DE GRUYTER Journal of Basic and Clinical Physiology and Pharmacology

A Study Of Anticoagulant Therapy In Patients With Coronary Artery Disease

Journal:	*Journal of Basic and Clinical Physiology and Pharmacology*
Manuscript ID	JBCPP.2020.0486.R2
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Puspitasari, Arina; Universitas Airlangga Fakultas Farmasi, Clinical Pharmacy Salean, Daniel DC; Universitas Airlangga Fakultas Farmasi, Clinical Pharmacy Hasmono, Didik; Universitas Airlangga Fakultas Farmasi, Clinical Pharmacy Hartono, Rudy; Bhayangkara Hospital Surabaya Ardiana, Meity; Bhayangkara Hospital Surabaya, Cardiology
Section/Category:	• Cardiovascular-Pulmonary Interactions
Keywords:	anticoagulants, coronary artery disease, fondaparinux, enoxaparin, warfarin, drp
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. Result: Most patients were male (80%) and aged 61-70 years old (37.5%). Fondaparinux was administered to 18 patients at a dose of 1x2.5 mg SC. Furthermore, enoxaparin was administered to 15 patients at a dose of 2x60 mg SC, and 7 patients received warfarin at a dose of 1x2-4 mg per oral. Conclusion: The anticoagulants used in this study were fondaparinux 1x2.5 mg SC (45%), enoxaparin 2x60 mg SC (37.5%), and warfarin 1x2-4 mg PO (17.5%). Side effects of the anticoagulants were absent. However, drug interactions with aspirin, clopidogrel, and allopurinol increased the risk of bleeding.

DE GRUYTER Journal Abbreviation. Year; short doi

Arina D. Puspitasari[1,2]*; Daniel Dwi Christiananta Salean[3]; Didik Hasmono[1]; Rudy Hartono[4]; Meity Ardiana[4]

A Study Of Anticoagulant In Patients With Coronary Artery Disease

DOI: https://doi.org/xxxxx/xxxxxxxxxx
Received: Month Day, Year; **Accepted**: Month Day, Year

Abstract

Objectives: One of the therapies for CAD is giving an anticoagulant which inhibits the formation and activation of clotting factors. The use of anticoagulants in patients with coronary heart disease must be monitored and evaluated because the greatest side effect is the risk of bleeding. The purposes of this research were to analyze anticoagulant used and identify potensial Adverse Drug Reaction and Drug Interaction.
Methods: This was is an observational study and data collection was taken retrospectively at Bhayangkara Hospital Surabaya. Patient data had to meet the inclusion criteria, such as patients with or without complications and comorbid diseases treated with a diagnosis of coronary heart disease and anticoagulant therapy. The data were then processed descriptively.
Results: Data were obtained from 40 patient medical records.The results reveal that the majority of patients were male (80%) and aged 61-70 years old (37.5%). The fondaparinux was given to 18 patients at a dose of 1 x 2.5 mg sc. Further, the enoxaparin was provided to 15 patients at a dose of 2 x 60mg sc, and 7 patients used warfarin at a dose of 1 x 2-4mg per oral.
Conclusions: The anticoagulants used in this study were Fondaparinux 1x2,5 mg sc (45%), Enoxaparin 2x60 mg sc (37,5%), and Warfarin 1x 2-4 mg po (17,5%). Side effects of the anticoagulants were absent, but drug interactions with aspirin, clopidogrel, and allopurinol will increase the risk of bleeding.

Keywords: anticoagulants; coronary artery disease; fondaparinux; enoxaparin; warfarin; drp

Introduction

Coronary artery disease (CAD) is an abnormality of coronary arteries which 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 (Dobesh, 2019). Blockages in blood vessels can cause various diseases based on the location of the blockages (Tubaro, 2018).

Acute coronary syndrome, which usually consists of myocardial infarction (MI) and unstable angina (UA), is the form of coronary artery disease (CAD) causing the majority of deaths. The 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 (Dipiro, 2019).

The prevalence of deaths caused by cardiovascular disease according to the data of the World Health Organization (WHO) in 2017 were at 31% or 17.9 million deaths worldwide. Coronary artery disease has caused 42.3% deaths (7.4 million) with a prevalence of 1.5% in Indonesia according to the 2018 Basic Health Research. According to the latest WHO data in 2018, deaths due to coronary heart disease in Indonesia reached 318,820 or 18.73% of the total deaths. The death 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 required to be monitored (Anderson, 2013). Bleeding can increase the risk of death. An anticoagulant therapy should be done to minimize the risk of bleeding (Trailokya, 2015). Several types of anticoagulants used include LMWH (Low Molecular Weight Heparin), UFH (Unfractionated Heparin), Vitamin K Antagonists, Direct Thrombin Inhibitor, and Factor Xa Inhibitor (Harter, 2015). There are many pharmacological advantages of LMWH, such as reduced monitoring, ease of use, and a lower risk of thrombocytopenia (Puymirat et al., 2013).

The use of anticoagulants in patients with coronary artery disease must be monitored and evaluated since it may result in the risk of bleeding. Problems related to anticoagulant drugs occur due to the selection of anticoagulant types, their side effects, their dosage, the possibility of occurrence of interactions between anticoagulants and other drugs. This study was expected to identify the pattern of anticoagulant drug use in patients with CAD at Bhayangkara Hospital Surabaya to improve pharmaceutical services.

***Corresponding author:** Arina D. Puspitasari, Department of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga; Universitas Airlangga Hospital, Surabaya Tel:+628132659919 E-mail: arinadery@ff.unair.ac.id
Dwi Christiananta Salean: Faculty of Pharmacy, Universitas Airlangga, Surabaya
Didik Hasmono: Department Clinical Pharmacy Department, Faculty of Pharmacy, Universitas, Surabaya
Rudy Hartono: Bhayangkara Hospital, Surabaya
Meity Ardiana: Bhayangkara Hospital, Surabaya

Materials and methods

This study was an observational study and collected data retrospectively from 1st January-31st December 2019 at Bhayangkara Hospital Surabaya. Inclusion criteria of the data included all medical records of patients with or without complications and comorbid diseases treated with a diagnosis of coronary artery disease and anticoagulant therapy at the Inpatient Cardiac Installation of Bhayangkara Hospital Surabaya. Data analysis was carried out descriptively. The data analyzed involved patient profile (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 data was 35 based on Lemeshow formula.

Results

There were 40 medical records found in this study. Table 1 showed 80% of the patients were male, and most patients with CAD were 60-69 years old (42.5%).

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. Lenght 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

Table 2 explains most of the patients with CAD were treated for 4 days (52.5%). From the CAD classification, most patients were diagnosed with STEMI (37.5%) as shown in Figure 1.

