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Cardiovascular risk assessment in HIV-infected male patients: a comparison of Framingham, SCORE, PROCAM and DAD risk equations

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Abstract

Introduction: Traditional cardiovascular (CVD) risk assessment algorithms such as the Framingham Risk Score (FRS), Systematic Coronary Risk Evaluation (SCORE) and Prospective Cardiovascular Munster (PROCAM) were developed for general populations, their usefulness in HIV-infected population has not been confirmed. DAD algorithm was developed specifically for HIV-infected patients. The aim of our study was to evaluate the performance of risk assessment algorithms in HIV-infected population.
Methods: A prospective cross-sectional national study that included 83 HIV-infected male patients from Slovenia below the age of 55 was performed. CVD risk was assessed using four algorithms, the presence of subclinical atherosclerosis was determined by measuring carotid intima-media thickness (CIMT); patients were followed up for 5 years.
Results: High proportion of patients with low CVD risk according to FRS (61.9%) and PROCAM (81.0%) and only 7.1% according to SCORE had evidence of subclinical atherosclerosis. Only 7.1% of patients with low CVD risk according to DAD algorithm had evidence of subclinical atherosclerosis.
Conclusion: Our study has shown that SCORE and DAD algorithm were superior to FRS and PROCAM. In younger HIV-infected patients, even with moderate CVD risk, CIMT assessment should be employed in a complete clinical evaluation as a more aggressive prevention and treatment approach is warranted.

Keywords: HIV infection, Framingham Risk Score, PROCAM, SCORE, 5-year DAD risk equation

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Introduction

Introduction of combination antiretroviral therapy (CART) has led to a markedly reduced morbidity and mortality among HIV-infected persons (1). The increase in life expectancy appears to be coupled with increased incidence of cardiovascular disease (CVD) as a significant cause of morbidity and mortality among HIV-infected patients treated with CART. The extent to which increased CVD risk among HIV-infected patients can be attributed to the traditional risk factors, HIV infection itself, or the use of CART is unclear (2, 3). Various studies have demonstrated that HIV-infected patients had an increased prevalence of subclinical atherosclerosis when compared to HIV-uninfected control groups, even after accounting for traditional CVD risk factors (4-6). Pathogenesis of accelerated atherosclerosis in HIV infection is complex and probably differs between treatment-naïve and patients receiving CART. Before initiation of CART inflammatory processes and HIV infection itself probably play a more significant role, while metabolic factors may become more important in patients receiving CART (7).

As the life expectancy of HIV-infected population increases and population ages, assessment of individual's CVD risk has become an important part of routine clinical evaluation as a more aggressive treatment approach in high-risk patients aimed to delay the progression of atherosclerosis may be warranted.

Traditional cardiovascular risk assessment algorithms such as the Framingham Risk Score (FRS) were developed for general populations and their usefulness in HIV-infected population has not been confirmed (8, 9). Various studies have compared usefulness of different approaches to estimate CVD risk in HIV-infected populations, mainly using the FRS, Prospective Cardiovascular Munster (PROCAM) risk score and Systematic Coronary Risk Evaluation (SCORE) equations (10-14). One algorithm based on the results of a large multicentre cohort study (Data Collection on Adverse Effects on Anti-HIV Drugs Cohort; DAD) was specifically developed for HIV-infected patients (15). Few studies have evaluated usefulness of DAD risk equation for routine CVD risk estimation so far (12, 14, 16).

Slovenia has relatively low incidence of HIV infection compared to most other countries in the European Union (21.9/1.000.000 in 2013), with consistent predominance of males among the infected population (86.5%). As our HIV-infected population is ageing, CVD risk assessment has become an important part of routine clinical evaluation. Between 1986-1995 29.7% of the patients were over the age of 40 and 10.8% over 50. In the last decade 40.5% of Slovenian HIV-infected patients were over the age of 40 and 15.1% over 50 (17, 18). All Slovenian HIV-infected patients are followed up centrally at the Department of Infectious Diseases, University Medical Centre Ljubljana (UMCL).

