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Pattern of statin use in several Hospitals in Jakarta. A cross sectional study

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KEYWORDS *statins; efficacy; hypercholesterolemia; drug combination*

ABSTRACT *A preliminary, cross-sectional study on the pattern of statins use in three hospitals in Jakarta was conducted to see the responder rate of the patients who took statins. Data were taken from the Medical Records from May-July 2004 of each hospital. The inclusion criteria were outpatients diagnosed with dyslipidemia treated with statins either as first choice or add-on therapy to the other lipid-lowering drugs given. Two hundred and forty three cases were recorded during the 3-month period of examination, 127 male and 116 female. The average age of both group of patients were 56 ± 12 years (male) and 55 ± 12 years (female). The most commonly used statins as first choice and as add-on was atorvastatin (38.1%, and 1.6%, respectively), followed by rosuvastatin (20.5%), fluvastatin (11.5%), pravastatin (10.7%); whereas lovastatin (0.4%) and simvastatin (3.7%) were least prescribed. Patients' total cholesterol levels were reduced significantly (241 ±57 vs 207 ±38 mg/dL, $p < 0.0001$), whereas triglyceride levels were not significantly reduced (174 ±86 vs 160 ± 71 mg/dL). Around 46% cases (72 out of 243 cases) met the NCEP ATP III goals on total cholesterol level. The most common combinations used, with respect to atorvastatin, were fenofibrate (11.3%), pravastatin (9.3%), rosuvastatin (3%), gemfibrozil (2%), whereas, with regard to rosuvastati, were gemfibrozil (9%), ciprofibrate (5%), and atorvastatin (3%). Large numbers of patients were not regularly checked up or low in compliance. In conclusion, statins usage in some hospitals in Jakarta had been inappropriately used, due to multiple factors, such as, prescribers, patients' aspects, and the national health system. Therefore, in order to observe the efficacy of statins in clinical setting, a large scale study on the pattern of statin use should be conducted.*

Many studies reveal that low blood cholesterol concentration substantially lowers the incidence of myocard infarct and any other cardiovascular diseases (Levine *et al*, 1995; Hughes 1997). The first effort offered for patients to lower their cholesterol level in blood is by changing life styles, which include reducing body weight, more vigorous daily activity and smoking cessation. However, these efforts could only reduce the cholesterol level up to 15%. For most of the cases, pharmacological approach, in the end, is considered by giving a specific lipid lowering drug. There are 5 classes of lipid-lowering drugs obtainable i.e. statins, niacin, bile-acids binding resins, fibrates, and cholesterol absorption inhibitor (ezetimibe) [Mahley and Bersot, 2001].

Statins (3-OH-3-methylglutaryl-CoA reductase inhibitor) are group of lipid lowering drugs, which are very effective in lowering the coronary artery incidence shown in many primary and secondary prevention studies. There are now at least seven types of statins, which are available in the market. The first obtainable statins are lovastatin, pravastatin and simvastatin, all of which have shown some remarkable results on lowering the incidence of cardiovascular diseases (Anonymous, 1999; LIPID, 1998; Heart Protection Study Collabora-tive Group,

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2002; Ballantyne *et al.* 2003). The development of new generation of statins is ever increased since the last 10 years; fluvastatin, atorvastatin and rosuvastatin are some of the newly developed statins, which according to the producers are somehow more powerful and have less side effects.

Though in many controlled studies, with very rigorous protocols, statins have proved to be effective in lowering coronary heart diseases (CHDs), however, the use of statins in clinical practice especially in developing countries are not yet fully explored, although in developed country such assessment has been done recently (Packham *et al,* 2000). Thus, the aim of the study was to investigate the pattern of statins' use in several hospitals in Jakarta greater area.

MATERIALS AND METHODS

A cross-sectional data of medical records from May to July 2004 were taken from three private hospitals in Jakarta greater area. The inclusion criteria for selecting and collecting data are out-patients diagnosed with hypercho-lesterolemia or hyperlipidemia either with or without any other complications or accompa-nying diseases who are treated with statins. The statins used can be either as first choice or add-on to any other lipid lowering drugs, such as fibrates or niacin. Responder is defined as patient whose Total cholesterol level (TC) during or after treatment meet the level as it is suggested by the NCEP ATP III criteria. Statistics were used as long as data collected were appropriate using SPSS vers. 11.0

RESULTS

At first, 256 cases were collected, but, after re-scrutinizing the data, for lacking of important items such as date of follow-ups, dosage, etc, only 243 cases were included for the study.

