Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multi-site UK acute Hospital Trust

Authors

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Abstract:

Background: The SARS-Cov2 virus binds to the ACE2 receptor for cell entry. It has been suggested that ACE-inhibitors, which are commonly used in patients with hypertension or diabetes and which raise ACE2 levels, may increase the risk of severe COVID-19 infection.

Methods: We evaluated this hypothesis in an early cohort of 205 acute inpatients with COVID-19 at King's College Hospital and Princess Royal University Hospital, London, UK with the primary endpoint being death or transfer to a critical care unit for organ support within 7-days of symptom onset.

Findings: 53 patients out of 205 patients reached the primary endpoint. Contrary to the hypothesis, treatment with ACE-inhibitors was associated with a reduced risk of rapidly deteriorating severe disease. There was a lower rate of death or transfer to a critical care unit within 7 days in patients on an ACE-inhibitor OR 0·29 (CI 0·10-0·75, p<0·01), adjusting for age, gender, comorbidities (hypertension, diabetes mellitus, ischaemic heart disease and heart failure).

Interpretation: Although a small sample size, we do not see evidence for ACE-inhibitors increasing the short-term severity of COVID-19 disease and patients on treatment with ACE-inhibitors should continue these drugs during their COVID-19 illness. A potential beneficial effect needs to be explored as more data becomes available.

Introduction

Early data from China during the SARS-Cov2 pandemic suggest that patients with hypertension or diabetes have an increased risk of severe COVID-19 disease.[1] It has been hypothesized that treatment with ACE-inhibitors (ACEi) or angiotensin receptor blockers (ARB) in such patients may increase the expression of ACE2, the receptor for SARS-Cov2 binding

and entry into cells.[1,2] However, reduced activation of the renin angiotensin system (RAS) and/or increased levels of ACE2 may be protective during severe lung injury.[3] The effect of ACEi and ARB during infection with SARS-CoV-2 is therefore controversial but needs urgent clarification.[4–7]

We tested for association between treatment with ACEi or ARB and disease severity in the first 205 patients with COVID-19 disease admitted to a multi-site acute NHS Trust in the United Kingdom (King's College Hospital NHS Foundation Trust). We used an informatics pipeline to allow rapid evaluation of disease concepts during the rapidly evolving pandemic.

Methods:

This project operated under London South East Research Ethics Committee (reference 18/LO/2048) approval granted to the King's Electronic Records Research Interface (KERRI); specific work on COVID-19 research was reviewed with expert patient input on a virtual committee with Caldicott Guardian oversight.

Study Design:

The study cohort was defined as all inpatients testing positive for SARS-Cov2 by RT-PCR at King's College Hospital and Princess Royal University Hospital from 1 March to 22nd March 2020. Only patients symptomatic and requiring inpatient admission were included. The primary endpoint was defined as death or admission to a critical care unit for organ-support within 7 days of symptoms onset (symptoms defined as fever, cough, dyspnoea, myalgia, chest pain or delirium). Patients were stratified according to drug exposure to ACEi or ARB within 7 days before symptoms or during inpatient treatment (prior to an endpoint being reached). Specifically, we divided the total cohort into patients with prescription and/or mention in any text record of (1) ACEi (Ramipril, Perindopril, Lisinopril, Enalapril, Captopril, Quinapril, Imidapril, Fosinopril, Trandolapril) and (2) ARB (Candesartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan) up to 7days before or after symptom onset. We considered patients whose medication was withheld during admission as positive for drug exposure. Patients with no medication orders or clinical documents created in the study period (because never admitted) were excluded. One newborn was also excluded. The primary endpoint was manually verified by a clinician review of the electronic health record.

