Atorvastatin in Low-Density Lipoprotein Apheresis-Treated Patients With Homozygous and Heterozygous Familial Hypercholesterolemia

Andreas Goldammer, Stefanie Wiltschnig, Gottfried Heinz, Martin Jansen, Thomas Stulnig, Walter H. Hörl, and Kurt Derfler

To further reduce low-density lipoprotein-cholesterol (LDL-C), atorvastatin treatment was investigated in patients with homozygous (n = 4) and heterozygous (n = 10) familial hypercholesterolemia (FH) undergoing LDL-apheresis. After a wash-out period of 4 weeks, atorvastatin therapy was administered in escalating doses (10 up to 80 mg/d). LDL-apheresis was performed at weekly intervals during the entire study period. The LDL-C concentration decreased from 240 ± 35 mg/dL after the wash-out period to 206 ± 63 mg/dL during treatment with 10 mg atorvastatin. Four weeks of treatment with 80 mg atorvastatin resulted in an additional 24% ($P < .05$) reduction in LDL-C. LDL-C increased from 28.8 ± 14.2 mg/dL immediately after apheresis to 156.6 ± 25.5 mg/dL at day 7. LDL-C values remained below the recommended target range for an extended duration of 48 hours in atorvastatin-treated patients, but not in those without concomitant lipid-lowering drug therapy. The levels of high-density lipoprotein-cholesterol (HDL-C) and plasma fibrinogen were unchanged during the entire study period. No adverse events were observed with atorvastatin treatment. Finally, high-dose atorvastatin therapy resulted in a 40% reduction in LDL-apheresis sessions in these patients. Our results show that LDL-C reduction by atorvastatin is a safe and effective therapy in LDL-apheresis patients with severe heterozygous or homozygous FH.

IN AN EFFORT TO reduce markedly elevated low-density lipoprotein-cholesterol (LDL-C) levels, LDL-apheresis is combined with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors.[1-7] In patients with homozygous familial hypercholesterolemia (FH), lovastatin, pravastatin, or simvastatin reduces LDL-C only by an additional 11.5% to 16% over the values achieved with LDL-apheresis alone.[2,8-10] In patients with serious heterozygous FH, an inadequate response to conventional lipid-lowering therapy requires combined treatment with LDL-apheresis to prevent progression of atherosclerotic vascular disease.[2,5,6] Even in LDL-apheresis patients, drugs with enhanced lipid-lowering capacity are needed to achieve target LDL-C values of less than 100 mg/dL.[2,4,5,6,8,11,12]

Atorvastatin, a synthetic and enantiomerically pure compound HMG-CoA reductase inhibitor, has been proven to suppress hepatic cholesterol synthesis. This effect is dose dependent, resulting in a reduction of LDL-C levels between 41% and 61%.[13-16] Thus, atorvastatin provides the highest reduction rate in LDL-C and triglycerides as compared with other available statins at the currently approved dosage.[13,15,16]

The effect of atorvastatin therapy in FH patients treated by LDL-apheresis is still a matter of dispute.[7,12,17] In a prospectively designed study, we examined the efficacy and safety of atorvastatin at a daily dose of 10 mg, 20 mg, 40 mg, 60 mg, or 80 mg in FH patients treated with LDL-apheresis. These effects were compared with the same patients treated with 40 mg of simvastatin/day (n = 13) or gemfibrozil (n = 1), as well as to the values obtained during the wash-out period. The effect of lipid-lowering drug therapy on the frequency of apheresis sessions and the associated health-care costs were also evaluated.

From the Divisions of Nephrology and Dialysis, Apheresis Unit and Endocrinology, Department of Medicine III, and the Division of Cardiology, Department of Medicine II, University Hospital, Vienna, Austria.

Submitted June 25, 2001; accepted February 23, 2002.

Address reprint requests to Kurt Derfler, MD, Department of Medicine III, Division of Nephrology and Dialysis, Apheresis Unit, Währinger Gürtel 18-20, A-1090 Vienna, Austria.

