



Biomarker panels versus single biomarkers to predict clinical endpoints.

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Clinical trials of chronic disease prevention

- Primary or secondary prevention of CVD, diabetes, cancers, degenerative diseases
- Expensive
- Very long time
- Single dose
- Patient selection
- Multifactor diseases
- Multiple drug effects

Benefits of predictive models in chronic disease clinical trials

- Summarize and weight major risk factors and biomarkers
- Identify high-risk subjects
- Predict long-term outcomes from drug effect on short-term biomarkers
- Capture drug pleiotropic effects
- Predict effect of alternate doses

BioSignia, Inc.

- Develops evidence-based, statistical models to better predict the onset and progression of chronic, preventable diseases
- www.knowyournumber.com is a clinical tool for estimating risk for vascular diseases (CHD, stroke, diabetes) and cancers (breast, colon, lung, prostate) and suggesting interventions
- Life insurance actuarial tools and health insurance claims analysis tools
- Disease prediction tools for pharmaceutical research

Presentation Objectives

- To simulate long-term outcomes from simvastatin trials with alternate doses similar to the 4S trial
 - Develop a predictive model of CHD onset to include newest biomarkers
 - Develop a “Composite Biomarker” of statin effect on CHD onset
 - Develop a dose model for pleiotropic effects of simvastatin
 - Demonstrate possible long-term dose response of simvastatin on CHD and its implications

Definitions

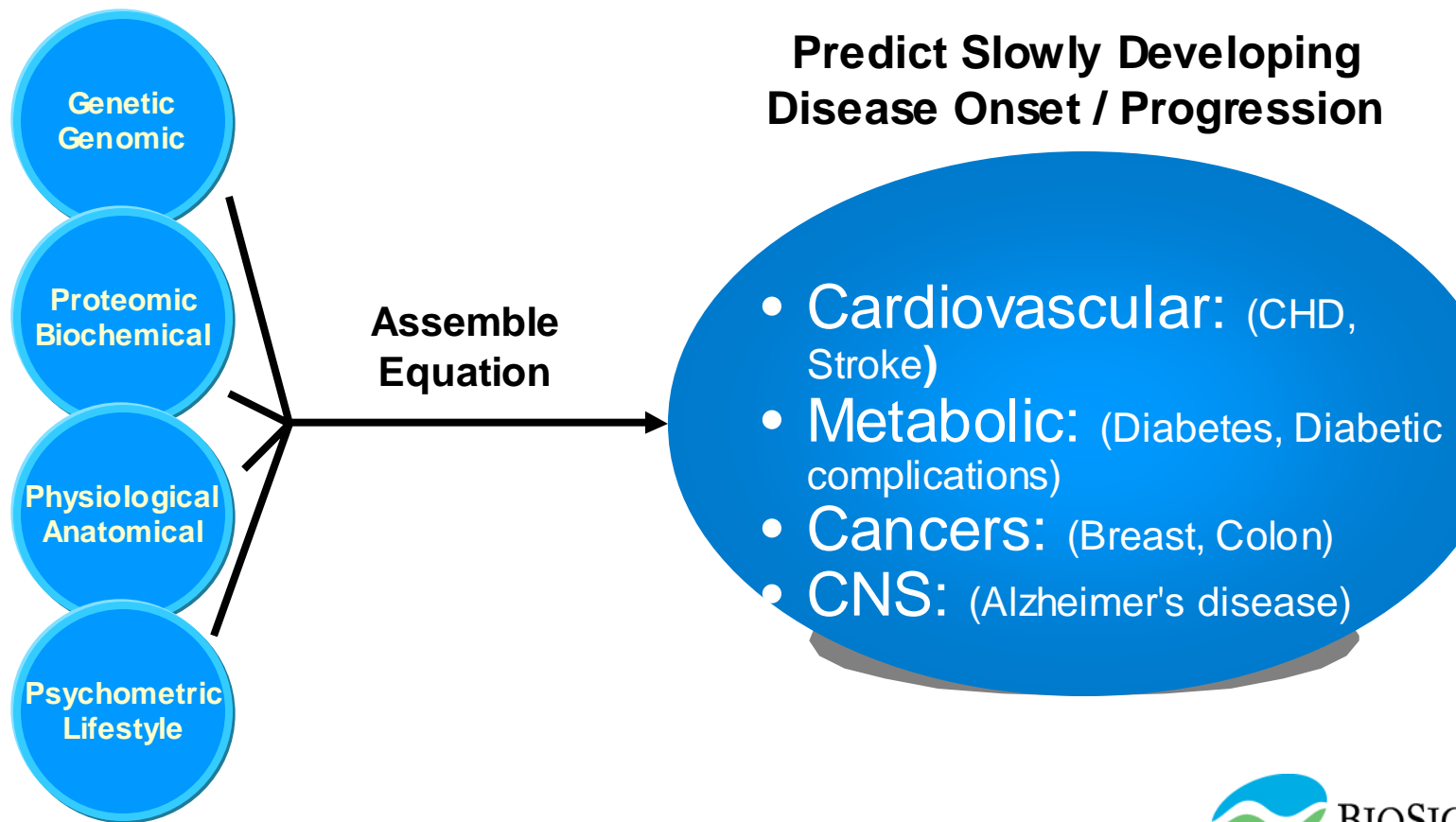
- Biomarker- A physiological, anatomical or clinical measurement that reflects information about the state of health or disease of an organism.
- Composite Biomarker- An equation that predicts a drug's effect on a disease through its effect on a panel of disease-related biomarkers.
- Risk Factor- Information (including biomarkers) that helps refine risk estimates for a disease.
- Pleiotropic Effects- The multiple effects of a drug on disease biomarkers.
- 4S- Scandinavian Simvastatin Survival Study, a secondary CHD prevention clinical trial, 5.4 years.

