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

by Turnitin Check

Submission date: 03-Oct-2023 12:23PM (UTC-0500)
Submission ID: 2184514465
File name: Anticoagulants_and_Warfarin_in_Atrial_Fibrillation_Patients.docx (396.41K)
Word count: 4707
Character count: 27494

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

Tren Penggunaan Antikoagulan Oral Direk dan Warfarin pada Pasien Fibrilasi Atrium

Abstrak : Pengobatan yang digunakan dalam terapi fibrilasi atrium, seperti yaitu antikoagulan, yang terdiri dari antagonis vitamin K (warfarin) dan antikoagulan oral direk (dabigatran, apixaban, rivaroxaban, dan edoxaban). Penggunaan warfarin membutuhkan pemantauan rutin *protrombin time* (PT) dan *international normalized 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

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 normalized 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 the 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 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 are obtained. The opposite was true in 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

INTRODUCTION

Atrial fibrillation increased with age, around 70% at ages 65-85 years and 84% at ages over 85 years. In 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 in data at the national cardiovascular center Harapan Kita hospital which shows that the percentage of atrial fibrillation events in outpatients always increases every year, which is 7.1% in 2010, it increased 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) is 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 is approximately 25% [(3)]. Therefore, it is 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)].

Treatment used in atrial fibrillation therapy, such as anticoagulants, which consist of vitamin K antagonists (warfarin) and new anticoagulants. Warfarin is 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 are frequently prescribed oral anticoagulants for the treatment of atrial fibrillation. However, some healthcare professionals exhibit hesitancy in 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 appropriate dosage. The correlation between warfarin dosage and patient response is 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 is a significant challenge. Following beginning, the dosage of warfarin is adjusted according to the outcomes of the international normalised ratio (INR). The requirement for meticulous surveillance and repeat of laboratory test findings represents a drawback associated with warfarin. A broad range of dosage is required in order to achieve and sustain a therapeutic International Normalised Ratio (INR) at relatively low doses, which are frequently necessary for individuals who are 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) is a laboratory test that quantifies the time required for blood coagulation to occur. The international normalised ratio (INR) is 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 are contingent upon the indication, environmental circumstances, patient history, and provider preferences. The recommended target International Normalised Ratio (INR) range for most indications is between 2 and 3. The attainment of INR objectives is a dynamic undertaking that necessitates regular monitoring, often multiple times per week. This is particularly crucial at the first stages of treatment or in instances of acute sickness, which may contribute to fluctuations in INR levels. The 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 can reduce the risk of bleeding [8].

The use of vitamin K antagonists in Indonesia experiences 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]. While the monitoring of body weight, age, sex, race, or demographic differences is 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, shorter half-life, and 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 is 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 is characterised by a set dose, meaning that the prescribed dosage is not meant to be modified in response to coagulation laboratory parameters. The suppression of Factors Xa by apixaban, rivaroxaban, and edoxaban has been observed to prolong several coagulation tests, such as PT/INR and aPTT. Nevertheless,

this alteration is of minor magnitude and is contingent upon variability, so rendering it impractical for the purpose of monitoring these pharmaceutical substances [10].

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

MATERIAL AND METHODS

Material

Sample

This study uses purposive sampling techniques. A large sample of 380 medical records, with inclusion criteria; patients aged 25 to ≥ 85 years, patients taking direct oral anticoagulant drugs or warfarin, and exclusion criteria; inaccessible and incomplete patient medical records.

Research Ethics

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

Method

This study uses a qualitative approach with a longitudinal method. Data are retrospective, through tracing medical record data for atrial fibrillation patients using warfarin and direct oral anticoagulants, the period 2014 to 2018 at one of the public hospital in Jakarta. Data was collected from February to April 2020.

Data Analysis

This study uses secondary data from a patient's medical record. The Data Obtained is assessed and the Results are 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 occurred in the age range of 51-60 years by 32.4% and 61-70 years by 24.9% [12].

