Evaluation of sudden death and non-haemorrhagic stroke and their association with HIV protease inhibitor (PI) usage


On behalf of the D:A:D study group
Background-I

- Concerns have evolved about potential adverse effects of protease inhibitors (PIs) on cardiac conductivity
  - May manifest as prolongation of Q-T and P-R interval durations on standard electrocardiogram (ECG)
  - FDA has issued warnings that some PIs [LPV/r, SQV/r] may have an effect on cardiac electric conductivity*

*U.S. Food and Drug Administration:
Concerns have evolved about potential adverse effects of protease inhibitors (PIs) on cardiac conductivity

- May manifest as prolongation of Q-T and P-R interval durations on standard electrocardiogram (ECG)
- FDA has issued warnings that some PIs [LPV/r, SQV/r] may have an effect on cardiac electric conductivity
- In SMART**, N=3719 all PI-based regimens (whether boosted or non-boosted) were associated with prolongation of P-R
- Average Q-T was significantly lower for any PI/r group compared to the NNRTI

**Soliman EZ, Lundgren JD et al. On behalf of SMART; Poster H-218, ICCAC 2010, AIDS in press
• Q-T prolongation may increase risk of sudden death

• It has been suggested that prolonged P-R interval may be a predictor of atrial fibrillation - associated with stroke and mortality*, no causal relationship has been established

• The possible clinical consequences of these ECG abnormalities in HIV-positive persons have not been assessed

  • Neither good ascertainment of ECGs nor good descriptions of ECGs in HIV+

  • Sudden deaths are rare events

*Soliman EZ, Prineas RJ et al. *Stroke* 2009
Scjabel RB, Sullivan LM et al. *Lancet* 2009,
Cheng S, keyes et al. *JAMA* 2009
Hypothesis

- Sudden death and non-haemorrhagic strokes may be rare ‘end-stage’ outcomes of prolonged Q-T or P-R intervals
- If exposure to PIs (as a class) does indeed cause these ECG abnormalities, we may expect to see an excess risk of sudden deaths/non-haemorrhagic strokes in patients exposed to PIs
Methods

• Centrally validated (with cardiologist input) cases of sudden deaths and non-haemorrhagic strokes were identified using standard case-definitions

• Person-years (PY) calculated from D:A:D entry to first event, death, 6 months after last visit or Feb 2009

• Association between combined endpoint and current/recent (any use in previous year) exposure to PIs (+/-ritonavir boosting) investigated using Poisson regression, adjusting for confounders (age, sex, body mass index, family and personal history of CVD)

• Sensitivity analyses assessed associations with sudden deaths alone
Results

- 49,727 patients followed for total of 234,818 PY
- 78 sudden deaths
  - Event rate: 0.34/1000 PY
- 172 non-haemorrhagic strokes
  - Event rate: 0.73/1000 PY
- 250 combined endpoint
  - Event rate: 1.06/1000 PY
Results

- 49,727 patients followed for total of 234,818 PY
- 78 sudden deaths
  - Event rate: 0.34/1000 PY
- 172 non-haemorrhagic strokes
  - Event rate: 0.73/1000 PY
- 250 combined endpoint
  - Event rate: 1.06/1000 PY
- Associations with PI class
  - In patients currently/recently exposed to PIs rates of 1.23 /1,000 PY
  - In patients not exposed to PIs rates of 0.92 /1,000 PY
## Characteristics at D:A:D entry

<table>
<thead>
<tr>
<th></th>
<th>Sudden deaths N=78</th>
<th>Non-haem strokes N=178</th>
<th>DAD overall N=49,737</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>Gender, (%)</td>
<td>Male 84.6</td>
<td>85.5</td>
<td>73.5</td>
</tr>
<tr>
<td>Race, (%)</td>
<td>White 59.0</td>
<td>47.7</td>
<td>50.4</td>
</tr>
<tr>
<td></td>
<td>Black 7.7</td>
<td>11.6</td>
<td>9.8</td>
</tr>
<tr>
<td>BMI kg/m², (%)</td>
<td>26-30 10.3</td>
<td>11.1</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>&gt;30 6.4</td>
<td>5.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Lipids (mmol/L),</td>
<td>TG 2.3</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>CHOL 5.5</td>
<td>5.2</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>HDL 1.1</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Smoking Status, (%)</td>
<td>Current/EX-smoker 35.4/60.3</td>
<td>41.3/58.1</td>
<td>30.0/51</td>
</tr>
<tr>
<td>Fam history of CVD, (%)</td>
<td>5.1</td>
<td>7.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Previous CVD event, (%)</td>
<td>7.7</td>
<td>9.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Diabetes Mellitus, (%)</td>
<td>7.7</td>
<td>14.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Anti hyp medication, (%)</td>
<td>6.4</td>
<td>12.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Lipid lowering drugs, (%)</td>
<td>7.7</td>
<td>7.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>
## Characteristics at D:A:D entry

