Statin therapy in people with diabetes and high-risk patients

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Lipid lowering forms part of the treatment of atherosclerosis. Primary prevention is dependent on identification and treatment of patients at high risk of which patients with diabetes are the clearest example. This article reviews the role of lipid lowering in high-risk individuals.

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The role of statin therapy in the treatment of patients with coronary heart disease is well established (*Table 1*) and forms part of the National Service Framework (NSF) for Coronary Heart Disease (Department of Health, 2000). It is recommended that all primary prevention patients are screened for cardiovascular risk factors, their risk assessed with the charts printed in the back of the British National Formulary and treated as appropriate.

Accepted interventions include the use of aspirin, antihypertensives (in varying contexts) and lipid-lowering therapies. In primary prevention, studies have shown the benefit of cholesterol reduction in high-risk men (West of Scotland Study; Shepherd et al, 1995) and in a population with low high density lipoprotein (HDL) (Air Force/Texas Coronary Atherosclerosis Prevention Study (AF/TexCAPS); Downs et al, 1998). The statins used in these studies not only reduce cholesterol but seem to have anti-inflammatory effects that reduce the inflammation present in atherosclerotic lesions and thus directly benefit plaque stability.

RISK OF EVENTS IN DIABETES

One of the highest risk groups for atherosclerotic events is patients with diabetes. The risk of coronary heart disease in patients with type 2 diabetes is in a similar range to that found in patients with established coronary heart disease (Haffner et al, 1998; Evans et al, 2002). In diabetes patients develop macrovascular disease, which is mostly

TABLE 1.
Summary of major end-point trials

		Number		Starting (mmol/litre)		Reduction (%)		Events		
Primary	Treatment	Men	Women	LDL	TG	LDL	TG	PTCA/CABG	MI	Death
LRC	Cholestyramine	10627	–	5.3	1.70	8	+3	–	25	20
WHO	Clofibrate	3806	–	~5	–	9	–	–	19	19
HHS	Gemfibrozil	4081	–	5.37	2.01	11	35	–	34	37
VA-HIT	Gemfibrozil	2531	–	2.90	1.81	0	25	9	22	22
4S	Simvastatin	3617	827	4.87	1.51	35	10	37	34	42
CARE	Pravastatin	3583	576	3.60	1.00	28	14	27	27	24
LIPID	Pravastatin	7498	1516	3.89	1.56	25	11	20	29	22
WOSCOPS	Pravastatin	6595	–	5.00	1.70	26	12	37	31	32
AF/TexCAPS	Lovastatin*	5608	997	3.89	1.78	25	15	33	40	N/A
Post-CABG	Lovastatin* ±cholestyramine	1243	108	3.98	1.76	14 *vs* 38	–	N/A	12.5	10
HPS	Simvastatin	15454	5082	3.5	2.0	31	23	24	26	13
GREACE	Atorvastatin	1256	344	4.65	2.08	46	31	51	59†	43

*Lovastatin is not licensed in the UK. †non-fatal. 4S = Scandinavian Simvastatin Survival Study; AF/TEX Caps = Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE = Cholesterol And Recurrent Events; GREACE = GREek Atorvastatin and Coronary-heart-disease Evaluation; HHS = Helsinki Heart Study; HPS = Heart Protection Study; LDL = low density lipoprotein cholesterol; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; LRC = Lipid Research Clinics; MI = myocardial infarct; Post-CABG = Post-coronary artery bypass graft study; PTCA = percutaneous transluminal coronary angioplasty; TG = triglycerides; VA-HIT = Veterans Affairs HDL-intervention trial; WHO= World Health Organisation; WOSCOPS = West of Scotland Coronary Prevention Study.

related to accelerated atherosclerosis, or microvacular disease, which leads to nephropathy, retinopathy and neuropathy. Microvascular complications are generally related to the extent of glycaemic control while macrovascular disease is strongly related to cardiovascular risk factors including hyperlipidaemia.

Most data in the field of diabetes and coronary heart disease relate to patients with type 2 diabetes. In type 1 diabetes, lipid levels tend to be normal, often with an elevated HDL, although this population still shows a vastly increased risk of coronary heart disease. The driving factors behind atherosclerosis in type 1 diabetes are unclear but it certainly seems that the presence of albuminuria and/or proteinuria plays a role in increasing cardiovascular risk in a manner analogous to that seen in patients with chronic renal disease.

LIPID PROFILES IN DIABETIC DYSLIPIDAEMIA

Macrovascular disease is the principal cause of morbidity in type 2 diabetes. One of the distinguishing features of type 2 diabetes is an atherogenic lipid profile comprising low levels of HDL, mild hypertriglyceridaemia and alterations in atherogenicity of low-density lipoprotein (LDL) caused by the hypertriglyceridaemia and the effects of hepatic lipase and cholesterol ester transfer protein (Laasko, 1995).

