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Predicting The Risk of Coronary Heart Disease (CHD) in HIV-infected patients: The D:A:D CHD Risk Equation

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BACKGROUND

- Prevention strategies for CHD require reliable estimates of CHD risk
- No such equations exist for HIV-positive persons, where components of antiretroviral therapy may contribute to this risk
- We developed a CHD risk equation tailored to HIV-positive patients

METHODS

- The D:A:D study is a prospective, multi-national observational study formed by the collaboration of 11 cohorts of HIV-infected patients. The primary objective of the study is to establish whether the use of combination antiretroviral therapy is associated with an increased risk of cardiovascular disease
- 23,437 HIV-infected individuals are followed at 188 clinics in Europe, the US and Australia **[Table 1]**
- The composite coronary heart disease endpoint (CHD) was defined as: myocardial infarction (MI), invasive coronary artery procedure (including coronary artery by-pass or angioplasty/stenting), or death from other coronary heart disease **[Table 2]**
- Model developed based on 9023 subjects who had full covariate data and were free of cardiovascular disease (CHD and stroke) at entry into the study **[Table 1]**
- The risk equation to predict CHD was developed based on parametric survival models. Different parametric models were initially considered (e.g. exponential, gompertz, weibull, log-logistic, gamma), with covariates fitted using proportional hazards and accelerated failure time models. The best fitting model was then chosen based on likelihood, Akaike's information criterion (AIC) and Schwarz's Bayesian information criterion (BIC)
- The underlying time scale was prospective follow up from baseline, and till the time of the first CHD event, the time of death, time of last follow-up visit in the study or Feb 1st, 2005, whichever occurred first
- Traditional CHD risk factors for inclusion in the model were chosen à priori and included: Age, sex, serum total cholesterol, serum HDL cholesterol, (total chosterol:HDL ratio), blood pressure, family history of CHD, smoking (current, former, never), and diabetes mellitus
    - In addition, the following covariates were considered for inclusion: duration of PI and NNRTI exposure, triglycerides, CD_4-count, HIV viral load, body-mass index, reported lipodystrophy, HIV-exposure category, geographical region (three regions were determined based on the risk in the background populations based on WHO CVD mortality rates; stratified into low (<23 per 100.000 men aged 35-55 years), intermediate (23-30 per 100.000) and high (>30 per 100.000) back-ground CVD risk). Among the latter, covariates were selected using backward selection and were included in the model only if the association with the outcome was significant (p<0.05)
    - Age, smoking status, PI and NNRTI exposure were fitted as time-updated, while all other covariates took the fixed value at baseline for the analyses
- Estimates from the risk equation and the corresponding hazard ratios (HR) from a Cox model are reported
- The performance of the equation was assessed on this development dataset by testing the prognostic system's discrimination, calibration, and accuracy
- We further assessed overfitting using a heuristic estimate of model shrinkage, given by:
    - (total model chisquare – number of parameters considered) / total model chisquare
- The predictive performance was also compared to that of a conventional prediction model (the Framingham CHD risk equation[1])
    - When comparing our risk estimates to those obtained from the Framingham equation, particular attention should be made to differences in demographics and outcome definition used in each of the studies. In this respect, the composite CHD endpoint used in the Framingham equation is broader than the endpoint used in D:A:D **[Table 2]**
- The final D:A:D CHD risk equation was further used to obtain absolute risk estimates. The proportions that were at low (<1%), moderate (1-5%), high (5-10%) and very high (>10%) risk of CHD over a 5-year period were estimated

RESULTS

The D:A:D CHD Risk Equation

- Among the 9,023 individuals, 157 cases of CHD occurred over 33,594 person-years
- The best fitting parametric model was log-logistic, and included the conventional risk factors of: age, sex, family history of CHD, systolic blood pressure, smoking status (current, former, never), the ratio of TC/HDL, diabetes (fitted separately by sex due to interaction), and in addition duration of PI exposure
- The parameterization of the model (β-coefficients from the log-logistic accelerated failure model, and – for interpretability - corresponding HRs from a Cox model) is illustrated in **Table 3**

Table 1

Follow-up information and baseline characteristics of the included population and of the entire D:A:D Study population

