Eduvest – Journal of Universal Studies
Volume 5 Number 3, March, 2025
p- ISSN 2775-3735- e-ISSN 2775-3727

IDENTIFICATION OF ADVERSE DRUG REACTION INCIDENTS IN STATIN USE IN DEPOK HOSPITAL INPATIENT

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ABSTRACT

One of the adverse drug reactions that occur in patients who receive treatment therapy is drug side effects. Statins are the first choice in cholesterol-lowering therapy. Although statins are safe and well tolerated, they have the potential for side effects. The purpose of this study is to determine the prevalence of adverse drug reactions, the incidence of adverse drug reactions that occur, and the probability score of adverse drug reactions based on the Naranjo Algorithm instrument in patients with inpatient atherosclerosis cardiovascular disease who use statin therapy at RSUI. The method used in this study is a prospective observational descriptive method with observation through patient interviews and medical record data collection as well as causality analysis using the Naranjo Algorithm. The results of this study were obtained from 116 patients who used statin therapy in the RSUI inpatient room in accordance with the inclusion and exclusion criteria. Of the 116 patients, as many as 14 patients (12.07%) experienced adverse drug reactions statins. Adverse drug reactions felt included shoulder pain (3.40%), nausea (2.60%), muscle pain (1.70%), blurred vision, difficulty sleeping, chest palpitations, joint pain, dizziness and body aches as much as 0.9% each. The total probability score of the Naranjo algorithm is a probable score of 5-8 in 7 patients (50%) and a possible score of 1-4 (50%). The conclusion of this study was that the prevalence of adverse drug reactions was 12.07%, the ADR events that occurred were shoulder pain, nausea, muscle pain, blurred vision, difficulty sleeping, chest palpitations, joint pain, dizziness and body aches. The probability score of the Naranjo algorithm is probable 5-8, meaning that the perceived adverse drug reaction can occur from the use of statins and the possible score of 1-4, which means that the perceived adverse drug reaction is not certain to occur from the use of statins.

KEYWORDS *Adverse Drug Reaction (ADR), Drug Side Effects, Statins, Naranjo Algorithm*

How to cite: Nurhikmah R. et all. (2025). Identification of Adverse Drug Reaction Incidents in Statin Use in Depok Hospital Inpatient. *Journal Eduvest*. *5*(3), 3416-3423
E-ISSN: 2775-3727

INTRODUCTION

Atherosclerotic cardiovascular disease is still the leading cause and contributes to 85% of the world's high mortality rate. In Indonesia, based on riskesdas data in 2018, the prevalence of cardiovascular diseases is around 12% of the population has high and very high LDL cholesterol levels. One of the risk factors for atherosclerotic cardiovascular disease is hypercholesterol (PERKI, 2022). To overcome this, statin therapy can be given. Statins are the main therapy of choice in overcoming the problem of imbalance of lipid levels in the body and have been proven to be effective in significantly lowering LDL cholesterol levels, triglycerides and increasing HDL cholesterol levels. Nonetheless, statins have the potential to cause drug-related problems such as side effects. Reported side effects include muscle pain, impaired liver function and an increased risk of type 2 diabetes mellitus (Arfania et al., 2023). Other studies showed results that simvastatin and atorvastatin cause myalgia of mild to moderate severity (Mahwal et al., 2022).

The use of drug therapy in patients generally has therapeutic effects and side effects. Side effects are other adverse effects of therapy that can interfere with expected clinical outcomes and adherence levels. Although the side effects are detrimental, not all patients experience them (Jutley et al., 2024). According to the WHO, drug side effects are defined as responses to unwanted drugs that occur at doses that are typically used for disease prevention, diagnosis or therapy. The high prevalence of drug side effects can increase morbidity and mortality (BPOM, 2020). The incidence of adverse drug reactions in the world from various studies is 6-20% (Shukla et al., 2021). In Indonesia, the incidence of drug side effects is around 0.9% to 99% based on the drug, duration of treatment and drug dose (Maharani & Yugatama, 2023). Drug side effects are difficult to distinguish whether they are caused by drugs or just the symptoms felt by the patient related to the disease suffered (Jutley et al., 2024). To help determine this, the naranjo algorithm can be used. The naranjo algorithm is one of the most widely used causality assessment methods and was developed to standardize the causality assessment of adverse drug reactions (Shukla et al., 2021). The naranjo algorithm can be used in monitoring drug side effects, consisting of ten questions with each point. The results of the point calculation will be categorized in four scales, namely highly probable, probable, possible and doubthful (BPOM, 2020).

