Supplementary Online Content


eAppendix. Supplemental text

eReferences

eTable. Annual probabilities, relative risks, and quality of life

eFigure. State transition diagrams for cardiac events, ischemic cerebral events, and intracranial hemorrhage events

This supplementary material has been provided by the authors to give readers additional information about their work.
Supplemental Text

Decision Model Structure

The Markov model consists of three interdependent, simultaneous random processes associated with ischemic cardiac events (6 states), ischemic cerebral events (4 states), and ICH events (2 states) (see Supplementary Figure 1). Death from any cause is considered a single absorbing state, and thus our model contains a total of 49 states (6x4x2+1). The three sub-models are shown separately for visual convenience; in the actual model, patients can experience any combination of ischemic cardiac, ischemic cerebral, and ICH events in a given cycle. Events may lead to death, a decrease in quality of life and/or a change in probability of future events, or leave current quality of life and future event probabilities unchanged. The non-fatal health states within each of the three categories outlined above are as follows (the abbreviations refer to Supplemental Figure 1):

A. Cardiac: (1) “NCH”, no cardiac history; (2) “SA”, stable angina; (3) “UA1”, unstable angina, within the first year after onset; (4) “UA2”, unstable angina, >1 year after onset; (5) “MI1”, within the first year after the most recent MI; (6) “MI2”, post MI, >1 year after the most recent one.

Patients have a transient higher risk of ischemic cardiac and ischemic stroke events during the first year after MI (MI1).

B. Stroke: (1) “NSH”, no history of ischemic stroke or TIA; (2) “TIA”, have had at least one TIA; (3) “S1”, within the first year after the most recent stroke; (4) “S2”, post ischemic stroke, >1 year after the most recent ischemic stroke. Patients have a transient higher risk of ischemic cardiac and ischemic stroke events during the first year after stroke (S1).
C. Hemorrhage: (1) “H+”, recurrent ICH within the current cycle, (2) “H-”, no recurrent ICH within the current cycle. Since the base case has a history of ICH, all hemorrhages in the model are considered recurrent. Although health states within each category are assumed to be mutually exclusive, health states from different categories can co-occur. Note that “events” (such as stable angina) are actually treated as risk categories in the model. As illustrated in the state transition diagrams (Figure 1), patients cannot transition “backward” from a more severe to a less severe risk category. For example, within the cardiac category, the transition sequence NCH $\rightarrow$ SA $\rightarrow$ MI1 is possible, but from the risk category of MI1 or MI2, a patient cannot revert back to the lower risk status of SA. In other words, although a patient with a history of MI may develop stable angina in clinical practice, in our model the risk category of “MI” trumps that of stable angina. The clinical impact of recurrent angina in a patient with prior MI, for example, is taken into account by an adjustment factor (see sixth assumption below). The exception is that the states MI1 and S1 are transient high risk categories and treated more like an actual event: both revert to a chronic risk category of MI2 and S2 after 1 year (1 cycle), but patients can re-visit these states as additional events occur over their lifetime.

Cerebrovascular events confer higher risk for future cardiovascular events, and vice versa. In the event that a patient’s health state contains prior history of both cardiac and stroke-related events, the transition probabilities for future events are derived by taking the maximum probability conferred by either category. For example, in a patient with a recent ischemic stroke (<1 year ago) and stable angina, the annual probability of stroke would be 0.0481, which is the probability of stroke conferred by having had a prior stroke (higher than the stroke risk of 0.006 in a patient with stable angina).
**Decision Model Assumptions**

First, we assume that patients on a statin tolerate therapy without any significant systemic side effects or negative impact on quality of life\(^1,2\). Complaints of myalgias and discontinuation of statin therapy for any reason are infrequent (~1\%) \(^3\), and serious reactions are rare, with rates for hepatotoxicity, rhabomyolysis, and any life-threatening event all <0.1\% \(^4\). There is no evidence that such adverse events are more prevalent in ICH survivors, thus we do not model systemic adverse effects of statin therapy. We also assume that the relative risk (RR) of ICH among patients receiving statins is the same for patients with or without a history of prior ICH. Moreover, we assume that the treatment status (on versus off statin therapy) after the initial ICH is maintained for life (regardless of subsequent events).

Second, we assume that statins are given at their maximum recommended dose, and that patients are fully compliant (see below), in keeping with prior analyses\(^5\). However, because it is likely that the type of statin and actual dose will vary with local practice patterns and with specific indications, and because it is unknown how ICH risk may vary with statin type and dose, we performed sensitivity analyses, varying the RR of ICH conferred by statin therapy.

