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# Safety assessment of statin-drug interaction effects in cardiology outpatient in Teaching Hospital at Surabaya

## *(Penilaian keamanan efek interaksi obat statin pada pasien kardiovaskular rawat jalan RS Pendidikan di Surabaya)*

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## ABSTRACT

**Background:** HMG-CoA inhibitors, more commonly known as statins, are lipid-lowering agents that have benefits in cardiovascular therapy. Statins are associated with two significant side effects that are asymptomatic elevations of liver enzymes and myopathy. Myopathy is the most likely to occur when statins are prescribed with other drugs. **Objectives:** To evaluate the effect of drug interactions between statins and concomitant drugs in outpatient cardiovascular patients. **Methods:** This study conducted in a prospective cohort. Drug interactions was checked by using lexicomp drug interactions software and patient's complaints were taken through interviews. **Results:** There were 69 patients included in this study as sample. A total of 16 patients received atorvastatin, and 53 patients received simvastatin. More than half of sample (59%) showed statin-drug interactions. The most drug interactions were severe (41%), followed by moderate (22%) and mild (10%). The most interacting drugs were amlodipine and diltiazem. Based on the results of interview, there were no complaint of myopathy felt by patient. **Conclusion:** The effects of drug interactions still need to be considered even though the patients did not complain myopathy. Several factors can determine the impact of drug interactions that is not experienced by the patients.



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## ABSTRAK

Latar belakang: Inhibitor HMG-CoA, lebih dikenal sebagai statin, adalah agen penurun lipid yang memiliki manfaat dalam terapi kardiovaskular. Statin dikaitkan dengan dua efek samping yang signifikan yaitu peningkatan enzim hati tanpa gejala dan miopati. Miopati adalah yang paling mungkin terjadi ketika statin diresepkan dengan obat lain. Tujuan: Untuk mengevaluasi efek interaksi obat antara statin dan obat penyerta pada pasien kardiovaskular rawat jalan. Metode: Penelitian ini dilakukan dalam kohort prospektif. Pengecekan interaksi obat dilakukan melalui software Lexicomp Drug Interactions dan keluhan pasien diwawancarai secara menyeluruh. Hasil: Ada 69 pasien yang termasuk dalam sampel penelitian. Sebanyak 16 pasien mendapat atorvastatin, dan 53 pasien mendapat simvastatin. Lebih dari setengah sampel (59%) memiliki interaksi obat statin. Interaksi obat yang paling banyak adalah yang parah (41%), diikuti sedang (22%) dan ringan (10%). Obat yang paling berinteraksi adalah amlodipine dan diltiazem. Berdasarkan hasil wawancara, tidak ada keluhan miopati yang dirasakan pasien. Kesimpulan: Efek interaksi obat masih perlu diperhatikan meskipun pasien tidak mengeluh miopati. Beberapa faktor dapat menentukan dampak interaksi obat yang tidak dialami oleh pasien.


Kata kunci: DDIs; interaksi obat; HMG-CoA reduktase; miopati; rhabdomiolisis.

## INTRODUCTION

Drug interactions are one of the most common drug-related problems in patients with polypharmacy. Some drug interactions can provide benefits but can also be detrimental to the patient. In some cases, drug interactions can be prevented, or adverse drug reactions can be minimized with the pharmacist's role (Khandeparkar, 2017). *Comorbidity* is a condition that often causes patients to experience disability, poor quality of life, and polypharmacy that can increase the risk of drug interactions. Drug interactions often go unnoticed during patient care, while interactions can have good or bad effects on patients. Therefore, pharmacists play a role in identifying, minimizing, and preventing the effects of unwanted drug interactions so that patients receive effective and safe drug therapy (Faizah, 2021). Drug interactions in the statin group can increase level of statin which increase the risk of rhabdomyolysis (Baxter, 2019).

