Drug Treatment of Hypercholesterolaemia

J C Tay,* *MBBS, MRCP (UK)*, Y C Chee,** *FAMS, FRCP (Lond), FRACP*

Abstract

We review the current drug treatment of hyperlipidaemia at our specialist out-patient clinics between October 1995 and December 1995. During this period, 523 patients received one or more lipid-lowering drugs. Each patient was assessed for his vascular risk, the number of lipid measurements before and after treatment and the type, duration and outcome of drug treatment. Only 30% patients achieved the low-density lipoprotein cholesterol (LDL-C) targets recommended by the National Cholesterol Education Program II: 14%, 37% and 71% of the high, moderate and low risk patients achieved the targets respectively. Most patients (62.7%) were treated after only one lipid measurement and less than 50% of patients had a post-treatment lipid measurement within 3 months. Although the majority of patients did not achieve the recommended LDL-C targets, their LDL-C was significantly reduced by 20%. A greater reduction of LDL-C (32%) was achieved by simvastatin monotherapy.

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Key words: Cholesterol targets, Coronary heart disease, Lipid lowering drugs, Vascular risks

Introduction

Serum cholesterol has been established as a major risk factor for coronary heart disease (CHD). There is a linear association between serum cholesterol level and CHD mortality and morbidity. Cholesterol-lowering therapy has been shown to reduce CHD mortality and morbidity in primary and secondary prevention trials.[1-3] However in view of the cost, side effects and long-term safety of drug treatment, it is recommended to start drug therapy after adequate and careful assessment before committing patients to long-term or life-long therapy. Despite numerous guidelines[4-6] published to assist physicians in their management, studies have shown that many eligible patients were not treated for hypercholesterolaemia[7-10] and in those who were treated with lipid-lowering drugs, many were inadequately treated to achieve the recommended target levels.[9-12]

The purpose of the study was to assess the current clinical practice and compare with the guidelines provided by the National Cholesterol Education Program (NCEP) (Adult Treatment Panel II).[4] The NCEP II guidelines are widely accepted algorithm for current management of dyslipidaemia and recent studies[9-12] have used the guidelines to assess clinical practice and adherence to the recommendations.

Patients and Methods

Patients who received lipid-lowering drugs for hyperlipidaemia at our specialist out-patient clinics between the period from October 1995 to December 1995 were selected from the hospital records. The lipid-lowering agents were gemfibrozil, bezafibrate, cholestyramine, nicotinic acid and simvastatin. These agents were available in the hospital formulary and were the most commonly prescribed lipid-lowering drugs.

Patients were assessed and stratified according to their risk status. Patients were considered high risk if they had a prior vascular event i.e. a definite myocardial infarction, stroke or peripheral arterial disease. Those without evidence of CHD but had two or more risk factors were considered moderate risk. Low risk patients were those without CHD and with less than two risk factors. The positive risk factors were:

1) male above the age of 45 years and female above the age of 55 years,
2) family history of premature coronary heart disease,
3) hypertension,
4) diabetes mellitus,
5) low high-density lipoprotein cholesterol (HDL-C) (<0.9 mmol/L), and
6) current cigarette smoking.

The negative risk factor was a high HDL-C (>1.6 mmol/L).[4]

The type and duration of drug treatment, the number of lipid measurements before and after drug treatment,

* *Registrar*
** *Head and Senior Consultant*
Department of General Medicine
Tan Tock Seng Hospital
Address for Reprints: Dr J C Tay, Department of General Medicine, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433.

and the outcome of each patient were recorded and compared to the NCEP II guidelines. Patients whose treatment was started before October 1995 were analysed retrospectively. Patients treated for at least 3 months and had at least one post-treatment low-density lipoprotein cholesterol (LDL-C) level were analysed for achieving the recommended targets according to their risks. The NCEP II recommended targets were LDL-C <2.6 mmol/L, <3.4 mmol/L and <4.1 mmol/L for high, moderate and low risk patients respectively. A subgroup of patients who started treatment between January 1994 and October 1995, who were treated for at least 3 months and who had pre- and post-treatment lipid measurements, were analysed for lipid changes before and after treatment. These patients were stratified according to their risks, type of treatment and duration of treatment. The lipid measurements included total cholesterol (TC), HDL-C, triglyceride (TG) and calculated LDL-C.

