SUPPLEMENTAL MATERIAL

Example of a decision analysis model used to evaluate clinical utility of a biomarker

In 2003, Blake, Ridker and Kuntz published results of a decision analytic model for evaluating proposed use of C-reactive protein (CRP) to target statin therapy in persons without overt hyperlipidemia (LDL<149 mg/dL)[1]. Here we describe how this model fits within our framework, and provide a brief critique following the subsections in our review.

Supplemental Figure 1 demonstrates how the authors' model fits into the basic framework we present in Figure 3, and illustrates some of the key assumptions and tradeoffs. In Strategy S_2, for example, the cost of the CRP test is incurred, but this allows targeting of statins only to persons with high CRP, who should benefit more from statins than those with a low CRP.

The base case scenario was a 58 year-old man with LDL cholesterol < 149 mg/dL. This LDL cutoff, as well as the CRP cutoff for treatment, CRP-specific event rates for men and women, and CRP-specific statin efficacy, were derived from single primary prevention statin trial[2] and a post-hoc analysis of that trial[3]. The analysis considered other scenarios varying age and sex, with event rates adapted from other population-based studies. The scenarios tested were defined broadly in terms of the LDL cholesterol level and overall coronary heart disease (CHD) risk level. For example, one might consider statin therapy for a 58 year-old man with LDL cholesterol level of 140 if he were also a diabetic hypertensive smoker (and thus at very high CHD risk), but not for a person at lower risk and/or lower LDL cholesterol level. Considering a wider range of more narrowly-defined scenarios might have provided more clinically relevant, actionable results. Sensitivity analyses varying 10-year risk ameliorate this concern to some extent.

The full range of strategies is compared in the base-case scenario (Treat None, Test-and-Treat, and Treat All, see Supplemental Figure 1). No attempt was made to compare the Treat All to Treat None strategy (to validate the model in terms of the overall cost-effectiveness of statin therapy, which can then be compared with prior similar estimates); using numbers provided in Table 3 of the publication[1], this estimate would be $97,500 per quality-adjusted life-year (QALY). Also, different CRP cutoffs were not considered.

Sub-scenarios (persons with high vs. low CRP) were modeled explicitly, and presumably with parallel methodology for each strategy. The prevalence of a CRP level ≥ 0.16 was 50% (median split) for the base-case scenario (Supplemental Figure 1). It is unclear, however, if this key biomarker distribution parameter was varied in the different scenarios. If the prevalence of a high CRP level is very low in some age/sex groups, this would be expected to negatively impact the cost-effectiveness of the Test-and-Treat strategy (many more tests performed to find one that is positive).

The post-test risk of events and effects of treatment were modeled carefully in the base-case scenario using data from the statin trial analysis. We derived risk estimates from the tables of assumptions in the publication to show post-test risks both with and without statin treatment in persons with high and low CRP, and show these in the Supplemental Figure 1. Note that statin treatment effectiveness for myocardial infarction (MI) is assumed to be higher in persons with high CRP vs. low CRP for two reasons: the post-test risk is higher (6.30 vs. 2.90 per 1000 person-years), and the treatment effectiveness is higher (relative risk reduction of 45% vs. 0%). In contrast, statin treatment effectiveness for stroke is higher only because post-test stroke risk is higher in persons with high vs. low CRP (2.21 vs. 1.74 per 1000 person-years); the relative risk reduction is assumed to be constant for these two groups (10%).

Outcomes were modeled using a simple and logical Markov Model with 5 different states: event-free, post-MI, post-stroke, both post-MI and post-stroke, and dead. The key transition probabilities varied in the different treatment strategies were those leading from the event-free state to post-MI and to post-stroke states (see “post-test risks”, above); other transitions were based on other data sources (e.g., U.S. life tables) and were not varied by strategy. Costs and utility penalties for events were age- and sex-specific and not varied. It is unclear if total costs and event rates for the outcome model were calibrated or validated against population-level estimates from external sources. Model results were presented in terms of incremental cost-effectiveness ratios.

Most assumptions were data-driven. Key assumptions were derived from a single statin trial (because it had been used in a prior analysis of the interaction between statin effectiveness and CRP level[3]); others were derived for various external sources such as population-based cohort studies and national vital statistics, as is typical for this type of analysis model. Assumptions about the cost of statins

were derived from the average wholesale price of statins in 2000 by standard methods. Some assumptions were made with imperfect, anecdotal, or completely missing data, as is typical; this includes the price of CRP testing, a key assumption.

The authors performed a set of one-way sensitivity analyses varying key parameters and a three-way analysis varying 10-year risk of MI, statin efficacy and statin price. An important shortcoming is that the results of these sensitivity analyses were presented almost exclusively in terms of Test-and-Treat compared with Treat None; the Treat All strategy, which would be expected to dominate other strategies when statin prices are very low, was mostly not considered in sensitivity analyses. Also, note that the analysis results were not sensitive to the cost of the CRP test itself; the primary downside of the Test-and-Treat strategy, the way the model was structured, is the cost of statins.

This decision analysis model provides potentially important information about the clinical utility of CRP measurement. In short, CRP measurement in persons with LDL<149 mg/dl who are not already on a statin, and initiation of statin therapy when the CRP measurement is high, should lead to important improvements in health outcomes (fewer MIs, strokes and deaths). These improvements are worth the additional costs associated with this strategy when 10-year risk is relatively high and/or the cost of statins is relatively low. Key assumptions are based on a single analysis showing an interaction between CRP and statin effectiveness, and the analysis does not provide an adequate comparison of the Test-and-Treat strategy with the Treat All strategy.

