



Improving glucose management: Ten steps to get more patients with type 2 diabetes to glycaemic goal

Recommendations from the *Global Partnership for Effective Diabetes Management*

S. DEL PRATO,¹ A-M. FELTON,² N. MUNRO,³ R. NESTO,⁴ P. ZIMMET,⁵ B. ZINMAN⁶ ON BEHALF OF THE GLOBAL PARTNERSHIP FOR EFFECTIVE DIABETES MANAGEMENT*

University of Pisa,¹ Pisa, Italy, Federation of European Nurses in Diabetes,² London, UK, Primary Care Diabetes Europe,³ Surrey, UK, Lahey Clinic,⁴ Burlington, MA, USA, International Diabetes Institute,⁵ Caulfield, Australia, and Mount Sinai Hospital,⁶ University of Toronto, Toronto, Canada

SUMMARY

Despite increasingly stringent clinical practice guidelines for glycaemic control, the implementation of recommendations has been disappointing, with over 60% of patients not reaching recommended glycaemic goals. As a result, current management of glycaemia falls significantly short of accepted treatment goals. *The Global Partnership for Effective Diabetes Management* has identified a number of major barriers that can prevent individuals from achieving their glycaemic targets. This article proposes 10 key

practical recommendations to aid healthcare providers in overcoming these barriers and to enable a greater proportion of patients to achieve glycaemic goals. These include advice on targeting the underlying pathophysiology of type 2 diabetes, treating early and effectively with combination therapies, adopting a holistic, multidisciplinary approach and improving patient understanding of type 2 diabetes. Implementation of these recommendations should reduce the risk of diabetes-related complications, improve patient quality of life and impact more effectively on the increasing healthcare cost related to diabetes.

Keywords: Glycaemic control; glycaemic targets; patient management; type 2 diabetes

© 2005 Blackwell Publishing Ltd

**Global Partnership for Effective Diabetes Management* Members: George Alberti, University of Newcastle upon Tyne, Newcastle upon Tyne, UK; Pablo Aschner, Javeriana University School of Medicine, Bogota, Colombia; Cliff Bailey, Aston University, Birmingham, UK; Lawrence Blonde, Oschner Clinic Foundation, New Orleans, LA, USA; Stefano Del Prato, University of Pisa, Pisa, Italy (Chair); Anne-Marie Felton, Federation of European Nurses in Diabetes, London, UK; Barry Goldstein, Jefferson Medical College of Thomas Jefferson University, PA, USA; Ramon Gomis, Hospital Clinic, Barcelona, Spain; Edward Horton, Joslin Diabetes Center, Boston, MA, USA; James LaSalle, Medical Arts Research Collaborative, Excelsior Springs, MO, USA; Hong-Kyu Lee, Seoul National University, College of Medicine, Seoul, Korea; Lawrence Leiter, St Michael's Hospital, Toronto, ON, Canada; Stephan Matthaer, Diabetes-Zentrum Quakenbruck, Quakenbruck, Germany; Marg McGill, Diabetes Centre, Royal Prince Alfred Hospital, Sydney, Australia; Neil Munro, Primary Care Diabetes Europe, Surrey, UK; Richard Nesto, Lahey Clinic, Burlington, MA, USA; Paul Zimmet, International Diabetes Institute, Caulfield, Australia; and Bernard Zinman, Mount Sinai Hospital, University of Toronto, Toronto, Canada.

Correspondence to:

Professor Stefano Del Prato, MD, Department of Endocrinology and Metabolism, Section of Diabetes-Ospedale Cisanello, Via Paradisa, 2, I-56124 Pisa, Italy
Tel.: + 39 (050) 995103
Fax: + 39 (050) 541521
Email: delprato@immr.med.unipi.it

CURRENT CHALLENGES IN TYPE 2 DIABETES: A GLOBAL CALL TO ACTION

Around 190 million people worldwide are now estimated to have diabetes, with over 330 million predicted to have the condition by 2025 (1). These figures, however, may significantly underestimate the extent of the problem, since up to 50% of the population with diabetes are thought to remain undiagnosed and therefore untreated (2). Thus, there is likely to be a substantial increase in the number of individuals presenting with diabetes-associated micro- and macrovascular complications. It is known from the United Kingdom Prospective Diabetes Study (UKPDS) that intensive glycaemic control can reduce the risk of complications (3,4). However, despite increasingly stringent guidelines, over 60% of patients are not reaching glycaemic targets, and urgent steps are required in order to increase the proportions of patients achieving their glycaemic goals (5,6).

The Global Partnership for Effective Diabetes Management, a multidisciplinary group from leading institutions and diabetes organisations worldwide, is supported by GlaxoSmithKline

plc and was launched in 2004 with the objective of providing practical guidance to facilitate improved treatment outcomes for people with type 2 diabetes. As many treatment algorithms and guidelines currently exist and vary between countries and within regions, the aim of the *Partnership* is not to provide new guidelines, but to give practical advice on how to get more patients to recommended treatment goals. The *Partnership* recognises and recommends a holistic approach to treatment; however, the discussion of aspects beyond glycaemic control is outside the scope of this article. As an initial step, the *Partnership* has identified major barriers that must be overcome to increase the number of patients who achieve glycaemic targets (Table 1) and has developed 10 key recommendations (Table 2) to aid physicians with this important aim. While appreciating that not all regions will be able to implement all 10 recommendations, the *Partnership* hopes that physicians will recognise the importance of tight glycaemic control and implement or adopt as many recommendations as is feasible locally.

OVERCOMING THE BARRIERS TO EFFECTIVE GLUCOSE MANAGEMENT: KEY RECOMMENDATIONS

Achieving Optimal Glycaemic Control

Serious micro- and macrovascular complications of type 2 diabetes adversely affect quality of life and impose a heavy burden on healthcare systems (7–9). For example, diabetes-related complications account for most hospitalisations; these represented 55% of total costs in the Cost of Diabetes in Europe – Type 2 (CODE-2) study, whereas expenditure on oral antidiabetic agents and insulin accounted for only a small proportion (7%) of healthcare costs (7). Notably, in the UKPDS, 50% of diabetes patients already had evidence of complications at diagnosis (10), emphasising the importance of early detection and treatment of diabetes. In the Nurses' Health Study, participants were found to have a substantially increased risk of cardiovascular disease (CVD) prior to clinical diagnosis of diabetes (11). Furthermore, individuals with prediabetes, in particular those

with impaired glucose tolerance (IGT), have an increased risk of CVD and mortality (12).

