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# Finding the Balance Between Benefits and Harms When Using Statins for Primary Prevention of Cardiovascular Disease

## A Modeling Study

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**Background:** Many guidelines use expected risk for cardiovascular disease (CVD) during the next 10 years as a basis for recommendations on use of statins for primary prevention of CVD. However, how harms were considered and weighed against benefits is often unclear.

**Objective:** To identify the expected risk above which statins provide net benefit.

**Design:** Quantitative benefit–harm balance modeling study.

**Data Sources:** Network meta-analysis of primary prevention trials, a preference survey, and selected observational studies.

**Target Population:** Persons aged 40 to 75 years with no history of CVD.

**Time Horizon:** 10 years.

**Perspective:** Clinicians and guideline developers.

**Intervention:** Low- or moderate-dose statin versus no statin.

**Outcome Measures:** The 10-year risk for CVD at which statins provide at least a 60% probability of net benefit, with baseline risk, frequencies of and preferences for statin benefits and harms, and competing risk for non-CVD death taken into account.

**Results of Base-Case Analysis:** Younger men had net benefit at a lower 10-year risk for CVD than older men (14% for ages 40 to 44 years vs. 21% for ages 70 to 75 years). In women, the risk required for net benefit was higher (17% for ages 40 to 44 years vs. 22% for ages 70 to 75 years). Atorvastatin and rosuvastatin provided net benefit at lower 10-year risks than simvastatin and pravastatin.

**Results of Sensitivity Analysis:** Most alternative assumptions led to similar findings.

**Limitation:** Age-specific data for some harms were not available.

**Conclusion:** Statins provide net benefits at higher 10-year risks for CVD than are reflected in most current guidelines. In addition, the level of risk at which net benefit occurs varies considerably by age, sex, and statin type.

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For author affiliations, see end of text.
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Most guidelines recommend statins for primary prevention of cardiovascular disease (CVD) if 10-year risk exceeds 7.5% to 10%, often in addition to such other criteria as high cholesterol level or presence of at least 1 specific risk factor (1–5). However, use of statins for primary prevention of CVD is controversial and varies greatly among countries because of several factors, such as uncertainty about the applicability of the results of randomized controlled trials (RCTs) on primary prevention to real-world populations, the definition of eligible persons likely to benefit, and potential differential reporting of harms (6–9).

Nevertheless, guidelines must make recommendations and deal with the uncertainties of the existing evidence base. Guidelines should consider multiple factors that influence the balance of benefits and harms of statins, including preventive effects and harms, baseline risks for benefit and harm outcomes, and outcome preferences of persons who may benefit from statins for primary prevention of CVD (10, 11). However, none of the current guidelines used a systematic assessment of the benefit–harm balance of statins that considered these factors (12). In addition, whether the currently recommended risk thresholds of 7.5% and 10% are justified is unclear. Therefore, this study aimed to assess the balance of benefits and harms of statins for primary prevention of CVD and determine age- and sex-specific 10-year risk thresholds at which the net benefits of statins outweigh the net harms. Because not all statins have the same benefit and harm profiles (13–15), we analyzed 4 commonly used statins separately.

## METHODS

### Target Population and Setting

We performed a quantitative benefit–harm balance modeling study on use of statins for primary prevention of CVD for persons in the general population aged 40 to 75 years with no history of CVD events. We excluded persons older than 75 years because of scarce data in this age group. Our study evaluated the balance of benefits and harms and accounted for baseline risks for the benefit and harm outcomes, the magnitude of the increase or decrease in risk due to statins, the relative importance of the outcomes, and a specific time horizon.

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Supplement

## Statins and Benefit and Harm Outcomes

This analysis focused on low- or moderate-dose statins, which are frequently prescribed for primary prevention of CVD (3), and excluded high-dose statins. We performed the benefit–harm analysis for 4 statins (atorvastatin, simvastatin, pravastatin, and rosuvastatin) for which there were sufficient data from RCTs about their effects. We selected clinically relevant benefit and harm outcomes from systematic reviews (14, 16) and quantified their relevance in a preference-eliciting survey reported elsewhere (17). Benefit outcomes (those favoring statin use) were fatal and nonfatal CVD events. Harm outcomes (adverse effects of statins) were myopathy, hepatic and renal dysfunction, cataracts, hemorrhagic stroke, type 2 diabetes, any cancer, nausea or headache, and treatment discontinuation due to adverse effects. We considered non-CVD mortality as a competing risk because we found insufficient evidence that statins reduce deaths due to causes other than CVD. Although it would be possible to use specific CVD events in the benefit–harm balance modeling, we considered a composite outcome of CVD events as the end point because most clinical guidelines and risk scores refer to such a composite outcome. This study did not consider costs associated with statins.

## Data Sources

We systematically selected evidence on the following input parameters needed for the quantitative benefit–harm balance modeling (18).

### *Preventive or Adverse Effects of Statins*

We based estimates of statin effects on a network meta-analysis of CVD events and harm outcomes in a primary prevention population that we performed previously for the purpose of the current study (**Figures 1** to **3** of the **Supplement**, available at Annals.org). We obtained information on preventive effects on cataracts and hemorrhagic stroke from 2 RCTs (HOPE-3 [Heart Outcomes Prevention Evaluation-3] [19] and MEGA [Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese] [20], respectively) because there were not enough trials for a meta-analysis. Data on harm outcomes from trials might be incomplete because of short follow-up or limited external validity or may be affected by differential reporting bias (8, 21). Observational studies may be more suitable for providing real-world estimates of harms, but they are often inherently biased (8, 21). We thus considered combined statin effect estimates for the harm outcomes from large observational studies and RCTs using a Bayesian inverse variance–weighted averaging method (**Appendix Table 1** [available at Annals.org] and **Table 1** of the **Supplement**) (22–25). The preventive effects from observational studies contributed less to the pooled effect due to higher variances. We also performed a sensitivity analysis using estimates of statin effects on harms from RCTs only.

### *Baseline Outcome Risks in the Population*

Population-based baseline risks are favored over event rates in control groups of RCTs because they better reflect the real-world population (18). We extracted age- and sex-specific baseline rates of type 2 diabetes, any cancer, hemorrhagic stroke, and non-CVD mortality from Global Burden of Disease estimates for Switzerland (26) and rates of myopathy, renal and hepatic dysfunction, and cataracts from other observational data (age- or country-specific rates were not available for these) (23) (**Table 2** of the **Supplement**). We chose Switzerland for some of these age- and sex-specific risks because the weights of the outcomes were elicited there and because outcome risks are moderate there, except for competing risk for death, which is low compared with other countries. However, we also performed the analysis for the United States and the United Kingdom (see Sensitivity Analyses). Because baseline risks for nausea or headache and treatment discontinuation were not available, we used rates from control groups of RCTs.

### *Outcome Preferences*

We considered population average preference weights from a preference-eliciting study designed to inform the current study. The best–worst scaling survey elicited preferences for benefit and harm outcomes of statins from a primary prevention population in Switzerland and Ethiopia (17). We considered preference weights reported as the surface under the cumulative ranking curve (SUCRA) (analyzed using a network meta-analytic approach) for the base-case analysis (27) and additional preference scales, including best–worst score and log-odds, for sensitivity analyses. The SUCRA indicates the probability of an outcome that patients would rather avoid or a weight showing the relative importance of an outcome to patients (larger values correspond to more important outcomes) (**Appendix Table 2**, available at Annals.org).