The aim of our study was to determine the CVD risk using three different scoring systems which determine 10-year risk of CVD – FRS, PROCAM, SCORE – as well as 5-year risk of CVD based upon DAD risk equation and to compare these results with the presence of early atherosclerosis as determined by carotid intima-media thickness (CIMT) in younger HIV-infected patients below the age of 55. The study group was followed up for 5 years and monitored for signs of CVD.

Patients and Methods

A prospective cross-sectional national study was performed at the

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Department of Infectious Diseases, UMCL, Slovenia. The investigation was approved by the Ethics Committee For Clinical Research.

Patients

Eighty-six consecutive HIV-infected male patients who were diagnosed as HIV-positive between 1986 and 2006 participated in our study. The study population is described in detail elsewhere (19). Patients lacking all required data for risk assessment evaluations were excluded from this post hoc analysis; in total 83 HIV-infected male patients were included. Inclusion criteria were HIV infection for more than one year, male gender and age below 55 years. Exclusion criteria were overt cardiovascular diseases, diabetes mellitus type 1, active opportunistic diseases and malignancy. Patients' history was recorded; physical examination and routine laboratory tests were performed in all subjects. All patients included in our study continued with regular routine check-ups at the Department of Infectious Diseases. Patients were followed up for 5 years.

CVD risk score

FRS is based on age, gender, systolic and diastolic blood pressure, total and HDL cholesterol levels, the presence of diabetes and smoking status. The patients were classified as having low (< 10%), medium (10 to 20%) or high (> 20%) cardiovascular risk (20).

PROCAM takes into account gender, age, serum HDL and LDL cholesterol and triglyceride levels, smoking status, diabetes, family history of coronary heart disease and systolic blood pressure. The patients were classified as having low (< 10%), medium (10 to 20%) or high (> 20%) cardiovascular risk (21).

SCORE is based upon gender, age, systolic blood pressure, smoking status and total cholesterol/HDL cholesterol ratio. As Slovenia is among low-risk regions of Europe, the risk chart for low-risk countries was used. The patients were classified as having low (< 1%), medium (≥ 1 to < 5%), high (≥ 5 to < 10%) or very high (≥ 10%) cardiovascular risk (22).

DAD risk equation takes into account age, gender, total and HDL cholesterol, smoking status (current or past), blood pressure, history of diabetes, family history of CVD, and exposure to indinavir, lopinavir and abacavir. They were classified as having low (< 1%), moderate (1 to 5%), high (5 to 10%) or very high (>10%) risk of CHD over a 5-year period (15). DAD risk score was calculated using web based risk calculator (http://www.cphiv.dk/TOOLS/tabid/437/Default.aspx). High- and very high-risk patients were subsequently grouped into a single high-risk category (≥ 5%) to simplify comparison.

Carotid intima media thickness measurement

CIMT was assessed by the B-mode high-resolution ultrasound technique (Diasonics VST ultrasound system) with a 10 MHz linear probe following a standard procedure as described previously (23, 24). Increased CIMT was defined as more than 0.8 mm thick carotid intima media ($CIMT_{>0.8mm}$) (25, 26). Plaque was defined as a focal structure that encroached into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrated a thickness 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface (27).

Statistical analysis

Statistical analysis was performed using statistical software IBM SPSS Statistics version 20.0 (IBM corp., NY, USA). We used Mann–Whitney U-test to compare continuous variables and Fisher's exact test or chi-squared test for categorical variables. Concordance between different CVD risk assessment algorithms was assessed using the kappa coefficient.

Results

The main baseline characteristics of 83 HIV-infected participants are shown in Table 1. Majority of the patients were determined to have low 10-year CVD risk according to FRS and PROCAM (72.3 and 88.0% respectively), while SCORE placed majority of the patients (66.3%) in moderate risk group. High 10-year CVD risk was found in 8.4% of the patients according to FRS and 7.2% according to SCORE risk evaluations. The observed agreement between FRS and PROCAM was 77.1% (κ 0.329; p 0.000), between FRS and SCORE 50.6% (κ 0.268; p 0.000) and between PROCAM and SCORE 32.5% (κ 0.018; p 0.000).

