Simulation

We simulated outcomes for 4,000 people with equivalent pre-trial five-year CVD risk estimates for those who were randomized to have a statin or placebo. First, we set our simulation to include 2,000 people with baseline five-year risk of CVD mortality of 5% (high risk group) and 2,000 people with five-year risk of CV mortality of 1% (low risk group). Second, within the two risk groups we randomized individuals to statin or placebo at a ratio of 1:1. Third, we applied a relative risk reduction on CVD mortality of 0.80 for individuals randomized to statin for the five years of the trial period. Fourth, we applied 0.90 relative risk reduction for the scenario of a legacy effect (eFigure 1A & 1B) and applied no relative risk reduction for the scenario of no legacy effect (eFigure 1C & 1D). After the trial, all individuals were followed until they had an event, up to a further 20 years. For simplicity, we did not include any effects for aging in the model. The simulation was run 1000 times in R 3.3.1. Survival and hazard curves were generated by calculating the average results.

eFigure 1. Survival and Hazard curves using simulated data.

Fig 1A. Survival curves using simulated data where there is a legacy effect.

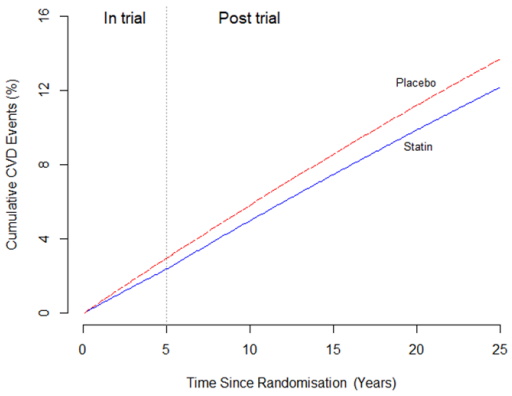


Fig 1B. Hazard curves using simulated data where there is a legacy effect.

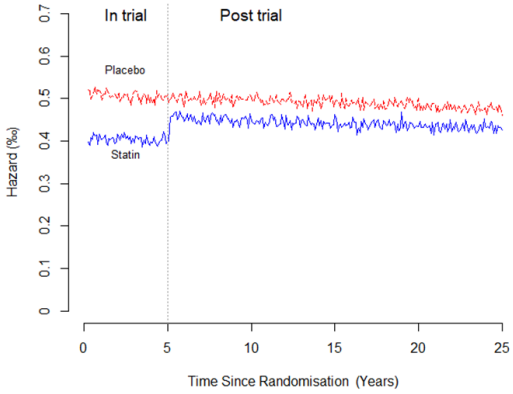


Fig 1C. Survival curves using simulated data where there is no legacy effect.

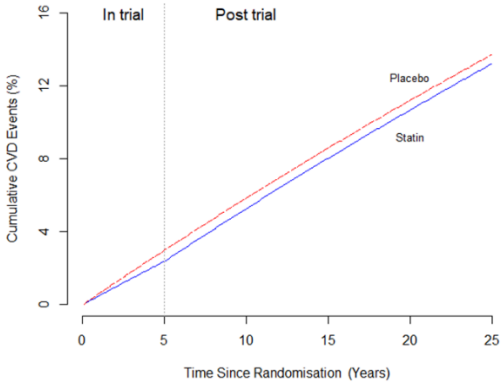
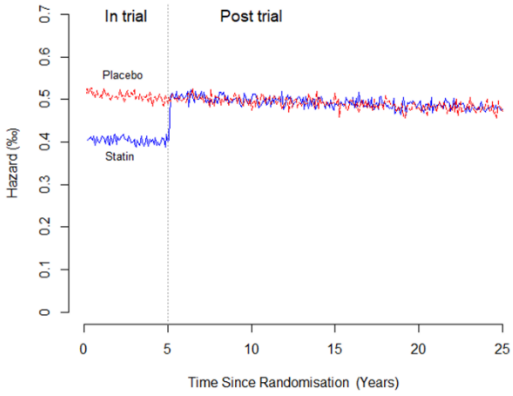


Fig 1D. Hazard curves using simulated data where there is no legacy effect.



