Figure 1: Risk of Bias Graph

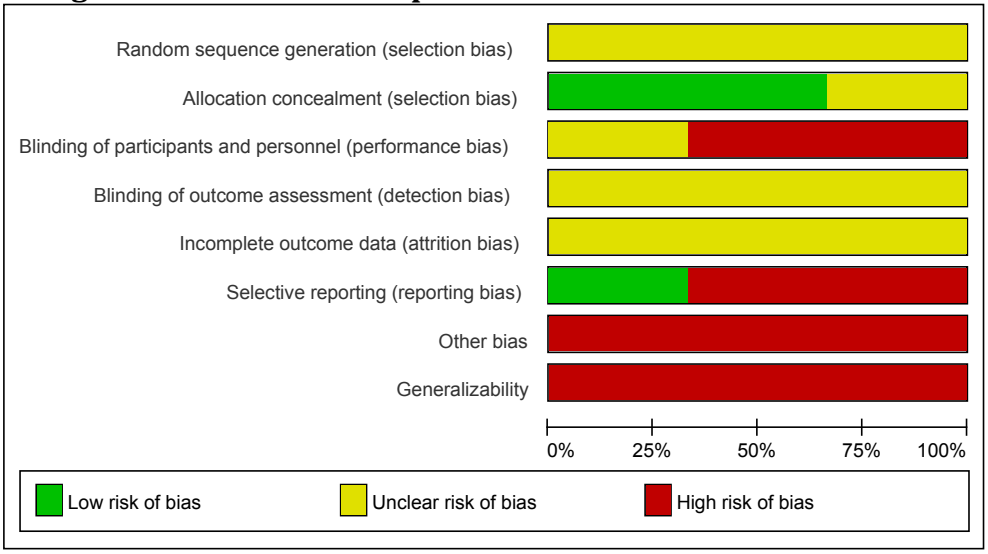

Figure 2: Detailed Summary of Findings (Overall)

High Dose versus Standard Dose Statins in Patients with Stable Coronary Heart Disease

Outcome	Participants (studies); Follow up	Relative Effect (95% CI)	Risk with Standard Dose	Risk with High Dose	Quality of the Evidence
Total Mortality	30 953 (1 RCT); 4.8 - 6.7 years	RR 0.99 [0.93, 1.06]	10.5%[a] 105 deaths per 1000	**No significant difference** 1 fewer death per 1000 (from 7 fewer to 6 more)	**High quality**[1]
Total Serious Adverse Events	12 064 (1 RCT); 6.7 yrs	RR 1.00 [0.98, 1.01]	83.5%[b] 835 SAEs per 1000	**No significant difference** No fewer SAEs per 1000 (from 17 fewer to 8 more)	**Low quality** due to study limitations and publication bias[2]
Non-Fatal Myocardial Infarction	30 953 (1 RCT); 4.8 - 6.7 years	RR 0.83 [0.76, 0.91]	7.1%[a] 71 NFMI per 1000	**12 fewer NFMI per 1000** (from 6 fewer to 17 fewer)	**Moderate quality** due to study limitations[3]
Withdrawals due to Adverse Events	30 953 (3 RCTs); 4.8 - 6.7 years	RR 1.45 [1.34, 1.58]	5.5%[a] 55 Withdrawals due to AEs per 1000	**25 more Withdrawals due to AEs per 1000** (from 19 more to 32 more)	**Moderate quality** due to study limitations[4]

[a]Control group event rate (i.e. standard dose statin) comes from this meta-analysis.
[b]Control group event rate (i.e. standard dose statin) comes from one RCT reporting this outcome, SEARCH (*Lancet* 2010;376:1658-69).

[1]Validity judged not to be significantly affected by the following study limitations: selection bias, performance bias, detection bias (Savocic *Ann Intern Med* 2012;157:429-438). Validity judged not to be appreciably affected by attrition bias since two of three RCTs contributing 82.7% of the weight to this outcome analysis report establishing vital status for all but <1% of participants. Not rated down for imprecision since 95% CI excludes appreciable benefit or harm.

[2]Risk of bias (-2): Validity of findings for some of the components of this composite judged to be affected by study limitations. Study limitations include unclear random sequence generation (selection bias); lack of blinding of clinicians to lipid parameters (performance bias); unclear blinding of outcome assessors to lipid parameters (detection bias); imbalance in total withdrawals between treatment groups (attrition bias). Validity of findings further affected by publication bias (2 of 3 RCTs do not contribute to this analysis; data missing for 61% of total participants).

