Trends in use of Direct Oral Anticoagulants and Warfarin in Atrial Fibrillation Patients

(Tren Penggunaan Antikoagulan Oral Direk dan Warfarin pada Pasien Fibrilasi Atrium)

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Abstract : Treatments used in atrial fibrillation therapy, such as those of anticoagulants, consist of vitamin K antagonists (warfarin) and direct oral anticoagulants (dabigatran, apixaban, rivaroxaban, and edoxaban). The use of warfarin requires regular monitoring of prothrombin time (PT) and international normalised ratio (INR). The therapeutic dose range is narrow, but the price is cheaper. Oral anticoagulants are directed, the incidence of major bleeding is lower, ease of use, food and drug interactions are minor, the half-life is shorter, and there is a lack of laboratory monitoring needs. Based on this problem, researchers conducted a study to determine the trend of using warfarin and oral anticoagulants in patients with atrial fibrillation at a public hospital in Jakarta. This study uses a qualitative approach, with longitudinal methods and retrospective data using outpatient medical records for the period 2014 to 2018. The trend of using warfarin anticoagulants decreased from 82.3% in 2014 to 62% in 2016, while oral anticoagulants were reduced. Direct oral anticoagulants are rivaroxaban and dabigatran, which are more widely used than apixaban, and edoxaban; no data on their use has been obtained. The opposite was true from 2017 to 2018, when the use of warfarin increased and caused a decrease in the use of direct oral anticoagulants. This research is expected to contribute to various parties, both health practitioners and academics, in terms of selecting therapies for atrial fibrillation.

Keywords: Anticoagulant, direct oral anticoagulants, atrial fibrillation, warfarin.

Abstrak : Pengobatan yang digunakan dalam terapi fibrilasi atrium, seperti yaitu antikoagulan, yang terdiri dari antagonis vitamin K (warfarin) dan antikoagulan oral direk (dabigatran, apiksaban, rivaroksaban, dan edoksaban). Penggunaan warfarin membutuhkan pemantauan rutin *protrombin time* (PT) dan *international normalised ratio* (INR), rentang dosis terapi sempit, namun harganya lebih murah. Antikoagulan oral direk, insiden perdarahan mayor lebih rendah, kemudahan penggunaan, interaksi makanan dan obat minor, waktu paruh lebih pendek, dan kurangnya kebutuhan pemantauan laboratorium. Berdasarkan masalah tersebut, peneliti melakukan kajian untuk mengetahui tren penggunaan warfarin dan antikoagulan oral direk pada pasien fibrilasi atrium pada salah satu rumah sakit di Jakarta. Penelitian ini menggunakan pendekatan kualitatif, dengan metode longitudinal dan data bersifat retrospektif menggunakan rekam medis pasien rawat jalan periode tahun 2014 sampai tahun 2018. Tren penggunaan antikoagulan warfarin mengalami penurunan dari 82,3% tahun 2014 menjadi 62% tahun 2016, sedangkan antikoagulan oral direk mengalami peningkatan. Antikoagulan oral direk rivaroksaban dan dabigatran lebih banyak digunakan dibandingkan apiksaban, dan edoksaban tidak diperoleh data penggunaannya. Hal sebaliknya pada tahun 2017 sampai 2018, dimana penggunaan warfarin mengalami peningkatan dan menyebabkan penurunan penggunaan antikoagulan oral direk. Penelitian ini diharapkan dapat memberikan kontribusi kepada berbagai pihak baik praktisi kesehatan maupun akademisi dalam hal pemilihan terapi untuk fibrilasi atrium.

Kata kunci: Antikoagulan, antikoagulan oral direk, fibrilasi atrium, warfarin.

