Development of Appropriate Coronary Heart Disease Risk Prediction Models in HIV-Infected Patients

Morris Schambelan, MD, Co-Chair; Peter W.F. Wilson, MD, Co-Chair; Kevin E. Yarasheski, PhD, Co-Chair; W. Todd Cade, PhD; Victor G. Dávila-Román, MD; Ralph B. D'Agostino, Sr, PhD; Tarek A. Helmy, MD; Matthew Law, MD; Kristin E. Mondy, MD; Sharon Nachman, MD; Linda R. Peterson, MD, FAHA; Signe W. Worm, MD; for Working Group 5

Prediction equations for coronary heart disease (CHD) risk are useful tools that inform clinicians and patients about the absolute risk for developing CHD. A basic principle in CHD prevention is that the intensity of risk-reducing interventions should be based on the individual patient's absolute CHD risk. In the current era of human immunodeficiency virus (HIV) infection and highly active antiretroviral therapy (HAART), knowing one's CHD risk and acting to reduce it have become imperative to long-term survival. Given the increased life expectancy as a result of HAART, more HIV-infected persons will experience complications not related to HIV per se and will reach an age at which they are at increased risk for developing CHD.

However, existing CHD risk prediction equations were not developed in HIV-infected adults or children. In the general population, CHD risk prediction models derived from the Framingham Heart Study estimate the risk of total CHD (angina pectoris, myocardial infarction [MI], CHD death)[1] or estimate the risk for hard CHD end points (MI, CHD).[2] The traditional risk factors used to predict CHD risk and how risk factor alterations affect CHD outcomes in HIV-infected and HIV-seronegative people are summarized in the Table. The estimates of the relative effects of traditional risk factors on CHD outcomes appear similar between HIV- and non–HIV-infected patients. However, they are based on only 2 studies in HIV-infected patients. Although traditional CHD risk factors may operate in the same manner in HIV patients as in the general population, there may still be a need to identify and evaluate HIV-specific CHD risk factors and equations, to refine existing CHD prediction equations, and to develop new HIV-specific CHD prediction equations for adults, adolescents, and children. To date, Framingham CHD risk predictions have performed reasonably well when applied to HIV-infected patients. We need to evaluate whether new HIV-specific CHD risk prediction approaches perform better than existing algorithms. This task represents a formidable challenge but is crucial to improving care and reducing healthcare costs for people living with HIV.

Existing CHD Prediction Equations

Historically, CHD prediction equations have been derived to estimate risk for an initial coronary event in a population with minimal CHD risk at the beginning of the observation period,[1,3,4] generally from data obtained in middle-aged adults. Such equations may not provide suitable predictions for young people living with HIV. Of concern, adolescents have been and continue to be infected with HIV, and despite substantial reductions in mother-to-child transmission in the United States, infants in resource-limited regions of the world continue to be infected with HIV, and adolescents continue to experiment with intravenous drugs, share needles, and engage in unprotected sex. Existing equations predict the 10-year CHD risk based on longitudinal observational data. Observational data are limited in their ability to predict adverse events.[5] HIV was identified in the 1980s, and HAART has been available only for ≈10 years, so predicting 10-year

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Table. Do Traditional Main Cardiovascular Risk Factors Predict the Risk of CHD/CVD Similarly in HIV-Infected and HIV-Uninfected Persons?

		Increase in Risk per Unit for Each Study, % (n Studies)		
CV Risk Factor	Unit	HIV Positive		HIV Negative
Age	Per 1 y older	9	6	6–9 (7)
Sex	Male vs female	NS	110	110–160 (2)
Diabetes	Yes vs no	260	90	140–252 (3)
Smoking	Yes vs no	140	290	70–290 (3)
Hypertension	Yes vs no	30	80	80–90 (3)
Total cholesterol	Per 1 mmol/L* increase	...	26	25–33 (3)
HDL cholesterol	Per 1 mmol/L* increase	...	−28	−52 (1)

CVD indicates cardiovascular disease; HDL, high-density lipoprotein.

