UNIT NO. 2

REVIEW OF EVIDENCE ON THE EFFICACY OF TREATMENT OF HYPERLIPIDEMIA

A/Prof Goh Lee Gan, Dr Peter Yan Chee Hong

INTRODUCTION

Total cholesterol was once implicated as the cause of CHD but it is now clear that it is the LDL cholesterol that is important[1]. The power of elevated LDL to cause CHD is shown most clearly in persons with genetic forms of hypercholesterolemia[2]. Thus, the Expert Panels of the National Cholesterol Education Programme (NCEP) have focussed on this in its Adult Treatment Panel (ATP) Reports. ATP I and ATP II identified serum LDL as the primary target for cholesterol-lowering therapy, and ATP III continues this emphasis.

At any level of LDL cholesterol, the CAD risk is magnified logarithmically as other CAD risk factors are added sequentially. The chief CAD risk factors are smoking, hypertension, and low levels of high-density lipoprotein (HDL) cholesterol. Diabetes mellitus is also a major risk factor. Reduction of LDL cholesterol reduces the CHD mortality and CHD incidence. It does not seem to matter how LDL cholesterol is lowered, whether by lifestyle modification, lipid lowering drugs, or surgery (ideal bypass surgery). Each way of lowering LDL cholesterol lowers CAD risk, although to different degrees[3].

This paper reviews the evidence on the efficacy of the various modalities of treatment in secondary prevention and also in primary prevention. The rationale of combination therapy for elevated non-LDL cholesterol is also commented upon.

LEARNING OBJECTIVES

At the end of this reading, the reader will have an understanding of:

- Cholesterol and Coronary heart disease (CHD)
- Efficacy of secondary prevention through reduction of LDL Cholesterol
- Efficacy of primary prevention through reduction of LDL Cholesterol
- Treatment of Coronary Heart Disease
- Combination therapy for reduction non-HDL Cholesterol

CHOLESTEROL AND CORONARY HEART DISEASE (CHD)

Several observational studies point to the link between serum levels and coronary heart disease namely:

- Framingham Study
- Seven Countries Study
- Multiple Risk Factor Intervention Trial (MRFIT)

GOH LEE GAN, Department of Community, Occupational & Family Medicine, National University of Singapore

PETER YAN CHEE HONG, Senior Consultant Cardiologist, Gleneagles Medical Centre

Framingham Heart Study

The link between serum cholesterol levels and CHD was first observed in the Framingham Heart Study. This study was started in 1948 and is ongoing. The Cholesterol-CHD relationship is now established to follow a curvilinear pattern, with diminishing levels of CHD risk with diminishing serum cholesterol levels down to probably less than 100 mg/dL[3,4].

Seven Countries Study

This study[5] was set up to compare the relationship between serum total cholesterol and long term mortality from coronary heart disease in different cultures. It was found that across cultures:

- CHD mortality is linearly related to serum cholesterol levels
- The relative increase in CHD mortality rates with a given cholesterol increase is the same
- The large difference in absolute CHD mortality rates at a given cholesterol level; this indicates that other factors such as diet, which are typical for cultures with a low CHD risk are also important with respect to primary prevention.

People who migrate from regions where average serum cholesterol in the general population is low to areas with high cholesterol levels show increases in their cholesterols as they acculturate. These higher levels in turn are accompanied by more CHD. For example, the Japanese in Japan had the lowest cholesterol levels, with the Japanese in Hawaii as intermediate and the Japanese in California had the highest levels. The group that was most acculturated to Western culture had a three to five-fold excess in CHD prevalence. This difference in CHD rate between most and least acculturated groups could not be accounted for by differences in the major coronary risk factors[6].