Data Processing:

The data (demographic, emergency department letters, discharge summaries, clinical notes, radiology reports, medication orders, lab results) was retrieved and analyzed in near real-time from the structured and unstructured components of the electronic health record (EHR) using a variety of natural language processing (NLP) informatics tools belonging to the CogStack ecosystem,[8] namely DrugPipeline,[9] MedCAT[10] and MedCATTrainer.[11] The CogStack NLP pipeline captures negation, synonyms, and acronyms for medical SNOMED-CT concepts as well as surrounding linguistic context using deep learning and long short-term memory networks. DrugPipeline was used to annotate medications and MedCAT produced unsupervised annotations for all SNOMED-CT concepts under parent terms Clinical Finding, Disorder, Organism, and Event with disambiguation, pre-trained on MIMIC-III.[12] Further supervised training improved detection of annotations and meta-annotations such as experiencer (is the concept annotated experienced by the patient or other), negation (is the

concept annotated negated or not) and temporality (is the concept annotated in the past or present) with MedCATTrainer. Meta-annotations for hypothetical and experiencer were merged into Irrelevant meaning that any concept annotated as either hypothetical or where the experiencer was not the patient was annotated as irrelevant. Performance of the MedCAT NLP pipeline for disorders mentioned in the text was evaluated on 138 documents by 4 annotators (TS, ZK, DB, AS) and F1, precision and recall recorded. Additional full case review for correct subsequent diagnosis assignment was performed by 3 clinicians (JT, KOG, RZ) for key comorbidities: Diabetes Mellitus, Hypertension, Heart Failure and Ischaemic Heart Disease. Performance of DrugPipeline has previously been described.[9] All detected drug mentions were manually reviewed to exclude false positives (e.g. allergy).

Statistical Analysis:

In order to investigate the association between ACEi and disease severity measured as critical care admission or death, we performed a series of logistic regressions applying Firth's correction.[13] This procedure has shown to be robust for low prevalence events and low-dimensional settings.[14,15] In a first step, we explored independently the association for ACEi (Baseline model). In a second step, we adjusted the model for age and sex (Model 1). Then, we additionally adjusted for hypertension (Model 2), and additionally adjusted by other comorbidities diabetes and ischemic heart disease or heart failure (Model 3). We also explored the independent association for hypertension following the same modelling approach. Sensitivity analyses were performed i) using exact logistic regression with models adjusted variable by variable; ii) requiring at least two detections of medication for positive exposure; iii) using only structured data on in-hospital medication orders; iv) ignoring our 7 day window for medications; v) testing sensitivity to unmeasured confounders.

Role of the funding source:

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results:

Our total cohort consists of 205 confirmed positive symptomatic inpatients aged 63±20 (SD) years and 52% males (Table 1). Baseline characteristics are 51·2% with hypertension, 30·2% with diabetes and 14·6% with ischaemic heart disease or heart failure. The percentage of patients that have a positive mention of a certain disorder in each of the two groups (Dead or Critical Care, Other) derived via the NLP for medical concept annotations with F1 > 80% and more than 10 annotated mentions are shown in Figure 1 (performance shown in Figure 2). All NLP-detected positive mentions of hypertension, diabetes, ischaemic heart disease or heart failure were manually reviewed at a patient level and false positive rates calculated 1·9%, 3·2%, 31%, 0% respectively.

Of the 205 patients, 53 patients died or required critical care support within 7 days of symptoms and 152 patients did not. The inclusion criteria of only patients needing admission is likely why this critical outcome figure is relatively high (25·9%) compared to fatality rate in population studies[16] but is comparable to hospital case series.[17] 14% (5/37) patients with exposure to an ACE-inhibitor died or required critical care support compared to 29% (48/168) for patients without such exposure.

Findings from unadjusted logistic regression models indicated that individuals on ACEi had lower likelihood of severe disease (OR 0·42 (CI 0·14-1·00), p=0·058). These associations were only partially attenuated when adjustments for gender and age were included (Model 1 in Table 2). Furthermore, these associations remained significant and were only partially attenuated when the model was additionally adjusted for hypertension (Model 2 in Table 2) and further for other comorbidities diabetes and ischaemic heart disease or heart failure (Model 3 in Table 2). Odds ratios and p-values for all variables in each model are shown in Supplementary Table 1. Males were found to have a higher likelihood of severe disease in Model 3 (OR 2.00 (CI 1.00-4.00), p=0.037).

We also examined the independent association between hypertension and disease severity. Our results showed that individuals diagnosed with hypertension had a similar likelihood of developing severe disease as those that were not diagnosed with hypertension, either in unadjusted models (OR 1·60 (CI 0·88-3·10); p=0·12) or models adjusted for age and gender (OR 1·80 (CI 0·83-3·80); p=0·14).

