Plasma Fibrinogen as a Biomarker for Mortality and Hospitalized Exacerbations in People with COPD

Online Supplement: Appendix 3 Supplemental Analysis Results
**Figure 1.**

**Distribution of Baseline Fibrinogen in ARIC**

(n= 1789)

- Hospitalized exacerbations within 12 months
- No hospitalized exacerbations within 12 months
Figure 2.

**Distribution of Baseline Fibrinogen in CHS (n=1292)**

- Hospitalized exacerbations within 12 months
- No hospitalized exacerbations within 12 months

Histories of Baseline Fibrinogen Levels:
- <=199 mg/dL: 0.8% (0.4% hospitalized, 2.5% non-hospitalized)
- 200-249 mg/dL: 7.7% (8.5% hospitalized, 7.7% non-hospitalized)
- 250-299 mg/dL: 26.4% (25.4% hospitalized, 26.4% non-hospitalized)
- 300-349 mg/dL: 29.7% (17.4% hospitalized, 14.8% non-hospitalized)
- 350-399 mg/dL: 19.4% (14.8% hospitalized, 11.3% non-hospitalized)
- 400-449 mg/dL: 11.3% (1.3% hospitalized, 1.1% non-hospitalized)
- 450-499 mg/dL: 2.5% (1.1% hospitalized, 2.2% non-hospitalized)
- 500+ mg/dL: 0.0% (0.0% hospitalized, 0.0% non-hospitalized)
Figure 3.

Baseline Fibrinogen Levels of ECLIPSE Participants With No Prior History of Exacerbations
(n=1114)

- Hospitalized exacerbations within 12 months
- No Hospitalized exacerbations within 12 months

Baseline Fibrinogen Levels:
- <=199 mg/dL: 1.0%
- 200-249 mg/dL: 2.2%
- 250-299 mg/dL: 6.4%
- 300-349 mg/dL: 9.8%
- 350-399 mg/dL: 19.1%
- 400-449 mg/dL: 22.3%
- 450-499 mg/dL: 25.5%
- 500+ mg/dL: 23.4%

Hospitalized exacerbations within 12 months:
- <=199 mg/dL: 0.0%
- 200-249 mg/dL: 0.0%
- 250-299 mg/dL: 1.0%
- 300-349 mg/dL: 2.2%
- 350-399 mg/dL: 9.8%
- 400-449 mg/dL: 19.1%
- 450-499 mg/dL: 22.3%
- 500+ mg/dL: 23.4%
Figure 4.

Baseline Fibrinogen Levels of ECLIPSE Participants with >=1 Prior Exacerbations (n=1004)

<table>
<thead>
<tr>
<th>Fibrinogen Levels (mg/dL)</th>
<th>Hospitalized exacerbations within 12 months</th>
<th>No Hospitalized exacerbations within 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=199</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>200-249</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>250-299</td>
<td>1.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>300-349</td>
<td>2.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>350-399</td>
<td>9.7%</td>
<td>9.7%</td>
</tr>
<tr>
<td>400-449</td>
<td>13.7%</td>
<td>13.7%</td>
</tr>
<tr>
<td>450-499</td>
<td>19.8%</td>
<td>19.8%</td>
</tr>
<tr>
<td>500+</td>
<td>20.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td></td>
<td>23.9%</td>
<td>23.9%</td>
</tr>
<tr>
<td></td>
<td>27.8%</td>
<td>27.8%</td>
</tr>
<tr>
<td></td>
<td>18.0%</td>
<td>18.0%</td>
</tr>
<tr>
<td></td>
<td>19.5%</td>
<td>19.5%</td>
</tr>
<tr>
<td></td>
<td>12.3%</td>
<td>12.3%</td>
</tr>
<tr>
<td></td>
<td>14.5%</td>
<td>14.5%</td>
</tr>
<tr>
<td></td>
<td>14.2%</td>
<td>14.2%</td>
</tr>
</tbody>
</table>
Figure 5.

Baseline Fibrinogen Levels of ECLIPSE Participants with >=2 Prior Exacerbations (n=469)
Figure 6.

