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Protease Inhibitor (PIS) Exposure Time And Risk Of Cardiovascular Disease (CVD) In Human Immunodeficiency Virus (HIV) Infected Patients

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ABSTRACT

Background: Some PIs are associated with hyperlipidemia, insulin resistance, hypertension (HTN) and diabetes mellitus (DM), which in turn are risk factors for CVD. Our objective was to quantify the effect of PI exposure time on subsequent CVD events.

Methods: The study population was derived from the HIV Insight™ database with data collection from centers funded by the HIV Outpatient Study, and the sponsoring agency for the database, Cerner Inc.™ Patients (age ≥18) from 01/01/1996 to 06/31/2003 were eligible. Patients were followed to the first CVD event (myocardial infarction, angina, coronary artery disease, PTCA/CABG, Stroke, TIA, PVD) or censored at end of follow-up. Covariates included age, gender, race, weight, hyperlipidemia, CVD, DM, HTN, smoking, IV drug (IVDU) and Cocaine use. Exposure time was specified as cumulative PI exposure days, calculated at each CVD event or censoring. Time-dependent Cox proportional hazards regression was used to estimate the adjusted hazards ratio (HR_{adj}) of time to the first CVD event.

Results: Among 7542 patients, PI use was reported in 77% and 127 (1.7%) had at least one CVD event. Baseline demographic distributions were as follows: 86% male; 58% white; 27% African-American; mean age, 39 yrs; mean weight, 169 lbs. For the PI and non-PI groups, CVD events/1,000 patient-years were: 9.8 and 6.5, respectively, overall; and 11.5 and 7.9 in a subset aged 35-65 yrs. For PI exposure ≥60 days, HR_{adj} (95%CI) for CVD was 1.71 (1.07-2.74, p=.03) overall and 1.90 (1.13-3.20, p=.02) in the 35-65 subset. In a model defining PI exposure as 1-180; 181-365; >365 the HR_{adj} (95%CI) for CVD were 1.03 (0.70-1.53); 1.13 (0.75-1.70); 1.51 (0.98-2.32, p=.06) overall, and 0.91 (0.59-1.4); 1.05 (0.67-1.64); 1.63 (1.01-2.63, p=.05), in the 35-65 subset.

Conclusion: PI exposure was found to increase CVD risk in this study. CVD risk was also shown to increase with cumulative PI exposure. Further long-term follow-up data will be needed to confirm these findings. Evaluating HIV-infected patients for CVD risk factors may be important in selecting HAART regimens.

Keywords: Cardiovascular disease, Protease Inhibitor therapy, Treatment Complications.

INTRODUCTION

Highly active antiretroviral therapy (HAART) has dramatically changed the survival patterns of HIV-infected patients [1-3]. In some reports, death from non-AIDS causes exceed those from AIDS causes [2, 4, 5], and CVD events are increasing as a cause of death in these patients [1, 2, 6]. Controversy exists over the association of HAART (and particularly PI therapies) with cardiovascular disease risk [7-9]. Longer life expectancy, PI-related metabolic complications [10,11] and a higher prevalence of traditional CVD risk factors such as smoking in HIV-infected persons [12] make it necessary to determine if PI exposure increases risk of CVD in HIV-infected patients.

METHODS

Data Source Description

- The study population was derived from HIV Insight™, a prospective observational database of HIV-infected patients, consisting of primary care clinicians' outpatient medical records.
- The data source comprises all centers funded by the CDC's HIV Outpatient Study (HOPS) and additional physician offices/clinics funded by the sponsoring agency, Cerner, Inc. There are currently 19 sites (10 from HOPS) participating in ongoing abstraction of patient medical records.

Patient Selection and Variable Definition

- Adult patients ≥18 years old with more than 2 office visits from 1/1/1996 to 6/30/2003.
- PI exposure was categorized in two ways; first as a cumulative exposure ≥60 days, and as a progressively increasing exposure duration (1 to <180 days; 180 to <365 days; ≥365 days).
- Patients starting PI therapy during the observation period could only contribute data to the PI exposed group.
- CVD events were defined as any one of the following: acute myocardial infarction (AMI), angina pectoris, coronary artery disease (CAD), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), cerebrovascular accident (CVA), transient ischemic attack (TIA), and peripheral vascular disease (PVD).