We did not run the regression analysis on the ARB group as there are only 9 patients in our cohort. We intend to carry out this analysis as our cohort grows.

Sensitivity analyses showed similar results when compared with the results from exact logistic regression analyses with univariate adjustment. We also compared our results to those using the penalised regression model and criteria for ACEi exposure that were either more strict (requiring multiple mentions or using only medications ordered in hospital) and less strict (including any detection of ACEi outside our 7 day window). In all cases we found that estimates of the impact of ACEi exposure were consistently in the same direction as those in Table 2 but were not significant.

We assessed the robustness to unmeasured confounders of the fully adjusted estimate of ACEi protective effect using the e-value approach.[18] An e-value of 3.32 for the point estimate indicated that it was robust to plausible residual confounding that might explain away the estimate. However, the e-value of 1.58 for the upper confidence of 0.75 showed that in the presence of residual confounding of a level often considered plausible, this study could not fully exclude the possibility of small harmful effects.

Discussion:

This study suggests that ACE-inhibitors do not increase the severity of COVID-19 disease as hypothesised [4–7] but may reduce severity. This holds true even after adjusting for conditions where ACEi may be used (hypertension, diabetes mellitus, ischaemic heart disease and heart failure). No meaningful comment can be made about ARB effect given the low prevalence of their use in this cohort, although ARB have a different mechanism of action compared to ACEi.

This study used an NLP approach to perform very rapid analysis of high volume, unstructured real world clinical data. This however introduces the possibility of missing circumlocutory mentions of disease, symptoms or medications. We have mitigated against this by manually validating annotations in a subset of records and also verified ACEi and ARB annotations

against inpatient electronic prescription data. Moreover, we have performed sensitivity analyses to test the impact of different criteria to define the ACEi exposed cohort on our results, finding that although not significant the OR remained <1.0 for ACEi exposure in all analyses. The lack of significance in the more strict analyses is likely due to the loss of power as some detections of ACEi medication are excluded. For the less strict analysis, the lack of significance may be due to noise introduced (e.g. prescription halted before the study period). The NLP output in the less strict analysis is also not manually reviewed and is highly likely to contain some irrelevant mentions e.g. previous allergic reaction. While the findings of robustness to bias due to unmeasured confounding increased our confidence, the need for replication in a larger sample remains.

One limitation with this study is the relatively small sample taken from a single UK centre over a short follow-up. Although we have used statistical procedures to provide robust results with our current sample, as numbers increase further updates to the analysis will be required to better understand our findings and confirm the directionality of these associations. Our group will provide regular updates during the pandemic to the analysis at the link https://cogstack.org/cogstack-kch-covid-19-analyses/ including longer follow-up and pooled analysis with other organisations. Whether these results also apply to infection severity in the non-hospital setting or to different global populations requires further study.

A tentative favourable association of ACE-inhibitors with less severe early outcomes is suggested by this study. A putative mechanism could be reduced RAS activation in patients on ACE-inhibitors, which is considered protective in Acute Respiratory Distress Syndrome, ARDS.[3] Furthermore, elevation of ACE2 also reduces RAS activation and is protective in acute lung injury,[19] including in ARDS of SARS1 infection.[20]

In summary, based on these early results and the absence of any evidence suggesting harm, patients on treatment with ACE-inhibitors should continue these drugs during their COVID-19 illness as per current guidelines.[21] Active research is merited on whether ACE inhibition or enhancement of ACE2 may have a therapeutic role in severe COVID-19 disease.

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Declaration of Interests:

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Author Contributions:

JTHT, RJBD, DMB, ZK, TS, AF conceived the study design
DMB, ZK, AS, TS, JTHT, LR, KN performed data processing and software development
KOG, RZ, JTHT performed data validation
DMB, AP, RB performed statistical analysis
JTHT, DMB, ZK, TS, AF, RJBD, AMS performed critical review
JTHT, RJBD, DMB, AMS, ZK, TS, AF, DMB, AP, RB wrote the manuscript

