Influence of Renin-Angiotensin System Inhibitors on Lower–Respiratory Tract Infections in Type 2 Diabetes: The Fremantle Diabetes Study Phase II

Timothy M.E. Davis and Wendy A. Davis

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OBJECTIVE

To determine whether ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) protect against lower–respiratory tract infections complicating type 2 diabetes.

RESEARCH DESIGN AND METHODS

Of 1,732 participants with diabetes recruited to the longitudinal observational Fremantle Diabetes Study Phase II (FDS2) between 2008 and 2011, 1,482 had confirmed type 2 diabetes (mean age 65.8 years and median diabetes duration 9.0 years; 51.6% were male). All were followed for hospitalizations for or with, or deaths from, pneumonia/influenza, ascertained from validated administrative data linkage from study entry to end of 2016. Cox regression and competing risk regression were used to identify independent predictors of this outcome.

RESULTS

Two-thirds of participants (n = 982) were taking an ACEi and/or ARB at study entry (498 [33.6%] ACEi, 408 [27.5%] ARB, 76 [5.1%] both). During 9,511 person-years of follow-up (mean ± SD 6.4 ± 2.0 years), 174 participants had incident pneumonia/influenza (156 hospitalizations and 18 deaths without hospitalization). In Cox regression analysis, baseline ACEi/ARB use was independently associated with a reduced risk of incident pneumonia/influenza (cause-specific hazard ratio [HR] 0.64 [95% CI 0.45, 0.89], P = 0.008). Allowing for the competing risk of death did not change this finding (subdistribution HR 0.67 [0.48, 0.95], P = 0.024), and similar reductions were seen for ACEi, ARB alone, and ACEi/ARB combination therapy. There was no significant change in use of ACEi/ARB during follow-up [interaction with ln(time), P = 0.70]. Other significant predictors of incident pneumonia/influenza were previously reported, clinically plausible variables.

CONCLUSIONS

ACEi/ARB reduce the risk of pneumonia/influenza in people with type 2 diabetes.

Medical School, University of Western Australia, and Fremantle Hospital, Fremantle, Western Australia, Australia

Corresponding author: Timothy M.E. Davis, tim.davis@uwa.edu.au

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The weight of evidence suggests that the risk of lower–respiratory tract infections is increased in people with type 2 diabetes (1–3) and that the associated mortality is greater than in people without diabetes (4). In addition, although the incidence of the chronic vascular complications of diabetes has declined over the past two decades (5), this trend has not been observed with infections. In contrast to a steady reduction in adults without diabetes, the rate of hospitalizations for pneumonia has remained relatively stable in people with diabetes in the U.S. over recent years (6). As diabetes is a strong risk factor for the development of pulmonary complications of coronavirus disease 2019 (COVID-19) (7), this divergence should become more marked with time.

One factor that has been identified as possibly affording protection against community-acquired infections is use of drugs that inhibit the renin-angiotensin system (RAS) and thus attenuate the adverse effects of RAS-mediated oxidative stress and inflammation (8). In the case of lower–respiratory tract infections, the results of a meta-analysis suggested that ACE inhibitors (ACEi), but not angiotensin receptor blockers (ARB), protect against pneumonia in general population studies (9). However, a more recent study showed that ARB were more effective than ACEi in preventing pneumonia in people with chronic obstructive pulmonary disease (COPD) (10). One primary care–based U.K. study in people with diabetes found that ACEi prevented community-acquired pneumonia (11). There have been no equivalent studies of ARB in diabetes, but because diabetes is associated with progressive pulmonary dysfunction (12), the response to this class versus ACEi may be similar to that in COPD (10).

In view of the inconsistent and incomplete diabetes-specific data, the aim of the current study was to examine whether use of ACEi or ARB is associated with a reduction in the incidence of hospitalization for lower–respiratory tract infections in representative people with type 2 diabetes. Because there are a large number of other recognized risk factors for this type of infection (13), it is important to include possible confounding variables in assessment of the independent contribution of RAS inhibitors, a limitation of previous studies (9–11). RAS inhibitors are commonly used as antihypertensive agents and for renoprotection in type 2 diabetes (14), but a beneficial effect on the incidence of lower–respiratory tract infections may justify their wider use.

