Progress in Microbes and Molecular Biology

HH PUBLISHER

Original Research Article

Comparison of the factors that influence the pattern of procurement and usage of antithrombotic drugs

Mohamed Mansor Manan[1], Aswani Yanti Baharuddin[1], Qi Ying Lean[1], Jagjit Singh Dhaliwal[2], Sachinjeet Kaur Sodhi Dhaliwal[2], Muhammad Junaid Farrukh[3], Ching Siang Tan[4], Long Chiau Ming[5]*

Article History

Received: 28 November 2022;

Received in Revised Form: 18 December 2022;

Accepted: 20 December 2022;

Available Online: 22 December 2022

[1]Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam, Malaysia; mansormanan@uitm.edu.my (MMM), clinpharms@gmail.com (AYB); leanqiying@yahoo.com (QYL)

[2]Pengiran Anak Puteri Rashidah Sa'adatul Bolkiah Institute of Health Sciences, Universiti Brunei Darussalam, Brunei Darussalam; jagjit.dhaliwal@ubd.edu.bn (JSD); molars14@hotmail.com (SKSD)

[3]Faculty of Pharmaceutical Sciences, UCSI University, 56000 Cheras, Malaysia; junaid@ucsiuniversity.edu.my (MJF)

[4]School of Pharmacy, KPJ Healthcare University College, Nilai 71800, Malaysia; tcsiang@kpjuc.edu.my (CST)

[5]School of Medical and Life Sciences, Sunway University, 47500 Sunway City, Malaysia

*Corresponding author: Long Chiau Ming; School of Medical and Life Sciences, Sunway University, Sunway City 47500, Selangor, Malaysia; chiaumingl@sunway.edu.my / longchiauming@gmail.com

Abstract: Antithrombotics are used for many indications in prophylaxis and therapeutic treatment. It is often associated with a higher risk of adverse effects; hence a drug utilization evaluation is essential. The main aim was to describe the utilization of antithrombotic drugs. The specific objectives are to compare the pattern of procurement and usage of antithrombotic drugs, estimate the Defined Daily Dose (DDD), and to compare the usage of antithrombotic drugs with the WHO recommended standard. This was a retrospective study evaluating the utilization of antithrombotics at a public tertiary care hospital in the urban city of Klang Valley, Malaysia. A defined daily dose (DDD) per 1000 inhabitants/day was calculated to estimate patients with thromboembolic disorders receiving standard treatment on a daily basis. Expenditures on all antithrombotic drugs were also assessed. The DDD was examined for correlation with gender, race, and age group. Malaysian Clinical Practice Guideline on the Prevention and Treatment of Venous Thromboembolism was used as a tool to evaluate the quality of prescribing. During the study period, among anticoagulants prescribed, warfarin was the most commonly utilized for treatment and prophylaxis in various disciplines, with 1.82 DDD. Enoxaparin was the second most utilized anticoagulant, with 1.05 DDD, followed by tinzaparin, with 0.39 DDD. For antiplatelet drugs, acetylsalicylic acid was the most utilized antiplatelet with 8.5 DDD followed by clopidogrel

(1.42 DDD) and ticlopidine (0.16 DDD). The utilization pattern for all the antithrombotic drugs was in accordance with the WHO DDD guidelines. The pattern of antithrombotic drug procured was based on the demand for the drug supplies. Age, gender, and race were determinant factors that influenced the choice of antithrombotic drugs and further affected the antithrombotic drug utilization pattern. Still, additional information regarding patient's status and concomitant disease condition is needed to establish the impact of utilization of antithrombotics fully. DDD analysis is an excellent practice to be conducted at planned intervals. It is a tool to update the changing or even new pattern of drug usage, which will assist in the justification of rational use of drugs. The mean difference in terms of DDDs of the studied antithrombotic drugs impacts patient demographic characteristics, smoking history, presence of atherosclerotic diseases and peripheral artery diseases, comorbidity, patient compliance, and bleeding history. It is useful to evaluate trends and expenditures, which will ultimately avoid untoward adverse effects and unnecessary costs.

Keywords: Drug utilization review; health outcomes; anticoagulant; antiplatelet; heart disease; myocardial infarction; healthcare delivery

1. Introduction

Drug utilization, one of the areas within pharmacoepidemiology has been given more emphasis in the current economic climate, to recognize the variation among prescribing practices that could optimise healthcare expenditure. Such utilization acts as indicators where these indicators provide information and give much input in strategic planning to healthcare managers to improve the quality of drug use, improvement of treatment guidelines and prescribing patterns, and development of national drug policy. They reflect the status of a vital characteristic of healthcare services [1,2].

