Cardiovascular risk in patients without known cardiovascular disease

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Abstract. – Understanding the risks of atherosclerotic cardiovascular disease (CVD) allows for better patient education and management. Multiple risk models have been validated in large patient populations and provide insights into the risks associated with CVD. When assessing such risks, we suggest using a model that predicts myocardial infarction, cardiovascular death, and/or cerebrovascular events. In this review, we analyze several risk models and stratify the risks associated with CVD. We suggest that appropriate profiling of patients at-risk of CVD will lead to better physician recognition and treatment of modifiable risk factors, appropriate application of ATP III treatment for hyperlipidemia, and achieving optimal blood pressure control.

Key Words:
   Coronary heart disease, Cardiovascular disease, Cardiovascular multiple risk factors, C Reactive Protein, Myocardial infarction, Borderline risk factors.

Introduction

Atherosclerotic cardiovascular disease (CVD) afflicts the majority of adults over the age of 60 years and the prevalence of coronary heart disease (CHD) is approximately one-half that of total CVD[1]. The presence of atherosclerosis in one organ system is predictive of atherosclerosis in other vascular beds. As such, the presence of non-coronary atherosclerotic disease is a CHD risk equivalent[2]. According to the Framingham Heart Study, the lifetime risk for CHD in individuals age 40 was 49% and 32% for men and women, respectively. In patients free from CHD at age 70, the lifetime risk for males and females is 35% and 24%, respectively. The lifetime risk of CHD is commensurate with the burden of risk factors (Figure 1)[3]. According to

the worldwide INTERHEART study, many of these factors are modifiable, as nine such risk factors accounted for over 90 percent of the population attributable risk of a first MI[4]. These factors include smoking, alcohol, dyslipidemia, hypertension, diabetes mellitus, obesity, psychosocial factors, consumption of fruits and vegetables, and physical activity.

In this review we discuss the predictive value of the risk factors and the use of multivariate risk models to estimate cardiovascular risks. We highlight the utility of these risk models in patient management, particularly in primary prevention of CVD events.

Methods

Population based studies and guidelines on risk stratification and prediction of cardiovascular disease, published from 1998 to 2012, were reviewed. While, little substantive information was found, the systematic review of Willis et al[5] assesses the effectiveness of recruiting participants using CVD risk scores and offers advice on modifications to reduce CVD morbidity and mortality.

Who Should Undergo Risk Estimation

Patients at High Risk

Individuals with established CVD; diabetes mellitus; chronic renal failure; and hereditary dyslipidemias are at high risk for the development of CVD events and do not need additional risk stratification.

Patients at Increased Risk

The United States National Cholesterol Education Program Expert Panel on Detection, Evalua-
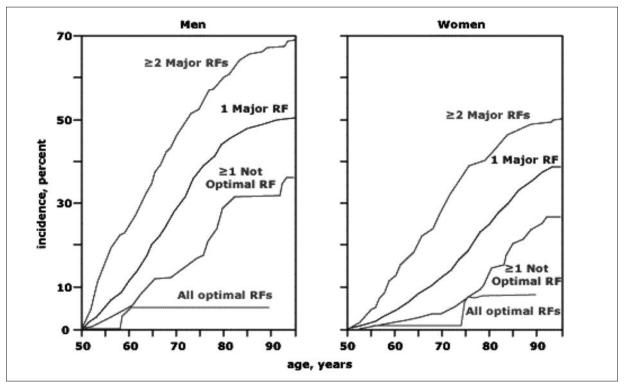
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Figure 1. Lifetime risk of cardiovascular disease. Cumulative lifetime incidence of cardiovascular disease, adjusted for the competing risk of death, according to the aggregate risk factor (RF) burden in men and women in the Framingham Heart Study at age 50 who did not have clinical cardiovascular disease. The lifetime risk ranged from 5 percent in men and 8 percent in women with all optimal risk factors to 69 percent in men and 50 percent in women with 2 major risk factors.

tion, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) guidelines recommend estimating risk in individuals with two or more risk factors[1]. However, this approach excludes many individuals who are at increased lifetime risk and for whom primary preventative strategies would be of value. Future revision of such guidelines is likely to include estimation of risk in individuals, with only one risk factor.

