

# Augmentation Therapy for Severe Alpha-1 Antitrypsin Deficiency Improves Survival and Is Decoupled from Spirometric Decline—A Multinational Registry Analysis

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## Abstract

**Rationale:** Intravenous plasma-purified alpha-1 antitrypsin (IV-AAT) has been used as therapy for alpha-1 antitrypsin deficiency (AATD) since 1987. Previous trials (RAPID and RAPID-OLE) demonstrated efficacy in preserving computed tomography of lung density but no effect on FEV<sub>1</sub>. This observational study evaluated 615 people with severe AATD from three countries with socialized health care (Ireland, Switzerland, and Austria), where access to standard medical care was equal but access to IV-AAT was not.

**Objectives:** To assess the real-world longitudinal effects of IV-AAT.

**Methods:** Pulmonary function and mortality data were utilized to perform longitudinal analyses on registry participants with severe AATD.

**Measurements and Main Results:** IV-AAT confers a survival benefit in severe AATD ( $P < 0.001$ ). We uncovered two distinct AATD phenotypes based on an initial respiratory diagnosis: lung

index and non-lung index. Lung indexes demonstrated a more rapid FEV<sub>1</sub> decline between the ages of 20 and 50 and subsequently entered a plateau phase of minimal decline from 50 onward. Consequentially, IV-AAT had no effect on FEV<sub>1</sub> decline, except in patients with a Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 lung index.

**Conclusions:** This real-world study demonstrates a survival advantage from IV-AAT. This improved survival is largely decoupled from FEV<sub>1</sub> decline. The observation that patients with severe AATD fall into two major phenotypes has implications for clinical trial design where FEV<sub>1</sub> is a primary endpoint. Recruits into trials are typically older lung indexes entering the plateau phase and, therefore, unlikely to show spirometric benefits. IV-AAT attenuates spirometric decline in lung indexes in GOLD stage 2, a spirometric group commonly outside current IV-AAT commencement recommendations.

**Keywords:**  $\alpha$  1-proteinase inhibitor; forced expiratory volume; Kaplan-Meier survival curve; universal health care

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Since the discovery of alpha-1 antitrypsin deficiency (AATD) in 1963 (1) and the confirmation of its key role in the development of emphysema in 1967 (2), our understanding of the biochemical nature of the lung disease has progressed steadily.

Plasma-purified intravenous AAT (IV-AAT) as augmentation therapy for severe AATD was shown to be biochemically effective as early as 1981 (3), increasing levels of AAT in blood and in the lung epithelial lining fluid (ELF). A further study by Wewers and colleagues in 1987 (4) showed that IV-AAT, administered once weekly at a dose of 60 mg/kg, increased AAT levels in blood and ELF above a putative protective threshold throughout the course of treatment, leading to approval by the U.S. Food and Drug Administration in 1987. However, randomized clinical trials (RCTs) have failed to demonstrate significant clinical efficacy (5), in part because of low statistical power as a consequence of AATD being a rare genetic condition (6). The lack of

conclusive RCT data has hampered acceptance of this therapeutic approach, and IV-AAT is not reimbursed by insurers or national health systems in many parts of the world.

Various metrics have been evaluated to assess the clinical effectiveness of IV-AAT, including decline in FEV<sub>1</sub> (7–13), lung densitometry (5, 14–16), pulmonary exacerbations (17), quality of life, and survival (7, 12, 18). The overall conclusions of these papers are that severe AATD deficiency, in itself, does not predict clinical outcomes and that there is significant heterogeneity in disease progression as well as response to IV-AAT, thus making studying the effects of IV-AAT challenging and potentially cost prohibitive (19–21). Power calculations suggest that studies would require 300–500 subjects with a follow-up time period of at least 3 years to show a benefit in FEV<sub>1</sub> decline (6), whereas 342 subjects per treatment arm would be needed to detect a 40% reduction in

mortality in a 5-year study of subjects with a baseline FEV<sub>1</sub> of 35–49% predicted (22). Other clinical endpoints such as DL<sub>CO</sub> are considered unsuitable for large multicenter studies, in part because of the irreproducibility of the data.

To date, the only parameter shown to be significantly affected by IV-AAT is lung densitometry, as measured by computed tomography (CT) scan. In the RAPID (14) and RAPID-OLE (15) studies, IV-AAT, administered at a dose of 60 mg/kg, was shown to decrease the loss of lung density, compared with placebo. Although this result was encouraging, there was no effect of IV-AAT on other parameters such as spirometry, exacerbations, hospitalizations, or survival. However, the studies were underpowered to detect differences in these more widely accepted clinical parameters. Consequently, there has been limited acceptance of the use of lung densitometry as a meaningful clinical endpoint. In addition, given the potential clinical efficacy of

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This article has an online supplement, which is accessible from this issue's table of contents at [www.atsjournals.org](http://www.atsjournals.org).

## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Severe alpha-1 antitrypsin deficiency (AATD) is a heterogeneous condition with variable lung function decline. In people with severe AATD, plasma-purified intravenous AAT (IV-AAT) has been proven by computed tomography lung densitometry to slow lung parenchymal loss but has not been shown definitively to have any other beneficial effect. Previous clinical trials have mainly recruited older symptomatic patients with more advanced lung disease.

### What This Study Adds to the

**Field:** We show that IV-AAT has a beneficial effect on mortality that is largely decoupled from its effect on lung function. This study also shows that FEV<sub>1</sub> is not a useful metric for assessing the efficacy of IV-AAT, especially in an older symptomatic cohort. People with AATD are diagnosed too late in their disease course to show an effect of treatment on FEV<sub>1</sub>, as by then their lung function decline has plateaued. A subgroup of people with AATD called “lung indexes” are at particular risk of rapid decline, and special consideration should be given to this group regarding therapeutic interventions.

IV-AAT shown in the RAPID studies, a long-term placebo-controlled trial now seems unethical.

In this study, we evaluated one of the largest cohorts, to date, of individuals with severe AATD over a prolonged period in countries with similar access to medical care and chronic obstructive pulmonary disease (COPD) treatments but unequal access to IV-AAT.

## Methods

Our retrospective observational study analyzed lung function decline and mortality in people with severe AATD who were enrolled in AATD registries in three

countries in Europe (Ireland, Switzerland, and Austria) with similar socialized healthcare systems. AATD testing, diagnosis, basic treatment, and access to care were widely similar across each country, although the criteria for commencing IV-AAT differed; that is, they were available and reimbursed in Switzerland and Austria once the criteria were met but were not reimbursed in Ireland. The criterion for commencing IV-AAT in both Switzerland and Austria was an FEV<sub>1</sub> percent predicted between 30 and 65%.

