Angiotensin-Converting Inhibitors and Angiotensin II Receptor Blockers and Longitudinal Change in Percent Emphysema on Computed Tomography

The Multi-Ethnic Study of Atherosclerosis Lung Study

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Abstract

Rationale: Although emphysema on computed tomography (CT) is associated with increased morbidity and mortality in patients with and without spirometrically defined chronic obstructive pulmonary disease, no available medications target emphysema outside of alpha-1 antitrypsin deficiency. Transforming growth factor-β and endothelial dysfunction are implicated in emphysema pathogenesis, and angiotensin II receptor blockers (ARBs) inhibit transforming growth factor-β, improve endothelial function, and restore airspace architecture in murine models. Evidence in humans is, however, lacking.

Objectives: To determine whether angiotensin-converting enzyme (ACE) inhibitor and ARB dose is associated with slowed progression of percent emphysema by CT.

Methods: The Multi-Ethnic Study of Atherosclerosis researchers recruited participants ages 45–84 years from the general population from 2000 to 2002. Medication use was assessed by medication inventory. Percent emphysema was defined as the percentage of lung regions less than −950 Hounsfield units on CTs. Mixed-effects regression models were used to adjust for confounders.

Results: Among 4,472 participants, 12% used an ACE inhibitor and 6% used an ARB at baseline. The median percent emphysema was 3.0% at baseline, and the rate of progression was 0.64 percentage points over a median of 9.3 years. Higher doses of ACE or ARB were independently associated with a slower change in percent emphysema ($P = 0.03$). Over 10 years, in contrast to a predicted mean increase in percent emphysema of 0.66 percentage points in those who did not take ARBs or ACE inhibitors, the predicted mean increase in participants who used maximum doses of ARBs or ACE inhibitors was 0.06 percentage points ($P = 0.01$). The findings were of greatest magnitude among former smokers ($P < 0.001$). Indications for ACE inhibitor or ARB drugs (hypertension and diabetes) and other medications for hypertension and diabetes were not associated independently with change in percent emphysema. There was no evidence that ACE inhibitor or ARB dose was associated with decline in lung function.

Conclusions: In a large population-based study, ACE inhibitors and ARBs were associated with slowed progression of percent emphysema by chest CT, particularly among former smokers. Randomized clinical trials of ACE and ARB agents are warranted for the prevention and treatment of emphysema.

Keywords: lung; emphysema; pharmacoepidemiology

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Chronic obstructive pulmonary disease (COPD) and emphysema are, jointly, the third leading cause of death in the United States and globally (1). COPD is defined by incompletely reversible airflow obstruction on spirometry (2). Pulmonary emphysema is characterized by airspace enlargement with destruction of alveolar walls (2). Strategies for the prevention and treatment of chronic lung disease to supplement smoking cessation and avoidance are urgently needed, particularly for former smokers (3).

Emphysema is common in the general population (4) among patients with and without COPD (5). The percentage of emphysema-like lung (hereafter called *percent emphysema*) on computed tomography (CT) predicts morbidity and mortality independent of lung function among patients with COPD (6, 7). Percent emphysema is also associated with incident airflow obstruction (8), symptoms of dyspnea (9), and increased mortality among patients without COPD (10).

Almost all medications for COPD target the airways rather than emphysema (3); however, none is proven to reduce mortality or to prevent incident COPD. Most animal models of COPD assess emphysema rather than airflow limitation; therefore, translation of therapeutic successes in murine models to emphysema progression rather than lung function decline in humans is an appealing strategy that has recently proved successful in alpha-1 antitrypsin deficiency (11).

Murine models demonstrate that altered transforming growth factor-β (TGF-β) signaling increases airspace enlargement and distorts alveolarization via changes to the extracellular matrix structure (12, 13). Angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors antagonize TGF-β signaling by inhibiting the renin-angiotensin system (14, 15). More complete blockage of the angiotensin receptor leads to greater reduction in TGF-β expression (16), emphasizing the importance of the dose of these drugs. Administration of ARBs in murine models reduces TGF-β expression and reverses emphysema (17). ACE inhibitors and ARBs also improve endothelial function (18, 19), which is implicated in emphysema pathogenesis in animal experiments (20) and human studies (21). A recent small clinical trial showed a nonsignificant decrease in percent emphysema after 12 months of ARB therapy among those with baseline emphysema (22).

We therefore hypothesized that the use and greater doses of ACE inhibitors or ARBs would be associated with a slowed decline in the progression of emphysema assessed quantitatively on the basis of CT over approximately a decade in a large, prospective cohort study. Preliminary results of this study were previously reported in the form of an abstract (23).

Methods

The Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) researchers recruited 6,814 participants ages 45–84 years from the general population in 2000–2002 (24). The MESA Air Pollution Study recruited an additional 257 participants in 2004–2007 (25). Exclusion criteria were clinical cardiovascular disease, weight over 136.1 kg, pregnancy, and impediments to long-term participation.

