Lipid Treatment Assessment Project (L-TAP) Study : a survey in 13 cities in Indonesia to evaluate the percentages of dyslipidemic patients achieving NCEP LDL-C target goals after treatment

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Abstrak

Berbagai uji klinik telah membuktikan bahwa penurunan kadar LDL-C sangat bermanfaat baik untuk pencegahan PJK primer maupun sekunder. Meskipun demikian di Amerika Serikat banyak penderita dislipidemia yang tidak diobati menurut petunjuk pelaksanaan yang dibuat NCEP. Pada tahun 1996 di Indonesia telah dibuat petunjuk pelaksanaan penanggulangan dislipidemia untuk pencegahan PJK oleh PERKI. Sampai saat ini pengobatan dislipidemia belum diketahui dengan pelaksanaannya di tempat praktek dokter. Tujuan penelitian adalah menentukan persentase penderita dislipidemia yang mencapai target LDL-C menurut NCEP setelah mendapat terapi minimal 3 bulan. Studi ini dilakukan dengan cara survei potong lintas yang mengikut sertakan dokter yang biasa mengobati penderita dislipidemia di 13 kota di Indonesia. Dokter yang ikut serta dalam penelitian diminta untuk mengisi kuesioner mengenai petunjuk NCEP dan mengisi formulir pencatatan kasus untuk setiap penderita. Terdapat 188 dokter (dari 400 yang diundang) berpartisipasi dalam survei ini dan mengikut sertakan 1420 penderita yang mendapat terapi statin (1082 orang), fibrat (301 orang), kombinasi obat (14 orang) dan non farmakologik 23 orang. Secara keseluruhan terdapat 49 % penderita yang berhasil mencapai target kadar LDL-C yang berkisar dari 14.8 % pada penderita PJK 43.6 % pada penderita risiko tinggi dan 73.0 % pada penderita risiko rendah. Dibanding dengan terapi lain, penderita yang mendapat statin lebih banyak yang mencapai target kadar LDL-C yaitu keseluruhan penderita 55 %, golongan risiko rendah 78 %, risiko tinggi 50 % dan PJK 19 %. Hanya 14 % dari dokter yang ikut penelitian memakai target kadar LDL-C seperti dalam petunjuk pelaksanaan NCEP. Kesimpulan : sebagian besar penderita dislipidemia yang diobati di praktek rutin tidak mencapai kadar target LDL-C. Banyak dokter yang belum memakai NCEP. ***(Med J Indones 2001; 10: 103-9)***

Abstract

Clinical trials have demonstrated significant benefit from low density lipoprotein cholesterol (LDL-C) lowering for primary and secondary prevention of cardiovascular disease. In the US, it is well recognized that a substantial number of hypercholesterolemic patients were not treated to the LDL-C goals recommended by the National Cholesterol Education Program (NCEP) guidelines. In 1996, the Indonesian Heart Association (PERKI) has issued guidelines recommending goals for screening and lipid treatment in Indonesia adopted from NCEP guidelines ; however, the frequency of undertreatment in Indonesia is not known. The ***objective*** *of this study was to determine the percentage of patients treated with lipid-lowering therapy who reached LDL-C goals as defined by NCEP guidelines in routine clinical practice. This was a cross-sectional survey targeted physicians who regularly treated dyslipidemic patients in 13 cities in Indonesia. Participating doctors were asked on their awareness of NCEP guidelines and to complete the case record form (CRF) of the enrolled patients. One-hundred and eighty-eight (188) out of four hundreds (400) physicians who were invited, have participated in this study. Among the evaluable 1420 CRF, 1082 patients received statins, 301 used fibrates, 14 patients used combination drugs, and 23 others received non-drug treatments only. Success rates on achieving target LDL-C in low-risk, high-risk, and CHD groups were 73.0 %, 43.6 %, and 14.8 %, respectively. Overall success rate in patients using statins was 55.1 %, while in low-risk group, high-risk group, and CHD patients, the success rates with statin were 77.8 %, 50.1 %, and 18.6 %, respectively. Atorvastatin showed the highest success rate (77.4 %) if compared to other statins. Only 14 % of physicians were knowledgeable about the NCEP goals.* ***Conclusion*** *: A large number of dyslipidemic patients who were on lipid-lowering therapy were not achieving the recommended LDL-C target levels. Success rates were lower in CHD patients and high risk group. Atorvastatin seemed more effective in lowering the LDL-C to target levels. There are still many physicians in Indonesia who do not aware about the NCEP guidelines and LDL-C treatment goals.* ***(Med J Indones 2001; 10: 103-9)***

Keywords: *lipid treatment assessment project (L-TAP), dyslipidemia, coronary heart disease (CHD) risk, routine practice*

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12 weeks prior to enrollment were excluded, as well as those who had an acute infection that required current antibiotic therapy or a recent or an abrupt change in their usual diet, exercise and body weight within the preceeding month. Women who were pregnant, breast-feeding, or ≤ 6 months post partum were also excluded.