Incidence of atrial fibrillation increases with 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 is 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 is 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 is 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 is 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 in 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 of 59.5% in men and 40.5% of women [12]. This is 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, lifestyle in men tends to be less good compared to women such as consuming alcohol and smoking for a long time can increase the risk factor for atrial fibrillation. The aetiology of acute alcohol-induced atrial fibrillation include 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 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) or public insurance and companies (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 formularies and hospital formularies [15]. Anticoagulant drugs borne by national health insurance are warfarin, dabigatran and rivaroksaban [16]. Drug selection is 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 Use of Anticoagulant

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).

Trend Warfarin (Antagonist Vitamin K)

Warfarin, a vitamin K antagonist, exerts its inhibitory effects on vitamin K complex reductase epoxide 1 (VKORC1), a crucial enzyme responsible for the activation of endogenous vitamin K within the body, by 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 in their use. Warfarin use decreased in 2014 to 2016 from 82.3% to 62% although its use remains the most widely used therapeutic option compared to oral anticoagulants, but in 2017 the use of warfarin again increased to 78.8% and in 2018 its use was 80.6%. This decrease is in line with the increased in the use of direct oral anticoagulants which increased during the period 2014 to 2016. Likewise with the increased use of warfarin in 2017 to 2018 which is in line with the decreased in the use of direct oral anticoagulants.

Warfarin is the most widely used anticoagulant in therapy for atrial fibrillation due to its availability in the general form (in this case there are tablet preparations and injections) and unlike direct oral anticoagulants [19]. Another factor of consideration is 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 in long-term use [20]. The use of therapy with warfarin is cheaper than oral anticoagulants. Where the difference ranges from $3000 to $4000 [21]. Warfarin is also preferred for medical reasons, such as the controlled INR (International Normalised Ratio) which is maintained in the use of warfarin, it is 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 in the elderly, when compared to aspirin [22]. In patient atrial fibrillation with haemodialysis, warfarin becomes a more suitable oral anticoagulant alternative

compared to oral anticoagulants recommended although in their use it is necessary to monitor closely especially at risk of bleeding [23]. In patients valve abnormalities also often cause atrial fibrillation. Paroxysmal and permanent atrial fibrillation is an indication for early intervention in valve abnormalities. Valve abnormalities with atrial fibrillation are indicative for 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 is too high, 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 is 2 mg with a duration of use of 7-10 days or less than 10 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, in 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 is necessary to reduce the dose by 10-20% [24,25].

Trends in Direct Oral Anticoagulant

The use of direct oral anticoagulant has increased and decreased in their use (figure 2). Decreased warfarin (figure 1), illustrates a change in the use of anticoagulants (figure 2) an increase in the use of direct oral anticoagulant was during the period 2014 to 2016. The direct oral anticoagulant rivaroxaban and dabigatran mostly used than apixaban, meanwhile edoxaban is not obtained data in their use (figure 2). Direct oral anticoagulants are superior to warfarin, including rapid onset and covering losses from anticoagulant effects, fixed doses, less drug and food interactions and no requirements in monitoring; this makes it an attractive alternative to anticoagulation. The recommended types of direct oral anticoagulants such as 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 is 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 where in 2014 the use was 8.1%, in 2015 the use was 11.6%, 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 favourable tolerability, characterised 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%, this decrease along with the use of warfarin which again increased in the year.

Studies have demonstrated that dabigatran is effective in mitigating the occurrence of thromboembolic consequences in individuals diagnosed with non-valvular atrial fibrillation. The utilisation of dabigatran has been associated with several adverse effects, including gastrointestinal bleeding. Renal insufficiency is 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 there is 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 are 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 haemorrhagic 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].

Apiksaban is direct oral anticoagulants approved by the FDA (*Food and Drug Administration*) in 2012. The mechanism of apixaban is 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% only. Not much use of apixaban can be caused by the price of the drug. Apixaban for indication of atrial fibrillation is 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 is also not covered by JKN, unlike other direct oral anticoagulants (in this case are rivaroxaban and dabigatran) and warfarin.