## Time Horizon

Although data from RCTs are available for follow-up less than 5 years, we extended the time horizon to 10 years with the assumption of smaller CVD risk accumulation and similar effects of statins over the period in low- to moderate-risk persons.

## Subgroups

We modeled the balance of benefits and harms and determined risk thresholds for 350 subgroups according to age and sex across 10-year CVD risks ranging from 1% to the value above which the benefits consistently outweighed the harms. We did not need to predict 10-year CVD risks because we repeated the analysis for each percentage point increase up to 25% (all statins) or 40% (specific statins). Although not relevant to this study, the use of well-calibrated risk scores is important for clinical practice to determine a person's risk and whether this risk justifies use of statins.

## Statistical Analysis

### *Benefit–Harm Balance Index*

We used a benefit–harm balance model developed by Gail and colleagues at the National Cancer Institute (NCI) (28, 29) and extended it to fit our research question of determining risk thresholds. A detailed description of our model is provided in the Appendix (available at Annals.org). In brief, we estimated the expected age- and sex-specific number of benefit and harm outcome events per 1000 persons not using statins over 10 years by using an exponential model that assumed constant risk rates over the time horizon and accounted for competing risk for non-CVD death. We then calculated the corresponding number of expected events for each outcome among statin recipients by using the same model but with consideration of estimates of statin effects. The differences in expected events with and without statin use provided attributable absolute events for each benefit and harm outcome. We then weighted the differences by their respective preference weights and summed them to yield a single benefit–harm index. The resulting index could have any negative (harms outweighed benefits), zero (harms equaled benefits), or positive (benefits outweighed harms) value on an arbitrary scale. To account for statistical uncertainty of the input parameters, we repeated the analysis 100 000 times for each subgroup with resampling of the parameters independently from normal distributions defined by their mean estimates (log risk ratio, SUCRA, and baseline risks) and their SEs.

### *Determining 10-Year Risk Thresholds for Net Benefits*

We calculated the probability of net benefits as the proportion of repetitions for which the benefit–harm index was positive (benefits outweighed harms). This probability could have any value between 0% and 100%. We defined statins as having net benefits if the probability of the index exceeding zero was at least 60% and net harms if the probability was less than 40%. Thus, probabilities of at least 40% but less than 60% (assuming an arbitrary 10% probability of uncertainty instead of defining the cutoff at exactly 50%) represented neither net benefits nor net harms. The probabilities were computed across the spectrum of CVD risks, from which we could identify risk thresholds for different subgroups. We performed all analyses using R, version 3.3.2 (R Foundation for Statistical Computing) (30).

### *Sensitivity Analyses*

We performed sensitivity analyses using different alternative assumptions. We tested the effect that different preference weights, including log-odds from a conditional logit model and best–worst scores, had on the balance of benefits and harms (17). We repeated the analysis with statin effects on harms from RCTs only instead of convergent estimates from RCTs and observational data. We checked whether excluding RCTs in high-risk primary prevention populations and considering baseline risks from the United States and the United Kingdom affected the balance of benefits and harms. We also tested the assumption of a constant risk rate over 10 years by using a piecewise exponential model (31). Although it is reasonable to assume constant risk for CVD events over 10 years (and most prediction models for CVD events do so), risk for some harms may change over time. In particular, the data used in our meta-analyses (not shown) suggested that risks for headache or nausea, myopathy, and renal and hepatic dysfunction may be highest at treatment initiation and decrease constantly over time. Therefore, we used a 1-year time horizon in each piecewise exponential model for these outcomes where we allowed the risk rates to decrease by 10% per year. Finally, the outcomes are not independent of each other, but we could not find data showing empirical correlations among them. Thus, we tested the effect on the risk thresholds by assuming moderate to strong correlation between CVD and diabetes and between diabetes and renal dysfunction. The correlations we used are probably too strong, but we decided to err on the side of caution to avoid underestimating the effect of correlations among outcomes (Figure 5 of the Supplement).

## Ethics

This study was based on published and aggregated data for which no ethical approval was needed.

## Role of the Funding Source

The Swiss Government Excellence Scholarship Office, the Béatrice Ederer-Weber Foundation, and the North-South Cooperation at the University of Zurich had no role in the design or conduct of the study or the decision to submit the manuscript for publication.

# RESULTS

## Expected Number of Benefit and Harm Outcome Events

Tables 1 and 2 show the expected number of benefit and harm outcome events per 1000 men and women over 10 years with and without use of all statins. The expected number of events among persons not using statins increased for diabetes, any cancer, and hemorrhagic stroke due to age, whereas the increase in these events in the statin group was due to the effect of statins in addition to age. The increase in events with age in the statin and nonstatin groups accounted for the competing risk for non-CVD death, whose effect on attenuation of the outcome risks was smaller than the effect of age on risk for diabetes, any cancer, and hemorrhagic stroke. There was no increase in myopathy, cataracts, or renal and hepatic dysfunction with age because we had to rely on average estimates given that age-specific estimates were not available; instead, risks decreased slightly with age due to the competing risk. The differences in expected events between men and women resulted from differences in baseline risks for the outcomes, differential statin effects on some outcomes, and higher competing risk for death in men. Tables 1 and 2 also show the expected number of CVD

*Table 1.* Number of Expected Benefit and Harm Outcome Events per 1000 Men in Switzerland Over 10 Years With and Without Use of Statins*

