

# Occurrence of the Triple Whammy in an Outpatient Clinic of a Tertiary Hospital

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## ABSTRACT

**Background:** The combination of Non-steroidal Anti-inflammatory Drugs (NSAIDs), Angiotensin-Converting Enzyme Inhibitors (ACEIs) and diuretics, among patients is common. The combination of these drugs can lead to renal disease and kidney failure over a long term use. **Objectives:** To identify the occurrence of the concomitant prescription of NSAIDs, ACEIs and diuretics, usually referred to as triple whammy, received by out-patients at a Malaysian tertiary hospital. It also aimed to identify the occurrence of triple whammy among the population of the elderly. **Methods:** A retrospective study was performed in a tertiary care hospital, situated in the state of Selangor, Malaysia. The patients' prescriptions with NSAIDs, ACEIs and diuretics, from the outpatient pharmacy department were reviewed and recorded. The association between the prescriptions with age was investigated using the chi-square test. A value of  $P < 0.05$  was considered significant. **Results:** A total of 424 prescriptions (56.1% male) were included in this study. The findings showed that 422 prescriptions were with one or more of NSAIDs, ACEIs and diuretic, and only 2 prescriptions were with all three drugs. Majority of the prescriptions (40.1%) were with the combination of ACEIs and diuretics. A combination of ACEI and diuretics were mainly (21.7%) prescribed to patients above 65 years of age, albeit, it is statistically not significant. **Conclusion:** The occurrence of triple whammy at a tertiary hospital during the period of data collection is low. This is indeed a good predictor of safe prescribing of drugs among physicians, as concomitant use of these three medications may impair renal function, especially in the elderly and dehydrated patients.

**Key words:** Non-steroidal anti-inflammatory drugs, Angiotensin-converting enzyme inhibitors, Diuretics, Kidney failure, Renal impairment.

## INTRODUCTION

The use of medicine need constant evaluation and monitoring, otherwise, might result in adverse effects or even pose significant risk of morbidity and death.<sup>1,2</sup> Nowadays, many pharmaceutical substances can lead to nephrotoxic effect and it is highly impossible for the prescribers to trace and track the use of these medicines among patients.<sup>3</sup> American Heart Association and the European Society of Cardiology, recommend Grade I with a level A evidence, denoting an effective clinical data derived from the multiple randomized clinical trials or from the meta analyses of using Angio-

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tenzin-Converting Enzyme Inhibitors (ACEIs) for coronary heart disease and heart failure.<sup>4,5</sup> ACEIs had been shown to improve the survival and quality of life in all classes of heart failure.<sup>6</sup> Another group of drugs normally used, either from prescription or through pharmacy counter are the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Approximately, 40% to 60% of the people who use NSAIDs are 60 years of age and above. NSAIDs are the most commonly prescribed drugs, and is also readily available over the counter in certain countries, such as in the United Kingdom and Australia.<sup>7,8</sup> Study had shown a positive link between stress scale scores, and people with medical problem. They also found that higher perceived stress scale scores are associated with greater pain intensity and interference.<sup>9</sup>

Furthermore, symptomatology in Heart Failure (HF) is complex and multi-factorial in etiology.<sup>10,11</sup> Pain is common in HF populations. Some recent studies had shown that 51% to 84% of patients with heart failure, suffer from various painful conditions.<sup>10,12,13</sup> Furthermore, study also reported that heart failure also induced pain, even patient's conditions were controlled with heart medication.<sup>14</sup>

Regardless of that, diuretics are among the most frequently used drugs among older individuals, being used by approximately 25% to 40% of those aged 65 years old and above.<sup>15</sup> A combination of ACEI, NSAIDs and diuretics among patients is common. For example, patients with hypertension or heart failure are regularly prescribed with an ACEIs and a diuretic. In addition, if these patients suffer from arthritis and muscular pain at the same time, it is conceivable that they often take NSAIDs, either by prescription or Over The Counter (OTC).<sup>16</sup> There are some sporadic report on the synergistic renal impairment of this drug combination.<sup>17,18</sup> However, more research data on the synergistic renal impairment of this combination are needed, especially among the elderly in the Asian region.

