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Original Research Article

Symptoms of Statin-Induced Adverse Drug Reactions on Muscle on Older Patients

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ABSTRACT

Older patients are susceptible to Adverse Drug Reactions (ADR) resulting from age-related decline in body physiological conditions. This condition also has an impact on the emergence of degenerative diseases, which generally require supportive therapy in the form of statin drugs. However, this medication has the highest prevalence of ADR, often presented in the form of muscular symptoms. This study determined the Odds Ratio (OR) value of the muscle symptoms resulting from statin drug use observed in older patients compared to non-older patients. The influencing confounding factors were also evaluated. The study used a case-control design. The study was carried out from February to May 2020 and involved 36 older and 36 non-older patients. The selection was preceded by an interview, and the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) questionnaire was used to assess the muscle symptoms experienced. The results showed a statistically significant relationship between age and muscle symptoms in patients. The incidence of muscular ADR symptoms was higher in the older than in the non-older patients (OR = 18.74, p = 0.008). Therefore, the use of statin drugs in older patients needs regular monitoring to minimize the risk of muscular ADR symptoms.

Keywords: Adverse drug reactions, Atorvastatin, SAMS-CI, Simvastatin.

Introduction

Drug-Related Problems (DRPs) is an incidence characterized by potential challenges towards treatment success. This incidence includes adverse drug reactions (ADR), known as dangerous or unexpected drug responses, observed after administering the normal doses. In addition, the related data have substantial application in diagnosis, as prophylactic and disease therapy, or during attempts to improve the body's physiology.[1] Several factors, including age, especially the older (≥ 60 years), influence the increased ADR risk. This group of patients are more susceptible due to declining body's physiological conditions, connected with the potential change of drug pharmacodynamic and pharmacokinetic profile.

Wulandari et al. (2016) reported a 3.6 times greater risk of ADR in older, compared to non-older patients (< 60 years), and another study stipulated 7 times higher.[2] These statistics indicate the need for special attention.[1] Conversely, the overall organ function of the individual also decreases, thus instigating the incidence of degenerative diseases in the older, including dyslipidemia, coronary heart disease, heart failure, stroke, and type 2 diabetes mellitus (DM).[3]

Statins are an LDL cholesterol-lowering class of drugs that can inhibit the mechanisms in the HMG-CoA reductase enzyme and are known to play a major role in cholesterol synthesis.[4] These drugs act as pleiotropic agents or stabilizers for LDL cholesterol, the dominant component of atherosclerotic plaque, observed in dyslipidemia or DM cases with cardiovascular disease complications. In addition, statin use increases with age, especially for people over 65 years, and the ADR from therapy potentially outweighs the benefits.

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This situation has prompted the need for proper monitoring during treatment.[5] The most common ADR symptoms are related to the muscles, reaching 72%,[6] and are divided into four groups, including myalgia (5-10%), myopathy (1.5-5%), myositis (0.1-0.2%), and myonecrosis (rare).[5] The presentation is typically observed in symmetrical patterns and located in the proximal area of large muscles, including the thighs, calves, arms, buttocks, and back.[7,8] These symptoms usually appear in the first 4-6 weeks of therapy, although some report their occurrence after several years of treatment. The statin-induced muscle symptoms have more impact on the older than non-older due to the decline in mass, strength, and mobility of the individuals' muscles.[5,8]

Several previously conducted studies tend not to adopt the SAMS-CI questionnaire during the assessment of side effects in the form of muscle symptoms resulting from statin drug use.[9-12] The questionnaire is relatively easy to develop and practical to use by physicians and pharmacists in detecting side effects in suspected patients, especially in the form of muscle symptoms. Physicians and pharmacists need to be aware and able to detect the incidence of SAMS (statin-associated muscle symptoms) because these ADRs decrease patient adherence to taking statin. This study evaluated the differences in muscular symptom incidence between patients aged < 60 and ≥ 60 years old.

Materials and Methods

Study Design

This study is quantitative, using a case-control observational design. The study was undertaken from February to May 2020. The progress of each patient was followed up for three consecutive months. The study population included all patients using statin drugs in the Cardiology and Vascular Clinic of UNISMA Hospital Malang and Bunga Melati Clinic, Malang, Indonesia.

