ONLINE SUPPLEMENTAL MATERIAL

eTable 1. Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating renin-angiotensin system blockade according to clinical guideline recommendations, overall and in most recent calendar period (extended version of Table 3)

	Clinical guidelines						All initiators		Continuing users*	
	NICE Heart Failure	NICE CKD	NICE Hypertension	NICE MI	UK Renal Association	GP Notebook	Generous baseline interpretation (≤12 month)	Strict baseline interpretation (≤1 month)	Generous baseline interpretation (≤12 month)	Strict baseline interpretation (≤1 month)
2004-2014							n=223,814 (100%)		n=173,244 (100%)	
Baseline testing	x	x	x	x	x	x	169,218 (76%)	75,476 (34%)	132,156 (76%)	58,668 (34%)
Follow-up test (≤2 weeks)†	x	x	n/a	x	x	x	46,486 (21%)	19,679 (9%)	43,420 (25%)	18,457 (11%)
+ At least within one year after				x			36,424 (16%)	15,642 (7%)	34,336 (20%)	14,800 (9%)
+ 1 month thereafter‡						x	11,866 (5%)	5,643 (3%)	11,298 (7%)	5,388 (3%)
+ 1 and 3 months thereafter ‡						x	5,787 (3%)	2,933 (1%)	5,516 (3%)	2,791 (2%)
+ 1, 3, and 6 months thereafter ‡						x	3,390 (2%)	1,807 (1%)	3,201 (2%)	1,703 (1%)
+ 1, 3, 6, and 12 months thereafter‡						x	2,618 (1%)	1,439 (1%)	2,464 (1%)	1,353 (1%)
Follow-up test (≤3 weeks)§							70,792 (32%)	30,451 (14%)	66,340 (38%)	28,644 (17%)
2009-2014							n=87,623 (100%)		n=68,042 (100%)	
Baseline testing	x	x	x	x	x	x	67,649 (77%)	30,576 (35%)	52,760 (78%)	23,716 (35%)
Follow-up test (≤2 weeks)†	x	x	n/a	x	x	x	20,172 (23%)	8,707 (10%)	18,862 (28%)	8,169 (12%)
+ At least within one year after				x			15,416 (18%)	6,726 (8%)	14,557 (21%)	6,377 (9%)
+ 1 month thereafter‡						x	5,373 (6%)	2,607 (3%)	5,123 (8%)	2,500 (4%)
+ 1 and 3 months thereafter ‡						x	2,614 (3%)	1,365 (2%)	2,492 (4%)	1,302 (2%)
+ 1, 3, and 6 months thereafter ‡						x	1,525 (2%)	841 (1%)	1,437 (2%)	792 (1%)
+ 1, 3, 6, and 12 months thereafter‡						x	1,152 (1%)	650 (1%)	1,079 (2%)	606 (1%)
Follow-up test (≤3 weeks)§							31,007 (35%)	13,511 (15%)	29,081 (43%)	12,726 (19%)

Abbreviations: CKD, chronic kidney disease; GP, General Practice; MI, myocardial infarction; n/a, not specified

* A patient was considered continuous users 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 stock piling and irregular use)

†Follow-up test among those with baseline measurements

‡Within additional 1, 3, 6, and 12 months after correspond to within 1.5, 3.5, 6.5, and 12.5 months after ACE/ARB initiation, respectively.

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

eTable 2. Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating angiotensin converting-enzyme inhibitors or angiotensin-receptor blockers, overall and most recent calendar period (extended version of Table 1)

	S-Creatinine, ≥1 test, n (%)	
	Total cohort (n=223,814)	2009-2014 cohort (n=87,623)
Baseline testing		
≤12 months before	169,218 (75.6)	67,649 (77.2)
≤3 months before	115,348 (51.5)	46,925 (53.6)
≤1 months before	75,476 (33.7)	30,576 (34.9)
Follow-up testing		
≤2 weeks after	65,090 (29.1)	27,933 (31.9)
≤1 month after	114,244 (51.0)	48,877 (55.8)
≤2 months after	139,044 (62.1)	58,334 (66.6)

eTable 3. Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating renin-angiotensin system blockade according to clinical guideline recommendations