RESEARCH DESIGN AND METHODS

Study Site, Participants, and Approvals

The Fremantle Diabetes Study Phase II (FDS2) is a longitudinal observational study conducted in a zip code–defined urban community of 157,000 people surrounding the city of Fremantle in the state of Western Australia (WA) (15). Socioeconomic data relating to income, employment, housing, transportation, and other variables in the study area show an average Index of Relative Socio-Economic Advantage and Disadvantage of 1,033 with a range by zip code of 977–1,113, figures similar to the Australian national mean ± SD, which are set at 1,000 ± 100 (16).

Descriptions of FDS2 recruitment, sample characteristics, and details of nonrecruited individuals with diabetes have previously been published (15). In brief, individuals resident in the catchment area with a clinician-verified diagnosis of diabetes (excluding gestational diabetes mellitus) were identified through all available hospital and community sources. Of 4,639 with known diabetes identified between 2008 and 2011, 1,668 (36.0%) were recruited to FDS2. Former FDS Phase I participants recruited between 1993 and 1996 who had moved out of the catchment area ($n = 64$) were also recruited, for a total cohort of 1,732. The mean ± SD baseline age of those recruited to the FSD2 was 62.0 ± 13.8 vs. 61.3 ± 17.4 years in patients identified but not recruited; 52.2% and 52.4%, respectively, were male; and 90.1% and 89.5%, respectively, had type 2 diabetes ($P \geq 0.17$ in each case) (17).

Study Procedures

All FDS2 participants were invited to face-to-face assessments at entry and then biennially, interspersed with biennial postal questionnaires (15). Face-to-face assessments included a standardized comprehensive questionnaire and physical examination, as well as fasting biochemical tests performed in a single nationally accredited laboratory. It was requested that participants bring all medications/prescriptions to each visit, and details were verified and recorded. Smoking, alcohol consumption, and vaccination histories were documented. BMI was determined together with a body shape index (ABSI), which represents a more reliable estimate of visceral adiposity (18). Pulmonary function testing was performed to American Thoracic Society spirometry standards (19).

Type 2 diabetes in participants was ascertained based on diabetes treatment history (especially insulin and its initiation relative to diagnosis), BMI, age at diagnosis, nature of first presentation, and/or self-identification. Among the 1,551 with clinically defined type 2 diabetes, subsequent testing for anti-GAD antibodies and monogenic diabetes reduced this number to 1,482 with true type 2 diabetes (16). Racial/ethnic background was categorized based on self-selection, country/countries of birth and parents'/grandparents' birth, and language(s) spoken at home as Anglo-Celt, Southern European, Other European, Asian, Aboriginal, or mixed/other.

Complications of diabetes were identified using standard definitions (20). Albuminuria was assessed by early-morning spot urine albumin-to-creatinine ratio (ACR) measurement and renal impairment from the estimated glomerular filtration rate (eGFR) (21). Peripheral sensory neuropathy was defined using the clinical portion of the Michigan Neuropathy Screening Instrument. Retinopathy was defined as one microaneurysm in either eye or worse, previous laser treatment on fundus photography, or ophthalmologist assessment. Participants were classified as having coronary heart disease if there was a history of myocardial infarction, angina, coronary artery bypass grafting, or angioplasty and as having cerebrovascular disease if there was a history of stroke or transient ischemic attack. Peripheral arterial disease was defined as an ankle brachial index ≤0.90 or a diabetes-related lower-extremity amputation.

Ascertainment of Outcomes

The Hospital Morbidity Data Collection (HMDC) contains information regarding all public/private hospitalizations in WA since 1970, while the Registry for Births, Deaths and Marriages records details of all deaths in WA (22). The FDS2 has been linked through the Western Australia Data Linkage System (WADLS) to these databases, as approved by the WA Department of Health Human Research Ethics Committee, to provide validated data on incident events to end of 2016.

The outcomes of interest during follow-up were hospitalizations for the main bacterial and viral lung parenchymal infections pneumonia or influenza using the ICD-10, Australian Modification (ICD-10-AM) codes J10–J18, which have previously been validated (23). Deaths from or with pneumonia/influenza, based on the death certificate or coroner's determination, were also identified.

The Hospital Morbidity Data Collection was used to supplement data obtained through FDS2 assessments relating to prevalent/prior disease during the 5 years prior to study entry. These data were used to calculate the Charlson comorbidity index (CCI) (24), which includes a history of myocardial infarction, heart failure, cerebrovascular disease, peripheral arterial disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, hemiparesis or paraparesis, renal disease, liver disease, and cancer. For the purposes of the current study, we excluded conditions coded as diabetes-specific chronic complications (ICD-9, clinical modification [ICD-9-CM] 250 and ICD-10-AM E10–E14 codes).

