Hepatitis C Virus Infection and the Risk of Coronary Disease

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Background

▪ Several infectious etiologies for CAD have been proposed based on epidemiological associations, but there is no consensus regarding a causative role (1-3)
  – C. pneumoniae, Cytomegalovirus, H. pylori. M. pneumoniae

▪ HIV infected persons have been reported to have a higher risk of CAD, which is at least partly attributed to antiretroviral therapy, lipid abnormalities and higher levels of inflammation in these persons (4)

▪ Studies on the association between HCV and CAD have shown conflicting results (5-7)

(3) Fong CMAJ. 2000;163:49-56.
Aims

- To determine whether HCV infection is associated with an increased incidence of coronary artery disease
- Compare risk factors and predictors for CAD in HCV infected and uninfected persons
Methods: Creation of ERCHIVES

- Study was conducted in the ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans)

DATA SOURCE

- National Patient Care Database (NPCD)
  - Demographics
  - Clinical diagnoses

Pharmacy Benefits Management (PBM) Database
  - Treatment prescription and duration

Decision Support System (DSS) Database
  - Selected labs

Beneficiary Identification Records Locator Subsystem (BIRLS)
  - Mortality data

MERGED

Butt J Viral Hepat. 2007;14:890-896.
# Methods: Definitions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV</strong></td>
<td>Any positive HCV antibody, OR positive HCV RNA</td>
</tr>
</tbody>
</table>
| **Coronary artery disease (CAD)** | 2 or more of the following in any combination, any time:  
  • ICD-9 code for CABG (coronary artery bypass grafting)  
  • Procedure code for CABG  
  • ICD-9 code for PTCA (percutaneous transluminal coronary angioplasty)  
  • Procedure code for PTCA  
  • ICD-9 code for myocardial infarction (MI) |
| **Comorbidities**       | ≥ 1 inpatient or ≥ 2 outpatient ICD-9 codes anytime                                                                                       |
| **Anemia**              | Hemoglobin <13 g/dl for men, <12g/dl for women                                                                                             |
| **Dyslipidemia**        | Any of the following  
  1. total cholesterol > 200 mg/dl on 2 separate occasions  
  2. total cholesterol > 200 mg/dl once PLUS LDL-C > 130 mg/dl once anytime  
  3. prescription of cholesterol lowering medication > 30 days |
| **Renal Failure**       | Estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m²                                                                            |
| **Diabetes**            | Any of the following  
  1. Glucose ≥ 200 mg/dl on two separate occasions;  
  2. ICD-9 codes (two outpatient OR one inpatient) PLUS treatment with an oral hypoglycemic or insulin for ≥ 30 days  
  3. ICD-9 codes (two outpatient OR one inpatient) PLUS glucose ≥ 126 mg/dl on two separate occasions  
  4. Glucose ≥ 200 mg/dl on one occasion PLUS treatment with a hypoglycemic for > 30 days. |
Methods

- Cases and controls retrieved from 2001-2006
- *Baseline/t₀ was the date of first* HCV diagnosis
- Exclude HIV+
- Exclude prevalent cases of CAD
Results

A flow chart depicting the number of subjects included in the study.

- **HCV antibody or RNA +**: 154,081
  - Complete clinical and lab data available: 105,375
    - Exclude HIV+: 3,779
      - Prevalent CAD: 19,153
    - 82,083

