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Who Should Receive HMG CoA Reductase Inhibitors?

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Abstract

During the last decade, the development of the HMG CoA reductase inhibitors, commonly referred to as 'statins', has contributed greatly to cholesterol lowering therapy and cardiovascular risk reduction. These agents are well tolerated and efficacious. Data on nearly 30 000 patients from five long-term randomised, placebo-controlled trials of statins have clearly demonstrated that a broad range of individuals can benefit from such therapy. These include men or women, younger or older individuals, those with elevated or normal cholesterol levels, with or without myocardial infarction or symptomatic coronary heart disease, with or without hypertension or diabetes mellitus, and those who are smokers or non-smokers. Benefits include reductions in the risks for myocardial infarction, and coronary, cardiovascular and all-cause mortality, stroke and the need for coronary revascularisation. Results of the recently completed Heart Protection Trial have clearly confirmed the results of the earlier trials and support the use of statin therapy in secondary prevention. The role of statins in acute coronary syndromes is being actively evaluated and appears promising. In primary prevention, the data are not as convincing and generalisations cannot be made as to whether, and in which subgroup, drug therapy to lower low density lipoprotein (LDL) cholesterol should be initiated. There are important cost implications to consider and the use of statin therapy has to be judged on an individual basis, particularly in those with high or very high LDL cholesterol levels and/or with multiple risk factors rendering them at high short- and long-term risk of coronary heart disease. There is evidence of a 'care gap' in translating trial data into practice, even in secondary prevention, and this needs closing in order to improve patient outcomes.

During the last decade, the development of the HMG CoA reductase inhibitors, commonly referred to as 'statins', has contributed greatly to cholesterol lowering therapy and cardiovascular risk reduction.[1,2] Extensive research has demonstrated: (i) the mechanistic role of lipids in atherosclerosis formation; and (ii) the epidemiology of cholesterol as a cardiovascular risk factor. Clinical trials have shown that lipid lowering therapy reduces morbidity and mortality secondary to coronary artery disease in individuals with elevated or normal cholesterol levels. The link between lipid levels and risk of cardiovascular disease is now widely accepted. Preventive measures are commonly used in individuals at risk. This has not always been the case.

Although earlier trials of less efficacious and less well tolerated cholesterol lowering agents have shown that high-risk individuals with high cholesterol levels benefited from cholesterol lowering therapy, the results of many of these trials were

inconclusive, particularly for individuals with mildly elevated or normal cholesterol levels.[3,4] There were controversies as to whether it was safe to lower cholesterol levels so much (total cholesterol <5.20 mmol/L) in this latter group.[4] With the introduction of the statins and the completion of several key clinical trials with these agents, the benefits of cholesterol lowering have been conclusively shown in individuals at risk.[5-9] With two exceptions,[8,9] these were carried out as secondary prevention trials. Concurrent angiographic studies and animal and laboratory studies have corroborated the results from the clinical trials and have provided insights into the mechanisms of the benefits of statin therapy.[10-16]

The issues now are not whether treatment with statins is beneficial but who should be treated and whether such treatment would reduce the risk of other clinical events besides those that can be directly attributed to coronary heart disease. Until recently, there was a debate as to whether there is a threshold level below which low density lipoprotein (LDL) cholesterol lowering is not beneficial. This has been settled with the completion and report of the Heart Protection Trial.[17] There are also suggestions that other mechanisms of action of the statins, besides cholesterol lowering, may have contributed to the benefits seen in these trials. A review of the results from the major trials and other studies will answer some of these questions.

Statins lower cholesterol levels by suppression of hepatic cholesterol synthesis, leading to an increase in hepatic LDL receptors and an alteration in the formation of very-low-density lipoprotein (VLDL) particles. The commonly available statins include lovastatin, pravastatin, simvastatin, fluvastatin and atorvastatin. A fifth, cerivastatin, has been withdrawn from the market recently because of an excess of adverse effects. Many studies have shown that the efficacy of these agents in lowering LDL cholesterol varies greatly when using published recommended doses. Only three of these agents, simvastatin, pravastatin and lovastatin have been used in published major clinical trials (see section 1).[5-9] While the evidence supports the view that the benefits of the statins are probably a class effect, differences among agents cannot be easily resolved in the absence of large 'head to head' comparative trials. Nevertheless, there is more than adequate information from this large database to draw useful conclusions.