The mean of patients' age was shown in Table 1. As we see from the table, male and female patients came from the same age group. However, there was one patient whose age was only 17 years old with total cholesterol level 243 mg/dL. She probably had a genetic type of hypercholesterolemia which could be assessed through genotyping.

The most commonly used statins as first choice and as add-on to the subsequent cases was depicted in Table 2. Atorvastatin (38.1% as first choice and 1.6% as add-on) seems to be the most prescribed statin, whereas lovastatin and simvastatin were least prescribed.

Total cholesterol (TC) and Triglycerides (TG) concentrations were depicted in Table 3 and 4. Only 84 out of 243 cases of Low-density lipoprotein cholesterol (LDL-C) level were regularly measured, whereas, the measurements of High-density lipoprotein cholesterol (HDL-C) were even more scarce (18 cases). Therefore, due to the inadequate data, both lipoprotein levels could not be shown and analyzed.

With respect to the NCEP ATP III criteria of cholesterol levels, the effect of various statins on TC and TG concentrations were depicted in Fig. 1 and 2. The percentage of patients whose TC level meet the criteria of ATP (responders) was shown in Table 5.

As it is often seen in the clinics, statins are usually prescribed in combination with other lipid-lowering drugs, such as fibrates, nicotinic acid and recently with ezetimibe, as a cholesterol absorption inhibitor. In this study, this combination was shown in Table. 6.

All statins significantly decreased the plasma TC level compared to the pretreatment level, but not for TG. The most frequently prescribed statins were atorvastatin (39.7%, 97 cases), rosuvastatin (22.5%, 55 cases), pravastatin (14.5%, 37 cases), fluvastatin (13%, 34 cases), simvastatin (3.7%, 9 cases), lovastatin (0.4%, 1 case), and the most frequent combination used for atorvastatin was fenofibrate, whereas for rosuvastatin was gemfibrozil.

Table 1. Demographic data of the patients

	Male	Female	Total
Age (years) (Mean ± SD)	56 ± 12	55 ± 12	55 ± 12
Number of cases	127	116	243

Table 2. The most frequently prescribed statins in the particular hospitals setting

Type of statins	As first choice	As add-on
Simvastatin	3.7 %	-
Pravastatin	10.7 %	4.5 %
Fluvastatin	11.5 %	2.5 %
Atorvastatin	38.1 %	1.6 %
Rosuvastatin	20.5 %	2.0 %
Lovastatin	0.4 %	-

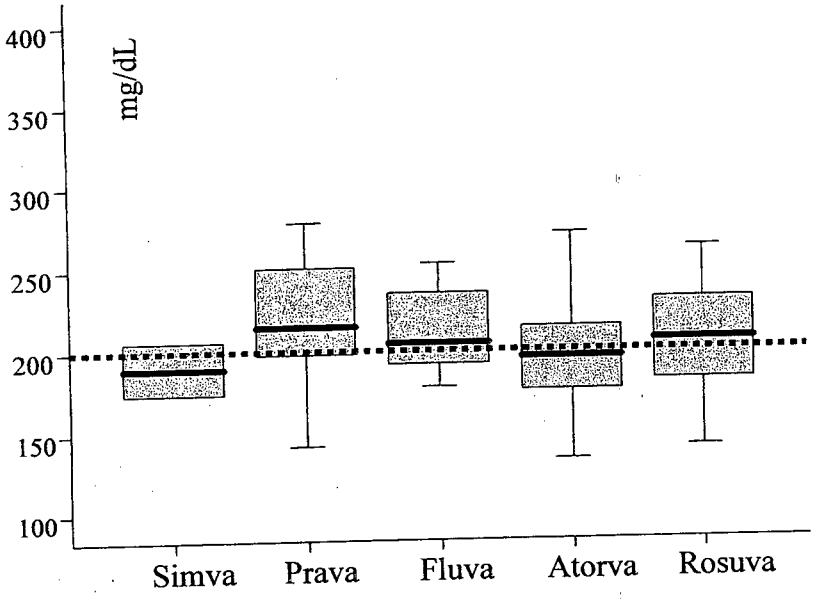

Figure 1. The effect of various statins on the level of Total Cholesterol. The dotted line shows the minimum level of TC according to the NCEP ATP III goals.

