Review Article

Management of the Elderly Patient with Hyperlipidaemia: Recent Concerns

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Key words:
Cardiovascular disease, elderly, hyperlipidaemia, management.

Manuscript received:
September 10, 2005;
Accepted:
January 17, 2006.

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People over 65 make up an ever-growing section of the community. It is estimated that these individuals account for 20% of the population in Europe and 14% in the United States of America.[1,2] It has been predicted that by 2050 those aged over 80 years will represent about 25% of the elderly and 5% of the total population of the USA.[2] In Greece, 11.5% of the general population is aged over 70 years.

The consequences of this increasing number of elderly people are of great importance for public health care systems.[4,5]

Cardiovascular disease in the elderly

Cardiovascular disease is a significant cause of morbidity and mortality in the elderly, defined as individuals aged over 65 years.[4] Indeed, about 85% of people who die from coronary artery disease (CAD) are aged 65 or over.[6] Similarly, cerebrovascular stroke mainly affects the elderly.[7] Coronary artery atherosclerosis is more severe and extensive in the elderly than in younger patients.[8,9] At the age of 65, CAD is more common in men than in women, but by the age of 80 the incidence of symptomatic CAD is almost the same in both sexes.[10]

In spite of its high prevalence, only 10-20% of people over 65 years of age have clinically documented CAD. The mechanisms that govern this discrepancy between the anatomical and clinical manifestations of CAD are not fully understood. Factors that could contribute include the following: the lack of specific data concerning CAD in the elderly; false diagnosis of the disease; the high incidence of "silent disease"; reduced physical exercise; and that fact that the risk factors have not been modified for elderly individuals.[1]

Cardiovascular disease has a multifactorial aetiology, and smoking, hypertension, type 2 diabetes mellitus and dyslipidaemia are the main well-established modifiable risk factors.[11] Increasing age is one of the most significant risk factors for the development of cardiovascular disease. The degree to which age merely reflects the duration of exposure to other cardiovascular risk factors remains the subject of discussion and debate.

Epidemiological studies have shown that the metabolic risk factors tend to increase with age.[12] It should be stressed that the relative risk does not indicate the incidence of CAD in relation to the elevated total cholesterol in the elderly, because it fails to take account of the high incidence of CAD at that age. In contrast, the attributed risk (absolute risk of individuals with high levels of total cholesterol – absolute risk of individuals with reduced total cholesterol) indicates the contribution of elevated total cholesterol to the absolute risk in a particular age group. Interventional studies have noted that modifying the cardiovascular risk factors reduces the incidence of major cardiovascular events. Indeed, risk factor man-

agement seems to be particularly effective in the elderly, especially in those who have multiple risk factors.[13] However, the number of interventional studies involving elderly subjects is limited (Table 1).

Dyslipidaemia as a modifiable risk factor in the elderly

Total cholesterol

The relationship between dyslipidaemia and the occurrence of CAD was described as long ago as 1960, when observational studies proved that increased plasma cholesterol levels were correlated with an increased risk of developing cardiovascular disease.[14] To date, a large amount of epidemiological data have established dyslipidaemia as a significant and independent cardiovascular risk factor.[15-20] In spite of this, the relationship between cholesterol and cardiovascular risk in the elderly appears to be different. Even though total cholesterol concentrations represent a significant cardiovascular risk factor in the elderly (>65 years), the relationship weakens progressively to the point where cholesterol levels do not appear to contribute to the risk of cardiovascular or overall mortality beyond the age of 70 years.[21,22] At an advanced age (>80 years) this "paradox" may lead to an inverse correlation between lipid levels and mortality risk. For example, in one study of chronically bedridden elderly patients high levels of cholesterol were correlated with an increase in expected survival.[23] It has also been reported that low total cholesterol levels are correlated with increased mortality in men and women aged 65-95 years.[24] There are indications that the levels of total cholesterol, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) are low in patients with severe diseases, especially in elderly patients with severe acute or chronic pathological conditions (e.g. infections, neoplasias).[25,26] In this clinical context, the finding of very low cholesterol levels is considered to be a manifestation of the severity of the disease and a predictor of an unfavourable outcome, especially in elderly patients.[23,27-29]

LDL cholesterol

Serum levels of LDL-C increase with age,[30] although the underlying mechanisms have not been fully elucidated. There are, however, indications that a reduction in the rate of catabolism of low density lipoprotein particles, as a result of reduced hepatic LDL receptor activity, plays a significant role.[31]