Third, we assume that patients are not receiving anticoagulation therapy.\(^6\)

Fourth, we assume that ICH events occur at a constant rate throughout the patient’s lifetime (that is, no effect of age) and that ICH events have no effect on subsequent cardiac or cerebral ischemic events.

Fifth, as in previous work\(^6\), we assume that recurrent ICH is of the same type as the initial event: patients who initially present with deep ICH are subsequently at risk for recurrent deep ICH, but not lobar ICH, and vice versa. This assumption is based on the different pathophysiology:
hypertension as the primary risk for deep ICH, versus cerebral amyloid angiopathy as the primary risk for non-traumatic lobar ICH.

Sixth, we adopted quality of life adjustment factors (Q) for cardiac and cerebral ischemic events from a recent systematic review. These factors account for reduced quality of life for different states of health by introducing a fractional down-scaling for each subsequent year of life (death has a Q=0). Quality of life adjustment factors for cardiac health states were as follows: stable angina, Q=0.81; unstable angina, Q=0.77, status-post myocardial infarction, Q=0.76. For ischemic stroke, we used a value based on results from a meta-analysis that considered both the distribution of outcomes (mild long term disability, 19%; moderate long term disability, 27%; and severe long-term disability, 54%) and the corresponding quality adjustment factors (0.87, 0.68, 0.52, respectively), yielding a weighted quality adjustment factor of Q=(0.19*0.87+0.27*0.68+0.54*0.52) = 0.63. Quality adjustment factors for ICH were based on data from our own institution and are the same as in a previous decision analysis of warfarin use after ICH. Among survivors of lobar ICH, the distribution of outcomes and associated quality adjustment factors used were: good recovery, 23%, Q=1; mild long-term disability, 24%, Q=0.76; severe long-term disability, 53%, Q=0.11. These values yield a weighted quality of life adjustment factor among lobar ICH survivors of Q=0.47. For deep ICH the corresponding values are: good recovery, 21%, Q=1; mild long-term disability, 24%, Q=0.76; severe long-term disability 55%, Q=0.11, yielding a weighted quality of life adjustment factor for deep ICH survivors of Q=0.45. Death probabilities in ICH were 19.0% for lobar ICH, and 20.7% for deep ICH.

Seventh: For secondary prevention sensitivity analysis, we scaled both the acute (first year after an event) and the chronic (subsequent years) riskin concert, by multiplying each by a scaling factor. Thus, both rates (off statin) were multiplied by a factor, α, varied between 1 and 6.
Finally, we assume that, when patients suffer morbidity from multiple clinical events, the quality adjustment factors accrue multiplicatively. For example, the sequence of events over four cycles “SA → S → MI → death” would lead to the following sequence of life quality adjustments: 1 → 1*0.81=0.81 (for SA), then 0.81*0.63=0.51 (for the subsequent stroke), then 0.51*0.76=0.39 (for the subsequent MI), then 0.39*0=0 (for death).

Review of the Data

Numbers discussed here are summarized in Supplemental Table 1.

Recurrence Rate and Outcomes of ICH: Recurrence probabilities for deep and lobar ICH were the same as in a prior analysis by two of the authors. The annual recurrence probability for lobar ICH was based on data from a prospective cohort of 435 consecutive ICH patients; the corresponding annual probability for recurrent deep ICH was taken from a review of data from 4 studies involving 823 survivors of deep hemispheric ICH. The annual rates from these studies were 0.140 for lobar ICH and 0.021 for deep ICH. The 1-year transition probabilities, Pr, are calculated from these rates, R, by the formula Pr=1-e(-R\times T); where T is 1 year, yielding 1-year event probabilities for lobar and deep ICH of 0.14 and 0.021, respectively. Probabilities for various functional outcomes of deep and lobar ICH are given above in the “assumptions” section.

We note that the recurrence rate for lobar ICH used here is higher than in other published studies. As in a prior decision analysis, we used 14% as the annual recurrence rate of lobar ICH based on our own data, to ensure consistency with the outcomes of ICH in the same patient population. The higher recurrence rates in our data may be attributable to a more stringent definition of lobar ICH, which excludes even slight involvement of the basal ganglia, thalamus, or brainstem and thus likely enriches the proportion of lobar hemorrhages attributable to cerebral
amyloid angiopathy. We address the possibility that 14% represents an overestimate via sensitivity analysis for risk of recurrent lobar ICH (Fig. 1).