Comparison of the changes in the lipid levels before and after treatment was performed using paired Student's *t*-test. Analysis of covariance was performed to compare the effects of simvastatin and gemfibrozil on percent change from baseline (pre-treatment) between the two different treatment groups and in the three different treatment duration groups, and to compare the LDL-C percent change from baseline in the three risk groups. The pre-treatment lipid levels were included as a covariate. Differences between simvastatin and gemfibrozil treatment in high risk patients in achieving the goal LDL-C were determined by using Chi-square procedure.

Patients whose drug treatment was started between October and December 1995 were followed up prospectively over 1 year to assess the outcome of their clinical management at the specialist out-patient clinics. No attempt was made to modify the lipid management during the study.

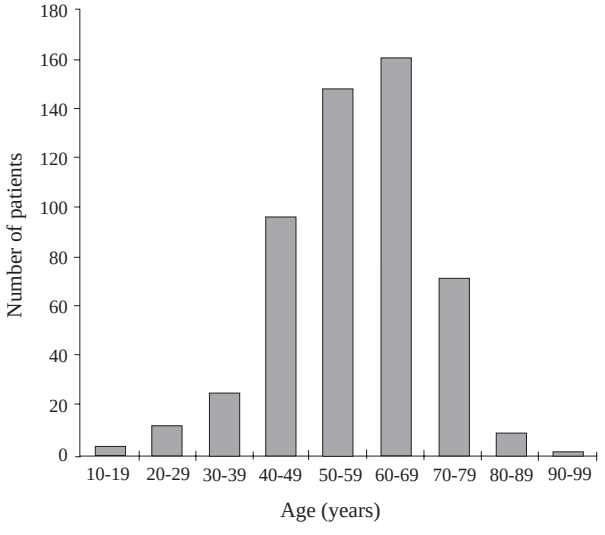

Fig. 1. Distribution of patients by age.

Results

During the period from October 1995 to December 1995, a total of 523 patients were treated with one or more antihyperlipidaemic drugs. There were 287 (54.9%) males and 236 (45.1%) females. There were 72.1% Chinese, 8.8% Malays, 14.9% Indians and 4.2% Others. The distribution of patients according to age is shown in Figure 1. The mean age was 57.4 years. A summary of the various lipid-lowering drugs is shown in Table I.

There were 463 patients treated before October 1995. The results of those who were analysed for achieving the targets are shown in Table II. There were 121 patients (26%) who were not analysed because of no LDL-C levels or LDL-C levels were done within 3 months of treatment. Analysis of percent changes in the lipid levels was done in 189 patients who had treatment started between January 1994 and October 1995 and had pre- and post-treatment lipid levels including LDL-C. The results are shown in Tables III to V and Figures 2 and 3.

There was a significant reduction in overall TC, TG and LDL-C by 18%, 13% and 20% respectively. HDL-C was elevated by about 6% but the result was not statistically significant. Simvastatin reduced TC and LDL-C significantly more than gemfibrozil (23% versus 11% and 32% versus 3% respectively), whereas a greater reduction of TG was achieved with gemfibrozil (42%

TABLE I: LIPID-LOWERING DRUGS

Drugs	No.	%
Simvastatin	264	50.5
Gemfibrozil	212	40.5
Nicotinic acid	15	2.9
Bezafibrate	12	2.3
Cholestyramine	2	0.4
Combined	18	3.4
Total	523	100

TABLE II: NUMBER AND PERCENTAGE OF PATIENTS ACHIEVING RECOMMENDED TARGETS ACCORDING TO RISKS

Risk		No. achieving target	Total no.	% achieving target
High	Total	28	200	14
	Simvastatin	21	106	20
	Gemfibrozil	5	67	7*
Moderate		29	79	37
Low		45	63	71
Total		102	342	30

* Significantly different from simvastatin group, P <0.05.

