Hospital Pharmacy[1], RWTH Aachen, University Hospital, Aachen; Department of Surgery[2], Städtisches Krankenhaus Heinsberg; Institute of Clinical Pharmacology[3], RWTH Aachen University Hospital, Aachen, Germany

The prevalence of 'triple whammy' prescriptions in surgical inpatients and associated pharmacist recommendations

J. A. Koeck[1, *], N. Mastragelopoulos[2], K. S. Just[3], A. Eisert[1, 3]

Received January 14, 2021, accepted April 29, 2021

**Corresponding author: Joachim A. Koeck, Hospital Pharmacy, RWTH Aachen University Hospital, Steinbergweg 20, 52074 Aachen, Germany*
jkoeck@ukaachen.de

Pharmazie 76: 317-327 (2021) *doi: 10.1691/ph.2021.1323*

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are beneficial in surgical settings, they may however lead to adverse drug reactions including decreased renal function, a risk, which is exacerbated by combination with other nephrotoxics, and particularly when NSAIDs are given as part of a so-called 'Triple Whammy' (TW) with diuretics and renin-angiotensin system blockers. The objective of this study was to identify the prevalence of TW-prescriptions in a surgical inpatient setting and to document the changes in renal function after pharmacist recommendations. A prospective, observational single centre pilot study was performed using a series of eleven weekly Point-Prevalence Analyses (PPA). Adult surgical inpatients were screened for a TW-prescription by a clinical pharmacist, who made one of two recommendations on identification of a TW: for patients with eGFR > 60 ml/min/1.73m^2 close monitoring of renal function; for patients with eGFR ≤ 60 ml/min/1.73m^2 discontinuation of NSAID. A TW was identified in 18 of 317 patients (prevalence 5.7%; mean age 75 years). NSAID discontinuation was recommended for 7/18 patients (39%) and implemented for six (33%). In cases where the NSAID was de-prescribed, an improvement in renal function until the time of discharge was observed, whilst in patients with eGFR > 60 ml/min/1.73m^2 for whom monitoring was recommended eGFR remained stable. TW-prescriptions were found to be a potential problem in the studied group of older surgical inpatients. Clinical pharmacists are well placed to identify patients who are prescribed a TW, and to advise on the management of these patients.

1. Introduction

The concurrent prescription and administration of medications affecting the renin-angiotensin aldosterone system (Angiotensin Converting Enzyme Inhibitors [ACEI]) or Angiotensin II Receptor Blockers [ARBs]) alongside diuretics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) has been shown to increase the risk of impaired renal function, largely due to the multiple nephrotoxic actions of the medications involved. Thomas and Boyd named this combination the 'Triple Whammy' (TW) and highlighted the particularly high risk of Acute Kidney Injury (AKI) when medications from all three of these classes are given in combination compared with, for example, co-administration of medications from two of the three groups (Boyd et al. 2000; Thomas 2000). It is not well understood whether a TW-prescription is more likely to cause an AKI in specific patient groups (Prieto-Garcia et al. 2016) and although several studies have investigated the prevalence of TW-prescriptions (Camin et al. 2015; Mangoni et al. 2017; Lind et al. 2019), none of these studies focused on the surgical inpatient setting, where patients may also be at risk.

NSAIDs are routinely prescribed on surgical wards, primarily for the management of post-operative pain, as well as for their anti-inflammatory and opioid-sparing properties (Gabriel et al. 2019) and ACEI, ARB and diuretics remain some of the mainstays in the treatment of hypertension (Williams et al. 2018) a condition whose prevalence increases with age (Neuhauser et al. 2015). As a result, we would expect TW-prescriptions to occur relatively commonly in the post-operative setting, particularly in older patients.

Clinical pharmacy services have the ability to significantly improve inpatient medication safety, in part through the identification and management of potential Drug-Related Problems (DRP) by the clinical pharmacist and the subsequent avoidance of potential adverse drug events. NSAIDs are commonly involved in DRPs (Bilge et al. 2013). This study aimed to identify the prevalence of TW-prescriptions on three surgical wards at a teaching hospital in Aachen, Germany and observe changes in patients´ eGFR, following review and recommendations made by a clinical pharmacist in cases where a TW-prescription is identified.

2. Investigations and results

2.1. Patients, setting, and 'triple whammy' prevalence

Eleven consecutive Point-Prevalence Analyses (PPA) were completed weekly on three surgical wards. In total 317 patient records were screened, 100 patients were prescribed an NSAID and a TW-prescription was identified in 18 patients (5.7%, Fig. 1). A TW-prescription was detected in up to 8.1% of adult surgical inpatients at any time point (Table 1).

The characteristics of the surgical inpatients are shown in Table 2. As expected, TW-prescriptions were more common in those aged over 65; 90% of patients with a TW-prescription were >65 and patients with a TW-prescription were a median of five years older than the average age of all screened patients. The initial indications for surgery in patients with a TW-prescription were endoprosthesis of the knee or hip (seven patients), repositioning and stabilization of fractures (five patients), and other reasons (six patients, Table 3).

2.2. Pharmacist recommendations for patients prescribed NSAIDs as a part of a 'triple whammy'

A TW-prescription was detected in 18 patients (median stay on ward 12 days; Table 3 and supplement, patients 1-18). TW-prescriptions are shown in Table 4. The most frequently identified TW-combination was ibuprofen with candesartan and hydrochlorothiazide

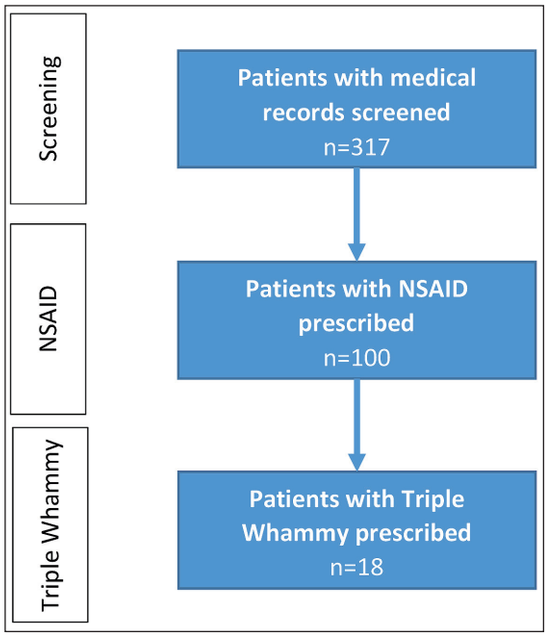


Fig. 1: Flow chart of patient inclusion process. NSAID= Non-Steroidal Anti-Inflammatory Drug.

(three patients). The most commonly prescribed TW-drugs were hydrochlorothiazide and ibuprofen (Table 5; 14 prescriptions, respectively). All patients with a TW-prescription were admitted to the hospital with a co-prescription of ACEI/ARB and diuretics (the so-called 'Double Whammy'). Six of these (patients 2-4, 8, 12, and 16) were already prescribed a TW-prescription prior to the surgical procedure (33% of TW-patients, 2% of all patients), highlighting the potential prevalence of TW-prescriptions in the ambulant population as well.

For 7 of 18 TW-patients (39%), the discontinuation of NSAID was recommended: of these patients six received NSAID with an eGFR ≤ 60 ml/min/1.73m^2 at admission (patients 3-6, 11, and 15) whilst one additional patient experienced a decrease in renal function ≤ 60ml/min/1.73m^2 during treatment (patient 17) triggering the recommendation to stop. For the remaining 11 patients monitoring of renal function was recommended and observed to be appropriate as renal function stayed stable. The recommendation to discontinue NSAID was accepted and actioned in six of seven patients. One patient (patient 15) was prescribed indomethacin for prophylaxis of periarticular heterotopic ossification, rather than for the management of post-operative pain/inflammation as would usually be the case. According to the physician´s discharge letter, this medication was to be discontinued four days after discharge. The pharmacist recommended the discontinuation of NSAIDs for two of the six patients, who were admitted with a TW-prescription (patients 3 and 4). Both received a second NSAID post-operatively (ibuprofen 1800mg/d, respectively). Four patients received NSAIDs prior to admission, this was continued pre- and post-operatively; the renal function was observed to stay stable during the hospitalisation.

