

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

### **Online Supplement: Appendix 4, Cox Model Tabular Results**

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**Table 1. COX Model for Patients with a COPD<sup>a</sup> Exacerbation within 12 Months (Fibrinogen Threshold = 250 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         |                                     |         |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|
|                                      | Total Population (N = 5199) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         |
|                                      | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value |
| <b>Number of Events</b>              | 667                         |         | 96                          |         | 236                         |         | 335                         |         | 94                                     |         | 241                                 |         | 127                                 |         |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |
| Yes (Unadjusted)                     |                             |         |                             |         |                             |         | 3.11<br>(2.45, 3.95)        |         | <0.0001                                |         |                                     |         |                                     |         |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| Fibrinogen Level < 250 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                   |         | 1                                   |         |
| Fibrinogen Level ≥ 250 (Unadjusted)  | 1.41<br>(0.97, 2.05)        | 0.07    | 1.99<br>(0.87, 4.56)        | 0.1     | 0.97<br>(0.62, 1.52)        | 0.89    | 4.24<br>(1.06, 17.01)       | 0.0418  | >999.99<br>(0.00, >999.99)             | 0.97    | 2.39<br>(0.59, 9.60)                | 0.22    | 1.45<br>(0.20, 10.32)               | 0.71    |
| Fibrinogen Level ≥ 250 (Adjusted)    | 1.41<br>(0.97, 2.05)        | 0.07    | 1.99<br>(0.87, 4.56)        | 0.1     | 0.97<br>(0.62, 1.52)        | 0.89    | 3.19<br>(0.80, 12.83)       | 0.1     | >999.99<br>(0.00, >999.99)             | 0.98    | 1.93<br>(0.48, 7.76)                | 0.36    | 1.18<br>(0.16, 8.44)                | 0.87    |
| FEV <sub>1</sub> (baseline)          |                             |         |                             |         |                             |         | 0.25<br>(0.19, 0.33)        | <0.0001 | 0.22<br>(0.13, 0.37)                   | <0.0001 | 0.35<br>(0.25, 0.50)                | <0.0001 | 0.45<br>(0.28, 0.73)                | 0.0012  |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc., (reference 20 in manuscript).

(2) Exacerbation definition: In ARIC and CHS hospitalizations with ICD-9 codes (490, 491, 492 and 496), in the rest of the databases the CE event file was used to identify exacerbations based on a indicator variable marked as valid exacerbation and the variable.

CETERM = 'COPD Exacerbation' or HOSCAT = 'COPD' in the hospitalization file. ECLIPSE uses the SUPPCE to find hospitalizations due to COPD exacerbations by using variable QNAM = 'EXACHOSP'

(3) The unadjusted HR for Fibrinogen level was derived from a model including age as a covariate.

(4) Variable selection process: Covariates with p-value < 0.2 in univariate analyses were entered into the model with fibrinogen level and age. Any covariates that modified the HR of fibrinogen level by at least 10% were selected for multivariate analysis.

The multivariate Cox model was stratified by study class and backward selection was performed with fibrinogen level and age as forced covariates.

<sup>a</sup>COPD patient definition: FEV<sub>1</sub>/FVC < 70%, FEV<sub>1</sub> % predicted < 80% and age 40+

ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity

**Table 2. COX Model for COPD<sup>a</sup> Patients with All-cause Mortality within 36 Months (Fibrinogen Threshold = 250 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|---------|--------|--|----------------------|--|--------|--|----------------------|--|----------------------|--|----------------------|--|--------|--|----------------------|--|---------|--|
|                                      | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
|                                      | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value | HR (95% CI)                 | p-value |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
| <b>Number of Events</b>              | 585                         |         | 86                          |         | 120                         |         | 220                         |         | 108                                    |         | 112                                 |         | 59                                  |         | 13                         |         | 146                         |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |                            |         |                             |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
| Yes (Unadjusted)                     |                             |         |                             |         |                             |         | 1.16<br>(0.89, 1.52)        |         | 0.26                                   |         |                                     |         |                                     |         |                            |         |                             |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
| Fibrinogen level < 250 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                   |         | 1                                   |         | 1                          |         | 1                           |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |
| Fibrinogen level ≥ 250 (Unadjusted)  | 1.71<br>(1.14, 2.56)        |         | 0.0092                      |         | 2.68<br>(0.98, 7.30)        |         | 0.05                        |         | 2.68<br>(0.99, 7.25)                   |         | 0.05                                |         | 0.66<br>(0.29, 1.48)                |         | 0.31                       |         | 0.76<br>(0.24, 2.40)        |         | 0.64   |  | 0.53<br>(0.17, 1.66) |  | 0.28   |  | 0.40<br>(0.05, 2.87) |  | 0.36                 |  | 0.92<br>(0.12, 7.10) |  | 0.94   |  | 1.69<br>(0.89, 3.21) |  | 0.11    |  |
| Fibrinogen level ≥ 250 (Adjusted)    | 1.65<br>(1.10, 2.47)        |         | 0.0157                      |         | 2.68<br>(0.98, 7.30)        |         | 0.05                        |         | 2.68<br>(0.99, 7.25)                   |         | 0.05                                |         | 0.56<br>(0.25, 1.26)                |         | 0.16                       |         | 0.57<br>(0.18, 1.81)        |         | 0.34   |  | 0.39<br>(0.12, 1.25) |  | 0.11   |  | 0.25<br>(0.03, 1.86) |  | 0.18                 |  | 0.92<br>(0.12, 7.10) |  | 0.94   |  | 1.69<br>(0.89, 3.23) |  | 0.11    |  |
| Gender (Reference = Male)            | 0.46<br>(0.37, 0.55)        |         | <0.0001                     |         |                             |         |                             |         | 0.64<br>(0.47, 0.86)                   |         | 0.0031                              |         |                                     |         |                            |         |                             |         |        |  |                      |  |        |  |                      |  | 0.40<br>(0.27, 0.59) |  | <0.0001              |  |        |  |                      |  |         |  |
| Age                                  | 1.05<br>(1.04, 1.06)        |         | <0.0001                     |         | 1.08<br>(1.03, 1.12)        |         | 0.0012                      |         | 1.08<br>(1.04, 1.11)                   |         | <0.0001                             |         | 1.05<br>(1.03, 1.07)                |         | <0.0001                    |         | 1.06<br>(1.03, 1.10)        |         | 0.0003 |  | 1.06<br>(1.03, 1.09) |  | 0.0002 |  | 1.07<br>(1.02, 1.11) |  | 0.0036               |  | 1.18<br>(1.07, 1.30) |  | 0.0008 |  | 1.06<br>(1.04, 1.08) |  | <0.0001 |  |
| BMI                                  | 0.98<br>(0.96, 1.00)        |         | 0.0135                      |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |         |        |  |                      |  |        |  |                      |  |                      |  | 0.95<br>(0.92, 0.99) |  | 0.008  |  |                      |  |         |  |
| Diastolic BP                         | 0.99<br>(0.98, 0.99)        |         | 0.0012                      |         |                             |         |                             |         | 0.98<br>(0.96, 0.99)                   |         | 0.0026                              |         | 0.97<br>(0.95, 0.99)                |         | 0.0047                     |         |                             |         |        |  |                      |  |        |  |                      |  |                      |  |                      |  |        |  |                      |  |         |  |

