Algorithms to Predict Cardiovascular Events in the General Population and HIV Patients

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Abstract

Objectives

To assess the accuracy of risk prediction algorithms used in the general population and an HIV-specific algorithm to predict hard cardiovascular events.

Methods

We compared the pooled equation algorithm (PE) proposed by the American Heart Association with the Framingham risk score (FRS) and the HIV-specific DAD (Data Collection on Adverse Effects of Anti-HIV Drugs) algorithm in a cohort of 2550 HIV+ patients followed for 17 337 patient-years.

Results

During follow-up we recorded 67 myocardial infarctions and 2 cardiovascular deaths. PE and FRS identified and missed the same number of events (44 of 69 identified by PE and 49 of 69 by FRS). Similarly, DAD and FRS predicted and missed the same number of events (38 of 64 and 44 of 64 identified, respectively). All algorithms showed moderate sensitivity, specificity and positive predictive values, but high negative predictive values. However, PE and DAD identified more patients with no events than FRS (13.8% and 9.3% net reclassification improvement, respectively).

Conclusions

All algorithms showed a modest predictive ability, although the PE and DAD algorithms identified more patients at low risk.

Introduction

Since cardiovascular disease has become a leading cause of mortality and morbidity in HIV+ patients [1], an accurate risk assessment is essential to implement risk reduction therapies. The algorithms used in the general population probably underestimate the severity of disease in HIV+ patient [2]. In fact, both the new pooled equation algorithm (PE) and the older Framingham risk score (FRS) failed to identify subclinical atherosclerosis in HIV+ patients [3]. To date there has not been a comparison of algorithms developed for the general population and HIV-specific algorithms to predict hard events, specifically the DAD (Data Collection on Adverse Effects of Anti-HIV Drugs) algorithm [4], that weighs in the contribution of ART to cardiovascular disease development in HIV+ patients. In this study, we report the observed incidence of hard cardiovascular events in a cohort of 2550 HIV+ patients followed for an average of 6.5 years and compare the risk predictions obtained with the FRS, new PE and DAD algorithm.

Methods

The risk profile of 2550 HIV-infected patients (34% women) was assessed at the Modena HIV Metabolic Clinic in Italy between January 2003 and September 2013. All data were stored in an electronic database, as previously described [5]. We excluded patients with prior cardiovascular events and patients <40 years of age, since the PE score cannot be calculated below this age. Diabetes mellitus was defined by the presence of a fasting glucose ≥126 mg/dL or the use of hypoglycaemic drugs. Hypertension was defined as a blood pressure >140/90 mmHg, in the seated position, or by the use of antihypertensive medications. Smoking was assessed as current smoking, non-smoking and pack-year history of smoking.

Biochemical parameters routinely collected included: serum creatinine, blood urea nitrogen, glucose, sodium, potassium, magnesium and a fasting lipid profile (total cholesterol, HDL and LDL cholesterol, triglycerides). Homeostatic model assessment (HOMA) was calculated according to the formula HOMA-IR [(glucose, mmol/L × 0.05551) × (insulin, mU/L)/22.5 g] [6]. BMI was calculated according to the formula: body weight (kg)/height2 (m). The FRS [7], PE risk score [8] as well as DAD risk score [4] were calculated for each patient according to the published equations, based on data collected during the first patient encounter, before any event had occurred.

The HIV stage was defined according to the CDC categories [10]. Cumulative time exposure to HAART drug classes (in months) and duration of known HIV status were recorded. All patients had received stable doses of HAART for a minimum of 6 months prior to study entry. Immunological biomarkers included complete blood cell count, CD4+ lymphocytes count, CD4+ nadir and HIV viral load. Non-fatal myocardial infarction and cardiovascular death were assessed via review of the medical records and death certificates and further verified during a clinic visit for non-fatal events.