In cases where the NSAID was de-prescribed, an increase in the median eGFR from 36 to 58 ml/min/1.73m^2 was observed, representing a median increase of 43% across all six patients (Fig. 2a). In the twelve patients for whom monitoring alone was the recommended (or physician selected), no relevant change in eGFR was observed, indicating the adequacy of monitoring in these patients (Fig. 2b). The median time from admission to the recommendation

Table 1: Patient characteristics and prescriptions in each of the eleven consecutive point-prevalence analyses

PPA no.	1	2	3	4	5	6	7	8	9	10	11
Patients with medical records screened	46	37	45	44	28	22	25	51	41	49	38
≥65 years [no.] (%)	32 (69.6)	21 (56.8)	33 (73.3)	36 (81.8)	16 (57.1)	15 (68.2)	16 (64.0)	32 (62.7)	25 (61.0)	27 (55.1)	24 (63.2)
Patients with NSAID prescribed	13	11	6	8	7	7	4	13	11	20	17
≥65 years [no.] (%)	9 (69.2)	4 (36.4)	6 (100)	5 (62.5)	4 (57.1)	6 (85.7)	4 (100)	6 (46.2)	5 (45.5)	9 (45.0)	10 (58.8)
No. of patients with GFR ≤ 60ml/min/1.73m^2	13	11	10	12	9	11	8	15	10	13	9
≥65 years [no.] (%)	12 (92.3)	9 (81.8)	9 (90.0)	12 (100)	7 (77.8)	11 (100)	8 (100)	15 (100)	10 (100)	12 (92.3)	9 (100)
No. of patients who were NSAID prescribed with GFR ≤ 60ml/min/1.73m^2	2	1	0	1	2	3	2	2	1	1	3
≥65 years [no.] (%)	2 (100)	1 (100)	0	1 (100)	2 (100)	3 (100)	2 (100)	2 (100)	1 (100)	1 (100)	3 (100)
Patients with TW prescribed	3	3	2	1	2	0	1	2	3	3	3
≥65 years [no.] (%)	3 (100)	2 (66.7)	2 (100)	1 (100)	2 (100)	0	1 (100)	1 (50.0)	2 (66.7)	3 (100)	3 (100)
Prevalence of TW (%)	6.5	8.1	4.4	2.3	7.1	0.0	4.0	3.9	7.3	6.1	7.9

NSAID= Non-Steroidal Anti-Inflammatory Drug; PPA= Point-Prevalence Analyses; TW= Triple Whammy.

Table 2: Baseline characteristics of included surgical inpatients

	Patients with medical records screened	Patients with NSAID prescribed	Patients with Triple Whammy prescribed
Characteristic	**N=317**	**N=100**	**N=18**
Median age [years] (IQR)	70.0 (24.0)	67.5 (28.0)	75.0 (14.5)
<65 years [no.] (%)	122 (38.5)	45 (45.0)	2 (11.1)
65-74 years [no.] (%)	64 (20.2)	21 (21.0)	7 (38.9)
75-84 years [no.] (%)	78 (24.6)	21 (21.0)	5 (27.8)
≥85 years [no.] (%)	53 (16.7)	13 (13.0)	4 (22.2)
Female sex [no.] (%)	163 (51.4)	53 (53.0)	11 (61.1)

IQR=interquartile range; NSAID= Non-Steroidal Anti-Inflammatory Drug.

Table 3: Characteristics of 18 included TW-patients with initial indication for surgery, sex, age, inpatient days, and pharmaceutical recommendation (details: see text)

TW-patient no.	Sex	Age group [years]	Main surgical indication	Inpatient days on surgical ward	Pharmaceutical intervention
1	Male	75-84	Cholecystectomy	9	Monitoring
2	Male	65-74	Repositioning of dislocation fracture in the upper ankle joint (1st-3rd surgery)	21	Monitoring
3	Female	75-84	Total endoprosthesis of the knee (1st surgery) with excision of wound margin necrosis (2nd surgery)	24	Termination of NSAIDs recommended (accepted)
4	Female	≥85	Repositioning and osteosynthesis of femur fracture	12	Termination of NSAIDs recommended (accepted)
5	Female	75-84	Dual head prosthesis after fracture of the femoral neck	12	Termination of NSAIDs recommended (accepted)
6	Female	≥85	Repositioning and osteosynthesis of femur fracture	12	Termination of NSAIDs recommended (accepted)
7	Male	<65	Reinsertion of biceps tendon with reconstruction of rotator cuff	6	Monitoring
8	Female	≥85	Dual head prosthesis after fracture of the femoral neck	16	Monitoring
9	Female	75-84	Repositioning and stabilization with a plate of a radius comminuted fracture	4	Monitoring
10	Male	65-74	Rectum stump resection, puncture of pancreatic pseudocyst, sacroiliac blockage, and lumbago with scatica	40	Monitoring
11	Female	75-84	Lower leg contusion with starting dermal necrosis	14	Termination of NSAIDs recommended (accepted)
12	Female	<65	Surgical closure of incisional hernia with foreign body infection	8	Monitoring
13	Male	65-74	Endoprosthesis of the knee	9	Monitoring
14	Male	65-74	Diabetes mellitus with femoropedal bypass (1st surgery), amputation of one toe (2nd surgery), and re-amputation (3rd surgery), prolonged course due to wound healing disorder	75	Monitoring
15	Female	75-84	Repositioning and osteosynthesis of a comminuted fracture of the humerus	15	Termination of NSAID recommended (not accepted, continuation of indomethacin for 4 days after discharge)
16	Female	65-74	Total hip endoprosthesis	11	Monitoring
17	Female	≥85	Total hip endoprosthesis	10	Termination of NSAID due to decline in GFR throughout therapy (2nd pharmacist round, accepted)
18	Male	65-74	Total hip endoprosthesis (1st surgery) with debridement (2nd surgery)	25	Monitoring

NSAID= Non-Steroidal Anti-Inflammatory Drug; TW= Triple Whammy.

to stop NSAIDs or to exclusive recommendation to monitor renal function was three days.

Alongside their recommendation to discontinue NSAIDs, the clinical pharmacist suggested prescribing an increased dose of metamizole to manage potential increases in post-operative pain. Additional prescriptions were not needed and no adverse events (increased pain or inflammation) were observed in the patients for whom NSAID was stopped.