### Study Participants

The participants were patients with severe AATD, as defined by genotype being any combination of Z, functionally Z-like mutations (e.g., M<sub>malton</sub>) or null (Q0) mutations, rather than AAT level alone (23). Individuals with an S or S-like mutation (or mutations) were excluded (24, 25). A comprehensive list of the clinical characteristics recorded at each visit are outlined in the online supplement.

All participants provided written informed consent to be enrolled in each country’s respective registry and to have their data used for research.

Lung index status was defined as anyone undergoing AATD testing specifically for respiratory reasons (as opposed to liver or family screening reasons) or those who had airflow obstruction on initial spirometry.

### AATD Laboratory Diagnosis

AATD was diagnosed by a combination of AAT level, phenotype, genotype, and *SERPINA1* sequencing (26). A full description can be found in the methods section of the online supplement.

### Pulmonary Function Testing (PFT)

PFT was in accordance with American Thoracic Society/European Respiratory Society standards (27). All three countries use the single-breath method for measuring DL<sub>CO</sub>.

### Statistical Analyses and FEV<sub>1</sub> Decline Modeling

We compared demographics, clinical characteristics, and lung function in registry participants across the three countries. Student’s *t* test and ANOVA were used to compare continuous variables, and a chi-square test was used for proportions.

We then performed stratified analyses by lung index and augmentation status

across the three countries. We estimated yearly FEV<sub>1</sub> decline using multivariable linear mixed models with random intercepts and random slopes, adjusted for sex, height, and ever-smoking status, using the R nlme package. We normalized yearly FEV<sub>1</sub> decline by dividing by the FEV<sub>1</sub> measured at baseline for each individual.

We produced Kaplan-Meier curves using the R survival and survminer packages. We performed time-to-event (either transplant or death) analyses adjusted for age at diagnosis, sex, smoking status, augmentation status, lung index status, and country. For Cox regression, we tested for proportionality using the global and individual Schoenfeld tests.

Statistical analyses were performed using R (version 4.1.0; R Foundational for Statistical Computing).

## Results

### Participant Characteristics

A total of 615 individuals with severe AATD were included in the study. The vast majority (97.7%) were individuals with the ZZ genotype. The other severe deficiency genotypes included are outlined elsewhere (see Table E1 in the online supplement). Mean follow-up time and duration of IV-AAT therapy were significantly different across the three countries (Table 1). In total, 1,768, 561, and 933 PFTs were performed in Ireland, Switzerland, and Austria, respectively. Means of 1.46, 1.88, and 0.65 PFTs per person follow-up years were performed in each country, respectively.

There was no difference in age at diagnosis, proportion of males, smoking status, smoking pack-years, liver ascertainment, or AAT level. A significantly higher proportion of individuals were tested for AATD for family screening reasons in Ireland (37%), compared with those in Switzerland (7%) and Austria (16%) ( $P < 0.001$ ). Conversely, Irish individuals were significantly less likely to be diagnosed with COPD or to be lung indexes at their baseline visit.

We also compared lung indexes to non-lung indexes (Table 2). Both groups had similar follow-up times ( $P = 0.084$ ). At diagnosis, lung indexes were older, male former smokers with a low body mass index and higher smoking pack-years. Lung indexes had lower percent predicted value for FEV<sub>1</sub>, forced expiratory flow between

**Table 1.** Participant Characteristics by Country

| Characteristic                            | Ireland       | Switzerland   | Austria       | P Value |
|---|---------------|---------------|---------------|---------|
| <i>n</i>                                  | 211           | 109           | 295           | —       |
| Age at diagnosis, yr                      | 44.94 (16.31) | 44.47 (14.13) | 45.09 (15.43) | 0.940   |
| Follow-up time, yr                        | 9.69 (4.87)   | 5.78 (2.48)   | 11.91 (6.34)  | <0.001  |
| Male sex, %                               | 116 (55.0)    | 61 (56.0)     | 176 (59.7)    | 0.545   |
| Smoking status, %                         |               |               |               |         |
| Never-smoker                              | 78 (37.0)     | 29 (26.6)     | 97 (33.7)     | 0.177   |
| Former smoker                             | 128 (60.7)    | 76 (69.7)     | 175 (60.8)    | 0.213   |
| Current smoker                            | 5 (2.4)       | 4 (3.7)       | 16 (5.6)      | 0.201   |
| Smoking pack-years                        | 13.18 (17.38) | 16.53 (16.58) | 14.27 (16.67) | 0.255   |
| Lung index, %                             | 109 (52.4)    | 90 (82.6)     | 232 (79.5)    | <0.001  |
| Reason for AATD testing, %                |               |               |               |         |
| Family screening                          | 77 (36.5)     | 8 (7.3)       | 47 (15.9)     | <0.001  |
| Lung symptoms                             | 109 (51.7)    | 88 (80.7)     | 205 (69.5)    | <0.001  |
| Liver abnormalities                       | 16 (7.6)      | 7 (6.4)       | 16 (5.4)      | 0.617   |
| Alpha-1 antitrypsin level, g/L            | 0.25 (0.09)   | 0.23 (0.09)   | 0.25 (0.10)   | 0.217   |
| Augmentation status, %                    |               |               |               |         |
| Never                                     | 191 (90.5)    | 44 (40.4)     | 130 (44.1)    | <0.001  |
| Past                                      | 0 (0.0)       | 11 (10.1)     | 26 (8.8)      | <0.001  |
| Current                                   | 20 (9.5)      | 54 (49.5)     | 139 (47.1)    | <0.001  |
| Duration of augmentation, yr              | 13.41 (2.57)  | 7.35 (4.80)   | 13.36 (7.76)  | <0.001  |
| COPD diagnosis, %                         | 136 (64.8)    | 92 (85.2)     | 184 (73.9)    | <0.001  |
| FEV <sub>1</sub> , L                      | 2.29 (1.22)   | 1.85 (1.03)   | 2.06 (1.18)   | 0.005   |
| FEV <sub>1</sub> , % predicted            | 70.30 (32.14) | 53.17 (24.27) | 60.88 (30.32) | <0.001  |
| Bronchodilator response at initial PFT, % | 16 (27.6)     | 20 (24.1)     | 16 (11.0)     | 0.005   |
| DL <sub>CO</sub> , mmol/(min · kPa)       | 6.51 (3.05)   | 5.27 (2.50)   | —             | 0.001   |
| DL <sub>CO</sub> , % predicted            | 69.91 (25.61) | 53.34 (20.97) | —             | <0.001  |
| FEF <sub>25–75</sub> , L                  | 1.64 (1.44)   | —             | —             | —       |
| FEF <sub>25–75</sub> , % predicted        | 42.15 (34.60) | —             | —             | —       |
| FEV <sub>1</sub> Q                        | 5.04 (2.66)   | 4.07 (2.26)   | 4.49 (2.54)   | 0.003   |

*Definition of abbreviations:* AATD =  $\alpha$ -1 antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; FEF<sub>25–75</sub> = forced expiratory flow between 25% and 75% of vital capacity; FEV<sub>1</sub>Q = FEV<sub>1</sub> quotient; PFT = pulmonary function test.

