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A study of anticoagulant therapy in patients with coronary artery disease

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Abstract

Objectives: One of the methods used to treat coronary artery disease (CAD) is anticoagulant therapy, which involves administering anticoagulants to patients that inhibit the arrangement and actuation of clotting factors. Anticoagulant therapy in patients with CAD must be monitored and evaluated because its greatest side effect is the risk of bleeding. The research aimed to analyze anticoagulants used in therapy for CAD patients and identify potential adverse drug reactions and adverse drug interactions.

Methods: This was an observational study which collected data retrospectively at Bhayangkara Hospital Surabaya. Patient data had to meet the requirements for inclusion, which were patients treated for a diagnosis of CAD with anticoagulant therapy and were in conditions with or without complications and comorbid diseases. Data were obtained from 40 patient medical records. The data were then processed descriptively.

Results: Most patients were male (80%) and aged 61–70 years old (37.5%). Fondaparinux was administered to 18 patients at a dose of 1 × 2.5 mg SC. Furthermore, enoxaparin was administered to 15 patients at a dose of 2 × 60 mg SC, and seven patients received warfarin at a dose of 1 × 2–4 mg per oral.

Conclusions: The anticoagulants used in this study were fondaparinux 1 × 2.5 mg SC (45%), enoxaparin 2 × 60 mg SC (37.5%), and warfarin 1 × 2–4 mg PO (17.5%). Side effects of the anticoagulants were absent. However, drug interactions with aspirin, clopidogrel, and allopurinol increased the risk of bleeding.

Keywords: anticoagulants; coronary artery disease; drug-related problems; enoxaparin; fondaparinux; warfarin.

Introduction

Coronary artery disease (CAD) is an abnormality of coronary arteries that occurs when they are narrowed or obstructed. It causes an imbalance between blood supply and oxygen, which can cause myocardial ischemia. Coronary artery disease is classified into acute coronary syndrome (ACS) and chronic stable angina pectoris [1]. Blockages in blood vessels can cause various diseases depending on the location of the blockages [2].

ACS, which usually consists of myocardial infarction and unstable angina, is the form of CAD causing the majority of deaths. ACS occurs due to the rupture or erosion of atherosclerotic plaque in the coronary arteries with the continuing activation and aggregation of extrinsic blood clots [3].

According to data from the World Health Organization (WHO), 31% or 17.9 million deaths worldwide in 2017 were caused by cardiovascular disease. CAD has caused 42.3% of deaths (7.4 million) with a prevalence of 1.5% in Indonesia according to Basic Health Research (2018). According to the WHO, in 2018, deaths due to CAD in Indonesia reached 318,820 or 18.73% of total deaths. The mortality rate based on age was 181.43 per 100,000 population.

The use of anticoagulants can reduce the occurrence of myocardial ischemia, but anticoagulants can also cause bleeding in CAD patients, thus its administration and effects on patients must be monitored [4]. Bleeding can increase the risk of death. Anticoagulant therapy should be done to minimize the risk of bleeding [5]. Several types of anticoagulants used include vitamin K antagonists, low-molecular-weight-heparin (LMWH), unfractionated heparin (UFH), direct thrombin inhibitors, and factor Xa inhibitors [6]. There are many pharmacological advantages

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of LMWH, such as reduced monitoring, ease of use, and a lower risk of thrombocytopenia [7]. During the administration of LMWH and UFH anticoagulants, minor bleeding occurred in 53% of the 230 hospitalized patients, moderate bleeding occurred in 32%, and 15% suffered major bleeding, such as intracranial bleeding. Major gastrointestinal bleeding occurred in 52% of the 56 patients, 34% suffered intracranial bleeding, and 14% experienced bleeding in other areas with the use of factor Xa inhibitors [8]. The use of the vitamin K antagonists' class of anticoagulants had a major bleeding incidence rate of 1,729 events, 338 incidences of intracranial bleeding, and 649 incidences of major gastrointestinal bleeding [9]. With the use of bivalirudin, major bleeding occurred in 1% of patients and minor bleeding occurred in 2–4% of patients [10].

