

ORIGINAL ARTICLE

The effect of initiation of renin–angiotensin system inhibitors on haemoglobin: A national cohort study

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Aims: To determine whether initiation of treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARBs) is associated with a subsequent reduction in haemoglobin in the general population.

Methods: We undertook a national cohort study over a 13-year period (2004–2016), using routine primary healthcare data from the UK Clinical Practice Research Datalink. We compared ACEI/ARB initiation with calcium channel blocker (CCB) initiation, to minimise confounding by indication. We included all first ACEI/ARB or CCB prescriptions in adults with at least 1 haemoglobin result in the 12 months before and 6 months after drug initiation. Our primary outcome was a ≥ 1 g/dL haemoglobin reduction in the 6 months after drug initiation.

Results: We examined 146 610 drug initiation events in 136 655 patients. Haemoglobin fell by ≥ 1 g/dL after drug initiation in 19.5% (16 936/86 652) of ACEI/ARB initiators and 15.9% (9521/59 958) of CCB initiators. The adjusted odds ratio of a ≥ 1 g/dL haemoglobin reduction in ACEI/ARB initiators vs CCB initiators was 1.15 (95% confidence interval 1.12–1.19).

Conclusion: ACEI/ARBs are associated with a modest increase in the risk of a haemoglobin reduction. For every 100 patients in our study that initiated a CCB, 16 experienced a ≥ 1 g/dL haemoglobin decline. If the effect is causal, 3 additional patients would have experienced this outcome if they had received an ACEI/ARB. This may have implications for drug choice and monitoring for many patients in primary care. Further research could identify patients at higher risk of this outcome, who may benefit from closer monitoring.

KEYWORDS

cardiovascular, chronic kidney disease, haematology, pharmacoepidemiology, primary care

Dr Greenhall and Dr Mansfield wish to be listed as joint first authors of this paper. The authors confirm that the principal investigator for this paper is Dr Laurie Tomlinson.

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1 | INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor II blockers (ARBs) are widely used for the treatment of heart failure, hypertension, ischaemic heart disease and proteinuric chronic kidney disease (CKD).^{1–4} In health, the renin–angiotensin system affects renal erythropoietin production and bone marrow haematopoiesis.⁵ Randomised data from clinical trials suggests that ACEI/ARB use is associated with a reduction in haemoglobin.^{6–8} However, most studies are restricted to specific populations, such as patients with heart failure, advanced CKD or erythrocytosis after renal transplantation. Observational data in this area are inconsistent and limited to restricted patient groups.^{9–14} There is a lack of evidence on the effect of ACEI/ARBs on haemoglobin in routine care populations.

Renal insufficiency and elevated baseline haemoglobin may modify the effect of ACEI/ARBs on haemoglobin, and the effects of ACEIs and ARBs may differ. However, evidence in these areas is conflicting.^{15–18}

We examined the association between ACEI/ARBs and haemoglobin in the UK primary care population. We hypothesised that initiation of ACEI/ARBs would be associated with a subsequent haemoglobin reduction. To minimise confounding by indication (which could give rise to an association between ACEI/ARB initiation and haemoglobin reduction that is in fact due to the indication for ACEI/ARB treatment, rather than the drug itself), we compared patients commencing ACEI/ARBs with patients commencing calcium channel blockers (CCBs).

2 | METHODS

2.1 | Study design and setting

We performed a cohort study of patients starting treatment with ACEI/ARBs or CCBs, using the Clinical Practice Research Datalink (CPRD Gold) as our source population. The CPRD contains real-world data from over 600 primary care practices, covering a representative sample of 7% of the UK population.¹⁹ The study period was 1 January 2004 to 31 December 2016. We chose this period because CKD is important in our study and serum creatinine testing became more frequent after the introduction of the Quality and Outcomes Framework in 2004.²⁰

2.2 | Population, exposure and outcome

We used electronic records of prescriptions and investigation results to identify patients in CPRD aged ≥ 18 years that received a new ACEI/ARB or CCB prescription (Table S1 in the Appendix shows all generic drug names used) during the study period, and had at least 1 haemoglobin result recorded in primary care in the 12 months before and 6 months after the date of prescription. To be confident that prescriptions were truly new and to ensure complete recording

What is already known about this subject

- Anaemia is associated with worse outcomes in patients with cardiovascular disease.
- Clinical trial evidence suggests that angiotensin converting enzyme inhibitors and angiotensin II receptor blockers (ACEI/ARBs) can cause a reduction in haemoglobin in restricted patient groups.
- The effect of ACEI/ARB initiation on haemoglobin in routine care populations is unknown.

What this study adds

- Compared to initiation of a calcium channel blocker, initiation of ACEI/ARB treatment was associated with a 15% increase in the risk of a ≥ 1 g/dL haemoglobin reduction.
- If causal, this could impact the quality of life of many patients who take these widely prescribed medications and may influence drug choice and monitoring.

of covariates, we excluded patients with <12 months of continuous practice registration prior to their first ACEI/ARB or CCB prescription.

Our exposure was ACEI/ARB initiation; our control condition was CCB initiation. We assumed that patients initiated medications on the date of the first prescription. We treated ACEI/ARB initiation and CCB initiation in the same patient as independent events, if separated by at least 6 months. We considered patients who commenced both an ACEI/ARB and a CCB within the same 6-month period to be exposed to the first drug prescribed only.