Guidelines from diabetes organisations, including the American Diabetes Association (ADA), European Diabetes Policy Group, Canadian Diabetes Association (CDA), American Association of Clinical Endocrinologists, Latin American Diabetes Association and the Asian-Pacific Type 2 Diabetes Policy Group, recommend targets for HbA_{1c} < 6.0%–7.0% in patients with type 2 diabetes (13–18). These guidelines emphasise the impact of improved glycaemic control on micro- and macrovascular complications, as demonstrated by epidemiologic analysis of the UKPDS data, which clearly indicated that every 1% drop in HbA_{1c} is associated with a significant reduction in risk of 21% for any diabetes-related endpoint, 21% for deaths related to diabetes, 14% for myocardial infarction and 37% for microvascular complications (19). No threshold of risk was observed for any endpoint, suggesting that the lowest risk of complications would be in those with HbA_{1c} values in the normal range (<6.0%) (19), although the benefits of intensive glycaemic control strategies should always be weighed against the risk of hypoglycaemia in some groups of patients.

However, despite publication of increasingly stringent glycaemic guidelines (13–16), several large-scale studies have shown that the current management of glycaemia is falling significantly short of accepted treatment goals (5,6,20–23). Of concern, there was little improvement in the proportion of patients achieving good glycaemic control between the US-based National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 1999–2000 (5). In NHANES and in the European CODE-2 study, only 37% and 31% of patients, respectively, achieved glycaemic targets (5,6). However, even when physicians are dissatisfied with their results, there may be a reluctance to change practices. For example, in the Diabetes in Canada Evaluation (DICE) study, although the majority of physicians were not satisfied with an HbA_{1c} of > 7%, most favoured conservative approaches to achieving glycaemic targets. Of note, 68% opted to reinforce lifestyle therapy, 27% augmented the use of oral antidiabetic agents and only 8% increased the use of insulin therapy (24).

A number of factors may underlie these observations, and we have identified several areas that, if addressed, should help increase the proportion of patients achieving good glycaemic control.

Clarify Definition of Good Glycaemic Control. Globally, guidelines may differ in the glycaemic goals they recommend, and the *Partnership* therefore recommends setting a universal glycaemic target to simplify and improve patient management. The benefits of good glycaemic control are well documented and are discussed in more depth in this issue (25), with a substantial body of evidence indicating that targeting therapy to achieve an

Table 1 Barriers to effective glucose management

Conservative management
Ineffective diet/exercise initiatives
Delayed efficacy due to a slow traditional stepwise approach
Suboptimal healthcare systems impede achievement of glycaemic goals
Lack of perceived efficacy
Insufficient communication with patient
Poor adherence to antidiabetic regimens
Lack of knowledge of underlying pathophysiology
Inappropriate prescription of medication

Table 2 Ten steps to get more type 2 diabetes patients to goal

1. Aim for good glycaemic control, defined as $HbA_{1c} < 6.5\%$ *
2. Monitor HbA_{1c} every 3 months in addition to regular glucose self-monitoring
3. Aggressively manage hyperglycaemia, dyslipidaemia and hypertension with the same intensity to obtain the best patient outcome
4. Refer all newly diagnosed patients to a unit specialising in diabetes care where possible
5. Address the underlying pathophysiology, including the treatment of insulin resistance
6. Treat patients intensively so as to achieve target $HbA_{1c} < 6.5\%$ * within 6 months of diagnosis
7. After 3 months, if patients are not at target $HbA_{1c} < 6.5\%$,* consider combination therapy
8. Initiate combination therapy or insulin immediately for all patients with $HbA_{1c} \geq 9\%$ at diagnosis
9. Use combinations of oral antidiabetic agents with complementary mechanisms of action
10. Implement a multi- and interdisciplinary team approach to diabetes management to encourage patient education and self-care and share responsibility for patients achieving glucose goals

*Or fasting/preprandial plasma glucose < 110 mg/dl (6.0 mmol/l) where assessment of HbA_{1c} is not possible.

$HbA_{1c} < 6.5\%$ would provide significant benefits in terms of reducing the risk of micro- and macrovascular complications (3,19,26,27). A goal for fasting/preprandial plasma glucose is also provided. However, we recognise the important role of clinical judgement to determine the patients who can reasonably and safely achieve these targets, giving consideration to individual risk factors such as the patient's age, prognosis, the presence of diabetes complications or comorbidities and the patient's risk for, and ability to recognise, symptoms of hypoglycaemia.

Recommendation 1: Aim for good glycaemic control, defined as $HbA_{1c} < 6.5\%$.¹

Ensure frequent monitoring of glycaemia and HbA_{1c} . Frequent monitoring of glycaemia is essential for effective management, particularly in patients newly diagnosed with type 2 diabetes. Many guidelines, however, do not always provide specific or consistent guidance on this topic. For example, the European Diabetes Policy Group recommends a 'regular review' of HbA_{1c} , whereas the ADA advocates HbA_{1c} monitoring every 3–6 months (14,28). Monitoring is often perceived to be time consuming and requires considerable motivation of all parties – from specialist to patient. However, regular assessment of glycaemia should lead to more proactive management of diabetes, and, for example, two consecutive measurements of $HbA_{1c} \geq 7.0\%$ should lead to a review of treatment.

Regular self-monitoring of blood glucose by the patient, according to a programme agreed by the healthcare professional (HCP) and patient, also constitutes a key component of diabetes self-management and can improve the proportion of patients achieving their glycaemic targets (14,16,28,29). Given the well-established link between elevated postprandial glucose (PPG) levels and cardiovascular risk (30–32), it is also important that patients monitor PPG and regularly

report results. The benefits of regular self-monitoring, which include improved glycaemic control, avoidance of hypoglycaemia and increased lifestyle flexibility, are enhanced by changes in self-care behaviour (16). In addition, regular monitoring of HbA_{1c} by the diabetes care provider should be undertaken. Patients who are aware of their own HbA_{1c} value can more accurately assess their diabetes control and have a better understanding of diabetes care, and the use of regular glucose monitoring results will aid patients in achieving HbA_{1c} targets. This may improve their self-confidence and motivation to manage the disease (33). The following recommendation is designed to encourage proactive management.

