Prescribe by Risk: The Utility of a Biomarker-Based Risk Calculation in Disease Management to Prevent Heart Disease

Authors: **MARTIN ROOT, Ph.D.**, and TIMOTHY SMITH, Ph.D.

Abstract

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ABSTRACT

Preventive treatment for those most at risk of heart disease rather than those with the highest blood pressure or cholesterol values may be a more efficacious strategy for disease management. This depends on accurate biomarker-based risk assessment tools. An evidence-based model of heart disease risk was developed using the Framingham model with an additional five risk factors, including three of the newer blood biomarkers. This was applied to the adult population of the 3rd National Health and Nutrition Examination Survey cohort. Additionally, the selection criteria for therapeutic intervention from the Adult Treatment Panel III guidelines (for hyperlipidemia) and the 7th Report of the Joint National Committee (for hypertension) were applied to the same subjects. Of this cohort 54% qualified for at least one of these medications while 18% qualified for both. Using this 18% cutoff, the 18% of the subjects with the highest calculated heart disease risk were also identified using the developed risk model. We applied established therapeutic reductions in heart disease probability to those identified by guidelines and to those identified by risk. Applying both drugs to the high-risk group (one third the size of the guidelines group) achieved the same reduction in population risk (about one fourth) as applying the drugs to the guideline groups and required only half as many prescriptions. Intermediate results were found when an intervention group was identified by a combination of both high risk and high levels of risk factors. In this simulation, identifying patients by heart disease risk level resulted in substantially fewer people being treated with fewer drugs and achieving a similar reduction in disease risk.

INTRODUCTION

CORONARY HEART DISEASE (CHD) is a prevalent, expensive, and preventable disease, and is a major focus of disease management organizations. Evidence based guidelines for the prevention of CHD have been developed and updated from time-to-time by national organizations. The National Cholesterol Education Program recently promulgated the third version of the Adult Treatment Plan (ATP III) guidelines[1] for the treatment of hyperlipidemia. The Seventh Report of the Joint National Committee on hypertension treatment (JNC7) was released in 2003.[2] These guidelines are not entirely intended for the prevention of

heart disease directly but for the reduction of subclinical risk factors. Thus, action levels of LDL cholesterol and blood pressure are presented and not, primarily, scores from such risk as sessment tools as the Framingham heart dis ease model. Several authors have suggested changes that would incorporate more risk-based assessments.[3–6] Several British societies combined their recommendations for risk fac tor intervention around risk assessments,[7] and several American authors have suggested the same for American recommendations.[8,9] The ATP III guidelines now include the Framing ham score as a secondary criteria.

Disease management is most successful for those conditions in which future suffering and costs can be lowered through efficacious self-care efforts. Disease management also works most effectively when supporting a physician's plan of care. Disease management thus rests on the twin pillars of accurate identification of those at risk of future suffering and cost, and of cost-effective intervention for those identi fied individuals. Thus, medical costs in a whole population can be managed by working with a small subgroup at highest risk. For example, this cost-effectiveness recently has been shown for the drug treatment of a series of conditions traditionally under disease management.[10] This type of care must involve collaborative practice models that include physicians in pa tient self-management education, particularly in compliance with drug therapies for which there is no immediate visible benefit.

The benefits of preventive programs are most observable and cost-effective among those at highest risk.[11–15] There are differences of opinion about how to assess this risk. Some suggest age alone,[14] whereas others suggest preexisting disease.[11,15] Yet others suggest more complex risk analysis such as with the Framingham heart disease risk score[4,13] or with additional newer risk factors.[12,16,17] It is im portant to note that most of these risk factors are not modifiable. In fact, the results of the large statin drug trials show minimal effect dif ferences between patient subgroups defined by non-modifiable risk factors. For example, in the Heart Protection Study, a 25% drop in risk was fairly consistent whether or not a person had a preexisting condition.[18] In a pooled analysis of pravastatin trials, only subgroups based on hypertension or LDL level had modest subgroup effects. Among those groups defined by non-modifiable risk factors (age, diabetes, gender, etc), there were no differences. This suggests that treatment lowers risk by a fixed percent in a population independent of the sources of that risk.[15] This is not only a convenient product of the mathematical nature of logistic risk models but also is a clinical reality that can be the ba sis of a new paradigm in cardiovascular dis ease prevention.[14] While the relative reduction in risk may be constant across the range of dis ease risk, the absolute reduction in events is markedly different in high and low risk groups. This concentration of a large number of future events in the high risk stratum makes this group an especially appealing target by which to lower the absolute number of events in the population relatively cost effectively.