According to a fact sheet by World Health Organization, more than 50% of all medicines are not prescribed, dispensed, and sold correctly and more than 50% of patients are not taking their drugs correctly. The situation is worse in developing countries, with 60-70% of patients not being treated according to clinical guidelines. The approach to rationalizing the use of medicines should address all the factors that contribute to the irrational use of medicines, including patient-centred factors, prescriber-related factors, social and economic factors, healthcare system factors, and disease factors [3].

Antithrombotic therapy is fundamental in treating arterial and venous thrombotic diseases and in percutaneous coronary intervention. It has had an enormous impact in several significant ways where anticoagulant becomes the cornerstone of treatment for thromboembolic disorders, either as prophylaxis or for treatment purposes, whilst antiplatelet therapy becomes a cornerstone in coronary artery disease management. The landscape of anticoagulant therapy for atrial fibrillation has changed significantly with the availability of targeted new oral anticoagulants that are safer than warfarin. Antiplatelet therapy is essential to treating acute coronary syndrome and preventing ischemic complications of percutaneous

coronary intervention. Both antiplatelets and anticoagulants work to prevent clots in the blood vessels, but they work in different mechanisms of action [4].

Anticoagulant use is often associated with risks and complications such as venous thromboembolism (VTE) and pulmonary embolism (PE). Patients with acute coronary syndrome remain at risk of recurrent cardiovascular events despite the advances in medical therapy like antiplatelet therapy [5].

The findings would inform healthcare administration on the current status of anticoagulant drugs and antiplatelet drug utilization and the appropriateness of those drugs prescribed in the tertiary hospital setting. The study's outcome would be beneficial in updating the hospital drug formulary. It can also improve current policy on the utilization of anticoagulants and antiplatelet drugs in the Hospital. Despite the availability of comprehensive and evidence-based guidelines such as the Malaysian Clinical Practice Guidelines (CPG) on the Prevention and Treatment of Venous Thromboembolism 2013 [6], much of the care provided is not in line with CPG. Published literature has shown that in a study performed to look at and monitor the appropriateness of care (care in line with evidence-based or consensus-based guidelines) at healthcare delivery in Australia, it was found out that the percentage of VTE compliance in healthcare delivery in Australia was reported at only 58% [7]. With the new entry of medications to treat and prevent thromboembolism to the hospital formulary list, little is known about its utilization pattern. Looking at the importance of anticoagulant and antiplatelet use and the associated risks of this therapy together with the shortage of budgetary resources and the increased cost of today's complex treatment of thrombosis, drug utilization evaluation of anticoagulant and antiplatelet medications is highly warranted. This study aimed to describe the utilization of anticoagulant and antiplatelet medications supplied to patients from various disciplines with a variety of underlying conditions and to compare the Defined Daily Dose (DDD) of anticoagulant and antiplatelet medications prescribed with the WHO’s standard DDD to examine the appropriateness of the prescription.

2. Materials and Methods

2.1. Study Design

This study was conducted at a tertiary public hospital located in the state of Selangor, Malaysia. This was a retrospective study on the utilization of selected anticoagulant medications. The drugs selected were warfarin, fondaparinux, tinzaparin, or enoxaparin) and selected antiplatelet medications such as acetylsalicylic acid, acetylsalicylic acid & glycine, clopidogrel, dipyridamole or ticlopidine. The data were obtained from dispensed prescriptions from the outpatient pharmacy department. The prescriptions were from several disciplines with various underlying conditions from January 2017 to December 2019. The selected hospital is a referral centre for haematology. It is a fully Information Technology (IT) hospital using an established online healthcare application known as electronic Hospital Information System (eHIS). The total number of patients in the Outpatient Pharmacy is

roughly 1000 patients per day from various disciplines and departments.

Record of all outpatient patients from all disciplines with a variety of underlying conditions who received at least one anticoagulant medication (i.e. warfarin, fondaparinux, tinzaparin or enoxaparin) or one antiplatelet (i.e. acetylsalicylic acid, acetylsalicylic acid & glycine, clopidogrel, dipyridamole, and ticlopidine) from the outpatient pharmacy during the study period was obtained from eHIS. Relevant data including patients' clinical and demographic data such as age, gender, race, medications use, anticoagulants use, antiplatelets use, diagnosis, prescribed drugs, dosing and indication, duration of therapy and cost of the drug were collected. The drug price was obtained from the medication purchase system. Patients' identities remained anonymous, and only relevant information was retrieved from the records.

2.2. Data Collection

The electronic Hospital Information System (eHIS) was utilized to generate the list of all outpatient patients with various underlying conditions from all disciplines from January 2017 to December 2019 that was prescribed with at least one of the anticoagulants or antiplatelets studied. Patients were then sorted and listed according to their registration numbers. Randomization was conducted by employing the method by Edward Fury, 2011 [32]. The final list was computer generated with each patient's identification number only. The identification number was used to retrieve each patient’s dispensing records, such as the prescribed medicine, dose, indication, and frequency, and transcribed into the data collection form. Additional information, such as demographic information and Procurement and Supply Data (2017 - 2019), was used to quantify the cost of drug usage and to see the pattern in drug procurement.