Data Analysis

- CVD observed event rates were calculated per 1000 person-years of follow up (PFYU) for both exposure groups.
- A time-dependent Cox proportional hazards multivariable model was used to compute the relative hazard of a first CVD event. To avoid double counting, only the first CVD event was considered.
- Covariates adjusted for were age category, gender, race, smoking, intravenous drug use (IVDU), cocaine use, hypertension, diabetes mellitus, pre-existing CVD, pre-existing hyperlipidemia, and weight. Weight was imputed for a small minority of patients (<5%) with missing information using the mean weight from the patient cohort with complete weight data.
- The primary analytic dataset comprised all 7,542 patients, and analyses were also repeated in a subset of patients, aged between 35 and 65 years (N=5,200). Sensitivity analyses truncating the observation period for the PI group were conducted.
- All statistical analyses were performed using SAS version 8.1 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

- A total of 7,542 patients met enrollment criteria. A total of 127 CVD events were observed, with 112 in the PI group for an adjusted incidence rate of 9.8/1000 PYFU, and 15 in the non-PI group for an adjusted incidence rate of 6.5/1000 PYFU (p=0.0008). Among patients in the 35-65 year old subset CVD event rates were also higher in the PI exposed group (11.5/1000 PYFU vs. 7.9/1000 PYFU; p=0.01).
- The median duration of follow-up was 3.5 years (mean 3.5 years; maximum 7.4 years) and 2 years (mean 2.5 years; maximum 7.4 years) for the PI and non-PI groups respectively. The median PI exposure time was 1.7 years (mean 2 years). Over 95% of the study patients in the PI arm had a minimum of one month of PI exposure, and over 75% had greater than 6 months of PI exposure. In the non-PI group, 67% were exposed to non-nucleoside reverse transcriptase inhibitors (NNRTI); and the others were treated with nucleoside reverse transcriptase inhibitors (NRTI) only.
- As shown in **Table 1**, significant demographic differences were observed between the exposure groups.

Table 1. Demographics and Risk Factor Distribution

Characteristics	PI Group (N=5787)	Non-PI Group (N=1755)	p-value
Median duration of follow-up (years)	3.5	2.0	<0.0001
Age (years)			
Mean (sd)	39.4 (8.30)	38.7 (8.90)	0.0012
Age in years N(%)			
18-34	1679 (29%)	604 (34%)	<0.0001
35-49	3461 (60%)	951 (54%)	<0.0001
50-64	600 (10%)	188 (11%)	NS
65+	47 (1%)	12 (1%)	NS
Males N(%)	5078 (88%)	1402 (80%)	<0.0001
Race N(%)			
Whites	3501 (61%)	883 (50%)	<0.0001
African American	1430 (25%)	587 (33%)	<0.0001
Smokers N(%)			
Current	1953 (34%)	678 (39%)	0.0002
Past	787 (14%)	230 (13%)	NS
Weight mean (sd)	169.1 (32.8)	170.1 (33.1)	NS
IVDU N(%)	42 (1%)	17 (1%)	NS
Cocaine N(%)	110 (2%)	39 (2%)	NS
Hypertension N(%)	271 (5%)	109 (6%)	0.01
Diabetes Mellitus N(%)	65 (1%)	16 (1%)	NS
Pre-existing CVD N(%)	7 (<1%)	1 (<1%)	NS
Pre-existing hyperlipidemia N(%)	553 (10%)	83 (5%)	<0.0001

- Results of univariate and multvariate analyses are shown in Table 2

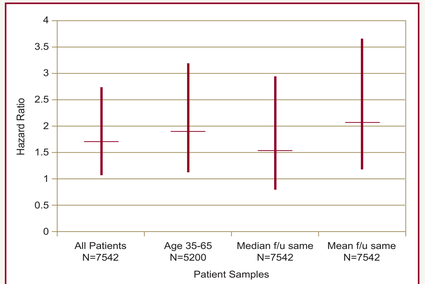
Table 2. Cox Proportional Hazards Regression Model: Significant Predictors of Time to First CVD Event for Patients with Cumulative PI Exposure ≥60 days (N=7542)

