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Lin, Sharon X; Phillips, Thomas; Culliford, David; Edwards, Christopher; Holroyd, Christopher; Ibrahim, Kinda; Barrett, Ravina; Howard, Clare; Johnson, Ruth; Adams, Jo; Stammers, Mathew; Rischin, Adam; Rutter, Paul; Barnes, Nicola; Roderick, Paul; Fraser, Simon D

DOI: https://doi.org/10.3399/BJGPO.2021.0208

To access the most recent version of this article, please click the DOI URL in the line above.

Received 25 October 2021
Revised 25 October 2021
Accepted 27 October 2021

Author Accepted Manuscript

This is an 'author accepted manuscript': a manuscript that has been accepted for publication in BJGP Open, but which has not yet undergone subediting, typesetting, or correction. Errors discovered and corrected during this process may materially alter the content of this manuscript, and the latest published version (the Version of Record) should be used in preference to any preceding versions

Characterising risk of non-steroidal-anti-inflammatory drug related acute kidney injury: a retrospective cohort study

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Abstract

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for pain and inflammation. NSAID complications include acute kidney injury (AKI), causing burden to patients and health services through increased morbidity, mortality, and hospital admissions.

Aim

This study aimed to measure the extent of NSAID prescribing in an adult population, the degree to which patients with potential higher risk of AKI were exposed to NSAIDs, and to quantify their risk of AKI.

Design and Setting

Retrospective two-year closed-cohort study.

Method

A retrospective cohort of adults was identified from a pseudonymised electronic primary care database in Hampshire, UK. The cohort had clinical information, prescribing data and complete GP- and hospital- ordered biochemistry data. NSAID exposure (minimum one prescription in a two-month period) was categorised as never, intermittent and continuous, and first AKI using the national AKI eAlert algorithm. Descriptive statistics and logistic regression were used to explore NSAID prescribing patterns and AKI risk.

Results

The baseline population was 702,265. NSAID prescription fell from 19,364 (2.8%) to 16,251 (2.4%) over two years. NSAID prescribing was positively associated with older age, women, greater socioeconomic deprivation, and certain comorbidities (diabetes, hypertension, osteoarthritis and rheumatoid arthritis) and negatively with cardiovascular disease (CVD) and heart failure. Among those prescribed NSAIDs, AKI was associated with older age, greater deprivation, CKD, CVD, heart failure, diabetes, and hypertension.

Conclusions

Despite generally good prescribing practice, we identified NSAID prescribing in some people at higher risk of AKI (CKD, older people) for whom medication review and NSAID de-prescribing should be considered.

How this fits in

Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed and taken 'over the counter' for pain and inflammation. Many NSAID risks, including gastro-intestinal bleeding and acute kidney injury (AKI), are well documented and there are clear prescribing guidelines to reduce NSAID-related harm. However, there remains some NSAID prescribing among people at high AKI risk. Quantifying the AKI risk associated with NSAIDs in different groups and examining NSIAD prescribing patterns would be useful to guide practice. This study used two years' data from a large primary care database in Hampshire to explore NSAID prescribing practice and associated AKI risk. We found that, while NSAID prescribing generally declined over a two year period and NSAIDs were prescribed less frequently in at risk groups such as those with cardiovascular disease (CKD) and heart failure, some NSAID prescribing among people at risk remained, and this was associated with greater AKI risk. Older people, those living in more socioeconomically deprived areas and thosewithcomorbidities (including CKD, CVD, heart failure, diabetes and hypertension) were at higher AKI risk.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed or bought 'over the counter' for a wide range of conditions and have analgesic and anti-inflammatory effects through inhibition of cyclo-oxygenase-1 (Cox-1) and Cox-2 enzymes, which are involved in prostaglandin synthesis.[1] An estimated 6 million people aged over 65 in the UK suffer from a musculoskeletal problem such as osteoarthritis.[2,3] Safe pharmacological pain relief options for these conditions are limited and NSAIDs are often prescribed[4]. NSAID safety concerns, especially for older people are known, and their complications well described, risk of which increase with age, dose and duration of use.[5-8] In a multimorbid, ageing population, complications such as bleeding, acute kidney injury (AKI), worsening chronic kidney disease (CKD), worsening heart failure, anaemia, myocardial infarction and stroke are key risks that lead to additional morbidity burden for patients, mortality and high health service use.[1] All NSAIDs increase risk of adverse events, though there is variation in side effect risk profile. For example, Cox-2 selective inhibitors and diclofenac are associated with higher risk of thrombotic events than naproxen and piroxicam is associated with higher gastro-intestinal risk than ibuprofen.[6,9] A systematic review and meta-analysis of five observational studies exploring risk of individual NSAID-related AKI risk did not identify a significant risk difference between specific agents.[10] AKI risk is common, particularly among older people and those