| Patient Characteristics  | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |         |
|--|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|---------|
|  | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |         |
|  | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value | HR (95% CI)                 | p-value |
| Systolic BP  | 1.01 (1.00, 1.01)           | 0.0003  |                             |         |                             |         | 1.01 (1.00, 1.02)           | 0.0282  | 1.02 (1.01, 1.03)                      | 0.0028  |                                     |         |                                     |         |                            |         |                             |         |
| History of COPD  | 1.27 (1.01, 1.60)           | 0.0437  |                             |         |                             |         |                             |         | 0.23 (0.07, 0.72)                      | 0.0115  |                                     |         |                                     |         |                            |         | 1.86 (1.32, 2.62)           | 0.0004  |
| Diabetes   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         | 1.86 (1.22, 2.84)           | 0.0037  |
| Asthma   |                             |         |                             |         |                             |         |                             |         | 1.79 (1.22, 2.63)                      | 0.0029  |                                     |         | 0.45 (0.25, 0.81)                   | 0.008   |                            |         |                             |         |
| Pulmonary or Chest Illness   | 0.66 (0.53, 0.83)           | 0.0003  |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Cardiovascular Disease   | 1.24 (1.01, 1.51)           | 0.036   |                             |         |                             |         | 1.36 (1.03, 1.81)           | 0.0311  |  |         | 1.49 (1.00, 2.22)                   | 0.0484  |                                     |         |                            |         |                             |         |
| FEV <sub>1</sub> (baseline)  | 0.48 (0.40, 0.57)           | <0.0001 |                             |         |                             |         | 0.29 (0.20, 0.42)           | <0.0001 | 0.39 (0.25, 0.62)                      | <0.0001 | 0.27 (0.15, 0.46)                   | <0.0001 | 0.20 (0.08, 0.49)                   | 0.0004  |                            |         | 0.60 (0.42, 0.86)           | 0.0061  |
| <b>Fibrinogen Threshold Model with History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level < 250 (Reference)                                   |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 250 (Unadjusted)                                  |                             |         |                             |         |                             |         | 0.66 (0.29, 1.48)           | 0.31    |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 250 (Adjusted)                                    |                             |         |                             |         |                             |         | 0.56 (0.25, 1.26)           | 0.16    |  |         |                                     |         |                                     |         |                            |         |                             |         |

| Patient Characteristics       | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |  |
|-------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|--|
|                               | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |  |
|                               | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value |                             |  |
| History of COPD Exacerbations |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |
| No (Reference)                |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Yes                           |                             |         |                             |         |                             |         | 1.00 (0.77, 1.31)           | 0.99    |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Gender (Reference = Male)     |                             |         |                             |         |                             |         | 0.64 (0.47, 0.86)           | 0.0031  |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Age                           |                             |         |                             |         |                             |         | 1.05 (1.03, 1.07)           | <0.0001 |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Diastolic BP                  |                             |         |                             |         |                             |         | 0.98 (0.96, 0.99)           | 0.0026  |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Systolic BP                   |                             |         |                             |         |                             |         | 1.01 (1.00, 1.02)           | 0.0282  |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Cardiovascular Disease        |                             |         |                             |         |                             |         | 1.36 (1.03, 1.81)           | 0.0312  |  |         |                                     |         |                                     |         |                            |         |                             |  |
| FEV <sub>1</sub> (baseline)   |                             |         |                             |         |                             |         | 0.29 (0.20, 0.42)           | <0.0001 |  |         |                                     |         |                                     |         |                            |         |                             |  |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc., (reference 20 in manuscript).

(2) Exacerbation definition: In ARIC and CHS hospitalizations with ICD-9 codes (490, 491, 492 and 496), in the rest of the databases the CE event file was used to identify exacerbations based on an indicator variable marked as valid exacerbation and the variable.

CETERM = 'COPD Exacerbation' or HOSCAT = 'COPD' in the hospitalization file. ECLIPSE uses the SUPPCE to find hospitalizations due to COPD exacerbations by using variable QNAM = 'EXACHOSP'

(3) The unadjusted HR for Fibrinogen level was derived from a model including age as a covariate.

(4) Variable selection process: Covariates with p-value < 0.2 in univariate analyses were entered into the model with fibrinogen level and age. Any covariates that modified the HR of fibrinogen level by at least 10% were selected for multivariate analysis.

The multivariate Cox model was stratified by study class and backward selection was performed with fibrinogen level and age as forced covariates.

