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RESEARCH ARTICLE

Study of Co-Prescription of Drugs Potentially Interacting with Warfarin in Indonesian Ambulatory patients

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ABSTRACT:

Background: Despite the growing use of Direct Oral Anticoagulant (DOAC), the most prescribed oral anticoagulant currently in Indonesia is warfarin. Efficacy and safety of warfarin are influenced by various factors including drug-drug interactions. Patients in ambulatory care often receive more than one prescription leading to potential drug-drug interactions. However, there is no data from Indonesia has been published. This study aimed to assess the prevalence of other drugs potentially interacting with warfarin and their interaction risk. **Method**: It was a descriptive cross-sectional study. We identified warfarin prescriptions issued between January 2015 and December 2019 using electronic prescription and electronic medical records. Analysis of interaction risk was performed using Medscape. **Result**: During 4 years, there were 50 patients fulfilling inclusion criteria with 715 prescriptions issued. From 50 patients, 94 % at least received 1 concomitant drug. The four most commonly interacting drugs prescribed during warfarin therapy were spironolactone (58%), simvastatin (54%), allopurinol (32%) and low dose acetylsalicylic acid (20%). Furthermore, there were 38% of patients received concomitant drugs classified as serious interaction as follows allopurinol, amiodarone, and fenofibrate. As much as 16% of patients had adverse outcomes and some of this may be associated with warfarin-drug interaction. **Conclusion:** This study indicates that the prevalence of co-prescription with potentially interacting drugs during warfarin therapy in ambulatory patients is high. Strategy to identify and manage warfarin-drugs interaction is warranted to avoid potential adverse events.

KEYWORDS: Warfarin, Co-Prescription, Drug-drug interaction, Indonesian, Ambulatory Patients.

INTRODUCTION:

Background:

Warfarin has been the mainstay of oral anticoagulant worldwide, including in Indonesia. Although DOAC does not generally need regular international normalized ratio (INR) monitoring [1] and has a faster onset and offset of action, but concerns about safety and high cost[2] diminish their use particularly in low-middle income countries, including in Indonesia.

Despite its effectiveness, warfarin is related to serious adverse effect e.g. bleeding which is estimated up to 15%[3,4]. Co-prescription of interacting medications with warfarin can decrease time in therapeutic range (TTR)[5] and was associated with increased risk of bleeding[6,7]. Given the above, it is essential to examine other drugs commonly prescribed with warfarin and their potency to produce interaction. To best of our knowledge, it is the first study in Indonesia providing new data that can be different from other countries. Indonesia is a developing nation with the fourth largest number of population in the world. However, the number of health workers available is still limited. This condition makes the burden of them is high, sometimes can lead to drug-drug interactions overrides. Also, the use of technology e.g. medication interactions alert is seldom. The result of this study will be valuable information for health care team

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particularly cardiologists and pharmacists in Indonesia as they will be aware of what the most common interacting medications and their risks. Furthermore, it can stimulate them to initiate a strategy to prevent potential adverse outcomes.

Methods:

Study Design and Population

This is a descriptive cross-sectional study conducted at Universitas Airlangga Teaching Hospital. Inclusion criteria was all patients taking warfarin visiting cardiology ambulatory clinic between January 2015 and December 2019. Research Ethics Committee of Universitas Airlangga Teaching Hospital approved this study in April 2019 (No. 118/KEH/2019).

Study Protocol:

Identification of patients fulfilling inclusion criteria was performed by using a hospital management information system called SIMRS. This program was able to identify patients visiting a cardiology clinic receiving warfarin. We also collected patients' characteristics including diagnosing, warfarin indication, gender, age and the number of medications per prescription (mean) from the electronic medical records. Analysis for potential drug-drug interaction was done using Medscape Program classifying drug-drug interaction by clinical relevance as follows[8]: Serious (drug combination should be avoided or use alternative drugs), use with caution or monitor closely (the combination can be handled e.g. by dose adjustments, close monitoring is required) and minor (significance unknown)

STATISTICAL ANALYSIS:

Descriptive statistics were used to describe continuous (Mean ± SD) and categorical variables (frequency and percent).

