ORIGINAL RESEARCH

Burden of Renal Events Associated with Nonsteroidal Anti-inflammatory Drugs in Patients with Osteoarthritis and Chronic Low Back Pain: A Retrospective Database Study

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ABSTRACT

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) have long-term benefits but are limited by side effects. We assessed the health and economic burden of renal events associated with NSAID use in patients with osteoarthritis (OA) and/or chronic low back pain (CLBP).

Methods: This retrospective, large-scale, medical claims database study of Japanese patients receiving NSAIDs for OA and/or CLBP between 2009 and 2018 assessed the incidence of renal events and effect of treatment duration, mode of administration, and usage consistency of NSAIDs.

Results: Of 180,371 patients, NSAIDs were prescribed as first-line analgesics in 89.3%.

Incidence per 10,000 person-years (95% confidence interval [CI]) for renal events was 23.46 (21.84–25.08) and for progression of chronic kidney disease (CKD) was 267.12 (189.93–344.32). Longer treatment duration (> 1 to ≤ 3 years, risk ratio [RR] 1.32, 95% CI 1.12–1.54; $P = 0.0007$; > 3 to ≤ 5 years, RR: 1.38, 95% CI 1.04–1.84; $P = 0.0254$ vs. < 1 year) and consistent use (RR: 1.24, 95% CI 0.99–1.55; $P = 0.0595$) increased the risk of renal events but the latter did not reach statistical significance. The risk was similar in patients using patch/oral NSAIDs and high in elderly patients and in those with diabetes, hypertension, and other cardiovascular disease. Following a renal event, median 1-year cost of drug treatment was $27.90; hospitalization, $1779.40; and dialysis, $33,018.40.

Conclusions: Risk of renal events significantly increased with prolonged and consistent NSAID use (irrespective of mode of administration), with age, and in patients with certain comorbidities. Careful NSAID use is recommended in patients with CKD and those at high risk for CKD.

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PLAIN LANGUAGE SUMMARY

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in patients with osteoarthritis (OA) and/or chronic low back

pain (CLBP) for pain relief but their use is limited by side effects. These side effects may include abdominal, heart, and kidney problems. This article presents the results from a large claims database study in Japan that assessed the incidence of renal events and the associated healthcare cost. Impact of NSAIDs treatment duration, mode of administration, and usage consistency on the risk of developing renal events was evaluated. Results showed high incidence of renal events and progression of chronic kidney disease. Longer treatment duration and consistent use increased the risk of developing renal events. The risk was similar in patients using patch/oral NSAIDs and high in elderly patients and those with diabetes, hypertension, and other heart diseases. The estimated cost of drug treatment, hospitalization, and dialysis was also high. The author of the study would recommend NSAIDs to be used carefully in patients at risk for (or with) chronic kidney disease.

Key Summary Points

Why carry out this study?

Patients with osteoarthritis (OA) and/or chronic low back pain (CLBP) require long-term nonsteroidal anti-inflammatory drugs (NSAIDs) use. However, the side effects of long-term NSAIDs use limits its benefits in these patients.

Additionally, the data concerning the risk of renal events and the associated cost of renal events with long-term NSAID use in terms of treatment duration, usage consistency, and the mode of administration in these patients are limited.

We aimed to assess the health and economic burden of renal events associated with NSAID use in patients with OA and/or CLBP.

What was learned from the study?

This retrospective database study shows that prolonged and consistent NSAID use increases the risk of renal events.

Elderly patients and patients with diabetes, hypertension, and other cardiovascular disease are at increased risk of developing renal events.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and a plain language summary, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13469 589.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesic agents for treating pain associated with osteoarthritis (OA) and chronic low back pain (CLBP) [1, 2]. In Japan, ~ 25.3 million people aged > 40 years have OA, and the prevalence of CLBP is $\sim 15.4\%$ in people aged > 50 years [3, 4]. As the elderly population is expected to rise in Japan, one would also expect to see an increase in the prevalence of patients with OA and CLBP. Currently, NSAID formulations, including oral pills and patches, are widely used to treat patients with OA and CLBP. Transdermal NSAID patches have demonstrated a superior safety profile over oral NSAIDs, and are recommended as first-line treatment for knee [5] and hip OA by the Osteoarthritis Research Society International (OARSI) guidelines [6]. In Japan, NSAIDs are also the commonly recommended and prescribed analgesics for CLBP [7].