<sup>a</sup>COPD patient definition: FEV<sub>1</sub>/FVC < 70%, FEV<sub>1</sub> % predicted < 80% and age 40+

<sup>b</sup>We used prediction equations from Hankinson et al (reference 18 in manuscript) to derive FEV<sub>1</sub> percent predicted for NHANES subjects. Because the integrated database classifies ethnicity as white/nonwhite, Mexican Americans in NHANES were classified as white in computing FEV<sub>1</sub> percent predicted. We then applied the definition of COPD (including <80% FEV<sub>1</sub> % predicted) and identified 1032 patients as having COPD, as compared with 1071 patients in Valvi et al (reference 19 in manuscript), a loss of 39 patients or  $(1071-1032/1071*100)$  3.6%.

ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, blood pressure; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV<sub>1</sub>, forced expiratory volume in 1 second; FHSOC, Framingham Heart Study Offspring Cohort; FVC, forced vital capacity; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey

**Table 3. COX Model for Patients with a COPD<sup>a</sup> Exacerbation within 12 Months (Fibrinogen Threshold = 300 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         |                                     |         |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|
|                                      | Total Population (N = 5199) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         |
|                                      | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value |
| <b>Number of Events</b>              | 667                         |         | 96                          |         | 236                         |         | 335                         |         | 94                                     |         | 241                                 |         | 127                                 |         |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |
| Yes (Unadjusted)                     |                             |         |                             |         |                             |         | 3.11<br>(2.45, 3.95)        | <0.0001 |  |         |                                     |         |                                     |         |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| Fibrinogen level < 300 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                   |         | 1                                   |         |
| Fibrinogen level ≥ 300 (Unadjusted)  | 1.49<br>(1.21, 1.82)        | 0.0001  | 2.24<br>(1.41, 3.56)        | 0.0006  | 1.03<br>(0.79, 1.35)        | 0.81    | 2.39<br>(1.49, 3.85)        | 0.0003  | 1.84<br>(0.85, 3.96)                   | 0.12    | 2.55<br>(1.39, 4.67)                | 0.0024  | 3.34<br>(1.24, 9.05)                | 0.0175  |
| Fibrinogen level ≥ 300 (Adjusted)    | 1.49<br>(1.21, 1.82)        | 0.0001  | 2.24<br>(1.41, 3.56)        | 0.0006  | 1.03<br>(0.79, 1.35)        | 0.81    | 2.00<br>(1.24, 3.22)        | 0.0042  | 1.48<br>(0.68, 3.21)                   | 0.32    | 2.28<br>(1.24, 4.17)                | 0.0077  | 2.98<br>(1.10, 8.08)                | 0.0317  |
| FEV <sub>1</sub> (baseline)          |                             |         |                             |         |                             |         | 0.25<br>(0.19, 0.33)        | <0.0001 | 0.22<br>(0.13, 0.37)                   | <0.0001 | 0.36<br>(0.25, 0.51)                | <0.0001 | 0.47<br>(0.29, 0.77)                | 0.0026  |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc., (reference 20 in manuscript).

(2) Exacerbation definition: In ARIC and CHS hospitalizations with ICD-9 codes (490, 491, 492 and 496), in the rest of the databases the CE event file was used to identify exacerbations based on a indicator variable marked as valid exacerbation and the variable

CETERM = 'COPD Exacerbation' or HOSCAT = 'COPD' in the hospitalization file. ECLIPSE uses the SUPPCE to find hospitalizations due to COPD exacerbations by using variable QNAM = 'EXACHOSP'



(3) The unadjusted HR for Fibrinogen level was derived from a model including age as a covariate.

(4) Variable selection process: Covariates with p-value < 0.2 in univariate analyses were entered into the model with fibrinogen level and age. Any covariates that modified the HR of fibrinogen level by at least 10% were selected for multivariate analysis.

The multivariate Cox model was stratified by study class and backward selection was performed with fibrinogen level and age as forced covariates.

<sup>a</sup> COPD patient definition:  $FEV_1/FVC < 70\%$ ,  $FEV_1$  % predicted < 80% and age 40+

ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints;  $FEV_1$ , forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio

**Table 4. COX Model for COPD<sup>a</sup> Patients with All-cause Mortality within 36 Months (Fibrinogen Threshold = 300 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                      |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |         |         |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|--------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|---------|---------|
|                                      | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbations (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |         |         |
|                                      | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                          | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value |                             |         |         |
| <b>Number of Events</b>              | 585                         |         | 86                          |         | 120                         |         | 220                         |         | 108                                    |         | 112                                  |         | 59                                  |         | 13                         |         | 146                         |         |         |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                      |         |                                     |         |                            |         |                             |         |         |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                      |         |                                     |         |                            |         |                             |         |         |
| Yes (Unadjusted)                     |                             |         |                             |         |                             |         | 1.16 (0.89, 1.52)           |         | 0.26                                   |         |                                      |         |                                     |         |                            |         |                             |         |         |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                      |         |                                     |         |                            |         |                             |         |         |
| Fibrinogen level < 300 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                    |         | 1                                   |         | 1                          |         | 1                           |         |         |
| Fibrinogen level ≥ 300 (Unadjusted)  | 1.83 (1.47, 2.29)           | <0.0001 | 2.19 (1.34, 3.59)           | 0.0018  | 2.71 (1.67, 4.38)           | <0.0001 | 1.19 (0.74, 1.90)           | 0.48    | 1.13 (0.59, 2.18)                      | 0.71    | 1.22 (0.62, 2.41)                    | 0.57    | 5.34 (0.74, 38.52)                  | 0.1     | 1.89 (0.41, 8.64)          | 0.41    | 1.56 (1.06, 2.28)           | 0.0224  |         |
| Fibrinogen level ≥ 300 (Adjusted)    | 1.76 (1.41, 2.20)           | <0.0001 | 2.19 (1.34, 3.59)           | 0.0018  | 2.71 (1.67, 4.38)           | <0.0001 | 1.02 (0.64, 1.64)           | 0.93    | 0.84 (0.43, 1.64)                      | 0.61    | 1.12 (0.57, 2.22)                    | 0.74    | 4.64 (0.64, 33.42)                  | 0.13    | 1.89 (0.41, 8.64)          | 0.41    | 1.39 (0.95, 2.05)           | 0.09    |         |
| Gender (Reference = Male)            |                             |         |                             |         |                             |         | 0.63 (0.47, 0.85)           |         | 0.0026                                 |         |                                      |         |                                     |         |                            |         | 0.40 (0.27, 0.60)           |         | <0.0001 |
| Age                                  | 1.07 (1.06, 1.08)           | <0.0001 | 1.07 (1.02, 1.12)           | 0.0024  | 1.08 (1.04, 1.11)           | <0.0001 | 1.05 (1.03, 1.07)           | <0.0001 | 1.06 (1.03, 1.10)                      | 0.0004  | 1.06 (1.03, 1.10)                    | <0.0001 | 1.07 (1.03, 1.12)                   | 0.0011  | 1.17 (1.07, 1.29)          | 0.0011  | 1.06 (1.04, 1.08)           | <0.0001 |         |
| BMI                                  |                             |         |                             |         |                             |         |                             |         |  |         |                                      |         |                                     |         |                            |         | 0.95 (0.92, 0.99)           |         | 0.0102  |
| Diastolic BP                         |                             |         |                             |         |                             |         | 0.98 (0.96, 0.99)           |         | 0.0027                                 |         | 0.97 (0.95, 0.99)                    |         | 0.0046                              |         |                            |         |                             |         |         |

