Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin–angiotensin system inhibitors in the community increases the risk of acute kidney injury

Tobias Dreischulte[1,2], Daniel R. Morales[1], Samira Bell[1] and Bruce Guthrie[1]

[1]Population Health Sciences Division, Medical Research Institute, University of Dundee, Dundee, UK and [2]NHS Tayside Medicines Governance Unit, Dundee, UK

Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of acute kidney injury (AKI) when used in triple combination with renin–angiotensin system inhibitors and diuretics, but previous research reported that NSAIDs in dual combinations with either renin–angiotensin system inhibitors or diuretics alone were not. However, earlier studies relied on hospital coding to define AKI, which may underestimate true risk. This nested case–control study characterized the risk of community-acquired AKI associated with NSAID use among 78,379 users of renin–angiotensin system inhibitors and/or diuretics, where AKI was defined as a 50% or greater increase in creatinine from baseline. The AKI incidence was 68/10,000 person-years. The relative increase in AKI risk was similar for NSAID use in both triple (adjusted rate ratio 1.64 (95% CI 1.25–2.14)) and dual combinations with either renin–angiotensin system inhibitors (1.60 (1.18–2.17)) or diuretics (1.64 (1.17–2.29)). However, the absolute increase in AKI risk was higher for NSAIDs used in triple versus dual combinations with renin–angiotensin system inhibitors or diuretics alone (numbers needed to harm for 1 year treatment with NSAID of 158 vs. over 300). AKI risk was highest among users of loop diuretic/aldosterone antagonist combinations, in those over 75 years of age, and in those with renal impairment. Thus, the nephrotoxic potential of both dual and triple combinations of NSAIDs with renin–angiotensin system inhibitors and/or diuretics yields a higher incidence of AKI than previously thought.

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KEYWORDS: acute kidney injury; angiotensin-converting enzyme inhibitor; angiotensin II type 2 receptor blockers; diuretics; nonsteroidal anti-inflammatory agents

Correspondence: *Tobias Dreischulte, NHS Tayside Medicines Governance Unit c/o University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee DD2 4BF, UK. E-mail: t.dreischulte@dundee.ac.uk*

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The incidence of acute kidney injury (AKI) is rising globally and it is increasingly recognized that even relatively small rises of serum creatinine are associated with subsequent chronic and end-stage kidney disease and death.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) are estimated to account for up to 7% of all cases of AKI and up to 36% of drug-induced cases.[2,3] NSAID exposure has been reported to increase the risk of AKI between 1.3- and 4.1-fold and the number needed to harm (NNH) with recent NSAID treatment has been estimated to range from 400 to 12,000 per year, depending on study populations and definitions of AKI used.[4–9]

The adverse renal effects of NSAIDs are primarily mediated by inhibiting the prostaglandin-mediated dilation of the afferent renal arteriole.[10] Prostaglandins do not usually have a major role in maintaining renal blood flow, but their effect may become crucial in situations of volume depletion, especially when the angiotensin-II-mediated constriction of the efferent renal arteriole is blocked. The renal risks of NSAIDs may therefore be particularly high in users of renin–angiotensin system inhibitors (RASIs) and/or diuretics, and the term 'triple whammy' was first coined in 2000 to highlight the potential nephrotoxic effects of combining all three drug classes.[11] A single case–control study demonstrated the renal adverse effects of the 'triple whammy' combination but did not find an increased AKI risk for dual combinations of NSAIDs with RASIs or diuretics alone.[8] However, similar to previous studies of NSAID-associated AKI risk,[4–9] this study relied on hospital discharge coding to identify AKI, which may underestimate true AKI risk, because AKI is commonly under-recorded in hospital discharge data.[12]

NSAIDs are effective analgesics and widely used in the management of acute and chronic pain, especially in the elderly, who also often take RASIs and diuretics for heart failure or cardioprevention. In a recent large cross-sectional study in the United Kingdom, 8.8% of patients aged 65 years and over prescribed RASIs and diuretics received at least one NSAID prescription per year.[13] Clinicians and patients therefore need robust information on the magnitude of renal risk associated with NSAIDs in this scenario. The aim of this

nested case–control study was to examine the risk of community-acquired AKI (measured using laboratory data) associated with exposure to NSAIDs among users of RASIs and/or diuretics and variations in AKI risk by diuretic regimen, baseline renal function, and age.