In edoxaban therapy, in this study no data on its use were obtained. Edoxaban is a fast and selective non-vitamin K antagonist drug. Edoxaban can be used once a day orally. Edoxaban

undergoes biotransformation into various metabolites. Edoxaban is eliminated in faeces and urine [30,32]. The reason for the use of direct oral anticoagulants which is less than warfarin can be caused by a decrease in kidney function reported by 25.7% of doctors. It is 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 is also not uncommon for clinician misfortune. In addition, research, strategy, and standardization of therapy related to direct oral anticoagulant are still limited and thus far also oral anticoagulant are 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 increased in use from 2014 to 2016. The decrease in warfarin use may be influenced by tight monitoring of routine prothrombin time (PT) and international normalized ratio (INR). This makes it difficult for outpatients, but also the availability of direct anticoagulants oral is recommended which use is easier because it does not require close monitoring. Direct oral anticoagulants are rivaroxaban and dabigatran is more widely used than apixaban, while edoxaban did not obtain data on their use. The opposite was true in 2017 to 2018, when the use of warfarin increased and caused a decrease in the use of direct anticoagulant oral. This increase may be related to the high price of direct oral anticoagulants.

ACKNOWLEDGEMENTS

Researcher want to acknowledge to one of the public hospital for granting permission to conduct research and facilitate data collection.

REFERENCE

1. Hartono B, Hanafy DA, Yugo D, Maharani E, Antara IMPS, Raharjo SB. Pedoman Tatalaksana Fibrilasi Atrium Non-valvular. Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI). Edisi Kedua, Cetakan Pertama. Trans Medical International. 2019. p. xviii–144.
2. Centers for Disease Control and Prevention. Atrial Fibrillation [Internet]. 2023. p. 3–6. Available from: https://www.cdc.gov/heartdisease/atrial_fibrillation.htm#. Diakses Februari 2023.
3. Xu X, Wei S, Ma C, Luo K, Zhang L, Liu C. Atrial Fibrillation Beat Identification Using the Combination of Modified Frequency Slice Wavelet Transform and Convolutional Neural Networks. *J Healthc Eng*. 2018:1-8..
4. World Health Organization. Cardiovascular diseases (CVDs) [Internet]. 2021. p. 1–5. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Diakses Februari 2023
5. Lippi G, Mattiuzzi C, Cervellin G, Favaloro EJ. Direct oral anticoagulants: Analysis of worldwide use and popularity using Google Trends. *Ann Transl Med*. 2017;5(16):1–8. Doi: 10.21037/atm.2017.06.65.
6. Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: A Review of the Pharmacology, Dosing, and Complications. *Curr Emerg Hosp Med Rep*. 2013;1(2):83–97. Doi: 10.1007/s40138-013-0014-6.
7. Patel S, Singh R, Preuss C V, Patel N. Warfarin [Internet]. Vol. 1. StatPearls [Internet]; 2022. 1–7 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470313/. Diakses Februari 2023.
8. Shendre A, Parmar GM, Dillon C, Beasley TM, Limdi NA. Influence of Age on Warfarin Dose, Anticoagulation Control, and Risk of Hemorrhage. *Pharmacotherapy*. 2018;38(6):588–96. Doi:10.1002/phar.2089.
9. Suriapranata IM, Tjong WY, Wang T, Utama A, Raharjo SB, Yuniadi Y, Tai SSW. Genetic factors associated with patient-specific warfarin dose in ethnic Indonesians. *BMC Med Genet*. 2011;12(80):2-9.
10. Ten Cate H, McHenskens Y, Lancé MD. Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants. *Vasc Health Risk Manag*. 2017;13:457–67.
11. Myers K, Lyden A. A review on the new and old anticoagulants. *Orthop Nurs*. 2019;38(1):43–52.
12. Adeyana S, Haryadi H, Wijaya C. Hubungan kejadian fibrilasi atrium dengan diameter atrium kiri pada fibrilasi atrium valvular dan fibrilasi atrium non-valvular di RSUD Arifin Achmad. *J Ilmu Kedokt*. 2017;11(1):31–8.
13. Dharma Rao V, Rajaneesh Reddy M, Srikanth K, Raj Kumar Prakash B, Satya Prasad A, Guru Prasad SS. To Study The Prevalence and Clinical Profile of Chronic Atrial Fibrillation in Hospitalized Patents. *Nitte Univ J Heal Sci*. 2014;4(2):17–20.
14. Sankaranarayanan R, Kirkwood G, Dibb K, Garratt CJ. Comparison of atrial fibrillation in the young versus that in the elderly: A review. *Cardiol Res Pract*. 2013. Doi: 10.1155/2013/976976.