Synthesis Analysis

- A novel method to assemble multivariate regression equations for predicting diseases (patented)
- Enables compilation of new models from diverse research studies examining a variety of single biomarkers/risk factors known to be associated with the same disease state (evidence-based models)
- Creates epidemiologically based prediction models, Composite Biomarkers, for drug effect on disease morbidity or mortality

Synthesis Analysis

Disease Risk Factors & Biomarkers



Method Overview

STEP 1

- Select disease and predictors

STEP 2

- Identify completed outcomes studies with univariate relative risk for each factor and disease outcome
- Combine univariate relative risks by meta-analysis

STEP 3

- Adjust for co-linearity between factors with cross-sectional study, and
- Generate multivariate risk equation for all factors

Synthesis Model: Expanding on Framingham

Framingham Variables

- Age
- Gender
- Smoking
- Total Cholesterol
- HDL
- SBP
- LVH
- Diabetes

Additional Variables

- Exercise
- Aspirin
- Family History
- Homocysteine
- C-Reactive Protein
- Fibrinogen
- Lipoprotein (a)
- Albumin

Effect of Other Risk Factors on CHD

Physical exercise RR = 1.9, 36 cohort studies

Fibrinogen RR = 1.8 (0.1g/dL), 18 studies

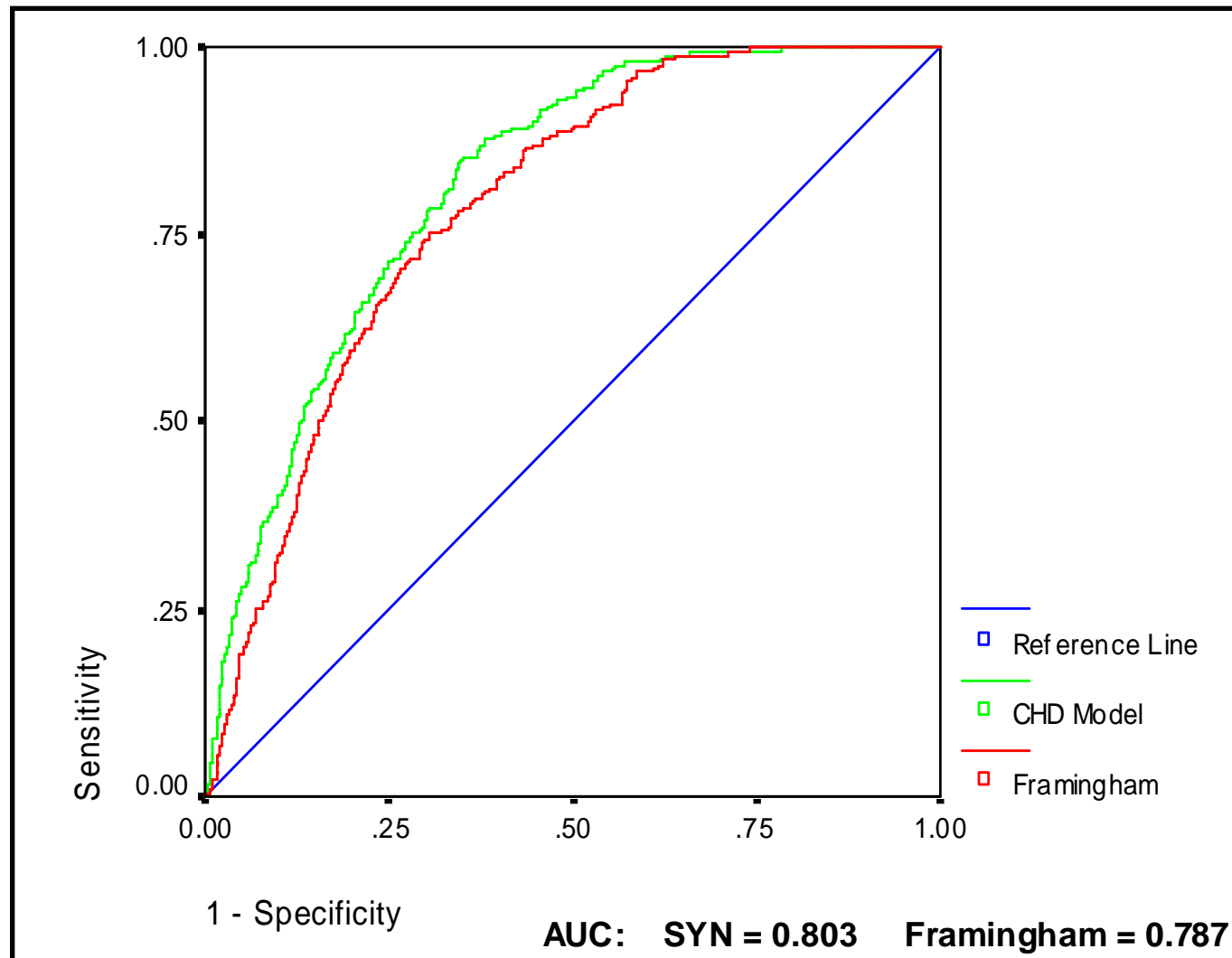
Albumin RR = 0.67 (4g/L), 8 studies

Lipoprotein(a) RR = 1.18 (log), 15 studies