| Patient Characteristics  | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                      |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |         |
|--|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|--------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|---------|
|  | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbations (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |         |
|  | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                          | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value | HR (95% CI)                 | p-value |
| Systolic BP  |                             |         |                             |         |                             |         | 1.01<br>(1.00, 1.02)        | 0.0274  | 1.02<br>(1.01, 1.03)                   | 0.0027  |                                      |         |                                     |         |                            |         |                             |         |
| History of COPD  |                             |         |                             |         |                             |         |                             |         | 0.23<br>(0.07, 0.73)                   | 0.0122  |                                      |         |                                     |         |                            |         | 1.84<br>(1.30, 2.60)        | 0.0005  |
| Diabetes   |                             |         |                             |         |                             |         |                             |         |  |         |                                      |         |                                     |         |                            |         | 1.84<br>(1.21, 2.80)        | 0.0046  |
| Asthma   |                             |         |                             |         |                             |         |                             |         | 1.79<br>(1.22, 2.63)                   | 0.0031  |                                      |         |                                     |         |                            |         |                             |         |
| Cardiovascular Disease   |                             |         |                             |         |                             |         | 1.35<br>(1.02, 1.80)        | 0.0347  |  |         |                                      |         |                                     |         |                            |         |                             |         |
| FEV <sub>1</sub> (baseline)  | 0.64<br>(0.55, 0.76)        | <0.0001 |                             |         |                             |         | 0.29<br>(0.21, 0.42)        | <0.0001 | 0.39<br>(0.25, 0.62)                   | <0.0001 | 0.28<br>(0.16, 0.49)                 | <0.0001 | 0.23<br>(0.10, 0.56)                | 0.0011  |                            |         | 0.61<br>(0.42, 0.88)        | 0.0081  |
| <b>Fibrinogen Threshold Model with History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                      |         |                                     |         |                            |         |                             |         |
| Fibrinogen level < 300 (Reference)                                   |                             |         |                             |         |                             |         | 1                           |         |  |         |                                      |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 300 (Unadjusted)                                  |                             |         |                             |         |                             |         | 1.19<br>(0.74, 1.90)        | 0.48    |  |         |                                      |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 300 (Adjusted)                                    |                             |         |                             |         |                             |         | 1.02<br>(0.64, 1.64)        | 0.93    |  |         |                                      |         |                                     |         |                            |         |                             |         |
| History of COPD Exacerbations  |                             |         |                             |         |                             |         |                             |         |  |         |                                      |         |                                     |         |                            |         |                             |         |

| Patient Characteristics     | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                      |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |  |
|-----------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|--------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|--|
|                             | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbations (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |  |
|                             | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                          | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value |                             |  |
| No (Reference)              |                             |         |                             |         |                             |         | 1                           |         |  |         |                                      |         |                                     |         |                            |         |                             |  |
| Yes                         |                             |         |                             |         |                             |         | 1.00 (0.76, 1.31)           | 0.99    |  |         |                                      |         |                                     |         |                            |         |                             |  |
| Gender (Reference = Male)   |                             |         |                             |         |                             |         | 0.63 (0.47, 0.85)           | 0.0026  |  |         |                                      |         |                                     |         |                            |         |                             |  |
| Age                         |                             |         |                             |         |                             |         | 1.05 (1.03, 1.07)           | <0.0001 |  |         |                                      |         |                                     |         |                            |         |                             |  |
| Diastolic BP                |                             |         |                             |         |                             |         | 0.98 (0.96, 0.99)           | 0.0028  |  |         |                                      |         |                                     |         |                            |         |                             |  |
| Systolic BP                 |                             |         |                             |         |                             |         | 1.01 (1.00, 1.02)           | 0.0274  |  |         |                                      |         |                                     |         |                            |         |                             |  |
| Cardiovascular Disease      |                             |         |                             |         |                             |         | 1.35 (1.02, 1.80)           | 0.0347  |  |         |                                      |         |                                     |         |                            |         |                             |  |
| FEV <sub>1</sub> (baseline) |                             |         |                             |         |                             |         | 0.29 (0.21, 0.42)           | <0.0001 |  |         |                                      |         |                                     |         |                            |         |                             |  |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc., (reference 20 in manuscript).

(2) Exacerbation definition: In ARIC and CHS hospitalizations with ICD-9 codes (490, 491, 492 and 496), in the rest of the databases the CE event file was used to identify exacerbations based on a indicator variable marked as valid exacerbation and the variable.