15. Mendrofa DE, Suryawati C. Analisis Pengelolaan Obat Pasien BPJS Di Instalasi Farmasi Rumah Sakit Panti Wilasa Citarum Semarang. *J Manaj Kesehat Indones*. 2016;4(3):214–21.
16. Kementerian Kesehatan Republik Indonesia. KEPMENKES Nomor 328/MENKES/SK/VIII/2013 tentang Formularium Nasional. 2013;53(9):100. Available from: https://bpjs-kesehatan.go.id/bpjs/dmdocuments/a85e064985b713815222f9a4ca213f94.pdf
17. Unger EF. Atrial fibrillation and new oral anticoagulant drugs. Oct 2016 [Internet]. 2015;2015:1–3. Available from: https://www.fda.gov/drugs/newsevents/ucm405148.htm.
18. Zimetbaum Peter MD. DOACs now recommended over warfarin to prevent blood clots in people with atrial fibrillation. Harvard Heal Publ [Internet]. 2019;1–13. Available from: https://www.health.harvard.edu/blog/doacs-now-recommended-over-warfarin-to-prevent-blood-clots-in-people-with-atrial-fibrillation-2019121618354. Diakses Juli 2020.
19. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *Am J Heal Pharm*. 2017;74(16):1237–44. Doi: 10.2146/ajhp160756
20. Ikeda T, Yasaka M, Kida M, Imura M. A survey of reasons for continuing warfarin therapy in the era of direct oral anticoagulants in Japanese patients with atrial fibrillation: The SELECT study. *Patient Prefer Adherence*. 2018;12:135–43.
21. Coyle D, Coyle K, Cameron C, Lee K, Kelly S, Steiner S, Wells GA. Cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. *Value Heal* [Internet]. 2013;16(4):498–506. Doi: 10.1016/j.jval.2013.01.009.
22. Yuniadi Y, Hanafy DA, Rahardjo SB, Tondas AE, Maharani E, Hermanto DY, Munawar M. 2014 Indonesian Heart Association Guidelines of Management of Atrial Fibrillation. *Indones J Cardiol*. 2015;35(2):102–33.
23. Erlanda W, Karani Y. Penggunaan Antikoagulan Pada Penyakit Ginjal Kronik. *J Kesehat Andalas*. 2018;7(Supplement 2):168.
24. Khairunnisa, Dini, Sari, Ika Puspita, dan Gofir A. Hubungan Dosis Dan Durasi Penggunaan Warfarin Terhadap Target Inr (International Normalized Ratio) 1,5-2,0 Pada Pasien Stroke Iskemik dengan Atrial Fibrilasi the Corelation Between Dose and Duration in Warfarin Administration. *J Manaj dan Pelayanan Farm*. 2013;3(4):269–72.
25. Furdiyanti NH. Evaluasi dosis warfarin dan hasil terapi pada pasien rawat jalan. *J Manaj dan Pelayanan Farm*. 2014;4(3):176–80.
26. Sikorska J, Uprichard J. Direct oral anticoagulants: A quick guide. *Eur Cardiol Rev*. 2017;12(1):40–5. Doi: 10.15420/ecr.2017:11:2.
27. Vimalesvaran K, Dockrill SJ, Gorog DA. Role of rivaroxaban in the management of atrial fibrillation: Insights from clinical practice. *Vasc Health Risk Manag*. 2018;14:13–21.
28. Leung TS, Fradette M, Thompson A, Koshman SL. Dabigatran in atrial fibrillation: New kid on the block. *Can Pharm J*. 2012;145(2):83–8
29. Ahmad Y, Lip GYH. Anticoagulation in Atrial Fibrillation. *Arrhythm Electrophysiol Rev* [Internet].

2012;1(1):12–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4711491/.

