

## Original Article

# Safe use of NSAIDs and RAS-inhibitors at Agogo Presbyterian Hospital, Ghana

Lieke G. Meulendijks<sup>1</sup>, Emmanuel A. Adomako<sup>2</sup>, Emmanuel B. Appiah<sup>3</sup>, Cornelis Kramers<sup>1,4,5</sup>

<sup>1</sup>Department of Pharmacology-Toxicology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands <sup>2</sup>Department of Medicine, Agogo Presbyterian Hospital, Agogo Asante-Akyem, Ghana <sup>3</sup>Pharmacy Department, Agogo Presbyterian Hospital, Agogo Asante-Akyem, Ghana. <sup>4</sup>Department of Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands. <sup>5</sup>Department of Clinical Pharmacy, Canisius Wilhelmina Ziekenhuis, Nijmegen, the Netherlands.

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Corresponding author: Lieke G Meulendijks

E-mail: [l.meulendijks@student.ru.nl](mailto:l.meulendijks@student.ru.nl)

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## SUMMARY

**Background:** Preventable adverse events of medication are an important cause of hospital admissions in the developed world, in which non-steroidal anti-inflammatory drugs (NSAIDs) and renin-angiotensin system (RAS-) inhibitors are frequently involved. NSAIDs and RAS-inhibitors are also often used in Ghana. The purpose of this study is to assess whether biochemical monitoring in patients on RAS-inhibitors, and co-administration of gastro protective agents (GPAs) in patients on NSAIDs, is done properly in Ghana.

**Material and methods:** Two retrospective cross-sectional studies were carried out at the Agogo Presbyterian Hospital, Ghana, in 2013. In 114 out-and inpatients who are on NSAIDs, the risk for gastrointestinal side effects and the frequency of co-administration of GPAs were determined. In 301 outpatients who are on RAS-inhibitors, the risk for renal dysfunction and the frequency of biochemical monitoring were determined. Fisher's exact test was used to determine the statistical strength.

**Results:** Co-administration of GPAs was done in 1.8% of patients on NSAIDs. Serum creatinine and potassium monitoring within one month after initiation of treatment with RAS-inhibitors were performed in 6.3% and 3.7%, respectively. Risk factors were neither associated with prescription of a GPA in patients on NSAIDs ( $p=0.134$ ), nor in performing biochemical monitoring in patients on RAS-inhibitors ( $p=0.219$  for creatinine,  $p=0.062$  for potassium).

**Conclusions:** Biochemical monitoring in patients on RAS-inhibitors and use of GPAs in patients on NSAIDs is poorly performed at the Agogo Presbyterian Hospital in Ghana. Improving the already existing Ghanaian guidelines, especially those for RAS-inhibitors, and encouraging their widespread use among prescribers should be pursued.

**Keywords:** Ghana, Non-Steroidal Anti-Inflammatory Agents, Anti-Ulcer Agents, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Antagonists, Drug monitoring

## INTRODUCTION

Medication use is associated with drug related problems. Preventable adverse events of medication are an important cause of hospital admissions in the developed world.<sup>1</sup> In addition, studies on hospital care in developed countries have shown an adverse event rate of about 10% in patients admitted to hospitals, with many of these medication related.<sup>2-8</sup> Little research has been done concerning medication related adverse events in developing countries.

A study in eight developing African countries found that 8.2% (2.5 – 18.4 %) of the patients on admission had an adverse event, of which 83% were preventable whilst

about 30% resulted in death. Almost 40% of the adverse events were therapeutic errors or drug related. Among patients taking any regular drug and patients with chronic illnesses, the adverse event rate is even higher.<sup>2</sup> In developed countries non-steroidal anti-inflammatory drugs (NSAIDs) and renin-angiotensin system (RAS-) inhibitors (angiotensin-converting-enzyme (ACE)-inhibitors and angiotensin-receptor blockers) are among the top 4 of drugs most commonly involved in adverse drug reactions (ADRs), accounting for 29.6% and 7.7% respectively.<sup>10</sup>

NSAIDs can cause serious gastro-intestinal (GI) complications.<sup>11,12</sup> To prevent these complications it is important to assess risk factors and consequently prescribe gastro protective agents (GPAs) in high risk patients.<sup>11,13</sup> Guidelines of developed countries recommend that patients who are at high risk should receive alternative therapy, or if anti-inflammatory treatment is absolutely necessary, co-therapy with a proton-pump inhibitor (PPI) or misoprostol. They also recommend to use a cyclooxygenase (COX)-2 inhibitor with caution, because its use has been limited by its adverse cardiovascular side effects.<sup>14-16</sup> However, not all high risk patients receive GPAs. Prescription of an effective GPA is seen in only about a third of the high risk patients in developed countries.<sup>17-19</sup>