Predictive Value of Risk Factors

In the general population, most have one or more risk factors for CHD and over 90% of CHD events occur in individuals with at least one risk factor[4,6]. Stamler et al[7] reviewed data from the Multiple Risk Factor Intervention Trial (MRFIT) and the Chicago Heart Association Project in Industry. When comparing the group with > 1 risk factor to the low risk group, after an average follow-up of 16 years for MRFIT and 22 years for the Chicago trial, patients with > 1 factor had significantly higher CHD mortality (0.2% to 8.8% versus 1.5% to 38% percent for those with ≥ 1 risk factor).

Key Point: Individuals with more than one risk factor for CHD should undergo risk stratification.

Borderline Risk Factors

The frequency and predictive value of blood pressure, LDL and HDL cholesterol, glucose intolerance, and smoking was evaluated in a study of white individuals 35 to 74 years of age without CHD in the Framingham Heart Study and the Third National Health and Nutrition Examination Survey (NHANES III). Six CHD events occurred in more than 90% of individuals who had at least one risk factor and 8% occurred in individuals who had borderline levels of multiple risk factors. In NHANES III, approximately 60% of men and 50% of women had one or two risk factors, and 26% of men and 41% of women had at least one borderline risk factor.

The available evidence in the present guidelines does not support the use of multiple risk factor interventions in the low to medium risk individuals. No guidelines address the lowest risk population, which may benefit from early recognition and intervention.

Key Point: We suggest that patients deemed low risk for CVD events may also benefit from early early recognition and intervention.

Multiple Risk Factors

In addition to the ATP III study, the increase in risk when multiple risk factors exist, has also been noted by other in both Western and Asian populations[8-10]. When a combination of cholesterol ≥ 200 mg/dL (≥ 5.2 mmol/L), hypertension, and cigarette smoking were present, both men and women had an increase in the relative risk of CHD 5.5 and 5.7, respectively, cardiovascular disease 4.1 and 4.5, respectively, and all-cause mortality 3.2 and 2.3, respectively. The independent effects of systolic pressure and total cholesterol were illustrated in a larger study of 380,000 individuals from Asia, Australia, and New Zealand[10]. This study demonstrated for every 10 mmHg increase in systolic pressure, there was an associated 21% to 34% increase in risk at all levels of serum cholesterol. Adjustment for other risk factors had no effect on these findings. Patients with higher levels total cholesterol (≥ 240 mg/dL []) and systolic pressure (≥ 160 mmHg) had a seven-fold increase in CHD and an eight-fold increase in stroke, compared to patients with lower levels of total cholesterol (< 183 mg/dL) and systolic pressure (< 130 mmHg).
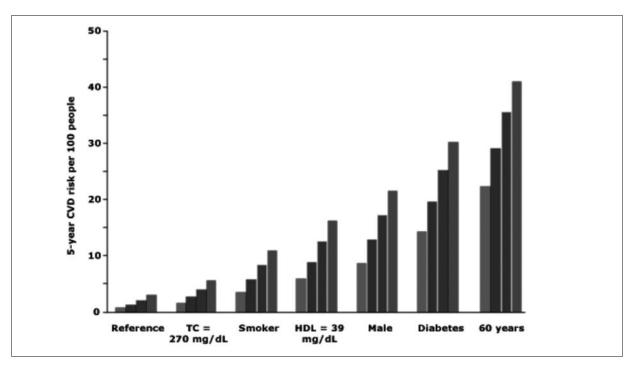
Key Point: The presence of multiple risk factors portends a significantly higher risk for cardiovascular disease and mortality.

Multivariate Risk Models

A number of multivariate risk models have been developed for estimating the risk of cardiovascular events in apparently healthy, asymptomatic individuals based upon assessment of multiple variables[4,6-10]. Many of the risk factors are recognized as producing a graded increase in risk (Figure 2)[8]. These models estimate risk of an individual over the next ten years.