30. Krisnayanti MW. Penggunaan Antikoagulan Oral Baru Pada Fibrilasi Atrium. *J Farm Udayana*. 2019;8(1):1. Doi: 10.24843/JFU.2019.v08.i01.p01.

31. Irawati S. Apixaban: Antikoagulan Oral Baru- Penghambat Spesifik Faktor Xa. Medikamen. 2014;(22):1.

32. Schwarb H, Tsakiris DA. New direct oral anticoagulants (DOAC) and their use today. *Dent J*. 2016;4(1):1–11. Doi: doi:10.3390/dj4010005.

TABLE

Table 1. Patient Characteristic

Characteristic	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

FIGURES

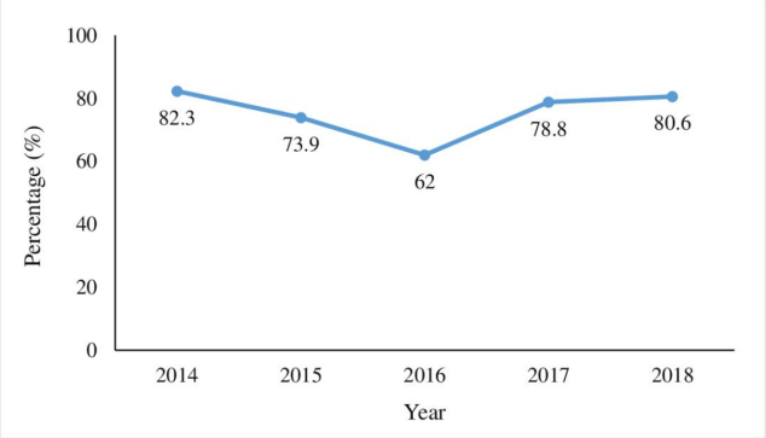

Figure 1. Tren in Warfarin Use

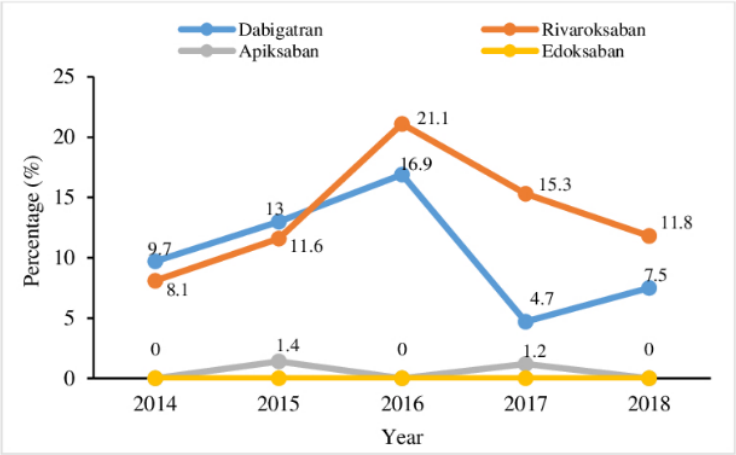

Figure 2. Trend of Direct Oral Anticoagulant

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

ORIGINALITY REPORT

17%	13%	12%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.wjgnet.com Internet Source	1%
2	nursing.ceconnection.com Internet Source	1%
3	Kayla Myers, Abbie Lyden. "A Review on the New and Old Anticoagulants", Orthopaedic Nursing, 2019 Publication	1%
4	Submitted to University of Wales Institute, Cardiff Student Paper	1%
5	www.discoveryjournals.org Internet Source	1%
6	M Eliana, N Nuryani. "Identification of atrial fibrillation using electrocardiographic RR-interval difference", Journal of Physics: Conference Series, 2017 Publication	1%
7	www.science.gov Internet Source	