RAS-inhibitors have many potential beneficial effects because of the widespread actions of the renin-angiotensin-aldosterone system (RAAS): they decrease morbidity and mortality in patients with hypertension, heart failure and renal disease.<sup>20-25</sup> Although they are largely considered to be nephroprotective, they can also cause serious adverse effects, such as hypotension, hyperkalemia and renal function decline.<sup>10,14,26-29</sup> Guidelines and advisory groups in developed countries recommend monitoring of serum potassium and creatinine before initiation of RAS-inhibitors in patients with known risk factors. After initiation patients should be monitored within two weeks. Some guidelines recommend periodic monitoring, depending on the risk factors.<sup>14,30-32</sup> If there is a risk for hyperkalemia, use of concurrent NSAIDs should be avoided if possible. In spite of the largely beneficial effects of RAS-inhibitors, the potential risk of kidney failure in high risk patients should always be considered.<sup>14</sup> In 2006 it was demonstrated that 68,4% of patients on RAS-inhibitors in the US did have at least one serum potassium and one serum creatinine monitoring in a 1-year period.<sup>33</sup> In 2011 it was demonstrated in the Netherlands that, in patients who were started on RAS-inhibitors therapy, only 34% had serum creatinine level measurements within 3 weeks after onset of treatment, whilst serum potassium level was assessed in only 28% of the patients. In high risk patients the frequency of creatinine monitoring was even lower, at 22%.<sup>34</sup>

NSAIDs and RAS-inhibitors are also available and frequently used in Ghana. However, there is hardly any literature describing the frequency of their use and whether prescribers take into account risk factors when deciding to perform biochemical monitoring in patients on RAS-inhibitors, and when deciding to co-administer GPAs in patients on NSAIDs. A review showed that the prevalence of hypertension in Ghana (BP  $\geq$  140/90 mmHg) ranged from 19% to 48%.<sup>35</sup> Among out-patients

with hypertension in Ghana, renal disease is an important complication, especially in those with severe hypertension; 30.2% developed a creatinine  $>$  140 mmol/L.<sup>36</sup> Another study in Ghana showed that chronic kidney disease (CKD) is common in hypertensive patients, with a prevalence of 46.9%.<sup>37</sup>

The Ministry of Health in Ghana has developed Standard Treatment Guidelines, which are designed to be used as a guide on treatment choices and as a reference to help in the overall management of patients. The guidelines list the preferred treatments for common health problems, but give, especially for RAS-inhibitors, limited advice about monitoring and the safe use of medication.<sup>38</sup> If preventive measures whilst using NSAIDs and RAS-inhibitors are not taken, it may increase the risk of serious nephrotoxicity and GI toxicity, which may even be fatal. This presents a dire scenario in a developing country like Ghana, where renal replacement therapy is mostly not an option and blood transfusions for GI bleeding may not always be available. There is therefore an urgent need to characterize this problem in order to be able to develop and implement strategies including guidelines which would promote safe use of NSAIDs and RAS-inhibitors.

## METHODS

### Setting

The study took place at the Agogo Presbyterian Hospital in Agogo, Ghana. It is the second largest hospital in the Ashanti Region of Ghana and a referral center for many hospitals. Although it is officially designated as a district hospital, its size, range of service provision and service outputs easily place it in the category of regional hospitals. It covers the Asante-Akim Area, which spans three administrative districts with a population of 169,976 (2010 census).<sup>39</sup> The hospital has 233 beds.

### Study population

#### *NSAID*

Among outpatients, patients aged  $\geq$ 18 years who visited the outpatient department between 16-Oct-2013 and 18-Dec-2013 and received a prescription of an NSAID were included. Inclusion criteria were a new prescription of an NSAID for at least 5 days, and one other prescription for an NSAID in the last three months. Among inpatients, post-operative patients aged  $\geq$ 18 years who received an NSAID between 08-Oct-2013 and 21-Dec-2013 were included. They usually receive an NSAID initially for about 5-7 days.

#### *RAS-inhibitors*

Patients aged  $\geq$ 18 years who visited the outpatient department between 14-Oct-2013 and 04-Dec-2013 and received a prescription of a RAS-inhibitor were included.

ed. Inclusion criteria were prescription of the RAS-inhibitor for at least one month.