One third of patients prescribed a TW were also discharged with a TW-prescription (6 of 18 patients). Five had an eGFR > 60 ml/min/1.73m^2

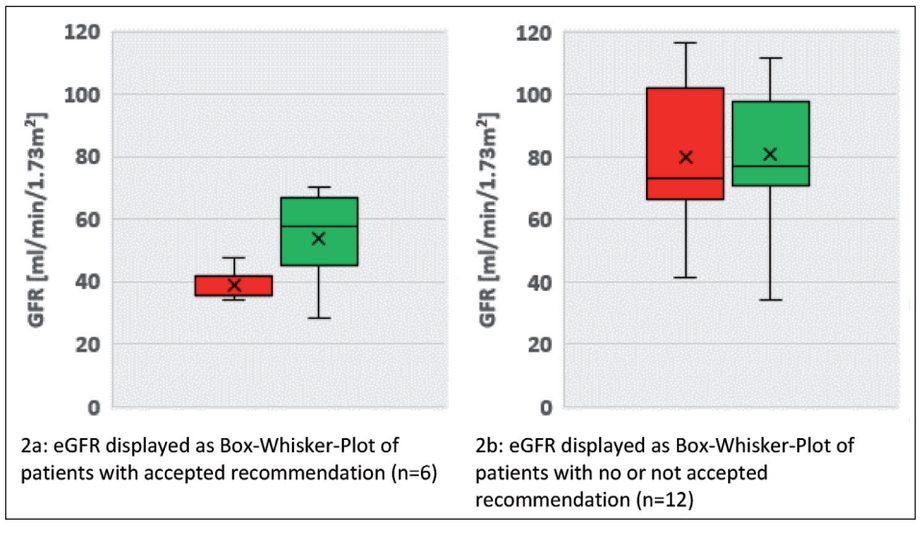


Fig. 2: Development in estimated Glomerular Filtration Rate (eGFR) from date of recommendation (red box-whisker-plots) to date of discharge (green box-whisker-plots). Figure 2a shows six patients for whom a discontinuation of NSAID (Non-Steroidal Anti-Inflammatory Drug) was recommended by pharmacist and accepted by surgeon. Figure 2b shows twelve patients for whom a discontinuation of NSAID was recommended by pharmacist and not accepted by surgeon or for whom monitoring of renal function was recommended only.

Table 4: TW-prescriptions for 18 included patients

Patient no.	Visit no.	NSAID (ATC)	ACEI/ARB (ATC)	Diuretics (ATC)
1	**1**	Ibuprofen 1800mg/d (M01AE01)	Candesartan 16mg/d (C09CA06)	HCT 12.5mg/d (C03AA03); Furosemide 10mg/d (C03CA01); Spironolactone 50mg/d (C03DA01)
2	**1**	Ibuprofen 1800mg/d (M01AE01)	Ramipril 5mg/d (C09AA05)	HCT 12.5mg/d (C03AA03)
3	**1**	Meloxicam 7,5mg/d (M01AC06)	Lisinopril 20mg/d (C09AA03)	Torasemide 7.5mg/d (C03CA04)
4	**1**	Ibuprofen 1800mg/d (M01AE01); Naproxen 1000mg/d (M01AE02)	Lisinopril 20mg/d (C09AA03)	HCT 12.5mg/d (C03AA03); Torasemide 20mg/d (C03CA01)
5	**1**	Ibuprofen 1800mg/d (M01AE01)	Ramipril 10mg/d (C09AA05)	HCT 12.5mg/d (C03AA03)
6	**1**	Etoricoxib 90mg/d (M01AH05)	Ramipril 5mg/d (C09AA05)	Torasemide 5mg/d (C03CA04); Spironolactone 25mg/d (C03DA01)
7	**1**	Ibuprofen 1800mg/d (M01AE01)	Valsartan 160mg/d (C09CA03)	HCT 12.5mg/d (C03AA03)
8	**1**	Naproxen 500mg/d (M01AE02)	Ramipril 2.5mg/d (C09AA05)	Torasemide 20mg/d (C03CA04)
9	**1**	Ibuprofen 1800mg/d (M01AE01)	Enalapril 10mg/d (C09AA02)	HCT 12.5mg/d (C03AA03)
10	**1**	Etoricoxib 60mg/d (M01AH05)	Ramipril 5mg/d (C09AA05)	Spironolactone 25mg/d (C03DA01)
11	**1**	Etoricoxib 90mg/d (M01AH05)	Valsartan 320mg/d (C09CA03)	HCT 12.5mg/d (C03AA03); Furosemide 40mg/d (C03CA01)
12	**1**	Diclofenac 75mg/d (M01AB05)	Valsartan 160mg/d (C09CA03)	HCT 25mg/d (C03AA03)
13	**1**	Ibuprofen 1800mg/d (M01AE01)	Candesartan 16mg/d (C09CA06)	HCT 25mg/d (C03AA03); Triamterene 50mg/d (C03DB02)
13	**2**	Ibuprofen 1800mg/d (M01AE01)	Candesartan 16mg/d (C09CA06)	HCT 25mg/d (C03AA03); Triamterene 50mg/d (C03DB02)
14	**1**	Ibuprofen 1800mg/d (M01AE01)	Ramipril 5mg/d (C09AA05)	Spironolactone 25mg/d (C03DA01)
14	**2**	Ibuprofen 1800mg/d (M01AE01)	Ramipril 5mg/d (C09AA05)	Spironolactone 25mg/d (C03DA01)
15	**1**	Indomethacin 50mg/d (M01AB01)	Candesartan 16mg/d (C09CA06)	HCT 12.5mg/d (C03AA03)
16	**1**	Ibuprofen 600mg/d (M01AE01)	Candesartan 32mg/d (C09CA06)	HCT 12.5mg/d (C03AA03)
16	**2**	Ibuprofen 600mg/d (M01AE01)	Candesartan 32mg/d (C09CA06)	HCT 12.5mg/d (C03AA03)
17	**1**	Ibuprofen 1800mg/d (M01AE01)	Losartan 100mg/d (C09CA01)	HCT 25mg/d (C03AA03)
18	**1**	Ibuprofen 1800mg/d (M01AE01)	Losartan 12.5mg/d (C09CA01)	Torasemide 30mg/d (C03CA04)
18	**2**	Ibuprofen 1800mg/d (M01AE01)	Losartan 12.5mg/d (C09CA01)	Torasemide 30mg/d (C03CA04); Spironolactone 100mg/d (C03DA01)
18	**3**	Ibuprofen 1800mg/d (M01AE01)	Losartan 12.5mg/d (C09CA01)	Torasemide 30mg/d (C03CA04); Spironolactone 100mg/d (C03DA01)

ACEI= angiotensin-converting enzyme inhibitors; ARB= angiotensin II receptor blockers; ATC=Anatomical, Therapeutic, and Chemical Classification; HCT= Hydrochlorothiazide; NSAID= Non-Steroidal Anti-Inflammatory Drug; TW= Triple-Whammy.

and the final patient was taking an NSAID for a non-pain indication at the discretion of the prescribing surgeon. The clinical pharmacist is not currently involved in the medicines reconciliation process on discharge from hospital.

3. Discussion

A TW-prescription was relatively common in our post-operative inpatient population and was shown to be potentially clinically relevant. Clinical pharmacy services can help to identify patients at risk of renal impairment due to a TW-prescription, monitor treatment and ensure the ongoing suitability of prescribed medicines for each individual patient.

In this pilot study we observed substantial improvements in renal function following acceptance of pharmacist advice to de-prescribe NSAIDs in a specific group of patients with reduced renal function, for whom the risk of ongoing NSAID therapy was likely to outweigh the benefit. The improvement in renal function following discontinuation of NSAID is to be expected, based on the known pharmacology of NSAIDs and their established and usually reversible effects on renal function (Prieto-Garcia et al. 2016). When NSAIDs are stopped, prostaglandin synthesis has the opportunity to recover, resulting in an improved eGFR. However, the improvement in renal function cannot be solely attributed to the clinical pharmacist's recommendation. The foundation 'Kidney Disease improving global outcomes' specified (amongst others) surgeries, dehydration, advanced age, and chronic heart diseases as risk factors for AKI, which also were present in parts of included patients (Kidney Disease Improving Global Outcome 2012).

We also observed in this study that only one third of TW-patients experienced a decreased renal function ≤ 60 ml/min/1.73m^2. Lapi et al. (2013) identified 18% of all TW-prescriptions with AKI, which is a similar percentage to our results. However, the observation of successful continuation of TW-prescriptions for two thirds of patients demonstrates that this combination may safely be used accompanied by ongoing monitoring during treatment.