*1 mmol/L=39 mg/dL.

Adapted from J. Lundgren (Chicago, Ill; June 2007). Data compiled from references 14, 36, and 49 to 54.

CHD risk with limited HAART experience will challenge existing CHD prediction equations.

Despite these limitations, existing CHD prediction algorithms have been applied to HIV-infected people[6–13] and have performed reasonably well.[14–17] Of note, there appears to be a significant but modest concordance among 3 popular CHD risk stratification algorithms when applied to HIV.[10] For the time being, it appears that the Framingham Risk Score calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp) can be used effectively to rank CHD risk in HIV-infected people; the only data required are age, smoking status, and fasting lipid profile. Most[6–9] but not all studies[11,13] found a slightly greater CHD risk in HIV-infected people taking HAART and experiencing abnormal adipose tissue distribution compared with "matched" HIV-seronegative controls. The contributions of type and duration of individual anti-HIV drugs and their differential effects on serum lipids/lipoproteins to CHD risk are still debated.[14,17–23] When actual CHD events (acute MI, cardiac death) are documented, the limited data suggest that CHD risk factors were more prevalent and acute MI rates were higher in HIV compared with age-matched non-HIV patients[12,14,20,24] (Figure 1). In these reports, however, the absolute risk of MI was low compared with the known benefits of HAART in terms of reducing AIDS-related mortality.[21,25,26] Given the limitations of existing CHD prediction equations, the evolving nature of the cardiometabolic syndrome in HIV, and the relative infancy of this area of inquiry, it is important to grasp this window of opportunity and move forward with the refinement of existing or the development of new HIV-specific CHD prediction equations.

HIV-Specific CHD Risk Factors

Whether HIV infection per se is an independent CHD risk factor or the increased CHD risk is due solely to HAART remains controversial. CHD risk is increased in autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus,[27,28] so HIV-related chronic proinflammatory processes and altered immune function may impart greater CHD risk than in the general population. Even before HAART became available, HIV infection was associated with a proatherogenic lipid profile: low high-density lipoprotein and elevated small dense low-density lipoprotein particles and triglyceride levels.[29,30] However, it may be difficult to delineate among CHD risk associated with HIV, HAART, and traditional risk factors because the vast majority of HIV-infected patients will receive HAART in the course of their disease.

Among traditional CHD risk factors, the prevalence and intensity of substance abuse (especially tobacco and recreational drugs) are greater in patients with HIV than in the general population.[6–8,11–13,31–33] In HIV, HAART, other medications, and poor lifestyle/behavioral choices (diet, physical inactivity, and substance abuse) may adversely affect (directly and indirectly) traditional coronary risk factors: lipid/lipoprotein levels, regional adipose tissue distribution, and insulin sensitivity. The increased CHD risk seen in some patients on HAART may be related primarily to the effects of HAART on traditional CHD risk factors. But other as-yet unidentified mechanisms may contribute to the increased CHD risk (eg, direct effect of HAART on the vasculature).[34] Evidence from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) and other studies indicates that