Risk Factors	CVD Events		Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)
	Yes (n=127), n (%)	No (n=7415), n (%)		
PI exposure ≥60 days				
Y	105 (82.7)	4707 (63.5)	1.69 (1.07-2.68)	1.71 (1.07-2.74)
N	22 (17.3)	2708 (36.5)	Reference	Reference
Smoking				
Current	56 (44.1)	2575 (34.7)	1.62 (1.14-2.30)	2.40 (1.59-3.64)
Past	29 (22.8)	988 (13.30)	1.80 (1.18-2.69)	1.74 (1.06-2.84)
Never	42 (33.1)	3852 (52)	Reference	Reference
Age (years)				
35-49	65 (51.2)	4347 (58.6)	2.90 (1.53-5.49)	2.57 (1.35-4.88)
50-64	42 (33.1)	746 (10.1)	10.93 (5.63-21.23)	8.09 (4.04-16.19)
≥65	9 (7.1)	50 (0.7)	38.97 (16.14-94.07)	32.04 (12.94-79.34)
<35	11 (8.7)	2272 (30.6)	Reference	Reference
Hypertension				
Y	19 (15)	361 (4.9)	3.68 (2.26-5.99)	1.80 (1.07-3.03)
N	108 (85)	7054 (95.1)	Reference	Reference
Diabetes Mellitus				
Y	5 (3.9)	76 (1)	5.25 (2.15-12.86)	3.59 (1.44-8.95)
N	122 (96.1)	7339 (99)	Reference	Reference
Evidence of pre-existing CVD				
Y	8 (6.3)	0 (0)	69.17 (33.7-141.94)	19.88 (8.68-45.55)
N	119 (93.7)	7415 (100)	Reference	Reference
Evidence of hyperlipidemia				
Y	21 (16.5)	615 (8.3)	1.63 (1.02-2.60)	1.11 (0.69-1.80)
N	106 (83.5)	6800 (91.7)	Reference	Reference

Other variables adjusted for but not significant predictors include gender, ethnicity, weight, cocaine use and intravenous drug use.

- **Sensitivity Analyses:** In a multivariate regression model fit for the subset 35-65 years of age (N=5200), adjusting for all risk factors, cumulative protease inhibitor exposure ≥60 days was also associated with an increased risk of CVD (HR_{adj}, 1.90; 95% CI, 1.13-3.20). Follow-up time for the PI group was truncated in two different analyses to achieve the same median and mean follow-up times as the non-PI group. As shown in **Figure 1**, PI exposure ≥60 days was still associated with increased risk of CVD events ([similar median follow-up times HR_{adj} 1.53; 95% CI 0.79-2.95] and [similar mean follow-up times HR_{adj} 2.07; 95% CI 1.18-3.66]).

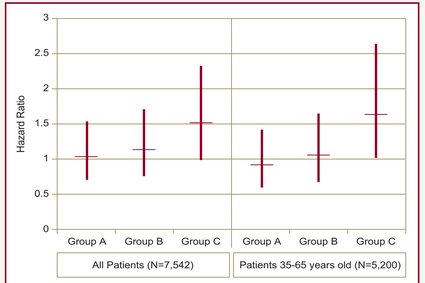
Figure 1: Cox proportional Hazards Regression Model: Sensitivity Analyses of PI Exposure ≥60 Days and Adjusted Risk of CVD events



(All models adjusted for age, gender, ethnicity, smoking status, weight, cocaine, IVDU, hypertension, diabetes mellitus, pre-existing CVD and hyperlipidemia; f/u = follow-up)

- The PI exposure variable was redefined to determine whether increasing exposure duration had an impact on CVD risk. Three exposure categories were defined as follows; PI exposure of 1 to <180 days (group A); 180 to <365 days (group B); ≥365 days (group C). In the multivariate regression model adjusting for all risk factors, only group 3 patients had an increased risk of CVD events (HR, 1.51; 95% CI, 0.98-2.32). Applying this model to the 35-65 year old subset, resulted in similar results; group 3 patients had an increased risk of CVD events (HR, 1.63; 95% CI, 1.01-2.63).

Figure 2: Cox Proportional Hazards Regression Model: Sensitivity Analyses of PI Exposure Days 1<180 (Group A); 180<365 (Group B); 365 (Group C) and Adjusted Risk of CVD Events



(All models adjusted for age, gender, ethnicity, smoking status, weight, cocaine, IVDU, hypertension, diabetes mellitus, pre-existing CVD and hyperlipidemia; f/u = follow-up)

CONCLUSIONS

- The results of this analysis suggests an increased risk of CVD events in HIV-infected patients exposed to PI therapies.
- This association was shown in the overall population but the risk was greater in the subset between 35 and 65 years of age.
- Although the effect of PI treatment on CVD risk was evident in this analysis, the demonstrated benefits of HAART therapy still outweigh the risk of subsequent cardiovascular events [13].
- Physicians should consider CVD risk when selecting treatment regimens for patients. In addition, steps designed to modify CVD risk factors among HIV-infected patients should be part of the routine clinical care for these patients.
- Further studies are needed to confirm this association as well as understand what the causal pathway may be.

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