Data are presented as mean (SD) or *n* (%). We performed a Student's *t* test and ANOVA to test for differences in means in continuous data and a chi-square test to test for differences in proportions in categorical data. Data for smoking status were missing for seven people (all Austrian). Three people (all Austrian) had neither smoking status nor lung index status recorded.

25% and 75% of vital capacity (FEF<sub>25–75</sub>), and DL<sub>CO</sub>, as well as lower FEV<sub>1</sub> quotient (FEV<sub>1</sub>Q), and were less likely to demonstrate a bronchodilator response ( $P < 0.001$ ). Seven patients could not be categorized.

When comparing only lung indexes between the three countries, there was no difference in age at diagnosis, proportion of males, or FEV<sub>1</sub> percent predicted. However, there was a significantly lower proportion of lung indexes currently receiving IV-AAT in Ireland, compared with the other two countries ( $P < 0.001$ ), and Irish patients had a higher DL<sub>CO</sub> percent predicted ( $P = 0.01$ ) (see Table E2).

### Pulmonary Function Decline by Age

A total of 615 participants were followed for a mean of 58 months ( $\pm 59$  months; maximum, 286 mo). Over this time period, 3,193 FEV<sub>1</sub>, 1,844 DL<sub>CO</sub>, and 1,212 FEF<sub>25–75</sub> measurements were undertaken and graphed according to the age at which the PFT was performed (Figures 1A–1D and E1A–E1D and E2A–E2D). A total of 1,005 (31.95%)

FEV<sub>1</sub> measurements occurred for patients between the ages of 20 to 50 years old, and 2,141 (68.05%) FEV<sub>1</sub> measurements occurred for patients age 50 years and older.

An initial analysis found that there was a significant difference in lung function decline in those diagnosed because of respiratory reasons (lung index) when compared with those diagnosed for nonrespiratory reasons (non–lung index), even though lung indexes had stopped smoking at the time of entry into this study. As a result, these two groups were separated for the analysis of lung function decline. The majority (70%) of participants were lung indexes. Figures 1A–1D demonstrate that lung indexes reach a lower FEV<sub>1</sub> (in liters) and percent predicted, compared with their non–lung index counterparts at each given age and decline more rapidly initially before reaching a plateau.

The absolute rate of decline in FEV<sub>1</sub> (in milliliters) in lung indexes is greater than in non–lung indexes between the ages of 20 and 50 years old (41 ml vs. 31 ml/yr;

difference, 10.7 ml/yr; 95% confidence interval [CI], 4.5–16.8;  $P < 0.001$ ), whereas the rate of decline in non–lung indexes is greater between the ages of 50 to 80 years old (47 ml vs. 36 ml/yr; difference, 10.8 ml/yr; 95% CI, 4.3–17.4;  $P = 0.001$ ) (see Figure E3).

We also compared estimated yearly FEV<sub>1</sub> decline normalized for baseline FEV<sub>1</sub> by age group, as defined in previous clinical trials. There was a significant difference in normalized FEV<sub>1</sub> decline between lung indexes and non–lung indexes in both age groups ( $P < 0.001$  and  $P = 0.005$ , respectively), with lung indexes declining more rapidly (see Figure E4).

### The Effect of Augmentation Therapy on Pulmonary Function Decline

In total, 250 people had ever received IV-AAT, with 213 actively receiving IV-AAT. A total of 365 had never received IV-AAT throughout the course of the observation period. Lung indexes accounted for 199 of the 213 (93.4%) who actively received

**Table 2.** Participant Characteristics by Lung Index versus Non-Lung Index Status

| Characteristic                            | Lung Index    | Non-Lung Index | P Value |
|---|---------------|----------------|---------|
| N   | 431           | 178            | —       |
| Age at diagnosis, yr                      | 48.09 (12.46) | 37.38 (19.19)  | <0.001  |
| Male sex, %                               | 264 (61.3)    | 84 (47.2)      | 0.002   |
| Follow-up time, yr                        | 10.34 (5.92)  | 9.44 (5.38)    | 0.084   |
| Country, %                                |               |                |         |
| Ireland                                   | 109 (25.3)    | 99 (55.6)      | <0.001  |
| Switzerland                               | 90 (20.9)     | 19 (10.7)      | 0.004   |
| Austria                                   | 232 (53.8)    | 60 (33.7)      | <0.001  |
| Smoking status, %                         |               |                |         |
| Never-smoker                              | 109 (25.5)    | 95 (53.4)      | <0.001  |
| Former smoker                             | 304 (71.2)    | 72 (40.4)      | <0.001  |
| Current smoker                            | 14 (3.3)      | 11 (6.2)       | 0.16    |
| Smoker pack-years                         | 17.21 (17.26) | 7.28 (13.87)   | <0.001  |
| Augmentation status, %                    |               |                |         |
| Never                                     | 197 (45.7)    | 162 (91.0)     | <0.001  |
| Past                                      | 35 (8.1)      | 2 (1.1)        | 0.002   |
| Current                                   | 199 (46.3)    | 14 (7.9)       | <0.001  |
| BMI, kg/m <sup>2</sup>                    | 24.69 (4.22)  | 25.75 (5.52)   | 0.014   |
| FEV <sub>1</sub> , L                      | 1.70 (0.92)   | 3.02 (1.19)    | <0.001  |
| FEV <sub>1</sub> , % predicted            | 51.75 (25.02) | 88.23 (27.57)  | <0.001  |
| Bronchodilator response at initial PFT, % | 34 (14.5)     | 18 (34.6)      | 0.001   |
| DL <sub>CO</sub> , mmol/(min · kPa)       | 4.90 (2.27)   | 7.79 (2.93)    | <0.001  |
| DL <sub>CO</sub> , % predicted            | 53.00 (20.32) | 79.72 (23.45)  | <0.001  |
| FEF <sub>25–75</sub> , L                  | 1.00 (1.17)   | 2.34 (1.38)    | <0.001  |
| FEF <sub>25–75</sub> , % predicted        | 27.30 (30.68) | 58.20 (31.49)  | <0.001  |
| FEV <sub>1</sub> Q                        | 3.67 (1.94)   | 6.75 (2.54)    | <0.001  |

