

# CASE STUDY

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## **THE COMPOSITE BIOMARKER: A NOVEL TECHNOLOGY TO PREDICT STATIN DISEASE PREVENTION EFFICACY, LONGITUDINAL OUTCOMES, AND PHARMACOECONOMIC IMPACT**

*Evaluating changes in cholesterol levels alone may not provide an accurate assessment of a statin drug's cost effectiveness and true efficacy for preventing coronary heart disease onset*

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### **THE CHALLENGE FOR PROVIDERS AND PAYORS**

Health care providers and payors are ultimately interested in preventing disease onset and progression, not just treating individual disease risk factors. For example, reducing cholesterol has no real intrinsic value if it does not help to prevent coronary heart disease or stroke. Unfortunately, demonstrating a drug's disease prevention efficacy versus its pharmacological efficacy is a complicated and time-consuming endeavor.

In many instances, the disease prevention outcomes are not known when a new drug is marketed. Providers and payors are frequently faced with the challenges of selecting prevention drugs, making decisions on reimbursement, and forecasting disease prevention expectations with limited information.

These challenges are exacerbated by other factors, including these:

(1) disease prevention often involves treating multiple risk factors that in concert reduce disease risk;

(2) target risk factors may have pleiotropic effects on the onset of diseases;

(3) there is difficulty in determining product superiority when multiple drugs within a class are available on the market.

There is a tremendous need in today's healthcare marketplace for providers and payors to establish and monitor disease prevention initiatives. To support their selection of the most appropriate drugs for cost-effective prevention of multiple diseases in large populations, it is crucial for providers and payors to have information regarding the most informative indicators of a drug's true prevention potential as well as its short-term and long-term pharmacoeconomic impact.

## PRODUCT POSITIONING CHALLENGES...AND THE SOLUTION FOR PRODUCT MANAGERS

Positioning prevention drugs to providers and payors requires both evidence that the drug prevents disease and evidence that a product has market superiority. In general, new drugs enter the market with evidence of disease prevention “intentions”; ie, intended reduction of disease risk through intervention of a novel risk factor. However, there is usually little evidence for disease prevention outcomes at this stage. Once a market has been established for a drug class, the burden for later or “next generation” drug entries is to establish product superiority.

While disease outcomes and corresponding economic data could provide the evidence needed to position a new drug with providers and payors, long-term outcomes studies executed prior to product launch are impractical since they extend the drug development timeline too many years after clinical efficacy and safety have been established.

A solution to the challenging task of providing timely outcome and economics data to inform provider and payor decision-making is the use of the Composite BioMarker, a novel analysis tool for the evaluation and prediction of a drug’s impact on long-term disease prevention.

## THE COMPOSITE BIOMARKER ANALYSIS CONCEPT

The Composite BioMarker is a multivariate prediction algorithm consisting of individual disease risk factors and biomarkers. A subset of these components includes the biomarker that has been shown to be either directly or indirectly a part of the drug’s mechanism of action.

Each biomarker captures a different pharmacodynamic aspect of a drug’s multiple effects. While *individually* each biomarker only provides limited predictive information about the drug’s true disease prevention efficacy, the *composite* set of biomarkers can predict the drug’s actual therapeutic efficacy for preventing disease onset.

Before the availability of the Composite BioMarker, several years of outcomes research would have been necessary to provide the same information on disease prevention.

## COMPOSITE BIOMARKER BETTER PREDICTS *PREVENTION EFFICACY* THROUGH THE ASSESSMENT OF MULTIPLE RISK FACTORS

Through the use of the Composite BioMarker, it can be shown that some statin drugs may be more effective at reducing heart disease risk than is predicted by their effect on cholesterol metabolism alone. Estimates of a statin’s impact on heart disease risk are revealed through a comprehensive analysis of the

non-lipid pharmacodynamic properties of the drug.