The MESA Lung Study researchers enrolled 3,965 MESA participants (26) and all MESA Air Pollution Study participants at one site (n = 100) in 2004–2007, as well as an additional 409 MESA participants in 2010–2012 (Figure 1). Seventy-six

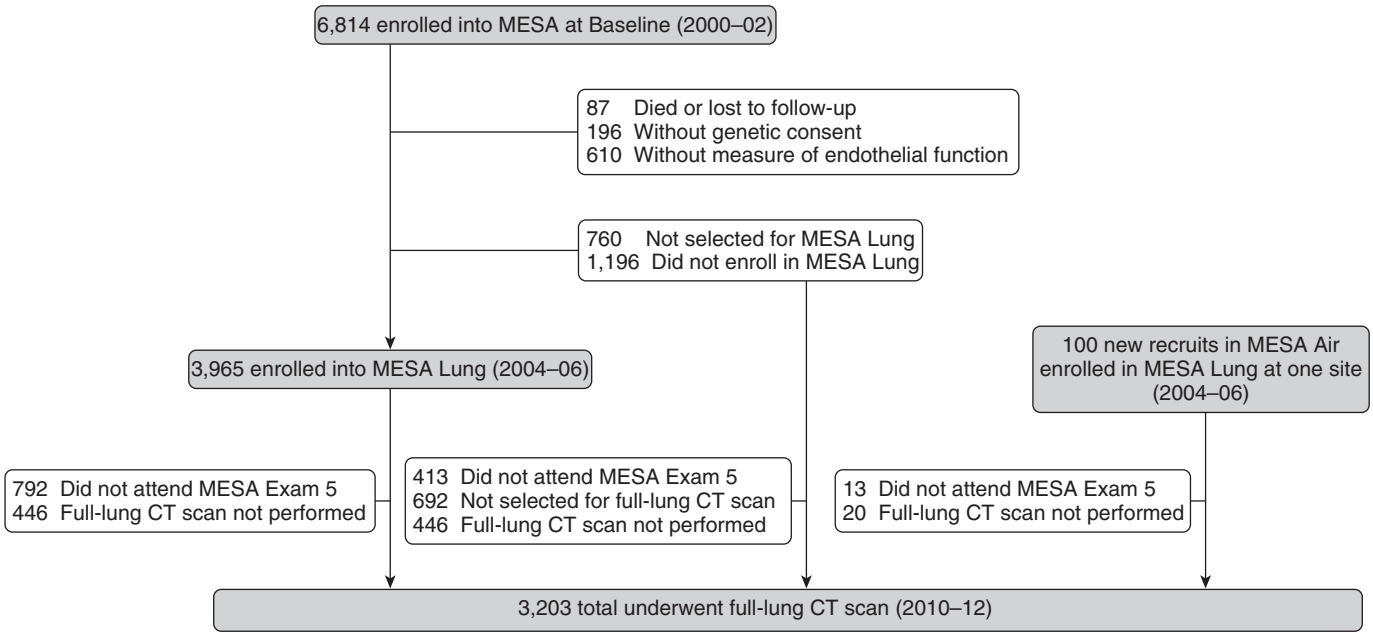

Figure 1. Flowchart of computed tomographic (CT) scans and percent emphysema measures included in longitudinal analysis. The longitudinal study included 4,472 subjects, 12,040 observations from examinations 1–5, and a median of 9.3 years of follow-up time. MESA = Multi-Ethnic Study of Atherosclerosis.

percent of those enrolled in 2004–2007 were reexamined in 2010–2012.

The protocols of MESA and all studies described were approved by the institutional review boards of collaborating institutions and the National Heart, Lung, and Blood Institute. Written informed consent was obtained from all participants.

ACE Inhibitor and ARB Dose

Medication use was assessed at enrollment into MESA using a medication inventory (27). Participants were instructed to bring with them all prescription and over-the-counter medications used in the 2 weeks prior to the visit. Staff recorded the name, strength, and frequency of use for each medication. If a participant forgot to bring medications to the visit, the information was obtained by a subsequent telephone interview.

Specific medications were grouped as ACE inhibitors and ARBs using standard pharmacopeia; combination pills that included either class of medication were included in the relevant category. Dose was assessed as the proportion of the maximum daily recommended dosage of each specific medication. If a patient used more than one ACE inhibitor or ARB medication, then cumulative dose was used in the analysis.

Measurement of Emphysema on Chest Computed Tomographic Images

All participants underwent cardiac CT at enrollment into MESA and were invited to undergo repeat cardiac scans though 2007 following a standardized protocol (28) after coaching to full inspiration on electron-beam and multidetector CT scanners. Forty-five scans acquired using an incorrect protocol were excluded, as were 312 scans acquired on Toshiba (Tokyo, Japan) scanners, which do not produce reliable lung density measures. Full-lung scans were performed for 3,203 MESA Lung Study participants in 2010–2012 at full inspiration on 64-slice multidetector CT scanners following the MESA Lung Study/Subpopulations and Intermediate Outcomes in COPD Study protocol (29).