0026-0495/02/5108-0005$35.00/0
doi:10.1053/meta.2002.34016

MATERIALS AND METHODS

Patients

All study patients (n = 14) were maintained on long-term LDL-apheresis at weekly intervals (Immunoadsorption; LDL-Therasorb, Plasma-Select, Teterow, Germany) for treatment of homozygous (n = 4) or severe heterozygous (n = 10) FH. The clinical characteristics of these patients are summarized in Table 1. The mean lipoprotein levels prior to LDL-apheresis treatment were as follows: total cholesterol (TC) 341 ± 74 mg/dL, LDL-C 264 ± 65 mg/dL, high-density lipoprotein-cholesterol (HDL-C) 36 ± 13 mg/dL, and triglycerides 206 ± 118 mg/dL. Thirteen patients suffered from cardiovascular disease, 5 had a history of myocardial infarction, 5 required percutaneous transluminal coronary angioplasty (PTCA), and 8 underwent coronary artery bypass graft surgery.

Thirteen patients were on simvastatin treatment (40 mg/d) before inclusion into the study (Table 2). One patient was on gemfibrozil medication due to myositis (creatine phosphokinase > 300 U/L) and gastrointestinal side effects during lovastatin and simvastatin therapy. The LDL-C level of this patient was 177 ± 18 mg/dL with gemfibrozil and LDL-apheresis therapy.

All patients were switched to atorvastatin. Patients were excluded from the study if they had significant liver, renal (nephrotic syndrome) or endocrine disease (hypothyroidism, diabetes mellitus), uncontrolled hypertension, risk of conception, poor compliance during the former treatment period, as well as acute myocardial infarction, coronary angioplasty, coronary artery bypass grafting, or unstable angina pectoris during the last 3 months before investigation. All subjects had been on the Step 1 diet according to the US National Cholesterol Education Program (NCEP) and continued their dietary restrictions throughout the study period.[18]

Study Design

The study protocol was approved by the local ethical committee. All 14 patients treated by LDL-apheresis in our unit were included in the study after informed consent was obtained.

Table 1. Patient Characteristics at Study Entry

Patients	N = 14
Age (yr)	48 ± 14 (18-69)*
Sex	F: n = 4
	M: n = 10
BMI (kg/m^2)	24 ± 2.6 (19-25)*
Coronary artery disease	n = 13 (93%)
Peripheral arterial disease (stage I to II)	n = 12 (86%)
Cerebrovascular disease	n = 12 (86%)
No. of LDL-apheresis treatments at study entry	187 ± 87 (29-290)*
Duration of LDL-apheresis therapy at study entry (mo)	48 ± 28 (6-89)*
Desorbed plasma volume/LDL-apheresis session (mL)	5,710 ± 490 (5,500-6,000)*

Abbreviations: BMI, body mass index; FH, familial hypercholesterolemia

*Range.

All patients discontinued their lipid-lowering drugs for 4 weeks (wash-out period), whereas LDL-apheresis was continued at weekly intervals. During the fourth week, the increase in postapheresis lipoprotein level was evaluated daily until the next LDL-apheresis procedure. Thereafter, all patients were placed on a standardized regimen of atorvastatin. The starting daily dose of 10 mg was increased every 4 weeks to 20, 40, 60, or 80 mg. At the end of the study period (all patients on 80 mg atorvastatin for 4 weeks), the postapheresis changes in lipoproteins were again evaluated (Table 2).

Lipoprotein values were obtained at the end of the wash-out period and at weeks 4, 8, 12, 16, and 20 according to the dose escalation of atorvastatin.

Depending on the individual LDL-C levels achieved at the end of the study period (4 weeks on 80 mg of atorvastatin), LDL-apheresis was reduced or even terminated if LDL-C values remained at the recommended target value (<100 mg/dL) for secondary prevention of coronary artery disease (CAD).

Safety measures. Adverse events were recorded weekly at each LDL-apheresis treatment. Patients were asked for adverse events, such as constipation, flatulence, dyspepsia, abdominal pain, or myalgia. Symptoms were rated as definitely, probably, or not drug related. Aspartate aminotransaminase (AST), alanine aminotransferase (ALT), and creatine phosphokinase levels were also measured.

