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STATINS DRUG USE AND DRUG-DRUG INTERACTIONS

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INTISARI

Dislipidemia merupakan penyebab paling umum penyakit aterosklerosis. Terapi utama pada dislipidemia adalah obat golongan statin yang diresepkan secara luas pada pasien di Indonesia. Penelitian ini bertujuan memberikan gambaran penggunaan statin dan interaksinya dengan obat-obat lain yang diberikan bersamaan. Penelitian ini deskriptif evaluatif, menggunakan teknik pengambilan sampel secara *purposive sampling* dan data diambil secara retrospektif. Kriteria inklusi meliputi semua pasien rawat jalan yang mendapatkan terapi obat golongan statin pada bulan April 2017 di Instalasi Rawat Jalan RSUD Tugurejo Semarang. Ada 334 pasien yang memenuhi kriteria inklusi, terbanyak perempuan (63,28%). Rentang usia pasien terbanyak adalah 60-69 tahun sebanyak 129 pasien (38,62%). Seratus tiga puluh satu pasien (39,22%) terdiagnosis dislipidemia tunggal. Kisaran dosis simvastatin dan rosuvastatin adalah 10 sampai 20 mg sekali sehari, sedangkan rosuvastatin diberikan 10 mg sekali sehari. Penggunaan terbanyak adalah 10 mg simvastatin per hari, diresepkan untuk 231 pasien (69,16%). Ada 177 pasien (52,99%) yang memiliki potensi interaksi statin dengan obat lain. Potensi interaksi terbanyak adalah interaksi simvastatin-amlodipin yang terjadi pada 104 pasien (31,14%). Hasil penelitian menunjukkan bahwa pengguna statin terbanyak adalah pasien usia lanjut. Statin digunakan tidak hanya pada pasien dislipidemia. Ada banyak potensi interaksi statin dengan obat lain, tetapi dosis statin yang diresepkan cukup rendah dan tidak melebihi dosis standar.

Kata kunci: dislipidemia, statin, interaksi obat

ABSTRACT

Dyslipidemia is the commonest cause of many atherosclerotic diseases. Statins are the mainstay of the management of dyslipidemia, and it is widely prescribed for patients in Indonesia. This study aims to give an overview, the use of statin, and its drug-drug interactions. The study method was descriptive, using a purposive sampling technic. The inclusion criteria were patients who received statins therapy, in the outpatient installation of Tugurejo Regional Public Hospital, Semarang, during April 2017. There were 334 patients meet the inclusion criteria, most of them were women (63,28%). The highest patients' range was 60-69 years old of 129 patients (38,62%). One hundred and thirty-one patients (39,22%) were diagnosed with dyslipidemia only. The dosage range of simvastatin and rosuvastatin was 10 to 20 mg once daily, but rosuvastatin was only given 10 mg once daily. The most dose was 10 mg simvastatin per day, prescribed for 231 patients (69,16%). There were 177 patients (52,99%) who has the potentiate of statin drug interactions. The most were simvastatin-amlodipine interactions, occurs in 104 patients (31,14%). This study shows that most statin users are elderly patients. Statin is used not only in dyslipidemia patients. There are many potential statin drug-drug interactions, but the statin dose is low and not over the standard doses.

Keyword: *dyslipidemia, statins, drug interactions*

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INTRODUCTION

According to the 2013 Basic Health Research Data (Riskesdas), coronary heart disease is the 7th ranked throughout Indonesia. Dyslipidemia is a major risk factor for cardiovascular events (Armitage et al., 2010). Household Health Survey Data (SKRT) in 2004 states that the prevalence of dyslipidemia in Indonesia reaches 14%. Although various drugs can be plasma cholesterol reducer, the best evidence in preventing cardiovascular morbidity and mortality comes from statins (Redondo et al., 2013).