Prior to the investigation, informed consent was declared following the WHO Standards in 2011. Ethical approval (with number 08/I/2020/KEPK.RSIUNISMA) was obtained from the Health Research Ethics Committee of Malang Islamic Hospital, Indonesia.

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Samples and Sampling Techniques

The sample size was determined based on the following formula:

$$n1 = n2 = \left(\frac{Z\alpha\sqrt{2PQ} + Z\beta\sqrt{P1Q1 + P2Q2}}{P1-P2}\right)^2$$

The sample size was calculated using the formula for unpaired categorical comparability, as follows:[13]

$$n1 = n2$$

$$= \left(\frac{1.96\sqrt{2(0.555)\,(0.445)} + 1.28\sqrt{(0.74)(0.26) + (0.37)(0.63)}}{0.74 - 0.37}\right)^2$$

$$= 35.75 \approx 36$$

Description:

n1 = the number of older patients
n2 = the number of non-older patients
α = type one error of 5%
Zα = the standard value of α 5% is 1.96
β = type two error of 10%
Zβ = the standard value of β 10% is 1.28
P1 = the proportion of older with muscle symptoms due to statins is 74%[9]
Q1 = 1 – P1 = 1 – 0.74 = 0.26
RR = P1/P2 = 2
P2 = the proportion of older without muscle symptoms due to statins is 37%
Q2 = 1 – P2 = 1 – 0.37 = 0.63
P1 – P2 = 0.74 – 0.37 = 0.37
P = (P1 + P2)/2 = (0.74 + 0.37)/2 = 0.555
Q = 1 – P = 1 – 0.555 = 0.445

The samples were obtained using the purposive sampling method resulting in a total of 72 patients, comprising 36 older (aged ≥ 60 years) and 36 non-older (aged < 60 years). The inclusion criteria were males or females aged ≥ 25 years receiving statin therapy (simvastatin 10 mg, simvastatin 20 mg, atorvastatin 10 mg, or atorvastatin 20 mg) for at least one month. The exclusion criteria were patients taking other drugs that induce muscle symptoms as side effects, such as alcohol, cocaine, opioids, neuroleptics and psychotropic agents (haloperidol, risperidone), immunosuppressants (cyclosporine A, azathioprine), antiviral agents (zidovudine, ritonavir, didanosine), analgesics and antiinflammatory drugs (salicylates, nonsteroidal antiinflammatory drugs, glucocorticoids), fibrates (gemfibrozil, fenofibrate), anesthetics and neuromuscular blocking agents (propofol, ketamine, succinylcholine).[14] Individuals with other ailments with related symptoms, including rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, and hypothyroidism, were not included. The confounding variables assumed to influence muscle symptom occurrence after the administration of statin drug include the type and dosage of medication, duration of treatment, gender, body mass index (BMI), DM and dyslipidemia, and smoking habit. Other medications taken by patients besides statin for cardiovascular disease include aspirin, nitroglycerin, captopril, clopidogrel, amlodipine, and nifedipine. However, these drugs caused no muscle symptoms and therefore were not included as a confounding variable. The cardiologist collected and assessed the data on muscle symptoms through interviews with patients, using the SAMS-CI (Statin-Associated Muscle Symptom Clinical Index) questionnaire. It evaluated the recent experiences or the worsening situation after receiving a statin drug regimen. The assessment outcome showed the presence of aches, cramps, heaviness, discomfort, weakness, or stiffness, and the parameters examined include 1) location and pattern of muscle symptoms, 2) timing of muscle symptom onset concerning starting the statin regimen, 3) timing of muscle symptom improvement after withdrawal of statin, and 4) timing of recurrence of similar muscle symptoms concerning starting the second regimen. The score categories include "unlikely" for 2-6, "possible" for 7-8, and "probable" for 9-11. The classification of "possible" or "probable" indicated the tendency for muscle symptoms experienced by patients induced by statin drug use. The questionnaire was adapted from the research by Rosenson et al. (2017) and Taylor et al. (2017).[15,16]

Statistical Analysis

The assessments were performed using the Pearson Product Moment formula and Cronbach's Alpha method. The Pearson's correlation test was used to access the validity of each item on the questionnaire. The calculations were carried out by correlating the score of each item with the total. From the results, a coefficient was obtained and used to measure the item validity level and determine its suitability. Each items outlined in the questionnaire was considered valid when the $p < 0.05$.[17] Subsequently, univariate analysis was used to determine the description of patient characteristics.