The data collection form was designed so that all appropriate information is not missed for further data analysis. These data were utilized to calculate each drug's Defined Daily Dose (DDD) per 1000 inhabitants per day. Malaysian CPG was referred to evaluate the quality of prescribing. The DDD was compared between drugs with respect to the patient's demographic characteristics.

2.3. Patient Selection Criteria

2.3.1. Inclusion Criteria

Outpatient patients aged 18 years and above from all disciplines with various underlying conditions received at least one antithrombotic medication from an outpatient pharmacy from January 2017 to December 2019. Patients with at least three (3) consecutive visits dose including during inpatient and outpatient visits to ensure the consistency and applicability of DDD except for tinzaparin and enoxaparin which 1 visit dose was sufficient.

2.3.2. Exclusion Criteria

Rivaroxaban (Non-formulary item). Heparin is given to patients for a short term during their stay in the ward. Patients on Dental prescriptions, haemodialysis, patients referred from other facilities, incomplete data.

2.4. Sample Size and Sampling Method

The sample size was determined using the sample size formula [33]. The significance level was set at $\alpha = 0.05$ (two-tailed), and confidence interval (CI) was set as 95% for the calculation of sample size by using the formula above. The calculated sample size was based on the proportion of patients who received antithrombotic agents in the chosen hospital. A total of 176 patients on antithrombotic agents for the year 2019, 135 patients for the year 2018, and 156 patients for the year 2017 were sampled from eHIS after considering approximately 20% for the drop-out patients following the inclusion and exclusion criteria.

Table 1. Characteristics of patients receiving antithrombotic agents.

Variables		**All (N=673)**		**Anticoagulants (n=262)**		**Antiplatelets (n=402)**		**Both (n=9)**		**X^2 (df)**	**P-value***
		N	**%**	**n**	**%**	**N**	**%**	**n**	**%**		
Gender	Male	309	45.9	60	22.9	243	60.4	6	66.7	91.63 (2)	<0.001
	Female	364	54.1	202	77.1	159	39.6	3	33.3		
Age (years)	18-30	52	7.7	46	17.6	4	1.0	2	22.2	201.46 (6)	<0.001
	31-45	146	21.7	111	42.4	34	8.5	1	11.1		
	46-60	150	22.3	31	11.8	118	29.4	1	11.1		
	>61	325	48.3	74	28.2	246	61.2	5	55.6		
	Mean age (SD)	57.03±17.41		47.32±18.55		63.36±13.24		56.33±18.74			
Ethnicity	Malay	375	55.7	174	66.4	197	49.0	4	44.4	29.10 (6)	<0.001
	Chinese	219	32.5	64	24.4	152	37.8	3	33.3		
	Indian	51	7.6	10	3.8	39	9.7	2	22.2		
	Others	28	4.2	14	5.3	0	0	0	0		
Diagnosis	CVS Conditions	521	77.4	114	43.5	398	99.0	9	100	288.38 (4)	<0.001
	Non-CVS Conditions: O&G	142	21.1	142	54.2	0	0	0	0		
	Non-CVS Conditions: Others	10	1.5	0	2.3	4	1.0	0	0		

*Chi-Square test

2.5. Medicine list

Anticoagulants available in the Ministry of Health Formulary are coumarins and indandiones group such as warfarin 1mg tablet, warfarin 2mg tablet, warfarin 3mg tablet, and warfarin 5mg tablet. Another available anticoagulant medication is the Factor Xa inhibitors group i.e. fondaparinux 2.5mg/0.5ml injection and rivaroxaban 10mg, 15mg, and 20mg tablets. Rivaroxaban is a control item purchased under the haematology discipline in this hospital, but patients are required to buy the medication out-of-pocket.

2.6. Outcome Parameter

The data was expressed in defined daily dose (DDD) per 1,000 inhabitants per day. The DDD result was then compared with the current WHO classification of ATC/DDD for the DDD analysis, obtained from the ATC/DDD Index 2020 [8]. For this study, the quantity of use of medicine was expressed as the number of DDDs per 1000 inhabitants per day.

2.7. Statistical analysis and Interpretation

Data were analysed using IBM Statistical Package for Social Science (SPSS) programme version 25 and Microsoft Excel version 2016. The patient's prescribing record and demographic data were descriptively presented, such as the frequency, percentage, mean and standard deviation. The variables evaluated were patients' age, gender, and race. The variables' distribution was assessed with the Kolmogorov-Smirnov test. Results would be statistically significant if the p-value were < 0.05.