Framingham Risk Scores

We are going to keep a validation study on the first Framingham CHD found that the predictor performed well for prediction of CHD events in black and white women and men[11,12]. The Framingham risk score was modified by ATP III for use in their recommendations for screening for and treatment of dyslipidemia (Table I a-b)[1]. The modifications included elimination of diabetes mellitus from the algorithm, broadening of the

Figure 2. Cumulative absolute risk of cardiovascular disease at five years. Cumulative absolute risk of cardiovascular disease (CVD) at five years according to systolic blood pressure and specified levels of other risk factors. The reference category is a no diabetic, nonsmoking 50 year old woman with a serum total cholesterol (TC) of 154 mg/dL (4.0 mmol/L) and HDL-cholesterol of 62 mg/dL (1.6 mmol/L).

Table Ia. Framingham/ATP III point scores in men.

Age, years	Points	Total cholesterol mg/dL (mmol/L)				
		Age 20 to 39	Age 40 to 49	Age 50 to 59	Age 60 to 69	Age 70 to 79
20 to 34	-9					
35 to 39	-4					
40 to 44	0					
45 to 49	3					
50 to 54	6					
55 to 59	8					
60 to 64	10					
65 to 69	11					
70 to 74	12					
75 to 79	13					
< 160 (3.4)		0	0	0	0	0
160 to 199 (3.4 to 5.15)		4	3	2	1	0
200 to 239 (5.17 to 6.18)		7	5	3	1	0
240 to 279 (6.2 to 7.21)		9	6	4	2	1
≥ 280 (7.24)		11	8	5	3	1
		Age 20 to 39	Age 40 to 49	Age 50 to 59	Age 60 to 69	Age 70 to 79
Nonsmoker		0	0	0	0	0
Smoker		8	5	3	1	1

Systolic blood pressure mmHg	Untreated	Treated
< 120	0	0
120 to 129	0	1
130 to 139	1	2
140 to 159	1	2
≥ 160	2	3

HDL cholesterol mg/dL (mmol/L)	Points
≥ 60 (1.55)	-1
50 to 59 (1.29 to 1.53)	0
40 to 49 (1.03 to 1.27)	1
< 40 (1.03)	2

Point total	10-years risk, percent
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4

Point total	10-year risk, percent
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥ 17	≥ 30

These risk estimates for the development of coronary heart disease do not account for all important cardiovascular risk factors. Not included are diabetes mellitus (which is considered a CHD equivalent), family history of CHD, alcohol intake, and the serum C-reactive protein concentration. Adapted from Adult Treatment Panel III at http://www.nhlbi.nih.gov/ The point total is determined in each category and the 10-year risk determined in the bottom row.

Table Ib. Framingham/ATP III point scores in women.

Age, years	Points
20 to 34	-7
35 to 39	-3
40 to 44	0
45 to 49	3
50 to 54	6
55 to 59	8
60 to 64	10
65 to 69	12
70 to 74	14
75 to 79	16

Total cholesterol mg/dL (mmol/L)

	Age 20 to 39	Age 40 to 49	Age 50 to 59	Age 60 to 69	Age 70 to 79
< 160 (3.4)	0	0	0	0	0
160 to 199 (3.4 to 5.15)	4	3	2	1	1
200 to 239 (5.17 to 6.18)	8	6	4	2	1
240 to 279 (6.2 to 7.21)	11	8	5	3	2
≥ 280 (7.24)	13	10	7	4	2

	Age 20 to 39	Age 40 to 49	Age 50 to 59	Age 60 to 69	Age 70 to 79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL cholesterol mg/dL (mmol/L)	Points
≥ 60 (1.55)	-1
50 to 59 (1.29 to 1.53)	0
40 to 49 (1.03 to 1.27)	1
< 40 (1.03)	2

Systolic blood pressure mmHg	Untreated	Treated
< 120	0	0
120 to 129	1	3
130 to 139	2	4
140 to 159	3	5
≥ 160	4	6

Point total	10-years risk, percent
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4

Point total	10-year risk, percent
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥ 25	≥ 30

These risk estimates for the development of coronary heart disease do not account for all important cardiovascular risk factors. Not included are diabetes mellitus (which is considered a CHD equivalent), family history of CHD, alcohol intake, and the serum C-reactive protein concentration. Adapted from Adult Treatment Panel III at http://www.nhlbi.nih.gov/ The point total is determined in each category and the 10-year risk determined in the bottom row.

age range, and inclusion of hypertension treatment and age-specific points for smoking, and total cholesterol.