Statins as the mainstay in the management of dyslipidemia, are widely prescribed in Indonesia, based on their potential to prevent adverse cardiovascular events. Hypolipidemic effect of statins happened by inhibiting hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase (Uransilp et al., 2018) and decreases LDL-C (Low-Density Lipoprotein Cholesterol) concentration due to the upregulation of LDL receptor activity (Nickenig, 2004). Early studies using statins to lower LDL cholesterol have shown reduced CHD (Coronary Heart Disease) rates and total mortality as well as reduced myocardial infarction, stroke, and peripheral vascular disease. Statins should be prescribed up to the maximum recommended dose or that can be tolerated to reach the target of LDL cholesterol (PERKAI, 2013).

Although statins were widely used to lower cholesterol and reduce cardiovascular morbidity and mortality, nonadherence to statin therapy remains an ongoing problem, because of the statin-associated muscle symptoms (i.e myopathy) and a range of other statin-induced side effects that also exist (Ward et al., 2019). Elderly patients usually have to take several different types of medications at the same time, because of the degenerative illness among them. Drug-drug interactions (DDI) is one of the most important components in safety therapy, including statins. In this article, we reviewed the use of statins, and focus on its drug-drug interactions, cause the majority of statins users were older people (Mortensen and Falk, 2018).

MATERIALS AND METHODS

The present study was carried out in Tugurejo Regional Public Hospital, Semarang. The method was descriptive, using a purposive sampling technic. The inclusion criteria were all patients who received statins therapy, during April 2017, in the outpatient installation of Tugurejo Regional Public Hospital, Semarang, and the data in its medical record could be accessed.

This was a retrospective study focusing on patients receiving statins treatment and meet the inclusion criteria. Different types of statins including atorvastatin, simvastatin, and rosuvastatin prescription were analyzed by diagnosed, doses, and DDI (Drug-Drug Interactions). We analyzed the statins DDI using “Medscape Drug Interaction Checker” online (accessed in March 2017).

RESULTS AND DISCUSSION

In April 2017, there were 334 patients who received statins for their therapy. The characteristics of the patients according to age and gender were shown in Table I. Most of the patients who recieved statins therapy were women, 212 patients, 63,28%. The gender distribution of the patients who received statins was shown in Figure 1.

Table I. Characteristic of the patients

Age	Gender		Percentage	
	Men	women	Men	Women
10 -19	1	0	0,3 %	0%
20 – 29	0	0	0%	0%
30 – 39	2	2	0,6 %	0,6 %
40 – 49	16	39	4,78 %	11,64 %
50 – 59	**37**	**82**	**11,04 %**	**24,48 %**
60 – 69	52	77	15,52 %	22,98 %
70 – 79	13	12	3,88 %	3,58 %
80 – 89	1	0	0,3 %	0%
Total	122	212	36,42 %	63, 28 %

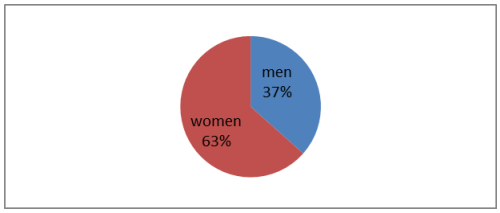

Fig 1. Gender distribution of the patients

It corresponds with the research conducted by Kamso et al., 2002, which was based on research conducted on 656 respondents in 4 major cities in Indonesia (Jakarta, Bandung, Yogyakarta, and Padang), which the prevalence of dyslipidemia in women was greater than in men. Dyslipidemia occurrence in women increased at the onset of menopause. The median age at menopause among women ranges between 50 and 52 years (Gold, 2012). In this study, 171 women patients (51,20%) were in this menopause category. The loss of female sex hormones plays a role in the increase in cardiovascular morbidity and mortality in postmenopausal women (Trapani and Pallottini, et al., 2011)

Almost half (49,40%) of the patients are elderly (above 60 years old). The range of age distribution of the patients was shown in Fig 2.

