

BMJ Open Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin-angiotensin system blockade: a UK general practice-based cohort study

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ABSTRACT

Objectives: To examine adherence to serum creatinine and potassium monitoring and discontinuation guidelines following initiation of treatment with ACE inhibitors (ACEI) or angiotensin receptor blockers (ARBs); and whether high-risk patients are monitored.

Design: A general practice-based cohort study using electronic health records from the UK Clinical Practice Research Datalink and Hospital Episode Statistics.

Setting: UK primary care, 2004–2014.

Subjects: 223 814 new ACEI/ARB users.

Main outcome measures: Proportion of patients with renal function monitoring before and after ACEI/ARB initiation; creatinine increase $\geq 30\%$ or potassium levels >6 mmol/L at first follow-up monitoring; and treatment discontinuation after such changes. Using logistic regression models, we also examined patient characteristics associated with these biochemical changes, and with follow-up monitoring within the guideline recommendation of 2 weeks after treatment initiation.

Results: 10% of patients had neither baseline nor follow-up monitoring of creatinine within 12 months before and 2 months after initiation of an ACEI/ARB, 28% had monitoring only at baseline, 15% only at follow-up, and 47% both at baseline and follow-up. The median period between the most recent baseline monitoring and drug initiation was 40 days (IQR 12–125 days). 34% of patients had baseline creatinine monitoring within 1 month before initiating therapy, but $<10\%$ also had the guideline-recommended follow-up test recorded within 2 weeks. Among patients experiencing a creatinine increase $\geq 30\%$ ($n=567$, 1.2%) or potassium level >6 mmol/L ($n=191$, 0.4%), 80% continued treatment. Although patients with prior myocardial infarction, hypertension or baseline potassium >5 mmol/L were at high risk of $\geq 30\%$ increase in creatinine after ACEI/ARB initiation, there was no evidence that they were more frequently monitored.

Strengths and limitations of this study

- This is the largest monitoring study until now, examining both adherence to creatinine and potassium monitoring and discontinuation guidelines following initiation of ACE inhibitors or angiotensin receptor blockers in UK primary care, and whether patients are monitored in accordance with their individual risk profile.
- Use of the UK Clinical Practice Research Datalink and Hospital Episode Statistics ensured that the study was population-based and not restricted to specific demographic, hospital or insurance groups.
- Blood tests performed in hospital systems were not recorded in the Clinical Practice Research Datalink, but the results were consistent for patients with no recent hospital admissions.
- If the recording of creatinine levels was not missing completely at random, the associations between patient characteristics and creatinine increase may have been underestimated.

Conclusions: Only one-tenth of patients initiating ACEI/ARB therapy receive the guideline-recommended creatinine monitoring. Moreover, the vast majority of the patients fulfilling postinitiation discontinuation criteria for creatinine and potassium increases continue on treatment.

INTRODUCTION

Renin angiotensin system blockade using ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs) is a mainstay in treatment of hypertension,¹ heart failure,² diabetic microalbuminuria or proteinuric

renal diseases,³ and after myocardial infarction.⁴ However, some patients experience a sudden decline in kidney function when initiating these drugs, presumably due to antagonism of the angiotensin II-mediated efferent arteriolar constriction or impaired kidney excretion of potassium.^{5 6}

The potential impact on kidney function should be evaluated by comparing preinitiation and postinitiation levels of serum creatinine and potassium.⁷ Discontinuation is recommended if the rise in creatinine exceeds 30% above baseline or if hyperkalaemia develops.⁸ It is unclear whether these recommendations are routinely followed in clinical practice.⁹

A few studies have compared baseline and follow-up monitoring results,⁹ but large studies using contemporary data with reference to current guidelines are lacking, and it is unknown whether patients' individual risk of renal impairment influences their likelihood of being monitored.⁹ We therefore examined adherence to creatinine and potassium monitoring and treatment discontinuation guidelines following ACEI/ARB initiation in UK primary care, and whether patients are monitored in accordance with their individual risk profile.

METHODS

Data sources

We used the UK's Clinical Practice Research Datalink (CPRD) linked to hospital record data from the Hospital Episode Statistics (HES) database. The CPRD database contains primary care electronic health record data from 7% of the UK population (~15 million patient lives, with ~8 million currently under follow-up).¹⁰ Patients included in the CPRD are largely representative of the UK population in terms of age, sex and ethnicity.^{10 11} Information recorded in the database includes demographics such as sex and year of birth, the location of the general practice, medical diagnoses (based on 'Read' codes), drug prescriptions and a range of routine laboratory test results. HES records cover all hospital admissions for patients covered by the National Health Service (NHS) who receive treatment either from English NHS trusts or independent providers.^{10 11} Fifty-eight per cent of general practices included in the CPRD have agreed to HES linkage.¹⁰ We obtained linked data on socioeconomic status (index of multiple deprivation) based on area of residence.