### Data collection

#### NSAIDs

Medical records of outpatients were reviewed in the hospital pharmacy, where patients came to pick up their new medication after outpatient department (OPD) visits. If patients had a treatment window of more than six months, data of the last treatment episode was used for the study. Medical records of inpatients were reviewed on the two surgical wards and the intensive care unit of the hospital, the day after the surgery. Information was obtained on demographic characteristics, co-morbidity, co-medication, the dose of the NSAID, chronic use (defined as NSAIDs described  $\geq 15$  days during the last month or a new prescription of  $\geq 15$  days) and prescription of a GPA. Side effects of GI-bleeding, other bleeding and pain in stomach area, including symptoms of epigastric pain, GI ulcer and gastritis, were recorded. For inpatients, data was collected on the day after the surgery and therefore GI side effects after initiation of therapy were not included in the analysis.

#### RAS-inhibitors

Medical records were reviewed in the hospital pharmacy, where patients came to pick up their new medication after OPD visits. If patients had a treatment window of more than six months, data of the last treatment episode was used for the study. Information was obtained on demographic characteristics, co-morbidity, co-medication, measurements of serum creatinine and potassium within 6 months before start of therapy, and measurements of serum creatinine and potassium after start of therapy, within and after one month. Side effects of high creatinine (serum creatinine level  $>125.0$  mmol/L) and hyperkalemia (serum potassium level  $> 5.4$  mmol/L) were recorded. If biochemical monitoring was done more than once, the date of the last value before start of therapy was used, and the date of the first value after start of therapy was used for defining the time within which monitoring was done.

### Prevalence of risk factors

#### NSAIDs

The number of risk factors for GI-problems was determined. Risk factors for GI-problems included: high dose of NSAID, multiple NSAIDs, age  $> 70$  years, history of GI-ulcer, co-morbidity of diabetes, heart failure or severe rheumatoid arthritis, concomitant use of anticoagulant, acetyl salicylic acid (including low dose) or corticosteroids. The total number of risk factors were enumerated. High risk patients were defined as patients who have  $>2$  risk factors, are  $>70$  years old or have a history of GI-ulcer.

#### RAS-inhibitors

The number of risk factors for renal dysfunction was determined. Risk factors included: age  $> 70$  years, co-morbidity of renal dysfunction, heart failure or diabetes mellitus and concomitant use of diuretics or NSAIDs. The total number of risk factors were enumerated. High risk patients were defined as patients who have  $>2$  risk factors.

### Ethical consideration

The Committee on Human Research, Publication and Ethics of the Kwame Nkrumah University of Science and Technology (KNUST) School of Medical Sciences & Komfo Anokye Teaching Hospital in Kumasi, Ghana, gave approval for the study. Patient data were collected anonymously.

### Data analysis

#### NSAIDs

The frequency of a prescription of a GPA was determined. Fisher's exact test was used to determine the statistical strength of the associations between risk groups or single risk factors and prescription of a GPA.

#### RAS-inhibitors

The frequencies of serum creatinine and potassium monitoring before and after initiation of RAS-inhibitor therapy were determined. The main outcome was the frequency of biochemical monitoring within 1 month after initiation of RAS-inhibitor therapy. Fisher's exact test was used to determine the statistical strength of the associations between risk groups or single risk factors and biochemical monitoring after initiation of therapy.

Variables that were associated with a p-value lower than 0.05 were considered statistically significant. Univariate analysis was used to calculate odds ratios for the various risk groups and single risk factors. All analyses were performed using the SPSS statistical software version 21.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### NSAIDs

#### Cohort

In the timeframe of the study 117 patients received a prescription of an NSAID; 53 of them were outpatients. 3 patients were excluded because of missing data, which resulted in a population of 114 patients for the study (Table 1). The mean age of the study population was 54 years (range 18-98 years) and among this population 55,3% were female.

**Table 1** Baseline characteristics of patients on NSAID

Characteristic (NSAID)	Value [n (%)]
Total no. of patients	114
Outpatients	47 (41.2%)
Inpatients	67 (58.8%)
Sex	
Male	51 (44.7%)
Female	63 (55.3%)
Age [y]	54 (18-98) <sup>a</sup>
Medical history	
Heart failure	2 (1.8%)
GI-ulcer	14 (12.3%)
Diabetes mellitus	11 (9.6%)
Severe rheumatoid arthritis	0
Co-medication	
Anticoagulant	0
Concomitant acetyl salicylic acid	7 (6.1%)
Corticosteroids	0
Dose	
Normal recommended dose	86 (75.4%)
High dose	28 (24.6%)
Multiple NSAIDs	1 (0.9)
Risk group gastrointestinal toxicity	
High risk <sup>b</sup>	34 (29.8%)
Intermediate risk <sup>c</sup>	25 (21.9%)
Low risk <sup>d</sup>	55 (48.2%)

a mean (range)

b defined as >2 risk factors, >70 years old or history of GI-ulcer.

c defined as 1-2 risk factors

d defined as no risk factors

*Gastroprotective agent*

Among all NSAIDs patients, 34 (29.8%) were defined as high risk for gastrointestinal toxicity and 25 (21.9%) as intermediate risk. GPAs were prescribed in 2 patients (1.8%) receiving an NSAID, these were both high risk patients. Of the chronic users one out of eight patients (12.8%) received a GPA. There was no statistically significant association found between the different risk groups and the use of a GPA (p = 0.134) (Table 2). Univariate analysis showed that none of the variables were associated with prescription of a GPA.

