Acta Diabetol (2002) 39:S29–S34

M.R. Taskinen

Controlling lipid levels in diabetes

Abstract Coronary heart disease (CHD) is associated with a 2- to 4-times greater risk of morbidity and mortality in patients with type 2 diabetes than in non-diabetic individuals. Dyslipidaemia is an important CHD risk factor in diabetic patients. The key atherogenic features of diabetic dyslipidaemia are elevated levels of serum triglycerides, low levels of high density lipoprotein (HDL) cholesterol, and the preponderance of small, dense low density lipoprotein (LDL). As a result, treatment guidelines for diabetic dyslipidaemia recommend elevated LDL cholesterol and triglyceride levels and low HDL cholesterol levels as targets of therapy. Unfortunately, however, these lipid abnormalities often persist despite best efforts to control hyperglycaemia, improve diet, and increase physical exercise, and therefore demand specific therapeutic intervention. Statins are the first choice for LDL cholesterol lowering as they are effective and well tolerated, and do not have adverse effects on glycaemic control. Furthermore, recent evidence suggests that statins may also be employed to treat moderately elevated levels of triglycerides. An increasing number of primary and secondary prevention trials have shown that lipid-lowering therapy with statins can significantly reduce the risk of CHD events in patients with diabetic dyslipidaemia.

Key words Diabetic dyslipidaemia • Low density lipoprotein • Coronary heart disease • Lipid-lowering • Statins

M.R. Taskinen (✉)
University of Helsinki
Department of Medicine, Biomedicum
Haartmaninkatu 8
FIN-00290, Helsinki, Finland

Introduction

Diabetes is a leading cause of morbidity and mortality worldwide, primarily through an increased incidence of coronary heart disease (CHD). Approximately three-quarters of all patients with diabetes will die of a cardiovascular event, compared with only one-third of non-diabetic subjects [1]. The risk of myocardial infarction (MI) is increased three- to four-fold in patients with type 2 diabetes and, for those diabetic patients who survive their first MI, short-term and one-year prognoses are poor compared with non-diabetic individuals [2, 3]. This greater propensity to CHD reflects the higher occlusion rate in diabetic than in non-diabetic patients, which is probably due to an excess of vulnerable plaques [4].

In the 12-year follow-up of men screened for the Multiple Risk Factor Intervention Trial (MRFIT), the three major CHD risk factors (hypercholesterolaemia, hypertension, and cigarette smoking) could not account for the excess risk observed in the diabetic cohort [5]. As a result, more recent research has focused on the identification of diabetes-specific risk factors for CHD. Potential candidates include hyperglycaemia, dyslipidaemia, insulin resistance, oxidative stress, and endothelial dysfunction. Of these, it is likely that diabetic dyslipidaemia, in particular, contributes to the increased risk of CHD observed in patients with type 2 diabetes.

Key features of diabetic dyslipidaemia and their impact on CHD risk

Two core components of diabetic dyslipidaemia are elevated plasma triglyceride levels and low levels of high density lipoprotein (HDL) cholesterol, both of which are major predictors of CHD risk. For example, in patients with type 2 diabetes included in the Finnish cohort of the Multinational

Monitoring of Trends and Determinants of Cardiovascular Disease (FINMONICA) MI registry, elevated triglyceride levels (>2.3 mmol/l; 204 mg/dl) and low HDL cholesterol levels (<1.0 mmol/l; 39 mg/dl) were associated with a two-fold increase in the risk of CHD mortality and morbidity [6]. This increased CHD risk was independent of other cardiovascular risk factors.

Elevated low density lipoprotein (LDL) cholesterol is also strongly correlated to CHD risk in both diabetic and non-diabetic patients [7]. However, the excess vascular risk associated with diabetes cannot be explained by any quantitative difference in the level of LDL cholesterol, the concentration of which in patients with type 2 diabetes is usually not significantly different from that found in non-diabetic individuals. Rather, recent research suggests that the higher rate of atherosclerosis associated with diabetes manifests from several qualitative, pro-atherosclerotic changes in LDL cholesterol and other lipoproteins [8]. For example, postprandial lipaemia is an inherent feature of diabetic dyslipidaemia, and precipitates a number of highly atherogenic metabolic events. These include the accumulation of chylomicron remnant particles, and the preponderance of small, dense LDL particles [8]. The latter, in particular, are highly susceptible to glycation and oxidation, both of which are processes central to the development of an atherosclerotic plaque.