NSAIDs show potential benefits as opiate sparing analgesics and anti-inflammatories what justifies their appropriate use in some cases of surgery (Gabriel et al. 2019). Thus, we cannot simply apply a general rule to 'avoid NSAID use in the elderly'. Knee or hip replacement surgeries are primarily carried out in the 65 to 75 year age group (Bleß and Kip 2017), and the incidence of fractures also increases with age (Amin et al. 2014). A large proportion of the patients in our study, in whom a TW-prescription was identified, were admitted for orthopaedic surgery, and could therefore potentially benefit from NSAID therapy. There is a need to identify the patients for whom an NSAID (alongside other nephrotoxic medications) is inappropriate, and also consider the prevention of AKI, as well as reacting after reductions in renal function are observed.

We observed that one third of the TW-patients were discharged with a TW-prescription. The risk of developing an AKI has been

Table 5: Drugs involved into "Triple Whammy": frequency of prescription and dosing

Drug	ATC-Code	Number of prescriptions	DDD [mg]	Mean prescribed DDD [%]
Hydrochlorothiazide	C03AA03	14	25	64
Ibuprofen	M01AE01	14	1200	136
Ramipril	C09AA05	7	2,5	214
Torasemide	C03CA04	6	15	136
Candesartan	C09CA06	6	8	267
Spironolactone	C03DA01	5	75	40
Furosemide	C03CA01	3	40	58
Valsartan	C09CA03	3	80	267
Etoricoxib	M01AH05	3	60	133
Triamterene	C03DB02	2	100	50
Lisinopril	C09AA03	2	10	200
Losartan	C09CA01	2	50	113
Naproxen	M01AE02	2	500	150
Enalapril	C09AA02	1	10	100
Indomethacin	M01AB01	1	100	50
Diclofenac	M01AB05	1	100	75
Meloxicam	M01AC06	1	15	50

ATC=Anatomical, Therapeutic, and Chemical Classification; DDD= Daily Defined Dose.

shown to be highest within the first 30 days of TW-therapy (Lapi et al. 2013) and TW-patients in this study stayed on the ward for a median of 12 days (Table 3) indicating that they were still at high risk on discharge from hospital, and reinforcing the importance of effective communication to primary care providers, in terms of plans for ongoing prescribing and monitoring. This represents another opportunity for our clinical pharmacist to get involved in improving management of these patients in future. Tong et al. (2017) have previously shown in a randomized controlled trial that clinical pharmacist involvement in medicines reconciliation on discharge from hospital can help to improve patient safety.

To our knowledge, inpatient studies of the prevalence of TW-prescriptions are lacking. When compared to the nomenclature of adverse events (European Commission 2009), the TW-prescription was revealed in our study to be a 'common' phenomenon at almost 6%. Interestingly, 2% of all patients were admitted to the hospital receiving a TW-prescription, whilst 4% of patients received a 'double whammy' of RAAS inhibitor and diuretic, with the third part to the TW-prescription – the NSAID – being added post-operatively. Three studies from various settings support this finding: the prevalence of TW-prescriptions was found as being between 1.7 and 9.9% (Camin et al. 2015; Mangoni et al. 2017; Lind et al. 2019). To our knowledge, this is the first data on the TW-prescriptions in an inpatient surgical population. Our results therefore add to the existing knowledge that TW-prescriptions are relatively common and present a particular risk for AKI. AKI has in turn been shown to increase hospital length of stay, morbidity and mortality, making prevention as well as treatment important (Khadzhynov et al. 2019). Based on the identified prevalence of TW-prescriptions in our patients we recommend increased awareness of the risks of this combination and suggest that a clinical pharmacist might be well placed to identify at risk patients and work with the multidisciplinary team to reduce risks.

The limitations of this study are predominantly based on the screening of patients in an observational single centre design. The decrease in renal function is usually a result of multiple factors. One common factor in surgical inpatients is the shift of body water during a surgical procedure. This effect is most common within the first post-operative day (Maciel et al. 2016). In our study, blood sampling was performed on average twice per week. Our results showed a creatinine increase up to six days after surgical intervention, indicating that surgery-independent factors are also likely to be involved. However, this factor would have affected both groups in our study. The assessment of additional clinical parameters (e.g. urine output) would have enabled further pharmacist recommendations – e.g. to stop ACEI in case of an AKI. Due to the screening nature of the methods described, a comprehensive pharmaceutical review of the medication was out of scope. So, we focused on the NSAID medication which was prescribed as part of a TW-prescription. The limited number of cases encompassing a wider range of diagnoses and lengths of stay may have influenced the results, therefore the results of this observational study should be verified in larger trials with modified study designs.

In conclusion, the co-prescription of an NSAID, ACEI/ARB and diuretic – the so-called 'triple whammy' – is a clinically relevant risk factor for decreased renal function, which occurred in 5.7% of the included surgical inpatients. Risk of receiving a TW-prescription appears to increase with age. Clinical pharmacists can play an important role in identifying patients at risk of reduced renal function due to TW-prescriptions. In patients with reduced eGFR and TW-prescription, discontinuation of NSAIDs (especially in settings with limited pharmacist's resources) may contribute to improvements in renal function.

4. Experimental

4.1. Ethics approval

This study was approved by the local ethics committee for quality assurance purposes (University Hospital RWTH Aachen, EK 20-257).

4.2. Patients and setting

The study was performed on three general surgical wards within a 187-bed teaching hospital of Aachen University. The hospital uses an electronic patient record (iMedOne®, Deutsche Telekom Healthcare and Security Solutions GmbH, Bonn, Germany). The hospital's laboratory program is connected to iMedOne® and results are shown in the patient record. Medications are prescribed on a paper drug chart on the surgical wards. A stand-alone clinical decision support system is used by all surgical health care professionals when needed (AIDKlinik®, Dosing GmbH, Heidelberg, Germany). This study documented routine data of pharmaceutical interventions in an observational pilot study. Older patients were defined as those aged ≥65 years and were subdivided into three groups (65-74 years, 75-84 years, and ≥85 years) (Radosavljevic et al. 2013).

4.3. Point-prevalence analyses

The clinical pharmacist was present on the wards three times per week, for this reason a point-prevalence analysis was more feasible than an incidence analysis. PPA were performed weekly from November 2018 to February 2019 as follows: on each day of PPA the demographic data and the last documented eGFR (automatically calculated with MDRD-formula, (Levey et al. 1999), [ml/min/1.73m^2]) were extracted for every surgical inpatient. Medication data was then collected from the paper-based medical records: if a patient received a NSAID (excluding low-dose aspirin), the medical records were searched for the remaining components of the TW (ACEI/ARB and diuretics). A TW-prescription was confirmed, when at least one drug from each of the TW components (NSAID, ACEI/ARB, diuretics) was identified. When records were not available on the ward (e.g. due to an examination of the patient) or when the patient was discharged the same day, their medical records were not screened. All patients with an identified TW-prescription were discussed with the surgeon on duty. Pharmacist recommendations were documented and handed over.

The daily prescriptions of NSAIDs, ACEIs/ARBs and diuretics for included patients were extracted from medical records with specific dosing. Anatomical, Therapeutic, and Chemical Classification (ATC-Code) and oral Daily Defined Doses (DDD) were sought from WHO 'ATC/DDD Index 2020' (WHO Collaborating Centre for Drug Statistics Methodology 2019).

4.4. Pharmacist recommendations

The local pain management practice for surgical inpatients who are transferred post-operatively to standard care includes the prescription of oxycodone (delayed release) 10 mg twice daily; metamizole 500 mg, three to four times daily, and ibuprofen 600 mg, three times daily.