*Definition of abbreviations:* BMI = body mass index; FEF<sub>25–75</sub> = forced expiratory flow between 25% and 75% of vital capacity; FEV<sub>1</sub>Q = FEV<sub>1</sub> quotient; PFT = pulmonary function test. Data are presented as mean (SD) or *n* (%). A Student's *t* test and ANOVA were performed to test for differences in means in continuous data, and a chi-square test was performed to test for differences in proportions in categorical data. Lung index status data were missing for six (three Irish and three Austrian) people. Smoking status data were missing for four people (all Austrian) in the lung index group. Three people (all Austrian) had neither smoking status nor lung index status recorded.

IV-AAT. Of those actively receiving IV-AAT, 20, 54, and 139 were Irish, Swiss, and Austrian, respectively (see Table E3). Mean duration for patients receiving IV-AAT across the three countries was 12.8 ( $\pm$ 7.2) years. A higher proportion of those actively receiving IV-AAT in Austria began treatment at GOLD stage 2 for COPD ( $P=0.02$ ), compared with those from Ireland and Switzerland. There was no significant difference in the proportions of those commencing in GOLD stage 3 when comparing patients across the three countries.

Of the 197 lung indexes who never received IV-AAT, 93 were Irish, 31 were Swiss, and 73 were Austrian. Baseline clinical characteristics are presented elsewhere (see Table E4). Of the 31 Swiss and 73 Austrians, 22 and 32 individuals, respectively, technically met the FEV<sub>1</sub> percent predicted inclusion criteria for IV-AAT at baseline, although it is unclear why they did not commence IV-AAT at the time.

When comparing FEV<sub>1</sub> decline (in milliliters) between those actively and

never receiving IV-AAT, GOLD stage 2 ( $50\% \leq \text{FEV}_1 < 80\%$ ) lung indexes were the only group to show a significant reduction in FEV<sub>1</sub> decline (Table 3). This suggests a need to consider IV-AAT earlier in disease progression if evaluating FEV<sub>1</sub> as an outcome measure.

### The Effect of Lung Index Status and Country On Time-to-Terminal-Event (TTE) Analyses

Patients were assessed by TTE analysis specifically from first PFT to terminal event (either lung transplant or death). Of the 615 patients observed over a maximum of 286 months, 96 experienced a terminal event (37 people received a lung transplant, and 59 died having never received a lung transplant). Of this group, the cause of the terminal event was respiratory in 64 (66.7%) patients, liver related in 3 (3.1%) patients, and other causes in 12 (12.5%) patients. Cause of death was unknown for 17 (17.7%) individuals.

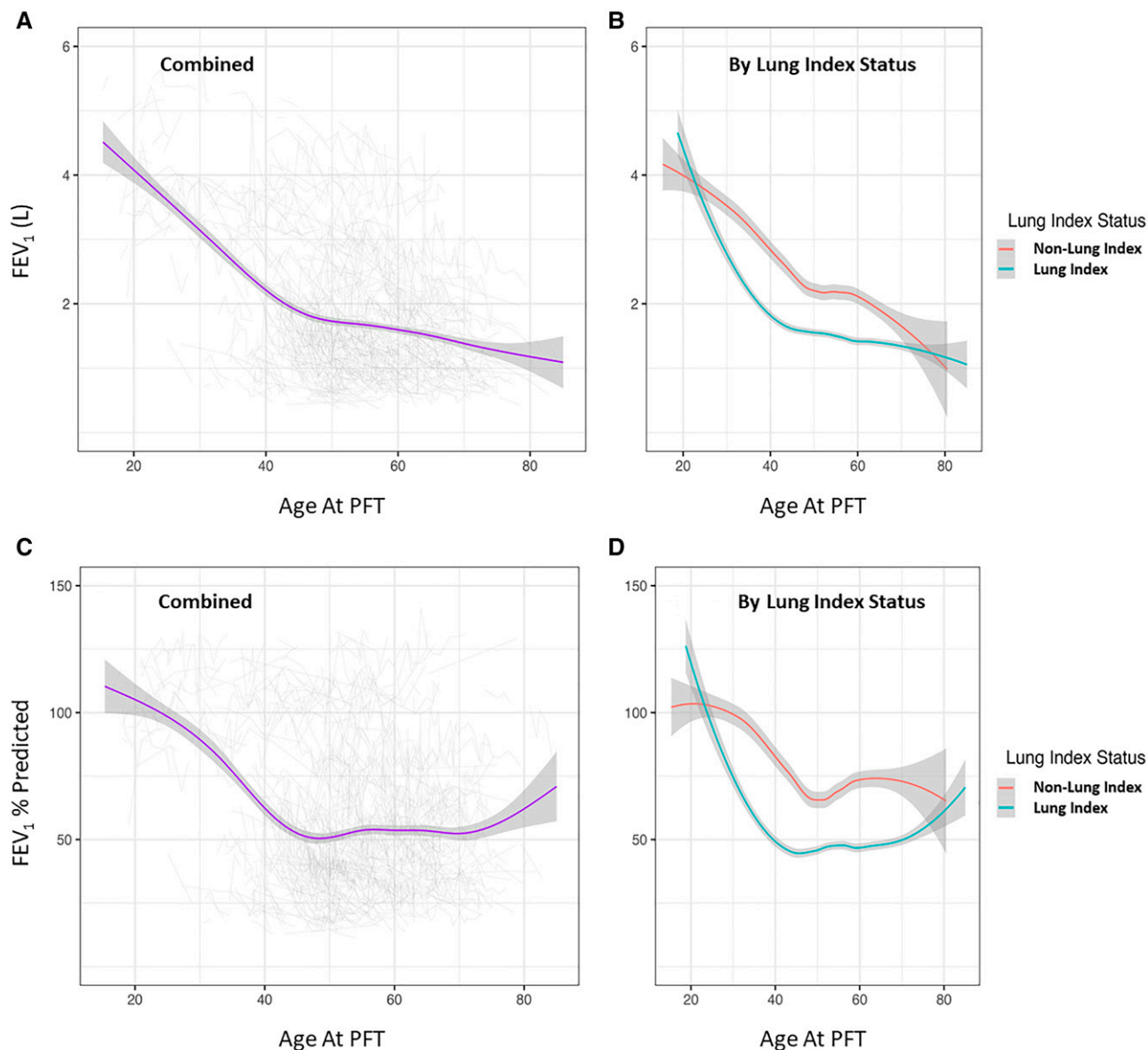
We first compared TTE between all lung indexes and non-lung indexes