Recommendation 2: Monitor HbA_{1c} every 3 months in addition to regular glucose self-monitoring.

Adopt a holistic approach to disease management. In addition to hyperglycaemia, it is important to address the comorbidities of type 2 diabetes that contribute to the severe complications associated with this disease. For example, in the large cohort of men screened for the Multiple Risk Factor Intervention Trial, serum cholesterol levels and systolic blood pressure, as well as cigarette smoking, were identified as significant predictors of CVD mortality, particularly in subjects with diabetes (34). In addition, several studies have demonstrated the benefits of managing hypertension and dyslipidaemia (20,35–38).

Hence, management strategies must acknowledge that individuals with diabetes should receive intensive and effective treatment for all metabolic disturbances, including hyperglycaemia (13,14). While we appear to be making progress in treating some risk factors, however, less progress is being made in treating obesity and diabetes. For example, in a recent model investigating the decline in coronary heart disease (CHD) deaths in England and Wales between 1981 and 2000, 58% of the decrease in CHD mortality was attributed to reductions in risk factors, such as smoking, blood pressure and cholesterol, whereas 42% was attributed to medical treatments. This decrease in CHD mortality rates resulted in an

¹Or fasting/preprandial plasma glucose < 110 mg/dl (6.0 mmol/l) where assessment of HbA_{1c} is not possible.

estimated 68,230 fewer deaths in 2000. In contrast, however, obesity and diabetes had an opposite effect on CHD mortality, with each being associated with around 2000–3000 additional deaths (39). The difficulties of managing hyperglycaemia are highlighted by findings from the Steno-2 study, in which only 15% of diabetes patients in the intensive treatment group achieved their HbA_{1c} goal of less than 6.5%, with notably fewer patients achieving glycaemic targets compared with those reaching goals for cholesterol levels (72%) or systolic/diastolic blood pressure (46% and 72%, respectively; Figure 1) (20).

Several factors could help explain these findings. For example, the relative complexity of managing hyperglycaemia or differences in the efficacy of available antidiabetic medications may account for the lower proportions of patients reaching glycaemic goals, compared with lipid and blood pressure targets. Of note, the UKPDS and other key diabetes trials have demonstrated an inevitable increase in HbA_{1c} in the long term, whereas lipid and blood pressure control can generally be achieved and sustained through polypharmacy (35,40,41). Also, there is a greater public awareness and acceptance of the general health benefits of lowering lipids and blood pressure, compared with the lower profile that the benefits of good glycaemic control receive.

An important role of the diabetes care team is to ensure that glycaemic control remains the cornerstone of diabetes management. The *Partnership* therefore recommends a holistic approach to disease management in which the treatment of hyperglycaemia has equal priority to the management of dyslipidaemia and hypertension.

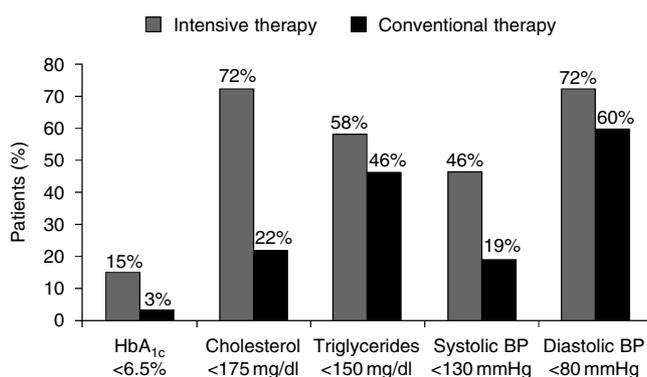


Figure 1 Patients achieving treatment goals for glycaemia, lipids and blood pressure (BP) in the Steno-2 study (20). Intensive treatment of hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria plus secondary prevention of cardiovascular disease with aspirin; conventional treatment of multiple risk factors in accordance with national guidelines [1988 recommendations of the Danish Medical Association (95), revised in 2000 (20)]. Mean follow-up = 7.8 years. Adapted with permission from Gaede et al. *N. Engl. J. Med* 2003; 348: 383–399. Copyright © 2003 Massachusetts Medical Society. All rights reserved

Recommendation 3: *Aggressively manage hyperglycaemia, dyslipidaemia and hypertension with the same intensity to obtain the best patient outcome.*

Increase involvement of specialist care units. Given the complexity of type 2 diabetes, relevant expertise is essential to identify the needs of the patient, including his or her phenotypic profile. Useful indicators of metabolic status include the degree of insulin deficiency vs. insulin resistance (indicative of β -cell function and the extent of disease progression) and the severity of the associated central obesity and other components of the metabolic syndrome (42–44). An additional indicator of phenotype is the degree of the patient's postprandial hyperglycaemia (45).

Extensive knowledge of the pathophysiological basis of type 2 diabetes, combined with a thorough awareness of the efficacy and tolerability of antidiabetic medications available, enables physicians to best match medication to patient phenotype. Most patients will be on complex drug regimens, requiring expert input in order to achieve the most appropriate balance of drugs, including antidiabetic, antihypertensive and lipid-lowering agents, aspirin and anti-obesity drugs. Such complicated regimens require careful review, within the monitoring process.

Involvement of HCPs with experience and expertise in type 2 diabetes will facilitate more patients in achieving their glycaemic targets. This recommendation is supported by a study in which specialist cardiology involvement increased the number of coronary artery disease patients achieving goals for cholesterol and blood pressure (46). Similarly, the Verona Diabetes Study demonstrated that specialist input in care of patients with type 2 diabetes results in greater achievement of glycaemic goals and better outcome. This survey, which evaluated nearly 7500 diabetes patients, compared survival between those who exclusively consulted their family physician and those who also attended diabetes centres. The study found a 17% increase in survival in those patients receiving specialist diabetes care. Moreover, multivariate analysis by Cox regression model showed that attending diabetes centres was an independent predictor of survival even after adjusting for sex, age and diabetes therapy (47).