RESULTS:

This study is the first to assess the prevalence of co-prescription of drugs potentially interact with warfarin in ambulatory patients in Indonesia. Over 4 years, a total of 50 patients at the Cardiology Clinic of Universitas Airlangga Teaching Hospital received warfarin. The most common indication of warfarin was the primary prevention of stroke in both non-valvular atrial fibrillation and valvular atrial fibrillation (98%). More than half of the patients were older than 60 years with a mean age of 61.66 ± 8.19 years (**Table 1**).

Table 1. Sociodemographic and clinical characteristic of warfarin users

Socio-demographic and clinical characteristic	N	%
Age (Years)		
Mean ± SD	61.7±8.2	-
Median	60	-
Gender		
Male	24	48
Female	26	52
Indication		
Atrial Fibrillation	42	84
Atrial Fibrillation and Emboli Stroke	1	2
Atrial Fibrillation and Mitral Stenosis	7	14
Duration of Therapy (Month) Mean (Min-Max)	19.3 (1-48)	
Number of Medications Mean (Min-Max)	4.5 (1-11)	

There were 94% of patients were prescribed at least one interacting drug during the period of study, ranging from 1 to 5 (mean= 1.42). The most commonly co-prescribed medications interacting with warfarin were spironolactone (58%), simvastatin (54%), allopurinol (32%) and low dose acetylsalicylic acid (20%). In addition, allopurinol, amiodarone, and fenofibrate are prescribed in 38% of patients and categorized as serious interaction that should be avoided or requiring alternative drugs (**Table 2**).

Table 2. Potentially Interacting Drugs Prescribed During Warfarin Therapy

Drug	N	%	Interaction Category and Recommendation	Probable Clinical Effect
Spironolactone	29	58	Monitor closely	Decreased effect of warfarin
Simvastatin	27	54	Monitor closely	Either increases effect of the other
Allopurinol	16	32	Serious -Use alternative	Increased effect of warfarin
Acetylsalicylic acid	10	20	Monitor closely	Increased risk of bleeding
NSAID	8	16	Monitor closely	Increased risk of bleeding
Clopidogrel	7	14	Monitor closely	Increased risk of bleeding
Omeprazole	4	8	Monitor closely	Increased effect of warfarin
Acetaminophen	3	6	Monitor closely	Increased effect of warfarin
Amiodarone	2	4	Serious-use alternative	Increased effect of warfarin
Fenofibrate	1	2	Serious-use alternative	Increased effect of warfarin

Note: The Acetylsalicylic acid dose was 100 mg/tablet
The percentage was calculated based on patients number

From 715 prescriptions identified, there were only 19.16% prescriptions that did not contain warfarin interacting medications (**Table 3**), indicating a high prevalence of potential warfarin-drug interaction. Furthermore, it was observed that 79.02% of

prescriptions had at least one interacting drug requiring close monitor intervention and action to use an alternate drug (**Table 4**). Finally, it was found that 16% of patients developed adverse outcomes (**Table 5**). There were 2 patients had a complaint of gastrointestinal bleeding with increased INR (up to 9.2),1 patient complained bleeding in the tongue and 5 patients had increased INR up to 7.3. Tongue bleeding appeared after patients had taken amiodarone concomitantly with warfarin 2 mg during 2 weeks and the bleeding gradually stopped after amiodarone has withdrawn. Similar to this, there was another patient had increased INR up to 7,3 after received amiodarone for 1 month simultaneously with warfarin 2 mg. After the amiodarone stopped, INR slowly decreased.

Meanwhile, 1 patient with gastrointestinal bleeding and increased INR had concomitant interacting drugs that were low dose acetylsalicylic acid. Finally, 2 patients with increased INR had concomitant therapy with simvastatin and allopurinol.

Table 3. Percentage of total prescription contain warfarin-drug interaction

Prescription	N	%
With Interaction	578	80.8
Without Interaction	137	19.2
Total	715	100

Table 4. Percentage of Prescription Containing other Drugs Interacting with Warfarin

Drug	N	%
Spironolactone	263	36.8
Simvastatin	259	36.2
Allopurinol	85	11.9
Acetylsalicylic acid	68	9.5
Clopidogrel	49	6.9
NSAID	9	1.3
Acetaminophen	5	0.7
Omeprazole	5	0.7
Amiodarone	2	0.3
Fenofibrate	1	0.1

Note: 1 prescription could contain more than 1 potentially interacting drug

The percentage was calculated based on total prescriptions

Table 5. Adverse Outcomes Manifestations

Adverse Outcomes	N	%
Increased INR	5	10
Increased INR (9,2) and Gastrointestinal Bleeding	2	4
Increased INR and Tongue Bleeding	1	2
Total	8	16