RESULTS

Background incidence of AKI

The dynamic study cohort comprised 78,379 patients aged 30 years or older (without prior AKI or otherwise unstable renal function) prescribed RASIs or diuretics at cohort entry (Figure 1). A total of 2804 cases of community-acquired AKI were identified, of which 2226 cases occurred during 327,491 person-years of exposure to RASIs and/or diuretics (incidence rate 68/10,000 patient years), and 1952 cases occurred during RASIs and/or diuretic exposure without concurrent NSAID exposure. Table 1 shows that the background AKI incidence was comparable under monotherapy with RASIs and diuretics, but doubled under treatment with both (99/10,000 patient years). Among diuretic regimens, AKI incidence was highest under loop diuretic/aldosterone antagonist treatment. Background AKI incidence was higher in people with renal impairment than without and increased with age. When only AKI events with emergency hospital admission were considered, incidence rates were considerably lower, but the relative differences among diuretics, renal function, and age strata were similar.

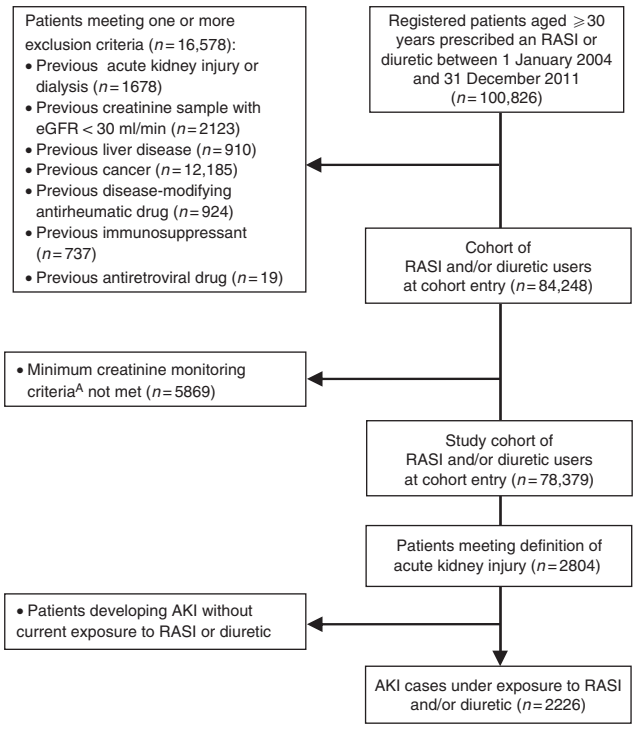

Figure 1 | Flow chart of the study. eGFR, estimated glomerular filtration rate; RASI, renin–angiotensin system inhibitor; A, at least one creatinine sample during follow-up and at least one further sample (at least 7 days apart) during follow-up or within a year before cohort entry.

Baseline characteristics of cases and matched controls

Table 2 shows the demographics of the 2226 cases of AKI identified and 21,206 matched controls. Compared with controls, cases were older, had lower baseline renal function at their respective index dates, and were more frequently dispensed drugs for intercurrent illness, started on a diuretic, and admitted to hospital recently, and more likely to have a history of vascular disease, and to have used insulin or oral corticosteroids within the previous year.

AKI outcomes

Table 3 shows that AKI cases were much more likely than matched controls to be hospitalized as an emergency within 7 days (1304 (58.6%) cases vs. 939 (4.4%) controls) and to die within 30 days (309 (13.9%) cases vs. 60 (0.3%) controls) of their respective index dates (i.e. AKI onset for cases, selection date for controls). Hospitalized patients had more severe AKI and higher 30-day mortality rates than patients managed in ambulatory care (20.7% vs. 4.2%), but non-admitted patients with AKI had a much higher mortality than controls (4.2% vs. 0.16%). Of hospitalized patients with laboratory-defined AKI, only 43.4% had any AKI discharge code.

AKI risk associated with NSAIDs

Table 4 shows the stratum-specific rate ratios and NNHs associated with NSAID exposure. Among users of any combination of RASI and/or diuretics, NSAID use was associated with a 66% increased risk of AKI (adjusted rate ratio 1.66; NNH for treatment with an NSAID for 1 year, 237). When we stratified by single or combined use of RASIs and diuretics, the adjusted rate ratios were similar and significantly elevated for both dual and the triple combination, but the absolute risk difference was much higher (NNH 158 vs. >300) for the triple combination, owing to the higher background AKI incidence under RASI/diuretic combination therapy (Table 1).

Stratification by diuretic regimen showed elevated adjusted rate ratios for NSAIDs among users of all diuretic regimens (statistically significant for thiazides and loop diuretic/aldosterone antagonist combinations), where the risk was highest for NSAID use among users of loop diuretic/aldosterone antagonist combinations (adjusted rate ratio 3.98; NNH = 10).

Stratification by renal function showed significantly elevated adjusted rate ratios irrespective of baseline renal function, but a higher risk among those with than those without renal impairment (adjusted rate ratio 2.51 vs. 1.60; NNH = 75 vs. 309).