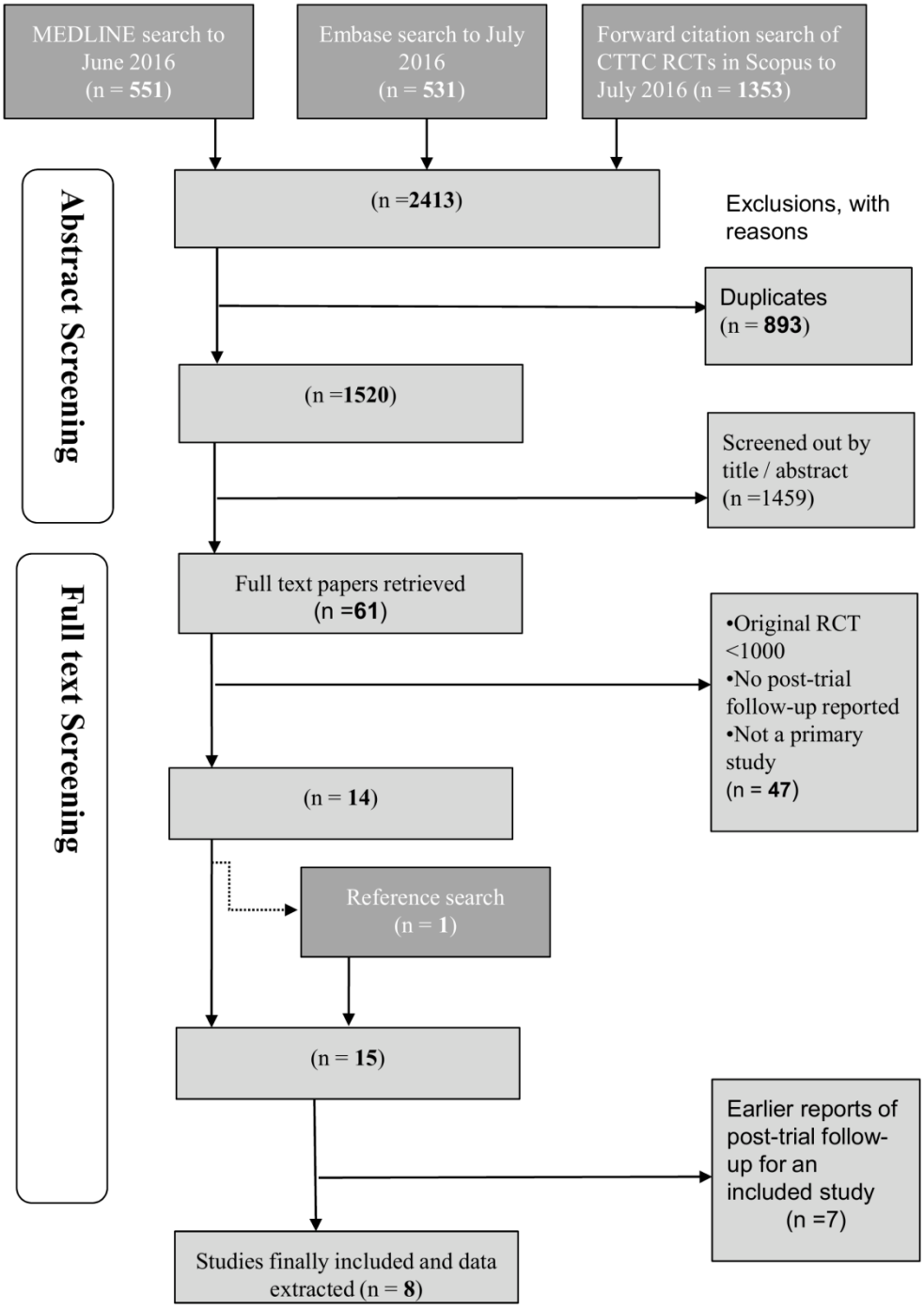
1A: Survival Curves, legacy effect; 1B: Hazard Curves, legacy effect; 1C: Survival Curves, no legacy effect; 1D: Hazard Curves, no legacy effect

During RCT period (5 years): Relative Risk Reduction for CVD mortality=0.80; during post-trial period (20 years): Relative Risk Reduction for CVD mortality =1 (i.e. no legacy effect).

Exaggeration of apparent legacy benefit is observed in the Survival Curves because of contribution of within-trial treatment effects on cummalitve incidence. Unbiased estimation

of post-trial legacy effects are shown in the Hazard Curves (note that these are curves of the instantaneous hazard at each time point, and are not curves of hazard ratios).

eFigure 2. Selection of primary studies



CTTC = Cholesterol Treatment Trialists' Collaboration