

# The Impact of Concurrent Use of Diuretics, RAAS Inhibitors with Non-steroidal Anti-inflammatory Drugs “Triple Whammy” on Renal Function

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## Abstract

**Objective:** This study aimed to evaluate the concomitant use of diuretics, angiotensin-converting-enzyme inhibitors/angiotensin receptor blocker (ACEIs/ARBs) and non-steroidal anti-inflammatory drugs, frequently termed as “Triple Whammy,” prescribed among out-patients. It also aimed to determine the impact of this combination on patients’ renal function. **Methodology:** A retrospective and observational study was conducted in a hospital located in the state of Selangor, Malaysia. Patients who were receiving two or more of triple whammy agents were reviewed and analyzed. The associations between the prescriptions and patients’ demographics and comorbidities were tested using the Chi-square test. On the other hand, a paired sample *t*-test was used to determine the impact of prescriptions on renal function with a consideration of statistical significance when  $P < 0.05$ . **Results:** Out of 412 prescriptions (60.2% male) were included in this study, 407 prescriptions were containing two of the mentioned medication with only 5 prescriptions for triple whammy. The majority of prescriptions had (64.1%) ACEIs/ARBs and diuretics, and it was mainly prescribed to hypertensive patients (98.5%) aged less than 65 years old (38.3%). Furthermore, males were more likely to receive this combination of ACEIs/ARB and diuretics than females ( $P < 0.001$ ) due to the fact that the male gender is considered as a risk factor for cardiovascular conditions that require ACEIs/ARBs + diuretics. In addition, there was a statistically significant decrease in CrCl after these risky combinations were initiated. **Conclusion:** The prescribing trend of triple whammy during the period of data collection was low compared to prescriptions of two risky combinations. This is indeed a good predictor of safe prescribing of drugs among physicians, as concomitant use of these three medications may impair renal functions.

**Key words:** Angiotensin-converting-enzyme inhibitors, Angiotensin receptor blockers, Diuretics, Non-steroidal anti-inflammatory drugs, Triple whammy

## INTRODUCTION

Medications are one of the most important necessities of life as they diminish the dangers caused by diseases; however, the use of medications adds an additional risk of harmful effects. Nowadays, the use of nephrotoxic medications, whether as monotherapy or in combination, needs constant evaluation and monitoring; otherwise, might result in adverse drug reactions which may lead to renal impairment.<sup>[1-3]</sup> Non-steroidal

anti-inflammatory drugs (NSAIDs) are one of the most commonly used medications in the world because of their

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well-established efficacy in reducing pain and inflammation, which has been proven by numerous studies in medical conditions such as various types of bone diseases as well as dental pain and headache. Mechanism of action of NSAIDs is the inhibition of the pro-inflammatory enzyme cyclooxygenase.<sup>[1-4]</sup> NSAIDs, both selective and nonselective agents, have a prominent effect on the kidney that will lead to renal impairment. They act by constricting the blood flow into the glomerulus through the afferent arteriole by inhibiting these prostaglandins.<sup>[5,6]</sup> Most of the NSAIDs are available as over-the-counter in most countries, this availability of such drugs encourages patients for self-prescribing, hence, adds on the risk to develop side effects, especially if the patient is on other nephrotoxic drugs.<sup>[7]</sup>

Furthermore, angiotensin-converting-enzyme inhibitors (ACEIs) are recommended as first-line treatment of hypertension as well as in patients with different comorbidities, such as high coronary disease risk or history of diabetes, stroke, heart failure (HF), myocardial infarction, or chronic kidney disease.<sup>[3-6]</sup> The mechanism of action of ACEIs in lowering blood pressure is by reducing peripheral vascular resistance without increasing cardiac output, heart rate, or contractility.<sup>[5-7]</sup> These drugs block the ACE enzyme, which converts angiotensin I to the potent vasoconstrictor angiotensin II, resulting in vasodilation of both arterioles and veins.<sup>[7-9]</sup> Angiotensin receptor blockers (ARBs), on the other hand, are orally active compounds that are competitive antagonists of the angiotensin II receptor. They have the advantage of complete blockage of angiotensin II action because ACEIs inhibit only one enzyme responsible for the production of angiotensin II. Furthermore, ARBs do not affect bradykinin levels. Although ARBs have actions similar to those of ACEIs, they are not therapeutically identical.<sup>[8,9]</sup> Even so, ARBs are a suitable alternative for ACEIs in those patients who cannot tolerate ACEIs. Renal impairment is a significant potential adverse effect of all ACEIs as well as ARBs which consider as type 1. Therefore, serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. However, an increase in serum creatinine of not greater than 30% above baseline is acceptable and by itself does not warrant discontinuation of treatment.<sup>[6-10]</sup>