Multiple Risk Factor Intervention Trial (MRFIT)

This study[7] reported the relationship between serum cholesterol and risk of premature death from coronary heart disease based on the findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). It was found that:

- Of all CHD deaths, 46% were estimated to be excess deaths attributable to serum cholesterol levels 180 mg/dL or greater (greater than or equal to 4.65 mmol/L), with almost half the excess deaths in serum cholesterol quintiles 2 through 4
- The pattern of a continuous, graded, strong relationship between serum cholesterol and six-year age-adjusted CHD death rate prevailed for non-hypertensive non-smokers, non-hypertensive smokers, hypertensive non-smokers, and hypertensive smokers

- The relationship between serum cholesterol and CHD is not a threshold one, with increased risk confined to the two highest quintiles, but rather is a continuously graded one that powerfully affects risk for the great majority of middle-aged American men.

CHOLESTEROL LOWERING TRIALS

The trials for testing the effects of cholesterol reduction can be divided into two groups. In secondary prevention trials, the aim is to prevent another cardiovascular event or cardiovascular mortality. In primary prevention trials, the aim is to prevent well subjects from getting a cardiovascular event or mortality.

EFFICACY OF SECONDARY PREVENTION THROUGH REDUCTION OF LDL CHOLESTEROL

Controlling Risk Factors

In the prevention of a subsequent cardiovascular event in patients with post myocardial infarction, the risk factors that must be controlled are diabetes mellitus (if present), hypertension, hyperlipidemia and obesity.

Obesity has an adverse influence on a number of cardiovascular risk factors including blood pressure, cholesterol, triglycerides and glucose intolerance. There is an inverse relationship between relative weight and long term risk of re-infarction[8]. There have been no studies of reducing obesity in patients with coronary heart disease despite the fact that it is a common problem – 23% of men and 33% of women with coronary heart disease remain significantly obese[9]. Weight reduction is important in obese patients with coronary heart disease and prevention of obesity by altered diet and exercise is therefore essential.

Serum cholesterol and LDL cholesterol are major risk factors for recurrent cardiac events in patients following MI[10]. These risks are multiplied if other risk factors for vascular disease are present.

Dietary Modification

Oslo Diet Heart Study; Oslo Diet Smoking Study; Meta-analysis of 27 studies. Dietary modification lowers cholesterol but the changes are relatively small – in the order of 9% if persisted over 2 years[11]. Diet modification tends to be poorly maintained as a consequence of limited motivation and non-compliance with stringent dietary restriction.

Bile acid sequestrants (BAS) And Fibrates

Lipid Research Clinics; Helsinki Heart Study. Early studies using cholestyramine or fibrates demonstrated that patients with coronary heart disease did benefit from cholesterol reduction[12,13,14]. Meta-analysis of these studies, which pre-date the major statin trials, demonstrated that mortality could be reduced by some 10% in patients who received active intervention[14].

Statins

Scandinavian Simvastatin Survival Study (4S), LIPID, CARE. These three studies using HMG Co-A reductase inhibitors (statins) have shown falls in cholesterol of 20-30% and clear benefit in both reduction of vascular events and all cause mortality[15,16,17].

The Scandinavian Simvastatin Survival Study (4S). This trial randomized 4,444 patients with total cholesterol in the range 5.5-8.0 mmol/l after dietary intervention to receive either simvastatin or placebo[15]. The majority of the patients had had an MI at least six months previously or had angina with a positive exercise test. Patients were aged between 35 and 70 years and 18% were women. The aim of the study was to reduce serum cholesterol to between 5.2 and 3.0 mmol/l. The dosage of simvastatin was titrated between 20 and 40 mg daily to achieve the target cholesterol. The mean follow-up was 5.4 years and the mean cholesterol reduction was 28%. Total mortality was reduced by 30% in the treatment group due to a 42% decrease in coronary heart disease deaths and the combined endpoint of morbidity and mortality (coronary death, non-fatal definite or probable MI, silent MI or resuscitated cardiac arrest) was reduced by 34%. The need for coronary artery surgery or coronary angioplasty was reduced by 37%. These benefits applied to older as well as younger patients.

Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study. This was the largest study of statins in patients with established coronary heart disease, either myocardial infarction or unstable angina[17]. A total of 9,014 patients (17% women) whose total cholesterol levels were in the range 4.0-7.0 mmol/l were randomized to receive either pravastatin 40 mg daily or placebo.

The duration of the trial was 6.1 years and the mean cholesterol reduction in the pravastatin group was 18%, with a reduction in LDL cholesterol of 25%. Overall mortality was 22% lower in the pravastatin group, with a 24% reduction in deaths from coronary heart disease and 25% reduction in deaths from other cardiovascular causes. In the subgroup with previous MI, mortality from coronary heart disease was 23% lower in the pravastatin group.

Other secondary endpoints specified included myocardial infarction, which was reduced by 29% and the incidence of stroke, which was reduced by 19%. The need for revascularisation was reduced by 20%. These results confirm and extend the findings of the 4S study in a much larger series of patients.

The Cholesterol and Recurrent Events (CARE) study. This study was designed to determine whether cholesterol lowering was of benefit for patients with average cholesterol levels[16]. A total of 4,159 patients (14% women) with serum cholesterol levels of less than 6.2 mmol/l were randomised to receive either pravastatin 40 mg daily or placebo over five years. Serum cholesterol was 20% lower in the pravastatin treated group, with a decrease of 28% in LDL cholesterol. CHD events and

CHD mortality decreased by 24% and 20% respectively in the pravastatin treated group and the need for coronary revascularisation fell by 27%. Overall mortality, however, was not significantly reduced.

A retrospective sub-group analysis of the combined endpoints of fatal and non-fatal myocardial infarction and coronary revascularization procedures in the CARE study suggested there was no benefit in a sub-group whose baseline LDL cholesterol was less than 3.2 mmol/l, equivalent to a total cholesterol of less than 5.0 mmol/l[16].

The results of these three major secondary prevention statin trials are summarised in Table 1.

EFFICACY OF PRIMARY PREVENTION THROUGH REDUCTION OF LDL CHOLESTEROL

The case for primary prevention of coronary heart disease

Atherosclerosis generally can first be identified by gross pathological examination of coronary arteries in adolescence or early adulthood. The subsequent rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels. Moreover, the cholesterol level in young adulthood predicts development of CHD later in life. In three prospective studies with long-term follow-up, detection of elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle-age[1].

Lipids in the context of other CHD risk factors

Increased total cholesterol and triglycerides have detrimental effects. Increased high density lipoprotein (HDL) cholesterol levels have protective effects. Serum total cholesterol alone is nevertheless a poor predictor of individual CHD risk. The risk is much increased beyond that due to high cholesterol when multiple risk factors are present.

Population and high risk strategies

Risk factors such as serum cholesterol and blood pressure are normally distributed within the population, with a slight skew to the right. Population strategies seek to prevent or delay the onset of CHD by shifting the whole distribution of risk factors such as cholesterol to the left, whereas the high risk approach concentrates its efforts on the smaller number of individuals with cholesterol or blood pressure levels above a certain threshold defining "hypercholesterolemia" or "hypertension". The notion of primary prevention embraces all valid activities which reduce the risk of CHD. It is recognized that effective coronary heart disease prevention must involve population as well as high risk approaches, and that these are not mutually exclusive.

Table 1. Major trials of statins in coronary heart disease

		4S		LIPID		CARE	
		placebo	simvastatin 20-40 mg/day	placebo	pravastatin 40 mg/day	placebo	pravastatin 40 mg/day
Trial duration (years)		5.4		6.1		5.0	
TOTAL MORTALITY	n	256	182	633	498	196	180
	%	11.5%	8.2%	14.1%	11.0%	9.4%	8.7%
	Relative risk reduction (95% CI)	30% (p<0.001) (15-42)		22% (ns) (13-31)		9% (ns) (-12-26)	
	Absolute risk reduction	3.3%		3.1%		0.7%	
	NNT over trial duration	30		32		143	
CHD MORTALITY	n	189	11	373	287	119	96
	%	8.5%	5.0%	8.3%	6.4%	5.7%	4.6%
	Relative risk reduction (95% CI)	42% (p<0.001) (27-54)		24% (p<0.001) (12-35)		20% (ns) (-5-39)	
	Absolute risk reduction	3.5%		1.9%		1.1%	
	NNT over trial duration	29		53		91	
CHD EVENTS*	n	622	431	715	557	274	212
	%	28%	19%	15.9%	12.3%	13.2%	10.2%
	Relative risk reduction (95% CI)	34% (p<0.001) (25-41)		24% (p<0.001) (15-32)		24% (p=0.003) (9-36)	
	Absolute risk reduction	9%		3.6%		3%	
	NNT over trial duration	11		28		33	