Lipid Profile Determination

Lipid profile information (serum level of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) at baseline and after treatment was taken from individual patients medical record. Initial lipid profile has been used as the basic for the investigators to establish the diagnosis of dyslipidemia and to begin treatment. Lipid profile post-treatment was lipid concentrations after a minimum of 3-months of treatment. Blood samples were sent to Prodia Laboratory for lipid profile measurements. Total cholesterol, HDL-C and triglycerida serum levels were determined by chod-pap enzymatic immuno-assay method using automatic photometer Hitachi equipment. LDL-C was calculated based on Friedewald's formula : LDL-C = total cholesterol - HDL-C - Triglycerida / 4.

Data Analysis

The primary study end-point was the proportion of patients on lipid-lowering therapy who achieved LDL-C target levels as defined by the NCEP guidelines. Treatment was successful if the LDL-C level after treatment reached the NCEP target level or lower.

Descriptive statistic of patients and investigators demographics, lipid profiles and success rates are presented. Analytical statistics was used to compare the success rates among risk groups using *chi-square test* and *analysis of variance (ANOVA).*

RESULTS

Investigators Demographics

One hundred eighty eight out of 400 physicians who were invited has participated in this study. Most of the them were males (74 %) and practiced as general practitioners 67%, internist 15 %, cardiologist 5 %, neurologist 3 % and other specialties 10 %. The mean age was 47.9 years with mean years practice of 23 years. Only 14% of investigators answered the questionnaires correctly which indicated their knowledge on NCEP guidelines.

Patients Demographics

There were 1633 case report forms obtained with complete lipid profile from 13 cities. Because of incomplete data on treatment and patients demographics, 213 forms were excluded from the analysis.

Among 1420 evaluable patients, there were 366 patients in low-risk group, 939 patients in high-risk groups, and 115 CHD patients. As many as 98.4 % of patients received lipid-lowering drugs whereas 1.6 % of patients underwent dietary therapy and exercises only (Table 1)

Table 1. Patient's demographics and treatment

Risk Group	Mean Age (± SD years)	Sex (male)	Number of patients and drugs used				
			Statins	Fibrates	Combination	Non-Drugs	Total
Low-risk	43.1 ± 9.6	51.3 %	293	65	5	3	366
High-risk	52.4 ± 10.1	61.0 %	703	211	7	18	939
CHD	54.3 ± 11.5	59.6 %	86	25	2	2	115
Over-all	50.3 ± 10.9	58.4 %	1082	301	14	23	1420

Low-risk : No CHD, < 2 risk factors, High-risk : No CHD, ≥ 2 risk factors, CHD : Coronary Heart Disease
Success Rate by risk groups

There were 48.8 % of overall patients who reached target LDL-C goals.The mean levels of LDL-C after treatment in patients who reached target goals and those who did not reach target-levels were shown in table 3. The highest success rate was shown in low-risk group (73.0 %), whereas the lowest success rate was found in patients with CHD patients group (14.8%) (Table 2).

The mean levels of LDL-C after treatment among high risk and CHD patients who did not reach target LDL-C were in fact still higher than the level for initiating drug treatment as recommended by NCEP.

Success rate by treatment

Among patients using statins, 55.1 % patients could reach the LDL-C target level. This was the highest if compare to other treatment (Tabel 3).

Tabel 3 shows success rates by treatment and by risk group. More patients who received statin achieved LDL-C target goals compared to other class of lipid lowering drugs for over all patients and for every risk group of patient.

Success rate by risk and by drug among patients who received statin for each individual drug was : 31.0 % for fluvastatin, 35.6 % for lovastatin, 25.5 % for pravastatin, 40.6 % for simvastatin and 77.4 % for atorvastatin.