Monitoring guidelines

Consistent with other international guidelines, the National Institute for Health and Care Excellence (NICE) recommends baseline testing of creatinine when initiating ACEI/ARB therapy in patients with hypertension,¹ heart failure,² myocardial infarction⁴ or chronic kidney disease (CKD).³ The time interval for baseline testing is not further specified.¹⁻⁴ Among patients with heart failure, myocardial infarction and CKD, NICE recommends follow-up monitoring within 2 weeks of

treatment initiation,²⁻⁴ and for patients with myocardial infarction at least annually thereafter.⁴ A baseline assessment and follow-up test within 2 weeks is also recommended by the UK Renal Association,¹² as well as the frequently used online web resource General Practice (GP) Notebook.¹³ GP Notebook additionally recommends monitoring 1, 3, 6 and 12 months after the first follow-up test.¹³ NICE recommends not to initiate ACEI/ARBs in patients with a baseline potassium level >5 mmol/L and to discontinue therapy if potassium rises above 6 mmol/L.

ACEI/ARB initiators

We identified a cohort of all HES-linked CPRD patients aged ≥18 years, who initiated ACEI/ARB treatment between 1 January 2004 and 31 March 2014. We did not include earlier calendar periods, as laboratory data before 2004 were incomplete due to interface problems between laboratory reporting software and GP practice management software.¹⁴ Also, creatinine testing was incentivised in 2004 with the introduction of the diabetes Quality and Outcomes Framework (QOF) and further in 2006 with the CKD QOF.¹⁴ To rule out any potential influence of incomplete data around 2004, we also examined the most recent 5-year calendar period separately in a sensitivity analysis. New users were defined as persons with at least 1 year of continuous registration in the CPRD before their first recorded ACEI/ARB prescription.

Laboratory data

All creatinine test results were extracted from the general practice records of the study population, using creatinine-specific codes in CPRD. Cross-reference was then made to creatinine test results identified from a broad Read code search. Any irrelevant codes were excluded. Renal function testing in the UK includes creatinine and potassium, so it can be inferred that testing frequency is similar to creatinine for potassium. When we conducted analyses related to potassium levels, we repeated the procedure used to identify creatinine levels for potassium test results.

Patient characteristics

We obtained information for all patients on age, sex, calendar period of ACEI/ARB initiation (2004–2008 and 2010–2014), socioeconomic status (quintiles of the 2004 index of multiple deprivation scores), lifestyle factors (smoking, alcohol intake and body mass index), baseline potassium level (≤5 or >5 mmol/L), CKD, cardiovascular comorbidities (heart failure, myocardial infarction, hypertension, peripheral arterial disease and arrhythmia) and diabetes.¹⁵ We used algorithms for smoking status, alcohol intake and body mass index based on the most recent records in the CPRD before ACEI/ARB initiation.^{16 17} As measures of baseline creatinine and potassium levels, we used the single most recent measurement within 12 months before the first ACEI/ARB

prescription. We calculated the estimated glomerular filtration rate (eGFR) level from the most recent creatinine measurement and CKD stage from the CKD Epidemiology Collaboration (CKD-EPI) equation.¹⁸ Cardiovascular comorbidities and diabetes were identified from both the CPRD and HES based on diagnoses recorded prior to ACEI/ARB initiation. The code lists for all variables are provided in the online supplementary appendix.

Patient involvement

The study included no patient involvement.

Statistical analysis

We described ACEI/ARB users according to patient characteristics, both overall and according to creatinine monitoring status (no baseline or follow-up monitoring, baseline only, follow-up only, and both baseline and follow-up monitoring). Baseline monitoring was defined as a test performed on the date of drug initiation or within either 12 months before (wide interval) or 1 month before initiation (more ideal interval assumed to be driven by planned ACEI/ARB initiation). To accord with the postinitiation monitoring interval recommended from previous trial data, we considered only follow-up monitoring within the first 2 months after drug initiation.⁸

We calculated the proportion of persons in the total cohort of new users who had baseline and follow-up monitoring (within 1, 3 and 12 months before drug initiation and within 2 weeks, 1 month and 2 months after initiation). We then computed the proportion of persons with both baseline and initial follow-up monitoring within the guideline-recommended interval of 2 weeks following drug initiation.

We repeated the analyses for continuing users, in order to examine adherence to the stricter guideline recommendations for ongoing monitoring (*ie*, monitoring within 1, 3, 6 and 12 months after the first retest).¹³ Continuation was defined as ACEI/ARB use beyond 30 days following the monitoring date, *that is*, when the end date of the first continuous course of therapy was after the date of the first monitoring date plus 30 days (to allow for stockpiling). The end date of each prescription was calculated by adding the prescription duration (total number of tablets prescribed divided by the specified number of tablets per day) to the prescription date. In identifying continuous courses of therapy, we allowed for a 30-day gap between the end date of one prescription and the start of the next consecutive prescription.