NSAIDs exert anti-inflammatory, analgesic, and antipyretic effects by inhibiting cyclooxygenases (COX-1 and COX-2) and this consequently suppresses prostaglandin and thromboxane synthesis [8]. Prostaglandins play a crucial role in the regulation of renin release, electrolyte balance, and vascular tone [9]. Thus, patients using NSAIDs are susceptible to renal adverse events such as reduced glomerular filtration rate, acute kidney injury (AKI), renal papillary necrosis, nephrotic syndrome, acute interstitial nephritis (mainly due to hypersensitivity reaction), and chronic kidney disease (CKD), in addition to fluid and electrolyte retention [10]. Between 1% and 5% of NSAID users develop renal adverse effects [11]. Evidence indicates an approximately two–to–threefold increase in the risk of AKI in patients treated with NSAIDs, and this risk is reported to further increase in older adults with pre-existing CKD and in those using high-dose or longer half-life NSAIDs [12–18]. Progression of CKD can trigger the need for dialysis, the medical cost of which is a critical problem in Japan. There are approximately 320,000 patients receiving dialysis in Japan as of 2017, and the annual medical costs for dialysis are estimated at 1.6 trillion yen [19]. Japan has the most rapidly aging elderly population in the world; consequently, the population on dialysis is also growing.

An association between NSAID use and occurrence of renal events has been demonstrated in numerous large-scale, real-world database studies [16, 20–24]. However, these studies did not assess the impact of duration of NSAID use on the risk of renal events, which is particularly important for patients with OA and CLBP as these conditions usually require long-term treatment. Continuous or intermittent use as identified by prescription re-fill is also likely to affect the risk of renal events that has not been accounted for in previous studies. Although patch NSAIDs are considered safe, the risk of developing renal events in patients using a patch compared to oral NSAIDs when used for longer duration has not been evaluated so far. In addition, data concerning the cost of renal events associated with long-term use of NSAIDs

remain scarce. To address this knowledge gap, we conducted a large database study evaluating the safety profile of NSAIDs in employed patients with CLBP and/or OA using data from the Japan Medical Data Center Co, Ltd (now JMDC Inc.). The study aimed to assess NSAID treatment characteristics that could increase the risk of renal events and identify patients who are at high risk of developing renal events. We also report the incidence of progression of CKD in a subgroup of patients who had renal comorbidities at baseline.

METHODS

Study Design and Population

This was a retrospective database analysis using anonymized claims data from the JMDC database. It is the largest claims database commercially available in Japan, and contains all claims across multiple medical institutions and can track patients who have changed institutions. It contains claims data from health insurance associations for company employees and their family members. Japan has a universal healthcare system, and the National Health Insurance covers people ≥ 75 years old and the membership to the original health insurance society is terminated upon reaching the age of 75 years, so JMDC does not cover claims of patients who are ≥ 75 years old.

The inclusion criteria were patients aged ≥ 18 years at index date with an initial diagnosis of OA or CLBP (per World Health Organization International Classification of Diseases, 10th revision, ICD-10) who visited healthcare facilities between 2009 and 2018. The index date was defined as the date when the first prescription of analgesic was given after the initial diagnosis of OA or CLBP. Patients taking ≥ 2 prescriptions of the same or different analgesics with ≥ 1-month gap after initial OA/CLBP diagnosis were included. These patients were not required to have any prescriptions for analgesics in the baseline period (6 months from the index date). Patients were excluded if they had malignancy (ICD10 codes: C00-C97,

D00-D09) after the initial diagnosis of OA or CLBP. The ICD-10 diagnosis of OA was defined by the codes M16 and M1, and CLBP was confirmed by at least two ICD-10 low back pain diagnoses (M40, M41, M43, M45–M48, and M50–M54). Diseases excluded from chronic low back pain are included in Table S1 (see in the electronic supplementary material).