**Table 2** Use of gastroprotective agent (GPA) during NSAID therapy

Variable	Use of GPA [n (%)] <sup>a</sup>
High risk (n=34)	2 (5.9%)
Intermediate risk (n=25)	0
Low risk (n=55)	0
Total (n=114)	2 (1.8%)

GPA = Gastroprotective agent

a = Fisher's exact test: p = 0.134

*Gastrointestinal complaints*

In outpatients who were on NSAIDs, GI-bleedings and other bleedings were not seen. Complaints of pain in stomach area were seen in 8 patients (17.0%). None of these patients was using a GPA. Among high risk patients 2 patients (5.9%) had complaints of pain in the stomach area.

**RAS-inhibitors**

*Cohort*

In the timeframe of the study 305 patients received a prescription of a RAS-inhibitor. Of this population, 4 patients were excluded because of missing data, which resulted in a population of 301 patients for the study (Table 3). The mean age of the study population was 62 years (range 22-93 years) and among this population 73.8% were female.

**Table 3** Baseline characteristics of patients on RAS-inhibitors

Characteristic (RAS-I)	Value [n (%)]
Total no. of patients	301
Sex	
Male	79 (26.2%)
Female	222 (73.8%)
Age [y]	62 (22-93) <sup>a</sup>
Medical history	
Heart failure	15 (5.0%)
Chronic kidney disease	7 (2.3%)
Diabetes mellitus	72 (23.9%)
Co-medication	
NSAIDs	66 (21.9%)
Loop diuretics	12 (4.0%)
Thiazide diuretics	78 (25.9%)
Potassium-sparing diuretics	4 (1.3%)
Risk group kidney function decline	
High risk (>2 risk factors)	19 (6.3%)
Intermediate risk (1-2 risk factors)	200 (66.4%)
Low risk (no risk factors)	82 (27.2%)

a mean (range)

RAS-I = renin-angiotensin system inhibitor

*Serum creatinine and potassium monitoring*

The serum creatinine level was measured in 12 patients (4.0%) within less than 6 months before initiation of therapy. After initiation of therapy, it was measured in 19 patients (6.3%) within 1 month and in 57 patients (18.9%) at least once after initiation of therapy (table 4). The serum potassium level was measured in 4 patients (1.3%) within less than 6 months before initiation of therapy. After initiation of therapy, it was measured in 11 patients (3.7%) within 1 month and in 28 patients (9.3%) at least once after initiation of therapy (Table 5).

Among all RAS-inhibitor patients, 19 (6.3%) were defined as high risk for kidney function decline and 200 (66.4%) as intermediate risk. Among high risk patients, creatinine monitoring was measured in 1 patient (5.3%) within 1 month after initiation of therapy. In intermediate risk patients and low risk patients this was respectively 16 patients (8.0%) and 2 patients (2.4%). Potassium monitoring within 1 month was never measured in high risk and low risk patients and in 11 intermediate

risk patients (5.5%). There was no statistically significant association found between the different risk groups and creatinine monitoring <6 months before start of therapy ( $p = 0.373$ ), <1 month after start of therapy ( $p = 0.219$ ) and ever after start of therapy ( $p = 0.078$ ) (Table 4). Univariate analysis showed that none of the variables were associated with the frequency of creatinine monitoring within one month after initiation of therapy.