Statins (HMG-CoA reductase) are lipid-lowering drugs that effectively lower LDL levels, thereby significantly reducing the incidence and mortality from CHD. Statins can also increase HDL cholesterol (5-15%) and lower TG (7-30%) (NCEP, 2002). Statins inhibit the action of the enzyme HMG-CoA reductase, which plays a role in the formation of cholesterol. These statin drugs include lovastatin, pravastatin, fluvastatin, pitavastatin, rosuvastatin, atorvastatin, and simvastatin. In addition to their effectiveness in lowering lipid levels, statins also have unwanted side effects related to muscle. Statins have long been associated with myotoxicity events such as myalgia, myopathy, myositis, and rhabdomyolysis (Hirota, 2015). The incidence of rhabdomyolysis is rare but has severe and life-threatening effects on the patient. This is due to the breakdown of skeletal muscle, causing the release of intracellular toxins into the blood circulation and causing acute renal failure. Approximately 60% of rhabdomyolysis associated with statins is reported to be due to drug interactions (Dybro, 2016).

Studies on the prevalence of statin drug interactions in Indonesia is still limited. Therefore, this study aims to analyze the interaction of statin drugs in a teaching hospital at Surabaya, Indonesia, and investigate the incidence of myotoxicity associated with statin drug interactions.

## METHODOLOGY

### Study design

The data were prospectively retrieved from prescriptions of patients receiving statins with other drugs. Prescriptions included in this study were prescriptions for outpatients at the Cardiology Clinic for three months. Statin-drug interactions were screened for Lexicomp Drug Interactions and Stockley's Drug Interactions. The classification analyzed in this study was taken based on Lexicomp Drug Interactions, including no action needed (B), monitor therapy (C), consider modification therapy (D), and avoid combination (X). Furthermore, we identified the occurrence of myopathy or rhabdomyolysis associated with statin-drug interactions through patient interviews.

### Ethical approval

The study was approved by the Hospital Ethics Committee (RI-260).

## RESULTS AND DISCUSSION

There were 69 patients involved in this study, and 59% of patients identified potential statin interactions. Demographic data are shown in Table 1, and there are more male patients than female patients. The age of the patients was dominated in the group of 46-65 years. Most of the patients were prescribed simvastatin 20 mg/day (43 patients). More than half of the patients had comorbidities such as HHD, CHD, and hypertension. The drugs most frequently used on prescription were amlodipine (42%) and diltiazem (38%).

Table 1. Demographic data of patients

| | | N | % |
|---|---|---|---|
| Gender | Man | 40 | 57 |
| | Woman | 29 | 43 |
| Age | 26-35 y.o | 3 | 4 |
| | 36-45 y.o | 13 | 19 |
| | 46-65 y.o | 43 | 63 |
| | >65 y.o | 10 | 14 |
| Comorbid | HHD | 21 | 31 |
| | CHD | 13 | 19 |
| | Hypertension | 10 | 14 |
| | Without comorbid | 25 | 36 |
| The highest medicine prescribed | Amlodipine | 29 | 42 |
| | Diltiazem | 26 | 38 |

From this study, there are 50 potential statin-drug interactions based on the *Lexicomp Drug Interaction Software*. Each drug prescription has a different number of statin-drug interactions, as shown in Table 2. Based on previous studies, the greater the number of drugs on the prescription, The increasing number of potential drug interactions. There is a significant relationship between polypharmacy and the number of potential drug interactions (Bojuwoye, 2022).

Table 2. Number of potential statin-drug interaction

| **Number of statin-interaction in every prescription** | **N** | **%** |
|---|---|---|
| None | 19 | 28 |
| 1 | 24 | 35 |
| 2 | 3 | 5 |
| 3 | 1 | 1 |

Most of the simvastatin drug interactions included in the interaction with level D are calcium channel blockers (amlodipine and diltiazem). The result is the same as Yan's research, which showed that 65.2% of patients identified a potential interaction of statins with calcium channel blockers (Yan, 2018). Meanwhile, the atorvastatin interaction was dominated by group B and followed by group C, as shown at Table 3 and Table 4. The entire mechanism of statin interaction was pharmacokinetic. The mechanism of interaction of simvastatin with CCB is inhibition of CYP3A4, an enzyme in simvastatin metabolism, thereby increasing the concentration of simvastatin in serum (Neuvonen, 2006). FDA is recommended that if simvastatin and amlodipine are used together, the dose of simvastatin is not more than 20 mg per day. In addition, laboratory and symptoms monitoring of rhabdomyolysis are required, such as creatinine kinase and muscle pain (Tomaszewski, 2011; Siriangkhawut, 2017).