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INTRODUCTION

ATRIAL fibrillation increased with age, with around 70% at ages 65–85 and 84% at ages over 85. The urban population in Jakarta shows an atrial fibrillation incidence rate of 0.2% with a ratio of men and women (3:2). Given the significant increase in the percentage of the elderly population in Indonesia from 7.74% (in 2000–2005) to 28.68% (WHO estimates for 2045–2050), the incidence of atrial fibrillation will also increase significantly. On a smaller scale, reflected data at the National Cardiovascular Centre Harapan Kita Hospital shows that the percentage of atrial fibrillation events in outpatients always increases every year, from 7.1% in 2010 to 9.0% (2011), 9.3% (2012), and 9.8% (2013)[1]. Atrial fibrillation may occur in short episodes, or it may be a permanent condition[2]. Atrial fibrillation (AF) was the most common type of arrhythmia in clinical diseases and gradually becomes an increasing healthcare burden in the world. According to the Framingham Heart Study, the risk of lifetime atrial fibrillation was approximately 25%[3]. Therefore, it was important to detect the disease early so that management with counselling and medication can be started. Early detection and appropriate treatment can prevent premature death[4].

Treatments used in atrial fibrillation therapy include anticoagulants, which consist of vitamin K antagonists (warfarin) and new anticoagulants. Warfarin was the most widely used anticoagulant drug for the prevention of strokes in atrial fibrillation. At present, there are three new types of anticoagulants on the Indonesian market, namely dabigatran, rivaroxaban, and apixaban. Dabigatran works by inhibiting thrombin directly, while rivaroxaban and apixaban both work by inhibiting the Xa factor[1]. Rivaroxaban and apixaban were frequently prescribed oral anticoagulants for the treatment of atrial fibrillation. However, some healthcare professionals exhibit hesitancy when prescribing these medications due to apprehensions regarding bleeding and reversibility. This reluctance persists despite recent evidence indicating a more favourable safety profile, including a nearly 50% reduced risk of intracranial bleeding compared to warfarin[5].

The administration of warfarin has historically posed challenges due to substantial interpatient variability in response, hence complicating the determination of an appropriate dosage. The correlation between warfarin dosage and patient response was subject to the influence of several genetic and environmental factors, including but not limited to food, drug interactions, and acute illnesses. Consequently, accurately predicting therapeutic doses

was a significant challenge. Following the beginning, the dosage of warfarin was adjusted according to the outcomes of the international normalised ratio (INR). One problem with warfarin was that it needs to be closely watched and multiple lab tests need to be done to confirm the results. A broad range of dosages was required in order to achieve and sustain a therapeutic International Normalised Ratio (INR) at relatively low doses, which were frequently necessary for individuals who were parents or patients with underlying comorbidities. The metabolism of warfarin primarily occurs in the liver, and its elimination predominantly takes place through the kidneys in the form of metabolites[6].

The laboratory measurements employed for the purpose of monitoring the safety and effectiveness of warfarin include prothrombin time (PT) and international normalised ratio (INR). The prothrombin time (PT) was a laboratory test that quantifies the time required for blood coagulation to occur. The international normalised ratio (INR) was a metric used to standardise PT values. The incidence rate ratio for patients with INR who did not get warfarin medication was approximately 1.0. If a patient exhibits an International Normalised Ratio (INR) of 2.0 or 3.0, this suggests that the individual's blood coagulation process takes two to three times longer in comparison to an individual who does not utilise anticoagulant medication. The therapeutic international normalised ratio (INR) serves several purposes, which were contingent upon the indication, environmental circumstances, patient history, and provider preferences. The recommended target International Normalised Ratio (INR) range for most indications was between 2 and 3. The attainment of INR objectives is a dynamic undertaking that necessitates regular monitoring, often multiple times per week. This was particularly crucial at the first stages of treatment or in instances of acute sickness, which may contribute to fluctuations in INR levels. Regular surveillance of patients has the capacity to negatively impact their quality of life while also imposing substantial financial burdens on the healthcare system and placing additional demands on healthcare providers[7]. Lower INR (1.6-2.6) in patients over 70 years old can reduce the risk of bleeding[8].