HDL cholesterol

A study of aged patients with or without CAD investigated the relationship between cardiovascular risk factors and the occurrence of new coronary episodes in 664 men, mean age 80 years, and 1488 women, mean age 82 years.[11] The relative risk of occurrence of a new coronary episode was 1.70 in men and 1.95 in women, for a reduction in HDL-C of 10 mg/dL.[11] Also, in the PROSPER trial (PROspective Study of Pravastatin in the Elderly at Risk) there was an inverse correlation between initial HDL-C levels and the risk of occurrence of the primary endpoint (hazard ratio 0.64, 95% CI 0.52-0.80, p=0.0069), while the benefit from pravastatin administration mainly accrued to those with the lowest initial HDL-C levels (<43 mg/dL).[32]

Triglycerides

A prospective study investigated the relationship between coronary risk factors and the occurrence of new events in 192 elderly men and 516 elderly women (mean age 82 ± 8 years, mean follow up 41 ± 6 months). Multifactorial analysis found that the significant risk factors in both men and women with a history of CAD were increased age, smoking, diabetes mellitus, serum levels of total cholesterol, HDL-C and triglycerides. Also, triglyceride levels were correlated with an increase risk of coronary events in women with no previous history of CAD.[33]

Apolipoproteins

In the AMORIS trial, in which 175,553 subjects took part, elevated levels of apolipoprotein (Apo) B and the Apo B:Apo A-I ratio were positively correlated with the risk of fatal acute myocardial infarction,[34] while Apo A-I had a protective effect (as did HDL-C), even above the age of 70 years (about 7.5% of the study population).

Other risk factors

Observational studies have shown that the prevalence of arterial hypertension (and especially of isolated systolic hypertension) increases with age,[35] while interventional studies of elderly subjects aged over 80 years found that the risk of stroke and signs of CAD reduces by 30% for each 20 mmHg reduction in blood pressure.[36]

About 20% of those aged over 70 years suffer from diabetes mellitus. However, there are indications that

Table 1. Studies evaluating the effect of lipid-lowering therapy on cardiovascular disease, showing the percentage of the study population comprised by elderly patients.

Primary prevention					
Study	Treatment	Population	Elderly	Reduction in relative risk	p
1. WOSCOPS	Pravastatin	6595 (45-64)	–	29% MACE 23% overall mortality	<0.042
2.AFCAPS/TexCAPS	Lovastatin	6605 (45-73)	>65 (21%)	40% incidence of fatal and non-fatal AMI	<0.001
3. CHS	Statins	1914 (>65)	>65 (100%)	56% cardiovascular disease 44% overall mortality	
4. CARDS	Atorvastatin	2838 (40-75)	>70 (12%)	37% cardiovascular events 36% acute coronary heart disease events 31% coronary revascularisation procedures 48% stroke 27% death	0.001 0.059
5. ASCOT-LLA	Atorvastatin	19342 (40-79)	–	36% primary endpoints[1]	0.0005
Secondary prevention					
Study	Treatment	Population	Elderly	Reduction in relative risk	p
1. 4S	Simvastatin	4444 (35-70)	–	35% overall mortality	<0.00001
2. CARE	Pravastatin	4159 (21-75)	>65 (31%)	24% MACE	<0.003
3. LIPID	Pravastatin	9014 (31-75)	>65 (36%)	25% MACE	<0.001
4. LIPS	Fluvastatin	1677 (18-80)	–	20% MACE	0.006
5. MIRACL	Atorvastatin	3086 (18-80)	–	16% primary endpoints[2]	0.048
6. GREACE	Atorvastatin	1600 (<75)	–	49% primary endpoints [3] (age 60-70)	0.0042
7. ALLIANCE	Atorvastatin	2442 (18-78)	–	17% primary endpoints[4]	0.02
8. TNT	Atorvastatin	10001 (35-75)	–	22% primary endpoints[5]	0.001
Primary and secondary prevention					
Study	Treatment	Population	Elderly	Reduction in relative risk	p
1. HPS	Simvastatin	>20000 (40-80)	>70 (29%)	25-30% MACE	<0.0001
2. PROSPER	Pravastatin	5804 (70-82)	>70 (100%)	15% coronary mortality, non-fatal AMI, fatal or non-fatal stroke	0.014