**Table 4** Creatinine monitoring in different risk groups before and during renin-angiotensin system inhibitor (RASi) therapy

Variable	Monitoring <6 months before start of therapy ([n (%)] <sup>a</sup> )	Monitoring after start of therapy ([n (%)]		
		<1 month <sup>b</sup>	>1 month	Total <sup>c</sup>
High risk (n=19)	1 (5.3%)	1 (5.3%)	2 (10.5%)	3 (15.8%)
Intermediate risk (n=200)	6 (3.0%)	16 (8.0%)	29 (14.5%)	45 (22.5%)
Low risk (n=82)	5 (6.1%)	2 (2.4%)	7 (8.5%)	9 (11.0%)
Total (n=301)	12 (4.0%)	19 (6.3%)	38 (12.6%)	57 (18.9%)

Fisher's exact test:  
a  $p = 0.373$   
b  $p = 0.219$   
c  $p = 0.078$

There was found a statistically significant association between the different risk groups and potassium monitoring performed at least once after initiation of therapy ( $p = 0.022$ ). No statistically significant association was found between the different risk groups and potassium monitoring <6 months before start of therapy ( $p =$

0.679) and <1 month after start of therapy ( $p = 0.062$ ) (Table 5). Univariate analysis showed that none of the variables were associated with the frequency of potassium monitoring within one month after initiation of therapy.

**Table 5** Potassium monitoring in different risk groups before and during renin-angiotensin system inhibitor (RASi) therapy

Variable	Monitoring <6 months before start of therapy ([n (%)] <sup>a</sup> )	Monitoring after start of therapy ([n (%)]		
		<1 month <sup>b</sup>	>1 month	Total <sup>c</sup>
High risk (n=19)	0	0	2 (10.5%)	2 (10.5%)
Intermediate risk (n=200)	2 (1.0%)	11 (5.5%)	13 (6.5%)	24 (12.0%)
Low risk (n=82)	2 (2.4%)	0	2 (2.4%)	2 (2.4%)
Total (n=301)	4 (1.3%)	11 (3.7%)	17 (5.6%)	28 (9.3%)

Fisher's exact test:  
a  $p = 0.679$   
b  $p = 0.062$   
c  $p = 0.022$

Of the RAS-inhibitor patients, 20 patients (6.6%) received the combination of a RAS-inhibitor together with a diuretic and an NSAID, the so called 'triple whammy', what is associated with an increased risk of acute kidney injury.<sup>40, 41</sup> These patients neither had measurement of serum creatinine or potassium within 6 months before initiation of therapy nor within 1 month after initiation of therapy. In 2 patients (10.0%) serum creatinine was measured at least once after initiation of therapy.

Serum potassium was never measured after initiation of therapy. No statistically significant association was found.

*Results of biochemical monitoring*

Among all RAS-inhibitor patients there were 2 patients (0.7%) who were both monitored for serum creatinine within 6 months before and within 1 month after initiation of therapy. These two patients had no kidney function decline. For serum potassium, there were no patients who were monitored this way.

In patients who had measurement of serum creatinine within one month after initiation of therapy, 4 patients (25.0%) developed a high serum creatinine within this period. These were all intermediate risk patients. In patients who had at least one measurement of serum creatinine after initiation of therapy, 18 patients (31.6%) developed a high serum creatinine. These were all intermediate risk patients as well.

None of the patients who had measurement of serum potassium within one month after initiation of therapy developed hyperkalemia within this period. In patients who had at least one measurement of serum potassium after initiation of therapy, 2 patients (7.1%) developed hyperkalemia. These were both intermediate risk patients.

### DISCUSSION

This is the first study to assess whether prescribers in sub-Saharan Africa take into account risk factors in their decision to perform biochemical monitoring in patients on RAS-inhibitors, and whether co-administration of GPAs in patients on NSAIDs is done properly. Although the risks of kidney function decline and hyperkalemia due to RAS-inhibitors, as well as the GI side effects of NSAIDs, are well known, we found that prescribers at the Agogo Presbyterian Hospital barely took these risks into account when prescribing these drugs. Biochemical monitoring in patients on RAS-inhibitors and co-administration of GPAs in patients on NSAIDs were scarcely done.

#### *NSAIDs*

Among all patients on NSAIDs, only 2 patients (1.8%) received a GPA. None of the five people who were at high risk for gastrointestinal toxicity received a GPA. Compared with literature from developed countries, that reported that about one-third of high risk patients were treated with a GPA, the number we found is remarkably low.<sup>17,18</sup> However, one has to take into account that the standard Ghanaian treatment guidelines only recommend a GPA when an NSAID is used for more than two weeks.<sup>38</sup> So in this respect there was no guideline violation. However, in the US, Canadian and Dutch guidelines there is no duration of NSAID treatment given at which one should start a GPA.<sup>14,15,42</sup> The national health service (NHS) of the United Kingdom has the statement that there is an increased risk of serious GI adverse events as soon as NSAID treatment is initiated and therefore concludes that prescription of a GPA is independent of the duration of NSAID use.<sup>43</sup> In our study there were only 6 out of 114 patients who used the NSAID > 14 days and none of them used GPA.