Stratification by age showed elevated adjusted rate ratios for NSAID users of all ages (statistically significant for patients aged 60 years or older), but a higher adjusted rate ratio (2.64 vs. <1.50) and much higher absolute risk difference in patients aged 75 years or older (NNH = 68 vs. >400).

Sensitivity analyses

In several prespecified sensitivity analyses, we found results generally consistent with the primary analyses, when (1) restricting the cohort to incident users of RASIs or diuretics;

Table 1 | Stratum-specific background incidence rates of community-acquired AKI in a dynamic cohort of RASI or diuretic users (*n* = 78,379) followed up for a total of 444,127 person-years

Exposure	Person-years exposed (% of total)	No. of community-acquired AKI events (incidence/10,000 years exposed (95% CI))	
		Any AKI	AKI with emergency admission within 7 days of AKI onset
Any RASI or diuretic without concurrent NSAID	304,121 (68.5)	1952 (64 (61, 67))	1158 (38 (36, 40))
Stratification by dual/triple combination			
RASI only without concurrent NSAID	117,373 (26.4)	559 (48 (44, 51))	321 (27 (24, 31))
Diuretic only without concurrent NSAID	85,205 (19.2)	389 (46 (41, 50))	258 (30 (27, 34))
RASI plus diuretic without concurrent NSAID	101,544 (22.9)	1004 (99 (93, 105))	579 (57 (52, 62))
Stratification by diuretic regimen			
Thiazide without loop diuretic or aldosterone antagonist without concurrent NSAID[a]	133,811 (30.1)	541 (40 (37, 44))	279 (21 (18, 23))
Loop diuretic without aldosterone antagonist without concurrent NSAID[b]	46,820 (10.5)	605 (129 (119, 139)	392 (84 (76, 92))
Loop diuretic plus aldosterone antagonist without concurrent NSAID[b]	6117 (1.4)	199 (325 (283, 374))	135 (221 (186, 261))
Stratification by renal function			
RASI and/or diuretic with eGFR 30–59 ml/min without concurrent NSAID	93,679 (21.1)	824 (88 (82, 94))	560 (60 (55, 65))
RASI and/or diuretic with eGFR ≥ 60 ml/min without concurrent NSAID	210,442 (47.4)	1128 (54 (50, 57))	598 (28 (26, 31))
Stratification by age			
RASI and/or diuretic without concurrent NSAID and aged <60 years	78,153 (17.6)	335 (43 (38, 48))	179 (23 (20, 27))
RASI and/or diuretic without concurrent NSAID and aged 60–74 years	133,190 (30.0)	782 (59 (55, 63))	435 (32 (30, 36))
RASI and/or diuretic without concurrent NSAID and aged 75 years or older	92,778 (20.9)	835 (90 (84, 96))	586 (59 [(54, 64))

Abbreviations: AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; RASI, renin–angiotensin system inhibitor.
[a]Includes cotreatment with amiloride or triamterene.
[b]Includes cotreatment with thiazides and/or amiloride triamterene.

(2) excluding people with hospitalization during the 30-day risk window; excluding cases (3) who died within 30 days, (4) with AKI stage 1, (5) without emergency admissions; (6) dropping the continuous exposure assumptions for RASIs and thiazide diuretics; (7) restricting exposures to those overlapping the index date; (8) additionally matching cases and controls by general practice; (9) excluding patients who were started on an RASI or diuretic during the risk window, distinguishing between (10) chronic and (11) acute NSAID exposure; and (12) when adjusting by a propensity score for NSAID exposure. However, there were three partial exceptions. First, acute NSAID exposure was associated with a higher risk of AKI than chronic NSAID exposure among patients treated with diuretics alone (3.40 vs. 1.32). Second, restricting the case definition to AKI stages 2 and 3 yielded a considerably lower adjusted rate ratio for the dual combination of NSAIDs with RASIs (0.89 vs. 1.60). Third, restricting the case definition to those with emergency admissions yielded lower adjusted rate ratios (ranging from 1.27 to 1.40), which is similar to a previous hospital-based study.[8] When we (13) extended the risk window of exposure to 60, 90, 180, and 360 days and the entire follow-up period, the risk estimates increased as the risk window became narrower, which is consistent with increasing exposure misclassification and supports the 30-day risk window. See Supplementary Material online for details.

DISCUSSION

Within a cohort of RASI and/or diuretic users (aged 30 years or older), the incidence of community-acquired AKI measured using laboratory data was 68/10,000 patient years, which was much higher than in previous studies in the general population relying on hospital discharge coding of AKI (0.25 to 7/10,000 patient years).[4,5,7–9] Of those developing AKI in this study, more than half (58.6%) were hospitalized as an emergency within 7 days, and 13.9% died within 30 days (13 and 49 times more than controls, respectively). Even among those with AKI who were not admitted, 30-day mortality was 4.2%, underlining the clinical significance of identified AKI events.