In sensitivity analyses, we repeated the analyses (1) extending the follow-up window for the first follow-up monitoring from 2 to 3 weeks to account for minor delays; (2) including only the most recent calendar period (2009–2014) to account for temporal changes in data completeness and quality of care; (3) excluding patients with a hospital admission or discharge date

within 1 month before or after their first ACEI/ARB prescription, in order to account for drug initiation and any subsequent renal function tests occurring in the hospital and therefore not captured in the CPRD; (4) focusing on specific patient subgroups (heart failure, myocardial infarction, hypertension, CKD (eGFR<60 mL/min/1.73 m²), peripheral arterial disease and diabetes); and (5) defining drug use continuation as ACEI/ARB use beyond 90 days (instead of 30 days) after the first retest date.

We used the subcohort of patients with both baseline and follow-up monitoring to calculate the proportion of patients with creatinine increases $\geq 30\%$ or potassium levels >6 mmol/L at the first follow-up monitoring within 2 months after initiation, as well as the proportion of patients continuing treatment despite these contraindications for use.

Finally, we fitted a logistic regression model to identify patient characteristics associated with a severe decline in renal function (creatinine increase $\geq 30\%$ or potassium level >6 mmol/L) and compared these characteristics with those associated with receiving postinitiation follow-up monitoring within 2 weeks. The model included age, sex, CKD stage, cardiovascular comorbidities, diabetes and baseline potassium level (>5 vs ≤ 5 mmol/L). In three additional model-based sensitivity analyses, we repeated the analyses (1) excluding patients with a recent hospitalisation (as defined above); (2) omitting baseline potassium from the model to examine the extent of potential overfitting when both baseline potassium and CKD stage were kept in the model; and (3) also adjusting additionally for ethnicity.

All analyses were performed using the STATA 14 statistical software package.

RESULTS

Serum creatinine monitoring before and after ACEI/ARB initiation

We identified 223 814 new users of ACEI/ARB. We compared these patients in four groups: 21 411 (10%) had no baseline or follow-up creatinine tests within 12 months before and 2 months after treatment initiation, 63 359 (28%) had only a baseline test, 33 185 (15%) had only follow-up tests, and 105 859 (47%) had both baseline and follow-up tests ([table 1](#)). Median age varied only slightly between the groups (60, 62, 59 and 63 years, respectively) and there were no substantial differences in socioeconomic status, lifestyle factors or peripheral arterial disease. Compared with patients with neither preinitiation nor postinitiation monitoring, patients with both were more likely to have diagnosed hypertension (76% vs 61%) and diabetes (20% vs 7%), but less likely to have diagnosed heart failure (4% vs 7%), myocardial infarction (4% vs 18%) and arrhythmia (7% vs 10%). Among patients with baseline monitoring, 83% did not have CKD, 13% stage 3a, 3% stage 3b, 0.5% stage 4 CKD. In the same population, 7% started

Table 1 Characteristics of patients initiating ACE inhibitors or ARBs in the UK primary care during 2004–2014, by monitoring groups