2.8. Ethical Considerations

The ethical approval application was obtained from UiTM's Ethics Committee and Medical Research & Ethics Committee (MREC) before commencing this study (Approval REC/04/2021), dated 30th April 2021. All the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines were followed. All the data obtained from eHIS, such as patients' profiles and medical records, was restricted only to the investigators and kept confidential.

3. Results

The eHIS database showed that the participating pharmacy unit in the hospital dispensed anticoagulant and antiplatelet agents to 37,314 patients from January 2017 to December 2019. Based on the general inclusion and exclusion criteria, 27,471 patients were eligible for further investigation of their medication dispensing records. This resulted in 73.8% of patients receiving antithrombotic drugs throughout the study. Out of 9843 patients excluded, some had incomplete dispensed prescription information and not meeting the criteria. The final randomization resulted in the screening are 673 patient’s records that constitute 2.4% of the total population who received antithrombotic drugs in the hospital which this study was conducted (Table 2).

Table 2. Use of antithrombotic in DDD/1000 inhabitants/day and total expenditure.

Anti-Thrombotic Drugs	ATC Code	Year	DDD/1000 inhabitants/day
Warfarin Tablet	B01AA03	2017	1.3153
		2018	2.0447
		2019	3.1305
Enoxaparin Injection	B01AB05	2017	1.3699
		2018	0.8173
		2019	1.5732
Fondaparinux Injection	B01AX05	2017	0.0023
		2018	0.0009
		2019	0.0000
Tinzaparin Injection	B01AB10	2017	0.4820
		2018	0.3304
		2019	0.3012
Acetylsalicylic Acid Tablet	B01AC06	2017	7.9451
		2018	7.4489
		2019	6.4526
Acetylsalicylic Acid and Glycine	B01AC06	2017	7.9451
		2018	7.4489
		2019	6.4526
Clopidogrel Tablet	B01AC04	2017	0.8418
		2018	1.7177
		2019	0.6883
Dipyridamole Tablet	B01AC07	2017	0
		2018	0
		2019	0
Ticlopidine Tablet	B01AC05	2017	0.3752
		2018	0.0463
		2019	0.0755
Total		2017	-
		2018	-
		2019	-

3.1. Patients' Socio-demographic Characteristics

The selected demographic data of patients who received antithrombotic agents (anticoagulant and/or antiplatelet agents) is summarised in Table 3.

Table 3. Summary of the mean difference in DDD in relation to age group, gender, and race.

Antithrombotic Drugs	Variables	Number of samples (n)	Mean DDD (SD)	P value
Warfarin	Male	57	0.0518(0.2736)	t=1.185, P=0.239
	Female	47	0.0215(0.9056)	No significant difference
	18-30	2	0.0518(0.2736)	
	31-45	10	0.0215(0.9056)	F=0.405, P=0.75
	46-60	24	0.0356(0.6316)	No significant difference
	>61	68	0.0355(0.6023)	
	Chinese	48	0.0393(0.5689)	F=1.753, P=0.161
	Indian	6	0.0984(0.4930)	No significant difference
	Malay	49	0.0260(0.6913)	
Enoxaparin	Male	2	0.0453(0.5027)	t=-1.130, P=0.260
	Female	152	0.0188(0.4748)	No significant difference
	18-30	46	0.0186(0.4256)	
	31-45	100	0.0168(0.4173)	F=10.739, P<0.001
	46-60	4	0.0430(0.9244)	
	>61	4	0.2697(0.4144)	
	Chinese	15	0.0294(0.6728)	F=2.247, P=0.085
	Indian	4	0.0279(0.6712)	No significant difference
	Malay	122	0.0190(0.4510)	
	Others	13	0.0106(0.2575)	
Acetylsalicylic Acid	Male	237	0.0583(0.4737)	t=0.524, P=0.601
	Female	146	0.0620(0.4975)	No significant difference
	18-30	5	0.0256(0.3911)	
	31-45	35	0.0411(0.4826)	F=3.103, P=0.027
	46-60	113	0.0564(0.4836)	
	>61	230	0.0662(0.4767)	
	Chinese	144	0.0736(0.4423)	F=8.426, P<0.001
	Indian	36	0.0611(0.5117)	
	Malay	190	0.0554(0.4779)	
	Others	13	0.0162(0.5028)	
Clopidogrel	Male	74	0.0325(0.5713)	t=2.152, P=0.034
	Female	42	0.0570(0.6094)	
	18-30	3	0.0421(0.5278)	F=1.290, P=0.281
	31-45	9	0.0169(0.4679)	No significant difference
	46-60	31	0.0412(0.1316)	
	>61	73	0.0435(0.5385)	
	Chinese	37	0.0649(0.6368)	F=4.384, P=0.006
	Indian	13	0.0412(0.7087)	
	Malay	58	0.0345(0.5047)	
	Others	8	0.0114(0.4178)	

3.2. Defined Daily Dose (DDD) of Antithrombotic Drugs

To estimate the DDD of antithrombotic drugs prescribed, 673 prescriptions sampled after randomization according to years from 2017 to 2019 were screened for all anticoagulant and antiplatelet drugs. DDDs values were calculated from the information on dosage per day.