Our outcome was a ≥ 1 g/dL haemoglobin reduction in the 6 months following drug initiation. We chose this outcome because we aimed to study a biological effect of ACEI/ARB initiation that could be seen at any initial level of haemoglobin, beyond the influence of natural variation or laboratory measurement error. Previous studies have demonstrated haemoglobin reductions of this magnitude after ACEI/ARB initiation.^{8,21} We calculated haemoglobin change as the difference between the last result in the 12 months prior to drug initiation (pre-initiation haemoglobin) and the result closest to 115 days in the 6 months after drug initiation (post-initiation haemoglobin). We used this method because 115 days is the average lifespan of a red blood cell.²²

2.3 | Covariates

We used clinical knowledge and findings from previous research to construct a conceptual framework of the relationship between ACEI/ARB initiation and haemoglobin change (see Figure S1 in the Appendix). We used this framework to select covariates associated

with ACEI/ARB use that are independent risk factors for haemoglobin reduction.

We used the most recent serum creatinine result in the 12 months prior to drug initiation to calculate estimated glomerular filtration rate (eGFR), using the CKD Epidemiology Collaboration equation,²³ without ethnicity adjustment. We corrected creatinine results to account for the standardisation of laboratory measurement.²⁴ We classified CKD stage as stage 3a, 3b, 4 and 5 (eGFR 45–59, 30–44, 15–29 and <15 mL/min/1.73m², respectively).²⁵

We used primary care morbidity coding (Read codes) to identify comorbidities at drug initiation. These were: hypertension, diabetes mellitus, ischaemic heart disease, heart failure and conditions that cause chronic hypoxia (e.g. chronic obstructive pulmonary disease, cyanotic heart disease). Complete morbidity code lists are available at <https://doi.org/10.17037/data.00001039>. We used electronic records to identify concurrently prescribed medications that can cause bone marrow suppression or bleeding (see Table S1 in the Appendix). We recorded calendar period to account for temporal changes in coding and clinical practice.

2.4 | Statistical analysis

We used *t*-tests and χ^2 tests to compare baseline characteristics between ACEI/ARB initiators and CCB initiators. For our main analysis, we used multivariable logistic regression to estimate the adjusted odds ratio (OR) of a ≥ 1 g/dL haemoglobin reduction, comparing ACEI/ARB initiators and CCB initiators. We initially adjusted for age group, sex and pre-initiation haemoglobin (<12, 12–13.9, 14–15.9, ≥ 16 g/dL; minimally adjusted model), before additionally adjusting for comorbidities (hypertension, diabetes, ischaemic heart disease, heart failure, CKD, chronic hypoxic conditions), co-prescribed medications (oral bone marrow suppressing drugs, drugs that can cause bleeding) and calendar period (2004–2006, 2007–2009, 2010–2012, 2013–2016), and accounting for clustering at the primary care practice level with robust standard errors (fully adjusted model).

We handled missing data by performing a complete case analysis. We performed all analyses using Stata 15.1 (StataCorp, USA) and R 3.3.3 (R Foundation, Austria). All statistical tests were 2-sided and conducted at a 5% significance level.

2.5 | Sensitivity analyses

In a series of sensitivity analyses, we examined the influence of: (i) including lifestyle factors (smoking, alcohol intake and body mass index); (ii) including patients with unknown renal function; (iii) excluding patients with heart failure and patients taking diuretics; and (iv) excluding patients initiating both ACEI/ARBs and CCBs on our results. We also restricted our study cohort by shortening our pre-initiation period and then by excluding the first 4 weeks from our post-initiation period. *Posthoc*, we included only individuals with pre-

initiation haemoglobin measured within 1 week of drug initiation (Table S2).

2.6 | Propensity score analysis

We performed a propensity score analysis to account for imbalances in confounders. We calculated propensity scores using a logistic mixed model including a practice-specific random effect, in which the outcome was treatment (ACEI/ARB vs CCB) and the covariates were the same as those in our fully adjusted model. We then used inverse probability of treatment weighting to create a pseudo-population. To ensure that we achieved a good balance between treatment groups, we estimated standardised differences for each covariate before and after propensity score weighting. We then estimated the average ACEI/ARB treatment effect using a weighted logistic regression model that included only the primary exposure and outcome.

2.7 | Additional analyses

We undertook a series of additional analyses to explore further the relationship between ACEI/ARB initiation and haemoglobin reduction.

2.7.1 | Effect modification

We assessed whether advanced CKD (eGFR <30 mL/min/1.73m²) or elevated pre-initiation haemoglobin (≥ 16 g/dL) modified the effect of ACEI/ARB initiation (compared to CCB initiation) on a ≥ 1 g/dL haemoglobin reduction, using Wald tests. *Posthoc*, we tested for an interaction between sex and ACEI/ARB initiation in our fully adjusted model, as there is some evidence that sex modifies erythropoietin responsiveness.²⁶

2.7.2 | ARB vs ACEI

Because ACEIs and ARBs may affect haemoglobin in different ways,⁵ we compared the odds of a ≥ 1 g/dL haemoglobin reduction between ARB initiators and ACEI initiators, with adjustment for the same covariates included in our fully adjusted model. We excluded from this analysis patients who started both an ACEI and an ARB during the study period.