with certain long term conditions, such as chronic kidney disease and heart failure, and is associated with several adverse outcomes including worsening of chronic kidney disease (CKD), higher healthcare costs, hospital admission and mortality.[7] More recent work reaffirms the association between NSAID prescribing and AKI **risk** in people aged 60 and above in both hospital and primary care settings.[11]

The Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health and Clinical Excellence (NICE) have published guidance on NSAID use, and NSAIDs are included in the American Geriatric Society Beers Criteria for Potentially Inappropriate Medication for use in older adults.[8,9,12] Despite awareness of risk among clinicians and presence of this guidance, NSAID use is still common, perhaps in part due to the limited pain-relief options available.[5] In the population-representative Health Survey for England 2016, 11% of the total population were taking some form of analgesia or NSAID.[13] Self-medication with NSAIDs is also common; in a Dutch study, about 30% of the general population sample and 13% of a 'high risk' sample reported NSAID use within the preceding four weeks.[14] Around 90,000 hospital admissions in England each year are related to adverse drug reactions and approximately 30% of those in older people are thought to be due to NSAIDs, mostly commonly GI bleeding, but renal impairment is also an important cause.[15,16]

There is some evidence of a changing pattern of NSAID prescribing over time, with reduction in certain key groups in which there are safety concerns, probably relating to MHRA and NICE guidance to General Practitioners (GPs).[17,18] The PINCER trial demonstrated that an pharmacist-led intervention was effective at reducing non-selective NSAID prescribing in people with a history of peptic ulcer without co-prescription of a proton-pump inhibitor.[19] National roll out of the PINCER intervention in the UK has led to demonstrable reductions in NSAID prescribing to those at risk of gastrointestinal bleeding.[20] However, the extent of NSAID prescribing for groups at higher risk of non-gastrointestinal adverse outcomes, such as AKI is not so well described. Identifying those at high risk would further inform NSAID medicines optimisation / de-prescribing endeavours. The aim of this study was to establish the extent of NSAID prescribing in a large primary care population, to identify the characteristics of those at high risk of AKI and to quantify their AKI risk in order to address the concern of ongoing risk of AKI among people still being prescribed NSAID.

Method

Population

The study population was drawn from the Care and Health Information Analytics database (CHIA), a pseudonymised electronic database containing linked primary care data for approximately 1.4 million patients across Hampshire (UK) and clinical biochemistry results (only using creatinine and AKI eAlert data for the purpose of this study) from two large hospital laboratories (University Hospital Southampton NHS Foundation Trust and Portsmouth Hospitals University NHS Trust). A two-year (from 1 October 2017 to 30 September 2019) retrospective cohort of individuals aged 18 years and over for whom complete GP-ordered tests and all hospital-ordered tests were available for the duration of the study was used to explore the relationship between NSAID exposure and AKI alerts (both defined below).[21]The study population consisted of adults registered with GP practices in Hampshire that consistently sent all laboratory data to one of the two hospitals (Southampton and Portsmouth) for the duration of the study (in order to allow capture of all AKI alerts) and who were alive on 1st October 2017 and survived until 30 September 2019. It was therefore a 'closed' cohort. 'Baseline' was defined as the first two-month period of the study for the purposes of describing NSAID exposure.

NSAID prescribing

NSAID exposure was defined as having at least one primary care–issued prescription of any oral NSAID (any drug within British National Formulary section 10.1.1: 'Non-steroidal anti-inflammatory drugs') recorded in a two-month period.[22] Two-month periods were chosen because repeat prescribing in the UK commonly adopts a one or two-month prescription pattern. It was not possible to assess 'over the counter' NSAID consumption as pharmacy sales data were not available in CHIA. NSAID exposure was therefore characterised based on prescriptions issued as 'never prescribed' (no NSAID prescriptions in the entire two-year study period), 'single prescription only' (any one NSAID prescription in any two-month period of the two-year study period), 'multiple prescriptions in the prevalent NSAID group' (more than one NSAID prescription in any two-months of the two-year study period in those who were prescribed NSAID at baseline), or 'multiple prescription in the incident NSAID group' (more than one NSAID prescription in any two-months of the two-year study period in those who were not prescribed NSAID at baseline). Age was defined in years based on birth date prior to pseudonymisation (full date of birth was not available to the study team). Ethnicity, where available, was categorised into white, Indian/Bangladeshi/Pakistani, African/Caribbean, Mixed and other). Socioeconomic status was defined using the 2019 Index of Multiple Deprivation (IMD) quintiles.[23] The IMD is a small-area measure of

