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Risco cardiovascular estimado em doente com VIH

Estimated cardiovascular disease risk in HIV-infected patients

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/ Resumo

Introdução: As recomendações atuais preconizam a avaliação do risco de doença cardiovascular (DCV) em pessoas que vivem com VIH de forma rotineira e regular, usando modelos convencionais de predição de risco. No entanto, os calculadores de risco desenvolvidos na população geral podem ser imprecisos para estimar o risco de DCV em pessoas com VIH. O objetivo do estudo é avaliar o risco cardiovascular em pessoas com HIV utilizando diferentes calculadores de risco e comparar a ocorrência estimada e real de eventos cardiovasculares.

Métodos: Estudo longitudinal em pessoas com VIH com idades entre os 30 e os 75 anos, que frequentam consulta hospitalar num hospital terciário. Dados coletados a partir dos registos médicos durante um período de 5 anos. Os algoritmos de risco clínico (Framingham, modelo D:A:D completo e reduzido) foram calculados e comparados com a ocorrência real de eventos cardiovasculares durante o período de seguimento.

Resultados: Oitenta e sete pesssoas com VIH foram incluídas; a mediana de idade foi de 44 anos, sendo 60,9% do sexo masculino. A mediana do risco foi de 2% para o *score* de Framingham, 3% para D:A:D completo e 2% para o D:A:D reduzido. Seis doentes (6,9%) apresentaram eventos cardiovasculares. A equação de Framingham apresenta uma forte correlação com o modelo completo D:A:D e correlação muito forte com o modelo D:A:D reduzido; os modelos D:A:D completo e reduzido apresentam uma correlação muito forte entre si.

Conclusão: Os calculadores de risco cardiovascular subestimaram o risco cardiovascular nesta população (6,9% vs 2,5-3,5%), embora as três pontuações apresentem uma correlação muito boa entre si.

Palavras-chave: VIH; risco cardiovascular; Terapia anti-retroviral; enfarte agudo do miocárdio; Doença cerebrovascular

/ Abstract

Background: *Current guidelines recommend assessment of cardiovascular disease (CVD) risk in HIV-infected patients routinely and regularly, using conventional risk prediction models. However, cardiovascular risk score developed in non-HIV population may be inaccurate to estimate CVD risk in HIV-patients. The aim of the present study is to evaluate the prevalence of cardiovascular risk factors among HIV patients using different risk score and compare the estimated and real occurrence of cardiovascular events.*

Methods: *Cross-sectional study in HIV-infected patients aged between 30 and 75 years old attending the public HIV clinic in a tertiary Portuguese hospital. Data were collected from the medical records of the patients who attended in 2011. Medical records were reviewed during 5 years follow-up regarding the occurrence of new cardiovascular events. Clinical risk scores (Framingham, D:A:D full and reduced model) were calculated at baseline assessment and compared among each other and with the real occurrence of cardiovascular events during follow-up period.*

Results: *Eighty-seven HIV patients were included, median age was 44 years, 60.9% male. The median cardiovascular risk score was 2% for Framingham score, 3% for D:A:D full and 2% for D:A:D reduced model. Six patients (6.9%) presented cardiovascular events. Cardiovascular risk scores were significantly higher in these patients ($p<0.05$). Framingham score presents a strong correlation with D:A:D full model and very strong correlation with D:A:D reduced model; D:A:D full and reduced model present a very strong correlation.*

Conclusion: *We observed that cardiovascular risk scores underestimated the cardiovascular risk in this population (6.9% vs 2.5-3.5%). Although the three scores present a very good correlation among themselves.*

Keywords: *HIV; Cardiovascular risk; Antiretroviral therapy; Acute myocardial infarction; Cerebrovascular disease*

/ Background

Over the last decades, the increase in survival of people living with HIV has contributed to the emergence of cardiovascular and metabolic diseases.[1,2,3,4,5] Although highly active anti-retroviral therapy (HAART) has reduced morbidity and mortality among HIV patients, it is recognized as independent cardiovascular risk factor.[1,2,3,4,6]

A recent systematic review and meta-analysis conclude that HIV patients have a higher risk of death and vascular disease that uninfected population.The magnitude of the risk differs by region (USA HIV patients present a higher risk that European).[7]

HIV has been linked to arterial stiffness, pro-inflammatory activation, hypertension which may lead to vascular dysfunction.[1] The mechanism of the increased risk of cardiovascular disease (CVD) among people with HIV infection is multifactorial, mainly supported by dyslipidemia and insulin resistance.[3]

Observational studies have consistently demonstrated that HIV increases the risk of coronary heart disease, heart failure, ischemic stroke and sudden cardiac death.[3,6] Although the majority of participants were men, another article confirms HIV-infected women also have an increased risk.[8]

