

# THE GUIDELINE

## 4 Diagnosis

### 4.1 Rationale

The diagnosis of Type 1 diabetes would not appear to present any problems. It is, however, a lifelong condition requiring treatment with a therapy of considerable health and social impact (insulin injections) so it is important that the diagnosis is secure. Considerations also arise over differentiating the types of diabetes.

### 4.2 Evidence

Diagnosis, in regard of types of diabetes, is generally not addressed by the WHO report.<sup>8</sup> That report notes that children present with severe symptoms, and that diagnosis is simply confirmed by blood glucose measurement (advice that may be regarded as dated) (IV).

WHO otherwise concentrates mainly on the situation pertaining to Type 2 diabetes, in doing so noting (by reference to the 1985 report) the lack of need for challenge testing when plasma glucose levels are high in the absence of other metabolic stress, and are confirmed by a second laboratory measurement or classic symptoms.

### 4.3 Comment

Type 1 diabetes is, for the most part, easily recognised and diagnosed, requiring hyperglycaemia to a significant degree (risk of microvascular complications), and islet B-cell destruction which may be detected as pathogenetic markers or poor insulin secretion.

Where the diagnosis of diabetes is equivocal, and hyperglycaemia is by definition marginal, management will generally follow guidelines for Type 2 diabetes. In some patients with 'Type 2 diabetes' or diabetes of uncertain type, management will be by clinical stage even if auto-immune markers of Type 1 diabetes are detected.

If Type 1 diabetes is suspected, referral should be more urgent than with most other types of diabetes diagnosed in adults.

### 4.4 Consideration

The group endorsed the commentary discussed above, and concluded that simple recommendations were all that were required. Although in this condition diagnosis of diabetes is rarely in doubt, errors do arise in attribution of diabetes type on occasions, and this is known to result in negative consequences including failure to anticipate ketoacidosis or unnecessary insulin therapy. Accordingly the group felt that cautionary recommendations were in order. The group noted that formal evidence of the utility of tests to distinguish type of diabetes by auto-immune markers or measures of islet B-cell function was not positive, and that these tests were not routinely performed.

The group were keen to reiterate the importance of laboratory glucose estimation in line with WHO recommendations to avoid the very rare misdiagnoses with lifelong consequences. The

role of symptoms and of HbA<sub>1c</sub> estimation were seen as useful but only supportive, as both lack absolute specificity.

## RECOMMENDATIONS

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| <b>R1</b> | Diabetes should be confirmed by a single diagnostic laboratory glucose measurement in the presence of classical symptoms, or by a further laboratory glucose measurement. The diagnosis may be supported by a raised HbA <sub>1c</sub> .   | <b>D</b> |
| <b>R2</b> | Where diabetes is diagnosed, but Type 2 diabetes suspected, the diagnosis of Type 1 diabetes should be considered if: <ul style="list-style-type: none"><li>● ketonuria is detected, or</li><li>● weight loss is marked, or</li><li>● the person does not have features of the metabolic syndrome or other contributing illness.</li></ul> | <b>D</b> |
| <b>R3</b> | When diabetes is diagnosed in a younger person, the possibility that the diabetes is not Type 1 diabetes should be considered if they are obese or have a family history of diabetes, particularly if they are of non-white ethnicity.   | <b>D</b> |
| <b>R4</b> | Tests to detect specific auto-antibodies or to measure C-peptide deficiency should not be regularly used to confirm the diagnosis of Type 1 diabetes. Their use should be considered if predicting the rate of decline of islet B-cell function would be useful in discriminating Type 1 from Type 2 diabetes.                             | <b>D</b> |

## 5 Care process and support

### 5.1 Scope of this chapter

It is outside the scope of this guideline to consider service delivery issues. Accordingly no recommendations are made regarding site of care; the emphasis is on the process of care necessary for a person with Type 1 diabetes to achieve optimal yet cost-effective outcomes. For example, while it is evidence-based that multidisciplinary team care leads to a reduced rate of complications, and it is known that no health professional alone possesses all the necessary skills, no recommendation is made about the membership of multidisciplinary teams or where they are sited. Nevertheless, where an evidence base exists for an activity associated with a health professional this has been appraised (because it influences the skillmix required), even if it is not used directly in the recommendations.

Equally, a term such as ‘diabetes centre’ should be read as a group of people working together as a resource with access to appropriate healthcare equipment and supporting all those in the local area providing diabetes care. This should not be interpreted as buildings sited in a primary or secondary care environment, or to sole sites of care. Some items of equipment (telephones, structured records, diabetes recall registers) are necessary components for the processes of care (for example retinopathy screening) discussed in other parts of this guideline.

### 5.2 Optimal healthcare processes

#### ▷ Rationale

The management of diabetes is multidimensional, and each dimension is multifaceted. Notable dimensions include diagnosis and associated management, preventative long-term care, hospital and emergency management, and detection and management of late-developing complications. With each of these dimensions a number of care areas are found (for example in long-term prevention, glucose control, blood pressure control, risk factor surveillance, blood lipid control and smoking), and for each care area a number of deliverables addressed (for example in blood glucose control: knowledge and basis of targets, injection skills, self-monitoring, dose adjustment, dietary matching, hypoglycaemia management, sick day management) by a number of different members of a multidisciplinary team. This multidimensional care delivery requirement has spawned diverse attempts aimed at ensuring optimal care is available to all those with diabetes. This section of the guideline seeks to examine what evidence is available to support some of these approaches.

#### ▷ Evidence review

It was recognised that the systems underlying structured organisation of care (for example diabetes centres) do not easily lend themselves to comparison by higher level studies (RCTs and cohort studies). Some technologies within such systems (for example a foot care information initiative) may on occasion be so approachable, but for the most part such technologies are offered and may only be applicable as part of an integrated care package. Accordingly, for the

purposes of evidence review, no limits to study type were placed on the papers sought. Of 348 titles identified, 58 were selected as relevant for critical appraisal.

Additionally the major national and international guidelines were reviewed for consistency of recommendations. As the current question was considered at the end of the guideline process, a review of generic structures of care already inherent or explicit in agreed recommendations within the current guideline was also made.

Only rarely did the primary literature distinguish type of diabetes. On occasion, insulin-treated people from both major types of diabetes were considered separately from people with Type 2 diabetes managed without insulin injections. Historically, people using insulin have been managed in specialist care; papers addressing issues of delivery of care by family doctors without reference to insulin-treated diabetes were also excluded from consideration, except in regards of complications surveillance.

▷ Evidence statements

*Multidisciplinary care*

The Diabetes Control and Complications Trial (DCCT),<sup>9</sup> and smaller RCTs using improved management to judge the effect on patient outcomes, used multidisciplinary team input (in particular from specialist nurses and dietitians) as part of an integrated package to improve metabolic intermediate outcomes. A Cochrane review<sup>10</sup> of diabetes specialist nurse input identified six heterogeneous studies unsuitable for meta-analysis, and found little evidence of longer-term impact on intermediate outcomes. An RCT<sup>11</sup> of the impact of structured team care as compared to usual care showed improved satisfaction and blood glucose control at six months. An RCT<sup>12</sup> of the use of diabetes specialist nurses to adjust insulin doses over the telephone showed improved blood glucose control (Ib).

A nurse specialist approach has been justified by a number of before-and-after studies and case series with such input<sup>13–17</sup> (II).

A number of studies of variable quality address the impact of inclusion of podiatrists compared to normal care within what is then usually called a diabetes foot care team. These studies included one RCT showing more patient knowledge and less callosities at one year, and a controlled study<sup>18</sup> (it is unclear whether that study is randomised) showing less foot ulceration (Ib).

A number of historically-controlled or descriptive studies support this approach, mainly reporting on patient preference outcomes<sup>15,19–21</sup> (IV).

The current guideline and all examined guidelines advise the use of members of a multidisciplinary team or, more specifically, nurses with training in teaching skills and adult education in a number of aspects of patient education, and formally trained dietitians and podiatrists within the specifically relevant areas of diabetes care (IV).

*Annual review*

No RCTs address the concept of integrated annual review. Newly-implemented structured annual review has been subject to a descriptive review,<sup>22</sup> suggesting improved satisfaction with care and improved patient motivation. Few full-length descriptions of the review process are available,<sup>23</sup> most references being editorials and letters (IV).

The current guideline suggests annual surveillance of a number of potentially developing late complications (as do all other guidelines for the most complications). The International Diabetes Federation's European guideline recommends integration of these activities into one patient visit.<sup>24</sup> Annual review is also the basis of many quality control structures proposed for diabetes care,<sup>25</sup> including (implicitly) that of the UK Audit Commission (IV).

#### *Diabetes registers*

A series of descriptive papers appear to demonstrate the feasibility of establishing population-based and clinic-based diabetes registers, with varying densities of information.<sup>26–36</sup> A system of database-driven recall for complications surveillance is implicit in the recommendations for annual complications surveillance of this and published guidelines. Issues of data security and confidentiality are not reported to have proved to be problematic obstructions to the deployment of diabetes registers (IV).

#### *Diabetes centres and structured care*

Most papers in this area are descriptive, and there is inevitable overlap with deployment of multidisciplinary teams and provision of diabetes information and foot care. Using historical controls a study<sup>37</sup> suggests improved blood glucose control, while another non-randomised study suggests improved survival (presumably mainly in people with Type 2 diabetes) (I**b**).

#### *Structured records and care cards*

Although papers were ascertained addressing these areas,<sup>38–44</sup> the papers were descriptive with no useful analysis of patient-related outcomes (IV).

#### *Electronic patient records and computer data analysis*

A number of descriptive papers were identified,<sup>45–48</sup> suggesting such approaches can be feasible and have utility, but not demonstrating comparative advantage to traditional approaches (IV).

However when such records were used to send judgemental letters to people with diabetes,<sup>49</sup> randomising sites of care, intermediate outcomes were significantly improved (probably mainly in people with Type 2 diabetes) (I**b**).

#### *Telemedicine*

A number of approaches to medical care without direct patient contact are described in the literature. One RCT of a telecare system for insulin<sup>50</sup> provided equivalent control at reduced cost, while another study<sup>12</sup> using nurses resulted in improved blood glucose control (I**b**).

In more rural and remote situations telemedicine can similarly provide apparent time and cost savings where images of foot problems<sup>51</sup> and eye photographs<sup>52</sup> need to be reviewed by specialists (I**b**).

### *Inpatient care*

Three papers using historical controls or randomised controls address the value of multidisciplinary teams with a specialist interest in diabetes management in the care of inpatients on non-diabetes wards.<sup>53–55</sup> Reduced length of inpatient stay is consistently reported. One study suggests improved glucose control.<sup>55</sup> One study, also using historical controls, addresses length of stay in a developing country in newly-diagnosed people with diabetes, showing much reduced stays with multidisciplinary team input (Ib/IIa).

### *Guidelines*

No literature on the deployment or impact of diabetes guidelines was identified.

#### ▷ Health economic evidence

Two potentially useful papers consider the type of treatment facility used to deliver care to those with Type 1 diabetes.<sup>334,335</sup> One German study<sup>334</sup> found that the treatment facility (polyclinics, specialist clinics or general practitioners) makes no difference to diabetes-specific knowledge when this was controlled for age, sex and education. One UK study<sup>335</sup> found no difference between hospital- and general practice-based care on a range of outcome measures for metabolic control, satisfaction with treatment or beliefs about diabetic control for a mixed diabetic population. Some differences were observed in the surveillance for complications, with more frequent testing in integrated care. Whilst costly, it is worth noting that fewer patients defaulted from general practice-based care than conventional care. Avoided complications may offset the increased cost of general practice-based care, although this cannot be established on the basis of this study.

One UK-based study<sup>297</sup> suggested that the provision of a hospital-based diabetes specialist nurse lowered the cost per patient admission without producing a significant difference in readmission, quality of life or patient satisfaction.

#### ▷ Consideration

The group endorsed the approaches suggested by the evidence, but noted that attempts to implement some of the recommendations in the past had been inhibited by funding difficulties. This however was not felt to be a barrier to reiterating the health gains to be obtained. It was noted that recent publications (beyond the cut-off date of the searches) supported some of the recommendations further, including those relating to specialist nurses. The UK's national service framework for diabetes was noted to have endorsed diabetes registers. The group recognised the lack of any kind of formal evidence relating to walk-in, telephone-request and out-of-hours services.

## RECOMMENDATIONS

- R5** Advice to adults with Type 1 diabetes should be provided by a range of professionals with skills in diabetes care working together in a coordinated approach. A common environment (diabetes centre) is an important resource in allowing a diabetes multidisciplinary team to work and communicate efficiently while providing consistent advice. **D**

R6	Open access services should be provided on a walk-in and telephone-request basis during working hours to adults with Type 1 diabetes, and a helpline staffed by people with specific diabetes expertise should be provided on a 24-hour basis. Adults with diabetes should be provided with contact information for these services.	C
R7	An individual care plan should be set up and reviewed annually, modified according to changes in wishes, circumstances and medical findings, and the details recorded. The plan should include aspects of: <ul style="list-style-type: none"> <li>● diabetes education including nutritional advice (see section 6.1, ‘Education programmes for adults with Type 1 diabetes’ and 6.3, ‘Dietary management’)</li> <li>● insulin therapy (see section 7.3, ‘Insulin regimens’ and 7.4, ‘Insulin delivery’)</li> <li>● self-monitoring (see section 6.2, ‘Self-monitoring of blood glucose’)</li> <li>● arterial risk factor surveillance and management (see chapter 8, ‘Arterial risk control’)</li> <li>● late complications surveillance and management (see sections on late complications)</li> <li>● means and frequency of communication with the professional care team</li> <li>● follow-up consultations including next annual review.</li> </ul>	D
R8	Population, practice-based and clinic diabetes registers (as specified by the national service framework) should be used to assist programmed recall for annual review and assessment of complications and vascular risk.	D
R9	Conventional technology (telephones), or newer technologies for high-density data transmission of images, should be used to improve process and outcomes.	A
R10	The multidisciplinary team approach should be available to inpatients with Type 1 diabetes, regardless of the reason for admission (see section 13.3, ‘Inpatient management’).	D

### 5.3 Support groups

#### ▷ Rationale

As having Type 1 diabetes can have a major impact on lifestyle and self-esteem, it would appear that support groups could have a role in providing for some needs outside the professional environment and even separately from immediate carers. The range of such potential input is large and might stretch from simply fulfilling a need for belonging, through to helping with diabetes-related financial problems (such as insurance), and even providing a further source of diabetes-related information.

Coping with diabetes, or any other condition, is influenced not only by psychological characteristics of the individual but also by social relationships (eg support and communication by healthcare team, family and friends). Informal interpersonal variables, such as social resources and support, have been found to be associated with better diabetes self-management,<sup>56–7</sup> family environment,<sup>58–60</sup> and marital interaction.<sup>61</sup> A medical condition is only one aspect that affects the make-up of an individual’s personal identity, and for some may be perceived as a minor factor compared to their environmental and social circumstances.

A ‘support group’ is defined in this guideline as a group of people with Type 1 diabetes that comes together to provide support to themselves and others in their locality. Members are usually unpaid and many will be supported under the auspices of national (or local) voluntary organisations. Support groups have become commonplace throughout health and social care.

Patients and carers may choose to contact or be involved with support groups to gain information and support to benefit their own needs, or with a wider altruistic aim of helping other people within the local community. It was not possible to find specific research identifying patient and carer preferences for support groups, or indeed to identify specific groups or types of people who may benefit more than others. Some people attend meetings of groups regularly whilst other individuals are reassured by being aware of a group's existence and the opportunity to contact the group at a later date if problems arise and/or support is required. Preferences are dependent on what stage people are at in their lives and what information is taken (or needs to be taken) on board.

▷ Evidence statements

The Diabetes Attitudes, Wishes and Needs (DAWN) questionnaire study<sup>62</sup> highlighted that emotional support, along with family support, was a key factor in how well people with diabetes manage their condition, with support networks being considered at least as important as the medication they take in helping them manage their diabetes. Interim results also indicate that people who do not have access to a community of support, especially the young or elderly living alone, may be less likely to be concordant with their medication regimes, putting them at risk of inadequate control of their diabetes (III).

There are still significant numbers of people emerging from the confirmation of a diagnosis who are underinformed and unsupported.<sup>63</sup> Qualitative research of various designs examining the views and experiences of people with diabetes and carers has identified that many perceived benefits exist from meeting other people with diabetes. It has helped many to overcome the feelings of isolation and is seen as an opportunity to talk to others going through the same experience<sup>64</sup> (IV).

Research evaluating the effectiveness of support groups for patients and carers, across numerous conditions and groups (not necessarily diabetes), has shown specific benefits including (III):

- psychological and emotional benefits<sup>65</sup> including lower pain perception and improved ability to cope with stress<sup>63,66-7</sup>
- reduction of carers' burdens and stresses<sup>68-9</sup>
- improvement in quality of life<sup>70-71</sup>
- improved self-care through health promotion strategies which have been helpful in smoking cessation and management of chronic conditions<sup>72-3</sup>
- improved access to health service provision<sup>74</sup>
- reduced isolation, overcoming depression and loss of self-esteem<sup>64</sup>
- better understanding of conditions, symptoms and healthcare systems through education and information.<sup>67</sup>

The Diabetes UK network of support groups recorded 175,426 members in July 2003, with around 7% under the age of 20 years and around 30% aged 70 years or over. Around 40% had paid for annual adult membership, 50% had a reduced rate membership (including children), and 10% had chosen life membership. The Diabetes UK Careline is, at the time of writing, one of the busiest sources of information for all people with Type 1 diabetes in the UK. In 2002, Careline were contacted 40,747 times (81% telephone, 13% e-mail, 6% post).

The five most frequent topics of enquiry recorded were (III):<sup>67a</sup>

- diet
- insulin
- medicines other than insulin
- new diagnosis
- travel.

▷ Health economic evidence

Two studies were identified as potentially useful in this area.<sup>336–7</sup> As neither paper included cost information, the cost-effectiveness of support interventions cannot be ascertained.

## RECOMMENDATION

- R11 At the time of diagnosis and periodically thereafter, adults with Type 1 diabetes should be offered up-to-date information on the existence of and means of contacting diabetes support groups (local and national) and the benefits of membership. C

### 5.4 Quality audit and monitoring

▷ Rationale

It is generally accepted now that any system delivering a product, including healthcare systems, can benefit from review of its performance. The diabetes care espoused by this guideline is both complex and systematic, and thus lends itself to the kind of data collection needed for quality development. That very complexity, however, means that monitoring the structures, process and outcomes of all sectors can seem overwhelming, necessitating consideration of how limited monitoring activity can be undertaken without distorting the areas gaining attention for improvement. Monitoring of quality of life would seem *a priori* to be of particular importance in diabetes care, but presents its own difficulties of data acquisition and of analysis of temporally different outcomes.

Audit criteria are suggested in section 3.3 of this guideline to assist local users in promoting implementation and monitoring ongoing improvements in process and outcome. They have been informed where possible by existing validated measures, principally those of the National Centre for Health Outcome Development.<sup>75</sup>

## 6 Education programmes and self-care

### 6.1 Education programmes for adults with Type 1 diabetes

#### ▷ Rationale

Having diabetes involves acquiring a great range of new skills and knowledge, including insulin therapy, dietary changes, self-monitoring, hypoglycaemia, jobs, travel, physical exercise, coping with concurrent illness, foot care, arterial risk control and avoiding complications. The history of education and information giving in diabetes care goes back to the earliest dietary interventions several centuries ago, and the use of education professionals to impart skills associated with insulin therapy dates from the time of discovery and isolation of insulin. Accordingly patient education is a true cornerstone that enables self-management of diabetes, and most diabetes management is self-management. Review of other parts of this NICE guideline will reveal that education and information giving are parts of nearly all of them, from enabling patient choice in determining features of self-management, to acquisition of skills needed to perform tasks and make judgements, to self-care where high risk complications have developed, and to skills in handling healthcare professionals to ensure that issues of importance to the person with Type 1 diabetes are addressed.

#### ▷ Evidence statements

##### *Content of education*

There were no trials located in newly-diagnosed people with Type 1 diabetes specifically, or concerned with the initial content of education. The American Diabetes Association (ADA) guidelines<sup>76</sup> suggest that as part of initial visit people should be referred to a diabetes educator if education is not provided by the physician or practice staff, but content of this education is not defined (IV).

##### *Educational setting*

One small randomised controlled trial<sup>77</sup> comparing the efficacy of classroom teaching of diabetes skills, compared to individualised learning, found that classroom teaching led to a greater level of awareness about diabetes self-care. However, there was no significant difference in terms of the level of use of self-care practices. Furthermore, the two education techniques provided no different outcome of levels of technical skill in self-care. However this study made no analysis of comparability of study groups at baseline and was not blinded (Ib).

##### *Technology interventions*

One randomised controlled study compared two interactive computer schemes to reinforce an educational video. The first gave additional feedback and information on the correct answers, the second only the correct answers.<sup>78</sup> People with diabetes in the interactive group scored significantly better in a follow-up test of diabetes knowledge than those following the standard scheme. There were no significant differences in user ratings for the two software packages, but

the people in the additional feedback group had a better diabetes knowledge at baseline, so the results may be biased by this confounding factor (Ib).

#### *Guidelines for self-management education*

An update of the US standards for diabetes self-management education<sup>79</sup> based on a literature review covered the organisation of diabetes self-management education, its content and provision. A multiprofessional task force encompassing all the major interested stakeholders agreed the following standards (IV).

- Education and information-giving will involve the interaction of the individual with diabetes with a multifaceted education instructional team, which may include a behaviourist, exercise physiologist, ophthalmologist, optometrist, pharmacist, physician, podiatrist, registered dietitian, registered nurse, other healthcare professionals, and paraprofessionals.
- Instructors will obtain regular continuing education in the areas of diabetes management, behavioural interventions, teaching and learning skills and counselling skills.
- Assessed needs of the individual will determine which of the following content areas are delivered:
  - describing the diabetes disease process and treatment options
  - incorporating appropriate nutritional management
  - incorporating physical activity into lifestyle
  - utilising medications (if applicable) for therapeutic effectiveness
  - monitoring blood glucose and urine ketones (where appropriate) and using results to improve control
  - preventing, detecting and treating acute complications
  - preventing (through risk reduction behaviour), detecting and treating chronic complications
  - goal-setting to promote health, and problem-solving for daily living
  - integrating psychosocial adjustment to daily life
  - promoting preconception care, management during pregnancy and gestational diabetes management (if applicable).
- An individualised assessment, development of an education plan and periodic reassessment between participant and instructor will direct the selection of appropriate educational materials and interventions.
- The assessment includes relevant medical history, cultural influences, health beliefs and attitudes, diabetes knowledge, self-management skills and behaviours, readiness to learn, cognitive ability, physical limitations, family support and financial status.
- There shall be documentation of the individual's assessment, education plan, intervention, evaluation and follow-up in the permanent confidential education record.

#### *General education programmes*

Within an overall review of patient education models for diabetes (not type-specific) one health technology assessment<sup>80</sup> reviewing four controlled trials of a range of education programmes including items of self-management, self-monitoring, diet and the effects of insulin and exercise, taught by a variety of staff or self-taught, and as an initial intense course or as ongoing

programmes, reported a variety of positive outcomes compared to normal care. This review found that one study had demonstrated improvements over 10 years in diabetic control, in terms of reduced HbA<sub>1c</sub> levels. In another study, an intensive five-day training course was found to be effective in reducing HbA<sub>1c</sub> levels. In one study there was no difference in blood glucose control with education compared to usual care, while there were no between-group comparisons made in another other study. Education was also shown to improve blood pressure. There is limited evidence to suggest a reduced rate of ketoacidosis and reduced hospitalisation. However, there was no evidence to indicate that education can reduce body mass index. There is some data to suggest increased incidence of hypoglycaemic episodes. Long-term outcomes of retinopathy or neuropathy were not found to be significantly affected by education, but there is some limited evidence to suggest nephropathy incidence is improved, although rates were low. Unsurprisingly, diabetes knowledge was significantly improved with education, although this was not true of quality of life. Overall the included trials were of moderate methodological rigour. Three of the trials included were investigating education in the context of intensification of treatment compared to normal care, and it is difficult to be sure that the benefits reported are directly attributable to the education aspect of the intervention (NICE).

Metabolic control and quality of life were not found to be significantly affected by a structured outpatient programme of education led by a nurse, dietitian and other people with diabetes over four weeks in a large randomised trial as compared to conventional care<sup>81</sup> (Ib).

A medium-sized randomised controlled trial<sup>82</sup> of a monthly education programme at which different aspects of diabetes treatment and technical skills were considered found that after one year of education HbA<sub>1c</sub> levels were reduced compared with normal clinical care in people with Type 1 diabetes. However, age differences between the control and intervention groups at baseline mean that this study is possibly methodologically limited (Ib).

Another moderate-sized systematic review of eight trials encompassing over 3,000 patients with either Type 1 or Type 2 diabetes,<sup>83</sup> found that intensive *vs* brief education on foot care provided a significant decrease in incidence of foot ulcers, and in one trial amputations, but no difference in the same outcomes over seven years in another study. This is despite three trials reporting successful uptake of messages regarding foot care behaviour. Another trial reported in this review found that an intensive educational intervention including both people with diabetes and doctors improved the prevalence of serious foot lesions compared to usual care, although the composite outcome of all foot lesions and amputations was not significantly improved. Authors of the review noted methodological limitations of the included studies, and outcome reporting times varied between individual trials (Ia).

### *Diabetes self-management education*

Evaluation, in a large systematic review,<sup>84</sup> of a range of diabetes self-management education (DSME) programmes compared to normal routine levels in populations of people with diabetes found that interventions based in community gathering places were able to reduce blood glycosylated haemoglobin (GHb) and fasting blood glucose levels. There is some evidence that they can also improve diabetes knowledge and improve physical activity (minutes of walking). Other trials reviewed that were based in the home setting – half of which included children or adolescents – showed a significant decrease in GHb after DSME, and a borderline

beneficial effect on weight for people undergoing DSME as compared to conventional care. Specific analysis in patients with Type 1 diabetes found no significant change in diabetes knowledge with such programmes (Ia).

#### *Other educational interventions*

A small randomised controlled trial<sup>12</sup> in people with Type 1 diabetes found that an intervention whereby patients received regular telephone contact with a diabetes nurse to alter insulin regimen decreased HbA<sub>1c</sub> over six months compared to usual care. This difference was not found to be affected by age, sex or type of diabetes (Ib).

#### *Behavioural and education interventions*

There are no systematic reviews and few prospective randomised studies that report on methods to improve concordance in self-management in people with Type 1 diabetes. One small unblinded study,<sup>85</sup> which was methodologically limited owing to high drop-out rates and inequalities in patient characteristics at baseline, found that an intervention of a self-taught study programme to improve self-control behaviour was able to demonstrate improved adherence to goals of self-monitoring of blood glucose level over 12 weeks. The intervention included a wide range of educational and behavioural choice items, and the relative effectiveness of any of these is hard to define. The methodological limitations of the study would not form a rigorous basis for recommending such an approach (Ib).

A similar intervention among adolescents (mean age 18 years) in India enrolled in a prospective randomised trial,<sup>86</sup> with an intervention of 15 hours of individualised learning over three months comprising both behavioural and cognitive strategies based on an operant learning model, found improved adherence on a composite three-item scale, compared to usual care. This improved adherence was mirrored in significantly improved blood glucose level compared to people in the control group. However, this study had a small sample size and was unblinded, and it was not possible to determine whether benefits persist after the cessation of the intervention (Ib).

#### *Education interventions*

One small- to medium-sized randomised trial of a specialist education programme delivered to people with Type 1 diabetes by a team of physicians, dietitians and specialist nurses found there to be no statistically significant differences in diabetes knowledge or adherence to dietary advice compared to a control group who received conventional diabetes education. Both groups improved in both measures immediately after the completion of the education intervention but then knowledge and adherence fell away with time. This trial was sited in Finland and there may be differences in content of conventional diabetes education compared to that of the UK care setting<sup>87</sup> (Ib).

#### *Monitoring devices*

There were no significant differences in adherence to glucose self-monitoring or in blood glucose levels reported at six months between two interventions with novel glucose monitoring devices and control with a standard device from a medium-sized multicentre randomised

trial.<sup>88</sup> The trial included a population of people with Type 1 diabetes who had had the condition for an average of 14 years. The study was blinded between the two novel monitoring machines, but the people in the control group would have been aware that they were not receiving the intervention as they continued to use their usual machine. To evaluate adherence all patients were asked to keep diaries of self-monitoring behaviour and this may have stimulated greater adherence even in the control group than under normal everyday self-monitoring conditions (Ib).

#### ▷ Health economic evidence

Assessing the cost-effectiveness of patient education is complicated by the fact that patient education is rarely assessed in isolation. Recent NICE guidance<sup>338</sup> into patient education models considered the health economic evidence for interventions in terms of self-care, quality of life and the long-term complications of diabetes. Interventions improving knowledge of diabetes were excluded from consideration, as improved knowledge of diabetes does not necessarily affect subsequent outcomes.

The NICE appraisal found only two published health economic papers suitable for assessing patient education.<sup>339,340</sup> Of these, only one<sup>339</sup> included Type 1 diabetes patients, and this established cost-effectiveness ratios for altering food habits.

