Diabetologia (2002) 45:S23–S28
DOI 10.1007/s00125-002-0863-0

Diabetologia

Evaluation of risk factors for development of complications in Type II diabetes in Europe

A. Liebl[1], M. Mata[2], E. Eschwège[3]*

[1] Diabetes Center, Bad Heilbrunn, Bad Heilbrunn, Germany
[2] Primary Health Care Centre La Mina, Barcelona, Spain
[3] INSERM, Unit 258, Villejuif, France

Abstract

Aims/hypothesis. The Cost of Diabetes in Europe – Type II study is the first large coordinated attempt to measure the current standard of care and determine the costs of managing patients with Type II (non-insulin-dependent) diabetes mellitus.
Methods. The study evaluated glycaemic control, blood lipid levels and blood pressure, all of which are risk factors for complications. Records of these clinical characteristics were collected from over 7000 patients during the 6-month study period.
Results. The mean HbA_{1c} value for the entire study population was 7.5%, ranging from 7.0% in Sweden to 7.8% in the United Kingdom. Only 31% of individuals achieved good glycaemic control ($HbA_{1c} \leq 6.5\%$) according to current European guidelines. Only 64% of the total study population were tested for HbA_{1c} values at least once within the 6-month study period (ranging from 49% in Spain to 71% in the UK), although HbA_{1c} testing every 3 months is recommended for all patients, by European Diabetes Policy Group guidelines. The majority of patients had borderline total cholesterol values, with a mean value of 5.7 mmol/l. Overall, 21% of patients were classified as having low risk cholesterol levels (<4.8 mmol/l). Good triglyceride levels (<1.7 mmol/l) were achieved by 47% of the total study population. During the study period, 81% of patients had their blood pressure measured, with 35% and 53.3% of the patients reaching the recommended targets for systolic and diastolic blood pressure, respectively.
Conclusion/interpretation. This study showed that a high proportion of patients with risk factors for diabetes-related complications are not adequately controlled. Improvements in disease management and monitoring are therefore required to ensure that guideline targets are met, thus reducing the long-term complications of Type II diabetes. [Diabetologia (2002) 45:S23–S28]

Keywords Type II diabetes, management, monitoring, control.

Published online: 19 June 2002

*The authors wrote on behalf of the CODE-2 Advisory Board

Corresponding author: Dr. A. Liebl, Diabetes Center, Fachklinik Bad Heilbrunn, Wörnerweg 30, D-83670 Bad Heilbrunn, Germany, E-mail: dr.liebl@t-online.de
Abbreviations: CODE-2, Cost of Diabetes in Europe-Type II; EDPG, European Diabetes Policy Group; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, distolic blood pressure.

Type II (non-insulin-dependent) diabetes is a chronic progressive disease that brings a considerable economic burden on worldwide healthcare resources. Both the major risks to health and the high management costs are predominantly due to the long-term complications of diabetes, which include cardiovascular and renal disease [1, 2].

Attaining and maintaining adequate glycaemic metabolic control has been the principal aim of disease management in Type II diabetes mellitus, which has usually employed a stepwise management strategy, typically beginning with a regimen of diet and exercise. The progressive deterioration in glycaemic con-

trol leads to the use of an oral pharmacological treatment (alone or in combination) and, finally, insulin, either alone or in combination with an oral agent, can become necessary. The issue of when to start, add or switch diabetic therapies is often a difficult decision for both general practitioners and diabetes specialists and can have a considerable influence on patient care and the cost of management. Evidence of the importance of glycaemic and blood pressure control in the management of diabetes is accumulating, particularly with respect to the development of chronic complications. The United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive treatment regimens for both blood glucose and blood pressure control reduces the incidence of long-term macrovascular and microvascular complications [3–7]. It also showed that the degree of control achieved by standard treatment protocols has not been satisfactory [3–6], making it unlikely that the recommendations of the St Vincent Declaration [8] be met in practice [9]. This is also of particular relevance economically, as a substantial proportion of the overall cost of the management of Type II diabetes arises as a consequence of the treatment of chronic complications, particularly cardiovascular and renal diseases [10]. The effect of complications on the total costs for management of Type II diabetes is discussed elsewhere in this supplement [11].

