Cardiovascular risk prediction in patients with HIV infection

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“The identification of the most appropriate tool for estimating cardiovascular risk is of paramount importance to curb the increasing incidence of CVD in patients with HIV infection.”

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In recent years, several studies have shown that patients with HIV infection have increased risk for cardiovascular events [1–3]. A meta-analysis of 80 longitudinal studies concluded that patients living with HIV have 2.16-times higher risk for cardiovascular disease (CVD) than individuals without HIV [1]. In addition, CVD has become a leading cause of mortality in patients with HIV infection [4,5].

Guidelines for the management of cardiovascular risk factors including hypertension and dyslipidemia emphasize that treatment goals depend on the total cardiovascular risk [6,7]. In patients with higher cardiovascular risk, cardiovascular risk factors should be managed more aggressively whereas treatment targets are less strict in lower-risk subjects [6,7]. Cardiovascular risk estimation is therefore essential for defining treatment targets [6,7].

The most widely used tools for estimating cardiovascular risk in the general population are the European Systematic Coronary Risk Evaluation score (SCORE) and the Pooled Cohort Equations, which are recommended by the European Society of Cardiology and the American College of Cardiology/American Heart Association, respectively [8,9]. However, these equations include only traditional cardiovascular risk factors, in other words, age, gender, smoking status, blood pressure and cholesterol levels [8,9]. This represents a major limitation when applying these equations in patients with HIV infection because HIV infection-specific risk factors also contribute to the increased risk of cardiovascular events in this population. Indeed, subclinical inflammation and low CD4 counts are independently associated with cardiovascular morbidity in patients with HIV infection [10–12]. Moreover, several classes of antiretroviral agents, including protease inhibitors and NRTIs, also appear to increase the cardiovascular risk of this population, partly due to their adverse metabolic effects [13,14]. Accordingly, two recent studies performed in the US reported that the Pooled Cohort Equations have moderate discrimination, poor calibration and underestimate cardiovascular risk in patients with HIV infection [15,16].

The D:A:D study equation versus SCORE & the pooled cohort equations

To overcome these limitations of cardiovascular risk estimation equations, the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study equation has been developed [17]. This equation derives from the study of patients with HIV infection followed up in 20 European countries and Australia and includes both traditional cardiovascular risk factors (age, sex, smoking status, blood pressure, cholesterol levels, diabetes mellitus and family history of CVD) and HIV-related risk factors, namely CD4 cell count, present treatment with abacavir and protease inhibitor and NRTI exposure [17]. An additional advantage of the D:A:D study equation is that it predicts cardiovascular risk in patients 18–40 years old whereas both the SCORE and the Pooled Cohort Equations are limited to patients older than 40 years old [8,9,17].

Despite the strengths of the D:A:D study equation, it is however unclear as to whether it predicts cardiovascular risk more accurately than the SCORE and the Pooled Cohort Equations. Only one study thus far has compared

the predictive ability of these three equations, which reported that the Pooled Cohort Equations and the D:A:D score have similarly high levels of discrimination, but both have moderate calibration levels and underestimate cardiovascular risk [18]. In contrast, the SCORE showed worse discrimination and calibration and overestimated cardiovascular risk [18]. Even though this study was relatively large ($n = 2283$), it has a number of limitations. First, since it was performed in the US, it was somewhat expected that the SCORE would not be as accurate as the Pooled Cohort Equations, given that the former was developed in European populations and the latter in the US. Second, the median follow-up of this study was rather short (6.5 years) and only 30.3% of the patients ($n = 692$) had ≥ 10 years of follow-up [18]. Given that the SCORE and the Pooled Cohort Equations predict 10-year risks, the authors had to hypothesize that cardiovascular risk remains constant over time, which might have affected their findings. Third, 34% of the study population was Black and 12.9% was Hispanic; it is therefore unclear whether these findings can be extrapolated to other populations [18]. In another large study from Italy ($n = 2550$), the Pooled Cohort Equations and the D:A:D study equation showed comparable predictive value [19]. However, this study also had a relatively short follow-up (6.5 years) and did not evaluate the performance of the SCORE [19]. Notably, several small cross-sectional studies reported that the D:A:D study equation, the SCORE and the Pooled Cohort Equations show only moderate agreement [20–24].

Role of other biomarkers in risk prediction

In addition to these cardiovascular risk prediction equations, other cardiovascular risk markers have also been proposed as a tool for improving risk stratification. In the general population, elevated levels of hsCRP, a marker of subclinical inflammation, are associated with increased incidence of cardiovascular events [25,26]. In a meta-analysis of 54 observational studies ($n = 160,309$ subjects without established CVD), each threefold increase in hsCRP levels was associated with a 37% increase in the risk for coronary heart disease and with a 55% increase in the risk for cardiovascular mortality [25]. However, in a more recent meta-analysis of 52 observational studies ($n = 246,669$ subjects without established CVD), measurement of hsCRP levels changed the risk category in only 1.5% of patients and it was estimated that hsCRP levels should be measured in 440 moderate-risk patients to prevent one cardiovascular event within the next decade [26]. In patients with HIV infection, conflicting results have been reported regarding the predictive value of hsCRP levels [27]. More importantly, it is unclear whether measuring hsCRP levels improves risk stratification in this population when added to a predictive risk equation [27]. Markers of subclinical atherosclerosis have also been shown to predict cardiovascular events in the general population [28–30]. In a meta-analysis of eight observational studies ($n = 37,197$ subjects without established CVD), each increase in carotid intima-media thickness (cIMT) by 0.1 mm was associated with a 15% increase in the incidence of coronary heart disease and with an 18% increase in the incidence of ischemic stroke [28]. However, in a more recent and larger meta-analysis of 14 observational studies ($n = 45,828$ subjects without established CVD), measuring cIMT resulted in risk category reclassification in only 3.6% of moderate-risk subjects [29]. In patients with HIV infection, a recent meta-analysis of 17 cross-sectional studies showed that these patients have higher cIMT than uninfected controls [31]. However, the progression of cIMT did not differ between the two groups in a meta-analysis of five cohort studies [31]. More importantly, it is unclear whether measurement of cIMT in these patients improves risk stratification when incorporated in risk prediction equations. A higher coronary artery calcium score is also associated with increased cardiovascular risk in the general population and its measurement resulted in a change in risk category of 14–24% intermediate risk patients in a meta-analysis of four observational studies ($n = 13,969$ subjects without established CVD [30]. However, this marker of subclinical atherosclerosis appears to be of limited value in young subjects [30].

Conclusion

In conclusion, it is unclear which equation is the most accurate for cardiovascular risk prediction in patients with HIV infection. Limited data suggest that the D:A:D study equation is not superior than the Pooled Cohort Equations both in the US and in Europe. However, it is unknown whether the D:A:D study equation is better, worse and equivalent with the SCORE for risk prediction in European populations. Therefore, there is a pressing need for more studies that will compare the discrimination and calibration of these three equations in patients with HIV infection. More studies are also needed to clarify the role of other biomarkers or markers of subclinical atherosclerosis in risk prediction in this high-risk population. The identification of the most appropriate tool for estimating cardiovascular risk is of paramount importance to curb the increasing incidence of CVD in patients with HIV infection.

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