Each LDL particle contains one molecule of apolipoprotein (apo) B. Thus, given the same level of plasma LDL cholesterol, small, dense LDL is associated with more apo B than large, buoyant LDL particles. The ratio of LDL to apo B can, therefore, be used to evaluate the presence of small, dense LDL in patients with apparently normal levels of LDL cholesterol [9]. Specifically, the combination of raised apo B (>115 mg/dl) and triglycerides (>1.7 mmol/l) identifies patients who require LDL cholesterol-lowering therapy. This diagnostic combination is especially common in women with type 2 diabetes (49.3%) compared with diabetic men (39.7%) (Taskinen et al., unpublished observations).

Treatment targets for lipid management

In individuals with diabetic dyslipidaemia, LDL cholesterol is the principal atherogenic lipoprotein and, thus, the primary target of any therapeutic intervention [7]. The latest National Cholesterol Education Program (NCEP) guidelines recognize that patients with diabetes have the same high risk of experiencing a CHD event as patients with established CHD [7]. As a consequence, the NCEP guidelines recommend an optimal LDL cholesterol goal of <2.6 mmol/l (100 mg/dl), which is in accordance with the recommendations of the American Diabetes Association (ADA) [10].

Once LDL cholesterol levels have been lowered to target, the secondary aim of lipid management is to reduce the levels of plasma triglycerides, and to raise the level of HDL cholesterol [10]. The ADA guidelines recommend an HDL cholesterol treatment goal of >1.15 mmol/l (45 mg/dl) in both genders. In addition, the latest ADA guidelines define a desirable level of triglycerides as <1.7 mmol/l (150 mg/dl). The rationale for this stringent target is that a triglyceride concentration in the range 1.5–1.7 mmol/l (130–150 mg/dl) represents the threshold above which there is a preponderance of small, dense LDL [11].

Prevalence of dyslipidaemia in type 2 diabetes

Achieving the target goals outlined above is a daunting task. This is partly because a large percentage of the diabetic population has lipid and protein values above the recommended treatment targets. According to the results from the Third National Health and Nutrition Examination Survey (NHANES III), for example, 84.6% of patients with type 2 diabetes had LDL cholesterol levels above the optimal NCEP treatment goal of 2.6 mmol/l (100 mg/dl), 41.9% had triglyceride levels >2.3 mmol/l (>200 mg/dl), and 62.1% had HDL cholesterol levels <1.15 mmol/l (<45 mg/dl) [12]. Furthermore, employing the more stringent target level for triglycerides (1.7 mmol/l [150 mg/dl] defined by ADA) would increase the percentage of patients defined as having elevated triglycerides.

Treating patients with type 2 diabetes to lipid targets is also complicated by the fact that diabetic dyslipidaemia is frequently under-diagnosed and under-treated. In NHANES III, for example, it was revealed that 40% of the patients identified as having diabetic dyslipidaemia were previously undiagnosed and thus not receiving any lipid-lowering therapy [12]. Of the patients with type 2 diabetes who had previously been diagnosed with dyslipidaemia, 59% still had an LDL cholesterol level ≥3.4 mmol/l (130 mg/dl), despite 89% of the patients having been treated with a lipid-lowering medication or diet [12]. Those taking medication were probably not having their dosage titrated to achieve the treatment goal [13].

The poor diagnosis and treatment of diabetic dyslipidaemia may reflect the requirement for early and aggressive screening. Recent studies have shown that the lipid abnormalities associated with diabetic dyslipidaemia begin to develop prior to the clinical onset of type 2 diabetes, at a time when blood glucose concentrations are relatively normal. For example, an examination of lipids and lipoproteins by glucose tolerance in 3606 subjects participating in the Botnia study revealed a stepwise increase in plasma triglycerides, and a stepwise lowering of HDL cholesterol, as glucose tolerance declined [14]. It follows that the implementation of effective anti-hyperlipidaemic treatment to the diabetic population requires an intensive approach.

Treatment strategies for diabetic dyslipidaemia

ADA recommends that the treatment of diabetic dyslipidaemia comprises a series of stepwise strategies [10]. The first step consists of both medical nutrition therapy and physical activity. Weight loss and increased physical activity will lead to decreased triglyceride and increased HDL cholesterol levels, and also to modest lowering of LDL cholesterol levels [15, 16]. If these strategies prove insufficient, the second step is to improve glycaemic control.