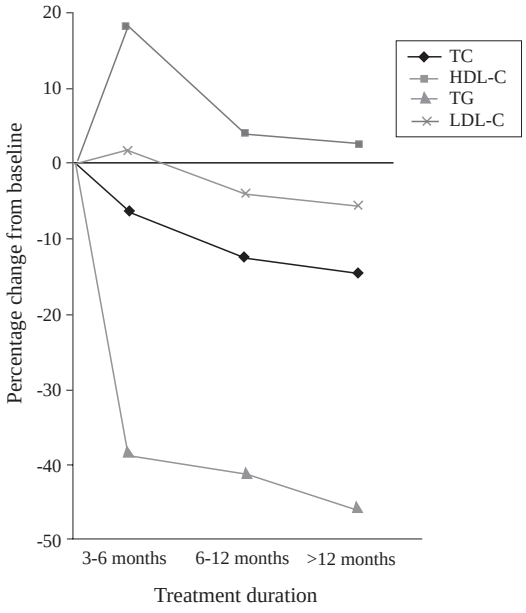

Fig. 2. Percentage change of TC, HDL-C, TG and LDL-C from baseline in 3 different gemfibrozil treatment duration groups.

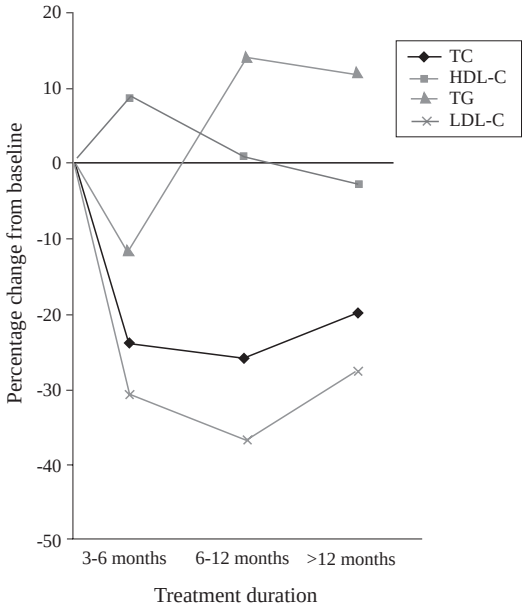

Fig. 3. Percentage change of TC, HDL-C, TG and LDL-C from baseline in 3 different simvastatin treatment duration groups.

TABLE III: EFFECT OF DRUG TREATMENT ON SERUM LIPIDS

	Overall	Simvastatin	Gemfibrozil
No. of patients	189	94	65
Duration of treatment (months)	10.6 ± 5.6	10.3 ± 5.3	10.6 ± 5.5
TC			
Pre	6.99 ± 1.23	7.15 ± 1.19	6.68 ± 1.07
Post	5.67 ± 1.10	5.46 ± 1.06	5.88 ± 1.09
% change	-17.7 ± 16.1*	-23.1 ± 13.1*	-11.1 ± 14.6*†
HDL-C			
Pre	1.19 ± 0.39	1.29 ± 0.39	1.05 ± 0.36
Post	1.22 ± 0.37	1.28 ± 0.32	1.10 ± 0.27
% change	6.0 ± 24.2	2.3 ± 20.6	8.8 ± 23.4
TG			
Pre	2.30 ± 0.97	1.84 ± 0.73	3.01 ± 0.90
Post	1.76 ± 0.86	1.78 ± 0.85	1.66 ± 0.78
% change	-13.3 ± 49.9*	4.9 ± 52.3	-41.5 ± 26.8*†
LDL-C			
Pre	4.75 ± 1.17	5.02 ± 1.11	4.27 ± 0.96
Post	3.66 ± 0.99	3.39 ± 0.94	4.03 ± 0.99
% change	-19.6 ± 26.3*	-31.5 ± 17.1*	-3.1 ± 23.2†

All lipid measurements were in mmol/l.
Results expressed as mean ± SD.
Pre and post referred to before and after drug treatment respectively.
% change referred to the percentage change in the lipid measurement after treatment.
* Significantly different from pre-treatment, P <0.05.
†Significantly different from simvastatin group, P <0.05.