LDL-Immunoadsorption Apheresis

For the entire study period, LDL-apheresis treatments were scheduled at weekly intervals. The detailed procedure of LDL-immunoadsorption has been recently described.[5,19]

Peripheral venous blood was drawn from an antecubital vein at a flow rate of 50 to 80 mL/min. For primary plasma separation, the Autopheresis-C therapeutic plasma system (TPS; Baxter, Deerfield, IL) was used. Standard sodium heparin at a rate of 1,000 U/h and acid citrate dextrose (ACD) (formula A; Baxter, Munich, Germany) at a volume ratio of 1:20 (5%) to whole blood were added for anticoagulation. LDL-Therasorb columns (Therasorb, Munich, Germany) were used for the removal of LDL-particles. A total of 6 cycles (1,000 mL plasma each) were performed at each treatment session.

Laboratory Methods

Lipoproteins were separated by microsample ultracentrifugation at density 1.006 g/mL. The top layer containing very–low-density lipoprotein (VLDL) was removed from the subnatant covering LDL and HDL by cutting with a tube slicer. Total cholesterol and triglycerides were determined enzymatically in the whole serum, as well as in the lipoprotein fractions using a commercial kit (Roche, Mannheim, Germany). HDL-C was quantified using polyethylene glycol modified enzymes (Roche). LDL-C was determined as the difference of cholesterol content of the bottom fraction after ultracentrifugation minus HDL-C of the whole serum. Lipoprotein(a) [Lp(a)] was determined quantitatively using an enzyme immunoassay [Innotest Lp(a); Innogenetics, Gent, Belgium]. Fibrinogen was determined according to the method of Clauss.[20]

Statistical Analysis

Values are presented as means ± SD unless otherwise noted. Differences between pre- and postapheresis treatment and different dosages of atorvastatin were compared by 1-way analysis of variance (ANOVA) and Tukey multiple range comparison test. Changes in lipoproteins versus baseline were tested for statistical significance by 1-way ANOVA. *P* values less than .05 were considered significant.

RESULTS

Changes in lipoprotein values in 14 FH patients on LDL-apheresis with or without atorvastatin therapy are summarized in Table 3.

Effects on LDL-C

Dose escalation of atorvastatin resulted in a continuous lowering of LDL-C preapheresis values. At the end of the study

Table 2. Study Protocol

Duration (wk)	Oral Lipid-Lowering Treatment (daily)	Frequency of LDL-Apheresis	Dietary Recommendations
4	40 mg simvastatin (n = 13) 900 mg gemfibrozil (n = 1)	1 × per week	NCEP-Step 1 diet
4	Wash-out period*	↓	↓
4	10 mg atorvastatin		
4	20 mg atorvastatin		
4	40 mg atorvastatin		
4	60 mg atorvastatin		
4	80 mg atorvastatin		

Abbreviation: NCEP, US National Cholesterol Education Program.

*Without lipid-lowering drug treatment.

Table 3. Mean Lipoprotein Values During LDL-Apheresis With Different Concomitant Statin Applications in Patients With FH (n = 14)

			C				
	A	B	10 mg	20 mg	40 mg	60 mg	80 mg
TC (mg/dL)	293 ± 50 (211-386)	309 ± 34 (255-368)	282 ± 64 (195-421)	245 ± 56 (159-372)	241 ± 45 (179-346)	216 ± 44 (138-331)	210 ± 33 (169-293)
LDL-C (mg/dL)	212 ± 38 (148-293)	240 ± 35 (195-310)	206 ± 63 (119-329)	185 ± 56 (94-326)	187 ± 42 (119-271)	167 ± 37 (97-250)	157 ± 26 (89-227)
HDL-C (mg/dL)	40 ± 9 (31-69)	41 ± 9 (34-69)	43 ± 7 (35-65)	41 ± 6 (32-58)	40 ± 8 (27-57)	40 ± 9 (29-60)	40 ± 9 (31-60)
TG (mg/dL)	154 ± 89 (40-323)	145 ± 56 (79-264)	183 ± 83 (59-351)	184 ± 111 (76-477)	140 ± 62 (63-283)	124 ± 55 (62-256)	125 ± 64 (52-263)

NOTE. Values are means ± SD with the range in parentheses. All laboratory investigations were applied immediately before LDL-apheresis. A, values during treatment with simvastatin (n = 13) or gemfibrozil (n = 1) plus weekly LDL-apheresis therapy; B, after 4 weeks without oral lipid-lowering drug treatment, but LDL-apheresis therapy; C, with escalating doses of atorvastatin (10 to 80 mg/d) plus LDL-apheresis therapy.