**Relative risk of ICH on statin**: The strongest evidence that statin therapy increases the risk of ICH comes from a post-hoc analysis of The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL) study, a randomized controlled trial of statins in patients with a history of stroke but without known coronary artery disease\(^1\),\(^2\). In this trial, 4,731 patients were randomized to atorvastatin 80 mg or placebo and followed for about 5 years. Of note, a small fraction of patients (93/4731, or ~2% of enrolled patients) had hemorrhagic stroke, but were enrolled if they were believed to be at risk for ischemic stroke or heart disease. In a post-hoc analysis, 55 (2.3%) patients in the atorvastatin-treated group developed hemorrhagic stroke during the 5-year follow-up, compared to 33 (1.4%) in the placebo-treated group (1.6-fold increased risk). A more detailed analysis using a Cox multivariable regression model estimated the RR of ICH on statin therapy (compared with placebo) to be 1.68 (95% CI 1.09 to 2.59), with no evidence of statistical interaction between the effect of statin therapy and other predictors of ICH (including ICH at study entry, male sex, age, and blood pressure)\(^2\),\(^15\). It is not known what effect varying the specific statin type or dose may have on the RR of ICH.

**Annual probabilities of ischemic events**: Annual probabilities for cerebral and cardiac ischemic events were taken from a recent Health Technology Assessment comprising a comprehensive systematic review and economic analysis of statin therapy\(^5\).

**Primary events**: The probability of developing ischemic cardiac or cerebral events depends on several factors, including age, blood pressure, smoking and diabetes status, LDL and HDL cholesterol levels, and family history\(^5\),\(^16\). We define cerebro-cardio-vascular disease (CVD) as the composite of all of the following: stable angina (SA), unstable angina (UA), myocardial infarction...
(MI), transient ischemic attack (TIA), and ischemic stroke (S). In our primary prevention analyses, the 65 year-old base-case patient was assumed to have a 10-year CVD risk of 20%, which translates into an annual CVD risk of 2.21%, via the formula $1-(1-0.2)^{(0.1)}=0.0221$. We also performed sensitivity analyses in which the 10-year CVD risk is varied between 0-80%. We used the following distribution over primary events in 65 year-old males with CVD: SA, 21.4%; UA, 8.3%; MI, 17.3%; death from MI (dMI), 9.7%, TIA, 10%; S, 27%; death from stroke (dS), 6.3%5. With regard to stroke, we used the given number as an estimate of the percentage of patients with CVD who have ischemic strokes, although the primary data from which these numbers were derived made no distinction between hemorrhagic and ischemic stroke. The error introduced by this assumption is probably small, as ICH comprises a relatively small fraction (7-20%) of all stroke17.

Secondary events: The rates of ischemic cerebral and cardiac events are increased in patients with established CVD, in a manner that generally depends on the specific past medical history of CVD. Risks of subsequent CVD events in patients with established CVD are listed in Table 15. As mentioned above, we modeled the risk of subsequent events in patients with a history of more than one CVD event (e.g. stroke and MI) by taking the risk of each future CVD event to be the maximum risk conferred by all elements of the past medical history.

Relative risks of primary and secondary ischemic events on statin: Values for RR of ischemic events on statin therapy were taken from a Bayesian meta-analysis (to account for possible correlations between treatment effects on different endpoints) of multiple primary and secondary prevention trials and are summarized in Table 15. While the differences between absolute risk reductions in these different clinical settings was substantial, no significant difference was found between relative risk reductions. The RR values were 0.59 for SA, 0.716 for UA, 0.656 for MI, 0.740 for dMI, 0.79 for TIA, and 0.769 for stroke. Most studies in the meta-analysis used the

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maximum recommended dose of the particular statin under study, and differences between benefits achieved with different specific statins were minimal. The RR for stroke related death (dS) was found to be 1. It has been postulated that this lack of benefit might be due to a cancellation involving a potential reduced rate of fatal ischemic stroke coupled with a simultaneous increased rate of fatal hemorrhagic stroke, since the studies on which this figure was based generally did not distinguish between ischemic and hemorrhagic stroke.