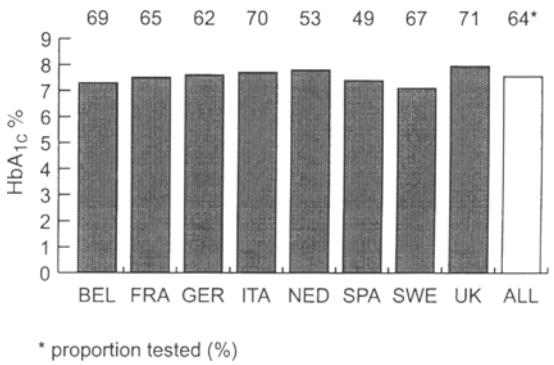

Fig. 1. Mean HbA_{1c} levels represented by country and for the total CODE-2 population

Table 1. European Diabetes Policy Group recommendations for HbA_{1c}, total cholesterol, high density lipoprotein, low density lipoprotein and triglyceride values [13]

Parameter	Low risk	Arterial risk	Microvascular risk
HbA_{1c}%	<6.5 Low risk	>6.5 At risk	>7.5 High risk
Total cholesterol			
mmol/l	<4.8	4.8–6.0	>6.0
mg/dl	<185	185–230	>230
Triglycerides			
mmol/l	<1.7	1.7–2.2	>2.2
mg/dl	<150	150–200	>200

The CODE-2 study

The Cost of Diabetes in Europe – Type II (CODE-2) study is the first large co-ordinated attempt to assess patient care together with the cost of patients with Type II diabetes throughout Europe. The methodology used by CODE-2 is described in an article in this supplement [12]. The CODE-2 study measured the standard of care and total healthcare costs in eight European countries – Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom using a prevalence-based design and involving over 7000 patients. The main objective was to measure the total healthcare costs of people with Type II diabetes in each of the specified countries. Secondary objectives included determining the current quality of care for Type II diabetes patients and benchmarking current clinical practice against glycaemic, lipid and blood pressure targets as recommended by current European diabetes practice guideline [13].

The 1999 European Diabetes Policy Group (EDPG) treatment guidelines were used in this analysis as an up-to-date European benchmark against which the CODE-2 data was compared [14]. The 1999 guidelines were selected as the target European benchmark for diabetes management because data for the CODE-2 study was collected between November 1998 and May 1999. Furthermore, the EDPG encompasses all the CODE-2 clinical characteristics which were collected in the physician survey, including fasting plasma glucose (FPG), haemoglobin A_{1c} (HbA_{1c}), total cholesterol (TC), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG), systolic (SBP) and diastolic blood pressure (DBP).

It is known that, in addition to hyperglycaemia and hypertension, blood lipids are important risk factors for macrovascular complications of diabetes mellitus [13, 15]. As a consequence, the CODE-2 study evaluated glycaemic control (HbA_{1c}), management of lipids, and hypertension, comparing the population findings with the targets set in the 1999 EDPG treatment guidelines.

National comparisons of HbA_{1c}. The degree of glycaemic control as determined by the evaluation of HbA_{1c} levels was found to be relatively consistent across all the participating countries (Fig. 1). The overall mean HbA_{1c} value for the entire CODE-2 population was 7.5%, ranging from a low of 7.0% in Sweden to a high of 7.8% in the United Kingdom. Of the patients having at least one HbA_{1c} test result in the 6 months surveyed, 42% of patients had HbA_{1c} levels above 7.5% placing them in the "microvascular risk" category according to the EDPG (Table 1). Data on

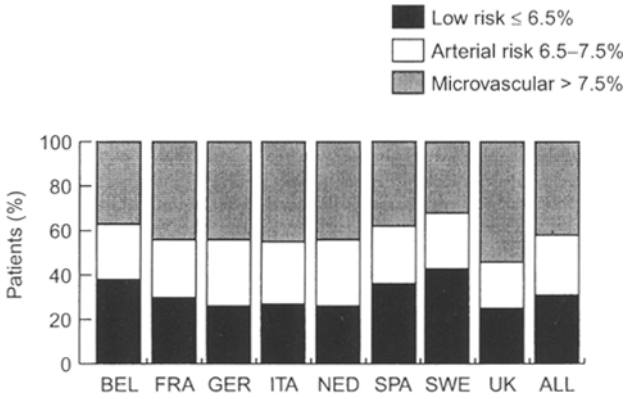

Fig. 2. Distribution of glycaemia by microvascular and arterial risk status, by country and for the total population

