Predicting Risk for Cardiovascular Disease:

Are we there yet?

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Internal Medicine Grand Rounds

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This is to disclose that Jarett Berry, MD has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Berry will not be discussing off-label uses in his presentation.

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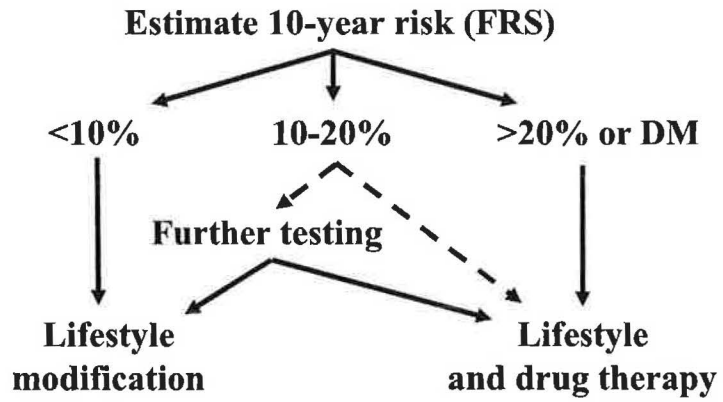
I. Introduction

The ability to quantify risk over the past three to four hundred years has transformed our culture, creating new foundations for our institutions, from the banking and finance industry to political decision-making and the world of sports. Similarly, the ability to quantify risk has transformed our approach to the prevention of common diseases such as cardiovascular disease (CVD), the leading cause of morbidity and mortality in the US and the developed world[1]. In the last two decades, there has been a paradigm shift in risk estimation for CVD. Initial efforts to estimate risk focused on single risk factors and the short-term relative risks associated with them. However, such an approach provides an incomplete and potentially misleading picture of short-term risk, as discussed in detail below. In the last two decades, increasing emphasis has been placed on estimating absolute risks for CVD using multivariable risk equations, which incorporates the synergistic interactions among all of the risk factors that can at times be less than intuitive[2, 3].

Therefore, based on the Adult Treatment Panel III guidelines[4], the approach should include the estimation of short-term risk using a version of the Framingham Risk Score that can be accessed online at http://hp2010.nhlbihin.net/atpiii/calculator.asp. After inserting a few basic variables, the risk estimator will provide a probabilistic estimate of the likelihood of developing fatal/non-fatal coronary heart disease over the next 10 years. Based on this estimate, the recommended approach to preventive intervention is quite straightforward for both low and high risk individuals, however, there remains some uncertainty regarding the approach for individuals in the intermediate risk category. Thus, the guidelines allow for the option of treatment or additional testing among intermediate risk patients depending on the clinical scenario as detailed in the figure below.

Current Paradigm for Risk Estimation and Treatment: ATP-III



Thus, the process of reducing risk for CVD requires a few sequential steps, as outlined in an editorial co-authored by Dr. Scott Grundy more than 10 years ago entitled, "Problems on the pathway from risk assessment to risk reduction"[3]:

1. Risk factor measurement
2. Risk interpretation
3. Intervention to promote risk reduction

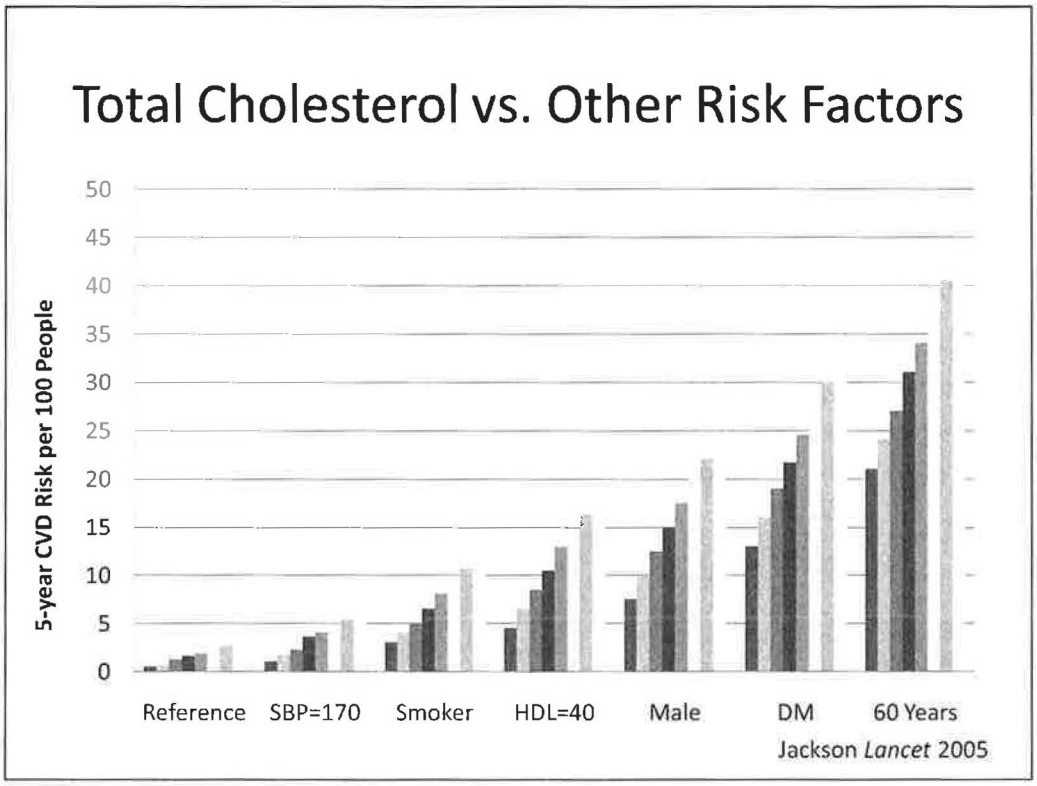
Of interest, much of the work in this area has been confined to the first of these steps, identifying novel risk factors to better identify those individuals at high risk. In fact, a paper published in the *Archives of Internal Medicine* several years ago identified an exponential increase to well over 1000 articles published per year with the terms "independent risk factor" or "independent predictor" in the abstract[5].