Anticoagulant therapy in patients with CAD must be monitored and evaluated since it may result in bleeding. Problems related to anticoagulant drugs occur due to the selection of anticoagulant types, their side effects, their dosage, and the possibility of interactions between anticoagulants and other drugs. This study aimed to analyze anticoagulants used and identify potential adverse drug reactions and drug interactions in patients with CAD at Bhayangkara Hospital Surabaya in order to improve pharmaceutical services.

Materials and methods

This observational study collected data retrospectively from January 1st to December 31st, 2019 at Bhayangkara Hospital Surabaya. Inclusion criteria of the data included all medical records of the patients treated for a diagnosis of CAD with anticoagulant therapy at the Inpatient Cardiac Installation of Bhayangkara Hospital Surabaya and in conditions with or without complications and comorbid diseases. Data analysis was carried out descriptively. The data analyzed involved patient profiles (name, age, weight, and height), patient history, patient treatments such as anticoagulant therapy and other drugs (dose, duration of use, route, and time of administration), diagnosis, clinical data, and laboratory data. The minimum number of samples needed was 35 based on the Lemeshow formula.

$$\text{Lemeshow Formula}: n = \frac{Z\alpha^2 \times p \times q}{d^2}$$

Description:

n=number of minimum sample; $Z\alpha$=standarize normal deviate; p=prevalence outcome; q=1 − p and d=clinically expected variation (precision) [11].

Medical record data, which usually included the patient's condition on that day, were used for identifying adverse drug reactions. Drug interactions were identified from patients' therapeutic profiles and searched in the literature for potential interactions from Stockley [12].

Results

There were 40 medical records reviewed for this study. Table 1 shows that 80% of the patients were male, and most patients with CAD were 60–69 years old (42.5%).

Table 2 shows that most of the patients with CAD were treated for four days (52.5%). Most patients were diagnosed with ST-elevation myocardial infarction (STEMI) (37.5%) as shown under the CAD classification in Figure 1.

The highest prevalence of comorbid disease that the patients had was diabetes mellitus (37.5%) as shown in Figure 2. Table 3 shows that the various kinds of anticoagulants found included fondaparinux, enoxaparin, and warfarin. Table 4 shows the potential drug interactions due to the polypharmacy patients experienced during treatment.

Potential drug interactions in this study, especially involving anticoagulants, are of great importance. Anticoagulants may cause bleeding as a side effect, and interactions with other drugs may increase the occurrence of bleeding. Potential anticoagulant drug interactions in this study with other drugs, namely aspirin, clopidogrel, and allopurinol. Interaction between fondaparinux and aspirin can result in increasing the incidence of bleeding. Table 5 shows the use of other therapies in patients with CAD.

Discussions

Table 1 illustrates 32 (80%) patients were male, while 8 (20%) were female. Men had a greater risk of developing CAD than women (American Heart Association, 2015). The morbidity of men with CAD is greater than in women due to the combination of estrogen and progesterone present in women that may act as secondary prevention of CAD.

Susceptibility toward CAD increases with age, especially in patients aged over 45 years old, while the

Table 1: Patient demographics.

Profile	Total, %
Gender:	
Men	32 (80%)
Women	8 (20%)
Age:	
40–49 years old	1 (2.5%)
50–59 years old	16 (40%)
60–69 years old	17 (42.5%)
70–79 years old	5 (12.5%)
≥80 years old	1 (2.5%)

Table 2: Length of stay (LOS) CAD patients.

LOS, days	Total patients	Percentage, %
2	1	2.5
3	10	25
4	21	52.5
5	7	17.5
6	1	2.5

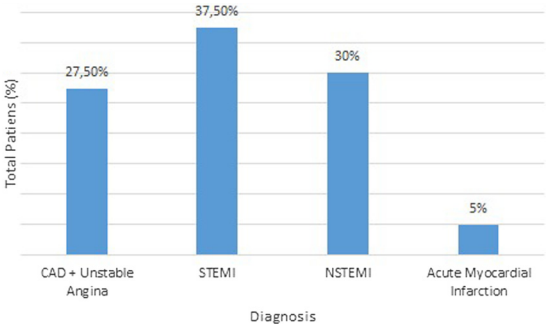

Figure 1: Distribution of CAD patients by diagnosis.