Prior to the surgical intervention, blood samples are taken to provide baseline laboratory results including renal function. Patients are moved to a standard care ward one day after surgery and blood samples are sent for routine laboratory analysis 2-3 times per week throughout their stay.

For patients with an eGFR > 60 ml/min/1.73m^2 in a patient prescribed a TW-prescription, the surgeon was informed about the risk of a reduced renal function and routine monitoring of the laboratory and clinical parameters for renal function was

continued. The clinical pharmacist re-assessed renal function during his visits (three times a week).

If an eGFR ≤ 60 ml/min/1.73m^2 was identified in a patient prescribed a TW-prescription, the pharmacist made the recommendation to stop the NSAID. As an alternative, an adjusted dose of metamizole up to 4 g daily was recommended, if necessary for pain management. If the NSAID was used for a non-pain/inflammation indication (e.g. prophylaxis of periarticular heterotopic ossification) the recommendation was made for the physician to decide on a case-by-case basis as there is no adequate pharmacological substitution.

Dates of admission, discharge, surgical interventions, and pharmacist recommendations were extracted from electronic patient records and discharge reports. The duration of NSAID therapy was extracted from medical charts. All available measurements for serum creatinine levels and eGFR were sought from the electronic patient record. Descriptive patient data is displayed as follows: age as median±interquartile range (IQR), ratio of gender of included patients as percentage. Differences in eGFR are summarized and compared using Box-Whisker-Plots (accepted recommendation to stop NSAID vs. not accepted recommendation to stop NSAID / recommendation to monitor renal function only). Other data is shown in percentages, as applicable.

All patients with a TW-prescription are summarized in individual graphical case reports (see supplement, patients 1-18). The patient ID was assigned randomly.

The change in eGFR from time of recommendation to the time of discharge was calculated as a percentage for every patient as follows: *percentage difference in eGFR [%] =eGFR [discharge]/eGFR [time of recommendation]*100-100*.

Acknowledgments: We greatly thank Ms. Nicola Jane Young for her language editing and proofreading of the manuscript as well as Dr. Claus-Joerg Cieslok for his support and encouragement.

Conflicts of interest: None declared.

References

European Commission (2009). "A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)". Available from: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf (last viewed March 2021).

Kidney Disease Improving Global Outcome (2012). KDIGO Clinical Practice Guideline for Acute Kidney

Injury. Kidney International Supplements 2: 124-138.

Bleß HH, Kip M (2017). Weißbuch Gelenkersatz. Versorgungssituation endoprothetischer Hüft- und Knieoperationen in Deutschland. Berlin p. 22.

WHO Collaborating Centre for Drug Statistics Methodology (2020) ATC/DDD Index 2020. Available from: https://www.whocc.no/atc_ddd_index/ (last viewed June 2020).

Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ 3rd (2014) Trends in fracture incidence: a population-based study over 20 years. J Bone Miner Res 29: 581–589.

Bilge U, Sahin G, Unluoglu I, Ipek M, Durdu M, Keskin A (2013) Inappropriate use of nonsteroidal anti-inflammatory drugs and other drugs in chronic kidney disease patients without renal replacement therapy. Ren Fail 35: 906–910.

Boyd IW, Mathew TH, Thomas MC (2000) COX-2 inhibitors and renal failure: the triple whammy revisited. Med J Aust 173: 274.

Camin RM, Cols M, Chevarria JL, Osuna RG, Carreras M, Lisbona JM, Coderch J (2015) Acute kidney injury secondary to a combination of renin-angiotensin system inhibitors, diuretics and NSAIDS: The Triple Whammy. Nefrologia 35: 197–206.

Gabriel RA, Swisher MW, Sztain JF, Furnish TJ, Ilfeld BM, Said ET (2019). State of the art opioid-sparing strategies for post-operative pain in adult surgical patients. Expert Opin Pharmacother 20: 949–961.

Khadzhynov D, Schmidt D, Hardt J, Rauch G, Gocke P, Eckardt KU, Schmidt-Ott KM (2019) The incidence of acute kidney injury and associated hospital mortality. Dtsch Arztebl Int 116: 397–404.

Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S (2013) Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ 346: e8525.

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130: 461–470.

Lind KE, Raban MZ, Georgiou A, Westbrook JI (2019) NSAID use among residents in 68 residential aged care facilities 2014 to 2017: An analysis of duration, concomitant medication use, and high-risk conditions. Pharmacoepidemiol Drug Saf 28: 1480–1488.

Maciel AT, Nassar AP Jr., Vitorio D (2016) Very transient cases of acute kidney injury in the early postoperative period after cardiac surgery: the relevance of more frequent serum creatinine assessment and concomitant urinary biochemistry evaluation. J Cardiothorac Vasc Anesth 30: 56–63.

Mangoni AA, Kholmurodova F, Mayner L, Hakendorf P, Woodman RJ (2017) The concomitant use of diuretics, non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (triple whammy), extreme heat, and in-hospital acute kidney injury in older medical patients. Adv Ther 34: 2534–2541.

Neuhauser HK, Adler C, Rosario AS, Diederichs C, Ellert U (2015) Hypertension prevalence, awareness, treatment and control in Germany 1998 and 2008-11. J Hum Hypertens 29: 247–253.

Prieto-Garcia L, Pericacho M, Sancho-Martinez SM, Sanchez A, Martinez-Salgado C, Lopez-Novoa JM, Lopez-Hernandez FJ (2016) Mechanisms of triple whammy acute kidney injury. Pharmacol Ther 167: 132–145.

Radosavljevic N, Nikolic D, Lazovic M, Petronic I, Milicevic V, Radosavljevic Z, Potic J, Ilic-Stojanovic O, Jeremic A (2013) Estimation of functional recovery in patients after hip fracture by Berg Balance Scale regarding the sex, age and comorbidity of participants. Geriatr Gerontol Int 13: 365–371.

Thomas M C (2000) Diuretics, ACE inhibitors and NSAIDs--the triple whammy. Med J Aust 172: 184–185.

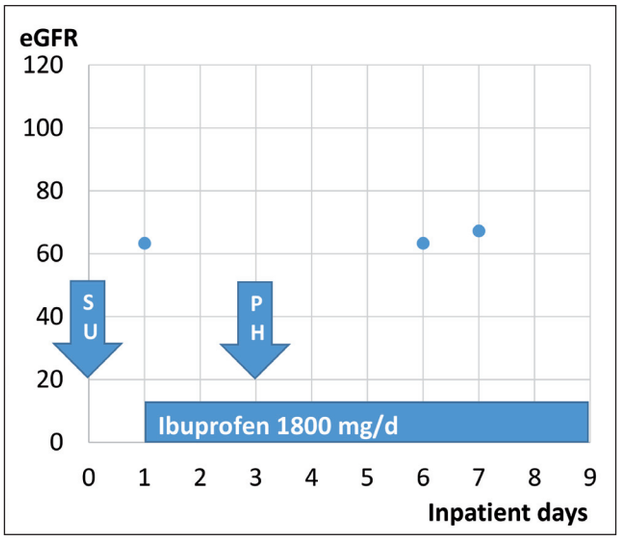
Tong EY, Roman CP, Mitra B, Yip GS, Gibbs H, Newnham HH, Smit V, Galbraith K, Dooley MJ (2017) Reducing medication errors in hospital discharge summaries: a randomised controlled trial. Med J Aust 206: 36–39.

Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 39: 3021–3104.