Recommendation 4: *Refer all newly diagnosed patients to a unit specialising in diabetes care where possible.*

Targeting the Underlying Pathophysiology of Type 2 Diabetes

Around 80%–85% of type 2 diabetes patients are insulin resistant (48,49), with β -cell defects such as maturity-onset diabetes of the young (MODY; poor insulin secretion due to defects such as glucokinase mutations) accounting for the majority of remaining cases (50). Transitions from normal glucose tolerance to IGT and from IGT to diabetes are both

accompanied by decreases in insulin sensitivity and β -cell function (51), whereas declining β -cell function is associated with deteriorating glycaemic control (3,52). Insulin resistance is also closely interlinked with numerous risk factors for CVD (53) and is an independent risk factor for CVD (54). Hence, both insulin resistance and β -cell dysfunction constitute important targets for therapeutic intervention to improve outcomes in type 2 diabetes (55).

When selecting a therapeutic regimen, it is important to consider whether agents address the underlying pathophysiology. Although sulphonylureas and metformin were successful in the UKPDS in the short term, glycaemic control was not achieved on a long-term basis, and combination therapy was required for the majority of patients (56). Loss of glycaemic control in this study correlated with deterioration in β -cell function (52). However, the potential for long-term glycaemic control is probably more feasible with the advent of new classes of agents that address the underlying pathophysiology of type 2 diabetes, such as thiazolidinediones (57–59), glucagon-like peptide-1 analogues, dipeptidyl peptidase IV inhibitors and protein tyrosine phosphatase 1B inhibitors (60,61).

Recommendation 5: Address the underlying pathophysiology, including treatment of insulin resistance.

Treating Early and Effectively with Combination Therapies

The traditional approach to type 2 diabetes management uses a 'stepwise approach' to control glycaemia. The first step is lifestyle modification, followed by treatment with a single oral antidiabetic agent, which is often uptitrated to maximal recommended doses before combination therapy is introduced (62). However, this conservative approach has a number of drawbacks and a more proactive approach that recognises the urgency of getting patients to achieve their glycaemic targets – tailoring therapy to the individual by methodically selecting agents – will optimise patient care.

Move from reactive, stepwise treatment to a more proactive approach. The stepwise approach often leads to unacceptable delays in both achieving and maintaining glycaemic goals. Several clinical trials have demonstrated the effectiveness of the first step – diet and exercise – in preventing diabetes and reducing disease progression (63,64), and such measures can provide substantial improvements in glycaemic control and in markers of vascular inflammation, such as C-reactive protein (65–68). However, in clinical practice, implementation of such a regimen is notoriously difficult to achieve and maintain, and glycaemic control is rarely achieved. Hence, in conjunction with pharmacologic approaches, lifestyle intervention strategies must be an integral component of diabetes management, but programmes should be tailored to accommodate diverse lifestyles.

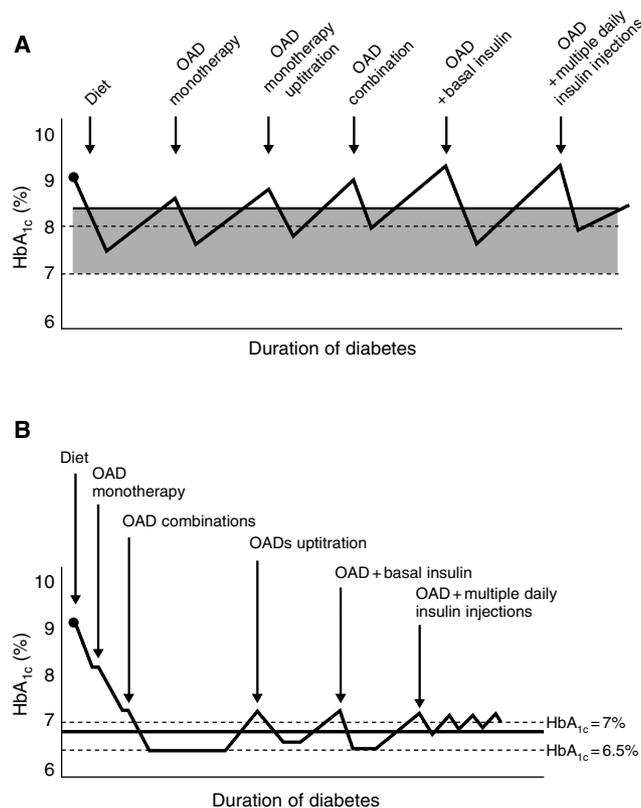


Figure 2 Conservative vs. proactive management: (A) traditional stepwise approach (62) and (B) early combination approach. OAD, oral antidiabetic drug. Adapted with permission from Campbell IW, Need for intensive early glycaemic control in patients with type 2 diabetes. *Br J Cardiol* 2000; 7: 625–631

Another problem with the stepwise approach is that delays often occur between stepping up from monotherapy to combination therapy (Figure 2A) (62). Taking this approach with an individual may lead to long periods of hyperglycaemia before treatment is stepped up – an unacceptable situation, given the evidence that even short periods of hyperglycaemia increase the risk of micro- and macrovascular complications (69–71). For example, data from the Kaiser Permanente Northwest database between 1994 and 2002 reveal that the average time between achieving the HbA_{1c} action point of 8% and switching to or adding a second oral antidiabetic agent for patients on metformin or sulphonylurea monotherapy was 14.5 or 20.5 months, respectively (Figure 3) (72,73). The authors concluded that: 'Clinicians should change glucose-lowering treatments in type 2 diabetes much sooner or use treatments that are less likely to fail', adding that 'An action point at 7.0% or lower is more likely to prevent additional deterioration than the traditional action point of 8.0%' (73). A more proactive schema is shown in Figure 2B. This represents the same sequence of events of treatment for the individual, but with each stage brought forward, to provide better and more rapid glycaemic control and therefore

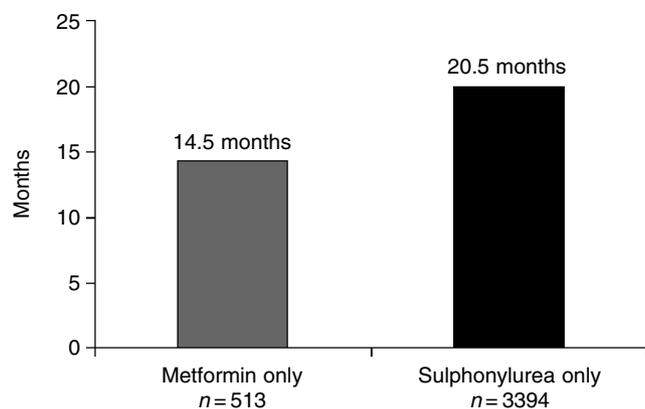


Figure 3 Length of time between first monotherapy $HbA_{1c} > 8.0\%$ * and switch/addition in therapy (73)*. *May include uptitration. Length of time between first $HbA_{1c} > 8\%$ and switch/addition in therapy could include periods where patients had subsequent HbA_{1c} test values below 8%. Based on non-randomised retrospective database analysis. Data from Kaiser Permanente Northwest 1994–2002. Patients had to be continuously enrolled for 12 months with HbA_{1c} laboratory values

improve the patient's glycaemic profile. This new approach can also be tailored to individual requirements and, importantly, avoids the delays that are the reality of present clinical experience.

