Lessons Learned From Cardiovascular Risk Models:

Experience from the Framingham Study

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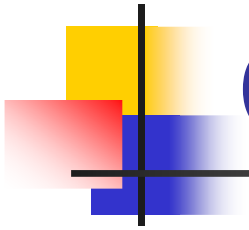


Outline

- Framingham Experience in Risk Prediction
- Guidelines for Developing Risk Prediction Models
- Example-NCEP ATP III
- Packaging Risk Models for Clinical Use
- Problems/Issues
- Next Steps

Framingham Experience in Risk Prediction

- Risk functions (HRAFs) are multivariable models
  - Predict likelihood that an individual will have an event (e.g., coronary heart disease) over a specified period of time (e.g., the next 10 years)
  - Impact of individual and combinations of readily available risk factors

Framingham History

- Modeling started in 1960's with discriminant function analysis and logistic regression analysis

-Truett J, Cornfield J, Kannel WB. A Multivariate analysis of the risk of coronary heart disease in Framingham. *J Chronic Dis* 1967; 20:511-524.

-Cornfield J, Gordon T, Smith W. Quantal response curves for experimentally uncontrolled variables. *Bull of Intl Stat Inst* 1961; 28: part 3.

-Walker S, Duncan D. Estimation of the probability of an event as a function of several independent variables. *Biometrika* 1967;54:167-179.

Framingham History Published Functions

- More data, longer follow-up, advances in statistical methods and computing – survival analysis was used

-Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* 1976; 38:46-51.

-Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation* 1991; 83:356-362

-Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97:1837-1847

Framingham History Disease-Specific Functions

- Coronary Heart Disease, Peripheral Artery Disease, Heart Failure, Stroke

  -Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991; 3:312-318.

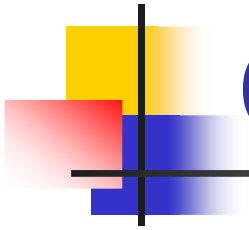
  -D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: Adjustment for antihypertensive medication. *Stroke* 1994; 25:40-43.

- Subsequent Events Functions

  -D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: New results from the Framingham Study. *Am Heart J.* 2000; 139:272-281.

Guidelines for Developing Risk Prediction Models

- Hypothesizing models that reflect biological pathways
- Collecting appropriate data
  - Identifying subjects (population at risk)
  - Defining and measuring risk factors and outcomes
  - Deciding on appropriate follow-up time
- Fitting and testing appropriate models

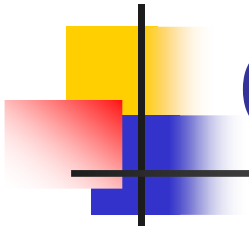


Objective

- To develop model that accurately reflects patterns in the data that are valid when applied to data in other, comparable settings
  - Based on biological model
- Methodologic Challenges
  - Changing definitions (DM)
  - Missing data-imputation techniques
  - Omission of risk factors
  - Incorrect specification of effects

Predictive Accuracy/Utility Components of Accuracy

- Calibration - how closely predicted probabilities agree numerically with actual outcomes (bias)
- Discrimination - ability of a predictive model to separate those who develop event from those who do not (ordering)
- Relationship
  - Poor discrimination – can't recalibrate to correct
  - Good discrimination – can recalibrate without losing discrimination



Calibration

- Dichotomous – form subgroups (deciles of predicted probabilities) and compare predicted and actual event probabilities
- Time to event – similar approach using KM estimates of actual probabilities

Discrimination

- Dichotomous or Time to Event –
  - c statistic – proportion of patient pairs in which predictions and actual outcomes are concordant (i.e., predicted survival higher for patient who actually survived longer)

Model Validation

- External Validation – frozen model applied to new data
- Internal Validation
  - Data Splitting
    - 75% sample: develop & freeze model, apply to remaining 25%, assess calibration and discrimination
  - Cross-Validation
    - Repeated data splitting (e.g., samples leaving out 50 observations each run, repeat 400 times, average results)
  - Bootstrapping
    - Large number of samples with replacement from original sample, estimate generalization error based on resampling

-Harrell F, Lee, Mark. Multivariable Prognostic Models: Issues in Developing Models, Evaluating Assumptions and Adequacy, and Measuring and Reducing Errors. *Stat Med* 2001; 15: 361-387.

Determining Risk Factors

- Framingham models designed to include risk factors that are readily available
- Age, sex, blood pressure, lipids, smoking, diabetes, treatment for hypertension & high cholesterol, obesity

Risk Factors (continued)

- Certain risk factors are important for specific events (e.g., Stroke: BP and LVH (-Lipids), CHD: BP, Lipids, Smoking, Diabetes)
- Different effects of risk factors in Men Vs Women
- Some risk factors have diminishing effect in older persons
- Specification of risk factors (e.g., Total Chol & HDL Vs Ratio Total/HDL, Raw Scores Vs Ln)
- Diabetes important – BMI?
- Treatment (Is SBP=120 same as SBP=120 on Rx?)