We found that NSAID use was associated with a significantly increased AKI risk overall (adjusted rate ratio 1.66; annual NNH = 237), where the annual NNH from NSAID use was much lower than in previous studies relying on hospital discharge coding of AKI (0.25 to 7/10,000 patient years; NNH > 4000).[4,5,7–9] We found that NSAID use is associated with a significantly increased AKI risk when used in triple combination with RASIs and diuretics but (in contrast to a recent study measuring AKI using hospital discharge codes[8]) also when used in dual combination with RASIs or diuretics alone. We found lower adjusted rate ratios more consistent with the previous study[8] when we restricted analysis to hospitalized cases of AKI in sensitivity analysis, demonstrating that relying on hospital discharge coding to define AKI and

Table 2 | Demographics of cases and controls matched by gender, follow-up time, incident user status, background treatment with RASIs and/or diuretics, and renal monitoring pattern

Variable	Control ($n = 21,206$)	Case ($n = 2226$)
Matching factors		
Male	9842 (46.4)	1040 (46.7)
Mean (s.d.) years of follow-up at index date	4.3 (2.2)	4.3 (2.2)
Cohort entry 2004–2006	19,001 (89.6)	1976 (88.8)
Cohort entry 2007–2009	1865 (8.8)	208 (9.3)
Cohort entry 2010–2012	340 (1.6)	42 (1.9)
Incident user of RASI or diuretic at cohort entry	7704 (36.3)	848 (38.1)
Exposure to RASI or diuretics in 30-day risk window		
RASI monotherapy	6265 (29.5)	629 (28.3)
Diuretic monotherapy	4215 (19.9)	463 (20.8)
Thiazide only	1647 (7.8)	169 (7.6)
Loop diuretic without aldosterone antagonist	2262 (10.7)	240 (10.8)
Loop diuretic plus aldosterone antagonist	248 (1.2)	38 (1.7)
'Other diuretic use'	58 (0.3)	16 (0.7)
RASI plus diuretic	10,726 (50.6)	1134 (50.9)
Thiazide only	4778 (22.5)	480 (21.6)
Loop diuretic without aldosterone antagonist	4221 (19.9)	439 (19.7)
Loop diuretic plus aldosterone antagonist	1429 (6.7)	176 (7.9)
'Other diuretic use'	298 (1.4)	39 (1.8)
Other potential confounders		
Creatinine measurements (as outpatients)		
Available before cohort entry	19,812 (93.4)	2091 (93.9)
Median (IQR) days between last creatinine measurement and cohort entry	114 (37, 287)	105 (30, 266)
NOT available before cohort entry	1394 (6.6)	135 (6.1)
Median (IQR) days between cohort entry and first creatinine measurement	79 (19, 291)	71 (20, 241)
Age and baseline renal function at index date		
Mean (s.d.) age at index date (years)	69.9 (11.7)	71.6 (11.7)
Mean (s.d.) baseline renal function at index date (eGFR in ml/min)	91.2 (25.9)	67.7 (21.7)
Previous hospital diagnoses		
Hypertension	5008 (23.6)	698 (31.4)
Peripheral arterial disease	1077 (5.1)	181 (8.1)
Stroke or transient ischemic attack	983 (4.6)	164 (7.4)
Acute coronary syndrome	2908 (13.7)	315 (14.2)
Heart failure	1842 (8.7)	265 (11.9)
Drug use within 30-day risk window		
Antibiotic	2264 (10.7)	605 (27.2)
Laxative	836 (3.9)	185 (8.3)
Drug used for diarrhea or vomiting	696 (3.3)	250 (11.2)
RASI started[a]	466 (2.2)	48 (2.2)
Diuretic started[a]	964 (4.5)	182 (8.2)
Previous hospital admission		
Within 30-day risk window	708 (3.3)	352 (15.8)
Within 31 to 180 days before index date	2351 (11.1)	480 (21.6)
Drug use within 360 days before index date		
Aspirin (without warfarin, clopidogrel, or dipyridamole)	6427 (30.3)	659 (29.6)
Clopidogrel or dipyridamole (without warfarin)	2615 (12.3)	365 (16.4)
Warfarin	2219 (10.5)	256 (11.5)
Statins	13,200 (62.2)	1345 (60.4)
β-Blocker	7982 (37.6)	890 (40.0)
Calcium channel blocker	12,696 (59.9)	1354 (60.8)
α-Blockers	1717 (8.1)	182 (8.2)
Antianginals	4476 (21.1)	514 (23.1)
Antiarrhythmics	276 (1.3)	27 (1.2)
Digoxin	1149 (5.4)	130 (5.8)
Oral antidiabetics (without insulin)	3892 (18.4)	399 (17.9)
Insulin	1082 (5.1)	165 (7.4)
Oral corticosteroid	1751 (8.3)	275 (12.4)

Abbreviations: IQR, interquartile range; RASI, renin–angiotensin system inhibitor.
Figures are numbers (percentages), unless stated otherwise.
[a]Dispensed prescription within 30-day risk window without a further dispensed prescription in the 180 days before the reference prescription.