The two multivariate analysis methods used were the Mantel-Haenzel stratification and logistic regression analysis. The Mantel-Haenzel stratification analysis method was used to control the effects of confounding variables. It was performed by grouping the samples that fall into the same category of variables. This analysis method was also used to control the effects of the confounding variables by grouping the subjects into homogeneous groups. The observed variables included gender, statin type, duration of statin consumption, BMI, history of diabetes mellitus (DM), history of dyslipidemia, and smoking habits.

The logistic regression analysis was used to test the effect of independent variables on the dependent variable using a binary nominal data scale. The results were considered statistically significant when the $p < 0.05$.

Results and Discussion

The study showed several patients' characteristics implicated as confounding factors in the incidence of muscle symptoms, including gender, statin drugs type and dosage, medication duration, BMI, DM and dyslipidemia, and smoking habits (Table 1). Based on gender, 55.6% of the older group receiving statin therapy was female, and 61.1% of the non-older was male. Based on the statin type and dose, simvastatin 20 mg was the most widely administered. As many as 77.8% of the older patients have been on medication for statins for a longer time (≥ 24 months) compared to short periods (1-23 months). Most patients (55.6%) in the non-older group were treated in the short term. Based on the patient's BMI, most of the older respondents had normal values (< 25 kg/m^2; 61.1%), and similar numbers of patients were normal and overweight BMI (obesity level 1) or obesity levels 2 and 3 (≥ 25 kg/m^2) for the non-older population. In terms of disease history, most participants had no DM, although there were reports of dyslipidemia. In addition, most respondents had no smoking habit.

The results showed validity of all items, as r count (0.768; 0.814; 0.871; 0.918) > r table (0.707), with $p < 0.05$. Therefore, the SAMS-CI instrument used is acceptable. The question items of a questionnaire are valid when r count > r table.[18] Based on the reliability test, the questionnaire alpha value was greater than 0.60, at 0.849, which is then confirmed reliable. Rosenson et al. (2017) showed that the SAMS-CI questionnaire was declared reliable due to its value of 0.77 (confidence interval 0.66-0.85).[15] Meanwhile, the reliability result in this study was set at 0.849; therefore, the SAMS-CI questionnaire used is also declared reliable.

The interviews performed using the SAMS-CI questionnaire led to the identification of seven patients with possible scores and two with probable scores in the older group. A total of two respondents in the non-older group had possible scores. These findings indicate a more common association between the occurrence of muscle symptoms and statin use among the older group, as shown in Table 4. Based on interviews by cardiologists, Table 4 shows the number of older and non-older patients with muscle symptoms resulting from statin use.

Until recently, there has been no gold standard for identifying the incidence of muscle symptoms due to statin use. Meanwhile, patients that experience these symptoms after taking statin stopped using the drugs. It increases the risk of morbidity and mortality associated with cardiovascular disease. Consequently, physicians and pharmacists need a standardized, practical, and applicable assessment instrument to accurately determine the muscle symptoms in patients due to statin use. For this reason, the NLA (National Lipid Association) Statin Muscle Safety Task Force devised a new method, known as SAMS-CI (Statin-Associated Muscle Symptom Clinical Index), for assessing the

incidence of muscle symptoms. It has four rankings, namely (1) location and pattern of muscle symptoms, (2) appearance of symptoms during the use of statin (starting), (3) symptoms improvement after stopping statin medication (dechallenge), and (4) the symptom recurrence when resuming statin medication (rechallenge).[14]

According to Taylor et al. (2017),[16] the classification of the events of muscle symptoms (unlikely, possible, probable) was based on four scales, namely location, pattern, timing of onset, and improvement after statin withdrawal. A study from the CoQ10 (Coenzyme Q10 in Statin Myopathy) on the use of SAMS-CI to assess the events of muscle symptoms due to the use of statin show that the instrument is effective in identifying patients who reported SAMS (statin-associated muscle symptoms) independently. This instrument also helps physicians and pharmacists promote adherence to statin medication in patients who believe they are intolerant due to muscle symptoms.[14]