| Variable | Aged 40–44 Years | | Aged 45–49 Years | | Aged 50–54 Years | | Aged 55–59 Years | | Aged 60–64 Years | | Aged 65–69 Years | | Aged 70–75 Years | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins |
| **Harm outcomes** | | | | | | | | | | | | | | |
| Myopathy | 4 | 5 | 4 | 5 | 4 | 5 | 4 | 5 | 3 | 5 | 3 | 5 | 3 | 4 |
| Renal dysfunction | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 9 | 7 | 9 | 7 | 9 | 7 | 9 |
| Hemorrhagic stroke | 3 | 3 | 5 | 6 | 6 | 7 | 7 | 9 | 10 | 12 | 14 | 16 | 22 | 26 |
| Hepatic dysfunction | 24 | 34 | 24 | 34 | 24 | 33 | 24 | 33 | 23 | 33 | 23 | 32 | 22 | 32 |
| Type 2 diabetes | 28 | 30 | 34 | 37 | 45 | 49 | 59 | 64 | 65 | 70 | 61 | 66 | 50 | 54 |
| Any cancer | 16 | 16 | 26 | 26 | 48 | 49 | 84 | 86 | 138 | 141 | 200 | 204 | 239 | 244 |
| Cataracts | 94 | 122 | 94 | 121 | 93 | 121 | 92 | 120 | 92 | 119 | 90 | 117 | 88 | 114 |
| Headache/nausea | 334 | 367 | 333 | 366 | 332 | 364 | 329 | 362 | 326 | 358 | 321 | 353 | 314 | 345 |
| Treatment discontinuation | 295 | 296 | 295 | 295 | 293 | 294 | 291 | 292 | 288 | 289 | 284 | 285 | 278 | 278 |
| **10-y CVD risk** | | | | | | | | | | | | | | |
| 1% | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 9 | 7 |
| 2% | 20 | 15 | 20 | 15 | 20 | 15 | 20 | 15 | 19 | 14 | 19 | 14 | 19 | 14 |
| 3% | 30 | 22 | 30 | 22 | 30 | 22 | 29 | 22 | 29 | 22 | 29 | 21 | 28 | 21 |
| 4% | 40 | 30 | 40 | 30 | 40 | 29 | 39 | 29 | 39 | 29 | 38 | 28 | 37 | 28 |
| 5% | 50 | 37 | 50 | 37 | 49 | 37 | 49 | 37 | 49 | 36 | 48 | 36 | 47 | 35 |
| 6% | 60 | 45 | 60 | 44 | 59 | 44 | 59 | 44 | 58 | 43 | 57 | 43 | 56 | 42 |
| 7% | 70 | 52 | 70 | 52 | 69 | 52 | 69 | 51 | 68 | 51 | 67 | 50 | 65 | 49 |
| 8% | 80 | 60 | 79 | 59 | 79 | 59 | 78 | 59 | 78 | 58 | 76 | 57 | 75 | 56 |
| 9% | 90 | 67 | 89 | 67 | 89 | 67 | 88 | 66 | 87 | 65 | 86 | 64 | 84 | 63 |
| 10% | 100 | 75 | 99 | 75 | 99 | 74 | 98 | 74 | 97 | 73 | 96 | 72 | 93 | 70 |
| 11% | 110 | 82 | 109 | 82 | 109 | 82 | 108 | 81 | 107 | 80 | 105 | 79 | 103 | 77 |
| 12% | 119 | 90 | 119 | 90 | 119 | 89 | 118 | 89 | 117 | 88 | 115 | 86 | 112 | 84 |
| 13% | 129 | 97 | 129 | 97 | 129 | 97 | 128 | 96 | 126 | 95 | 124 | 94 | 121 | 91 |
| 14% | 139 | 105 | 139 | 105 | 138 | 104 | 137 | 104 | 136 | 103 | 134 | 101 | 131 | 99 |
| 15% | 149 | 113 | 149 | 113 | 148 | 112 | 147 | 111 | 146 | 110 | 143 | 108 | 140 | 106 |
| 16% | 159 | 121 | 159 | 120 | 158 | 120 | 157 | 119 | 155 | 118 | 153 | 116 | 150 | 113 |
| 17% | 169 | 128 | 169 | 128 | 168 | 127 | 167 | 126 | 165 | 125 | 163 | 123 | 159 | 120 |
| 18% | 179 | 136 | 179 | 136 | 178 | 135 | 177 | 134 | 175 | 133 | 172 | 131 | 168 | 128 |
| 19% | 189 | 144 | 189 | 143 | 188 | 143 | 187 | 142 | 185 | 140 | 182 | 138 | 178 | 135 |
| 20% | 199 | 152 | 199 | 151 | 198 | 151 | 196 | 149 | 194 | 148 | 191 | 145 | 187 | 142 |
| 21% | 209 | 159 | 209 | 159 | 208 | 158 | 206 | 157 | 204 | 155 | 201 | 153 | 196 | 150 |
| 22% | 219 | 167 | 219 | 167 | 218 | 166 | 216 | 165 | 214 | 163 | 210 | 161 | 206 | 157 |
| 23% | 229 | 175 | 228 | 175 | 227 | 174 | 226 | 173 | 223 | 171 | 220 | 168 | 215 | 164 |
| 24% | 239 | 183 | 238 | 183 | 237 | 182 | 236 | 180 | 233 | 179 | 230 | 176 | 225 | 172 |
| 25% | 249 | 191 | 248 | 190 | 247 | 190 | 245 | 188 | 243 | 186 | 239 | 183 | 234 | 179 |

CVD = cardiovascular disease.
* Values are the predicted number of events with and without use of statins per 1000 men over 10 y based on participants' baseline risks, calculated using an exponential model and adjusted for non-CVD mortality as a competing risk. Some outcomes, such as myopathy, hepatic dysfunction, and renal dysfunction, had restrictive definitions in the observational data source (i.e., only moderate or serious cases were reported) and were average estimates (i.e., not age-specific).

events for each percentage point increase in CVD risk with and without statins.

### Benefit–Harm Balance and Risk Thresholds

We estimated the benefit–harm balance by sex and age group across 10-year CVD risk of 1% to 25% for all statins and 1% to 40% for specific statins until we obtained a probability above which the balance was consistently positive. Figure 1 shows the probabilities at which statins provide net benefit among 350 subgroups based on age and sex (mean benefit–harm balance indices are presented in Figure 4 of the Supplement). Statins demonstrated net benefits (green cells) starting at a CVD risk of 14% for men aged 40 to 44 years, and the threshold increased to 21% for those aged 70 to 75 years. Similar results were observed for women, but the risk thresholds were higher (17% for women aged 40 to 44 years and 22% for those aged 70 to 75 years). Persons at high risk for CVD (>21%) were likely to benefit from statins, regardless of sex or age.

Figures 2 and 3 illustrates the probabilities at which the benefits of specific statins outweighed the harms for 2240 subgroups based on age, sex, and CVD risk. As a result of differences in preventive effects on benefit or harm outcomes, atorvastatin had the most favorable benefit–harm balance, followed by rosuvastatin, especially for persons with low or medium CVD risk and age less than 60 years. The other statins did not demonstrate benefits at the same risk level for any of the age groups. For example, among men aged 45 to 49 years, net benefits were seen at a 10-year CVD risk of 15% for atorvastatin but at risk levels of 18% for rosuvastatin, 19% for pravastatin, and 21% for simvastatin.

With the exception of atorvastatin, the risk thresholds for the specific statins were all higher than for the overall statins due to differences in preventive effects and less precision (wider distributions) in the specific statins that could have led to greater variation in randomly sampled estimates during modeling and accordingly wider distributions of the resulting benefit–harm indices.

### Sensitivity Analyses

Results of the sensitivity analyses are presented in Figures 6 to 13 of the Supplement. Most showed thresholds similar to those estimated in the base-case analysis, with deviation of 0% or 1% (except U.S. men and women aged 55 to 59 years, who had 3% to 4% higher thresholds). However, the sensitivity analyses with the log-odds (not normalized) and with harm effects from RCTs only showed similar patterns (increases with age and in women), but with 3% to 4% lower risk thresholds (Figures 7 and 12 of the Supplement).