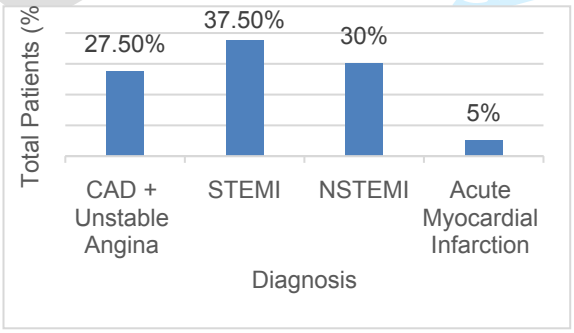


Figure 1. Distribution of CAD Patients by Diagnosis

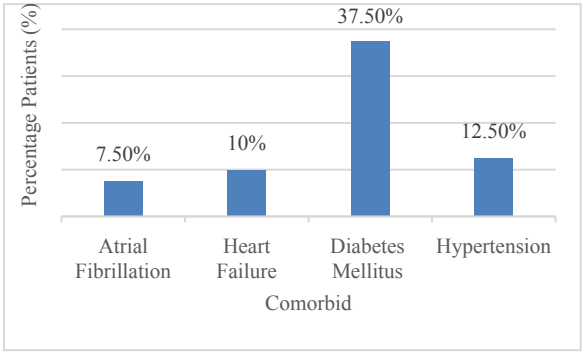


Figure 2. Distribution of Comorbidity by Diagnosis

The highest prevalence of comorbid disease that the patients had was Diabetes Mellitus (37.5%) as described in Figure 2. Table 3 shows various kinds of anticoagulants found included Fondaparinux, Enoxaparin, and Warfarin. Table 4 shows the potential drug interactions due to polypharmacy the patients experienced during treatment.

Table 3. Use of Anticoagulant Therapy

Drug Classification	Type of Medicine	Dosage	Route	Total
Anticoagulant	Warfarin	1x2-4mg	po	7
	Enoxaparin	2x60mg	sc	15
	Fondaparinux	1x2,5mg	sc	18

Discussion

Table 1 illustrates 32 (80%) patients were male, while 8 (20%) were female patients. Men have a greater risk of developing CAD than women (American Heart Association, 2015). The morbidity of men with CAD is greater than in women because there is a combination of women's hormones estrogen and progesterone as the secondary prevention of CAD.

The susceptibility of CAD increases by age, especially in the patients aged over 45 years old, while the 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, and thus the heart's pumping chamber will be stiffer and work less efficiently (American Heart Association, 2015).

All patients with CAD examined in this present study received inpatient care in <7 days (Table 2). A total of 21 patients (52.5%) were treated for 4 days. One study in 119,398 patients shows patients with CAD received a mean length of stay for 5.5 days with a median of 4 days. The length of care for CAD patients may depend on heart care procedures. The shorter period of treatment indicates good treatment procedures (Tickoo, 2016).

CAD Classification Based on Diagnosis

Coronary artery disease is categorized into NSTEMI, STEMI, unstable angina, and stable angina pectoris. Acute myocardial infarction is classified into STEMI and NSTEMI. Figure 1 shows15 patients were diagnosed with STEMI, 12 patients with NSTEMI, 11 patients with unstable angina, and 2 patients with acute myocardial infarction.

Based on the diagnosis of the patients with CAD, the patients experienced several comorbid diseases which the highest prevalence was Diabetes Mellitus (Figure 2) with a total of 15 patients (37.5%). A study has shown that Diabetes Mellitus was a risk factor worsening 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 that was no longer functioning properly, increased free fatty acids, subclinical inflammation, changes in the adipokine layers and the thrombosis and fibrinolysis systems (Al-Nozha, 2016).

Therapy in Patients with CAD

Given the types of anticoagulants in Table 3, 7 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 Xa factor resulted from antithrombin by not increasing the inhibition of thrombin (Bruins, 2018). Enoxaparin is an anticoagulant in the LMWH (Low Molecular Weight Heparin) 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 more specific degradation of Xa factor that enoxaparin inhibits, while heparin tends to focus on the inhibition of thrombin by antithrombin. A 2.5 mg of fondaparinux can be given to all patients once a day. The dose of fondaparinux therapy is given once a day, the half-life of fondaparinux is 15-17 hours by the subcutaneous route (Zehnder, 2012).

This study showed the patients received fondaparinux within 2-3 days, enoxaparin within 2-5 days, and warfarin in 2-3 days. Types of anticoagulants such as warfarin require monitoring using laboratory INR data; whereas, the use of fondaparinux and enoxaparin anticoagulants can use a PTT. This study discovers that the patients with complications caused by other diseases such as AF (atrial fibrillation) and heart failure were given more warfarin as an effective anticoagulant to prevent ischemic stroke according to PERKI (The Indonesian Heart Association). During the atrial fibrillation, there are blood stasis, atrial hypercontractility, remodeling of the atrial structures, and 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 anticoagulant is more common for several reasons. First, anticoagulant administration for this type is recommended for all patients receiving an antiplatelet therapy (PERKI 2015), which does not violate religious rules and drug prices. The use of enoxaparin in patients who had undergone PCI therapy was more effective than fondaparinux as thrombus could be formed more easily as the result of fondaparinux use. However, the risk of bleeding for using enoxaparin is greater than fondaparinux (Zhao, 2016).

Drug-Related Problems (DRPs)

Potential drug interactions in this study, especially anticoagulants, were of great importance. Anticoagulants resulted in bleeding side effects that often occur. Interactions with other drugs can increase the occurrence of bleeding. This study points out potential anticoagulant drugs could interact with other drugs, such as aspirin, clopidogrel, and allopurinol.

Conclusions

The anticoagulants used in this study were Fondaparinux 1x2,5 mg sc (45%), Enoxaparin 2x60 mg sc (37,5%), and Warfarin 1x 2-4 mg po (17,5%). There were no adverse effects found from using of Fondaparinux, Enoxaparin, and Warfarin in this study, but potential drug interactions with aspirin, clopidogrel, and allopurinol will increase the risk of bleeding.

References

1. Al-Nozha MM, Ismail HM, Al Nozha OM. Coronary artery disease and diabetes mellitus. J *Taibah Univ* Sci 2016:11(4):330–338.
2. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Chavey WE, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright R, Scott. 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(23):179-347.
3. Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database of Systematic Reviews 2018.
4. Dipiro Joseph T, Talbert Robert L, Yee Gary C, Matzke Gary A, Wells Barbara G, Posey L Michael. Pharmacotherapy a pathophysiologic approach 10th Ed, USA : McGraw – Hill Companies 2019: 761-826.
5. Dobesh Paul P. Stable ischemic heart disease. *In*: Dipiro Joseph T, Talbert Robert L, Yee Gary C, Matzke Gary A, Wells Barbara G, Posey L Michael. Pharmacotherapy A Pathophysiologic Approach 10th Ed, USA : McGraw – Hill Companies 2019: 691-760.
6. Harter, Katherine, Levine., Michael, Henderson, Sean O. Anticoagulation drug therapy: A review. West J Emerg Med: Integrating Emergency Care with Population Health 2015: 16(1): 11-17.
7. PERKI. Pedoman tatalaksana sindrom koroner akut, Indonesia: Perhimpunan Dokter Spesialis Kardiovaskular Indonesia 2015.
8. Puymirat E, Aissaoui N, Collet Jean-Philippe, Chaib A, Bonnet Jean-Louis, Bataille V, Drouet E, Mulak G, Ferrieres J, Didier B, Tabassome S, Danchin N. Comparisson of bleeding complications and one-year survival of low molecular weight heparin versus unfractioned heparin for acute myocardial infarction in elderly patients, Int J Cardiol 2013: 166: 106-110.
9. Tickoo S, Bhardwaj A, Fonarow Gregg C, Liang Li, Bhatt Deepak L, Cannon Christopher P. Relationship between length of stay and quality of care in patients with acute coronary syndromes. Am J Cardiol 2016: 117(2): 201–205.
10. Trailokya Abhijit, Dhall Anil, Kumbla DK. Fondaparinux in acute coronary syndromes. J Assoc Physicians India 2015: 63: 83-87.
11. Tubaro M, Vranckx P, Price S, Vrints C. The ESC Textbook of Intensive and Acute Cardiovascular Care 2nd ed., Eur Heart J 2018:1-43.
12. Zehnder JL. Obat yang digunakan pada gangguan koagulasi. In: B,G, Katzung (Ed). Farmakologi Dasar dan Klinik 12th Ed, Indonesia: McGraw-Hill Companies Inc 2012: 675-696.
13. Zhao X, Yang X.-X, Ji S.-Z, Wang X.-Z, Wang L, Gu C.-H, Han Y.-L. Efficacy and safety of fondaparinux versus enoxaparin in patients undergoing percutaneous coronary intervention treated with the glycoprotein IIb/IIIa inhibitor tirofiban. Military Medical Research 2016: 3(1).