The use of vitamin K antagonists in Indonesia faces obstacles, such as the unavailability of INR inspection facilities in peripheral areas. Other factors also need to be considered, such as genetics in ethnic Indonesians related to individual sensitivity to warfarin[9]. The monitoring of body weight, age, sex, race, or demographic differences was not necessary

for the administration of direct oral anticoagulant medication[10]. Direct oral anticoagulants, including dabigatran, apixaban, rivaroxaban, and edoxaban, exhibit several advantages. These advantages encompass a reduced occurrence of significant bleeding, enhanced user friendliness, minimal interactions with food and certain medications, a shorter half-life, and the absence of the requirement for laboratory monitoring[11]. The decision to forego monitoring requirements for International Normalised Ratio (INR) or other measures when using oral anticoagulants was a favourable option for individuals experiencing unstable INR levels due to warfarin usage or medication regimens that interact with warfarin. The administration of these medications was characterised by a set dose, meaning that the prescribed dosage was not meant to be modified in response to coagulation laboratory parameters. The suppression of Factor Xa by apixaban, rivaroxaban, and edoxaban has been observed to prolong several coagulation tests, such as PT/INR and aPTT. Nevertheless, this alteration was of minor magnitude and was contingent upon variability, rendering it impractical for the purpose of monitoring these pharmaceutical substances[10].

Based on this background, researchers were interested in analyzing trends in the use of warfarin anticoagulants and direct oral anticoagulants in atrial fibrillation patients at a public hospital in Jakarta. This research was expected to contribute to various parties, both health practitioners and academics, in the selection of therapies for atrial fibrillation.

MATERIALS AND METHODS

MATERIALS. This study have purposive sampling techniques. A large sample of 380 medical records was collected from one public hospital in Jakarta,, with inclusion criteria of patients aged 25 ≥ 85 years, patients taking direct oral anticoagulant drugs or warfarin, and exclusion criteria of inaccessible and incomplete patient medical records.

METHODS. Study Design. This study used a qualitative approach with a longitudinal method. The data were retrospective, tracing medical record data for atrial fibrillation patients using warfarin or direct oral anticoagulants for the period 2014–2018 at one of the public hospitals in Jakarta. Data was collected from February to April 2020.

Research Ethics. This research obtained ethical approval with number LB.02.01/VII/413/KEP.002/2020 from the Research Ethics Committee.

Data Analysis. This study used secondary data from a patient's medical record. The data obtained was assessed, and the results were displayed in tabular and graphical form. Data retrieval was carried out during the COVID-19 pandemic, causing limited data retrieval time.

RESULTS AND DISCUSSION

Patient Characteristics. Patient characteristics include age, sex, level of education, and patient payment methods, as in Table 1. The results of the study (table 1) showed that more atrial fibrillation occurred in the 55–64 age group and 65–74 years, respectively, by 30.3% and 25%. Other studies also obtained relatively similar results. Atrial fibrillation patients most commonly occur in the age range of 51–60 years (32.4%) and 61–70 years (24.9%)[12].

Table 1. Patient characteristic.

Characteristics	Number (n = 380)	Percentage (%)
Age		
25-34 year	2	0.5
35-44 year	45	11.8
45-54 year	92	24.2
55-64 year	115	30.3
65-74 year	95	25
75-84 year	30	7.9
≥85 year	1	0.3
Sex		
Male	219	57.6
Female	161	42.4
Education		
Not finished Elementary School	12	3.2
Elementary School	29	7.6
Junior High School	39	10.3
Senior High School	127	33.4
Diploma	57	15
Bachelor	116	30.5
Payment		
Private insurance	16	4.2
Public insurance	334	87.9
Personal payment	30	7.9

The incidence of atrial fibrillation increases with the duration of life; the majority of people suffer from atrial fibrillation after 50 years of age. According to epidemiological research, the prevalence of atrial fibrillation was very low among individuals below the age of 50. However, it exhibits a notable increase in occurrence, with a prevalence of 0.5% among those aged 50–59. This prevalence further escalates to 8.8% among individuals aged 80–89[13]. Age was the biggest trigger factor in atrial fibrillation. Increased age triggers variation and dilatation. Atrial muscular atrophy can interfere with conduction and contraction in the atrium so as to worsen the atrial condition. Advanced age was associated with a heightened susceptibility to atrial fibrillation, primarily due to

the presence of various cardiovascular conditions, including hypertension, coronary artery disease, heart valve abnormalities, and heart failure[12]. Moreover, it was worth noting that hyperthyroidism might serve as an additional etiological factor for the development of atrial fibrillation, particularly among the older population. According to a study, the occurrence of atrial fibrillation among hyperthyroid patients above the age of 60 was found to be 25%, whereas it was only 5% among those below the age of 60[14].