Distribution of Baseline Fibrinogen Levels in ARIC
(n= 1789)

- Died within 36 months (%)
- Alive through 36 months (%)

Distribution categories and corresponding percentages:
- <=199 mg/dL
  - Died: 1.2%, Alive: 3.5%
- 200-249 mg/dL
  - Died: 1.8%, Alive: 10.2%
- 250-299 mg/dL
  - Died: 19.8%, Alive: 15.1%
- 300-349 mg/dL
  - Died: 31.2%, Alive: 29.7%
- 350-399 mg/dL
  - Died: 25.6%, Alive: 15.9%
- 400-449 mg/dL
  - Died: 12.8%, Alive: 9.3%
- 450-499 mg/dL
  - Died: 6.9%, Alive: 2.3%
- 500+ mg/dL
  - Died: 2.1%, Alive: 2.1%
Figure 7.

Distribution of Baseline Fibrinogen Levels in CHS  
(n=1292)
Figure 8.

Distribution of Baseline Fibrinogen Levels in ECLIPSE
(n= 2118)

Died within 36 months (%)
Alive through 36 months (%)

[Bar chart showing the distribution of baseline fibrinogen levels in ECLIPSE, with percentage values for each fibrinogen level range.]
Figure 9.

Distribution of Baseline Fibrinogen Levels in FHSOC
(n=145)
Figure 10.

Distribution of Baseline Fibrinogen Levels in NHANES III (n= 1032)
Figure 11.

Time to First Hospitalized COPD Exacerbation within 12 months, ARIC Fibrinogen Threshold 250 mg/dL

Low Fibrinogen:
- # Patients: 207
- # Outcomes: 6
- % Outcomes: 2.8%

High Fibrinogen:
- # Patients: 1582
- # Outcomes: 90
- % Outcomes: 5.6%
Figure 12.

Time to First Hospitalized COPD Exacerbation within 12 months, CHS
Fibrinogen Threshold 250 mg/dL

<table>
<thead>
<tr>
<th>Fibrinogen Level</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Percentage of Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Fibrinogen</td>
<td>110</td>
<td>21</td>
<td>19%</td>
</tr>
<tr>
<td>High Fibrinogen</td>
<td>1182</td>
<td>215</td>
<td>18%</td>
</tr>
</tbody>
</table>
Figure 13.

Time to First Hospitalized COPD Exacerbation Within 12 months for ECLIPSE by Fibrinogen Classification, Fibrinogen Threshold 250 mg/dL

- **Low Fibrinogen**
  - # Patients: 51
  - # Outcomes: 2
  - % Outcomes: 3.9%

- **High Fibrinogen**
  - # Patients: 2,067
  - # Outcomes: 333
  - % Outcomes: 16.1%
Figure 14.

**Time to First Hospitalized COPD Exacerbation within 12 months, ARIC**
**Fibrinogen Threshold 300 mg/dL**

- **Low Fibrinogen:**
  - # Patients: 756
  - # Outcomes: 24
  - % Outcomes: 3.1%

- **High Fibrinogen:**
  - # Patients: 1033
  - # Outcomes: 72
  - % Outcomes: 6.9%
Figure 15.

Time to First Hospitalized COPD Exacerbation within 12 months, CHS
Fibrinogen Threshold 300 mg/dL

Low Fibrinogen:
# Patients: 449
# Outcomes: 81
% Outcomes: 18%

High Fibrinogen:
# Patients: 843
# Outcomes: 155
% Outcomes: 18.3%
Figure 16.

Time to First Hospitalized COPD Exacerbation Within 12 months for ECLIPSE by Fibrinogen Classification, Fibrinogen Threshold 300 mg/dL

<table>
<thead>
<tr>
<th>Fibrinogen Threshold 300 mg/dL</th>
<th>Low Fibrinogen</th>
<th>High Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>244</td>
<td>1,874</td>
</tr>
<tr>
<td># Outcomes</td>
<td>18</td>
<td>317</td>
</tr>
<tr>
<td>% Outcomes</td>
<td>7.4%</td>
<td>16.9%</td>
</tr>
</tbody>
</table>

Percentage of Patients with no event
Figure 17.

Time to First Hospitalized COPD Exacerbation Within 12 months, ARIC
Fibrinogen Threshold 350 mg/dL

- **Low Fibrinogen:**
  - # Patients: 1,275
  - # Outcomes: 49
  - % Outcomes: 3.8%

- **High Fibrinogen:**
  - # Patients: 514
  - # Outcomes: 47
  - % Outcomes: 9.1%
Figure 18.