socioeconomic status, ranked nationally, and comprises seven domains: income, employment, education/skills/training, health and disability, crime, barriers to housing and services, and living environment. Baseline comorbidities were defined as ever having had a diagnosis of the condition coded in the primary care record using a set of standard Read codes (used to record primary care diagnoses in England) as described in a previous paper using CHIA data.[21] Particular groups potentially at increased risk from NSAID-related AKI were identified including CKD (excluding kidney dialysis and transplant), cardiovascular disease (CVD) (including Cerebrovascular Disease, Ischaemic Heart Disease and Peripheral Vascular Disease), heart failure (including cor-pulmonale), and older people (classified as 60 years of age and above) and the number and proportion of each risk group prescribed NSAID in each two-month period of the study period were identified and described.

AKI risk

In the UK, the National Health Service (NHS) implemented an AKI detection algorithm, based on now widely used Kidney Disease: Improving Global Outcomes (KDIGO) creatinine change criteria, which generated electronic AKI alerts ('e-alerts') for clinicians.[24] This algorithm was used by the data provider prior to data extraction to identify AKI-alert occurrences in the cohort. Read codes for AKI were also identified and the main study outcome was AKI risk, defined as the rate of AKI occurrences in relevant sample populations. AKI in this study was defined as first occurrence of any AKI alert or Read Code (used to record primary care diagnoses)[24] during the study period, regardless of AKI stage.

Statistical analyses

Descriptive statistics were used to identify the prevalence of NSAID exposure in the whole cohort and the defined sub groups at baseline and in each two-months of the study period. Other medications were not considered (see limitations). The numbers and proportions of people having at least one AKI alert during the two year period, as well as within four months from the start of a prescription were described by NSAID exposure category (not prescribed, one prescription only, multiple prescriptions with and without a baseline prescription). Univariate logistic regression was used to explore baseline associations between patient characteristics and NSAID prescription. Multivariable logistic regression models were then fitted to assess the associations between NSAID exposure in each two-month prescribing period and first AKI alert occurring either in the same or subsequent two-month period. This was in order to capture NSAID exposure and AKI risk outcome for all of the differing patterns of NSAID exposure.

Finally absolute risk of first AKI was calculated for people aged over 60, with and without exposure to NSAIDs (either single or multiple prescriptions across the two years) and other key risks (being older, lower social economic status, presence of comorbidities). For this calculation, first AKI occurring at any point across two years was used to calculate AKI risk in their respective sample population. This was to reflect the real world possibility of people with any prescription of NSAID in a given period taking them sporadically rather than exactly as prescribed.

Results

The closed study population comprised 702,265 people registered with 85 GP practices at study baseline (Figure 1). Mean age was 52 years and 53.2% were female, about 15% lived in the most deprived quintile of IMD and the majority were of British/Mixed British ethnicity, though 35% of individuals had no ethnicity data recorded (see Table 1). The most common long-term conditions were hypertension and osteoarthritis and about 5.1%, 9.5% and 1.8% of the population had a history of CKD, CVD and heart failure respectively.

