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The effect of initiation of renin-angiotensin system inhibitors on haemoglobin

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Introduction:
We aimed to investigate whether initiation of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARBs) is associated with a reduction in haemoglobin. ACEI/ARBs are an established treatment for proteinuric chronic kidney disease (CKD), cardiac failure, ischaemic heart disease and hypertension. Lower haemoglobin is associated with poorer outcomes in patients with CKD and cardiovascular disease.[1 2]
The renin-angiotensin system has a role in erythropoiesis:[3] Some evidence supports the efficacy of ACEI/ARBs for the treatment of post-transplant erythrocytosis,[4] and ACEI/ARBs may influence responsiveness to erythropoiesis stimulating agents.[5] Studies in restricted patient groups suggest ACEI/ARBs may cause a reduction in haemoglobin.[6 7 8] There is little evidence on the effect of ACEI/ARBs on haemoglobin in the general population. Baseline haemoglobin or advanced CKD may modify the effect of ACEI/ARBs on haemoglobin, and the effects of ACEIs and ARBs on haemoglobin may be differential.[9]
We examined the relationship between ACEI/ARB initiation and haemoglobin change in the primary care population. We hypothesised that initiation of treatment with ACEI/ARBs would be associated with a subsequent reduction in haemoglobin.

Methods:
We undertook a national cohort study using primary care electronic health record data from the UK Clinical Practice Research Datalink. To minimise confounding by indication, we compared patients initiating ACEI/ARBs with those initiating calcium channel blockers (CCBs). Our study population included all adult patients receiving a first ACEI/ARB or CCB prescription between 2004 and 2016, with at least one haemoglobin result recorded in the twelve months before and one in the six months after drug initiation. Our primary outcome was a ≥1g/dL haemoglobin reduction in the six months after drug initiation.

Results:
146,610 eligible drug initiation events occurred in 136,655 individual patients (see Table). Haemoglobin fell by ≥1g/dL after drug initiation in 19.5% (16,936/86,652) of ACEI/ARB initiators and 15.9% (9,521/59,958) of CCB initiators. After adjusting for confounders, the odds of a ≥1g/dL haemoglobin reduction were 15% higher in ACEI/ARB initiators than CCB initiators (OR 1.15, 95%CI 1.12-1.19). Our results were consistent across a number of secondary outcomes and robust in a series of sensitivity analyses (see Figure). The association between ACEI/ARB initiation and haemoglobin decline was weaker among patients with a pre-initiation haemoglobin level above 16g/dL (OR 1.07, 95% CI 0.99-1.16) than among those with a pre-initiation level below 16g/dL (OR 1.17, 95% CI 1.13-1.21; p=0.03 for interaction). There was no evidence that advanced CKD modified the effect of ACEI/ARB initiation on haemoglobin reduction (p=0.31 for interaction). ACEIs were associated with a higher risk of haemoglobin reduction than ARBs (OR 1.13, 95% CI 1.05-1.22).

Discussion:
ACEI/ARBs increase modestly the risk of a clinically important haemoglobin reduction. For every 100 patients in our study that initiated a CCB, 16 experienced a ≥1g/dL haemoglobin decline. Assuming a causal

relationship, 3 additional patients would have experienced this outcome if they had received an ACEI/ARB instead. This may have implications for drug choice and monitoring in a large number of patients.