[3]Risk of bias (-1): Study limitations include unclear random sequence generation (selection bias); unclear allocation concealment (selection bias); lack of or unclear blinding of participants or clinicians to treatment assignment or lipid parameters (performance bias); unclear blinding of outcome assessors to lipid parameters (detection bias); imbalance in total withdrawals between treatment groups (attrition bias). We did not rate down for indirectness since the effect estimate was consistent across clinical trials despite variability in included NFMI events between RCTs (i.e. clinical, silent, procedural).

[4]Risk of bias (-1): Study limitations include unclear random sequence generation (selection bias); unclear allocation concealment (selection bias); lack of or unclear blinding of participants or clinicians to treatment assignment or lipid parameters (performance bias); imbalance in total withdrawals between treatment groups (attrition bias). We did not rate down for inconsistency because heterogeneity could be explained by inclusion of one RCT where participants were aware of treatment assignment.

Figure 3: Total Mortality

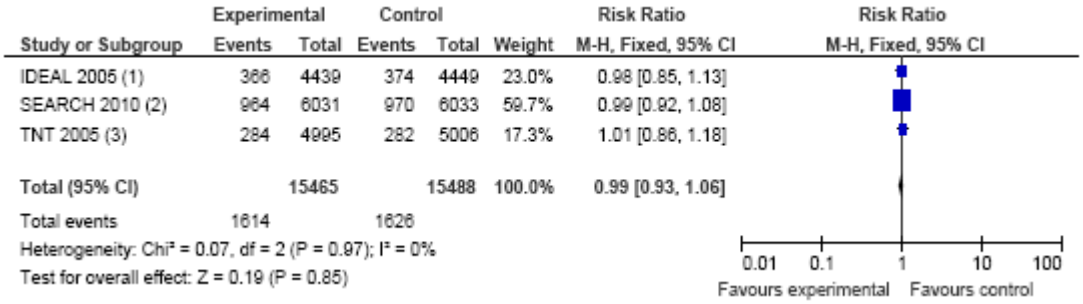

Figure 4: Non-Fatal Myocardial Infarction

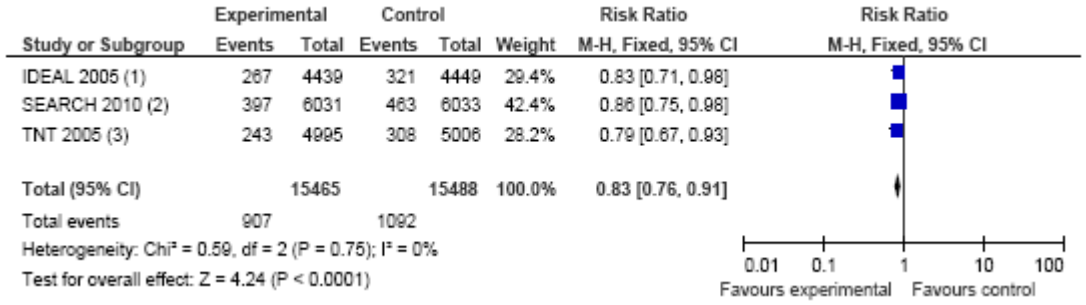

Figure 5: Total Serious Adverse Events

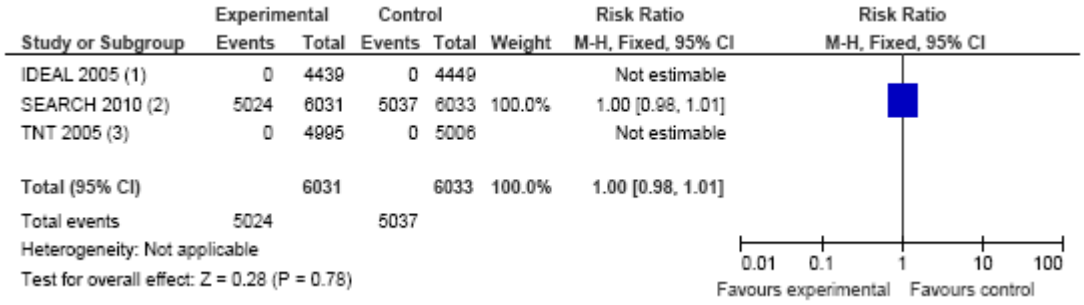

Figure 6: Total Mortality (Sex-Specific Analysis)