Although the improvement in risk prediction represents an important area for further study, much less is known about the second and third steps in the process. Therefore, the subject of the presentation today will be focused almost exclusively on the interpretation of risk and its potential implications for treatment and lifestyle interventions to lower CVD risk. In particular, I would like to review the strengths and weaknesses of the approach to 10-year risk prediction within the context of our research program here at UT Southwestern.

II. Rationale for multivariable risk equations

Current clinical practice guidelines and public health prevention efforts are aimed at individuals with high short-term risk for CVD, because of the underlying assumption that the intensity of prevention efforts should match the absolute risk of developing CVD. This short-term focus serves to identify those patients who will likely benefit most from drug therapy[4].

However, the correct identification of individuals at the highest short-term risk for CVD reflects the importance of more than just individual risk factor levels such as cholesterol and blood pressure[6-8]. Consider the effect of variable levels of serum total cholesterol in a hypothetical case of a 50-year old, non-smoking, non-diabetic female with normal blood pressure and a normal HDL in the accompanying figure. Although higher levels of cholesterol in isolation translate into incrementally higher short-term risks for CVD, the isolated effect of cholesterol is relatively modest in the absence of additional risk factors. When we add in a blood pressure of 170 mmHg, the effect of these differences in cholesterol become more pronounced. With each additional risk factor added, the effect of cholesterol becomes increasingly more pronounced. In the far right column, this reflects the baseline risk across all levels of serum cholesterol for a 60-year old diabetic, hypertensive, smoking male. The baseline risk across all levels of cholesterol are markedly higher in the latter scenario, such that the baseline risk for an optimal cholesterol level in this scenario is 4-5 fold the baseline risk of the first case with a cholesterol of 320 mg/dL[6].



This synergistic interaction among all CVD risk factors has been observed for decades and is consistent with our prior clinical experience as well. Nevertheless, recent large-scale clinical trials appear to miss this point, creating much confusion in the literature. For example, consider the recently published JUPITER trial in the *New England Journal of Medicine*[9]. In this trial, nearly 17,000 individuals with low LDL cholesterol but high C-reactive protein were randomized to rosuvastatin 20 mg vs. placebo. Although a full analysis of the JUPITER trial is beyond the scope of this presentation, it is interesting to consider the baseline risks in this study. As shown in the table below, the estimated Framingham Risk Score for a non-smoking male with average cholesterol, blood pressure, and HDL-cholesterol was 12%. In comparison to two previous primary prevention placebo-controlled trials (The West of Scotland Coronary Prevention Study[10] and AFCAPS/TexCAPS[11]), the Framingham Risk Score was surprisingly similar. This occurs because the mean age for JUPITER was 10 years greater than the previous studies. Thus, with JUPITER we have exchanged total cholesterol for age and conducted a very similar clinical trial with findings that should not be terribly surprising.

Comparison of Baseline Characteristics and Traditional Risk Factors Across Three Primary Prevention Statin Trials			
	JUPITER	WOSCOPS	AFCAPS/TexCAPS
	11,002 (men) 6,800 (women)	6595 (men) 0 (women)	5608 (men) 997 (women)
Age (years)	66.3	55.1	57
SBP (mmHg, mean)	134	136	138
TC (mg/dL, mean)	185	272	221
HDL-c (mg/dL, mean)	49	44	38
Current smoking (%)	15.8	44	12
Diabetes (%)	0	1	3.8
FRS (men, non-smokers)	12%	12%	12%

WOSCOPS: The West of Scotland Coronary Prevention Study
FRS: Framingham Risk Score (estimated)

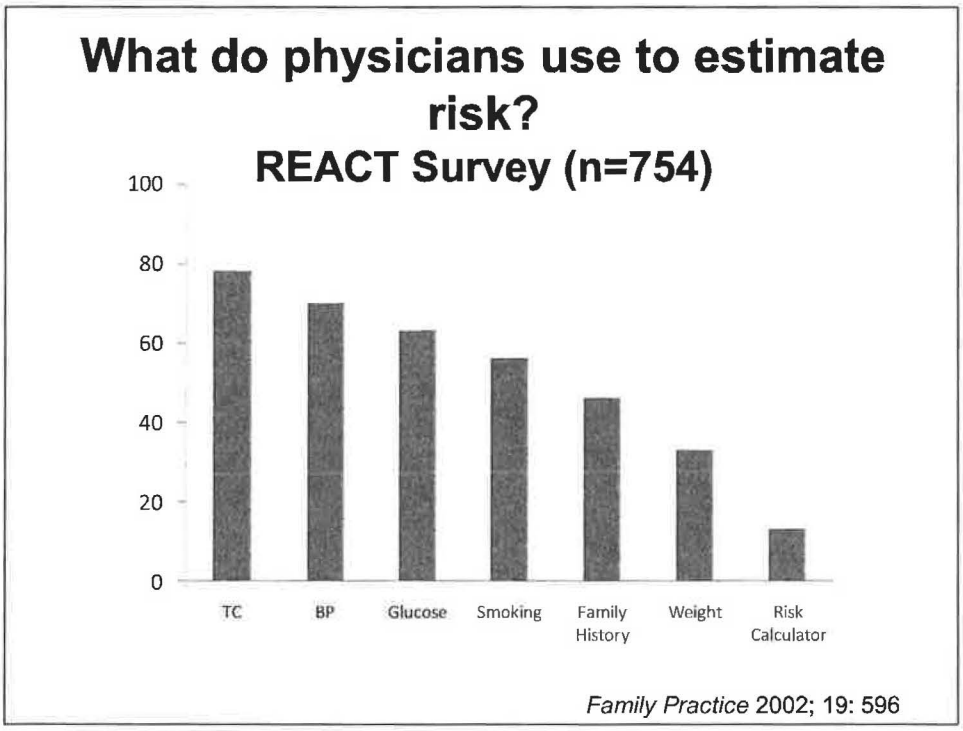
III. Risk equations not just efficient but necessary

When left to intuition, even the most experienced physicians are not successful at estimating risk. Several prior studies have assessed the ability of physicians to interpret patients' risk, demonstrating that an average, we are correct less than 50% of the time. For example, in a mail survey administered to 247 physicians (family practice, general internists, and cardiologists), physicians appeared to vastly overestimate both the baseline 5-year event rate as well as the potential clinical benefit from statin therapy. Although the baseline MI rate from the published literature for the hypothetical case was just 6%, family practice and general internist physicians on average estimated the event rate to be 20%, whereas cardiologists also overestimated the risk at 10%[12].