It was found that the top three most utilized anticoagulant drugs from the year 2017 to 2019 were warfarin with 1.82 DDD, followed by enoxaparin (1.05) and tinzaparin (0.39). This implied that warfarin was the most utilized anticoagulant drugs in the population about two times more than the second most utilized drug i.e. enoxaparin followed by tinzaparin. Fondaparinux was the least utilized anticoagulant drug in this study. The results for DDD of warfarin, enoxaparin, acetylsalicylic acid, clopidogrel according to gender, age and race were presented in Table 4. Comparison of DDD/1000 inhabitants'/day anticoagulant and antiplatelet drugs with MSOM 2015 – 2016 tabulated in Table 5.

Table 4. Association between antithrombotic drugs uses and demographic variables based on WHO defined daily dose (DDD) and Malaysian CPG on the Prevention and Treatment of Venous Thromboembolism 2013.

Antithrombotic Drugs	**Variables**	**Accordance to WHO DDD's**		**Accordance to CPG**	
		n	**%**	**n**	**%**
Warfarin	Male	57	100	57	100
	Female	47	100	47	100
	18-30	2	100	2	100
	31-45	10	100	10	100
	46-60	24	100	24	100
	>61	68	100	68	100
	Chinese	48	100	48	100
	Indian	6	100	6	100
	Malay	49	100	49	100
Enoxaparin	Male	2	100	2	100
	Female	152	100	152	100
	18-30	46	100	46	100
	31-45	100	100	100	100
	46-60	4	100	4	100
	>61	4	100	4	100
	Chinese	15	100	15	100

	Indian	4	100	4	100
	Malay	122	100	122	100
	Others	13	100	13	100
Acetylsalicylic Acid	Male	237	100	237	100
	Female	146	100	146	100
	18-30	5	100	5	100
	31-45	35	100	35	100
	46-60	113	100	113	100
	>61	230	100	230	100
	Chinese	144	100	144	100
	Indian	36	100	36	100
	Malay	190	100	190	100
	Others	13	100	13	100
Clopidogrel	Male	74	100	74	100
	Female	42	100	42	100
	18-30	3	100	3	100
	31-45	9	100	9	100
	46-60	31	100	31	100
	>61	73	100	73	100
	Chinese	37	100	37	100
	Indian	13	100	13	100
	Malay	58	100	58	100
	Others	8	100	8	100

Table 5. Comparison of DDD/1000 inhabitants'/day anticoagulant and antiplatelet drugs with MSOM 2015 – 2016.

Drugs (ATC Code)	**DDD in MSOM 2016 (Public sector)**	**MSOM Ranking 2016 (Top 50)**	**DDD/1000 inhabitants/day**		
			2017	**2018**	**2019**
Warfarin (B01AA03)	0.2852	-	1.3153	2.0447	3.1305
Enoxaparin (B01AB05)	0.0986	-	1.3699	0.8173	1.5732
Fondaparinux (B01AX05)	0.0259	-	0.0023	0.0009	0
Tinzaparin (B01AB10)	0.0184	-	0.4820	0.3304	0.3012
Acetylsalicylic Acid (B01AC06)	8.5408	6	7.9451	7.4489	6.4526
Clopidogrel (B01AC04)	0.6873	42	0.8418	1.7177	0.6883
Dipyridamole (B01AC07)	0.0219	-	-	-	-
Ticlopidine (B01AC05)	0.4728	-	0.3752	0.0463	0.0755

3.3. Factors/Determinants Influence Anticoagulant and Antiplatelet Drugs Pattern

It was found that both males and females in all age groups received antithrombotic drugs, and females were found to receive more antithrombotic agents than males for each year from the year 2017 to 2019. In terms of age, the patients' age ranged >61 years old, which were the highest number of patients who received the antithrombotic drug for both genders.

The highest anticoagulant received by the male population for the three years was warfarin which was almost two times more than females in 2017. As for 2018 and 2019, the prescription frequency of males to females receiving warfarin was similar. This was followed by tinzaparin, fondaparinux, and enoxaparin. The highest anticoagulant received by females for those three years was enoxaparin. Females in the age group 31-45 years old received enoxaparin the most, followed by the age group 18-30 years old for the years 2017 to 2019. This was followed by warfarin, tinzaparin, and fondaparinux.