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<tbody>
<tr>
<td><strong>Mode of infection, (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homo-sexual</td>
<td>52.6</td>
<td>49.4</td>
<td>43.6</td>
</tr>
<tr>
<td>Hetero-sexual</td>
<td>26.9</td>
<td>15.1</td>
<td>15.3</td>
</tr>
<tr>
<td>IDU</td>
<td>14.1</td>
<td>25.0</td>
<td>32.3</td>
</tr>
<tr>
<td><strong>Duration of previous exposure to ART, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>1.8</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>NRTIs</td>
<td>3.4</td>
<td>3.0</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Log HIV-1 RNA (copies/ml)</strong></td>
<td>3.4</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>CD4 counts (cells/mm³)</strong></td>
<td>307</td>
<td>351</td>
<td>402</td>
</tr>
</tbody>
</table>
Relative rate of non-haemorrhagic strokes or sudden deaths and current/recent PI exposure (unadjusted and adjusted)

Adjusted for:
age, sex, BMI, family and personal history of CVD

GREY bars: Unadjusted
BLACK bars: Adjusted

RR (95% CI)

1.34
1.19

Rates of the CE, currently/recently exposed to PIs
1.23 /1,000 PY

Sudden deaths and non-haem strokes
Relative rate of non-haemorrhagic strokes or sudden deaths and current/recent PI exposure (unadjusted and adjusted)

Adjusted for: age, sex, BMI, family and personal history of CVD
Limitations

- ECGs are not collected on a routine basis in D:A:D
- Sudden deaths are rare events – our study is only sufficiently powered to detect a strong signal between PIs (as a class) and this outcome
  - It remains possible that one or few individual drugs are associated with a markedly raised risk of sudden death.
- Even if relative rates of sudden death are close to 1, we cannot rule out the possibility that some patients might be adversely affected
- Inability to distinguish sudden death resulting from conduction disturbances caused by genetics, or secondary to ischemic heart disease
- The study has limited information on concomitant cocaine use, methadone or on use of anti-arrythmic drugs
Conclusions

- A small increased risk of sudden death/non-haemorrhagic stroke was observed with PI exposure in univariate analyses
  - this association (including sudden deaths) was not noted after adjustment for potential confounders
- These findings do not support the routine use of ECG monitoring for all patients on PIs, however, monitoring might be considered:
  - For patients receiving other drugs with known effects on cardiac conductivity
- In this study, we did not have sufficient power to examine the association between individual PIs and sudden death/non-haemorrhagic stroke
Acknowledgement

- **Cohort PI’s:** W E-Sadr * (CPCRA), G Calvo * (BASS), F Dabis * (Aquitaine), O Kirk * (EuroSida), M Law * (AHOD), A d’Arminio Monforte * (ICONA), L Morfeldt * (HivBIVUS), C Pradier * (Nice), P Reiss * (ATHENA), R Weber * (SHCS), S De Wit * (Brussels)

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- **Community representative:** S Collins *

- **DAD coordinating office:** S Worm, L Ryom, R Salbøl Brandt, JD Lundgren *¢

- **Steering Committee:** Members indicated w/*; ¢ chair; Additional members: R Rode*, D Butcher *, N Shortman *

- **Funding:** ‘Oversight Committee for The Evaluation of Metabolic Complications of HAART’ with representatives from academia, patient community, FDA, EMA and a consortium of “Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Viiv Heathcare, Merck, Pfizer, and Hoffman-La Roche”