Results of risk score calculation were compared to the presence of subclinical atherosclerosis. $CIMT_{>0.8mm}$ was found in 42 patients (50.6%), while carotid plaques were found in 12 (14.5%). The relationship between the presence of subclinical atherosclerosis and CVD risk is shown in Table 2. We found some concordance between FRS, PROCAM and SCORE CVD risk and subclinical atherosclerosis (60.2%, 56.6% and 69.9% respectively). High proportion of HIV-infected patients with low CVD risk as estimated by FRS and PROCAM already had evidence of subclinical atherosclerosis (61.9% and 81.0% respectively). SCORE risk assessment algorithm placed only three (7.1%) patients with subclinical atherosclerosis into low-risk group.

When 5-year DAD risk equation was applied, 21 (25.3%) patients were classified as having low CVD risk, 51 (61.4%) as medium risk, 7 (8.4%) as high risk and 4 (4.8%) a very high CVD risk. The observed agreement between 5-year DAD risk equation was 53.0% in case of FRS (κ 0.246; p 0.001), 37.3% in case of PROCAM (κ -0.045; p 0,304) and 32.5% in case of SCORE (κ was 0.533; p 0.000). Only three (7.1%) of HIV-infected patients who had low CVD risk according to 5-year DAD risk equation already had evidence of subclinical atherosclerosis (the same patients as those with low SCORE and $CIMT_{>0.8mm}$).

During the 5-year follow up majority of patients, 71 (85.5%), had shown no symptoms or signs of CVD, three (3.6%) have died due to non-CVD cause and six (7.2%) were lost to follow-up. Patient No. 12, age 49.2 years, smoker, suffered acute myocardial infarction (single-vessel disease) two years after inclusion in the study and developed peripheral arterial disease. He was on non-protease inhibitor based CART for 88 months at the initiation of the study, BMI was 24.4, CD4 cell count was 493 cells/mm3 with HIV RNA viral load below level of detection. Dyslipidemia was present with 6.2 mmol/dL total, 1.1 mmol/dL HDL and 4.7 mmol/dL LDL cholesterol serum levels and 1 mmol/dL triglycerides level. Increased CIMT with carotid plaques was found. All risk assessment algorithms have shown moderate 10-year CVD risk with FRS 16%, PROCAM 10% and SCORE 4%. 5-year CVD risk according to DAD was also moderate at 4.5%.

Discussion

We have investigated the usefulness of CVD risk assessment algorithms to improve clinical evaluation of young Slovenian HIV-infected patients below the age of 55 with no symptoms or signs of CVD by comparing it with results of CIMT measurements.

Table 1 | **Basic demographic and clinical characteristics of study participants.**

Species Group	HIV-infected patients (all)	Subclinical atherosclerosis		p value
		No	Yes	
Number (%)	83	41	42	
Gender	Male 83 (100.0)			
Age (SD)	39.6 (8.555)	34.8 (1.272)	43.8 (1.285)	0.000
Duration of HIV infection (%)	8.9 (6.44)	7.8 (1.07)	9.7 (1.108)	0.070
‹ 5 years	25 (30.1)	15 (36.6)	10 (23.8)	
5-10 years	15 (18.1)	9 (22.0)	6 (14.3)	
10-15 years	16 (19.3)	5 (12.2)	11 (26.2)	
› 15 years	13 (15.7)	4 (9.8)	9 (21.4)	
Not known	14 (16.9)	8 (19.5)	6 (14.3)	
Antiretroviral therapy (CART)	59 (71.1)	26 (63.4)	33 (78.6)	0.281
treatment-naive	24 (28.9)	15 (36.6)	9 (21.4)	
CART - PI based	27 (32.5)	11 (26.8)	16 (38.1)	
CART – non-PI	32 (38.6)	15 (36.6)	17 (40.5)	
Duration of exposure to CART, years (SD)	3.3 (3.16)	3.1 (0.49)	4.1 (0.581)	0.014
HIV RNA viral load ‹ 40 copies/mL (%)	50 (60.2)	23 (56.1)	27 (64.3)	0.505
CD4 cell count, cells/mm3 (study)	468.0 (259.02)	520.6 (46.956)	417.22 (40.845)	0.350
Body mass index, kg/m2	24.3 (2.404)	24.382 (0.448)	24.4 (0.468)	0.410
Waist-hip ratio	1.08 (0.073)	1.07 (0.016)	1.08 (0.01)	0.350
Dyslipidemia, No. (%)	24 (28.9)	7 (17.1)	17 (40.5)	0.029
Triglycerides, mmol/dL	2.89 (3.46)	3.4 (0.98)	2.7 (0.412)	0.290
HDL cholesterol, mmol/dL	1.2 (0.25)	1.2 (0.451)	1.2 (0.042)	0.243
Total cholesterol, mmol/dL	5.8 (1.44)	6.1 (0.228)	5.9 (0.253)	0.483
LDL cholesterol, mmol/dL	3.4 (1.03)	3.6 (0.196)	3.5 (0.169)	0.619
Hypertension, No. (%)	4 (4.8)	0 (0.0)	4 (9.5)	0.116
Diabetes mellitus, type II No. (%)	9 (10.8)	2 (4.9)	7 (16.7)	0.156
Family history of early coronary disease, No. (%)	4 (4.8)	1 (2.4)	3 (7.1)	0.616
Smoker, No. (%)	47 (56.6)	22 (53.7)	25 (59.6)	0.661