The interaction of simvastatin with diltiazem is the same as that of amlodipine, and based on the Lexicomp drug interaction; it can be considered to replace it with another drug. Atorvastatin is a statin that is less sensitive to CYP3A4 inhibition than simvastatin. Switching to statins that do not have strong cytochrome P450 interactions (such as pravastatin) may be more appropriate when combined with drugs that inhibit CYP3A4 (Mitchell, 2015). However, if used together, the dose of simvastatin should be limited to 10 mg per day and diltiazem limited to 240 mg per day, as shown in Table 5. When we use a combination of these two drugs, we need to be considered because it can increase the risk of simvastatin toxicity such as myopathy or rhabdomyolysis.

Table 3. Potential statin-drug interaction

| | | **Classification of drug interaction** | **N** |
|---|---|---|---|
| Simvastatin | Clopidogrel | B | 6 |
| | Diltiazem | D | 10 |
| | Amlodipine | D | 15 |
| | Ticagrelor | D | 3 |
| Atorvastatin | Clopidogrel | B | 9 |
| | Ticagrelor | C | 3 |
| | Spironolactone | C | 3 |
| | Diltiazem | C | 1 |

*B=no action needed, C=monitor therapy, D=consider modification therapy

The physicochemical properties of statins may also affect the myotoxic effect. Lipophilic statins such as atorvastatin, lovastatin, fluvastatin, pitavastatin, and simvastatin can diffuse nonselectively into extrahepatic tissues such as skeletal muscle (Ward, 2019). On the other hand, hydrophilic statins such as pravastatin and rosuvastatin have less penetration into the muscle and, therefore, a lower risk of developing muscle-related problems (Mueller, 2021).

Table 4. Classification of potential statin-drug interaction

| **Classification of drug interaction** | **N** | **%** |
|---|---|---|
| No action needed (B) | 15 | 31 |
| Monitor therapy (C) | 7 | 14 |
| Consider therapy modification (D) | 27 | 55 |
| Total | 49 | 100 |

Based on the interviews with patients, we did not find that the patient had signs and symptoms of myotoxicity. Therefore, we report that no rhabdomyolysis was associated with statin interactions in our study. This contrasts the results of studies from China experienced an adverse drug reaction of statins were 7.460% including gastrointestinal symptoms, liver disease, muscle and neurological symptoms (Tsui, 2022). It suggests that myotoxicity such as rhabdomyolysis is more common in elderly patients taking high-dose statins (Xiaou, 2020).

Although this study did not show the presence of rhabdomyolysis associated with statin drug interactions, the role of pharmacists in minimizing the undesirable effects of statin interactions is still needed. First, pharmacists are active in identifying drug interactions, especially in patients, who can experience it, namely the elderly and patients with decreased kidney function, and discuss with their doctor. Second, pharmacists provide drug replacement recommendations according to professional

decisions, which can reduce or prevent the effects of unwanted drug interactions. Third, the patient's condition is closely monitored when a 40 mg or higher statin dose is administered.

Table 5. Serious potential statin-drug interaction

| Drugs | Mechanism of drug interaction | Effect of drug interaction |
|---|---|---|
| Simvastatin-Amlodipine | Pharmacokinetic | Risk of rhabdomyolisis. Limit statin dose to no more than 20 mg/day |
| Simvastatin-Diltiazem | Pharmacokinetic | Increase level of statin. Limit dose for statin no more than 20 mg/day and diltiazem no more than 240 mg/day |

Since our research is observational studies, it has several limitations like the others. First, this research method has no control. Several variables outside of therapy still exist and can affect the results of the study. Second, we did not check creatinine kinase levels, which are laboratory data on myotoxicity. Another limitation of this study relates to insufficient data on herbal medicines taken by patients that may interact with statins.

## CONCLUSION

The effects of drug interaction still need to be considered even though the patients did not complain of myopathy in this study. Several factors can determine the impact of drug interactions not experienced by the patient.

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