[1] Non-fatal AMI, fatal CAD
[2] Death, non-fatal AMI, resuscitated cardiac arrest, recurrence of myocardial ischaemia needing rehospitalisation
[3] Death, non-fatal AMI, unstable angina, cardiovascular failure, revascularisation and stroke
[4] Cardiac death, non-fatal AMI, resuscitated cardiac arrest, revascularisation, unstable angina necessitating hospitalisation
[5] First MACE, CAD-related death, non-fatal AMI, resuscitated cardiac arrest, fatal or non-fatal stroke

AMI – acute myocardial infarction; MACE – major acute coronary events

WOSCOPS: West Of Scotland Coronary Prevention Trial
AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study
CHS: Cardiovascular Health Study
CARDS: Collaborative AtoRvastatin Diabetes Study
ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm
4S: Scandinavian Simvastatin Survival Study
CARE: Cholesterol And Recurrent Events trial
LIPID: Long-term Intervention with Pravastatin in Ischemic Disease
LIPS: Lescol Intervention Prevention Study
GREACE: GREek Atorvastatin and Coronary heart disease Evaluation trial
MIRACL: Myocardial Ischemia Reduction with Acute Cholesterol Lowering trial
ALLIANCE: Aggressive Lipid-Lowering Initiation Abates New Cardiac Events study
TNT: Treating to New Targets study
HPS: Heart Protection Study
PROSPER: PROSpective Study of Pravastatin in the Elderly at Risk

the contribution of diabetes to cardiovascular risk is smaller in the elderly than in those of younger age.[37] In one large study of elderly men and women (The Large Cohort of Very Elderly Patients With and Without Coronary Artery Disease) the relative risk of new coronary events in smokers was double that in non-smokers.[11]

Finally, psychological factors, such as depression or social isolation are of particular importance in elderly people, since their frequency and intensity increases with age. However, in the elderly, too, it is difficult to quantify the contribution of psychosocial factors to the occurrence of cardiovascular disease.[38,39]

Treatment of hyperlipidaemia in the elderly: are there indications?

According to the foregoing, treatment of dyslipidaemia in selected elderly patients with multiple risk factors is considered to be justifiable.[18,40-42] As regards the efficacy of the treatment, all studies that administered lipid-lowering agents to elderly patients found that the drugs were at least as effective at improving dyslipidaemia in the elderly as in younger individuals. However, the decision to treat a patient with hyperlipidaemia must be taken on the basis of the general rules of prescription in a geriatric population.

Most specialists agree that the decision to administer treatment to elderly patients with high or marginally high serum cholesterol concentrations must be individualised, guided by chronological and biological age. For example, a patient with low expected survival because of a coexistent pathological condition is not a logical candidate for treatment with lipid-lowering drugs. On the other hand, in a healthy elderly person treatment should not be withheld solely on the basis of age.[43]

There are some serious questions concerning the administration of lipid-lowering agents to the elderly, such as overmedication and its cost, and the increased probability of the occurrence of side effects (liver toxicity and myopathy related to statin treatment).[44]

Indeed, the risk of myotoxic action by statins is particularly high in the elderly.[45-46] The effect of age on the muscles, in combination with the increased probability of coexisting pathological conditions (e.g. hypothyroidism) or the simultaneous use of other medication, may increase the risk of myopathy.[47] A variety of other agents (e.g. antibiotics, β-blockers, corticosteroids) may cause myopathy and their administration in combination with statins is potentially dangerous.[48]

The findings of secondary prevention studies have shown that elderly patients with established CAD who do not have other severe concomitant diseases should receive adequate therapy.[18,49-51] Specifically, the main aim of lipid-lowering treatment in patients with established CAD or equivalent conditions (diabetes mellitus, carotid atherosclerosis, abdominal aortic aneurysm) is to achieve an LDL-C level below 100 mg/dL.[42,52] In general, it is accepted that aged patients with CAD should be treated in the same way as younger patients, and indeed, according to the revised guidelines the LDL-C target should be significantly lower, namely below 70 mg/dL, in patients with acute coronary episodes, CAD patients with diabetes mellitus, smokers with CAD, and CAD patients with metabolic syndrome.[53]

Treatment of hyperlipidaemia in the elderly

Health and dietary measures

Treatment with non-pharmaceutical means is considered the first choice in elderly patients with hyperlipidaemia. This includes dietary interventions and changes in lifestyle, aimed at modifying the risk factors, such as smoking, obesity, and a lack of physical activity.[43,52-56] Counselling about smoking cessation should be provided even in the very old. Apart from the direct advantages of giving up smoking, the results of statin studies show that the clinical benefit is greater in non-smokers.[57]

The kind of dietary intervention that could be of theoretical benefit concerns the replacement of saturated fats with monounsaturated (olive oil) or polyunsaturated (vegetable oils) fats.[55] However, dietary modifications require full compliance for many years and may entail a high cost. Most elderly people are attached to their dietary habits and way of life and do not easily accept suggestions for changes of diet.

