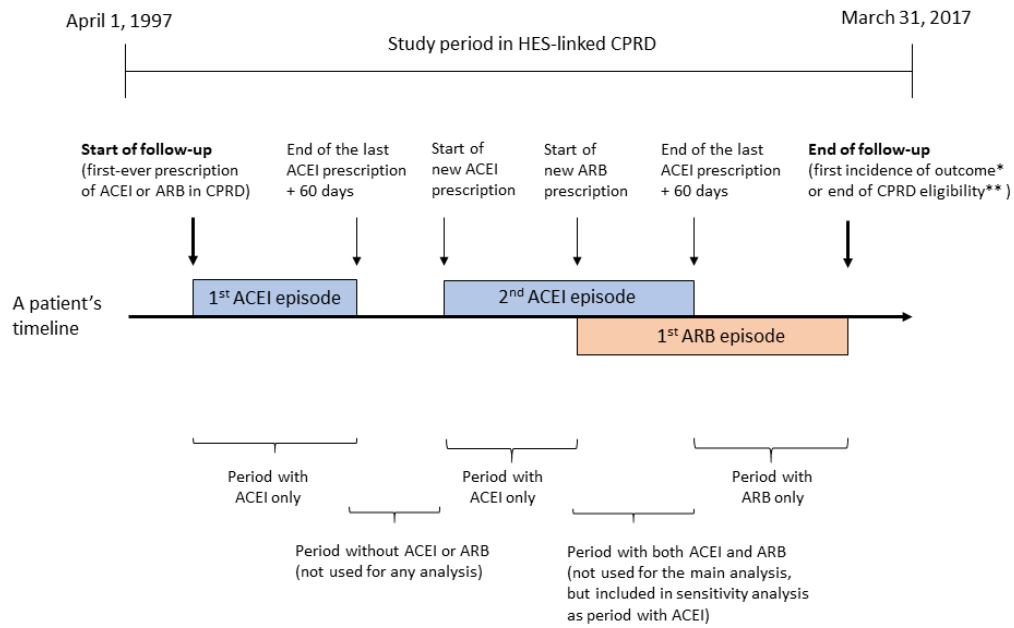


**Supplementary data for “Comparisons of Staphylococcus aureus infection  
and other outcomes between users of angiotensin-converting-enzyme  
inhibitors and angiotensin II receptor blockers: lessons for COVID-19 from a  
nationwide cohort study”**

**Supplementary Figure 1.** Diagram of study design with definition of exposure periods



ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin II receptor antagonist, CPRD = Clinical Practice Research Datalink, HES = Hospital Episode Statistics.

**Supplementary Table 1.** Characteristics of the 487,165 study participants during follow-up

	<b>Cohort during time exposed to ACEI treatment (PY) (% of 1,759,917 PY)</b>	<b>Cohort during time exposed to ARB treatment (PY) (% of 644,953 PY)</b>
<b>Age category (years):</b>		
<55	397,374 (22.6)	112,096 (17.4)
55-64	445,516 (25.3)	155,579 (24.1)
65-74	463,304 (26.3)	186,896 (29.0)
75-84	350,245 (19.9)	151,067 (23.4)
≥85	103,478 (5.9)	39,317 (6.1)
<b>Sex:</b>		
Men	972,606 (55.3)	278,890 (43.2)
Women	787,312 (44.7)	366,063 (56.8)
<b>Year:</b>		
1997-2001	157,853 (9.0)	34,096 (5.3)
2002-2006	593,273 (33.7)	213,373 (33.1)
2007-2011	734,484 (41.7)	280,502 (43.5)
2012-2016	274,307 (15.6)	116,982 (18.1)
<b>Hypertension</b>	<b>1,387,684 (78.8)</b>	<b>560,727 (86.9)</b>
<b>Diabetes</b>	<b>432,414 (24.6)</b>	<b>138,224 (21.4)</b>
<b>Myocardial infarction</b>	<b>197,100 (11.2)</b>	<b>47,323 (7.3)</b>
<b>Heart failure</b>	<b>117,119 (6.7)</b>	<b>34,701 (5.4)</b>
<b>Proteinuria diagnosis</b>	<b>56,933 (3.2)</b>	<b>21,382 (3.3)</b>
<b>Kidney function:</b>		
Not measured	88,491 (5.0)	23,392 (3.6)
eGFR ≥60 mL/min/1.73m <sup>2</sup>	1,292,122 (73.4)	454,076 (70.4)
eGFR 45-59 mL/min/1.73m <sup>2</sup>	254,536 (14.5)	109,623 (17.0)
eGFR 30-44 mL/min/1.73m <sup>2</sup>	101,337 (5.8)	45,439 (7.0)
eGFR <30 mL/min/1.73m <sup>2</sup>	20,652 (1.2)	10,566 (1.6)
On renal replacement therapy	2,778 (0.2)	1,856 (0.3)

ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin II receptor antagonist, eGFR = estimated glomerular filtration rate, PY = person years.

**Supplementary Table 2.** Crude rates and adjusted hazard ratio for the incidence of *Staphylococcus aureus* infections comparing periods prescribed angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers

	Period with ACEI prescription			Period with ARB prescription			Adjusted HR (ACEI vs ARB) (95% CI)
	No. of outcomes	Follow-up length (PY)	Crude rate (/1000 PY) (95% CI)	No. of outcomes	Follow-up length (PY)	Crude rate (/1000 PY) (95% CI)	
<b>Main analysis:*</b>	3,430	1,759,917	1.95 (1.88-2.02)	1,007	644,953	1.56 (1.47-1.66)	1.18 (1.10-1.27)
<b>Sensitivity analyses:</b>							
<b>Exposure:</b> Inclusion of time prescribed ACEI and ARB combined into time prescribed ACEI	3,518	1,795,479	1.96 (1.90-2.03)	1,007	644,953	1.56 (1.47-1.66)	1.19 (1.10-1.27)
<b>Exposure:</b> Grace period between prescriptions: 90 days	3,562	1,784,330	2.00 (1.93-2.06)	1,039	645,531	1.61 (1.51-1.71)	1.18 (1.10-1.26)
<b>Exposure:</b> Grace period between prescriptions: 30 days	3,202	1,710,676	1.87 (1.8-.94)	943	635,923	1.48 (1.39-1.58)	1.19 (1.11-1.28)
<b>Covariates:</b> Exclusion of patients with missing kidney function	2,409	134,4731	1.79 (1.72-1.86)	715	485,115	1.47 (1.37-1.59)	1.17 (1.08-1.28)
<b>Covariates:</b> Adjustment for additional potential confounders **	3,430	1,759, 917	1.95 (1.88-2.02)	1,007	644,953	1.56 (1.47-1.66)	1.20 (1.12-1.29)
<b>Outcome:</b> Restriction to <i>S. aureus</i> infection recorded in the 1 <sup>st</sup> HES episode	1,718	1,759,917	0.98 (0.93-1.02)	494	644,953	0.77 (0.70-0.84)	1.17 (1.06-1.30)
<b>Outcome:</b> Any <i>Staphylococcus</i> infection (ICD-10 code A41.0, B95.6, A41.0, G00.3, J15.2, or M00.0)	4,046	1,758,742	2.30 (2.23-2.37)	1,183	644,484	1.84 (1.73-1.94)	1.16 (1.09-1.24)
<b>Outcome:</b> Sepsis due to <i>S. aureus</i> (ICD-10 code A41.0)	390	1,766,015	0.22 (0.20-0.24)	122	647,258	0.19 (0.16-0.23)	1.09 (0.89-1.35)

ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin II receptor antagonist, CI = confidence interval, ICD-10 = International Statistical Classification of Diseases 10th revision, PY = person-years.