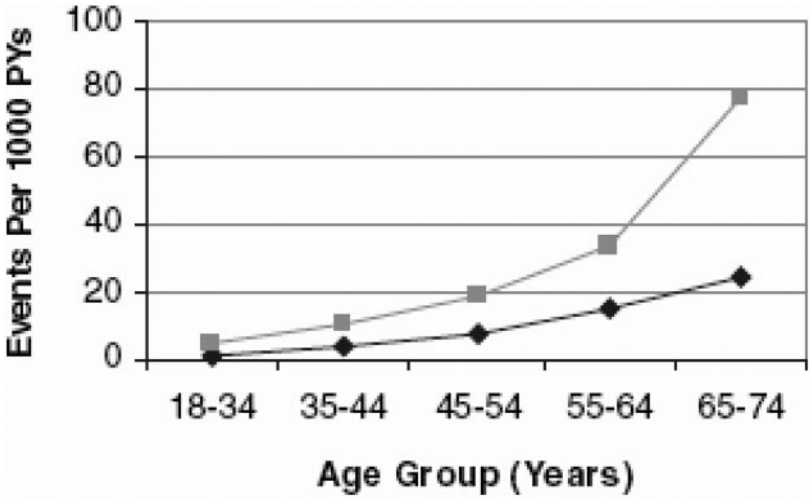

Figure 1. MI rates in HIV- and non–HIV-infected patients. Acute MI rates (events per 1000 patient-years [PYs]) were increased with advancing age in HIV vs non-HIV patients. Both genders are included. Gray line indicates HIV infected; black line, HIV-seronegative control group. Reprinted with permission from Triant et al.[24]

increased duration of protease inhibitor therapy leads to an increase in the rate of cardiovascular disease events.[20,35,36] HAART regimens are changed frequently, and each drug within a class (nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors) is associated with very different effects on traditional CHD risk factors.[8,37–39] New anti-HIV drugs and drug classes (entry, fusion, integrase, and maturation inhibitors) are introduced continuously. HAART prescribing practices are dynamic, variable, and complicated, and it is not certain whether they should be included in the HIV-specific CHD risk prediction models that are under development.[8,16,22] Conversely, we may need several separate CHD risk algorithms for people living with HIV (ie, HAART naive, history of HAART exposure, discontinued HAART, children, and adolescents). Finally, HIV is a global epidemic, and CHD prediction models will need to be adapted to the markedly different geographical, ethnic, and racial variations.[14,40]

Refining Existing Prediction Equations

The starting point for the development of a CHD risk prediction equation in patients with HIV is a comprehensive medical history and clinical examination with standardized collection of key predictor (independent) risk factors: age, sex, fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, ratio of total to high-density lipoprotein cholesterol), systolic blood pressure, history of diabetes mellitus treatment, fasting or postprandial glucose levels, and use of tobacco and other substances.[1,4,28] Most existing equations predict CHD morbidity (new MI, ischemic events, including stroke, coronary artery angioplasty, bypass surgery, carotid endarterectomy) and mortality (cardiac death). Such end points need to be defined a priori and captured in data collection (dependent variables). Baseline risk factors and treatments for hypertension, dyslipidemia, hyperglycemia, and other conditions need to be captured. In particular, specialized models have been developed for persons with type 2 diabetes that consider additional potential predictor variables: hemoglobin A1c, microalbuminuria, and duration of diabetes.[41–43] In HIV, a challenge is to allow for a higher prevalence of lipid- and glucose-lowering and antihypertensive therapies, as well as HIV-specific factors (ie, HIV RNA, CD4 cell count, duration of disease, and therapy).

In prospective studies, selecting risk factors and developing and assessing the utility of a new CHD prediction model typically involve a proportional-hazards regression model. The utility of the model can be assessed by several different performance measures.

Relative Risk

For each risk factor, proportional-hazards modeling yields regression coefficients for a study cohort. The relative risk of a variable is computed by exponentiation of the regression coefficient and is a measure of the increased risk for someone with a given risk factor (eg, tobacco use) compared with the risk for someone without that risk factor (eg, nonsmoker).

Discrimination

Discrimination is the ability of a prediction model to separate those who experience hard CHD events from those who do not. This is quantified by calculating the c statistic, analogous to the area under a receiver-operating characteristics curve.[44] This value represents an estimate of the probability that a model assigns a higher risk to those who develop CHD within a specified follow-up than to those who do not.

Calibration

Calibration measures how closely predicted outcomes agree with actual outcomes. For this, a version of the Hosmer-Lemeshow χ^2 statistic is used.[45] The χ^2 statistic is used to compare the differences between predicted and actual event rates. Small values indicate good calibration, and values >20 indicate significant lack of calibration.

Recalibration

An existing CHD prediction model can be recalibrated if it systematically overestimated or underestimates CHD risk in a new population but correctly ranks subjects in terms of CHD risk. For example, recalibrating the Framingham risk prediction equation would involve inserting the mean risk factor values and average incidence rate for the new population into the Framingham equation. Kaplan–Meier estimates can be used to determine average incidence rates.