AUTHOR FORM

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

INSTRUCTIONS

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. The submitting author is responsible for the accuracy and completeness of the submitted information. The form should be uploaded alongside with the submitted manuscript. The form is in four parts.

1 IDENTIFYING INFORMATION

Provide the date of submission and the title of your manuscript and the ID (in case you know it already). Give your full name and if you are NOT the corresponding author please check the box „no". Provide the full name and the initials of all co-authors and indicate, if applicable, the corresponding author.

2 THE WORK UNDER CONSIDERATION FOR PUBLICATION

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you and/or any co-authors received, either directly or indirectly (via your institution), to enable the completion of the work. Checking „No" means that you and any co-authors did the work without receiving any financial support from any third party - that is, the work was supported by funds from the same institution that pays the salary and that institution did not receive third-party funds with which to pay you and/or any co-authors. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check „Yes".

3 RELEVANT FINANCIAL ACTIVITIES OUTSIDE THE SUBMITTED WORK

This section asks about any financial relationships you or any co-authors might have with entities in the scientific arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. Report all sources of revenue paid (or promised to be paid) directly to you, any co-authors or related institutions on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so. For grants you or any co-authors have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. This section also asks about intellectual property such as patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

4 RELATIONSHIPS NOT COVERED ABOVE

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

SECTION 1.

IDENTIFYING INFORMATION - SUBMISSION

1. Effective Date (Day-Month-Year)

2. Manuscript Title A STUDY OF ANTICOAGULANT IN PATIENTS WITH CORONARY ARTERY DISEASE

3. Manuscript Identifying Number (if you know it)

IDENTIFYING INFORMATION - SUBMITTING AUTHOR

1. Given Name (First Name) ARINA DERY

2. Surname (Last Name) PUSPITASARI

3. Are you the corresponding author? Yes ☑ No ☐

Corresponding Author's Name

IDENTIFYING INFORMATION - CO-AUTHOR

Please add all co-authors of your manuscript. Please ensure that you collected all relevant information of your co-authors correctly, since the submitting author is responsible for the accuracy and completeness of the submitted information.

THE WORK UNDER CONSIDERATION FOR PUBLICATION		
Last name	First name	Initials
SALEAN	DANIEL DWI CHRISTIANANTA	
HASMONO	DIDIK	
HARTONO	RUDY	
ARDIANA	MEITY	

SECTION 2.

THE WORK UNDER CONSIDERATION FOR PUBLICATION

Did you, a co-author or your institution at any time receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? Yes ☐ No ☑

If yes, please fill out the appropriate information below. Complete each row by checking "No" or providing the requested information.
Indicate the recipient of the payment or the service by adding the initials in the respective row.

If the relevant information exceeds the available rows, please fill in an additional form and upload this as separate file to the submission system.

THE WORK UNDER CONSIDERATION FOR PUBLICATION						
Type	No	Recipient Initials	Money paid to you	Money paid to your Institution*	Name of Entity	Comments**
Grant	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Consulting fee or honorarium	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Support for travel to meetings for the study or other purposes	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Payment for writing or reviewing the manuscript	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		

Provision of writing assistance, medicines, equipment, or administrative support	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Other	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

SECTION 3.

RELEVANT FINANCIAL ACTIVITIES OUTSIDE THE SUBMITTED WORK

Place a check mark in the appropriate boxes in the table to indicate whether you or any co-author have financial relationships (regardless of the amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the „Add +“. You should report relationships that were present during the 36 months prior to submission. Indicate the person involved by adding the initials in the respective row.

Are there any relevant conflicts of interest? Yes ☐ No ☑

If yes, please fill out the appropriate information below. Complete each row by checking “No” or providing the requested information.
If the relevant information exceeds the available rows, please fill in an additional form and upload this as separate file to the submission system.

RELEVANT FINANCIAL ACTIVITIES OUTSIDE THE SUBMITTED WORK						
Type of Relationship	No	Initials	Money paid to You	Money paid to Your Institution*	Name of Entity	Comments**
Board Membership	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Consultancy	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Employment	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Expert testimony	☑		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		

Grants/grants pending	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Payment for lectures including service on speakers bureaus	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Payment for manuscript preparation	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Patents (planned, pending or issued)	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Royalties	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Payment for development of educational presentations	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Stock/stock options	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		

Travel/accommo-dations/meeting expenses unrelated to activities listed	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
Other	✔		☐	☐		
	☐		☐	☐		
	☐		☐	☐		
	☐		☐	☐		

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

SECTION 4.

OTHER RELATIONSHIPS

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

SOURCES

This form is based on the ICMJE Form for Disclosure of Potential Conflicts of Interest form (to be found here: http://www.icmje.org/conflicts-of-interest/).

Strictly adhere to the given format.
Statements on Informed consent and Ethical approval may be removed **if not applicable**.

Acknowledgments

Gratitude is due to the Bhayangkara Hospital Surabaya.

Research funding

The source of funds in this research is personal from the Authors

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests

There is no conflict of interest from this research.

Informed consent

Informed consent was obtained from all individuals included in this study.