While stepwise uptitration of monotherapy to the maximum recommended dose can be effective, in some cases the maximum recommended dose of agent is higher than the maximum effective dose (74). Moreover, uptitration may also lead to an increased incidence of adverse events, for example hypoglycaemia and gastrointestinal side-effects, without additional benefits on glycaemic control (75,76). In contrast, early use of combination of submaximal doses of agents can improve glycaemic control without significantly increasing side-effects (16,59,77–79). A precedent for this strategy comes from the antihypertensive arena, in which it has become commonplace to initiate therapy with a combination of drugs. However, patients are often reluctant to move to polypharmacy, and there may be compliance issues. There is therefore a continued need for discussion with and education of patients.

The *Partnership* recommends adopting a more proactive approach to type 2 diabetes management and advocates earlier use of combination therapy, in parallel with diet and exercise reinforcement. A suggested schema for glycaemic monitoring and initiation of combination therapy is shown in Figure 4 and is outlined in recommendations 6–8 below.

Recommendation 6: *Treat patients intensively so as to achieve target $HbA_{1c} < 6.5\%$ ² within 6 months of diagnosis.*

²Or fasting/preprandial plasma glucose < 110 mg/dl (6.0 mmol/l) where assessment of HbA_{1c} is not possible.

Recommendation 7: *After 3 months, if patients are not at target $HbA_{1c} < 6.5\%$,² consider combination therapy.*

Consider patient profile in selecting therapy. Where possible, treatment should be tailored to the phenotype of the patient at diagnosis, taking into account factors such as baseline HbA_{1c} , duration of diabetes, the presence of complications and risk of hypoglycaemia. Given that many patients, particularly those with high baseline glycaemia, may not attain their glycaemic targets with monotherapy or with late addition of combination therapy, their management regimens should aim for glycaemic targets as close to normal as possible and as early as possible. For example, in patients presenting with marked hyperglycaemia ($HbA_{1c} \geq 9\%$), the CDA Clinical Practice Guidelines recommend initiating first-line combination therapy with two complementary oral antidiabetic agents (16). In some circumstances, particularly if the patient is not morbidly obese, it may be desirable to give insulin to these patients in order to rapidly reduce HbA_{1c} , before transferring to an oral agent (16). Patients with long duration diabetes are likely to have limited β -cell function and therefore treatment with a secretagogue may not be appropriate, while in those with advanced disease and little residual β -cell function, insulin may be the only option although in obese individuals, successful weight reduction should always be encouraged.

Recommendation 8: *Initiate combination therapy or insulin immediately for all patients with $HbA_{1c} \geq 9\%$ at diagnosis.*

Choose the most appropriate combination of agents. One reason cited for the low proportion of patients achieving recommended glycaemic targets is a perceived lack of efficacy of some antidiabetic agents by some prescribers. Also, physicians may prescribe agents such as sulphonylureas and metformin over newer therapies because of familiarity and concerns regarding adverse events and costs. The first two factors can be overcome by raising awareness of the properties of agents and the third by considering the cost of managing the consequences of inadequate glycaemic control – micro- and macrovascular complications – that represent the largest expenditure for diabetes (7). There is evidence that effective disease management programmes that aim at preventing complications – in particular, CVD – are likely to significantly reduce the cost of managing diabetes (80).

While the need for efficacious agents is accepted, particular consideration should be paid to the patient's susceptibility to adverse events. For example, long-acting sulphonylureas should be used with caution in older patients because of the increased risk of hypoglycaemia (Table 3). In addition, the mechanism of action of these agents (primarily increasing insulin secretion rather than directly addressing insulin resistance) does not make them the agent of choice for use in obese, insulin-resistant individuals, who would most likely

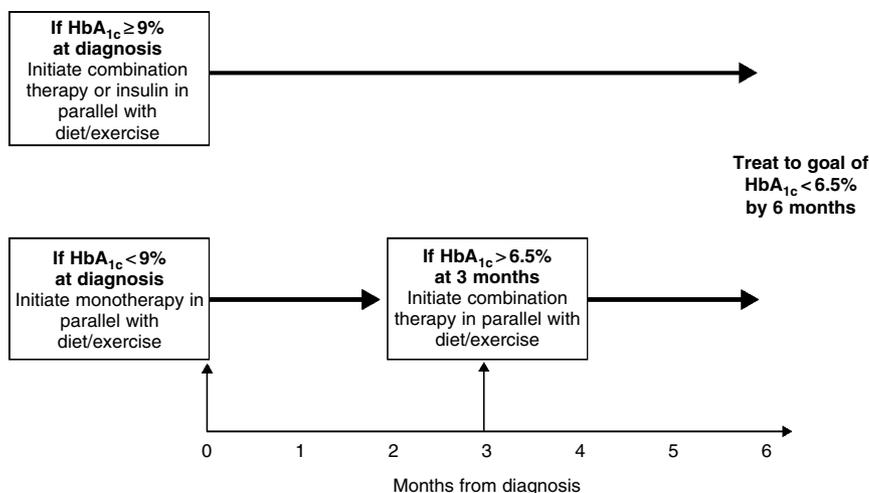


Figure 4 *Global Partnership* recommendations for management of glycaemia in newly diagnosed patients

benefit from an insulin sensitiser (81). Similarly, metformin is contraindicated for patients with renal impairment (82) and thiazolidinediones are contraindicated in Europe in patients with a history, or evidence, of heart failure, as well as in patients with New York Heart Association (NYHA) class III or IV heart failure, and in the USA in patients with NYHA class III or IV heart failure, due to the increased risk of oedema in these subjects (Table 3) (83,84).