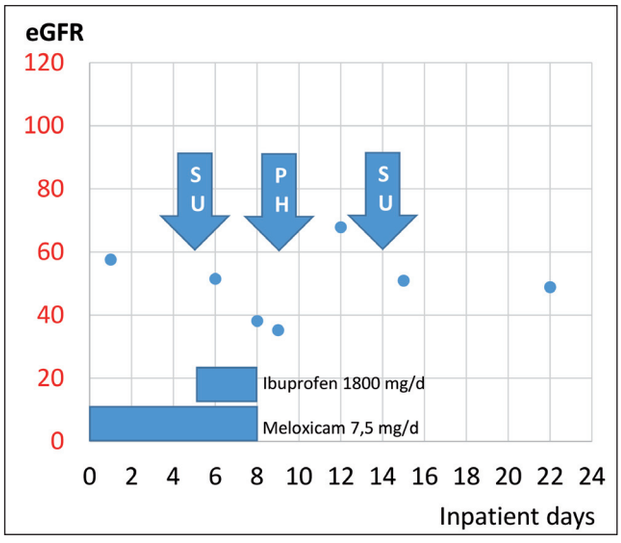
Supplement

The graphical case reports below show the progression of eGFR in relation to the specific inpatient days (day 0 = day of admission). eGFR is calculated as MDRD normalized to 1.73 m^2 (blue dots, [ml/min/1.73m^2]). As usual practice on regular surgical wards, blood samples were not taken every day. In case of eGFR below 60 ml/min/1.73 m^2 after pharmacists´ point prevalence analyses, y-axis was colored in red.

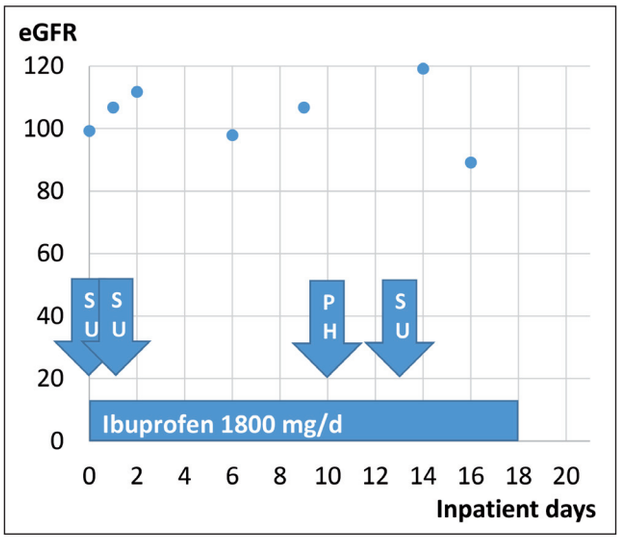
The dates of surgeries are marked with arrows ("SU"), as well as pharmacists´ point prevalence analyses ("PH").
The days of NSAID-prescription are presented using a bar with the drug name and daily prescribed dose.
The legend comprises the age of the patient, the main diagnosis, and the totaled inpatient days on surgical ward. In addition to that, the pharmaceutical recommendation and the physicians' acceptance is described.



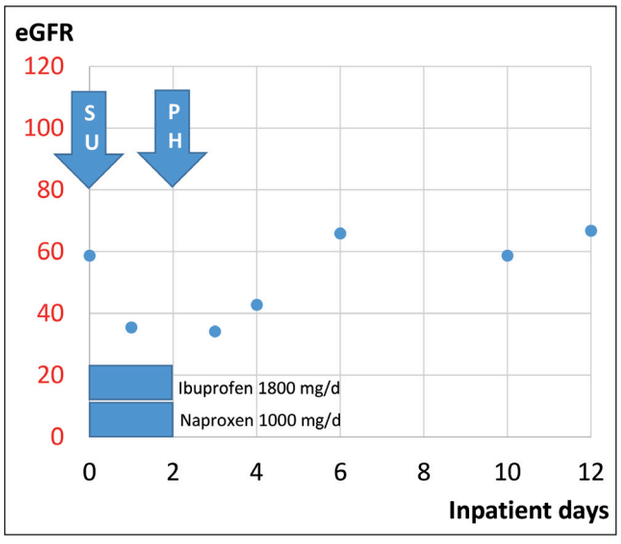
Patient 1: male, 75-84 years, Cholecystectomy, 9 inpatient days; pharmaceutical recommendation: monitoring



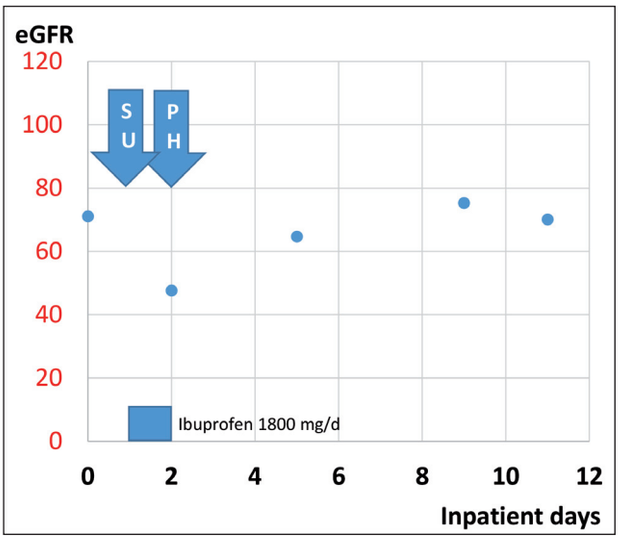
Patient 3: female, 75-84 years, total endoprosthesis of the knee (1st surgery) with excision of wound margin necrosis (2nd surgery), 24 inpatient days; pharmaceutical recommendation: termination of NSAIDs recommended (accepted)



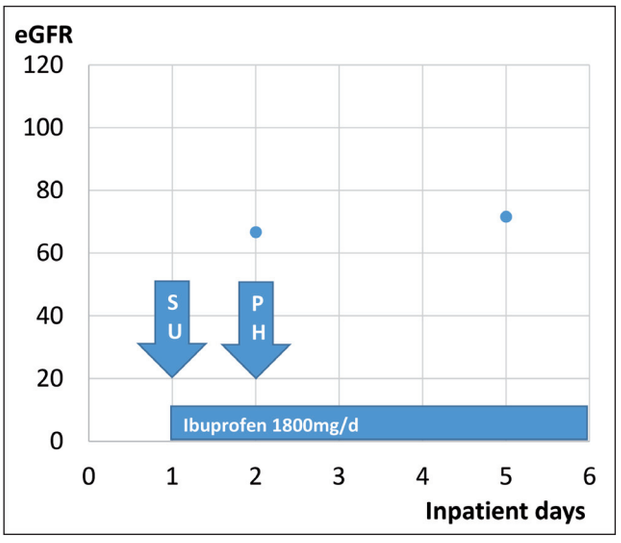
Patient 2: male, 65-74 years, repositioning of dislocation fracture in the upper ankle joint (1st-3rd surgery), 21 inpatient days; pharmaceutical recommendation: monitoring



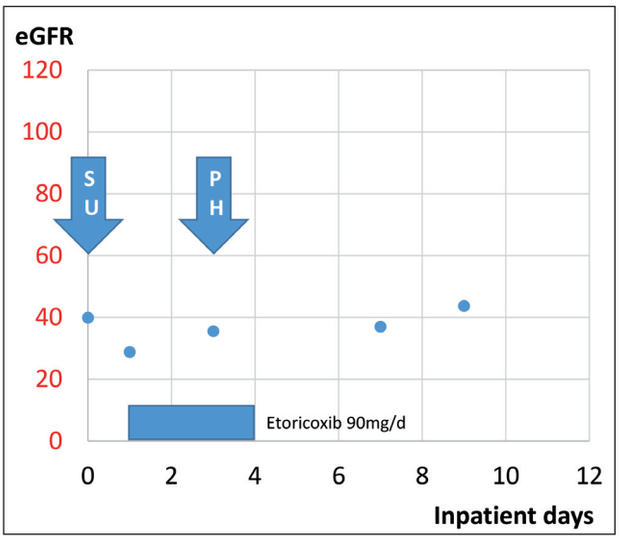
Patient 4: female, ≥85 years, repositioning and osteosynthesis of femur fracture, 12 inpatient days; pharmaceutical recommendation: termination of NSAIDs recommended (accepted)



