

Cardiovascular Disease Risk Assessment Tools in HIV-Infected Patients - Are They Adequate?

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Abstract

Cardiovascular disease (CVD) has become one of the leading causes of morbidity and mortality among HIV-infected patients with seropositive patients developing CVD at higher rates than seronegative patients. Therefore, it is critical to have inexpensive, non-invasive assessment tools for CVD risk assessment in HIV-infected patients. Nearly all CVD risk assessment tools were derived from the general population, and their ability to predict CVD in the HIV population has been variable. In order to more accurately predict CVD risk in HIV-infected patients, a new CVD risk assessment tool derived from the HIV population that accounted for factors specific to HIV infection, disease course, and/or sequelae of treatment with antiretroviral therapy is needed. An improved CVD risk assessment tool for HIV-infected patients will help determine which patients would most benefit from primary prevention strategies.

Keywords: HIV/AIDS; Cardiovascular disease; Heart disease; Cardiovascular disease risk; Cardiovascular disease risk scores; Coronary heart disease risk scores; Cardiovascular disease prevention

Introduction

The era of antiretroviral therapy (ART) has seen a shift in the morbidity and mortality among HIV-infected patients. The proportion of AIDS-related causes of death (i.e. opportunistic infections, AIDS-related malignancies) has decreased, while there has been an increase in non-AIDS causes of death [1-3]. In a large outpatient observational cohort study in the United States between 1996 and 2004, non-AIDS causes rose from 13.1% to 42.5% of deaths among HIV-infected patients, and of the non-AIDS causes, cardiovascular disease (CVD) was the most frequent cause of death [3]. Similar findings have been reported in numerous other studies, and CVD ranks as one of the leading causes of mortality among these patients currently [1,4].

Many studies suggest HIV-infected patients develop CVD at higher rates than their HIV-uninfected counterparts [5-7]. Freiberg et al. [5] conducted a six year prospective cohort study comparing acute myocardial infarction (AMI) incidence between HIV-infected and uninfected men in the Veteran's Aging Cohort Study Virtual Cohort, and found HIV-infected patients had approximately 50% increased risk of developing AMI (HR=1.48) compared to uninfected patients after controlling for demographics and traditional CVD risk factors. Triant et al. [6] found a comparable increased AMI risk (RR=1.75) for HIV-infected patients in Boston, Massachusetts. They found stratifying patients by gender further increased the relative risk of AMI in HIV-infected women (RR=2.98) but not in HIV-infected men. Currier et al. found HIV-infected patients had increased coronary heart disease (CHD) risk compared to HIV-negative patients using California Medicaid data [7]. The relative risk was especially great among younger patients ages 18-24 years old (RR=6.76 for men, RR=2.47 for women). Increased CVD risk in HIV-infected patients is believed to be multifactorial including traditional factors (dyslipidemia, diabetes, hypertension), lifestyle (increased rates of cigarette smoking, alcohol, and illicit drug use), and HIV-related risk factors (inflammation, hypercoagulability, immune activation, effects of ART) [4,8-10]. Nonetheless, an unexplained excess risk of CVD persists after adjustment for traditional CVD risk factors [4,7,11], and therefore necessitates accurate prediction models for developing CVD in order to guide prevention strategies.

Population-based CVD Prediction Models

A number of CVD prediction models have been developed for the general population. These models were created from large population studies and were usually validated for use in the countries from which they were derived. The United States has historically used the Framingham Risk Score (FRS), which was developed from the Framingham Heart Study, to predict individuals' 10 year risk of developing CHD [12]. The original Framingham Risk Equation was developed in 1998, and it created a risk assessment tool- the FRS- that evaluated several variables as predictors of CHD outcomes defined by angina, AMI, coronary insufficiency, and death attributable to CHD. The variables included were: age, gender, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), blood pressure category, diagnosis of diabetes mellitus, and current smoking status. The FRS has undergone a few revisions since then. The current 2008 FRS calculates the 10 year risk of developing CVD defined by coronary artery disease, stroke, peripheral vascular disease, congestive heart failure, and cardiac death by including slightly adjusted variables: age, gender, total cholesterol, HDL-c, current smoking status, systolic blood pressure, and hypertension treatment status into its calculus [13]. In 2013, the Atherosclerotic CVD (ASCVD) risk score derived from the Pooled Cohort Equation was developed by the American College of Cardiology and American Heart Association and has begun replacing the FRS [14]. The ASCVD risk score includes the variables in the FRS plus diabetes mellitus diagnosis or treatment.