NSAID Prescription

A total of 19,364 (2.8%, n = 702,265) people were prescribed oral NSAID at baseline (Table 1). This had fallen to 16,251 (2.4%, 686,057) excluding the deceased during the two-year study perod. During the two-year follow up period 620,887 (88.4%) were never prescribed NSAIDs at any point (Figure 2, Supplementary Table 3), 47,740 (6.82%) were prescribed NSAIDs once ('single NSAID group') , 13,981 (1.99%) were prescribed NSAIDs multiple times including a baseline prescription ('prevalent NSAID group') and 19,657 (2.80%) were also prescribed NSAIDs multiple times, but not at baseline ('incident NSAID group'). In the groups at potentially higher risk of AKI (older age, CKD, CVD, heart failure), NSAID prescribing fell over the study period (Figure 2). For example, among people with CKD, baseline prescription rate of 2.8% fell to2.2% at the end of two years. The total number of patients with heart failure, cardiovascular disease or CKD prescribed NSAID more than once was still 4686 (Supplementary Table 3). NSAID prescription at baseline was associated with older age, being female, greater socioeconomic deprivation, history of diabetes, hypertension, osteoarthritis and rheumatoid arthritis (Table 2). Those with CVD (OR:0.80, 95% CI:076-0.85,p<0.001) or heart failure (OR:0.51, 95%CI:0.44-0.59,p<0.001) were less likely to be prescribed NSAID and there was no association (either positive or negative) with having CKD (OR:1.00, 95%CI:0.94-1.06, p=0.96).

AKI risk

The highest proportion of first AKI alert, hence AKI risk in NSAID prescription groups was 3.57% in the 'prevalent NSAID group'(Figure 3), followed by 2.79% in the 'no prescription group', 2.51% in the 'incident NSAID group' and 2.06% in the 'single prescription group'. The same order of AKI risk was also found in the subgroups within four months of prescription: 2.78%, 1.26% and 0.58% (by definition the group not prescribed NSAID did not have a value).

Associations with AKI risk

Among those prescribed NSAIDs at any point (single, prevalent and incident NSAID groups) through the study people of older age groups experienced between 65% (OR 1.65,95% CI:1.27-2.18, p<=0.001) and 657% (OR 7.57, 95% CI: 5.53-10.42, p<=0.001) more risk of AKI alerts within four months of prescription than the youngest group, those with greater social deprivation were more likely to have AKI alerts (29% to 69%), , the disease group with history of CKD, CVD, heart failure, diabetes and hypertension were around 50% more likely to have AKI alerts (Table 3). No significant differences were present between male and female groups. Absolute risk of first AKI was highest among those over 80 with greater combinations of hypertension, diabetes, CKD, CVD and heart failure and those from lower socioeconomic groups (Supplementary Table 1 and Supplementary Figure 3).

Discussion

Summary

This retrospective cohort study identified the extent and distribution of NSAID prescribing and estimated the risk of AKI in a large primary care population. There were indicators of good practice in concordance with new guidance on NSAID prescribing. Overall fewer patients in high risk groups received these medications and the incidence of prescribing fell during the study period (Figure 2) despite natural ageing of the population in this closed cohort. Patients with known risk factors of AKI, particularly in the context of NSAID prescribing, such as cardiovascular disease and heart failure were all prescribed NSAIDs less frequently than those without those risk factors. However there was still an important minority of those with known risk factors, including heart failure, cardiovascular disease or CKD who were prescribed NSAID. The lack of association between NSAID prescribing and having CKD maybe a concern. The association was not negative as it was for cardiovascular

disease and heart failure, which may suggest that patients having CKD is not as strong a deterrent for NSAID prescribing by GPs as cardiovascular disease or heart failure.

Established risk factors for AKI were also reflected in this dataset – older age, lower socioeconomic status, CKD, cardiovascular disease, heart failure, diabetes and hypertension all showed increased AKI rates within four months of NSAID prescription. Our cohort identified NSAID prescription at baseline positively associated with older age, being female, greater socioeconomic deprivation, history of diabetes, hypertension, osteoarthritis and rheumatoid arthritis potentially reflecting greater need for pain relieve in these groups. We suspect (though did not demonstrate) that people with diabetes and hypertension were also more likely to be co-prescribed renin-angiotensin system inhibitors or diuretics which may further increase the risk of AKI.[26,27]

We explored the development of an NSAID-related AKI risk tool, based on absolute risk of first AKI among those of old age, low socio-economic status, and combinations of comorbidities (hypertension, diabetes, CKD, CVD and heart failure). This pointed to the potential value of identifying those with higher risk combinations of these exposures in informing de-prescribing endeavours, but further work is needed to validate this risk tool (Supplementary Figure 3). For example, the calculation of absolute risk was limited by the lack of knowledge about when exactly people took NSAIDs.

Strengths and limitations

Strengths of this study include a large primary care cohort with detailed NSAID prescribing data and its linked hospital and GP biochemical tests including creatinine which enabled the characterisation of NSAID exposure and AKI risk.