2.7.3 | Secondary outcomes

To test the consistency of the relationship between ACEI/ARB initiation and haemoglobin reduction, we repeated our fully adjusted model using incident anaemia (defined as haemoglobin <13 g/dL in men and <12 g/dL in women)²⁷ following drug initiation as the outcome. We then used multivariable linear regression to compare absolute

haemoglobin change between ACEI/ARB and CCB initiators, with adjustment for the same covariates included in our fully adjusted model. We also examined the association between ACEI/ARB initiation and diagnosed bone marrow suppression (identified using morbidity codes; see <https://doi.org/10.17037/data.00001039>) between 1 and 12 months after drug initiation, with adjustment for age, pre-initiation haemoglobin and use of oral bone marrow suppressing drugs.

2.7.4 | Haemoglobin variation

We explored whether variation in haemoglobin biased our results, with two further analyses. Firstly, we predicted that patients with decreasing haemoglobin prior to drug initiation would be more likely to experience a haemoglobin reduction after drug initiation. If the haemoglobin trajectory prior to drug initiation differed between

ACEI/ARB and CCB initiators, our outcome definition could incorrectly attribute a haemoglobin reduction to drug initiation. We assessed this by comparing the average (unadjusted) haemoglobin change prior to drug initiation (defined as the coefficient of the regression line of all haemoglobin results in the 12 months prior to drug initiation) between ACEI/ARB and CCB initiators. We restricted this analysis to patients with at least 3 haemoglobin results in the pre-initiation period, so that we had sufficient data to determine a trend. Any between-group differences in this analysis would suggest that our outcome definition biased our estimate of the association between ACEI/ARB initiation and haemoglobin reduction.

Secondly, we hypothesised that a post-initiation haemoglobin reduction would be more likely in patients with greater *natural* haemoglobin variation (i.e. variation over time), due to the phenomenon known as *regression to the mean*.²⁸ If ACEI/ARB initiators had greater natural haemoglobin variation than CCB initiators, the likelihood of a ≥ 1 g/dL haemoglobin reduction (our primary outcome)

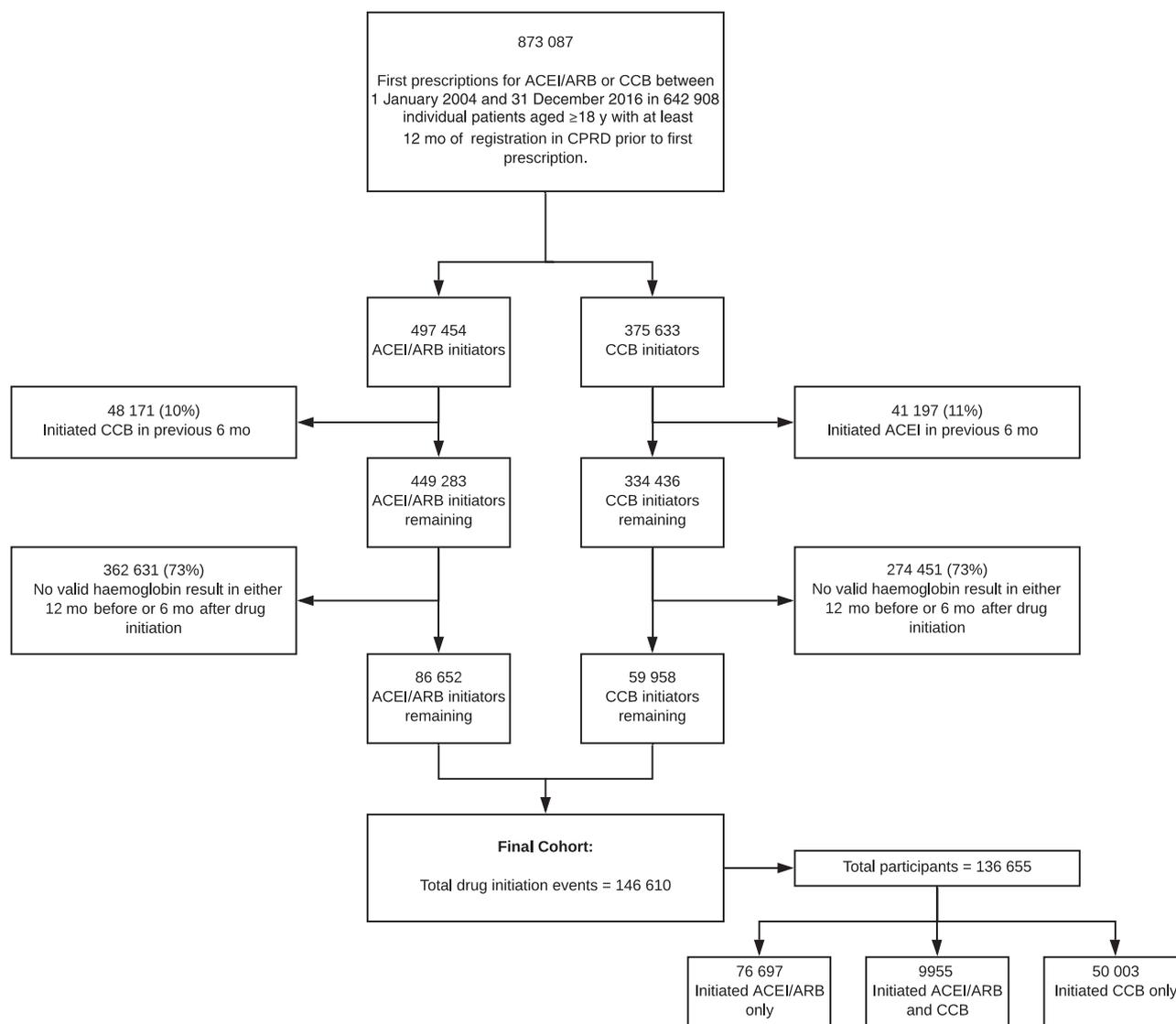


FIGURE 1 Flowchart of cohort creation ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; CPRD, clinical practice research datalink