The atherogenic LDL in diabetes is termed 'small dense' LDL and the presence of these small particles as seen on gel chromatography or sized directly by nuclear magnetic resonance techniques is associated with a 5–7-fold excess risk of cardiovascular events. However, the lipid profile is more complicated as triglyceride-rich remnants of larger post-prandial particles, e.g. intermediate density (IDL) and very low density lipoprotein (VLDL) are also increased (Grundy, 1997). These remnants also form different small dense particles containing apolipoprotein C3, which are also associated with increased risk of cardiovascular events. It is currently disputed as to whether triglyceride-rich remnants or small dense LDL are responsible for cardiovascular risk in diabetes. It is likely that both contribute, along with low dysfunctional HDL.

Statins reduce LDL and triglycerides, and moderately raise HDL, especially in populations with reduced levels. There is also some evidence that statins improve the atherogenicity of LDL by increasing LDL size, inhibit cholesterol ester transfer protein, and promote cholesterol efflux (Frost et al, 2001; Guerin et al, 2002). Fibrates have larger effects on triglycerides, HDL and in improving LDL subfraction profiles but a far lesser effect on the LDL concentration (Frost et al, 2001). In patients with diabetes in the UK, the UK Prevention of Diabetes Study (UKPDS) showed that the cardiovascular risk profile comprised patients with both raised LDL and reduced HDL (Stevens et al, 2001). Thus treatment of cardiovascular risk profiles in diabetes is likely to be controversial as there are theoretical benefits for both raising HDL and lowering triglycerides, which is best performed with fibrates, or aggressively reducing LDL, which is an indication for statins. Combination therapy, although reported in small-scale studies in specialist units, has not been comprehensively assessed in large-scale studies.

LIPID-LOWERING THERAPY IN CARDIOVASCULAR DISEASE

The data from the statin trials in cardiovascular diseases are summarized in *Table 1*. The AFTexCAPS study used lovastatin 20 mg in primary prevention in patients with low HDL while the Post-CABG study used doses of lovastatin 40 mg plus bile acid sequestrants to reduce LDL to a target of 2.5 mmol/litre.

Recently the Heart Protection Study (HPS) of 20 000 patients using simvastatin 40 mg had a substantial drop-in rate to treatment such that the study in fact investigated the effects of a 1 mmol/litre reduction in LDL. It showed a 24% reduction in events in all major sub-groups including patients with stroke, peripheral vascular disease and diabetes (MRC/BHF Heart Protection Study Group, 2002). The diabetes sub-group data from this study have not yet been published but they may show disproportionate benefit even at lower LDL levels compared to normoglycaemic patients. The analysis will also allow the relative effects of low HDL and high LDL in patients with diabetes to be identified, so any recommendation for blanket treatment with statins in diabetes before this analysis has been completed may be premature.

The effects of larger reductions in LDL and lower LDL targets are being tested in major studies, which are currently underway. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) study is comparing the effects of simvastatin 20 mg *vs* 80 mg with or without folic acid in secondary prevention patients while the Treatment to New Targets (TNT) and Incremental Decrease in Endpoints through Aggressive Lipid (IDEAL) studies are compar-

ing atorvastatin 80 mg with simvastatin 10 mg and 20–40 mg respectively in similar populations. Intriguing data on the possible results of these studies due in 2005 are provided by the GREek Atorvastatin and Coronary-heart disease Evaluation (GREACE) study, a secondary prevention study, that compared optimal treatment to target LDL of 2.6 mmol/litre with atorvastatin (average dose 24 mg) with usual care in 1600 secondary prevention patients (Athyros et al, 2002). In the usual care group only 14% received any lipid-lowering therapy and the study showed a 1.75 mmol/litre difference in LDL achieved, which resulted in a 50% reduction in cardiovascular events (*Figure 1*).

LIPID-LOWERING THERAPY IN DIABETES

Despite the high risk associated with diabetes there have been few trials in this area. A subgroup of 200 patients with established coronary heart disease in the Scandinavian Simvastatin Survival Study showed that statin therapy in patients with predominant hypercholesterolaemia and type 2 diabetes resulted in a 55% reduction in cardiovascular events, approximately double that seen in normoglycaemic patients (Pyorala et al, 1997). Analysis of the diabetic and impaired glucose tolerance cohort of this study suggested that statins may remove the excess cardiovascular risk associated with diabetes in this population.

However, in the less hypercholesterolaemic, more hypertriglyceridaemic cohorts of the Cholesterol And Recurrent Events (CARE; Cholesterol and Recurrent Events Trial investigators, 1996) and Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) (Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group, 1998) studies the relative risk reduction was similar between normoglycaemic and diabetic groups. Indeed, in this cohort, in contrast to others, large LDL (analogous to that found in familial hypercholesterolaemia) and not small dense LDL was associated with cardiovascular risk in diabetes (Sacks et al, 2002a). In this meta-analysis, all the benefit in the patients with LDL <3 mmol/litre was seen in the group of patients with diabetes.

In the HPS, all patients benefited from a 24% reduction in major vascular events, even those with an LDL of 2 mmol/litre, although no sub-group analyses have been published as yet to resolve the issue of heterogeneity of benefit in diabetes and normoglycaemia. In the GREACE study, benefits of atorvastatin were similar in diabetic (20%) and normoglycaemic (80%) populations, but given the increased baseline risk in the patients with diabetes this implies a higher absolute benefit in the diabetic sub-group.