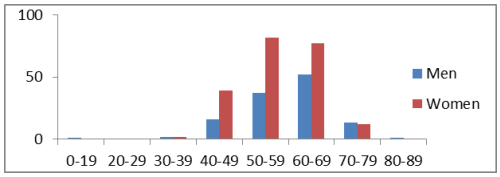

Fig 2. Range of age distribution of the patients

The prevalence of atherosclerosis increased with age and the number of cardiovascular events was higher in elderly patients due to due to the physiological changes induced by age, many comorbidities, and drug treatments (Mortensen and Falk, 2018). The youngest patient, 17 years old, was diagnosed with syndrome nephrotic. There was another one patient with syndrome nephrotic, 52 years old. The complication of nephrotic syndrome is dysregulated lipid metabolism and induce dyslipidemia, so the nephrotic syndrome' patients need statins. (Kwieterovich, 1999 and Aggrawal et al., 2018)

Only 3 types of statins were used for the patients. Most of all was simvastatin (n = 296 patients (88,62%), followed by atorvastatin (n= 34 patients 10,18 %), and the least was rosuvastatin which was only prescribed for 4 patients (1,2%) The type of statins used for the patients were shown by Fig 3.

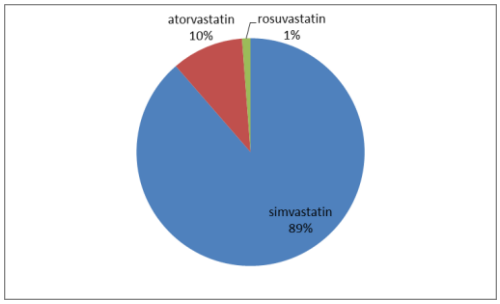

Fig 3. Type of statins used for the patients

The patients were BPJS participants which the prescribed recipe was based on Indonesian National Formularium (NF). It is restricted on NF, that clinician could prescribe atorvastatin and rosuvastatin, only after 3 months used of simvastatin and it could not able to reduce LDL < 100 mg/dL combine with a strict lipid diet. The maximal use of atorvastatin and rosuvastatin was only 3 months, if after 3 months didn't hit the target, the simvastatin must be used again.

The most diagnose for the patients who use statins were dyslipidemia as a single diagnosed (n=131 patients, 39,22%) followed by triple diagnosed: dyslipidemia+diabetes mellitus+ hypertension (n= 42 patients, 12,57%) , dyslipidemia with hypertension (n= 33 patients, 9,88%) and dyslipidemia with diabetes (n= 19 patients, 5,69%). The diagnose of the patients who used statins were shown in Fig 4.

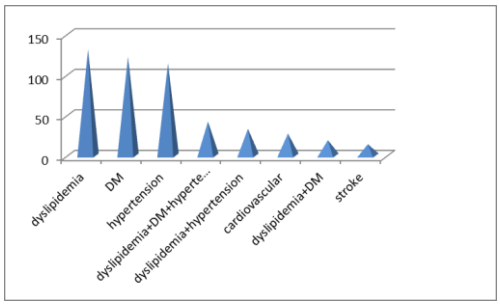

Fig 4. Diagnoses of the patients who used statins

One hundred and twenty-two patients (36,53%) were diagnosed DM, alone or with other diseases such as dyslipidemia, hypertension, stroke, and others. There was no evidence that the prevalence of hypercholesterolemia increased in DM patients, but mortality from coronary heart disease increased as a function of serum cholesterol levels, and lowering of cholesterol with statins reduces diabetic patients' relative cardiovascular risk (Mooradian and Arshag, 2009). In 2012, statins as a cholesterol-lowering drugs received a US Food and Drug Administration warning, regarding an increased risk of incident diabetes (Rajpathak et al., 2009). Atorvastatin and simvastatin are relatively lipophilic compounds while rosuvastatin is relatively hydrophilic. Lipophilic statins might be more diabetogenic as they can more readily penetrate extrahepatic cell membranes such as beta cells, adipocytes, and skeletal muscles (Aiman et al., 2014). In this research, it was not clear whether the patients had been on statins for a long time and had any consequences to become a diabetic patient.