Framingham Experience Validation

- Framingham participants are white, middle class
- Assessment of the validity of the Framingham CHD function in 6 ethnically diverse cohorts
- Results - the Framingham functions performed well in whites and blacks, with recalibration can be applied to other ethnic groups

-D'Agostino RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: Results of a multiple ethnic groups investigation. *JAMA* 2001; 296: 180-187.

Framingham Experience Validation (continued)

MEN		ARIC		PHS	HHP	PR	SHS
Discrimination (c)	FHS	W	B	W	JapAm	Hisp	NaAm
FHS Model	0.79	0.75	0.67	0.63	0.72	0.69	0.69
Study Model	0.79	0.76	0.70	0.64	0.74	0.72	0.77
Calibration (χ^2)							
FHS Model		13.8	6.2	---	66.0	142.0	10.6
Recalibrated		---	---	---	12.0	10.0	---

Recalibration

- Cox model $S_0(t)^{\exp[\hat{\beta}_1(X_1-M_1)+\hat{\beta}_2(X_2-M_2)+\ldots+\hat{\beta}_p(X_p-M_p)]}$

- Where β_i are the regression coefficients, X_i are individual's values on the risk factors, M_i are the FHS means of the risk factors, $S_0(t)$ is the FHS survival at the means of the risk factors
- Recalibration: Replace FHS means M_i and FHS $S_0(t)$ by study's means and survival

Packaging Risk Models for Clinical Use

- Framingham Experience
  - Have the risk factor data (risk factors measured serially with extensive QC, new measures continue to be added)
  - Outcomes assessed comprehensively
  - Validation
- How can we make these models useful in clinical practice?

National Cholesterol Education Program Adult Treatment Panel III

- Updated clinical guidelines for cholesterol testing and management
- Intended to inform but not replace clinical judgment (evidence based)
- Major focus on more intensive cholesterol lowering therapy in certain groups of people

NCEP ATP III - Treatment

- Intensive treatment for persons with CHD
- Focus on multiple risk factors using Framingham functions for 10 year absolute CHD risk
- Match intensity of treatment to absolute CHD risk
  - If risk estimate > 20% aggressive treatment
  - If risk estimate 10-20% moderated treatment

Executive Summary *JAMA* 2001; 285(19): 2486-2497.

New Framingham Functions for NCEP ATP III

- Outcome is Hard CHD (MI, coronary death)
- Population at Risk:
  - Persons free of CHD, IC and Diabetes
  - Age 30-79 years of age

New Framingham Functions for NCEP ATP III (continued)

MODEL DEVELOPMENT STRATEGY

- Separate models for men and women
- Cox regression analysis
- Investigate whether there is a decreasing effect of risk factors on risk among older persons
- Compare models using discrimination and calibration statistics

Points Systems to Estimate CHD Risk

- Generated score sheets for men and women based on Cox models
  - Assign integer "points" to risk factors to approximate $\Sigma\beta X$
  - Users compute a "point total" to reflect risk factor profile
  - Provide estimates of 10 year risk of CHD associated with each point total
  - Comparative risks also provided

ATP III Score Sheets: Men

Age	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
	-9	-4	0	3	6	8	10	11	12	13

Total Cholesterol	Age 30-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥ 280	11	8	5	3	1

Smoking	Age 30-39	40-49	50-59	60-69	70-79
No	0	0	0	0	0
Yes	8	5	3	1	1

ATP III Score Sheets: Men

HDL	
≥ 60	-1
50-59	0
40-49	1
< 40	2

Systolic Blood Pressure	If Untreated	If Treated
< 120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥ 160	2	3

Point Total	10 Year Risk
< 0	< 1%
0-4	1%
5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16 or more	>20%

ATP III Comparative Risks: Men

Age Group	Lowest (TC<160,HDL>60, Optimal BP,No Trt , Non-Smk)	Low (TC 160-199, HDL 50-59 Normal BP, No Trt, Non-Smk)
30-34	0%	0%
35-39	0%	1%
40-44	0%	1%
45-49	1%	2%
50-54	2%	4%
55-59	3%	6%
60-64	5%	8%
65-69	7%	10%
70-74	9%	13%
75-59	12%	16%

Example Risk Factor Profile

Risk Factors	Points
Age 65	11
Total Cholesterol 200	1
HDL 50	0
SBP 130	1
No Treatment for Htn	0
Non-Smoker	0
TOTAL	13 , Risk =12%

Comparative Risks: Lowest = 7%, Low = 10%

Score Sheets

- Provide accurate estimates of CHD risk
- Widely disseminated
- Simple to use

Algorithm for Generating Point Systems

- Estimate multivariable model
- Organize risk factors into categories
- Select a referent category for each risk factor (0 points, healthier <0, sicker >0 points)
- Determine the referent risk factor profile
- Determine constant = 1 point

  (constant=increase in risk associated with 5 year increase in age)

Algorithm for Generating Point Systems

- Determine points for each risk factor category:

Points = β_i(risk factor category-referent category)/constant

- Determine risks associated with point totals
  - Dependent on model used
  - "Add back" referent category
  - Interaction effects

-Sullivan LM, Massaro JM, D'Agostino RB. TUTORIAL IN BIOSTATISTICS: Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med* 2004; 23(10): 1631-1660.