Diuretics are recommended as 1<sup>st</sup> line therapy for hypertension unless there are compelling reasons to choose another agent.<sup>[10]</sup> Regardless of the diuretic class, the initial mechanism of action of diuretics is based upon decreasing blood volume, which ultimately leads to reduced blood pressure.<sup>[11]</sup> Established studies confirmed that low-dose diuretic therapy is safe and effective in preventing stroke, myocardial infarction, and HF.<sup>[8,9]</sup>

All three drugs are considered an excellent choice for the management of various comorbidities; therefore, its commonly prescribed together.<sup>[10]</sup> Nevertheless, it has a significant effect on causing renal impairment, the incidence

of such adverse effect would peak when prescribed all together within the first 30 days, and the risk will be presented even when only two of these medications are prescribed; such effect may lead to fatal interaction.<sup>[12,13]</sup> Recent studies have proven that the risk of renal injury is present when only two of the three drugs are prescribed.<sup>[3,7]</sup> In this study, prescriptions of two of triple whammy agents were termed as “risky combination.” Several mechanisms are responsible for causing renal impairment, including actions of each drug on the kidney. Angiotensin II, on the one hand, acts as a vasoconstrictor, by decreasing angiotensin II levels, ACEI and ARB dilate the efferent arteriole,<sup>[7,8]</sup> as well as on the other hand, NSAIDs constrict the blood flow into the glomerulus through the afferent arteriole by inhibition of prostaglandins mediated.<sup>[14,15]</sup> Eventually, diuretics act by promoting Na<sup>+</sup> and water excretion resulting in volume depletion. These alterations in renal hemodynamics will lead to a decline in the glomerular filtration rate.<sup>[14,15]</sup>

Pharmacovigilance reports confirmed the risk of triple whammy and risky combinations in the general population. Nevertheless, a survey was conducted in Australia 2006, presented minimal knowledge about this combination and its adverse effect among the public. However, locally, only one study was conducted to cover this clinical issue in Malaysian hospitals.<sup>[16]</sup> Therefore, the objectives of this study were to investigate the occurrence of triple whammy and its impact on renal function among patients. It also aimed to identify the factors that could affect the prescription of those risky combinations.

## METHODOLOGY

The study was a retrospective; cross-sectional observational study was conducted in a hospital located in Selangor state. This study data were retrieved retrospectively from the outpatient pharmacy department. Each patient’s clinical data, including patient’s demographic data, medical history, diagnosis, and medication prescribed during the clinic visit, were recorded. All adult patients (>18 years) with normal renal function who prescribed with two or three of the NSAIDs, ACEIs/ARBs, or diuretics were included in this study. The study protocol was reviewed in terms of methodological and ethical issues. The research ethics committee approved this study of the concerned hospital. The permission was taken from the concerned hospital before the commencement of the study.

### Data analyses

Data collected from the hospital database and analyzed using Statistical Package for the Social Sciences software version 24.0. Descriptive analysis involving frequencies and percentages were used to present the results of the analysis. Chi-square or Fisher’s exact was used when relevant to test

any associations between demographic data and types of risky combination of triple whammy. All reported  $P < 0.05$  were considered statistically significant. In addition, a paired *t*-test was used to determine any impact on CrCl after those risky combinations were prescribed.

## RESULTS

A total of 412 prescriptions were identified receiving two or three of the NSAIDs, ACEIs/ARBs, or diuretics during the study, 60.2% of them were males. The median age of the patients was 60 years ranging between the period between (30 and 87) years. The majority of prescriptions (98.5%) was for risky combinations, ACEIs/ARBs and diuretics (64.1%) were prescribed in highest frequency, compared to only five prescriptions for triple whammy, Table 1. Furthermore, Malay race (54.9%) received the majority of prescriptions followed by Chinese (23.8%) and Indians (21.4%); nevertheless, there was no significant association. In addition, hypertension 357 (86.6%) was the majority of diagnosed comorbidities among these study patients; nearly 98.5% of them were taking a risky combination of two drugs, and only 5 of them were prescribed with all three drugs combination together. The majority of patients received ACEI/ARB and diuretics followed by ACEI/ARB and NSAIDs. Arthritis diagnosed patients were 37.1% patients that were diagnosed with arthritis and almost all of them were taking a risky combination of two drugs; ACEI/ARB and NSAIDs were the majority of prescriptions in arthritis patients. About 4 of them were prescribed with all three drugs together; HF patients, on the other hand, were 15.5% of patient and all of them were taking a risky combination of two drugs, and none of them was prescribed with all three drugs together. The majority of HF patients in this study were prescribed with ACEI/ARB and diuretics 97% combination and only 1 prescription was for ACEI/ARB and NSAIDs as well as NSAIDs and diuretics combination which also prescribed once.

