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Risk of acute kidney injury by initiation of non-steroidal anti-inflammatory drugs in hospitalized patients treated with diuretics and renin angiotensin aldosterone system inhibitors

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Running title : non-steroidal anti-inflammatory drugs and risk of acute kidney injury

Keywords: Acute kidney injury, hospitalized patients, diuretics, non-steroidal anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, clinical pharmacy, adverse drug reactions.

Abstract

Objectives

Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) with diuretics and renin-angiotensin-aldosterone system inhibitors (RAASI) has been associated to an increased risk of developing acute kidney injury (AKI) in ambulatory setting. There is currently no information on AKI prevalence in hospitalized patients where initiation of NSAID prescription is quite frequent. The aim of our study was to assess the prevalence of AKI in patients treated with diuretics and/or RAASI in the hospital setting when NSAIDs are initiated.

Methods

Retrospective single center study on inpatients receiving triple or dual association. AKI was established according to evidence-based clinical practice guidelines in kidney disease (Kidney Disease Improving Global Outcome, KDIGO criteria) using the following criteria : increase in SCr by $\geq 0.3\text{mg/dL}$ (or $\geq 26.5\ \mu\text{mol/L}$) within 48 hours or increase in SCr to ≥ 1.5 times baseline occurring within the last 7 days.

Results

AKI was identified in 5 of 151 patients (3.3%) treated with both diuretics and RAASI in whom NSAIDs were initiated with a $49\ \mu\text{M}$ average increase in SCr within 48h compared to baseline. AKI was identified in 2 of 117 (1.7%) patients treated with diuretics and NSAIDs, and in 1 of 427 (0.23%) patients treated with RAASI and NSAIDs. The average increase in SCr within 2 days was $29\ \mu\text{M}$. No Aki was identified in a control group of 1,886 patients treated by diuretics and RAASI with no NSAIDs initiation during their hospitalization.

Conclusion

Initiation of NSAID therapy in hospitalized patients already treated with diuretics and RAASI is a risk factor for AKI. The risk of AKI with the triple association appeared higher than with the dual association.

Introduction

Non-Steroidal anti-inflammatory drugs (NSAIDs) are widely used either as prescription or as over-the-counter drugs. Over the last decade (from 2006 to 2016) NSAID use in France has been relatively stable: 30 Define Daily Dose (DDDs) /1000 inhabitants/day for NSAIDs. Ibuprofen, the second-most used non-opioid analgesic, contributed to one-third of the NSAID consumption (1).

While gastro-intestinal and cardio-vascular side effects are well-known, renal effects, although considered as rare, should be taken in account. Indeed the hemodynamic interaction of NSAIDs with other therapies is important, particularly with diuretics and inhibitors of the renin-angiotensin-aldosterone system (RAASI). Each drug can affect kidney function: NSAIDs cause renal afferent vasoconstriction mediated by prostacyclin inhibition, diuretics induce hypovolemia and RAASI reduce glomerular filtration (Supplementary material 1). This triple combination can therefore induce an episode of acute renal injury (AKI) especially in elderly or dehydrated subjects (2).

Epidemiological studies performed in ambulatory settings have shown a robust link between NSAIDs use and AKI in patients with a two-fold increase risk of acute renal injury (3). In general population, a modest higher risk in older people has been evidenced with an adjusted odds-ratio of 1.73 (95% CI 1.44-2.07) (4). In a subgroup of older people (> 50 years), a somewhat higher odds of AKI with NSAID exposure was reported (OR 2.01, 95%CI 1.52–2.68) (5).

The interaction between NSAIDs, diuretics and RAASI has been investigated in ambulatory studies showing that the combination of a NSAID with a diuretic or a RAASi was not associated with a higher risk of AKI compared to the use of diuretics or RAASi alone (RR =1.02) (6). On the other hand, the combination of NSAID with both diuretic and RAASi would result in a 31% higher risk of AKI (6).

In view of these elements and the fact that there is currently no evaluation in the hospital setting, it appeared relevant to assess the prevalence of AKI induced by hospital prescribing of NSAID in adults treated with diuretics and/or RAASI and to compare them.