New CHD Prediction Equations for HIV

In HIV, estimates of CHD risk have been reported and calibrated by the D:A:D investigators[8,14,15,17] and others,[20,22,24] and new HIV-specific CHD prediction algorithms have recently been proposed.[16,21,31] The D:A:D-derived HIV-specific CHD risk equations incorporated protease inhibitor exposure and traditional CHD risk factors (eg, age, tobacco use) and captured CHD events (including MI) as the dependent variable. Among 33 594 person-years, 157 CHD events occurred; the D:A:D equation predicted 153, and the Framingham equation predicted 187. The Framingham equation predicted remarkably well but tended to underestimate CHD events in HIV-positive tobacco users (Figures 2 and 3). The area under the D:A:D receiver-operating characteristics curve discrimination statistic was 0.78 (95% CI, 0.75 to 0.82), and the D:A:D prediction equations were accurate in men versus women and in tobacco users versus nonusers. Several lessons have been learned that can be applied. The receiver-operating characteristics curve discrimination statistic (0.78) was excellent, and whether it can be improved on by including additional traditional or HIV-specific risk factors needs to be evaluated. External validation of the D:A:D prediction model is warranted to determine whether it is generalizable among people living with HIV.

Finally, noninvasive, direct measures of carotid intima-media thickness or brachial artery reactivity/dilatation also have been used to evaluate cardiovascular disease risk[46–48] in HIV-infected adults and children. In theory, these measures may provide more predictive value for premature atherosclerosis and CHD in HIV. In support of this, 1 study using multivariate models has reported that Framingham risk stratification independently predicted carotid intima-media thick-

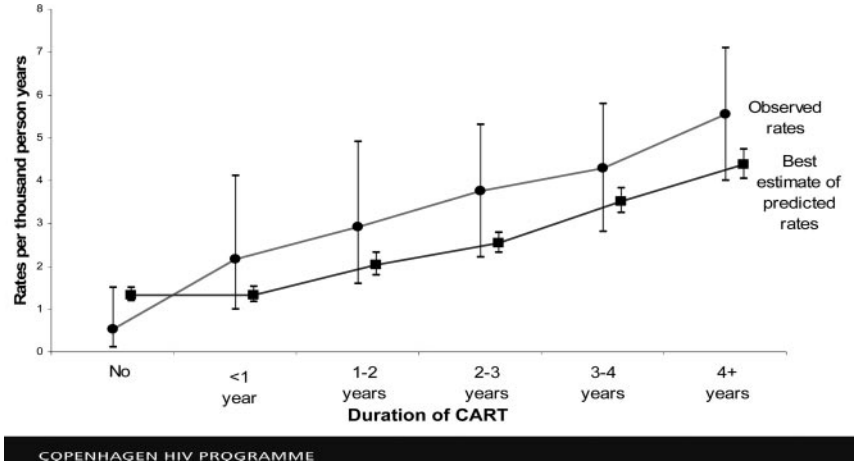

Figure 2. Comparison of observed rates in D:A:D and those predicted by the Framingham score. Based on duration of HAART and the Framingham CHD risk prediction, CHD events were underpredicted vs events observed in D:A:D. CHD events were MI according to the World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (WHO-MONICA) classification, monitored and verified by 2 independent physicians. A total of 126 MIs were observed. Reprinted with permission from D:A:D.[15]

ness in HIV-infected adults.[46] This suggests that additional research should focus on the utility, sensitivity, and specificity of these and other noninvasive surrogate measures (coronary vessel imaging) of premature CHD in HIV rather than waiting for the somewhat rare but hard CHD outcomes like MI, stroke, endarterectomy, or cardiac death to occur.