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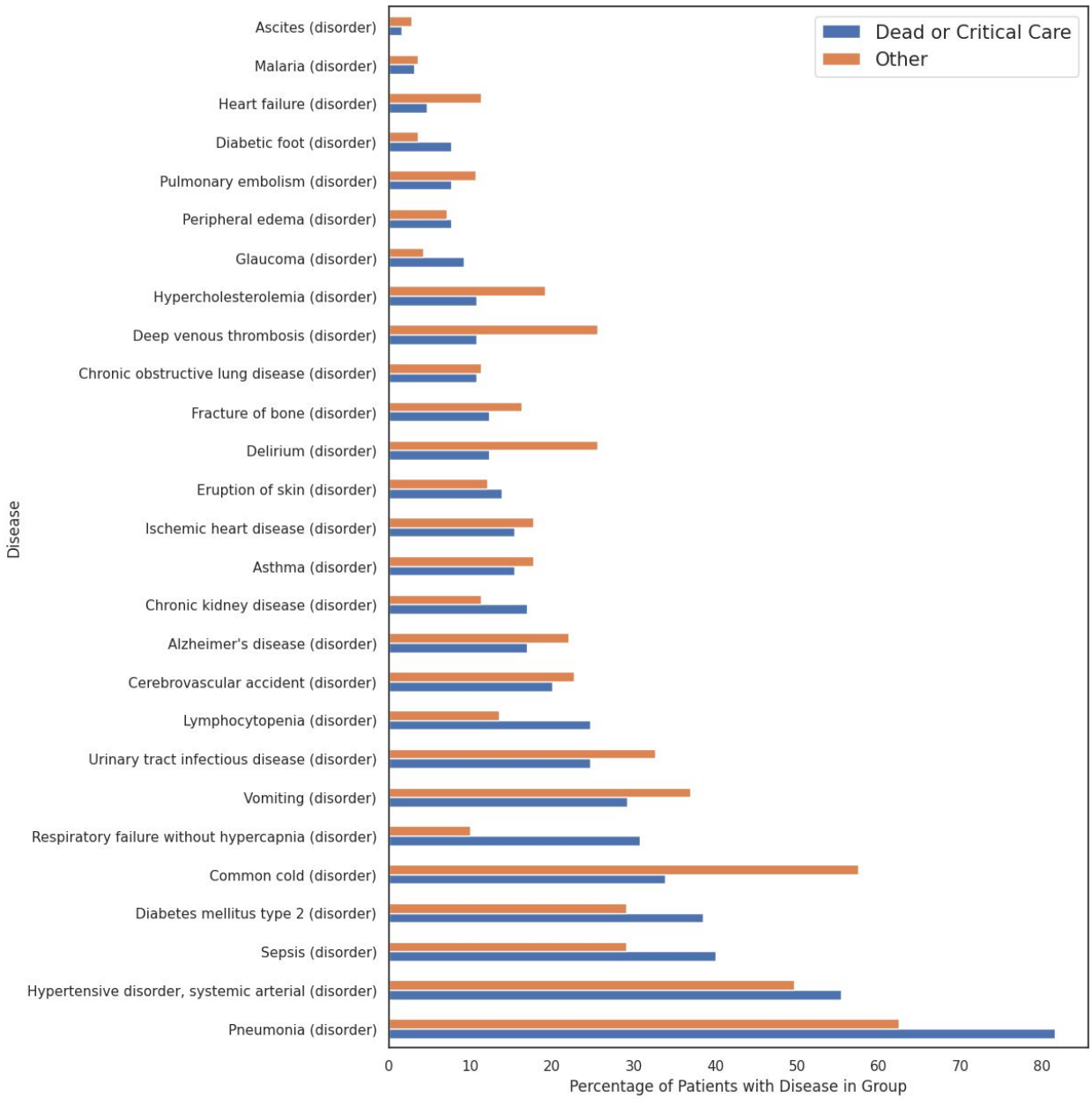

Figure 1. *The percentage of patients that have a positive mention of a disorder in each of the two groups (Dead or Critical Care, Other). Dead or Critical Care - patients that have died or that are in the Intensive Treatment Unit; and Other - patients that are neither dead nor in ITU at day 7. All diseases were extracted from free-text using Cogstack and MedCAT. Only medical concept annotations with F1 > 80% and more than 10 annotated samples are shown.*