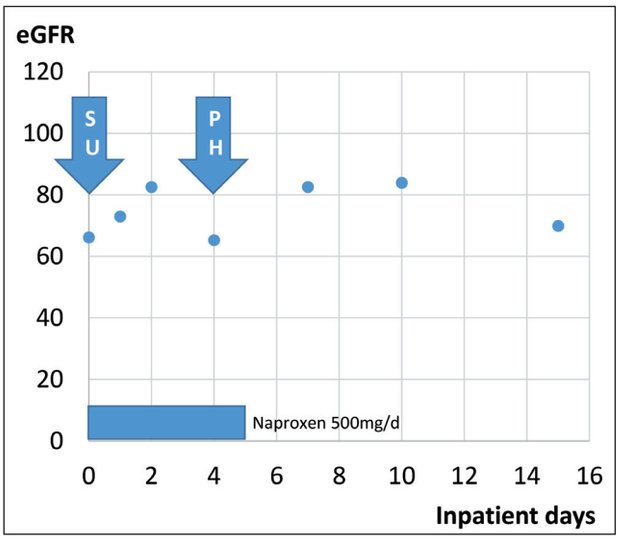
Patient 5: female, 75-84 years, dual head prosthesis after fracture of the femoral neck, 12 inpatient days; pharmaceutical recommendation: termination of NSAID recommended (accepted)



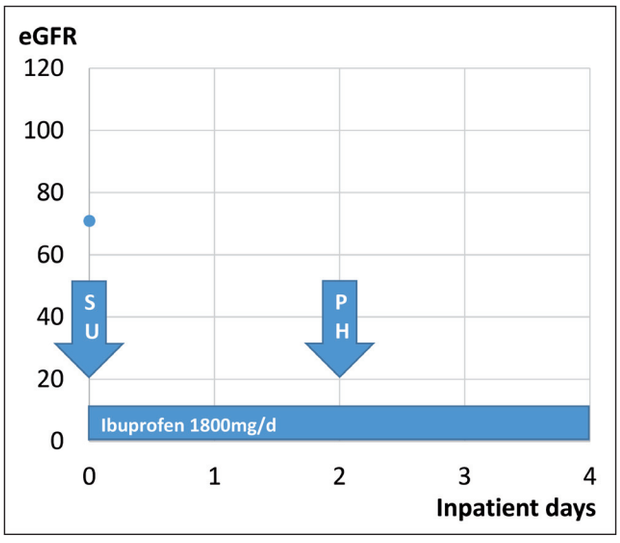
Patient 7:male, <65 years, reinsertion of biceps tendon with reconstruction of rotator cuff, 6 inpatient days; pharmaceutical recommendation: monitoring



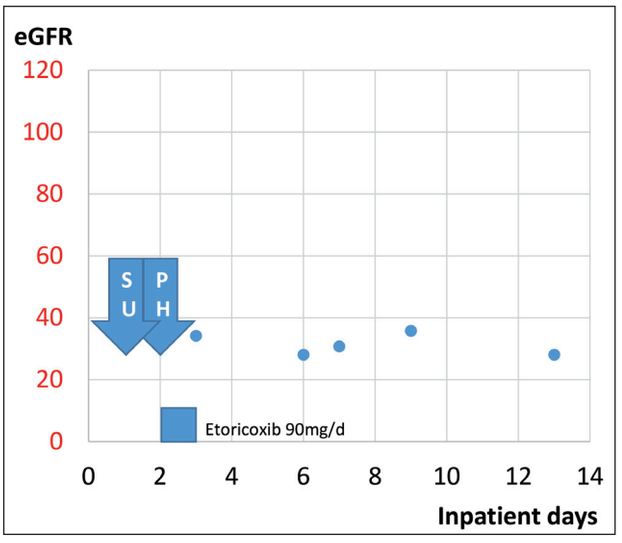
Patient 6: female, ≥85 years, repositioning and osteosynthesis of femur fracture, 12 inpatient days; pharmaceutical recommendation: termination of NSAID recommended (accepted)



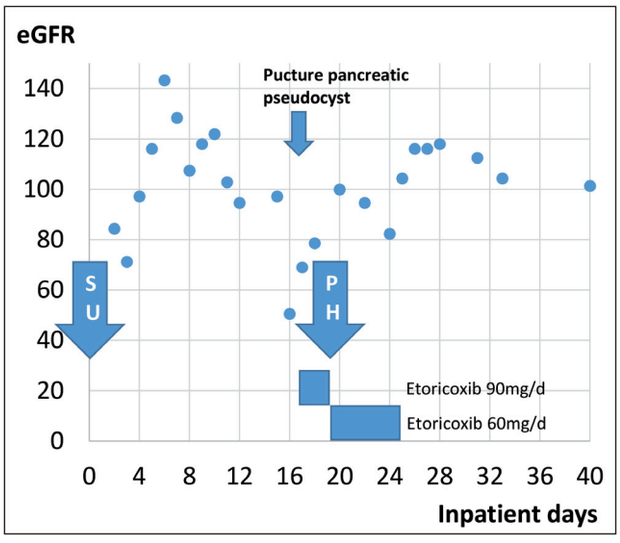
Patient 8: female, ≥85 years, dual head prosthesis after fracture of the femoral neck, 16 inpatient days; pharmaceutical recommendation: monitoring



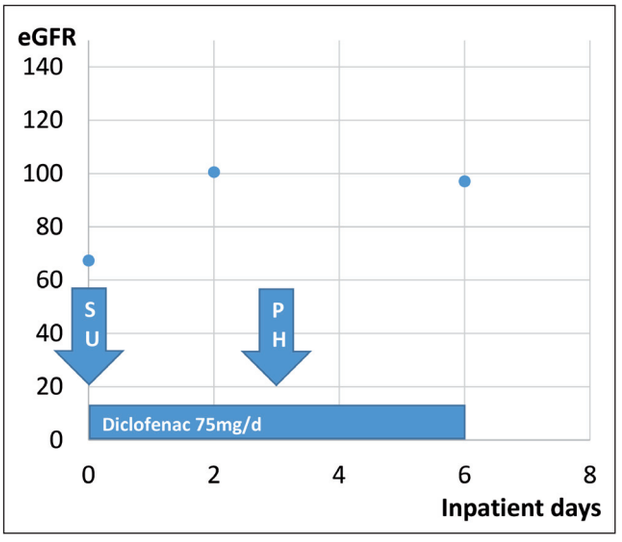
Patient 9: female, 75-84 years, repositioning and stabilization with a plate of a radius comminuted fracture, 4 inpatient days; pharmaceutical recommendation: monitoring



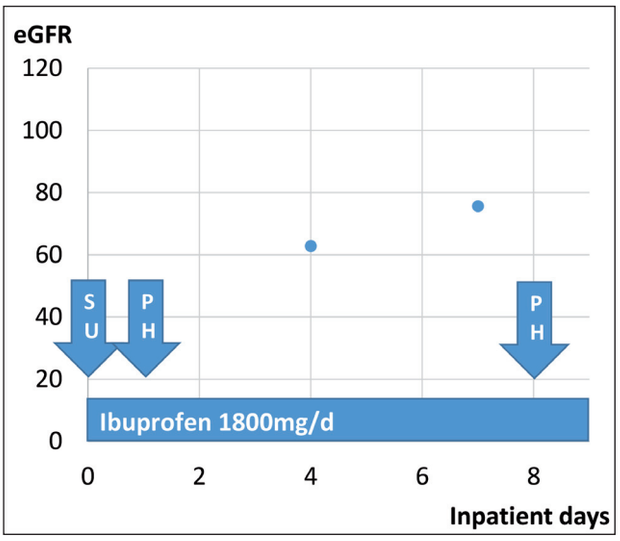
Patient 11: female, 75-84 years, lower leg contusion with starting dermal necrosis; 14 inpatient days; pharmaceutical recommendation: termination of NSAID recommended (accepted)