The males received the highest antiplatelet drug for three years. They were in the age group >61, followed by 46-60. The highest antiplatelet drug received by the male population for the three years was aspirin followed by cardiprin and clopidogrel. The pattern of receiving antiplatelet drugs in the female group was similar to the male patients. Ticlopidine and dipyridamole was the least antiplatelet drug that both groups received.

4. Discussions

4.1. Patients' Socio-Demographic Characteristics

The distribution of patients receiving antithrombotic agents was mainly from the medical department, O&G department and haematology department of this hospital which is also a referral hospital for haematology. The number of patients load is about 1000 patients per day. The percentage of patients who received antithrombotic drugs showed an increasing trend for antiplatelets, of which 5.5% for 2017 and 7.7% for 2019. For anticoagulants, the percentage also increased from 2.2% in 2018 to 2.46% in 2019.

The patients were predominantly Malay and Chinese; most were >61 years old, followed by the age group between 45-60 and 31-45 years old. The distribution of patients resembled the demographics of patients reported by the Department of Statistics, Malaysia, 2019 under the Statistics on Causes of Death, 2019 [21]. The report showed that ischaemic heart diseases contributed to the highest principal causes of death in 41-59 years old and >60 years old in 2018.

4.2. Appropriateness and Rational Use of Antithrombotics

In this study, the DDD for all antithrombotic drugs studied were in accordance with WHO DDD's, i.e. lower than WHO DDD's. All antithrombotic drugs were prescribed in compliance with the Malaysian CPG on the Prevention and Treatment of Venous Thromboembolism 2013. This finding was inconsistent with a previous study done in Canada by Lloyd et al. where the management of deep vein thrombosis (DVT) despite the recommendation to support deep vein thrombosis (DVT) risk assessment and appropriate use of prophylaxis in medical inpatients. The authors further stated it was either neglected or prescribed unnecessarily by the clinicians [9].

The proportion of outpatient patients who received anticoagulants was 2.46% in 2019, which increased from 2018 to 2.2%. However, in 2017, the proportion of outpatient patients who received anticoagulants was 3.36%. The proportion of outpatient patients who received antiplatelets are 7.7% in 2019, which also showed an increasing trend from 2018, which was 5.4%, and 5.5% in 2017.

Among all the antithrombotic drugs, enoxaparin injection was the highest item purchased in 2019 (RM755, 992.49) where the total purchasing value had increased by about 32% from 2018. It was found that RM1, 528,234.14 had been allocated for antithrombotic drugs purchased in 2019 (about 2% of the total expenditure). This was fair in terms of budgetary implications since there were no significant changes in the drug price from 2017 to 2019 for most of the antithrombotic drugs studied. This showed that the pattern of drugs procured was based on demand.

The evaluation of purchasing of anticoagulant drugs from 2017 to 2019 found that the total expenditure spent on the purchase of warfarin was in accordance with the usage pattern.

The total cost of warfarin usage was also in line with the DDD/1000population/day of warfarin from 2017 to 2019. This was consistent with a study by Kirley et al., and Theodorou et al. that stated although prescribing of NOACs is increasing, recent data available suggested that warfarin remains the most commonly utilized oral anticoagulant in outpatient settings [10.11].

For enoxaparin, the second highest utilized anticoagulant drug, the total expenditure spent on purchasing this drug was appropriate with the total cost usage. From the total cost of enoxaparin usage, the decreasing pattern from 2017 to 2018 later rebounded from 2018 to 2019. This was in line with the DDD/1000population/day of enoxaparin from 2017 to 2019. The decreasing pattern of the usage of enoxaparin from 2017 to 2018 was due to the purchase of enoxaparin in 2017 (RM1, 267,153.20) constituted a 2.1% budget spent on drugs for that year. This has made it a controlled item and is strictly monitored by the pharmacy department. This control was with the agreement with the O&G department, where prescribing and supplying enoxaparin must be according to the scoring and criteria of post-natal patients upon discharge after delivery. This approach impacted the reduced budget spent on enoxaparin in 2018 (RM 512,909.20) i.e. only 0.8% of the budget was spent on drugs for that year. However, the total expenditure on enoxaparin increased from 2018 to 2019 due to the increase in deliveries in this hospital.

Tinzaparin, the second costliest anticoagulant drug, the total cost of usage for the outpatient setting was more than the total purchase for the total number of patients. This was contrary to fondaparinux, where total expenditure spent on it was high, but the actual total usage was very low. Both tinzaparin and fondaparinux total cost usage were not in line with the DDD from 2017 to 2019. This highlighted the amount of money that could be saved to purchase other drugs, such as enoxaparin.