#### *RAS-inhibitors*

Creatinine monitoring within one month after initiation of therapy was only performed in about one-sixteenth (6.3%) of the patients. In patients at high risk for renal dysfunction this was 5.3%. Potassium monitoring was even less frequently done, namely in 3.7% of patients. Irrespective of the period since initiation of therapy, creatinine was monitored at least once in 18.9% of patients, potassium in 9.3%. Compared with two other studies, which were done only in developed countries, these numbers are remarkably low. In a Dutch study, serum creatinine monitoring within 3 weeks after initiation of therapy was measured in 34% of patients and in a study from the US 68.4% of patients were monitored for serum creatinine within 1 year.<sup>33,34</sup> The only significant association found was the association between the risk group categories and potassium monitoring ever performed after initiation of therapy. Considering that the study did not find rigorous and consistent biochemical monitoring, this finding was perhaps a chance event. High creatinine was found in 21.1% of patients who were monitored for serum creatinine within one month after initiation of RAS-inhibitor therapy. This suggests that among these patients, an important number may have kidney function decline. However, there was no baseline serum creatinine level known and therefore we cannot say anything about whether the use of the RAS-inhibitor is the cause of high creatinine.

We do not know why prescribers perform so little biochemical monitoring and why there is so little co-administration of GPAs. A possible cause is that only 35% of the Ghanaian population has a total active membership of the National Health Insurance.<sup>44</sup> Monitoring of serum creatinine and potassium are reimbursed. Although, for the two-third of the population who do not have health insurance, it could be that patients are not able to pay for it or prescribers may consider biochemical monitoring to be too expensive for the patients.

PPIs and H<sub>2</sub>-antagonists are only covered for treating ulcers and not as preventive drugs. This could be the reason of the remarkably low number of their prescriptions. Another possible cause may be the lack of appreciation of drug safety and monitoring among prescribers. Next to that, a possible cause is that there are, especially for RAS-inhibitors, no clear guidelines. There are guidelines in Ghana, which are developed by the Ministry of Health, but these are limited: For NSAIDs it is mentioned that patients with chronic kidney disease and heart failure should not be given NSAIDs, and a PPI should be given if treatment is going to exceed 2 weeks. There is not much said about biochemical monitoring in patients on RAS-inhibitors; the guidelines state that serum creatinine is one of the investigations to be per-

formed when patients are diagnosed with hypertension and that potassium should be monitored periodically. There is no time frame mentioned.<sup>38</sup> This leads to a situation where every prescriber may take their own individual approach. This can result in alterations in medication with every patient visit, as well as confusion among prescribers and patients. Our study was done in a hospital which has the capacity to undertake biochemical monitoring, a service which may be unavailable in many district hospitals in Ghana.

The results of this study show that a lot needs to be done to improve the safe use of RAS-inhibitors and NSAIDs in Ghana. We think that improving the existing Ghanaian guidelines and encouraging their widespread use among prescribers should be pursued. In order to develop these guidelines it is important to investigate why prescribers perform so little biochemical monitoring and why they prescribe so little GPAs. Future studies should be multi-centered, using hospitals with capacity to undertake biochemical monitoring. While developing these guidelines, it is important to take into account the best options suited to the Ghanaian situation, where health care has less possibilities than in developing countries. It should be noted that in the coming years, access to healthcare may improve and the incidence of mainly Western diseases will increase.<sup>45,46</sup> Consequently the incidence of medication related adverse events will maybe also increase.

### Limitations

Our study may have several limitations. First, we did not investigate whether the prescriber ordered laboratory tests that the patient did not complete. It is possible that patients did not want to do an ordered blood test or did not understand the need for it. Secondly, handwritten medical records were used. Mistakes in reading by prescribers or by researchers while collecting data is possible. Thirdly, the study was performed in one hospital and with a relatively small number of patients. Despite this, we think that our results may also reflect other hospitals in Ghana and maybe even hospitals in other developing countries, because the Agogo Presbyterian Hospital is typical in its function as a large district hospital and is a place where patients from a large region in the country are seen. Fourthly, we did not have information about medication history or laboratory testing outside the Agogo Presbyterian Hospital. It is possible that this information was known among prescribers, but was not recorded in the patient medical record of the Agogo Presbyterian Hospital. Lastly, NSAIDs are readily available in Ghana without prescription. In our study we did not have information about the use of non-prescribed NSAIDs in addition to the prescribed NSAIDs. This combination can result in a higher dose

or a prolonged use and consequently a higher risk for kidney function decline and GI toxicity. On the other hand, we did not know if patients really used their prescribed medication and whether they used it in the right way.