Statins

Statins are the lipid-lowering drugs *par excellence*, in that they have been shown to be effective in reducing LDL-C levels and have a significant clinical benefit in the elderly.

The Cholesterol Reduction In Seniors Program (CRISP)[58] investigated to what extent it was possible to study the reduction of cholesterol levels in an elderly population. The study involved 431 individuals aged >65 years, with LDL-C levels 159-221 mg/dL, who were randomised to receive treatment with lovastatin (either 20 or 40 mg daily) or placebo. In the patients who took lovastatin there was a reduction in total cholesterol by 17% and 20% and in LDL-C by 24% and 28%, in the 20

mg and 40 mg groups, respectively. There were no differences in the changes of lipid parameters between patients aged 65-70 years and those over 70 years.

Lipid-lowering interventions have a proven correlation with a significant reduction in morbidity and mortality in the elderly (Table 1). However, the improvement in cardiovascular risk, according to clinical studies of statins, cannot be attributed solely to a reduction in cholesterol levels. A wide spectrum of beneficial effects from these drugs on the arterial wall, the endothelium, on indexes of thrombosis and inflammation (pleiotropic actions) are currently under investigation.[59]

In the elderly the half life of statins is prolonged. In addition, the patients may be taking other drugs that are metabolised to the same cytochrome, rendering it more prudent to give small or medium doses of statins (initially as monotherapy and/or in combination with ezetimibe) in order to achieve the desired reduction in LDL-C.

Newer therapeutic options

The development of new drugs, which are effective in smaller doses and have fewer side effects and interactions with other drugs, has increased the available options for elderly patients. Rosuvastatin, a powerful inhibitor of HMG-CoA reductase, may prove useful in the treatment of elderly dyslipidaemic patients once its safety has been proved in this category of patients.[60-63] In addition, the combination of low doses of a statin with ezetimibe may be another desirable option in the elderly, since it can improve the lipid profile significantly. A meta-analysis of four multi-centre, randomised, double blind studies examined the efficacy and safety of statin monotherapy compared to treatment with 10 mg ezetimibe plus a statin in elderly and younger patients with primary hypercholesterolaemia. The combination of ezetimibe and statin was well tolerated and led to a significant reduction in LDL-C levels compared with statin monotherapy in all age groups. The reduction in LDL-C, triglycerides and HDL-C was found to be independent of age.[64]

Conclusions

Interventional studies in the elderly, as well as analysis of study subgroups, have shown a stable reduction of risk of CAD as a result of lipid-lowering therapy. Although observational studies have noted that the prognostic value of hypercholesterolaemia is limited at an advanced age, according to the results of interventional studies the benefit from reducing elevated levels of LDL-C is similar in middle-aged and elderly patients over a five-year period.

Questions related to age, expected survival, coexisting pathological conditions, the incidence of side effects, and the cost all have a significant effect on therapeutic decisions concerning the administration of special lipid-lowering treatment in clinical practice. The ultimate choice of treatment for the elderly patient with hyperlipidaemia should be taken on the basis of the risk-benefit ratio, the patient's general state of health, and his/her attitude to undergoing long-term or lifelong and expensive treatment. The role of the treating physician remains pivotal.