Statistical Analysis

The computer packages IBM SPSS Statistics 25 (IBM Corporation, Armonk, NY) and Stata/SE 15 (StataCorp, College Station, TX) were used for statistical analysis. Data are presented as proportions, mean ± SD, geometric mean (SD range), or, when variables did not conform to a normal or log-normal distribution, median and interquartile range. For independent samples, two-way comparisons for proportions were by Fisher exact test, for normally distributed variables by Student *t* test, and for non–normally distributed variables by Mann-Whitney *U* test. Multiple logistic regression (backward stepwise conditional modeling with $P < 0.05$ for variable entry and ≥ 0.05 for removal) was used to determine associates of baseline ACEi/ARB use.

Cox regression modeling was used to determine independent predictors of time to first hospitalization for or with or death from or with pneumonia/influenza. Variables were included if they were clinically plausible with a bivariable $P < 0.20$. They were removed one at a time, those with least statistical significance first, until all variables in the model were significant at $P < 0.05$. The use of ACEi/ARB at study entry was then added to the model as a binary variable (no ACEi/ARB use, ACEi/ARB use) and as a categorical variable (no ACEi/ARB use, ACEi only, ARB only, both ACEi and ARB). Fine and Gray competing risk regression modeling was performed similarly to take account of the competing risk of death from causes other than pneumonia or influenza (25). The proportional hazards assumption was checked for each model using Schoenfeld residuals for individual covariates and globally and using time-varying covariates. Thirty-four participants (2.3%) had missing data for one or more variables in the final models. As a sensitivity analysis, the six variables with missing data were multiply imputed (×20) and the analyses rerun with imputed data.

RESULTS

Baseline Characteristics

At study entry, the 1,482 FDS2 participants with type 2 diabetes had a mean ± SD age of 65.8 ± 11.6 years a median diabetes duration of 9.0 years (interquartile range 3.0–16.0), and 51.6% were male. Two-thirds ($n = 982$) were taking an ACEi and/or ARB at study entry (498 [33.6%] ACEi, 408 [27.5%] ARB, and 76 [5.1%] both). The independent associates of baseline use of ACEi and/or ARB are shown in Table 1 (see Supplementary Table 1 for bivariable comparisons). ACEi/ARB use was associated with longer diabetes duration and higher BMI and clustered with other pharmacotherapies including lipid-modifying agents (with an additional inverse association with total serum cholesterol), calcium channel blockers, diuretics, and aspirin. There was a graded increase in use with increasing urine albumin excretion, while participants with an eGFR ≥45 and <60 mL/min/1.73 m^2 were more likely to be taking ACEi/ARB than were those with an eGFR outside this range. Although participants with peripheral arterial disease were more likely to be treated with an ACEi/ARB than those without, those with a CCI ≥3 were less likely to be taking these agents than those with a lower comorbidity burden.

Incident Pneumonia/Influenza and Changes in RAS Inhibitor Use

During 9,511 person-years of follow-up (mean ± SD 6.4 ± 2.0 years) to first incident hospitalization for or with pneumonia or influenza, death, or end of December 2016—whichever came first—174 (11.7%) participants had incident pneumonia or influenza (156 hospitalizations for or with pneumonia/influenza and 18 deaths from or with pneumonia/influenza without hospitalization [crude incidence 18.3/1,000 person-years]).

The baseline characteristics of the cohort classified by incident pneumonia/influenza status are shown in Table 2. Compared with participants who remained free of lower–respiratory tract infections during follow-up in bivariable analyses, those with incident pneumonia/influenza were older and less well educated at baseline, were less likely to be married or in a de facto relationship, were less likely to be Anglo-Celt and more likely to be indigenous, and consumed less alcohol. They had longer duration of diabetes and greater abdominal obesity,

Table 1—Odds ratios 95% CIs for independent baseline associates of ACEi/ARB use in FDS2 participants with type 2 diabetes