Similar studies have been reported in which physicians were given a series of cases across the distribution of risk, finding similar results. For example, in one study 162 physicians estimated risk on 3,120 patients in their practice. Physicians were asked to estimate the patients' risk as "mild", "moderate", "high", or "very high" and these estimates were compared to a estimated risk from the SCORE risk prediction algorithm used by the European prevention guidelines. Fewer than ½ of physicians estimated risk accurately, with nearly 1/3 overestimating and 1/3 underestimating risk[13].

This is particularly important given the infrequency with which physicians use risk prediction tools in clinical practice. In the Reassessing European Attitudes about Cardiovascular Risk (REACT) survey[14], 754 randomly selected primary care physicians across Europe were interviewed in a semi-structured telephone interview process to determine their beliefs and

practices with regard to CVD risk. Most physicians reported difficulty in adhering to CVD prevention guidelines secondary to time constraints. Of interest, when asked which tests were used to assess CVD risk, most respondents reported the frequent use of individual risk factors with only a small percentage reporting the frequent use of multivariable risk equations.



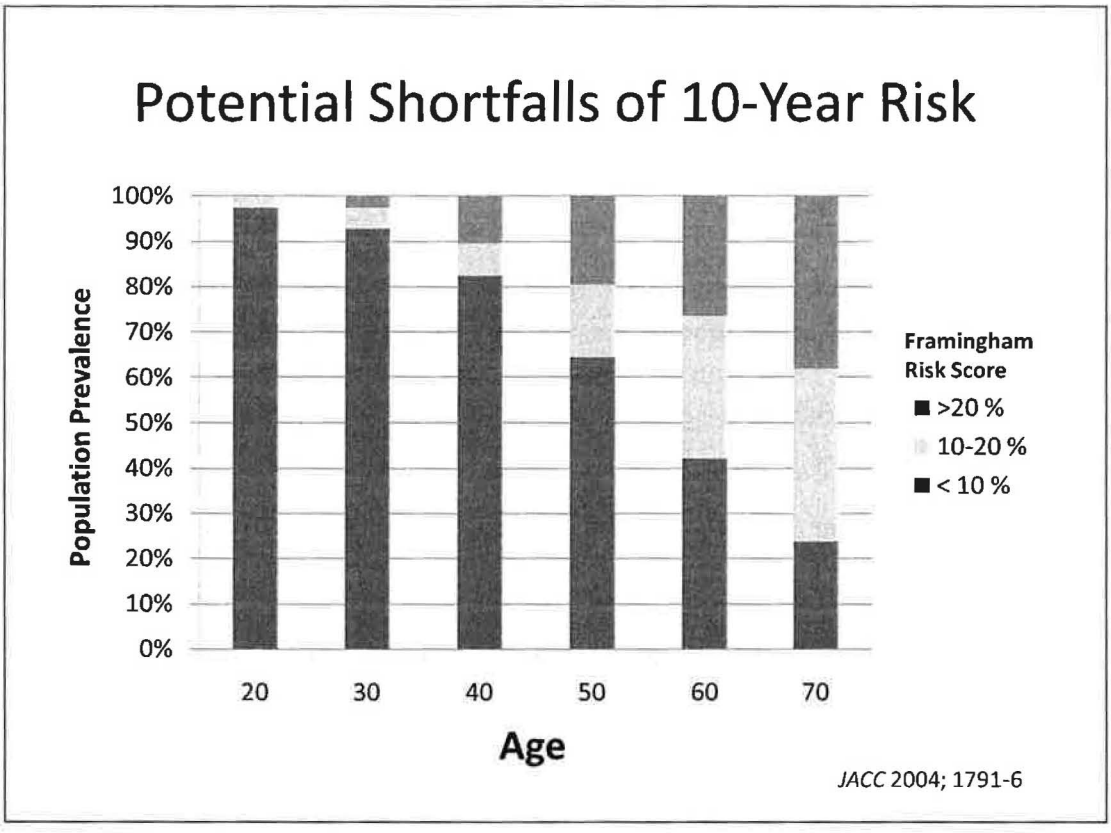
Thus, risk estimation is critical for good clinical decision-making, but it is not intuitive, reflecting a complex interaction among age, sex, smoking and treatable risk factors. In addition, the infrequent use of risk prediction tools by physicians likely facilitates propagating these biases into clinical decisions in which we overtreat low risk patients and undertreat high risk patients[15, 16].

IV. Limitations of Short-term Risk Estimates: the problem of age

Although these risk equations represent an important advance in the primary prevention of CVD, they are not without limitations, particularly among younger adults. Consider two hypothetical cases of 45-year old men with significant differences in blood pressure and cholesterol. In spite of these differences, their short-term risks are quite similar and would be considered low risk by current clinical criteria[17, 18].

Short-term Risk Estimates in two hypothetical cases: a problem of Risk Discrimination	
	10-year risk (CHD)
Case 1: 45 yo male, TC 240 mg/dL, SBP 115 mm Hg on treatment, HDL 40 mg/dL, no DM, non-smoking	4%
Case 2: 45 yo male, TC 180 mg/dL, SBP 115 mmHg, HDL 40 mg/dL, no DM, non-smoking	2%

Similarly, with advancing age, a higher percentage of adults will exceed treatment thresholds of 10% or 20% regardless of risk factor burden. For example, at age 30 years, less than 5% of adults are at high 10-year risk (or have diabetes) in contrast to more than 40% of adults age 70 years with high 10-year risk[19].



Although short-term event rates and hence, absolute event rates in individuals <30 years are low, multiple prior observational studies from Framingham[20], the Chicago Heart Association[21, 22] and other cohorts have demonstrated that individual risk factors measured at younger ages are significant and strong predictors of future clinical events. For example, among

1017 male medical students in the Johns Hopkins study[23], serum total cholesterol was a strong and independent predictor of future CVD events over the course of 27 to 42 years of follow-up. Forty years of follow-up from 595 young adults (age 30-39 years) in the Framingham Heart Study[20] found similar associations between total cholesterol and both cardiovascular and all-cause mortality.