(Figure 2A) and between the three countries combined (Figure 2B). Lung indexes had significantly lower survival probability compared with non-lung indexes ( $P=0.009$ ). Individuals in Ireland also had significantly lower survival probability compared with individuals in the other two countries ( $P=0.035$ ). After stratification for lung index status, the significant difference in TTE appears to be strongly influenced by the difference in TTE between Ireland and Austria for lung indexes ( $P=0.004$ ), which is likely influenced by variable access to IV-AAT in these countries (Figure 3A). This difference was not evident in non-lung indexes ( $P=0.4$ ) (Figure 3B).

### The Effect of Augmentation Therapy on TTE Analyses

There was a significant survival benefit for individuals actively receiving IV-AAT compared with individuals who had never received IV-AAT in the overall study cohort ( $P=0.00076$ ) (Figure 4A).

We performed Cox proportional hazard modeling to test the independent



**Figure 1.** (A) FEV<sub>1</sub> (in liters; L) at age of pulmonary function testing (PFT) in all study participants. (B) FEV<sub>1</sub> (L) at age of PFT stratified by lung index status. (C) FEV<sub>1</sub> percent predicted at age of PFT in all study participants. (D) FEV<sub>1</sub> percent predicted at age of PFT stratified by lung index status. Gray shading represents 95% confidence interval of the mean.

effects of each covariate of interest. Increased age (hazard ratio [HR], 1.03; 95% CI, 1.01–1.05) and lung index status (HR, 2.93; 95% CI, 1.39–6.21) were associated with lower survival probability, whereas IV-AAT was associated with higher survival probability (HR, 0.61; 95% CI, 0.45–0.83). There was no significant association with sex, smoking status, or country. We observed similar findings in sensitivity analyses adjusted for FEV<sub>1</sub>, except that lung index status was no longer significant.

Irish patients who never received IV-AAT appeared to fare worse than their Swiss and Austrian counterparts, although not significantly so (Figure 4B). Individuals in Austria and Switzerland with stable pulmonary function were deemed not to require IV-AAT over the course of the study; in both of these countries, people with AATD demonstrating pulmonary deterioration were commenced on IV-AAT. In Ireland, patients showing deterioration in their condition had no access to IV-AAT outside of clinical trials.

The presence of COPD at study entry independently conferred a poorer overall survival compared with the findings for those who did not have COPD (see Figure E5A). This has been described in previous studies (12, 28). Increasing GOLD stage also predicted mortality ( $P=0.022$ ) (Figure E5B).

It is interesting that being a never-smoker did not confer a survival benefit over those who were past or active smokers. The reasons for this remain unclear, although a higher percentage of those who smoked went on to receive IV-AAT. This finding is not in

**Table 3.** Mean Yearly Decline in FEV<sub>1</sub> (in Milliliters) Categorized by GOLD Stage from the Time of First Pulmonary Function Test

| GOLD Stage | Lung Index Status |                |                    |                |         |                 |                |                    |                |         |
|------------|-------------------|----------------|--------------------|----------------|---------|-----------------|----------------|--------------------|----------------|---------|
|            | Non-Lung Index    |                |                    |                |         | Lung Index      |                |                    |                |         |
|            | Never Augmented   |                | Actively Augmented |                | P Value | Never Augmented |                | Actively Augmented |                | P Value |
| n          | Δml               | n              | Δml                | n              |         | Δml             | n              | Δml                |                |         |
| 1          | 12                | -43.53 (17.48) | 0                  | —              | —       | 14              | -33.16 (13.84) | 6                  | -22.78 (24.29) | 0.36    |
| 2          | 21                | -41.47 (36.49) | 7                  | -29.73 (44.48) | 0.54    | 46              | -45.21 (22.32) | 54                 | -32.77 (22.19) | 0.007   |
| 3          | 11                | -43.32 (21.91) | 5                  | -53.52 (6.38)  | 0.18    | 45              | -43.69 (19.01) | 80                 | -41.22 (15.62) | 0.46    |
| 4          | 4                 | -59.23 (12.34) | 1                  | -36.41 (NA)    | —       | 37              | -47.04 (15.03) | 21                 | -49.45 (11.66) | 0.5     |
| Normal     | 101               | -34.88 (20.15) | 1                  | 88.06 (NA)     | —       | 34              | -43.51 (22.51) | 7                  | 2.87 (78.29)   | 0.17    |
| PRISm      | 6                 | -61.34 (43.79) | 0                  | —              | —       | 7               | -15.65 (76.77) | 5                  | -40.94 (19.24) | 0.43    |

Definition of abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRISm = preserved ratio impaired spirometry.

keeping with previous research (29), where a survival benefit was found among never-smokers (see Figure E6). Sex had no influence on survival, despite males constituting 61.4% of the lung indexes (see Figure E7).

## Discussion

In this study, we show that IV-AAT has a significant survival advantage, which is distinct from its effect on lung function, and that there are two distinct clinical populations of people with severe AATD. The two populations can be separated on the basis of initial respiratory referral: lung indexes and non-lung indexes. The characteristic lung index individual is more likely to have a lower body mass index and be a male former smoker with COPD and a diminished bronchodilator response. The lung-index individual will have a lower survival probability, and overall lung indexes demonstrate a lung function decline profile that is not continuous throughout life but, instead, occurs in distinct, predictable phases of active and minimal decline and that is more pronounced than in their non-lung index counterparts. This is of major importance in designing therapeutic trials for AATD using FEV<sub>1</sub> as an endpoint.