	Population used for derivation of the D:A:D equation	D:A:D Study population
No.of subjects	9,023	23,437
Median follow up (years)	4.2 (3.2-4.6)	4.5 (3.8-4.8)
Time at risk (person-years)	33,594	94,469
Baseline date	June 2000 (Feb-Aug 2000)	May 2000 (Feb-Dec 2000)
Median (IQR)		
Age (years)	39 (3346)	39 (3445)
Pi exposure (years)	2.1 (0.0-3.3)	1.6 (0.0-2.9)
Systolic BP (mmHg)	120 (110-130)	120 (110-130)
Diastolic BP (mmHg)	80 (70-85)	80 (70-80
Total cholesterol (mmol/l)	5.1 (4.3-6.1)	5.0 (4.2-6.0)
HDL cholesterol (mmol/l)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
Non-HDL Cholesterol (mmol/l)	3.9 (3.0-4.9)	3.9 (3.1-5.0)
Ratio Total:HDL cholesterol	4.5 (3.4-5.8)	4.4 (3.4-5.6)
Triglyceride (mmol/l)	1.7 (1.2-2.9	1.7 (1.2-2.8)
BMI (kg/m²)	22.9 (20.9-25.1)	23.0 (21.0-25.2)
%		
Female	25.6	24.1
Family history of CVD	8.0	6.0
Prior CVD	0	1.4
Diabetes	3.3	3.1
Current cigarette smoker	52.9	44.9
Ex-smoker	14.0	11.2
Transmission group		
Heterosexual	30.6	25.9
homosexual	43.0	45.2
Intravenous drug use	21.5	20.1
Region		
I (low background incidence)	49.1	37.1
II (medium background incidence)	31.0	26.3
III (high background incidence)	19.9	36.7
Ethnicity		
White	57.3	47.5
Nonwhite	8.6	13.5
Unknown	34.1	39.0

See Box 1 for conversion of units

Table 2

Description of characteristics and outcome variables used in the model development datasets from the D:A:D and Framingham Cohorts

Cohort	Setting	Study population	Year of baseline examination and followup	Definition of fatal and non fatal myocardial infarction (MI)	Definition of coronary heart disease (CHD)*
D:A:D Study	Cohort collaboration; clinics in 21 countries in Europe and Australia	HIV-infected persons; 6716 men and 1307 women; aged 17 to 84 years at baseline	Baseline: 2000; maxiMfollowup 4.2 years	Fatal and non fatal MI, including sudden death	MI, invasive coronary artery procedure, CHD death
Framingham Heart Study	Town of Framingham, Massachusetts, USA	2590 men and 2983 women from original and offspring cohorts, aged 30 to 74 years at baseline	Baseline: 1968 to 1971 (original cohort), 1971 to 1975 (offspring cohort); maximum followup approximately 12 years	Fatal and non fatal MI, including silent MI	MI, angina pectoris, coronary insufficiency, CHD death incl. sudden death

*: proportion MI of CHD endpoint, ~70% in D:A:D versus ~50% in Framingham

Table 3

The D:A:D CHD Prediction Equation* and Corresponding Hazard Ratios (HR) from a Cox Model

Model	Log-logistic Accelerated failure*		Cox	
	Coefficient β	SE	HR	95% CI
predictor				
Cumulative PI exposure (per additional year)	-0.1139	0.04	1.13	1.05 -1.23
Male gender	-0.7304	0.31	2.35	1.26 -4.38
Age (per 5 years older)	-0.3357	0.05	1.42	1.31 -1.54
Current cigarette smoking	-1.0416	0.22	2.97	1.93 -4.57
Ex -smoking	-0.5458	0.25	1.78	1.07 -2.96
Family history of CVD	-0.4777	0.23	1.66	1.05 -2.63
Diabetes in men	-0.6833	0.27	1.94	1.15 -3.28
Diabetes in women	-1.3489	1.05	4.04	0.51 -31.46
Ratio of TC/HDL (per unit higher)	-0.1438	0.03	1.16	1.08 -1.23
Systolic blood-pressure (per 10mmHG higher)	-0.0502	0.05	1.05	0.95 -1.16
Constant	11.4984	1.07		
shape parameter	γ			
gamma	0.9333	0.07		

RESULTS (continued)