Homocysteine RR = 1.10 (mmol/L), 13 studies

C-Reactive Protein RR = 1.42 (log), 6 studies

ROC of Synthesis Analysis in NHEFS



Synthesis Analysis = “Multivariate Meta-Analysis”

- Enables creation of a customized disease risk algorithm
- Applicable to any defined disease state backed by epidemiological research data
- Limitations:
 - Validity of epidemiology evidence
 - Approximation vs. empirical model
 - Assume same underlying population

Composite Biomarker

- Predicts a drug's impact on the incidence of future disease events (multivariate logistic regression)
 1. Predict baseline risk of disease events
 2. Predict reduced risk of disease events from drug intervention
- Utilizes clinical trial data collected in relatively short time frames (months) to capture the drug's effect on disease-related biomarkers, and subsequently, to predict the drug's long-term effect (years) on reducing the risk of disease
- Assumptions
 - Synthesis Analysis assumptions
 - All biomarkers are critical to causal pathways to disease
 - Equation betas accurately reflect biological importance of variable
 - Each disease-drug class model needs to be validated anew

Predicting Therapeutic Efficacy

Goal:

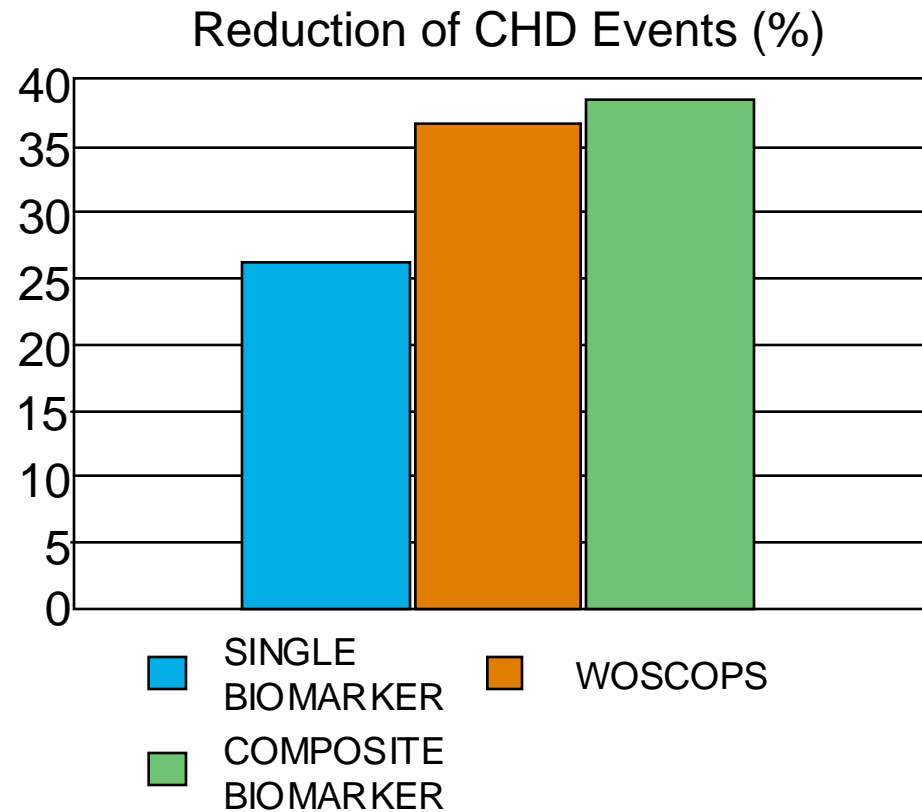
Determine if CHD composite biomarker more accurately predicts efficacy of statins in preventing CHD events than any single biomarker.