1. Clinical Trials

Five key, adequately powered, long-term clinical outcomes trials have been conducted and these have exerted the greatest impact on clinical practice (table I). They are the three secondary prevention trials, the Scandinavian Simvastatin Survival Study (4S),[5] the Cholesterol and Recurrent Events (CARE) trial[6] and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial,[7] and the two primary prevention trials, the West of Scotland Coronary Prevention Study (WOSCOPS)[8] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[9] A number of angiographic trials have also been carried out evaluating the effects of statin treatment on the progression of coronary atherosclerosis and their results are in concordance with the major clinical trials.[10-16]

The spectrum of the 29 820 patients enrolled in these five trials ranged from high-risk patients with myocardial infarction and/or unstable angina pectoris and with cholesterol levels up to 8.0 mmol/L to those without clinical evidence of vascular disease and normal cholesterol levels (table I). In these trials, LDL cholesterol levels were reduced by approximately 25 to 35% during the long-term follow-up of 5 to 6 years. The primary trial endpoints varied among the trials, since the choice of primary endpoint in any trial is greatly influenced by the sample size, the duration of treatment and the baseline risk profile of the patients. Thus, the primary endpoints were: total all cause mortality in the 4S trial; a composite of coronary heart disease mortality or non-fatal myocardial infarction in the CARE trial; coronary heart disease mortality in the LIPID trial; a composite of coronary heart disease mortality or non-fatal myocardial infarction in WOSCOPS; and a composite of fatal or

Table I. Summary of baseline characteristics of patients enrolled in five major randomised, placebo-controlled clinical trials of HMG Co-A reductase inhibitors

Variables	4S[5]	CARE[6]	LIPID[7]	WOSCOPS[8]	AFCAPS/ TexCAPS[9]
No. pts	4444	4159	9014	6595	5608
Start date	May 1988	Dec 1989	Jun 1990	Feb 1989	May 1990
Completion date	Aug 1994	Feb 1996	Sep 1997	May 1995	Sep 1997
Average follow-up (y)	5.4	5.0	6.1	4.9	5.2
Active treatment (mg/day)	Simvastatin 20-40	Pravastatin 40	Pravastatin 40	Pravastatin 40	Lovastatin 20-40
Average age (y)	51% ≥60[a]	59	62	55	58
Female (%)	19	14	17	0	15
MI (%)	79	100	64	[b]	[c]
UAP (%)	38	20	36	5[b]	[c]
Current smoker (%)	27	21	10	44	12
Hypertension (%)	26	43	42	15	22
Diabetes mellitus (%)	5	15	9	1	4
PTCA alone (%)		28	11		
CABG alone (%)		32	27		
PTCA or CABG (%)	8	54	35		
Concomitant medication (%)					
Aspirin	37	83	82		17
β-Blockers	57	39	47		5
Calcium channel antagonists	30	38	36		5
ACE inhibitors		14	16		8
Lipid levels mmol/L (% change)[d]					
Total cholesterol	6.75 (–25)	5.40 (–20)	5.64 (–18)	7.03 (–20)	5.71 (–18)
LDL cholesterol	4.87 (–35)	3.60 (–28)	3.88 (–25)	4.97 (–26)	3.89 (–25)
HDL cholesterol	1.19 (+8)	1.01 (+5)	0.93 (+5)	1.14 (+5)	0.94 (+6)
Triglycerides	1.51 (–10)	1.75 (–14)	1.56 (–11)	1.85 (–12)	1.78 (–15)

a 51% of patients in 4S were 60 years of age or older, suggesting a median age of just over 60 years.

b None of the patients had a history of MI, but 5% had stable angina pectoris not requiring hospitalisation during previous 12 months.

c Patients with MI, angina pectoris or other clinical vascular disease were excluded.

d Percent change from baseline in patients on active treatment or comparison of lipid levels between active and placebo groups during the trial.