RSUI is one of the hospitals in the city of Depok that serves BPJS patients who are dominated by patients with atherosclerotic cardiovascular disease so that there are many patients who use statin therapy such as simvastatin, atorvastatin and rosuvastatin. However, research on the side effects of statin drugs at RSUI has never been conducted. Based on the background description above, this study was conducted to determine the prevalence of adverse drug reactions, the incidence of adverse drug reactions that occurred and the probability score of adverse drug reactions based on the Naranjo Algorithm instrument in patients with inpatient atherosclerosis cardiovascular disease who use statins at RSUI.

RESEARCH METHOD

This study uses a prospective observational descriptive method by direct observation of patients through patient interviews and causality analysis with the Naranjo Algorithm. The population and sample of the study were patients who met

the inclusion and exclusion criteria. The inclusion criteria are inpatients who use statin therapy, adult age is 25-60 years old and the elderly are over 60 years old, male or female gender and willing to be a respondent. The exclusion criteria are patients who are not willing to be respondents. Samples are selected based on purposive sampling. The research was carried out in April – July 2024 in the inpatient ward. Subjects who are willing to become respondents will then be interviewed and observed medical record data then identified for the occurrence of adverse drug reactions and the calculation of probability scores with the help of the Naranjo Algorithm questionnaire. This research has received ethical approval from the RSUI ethics committee with permit number S-033/KETLIT/RSUI/II/2024.

RESULT AND DISCUSSION

Characteristics Responden

Based on the results of the data that has been collected, there are 116 patients who use statins in the hospital and are willing to be respondents. The results of the study can be seen in table 1 below:

Table 1. Description of Respondent Characteristics

Characteristic	Number of Respondents	Percentage (%)
Age		
Adult (25-60 years)	63	54,3
Senior (>60 years old)	53	45,7
Gender		
Man	72	62,1
Woman	44	37,9
Type of Drug		
Simvastatin	17	14,7
Atorvastatin	91	78,4
Rosuvastatin	8	6,9
Drug Dosage		
10 mg/day	6	5,2
20 mg/day	88	75,9
>20 mg/hari	22	19,0
Duration of Treatment		
<4 weeks	51	44,0
4-6 weeks	32	27,6
7-12 weeks	8	6,9
>12 weeks	25	21,6
Total	116	100

In table 1, the description of the characteristics of the respondents can be seen that in the age category that has the most or dominates in the use of statins is the adult age, namely 25-60 years old, as many as 63 respondents (54.3%). This is relevant to previous research that the majority of coronary heart disease patients who use statins in the age range of 41-60 years are 55.55%. The adult age group is

the highest risk group for cardiovascular disease because as we age, the function of the body's organs decreases (Pradina et al., 2023).

In the gender category, there are more male patients than women where 77 male patients (62.1%) while female patients are 44 (37.9%). Based on the literature in the atherosclerotic cardiovascular guidelines, gender is one of the risk factors in the clinical assessment of atherosclerotic cardiovascular disease where in the male sex they experience the disease faster than women because women have premenopausal hormones that can slow down the occurrence of atherosclerotic disease (PERKI, 2022). This is relevant to the previous study where male respondents were nominated 68.8% more than women 31.11%. Men are more likely to experience increased cholesterol because they do not have the hormone estrogen that functions as a protector of the heart (Pradina et al., 2023).

In the category of the type of drug most used by respondents, atorvastatin was 91 respondents (78.4%), simvastatin was 17 respondents (14.7%) and rosuvastatin was 8 respondents (6.9%). Meanwhile, in the drug dose category, the most widely used by respondents was the dose of 20 mg per day for 88 respondents (75.9%). The choice of statin therapy is adjusted to the patient's condition where statins with moderate intensity such as atorvastatin 20 mg have the ability to reduce LDL cholesterol values by 30% to below 50% and are most commonly chosen compared to rosuvastatin. Rosuvastatin 20 mg as a high-intensity statin may be given to patients with conditions that have been proven to have coronary heart disease. This is related to the response to side effects that occur because the higher the dose of statins received, the greater the potential for the patient to experience side effects (Perkeni, 2021).