Predicting Therapeutic Efficacy (con't)

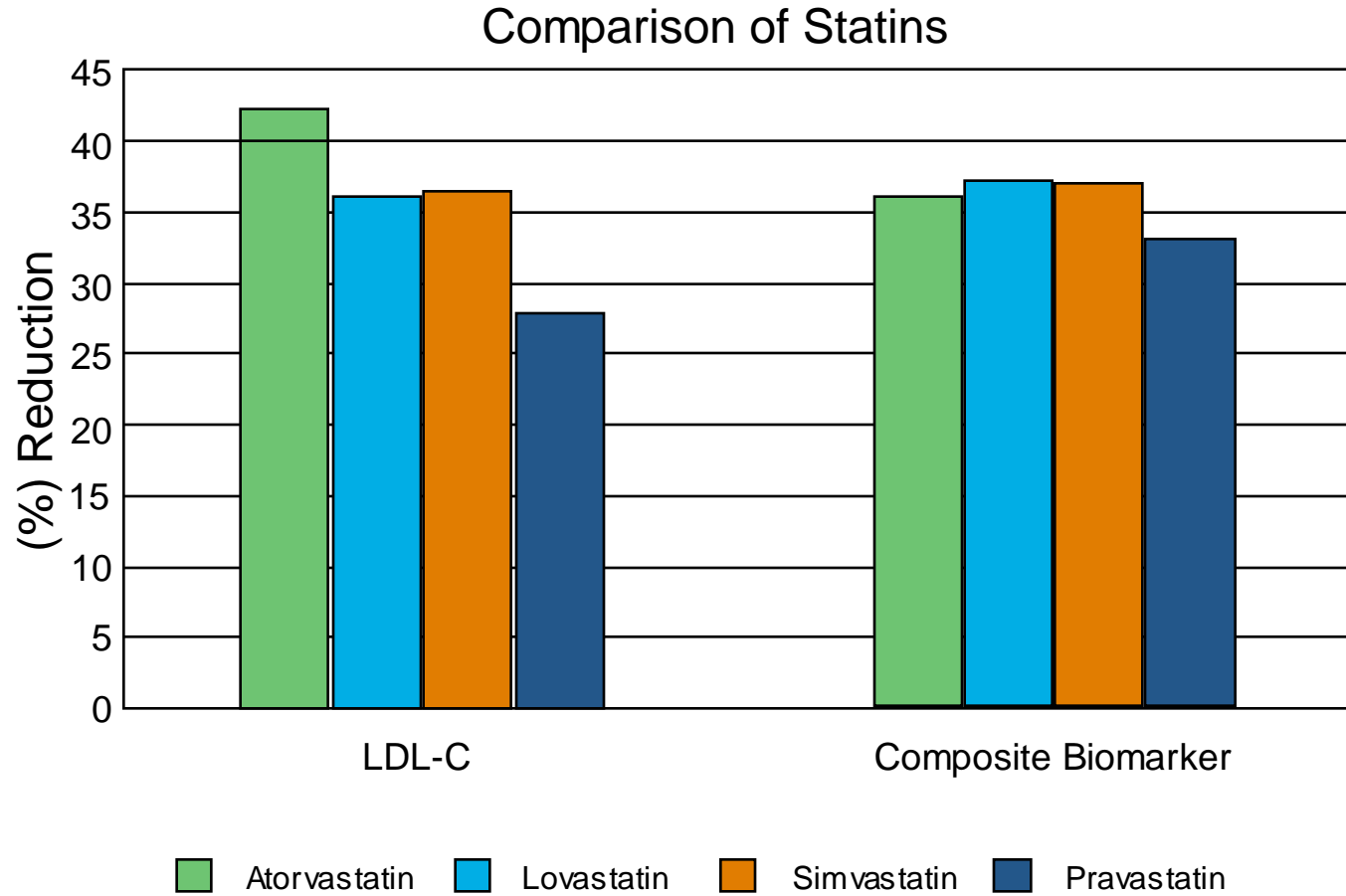
- Benchmark for Validation
 - WOSCOPS outcomes data for pravastatin
- Method
 - Created cohort from NHANES III
 - Treatment A: Risk of CHD based on Composite Biomarker
 - Treatment B: Risk of CHD based on lowering cholesterol alone
 - Treatment C: Risk of CHD based on altering multiple biomarkers