would be higher in ACEI/ARB initiators at any time in our study period, irrespective of drug initiation (see Figure S2 in the Appendix for a graphical illustration of this). We investigated this by comparing the odds of a ≥ 1 g/dL haemoglobin reduction after an arbitrarily chosen date (1 January 2010), between patients who initiated ACEI/ARBs or CCBs at another time in the study period. We restricted this analysis to patients who only initiated an ACEI/ARB or a CCB and had at least 1 haemoglobin result in the 12 months before and 6 months after 1 January 2010. We adjusted this analysis for age, sex and initial haemoglobin (the most recent result before 1 January 2010). Any between-group difference in this model would be attributable to natural variation alone, and therefore argue against a causal drug effect in our main analysis.

3 | RESULTS

The study cohort comprised a total of 146 610 drug initiation events (86 652 ACEI/ARB and 59 958 CCB) in 136 655 individual patients. Of these, 9955 patients initiated both an ACEI/ARB and a CCB, and therefore contributed 2 drug initiation events. Figure 1 shows the development of the cohort.

The mean age at drug initiation was 64.7 years. Male sex, younger age, ischaemic heart disease, heart failure and diabetes were more common in ACEI/ARB initiators than CCB initiators (Table 1). The distribution of lifestyle variables (smoking, alcohol, body mass index) did not differ meaningfully between ACEI/ARB initiators and CCB initiators (see Table S3 in the Appendix).

The mean number of haemoglobin results in the pre-initiation and post-initiation periods was similar in ACEI/ARB initiators and CCB initiators. Pre-initiation haemoglobin was 0.19 g/dL (95% confidence interval [CI] 0.17–0.21) higher in patients initiating ACEI/ARBs compared to CCBs. The prevalence of anaemia at drug initiation was lower in ACEI/ARB initiators than CCB initiators (15.8 vs 16.7%; OR 0.94, 95% CI 0.91–0.97; Table 2).

A ≥ 1 g/dL haemoglobin reduction following drug initiation occurred in 19.5% (16,936/86,652) of ACEI/ARB initiators and 15.9% (9,521/59,958) of CCB initiators (OR 1.29, 95% CI 1.25–1.32). The minimally adjusted OR (adjusted for age, sex and pre-initiation haemoglobin) of a ≥ 1 g/dL haemoglobin reduction after drug initiation comparing ACEI/ARB initiators to CCB initiators was 1.24 (95% CI 1.21–1.28). The fully adjusted OR (additionally adjusted for comorbidities, co-prescribed medications and calendar period) was 1.15 (95% CI 1.12–1.19; Table 3. Table S4 in the Appendix shows the mutually adjusted ORs of all covariates in the fully adjusted model).

3.1 | Sensitivity analyses

Our results did not differ meaningfully in any of our sensitivity analyses, although restriction of the pre-initiation period attenuated the association between ACEI/ARB initiation and haemoglobin reduction. In the *posthoc* analysis restricted to individuals with a pre-initiation

TABLE 1 Characteristics of the study population at drug initiation. Data are *n* (column %)

	ACEI/ARB initiators (<i>n</i> = 86 652)	CCB initiators (<i>n</i> = 59 958)
Male sex	41 222 (47.6)	24 631 (41.1)
Age (y)		
18–44	8395 (9.7)	4640 (7.7)
45–49	7466 (8.6)	3363 (5.6)
50–54	9067 (10.5)	4557 (7.6)
55–59	8963 (10.3)	6473 (10.8)
60–64	10 181 (11.7)	8094 (13.5)
65–69	10 430 (12.0)	8563 (14.3)
70–74	10 048 (11.6)	8150 (13.6)
75–79	9360 (10.8)	7327 (12.2)
80–84	7211 (8.3)	5234 (8.7)
85+	5531 (6.4)	3557 (5.9)
Calendar period		
2004–2006	22 925 (26.5)	11 834 (19.7)
2007–2009	25 386 (29.3)	14 792 (24.7)
2010–2012	20 406 (23.5)	16 088 (26.8)
2013–2016	17 935 (20.7)	17 244 (28.8)
Comorbidities		
Hypertension	54 917 (63.4)	42 816 (71.4)
Ischaemic heart disease	20 542 (23.7)	11 591 (19.3)
Heart failure	5428 (6.3)	1082 (1.8)
Diabetes	21 957 (25.3)	11 447 (19.1)
Chronic hypoxic conditions	16 813 (19.4)	12 900 (21.5)
CKD		
None	66 335 (76.6)	45 602 (76.1)
Stage 3a	11 267 (13.0)	6812 (11.4)
Stage 3b	3898 (4.5)	2702 (4.5)
Stage 4	791 (0.9)	913 (1.5)
Stage 5	120 (0.1)	244 (0.4)
Missing	4241 (4.9)	3685 (6.1)
Co-prescribed medication		
Oral bone marrow suppressing drugs ^a	1713 (2.0)	1495 (2.5)
Drugs that can cause bleeding ^a	29 455 (34.0)	16 274 (27.1)
Pre-initiation haemoglobin (g/dL)		
<12	10 680 (12.3)	7960 (13.3)
12–13.9	32 848 (37.9)	25 734 (42.9)
14–15.9	35 093 (40.5)	22 127 (36.9)
≥ 16	8031 (9.3)	4137 (6.9)

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease.