Source: SIGN 41, 2000.
Footnotes: n = total number of events
NNT = number needed to treat to prevent one event over trial period
** 4S: CHD death, non-fatal definite or probable MI, silent MI, resuscitated cardiac arrest*
CARE: CHD death or symptomatic non-fatal MI (except during cardiac surgery)
LIPID: CHD death or silent or symptomatic non-fatal MI

Population interventions

A mass population intervention strategy, initiated during the 1970s in North Karelia, Finland, has been associated with a significant fall in CHD mortality of about 50% in that region[18,19]. The North Karelia project was not a randomised trial of multifactorial intervention but nevertheless supports the view that lifestyle measures may impact on CHD morbidity and mortality if individuals and local populations are willing and able to make the necessary changes. Population interventions, such as the North Karelia project, must also address the social, economic and environmental circumstances which influence health.

Lipid lowering drugs for high risk patients

Early trials using anion exchange resins or fibrates of limited potency recorded small reductions in fatal and non fatal CHD events with an increase in non cardiovascular mortality (WHO Clofibrate Study[20,21], Lipid Research Clinics Coronary Primary Prevention Trial[22,23] and the Helsinki Heart Study[24].

Two primary prevention studies – the West of Scotland Coronary Prevention Study (WOSCOPS)[25] and the Air Force/ Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS)[26] – and three secondary prevention studies – the Scandinavian Simvastatin Survival Study (4S)[15], the Cholesterol and Recurrent Events (CARE) study[16], and the Long-term Intervention with Pravastatin and Ischaemic Disease (LIPID) study[17] – using statins (HMG CoA reductase inhibitors) have since shown clinically and statistically significant falls in fatal and non fatal CHD. Because there were no adverse outcomes with statins in these trials, three of the five (WOSCOPS, 4S, and LIPID) were also able to show significant reductions in all cause mortality.

That lipid lowering with statins has produced beneficial effects is no longer in doubt, but it is only one of the mechanisms that contribute to coronary heart disease. The challenge now is to decide which patients should be targeted for drug therapy and how they should be managed effectively.

COMPARISON OF PRIMARY AND SECONDARY PREVENTION TRIALS

Table 2 shows baseline risk factors, major CHD event rates and number needed to treat in AFCAPS/TexCAPS, WOSCOPS, CARE, LIPID and 4S to save one major coronary event during the duration of each trial[27].

The reduction in coronary heart disease event rates in the major statin trials, primary and secondary, has also been summarised graphically by Illingworth[28]. This is reproduced as Figure 1.

PATIENTS WITH CORONARY HEART DISEASE

The results of the post-coronary artery bypass graft trial (Post-CABG) Trial, the Atorvastatin versus revascularization treatment trial (AVERT), and the Myocardial ischaemia reduction with aggressive lowering (MIRACL) study, together provided additional evidence on the benefits of reducing LDL-Cholesterol levels in patients with coronary artery disease to less than 100 mg/dL[29].