## Discussion

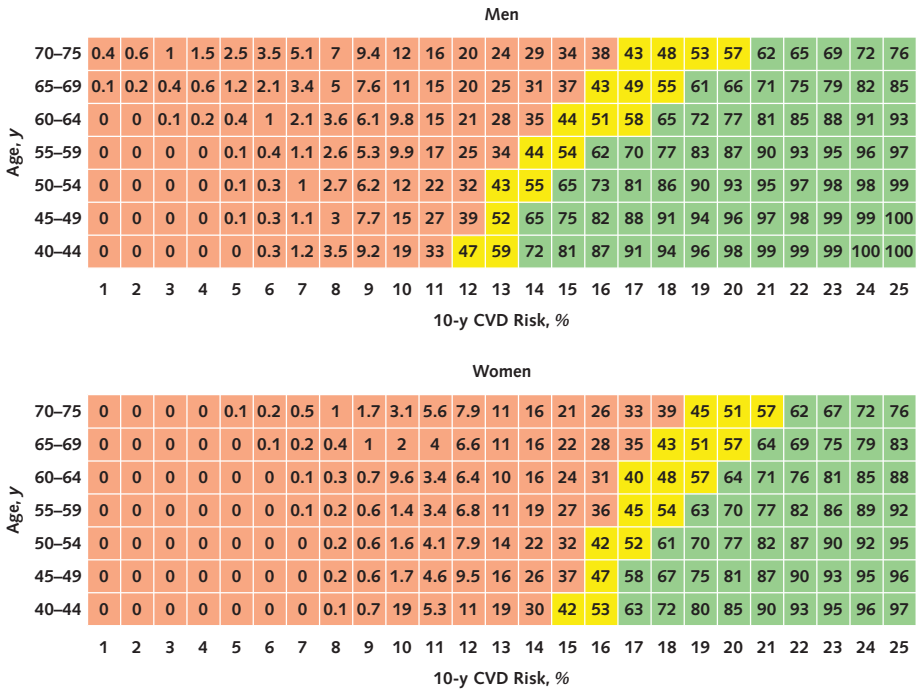
To our knowledge, this is the first quantitative benefit–harm balance modeling study on statins for primary prevention of CVD and the first study to determine 10-year risk thresholds above which the benefits outweigh the harms over 10 years. We found that statins are likely to provide net benefits at substantially higher risk thresholds than the 7.5% to 10% thresholds to which most guidelines refer. Depending on age and sex, the risk thresholds varied between 14% and 22%. The thresholds were lower for atorvastatin and rosuvas-

*Table 2.* Number of Expected Benefit and Harm Outcome Events per 1000 Women in Switzerland Over 10 Years With and Without Use of Statins*

| Variable | Aged 40–44 Years | | Aged 45–49 Years | | Aged 50–54 Years | | Aged 55–59 Years | | Aged 60–64 Years | | Aged 65–69 Years | | Aged 70–75 Years | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins | No Statins | Statins |
| **Harm outcomes** | | | | | | | | | | | | | | |
| Myopathy | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 |
| Renal dysfunction | 6 | 8 | 6 | 8 | 6 | 8 | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 7 |
| Hemorrhagic stroke | 3 | 3 | 5 | 5 | 6 | 7 | 7 | 8 | 8 | 10 | 11 | 13 | 18 | 21 |
| Hepatic dysfunction | 24 | 34 | 24 | 34 | 24 | 34 | 24 | 34 | 24 | 33 | 24 | 33 | 23 | 33 |
| Type 2 diabetes | 21 | 22 | 22 | 24 | 29 | 32 | 42 | 45 | 48 | 52 | 48 | 52 | 41 | 45 |
| Any cancer | 24 | 24 | 38 | 39 | 52 | 53 | 70 | 71 | 91 | 93 | 116 | 118 | 131 | 134 |
| Cataract | 161 | 204 | 161 | 204 | 160 | 203 | 160 | 202 | 159 | 201 | 157 | 199 | 155 | 196 |
| Headache/nausea | 334 | 367 | 334 | 367 | 333 | 366 | 331 | 364 | 330 | 362 | 326 | 359 | 322 | 354 |
| Treatment discontinuation | 296 | 297 | 295 | 296 | 294 | 295 | 293 | 294 | 291 | 292 | 289 | 289 | 285 | 286 |
| **10-y CVD risk** | | | | | | | | | | | | | | |
| 1% | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 |
| 2% | 20 | 15 | 20 | 15 | 20 | 15 | 20 | 15 | 20 | 15 | 19 | 14 | 19 | 14 |
| 3% | 30 | 22 | 30 | 22 | 30 | 22 | 30 | 22 | 29 | 22 | 29 | 22 | 29 | 21 |
| 4% | 40 | 30 | 40 | 30 | 40 | 30 | 39 | 29 | 39 | 29 | 39 | 29 | 38 | 29 |
| 5% | 50 | 37 | 50 | 37 | 50 | 37 | 49 | 37 | 49 | 37 | 49 | 36 | 48 | 36 |
| 6% | 60 | 45 | 60 | 45 | 60 | 44 | 59 | 44 | 59 | 44 | 58 | 43 | 57 | 43 |
| 7% | 70 | 52 | 70 | 52 | 69 | 52 | 69 | 52 | 69 | 51 | 68 | 51 | 67 | 50 |
| 8% | 80 | 60 | 80 | 60 | 79 | 59 | 79 | 59 | 79 | 59 | 78 | 58 | 77 | 57 |
| 9% | 90 | 67 | 90 | 67 | 89 | 67 | 89 | 67 | 88 | 66 | 87 | 66 | 86 | 65 |
| 10% | 100 | 75 | 100 | 75 | 99 | 74 | 99 | 74 | 98 | 74 | 97 | 73 | 96 | 72 |
| 11% | 110 | 82 | 109 | 82 | 109 | 82 | 109 | 82 | 108 | 81 | 107 | 80 | 105 | 79 |
| 12% | 120 | 90 | 119 | 90 | 119 | 90 | 119 | 89 | 118 | 89 | 117 | 88 | 115 | 87 |
| 13% | 130 | 98 | 129 | 97 | 129 | 97 | 128 | 97 | 128 | 96 | 126 | 95 | 125 | 94 |
| 14% | 140 | 105 | 139 | 105 | 139 | 105 | 138 | 104 | 137 | 104 | 136 | 103 | 134 | 101 |
| 15% | 150 | 113 | 149 | 113 | 149 | 112 | 148 | 112 | 147 | 111 | 146 | 110 | 144 | 109 |
| 16% | 160 | 121 | 159 | 120 | 159 | 120 | 158 | 120 | 157 | 119 | 156 | 118 | 153 | 116 |
| 17% | 170 | 128 | 169 | 128 | 169 | 128 | 168 | 127 | 167 | 126 | 165 | 125 | 163 | 124 |
| 18% | 180 | 136 | 179 | 136 | 179 | 136 | 178 | 135 | 177 | 134 | 175 | 133 | 173 | 131 |
| 19% | 189 | 144 | 189 | 144 | 189 | 143 | 188 | 143 | 187 | 142 | 185 | 140 | 182 | 138 |
| 20% | 199 | 152 | 199 | 152 | 198 | 151 | 198 | 150 | 196 | 149 | 195 | 148 | 192 | 146 |
| 21% | 209 | 160 | 209 | 159 | 208 | 159 | 207 | 158 | 206 | 157 | 204 | 156 | 201 | 154 |
| 22% | 219 | 168 | 219 | 167 | 218 | 167 | 217 | 166 | 216 | 165 | 214 | 163 | 211 | 161 |
| 23% | 229 | 175 | 229 | 175 | 228 | 175 | 227 | 174 | 226 | 173 | 224 | 171 | 221 | 169 |
| 24% | 239 | 183 | 239 | 183 | 238 | 182 | 237 | 182 | 236 | 180 | 233 | 179 | 230 | 176 |
| 25% | 249 | 191 | 249 | 191 | 248 | 190 | 247 | 189 | 246 | 188 | 243 | 187 | 240 | 184 |

CVD = cardiovascular disease.
* Values are the predicted number of events with and without use of statins per 1000 women over 10 y based on participants' baseline risks, calculated using an exponential model and adjusted for non-CVD mortality as a competing risk. Some outcomes, such as myopathy, hepatic dysfunction, and renal dysfunction, had restrictive definitions in the observational data source (i.e., only moderate or serious cases were reported) and were average estimates (i.e., not age-specific).