The results showed a statistically significant relationship between age and the prevalence of muscle symptoms following statin use (Table 3). Table 3 shows that all confounding variables, including the comorbidities of diabetes mellitus and dyslipidemia, have no statistically significant relationship with the muscle symptoms incidence ($p > 0.05$). All confounding variables were not statistically significant and had no effect on the events of muscle symptoms. The occurrence probability has a greater impact on the older than the non-older. In addition, muscle strength is assumed to decrease by 3% every year at old age. The size of cells, tissues, and fibers also decreases due to reduced protein production ability. The effect was further observed in all major muscle groups, including the deltoid, biceps, triceps, hamstrings, and calf.[19] A typical ability to produce free radicals is accelerated with increasing age because of declined mitochondrial function and increased electron movement to the transport chain. These events subsequently stimulate the generation of Reactive Oxygen Species in the mitochondria, thus augmenting the susceptibility to oxidative damage. In addition, there is a possibility of further dysfunction in the form of poor capacity to efficiently produce the energy needed by the muscle cells. These conditions lead to a decline in function, as observed in muscle contractility dysfunction, regulation changes, and protein degradation.[20] However, the mass and strength and reduced mobility have been implicated in the higher disposition to side effects in older patients. Those were observed in the form of statin drug-related muscle symptoms, compared to the results obtained for non-older patients.

The mechanism of statin-induced muscle symptom incidence is allegedly due to HMG-CoA reductase enzyme inhibition and is assumed to interfere with farnesyl pyrophosphate formation. It subsequently causes ubiquinone deficiency or Coenzyme Q10 (CoQ10), which plays an important role in energy production from mitochondria to muscle cells. Therefore, a decline in quantity triggers muscle cells dysfunction, followed by an increase in the yield of free radicals, predominantly observed in older people. Consequently, the mitochondrial function is damaged, and susceptibility to the symptoms increases after administering statin drugs.[8]

Based on the crude RR (Relative Risk) calculation (Table 2), the risk of developing muscle symptoms in non-older due to statin drugs was 0.222 times lower than the older. Table 3 indicates that the regression coefficient due to the effect of age on muscle symptoms was 18.74. It shows that age exerts a significantly positive effect on muscle symptoms. Therefore, based on these results, older patients have a greater possibility of experiencing muscle symptoms than non-older. Several previous studies showed greater ADR risks in the older. This is also congruent with the results obtained in the report of Alomar (2014) and Wulandari *et al*. (2016).[1,2] A meta-analysis investigation showed a 4 times higher tendency for hospitalization of older people, following an adverse event.[21]

PRIMO (Prediction of Muscular Risk in Observational conditions) studies showed an incidence of muscle symptoms by 10.5%. Meanwhile, data collection was carried out by interviewing hyperlipidemic patients receiving high-dose statin therapy.[22] Another study also reported a greater incidence of muscle symptoms by 23% in statins patients. Similarly, data collection was also done by interview.[23] A study in Jordan using an interview method for patients on statin drugs showed that the prevalence of muscle symptoms was 27.9%. In the aforementioned study, the types of statins used were simvastatin (18.8%), atorvastatin (75.8%), rosuvastatin (1.6%), fluvastatin (0.9%), and pravastatin (2.9%). Meanwhile, the statins daily doses used were 10 mg (14.5%), 20 mg (78.8%), 40 mg (6.1%), and 80 mg (0.6%).[9] The prevalence of muscle symptoms due to statin use in this study was 15.3%. The results showed that the muscle symptom risk in patients that uses atorvastatin was 1.22 times higher than those using simvastatin (crude RR = 1.22; 95% CI 0.396-3.747). By considering the effect of drug doses, patients with atorvastatin were 1.30 times more likely to experience muscle symptoms than those with simvastatin (adjusted RR = 1.30; 95% CI 0.460-3.662). Furthermore, the differences in SAMS incidence could be due to differences in statin types; therefore, the greatest risk of SAMS is associated with lipophilic statins such as simvastatin, atorvastatin, and lovastatin owing to their ability to diffuse non-selectively into extrahepatic tissues, such as skeletal muscle. In contrast, hydrophilic statins, such as pravastatin and fluvastatin, penetrate less into the muscles; therefore, the risk of SAMS is also lower. Furthermore, differences in ethnicity and genetic factors also influenced the incidence of SAMS. It occurred due to these factors' involvement in changing skeletal muscle membrane stability, fluidity, and protein signaling and activity. In addition, they also affect mitochondrial function and lowers membrane cholesterol content. Therefore, changes in statin uptake or metabolism can increase exposure to skeletal muscle deformity, caused by changes in mitochondrial function, calcium signaling, and cell cycle pathways.[6]