People who are under medication for high blood pressure are being warned to beware of any dangerous drug combination that can lead to kidney failure, over a long term use. A survey by Kidney Health Australia, has found that as much as 10% of people with blood pressure problems are taking these three drugs: NSAID, ACEIs and diuretics, that have a potentially fatal interaction.<sup>17,19</sup> Several mechanisms responsible for the renal effect are involved, including the inhibition of prostaglandin-mediated afferent arteriolar vasodilation by ACEIs as well as the inhibition of angiotensin II-mediated efferent arteriolar vasoconstriction by

NSAIDs. Eventually, diuretics decrease the plasma volume. All the combination of mechanisms lead to a reduction in the renal blood flow and renal dysfunction.<sup>20</sup>

According to the Australian Adverse Drug Reactions Committee, a new survey by Australians on the anti-hypertensive found out that there was a lack of public awareness about the interaction in the year 2006.<sup>21</sup> Doctors or other prescribers have been reminded of the risks involved by the concurrent use of these three drugs, with research suggesting that as much as 1 in 10 hypertensive patients, is taking the potentially lethal mix. However, locally, no studies were ever performed in Malaysia to look into this issue. Therefore, the objectives of this study were to identify the occurrence of the concomitant prescribing of NSAIDs, ACEI and diuretics, referred to as triple whammy, received by out-patients at a Malaysian tertiary hospital. It also aimed to identify the relationship between the prescriptions of triple whammy with a specific age.

## METHODOLOGY

This observational, descriptive and non-interventional study was conducted at a 306 bedded government-funded district hospital located in the central part of Klang Valley, Malaysia. It provides primary and specialist health care services for most illnesses and accidents. This study retrospectively gathered data from the hard copy prescriptions, located at the Outpatient Pharmacy Department. A range of clinical data was extracted from the prescriptions, including patient's demographic data, medical history, diagnosis and medication prescribed during the clinic visit. All prescriptions of adult patients (>18 years old) combined with NSAIDs, ACEIs or diuretics in Outpatient Pharmacy Department of a tertiary hospital, between January-March 2012, were included in this study. This allowed sufficient number of prescriptions to be collected in order to provide baseline information regarding the usage of NSAIDs, ACEIs and diuretic. Pediatric patients and those who were not under any of the medications, such as the NSAIDs, ACEIs and diuretics were excluded from the study. The study protocol was reviewed in terms of methodological and ethical issues. An institutional ethical committee approval was obtained by the Medical Research Ethics Committee of the Ministry of Health, Malaysia (NMRR-12-760-12373) and Research Management Institute Universiti Teknologi MARA (600-RMI (5/1/6/01) before the commencement of the study. Confidentiality and non-disclosure were strictly maintained.

## Data Analysis

The data collected was analyzed at the end of the data collection period. SPSS version 20 was used to analyze the data. Descriptive analysis involving frequencies and percentages were used to present the results of the analysis. The association between the drug of choice and specific factors was obtained, using chi-square test. A value of  $P < 0.05$  was considered significant. Fisher's exact test was used when the frequency of the variable was less than 5.

## RESULTS

A total of 424 prescriptions within the 3-month study period were identified to be given, with any of the drug groups described (NSAIDs, ACEIs or diuretics). Among the recipients of the prescriptions that were involved in this study, 56.1% were male. The mean age of the patients recorded in the prescription was 55.5 years old with 218 of them (51.4%) being above 65 years of age. Meanwhile, only three patients were in the range of 20-29 years of age. Patients with Heart Failure (HF) accounted for 25% of the clinic visit (Table 1). This was followed by the combination of hypertension and diabetes mellitus, which constituted 20% and hypertension alone, 17.7%. 3 patients were diagnosed as having myocardial infarction.

For one drug of choice, 14.4% of the prescriptions were on NSAIDs only, whereas, 21% of them were on ACEIs only, and 10.1% were on diuretics only. While for two drugs of choice, 16 prescriptions were a com-

bination of NSAIDs and a diuretic, while 170 prescriptions were a combination of ACEIs and diuretic, and 45 prescriptions were a combination of NSAIDs and ACEIs. Only 2 prescriptions combined all three drugs of choice at the same time. The combination of diuretics and ACEIs has the highest percentage for ages below and above 65 years with 18.4% and 21.7%. Then, it was followed by ACEIs, having only 11.1% for ages below 65 years and 9.9% for ages above 65 years. NSAID was the third highest drugs that were prescribed. All the age groups are not statistically significant (Table 2).