CETERM = 'COPD Exacerbation' or HOSCAT = 'COPD' in the hospitalization file. ECLIPSE uses the SUPPCE to find hospitalizations due to COPD exacerbations by using variable QNAM = 'EXACHOSP'

(3) The unadjusted HR for Fibrinogen level was derived from a model including age as a covariate.

(4) Variable selection process: Covariates with p-value < 0.2 in univariate analyses were entered into the model with fibrinogen level and age. Any covariates that modified the HR of fibrinogen level by at least 10% were selected for multivariate analysis.

The multivariate Cox model was stratified by study class and backward selection was performed with fibrinogen level and age as forced covariates.

<sup>a</sup>COPD patient definition: FEV<sub>1</sub>/FVC < 70%, FEV<sub>1</sub> % predicted < 80% and age 40+

<sup>b</sup>We used prediction equations from Hankinson et al (reference 18 in manuscript) to derive FEV<sub>1</sub> percent predicted for NHANES subjects. Because the integrated database classifies ethnicity as white/nonwhite, Mexican Americans in NHANES were classified as white in computing FEV<sub>1</sub> percent predicted. We then applied the definition of COPD (including <80% FEV<sub>1</sub> % predicted) and identified 1032 patients as having COPD, as compared with 1071 patients in Valvi et al (reference 19 in manuscript), a loss of 39 patients or  $(1071-1032/1071*100)$  3.6%.

ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, blood pressure; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV<sub>1</sub>, forced expiratory volume in 1 second; FHSOC, Framingham Heart Study Offspring Cohort; FVC, forced vital capacity; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey

**Table 5. COX Model for Patients with a COPD<sup>a</sup> Exacerbation within 12 Months (Fibrinogen Threshold = 350 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         |                                     |         |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|
|                                      | Total Population (N = 5199) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         |
|                                      | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value |
| <b>Number of Events</b>              | 667                         |         | 96                          |         | 236                         |         | 335                         |         | 94                                     |         | 241                                 |         | 127                                 |         |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |
| Yes (unadjusted)                     |                             |         |                             |         |                             |         | 3.11 (2.45, 3.95)           |         | <0.0001                                |         |                                     |         |                                     |         |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| Fibrinogen level < 350 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                   |         | 1                                   |         |
| Fibrinogen level ≥ 350 (Unadjusted)  | 1.64 (1.39, 1.93)           | <0.0001 | 2.45 (1.64, 3.66)           | <0.0001 | 1.11 (0.85, 1.44)           | 0.45    | 2.04 (1.56, 2.67)           | <0.0001 | 1.65 (1.04, 2.63)                      | 0.0338  | 2.04 (1.46, 2.84)                   | <0.0001 | 2.02 (1.23, 3.33)                   | 0.0057  |
| Fibrinogen level ≥ 350 (Adjusted)    | 1.64 (1.39, 1.93)           | <0.0001 | 2.45 (1.64, 3.66)           | <0.0001 | 1.11 (0.85, 1.44)           | 0.45    | 1.72 (1.31, 2.26)           | <0.0001 | 1.39 (0.87, 2.22)                      | 0.16    | 1.80 (1.29, 2.51)                   | 0.0006  | 2.02 (1.23, 3.33)                   | 0.0057  |
| FEV <sub>1</sub> (baseline)          |                             |         |                             |         |                             |         | 0.26 (0.20, 0.35)           |         | <0.0001                                |         | 0.23 (0.13, 0.38)                   |         | <0.0001                             |         |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc.

(2) Exacerbation definition: In ARIC and CHS hospitalizations with ICD-9 codes (490, 491, 492 and 496), in the rest of the databases the CE event file was used to identify exacerbations based on a indicator variable marked as valid exacerbation and the variable.

CETERM = 'COPD Exacerbation' or HOSCAT = 'COPD' in the hospitalization file. ECLIPSE uses the SUPPCE to find hospitalizations due to COPD exacerbations by using variable QNAM = 'EXACHOSP'

(3) The unadjusted HR for Fibrinogen level was derived from a model including age as a covariate.

(4) Variable selection process: Covariates with p-value < 0.2 in univariate analyses were entered into the model with fibrinogen level and age. Any covariates that modified the HR of fibrinogen level by at least 10% were selected for multivariate analysis.

The multivariate Cox model was stratified by study class and backward selection was performed with fibrinogen level and age as forced covariates.

<sup>a</sup>COPD patient definition:  $FEV_1/FVC < 70\%$ ,  $FEV_1$  % predicted < 80% and age 40+

ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints;  $FEV_1$ , forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio

**Table 6. COX Model for COPD<sup>a</sup> Patients with All-cause Mortality within 36 Months (Fibrinogen Threshold = 350 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|--|--------|--|-------------------|--|---------|--|-------------------|--|-------|--|-------------------|--|--------|--|-------------------|--|---------|--|
|                                      | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
|                                      | HR (95% CI)                 | P-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| <b>Number of Events</b>              | 585                         |         | 86                          |         | 120                         |         | 220                         |         | 108                                    |         | 112                                 |         | 59                                  |         | 13                         |         | 146                         |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |                            |         |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| Yes (Unadjusted)                     |                             |         |                             |         |                             |         | 1.16 (0.89, 1.52)           |         | 0.26                                   |         |                                     |         |                                     |         |                            |         |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| Fibrinogen level < 350 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                   |         | 1                                   |         | 1                          |         | 1                           |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| Fibrinogen level ≥ 350 (Unadjusted)  | 2.02 (1.62, 2.41)           |         | <0.0001                     |         | 3.82 (2.48, 5.89)           |         | <0.0001                     |         | 2.07 (1.44, 2.95)                      |         | <0.0001                             |         | 1.72 (1.23, 2.38)                   |         | 0.0013                     |         | 1.93 (1.21, 3.10)           |  | 0.0062 |  | 1.48 (0.94, 2.34) |  | 0.09    |  | 1.42 (0.72, 2.80) |  | 0.32  |  | 1.07 (0.35, 3.29) |  | 0.9    |  | 1.68 (1.22, 2.33) |  | 0.0017  |  |
| Fibrinogen level ≥ 350 (Adjusted)    | 1.94 (1.62, 2.31)           |         | <0.0001                     |         | 3.82 (2.48, 5.89)           |         | <0.0001                     |         | 2.07 (1.44, 2.95)                      |         | <0.0001                             |         | 1.49 (1.07, 2.08)                   |         | 0.0176                     |         | 1.67 (1.04, 2.68)           |  | 0.0352 |  | 1.30 (0.82, 2.06) |  | 0.27    |  | 1.28 (0.65, 2.53) |  | 0.47  |  | 1.07 (0.35, 3.29) |  | 0.9    |  | 1.56 (1.12, 2.17) |  | 0.0079  |  |
| Age                                  | 1.07 (1.06, 1.08)           |         | <0.0001                     |         | 1.07 (1.02, 1.12)           |         | 0.003                       |         | 1.08 (1.04, 1.11)                      |         | <0.0001                             |         | 1.05 (1.03, 1.08)                   |         | <0.0001                    |         | 1.06 (1.02, 1.09)           |  | 0.001  |  | 1.06 (1.03, 1.10) |  | <0.0001 |  | 1.07 (1.03, 1.12) |  | 0.001 |  | 1.18 (1.07, 1.30) |  | 0.0008 |  | 1.08 (1.06, 1.10) |  | <0.0001 |  |
| Diastolic BP                         |                             |         |                             |         |                             |         |                             |         | 0.98 (0.97, 0.99)                      |         | 0.008                               |         | 0.97 (0.95, 0.99)                   |         | 0.0069                     |         |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |
| Systolic BP                          |                             |         |                             |         |                             |         |                             |         | 1.01 (1.00, 1.02)                      |         | 0.0492                              |         | 1.02 (1.01, 1.03)                   |         | 0.0033                     |         |                             |  |        |  |                   |  |         |  |                   |  |       |  |                   |  |        |  |                   |  |         |  |



| Patient Characteristics  | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |         |
|--|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|---------|
|  | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |         |
|  | HR (95% CI)                 | P-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value | HR (95% CI)                 | p-value |
| History of COPD  |                             |         |                             |         |                             |         |                             |         | 0.24 (0.07, 0.75)                      | 0.0141  |                                     |         |                                     |         |                            |         | 2.01 (1.44, 2.81)           | <0.0001 |
| Diabetes   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         | 1.82 (1.21, 2.73)           | 0.0041  |
| Asthma   |                             |         |                             |         |                             |         |                             |         | 1.72 (1.17, 2.53)                      | 0.0054  |                                     |         |                                     |         |                            |         |                             |         |
| Cardio-vascular Disease  |                             |         |                             |         |                             |         | 1.34 (1.01, 1.78)           | 0.0405  |  |         |                                     |         |                                     |         |                            |         |                             |         |
| FEV <sub>1</sub> (baseline)  | 0.66 (0.56, 0.78)           | <0.0001 |                             |         |                             |         | 0.35 (0.25, 0.50)           | <0.0001 | 0.42 (0.27, 0.66)                      | 0.0002  | 0.29 (0.17, 0.50)                   | <0.0001 | 0.23 (0.10, 0.55)                   | 0.0009  |                            |         |                             |         |
| <b>Fibrinogen Threshold Model with History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level < 350 (Reference)                                   |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 350 (Unadjusted)                                  |                             |         |                             |         |                             |         | 1.72 (1.23, 2.38)           | 0.0013  |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 350 (Adjusted)                                    |                             |         |                             |         |                             |         | 1.49 (1.07, 2.08)           | 0.0175  |  |         |                                     |         |                                     |         |                            |         |                             |         |
| History of COPD Exacerbations  |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |         |
| No   |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |                            |         |                             |         |

| Patient Characteristics     | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |  |
|-----------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|--|
|                             | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |  |
|                             | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value |                             |  |
| (Reference)                 |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Yes                         |                             |         |                             |         |                             |         | 0.98 (0.75, 1.29)           | 0.91    |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Age                         |                             |         |                             |         |                             |         | 1.05 (1.03, 1.08)           | <0.0001 |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Diastolic BP                |                             |         |                             |         |                             |         | 0.98 (0.97, 0.99)           | 0.0082  |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Systolic BP                 |                             |         |                             |         |                             |         | 1.01 (1.00, 1.02)           | 0.0493  |  |         |                                     |         |                                     |         |                            |         |                             |  |
| Cardio-vascular Disease     |                             |         |                             |         |                             |         | 1.34 (1.01, 1.78)           | 0.0404  |  |         |                                     |         |                                     |         |                            |         |                             |  |
| FEV <sub>1</sub> (baseline) |                             |         |                             |         |                             |         | 0.35 (0.25, 0.50)           | <0.0001 |  |         |                                     |         |                                     |         |                            |         |                             |  |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc., (reference 20 in manuscript).

(2) Exacerbation definition: In ARIC and CHS hospitalizations with ICD-9 codes (490, 491, 492 and 496), in the rest of the databases the CE event file was used to identify exacerbations based on a indicator variable marked as valid exacerbation and the variable.

CETERM = 'COPD Exacerbation' or HOSCAT = 'COPD' in the hospitalization file. ECLIPSE uses the SUPPCE to find hospitalizations due to COPD exacerbations by using variable QNAM = 'EXACHOSP'

(3) The unadjusted HR for Fibrinogen level was derived from a model including age as a covariate.

(4) Variable selection process: Covariates with p-value < 0.2 in univariate analyses were entered into the model with fibrinogen level and age. Any covariates that modified the HR of fibrinogen level by at least 10% were selected for multivariate analysis.

The multivariate Cox model was stratified by study class and backward selection was performed with fibrinogen level and age as forced covariates.