#### ▷ Consideration

The group noted that patient education was a necessary and logical part of most aspects of diabetes self-care, and that self-care was a social, health and economic necessity in the management of the condition. Specific recommendations related to aspects of care such as self-monitoring, insulin therapy, foot care and nutrition were thought best presented in the individual sections of this guideline. The group noted inappropriateness of the classical clinical trial model when just one feature of an integrated package was varied, and one of many possible outputs monitored as primary outcome. There is also the difficulty of, and lack of funding for, the larger, longer-term trials used for pharmaceutical interventions. Equally, the central role of education in achieving success in blood glucose control and health outcomes (DCCT and other key studies) could not be ignored. Such information suggested that educational interventions were likely to be cost-effective, but it was impossible to make comparative judgements of different education models, a conclusion seemingly also reached by the NICE Appraisal Committee on the basis of a report from the University of Southampton's health technology assessment unit.

Issues of information overload at the stressful time of diagnosis, the size of the longer-term educational needs of individuals, the diversity of individual needs, and the retention of the information needed to make informed choices, and the group's experience of these in practice, served to guide recommendations broadly in line with those of Diabetes UK and the International Diabetes Federation (Europe).

## RECOMMENDATIONS

Specific recommendations on patient education and information-giving in particular aspects of care are given in individual sections of this guideline.

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|-----|---|---|
| R12 | A programme of structured diabetes education covering all major aspects of diabetes self-care and the reasons for it should be made available to all adults with Type 1 diabetes in the months after diagnosis, and periodically thereafter according to agreed need following yearly assessment.   | A |
| R13 | Education programmes for adults with Type 1 diabetes should be flexible so that they can be adapted to specific educational, social and cultural needs. These needs should be integrated with individual health needs as dictated by the impact of diabetes and other relevant health conditions on the individual.   | D |
| R14 | Education programmes for adults with Type 1 diabetes should be designed and delivered by members of the multidisciplinary diabetes team in accordance with the principles of adult education.   | D |
| R15 | Education programmes for adults with Type 1 diabetes should include modules designed to empower adults to participate in their own healthcare through: <ul style="list-style-type: none"> <li>● enabling them to make judgements and choices about how they effect that care</li> <li>● obtaining appropriate input from the professionals available to advise them.</li> </ul> | D |
| R16 | Professionals engaged in the delivery of diabetes care should consider incorporating educational interchange at all opportunities when in contact with a person with Type 1 diabetes. The professional should have the skills and training to make best use of such time.   | D |
| R17 | More formal review of self-care and needs should be made annually in all adults with Type 1 diabetes, and the agenda addressed each year should vary according to the priorities agreed between the healthcare professional and the person with Type 1 diabetes.  | D |

### 6.2 Self-monitoring of blood glucose

#### ▷ Rationale

Insulin therapy has to be adjusted with lifestyle, insulin dose requirements vary from individual to individual, and the effects of insulin injections are notoriously erratic. It might seem obvious that being able to keep an hour-to-hour or day-to-day check on actual blood glucose levels would be to the advantage of any person using insulin therapy. Potential should exist here to assist with diabetes self-education, dose optimisation, reassurance over hypoglycaemia and helping professionals give optimum advice on insulin regimens.

#### ▷ Evidence statements

##### *Reliability and validity*

Papers contained within a systematic review<sup>89</sup> suggest that the evidence on issues of observer training, interdevice variability, the effects of long-term use and patient acceptability have not been adequately addressed (IV).

**Table 2 Some appropriate content of education programmes for people with Type 1 diabetes and those personally involved with helping in their day-to-day care\***

**Around time of diagnosis**

- The aims of management and outcome of good self-management
- Self-injection and self-monitoring skills
- Nutritional information for people on insulin injection therapy
- Detection and management of hypoglycaemia
- Establishing healthy lifestyle

**In the period following diagnosis**

- Reinforcement of above
- Use of professional advisors and the healthcare system
- Integration of flexible eating and insulin dosing
- Goals of self-management
- Long-term risks and their amelioration (including arterial risk)
- Management of intercurrent illness and developing complications
- Role of preventative therapeutic interventions, side effects and importance
- Lifestyle issues including employment, travel (including across time zones), driving
- Contraception, pregnancy and children

**In the longer term**

- Self-care of late complications including foot care
- Reinforcement based on annual review of need

*\*See also the recommendations of IDF (Europe)<sup>24</sup> and Diabetes UK.<sup>282</sup>*

One study within the systematic review<sup>89</sup> comparing self-reported readings against a memory meter showed that inaccuracies in readings were common. This was due to rounding of values, omission of outlying values and reporting of results when no test had been performed. These findings were confirmed in another reviewed study of 14 people who recorded lower blood glucose values in logbook records than meter memories (Ia).

Reported within the systematic review, one trial<sup>89</sup> suggested that patients needed to be informed of the memory capacity of their meters to improve accuracy. A further study reported in the review argued that the true diurnal variability in glycaemia in people with Type 1 diabetes is too great to be measured, even when self-monitoring of blood glucose (SMBG) is repeated seven times daily (Ia).

Patient factors (as described below) were shown to have an impact (both positive and negative) on the reliability of monitoring in five studies.<sup>89</sup>

Reliability can be improved through proper training of patients, and was shown in sub-group analysis to be equally as good in older people, and people with visual impairments (on condition that extensive instruction has been provided).

One study concluded that impairment of colour vision affects the ability to interpret self-monitoring with visually read strips, suggesting that all patients should be screened for colour vision before self-monitoring begins (Ia).

#### *Clinical effectiveness of blood glucose monitoring*

Four trials contained within a systematic review<sup>89</sup> failed to show with sufficient power a demonstrated effect of SMBG on blood glucose control (Ia).

Two trials comparing urine and blood testing showed no clinical difference in the two tests<sup>89</sup> (Ia).

A systematic review<sup>89</sup> reported on patient preferences for different monitoring techniques. One trial reported patients preferring blood testing, or a combination of blood and urine testing, compared to urine testing alone. No preference was stated for visual strips or strips with meters (Ia).

One methodologically-limited crossover study<sup>90</sup> comparing blood glucose meters with visual test strips showed patients found the two techniques equally convenient to use, although overall more patients preferred the blood glucose meter.

Preferences were based on: accuracy, confidence in test result, no judgement by patient, inability to cheat with result and use of the built in timer (Ib).

One methodologically-limited comparative study<sup>91</sup> showed that fructosamine self-test results correlated well with laboratory test with very low bias. Imprecision of the self-test was higher than the laboratory test, but could still identify patients with good *vs* poor glycaemic control (DS).

A further methodologically-limited diagnostic study<sup>92</sup> in people with Type 2 diabetes showed self-testing of fructosamine to be comparable in accuracy to laboratory fructosamine and GHb values (CDS).

One trial with 25 patients<sup>93</sup> showed no significant difference in glucose control or patient practice based on frequency of testing. The authors stated that they are unable to identify any optimal frequency for blood glucose self-monitoring in typical diabetic population. There is little or no relationship between the frequency of blood glucose monitoring, the frequency of insulin dose adjustments and the level of metabolic control (Ib).

A study of the preferences of 18 patients within a systematic review<sup>89</sup> reported a preference for testing four times daily twice weekly, or four times daily once a week, compared to twice daily every day of the week (Ib).

One study from a systematic review reported fasting plasma glucose to be less useful as an accurate mode of monitoring in insulin-treated people with diabetes than in other people<sup>89</sup> (IIa).

#### ▷ Health economic evidence

The DCCT included self-monitoring of blood glucose as part of intensive treatment. Self-monitoring is only likely to have an effect on blood glucose control when used to inform the management of diabetes. As such, it is not feasible to analyse its cost-effectiveness in isolation from the requirements of subsequent management strategies.

A recent HTA report<sup>89</sup> identifies one paper considering the cost-effectiveness of blood or urine glucose monitoring against ‘conventional dietary control’ amongst those with Type 1 diabetes.<sup>341</sup> This paper is based on Russian conditions and also includes education in the intervention technologies. The GDG felt that differences in international healthcare systems mean little weight could be placed on its assertions that no significant difference exists between blood and urine glucose monitoring.

#### ▷ Consideration

Self-monitoring does not, in itself, appear to improve blood glucose control. However, the group noted that it was an essential component of the markedly improved blood glucose control with improved outcomes demonstrated in the landmark DCCT study, and indeed in the other smaller studies of blood glucose control and complications. Indeed it was difficult for members of the group to conceive how modern flexible insulin dosage regimens could be adopted without it. However, the technique is not easy, painless or convenient, and as a result no one system is found appropriate for use by all individuals. Improved technical facility could be identified from clinical experience. Nevertheless appropriate training and quality of skills review is agreed as necessary and normal practice. Different individuals are noted to use this technology with different frequencies and for different needs according to personal preferences. Given the nature of the technology it is rarely abused.

A newer approach, using smaller blood samples from non-finger-prick sites, was not judged to have adequate evidence of reliability, particularly in the situation of hypoglycaemia, to allow a general recommendation.

## RECOMMENDATIONS

- |     |   |   |
|-----|---|---|
| R18 | Self-monitoring of blood glucose levels should be used as part of an integrated package that includes appropriate insulin regimens and education to help choice and achievement of optimal diabetes outcomes.   | D |
| R19 | Self-monitoring skills should be taught close to the time of diagnosis and initiation of insulin therapy.   | D |
| R20 | Self-monitoring results should be interpreted in the light of clinically significant life events.   | D |
| R21 | Self-monitoring should be performed using meters and strips chosen by adults with Type 1 diabetes to suit their needs, and usually with low blood requirements, fast analysis times and integral memories.  | D |
| R22 | Structured assessment of self-monitoring skills, the quality and use made of the results obtained and the equipment used should be made annually. Self-monitoring skills should be reviewed as part of annual review or, more frequently, according to need and reinforced where appropriate. | D |
| R23 | Adults with Type 1 diabetes should be advised that the optimal frequency of self-monitoring will depend on: <ul style="list-style-type: none"> <li>● the characteristics of their blood glucose control</li> </ul>  | D |

- the insulin treatment regimen
  - personal preference in using the results to achieve the desired lifestyle.
- R24 Adults with Type 1 diabetes should be advised that the optimal targets for short-term glycaemic control are: D
- a pre-prandial blood glucose level of 4.0–7.0 mmol/l and
  - a post-prandial blood glucose level of less than 9.0 mmol/l.
- Note: These values are different to those given in the recommendations for children and young people with Type 1 diabetes because of clinical differences between these two age groups.
- R25 Monitoring using sites other than the finger tips (often the forearm, using meters that require small volumes of blood and devices to obtain those small volumes) cannot be recommended as a routine alternative to conventional self-blood glucose monitoring. D

### 6.3 Dietary management

#### ▷ Rationale

The imperfect nature of insulin replacement therapy, and in particular the prospective, erratic and inappropriate profiles of insulin absorption, make it necessary to understand the effects of different foods on glucose excursions if these excursions are to be appropriately minimised. Furthermore, people with Type 1 diabetes are at high arterial risk, which might be ameliorated by appropriate nutritional choices, while some associated conditions can be partly managed through nutritional advice.

#### ▷ Evidence statements

##### *Changes to diet*

Four small randomised controlled trials<sup>94–97</sup> were identified examining different diet regimens in people with Type 1 diabetes. One randomised controlled study<sup>94</sup> found that a high fibre diet (50 g/day) for 24 weeks compared to a low fibre diet (15 g/day) improved blood glucose profile, and number of hypoglycaemic events, although HbA<sub>1c</sub>, cholesterol, body weight and insulin dose were not affected (**Ib**).

A high carbohydrate, high fibre and low fat diet, compared to conventional low carbohydrate diet, taught by a dietitian in an unblinded randomised controlled trial<sup>97</sup> was seen at 12 months to improve HbA<sub>1c</sub> (**Ib**).

The addition of vitamin E to the normal diet has been shown to provide no benefit in terms of cholesterol level, HbA<sub>1c</sub>, body mass index (BMI), insulin dose or blood pressure over a 12-month period<sup>96</sup> (**Ib**).

There were significant improvements in glomerular filtration rate, and a decline in albuminuria after four weeks of a low protein diet compared to a normal protein diet in a randomised prospective trial in people with overt diabetic nephropathy.<sup>95</sup> Outcomes of urinary sodium excretion, blood pressure, BMI and HbA<sub>1c</sub> were not significantly different between the diets (**Ib**).

*Therapy adjustment for normal eating*

Canadian clinical practice guidelines<sup>98</sup> recommend that all people with diabetes on fixed-dose insulin regimen should have an individualised meal and activity plan developed. Two studies showed that patients should be taught how to adjust insulin dosage, diet and physical activity in response to blood glucose levels to reduce incidence of hypoglycaemia (Ia).

A medium-sized randomised controlled trial<sup>99</sup> of a five-day outpatient programme to enable patients to replace insulin by matching it to desired carbohydrate intake amongst adults with Type 1 diabetes found that the intervention improved HbA<sub>1c</sub> compared to a control of normal care to six months. Positive effects were also seen in weighted quality of life and total well-being. There was no effect on incidence of severe hypoglycaemia, weight or total cholesterol. This trial enrolled people with poorly-controlled diabetes (Ib).

A similar small trial<sup>96</sup> in which intensified insulin plus simplified diet was compared to conventional therapy and diet found HbA<sub>1c</sub> to be significantly reduced, although there was no differences between the study groups for outcomes of body weight, BMI, cholesterol or triglycerides (Ib).

*Undefined diet*

A large cohort study<sup>100</sup> comparing degree of liberalisation of diet away from a specific controlled diet after a treatment and teaching programme with estimation of carbohydrate intake and subsequent insulin self-adjustment found that there was no significant relationship between BMI and degree of diet liberalisation. In addition there was no relationship with HbA<sub>1c</sub> level or severe hypoglycaemia. However there was a relationship between liberalised diet and higher cholesterol levels, and an inverse relationship with tendency to monitor blood glucose more than three times a day (IIa).

*Other evidence*

The recent evidence-based guidelines for nutrition principles developed by the ADA,<sup>76</sup> provide a broad overview of research in the area of improved diabetes care for people with Type 1 diabetes through beneficial nutritional therapies. There are recommendations based on well-performed RCTs showing significant effectiveness of interventions for areas such as carbohydrates, dietary fat, energy balance and obesity, nutritional therapy for the treatment or prevention of acute complications, and hypertension. Recommendations in other key areas are based on cohort or uncontrolled studies (Ia).

## ▷ Health economic evidence

The recent NICE Technology Appraisal<sup>101</sup> into patient education models ([www.nice.org.uk/cat.asp?c=68326](http://www.nice.org.uk/cat.asp?c=68326)) recommends dose adjustment for normal eating (DAFNE), and the intensified treatment required by DAFNE, as cost effective.

▷ Consideration

The group was impressed by the systematic approach to nutritional recommendations published by the ADA,<sup>76</sup> and the consistency of that approach with the new recommendations from Diabetes UK.<sup>107</sup> Consideration of the existing guidelines in the area did not lead the group to any divergent recommendations on nutrition. Furthermore, recent NICE guidance on education models for people with Type 1 diabetes had particularly addressed the relevance of one programme for mealtime insulin dose adjustment (DAFNE) and, after due discussion of some of the issues surrounding that study including the health economic issues, it was felt inappropriate to recommend modification of any of the appraisal's conclusions. Accordingly the recommendations agreed by the group are mainly those of emphasis and approach appropriate to people with Type 1 diabetes, but reflecting both management of blood glucose excursions and arterial risk.

## RECOMMENDATIONS

- |     |   |   |
|-----|---|---|
| R26 | Nutritional information sensitive to personal needs and culture should be offered from the time of diagnosis of Type 1 diabetes.  | D |
| R27 | Nutritional information should be offered individually and as part of a diabetes education programme (see 'Patient Education' recommendations in this chapter (R12-17). Information should include advice from professionals with specific and approved training and continuing accredited education in delivering nutritional advice to people with health conditions. Opportunities to receive nutritional advice should be offered at intervals agreed between adults with Type 1 diabetes and their advising professionals. | D |
| R28 | The hyperglycaemic effects of different foods a person with Type 1 diabetes wishes to eat should be discussed in the context of the insulin preparations chosen to match those food choices.  | A |
| R29 | Programmes should be available to adults with Type 1 diabetes to enable them to make: <ul style="list-style-type: none"> <li>● optimal choices about the variety of foods they wish to consume</li> <li>● insulin dose changes appropriate to reduce glucose excursions when taking different quantities of those foods.</li> </ul>   | A |
| R30 | The choice of content, timing and amount of snacks between meals or at bedtime available to the person with Type 1 diabetes should be agreed on the basis of informed discussion about the extent and duration of the effects of consumption of different food types and the insulin preparations available to match them. Those choices should be modified on the basis of discussion of the results of self-monitoring tests.   | D |
| R31 | Information should also be made available on: <ul style="list-style-type: none"> <li>● effects of different alcohol-containing drinks on blood glucose excursions and calorie intake</li> <li>● use of high calorie and high sugar 'treats'</li> <li>● use of foods of high glycaemic index.</li> </ul>   | D |

- R32 Information about the benefits of healthy eating in reducing arterial risk should be made available as part of dietary education in the period after diagnosis, and according to need and interest at intervals thereafter. This should include information about low glycaemic index foods, fruit and vegetables, and types and amounts of fat, and ways of making the appropriate nutritional changes. D
- R33 Nutritional recommendations to individuals should be modified to take account of associated features of diabetes, including: D
- excess weight and obesity
  - underweight
  - eating disorders
  - raised blood pressure
  - renal failure.
- R34 All healthcare professionals providing advice on the management of Type 1 diabetes should be aware of appropriate nutritional advice on common topics of concern and interest to adults living with Type 1 diabetes, and should be prepared to seek advice from colleagues with more specialised knowledge. Suggested common topics include: D
- glycaemic index of specific foods
  - body weight, energy balance and obesity management
  - cultural and religious diets, feasts and fasts
  - foods sold as ‘diabetic’
  - sweeteners
  - dietary fibre intake
  - protein intake
  - vitamin and mineral supplements
  - alcohol
  - matching carbohydrate, insulin and physical activity
  - salt intake in hypertension
  - co-morbidities including nephropathy and renal failure, coeliac disease, cystic fibrosis or eating disorders
  - use of peer support groups.

## 6.4 Physical activity

### ▷ Rationale

Many people wish to perform varying amounts of physical exercise, but this can interact to disturb blood glucose levels in people on insulin therapy. Physical exercise is usually recommended to the general population as part of a package of lifestyle measures to improve future health, in particular reduction of arterial risk, which is markedly elevated in people with Type 1 diabetes.

▷ Evidence statements

*Aerobic exercise*

One small randomised controlled trial<sup>102</sup> was identified that assessed the effect of a 16-week aerobic exercise programme on fitness and lipid profile in young men with Type 1 diabetes. There were significant differences in  $VO_{2max}$  and serum total cholesterol compared to no training. There were no significant changes in outcomes of HbA<sub>1c</sub> and plasma glucose. The study was not blinded due to the nature of the intervention (Ib).

A small cross-sectional study<sup>103</sup> evaluating the effect of three months of individualised aerobic exercise in altering blood pressure and lipid profile found that HbA<sub>1c</sub>, fructosamine and total blood glucose did not change significantly from baseline levels. The design of the study would not represent a sound basis for supporting a recommendation for advocating exercise as therapy (IIa).

Another study with a similar intervention<sup>102</sup> found that four months of aerobic training provided no changes in terms of HbA<sub>1c</sub> or total cholesterol, although there were benefits of exercise compared to control in terms of peak oxygen uptake (IIb).

A prospective non-randomised study<sup>104</sup> with a before and after design found that steady-state plasma glucose was significantly decreased compared to baseline as was plasma insulin with supervised exercise program (at least 135 minutes/week) for three months compared to no exercise. Also cholesterol decreased significantly, however there were no reported significant changes in fasting blood glucose, HbA<sub>1c</sub> and microalbuminuria (IIb).

*Education and exercise*

A medium-sized randomised controlled trial<sup>105</sup> of intensive advice and lifestyle programme with specified diet and exercise prescriptions compared to conventional care found that HbA<sub>1c</sub> decreased from baseline measurements significantly over six months in the control group but remained relatively stable in the intervention group, but no between-group comparison was made. Also, HDL cholesterol and triglycerides were not significantly different between groups at any phase of the study. However exercise sessions were not standardised in the study and a lack of blinding limited the validity of the trial (Ib).

A small before and after study<sup>106</sup> found that an intervention of 10 hours of education and physical training three or four times a week produced no metabolic response at three months with fasting plasma glucose levels and serum cholesterol not changing significantly. Without blinding or randomisation this evidence is not sufficient to support the use of a mixed education and exercise intervention for people with Type 1 diabetes (IIb).

*Other exercise*

A non-randomised prospective controlled study<sup>103</sup> to assess whether exercise is related to better diabetes control was reviewed. There was no significant correlation between the exercise expenditure and HbA<sub>1c</sub> in all Type 1 diabetes patients, nor was there any relationship to the frequency of mild hypoglycaemic events (IIa).

*Guidelines on exercise*

The ADA<sup>76</sup> guidelines present recommendations based on a good evidence-based review. They recommend that a thorough evaluation be undertaken of patients before exercise is initiated. General recommendations for how to exercise safely include:

- metabolic control before activity
- blood glucose monitoring before and after physical activity
- food intake to be considered with added carbohydrate as necessary (Ia).

## ▷ Health economic evidence

No evidence was found on the cost-effectiveness of programmes encouraging physical activity for Type 1 diabetes.

## ▷ Consideration

The group noted that the evidence for an improved arterial risk profile in people with Type 1 diabetes was consistent with that for other diabetic and non-diabetic people. Evidence of a consistent effect in improving blood glucose control was absent, although by analogy with people with Type 2 diabetes the overweight/insulin-resistant person might benefit from an exercise programme as part of a lifestyle improvement initiative. Some people will undertake significant exercise by choice and would benefit from support in so doing.

**RECOMMENDATIONS**

- |     |  |   |
|-----|--|---|
| R35 | Adults with Type 1 diabetes should be advised that physical activity can reduce their enhanced arterial risk in the medium and longer term.  | C |
| R36 | <p>Adults with Type 1 diabetes who choose to integrate increased physical activity into a more healthy lifestyle should be offered information about:</p> <ul style="list-style-type: none"> <li>● appropriate intensity and frequency of physical activity</li> <li>● role of self-monitoring of changed insulin and/or nutritional needs</li> <li>● effect of activity on blood glucose levels (a fall is likely) when insulin levels are adequate</li> <li>● effect of exercise on blood glucose levels when hyperglycaemic and hypoinsulinaemic (risk of worsening of hyperglycaemia and ketonaemia)</li> <li>● appropriate adjustments of insulin dosage and/or nutritional intake for exercise and post-exercise periods, and the next 24 hours</li> <li>● interactions of exercise and alcohol</li> <li>● further contacts and sources of information.</li> </ul> | D |

**6.5 Cultural and individual lifestyle**

## ▷ Rationale

Cultural and genetic differences between ethnic groups are known to affect health and response to healthcare for many diseases. In regard of Type 1 diabetes this is particularly true of eating

habits, while arterial risk is known to differ for the general population and people with Type 2 diabetes. Other care issues seem likely.

▷ Consideration

The group were aware of a systematic review designed to detect issues of relevance (rather than trials of interventions) and identified papers concerning differences in incidence, attitudes to complications, degree of response to education programmes, blood glucose control, religious fasting and feasting, and hospitalisation.

The group noted that cultural and genetic issues affected diabetes healthcare delivery in the areas of:

- patient education and self-care
- nutritional advice
- insulin therapy (including religious feasts and fasts)
- arterial risk
- blood pressure management
- hospitalisation.

In some areas there was overlap with social/deprivation issues. The group's recommendations address cultural/religious issues in the appropriate sections of this guideline, emphasising the primacy of the individual in this regard.

## RECOMMENDATION

- R37 Each adult with Type 1 diabetes should be managed as an individual, rather than as a member of any cultural, economic or health-affected group. Attention should be paid to the recommendations given elsewhere in this guideline with respect to the cultural preferences of individual adults with Type 1 diabetes. D

# 7 Blood glucose control and insulin therapy

## 7.1 Clinical monitoring of blood glucose

### ▷ Rationale

Type 1 diabetes is for most of the time asymptomatic once effective therapy is instituted. However, it is generally understood that there is a relationship between blood glucose control and the late complications of the condition. Together these observations suggest that some means of monitoring blood glucose control should help healthcare professionals advise people with diabetes to best effect on insulin doses, regimens and associated lifestyle issues.

### ▷ Evidence statements

#### *Glycated haemoglobin testing*

A Diabetes UK consensus statement recommended that only HbA<sub>1c</sub> should be used in the monitoring of blood glucose control. Other studies reported within a systematic review<sup>89</sup> have shown discrepancies in the classification of patients between HbA<sub>1c</sub> and HbA<sub>1</sub> assays (IV).

Two studies in a systematic review<sup>89</sup> showed high inter-individual variability for GHb assays in non-diabetic and in diabetic subjects with stable or variable control. One of these studies suggested an association between clinical control and sampling interval (IIa).

The same systematic review<sup>89</sup> reported on randomised controlled trial evidence supporting the use of GHb measurements, in particular results cited from the DCCT demonstrated the usefulness of these assays in contributing to improved long-term blood glucose control and a reduction in morbidity (Ia).

A Danish systematic review<sup>108</sup> reported that HbA<sub>1c</sub> values allowed clinicians to identify patients with poor glycaemic control, concluding that GHb is the most clinically appropriate test of long-term glycaemia and should be used in routine management of Type 1 diabetes (Ia).

#### *Frequency of monitoring*

The optimal frequency of testing has not been established.

One study within a systematic review<sup>89</sup> recommended that no more than six GHb assays were necessary in a given year (IV).

ADA recommendations<sup>76</sup> advise GHb measurements are performed in accordance with clinical judgements. ADA consensus recommends GHb testing at least twice a year in patients with stable glycaemic control who are meeting treatment goals. Testing should be more frequent (quarterly) in patients whose therapy has changed or who are not meeting glycaemic control targets (IV).

### *Fructosamine testing*

There are discrepancies in the evidence surrounding the use of fructosamine testing.

One study within a systematic review<sup>89</sup> reported fructosamine testing as able to detect shorter or more recent fluctuations in blood glucose compared to GHb. Fructosamine testing does not have the problems of standardisation associated with GHb, thus results are comparable between laboratories (IIa).

Two studies within a systematic review<sup>89</sup> described a high correlation between fructosamine and HbA<sub>1c</sub>, however later studies debated this claim. One study suggested that although fructosamine correlates with HbA<sub>1c</sub>, the value of HbA<sub>1c</sub> in an individual cannot routinely be inferred with reliability from the level of fructosamine (IIa).

Two studies contained within a systematic review,<sup>89</sup> in patients with renal failure and elderly Type 2 diabetes patients with liver cirrhosis and nephrotic syndrome, suggest the influence of chronic conditions rather than metabolic control on fructosamine levels is the source of unreliability in test result. The systematic review concludes that more evidence is needed to resolve these issues (IV).

One correlation study within a review<sup>89</sup> showed no significant correlation between HbA<sub>1c</sub> and fructosamine results over a six month follow-up (III).

### *Frequency of monitoring*

ADA recommendations<sup>76</sup> state that assays of glycated serum protein would have to be performed on a monthly basis to gather the same information as measured in GHb three to four times per year (IV).

A systematic review<sup>89</sup> urges caution in using fructosamine testing, in light of the fact that fructosamine values can be improved by increased concordance a week or two before testing (IV).

Another study found that fasting blood glucose level (FBG) and serum fructosamine are not as useful as HbA<sub>1c</sub> for monitoring diabetic control, but are additional extras for assessing control over short and long periods<sup>89</sup> (IIa).

### *Continuous glucose monitoring systems*

Three observational studies<sup>109–111</sup> compared continuous glucose monitoring systems (CGMS) with SMBG. Studies demonstrated good correlation of CGMS with plasma and capillary measures of blood glucose over a range of blood glucose values. Error grid analysis showed the majority of readings fell within a clinically acceptable margin of error across all studies (III).

One study<sup>111</sup> reported acceptable level of comfort with CGMS. However, none of these studies address viable outcomes of glycaemic control or long-term use. Study methodology is not clearly reported (III).

### *Near patient testing*

In this guideline, 'near patient testing' is defined as a biochemical or other test at or near (in time and place) the clinical consultation, such that the result is available at the consultation.

One controlled trial within a systematic review<sup>112</sup> demonstrated that near patient testing led to an increase in management changes for patients with poor glucose control. Near patient testing for HbA<sub>1c</sub> improved the process of care of patients (IIa).

In the same review,<sup>112</sup> questionnaires recording patient satisfaction of near patient testing concluded that the introduction of near patient testing for HbA<sub>1c</sub> improves the likelihood of monitoring and discussion of glycaemic control at patient visits. Patients reported that this was important to them and resulted in greater satisfaction with the test information provided (III).

Within the health technology assessment,<sup>112</sup> a retrospective cohort study showed that, after allowing for confounding factors, mean HbA<sub>1c</sub> level was lower following near patient testing and the immediate availability of results. In order to precisely quantify the effect of the testing system on HbA<sub>1c</sub> level, further, prospective studies are required (IIa).

A systematic review<sup>89</sup> reported four studies on the effectiveness of benchtop analysers compared with traditional laboratory methods. Two studies showed comparable results between the two techniques when operated by non-medical personnel. One study found that the benchtop analyser, although reliable, tended to slightly underestimate HbA<sub>1c</sub>, compared with high performance liquid chromatography (HPLC) (IIa).

#### ▷ Health economic evidence

An HTA report<sup>112</sup> produced cost estimates for near patient testing conducted by a laboratory or nurse against conventional testing. However, little data was available on the effects of near patient testing on clinical or quality of life outcomes. For health economics to provide guidance in this area, the long-term effects of different types of clinical monitoring on glycaemic control and subsequent complications must be known.