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; Lp(a), lipoprotein (a).

period (all patients on 80 mg atorvastatin for 4 weeks), LDL-C preapheresis levels were reduced by an additional 24% ($P < .05$) as compared with the values obtained by 10 mg atorvastatin (Table 3).

In the individuals with homozygous FH, the LDL-C levels at the end of the wash-out period were 254 ± 38 mg/dL (range, 226 to 310 mg/dL), while the heterozygous FH group showed LDL-C levels of 229 ± 48 mg/dL (range, 195 to 284 mg/dL; P = not significant [NS]). After 4 weeks on 80 mg atorvastatin, LDL-C values were comparable in patients with homozygous FH (168 ± 26 mg/dL; range, 133 to 190 mg/dL) and heterozygous FH (152 ± 38 mg/dL; range, 89 to 227 mg/dL; P = NS) representing an identical 34% reduction in LDL-C preapheresis values.

LDL-C Recovery After LDL-Apheresis Treatment

The recovery of LDL-C after LDL-apheresis treatment was evaluated twice, at the end of the wash-out period and after 4 weeks on 80 mg atorvastatin (Table 4). Postapheresis LDL-C levels were below the recommended target concentration for secondary prevention of CAD in all patients. LDL-C remained less than 100 mg/dL for an extended duration of almost 48 hours during atorvastatin treatment as compared with the wash-out period. The increase of LDL-C was highest during the first 24 hours after LDL-apheresis treatment and, thereafter, the day-by-day increase was comparable. The LDL-C levels in between the 2 apheresis treatments were on average 37% ± 4.3% lower when patients were on atorvastatin (Table 4).

Effects on Triglycerides, Lp(a), and Plasma Fibrinogen

Triglyceride levels were highest before initiation of LDL-apheresis. Atorvastatin caused a dose-dependent triglyceride lowering ($F = 2.06$, $P = .06$).

Lp(a) levels showed considerable fluctuations during the entire study period, but these were not statistically significant. The levels of HDL-C and fibrinogen remained unchanged during the entire study period (P = NS). Plasma fibrinogen values were comparable during simvastatin (40 mg: 256 ± 47 mg/dL) and atorvastatin treatment at escalating dosages (10 mg: 266 ± 52; 40 mg: 262 ± 42; 80 mg: 248 ± 48 mg/dL).

Cost Effectiveness of 80 mg Atorvastatin Therapy in LDL-Apheresis Patients

At the end of the study period, the specific combination of lipid-lowering interventions was re-examined. Reduction in the frequency of LDL-apheresis from 1 treatment/week to 1 treatment every second week was achieved in 5 patients (including

Table 4. Recovery of LDL-C After LDL-Apheresis Treatments in Patients With FH With and Without Atorvastatin Therapy

	α (mg/dL)	β (mg/dL)	α v β
Pre-LDL-apheresis	256.8 ± 32.1	155.7 ± 29.1	−39%
Post-LDL-apheresis			
0 h	53.8 ± 18.1	28.8 ± 14.2	−47%
24 h	100.4 ± 16.6	67.0 ± 16.4	−33%
48 h	132.3 ± 17.9	88.4 ± 21.9	−33%
72 h	160.1 ± 25.1	103.6 ± 24.2	−35%
96 h	185.2 ± 30.8	116.3 ± 27.2	−37%
120 h	210.1 ± 27.6	128.9 ± 27.8	−39%
144 h	223.2 ± 27.6	139.0 ± 29.6	−38%
168 h	239.9 ± 35.0	156.6 ± 25.5	−35%

NOTE. Measurement of LDL-C immediately before and after apheresis treatment followed by determinations in 24-hour intervals until to the next apheresis session 1 week later. α = wash out period (4 weeks without concomitant oral lipid-lowering treatment), β = 4 weeks on oral therapy with 80 mg atorvastatin, α v β = mean difference (%) comparing value α with value β.