The third-ranked diagnosing was hypertension: 114 patients (34,13%). Some clinical evidence showed that statins, apart from lowering cholesterol levels, also have an antihypertensive effect (Morgado et al., 2006). Statins had other mechanisms such as effects on the renin-

angiotensin system or endothelial vasoreactivity so it could decrease the blood pressure (Milionis et al., 2011 and Golomb et al., 2008). May be due to some physiologic effects of statins, including improved endothelial function, increased nitric oxide (NO) bioavailability, antioxidant properties, stabilization of atherosclerotic plaques, and anti-inflammatory effects (King et al., 2007)

Fourteen patients were diagnosed with post stroke non haemorrhagic. The use of statins in patients at Bethesda Hospital Yogyakarta with recurrent ischemic stroke can provide good functional outcomes (Alexxander et al., 2016). Statins showed efficacy in reducing the incidence of fatal stroke and hemorrhagic stroke (Wang and Zhang, 2014) and clinicians also prescribed statins for stroke prevention (Guerra et al., 2019).

Of all the patients who received statin during the study period, the majority received treatment of simvastatin 10 mg once a day (n = 231 patients (69,16%), followed by simvastatin 20 mg (n=65, 19,46%). The other drugs atorvastatin 20 mg (n= 18, 5,39 %), atorvastatin 10 mg (n= 16, 4,79 %) and least of all, rosuvastatin 10 mg once a day, which was only prescribed for 4 patients (1,2%). The doses of all statins prescribed for the patients were shown in Fig 5.

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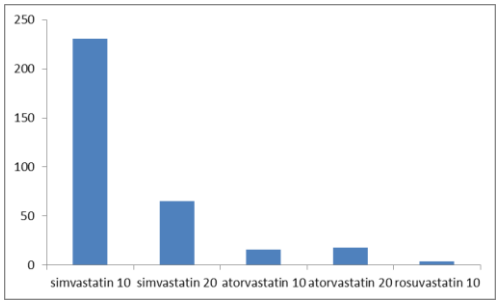

Fig 5. Doses of statins prescribed for the patients

According to ACC=American College of Cardiology; AHA=American Heart Association, 2003: the statin therapy doses were at low and moderate intensity, none of the therapy in this study include very high intensity. High-intensity statins have demonstrated consistent benefits for secondary prevention of adverse cardiovascular events compared with moderate-intensity statins in several randomized trials (Stone et al., 2013) ,

The elderly commonly received a lot of medication together. Concerned of possible drug interactions is important because comorbidity is common in the elderly as statin users (Mortensen and Falk, 2017). This present study showed the number of drugs per recipe sheet that the patients received was variated from 2 to 10 kinds of drugs, and the average was 4,94 drugs per recipe sheet. Interactions may increase the risk of serious adverse reactions (such as myopathy or rhabdomyolysis) or, in some cases, but very rare, the effect of the interaction could reduce the effectiveness of statins treatment. So, statin DDIs are often unavoidable and should be clinically managed. There were 177 patients (52,99 %) who have the potential of statin DDIs. The type of statins drug drug interactios were shown in Figure 6.

The change of the pharmacokinetic parameters (AUC, Cmax, and Tmax) of simvastatin as HMG-CoA reductase inhibits its activity. The most were simvastatin-amlodipine interactions, occurred in 104 patients (31,14%). Coadministered with amlodipine 10 mg increased almost half (46%) simvastatin bioavailability and decreased the simvastatin clearance by 13%. To minimize the interaction with amlodipine 10 mg, the optimal simvastatin dose should be 60% of the usual dose. Simvastatin 24 mg was an optimal dose in coadministration with amlodipine 10 mg (Son et al., 2013). In this study, the maximum simvastatin's doses were 20 mg, so it still a safe use of statins.