The post-coronary artery bypass graft trial. The Post-Coronary Artery Bypass Graft (Post-CABG) Trial, supported by the National Heart, Lung, and Blood Institute, compared moderate and aggressive lowering of LDL-C to determine the effects on atherosclerotic changes in coronary artery bypass

Table 2. Comparison Of Primary And Secondary Prevention Trials

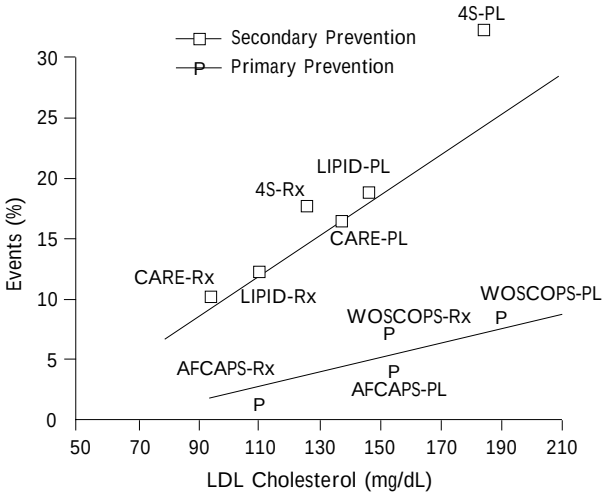
	AFCAPS/TexCAPS	WOSCOPS	CARE	LIPID	4S
Subjects (% male)	6605 (85%)	6595 (100%)	4159 (86%)	9014 (83%)	4444 (81%)
Average age (range) years	57 (43-73)	55 (45-64)	59 (21-75)	62 (31-75)	59 (35-70)
Previous CHD	0%	5% (no MI)	100% (all MI)	100% (64% MI / 36% UAP)	100% (81%MI)
Previous CABG/PTCA	0%	0%	54%	44%	8%
Baseline cholesterol (mmol/l)	5.7 (HDL<1.2)	7.0 (6.5-8.0)	5.5 (<6.2)	5.6 (4.0-7.0)	6.8 (5.5-8.0)
Active treatment (mg/day)	Lovastatin 20-40 mg	Pravastatin 40 mg	Pravastatin 40 mg	Pravastatin 40 mg	Simvastatin 20-40 mg
Average cholesterol reduction (mmol/l)	1.0	1.4	1.1	1.0	1.7
Placebo event rate*	5.5%	7.9%	13.2%	15.9%	28.0%
Statin event rate	3.4%	5.5%	10.2%	12.3%	19.4%
Relative risk reduction (95% CI)	37 (21-50) %	31 (17-43)%	24 (9-36)%	24 (15-32)%	34 (25-41)%
Absolute risk reduction	2.0%	2.4%	3.0%	3.6%	8.6%
Number needed to treat	50	42	33	28	11

Source: SIGN 40, 1999.

Key to abbreviations:CHD = coronary heart disease; MI = myocardial infarction; UAP = unstable angina pectoris;CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; The event rates in WOSCOPS, LIPID and 4S are for definite CHD death or non fatal MI; in CARE for definite and suspect CHD death or definite non fatal MI; and in AFCAPS/TexCAPS for fatal and non fatal MI, unstable angina or sudden death. Relative risk reductions are similar for all five trials. The number needed to treat (NNT) for five years to save one event is the reciprocal of the absolute risk reduction. The patients who benefited most were those at highest risk initially.*

FIGURE 1. Coronary heart disease event rates and mean low-density lipoprotein (LDL) cholesterol levels in major statin trials.

AFCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE = Cholesterol and Recurrent Events trial; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease trial; PL = placebo; Rx = statin-treated; 4S = Scandinavian Simvastatin Survival Study; WOSCOPS = West of Scotland Coronary Prevention Study. (Reproduced Med Clin North Am. 2000;84:23-42.)



