

## **Online Appendix**

### **Real-life evaluation of European and American high-risk strategies for primary prevention of cardiovascular disease in patients with first myocardial infarction**

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## Supplementary Methods

### Estimation of predicted risk and eligibility for statins

The guideline-recommended risk equations and web calculators used to determine predicted risk, risk factors (predictors), clinical endpoints, definitions of high-risk and recommended decision thresholds above which statin therapy should be considered are shown in Table 1 in the printed article and described below.

The 2012 ESC recommendations for primary prevention are based on the SCORE model introduced in 2003 that predicts 10-year risk for fatal CVD in people 40 to 65 years of age.[1] Two standard SCORE risk charts/equations are available, one for countries with a high incidence of fatal CVD, the other for countries with a low incidence. Denmark, together with many other European countries, was reclassified from “high-risk” to “low-risk” in 2012 and recommended to use the SCORE low-risk equation instead of the high-risk equation. As another novelty, HDL-adjusted risk estimates became available in 2012, either as risk charts or the electronic version of SCORE, *HeartScore*. [2] HeartScore allows entry of age up to 100 years but the age-dependent risk is capped at age 65. The LDL-C dependent eligibility for statin therapy is based on both estimated 10-year risk and age, expressed in the following way: “In general, those with a risk of CVD death of  $\geq 5\%$  qualify for intensive advice, and may benefit from drug treatment. At risk levels  $>10\%$ , drug treatment is more frequently required. In persons older than 60, these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other cardiovascular risk factor levels are ‘normal’.” [1] While no universally applicable risk threshold for statin therapy is given, a common interpretation is that statin therapy should be considered at SCORE  $\geq 5\%$  (defined as high risk) below age 60 and  $\geq 10\%$  (defined as very high risk) above 60.

The 2013 ACC/AHA recommendations for primary prevention are based on the newly developed PCE that predict 10-year risk for atherosclerotic CVD (ASCVD) defined as nonfatal MI, CHD death, and fatal and nonfatal stroke.[3,4] The downloadable PCE-based risk calculator provides race- and sex-specific 10-year and lifetime risks of ASCVD in nonhispanic Whites and nonHispanic African Americans.[5] For other ethnic groups, use of the sex-specific estimates calculated for nonhispanic Whites may be considered (expert opinion/IIb recommendation).[4] In adults 40 to 75 years of age, eligibility for statin therapy is PCE  $\geq 7.5\%$  (strong/class I recommendation) and 5% to  $<7.5\%$  (weak/class IIa recommendation).[4]

The 2013 ACC/AHA guideline replaced the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program.[6,7] ATP III-based risk assessment used a Framingham-derived risk equation that predicted 10-year risk for hard coronary heart disease (CHD) defined as nonfatal MI and fatal CHD. The web-based risk calculator is still available.[8] The treatment algorithm for primary prevention with statins was complicated, depending on number of risk factors, low-density lipoprotein cholesterol (LDL-C) levels, and estimated 10-year risk ( $>20\%$ : nearly unconditional treatment; 10-20%: conditional treatment).[6,7]

The 2010 revision of the NICE (National Institute for Health and Care Excellence) guideline recommended to estimate 10-year risk for CVD, defined by QRISK as CHD (angina and MI), stroke, and transient ischemic attack.[9,10] The latest version of the risk calculator, QRISK<sup>®</sup>2-2013, was used for this study.[11] When QRISK2 is used outside UK, an average value for social deprivation (UK postcode) is used to calculate the score. For primary prevention in people aged 40-74, statin therapy was recommended at QRISK  $\geq 20\%$  (defined as high risk). The 2014 revision of the NICE guideline recommends to lower the risk-based threshold for primary prevention with statins from 20% to 10% in people  $\leq 84$  years of age,[12] endorsed by the third Joint British Societies’ (JBS3) consensus recommendations for the prevention of CVD.[13] Beyond age 84, the new recommendation 55 reads as follows; “For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 48)”.[12]

## Comparison of CVD prevention guidelines

We evaluated and compared the performance of the American and European primary prevention guidelines shown in Table 1 in the printed article. For each patient we calculated the absolute 10-year risk for the predicted outcomes using the recommended risk equations or calculators. In accordance with the SCORE risk charts [1] and the online risk calculator HeartScore,[2] the age-dependent risk was capped at age 65 when estimating risk using the SCORE algorithms. The guidelines were compared in three steps as described below.