Table 1: Demographic characteristics of patients receiving statin drugs

Variables	Older (36 patients) n%	Non-Older (36 patients) n%
Gender		
Male	16 (44.4%)	22 (61.1%)
Female	20 (55.6%)	14 (38.9%)
Statin Type		
Simvastatin 10 mg	6 (16.7%)	4 (11.1%)
Simvastatin 20 mg	19 (52.8%)	20 (55.6%)
Atorvastatin 10 mg	3 (8.3%)	7 (19.4%)
Atorvastatin 20 mg	8 (22.2%)	5 (13.9%)
Duration of Taking Statins		
1-23 months	8 (22.2%)	20 (55.6%)
≥ 24 months	28 (77.8%)	16 (44.4%)
BMI		
< 25 kg/m^2	22 (61.1%)	18 (50.0%)
≥ 25 kg/m^2	14 (38.9%)	18 50.0%)
DM History		
No	22 (61.1%)	26 (72.2%)
Yes	14 (38.9%)	10 (27.8%)
Dyslipidemia History		
No	4 (11.1%)	5 (13.9%)
Yes	32 (88.9%)	31 (86.1%)
Smoking Habit		
No	28 (77.8%)	23 (63.9%)
Yes	8 (22.2%)	13 (36.1%)

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Table 2: Crude and adjusted RR analysis of age and confounding variables

Variable	Experiencing Muscle Symptoms		RR crude (CI 95%)	RR adjusted (CI 95%)
	Yes (11 patients)	No (61 patients)		
Age				
Older	9 (81.8%)	27 (44.3%)	0.22	-
Non-older	2 (18.2%)	34 (55.7%)	(0.051-0.958)	
Confounding Variables				
Gender				
Male	8 (72.7%)	30 (49.2%)	0.42	0.43
Female	3 (27.3%)	31 (50.8%)	(0.121-1.454)	(0.128-1.473)
Statin Type				
Simvastatin 10 mg	2 (18.2%)	8 (13.1%)		
Simvastatin 20 mg	5 (45.5%)	34 (55.7%)	1.22	1.30
Atorvastatin 10 mg	1 (9.0%)	9 (14.8%)	(0.396-3.747)	(0.460-3.662)
Atorvastatin 20 mg	3 (27.3%)	10 (16.4%)		
Duration of Taking Statins				
1-23 months	6 (54.5%)	22 (36.1%)	0.51	0.39
≥ 24 months	5 (45.5%)	39 (63.9%)	(0.164-1.595)	(0.126-1.233)
BMI				
< 25 kg/m^2	7 (63.6%)	33 (54.1%)	0.71	0.82
≥ 25 kg/m^2	4 (36.4%)	28 (45.9%)	(0.229-2.227)	(0.272-2.493)
DM History				
No	8 (72.7%)	40 (65.6%)	0.75	0.64
Yes	3 (27.3%)	21 (34.4%)	(0.219-2.574)	(0.188-2.142)
Dyslipidemia History				
No	0 (0.0%)	9 (14.8%)	-	-
Yes	11 (100.0%)	52 (85.2%)		
Smoking Habit				
No	7 (63.6%)	44 (72.1%)	1.39	1.75
Yes	4 (36.4%)	17 (27.9%)	(0.453-4.247)	(0.604-5.092)

Table 3: Multiple logistic regression analysis of age and confounding variables

Variables	Odds Ratio	p	95% CI	
Age	18.74	0.008	2.176	161.470
Gender	0.26	0.155	0.040	1.666
Statin Type	1.37	0.436	0.623	3.001
Duration of Taking Statin	0.19	0.066	0.032	1.116
BMI	0.38	0.304	0.059	2.420
DM History	0.27	0.216	0.035	2.129
Dyslipidemia History	1.00	-	-	-
Smoking Habit	2.37	0.361	0.372	15.067
Constant	0.09	0.080	0.006	1.333

