Supplementary Online Content


eAppendix. Sensitivity Analyses

This supplementary material has been provided by the authors to give readers additional information about their work.
We performed five sensitivity analyses to adjust the observed risk estimates for the use of statins and/or revascularization procedures. Details of the five methods of adjustment for statins are as follows:

1) *Adjustment for risk reduction due to statin use.*

We increased the rate among those using statins inversely proportional to the estimated effect of statins on ASCVD. In a meta-analysis of randomized trials, among those without prior vascular disease, statins reduced the risk of major vascular events by an aggregate 25% per mmol/L reduction in LDL cholesterol, similar to the effect of a typical dose. We thus increased the rate of ASCVD among those using statins proportionately. The rate was increased for each year of follow-up separately then aggregated in a life table analysis.

Let \( r_T \) be the true rate that we would see if no one was using statins, \( r_{\text{obs}} \) be the observed rate, and let \( p_s \) be the proportion of women using statins. Then if \( \text{RR}_s \) is the rate ratio associated with statin use, we can write

\[
r_{\text{obs}} = (1 - p_s) r_T + p_s \text{RR}_s r_T.
\]

We can solve for \( r_T \), the underlying or ‘true’ rate of ASCVD without statins, as

\[
r_T = r_{\text{obs}} / (1 + p_s (\text{RR}_s - 1)).
\]  

(1)

In the calculations we assume that \( \text{RR}_s = 0.75 \), based on the meta-analysis of statin trials.

2) *Adjustment for risk reduction due to statin use and confounding by indication.*

Because of potential confounding by indication, statin users may be at higher risk of ASCVD than
those at the same estimated baseline level of risk by conventional risk factors. For example, those who were prescribed statins may have a family history of ASCVD, high CRP, or their lipids may have increased over time. We therefore increased the rate further in this group by doubling it, in addition to accounting for the statin effect as in analysis 1).

Let \( r_0 \) be the rate among women who are not prescribed statins and \( \text{RR}_{\text{ind}} \) be the extent of confounding by indication. That is, \( \text{RR}_{\text{ind}} \) is the rate ratio comparing those who are and are not prescribed statins. Then

\[
\begin{align*}
\text{RR}_{\text{obs}} &= (1 - p_s) r_0 + p_s \text{RR}_s \text{RR}_{\text{ind}} r_0 \\
\end{align*}
\]

where the other terms are defined as above. The true rate that we would like to estimate can be written as

\[
\begin{align*}
\text{RR}_T &= (1 - p_s) r_0 + p_s \text{RR}_{\text{ind}} r_0 \\
&= \frac{\text{RR}_{\text{obs}}}{1 + p_s (\text{RR}_{\text{ind}} - 1)}.
\end{align*}
\]

We assume as above that \( \text{RR}_s = 0.75 \), and also that \( \text{RR}_{\text{ind}} = 2.0 \). Note that \( \text{RR}_{\text{ind}} \) is conditional on (in addition to) baseline risk factors, including age and cholesterol level.

3) **Adjustment for risk reduction due to statin use and revascularization and for confounding by indication for each.**

We adjusted for the potential effects of revascularization therapy using similar methods. First, we conservatively estimated that such procedures would reduce rates of ASCVD by 25%. This estimate is optimistic since randomized trials comparing these procedures to optimal medical therapy suggest little difference in the occurrence of ASCVD endpoints. Second, we allowed for confounding for indication similar to that for statins by doubling the observed risk. These analyses accounted for the risk reductions due to statins and to revascularization procedures as
well as the potential confounding by indication for both statins and revascularization.

In addition to the terms above, let $RR_v$ be the rate ratio associated with revascularization, $RR_{indv}$ be the rate ratio for indication for these procedures, and $RR_{indsv}$ be the rate ratio associated with indication for both. Then let $p_0$, $p_s$, $p_v$, and $p_{sv}$ be the proportions not on statin with no procedures, on statins only, with revascularization only, and with both, respectively. The observed risk can be written as

$$r_{obs} = p_0 r_0 + p_s RR_s RR_{inds} r_0 + p_v RR_v RR_{indv} r_0 + p_{sv} RR_s RR_v RR_{indsv} r_0.$$  

The 'true' risk can then be estimated as

$$r_T = r_0 (p_0 + p_s RR_{inds} + p_v RR_{indv} + p_{sv} RR_{indsv}) = r_{obs} \frac{c_1}{c_2}$$  

where

$$c_1 = p_0 + p_s RR_{inds} + p_v RR_{indv} + p_{sv} RR_{indsv}$$

$$c_2 = p_0 + p_s RR_s RR_{inds} + p_v RR_v RR_{indv} + p_{sv} RR_s RR_v RR_{indsv}.$$  

Here we make the assumption that all those who undergo a revascularization procedure will also be prescribed statins, so that the proportion with revascularization only is zero, or $p_v=0$. We assume as above that $RR_s = 0.75$ and $RR_{inds} = 2.0$, and also that $RR_v=0.75$ and $RR_{indsv}=RR_{indsv}=2$.

4) **Censoring at use of cholesterol-lowering medication.**

In a separate sensitivity analysis we censored women at the time of initiation of cholesterol-lowering medications. While this would account for the beneficial effect of statins, it would not account for confounding by indication.

5) **Censoring at cholesterol-lowering medication use or revascularization.**

We performed an additional sensitivity analysis censoring women when they began using cholesterol-lowering medications or underwent revascularization, by definition prior to ASCVD.
Note that while this would account for the beneficial effect of both statins and revascularization, it would not account for confounding by indication.

In our initial analyses, we adjusted for use of statins only because those agents have been found to reduce cardiovascular risk. In alternate analyses, we substituted use of any cholesterol-lowering agent for statins. In addition, since the risk equations are meant to be used clinically for those who are not diabetic, not on cholesterol-lowering medications at baseline, and with LDL in the range 70 to 189 mg/dL, we additionally subset to that group.

Finally, we estimated what the size of effects would be necessary to reconcile any differences in event rates, using the above equations. In particular, we estimated the numbers of events that would have to be missed through inadequate ascertainment in order to reconcile remaining differences between observed and predicted rates.