Exposure

The exposure period of NSAIDs ended on the day when the first event occurred in patients with a renal event. The NSAID treatment variables were duration of treatment, mode of administration (oral drugs, patch, other transdermal drugs), and consistency of NSAID use. Categories of treatment duration were > 0 to 1 year, > 1 to ≤ 3 years, > 3 to ≤ 5 years, and > 5 years. Consistent NSAID use was defined as a percentage of the number of supply days in a total treatment duration of ≥ 70%, and intermittent use was identified as a percentage of the number of supply days in a total treatment duration of < 70%.

Study Outcomes

Incidence of renal disease (renal events) and progression of CKD, and their medical costs were assessed. Renal events included acute/chronic tubulointerstitial nephritis, NSAID nephropathy, drug-induced renal disease, AKI, CKD, and end-stage renal failure (see Table S2 in the electronic supplementary material). Although the disease names of interstitial nephritis and drug-induced renal disease should be the events related to NSAID use, broad terms of acute/chronic renal failure or kidney disease are commonly used in medical practice; thus, 'renal events' included these conditions in patients who did not have them at baseline. Progression of CKD was defined as initiation of dialysis after treatment with NSAIDs in patients with comorbidity of renal disease without dialysis at baseline.

Costs of drug treatment, dialysis, and hospitalization constituted healthcare resource utilization data. The total costs of drug treatment and hospitalization were calculated for 12 months after onset of the event. The basic direct cost of dialysis started when a patient underwent dialysis for 12 months after NSAID treatment.

Statistical Analysis

All analyses were done using SAS version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables are summarized using descriptive statistics or frequencies for dichotomous and polychotomous variables of categorical data. An alpha level of < 0.05 was considered statistically significant. The crude incidence (per 10,000 person-years) of renal events with its 95% confidence interval (CI) was calculated. An overdispersed Poisson regression model using the SAS GLIMMIX procedure was used to identify factors affecting incidence of renal events with covariates of age at index date, gender, baseline comorbidities of diabetes mellitus, gastrointestinal, and cardiovascular (CV) disease. However, model analysis was not performed for the progression of CKD because of the anticipated small sample size owing to a low percentage of patients with renal disease at baseline.

Ethics Statement

As this study involved anonymized structured data, which according to applicable legal requirements did not contain data subject to privacy laws, obtaining informed consent from patients was not required. As Japanese Ethical Guidelines [25] for 'Medical and Health Research Involving Human Subjects' do not apply to studies that use anonymized secondary data, this study was not reviewed by an institutional review board/research ethics committee.