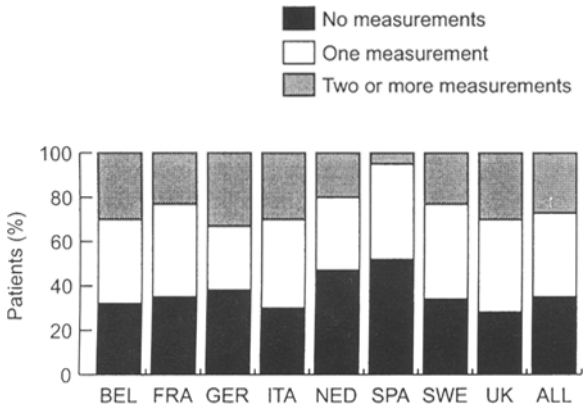

Fig. 3. Number of HbA_{1c} measurements during the 6 months of data collection, represented by country and for the total CODE-2 population

the degree of glycaemic control according to the European guidelines shows that only 31% of the study population achieved glycaemic control at or below 6.5% (Fig. 2). The proportion of the tested patient population with poor control (arterial risk + microvascular risk) was found to be lowest in Sweden (57.4%) and highest in the United Kingdom (75.2%).

The EDPG state a fasting blood glucose of less than 6.0 mmol/l for "low risk", and the overall FBG in the CODE-2 population was 9.1 mmol/l, ranging from 8.6 mmol/l in Germany to 11.2 mmol/l in the United Kingdom.

Frequency of HbA_{1c} assessment. The 1999 European Diabetes Policy Group guidelines recommend the evaluation of HbA_{1c} every 2–6 (of control vs stable) months. Results from the CODE-2 study indicate that only about 64% of the total study population were tested at least once within the 6-month study period (ranging from 49% in Spain to 71% in the UK) (Fig. 3). At a national basis, Spain and the Netherlands both emerged as having substantially less blood HbA_{1c} testing than other countries, while patients in the United Kingdom and Italy received more frequent

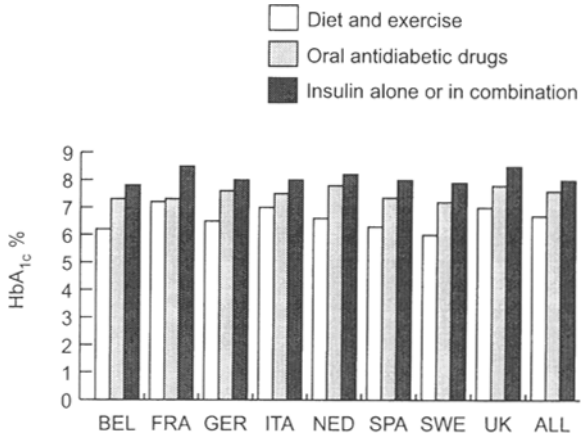

Fig. 4. Mean HbA_{1c} values represented by type of diabetes treatment

testing with 30.4% and 33.3% respectively, receiving two or more HbA_{1c} evaluation tests within the 6 month study period. On average, about one third of the entire study population received no blood HbA_{1c} testing at all over the 6-month study period. This comparison reveals substantial national variation in achieving the stated EDPG objectives for HbA_{1c} testing.

HbA_{1c} and type of diabetes treatment. When glycaemic control was considered by treatment type, a similar pattern emerged for each country (Fig. 4). Overall, patients treated with a regimen of diet and exercise only, oral antidiabetic drugs, or insulin alone or in combination achieved mean HbA_{1c} values of 6.7%, 7.5%, 8.1%, respectively. Consequently, the majority of insulin-treated patients, and a substantial proportion of those receiving oral antidiabetic drugs, remain poorly controlled despite therapy.