In the treatment duration category, the most treatment duration was in respondents who used statins for less than 4 weeks as many as 51 respondents (44.0%). This is because the patient only received statin therapy while in the hospital. Previously, patients only took other drugs such as antihypertensive or oral antidiabetics but had not checked cholesterol levels or needed statin therapy. Based on the literature, the duration of statin use for 4-12 weeks can routinely show the results of therapy effectiveness and the occurrence of side effects. However, not everyone experiences side effects in this time span because statins are well tolerated (Perkeni, 2021).

Prevalensi Adverse Drug Reaction Statin

Based on Figure 1, the prevalence of adverse drug reactions to statin use was obtained, out of 116 respondents, only 14 respondents felt adverse drug reactions from statins with a prevalence value of 12.07%. The results of this study are not much different from previous studies where adverse drug reactions occurred in patients taking statins by 7.46% (Tsui et al., 2023).

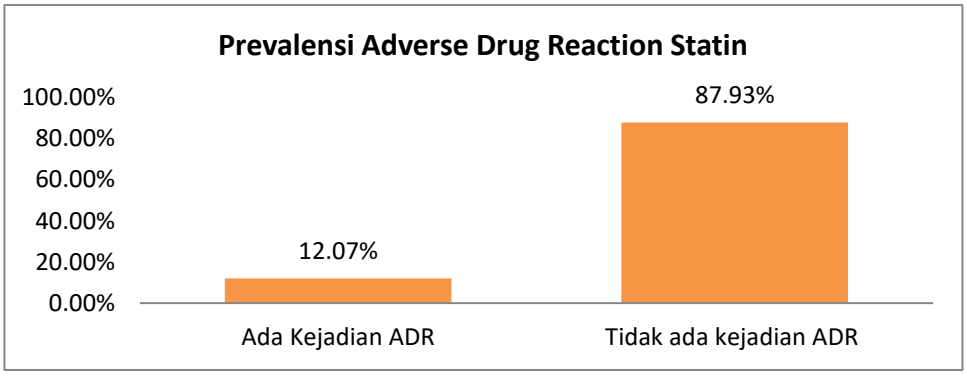

Figure 1. Diagram Prevalensi Adverse Drug Reaction Statin

From these results, it can be concluded that almost all respondents are suitable for the use of statins as a therapy for atherosclerotic cardiovascular disease. The types of statins that cause adverse drug reactions in 14 respondents can be seen in table 2 below.

Table 2. Types of Statins That Cause Adverse Drug Reactions

Drug Name	Drug Dosage	Number of respondents	Percentage
Atorvastatin	20 mg	9	64,29%
Atorvastatin	40 mg	2	14,29%
Rosuvastatin	20 mg	2	14,29%
Atorvastatin	80 mg	1	7,14%
Total		14	100,00%

Based on table 2, it shows that the types of statins that cause adverse drug reactions in this study are 64.29% of atorvastatin 20 mg, 14.29% of atorvastatin 40 mg, 7.14% of atorvastatin 80 mg and 14.29% of rosuvastatin 20 mg. This is relevant to previous research on hypercholesterolemia patients as many as 19 respondents (41.30%) who used atorvastatin at a dose of 20-40 mg/day experienced myalgia (Mahwal et al., 2022). Other studies show that adverse drug reactions related to muscle symptoms such as muscle pain are most common in the use of atorvastatin at 1.67%, followed by simvastatin at 1.03% and rosuvastatin at 0.92% (Tsui et al., 2023). Choosing the wrong dose can increase the risk of side effects. Higher doses are not recommended on initial statin therapy because they increase the risk of muscle disorders. This is excluded if the patient has been taking statins at that dose for more than 12 consecutive months without any symptoms or muscle disorders (Perkeni, 2021). In addition to the type of drug and the dosage of the drug, the duration of treatment also affects the occurrence of side effects. In previous studies, respondents who took statins long-term for more than 12 months experienced symptoms of muscle pain and stopped treatment after experiencing symptoms (Howard et al., 2021).