These risk factors are associated with future clinical events in part because of their ability to promote subclinical atherosclerosis at very young ages. Autopsy studies from the Korean[24] and Vietnam[25] wars were the first to document the presence of significant subclinical coronary atherosclerosis among young individuals who died of non–CVD-related causes[26]. Premature atherosclerosis does not affect all young adults equally and varies according to the presence of major cardiovascular risk factors. More recently, the Bogalusa Heart Study[27] has shown that smoking, blood pressure, blood cholesterol, and age are significantly associated with the accumulation of aortic and coronary atherosclerosis among a younger population (age 2-39 years).

Thus, our approach to CVD risk prevention among younger adults is at odds with the biology of the disease process. This translates into two fundamental problems:

1. Younger adults with high risk factor burden are given misleading messages regarding the true nature of their CVD risk.

2. Short-term risk estimates bias treatment away from younger adults with risk factors and in favor of treating nearly all older adults regardless of risk factor burden.

These considerations raise potentially important questions regarding treatment and primary prevention interventions. Might we consider risk for CVD beyond the 10-year window to consider the remaining lifespan? Do we want to lower event rates in the elderly? Or, do we want to add life-years to younger adults with high risk factor burden who will no doubt become high risk across their lifespan?

There are a variety of different approaches to address the problem of age-dependency with short-term risk estimates, but they generally fall into three broad categories: (1) testing with biomarkers and/or imaging, (2) lowering the absolute risk treatment threshold, and/or (3) modifying/supplementing the absolute risk estimate with an additional method.

V. Lifetime risk estimation

Our research program has sought to address this limitation directly, by extending the time horizon for risk estimation beyond 10-years to include the remaining lifespan. Fundamentally, lifetime risk estimates allow the patient and the physician to answer a simple question: what is the absolute risk of developing a given disease across the lifespan[28-32]? By examining absolute

risk across the lifespan, this approach removes the effect of age from the risk estimate, thereby avoiding some of the limitations of other absolute risk approaches[33]. Furthermore, widespread behavior change and increased public health awareness have been attributed to its application in other disease processes: dissemination of data on lifetime risk for breast cancer[34] was associated with an increase in both public awareness of breast cancer and mammography screening rates[35]. Thus, knowledge of the association between risk factors and lifetime risks for CVD may offer substantial clinical and public health benefits by improving risk communication strategies.

In response, European guidelines[36] as well as national guidelines from the National Cholesterol Education Program[4] and the American Heart Association[37] suggest that clinicians consider current risk factor burden within the context of long-term or lifetime risk for cardiovascular disease CVD. The majority of prior reports on lifetime risk estimates for CVD are confined to data from a single cohort with analyses restricted to risk factors measured at a single age. In addition, there are limited data available for non-whites[38].

Thus, we pooled individual-level data from participants in 17 diverse observational cohorts to create the **Cardiovascular Lifetime Risk Pooling Project** using data from the National Heart, Lung, and Blood Institute and other sources[39-58]. Our objective was to determine the lifetime risks for CVD death, fatal/non-fatal coronary heart disease, fatal/non-fatal stroke, and total atherosclerotic cardiovascular disease for risk factors measured at four index ages: 45, 55, 65, and 75 years. We analyzed 254,402 black and white men and women with risk factors measured at or near index each index age, providing extensive follow-up and a large number of events. For example, in the pooled cohort for the CVD death analysis, there were *more than 20,000 CVD deaths with over 2.5 million person-years of follow-up*. We grouped participants according to risk factor levels as measured within three years of each index age. For example, risk factors measured between ages 42 and 48 were included in the analyses for age 45. Risk factors were categorized individually as well as in aggregate based on our previously published algorithm[59] (see Table).

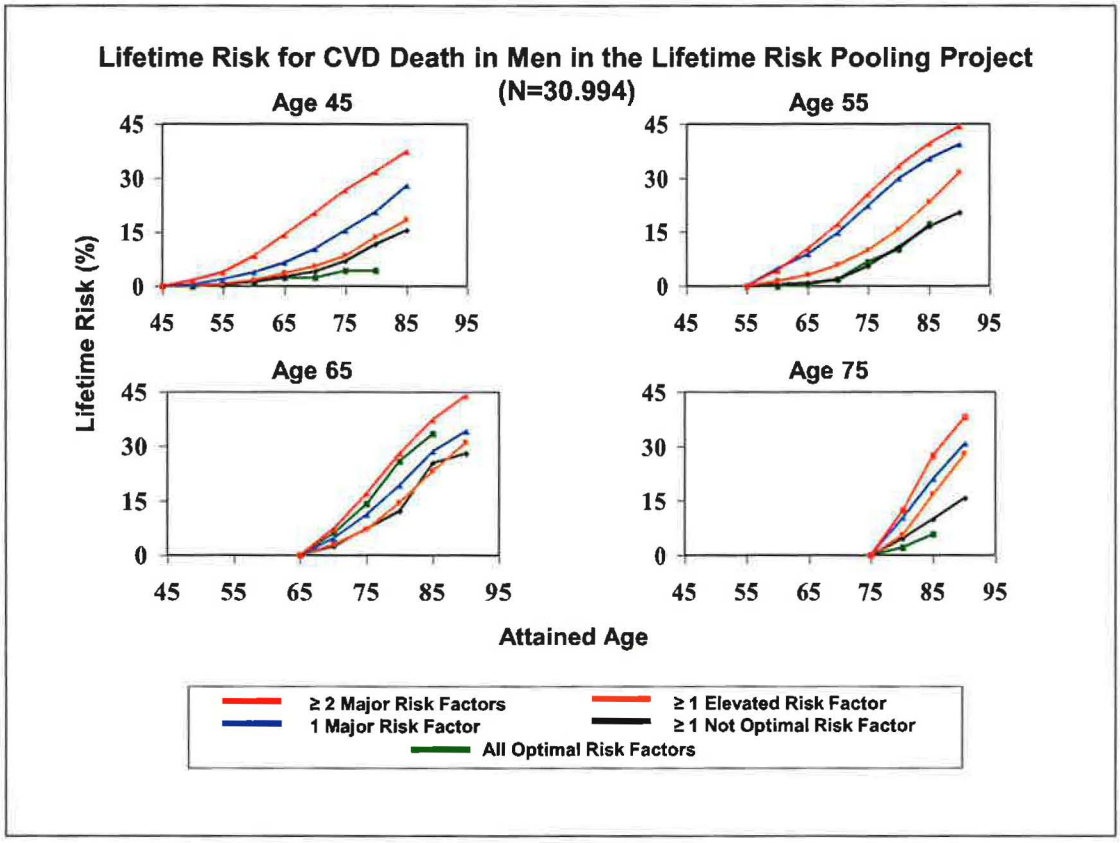
In these types of analyses, participants contribute information on the incidences of CVD and death free of CVD for each age they attain during follow up[33, 60]. Each subject in the study sample is followed from study entry until the occurrence of a first CVD event, death, or attainment of age 95. These analyses were extended until age 80 years (for index ages 45 and 55 years) and 90 years (for index ages 65 and 75 years).