First, we assessed the concordance in CVD risk characterization between the PCE and the four other risk equations/calculators (ATP III, QRISK2, SCORE+HDL low-risk and SCORE+HDL high-risk) by computing the Spearman rank-order correlation coefficients (Spearman's rho). Secondly, the new American ACC/AHA risk thresholds of 5% and 7.5% were translated to risks estimated by the other risk equations/calculators. The risk values estimated by ATP III, QRISK2 and SCORE+HDL that corresponded to PCE risks of 5% and 7.5% were determined from sex-specific linear regression equations derived from pairwise comparisons of predicted risk in persons with a PCE risk <7.5%. Finally, we determined the proportion of patients with a first MI who would have been eligible for primary prevention with statins based on recommendations in the former and the new American and European guidelines. Men and women were analyzed separately, and stratified by pre-specified age groups (40 to 60 years and 60 to 75 years).

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## Supplementary Table

**Supplementary Table. Proportion of patients (detection rate) with first MI who had a predicted risk of atherosclerotic CVD above which primary prevention with statins should be considered.**

| Guideline Algorithm                                                    | Risk threshold | Detection rate (%) |               |                    |               |
|------------------------------------------------------------------------|----------------|--------------------|---------------|--------------------|---------------|
|                                                                        |                | 40-60 years of age |               | 60-75 years of age |               |
|                                                                        |                | Men<br>n=65        | Women<br>n=31 | Men<br>n=97        | Women<br>n=54 |
| 2012 ESC European Guideline SCORE+HDL Low-Risk <sup>1</sup>            | 5%             | 2                  | 0             | /                  | /             |
|                                                                        | 10%            | /                  | /             | 12                 | 2             |
| 2012 ESC European Guideline SCORE+HDL High-Risk <sup>1</sup>           | 5%             | 31                 | 0             | /                  | /             |
|                                                                        | 10%            | /                  | /             | 43                 | 22            |
| 2013 ACC/AHA <sup>2</sup><br>Pooled Cohort Equations/White             | 5%             | 78                 | 32            | 100                | 98            |
|                                                                        | 7.5%           | 62                 | 13            | 100                | 85            |
| Adult Treatment Panel III <sup>3</sup><br>Modified Framingham Equation | 10%            | 60                 | 10            | 98                 | 22            |
|                                                                        | 20%            | 12                 | 0             | 38                 | 4             |
| 2010 & 2014 NICE/UK <sup>4,5</sup><br>QRISK2-2013/White                | 10%            | 40                 | 6             | 100                | 91            |
|                                                                        | 20%            | 2                  | 0             | 69                 | 22            |

<sup>1</sup>Statin therapy should be considered at SCORE  $\geq 5\%$  below age 60 and  $\geq 10\%$  above 60.[1]

<sup>2</sup>Recommendations for statin therapy are 10-year risk  $\geq 7.5\%$  (strong/class I) and 5% to  $<7.5\%$  (weak/class IIa).[2]

<sup>3</sup>Recommendations for statin therapy depending on risk factors, cholesterol level, and 10-year risk  $>20\%$  (~unconditional treatment) and 10-20% (conditional treatment).[3]

<sup>4,5</sup>Indication for statin therapy in UK was 10-year risk  $\geq 20\%$  until 2014,[4] then lowered to  $\geq 10\%$  in the 2014 NICE guideline.[5]