	All initiators n=223,814 (100%)	
	Generous baseline interpretation (≤12 month)	**Strict baseline interpretation** (≤1 month)
Overall (n=223,814)		
Baseline testing	169,218 (76%)	75,476 (34%)
+ Follow-up test ≤2 weeks*	46,486 (21%)	19,679 (9%)
+ Follow-up test ≤3 weeks†	70,792 (32%)	30,451 (14%)
Overall, no recent hospitalization (n=197,291)		
Baseline testing	153,353 (78%)	68,883 (35%)
+ Follow-up test ≤2 weeks*	42,967 (22%)	18,222 (9%)
+ Follow-up test ≤3 weeks†	65,881 (33%)	28,375 (14%)
Heart failure patients (n=10,807)		
Baseline testing	7,853 (73%)	3,277 (30%)
+ Follow-up test ≤2 weeks*	2,229 (21%)	951 (9%)
+ Follow-up test ≤3 weeks†	3,085 (29%)	1,340 (12%)
Myocardial infarction patients (n=16,357)		
Baseline testing	9,273 (57%)	3,766 (23%)
+ Follow-up test ≤2 weeks*	1,816 (11%)	726 (4%)
+ Follow-up test ≤3 weeks†	2,645 (16%)	1,078 (7%)
Hypertension patients (n=162,437)		
Baseline testing	125,219 (77%)	54,174 (33%)
+ Follow-up test ≤2 weeks*	35,502 (22%)	14,559 (9%)
+ Follow-up test ≤3 weeks†	54,585 (34%)	22,710 (14%)
CKD patients (n=31,399)		
Baseline testing	27,961 (89%)	13,913 (44%)
+ Follow-up test ≤2 weeks*	8,457 (27%)	4,198 (13%)
+ Follow-up test ≤3 weeks†	12,482 (40%)	6,324 (20%)
PAD patients (n=5,131)		
Baseline testing	4,137 (81%)	1,671 (33%)
+ Follow-up test ≤2 weeks*	1,198 (23%)	458 (9%)
+ Follow-up test ≤3 weeks†	1,751 (34%)	698 (14%)
Diabetes patients (n=38,525)		
Baseline testing	35,134 (91%)	15,907 (41%)
+ Follow-up test ≤2 weeks*	9,161 (24%)	3,794 (10%)
+ Follow-up test ≤3 weeks†	14,093 (37%)	5,994 (16%)

Abbreviations: CKD, chronic kidney disease

*Follow-up test among those with baseline measurements

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

eTable 4: Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating renin-angiotensin system blockade according to clinical guideline recommendations, stratified by year of ACEI/ARB initiation, 2004-2014

	All initiators n=223,814		**2004/2005** n=51,529		**2006/2007** n=59,881		**2008/2009** n=47,472		**2010/2011** n=37,183		**2012/2014** n=27,749	
	Wide baseline interval (≤12 month)	Ideal baseline interval (≤1 month)	Wide baseline interval (≤12 month)	Ideal baseline interval (≤1 month)	Wide baseline interval (≤12 month)	Ideal baseline interval (≤1 month)	Wide baseline interval (≤12 month)	Ideal baseline interval (≤1 month)	Wide baseline interval (≤12 month)	Ideal baseline interval (≤1 month)	Wide baseline interval (≤12 month)	Ideal baseline interval (≤1 month)
Baseline testing	169,218 (76%)	75,476 (34%)	36,649 (71%)	14,710 (29%)	45,801 (76%)	21,079 (35%)	36,585 (77%)	17,265 (36%)	28,740 (77%)	13,045 (35%)	21,443 (77%)	9,377 (34%)
+ Follow-up test ≤2 weeks*	46,486 (21%)	19,679 (9%)	8,139 (16%)	2,929 (6%)	12,587 (21%)	5,509 (9%)	10,595 (22%)	4,769 (10%)	8,609 (23%)	3,720 (10%)	6,556 (24%)	2,752 (10%)
+ Follow-up test ≤3 weeks†	70,792 (32%)	30,451 (14%)	12,222 (24%)	4,550 (9%)	19,102 (32%)	8,504 (14%)	16,229 (34%)	7,392 (16%)	13,185 (35%)	5,768 (16%)	10,054 (36%)	4,237 (15%)

*Follow-up test among those with baseline measurements

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

eTable 5. Proportion of new users of ACEI/ARB who continue or discontinue treatment according to guideline recommended cut-off levels of serum creatinine and potassium at follow-up testing

	Wide monitoring interval (12 month before to the first monitoring within 2 month after)			**Narrow monitoring interval (1 month before to the first monitoring within 2 month after)**		
	Continuation*	Discontinuation*	Total	Continuation*	Discontinuation*	Total
+ 30 day window						
Total number, %	113,210 (92.5)	9,170 (7.5)	122,380 (100)	48,772 (93.0)	3,676 (7.0)	52,448 (100)
S-creatinine increase ≥30%, n (%)	1,679 (80.7)	401 (19.3)	2,080 (100)	541 (81.5)	123 (18.5)	664 (100)
S-potassium >6 mmol/L, n (%)	472 (81.9)	104 (18.1)	576 (100)	204 (80.6)	49 (19.4)	253 (100)
+ 90 day window						
Total number, %	86,620 (81.8)	19,239 (18.2)	105,859 (100)	37,920 (82.2)	8,200 (17.8)	46,120 (100)
S-creatinine increase ≥30%, n (%)	1,111 (64.7)	605 (35.3)	1,716 (100)	372 (65.6)	195 (34.4)	567 (100)
S-potassium >6 mmol/L, n (%)	261 (61.0)	167 (39.0)	428 (100)	110 (57.6)	81 (42.4)	191 (100)

Calculated from the measurements closest to the first prescription date in the corresponding intervals, i.e., the most recent baseline measurements and the first follow-up measurement.