4S = Scandinavian Simvastatin Survival Study; **ACE** = angiotensin converting enzyme; **AFCAPS/TexCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **CABG** = coronary artery bypass graft surgery; **CARE** = Cholesterol and Recurrent Events; **HDL** = high density lipoprotein; **LDL** = low density lipoprotein; **LIPID** = Long-term Intervention with Pravastatin in Ischaemic Heart Disease; **MI** = myocardial infarction; **PTCA** = percutaneous transluminal coronary angioplasty; **UAP** = unstable angina pectoris; **WOSCOPS** = West of Scotland Coronary Prevention Study.

non-fatal myocardial infarction, unstable angina or sudden cardiac death in AFCAPS/TexCAPS. In each trial, a clear and consistently significant reduction in risk of the primary endpoint was found in patients on active treatment compared with placebo.[5-9]

As summarised in table II, statistically significant, or strong trends toward significant, risk reductions were seen in myocardial infarction, in deaths from coronary heart disease, cardiovascular or all-causes, in stroke and in the need for revascularisation in the patients receiving statins compared with controls. These data can be interpreted as indicating that statin therapy is beneficial in a wide range of patients, irrespective of gender, age, cholesterol levels, smoking status, or history of

Table II. Relative risk reductions (95% confidence interval) in clinical outcomes in five major randomised, placebo-controlled clinical trials of HMG Co-A reductase inhibitors

Outcome	4S[5]	CARE[6]	LIPID[7]	WOSCOPS[8]	AFCAPS/ TexCAPS[9]a
Non-fatal MI	37 (27-46)	23 (8-39)		31 (15-45)	
Any MI		25 (8-39)	29 (18-38)		40 (17-57)
Mortality from:					
CHD	42 (27-54)	20 (–5-39)	24 (12-35)	28 (–10-52)	
CV	35 (20-40)	15 (–11-35)	25 (13-35)	32 (3-53)	
non-CV	5 (–41-37)	11 (–22-35)		11 (–28-38)	
all-cause	30 (15-42)	9 (–12-26)	22 (13-31)	22 (0-40)	
Stroke	30 (4-48)	27 (15-37)	19 (0-34)	11 (–11-40)	
Revascularisation	37 (26-46)	31 (3-52)	20 (10-28)	37 (11-56)	33 (15-48)

a Significant reductions were found in the primary composite endpoint of first major coronary event (fatal or non-fatal MI, unstable angina pectoris or sudden cardiac death) and other cardiovascular events.

4S = Scandinavian Simvastatin Survival Study; **AFCAPS/TexCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **CARE** = Cholesterol and Recurrent Events; **CHD** = coronary heart disease; **CV** = cardiovascular; **LIPID** = Long-term Intervention with Pravastatin in Ischaemic Heart Disease; **MI** = myocardial infarction; **WOSCOPS** = West of Scotland Coronary Prevention Study.

hypertension, diabetes mellitus, myocardial infarction, or the presence or absence of coronary disease symptoms.

In the interpretation of trial data, whether or not some patients with some particular baseline characteristics will benefit from statin therapy can be determined by subgroup analysis. However, such analyses can be fraught with statistical type I and type II errors, and any results should be interpreted cautiously. In randomised trials, the reliable detection of modest, but important, differences between active and control treatments requires large number of patients and events. To further detect significant treatment differences between subgroups, substantially more patients are required. No study is designed such that there is adequate power to reliably detect subgroup differences. To overcome this concern about lack of statistical power, pooling of the data from several trials has been carried out and data from other trials can be examined for consistency of outcomes. A formal analysis of the pooled data from the three pravastatin trials (CARE, LIPID and WOSCOPS) has reported that active treatment in these trials significantly reduced the risk of coronary heart disease death or nonfatal myocardial infarction in younger (<65 years) and older (≥65 years) patients, men and women, smokers and non-smokers, and patients with and without diabetes or hypertension.[18] Significant relative risk reductions were seen in the various pre-defined categories of baseline lipid levels.[18] Subgroup analyses from the 4S trial confirm these findings.[5,18-21]