As for antiplatelet drugs, from 2017 to 2019, the total expenditure spent on the purchase of aspirin and cardiprin was in accordance with the usage pattern. However, the total cost of aspirin and cardiprin was not in line with the DDD/1000 population/day of acetylsalicylic acid from 2017 to 2019. This finding was consistent with a study in the United States by Ansa et al. that showed that not all groups of individuals are leveraging the benefits from the recommended use of aspirin and may consequently be at higher risks for cardiovascular events and premature death [12].

The total cost usage was in line with the DDD calculated for clopidogrel from 2017 to 2018 and not from 2018 to 2019. However, the total expenditure spent on the purchase of this drug was appropriate with the total cost usage. The drop in the DDD of clopidogrel from 2018 to 2019 might be contributed by the lack of awareness at the prescriber side on the availability of the generic clopidogrel which allows the prescriber to start prescribing clopidogrel for lifelong treatment from March 2010 onwards. This was due to the high budget implications since the cost of original clopidogrel for lifelong treatment would be RM2007.50 per patient/year. This is about eighteen times higher as compared to RM110 per patient per year for generic clopidogrel [13]. The usage of generic clopidogrel led to total

expenditure for the whole year 2019 for generic clopidogrel was only RM58, 344 or 0.1% of the budget spent on drugs in 2019.

4.3. Defined Daily Dose (DDD) of Antithrombotic Drugs

The DDDs found in this study were based on the population sample at the outpatient pharmacy of the chosen hospital. The national reports (MSOM) include the utilization of the whole population data for public health institutions but sample population data for private health institutions. Therefore, the comparison of the DDD from the study with the national reports was not comparable.

Overall, from 2017 to 2019, there was a fluctuation in the usage of antithrombotic agents, except for the use of warfarin from 2017 to 2019, which showed an increasing pattern. This was due to warfarin remaining the gold standard oral anticoagulant since the availability of other oral anticoagulants (DOAC), such as rivaroxaban, was purchased for the haematology patient only. Hence warfarin is the preferred choice for the prescriber. The findings on warfarin being the highest DDD utilized, were in accordance with the current recommendations. Warfarin was recommended for use as an initial treatment for venous thromboembolism (VTE), a common cardiovascular disease after myocardial infarction and stroke [14].

Enoxaparin, a low molecular weight heparin, was the second most utilized anticoagulant drug from 2017 to 2019. LMWH was proven in a few studies to be more effective than unfractionated heparin in preventing thrombosis without increasing the risk of bleeding [15-18]. These findings were consistent to another study that found enoxaparin was among commonly used anticoagulant drugs for various diagnoses such as ischemic heart disease (IHD), deep vein thrombosis (DVT), pulmonary embolism (PE), cardiovascular accident and others [18]. However, the high usage of enoxaparin was mainly utilized by females aged 31-45 and 18-30 years old for the indication for pregnancy and post-partum. This was consistent with current recommendations suggesting LMWH as the preferred agent during pregnancy for prophylaxis and VTE treatment [19].

The least utilized antithrombotic agents at the outpatient pharmacy from 2017 to 2019 were tinzaparin and fondaparinux. This was due to the high budget implications of these drugs. Its low utilization was monitored and presented during drug therapeutic committee meetings to the hospital departments, which created heightened awareness to the prescriber in prioritizing its use on patients.

Acetylsalicylic acid (aspirin) remained the most widely used agent for antiplatelet drugs since 2017. This was followed by cardiprin, clopidogrel, ticlopidine and dipyridamole. The usage pattern of antiplatelet drugs from 2017 to 2019 was consistent with the usage pattern of antiplatelet drugs from 2015 to 2016 that was reported in the Malaysian Statistics on Medicines (MSOM) 2015 to 2016 [20].

4.4. Factors and determinants influence the antithrombotic drugs pattern

Regarding the finding on patient characteristics, it was found that the treatment intensity increased with age. Patients in the age range >61 years old had the highest number of patients who received antithrombotic followed by patients in the age group 46-60 and 31-45. The lowest range of age received antithrombotic was 18-30 years old. This was consistent with the study performed by Man-Son-Hing et al. where among all age groups, elderly persons received the most significant absolute benefit from warfarin or aspirin prophylaxis [23]. Man-Son-Hing et al., in the study, also highlighted a recommendation from an expert panel that for long-term warfarin treatment, all elderly people with atrial fibrillation should be treated, unless there was a contraindication.