TABLE IV: PERCENT CHANGE OF LDL-C IN DIFFERENT RISK GROUPS

	High risk	Moderate risk	Low risk
No. of patients	112	43	34
LDL-C			
Pre	4.81 ± 1.07	4.51 ± 1.10	4.86 ± 1.49
Post	3.65 ± 1.08	3.68 ± 0.90	3.67 ± 0.79
% change	-21.5 ± 26.1	-14.0 ± 29.5	-20.3 ± 22.1

All lipid measurements were in mmol/l.
Results expressed as mean ± SD.
Pre and post referred to before and after drug treatment respectively.
% change referred to the percentage change in LDL-C after treatment.

versus 5%). Among the three risk groups, LDL-C was reduced by an average of 14% to 22%. There were no significant differences in their pre-treatment and percent reduction of LDL-C among the three groups. Among the different treatment duration groups, most lipid changes occurred within the first 3 to 6 months. A greater reduction in LDL-C was seen in the simvastatin group treated from 7 to 12 months than those treated for more than 12 months (37% versus 27%). The other lipid changes were not statistically significant among the three different treatment duration groups.

Analysis of adherence to the guidelines in initiation of treatment and monitoring of lipid levels after treatment was done in 158 patients. About 63% of patients were treated based on a single lipid measurement and another 22% were treated after two lipid results. About 50%, 61% and 68% of patients were treated within 1, 3 and 6 months after their first lipid measurement respectively. After treatment, only 11% and 47% had lipid measurements within 6 weeks and 3 months respectively, and only 39% of high risk, 53% of moderate risk and 67% of low risk patients had a lipid measurement

TABLE V: EFFECT OF DRUG TREATMENT IN DIFFERENT TREATMENT DURATION GROUPS

	Simvastatin			Gemfibrozil		
Duration group (months)	3-6	7-12	>12	3-6	7-12	>12
Mean duration of treatment (months)	4.3	9.7	16.3	4.5	9.8	17.0
No. of patients	30	31	33	20	23	22
Percent change (%)						
TC	-24	-26	-20	-6	-12	-14
HDL-C	9	1	-3	18	5	4
TG	-11	14	12	-38	-41	-46
LDL-C	-31	-37	-27*	1	-4	-6

* Significantly different from 7-12 months treatment group, $P < 0.05$.

within 3 months of treatment. Up to 27% of patients had no follow-up lipid measurements within 6 months of treatment.

Sixty patients started treatment during the period from October 1995 to December 1995 and were followed up for 1 year. There were 29 males and 31 females. Forty-two patients (70%) were treated based on a single lipid measurement and 2 patients were treated without any documented results. After treatment, 28 patients (47%) had no follow-up measurements. Of the 32 patients with follow-up measurements, 31 patients (97%) had no measurements within 6 weeks and only 12 patients (38%) had measurements within 3 months. Nine patients were discharged and 5 patients defaulted follow-up after starting treatment. Of the 46 patients who were on follow-up after starting treatment, 10 patients were subsequently discharged after a mean follow-up of 6.2 months and another 10 defaulted after a mean follow-up of 6.7 months. Of the 10 defaulters, only one low-risk patient achieved the target. None of the 10 discharged patients achieved the recommended targets (8 high risk, 1 moderate risk, 1 low risk). Of these 20 discharged and defaulted patients 9 had no follow-up measurements. Twenty-six patients (43%) were still on follow up as at the end of 1996. Five patients had no follow-up measurements and drug treatment was stopped in 2 patients. Nineteen patients (7 high risk, 7 moderate risk and 5 low risk) were treated for a mean duration of 13.5 months. Only 5 patients (26%) (1 high risk, 3 moderate risk and 1 low risk) achieved the recommended targets.