**Probability of death, including death from other causes**: We used mortality rate data from life tables to model annual probability of death from causes not directly related to cardio-cerebrovascular disease. This probability is updated with each time step of our simulation as the patients age. The overall probability of death (Pd) in any given health state depends on three different annual death probabilities, namely the probability of death from cardiac (Pc), stroke (Ps), hemorrhage (Ph), or other causes (Po), and is given by Pd = 1-(1-Pc)(1-Ps)(1-Ph)(1-Po).
BIBLIOGRAPHY FOR SUPPLEMENTAL MATERIAL


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**Supplemental Table 1. Annual probabilities, Relative Risks, and Quality of Life**

**Distribution of primary CVD events (%)**

<table>
<thead>
<tr>
<th>Event:</th>
<th>SA</th>
<th>UA</th>
<th>MI</th>
<th>dMI</th>
<th>TIA</th>
<th>S</th>
<th>dS</th>
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<tbody>
<tr>
<td>%</td>
<td>21.4</td>
<td>8.3</td>
<td>17.3</td>
<td>9.7</td>
<td>10.0</td>
<td>27.0</td>
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**Annual transition probabilities (off statin)**

<table>
<thead>
<tr>
<th>PMH</th>
<th>SA</th>
<th>UA</th>
<th>MI</th>
<th>cD</th>
<th>TIA</th>
<th>S</th>
<th>sD</th>
</tr>
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<tbody>
<tr>
<td>No hx</td>
<td>0.0047</td>
<td>0.0018</td>
<td>0.0038</td>
<td>0.0021</td>
<td>0.0022</td>
<td>0.0060</td>
<td>0.0014</td>
</tr>
<tr>
<td>SA</td>
<td>*</td>
<td>0.0060</td>
<td>0.0110</td>
<td>0.0070</td>
<td>0.0022</td>
<td>0.0060</td>
<td>0.0014</td>
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<tr>
<td>UA1</td>
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<td>*</td>
<td>0.0488</td>
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<td>UA2</td>
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<td>*</td>
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<td>MI1</td>
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<td>0</td>
<td>0.0185</td>
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<td>TIA</td>
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<td>0.0018</td>
<td>0.0055</td>
<td>0.0185</td>
<td>*</td>
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<tr>
<td>S1</td>
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<td>0.0018</td>
<td>0.0055</td>
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<td>0.0481</td>
<td>0.0260</td>
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<tr>
<td>S2</td>
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<td>0.0018</td>
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<td>0</td>
<td>0.0223</td>
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**Annual probability of recurrent ICH (off statin)**

<table>
<thead>
<tr>
<th>Type</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lobar</td>
<td>0.1128</td>
<td>0.0265</td>
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<tr>
<td>Deep</td>
<td>0.0165</td>
<td>0.0043</td>
</tr>
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</table>

**Relative risks on statin therapy**

<table>
<thead>
<tr>
<th>Event:</th>
<th>SA</th>
<th>UA</th>
<th>MI</th>
<th>dMI</th>
<th>TIA</th>
<th>S</th>
<th>dS</th>
<th>H</th>
<th>dH</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Event:</th>
<th>SA</th>
<th>UA</th>
<th>MI</th>
<th>dMI</th>
<th>TIA</th>
<th>S</th>
<th>dS</th>
<th>H(L)</th>
<th>H(D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q</td>
<td>0.808</td>
<td>0.770</td>
<td>0.760</td>
<td>0</td>
<td>1</td>
<td>0.630</td>
<td>0</td>
<td>0.471</td>
<td>0.454</td>
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</table>

**Legend:** CVD, cardio-cerebro-vascular disease. SA, stable angina; UA, unstable angina; MI, myocardial infarction; TIA, transient ischemic attack; S, ischemic stroke; H, hemorrhagic stroke; H(L), lobar hemorrhagic stroke; H(D), deep hemorrhagic stroke; dMI, death from MI; dS, death from stroke; dH, death from intracerbral hemorrhage; PMH, past medical history; Q, quality adjustment factor; RR, relative risk. Suffixes 1 or 2 (after UA or MI) indicate either ≤ 1 year or >1 year after an event, respectively. Darkly shaded boxes contain event probabilities that vary with 10-year CVD risk (here set to 20%). Asterisks (*) represent states with values that vary over time with the age-dependent probability of death from other causes.
Legend:

Supplemental Figure 1. State transition diagrams for cardiac events (a), ischemic cerebral events (b), and intracranial hemorrhage events (c). Abbreviations: dMI, death from cardiac causes; NCH, no prior cardiac history; SA, stable angina; UA1, unstable angina within 1 year of onset; UA2, unstable angina >1 year after onset; MI1, myocardial infarction less than one year after event; MI2, myocardial infarction, >1 year after event; NSH, no prior history of stroke; TIA, transient ischemic attack; S1, stroke less than one year after event; S2, ischemic stroke >1 year after event; dS, death due to ischemic stroke; H-, no intracerebral hemorrhage (ICH); H+, ICH; dH, death from ICH.
Supplemental Figure 1

(a)

(b)

(c)