Composite Biomarker Accuracy

- Composite biomarker prediction of statin's efficacy correlates well with published outcomes studies
- Composite biomarker is more predictive of disease events than cholesterol alone



Statin Effectiveness: LDL-C vs. CHD Risk



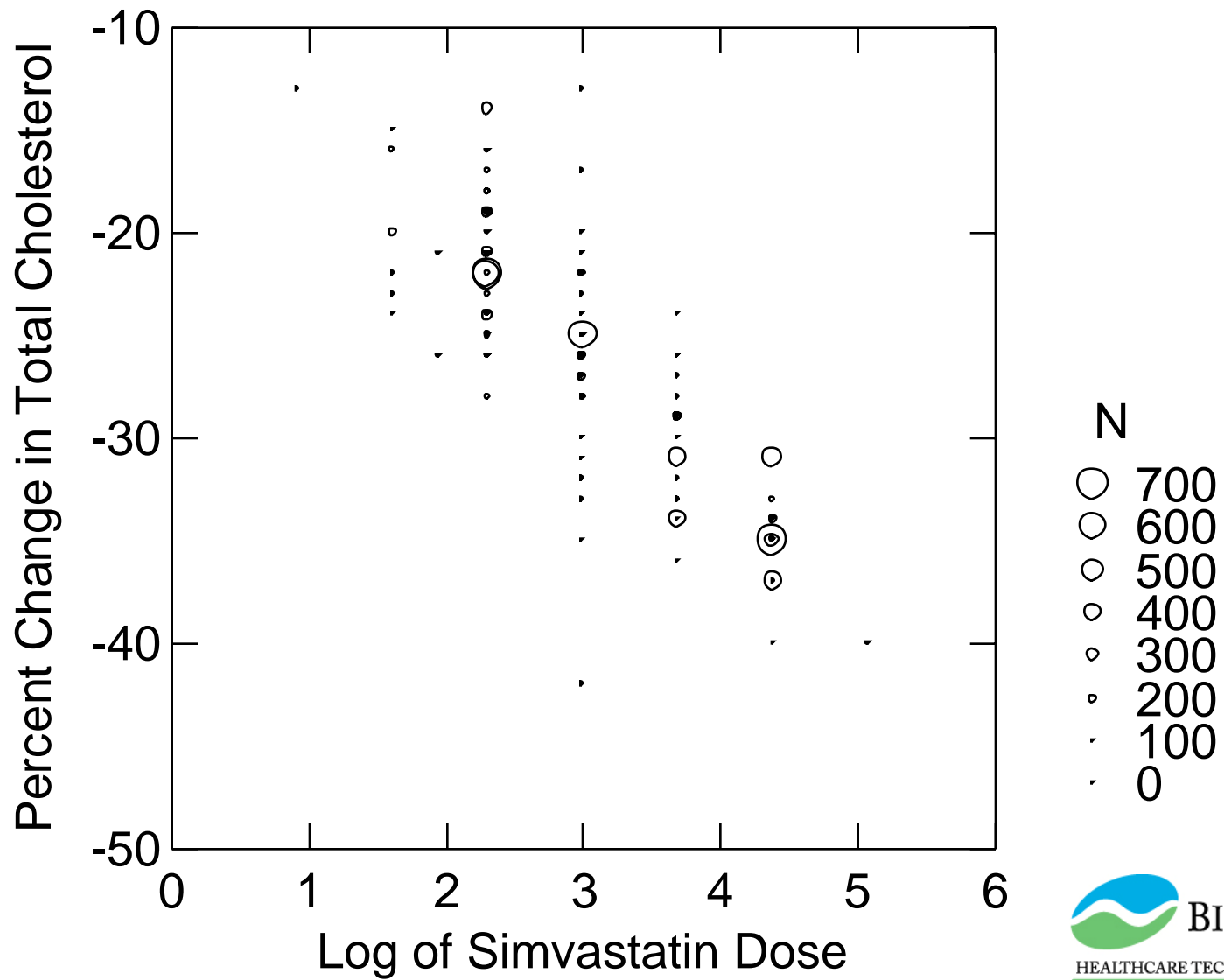
Method for Dose-Response Model

- Collect reports on lipid and non-lipid effects of simvastatin in short-term clinical trials.
- Meta-analyze simvastatin effect on each biomarker for dependence on dose, length of study, initial biomarker value, and weighted by study sizes.
- Develop 6 dose equations for biomarkers based on measurement at 12 weeks.
- Model CHD effect of each dose using composite biomarker by dose effects on the 6 biomarkers.