Interventions to improve blood glucose control have a modest effect on triglyceride levels in patients with type 2 diabetes [17, Taskinen et al., unpublished observations]. In the Botnia study (Fig. 1), for example, patients with hyperglycaemia that is reasonably controlled (glycosylated haemoglobin (HbA_{1c}) concentration ≤8.5%) had lower levels of plasma triglycerides compared with patients with very poor metabolic control (HbA_{1c} ≥8.5%). However, glycaemic control was found to have no effect on LDL cholesterol. Indeed, it is a common misconception that diabetic dyslipidaemia is completely reversed if glucose control is improved.

In practice, lifestyle modifications and improved glycaemic control often do not produce desirable lipid levels. Therefore, most patients with type 2 diabetes eventually require intensive lipid-lowering management (Fig. 2). HMG-CoA reductase inhibitors (statins) are considered the drugs of choice to reduce LDL cholesterol levels [10]. Statins have proven to be highly effective and well tolerated with a good safety profile, and they do not adversely influence glycaemic control [18]. Accordingly, the NCEP guidelines for the management of CHD or CHD risk equivalents (including diabetes) recommend that patients in this category with LDL cholesterol levels ≥3.4 mmol/l (130 mg/dl) are immediate candidates for statin therapy [7].

In patients with LDL cholesterol levels between 2.6 and 3.4 mmol/l (100 and 129 mg/dl), exercise and dietary changes should be implemented and lipid-lowering drugs considered. The clinician's choice of lipid-lowering agent should depend on the concentration of other lipid levels, particularly plasma triglycerides (Fig. 2). Generally, if triglycerides are markedly elevated (>4.5 mmol/l [400 mg/dl]), the first drug introduced should be a fibrate. Statin therapy should be considered if target LDL cholesterol levels are not achieved with fibrate monotherapy. If triglycerides are moderately raised (>2.3 mmol/l [200 mg/dl]), however, statin and/or fibrate treatment may be employed.

Recent studies have provided the rationale that statins can be employed in diabetic patients with a moderate elevation in triglyceride levels. The Diabetes Atorvastatin Lipid Intervention (DALI) trial was a randomized, double-blind, placebo-controlled study designed to assess the effect of the lowest and highest daily dose of atorvastatin (10 mg and 80 mg) on plasma triglyceride levels in patients with concurrent type 2 diabetes and dyslipidaemia [19]. As illustrated in Fig. 3, atorvastatin 10 mg and 80 mg produced significant reductions from baseline in plasma triglyceride levels (-25% [$p<0.001$] and -35% [$p<0.001$], respectively) compared with placebo. The difference in triglyceride reduction between the two doses was not statistically significant. Atorvastatin 10 mg and 80 mg also provided significant reductions from baseline in LDL cholesterol (-40% [$p<0.001$] and -52% [$p<0.001$]), and significantly increased HDL cholesterol (+6% [$p<0.005$] and +5.2% [$p<0.005$]). Both doses of atorvastatin were well tolerated [19].