Within the disease management context, reducing disease costs for a population is achieved by working most intensively with those at highest risk of future disease and the associated cost. Thus, making the most accu rate identification of those at truly highest risk would be of paramount importance. Since 1991 when the Framingham model was published in its present form,[19] many new biological risk factors of heart disease have been discov ered.[20–22] Combining these with the Framingham model would produce an advanced and credible prediction tool for CHD risk.[16,17] For example, three studies have specifically shown how C-reactive protein would supplement the Framingham score in identifying those at high risk.[23–25]

We have developed such a tool and use it to demonstrate, in a representative population, the benefits of prescribing CHD preventive measures by risk level rather than by risk factor levels.

MATERIALS AND METHODS

Applying guidelines to NHANES III

The 3rd National Health and Nutrition Ex amination Survey (NHANES III) is a nationwide weighted survey of individuals in the

United States performed between 1988 and 1994. The results of the survey were used in their unweighted form to assess the performance of the ATP III and JNC7 guidelines. Adult subjects aged 40–75, inclusive, were used. The following variables were assessed for inclusion in the eligible group for ATP III: LDL cholesterol, age, gender, history of CHD and diabetes, current smoking, and a family history of CHD. The NHANES III family history question identified those whose parents had a heart attack before the age of 50 while the ATP III family history question identifies a mother with heart disease before age 65 or a father be fore age 55. This difference may result in fewer people being identified at high risk than if the ATP III definition was used. The remaining variables used in the Framingham score[19] were used: systolic blood pressure, total cholesterol, HDL cholesterol, and left ventricular hypertro phy. In addition several newer risk factors were added: lipoprotein(a), C-reactive protein, homocysteine, and subjective assessment of exer cise level (three levels). The JNC7 also required diastolic blood pressure. Using these variables, the guidelines of ATP III and JNC7 were ap plied with particular attention to those for whom drug therapy was recommended.

Creation of CHD risk model

The Framingham CHD risk score is a well-known and validated tool for assessing future CHD risk. Our goal was to add to this model the newer risk factors in such a way that the credibility of the Framingham model would be retained while adding newer risk information. The novel method for the creation of this extended risk model has been termed "synthesis analysis" and has been demonstrated in a simplified clinical context.[26] Here is the method in brief. The age and gender-adjusted odds ratios or relative risks for novel risk factors are de termined from published meta-analyses or from our own meta-analyses of the epidemiologic literature. These new risk factors are added in a stepwise fashion to the existing model (starting with Framingham) adjusting for the colinearity between the added variable and the existing model at each step. The dataset utilized in this process is from NHANES III. First, the 5-year probability of CHD is calcu lated among the adult NHANES subjects using the Framingham risk equation. Then a linear regression model is run comparing that probability against the first added variable, in this case family history. The beta for family history was 0.088 which is a measure of the colinearity between the added variable and the previous variables. This value is subtracted from the univariate beta from the medical literature (0.262) to obtain the beta used for family history in the stepwise model (0.0174). The resulting logistic model after this step contains the Framingham variables and family history with a beta of 0.0174. In the next step, a new variable is adjusted by a similar subtraction and added to the model. When all the candidate variables are entered, or cannot be added due to excessive colinearity, then the model is complete. For a summary of the univariate and stepwise multivariate adjusted odds ratios used in the model, see Table 1.