While taking these factors into account, additional benefits are more likely to be achieved by choosing agents with complementary modes of action, which can be selected depending on the phenotype of the patient. Such combinations have been demonstrated clinically to improve the proportion of patients reaching glycaemic targets, for example metformin in combination with a sulphonylurea (85) or in combination with a thiazolidinedione (59). In future, it may prove more beneficial to incorporate at least one agent that addresses the underlying pathophysiology of the disease (Table 3).

Recommendation 9: Use combinations of oral antidiabetic agents with complementary mechanisms of action.

Improving Cross-Disciplinary Collaboration and Patient Communication

Many physicians consider poor patient adherence to be the greatest barrier to achieving effective glycaemic control. However, this is frequently subjective and it is difficult to achieve reliable assessments (86). Adherence to oral antidiabetic agents is, however, often lower than with other therapies (e.g. lipid-lowering agents). This may be linked with adverse events associated with oral antidiabetic agents or a lack of confidence in the immediate or future benefits of medication (87). Other factors include a lack of acceptance of the seriousness of type 2 diabetes due to the absence of symptoms.

Unfortunately, the complexity of the disease and limited physician consultation time restrict communication between HCP and patient, compounding the lack of understanding of the severity of the disease and of the importance of adherence. For example, in a survey of diabetes patients and non-specialist HCPs, including primary care professionals (PCPs), nurses and pharmacists, assessing their knowledge about oral

Table 3 Characteristics of oral antidiabetic agents

	<i>Insulin secretagogues</i>	<i>Metformin</i>	<i>α-Glucosidase inhibitors</i>	<i>Insulin</i>	<i>TZDs</i>	<i>Insulin</i>
Efficacy						
Effect on FPG/HbA _{1c} (82)	↓	↓	↓	↓	↓	↓
Effect on plasma insulin (82,93)	↑	↓	–	↑	↓	↑
Effect on insulin resistance (81)	–	↓/–	–	–	↓	–
Effect on β-cell function (94)	–	–	–	–	↑	–
Safety and tolerability						
Risk of hypoglycaemia (3,82)	✓	–	–	✓	–	✓
Weight gain (3,82)	✓	–	–	✓	✓	✓
Gastrointestinal side-effects (82)	–	✓	✓	–	–	–
Lactic acidosis (82)	–	✓	–	–	–	–
Oedema (84)	–	–	–	–	✓	–

Efficacy: ↓, reduced levels; ↑, increased levels; –, no documented change. Safety and tolerability: ✓, treatment-related adverse event; –, no documented association with treatment. FPG, fasting plasma glucose; TZDs, thiazolidinediones.

antidiabetic agents, only 35% of patients recalled receiving advice about their medication. Only 10% of patients using sulphonylureas appreciated the risk of hypoglycaemia and just 20% of those taking metformin were aware of potential gastrointestinal side-effects. PCPs, nurses and pharmacists also had important gaps in their knowledge, with, for example, only 50% answering questions correctly on the timing of metformin dosing in relation to food (88). Thus, continued education of all groups, including consistency of information from members of primary and secondary teams, is an essential feature of diabetes care.

The use of a multidisciplinary team approach to diabetes care – involving diabetologists, PCPs, diabetes specialist nurses, pharmacists, dieticians and health educators, among others, with the patient at the centre of the team – has been demonstrated to improve both glycaemic control and patient quality of life (89). For example, in the UKPDS, patients receiving intensive therapy delivered by a multidisciplinary team had significant benefits in glycaemic control and outcome compared with patients on standard therapy (3). Also, in a study of poorly controlled type 2 diabetes patients, a multidisciplinary team approach for delivering outpatient case management was found to provide significantly greater reductions in HbA_{1c} and in the use of healthcare resources compared with conventional PCP intervention (90). Such patient-centred approaches focusing on teamwork and patient education are currently being developed by several organisations (91,92).

While there may be challenges in applying these approaches globally, due to variations between countries and healthcare systems, greater involvement of patients (and their families) within the diabetes care team is pivotal to improving the proportion of individuals achieving their glycaemic goals. Physicians and other PCPs should recognise their important role in enabling and empowering patients to take control of their condition by providing effective communication, education and support, including the use of positive language, and by encouraging patient self-management.

Recommendation 10: Implement a multi- and interdisciplinary team approach to diabetes management to encourage patient education and self-care and share responsibility for patients achieving glucose goals.

CONCLUSIONS

Basic and clinical research have greatly increased the understanding of type 2 diabetes, and there has been substantial progress over the last decade in the development of new agents to treat the underlying pathophysiology. The benefits of good glycaemic control are well documented, and modern guidelines for glycaemic targets reflect the need for a tighter control as an important component of diabetes management. Given the current shortfall in the proportion of patients

achieving goals for glycaemia compared with other risk factors such as lipids and blood pressure, the *Global Partnership for Effective Diabetes Management* has developed 10 practical recommendations to help HCPs control hyperglycaemia (Table 2). The sense of urgency and the proactive approach to patient management reflected in these recommendations should be incorporated into clinical practice and management guidelines to maximise the number of patients with type 2 diabetes who achieve and maintain all recommended therapeutic goals: glucose, lipids and blood pressure.

ACKNOWLEDGEMENT

The Global Partnership for Effective Diabetes Management, including development of this manuscript, is sponsored by GlaxoSmithKline plc.

REFERENCES

- 1 International Diabetes Federation. *Facts & Figures 2004*. [Available at <http://www.idf.org/home/>].
- 2 Gonzalez-Clemente JM, Galdon G, Mitjavila J et al. Translation of the recommendations for the diagnosis of diabetes mellitus into daily clinical practice in a primary health care setting. *Diabetes Res Clin Pract* 2003; **62**: 123–9.
- 3 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–53.
- 4 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**: 854–65.
- 5 Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004; **291**: 335–42.
- 6 Liebl A, Mata M, Eschwege E. Evaluation of risk factors for development of complications in Type II diabetes in Europe. *Diabetologia* 2002; **45**: S23–8.
- 7 Jonsson B. Revealing the cost of Type II diabetes in Europe. *Diabetologia* 2002; **45**: S5–12.
- 8 American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care* 2003; **26**: 917–32.
- 9 Koopmanschap M. Coping with Type II diabetes: the patient's perspective. *Diabetologia* 2002; **45**: S18–22.
- 10 UK Prospective Diabetes Study (UKPDS) Group. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia* 1991; **34**: 877–90.
- 11 Hu FB, Stampfer MJ, Haffner SM et al. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care* 2002; **25**: 1129–34.
- 12 Irons BK, Mazzolini TA, Greene RS. Delaying the onset of type 2 diabetes mellitus in patients with prediabetes. *Pharmacotherapy* 2004; **24**: 362–71.