### Conclusions

We demonstrated that biochemical monitoring in patients on RAS-inhibitors and co-administration of GPAs in patients on NSAIDs is poorly performed. The low numbers of biochemical monitoring and co-administration of GPAs clearly demonstrate the need for improvement. Especially in Ghana, where healthcare options may be limited, this is a serious situation. Our findings stress the need to investigate in a multi-centered study why these numbers are so low. However, one has to take into account that the standard Ghanaian treatment guidelines only recommend a GPA when an NSAID is used for more than two weeks.<sup>38</sup> So in this respect there was no guideline violation. Improving the already existing Ghanaian guidelines, especially those for RAS-inhibitors, and encouraging their widespread use among prescribers should be pursued.

### Statement

Our work has been presented as a poster presentation at the European Association for Clinical Pharmacology and Therapeutics (EACPT) 2015 meeting in Madrid. Only the abstract has been published, there was no access to our manuscript. There will be no other publication than in Ghana Medical Journal.

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### REFERENCES

1. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365(21):2002-12.
2. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ*. 2004;170(11):1678-86.
3. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med*. 1991;324(6):370-6.
4. Davis P, Lay-Yee R, Briant R, Ali W, Scott A, Schug S. Adverse events in New Zealand public

- hospitals I: occurrence and impact. *N Z Med J*. 2002;115(1167):U271.
5. Davis P, Lay-Yee R, Briant R, Ali W, Scott A, Schug S. Adverse events in New Zealand public hospitals II: preventability and clinical context. *N Z Med J*. 2003;116(1183):U624.
  6. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med care*. 2000;38(3):261-71.
  7. Levinson D Department of Health and Human Services. Adverse events in hospitals: National incidence among medi-care beneficiaries. United States, 2010. Available from: <http://oig.hhs.gov/oei/reports/oei-06-09-00090.pdf>.
  8. Soop M, Fryksmark U, Koster M, Haglund B. The incidence of adverse events in Swedish hospitals: a retrospective medical record review study. *Int J Qual Health Care*. 2009;21(4):285-91.
  9. Wilson RM, Michel P, Olsen S, Gibberd RW, Vincent C, El-Assady R, et al. Patient safety in developing countries: retrospective estimation of scale and nature of harm to patients in hospital. *BMJ*. 2012;344:e832.
  10. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-9.
  11. Dubois RW, Melmed GY, Henning JM, Bernal M. Risk of Upper Gastrointestinal Injury and Events in Patients Treated With Cyclooxygenase (COX)-1/COX-2 Nonsteroidal Antiinflammatory Drugs (NSAIDs), COX-2 Selective NSAIDs, and Gastroprotective Cotherapy: An Appraisal of the Literature. *J Clin Rheumatol*. 2004;10(4):178-89.
  12. Gutthann SP, Garcia Rodriguez LA, Raiford DS. Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiology*. 1997;8(1):18-24.
  13. Adebajo A. Non-steroidal anti-inflammatory drugs for the treatment of pain and immobility-associated osteoarthritis: consensus guidance for primary care. *BMC Fam Pract*. 2012;13:23.
  14. Ministerie van Volksgezondheid, Welzijn en Sport (VWS); Expert Group Medicatieveiligheid. Hospital admissions related to medication (HARM) wrestling rapport: Een voorstel van de Expertgroep Medicatieveiligheid m.b.t. concrete interventies die de extramurale medicatieveiligheid op korte termijn kunnen verbeteren. The Netherlands, 2009. Available from: <http://www.rijksoverheid.nl/documenten-en-publicaties/rapporten/2008/02/25/rapport-expertgroep-medicatieveiligheid.html>
  15. Lanza FL, Chan FK, Quigley EM, Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104(3):728-38.
  16. College voor Zorgverzekeringen. Farmacotherapeutisch Kompas: prostaglandinesynthetaseremmers. The Netherlands [Accessed 2014 Feb 24]; Available from: <http://www.fk.cvz.nl/inleidendeteksten/i/inl%20prostaglandinesynthetaseremmers.asp>.
  17. Kolarz G, Mayrhofer F, Neumann K, Singer F. Adverse effects of non-steroidal anti-inflammatory drugs. A prevalence study in Austria. *Wien Klin Wochenschr*. 2003;115(1-2):41-6.
  18. Cote GA, Norvell JP, Rice JP, Bulsiewicz WJ, Howden CW. Use of gastroprotection in patients discharged from hospital on nonsteroidal anti-inflammatory drugs. *Am J Ther*. 2008;15(5):444-9.
  19. Valkhoff VE, van Soest EM, Sturkenboom MC, Kuipers EJ. Time-trends in gastroprotection with nonsteroidal anti-inflammatory drugs (NSAIDs). *Aliment Pharmacol Ther*. 2010;31(11):1218-28.
  20. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet*. 2001;358(9290):1305-15.
  21. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet*. 2003;361(9372):1843-8.
  22. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet*. 2000;355(9200):253-9.
  23. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327(10):669-77.
  24. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet*. 1999;354(9176):359-64.
  25. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med*. 1996;334(15):939-45.
  26. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause pre-