Table 5. Effect of Atorvastatin Therapy (80 mg/d) on Costs and Frequency of LDL-Apheresis

LDL-Apheresis Performed at	Patients (%)	Cost Accounting
7-day intervals	6 of 14 (43)	+$9,818
14-day intervals	5 of 14 (36)	−$61,668
Without LDL-apheresis	3 of 14 (21)	−$76,741
		Total − $128,591

NOTE. The reduction in expenses was calculated for 1 year due to the 40% lower frequency in LDL-apheresis treatments required for patients with FH (n = 14).

1 with homozygous FH). In 3 cases (all with heterozygous FH), extracorporeal treatments were terminated. In total, the improvement in LDL-C due to atorvastatin therapy resulted in a 40% reduction of LDL-apheresis (Table 5).

Adverse Events

No complications or adverse events were reported during the entire study period. The clinical observations were verified by regular laboratory investigations of the safety parameters.

DISCUSSION

Recently published data suggest that more aggressive lipid-lowering interventions result in a reduction of cardiovascular morbidity and mortality.[9,10,15,21-23] In patients maintained on LDL-apheresis, the addition of HMG-CoA reductase inhibitors, other than atorvastatin, has been shown to cause delayed reincrease in LDL-C.[2,4,6,12,17,24] Despite the proven benefit in primary and secondary prevention of CAD, the high cost of the LDL-apheresis procedure restricts its application to a few patients with serious FH.[3,5] Thus, drugs with enhanced lipoprotein-lowering capacity are still needed to assure that LDL-C levels are maintained below the US NCEP target values, particularly in patients with homozygous and severe heterozygous FH.[18]

This prospective study was aimed at assessing the effectiveness of atorvastatin in the treatment of FH in patients maintained on long-term LDL-apheresis at weekly intervals. During administration of 10 mg atorvastatin or 40 mg simvastatin, comparable LDL-C values were obtained (Table 3). When the dosage of atorvastatin was increased to 80 mg/day, a further 24% reduction in LDL-C values could be achieved. In patients with FH on sole statin therapy, atorvastatin was also more effective than simvastatin.[25]

Only 6 of 14 patients continued apheresis at a frequency of 1 session/week. In 8 individuals, LDL-apheresis treatments could be reduced to every second week (n = 5) or could be terminated (n = 3). A similar rate of reduction in LDL-C (-79%) at the end of the wash-out period and with high-dose atorvastatin therapy (-82%) was achieved by desorption of 6 L of plasma during each apheresis session. The reduction in preapheresis LDL-C values resulted from a delayed recovery in serum lipids induced by 80 mg atorvastatin (Table 4).

There are only limited data available regarding the effect of atorvastatin in patients treated by LDL-apheresis.[12,17,26,27] In 9 patients with homozygous FH undergoing LDL-apheresis every second week, Yamamoto et al[27] observed an additional 20% reduction in LDL-C values with 40 mg atorvastatin. However, in contrast to 4 of 4 receptor-defective patients, only 1 of 5 receptor-negative patients responded. Atorvastatin therapy was more effective in the present study. This may be due to the inclusion of patients with both homozygous FH (n = 4) and heterozygous FH (n = 10) on LDL-apheresis at weekly intervals. Marais et al[12] compared 80 mg atorvastatin to placebo in LDL-apheresis patients (n = 7) with homozygous FH. In agreement with our results, a mean decrease in LDL-C of 31% was observed with atorvastatin as compared with placebo.[12] We performed combined statistical analysis of the study results for patients suffering from homozygous and serious heterozygous FH, because atorvastatin caused comparable LDL-C reduction in these 2 groups.