^aSee Table S1 for full list of medications.

TABLE 2 Haemoglobin results by exposure group

	ACEI/ARB initiators (n = 86 652)	CCB initiators (n = 59 958)
Number of haemoglobin results (mean [SD])		
Pre-initiation period	2.0 (2.1)	2.1 (2.3)
Post-initiation period	1.5 (1.2)	1.6 (1.3)
Haemoglobin level (g/dL) (mean [SD])		
Pre-initiation	13.9 (1.7)	13.7 (1.7)
Post-initiation	13.6 (1.7)	13.5 (1.6)
Anaemia^a (n [%])		
Pre-initiation (prevalence)	13 709 (15.8)	9989 (16.7)
Post-initiation (incidence) ^b	6384 (8.8)	3985 (8.0)

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; SD, standard deviation.

Pre-initiation period: 12 months prior to drug initiation; post-initiation period: 6 months following drug initiation.

^aHaemoglobin <13 g/dL in men or <12 g/dL in women.

^bIncidence expressed as n (%) of new cases among patients who were not anaemic prior to drug initiation.

haemoglobin within 1 week of drug initiation, a ≥ 1 g/dL haemoglobin reduction was associated with CCB initiation (Figure 2; Table S2 in the Appendix).

3.2 | Propensity score analysis

Our propensity score analysis showed that, after accounting for potential confounders, the OR of a ≥ 1 g/dL haemoglobin reduction after drug initiation comparing ACEI/ARB initiators to CCB initiators was 1.15 (95% CI 1.11–1.20). Table S5 in the Appendix shows cohort characteristics before and after propensity score weighting).

TABLE 3 Multivariable adjusted odds ratio of a ≥ 1 g/dL haemoglobin reduction in ACEI/ARB initiators vs CCB initiators

Model	Minimally adjusted ^a		Fully adjusted ^b	
Observations	146 610		138 684	
	Adjusted OR	95% CI	Adjusted OR	95% CI
CCB initiators	Reference		Reference	
ACEI/ARB initiators	1.24	[1.21–1.28]	1.15	[1.12–1.19]

OR, odds ratio; CI, confidence interval; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker.

^aAdjusted for age, sex and pre-initiation haemoglobin.

^bAdditionally adjusted for comorbidities (hypertension, ischaemic heart disease, heart failure, diabetes, chronic hypoxic conditions, chronic kidney disease), medications (oral bone marrow suppressing drugs, drugs that can cause bleeding), calendar period and clustering at primary care practice level.

3.3 | Additional analyses

3.3.1 | Effect modification

The association between ACEI/ARB initiation and haemoglobin reduction was weaker among patients with pre-initiation haemoglobin ≥ 16 g/dL (OR 1.07, 95% CI 0.99–1.16) than among those with pre-initiation haemoglobin <16 g/dL (OR 1.17, 95% CI 1.13–1.21; $P = .03$ for interaction). There was no evidence that advanced CKD (eGFR <30 mL/min/1.73m²) modified the effect of ACEI/ARB initiation on haemoglobin reduction ($P = .31$ for interaction; Figure 2). Our *posthoc* analyses showed that the association between ACEI/ARB initiation and haemoglobin reduction was more pronounced in women (OR 1.23, 95% CI 1.18–1.28) than in men (OR 1.08, 95% CI 1.04–1.13; $P < .001$ for interaction; Figure 2).

3.3.2 | ARB vs ACEI

Among the 86 652 ACEI/ARB initiators, there were 80 911 ACEI initiators and 5710 ARB initiators; 31 individuals initiated both an ACEI and an ARB during the study period. There were no major differences between ACEI initiators and ARB initiators (see Table S6 in the Appendix). 19.5% (15,787/80,911) of ACEI initiators and 19.9% (1,135/5,710) of ARB initiators experienced a ≥ 1 g/dL haemoglobin reduction after drug initiation. The fully adjusted OR of a ≥ 1 g/dL haemoglobin reduction comparing ARB initiators to ACEI initiators was 1.13 (95% CI 1.05–1.22).

3.3.3 | Secondary outcomes

The incidence of anaemia (defined as haemoglobin <13 g/dL in men and <12 g/dL in women)²⁷ after drug initiation was 8.8% (6384/72 943) in ACEI/ARB initiators and 8.0% (3985/49 969) in CCB initiators. The fully adjusted OR of incident anaemia in ACEI/ARB initiators compared to CCB initiators was 1.12 (95% CI 1.07–1.17). The fully adjusted absolute haemoglobin reduction was 0.05 g/dL (95% CI 0.04–0.06) greater in ACEI/ARB initiators compared to CCB initiators.