	OR (95% CI)	*P*
Lipid-modifying medication	2.11 (1.58, 2.82)	<0.001
Calcium channel blocker therapy	2.23 (1.55, 3.21)	<0.001
Diuretic therapy	6.68 (4.54, 9.82)	<0.001
Aspirin therapy	1.87 (1.41, 2.47)	<0.001
Diabetes duration (increase of 1 year)	1.03 (1.01, 1.04)	0.001
Total serum cholesterol (increase of 1 mmol/L)	0.83 (0.73, 0.93)	0.002
Peripheral arterial disease	1.61 (1.16, 2.25)	0.005
BMI (increase of 1 kg/m^2)	1.03 (1.00, 1.05)	0.020
eGFR 45–59 mL/min/1.73 m^2	1.84 (1.09, 3.12)	0.022
Albuminuria category		0.025
Normoalbuminuria (ACR <3.0 mg/mmol)	1.00 (reference)	
Microalbuminuria (ACR 3.0–29.9 mg/mmol)	1.34 (1.01, 1.78)	0.042
Macroalbuminuria (ACR ≥30.0 mg/mmol)	1.90 (1.05, 3.44)	0.033
CCI ≥3	0.58 (0.34, 0.97)	0.040

OR, odds ratio.

and they were more likely to be insulin treated. They had a higher resting pulse rate and lower diastolic blood pressure, a greater urinary albumin excretion, and a lower eGFR and were more likely to have chronic vascular complications of diabetes. They were more likely to have been hospitalized with pneumonia/influenza before study entry, were more likely to have had both influenza and pneumococcal vaccinations, and had worse pulmonary function.

Predictors of First Hospitalization With or Death From Pneumonia/Influenza

The results of the Cox regression modeling are summarized in Table 3. After adjustment for the most parsimonious model of independent associates of first incident hospitalization for or with or death from or with pneumonia or influenza, use of ACEi or ARB at baseline was associated with a significant, 36%, reduced risk of incident pneumonia/influenza (cause-specific hazard ratio [csHR] 0.64 [95% CI 0.45, 0.89], $P = 0.008$). Other significant variables in the model were older age, indigenous and other European ethnicity, increasing HbA_{1c} and ABSI, increasing heart rate and lower diastolic blood pressure, increasing urinary albumin excretion and stage 3 or 4 chronic kidney disease, proton pump inhibitor use, increased CCI, and prior hospitalization with pneumonia/influenza.

To explore whether there were differences by type of RAS inhibitor, we used categorical variables for ACEi/ARB use (i.e., no ACEi/ARB, ACEi only, ARB only, both ACEi and ARB) in the same Cox model. The respective adjusted csHRs with no ACEi/ARB use as reference were 0.66 (95% CI 0.45, 0.97) ($P = 0.036$), 0.62 (0.41, 0.93) ($P = 0.020$), and 0.60 (0.30, 1.17) ($P = 0.13$), respectively. Taking the competing risk of death from other causes during follow-up into account attenuated the risk reduction, but it remained significant (subdistribution hazard ratio [sdHR] 0.67 [95% CI 0.48, 0.95], $P = 0.024$). (See Table 3.) The proportional hazards assumption was not violated for any of the variables in the models ($P \geq 0.31$) or overall ($P = 0.65$).

The models using multiply imputed data produced similar results. For the Cox model, the adjusted csHR for ACEi/ARB use was 0.61 (95% CI 0.44, 0.85) ($P = 0.003$), and for the competing risk model the adjusted sdHR was 0.70 (0.50, 0.98) ($P = 0.039$). At biennial face-to-face assessments, similar proportions of participants were taking an ACEi or ARB compared with baseline (68.3% of 1,152 at year 2, 69.5% of 893 at year 4, and 71.3% of 739 at year 6). The binary variable ACEi/ARB use did not vary over time [interaction with ln(time), $P = 0.70$].

Mortality

Of the participants who had an episode of pneumonia/influenza, 88 were hospitalized and were still alive at the end of follow-up (end-2016), 68 were hospitalized but had died by end-2016, and 18 died of or with pneumonia but had no hospital admission. Of the 68 hospitalized patients who died during follow-up, the mean ± SD time between hospitalization and death was 586 ± 626 days, with no significant difference by ACEi/ARB treatment status (21 not treated, 563 ± 600 days, vs. 47 treated, 597 ± 644 days; Mann-Whitney *U* test, $P = 0.98$). Three participants who were not taking ACEi/ARB (14.3%) vs. 10 who were (21.3%) died within 30 days of first hospitalization for or with pneumonia/influenza ($P = 0.74$).