The Composite BioMarker algorithm is an adaptation of the Framingham coronary risk equation to include all biomarkers identified to date as capturing statin effects. (For information on the algorithm used, see Appendix A)

The effects of three statins on reduction of coronary heart disease risk were studied on a simulated population created from the NHANES III cohort (representative Americans, age 40-75 with an LDL cholesterol >155 mg/dL and no history of previous heart disease, were selected). The simulated study was five years long. Baseline coronary risk was determined from analyzing the population's risk factors and biomarkers with the Composite BioMarker. The effects of administering statin therapy were simulated by modifying the population's biomarkers using the Composite BioMarker algorithm (See Appendix A) and then recalculating the population risk.

The effects of the three statins on coronary heart disease risk factors were determined using results from a number of recent clinical trials and data obtained through an extensive review of the literature. The usual lipid effects of the statins were obtained from a well-conducted trial of five statins that brought subjects below the National Cholesterol Education Program (NCEP) guidelines for LDL cholesterol.<sup>1</sup>

Table 1 shows how the coronary heart disease risk factors were modified by each drug. Negative numbers indicate that the drug lowered biomarker levels. Numbers in parentheses are the number of studies whose results were averaged to obtain each value. Notice that while atorvastatin demonstrates the greatest reduction in LDL cholesterol (42%), other statins show better trends in reduction of fibrinogen, C-reactive protein and blood pressure.

**Table 1. Differential effects of statins on coronary biomarkers.**

Biomarker	Units	Prava- statin	Simva- statin	Atorva- statin
Cholesterol	%	-20	-25	-31
HDL cholesterol	%	+6	+6	+5
LDL cholesterol	%	-28	-36	-42
Triglycerides	%	-9	-13	-19
Systolic BP	Mm Hg	-7 (4)	-5 (5)	-3 (3)
Fibrinogen	mg /dL	-1 (16)	-4 (25)	+24 (16)
C-reactive protein	%	-14 (11)	-13 (7)	-9 (4)
Lipoprotein (a)	%	+1 (10)	0 (17)	+2 (6)

In Table 2, a summary of the Composite BioMarker-simulated statin impact on reducing coronary heart disease risk (CHD) is presented for 1,951 subjects. At baseline, the average 5-year risk of heart disease was 8.1%. The Composite BioMarker simulation showed that treatment with any of the three statins resulted in a reduction of the 5-year CHD risk to approximately 5%. Conversely, LDL-cholesterol reduction varied considerably among drugs.

It is interesting to note, that the underlying clinical outcomes study (Andrews *et al*) showed that 76% of atorvastatin subjects reached the NCEP guidelines after one year of treatment, compared with only 58% for simvastatin and 34% for pravastatin. However, the Composite BioMarker comparison of the three statins predicts *equivalent* efficacy for reducing coronary risk. The superior effect of atorvastatin on LDL reduction appears to be mitigated by its large increase in fibrinogen and less impressive effect on C-reactive protein and blood pressure.

longitudinal outcomes studies. The Scandinavian Simvastatin Survival Study showed a 34% reduction in recurrent major coronary events; this finding is consistent with the Composite BioMarker’s prediction of a 37% risk reduction of CHD.<sup>2</sup> The predicted effects of pravastatin (33% reduction) also compare well with the WOSCOP primary prevention trial of pravastatin (31% reduction).<sup>3</sup> A primary prevention trial with atorvastatin has not been undertaken, but we predict a risk reduction of such a trial, in a dose-to-goal format, of about 36%.

**COMPOSITE BIOMARKER BETTER PREDICTS PHARMACOECONOMIC IMPACT THROUGH THE ASSESSMENT OF MULTIPLE RISK FACTORS**

The Composite BioMarker’s validated predictions of the effects of statins on CHD risk can also be used to estimate both short- and long-term economic impact of statin treatment on healthcare budgets. A simple pharmacoeconomics assessment based on the results of the simulated statin prevention trial is presented in Table 3. (For assumptions and calculations, see Appendix B.) While more rigorous health economics evaluations can be developed from the Composite BioMarker predictions, this basic analysis is presented here for illustrative purposes.