Methods

The study was performed as a retrospective (48 month-period from January 2017 to December 2018), observational, single-center study on 37,873 adult inpatients of Rennes University Hospital.

Inclusion criteria were: complete hospitalization, age over 18 years, absence of pre-existing renal disease or disease associated with impaired renal function, and co-prescription of other nephrotoxic treatments (list based on the recommendations of the national “Guide de Prescription et Rein”, GPR available at <http://sitegpr.com/fr/>).

Exclusion criteria were : Use of NSAID at hospital admission, complete hospitalization in the following departments : nephrology, dialysis and intensive care because patients in these departments have several medications correcting renal function impairment, and hematology and emergency department because they used a different CPOE system.

Drug prescription data was extracted from the computerized physician order entry database (CPOE, DxCare® Software). This database also indicates the real-time administration of drugs to patients by the nurses that was recorded for the drugs of concern in this study.

3 groups of patients were identified and defined as follows:

- Triple association: Patients treated with diuretics and RAASI who were initiated with NSAIDs (IV or VO) (minimum overlap of 24 hrs).
- Dual association: Patients treated with diuretics or RAASI and who were initiated with NSAIDs (IV or VO) (minimum overlap of 24 hrs).

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3 - Control: Patients treated with diuretics and RAASI with no NSAID's initiation.
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6 The decrease in renal function was based on serum creatinine (SCr) measurement extracted from
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8 hospital biological database. According to evidence-based clinical practice guidelines in kidney disease
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10 (7), AKI is defined by the increase in SCr (absolute or relative increase) or by the decrease in urine
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12 output. AKI is staged in 3 levels, stage 1 corresponding to the first level of acute renal impairment.
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15 AKI not graded is defined as any of the following (7) :

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18 - Increase in SCr by ≥ 0.3 mg/dL (or ≥ 26.5 μ mol/L) within 48 hours or
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20 - Increase in SCr to ≥ 1.5 times baseline occurring within the last 7 days, or
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22 - Diuresis less than <0.5 ml/kg/h for at least 6 hours.
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25 In our study, we only used SCr as criteria for detecting AKI because the urine output is not usually
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27 measured in hospitalized patients excepted patients in intensive care units, nephrology and dialysis
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29 departments.
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32 The prevalence of AKI in patients with the dual association and in the control group was checked in
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34 patients from the departments where AKI was identified under the triple association (i.e., department
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36 of Orthopedic surgery, Pneumology, Neurology and Thoracic surgery). This was done to decrease the
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38 heterogeneity between groups. Indeed, including patients other medical or surgical departments in
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40 the control groups or in the dual association group may likely increase the heterogeneity, and hence
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42 the variability between groups.
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48 The three groups were evaluated for differences in the prevalence of AKI by Fisher's exact test followed
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50 by Bonferroni pairwise comparisons. A p-value < 0.05 was considered significant.
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59 **Results**
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5 The hospital data base recorded 37,874 patients in 2 years with at least one of the drugs of interest
6 (NSAIDs and/or diuretics and/or RAASI). Among these patients, 6,281 (mean age 74 ± 12.7 years) were
7 treated by the association (395 NSAIDs + diuretics, 1,015 NSAIDs + RAASI, 4,871 diuretics + RAASI) and
8 151 (mean age 73 ± 11 years) by triple association (NSAIDs + diuretics + RAASI).
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16 Five (3.3 %) of the patients from the triple association group had an episode of AKI and were
17 hospitalized in 4 different departments (Neurology, Cardio-Thoracic Surgery, Pneumology and
18 Orthopedics). The evaluation of SCr as a function of time for these 5 patients is depicted in Figure 1A.
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23 Dual association group in the four departments included 544 patients: 117 patients received NSAIDs
24 and diuretics and 427 received NSAIDs and RAASI. An AKI episode was detected in 3 patients during
25 their hospital stay (2 patients had diuretics + NSAIDs and 1 patient had RAASI + NSAIDs). The evaluation
26 of SCr as a function of time for these 3 patients is depicted in Figure 2B. Their mean SCr values at the
27 admission, 48h after initiation of NSAID therapy and at discharge are presented in supplementary
28 material (cf Supplementary material 2 data file).
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36 The characteristics of the patients with AKI and the drug treatment chronology are summarized in
37 supplementary material (cf supplementary material 3 data file).
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3 No AKI episode was detected among the 1,886 patients treated by diuretics and RAASI with no NSAIDs
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5 initiation during their hospitalization in the above-mentioned departments.
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10 In our study, the prevalence of AKI for the triple association was 3.3% with a 49 μM average increase
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12 in SCr within 48h compared to baseline. The prevalence of AKI for the dual association was 1.7% for
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14 patients treated with NSID and diuretics and was 0.23% for patients treated with NSAID and RAASI.
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16 The average increase in SCr within 2 days was 29 μM .
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21 The risk of AKI was significantly different between the 3 groups (triple association, dual association and
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23 control patients, $p < 0.001$) with significant differences between triple and dual association ($p = 0.043$),
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25 triple association and control ($p < 0.001$) and double association and control ($p = 0.034$).
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30 **Discussion**