The 4S trial, which included patients with higher cholesterol levels than those in the other trials, reported similar treatment sizes were seen in the patients regardless of baseline cholesterol levels,[5] whereas the CARE trial suggested that patients with baseline LDL cholesterol levels lower than 3.25 mmol/L did not benefit from treatment.[6] This latter observation has not been confirmed in other trials. It may be that individuals with these low baseline levels were at a much lower risk and therefore that the sample size in this particular subgroup did not have sufficient statistical power to show a difference between the active and control groups. Another explanation may be that there really is a biological basis for the apparent lack of effect.[22] On balance, the former explanation is more likely. In general, in these trials, the likelihood of benefit is greater in the secondary prevention trials enrolling higher risk patients, than in the primary prevention trials that enrol lower risk patients. In the primary prevention trials, the WOSCOPS trial, which enrolled higher risk patients, showed a greater likelihood of, and larger

absolute, benefit than in the AFCAPS/TexCAPS trial which evaluated lower risk patients.

The contribution of statins appears promising in patients with acute ischaemic syndromes. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study randomised 3086 patients to atorvastatin 80 mg/day or placebo 24 to 96 hours after an acute ischaemic syndrome.[23] After a follow-up period of up to 16 weeks, the difference in the primary composite outcome of death, nonfatal myocardial infarction, cardiac arrest with resuscitation, or recurring symptomatic myocardial ischaemia with objective evidence and requiring emergency hospitalisation between the atorvastatin group (14.8%) and the placebo group (17.4%) was nominally significant ($p = 0.048$). There were no significant differences between the groups for each of the individual endpoints except for a significantly lower risk in symptomatic ischaemia requiring hospitalisation (6.2 *vs* 8.4%, $p = 0.02$).[23] Several ongoing trials are currently actively evaluating the role of the statins in acute ischaemic syndromes.

2. Angiographic Trials

Angiographic trials of cholesterol lowering therapy have also shown consistently that patients randomised to active treatment benefited with a slowing of progression, or even an enhancement of regression, of coronary atherosclerosis.[10-16] Early coronary angiographic trials enrolled only patients with high cholesterol levels.[10-12] More recent trials have enrolled patients with moderately elevated levels.[13-16] One trial has reported a neutral effect on angiographic endpoints in patients with normal cholesterol levels,[24] but another with a larger sample size and longer follow-up showed clearly that patients with normal or slightly elevated cholesterol levels clearly benefited angiographically from long-term (average follow-up of 4 years) statin therapy.[15]

Subgroup analysis of the data from the latter trial also showed convincingly that the benefits could be seen in important subgroups including men or women, younger or older individuals, those with hypertension and those without, individuals with diabetes and those without, smokers or non-smokers, and those with or without advanced lesions.[16] These data are clearly consistent with the overall data from the clinical trials with clinical endpoints.

The Heart Protection Trial, the preliminary results of which were reported at the American Heart Association Annual Scientific Meeting in November 2001, studied the effects of simvastatin 40 mg/day and antioxidant vitamin supplementation on mortality in a wide range of 20 536 patients at high risk of coronary heart disease, that is, those with previous myocardial infarction or other coronary heart disease, other occlusive non-coronary atherosclerotic disease, diabetes or hypertension.[17] At baseline, 42% of patients had LDL cholesterol levels of ≥3.5 mmol/L, 25% had levels between 3.0 and 3.5 mmol/L and 33% had levels <3.0 mmol/L. In addition, 24% of the patients were between 65 and 69 years of age and 28% were 70 years or older. While the vitamin supplementation had a neutral effect on outcomes, treatment with simvastatin was associated with a highly significant 17% relative risk reduction in vascular mortality ($p < 0.0002$) and a 12% reduction in all cause mortality ($p < 0.001$). Stroke was reduced by 27% ($p < 0.00001$). Highly significant reductions are seen in the major pre-specified subgroups of those patients with myocardial infarction, those without coronary heart disease but with cerebrovascular disease, peripheral vascular disease or diabetes. Similar reductions in risk of vascular events after treatment with simvastatin were seen in male and female patients, and in all age groups, that is, in those who were younger than 65 years, 65 to 69 years, 70 to 74 years and those 75 years or older. Comparable benefits were also seen in patients irrespective of their baseline LDL cholesterol levels.