Limitations of this data were: an inability to identify and track over the counter NSAID sales and use, nor to capture patients who may vary the use of NSAIDs or stop and start them according to symptoms, or continue at a lower dose. Some people would have moved out of the area during the study period which means their data would no longer be captured and may therefore potentially decrease the prescription rate and death rate in this closed cohort. There was potential for further confounding arising from exposures that we were unable to consider including other comorbidities and medications, such as renin-angiotensin system inhibitors and diuretics. Individual NSAIDs were not specified, although a recent review shows no appreciable AKI risk difference between agents.[10] Other medications were not considered in this study, which might introduce additional risk. There were also a high proportion of missing ethnicity data which hampers broader application of this data in

different sub-populations and conclusions as to ethnicity as a non-modifiable risk factor. The baseline comorbidities were recorded to include all historic, therefore some may no longer be currently 'active'. We did not explore severe AKI, which is relatively common in people with a history of kidney disease. In our study 6400 had more severe AKI, useful to support future work between NSAID and severity of AKI. Our data were limited in geography to the south of England. In other settings, such as areas of greater deprivation or those with higher rates of CVD/CKD, there may be larger numbers of patients at risk.

Similarly to our findings, a Scandinavian study investigating NSAIDs in patients with CVD showed that prescribing is still as high (around 10%), but has been decreasing with time. Diabetes and hypertension also predispose to higher NSAID prescription rates in this study.[28] Over the counter sales of available NSAIDs in the region have also been noted to have increased.[29] Another European study identified a fall in diclofenac prescribing after regulatory advice was issued, but the gradient of this reduction was slowing in more recent years, particularly in those with diabetes and hypertension.[30]

Implications for research and practice

The practical implications of these findings are that it is still important to review NSAID prescribing, particularly for those in high risk groups for AKI. It may be advisable to flag patients in these groups in primary care to avoid or reduce the number of prescriptions. Further exploration would be valuable of the process of initiation and review of NSAID prescriptions during clinical consultations and medication reviews. It would also be valuable to investigate the extent to which an AKI alert leads practitioners to cease NSAID prescription. There is clearly a burden of musculo-skeletal disease for which many still rely on NSAIDs and alternative, effective medicines may be lacking. Non-pharmacological pain management strategies that address the whole person involving behaviour research could be explored. Topical NSAIDs have been shown to be associated with a lower risk of AKI than oral NSAIDs, even when the oral NSAIDs were short course only (analogous to our intermittent prescribing group).[11] Changing to topical NSAIDs may represent one strategy for de-prescribing or not initiating oral NSAID prescription among those at highest risk. De-prescribing NSAIDs has been shown to be pragmatic, cost effective and potentially beneficial to patients in other settings as well as in the UK.[31,32] Other pharmaceutical agents for pain relief or other alternative pain relief approaches need further exploration.Non-pharmacological pain management strategies that address whole person needs require further exploration for the groups of patients we have identified but are beyond the remit of this paper.

Conclusions

This large retrospective cohort study using routine primary care and laboratory data identified that while NSAID usage was falling overall, some people in the population with high risk of developing AKI were still being prescribed NSAIDs and they were shown to be at greater risk of AKI. These findings support targeted NSAID de-prescribing efforts in high-risk groups and highlight which patients are most at risk.

Funding

The study is an independent research funded by the National Institute for Health Applied Research Collaboration Wessex. The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

Ethical approval

Ethical approval for the study was obtained from the University ofSouthampton Faculty of Medicine research Ethics Committee (Submission ID:53312), and the UK Health Research Authority (19/HRA/6613).

Approval for the extraction of data from the Care and Health Information Analytics database was provided by the Care and Health Information Exchange Information Governance Group.

Acknowledgements

The authors are grateful for the help from MOIRA (Medicines optimisation: improving safety and reducing treatment burden among people taking non-steroidal anti-inflammatory drugs or disease modifying antirheumatic drugs) Study Group: James Bachelor, Mary O'Brien, IT support from FlorinaBorca, Hang Phan, and implementation advice from David Kryl.