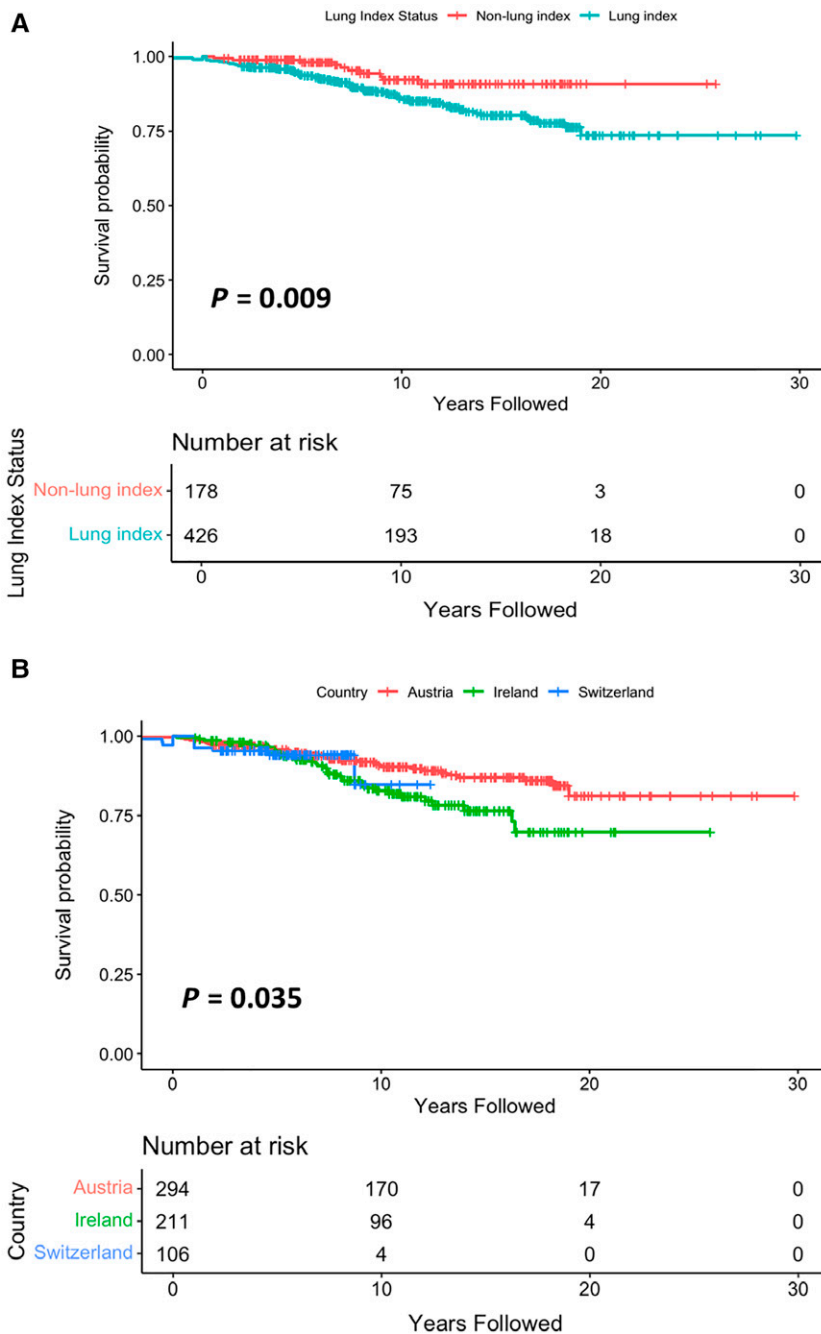
IV-AAT was associated with an HR of 0.64 in favor of a mortality reduction. The distinct survival advantage conferred by IV-AAT was apparent, even though the majority (93%) of those receiving IV-AAT were lung indexes, who, as noted previously, have a lower survival probability than non-lung indexes. These differences were

apparent even when adjusted for FEV<sub>1</sub> in Cox proportional hazard modeling. The survival benefit of IV-AAT is further supported when examining lung indexes in each country, where the benefit of having access to IV-AAT is the likely driver behind the increased survival probability in Switzerland and Austria. This idea is further strengthened when looking at non-lung indexes in each country, the vast majority having never received IV-AAT, where we see no difference in survival. Overall, Irish non-lung indexes (detected by the national targeted detection program) fared much the same as their never-augmented Austrian and Swiss counterparts, arguably because of the fact that these Austrian and Swiss individuals were a self-selected group with nonprogressive COPD. Austria and Switzerland have the opportunity to place patients with AATD on IV-AAT as the need arises. These data show a survival advantage that is largely decoupled from pulmonary function decline.

This study also investigated the effects of IV-AAT on preserving lung function. Given the positive results of the RAPID studies (14, 15), it is now ethically questionable to initiate long-term trials of IV-AAT with a placebo arm. Very few Irish patients with severe AATD receive IV-AAT, whereas Swiss and Austrian patients receive IV-AAT if they meet the criteria. The mean age of those who commenced IV-AAT was 50 (±10) years old, and, 234 (93%) of the 250 patients who had ever received IV-AAT were lung indexes. From the data shown, those patients who received IV-AAT had arguably entered, or were close to entering, the plateau phase of lung function decline;

therefore, the potential for IV-AAT to show a meaningful effect on lung function decline would be unlikely. The only group to show a significant difference in FEV<sub>1</sub> decline were lung indexes with GOLD stage 2 COPD (50% ≤ FEV<sub>1</sub> < 80%) at the time of commencement of IV-AAT, a spirometric class that is not currently recommended for IV-AAT (30). It may be more beneficial to commence IV-AAT earlier than current guidelines suggest if preservation of lung function is the aim, although we do acknowledge that the cost associated with conducting prospective, placebo-controlled, clinical trials with participants who are younger and have a preserved FEV<sub>1</sub> may be prohibitive from the point of view of a drug sponsor and may not meet other clinical endpoints, such as quality of life or mortality metrics. Consideration, however, should be given to the bigger picture, where people receive potentially preventative disease-modifying treatment before a significant disease burden has been established because of AATD. Consideration must also be given to the knock-on effects that this morbidity has for the individuals at risk, as well as for society, in terms of economic loss because of AATD-related disability later in life.

Compared with other studies investigating the use of IV-AAT to slow the rate of FEV<sub>1</sub> decline, we found that IV-AAT had a significant effect on FEV<sub>1</sub> decline at a lower GOLD stage than had been previously described (8, 10). Our cohort declined at a slower rate than observed in previous studies, regardless of lung index status, although the use of lung index status to subtype the groups makes direct comparisons more difficult. Our



**Figure 2.** (A) Kaplan-Meier survival analysis categorized by lung index status showing an increased survival probability for non-lung index individuals compared with lung-index individuals ( $P=0.009$ ). (B) Kaplan-Meier survival analysis categorized by country showing an increased survival probability, mainly among Austrian individuals compared with Irish individuals (including lung index and non-lung index individuals) ( $P=0.035$ ).

study also found effects on survival that were similar to the findings of a previous study (12), with an HR of 0.64 in favor of mortality reduction found in that study and 0.61 in ours.