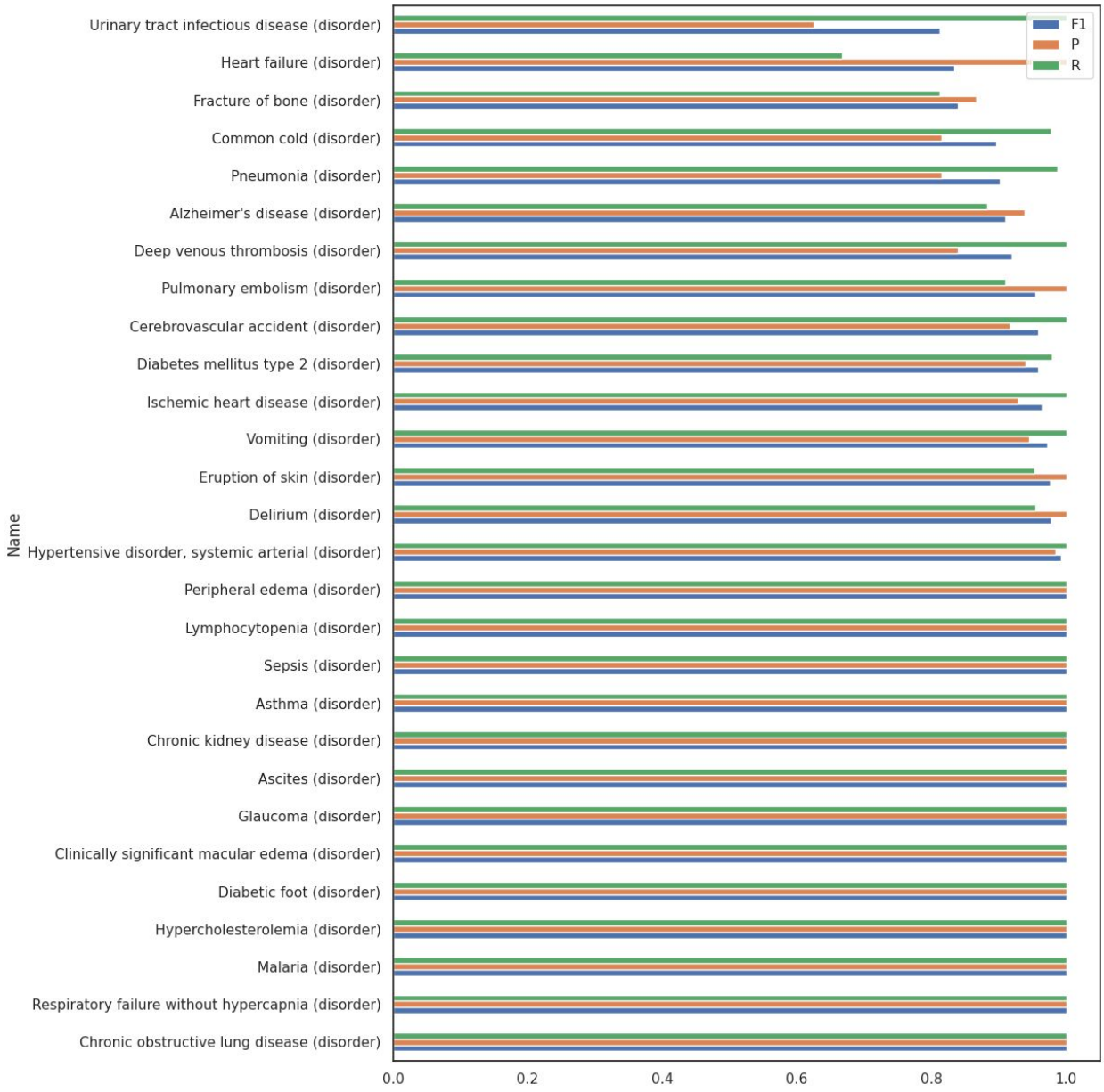

***Figure 2**. Performance of the CogStack and MedCAT NLP pipeline in detecting disease mentions within the electronic health record text. Precision (P), Recall (R) and F1 (harmonic mean of precision and recall). Only medical concept annotations with F1 > 80% and more than 10 annotated samples are shown.*