***Figure 1.*** Probabilities at which statin therapy for primary prevention of CVD is likely to provide net benefits among 350 subgroups based on age, sex, and CVD risk (1% to 25%).




Pink, yellow, and green cells indicate risk thresholds at which the probability indicates that harms outweigh benefits (<40%), harms equal benefits (40% to 60%), and benefits outweigh harms (≥60%), respectively. The analyses accounted for age- and sex-specific non-CVD mortality as a competing risk. CVD = cardiovascular disease.

tatin than for simvastatin and pravastatin across all age groups and for men and women, indicating that they had a more favorable benefit–harm balance.

Our results suggest that higher 10-year risk thresholds for prescription of statins may be warranted than what current guidelines recommend and that the thresholds vary considerably by age, sex, and statin type. Guidelines emphasize benefits, and although harms are not ignored, they seem to have little effect on recommendations (12). The problem with such an approach is that eligibility for statins increases with age because more events can be prevented in elderly persons who are at higher CVD risk, as a recent study showed (32). However, when harm outcomes, which also increase with age, are considered, the benefit–harm balance of statins becomes less favorable. Indeed, our results show that the thresholds of 10-year CVD risk above which statins provide more benefits than harms are higher in elderly than younger persons. Precautions must be taken when prescribing statins to older persons, especially those older than 65 years, because the 10-year risk prediction models are heavily influenced by age (33), which is a nonmodifiable risk factor, and thus many in this age group may be eligible for statins even in the absence of other risk factors, such as hyperlipidemia (34, 35). The small differences in risk thresholds between men and women were due to variation in baseline risk for other outcomes, such as diabetes, any cancer, and cataracts, as well as the differential effect of statins on myopathy and renal dysfunction.

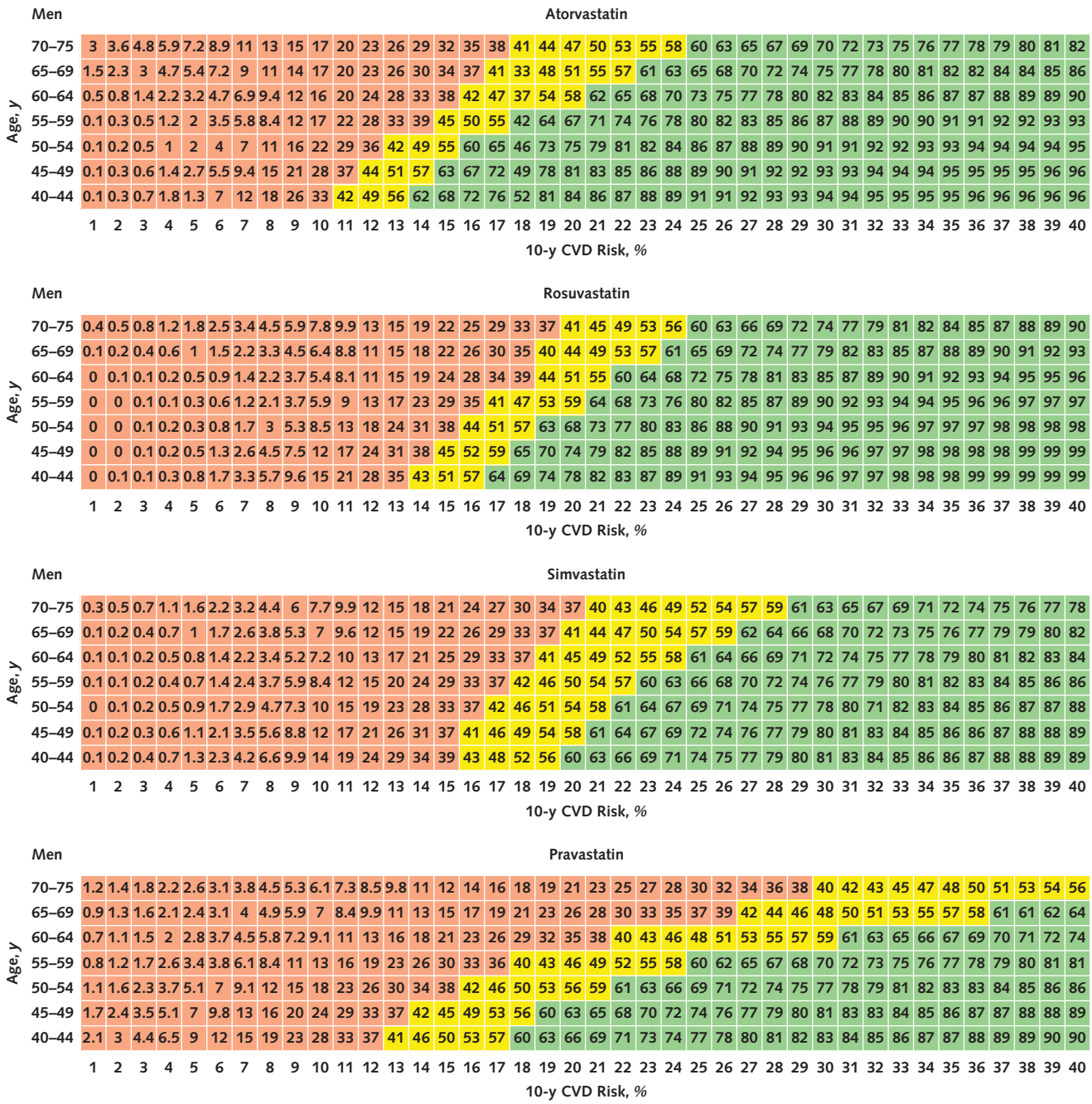
The sensitivity analyses testing different assumptions demonstrated similar risk thresholds (**Figure 14** of the **Supplement**). Some of these thresholds were slightly higher and others were slightly lower than the results of the base-case analysis, but all, including the analyses that considered treatment effects of harms from RCTs only, showed higher thresholds than those commonly recommended by guidelines. Most of our analyses also showed that harm outcomes had less effect on the balance of benefits and harms because of small statin effects or smaller preference weights. However, our models probably still underestimated the risk thresholds because of potentially unmeasured harms (such as rhabdomyolysis or neurologic effects), relatively low baseline risks for some harm outcomes due to restrictive definitions (reporting of only moderate or serious cases) in our data sources, and unavailability of age-specific risks for these outcomes, which would make statins even less favorable for older persons.

Redefining the risk thresholds would have important clinical implications. Current practice indicates statin use for a large proportion of the healthy population. For example, on the basis of the Copenhagen General Population Study (32), 31% to 44% (depending on the guideline) of persons aged 40 to 75 years would be eligible for statins for primary prevention at a 10-year

CVD risk of 10%. However, the proportion would be substantially smaller if our age-, sex-, and statin-specific recommendations were followed, especially if pravastatin and simvastatin, for which our model showed higher risk thresholds, were recommended. More benefits were demonstrated with atorvastatin and rosuvastatin; these had lower risk thresholds due to differences in their effect on CVD and some harm outcomes. These results are consistent with the fact that atorvastatin and rosuvastatin have more potent pharmacologic properties in reducing cholesterol levels than the other statins (15).