In the biggest studies of IV-AAT to date (RAPID studies), there was a significant effect on the loss of lung density as measured by computed tomography scan but no appreciable effect on spirometric decline.

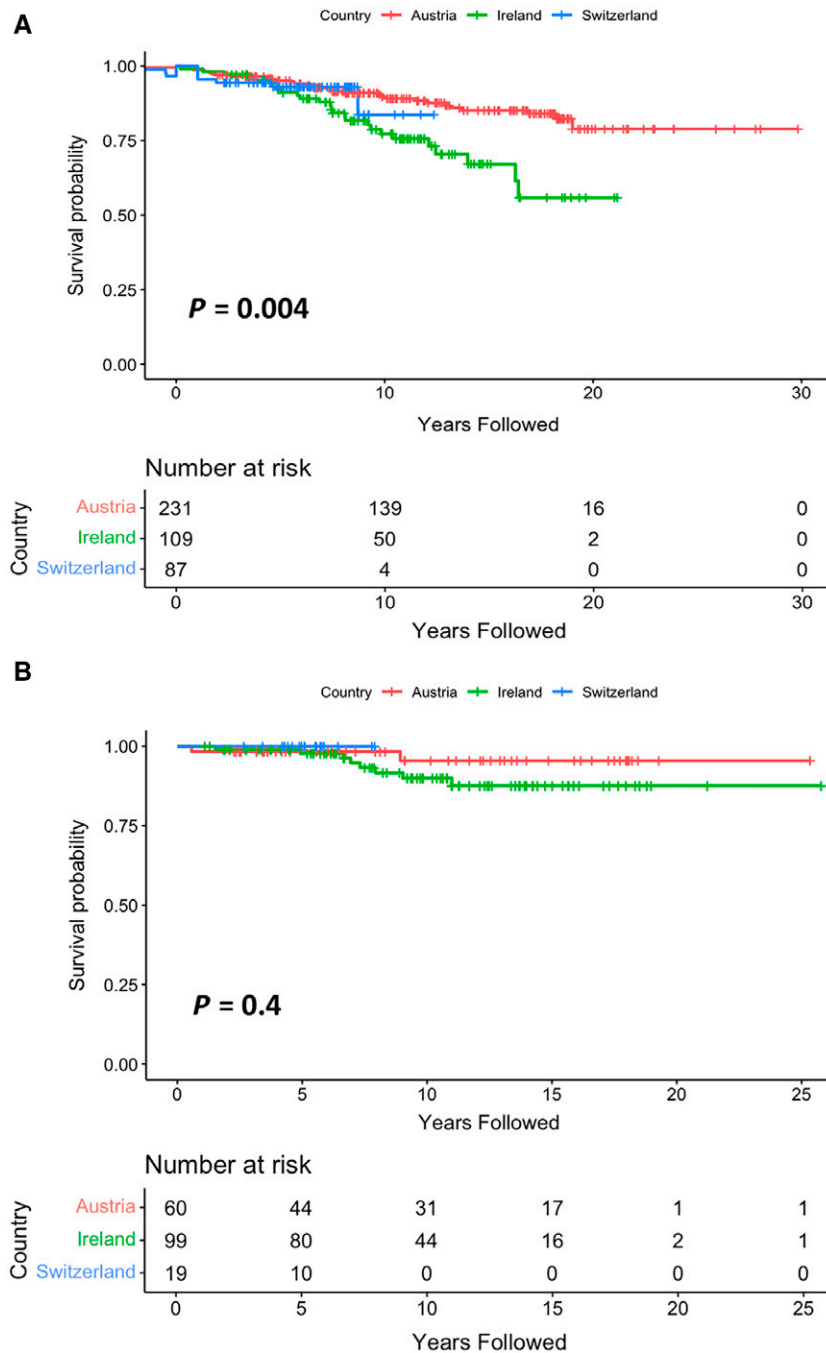
On review of the patient populations in these studies, it is clear that most are lung indexes over 50 years old, a group in a lower, static “plateau” phase of spirometry, as evidenced by our multinational data (mean age at trial commencement in RAPID, 53.8). The present study shows a decoupling of survival from change in FEV<sub>1</sub>.

Table E3, in particular, would suggest that the optimal individual for a clinical trial, using FEV<sub>1</sub> as an endpoint, is a lung-index individual between the ages of 20 and 50 or a non-lung-index individual between the ages of 50 and 80. It is possible that younger lung indexes are in the rapid decline phase, as seen in Figure 1B, and then enter a phase of relatively less rapid decline that may indicate a parenchymal elastin burnout effect. Non-lung indexes appear to have a rate of decline that accelerates with age to a rate that is similar to that of younger lung indexes, possibly because of having preserved lung function/elastin when younger and relatively more to lose later in life. Using normalized FEV<sub>1</sub> decline as the primary endpoint, as outlined in Table E4, could represent the basis of an alternative clinical trial recruitment strategy.

This study also raises questions about the efficacy of screening for AATD in the absence of access to IV-AAT. The Irish registry benefits from a national targeted detection program, with 37% of the severe AATD population in the Irish registry identified by family screening, compared with 16% in Austria and 7% in Switzerland. This does not mean that targeted detection programs confer no benefit. Of the 77 Irish people picked up by family screening, 27% fit the criteria for IV-AAT commencement at diagnosis. In Austria or Switzerland, this same cohort would be offered IV-AAT with the potential for improved survival. This emphasizes that targeted detection programs need to be linked to effective interventions beyond smoking cessation. These data also show that, despite the increased awareness of AATD, the impact of targeted detection programs, and the potential efficacy of new treatments, we are still diagnosing people with severe AATD in their mid-40s with established COPD. As this, and other studies (28) show, COPD at diagnosis independently predicts increased mortality.

Diagnosing AATD before COPD is established, and the added potential to initiate therapy at the time of rapid lung function decline, is very attractive. That will





**Figure 3.** (A) Kaplan-Meier survival analysis of lung-index individuals categorized by country showing an increased survival probability, mainly among Austrian lung-index individuals compared with Irish lung-index individuals ( $P=0.004$ ). (B) Kaplan-Meier survival analysis of non-lung index individuals categorized by country showing a similar survival probability among non-lung index individuals across all three countries ( $P=0.4$ ).