The choice of antithrombotic drugs was influenced by the patient's factors that can affect the antithrombotic drug utilization pattern as well as the outcome of the treatment. Determinant factors include age, gender, race, smoking history, presence of atherosclerotic diseases & peripheral artery diseases, comorbidity, patient compliance, and bleeding history. Patients in the presence of atherosclerotic diseases like angina and peripheral artery disease constitute the major determinants of the selection of antithrombotic monotherapy. Comorbidity of cardiovascular risk factors (heart failure, hypertension, stroke, transient ischaemic attack (TIA), systematic thromboembolism, pulmonary thromboembolism, deep vein thrombosis, peripheral artery diseases, myocardial infarction (MI) and angina were among the major determinants on the selection of antiplatelet and anticoagulant drugs (Rauch, 2012). Prescribing of anticoagulants was mentioned to be influenced to a greater extent by bleeding risk than it was by the risk of stroke [24]. Another study also showed that changes in anticoagulant regimens were influenced by a history of bleeding [25].

For the anticoagulants studied, warfarin was the highest utilized anticoagulant for the three years. The mean difference in DDD was not statistically significant in relation to gender, age group, and race. This was supported by two studies in patients with atrial fibrillation (AF) that demonstrated the factors for the usage of oral anticoagulants and their consistent use in these AF patients. Evidence suggested that oral anticoagulants, such as Vitamin K antagonists (VKA) or NOAC, were influenced by old age, race, and patient-related and provider-related factors [26,27].

Enoxaparin, the second most utilized antithrombotic drug from 2017 to 2019, the mean difference of DDD for enoxaparin was statistically significant only with age group but not statistically significant with gender and race. Enoxaparin was mainly used for the indication of pregnancy and post-partum in women. This was supported by a study by Ellison et.al that highlighted the use of enoxaparin in pregnancy was associated with a low incidence of complications and a dose of 40 mg once daily throughout pregnancy provides satisfactory anti-factor Xa levels and appears effective in preventing venous thromboembolism [28].

Enoxaparin's highest female population to receive was in the age group of 31-45 followed by those in the age group between 18-30 years old. This was because 18-45 years

old was the child-bearing age that supported the high utilization of enoxaparin in that age range. This was consistent with the study highlighting the average female age of first-time pregnancy in the United States of America increased from 21 to 25 years in the 40 years after 1970, with a decline in the number of mothers under the age of 20 and a substantial rise in those over the age of 35 [29].

The highest utilized antiplatelet for the three years was acetylsalicylic acid. The mean difference in DDD was statistically significant in relation to age group and race but not statistically significant in gender. For clopidogrel, the second highest utilized antiplatelet for the three years of 2017, 2018, and 2019 the mean difference in DDD was statistically significant in relation to gender and race, but the mean difference of DDD was not statistically significant in relation to age group. This was consistent with the findings in the study by Ahmed et al. that found there were differences in prescribing antiplatelet agents between different gender and different ages. The study reported that clopidogrel and aspirin were prescribed mainly for patients over 50 years old, and generally, majority of the male patients received antiplatelet agents [30].

This is the first study conducted in the region assessing the usage of antithrombotic agents, and the DDD values could serve as the standard for comparison with other studies. Even though this study was only conducted in one particular hospital, we collected data for consecutive three years' data to examine the continuous usage pattern. The study's outcome would be beneficial in developing a cost-effective hospital drug formulary and improving current policy on the utilization of anticoagulants and antiplatelets. This research could highlight the utilization pattern of anticoagulants and antiplatelets in a tertiary hospital in Malaysia and its appropriateness in terms of DDD.

5. Conclusions

The findings on the trend of high warfarin utilization, a high risk medication that requires close monitoring to prescribe this medication through the effective collaboration among prescribers and pharmacists in managing thrombotic diseases. Warfarin was also an efficient and cost-effective alternative due to favorable tolerability with fewer side effects than DOAC. Aspirin and cardiprin were the highest utilized antiplatelet drugs, followed by clopidogrel and ticlopidine. This study showed that the mean difference in terms of DDDs of the studied antithrombotic drugs have an impact of patient demographic characteristics in terms of age, gender, race, smoking history, presence of atherosclerotic diseases and peripheral artery diseases, comorbidity, patient compliance and bleeding history that affected the choice and utilization of antithrombotic drugs. Future drug use evaluation should also have prospectively assessed the appropriateness of antithrombotic drug indications, drug selection, duration of treatment, drug interactions, and outcomes of treatment.

Author Contributions: Conceptualization, MMM, AYB, LCM ; methodology, MMM, QYL, KSL, LCM ; software, AYB, QYL; validation, MMM, AYB, QYL, LCM; formal analysis, MMM, AYB, LCM ; investigation, MMM, AYB, QYL, LCM ; resources, QYL, KSL, LCM ; data curation, MMM, AYB, QYL, KSL, LCM ; writing-original draft preparation, MMM, AYB; writing-review and editing, QYL, JSD, SKSD, MJF, KSL, LCM

Funding: No external funding was provided for this research.

Conflicts of Interest: The authors declare no conflict of interest.

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