A recent HTA report<sup>89</sup> recommended further research into the cost-effectiveness of near patient testing for diabetes, FBG and fructosamine testing. No other paper in the health economics searches specifically addressed the issue of clinical monitoring.

#### ▷ Consideration

The group endorsed the utility of having a frame of reference against which people with diabetes and the professionals advising them could assess risk and risk threshold for micro- and macro-vascular disease in terms of blood glucose control. This was a core component of intensification of therapy in studies showing improved long-term outcomes. HbA<sub>1c</sub> is the only measure for which quantitative information linking glucose control to complications is available, and then only when standardised to the assay used in the DCCT study. Near patient testing was felt to be a core component of making optimal and relevant use of HbA<sub>1c</sub> results. Continuous glucose monitoring systems were considered to not yet have established their usefulness beyond problem-solving in the occasional person with recurrent blood glucose control problems at the same time of day.

## RECOMMENDATIONS

- |     |  |   |
|-----|--|---|
| R38 | Clinical monitoring of blood glucose levels by high precision DCCT-aligned methods of haemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) should be performed every two to six months depending on: <ul style="list-style-type: none"> <li>● achieved level of blood glucose control</li> <li>● stability of blood glucose control</li> <li>● change in insulin dose or regimen.</li> </ul> | D |
| R39 | Site-of-care measurement, or measurement before clinical consultation, should be provided.   | D |
| R40 | HbA <sub>1c</sub> results should be communicated to the person with Type 1 diabetes after each measurement. The term 'A1c' can be used for simplicity.   | D |
| R41 | Total glycated haemoglobin (GHb) estimation, or assessment of glucose profiles, should be used where haemoglobinopathy or haemoglobin turnover invalidate HbA <sub>1c</sub> measurement.   | A |
| R42 | Fructosamine should not be used as a routine substitute for HbA <sub>1c</sub> estimation.  | B |
| R43 | Continuous glucose monitoring systems have a role in the assessment of glucose profiles in adults with consistent glucose control problems on insulin therapy, notably: <ul style="list-style-type: none"> <li>● repeated hyper- or hypoglycaemia at the same time of day</li> <li>● hypoglycaemia unawareness, unresponsive to conventional insulin dose adjustment.</li> </ul>         | B |

## 7.2 Glucose control assessment levels

### ▷ Rationale

The DCCT, and a number of smaller studies which are potentially underpowered,<sup>113</sup> suggest that more intensive management of people with Type 1 diabetes (by themselves, with advice) reduces the rate of development of microvascular complications over a period of years. The primary metabolic improvement in the DCCT was lowering of blood glucose level, and this was the measure used in that study to drive the intensification of therapy. This suggests that using measures of blood glucose control in the routine management of therapy in people with Type 1 diabetes is well founded.

A question then arises as to what level of blood glucose control people with diabetes should choose to strive for. A closely related question is what level(s) of glucose control should be used in assessing the performance of diabetes services.

'Targets' have been criticised by some as not giving flexibility for individuals with particular problems (eg hypoglycaemia) to be content with higher HbA<sub>1c</sub> levels, which allows some longer-term risk for a gain in current well-being. It is clearly useful to be able to identify those in whom newer and more expensive technologies could be tried in an attempt to reduce microvascular risk, and to distinguish them from those who already achieve safe (or safer) levels on their current therapy. People with diabetes need information on what blood glucose level they need to attain if they wish to minimise vascular risk.

▷ Evidence statements – guidelines

In 1989, the European NIDDM Policy Group (Type 2 diabetes) suggested HbA<sub>1c</sub> was good <8.5%, acceptable 8.5–9.5%, poor >9.5% (equivalent to HbA<sub>1c</sub> of <6.9, 6.9–7.7, >7.7%). No evidence for these limits was given, and it was not clear whether the intent was for micro- or macrovascular protection or both. However, the need to individualise by life expectancy was acknowledged<sup>114</sup> (IV).

In 1993, the above guidelines were revised to HbA<sub>1c</sub> <6.5%, 6.5–7.5%, and >7.5%. The European IDDM Policy Group (Type 1 diabetes) (WHO, IDF, St Vincent) met concurrently and agreed these, but using the terminology ‘good’, ‘borderline’ and ‘poor’ to describe the groups. These pre-DCCT recommendations are not justified in the text<sup>115</sup> (IV). See Table 3, below, for how that guideline maps these assessment levels to self-monitored blood glucose equivalents.

**Table 3 Blood glucose equivalents (self-monitored) of HbA<sub>1c</sub> assessment levels, as given in the 1993 European IDDM Policy Group guideline**

HbA <sub>1c</sub> (%)	Pre-prandial (mmol/l)	Post-prandial (mmol/l)
6.5	6.1	8.0
7.5	8.0	10.0

In 1998, the European Diabetes Policy Group revised its terminology to ‘assessment levels’, giving advice on how to use assessment levels to set targets for individuals. These were, for HbA<sub>1c</sub>: adequate 6.2–7.5%, inadequate >7.5%. However the relation of this 7.5% to glucose levels was then revised to equivalent to a self-monitored pre-prandial level of 6.5 mmol/l and post-prandial 9.0 mmol/l. These post-DCCT recommendations are not justified in the text<sup>115</sup> (III).

The NICE (inherited) Type 2 diabetes guideline on glucose control reads (NICE):

*Evidence: narrative*

The UKPDS showed that the reduction over a median of 10 years in HbA<sub>1c</sub> from 7.9 to 7.0% using sulphonylureas or insulin provided much of the benefit that could be expected from that degree of improved glycaemic control. However it also illustrated the difficulties in being able to reach this level (7.0%) in a substantial proportion of people. Thus providing only one target is likely to encounter a significant number of people who ‘fail’ to meet that target. Similarly for some individuals an even lower target is desirable as they may have additional risk factors which necessitates even tighter blood glucose control. The UKPDS also suggested that there were no thresholds for cessation of benefit and that the lower the level of mean HbA<sub>1c</sub> the better.

*Working group commentary*

The Working group tried to reflect these issues when deciding upon a target HbA<sub>1c</sub>. They concluded that a range was the best option, recognising the difficulty in achieving a low target whilst recognising the importance of trying to achieve as near normal an HbA<sub>1c</sub> level as possible, and in particular recognising that additional risk factors made the lower limit even more important for many individuals. While no study suggests clear thresholds, the group noted on the basis of the epidemiological evidence in the DCCT (Type 1 diabetes) and UKPDS that microvascular risk was low once average HbA<sub>1c</sub> was around 7.0–8.0% while arterial risk continued to fall down to 6.0 to 7.0% (DCCT standardised).

Thus the target for each individual should be set which fully takes into account: their assessed risk factors, including: age, BMI, blood pressure and lipid status, side effects of therapy, other individual factors, patient choice.<sup>382</sup>

The NICE Type 2 diabetes guidelines therefore recommended 6.5% to 7.5% as ideal targets, individualised by balance of macrovascular (tend to 6.5%) and microvascular (7.5%) risk (NICE).

The ADA has republished its recommendations yearly.<sup>76</sup> These choose a 'glycaemic goal' of HbA<sub>1c</sub> <7.0% for adults (type of diabetes not specified), equating this to pre-prandial <7.2 mmol/l and peak post-prandial <10.0 mmol/l. However, a table in the same paper suggests that an HbA<sub>1c</sub> of 7.0% equates to mean self-monitored plasma glucose of 9.5 mmol/l<sup>116</sup> (IV).

However in the same issue (January 2003),<sup>76</sup> the ADA notes in a chapter on 'Implications of the DCCT' that the level of glucose control to be sought under ideal circumstances is an HbA<sub>1c</sub> of around 7.2% (average glucose 8.6 mmol/l). This argument is based on that achieved in the DCCT, and is thus not theoretically justified (IV).

The microvascular risk threshold is what determines the diagnostic threshold for diabetes. In theory, oral glucose tolerance test (OGTT) findings should give some guidance as to this threshold. Unfortunately these are mainly based on non-physiological glucose load findings, and set a top limit of risk for 2h post-prandial levels. Fasting levels have been set as a microvascular threshold of 7.0 mmol/l (based on epidemiological equivalence with 2h OGTT levels), which would map to a DCCT-harmonised HbA<sub>1c</sub> of about 7.7% (IV).

▷ Evidence statements

Simple direct findings indicating the microvascular risk level for people with Type 1 diabetes are not available.

The DCCT data has never been satisfactorily analysed with a view to answering this question. A graph in the original main paper<sup>117</sup> suggests a curvilinear relationship between control and complications, giving the conclusion that lower is always better (ignoring the hypoglycaemia issue for this purpose), down at least to the levels measured in the study (5.5%). This conclusion is called into question because (IIa):

- it is based on study averages, and even people at lower levels over nine years may have been at high levels at times
- it takes no account of pre-trial levels
- incident retinopathy is counted only in a forward (worsening) direction, which makes no allowance for false negative retinopathy at baseline
- worsening retinopathy is known to occur in the first two years after improvement of blood glucose control, and this is not discounted.

Further analysis was published in 1995.<sup>118</sup> Unfortunately, this is mostly in the form of a series of fitted curves without the data on which they are based. Curves of risk *vs* time suggest that retinopathy progression in the intensively managed group did not increase with time with a mean HbA<sub>1c</sub> of 8.0%, and increased little at this level in the conventionally managed group with time (IIa).

Reanalysis of the published DCCT curve<sup>118</sup> suggests no worsening of retinopathy rates from normal levels until HbA<sub>1c</sub> >8.0%; the 'low' rates (2% per 100 patient years) below that may be

artefact for the reasons given above. The UKPDS (epidemiological analysis, Type 2 diabetes, microvascular disease) suffers much the same problems.<sup>119</sup> A similar level is found for retinopathy of 2% per 100 patient years at an HbA<sub>1c</sub> of 7.5% and of 1% per 100 patient years at a level of 6.5% (III).

One study (1989)<sup>120</sup> studied HbA<sub>1</sub> and retinopathy incidence long term in Belfast. While some clear relationships were established the data showing no proliferative retinopathy below an HbA<sub>1</sub> of 10.0% (HbA<sub>1c</sub> 8.5%) are compromised by very small numbers, and only interquartile ranges are given for non-proliferative retinopathy (III).

Neither the Oslo nor Stockholm studies of control and complications in Type 1 diabetes<sup>121</sup> give useful data on targets and thresholds, beyond showing that people with lower levels on average do better (III).

A non-randomised controlled study<sup>122</sup> looked prospectively at glycated Hb and micro-albuminuria risk in people with Type 1 diabetes attending their clinic. Their data did suggest a threshold effect (small and unchanging incidence below threshold, sharp rise above), at 7.9–8.5% HbA<sub>1c</sub> (the authors chose to centre on 8.1%) (IIa).

A non-randomised controlled study<sup>123</sup> looked at how glycated Hb measurement related to OGTT results, performing a meta-analysis on 18 studies. Unfortunately most of these were published before any kind of GHb standardisation, rendering the results uninterpretable (IIa).

A further cohort study<sup>124</sup> looked in more detail at GHb, fasting and 2h glucose as diagnostic methods (and thus mainly Type 2 diabetes), using retinopathy and nephropathy as outcome measures. It may be noted that the Wisconsin data suggested that the microvascular/glucose control relationships were the same in Type 1 and Type 2 diabetes. The data presentations are strongly reminiscent of previous work,<sup>122</sup> with low and unchanging incidence of microvascular disease up to an inflection point, then sharply rising rates. The thresholds for fasting glucose appear to be somewhere above 6.8 mmol/l (consistent with older OGTT data), and HbA<sub>1c</sub> somewhere above 7.4% (and below 9.1%) (IIa).

### *Glucose equivalents*

Two non-randomised controlled studies<sup>116,125</sup> report the relationship between HbA<sub>1c</sub> and self-monitored pre- and post-prandial glucose levels. The reports are consistent and can be related to DCCT-harmonised assays. It must be noted that these studies used pre-determined, self-monitored profiles taken from memory meters, and cannot easily be translated into patient-selected estimations, or only pre-prandial monitoring. They also omit the effects of night-time glucose profiles between bedtime and pre-breakfast readings. These data give the most robust evidence of the relationship between HbA<sub>1c</sub> and the toxic glucose concentrations which actually cause the microvascular damage (IIa).

### ▷ Consideration

There must be a threshold for glucose control and the development of microvascular complications, or non-diabetic people would get complications. Indeed, this threshold must be well above the normal range as people with impaired glucose tolerance (IGT) do not (by

definition) get microvascular complications. As people with IGT have HbA<sub>1c</sub> levels of up to 7.0%, this by itself sets a lower limit of microvascular risk.

The microvascular thresholds of HbA<sub>1c</sub> 7.5% set around 10 years ago have stood the test of all data published since. If anything the DCCT, Krolewski and McCance data suggest a figure closer to 8.0%.

Recommendations from the ADA (7.0%) and American College of Endocrinologists (6.5%) are not specific to type of diabetes; data does suggest macrovascular protection is gained by lowering blood glucose levels into the normal range, and the NICE (inherited) guidelines for Type 2 diabetes go for HbA<sub>1c</sub> 6.5% in these higher arterial risk individuals.

Some people with Type 1 diabetes are at higher arterial risk, notably those with developing nephropathy. This can be identified by increased albumin excretion rate. The presence of features of the metabolic syndrome will also predict higher arterial risk. It may be appropriate to consider tighter targets for glucose control (if feasible) in people in these categories.

However, these levels are better considered as *assessment levels*, to be used in setting realistic targets for the individual. Major diabetes services in Europe currently only get about 20% of people with Type 1 diabetes into the sub-7.5% bracket. UK composite data (UKDIABS) shows some services doing better, but this may only represent non-standardised GHb estimation.

That current technologies of diabetes care markedly limited the proportion of people on insulin who were able to manage themselves to ideal levels was not seen as a bar to setting such assessment levels. It was noted that arterial risk would be likely to have a different relationship in this regard from microvascular risk, and that for the former there was little direct information available for people with Type 1 diabetes, but that the understandings gained in Type 2 diabetes and people without diabetes gave strong guidance in this respect. It was felt that as the assessment of the evidence available pointed to target definition in the same range as other published guidelines, and in particular the NICE inherited guidelines for Type 2 diabetes, there was practical utility for practice of care in having matching recommendations. Lastly the problem of hypoglycaemia in limiting was what achievable in any individual should be addressed within any recommendations, to assuage inappropriate attempts to achieve tight control and counter impressions of failure if targets are not attained.

## RECOMMENDATIONS

- |     |  |      |
|-----|--|------|
| R44 | Adults with Type 1 diabetes should be advised that maintaining a DCCT-harmonised HbA <sub>1c</sub> below 7.5% is likely to minimise their risk of developing diabetic eye, kidney or nerve damage in the longer term.  | B    |
| R45 | Adults with Type 1 diabetes who want to achieve an HbA <sub>1c</sub> down to, or towards, 7.5% should be given all appropriate support in their efforts to do so.  | D    |
| R46 | Where there is evidence of increased arterial risk (identified by a raised albumin excretion rate, features of the metabolic syndrome, or other arterial risk factors) people with Type 1 diabetes should be advised that approaching lower HbA <sub>1c</sub> levels (for example 6.5% or lower) may be of benefit to them. Support should be given to approaching this target if so wished. | NICE |

- R47 Where target HbA<sub>1c</sub> levels are not reached in the individual, adults with Type 1 diabetes should be advised that any improvement is beneficial in the medium and long term, and that greater improvements towards the target level lead to greater absolute gains. B
- R48 Undetected hypoglycaemia and an attendant risk of unexpected disabling hypoglycaemia or of hypoglycaemia unawareness should be suspected in adults with Type 1 diabetes who have: D
- lower HbA<sub>1c</sub> levels, in particular levels in or approaching the normal reference range (DCCT harmonised <6.1%)
  - HbA<sub>1c</sub> levels lower than expected from self-monitoring results.
- R49 Where experience or risk of hypoglycaemia is significant to an individual, or the effort needed to achieve target levels severely curtails other quality of life despite optimal use of current diabetes technologies, tighter blood glucose control should not be pursued without balanced discussion of the advantages and disadvantages. D

*Note: A new chemical standard for HbA<sub>1c</sub> has been developed by the International Federation of Clinical Chemistry (IFCC). This reads lower by around 2.0% (units), and will be the basis of primary calibration of instruments from 2004 onwards. However, this does not preclude the use of DCCT-harmonised levels, and views from patient organisations and professional bodies at a recent Department of Health meeting (July 2003) are that all HbA<sub>1c</sub> reports should be DCCT aligned, pending some internationally concerted policy change.*

### 7.3 Insulin regimens

#### ▷ Rationale

Type 1 diabetes is an insulin deficiency disease. Physiological insulin delivery is regulated on a minute-to-minute basis, while therapeutic insulin is given a small number of times a day. Furthermore subcutaneous depot insulin preparations have, until recently, not come close to providing the physiological plasma insulin profiles occurring at mealtimes or in the interprandial basal state. A number of preparations of mealtime and extended-acting insulins are available, and combining these to suit individual needs, while taking account of preferences for numbers of injections, gives a variety of possible insulin regimens of differing characteristics.

While insulin deficiency is the hallmark of Type 1 diabetes, a few people retain some insulin secretion for a short time (and might therefore benefit from insulin secretagogues). Some glucose-lowering drugs work on gut absorption of nutrients or on the insulin effector tissues, and might therefore be expected to be of benefit in some individuals even when completely insulin deficient and managed on insulin replacement therapy.

#### ▷ Evidence statements

##### *Insulin and insulin analogues*

Insulin with the molecular structure of human and animal insulins is currently available. Evidence from the majority of studies<sup>126–8</sup> reports no significant differences in hypoglycaemic episodes and glycaemic control between the insulin of human and animal chemical structures (Ia).

Conventional two-dose insulin regimens may result in a high frequency of nocturnal hypoglycaemia. Intensified three-dose insulin regimens improve glycaemic control, but often do not improve morning blood glucose<sup>129</sup> (Ia).

Continuous subcutaneous insulin infusion (CSII) improves nocturnal and morning glycaemic control compared with multiple daily injection (MDI) regimens. With multiple injection regimens the morning injection must not be delayed. Total and bolus insulin doses required are lower with CSII compared with MDI<sup>130</sup> (Ib).

Mortality from acute metabolic causes (ketoacidosis) was reported as significantly increased with intensified treatment; odds ratio 7.20 (pumps) 1.13 (multiple daily injection).<sup>129</sup> The pump data is however based on early pump technologies (Ia).

Similar glycaemic control results from either lente or isophane (NPH) insulin when used as basal insulin for multiple injection regimens together with a short-acting insulin preparation before meals<sup>131</sup> (Ib).

On the balance of effectiveness and cost-effectiveness evidence, insulin glargine, which has a peakless action profile, is also recommended as a long-acting preparation for people with Type 1 diabetes;<sup>132</sup> some studies in this review show significantly lower fasting blood glucose with insulin glargine than isophane (NPH) insulin and others suggest that people on insulin glargine may experience fewer hypoglycaemic events than people receiving once-daily isophane (NPH) insulin<sup>132</sup> (NICE).

Evidence from a large multicentred study suggests that people commonly inject insulin closer to mealtime than the recommended 30 minutes. Due to slow absorption and delayed action, the use of unmodified ('soluble') human insulin as pre-meal dose results in high and variable post-breakfast blood glucose concentrations, which together with the incidence of later hypoglycaemia suggests that this regimen does not give satisfactory post-prandial blood glucose control in many patients<sup>133</sup> (Ib).

Rapid acting insulin analogues allow injection closer to mealtimes due to their pharmacokinetic profile<sup>134-6</sup> (Ib).

A meta-analysis<sup>137</sup> and several open-label trials<sup>133,138-145</sup> show that insulin lispro is more effective than unmodified ('soluble') human insulin in improving post-prandial glucose control, without an increase in the rate of hypoglycaemic episodes (Ia).

Two studies<sup>146-7</sup> show reduced frequency of nocturnal hypoglycaemia<sup>148</sup> with insulin lispro compared to unmodified ('soluble') human insulin (Ib).

Two studies<sup>148-9</sup> show reduced frequency of severe hypoglycaemia with insulin lispro compared to unmodified ('soluble') human insulin (Ia).

Patients perceive an improvement in their well-being and quality of life with rapid-acting insulin analogues due to flexibility of injection times and less frequent hypoglycaemic reactions<sup>128,141,146</sup> (Ib).

The effects of insulin lispro on HbA<sub>1c</sub> levels (overall glycaemic control) have not been firmly established.<sup>133,137,149</sup> The long-term safety profile is as yet unknown (Ia).

Two multicentre randomised studies<sup>149–50</sup> and one RCT<sup>135</sup> showed insulin aspart to improve post-prandial glucose control more effectively than unmodified ('soluble') human insulin, without an increase in the rate of hypoglycaemic episodes. Fewer major hypoglycaemic episodes were observed (Ia).

A before-and-after study has shown that a lower dose of mealtime insulin can be taken along with an increase in basal dose, with no increase in hypoglycaemic episodes when insulin lispro is used as a replacement for human insulin as mealtime injection therapy<sup>142</sup> (IIb).

Two randomised trials have shown that it is possible to replace mealtime unmodified ('soluble') human insulin with insulin lispro or insulin aspart without detriment to glycaemic control if care is taken to replace basal insulin delivery more physiologically<sup>151–2</sup> (Ib).

A multi-arm randomised trial found that adding a few units of isophane (NPH) insulin to insulin lispro at each meal, in combination with bedtime NPH insulin improves blood glucose concentrations compared to an unmodified ('soluble') human insulin regimen in a multidose regimen<sup>136</sup> (Ib).

Splitting the evening administration of insulin to short-acting insulin at dinner and isophane (NPH) insulin at bedtime has a number of advantages over mixed administration of short-acting insulin and isophane (NPH) at dinner. Compared with the mixed mealtime regimen, the evening split regimen reduced by more than 60% the risk of nocturnal hypoglycaemia;<sup>153–4</sup> improved long-term control of blood glucose levels, decreased variability of blood glucose levels in fasting state and led to improvement in preserved hormonal, symptom and cognitive function responses to hypoglycaemia (Ib).

When basal insulin replacement is by either continuous subcutaneous insulin infusion (CSII) or multiple daily administrations of isophane (NPH) insulin, the long term administration of lispro at mealtime reduces HbA<sub>1c</sub>;<sup>130</sup> however, compared with multiple daily injections, patients using continuous subcutaneous administration of insulin (mainly those using older systems) have been at a significantly higher risk of ketoacidosis (Ib).

Frequency of hypoglycaemic reactions was found to be similar on patient-mixed and premixed insulins.<sup>143,155</sup> One randomised controlled trial showed premixed preparations of insulin analogues to be well suited for those who wish to limit the number of daily injections;<sup>155</sup> 83% of people expressed a preference for premixed insulins throughout the trial (Ib).

Few studies have addressed the needs of people with diabetes with suboptimal glucose control, and none of suitable design from the evidence hierarchy were found for review.

In a group of people with Type 1 diabetes with poor glucose control, the introduction of more intensive insulin regimens may lead to high loss to follow-up.<sup>156</sup>

Poor outcome appears to be due to the people refusing the constraints of multiple daily injections, effective blood glucose self-monitoring and regular clinic visits at short time intervals. It was suggested that people should be given clear and concise information on treatment goals and the ways in which these goals are to be attained as well as an explanation of the advantages and disadvantages (IV).

Few studies addressed the needs of people newly diagnosed with diabetes and none of suitable design from the evidence hierarchy were found for review.

### *Acarbose and insulin combination therapy*

Four randomised controlled trials, two large parallel groups,<sup>157–8</sup> and two small crossover designs<sup>159–60</sup> were identified that examined the use of acarbose in conjunction with insulin therapy compared to insulin and placebo in each case, in people with Type 1 diabetes. A multicentred study<sup>157</sup> with variable doses titrated up to 300 mg three times a day for 24 weeks, found a significant reduction in HbA<sub>1c</sub> levels with acarbose compared to placebo, and decreases in fasting and post-prandial glucose levels to two hours. There were no differences between groups for daily insulin dose or hypoglycaemic events, although adverse events of abdominal pain, diarrhoea and flatulence were more common with acarbose. This led to more frequent treatment discontinuation in the acarbose group than the placebo group. A similar Italian trial<sup>158</sup> with up to 100 mg acarbose three times daily for 24 weeks found no difference in HbA<sub>1c</sub> levels, daily insulin dose, fasting glycaemia and total cholesterol. However, a significant decrease was found in two-hour post-prandial plasma glucose level, and HDL cholesterol levels were lower in people on acarbose than placebo. Again minor adverse events were more common in the acarbose group, but hypoglycaemic episodes were similar in both groups. Although care was taken not to alter baseline insulin doses, this could be adjusted if glucose levels exceeded 11.1 mmol/l or reduced with hypoglycaemic episodes (Ib).

The two crossover trials with 100 mg acarbose three times a day over relatively short time periods did not assess requirement for wash out periods (although analysis in one found no effect of treatment order) and did not account for study withdrawals. One study found a benefit in terms of HbA<sub>1c</sub> with acarbose,<sup>160</sup> while the other found no significant differences between groups.<sup>159</sup> Potential methodological limitations of these trials would not permit them to be used as an evidence base to inform recommendations in this area (Ib).

### *Sulfonylurea and insulin combination therapy*

Two small randomised controlled trials investigated the use of glibenclamide (called 'glyburide' as the trials were conducted in the USA) in the therapy for Type 1 diabetics. A study using 5 mg glyburide (orally) for 12 weeks compared to placebo after a 12-week open-label insulin stabilisation run-in period<sup>161</sup> found fasting blood glucose declined significantly at 12 weeks from baseline, although no comparison was made between groups. No differences were found in daily insulin dose or glycated haemoglobin levels at any stage of the study. A randomised study without comparison between groups at baseline with 5 mg glyburide daily for 24 weeks compared to placebo<sup>162</sup> found no differences in plasma C-peptide levels between groups, nor difference in plasma glucose concentrations at any time point. Although HbA<sub>1c</sub> levels were reported to have changed more from baseline in the glyburide treated group at six weeks, potential methodological limitations of these trials would not permit them to be used as an evidence base to inform recommendations in this area (Ib).

Comparison of 15 mg of glibenclamide daily with placebo in addition to insulin therapy in a small sample of people with Type 1 diabetes in a randomised double-blind crossover study<sup>163</sup> found mean blood glucose level, HbA<sub>1c</sub> and blood glucose variability to be significantly lower with the intervention among people who retained endogenous insulin production. No such differences were found in a subgroup who were C-peptide negative. Although the study had a medium-term intervention period of three months, it did not provide analysis of the cohort as a whole for glibenclamide vs placebo and thus cannot be used for recommendations given the

small sample sizes of the subgroups, and the inherent difficulties of extrapolating such findings to a wider population (Ib).

A reduced insulin requirement at 18 months was found in patients given 80 mg gliclazide twice a day compared to placebo in a small sample in a long-term study.<sup>164</sup> Although glycated haemoglobin both fasting and one hour post-breakfast were found to be very similar in both groups, the gliclazide group had C-peptide levels significantly higher than people on placebo for the same test times of the day, at six-monthly assessment points to 18 months. This study only applies to people with retained endogenous insulin secretion, and thus not the overwhelming majority of people with Type 1 diabetes (Ib).

### *Metformin*

A medium-sized randomised controlled study found that the addition of metformin to an insulin regimen provided by CSII was able to reduce the total IR required by the person with Type 1 diabetes (including reduced basal therapy) as compared to placebo over a period of six months. This was achieved without significant change to HbA<sub>1c</sub> or increased incidence of hypoglycaemia (Ib).

## ▷ Health economic evidence

The health economic searches produced no studies giving guidance on appropriate insulin regimens for those newly-diagnosed with Type 1 diabetes or for the management and prevention of hypoglycaemia, with the exception of the NICE appraisal of insulin glargine.

The health economic searches found no published papers dealing with insulin glargine or NPH insulin. A recent NICE technology appraisal<sup>132</sup> recommended insulin glargine as a long-acting preparation for people with Type 1 diabetes alongside insulin NPH. The crucial issue for the cost-effectiveness of insulin glargine is the amount of utility associated with reducing the fear of hypoglycaemia.

Two cost-benefit studies were identified that considered the role of insulin lispro.<sup>342,380</sup> Neither paper was based in the UK (Canada, Australia), and both suggest that the willingness to pay for insulin lispro will outweigh its additional cost. The cost-effectiveness of lispro is unclear and is likely to be most favourable amongst those who require increased flexibility in setting mealtimes, or those for whom mealtimes are often unpredictable.

The issue of the cost-effectiveness of intensive insulin therapy is complicated by a shortage of unconfounded data. The DCCT showed that a series of interventions including intensive insulin therapy reduces the rate of diabetic complications and increases life expectancy amongst an unrepresentative sample of adults and adolescents with Type 1 diabetes. Because of the complexity of this intervention, health economic analysis of the DCCT data has typically assumed that these reductions are primarily due to intensive insulin regimens.

The health economic searches found three models designed to find the cost-effectiveness of intensive treatment,<sup>343–4,381</sup> of which two attempted to form QALYs. The health utility values in each of the studies are poor: in one study<sup>343</sup> non-preference-based values are used; in another<sup>381</sup> only a very small sample was used to find health utilities. Both studies considered only a small number of health states and both suggest that intensive therapy is cost-effective.