Current guidelines recommend assessment of CVD risk routinely and regularly, using conventional risk prediction models, such as Framingham, or using prediction model tailored to the HIV-infected population, such as D:A:D model. However, cardiovascular risk score developed in non-HIV population may be inaccurate to estimate CVD risk in HIV-patients, since they do not take into account HIV-parameters (ie. HAART, chronic inflammation, immune activation).[5,6]

D:A:D group developed a full model that incorporates TCD4 lymphocytes count and exposure to HAART and a reduced model that is based on conventional cardiovascular risk factors and TCD4 lymphocytes count only.[6]

The aim of this study is to evaluate the prevalence of cardiovascular risk factors among HIV patients attending an HIV clinic in Portugal, using different cardiovascular risk scores and to compare the estimated risk with the real occurrence of cardiovascular events.

/ Methods

A cohort study was conducted involving HIV-infected patients aged between 30 and 75 years old attending the public HIV clinic in a tertiary hospital.

The data were collected from the medical records of all patients who attended between January and December 2011 to their doctor's appointment (CS). The first medical appointment during 2011 for each patient was selected.

Patients were excluded if had no medical records from 2011, if were infected with HIV-2 and were younger than 30 or older than 75, due to inability to calculate cardiovascular risk score and if they had had previous cardiovascular event.

Data collected included demographic, analytical and therapeutic data required to calculate three cardiovascular risk scores (Framingham, D:A:D full and reduced model) – age, gender, history of smoking, family CVD history, diabetes, treatment with abacavir, years of exposure to nucleoside reverse-transcriptase inhibitors (NRTI) and Protease inhibitors (PI), Blood pressure lowering treatment, TCD4 lymphocytes count, systolic blood pressure, total cholesterol and HDL. For better characterization of the population nationality, ethnicity, age of diagnose and duration of disease, duration of HAART therapy and plasma VIH RNA level (viral load) were also collected.

Blood pressure was measured using a calibrated automated machine in a sitting position by the nurse team before medical appointment.

During 5 years follow-up (since 2011 till 2016) medical records were reviewed regarding the occurrence of new cardiovascular events (i.e., stroke, acute coronary syndrome, peripheral arterial disease).

Clinical risk scores were calculated and compared among each other and with the real occurrence of cardiovascular events.

Data analyses included descriptive statistics with numbers (proportions) for categorical variables and median (Q25-Q75) for continuous variables. Categorical variables were compared using a chi-squared test or Fisher exact test and quantitative variables by Mann-Whitney test. Continuous variables were correlated using Spearman correlation. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed in SPSS v21.

/ Results

Characteristics of the study population

Ninety-nine HIV-patients were analyzed, 12 patients were excluded due to age, HIV-2 infection or missing data. Eighty-seven patients included, median age was 44 [40-54] years, 60.9% were male, 74,7% were Portuguese. The majority of participants (88.5%) were on continuous HAART. The median time since diagnosis of HIV infection was 10 [7-12.25] years.

The study population's characteristics are presented in table 1.

Assessment of the 5-year risk of CVD and Cardiovascular events

The median cardiovascular risk score was 2% [1-4%] for Framingham score, 3% [1-5%] for D:A:D full and 2% [1-3%] for D:A:D reduced model (Table 1).

Six patients (6.9%) presented cardiovascular events – 5 coronary heart disease and 1 peripheral artery disease. No patient present stroke. Cardiovascular risk scores were significantly higher in these patients ($p<0.05$). Five of the six patients were male and born in Portugal and age varies from 42 to 73 years old. Four of six were current smoker and one was previous smoker. None of them had type 2 diabetes mellitus and three had hypertension. All these patients had controlled infection with no detectable viral load and TCD4 lymphocytes > 200 cells. Two patients were previously exposed to abacavir, three patients were on protease inhibitors from 4 to 10 years and all patients were on nucleoside reverse transcriptase inhibitors from 7 to 14 years. Framingham score varies from 3.52% till 13.46%, DAD full from 3.01% till 15.97% and DAD reduced model from 3.01% till 8.56%.

Correlation among CVD risk scores

Regarding all population, Framingham score presents a strong correlation with D:A:D full model ($r=0.857$ $p<0.0001$) and very strong correlation with D:A:D reduced model ($r=0.909$ $p<0.0001$). D:A:D full and reduced model present a very strong correlation ($r=0.944$, $p< 0.0001$).

/ Discussion

The general objective of this study was to evaluate accuracy of CV risk scores for predicting cardiovascular events in HIV patients.