Table 2 | **Relationship between the presence of subclinical atherosclerosis and CVD risk as determined by 5- and 10-year CVD risk assessment algorithms. Moderate- and high risk scores were grouped into single category.**

	Subclinical atherosclerosis ($CIMT_{>0.8mm}$)				
	No		Yes		
Risk score	Low	Moderate/high	Low	Moderate/high	p value (Fisher's Exact Test)
10-year risk					
FRS	34 (82.9)	7 (17.1)	26 (61.9)	16 (38.1)	0.049
PROCAM	39 (95.1)	2 (4.9)	34 (81.0)	8 (19.0)	0.088
SCORE	19 (46.3)	22 (53.7)	3 (7.1)	39 (92.9)	0.000
5-year risk					
DAD	18 (43,9)	23 (56,1)	3 (7,1)	39 (92,9)	0.000

In our study 27.7% of HIV-infected patients had 10-year CVD risk over 10% according to FRS which is similar to several other studies of FRS in HIV-infected patients (10,11,28,29). De Socio et al have analysed treatment-naïve HIV-infected patients and found that FRS had slightly better predictive value than SCORE and that 55% of patients with intermediate risk already had subclinical carotid lesions (30). The prevalence of HIV-infected patients with medium 10-year CVD risk according to PROCAM was much lower (12.0%) and none of the patients were found to be at high risk. This is lower than some other studies, these have however included larger patient population (10,11). The prevalence of HIV-infected patients with medium 10-year CVD risk according to SCORE was much higher (66.3%) and 7.2% were found to be at high risk. This is higher than some other studies which have, however, stratified patients according to older European Society of Cardiology (ESC) guidelines (10,11,30). The agreement between different 10-year risk assessment algorithms was fair between FRS and SCORE (κ 0.268), FRS and PROCAM (κ 0.329) and poor between PROCAM and SCORE (κ 0.018). Similar results regarding FRS and PROCAM were reported by two other studies, while results for SCORE cannot be compared as we have followed newer ESC guidelines (10,11).

The usefulness of these CVD risk assessment algorithms which were developed by studying general population for CVD risk assessment in HIV-infected patients remains unclear (8). We have evaluated the agreement of 10-year CVD risk assessment algorithms with the presence of subclinical atherosclerosis in Slovenian HIV-infected patients below the age of 55. We have found that FRS and PROCAM evaluated CVD risk as low in a high proportion of HIV-infected patients with evidence of subclinical atherosclerosis as measured by CIMT (61.9% and 81.0% respectively). Several studies have similarly found that a high proportion of patients with an estimated low risk had subclinical atherosclerosis and that FRS underestimated the presence of subclinical atherosclerosis as defined by CIMT measurement (30,31). According to SCORE only 7.1% of HIV-infected patients with evidence of subclinical atherosclerosis as measured by CIMT were assigned low CVD risk. Our results have shown that FRS and PROCAM algorithms underestimate CVD risk as they fail to identify a large proportion of patients which could benefit from more vigorous prevention and eventually treatment measures. CVD risk assessment using SCORE algorithm interpreted according to ESC 2012 guidelines identified majority (92.9%) of patients with subclinical atherosclerosis as moderate to high risk patients. SCORE algorithm thus appears to improve clinical assessment of CVD risk HIV-infected patients.