Two models analysed intensive treatment in cost-per-life-year terms, and differed in their results. One study<sup>343</sup> produced a cost-per-life-year figure of US\$28,661 at 1994 prices, whilst another<sup>344</sup> found a figure several times larger. Neither study used UK costs. Note that as several diabetic complications will affect quality of life but will not significantly shorten life expectancy, the cost-per-QALY figure may be lower than the corresponding cost-per-life-year figure. Two cost analyses also suggest that the DCCT cost estimates may be overestimates.<sup>345-6</sup> Few inferences can be drawn because these studies are limited but it appears likely that intensive treatment, including intensive insulin regimens, will be cost-effective.

▷ Consideration

It was noted that Type 1 diabetes is a hormone deficiency disease. The problems faced by people with the condition (injections, hypoglycaemia, hyperglycaemia, consequences of capricious control, late complications) were noted to be solely a function of the poor state of insulin replacement therapy.

The group noted that the use of insulin injections in people with Type 1 diabetes is not RCT-based and never could be. It was also noted that, prior to the introduction of short- and long-acting insulin analogues, the use of insulin regimens based on a combination in various forms of unmodified (soluble) human insulin before meals and human isophane (NPH) insulin for basal supply had become widespread, and that, the analogues aside, there was no evidence to challenge that conventional practice. Long-acting analogues, or rather insulin glargine, are covered by NICE appraisal guidance, and this recommends their availability for use in people with Type 1 diabetes. Rapid-acting insulin analogues are supported by an evidence base for less hypoglycaemia at night and at some other times, reduced hyperglycaemic excursions after meals and small improvements in HbA<sub>1c</sub>, suggesting that these too should have an increasing role in people with Type 1 diabetes.

The group was aware that the evidence for combining the advantages of rapid- and long-acting insulin analogues was evolving as the knowledge base to use these technologies improves. This combination would be particularly suitable to matching with active mealtime insulin dose adjustment (AMIDA, see dietary recommendations in 6.3). Some recent NICE technology appraisals provided a health economic basis for supporting this regimen, should appropriate improvements in HbA<sub>1c</sub> be demonstrated. Accordingly the recommendations were drafted to allow choice of human or combined analogue regimens including from the time of diagnosis.

The group noted the potential usefulness of the new insulins in some special situations, including religious feasts and fasts, and shift work. A need to address insulin starters and people who wished for smaller numbers of injections was identified. A need to caution against using newer, more expensive insulins in people with control problems without proper assessment of underlying causes was felt appropriate. The NICE appraisal of insulin pumps (effectively an insulin regimen rather than a device) was noted, and no elaboration felt to be needed on that.

The group found the evidence for the general recommendation of any glucose-lowering drug in combination with insulin to be unconvincing. While there may be a small gain in overall glucose control evidenced inconsistently in the acarbose studies, the size of this gain, the prevalence of intolerance, and the suggestion of increased hypoglycaemia, together were taken as indicating that no recommendation for the general use of this drug in this context could be made.

The use of metformin and insulin sensitisers in people with Type 1 diabetes and the metabolic syndrome has not been adequately investigated.

The group was aware of the concern that arterial complications in people with Type 1 diabetes were associated with features of the metabolic syndrome as seen in Type 2 diabetes, and that there was evidence of benefit in people with Type 2 diabetes for some drugs, notably metformin (UKPDS study) and PPAR- $\gamma$  agonists (see NICE guidance). While not endorsing the general use of such drugs in people with Type 1 diabetes and features of the metabolic syndrome (see section 8.2, 'Arterial disease management'), the group noted that further investigation might support the high *a priori* likelihood of benefit in this high-risk situation.

## RECOMMENDATIONS

- |     |  |   |
|-----|--|---|
| R50 | Adults with Type 1 diabetes should have access to the types (preparation and species) of insulin they find allow them optimal well-being.  | A |
| R51 | Cultural preferences need to be discussed and respected in agreeing the insulin regimen for a person with Type 1 diabetes.   | D |
| R52 | Multiple insulin injection regimens, in adults who prefer them, should be used as part of an integrated package of which education, food and skills training should be integral parts.   | A |
| R53 | Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes.   | D |
| R54 | Mealtime insulin injections should be provided by injection of unmodified ('soluble') insulin or rapid-acting insulin analogues before main meals.   | D |
| R55 | Rapid-acting insulin analogues should be used as an alternative to mealtime unmodified insulin: <ul style="list-style-type: none"> <li>● where nocturnal or late inter-prandial hypoglycaemia is a problem</li> <li>● in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired.</li> </ul>   | A |
| R56 | Basal insulin supply (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogues (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogues are given at mealtimes or the midday insulin dose is small or lacking, the need to give isophane (NPH) insulin twice daily (or more often) should be considered. | D |
| R57 | Long-acting insulin analogues (insulin glargine) should be used when: <ul style="list-style-type: none"> <li>● nocturnal hypoglycaemia is a problem on isophane (NPH) insulin</li> <li>● morning hyperglycaemia on isophane (NPH) insulin results in difficult daytime blood glucose control</li> <li>● rapid-acting insulin analogues are used for mealtime blood glucose control.</li> </ul>                               | D |
| R58 | Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life: <ul style="list-style-type: none"> <li>● biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance</li> </ul>   | D |

- biphasic rapid-acting insulin analogue pre-mixes may give an advantage to those prone to hypoglycaemia at night.

Such twice daily regimens may also help:

- those who find adherence to their agreed lunchtime insulin injection difficult
- adults with learning difficulties who may require assistance from others.

R59	Adults whose nutritional and physical activity patterns vary considerably from day-to-day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations (see R55–7) and consideration of unusual patterns and combinations.	D
R60	For adults undergoing periods of fasting or sleep following eating (such as during religious feasts and fasts or after night-shift work), a rapid-acting insulin analogue before the meal (provided the meal is not prolonged) should be considered.	D
R61	For adults with erratic and unpredictable blood glucose control (hyper- and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered: <ul style="list-style-type: none"> <li>• resuspension of insulin and injection technique</li> <li>• injection sites</li> <li>• self-monitoring skills</li> <li>• knowledge and self-management skills</li> <li>• nature of lifestyle</li> <li>• psychological and psychosocial difficulties</li> <li>• possible organic causes such as gastroparesis.</li> </ul>	D
R62	Continuous subcutaneous insulin infusion (insulin pump therapy) is recommended as an option for people with Type 1 diabetes provided that: <ul style="list-style-type: none"> <li>• multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed;* and</li> <li>• those receiving the treatment have the commitment and competence to use the therapy effectively.</li> </ul>	NICE
R63	Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some mealtime insulin) should be considered for adults starting insulin therapy, until such time as islet B-cell deficiency progresses further.	D
R64	Clear guidelines and protocols ('sick day rules') should be given to all adults with Type 1 diabetes to assist them in adjusting insulin doses appropriately during intercurrent illness.	D
R65	Oral glucose-lowering drugs should generally not be used in the management of adults with Type 1 diabetes.	D

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\* People for whom multiple-dose therapy has failed are considered to be those for whom it has been impossible to maintain an HbA<sub>1c</sub> level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occurring, despite a high level of self-care of their diabetes. 'Disabling hypoglycaemia', for the purpose of this guidance, means the repeated and unpredicted occurrence of hypoglycaemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life.

## 7.4 Insulin delivery

### ▷ Rationale

As a large protein, insulin cannot be taken orally (it is digested) and is only absorbed across mucous membranes (of the nose or inside cheeks for example) very poorly. As a result, it generally has to be injected or infused into the subcutaneous fat. Self-use of injection devices is not something most people adopt happily by choice, and since the late 1970s various solutions to making this easier and more satisfactory have been developed.

### ▷ Evidence statements

NICE guidance<sup>165</sup> concluded that, compared to optimised MDI therapy, CSII results in a modest but worthwhile improvement in GHb and quality of life (by allowing greater flexibility of lifestyle), and reduction of other problems such as hypoglycaemia and rising blood glucose levels at the end of the night. In routine practice, patients who go on to pumps are carefully selected, and to a large degree self-selected. Overall, insulin pumps appear to be a useful advance for patients having particular problems, rather than a dramatic breakthrough in therapy, and would probably be used only in a small percentage of patients (NICE).

There is a paucity of trials of sufficient sample size in comparing insulin injection pens to other forms of insulin delivery.

One randomised trial<sup>166</sup> of medium sample size compared a multiple injection regimen from a pen injector with conventional treatment with twice-daily syringe injection. No significant differences were seen in GHb values, blood glucose values or hypoglycaemic episodes. Patient satisfaction with pen injectors was high and most patients opted to continue on this delivery system following termination of the trial. However, this study has some methodological limitations (**Ib**).

One randomised crossover trial<sup>167</sup> compared two types of insulin regimen injected in the abdomen with the same regimen injected in the thigh. Regular insulin injections in the abdomen resulted in significantly lower post-prandial plasma glucose values, peak plasma glucose and increment in plasma glucose compared to time periods following injection in the thigh. Significantly higher serum free insulin values were also seen following abdominal injection of regular insulin, compared with injections administered at the thigh. No differences were recorded between injections at either site following injections containing both isophane (NPH) and unmodified ('soluble') insulin (**Ib**).

One prospective study<sup>168</sup> comparing the absorption of insulin injected superficially and deep subcutaneously at the fat-muscle boundary showed no significant difference between the two techniques. A sub-group of 10 participants showed no difference in overall serum free insulin or plasma glucose values following superficial and deep subcutaneous injection (**IIa**).

One study<sup>169</sup> reported benefits associated with injection through clothing, compared with conventional injection practice with skin preparation over a 20-week trial period. This study had some methodological limitations (**Ib**).

Outside of the recommendations made on continuous subcutaneous insulin infusion,<sup>165</sup> no studies were identified that specifically addressed the insulin delivery needs of people with Type 1 diabetes with poor blood glucose control.

▷ Health economic evidence

The health economic searches produced three published papers<sup>347–9</sup> considering the use of insulin pens. None of the three papers compare their benefits (patient satisfaction, or improved HbA<sub>1c</sub>) against their costs.

▷ Consideration

Insulin injection pens were noted to be the overwhelming norm in the UK for insulin delivery for reasons of convenience, ease of teaching and portability. Some devices with particular design characteristics can be used by people with disabilities, where otherwise a third party would have to give injections. The desirability and often cost-effectiveness of this was noted. Injection into deep subcutaneous fat, and on the basis of many studies into the tissues of the abdominal wall for mealtime unmodified human insulin, are generally advised and logically based. However the needs and beliefs of individuals in giving their own insulin were felt to be of importance. Simple logic also leads to the conclusion that rotation of injection sites should be within one region rather than between regions. Group members (both clinicians and people with diabetes) expressed a widespread experience of repeated self-injection with the same needle without problems arising. The group considered the utility of recommending advice on cleanliness for those who choose to re-use needles, but noted the regulatory position from the Medicines and Healthcare Products Regulatory Agency (MHRA, formerly the Medical Devices Agency) in the bulletin DB2000(04). Consequently, the guideline cannot make such a recommendation. Other common sense issues included provision for sharps disposal, and check on the condition of injection sites annually or if blood glucose control problems worsen.

## RECOMMENDATIONS

R66	Adults with Type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen.	D
R67	Adults with Type 1 diabetes who have special visual or psychological needs should be provided with injection devices or needle-free systems that they can use independently for accurate dosing.	D
R68	Insulin injection should be made into the deep subcutaneous fat. To achieve this, needles of a length appropriate to the individual should be made available.	D
R69	Adults with Type 1 diabetes should be informed that the abdominal wall is the therapeutic choice for mealtime insulin injections.	D
R70	Adults with Type 1 diabetes should be informed that extended-acting suspension insulin (for example isophane (NPH) insulin) may give a longer profile of action when injected into the subcutaneous tissue of the thigh rather than the arm or abdominal wall.	D
R71	Adults with Type 1 diabetes should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within that area.	D

- R72 Adults with Type 1 diabetes should be provided with suitable containers for the collection of used needles. Arrangements should be available for the suitable disposal of these containers. D
- R73 Injection site condition should be checked annually, and if new problems with blood glucose control occur. D

## 7.5 Hypoglycaemia: prevention of hypoglycaemia, problems related to hypoglycaemia and management of symptomatic hypoglycaemia

### ▷ Rationale

Hypoglycaemia is, for most people using insulin therapy, an inevitable consequence of the erratic absorption of insulin from subcutaneous tissue after depot injection or infusion, coupled with absence of feedback to insulin need when changes in planned activity or eating occur once the injection has been given. Hypoglycaemia is usually unpleasant, often becomes a source of fear, and can be an embarrassment as well as a safety risk. Accordingly, while careful choice of insulin regimen (section 7.3) informed by self-monitoring (section 6.2) is important in ameliorating this problem, other preventative measures are of importance. A higher level of optimised management is needed when hypoglycaemia and its related problems do occur.

### ▷ Evidence statements

#### *Management of hypoglycaemia*

Canadian clinical practice guidelines<sup>98</sup> reported four studies supporting the use of 15 g glucose (monosaccharide) (orally) for the treatment of moderate hypoglycaemia. Two studies within the guidelines explored a 20 g oral glucose dose for recovery of blood glucose levels. Recovery was slower following treatment with milk and orange juice. The use of glucose gel also delivered slower recovery in the latter study and required swallowing to have a significant effect. A further study showed no support for buccal administration of glucose (Ia).

One study within the Canadian guidelines<sup>98</sup> reported on the special needs of people taking alpha-glycosidase inhibitors when treating hypoglycaemia, recommending the use of glucose (dextrose) tablets, or milk or honey if these are unavailable (IV).

#### *Nocturnal hypoglycaemia*

A bedtime snack may be needed to avoid nocturnal hypoglycaemia. Two studies from a systematic review<sup>98</sup> showed prepared cornstarch snack bars have some benefit in overnight reduction of hypoglycaemia, but the number of events were not significantly reduced (Ia).

#### *Hypoglycaemia unawareness*

Canadian clinical practice guidelines<sup>98</sup> report one paper on the link between incidence of prior hypoglycaemic episodes and worsening in the defect of the hormonal responses to hypoglycaemia, leading to a reduction in the self-detection of hypoglycaemia. Eight papers report the benefits of strict avoidance of hypoglycaemia in improving recognition of severe hypoglycaemia or the responses of counter-regulatory hormones (Ia).

### *Blood glucose awareness training*

A randomised controlled study<sup>170</sup> compared blood glucose awareness training (BGAT) with no training on the increased hypoglycaemia after initiation of more intensive diabetes management. The counter-regulatory hormone epinephrine (adrenaline) response was not impaired following BGAT despite an increase in frequency of hypoglycaemia induced by intensive diabetes management. No difference was seen in awareness of the symptoms of hypoglycaemia following BGAT, compared with controls, although BGAT does lead to a better detection of low blood glucose levels in people starting intensive diabetes management (Ib).

An observational study<sup>171</sup> compared blood glucose sensitivity and prediction accuracy in inpatients before and after blood glucose awareness training, showed no additional effect on the improvement of HbA<sub>1c</sub>. The decrease in HbA<sub>1c</sub> was not however accompanied by a change in the accuracy of blood glucose estimation or sensitivity of recognition of low blood glucose levels (IIa).

Canadian clinical practice guidelines<sup>98</sup> cite five studies demonstrating a positive effect of BGAT on accurate detection and treatment of hypoglycaemia, and allowing reduced-awareness subjects to detect a greater percentage of low blood glucose levels. These BGAT programmes involve instruction in interpretation of physical symptoms and instruction on food, exercise, insulin dosage and action, and the impact of time of day and last blood glucose measurements on estimations of blood glucose (Ia).

### *Long-term complications of hypoglycaemia*

Evidence on the impact of hypoglycaemia on cognitive function is not clear. Two prospective studies reported within the Canadian guidelines<sup>98</sup> did not find association between intensive diabetes management and cognitive function. However, six retrospective studies found subjects with recurrent hypoglycaemia performed more poorly in a range of intellectual tests (IIa).

### *Medical intervention of hypoglycaemia*

Two randomised studies compared the use of glucagon and dextrose in the treatment of severe hypoglycaemia. One study<sup>172</sup> compared intramuscular administration of 1 mg glucagon with 50 ml 50% IV dextrose in people with hypoglycaemic coma. A second study<sup>173</sup> compared intravenous administration of 1 mg glucagon vs 50 ml 50% dextrose in people with hypoglycaemic coma. Both studies showed a significantly slower recovery to a normal level of consciousness in the glucagon treated group (Ib).

Two glucagon-treated patients in each study (7% and 4% respectively) and two dextrose-treated patients in the second study (4%) required additional administration of 12.5 g IV dextrose following failing to recover consciousness after 15 minutes. In the first study average duration of hypoglycaemic coma was not different between the two treatment groups (Ib).

No correlation was seen between time taken to recovery of consciousness and initial plasma glucose concentration or duration of hypoglycaemia in either of the studies. Side effects were similar among the treatment groups (Ib).

These two small studies suggest that intravenous glucose gives a clinically non-significant advantage over intramuscular glucagon in time to recovery of consciousness in people with Type 1 diabetes in hypoglycaemic coma (Ib).

▷ Health economics evidence

No health economic evidence on the prevention or management of hypoglycaemia was identified in the literature review.

▷ Consideration

The group noted this was an area of considerable importance to people with Type 1 diabetes, but that prevention of hypoglycaemia was considered appropriately under insulin therapy recommendations, and secondarily under education and lifestyle issues. The group noted issues related to absorption and ingestion of free carbohydrate in people with decreased conscious level. They were concerned that recurrent hypoglycaemia was properly considered in a medical context, and not simply attributed to lifestyle problems secondary to insulin therapy.

Hypoglycaemia unawareness was also noted to be an important issue, and be partially reversible and capable of useful management, as now is nocturnal hypoglycaemia (it was noted that the recommendations on insulin therapy and clinical monitoring addressed other aspects of such management). No useful hard evidence was available for cognitive decline occurring in people with Type 1 diabetes, but the possibility of recurrent severe hypoglycaemia being a contributory factor was felt worth mentioning.

The group noted that the ease and safety of administration of glucagon compared to IV glucose (risk of extravasation) meant that in most situations it was the treatment of choice. While it was recognised that there were groups of people to whom the identified studies do not apply (starvation, alcohol toxic), and that these people would not be expected to respond well to glucagon, it was agreed that the best means of detecting this was by absence of a response to glucagon at 10 minutes. Safe follow-up management after either therapy should include oral carbohydrate and awareness of risk of relapse. Users of glucagon injections need appropriate education and training.

## RECOMMENDATIONS

- |     |   |   |
|-----|---|---|
| R74 | Adults with Type 1 diabetes should be informed that any available glucose/sucrose containing fluid is suitable for the management of hypoglycaemic symptoms or signs in people who are able to swallow. Glucose containing tablets or gels are also suitable for those able to dissolve or disperse these in the mouth and swallow the products.  | A |
| R75 | When a more rapid-acting form of glucose is required, purer glucose-containing solutions should be given.   | D |
| R76 | <p>Adults with decreased level of consciousness due to hypoglycaemia who are unable to take oral treatment safely should be:</p> <ul style="list-style-type: none"> <li>● given intramuscular glucagon by a trained user (intravenous glucose may be used by professionals skilled in obtaining intravenous access)</li> <li>● monitored for response at 10 minutes, and then given intravenous glucose if the level of consciousness is not improving significantly</li> <li>● then given oral carbohydrate when it is safe to administer it, and placed under continued observation by a third party who has been warned of the risk of relapse.</li> </ul> | D |

- R77** Adults with Type 1 diabetes should be informed that some hypoglycaemic episodes are an inevitable consequence of insulin therapy in most people using any insulin regimen, and that it is advisable that they should use a regimen that avoids or reduces the frequency of hypoglycaemic episodes while maintaining as optimal a level of blood glucose control as is feasible. Advice to assist in obtaining the best such balance from any insulin regimen should be available to all adults with Type 1 diabetes. (see section 7.2, ‘Insulin regimens’ and 7.2, ‘Insulin delivery’). **B**
- R78** When hypoglycaemia becomes unusually problematic or of increased frequency, review should be made of the following possibly contributory causes: **D**
- inappropriate insulin regimens (incorrect dose distributions and insulin types)
  - meal and activity patterns including alcohol
  - injection technique and skills including insulin resuspension
  - injection site problems
  - possible organic causes including gastroparesis
  - changes in insulin sensitivity (the latter including drugs affecting the renin-angiotensin system and renal failure)
  - psychological problems
  - previous physical activity
  - lack of appropriate knowledge and skills for self-management.
- R79** Hypoglycaemia unawareness should be assumed to be secondary to undetected periods of hypoglycaemia (<3.5 mmol/l, often for extended periods, commonly at night) until these are excluded by appropriate monitoring techniques. If present, such periods of hypoglycaemia should be ameliorated. **D**
- R80** Specific education on the detection and management of hypoglycaemia in adults with problems of hypoglycaemia awareness should be offered. **D**
- R81** Nocturnal hypoglycaemia (symptomatic or detected on monitoring) should be managed by: **D**
- reviewing knowledge and self-management skills
  - reviewing current insulin regimen and evening eating habits and previous physical activity
  - choosing an insulin type and regimen with less propensity to induce low glucose levels in the night hours, such as:
    - isophane (NPH) insulin at bedtime
    - rapid-acting analogue with the evening meal
    - long-acting insulin analogues (insulin glargine)
    - insulin pump.
- R82** Adults with Type 1 diabetes should be informed that late post-prandial hypoglycaemia may be managed by appropriate inter-prandial snacks, or the use of rapid-acting insulin analogues before meals. **D**
- R83** Where early cognitive decline occurs in adults on long-term insulin therapy, normal investigations should be supplemented by consideration or investigation of possible brain damage due to overt or covert hypoglycaemia, and the need to ameliorate this. **D**

## 8 Arterial risk control

### 8.1 Identification of arterial risk

#### ▷ Rationale

People with Type 1 diabetes are generally recognised to be at greatly increased risk of arterial disease (CVD) in middle age. While the literature on arterial risk factors and markers in the general population is large, it would not appear to follow that the findings can be simply carried over to people with Type 1 diabetes. Similarly, the tools used to quantify arterial risk in the general population are known not to work well in people with Type 2 diabetes, and seem even less likely to be valid in Type 1 diabetes.

#### ▷ Evidence statements

##### *Arterial risk factors*

The Scottish intercollegiate guidelines<sup>174</sup> identify specific risk factors for arterial disease as cigarette smoking, dyslipidaemia, hypertension, hyperglycaemia, obesity and microalbuminuria (IV).

The guideline<sup>174</sup> reports on non-randomised studies showing that smoking is an independent arterial risk factor in people with diabetes. Additional observational studies reported dyslipidaemia. An increased concentration of LDL cholesterol or total cholesterol has also been identified as an independent risk factor for arterial morbidity and mortality and each 1.0 mmol/l reduction of LDL cholesterol represents a 36% reduction in risk of arterial disease (IIa).

Two controlled but not randomised studies reported within the guideline<sup>174</sup> demonstrated the positive relationship between hypertension and risk of arterial death, with a progressive increase in risk with rising systolic pressure. Each 10 mmHg reduction in systolic pressure is associated with a 15% (95% CI: 12–18) reduction in risk of arterial death over 10 years (IIa).

The link between glycaemia and arterial morbidity and mortality was also reported in two studies reviewed in the SIGN guidelines.<sup>174</sup> In one study each 1% reduction in HbA<sub>1c</sub> was associated with a 21% (95% CI: 15–27) reduction in the risk of diabetes-related death and a 14% reduction for myocardial infarction over 10 years (IIa).

Evidence for the other risk factors is sparse. In the SIGN guidelines,<sup>174</sup> no studies were identified for linking obesity as an independent risk factor in established diabetes. One observational study reported microalbuminuria as an independent marker associated with doubling in arterial risk, however, there is insufficient evidence to determine whether reducing albumin excretion rate specifically reduces arterial morbidity or mortality (IIa).

A meta-analysis<sup>175</sup> aimed at defining risk factors for arterial disease from studies in people with diabetes, showed that, adjusted for age, both total mortality and death from all vascular causes increased significantly with total cholesterol level and systolic blood pressure, and decreased with percentage of women. Duration of diabetes and mean HbA<sub>1c</sub> were not considered to be associated with mortality. However, this meta-analysis did not contain a critical appraisal of

included studies or details of approaches used to ensure study quality before inclusions and should therefore not be used as the basis for clinical recommendations (IIa).

### *Screening tests*

One systematic review<sup>176</sup> examined 67 studies, addressing both screening for primary detection of arterial risk factors and treatment of lipid abnormalities in asymptomatic people both with and without diabetes. Reliability and effectiveness of each screening strategy for identifying lipid disorders was investigated, and showed that total cholesterol measurements generally have good reliability, with an analytic variability of less than or equal to 3% and a mean total biologic variability of the order of 6%. A total cholesterol level within 10% of the true value can be determined with two separate measurements, which do not differ significantly between fasting or non-fasting venous blood (III).

Evidence within this systematic review<sup>176</sup> for HDL cholesterol showed a higher analytical (6%) and biological (7.5%) variation than total cholesterol, however, two or three values were required to estimate true HDL cholesterol levels to within 10 to 15%. Variations were also found between non-fasting and fasting blood samples as HDL cholesterol is 5%–10% lower in the non-fasting state, suggesting that non-fasting measurement may slightly overestimate coronary heart disease risk, but not enough to make accuracy of screening unacceptable (III).

Additional studies within this systematic review<sup>176</sup> considered triglyceride screening. Values measured varied by 20%–30% between fasting and non-fasting states. LDL cholesterol is calculated from total and HDL cholesterol and triglycerides measurements and application of the Friedewald equation. However, this equation has been found to be inaccurate at triglyceride levels greater than or equal to 4.5 mmol/l when special techniques must be employed (eg ultracentrifugation) (III).

Also considered in this systematic review<sup>176</sup> was the comparable accuracy of total and HDL cholesterol from capillary blood samples. These were found to be less reliable without proper attention to calibration and proper testing techniques. One study found that a Framingham-based coronary risk model was the best predictor of IHD mortality. Guidelines reported in the review concluded that the LDL:HDL cholesterol and the total:HDL cholesterol ratios performed equally well in determining arterial outcomes, and the least accurate screening test was that of measuring total cholesterol alone (III).

Other studies included in this review<sup>176</sup> assessing characteristics of the screening tests showed that non-fasting total cholesterol alone is the easiest to perform for the patient and provider. Total:HDL cholesterol ratio is easy for patients to obtain and for providers to interpret and performs equally accurately as the LDL:HDL cholesterol ratio strategy. However, one study in the review demonstrated that risk-based algorithms which directly incorporate age, other risk factors and measures of total and HDL cholesterol are the most accurate approach to screening. These processes are difficult to access and so supplemental tables, such as the Sheffield table, can improve the feasibility of a risk-based strategy (III).

There was no evidence from this systematic review<sup>176</sup> to inform the question of appropriate frequency of screening. National guidelines recommend a five-year interval for people with previous normal results and more frequent screening in those with borderline values (IV).

*Prediction of arterial risk*

Six studies all published by the same group addressed the relative specificity and sensitivity of the different methods for predicting arterial risk (Sheffield, Modified Sheffield, Joint British Guidelines, Canadian, Framingham categorical, New Zealand, and Joint European guidelines, but not including the UKPDS risk engine).

One study<sup>177</sup> comparing the Sheffield tables to the computer-calculated Framingham equation revealed a low sensitivity and specificity for the Sheffield tables (35% (95% CI 28 to 42) and 98% (95% CI 97 to 99) respectively). The old tables only included patients with systolic blood pressure <160 mmHg, and cholesterol greater than 5.5 mmol/l. Adopting these exclusion criteria led to a substantial reduction in the number of patients eligible for screening without improving detection of risk assessment (DS).

Another evaluation<sup>178</sup> studied all seven guidelines against the calculated Framingham equation in 906 people with diabetes, showing Modified Sheffield tables have higher sensitivity (95% *vs* 37%) with a slight reduction in specificity (90% *vs* 97%) compared with the original tables, with a slightly better positive predictive value than the original version (80% *vs* 71%). The Joint British tables have good specificity (99%), but low sensitivity (77%) but the tables perform well at the lower CHD risk of greater than or equal to 15% over 10 years (specificity 92%, sensitivity 96%). Canadian tables perform poorly at the  $\geq 30\%$  risk, and only slightly better at the greater than or equal to 15% level of risk (specificity 100%, sensitivity 5%, and 85% and 98%, respectively). The Framingham categorical tables have a lower specificity (83%) for the identification of high-risk individuals (although risk is greater than or equal to 27% not greater than or equal to 30%) and this deteriorates for identification of those at  $\geq 15\%$  risk (specificity 77%). New Zealand tables had a sensitivity of 69% and specificity of 88% at a greater than or equal to 20% level of risk, at the  $\geq 10\%$  level of risk, specificity deteriorates to 58%. The Joint European tables have a sensitivity of 89% for risk levels greater than or equal to 20% but specificity of only 71%. This means that one in four patients would be incorrectly identified as having a risk above the 20% threshold (DS).

A further study from the same investigators<sup>179</sup> assessed the PROCAM program against that of the Framingham equation. Only 56% of the study population were eligible for evaluation with PROCAM. This evaluation also systematically underestimates risk in comparison with the Framingham equation at low levels of absolute risk but overestimates at higher risk levels (DS).