Furthermore, results in Table 1 also showed that patients aged <65 years received a higher number of risky combinations, almost double, as compared to only one-third of elderly patients with risky combinations. Nevertheless, there was no statistically significant. As for the gender, males were more likely to receive this combination of ACEIs/ARBs and diuretics than females ( $P < 0.001$ ). On the other hand, ACEIs/ARB and NSAIDs combination was prescribed slightly more frequently in females than males ( $P < 0.001$ ) Table 1.

Dramatically, there was a statically significant reduction in CrCl from baseline to 1<sup>st</sup> follow-up by about 8 ml/min/1.73 m<sup>2</sup> ( $P < 0.001$ , 95% confidence interval [CI] 5.964, 9.621). Descriptively, 12% of the patients who were on stage I at baseline moved down to more advanced stages after risky combinations were initiated in Table 1. More specifically, ACEI/ARB and diuretics combination caused a statically significant decrease in CrCl from baseline to 1<sup>st</sup> follow-up. The

**Table 1: The association of risky combination and patients' demographics**

Type of combination	Frequency (%)		Age		Race			Gender		
	Non-elderly n (%)	Elderly n (%)	P-value	Malay n (%)	Indian n (%)	Chinese n (%)	P-value	Male n (%)	Female n (%)	
ACEI/ARB + Diuretics	264 (64.1)	106 (25.7)	0.067 <sup>a</sup>	140 (34.9)	63 (15.2)	61 (14.8)	0.253 <sup>a</sup>	176 (42.7)	88 (21.4)	<0.001 <sup>a</sup>
ACEI/ARB + NSAIDs	102 (24.8)	31 (7.5)	0.134 <sup>a</sup>	61 (14.8)	15 (3.6)	26 (6.3)	0.185 <sup>a</sup>	43 (10.4)	58 (14.1)	<0.001 <sup>a</sup>
Diuretics + NSAIDs	41 (9.9)	11 (2.7)	0.159 <sup>a</sup>	23 (5.5)	9 (2.2)	9 (2.2)	0.959 <sup>a</sup>	25 (6.1)	16.3 (3.9)	0.914 <sup>a</sup>
ACEI/ARB+Diuretics + NSAIDs	5 (1.2)	3 (0.7)	0.363 <sup>b</sup>	2 (0.5)	1(0.24)	2 (0.5)	- - -	3 (0.7)	2 (0.5)	0.681 <sup>b</sup>

<sup>a</sup>Pearson Chi-square test, <sup>b</sup>Fisher's exact test. ARB: Angiotensin receptor blockers, ACEIs: Angiotensin-converting-enzyme inhibitors, NSAIDs: Non-steroidal anti-inflammatory drugs

mean decrease in CrCl was about 7 ml/min/1.73 m<sup>2</sup> ( $P < 0.001$ , 95% CI 4.92, 9.21). Further analysis showed that 6.5% of the patients who were on stage I at baseline moved down to more advanced stages after ACEI/ARB and diuretic combinations were initiated. In addition, the percentage of patients' number who were on stage III increased by about 7.3%. Furthermore, ACEI/ARB and NSAIDs did not differ much from the previous ACEI/ARB and diuretics combination. There was a statistically significant decrease in CrCl from time one (baseline) to time two (1<sup>st</sup> follow-up). The mean decrease in CrCl was again about 7 ml/min/1.73 m<sup>2</sup> ( $P < 0.001$ , 95% CI 3.53, 11.16). Further analysis also showed that 3.4% of the patients who were on stage I at baseline moved down to more advanced stages after ACEI/ARB and NSAIDs combination were initiated. In addition, the percentage of patients' number who were on stage III increased by about 2.0%. In addition, diuretics and NSAIDs combination was prescribed in relatively fewer cases as compared to other combinations; however, a similar impact was found. There was a statically significant decrease in CrCl from baseline to 1<sup>st</sup> follow-up by about 10 ml/min/1.73 m<sup>2</sup> ( $P = 0.005$ , 95% CI 3.28, 17.35). Further analysis showed that 3.3% of the patients who were on stage I at baseline moved down to more advanced stages after ACEI/ARB and NSAIDs combination were initiated. In addition, the percentage of patients who were on stage III increased by about 2.0 %, Table 2.

## DISCUSSION

The use of cardiac medication such ACEIs/ARBs as well as diuretics as whether as monotherapy or in a combination, is in the increasing trend,<sup>[16]</sup> as it keeps showing tremendous impact in reducing mortality as well as morbidity that associated with cardiovascular comorbidities such as hypertensive and HF.<sup>[17]</sup> This positive improvement as a negative impact related to its ability to cause renal impairment, especially when prescribed with NSAIDs. Based on this study, only 1.2% of the patient was taking all the three drugs that are known to be associated with renal impairment. The occurrence of the concomitant use of triple whammy is low. However, about 98.7% of the patients were prescribed with risky combinations.