Our current model includes the following variables in addition to those in the Framingham model: prior CHD diagnosis, lipoprotein(a), C-reactive protein, homocysteine, as sessment of exercise level, and family history of CHD. The addition of a prior CHD diagno sis as a risk factor was done following the cal culation of first and subsequent CHD risk for the Framingham cohort.[27] For the remaining additional variables a relative risk per unit of measure of the risk factor was calculated, then each was modified and added in a stepwise fashion (Table 1). The lipoprotein(a) relative risk of 1.15 per log unit of mg/dL was derived from a meta-analysis by Danesh et al.[28] The C-reactive protein relative risk of 1.175 per log unit of mg/L was derived from another Danesh meta-analysis.[29] The homocysteine rel ative risk of 1.042 per μ,mole/L was derived from a recent meta-analysis by D.S. Wald et al.[30] The relative risk for a family history of CHD came from a study from Framingham[31] and the relative risk for three subjective steps of exercise came from a review of Powell et al.[32]

Effects of therapeutic agents

A meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration found

Table 1. Original Relative Risks and Step-Wise Multivariate Adjusted Relative Risks for Variables in the Complete CHD Risk Assessment Model

Risk factors	*Units*	*Original relative risk*	*Multivariate relative risk*
CHD family history	No = 0; yes = 1	1.30	1.19
Exercise	3 levels	0.72	0.85
Logarithm of C-Reactive Protein	mg/L	1.58	1.11
Homocysteine	μ,mol/L	1.042	1.036
Logarithm of Lipoprotein(a)	mg/dL	1.15	1.12

that, in general, antihypertensives reduce CHD events by 19%.[33] A meta-analysis by LaRosa et al in 1999[34] concluded that statins as a group lowered major CHD events by 31%. The calculated combined effect of the two medications together would be a 44% reduction in CHD.

RESULTS

Restricting the final dataset to those for whom all the variables were available and for the ages used in the original Framingham study, limited the age range to 40–75 and the total number to 2890. The subjects, in their treatment groups, are described in Table 2. Of these subjects with complete data, 30% were eligible for cholesterol treatment by ATP III and 42% were eligible for hypertension treatment by JNC7 (Table 3). Thus, 54% of the population was eligible for one or both treatments, and 18% were eligible for both. When CHD risk was used as the criteria, the 18% of the subjects with the highest risk were eligible for both medications. The remaining subjects received no treat ment.

Table 2. Description of NHANES III Adult Subjects before Simulated Treatment by ATP III and JNC7 Guidelines, by CHD Risk Alone, or by a Combination

Variables	*Adult*	*Guidelines*	*Risk*	*Combination*
N	2890	1556	518	799
Age	56	59	64	62
Female (%)	54	52	35	45
Prior CHD (%)	5	8	18	13
Diabetes (%)	11	18	29	22
Family history CHD (%)	7	7	8	6
Smokers (%)	28	31	45	36
Exercise (1–3)	2.1	2.1	2.0	2.0
Systolic BP	131	141	143	145
Albumin (mg/dL)	4.0	4.0	3.9	3.9
Lipoprotein(a)[a] (mg/dL)	11	11	22	17
Fibrinogen (mg/dL)	312	324	376	353
Total cholesterol (mg/dL)	216	228	229	237
HDL cholesterol (mg/dL)	50	48	42	45
C-Reactive Protein[a] (mg/dL)	3.6	4.0	6.0	4.9
Homocysteine (μ,mol/L)	10	11	12	11

[a]Mean of logarithm-transformed variable.

Table 3. Comparison of Hypertension Treatment Eligibility by JNC7 (Rows) and Cholesterol Treatment Eligibility by ATP III (in Columns) Among NHANES III Adults

	ATP III		
	Non-eligible	*Eligible*	*Total*
JNC7			
Non-eligible	1334	352	1686
	686	518	1204
Eligible	2020	870	2890

When the estimated risk reductions were applied to the appropriate groups, the reduction of risk when treating by the guidelines was 27%, and from a group average risk of 6.2% in 5 years to 4.6%. A similar risk reduction of 27% was found when the treated group was identified by CHD risk level (Fig. 1). Thus, when us ing CHD risk rather than the guidelines in guiding therapy, one third of the number of pa tients with roughly one half as many prescrip tions were needed and the CHD risk reduction was an equivalent amount.