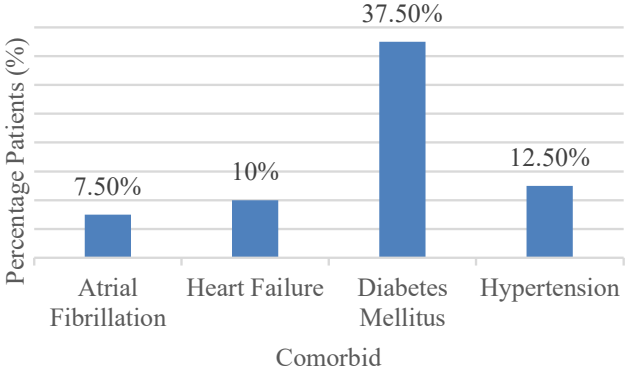

Figure 2: Distribution of comorbidity by diagnosis.

Table 3: Use of anticoagulant therapy.

Drug classification	Type of medicine	Dosage	Route	Total
Anticoagulant	Warfarin	1 × 2–4 mg	po	7
	Enoxaparin	2 × 60 mg	sc	15
	Fondaparinux	1 × 2.5 mg	sc	18

incidence of CAD is very rare in patients under 40 years old. As a person grows older, changes in the physiology of the heart and blood vessels will occur despite the absence of disease. The myocardium of the aging heart sometimes rests imperfectly between heartbeats, thus the heart's pumping chamber will become stiffer and work less efficiently (American Heart Association, 2015).

All patients with CAD examined in this study received inpatient care for less than seven days (Table 2). A total of 21 patients (52.5%) were treated for four days. One study with 119,398 samples showed that patients with CAD received a mean length of stay of 5.5 days and with a median of four days. The length of care for CAD patients may depend on heart care procedures. The shorter period of treatment indicates good treatment procedures [13].

CAD classification based on diagnosis

CAD is categorized into non-ST-elevation myocardial infarction (NSTEMI), STEMI, unstable angina, and stable angina pectoris. Acute myocardial infarction is classified into STEMI and NSTEMI. Figure 1 shows 15 patients were diagnosed with STEMI, 12 patients with NSTEMI, 11 patients with unstable angina, and two patients with acute myocardial infarction.

Patients experienced several comorbid diseases, with the most prevalent being diabetes mellitus (Figure 2) with a total of 15 patients (37.5%). A study has shown that diabetes mellitus was a risk factor that could worsen the condition of patients with CAD. This comorbid disease occurs due to the interaction of metabolic changes in the pre-diabetic level, such as the presence of atherogenic dyslipidemia, the endothelial function no longer functioning properly, increased free fatty acids, subclinical inflammation, changes in the adipokine layers and the thrombosis, and fibrinolysis systems [14].

Therapy in patients with CAD

Table 3 shows that, seven patients (17.5%) used warfarin, 18 patients (45%) were given fondaparinux, and 15 patients (37.5%) used enoxaparin. Fondaparinux is a drug that catalyzes the inhibition of factor Xa by antithrombin and does not increase the inhibition of thrombin [15]. Enoxaparin is an anticoagulant in the LMWH group, and it has a mechanism of action similar to heparin, which affects the activity of antithrombin (AT III). What distinguishes heparin from enoxaparin is the more specific degradation of factor Xa that enoxaparin inhibits, while heparin tends to focus on the inhibition of thrombin by antithrombin. Fondaparinux in doses of 2.5 mg may be given to all patients once a day, with a half-life of 15–17 h by the subcutaneous route [16].

This present study shows the patients received fondaparinux within 2–3 days, enoxaparin within 2–5 days, and warfarin in 2–3 days. Several types of anticoagulants,

Table 4: Potential drug interactions (n=40).