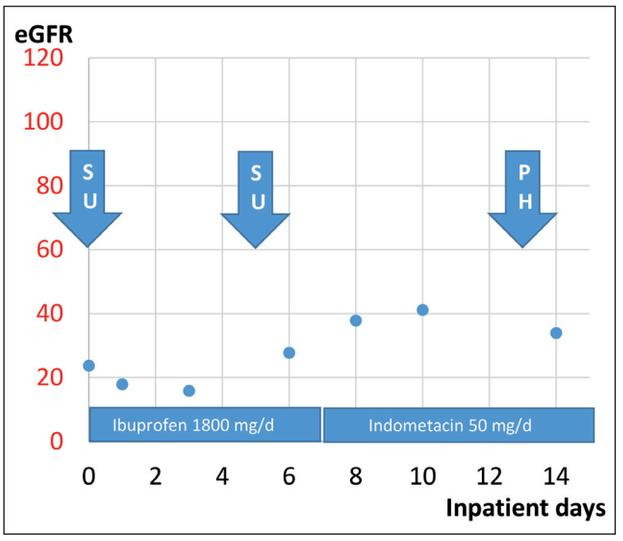
Patient 10: male, 65-74 years, rectum stump resection, puncture of pancreatic pseudocyst, sacroiliac blockage, and lumbago with scatica, 40 inpatient days; pharmaceutical recommendation: monitoring



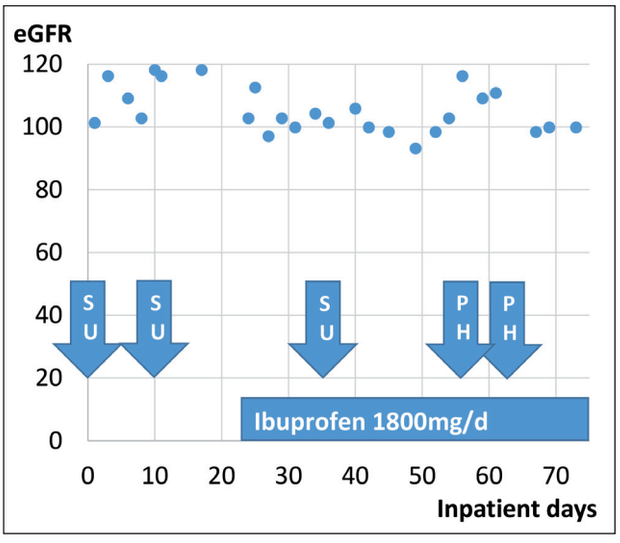
Patient 12: female, <65years, surgical closure of incisional hernia with foreign body infection, 8 inpatient days; pharmaceutical recommendation: monitoring



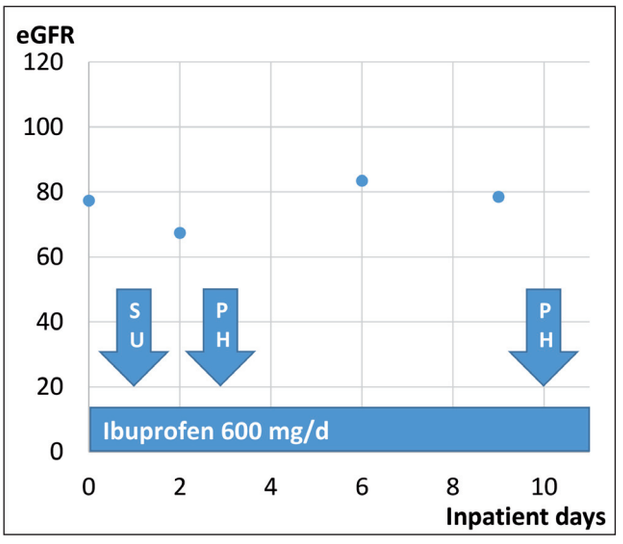
Patient 13: male, 65-74 years, endoprosthesis of the knee, 9 inpatient days; pharmaceutical recommendation: monitoring



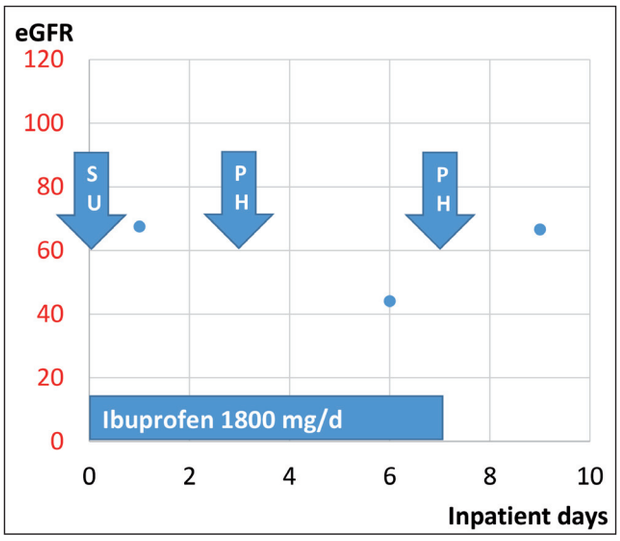
Patient 15: female, 75-84 years, repositioning and osteosynthesis of a comminuted fracture of the humerus, 15 inpatient days; pharmaceutical recommendation: termination of NSAID recommended (not accepted, continuation of indometacin for 4 days after discharge)



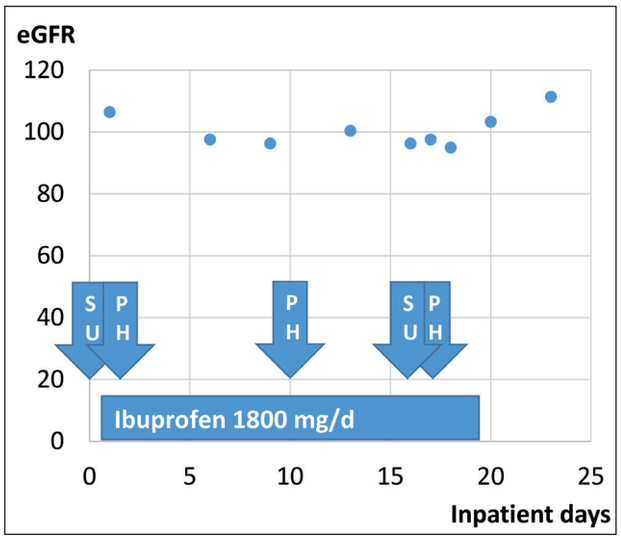
Patient 14: male, 65-74 years, diabetes mellitus with femoropedal bypass (1st surgery), amputation of one toe (2nd surgery), and re-amputation (3rd surgery), 75 inpatient days (prolonged course due to wound healing disorder); pharmaceutical recommendation: monitoring



Patient 16: female, 65-74 years, :total hip endoprosthesis, 11 inpatient days; pharmaceutical recommendation:: monitoring



Patient 17: female, ≥85 years, total hip endoprosthesis, 10 inpatient days; pharmaceutical recommendation: termination of NSAID due to decline in GFR throughout therapy (2nd pharmacist round, accepted)



Patient 18: male, 65-74 years, total hip endoprosthesis (1st surgery) with debridement (2nd surgery), 25 inpatient days; pharmaceutical recommendation: monitoring