	Serum creatinine monitoring*				Total
	No baseline or follow-up tests	Baseline test only	Follow-up test only	Baseline and follow-up tests	
Total number	21 411 (100)	63 359 (100)	33 185 (100)	105 859 (100)	223 814 (100)
Female sex	8882 (41)	27 722 (44)	14 570 (44)	49 109 (46)	100 283 (45)
Age (years)					
<50	5019 (23)	13 697 (22)	8732 (26)	19 910 (19)	47 358 (21)
50–59	5485 (26)	15 135 (24)	9115 (27)	24 866 (23)	54 601 (24)
60–69	4863 (23)	15 586 (25)	7776 (23)	27 790 (26)	56 015 (25)
70–79	3579 (17)	12 193 (19)	5066 (15)	22 152 (21)	42 990 (19)
80+	2465 (12)	6748 (11)	2496 (8)	11 141 (11)	22 850 (10)
Calendar period					
2004–2008	14 814 (69)	40 667 (64)	19 808 (60)	60 902 (58)	136 191 (61)
2009–2014	6597 (31)	22 692 (36)	13 377 (40)	44 957 (42)	87 623 (39)
SES quintiles					
1 (low)	5153 (24)	15 290 (24)	8533 (26)	25 577 (24)	54 553 (24)
2	4725 (22)	14 331 (23)	7887 (24)	24 851 (23)	51 794 (23)
3	4341 (20)	13 028 (21)	6890 (21)	22 629 (21)	46 888 (21)
4	4254 (20)	12 140 (19)	5931 (18)	19 318 (18)	41 643 (19)
5 (high)	2925 (14)	8508 (13)	3898 (12)	13 359 (13)	28 690 (13)
Missing	13 (0)	62 (0)	46 (0)	125 (0)	246 (0)
Smoking status					
Never	7860 (37)	22 496 (36)	12 229 (37)	36 895 (35)	79 480 (36)
Ever	13 433 (63)	40 797 (64)	20 915 (63)	68 939 (65)	144 084 (64)
Missing	118 (1)	66 (0)	41 (0)	25 (0)	250 (0)
Alcohol intake					
No use	2556 (12)	7819 (12)	3409 (10)	11 088 (10)	24 872 (11)
Current	15 495 (72)	47 322 (75)	25 656 (77)	82 870 (78)	171 343 (77)
Former	1328 (6)	4499 (7)	1933 (6)	7490 (7)	15 250 (7)
Missing	2032 (9)	3719 (6)	2187 (7)	4411 (4)	12 349 (6)
BMI groups					
Underweight	282 (1)	700 (1)	304 (1)	1008 (1)	2294 (1)
Healthy weight	5666 (26)	15 406 (24)	8089 (24)	24 972 (24)	54 133 (24)
Overweight	7677 (36)	23 755 (37)	12 484 (38)	40 556 (38)	84 472 (38)
Obesity	6009 (28)	20 660 (33)	10 527 (32)	35 887 (34)	73 083 (33)
Missing	1777 (8)	2838 (4)	1781 (5)	3436 (3)	9832 (4)
CKD (eGFR)†					
Stage ≤2 (≥60)	10 326 (48)	53 773 (85)	19 470 (59)	87 484 (83)	171 053 (76)
Stage 3a (45–59)	1137 (5)	7382 (12)	1766 (5)	13 913 (13)	24 198 (11)
Stage 3b (30–44)	217 (1)	1885 (3)	265 (1)	3854 (4)	6221 (3)
Stage 4 (15–29)	24 (0)	319 (1)	29 (0)	608 (1)	980 (0)
Not measured	9707 (45)	0 (0)	11 655 (35)	0 (0)	21 362 (10)
CV comorbidities‡					
Heart failure	1568 (7)	3270 (5)	1386 (4)	4583 (4)	10 807 (5)
Myocardial infarction	3881 (18)	4653 (7)	3203 (10)	4620 (4)	16 357 (7)
Hypertension	13 023 (61)	44 273 (70)	24 195 (73)	80 946 (76)	162 437 (73)
Peripheral arterial disease	471 (2)	1590 (3)	523 (2)	2547 (2)	5131 (2)
Arrhythmia	2057 (10)	4973 (8)	2000 (6)	7123 (7)	16 153 (7)
Diabetes mellitus	1399 (7)	13 586 (21)	1992 (6)	21 548 (20)	38 525 (17)

*Monitoring groups based on baseline (within 12 months before) and follow-up (within 2 months after) serum creatinine monitoring.

†Calculated from most recent creatinine measurement within 12 months before the first prescription date.

‡Diagnosis ever registered before ACE/ARB initiation in CRPD or HES.

ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HES, Hospital Episode Statistics; SES, socioeconomic status.

ACEI/ARB therapy despite baseline potassium above 5 mmol/L. The median number of days between baseline monitoring and first prescription date was 40 days (IQR 12–125 days).

Among all patients initiating ACEI/ARB therapy, the proportion of patients receiving creatinine testing before initiation was 76% within 12 months of treatment initiation, declining to 34% within 1 month before initiation

Table 2 Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating ACE inhibitors or angiotensin receptor blockers, 2004–2014

Total number	Serum creatinine, ≥ 1 test n=223 814 (100%)
Baseline testing	
≤ 12 months before	169 218 (76%)
≤ 3 months before	115 348 (52%)
≤ 1 month before	75 476 (34%)
Follow-up testing	
≤ 2 weeks after	65 090 (29%)
≤ 1 month after	114 244 (51%)
≤ 2 months after	139 044 (62%)

(table 2). The proportion with follow-up testing after treatment initiation was 29% within 2 weeks, increasing to 62% within 2 months. Among ACEI/ARB initiators who had a baseline test within 12 months, 21% also had a follow-up test within 2 weeks after starting treatment (table 3). However, among patients undergoing testing within 1 month prior to treatment initiation, only 9% had also the recommended follow-up test within 2 weeks of treatment start. When we extended the follow-up window to 3 weeks, this proportion increased to only 14% (table 3). Among patients continuing treatment, only 1% had follow-up measurements at 1, 3, 6 and 12 months after the first retest, in compliance with the strictest recommendation (eTable 1). These results were unchanged when the analysis was restricted to the most recent

calendar period (eTables 1–2) and to patients with heart failure, myocardial infarction, hypertension, peripheral arterial disease, diabetes or no recent hospitalisation (eTable 3). Only patients with CKD received a slightly higher degree of monitoring (13%) within 2 weeks following treatment initiation (eTable 3). The proportion with follow-up testing after treatment initiation was also unchanged when results were stratified by date of ACEI/ARB initiation in 2-year intervals (eTable 4).