An alternative therapeutic approach exists to the joint low HDL and low LDL cohort, which includes many patients with diabetes or obesity. The secondary prevention Veterans Affairs HDL Intervention Trial (VA-HIT) raised HDL by 8% and reduced triglycerides by 25% and showed a

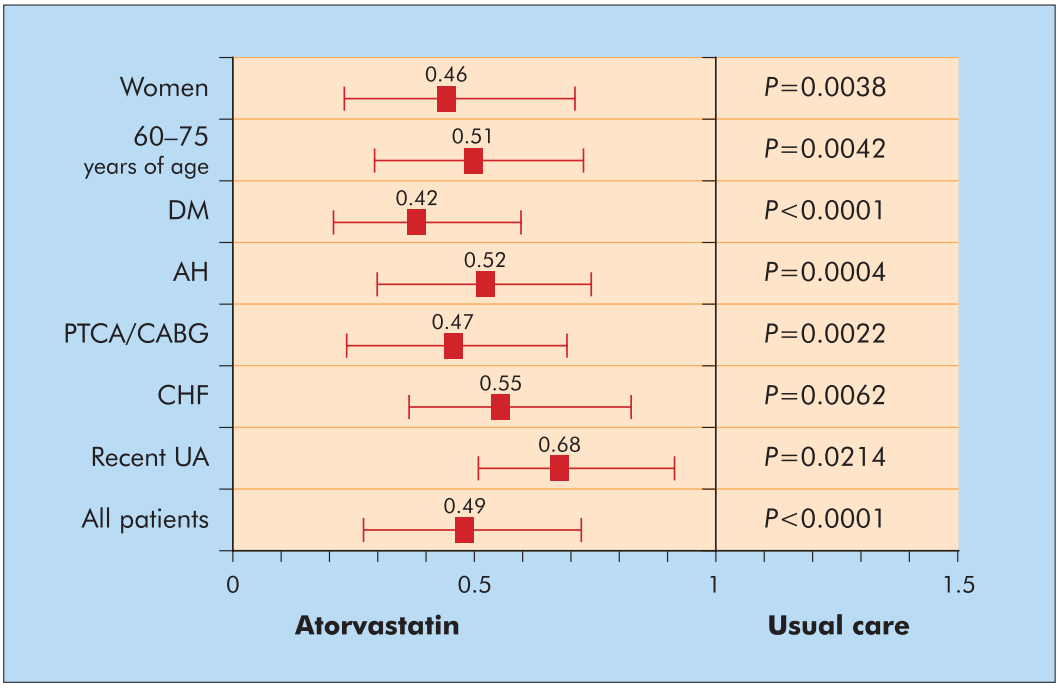

Figure 1. Risk ratios for all events in patient subgroups: atorvastatin vs usual care (Athyros et al, 2002). AH = arterial hypertension; CABG = coronary artery bypass graft; CHF = chronic heart failure; DM = diabetes mellitus; PTCA = percutaneous transluminal coronary angioplasty; UA = unstable angina.

corresponding 24% benefit in coronary heart disease event rates in both diabetic and non-diabetic groups (Rubins et al, 1999).

Definitive evidence in patients with diabetes will come from two studies currently underway. The Fenofibrate and Ischemic Event Lowering in Diabetes (FIELD) study in 9500 patient with diabetes and the Collaborative AtoRvastatin Diabetes Study (CARDS) in 6000 patients (Colhoun et al, 2002) will answer definitively which therapy is efficacious in the treatment of cardiovascular risk in diabetes.

MANAGEMENT OF HIGH-RISK PATIENTS

The NSF prioritizes patients with established coronary heart disease and those at high risk of events for treatment. Patients with diabetes are the most easily identified group of high-risk patients for primary prevention as they are already managed in dedicated clinics in both primary and secondary care. Data from recent studies suggests that LDL should be reduced to 2.5 mmol/litre in high risk groups or if they have reduced HDL (<1 mmol/litre) and low LDL (<3 mmol/litre) that HDL should increased to >1 mmol/litre (Sacks et al, 2002b).

The management of lipids in patients with diabetes should be given high priority in parallel to control of glucose and blood pressure. Both primary and secondary care need to improve their surveillance of patients with established coronary heart disease or at high risk of coronary heart disease as only 40–60% of patients with established disease receive lipid-lowering therapy while only 2–30% of primary prevention patients at high risk are treated. Shared care protocols targeting lipid lowering as a priority in these groups need to be developed and systematically implemented so that rates of treatment exceed 90% in both groups. HM

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KEY POINTS

- Lipid lowering is part of the treatment of atherosclerosis.
- All forms of atherosclerosis benefit equally from lipid-lowering therapy with statins.
- Diabetes is a high risk condition for atherosclerosis.
- Statins or fibrates can benefit patients with diabetes.
- Aggressive treatment leads to greater benefits.