References

1. Lye M, Donellan C: Heart disease in the elderly. Heart 2000; 84: 560-566.
2. US Census Bureau: sixty five plus in America.
3. Greek Statistical Service: 2001 census.
4. Wei JY, Gersh BJ: Heart disease in the elderly. Curr Probl Cardiol 1987; 12: 1-65.
5. Chrischilles EA, Foley DJ, Wallace RB, et al: Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly. J Gerontol 1992; 47: M137-144.
6. American Heart Association: 2000 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association; 1999.
7. Shepherd J: Issues surrounding age: vascular disease in the elderly. Curr Opin Lipidol 2001; 12: 601-609.
8. Stone PH, Thompson, B, et al: Influence of race, sex and age on the management of unstable angina and non Q-wave myocardial infarction. The TIMI III registry. JAMA 1996; 275: 1104-1112.
9. Williams MA, Fleg JL, Ades PA, et al: Secondary prevention of coronary heart disease in the elderly (with emphasis on patients 75 years of age): an American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2002; 105: 1735-1743.
10. Lerner DJ, Kannel WB: Patterns of coronary heart disease morbidity and mortality in the sexes. A 26 year follow up of the Framingham population. Am Heart J 1986; 111: 383-390.
11. Aronow WS, Ahn C: Risk factors for new coronary events in a large cohort of very elderly patients with and without coronary artery disease. Am J Cardiol 1996; 77: 864-866.
12. Milionis HJ, Rizos E, Goudevenos J, et al: Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. Stroke 2005; 36: 1372-1376.
13. Tuomilehto J: Impact of age on cardiovascular risk: implications for cardiovascular disease management. Atheroscler Suppl 2004; 5: 9-17.
14. Kannel WB, Castelli WP, Gordon T, et al: Serum cholesterol, lipoproteins and the risk of coronary heart disease. The Framingham Study. Ann Intern Med 1971; 74: 1-12.
15. Downs JR, Clearfield M, Weis S, et al: Primary prevention of acute coronary events with lovastatin in men and women with

average cholesterol levels: results of AFCAPS/TexCAPS Air Force/ Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279: 1615-1622.
16. Cholesterol, diastolic blood pressure, stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. Lancet 1995; 346: 1647-1653.
17. Shepherd J, Cobbe SM, Ford I, et al: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333: 1301-1307.
18. 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: 1383-1389.
19. Pfeffer MA, Sacks FM, Moye LA, et al: Cholesterol and recurrent events: a secondary prevention trial for normolipidemic patients. CARE Investigators. Am J Cardiol 1995; 76: 98C-106C.
20. Prevention of cardiovascular events, death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels: The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998; 339: 1349-1357.
21. Krumholz HM, Seeman TE, Merrill SS, et al: Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA 1994; 272: 1335-1340.
22. Kronmal R, Cain K, Ye Z, et al: Total serum cholesterol levels and mortality risk as a function of age: a report based on the Framingham data. Arch Intern Med. 1993; 153: 1065-1073.
23. Forette B, Tortrat D, Wolmark Y: Cholesterol as risk factor for mortality in elderly women. Lancet 1989; i: 868-870.
24. Casiglia E, Mazza A, Tikhonoff V, et al: Total cholesterol and mortality in the elderly. J Intern Med 2003; 254: 353-362.
25. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, et al: Total cholesterol and risk of mortality in the oldest old. Lancet 1997; 350: 1119-1123.
26. Pekkanen J, Nisssinen A, Vartiainen E, et al: Changes in serum cholesterol level and mortality: a 30-year follow-up. Am J Epidemiol 1994; 139: 155-156.
27. Hazzard WR, Ettinger WH: Aging and atherosclerosis: changing considerations in cardiovascular disease prevention as the barrier to immortality is approached in old age. Am J Geriatr Cardiol 1995; 4: 16-36.
28. Noel M, Smith T, Ettinger W: Characteristics and outcomes of hospitalized older patients who developed hypocholesterolemia. J Am Geriatric Soc 1991; 39: 455-461.
29. Ettinger W, Harris T: Causes of hypocholesterolemia. Coron Artery Dis 1993; 4: 854-859.
30. Kreisberg RA, Kasim, S: Cholesterol metabolism and aging. Am J Med 1987; 82: 54-60.
31. Ericsson S, Eriksson M, Vitols S, et al: Influence of age on the metabolism of plasma low density lipoproteins in healthy males. J Clin Invest 1991; 87: 591-596.
32. Shepherd J, Blauw GL, Murphy MB, et al, study group: PRO spective Study of Pravastatin in Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623-1630.
33. Aronow WS, Herzig AH, Etienne F, et al: 41-month follow-up of risk factors correlated with new coronary events in 708 elderly patients. J Am Geriatr Soc 1989; 37: 501-506.
34. Walldious G, Jungner I, Holme I, et al: High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001; 358: 2026-2033.
35. Bots ML, Witteman JC, Hofman A, et al: Low diastolic blood pressure and atherosclerosis in elderly subjects. The Rotterdam Study. Arch Intern Med 1996; 156: 843-848.
36. Lewington S, Clarke R, Qizilbash N, et al: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-1913.
37. Ezenwaka CE, Offiah NV: Differences in cardiovascular disease risk factors in elderly and younger patients with type 2 diabetes in the West Indies. Singapore Med J 2002; 43: 497-503.
38. Rozanski A, Blumenthal JA, Kaplan J: Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999; 99: 2192-2217.
39. Rozanski A, Blumenthal JA, Davidson KW, et al: The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice. J Am Coll Cardiol 2005; 45: 637-651.
40. Davidson MH, Kurlandsky SB, Kleinpell RM, et al: Lipid management and the elderly. Prev Cardiol 2003; 6:128-33; 134-135.
41. Papadakis JA, Milionis HJ, Press M, et al: Treating dyslipidaemia in non-insulin dependent diabetes mellitus - a special reference to statins. J Diabetes Complic 2001; 15: 211-226.
42. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-2497.
43. Grundy SM, Cleeman JI, Rifkind BM, et al: Cholesterol lowering in the elderly population. Coordinating Committee of the National Cholesterol Education Program. Arch Intern Med 1999; 159: 1670-1678.
44. Hazzard R: Dyslipoproteinemia in the elderly: To treat or not to treat? Am J Med 1999; 107: 51-53.
45. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al: ACC/ AHA/ NHLBI clinical advisory on the use and safety of statins. Circulation 2002; 106:1024-1028.
46. Rosenson RS: Statins and the risk of rhabdomyolysis. J Endocrinol Invest 2002; 25: 577.
47. Rosenson RS: Current overview of statin-induced myopathy. Am J Med 2004; 116: 408-416.
48. Sica DA, Gehr TW: Rhabdomyolysis and statin therapy: relevance to the elderly. Am J Geriatr Cardiol 2002; 11: 48-55.
49. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
50. Miettinen TA, Pyorala K, Olsson AG, et al, for the Scandinavian Simvastatin Study Group: Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: Findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 1997; 96: 4211-4218.
51. Hunt D, Young P, Simes J, et al: Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. Ann Intern Med 2001; 134: 931-940.
52. Grundy SM, Pasternak R, Greenland P, et al: Assessment of cardiovascular risk by use of multiple-risk factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 1999; 100: 1481-1492.