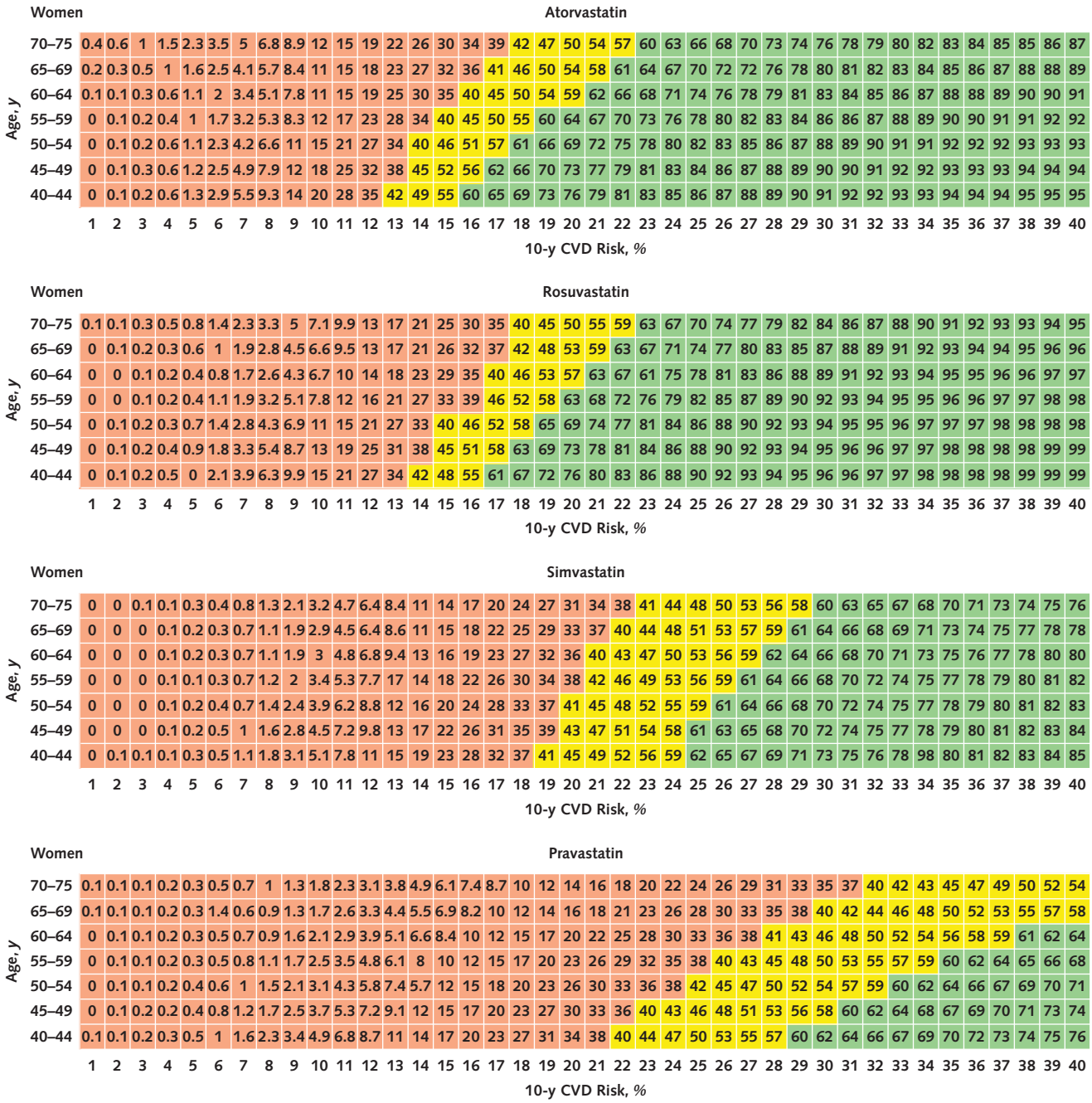
Although the importance of shared decision making in clinical practice is well known, none of the guidelines refer to a decision aid for fully informed decisions (6). Our

***Figure 2.*** Probabilities at which statin therapy for primary prevention of CVD is likely to provide net benefits among 1120 subgroups of men based on age, CVD risk (1% to 40%), and statin type.




Pink, yellow, and green cells indicate risk thresholds at which the probability indicates that harms outweigh benefits (<40%), harms equal benefits (40% to 60%), and benefits outweigh harms (≥60%), respectively. The analyses accounted for age- and sex-specific non-CVD mortality as a competing risk. CVD = cardiovascular disease.

***Figure 3.*** Probabilities at which statin therapy for primary prevention of CVD is likely to provide net benefits among 1120 subgroups of women based on age, CVD risk (1% to 40%), and statin type.




Pink, yellow, and green cells indicate risk thresholds at which the probability indicates that harms outweigh benefits (<40%), harms equal benefits (40% to 60%), and benefits outweigh harms (≥60%), respectively. The analyses accounted for age- and sex-specific non-CVD mortality as a competing risk. CVD = cardiovascular disease.

granulated risk heat maps could be a first step toward promoting patient-centered decision making combined with valuable clinical judgment and experience. Our model assumed average age- and sex-specific baseline risks for the harm outcomes, but this could be individualized and integrated into interactive decision aids or electronic medical records to incorporate individual-patient preferences and baseline risks for the outcomes to predict a personalized benefit–harm balance (11). For example, a woman with no net benefits (based on average population preferences) at a 10-year CVD risk of 15% may have net benefits if she places a higher value on CVD or a lower value on harm outcomes or if she has a lower risk for harms than the general population. Thus, additional

studies may be required to test the sensitivity of the thresholds to individual-patient preferences as well as to assess the effect of the new thresholds on perceived health status, such as quality of life.

Our study has limitations that must be considered when interpreting the results. We did not test how the risk thresholds changed across varying risks for harm outcomes (as we did for the different CVD risk levels); instead, we took age- and sex-specific average risks from population data. We were unable to obtain enough data on all possible harms and age-specific data on some harm outcomes, so the risk thresholds we determined may still be too low. In addition, the balance of benefits and harms might change if different countries were considered, but we would expect the thresholds to be similar or higher because Switzerland has moderate risks for the harm outcomes. To apply our findings, valid and well-calibrated CVD risk prediction models that are context-specific are needed. The risk scores for fatal CVD only used by the guideline from the European Society of Cardiology and the European Atherosclerosis Society cannot be used because we considered the risks for fatal and nonfatal CVD events combined (36). Another limitation is that although studies show that preferences do not significantly vary by age or sex or across populations (17, 37), our study did not extensively examine whether the benefit–harm balance is preference-sensitive, which would indicate the need for individualized decision-making tools to determine the balance of benefits and harms. Finally, our findings apply to low- and moderate-dose statins only.

In conclusion, our results suggest that guidelines should use higher 10-year risk thresholds when recommending statins for primary prevention of CVD and should consider different recommendations based on sex, age group, and statin type. Such recommendations would substantially improve selection of persons eligible for statin therapy for primary prevention of CVD.

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## Appendix: Technical Details

This appendix describes the statistical approach used for the benefit–harm balance modeling and summarizes the input data. Details on data use are provided in the Supplement.