Table 4: Muscle symptom score based on the SAMS-CI questionnaire

Muscle Symptom Score	Number of Patients on Older Group	Number of Patients on Non-Older Group
	Unlikely Group	
2	3	5
3	6	9
4	6	3
5	8	9
6	4	8
	Possible Group	
7	4	1
8	3	1
	Probable Group	
9	1	0
11	1	0
Total	36	36

Interactions between drugs occur when the pharmacokinetics or pharmacodynamics of one drug is altered by another administered previously or simultaneously. It leads entirely to different effects compared to when each drug is administered separately. Meanwhile, the most clinically significant drug interactions are the pharmacokinetic changes due to induction or inhibition of drug-metabolizing enzymes and transporters. Most statins were subjected to extensive microsomal metabolism by CYP450 isoenzymes. The potent inhibitors of CYP3A4 can significantly increase the active and concentrated forms of atorvastatin, simvastatin, and lovastatin. Moreover, genetic variations in the liver, gut, and muscle transporters probably contribute to drug interactions through changes in bioavailability, metabolism, and statin clearance and concentrations in tissues.[6] Approximately 75% of drugs were metabolized by CYP, while about half by CYP3A4 isoenzymes. Drugs metabolized by CYP3A4 are likely to increase serum statin concentrations through competition for catabolism. These drugs include azole antifungals, macrolide or "mycin" antibiotics, tricyclic antidepressants, protease inhibitors, and calcium-channel blockers such as amlodipine.[24] Also, some patients in this study took amlodipine that was unavoidable because they had cardiovascular disease requiring treatment. However, the maximum dose of simvastatin used was 20 mg per day. Meanwhile, the use of simvastatin 20 mg/day together with amlodipine did not increase SAMS risk. Another statin drug used in this study was atorvastatin, which does not also interact with amlodipine.[25] The serum creatinine levels in this research were not examined, leading to difficulties in categorizing the muscle symptoms recorded into myalgia, myopathy, myositis, or myonecrosis (rhabdomyolysis). It is because the physicians only measured the complaints and location of muscle symptoms, and the serum creatinine levels were not examined using the SAMS-CI questionnaire.

The prevalence of muscle symptoms resulting from statin use in this research was 15.3%. This condition instigated attention from physicians because the side effects can potentially inhibit patient compliance during simvastatin administration.[9] In addition, it is important for physicians and pharmacists to educate patients on the necessity of reporting the manifestation of any consequent muscle symptoms. The statin dose adjustments, changes in the type of statin drug, or temporary termination of therapy were also considered after reflecting on the medical benefits and risks for the patient.[9]

Conclusion

The muscle symptom incidence resulting from statin drug use is higher in the older patient group than that in the non-older patients. In addition, age is considered to be the only influencing variable among others.

Conflict of Interest

The authors declare no conflicts of interest.