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Figure 1 - Flow diagram of study participants

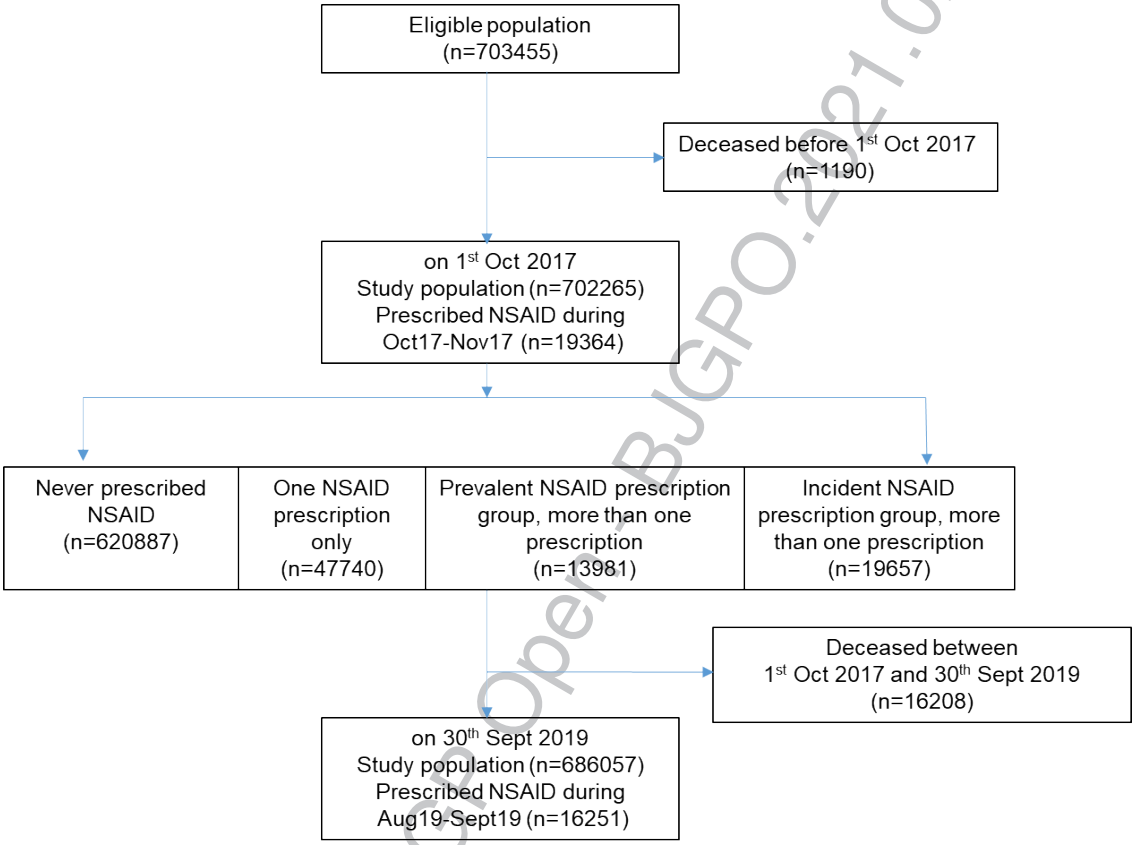


Figure 2 - Proportion of patients in each of the risk groups prescribed NSAID in each 2 month time period of follow up