Discussion

Our study shows that drug treatment for hyperlipidaemia is most frequently given to those in the 50 to 69 years age group. However, the ages of patients on drug treatment can range from as young as 12 years old to as old as 90 years old. In our study 15.5% of patients were above the age of 70 years and 7.5% were below the age of 40 years. Drug treatment in the elderly is still controversial as most major large-scale studies were done in high risk middle-age patients.[1-3] There was slightly more men (54.9%) than women (45.1%) and a higher percentage of Indians (14.9%) and less Malays (8.8%) on drug treatment. This is interesting as most previous studies have shown that females are generally undertreated with lipid-lowering drugs.[10-12] Both simvastatin and gemfibrozil were most frequently used accounting to about 91% of drugs used.

Our study shows that only a small minority of patients (30%) on lipid-lowering drugs achieved the targets recommended by the NCEP II especially the high risk group (14%) despite the fact that the guideline was published in 1993. The success in the prospective group was even lower (26%). The finding is consistent with recent studies which generally show less than one-third to half of their patients and one-quarter to one-third of their high-risk patients achieve the recommended goals.[10-13] Furthermore, many patients were not adequately assessed and given a trial of diet therapy before starting drug treatment. Many of them (63%) were treated based on just a single lipid measurement and drug treatment was started as soon as the results were available. Furthermore, patients on drug therapy were not carefully monitored. There was minimal documentation of compliance to the drugs or diet. More than 50% of patients did not have a follow-up measurement within 2 to 3 months after starting treatment. Poor adherence to the guidelines in monitoring efficacy and toxicity of drug treatment is also reflected in recent studies.[10,11]

There are many reasons for not achieving the targets. Firstly, there is a failure to use the appropriate type and dose of lipid-lowering drugs. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are presently the most effective drugs in reducing cholesterol levels. Bile acid sequestrants (resins) and nicotinic acid lower cholesterol levels moderately while fibrates are considered to have only a mild effect on cholesterol lowering.[4] In clinical trials during which the administration of drugs is tightly controlled, monitored and titrated to the optimal dose, a reduction of 25% to 60% of LDL-C can be achieved by using statins as monotherapy.[1-3,14] However, in clinical practice, the results are often less impressive, partly because of failure to titrate the dosage and of non-compliance to treatment and dietary control. In our study, we find that there was an overall significant 20% LDL-C reduction. A greater reduction (32%) of LDL-C was seen in patients taking simvastatin monotherapy. Patients taking gemfibrozil had a non-significant reduction of LDL-C of only 3%. As expected, in the high risk group, a higher percentage of patients on simvastatin achieved the LDL-C target than those on gemfibrozil (20% versus 7%). Despite the poor reduction of LDL-C with gemfibrozil, a large proportion of our patients (40.5%) were treated with this medication as a

result of its low cost. In patients who were treated with simvastatin, the drug was not adjusted to the maximal dose in most of them. The majority were only on 5mg of simvastatin. Even then, a remarkable 32% reduction of LDL-C was achieved with simvastatin monotherapy.

Although the duration of treatment plays a role in cholesterol lowering, optimal reduction is usually achieved within 6 weeks of treatment and monitoring of efficacy and response can usually be performed within 6 weeks and 3 months of treatment.[4] In our study, we find that most lipid changes were seen in the first 3 to 6 months. A longer treatment duration produced only slight changes in the lipid levels. The failure to produce a greater cholesterol lowering with longer duration of treatment highlights the lack of drug and dosage titration to obtain an optimal response. In fact the higher LDL-C seen in those treated with simvastatin for more than 12 months may be related to noncompliance to drug or dietary treatment.