- 13 American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004; 27 (Suppl. 1): S15–34.
- 14 European Diabetes Policy Group. A desktop guide to type 2 diabetes. *Diabet Med* 1999; 16: 716–30.
- 15 American Association of Clinical Endocrinologists. Medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management – 2002 update. *Endocr Pract* 2002; 8 (Suppl. 1): 40–82.
- 16 Canadian Diabetes Association. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2003; 27 (Suppl. 2): S1–152.
- 17 Latinamerican Diabetes Association (ALAD). Guidelines for the diagnosis, control and treatment of type 2 diabetes mellitus. *Revista de la Asociación Latinoamericana de Diabetes* 2000; 8 (Suppl. 1): 101–67.
- 18 Asian-Pacific Type 2 Diabetes Policy Group. *Type 2 Diabetes: Practical Targets and Treatments*, 3rd edn, 2002. Health Communications Australia Pty Limited and In Vivo Communications Pty Limited, Sydney, Australia, on behalf of the Asian-Pacific Type 2 Diabetes Policy Group.
- 19 Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321: 405–12.
- 20 Gaede P, Vedel P, Larsen N et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383–93.
- 21 Monnier L, Grimaldi A, Charbonnel B et al. Management of French patients with type 2 diabetes mellitus in medical general practice: report of the Mediab observatory. *Diabetes Metab* 2004; 30: 35–42.
- 22 Charpentier G, Genes N, Vaur L et al. Control of diabetes and cardiovascular risk factors in patients with type 2 diabetes: a nationwide French survey. *Diabetes Metab* 2003; 29: 152–8.
- 23 Rothenbacher D, Ruter G, Saam S et al. Younger patients with type 2 diabetes need better glycaemic control: results of a community-based study describing factors associated with a high HbA1c value. *Br J Gen Pract* 2003; 53: 389–91.
- 24 Harris S, Ekoé J-M, Webster-Bogaert S. The Diabetes in Canada Evaluation (DICE) study: are primary care physicians achieving target A1c? *Diabetes* 2003; 52 (Suppl. 1): A499.
- 25 Bailey C, Del Prato S, Eddy DM et al. Earlier intervention in type 2 diabetes: the case for achieving early and sustained glycaemic control. *Int J Clin Pract* (doi: 10.1111/j.1742-1241.2005.00675.x).
- 26 Standl E, Balletshofer B, Dahl B et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia* 1996; 39: 1540–5.
- 27 Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 1995; 44: 968–83.
- 28 American Diabetes Association. Tests of glycemia in diabetes. *Diabetes* 2004; 27 (Suppl. 1): S91–3.
- 29 Blonde L, Ginsberg BH, Horn S et al. Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care* 2002; 25: 245–6.
- 30 Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in type 2 diabetes? *Eur J Clin Invest* 2000; 30 (Suppl. 2): 3–11.
- 31 Bonora E, Muggeo M. Postprandial blood glucose as a risk factor for cardiovascular disease in Type II diabetes: the epidemiological evidence. *Diabetologia* 2001; 44: 2107–14.
- 32 Hanefeld M, Koehler C, Henkel E et al. Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid intima-media thickness: the RIAD Study. *Diabet Med* 2000; 17: 835–40.
- 33 Heisler M, Piette JD, Spencer M et al. The relationship between knowledge of recent HbA1c values and diabetes care understanding and self-management. *Diabetes Care* 2005; 28: 816–22.
- 34 Stamler J, Vaccaro O, Neaton JD et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16: 434–44.
- 35 UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: (UKPDS 38). *BMJ* 1998; 317: 703–13.
- 36 UK Prospective Diabetes Study (UKPDS) Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: (UKPDS 39). *BMJ* 1998; 317: 713–20.
- 37 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005–16.
- 38 Owen OG. The collaborative atorvastatin diabetes study: preliminary results. *Int J Clin Pract* 2005; 59: 121–3.
- 39 Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004; 109: 1101–7.
- 40 Lazarus JM, Bourgoignie JJ, Buckalew VM et al. Achievement and safety of a low blood pressure goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. *Hypertension* 1997; 29: 641–50.
- 41 Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; 351: 1755–62.
- 42 Del Prato S, Marchetti P. Targeting insulin resistance and β -cell dysfunction: the role of thiazolidinediones. *Diabetes Technol Ther* 2004; 6: 719–31.
- 43 Kahn SE, Haffner SM, Zinman B et al. Lack of concordance of NCEP and WHO criteria for the diagnosis of the metabolic syndrome in recently diagnosed diabetes in North America and Europe in the ADOPT study cohort. *Diabetes* 2003; 52 (Suppl. 1): A222.
- 44 Herman W, Freed M, Heise M et al. The ADOPT study: symptoms and health status in a recently-diagnosed type 2 diabetic population. *Diabetes* 2003; 52 (Suppl. 1): A263.