- **HCV uninfected controls**: 103,445
  - Complete clinical and laboratory data available: 103,445
    - Exclude HIV+: 1,255
      - Prevalent CAD: 12,608
    - 89,582
### Results:
**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>HCV+ (n=82,083)</th>
<th>HCV- (n=89,582)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>51.2 (7.3)</td>
<td>51.8 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>55.4</td>
<td>55.8</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>29.5</td>
<td>29.5</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.9</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>13.2</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Gender, % male</td>
<td>97.1</td>
<td>97.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td><strong>41.6</strong></td>
<td><strong>50.4</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.8</td>
<td>21.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td><strong>39.4</strong></td>
<td><strong>72.2</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol: Mean, (SD)</td>
<td>175 (40.8)</td>
<td>198 (41.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C: Mean, (SD)</td>
<td>102 (36.8)</td>
<td>119 (38.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dl): Mean, (SD)</td>
<td>144 (119)</td>
<td>179 (151)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dl): Mean, (SD)</td>
<td>46 (16.8)</td>
<td>46 (15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2.6</td>
<td>1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>38.6</td>
<td>19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug abuse or dependence</td>
<td>31.4</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
# Results:

Factors associated with CAD (multivariable Cox)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>HCV+</th>
<th>HCV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td><strong>1.27 (1.22-1.31)</strong></td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Age (5 year increment)</td>
<td>1.14 (1.13-1.16)</td>
<td>1.14 (1.12-1.15)</td>
<td>1.15 (1.13-1.17)</td>
</tr>
<tr>
<td>Race (comparator: white)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.89 (0.86-0.93)</td>
<td>0.90 (0.85-0.95)</td>
<td>0.89 (0.84-0.94)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.71 (0.62-0.81)</td>
<td>0.58 (0.47-0.73)</td>
<td>0.81 (0.68-0.96)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>0.75 (0.70-0.80)</td>
<td>0.64 (0.58-0.70)</td>
<td>0.87 (0.80-0.95)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.70 (0.62-0.81)</td>
<td>0.72 (0.60-0.86)</td>
<td>0.69 (0.56-0.84)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.37 (1.32-1.43)</td>
<td>1.50 (1.42-1.58)</td>
<td>1.25 (1.18-1.32)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.46 (1.39-1.54)</td>
<td>1.44 (1.34-1.54)</td>
<td>1.48 (1.38-1.59)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.82 (1.75-1.90)</td>
<td>1.79 (1.69-1.89)</td>
<td>1.87 (1.76-1.98)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2.08 (2.00-2.18)</td>
<td>2.06 (1.95-2.17)</td>
<td>2.14 (1.97-2.31)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2.78 (2.57-3.00)</td>
<td>2.82 (2.56-3.11)</td>
<td>2.57 (2.25-2.94)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.37 (1.30-1.44)</td>
<td>1.42 (1.32-1.53)</td>
<td>1.32 (1.22-1.43)</td>
</tr>
<tr>
<td>Alcohol abuse or dependence</td>
<td>1.04 (0.99-1.09)</td>
<td>1.06 (0.99-1.13)</td>
<td>1.01 (0.93-1.10)</td>
</tr>
<tr>
<td>Drug abuse or dependence</td>
<td>1.10 (1.04-1.16)</td>
<td>1.10 (1.03-1.17)</td>
<td>1.07 (0.96-1.19)</td>
</tr>
</tbody>
</table>
Results:
Risk of CAD in HCV infected and uninfected subjects. (P<0.0001)

Incident CAD by HCV- vs. HCV+

Adjusted for Age, Race, Gender, HTN, Diabetes, Hyperlipidemia, COPD

% without CAD

Time in Years

HCV- HCV+
Conclusions

- Despite a favorable risk profile, HCV is associated with an increased risk of incident CAD
Implications/Future Directions

- HCV infected persons should be specifically targeted for early evaluation and intervention for CAD
- In HCV infected persons, such evaluation and intervention might need to be triggered even when the classic risk factors are absent
- Further studies to understand the mechanism of CAD in HCV infected persons are warranted
Strengths and Limitations

- Largest known study to our knowledge
- National population
- Centralized data recording
- Longitudinal follow up
- Strengths of the VHA system

- Analysis of administrative database
- Exact time of HCV infection unknown
- CAD diagnosis based on ICD-9 codes
- Lack of BMI/anthropometric measures
- ?Point-of-care bias for CAD care
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