Controversial Issues, Gaps in Knowledge, and Future Research Priorities

Given limited data, the estimation of the relative effects of traditional risk factors on CHD outcomes appears similar between HIV-infected and non–HIV-infected patients. To date, Framingham CHD risk predictions have performed reasonably well when applied to HIV-infected patients. There is an important need to identify HIV-specific risk factors and to test whether new HIV-specific CHD risk prediction approaches perform better than existing algorithms. In this regard, the following research needs and priorities were identified:

- Perform a large, multicenter, multinational prospective study that captures a core set of traditional and HIV-specific variables that are all collected at standard intervals in HAART-naive and treated HIV-infected children, adolescents, and adults to determine with certainty the optimal HIV-specific risk prediction algorithm and the relative contribution of HIV infection and HAART to CHD in this population. Ideally, such a study or related studies would obtain fundamental data on (1) the relative contribution of HIV infection (replication, altered immunity, and inflammation), HAART component(s), central adiposity, peripheral lipoatrophy, and metabolic dysregulation to CHD risk in HIV and (2) the safety and efficacy of standard treatments (diet, weight loss, physical activity) and more intensive therapies (antiinflammatory agents; glucose-, lipid-, and blood pressure–lowering agents; switching HAART regimens) for CHD in HIV.
- Consider the use of large administrative databases/registries as interim data sources to develop and refine HIV-specific CHD risk prediction equations because a prospective study would require many years of follow-up. Participants should be enrolled from developed and

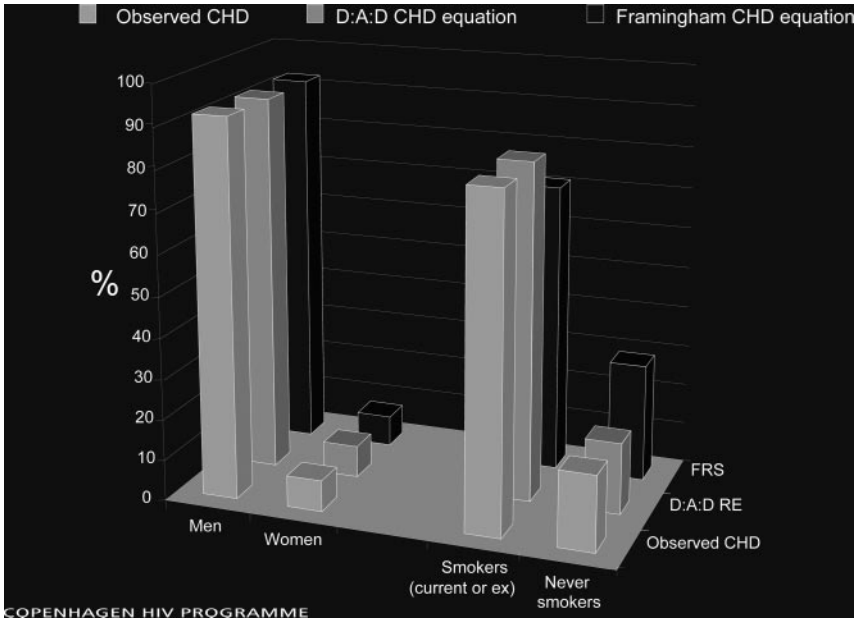

Figure 3. Proportional distribution of CHD in subgroups: observed and predicted. When subdivided on the basis of gender and tobacco use, Framingham CHD risk prediction appeared to underestimate observed CHD events in D:A:D for tobacco users and to overestimate CHD events for HIV-infected patients who reported never using tobacco. CHD events represent a composite end point, including MI, invasive coronary artery procedure, including coronary artery bypass or angioplasty/stenting, or death from other CHD.[16] Reprinted with permission from D:A:D.[16-18]

resource-limited regions of the world where HAART regimens are more standardized.

- Develop novel database integration techniques to combine ongoing cohorts and recalibrate existing models (D:A:D, Strategies for Management of Retroviral Therapy [SMART], Multicenter AIDS Cohort Study [MACS], Veterans Administration AIDS Clinical Trial Group [ACTG]). A focus of current HIV observational and cohort studies should be the implementation of standardized, prospective, validated CHD end points, together with core HIV markers and treatment and traditional CHD risk factors, to allow such integration to be undertaken.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary, which is available online at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189622.

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