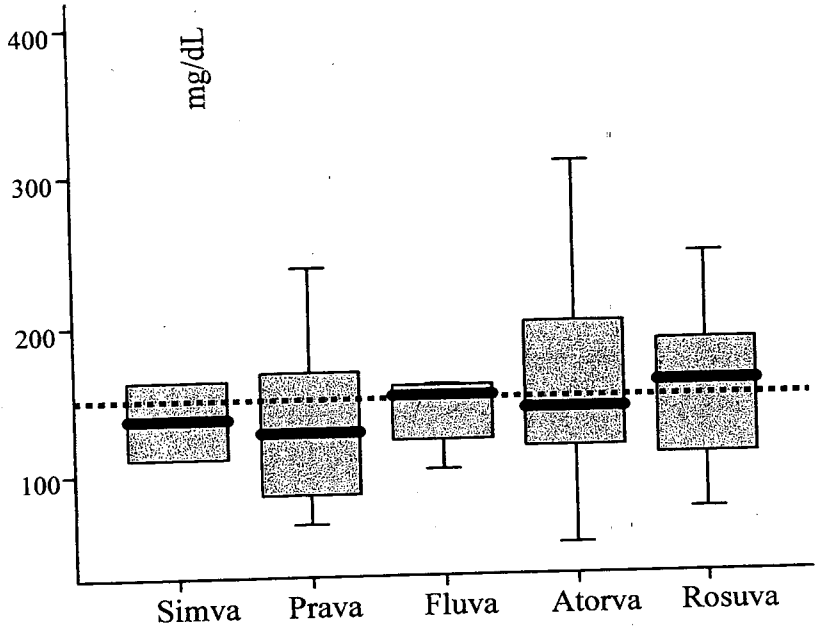

Figure 2. The effect of various statins on the level of Triglycerides. The dotted line shows the minimum level of TC according to the NCEP ATP III goals.

Table 3. The effect of various statins on total cholesterol level

Type of statins	Total Cholesterol (mg/dL; Mean ± SD)	
	Pre treatment	During & Post treatment
Simvastatin	226.5 ± 45	190 ± 22.7
Pravastatin	220 ± 40	215 ± 40
Fluvastatin	236 ± 41.5	205 ± 28
Atorvastatin	227 ± 52.6	196 ± 35
Rosuvastatin	247 ± 109	206 ± 51
Total	241 ± 57	207 ± 38*

* $p < 0.001$

Table 4. The effect of various statins on triglycerides level

Type of statins	Triglycerides (mg/dL; Mean ± SD)	
	Pre treatment	During & Post treatment
Simvastatin	203.5 ± 45	136 ± 37
Pravastatin	138 ± 30	127 ± 74
Fluvastatin	234 ± 61.5	151 ± 60
Atorvastatin	141 ± 68	142 ± 68
Rosuvastatin	176 ± 61	159 ± 65
Total	174 ± 86	160 ± 71

Table 5. The percentage of responders in accordance with the ATP III criteria

	Percentage of responder population
All type of statins	46.45% (72 out of 155 cases)
Simvastatin	0.65%
Pravastatin	3.22%
Fluvastatin	1.33%
Atorvastatin	17.42%
Rosuvastatin	5.16%
Atorva + (prava., fibrate, gemfibrozil)	0.65%, 0.65%, 0.65%, respectively

Table 6. The most lipid-lowering drug combinations used with statins

	Atorvastatin (94 cases)	Rosuvastatin (55 cases)
Fenofibrate	11.3% (11)	-
Pravastatin	9.3% (9)	-
Rosuvastatin	3.0% (3)	-
Gemfibrozil	2.0% (2)	9.0% (5)
Fluvastatin	1.0% (1)	-
Ciprofibrate	1.0% (1)	5.0% (3)
Atorvastatin	-	3.0% (2)

DISCUSSION

From Figure 1 and Table 3 we can see that TC level was significantly reduced. But, to some extent, the decrease was not yet optimal. In this study, the total cholesterol and triglyceride levels were lower compared to the pretreatment level, though only 46.45% of patients whose total cholesterol level achieved the NCEP ATP III goal (See Table 5.). In contrast, atorvastatin (17.42%) seemed to be the most significant contributor which gave the result. This result, surprisingly, is lower than the other result (Nash, 1996). Brown *et al.*, (1998), however, showed that a significant number of patients treated with atorvastatin reached the target LDL cholesterol level than patients treated with fluvastatin and lovastatin. In this study, atorvastatin was the most frequently prescribed drug in the three hospitals.

The results of many controlled trials on dyslipidemia indicated that CHD mortality was reduced as much as 30% to 40% when hypercholesterolemic patients were treated with moderate dose of lipid-lowering drugs. Thus, it was very important that the ultimate goal for treating patients with hypercholesterolemia was that their cholesterol level could achieve the NCEP ATP III goals.

