



## **Effect of Aspirin on the International Normalized Ratio in Elderly Patients with Atrial Fibrillation on Concurrent Warfarin Therapy**

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### **ABSTRACT**

**Introduction:** Aspirin and warfarin are frequently taken together to enhance antithrombotic efficacy and prevent cardiovascular events. The initiation of aspirin in elderly patients with atrial fibrillation (AF) on warfarin therapy affects the International Normalized Ratio (INR). The aim of the study was to determine the changes in INR and the prevalence of INR adherence before and after aspirin initiation in elderly patients with AF on warfarin therapy.

**Methods:** A cross-sectional study was conducted in the Anticoagulant Medication Therapy Adherence Clinic in Hospital Tuanku Ampuan Najihah from January to March 2021. In this study, we included elderly patients with AF on concurrent use of aspirin and warfarin for at least four weeks. A total of 350 patients with AF were screened for eligibility and 81 of them were included in this study. A data collection form was used to collect their demographic data as well as their INR before and after aspirin initiation. Descriptive statistics summarised the demographics and INR distribution. Paired t-test was used to assess the differences in INR before and after aspirin initiation.

**Results:** Most of the patients were female (n=44, 54.3%), Malay (n=74, 91.4%), with a mean age of  $74.94 \pm 8.14$  years old. There was a significant difference in the INR before and after aspirin initiation,  $2.27 \pm 0.79$  and  $3.59 \pm 0.70$ , respectively ( $P < 0.001$ ). Before aspirin initiation, 32 (39.5%) patients achieved their targeted INR range of 2.0 to 3.0, meanwhile 33 (40.7%) and 16 (19.8%) patients had subtherapeutic and supratherapeutic INR ranges, respectively. In contrast, only 16 (19.8%) patients achieved their INR target range, after aspirin initiation. Furthermore, INR rose in 58 (71.6%) patients and 49 (60.5%) patients had their INR increased to above 3.0.

**Conclusion:** This study showed that aspirin initiation increased the INR significantly in elderly patients with AF on warfarin therapy. Thus, healthcare professionals should monitor INR closely when aspirin is prescribed concurrently with warfarin in elderly patients with AF. Improvements in the patient counselling points checklist have to be made to ensure optimal health outcomes in and prevent potential bleeding incidence.

**Keywords:** Atrial Fibrillation, aspirin, elderly, INR, warfarin

## INTRODUCTION

Atrial fibrillation is one of the common cardiovascular diseases among elderly patients (1). Warfarin is one of the anticoagulants utilized for the management of patients with a variety of thromboembolic conditions (2). It plays a crucial role in the treatment and prevention of stroke specifically due to atrial fibrillation (AF) in elderly patients (2). Nevertheless, it has many drug-drug interactions (2).

Aspirin and warfarin are widely used concurrently for better antithrombotic effects or the prophylaxis of cardiovascular events (3). This leads to more bleeding episodes compared to warfarin therapy alone (3). In addition, International Normalized Ratio (INR) level increased in patients with bleeding episodes (4). Physiological changes of aging aggravate the side effect profile of aspirin in elderly patients (5). Maximizing INR between 2.0 to 3.0 has been shown to provide the most advantage for preventing major hemorrhage, stroke, and death (6). Subtherapeutic and supratherapeutic anticoagulation problems often require hospital admission (7). Maintaining INR within the therapeutic range is a known problem in primary care due to the interaction of warfarin with other drugs. (8).

For the best management of numerous vascular conditions that may result in thrombosis or embolism in elderly patients, the use of oral anticoagulant medication, such as warfarin is essential (9). Contrary to warfarin alone, the concurrent use of antiplatelet medication will cause bleeding episodes to increase 1.5 to 2 times more frequently than with warfarin alone (10,11). This is observed that in Japanese patients who received the best anticoagulant therapy (9), both the regulated prothrombin time (PT) - INR value and age were significant factors that increased the sensitivity to warfarin. As a result, greater care should be taken while determining the dosing regimen for such older patients (9).

To the best of the authors' knowledge, limited data is available in Malaysia regarding the effect of aspirin on INR in elderly patients with AF on concurrent warfarin. Therefore, we aimed to determine the change in INR and the prevalence of INR adherence before and after aspirin initiation in the elderly with AF on warfarin therapy.