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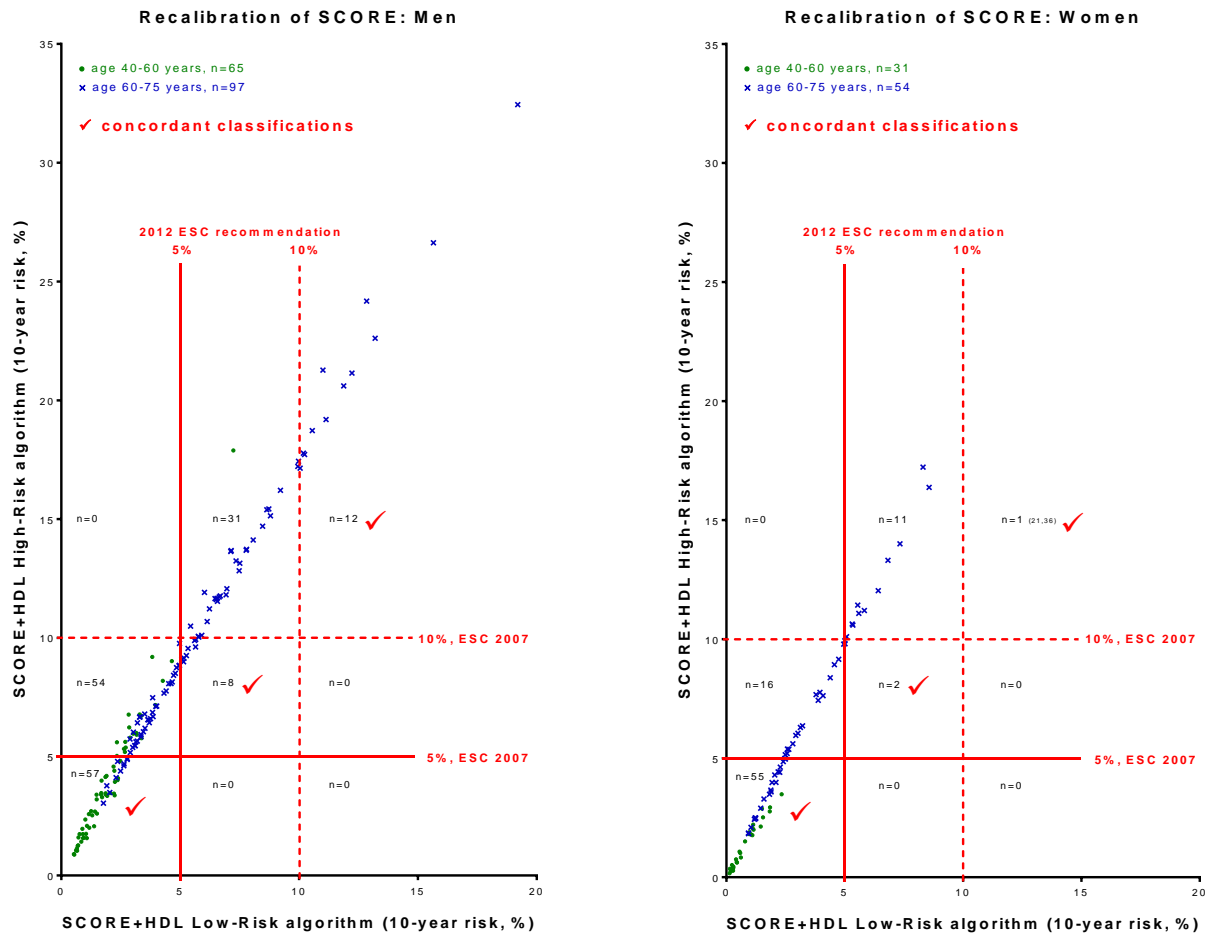
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## Supplementary Figure



### Supplementary Figure. Eligibility for statin therapy by high-risk versus low-risk SCORE equation.

Predicted risk estimated by the High-Risk and Low-Risk SCORE equations correlated perfectly (Spearman's  $\rho \geq 0.99$ ;  $R^2 = 0.99$ ;  $p < 0.0001$ ). The High-Risk equation consistently overestimates risk compared with the Low-Risk equation. Classification based on the guideline-defined decision thresholds of 5% and 10% was discordant in 85 of 162 males (52%) and 27 of 85 females (32%), with potential loss of indication for statin therapy by recalibration of SCORE to fit a lower mortality of cardiovascular disease. ESC: European Society of Cardiology.