\*In the main analysis, outcome was defined as hospitalisation with ICD-10 code A41.0 ("Sepsis due to *Staphylococcus aureus*") or ICD-10 code B95.6 ("*Staphylococcus aureus* as the cause of diseases classified to other chapters") at any code position at any episode during hospitalisation, periods with ACEI prescription only and ARB prescription only were compared (ie. period with both ACEI and ARB was excluded from the analysis), drug grace period was assumed to be 60 days, and adjusted covariates were age (<55, 55-64, 65-74, 75-84, and ≥85 years), sex, year (1997-2001, 2002-2006, 2007-2011, 2012-2016), kidney function (in which period without serum creatinine measurement was grouped into period with eGFR ≥60 mL/min/1.73m<sup>2</sup>), diagnoses of hypertension, diabetes, myocardial infarction, heart failure, and proteinuria (all covariates were time-updated).

\*\*Additionally adjusted for diagnoses of cancer, rheumatoid arthritis, systematic lupus erythematosus, inflammatory bowel disease, chronic liver disease, chronic pulmonary disease, human immunodeficiency virus infection and acquired immune deficiency syndrome, prescription of other antihypertensives (beta blockers, calcium channel blockers, and diuretics), statins, and oral corticosteroids, and life-style factors (smoking status, alcohol status, and body mass index). The presence or absence of each diagnosis (anytime from the CPRD registration) and prescription (in the past year) was judged at cohort entry and not time-updated. Information on life-style factors was based on that recorded at the closest time point to the cohort entry and not time-updated.

**Supplementary Table 3.** Crude rates and adjusted hazard ratio for the incidence of *Staphylococcus aureus* infection, comparing periods prescribed angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers, stratified by calendar period and smoking status

	Period with ACEI prescription			Period with ARB prescription			Adjusted HR (ACEI vs. ARB) (95% CI)
	No. of outcomes	Follow-up length (PY)	Crude rate (/1000 PY) (95% CI)	No. of outcomes	Follow-up length (PY)	Crude rate (/1000 PY) (95% CI)	
<b>Subgroup analysis* by year:</b>							
1997-2001	342	157,853	2.17 (1.95 – 2.41)	59	34,096	1.73 (1.34 – 2.23)	0.94 (0.71 – 1.24)
2002-2006	1,208	593,273	2.04 (1.92 – 2.15)	329	213,373	1.54 (1.38 – 1.72)	1.17 (1.04 – 1.33)
2007-2011	1,315	734,484	1.79 (1.70 – 1.89)	412	280,502	1.47 (1.33 – 1.62)	1.22 (1.09 – 1.37)
2012-2016	565	274,307	2.06 (1.90 – 2.24)	207	116,982	1.77 (1.54 – 2.03)	1.18 (1.00 – 1.39)
<b>Subgroup analysis* by smoking status:**</b>							
Never smoker	1,365	798,401	1.71 (1.62 – 1.80)	448	330,618	1.36 (1.24 – 1.49)	1.22 (1.10 – 1.36)
Ex-smoker	924	489,112	1.89 (1.77 – 2.02)	284	169,205	1.68 (1.49 – 1.89)	1.09 (0.95 – 1.25)
Current smoker	954	459,422	2.08 (1.95 – 2.21)	251	142,379	1.76 (1.56 – 2.00)	1.16 (1.01 – 1.34)

ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin II receptor antagonist, CI = confidence interval, PY = person-year.

\*In the same way as the main analysis (except for adjustment of year for the subgroup analysis by year): outcome was defined as hospitalisation with ICD-10 code A41.0 (“Sepsis due to *Staphylococcus aureus*”) or ICD-10 code B95.6 (“*Staphylococcus aureus* as the cause of diseases classified to other chapters”) at any code position at any episode during hospitalisation, periods with ACEI prescription only and ARB prescription only were compared, drug grace period was assumed to be 60 days, and adjusted covariates were age (<55, 55-64, 65-74, 75-84, and ≥85), sex, year (1997-2001, 2002-2006, 2007-2011, 2012-2016), kidney function (in which period without serum creatinine measurement was grouped into period with eGFR ≥60 mL/min/1.73m<sup>2</sup>), diagnoses of hypertension, diabetes, myocardial infarction, heart failure, and proteinuria (all covariates were time-updated).

\*\* Information on smoking status was based on that recorded at the closest time point to the cohort entry (either before or after the cohort entry) and not time-updated, and patients with missing information on smoking status (n = 6,704) were excluded.