Secondly, baseline lipid levels are an important predictor of achieving target.[12] About 75% of those with baseline LDL-C ≤3.4 mmol/L and less than 50% of those >3.4 mmol/L achieve the target levels.[12] The recent NCEP II guidelines based on recent studies on CHD morbidity and mortality recommend a more aggressive lowering of LDL-C to <2.6 mmol/L in secondary prevention. Thus, as expected, less patients in the high risk group will achieve the target compared to those with mild to moderate risk.[11] In our study, we find that the pre-treatment LDL-C was rather high with a mean of 4.75 mmol/L. This is comparable to the Western population. The pre-treatment LDL-C was similar in the three risk groups. After treatment, an average 20% reduction of LDL-C was achieved. Post-treatment LDL-C was also comparable in the three risk groups. Although different LDL-C targets were set for the different risk groups, we find that the percent reduction in LDL-C was similar in the three groups implicating that all patients with different risks were treated similarly to the same extent when they were on lipid lowering medication. Therefore, if LDL-C is reduced to the same extent, then a greater percentage of low risk patients will reach the less stringent LDL-C target and conversely, less high risk patients will achieve the lower LDL-C target. In our high risk group, an average 43% reduction of LDL-C was required to achieve the target of <2.6 mmol/L. Therefore a more aggressive approach in this high-risk group of patients is needed to achieve the goal and to prevent future CHD morbidity and mortality. In clinical trials using statin as monotherapy, participants achieved 32% to 38% lowering in the mean LDL-cholesterol level.[1,3] In our study, we find that patients on simvastatin had an average of 32% reduction in LDL-C. This is consistent with other clinical practice.[12] However such reduction of LDL-C is often not adequate for most high-risk patients who have high baseline LDL-C levels. They often require >45% reduction of LDL-C to achieve the target.[10-12] A greater LDL-C reduction may be achieved by drug combination and newer statins such as atorvastatin.[14-17] Combination drug therapy has been recommended if single agents fail to achieve LDL-C targets.[4,12]

Thirdly, patient compliance to long-term drug and dietary therapy can have a significant impact in achieving the goals. Dietary and drug compliance is often not well documented in many studies. Even in a tertiary centre with a multidisciplinary team approach, a noncompliant rate of 31% can be seen.[11] In our study we find that a significant number of patients were lost on one-year follow-up. Even in those who were on follow-up, documentation of ensuring compliance was often lacking. It is a well-known fact that most of our local patients are not keen on long-term Western drugs and are poorly motivated to change their dietary habits. Although dietary restriction is important in lowering cholesterol, studies have shown that unless there is an intensive counselling, the reduction of cholesterol by dietary therapy is quite modest.[18] Drug therapy is effective but it is also expensive and not without side effects. Patient education is essential in ensuring compliance particularly if physicians are considering initiating long-term drug therapy. More studies are needed to assess drug and dietary compliance in achieving the recommended goals and whether a multidisciplinary team approach such as a lipid clinic will improve drug compliance and outcome of treatment.[19]

Recent reviews have indicated that a 1 percentage reduction in total cholesterol is accompanied by a 2 to 3 percentage reduction in the risk of coronary disease. Thus, based on our study, we can estimate that most patients may achieve a CHD risk reduction of about 30% to 60%. However, a greater reduction in LDL-C and a greater percentage of our high risk patients may achieve the target of less than 2.6 mmol/L by using statins or even drug combination in optimal doses. Patient education and compliance to treatment and dietary modification will help maintain a long-term cholesterol lowering.

Our results may not be generalizable to other settings with different types of patients, treatment protocols and different lipid goals. Nevertheless, recent studies have also reported on poor adherence to the guidelines and target rate even in a multidisciplinary lipid clinic.[10-12] Thus, there is a need to review our current lipid management strategy to improve treatment especially in high risk patients if we are to reduce future cardiovascular morbidity and mortality significantly. Besides initiating drug treatment, physicians should also ensure drug compliance and adhere to the recommended guidelines.

Conclusion

At the time of study, most patients with hyperlipidae-

mia were treated with drugs based on a single lipid measurement without adequate dietary advice. Follow-up measurements after treatment were often inadequate and compliance to drugs and diet was often not ensured. Furthermore, patients were often discharged (32%) without achieving targets and there was a high rate of defaulters (25%). Although the majority of patients (70%) did not achieve the recommended LDL-C targets, the treated group had a significantly lower TC, LDL-C and TG. This is often evident as early as 3 to 6 months after therapy. A greater reduction of LDL-C may be achieved with a statin or drug combination.