CONCLUSIONS

The current study shows that use of ACEi and/or ARB was protective against hospitalization for pneumonia and influenza independently of a range of recognized risk factors over an average follow-up period of >6 years in a representative, community-based cohort of people with type 2 diabetes. The two classes of RAS inhibitor therapy, whether as monotherapy or in combination, had similar effects, providing a ≥30% reduction in the incidence of these lower–respiratory tract infections after adjustment. The competing risk of death had only a marginal effect on the magnitude of benefit, and there was no time-dependent influence of use of ACEi/ARB medications. These data have implications for management, especially in an era in which lower–respiratory tract infections remain a major cause of hospitalization for infection in people with diabetes (1,6) which is increasingly due to COVID-19 (7).

The published evidence to date that RAS inhibitor use may be beneficial in this way is inconsistent. A meta-analysis of general population studies found a 34% reduction in pneumonia with ACEi, close to the 36% protection with any RAS inhibitor in the current study, but no significant benefit with ARB use (9). The only diabetes-specific study, a retrospective study involving the large U.K. General Practice Research Database, found a smaller but still significant protective effect of 28% with ACEi, but ARB were not considered, there was no differentiation by type of diabetes, and there was limited availability of confounding variables (11). A recent Taiwanese study showed that ARB were more effective than ACEi in preventing pneumonia in COPD (10), and we were concerned that this finding may be relevant to type 2 diabetes because of the progressive, largely restrictive, pulmonary dysfunction that has been consistently reported (12). Nevertheless, despite the conflicting results for ARB in previous studies (9,10), we found that ARB and ACEi had similar effects in our well-characterized cohort of people with type 2 diabetes.

Although there is evidence that the combination of ACEi and ARB is beneficial for proteinuria (26) and heart failure (27), there are also adverse effects including acute kidney injury (AKI), hyperkalemia, and hypotension (28). Consistent with studies in other countries (29,30), 1 in 13 of our participants who were taking an RAS inhibitor were on combination therapy. This subgroup appeared, within the limitations of a small sample size and thus low statistical power, to have benefits to similar to those of monotherapy for prevention of pneumonia/influenza (a 40%, nonsignificant, reduction). Guidelines conventionally recommend temporary cessation of RAS inhibitor therapy during intercurrent illness such as pneumonia/influenza because of the risk of AKI and its sequelae, but the justification for this practice has been questioned (31). We did not have detailed data concerning inpatient and postdischarge management including RAS inhibitor use but did not find a significant difference in mortality by prior ACEi/ARB treatment status including at 30 days after discharge.

The other significant independent predictors of first hospitalization for, or death from, pneumonia/influenza in our multivariable models were consistent with those reported previously in studies of pneumonia in both the general population (13,32–34) and population with diabetes (3), including age, Australian indigenous ethnicity, overweight, chronic renal disease and albuminuria,

Table 2—Baseline associates of incident hospitalization for or with or death from or with pneumonia or influenza in FDS2 participants with type 2 diabetes