Thus, this trial confirms the finding from the earlier trials. A consistent finding is that high-risk patients benefit from statin therapy irrespective of gender, age and baseline LDL cholesterol levels. Unlike a previous trial suggesting that there is a level of LDL cholesterol (3.25 mmol/L) below

which further LDL cholesterol lowering is not associated with benefits,[6] this trial showed that even in patients with LDL cholesterol levels which are 3.0 mmol/L or less, benefits of treatment can be obtained.

3. Other Outcomes

Interpretation of the data on the effects of statin treatment on other outcomes must be qualified by the comments on subgroup analysis. However, statin treatment has also been consistently observed to reduce the incidence of stroke and the need for revascularisation in the trials discussed here (table II). While reduction of the need for revascularisation may be seen to be part of the 'anti-atherosclerosis' effect of statins, it is less easy to explain the reduction in stroke risk.

Stroke and coronary heart disease share many of the same risk factors, but the correlation between cholesterol levels and either ischaemic or haemorrhagic stroke has been shown to be weak.[25] That statin therapy can reduce the incidence of stroke by approximately 30%[25] can perhaps be attributed to anti-atherosclerotic effects or to other mechanisms of the statins.

4. Other Mechanisms of Benefit from Statin Therapy

Several studies have suggested that statins are associated with a number of potential mechanisms of benefit other than cholesterol lowering. These include anti-inflammatory and antiatherothrombotic properties.[26-28] It has been suggested that the reason the clinical benefits of statin therapy are much greater than that which could be extrapolated from the effects of the treatment on angiographic endpoints may be due to these mechanisms, which are unrelated to cholesterol lowering. However, other investigators suggest that the reason patients benefit from statins is that cholesterol lowering results in shrinkage, or in slowing of progression, of the atherosclerotic plaque and stabilisation of the lipid rich plaque.[29,30] Thus, while the possible role of the non-cholesterol lowering mechanisms appears interesting, their contribution to the clinical benefits remains to be demonstrated.

5. Cholesterol Lowering Therapy in Clinical Practice: Primary versus Secondary Prevention

The data have thus far been reviewed in terms of risk levels. Data from the trials have shown that individuals at high risk of developing cardiovascular disease such as those enrolled in the 4S, derived greater benefits from statin therapy than the patients at lower risk in the AFCAPS/TexCAPS. In clinical practice, it is more usual to make decisions about drug cholesterol lowering therapy in terms of primary or secondary prevention. Most of the data demonstrating the effectiveness of statin therapy have been obtained from trials of secondary prevention. Only the data from WOSCOPS and AFCAPS/TexCAPS are available on primary prevention. Whether or not drug therapy should be initiated in primary prevention remains controversial.[31] Because of the smaller number of lower risk individuals who experienced fewer events in these two trials, data from subgroup analyses as to whether particular subgroups would benefit from treatment remain inconclusive. This is in contrast to secondary prevention trials, in which convincing data show that a broad range of individuals will benefit from treatment. It has been pointed out that a decision to initiate statin therapy as primary prevention in an individual may be guided by data from cost effectiveness analyses.[31] While this is logical, for the practising physician, such analyses may not be readily available nor specifically applicable to the individual situation and there is no simple guide from the trial data with which to help with decision making. The Third Report of the National Cholesterol Education Program (NCEP III) has adopted an approach that appears reasonable.[32]

6. Third Report of the National Cholesterol Education Program (NCEP III)

The NCEP III guidelines on the detection, evaluation and treatment of high cholesterol in adults

in the management of cholesterol as a cardiovascular risk factor has been updated in light of current data, and recently published.[32] This document emphasises the importance of risk assessment of all individuals, primary and secondary prevention, LDL cholesterol lowering, and also raises the issue of cost-effectiveness of treatment of individuals in the various risk groups. Treatment goals for LDL cholesterol are indicated depending on the individual's risk category.