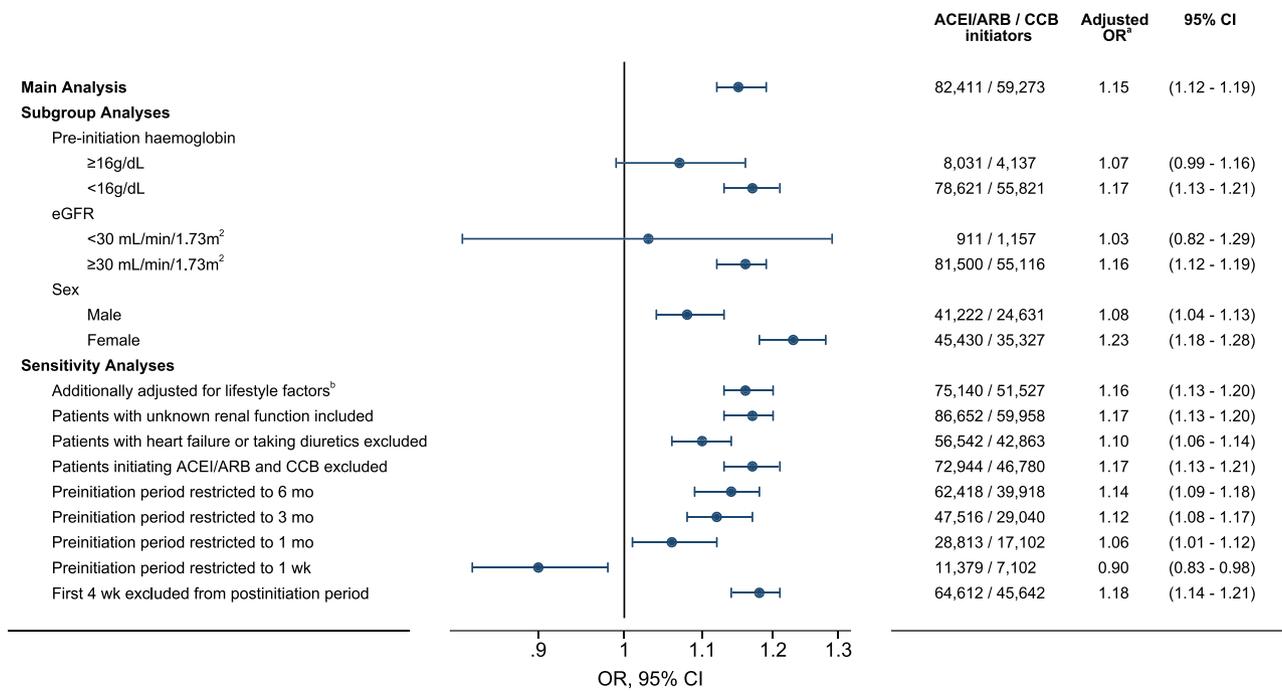


FIGURE 2 Forest plot of main, subgroup and sensitivity analyses: adjusted odds ratio of ≥ 1 g/dL haemoglobin reduction in ACEI/ARB initiators vs CCB initiators. ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate. ^a Adjusted for age, sex and pre-initiation haemoglobin, comorbidities (hypertension, ischaemic heart disease, heart failure, diabetes, chronic hypoxic conditions, chronic kidney disease), medications (oral bone marrow suppressing drugs, drugs that can cause bleeding), calendar period and clustering at primary care practice level. ^b Additionally adjusted for smoking status, alcohol intake and body mass index

A diagnosis of bone marrow suppression was received by 0.15% (128/86 652) of ACEI/ARB initiators and 0.19% (112/59 958) of CCB initiators between 1 and 12 months after drug initiation. After adjustment for age, sex and use of oral bone marrow suppressing drugs, there was no difference in the odds of diagnosed bone marrow suppression between ACEI/ARB initiators and CCB initiators (OR 0.82, 95% CI 0.63–1.08)

3.3.4 | Haemoglobin variation

There were 16 040 ACEI/ARB initiators and 12 065 CCB initiators with 3 or more haemoglobin results in the pre-initiation period. Among these patients, there was no difference in the average haemoglobin change prior to drug initiation between ACEI/ARB initiators (0.28 g/dL/y) and CCB initiators (0.29 g/dL/y; difference 0.01, 95% CI -0.17 to 0.20).

There were 34 257 individuals with at least 1 haemoglobin result in the 12 months before and 6 months after 1 January 2010 (our arbitrarily chosen date). After adjustment for age, sex and initial haemoglobin, there was no difference in the odds of a ≥ 1 g/dL haemoglobin reduction after 1 January 2010 between patients who, at another time in the study period, initiated ACEI/ARBs or CCBs (OR 1.02, 95% CI 0.95–1.09).

4 | DISCUSSION

In this large new-user cohort study, we found strong evidence for an association between ACEI/ARB initiation and subsequent haemoglobin reduction. After adjustment for confounders, ACEI/ARB initiators compared to CCB initiators had 15% higher odds of a ≥ 1 g/dL haemoglobin reduction, and 12% higher odds of incident anaemia. Of 100 CCB initiators in our study, 16 experienced a ≥ 1 g/dL haemoglobin decline. If the relationship with drug exposure was causal, 3 additional patients would have experienced this outcome if the same 100 patients had initiated an ACEI/ARB instead. In our study population, approximately 8% of the incidence of our primary outcome was attributable to ACEI/ARB initiation.

To our knowledge, this is the largest study on this topic, and the first in a national primary care cohort. Restricting to new users and examining a longitudinal outcome increases the strength of our findings, and we accounted for the influence of several important covariates. Our findings were consistent across several secondary outcomes and sensitivity analyses. Differences in the pre-initiation trajectory or the natural variation of haemoglobin between ACEI/ARB and CCB users did not appear to explain our results.

