Appendix 2. Calculation example of Net Benefit

Strategy	Treat no patients, regardless of predicted treatment effect	Treat all patients, regardless of predicted treatment effect	Framingham risk score prediction-based treatment
Number of patients	8875	8853	8832
2 year event rate	2.47%	1.39%	1.84%
10 year event rate	11.75%	6.77%	8.88%
Decrease in 10 year event rate	0%	4.99%	2.87%
Number of treatments (treatment rate)	0 (0%)	8853 (100%)	4106 (46.5%)
Net benefit	0	-0.0001	0.0054

The net benefit assessment method is described in detail by Vickers et al.[1] Here we provide an example of how we applied this method to our data. In this example, the number willing to treat (NWT) is set to 20. This means that the decision-threshold (T) is a 5% absolute risk reduction or more. The net benefit of Framingham risk score-prediction based treatment compared to treat all patients is calculated as follows:

1) First we observe the 2-year event rate in the placebo treated group, which is the event rate in the situation that no one is treated with rosuvastatin. The event rate of 2.47% in this example can be extrapolated to an event rate of 11.75% over 10 years follow up.

2) Second we observe the 2-year event rate in the rosuvastatin treated group. This is the event rate in the situation that everybody is treated with rosuvastatin. The event rate in the present example (1.39%) can be extrapolated to an event rate of 6.77% over 10 years follow up. The decrease in event rate of 4.99% was achieved at the cost of a treatment rate of 100%.

3) The net benefit of treat all patients versus treat no one (decrease in event rate – treatment rate x T) is, thus, 0.0499 - 1 x 0.05 = -0.0001. Notably, the minus sign means that in if the NWT is 20, treating no one is preferable over treating everyone.

4) Next, we observe the event rate in patients whose treatment allocation was congruent to their predicted treatment effect. This includes 4,106 intervention group patients whose predicted 10-year treatment effect exceeded the decision-threshold (i.e. 5% absolute risk

reduction) and 4,726 control group patients whose predicted 10-year treatment effect was lower than the decision-threshold. The 2-year event rate in these groups of patients combined (n=8,832) was 1.84% (8.88% if extrapolated to 10 years). This means that Framingham risk score prediction-based treatment compared to treating no one reduced the event rate by 2.87% at the cost of a treatment rate of 46.5%.

5) The net benefit of treatment according to Framingham based predictions versus treat no one (decrease in event rate – treatment rate x T) is, thus, 0.0287 - .465 x 0.05 = 0.0054. This figure can also be found in results table 3 of the article. Notably, it means that if the NWT is 20, Framingham risk score prediction-based treatment is preferable over both treating everyone and treating no one.

1 Vickers AJ, Kattan MW, Daniel S. Method for evaluating prediction models that apply the results of randomized trials to individual patients. *Trials* 2007;8:14.