The Framingham/ATP III criteria were used to estimate the distribution of CHD risk in the United States in NHANES III among 11,611 patients without self-reported CHD, stroke, peripheral arterial disease, or diabetes[13]. Patients were categorized based on risk of CHD at 10 years – low (< 10%), intermediate (10-20%), and high risk (> 20%). 82% of the patients were found to be the low risk, 16% were intermediate, and 3% were in the high risk group. Predictably, high risk was associated with increased age and the male gender.

The Framingham risk scores do not include all of the potential adverse consequences of atherosclerosis such as stroke, transient ischemic attack, claudication, and heart failure. These outcomes were considered in the development of the 2008 Framingham general cardiovascular risk score, which was shown to have reliable predictive ability (Table II a-b)[14]. The estimated risk of developing a cardiovascular event will be higher with this risk score than with those that predict only CHD events.

Several studies suggest that the Framingham criteria either overestimate or underestimate the risk of initial CHD events in other ethnic populations and in patients older than age 85 years[12,15-22]. It is unclear if these differences are real or if they are due to differences in research methodology[15,22]. Multiple models, including SCORE and QRISK2, have been developed in an attempt to provide better predictive accuracy for European patients[18-24].

Key Point: Framingham Risk score performs well for risk prediction of CHD events in black and white women and men. Its validity for other ethnic groups is not well established.

Score

SCORE included data on more than 200,000 patients pooled from cohort studies in 12 European countries[18-22]. Variables included age, gender, systolic blood pressure, total cholesterol, HDL cholesterol, and cigarette smoking. The mean follow-up was 13 years, with the end point being cardiovascular death. A unique aspect of SCORE is that separate risk scores were calculated for high- and low-risk regions of Europe. The predictive value of SCORE was high in each component study cohort. SCORE differs from the earlier Framingham risk models in two ways: it estimates the ten-year risk of any first fatal atherosclerotic event and it estimates only CVD mortality. SCORE was recommended in the 2007 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice[21].

Discussion

While the current risk models provide good stratification and definition of high-risk CVD patients, they provide false reassurance for those deemed low risk (Figure 1)[3,6]. Patients with less than 10% likelihood of developing CVD are considered low risk. However, this does not consider

Table IIa. Formula Risk Factors = (ln(Age) *2.32888) + (ln(TotalChol) *1.20904) – (ln(HDLChol) * 0.70833) + (ln(SysBP) *SysBPFactor) + Cig + DM – 26.1931 Risk = 100 * (1 – 0.9501 e (RiskFactors).

Input:			Results:		
Age		yr ▼	Risk Factors		
Sys BP		mmHg ▼	Risk	%	▼
Total Chol		mg/dL ▼	Decimal precision	2	▼
HDL Chol		mg/dL ▼			
On hypertension medication	No (2.76157) ▼				
Cigarette smoker	No (0) ▼				
Diabetes present	No (0) ▼				

Framingham 10 Year Risk of General Cardiovascular Disease in Women. This risk assessment tool is based on the Cox regression model of proportional hazards. Cardiovascular disease includes coronary disease, cerebrovascular disease, peripheral vascular arterial disease and heart failure. It may be applied to women who have had no prior history of cardiovascular disease.

Table IIb. Formula Risk Factors = (ln(Age) *3.06117) + (ln(TotalChol) * 1.12370) – (ln(HDLChol) *0.93263) +(ln(SysBP) *SysBPFactor) + Cig + DM - 23.9802. Risk = 100 * (1 – 0.88936 e (RiskFactors).