Ethical approval

This research has complied with all the relevant national regulations and institutional policies. (Universitas Airlangga, Number: No.05/IV/2020/KEPK/RUMKIT

TABEL COMMENT AND RESPONSE

REVIEWER 1

Comment	Response
title: A Study of Anticoagulant (Use/Therapy) in Patients with.....	A STUDY OF ANTICOAGULANT THERAPY IN PATIENTS WITH CORONARY ARTERY DISEASE
line 22: revealed	The results revealed that the majority
line 23: furthermore	Furthermore, the enoxaparin was provided
line 25: the first letter in the name of medication should not in capital	We have corrected
where are the results about ADR and DI?	We have added table 4 and table 5
introduction: please add more evidence in anticoagulant caused bleeding in CAD patients	We have added the evidence in anticoagulant caused bleeding "the administration of LMWH and UFH anticoagulants was 53% of the 230 hospitalizations having minor bleeding, 32% had moderate bleeding, and 15% had major bleeding such as intracranial bleeding."
Materials and methods: -please add the procedure of checking ADR and drug interaction also literature used -please add analysis method (e.g table consist of frequency and percentage, etc)	We have added the procedure "For identifying the adverse drug reaction based on medical record data which usually includes the patient's condition on that day. Drug interactions were known on the patient's therapeutic profile and searched in the literature for potential interactions from Stockley (Stockley, 2010)."
line 6 : The first sentence was grammatically error, should be "This observational study collected data..."	This observational study collected data retrospectively from 1st January-31st December
line 12: Which one of Lemeshow formula?	We have added Lameshow's formula
Results: Where is the results regarding ADR and drug interaction?	We have added table 4 and table 5 to show the potential drug interaction and adverse drug reaction.
Discussion: line 31: should add a reference (citation) for this sentence please add more on the benefit of knowing the results of this study to the improvement of pharmaceutical services (as mention in the last part of introduction)	We have added a reference for that sentences from PERKI We have added the benefit to improve pharmaceutical services "From this research, pharmacist can improve pharmaceutical services by monitoring and evaluating the effects that can be caused by potential drug interactions.

REVIEWER 2

Comment	Response
the abstract states that there are drug interactions with other anticoagulants, were there any of the patients received double anticoagulants?	We could not find the sentence you meant, please indicate which line it is on.
the results of the study did not indicate patient drug therapies as mentioned in method, so there are no data to conclude the existence of drug interactions	We have added table 4 and table 5 to show the potential drug interaction and adverse drug reaction.
3. Please explain in detail about the sample size calculation using Lameshow's formula	We have added Lameshow's formula

EDITOR

Comment	Response
Based on the result of similaity check your article has 30% similarity index (file attached), which is above the requirement of the journal (30%). We suggest you to rewrite/paraphrase some sentences to fulfill this requirement.	We have paraphrased some sentences
Please be sure to correct any grammatical errors or typographical errors in the manuscript	We have corrected the grammatical error.
Please format the reference according to the journal guideline, especially for journal name's abbreviation and page number of the cited articles or book chapter	We have corrected according to journal guideline

Arina D. Puspitasari[1,2]; Daniel Dwi Christiananta Salean[3]; Didik Hasmono[1]; Rudy Hartono[4]; Meity Ardiana[4]

A STUDY OF ANTICOAGULANT THERAPY IN PATIENTS WITH CORONARY ARTERY DISEASE

[1]Clinical Pharmacy Department, Faculty of Pharmacy, Universitas Airlangga
[2]Universitas Airlangga Hospital Surabaya
[3] Faculty of Pharmacy, Universitas Airlangga
[4]Bhayangkara Hospital Surabaya

Abstract

Objectives: One of the therapies for CAD is giving an anticoagulant which inhibits the arrangement and actuation of clotting factors. Anticoagulant therapy in patients with coronary artery disease must be monitored and evaluated because the greatest side effect is the risk of bleeding. The purposes of this research were to analyze anticoagulant used and identify potential Adverse Drug Reaction and Drug Interaction.

Methods: This was is an observational study and data collection was taken retrospectively at Bhayangkara Hospital Surabaya. Patient data had to meet the requirements for inclusion, such as patients with or without complications and comorbid diseases treated with a diagnosis of coronary artery disease and anticoagulant therapy. The data were then processed descriptively.

Result: Data were obtained from 40 patient medical records. The results revealed that the most of patients were male (80%) and aged 61-70 years old (37.5%). The fondaparinux was given to 18 patients at a dose of 1 x 2.5 mg sc. Furthermore, the enoxaparin was provided to 15 patients at a dose of 2 x 60mg sc, and 7 patients used warfarin at a dose of 1 x 2-4mg per oral.

Conclusion: The anticoagulants used in this study were fondaparinux 1x2,5 mg sc (45%), enoxaparin 2x60 mg sc (37,5%), and warfarin 1x 2-4 mg po (17,5%). Side effects of the anticoagulants were absent, but drug interactions with aspirin, clopidogrel, and allopurinol will increase the risk of bleeding.

Keywords: anticoagulants, coronary artery disease, fondaparinux, enoxaparin, warfarin, drp

***Corresponding author:** Arina D. Puspitasari**,** Clinical Pharmacy Department, Faculty of Pharmacy, Universitas Airlangga Hospital, Universitas Airlangga, Surabaya Tel:, E-mail: arinadery@ff.unair.ac.id
Dwi Christiananta Salean: Faculty of Pharmacy, Universitas Airlangga, Surabaya
Didik Hasmono**:** Clinical Pharmacy Department, Faculty of Pharmacy, Universitas, Surabaya
Rudy Hartono**:** Bhayangkara Hospital, Surabaya
Meity Ardiana: Bhayangkara Hospital, Surabaya

Introduction

Coronary artery disease (CAD) is an abnormality of coronary arteries which 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 (Dobesh, 2019). Blockages in blood vessels can cause various diseases based on the location of the blockages (Tubaro, 2018).

Acute coronary syndrome, which usually consists of myocardial infarction (MI) and unstable angina (UA), is the form of coronary artery disease (CAD) causing the majority of deaths. The 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 (Dipiro, 2019).

The prevalence of deaths caused by cardiovascular disease according to the data of the World Health Organization (WHO) in 2017 were at 31% or 17.9 million deaths worldwide. Coronary artery disease has caused 42.3% deaths (7.4 million) with a prevalence of 1.5% in Indonesia according to the 2018 Basic Health Research. According to the latest WHO data in 2018, deaths due to coronary artery disease in Indonesia reached 318,820 or 18.73% of the total deaths. The death 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 required to be monitored (Anderson, 2013). Bleeding can increase the risk of death. An anticoagulant therapy should be done to minimize the risk of bleeding (Trailokya, 2015). Several types of anticoagulants used include Vitamin K Antagonists, LMWH (Low Molecular Weight Heparin), UFH (Unfractionated Heparin), Direct Thrombin Inhibitor, and Factor Xa Inhibitor (Harter, 2015). There are many pharmacological advantages of LMWH, such as reduced monitoring, ease of use, and a lower risk of thrombocytopenia (Puymirat et al., 2013). The bleeding that occurred during the administration of LMWH and UFH anticoagulants was 53% of the 230 hospitalizations having minor bleeding, 32% had moderate bleeding, and 15% had major bleeding such as intracranial bleeding. Major gastrointestinal bleeding was 52% of 56 patients, 34% intracranial bleeding, and 14% bleeding in other areas with the use of

factor Xa inhibitor (Milling, 2018). The use of vitamin K Antagonists class of anticoagulants has a major bleeding incidence rate of 1729 events, 338 intracranial bleeding, 649 major gastrointestinal bleeding (Adeboyeje, 2017). In bivalirudin, major bleeding occurs in 1% and minor bleeding 2-4% (Vivian, 2016).

Anticoagulants therapy in patients with coronary artery disease must be monitored and evaluated since it may result in the risk of bleeding. Problems related to anticoagulant drugs occur due to the selection of anticoagulant types, their side effects, their dosage, the possibility of occurrence of interactions between anticoagulants and other drugs. The aim of this study to analyze anticoagulant used and identify potential adverse drug reaction and drug interaction in patients with CAD at Bhayangkara Hospital Surabaya to improve pharmaceutical services.