Table 3 | Outcomes of cases of AKI and controls, differentiating between those with and without emergency hospital admission within 7 days of AKI onset (for cases) and selection date (for controls)

Patients	Controls ($n = 21,206$)	Cases of AKI			
		All stages ($n = 2226$)	Stage 1 ($n = 1356$)	Stage 2 ($n = 467$)	Stage 3 ($n = 403$)
Admitted to hospital					
Total	939 (100.0)	1304 (100.0)	591 (100.0)	355 (100.0)	358 (100.0)
AKI recorded at discharge	6 (0.64)	566 (43.4)	148 (25.0)	173 (48.7)	245 (68.4)
Died within 30 days	28 (3.0)	270 (20.7)	77 (13.0)	95 (26.8)	98 (27.4)
Not admitted to hospital					
Total	20,267 (100.0)	922 (100.0)	765 (100.0)	112 (100.0)	45 (100.0)
Died within 30 days	32 (0.16)	39 (4.2)	17 (2.2)	13 (11.6)	9 (20.0)

Abbreviation: AKI, acute kidney injury.

Table 4 | Stratum-specific current use of NSAIDs and associated risk of AKI among users of renin–angiotensin system inhibitors and/or diuretics

Exposure		Controls (%), $n = 21,206$	Cases (%), $n = 2226$	RR crude[a]	RR adjusted[a,b]	NNH/year
Background treatment	**NSAID**					
Overall						
Any RASI or diuretic	No	19,461 (91.8)	1952 (87.7)	1.59**	1.66**	237
	Yes	1745 (8.2)	274 (12.3)	(1.38, 1.82)	(1.40, 1.97)	
Stratification by single/combined use of RASI/diuretic						
RASI only	No	5803 (92.6)	559 (88.9)	1.58**	1.60**	347
	Yes	462 (7.4)	70 (11.1)	(1.21, 2.06)	(1.18, 2.17)	
Diuretic only	No	3774 (89.5)	390 (84.0)	1.69**	1.64**	340
	Yes	441 (10.5)	74 (16.0)	(1.28, 2.21)	(1.17, 2.29)	
RASI plus diuretic	No	9884 (92.1)	1004 (88.5)	1.54**	1.64**	158
	Yes	842 (7.9)	130 (11.5)	(1.26, 1.87)	(1.25, 2.14)	
Stratification by diuretic regimen						
Thiazide alone[c]	No	5866 (91.3)	541 (83.4)	2.10**	1.97**	258
	Yes	559 (8.7)	108 (16.6)	(1.68, 2.63)	(1.49, 2.61)	
Loop diuretic without aldosterone antagonist[d]	No	5886 (90.8)	605 (89.1)	1.20	1.18	431
	Yes	597 (9.2)	74 (10.9)	(0.93, 1.55)	(0.83, 1.66)	
Loop diuretic plus aldosterone antagonist[d]	No	1575 (93.9)	199 (93.0)	1.24	3.98*	10
	Yes	102 (6.1)	15 (7.0)	(0.68, 2.24)	(1.20, 13.2)	
Stratification by renal function						
Any RASI or diuretic and eGFR ≥ 60 ml/min	No	18 050 (91.9)	1 128 (87.0)	1.76**	1.60**	309
	Yes	1598 (8.1)	168 (13.0)	(1.43, 2.10)	(1.31, 1.95)	
Any RASI or diuretic and eGFR 30–59 ml/min	No	1 411 (90.6)	824 (88.6)	0.86	2.51*	75
	Yes	147 (9.4)	106 (11.4)	(0.53, 1.38)	(1.09, 5.78)	
Stratification by age						
Any RASI or diuretic and aged <60 years	No	4074 (89.7)	335 (84.8)	1.53*	1.34	684
	Yes	467 (10.3)	60 (15.2)	(1.05, 2.24)	(0.86, 2.07)	
Any RASI or diuretic and aged 60–74 years	No	8398 (90.5)	782 (85.9)	1.52**	1.41*	413
	Yes	877 (9.5)	128 (14.1)	(1.21, 1.90)	(1.07, 1.87)	
Any RASI or diuretic and aged 75 years or older	No	6989 (94.6)	835 (90.7)	2.04**	2.64**	68
	Yes	401 (5.4)	86 (9.3)	(1.54, 2.71)	(1.50, 4.64)	

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; NNH, number needed to harm; NSAID, nonsteroidal anti-inflammatory drug; RASI, renin–angiotensin system inhibitor; RR, rate ratio.