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34 AKI occurs in nearly 20% (8) of hospitalizations and can reach a 60% rate in critically ill patients (9). This
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36 occurrence may therefore increase mortality, hospital length of stay and also health care cost, making
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38 it a major public health concern (9). Indeed, it has recently been shown that patients in whom AKI
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40 occurred had a higher risk of developing chronic kidney disease (CKD): 70% of elderly patients
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42 developed CKD within 2 years after their episode of AKI (10).
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48 The known risks associated with the triple association between NSAIDs, diuretics and RAASI are
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50 currently based on studies achieved in ambulatory patients. Lapi et al. (6) showed a 31% increased risk
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52 of developing AKI in patients treated by NSAIDs, diuretics and RAASI compared to patients treated by
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54 diuretics or RAASI alone. However, they found that the dual associations (diuretics + NSAIDs or RAASI
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56 + NSAIDs) did not increase the risk of AKI. Dreischulte et al. (11) showed that NSAIDs use was associated
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3 with a 66% increased risk of AKI when used either in triple association or in dual association. Hence,
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5 the impact of the dual association should be further studied to confirm or not its negative effect.
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10 Our study showed that NSAIDs initiation in hospitalized patients treated with diuretics and/or RAASI is
11 deleterious for the renal function. Comparison with the literature is not possible since to our
12 knowledge this has not been previously studied in hospital setting. However, these results are in
13 agreement with studies performed in ambulatory patients that showed that the triple association
14 increased the risk of AKI (6,11). Furthermore, it should be noticed that the dual association led to a
15 smaller increase in the prevalence of AKI in patients in comparison with the triple association. It should
16 be noticed that half of the patients had an increase in furosemide dosing regimen throughout their
17 stay, and this may question a role of furosemide in AKI development. However, the impact of
18 furosemide on AKI can be reasonably ruled out since furosemide is sometimes used in AKI. Indeed, a
19 recent systematic review and meta-analysis comparing the role of furosemide in prevention and
20 treatment at any stage of AKI concluded that furosemide had neither an impact on mortality nor
21 requirement of renal replacement therapy (12). Moreover, a recent systematic review and meta-
22 analysis in adult surgical patients has shown the use of furosemide in AKI was associated to very low
23 to no firm evidence for benefit or harm (13).
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44 The limitations of our study arise from the fact that it is a retrospective study, which results in some
45 limitations of data collection. Indeed, SCr values were not available every 48h in all patients so that
46 the number of patients, and therefore the prevalence and intensity of AKI may have been
47 underestimated. Furthermore, the urine output is not measured in all the patients in our hospital and
48 was not retained as a marker of AKI. This is a limitation because some patients could meet this criteria
49 without increased SCr and might have underestimated the prevalence of AKI. It is well known that
50 creatinine is secreted at the tubular kidney level so that a significant decrease in GFR is required to
51 translate in an increase of SCr (i.e., when creatinine secretion is saturated).
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3 In addition, the study was conducted on a rather limited number of patients and future studies should
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5 take into account and control comorbidity (i.e., hypertension, diabetes, CKD, aging, dehydration) that
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7 are factors involved in AKI.
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10 **Conclusion**