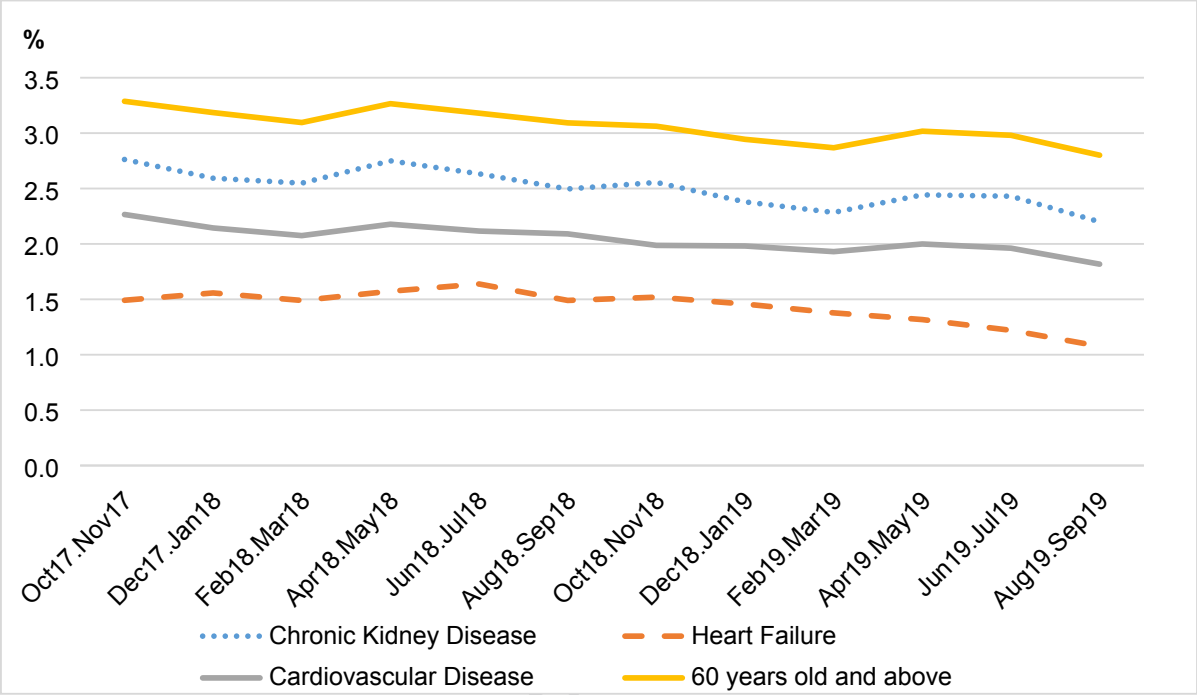
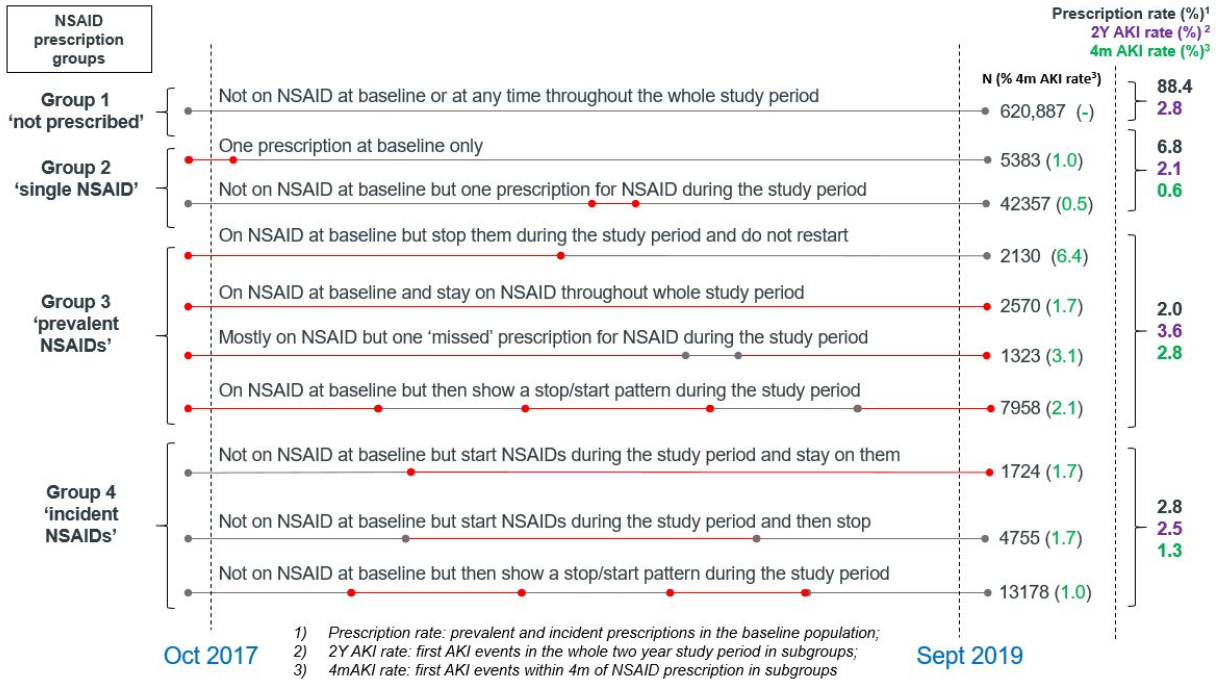