		1 %
8	link.springer.com Internet Source	1 %
9	lib.bioinfo.pl Internet Source	1 %
10	"Anticoagulation Therapy", Springer Science and Business Media LLC, 2018 Publication	1 %
11	e-journal.unair.ac.id Internet Source	1 %
12	www.clinmedkaz.org Internet Source	1 %
13	repository.unj.ac.id Internet Source	<1 %
14	Scott W. Yates. "Apixaban for Stroke Prevention in Atrial Fibrillation: A Review of the Clinical Trial Evidence", Hospital Practice, 2015 Publication	<1 %
15	www.mdpi.com Internet Source	<1 %
16	eprints.ums.ac.id Internet Source	<1 %

17	Mei Wang, Anne Holbrook, Munil Lee, Jiayu Liu, Alvin Leenus, Nora Chen, Lawrence Mbuagbaw, Lehana Thabane. "Barriers and facilitators to optimal oral anticoagulant management: a scoping review", Journal of Thrombosis and Thrombolysis, 2020 Publication	<1 %
18	myassignmenthelp.com Internet Source	<1 %
19	dergipark.org.tr Internet Source	<1 %
20	scindeks.ceon.rs Internet Source	<1 %
21	www.innovationsincrm.com Internet Source	<1 %
22	www.repository.trisakti.ac.id Internet Source	<1 %
23	Aditi Shendre, Gaurav M. Parmar, Chrisly Dillon, Timothy Mark Beasley, Nita A. Limdi. "Influence of Age on Warfarin Dose, Anticoagulation Control, and Risk of Hemorrhage", Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2018 Publication	<1 %

24	Bridget M. Nugent, Rajanikanth Madabushi, Barbara Buch, Vasum Peiris et al. "Heterogeneity in treatment effects across diverse populations", Pharmaceutical Statistics, 2021 Publication	<1 %
25	www.binasss.sa.cr Internet Source	<1 %
26	www.fip.org Internet Source	<1 %
27	Kathleen A Hazlewood, Christy M Weiland. "Advances in oral anticoagulants: focus on dabigatran etexilate", Expert Review of Clinical Pharmacology, 2014 Publication	<1 %
28	core.ac.uk Internet Source	<1 %
29	diapharma.com Internet Source	<1 %
30	www.researchgate.net Internet Source	<1 %
31	Giuseppe Lippi, Camilla Mattiuzzi, Dorothy Adcock, Emmanuel J. Favaloro. "Oral anticoagulants around the world: an updated state-of-the art analysis", Annals of Blood, 2018	<1 %

	Publication	
32	Mukesh Singh, Sasikanth Adigopula, Pawan Patel, Kranti Kiran, Sandeep Khosla. "Recent advances in oral anticoagulation for atrial fibrillation", Therapeutic Advances in Cardiovascular Disease, 2010 Publication	<1 %
33	bradscholars.brad.ac.uk Internet Source	<1 %
34	dokumen.pub Internet Source	<1 %
35	ecommons.aku.edu Internet Source	<1 %
36	wikidoc.org Internet Source	<1 %
37	www.grafiati.com Internet Source	<1 %
38	Ameenathul M Fawzy, Gregory Y. H. Lip. "Pharmacokinetics and pharmacodynamics of oral anticoagulants used in atrial fibrillation", Expert Opinion on Drug Metabolism & Toxicology, 2019 Publication	<1 %
39	Takanori Ikeda, Masahiro Yasaka, Makoto Kida, Miki Imura. "A survey of reasons for continuing warfarin therapy in the era of	<1 %

direct oral anticoagulants in Japanese patients with atrial fibrillation: the SELECT study", 'Dove Medical Press Ltd.', 2018
Internet Source

---

40 P. Bahrmann, M. Wehling, D. Ropers, J. Flohr, A. Leischker, J. Röther. "Optimal Stroke Prevention in the Geriatric Patient with Atrial Fibrillation: Position Paper of an Interdisciplinary Expert Panel", Drug Research, 2014
Publication

<1%

---

41 Sabir, Ian, Kaivan Khavandi, Jack Brownrigg, and A. John Camm. "Oral anticoagulants for Asian patients with atrial fibrillation", Nature Reviews Cardiology, 2014.
Publication

<1%

---

42 Schwarb, Heike, and Dimitrios Tsakiris. "New Direct Oral Anticoagulants (DOAC) and Their Use Today", Dentistry Journal, 2016.
Publication

<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		