* A patient was considered continuous users when the end date of the first continuous course of therapy was larger than the date of the first follow-up monitoring + 30 days or + 90days (to allow for stock piling and irregular use)

eTable 6. Association between patient characteristics and serum creatinine increase ≥30% and follow-up monitoring within 2 weeks following initiation of renin-angiotensin system blockade

	Adjusted odds ratio (95% confidence intervals)					
	Additional adjustment for ethnicity†			Excluding patient with hospitalisation within 30 days†		
Characteristics	**S-creatinine monitoring within 2 weeks**	**S-creatinine increase ≥30%***	**S-potassium >6 mmol/L***	**S-creatinine monitoring within 2 weeks**	**S-creatinine increase ≥30%***	**S-potassium >6 mmol/L***
Female sex	1.04 (1.01-1.08)	1.91 (1.64-2.23)	1.09 (0.70-1.71)	1.06 (1.04-1.09)	1.66 (1.48-1.86)	0.94 (0.69-1.27)
Age (years)						
< 50 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
50-59 years	0.97 (0.92-1.02)	0.91 (0.71-1.16)	1.65 (0.77-3.52)	0.99 (0.95-1.03)	0.86 (0.71-1.05)	1.17 (0.70-1.98)
60-69 years	1.04 (0.99-1.10)	0.86 (0.68-1.10)	1.23 (0.57-2.65)	1.07 (1.02-1.11)	1.05 (0.87-1.26)	0.98 (0.58-1.64)
70-79 years	1.22 (1.15-1.30)	1.22 (0.96-1.55)	0.83 (0.36-1.95)	1.19 (1.14-1.24)	1.40 (1.16-1.68)	0.72 (0.41-1.27)
80+ years	1.15 (1.06-1.24)	1.61 (1.21-2.14)	0.58 (0.21-1.58)	1.17 (1.11-1.24)	2.16 (1.76-2.66)	0.71 (0.38-1.33)
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 (0.94-1.06)	0.51 (0.39-0.66)	1.82 (0.93-3.55)	1.00 (0.96-1.04)	0.58 (0.49-0.70)	2.40 (1.57-3.68)
Stage 3b (30–44)	1.06 (0.95-1.17)	0.99 (0.71-1.39)	5.66 (2.70-11.9)	0.98 (0.92-1.06)	0.92 (0.73-1.17)	5.15 (3.09-8.58)
Stage 4 (15–29)	1.51 (1.17-1.94)	1.65 (0.87-3.12)	15.0 (5.84-38.8)	1.42 (1.20-1.70)	1.86 (1.23-2.81)	12.2 (6.29-23.7)
Comorbidities*						
Heart failure	1.10 (0.99-1.21)	3.07 (2.41-3.91)	2.16 (0.96-4.85)	1.15 (1.06-1.24)	2.57 (2.11-3.13)	2.68 (1.59-4.51)
MI	0.78 (0.72-0.86)	1.76 (1.35-2.30)	1.10 (0.46-2.63)	0.89 (0.82-0.97)	1.59 (1.23-2.06)	1.89 (1.05-3.41)
Hypertension	0.97 (0.90-1.05)	1.51 (1.19-1.92)	1.01 (0.44-2.30)	1.04 (0.99-1.11)	1.40 (1.16-1.68)	0.81 (0.46-1.42)
PAD	1.09 (0.96-1.23)	1.63 (1.13-2.35)	1.52 (0.54-4.29)	1.16 (1.06-1.26)	1.74 (1.34-2.27)	1.75 (0.92-3.32)
Arrhythmia	0.96 (0.92-1.01)	0.84 (0.71-0.99)	0.72 (0.44-1.17)	0.98 (0.94-1.01)	0.80 (0.71-0.91)	0.74 (0.53-1.03)
Diabetes mellitus	0.91 (0.87-0.96)	1.15 (0.96-1.37)	0.58 (0.31-1.09)	0.93 (0.90-0.96)	1.06 (0.93-1.22)	0.93 (0.64-1.35)
Baseline K>6 mmol/L	1.05 (0.98-1.13)	0.86 (0.63-1.15)	7.98 (5.06-12.6)	1.03 (0.98-1.08)	1.01 (0.82-1.24)	6.44 (4.69-8.84)

Abbreviations: CKD, chronic kidney disease; MI, myocardial infarction; PAD, peripheral arterial disease

* 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).

† The main model was adjusted for sex, age, CKD, heart failure, MI, hypertension, PAD, arrhythmia, diabetes, and calendar period of prescription start