RESULTS

Patient Disposition and NSAID Treatment

Of 628,488 patients diagnosed with OA or CLBP who used analgesics at least once in the JMDC
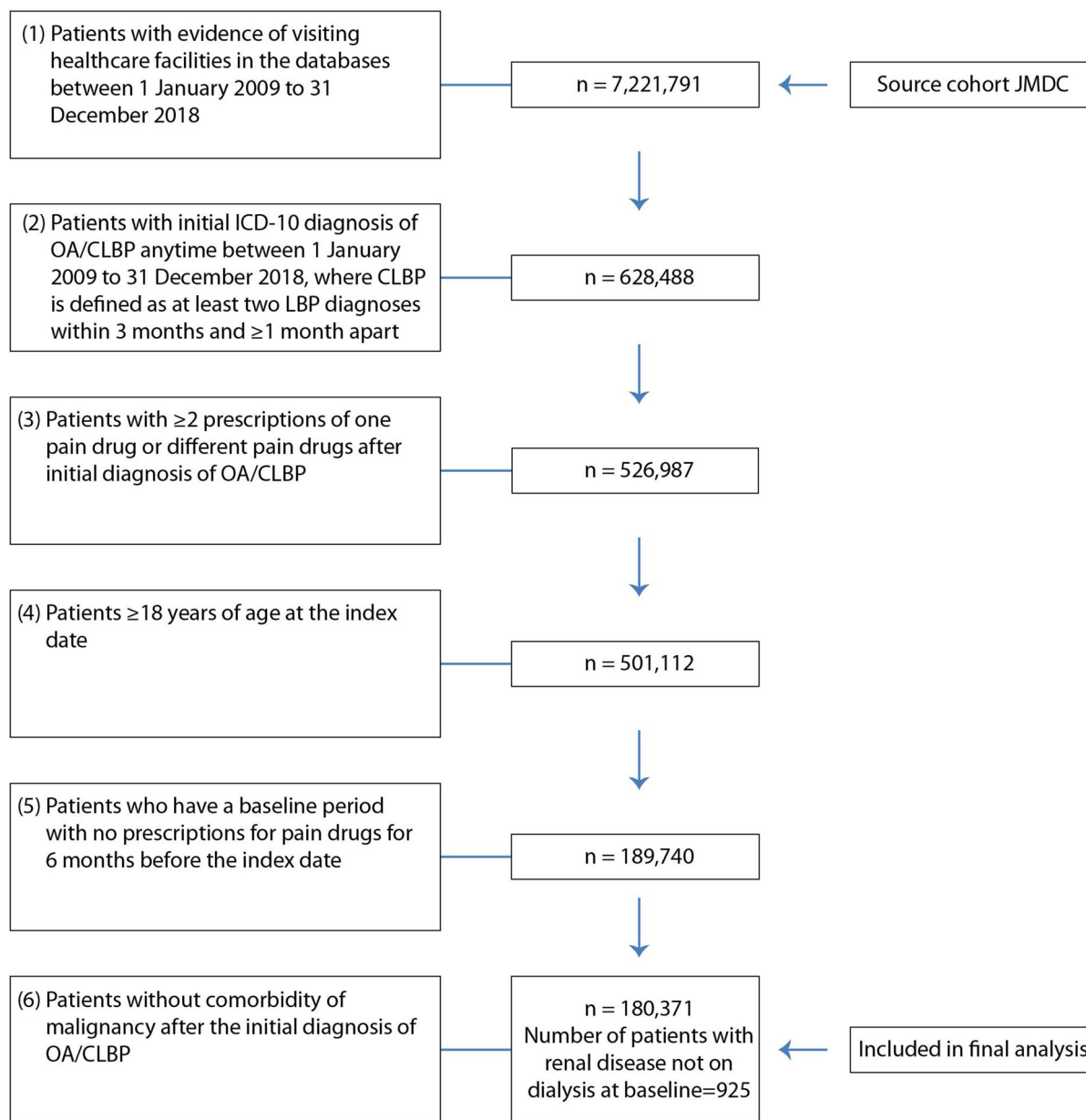
Fig. 1 Patient disposition. *CLBP* chronic low back pain, *ICD-10* International Classification of Disease-10, *JMDC* Japan Medical Data Center, *LBP* low back pain, *OA* osteoarthritis

database, 180,371 met the eligibility criteria and were included in this analysis (Fig. 1). A total of 32.9% patients had OA, 53.8% had CLBP, and 13.4% had both OA and CLBP. Diabetes was reported in 11.8% patients, and hypertension in 21.9%. Renal comorbidities were present in 1454 (0.8%) patients (Table 1).

NSAIDs were prescribed as first-line analgesics to 161,152 (89.3%) patients: oral to

90.3%; patches to 80.4%; and other transdermal drugs to 24.0% (see Table S3 in the electronic supplementary material). In a subgroup of patients with renal comorbidities at baseline ($n = 1186$), 76.9% were administered oral NSAIDs and 85.6% received NSAIDs patches as the first-line analgesic (see Table S3 in the electronic supplementary material). A total of 83.8% and 77.5% of patients used NSAIDs for