Trained readers performed percent emphysema measurements at a single reading center without knowledge of other participant information using modified Pulmonary Analysis Software Suite (PASS) software (30) for cardiac scans and Apollo 1.2 (an updated version of PASS; VIDA Diagnostics, Coralville, IA) for full-lung scans. Percent emphysema was defined as the percentage of voxels in the lung below −950 Hounsfield units (HU), a threshold chosen on the basis of pathologic comparisons (31), validity in longitudinal studies (32), and prognostic significance in this cohort (10). The −950-HU threshold was adjusted for attenuation of air outside the chest to help account for scanner changes (33). Cardiac CT scans approximately 66% of lung volume from the carina to the lung bases (34); the upper third of each full-lung scan was therefore excluded to compare the same lung regions over time.

Percent emphysema on cardiac CT scans has been validated previously against full-lung scans in this cohort (34). Examination of monthly averages of air outside the chest from all scans demonstrated little scanner drift over more than 11 years, with the exception of one scanner (*see* E2 in the online supplement). The scan–rescan reliability of percent emphysema previously assessed with interclass correlation was high: 0.89 (34). The reproducibility of the imaged lung volume over the five examinations was somewhat more variable (Table E7). Lung density at the lower 15th percentile, measured as the HU level below which 15% of all lung voxels have a lower density value (32), was used as a secondary endpoint.

Spirometry

Spirometry was conducted in the MESA Lung Study sample in 2004–2007 and repeated in 2010–2012 in accordance with American Thoracic Society/European Respiratory Society guidelines (35). All participants attempted at least three acceptable maneuvers on the same dry rolling seal spirometers (Occupational Marketing Inc., Houston, TX); all examinations were reviewed by one investigator (36).

Smoking and Other Covariates

Age, sex, race/ethnicity, educational attainment, secondhand smoke exposure, family history of emphysema, health insurance, and asthma prior to the age of 45 years were self-reported at baseline. Smoking status was defined at each examination as follows: ever smoking as more than 100 cigarettes lifelong; current smoking as a cigarette in the last 30 days or, at baseline and 10-year follow-up, positive urinary cotinine levels, as previously described (26); and former smokers as ever smokers who were not current smokers. Height, weight, blood pressure, and fasting plasma glucose were measured using standard techniques. Diabetes and hypertension were defined by self-reported physician diagnosis, the indication for most ACE or ARB use.

Statistical Analysis

Generalized mixed models with random intercepts were used to assess the relationship of medication dose and change in percent emphysema over time (37). Initial analyses examined dose of both medication classes combined; subsequent analyses examined each class of medication separately. Hypothesis tests treated dose as a proportion; it was also dichotomized for descriptive purposes as low dose (daily intake of less than 50% of maximum recommended dose) and full dose (daily intake of 50% or greater of the maximum recommended dose).

The initial model included CT scanner model, voxel size, and milliamperes as time-varying covariates. The subsequent model adjusted for age; sex; race/ethnicity; baseline pack-years of smoking; and time-varying measures of height, weight, and cigarettes per day. The final model also included baseline measures of systolic blood pressure, diastolic blood pressure, secondhand smoke exposure, family history of emphysema, socioeconomic status, health insurance, diabetes, asthma prior to the age of 45 years, statin use, aspirin use, diuretic use, and female hormone use.

Effect measure modification over time was evaluated for sex, smoking status, and race/ethnicity. Analyses for lung function used a similar statistical approach. To further address potential confounding by indication, propensity scores were calculated according to category of ACE inhibitor or ARB dose, and analyses were weighted by propensity score (38, 39). Statistical significance was defined as a two-tailed P value less than 0.05. Analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

Results

The 4,472 participants included in the analysis differed modestly with respect to demographic and anthropomorphic factors

from the MESA participants who were not included; however, smoking history and ACE or ARB drug use were similar (Table E1). The included participants had a mean age of 61 ± 10 years at baseline, and 49% were male. Fourteen percent were current smokers, 40% were former smokers, and 46% had never smoked. The race/ethnicity distribution was 38% white, 27% African American, 21% Hispanic, and 15% Chinese. The median percent emphysema was 3.0% (interquartile range, 1.2 to 5.9%).

Twelve percent used an ACE inhibitor at baseline, and 6% percent used an ARB; 0.2% took both medications. Use of ACE inhibitors or ARBs was fairly consistent over time, with 81% of participants who reported use of the medication at baseline also reporting it at one or more follow-up visits.