Patients with male sex had the highest number of cases of atrial fibrillation, as many as 219 people (57.6%) and women as many as 161 people (42.4%). Other studies also had relatively similar results: 59.5% in men and 40.5% in women[12]. This was due to the man having an expression of excessive ion channel repolarization so as to accelerate atrial repolarization, shortening of the atrial refractory period, and the mechanism of in and out of ions. Men also have a greater diameter of the left atrium compared to the diameter of the female left atrium[12]. Another factor was that the lifestyle of men tends to be less good compared to women, such as consuming alcohol and smoking for a long time, which can increase the risk factor for atrial fibrillation. The aetiology of acute alcohol-induced atrial fibrillation includes metabolic acidosis, catecholamine release, and electrolyte imbalances, whereas chronic excessive alcohol use leads to myocardial fibrosis, dilatation, and alterations in autonomic function. Numerous studies have demonstrated a causal relationship between smoking and the development of atrial fibrosis, a well-established marker for the presence of atrial fibrillation [14]. In terms of educational characteristics, as many as 33.4% of patients undertake high school education, and 30.5% of scholars or colleges.

Payment methods for patients such as national health insurance (JKN), public insurance, and private insurance. The large number of JKN patients causes hospitals to have to regulate the efficiency of spending for these patients to run well, including in providing drug therapy in accordance with national and hospital formularies[15]. Anticoagulant drugs borne by JKN were warfarin, dabigatran, and rivaroxaban[16]. Drug selection was in accordance with the national formulary for JKN patients so that it can be claimed by the hospital, whereas for private and corporate patients, it does not depend on the national formulary.

Trends in the Use of Anticoagulants. This study was conducted to examine trends in the use of anticoagulants, including warfarin (vitamin K antagonists; Figure 1) and direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban (Figure 2).
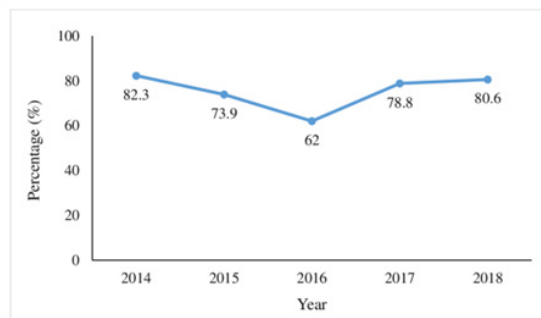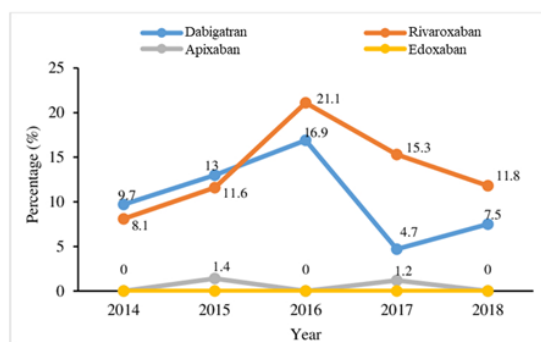

Figure 1. Trend in warfarin use.

Figure 2. Trend of direct oral anticoagulant.

Trend Warfarin (Antagonist Vitamin K). Vitamin K antagonist warfarin blocks vitamin K complex reductase epoxide 1 (VKORC1), an important enzyme that turns on vitamin K produced by the body, by engaging in competitive inhibition. Warfarin has the ability to deplete functional vitamin K stores, resulting in a reduction in the synthesis of active clotting components[7,6]. Trends in the use of warfarin (Figure 1) have increased and decreased. Warfarin use decreased from 2014 to 2016 from 82.3% to 62%, although its use remains the most widely used therapeutic option compared to oral anticoagulants. In 2017, the use of warfarin again increased to 78.8%, and in 2018, its use was 80.6%. This decrease was in line with the increase in the use of direct oral anticoagulants, which increased during the period 2014–2016. Similarly, the increased use of warfarin from 2017 to 2018 parallels the declining use of direct oral anticoagulants.