Drug therapy for hyperlipidaemia is effective. However, it should not be taken lightly in view of the potential side effects and the cost of long-term treatment. Patients should be adequately assessed and given a trial of dietary therapy before committing them to long-term drug therapy. In view of the poor achievement of the targets set by NCEP II, we should review our current lipid management strategy in order to maximize the cost-effectiveness of drug therapy. Local guidelines in lipid management would certainly help our doctors to better manage hyperlipidaemic patients.

REFERENCES

1. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383-9.
2. Shepherd J, Cobbe S M, Ford I, Isles C G, Lorimer A R, MacFarlane P W, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333:1301-7.
3. Sacks F M, Pfeffer M A, Moye L A, Rouleau J L, Rutherford J D, Cole T G, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335:1001-9.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 1993; 269:3015-22.
5. Betteridge D J, Dodson P M, Durrington P N, Hughes E A, Laker M F, Nicholls D P, et al. Management of hyperlipidaemia: guidelines of the British Hyperlipidaemia Association. Postgrad Med J 1993; 69:359-69.
6. Pyorala K, Backer G D, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J 1994; 15:1300-31.
7. Schrott H G, Bittner V, Vittinghoff E, Herrington D M, Hulley S. Adherence to National Cholesterol Education Program Treatment Goals in Postmenopausal Women with Heart Disease. JAMA 1997; 227:1281-6.
8. Cohen M V, Byrne M J, Levine B, Gutowski T, Adelson R. Low rate of treatment of hypercholesterolemia by cardiologists in patients with suspected and proven coronary artery disease. Circulation 1991; 83:1294-304.
9. Hoerger T J, Bala M V, Bray J W, Wilcosky T C, LaRosa J. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. Am J Cardiol 1998; 82:61-5.
10. Danias P G, O'Mahony S, Radford M J, Korman L, Silvermn D I. Serum cholesterol levels are underevaluated and undertreated. Am J Cardiol 1998; 81:1353-6.
11. Marcelino J J, Feingold K R. Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. Am J Med 1996; 100:605-10.
12. Schectman G, Hiatt J. Drug therapy for hypercholesterolemia in patients with cardiovascular disease: factors limiting achievement of lipid goals. Am J Med 1996; 100:197-204.
13. Kellick K A, Burns K, McAndrew E, Haberl E, Hook N, Ellis A. Outcome monitoring of fluvastatin in a department of veterans affairs lipid clinic. Am J Cardiol 1995; 76:62A-4A
14. Nawrocki J W, Weiss S R, Davidson M H, Sprecher D L, Schwartz S L, Lupien P J, et al. Reduction of LDL-cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. Arterioscler Thromb Vasc Biol 1995; 15:678-82.
15. Cashin-Hemphill L, Mack W J, Pogoda J M, Sanmarco M E, Azen S P, Blankenhorn D H. Beneficial effects of colestipol-niacin on coronary atherosclerosis: a 4-year follow-up. JAMA 1990; 264:3013-7.
16. Schrott H G, Stein E A, Dujovne C A, Davidson M H, Goris G B, Oliphant T H, et al. Enhanced low-density lipoprotein cholesterol reduction and cost-effectiveness by low dose colestipol plus lovastatin combination therapy. Am J Cardiol 1994; 75:34-9.
17. Pasternak R C, Brown L E, Stone P H, Silverman D I, Gibson C M, Sacks F M. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. Ann Intern Med 1996; 125:529-40.
18. Hunninghake D B, Stein E A, Dujovne C A, Harris W S, Feldman E B, Miller V T, et al. The efficacy of intensive dietary therapy alone or combined with lovastatin in outpatients with hypercholesterolemia. N Engl J Med 1993; 328:1214-9.
19. Harris D E, Record N B, Gipson G W, Pearson T A. Lipid lowering in a multidisciplinary clinic compared with primary physician management. Am J Cardiol 1998; 81:929-33.