The Composite BioMarker analysis reveals that cost effectiveness (measured as cost per CHD event prevented) for the three drugs is similar, despite their large

**Table 2. Composite BioMarker Predictions of Statin Risk Reduction for Coronary Heart Disease.**

N=1951 cases	Mean Baseline CHD risk	Prava-statin CHD risk	Simva-statin CHD risk	Atorva-statin CHD risk
	8.1 %	5.4 %	5.1 %	5.2 %
Composite BioMarker Risk Reduction		33%	37%	36%
% Meeting NCEP goal		34%	58%	76%
LDL-C Reduction		28%	36%	42%

Thus, the Composite BioMarker simulation demonstrates that evaluation of statin differential effectiveness on disease prevention based on cholesterol reduction alone is misleading. The Composite BioMarker more fully captures the drug’s predicted prevention efficacy through the assessment of multiple biomarkers.

Most significantly, the Composite BioMarker disease prevention predictions are validated by published results of

**Table 3. Cost Effectiveness (CE) of statins based on coronary heart disease (CHD) risk.**

	Prava- statin	Simva- statin	Atorva- statin
Number needed to treat	37	33	34
Number CHD predicted	106	100	102
Total CHD costs (\$M)	\$2.18	\$2.05	\$2.10
Prevention cost/dose <sup>1</sup>	\$2.18	\$2.29	\$1.97
Prevention cost (\$M)	\$7.76	\$8.15	\$14.0
Cost/CHD prevented	\$73,242	\$81,690	\$68,625
Total Cost (\$M)	9.95	10.2	9.12
\$M	3.66	3.37	3.13
CE/person (\$/Yr) <sup>2</sup>	1,876	1,725	1,606
CE/person (\$/Yr) LDL <sup>3</sup>	2,273	1,791	1,335

1. Drug cost information is obtained from 2000 Red Book. Average wholesale price is used and no discount is applied.
2. CE = Sum (total CHD cost + drug cost) / % risk reduction as calculated from the Composite BioMarker analysis.
3. CE = Sum (total CHD cost + drug cost) / % reduction in LDL-Cholesterol.

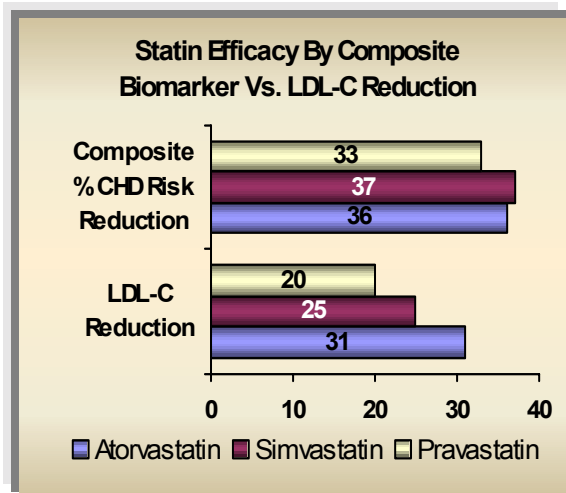
differences in LDL-cholesterol reduction efficacy. However, if cost-effectiveness is measured as cost per percentage reduction in LDL-cholesterol, the pharmacoeconomics evaluation would suggest a substantial difference in the three drugs' costs to prevent disease.

If only LDL-cholesterol improvement is considered, a health economics assessment would suggest that to provide the same level of benefit, pravastatin would cost an additional \$938 per year as compared to atorvastatin. Incremental costs for pravastatin to achieve the same CHD risk reduction as that achieved by atorvastatin decline to almost \$200 per

person per year when considering Composite BioMarker-predicted coronary risk reduction as the measure of statin effectiveness.