	No pneumonia/influenza	Incident pneumonia/influenza	*P*
Number (%)	1,308 (88.3)	174 (11.7)	
Age (years)	65.1 ± 11.3	70.3 ± 12.1	<0.001
Male (%)	51.4	52.9	0.75
Education beyond primary level (%)	87.9	76.5	<0.001
Not fluent in English (%)	10.2	14.4	0.11
Married/de facto relationship (%)	63.6	52.9	0.008
Ethnic background (%)			
Anglo-Celt	54.1	47.7	
Southern European	12.5	13.8	
Other European	6.7	8.6	0.005
Asian	4.7	2.3	
Aboriginal/TSI	6.3	14.4	
Mixed/other	15.7	13.2	
Smoking status (%)			
Never	43.3	35.8	
Former	46.3	50.9	0.13
Current	10.3	13.3	
Alcohol consumption (standard drinks/day)	0.1 [0–1.2]	0.1 [0–0.9]	0.024
Age at diabetes diagnosis (years)	55.4 ± 11.9	56.9 ± 14.1	0.17
Diabetes duration (years)	8.0 [2.1–15.4]	14.1 [6.0–19.1]	<0.001
Diabetes treatment (%)			
Lifestyle/diet	25.1	17.2	
OGLM	54.1	50.6	0.002
Insulin alone	4.9	10.3	
Insulin+OGLM	15.9	21.8	
HbA_{1c} (%)	7.1 [6.1–8.7]	7.5 [6.1–9.5]	0.16
HbA_{1c} (mmol/mol)	54 [43–72]	58 [54–80]	0.16
Fasting serum glucose (mmol/L)	6.8 [6.2–7.7]	7.1 [6.3–8.0]	0.015
ABSI ($m^{11/6} \cdot kg^{-2/3}$)	0.081 ± 0.005	0.083 ± 0.005	<0.001
BMI (kg/m^2)	31.2 ± 6.0	31.1 ± 6.4	0.79
Heart rate (bpm)	69 ± 12	74 ± 14	<0.001
Supine systolic blood pressure (mmHg)	146 ± 21	148 ± 25	0.28
Supine diastolic blood pressure (mmHg)	80 ± 12	78 ± 14	0.040
Antihypertensive medication (%)	74.3	77.9	0.35
ACEi/ARB use (%)	66.4	63.2	0.44
Total serum cholesterol (mmol/L)	4.4 ± 1.1	4.2 ± 1.1	0.10
Serum HDL cholesterol (mmol/L)	1.24 ± 0.34	1.19 ± 0.36	0.08
Serum triglycerides (mmol/L)	1.5 (0.9–2.5)	1.6 (1.0–2.6)	0.25
Lipid-lowering medication (%)	69.0	71.5	0.54
Aspirin (%)	37.3	42.1	0.24
Urinary ACR (mg/mmol)	3.0 (0.8–11.1)	6.8 (1.4–34.1)	<0.001
eGFR category (%)			
≥90 mL/min/1.73 m^2	39.9	23.6	
60–89 mL/min/1.73 m^2	46.0	37.9	
45–59 mL/min/1.73 m^2	8.5	13.2	<0.001
30–44 mL/min/1.73 m^2	3.8	15.5	
<30 mL/min/1.73 m^2	1.8	9.8	
Any retinopathy (%)	36.2	47.0	0.008
Peripheral sensory neuropathy (%)	57.1	69.5	0.002
Prior coronary heart disease (%)	27.4	44.8	<0.001
Prior cerebrovascular disease (%)	7.3	17.8	<0.001
Peripheral arterial disease (%)	21.8	29.3	0.034
CCI (%)			
0	78.3	48.9	
1–2	15.4	31.6	<0.001
3+	6.3	19.5	

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Table 2—Continued

	No pneumonia/influenza	Incident pneumonia/influenza	*P*
Prior pneumonia/influenza hospitalization (%)	1.8	9.2	<0.001
Influenza vaccination within last year (%)	70.6 (n = 1,261)	82.9 (n = 158)	0.001
Pneumonia vaccination within last 5 years (%)	40.7 (n = 1,245)	57.4 (n = 155)	<0.001
FVC (% predicted)	86.9 ± 17.7 (n = 1,210)	80.2 ± 17.5 (n = 136)	<0.001
FEV_1 (% predicted)	83.7 ± 18.7 (n = 1,210)	76.7 ± 19.7 (n = 136)	<0.001
FEV_1/FVC (%)	78.1 ± 1.9 (n = 1,210)	77.4 ± 1.9 (n = 136)	<0.001

Data are means ± SD, geometric means (SD range), or median [interquartile range] unless otherwise indicated. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; OGLM, oral glucose-lowering medications and noninsulin injectables; TSI, Torres Strait Islander.

prior hospitalization for respiratory infection, proton pump inhibitor therapy, and glycemic control. Smoking and COPD are other recognized risk factors in general population studies (13) but not in the current study. However, COPD is likely to have been captured under CCI categories, or resting pulse rate (35), especially as pulmonary function was not a significant predictor in our models, while the low rate of smoking in our participants (less than one in eight) may have obscured an association. The inverse association with diastolic blood pressure and, by implication, a wide pulse pressure may indicate an association with cardiovascular disease that has been inconsistent in general population studies (13). Participants whose ethnicity was from parts of Europe other than the U.K./Ireland and Southern European countries had an increased risk of pneumonia/influenza that reflects regional European general population differences (36). Neither pneumococcal nor influenza vaccination was predictive, reflecting general population studies (13).

There is debate as to whether use of ACEi/ARB prescribed for conventional indications may facilitate the COVID-19 infection and its complications or, alternatively, confer cardiorespiratory protection (37), but most guidelines recommend that they not be stopped as a precaution (38). In addition, available information suggests that, although COVID-19 itself causes pneumonia, secondary bacterial pulmonary infection may complicate up to one-half of fatal cases (39). The present data provide some support for maintaining ACEi or ARB therapy in patients at risk or those with mild symptoms who are at low risk of AKI due to fluid loss (31).

The current study had limitations. The FDS data were observational, but there is little evidence that estimates of intervention effects in well-conducted observational studies are consistently larger than, or qualitatively different from, those from randomized controlled trials (40). We did not examine dose-response relationships, as our aim was to assess whether usual-care ACEi/ARB prescription was associated with pneumonia/influenza hospitalizations and deaths. The choice of dose will depend on tolerability as well as cardiovascular and renal indications, which are independent of infection concerns. Independent associates of baseline ACEi/ARB use were largely consistent with cardiovascular/renal indications and warnings/contraindications that were not directly linked to infection, thus minimizing the risk of confounding by indication. The strengths of the current study include the prospective design, large patient numbers, detailed assessments, and ascertainment of end points through validated data linkage.

Table 3—Models of independent baseline predictors of first incident hospitalization for or with or death from or with pneumonia or influenza

	Cox model, csHR (95% CI)	*P*	Fine and Gray model, sdHR (95% CI)	*P*
Age at study entry (increase of 1 year)	1.05 (1.03, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
Australian Aboriginal ethnicity	2.60 (1.44, 4.67)	0.001	2.04 (1.15, 3.64)	0.016
Other European ethnicity[a]	1.82 (1.03, 3.20)	0.039	1.83 (1.05, 3.16)	0.032
HbA_{1c} (increase of 1% or 11 mmol/mol)	1.16 (1.04, 1.29)	0.006	1.18 (1.06, 1.31)	0.002
ABSI (increase of 10^{-3} for units of $m^{11/6} \cdot kg^{-2/3}$)	1.04 (1.01, 1.07)	0.011	1.03 (0.996, 1.06)	0.090
Heart rate (increase of 1 bpm)	1.02 (1.01, 1.03)	0.001	1.02 (1.004, 1.03)	0.011
Diastolic blood pressure (increase of 1 mmHg)	0.98 (0.97, 0.995)	0.007	0.98 (0.97, 0.997)	0.016
ln(urinary ACR [mg/mmol])[b]	1.19 (1.06, 1.33)	0.003	1.18 (1.05, 1.33)	0.005
eGFR[c] 30–44 mL/min/1.73 m^2	2.02 (1.28, 3.20)	0.003	2.03 (1.27, 3.24)	0.003
eGFR[c] <30 mL/min/1.73 m^2	2.52 (1.31, 4.87)	0.006	1.73 (0.83, 3.61)	0.145
PPI use	1.48 (1.05, 2.10)	0.027	1.43 (1.00, 2.05)	0.050
CCI[d] 1 or 2	2.19 (1.51, 3.18)	<0.001	1.98 (1.34, 2.91)	0.001
CCI[d] ≥3	2.42 (1.52, 3.86)	<0.001	2.08 (1.25, 3.46)	0.005
Prior hospitalization for/with pneumonia or influenza	2.67 (1.44, 4.98)	0.002	1.76 (0.94, 3.33)	0.079
ACEi or ARB use	0.64 (0.45, 0.89)	0.008	0.67 (0.48, 0.95)	0.024

PPI, proton pump inhibitor. [a]European other than Anglo-Celt and Southern European. [b]A 2.72-fold increase in ACR corresponds with an increase of 1 in ln(ACR). [c]Using eGFR ≥45 mL/min/1.73 m^2 as reference. [d]Using CCI of 0 as reference.

The present data represent a robust extension and clarification of published studies examining the relationship between ACEi/ARB use and lower respiratory infections in the context of type 2 diabetes. The detailed nature of FDS2 data permits the beneficial effects of RAS inhibitor therapies to be assessed independently of important confounding variables, while we have also allowed for time-dependent use of these therapies and the competing risk of death. Our findings suggest that prevention of pneumonia/influenza in people with diabetes may represent a novel indication for these therapies, especially in situations such as the current COVID-19 pandemic where pulmonary infections are a particular concern.

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