	Overall	On ACEi	Not on ACEi	On ARB	Not on ARB	Primary endpoint reached	Primary endpoint not reached
N	205	37	168	9	196	53	152
Age	62.95 (19.94)	74.51 (13.41)	60.4 (20.27)	65.0 (13.53)	62.85 (20.21)	64.91 (17.4)	62.26 (20.77)
Male	106 (51.7%)	22 (59.5%)	84 (50.0%)	3 (33.3%)	103 (52.6%)	33 (62.3%)	73 (48.0%)
On ACEi	37 (18.0%)	37 (100.0%)	0 (0.0%)	0 (0.0%)	37 (18.9%)	5 (9.4%)	32 (21.1%)
On ARB	9 (4.4%)	0 (0.0%)	9 (5.4%)	9 (100.0%)	0 (0.0%)	4 (7.5%)	5 (3.3%)
Hypertension	105 (51.2%)	31 (83.8%)	74 (44.0%)	7 (77.8%)	98 (50.0%)	32 (60.4%)	73 (48.0%)
Diabetes mellitus	62 (30.2%)	17 (45.9%)	45 (26.8%)	6 (66.7%)	56 (28.6%)	20 (37.7%)	42 (27.6%)
Ischaemic heart disease or heart failure	30 (14.6%)	11 (29.7%)	19 (11.3%)	2 (22.2%)	28 (14.3%)	6 (11.3%)	24 (15.8%)
Primary Endpoint	53 (25.9%)	5 (13.5%)	48 (28.6%)	4 (44.4%)	49 (25.0%)	53 (100.0%)	0 (0.0%)

Table 1. Characteristics of study cohort. *All patients are positive for COVID-19. All variables are shown as N (% of column) except age which is mean (SD). ACEi = Angiotensin converting enzyme inhibitor; ARB = Angiotensin 2 Receptor Blocker.*

Model	Adjustments	OR (95% CI) on ACEi vs Not on ACEi	p
Baseline	-	0.42 (0.14-1.00)	0.058
Model 1	Age, sex	0.34 (0.11-0.86)	0.02
Model 2	Age, sex, hypertension	0.28 (0.09-0.73)	<0.01
Model 3	Age, sex, hypertension, diabetes mellitus, ischaemic heart disease, heart failure	0.29 (0.10-0.75)	<0.01

Table 2. Summary of odds ratios for ACE inhibitor drug exposure and primary endpoint. *Odds ratios and p-values calculated from logistic regressions applying Firth's correction (Firth, 1993). Baseline no adjustments; Model 1 adjusted for age and gender; Model 2 additionally adjusted for hypertension; Model 3 additionally adjusted for hypertension, diabetes mellitus, ischaemic heart disease or heart failure. ACEi = Angiotensin converting enzyme inhibitor. OR = Odds ratio.*

Model	Variable	OR (95% CI)	P-value
Baseline	On ACEi	0.42 (0.14-1.00)	0.058
Model 1	On ACEi	0.34 (0.11-0.86)	0.022
Model 1	Age per 10 years	1.10 (0.94-1.30)	0.21
Model 1	Male	1.80 (0.95-3.40)	0.074
Model 2	On ACEi	0.28 (0.09-0.73)	<0.01
Model 2	hypertension	2.20 (1.00-4.90)	0.047
Model 2	Age per 10 years	1.00 (0.82-1.20)	0.98
Model 2	Male	2.00 (1.00-3.90)	0.038
Model 3	On ACEi	0.29 (0.10-0.75)	<0.01
Model 3	Age per 10 years	1.00 (0.85-1.30)	0.72
Model 3	Male	2.00 (1.00-4.00)	0.037
Model 3	diabetes	1.50 (0.71-3.00)	0.29
Model 3	hypertension	2.10 (0.90-4.80)	0.085
Model 3	ischaemic heart disease or heart failure	0.53 (0.18-1.40)	0.22
Hypertension unadjusted	hypertension	1.60 (0.88-3.10)	0.12
Hypertension adjusted	hypertension	1.80 (0.83-3.80)	0.14

Hypertension adjusted	Age per 10 years	0.98 (0.81-1.20)	0.84
Hypertension adjusted	Male	1.80 (0.97-3.50)	0.064

Supplementary Table 1. Odds ratios and p-values for all variables and primary endpoint. *Odds ratios and p-values calculated from logistic regressions applying Firth's correction[1]. ACEi = Angiotensin converting enzyme inhibitor. OR = Odds ratio.*

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