Table 1 Patient demographic and clinical characteristics

Characteristics	All patients (N = 180,371)	Patients with renal disease not on dialysis at baseline (n = 925)
Age at index date (years), mean ± SD	49.3 ± 11.8	56.3 ± 10.18
Age categories (years), n (%)		
18 to < 30	12,244 (6.8)	12 (1.3)
30 to < 40	24,319 (13.5)	49 (5.3)
40 to < 50	47,068 (26.1)	156 (16.9)
50 to < 60	59,447 (33.0)	323 (34.9)
60 to < 70	32,646 (18.1)	307 (33.2)
70 to ≤ 75	4647 (2.6)	78 (8.4)
Male gender, n (%)	92,650 (51.4)	615 (66.5)
Diagnosis, n (%)		
OA	59,318 (32.9)	243 (26.3)
CLBP	96,959 (53.8)	527 (57.0)
Both OA and CLBP	24,094 (13.4)	155 (16.8)
Affected joints in OA patients, n (%)		
Coxarthrosis	11,765 (14.1)	47 (5.1)
Gonarthrosis	71,647 (85.9)	286 (30.9)
Comorbidities, n (%)		
GI disease	14,285 (7.9)	184 (19.9)
Renal disease	1454 (0.8)	NA
CV disease (excluding hypertensive disease)	24,238 (13.4)	420 (45.4)
Hypertension	39,413 (21.9)	672 (72.6)
Diabetes mellitus	21,240 (11.8)	428 (46.3)

CLBP chronic low back pain, *CV* cardiovascular, *GI* gastrointestinal, *OA* osteoarthritis, *NA* not applicable

up to 1 year in the total study population and those who had renal comorbidities at baseline, respectively. Combination of oral and patch NSAIDs was used by 65.1% and 52.7% of patients in the whole study population and those who had renal comorbidities at baseline, respectively (see Table S4 in the electronic supplementary material).

Renal Events

The incidence rate of renal events was 23.46/ 10,000 person-years (95% CI 21.84–25.08) in the study population. Of 806 renal events, the most common were CKD (45.2%), chronic renal failure (35.7%), and acute renal failure (8.8%) (see Table S5 in the electronic supplementary material).

The event rate was higher in patients who used NSAIDs for ≥ 1 year: > 0 to ≤ 1 year, 20.37 (95% CI 18.59–22.14); > 1 to ≤ 3 years, 30.64 (95% CI 26.67–34.61); > 3 to ≤ 5 years, 36.10 (95% CI 26.73–45.47); and ≥ 5 years, 29.95 (95% CI 14.79–45.10). However, it should be noted that the number of patients who used NSAIDs for ≥ 5 years in this study was very low (15 events/755 patients). The incidence was also higher in patients who used NSAIDs consistently compared to those who did not (37.45 [95% CI 30.28–44.61] vs. 22.22 [95% CI 20.58–23.87]). Similarly, the risk of renal events was higher in patients who only used patch NSAIDs compared to oral NSAIDs only (32.49 [95% CI 22.16–42.82] vs. 19.76 [95% CI 14.88–24.64]) (Table 2). After adjusting the covariates, age, sex, and comorbidities in the multivariate analysis, the duration of treatment was a significant factor that increased the risk of developing renal events (> 1 to ≤ 3 years, risk ratio [RR] 1.32, 95% CI 1.12–1.54; P = 0.0007; > 3 to ≤ 5 years, RR: 1.38, 95% CI 1.04–1.84; P = 0.0254) while consistency of use was not statistically significant but showed a trend towards increasing the risk of developing renal events (RR: 1.24, 95% CI 0.99–1.55; P = 0.0595) (Table 3). The risk of developing renal events was similar in patients using only patch or only oral NSAIDs (RR: 0.97, 95% CI 0.64–1.46; P = 0.8650) in the multivariate

Table 2 Incidence of renal events stratified as per treatment duration, consistency of use, and mode of administration

Treatment characteristic	Renal events		
	N	n of patients with event	Incidence rate per 10,000 person-years (95% CI)
Total	159,966	806	23.46 (21.84–25.08)
NSAID treatment duration, years			
> 0 to ≤ 1	134,117	505	20.37 (18.59–22.14)
> 1 to ≤ 3	21,908	229	30.64 (26.67–34.61)
> 3 to ≤ 5	3186	57	36.10 (26.73–45.47)
≥ 5	755	15	29.95 (14.79–45.10)
Percentage of supply days during treatment period			
< 70%	126,467	701	22.22 (20.58–23.87)
≥ 70%	33, 499	105	37.45 (30.28–44.61)
Mode of administration			
Oral	21,536	63	19.76 (14.88–24.64)
Patch	11,096	38	32.49 (22.16–42.82)
Combination of oral and non-oral[a]			
Yes	69,377	316	21.83 (19.42–24.24)
No	90,589	490	24.65 (22.47–26.84)