Categories of Aggregate Risk Factor Burden in the Cardiovascular Lifetime Risk Pooling Project

	All Optimal Risk Factors	≥ 1 Not Optimal Risk Factors	≥ 1 Elevated Risk Factors	Major Risk Factor
Systolic/Diastolic (mmHg)	< 120/80	120-139/ 80-89	140-159/ 90-99	≥160 ≥100 (or treated)
Total Cholesterol (mg/dL)	< 180	180-199	200-239	≥ 240 (or treated)
Diabetes	No	No	No	Yes
Smoking	No	No	No	Yes

Lifetime risk estimates raise novel analytic challenges because of the role of competing causes of death across the lifespan. In general, survival analyses can be considered generically to be a function of the cumulative effect of a hazard times the probability of surviving across the lifespan. In traditional analyses such as the Kaplan-Meier estimate, this second, "survival probability" term is a function of the events of interest only (i.e. CVD death) and ignores other causes of death (i.e. cancer death). In contrast, this "survival probability" term in the lifetime risk estimate is a function of both the events of interest and competing causes of death (i.e. cancer death). Thus, over the short term, when the number of "other deaths" (i.e. competing risks) remains low, Kaplan-Meier and Lifetime Risk estimates are similar. However, across the lifespan competing risks can be substantial and ignoring them translates into marked differences in long-term risk estimates.

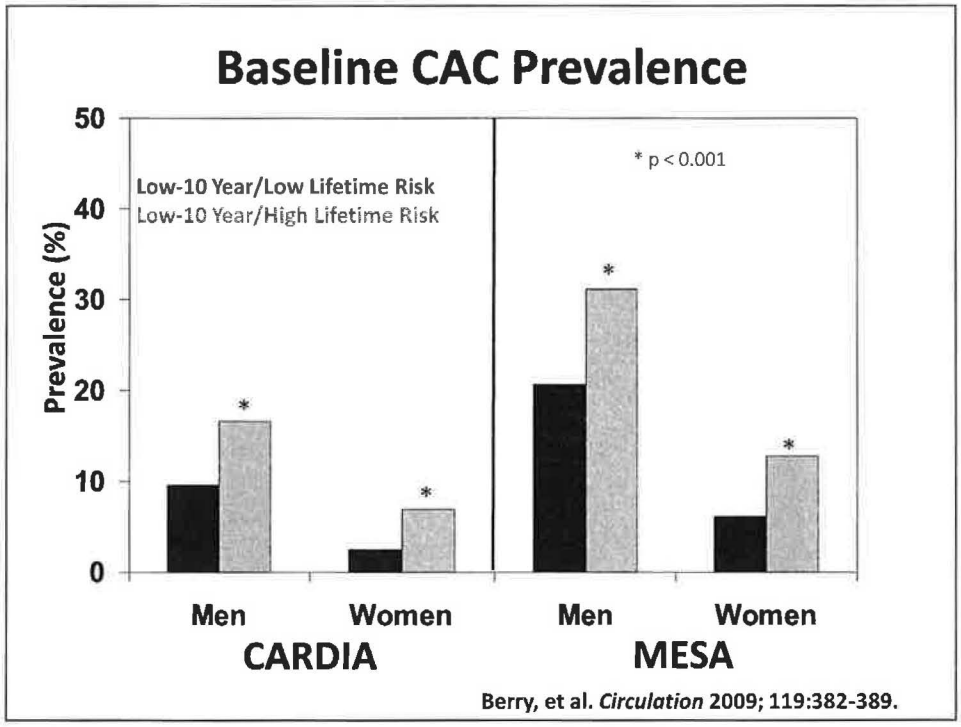
The figure below provides a summary of the lifetime risks for CVD death by aggregate risk factor burden at selected ages in men. Higher risk factor burden is associated with a higher lifetime risk for CVD death for risk factors measured at age 45, 55, 65, or 75 years. In spite of the similarity of risk in the first 10 to15 years across all risk strata, there were marked differences in the observed lifetime risk for CVD death. In addition, lifetime risks tended to be very low for those with all optimal risk factor levels at all index ages. A similar pattern of results was noted for both fatal/non-fatal CHD and fatal/non-fatal stroke in both men and women for risk factors measured at age 45, 55, 65, and 75 years.