Drug interactions	Mechanisms and effects of drug interactions	Total	Troubleshooting
Fondaparinux + aspirin and NSAIDs	In general, fondaparinux as an anticoagulant can cause bleeding because of its mechanism of action. The use of antiplatelet and NSAIDs can also increase the incidence of bleeding → combined use with fondaparinux can increase the risk of bleeding and the severity of bleeding.	16 (40%)	More closer monitoring is warranted when using fondaparinux with antiplatelet or NSAIDs. The time of drug administration can be spaced.
Enoxaparin + clopidogrel	Clopidogrel inhibits platelet aggregation thereby prolonging bleeding time → increases the risk of bleeding when used concurrently.	8 (20%)	The administration of drugs has the potential for bleeding, so it can be overcome by administering different times for the two drugs.
Warfarin + allopurinol	Allopurinol can increase the half-life and work of the anticoagulant → the longer the half-life can increase the duration of warfarin action so that possible side effects of warfarin.	2 (5%)	Concomitant use of allopurinol with the anticoagulant warfarin can reduce the side effects of warfarin.
Warfarin + aspirin + clopidogrel	Aspirin and clopidogrel are antiplatelet agents that work to inhibit platelet aggregation → the use of aspirin and clopidogrel in combination with warfarin can increase the risk of bleeding	6 (15%)	The use of anticoagulants can be given an interval of administration so that they are not simultaneously used.

Table 5: Use of other therapies in patients with CAD (n=40).

Drug classification	Type of medicine	Dosage	Route		Total
Vasodilator nitrat	ISDN	2.5–5 mg	po	26	(65%)
Fibrinolitic	Streptokinase	1,500,000 IU	iv	4	(10%)
	Alteplase	15 mg	iv	2	(5%)
Antiplatelet	Aspirin	100 mg	po	34	(85%)
	Clopidogrel	75 mg	po	34	(85%)
	Ticagrelor	90 mg	po	3	(7.5%)
β-blocker	Bisoprolol	1.25–5 mg	po	24	(60%)
ACE inhibitor	Lisinopril	5–10 mg	po	9	(22.5%)
	Ramipril	2.5–5 mg	po	7	(17.5%)
Antidyslipid	Atorvastatin	20–40 mg	po	39	(97.5%)
	Fenofibrate	300 mg	po	1	(2.5%)
ARB	Candesartan	8–16 mg	po	2	(5%)
Diuretic	Furosemide	40 mg	po, iv	6	(15%)
	Spironolakton	25–50 mg	po	7	(17.5%)
Sedative	Alprazolam	0.5–1 mg	po	19	(47.5%)
Other drug	Allupurinol	100–300 mg	po	11	(27.5%)
	Digoxin	0.25 mg	po	5	(12.5%)
	Glimepiride	2–4 mg	po	4	(10%)
	Metformin	500 mg	po	2	(5%)
	Lantus	4–20 IU	sc	5	(12.5%)
	Apidra	3 × 4–12 IU	sc	4	(10%)

such as warfarin, require monitoring using laboratory international normalized ratio data, whereas fondaparinux and enoxaparin anticoagulants can use partial thromboplastin time. This study found that the patients with complications caused by other diseases, such as atrial fibrillation (AF) and heart failure, were given more warfarin as an effective anticoagulant to prevent ischemic stroke according to the Indonesian Heart Association (2015). During AF, there is blood stasis, atrial hypercontractility, and remodeling of the atrial structures, platelet activation, and the coagulation cascade. These conditions will increase the risk of thrombus formation and the occurrence of ischemic stroke. The use of fondaparinux anticoagulants is more common for several reasons. First, anticoagulant

administration of this type is recommended for all patients receiving antiplatelet therapy (Indonesian Heart Association, 2015), which does not violate religious rules and drug prices. The use of enoxaparin in patients who had undergone percutaneous coronary intervention therapy was more effective than fondaparinux, as thrombus could be formed more easily when fondaparinux was used. However, the risk of bleeding when using enoxaparin was greater than when using fondaparinux [17].

Drug-related problems (DRPs)

Potential drug interactions in this study, especially involving anticoagulants, were of great importance. The administration of anticoagulants often resulted in bleeding as a side effect. Interactions with other drugs increased the occurrence of bleeding. This study points out potential anticoagulant drugs could interact with other drugs, such as aspirin, clopidogrel, and allopurinol. This research can allow pharmacists to improve pharmaceutical services by monitoring and evaluating the effects caused by potential drug interactions.