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15 Our study indicates that the initiation of NSAID therapy in hospitalized patients already treated with
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17 diuretics and RAASI is a risk factor for AKI. The risk of AKI with this triple association appeared higher
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19 than with a dual association. Hospital pharmacists should inform clinicians of the potential risk of AKI
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21 with NSAID initiation in patients treated with diuretics and RAASI, as well as patients to prevent NSAID
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23 self-medication, especially those who experimented an AKI episode during hospitalization.
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28 **Ethical approval retrospective studies**

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33 This study was approved by the hospital's Ethics Committee (number 19.107)
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37 **Conflict of interest**

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42 The authors declare that they have no conflict of interest.
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46 **Data availability statement**

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51 All data relevant to the study are included in the article or uploaded as supplementary material
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55 **Source of Funding**

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60 None.

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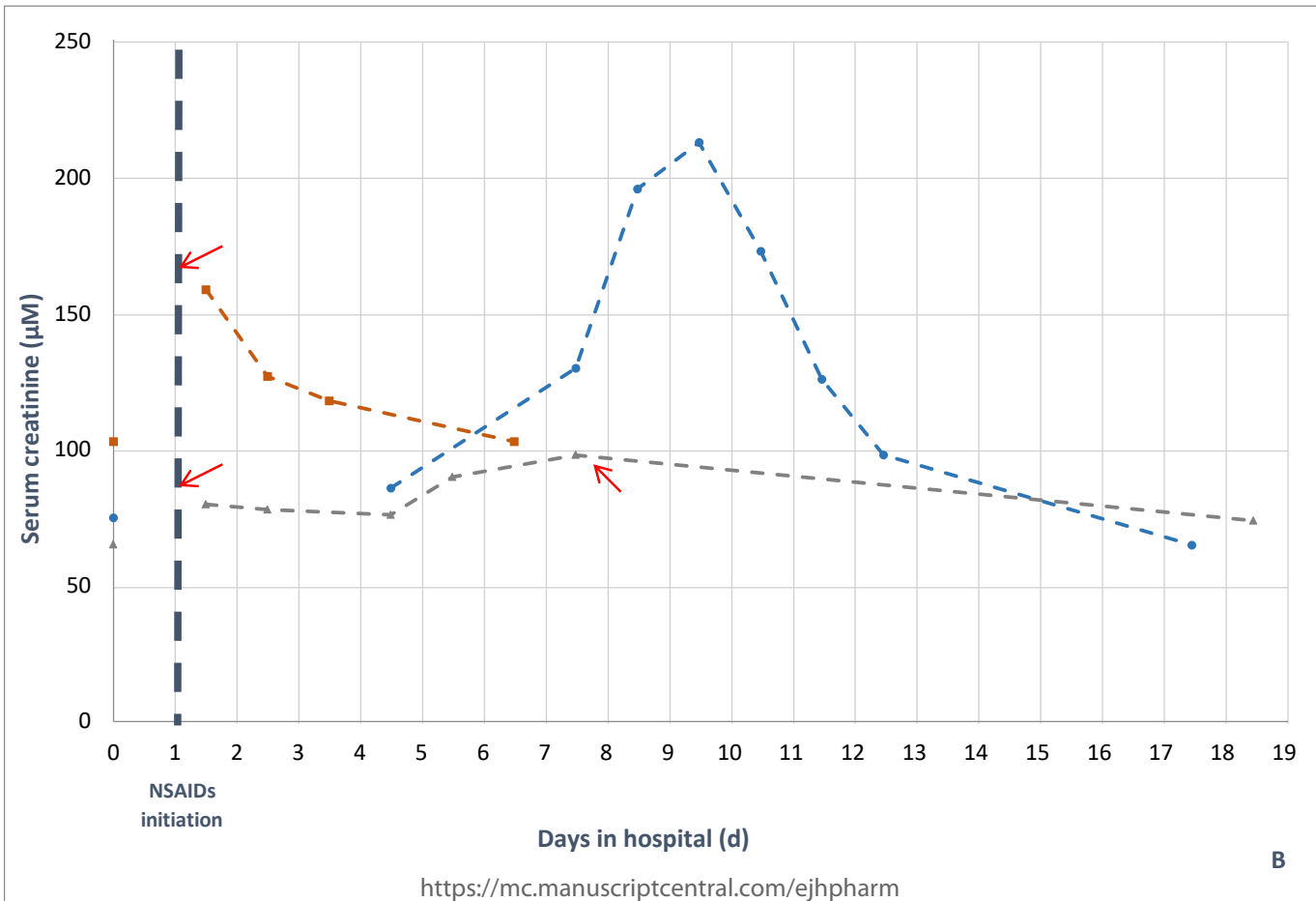
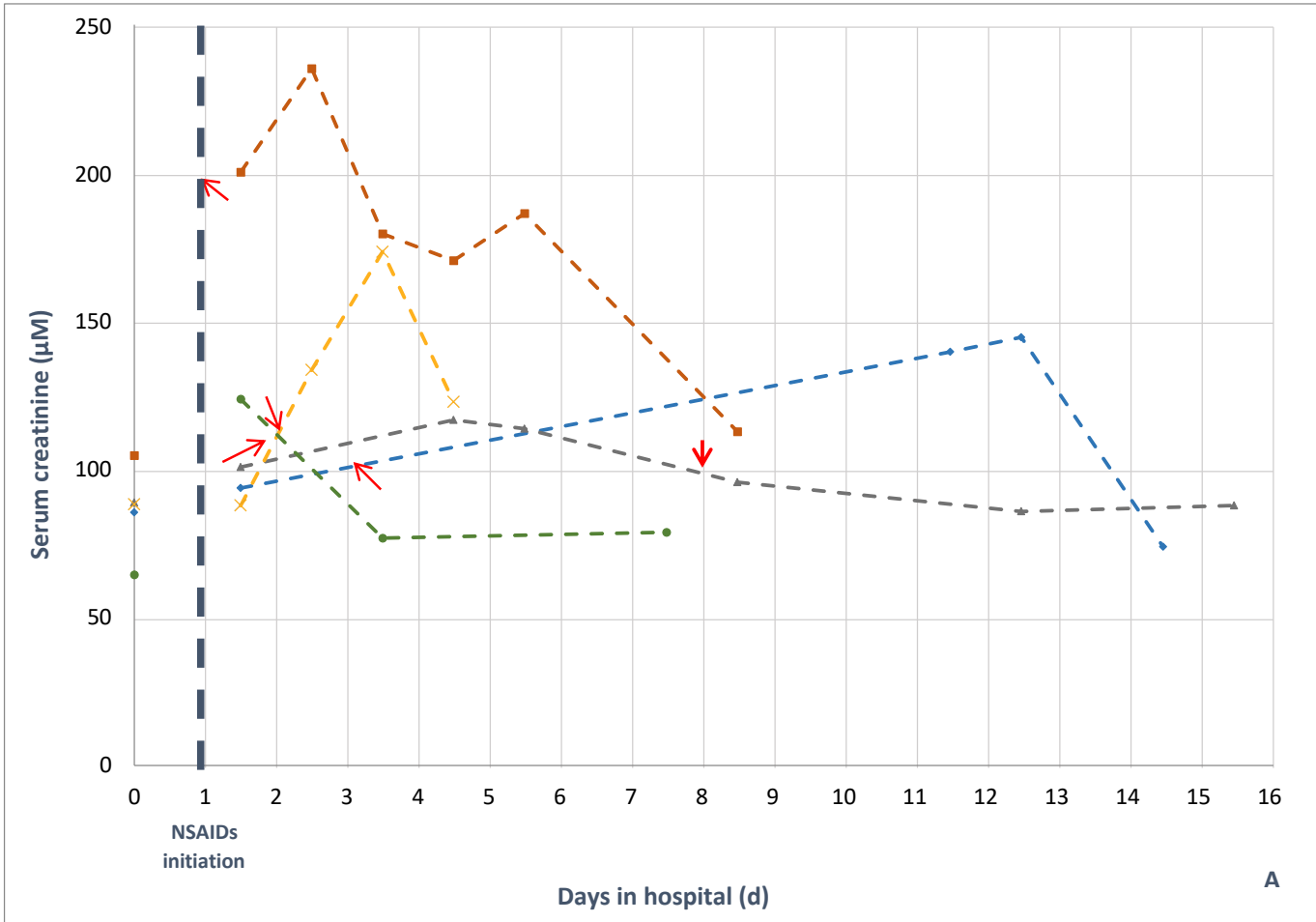
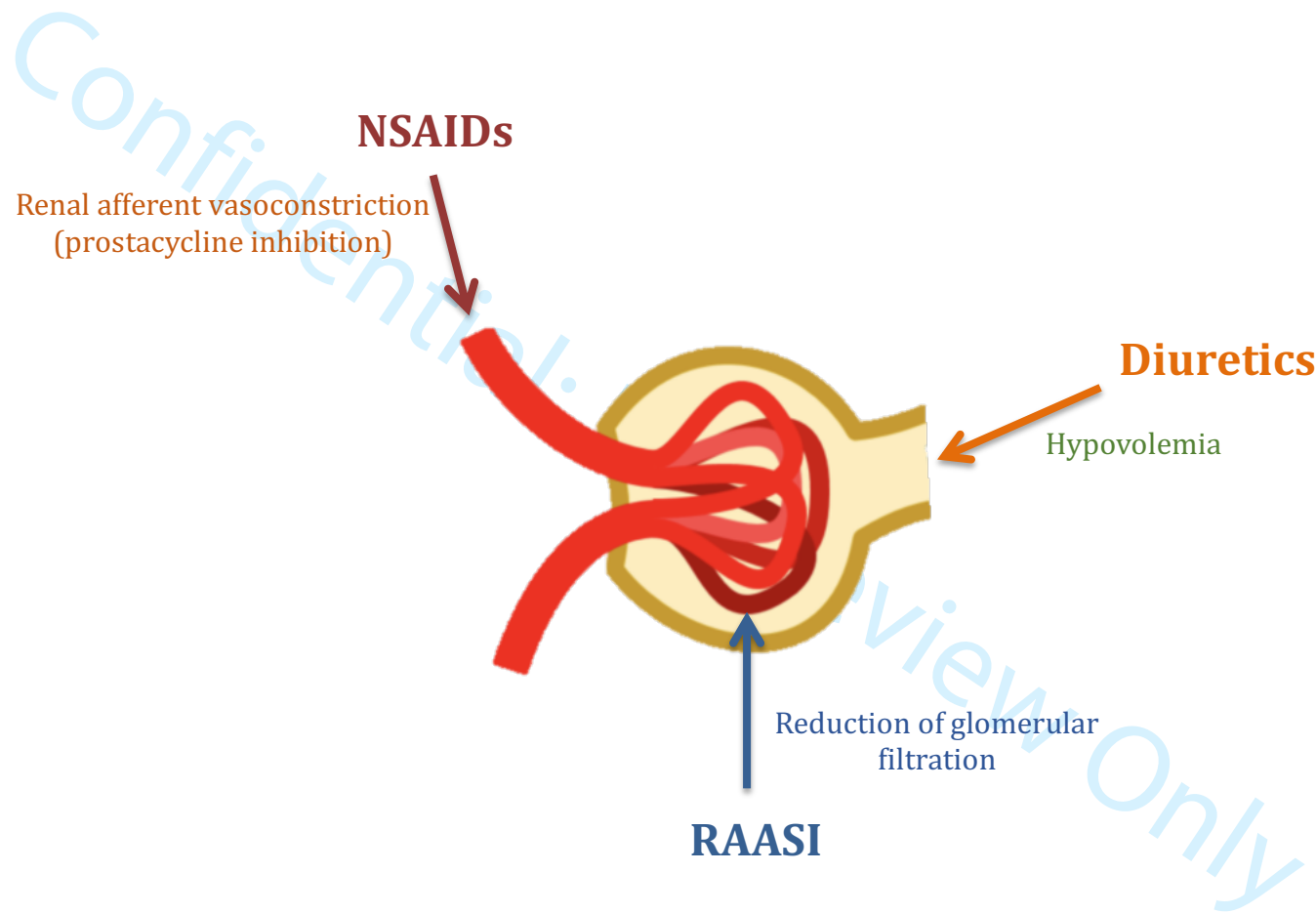