There is a significant association between the combination of ACEIs and diuretic, heart failure patients ( $P < 0.05$ ) and hypertension patients ( $P = 0.005$ ). 75.4% of patients in pain were given NSAIDs ( $p < 0.001$ ). About 11.5% of patients screened with the prescription and receiving NSAIDs, have heart failure (Table 3).

## DISCUSSION

The use of ACEIs is increasing, including the use of tablets in combination, containing ACEIs, plus diuretics. Episodes of renal failure can appear to be precipitated by mild stress inpatients taking the triple combination or by the addition of the third drug, usually NSAIDs. This is in agreement with the previous study conducted.<sup>21</sup> A survey of more than 600 people on high blood pressure medication found that 9% were taking a risky combination. Only half of them could recall, being warned by their healthcare provider about the risk associated with the combination of these three drugs.<sup>21</sup> However, it is not known how often and when renal dysfunction occurs in patients, using a combination of these three drugs.<sup>22,23</sup> As reported in this study, only 0.5% of them were taking all the three drugs that are known to be associated with impaired renal function. The occurrence of the concomitant use of NSAIDs, ACEIs and diuretics known as "triple whammy" is low.

Based on this study, 75% of screened prescriptions indicated that NSAIDs ( $P < 0.05$ ) were given to patients for pain management. About 12% of the prescriptions with an indication of heart failure were given NSAIDs alone ( $P < 0.05$ ). Furthermore, 3% of the prescriptions with an indication of heart failure were given in combination with NSAIDs and ACEIs. Although, this relationship is insignificant ( $P = 0.785$ ), it should be noted that, NSAIDs should be avoided in patients that are prone to heart failure because it can cause vasoconstriction, fluid retention and renal dysfunction.<sup>22,24</sup>

According to the study done by Taddei, ACEIs enhance the antihypertensive effects of diuretics, though the interaction appears more additive than synergistic.

**Table 1: Diagnosis for the study population**

Type of disease	n (%)
Heart failure	106 (25.0)
Type II diabetes mellitus+Hypertension	85 (20.0)
Hypertension	75 (17.7)
Type II diabetes mellitus	34 (8.0)
Type II diabetes mellitus+Ischemic heart disease+Hypertension	27 (6.4)
Ischemic heart disease	20 (4.7)
Pain	19 (4.5)
Type II diabetes mellitus+Ischemic heart disease	18 (4.2)
Type II diabetes mellitus+Hypertension+Dyslipidemia	11 (2.6)
Type II diabetes mellitus+Hypertension+Chronic kidney disease	9 (2.1)
Type II diabetes mellitus+Ischemic heart disease+Atrial fibrillation+Hypertension	7 (1.7)
Chronic kidney disease	6 (1.4)
Type II diabetes mellitus+Dyslipidemia	4 (0.9)
Myocardial infarction	3 (0.7)

**Table 2: Drug of choice versus age**

	n (%) Less than or equal to 65 years old	N (%) Above 65 years old	P value
Diuretics+ACEI	78 (18.4)	92 (21.7)	0.362
ACEI	47 (11.1)	42 (9.9)	0.370
NSAIDs	26 (6.1)	35 (8.3)	0.314
Diuretics	24 (5.7)	19 (4.5)	0.317
ACEI+NSAIDs	20 (4.7)	25 (5.9)	0.557
NSAIDs+Diuretics	11 (2.6)	5 (1.2)	0.100
ACEI+Diuretics+NSAIDs	0 (0)	2 (0.5)	0.499

**Table 3: Drug of choice versus type of diseases**

	n (%) Heart failure	n (%) Hypertension	n (%) Pain
NSAIDs	7 (11.5)*	0 (0)	46 (75.4)*
NSAIDs+ACEIs	12 (2.8)	19 (4.5)*	12 (26.7)
ACEIs+Diuretics	15 (3.5)*	41 (9.7)*	0 (0)

\*P&lt;0.05.