Plasma lipid levels. LDL-cholesterol has recently emerged as a very strong predictor for coronary heart disease [16]. The EDPG guidelines specify LDL values of 3.0 or less, more than 3.0 but equal to or less than 4.0, and more than 4.0 mmol/l as low risk, at risk and high risk, respectively and recommend lipid-lowering therapy in patients with LDL values of 3.0 mmol/l or more [13]. American Heart Association guidelines for cardiovascular risk factors in diabetic patients, state that LDL values should be maintained under 2.6 mmol/l or 2.0 mmol/l if multiple risk factors are present [17]. In the CODE-2 study, LDL measurements were carried out in only 27% of patients. The available LDL data for the 2029 CODE-2 patients showed a mean value of 3.6 mmol/l.

The overall degree of total cholesterol (TC) control and the proportion of patients tested within the 6 months of data collection are shown by country in Fig. 5. The majority of tested patients were found to have a mean value for TC across the CODE-2 popula-

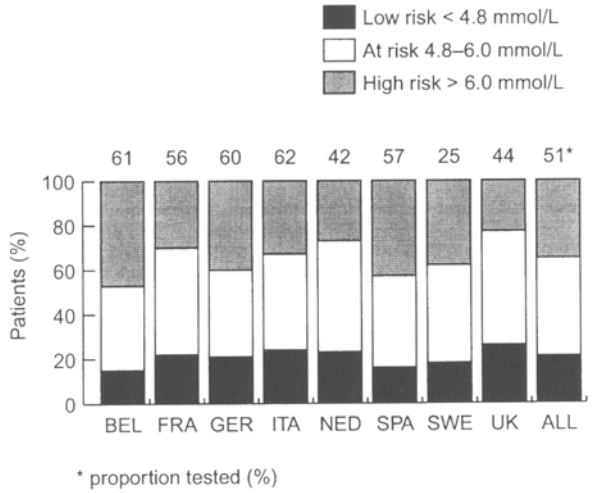

Fig. 5. Distribution by risk status, as assessed by total cholesterol, by country and for the total population

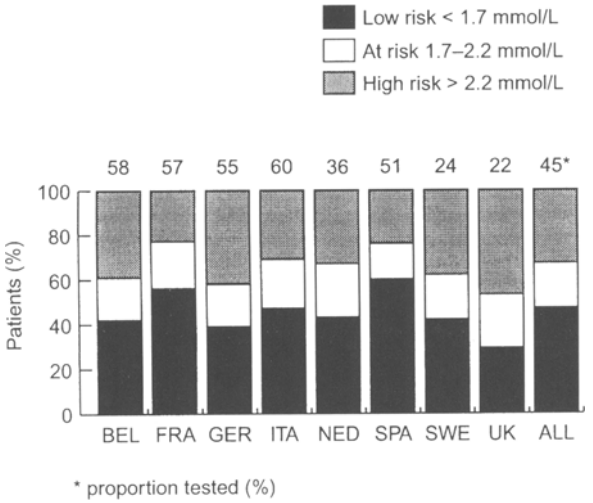

Fig. 6. Distribution by risk status, as assessed by triglycerides, by country and for the total population

tion of 5.7 mmol/l (range: from 5.5 mmol/l in the UK to 5.9 mmol/l in Belgium). Overall, only 21% of patients had TC values below the 4.8 mmol/l (low risk) level, while about 35% of tested patients had TC values exceeding 6.0 mmol/l (high risk). It is worth noting that these results included the 13.5% of patients receiving lipid-lowering medication along with untreated patients. The use of lipid lowering agents was highest in the United Kingdom (24.4%), while only 0.3% in France were receiving these agents. On average, 51% of the CODE-2 patients had undergone evaluation of TC within the 6-month study period.

The average HDL value of the tested CODE-2 patients was 1.27 mmol/l. About 26% of patients had HDL values in the high risk category of less than 1 mmol/l. Of note, two-thirds of all CODE-2 patients did not receive a HDL evaluation during the 6-month study period.