Participants taking full-dose ACE inhibitors or ARBs were more likely to be older, African American, and obese and had greater pack-years, but were similar with regard to sex, socioeconomic status, and smoking status, compared with participants not taking these medications (Table 1). As expected, participants taking ACE inhibitors or ARBs were much more likely to have hypertension and diabetes. Compared with participants not taking ACE inhibitors/ARBs, their FEV_1 was lower, their FEV_1/FVC ratio similar, and their percent emphysema at baseline slightly higher.

ACE Inhibitor/ARB and Longitudinal Change in Percent Emphysema

The 4,472 participants were scanned a median of three times over a median of 9.3 years (interquartile range, 4.6–9.7), resulting in 12,040 measures of percent emphysema. The mean increase in percent

Table 1. Baseline clinical characteristics of participants in the Multi-Ethnic Study of Atherosclerosis Lung Study, stratified by angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker dose

	No ACE Inhibitor/ARB Use (*n = 3,693*)	Low Dose (*n = 430*)	Full Dose (*n = 349*)
Age, yr, mean ± SD	60.6 ± 9.8	64.4 ± 9.2	64.9 ± 9.0
Male sex, n (%)	1,782 (48.2)	228 (53.0)	169 (48.2)
Race/ethnicity			
White, n (%)	1,435 (38.9)	151 (35.1)	92 (26.7)
African American, n (%)	921 (24.9)	145 (33.7)	144 (41.2)
Asian, n (%)	573 (15.5)	41 (9.5)	38 (10.9)
Hispanic, n (%)	765 (20.7)	93 (21.6)	74 (21.2)
Educational attainment			
Less than high school degree, n (%)	576 (15.6)	71 (16.5)	57 (16.3)
High school degree, n (%)	646 (17.5)	84 (19.5)	78 (22.4)
Some college/associate's degree/vocational school, n (%)	1,022 (27.7)	130 (30.2)	102 (29.2)
College degree or higher, n (%)	1,442 (39.3)	145 (33.7)	112 (32.1)
Height, cm, mean ± SD	166.7 ± 10.0	167.0 ± 10.3	166.6 ± 10.3
Weight, kg, mean ± SD	77.3 ± 16.8	81.9 ± 17.0	85.2 ± 18.0
Body mass index, kg/m^2, mean ± SD	27.7 ± 5.2	29.3 ± 5.1	30.6 ± 5.7
Cigarette smoking status, n (%)			
Never	1,727 (46.8)	193 (44.9)	155 (44.4)
Former	1,449 (39.2)	180 (41.9)	145 (41.6)
Current	517 (14.0)	57 (13.2)	49 (14.0)
Pack-years of smoking, median (IQR)	23.5 (11 0.0–42.0)	32.3 (11.7–46.5)	30.0 (17.0–56.0)
LDL, mg/dl, mean ± SD	118.4 ± 30.6	111.3 ± 30.7	110.6 ± 31.7
HDL, mg/dl, mean ± SD	51.43 ± 15.0	49.3 ± 13.8	48.9 ± 13.4
Systolic blood pressure, mm Hg, mean ± SD	122.9 ± 19.6	132.0 ± 20.3	135.7 ± 20.2
Diastolic blood pressure, mm Hg, mean ± SD	71.4 ± 10.0	73.7 ± 10.4	73.7 ± 10.7
Hypertension, n (%)	1,152 (31.2)	408 (94.9)	341 (97.7)
Fasting plasma glucose, mg/dl, median (IQR)	88.0 (82.0–96.0)	94.0 (863.0–111.0)	97.0 (88.0–114.0)
Diabetes mellitus, n (%)	231 (6.2)	118 (27.4)	101 (28.9)
Medication use, n (%)			
Statins	449 (12.2)	114 (26.5)	108 (31.0)
Calcium channel blockers	326 (8.8)	91 (21.2)	108 (31.0)
β-Blockers	298 (8.1)	62 (14.4)	43 (18.3)
Any diuretics	366 (9.9)	136 (31.6)	203 (58.2)
Aspirin	864 (23.4)	149 (34.7)	127 (36.4)
Female hormone use	588 (31.6)	69 (34.2)	57 (32.0)
FEV_1 percent predicted*, mean ± SD (n = 3,889)	94.8 ± 17.7	92.1 ± 19.5	90.8 ± 18.1
FVC percent predicted*, mean ± SD (n = 3,813)	96.7 ± 16.1	94.3 ± 16.4	92.3 ± 16.0
FEV_1/FVC ratio*, mean ± SD (n = 3,813)	0.75 ± 0.08	0.73 ± 0.10	0.75 ± 0.09
Percent emphysema −950 HU, median (IQR)	3.0 (1.2–5.9)	3.0 (1.3–5.7)	3.1 (1.3–5.8)

Definition of abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; HDL = high-density lipoprotein; HU = Hounsfield units; IQR = interquartile range; LDL = low-density lipoprotein.

Low dose is defined as daily intake of less than 50% of the maximum recommended dose. Full dose is defined as daily intake less than or equal to 50% of the maximum recommended dose.