Materials and methods

This observational study collected data retrospectively from 1st January-31st December 2019 at Bhayangkara Hospital Surabaya. Inclusion criteria of the data included all medical records of patients with or without complications and comorbid diseases treated with a diagnosis of coronary artery disease and anticoagulant therapy at the Inpatient Cardiac Installation of Bhayangkara Hospital Surabaya. The study protocol was approved by the Health Research Ethics Committee R.S. Bhayangkara H.S. Samsoeri Mertojoso Surabaya No. 05/IV/2020/KEPK/RUMKIT.

Data analysis was carried out descriptively. The data analyzed involved patient profile (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 data was 35 based on Lemeshow formula.

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

For identifying the adverse drug reaction based on medical record data which usually includes the patient's condition on that day. Drug interactions were known on the patient's therapeutic profile and searched in the literature for potential interactions from Stockley (Stockley, 2010).

RESULTS

There were 40 medical records found in this study. Table 1 showed 80% of the patients were male, and most patients with CAD were 60-69 years old (42.5%).

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. Lenght 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

Table 2 explains most of the patients with CAD were treated for 4 days (52.5%). From the CAD classification, most patients were diagnosed with STEMI (37.5%) as shown in Figure 1.

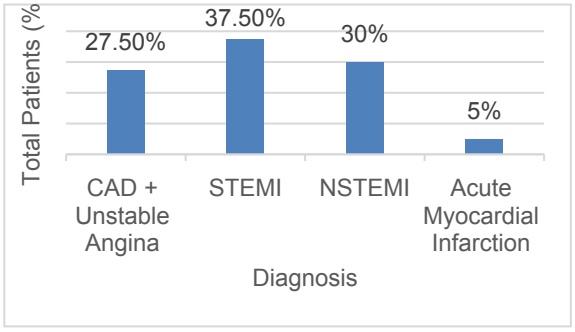


Figure 1. Distribution of CAD Patients by Diagnosis

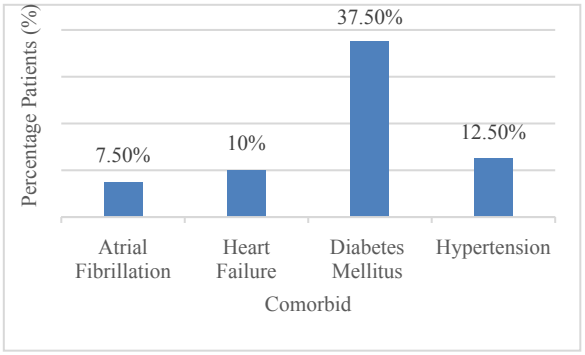


Figure 2. Distribution of Comorbidity by Diagnosis

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

Table 3. Use of Anticoagulant Therapy

Drug Classification	Type of Medicine	Dosage	Route	Total
Anticoagulant	Warfarin	1x2-4mg	po	7
	Enoxaparin	2x60mg	sc	15
	Fondaparinux	1x2,5mg	sc	18

Tabel 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 close 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 + Allupurinol	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.

Potential drug interactions in this study, especially anticoagulants, are of great importance. Anticoagulants have bleeding side effects that most often occur with use, so interactions with other drugs that can increase the occurrence of bleeding can occur. Potential anticoagulant drug interactions in this study with other drugs, namely aspirin, clopidogrel, and allopurinol. Fondaparinux and aspirin can interact with the effect of increasing the incidence of bleeding. Table 5 shows the use of other therapies in patients with CAD.

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	1,5jt/IU	iv	4 (10%)
	Alteplase	15 mg	iv	2 (5%)
Antiplatelet	Aspirin	100 mg	po	34 (85%)
	Klopidogrel	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	0,25mg	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	3x4-12 IU	sc	4 (10%)

DISCUSSIONS

Table 1 illustrates 32 (80%) patients were male, while 8 (20%) were female patients. Men have a greater risk of developing CAD than women (American Heart Association, 2015). The morbidity of men with CAD is greater than in women because there is a combination of women's hormones estrogen and progesterone as the secondary prevention of CAD.

The susceptibility of CAD increases by age, especially in the patients aged over 45 years old, while the 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, and thus the heart's pumping chamber will be stiffer and work less efficiently (American Heart Association, 2015).

All patients with CAD examined in this present study received inpatient care in <7 days (Table 2). A total of 21 patients (52.5%) were treated for 4 days. One study in 119,398 patients shows patients with CAD received a mean length of stay for 5.5 days with a median of 4 days. The length of care for CAD patients may depend on heart care procedures. The shorter period of treatment indicates good treatment procedures (Tickoo, 2016).

CAD Classification Based on Diagnosis

Coronary artery disease is categorized into NSTEMI, STEMI, unstable angina, and stable angina pectoris. Acute myocardial infarction is classified into STEMI and NSTEMI. Figure 1 shows15 patients were diagnosed with STEMI, 12 patients with NSTEMI, 11 patients with unstable angina, and 2 patients with acute myocardial infarction.

Based on the diagnosis of the patients with CAD, the patients experienced several comorbid diseases which the highest prevalence was Diabetes Mellitus (Figure 2) with a total of 15 patients (37.5%). A study has shown that Diabetes Mellitus was a risk factor worsening 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 that was no longer functioning properly, increased free fatty acids, subclinical inflammation, changes in the adipokine layers and the thrombosis and fibrinolysis systems (Al-Nozha, 2016).

Therapy in Patients with CAD

Given the types of anticoagulants in Table 3, 7 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 Xa factor resulted from antithrombin by not increasing the inhibition of thrombin (Bruins, 2018). Enoxaparin is an anticoagulant in the LMWH (Low Molecular Weight Heparin) 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 more specific degradation of Xa factor that enoxaparin inhibits, while heparin tends to focus on the inhibition of thrombin by

antithrombin. A 2.5 mg of fondaparinux can be given to all patients once a day. The dose of fondaparinux therapy is given once a day, the half-life of fondaparinux is 15-17 hours by the subcutaneous route (Zehnder, 2012).

This study showed the patients received fondaparinux within 2-3 days, enoxaparin within 2-5 days, and warfarin in 2-3 days. Types of anticoagulants such as warfarin require monitoring using laboratory INR data; whereas, the use of fondaparinux and enoxaparin anticoagulants can use a PTT. This study discovers that the patients with complications caused by other diseases such as AF (atrial fibrillation) and heart failure were given more warfarin as an effective anticoagulant to prevent ischemic stroke according to PERKI (The Indonesian Heart Association, 2015). During the atrial fibrillation, there are blood stasis, atrial hypercontractility, remodeling of the atrial structures, and 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 anticoagulant is more common for several reasons. First, anticoagulant administration for this type is recommended for all patients receiving an antiplatelet therapy (PERKI 2015), which does not violate religious rules and drug prices. The use of enoxaparin in patients who had undergone PCI therapy was more effective than fondaparinux as thrombus could be formed more easily as the result of fondaparinux use. However, the risk of bleeding for using enoxaparin is greater than fondaparinux (Zhao, 2016).

