgroup	No of patients: Statin group	No of patients: Control group	Odds ratio (95% CI)	Odds ratio (95% CI)
Sex				
Men	13 413	13 508		0.95 (0.86 to 1.06)
Women	10 372	10 445		0.91 (0.76 to 1.08)
P for heterogeneity = 0.62				
Age				
‹65	12 889	13 129		0.89 (0.74 to 1.04)
›65	10 896	10 824		0.95 (0.80 to 1.12)
P for heterogeneity = 0.57				
Diabetes mellitus				
No	16 672	16 890		0.96 (0.76 to 1.21)
Yes	3809	3762		0.95 (0.84 to 1.07)
P for heterogeneity = 0.94				

0.5 1 2
Favours statin | Favours control

Major coronary events

Subgroup	No of patients: Statin group	No of patients: Control group	Odds ratio (95% CI)	Odds ratio (95% CI)
Sex				
Men	13 413	13 508		0.72 (0.61 to 0.86)
Women	10 372	10 445		0.79 (0.56 to 1.13)
P for heterogeneity = 0.65				
Age				
‹65	10 300	10 529		0.62 (0.42 to 0.87)
›65	10 181	10 123		0.86 (0.67 to 1.09)
P for heterogeneity = 0.11				
Diabetes mellitus				
No	16 672	16 890		0.76 (0.57 to 1.01)
Yes	3809	3762		0.88 (0.69 to 1.13)
P for heterogeneity = 0.45				

0.25 0.5 1 2
Favours statin | Favours control

Major cerebrovascular events

Subgroup	No of patients: Statin group	No of patients: Control group	Odds ratio (95% CI)	Odds ratio (95% CI)
Sex				
Men	7949	8060		0.77 (0.44 to 1.36)
Women	7362	7407		0.74 (0.54 to 1.00)
P for heterogeneity = 0.90				
Age				
‹65	7989	8192		0.62 (0.42 to 0.89)
›65	7322	7275		0.79 (0.53 to 1.18)
P for heterogeneity = 0.37				
Diabetes mellitus				
No	13 357	13 488		0.71 (0.48 to 1.04)
Yes	1954	1979		0.88 (0.60 to 1.28)
P for heterogeneity = 0.43				

0.25 0.5 1 2
Favours statin | Favours control

Cancer

Subgroup	No of patients: Statin group	No of patients: Control group	Odds ratio (95% CI)	Odds ratio (95% CI)
Sex				
Men	10 754	10 863		0.95 (0.84 to 1.08)
Women	7861	7905		1.09 (0.91 to 1.30)
P for heterogeneity = 0.22				
Age				
‹65	10 578	10 792		0.92 (0.78 to 1.07)
›65	8037	7976		1.05 (0.87 to 1.28)
P for heterogeneity = 0.30				
Diabetes mellitus				
No	13 357	13 488		0.99 (0.81 to 1.22)
Yes	1954	1979		1.34 (0.85 to 2.13)
P for heterogeneity = 0.24				

0.5 1 2 4
Favours statin | Favours control

Brugts et al. BMJ 2009;338:2376-89

Statin use and risk of diabetes

Pairwise meta-analysis including 113 698 patients.

Statins as a class showed a statistically significantly **higher risk of diabetes** versus placebo (OR, 1.09; 95% CI 1.02–1.16; I^2, 2.8%).

Rosuvastatine showed the highest risk of diabetes compared to placebo (OR, 1.16; 95% CI, 1.02–1.31; I^2, 0.0%).

No significant differences between individual statins at different dosages.

Statin use and risk of cancer

Pairwise meta-analysis including 100 523 participants
In which 5511 cancer events (5.2 %) occurred.

No elevated risk of cancer by using statins as a class:
OR 0.96; 95% CI 0.91–1.02; I^2, 0.0%) versus placebo

No evidence of potential head-to-head or dose differences in the incidence of cancer between individual statins