Statistical Methods

The primary aims of the study were to (i) compare a 10 year FRS ≥6% threshold with a PE ≥7.5% threshold for the prediction of hard cardiovascular events, and (ii) compare a 5 year FRS ≥5.5% with a DAD ≥4.5% for the prediction of hard cardiovascular events in the same population (the DAD can only be calculated at 5 years). The 6% threshold for the FRS was chosen to verify whether lowering the threshold of the FRS algorithm to 6% may be equivalent to using the 7.5%

risk threshold proposed by the new PE algorithm [8]. The thresholds of 5.5% for FRS and 4.5% for the DAD score were the respective 75th percentile for each algorithm in the study population, and were therefore adopted as markers of high 5 year risk. Sensitivity, specificity and positive and negative predictive values were calculated for all algorithms. Differences in prediction were assessed using the net reclassification index (NRI) for events and non-events, corresponding to the changes in the true- and false-positive rates, respectively.

Results

During a follow-up of 17 337 patient-years, 67 non-fatal myocardial infarctions and 2 cardiovascular deaths were recorded (event rate of 3.98/1000 patient-years). Table 1 shows the clinical characteristics of the study cohort.

Test performance for 10-year risk models

A similar number of events was correctly predicted and missed by the PE ≥7.5% and FRS ≥6.0%; 44 of 69 and 49 of 69 events were correctly predicted, and 25 of 69 and 20 of 69 events were missed, respectively (Table 2). Only seven patients with events were classified differently by the two risk models: six patients were correctly classified as high risk by FRS but low risk by PE, while one was classified as high risk by PE but low risk by FRS. Among the patients who did not suffer an event, 30 were considered high risk by PE but not by FRS and 372 by FRS but not by PE. The test characteristics are shown in Table 2.

Test performance for 5-year risk models

Owing to the lack of all necessary information, the risk of cardiovascular events at 5 years with the DAD and FRS algorithms was calculated in 2314 of the 2550 patients in the cohort; among these 64 suffered events during follow-up and 2250 did not. A similar number of events was correctly predicted and missed by the DAD ≥4.5% and FRS ≥5.5% methods (Table 2). Only eight patients with events were classified differently with the two methods: seven patients were correctly classified as high risk using FRS ≥5.5% and one using DAD ≥4.5%. Among patients who did not suffer an event, 238 were considered high risk by FRS but not by DAD and 28 by DAD, but not by FRS.

Net reclassification Improvement

The NRI for non-events was 13.8% and 9.3% for PE and DAD, respectively, suggesting that they correctly classified more individuals without events, compared with FRS. In contrast, FRS was better in the prediction of events at both 5 and 10 years since both PE and DAD correctly predicted a smaller proportion of events (NRIs for events: −7.2% and −9.4%, for PE and DAD, respectively).

Discussion

In a large observational cohort of HIV+ patients the algorithms developed for the general population to estimate risk and the new DAD algorithm performed equally for the prediction of events. However, the PE and DAD models were slightly more accurate than the previous FRS at excluding risk. Therefore, the small benefit of employing the PE or DAD algorithms may reside in a more accurate identification of patients at low risk of events. This may allow the use of drugs with potential adverse cardiovascular effects in patients deemed at low cardiovascular risk intolerant of other HAART drugs. However, this assumption remains completely speculative at this time.

To estimate risk accurately in the general population, modelling trends and risk-equation algorithms were developed both in North America and in Europe [7,8] [11]. A new approach to the assessment of cardiovascular risk in HIV+ patients was proposed by the DAD investigators [4]. In the new DAD risk equations, the investigators included both traditional and HIV-specific risk factors such as the exposure to HAART. In clinical practice risk assessment, algorithms are utilized to select patients that need preventive interventions, or need to be referred for a cardiovascular consultation or advanced diagnostic testing. In view of the low positive predictive value of all three algorithms considered in this study, none of the models will likely increase the number of patients referred for further testing over the other. The new PE algorithm has been the target of conflicting criticism. According to Ridker and Cook [13] the new algorithm overestimates the actual risk by 75%–150%, likely because the writers of the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines took into