CI confidence interval, *NSAID* nonsteroidal anti-inflammatory drug

[a] Non-oral includes topical including patch, other transdermal drugs (cream, gel, liquid, lotion, ointment), and suppository

Table 3 Multivariate model analysis with covariates for the renal event

Covariates	Risk ratio (95% CI)	P value
Age, years vs. 18 to < 30 years		
30 to < 40	1.03 (0.59–1.80)	0.9249
40 to < 50	2.08 (1.26–3.42)	0.0041
50 to < 60	2.96 (1.81–4.83)	< 0.0001
60 to < 70	4.10 (2.49–6.74)	< 0.0001
70 to ≤ 80	6.88 (3.91–12.09)	< 0.0001
Gender, male vs. female	1.88 (1.62–2.18)	< 0.0001
Baseline GI	0.92 (0.64–1.32)	0.6576
Baseline CV	1.46 (1.15–1.87)	0.0022
Baseline hypertension	1.63 (1.26–2.10)	0.0002
Baseline diabetes mellitus	1.97 (1.53–2.55)	< 0.0001
Duration of treatment, years vs. < 1 year		
> 1 to ≤ 3	1.32 (1.12–1.54)	0.0007
> 3 to ≤ 5	1.38 (1.04–1.84)	0.0254
≥ 5	1.19 (0.70–2.01)	0.5298
Consistent use of NSAIDs, percentage of supply days ≥ 70% vs. < 70%	1.24 (0.99–1.55)	0.0595
Method of administration compared to oral		
Patch	0.97 (0.64–1.46)	0.8650
Other[a]	0.99 (0.75–1.30)	0.9321
Combination use	0.88 (0.76–1.02)	0.0963

CI confidence interval, *CV* cardiovascular, *GI* gastrointestinal, *NSAIDs* nonsteroidal anti-inflammatory drugs

[a] Other is transdermal drugs other than patch (cream, gel, liquid, lotion, ointment) and suppository

analysis. The risk of renal events was found to significantly increase with increasing age, and the risk was threefold higher in patients aged 70–80 years compared to those who were 40–50 years (40 to < 50 years, RR: 2.08, 95% CI 1.26–3.42; *P* = 0.0041; 70 to ≤ 80 years, RR: 6.88, 95% CI 3.91–12.09; *P* < 0.0001). Among other comorbid conditions (hypertension and other CV diseases), diabetes was shown to increase the risk twofold (RR: 1.97, 95% CI

1.53–2.55; *P* < 0.0001). The incidence of progression of CKD was 267.12/10,000 person-years (95% CI 189.93–344.32) (Table 4). Compared with the whole study population, patients with renal disease at baseline were older, predominantly men, and had higher prevalence of

Table 4 Incidence of progression of CKD in patients with renal disease not on dialysis at baseline

Treatment characteristic	Progression of CKD		
	N	n of patients with event	Incidence rate per 10,000 person-years (95% CI)
Total	925	46	267.12 (189.93–344.32)
NSAID treatment duration, years			
> 0 to ≤ 1	737	29	254.38 (161.79–346.96)
> 1 to ≤ 3	158	12	268.83 (116.73–420.93)
> 3 to ≤ 5	23	4	413.00 (8.26–817.74)
≥ 5	7	1	257.95 (0.00–763.49)
Percentage of supply days during treatment period			
< 70%	675	41	278.28 (193.10–363.46)
≥ 70%	250	5	201.05 (24.83–377.27)
Mode of administration			
Oral	102	0	NC
Patch	140	3	207.57 (0.00–442.45)
Combination of oral and non-oral			
Yes	354	13	189.15 (86.33–291.97)
No	571	33	318.91 (210.10–427.72)

Lower limit of confidence interval was truncated at zero
CI confidence interval, *CKD* chronic kidney disease, *NC* confidence interval was not computed as there was no event in patients using oral NSAIDs, *NSAID* nonsteroidal anti-inflammatory drug

diabetes, hypertension, and other CV disease (Table 1). The pattern of renal events and that of progression of CKD remained similar for both OA and CLBP patients (see Tables S6 and S7 in the electronic supplementary material).