Agreement Between Points System and Function

		Points System		
		<10%	10-20%	>20%
Function	<10%	1642	10	0
	10-20%	110	410	569
	>20%	0	69	193

κ=0.87 (95% CI κ: 0.85-0.88)

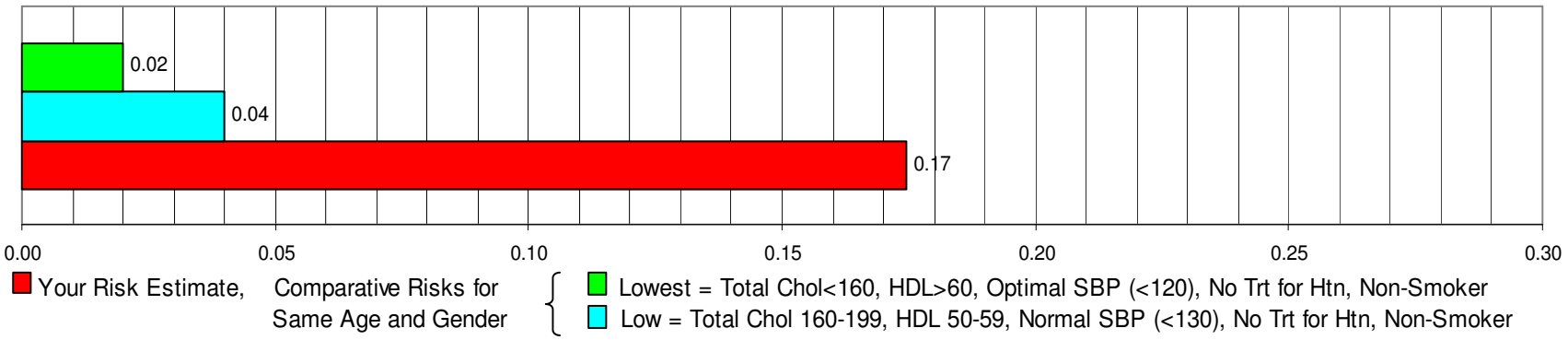
Dissemination

- NCEP ATP III report
  http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm
  - Score sheets
- American Heart Association website

  http://www.americanheart.org
  - Are you at risk for a Heart Attack? Find your risk.
  - Downloadable program (MS Excel) – Function
  - Palm pilot application

MS Excel Program for Risk Assessment

From The Framingham Heart Study	Enter Values Here		
CHD(MI and Coronary Death) Risk Prediction			***National Cholesterol Education Program Adult Treatment Panel III***
Risk Factor	**Units**	**(Type Over Placeholder Values in Each Cell)**	**Notes**
Gender	male (m) or female (f)	M	
Age	years	52	
Total Cholesterol	mg/dL	220	
HDL	mg/dL	45	
Systolic Blood Pressure	mmHg	146	
Treatment for Hypertension {Only if SBP≥120}	yes (y) or no (n)	N	
Current Smoker	yes (y) or no (n)	Y	
Time Frame for Risk Estimate	10 years	10	
Your Risk (The risk score shown is derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.)		17%	*If value is < the minimum for the field, enter the minimum value. If value is > the maximum for the field, enter the maximum value.*



These functions and programs were prepared by Ralph B. D'Agostino, Sr., Ph.D. and Lisa M. Sullivan, Ph.D., Boston University and The Framingham Heart Study and Daniel Levy, M.D., Framingham Heart Study, National Heart, Lung and Blood Institute.

Summary

- Framingham has been a leader in the development and dissemination of multivariable models to estimate CHD risk
- Points system makes complex models useful in practice
- Patients can also assess CHD risk over time

Problems/Issues

- "Points" system Vs. Function
- Comparing Functions
  - Population at risk
  - Outcome (CHD, HCHD, Coronary Death)
  - Risk Factors
  - Parameterization of Risk Factors (categories, continuous)

Next Steps

- Adding novel risk factors (e.g., CRP, Nutrition, Family History)
  - Statistical Significance Vs. Improving Prediction
  - Measurement Issues (missing/incomplete data)
- CI around risk estimates
  - How to add CI to guidelines?
  - Treatment depends on absolute risk

    < 10%, 10-20%, >20%
- Continuing validation work