VI. Short-term vs. long-term risk

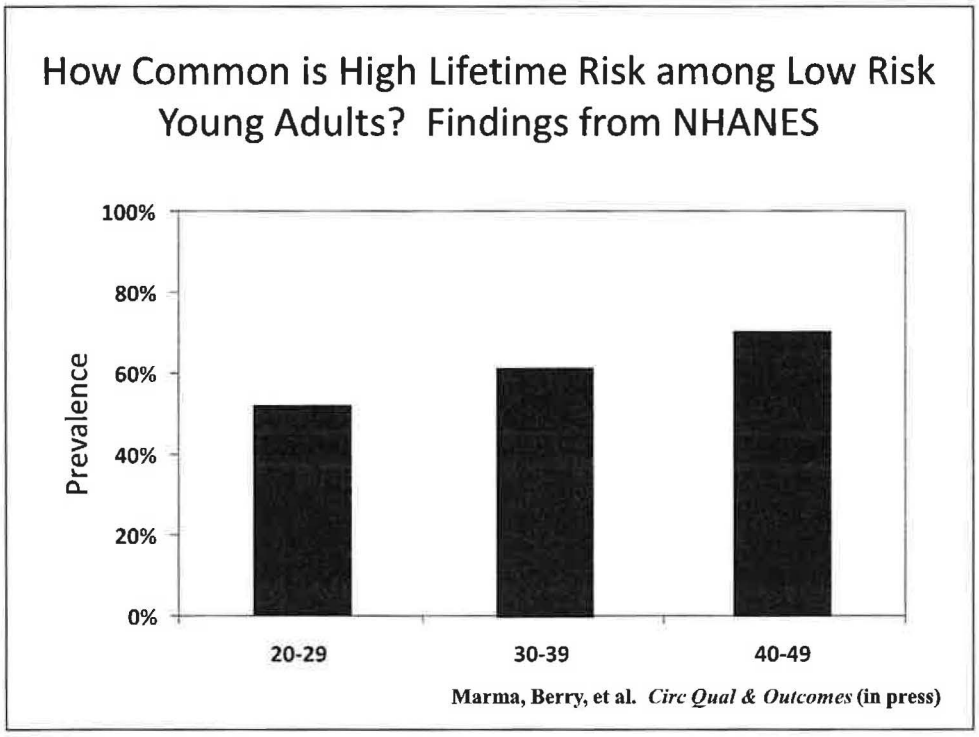
Because of the marked difference in risk between short- and long-term follow-up periods, we sought to determine the potential advantage of identifying a higher risk subset of individuals using a process of lifetime risk stratification[2]. First, we calculated the Framingham Risk Score for all adults less than 50-years of age in two unique, NHLBI-sponsored observational cohorts (CARDIA[61] and MESA[62]). We first classified individuals with diabetes or calculated 10-year risk of ≥ 10% as "high short-term risk". We subsequently estimated the lifetime predicted risk among individuals with low short-term risk, thereby creating three mutually exclusive risk categories: (1) low short-term, low lifetime predicted risk; (2) low short-term, high lifetime predicted risk, and (3) high short-term risk.

We subsequently compared the overall burden and progression of subclinical atherosclerosis using coronary artery calcium and carotid intima-media thickness (IMT). In all cases, in both men and women and in both studies, individuals with low short-term but high lifetime predicted risk had a greater burden and progression of subclinical atherosclerosis compared to individuals with low short-term and low lifetime predicted risk. Representative data shown are for baseline CAC prevalence in the CARDIA study.



Thus, without any additional testing, we would predict that an individual with low short-term but high lifetime predicted risk would have a greater burden and progression of subclinical atherosclerosis compared to an individual with an optimal cholesterol and blood pressure. These results suggest a potential benefit of aggressive prevention efforts for individuals < 50 years with low short-term but *high* lifetime predicted risk.

To determine the population prevalence of this phenotype, we determined the population prevalence of individuals with low short-term but high lifetime risk[63]. As can be seen from the figure, nearly 50% of individuals less than 50-years of age have low short-term but high lifetime predicted risk. Short-term risk is highly influenced by age, however, long-term risk essentially removes the problem of age and demonstrates the singular importance of traditional risk factors and risk for CVD across the lifespan.



VII. The Perception of Lifetime Risk in the General Population

Little direct information is known about the role that perceived lifetime risk plays in influencing patient and/or physician behavior for CVD or other non-CVD endpoints. However, nationally representative surveys make clear that most adults consider their risk for cancer to be substantially higher than their risk for CVD[64]. For example, among a nationally representative sample of women in the United States, only 13% identified CVD as their greatest personal health risk whereas 51% identified cancer as their greatest health risk[64]. This is in contrast to the markedly lower lifetime risks for breast cancer compared to total atherosclerotic CVD (12.5% vs. 40%)[34, 37].

Self perception of low cardiac risk also lowers young adults' motivation to engage in lifestyle modification. In a survey of 1,008 women, knowledge that CVD was the leading cause of death for women was associated with greater odds of exercise and weight loss (OR 1.35 [95% CI, 1.00-1.83] and 1.47 [95% CI, 1.14 to 2.02], respectively)[65]. Thus, although better education strategies will not guarantee success, available data suggest that much work remains regarding education with some potential benefit to improve future CVD risk.

Little is known about the nature of perceived lifetime risk for CVD in the general population. Therefore, we have sought to answer this question using data from the Dallas Heart Study[66]. At study entry, participants were asked to rate their perceived lifetime risk for CVD on a 5 point scale (1—unlikely; 5—most likely). We were also able to estimate the predicted lifetime risk using our previously published algorithm, thereby allowing for us to compare the

perceived and predicted lifetime risk within a population-based sample of participants in Dallas County.

Therefore, we included 3,022 participants from the Dallas Heart Study and classified them according to their perceived and predicted lifetime risk for CVD. We observed several interesting findings. First, among the 1,960 participants (65% of study sample) with high predicted lifetime risk, 898 (45.8%) of participants had a low perceived lifetime risk for CVD, **indicating a high prevalence of underestimated risk in the general population**. Second, this discordance was quite unrelated to risk factor burden and was more closely related to race and psychosocial variables. Of particular interest, underestimated lifetime risk for CVD was strongly associated with physician behavior. And, after multivariable adjustment for age, demographics, risk factors, and psychosocial variables, participants who reported receiving lifestyle counseling from their physicians were more likely to have a correct understanding of their lifetime risk for CVD [odds ratio (95% confidence interval): 1.47 (1.16-1.85).