*Spirometry measured approximately 4 years after baseline.

Table 2. Predicted change of emphysema over 10 years, by baseline angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker dose

	Medication Dose Percentage of Maximum Recommended Dose			Change per Maximum Dose over 10 Yr in Percent Emphysema (95% CI)	*P* Value
	None	Low Dose	Full Dose		
ACE inhibitor/ARB dose	(n = 3,693)	(n = 430)	(n = 349)	(n = 4,472)	
Model 1, mean difference	Reference	−0.19	−0.40	−0.68 (−1.28, −0.09)	0.02
Model 2, mean difference	Reference	−0.16	−0.45*	−0.76 (−1.34, −0.18)	0.01
Model 3, mean difference	Reference	−0.16	−0.43*	−0.74 (−1.32, −0.16)	0.01
ACE inhibitor dose	(n = 3,934)	(n = 396)	(n = 142)		
Model 1	Reference	−0.29	−0.86*	−1.24 (−2.22, −0.26)	0.01
Model 2	Reference	−0.22	−0.77*	−1.10 (−2.06, −0.14)	0.02
Model 3	Reference	−0.22	−0.76*	−1.09 (−2.05, −0.13)	0.03
ARB dose	(n = 4,223)	(n = 40)	(n = 209)		
Model 1	Reference	0.96	−0.02	−0.34 (−1.06, 0.38)	0.35
Model 2	Reference	0.69	−0.16	−0.53 (−1.23, 0.17)	0.14
Model 3	Reference	0.66	−0.14	−0.50 (−1.20, 0.20)	0.16

Definition of abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CI = confidence interval.
Model 1 adjusted for scanner model, voxel size, and high milliamperes. Model 2 adjusted for variables in model 1 in addition to age, sex, race/ethnicity, height and weight, cigarettes per day, pack-years, sex × time interaction, race × time interaction, and pack-years × time interaction. Model 3 adjusted for variables in model 2 in addition to systolic blood pressure, diastolic blood pressure, environmental tobacco smoke, family history of emphysema, educational attainment, health insurance, diabetes, asthma, statin use, female hormone use, aspirin use, and diuretic use.
*$P < 0.05$.

emphysema over 10 years was 0.64 percentage points (95% confidence interval [CI], 0.35 to 0.93%; $P < 0.001$) in this mostly healthy sample.

Use of a full dose of an ACE inhibitor or ARB was significantly associated with slowed progression of percent emphysema compared with not taking an ACE inhibitor or ARB in the minimally adjusted models (−0.68% per 10 yr; 95% CI, −1.28 to −0.09%; $P = 0.02$). Over 10 years, in contrast to a predicted mean increase in percent emphysema of 0.66 percentage points in those who did not take ARBs or ACE inhibitors, the predicted mean increase in participants who used the full doses of ARBs or ACE inhibitors was 0.06 percentage points. These results were largely unchanged in the fully adjusted model (Table 2). Participants taking low doses of an ACE inhibitor or ARB had a

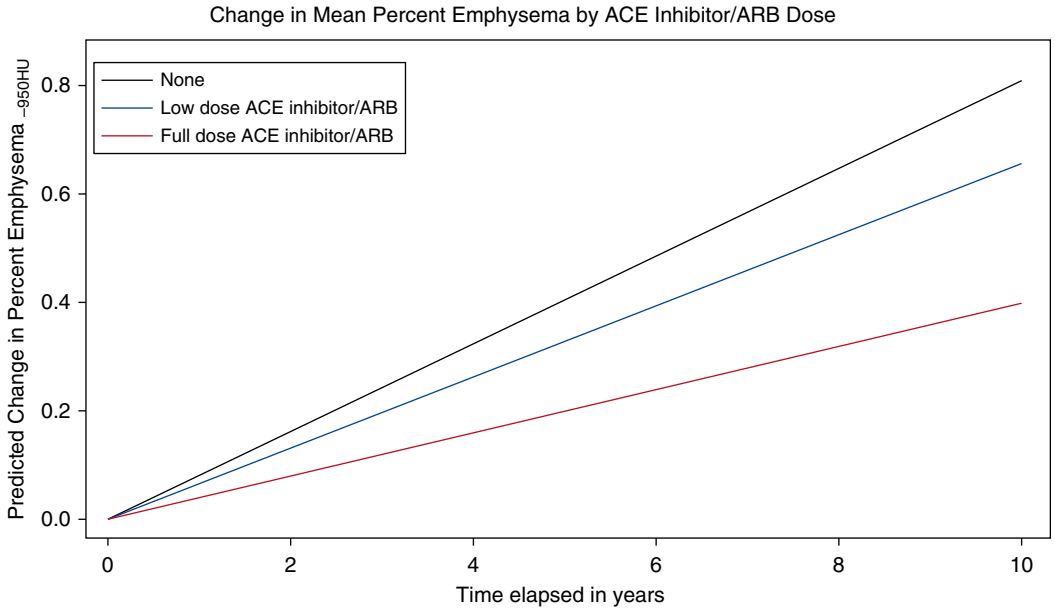

Figure 2. Predicted change in percent emphysema over time, by angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) dose. Low dose is defined as daily intake less than 50% of the maximum recommended dose. Full dose is defined as daily intake of at least 50% of the maximum recommended dose. HU = Hounsfield units.

nonsignificantly slower rate of progression in percent emphysema over time than participants not taking an ACE inhibitor or ARB. The change in percent emphysema for patients taking low and full ACE inhibitor or ARB doses was slower than the change for patients not taking either medication (Figure 2).