5-year DAD risk equation was developed in HIV-infected population and takes into account traditional risk factors as well as exposure to three different HIV medications. When applied to our study group only three (7.1%) of HIV-infected patients who had

low CVD risk according to 5-year DAD risk equation already had evidence of subclinical atherosclerosis as measured by CIMT, majority of patients with $CIMT_{>0.8mm}$ were classified into either moderate or high/very high risk group. This algorithm appears to be better suited for estimation of CVD risk in HIV-infected population than FRS or PROCAM. Interestingly both 5-year DAD risk equation and 10-year CVD risk equation using SCORE have identified 74.7% and 73.5% respectively as moderate to high risk patients, both algorithms have assigned low CVD risk to only three (7.1%) of HIV-infected patients who already had evidence of subclinical atherosclerosis as measured by CIMT.

When assessing the usefulness of CVD risk assessment algorithms in comparison with CIMT measurements, one must consider the fact that these algorithms were not developed to predict coronary or carotid atherosclerosis, but rather cardiovascular events such as myocardial infarction or sudden cardiac death depending on the algorithm. Thus direct comparison with subclinical atherosclerosis as assessed by CIMT may show discordant results, nonetheless these algorithms aid clinical assessment of the patient to determine how intensively to intervene on lifestyle and whether medication in correspondence with individual's cardiovascular risk factors is indicated.

During the 5-year follow-up three patients developed symptoms and signs of CVD, one patient suffered AMI and developed PAD, the other two patients developed angina pectoris. Angina pectoris is not an endpoint in risk assessment algorithms but indicates more advanced cardiovascular lesions. All 10-year CVD risk scores and 5-year DAD risk equation have classified the patient who developed AMI and PAD in moderate-risk category. One of the patients with angina pectoris was classified into moderate risk group, the other patients into low-risk group by FRS and PROCAM risk assessment tools and in moderate-risk group by SCORE and 5-year DAD risk equation.

In HIV-infected patients with early atherosclerosis a more aggressive prevention and treatment measures aimed to delay the progression of atherosclerosis may be warranted. All patients that have participated in our study with $CIMT_{>0.8mm}$ have been placed on active primary prevention regime to reduce CVD risk in correspondence with individual's cardiovascular risk factors – implementation of antihypertensive, lipid-lowering or anti-aggregative medication, if indicated, maintenance of normal levels of serum glucose in combination with promotion of healthier lifestyle, especially smoking cessation and encouragement of physical activity. During the five-year follow-up six patients were lost to follow-up, three have died from non-CVD related illness. Among the remaining patients two patients developed angina pectoris and one patient had both myocardial infarction and PAD. Follow up is on-going.

The main limitation of our study is that only male patients were included and that the results therefore cannot reflect the situation or simply be transferred to female or mixed HIV-infected population. On the other hand at the end of 2013 86.5% of all HIV-infected individuals in Slovenia were male and therefore these results are very useful for Slovenian HIV-infected population.

Conclusion

CVD risk assessment algorithms were developed in general populations to aid clinicians in clinical evaluation of the patients. These algorithms may not accurately predict CVD risk for HIV-infected patients as additional HIV-related risk factors are present such as chronic inflammation and metabolic syndrome. Due to notable extension of life expectancy in HIV-infected patients CVD complications are becoming more frequent as this population ages. This indicates the necessity of routine screening, appropriate monitoring and management of the broad spectrum of risk factors contributing to CVD complications. Our study which included young Slovenian HIV-infected male patients below the age of 55 has demonstrated that SCORE and DAD risk equation were superior to FRS and PROCAM. In younger HIV-infected male patients even with moderate CVD risk CIMT assessment should be employed in complete clinical evaluation. In HIV-infected male patients with early atherosclerosis a more aggressive prevention and treatment approach in correspondence with individual's cardiovascular risk factors is necessary.

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