The sensitivity and specificity of various risk prediction tables and charts was also investigated in one comparative study.<sup>180</sup> Compared to the Framingham equation the Sheffield tables had a low sensitivity (40% eligible for cholesterol lowering treatment would be identified), but with high specificity and thus low false positive rates. The New Zealand tables had similar sensitivities and specificities to the Sheffield tables, but a 10% level of risk prediction of five-year arterial disease risk threshold specificity is significantly lower than the Sheffield tables. The European tables have better sensitivity than Sheffield and New Zealand tables but specificity is significantly worse than other risk assessment levels leading to an equally low sensitivity. The joint British Societies table has significantly better specificities at greater than or equal to 15% and greater than or equal to 30% 10-year CHD risk than the modified Sheffield tables. Sensitivity is generally low, but high at the 15% 10-year CHD/10% five-year CVD risk level. Canadian tables are not reliable at greater than or equal to 30% risk but are comparable with the modified Sheffield tables at 154% risk threshold. The Framingham equation had the best

performance with sensitivity and specificity comparable to that of the modified Sheffield and joint British Society methods, respectively (DS).

▷ Consideration

The group recognised the very considerable difficulties in reaching conclusions from the evidence in this area. Very little direct information pertaining to people with Type 1 diabetes can be ascertained, whilst the importance of the issue is emphasised by the very high early arterial disease (CVD) risk run by people with Type 1 diabetes. Nevertheless certain sub-groups are known to be at particularly high risk (people with raised albumin excretion rate (micro-albuminuria)), while others combine Type 1 diabetes with combinations of classic risk factors typical of the metabolic syndrome and known to be predictors of high arterial risk in people with Type 2 diabetes and indeed non-diabetic populations. A further group of people will combine Type 1 diabetes with a single arterial risk factor or risk marker, while yet others will have Type 1 diabetes but appear low risk otherwise.

Accordingly the important factors for surveillance are urinary albumin excretion (most important), other classical risk factors including full lipid profile, and risk markers such as age, family history and some ethnic groups. In accordance with the principle of unified organisation of care, monitoring of these factors annually is to be recommended, but it was recognised that in low risk individuals technology might become capable of programming longer review intervals for serum lipids.

The group recognised that different ways of using information from a full lipid profile (calculated LDL and HDL separately, calculation of total: HDL cholesterol ratio, calculation of non-HDL cholesterol) are in use. While the group preferred the first of these as not mixing lipid abnormalities of different pathogenesis, and being a better route to using the treatments for different lipid disorders rationally, it was recognised that there was not good evidence to suggest supporting one approach over the others.

The group could find no confidence in any risk table, engine or equation when applied to people with Type 1 diabetes.

## RECOMMENDATIONS

- |     |  |    |
|-----|--|----|
| R84 | Arterial risk factors should be assessed annually, and the assessment should include: <ul style="list-style-type: none"><li>● albumin excretion rate</li><li>● smoking</li><li>● blood glucose control</li><li>● blood pressure</li><li>● full lipid profile (including HDL and LDL cholesterol and triglycerides)</li><li>● age</li><li>● family history of arterial disease (CVD)</li><li>● abdominal adiposity.</li></ul> | C  |
| R85 | Arterial risk tables, equations or engines for calculation of arterial risk should not be used because they underestimate risk in adults with Type 1 diabetes.   | DS |

- R86** Adults with raised albumin excretion rate (microalbuminuria), or two or more features of the metabolic syndrome (see Table 4), should be managed as the highest risk category (as though they had Type 2 diabetes or declared arterial disease). **D**

**Table 4 Features of the metabolic syndrome suggesting high arterial risk in people with Type 1 diabetes**

Feature	Women	Men
Blood pressure average (mmHg)	>135/80	>135/80
Waist circumference (m) ( <i>use 0.10m lower figures for people of South Asian extraction</i> )	>0.90	>1.00
Serum HDL cholesterol (mmol/l)	<1.2	<1.0
Serum triglycerides (mmol/l)	>1.8	>1.8

Raised albumin excretion rate is not included because in Type 1 diabetes it is a marker of developing nephropathy and nephropathy alone is associated with extreme risk of ischaemic heart disease.  
Glucose intolerance cannot be assessed in adults with Type 1 diabetes, but higher insulin doses in adults >20 years (>1.0 U/kg/day) suggest insulin insensitivity.

- R87** Adults with Type 1 diabetes who are not in the highest risk category but who have other arterial risk factors (increasing age over 35 years, family history of premature heart disease, of ethnic group with high risk or with more severe abnormalities of blood lipids or blood pressure) should be managed as a moderately high risk group. **D**
- R88** Where there is no evidence of additional arterial risk, the management of lipids and blood pressure should follow normal procedures for the non-diabetes population, using appropriate clinical guidelines. **D**

## 8.2 Interventions to reduce risk and to manage arterial disease

### ▷ Rationale

Prevention of arterial risk in people with Type 1 diabetes, through attention to blood glucose control (insulin therapy, patient education, nutrition, self-monitoring) is considered elsewhere in this guideline, and blood pressure management in 8.3, below. However, in the general population (at much lower risk) and in people with Type 2 diabetes other therapies are known to reduce the risk of arterial events. The current section therefore deals with these approaches as applied to people with Type 1 diabetes.

### ▷ Evidence statements

#### *Lipid lowering therapy*

The Scottish intercollegiate guidelines<sup>174</sup> identify a role for lipid-lowering drugs in reducing ischaemic heart disease events but not all cause mortality in people with no known arterial disease, compared with placebo (Ia).

SIGN guidelines on lipids<sup>181</sup> and the prevention of ischaemic heart disease detail studies targeted at people with Type 2 diabetes. However, secondary prevention trials of lipids reported

in the guideline have shown significant reduction in arterial disease in both Type 1 and Type 2 diabetes. These guidelines recommend the loss of weight, reduction of intake of saturated fat, increased consumption of fruit and vegetables, regular exercise and the introduction of lipid-lowering drug treatment for primary prevention of arterial problems in high-risk people with diabetes. The guidelines also report a study raising concern about underestimating diabetic ischaemic heart disease risk, particularly in people with Type 1 diabetes (Ia).

The SIGN guidelines<sup>174</sup> report on a number of therapeutic studies. The CARE study demonstrated a significant reduction in coronary events with pravastatin *vs* placebo, although the magnitude of effect was lower than in the 4S study. The LIPID study also showed a trend to reduction in recurrent coronary events but numbers of people with diabetes in this study were too low to demonstrate statistical significance. The VA-HIT study showed significant secondary prevention of coronary events in men with diabetes aged less than 74 years, taking a fibrate (gemfibrozil) for a mean follow-up of 5.1 years (Ia).

Three randomised controlled trials<sup>182–184</sup> reported on the positive effect of pravastatin on arterial outcomes in people with diabetes. One study<sup>182</sup> reported a significant change in total and LDL cholesterol, HDL cholesterol and triglycerides *vs* placebo. After 24 weeks the reduction in total cholesterol from baseline was 22%, LDL cholesterol 26%, and triglycerides decreased by 2%, accompanied by an increase in HDL cholesterol of 14%. Pravastatin was well tolerated throughout the study (Ib).

Similar results were seen in the further two trials. One study<sup>183</sup> reported reductions in LDL cholesterol and VLDL cholesterol of 30% and 13% respectively with pravastatin compared with placebo and significant increases in HDL cholesterol at eight and 16 weeks. The final study<sup>184</sup> was in a majority of sulfonylurea treated people with Type 2 diabetes, and pravastatin reduced total and LDL cholesterol by 19% and 27% in the diabetes group. Compared with placebo pravastatin caused a 13% decrease in triglycerides and a 4% increase HDL cholesterol in people with diabetes. Results were similar to those in people without diabetes, and were unaffected by adjustment for age and sex (Ib).

The SIGN management of arterial disease in diabetes guidelines<sup>174</sup> cite results from the Scandinavian Simvastatin study, which contained 204 people with diabetes (of a study population of 4,444), and demonstrated that cholesterol-lowering therapy was highly effective compared with placebo in those undergoing revascularisation procedures, especially in those with diabetes (risk reduction 55% *vs* 32% in non-diabetes) (Ia).

Two RCTs reported the effect of simvastatin in people with diabetes. Total and LDL cholesterol levels and the ratio between LDL and HDL cholesterol were decreased following treatment in one study<sup>185</sup> of 25 people with diabetes, whereas no difference was seen following placebo, no between group comparison was made. The second study, containing 26 people with Type 1 diabetes<sup>186</sup> also reported a significant reduction in the plasma concentrations of total cholesterol, LDL cholesterol and apolipoprotein B after 12 weeks simvastatin treatment, whereas no changes were observed after placebo treatment (Ib).

One study reported the effect of bezafibrate on arterial outcomes in 36 people with Type 1 diabetes.<sup>187</sup> However, there are some potential methodological limitations in this study, which does not make this evidence a reliable basis for a clinical recommendation (Ib).

*Antiplatelet therapy*

The SIGN guidelines<sup>174</sup> report uncertainty about the role of aspirin in primary prevention. Citing the HOT study (a randomised controlled trial) and the further reduction in arterial risk in well-controlled hypertensive patients with diabetes, they note the importance of balancing this reduction against the risk of bleeding (Ia).

The North of England guidelines<sup>188</sup> on aspirin for the secondary prophylaxis of vascular disease in primary care reported a pooled risk ratio by combining the meta-analysis of the Antiplatelet Collaborative Group with trials published after 1990 to establish the impact of antiplatelet therapy on subsequent myocardial infarction (MI), stroke and vascular death. This provided strong evidence for a general protective effect of aspirin as antiplatelet therapy in patients at raised vascular risk. Few studies were found containing comparisons of aspirin and alternative antiplatelet agents to enable comparison of their relative effectiveness (Ia).

For evidence relating specifically to people with diabetes the North of England guidelines<sup>188</sup> identified eight trials contributing to an overall estimate of risk difference for arterial morbidity of 1.2% with aspirin compared to placebo or other antiplatelet agent. These trials were homogeneous with a pooled incidence rate difference (by random effects model) of a 0.3% reduction in the risk of MI, stroke or vascular death from antiplatelet therapy for one year. This is not a statistically significant difference, and in summary authors state that aspirin given to patients with diabetes appears to have a small and statistically uncertain effect upon the risk of experiencing a subsequent vascular event. They also suggest that the similar relative risk for MI, stroke and vascular death found in diabetes trials and other trials of patients at raised vascular risk, indicates that patients with diabetes alongside other indications of vascular risk are likely to benefit from routine aspirin therapy (Ia).

American Diabetes Association guidelines<sup>76</sup> indicate that meta-analysis and large-scale collaborative trials in men and women with diabetes support the view that low-dose aspirin therapy should be prescribed as a secondary prevention strategy if no contraindications exist. The guidelines also point to substantial evidence suggesting that low-dose aspirin therapy should be used as a primary prevention strategy in men and women with diabetes who are at a high risk for arterial events.

The meta-analysis of 145 prospective controlled trials of antiplatelet therapy by the Antiplatelet Trialists Group reported in the ADA guidelines<sup>76</sup> showed a trend toward increased risk reductions with doses of aspirin  $\leq 325$  mg/day, but the difference was not statistically significant. An estimated  $38 \pm 12$  vascular events per 1,000 patients with Type 1 diabetes would have been prevented if they were treated with aspirin as a secondary prevention strategy (Ia).

The ADA guidelines<sup>76</sup> also reported on the HOT study, which showed a reduction in arterial events following aspirin therapy compared to placebo of 15% and a 36% reduction in myocardial infarction. This study also showed that fatal bleeding including intracerebral bleeding were equal in aspirin and control groups, whereas non-fatal minor bleeding episodes were more frequent in patients receiving aspirin. The US Physicians Health study reported in the same guideline compared aspirin (325 mg/day) with placebo in male physicians (without diabetes), resulting in a 44% risk reduction in MI among the treated group. In a subgroup of people with diabetes there was a reduction in MI from 10% to 4% yielding a relative risk of 0.39 for men with diabetes randomised to aspirin therapy (Ia).

The ADA guidelines<sup>76</sup> also addressed the safety of aspirin use and reported several prospective randomised studies in which a trend for an increase in haemorrhagic stroke followed aspirin therapy, although this has not reached statistical significance (Ia).

Contraindications reported<sup>76</sup> include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding and clinically active hepatic disease (Ib).

Relative risk of MI reported by the ETDRS group<sup>189</sup> in which roughly 48% of men and women with diabetes had a history of arterial disease was lowered significantly in the first five years in those randomised to aspirin therapy (Ib).

In the management of people with diabetes and new or established vascular disease, the SIGN guidelines<sup>174</sup> refer to a meta-analysis of platelet inhibitor therapy demonstrating a 31% reduction in non-fatal reinfarction, a 42% reduction in non-fatal stroke and a 13% reduction in arterial mortality (Ia).

One meta-analysis<sup>190</sup> of six randomised, double-blind, placebo-controlled trials showed a significant pooled reduction in mortality following treatment with platelet glycoprotein inhibitors. The most marked benefit was seen in patients undergoing percutaneous coronary intervention. A significant reduction in composite death or MI at 30 days was also seen following treatment in people with diabetes. However, potential methodological limitations of the trials included would not permit this analysis to be used as a evidence base to inform recommendations in this area (Ia).

Also reported in the SIGN guideline<sup>174</sup> is a sub-study analysis of a large RCT demonstrating that addition of clopidogrel to aspirin over 3–12 months reduces the risk of fatal or non-fatal MI or stroke by 20% in patients with a past history of coronary heart disease presenting with acute coronary syndromes (without electrocardiographic ST elevation). This risk reduction was however associated with an additional risk of bleeding (Ia).

The ADA guidelines<sup>76</sup> also report from the CAPRIE study which showed that clopidogrel was slightly more effective than aspirin in reducing the combined risk of stroke, MI or vascular death in people with and without diabetes (effect sizes not stated) (Ia).

### *Management of arterial disease*

One randomised controlled study reviewed in the ADA guideline<sup>76</sup> showed that thrombolytic therapy reduced mortality after acute MI in subjects with diabetes by  $\leq 42\%$  with no increase in risk of bleeding or stroke, and should not be withheld due to concern about retinal haemorrhage in patients with retinopathy. This study also demonstrated that the indications and contraindications for thrombolysis in patients with diabetes are the same as those without (Ia).

The SIGN guideline<sup>174</sup> reports on the results of the beta-blocker adrenergic pooling project study, which demonstrated that diabetes is not a contraindication to the use of beta-blockers, and that these reduce mortality, sudden cardiac death and re-infarction when given after acute MI. The guideline also cites the 1995 Collaborative Group on ACE inhibitor trials meta-analysis of nearly 100,000 patients which showed that receiving therapy with an ACE inhibitor within 36 hours of acute MI for  $\geq 4$  weeks, reduced mortality post MI. The majority of benefits occurred within the first few days when mortality was highest, benefiting patients at a higher risk to a greater absolute extent (Ia).

Three large trials (AIRE, SAVE and TRACE studies)<sup>174</sup> also reviewed within the SIGN guideline have shown consistent reductions in mortality when ACE inhibitor therapy is given to people after acute MI with clinical evidence of heart failure or a reduced ejection fraction. A fourth study (SOLVD) demonstrated an absolute risk reduction for mortality of 4.5% in patients with diabetes and chronic heart failure given an ACE inhibitor compared to placebo over a mean follow-up of 4.5 years (Ia).

A predefined subgroup analysis of 3,577 people over 55 with diabetes (the majority of whom had Type 2 diabetes) in the large multinational HOPE randomised controlled trial<sup>191</sup> showed the effect of ramipril on arterial outcomes in people with diabetes. The rate of combined primary outcome of MI, stroke or arterial death was significantly lower in the ramipril groups than in those receiving placebo. Total mortality was reduced by 24%. Adjustment for changes in systolic and diastolic blood pressures did not change the magnitude of the effect (Ib).

Other results from the HOPE study<sup>192</sup> in which patients aged over 55 years, with and without diabetes, who were randomised to receive 400 IU vitamin E for an average follow-up of 4.5 years, showed no effect of antioxidant over placebo. Primary outcomes of MI, stroke or arterial death, or secondary outcomes of hospitalisations for angina or heart failure, were similar following treatment with vitamin E and placebo. No differences were observed in the frequency of outcomes in people with diabetes in the two treatment groups (Ib).

#### *Management of acute stroke*

SIGN guidelines<sup>174</sup> state that clinical presentation of stroke in people with diabetes is similar to that in people without diabetes. There is little evidence specific to people with diabetes let alone specific to Type 1 diabetes, suggesting that the management of stroke should be similar to that in people without diabetes (IV).

#### ▷ Health economic evidence

Whilst economic analyses have been conducted on trials of lipid-lowering agents, no evaluation has specifically considered Type 1 diabetes. Three papers were identified within the health economic literature dealing with mixed diabetic populations.<sup>350–52</sup> An economic analysis<sup>350</sup> of simvastatin using the 4S trial data suggests that it would provide cost-effective mortality reduction in the UK amongst a similar population. A second cost-effectiveness paper<sup>351</sup> also suggests that the simvastatin may be cost-effective in the UK for those aged 40 to 70 years with elevated cholesterol even if they have not been diagnosed with arterial disease. A third paper based outside the UK suggests that the benefits of simvastatin to diabetics with elevated lipid levels and arterial disease outweigh the benefit to those with elevated lipid levels and no prior arterial disease.<sup>352</sup>

As the GDG has no confidence in any existing risk table, engine or equation when applied to those with Type 1 diabetes, the degree to which models that make use of such equations can be relied upon is extremely limited.

▷ Consideration

The data on arterial risk management in people with Type 1 diabetes are few, though it is noted that studies in people with and without Type 2 diabetes point to clinically effective interventions for those groups. In the absence of quantitative risk assessment and noting the economic evidence placed before the group it seemed clear that interventions in people with Type 1 diabetes must be recommended considering their semi-quantitative arterial disease risk: high, moderate or no risk.

Given the high arterial risk of many people with Type 1 diabetes, smoking was considered to be particularly disadvantageous.

## RECOMMENDATIONS

These recommendations assume that arterial risk has been assessed according to the recommendations in section 8.1. Blood glucose control, blood pressure control and education programmes are considered elsewhere in this guideline (see 7, 8.3, 6.1 respectively).

- |     |   |   |
|-----|---|---|
| R89 | Adults with Type 1 diabetes who smoke should be given advice on smoking cessation and use of smoking cessation services, including NICE guidance-recommended therapies. The messages should be reinforced in continuing smokers yearly if pre-contemplative of stopping, and at all clinical contacts if there is a prospect of their stopping. | D |
| R90 | Young adult non-smokers should be advised never to start smoking.   | D |
| R91 | Aspirin therapy (75 mg daily) should be recommended in adults in the highest and moderately-high risk categories.   | B |
| R92 | A standard dose of a statin should be recommended for adults in the highest risk and moderately-high risk groups. Therapy should not be stopped if alanine aminotransferase (ALT) is raised to less than three times the upper limit of reference range.  | B |
| R93 | If several statins are not tolerated, fibrates and other lipid-lowering drugs should be considered as indicated according to assessed arterial risk status.   | D |
| R94 | Fibrates should be recommended for adults with hypertriglyceridaemia according to local lipid-lowering guidelines, and arterial disease risk status.  | D |
| R95 | Responses to therapy should be monitored by assessment of lipid profile. If the response is unsatisfactory, the following causes should be considered: non-concordance, inappropriate drug choice and the need for combination therapy.   | D |
| R96 | Adults who have had myocardial infarction or stroke should be managed intensively, according to relevant non-diabetes guidelines. In the presence of angina or other ischaemic heart disease, $\beta$ -adrenergic blockers should be considered (for use of insulin in these circumstances, see R165.)  | D |

### 8.3 Blood pressure

#### ▷ Rationale

Blood pressure is an accepted arterial risk factor. Some drugs used in blood pressure management have been suggested as having metabolic effects or interacting with insulin therapy. Accordingly blood pressure management in people with Type 1 diabetes might be different from people who do not have diabetes. However, those with developing diabetic kidney disease may have different needs again, and are considered separately in chapter 10.

#### ▷ Evidence statements

##### *Drug therapy*

A significant amount of research has been conducted into the treatment of hypertension in recent years. Primary endpoints for this research are the reduction of arterial and microvascular complications by the reduction of blood pressure to within target levels.

Three sets of national clinical guidelines have been published in the last two years – Canadian,<sup>193</sup> American,<sup>76</sup> and Scottish<sup>194</sup> – presenting rigorous systematic reviews of evidence in this area to date.

The UKPDS<sup>195</sup> randomised controlled trial (in people with Type 2 diabetes) showed that lowering blood pressure in people with diabetes reduces the risk of macrovascular and microvascular disease (Ib).

British Hypertension Society guidelines<sup>196</sup> recommend a threshold for initiating antihypertensive treatment in people with diabetes at  $\geq 140/90$  mmHg. Target blood pressure for this group of people is advised at  $<140/80$  mmHg unless nephropathy or proteinuria ( $>1$  g/24h) is present when this target is lowered to  $<130/80$  mmHg and  $<127/75$  mmHg, respectively. The guidelines also recommend that blood pressure reduction and ACE inhibitors can be employed to reduce the rate of decline in renal function in people with hypertension and diabetic nephropathy (IV).

British Hypertension Society guidelines<sup>196</sup> suggest that treatment should essentially be the same in people with Type 1 and Type 2 diabetes. Several studies are cited which provide evidence for the safety and efficacy of ACE inhibitors, dihydropyridine calcium channel blockers, low dose thiazide diuretics and  $\beta$ -adrenergic blockers in the treatment of hypertension in people with diabetes. The guidelines recommend that the choice among these drug classes should be determined using the criteria set out for people without diabetes (IV).

The large multicentre randomised ALLHAT trial<sup>197</sup> showed no superiority of a calcium channel blocker (amlodipine) or an ACE inhibitor (lisinopril) over a thiazide diuretic (chlorthalidone) in preventing major coronary events or in increasing survival in older people both with and without Type 2 diabetes. This RCT of long duration<sup>197</sup> found that lisinopril therapy had a 15% higher risk for stroke and a 10% higher risk of combined CVD compared to chlorthalidone in a mixed population with 36% of people with diabetes. The six-year absolute risk difference for combined CVD was 2.4%, which included a 19% higher risk of heart failure and 10% higher risk of hospitalised/fatal heart failure (not statistically significant), also a 11% higher risk for treated angina and 10% higher risk of coronary revascularisation were statistically significant

outcomes. Patients assigned to amlodipine had a 38% higher risk of heart failure, a six-year absolute risk difference of 2.5% and a 35% higher risk of fatal heart failure compared to those on chlorthalidone. Further long-term outcomes reported in this study showed that diuretic was superior to the calcium channel blocker in preventing major coronary events or increasing survival, although their effect on overall CVD prevention was comparable. Diuretic treatment was superior to ACE inhibitor lowering of blood pressure and in preventing aggregate arterial events (mainly stroke, heart failure, angina and coronary revascularisation) in both people with and without Type 2 diabetes (Ib).

Two meta-analyses of randomised controlled trials cited in the Scottish guidelines,<sup>194</sup> demonstrated that thiazides, beta-blockers, ACE inhibitors and calcium channel blockers are all effective in lowering blood pressure and reducing the risk of arterial events (Ia).

A large randomised controlled study of the use of an angiotensin II receptor antagonist compared to a  $\beta$ -adrenergic blocker in people with diabetes (predominantly Type 2 diabetes) found the angiotensin II receptor antagonist significantly reduced the risk of arterial mortality or stroke, and MI over four or more years of follow-up (Ia).

Randomised controlled trials reported within the SIGN guidelines<sup>194</sup> state that combination therapy is often required to reach target blood pressure, either with the same class of drug or in combination with another type of drug. The superiority of one combination regimen over another has not been examined or documented in Type 1 diabetes (Ia).

Several trials report the benefit of ACE inhibitors in producing highly significant and clinically important reductions in endpoints of MI, stroke and arterial death.

Multiple trials and systematic reviews<sup>76,174,193,198</sup> have consistently demonstrated substantial benefits from ACE inhibitors in people with Type 1 diabetes with hypertension and diabetic nephropathy. In diabetic nephropathy these antihypertensives reduce progression from micro- to macroalbuminuria and to end stage renal disease compared to placebo as reported in a well developed systematic review<sup>193</sup> (Ia).

Two sets of SIGN guidelines<sup>174,194</sup> recommend ACE inhibitors as first-line therapy in patients with microalbuminuria due to their additional benefit on renal function, based on a review of RCT-based evidence (Ia).

Adverse effects of ACE inhibitors described in clinical trials and found to be problematic in clinical use include a persistent cough (IV).

The ADA technical review<sup>76</sup> and one randomised controlled study in the Canadian guidelines<sup>193</sup> suggest that if ACE inhibitors are prescribed, serum creatinine and potassium levels should be measured at baseline and one to two weeks after initiation (Ia).

The UKPDS showed apparent equivalence of beta-blockers (atenolol) with ACE inhibitors (captopril) to moderate blood pressure in people with diabetic nephropathy; this study was in people with Type 2 diabetes and had insufficient power to show any change of clinical significance<sup>174</sup> (Ia).

Three randomised studies have shown similar reductions in proteinuria in diabetic antihypertensive patients with beta-blockers and ACE inhibitors as reported in a systematic review<sup>76</sup> (Ia).

Concern around the blunting of recovery from hypoglycaemia by beta-blockers was not

confirmed in a large randomised study on people with Type 2 diabetes, but caution is urged when prescribing to insulin-treated people with a history of severe hypoglycaemia<sup>76</sup> (Ia).

There is no robust evidence to recommend the use of alpha-blockers as first-line treatment in antihypertensive therapy. One ongoing multicentre trial is reported in a systematic review as having discontinued the alpha-blocker arm of the study due to increased incidence of arterial events in this treatment group<sup>76</sup> (Ia).

A recent meta-analysis suggests that dihydropyridine calcium channel blockers may be equivalent in protecting against stroke, but less effective in reducing MI and coronary events than ACE inhibitors, beta-blockers or diuretics<sup>76</sup> (Ia).

One randomised study<sup>199</sup> found no difference between dihydropyridine calcium channel blockers and other antihypertensive drugs with respect to diabetic nephropathy. In addition, the American guidelines<sup>76</sup> urge caution as it is difficult to compare trials studying different calcium channel blockers due to their diverse pharmacological effects (Ia).

Evidence for the use of thiazide diuretics is not as robust as for other antihypertensive therapies.<sup>193</sup> Treatment has been associated with hypokalaemia, hyponatraemia, volume depletion, hypercalcaemia and hyperuricaemia. Two retrospective studies reported in the American guidelines<sup>76</sup> suggested increased arterial mortality, and other studies have shown that thiazides may not be as effective in subjects with significantly decreased renal function (IV).

#### *Target blood pressure*

Two large multicentre trials included in a systematic review<sup>193</sup> showed an improvement in arterial and microvascular outcome in patients randomised to lower target blood pressures compared to those with less intensive blood pressure lowering. Evidence supports a treatment goal of diastolic BP <80 mmHg (Ia).

No evidence exists on the appropriate target systolic blood pressure for people with Type 1 diabetes. Consensus recommendations from the Canadian Hypertension Recommendations working group<sup>193</sup> is that systolic blood pressure should be <130mmHg (IV).

The SIGN hypertension guidelines<sup>194</sup> note that RCTs use target blood pressures of <130/80 mmHg in major outcome trials or 125/75 mmHg when proteinuria >1g/24h is present (IV).

#### *Behavioural therapy*

A rigorous systematic review performed in the production of the American Diabetes Association guidelines<sup>76</sup> on the treatment of hypertension in diabetes reported one meta-analysis of RCTs showing that dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension. However, this has not been tested in a diabetic population. No evidence exists for significant benefit of magnesium supplementation or calcium supplementation in people with diabetes (Ia).

Weight reduction has also been shown in a systematic review of non-randomised controlled trials<sup>76</sup> to reduce blood pressure independently of sodium intake and to improve glucose and lipid levels (IIa).

Smoking cessation, moderation of alcohol intake and mild physical activity have been recommended by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure to reduce blood pressure<sup>76</sup> (IV).

The American Diabetes Association guidelines<sup>76</sup> recommend that patients with a systolic blood pressure of 130–139 or diastolic blood pressure of 80–89 mmHg should be given lifestyle/behavioural therapy as first-line treatment for a maximum of three months, based on evidence from large scale RCTs (Ia).

▷ Health economic evidence

The health economic literature on Type 1 diabetes does not assess the cost-effectiveness of ACE inhibitors in lowering blood pressure in isolation. The effect of ACE inhibitors in lowering blood pressure is linked in these studies to its effects in delaying kidney damage, and the GDG felt that no recommendations in regard of blood pressure lowering alone could be drawn from the existing evidence.

▷ Consideration

The finding of raised blood pressure in people with diabetes is felt to be of different significance in the presence of nephropathy, if features of the metabolic syndrome are present, or in the absence of these findings. Other risk factors (age, ethnic group, family history, smoking) will be relevant in the last group, in whom it was felt management should echo that of non-diabetic people of the same age, but regarding the diabetes as a further substantial risk factor. (Formal risk calculation was considered above under arterial disease surveillance, and is not recommended.) The combination of raised blood pressure and nephropathy or features of the metabolic syndrome is however known to be very high risk indeed for premature arterial disease in early middle age. Accordingly intervention levels and targets should be lower and more strictly applied than for the person with 'simple' hypertension. Very many suggestions for intervention levels based on evidence have been put forward by other groups, with (allowing for the gradual evolution of evidence) considerable coherence. The group assessed all the available recommendations in this area and reached a consensus based on small differences between these.

The problems of motivating professionals and people with diabetes to manage blood pressure appropriately, despite the clear arterial and macrovascular protection to be gained, were noted to be multifactorial. Accordingly, recommendations emphasising intervention levels, targeting, informed discussions and patient-held record cards were discussed. The problem of potential and minor side effects inhibiting the achievement of major clinical gains was felt to be worth mentioning. It was noted that lifestyle interventions have a role in blood pressure management (considered in more detail in other parts of this guideline).