Figure 3: NSAID prescription patterns throughout the study period



Tables

Table 1: Cohort characteristics at baseline

Characteristic		Number	Percentage (unless stated otherwise)
Age (years)	Median (IQR)	52	36,66
	Mean (SD)	52	19
Age groups (years)	18 to 39	210,047	29.9
	40 to 59	241,831	34.4
	60 to 79	194,168	27.6
	80 & above	56,219	8.0
Sex	Male	328,712	46.8
	Female	373,553	53.2
Socioeconomic status (IMD quintile)	1 (most deprived)	102,796	14.6
	2	126,069	18.0
	3	132,262	18.8
	4	146,622	20.9
	5 (least deprived)	186,284	26.5
	Missing	8232	1.2
Ethnicity	British & Mixed British/Irish/Other White	427,019	61.8
	Mixed (White & Asian/ White and Black African/White and Black Caribbean/Other Mixed)	3863	0.6
	Indian/Bangladeshi/Pakistani/other Asian	13,180	1.9
	African/Caribbean/Other Black	5251	0.7
	Other	7236	1.0
	Missing	245,716	35.0
Long term conditions diagnosed at the point of baseline	Chronic kidney disease	36,059	5.1
	CVD (Ischaemic Heart Disease, Cerebrovascular disease, Peripheral Cardiovascular Disease)	52,985	9.5
	Heart failure	12,799	1.8
	Diabetes	62,767	8.9
	Hypertension	150,458	21.4
	Osteoarthritis	95,294	13.6
	Rheumatoid arthritis	6723	1.0

Prescribed at baseline	NSAID	19,364	2.8

Abbreviations: SD – standard deviation, IMD – Index of Multiple Deprivation, CVD – cardiovascular disease, NSAID – non-steroidal anti-inflammatory drug.

Table 2: Univariate associations with NSAID prescription at baseline

Characteristic		**Odds ratio**	**95% confidence interval**		**p value**
Age groups (vs. 18 to 40)	40 to 59	2.20	2.11	2.29	0.02
	60 to 79	2.59	2.48	2.71	<0.001
	80 & above	1.29	1.20	1.39	<0.001
Sex (vs. male)	Female	1.22	1.19	1.26	<0.001
Socioeconomic status IMD quintile (vs. 5, least deprived)	4	1.06	1.01	1.10	<0.001
	3	1.15	1.10	1.20	<0.001
	2	1.29	1.23	1.35	<0.001
	1 (most deprived)	1.54	1.47	1.61	<0.001
CKD (vs. no CKD)		1.00	0.94	1.06	0.96
CVD (vs. no CVD)		0.80	0.76	0.85	<0.001
Heart failure (vs. no heart failure)		0.51	0.44	0.59	<0.001
Diabetes (Type 1 or 2 vs. no diabetes)		1.31	1.26	1.37	<0.001
Hypertension (vs. no hypertension)		1.44	1.39	1.49	< 0.001
Osteoarthritis (vs. no osteoarthritis)		2.82	2.73	2.91	<0.001
Rheumatoid arthritis (vs. no rheumatoid arthritis)		5.08	4.71	5.47	<0.001

Footnote: for those with multiple categories odd ratios are compared to base groups.

Abbreviations: IMD – Index of Multiple Deprivation, CKD – chronic kidney disease, CVD – cardiovascular disease.

Table 3: Multivariate logistic model on associations between NSAID prescription and AKI within four months from the start of prescription period

Characteristic		Odds ratio	95% confidence interval		p value
Age group (vs. 18 to 40) (years)	40 to 59	1.65	1.27	2.18	< 0.001
	60 to 79	3.98	3.07	5.22	< 0.001
	80 & above	7.57	5.53	10.42	< 0.001
Sex (vs. male)	Female	1.11	0.97	1.27	0.13
Socioeconomic status (by IMD) vs 5 (least deprived)	4	1.19	0.96	1.46	0.11
	3	1.29	1.04	1.59	0.02
	2	1.64	1.34	2.01	< 0.001
	1 (most deprived)	1.69	1.36	2.09	< 0.001
CKD (vs. no CKD)		1.61	1.30	1.97	< 0.001
CVD (vs. no CVD)		1.78	1.47	2.14	< 0.001
Heart failure (vs. no heart failure)		1.78	1.23	2.51	0.001
Diabetes (Type 1 or 2 vs. no diabetes)		1.50	1.25	1.78	< 0.001
Hypertension (vs. no hypertension)		1.41	1.21	1.64	< 0.001

Cohort N: 77422, AKI N: 915