Conclusions

The anticoagulants used in this study were fondaparinux 1×2.5 mg SC (45%), enoxaparin 2×60 mg SC (37.5%), and warfarin 1×2–4 mg PO (17.5%). There were no adverse effects found from using fondaparinux, enoxaparin, and warfarin, however, potential drug interactions with aspirin, clopidogrel, and allopurinol were found to increase the risk of bleeding.

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References

1. Dobesh PP. Stable ischemic heart disease. In: Dipiro JT, Talbert RL, Yee GC, Matzke GA, Wells BG, Posey LM, editors. Pharmacotherapy a pathophysiologic approach, 10th ed. USA: McGraw – Hill Companies; 2019:691–760 pp.
2. Tubaro M, Vranckx P, Price S, Vrints C. The ESC textbook of intensive and acute cardiovascular care, 2nd ed. UK: Oxford University Press; 2018:1–43 pp.
3. Dipiro JT, Talbert RL, Yee GC, Matzke GA, Wells BG, Posey LM. Pharmacotherapy a pathophysiologic approach, 10th ed. USA: McGraw – Hill Companies; 2019:761–826 pp.
4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. Management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:179–347.
5. Trailokya A, Dhall A, Kumbla DK. Fondaparinux in acute coronary syndromes. J Assoc Phys India 2015;63:83–7.
6. Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: a review. West J Emerg Med 2015;16:11–7.
7. Puymirat E, Aissaoui N, Collet J-P, Chaib A, Bonnet J-L, Bataille V, et al. Comparisson of bleeding complications and one-year survival of low molecular weight heparin vs. unfractioned heparin for acute myocardial infarction in elderly patients. Int J Cardiol 2013;166:106–10.
8. Milling TJ, Clark CL, Feronti C, Song SS, Torbati SS, Fermann GJ, et al. Management of factor Xa inhibitor-associated life-threatening major hemorrhage: a retrospective multi-center analysis. Am J Emerg Med 2018;36:396–402.
9. Adeboyeje G, Sylwestrzak G, Barron JJ, White J, Rosenberg A, Abarca J, et al. Major bleeding risk during anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban in patients with nonvalvular atrial fibrillation. J Manag Care Spec Pharm 2017;23:968–78.
10. Vivian NG, Baumbach A, Grinfeld L, Lincoff AM, Mehran R, Stone GW, et al. Impact of bleeding and bivalirudin therapy on mortality risk in women undergoing percutaneous coronary intervention. Am J Cardiol 2016;117:186–91.
11. Daniel WW. Biostatistics: a foundation for analysis in the health sciences, 7th ed. New York: John Wiley & Sons; 1999.
12. Stockley BK. Stockley's drug interactions, 9th ed. London: Pharmaceutical Pr; 2010.
13. Tickoo S, Bhardwaj A, Fonarow GC, Liang L, Bhatt DL, Cannon CP. Relationship between length of stay and quality of care in patients with acute coronary syndromes. Am J Cardiol 2016;117:201–5.
14. Al-Nozha MM, Ismail HM, Al Nozha OM. Coronary artery disease and diabetes mellitus. J Taibah Univ Med Sci 2016;11:330–8.
15. Bruins Slot KM, Berge E. Factor Xa inhibitors vs. vitamin K antagonists for preventing cerebral or systemic embolism in

patients with atrial fibrillation. Cochrane Database Syst Rev 2018; CD008980.
16. Zehnder JL. Obat yang digunakan pada gangguan koagulasi. In: Katzung BG, editor. Farmakologi Dasar dan Klinik, 12th ed. Indonesia: McGraw-Hill Companies Inc; 2012:675–96 pp.
17. Zhao X, Yang X-X, Ji S-Z, Wang X-Z, Wang L, Gu C-H, et al. Efficacy and safety of fondaparinux vs. enoxaparin in patients undergoing percutaneous coronary intervention treated with the glycoprotein IIb/IIIa inhibitor tirofiban. Mil Med Res 2016; 3:13.