## RECOMMENDATIONS

- R97 Intervention levels for recommending blood pressure management should be 135/85 mmHg unless the person with Type 1 diabetes has abnormal albumin excretion rate or two or more features of the metabolic syndrome (see Table 4), in which case it should be 130/80 mmHg. See also R116–18. D

- R98** To allow informed choice by the person with the condition, the following should be discussed: **D**
- reasons for choice of intervention level
  - substantial potential gains from small improvements in blood pressure control
  - possible negative consequences of therapy.
- See also R116–18 in chapter 10.
- R99** A trial of a low-dose thiazide diuretic should be started as first-line therapy for raised blood pressure, unless the person with Type 1 diabetes is already taking a renin-angiotensin system blocking drug for nephropathy (see Chapter 10). Multiple drug therapy will often be required. **D**
- R100** Adults with Type 1 diabetes should be offered information on the potential for lifestyle changes to improve blood pressure control and associated outcomes, and offered assistance in achieving their aims in this area. **D**
- R101** Concerns over potential side effects should not be allowed to inhibit advising and offering the necessary use of any class of drugs, unless the side effects become symptomatic or otherwise clinically significant. In particular: **D**
- selective  $\beta$ -adrenergic blockers should not be avoided in adults on insulin
  - low-dose thiazides may be combined with beta-blockers
  - when calcium channel antagonists are prescribed, only long-acting preparations should be used
  - direct questioning should be used to detect the potential side effects of erectile dysfunction, lethargy and orthostatic hypotension with different drug classes.

## 9 Management of late complications: diabetic eye disease

### 9.1 Retinopathy surveillance programmes

#### ▷ Rationale

Diabetes eye damage is the single largest cause of blindness before old age. The success of laser therapy in the treatment of sight-threatening retinopathy is an accepted part of ophthalmological care and has not been assessed for this guideline. Appropriate issues which need to be addressed are, however, how people with developing retinopathy can be selected for ophthalmological referral in time for optimal treatment, and whether preventative therapy other than good blood glucose and good blood pressure control can be useful in people with Type 1 diabetes. This section deals with the structure and success of surveillance programmes, while the methods used for detection of early retinopathy, the use of alternative preventative therapies and referral guidelines to ophthalmology are considered below.

#### ▷ Evidence statements

The SIGN guideline<sup>174</sup> suggested from two comparative studies that screening is effective at detecting unrecognised sight-threatening retinopathy. Onset of pre-proliferative retinopathy was identified in one study 3.5 years after diagnosis of Type 1 diabetes in post-puberty patients, and within two months of onset of puberty (IIa).

There are discrepancies in the recommended optimal frequency of testing for diabetic retinopathy. Annual review was considered appropriate by consensus in two guidelines.<sup>174,200</sup> Testing for other diabetic complications takes place annually, and this is considered an appropriate schedule for retinopathy screening (IV).

The NICE guidelines for Type 2 diabetes<sup>201</sup> reached consensus on a more frequent need for screening (three to six months) in patients who experienced worsening of lesions or scattered exudates more than one disc diameter from the fovea or in a person with changes in blood glucose control suggesting higher risk of progression of retinopathy (NICE).

Further research is needed in increasing this screening interval for low-risk patients. Evidence from non-randomised controlled studies considered in a systematic review found that patients with no retinopathy at baseline have a less than 1% chance of developing any retinopathy within two years<sup>174</sup> (IIa).

Evidence from patient focus groups and the grey literature suggests that success of screening depends on continued consistently high levels of uptake. Patients expressed importance in discussing fear of blindness and benefits of attending regular screening. Explanations of techniques and technologies for screening including new technologies under investigation were requested. The need for eye drops and transient effects on vision should also be communicated. Multiple patient reminders did not improve attendance at screening sessions. A range of education methods is needed to encourage non-attendees (IV).

SIGN guidelines<sup>174</sup> cite cohort studies with high risk of potential confounding in their design and expert opinion indicating that patients prefer screening to be performed at a site convenient to them. Low vision clinics and community self-help groups can improve the quality of life and functional ability of patients with visual impairment. Community support, low vision aids and training, and assistance to register as blind/partially sighted should be provided to people with diabetes and visual impairment (IV).

▷ Health economic evidence

The health economic searches produced nine papers of potential interest to the guideline that fall into three distinct sets. The first set of five papers<sup>354–8</sup> present US and Swedish simulations of the cost-effectiveness of the screening for and treatment of diabetic retinopathy using a similar model structure. All these papers consider retinopathy screening at a yearly or more frequent interval. Three of the papers<sup>354–6</sup> relate to a government perspective within the US, where the cost of federal benefits for blindness is argued to be greater than the costs of a yearly (or more frequent) screening regimen for those with retinopathy. A fourth paper relates the model to Sweden,<sup>357</sup> where it is argued that retinopathy screening is cost-saving to the government. A final paper,<sup>358</sup> also US based, considers only medical costs (a health insurer standpoint) and finds a cost-effectiveness ratio of \$1,996 per QALY (1990 prices) for the yearly screening of those without retinopathy and a six-monthly screening for those with retinopathy.

Two other related papers<sup>359–60</sup> consider national retinopathy screening using an alternative model. In one of these papers, only minimal glycaemic control is assumed (HbA<sub>1c</sub> at 10%) when evaluating retinopathy, whilst the other gives insufficient details of the model or alternative strategies to allow analysis. Both papers appear to produce findings consistent with the cost-effectiveness of screening for and treatment of diabetic retinopathy.

None of the above papers consider the potential role of digital photography in detecting diabetic retinopathy at low marginal cost.

Two papers<sup>361–2</sup> consider the screening methods used in dispersed or isolated populations. Of these, one relates to a mixed population with a very low proportion of Type 1 diabetes,<sup>362</sup> whilst the other uses highly-specific cost estimates.<sup>361</sup> As no large dispersed or isolated subgroup exists within the UK, the results of these papers are not relevant for the guideline.

▷ Consideration

Members of the group recognised that some people with long-standing stable eye condition (and unchanging metabolic and blood pressure control) did not necessarily justify annual eye surveillance, but that currently the practicalities and knowledge base for identification and selection and recall of such people meant that a universal minimum recommendation of annually was the correct judgement. More frequent assessment of some individuals with changing retinopathy was noted to be cost-effective as they would otherwise have to be referred to ophthalmologists. The group were aware that future developments in the evidence base may allow for longer intervals between assessments for low-risk individuals. The importance of education of people with diabetes as to the purpose of the surveillance was agreed, while the issue of convenience of site was noted to have significant cost consequences.

## RECOMMENDATIONS

R102	Eye surveillance for adults newly diagnosed with Type 1 diabetes should be started from diagnosis.	A
R103	Depending on the findings, structured eye surveillance should be followed by: <ul style="list-style-type: none"> <li>● routine review in one year, or</li> <li>● earlier review, or</li> <li>● referral to an ophthalmologist.</li> </ul>	B
R104	Structured eye surveillance should be at one-year intervals.	A
R105	The reasons and success of eye surveillance systems should be properly conveyed to adults with Type 1 diabetes, so that attendance is not reduced by ignorance of need or fear of outcome.	C

### 9.2 Screening tests for retinopathy

#### ▷ Rationale

The success of laser therapy in the treatment of sight-threatening retinopathy is an accepted part of ophthalmological care and has not been assessed for this guideline. The appropriate issue to be addressed is, however, how people with developing retinopathy can be selected for ophthalmological referral in time for optimal treatment. This section deals with the methods used for detection of early retinopathy, the structure of surveillance programmes having been covered in the previous section, while other therapy issues are covered in 9.3.

#### ▷ Evidence statements

##### *Ophthalmoscopy*

Direct ophthalmoscopy does not usually meet the required standards for retinopathy screening and review.<sup>201</sup> Sensitivity achieved by GP and optometrist screening with ophthalmoscopes is very low<sup>201–202</sup> (NICE).

##### *Ultra-wide angle screening laser ophthalmoscope*

Little evidence is available in this area. One comparative study conducted on healthy individuals reported in a systematic review is of limited applicability clinically<sup>202</sup> (Ia).

##### *Slit lamp biomicroscopy*

A diagnostic study quoted in a systematic review found that slit lamp biomicroscopes with dilated indirect ophthalmoscopy used by properly-trained individuals can achieve sensitivities similar to retinal photography, with a lower technical failure rate<sup>202</sup> (DS).

A systematic review concluded that slit lamps are always needed for those not amenable to digital photography<sup>202</sup> (IV).

### *Retinal photography*

Retinal cameras have the highest level of accuracy of any practical screening method,<sup>203</sup> and provide permanent images for quality control. Retinal photography is more effective than direct ophthalmoscopy and can regularly achieve a sensitivity of 80%<sup>174</sup> (DS).

Photography is more accurate at detecting the presence of microaneurysms than ophthalmoscopy and may be of use in milder disease states<sup>203</sup> (Ib).

A low percentage of retinal photographs are ungradeable, although this may be improved by digital imaging. Accuracy is not dependent on the type of professional involved, but data from non-randomised controlled studies underlines the need for training in reading the photographs or images<sup>202</sup> (IIa).

Limited evidence exists on the number of fields that should be viewed with a retinal camera. One systematic review<sup>202</sup> considering diagnostic studies showed that single-field studies gave marginally better results than those with two or more fields (DS).

Digital cameras show similar accuracy to conventional photography but have advantages in image transfer and potential for automated grading.<sup>202</sup> Technical failure rates are lower with digital cameras (DS).

Further evaluation of digital imaging techniques is needed to prove the usefulness of this screening method<sup>174</sup> (IV).

There are inconsistent results and conclusions from randomised trials regarding the use of mydriasis in retinal photography reported in a systematic review<sup>202</sup> (Ia).

The Health Technology Board for Scotland assessment report<sup>202</sup> states that there is no clear evidence that mydriasis or the routine use of more than one image significantly alters the sensitivity or specificity of screening for the detection of sight-threatening retinopathy. The review concludes that there is little difference between the accuracy and failure rates of modern cameras when used with or without mydriasis; however, the analysis of failure after non-mydriatic photography may have favoured no difference to outcome. Comparable screening accuracy is achieved with digital cameras, with or without mydriasis, however direct comparisons suggest that mydriasis may occasionally result in a successful image when non-mydriatic imaging fails (DS).

A large diagnostic study of screening services in both hospital and district settings<sup>204</sup> found screening tests by trained retinal screeners to have a high sensitivity and very high specificity to detect sight-threatening diabetic retinopathy as assessed by slit lamp examination (DS).

NICE Type 2 diabetes guidelines<sup>201</sup> suggest that mydriatic 45° retinal photography is the most effective test when screening for diabetic retinopathy (NICE).

If more than one image per eye is required for screening then mydriasis is essential because of constriction of the pupil caused by the first photographic flash (IV).

Tropicamide (0.5%–1%), administered by a trained professional is a safe and appropriate way to perform mydriasis<sup>174</sup> (NICE).

The use of pilocarpine to reduce mydriasis is potentially harmful<sup>202</sup> (IV).

Blurred vision and sensitivity to light are complications of the instillation of eye drops for mydriasis. Other related side effects such as glaucoma and allergic reactions are rare<sup>205</sup> (IV).

**Table 5 Mydriasis with tropicamide**

Mydriasis with tropicamide:

- reduces the failure rate (inadequately interpretable photographs) in around 5% of eyes of people with diabetes (in particular in the second eye and in the elderly), and thus the need for recall for a further examination when tropicamide will be necessary
- allows follow-up ophthalmoscopy to be optimised reducing false-negative referrals to ophthalmologists
- carries no detectable risk to the eye except in the post-surgical period
- is briefly uncomfortable (stings)
- paralyses accommodation (near vision) and pupil constriction for 30–60 minutes (low dose), but in some people for much longer, giving problems with glare and bright light sufficient to impair vision to unsafe levels for some tasks (for example driving).

No studies reported whether differences found in sensitivities of healthcare professionals undertaking tests were statistically significant. Comparable sensitivity is achieved by GPs and optometrists using a direct ophthalmoscope through dilated pupils. Optometrists using slit lamp biomicroscopy only achieved moderate sensitivity (62% sensitivity at 95% specificity). The greatest sensitivity was found in comparative studies used in a systematic review with trained graders using mydriatic and non-mydriatic photography<sup>202</sup> (DS).

Initial data indicates that high-resolution automated grading systems compared to conventional grading can identify the absence of microaneurysms on digital images with a high sensitivity<sup>202</sup> (Ia).

A systematic review<sup>202</sup> included a descriptive study evaluating a system for referring photographs to the next level of expertise. Referral when the grader identified any potential sign of retinopathy, with the more experienced professionals involved in the second and third levels, helped maintain effective analysis of images (IV).

Diabetes UK consensus is that an effective screening system should achieve a technical failure rate of less than 5%<sup>206</sup> (IV).

A systematic review<sup>202</sup> reported inconsistent findings from controlled studies of the impact of disease condition and progression of disease on test failure rates (IIa).

Lower technical failure rates are achievable with digital photography compared to conventional slide photography. Failure rates for ophthalmoscopy do not differ greatly from photography in controlled studies reported within a systematic review<sup>202</sup> (IIa).

There is a lack of discrete evidence about the role and usefulness of visual acuity testing. The NICE Type 2 diabetes guideline retinopathy working-group<sup>201</sup> supported the consensus guidelines from the Royal College of Ophthalmologists on the usefulness of visual acuity testing as part of the overall eye care approach (NICE).

Diagnosis of macular oedema rests on the use of stereoscopic, slit lamp, indirect ophthalmoscopy in expert hands. Due to the difficulty of differentiating non-significant and clinically significant macular oedema, the use of visual acuity testing is recommended for screening in routine practice. Reduced visual acuity is an indication for specialist referral<sup>201</sup> (NICE).

▷ Consideration

The group felt that earlier judgements (for example NICE Inherited Type 2 diabetes guideline) that digital photography best met the needs of appropriate sensitivity/selectivity, feasibility and opportunities for quality assurance were clearly endorsed by the evidence review and personal experience of Group members. Mydriasis was noted to be of particular importance in particular groups of people in whom some form of ophthalmoscopy was commonly required to complete a quality examination after photography, and appears safe if inconvenient to some people. It was strongly endorsed. Patient preference studies have suggested that mydriasis may reduce attendance for retinopathy screening because of its temporary effect on vision, but there is no recorded clinical evidence to suggest this. Visual acuity testing, while ill-evidenced, was noted to be fast and non-invasive (though requiring trained staff to test), and provided a useful function in helping detect unsuspected macular oedema, a critical but treatable condition.

## RECOMMENDATIONS

- |      |  |        |
|------|--|--------|
| R106 | Digital retinal photography should be implemented for eye surveillance programmes for adults with Type 1 diabetes.   | B      |
| R107 | Mydriasis with tropicamide should be used when photographing the retina, after prior agreement with the person with Type 1 diabetes following discussion of the advantages and disadvantages, including appropriate precautions for driving. | B<br>D |
| R108 | Visual acuity testing should be a routine part of eye surveillance programmes.   | D      |

### 9.3 Referral

▷ Rationale

The issues of surveillance programmes, screening technologies and non-blood glucose/non-blood pressure therapies for prevention are considered in the immediately prior and following sections of this guideline. This section considers the issue of how quickly a person with diabetes should be seen by an ophthalmologist once potentially sight-threatening retinopathy is detected.

▷ Evidence statements

The SIGN guidelines<sup>174</sup> showed from controlled trials that poor outcomes and severe visual loss are associated with a delay in treatment of over two years from diagnosis of sight-threatening diabetic retinopathy. This figure was one year for vitrectomy (IIa).

▷ Consideration

The group felt it inappropriate to derive and recommend new referral guidelines without detailed review of the ophthalmological literature, particularly as such guidelines were already published by the Royal College of Ophthalmologists and the National Screening Committee diabetic retinopathy screening group ([www.nscretinopathy.org.uk](http://www.nscretinopathy.org.uk)). In the area of assessment of macular oedema it was noted that retinal screening recommendations using digital photography (see section 9.2, 'Screening tests for retinopathy') could not inform the referral

process suggested by the RCO guideline; thus use of unexplained change in visual acuity was substituted, reflecting current practice.

## RECOMMENDATIONS

- R109** Emergency review by an ophthalmologist should occur for: **D**
- sudden loss of vision
  - rubeosis iridis
  - pre-retinal or vitreous haemorrhage
  - retinal detachment.
- R110** Rapid review by an ophthalmologist should occur for new vessel formation. **D**
- R111** Referral to an ophthalmologist should occur for: **D**
- referable maculopathy:
    - exudate or retinal thickening within one disc diameter of the centre of the fovea
    - circinate or group of exudates within the macula (the macula is defined here as a circle centred on the fovea, of a diameter the distance between the temporal border of the optic disc and the fovea)
    - any microaneurysm or haemorrhage within one disc diameter of the centre of the fovea, only if associated with a best visual acuity of 6/12 or worse
  - referable pre-proliferative retinopathy (if cotton wool spots are present, look carefully for the following features, but cotton wool spots themselves do not define pre-proliferative retinopathy):
    - any venous beading
    - any venous loop or reduplication
    - any intraretinal microvascular abnormalities (IRMA)
    - multiple deep, round or blot haemorrhages.
  - any unexplained drop in visual acuity.

## 9.4 Non-surgical treatment of diabetic retinopathy

### ▷ Rationale

The means and systems of detection of diabetic retinopathy in sufficient time to allow successful laser therapy are considered in the previous three sections. However, laser therapy is a destructive salvage therapy, and prevention by good blood glucose and good blood pressure control are not as yet absolutely successful. Accordingly it is important to consider whether other approaches can delay the development of retinopathy in people with Type 1 diabetes.

### ▷ Evidence statements

There is a lack of robust evidence for non-surgical, non-laser treatment of diabetic retinopathy. In general, trials in this area have limitations in their methodology.

The SIGN guideline<sup>174</sup> addressed the absence of good evidence for use of ACE inhibitors in diabetic eye disease. One multicentre RCT examined therein is methodologically limited. Trials

with ACE inhibitor therapy are ongoing but at present there is inconclusive evidence in this area (Ia).

There is limited evidence from trials with the antiplatelet agents ticlopidine<sup>207–208</sup> and dipyridamole<sup>209</sup> that measures for deterioration of retinopathy were significantly lower in patients treated with antiplatelet agents compared to placebo, although potential methodological limitations would prevent this evidence forming the basis of a clinical recommendation. Ticlopidine has a high incidence of side effects (Ib).

One three-year study<sup>210</sup> showed a sevenfold reduction in the number of definite annual microaneurysms compared to placebo in insulin-treated patients, and an inverse relationship between progression of microaneurysms and hypo-aggregability level in patients treated with ticlopidine. The trial in this treatment area is of moderate size (Ib).

A recent randomised controlled trial<sup>211</sup> showed high dose vitamin E significantly reduced mean circulation time and increased retinal blood flow in diabetic patients. No differences were seen in retinopathy level between the placebo and vitamin E groups (Ib).

▷ Consideration

Issues of blood glucose control, blood pressure control or smoking are covered in chapters 7 and 8. Outside these indications the evidence was not felt to be strong enough to justify any recommendation. As this is in line with current practice, no negative recommendations were felt to be needed.

# 10 Management of late complications: diabetic kidney disease

## 10.1 Kidney damage

### ▷ Rationale

Kidney damage in Type 1 diabetes is the largest cause of renal failure in the working age group. Primary prevention by good blood glucose and good blood pressure control is considered elsewhere in this guideline while this section deals with the early detection and management of developing diabetic nephropathy.

### ▷ Evidence statements

#### *Predictors of nephropathy*

One seven-year longitudinal study<sup>212</sup> showed the ability to predict progression to diabetic nephropathy by the presence of microalbuminuria may not be as reliable as previous studies have assumed. Approximately 19% to 24% of patients with microalbuminuria develop diabetic nephropathy. Systolic blood pressure, glycated haemoglobin and triglycerides were significantly higher in people with Type 1 diabetes who progressed to diabetic nephropathy, than for those who did not (III).

Five year follow-up<sup>213</sup> of microalbuminuric patients with Type 1 diabetes showed 19% progressed to diabetic nephropathy and 33% regressed to normoalbuminuria. Progressors had significantly higher HbA<sub>1c</sub> and mean blood pressure and incidence of proliferative retinopathy compared to non-progressors (III).

Another seven-year prospective study<sup>214</sup> in 148 normotensive people with diabetes showed that baseline albumin excretion rate (AER) is the predominant predictor for the development of microalbuminuria in Type 1 diabetes. Raised mean arterial blood pressure and HbA<sub>1c</sub> also were significantly related to progression to microalbuminuria (III).

A cohort study of two years follow-up<sup>215</sup> showed in sex-specific analysis that HbA<sub>1c</sub>, age and baseline AER were particularly important predictors of progression to nephropathy in men, whereas duration of diabetes and triglycerides were particularly important in women. Low-density lipoprotein (LDL) cholesterol was particularly important in people with shorter duration of diabetes and triglycerides in those with a longer diabetes duration (IIa).

A case-controlled study with 10-year follow-up<sup>216</sup> showed that baseline glomerular filtration rate (GFR), although not a predictor of end-point AER or microalbuminuria, was a significant predictor of end-of-study blood pressure level. Levels of AER and blood pressure were the main risk factors for renal outcome. A further five-year prospective study<sup>217</sup> showed that in patients with microalbuminuria decline in GFR was independently correlated to onset of diabetic nephropathy and baseline systolic blood pressure (IIa).

### *Screening and diagnosis*

The SIGN diabetes guidelines<sup>174</sup> include one comparative study showing that measurements of albumin loss and serum creatinine are the best screening tests for diabetic nephropathy (III).

Urine albumin concentration compared to urine albumin:creatinine ratio in a screening accuracy test<sup>218</sup> showed specificity and sensitivity for microalbuminuria of 77% and 82% and 77% and 92% and for macroalbuminuria levels of 84% and 90%, and 88% and 90%. No statistically significant difference was seen when comparing the performance of these two measures in detecting nephropathy (DS).

Both albumin concentration and albumin:creatinine ratio measured on a first-pass morning urine sample and compared against timed collection of urinary albumin excretion rate, showed high sensitivity and specificity for normal and elevated albuminuria.<sup>219</sup> Combining the two tests together in the same urine sample revealed the highest sensitivity (98%) and specificity (100%) (DS).

A comparative study reported in the SIGN guidelines<sup>174</sup> reports that first-pass morning urine samples best reflect a timed collection and provide adequate assessment of urinary albumin loss (III).

One test accuracy study comparing 24-hour urine collection with spot-urine samples<sup>220</sup> showed both samples were accurate for the screening and diagnosis of diabetic nephropathy. Urinary protein better correlates with the reference standard (urinary AER) in macroalbuminuric (0.95) and microalbuminuric (0.80) samples, than in normoalbuminuric samples (0.61) (DS).

A 10-year follow up study<sup>221</sup> showed the predication of microalbuminuria is most effective in a four-hour morning urine collection with a greater specificity than 24-hour collection (positive predictive value 91% vs 79%), and is similar to the overnight collection, but with a greater sensitivity (DS).

One screening test study<sup>222</sup> showed significant intraindividual variation of urinary albumin excretion between samples taken in triplicate for seven days. Mean coefficient of variation was 49%. Urinary albumin excretion >1.0 mg/mmol on the first specimen had a sensitivity of 97% and specificity of 82% for detection of those with a three sample mean >2.5 mg/mmol (DS).

A microalbumin analyser was shown in one screening test accuracy study<sup>223</sup> to have sensitivity, specificity, negative predictive and positive predictive values of 92%, 100%, 93% and 100% respectively, suggesting a high reproducibility and reliability for microalbuminuria detection. Another accuracy study<sup>224</sup> showed a different device to have sensitivity, specificity and negative and positive predictive value of 100%, 97%, 100% and 96% respectively (DS).

A semi-quantitative diagnostic test<sup>225</sup> reported sensitivity of 86% and specificity of 67% to estimate albumin excretion rate as a screening tool for microalbuminuria. This was considerably lower than the reference standard of albumin concentration (sensitivity 75% and specificity 94%) using the Micral test, which itself is not an effective screening tool for microalbuminuria. A further three studies<sup>226–228</sup> of similar design, predominantly comparing Micral test with urinary albumin excretion rates returned varying results in terms of accuracy. However all suggested a lower sensitivity of Micral test for the detection of albuminuria (DS).

One correlation study<sup>229</sup> reporting on self-testing with the Micral test found that 80% of patients classified themselves correctly. Using at least two positive test results increased the specificity and sensitivity to 81% and 92% with a positive predictive value 71% leading to 90% of all patients classifying themselves correctly (III).

One correlation study<sup>230</sup> showed that the dipstick testing method was insensitive or not adequately specific to detect abnormal overnight albumin excretion rate. This study had potential internal validity limitations and should not be used as the basis for a positive clinical recommendation (III).

One diagnostic study<sup>231</sup> of a Clinitek microalbumin test method performed in 302 people with diabetes demonstrated sensitivity and specificity of 79% and 81% and negative and positive predictive values of 46% and 95% for determining microalbuminuria (DS).

### *Management of nephropathy*

The SIGN guideline<sup>174</sup> reports results from the DCCT showing that a reduction in mean HbA<sub>1c</sub> from 9.0% to 7.3% was associated with a 39% and 54% reduction in the occurrence of microalbuminuria and proteinuria respectively over 6.5 years. However, no clear benefit was seen in the treatment of established microalbuminuria in people with Type 1 diabetes (Ia).

Three prospective studies within the SIGN guideline<sup>174</sup> reported reductions in AER with ACE inhibitors in people with both microalbuminuria and proteinuria. In the former group blood pressure of 112/73 and 122/79 mmHg was associated with a 30% and 18% reduction in AER at 30 and 24 months (Ia).

SIGN guidelines<sup>174</sup> report results from an RCT that ACE inhibitors are more effective than other agents in reducing urinary albumin loss. Three years therapy was associated with a 50% reduction in a combined end-point of death, dialysis or transplantation, this effect was independent of blood pressure (Ia).

A Cochrane systematic review<sup>232</sup> demonstrated the effect of ACE inhibitors on normotensive people with microalbuminuria or overt albuminuria, showing a reduction in albumin excretion rate in patients receiving ACE inhibition compared to placebo. Antihypertensive therapy also reduced blood pressure in treated patients, compared to placebo-treated controls, with no significant effect on GFR or HbA<sub>1c</sub>. All three ACE inhibitors included in this study had comparable effects (Ia).

A meta-analysis of individual patient data<sup>233</sup> demonstrated a marked benefit in terms of AER being 54% lower in patients receiving ACE inhibitor treatment, compared to those on placebo. Only a small fraction of this effect was due to a decrease in systolic blood pressure. There was a clear gradation in beneficial effect depending on baseline AER. The two-year difference for patients with baseline AER ~200 µg/min was 75% compared with 18% in patients with AER ~20 µg/min at baseline (Ia).

A medium-sized randomised controlled trial<sup>234</sup> of 89 normotensive patients failed to show any significant effect of ACE inhibitor treatment on mean arterial BP or creatinine clearance among people with Type 1 diabetes without microalbuminuria followed up for five years (Ib).

Three RCTs compared the effect of ACE inhibitors and calcium channel blockers<sup>235–7</sup> in people with Type 1 diabetes, over follow-up periods of one to four years. One study showed reductions

in blood pressure with either agent compared to placebo, but no effect on AER or GFR.<sup>235</sup> The other two studies showed a significantly greater decline in albuminuria in patients treated with the ACE inhibitor, but no other differences between the two treatments.<sup>236–7</sup> Some side effects of calcium channel blockers were seen in all of these studies (Ib).

No methodologically robust evidence exists on the use of angiotensin 2 receptor antagonists in the management for nephropathy in people with Type 1 diabetes specifically.

NICE guidelines on Type 2 diabetes<sup>201</sup> report an equally beneficial effect of angiotensin 2 receptor antagonists and ACE inhibitors on renal function in normotensive and hypertensive patients. However, the guidelines comment that the evidence base for angiotensin 2 receptor antagonists is still emerging and caution is urged when making specific recommendations for their use as first-line therapy (NICE).

SIGN guidelines<sup>174</sup> recommend angiotensin 2 receptor antagonists should be considered for people with Type 2 diabetes with microalbuminuria or proteinuria (Ia).

Two meta-analyses are reported in the SIGN guidelines.<sup>174</sup> These found a reduction of dietary protein to 0.6 to 0.8 g/kg/day was associated with a reduction in the rate of GFR loss in people with proteinuria and impaired renal function, and sensitivity analysis suggested this effect was greater in people with diabetes (Ia).

One Cochrane systematic review<sup>238</sup> showed a slight slowing of the decline in GFR following low protein diet for six to 24 months follow-up (mean change in GFR  $-1.0$  and  $-0.3$  (ml/min) for control and treatment groups respectively). All studies included in this review are small and an exact level of protein restriction has yet to be established (Ia).

One systematic review<sup>239</sup> that included randomised and non-randomised trials reported eight studies of which some showed significant delay in progression of nephropathy following protein-restricted diets, compared to conventional care. However, some of these studies were methodologically limited by not having sufficient follow-up time to detect particular outcomes (Ia).

Two additional RCTs<sup>240–1</sup> were identified in this area. In one study dialysis, transplantation and death occurred in 27% and 10% of patients receiving a usual protein vs a low protein diet respectively. Mean blood pressure during follow-up was higher in the usual protein diet group. GFR was comparable between the two groups. The second study found no significant difference in renal function following low protein diet but a significant decrease in body weight and obesity index were seen at the end of 12 months follow-up (Ib).