Warfarin was the most widely used anticoagulant in therapy for atrial fibrillation due to its availability in the general form (in this case, tablet preparations and injections) and unlike direct oral anticoagulants[19]. Another factor of consideration was cost; as many as 47.2% of patients prefer to use warfarin to be ward because of the high price of direct oral anticoagulants, and as much as 31.7% use warfarin because of positive experiences with long-term use[20]. Therapy with warfarin was cheaper than oral anticoagulants. The difference varies between $3000 and $4000[21].

Warfarin was also preferred for medical reasons, such as the controlled INR (International Normalised Ratio), which was maintained in the use of warfarin. It was necessary to monitor frequent laboratory and impaired kidney function[20].

The use of warfarin in atrial fibrillation also shows a decrease in the incidence of ischemic stroke and cardiovascular events, with only a slight increase in the incidence of severe bleeding. Warfarin has greater benefits for the elderly when compared to aspirin[22]. For a patient with atrial fibrillation on hemodialysis, warfarin becomes a more suitable oral anticoagulant alternative compared to the oral anticoagulants recommended, although in their use, it was necessary to monitor closely, especially at risk of bleeding[23]. In patients, valve abnormalities also often cause atrial fibrillation. Paroxysmal and permanent atrial fibrillation was an indication for early intervention in valve abnormalities. Valve abnormalities with atrial fibrillation are indicative of the administration of oral anticoagulants of vitamin K antagonists (warfarin)[22]. The use of warfarin must be done carefully; if the effect is too small, it will fail to prevent stroke in atrial fibrillation patients, whereas if the effect was too high, it will cause excessive bleeding. Thus, the dose of warfarin must be adjusted to keep the effect of blood retailers in the right range[17].

The average dose of warfarin used was 2 mg, with a duration of use of 7–10 days or less than ten days, so that it can later assist the clinician in making a decision regarding the dose of warfarin, warfarin duration, and appropriate INR targets in ischemic stroke patients with atrial fibrillation in Indonesia. The warfarin dose actually depends on the INR of the patient; patients who have not reached the INR target (2.0–3.0) need to increase the weekly dose by 10–20%, if necessary, given bridging therapy, whereas in patients whose INR has reached the target, it was necessary to reduce the dose by 10–20%[24,25].

Trends in Direct Oral Anticoagulants. The use of direct oral anticoagulants has increased and decreased (Figure 2). Decreased warfarin (Figure 1) illustrates a change in the use of anticoagulants (Figure 2); an increase in the use of direct oral anticoagulants occurred during the period 2014–2016. The direct oral anticoagulants rivaroxaban and dabigatran were used more than apixaban; meanwhile, edoxaban does not obtain data on their use (Figure 2). Direct oral anticoagulants were superior to warfarin, including rapid onset and covering losses from anticoagulant effects, fixed doses, fewer drug and food interactions, and no requirements for monitoring; this makes them an attractive alternative to anticoagulation. The recommended types of direct oral anticoagulants were dabigatran, rivaroxaban, edoxaban, and apixaban. The efficacy and safety of direct oral anticoagulants, based on trial and real data, for the purpose of counselling and special care for each patient[26]. Rivaroxaban functions as a direct oral inhibitor of the Xa factor. Rivaroxaban functions as an anticoagulant by specifically and directly blocking the Xa factor, which was involved in the formation of blood clots in human plasma. Notably, it achieves this without binding to antithrombin[27]. In rivaroxaban therapy, the number of uses increased in 2014; the use was 8.1%; in 2015, the use was 11.6%; and in 2016, the use was 21.1%. The observed rise can be attributed to the inherent capabilities and subsequent impact. Rivaroxaban has been observed to exhibit favorable tolerability, characterized by a consistent pharmacokinetic profile and the absence of laboratory monitoring requirements[27]. The decrease in rivaroxaban use in 2017 to 15.3% and in 2018 to 11.8%, along with the use of warfarin, which again increased in the year.