Table 2. Success rates and Mean LDL-C levels after treatment within risk groups

Risk Category	N	Success rates (%)	Mean LDL-C (mg/dL) after treatment		NCEP recommendation on LDL-C level (mg/dl)	
			Patients Reaching Target Levels	Patients Not Reaching Target Levels	Initiation of drug treatment	Target goal
Low-risk	366	73.0	123.7 ± 24.9 (N = 267)	182.7 ± 24.8 (N = 99)	≥ 190	≤ 160
High-risk	939	43.6	111.6 ± 17.6 (N = 409)	161.9 ± 27.8 (N = 530)	≥ 160	≤ 130
CHD	115	14.8	98.4 ± 28.4 (N = 17)	158.0 ± 44.6 (N = 98)	≥ 130	≤ 100

Low-risk : No CHD, < 2 risk factors, High-risk : No CHD, ≥ 2 risk factors,CHD : Coronary Heart Disease

Table 3. Success rate by treatment

	Statin		Fibrates		Combination		Non-Drugs	
	N	Success (%)	N	Success (%)	N	Success (%)	N	Success (%)
Low-risk	293	228 (77.8)^	65	35 (53.8)^	5	2 (40)	3	2 (66.7)
High-risk	703	352 (50.1)#	211	52 (24.6)#	7	2 (28.6)	18	3 (16.7)
C H D	86	16 (18.6)	25	1 (4.0)	2	0 (0)	2	0 (0)
Overall	1082	596 (55.1)*	301	88 (29.2)*	14	4 (28.6)	23	5 (21.7)

Low-risk : No CHD, < 2 risk factors, High-risk : No CHD, ≥ 2 risk factors,CHD : Coronary Heart Disease
** P < 0.001 (significant), ^ P< 0.001 (significant), # P < 0.001 (significant)*

Table 4. Mean LDL-C levels before and after treatment by treatment groups

Mean LDL-C levels	Statins (N = 1082)	Fibrates (N = 301)	Combination (N = 14)	Non-Drug (N = 23)
Initial (mg/dL)	191 ± 50*	184 ± 37*	183 ± 28	190 ± 42
Post treatment (mg/dL)	137 ± 36^	152 ± 31^	155 ± 24	172 ± 45

** p < 0.05 (significant), ^ p < 0.001 (significant)*

Lipid Profile

Patients who received statins had higher mean baseline LDL-C (191 + 51 mg/dl) as compared to those who were given fibrates (184 ± 37 mg/dl). However, mean LDL-C level after treatment was lower in those treated with statins rather than patients treated with fibrates (137 ± 36 mg/dl vs 152 ± 31 mg/dl)

The difference of initial mean LDL-C values varied among statin group. Initial mean LDL-C value in atorvastatin group was significantly higher than inital mean LDL-C value in simvastatin, lovastatin, and pravastatin, but not in fluvastatin group. After treatment, the mean LDL-C value in atorvastatin group was significantly different from the initial value. This value was also significantly lower than other statins (Tabel 5)

Drug Dosage

It is shown in Tabel 6, that most patients received the initial or low doses of statins. They were treated with atorvastatin 10 mg, pravastatin 20 mg, pravastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, and fluvastatin 40 mg.

Table 5. Mean LDL-C levels before and after treatment within statin groups

Mean LDL-C levels	Fluvastatin (N =58)	Lovastatin (N = 45)	Pravastatin (N = 282)	Simvastatin (N= 133)	Atorvastatin (N = 563)
Initial (mg/dL)	187 ± 57	179 ± 33	187 ± 39	180 ± 38	197 ± 57*
Post treatment (mg/dL)	159 ± 36^	154 ± 30^	160 ± 34^	153 ± 36^	118 ± 27*^

** p < 0.05 (significant), ^ p < 0.001 (significant)*

Table 6. Dosages of statin in the study (N = 1082)

	No data	5 mg	10 mg	20 mg	40 mg	Total
Fluvastatin	2 (1.9 %)		6 (10.2 %)	17 (29.4 %)	34 (58.6 %)	58 (100 %)
Lovastatin	4 (8.9 %)		9 (20.0 %)	26 (57.8 %)	6 (13.3 %)	45 (100 %)
Pravastatin	6 (2.1 %)	2 (0.7 %)	132 (46.8 %)	139 (49.3 %)	3 (1.1 %)	282 (100 %)
Simvastatin	8 (6.0 %)		81 (60.9 %)	25 (18.8 %)		133 (100 %)
Atorvastatin			528 (93.8 %)	35 (6.2 %)		563 (100 %)

DISCUSSION

The NCEP guidelines have defined LDL-C target levels for patients with dyslipidemia in order to reduce the risk of new or recurrent CHD.

Our data has shown that, like in the United States, many dyslipidemic patients failed to reach the NCEP target goals after treatment. The overall success rate in this study was only 48.8 % for all-risk groups. This was higher than the rate of US L-TAP study in 1996, which showed a success rate 38.4 %.[15] Another study in the United States, The Estrogen / Progestin Replacement in postmenopausal women with CHD (HERS) Study, reported that 63 % of patients did not reach LDL-C level below 130 mg/dL and 91 % did not reach LDL-C level below 100 mg/dL. [16] In this current study, 85.1 % CHD patients failed to reach the LDL- target level. This indicates that most patients were still having the risk for cardiovascular events or death especially the high-risk patients.