Time to First Hospitalized COPD Exacerbation within 12 months, CHS
Fibrinogen Threshold 350 mg/dL

Percentage of patients with no event

Low Fibrinogen:  
# Patients: 848  
# Outcomes: 151  
% Outcomes: 17.8%

High Fibrinogen:  
# Patients: 444  
# Outcomes: 85  
% Outcomes: 19.1%
Time to First Hospitalized COPD Exacerbation Within 12 months for ECLIPSE by Fibrinogen Classification, Fibrinogen Threshold 350 mg/dL

- **Low Fibrinogen**
  - # Patients: 684
  - # Outcomes: 66
  - % Outcomes: 9.6%

- **High Fibrinogen**
  - # Patients: 1,434
  - # Outcomes: 269
  - % Outcomes: 18.8%
Figure 20. 

Time to First Hospitalized COPD Exacerbation within 12 months, ARIC 
Fibrinogen Threshold 400 mg/dL 

- Low Fibrinogen: 
  - # Patients: 1567 
  - # Outcomes: 72 
  - % Outcomes: 4.5%

- High Fibrinogen: 
  - # Patients: 222 
  - # Outcomes: 24 
  - % Outcomes: 10.8%
Figure 21.

**Time to First Hospitalized COPD Exacerbation within 12 months, CHS Fibrinogen Threshold 400 mg/dL**

- **Low Fibrinogen:**
  - # Patients: 1094
  - # Outcomes: 192
  - % Outcomes: 4.5%

- **High Fibrinogen:**
  - # Patients: 198
  - # Outcomes: 44
  - % Outcomes: 22.2%
Figure 22.

**Time to First Hospitalized COPD Exacerbation Within 12 months for ECLIPSE by Fibrinogen Classification, Fibrinogen Threshold 400 mg/dL**

- **Low Fibrinogen**
  - # Patients: 1,189
  - # Outcomes: 137
  - % Outcomes: 11.5%

- **High Fibrinogen**
  - # Patients: 929
  - # Outcomes: 198
  - % Outcomes: 21.3%
Figure 23.

Time to Death within 36 months ARIC
Threshold 250 mg/dL

Percentage of Patients with no event

<table>
<thead>
<tr>
<th></th>
<th>Low Fibrinogen:</th>
<th>High Fibrinogen:</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>207</td>
<td>1582</td>
</tr>
<tr>
<td># Outcomes</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>% Outcomes</td>
<td>1.9%</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Time (Months)
Figure 24.

Time to Death within 36 months CHS
Threshold 250 mg/dL

Percentage of Patients with no event

Time (Months)

Low Fibrinogen:
# Patients: 110
# Outcomes: 4
% Outcomes: 3.6%

High Fibrinogen:
# Patients: 1182
# Outcomes: 116
% Outcomes: 9.8%
Figure 25.

**Time to Death within 36 months ECLIPSE**

Threshold 250 mg/dL

- **Low Fibrinogen:**
  - # Patients: 51
  - # Outcomes: 6
  - % Outcomes: 11.7%

- **High Fibrinogen:**
  - # Patients: 2067
  - # Outcomes: 214
  - % Outcomes: 10.3%
Figure 26.

Time to Death within 36 months FHSOC
Threshold 250 mg/dL

- Low Fibrinogen:
  - # Patients: 10
  - # Outcomes: 1
  - % Outcomes: 10.0%

- High Fibrinogen:
  - # Patients: 135
  - # Outcomes: 12
  - % Outcomes: 8.8%
Figure 27.

Time to Death within 36 months NHANES
Threshold 250 mg/dL

Percentage of Patients with no event

Time (Months)

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Low Fibrinogen:
# Patients: 142
# Outcomes: 10
% Outcomes: 7%

High Fibrinogen:
# Patients: 890
# Outcomes: 136
% Outcomes: 15.2%
Time to Death within 36 months ARIC
Threshold 300 mg/dL

Percentage of Patients with no event

Time (Months)

Low Fibrinogen:
# Patients: 756
# Outcomes: 21
% Outcomes: 2.7%

High Fibrinogen:
# Patients: 1033
# Outcomes: 65
% Outcomes: 6.2%
Figure 29.

Time to Death within 36 months CHS Threshold 300 mg/dL

Percentage of Patients with no event

- **Low Fibrinogen:**
  - # Patients: 449
  - # Outcomes: 20
  - % Outcomes: 4.4%

- **High Fibrinogen:**
  - # Patients: 843
  - # Outcomes: 100
  - % Outcomes: 11.8%
Figure 30.