Those eligible for treatment by the guidelines were combined by the number of prescriptions for which they were eligible: 0, 1, or 2. These groups were compared with the CHD risk-based eligibility (Table 4). Less than half of the subjects who met the eligibility of both sets of guidelines qualified as high-risk subjects (232 of 518). Conversely, 12% of the high-risk group qualified for no drugs by the guidelines (60 of 518).

An alternative was proposed in which both high CHD risk and high levels of risk factors were used to identify those eligible for treat ment. In addition to those at the top 18% of risk, we added those with LDL cholesterol over 190 mg/dL or those with systolic blood pressure over 160 mm Hg or diastolic blood pressure over 100 mm Hg (Table 5). Both drug treatment groups together comprised 28% of the popula tion, compared to 54% by the original guide lines and 18% by the original risk algorithm. By applying the appropriate drug treatments, the CHD risk was lowered 29%, slightly more than the other two strategies. The number of treated subjects was exactly half of the guidelines groups and about two thirds (64%) as many prescriptions were needed as in the guidelines groups.

These improvements in treatment efficiency by treating by risk are balanced by an increased number of probable CHD events in the low risk group (Table 6). The risk-defined group that receives no treatment is about twice as large as the therapeutic non-treated group. Since the average CHD risk is about the same in these two groups, the number of probable events is twice as many (71 versus 35) in the low-risk group. This is lowered to 56 probable events with the combined non-treated group.

DISCUSSION

The idea of prescribing by disease risk is not new. N.J. Wald and M.R. Law have forcefully put forward this idea[15] and implemented it in a most austere form in their Polypill concept.[14] Both American and British guidelines now use some version of risk assessment.[1,7,35] Others have shown that using the guidelines can be poor predictors of CHD risk.[5]

The advantages to disease management or ganizations of such a risk-based strategy are ev

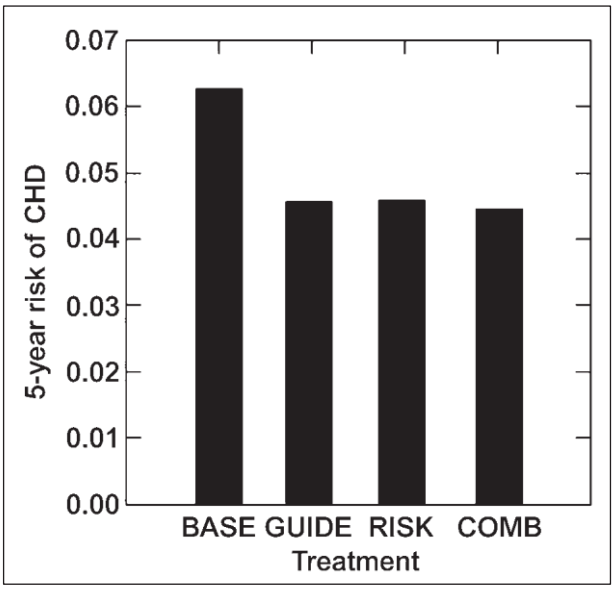

FIG. 1. CHD risk among NHANES III adult subjects at baseline and with simulated treatment by ATP III and JNC7 guidelines, by CHD risk alone, or by a combination. Base, baseline; guide, ATP III and JNC7 guidelines; risk, CHD risk alone; comb, combination of risks.

Table 4. Comparison of Number of Guideline Treatment Eligibilities (in Rows) and CHD Risk-Based Eligibility (in Columns) Among NHANES III Adults

	CHD risk-based eligibility		
	Non-eligible	*Eligible*	*Total*
Number of treatment eligibilities			
0	1274	60	1334
1	812	226	1038
2	286	232	518
Total	2372	518	2890

Table 6. Comparison of the Probable Number of CHD Events in 5 Years by Therapeutic Treatment Groups (in Rows) and CHD Risk-Based Treatment Groups (in Columns) Among NHANES III Adults

	CHD risk-based eligibility		
	Non-eligible	*Eligible*	*Total*
Number of treatment eligibilities			
0	24[a]	11	35
1	31	47	78
2	16	52	68
Total	71	110	181

[a]The probable number of events is the sum of the probabilities of CHD for the members of each cell from Table 3.

ident from the increased efficiency of treating fewer patients with fewer drugs for similar results. We have made assumptions about the efficacy of the two large classes of drugs to arrive at our estimates of reduced risk. However, even if these drugs are only a fraction as efficacious in clinical practice as in clinical trials, the relative benefit of risk-based eligibility is the same, though the absolute risk reduction and cost containment would be reduced.