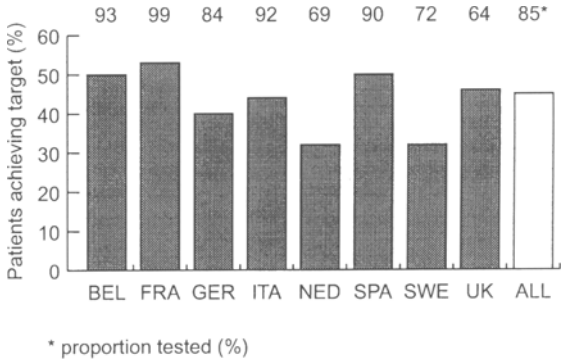

Fig. 7. Percentage of patients achieving systolic blood pressure targets, and the percentage tested at least once during the 6 months of data collection, represented by country and for the total CODE-2 population

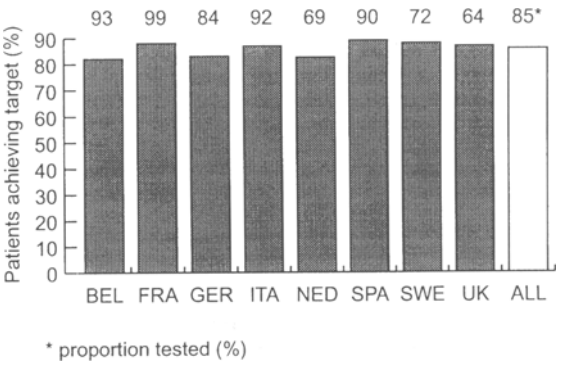

Fig. 8. Percentage of patients achieving diastolic blood pressure targets, represented by country and for the total CODE-2 population

The triglyceride values in the CODE-2 study population are presented in Fig. 6. In general, triglyceride values were more often within recommended ranges than TC, with 47.0% of the total patient population achieving a value less than 1.7 mmol/l. The mean value for all countries was 2.2 mmol/l, with a range of 1.8 mmol/l in France to 3.0 mmol/l for the United Kingdom.

Blood pressure. Of the total CODE-2 population, 25.9% were receiving anti-hypertensive agents. In total, 81% of the patients had their blood pressure measured within the 6-month study period. Figures 7 and 8 show the proportions of the CODE-2 patients that had blood pressure measurements that met the recommended targets for systolic and diastolic blood pressure (≤140 mmHg and ≤85 mmHg, respectively) and the proportion of the patients tested within the 6 months of data collection. Altogether 35% of the patients (range from 20.1% in the Netherlands to 53.4% in France) had systolic blood pressure values of less than or equal to 140 mmHg. The mean value for the total CODE-2 population was 145.97 mmHg (range: from 141.1 mmHg in Belgium to 151.1 mmHg in Sweden). The overall mean diastolic blood pressure was 82.3 mmHg.

Throughout the study population only 53% of patients had blood pressure (BP) within the target ranges set by EDPG. Given recent results from UKPDS highlighting the advantages of improving control of hypertension in Type II diabetic patients, enormous clinical benefits could be achieved [5].

Conclusions

An examination of the average results obtained from the CODE-2 practitioner survey showed that the overall glycaemic control in the Type II diabetic population in the eight participating countries was acceptable. However, when the CODE-2 management data were considered according to the proportion of patients achieving EDPG guideline targets the quality of the control is far from being optimal. A total of 42% of patients were classified as having HbA_{1c} values above 7.5%. Furthermore, 37% of the patients had not received HbA_{1c} testing within the 6-month study period, despite the EDPG recommendation for testing once every 3 months for optimal glycaemic control. There is a possibility that the degree of compliance to the guidelines observed in the CODE-2 study was affected by selection bias, as the study population could be expected to include an above-average proportion of especially conscientious practitioners and motivated patients. Differences between countries, in the way in which patients were selected could contribute to the apparent variations in outcome. For example, in some clinics, patients with poor glucose control could have attended the clinic more regularly and consequently included in the study more often. National variations in clinic populations could also lead to selection bias.

When glycaemic control was evaluated by treatment category, the mean HbA_{1c} value was higher in patients treated with insulin alone or in combination with pharmacotherapy, compared with oral antidiabetic drugs or diet and exercise alone. This does not suggest that diet and exercise is the optimal management regimen. Rather, it is indicative of the influence of disease progression and the stepwise increase in pharmacotherapeutic measures required to maintain glycaemic control. This result was expected and indicates that patients on insulin are inadequately controlled more frequently. Intensification of treatment reflects the natural progression of the disease and the management of patients requiring insulin is often challenging because of severe co-morbidity and complications due to long-standing disease and ageing. In contrast to previous studies which found the initiation of insulin therapy in patients with poor glycaemic control to be largely ineffective [3, 18], recent evidence suggests that the effective management of glycaemia with intensive insulin therapy can prevent the development of microvascular complications [19]. New treatment options, including the more recently developed thiazolidinedione agents and a combination of therapies with optimised insulin regimens, including insulin analogues and new delivery methods should improve control in this patient group.