Input:			Results:		
Age		yr ▼	Risk Factors		
Syst BP		mmHg ▼	Risk	%	▼
Total Chol		mg/dL ▼	Decimal precision	2	▼
HDL Chol		mg/dL ▼			
On hypertension medication	No (1.93393) ▼				
Cigarette smoker	No (0) ▼				
Diabetes present	No (0) ▼				

Framingham 10 Year Risk of General Cardiovascular Disease in Women. This risk assessment tool is based on the Cox regression model of proportional hazards. Cardiovascular disease includes coronary disease, cerebrovascular disease, peripheral vascular arterial disease and heart failure. It may be applied to women who have had no prior history of cardiovascular disease.

the lifetime risk, which may be high and amenable to early intervention[3,26-28]. Many of the current models were derived from cohort studies that included persons not on medications. The more frequent use of cholesterol lowering and antihypertensive medications in recent years and assessment of factors that might alter the risk for vascular events have become more complicated[29]. Some risk models do not include cardiovascular outcomes such as stroke, heart failure, or development of symptomatic peripheral arterial disease.

Potential Improvements to the Risk Models

Potential ways to enhance the estimation of cardiovascular risk include the addition of laboratory tests to the models or to estimate lifetime risk in individuals with a low ten-year risk[30]. Biomarkers such as CRP, imaging tests such as coronary calcium score or carotid intima-media thickness, exercise testing or screening for novel genotypes are potential improvements to current risk models.

Lifetime Risk

The Framingham Heart Study assessed long-term outcomes according to risk status in individual's age 50 years without known cardiovascular disease[3]. Participants were defined as having optimal risk factors – total cholesterol < 180 mg/dL (4.65 mmol/L), blood pressure < 120/< 80 mmHg, no smoking, and no diabetes. The risk increased progressively with the number and intensity of risk factors (Figure 1). Participants with optimal risk factors when compared to those with

≥ 2 major risk factors, had lower lifetime risks of cardiovascular disease (5% versus 69% in men, and 8% versus 50% in women), and longer median survivals (> 39 versus 28 years in men and > 39 versus 31 years in women). Although the difference was less pronounced, the lifetime cardiovascular risk was significantly lower in participants with optimal risk factors compared to those with ≥ 1 suboptimal risk factor (5% versus 36% in men and 8% versus 27% in women).

However, many individuals with a low ten-year risk have a high lifetime risk. This was illustrated in the MESA and CARDIA trials[29]. Ten year and lifetime risks were assigned to each individual and patients were then divided into three groups: low (< 10%) and low lifetime risk (< 39%); low ten year and high lifetime risk (≥ 39%); and high ten year risk or diabetes. The group with a low ten year and high lifetime risk had both a significantly greater burden of baseline subclinical atherosclerosis as well as a significantly higher rate of coronary artery calcification (CAC) progression than the group with a low ten year and low lifetime risk.

Key point: The use of additional tests to define the baseline atherosclerosis burden significantly improves the predictability power of the risk model.

Conclusions

Recommendations for Risk Assessment in a Presumed "Low Risk" Population Estimation of

cardiovascular risk using multivariate risk profiling were strongly endorsed by an AHA/ACC Scientific Statement in 1999[31]. The appropriate application of risk score assessment in patient management includes the following considerations: (1) The ATP III recommendations for the treatment of hyperlipidemia, which is modified by the coexistence of CHD and the number of cardiac risk factors[1]. (2) The goal blood pressure in patients at high risk for the development of CVD is controversial, with some experts suggesting use of risk models and others not[31]. (3) It has been suggested that determination of a patient's calculated cardiovascular risk profile, and presentation of the results to the patient, may improve compliance with risk reduction measures (Table I a-b). (4) It has also been suggested that determination of a patient's risk profile should improve physician recognition and treatment of modifiable risk factors.

Under-recognition of hypertension, hyperlipidemia and other risk factors, when presenting as a single, modifiable risk factor remains a common problem, particularly in the "low risk" population. Thus, routine risk assessment may appropriately identify even a presumed "low-risk" profile, leading to more appropriate, cost-effective intervention and improved outcomes.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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