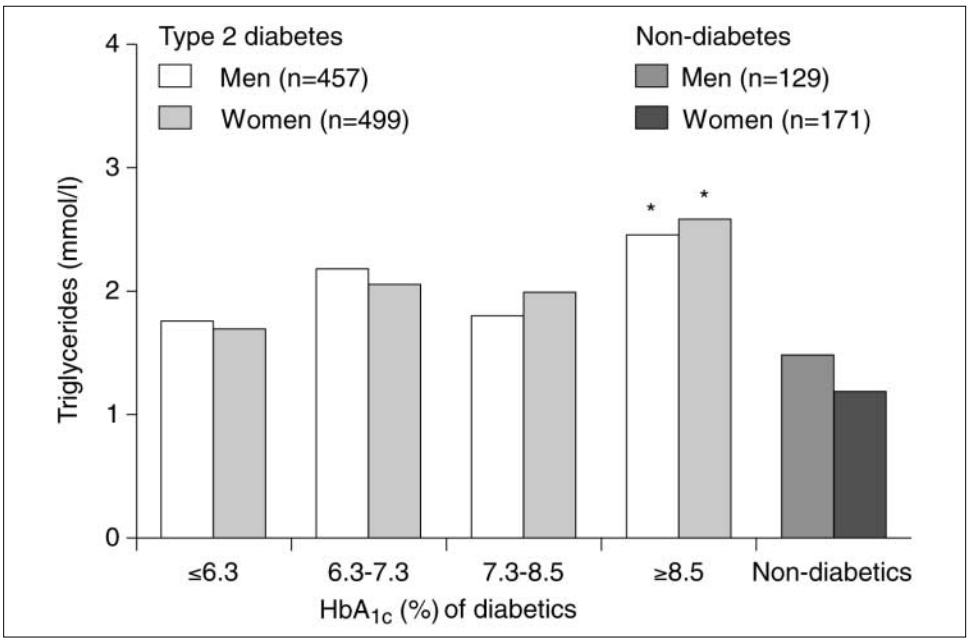

Fig. 1 The effect of glycaemic control on plasma triglycerides in patients with type 2 diabetes (Taskinen et al., unpublished observations). *$p<0.01$

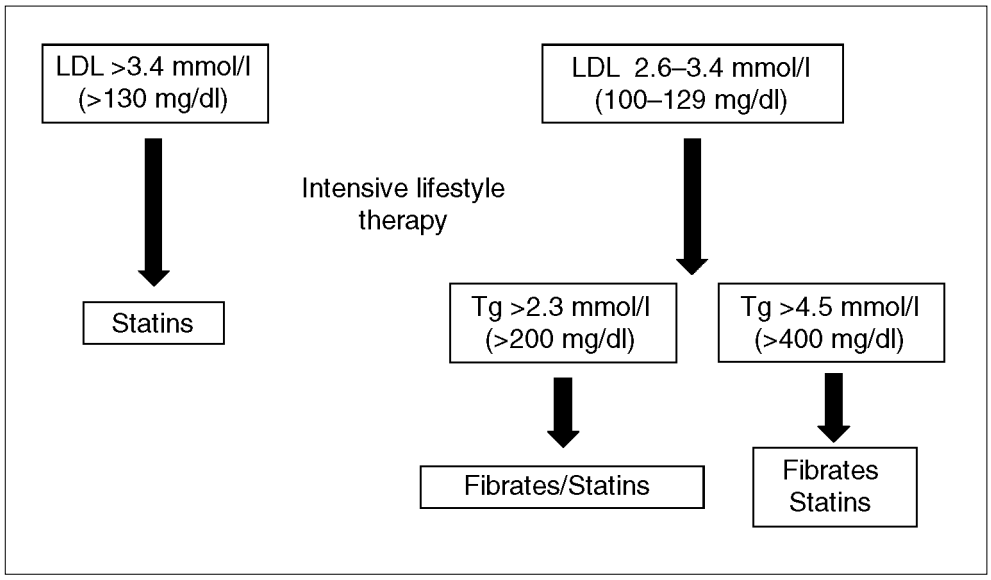

Fig. 2 Recommendations for the management of lipid levels in patients with diabetic dyslipidaemia. *LDL*, low density lipoprotein; *Tg*, triglycerides

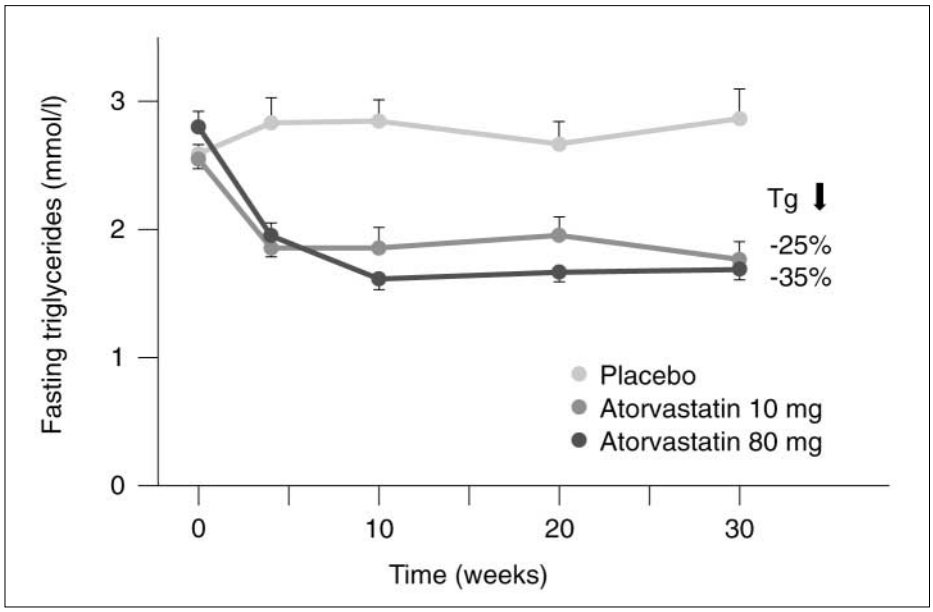

Fig. 3 Reduction of triglyceride levels by atorvastatin in patients with diabetic dyslipidaemia: the Diabetes Atorvastatin Lipid Intervention (DALI) study. *Tg*, triglycerides (Adapted with permission from [19])