In addition, ACEIs/ARBs and diuretic combinations were significantly more prone to be prescribed in male patients compared to the female gender, the male gender is considered

as a risk factor for cardiovascular conditions that require ACEI/ARB and diuretics to be prescribed.<sup>[18,19]</sup> ACEI/ARB and NSAIDs combination, on the other hand, were prescribed slightly more frequently in females than males, and that could be due to the fact that female gender is a risk factor for the bone diseases that require NSAIDs to be prescribed.<sup>[11]</sup> Despite this fact, it was found that there is no association between gender and prescribing trend of antihypertensive with NSAIDs.<sup>[20]</sup> However, other factors could affect the prescriptions patterns for both genders.

As for the impact of types of risky combinations on renal function, our result showed that renal function was significantly decreased after risky combination was prescribed. As over all, this result could indicate the potency of these combinations on deterioration renal function. This result was in line to another study which reported that risky combination had a significant association ( $P < 0.001$ ) with renal impairment. Double therapy combination was not associated with an increased rate of acute kidney injury (AKI).<sup>[21]</sup> Triple therapy combination was associated with a 31% higher rate of AKI as presented by another study.<sup>[22]</sup> Although many studies have shown the impact of such a risky combination on renal function, other facts may have a significant effect on renal function, such as increasing age and patient cardiovascular comorbidities.<sup>[23,24]</sup> This study also showed that patients' renal function deteriorated when patient prescribed with ACEI/ARB and diuretics combination in a way that the mean difference in CrCl after prescribing ACEI/ARB and diuretics combination was significantly lower than baseline. This maybe gives a hint that ACEI/ARB and diuretic combination have a higher risk to cause AKI, nevertheless, other factors such as pre-existing cardiovascular comorbidities may involve in decreasing function of kidneys.<sup>[24]</sup> However, it is also concluded prescriptions of two risky combinations were not associated with increased risk of AKI.<sup>[22,25]</sup> Despite these facts, during this study, one case of AKI was reported due administration of Captopril and Frusemide to a hypertensive Malay female patient. Furthermore, ACEI/ARB and NSAIDs combination was prescribed. In addition, we also observed that the mean difference in CrCl after prescribing ACEI/ARB and NSAIDs combination was lower than baseline. NSAIDs are considered as a nephrotoxic drug and increase the risk of renal impairment, especially when the patient has other risk factors such as dehydration, increased age, or concomitant

**Table 2:** The impact of risky combination on creatinine clearance

Variable	CrCl at baseline Mean±(SD)	CrCl at follow-up Mean±(SD)	Mean difference in CrCl (95% CI)	t-statistic (df)	P-value
Risky combinations	82.9 (21.06)	75.06 (19.05)	7.79 (5.964, 9.621)	8.378 (411)	<0.001*
ACEI/ARB + diuretics	81.7 (21.5)	74.6 (19.2)	7.065 (4.92, 9.21)	6.484 (263)	<0.001*
ACEI/ARB + NSAIDs	82.8 (17.96)	75.4 (16.62)	7.35 (3.53, 11.16)	3.82 (100)	<0.001*
Diuretics + NSAIDs	88.3 (24.5)	78.0 (23.53)	10.31 (3.28, 17.35)	2.97 (40)	0.005*

\*Paired t-test, CrCl in ml/min/1.73 m<sup>2</sup>. CI: Confidence interval, ARB: Angiotensin receptor blocker, ACEIs: Angiotensin-converting-enzyme inhibitors, NSAIDs: Non-steroidal anti-inflammatory drugs

administration with ACEI/ARB or any nephrotoxic drug.<sup>[3]</sup> On the other hand, dual therapy ACEI/ARB and NSAIDs did not show any significant increase in renal impairment. As for the 3<sup>rd</sup> type of risky combinations, NSAIDs and diuretic combinations, our research found that this combination renal function decreased in view of the regress of patients' CrCl after been prescribed with NSAIDs and diuretics combination because of the mean difference in CrCl after prescribing NSAIDs and diuretics combination was lower than baseline. This may be attributed to the fact, NSAIDs and diuretics combination carries similar risk to cause AKI.<sup>[25]</sup> Pointed that there was an early increase in AKI risk for a diuretic-NSAIDs combination. During this research, an AKI case was reported due to the use of frusemide and ibuprofen following a short period of prescription.

## CONCLUSION

The prevalence of triple whammy in the studied hospital was minimal compared to prescriptions of two risky combinations, which was the majority, concluding a safe prescribing trend within hospital's physicians, especially in a hypertensive patient who already on a combination of 2 risky agents. Nevertheless, prescriptions of two risky combinations caused two patients to be diagnosed with AKI as well as impairment to renal function in about all of the patients by a significant reduction in CrCl.

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