Examination of each medication class separately showed that ACE inhibitor dose was significantly associated with a decline in the progression of percent emphysema over time in the minimally adjusted model (Table 2). ARB dose was also associated with decline in the progression of percent emphysema over time; however, this association was of lesser magnitude and did not attain statistical significance.

Use of an ACE Inhibitor or ARB and Longitudinal Change in Percent Emphysema by Smoking Status

Associations were modified by smoking status (P-interaction = 0.02). There were highly statistically significant associations among former smokers for doses of ACE inhibitor or ARB in addition to ARB with a consistent although nonsignificant association for ACE inhibitors (Table 3). Findings for current smokers were also consistent but nonsignificant. There was no evidence for association among never smokers. A subgroup analysis of patients with significant emphysema at baseline, defined as percent emphysema above the upper limit of normal, yielded associations of stronger magnitude but did not attain statistical significance (Table 4).

Findings were also of greater magnitude among males than among females (P-interaction < 0.001) (Figure E1). There was no evidence for effect modification, although there were modest differences across strata of race/ethnicity, body mass index, age, scanner type, site, diabetes, and hypertension (Figure E1). Findings were consistent among patients with an FEV_1/FVC less than 0.70 and were not altered by adjustment for renal function (Figure E1).

Additional Analyses

The major indications for ACE inhibitors and ARBs are hypertension and diabetes. There was no evidence that a physician's diagnosis of either hypertension or diabetes or other medications used for these conditions was associated independently with change in percent emphysema (Table 5). Use of a propensity score approach yielded consistent if not stronger results (Table E3), as did longitudinal change in lung density at the lower 15th percentile (Table E4), percent emphysema defined at the −910-HU threshold (Table E5), and exclusion of one scanner that had poor calibration (Table E6).

ACE Inhibitor/ARB and Longitudinal Change in Lung Function

Of the participants in the longitudinal cohort, 3,889 had valid spirometry. Over a median follow-up time of 4.8 years, the mean decline in the FEV_1 per year was 19 ml (95% CI, 18–21; $P < 0.001$). There was no significant association between baseline ACE inhibitor or ARB dose

Table 3. Predicted change of emphysema over 10 years, by baseline angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker dose, stratified by baseline smoking status

	Medication Dose Percentage of Maximum Recommended Dose			Change per Maximum Dose over 10 Yr in Percent Emphysema (95% CI)	*P* Value
	None	Low Dose	Full Dose		
Former smokers				(n = 1,774)	
Combined ACE inhibitor/ARB dose	(n = 1,449)	(n = 180)	(n = 145)		
	Reference	−0.28	−0.74*	−1.75 (−2.73, −0.77)	<0.001
ACE inhibitor dose	(n = 1,548)	(n = 167)	(n = 59)		
	Reference	−0.29	−0.81	−1.13 (−2.76, 0.49)	0.17
ARB dose	(n = 1,671)	(n = 18)	(n = 85)		
	Reference	0.87	−0.62	−1.86 (−3.03, −0.70)	0.002
Current smokers				(n = 623)	
Combined ACE inhibitor/ARB dose	(n = 517)	(n = 57)	(n = 49)		
	Reference	−0.93	−0.77	−0.95 (−2.62, 0.73)	0.27
ACE inhibitor dose	(n = 548)	(n = 51)	(n = 24)		
	Reference	−1.03	−0.92	−1.83 (−4.51, 0.85)	0.18
ARB dose	(n = 591)	(n = 6)	(n = 26)		
	Reference	−0.04	−0.53	−0.42 (−2.65, 1.82)	0.72
Never smokers				(n = 2,075)	
Combined ACE inhibitor/ARB dose	(n = 1,727)	(n = 193)	(n = 155)		
	Reference	0.15	0.07	0.26 (−0.52, 1.05)	0.51
ACE inhibitor dose	(n = 1,838)	(n = 178)	(n = 59)		
	Reference	0.06	−0.49	−0.58 (−1.89, 0.73)	0.39
ARB dose	(n = 1,961)	(n = 16)	(n = 98)		
	Reference	0.96	0.44	0.67 (−0.10, 0.86)	0.16

Definition of abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CI = confidence interval.
Models adjusted for scanner model, voxel size, high milliamperes, age, sex, race/ethnicity, height and weight, cigarettes per day, pack-years, sex × time interaction, race × time interaction, pack-years × time interaction, systolic blood pressure, diastolic blood pressure, environmental tobacco smoke, family history of emphysema, educational attainment, health insurance, diabetes, asthma, statin use, female hormone use, aspirin use, and diuretic use.
*$P < 0.05$.