One RCT<sup>242</sup> found no effect of fish oil supplementation on the progression of renal function and albuminuria in normotensive patients with diabetic nephropathy (Ib).

### *Referral*

There are no studies directly examining the appropriate timing of referral of people with Type 1 diabetes and diabetic nephropathy to a renal specialist.

Strong explicit consensus in the NICE guidelines<sup>243</sup> for Type 2 diabetes was for specialist referral when serum creatinine is greater than 150  $\mu\text{mol/l}$  (NICE).

SIGN guidelines<sup>174</sup> state that although no evidence exists on a time to referral, most renal physicians would prefer patients to be referred earlier rather than later (IV).

▷ Health economic evidence

The health economic literature relating to the method of surveillance for emerging kidney damage produced four papers.<sup>363–6</sup> Three of these papers concentrated on the costs of testing, and largely ignored later outcomes. The fourth of these papers<sup>366</sup> presents a cost-utility analysis of laboratory testing *vs* double dipstick testing plus laboratory assays where either result is positive. However, this paper employs a non-standard QALY measure and this limits the robustness of the conclusions.

Five studies<sup>367–71</sup> consider ACE inhibitor use for those found to have proteinuria following screening. One paper<sup>370</sup> was excluded as it was predicated on a significantly different healthcare system than that of the UK. The remaining four papers argued that ACE inhibitor treatment will be cost-saving in those found to exhibit proteinuria.

The cost-effectiveness of ACE inhibitor treatment of those with microalbuminuria<sup>372–5</sup> is also analysed in four papers based outside of the UK, of which two consider benefits from arterial disease in addition to the benefits of delaying or preventing nephropathy.<sup>374–5</sup> Two papers<sup>372,374</sup> suggest ACE inhibitor treatment will be cost-effective on both base case and sensitivity analysis. One cost-utility study<sup>373</sup> (interpretation of which is limited by possible typographic errors in the calculations) considers nephropathy benefits only and suggests ACE inhibitor treatment is cost-effective on their base case analysis but not in sensitivity testing. A final paper considers both nephropathy and arterial benefits and finds a high cost per life year saved.<sup>375</sup>

▷ Consideration

The issue of blood glucose control and its role in the development of microvascular complications is considered elsewhere in this guideline.

While there was no formal evidence on frequency of testing in the individual without previous evidence of nephropathy, organisational issues and the slow time course of progression of nephropathy suggested yearly surveillance in concert with eye and foot surveillance. For perceived reasons of convenience and adherence, spot urine specimens were considered more useful than timed collections, and, because of the effects of activity on albumin excretion rate, first-pass specimens on rising ('early morning urine') the most desirable. As urine concentration varies considerably between and within individuals, the general recommendation to measure an albumin:creatinine ratio was accepted, but if this was not organisationally practical a specific and sensitive concentration test could be used. Once positive, confirmation is recommended given the variability of albumin excretion rate from day to day. It was not felt that confirmation required a further clinic visit if one was already scheduled at three to four month intervals, unless there was evidence of renal impairment or non-diabetic renal disease. It seems sensible to measure serum creatinine annually at the same time. There is a need to consider the possibility of renal disease unrelated to diabetes.

Effectiveness and cost-effectiveness evidence suggests that ACE inhibitors should be used as first-line therapy in people with Type 1 diabetes once albumin excretion rate is detectably abnormal. Discussion of side effects noted the more serious of these (hyperkalaemia and acute renal impairment) related mostly to people with Type 2 diabetes. No direct evidence for angiotensin 2 receptor antagonists in Type 1 diabetes had been found, but as the microvascular complications

of diabetes seem independent of aetiology of diabetes, the Group felt that evidence from Type 2 diabetes could be extrapolated. However, being more expensive, these should be reserved as second-line therapy. Combination therapy seems likely to be effective but no recommendation is appropriate until more evidence on benefit and risk in this area is available.

While it was not found that a low protein diet was sufficiently well supported to be recommended for people with evidence of established diabetic nephropathy, it was felt that formal advice on a non-high protein diet should be given. In the absence of useful evidence, the group were unable to set an arbitrary referral cut-off based on one biochemical measure, but agreed to leave this to local collaborative arrangements between specialists.

## RECOMMENDATIONS

See also recommendations for blood pressure in section 8.3.

- |      |  |    |
|------|--|----|
| R112 | All adults with Type 1 diabetes, with or without detected nephropathy, should be asked to bring in a first-pass morning urine specimen once a year. This should be sent for estimation of albumin:creatinine ratio. Estimation of urine albumin concentration alone is a poor alternative. Serum creatinine should be measured at the same time. | D  |
| R113 | If an abnormal surveillance result is obtained (in the absence of proteinuria/urinary tract infection), the test should be repeated at each clinic visit or at least every three to four months, and the result taken as confirmed if a further specimen (out of two more) is also abnormal (>2.5 mg/mmol for men, >3.5 mg/mmol for women).      | DS |
| R114 | Other renal disease should be suspected: <ul style="list-style-type: none"> <li>● in the absence of progressive retinopathy</li> <li>● if blood pressure is particularly high</li> <li>● if proteinuria develops suddenly</li> <li>● if significant haematuria is present</li> <li>● in the presence of systemic ill health.</li> </ul>          | DS |
| R115 | The significance of a finding of abnormal albumin excretion rate should be discussed with the person concerned.  | D  |
| R116 | ACE inhibitors should be started and (with usual precautions) titrated to full dose in all adults with confirmed nephropathy (including those with microalbuminuria alone) and Type 1 diabetes.  | A  |
| R117 | If ACE inhibitors are not tolerated, angiotensin 2 receptor antagonists should be substituted. Combination therapy is not recommended at present.  | B  |
| R118 | Blood pressure should be maintained below 130/80 mmHg by addition of other anti-hypertensive drugs if necessary.   | D  |
| R119 | Adults with Type 1 diabetes and nephropathy should be advised about the advantages of not following a high protein diet.   | B  |
| R120 | Referral criteria for tertiary care should be agreed between local diabetes specialists and nephrologists.   | D  |

# 11 Management of late complications: diabetes foot problems

## 11.1 Screening and surveillance of diabetic foot problems

### ▷ Rationale

Foot ulceration, foot infection, foot and limb amputation and some forms of deformity (including Charcot arthropathy) are major forms of disability arising from Type 1 diabetes. Prevention and management of such problems depends on detection of risk factors, and of markers of predisposing problems including neuropathy and vascular disease, as well as more diverse factors such as poor footwear and skin condition. Accurate and programmed surveillance for such risk factors is required if efficient use is to be made of education programmes and the services of those with special expertise in management of individuals with particularly high risk of foot ulceration.

### ▷ Evidence statements

#### *Monitoring*

The major risk factors for foot complications have been identified in several systematic reviews<sup>174,244</sup> as history of ulceration and lack of sensation.

The NICE *Clinical guidelines for Type 2 diabetes*<sup>244</sup> reported inconsistent evidence of markers associated with foot complications from nine studies using a range of methods and patient data. These included: old age, duration of diabetes, neuropathy, peripheral vascular disease, renal disease, foot deformities, plantar callus, previous ulceration or amputation, poor vision, poor footwear, cigarette smoking, social deprivation and social isolation (NICE).

The NICE guideline<sup>244</sup> also reported five surveys investigating additional risk factors for the elderly, concluded that suboptimal supervision of elderly patients in hospital, residential care and general practice increases their risk of ulceration and amputation (NICE).

#### *Organisation of screening programmes*

The SIGN guidelines<sup>174</sup> note that absence of reliable symptoms and the high prevalence of asymptomatic disease make foot screening essential (IV).

One large comparative trial in a systematic review<sup>245</sup> of a combined screening and foot protection programme reported a statistically significant reduction in major amputations over a two-year period compared to normal organisation of care (Ia).

The NICE clinical guidelines<sup>244</sup> report a Cochrane review comparing trials of general practice vs hospital care for recall and review of foot problems, and conclude that despite the methodological flaws in these trials a system of shared care – joint participation between hospitals and general practices – provides levels of surveillance as good as hospital diabetic clinic attendance alone (NICE).

Information exchange between specialists is advocated in one review in the NICE Type 2 diabetes guidelines.<sup>244</sup> However, no evidence exists to specify the components of these procedures (NICE).

The guidelines foot care working party<sup>244</sup> also endorsed the findings of Diabetes UK that a multidisciplinary team of professionals should be available to promptly provide the full range of appropriate foot care services to patients (NICE).

#### *Detection of loss of foot sensation*

SIGN guidelines<sup>174</sup> concluded from three studies that neuropathy screening performed by using clinical neuropathy disability scores, 10 g monofilaments or vibration perception thresholds, alone or in combination, have benefits in selecting patients at increased risk of foot ulceration (DS).

Additional techniques available for assessing neuropathic deficit that are considered in SIGN guidelines<sup>174</sup> include tactile circumferential discriminator, the graduated tuning fork, thermal discrimination devices and others. These techniques have not been prospectively evaluated but generally compare with other techniques for detection of ulcers (IV).

There is general agreement in systematic reviews and guidelines<sup>174,244</sup> that the 5.07 monofilament (10g) is cheap and easy to use compared to other neuropathic tests and is the recommended screening test for neuropathy as a risk factor for diabetes foot ulcers (IV/NICE).

A systematic review<sup>246</sup> of a particular monofilament and other threshold tests for preventing ulceration and amputation in people with diabetes found this design of monofilament correlated best with the presence or history of an ulcer. Evidence varies as to the appropriate number of sites to use with this technique, the majority of studies testing at  $\geq 1$  site. The plantar surface of the forefoot provides the best discrimination between those who did and did not have ulcers (III).

Four prospective studies included in a systematic review<sup>246</sup> described a strong predictive ability of the monofilament test for future foot ulceration and amputation and a high reproducibility (DS).

Within a systematic review<sup>246</sup> two non-randomised studies reported physical symptoms of tingling, burning, hyperaesthesia and other uncomfortable sensations affecting >40% of people with diabetes after diagnosis. However, two separate studies reported poor correlation of pain symptoms with foot ulceration (III).

Prospective evidence is sparse for traditional clinical assessment,<sup>246</sup> using pinprick, tuning fork vibration or light touch with a cotton wisp. While the reproducibility of these investigations is low, replicability is slightly better for ankle jerks; however these tests are considered poor predictors of ulceration (DS).

Two-point discrimination was shown in one study in a well-produced systematic review<sup>246</sup> to be more sensitive but less specific than monofilament or vibration perception threshold (VPT) testing. Temperature sensation was found in two studies to be cumbersome and irritating and correlated less well with risk of ulceration compared to monofilament or VPT (DS).

One further medium-sized diagnostic study<sup>247</sup> described the comparability of a new technique combining a monofilament and pinprick test to reference standard tests. The new technique was found to have good correlation with VPT and a neuropathy disability score assessment, and a specificity and sensitivity of roughly 80% and 70% respectively in detecting both neuropathy disability score and VPT results identifying moderate to severe neuropathy (DS).

*Detection of peripheral vascular disease*

Screening for vascular insufficiency is less well documented than ulceration in existing reviews<sup>174</sup> (IV).

Two studies in the SIGN guidelines<sup>174</sup> note that absence of pedal pulses can be used in first-line screening as a guide to peripheral vascular disease. Evidence from one study urges caution when evaluating ankle pressure and pressure indices, which can be falsely elevated in people with diabetes (DS).

A systematic review<sup>248</sup> of observational studies noted a restricted accuracy of pedal pulses in identifying severe peripheral ischaemia (DS).

The validity of Doppler ultrasonography to determine ankle-brachial index as an indicator of peripheral blood flow was also questioned by one study in a systematic review.<sup>248</sup> The study noted that calcification of the media of the distal arteries, common in diabetes, may lead to artificially high systolic pressure in the ankle (DS).

▷ Health economic evidence

The health economic search found no papers specific to foot care screening or treatment in Type 1 diabetes. As the Type 2 diabetes foot care guideline will use all the information identified in the health economic searches, and may use other information excluded in the search process, the specific health economic recommendations from this guideline should be applied here.

The only exception to this comes in the cost-effectiveness of cultured human dermis where additional modelling was undertaken. Two economic evaluations<sup>376–7</sup> were identified from the literature for Dermagraft, of which one paper used UK cost data,<sup>377</sup> but the results were unpublished. The remaining paper<sup>376</sup> considers French cost-effectiveness in terms of cost per ulcer healed over 52 weeks. This model was replicated by the health economist in the GDG, but its findings could not be duplicated. No conclusion can therefore be drawn from these studies.

This replicated model was used to construct an estimate of the cost-effectiveness of Dermagraft in QALY terms using published health utility values. Dermagraft does not appear to be a cost-effective treatment for diabetic foot ulcers on the basis of this model. Furthermore, as the clinical data underlying this model relates to long-standing ulcers that may be less likely to heal with standard treatment, the general cost-effectiveness of Dermagraft for all non-recurrent ulcers free of infection is likely to be worse than the figures produced here.

▷ Consideration

The group noted that this area had been examined by other quality guideline groups both internationally and for Type 2 diabetes. No reason for being inconsistent with those recommendations could be found, although for the most part people with foot problems and Type 1 diabetes had predominantly neuropathic problems rather than neuroischaemic problems. Annual foot review was thought desirable for reasons of both foot surveillance and education. The simple and effective utility of the monofilament was noted.

## RECOMMENDATIONS

- |      |  |    |
|------|--|----|
| R121 | Structured foot surveillance should be at one-year intervals, and should include educational assessment and education input commensurate with the assessed risk.   | D  |
| R122 | The reasons for, and success of, foot surveillance systems should be properly conveyed to adults with Type 1 diabetes, so that attendance is not reduced by ignorance of need.   | D  |
| R123 | Inspection and examination of feet should include: <ul style="list-style-type: none"><li>● skin condition</li><li>● shape and deformity</li><li>● shoes</li><li>● impaired sensory nerve function</li><li>● vascular supply (including peripheral pulses).</li></ul> | D  |
| R124 | Use of a 10 g monofilament plus non-traumatic pin prick is advised for detection of impairment of sensory nerve function sufficient to significantly raise risk of foot ulceration.  | DS |

### 11.2 Management of foot ulceration and associated risk factors

#### ▷ Rationale

Diabetes foot problems lead to significant morbidity and healthcare costs from foot ulceration and limb amputation. In Type 1 diabetes the predominant risk factor is the development of somatic sensory neuropathy, although peripheral vascular disease may contribute to the risks in some people. Poor blood glucose control can interfere with healing and control of infection where skin damage occurs.

#### ▷ Evidence statements

There were no randomised controlled trials identified from the search of interventions for managing foot ulceration and infection in populations with Type 1 diabetes specifically. We therefore recommend following the Type 2 diabetes guideline for foot care, which considered evidence from trials with populations with Type 2 diabetes, and mixed Type 1 and Type 2 diabetes ([www.nice.org.uk](http://www.nice.org.uk)) (NICE).

#### ▷ Consideration

The group noted the draft recommendations of the updated Type 2 diabetes foot care guideline, and the differences between Type 1 and Type 2 diabetes in respect of this area, mainly arising as a result of the lesser impact of peripheral vascular disease in people with Type 1 diabetes. The importance of trained foot care personnel was noted from the evidence statements in chapter 5. Disappointingly there was little evidence on the effectiveness of the different antibiotic regimens employed. The sometimes rapid progression from the start of ulceration to cellulitis was felt to justify very rapid referral and review by a specialist team where ulceration is detected.

The economic analysis provided to the group was felt to be secure in suggesting that human cultured dermis was not a cost-effective option in the context of the current NHS.

At the time of review by the group the evidence on Charcot osteoarthropathy management was felt to be incomplete, and the group did not reach any conclusions on the subject. A recommendation was based on the draft of the updated NICE guideline on foot care in Type 2 diabetes.

## RECOMMENDATIONS

### *Foot complication surveillance*

- R125 On the basis of findings from foot care surveillance, foot ulceration risk should be categorised into: D
- low current risk (normal sensation and palpable pulses)
  - increased risk (impaired sensory nerve function or absent pulses, or other risk factor)
  - high risk (impaired sensory nerve function and absent pulses or deformity or skin changes, or previous ulcer)
  - ulcer present.

### *Foot care management*

- R126 For people found to be at increased risk or high risk of foot complications: B
- arrange specific assessment of other contributory risk factors including deformity, smoking, level of blood glucose control
  - arrange/reinforce specific foot care education, and review those at high risk as part of a formal foot ulcer prevention programme
  - consider the provision of special footwear, including insoles and orthoses, if there is a deformity, callosities or previous ulcer.
- R127 For people with an ulcerated foot: B
- arrange referral to a specialist diabetes foot care team incorporating specifically-trained foot care specialists (usually state-registered podiatrists) within one to two days if there is no overt infection of the ulcer or surrounding tissues, or as an emergency if such infection is present
  - use antibiotics if there is any evidence of infection of the ulcer or surrounding tissues, and continue these long-term if infection is recurrent
  - use foot dressings taking account of cost according to local experience, ensuring arrangements are in place to monitor and change dressings frequently (often daily) accordingly to need
  - remove dead tissue from diabetic foot ulcers
  - consider the use of off-loading techniques (such as contact casting) for people with neuropathic foot ulcers
  - do not use cultured human dermis (or equivalent), hyperbaric oxygen therapy, topical ketanserin or growth factors in routine foot ulcer management
  - consider ensuring complete and effective foot education through the use of graphic visualisations of the consequences of ill-managed foot ulceration in people with recurrent ulceration or previous amputation
  - review progress in ulcer healing frequently (daily to monthly) according to need
  - if peripheral vascular disease is detected, refer for early assessment by a specialist vascular team.

*Charcot osteoarthropathy*

- R128** Adults with suspected or diagnosed Charcot osteoarthropathy should be referred immediately to a multidisciplinary diabetes foot care team. **D**

# 12 Management of late complications: diabetes nerve damage

## 12.1 Diagnosis and management of erectile dysfunction

### ▷ Rationale

Erectile dysfunction in men with diabetes is common, and to a greater extent than in the matched general population. There is some debate as to whether professionals should actively ask about erectile problems on a recurrent basis (perhaps yearly), or only respond to self-reported problems. There have been dramatic changes in the approach to male erectile dysfunction in recent years, stimulated by the advent of the phosphodiesterase type 5 (PDE5) inhibitors.

### ▷ Evidence statements

#### *Significance of patient-reported sexual symptomatology in predicting actual physiological measures of sexual dysfunction*

A medium-sized cross-sectional cohort study<sup>249</sup> in people with diabetes mellitus evaluated the significance of patient-reported sexual symptomatology in predicting penile tip and base rigidity, tip and base duration of erectile episode. This study reports that the presence of morning erections was associated with increased Rigiscan values of tip rigidity ( $r=0.64$ ), base rigidity ( $r=0.58$ ), tip duration of erectile episode ( $r=0.65$ ) and base duration of erectile episodes ( $r=0.57$ ), all demonstrating significant relationships (IIa).

Reports of fuller erectile quality were also significantly associated with increased Rigiscan values of tip rigidity ( $r=0.58$ ), base rigidity ( $r=0.42$ ), tip duration of erectile episode ( $r=0.67$ ) and base duration of erectile episode ( $r=0.71$ ).<sup>249</sup> Other significant associations found in this cohort study included intact ejaculatory capacity being associated with increased Rigiscan measures of tip rigidity ( $r=0.45$ ). Tip duration of erectile episode ( $r=0.56$ ) and base duration of erectile episode ( $r=0.30$ ) were also related to Rigiscan measures in the same study.<sup>249</sup>

A significant inverse relationship was found between symptom frequency and the Rigiscan measure of base duration of erectile episodes, with greater symptom frequency being associated with diminished duration values of erectile episodes at the penile base ( $r=-0.39$ )<sup>249</sup> (IIa).

#### *Correlations of lower limb nerve fibre abnormalities with erectile dysfunction*

A medium-sized cross-sectional cohort study<sup>250</sup> aimed to characterise the neuropathy in erectile dysfunction, as well as to identify nerve fibre subtypes that may be preferentially affected. Patients were evaluated with a symptom questionnaire based on the Michigan Neuropathy Screening instrument questionnaire and examined clinically. Sural and peroneal nerve-conduction studies and quantitative sensory and autonomic tests (using the staging system of Dyck) were used to detect nerve abnormalities in the lower limbs. Various

methodological limitations inherent to the study limited the validity of the results derived from the trial (IIa).

*Relationship of symptoms of depression, sexual dysfunction and neuropathy in women*

A small cross-sectional cohort study<sup>251</sup> assessed the relationship between symptoms of depression (as measured by the Beck Depression Inventory and the Hamilton Psychiatric Rating Scale), sexual dysfunction (as measured by a questionnaire which asked patients to rate their symptoms on a scale from 0 to 10), and neuropathy (as measured by the visual analogue scale). However, various methodological limitations inherent to the study limit the validity of the results derived from the trial, and should not be used as the basis for a positive recommendation (IIa).

*Sildenafil*

One large multicentre study of sildenafil at 100 mg/day compared to placebo in men with erectile dysfunction and Type 1 or Type 2 diabetes<sup>252</sup> found significantly more men were able to achieve and to maintain erections with sildenafil than placebo at 12 weeks. Another 11 outcomes from questionnaire-based evaluation of male sexual function described significant improvement with the intervention drug, however there were no differences in indices of frequency and level of sexual desire. Erectile function was improved regardless of age, duration of erectile dysfunction, duration of diabetes or type of diabetes, and the incidence of adverse arterial events was similar in both groups (Ib).

A smaller prospective study from the UK<sup>253</sup> found that sildenafil at 25 mg or 50 mg, compared to placebo, significantly improved adjusted duration of penile rigidity at base and tip. In addition, there was an improved number of erections hard enough for sexual intercourse with either dose, with no serious adverse events being related to treatment (Ib).

▷ Consideration

The group noted the problems surrounding asking all men about impotence, but suggested a reasonable approach to this problem is to enquire as to whether individuals were ‘troubled by sexual dysfunction’. It was not felt that the current opportunities for assisting women with problems of organic sexual dysfunction secondary to diabetes could justify routine enquiry. The group noted the licensing in 2003 of two additional PDE5 inhibitors to sildenafil, and felt that the lack of comparative trials meant that any recommendations should be for the drug class rather than any individual agent. Men still having a problem after a trial of PDE5 inhibitors had failed might have their needs met by expertise available in a variety of care situations, suggesting that the site of such care and advice could not be specified.

## RECOMMENDATIONS

- |      |  |   |
|------|--|---|
| R129 | Men should be asked annually whether erectile dysfunction is an issue.   | D |
| R130 | A PDE5 (phosphodiesterase-5) inhibitor drug, if not contraindicated, should be offered where erectile dysfunction is a problem.                            | A |
| R131 | Referral to a service offering other medical and surgical management of erectile dysfunction should be discussed where PDE5 inhibitors are not successful. | D |

## 12.2 Diagnosis and management of autonomic neuropathy

### ▷ Rationale

Autonomic neuropathy is a late complication of diabetes that presents in diverse ways and affects a variety of organ symptoms including the skin (sweating), blood vessels (orthostatic hypotension), gastrointestinal tract (gastroparesis, diarrhoea), heart (cardiac arrest), bladder and sexual function. It may blunt the symptoms of hypoglycaemia. Considerable morbidity occurs as a result of many of these problems.

### ▷ Evidence statements

#### *Progression of autonomic neuropathy*

A long-term follow-up study measured the progression of symptoms of autonomic neuropathy in 76 people with Type 1 diabetes and over nine years.<sup>254</sup> This study found that of all the symptoms of autonomic neuropathy only gastroparesis was found to have increased in prevalence from baseline. At nine years after entering the study the only other symptoms reported were diarrhoea, impotence, loss of vaginal lubrication, hypoglycaemia unawareness and postural hypotension, and these were reported in not more than 9% of the study sample. There was a tendency for many symptoms such as hypoglycaemia unawareness to recover with time (III).

#### *Symptoms of autonomic neuropathy*

Two descriptive reviews were located that suggested possible symptoms due to autonomic neuropathy across diabetes populations. One review<sup>255</sup> suggested impotence, unexplained diarrhoea, faecal incontinence, unexplained urinary symptoms (increased period between micturition, muted sensation of bladder fullness, frequency, urinary incontinence, unexplained bladder dilation), postural dizziness or faintness, gustatory sweating, dry feet, unexplained bloating, early satiety, fullness, nausea, vomiting, unexplained dysphagia and unexplained ankle oedema. The authors suggested that tests for autonomic neuropathy may help in defining neuropathic aetiology. Another review<sup>256</sup> found that autonomic symptoms can be vague and may present insidiously, and that nerve damage can be found in people without symptoms being manifest. It is suggested that a mixed presentation is usual with a combination of postural hypotension, nocturnal diarrhoea, gastric problems, bladder symptoms, abnormal sweating, impotence or a failure to recognise that hypoglycaemia is likely. In addition people with severe symptoms may also have advanced retinopathy, nephropathy and somatic neuropathy (IV).

### *Aldose reductase inhibitors*

Three randomised controlled trials have investigated the effect of ponalrestat on autonomic nerve function in mixed diabetes cohorts. Two small and short-term studies found no benefit of ponalrestat over placebo in terms of heart rate variability<sup>257</sup> or standard tests of autonomic function,<sup>258</sup> although a vibration perception measure or peripheral neuropathy did show a significant improvement with the intervention drug after 16 weeks of therapy.<sup>257</sup> However the potential methodological limitations of this study would not recommend it for the basis for recommendations (Ib).

A larger multicentre trial<sup>259</sup> also testing the effect of 600 mg of ponalrestat compared to placebo found heart rate response to standing was significantly greater on the intervention drug while HbA<sub>1c</sub> remained constant throughout the period, and with no effect on frequency of adverse events, although only a third of the study population displayed abnormal autonomic neuropathy from tests, with the sample being drawn from people with diabetes and peripheral neuropathy (Ib).

A long-term study<sup>260</sup> found that there was a significant increase in indices of postural index and heart rate variability after two years of treatment with tolrestat compared with placebo, with changes in autonomic function not being influenced by changes in HbA<sub>1c</sub> level. This study was conducted in people with diabetes who displayed abnormalities in two or more standard autonomic function tests and used a dose of 200 mg/day tolrestat (Ib).

### *ACE inhibitors*

Two small studies with medium-term follow-up investigated the potential of the angiotensin converting enzyme inhibitor quinapril to improve the heart rate variability of people with diabetic autonomic neuropathy. One study<sup>261</sup> found total heart power (by 24-hour ECG) to be improved with quinapril compared to placebo as was high frequency power at six months. In addition there was a significant increase in the level of heart rate variability at both three and six months. A similar study for 12 months<sup>262</sup> found quinapril to have beneficial effects on all heart rate frequency domains, and the low frequency to high frequency power ratio to be lower (improved) with quinapril than placebo, and this held for analysis of morning, evening, or night-time comparisons. The study also found quinapril to reduce heart rate to 12 months although no effect was seen on blood pressure. No complications of diabetic autonomic neuropathy or hospitalisations were reported (Ib).

No studies were identified that determined the effects of quinapril on symptoms of autonomic neuropathy.

### *Indirect cholinergic agent cisapride*

A small crossover trial of 20 mg cisapride compared to placebo in a mixed diabetes population<sup>263</sup> found no increase in antral or duodenal motility with the intervention drug; however, antral-duodenal coordination was significantly improved when fasting, and at other meals (Ib).

*Erythromycin*

Three small crossover trials of erythromycin compared to placebo in people with Type 1 diabetes and documented gastroparesis found short-term improvement in emptying of solids and mixed results with liquids with oral<sup>264,265</sup> or intravenous<sup>266</sup> administration, without side effects. However no improvements in symptoms scores were reported and larger scale and longer trials will be required to prove efficacy (Ib).

▷ Health economic evidence

No health economic papers were found regarding the diagnosis of either autonomic neuropathy or gastroparesis. One paper<sup>378</sup> was identified in the cost-effectiveness of management for painful neuropathy. However, as a review of other evidence, specific cost-effectiveness data was limited to recommending intensive treatment to reduce complications.

▷ Consideration

The group noted that the manifestations of autonomic neuropathy often occurred independently of each other, with very significant overlap into many other super-specialties of medicine (for example dermatology, gastroenterology, urology). Accordingly, the topic addressed a wider range of diagnostic and management issues than could be tackled in a diabetes guideline. Nevertheless the importance of alertness to, and detection of, these conditions was clearly relevant to the practice of the diabetes team. Of specific relevance is gastroparesis because of the effect of this condition on blood glucose control, but the group recognised that the diagnosis of this condition was not easy or reliable, and the treatments available only partially and erratically successful.