Our study has some limitations. Although our choice of comparator group minimised confounding by indication because hypertension is the major indication for the prescription of both ACEI/ARBs and

CCBs, the greater degree of comorbidity among ACEI/ARB initiators makes residual confounding possible. Unmeasured confounders such as infection, chronic inflammation or nutritional deficiency, which are not captured reliably by our data source, may have been more prevalent in ACEI/ARB initiators. However, ACEI/ARB initiators were younger and had higher pre-initiation haemoglobin than CCB initiators, and we found no difference in the haemoglobin change of each group before drug initiation; these observations are not consistent with ACEI/ARB initiators being sicker in general, and therefore more likely to experience a haemoglobin reduction. We were unable to account for adherence to prescribed medication and did not examine for a dose–response effect due to limitations of the data. Restricting our study population to patients with haemoglobin results before and after drug initiation may have resulted in selection bias towards patients for whom there was a clinical concern over haemoglobin change, which may limit generalisability of our findings. Our sensitivity analyses involving shortening of the pre-initiation period showed a trend towards lower odds of a ≥ 1 g/dL haemoglobin reduction among ACEI/ARB initiators, and lower odds of a reduction in haemoglobin compared to CCB initiators for people with pre-initiation haemoglobin measured within 1 week of drug initiation. It is possible that this is due to misclassification of pre-initiation haemoglobin levels among people with more historic measures, and that the overall result of the study is due to residual confounding between users of the drug classes. However, it is also possible that using only individuals with recent haemoglobin measures exacerbated selection bias by using only information from the sickest participants with lower haemoglobin. Alternatively, this selection of more unwell people may have included a larger number with abnormal circulating volume where haemoconcentration occurred after ACEI/ARB initiation. Lastly, there is some evidence that CCBs may increase the risk of gastrointestinal bleeding²⁹; this could have led us to underestimate the association between ACEI/ARBs and haemoglobin reduction.

Previous studies have found a stronger association between ACEI/ARBs and haemoglobin reduction.⁹ This may be due to restriction to specific patient groups with a higher prevalence of comorbidities, such as the elderly¹⁰ or patients with heart failure,⁷ CKD,⁸ or diabetes.¹² However, it is noteworthy that advanced CKD did not modify the effect of ACEI/ARB initiation on haemoglobin reduction in our study. The greater effect that we observed in ARB initiators compared with ACEI initiators conflicts with the findings of a previous study in primary care.¹⁵

Our findings of an attenuated association between ACEI/ARB use and haemoglobin reduction among patients with higher pre-initiation haemoglobin, and a more substantial effect in women compared to men, warrant further examination.

A causal association between ACEI/ARB initiation and haemoglobin reduction is plausible. Alterations in intrarenal haemodynamics could inhibit erythropoietin secretion by increasing oxygen delivery to renal fibroblasts. A small study demonstrated a reduction in serum erythropoietin (but not haemoglobin) in healthy volunteers taking ACEIs,³⁰ which supports this mechanism. Experimental studies have also suggested a direct ACEI/ARB effect on bone

marrow.^{5,31,32} It is not possible to determine which of these explanations might underpin our findings.

Anaemia in older patients is associated with cognitive decline, decreased quality of life and increased mortality.³³ Because ACEI/ARBs account for 6% of English primary care prescriptions,³⁴ our findings may have a bearing on drug selection, monitoring and potentially quality of life for a large number of patients. Our results are relevant to the assessment of unexplained anaemia and may help to reduce invasive investigations in some patients. These findings should not influence treatment of patients where strong clinical trial evidence of prognostic benefit exists, such as those with heart failure and reduced left ventricular systolic function.^{35,36} However, they merit consideration when treating conditions where other drug classes are equally effective, particularly in patients with pre-existing anaemia.

In summary, we found a modest increase in the risk of haemoglobin reduction after initiation of ACEI/ARB treatment. For some patients, this degree of haemoglobin reduction could have clinical implications. Further study could identify patients at higher risk of this adverse outcome, who may benefit from closer monitoring.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Unrelated to the submitted work, D.N. and L.T. are involved in 2 GlaxoSmithKline (GSK) funded noninterventional studies investigating aspects of renal function in sub-Saharan Africa, L.S. has received grants from the Wellcome Trust, Medical Research Council, National Institute for Health Research, GSK, British Heart Foundation (BHF), and Diabetes UK; L.S. is a Trustee of the BHF.

CONTRIBUTORS

L.T., K.M., D.N., M.I., R.J. and L.S. conceived the study. K.M. wrote the original study protocol, extracted the data and developed the study cohort. G.G. reviewed the literature, carried out the statistical analyses and wrote the initial draft. C.L. performed the propensity score analyses. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version.

All authors were independent from funders and had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are not publicly available because this study used existing data from the UK CPRD electronic health record databases. This is accessible to researchers following protocol approval by the CPRD's Independent Scientific Advisory Committee.