## **METHODS**

### *Study Design and Participants*

This was a cross-sectional study conducted from January to March 2021 at Anticoagulant Medication Therapy Adherence Clinic (AC-MTAC) in Hospital Tuanku Ampuan Najihah (HTAN), Kuala Pilah, Negeri Sembilan. We included patients aged at least 60 years old, diagnosed with atrial fibrillation (AF), had a target INR of between 2.0 and 3.0, initiated on aspirin in addition to the warfarin therapy for at least four weeks, and had been followed up for more than two visits. The exclusion criteria included the patients who were started on aspirin from other healthcare facilities, or presented with other factors which could affect INR including poor or inconsistent adherence to the dietary recommendations, drugs, herbs, and alcohol consumption.

A total of 350 patients under the follow-up at AC-MTAC were screened for eligibility. Among the patients screened, 121 were elderly AF patients who fulfilled the inclusion criteria. Demographic data, diagnosis, target INR range, and INR before and after aspirin initiation taken of 121 patients were extracted from the Medical Outpatient Department card and recorded into the data collection form. The data collection form was adapted from the HTAN AC-MTAC counselling form and modified after an extensive review of the literature (3,11). All information collected was kept private and confidential. However, 40 patients were excluded from the study due to the exclusion criteria, therefore the final sample included in this study was 81.

### *Statistical Analysis*

The SPSS® version 21 was used for descriptive and inferential statistical analyses. Patients' demographic data and the distribution of INR before and after aspirin initiation was summarized as mean, standard deviation (SD), frequencies, and percentages. Paired t-test was used to assess differences in INR before and after aspirin initiation.

### *Ethical Approval*

This study was registered with National Medical Research Registry (NMRR-20-2635-57429) and approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MREC: KKM/NIHSEC/P20-2596(4)).

## RESULTS

### *Demographic Characteristics*

A total of 81 patients were included in the study. The mean age of the patients was  $74.94 \pm 8.14$  years old. The majority of them were female (n=44, 54.3%), and Malay (n=74, 91.4%). All patients received 75mg aspirin but were on various doses of warfarin. The mean duration of concurrent use of aspirin and warfarin was  $4.79 \pm 0.89$  weeks and the majority of patients took aspirin and warfarin concurrently for four weeks (n=60, 74.1%). The demographic characteristics of the patients are summarised in Table 1.

**Table 1:** Demographic characteristics (n=81)

Characteristics	Mean (SD)	n (%)
<b>Age (years)</b>	74.94 (8.14)	
60-69		24 (29.7)
70-79		30 (37.0)
80-89		23 (28.4)
90-99		4 (4.93)
<b>Gender</b>		
Female		44 (54.3)
Male		37 (45.7)
<b>Ethnicity</b>		
Malay		74 (91.4)
Chinese		7 (8.6)
<b>Duration of concurrent use of aspirin and warfarin (weeks)</b>	4.79 (0.89)	
4		60 (74.1)
6		19 (23.5)
8		2 (2.47)

*Differences in INR Before and After Aspirin Initiation*

There was a significant difference in the INR ( $P < 0.001$ ) before aspirin initiation ( $2.27 \pm 0.79$ ) and after aspirin ( $3.59 \pm 0.70$ ). Therefore, aspirin initiation significantly affected INR in elderly AF patients on warfarin therapy. The differences in INR before and after INR initiation are summarised below (Table 2).

**Table 2:** Differences in INR before and after aspirin initiation (n=81)

Variable	Mean (SD)		Mean Difference (95% CI)	t-statistic (df)	P-value
	Before	After			
<b>INR</b>	2.27 (0.79)	3.59 (0.70)	1.31 (1.12, 1.50)	13.65 (80)	< 0.001

*INR Adherence Before and After Aspirin Initiation*

Before aspirin initiation, 32 (39.5%) patients achieved the targeted INR range of 2.0 to 3.0, meanwhile 33 (40.7%) and 16 (19.8%) patients had subtherapeutic and supratherapeutic INR ranges, respectively. In contrast, only 16 (19.8%) patients achieved their INR target range, after aspirin initiation. Furthermore, INR rose in 58 (71.6%) patients and 49 (60.5%) patients had their INR increased to above 3.0. In addition, 65 (80.2%) patients had supratherapeutic INR level. Table 3 illustrates the findings.