Geiss et al[17] investigated 21 patients with heterozygous and severe combined hyperlipidemia who were being treated with 40 mg simvastatin and different extracorporeal devices for LDL-apheresis, including immunoadsorption, dextran sulfate adsorption, the heparin-mediated extracorporeal LDL-C precipitation (HELP) system, and the cascade filtration technique. The frequency of the apheresis treatments ranged from weekly to every second or even every third week. The investigators concluded that treatment with 60 mg or 80 mg atorvastatin was superior to 40 mg simvastatin when combined with extracorporeal lipoprotein-lowering therapy. However, Geiss et al[17] did not observe any additional effect on LDL-C reduction when atorvastatin dosage was increased from 60 mg to 80 mg/day. Furthermore, Geiss et al[17] processed a smaller amount of plasma as associated with a shorter duration of apheresis treatments. Our study was designed to achieve LDL-C values close to the recommended target range, because a more aggressive lipoprotein reduction has been assumed to improve the outcome of patients with CAD.[4,6,12,28-30]

Atorvastatin therapy may affect fibrinogen levels.[26,31-33] Wierzbicki et al[31] demonstrated consistently higher fibrinogen levels associated with atorvastatin therapy when compared with simvastatin in individuals suffering from severe polygenic or FH. These data are, however, in contrast to controlled investigations that describe no significant change in fibrinogen levels due to atorvastatin therapy.[16,26,34]

Our investigation shows no significant change in plasma fibrinogen for the entire study period. Banyai et al[33] recently described that atorvastatin improves blood rheology in patients with FH on long-term LDL-apheresis. The improvements in blood-flow properties were observed despite a slight increase of 5% ($P < .01$) in fibrinogen levels.

Administration of 80 mg atorvastatin rather than 40 mg simvastatin increases the cost of drug medication by 66%, but reduces LDL-apheresis therapy by 40%.[2,5] Due to the reduction of LDL-apheresis treatments, we observed an overall savings of about 35% of the calculated therapy cost by atorvastatin in this particular group of FH patients (Table 5).

In summary, atorvastatin efficiently reduces LDL-C in FH patients undergoing LDL-apheresis treatment. No side effects were observed when atorvastatin was administered in an escalating dose regimen. An atorvastatin dose of 80 mg enables lower LDL-C concentrations despite a 40% reduction in LDL-apheresis treatments. The long-term clinical effects of reduced LDL-C in FH patients require future study.

REFERENCES

1. Mellwig KP, Baller D, Gleichmann U, et al: Improvement of coronary vasodilatation capacity through single LDL-apheresis. Atherosclerosis 139:173-178, 1998

2. Gordon BR, Saal SD: Current status of low-density lipoprotein-apheresis for the therapy of severe hyperlipidemia. Curr Opin Lipidol 7:381-384, 1996

3. Jansen M, Banyai S, Schmaldienst S, et al: Direct adsorption of lipoproteins (DALI) from whole blood: First long-term clinical experience with a new LDL-apheresis system for the treatment of familial hypercholesterolaemia. Wien Klin Wochenschrift 112:61-69, 2000

4. Kroon AA, Aengevaeren WRW, van der Werf T, et al: LDL-Apheresis Atherosclerosis Regression Study (LAARS). Effect of aggressive versus conventional lipid lowering treatment on coronary atherosclerosis. Circulation 93:1826-1835, 1996

5. Schmaldienst S, Banyai S, Stulnig ThM, et al: Prospective randomised cross-over comparison of three LDL-apheresis systems in statin pretreated patients with familial hypercholesterolemia. Atherosclerosis 151:493-499, 2000

6. Thompson GR, Maher VMG, Matthews S, et al: Familial Hypercholesterolaemia Regression Study: A randomised trial of low-density-lipoprotein apheresis. Lancet 345:811-816, 1995

7. Yamamoto A, Kawaguchi A, Harada-Shiba M, et al: Apheresis technology for prevention and regression of atherosclerosis: An overview. Ther Apheresis 1:233-241, 1997

8. Tikkanen MJ: Statins: Within-group comparisons, statin escape and combination therapy. Curr Opin Lipidol 7:385-388, 1996

9. Shepherd J: Profiling risk and new therapeutic interventions: Looking ahead. Am J Med 104:19S-22S, 1998

10. Stein EA: Drug and alternative therapies for hyperlipidemia. Atherosclerosis 108:105-116, 1994

11. Wunsch H: Issue of lower limit for LDL cholesterol unresolved. Lancet 351:1257, 1998

12. Marais AD, Naoumova RP, Firth JC, et al: Decreased production of low-density lipoprotein by atorvastatin after apheresis in homozygous familial hypercholesterolemia. J Lipid Res 38:2071-2078, 1997