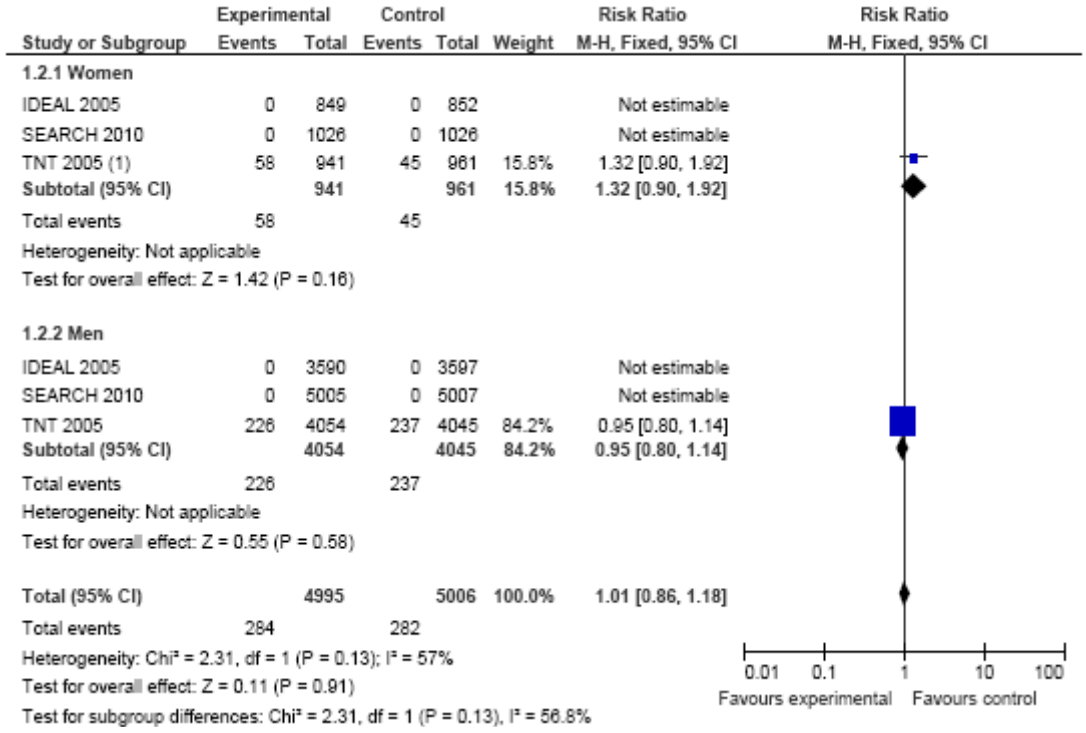

Figure 7: Non-Fatal Myocardial Infarction (Sex-Specific Analysis)