Serum creatinine and potassium changes after ACEI/ARB initiation

Among patients receiving the recommended renal function monitoring, 567 (1.2%) experienced a creatinine increase $\geq 30\%$ and 191 (0.4%) a potassium level >6 mmol/L at their first follow-up test within 2 months of treatment initiation (1.4% experienced the increase in creatinine and/or potassium) (table 4). Among these patients, 80% continued treatment beyond 30 days following the monitoring date (table 4). The sensitivity analysis showed that 65% of patients with a creatinine increase $\geq 30\%$ and 60% of those with a potassium level >6 mmol/L also continued treatment beyond 90 days after the monitoring date (eTable 5). The results remained consistent for longer baseline monitoring intervals (eTable 5).

Patients at high risk for creatinine increases $\geq 30\%$

When we examined patient characteristics associated with a creatinine increase $\geq 30\%$ and adjusted for the

Table 3 Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating ACE inhibitors or angiotensin receptor blockers according to clinical guideline recommendations

	Clinical guidelines					All initiators n=223 814 (100%)	
	NICE heart failure	NICE MI	NICE/UKRA hypertension	NICE CKD	GP Notebook	Wide baseline interval (≤ 12 -months)	Ideal baseline interval (≤ 1 month)
Baseline testing	x	x	x	x	x	169 218 (76%)	75 476 (34%)
+Follow-up test ≤ 2 weeks*	x	NA	x	x	x	46 486 (21%)	19 679 (9%)
+Follow-up test ≤ 3 weeks†						70 792 (32%)	30 451 (14%)

*Follow-up test among those with baseline measurements.

†Sensitivity analysis illustrating the importance of 2-week vs 3-week cut-off interval in follow-up test intervals.

CKD, chronic kidney disease; GP, general practice; MI, myocardial infarction; NA, not applicable; NICE, National Institute for Health and Care Excellence; UKRA, United Kingdom Renal Association.

Table 4 Proportion of new users of ACE inhibitors or angiotensin receptor blockers who continue or discontinue treatment according to guideline recommended cut-off levels of serum creatinine and potassium at follow-up testing*

	Continuation†	Discontinuation†	Total
Total number, %	42 942 (93.1)	3178 (6.9)	46 120 (100)
Serum creatinine increase $\geq 30\%$, n (%)	462 (81.5)	105 (18.5)	567 (100)
Serum potassium >6 mmol/L, n (%)	150 (78.5)	41 (21.5)	191 (100)

*Calculated from the most recent measurements within 1 month before and 2 months after drug initiation.

†A patient was considered a continuous user when the end date of the first continuous course of therapy was larger than the date of the first follow-up monitoring +30 days (to allow for stockpiling and irregular use).

Table 5 Association between patient characteristics and serum creatinine increase $\geq 30\%$ and follow-up monitoring within 2 weeks following initiation of ACE inhibitors or angiotensin receptor blockers

Characteristics	OR (95% CIs)					
	Serum creatinine monitoring ≤ 2 weeks		Serum creatinine increase $\geq 30\%^*$		Serum potassium increase $\geq 30\%^*$	
	Age-adjusted and sex-adjusted	Fully adjusted†	Age-adjusted and sex-adjusted	Fully adjusted†	Age-adjusted and sex-adjusted	Fully adjusted†
Female sex	1.07 (1.04 to 1.10)	1.07 (1.04 to 1.09)	1.39 (1.26 to 1.53)	1.63 (1.47 to 1.80)	0.87 (0.66 to 1.16)	0.94 (0.70 to 1.26)
Age (years)						
<50	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
50–59	0.98 (0.94 to 1.01)	0.98 (0.95 to 1.02)	0.88 (0.74 to 1.05)	0.86 (0.72 to 1.03)	1.29 (0.79 to 2.11)	1.10 (0.67 to 1.81)
60–69	1.05 (1.02 to 1.09)	1.05 (1.01 to 1.09)	1.03 (0.88 to 1.21)	1.00 (0.85 to 1.19)	1.35 (0.84 to 2.17)	0.97 (0.60 to 1.58)
70–79	1.18 (1.14 to 1.23)	1.18 (1.13 to 1.23)	1.49 (1.27 to 1.74)	1.36 (1.15 to 1.61)	1.65 (1.02 to 2.66)	0.74 (0.43 to 1.26)
80+	1.20 (1.14 to 1.25)	1.17 (1.11 to 1.23)	2.72 (2.32 to 3.20)	2.02 (1.68 to 2.44)	2.75 (1.67 to 4.53)	0.73 (0.41 to 1.32)
CKD stage						
No CKD (≥ 60)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Stage 3a (45–59)	1.00 (0.96 to 1.04)	1.00 (0.96 to 1.04)	0.62 (0.53 to 0.73)	0.60 (0.51 to 0.70)	2.48 (1.66 to 3.71)	2.06 (1.36 to 3.11)
Stage 3b (30–44)	0.99 (0.93 to 1.06)	1.01 (0.94 to 1.08)	1.01 (0.82 to 1.24)	0.88 (0.71 to 1.09)	7.51 (4.75 to 11.9)	5.10 (3.16 to 8.22)
Stage 4 (15–29)	1.42 (1.21 to 1.67)	1.41 (1.20 to 1.66)	2.16 (1.52 to 3.05)	1.72 (1.18 to 2.51)	24.0 (13.5 to 42.6)	11.4 (6.07 to 21.4)
Comorbidities*						
Heart failure	1.15 (1.09 to 1.23)	1.16 (1.08 to 1.23)	4.00 (3.49 to 4.58)	2.93 (2.51 to 3.42)	2.90 (1.90 to 4.42)	2.22 (1.38 to 3.58)
MI	0.80 (0.75 to 0.85)	0.77 (0.72 to 0.82)	2.33 (1.98 to 2.74)	1.57 (1.32 to 1.87)	2.12 (1.33 to 3.39)	1.35 (0.80 to 2.25)
Hypertension	1.00 (0.97 to 1.02)	1.05 (1.00 to 1.11)	0.62 (0.56 to 0.68)	1.58 (1.36 to 1.84)	0.60 (0.45 to 0.80)	1.02 (0.63 to 1.65)
PAD	1.09 (1.01 to 1.18)	1.11 (1.02 to 1.20)	2.10 (1.70 to 2.60)	1.87 (1.50 to 2.33)	2.14 (1.18 to 3.86)	1.53 (0.82 to 2.88)
Arrhythmia	1.09 (1.03 to 1.14)	0.98 (0.95 to 1.01)	2.37 (2.07 to 2.71)	0.77 (0.69 to 0.86)	1.41 (0.90 to 2.21)	0.77 (0.56 to 1.05)
Diabetes mellitus	0.93 (0.90 to 0.96)	0.93 (0.90 to 0.96)	1.09 (0.97 to 1.22)	1.04 (0.92 to 1.18)	0.97 (0.69 to 1.36)	0.90 (0.63 to 1.29)
Baseline K >5 mmol/L	1.04 (1.00 to 1.10)	1.04 (0.99 to 1.09)	1.04 (0.86 to 1.25)	0.97 (0.80 to 1.17)	8.22 (6.14 to 11.0)	6.68 (4.94 to 9.02)