*P-value <0.05; **P-value <0.01.

[a]No NSAID exposure served as the reference; cases and controls matched on calendar year of cohort entry, follow-up duration at index date, prevalent user status, renal monitoring pattern, and background treatment with RASIs and/or diuretic, with diuretics stratified as thiazide alone, loop diuretic without aldosterone antagonist, loop diuretic plus aldosterone antagonist, and 'other'.

[b]Adjusted for age at index date, baseline renal function at index date, and those potential confounders listed in Table 2 that were significantly associated with AKI in the multivariate model (at $P<0.05$ level) or altered the rate ratio for NSAID exposure by $\geqslant 10\%$.

[c]Excludes patients treated with loop diuretics or aldosterone antagonists.

[d]Includes patients also treated with thiazide diuretics.

excluding AKI events managed in the community may underestimate both AKI incidence and NSAID risk. Despite similar adjusted rate ratios, we nevertheless found that the absolute increase in AKI risk was much higher (and the annual NNH much lower) for NSAID use in triple than in dual combination with RASIs and/or diuretics (NNH = 158 vs. >300) because of the higher background AKI incidence rate under RASI/diuretic combination therapy.

Our study showed that the AKI risk associated with NSAIDs varied considerably (both in terms of adjusted rate ratios and NNH) by background diuretic regimen, baseline renal function, and age, suggesting that the risk of developing AKI is highest (in both absolute and relative terms) when NSAIDs are used in patients with additional risk factors for AKI, that is, advanced age, renal impairment, and loop diuretic/aldosterone antagonist combination treatment (which is typically used to treat heart failure).

A major strength of our study is the availability of creatinine data, which enabled us to implement current consensus definitions to identify AKI,[14] to adjust for current baseline renal function in statistical models, and to separately evaluate AKI risk in patients with moderate renal impairment (chronic kidney disease (CKD) stage 3). The large differences in AKI risk found for different diuretic regimens, levels of renal function, and age will help to identify patients who are particularly vulnerable to the adverse renal effects of NSAIDs. We also provide absolute AKI risk estimates (NNH) that were previously unavailable in this population of patients, supporting risk communication to clinicians and patients.[15]

Our study also has some limitations. First, using routine creatinine data to define AKI implies the risk of detection bias, which may affect both (1) background AKI incidence rates (and therefore NNH) and (2) adjusted rate ratios. However, with respect to (1), we found similar differences in AKI risk among strata of background treatment, baseline renal function, and age when only AKI events detected at hospital admission were considered (Table 1), where creatinine is routinely measured and detection bias is therefore not at issue. With respect to (2), we minimized the risk of detection bias by matching cases and controls on renal monitoring pattern (ensuring that AKI is detectable at the point of selection as controls), and additionally by matching on, or statistically adjusting for factors associated with AKI risk and therefore likely intensity of renal monitoring (e.g. age, baseline renal function, RASI/diuretic treatment regimen). Second, confounding by indication or contraindication is a general concern in pharmacoepidemiology, although matching on or adjusting for indications and relative contraindications (e.g. age, renal impairment, cardiovascular comorbidity) for NSAIDs will have minimized the risk of such confounding. Third, we were unable to control for exposure to iodinated radiocontrast media and other triggers of AKI (e.g. hypovolemia or sepsis) as potential confounders, although we adjusted for proxies of intercurrent illness (dispensation of antibiotics and drugs to treat diarrhea and vomiting within the risk window). Finally, we were unable to account for over-the-counter use of NSAIDs, although we expect such use to be relatively low in National Health Service (NHS) Scotland (during the period of analysis, all prescriptions were free to people aged 65 years or older and free or capped for many younger people with chronic diseases), and previous research suggests that even if the proportion of over-the-counter use was as high as 80%, it would not substantially alter our results.[16]

Our findings have important implications for research and practice. The higher incidence of AKI found in our study is concerning, especially since over half of all patients with AKI were hospitalized and AKI events managed in hospital and community were associated with much higher mortality than matched controls, with a 30-day mortality of 4.2% even in non-admitted AKI cases.[17] In addition, it is likely that our risk estimates are conservative, as patients with unstable renal function and those with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 ml/min) were excluded. Further research into the longer-term prognosis of AKI managed in ambulatory care is needed.