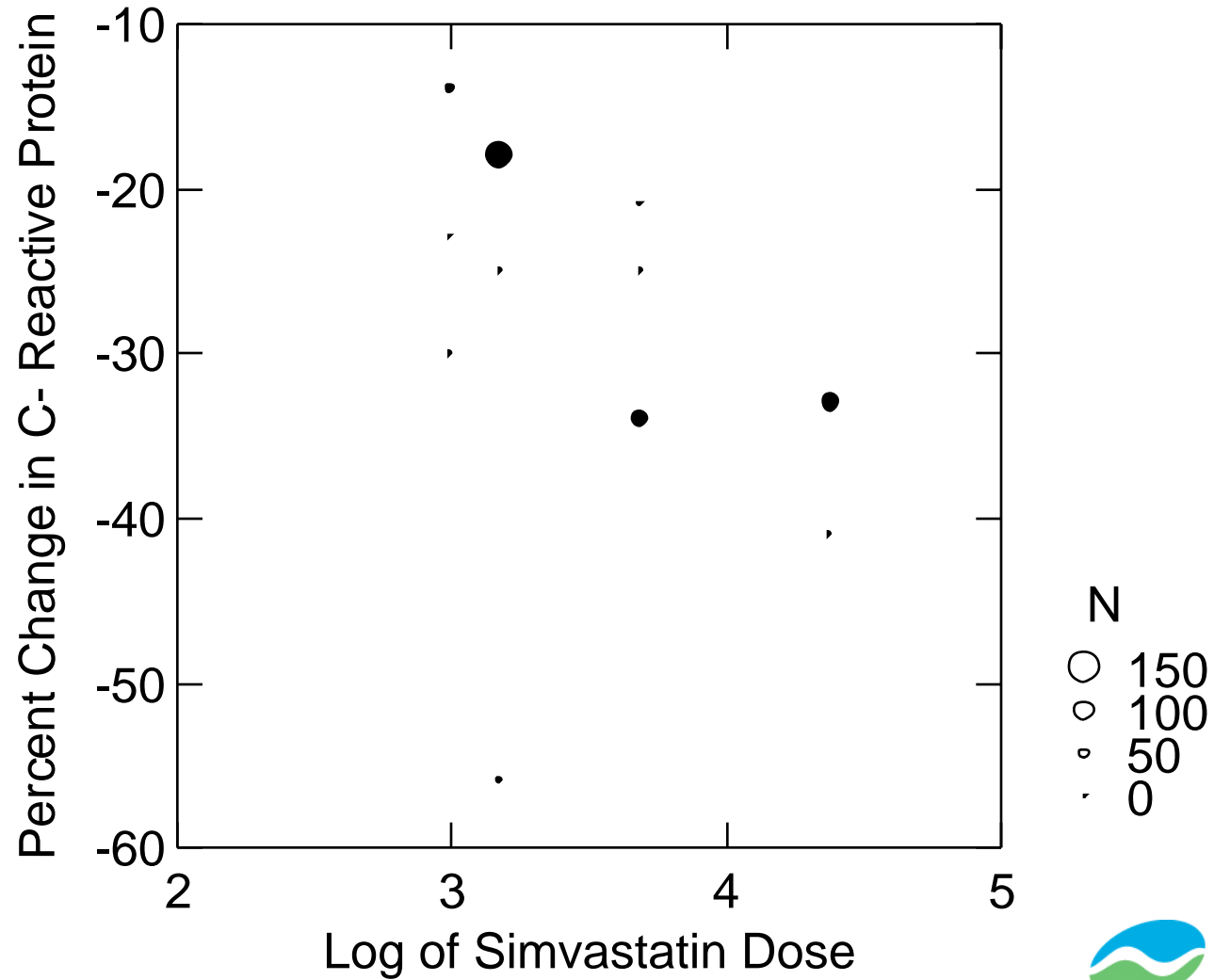
Biomarkers Affected by Simvastatin

<u>Biomarker</u>	<u>Doses</u>	<u>Total N</u>	<u>Units Changed</u>	<u>Change Equation</u>
Total Cholesterol	106	11605	%	$-6.25 \cdot \log(\text{dose})$
HDL Cholesterol	104	11912	%	$+0.77 \cdot \log(\text{dose}) - 0.104 \cdot \text{HDL}$ (12 wks)
Lipoprotein (a)	28	2520	%	+1.78 (12 wks)
Fibrinogen	18	723	mg/dL	-4.8
Systolic BP	17	211	mmHg	$20.7 - 0.16 \cdot \text{sbp}$ (12 wks)
C-Reactive Protein	11	517	%	-27.7