consideration 30-year-old publications. In contrast, Muntner et al. [14] compared the estimated and observed risk of cardiovascular events in contemporary patient cohorts and concluded that the new guidelines provide reliable predictions of risk in the general population. We were hoping to demonstrate that the DAD algorithm, that includes HAART use and considers a broader range of events inclusive of stroke (similar to PE), would offer an advantage over the others. In view of a lack of clear superiority of any of the three algorithms, further 'modifiers' might be necessary to assess cardiovascular risk in HIV+ patients. The power of subclinical atherosclerosis imaging is slowly emerging in HIV medicine [15] and the 2010 ACC Foundation/AHA Taskforce for assessment of cardiovascular risk in adults [16] and the recent ACC/AHA guidelines suggested that atherosclerosis imaging might be a desirable approach to refine risk assessment in intermediate risk patients.

There were a few limitations in our study. The 10 year FRS risk threshold was arbitrarily chosen to match the reduced cut-off point proposed by the ACC/AHA guidelines [8] and the 5 year thresholds for the DAD and FRS models were the median risk level in our population. The cardiovascular event rate in our cohort was low; however, recent evidence suggests that the cardiovascular risk in HIV+ patients in the USA may be decreasing. In conclusion, the recent PE and DAD equations showed improved negative predictive values compared with FRS. The potential to improve these performance statistics with the inclusion of atherosclerosis imaging warrants investigation, as recently shown in the general population [17].

Table 1

Demographic, HIV-specific and traditional cardiovascular risk factors of the cohort patients.

Variable	**Non-events (n=2481)**	**Events (n=69)**	***p*-value**
Age (years), median (IQR)	45 (42–49)	48 (44–53)	<0.01
Women, n (%)	858 (34.6)	9 (13.4)	<0.01
Years since HIV diagnosis, median (IQR)	15.8 (10.7–20.2)	13.9 (10.5–17.4)	0.03
Nadir CD4+ count (cells/µL), median (IQR)	178 (70–279)	169 (60–280)	0.67
LDL (mg/dL), median (IQR)	114 (90–142)	116 (98–141)	0.61
Triglycerides (mg/dL), median (IQR)	152 (108–219)	178 (139–261)	0.01
Diabetes, n (%)	177 (7.1)	11 (15.9)	<0.01
Smokers, n (%)	1077 (43.5)	38 (55.1)	0.04
Pack-year, median (IQR)	15 (2.0–26.0)	14.3 (5.2–27.0)	0.38
On statin, n (%)	357 (14.4)	38 (55.1)	<0.01
FRS 10 year risk score (%), median (IQR)	3.0 (1.0–7.0)	10.0 (5.0–16.0)	<0.01
PE 10 year risk score (%), median (IQR)	3.1 (1.4–6.0)	8.7 (4.4–13.6)	<0.01
FRS 5 year risk score (%), median (IQR)	4.7 (3.7–5.6)	6.1 (5.0–6.7)	<0.01
DAD 5 year risk score (%), median (IQR)	3.5 (2.7–4.3)	4.7 (3.9–5.2)	<0.01

Table 2

Event prediction and test characteristics of three algorithms tested in our HIV cohort

10-year risk prediction

	PE < 7.5%	*PE ≥ 7.5%*	*FRS < 6%*	*FRS ≥ 6%*
Non event	2030	451	1688	793
Event	25	44	20	49
Sensitivity		63.8%		71.0%
Specificity		81.8%		68.0%
Positive predictive value		8.9%		5.8%
Negative predictive value		98.8%		98.8%

5-year risk prediction

	DAD < 4.5%	*DAD ≥ 4.5%*	*FRS < 5.5%*	*FRS ≥ 5.5%*
Non event	1821	429	1611	639
Event	26	38	20	44
Sensitivity		59.4%		68.8%
Specificity		80.9%		71.6%
Positive predictive value		8.1%		6.4%
Negative predictive value		98.6%		98.8%

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