Table 4. Predicted change of emphysema over 10 years, by baseline angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker dose in patients with percent emphysema greater than the upper limit of normal

	Change per Maximum Dose over 10 Yr in Percent Emphysema (95% CI)	*P* Value
ACE inhibitor/ARB dose	(n = 602)	
Model 1, mean difference	−1.42 (−3.56, 0.71)	0.19
Model 2, mean difference	−1.73 (−3.82, 0.37)	0.11
Model 3, mean difference	−1.75 (−3.84, 0.35)	0.10
ACE inhibitor dose		
Model 1	−1.98 (−5.41, 1.45)	0.26
Model 2	−1.85 (−5.24, 1.55)	0.29
Model 3	−1.83 (−5.22, 1.57)	0.29
ARB dose		
Model 1	−0.96 (−3.51, 1.62)	0.47
Model 2	−1.46 (−3.96, 0.10)	0.25
Model 3	−1.48 (−3.98, 1.00)	0.24

Definition of abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CI = confidence interval.
Model 1 adjusted for scanner model, voxel size, and high milliamperes. Model 2 adjusted for variables in model 1 in addition to age, sex, race/ethnicity, height and weight, cigarettes per day, pack-years, sex × time interaction, race × time interaction, and pack-years × time interaction. Model 3 adjusted for variables in model 2 in addition to systolic blood pressure, diastolic blood pressure, environmental tobacco smoke, family history of emphysema, educational attainment, health insurance, diabetes, asthma, statin use, female hormone use, aspirin use, and diuretic use.

and change in lung function over time (Table E3).

Discussion

Greater dose of ACE inhibitors and ARBs was associated with slowed longitudinal change in percent emphysema in this population-based prospective cohort study with a median follow-up of 9.3 years. Findings were of greatest magnitude among former smokers and were specific to ACE inhibitors and ARBs among medications for hypertension and diabetes.

To our knowledge, this is the first study to examine the association between use of an ACE inhibitor or ARB and longitudinal decline in percent emphysema. Two prior studies demonstrated associations between use of an ACE inhibitor or ARB plus statin use with lowered rates of pulmonary hospitalization and mortality; however, the findings were nonspecific, and the studies used administrative data (40, 41), which is often subject to confounding (e.g., smoking history is poorly or not measured in administrative datasets). Given that percent emphysema is associated with increased risk of pulmonary hospitalization among smokers and mortality in the general population (8, 10), the present results are consistent with these prior studies for ACE inhibitors or ARBs but expand upon them with a much more specific endpoint and more detailed control for potential confounding factors.

Stratification by smoking status revealed that the association was of greatest magnitude among former smokers, consistent with the murine model that found that ARBs improved lung architecture in smoking-induced emphysema (17). Studies in patients with emphysema and COPD of varying severity have shown chronic cigarette smoke induces altered TGF-β signaling (42, 43). Additionally, genetic studies have demonstrated an association of gene polymorphisms in the *TGFB1* and *TGFB2* genes among smokers with COPD and emphysema (44, 45). Cigarette smoke–induced pulmonary emphysema is associated with matrix metalloproteinases and their inhibitors, which regulate extracellular matrix homeostasis (46). In emphysema, altered TGF-β signaling may lead to increased matrix metalloproteinase expression and subsequent extracellular matrix degradation (47, 48). Additionally, ACE inhibitors and ARBs improve endothelial dysfunction (18, 19), which is implicated in emphysema pathogenesis (21), and provide protection of end organs from microvascular disease (49, 50), which is also aberrant in emphysema (51).

Among current smokers, the ACE or ARB dose was associated nonsignificantly with slowed progression of emphysema. The lack of statistical significance in this group may have been due to the much smaller sample of current smokers, artifact that current smoking produces in quantitative measures of emphysema on CT images (52); greater ongoing damage from active smoking; or the lack of visualization of the lung apices on these CT scans that would miss early smoking-related centrilobular emphysema, which has an apical predilection.

In contrast to results for percent emphysema, there was no evidence of a relationship between ACE inhibitor or ARB use and slowed decline of lung function over 5 years. A prior study showed an association of ACE inhibitor use with lower odds of rapid FEV_1 decline among current and former smokers over a similar follow-up time (53); however, that study was considerably smaller and restricted to smokers. That said, the present sample with spirometry may have been less affected and, compared with the sample with percent emphysema, was smaller and had shorter follow-up, which may have resulted in insufficient power to detect a decline in lung function in the present study. Change in emphysema and change in lung function over time are likely due to distinct mechanisms (54, 55), and the present findings may reflect the divergent underlying biology of emphysema and airflow limitation.