### IMPLICATIONS FOR PROVIDERS, PAYORS, AND PRODUCT MANAGERS

Evaluating potential differences among three major statin products solely based on LDL cholesterol may be misleading in terms of the drug's intended therapeutic benefit for reducing coronary risk. These data show that probable disease outcomes can be confidently predicted with a Composite BioMarker that captures the multiple effects of statin drugs on several biomarkers and more fully predicts the therapeutic benefits compared to a single biomarker such as cholesterol. Predicted outcomes are consistent with published data for pravastatin and simvastatin, lending validity to this novel technique.



## **BENEFITS IN DRUG DEVELOPMENT AND PORTFOLIO MANAGEMENT**

Analysis of clinical trial data with a Composite BioMarker at or before drug launch could allow providers and payors to gain early insight into a drug's actual potential to prevent disease onset.

The benefit to pharmaceutical developers is the ability to forecast clinical outcomes prior to lengthy post-marketing morbidity and mortality studies. This information could improve product positioning, pricing, and go/no-go decision making on initiating outcomes research.

Additionally, clinical trials would provide a source of data to guide go/no-go decisions for pursuing new indications. A Composite BioMarker can be used to analyze a product's clinical trial data and predict the potential clinical efficacy and economic impact for new disease prevention indications. For example, cholesterol is a risk factor for stroke and Type II diabetes. The potential therapeutic efficacy of statins for reducing the risk of these outcomes could be accurately predicted with a Composite BioMarker.

As a result of applying this novel analytical technique to currently available data, undiscovered drug benefits could be teased out from a large population analysis. This is a definitive declaration of additional drug value, that previously had not been confirmed or quantified. Without performing even a single new clinical study, this analysis gives R&D executives

confidence that a new drug effect is real, ie, is demonstrated by actual patient data, not hypothetical modeling *in silico*. The result is increased confidence in decisions to proceed with clinical trials knowing the risk of failure is much reduced. Drug companies would be able to initiate phase IV clinical trials more quickly and with greater confidence to expand product indications and improve product competitiveness.

## References

1. Andrews et al. Achieving and Maintaining National Cholesterol Education Program Low-density Lipoprotein Cholesterol Goals with Five Statins. *Am J Med.* 2000;111:185.
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3. Shepherd et al. Prevention of Coronary Heart disease with Pravastatin in Men with Hypercholesterolemia. *NEJM.* 1995;333:1301.

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## Appendix

### A. The Composite BioMarker Algorithm

*The algorithm is constructed using the Synthesis Analysis modeling tool for creating what are essentially meta-analyzed multivariate risk models. This technique combines current epidemiological findings with a method for compensating for the colinearity of risk factors and allows the engineering of multivariate equations to predict a specific disease state from a selected set of risk factors and biomarkers. The resulting predictive equation is customized to accurately predict disease risk from all the available evidence and demonstrate the drug impact on reducing this risk.*

### B. Calculations for Pharmacoeconomic Assessment

*Based on the absolute reduction in risk for each statin, the numbers needed to treat (NNT) were calculated. This represents the number of subjects who need to be taking the statin for 5 years to avoid one coronary incident. The number of subjects multiplied by the risk of CHD in the simulated study yields the number of events in 5 years in this cohort if the entire cohort were taking the indicated statin. By comparison, the baseline risk would indicate 159 cases of CHD in 5 years with no statin treatment. The cost of CHD per*

*person per year was \$8,241. Medical cost information was obtained from the American Heart Association for 1999. The total CHD cost is the number of predicted CHD cases times \$8,241. The prevention cost/ dose was the cost of each daily dose of statin. The cost per CHD case prevented is the prevention cost divided by the number of predicted cases. Despite the slightly lower cost of atorvastatin and the greater number reaching the NCEP goal, the cost of CHD prevented is only slightly lower than for pravastatin and simvastatin. The total cost is the total CHD total plus the prevention cost. The cost effectiveness (CE) is the total cost divided by the % absolute reduction in risk for the statin treatment. This represents the cost of reducing the risk of CHD by 1% in the cohort of 1,951 people over 5 years. The CE/person is the cost of reducing the CHD risk by 1% for each subject and includes both direct and indirect medical costs.*