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

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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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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.

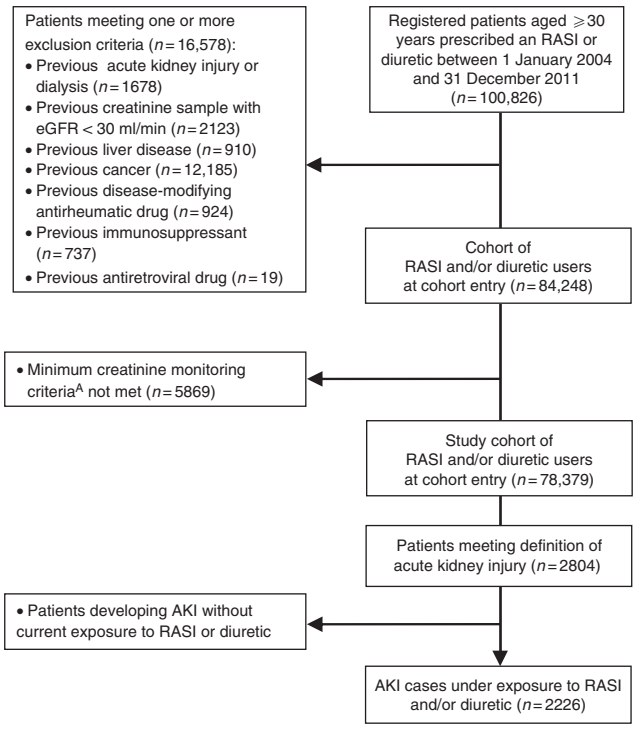

Figure 1 | Flow chart of the study. eGFR, estimated glomerular filtration rate; RASI, renin–angiotensin system inhibitor; A, at least one creatinine sample during follow-up and at least one further sample (at least 7 days apart) during follow-up or within a year before cohort entry.

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;