*The increase was based on the difference between the most recent baseline measurements within 12 months before and first follow-up measurement within 2 months after drug initiation. All analyses were restricted to those with both baseline and follow-up measurements (n=105 859).

†Adjusted for sex, age, CKD, heart failure, MI, hypertension, PAD, arrhythmia, diabetes and calendar period of prescription start. CKD, chronic kidney disease; K, potassium; MI, myocardial infarction; PAD, peripheral arterial disease.

other characteristics in a multivariable analysis (table 5), we found an increased OR for women (1.6-fold increased), for age above 70 years (at least 1.3-fold increased), for CKD stage 4 (1.6-fold increased), heart failure (2.9-fold increased), peripheral arterial disease (1.9-fold increased), myocardial infarction (1.6-fold increased) and hypertension (1.6-fold increased).

Patients at high risk for potassium >6 mmol/L

Baseline potassium level and CKD stage, but not age and sex, were associated with potassium levels >6 mmol/L after ACEI/ARB initiation. Thus, the OR was sevenfold increased for baseline potassium >5 mmol/L, twofold increased for CKD stage 3a, fivefold increased for stage 3b, and 11-fold increased for stage 4 (table 5). Among cardiovascular comorbidities, heart failure was associated with the strongest OR of a potassium level >6 mmol/L (2.22, 95% CI 1.38 to 3.58).

Monitoring high-risk patients

Some characteristics associated with increased odds of having $\geq 30\%$ rise in creatinine were also associated with a greater likelihood of having a follow-up test within 2 weeks following drug initiation. These included older age: persons aged 70 years or above compared with ≤ 50 years (1.18, 95% CI 1.13 to 1.23 for 70–79 years and 1.17, 95% CI 1.11 to 1.23 for 80+ years), CKD stage 4 compared with no CKD (1.41, 95% CI 1.20 to 1.66), heart failure (1.16, 95% CI 1.08 to 1.23) and peripheral arterial disease (1.11, 95% CI 1.02 to 1.20). However, other characteristics associated with increased odds of having $\geq 30\%$ rise in creatinine were not associated with a greater likelihood of having a follow-up test within 2 weeks following drug initiation: there was no substantially increased OR (>10%) associated with female sex (1.07, 95% CI 1.04 to 1.09), prior history of myocardial infarction (0.77, 95% CI 0.72 to 0.82), hypertension (1.05, 95% CI 1.00 to 1.11) or baseline potassium >5 mmol/L (1.04, 95% CI 0.99 to 1.09). When we excluded patients with a recent hospital admission, the reduced OR for myocardial infarction was no longer observed (0.93, 95% CI 0.80 to 1.08) (eTable 6). Finally, the results remained consistent when we omitted adjustment for baseline potassium (data not shown) and when we adjusted additionally for ethnicity (eTable 6).