Combining diuretics with ACEIs appear to be more effective than combining them with beta blockers for the treatment of hypertension.<sup>25,26</sup> As for heart failure, when ACEI are added to diuretics, they will improve symptoms, exercise tolerance, and survival, also reduce the hospital admission rates in chronic heart failure cases.<sup>27,28</sup>

Based on this study, most of the prescriptions screened to be given to patients above 65 years of age and NSAIDs were highly prescribed among elderly patients. It must be noted that NSAIDs prescribed to elderly patients is not recommended, and this was proven by a study that stated; the use of NSAIDs should be avoided as much as possible, among the elderly.<sup>20</sup> Most reports sent to Adverse Drug Reactions Advisory Committee on drug-induced renal failure focus on elderly patients, and this applies as well, to renal failure associated with the triple therapy (median age of 76 years).<sup>21</sup> Paracetamol seems to be preferred as an alternative for NSAIDs. In addition, when NSAIDs were combined with others drugs, it worsened the patients' condition, such as worsen kidney function, as well as gastrointestinal and cardiovascular side effects.<sup>29,30</sup>

In this research setting, the combination of ACEIs and diuretic were most widely prescribed among elderly patients. This is especially true if the patients are diagnosed with heart failure, because ACEIs and diuretics have been proven to be effective in the management of heart failure.<sup>31</sup> Notably, the patients should be handled with caution by monitoring the renal function frequently, especially among elderly patients, because most of their organ have deteriorated.<sup>30</sup>

### Limitation

The occurrence of triple whammy in the current setting is low might, due to several limitations. Firstly, it might be due to several prescriptions given to a patient at the same time. For example, a patient having chronic pain was usually referred to the orthopedic or surgical department and prescribed with NSAIDs, whereas, at the same time, the patient might also receive ACEIs and diuretic from the medical department. The patients might receive all three drugs but in a different prescriptions. Based on that, they might receive all three drugs concurrently, but it was not detected during the study period. Secondly, the patients might buy NSAIDs as an OTC drugs, and based on that, it was difficult to trace patients that were on NSAIDs in addition to the other two drugs of interest. So, the number of patients who might be on NSAIDs might be missed out.

### Recommendation

It is important to educate the doctors as the main prescribers, regarding the risks associated with the concurrent use of ACEIs, diuretic and NSAIDs. If possible, prescribers should avoid the combination of these drugs. However, if these drugs are necessary, prescribers should be alert and watch out for symptoms, such as illness, dehydration and also advice patients to seek medical advice during such episodes.<sup>19</sup> More so, patients that were combining two drugs should also be educated by doctors and pharmacists regarding the high risk of renal insufficiency of NSAIDs and triple whammy. Additional auxiliary label stating the potential renal impairment effect of these agents might be helpful to

reinforce this message. More study should be done in the future, especially prospective study in order to get more accurate patterns in Malaysia.

## CONCLUSION

The occurrence of triple whammy at a tertiary hospital during the period of data collection is low. This is indeed a good predictor of safe prescribing of drugs among physicians, as the concomitant use of these three medications may impair renal function, especially among the elderly and dehydrated patients. Patients with heart failure or hypertension above 65 years of age also tend to receive a combination of diuretics and ACEI.

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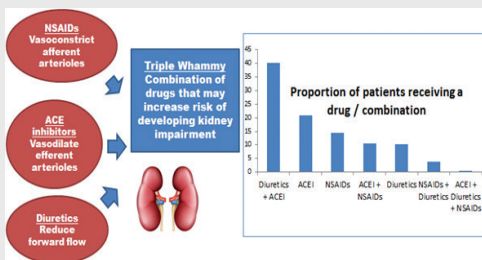
## CONFLICT OF INTERESTS

The author declare no conflict of interest.

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## PICTORIAL ABSTRACT



## SUMMARY

- The occurrence of the concomitant use of NSAIDs, ACEIs and diuretics known as “triple whammy” is very low in this study.
- Only 3% of the prescriptions with an indication of heart failure were including a combination of NSAIDs and ACEIs.
- Taking a combination of ACEIs and diuretic was associated with heart failure and hypertension.
- The combination of diuretics and ACEIs were mainly prescribed to elderly patients.

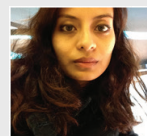
## ABBREVIATIONS USED

**NSAIDs:** Non-steroidal Anti-inflammatory Drugs; **ACEIs:** Angiotensin-Converting Enzyme Inhibitors; **HF:** Heart Failure; **OTC:** Over the Counter.

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