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


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 centers 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 CVD
- 37,432 HIV-infected individuals are followed at 88 sites in 19 countries in Europe, the US and Australia
- The composite coronary heart disease endpoint was defined as: myocardial infarction, invasive coronary procedure (including coronary artery bypass surgery), angina, or death from other coronary heart disease
- Model development was based on 20,730 subjects who had full covariate data and were free of cardiovascular disease (CHD) at study entry
- The risk equation to predict CHD was developed based on parametric survival models. Different parametric models were initially considered (e.g., exponential, gamma, Weibull, log-logistic), 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 the time of the first CHD event, the date of death, or at 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 a priori and included: Age, sex, serum total cholesterol, serum HDL cholesterol, total cholesterol/HDL ratio, blood pressure, family history of CHD, smoking (current, former, never), diabetes mellitus
- To exclude the following covariates were considered for inclusion: duration of HAART and NNRTI exposure, HIV viral load, CD4 count, HIV viral load, body mass index, reported lipodystrophy, HIV exposure category, geographic region (three regions were considered based on the first, second, and third highest percentages of HIV in 2000 and 2005), antiretroviral drug use (first, second, and third line of HAART), region at last follow-up visit in the study, and were using backward selection and were included in the model only if the association with the outcome was significant (p<0.05)
- Age, smoking status, HAART 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 the development dataset by testing the predicted system’s discrimination, calibration, and accuracy
- We further assessed overfitting using a heuristic estimate of model shrinkage, given by:
  \[ \text{shrinkage} = \frac{\text{total model chi-square} - \text{number of parameters considered}}{\text{total model chi-square}} \]

RESULTS (continued)

- The D:A:D CHD risk equation was used to obtain absolute 5-year risk estimates. Overall, 8.3% of the study population were estimated to be at a high risk, and 5.2% at very high risk, of developing CHD over a 5-year follow-up period (Figure 2). These proportions were lower in women (3.8% and 2.4% versus 11.1% and 5.1% in men), younger individuals (age <45 years in men/155 years in women; 2.5% and 1.3% versus 6.1% and 2.5% in older patients), and non-smokers (4.5% and 3.2% versus 7.1% and 4.9% 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 reflected Framingham – the estimated 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, the Framingham equation slightly underestimated the risk of CHD

- Bootstrapping, which refits the models, and consequences model fit, in 100 replicate data sets obtained from the original development dataset, will be performed as internal validation of the D:A:D CHD risk equation
- Internal validation of the model in 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

Table 1: Hazard ratios from a Cox model

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.7964</td>
<td>0.31</td>
<td>2.35</td>
</tr>
<tr>
<td>Age (per 5 years older)</td>
<td>0.3337</td>
<td>0.05</td>
<td>1.42</td>
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<tr>
<td>Current cigarette smoking</td>
<td>1.0416</td>
<td>0.22</td>
<td>2.97</td>
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<tr>
<td>Ex-smoking</td>
<td>0.5458</td>
<td>0.25</td>
<td>1.78</td>
</tr>
</tbody>
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Table 2: Overview of the characteristics and exposure to antiretroviral drugs of the D:A:D study population

- Distribution of CHD in Subgroups: Observed and Predicted

Figure 1: Follow-up information and baseline characteristics of the included population and of the entire D:A:D Study population

- Table 3: The Framingham equation

- Figure 2: Absolute observed and predicted number of CHD events, and proportion of 5% of older individuals, 10% of population, 30% of women, 40% of men, 50% of older individuals, and 60% of population 5% of women, 10% of population, 30% of women, 40% of men, 50% of older individuals, and 60% of population

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