Triglycerides and the risk of myocardial infarction in the D:A:D study

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

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Fontas E, et al. JID 2004; 189
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- HIV infection, insulin resistance, obesity and fatty liver disease can cause elevated TG levels as well

Grunfeld C el at. J Clin Endocrinol Metab. 1992; 74(5)
Fabbrini E et al. Hepatology. 2010;51(2)
Capaeu J Diabetes Metab. 2008 ;34(6 Pt 2)
Background

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- HIV infection, insulin resistance, obesity and fatty liver disease can cause elevated TG levels as well.
- It is unclear whether TG levels provide additional prognostic information regarding myocardial infarction (MI) risk once total cholesterol (TC) and HDL-cholesterol (HDL) are taken into account.
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- Elevated triglyceride (TG) levels are a common complication of antiretroviral therapy (ART)
- HIV infection, insulin resistance, obesity and fatty liver disease can cause elevated TG levels as well
- It is unclear whether TG levels provide additional prognostic information regarding myocardial infarction (MI) risk once total cholesterol (TC) and HDL-cholesterol (HDL) are taken into account
  - There is no evidence that reduction of elevated TG levels will translate into a reduction in MI risk in HIV-positive persons
Purpose

• Explore the relationship between TG levels and the risk of MI after adjustment for TC and HDL
Methods

- Follow-up counted from D:A:D enrolment until the first MI event, 1st February 2008 or 6 months after the patient’s last clinic visit (whichever occurred first)
- Covariates were time-updated at the start of each month
- The incidence of the first MI during prospective D:A:D follow-up was calculated according to the latest (time-updated) TG level
Methods

• TG levels were stratified into sixtiles

<table>
<thead>
<tr>
<th>mmol/L :</th>
<th>mg/dl :</th>
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<tbody>
<tr>
<td>&lt;0.90</td>
<td>&lt;80</td>
</tr>
<tr>
<td>0.90–1.25</td>
<td>80-110</td>
</tr>
<tr>
<td>1.25-1.70</td>
<td>110-150</td>
</tr>
<tr>
<td>1.70-2.30</td>
<td>150-200</td>
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<tr>
<td>2.30-3.45</td>
<td>200-300</td>
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<tr>
<td>&gt;3.45</td>
<td>&gt;300</td>
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</table>

• Multivariable Poisson regression models were used to describe the independent association between the latest TG level and MI risk

• TG assessed fasting and non-fasting*, continuous measurement, per doubling

* 27% fasting, 13% non-fasting, 60% unknown
Methods
adjustments in multivariable models

• Two sets of adjustments were made to explore the potential independent association between TG levels and risk of MI:

  i) non-lipid cardiovascular disease (CVD) risk factors (sex, age, race, body mass index, smoking, family history of CVD, previous CVD event, diabetes mellitus, receipt of lipid lowering drugs, hepatitis C status), calendar year, the latest HIV-RNA level and CD4 count and exposure to ART

  ii) as above, **plus** the latest TC and HDL level
Baseline characteristics of patients with at least one TG measurement over follow-up

Patients with at least one
TG measurement 30,703 (92.2)*
Age, Median value 39
Male sex % 74.1
Race %
  White 53.6
  Black 9.0
  Other 2.7
  Unknown 33.7
Smoking Status %
  Current smoker 37.0
  Ex-smoker 19.2
Family history of CVD % 7.4
Previous CVD % 1.7
Diabetes Mellitus % 2.9

* Out of total 33,308 patients
Baseline characteristics of patients with at least one TG measurement over follow-up

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<th>Value</th>
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<td>1.7</td>
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<tr>
<td>Diabetes Mellitus %</td>
<td>2.9</td>
</tr>
<tr>
<td>Mode of infection %</td>
<td></td>
</tr>
<tr>
<td>Homosexual/bisexual</td>
<td>43.2</td>
</tr>
<tr>
<td>IDU</td>
<td>18.2</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>31.5</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>7.6</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/ m²</td>
<td>4.1</td>
</tr>
<tr>
<td>Median value (IQR)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol **</td>
<td>1.1 (0.9 - 1.4)</td>
</tr>
<tr>
<td>Total cholesterol **</td>
<td>4.9 (4.1 - 5.9)</td>
</tr>
<tr>
<td>CD4 counts (cells/mm³)</td>
<td>407 (249 - 600)</td>
</tr>
<tr>
<td>HIV RNA, % suppressed</td>
<td>33</td>
</tr>
<tr>
<td>Any exposure to ART %</td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>60.3</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>34.3</td>
</tr>
<tr>
<td>NRTIs</td>
<td>75.3</td>
</tr>
</tbody>
</table>