53. Grundy SM, Cleeman JI, Merz CN, et al: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-239.
54. Lemaitre RN, Psaty BM, Heckbert SR, et al: Therapy with hydroxymethylglutaryl coenzyme a reductase inhibitors (statins) and associated risk of incident cardiovascular events in older adults: evidence from the cardiovascular health study. Arch Intern Med 2002; 162: 1395-1400.
55. National Cholesterol Education Program: Second report of the expert panel on detection, evaluation and treatment of high blood cholesterol (Adult Treatment Panel II). Circulation 1994; 89: 1329-1445.
56. Denke MA, Grundy SM: Hypercholesterolemia in elderly persons: resolving the treatment dilemma. Ann Intern Med 1990; 112: 780-792.
57. Milionis HJ, Rizos E, Mikhailidis DP: Smoking diminishes the beneficial effect of statins: observations from the landmark trials. Angiology 2001; 52: 575-587.
58. LaRosa JC, Applegate W, Crouse JR, et al: Cholesterol lowering in the elderly. Results of the Cholesterol Reduction In Seniors Program (CRISP) pilot study. Arch Intern Med 1994; 154: 529-539.
59. Milionis HJ, Elisaf MS, Mikhailidis DP: The effects of lipid-regulating therapy on haemostatic parameters. Curr Pharm Des 2003; 9: 2425-2443.
60. Scott LJ, Curran MP, Figgitt DP: Rosuvastatin: a review of its use in the management of dyslipidemia. Am J Cardiovasc Drugs 2004; 4: 117-138.
61. Milionis HJ, Gazi IF, Filippatos TD, et al: Starting with rosuvastatin in primary hyperlipidaemia - Is there more than lipid lowering? Angiology 2005; 56: 585-592.
62. Shepherd J, Hunninghake DB, Stein EA, et al: Safety of rosuvastatin. Am J Cardiol 2004; 94:882-888.
63. Alsheikh-Ali AA, Ambrose MS, Kuvin JT, et al: The safety of rosuvastatin as used in common clinical practice. A postmarketing analysis. Circulation 2005; 111: 3051-3057.
64. Lipka L, Sager P, Strony J, Yang B, Suresh R, Veltri E; Ezetimibe Study Group: Efficacy and safety of coadministration of ezetimibe and statins in elderly patients with primary hypercholesterolaemia. Drugs Aging 2004; 21: 1025-1032.