Drug-Related Problems (DRPs)

Potential drug interactions in this study, especially anticoagulants, were of great importance. Anticoagulants resulted in bleeding side effects that often occur. Interactions with other drugs can increase the occurrence of bleeding. This study points out potential anticoagulant drugs could interact with other drugs, such as aspirin, clopidogrel, and allopurinol. From this research, pharmacist can improve pharmaceutical services by monitoring and evaluating the effects that can be caused by potential drug interactions.

Conclusions

The anticoagulants used in this study were fondaparinux 1x2,5 mg sc (45%), enoxaparin 2x60 mg sc (37,5%), and warfarin 1x 2-4 mg po (17,5%). There were no adverse effects found from using of fondaparinux, enoxaparin, and Warfarin in this study, but potential drug interactions with aspirin, clopidogrel, and allopurinol will increase the risk of bleeding.

REFERENCE

1. 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. Journal of Managed Care & Specialty Pharmacy 2017; 23:968–978.
2. Al-Nozha MM, Ismail HM, Al Nozha OM. Coronary artery disease and diabetes mellitus. J Taibah Univ Sci 2016;11:330–338.
3. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Chavey WE, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright R, Scott. 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.
4. Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database of Systematic Reviews 2018.
5. Dipiro Joseph T, Talbert Robert L, Yee Gary C, Matzke Gary A, Wells Barbara G, Posey L Michael. Pharmacotherapy a pathophysiologic approach 10th ed, USA : McGraw – Hill Companies; 2019: 761-826 p.
6. Dobesh Paul P. Stable ischemic heart disease. *In*: Dipiro Joseph T, Talbert Robert L, Yee Gary C, Matzke Gary A, Wells Barbara G, Posey L Michael. Pharmacotherapy A Pathophysiologic Approach 10th ed, USA : McGraw – Hill Companies 2019; 691-760 p.
7. Harter, Katherine, Levine., Michael, Henderson, Sean O. Anticoagulation drug therapy: A review. West J Emerg Med: Integrating Emergency Care with Population Health 2015; 16: 11-17.
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. The American Journal of Emergency Medicine 2018; 36: 396–402.
9. PERKI. Pedoman tatalaksana sindrom koroner akut, Indonesia: Perhimpunan Dokter Spesialis Kardiovaskular Indonesia; 2015.
10. Puymirat E, Aissaoui N, Collet Jean-Philippe, Chaib A, Bonnet Jean-Louis, Bataille V, Drouet E, Mulak G, Ferrieres J, Didier B, Tabassome S, Danchin N. Comparisson of bleeding complications and one-year survival of low molecular weight heparin versus unfractioned heparin for acute myocardial infarction in elderly patients, Int J Cardiol 2013: 166: 106-110.
11. Stockley., Baxter, K., Stockley's Drug Interactions: 9th Edition. Pharmaceutical Pr, London 2010.
12. Tickoo S, Bhardwaj A, Fonarow Gregg C, Liang Li, Bhatt Deepak L, Cannon Christopher P. Relationship between length of stay and quality of care in patients with acute coronary syndromes. Am J Cardiol 2016: 117(2): 201–205.
13. Trailokya Abhijit, Dhall Anil, Kumbla DK. Fondaparinux in acute coronary syndromes. J Assoc Physicians India 2015: 63: 83-87.
14. Tubaro M, Vranckx P, Price S, Vrints C. The ESC Textbook of Intensive and Acute Cardiovascular Care 2nd ed., Eur Heart J 2018:1-43.

15. Vivian NgG, 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. The American Journal of Cardiology 2016;117:186–191.
16. Zehnder JL. Obat yang digunakan pada gangguan koagulasi. In: B,G, Katzung (Ed). Farmakologi Dasar dan Klinik 12th ed. Indonesia: McGraw-Hill Companies Inc 2012; 675-696 p.
17. Zhao X, Yang X-X, Ji S-Z, Wang X-Z, Wang L, Gu C-H, Han Y-L. Efficacy and safety of fondaparinux versus enoxaparin in patients undergoing percutaneous coronary intervention treated with the glycoprotein IIb/IIIa inhibitor tirofiban. Military Medical Research 2016: 3(1).

Arina D. Puspitasari[1,2]; Daniel Dwi Christiananta Salean[3]; Didik Hasmono[1]; Rudy Hartono[4]; Meity Ardiana[4]

A STUDY OF ANTICOAGULANT THERAPY IN PATIENTS WITH CORONARY ARTERY DISEASE

[1]Clinical Pharmacy Department, Faculty of Pharmacy, Universitas Airlangga
[2]Universitas Airlangga Hospital Surabaya
[3] Faculty of Pharmacy, Universitas Airlangga
[4]Bhayangkara Hospital Surabaya

Abstract

Objectives: One of the ~~therapy~~ methods used to treat~~ies~~ ~~for~~ coronary artery disease (CAD) is anticoagulant therapy~~involvesis giving an anticoagulants to patients,~~ which involves administering anticoagulants to patients that inhibit~~s~~ the arrangement and actuation of clotting factors. Anticoagulant~~s~~ therapy in patients with CAD must be monitored and evaluated because its~~the~~ greatest side effect is the risk of bleeding. The research aimed to analyze anticoagulants used in therapy for CAD patients and identify poten~~t~~s~~s~~ial a~~A~~dverse d~~D~~rug r~~R~~eactions and adverse d~~D~~rug i~~I~~nteractions.

Methods: This was ~~is~~ an observational study which collected data retrospectively~~datawhich whereinand data collection werewas collectedtaken retrospectively~~ at Bhayangkara Hospital Surabaya. Patient data had to meet the requirements for inclusion, which were~~such as~~ patients ~~with or without complications and comorbid diseases~~ treated for~~with~~ a diagnosis of CAD~~coronary artery disease~~ with~~and~~ 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.

Result: ~~Data were obtained from 40 patient medical records.~~ M~~ost of~~ patients were male (80%) and aged 61-70 years old (37.5%). F~~The f~~ondaparinux was administered~~given~~ to 18 patients at a dose of 1 x 2.5 mg SC~~sc~~. Furthermore, ~~the~~ enoxaparin was administered~~provided~~ to 15 patients at a dose of 2 x 60 mg SC~~sc~~, and 7 patients received~~used~~ warfarin at a dose of 1 x 2-4 mg per oral.

Conclusion: The anticoagulants used in this study were fondaparinux 1x2.5 mg SC~~sc~~ (45%), enoxaparin 2x60 mg SC~~sc~~ (37.5%), and warfarin 1x 2-4 mg PO~~po~~ (17.5%). Side effects of the anticoagulants were absent. H~~,~~ ~~however,but~~ drug interactions with aspirin, clopidogrel, and allopurinol ~~will~~ increase~~d~~ the risk of bleeding.

Keywords: anticoagulants, coronary artery disease, fondaparinux, enoxaparin, warfarin, drug-related problems~~drp~~

***Corresponding author:** Arina D. Puspitasari, Clinical Pharmacy Department, Faculty of Pharmacy, Universitas Airlangga Hospital, Universitas Airlangga, Surabaya Tel:, E-mail: arinadery@ff.unair.ac.id
Dwi Christiananta Salean: Faculty of Pharmacy, Universitas Airlangga, Surabaya
Didik Hasmono: Clinical Pharmacy Department, Faculty of Pharmacy, Universitas, Surabaya
Rudy Hartono: Bhayangkara Hospital, Surabaya
Meity Ardiana: Bhayangkara Hospital, Surabaya

Introduction

Coronary artery disease (CAD) is an abnormality of coronary arteries that occurs when theywhich 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 (Dobesh, 2019). Blockages in blood vessels can cause various diseases dependingbased on the location of the blockages (Tubaro, 2018).