Performance of The D:A:D CHD Risk Equation & Comparison with Framingham

- The model performed well on the development dataset with regards to discriminating risks: area under the receiver-operator curve (AUROC) discrimination statistics 0.78 (95% CI 0.75-0.82) **[Figure 1]**
- The calibration was assessed by visually comparing Kaplan–Meier cumulative survival curves for risk of CHD and the corresponding predicted curve calculated from the D:A:D model, and found good concordance (data not shown)
- The heuristic estimate of model shrinkage estimate was <3%, suggesting that model overfitting is not likely to lead to materially poorer predictions in independent data samples.
- Overall, the D:A:D equation predicted 153 CHD events (112 MI), compared with 157(114) observed, whereas 187 (103) events were predicted by the Framingham equation **[Figure 2]**
- The proportional distributions in subgroups of observed and predicted CHD events by the D:A:D and Framingham risk equations, respectively, are illustrated in **Figure 3**
- Predictions by the D:A:D equation were accurate in sub-groups of patients according to gender and smoking status
- The Framingham equation tended to underestimate the risk in smokers **[Figure 3]**, and among the lowest risk tertile (data not shown)

Absolute 5-Year CHD Risk Estimates

- The D:A:D CHD risk equation was used to obtain absolute 5-year CHD risk estimates. Overall, 8.5% of the study population were estimated to be at a high risk, and 3.2% at very high risk, of developing CHD over a 5-year follow- up period **[Figure 4]**
- These proportions were lowest in women (0.8% and 0.4% versus 11.1% and 4.1% in men), younger individuals (age <45 years in men/<55 years in women; 2.5% and 0.3% versus 28.1% and 12.5% in older), and non-smokers (4.2% and 1.5% versus 10.2% and 3.7% in current smokers)

CONCLUSIONS

- The D:A:D equation, developed on HIV-positive subjects and incorporating PI exposure as well as conventional CHD risk parameters, accurately predicted CHD outcomes in the development dataset
- The model also - more accurately than Framingham - estimated the risk of CHD in subgroups
- The Framingham equation tended to overestimate absolute CHD risk in the D:A:D study population, which may largely be due to differences in CHD endpoint definitions
    - However, consistent with our earlier paper[2], the Framingham equation slightly underpredicted the risk of MI
- Bootstrapping, which refits the models, and reassesses model fit, on 100 replicate data sets obtained from the original development dataset, will be performed as internal validation of the D:A:D CHD risk equation
    - However, validation of the model on independent datasets is warranted to determine whether this D:A:D equation can be generalized among HIV infected individuals, and subsequently be introduced into clinical practice

References
1. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991; 121(1 Pt 2):293-298.
2. Law MG, Friis-Møller N, El-Sadr WM et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. HIV Med 2006; 7(4):218-230.

Box 1. Converting units for cholesterol and triglycerides

Cholesterol	mmol/L to mg/dl: multiply by 38.5	mg/dl to mmol/L: divide by 38.5
Triglycerides	mmol/L to mg/dl:multiply by 87.7	mg/dl to mmol/L:divide by 87.7

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Figure 1

Discrimation of the CHD prediction model – assessed by the Receiver-Operator Characteristic (ROC) Curve

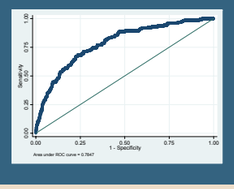


Figure 2

Absolute observed and predicted number of CHD events, and proportion MI

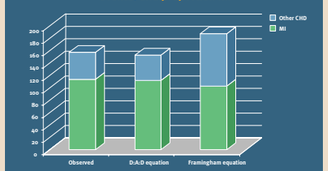


Figure 3

Proportional Distribution of CHD in Subgroups – Observed and Predicted

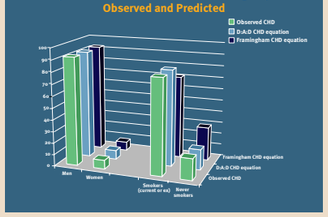
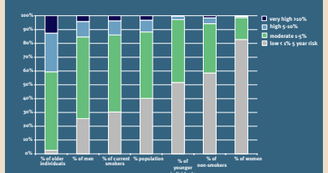


Figure 4

CHD 5-year risk stratification



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