Unfortunately, according to Primatesta *et al* (2000), only 1 out of 50 English adults used a lipid lowering agent (30% of people with a history of cardiovascular disease and 3% of people with a 10 year risk of coronary heart disease of >30%). And this was also confirmed by Hulley (2000) and Packham *et al.* (2000). As shown in these studies, patients who supposed to be treated with statins accordingly received no proper treatment.

As was depicted in Table 6, there were 11 cases where combination of statins with fibrate were used. In addition, there were also combinations of two different statins, like atorvastatin with pravastatin (9 cases), and atorvastatin and rosuvastatin (3 cases). It was well documented elsewhere, that the combinations of statins with other lipid-lowering drugs, such as bile-acid binding resins, niacin were beneficial, but, to put two statins together in one therapy regime was not yet well practiced. Unfortunately, some drug combinations were prone to intensify their side effects. The most frequent side-effects predicted were myopathy which could lead to rhabdomyolysis (Duell *et al*, 1998; Garnett, 1995; Miller & Spence 1998). In this study, it was not clear whether the patients observed experienced some effects resembling myopathy, while no notices were seen in the medical record. Some studies revealed that myopathy apparently occurred due to pharmacodynamic and pharmacokinetics interactions (Corsini *et al.*, 1999; Mahley & Bersot, 2001).

The measurement of the concentration of lipoprotein cholesterol should comprise not only total cholesterol, but LDL-C and HDL-C as well, especially for patients who had other risk factors as mentioned in NCEP ATP III criteria. In this study, quite a lot of patients had been checked only for their TC level and triglyceride level, whereas the level of HDL-C was also not properly checked. There were 28.2% (49 out of 174 patients) who had their pretreatment HDL-C level ≤ 40 mg/dL (data was not shown), which was also considered as one of the important predisposing factor for CHD (Ballantyne *et al.*, 2003; Kreisberg, 2002; Kreisberg, 2003). Other predisposing factors, such as BMI, smoking habits, family history were not very well documented. As suggested in the NCEP ATP III guideline, all these factors should always be taken into account for the treatment of dyslipidemia.

On the other hand, many cases were difficult to retrieve due to irregular check ups or no follow-ups; therefore, these factors, at the end, gave an incomplete information on the efficacy of the respective statins. There were some possible answers to this problems, i.e. among others, lack of comprehensive information from the care providers to the patients on the importance of the continuity of the drugs prescribed, and patients refused to come for check ups due to economic backgrounds (Fairhurst & Huby, 1998; Schwed *et al*, 1999). Furthermore, most of the patients in Indonesia were not covered by insurance, or patients who felt better due to various reasons were refused to come for follow ups,

The choice of statins should be based on efficacy and cost. Could the dose of a particular statin reduce the patient's LDL-C to the target level? With regards to the decrease of LDL-cholesterol level, nowadays, a combination of statins and a cholesterol absorption inhibitor i.e. 'ezetimibe, was proven to be superior compared to statins alone or statins with other lipid-lowering drugs, such as fibrates. The combina-tion of ezetimibe and simvastatin could reduce the LDL-C level up to 38% (Goldberg *et al.*, 2004), which gave a greater proportion of patients to reach the target level according to the NCEP ATP III criteria. Cost should be the next discerning factor, if once drug treatment is initiated, it is almost always lifelong (Ulrich *et al*, 2000). Combination of statins and other lipid lowering drugs also had a beneficial aspect which could reduce the possibility of statins'

side effects while the statin dosage used in combination was lower than statin monothe-rapy.

The use of evidence from controlled clinical trials to support routine practice was obvious to be a key factor of achieving a cost effective health service (Van Hout and Simoons, 2001). Treatment guidelines offer the prescribers a rational way to choose and maintain their treatment for particular diseases, including hy-perlipidemia, but, nevertheless, doctors should pursue the new trends and developments in their respective areas, as in the treatment of lipid disorders. The development and use of statins were an example of the very rapid progression in the management of dyslipidemia.

CONCLUSION

A cross-sectional study of pattern use of statins in several hospital in Jakarta was conducted. Although total cholesterol levels decreased significantly, the responders rate was still small. The dose of statins (rosuvastatin, fluvastatin) needs to be increased to meet the therapeutic goal in lowering Triglyceride level (ATP III). A prospective large scale study should be performed to assess the pattern use of statins with respect to clinical settings in Indonesia, thus, the efficacy and other beneficial aspects of statins could be rigorously measured.

ACKNOWLEDGEMENT

The authors wish to thank Ms. Lien Naiborhu, Ns. Yuni Sulistyowati, for their efforts in collecting the data from the medical record. The study was funded by DIGM (German Indonesia Medical Society) and Faculty of Medicine of Universitas Kristen Indonesia.

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