ACScute coronary syndrome, which usually consists of myocardial infarction (MI) and unstable angina (UA), is the form of coronary artery disease (CAD) causing the majority of deaths. The 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 (Dipiro, 2019).

AThe prevalence of deaths caused by cardiovascular disease according to the data from of the World Health Organization (WHO), in 2017 waswere at 31% or 17.9 million deaths worldwide in 2017 were caused by cardiovascular disease. CADoronary artery disease has caused 42.3% of deaths (7.4 million) with a prevalence of 1.5% in Indonesia according to the 2018 Basic Health Research (2018). According to the latest WHO, data in 2018, deaths due to CADcoronary artery disease in Indonesia reached 318,820 or 18.73% of the total deaths. The mortality death 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 mustrequired to be monitored (Anderson, 2013). Bleeding can increase the risk of death. An anticoagulant therapy should be done to minimize the risk of bleeding (Trailokya, 2015). Several types of anticoagulants used include vVitamin K aAntagonists, LMWH (Llow- mMolecular- wWeight- hHeparin) (LMWH), UFH (Uunfractionated hHeparin) (UFH), dDirect tThrombin iInhibitors, and fFactor Xa iInhibitors (Harter, 2015). There are many pharmacological advantages of LMWH, such as reduced monitoring, ease of use, and a lower risk of thrombocytopenia (Puymirat et al., 2013). DThe bleeding that occurred during the administration of LMWH and UFH anticoagulants, minor bleeding occurred in was 53% of the 230 hospitalized patientsations having minor bleeding, 32% had

moderate bleeding occurred in 32%, and 15% sufferedhad major bleeding, such as intracranial bleeding. Major gastrointestinal bleeding occurred inwas 52% of the 56 patients, 34% suffered intracranial bleeding, and 14% experienced bleeding in other areas with the use of factor Xa inhibitors (Milling, 2018). The use of the vitamin K aAntagonists class of anticoagulants hads a major bleeding incidence rate of 1,729 events, 338 incidences of intracranial bleeding, and 649 incidences of major gastrointestinal bleeding (Adeboyeje, 2017). With the use ofIn bivalirudin, major bleeding occurreds in 1% of patients and minor bleeding occurred in 2-4% of patients (Vivian, 2016).

Anticoagulants therapy in patients with CADcoronary artery disease must be monitored and evaluated since it may result in the risk of bleeding. Problems related to anticoagulant drugs occur due to the selection of anticoagulant types, their side effects, their dosage, and the possibility of occurrence of interactions between anticoagulants and other drugs. The aim of this study was to analyze anticoagulants used and identify potentsial 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, 1st January-31st December 2019 at Bhayangkara Hospital Surabaya. Inclusion criteria of the data included all medical records of patients with or without complications and comorbid diseases treated forwith a diagnosis of CADcoronary artery disease withand anticoagulant therapy at the Inpatient Cardiac Installation of Bhayangkara Hospital Surabaya and in conditions, with or without complications and comorbid diseases, at the Inpatient Cardiac Installation of Bhayangkara Hospital Surabaya. 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, time of administration), duration of use, route, and diagnosis, clinical data, and laboratory data. The minimum number of samples neededdata was 35 based on the Lemeshow formula.

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

Medical record data, ~~For identifying the adverse drug reactions based on medical record data~~ which usually include~~ds~~ the patient's condition on that day, were~~was~~ used for identifying adverse drug reactions. Drug interactions were identified from~~known on the~~ patient~~'s~~' therapeutic profiles and searched in the literature for potential interactions from Stockley (Stockley, 2010).

RESULTS

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

Table 1. Patient Demographics

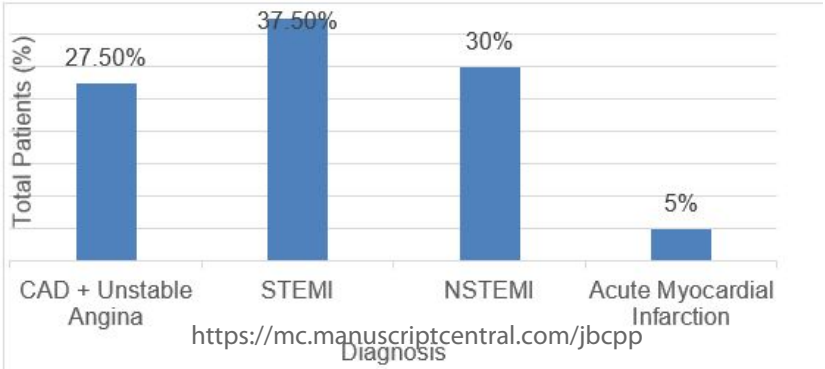
Profile	Total (%)
Gender:	
Men	32 (80%)
Women	8 (20%)
Age:	
40 – 49 years old	1 (2,5%)
50 – 59 years old	16 (40%)
60 – 69 years old	17 (42,5%)
70 – 79 years old	5 (12,5%)
≥ 80 years old	1 (2,5%)

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

Table 2 shows that~~explains~~ most of the patients with CAD were treated for 4 days (52.5%).

M~~From the most~~



~~CAD classification,~~ patients were

diagnosed with ST-elevation myocardial infarction (STEMI) (37.5%) as shown underin the CAD classification in Figure 1.

Figure 1. Distribution of CAD Patients by Diagnosis

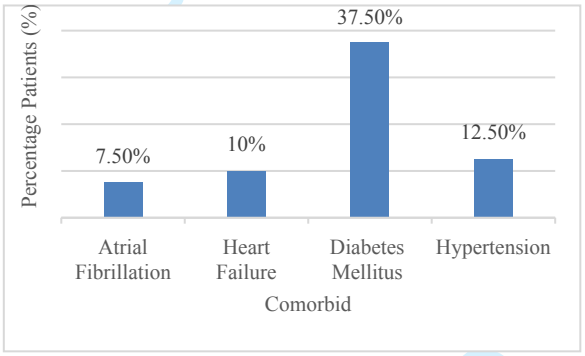


Figure 2. Distribution of Comorbidity by Diagnosis

The highest prevalence of comorbid disease that the patients had was dDiabetes mMellitus (37.5%) as showndescribed 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 the patients experienced during treatment.

Table 3. Use of Anticoagulant Therapy

Drug Classification	Type of Medicine	Dosage	Route	Total
Anticoagulant	Warfarin	1x2-4mg	po	7
	Enoxaparin	2x60mg	sc	15
	Fondaparinux	1x2,5mg	sc	18

Tabel 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 close 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 + Allupurinol	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.

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

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	1,5jt/IU	iv	4	(10%)
	Alteplase	15 mg	iv	2	(5%)
Antiplatelet	Aspirin	100 mg	po	34	(85%)
	Klopidogrel	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	0,25mg	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	3x4-12 IU	sc	4	(10%)

DISCUSSIONS

Table 1 illustrates 32 (80%) patients were male, while 8 (20%) were female ~~patients~~. Men had~~ve~~ 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~~because there is a~~ combination of ~~women's hormones~~ estrogen and progesterone present in women that may act as ~~the~~ secondary prevention of CAD.