<sup>a</sup>COPD patient definition: FEV<sub>1</sub>/FVC < 70%, FEV<sub>1</sub> % predicted < 80% and age 40+

**\*\*Reference category for comorbidities is the absence of the comorbidity**

<sup>b</sup>We used prediction equations from Hankinson et al (reference 18 in manuscript) to derive FEV<sub>1</sub> percent predicted for NHANES subjects. Because the integrated database classifies ethnicity as white/nonwhite, Mexican Americans in NHANES were classified as white in computing FEV<sub>1</sub> percent predicted. We then applied the definition of COPD (including <80% FEV<sub>1</sub> % predicted) and identified 1032 patients as having COPD, as compared with 1071 patients in Valvi et al (reference 19 in manuscript) a loss of 39 patients or  $(1071-1032/1071*100)$  3.6%.

ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, blood pressure; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV<sub>1</sub>, forced expiratory volume in 1 second; FHSOC, Framingham Heart Study Offspring Cohort; FVC, forced vital capacity; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey

**Table 7. COX Model for Patients with a COPD<sup>a</sup> Exacerbation within 12 Months (Fibrinogen Threshold = 400 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         |                                     |         |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|
|                                      | Total Population (N = 5199) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         |
|                                      | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value |
| <b>Number of Events</b>              | 667                         |         | 96                          |         | 236                         |         | 335                         |         | 94                                     |         | 241                                 |         | 127                                 |         |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |
| Yes (Unadjusted)                     |                             |         |                             |         |                             |         | 3.11 (2.45, 3.95)           |         | <0.0001                                |         |                                     |         |                                     |         |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |
| Fibrinogen level < 400 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                   |         | 1                                   |         |
| Fibrinogen level ≥ 400 (Unadjusted)  | 1.81 (1.54, 2.14)           | <0.0001 | 2.44 (1.54, 3.88)           | 0.0002  | 1.34 (0.97, 1.86)           | 0.08    | 1.97 (1.59, 2.46)           | <0.0001 | 1.73 (1.16, 2.60)                      | 0.0078  | 1.85 (1.43, 2.40)                   | <0.0001 | 1.80 (1.25, 2.59)                   | 0.0015  |
| Fibrinogen level ≥ 400 (Adjusted)    | 1.81 (1.54, 2.14)           | <0.0001 | 2.44 (1.54, 3.88)           | 0.0002  | 1.34 (0.97, 1.86)           | 0.08    | 1.61 (1.29, 2.01)           | <0.0001 | 1.36 (0.90, 2.05)                      | 0.14    | 1.64 (1.26, 2.13)                   | 0.0002  | 1.80 (1.25, 2.59)                   | 0.0015  |
| FEV <sub>1</sub> (baseline)          |                             |         |                             |         |                             |         | 0.27 (0.20, 0.36)           |         | <0.0001                                |         | 0.23 (0.14, 0.39)                   |         | <0.0001                             |         |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc., (reference 20 in manuscript).

(2) Exacerbation definition: In ARIC and CHS hospitalizations with ICD-9 codes (490, 491, 492 and 496), in the rest of the databases the CE event file was used to identify exacerbations based on a indicator variable marked as valid exacerbation and the variable

CETERM = 'COPD Exacerbation' or HOSCAT = 'COPD' in the hospitalization file. ECLIPSE uses the SUPPCE to find hospitalizations due to COPD exacerbations by using variable QNAM = 'EXACHOSP'

(3) The unadjusted HR for Fibrinogen level was derived from a model including age as a covariate.

(4) Variable selection process: Covariates with p-value < 0.2 in univariate analyses were entered into the model with fibrinogen level and age. Any covariates that modified the HR of fibrinogen level by at least 10% were selected for multivariate analysis.

The multivariate Cox model was stratified by study class and backward selection was performed with fibrinogen level and age as forced covariates.

<sup>a</sup>COPD patient definition: FEV<sub>1</sub>/FVC < 70%, FEV<sub>1</sub> % predicted < 80% and age 40+

ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; EDTA, Ethylenediaminetetraacetic acid; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio

**Table 8. COX Model for COPD<sup>a</sup> Patients with All-cause Mortality within 36 Months (Fibrinogen Threshold = 400 mg/dL)**