REFERENCES FOR SUPPLEMENTAL MATERIAL

1. Blake GJ, Ridker PM, Kuntz KM. Potential cost-effectiveness of C-reactive protein screening followed by targeted statin therapy for the primary prevention of cardiovascular disease among patients without overt hyperlipidemia. *Am J Med.* 2003;114(6):485-494.

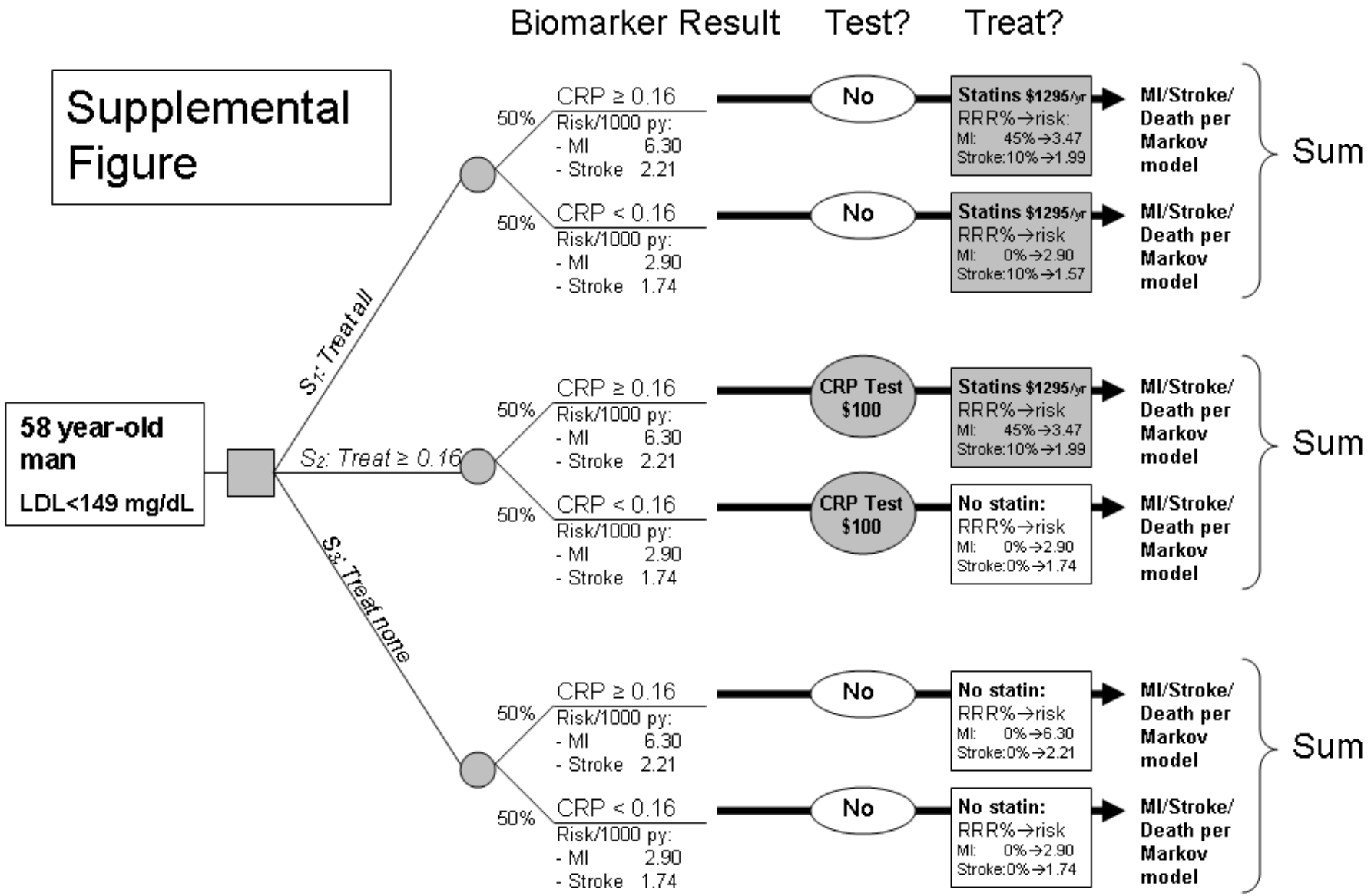
2. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM, Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA.* 1998;279(20):1615-1622.

3. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM, Jr. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med.* 2001;344(26):1959-1965.

SUPPLEMENTAL FIGURE LEGEND

Supplemental Figure 1. Example of a decision analysis model used for evaluating the clinical utility of C-reactive protein screening

Model structure and numeric parameters derived from a publication by Blake, Ridker and Kuntz[1].


Supplemental Figure
Biomarker Result
Test?
Treat?
58 year-old man
LDL<149 mg/dL
S1: Treat all
S2: Treat ≥ 0.16
S3: Treat none
50%
CRP ≥ 0.16
Risk/1000 py:
- MI 6.30
- Stroke 2.21
CRP < 0.16
Risk/1000 py:
- MI 2.90
- Stroke 1.74
No
CRP Test $100
Statins $1295/yr
RRR%→risk:
MI: 45%→3.47
Stroke:10%→1.99
RRR%→risk
MI: 0%→2.90
Stroke:10%→1.57
No statin:
RRR%→risk
MI: 0%→2.90
Stroke:0%→1.74
MI/Stroke/ Death per Markov model
Sum