Figure 1: Serum creatinine variations in patients treated by triple (A) and dual (B) association. Triple association has been defined as the concomitant use of NSAIDs with diuretics and RAASI and dual association as the use of NSAIDs and diuretics or RAASI. To be considered as dual or triple association the drugs of interest had to have an overlapping administration for at least 24 hours. SCr reference values are reported at day 0. NSAIDs initiation occurs at day 1. The arrow indicates the last administration of NSAID.

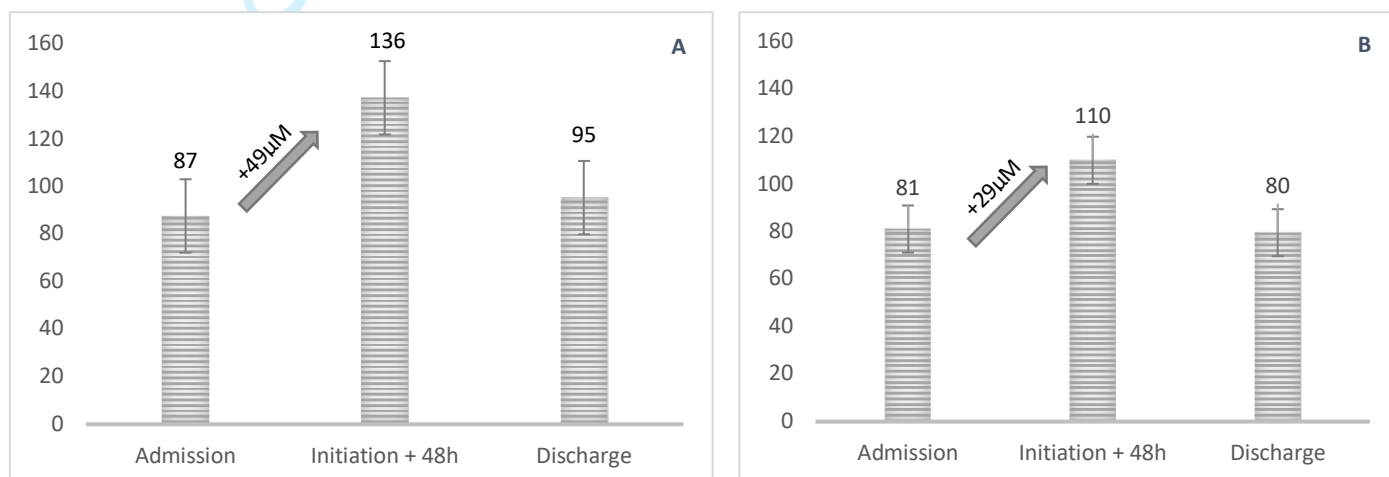
Foot note: Each curve corresponds to a patient identified as having an AKI during hospitalization. SCr reference values in patients was averaged from SCr value at admission and previous SCr values found in the patient record (up to 1 month before).

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Supplementary material 1 : Hemodynamic interactions of non-steroidal anti-inflammatory drugs (NSAIDs) with diuretics and renin angiotensin aldosterone system inhibitors (RAASI).



Supplementary material 2: Average serum creatinine values (\pm SD) in patients with an AKI episode and treated by triple (A) and dual (B) association.

AKI episode was defined according to KDIGO criteria: increase in SCr by $> 26.5 \mu\text{mol/L}$ (or 0.3mg/dL) within 48 hours or increase in SCr to > 1.5 times reference value occurring within the last 7 days.