13. Schwartz GG, Olsson AG, Ezekovitz MD, et al: Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study. JAMA 285:1711-1718, 2001

14. Simons LA, Sullivan D, Simons J, et al: Effects of atorvastatin monotherapy and simvastatin plus cholestyramine on arterial endothelial function in patients with severe primary hypercholesterolaemia. Atherosclerosis 137:197-203, 1998

15. Pitt B, Waters D, Brown WV, et al: Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. N Engl J Med 341:70-76, 1999

16. Jones P, Kafonek S, Laurora I, et al: Comparative dose efficacy study of atorvastatin with that of lovastatin, pravastatin, simvastatin, and fluvastatin in patients with hypercholesterolemia: The CURVES study. Am J Cardiol 81:582-587, 1998

17. Geiss HC, Parhofer KG, Schwandt P: Atorvastatin compared with simvastatin in patients with severe LDL hypercholesterolaemia treated by regular LDL-apheresis. J Intern Med 245:47-55, 1999

18. Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third 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 III). JAMA 285:2486-2497, 2001

19. Kostner K, Banyai S, Jansen M, et al: Low-density lipoprotein apheresis does not increase plasma lipid peroxidation products in vivo. Clin Chim Acta 288:21-30, 1999

20. Ebeling H: A rapid and precise determination of fibrinogen and its cleavage products. J Clin Chem Clin Biochem 14:205-211, 1976

21. Smilde TJ, Wissen S van, Wollersheim H, et al: Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): A prospective, randomised, double-blind trial. Lancet 357:577-581, 2001

22. Watts GF, Burke V: Lipid-lowering trials in the primary and secondary prevention of coronary heart disease: New evidence, implications and outstanding issues. Curr Opin Lipidol 7:341-355, 1996

23. Gotto AM Jr: Risk factor modification: Rationale for management of dyslipidemia. Am J Med 104:6S-8S, 1998

24. Pfohl M, Naoumova RP, Klass C, et al: Acute and chronic effects on cholesterol biosynthesis of LDL-apheresis with or without concomitant HMG-CoA reductase inhibitor therapy. J Lipid Res 35: 1946-1955, 1994

25. Smilde TJ, van Wissen S, Wollersheim H, et al: Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): A prospective, randomized, double-blind trial. Lancet 357:577-581, 2001

26. Otto C, Geiss HC, Donner MG, et al: Influence of atorvastatin versus simvastatin on fibrinogen and other hemorheological parameters in patients with severe hypercholesterolemia treated with regular low-density lipoprotein immunoadsorption apheresis. Ther Apheresis 4:244-248, 2000

27. Yamamoto A, Harada-Shiba M, Kawaguchi A, et al: The effect of atorvastatin on serum lipids and lipoproteins in patients with homozygous familial hypercholesterolemia undergoing LDL-apheresis therapy. Atherosclerosis 153:89-98, 2000

28. Falk E, Prediman KS, Fuster V: Coronary plaque disrupture. Circulation 92:657-671, 1995

29. Mabuchi H, Koizumi J, Shimizu M, et al: Long-term efficacy of low-density-lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Am J Cardiol 82:1489-1495, 1998

30. Sacks FM, Moye LA, Davis BR, et al: Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the cholesterol and recurrent events trial. Circulation 97:1446-1452, 1998

31. Wierzbicki AS, Lumb PJ, Chik G, et al: Fibrinogen response with simvastatin versus atorvastatin in familial hypercholesterolemia. Am J Cardiol 87:338-340, 2001

32. Haverkate F, Koopman J, de Maat MPM: Statins and fibrinogen. Lancet 351:1430-1432, 1998

33. Banyai S, Banyai M, Falger J, et al: Atorvastatin improves blood rheology in patients with familial hypercholesterolemia (FH) on long-term LDL-apheresis treatment. Atherosclerosis 159:513-519, 2001

34. Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, et al: Effect of atorvastatin versus simvastatin on lipid profile and plasma fibrinogen in patients with hypercholesterolaemia. Clin Drug Invest 16:219-227, 1998