In some patients with severe or incapacitating pain, NSAIDs may be the least bad option, but our findings suggest that combined use of NSAIDs with RASIs and diuretics should be restricted to clinical situations without acceptable alternatives, especially in people treated with both RASIs and diuretics, those taking combinations of loop diuretics and aldosterone antagonists, and those with renal impairment and older people. Where NSAIDs are considered to be essential, the risk of AKI may be reduced by stopping NSAIDs and other drugs during periods of volume depletion due to intercurrent illness or by intensifying monitoring.[4] It is also worth noting that people treated with RASIs or diuretics are very likely to have other relative contraindications to NSAIDs including an elevated risk of cardiovascular events and higher risk of gastrointestinal bleeding by virtue of age or antithrombotic coprescription.[18,19] These risks, in addition to the higher renal risks identified in this study, will need to be balanced against any expected benefits from NSAID use.[20]

MATERIALS AND METHODS

Study design and setting

The study design was a case–control study nested in a population cohort of adults aged 30 years or older who were prescribed a diuretic or RASI between January 2004 and December 2011 and were registered with an NHS general practitioner in Tayside, Scotland. The Tayside population comprises ~405,000 people (representative of Scotland in terms of age and socioeconomic status) and residents have universal access to free health care. We used fully anonymized data. NHS Research Ethics review was not required.

Data sources

We used health-care databases held by the University of Dundee/NHS Health Informatics Centre, which holds data on all Tayside residents registered with an NHS Tayside general practice (e.g. demographics, hospitalizations, dispensed prescriptions, laboratory tests obtained electronically from the central laboratory system, dates of registration/deregistration with a general practice). Registration

with a general practice is required to obtain NHS care and each patient has a unique identifier, which enables data linkage.

Study cohort

Cohort entry was the date of a first dispensed prescription of an RASI or diuretic, on or after 1 January 2004, after each subject's 30th birthday, and at least 1 year after registration with a Tayside general practice. Individuals prescribed an RASI or diuretic before cohort entry were defined as 'prevalent' users.

Exclusion criteria were a previous history of AKI, eGFR <30 ml/min, and conditions or drug exposures associated with acute renal deterioration (hepatitis or liver cirrhosis, cancer, use of immunosuppressants, disease-modifying antirheumatic drugs, or antiretroviral agents). All patients had to have at least two creatinine measurements (>7 days apart), of which at least one was during follow-up. Membership in the cohort was dynamic, that is, patients were allowed to move in and out of the cohort as they stopped and restarted treatment with RASIs or diuretics. Patients meeting the inclusion criteria were followed up until the first occurrence of either AKI, any of the above exclusion criteria (including a first eGFR <30 ml/min), death, deregistration with NHS Tayside, or end of the study period (31 December 2011). For an illustration of cohort and exposure definitions, see Figure 2.

Definition of baseline renal function and AKI

Cases were individuals who developed community-acquired AKI, defined as a ≥ 1.5-fold increase in creatinine from baseline.[21] To identify AKI cases, all creatinine samples taken in ambulatory care or within a day following hospitalization were included. Baseline renal function was calculated as the mean of all outpatient creatinine levels available within 8 to 360 days before the reference sample (samples taken within 7 days before AKI may underestimate baseline renal function) and, if not available, within 30 to 90 days after the reference sample (assuming AKI resolved).[22,23] The index date was the date of incident AKI. Using the maximum creatinine within 7 days of the index date, we staged AKI as stage 1 ($\geq$1.5- to $<$2-fold increased creatinine), stage 2 (2- to $<$3-fold increase), or stage 3 ($\geq$3-fold increase or maximum creatinine of 354 μmol/l or need for dialysis).[21] Details of the rationale for the case definition are provided in the Supplementary Material online.

Selection of controls

For each case, we selected up to 10 controls among those present in the cohort at the case index date and meeting the following matching criteria: sex, calendar year of cohort entry, prevalent user status, duration of follow-up ± 90 days, 'background treatment', and 'renal monitoring pattern'. 'Background treatment' comprised nine strata: RASI alone, diuretic alone (stratified as (a) thiazide without loop diuretic or aldosterone antagonist, (b) loop diuretic without aldosterone antagonist, (c) loop diuretic plus aldosterone antagonist, (d) any other regimen), and RASI plus diuretic with the same four diuretic strata. Matching on background treatment in this cohort of RASI and/or diuretic users aimed to further minimize confounding by indication (e.g. thiazide monotherapy is mainly used for hypertension, while RASI/loop diuretic combinations are commonly used in heart failure). Matching on 'renal monitoring pattern' aimed to minimize detection bias by requiring that eligible controls had to have at least two creatinine measurements (the minimum number required to detect AKI), that is, at least one within ± 90 days of the case index date (marking the 'control index date'), and at least one within 8 to 360 days of the control index date. At the point of being matched to a case, controls were thus alive, registered with an NHS Tayside general practice, had an equal duration of follow-up to cases, were on the same RASI/diuretic regimen as cases, and had no previous AKI or severe renal impairment but sufficient creatinine measurements to allow AKI detection (if it had occurred).