	High Predicted Lifetime Risk (N= 1,960)		
	Correct (perceived = predicted) N= 1,062	Underestimated Risk (perceived < predicted) N= 898	P-value
Age	45.8	45.5	0.4
Non-white, N (%)	676 (63.6%)	696 (77.5%)	<0.001
Total Cholesterol, mg/dL	190.4	190.3	0.96
Systolic Blood Pressure, mmHg	129.4	128.2	0.15
Current Smoker, N (%)	470 (44%)	379 (42%	0.39
Diabetes, N (%)	185 (17%)	135 (15%)	0.16
Low Perceived Stress, N (%)	61 (6%)	134 (15%)	<.0001
High Perceived Health	337 (32%)	418 (46.5%)	<.0001
Did not receive MD counseling to increase physical activity, (N, %)	477 (45%)	537 (60%)	<.0001

VIII. Lifetime risk estimates to target lifestyle variables: Cooper Center Longitudinal Study

Thus, for the past several years, much of our prior work has been focused on developing lifetime risk estimates for a variety of different clinical endpoints, stratified by age, race, sex, and risk factor burden. Because one of the primary purposes of these risk estimates is to facilitate risk communication and promote more effective preventive interventions, recently we have sought to address lifestyle variables more directly using our lifetime risk technique.

It is now well-documented that unfavorable lifestyle trends promoting weight gain and CVD risk factors are leading to an increase in some CVD risk factors such which may halt or even reverse the favorable trends in CVD death[1]. For example, only 1 in 2 adults achieve recommended moderate or vigorous activity levels in a given week[67]. It is hypothesized that more effective public health and clinical strategies are needed to communicate the importance of lifestyle factors such as physical activity in preventing cardiovascular disease.

Therefore, through an ongoing collaborative relationship between UT Southwestern and the Cooper Center Longitudinal Study[68, 69] here in Dallas, TX, we have sought to extend our lifetime risk work to determine the association between physical fitness and lifetime risk for CVD. The application of these novel survival analytic techniques could provide risk estimates that could be useful in clinical practice. More importantly, this type of analysis is particularly relevant given the well-established association between fitness and both CVD and non-CVD death[68-71], requiring more advanced survival analytic techniques that account for competing risks across the lifespan.

We analyzed available data from 11,049 men who underwent clinical examination at the Cooper Clinic in Dallas, TX before 1990 until the occurrence of CVD death, non-CVD death, or attainment of age 90. The presence of extensive follow-up time (281,469 person-years) and a large number of CVD deaths (1,106 CVD deaths) allowed for the estimation of lifetime risks for CVD death stratified by fitness levels and different fitness level/traditional risk factor combinations. Physical fitness was measured by a maximal treadmill exercise test using a Balke protocol and categorized into three groups based on age- and sex-specific cut points of Balke treadmill time: low, intermediate, and high fitness. Lifetime risk for CVD death determined by the National Death Index was estimated for fitness levels measured at different ages (45-, 55-, and 65-years) with non-CVD death as the competing event.

Table: Representative Baseline Characteristics Among 3,424 Male Participants in the Cooper Center Longitudinal Study

	Age 55		
	Low Fit N = 802	Moderate Fit N = 1,492	High Fit N = 1,130
Age, years	54.8	54.2	54.1
SBP, mmHg	129.2	124.3	123.6
TC, mg/dL	231.2	226.2	217.9
BMI, kg/m2	28.1	26.4	26.4
Smokers, %	29.6	21.9	9.8
Diabetes, %	7.9	5.8	3.2
METS, mean	7.4	9.6	12.6
CVD Deaths, N (%)	212 (26.4)	191 (12.8)	85 (7.5)

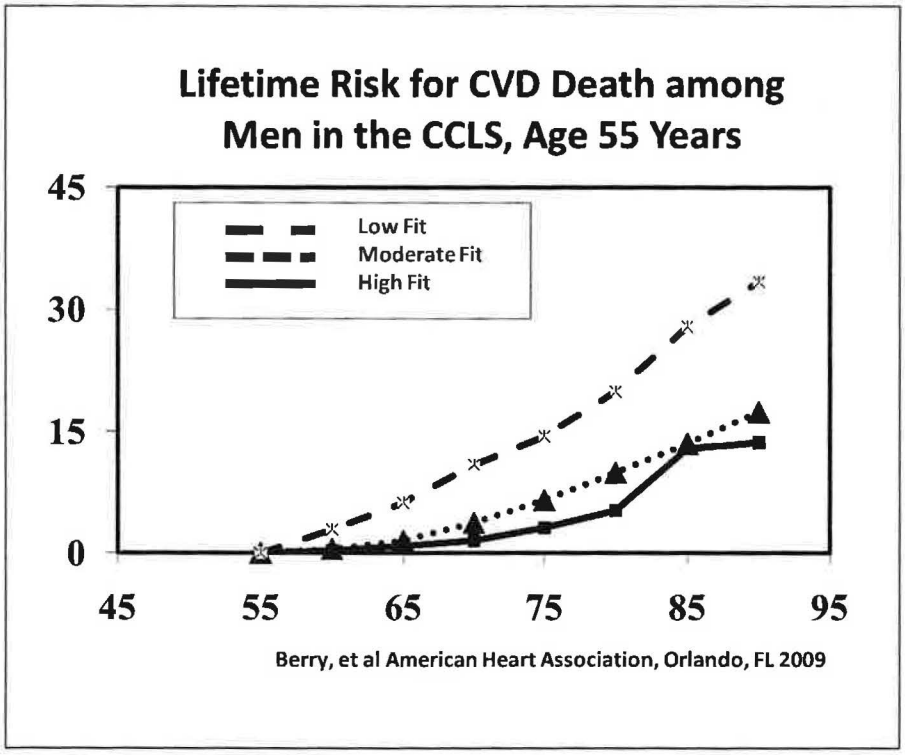
Representative data are shown for men age 55 years in the CCLS in the above table. As expected, traditional risk factors were lower among men with high fit participants, particularly current smoking rates. When we estimated the lifetime risks for CVD death across levels of fitness, we observed marked differences in lifetime risks, even after adjustment for competing risks. However, fitness was strongly associated with lifetime risks for CVD death across all levels of fitness measured at different index ages. Representative data are shown below for fitness levels measured at or around age 55 years (see figure).