Table 5 Health resource utilization due to renal events

Criteria	Cost ($)	
	N	Median (Q1–Q3)
Patients without renal disease at baseline who developed renal event		
Cost due to drug treatment for 1 year	60	27.90 (6.80–65.50)
Total cost of hospitalization due to renal events	9	1779.40 (1081.60–2857.00)
Patients with renal disease at baseline who underwent dialysis after treatment with NSAIDs		
Dialysis for the first month	44	2347.30 (1665.40–2657.60)
Dialysis for 1 year	26	33,018.40 (23,124.50–35,485.60)

NSAID nonsteroidal anti-inflammatory drug, *Q* quarter

Health Resource Utilization Due to Renal Events

The median (interquartile range [IQR]) cost of 1 year of drug treatment following a renal event was $27.90 (6.80–65.50). The median cost of hospitalization was $1779.40 (1081.60–2857.00) (Table 5). The median (IQR) length of hospital stay was 10 days (8–13). The cost of dialysis for the first month was $2347.30 (1665.40–2657.60) and for 1 year was $33,018.40 (23,124.50–35,485.60). The cost estimates remained similar for both OA and CLBP patients (see Table S8 in the electronic supplementary material).

DISCUSSION

This contemporary large-scale database study reports, for the first time, the incidence and economic burden of NSAID-associated renal events using claims data of medical insurance

beneficiaries employed by middle-to-large size companies in Japan. The incidence rate of renal events was 23.46 per 10,000 person-years (95% CI 21.84–25.08) that increased with longer duration of treatment. As expected, the incidence of renal events was higher in a subgroup of patients with renal comorbidities compared to the total study population.

The prevalence of CKD based on the glomerular filtration rates in Japanese adult population was estimated to be 13% [26]. As no studies have reported NSAID-associated renal events in the general Japanese population or in disease subgroups to date, our study may fill this gap and could contribute to optimal management of OA and CLBP patients in Japan. Although there are no data available even from outside of Japan to compare with the incidence rate in our study, the annual incidence of CKD was 13 per 10,000 for men and seven per 10,000 for women in a cohort study of the French general population [27]. The community-acquired incidence of AKI associated with NSAIDs was reported to be 68 per 10,000 person-years among 78,379 patients using renin–angiotensin system inhibitors and/or diuretics in the United Kingdom [28]. Our study results, showing an increased risk of renal events with longer duration of treatment, is consistent with previous studies that have shown that long-term use of NSAIDs is associated with unfavorable renal outcomes [20, 21]. This finding is quite important given the current guidelines recommend against long-term NSAID-use [5, 7]. The reasons for their long-term use in Japan may be due to the preference of patch NSAIDs over other forms of NSAIDs and that the upper limit to the number of patches that can prescribed at a time is regulated by the Japanese government. NSAIDs may decrease renal blood flow, induce precipitation of crystals leading to tubular obstruction, exert direct cytotoxicity, and activate cell-mediated immune injury mechanisms, resulting in AKI [29]. Interstitial nephritis is another common pathological change caused by NSAIDs that may require renal biopsy and specialist management with immunosuppressants, and may progress to CKD [29].