Studies have demonstrated that dabigatran was effective in mitigating the occurrence of thromboembolic consequences in individuals diagnosed with non-valvular atrial fibrillation. The utilization of dabigatran has been associated with several adverse effects, including gastrointestinal bleeding. Renal insufficiency was also observed in elderly people[28,19]. Decreased use of dabigatran can be due to increased use of rivaroxaban, in this case, competition in the direct oral anticoagulant market share; in addition, dabigatran also has a tendency to cause dyspepsia, which can limit its use in patients who have digestive disorders[29]. The increase in dabigatran can be due to the superiority it has. Dabigatran has a relatively fast start of work, interactions with food and with other drugs were less than warfarin, and dabigatran does not require intensive laboratory monitoring as in warfarin[30]. In dabigatran therapy, there was an increase in its use; in 2014, its use was 9.7%; in 2015, it was 13%; in 2016, it was 16.9%. However, in 2017, there was a very significant decrease in dabigatran to 4.7% and an increase back in 2018 to 7.5%, although, in use, it was still less than rivaroxaban. The RE-LY (Randomised Evaluation of Long-term anticoagulant therapy with dabigatran etexilate) study demonstrated that the administration of dabigatran at a dosage of 110 mg twice daily was found to be non-inferior to warfarin in terms of its efficacy. Furthermore, the use of dabigatran at a dosage of 150 mg twice daily was shown to be superior to warfarin in reducing the occurrence of stroke and systemic embolism in patients diagnosed with atrial fibrillation. The incidence of hemorrhagic stroke was found to be significantly reduced in both the

dabigatran treatment groups, namely the dabigatran 110 mg group and the dabigatran 150 mg group[28].

Apixaban was a direct oral anticoagulant approved by the FDA (food and drug administration) in 2012. The mechanism of apixaban was the same as rivaroxaban, which inhibits the Xa factor. In apixaban therapy, the number of uses was the least compared to other direct oral anticoagulants such as dabigatran and rivaroxaban; in 2015, its use was only 1.4%, and in 2017, its use was only 1.2%. Not much use of apixaban can be caused by the price of the drug. Apixaban for the indication of atrial fibrillation was more expensive than other oral anticoagulants for the same indication [31]. In addition, according to the Decree of the Minister of Health of the Republic of Indonesia Number 328/MENKES/SK/VIII/2013 concerning the National Formulary, the appendix was also not covered by JKN, unlike other direct oral anticoagulants (in this case, rivaroxaban and dabigatran) and warfarin.

In edoxaban therapy, in this study, no data on its use were obtained. Edoxaban was a fast and selective non-vitamin K antagonist drug. Edoxaban can be used once a day orally. Edoxaban undergoes biotransformation into various metabolites. Edoxaban was eliminated in faeces and urine[30,32]. The reason for the use of direct oral anticoagulants, which was less than warfarin, can be caused by a decrease in kidney function reported by 25.7% of doctors. It was advised that direct oral anticoagulants possess varying degrees of renal excretion. Among these medications, dabigatran exhibits the highest renal excretion rate at 80%, followed by edoxaban at 50%, rivaroxaban at 33%, and apixaban at 27%[20]. The use of direct oral anticoagulants by themselves was also not uncommon for clinician misfortune. In addition, research, strategy, and standardisation of therapy related to direct oral anticoagulants were still limited, and thus far, oral anticoagulants were still focused only on cases of atrial fibrillation[30].

CONCLUSION

The trend in the use of warfarin anticoagulants in atrial fibrillation patients decreased from 82.3% in 2014 to 62% in 2016, while direct oral anticoagulants experienced an increase in use from 2014 to 2016. The decrease in warfarin use may be influenced by tight monitoring of routine prothrombin time (PT) and international normalised ratio (INR). This makes it difficult for outpatients, but also, the availability of oral direct anticoagulants was recommended, whose use was easier because it does not require close monitoring. Direct oral anticoagulants were rivaroxaban, and dabigatran was more widely used than apixaban, while edoxaban did not obtain data on their use. The opposite was true from 2017 to 2018, when the use of warfarin increased and caused a decrease in the use of direct oral anticoagulants. This increase may be related to the high price of direct oral anticoagulants.

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