	Time (days)	Diuretics	RAASI	NSAIDs	SCr (μM)
Patient 1	0	Furosemide 40mg	Candesartan 4mg		86
	1 (NSAIDs initiation)	Cont'd	Cont'd	Ketoprofen 100mg IV	
	2	Cont'd	Cont'd	Cont'd	94
	3		Cont'd	Cont'd	
	4		Cont'd		
	5		Cont'd		
	6		Cont'd		
	7		Cont'd		
	8		Cont'd		
	9		Cont'd		
	10		Cont'd		
	11				
	12				140
	13				145
	14				
	15				74
Patient 2	0	Furosemide 20mg	Candesartan 8mg		105
	1 (NSAIDs initiation)	Furosemide 40mg	Cont'd	Ketoprofen 100mg PO	201
	2				236
	3				180
	4				171
	5				187
	6				
	7				
	8				113
Patient 3	0	Spironolactone 25mg	Perindopril 8mg		89
	1 (NSAIDs initiation)	Cont'd	Cont'd	Ibuprofen 400mg PO	
	2	Cont'd	Cont'd	Ibuprofen 800mg PO	
	3	Cont'd	Cont'd	Cont'd	
	4	Cont'd	Cont'd	Cont'd	
	5	Cont'd	Cont'd	Cont'd	
	6	Cont'd	Cont'd	Cont'd	101
	7	Cont'd	Cont'd	Ibuprofen 400mg PO	
	8	Cont'd	Cont'd	Cont'd	
	9	Cont'd	Cont'd		117
	10	Cont'd			114
	11	Cont'd			
	12	Cont'd			
	13	Cont'd	Perindopril 8mg		96
	14	Cont'd	Cont'd		
	16	Cont'd	Cont'd		
	17	Cont'd	Cont'd		86

	18	Cont'd	Cont'd		
	19	Cont'd	Cont'd		
	20	Cont'd	Cont'd		88
Patient 4	0	Furosemide 60mg + Spironolactone 25mg	Ramipril 2,5mg		88
	1 (NSAIDs initiation)	Furosemide 125 mg + Spironolactone 50mg	Cont'd	Profenid 100mg PO	88
	2	Cont'd	Cont'd	Cont'd	134
	3	Cont'd			174
	4	Furosemide 80mg + Spironolactone 25mg			123
Patient 5	0	Furosemide 40mg	Valsartan 40mg		64,5
	1 (NSAIDs initiation)	Furosemide 40mg	Cont'd	Ketoprofen 200mg PO + 50mg IV	
	2	Furosemide 40mg	Cont'd	Ketoprofen 200mg PO	124
	3		Cont'd		
	4		Cont'd		77
	5	Furosemide 40mg	Valsartan 60mg		
	6		Cont'd		
	7		Cont'd		
	8	Furosemide 40mg	Valsartan 40mg		79

A

	Time (days)	Diuretics	RAASI	NSAIDs	SCr (μM)
Patient 1	0	Furosemide 20mg			75
	1 (NSAIDs initiation)	Cont'd		Ketoprofen 50mg IV	
	2	Cont'd			
	3	Cont'd			
	4	Cont'd			86
	5	Cont'd			
	6				
	7				130
	8				196
	9				213
	10				173
	11				126
	12				98
	13				
	14				
	15				
	16				
17				65	
Patient 2	0		Candesartan 16mg		103
	1 (NSAIDs initiation)		Cont'd	Celecoxib 100mg PO	159
	2		Cont'd		127
	3		Cont'd		118
	4		Cont'd		
	5				
6				103	
Patient 3	0	Furosemide 40mg			65,21
	1 (NSAIDs initiation)	Furosemide 40mg + Spironolactone 25mg		Ibuprofen 400mg PO	80
	2	Furosemide 40mg			78
	3	Cont'd			
	4	Furosemide 60mg			76
	5	Cont'd			90
	6	Furosemide 40mg		Ketoprofen 100mg PO	
	7	Cont'd		Cont'd	98
	8	Cont'd		Ketoprofen 50mg PO	

18				74	

B

Supplementary material 3: Characteristics of patients with AKI and treated with triple association (A) and dual association (B). For each patient, gender, age, body mass index (BMI), co-morbidities, dosing regimen (daily dose) and SCr values were collected. Time column is based on NSAIDs initiation during hospital stay, day 0 corresponds to all SCr values and dosing regimen prior to NSAID initiation (baseline values). Cont'd means treatment continued with the same dosing regimen.