DISCUSSION

Only one-tenth of patients initiating ACEI/ARBs in UK primary care appear to receive the guideline-recommended creatinine monitoring. One in 15 patients started ACEI/ARBs despite baseline potassium above the recommended level, which was also shown to be a strong predictor for severe postinitiation hyperkalaemia. Among monitored patients, a creatinine increase $\geq 30\%$ or a potassium level >6 mmol/L occurred in almost 1.5% of patients, and most did not discontinue therapy despite guideline recommendations to stop. Although patients

with prior myocardial infarction, hypertension or a high baseline potassium level were at higher risk of sudden decline in kidney function after ACEI/ARB initiation, there was no evidence that these patient groups were monitored more frequently while initiating the drugs.

Strengths and limitations

Several issues should be considered when interpreting our study results. Its large sample size increased precision. Use of the CPRD ensured that the study was general practice-based and not restricted to specific demographic, hospital or insurance groups.

Over the time course of this study, multiple factors have impacted on the prescribing of ACEI/ARB and measurement of renal function in primary care, for example, the introduction of the relevant NICE guidelines, and QOF reimbursement for testing in certain subgroups. We also did not have information about clinical initiatives such as heart failure nurses and ACEI/ARB stopping rules ('sick-day rules'). While our main results provide summary measures over a 10-year period, sensitivity analyses confirm that despite these changes, the proportion receiving the guideline suggested that biochemical monitoring does not vary during the study period. We did not have access to blood tests performed in hospital systems, which may have been reported to GPs, but not recorded in CPRD. However, restricting the analysis to patients with no recent hospital admissions who were most likely to have had renal function measured and acted on in secondary care had little effect on our findings. We did not examine testing during initiation of dual blockade with ACEI and ARB as this combination is now used very infrequently for patients with severe comorbidities who are likely to be monitored in secondary care. Although some patients may also have been seen in outpatient specialty clinics, it is common practice for specialists to ask GPs to initiate new drugs such as ACEI/ARBs, with local biochemical monitoring, limiting misclassification.

Consistent with findings from other studies,¹⁹ we found that $\sim 50\%$ of all ACEI/ARB initiators were monitored both before and after treatment start. If GPs are retesting renal function in patients at higher risk of substantial biochemical changes, we may have overestimated the proportion of patients with high potassium levels or creatinine increases compared with the untested lower-risk general population.

GP system software is used for issuing prescriptions, ensuring the accuracy of prescription data. However, it cannot be inferred that all patients actually redeemed their prescription at the pharmacy and started medication on the same day that it was prescribed.^{18 20} Similarly, the estimated coverage of prescriptions may not be completely accurate due to such factors as stock-piling and irregular use. We also do not know whether GPs contacted patients with elevated laboratory results to advise them to stop taking the medication prior to the end of their prescriptions. However, 80% of patients



who developed creatinine increase $\geq 30\%$ after ACEI/ARB initiation were still issued a subsequent ACEI/ARB prescription.

We aimed to detect discontinuation related closely in time to the first follow-up monitoring and hence most likely resulting from an elevated creatinine or potassium result. We therefore defined continuation as ACEI/ARB use beyond 30 days (the median prescription duration) after the monitoring date. Extending the definition of continuous use beyond 90 days reduced the risk of misclassifying patients as continuing treatment when they had in fact stopped. However, extending the duration also increased the risk of identifying discontinuation due to other reasons than creatinine/potassium increase, for example, death or cough. Diagnoses recorded in the CPRD generally have been found to have adequate validity for research purposes,^{21 22} particularly in the domains assessed by the QOF.^{23 24}

In the logistic regression analysis to estimate factors associated with creatinine increase $\geq 30\%$, we excluded patients without pre and post measurements (complete case analysis). If the recording of creatinine levels was not missing completely at random, the associations between patient characteristics and creatinine increase may have been underestimated.²⁵ While this assumption could not be tested directly, examination of baseline characteristics revealed no major differences in age, sex, socioeconomic status, and lifestyle between patients with and without premonitoring and postmonitoring. Furthermore, the results were consistent for each individual patient group examined. Patients with no testing before or after treatment initiation (including those with potentially haemolysed samples) only accounted for 10% of all ACEI/ARB initiators.

Comparison with other studies

To the best of our knowledge, this is the largest study conducted until now on adherence to monitoring and discontinuation guidelines after ACEI/ARB initiation. Only one previous study¹⁹ examined monitoring according to guideline-recommended intervals (<14 days). All others have used longer intervals (eg, 30 days²⁶ or 6 months^{27 28}), which make interpretations and implications for clinical practice less clear. Poor adherence to monitoring guidelines after ACEI/ARB initiation is not restricted to the UK,^{19 28 29} but has also been reported in the USA,^{30–32} Canada³³ and the Netherlands.^{26 34} Owing to our sample size, we were able to show that the lack of monitoring occurred in all patient groups with an indication for ACEI/ARB therapy.