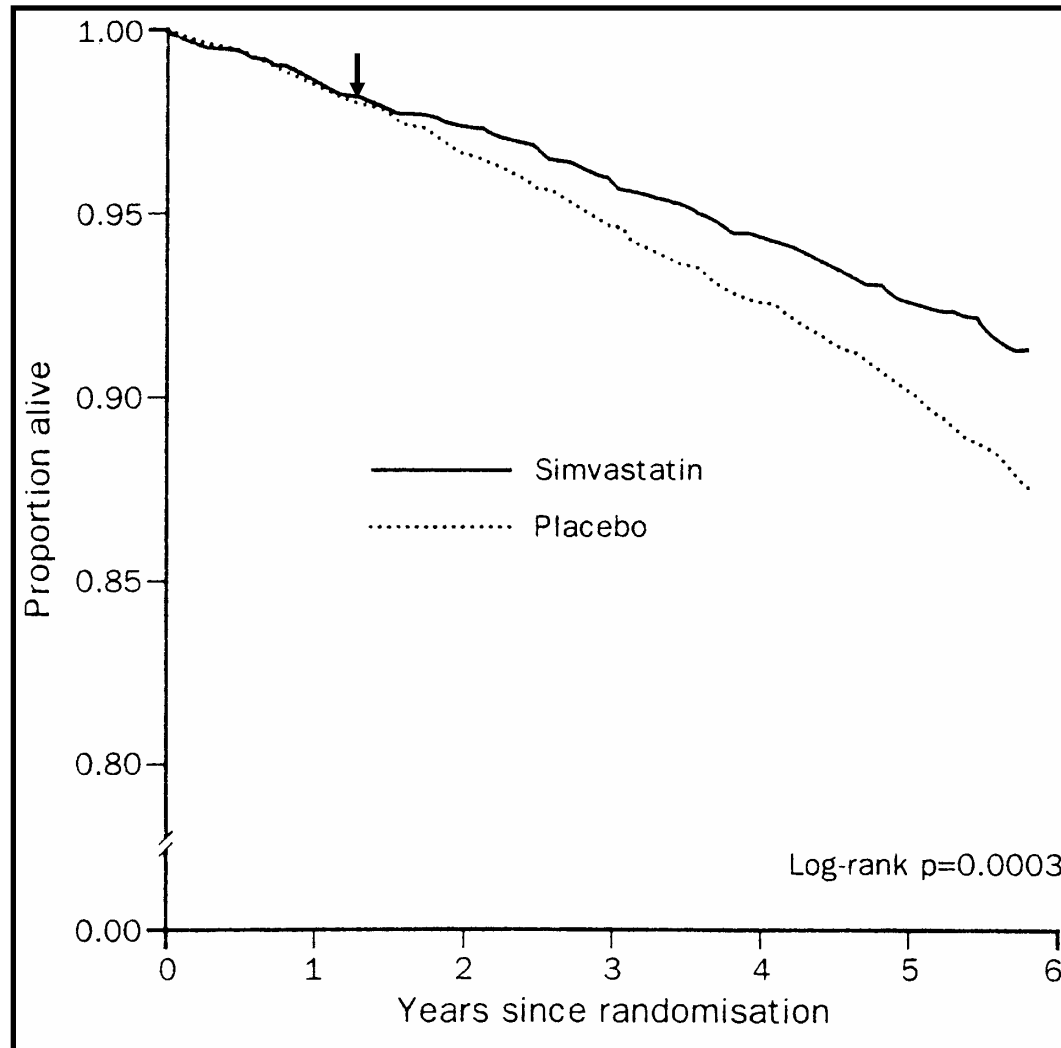
Total Cholesterol and Simvastatin Dose



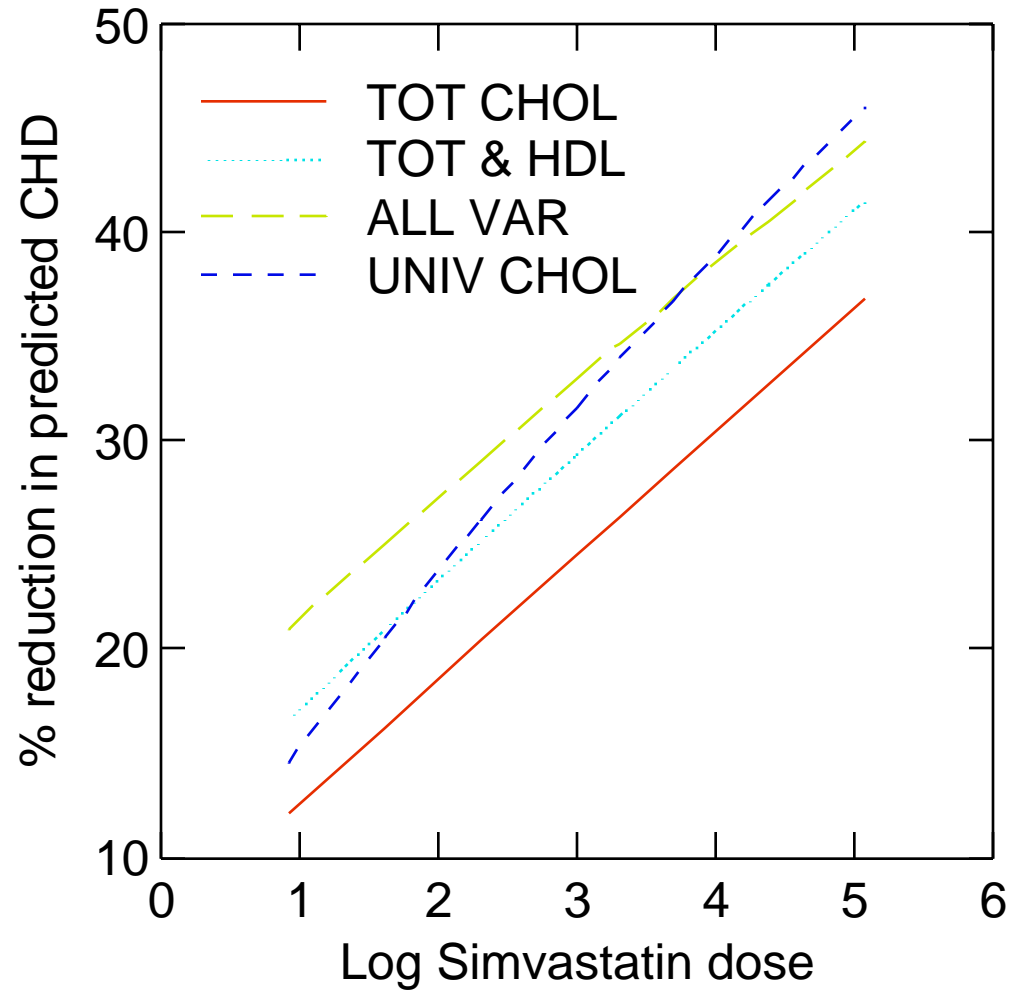
C-Reactive Protein and Simvastatin Dose



Survival Curve from 4S



Predicted Reduction in CHD Risk by Simvastatin



Drug Cost to Prevent One CHD Event

<u>Dose</u> (mg/day)	<u>Risk</u> <u>Reduction</u>	<u>Annual</u> <u>NNT</u>	<u>Pill</u> <u>Cost</u>	<u>\$ per Event</u> <u>Saved</u>
5	25.0	514	1.57	295,000
10	28.9	444	2.10	341,000
20	32.8	392	3.64	521,000
40	36.7	350	3.64	466,000
80	40.5	318	3.68	427,000

Pharmaco-Economic Messages

- Doctor: Prescribe “everyone” 5 mg
- Patient: Take 5 mg if no insurance
- Merck: 5 mg undervalued
- MCO: 10-80 mg overvalued
- FDA: OTC 5 mg?

Conclusions

- Synthesis Analysis technology is useful in compiling multivariate disease risk models.
- Composite biomarkers are possible with sufficient input data and acceptable assumptions.
- Low dose simvastatin (and possibly other statins) are probably more efficacious than previously thought.



Thank you very much for your kind attention.