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REFERENCES

- National Institute for Health and Care Excellence (NICE). Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease. 2013; Available from: www.nice.org.uk/guidance/cg172
- National Institute for Health and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management. 2015; Available from: www.nice.org.uk/guidance/cg182
- National Institute for Health and Care Excellence (NICE). Chronic heart failure in adults: management. 2010; Available from: www.nice.org.uk/guidance/cg108
- National Institute for Health and Care Excellence (NICE). Hypertension in adults: diagnosis and management. 2018; Available from: www.nice.org.uk/guidance/cg127
- Hubert C, Savary K, Gasc J-M, Corvol P. The hematopoietic system: a new niche for the renin-angiotensin system. *Nat Clin Pract Cardiovasc Med*. 2006;3(2):80-85.
- Beckingham IJ, Woodrow G, Hinwood M, et al. A randomized placebo-controlled study of enalapril in the treatment of erythrocytosis after renal transplantation. *Nephrol Dial Transplant*. 1995;10(12):2316-2320.
- Ishani A, Weinhandl E, Zhao Z, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2005;45(3):391-399.
- Mohanram A, Zhang Z, Shahinfar S, Lyle PA, Toto RD. The effect of losartan on hemoglobin concentration and renal outcome in diabetic nephropathy of type 2 diabetes. *Kidney Int*. 2008;73(5):630-636.
- Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. *Qjm*. 2015;108(11):879-884.
- Laudisio A, Marzetti E, Pagano F, et al. Introduction of angiotensin-converting enzyme inhibitors induces a fall in hemoglobin levels in elderly patients hospitalized with heart failure: a cohort study. *Aging Clin Exp Res*. 2012;24(2):145-151.
- Winkelmayer WC, Kewalramani R, Rutstein M, Gabardi S, Vonvisger T, Chandraker A. Pharmacoeconomics of anemia in kidney transplant recipients. *J Am Soc Nephrol*. 2004;15(5):1347-1352.
- Nishida Y, Takahashi Y, Nakayama T, Asai S. Comparative effect of angiotensin II type I receptor blockers and calcium channel blockers on laboratory parameters in hypertensive patients with type 2 diabetes. *Cardiovasc Diabetol*. 2012;11(1):53.
- Piccoli A, Pastori G, Pierobon E, et al. Anti-renin-angiotensin-system drugs and development of anemia in chronic kidney disease. *J Nephrol*. 2005;18(5):585-591.
- Dousdampanis P, Trigka K, Fourtounas C. Prevalence of anemia in patients with type II diabetes and mild to moderate chronic kidney disease and the impact of anti-RAS medications. *Saudi J Kidney Dis Transpl*. 2014;25(3):552-557.
- Ajmal A, Gessert CE, Johnson BP, Renier CM, Palcher JA. Effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on hemoglobin levels. *BMC Res Notes*. 2013;6(1):443.
- Inoue A, Babazono T, Iwamoto Y. Effects of the renin-angiotensin system blockade on hemoglobin levels in type 2 diabetic patients with chronic kidney disease. *Am J Hypertens*. 2008;21(3):317-322.
- Robles N, Angulo E, Grois J, Barquero A. Comparative effects of Fosinopril and Irbesartan on Haematopoiesis in essential Hypertensives. *J Clin Basic Cardiol*. 2003;6:45-47.
- Yildiz A, Cine N, Akkaya V, et al. Comparison of the effects of enalapril and losartan on posttransplantation erythrocytosis in renal transplant recipients: prospective randomized study. *Transplantation*. 2001;72(3):542-544.
- Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.
- Doran T, Kontopantelis E, Valderas JM, et al. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK quality and outcomes framework. *Br Med J [Internet]*. 2011 Jun [cited 2019 Jan 19];342:d3590. Available from: <http://www.bmj.com/content/342/bmj.d3590/suppl/DC1>
- Schievink B, De Zeeuw D, Parving HH, Rossing P, Heerspink HJL. The renal protective effect of angiotensin receptor blockers depends on intra-individual response variation in multiple risk markers. *Br J Clin Pharmacol*. 2015;80(4):678-686.
- Franco RS. Measurement of red cell lifespan and aging. *Transfus Med Hemotherapy*. 2012;39(5):302-307.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
- Mansfield KE, Nitsch D, Smeeth L, Bhaskaran K, Tomlinson LA. Prescription of renin-angiotensin system blockers and risk of acute kidney injury: a population-based cohort study. *BMJ Open*. 2016;6(12):e012690.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3:1-150.
- Ifudu O, Uribarri J, Rajwani I, et al. Gender modulates responsiveness to recombinant erythropoietin. *Am J Kidney Dis [Internet]*. 2001;38(3):518-522. <https://doi.org/10.1053/ajkd.2001.26842>
- World Health Organisation. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011; Available from: <http://www.who.int/vmnis/indicators/haemoglobin.pdf>
- Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. *Int J Epidemiol*. 2005;34(1):215-220.
- He Y, Chan EW, Leung WK, Anand S, Wong ICK. Systematic review with meta-analysis: the association between the use of calcium channel blockers and gastrointestinal bleeding. *Aliment Pharmacol Ther*. 2015 Jun;41(12):1246-1255.
- Pratt MC, Lewis-Barned NJ, Walker RJ, Bailey RR, Shand BI, Livesey J. Effect of angiotensin converting enzyme inhibitors on erythropoietin concentrations in healthy volunteers. *Br J Clin Pharmacol*. 1992;34(4):363-365.
- Macdougall IC. ACE inhibitors and erythropoietin responsiveness. *Am J Kidney Dis*. 2001;38(3):649-651.

32. Richmond RS, Tallant EA, Gallagher PE, Ferrario CM, Strawn WB. Angiotensin II stimulates arachidonic acid release from bone marrow stromal cells. *J Renin Angiotensin Aldosterone Syst.* 2004;5(4):176-182.
33. Denny SD, Kuchibhatla MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. *Am J Med.* 2006;119(4):327-334.
34. NHS Digital. Prescription Cost Analysis - England, 2017 [Internet]. England; 2018 [cited 2019 Jan 27]. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/prescription-cost-analysis-england-2017>
35. Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet.* 2000;355(9215):1575-1581.
36. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991 Aug;325(5):293-302.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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