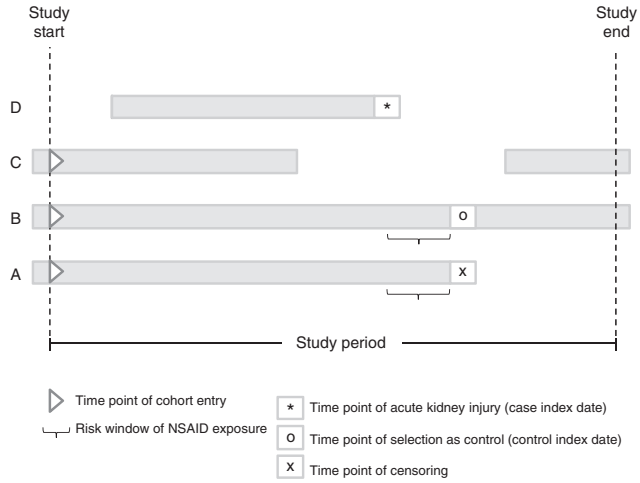

Figure 2 | Illustration of the dynamic study cohort and medication exposure. The figure shows four exemplary patients (A–D) who enter the cohort with their first prescription of a renin–angiotensin inhibitor (RASI) or a diuretic during the study period. Patient D is an incident user of an RASI or diuretic at the cohort entry, whereas the other patients are prevalent users. Only patient B remains a member of the cohort from the study start to end. Patient A exits the cohort at the point of developing acute kidney injury, patient C at the point of no longer being exposed to an RASI or a diuretic (but re-enters when diuretic or RASI treatment is restarted), and patient D is censored at the point of meeting one or more exclusion criteria. Only patient B is eligible as a control for patient A, because all other patients are not members of the cohort at the time that patient A became a case.

Exposure assessment

Drug exposures of interest were 'recent' use of NSAIDs (excluding low-dose aspirin and topicals) in combination with RASIs and/or diuretics. 'Recent' exposure was defined as drug coverage within 30 days before index dates. We chose a 30-day risk window, as lag effects are not plausible because of the likely mechanism of renal injury (inhibition of prostaglandin-mediated mechanisms in response to an acute reduction in renal perfusion) and the pharmacokinetic properties of NSAIDs (half-life is 24 h or less). The duration of drug coverage was calculated as the number of dispensed doses divided by the number of prescribed doses per day. For RASIs and thiazide diuretics, we assumed continuous exposure if a prescription was followed by a further prescription within 180 days. Otherwise, exposure ended with the last day of calculated drug coverage.

Potential confounders

In addition to the matching factors, we considered a number of factors that may influence exposure to NSAIDs, the risk of AKI or its detection. These included age at index date, baseline renal function at index date (the mean outpatient creatinine within 8 to 360 days before or (if not available) 30 to 90 days after index dates), history of cardiovascular morbidities (hospital diagnoses, use of antidiabetic, and cardiovascular drugs in the year before index dates), prior

hospital admission, proxies for intercurrent illness (current use of antibiotics or gastrointestinal drugs), and initiation of RASIs or diuretics during the risk window (as factors that may precipitate AKI) (see Table 2).[24,25]

Statistical analysis

We compared the risk of AKI associated with NSAID exposure to no NSAID exposure among users of the same background treatment with RASIs and/or diuretic regimen. We used PROC LOGISTIC, SAS version 9.3 (SAS Institute, Cary, NC),[26] for conditional logistic regression analyses, yielding odds ratios that (under the design of this nested case–control study) provided unbiased estimates of the rate ratios and 95% confidence intervals.[27] In addition to the matching variables on which the logistic regression was conditioned, all statistical models were adjusted for age and baseline renal function at index date and the confounders listed in Table 2.

The background AKI incidence rates in periods without NSAID exposure was calculated by dividing the number of incident cases by person-years spent in each stratum of RASI/diuretic exposure, renal function, and age.[28] These were multiplied by the adjusted rate ratios for NSAID exposure, yielding strata-specific adjusted AKI incidence rates under additional NSAID exposure. The absolute difference in AKI between periods exposed and unexposed to NSAIDs was used to calculate the number of patients needing to be treated for 1 year, for one additional AKI event to occur (NNH).

DISCLOSURE

Study design, data analysis, interpretation and publication were the responsibility of the research team who had sole access to the data. All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

TD and BG conceived of the study. TD led on the study design, wrote the study protocol, and conducted the data analysis, with input from DRM and BG. TD wrote the manuscript. All authors contributed to the interpretation of analysis findings, commented on iterative drafts of the manuscript, and approved the final manuscript version.

SUPPLEMENTARY MATERIAL

Figure S1. Illustration of how episodes of AKI were identified from creatinine data.

Figure S2. Distribution of propensity scores for NSAIDs for cases and controls.

Table S1. Sensitivity analyses.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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