- 45 Monnier L. The role of blood glucose-lowering drugs in the light of the UKPDS. *Diabetes Obes Metab* 1999; 1 (Suppl. 2): S14–23.
- 46 Ho PM, Masoudi FA, Peterson ED et al. Cardiology management improves secondary prevention measures among patients with coronary artery disease. *J Am Coll Cardiol* 2004; 43: 1517–23.
- 47 Verlato G, Muggeo M, Bonora E et al. Attending the diabetes center is associated with increased 5-year survival probability of diabetic patients: the Verona Diabetes Study. *Diabetes Care* 1996; 19: 211–3.
- 48 Haffner SM, Mykkanen L, Festa A et al. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation* 2000; 101: 975–80.
- 49 Bonora E, Kiechl S, Willeit J et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes* 1998; 47: 1643–9.
- 50 Bloomgarden ZT. Type 2 diabetes in the young: the evolving epidemic. *Diabetes Care* 2004; 27: 998–1010.
- 51 Weyer C, Bogardus C, Mott DM et al. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104: 787–94.
- 52 UK Prospective Diabetes Study (UKPDS) Group. UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995; 44: 1249–58.
- 53 Nesto RW. The relation of insulin resistance syndromes to risk of cardiovascular disease. *Rev Cardiovasc Med* 2003; 4 (Suppl. 6): S11–18.
- 54 Bonora E, Calcaterra F, Lombardi S et al. Plasma glucose levels throughout the day and HbA(1c) interrelationships in type 2 diabetes: implications for treatment and monitoring of metabolic control. *Diabetes Care* 2001; 24: 2023–9.
- 55 Gerich JE. Redefining the clinical management of type 2 diabetes: matching therapy to pathophysiology. *Eur J Clin Invest* 2002; 32 (Suppl. 3): 46–53.
- 56 Turner RC, Cull CA, Frighi V et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; 281: 2005–12.
- 57 Campbell IW. Long-term glycaemic control with pioglitazone in patients with type 2 diabetes. *Int J Clin Pract* 2004; 58: 192–200.
- 58 Jariwala S, Mather R, Walker L et al. Long term glycaemic control with rosiglitazone in combination with metformin. *Diabet Med* 2003; 20 (Suppl. 1): 105.
- 59 Rosenstock J, Porter LE, Heise M et al. The RESULT study in older type 2 diabetes: reaching durable glycemic goals with combination sulfonylurea and rosiglitazone. *Diabetes* 2004; 53 (Suppl. 2): A160.
- 60 Vahl TP, D'Alessio DA. Gut peptides in the treatment of diabetes mellitus. *Expert Opin Investig Drugs* 2004; 13: 177–88.
- 61 Taylor SD, Hill B. Recent advances in protein tyrosine phosphatase 1B inhibitors. *Expert Opin Investig Drugs* 2004; 13: 199–214.
- 62 Campbell IW. Need for intensive, early glycaemic control in patients with type 2 diabetes. *Br J Cardiol* 2000; 7: 625–31.
- 63 Tuomilehto J, Lindstrom J, Eriksson JG et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343–50.
- 64 Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346: 393–403.
- 65 Pastors JG, Warshaw H, Daly A et al. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 2002; 25: 608–13.
- 66 Boule NG, Haddad E, Kenny GP et al. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001; 286: 1218–27.
- 67 Kopp HP, Kopp CW, Festa A et al. Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arterioscler Thromb Vasc Biol* 2003; 23: 1042–7.
- 68 Esposito K, Pontillo A, Di Palo C et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003; 289: 1799–804.
- 69 Writing Team for the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003; 290: 2159–67.
- 70 Writing Team for the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002; 287: 2563–9.
- 71 Nathan DM, Lachin J, Cleary P et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003; 348: 2294–303.
- 72 Brown JB, Nichols GA. Glycemic burden of oral agent failure in type 2 diabetes. *Diabetes* 2003; 52 (Suppl. 1): A61–2.
- 73 Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care* 2004; 27: 1535–40.
- 74 Garber AJ. Using dose-response characteristics of therapeutic agents for treatment decisions in type 2 diabetes. *Diabetes Obes Metab* 2000; 2: 139–47.
- 75 Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; 334: 574–9.
- 76 Scheen AJ, Lefebvre PJ. Oral antidiabetic agents. A guide to selection. *Drugs* 1998; 55: 225–36.
- 77 Rosenstock J, Goldstein BJ, Wooddell M et al. Greater benefits of rosiglitazone (RSG) added to submaximal dose of metformin (MET) compared to maximizing metformin dose in type 2 diabetes (T2DM) patients. *Diabetes* 2004; 53 (Suppl. 2): A144.
- 78 Kerenyi Z, Samer H, Yan Y et al. Combination therapy with rosiglitazone and glibenclamide compared with upward titration of glibenclamide alone in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2004; 63: 213–23.

- 79 Baksi A, James RE, Zhou B et al. Comparison of uptitration of gliclazide with the addition of rosiglitazone to gliclazide in patients with type 2 diabetes inadequately controlled on half-maximal doses of a sulphonylurea. *Acta Diabetol* 2004; **41**: 63–9.
- 80 Selby JV, Ray GT, Zhang D et al. Excess costs of medical care for patients with diabetes in a managed care population. *Diabetes Care* 1997; **20**: 1396–402.
- 81 Matthaei S, Stumvoll M, Kellerer M et al. Pathophysiology and pharmacological treatment of insulin resistance. *Endocr Rev* 2000; **21**: 585–618.
- 82 DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; **131**: 281–303.
- 83 Barnett AH. Insulin-sensitizing agents – thiazolidinediones (glitazones). *Curr Med Res Opin* 2002; **18** (Suppl. 1): S31–9.
- 84 Nesto RW, Bell D, Bonow RO et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003; **108**: 2941–8.
- 85 Garber AJ, Larsen J, Schneider SH et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab* 2002; **4**: 201–8.
- 86 Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004; **27**: 1218–24.
- 87 Grant RW, Devita NG, Singer DE et al. Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care* 2003; **26**: 1408–12.
- 88 Browne DL, Avery L, Turner BC et al. What do patients with diabetes know about their tablets? *Diabet Med* 2000; **17**: 528–31.
- 89 Codispoti C, Douglas MR, McCallister T et al. The use of a multidisciplinary team care approach to improve glycemic control and quality of life by the prevention of complications among diabetic patients. *J Okla State Med Assoc* 2004; **97**: 201–4.
- 90 Sadur CN, Moline N, Costa M et al. Diabetes management in a health maintenance organization. Efficacy of care management using cluster visits. *Diabetes Care* 1999; **22**: 2011–7.
- 91 National Health Service. *National Service Framework for Diabetes: Standards 2004*. [Available at <http://www.dh.gov.uk/assetRoot/04/05/89/38/04058938.pdf>].
- 92 NHS Scotland. *Scottish Diabetes Framework 2004*. [Available at <http://www.scotland.gov.uk/library5/health/sdf.pdf>].
- 93 Lebovitz HE. Oral therapies for diabetic hyperglycemia. *Endocrinol Metab Clin North Am* 2001; **30**: 909–33.
- 94 Bell DS. Beta-cell rejuvenation with thiazolidinediones. *Am J Med* 2003; **115** (Suppl. 8A): 20S–23S.
- 95 Beck-Nielsen H, Damsgaard EM, Faber O et al. *Ikke-insulinkrævende diabetes mellitus: diagnostik og behandling* Copenhagen, Denmark: Dansk Selskab for Intern Medicin, 1988.

Paper received June 2005, accepted July 2005