- ventable admissions to hospital? A systematic review. *Br J Clin Pharmacol.* 2007;63(2):136-47.
27. Howard RL, Avery AJ, Howard PD, Partridge M. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. *Qual Saf Health Care.* 2003;12(4):280-5.
  28. Schneeweiss S, Hasford J, Gottler M, Hoffmann A, Riethling AK, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. *Eur J Clin Pharmacol.* 2002;58(4):285-91.
  29. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, Group HS. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med.* 2008;168(17):1890-6.
  30. Nederlands Huisartsen Genootschap (NHG). Standaard Diabetes mellitus type 2. The Netherlands, 2013 [Accessed 2014 Jan 26]; Available from: <https://www.nhg.org/standaarden/samenvatting/diabetes-mellitus-type-2>.
  31. Nederlands Huisartsen Genootschap (NHG) Standaard Cardiovasculair risicomanagement (CVRM). The Netherlands, 2012 [Accessed 2014 Jan 26]; Available from: <https://www.nhg.org/standaarden/samenvatting/cardiovasculair-risicomanagement>.
  32. Nederlands Huisartsen Genootschap (NHG). Standaard Hartfalen. The Netherlands, 2010 [Accessed 2014 Jan 26]; Available from: <https://www.nhg.org/standaarden/volledig/nhg-standaard-hartfalen>.
  33. Raebel MA, McClure DL, Simon SR, Chan KA, Feldstein A, Andrade SE, et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf.* 2007;16(1):55-64.
  34. Bootsma JE, Warle-van Herwaarden MF, Verbeek AL, Fussenich P, De Smet PA, Olde Rikkert MG, et al. Adherence to biochemical monitoring recommendations in patients starting with renin angiotensin system inhibitors: a retrospective cohort study in the Netherlands. *Drug Saf.* 2011;34(7):605-14.
  35. Bosu WK. Epidemic of hypertension in Ghana: a systematic review. *BMC Public Health.* 2010;10:418.
  36. Plange-Rhule J, Phillips R, Acheampong JW, Sagar-Malik AK, Cappuccio FP, Eastwood JB. Hypertension and renal failure in Kumasi, Ghana. *J Hum Hypertens.* 1999;13(1):37-40.
  37. Osafo C, Mate-Kole M, Affram K, Adu D. Prevalence of chronic kidney disease in hypertensive patients in Ghana. *Ren Fail.* 2011;33(4):388-92.
  38. Standard Treatment Guidelines, sixth edition. Ghana, 2010 [Accessed 2014 Feb 24]; Available from: [apps.who.int/medicinedocs/documents/s18015en/s18015en.pdf](http://apps.who.int/medicinedocs/documents/s18015en/s18015en.pdf)
  39. The Asante Akim Central Municipal. About this municipality. [Accessed 2015 Sept 12]; Available from: <http://asanteakimnorth.ghanadistricts.gov.gh/>.
  40. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. 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.* 2013;346:e8525.
  41. Loboz KK, Shenfield GM. Drug combinations and impaired renal function -- the 'triple whammy'. *Br J Clin Pharmacol.* 2005;59(2):239-43.
  42. Rostom A, Moayyedi P, Hunt R, Canadian Association of Gastroenterology Consensus G. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. *Aliment Pharmacol Ther.* 2009;29(5):481-96.
  43. National Health Service (NHS); East & South East England Specialist Pharmacy Services. Achieving Appropriate Prescribing of Non-Steroidal Anti-inflammatory Drugs (NSAIDs): Briefing paper for secondary care providers. United Kingdom, 2011. Available from: <http://www.medicinesresources.nhs.uk/en/Communities/NHS/SPS-E-and-SE-England/Meds-use-and-safety/Patient-safety/Learning-safety-solutions/NSAIDs/NSAIDs-Briefing-paper-for-secondary-care-providers---Aug11-/>
  44. National Health Insurance Authority. Annual Report 2012. Ghana. Available from: <http://www.nhis.gov.gh/files/2012%20NHIA%20ANNUAL%20REPORT.pdf>.
  45. Adeloye D, Basquill C. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. *PloS One.* 2014;9(8):e104300.
  46. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract.* 2014;103(2):137-49