| Patient Characteristics              | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |         |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
|--------------------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|--|---------|--|-------------------|--|---------|--|-------------------|--|-------------------|--|-------------------|--|--------|--|-------------------|--|---------|--|
|                                      | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |         | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
|                                      | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value |                             |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
| <b>Number of Events</b>              | 585                         |         | 86                          |         | 120                         |         | 220                         |         | 108                                    |         | 112                                 |         | 59                                  |         | 13                         |         | 146                         |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
| <b>History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
| No (Reference)                       |                             |         |                             |         |                             |         | 1                           |         |  |         |                                     |         |                                     |         |                            |         |                             |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
| Yes (Unadjusted)                     |                             |         |                             |         |                             |         | 1.16 (0.89, 1.52)           |         | 0.26                                   |         |                                     |         |                                     |         |                            |         |                             |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
| <b>Fibrinogen Threshold Models</b>   |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
| Fibrinogen level < 400 (Reference)   | 1                           |         | 1                           |         | 1                           |         | 1                           |         | 1                                      |         | 1                                   |         | 1                                   |         | 1                          |         | 1                           |  |         |  |                   |  |         |  |                   |  |                   |  |                   |  |        |  |                   |  |         |  |
| Fibrinogen level ≥ 400 (Unadjusted)  | 1.89 (1.58, 2.25)           |         | <0.0001                     |         | 3.89 (2.50, 6.07)           |         | <0.0001                     |         | 2.04 (1.35, 3.06)                      |         | 0.0007                              |         | 1.74 (1.33, 2.28)                   |         | <0.0001                    |         | 1.63 (1.11, 2.37)           |  | 0.0119  |  | 1.83 (1.24, 2.69) |  | 0.0023  |  | 1.64 (0.95, 2.81) |  | 0.07              |  | 0.82 (0.18, 3.69) |  | 0.79   |  | 1.48 (1.04, 2.10) |  | 0.0296  |  |
| Fibrinogen level ≥ 400 (Adjusted)    | 1.79 (1.50, 2.13)           |         | <0.0001                     |         | 3.89 (2.50, 6.07)           |         | <0.0001                     |         | 2.04 (1.35, 3.06)                      |         | 0.0007                              |         | 1.51 (1.15, 1.98)                   |         | 0.003                      |         | 1.40 (0.95, 2.06)           |  | 0.09    |  | 1.60 (1.08, 2.37) |  | 0.0183  |  | 1.48 (0.86, 2.54) |  | 0.16              |  | 0.82 (0.18, 3.69) |  | 0.79   |  | 1.27 (0.88, 1.82) |  | 0.2     |  |
| Gender (Reference = Male)            |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |         |  |                   |  |         |  |                   |  | 0.40 (0.27, 0.60) |  | <0.0001           |  |        |  |                   |  |         |  |
| Age                                  | 1.07 (1.06, 1.08)           |         | <0.0001                     |         | 1.07 (1.03, 1.12)           |         | 0.0018                      |         | 1.08 (1.05, 1.11)                      |         | <0.0001                             |         | 1.06 (1.04, 1.09)                   |         | <0.0001                    |         | 1.07 (1.04, 1.11)           |  | <0.0001 |  | 1.06 (1.03, 1.09) |  | <0.0001 |  | 1.07 (1.03, 1.12) |  | 0.0015            |  | 1.18 (1.07, 1.30) |  | 0.0008 |  | 1.06 (1.04, 1.08) |  | <0.0001 |  |
| BMI                                  |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |         |  |                   |  |         |  |                   |  | 0.96 (0.92, 0.99) |  | 0.0123            |  |        |  |                   |  |         |  |
| History of COPD                      |                             |         |                             |         |                             |         |                             |         |  |         |                                     |         |                                     |         |                            |         |                             |  |         |  |                   |  |         |  |                   |  | 1.85 (1.31, 2.62) |  | 0.0004            |  |        |  |                   |  |         |  |

| Patient Characteristics  | Total                       |         | ARIC                        |         | CHS                         |         | ECLIPSE                     |                   |  |         |                                     |         | FHSOC                               |         | NHANES <sup>b</sup>        |         |                             |         |
|--|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|-----------------------------|-------------------|--|---------|-------------------------------------|---------|-------------------------------------|---------|----------------------------|---------|-----------------------------|---------|
|  | Total Population (N = 6376) |         | Total Population (N = 1789) |         | Total Population (N = 1292) |         | Total Population (N = 2118) |                   | No History of Exacerbations (N = 1114) |         | One or More Exacerbation (N = 1004) |         | Two or More Exacerbations (N = 469) |         | Total Population (N = 145) |         | Total Population (N = 1032) |         |
|  | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value | HR (95% CI)                 | p-value           | HR (95% CI)                            | p-value | HR (95% CI)                         | p-value | HR (95% CI)                         | p-value | HR (95% CI)                | p-value | HR (95% CI)                 | p-value |
| Diabetes   |                             |         |                             |         |                             |         |                             |                   |  |         |                                     |         |                                     |         |                            |         | 1.86 (1.22, 2.84)           | 0.0038  |
| Asthma   |                             |         |                             |         |                             |         |                             | 1.72 (1.17, 2.52) | 0.0057                                 |         |                                     |         |                                     |         |                            |         |                             |         |
| FEV <sub>1</sub> (baseline)  | 0.66 (0.56, 0.78)           | <0.0001 |                             |         |                             |         | 0.36 (0.26, 0.52)           | <0.0001           | 0.41 (0.26, 0.66)                      | 0.0002  | 0.31 (0.18, 0.54)                   | <0.0001 | 0.24 (0.10, 0.57)                   | 0.0012  |                            |         | 0.62 (0.43, 0.89)           | 0.0099  |
| <b>Fibrinogen Threshold Model with History of COPD Exacerbations</b> |                             |         |                             |         |                             |         |                             |                   |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level < 400 (Reference)                                   |                             |         |                             |         |                             |         | 1                           |                   |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 400 (Unadjusted)                                  |                             |         |                             |         |                             |         | 1.74 (1.33, 2.28)           | <0.0001           |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Fibrinogen level ≥ 400 (Adjusted)                                    |                             |         |                             |         |                             |         | 1.51 (1.15, 1.99)           | 0.003             |  |         |                                     |         |                                     |         |                            |         |                             |         |
| History of COPD Exacerbations  |                             |         |                             |         |                             |         |                             |                   |  |         |                                     |         |                                     |         |                            |         |                             |         |
| No (Reference)   |                             |         |                             |         |                             |         | 1                           |                   |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Yes  |                             |         |                             |         |                             |         | 0.96 (0.74, 1.26)           | 0.8               |  |         |                                     |         |                                     |         |                            |         |                             |         |
| Age  |                             |         |                             |         |                             |         | 1.06 (1.04, 1.09)           | <0.0001           |  |         |                                     |         |                                     |         |                            |         |                             |         |
| FEV <sub>1</sub> (baseline)  |                             |         |                             |         |                             |         | 0.36 (0.25, 0.52)           | <0.0001           |  |         |                                     |         |                                     |         |                            |         |                             |         |

(1) Fibrinogen values for ECLIPSE have been corrected by -13.6% to account for the use of EDTA plasma instead of citrate plasma using data provided by Pacific Biomarkers Inc., (reference 20 in manuscript).

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<sup>a</sup>COPD patient definition: FEV<sub>1</sub>/FVC < 70%, FEV<sub>1</sub> % predicted < 80% and age 40+

<sup>\*\*</sup>Reference category for comorbidities is the absence of the comorbidity.

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ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, blood pressure; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV<sub>1</sub>, forced expiratory volume in 1 second; FHSOC, Framingham Heart Study Offspring Cohort; FVC, forced vital capacity; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey