Real-world Evidence of Time-varying Effects of Renin-angiotensin System Inhibitors on Pneumonia and Related Deaths: A Territory-wide Cohort Study in 252,616 Patients With Diabetes (2002-2019)

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Abstract

Background

Diabetes is associated with increased risk of respiratory infections. Renin-angiotensin system (RAS) inhibition with anti-fibrotic, anti-inflammatory effects may reduce pneumonia risk. Prior studies did not account for time-varying and cumulative exposure to RAS inhibitors (RASi), with short follow-up periods, nor compared angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) use in Asians. We investigated the association of long-term use of RASi with risk of pneumonia and related death in Chinese people with diabetes using electronic medical record (EMR) data.

Methods

This was a prospective analysis of EMR with overlap propensity-score weighting of a territory-wide cohort (n=252,616, 1.7 million person-years) and a register-based cohort (n=13,017, 0.1 million person-years) in Hong Kong. We compared new-users of RASi (ACEi/ARBs) following baseline assessment with non-RASi users and new-users of calcium-channel blockers as active comparator. The main outcome was first hospitalization and death from pneumonia.

Results

Amongst 252,616 patients with diabetes in the population-based cohort (mean age=61.0 [SD=12.2] years), 73,161 were new-ACEi-only users; 20,907 new-ARBs-only users; 38,778 ACEi/ARBs users; and 119,770 never-ACEi/ARBs users. Over a mean follow-up period of 6.7 years, 5.2% (n=13,057) of patients had pneumonia and 2.2% (n=5,480) died with pneumonia. Compared with non-RASi use, time-varying RASi exposure was associated with reduced risk of pneumonia (hazard ratio, HR, 95% CI): 0.78 (0.75-0.82) and pneumonia-related death (HR=0.49, 0.46-0.53). The respective HRs for ARBs-only were 0.70 (0.62-0.78) and 0.41 (0.33-0.52) and that of ACEi-only were 0.98 (0.91-1.05) and 0.77 (0.68-86). In the Aalen-additive hazards model, the effect of RASi use was time-invariant for pneumonia (P=0.340) and time-varying for related death (P<0.001) with prevention of 0.6 (0.2-0.9) and 1.4 (1.0-1.6) per-1000-person-years pneumonia events and related deaths, respectively.

Conclusions

Long-term use of RASi, notably ARB, was associated with reduced risk of pneumonia and related deaths in Chinese patients with diabetes.

Background

During the current pandemic of coronavirus-disease 2019 (COVID-19), there is renewed interest in the effects of renin-angiotensin system inhibitors (RASi) including angiotensin converting enzyme inhibitors or angiotensin receptor blocker (ACEi/ARBs) in pulmonary infections. These drugs are widely prescribed in patients with hypertension, multiple risk factors and cardiovascular-renal disease. ACE and ACE2 are

regulators of angiotensin II (Ang II), a potent vasoconstrictor that can activate widespread inflammatory responses. ACEi reduces the conversion from Ang I to Ang II while ARBs blocks the angiotensin type 1 receptor (AT1) to reduce the deleterious effects of Ang II which can contribute to the severity of pneumonia and viral respiratory infections [1]. Use of RASi were associated with neutral risks of COVID-19 infection and mortality in randomized controlled trials and observational studies [2].

A previous metanalysis suggested that ACEi, but not ARBs use was associated with reduced risk of pneumonia [3]. However, these findings were not always consistent [4]. In Australia, researchers reported similar risk reduction in incident pneumonia among ACEi/ARBs users with diabetes versus non-users [5]. In an observational study of 6000 Chinese patients from Taiwan with chronic obstructive pulmonary disease (COPD), ARBs were associated with lower rates of pneumonia, severe pneumonia, and mortality than ACEi [4]. Prior studies suffered from methodological limitations, including short follow-up periods, lack of consideration for time varying and cumulative exposure or treatment switching, or inclusion of an appropriate comparator [5, 6]. Some studies have highlighted inter-ethnic differences in responses to RASi, with Asians experiencing greater reductions in pneumonia as compared with non-Asians, however this remains inconclusive [3].

In areas with universal health coverage, such as Hong Kong, the incidence of cardiovascular disease (CVD) had declined with pneumonia becoming a leading cause of death [7]. Hyperglycaemia is associated with activation of inflammatory and vascular responses which can increase their risks of infections including pneumonia [8, 9]. Based on the premise that RASi possess immunomodulatory effects, we hypothesized that long-term RASi use might reduce the risk of first pneumonia hospitalisation and death from pneumonia in patients with diabetes. The clinical course of diabetes is punctuated by co-morbidities, notably chronic kidney disease (CKD) and use of multiple medications which might confound the risk association of RASi and pneumonia events [10, 11]. Using longitudinal data curated from a territory-wide electronic medical record (EMR) system, we evaluated the time-varying and cumulative effects of RASi on pneumonia and related deaths in a prospective population-based cohort and a diabetes register-based cohort of Chinese patients with diabetes, and differential effects between ACEi and ARBs and their comparative effects with calcium-channel blockers (CCB).

Methods

Study design and participants

Data sources

Hong Kong is a cosmopolitan city with 7.5 million people, mainly southern Chinese. The Hong Kong Hospital Authority (HA) provides about 90% of all healthcare services for chronic medical conditions and governs all hospitals and majority of clinics in the public sector. In 2000, the HA developed an EMR system to routinely collect clinical information and drug data of all patients managed in public hospitals, specialist out-patient clinics, and general out-patient clinics. Our analysis included 581,811 patients with

diabetes in the territory-wide Hong Kong Diabetes Surveillance Database (HKDSD) who underwent structured assessment using the Risk Assessment and Management Programme for Diabetes Mellitus (RAMP-DM) module [7, 12, 13]. We also repeated our analysis in a registry-based cohort the Hong Kong Diabetes Register (HKDR). The HDKR was first established at the Prince of Wales Hospital (PWH), the teaching hospital of the Chinese University of Hong Kong since 1995 as part of a quality improvement programme. Details of the register have been described elsewhere [12]. For both HKDSD RAMP-DM and HKDR cohorts, patients had structured assessments guided by a uniform template consisting of risk factor assessments including blood pressure, lipid profile, glycemic control and microvascular complications.

Population-based cohort (HKDSD RAMP-DM module)

In the population-based cohort, we included a prospective cohort of 558,177 patients with diabetes using data from the HKDSD RAMP-DM module between 2002 and 2019. We adopted a new-user design excluding prevalent users of RASi (ACEi/ARBs) at enrollment (n = 184,709) to reduce prevalent bias. In the remaining 558,177 participants, the index date refers to the first date of dispensing of RASi (ACEi/ARBs, 52.7%). For non-RASi users, the index date refers to the first date of dispensing of glucose-lowering drugs (GLDs) with 16.4% initiated upon enrollment and 30.9% after enrolment. The baseline period was defined as one-year prior to index date (**Figure S1**).

Exclusion criteria included incident RASi-users in 2019 which was the year of censor (n = 41,434), gestational diabetes mellitus and missing type of diabetes (n = 10,647), observation for < 1 year, age < 18 years at enrolment, missing year of diabetes diagnosis (n = 11,548), prior history of kidney failure, CVD, cancer, chronic obstructive pulmonary disease (COPD), and asthma[14] based on the International Classification of Diseases (ICD) codes (see later definition, n = 52,352) and RASi use for < 90 days (n = 5,501) throughout the observation period. A total of 252,616 adult patients with type 1 (0.7%, n = 1,800) and type 2 (99.3%, n = 250,816) diabetes enrolled in 2002–2018 and observed until 31 December 2019 were included for analysis (**Figure S2**).

Diabetes register-based cohort (HKDR cohort)

In this register-based cohort, we included 27,580 patients with diabetes at the Prince of Wales Hospital enrolled in 2002–2018 and observed until 2019. We adopted the new-user design and included 13,017 participants in this analysis (7,716 incident-RASi and 5,301 non-RASi users) **(Figure S2).**

Analysis of RASi and other medications

Patients from both cohorts had individual-level longitudinal dispensing data including RASi, GLDs, antihypertensive and lipid modifying drugs including drug name, dose, frequency, dispensing duration (in days), start and end dates from 2000 to 2019. Across both cohorts, medications were prescribed and dispensed from the HA outpatient pharmacy on the same day as their primary or secondary care outpatient visit until the next clinic follow-up. Dispensed drug quantity and duration were captured from the EMR system. We grouped RASi and other drugs according to the Anatomical Therapeutic Chemical

Classification System,[13] including antihypertensive, diuretics, statins and non-statin lipid-modifying drug, beta-blocker, CCB, alpha-blocker and GLDs including insulin, metformin, sulfonylurea, alpha-glucosidase inhibitor (AGI), thiazolidinedione (TZD), dipeptidyl peptidase 4 inhibitor (DPP-4i), glucagon-like peptide-1 receptor analogue (GLP-1RA), and sodium-glucose co-transporter 2 inhibitor (SGLT2i) (**Table S1**). A patient was defined as a RASi-user if he/she had been exposed to ACEi and/or ARBs for 90 days or longer during the observation period. Time-varying exposure to RASi and other drugs were based on start and end dates of dispensing records during each follow-up year.

Outcomes

We examined the associations of RASi exposure with first pneumonia hospitalisation and death from pneumonia according to discharge diagnoses (ICD-9) in the EMR system and death codes (ICD-10) from the HKDR. The first pneumonia hospitalisation was defined using principal discharge diagnoses ICD-9 codes 480–486 (http://www.icd9data.com/2007/Volume1/default.htm) and pneumonia-related death was defined as death due to pneumonia (ICD-10 code: J12-J18).

Covariates

Covariates included sociodemographic data, clinical measurements, comorbidities, and medications. Data captured in the RAMP-DM module and the HKDR included personal data (sociodemographic characteristics, use of tobacco and alcohol, age of diagnosis, family history of diabetes), clinical (systolic and diastolic blood pressure [SBP/DBP], body mass index [BMI), waist circumference) and laboratory assessments (lipids, triglyceride, total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], HbA1c, hemoglobin, and estimated-glomerular filtration rate [eGFR]) collected on the same day. History of comorbidities (CVD, acute myocardial infarction [AMI], ischemic heart disease [IHD], heart failure, stroke, and cancer), were based on self-report at enrolment or hospitalisation record (ICD-9 codes, **Table S2**) prior to enrolment. History of hypertension was defined as SBP/DBP $\geq$ 140/90 mmHg or taking antihypertensive medications at enrollment. In the HKDR, we retrieved the influenza and pneumococcal vaccination data using the PWH-EMR system independent of the HKDSD.

Statistical analysis

All descriptive statistics were reported as counts (percentages) or mean (standard deviation, SD). For between-group comparisons of demographic variables and comorbidities, independent-sample *t* tests were used for numeric variables, while χ^2 tests were used for categorical variables.

To address confounding by indication [15], we applied overlap propensity-score weighting to homogenize baseline data for comparing incident-RASi versus non-RASi users [16]. We calculated propensity-score using a multivariate logistic regression model, and used the effect size of selected covariates to assign weights to the relevant attributes for each patient using the overlap weighting approach [16]. This overlap weighting method creates an exact balance of every measured covariate at baseline, including the 10-year risk score for atherosclerotic cardiovascular disease (ASCVD) [17] (Table 1). Compared with the

classic propensity-score method of matching and inverse probability of treatment weighting, overlap weighting showed better performance with respect to target population, balance and precision [16]. We used the Cox-proportional hazards model to estimate the independent association of RASi exposure with first pneumonia hospitalisation and death from pneumonia in the overlap weighted cohort, presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

Table 1
Clinical profiles of patients by incident-RASi use before and after overlap-weighting in the population-based cohort.

Variables	Overall	Before overlap-weighting			After overlap-weighting		
		Non-RASi	RASi	SMD	Non-RASi	RASi	SMD
N	252616	119770 (47.4)	132846 (52.6)		119770	132846	
Men, %	119824 (47.4)	54777 (45.7)	65047 (49.0)	0.065	48.2	48.2	< 0.001
Age at index date, years	60.9 (12.1)	58.8 (12.1)	62.8 (11.7)	0.342	58.8 (12.1)	58.8 (12.1)	< 0.001
Duration of diabetes, years	5.3 (6.2)	3.5 (5.1)	6.9 (6.6)	0.582	3.5 (5.1)	3.5 (5.1)	< 0.001
Family history of diabetes, %	109024 (43.2)	51976 (43.4)	57048 (42.9)	0.009	42.2	42.2	< 0.001
Use of tobacco, %				0.088			< 0.001
Never	186734 (73.9)	90407 (75.5)	96327 (72.5)		74.0	74.0	
Ever	34508 (13.7)	14497 (12.1)	20011 (15.1)		13.5	13.5	
Current	31374 (12.4)	14866 (12.4)	16508 (12.4)		12.5	12.5	
Use of alcohol, %				0.046			< 0.001
Never	48549 (19.2)	23571 (19.7)	24978 (18.8)		19.3	19.3	
Ever	187621 (74.3)	89067 (74.4)	98554 (74.2)		74.2	74.2	
Current	16446 (6.5)	7132 (6.0)	9314 (7.0)		6.5	6.5	
Body mass index, kg/m^2	25.7 (4.1)	25.2 (4.0)	26.1 (4.2)	0.229	25.2 (4.0)	25.2 (4.0)	< 0.001
Waist, cm	89.0 (10.2)	87.6 (10.1)	90.2 (10.2)	0.254	87.6 (10.1)	87.6 (10.1)	< 0.001

SMD: standardized mean difference

Variables	Overall	Before overlap-weighting			After overlap-weighting		
Systolic BP, mmHg	132.2 (13.5)	128.0 (13.3)	135.9 (12.5)	0.614	128.0 (13.3)	128.0 (13.3)	< 0.001
Diastolic BP, mmHg	74.4 (8.3)	73.5 (8.3)	75.2 (8.3)	0.212	73.5 (8.3)	73.5 (8.3)	< 0.001
HDL-C, mmol/L	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	0.099	1.3 (0.4)	1.3 (0.4)	< 0.001
LDL-C, mmol/L	2.8 (0.9)	2.8 (0.9)	2.7 (0.9)	0.138	2.8 (0.9)	2.8 (0.9)	< 0.001
Total cholesterol, mmol/L	4.8 (1.0)	4.8 (1.0)	4.7 (1.0)	0.118	4.8 (1.0)	4.8 (1.0)	< 0.001
Triglyceride, mmol/L	1.6 (1.3)	1.6 (1.3)	1.7 (1.4)	0.069	1.6 (1.3)	1.6 (1.3)	< 0.001
Blood haemoglobin, g/dL	13.7 (1.6)	13.8 (1.5)	13.7 (1.6)	0.072	13.8 (1.5)	13.8 (1.5)	< 0.001
HbA1c, %	7.5 (1.6)	7.5 (1.6)	7.4 (1.5)	0.017	7.5 (1.6)	7.5 (1.6)	< 0.001
eGFR, mL/min/1.73m^2	85.3 (18.9)	88.9 (17.5)	82.2 (19.5)	0.362	88.9 (17.5)	88.9 (17.5)	< 0.001
Medications							
Antihypertensives	15865 (6.3)	5025 (4.2)	10840 (8.2)	0.165	5.9	5.9	< 0.001
Diuretics	20030 (7.9)	6340 (5.3)	13690 (10.3)	0.188	7.6	7.6	< 0.001
Beta-blockers	55769 (22.1)	20019 (16.7)	35750 (26.9)	0.249	21.6	21.6	< 0.001
Calcium-channel blockers	99971 (39.6)	34404 (28.7)	65567 (49.4)	0.433	38.8	38.8	< 0.001
Statins	77878 (30.8)	31940 (26.7)	45938 (34.6)	0.172	30.8	30.8	< 0.001
Non-statins lipid-modifying	8561 (3.4)	3051 (2.5)	5510 (4.1)	0.089	3.3	3.3	< 0.001
Alpha-blockers	5006 (2.0)	2184 (1.8)	2822 (2.1)	0.022	2.0	2.0	< 0.001
Glucose-lowering drugs (GLDs)							

SMD: standardized mean difference

Variables	Overall	Before overlap-weighting			After overlap-weighting		
Insulin	17125 (6.8)	6342 (5.3)	10783 (8.1)	0.113	5.8	5.8	< 0.001
Metformin	167748 (66.4)	69429 (58.0)	98319 (74.0)	0.344	65.2	65.2	< 0.001
Sulfonylureas	101882 (40.3)	36063 (30.1)	65819 (49.5)	0.405	38.1	38.1	< 0.001
AGIs	1108 (0.4)	364 (0.3)	744 (0.6)	0.039	0.4	0.4	< 0.001
TZD	1422 (0.6)	421 (0.4)	1001 (0.8)	0.054	0.5	0.5	< 0.001
DPP-4i	3795 (1.5)	1034 (0.9)	2761 (2.1)	0.101	1.3	1.3	< 0.001
GLP-1RA	2012 (0.8)	612 (0.5)	1400 (1.1)	0.062	0.7	0.7	< 0.001
SGLT2i	244 (0.1)	84 (0.1)	160 (0.1)	0.016	0.1	0.1	< 0.001
Number of GLDs				0.501			< 0.001
0	61395 (24.3)	38980 (32.5)	22415 (16.9)		25.3	25.3	
1	100053 (39.6)	50984 (42.6)	49069 (36.9)		41.6	41.6	
2	79595 (31.5)	26428 (22.1)	53167 (40.0)		29.4	29.4	
≥ 3	11573 (4.6)	3378 (2.8)	8195 (6.2)		3.8	3.8	
Hypertension history	151566 (60.0)	55648 (46.5)	95918 (72.2)	0.543	60.8	60.8	< 0.001
ASCVD 10-year risk score				0.423			< 0.001
Low (< 7.5)	35817 (14.2)	24007 (20.0)	11810 (8.9)		12.9	12.9	
Medium (7.5–19.9)	81295 (32.2)	43388 (36.2)	37907 (28.5)		33.2	33.2	
High (≥ 20)	135504 (53.6)	52375 (43.7)	83129 (62.6)		53.9	53.9	

SMD: standardized mean difference

Variables	Overall	Before overlap-weighting			After overlap-weighting	
Period of index year				0.200		< 0.001
2002–2006	21882 (8.7)	10418 (8.7)	11464 (8.6)		9.1	9.1
2007–2010	55753 (22.1)	24402 (20.4)	31351 (23.6)		22.6	22.6
2011–2014	84755 (33.6)	36362 (30.4)	48393 (36.4)		33.2	33.2
2015–2018	90226 (35.7)	48588 (40.6)	41638 (31.3)		35.2	35.2
SMD: standardized mean difference						

To address discontinuation of RASi use during follow-up, we performed Cox-proportional hazards model with time-varying RASi exposure in the overlap-weighted cohort adjusted for time-varying covariates including HbA1c, lipids, eGFR, use of medications, and incidence of CVD and cancer during the observation period.[18] To estimate the absolute treatment effects and time-varying effects of RASi on the risk of pneumonia and related deaths,[19] we fitted the Aalen-additive hazards model with time-varying RASi exposure and confounders in the overlap-weighted cohort. The *timereg* package was used to plot the estimated cumulative effects of treatment in the follow-up period [20]. Missing data for time-varying covariates (HbA1c, eGFR and lipids) was imputed using multiple imputations [21].

In the population-based cohort, we further compared the risk of pneumonia and related death in ACEi-only and ARBs-only versus non-RASi users, and between ARBs-only and ACEi-only users. Due to the modifying effect of RASi on kidney function and the high risk of pneumonia in patients with CKD [10, 22], we conducted subgroup analyses stratified by sex and baseline eGFR using CKD-Epidemiological collaboration (CKD-EPI) equation [23]: ≥60 (G1-2), 45–59 (G3a), 30–44 (G3b), and 15–29 (G4) mL/min/1.73 m^2. The use of influenza and pneumococcal vaccines might bias the association between RASi use and risk of pneumonia. In the register-based cohort, we adjusted for time-varying influenza and pneumococcal vaccine use (yes/no) in the Cox-model with time-varying RASi exposure.

Sensitivity analysis

We adopted active comparator new-user design [15] using restrictive study criteria to compare the risk of pneumonia and related death between incident-RASi and incident-CCB users in the HKDSD RAMP-DM module (**Figure S3**). The index date refers to the first date of dispensing of RASi or CCB after enrollment. We finally included 30,332 RASi-users and 18,511 CCB users enrolled in 2002–2018 and observed until 31 December 2019. We additionally performed sensitivity analysis among 250,816 patients with type 2 diabetes in the population-based cohort. All data was analyzed using R statistical software (version 4.0.0). A two-sided p value of < 0.05 was considered significant.

Results

In the main analysis, we included 252,616 patients extracted from the HKDSD RAMP-DM module including 132,846 (52.6%) incident-RASi users (73,161 ACEi-only users, 20,907 ARBs-only users, and 38,778 ACEi/ARBs users [~ 92% with switching from ACEi to ARBs]) and 119,770 (47.4%) never exposed to ACEi/ARBs (Figure S2). Overall, RASi users had worse risk factors and received more medications than non-RASi users (Table 1). Following overlap propensity-score weighting, all characteristics were well-balanced between groups. The mean (SD) sum of treatment year and follow-up year to death was 5.5 (SD = 3.6) and 6.4 (SD = 3.9) for RASi-users. The respective figures were 6.0 (SD = 3.9) and 7.4 (SD = 3.6) for ACEi-only users, and 3.3 (SD = 2.2) and 3.6 (SD = 2.2) for ARBs-only users (Table 2). Over a mean 6.7 (SD = 3.8) years of follow-up (1,680,174 person-years), 13,057 (5.2%) patients had first hospitalisations due to pneumonia with an incidence of 7.9 events per-1000-person-year. A total of 24,241 patients (9.6%) died and 5,480 (2.2%) deaths were due to pneumonia with respective incidence of 14.4 and 3.3 events per-1000-person-years (Table 2).

Table 2
Crude incidence of events and follow-up time in Chinese patients with diabetes

Outcomes	Overall	Treatment group	Comparator group
RASi versus non-RASi in the population-based cohort			
Number at risk	252,616	132,846	119,770
First pneumonia hospitalisation			
Events (%)	13,057 (5.2)	8,954 (6.7)	4,103 (3.1)
Crude incidence (1000 person-years)	7.9	10.0	5.4
Follow-up time, mean (SD)	6.5 (3.8)	6.3 (3.9)	6.7 (3.7)
Death from pneumonia			
All-cause deaths (%)	24,241 (9.6)	15,336 (11.5)	8,905 (7.4)
Crude incidence (1000 person-years)	14.4	16.8	11.6
Deaths from pneumonia (%)	5,480 (2.2)	3,634 (2.7)	1,846 (1.5)
Crude incidence (1000 person-years)	3.3	4.0	5.4
Follow-up time, mean (SD)	6.7 (3.8)	6.4 (3.9)	6.9 (3.7)
RASi versus non-RASi in the register-based cohort			
Number at risk	13,017	7,716	5,301
First pneumonia hospitalisation			
Events (%)	550 (4.2)	421 (5.5)	129 (2.4)
Crude incidence (1000 person-years)	5.3	6.4	3.3
Follow-up time, mean (SD)	8.0 (4.4)	7.3 (4.1)	8.5 (4.5)
Death from pneumonia			
All-cause deaths (%)	1,888 (14.5)	15,336 (11.5)	8,905 (7.4)
Crude incidence (1000 person-years)	17.9	22.9	9.2
Deaths from pneumonia (%)	416 (3.2)	350 (4.5)	66 (1.2)
Crude incidence (1000 person-years)	3.9	5.2	1.7
Follow-up time, mean (SD)	8.1 (4.4)	7.3 (4.1)	8.7 (4.5)

Outcomes	Overall	Treatment group	Comparator group
RASi versus CCBs in the population-based cohort			
Number at risk	48,843	30,332	18,511
First pneumonia hospitalisation			
Events (%)	1,641 (3.4)	896 (3.0)	745 (4.0)
Crude incidence (1000 person-years)	5.7	4.8	7.5
Follow-up time, mean (SD)	5.9 (3.4)	6.2 (3.6)	5.4 (2.9)
Death from pneumonia			
All-cause deaths (%)	3,355 (6.9)	1,382 (4.6)	1,973 (10.7)
Crude incidence (1000 person-years)	11.6	13.7	10.4
Deaths from pneumonia (%)	714 (1.5)	365 (1.2)	349 (1.9)
Crude incidence (1000 person-years)	2.5	1.9	3.5
Follow-up time, mean (SD)	5.9 (3.4)	6.3 (3.6)	5.4 (2.9)

RASi use and risk of pneumonia and deaths from pneumonia

In the population-based cohort, there were 8,954 (6.7%) and 4,103 (3.1%) first pneumonia hospitalisations with respective crude-incidence rate of 10.0 and 5.4 events per-1000-person-years in RASi and non-RASi users during a mean follow-up of 6.5 years (Table 2). In the Cox model applied to the overlap-weighted cohort, non-time-varying RASi use was associated with increased risk of first pneumonia hospitalisation compared with non-RASi users (HR = 1.12, 95% CI: 1.08–1.17, Fig. 1a). After adjusting for the time-varying RASi exposure and other time-varying risk factors and events, RASi use was associated with reduced risk of first pneumonia hospitalisation (HR = 0.78, 0.75–0.82) (Fig. 1a). During a mean follow-up of 6.7 years, 3,634 (2.7%) and 1,846 (1.5%) died from pneumonia with incidence rate of 4.0 and 2.4 events per-1000-person-years in RASi and non-RASi users. Compared with non-RASi users, RASi use was associated with reduced risk of death from pneumonia in both Cox models before (HR = 0.90, 0.85–0.95) and after (HR = 49, 0.46–0.53) adjusting for time-varying RASi exposure and covariates (Fig. 1a).

In the register-based cohort where data on vaccination were available, 32.8% of patients received influenza and pneumococcal vaccines with in 13,017 patients overall a mean 6.7 years of follow-up (mean/median frequency = 4 times). there were 7,716 incident-RASi users and 5,301 non-RASi users. There were 550 (4.2%) first pneumonia hospitalisations, 1,888 all-cause deaths (14.5%), and 416 (3.2%) deaths from pneumonia. After overlap-weighting the baseline characteristics between RASi and non-RASi

users (**Table S3**), long-term RASi use was associated with reduced risk of pneumonia hospitalisation (HR = 0.68, 0.54–0.86) and related death (HR = 0.50, 0.36–0.68) after multiple adjustments including time-varying influenza and pneumococcal vaccine use (Fig. 1a).

Sub-group analyses by sex and baseline eGFR categories

In the population-based cohort, after adjustment for the time-varying RASi exposure and other time-varying risk factors and events, RASi use was associated with reduced risk of first pneumonia hospitalisation in both men (HR = 0.72, 0.68–0.76) and women (HR = 0.87, 0.82–0.93), and all baseline eGFR categories, including advanced CKD stages (G4) (HR = 0.80, 0.60-1.00). RASi use was associated with reduced risk of death from pneumonia in both Cox models with or without adjustment for time-varying RASi exposure and covariates in both men and women and across all CKD stages (Fig. 1b).

Time-varying effects of RASi use and pneumonia risk

In addition to the Cox-proportional hazard model adjusted for time-varying RASi exposure, we fitted the Aalen-additive hazards model to estimate the absolute treatment effects of RASi and time-varying effects on pneumonia risk in this population-based cohort. Compared with non-RASi users, RASi use reduced the events of pneumonia hospitalisation by 0.6 (95% CI: 0.2–0.9) per-1000-person-years and pneumonia-related death by 1.4 (1.0-1.6) per-1000-person-years. Figure 3 shows the estimated number of events prevented by the use of RASi expressed as cumulative treatment effects over the follow-up time. The reduced risk association of RASi use was time-invariant for first pneumonia hospitalisation (*P* for time-invariant = 0.340) and time-varying for deaths from pneumonia (*P* for time-invariant < 0.001).

Comparison different treatment effects of ACEi and ARBs

After overlap-weighting the baseline characteristics amongst the ACEi-only, ARBs-only and non-RASi users in the population-based cohort (**Table S4**), use of ARBs-only (HR = 0.70, 0.62–0.78) but not ACEi-only (HR = 0.98, 0.91–1.05) was associated with reduced risk of first pneumonia hospitalisation in the Cox-proportional model adjusted for time-varying exposure to RASi and other confounders (Fig. 3). ACEi-only (HR = 0.77, 0.68–0.86) and ARBs-only (HR = 0.41, 0.33–0.52) use were both associated with reduced risk of death from pneumonia versus non-RASi. Compared with ACEi-only use, ARBs-only use was associated with reduced risk of first pneumonia hospitalisation and death from pneumonia (Fig. 3 **and Table S5**).

Sensitivity analysis

We adopted the active comparator new-user design to compare effects between 30,332 incident-RASi and 18,511 incident-CCB users. Over a mean 5.9 (SD = 3.4) years of follow-up (290,421 person-years), there were 1,641 (3.4%) first pneumonia hospitalisations, 3,355 all-cause deaths (6.9%), and 714 (1.5%) deaths from pneumonia. The respective incidence rates were 5.7, 11.6 and 2.5 events per-1000-person-years. After overlap-weighting the baseline characteristic between RASi and CCB users (**Table S6**), use of RASi was associated with reduced risk of pneumonia hospitalisation (HR = 0.84, 0.74–0.95) and death from

pneumonia (HR = 0.79, 0.64–0.98) versus CCB (Fig. 1a). Compared with CCB, RASi use reduced incidence of pneumonia hospitalisation by 5.3 (3.6–6.4) per-1000-person-years and deaths from pneumonia by 4.0 (2.9–5.1) per-1000-person-years in the Aalen-additive hazards model. Similar reduced risk associations of RASi use with pneumonia and related deaths were observed in patients with type 2 diabetes in the populations-based cohort (**Table S7**).

Discussion

The availability of EMR with documentation of clinical, laboratory, medications and hospitalisation data have provided a valuable opportunity to evaluate drug effects in real- world practice complementary to randomized clinical trials [24]. Using a territory-wide EMR with detailed documentation of these variables in over 0.2 million patients with diabetes followed up for an average of 6.7 years, we implemented multiple methodologies to adjust for time-varying exposures to RASi, multiple events and co-administered medications to explore the effects of RASi on pneumonia hospitalisation and related death in Chinese patients with diabetes. Our results indicated that long-term use of RASi was associated with reduced risk of both events. We also demonstrated that while the effect of RASi on pneumonia hospitalisation was time-invariant, that on pneumonia-related death was time-varying. These benefits appeared to be more robust with ARBs which was associated with reduced risk of hospitalisation and death when compared directly with ACEi. In a register-based cohort where we adjusted for time-varying exposure to vaccines against influenza and pneumonia, these benefits of RASi remained significant. In a sensitivity analysis between incident-RASi and incident-CCB users, the independent beneficial effects of RASi on risk of both events remained significant.

Given the high RAS activity in patients with diabetes, appropriate use of RASi is critical to protect the organs from the deleterious effects of Ang-II [25–27]. While both clinical trials and real-world evidence (RWE) had confirmed the benefits of RASi on cardiovascular-renal outcomes [28, 29], similar data on pneumonia as a major cause of morbidity and mortality in diabetes remain scarce. The COVID-19 pandemic has led to the revisiting of the immunomodulating effects of RASi [25] with several researchers reporting reduced risk of pneumonia and influenza-related death amongst patients treated with RASi [3, 30, 31]. There are a number of pharmacoepidemiological analyses exploring the RWE of RASi on pneumonia or pneumonia related deaths [3–6]. However, biases due to lack of active comparator [5] and adjustments for time-varying factors and cumulative effects of these drug exposures can lead to inconsistent or conflicting results [32].

In this analysis, all patients had undergone structured assessment of cardiometabolic risk factors, including renal function at baseline, which are major confounders of outcomes. We adopted new-user design and controlled for time-varying exposure and confounders [15]. In addition, we implemented advanced modelling [19] to estimate the absolute treatment effects and cumulative (time-varying) effects expressed as the number of pneumonia hospitalisation and deaths prevented by use of RASi. The benefits effects of RASi were also observed in both men and women and across all baseline CKD stages, including advanced CKD (G4).

There are few studies designed to compare use of ARBs-only with ACEi-only on pneumonia risk. In our direct comparison of ACEi-only and ARBs-only users who were well-matched for baseline characteristics, we found ARBs were superior to ACEi in reducing pneumonia events, which are consistent with some studies [25]. Both ARB and ACEi effectively block RAS, but only ARB selectively blocks the AT1-receptor and increases expression of ACE2 [26, 27]. The increased conversion of Ang-II to Ang 1–7 by ACE2 can promote anti-inflammatory and vasodilatory responses relevant to infective processes including pneumonia [27, 33]. By contrast, ACEi does not directly block the action of AII but only reduces its formation by inhibiting ACE1 which pre-empts the generation of Ang 1–7 from Ang-II [26, 27]. These differences may explain the superior effects of ARBs on reducing the risk of pneumonia and related mortality compared with ACEi.

Although the use of RASi was associated with reduced risk of pneumonia hospitalisation and related death, the cumulative treatment effects of RASi on pneumonia hospitalisation was time-invariant while that on pneumonia-related death was time-varying. Reasons underlying these differences was not immediately evident, although we postulate that the cumulative effects of RAS blockade on multiple systems over time might reduce the risk of death in the immediate post-pneumonia period. We cannot exclude the possibility that the reduction of pneumonia related death could be attributed at least in part due to a reduction of cardiovascular events in the immediate post-pneumonia period [34].

The strengths of this study include two prospective cohorts with long follow-up duration and comprehensive documentation of baseline and time-varying factors including duration of drug exposure, treatment switching and discontinuation, cardiometabolic indices, renal function, clinical events, use of multiple medications and vaccines. We adopted new-use design, restrictive study criteria, and robust analytic techniques to adjust for different biases. Healthy user bias may confound the association when comparing RASi versus non-RASi users, however our results were also robust when compared against new-CCB users as an active comparator group. We did not capture drug adherence and it remains possible that poorer adherence to ACEi, for example due to ACEi-related cough [35], may explain weaker associations between RASi use and pneumonia risk. Other limitations included residual confounding by indication despite propensity-score matching which negates inference for causality. Finally, this is one of the largest studies performed in Chinese patients with diabetes, however our observations may not generalize to other ethnicities.

Conclusions

In conclusion, long-term use of ACEi/ARBs was independently associated with reduced risk of pneumonia hospitalisation and related death in Chinese patients with diabetes. The use of ARBs was associated with lower risk of pneumonia and related death compared with ACEi. Our results suggested that the use of RASi might have benefits beyond cardiovascular-renal protection and that their effects on respiratory infections, including coronavirus and influenza, warrant further investigations.

Abbreviations

ACEi:	angiotensin converting enzyme inhibitor
AGI:	alpha-glucosidase inhibitor
AMI:	acute myocardial infarction
Ang II:	angiotensin II
ARB:	and angiotensin receptor blocker
ASCVD:	atherosclerotic cardiovascular disease
AT1:	angiotensin type 1 receptor
BMI:	body mass index
CCB:	calcium-channel blockers
CKD:	chronic kidney disease
COPD:	chronic obstructive pulmonary disease
COVID-19 :	coronavirus disease
CVD:	cardiovascular disease
DBP:	diastolic blood pressure
DPP-4i:	dipeptidyl peptidase 4 inhibitor
eGFR:	estimated-glomerular filtration rate
EMR:	electronic medical record
EMR:	electronic medical record
GLDs:	glucose-lowering drugs
GLP-1RA:	glucagon-like peptide-1 receptor analogue
HA:	hospital authority
HDL-C:	high-density lipoprotein cholesterol
HKDR:	Hong Kong Diabetes Registry
HKDSD:	Hong Kong Diabetes Surveillance Database
ICD:	international classification of diseases
IHD:	ischemic heart disease
LDL-C:	low-density lipoprotein cholesterol
PWH:	Prince of Wales Hospital
RAMP-DM:	Risk Assessment and Management Programme for Diabetes Mellitus

RASi:	renin-angiotensin system inhibition
SBP:	systolic blood pressure
SGLT2i:	sodium-glucose co-transporter 2 inhibitor
TZD:	thiazolidinedione

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

Consent for publication

Not applicable

Availability of data and materials

The datasets used in this study were only available in the Chinese University of Hong Kong.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AY, EC and JC contributed to conception of the article, statistical analysis, interpretation of results, drafting, revision and approval of the manuscript. HW, ESHL, MS, BF contributed to interpretation of results, revised the manuscript critically and approved the final version. APSK and RCWM contributed to conception of the article, revised the manuscript critically and approved the final version. AOYL contributed to conception of the article, interpretation of results, revised the manuscript critically and approved the final version. EC is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis. AOYL has full access to all the data in the study.

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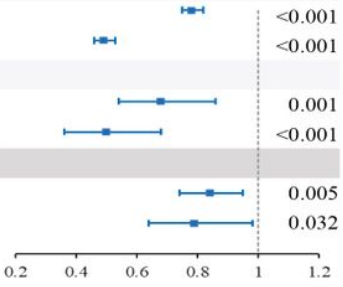
Figures

a

Outcomes	Event/No. at Risk		Hazard Ratio (95% CI)			P
	Treatment	Comparison	Model 1	Model 2	Model 3	
RASi versus non-RASi						
Population-based cohort						
First pneumonia hospitalisation	8954/132846	4103/119770	1.12 (1.08, 1.17)	0.79 (0.76, 0.82)	0.78 (0.75, 0.82)	<0.001
Death from pneumonia	3634/132846	1846/119770	0.90 (0.84, 0.95)	0.43 (0.41, 0.46)	0.49 (0.46, 0.53)	<0.001
Register-based cohort						
First pneumonia hospitalisation	421/7716	129/5301	1.10 (0.87, 1.39)	0.83 (0.66, 1.03)	0.68 (0.54, 0.86)	0.001
Death from pneumonia	350/7716	66/5301	1.26 (0.93, 1.70)	0.55 (0.41, 0.72)	0.50 (0.36, 0.68)	<0.001
RASi versus calcium-channel blockers (CCBs)						
First pneumonia hospitalisation	896/30332	745/18511	0.89 (0.80, 0.99)	0.86 (0.76, 0.97)	0.84 (0.74, 0.95)	0.005
Death from pneumonia	365/30332	349/18511	0.83 (0.70, 0.97)	0.77 (0.62, 0.95)	0.79 (0.64, 0.98)	0.032



b

Outcomes	Event/No. at Risk		Hazard Ratio (95% CI)			P
	Treatment	Comparison	Model 1	Model 2	Model 3	
First pneumonia hospitalisation						
Men	4628/65047	2245/54777	1.12 (1.06, 1.18)	0.74 (0.70, 0.78)	0.72 (0.68, 0.76)	*<0.001*
Women	4326/67799	1858/64993	1.13 (1.06, 1.20)	0.85 (0.80, 0.90)	0.87 (0.82, 0.93)	<0.001
eGFR categories (G)						
eGFR ≥60 (G1-G2)	5953/113967	3054/112180	1.18 (1.12, 1.24)	0.84 (0.80, 0.88)	0.80 (0.76, 0.84)	<0.001
eGFR 15-59 (G3-G4)	3001/18879	1049/7590	1.08 (1.00, 1.16)	0.77 (0.72, 0.83)	0.81 (0.75, 0.87)	<0.001
eGFR 45-59 (G3a)	1804/12867	643/5396	1.06 (0.97, 1.17)	0.78 (0.71, 0.85)	0.80 (0.73, 0.88)	<0.001
eGFR 30-44 (G3b)	939/4789	281/1585	1.10 (0.96, 1.27)	0.80 (0.70, 0.91)	0.82 (0.72, 0.94)	0.004
eGFR 15-29 (G4)	258/1223	125/609	1.16 (0.92, 1.45)	0.84 (0.67, 1.05)	0.80 (0.64, 1.00)	0.046
Death from pneumonia						
Men	1960/65047	1103/54777	0.88 (0.81, 0.96)	0.40 (0.36, 0.44)	0.45 (0.41, 0.49)	<0.001
Women	1674/67799	743/64993	0.93 (0.85, 1.03)	0.48 (0.44, 0.53)	0.55 (0.50, 0.61)	<0.001
eGFR categories (G)						
eGFR ≥60 (G1-G2)	2213/113967	1266/112180	0.93 (0.86, 1.01)	0.44 (0.41, 0.48)	0.48 (0.44, 0.52)	<0.001
eGFR 15-59 (G3-G4)	1421/18879	580/7590	0.93 (0.84, 1.03)	0.48 (0.43, 0.53)	0.54 (0.49, 0.60)	<0.001
eGFR 45-59 (G3a)	822/12867	347/5396	0.91 (0.80, 1.05)	0.48 (0.42, 0.55)	0.54 (0.46, 0.62)	<0.001
eGFR 30-44 (G3b)	473/4789	154/1585	1.04 (0.86, 1.27)	0.52 (0.43, 0.62)	0.57 (0.47, 0.70)	<0.001
eGFR 15-29 (G4)	126/1223	79/609	0.85 (0.63, 1.15)	0.45 (0.31, 0.64)	0.43 (0.30, 0.62)	<0.001

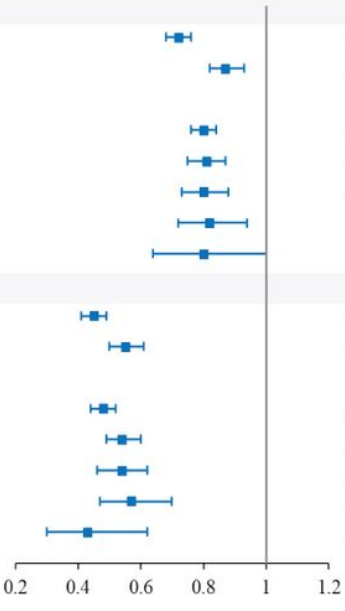


Figure 1

Associations of RASi use with pneumonia-related outcomes in the overlap-weighted cohorts Model 1: results were yielded using Cox proportional hazards model in the overlap-weighted cohort; Model 2: fitted with time-varying RASi use in the overlap-weighted cohort; Model 3: adjusted for time-dependent HbA1c, lipids, eGFR, and medications (antihypertensive, diuretics, statins and non-statins lipids modifying drugs, beta-blocking, calcium-channel blockers, alpha-blockers, insulin, metformin, and sulfonylureas) and comorbidities (CVD and cancer) based on Model 2. In the register-based cohort (Figure 1A), Model 3

adjusted for time-varying RASi use, and time-varying HbA1c, lipids, eGFR, medications (statins, insulin, metformin, and sulfonylureas), comorbidities (CVD and cancer) and use of influenza and pneumococcal vaccine.

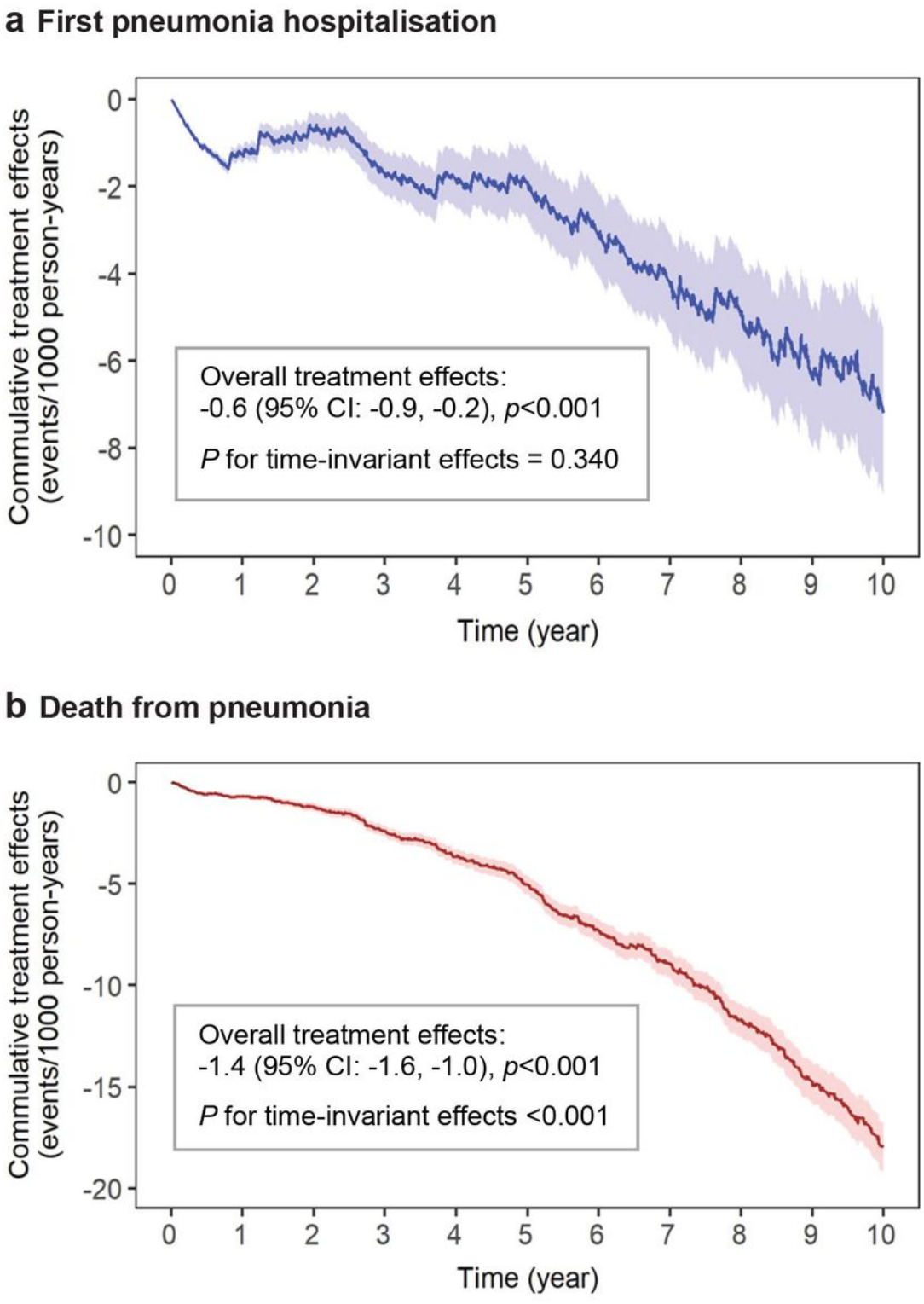


Figure 2

Cumulative treatment effects of RASi with 95% confidence intervals (CIs) in the Aalen-additive hazard model The models with time-varying RASi use were adjusted for time-varying HbA1c, lipids, eGFR,

medications (antihypertensive, diuretics, statins and non-statins lipids modifying drugs, beta-blockers, calcium-channel blockers, alpha-blockers, insulin, metformin, and sulfonylureas) and comorbidities (CVD and cancer) in the overlap-weighted population-based cohort. P-time-invariant effect was 0.340 for first pneumonia hospitalisation and <0.001 for death from pneumonia.

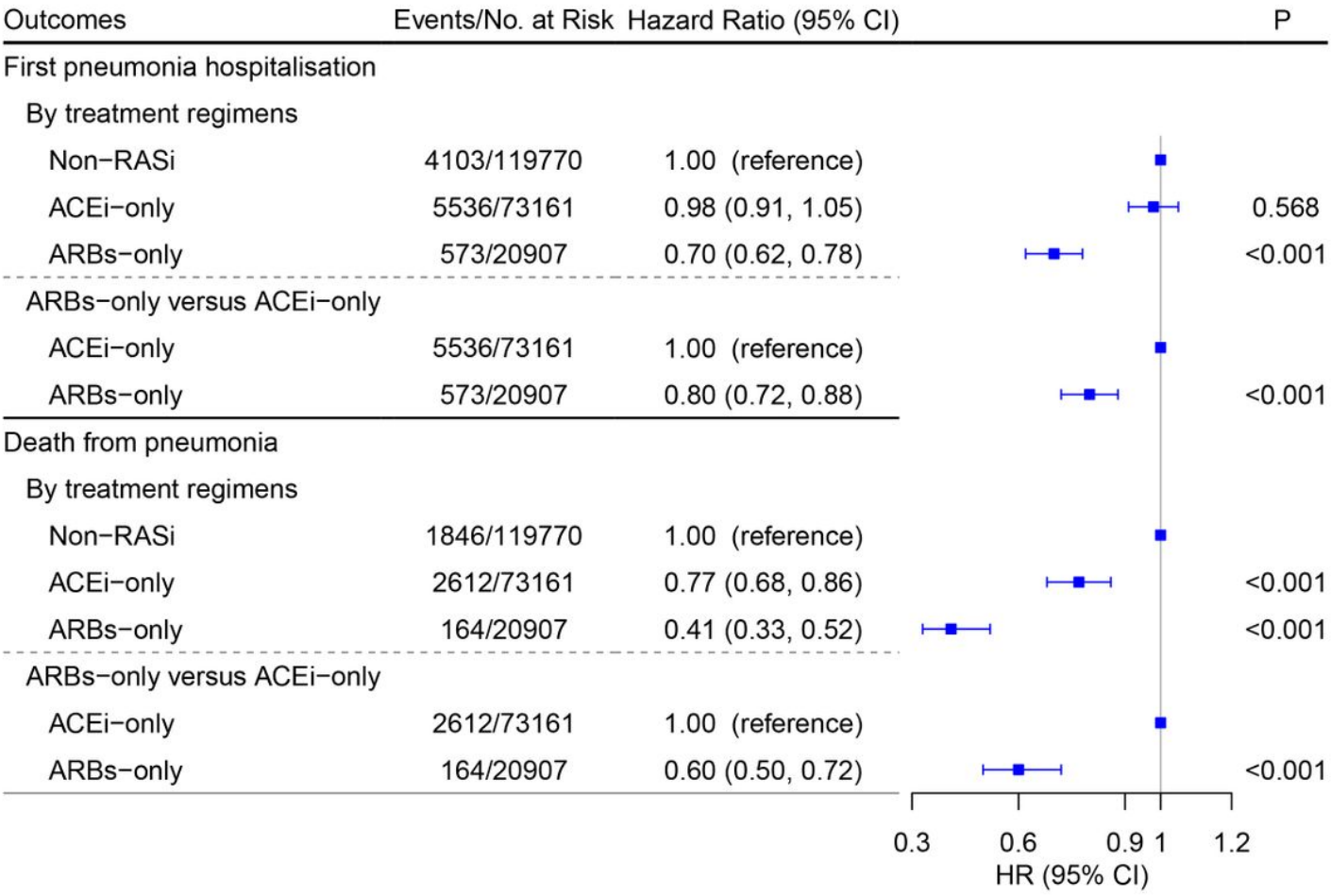


Figure 3

Comparison between ACEi-only and ARBs-only versus non-RASi users, and ARBs-only versus ACEi-only users In subgroup analyses by treatment regimens: results were yielded using the Cox-proportional hazard model with time-varying RASi use, adjusting for time-varying HbA1c, lipids, eGFR, medications (antihypertensive, diuretics, statins and non-statins lipids modifying drugs, beta-blockers, calcium-channel blockers, alpha-blockers, insulin, metformin, and sulfonylureas) and comorbidities (CVD and cancer) in the overlap-weighted cohort. Results of ARBs-only versus ACEi-only use were yielded using fixed-time Cox-proportional hazard model in the overlap-weighted population-based cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 3.RASpneumoniaRAMPSuppCardioDiab.docx