Time to Death within 36 months ECLIPSE
Threshold 300 mg/dL

Percentage of Patients with no event

Low Fibrinogen:
# Patients: 244
# Outcomes: 19
% Outcomes: 7.7%

High Fibrinogen:
# Patients: 1874
# Outcomes: 98
% Outcomes: 5.2%
Figure 31.

Time to Death within 36 months FHSOC
Threshold 300 mg/dL

Percentage of Patients with no event

Time (Months)

Low Fibrinogen:
# Patients: 42
# Outcomes: 2
% Outcomes: 4.7%

High Fibrinogen:
# Patients: 103
# Outcomes: 11
% Outcomes: 10.6%
Figure 32.

Time to Death within 36 months NHANES
Threshold 300 mg/dL

<table>
<thead>
<tr>
<th>Fibrinogen Level</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Outcome %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Fibrinogen</td>
<td>363</td>
<td>35</td>
<td>9.6%</td>
</tr>
<tr>
<td>High Fibrinogen</td>
<td>669</td>
<td>111</td>
<td>16.5%</td>
</tr>
</tbody>
</table>
Figure 33.

Time to Death Within 36 months ARIC Threshold 350 mg/dL

Percentage of Patients with no event

Low Fibrinogen:
# Patients: 1275
# Outcomes: 34
% Outcomes: 2.7%

High Fibrinogen:
# Patients: 514
# Outcomes: 52
% Outcomes: 10.1%
Figure 34.

Time to Death Within 36 months CHS
Threshold 350 mg/dL

Low Fibrinogen:
# Patients: 848
# Outcomes: 59
% Outcomes: 7.0%

High Fibrinogen:
# Patients: 444
# Outcomes: 61
% Outcomes: 13.7%
Figure 35.

Time to Death Within 36 months ECLIPSE
Threshold 350 mg/dL

Low Fibrinogen:
# Patients: 684
# Outcomes: 45
% Outcomes: 6.6%

High Fibrinogen:
# Patients: 1434
# Outcomes: 175
% Outcomes: 12.2%
Figure 36.

Time to Death Within 36 months FHSOC
Threshold 350 mg/dL

Low Fibrinogen:
# Patients: 95
# Outcomes: 8
% Outcomes: 8.4%

High Fibrinogen:
# Patients: 50
# Outcomes: 5
% Outcomes: 10.0%
Figure 37.

Time to Death Within 36 months NHANES
Threshold 350 mg/dL

Low Fibrinogen:
# Patients: 621
# Outcomes: 67
% Outcomes: 10.8%

High Fibrinogen:
# Patients: 411
# Outcomes: 79
% Outcomes: 19.2%
Figure 38.

Time to Death within 36 months ARIC
Threshold 400 mg/dL

Percentage of Patients with no event

Time (Months)

Low Fibrinogen:
#patients: 1567
#outcomes: 56
%Outcomes: 3.5%

High Fibrinogen:
#patients: 222
#outcomes: 30
%Outcomes: 13.5%
Figure 39.

**Time to Death within 36 months CHS**

**Threshold 400 mg/dL**

- **Low Fibrinogen:**
  - # Patients: 1094
  - # Outcomes: 89
  - % Outcomes: 8.1%

- **High Fibrinogen:**
  - # Patients: 198
  - # Outcomes: 31
  - % Outcomes: 15.6%
Figure 40.

Time to Death within 36 months ECLIPSE
Threshold 400 mg/dL

Percentage of Patients with no event

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Low Fibrinogen</th>
<th>High Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Patients: 1189</td>
<td># Patients: 929</td>
</tr>
<tr>
<td></td>
<td># Outcomes: 91</td>
<td># Outcomes: 57</td>
</tr>
<tr>
<td></td>
<td>% Outcomes: 7.6%</td>
<td>% Outcomes: 6.1%</td>
</tr>
</tbody>
</table>

Low Fibrinogen: 7.6%
High Fibrinogen: 6.1%
Figure 41.

Time to Death within 36 months FHSOC
Threshold 400 mg/dL

Low Fibrinogen:
# Patients: 121
# Outcomes: 11
% Outcomes: 9%

High Fibrinogen:
# Patients: 24
# Outcomes: 2
% Outcomes: 8.3%
Figure 42.

Time to Death within 36 months NHANES
Threshold 400 mg/dL

Percentage of Patients with no event

Time (Months)

Low Fibrinogen:
# Patients: 811
# Outcomes: 101
% Outcomes: 12.4%

High Fibrinogen:
# Patients: 221
# Outcomes: 45
% Outcomes: 20%