grafts[30]. Subjects had a history of bypass surgery (1 to 11 years earlier), LDL-C levels of 130 mg/dL to 175 mg/dL, and at least one patent vein graft at study entry. Participants who received the aggressive lipid-lowering regimen achieved a mean LDL-C level of 93 to 97 mg/dL, whereas those on the moderate lipid-lowering regimen achieved a mean LDL-C level of 132 to 136 mg/dL. After an average of 4.3 years, aggressively treated patients (LDL-C of 93 to 97 mg/dL) were compared with those in the moderate-treatment group. The aggressively treated patients had (1) less progression of atherosclerosis, (2) fewer new occlusions and lesions in grafted vessels, (3) less narrowing of lumen diameter, and (4) a lower rate of revascularization. Follow-up analysis of the data revealed that aggressive lowering of LDL-C was beneficial in all patients, regardless of age, gender, smoking status, or the presence of diabetes or hypertension. The investigators concluded that post-CABG patients derived long-term benefits from reducing their LDL-C levels to <100 mg/dL.

Atorvastatin versus revascularization treatment trial. Similarly, in the Atorvastatin Versus Revascularization Treatment (AVERT) trial, lowering LDL-C levels to <100 mg/dL in 341 relatively low-risk patients with ischemic heart disease and stable asymptomatic or mild-to-moderate angina resulted in a decreased risk for ischemic events. Subjects had an LDL-C level of =140 mg/dL at baseline and were randomly assigned to receive atorvastatin 80 mg/day or to undergo angioplasty followed by usual care, including lipid-lowering treatment. After 18 months, atorvastatin therapy reduced the mean LDL-C level by 46% (to 77 mg/dL) in the aggressive-treatment group. By contrast, mean LDL-C decreased by only 18% (to 119 mg/dL) in the angioplasty patients, 69% of whom were also receiving lipid-lowering therapy (usually a low dose of a statin) at study end. The atorvastatin-treated patients had a 36% lower incidence (p 0.048 not statistically significant) of ischemic events than did the revascularized patients, as well as a significantly longer time to first ischemic event. The investigators concluded that aggressive lipid lowering is at least as effective as angioplasty in reducing the incidence of ischemic events in the subset of relatively low-risk patients with stable coronary artery disease[31].

The myocardial ischemia reduction with aggressive cholesterol lowering study. This study suggests that benefit may be observed in people who already have coronary artery disease if their LDL-C levels are decreased to <80 mg/dL. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial enrolled 3,086 patients who had been hospitalized with unstable angina or a non-Q-wave myocardial infarction. Patients, who had an average LDL-C level of 123 mg/dL at baseline, were randomized to receive either 80 mg/day of atorvastatin or a placebo within 4 days of the qualifying event. At 16 weeks, the average LDL-C level had decreased to 72 mg/dL in the atorvastatin group but had increased slightly in the placebo group. The risk for the primary combined endpoint of death, recurrent myocardial infarction, cardiac arrest with resuscitation, or worsening of angina requiring hospitalization decreased by 16% (statistically significant) in the atorvastatin group[32].

COMBINATION THERAPY FOR REDUCTION NON-HDL CHOLESTEROL

In accordance with ATP III guidelines, the primary target of therapy is lowering LDL cholesterol. After LDL cholesterol is reduced in accordance with ATP III guidelines, reduction of non-HDL cholesterol becomes the secondary therapeutic objective[29].

Many patients with high concentrations of non-HDL cholesterol have the metabolic syndrome and/or type 2 diabetes and thus would benefit from therapeutic lifestyle changes, such as diet and exercise. Pharmacologic therapy for high levels of non-HDL cholesterol in statin-treated patients may include escalation of the statin dosage or combination therapy with nicotinic acid and/or a fibrate. The decision as to whether to combine a statin agent with a fibrate or niacin is influenced by baseline levels of triglycerides (fibrate therapy) and HDL cholesterol (niacin therapy)[30].

Although no formal recommendations have been advocated for increasing HDL cholesterol levels by pharmacological intervention, low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women) remains an important predictor of recurrent cardiovascular events in patients with CHD. Pharmacologic therapy in statin-treated patients with low HDL cholesterol or small LDL particles may include niacin; when the triglycerides are elevated, fibrates are effective HDL-increasing agents[30].