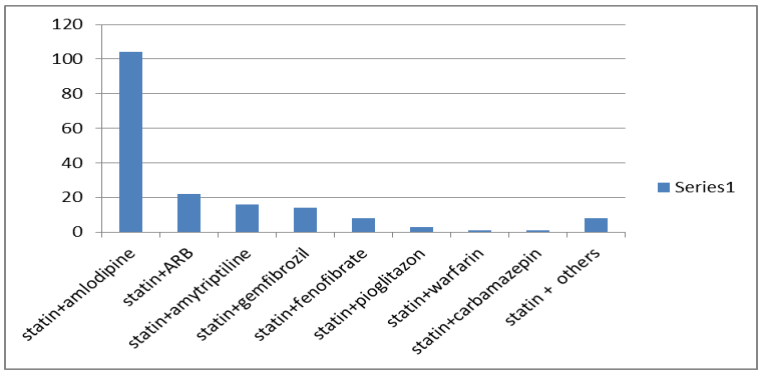

Fig 6. Statin drug-drug interactions

Concomitant use of certain drugs (fibrates, erythromycin, itraconazole) can increase blood levels of statins and, consequently, the risk for myopathy (Bellosta et al., 2004). The 2013 American College of Cardiology/American Heart Association "Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults" states that combination therapy with any statin and gemfibrozil should be avoided (Stone et al., 2013). This recommendation is because of concerns for the increased risk for muscle-related toxicity (Botorf, 2006). The use of rosuvastatin in combination with gemfibrozil is included in FDA-approved product labeling, but it is recommended that the daily dose of rosuvastatin be limited to 10 mg daily (Wiggins et al., 2016). In this research, none of the patients got erythromycin nor itraconazole, only 22 patients got fibrates. Furthermore, gemfibrozil increases systemic exposure to simvastatin, atorvastatin, and rosuvastatin so it could raise the risk of myopathy. The maximum daily dose of simvastatin is 10 mg daily when used with fibrates (except fenofibrate). For rosuvastatin, start with 5 mg and do not exceed 20 mg during use with fibrates (Gov.UK, 2008). In this research, rosuvastatin were prescribed 10 mg once a day. The risk of myopathy is dose-related and is increased by concomitant use of statins with cytochrome P-450 (CYP) 3A4 inhibitors, which raise serum concentrations of statins. Other agents such as gemfibrozil also increase the risk of myopathy, possibly by inhibiting the glucuronidation of statins (Self , 2004). The limitation of this study was the side effect such as myopathy was not recorded well.

Patients at risk from heart failure would probably be ideal candidates for combination therapy with an ARB and a statin. Twenty-two patients received ARBs. Statins reduced cholesterol concentration, atheroprotective, and improve endothelial function. ARBs are effective in controlling hypertension and associated CVD risks which blocking the binding of angiotensin II. They had a potentially synergistic mode of action, which could represent a potent and effective combination in a variety of patient populations (Nickening, 2004).

Antidepressant drugs were frequently used in the elderly, cause many of them had depressed with their illness. It usualy used in combination due to the high and growing incidence of cardiovascular diseases and psychiatric disorders worldwide, especially in the elderly. Sixteen patients in this research, got amytriptyline, a tricyclic antidepressant, which potentially interacts with statins but rarely clinically significant, the use of antidepressants with statins is still advisable (Palleria et al., 2019).

Coadministration of simvastatin with pioglitazone happened in 3 patients. The lack of pharmacokinetic effect of pioglitazone on simvastatin supports the expectation that this combination may be used safely (Thomayan et al., 2001). The mean AUC of simvastatin was reduced and by 82% by carbamazepine. Because of the pharmacokinetic profiles, only 1 patient in this study, he received only 10 mg per day, it should be given minimal 20 mg per day, otherwise, the effect of statins could not reduce the LDL cholesterol (Wiggins et al., 2016)

Most statins have been reported to slightly increase the anticoagulant effect of warfarin, requiring warfarin dosage reduction. Only 1 patient got 2 mg warfarin per day. The exact mechanisms of these interactions are unknown (Belosta et al., 2004). Inhibition of the partially CYP3A4- mediated metabolism of R-warfarin might explain the effects of simvastatin on

warfarin, but other mechanisms can be more important to the increased effect of anticoagulants. Several studies have demonstrated reduced warfarin dose requirements when coadministered with simvastatin (Hickmott et al., 2003).

CONCLUSION

This study shows that most statin user is elderly patients. Statins are used not only in dyslipidemia patients. There are many potential statin drug-drug interactions, but the clinicians give the statins in low-intensity doses and not over standard dose so the safety of the patients is maintained.

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