S~~The s~~usceptibility towards~~of~~ CAD increases with~~by~~ age, especially in ~~the~~ patients aged over 45 years old, while the 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, ~~and~~ thus the heart's pumping chamber will become stiffer and work less efficiently (American Heart Association, 2015).

All patients with CAD examined in this ~~present~~ study received inpatient care for less than ~~in <~~7 days (Table 2). A total of 21 patients (52.5%) were treated for 4 days. One study within~~in~~ 119,398 samples~~patients~~ showed~~s~~ patients with CAD received a mean length of stay offor 5.5 days, with a median of 4 days. The length of care for CAD patients may depend on heart care procedures. The shorter period of treatment indicates good treatment procedures (Tickoo, 2016).

CAD Classification Based on Diagnosis

CAD~~oronary artery disease~~ is categorized into non-ST-elevation myocardial infarction (NSTEMI)~~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 2 patients with acute myocardial infarction.

P~~Based on the diagnosis of the patients with CAD, the p~~atients experienced several comorbid diseases, with the most prevalent being ~~which the highest prevalence was D~~diabetes m~~M~~ellitus

(Figure 2) with a total of 15 patients (37.5%). A study has shown that dDiabetes mMellitus was a risk factor that could worsenworsening 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 that was no longer functioning properly, increased free fatty acids, subclinical inflammation, changes in the adipokine layers and the thrombosis and fibrinolysis systems (Al-Nozha, 2016).

Therapy in Patients with CAD

Table 3 shows thatGiven the types of anticoagulants in Table 3, 7 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 Xa factor Xa byresulted from antithrombin, and doesby not increaseing the inhibition of thrombin (Bruins, 2018). Enoxaparin is an anticoagulant in the LMWH (Low Molecular Weight Heparin) 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 Xa factor Xa that enoxaparin inhibits, while heparin tends to focus on the inhibition of thrombin by antithrombin. A 2.5 mg of fondaparinux can be given to all patients once a day. The dose of fFondaparinux in doses of 2.5 mgtherapy may beis given to all patients once a day, with athe half-life of fondaparinux is 15-17 hours by the subcutaneous route (Zehnder, 2012).

This present study showsed the patients received fondaparinux within 2-3 days, enoxaparin within 2-5 days, and warfarin in 2-3 days. Several tTypes of anticoagulants, such as warfarin, require monitoring using laboratory international normalized ratio (INR) data,; whereas, the use of fondaparinux and enoxaparin anticoagulants can use partial thromboplastin timea (PTT). This study founddiscovereds that the patients with complications caused by other diseases, such as AF (atrial fibrillation) (AF) and heart failure, were given more warfarin as an effective anticoagulant to prevent ischemic stroke according to the Indonesian Heart AssociationPERKI (The Indonesian Heart Association, 2015). During the atrial fibrillation, there isare blood stasis, atrial hypercontractility, and remodeling of the atrial structures, and 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 offor this type is recommended for all patients receiving an antiplatelet therapy (Indonesian Heart Association,PERKI 2015), which does not violate religious rules and drug prices. The use of enoxaparin in patients who had undergone percutaneous coronary intervention (PCI) therapy was more effective than fondaparinux, as thrombus could be formed more easily whenas athe result of fondaparinux was used. However, the risk of bleeding whenfor using enoxaparin waiis greater than when using fondaparinux (Zhao, 2016).

Drug-related problems (DRPs)

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

Conclusions

The anticoagulants used in this study were fondaparinux 1x2.,5 mg SCsc (45%), enoxaparin 2x60 mg SCsc (37.,5%), and warfarin 1x2-4 mg POpo (17.,5%). There were no adverse effects found from using of fondaparinux, enoxaparin, and wWarfarin in this study, however,but potential drug interactions with aspirin, clopidogrel, and allopurinol were found to will increase the risk of bleeding.

REFERENCE

1. 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. Journal of Managed Care & Specialty Pharmacy 2017; 23:968–978.
2. Al-Nozha MM, Ismail HM, Al Nozha OM. Coronary artery disease and diabetes mellitus. J Taibah Univ Sci 2016;11:330–338.
3. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Chavey WE, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright R, Scott. 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.
4. Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database of Systematic Reviews 2018.
5. Dipiro Joseph T, Talbert Robert L, Yee Gary C, Matzke Gary A, Wells Barbara G, Posey L Michael. Pharmacotherapy a pathophysiologic approach 10th ed, USA : McGraw – Hill Companies; 2019: 761-826 p.

6. Dobesh Paul P. Stable ischemic heart disease. *In*: Dipiro Joseph T, Talbert Robert L, Yee Gary C, Matzke Gary A, Wells Barbara G, Posey L Michael. Pharmacotherapy A Pathophysiologic Approach 10th ed, USA : McGraw – Hill Companies 2019; 691-760 p.
7. Harter, Katherine, Levine., Michael, Henderson, Sean O. Anticoagulation drug therapy: A review. West J Emerg Med: Integrating Emergency Care with Population Health 2015; 16: 11-17.
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. The American Journal of Emergency Medicine 2018; 36: 396–402.
9. PERKI. Pedoman tatalaksana sindrom koroner akut, Indonesia: Perhimpunan Dokter Spesialis Kardiovaskular Indonesia; 2015.
10. Puymirat E, Aissaoui N, Collet Jean-Philippe, Chaib A, Bonnet Jean-Louis, Bataille V, Drouet E, Mulak G, Ferrieres J, Didier B, Tabassome S, Danchin N. Comparisson of bleeding complications and one-year survival of low molecular weight heparin versus unfractioned heparin for acute myocardial infarction in elderly patients, Int J Cardiol 2013: 166: 106-110.
11. Stockley., Baxter, K., Stockley's Drug Interactions: 9th Edition. Pharmaceutical Pr, London 2010.
12. Tickoo S, Bhardwaj A, Fonarow Gregg C, Liang Li, Bhatt Deepak L, Cannon Christopher P. Relationship between length of stay and quality of care in patients with acute coronary syndromes. Am J Cardiol 2016: 117(2): 201–205.
13. Trailokya Abhijit, Dhall Anil, Kumbla DK. Fondaparinux in acute coronary syndromes. J Assoc Physicians India 2015: 63: 83-87.
14. Tubaro M, Vranckx P, Price S, Vrints C. The ESC Textbook of Intensive and Acute Cardiovascular Care 2nd ed., Eur Heart J 2018:1-43.
15. Vivian NgG, 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. The American Journal of Cardiology 2016;117:186–191.
16. Zehnder JL. Obat yang digunakan pada gangguan koagulasi. In: B,G, Katzung (Ed). Farmakologi Dasar dan Klinik 12th ed. Indonesia: McGraw-Hill Companies Inc 2012; 675-696 p.
17. Zhao X, Yang X-X, Ji S-Z, Wang X-Z, Wang L, Gu C-H, Han Y-L. Efficacy and safety of fondaparinux versus enoxaparin in patients undergoing percutaneous coronary intervention treated with the glycoprotein IIb/IIIa inhibitor tirofiban. Military Medical Research 2016: 3(1).