LEARNING POINTS

- LDL Cholesterol is the primary target for lowering cholesterol
- The order of cholesterol reduction in the different modalities of intervention is dietary modification 9%, bile sequentrants and fibrates 10%, statins 25-30%
- Secondary prevention and primary prevention strategies are both important
- Combination therapy may be needed to deal with non-LDL cholesterol reduction seen in diabetes mellitus.

REFERENCES

1. National Cholesterol Education Programme. Full Report of the Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). National Heart, Lung, And Blood Institute; Sep 2002:II-1.
2. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986:232:34-47.
3. McKenney J. Combination therapy for elevated low-density lipoprotein cholesterol: the key to coronary artery disease risk reduction. Am J Cardiology 2002;90(10 Suppl 2): 8-20.
4. Llyod-Jones DM et al. Lifestyle Risk of Coronary Heart Disease by Cholesterol Levels at Selected Ages. Arch Intern Med Sep 8 2003, 163:1966-1972.
5. Verschuren VM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five year follow-up of the seven countries study. JAMA 1995 Jul 12;274(2):131-6.
6. Marmot MG, Syme SL. Acculturation and coronary heart disease in Japanese-Americans. Am J Epidemiol 1976 Sep;104(3):225-47.
7. Stamler J, Wentworth D, Neatson JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986 Nov 28; 256(20):2823-8.
8. Wong ND, Cupples LA, Ostfeld AM, Levy D, Kannel WB. Risk factors for long-term coronary prognosis after initial myocardial infarction: the Framingham Study. Am J Epidemiol 1989; 130: 469-80.
9. SIGN 41. Secondary prevention of coronary heart disease following myocardial infarction, Jan 2000.
10. Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without pre-existing cardiovascular disease. N Engl J Med 1990;322:1700-7.
11. Hooper L et al. Dietary fat intake and prevention of cardiovascular disease; systematic review. BMJ 2001:322:757-63.
12. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 1994; 308: 367-72.
13. Huttunen JK, Manninen V, Manttari M, Koskinen P, Romo M, Tenkanen L, Heinonen OP, Frick MH. The Helsinki Heart Study: central findings and clinical implications. Ann Med 1991;23:155-9.
14. Rifkind BM. Gemfibrozil, lipids, and coronary risk. N Engl J Med 1987;317:1279-81.
15. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study Group (4S). Lancet 1994;344:1383-9.
16. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001-9.
17. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-57.
18. Puska P, Koskela K, Pakarinen H, Puumalainen P, Soininen V, Tuomilehto J. The North Karelia Project: a programme for community control of cardiovascular diseases. Scand J Soc Med 1976;4:57-60.
19. Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P. Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. BMJ 1994;309:23-7.
20. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. Br Heart J 1978;40:1069-118.
21. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Report of the Committee of Principal Investigators. Lancet 1984;15:600-4.
22. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251:351-64.
23. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984;251:365-74.
24. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45.
25. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, 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;333:1301-7
26. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, 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;279:1615-22.
27. SIGN 40. Lipids and the Primary Prevention of Coronary Heart Disease, 1999.
28. Illingworth DR. Management of hypercholesterolemia. Med Clin North Am 2000;84:23-42.
29. Castelli WP. Making practical sense of clinical data in decresing cardiovascular risk. Am J Cardiology Aug 16, 2001;88(4 SuppA):16F-20F.
30. Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Eng J Med 1998;336:153-52.
31. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease – Atovastatin Versus Revascularization Treatment Investigators. N Eng J Med 1999;341:70-76.
32. Schwartz GG, Oliver MF, Ezekowitz MD et al. Rationale and design of the Myocardial Ischemia. Reduction with Aggressive Cholersterol Lowering (MIRACL) Study that evaluates atorvastatin in unstable angina peotoris and in non-Q-wave acute myocardial infarction. Am J Caridiol 1998;81:578-81.
33. NCEP. Executive Summary of the Third Report of the National Cholesterol Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
34. Rosenson RS. The Rationale for Combination Therapy. Am J Cardiology 2002;90(suppl):2K-7K.