There has been some widely used CVD prediction models derived in Europe as well. The United Kingdom utilizes the QRISK2 score to predict 10-year risk of CVD defined in this case as CHD, stroke and

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transient ischemic attack [15]. In addition to the variables in the FRS, QRISK2 incorporates the total cholesterol/HDL-c ratio rather than the individual variables weighted separately and also include several other variables: body mass index, ethnicity, family history of CHD, deprivation (measured using the Townsend deprivation score), chronic kidney disease, rheumatoid arthritis, and atrial fibrillation. The Systematic Coronary Risk Evaluation (SCORE) is a risk estimator of 10 year fatal CVD derived from 12 European cohort studies mainly from general population settings [16]. It incorporates variables similar to the FRS except that it incorporates either total cholesterol or total cholesterol/HDL-c ratio with only minor differences observed between models that used one or the other, and it excludes diabetes mellitus and race. The SCORE plots an individual's predicted 10 year probability of CVD death into two sets of charts, one for high CVD risk countries and one for low-risk countries based on national data on CVD mortality rates among countries. The Prospective Cardiovascular Münster (PROCAM) score was derived from a German cohort of industrial employees to predict risk of CVD [17]. The PROCAM score includes the variables age, LDL-c, smoking status, HDL-c, systolic blood pressure, family history of AMI, diabetes mellitus diagnosis, and triglyceride level. Importantly, minorities, women, and men over aged 65 years old at time of cohort recruitment were not included in the cohort from which the PROCAM score was developed. Therefore, it is apparent that there are numerous differences in populations from which these risk assessment scores were developed, differences in variables included and statistical methods used, and differing outcomes being predicted (different definitions of CHD or CVD, or CVD events rather than attributable deaths) in the various CVD risk estimation models [18]. Nonetheless, the various risk prediction models also share some similarities with significant overlap of predictive variables and derivation from high-income European countries or American cohorts. Ultimately, the utility of these prediction models is the same: to identify individuals at high CVD risk, who may benefit from primary interventions to prevent CVD.

Applying CVD Prediction Models to HIV-Infected Patients

None of the CVD risk estimation tools described above were derived from HIV-infected populations, and therefore they may not adequately predict risk of developing CVD in HIV-infected patients. In order to assess their accuracy and utility, it is important to evaluate how they performed when applied to HIV-infected populations. FRS has predicted the increased CVD risk among HIV-infected patients in some but not all studies. In a Norwegian study, Bergersen et al. [19] found a greater proportion of HIV-infected patients had high 10 year CHD risk based on FRS >20% compared to uninfected controls (11.9% vs. 5.3%, respectively). Law et al. [20] found FRS increased with ART duration in HIV-infected patients enrolled in the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study. Falcone et al. [21] found higher FRS in HIV-infected patients correlated with markers of early atherosclerosis – increased carotid intima media thickness and coronary artery calcification. However, it is important to acknowledge that these are surrogate markers of subclinical disease that may not necessarily result in observed CVD events.

On the other hand, Regan et al. [22] observed that both ASCVD score and FRS under-predicted CVD risk in a Boston HIV-infected cohort. Freiberg et al. [5] found that HIV-infected veterans had 50% greater risk of developing AMI compared to uninfected veterans despite having similar mean FRS. Lo et al. found higher rates of subclinical atherosclerosis assessed by CT coronary angiography among the HIV-

infected patients compared to negative controls despite similar FRS in the two groups [23]. Although Law et al. [20] found that predicted AMI rates based on FRS increased in parallel with observed AMI rates with increasing duration of ART in the D:A:D cohort, FRS consistently underestimated the observed AMI rates. In contrast, Friis-Møller et al. [24] found FRS over-predicted observed CVD in their analysis of D:A:D study. In summary, FRS and other CVD risk scores variably predicted observed CVD events in HIV-infected patients by both over- and underestimating events across studies. In studies comparing FRS, SCORE, PROCAM, and other CVD risk estimates among HIV-infected cohorts, FRS consistently produced the highest risk estimates [25,26].