Event Adverse Drug Reaction Statin

In this study, the adverse drug reaction statins that occurred in 14 respondents can be seen in the following graphic image:

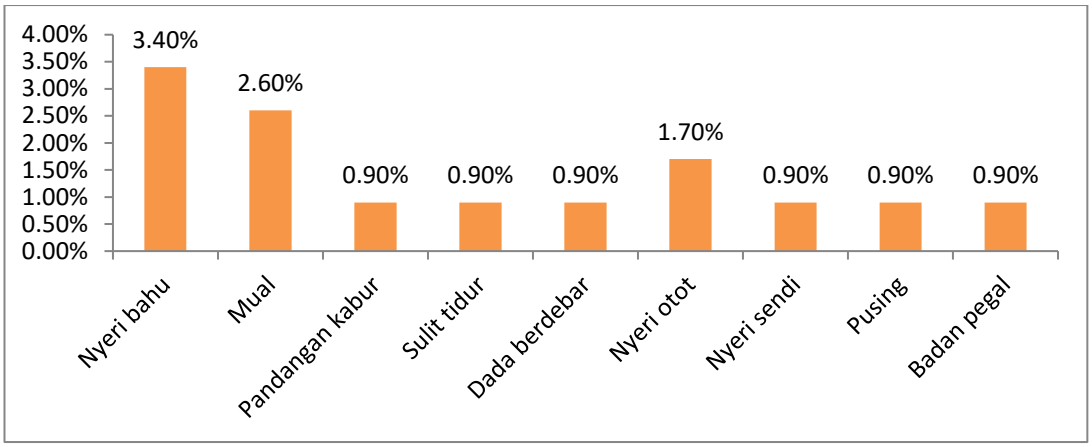

Figure 2. Event Adverse Drug Reaction Statin

A total of 3.40% of respondents experienced shoulder pain, followed by 2.60% of respondents experienced nausea, then 1.70% of respondents experienced muscle pain. Other adverse drug reactions felt by respondents were blurred vision 0.90%, difficulty sleeping 0.90%, chest palpitations 0.90%, joint pain 0.90%, dizziness 0.90% and body aches 0.90%. This is different from previous studies that reported ADR that occurred in statin use, namely gastrointestinal disorders 3.94%, followed by symptoms of liver disease 1.28%, muscle pain 1.17%, symptoms of neurological diseases 0.65%, symptoms of skin 0.21%, symptoms of cardiovascular disease 0.14% and others 0.01% (Tsui et al., 2023). Based on the literature, the use of statins has the potential to cause adverse drug reactions related to muscle disorders such as muscle pain, myopathy, and myalgia (PERKI, 2022). The mechanism of adverse drug reaction in the use of statins is related to the mechanism of action of statins, namely as inhibitors of the HMG-CoA enzyme. The HMG-CoA reductase enzyme not only inhibits the formation of cholesterol in the liver but also affects the production of ubiquinone or coenzyme Q10. Coenzyme Q10 plays an important role in the mitochondrial respiration process that produces energy for muscles. If there is a decrease in ubiquinone levels, it can cause muscle disorders (Hariadini, 2020). From the results of this study, it can be concluded that adverse drug reactions that occur in the use of statins are not only muscle disorders but also gastrointestinal disorders.

Skor Probabilitas Adverse Drug Reaction Statin

Based on the data of table 3, it was obtained that the probability score of adverse drug reaction in the use of statins by inpatients at RSUI was a probable score of 50% and a possible score of 50%. When compared to previous studies, the causal assessment of the occurrence of muscle disorders, namely myalgia, in patients who use statins, has a probable score of 16% and a possible score of 84% (Indumathi et al., 2017). The naranjo algorithm is used to help standardize causality assessments for all drug side effects because most adverse drug reactions are not

specific to a particular drug, so causality assessments are important (Shukla et al., 2021). Probability scores can help in determining whether drug side effects are really caused by drugs or due to other factors (BPOM, 2020).

Table 3. Statin Adverse Drug Reaction Probability Score

Naranjo Scale (score)	Respond	Percentage
Highly probable (skor 9 +)	0	0%
Probable (skor 5-8)	7	50%
Possible (skor 1-4)	7	50%
Doubthful (0 -)	0	0%
Total	14	100%

Description: Highly probable: very certain; Probable: can occur; Possible: not yet certain, Doubthful: doubtful

CONCLUSION

The prevalence of adverse drug reaction events in hospitalizations was 12.07%, with the incidence of adverse drug reactions felt after using statins including shoulder pain, nausea, muscle pain, blurred vision, difficulty sleeping, chest palpitations, joint pain, dizziness and body aches. The probability score of adverse drug reaction statin with the causality analysis of the naranjo algorithm in inpatients who use statins obtained probable scores of 7 respondents (50%) and possible scores of 7 respondents (50%). Based on the results of the study, it can be said that statins are safe to use as a therapy for atherosclerotic cardiovascular disease when viewed from the prevalence of adverse drug reactions that occurred in 14 respondents who experienced adverse drug reactions from a total of 116 respondents.

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