In secondary prevention, for those individuals with coronary heart disease and coronary heart disease risk equivalents (much like those enrolled in the Heart Protection Trial) the LDL cholesterol goal is <2.60 mmol/L (100 mg/dL), those with multiple (two or more) risk factors, the goal is <3.36 mmol/L (130 mg/dL) and those with zero to one risk factor, the goal is <4.15 mmol/L (<160 mg/dL). Although therapeutic lifestyle changes in LDL cholesterol lowering therapy are indicated in all categories, in order to achieve treatment goals, drug therapy is often indicated, particularly in those individuals in whom a low LDL cholesterol level is desirable. Because of efficacy in lowering cholesterol levels and clinical risk and high tolerability, the statins are generally accepted as drugs of first choice in this regard.

In a section on primary prevention and LDL cholesterol lowering therapy, lifestyle changes are seen as the most cost-effective means to reduce coronary heart disease. It is also noted that while the 'clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including: 1) reduced intakes of saturated fat and cholesterol, 2) increased physical activity, and 3) weight control, to lower population cholesterol levels and reduce coronary heart disease risk, … the clinical approach intensifies preventive strategies for higher risk persons'.[32] It is suggested that persons who are at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL cholesterol lowering drug therapy.[32] Such a recommendation is consistent with the interpretation of the available data on primary prevention.

7. Translation of Trial Results Into Practice

Despite the conclusiveness of the results from these and other trials, available evidence indicates that the results have not been translated into an optimal level of practice.[33-35] There are many reasons for this 'care gap'.[33] Awareness of and willingness to apply these data by the physicians, empowering patients to know their risk factors and to ask for appropriate treatment, and ensuring that patients have proper access (financially) to the medications are important factors. Innovative practice-enhancing measures, which can be incorporated seamlessly into traditional practices, may result in closure of the 'care gap' and improvement in patient outcomes.[33-36] These can be simple measures such as ensuring that appropriate treatments are started before patient discharge from hospital, patient management clinical paths and other systematic approaches to risk factor modifications.[33,36]

8. Conclusion

Data on nearly 30 000 patients from five long-term randomised, placebo-controlled trials of statins have clearly demonstrated that a broad range of individuals can benefit from such therapy. These include men or women, younger or older individuals, those with elevated or normal cholesterol levels, with or without myocardial infarction or symptomatic coronary heart disease, with or without hypertension or diabetes, and those who are smokers or non-smokers. Benefits include reductions in the risks for myocardial infarction, coronary, cardiovascular and all-cause mortality, stroke and the need for coronary revascularisation. Certainty of benefits is much clearer in higher risk coronary patients than in lower risk individuals without clinical evidence of vascular disease. Results of the recently completed Heart Protection Trial have clearly confirmed the results of the earlier trials and support the use of statin therapy in secondary prevention. The promising role of statins

in the management of patients with acute ischaemic syndromes is being actively evaluated.

In primary prevention, the data are not as convincing and generalisations cannot be made as to whether, and in which subgroup, drug therapy to lower LDL cholesterol should be initiated.

There are important cost implications and the use of statin therapy has to be judged on an individual basis, particularly in those with high or very high LDL cholesterol levels and/or with multiple risk factors placing them at high short- and long-term risk of coronary heart disease. There is evidence of a 'care gap' in translating trial data into practice, even in secondary prevention, and this 'care gap' needs closing in order to improve patient outcomes.

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