Statins and CHD risk reduction in patients with diabetes

There is a wealth of data that clearly demonstrates that LDL cholesterol reduction with statins is well tolerated, and reduces the risk of both CHD events and total mortality by 25%–35% in patients with and without existing CHD [20–23]. Currently, however, there are still limited data on the benefits of statins with respect to CHD in patients with diabetic dyslipidaemia. The majority of available data are from landmark secondary prevention trials of statins that contained a relatively small number of patients with type 2 diabetes (Table 1). These studies strongly suggest that patients with CHD and concurrent type 2 diabetes benefit from statin therapy at least as much as non-diabetic CHD patients. Several ongoing studies, such as the Atorvastatin Study for the Prevention of Coronary Disease Endpoints in Noninsulin-dependent Diabetes Mellitus (ASPEN) [24], and the Treating to New Targets (TNT) trial [25], will directly determine the efficacy of lipid-lowering treatment for the primary and secondary prevention of CHD in a large population of patients with type 2 diabetes.

Recent observations may reflect that, as the absolute risk of CHD is higher in patients with diabetes than in non-diabetic cohorts [26], the reduction of absolute risk afforded by statin therapy is likely to be more favourable in diabetic patients. For example, an extended analysis of the

Table 1 Risk reduction of coronary heart disease (CHD) in patients with diabetes: the landmark statin trials

Study	Diabetic patients, n	CHD risk reduction	
		Overall	Diabetes
Primary prevention			
AFCAPS/TexCaps [23]	239	-37%	-43%
Secondary prevention			
CARE [30]	586	-23%	-25%
4S [31]	202	-32%	-55%
LIPID [22]	782	-25%	-19%
4S-Extended [26]	483	-32%	-42%

Scandinavian Simvastatin Survival Study (4S) using the 1997 ADA diagnostic criteria showed that patients with type 2 diabetes (n=483; fasting glucose level >7.0 mmol/l) benefited more from statin treatment than patients with normal fasting glucose (n=3237; <6.0 mmol/l) [27]. In particular, greater reductions in total cardiovascular disease-related hospital days were observed in the diabetic cohort (55%) compared with study participants with normal fasting glucose (28%) [28].

Importantly, statin therapy in patients with type 2 diabetes, but without cardiovascular disease, appears to be just as cost-effective as treating non-diabetic individuals with cardiovascular disease (CVD). In the USA, for example, statin therapy in cardiovascular patients without diabetes costs between $8 799 and $21 628 per year of life saved [29]. An equivalent amount (between $5063 and $23 792 per year of life saved) is spent on statin therapy in diabetic individuals without CVD [29].

Conclusions

Type 2 diabetes is associated with important quantitative and qualitative changes in lipid and lipoprotein metabolism that are likely to contribute appreciably to the excess CHD risk allied with this condition. In particular, the coexistence of elevated plasma triglycerides, small, dense LDL, and low HDL cholesterol represents a lipid 'triad' that is highly atherogenic. While these lipid abnormalities are responsive to therapeutic intervention, the majority of patients with diabetic dyslipidaemia are under-diagnosed and under-treated, and the treatment necessitates a multifactorial stepwise approach. In addition to lifestyle changes and improved glycaemic control, aggressive lowering of LDL cholesterol is usually required. The lipid-lowering agents of choice in this regard are statins, and recent evidence suggests they may also be employed to treat moderately elevated levels of triglycerides.