DISCUSSION:

To best of our knowledge, it was the first study in Indonesia, identifying warfarin-drug interactions. Majority of warfarin users in this study older than 60 years old with a mean age of 61.66±8.19 years. Meanwhile, all patients had atrial fibrillation as an indication of warfarin treatment. The prevalence of nonvalvular (NVAF) atrial fibrillation has continually increased with age and reached 6.3% for those older than 75 years[9]. Similar to that, in the USA, the prevalence of NVAF in Medicare beneficiaries older than 65 years is estimated to be 8.6%[10]. Most patients with warfarin usually have other comorbidities that risk patients at polypharmacy. The result of this study is different from another study by Guidoni et al that showed enoxaparin was the most frequent interacting drug. This difference is likely caused by a different set of study which was done in hospitalized patients[3]. Although a most of interacting drugs in this study are not contraindicated, but there were 38% of patients received interacting drugs categorized as serious interaction including amiodarone, fenofibrate, and allopurinol. Amiodarone is one of the interacting medications that can cause serious negative outcome[8]. Amiodarone is frequently used for rhythm control in patients with AF, thus it is often co-administered with warfarin[11]. Studies showed that amiodarone inhibits the clearance of both (R) and (S) warfarin and it typically needs a dose reduction of warfarin 25-40%, depends on amiodarone maintenance dose[12,13]. Patients taking both of the drugs need INR monitoring more frequently, to avoid bleeding. In this study, there were 2 patients received amiodarone and both of them developed a negative effect. Low dose acetylsalicylic acid cannot influence INR but can increase bleeding[7,8]. Meanwhile, concurrent use of simvastatin and warfarin can increase the effect of the other by affecting hepatic CYP3A4. It may result in increased INR and increased risk of rhabdomyolisis[7-8,14]. The clinician should monitor INR once concomitant therapy started or change simvastatin to atorvastatin[7]. Similar to simvastatin, allopurinol can increase INR by decreasing warfarin metabolism[8]. Although the certainty of the effect of warfarin-drug interactions in this study cannot be validated because of the retrospective data, but this study gives us insight that some adverse outcomes occurred may be attributable to warfarin-drug interactions. In the future, well-designed research is needed on the clinical consequences of co-prescribing of interacting drugs with warfarin. The result of this study demonstrates the necessity of understanding the severity of drug interactions and its proper management. In our country, drug interactions alert has not been widely used. The high cost of the alert and low awareness of potential negative consequences of drug-drug interactions make it underutilized. In the future, it is reasonable to include an effective drug interaction alert that can distinguish between high-risk and low-risk warnings as a standard of hospital accreditation to improve patient safety. Furthermore, the finding from Feldstein et al that assessed the effect of using medication interactions alert

showed there was a moderate reduction of co-prescribing of interacting medications[15].

This study has some limitations including a small sample size. In addition, we may have underestimated the occurrence of co-prescription because we did not assess non-prescription medications that may be purchased by patients, e.g. painkillers, vitamins or supplements that may have significant chance to interact with warfarin. Beside of that, we may have overestimated the prevalence of co-prescription because no certainty of whether patients consumed warfarin and other concurrent medications potentially interact or not. Despite this, our data is important because it is the first study providing preliminary data on the co-prescription of warfarin and interacting medications in Indonesia. Our study results documented a high prevalence of co-prescription of warfarin potentially interacting medications. Even though most of interacting medications found in this study are not contraindicated, but 38% of patients received at least one concurrent medication classified as serious interaction. Also, the finding that some patients developed adverse outcomes and may associated with warfarin-amiodarone interaction highlight the importance of initiating an effective strategy to identify warfarin-drug interactions to avoid potential adverse events. Thus, it allows clinicians and pharmacists in Indonesia to be more ready to manage warfarin-drug interactions.

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CONFLICT OF INTEREST:
The authors state that they have no conflict of interest.

LIST OF ABBREVIATION:
Direct Oral Anticoagulant (DOAC)
International Normalized Ratio (INR)
Time in Therapeutic Range (TTR)
Nonvalvular Atrial Fibrillation (NVAF)
Atrial Fibrillation (AF)
Standard Deviation (SD)
Cytochrome 3A4 (CYP3A4)
Hospital Management Information System (SIMRS)

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