### Benefit–Harm Balance Modeling

We used an approach developed by Dr. Mitchell Gail at the NCI in the context of a benefit–harm assessment for tamoxifen for prevention of breast cancer (28). The benefit–harm balance indices for each risk combination according to sex, age, and 10-year CVD risk were calculated using the Gail/NCI approach based on an exponential model as described in the following equations:

Expected number of events without statin use ($N_{i,no\ statins}$) per 1000 persons over 10 years, taking into consideration baseline risk for each outcome ($I_i$) and competing risk for non-CVD death ($M$).

$$N_{i,no\ statins} = 1000\{I_i/(I_i + M)\}[1 - exp\{-10\ yrs(I_i + M)\}] \quad (1)$$

Expected number of events with statin use ($N_{i,statins}$) per 1000 persons over 10 years, taking into consideration baseline risk ($I_i$) and treatment effect of statins on each outcome ($RR$) and competing risk for non-CVD death ($M$).

$$N_{i,statins} = 1000\{RR_i \times I_i/(RR_i \times I_i + M)\}$$
$$[1 - exp\{-10\ yrs(RR_i \times I_i + M)\}] \quad (2)$$

The benefit–harm balance index for a given subgroup was obtained from the cumulative difference of the number of events between the treatment and control groups (calculated using equations 1 and 2) for each outcome and weighted by the respective weights that reflect patient preferences ($W_i$).

$$Benefit\text{–}harm\ index = \sum_{i}^{10\ outcomes} (N_{i,no\ statins} - N_{i,statins}) \times W_i \quad (3)$$

To account for the statistical uncertainty of the input parameters, we resampled each estimate of the input parameters 100 000 times from normal distributions defined by their mean estimates (log risk ratio, log rate, and SUCRA) and their SEs. From the distribution of the resulting benefit–harm index, we determined the probability above which the benefit–harm index was positive for at least 60% (an example is provided in the Appendix Figure). We performed this calculation for a range of 10-year CVD risks (1% to 25% for statins as a class and 1% to 40% for specific statins) and identified the threshold at which the net benefits outweighed the net harms.

### Example of the Gail/NCI Approach

The benefit–harm balance modeling was based on distributions of the input parameters. However, to illustrate the method, we present a manually calculated example with specific parameter values for 1 benefit end point (CVD outcome) and 1 harm outcome (diabetes) for 1 subgroup to answer the question, "Do men aged 55 to 59 years with risk for CVD of 10% over 10 years benefit from statins?" We assumed that statins did not have other harm risks. The risk for death due to causes other than CVD in this age group is 0.0038 person-year, which is considered a competing risk in the model.

The expected number of CVD events without use of statins, calculated with equation 1, is:

$$N_{CVD,no\ statin} = 1000\{0.0105/(0.0105 + 0.0038)\}$$
$$[1 - exp\{-10(0.0105 + 0.0038)\}] = 97.8. \quad (4)$$

This shows that men aged 55 to 59 years would be expected to have 97.8 CVD events per 1000 persons in 10 years if they did not take statins. Of note, the 10% probability of having CVD over 10 years was converted to 0.0105 person-year using the equation $(-1n[1 - p])/t$ (where $t$ is the time horizon and $p$ is the 10-year risk) to convert the probability to a rate (because, for example, a 10% 10-year risk does not equate to a 1% probability in 1 year).

The corresponding number of events after statin use (risk ratio of statins reducing CVD events is 0.74), calculated with equation 2, is:

$$N_{CVD,statin} = 1000\{0.74 \times 0.0105/(0.74 \times 0.0105$$
$$+ 0.0038)\}[1 - exp\{-10(0.74 \times 0.0105 + 0.0038)\}]$$
$$= 73.4. \quad (5)$$

The same cohort of men aged 55 to 59 years would be expected to have 73.4 CVD events if they were treated with statins for 10 years. Thus, taking statins for 10 years could prevent 24.4 CVD events per 1000 persons (97.8 − 73.4). It is then important to consider patient preferences (that is, the preference for taking statins to obtain particular benefits at the price of having certain risk for harms due to statins). Accordingly, 24.4 CVD events × 0.645 (preference value for CVD) yields 15.7 preference-adjusted CVD events prevented, which is used in the benefit–harm balance model.

Similarly, the expected numbers of diabetes cases with and without statin use are:

$$N_{diabetes,no\ statin} = 1000\{0.0062/(0.0062 + 0.0038)\}\left[1 - exp\{-10(0.0062 + 0.0038)\}\right] = 59.0. \quad (6)$$

$$N_{diabetes,statin} = 1000\{1.09 \times 0.0062/(1.09 \times 0.0062 + 0.0038)\}\left[1 - exp\{-10(1.09 \times 0.0062 + 0.0038)\}\right] = 64.3. \quad (7)$$

More than 5 diabetes cases per 1000 persons (59.0 − 64.3 = −5.3) that are attributable to preventive statin treatment are expected to occur over 10 years. The preference-adjusted rate of diabetes cases is 1.35 per 1000 persons (5.3 diabetes cases × 0.255 [preference value for diabetes]).

In this example, the benefit–harm balance (or net benefit) is 14.35 prevented events (15.7 CVD events − 1.35 diabetes cases).

***Appendix Table 1.*** Effect Estimates of Statins on Benefit and Harm Outcomes Considered From Randomized Controlled Trials and Observational Studies*

| Outcomes | RR (95% CI) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All Statins | | Simvastatin | | Atorvastatin | | Pravastatin | | Rosuvastatin | |
| | Men | Women | Men | Women | Men | Women | Men | Women | Men | Women |
| Myopathy | 1.33 (1.25–1.41) | 1.16 (1.09–1.23) | 1.29 (1.22–1.37) | 1.15 (1.08–1.22) | 2.94 (2.51–3.44) | 1.68 (1.39–2.02) | 1.81 (1.50–2.18) | 1.81 (1.5–2.18) | 1.18 (1.02–1.36) | 1.68 (1.47–1.90) |
| Renal dysfunction | 1.31 (1.19–1.44) | 1.26 (1.14–1.40) | 1.29 (1.17–1.42) | 1.23 (1.11–1.37) | 1.58 (1.29–1.92) | 1.51 (1.20–1.90) | 1.18 (1.05–1.33) | 1.18 (1.05–1.33) | 1.15 (1.02–1.30) | 1.14 (1.01–1.28) |
| Hemorrhagic stroke | 1.17 (0.58–2.37)† | | | | | | | | | |
| Hepatic dysfunction | 1.41 (1.32–1.50) | 1.40 (1.31–1.50) | 1.40 (1.30–1.50) | 1.38 (1.29–1.49) | 1.54 (1.38–1.71) | 1.5 (1.33–1.70) | 1.30 (1.06–1.59) | 1.30 (1.06–1.59) | 1.41 (1.04–1.92) | 1.31 (0.94–1.82) |
| Type 2 diabetes | 1.09 (0.96–1.22) | 1.09 (0.96–1.22) | 1.11 (1.04–1.19) | 1.11 (1.04–1.19) | 1.25 (1.22–1.28) | 1.25 (1.22–1.28) | 1.02 (0.98–1.06) | 1.02 (0.98–1.06) | 1.29 (1.15–1.45) | 1.29 (1.15–1.45) |
| Any cancer | 1.02 (0.95–1.10) | 1.02 (0.95–1.10) | 1.02 (0.95–1.10) | 1.02 (0.95–1.10) | 1.04 (0.89–1.22) | 1.04 (0.89–1.22) | 1.11 (0.96–1.28) | 1.11 (0.96–1.28) | 1.04 (0.92–1.16) | 1.04 (0.92–1.16) |
| Cataracts‡ | 1.32 (1.27–1.37) | 1.30 (1.25–1.34) | 1.31 (1.24–1.37) | 1.30 (1.24–1.36) | 1.31 (1.24–1.40) | 1.30 (1.23–1.36) | 1.36 (1.24–1.49) | 1.36 (1.24–1.49) | 1.38 (1.22–1.57) | 1.27 (1.12–1.43) |
| Nausea/headache§ | 1.12 (0.96–1.32) | 1.12 (0.96–1.32) | 1.12 (0.96–1.32) | 1.12 (0.96–1.32) | 1.05 (0.60–1.84) | 1.05 (0.60–1.84) | 1.46 (0.57–3.75) | 1.46 (0.57–3.75) | 1.36 (0.74–2.51) | 1.36 (0.74–2.51) |
| Treatment discontinuation due to AEs§ | 0.99 (0.83–1.21) | 0.99 (0.83–1.21) | 1.42 (0.67–3.02) | 1.42 (0.67–3.02) | 0.86 (0.64–1.15) | 0.86 (0.64–1.15) | 0.92 (0.68–1.25) | 0.92 (0.68–1.25) | 1.08 (0.77–1.51) | 1.08 (0.77–1.51) |
| CVD§ | 0.74 (0.68-0.81) | 0.74 (0.68-0.81) | 0.73 (0.58–1.91) | 0.73 (0.58–1.91) | 0.71 (0.56–0.90) | 0.71 (0.56–0.90) | 0.77 (0.63–0.93) | 0.77 (0.63–0.93) | 0.67 (0.53–0.85) | 0.67 (0.53–0.85) |