In an effort to incorporate these analyses into our prior approach with traditional risk factors, we further stratified individuals into four mutually exclusive risk factor categories: low fitness/high risk factor burden; low fitness/low risk factor burden; high fitness/high risk factor burden; and high fitness/low risk factor burden. *(Note: high risk factor burden is defined as the presence of at least one elevated or major risk factor according to the traditional risk factor stratification table detailed on the top of page 11)*

Lifetime risk for CVD death was lowest in the high fit/low traditional risk factors group for risk factors measured at each index age. The lifetime risks were highest for individuals with both low fitness level and high levels of traditional risk factors at each index age. In contrast, the lifetime risks and median survival were intermediate for groups with either low fitness or high traditional risk factors risk, but not both.

Compared with Kaplan-Meier cumulative incidence data for CVD death, adjustment for competing causes of death resulted in a decrease in the lifetime risks for CVD death across all age, fitness, and risk factor groups studied. However, the evidence for competing risks was most prominent at older ages and at lower levels of fitness where the rates of non-CVD death are highest. For example, among men with high fitness levels measured at age 55 years, the lifetime risks for CVD death were similar to the unadjusted, Kaplan Meier estimate (Kaplan-Meier

cumulative incidence 13.1% vs. lifetime risk 11.5%). At age 55 years, adjustment for competing risks among the group with very low fitness levels (≤ 6 METS) decreased lifetime risk estimates substantially (Kaplan-Meier cumulative incidence 44.0% vs. lifetime risk 35.7%).



Finally, to our knowledge, there have been only inconsistent reports of the association between physical activity and longevity[72, 73] and no available data regarding the association between fitness and longevity. We observed marked differences in median survival across levels of fitness (see table). A similar pattern of results was observed for fitness/risk factor combinations described above.

Table: Median Age at Death (95% CI) Across Fitness Levels and Measured at Age 55- and 65-Years in the Cooper Clinic Longitudinal Study

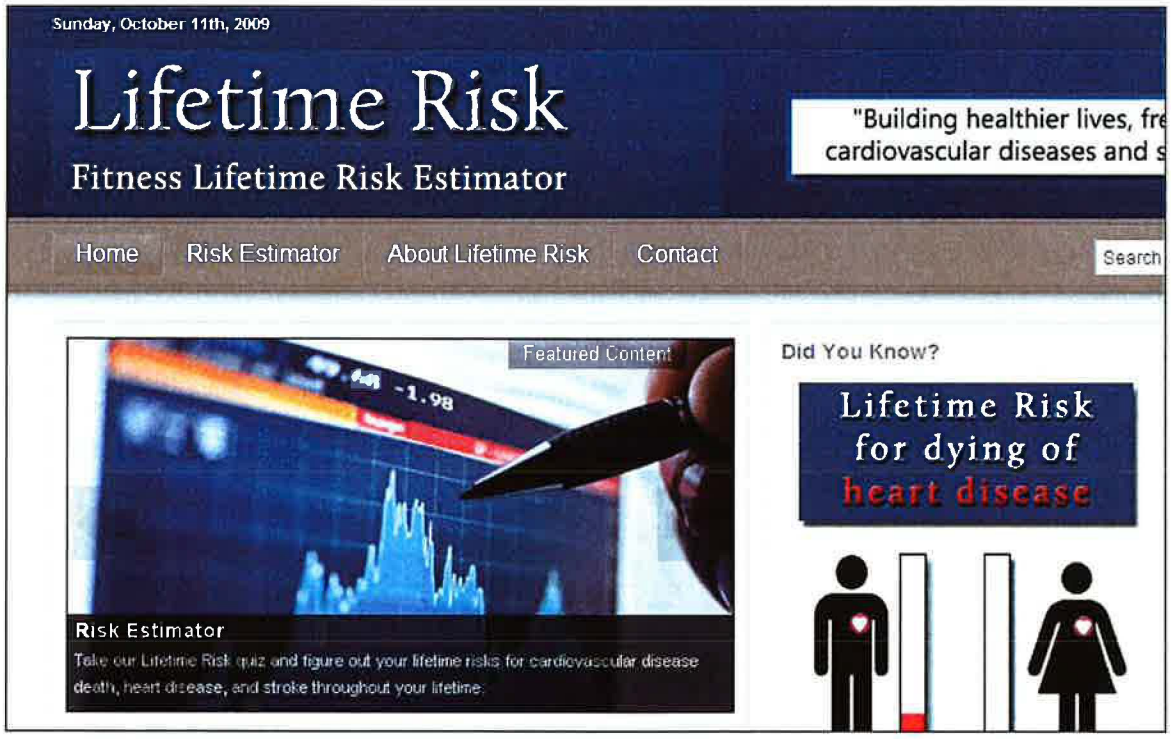
	High Fitness	Moderate Fitness	Low Fitness	Very Low Fitness (METS ≤ 6)
Age 55 Years	88.9	87.3	82.4	77.8
Age 65 Years	89.5	87.5	85.0	83.9

These data provide a clinically relevant and intuitive estimate of the association between fitness, traditional risk factors, and long-term risk. With the knowledge of a man's age, fitness, and risk factor status, clinicians can provide an estimate of the lifetime risk for CVD death and overall survival. In addition, these data could also be used by policy-makers to facilitate communication regarding the public health benefits of fitness. It is possible that a broader understanding of the associations between fitness and lifetime risks for CVD could translate into better public understanding of the importance of fitness, potentially motivating changes in physical activity patterns.

IX. Where do we go from here?

Risk estimation represents an important and indispensable tool for clinical interventions for CVD prevention. However, much of the prior emphasis in the literature has been in the area of the development of novel risk markers rather than on creating more effective tools to communicate risk and thereby lower risk. We believe that lifetime risk estimates represent an important tool that could serve as an adjunct to current short-term risk estimation strategies.

Toward this end, we have started developing a website through which we might be able to create a platform to facilitate communication between patients and physicians (www.lifetimerisk.org).



Once completed, physicians and/or patients will be able to enter their demographic and risk factor data to obtain a lifetime risk estimate for CVD. In addition, by incorporating data from the Rockport Walking Test or a clinically derived estimate of their physical fitness, patients would also be able to incorporate fitness data to further stratify their lifetime risk for CVD. We hope to obtain additional funding this next year to complete this website and create an interactive, online risk estimation platform in which patients and physicians here at UT Southwestern and beyond could use these data on traditional risk factors as well as physical fitness to create a more meaningful dialogue and thereby facilitate more effective preventive interventions.

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