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** mmol/L
Results

- 580 MIs over 178,835 person-years
- 405,756 TG measurements
- Regardless of fasting status, overall TG levels were
  - higher in men
  - increased with older age
  - higher in those with BMI > 30kg/m²
  - lower in patients with CD4 of < 300 cells/m³ compared to patients with >600 cells/m³
  - higher in patients with viral load less than 500 copies/ml
  - higher in patients currently on ART compared to patient not on ART
Incidence of MI according to TG group

![Graph showing the incidence rate per 1000 PY for different TG levels (mg/dl or mmol/L)].

- **Levels of TG**
  - mmol/L
  - mg/dl

- **Incidence rate per 1000 PY (95% CI)**

  - <0.90
  - 0.90-1.25
  - 1.25-1.70
  - 1.70-2.30
  - 2.30-3.45
  - >3.45

- **Incidence of MI according to TG group**
Incidence rates of MI per 100 PYRS

**TG and TC**

- TG (mmol/L)
  - < 2.3
  - 2.3 - 3.5
  - 3.5 - 4.0
  - > 4.0
- TC (mmol/L)
  - < 0.9
  - 0.9 - 1.3
  - 1.3 - 1.7
  - > 1.7

**TG and HDL**

- TG (mmol/L)
  - < 0.9
  - 0.9 - 1.3
  - 1.3 - 1.7
  - > 1.7
- HDL (mmol/L)
  - < 0.9
  - 0.9 - 1.3
  - 1.3 - 1.7
  - > 1.7
Relative rate of MI per doubling of TG levels

RR (95% CI)

Unadjusted
Relative rate of MI per doubling of TG levels

Unadjusted

Adjusted for CVD risk factors

Relative rate of MI per doubling of TG levels

Unadjusted

Adjusted for CVD risk factors

Relative rate (95% CI)

1.11 [1.01-1.23]

Further adjusted for HDL and TC

Adjusted for CVD risk factors
Further adjusted for HDL and TC

Adjusted for CVD risk factors

Unadjusted

Relative rate of MI per doubling of TG levels

1.67 [1.54-1.80]

1.32 [1.21-1.45]

1.11 [1.01-1.23]
Limitations

• Lack of repeated sampling, variability of TG levels could lead to regression dilution bias
  • -> also underestimate the effects of TC and HDL and hence the extent to which they attenuate the effect of TG
• Sensitivity analysis using fasting, non-fasting and unknown fasting status reached similar conclusions
• Although adjustments for ART was done, drug induced triglyceride elevations could not be compared to TG elevations due to other factors
• Causal link between triglyceride level and MI cannot be established due to the observational nature of study
Conclusions

- Higher TG levels were independently associated with an increased risk of MI in HIV-positive persons
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• However, the residual effect of TG levels after adjustment for non-lipid and lipid risk factors, of 11% is very small compared with the original unadjusted effect of 67%
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• Higher TG levels were independently associated with an increased risk of MI in HIV-positive persons
  • However, the residual effect of TG levels after adjustment for non-lipid and lipid risk factors of 11% is very small compared with the original unadjusted effect of 67%
• Thus, use of drugs that lower TG levels (e.g. fibrates, nicotinic acid) are unlikely to have major impact on the incidence of MI*

* EACS guidelines presented in Cologne, November 2009
Acknowledgements

- **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)

- **Cohort coordinators and datamanagers:** S Zaheri, L Gras (ATHENA), M Bruyand, S Geffard, (Aquitaine), K Petoumenos (AHOD), S Mateu, F Torres (BASS), M Delforge (Brussels), G Bartsch, G Thompsen (CPCRA), J Kjær, J Tverland (EuroSIDA), P Pezzotti (ICONA), E Fontas, C Caissotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach (SHCS)

- **Statisticians:** CA Sabin*, AN Phillips*, Alim Kamara

- **Community representative:** S Collins*

- **D:A:D coordinating office:** SW Worm, N Friis-Møller, R Brandt, JD Lundgren*¢

- **Steering Committee:** Members indicated w/*; ¢ chair;
  Additional members: S Storfer*, G Pearce*, R Rode*

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