Strengths and Limitations

The major strength of this study is the longitudinal design of repeated CT measures in a large, multiethnic population–based sample over 10 years. However, there are several potential limitations. Confounding by indication is a frequent flaw of observational studies of medication use. For example, prior studies of statins and lung function decline and exacerbations (41, 56) failed to replicate in a large randomized clinical trial (57). We think this to be an unlikely explanation for our results for several reasons. First, the endpoint (change in percent emphysema) was mostly subclinical in this cohort; emphysema (as opposed to COPD) is rarely diagnosed by

Table 5. Association with major indicators for angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and progression per 10 years in percent emphysema

Confounders	n (%)	Change per Maximum Dose per 10 Yr in Percent Emphysema (95% CI)	*P* Value
Diagnosed hypertension	1,682 (37.6)		
Model 1		−0.20 (−0.43, 0.03)	0.09
Model 2		−0.09 (−0.34, 0.16)	0.48
Diagnosed diabetes	450 (10.1)		
Model 1		0.19 (−0.19, 0.56)	0.32
Model 2		0.30 (−0.08, 0.68)	0.13
Antihypertensive medications	525 (11.7)		
Calcium channel blockers			
Model 1		−0.03 (−0.37, 0.32)	0.88
Model 2		0.01 (−0.29, 0.40)	0.75
β-Blockers	426 (9.5)		
Model 1		0.21 (−0.16, 0.58)	0.27
Model 2		0.26 (−0.11, 0.63)	0.17
Diuretics	705 (15.8)		
Model 1		−0.43 (−0.73, −0.12)	0.006
Model 2		−0.32 (−0.65, 0.003)	0.05
α-Blockers	170 (3.8)		
Model 1		−0.30 (−0.89, 0.03)	0.33
Model 2		−0.33 (−0.93, 0.26)	0.28
Diabetes medications	60 (1.3)		
Insulin			
Model 1		0.05 (−0.10, 0.92)	0.93
Model 2		0.11 (−0.86, 1.08)	0.83
Oral hypoglycemic agents	348 (7.8)		
Model 1		0.25 (−0.17, 0.68)	0.24
Model 2		0.33 (−0.10, 0.76)	0.14

Definition of abbreviation: CI = confidence interval.
Model 1 adjusted for scanner model, voxel size, and high milliamperes, age, sex, race/ethnicity, height and weight, cigarettes per day, pack-years, sex × time interaction, race × time interaction, pack-years × time interaction, and angiotensin-converting enzyme (ACE) or angiotensin II receptor blocker (ARB) doses. Model 2 adjusted for variables in model 1 in addition to ACE or ARB dose and ACE or ARB dose × time interaction.

clinicians; and neither emphysema nor COPD is an indication for an ACE inhibitor or ARB. Second, the two major indications for ACE or ARB drugs, hypertension and diabetes, were not significantly associated with emphysema progression. Third, there was little to no evidence that other medications with the same indications (i.e., antihypertensives and diabetes medications) were associated with emphysema progression; hence, the association was specific to ACE or ARB agents. Fourth, the association was specific to emphysema progression in this study; were the results due to characteristics of participants taking an ACE inhibitors or ARB, it would be likely that those same characteristics would have resulted in slowed decline in lung function. Fifth, propensity score analyses (which are not immune to confounding) also yielded significant results. Hence, the observed specific relationship for percent emphysema is unlikely to be due to confounding by indication.

The medication inventory to determine participant use of an ACE inhibitor or ARB did not include information on medicine adherence. However, nonadherence in this study should have introduced a conservative bias, and the medication inventory is more reliable than self-report in assessing prescription drug use (27). Detailed information on exacerbations and hospitalizations, as well as some medications, was not available and was not included in multivariate models.

There was evolution of scanners over the 12 years of the study. A large minority of scans included in this study were acquired on electron-beam scanners, which have a consistently different calibration of air. However, all scans were acquired under a tight quality control program, and attenuation of air outside the body on these scans remained stable over the 12-year study period. Modeling approaches accounted for much of the scanner differences, and sensitivity analyses of scans acquired on similar scanners showed consistent results. The lung apices were excluded; therefore, results are based on the lower two-thirds of the lung, which correlate well with measures from full-lung scans (34), and volume correction was not available, although analyses using alterative CT metrics were consistent.

Conclusions

ACE inhibitor or ARB dose was associated with a slowed progression of percent emphysema over 9.3 years in this large, prospective cohort study. Findings were of greatest magnitude among former smokers. These findings suggest that ACE inhibitors and ARBs might play an important role in the prevention and treatment of emphysema among humans, as suggested by animal models. Randomized clinical trials of medications targeting the renin-angiotensin system pathway and the endothelium are warranted in emphysema to determine their potential therapeutic benefits. ■

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