References

1. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB (1988) Mortality among diabetics in a national health sample. Am J Epidemiol 128:389–401
2. Kereiakes DJ (1985) Myocardial infarction in the diabetic patient. Clin Cardiol 8:446–450
3. Miettinen H, Lehto S, Salomaa VV, Mähönen M, Niemalä M, Haffner SM, Pyörälä K, Tuomilehto J (1998) Impact of diabetes on mortality after the first myocardial infarction. Diabetes Care 21:69–75
4. Ledru F, Ducimetière P, Battaglia S, Courbon D, Beverelli F, Guize L, Guermonprez J-L, Diéblod B (2001) New diagnostic criteria for diabetes and coronary artery disease: Insights from an angiographic study. J Am Coll Cardiol 37:1543–1550
5. Stamler J, Vaccaro O, Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Risk Group (1993) Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 16:434–444
6. Lehto S, Ronnemaa T, Haffner SM, Pyörälä K, Kallio V, Laakso M (1997) Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. Diabetes 46:1354–1359
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) 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 285:2486–2497
8. Syvänne M, Taskinen MR (1997) Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. Lancet 350[Suppl 1]:20–23
9. Sniderman AD, Scantlebury T, Clanflone K (2001) Hypertriglyceridemic hyperapoB: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. Ann Intern Med 135:447–459
10. American Diabetes Association (2002) Management of dyslipidemia in adults with diabetes (Position Statement). Diabetes Care 25:S74–S77
11. Demacker PN, Veerkamp MJ, Bredie SJ, Marcovina SM, de Graaf J, Stalenhoef AF (2000) Comparison of the measure-

ment of lipids and lipoproteins versus assay of apolipoprotein B for estimation of coronary heart disease risk: a study in familial combined hyperlipidemia. Atherosclerosis 153:483–490
12. Harris MI (2000) Health care and health status and outcome for patients with type 2 diabetes. Diabetes Care 23:754–758
13. Marcelino JJ, Feingold KR (1996) Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. Am J Med 100:605–610
14. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L (2001) Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 24:683–689
15. American Diabetes Association (2002) Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications (Position Statement). Diabetes Care 25:S50–S60
16. American Diabetes Association (2002) Diabetes mellitus and exercise (Position Statement). Diabetes Care 25:S64–S68
17. Tan CE, Chew LS, Chio LF, Tai ES, Lim HS, Lim SC, Jayakumar L, Eng HK, Packard CJ (2001) Cardiovascular risk factors and LDL subfraction profile in type 2 diabetes mellitus subjects with good glycaemic control. Diabetes Res Clin Pract 52:107–114
18. Vaughan CJ, Gotto AM Jr, Basson CT (2000) The evolving role of statins in the management of atherosclerosis. J Am Coll Cardiol 35:1–10
19. The Diabetes Atorvastatin Lipid Intervention (DALI) Study Group (2001) The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia. The DALI study: a double-blind randomized placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia. Diabetes Care 24:1335–1341
20. Scandinavian Simvastatin Survival Study Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383–1389
21. Sacks FM, Moyé LA, Davis BR, Cole TG, Rouleau JL, Nash DT, Pfeffer MA, Braunwald E (1998) Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial. Circulation 97:1446–1452
22. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998) 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 339:1349–1357
23. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr (1998) 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 279:1615–1622
24. Gmerek A, McLain R, Nawrocki J (1997) A 4-year, placebo-controlled study of atorvastatin as prevention of CHD endpoints in patients with non-insulin-dependent diabetes mellitus. Diabetes 46[Suppl 1]:363A
25. LaRosa JC for the TNT Steering Committee (1998) Effect of lowering LDL-C beyond currently recommended minimum targets – the Treating to New Targets (TNT) study. In: Thirteenth International Symposium on Drugs Affecting Lipid Metabolism, 30 May–3 June 1998, Florence, Italy (abstract)
26. Haffner SM, Lehto S, Ronnemaa T, Pyörälä K, Laakso M (1998) Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229–234
27. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyörälä K (1999) Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. Arch Intern Med 159:2661–2667
28. Herman WH, Alexander CM, Cook JR, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyörälä K (1999) Effect of simvastatin treatment on cardiovascular resource utilization in impaired fasting glucose and diabetes. Findings from the Scandinavian Simvastatin Survival Study. Diabetes Care 11:1771–1778
29. Grover SA, Coupal L, Zowall H, Alexander CM, Weiss TW, Gomes DR (2001) How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? Diabetes Care 24:45–50
30. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arrnold JM, Wun CC, Davis BR, Braunwald E, for the Cholesterol and Recurrent Events Trial Investigators (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 335:1001–1009
31. Pyörälä K, Pederson TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G for the Scandinavian Simvastatin Survival study (4S) Group (1997) Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 20:614–620