Underidentification and undertreatment still remain difficult clinical issues.[36] Only half of eligible patients have their cholesterol checked, and only half of those who meet the guidelines are put on the proper therapy. Of those on medication, three quarters do not reach their therapeutic goal and less than 30% of patients continue on therapy after a year.[36] Knowledge of disease risk scores has been shown to improve treatment,[37] although accurate assessment of coronary risk remains difficult for many doctors.[38] Even short visits with doctors and nurses are effective in changing lifestyle.[39] However, a recent study in Canada among the elderly showed that the probability of statin prescription actually decreases with advancing age and advancing risk.[40] One shortcoming of a risk-based approach is that it requires a computer and the time necessary to enter the required data. Unfortunately, the utilization of the ATP III guidelines is also a very complex algorithm that requires substantial patient information and is not easily performed in the presence of a waiting patient. The decision tree derived from ATP III has been computerized effectively.

Table 5. Comparison of Hypertension Treatment Eligibility (in Rows) and Cholesterol Treatment Eligibility (in Columns) Among NHANES III Adults Determined by a Combination of High CHD Risk and High Blood Pressure or High LDL Cholesterol

	Cholesterol treatment		
	Non-eligible	*Eligible*	*Total*
Hypertension treatment			
Non-eligible	2091	131	222
Eligible	136	532	668
Total	227	663	2890

This reported exercise is a simplification in several ways. It does not consider other pathological sequelae of hypertension and dyslipidemia. The guidelines address relatively rare conditions such as preeclampsia and obstructive liver disease that are not addressed in the CHD-risk approach. Also, for the purpose of this example, we did not consider other important outcomes such as kidney disease, cerebral vascular disease and heart failure. The optimal risk-based algorithm would need to be a composite of all the deleterious sequelae weighted by their severity or cost. We have begun this process by developing other risk mod

els for these diseases. Another simplification is that this was a simulation of outcomes and not a study of actual outcomes. Therefore, our dis ease risk algorithm was used both to identify those at risk and to assess the success of the in tervention (Table 6).

In administering care to a patient, clinicians must consider many factors beyond chronic disease risk, including adverse effects, com pliance, patient preferences and other com plicating presenting factors risks.[41] Numerous options are available to clinicians and not all options can be readily quantified. In disease management the prevailing findand-treat-high-risk paradigm may not necessarily focus on the same patients as a clinician. Thus, the risk-based tool suggested here may be more ap propriately used by a disease management or ganization than by a clinician. This type of risk assessment and disease management involves more collaborative practice models that include physician intervention and disease manage ment in patient self-management. The bio marker-based risk assessment encourages a more seamless approach to risk factor man agement to reduce incidence of future costly diseases.

The benefit of a biomarker-based risk model is that the newest risk factor information can be incorporated into the model and a more ac curate assessment of risk made. For example, the beta used for C-reactive protein was only very recently published[29] but was used in our updated risk model. The three new markers—C-reactive protein, lipoprotein(a), and homocysteine—played a key role in identifying those at highest risk. The cost of these markers is an added cost not encountered in the guidelines-based approach. Another cost of treating so few patients with a risk-based treatment plan (only 18%) is that an increased number of CHD events is likely in the larger untreated group. However, this increase is more than compen sated for by the 44% reduction in CHD events in the high-risk group.

The objective of this simplified simulation was to show the potential of a risk-based disease management approach. To make this a reality, more will need to be understood about how this process can be integrated into the physician's practice, how multiple disease risks can be incorporated, and how to further solve the continuing problem of underidentification and undertreatment.

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