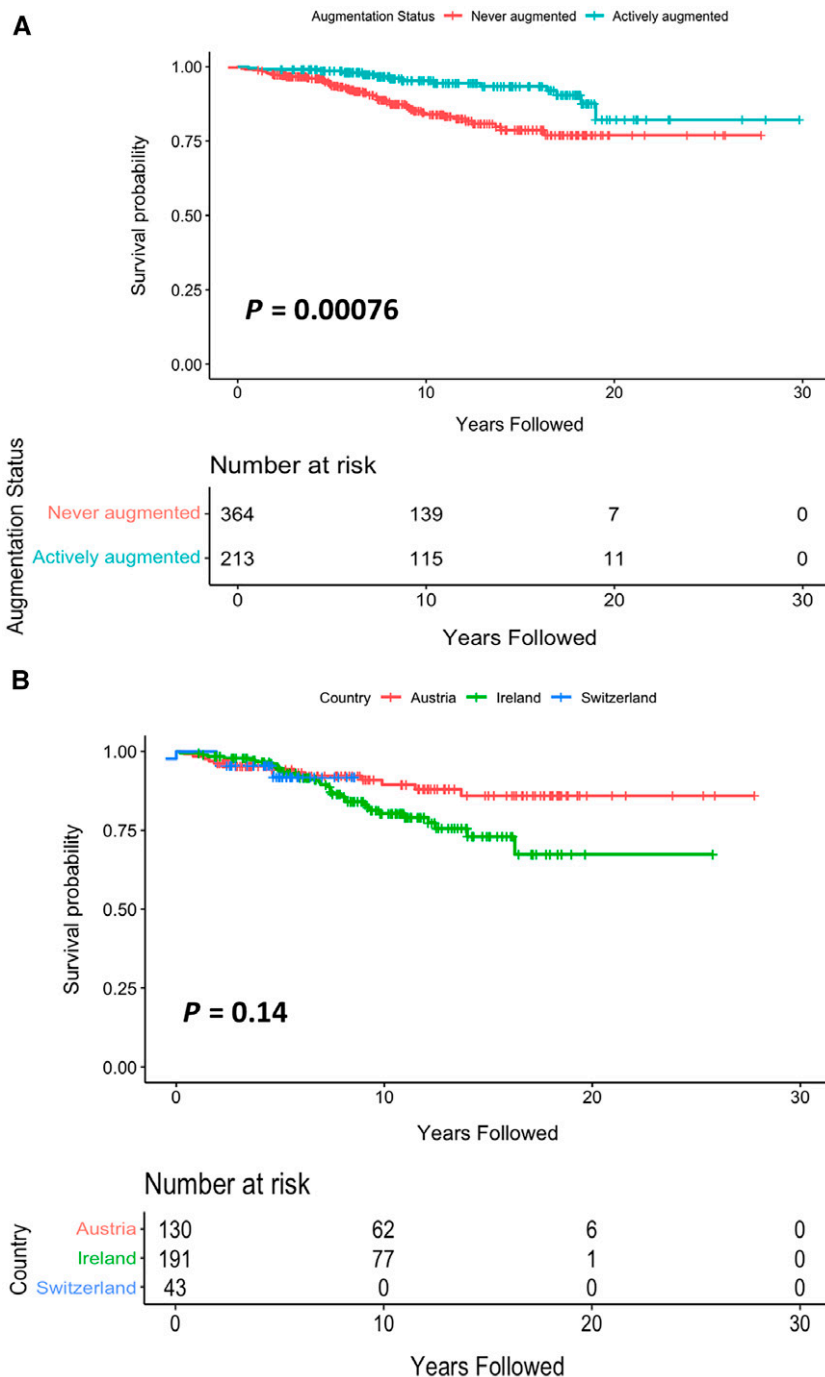
not be achievable with the present screening programs, which target people with emphysema, COPD, poorly responsive asthma, unexplained liver disease, and panniculitis and first-degree relatives of

people diagnosed with AATD (31–33). With the exception of children diagnosed shortly after birth because of jaundice, the majority of individuals with the ZZ genotype identified by targeted detection programs are

middle-aged, and their first-degree relatives are also diagnosed relatively late in life (34). To this point, the current mean age of detection ( $\pm$ SD) for individuals with the ZZ genotype in the Irish national targeted detection program is 44.13 years old ( $\pm$ 21.71). In the era of emerging therapies for AATD, it may be pertinent to revisit neonatal screening programs as a means of early detection.

Although this is one of the largest studies, to date, of the real-world effects of IV-AAT in severely deficient individuals, we acknowledge its limitations. This is a retrospective, observational study, although the reasons for conducting such a study have been outlined earlier. There are some discrepancies in the data collected across the three participating countries, limiting some analyses; notably,  $D_{LCO}$  was unavailable in Austria, and  $FEF_{25-75}$  measurements were only available in Ireland. Quality-of-life measures, which would add further valuable insights, were not available for analysis. Differences in follow-up length between the three countries may have reduced power to detect differences in survival. In addition, the observed decline by age of diagnosis may be a result of similar heterogeneity in follow-up length. A potential cause of this heterogeneity could be related to different characteristics between individuals who dropped out early and those who remained a part of the registry for a longer duration. We cannot account for differences because of additional genetic modifiers of *SERPINA1* expression that may exist in differing frequencies between the populations of the three countries, or because of ethnicity and socioeconomic status, as these were not captured in the registry data. Finally, we are unable to account for what medications or inhalers each participant was receiving at each time point in each country, although we note that prescribing practices were consistent and guideline-based across all three countries.

In summary, this study shows that people with AATD can be differentiated according to their index case status, with lung indexes having a more severe disease phenotype at diagnosis. IV-AAT confers a significant and demonstrable survival advantage in people with severe AATD, the majority of whom in this study are lung indexes. There is a disconnect between survival and spirometric lung function in AATD. Most RCTs of IV-AAT to date have been unable to show an effect of IV-AAT on



**Figure 4.** (A) Kaplan-Meier survival analysis categorized by augmentation status across all three countries showing an increased survival probability conferred by augmentation therapy ( $P=0.00076$ ). Those who were previously receiving augmentation therapy but stopped receiving it were excluded from analysis. (B) Kaplan-Meier survival analysis of individuals who never received intravenous alpha-1 antitrypsin, categorized by country, showing no difference in survival probability in those who never received augmentation therapy ( $P=0.14$ ).

lung function. But these studies enrolled predominantly lung indexes whose lung function had reached a low FEV<sub>1</sub> plateau, mitigating against showing a significant therapeutic effect of IV-AAT. This should

inform patient enrollment in future clinical studies. Detecting people with severe AATD as early as possible and initiating therapy before the establishment of COPD should be the goal in improving survival (35). That has

not been achieved to date, even with aggressive targeted detection programs. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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