AE = adverse effect; CVD = cardiovascular disease; RR = risk ratio.

* See the **Supplement** for data sources. The effect estimates in the table are combined excess risk of statins on harm outcomes (myopathy, renal dysfunction, hepatic dysfunction, cancer, diabetes, cataracts) from trials and observational data sources calculated using an inverse variance–weighted averaging equation, a Bayesian principle (equations 1 and 2) described elsewhere (22). This method combines treatment estimates from 2 distributions (defined by mean treatment, *log RR*, and variance, *var (log RR)*). The treatment effects are weighted by their inverse variance, 1/*var()*. As such, the estimates from observational data contributed less because of imprecise estimates. We assumed that estimates from both sources were adequately approximated by normal distributions defined by the respective *log RR* and *var (log RR)*. Variance of the combined effect is the total variance of both sources.

$$\log RR_{mixed} = \frac{\frac{1}{var(\log RR_{trial})}\log RR_{trial} + \frac{1}{var(\log RR_{obs})}\log RR_{obs}}{\frac{1}{var(\log RR_{trial})} + \frac{1}{\mathrm{var}(\log RR_{obs})}} \quad (1)$$

$$\mathrm{var}(\log RR_{mixed}) = \frac{1}{\frac{1}{var(\log RR_{trial})} = \frac{1}{\mathrm{var}(\log \mathrm{RR}_{\mathrm{obs}})}} \quad (2)$$

log $RR_{mixed}$ indicates log-transformed combined effect estimate from trials (log $RR_{trial}$) and observational data (log $RR_{obs}$). var (log $RR_{mixed}$) indicates that variance of the combined effect was defined by the inverse of total variance of statin excess effect from trials (var (log $RR_{trial}$)) and from observational data (var (log $RR_{obs}$)). Thus, CIs can be calculated using log $RR_{mixed}$ and var (log $RR_{mixed}$).

† The relative treatment effect was taken from the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) trial and was assumed to be similar for all subgroups due to unavailability of group-specific estimates (20).

‡ The treatment effect was taken from the HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial (19).

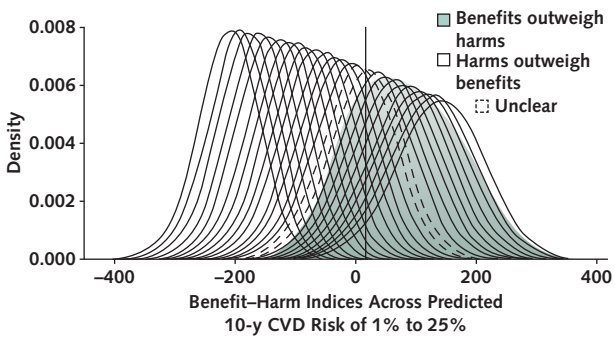
§ Treatment effects were available only from the meta-analysis of randomized trials (see **Figure 1** of the **Supplement**).

***Appendix Table 2.*** Preference Weights for Benefit and Harm Outcomes Considered for the Benefit–Harm Balance Modeling*

| Outcome | SUCRA (95% CI) | Best-Worst Score | Log-Odds (95% CI) |
|---|---|---|---|
| Myopathy | 0.255 (0.253–0.256) | 0.138 | 0.60 (0.37–0.83) |
| Renal dysfunction | 0.262 (0.242–0.293) | 0.110 | 0.67 (0.42–0.92) |
| Hemorrhagic stroke | 0.766 (0.644–0.818) | 0.582 | 3.75 (3.43–4.60) |
| Hepatic dysfunction | 0.378 (0.347–0.424) | 0.289 | 1.45 (1.20–1.69) |
| Type 2 diabetes | 0.47 (0.350–0.531) | 0.304 | 1.51 (1.25–1.75) |
| Any cancer | 0.859 (0.843–0.880) | 0.779 | 4.37 (4.03–4.71) |
| Cataracts | 0.378 (0.347–0.424) | 0.289 | 1.45 (1.20–1.69) |
| Nausea/headache | 0.065 (0.035–0.105) | 0.042 | 0.23 (0.0–0.47) |
| Treatment discontinuation | 0.085 (0.002–0.141) | 0.000 | 0.00† |
| CVD | 0.645 (0.553–0.692) | 0.518 | 3.20 (2.85–3.46) |

CVD = cardiovascular disease; SUCRA = surface under the cumulative ranking curve.
* Based on reference 17. The outcome preferences were elicited using a best–worst scaling survey in Switzerland and Ethiopia in which participants were asked to select 2 answers (most worrisome and least worrisome outcomes concurrently) from a different set of outcomes arranged using a balanced incomplete block design (17). The data were analyzed using different methods and thus presented in different scales, including SUCRA, standardized best–worst score, and log-odds. The SUCRA resulted from a multiple treatment comparison method (i.e., network meta-analysis) approach. The best–worst score was the difference in frequency at which an outcome was selected as most worrisome or least worrisome. Similarly, the log-odds was analyzed using a conditional logit model and was a measure of relative importance showing the odds that the selected outcome was the most worrisome given a set of other outcomes. The 3 measures are relative preference values indicating which outcomes patients would rather avoid. Higher values indicate more worrisome or more important outcomes to patients. The SUCRA was used for the base-case analysis, whereas best–worst score and log-odds were used for the sensitivity analyses. This study elicited preferences for the different harm outcomes and specific CVD events. We then assigned the preference for the composite outcome of CVD events from the preference values of specific CVD outcomes.
† Reference outcome in the conditional logit model.

***Appendix Figure.*** Distribution of benefit–harm indices of statins for men aged 55 to 59 y across different CVD risks.




The figure demonstrates how the distributions of benefit–harm balance indices across the range of 10-y risks for CVD of 1% to 25% shift from negative to zero and to positive, with men aged 55 to 59 y used as an example. The vertical line shows the risk threshold at which the probability of net benefits is ≥60%. CVD = cardiovascular disease.