A recent Dutch study, including 3353 patients initiating ACEI/ARBs between 2005 and 2011, found that 19% had creatinine measured within 30 days and 66% within 1 year.²⁶ Creatinine increases above 30% occurred in 1.6% of patients, and among these 70% did not discontinue treatment.²⁶ A Scottish study of 4056 patients with type 2 diabetes, prescribed an ACEI/ARB between

2005 and 2009, found that 19% had both a baseline (within 90 days) and follow-up measurement (within 2 weeks) of initiation. Within this cohort, 1.7% had both a creatinine increase of $\geq 30\%$ and potassium level ≥ 5.6 mmol/L.

The magnitude of the risk of severe renal impairment, as measured by creatinine increase in these observational studies, was consistent with our findings, but substantially higher than reported in clinical trials (eg, 0.2% in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)).³⁵ It is not clear from the literature how often harm occurs around the time of initiation, when the risk of nephrotoxicity is thought to be greatest.⁸ If physicians are to understand why follow-up monitoring within 2 weeks of treatment start matters, the short-term risks need to be clarified. Until now, most studies have reported only on cumulative risk over entire courses of treatment, such as the 1.1% 2-year risk for potassium of >6 mmol/L in the Studies of Left Ventricular Dysfunction (SOLVD) trials of patients with heart failure.³⁶ In contrast to clinical trial reviews, reporting a 0.2% (3/1818) risk of potassium >6 mmol/L, we found a 0.4% risk of hyperkalaemia already at the time of first retesting after ACEI initiation.

Extending the previous literature, our results support that advanced age, advanced CKD and heart failure, but not sex, increase the likelihood of being monitored.^{19 26 30} Consistent with some,^{26 30} but not all, previous studies,²⁸ we found no association for diabetes. However, these previous studies reporting an association for diabetes focused on monitoring within broader intervals (eg, 6 months),²⁸ where patients with diabetes, irrespective of ACEI/ARB initiation, were likely to receive blood testing owing to the diabetes QOF programme.

Determinants of increases in creatinine levels after ACEI/ARB initiation are less well understood than for hyperkalaemia, but increasing age is a consistently reported factor.¹⁹ Advanced CKD and a range of cardiovascular comorbidities (mostly associated with atherosclerosis) were also important determinants in our patient cohort. Consistent with previous studies, we found that the risk of hyperkalaemia was associated with CKD (most likely due to the impaired ability of the cortical collecting tubule to secrete potassium), heart failure (most likely due to the decreased delivery of sodium to the distal nephron), and high pretreatment potassium levels.^{6 8 19 37} We did not observe an association with diabetes or increasing age, as could have been expected due to diabetic nephropathy or age-dependent hyporeninaemic hypoaldosteronism.⁶

Clinical relevance

Several possible explanations exist for the divergence between the clinical guideline recommendations and the observed monitoring and response patterns in clinical practice. The first is *clinician non-adherence* to ordering tests. This may be due to inconsistent

recommendations for timing and frequency of monitoring over time,⁶ consensus-based (rather than evidence-based) monitoring guidelines, and a lack of guidelines tailored to particular high-risk patients, such as those with CKD and heart failure. Although we found that follow-up monitoring correlated well with the risk of renal impairment after ACEI/ARB initiation for most patient groups, it was not observed for patients with myocardial infarction or preinitiation high potassium. The second explanation may be *patient non-adherence* to ordered tests. This is particularly salient in UK primary care where blood samples may be taken in phlebotomy clinics that the patient has to visit rather than the GP practice. Patients may find it burdensome to have blood tests, and GPs have no direct economic incentives to ensure that they are done. A third barrier is *lack of evidence of the clinical importance* of monitoring and its cost-effectiveness. ACEI/ARB-induced renal impairment is rare in clinical trials, even among patients with multiple risk factors for atherosclerotic renal artery stenosis.^{8–38} Trial results may therefore have led to a general perception that the rarity of renal impairment obviates the need for close monitoring. However, as observed in our data, the risks in real-world practice may be somewhat higher and non-negligible. In addition, previous research has shown that potassium monitoring in high-risk patients with CKD and diabetes may reduce serious hyperkalaemia-associated adverse events.³⁹ Still, the extent to which an initial creatinine increase $\geq 30\%$ translates into adverse long-term outcomes in real-world patients remains to be clarified in future studies.

Generalisability, implications and conclusions

The majority of patients initiating treatment with ACEI/ARBs experience only minor changes in renal function. However, substantial increases in creatinine levels after ACEI/ARB initiation may not be as rare as previously suggested, reinforcing the need for adherence to clinical guidelines for both pre-initiating and post-initiating monitoring. Moreover, the postinitiation creatinine increase and potassium levels used in this study are widely recognised cut-off levels, making the results internationally applicable. The comparison with the previous literature also confirms that the lack of systematic monitoring is not exclusive to the UK. Of particular concern was that even when appropriate monitoring was performed, severe renal impairment only rarely led to treatment discontinuation. Individual patient counselling may also be helpful to ensure that those at highest risk are closely monitored. More work is needed to determine the prognostic importance of the changes in renal function that we have observed.

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