**Table 3:** INR adherence before and after aspirin initiation (n=81)

		After aspirin initiation		
		INR < 2	INR within therapeutic range (2.0-3.0)	INR > 3
<b>Before aspirin initiation</b>	INR < 2	0	9	24
	INR within therapeutic range (2.0-3.0)	0	7	25
	INR > 3	0	0	16

## DISCUSSION

The present study showed a significant effect of aspirin initiation on the INR among elderly AF patients on warfarin, whereby increase in INR was observed. In a previous study, the median INR rose from 1.05 to 1.10 in patients receiving the microdose of warfarin and from 1.04 to 1.11 in patients receiving the combination dose of warfarin and aspirin (12). Therefore, patients receiving warfarin with aspirin experience a similar increase in INR after one month (12). Despite this, aspirin may have a risk of significant bleeding that is comparable to that of warfarin therapy administered at an adjusted dose (13). However, previous study found that the combination of warfarin and aspirin was linked to a moderate risk of serious bleeding by 0.3% annually when compared to the use of either adjusted-dose warfarin or aspirin monotherapy (13). Yet, other studies found that bleeding incidence in elderly AF patients was due to the significant effect of aspirin on INR when combined with warfarin (10-11). This is because the interaction between aspirin and warfarin results in an additive effect on platelet function and interference with warfarin metabolism which contributes to an elevated INR level (14). From our findings, we recommend close monitoring on INR level in elderly AF patients on warfarin initiated on aspirin due to its significant effect on INR.

Notably, we found that only about one-fifth (19.8%) of our patients achieved their targeted INR after aspirin was initiated. A similar trend was seen among patients from a study in Miri, Sarawak in which only 14.3% patients achieved their INR targets (15). It was important to note that most of our patients' (80.2%) INR were supratherapeutic (>3.0) after aspirin was initiated. Another study has found that patients spent significant percentages of their maintenance time out of their target INR range: 1.2% at an INR of 4.5 or higher, 12.9% at an INR of 3.1 to 4.4, and 22.7% at an INR of 2.0 or less (16).

Previous studies have concluded that the risk of bleeding increased among patients with elevated INR levels when aspirin was concurrently prescribed with warfarin (3-8). Although an increase in INR value increased the risk of bleeding (13), another study has demonstrated that it may be safe to provide warfarin and aspirin to older people (17). Nevertheless, the rate of bleeding was higher in patients older than 75 years than in younger patients in a prospective cohort analysis of patients

with diverse conditions and more serious bleeding events occurred in the elderly patients (18). Old age is one of the factors that increase sensitivity to warfarin due to a reduction in vitamin K redox cycling activity (19-21). The dispute over older age as a potential risk factor for bleeding is significant since many individuals may not receive necessary warfarin medication because of their age (13).

In addition, the study of combined anticoagulant-antiplatelet use and major bleeding events in elderly AF patients proved that bleeding risk was moderately increased with combined warfarin-antiplatelet therapy (20). Hence, there are several actions which should be taken to increase the quality of warfarin treatment in elderly AF patients who require concurrent warfarin and aspirin treatment. Frequent INR monitoring and risk of bleeding need to be assessed in elderly warfarin users newly started with the antiplatelet. Furthermore, pharmacists' roles are crucial in providing counselling on the potential interaction between aspirin and warfarin, the signs and symptoms of bleeding, and the necessary actions when bleeding occur. Close INR monitoring following aspirin initiation is also of utmost importance to avoid bleeding incidences and optimise treatment.

## **LIMITATIONS**

However, there were several limitations to this study. Firstly, we had a small sample size as patients were only recruited from one hospital. The small sample size may have influenced our findings. Furthermore, the findings are not generalisable to the Malaysian population. Secondly, we did not assess the bleeding risk and incidence among the patients. Further studies exploring these aspects is therefore, welcomed.

## **CONCLUSION**

This study found that starting aspirin significantly raised the INR level of elderly patients with AF on warfarin therapy. To provide the best possible health outcomes for senior patients and reduce the risk of bleeding, healthcare practitioners should constantly monitor INR when aspirin is prescribed alongside warfarin in older patients with AF and make modifications to the patient counselling points checklist accordingly.

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## **CONFLICT OF INTERESTS**

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