Author's Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Alomar MJ. Factors affecting the development of adverse drug reactions (review article). Saudi Pharm J. 2014; 22(2):83-94.
2. Wulandari N, Andrajati R, Supardi S. Risk factor elderly age on incidence of adverse drug reaction in patients with hypertension, diabetes, dyslipidemic at three puskesmas in Depok. Indones Pharm J. 2016; 6(1):60-67.
3. Zaenurrohmah DH and Rachmayanti RD. Relationship between knowledge and hypertension history with blood pressure control in elderly. Period Epidemiol J. 2017; 5(2):174-184.
4. Erwinanto E, Santoso A, Putranto JNE, Tedjasukmana P, Sukmawan R, Suryawan R. Guidelines for dyslipidemia management 2017. Jakarta: Indonesian Heart Association (IHA); 2017. 1-80 p.
5. Hilmer S and Gnjidic D. Statins in older adults. Aust Prescr. 2013; 36(3):79-82.
6. Ward NC, Watts GF, Eckel RH. Statin toxicity mechanistic insights and clinical implications. Circ Res. 2019; 124(2):328-350.
7. Mlodinow SG, Onysko MK, Vandiver JW, Hunter ML, Mahvan TD. Statin adverse effects: sorting out the evidence. J Fam Pract. 2014; 63(9):497-506.
8. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgozoglu L, Nordestgaard BG, Bruckert E, Backer GD, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, Marz W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN. Statin-associated muscle symptoms: impact on statin therapy-European atherosclerosis society consensus panel statement on assessment, aetiology and management. Eur Heart J. 2015; 36(17):1012-1022.
9. Khlief Y, Hyassat D, Liswi M, Jaddou H, Ajlouni K. Prevalence of myopathy in subjects on statin therapy attending the National Center for Diabetes, Endocrinology and Genetics in Jordan. Endocrinol Metab Syndr. 2015; 4(4):1-6.
10. Castro PF, Ribeiro E, Dorea EL, Pinto GA, Hirata RDC. Factors associated with statin-related adverse muscular events in adult dyslipidemic outpatients. Braz J Pharm Sci. 2017; 53(4):1-10.
11. Jacobson TA, Cheeley MK, Jones PH, Forge RL, Maki KC, Lopez JAG, Xiang P, Bushnell DM, Martin ML, Cohen JD. The statin adverse treatment experience survey: experience of patients reporting side effects of statin therapy. J Clin Lipidol 2019; 13(3):415-424.
12. Hopewell JC, Offer A, Haynes R, Bowman L, Li J, Chen F, Bulbulia R, Lathrop M, Baigent C, Landray MJ, Collins R, Armitage J, Parish S. Independent risk factors for simvastatin-related myopathy and relevance to different types of muscle symptom. Eur Heart J. 2020; 41(35):3336-3342.
13. Dahlan MS. Besar sampel dalam penelitian kedokteran dan kesehatan. (5th ed). Jakarta: Epidemiologi Indonesia; 2016; 82-93 p.
14. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol. 2014; 8(3):S58-S71.
15. Rosenson RS, Miller K, Bayliss M, Sanchez RJ, Baccara-Dinet MT, Chibedi-De-Roche D, Taylor B, Khan I, Manvelian G, White M, Jacobson TA. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): revision for clinical use, content validation, and inter-rater reliability. Cardiovasc Drugs Ther. 2017; 31(2):179-186.
16. Taylor BA, Sanchez RJ, Jacobson TA, Chibedi-De-Roche D, Manvelian G, Baccara-Dinet MT, Khan I, Rosenson RS. Application of the Statin-Associated Muscle Symptoms-Clinical Index to a randomized trial on patients with an ICD remain at risk for painful shocks in last moments. J Am Coll Cardiol. 2017; 70(13):1680-1681.
17. Bina Nusantara University. Uji validitas dan reliabilitas. [Online]. 2021 [cited 2021 Jan 14]. Available from: https://qmc.binus.ac.id/2014/11/01/u-j-i-v-a-l-i-d-i-t-a-s-d-a-n-u-j-i-r-e-l-i-a-b-i-l-i-t-a-s/#.
18. Rahman TA. Analisis statistik penelitian kesehatan (prosedur pemilihan uji hipotesis penelitian kesehatan). Bogor: In Media; 2015. 107-108 p.
19. Amarya S, Singh K, Sabharwal M. Ageing process and physiological changes. Gerontology. London: IntechOpen; 2018. 1-24 p.

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20. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel J, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M. Sarcopenia: European consensus on definition and diagnosis. Age Ageing. 2010; 39(4):412-423.
21. Narvaez ED, D'Souza K, Rivera V. Common chronic conditions. In: Chun A (Eds.). Geriatric practice: a competency based approach to caring for older adults. Switzerland: Springer Nature Switzerland AG; 2019. 144 p.
22. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients-the PRIMO study. Cardiovasc Drugs Ther 2005; 19(6):403-414.
23. Buettner C, Rippberger MJ, Smith JK, Leveille SG, Davis RB, Mittleman MA. Statin use and musculoskeletal pain among adults with and without arthritis. Am J Med. 2012; 125(2):176-182.
24. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol. 2016; 67(20):2395-2410.
25. Medscape. Drug interaction checker. [Online]. 2021 [cited 2021 Jan 14]. Available from: https://reference.medscape.com/drug-interactionchecker.