In this study, elderly patients and patients with diabetes, hypertension, and other CV disease were at high risk of developing renal events, which is in agreement with previous reports [30, 31]. In these patients, the autoregulation of renal blood flow is impaired, and consistent long-term use of NSAIDs may aggravate the reduction in blood flow [32]. Further, as hypertension and heart failure are often prevalent in elderly patients with chronic pain, the co-prescription of angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, or diuretics with NSAIDs is common; this has the potential to compromise renal blood flow and contribute to worsening of renal ischemia [33, 34]. Interestingly, the risk of renal events was similar in patients using oral or patch NSAIDs in our study indicating that switching patients from oral to patch NSAIDs in these high-risk patients would not offer any additional benefits in reducing risk of renal events. Although systemic exposure of topical NSAIDs is reported to be lower than that of the oral NSAIDs, repeated use or a high dose of topical NSAIDs may increase systemic concentration approaching that of oral NSAIDs.

Importantly, studies show that numbers of adverse events, however low, are observed even in patients using topical NSAIDs [35, 36]. Moreover, data comparing renal adverse effects between topical and systemic NSAIDs when they are used consistently over the long term are lacking. Therefore, appropriate assessment of medical history regarding comorbid hypertension or heart failure should be performed if NSAIDs are required to relieve pain in patients with CKD or who are at higher risk of developing CKD. NSAIDs should be used for a limited period with careful monitoring of renal function, and if renal dysfunction is observed and the patient still needs pain relief, switching to an alternative analgesic should be considered [37].

Those patients with abnormal renal function at baseline have a three-to-fourfold increased risk of deterioration in renal function compared to those with normal renal function [38]. Although the severity of renal disease at baseline was unknown, the incidence of progression of CKD found in this study (267.12/10,000 person-years) was remarkably high compared to the prevalence rate for dialysis reported for the

general population (26.9/10,000 persons) in Japan [39]. The higher incidence rate may be due to a high-risk population. Patients who had renal disease at baseline were mainly men and had a higher prevalence of comorbidities, such as diabetes, hypertension, and other CV disease, and the risk was found to increase with increasing age. Despite the recommendation against the use of NSAIDs in CKD [40], several studies report that a significant percentage of patients still receive them. Approximately 15.4% of CKD patients were prescribed traditional NSAIDs or COX-2 inhibitors in the United States, 11.1% in the United Kingdom, and 15.9% in Australia [41–43]. Better quantification of risks is recommended in people with CKD when NSAIDs are used [44]. In this context, for patients at high risk of developing renal events, analgesics that do not influence renal COX mechanisms and are potent enough to relieve the pain associated with OA and CLBP may be of potential clinical relevance.

The monthly cost of dialysis was $2347.30 in our study. Although the dialysis cost in this study included only the direct cost and did not include the cost of medications, laboratory tests, diagnostic imaging, and management of dialysis-associated adverse events, the annual cost was considerable ($33,018.40). Takura et al. reported the annual direct medical cost including examination, consultation, and rehabilitation was $45,200 [45]. Moreover, the burden of dialysis is increasing worldwide [46] and it is also associated with a high degree of perceived caregiver burden [47].

There are some implicit database-related limitations of the study. In the absence of medical chart information, the severity of disease, dose of NSAIDs, and actual drug use could not be assessed. Since the database does not include information, which could confirm the diagnosis of renal events, we relied upon the physician's opinion/diagnosis. Data for patients > 65 years were limited and no data were available for patients > 75 years. Thus, we cannot generalize the study results to the entire Japanese population but they can be generalized for those between the ages 18 and 75 years. Patients who withdrew from the JMDC database could not be identified. There may be unmeasured confounding factors that limit interpretation of the model analysis. The study allows estimating the incidence of renal events but does not allow establishing causality with NSAIDs directly. The main strength of the study is that it provides robust real-world evidence from a large administrative claims database. The JMDC database allows an accurate estimation of the incidence because it issues a unique identifier to insured individuals enabling tracking of patient movement and treatment across medical institutions until they withdraw from their health insurance provider.

CONCLUSIONS

The risk of developing renal events was higher in older patients and in patients with diabetes, hypertension, and other CV diseases. Results showed that the risk increased with prolonged and consistent use of NSAIDs. The risk of renal events remained similar in patients using a patch or oral NSAIDs. Careful use of NSAIDs is recommended in patients with CKD and those who are at high risk for CKD.

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the work as a whole, and have given their approval for this version to be published.

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