As key findings, we observed that CV risk scores underestimated the cardiovascular risk in this population (6.9% vs 2.5-3.5%). Although, the three scores present a very good correlation among themselves. Our population is constituted by middle-aged man, under HAART and with 5 to 22 years of disease. It is interesting to note that none of the patients had cerebrovascular event. In Portugal, distinctly to other European countries, cerebrovascular events are more frequent than coronary heart disease[9]. This could be related to an increased predisposition of HIV-patients to cardiac events comparing to cerebrovascular events.

TABLE 1 – POPULATION CHARACTERISTICS (N=87)	
Age (median (Q25;Q75))	44 (40; 54)
Male gender (%)	60.9%
Nationality	
Portugal	74.7%
Angola	10.3%
Cape Verde	5.7%
Mozambique	4.6%
Guinea-Bissau	3.4%
(Unknown)	1.1%
Antihypertensive treatment (%)	9.6%
Systolic Blood pressure (median (Q25;Q75)) mmHg	120 (109; 133)
Diabetes mellitus (%)	4.8%
Cholesterol (median (Q25;Q75))	
Total cholesterol (mg/dL)	185,5 (157.75; 217,5)
High density lipoprotein (mg/dL))	46 (37.75; 56)
Smoke status (%)	
Former smoker	7.4 %
Smoker	46.9%
Family history of premature cardiovascular disease	3.4%
Years since HIV diagnosis (median (Q25;Q75))	10 (7; 12.5)
Antiretroviral therapy (%)	88.5%
Abacavir exposure	16%
NRTI	
Number of patients	79
Years of treatment (median (Q25;Q75))	7.5 (5; 9)
PI	
Number of patients	44
Years of treatment (median (Q25;Q75))	2 (0; 6)
TCD4 lymphocytes	
Absolute count (median (Q25;Q75))	595.3 (380; 756,8)
Percentage	28 (20; 34)
Undetected viral load (%)	73.3%
Cardiovascular risk score	
5 year Framingham score (median (Q25;Q75))	2 (1;4) %
DAD full model (median (Q25;Q75))	3 (1; 4) %
DAD reduced model (median (Q25;Q75))	2 (1; 3%)
Cardiovascular events 5 years follow-up	
Coronary heart disease (%)	5.7%
Peripheral artery disease (%)	1.15%
Stroke (%)	0 %

NRTI: nucleoside reverse-transcriptase inhibitors; PI Protease inhibitors.

Recent article regarding African population present an even lower estimated cardiovascular risk using Framingham and DAD score, 0.7% [0.2-2%] and 0.6% [0.3-1.3%]. This could be related to the relatively young age of their participants (44.4±9.8 years) and the high proportion of females (80%).[3]

As known, HIV population have a higher CV risk. It is documented an increased risk of arterial coronary disease in HIV patients, and at a younger age when compared with the general population.[10] Hypertension is common among HIV infected individuals and is more prevalent in older and obese adults.Previous study indicated that a similar pattern of behavior for hypertension and comorbidities in HIV patients in comparison to the general population.[1] No significant association was also found between the HIV RNA level or TCD4 lymphocytes count and hypertension in this population.[1] Some studies reported a higher incidence of diabetes mellitus in HIV patients with exposure to HAART, four times higher when compared with non-HIV patients.[11]

We should also consider pathophysiologic mechanisms related to the virus, based on the immunodeficiency persistence, immune dysregulation, and inflammation virus-related.[12]

Additionally, HAART cause metabolic changes that gives an additional risk to these patients, such as metabolic syndrome.[13] Therefore, HAART contributes, on one hand, to reduce the endothelial damage, but on the other hand, to endothelial activation through metabolic changes in glycose and lipids.[14]

The present study has some limitation. There are many cardiovascular risk factors that are not included in the analyzed scores and could be important in global cardiovascular risk of HIV patients (ex: obesity, hepatitis C status, alcohol and cocaine use). The present study was done in a single outpatient clinic, based on medical records that were analyzed retrospectively. Although there were no missing data, since medical records were very informative affirming or denying cardiovascular risk factors and the occurrence of cardiovascular events.

On the other hand, the study also has several strengths. It was conducted with population undergoing clinical follow-up and having reliable information on HAART use. It includes a 5 years follow-up which gives information about the real occurrence of cardiovascular events.

Despite the low value of the cardiovascular risk score, 6.9% (6 patients) presented cardiovascular events. Although specific HIV-risk score seems to be comparable to general cardiovascular risk scores, as Framingham score, in our population the real occurrence of cardiovascular event was higher than the estimated risk. Further research is needed, with larger sample size to confirm our results and look for other cardiovascular variable that are not considered in currently cardiovascular risk estimation. However, these data reinforce the need to prevent cardiovascular disease in these patients by adopting healthy lifestyle habits, screening and early treatment of comorbidities.

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