A CVD risk model for HIV-positive patients was derived from the D:A:D study by Friis-Møller et al. [24]. The variables included in their model included: age, sex, systolic blood pressure, smoking status, family history of CVD, diabetes mellitus, total cholesterol, HDL-c, indinavir (IDV), lopinavir/ritonavir (LPV/r), and abacavir (ABC) exposure. This model more accurately predicted observed MI, CHD, and CVD rates compared to FRS. Of note, CD4 cell count and HIV-RNA level did not improve the predictive ability of the model.

Recommendations and Conclusion

The increased CVD morbidity and mortality among HIV-infected patients warrants routine implementation of inexpensive and non-invasive risk assessment tools such as CVD risk estimation calculators. However, the predictability of existing, CVD risk calculators derived and generally validated in HIV-uninfected patient populations has been variable, with many studies suggesting they may underestimate CVD risk in HIV-infected patients [5,22]. A CVD risk calculator that includes variables that are more specific to HIV infection, disease course, and/or its sequelae of treatment should be derived and validated for implementation in the HIV population, which is at increased risk of CVD. The D:A:D score developed by Friis-Møller et al. [24] based on the D:A:D study incorporated some HIV-related factors (IDV, LPV/r, and ABC exposure) and was likely more valid for the HIV-positive population. However, IDV and LPV are no longer used as frequently as newer protease inhibitors, which limit the utility of the risk assessment tool. While they found factors such as CD4 count and viral load did not improve the predictability of their risk estimation model, these factors likely need to be re-tested in different settings than that represented in the D:A:D cohort. In the HIV Outpatient Study (HOPS), Lichtenstein et al. found patients with CD4<350 cells/mm³ had increased CVD events compared to those with CD4>500 cells/mm³ (HR=1.58), suggesting CD4 count may indeed be an independent predictor of CVD [27]. Other HIV disease-related factors should also be considered in future models. For example, low CD4:CD8 ratio has been associated with increased coronary artery disease risk in patients on ART achieving virologic suppression, making CD4:CD8 ratio of interest when investigating new CVD risk models [28]. Until a new CVD risk assessment tool has been derived and validated in the HIV population, we are left to applying the FRS or the newer ASCVD risk score to HIV-infected patients. CVD risk assessment should be performed regularly for HIV-infected patients, as recommended by the Infectious Diseases Society of America [29].

Developing a CVD risk estimation tool specifically for HIV-infected patients is essential for risk-stratifying patients and determining timely prevention strategies. Patients estimated at high risk should begin preventative measures such as statin therapy, blood pressure control, and weight-loss programs [14]. Strict LDL-c cut-off such as LDL-c<100 mg/dL (LDL<115 mg/dL is recommended by the European AIDS Clinical Society) should be set for high risk patients, and if LDL-c persists above these cutoffs or their ART regimen is suspected as

contributing to dyslipidemia, providers could consider modifying the ART regimen [30]. Those stratified as low risk may continue routine screening and lifestyle modification [14]. For patients at intermediate CVD risk, additional testing with non-invasive imaging modalities such as coronary computed tomography angiography or exercise stress test should be pursued to further stratify their risk. Markers of inflammation such as high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) have been associated with increased CVD risk in the general population, and both have been found to be elevated in HIV-positive patients compared to uninfected patients [31,32]. Testing hsCRP and IL-6 levels in HIV-infected patients at intermediate CVD risk may prove useful in selecting those that may benefit from initiating preventive therapy (i.e., patients calculated at intermediate CVD risk but with elevated inflammatory markers), and at the very least, such a strategy warrants further investigation. Soluble CD163 (sCD163), a marker of macrophage/monocyte activation, has been associated with atherosclerotic plaque formation in both the general and HIV populations [33,34]. Therefore, measuring levels of sCD163 level may help identify other patients who may benefit from starting preventive therapy if they appear ineligible for initiation of CVD preventive therapies based on non-invasive testing or hsCRP or IL-6. Such graded level testing using different inflammatory and immune markers should be investigated in future studies to inform clinicians how to discriminate among intermediate risk HIV-infected patients.

As the morbidity and mortality from CVD in the HIV population increases, so too must preventive and therapeutic efforts to provide these patients with the best care. This all begins with accurate CVD risk assessment.

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