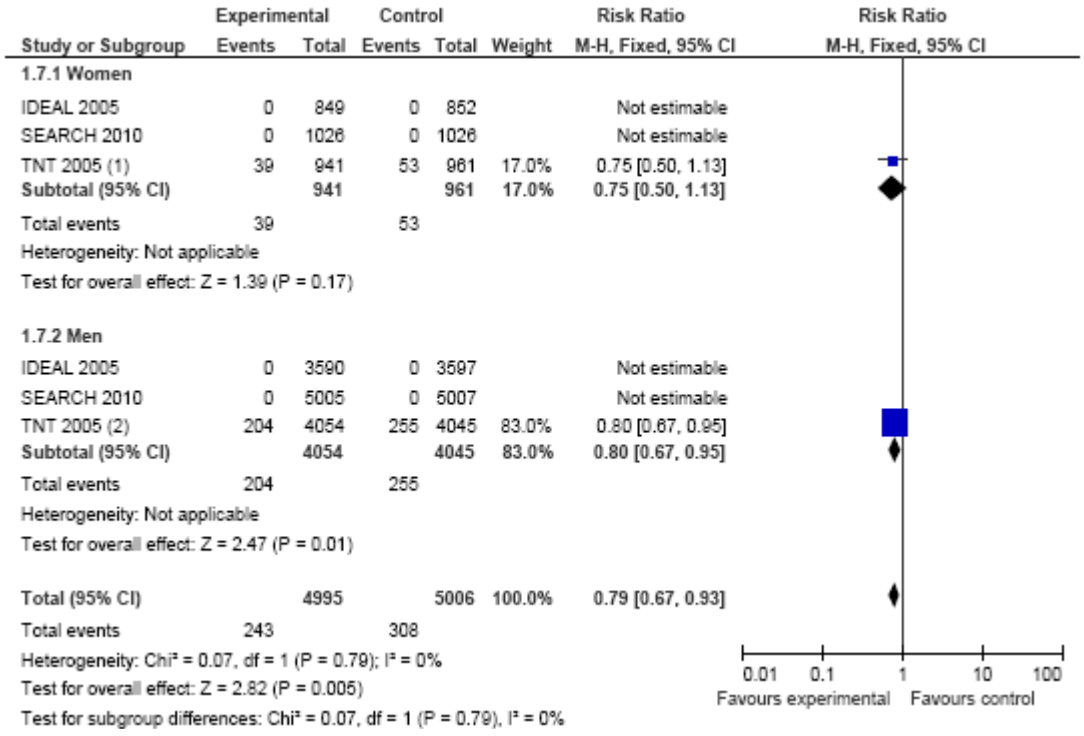

Figure 8: Detailed Summary of Findings (Sex-Specific Analysis)

High Dose versus Standard Dose Statins in Patients with Stable Coronary Heart Disease

Outcome	Participants (studies); Follow up	Relative Effect (95% CI)	Risk with Standard Dose	Risk with High Dose	Quality of the Evidence
Men					
Total Mortality	8099 (1 RCT); 4.9 years	RR 0.95 [0.80, 1.14]	5.9%[a] 59 deaths per 1000	**No significant difference** 3 fewer deaths per 1000 (from 12 fewer to 8 more)	**High quality**[1]
Non-Fatal Myocardial Infarction	8099 (1 RCT); 4.9 years	RR 0.80 [0.67, 0.95]	6.3%[a] 63 NFMI per 1000	**13 fewer NFMI per 1000** (from 3 fewer to 21 fewer)	**Moderate quality** due to study limitations[2]
Women					
Total Mortality	1902 (1 RCT); 4.9 years	RR 1.32 [0.90, 1.92]	4.7%[a] 47 deaths per 1000	**No significant difference** 15 more deaths per 1000 (from 5 fewer to 43 more)	**Moderate quality** due to imprecision and publication bias[3]
Non-Fatal Myocardial Infarction	1902 (1 RCT); 4.9 years	RR 0.75 [0.50, 1.13]	5.5%[a] 55 NFMI per 1000	**No significant difference** 14 fewer NFMI per 1000 (from 28 fewer to 7 more)	**Low quality** due to study limitations, imprecision and publication bias[4]

[a]Sex-specific control group event rate (i.e. standard dose statin) comes from one RCT contributing sex-specific data, TNT (*N Engl J Med* 2005;352:1425-35; *Heart* 2008;94:434-9)

[1]Validity for this outcome judged not to be significantly affected by the following study limitations: selection bias, performance bias, detection bias (Savocic *Ann Intern Med* 2012;157:429-438). Quality not rated down for attrition bias; although the RCT that contributes sex-specific data for this outcome does not report ascertainment of vital status for all participants and suffers from high total withdrawals (26%) with imbalance in total withdrawals between treatment groups (5%), the effect estimate is consistent with that of the overall analysis. Not rated down for imprecision since the 95% CI excludes appreciable benefit or harm and the optimal information size for this outcome was achieved (>400 events). The effect estimate for men was judged unlikely to be significantly affected by publication bias (2 of 3 RCTs do not contribute sex-specific data to this analysis) given consistency of the effect estimate with the overall analysis (where men account for 82% of participants).

[2]Risk of bias (-1): Study limitations include unclear random sequence generation (selection bias); unclear allocation concealment (selection bias); unclear blinding of participants or clinicians to treatment assignment (performance bias); unclear blinding of outcome assessors to lipid parameters (detection bias); imbalance in total withdrawals between treatment groups (attrition bias). We did not rate down for indirectness since the effect was similar across clinical trials despite variability in NFMI events included (i.e. clinical, silent, procedural). The effect estimate for men was judged unlikely to be significantly affected by publication bias (2 of 3 RCTs do not contribute sex-specific data to this analysis) given consistency of the effect estimate with the overall analysis (where men account for 82% of participants).

[3]Risk of bias (-1): As per footnote #1. In addition, the effect estimate for women was judged to be affected by imprecision (below optimal information size; estimate fails to exclude appreciable harm) and publication bias (2 of 3 RCTs do not contribute sex-specific data to this analysis; women under-represented in overall analysis). Overlap between imprecision and publication bias is anticipated.

[4]Risk of bias (-2). As per footnote #2. In addition, the effect estimate for women was judged to be affected by imprecision (below optimal information size; estimate fails to exclude appreciable benefit), and publication bias (2 of 3 RCTs do not contribute sex-specific data to this analysis; women under-represented in overall analysis). Overlap between imprecision and publication bias is anticipated.

Figure 9: Withdrawals Due To Adverse Events