Nearly half of the total CODE-2 population had not received any cholesterol monitoring during the 6-month study. When measurements were taken, only one fifth of patients had satisfactory total cholesterol values, and triglyceride values were within the low-risk level in less than half the patient population. Again, this finding shows that there are considerable setbacks in the implementation of current EDPG treatment guidelines for management of lipid abnormalities in Type II diabetic patients.

The assessment and treatment of hypertension in the CODE-2 study also highlighted problems with the control of hypertension, with almost two thirds of the patients not reaching the EDPG recommended target for systolic blood pressure. Moreover, the actual number of patients not reaching the target could be even higher, as 19% of the patients had not had their blood pressure measured within the 6-month study period.

In conclusion, the CODE-2 study shows that the proportion of European patients in whom cardiovascular risk factors are inadequately controlled is high, despite the relatively favourable overall mean HbA_{1c} value. A substantial proportion of the population is not monitored at the recommended frequency for important predictors of costly diabetic complications. Improved disease management with intensive therapeutic interventions aimed at controlling all risk factors and an increase in monitoring is therefore required in order to meet the EDPG guideline targets with the aim of reducing or preventing the long-term complications of Type II diabetes.

References

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D (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
2. Perneger TV, Brancati FL, Whelton PK, Klag MJ (1994) End-stage renal disease attributable to diabetes mellitus. Ann Intern Med 121: 912–918
3. UK Prospective Diabetes Study Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type II diabetes (UKPDS 33). Lancet 352: 837–853
4. UK Prospective Diabetes Study Group (1998) Intensive blood-glucose control with metformin on complications in overweight patients with Type II diabetes (UKPDS 34). Lancet 352: 854–865
5. UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in Type II diabetes (UKPDS 38). BMJ 352: 703–713

6. UK Prospective Diabetes Study Group (1998) Efficacy of atenolol and captopril in reducing risk of both macrovascular and microvascular complications in Type II diabetes (UKPDS 39). BMJ 317: 713–720
7. American Diabetes Association (1998) Implications of the United Kingdom prospective diabetes study. Diabetes Care 21: 2180–2184
8. Diabetes Care and Research in Europe (1990) The St Vincent Declaration. Diabetic Med 7: 360
9. Massi-Benedetti M (2000) Cost of diabetes in Europe – Type II (CODE 2) study. Diabetologia supplement [this issue]
10. Brown JB, Pedula KL, Bakst AW (1999) The progressive cost of complications in Type II diabetes mellitus. Arch Intern Med 159: 1873–1880
11. Williams R, Van Gaal L, Lucioni C (2000) Assessing the impact of complications on the costs of Type II diabetes. Diabetologia supplement [this issue]
12. Jönsson B (2000) Revealing the cost of Type II diabetes in Europe. Diabetologia supplement [this issue]
13. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G (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
14. European Diabetes Policy Group (1999) Guidelines for diabetes care: a desktop guide to type II diabetes mellitus. International Diabetes Federation (European Region). Diabet Med 16: 716–730
15. Sacks FM, Pfeffer MA, Moye LA et al. (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 335: 1001–1009
16. Howard BV, Robbins DC, Sievers ML et al. (2000) LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: The Strong Heart Study. Arterioscler Thromb Vasc Biol 3: 830–835
17. Kris-Etherton PM, AHA Science Advisory (1999) Monounsaturated fatty acids and risk of cardiovascular disease. American Heart Association. Nutrition Committee. Circulation 100: 1253–1258
18. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S (1997) Starting insulin therapy in patients with Type II diabetes. JAMA 278: 1663–1669
19. Ohkubo Y, Kishikawa H, Araki E et al. (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomised prospective 6-year study. Diabetes Res Clin Pract 28: 103–117