Our data showed success rates in achieving LDL-C targets by risk group as follow : 73 % for low-risk group, 43.6 % for high risk group and 14.8 % for CHD groups. The success rates in the US L-TAP study were 68 %, 37 % and 18 % for low-risk, high-risk and CHD patient groups respectively. Hoerger et al has found from the National Health and Nutrition Examination Survey III phase 2 that the success rates to reach LDL-C target level were 63 %, 55.4 %, and 17.5 % for low-risk, high-risk and CHD patient groups respectively.[17] In line with the US-studies mentioned above, our study has shown that the more the cardivascular risks they had, the lower the likehood of dyslipidemic patients reaching the LDL-C target levels.

In this study, 76 % of patients received statins, 21 % fibrates, 1 % combination drugs and the remaining 2% non-pharmacological therapy. It is clearly shown that most physicians prescribed statins as their preffered lipid-lowering drug. Unfortunately most of the patients received low dose or the starting dose recommended for each statin did not receive the dosage frequently used in clinical trails. The mean LDL-C levels after treatment in patients who did not reach LDL-C targets, was even higher than the recommended level to start therapy. The means of LDL-C level after treatment in high-risk group and CHD patients were 162 mg/dL and 158 mg/dL respectively. This clearly showed that their initial LDL-C levels were high. Cullen et al stated that a "log-linear" correlation exists between statin dosage or more-effective statin is needed to lower cholesterol level adequately in high-risk patients compared to the low-risk patients.[18]

The efficacy of statin therapy in both primary and secondary prevention reducing CHD mortality and other CHD events has been established by some mega trials. In this study, there were significantly more patients treated with statins who reached LDL-C target goals compared to patients treated with fibrates. It is not surprising since statins has been known to be more effective than fibrates in lowering toato cholesterol and LDL-C level, whereas fibrates were more effective in lowering triglyceride and increasing HDL-C level. In NCEP and European Atherosclerosis Society (EAS) recommendations, it was suggested to use fibrates in hypertriglyceridemic patients.[10]

In the present study, 1082 patients received HMG CoA-reductase inhibitor monotherapy, which included various doses of fluvastatin, lovastatin, pravastatin, simvastatin and atorvastatin. The success rate of atorvastatin was significantly higher than other statins, whereas in the US L-TAP study, simvastatin was the most effective drug (atorvastatin was not commercially availabel at that time). In the US L-TAP study, the success rates were 15.3 % for fluvastatin, 22 % for lovastatin, 24.4 % for pravastatin and 38.3 % for simvastatin.Hunninghake prospectively compared 344 patients without CHD who were treated with various statins and found that the success rates at week-12 were 16 % for fluvastatin, 34 % for lovastatin, 41 % for simvastatin and 71 % for atorvastatin.[19] In our study, success rates for atorvastatin was 93.4 % in low-risk patients, and 76.5% in high-risk patients. Both were statistically significant to other statins. In CHD patients, success rate for atorvastatin was 31 % only, but there was no significant differences to other statins. This might be due to small number of patients in this group. In the United States, Brown studied 318 patients with CHD and compared the results prospectively among statin groups. In week-12, the success rate of atorvastatin to reach LDL-C target level was 32 %. This was significantly higher than fluvastatin (1 %) and lovastatin (12 %), but not significantly higher than simvastatin (22 %).

Only 14 % of physicians who participated in this study indicated that they were aware of NCEP guidelines. This percentage is much lower than investigators awareness in th US L-TAP study which

was 95 %. Contradictory, the overall success rate in achieving the LDL-C targets is higher in Indonesia than in the United States (48.8 % vs 38 %), this may be due to the fact that many patients in this study (39%) received atorvastatin while no patient received atorvastatin in the US L-TAP study.

The results of this survey as presented here do not meet the classical criteria of a randomized, controlled clinical trial. Hence, no comparison can be made on the efficacy of different drugs used on this survey. However, this study mimics the real-life situation and provides information about practice of physicians in treating dyslipidemia.

In conclusion, this study revealed that the majority of dyslipidemic patients treated in routine clinical practice did not reach the NCEP target goals. The success rates were even lower in high risk patients and lowest in CHD patients. This was probably due to the lack of the understanding of the treating physicians with regard to the NCEP/PERKI guidelines and to the in adequate dosages of lipid modification drugs used in this survey.

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