## RECOMMENDATIONS

R132	In adults with Type 1 diabetes on insulin therapy who have erratic blood glucose control (or unexplained bloating or vomiting), the diagnosis of gastroparesis should be considered.	D
R133	In adults with Type 1 diabetes who have altered perception of hypoglycaemia the possibility of sympathetic nervous system damage as a contributory factor should be considered.	D
R134	In adults with Type 1 diabetes who have unexplained diarrhoea, particularly at night, the possibility of autonomic neuropathy affecting the gut should be considered.	D
R135	Care should be taken when prescribing antihypertensive drugs not to expose people to the risks of orthostatic hypotension as a result of the combined effects of sympathetic autonomic neuropathy and blood pressure lowering drugs.	D
R136	Adults with Type 1 diabetes who have bladder emptying problems should be investigated for the possibility of autonomic neuropathy affecting the bladder, unless other explanations are adequate.	D

- R137 The management of the symptoms of autonomic neuropathy should include standard interventions for the manifestations encountered (for example, for erectile dysfunction or abnormal sweating). D
- R138 For adults with Type 1 diabetes with diagnosed or suspected gastroparesis a trial of prokinetic drugs is indicated (metoclopramide or domperidone, with cisapride as third line if necessary). D

*Anaesthesia and autonomic neuropathy*

- R139 Anaesthetists should be aware of the possibility of parasympathetic autonomic neuropathy affecting the heart in adults with Type 1 diabetes who are listed for procedures under general anaesthetic and who have evidence of somatic neuropathy or other manifestations of autonomic neuropathy. D

### 12.3 Optimum management of painful neuropathy

▷ Rationale

Symptomatic neuropathy is unusual amongst the forms of diabetes tissue damage in that it is a relatively early manifestation of the effects of hyperglycaemia, which may go into remission with progression of nerve damage (nerve death) or recovery of nerve fibre function. The symptoms are protean in nature, and often very troublesome to the person with diabetes, especially if sleep is disturbed. Management can be difficult.

▷ Evidence statements

*Anticonvulsants*

One large meta-analysis<sup>267</sup> found a significant benefit of at least 50% pain relief with people with anticonvulsants compared to placebo. The relative risk estimates showed that anti-convulsants had a significantly increased incidence of adverse effects compared with placebo for minor but not major harm (Ia).

One small, randomised controlled trial of gabapentin<sup>268</sup> found an improvement over placebo control on a pain questionnaire at 12 weeks but with no significant improvement on a visual analogue pain scale, or present pain intensity. No significant adverse events were reported in either study arm but minor events drowsiness, fatigue and imbalance were more common in the population on gabapentin than on placebo (Ib).

The differences in mean pain intensities between the intervention and control groups were significant after eight weeks at lamotrigine doses of 200, 300 and 400 mg in a small-scale prospective randomised trial.<sup>269</sup> This study found no significant changes in assessment of McGill Pain Questionnaire, Beck Depression Inventory and Pain Disability Index (Ib).

*Antidepressants*

One large meta-analysis found a significant benefit of at least 50% pain relief with people with antidepressants compared to placebo<sup>267</sup> with pooled analyses of tricyclic antidepressants showing significant benefit but no benefit with selective serotonin re-uptake inhibitors.

Tricyclic antidepressants used were prescribed in doses in the low to moderate range for depression. Antidepressants had a significantly increased incidence of adverse effects compared with placebo with typical antimuscarinic effects of dry mouth, constipation and blurred vision. Also major events (leading to withdrawal from the trial) were more common with antidepressants than placebo, the number needed to harm (NNH) for a major adverse effect with antidepressants compared with placebo was 17 (Ia).

A small short-term randomised controlled trial<sup>270</sup> investigating mean pain intensity diary scores in a six-week within-patient comparison, showed that desipramine was superior to placebo. No significant difference between incidence of adverse events or withdrawals between desipramine and placebo groups (Ib).

### *Other therapies*

*Amantadine:* A small randomised controlled trial with a one-week follow-up<sup>271</sup> found amantadine infusion at 200 mg in 500 ml 0.9% saline infusion over three-hour period caused a significant clinically relevant reduction in pain score when compared with placebo, and caused a significant improvement in the neuropathy symptom score. Following amantadine, there was a clinically significant subjective tenfold improvement in pain relief (Ib).

*Capsaicin:* A meta-analysis<sup>272</sup> comparing a range of studies with outcomes from four to eight weeks found capsaicin cream produced significantly higher response rates than placebo cream for physician assessment of global pain in two of the trials, but not in the other two (Ia).

*Clonidine:* No statistically significant difference between intervention and control groups in patients' pain record diary or pain intensity levels in two randomised trials of clonidine.<sup>273,274</sup> In the patients completing the study, dry mouth and drowsiness tended to occur more commonly with clonidine than placebo<sup>273</sup> (Ib).

*Gamma-linolenic acid:* Compared with placebo, dietary supplementation with gamma-linolenic acid was reported as being associated with significant clinical, neuropsychological and quantitative sensory improvement in established distal diabetic polyneuropathy in the medium term.<sup>275</sup> A significant improvement in the gamma-linolenic acid group compared with the placebo group was seen in nine variables: symptom scores, median MCV (m/s), peroneal MCV (m/s), median CMAP (mV), peroneal CMAP (mV), median SNAP ( $\mu$ V), sural SNAP ( $\mu$ V), ankle HT ( $^{\circ}$ C), wrist HT ( $^{\circ}$ C). This study recruited only people with Type 2 diabetes (Ib).

A second trial<sup>276</sup> confirms this with gamma-linolenic acid being significantly superior in improving neuropsychological, neurological and thermal sensation parameters of diabetic neuropathy compared with placebo over a one-year period. A significant improvement in the gamma-linolenic acid group compared with the placebo group was seen in: peroneal MNCV, median MNCV, extensor digitorum brevis CMAP, thenar CMAP, sural SNAP, median SNAP, wrist heat threshold, wrist cold threshold, arm muscle strength, arm tendon reflexes, leg tendon reflexes, arm sensation, leg sensation. Subgroup analysis showed improvement of outcome parameters with the gamma-linolenic acid was greater in patients with initial HbA<sub>1c</sub> <10% than those with HbA<sub>1c</sub> >10% (Ib).

*Isosorbide dinitrate (ISDN):* A small crossover trial<sup>277</sup> showed significant reductions in pain and burning sensation using the ISDN spray compared with placebo. During the ISDN phase of the

study, two patients developed mild transient headaches, which resolved spontaneously and did not affect overall adherence with the spray (Ib).

*Mexiletine:* Trials of mexiletine have provided mixed results in terms of efficacy for pain reduction in people with diabetes and painful neuropathy. This difference in effect could be due to clinical differences in study populations, doses utilised or length of follow-up measured (Ib).

A significant reduction in pain during night-time (as estimated by the visual analogue scale score for pain) was observed in the mexiletine 675 mg group compared with the placebo group as was a significant reduction in sleep disturbances in a large multicentre randomised trial.<sup>278</sup> No significant difference between groups in daytime pain or global assessment of efficacy was recorded. However, another study<sup>279</sup> showed no improvement in the McGill Questionnaire or on the visual analogue scale for pain to five weeks (Ib).

In contrast a study of mexiletine compared to placebo for 26 weeks<sup>280</sup> found that the Five Item Symptom Scale Score was improved in all but one patient during treatment with mexiletine, but in only two patients during the placebo phase. Mexiletine significantly improved pain, dysaesthesia and paraesthesia. During treatment with mexiletine the visual analogue score fell significantly. Three patients had mild side effects when treated with mexiletine, including nausea, hiccough and tremor (Ib).

*Tramadol:* A medium-scaled prospective randomised trial<sup>281</sup> of tramadol at up to 200 mg/day found that by day 14 people in the tramadol group had less pain than patients in the placebo group. This benefit lasted through to the end of the trial at day 42. They also scored better on outcomes of physical and social functioning. No statistically significant differences between treatments were noted for current health perception, psychological distress, overall role functioning and the two overall sleep problem indexes and sleep subscales. The most common adverse events in the tramadol group were nausea (23%), constipation (22%), headache (17%) and somnolence (12%). Nine patients treated with tramadol and one treated with placebo discontinued due to adverse events. The most common adverse events leading to discontinuation of tramadol were nausea and dyspepsia. However, this study recruited only people with Type 2 diabetes (Ib).

▷ Consideration

The group noted that the severity of neuropathic symptoms varied considerably between individuals. Many of the well-established drugs were used outside licensed indications in contrast to the newest drugs. Established clinical practice, as in most areas of pain control, uses a stepped approach, and no reason for challenging that was found. Nevertheless, the group was also aware that prescribing habits and long review intervals could lead to suboptimal management where therapies proved ineffective, both through a failure to recognise an unsuccessful trial of therapy and through over-slow dose titration. In the absence of comparative studies, while gabapentin was believed more effective than tricyclic drugs, the need for dose titration and problems of intolerance together with cost suggested the older drugs to be worth a trial first. Other drugs were now felt by the group to be reserved for people failing trials of tricyclic drugs and gabapentin. The group were aware of difficulties with evidence on gamma-linolenic acid, which meant that it could not be considered further for this guideline. The group also noted the availability of local pain management teams for people whose pain does not respond to conventional measures.

**RECOMMENDATIONS**

- |      |   |   |
|------|---|---|
| R140 | Use of simple analgesics (paracetamol, aspirin) and local measures (bed cradles) are recommended as a first step, but if trials of these measures are ineffective, they should be discontinued and other measures should be tried.  | D |
| R141 | Where initial measures fail, a low to medium dose of a tricyclic drug should be used, timed to be taken before the time of day the symptoms are troublesome; adults with Type 1 diabetes should be advised that this is a trial of therapy.   | A |
| R142 | Where an adequate trial of tricyclic drugs fails, a trial of gabapentin should be started, and not stopped unless ineffective at the maximum tolerated dose or at least 1,800 mg per day.   | A |
| R143 | If treatment with gabapentin is unsuccessful, carbamazepine and phenytoin should be considered.   | D |
| R144 | Where severe chronic pain persists despite trials of other measures, opiate analgesia may be considered. At this stage the assistance of the local chronic pain management service should be sought.  | D |
| R145 | Professionals should be alert to the psychological consequences of chronic painful neuropathy, and offer appropriate management where they are identified.  | D |
| R146 | Where drug therapy is successful in alleviating symptoms, trials of reduced dosage and cessation of therapy should be considered after six months of treatment.   | D |
| R147 | Where neuropathic symptoms cannot be adequately controlled it is useful, to help individuals cope, to explain: <ul style="list-style-type: none"> <li>● the reasons for the problem</li> <li>● the likelihood of remission in the medium term</li> <li>● the role of improved blood glucose control.</li> </ul> | D |

# 13 Management of special situations

## 13.1 Adults who are newly diagnosed

### ▷ Rationale

The time following diagnosis is one of marked stress for many adults with diabetes. However, decisions taken at this time may have a long-term impact, and to be accurate and effective would appear to need fairly complete assessment of medical and lifestyle factors. These can be expected to affect choice of therapy and monitoring requirements, educational requirements, input from different members of the multidisciplinary team, site of care and the need for involvement of other health-related services and perhaps employers and other institutions.

### ▷ Evidence statements

#### *Organisation of initial assessment planning*

Consensus in the ADA guidelines<sup>76</sup> suggests that medical evaluation is made to classify the person presenting as a basis for a management plan and to assess complications. This is echoed by Diabetes UK recommendations for management in primary care<sup>282</sup> which indicate that a planned programme of diabetes care should include systems for ensuring assessment and acute management of all newly-diagnosed patients. In addition, American guidelines from the Department of Veterans Affairs<sup>283</sup> identify initial assessment as a useful tool to review systems and set priorities for care (IV).

#### *Content of the initial assessment plan*

All of the guidelines reviewed are aimed at a mixed diabetic population and do not specify any specific features of initial assessment that are particular to people with Type 1 diabetes. All guidance suggests that assessment should look for co-morbid conditions that people with diabetes are more commonly at risk from<sup>282-5</sup> and should consider factors that may affect the management of diabetes such as COPD, substance misuse and depression.<sup>283-5</sup> Factors that may precipitate diabetes secondary to other medical conditions should also be considered<sup>283</sup> (IV).

Other factors of initial assessment that can aid management planning that are widely suggested included physical examinations, laboratory tests including lipid profile, urinalysis and ECG.<sup>282-3,285</sup> Consideration for referral is advised for (IV):

- urgent hospitalisation if patient is clearly unwell,<sup>282</sup> or
- where specialist examination is required for eye exam, family planning, diabetes education, behavioural advice or foot disorders.<sup>285</sup>

Consistent documentation of assessment is widely recommended,<sup>282-3</sup> and initial assessment should be used for the baseline of an individualised management plan<sup>282,285</sup> (IV).

*Benefit of initial assessment plan*

No interventional studies were identified that assess the affect on outcomes of improved initial assessment planning. It may be assumed that benefits may accrue in terms of understanding and satisfaction with care, and potentially with adherence to management plans, although these cannot be quantified at this time (IV).

▷ Health economic evidence

The health economic searches produced no studies giving guidance on appropriate insulin regimens for those newly diagnosed with Type 1 diabetes.

▷ Consideration

The group noted that this was not an area in which to expect RCT evidence of different styles of initial management planning, and endorsed in general the views expressed in other recent guidelines for people with Type 1 diabetes. An overlap with the education recommendations of this guideline (see 6.1) was noted.

## RECOMMENDATIONS

**R148** At the time of diagnosis (or if necessary after the management of critically decompensated metabolism) the professional team should develop with, and explain to, the adult with Type 1 diabetes a plan for their early care. To agree such a plan will generally require: **D**

- medical assessment to:
  - ensure security of diagnosis of type of diabetes
  - ensure appropriate acute care is given when needed
  - review and detect potentially confounding disease and drugs
  - detect adverse vascular risk factors
- environmental assessment to understand:
  - social, home, work and recreational circumstances of the individual and carers
  - their preferences in nutrition and physical activity
  - other relevant factors such as substance use
- cultural and educational assessment to identify prior knowledge and to enable optimal advice and planning about:
  - treatment modalities
  - diabetes education programmes
- assessment of emotional state to determine the appropriate pace of education.

The results of the assessment should be used to agree a future care plan.

**R149** Elements of an individualised and culturally-appropriate plan will include: **D**

- sites and timescales of diabetes education including nutritional advice (see section 6.1, 'Education programmes for adults with Type 1 diabetes' and 6.3, 'Dietary management')
- initial treatment modalities (see section 7.3, 'Insulin regimens' and 7.4, 'Insulin delivery')
- means of self-monitoring (see section 6.2, 'Self-monitoring of blood glucose')

Table 6 Some items of the initial diabetes assessment

● Acute medical history	● General examination
● Social, cultural and educational history/lifestyle review	● Weight/body mass index
● Complications history/symptoms	● Foot/eye/vision examination
● Long-term/recent diabetes history	● Urine albumin excretion/urine protein/serum creatinine
● Other medical history/systems	● Psychological well-being
● Family history of diabetes/arterial disease	● Attitudes to medicine and self-care
● Drug history/current drugs	● Immediate family and social relationships and availability of informal support
● Vascular risk factors	
● Smoking	

- means and frequency of communication with the professional team
- follow-up consultations including surveillance at annual review (see the chapters on the management of late complications (chapters 9 to 12))
- management of arterial risk factors (see chapter 8, 'Arterial risk control').

**R150** After the initial plan is agreed, arrangements should be put in place to implement it without inappropriate delay, and to provide for feedback and modification of the plan over the ensuing weeks. **D**

## 13.2 Diabetic ketoacidosis

### ▷ Rationale

The management of diabetic ketoacidosis (DKA) is a topic which has attracted considerable attention over 40 years, because it can carry a high fatality risk if suboptimally managed. If optimally managed, the fatality and morbidity rates are very low. The topic is not easily addressed within a general diabetes guideline, being large enough for a guideline of its own. The approach below is to address some broad principles and specific topics of contention, rather than present a detailed protocol.

### ▷ Evidence statements

#### *Insulin therapy*

Continuous *vs* intermittent insulin therapy for DKA was evaluated in one small randomised study.<sup>286</sup> Insulin was administered as bolus injections (50 U/2h) compared to continuous insulin infusion (10 U/h) and low dose continuous insulin infusion (2 U/h) with an initial loading dose. To reduce plasma glucose concentrations, continuous infusion is as effective as intermittent insulin therapy at 10 U/h, with reduction to 5 U/h when plasma glucose <300 mg/100 ml. DKA recovery rate was significantly reduced following the very low dose continuous infusion regimen (**Ib**).

Another small study<sup>287</sup> showed that low doses of insulin given by intermittent intramuscular (IM) injection or by constant intravenous (IV) infusion after an initial IV loading dose are similarly effective in controlling DKA. Time to recovery of DKA and total insulin dose required did not differ between the two treatment groups (Ib).

A comparison<sup>288</sup> of different possible routes of insulin delivery in treating DKA showed similar efficacy for IV, IM and subcutaneous (SC) administered insulin therapy. No significant differences were seen for the time to metabolic recovery or total insulin dose or fluid replacement requirements. Patients receiving IM insulin were most likely to require additional insulin loading dose to achieve an adequate initial response. In this report a significantly higher rate of decrease in glucose and ketone bodies was observed in the first two hours following IV insulin, but these differences were not maintained over the rest of the recovery period (Ib).

No significant differences in recovery rates were seen following the administration of human and porcine insulin for treatment of DKA in a prospective trial with a small study population of people with both Type 1 and Type 2 diabetes<sup>289</sup> (Ib).

Continuation of insulin administration past the usually cut-off point of near-normoglycaemia vs conventional insulin regimen (rehydration, electrolyte replacement and insulin at 5 U/h to near-normoglycaemia, that is blood glucose less than or equal to 10 mmol/l, and then at a reduced rate until clinical recovery) in one small study,<sup>290</sup> significantly increased the resolution of ketosis, measured as duration of elevated blood 3-hydroxybutyrate levels, and acidosis (Ib).

### *Bicarbonate therapy*

Intravenous sodium bicarbonate therapy added to the treatment regimen for DKA was shown in a randomised trial with small sample size<sup>291</sup> to increase recovery of arterial pH and bicarbonate levels in the first two hours, but did not effect pCO<sub>2</sub> or blood glucose levels. All patients in the bicarbonate group developed hypokalaemia (Ib).

One study<sup>292</sup> compared the effect of two different intravenous bicarbonate doses (adjusted to initial arterial pH) on the recovery rate of DKA, with placebo. No significant differences were seen between the groups treated with bicarbonate or placebo (Ib).

In agreement with these studies, one small trial<sup>293</sup> showed intravenous bicarbonate therapy had no additional beneficial effect when compared to standard DKA therapy without bicarbonate supplementation (IIa).

No significant differences were seen after addition of phosphate therapy to treatment for DKA in a small trial.<sup>294</sup> A protective effect against hypophosphataemia was seen following phosphate treatment compared to placebo, but only on the first day of treatment (Ib).

An additional paper<sup>295</sup> also reported no evidence of clinical benefit of phosphate therapy compared to placebo (Ib).

### *Somatostatin therapy*

One small study<sup>296</sup> concluded that addition of the somatostatin analogue octreotide to low-dose insulin therapy reduced the time taken for correction of ketonuria. However, no such effect was seen on recovery rate of hyperglycaemia and acidosis (Ib).

▷ Health economic evidence

The health economic searches found only one US-based costing study.<sup>379</sup> As such, no specific health economic guidance can be provided here.

▷ Consideration

DKA management was noted to be based on a mixture of types of evidence, pathological, pharmacokinetic, clinical outcomes, cohorts and trials.

It was noted that DKA management is:

- quite detailed
- often performed under the supervision of diverse groups of specialists
- dependent on careful monitoring if catastrophic outcome is to be avoided.

There was broad consensus on issues of management, which largely seem to revolve around ameliorating the acidosis and hyperglycaemia without inducing the possibly fatal complications of cerebral oedema, hypokalaemia or aspiration pneumonia. Moderation in speed and methods of correcting dehydration, hyperglycaemia and ketosis is combined with a high intensity of monitoring of the changing condition of the patient.

The group noted that there was no evidence at all for the use of bicarbonate in any situation, and that the consensus recommendations for its use below a pH of 6.9 were poorly grounded in either clinical experience or any kind of evidence.

The group noted that the nature of insulin pharmacokinetics and pharmacodynamics suggested that the detailed studies of ways of starting insulin infusions had no logical basis.

Clinical experience of management in adults suggested that acute respiratory distress syndrome ('fluid on the lung') was seen not infrequently in addition to cerebral oedema. While the evidence that either of these could be ameliorated by using lower rates of saline replacement was not good, nor was there any impression that in the non-shocked patients such lower rates were harmful. Accordingly they are recommended.

Members of the group had seen examples of glucose concentration escape after reaching near-normal glucose levels, and felt that the evidence-based lesson of the Belfast paper<sup>290</sup> (that these insulin-resistant patients require continued administration of higher rates of insulin than other patients on insulin infusions) was worth noting.

## RECOMMENDATIONS

- R151 Professionals managing DKA should be adequately trained including regular updating, and familiar with all aspects of its management which are associated with mortality and morbidity. These topics should include: D
- fluid balance
  - acidosis
  - cerebral oedema
  - electrolyte imbalance
  - disturbed interpretation of familiar diagnostic tests (white cell count, body temperature, ECG)

- respiratory distress syndrome
- cardiac abnormalities
- precipitating causes
- infection management including opportunistic infections
- gastroparesis
- use of high dependency and intensive care units
- and the recommendations below.

Management of DKA should be in line with local clinical governance.

R152	Primary fluid replacement in DKA should be with isotonic saline, not given too rapidly except in cases of circulatory collapse.	D
R153	Bicarbonate should not generally be used in the management of DKA.	A
R154	Intravenous insulin should be given by infusion in cases of DKA.	A
R155	In the management of DKA, once plasma glucose concentration has fallen to 10–15 mmol/l, glucose containing fluids should be given (not more than two litres in 24 hours) in combination with higher rates of insulin infusion than used in other situations (for example 6 U/h – monitored for effect).	D
R156	Potassium replacement should begin early in DKA, with frequent monitoring for the development of hypokalaemia.	D
R157	Phosphate replacement should not generally be used in the management of DKA.	A
R158	In patients whose conscious level is impaired, consideration should be given to insertion of a nasogastric tube, urinary catheterisation to monitor urine production and heparinisation.	D
R159	To reduce the risk of catastrophic outcomes in DKA, monitoring should be continuous and review should cover all aspects of clinical management at frequent intervals.	D

### 13.3 Inpatient management

#### ▷ Rationale

People with Type 1 diabetes often find that time in hospital, or other institutional care, is somewhat stressful. The delicate equilibrium they may have established with their insulin therapy can be destroyed by the change in routine, change in nutrition and the effects of illness and procedures. They find too often that the expertise they bring to their diabetes management is underused by staff with less knowledge of the condition than themselves. Special insulin regimens may be needed to cope with procedures which interfere with eating patterns, or which cause enough metabolic stress to otherwise disturb control of diabetes. In some acute situations there is evidence that special insulin management may improve the outcomes of other medical conditions.

The overwhelming majority of admissions of people with diabetes are for non-diabetes related medical and surgical conditions. Indeed the problems discussed above are likely to be greater when care is outside the responsibility of the multidisciplinary diabetes team. Accordingly the evidence search and recommendations are intended to cover hospital and other institutional

care across all specialties. However, some aspects of continuing self-care will self-evidently not be relevant during extreme critical illness.

The principles espoused are seen as applying, in general, to other institutional care (prisons, residential and nursing homes) as well as hospital care.

#### ▷ Evidence statements

##### *Multidisciplinary team care*

One study<sup>297</sup> showed a significant reduction in length of stay in hospital following supervision by a diabetes specialist nurse. Significant differences were also seen in patient satisfaction and diabetes knowledge, although not for readmission frequency, referral rates or quality of life (Ib).

A cohort study<sup>298</sup> showed a significant reduction in length of stay in medical and surgery wards in patients with diabetes following the introduction of a diabetes nurse advisor (IIa).

A prospective randomised study examining the impact of a specialist diabetes team on inpatient management<sup>55</sup> demonstrated a significant increase in documentation of instructions for blood glucose monitoring, insulin administration, received education and nutritional consultation. Patients were significantly less likely to be readmitted within three months following supervision by a specialist diabetes team (Ia).

##### *Hospital procedures*

A small prospective randomised trial of aggressive IV insulin therapy with glucose level checks every 15 to 30 minutes compared to standard insulin therapy in a mixed diabetes cohort undergoing cardiopulmonary bypass<sup>299</sup> found that phagocytic activity decreased less with the aggressive regimen at one hour post operation. There was no measurement of clinical outcomes in this trial (Ib).

A cohort study from the United States in a mixed diabetic population<sup>300</sup> found that blood glucose levels on the day of operation to the third post-operative day were significantly lower with continuous insulin infusion compared to individualised subcutaneous insulin injection. Also the risk of deep sternal wound infection following cardiac surgery was independently associated with receiving continuous insulin infusion in multivariate analysis (IIa).

In another trial including people with both Type 1 and Type 2 diabetes,<sup>301</sup> continuous IV infusion of insulin from an electrically-driven syringe produced no significant differences in plasma beta-hydroxybutyrate:acetoacetate ratio, lactate:pyruvate ratio or concentrations of cortisol and catecholamine compared with a two-hourly bolus IV insulin injection. The total amount of insulin and rate given was similar in both groups (Ib).

Two small studies of IV delivery of insulin compared to subcutaneous injection in either minor<sup>302</sup> or major<sup>303</sup> surgery found that median blood glucose can be reduced on the first postoperative day with IV delivery although this did not hold true for all time points at which levels were tested, and that more measurements were found to be in the target range of 5–10 mmol/l, also haemoglobin levels were higher with the IV infusion regimen, although chest X-rays revealed no infective processes either pre- or postoperatively.<sup>302</sup> Alternatively the insulin to glucose ratio was significantly lower in people receiving IV insulin compared to the subcutaneous group, and the

number of dosage adjustments required was lower with the IV delivery method.<sup>303</sup> No significant hyper- or hypoglycaemic events were recorded in either trial (Ib).

The use of a two pump IV infusion technique in which a y-shaped cannula was connected to separate pumps delivering glucose and potassium and another providing insulin was compared to a standard IV regimen with variable amounts of insulin being added to a glucose and potassium infusion bag during a range of surgical procedures on people with Type 1 diabetes.<sup>304</sup> The former method provided lower glucose concentrations when people were being taken off infusion during the sliding scale period, and when on their normal insulin regimen postoperatively as compared to the standard method. However there were no significant differences between groups in the median length of time on the regimens, the length of stay or in the number of infections reported (Ib).

An experimental method for adjusting dose of infused insulin for critically ill diabetic patients using a fuzzy logic principle compared with standard algorithms was tested in a small randomised controlled trial.<sup>305</sup> Over 72 hours the adjustment using fuzzy logic produced lower mean blood glucose levels than the standard method, with level falling below 10 mmol/l in a shorter period. This appeared to be achieved by more frequent dose adjustments (Ia).

### *Myocardial infarction*

A large randomised controlled trial including 620 people<sup>306</sup> demonstrated a significant reduction in total mortality at three months, one year and three and a half years, and re-infarctions following insulin-glucose infusion, compared to controls (Ib).

One moderate-sized prospective randomised trial in an elderly mixed diabetic population (19% Type 1)<sup>307</sup> tested the use of 24 hours of infused insulin, followed by subcutaneous injections for three months. This was found to reduce glucose levels further than a control of no insulin during the first 24 hours of admission. However no significant differences in HbA<sub>1c</sub> were noted between the group to 24 hours. There was also excess incidence of hypoglycaemia among the insulin-treated patients (Ia).

An additional prospective controlled trial<sup>308</sup> showed a significant reduction in total mortality and the occurrence of complications (heart failure and arrhythmias) with continuous intravenous insulin therapy compared to conventional therapy, however, this population was predominantly people with Type 2 diabetes. Subgroup analysis showed that reductions in complications were only significant in patients treated with oral hypoglycaemic agents, no insulin or diet alone (IIa).

#### ▷ Health economic evidence

One UK-based study<sup>297</sup> suggested that the provision of a hospital-based diabetes specialist nurse lowered the cost per patient admission without producing a significant difference in readmission, quality of life or patient satisfaction.

#### ▷ Consideration

The evidence supporting the benefit of specialist multidisciplinary team advice in giving healthcare and cost gains to inpatients outside specialist diabetes wards was felt to be

conclusive. Professional and patient members of the group were sadly familiar with the failure of some wards to use the expertise of people with diabetes, and the distress this can cause when care becomes suboptimal as a result. This was noted to be particularly the case in relation to nutritional intake and insulin therapy.

The evidence base for optimal use of insulin therapy in people with diabetes suffering critical acute arterial (and non-arterial) emergencies comes mainly from cohorts of people with Type 2 diabetes. The pathophysiological situation in these circumstances was not thought to be significantly different in Type 1 diabetes, and that evidence was therefore taken as the basis for a clinical recommendation.

The group was aware that the most widely established technique for managing people requiring insulin through surgical and other procedures (the glucose–insulin–potassium infusion) was not identified by the literature search despite a significant descriptive literature. Nevertheless, the prevalent use of this technique throughout the UK was felt to be such that it would be inappropriate not to recommend its general use.

## RECOMMENDATIONS

- |      |   |   |
|------|---|---|
| R160 | From the time of admission, the person with Type 1 diabetes and the team caring for him or her should receive, on a continuing basis, advice from a trained multidisciplinary team with expertise in diabetes.  | B |
| R161 | Throughout the course of an inpatient admission, the personal expertise of adults with Type 1 diabetes (in managing their own diabetes) should be respected and routinely integrated into ward-based blood glucose monitoring and insulin delivery, using the person with Type 1 diabetes' own system. This should be incorporated into the nursing care plan.                                    | D |
| R162 | Throughout the course of an inpatient admission, the personal knowledge and needs of adults with Type 1 diabetes regarding their dietary requirements should be a major determinant of the food choices offered to them (except when illness or medical or surgical intervention significantly disturbs those requirements).  | D |
| R163 | Hospitals should ensure the existence and deployment of an approved protocol for inpatient procedures and surgical operations for adults with Type 1 diabetes. This should aim to ensure the maintenance of near-normoglycaemia without risk of acute decompensation, usually by the use of regular quality-assured blood glucose testing driving the adjustment of intravenous insulin delivery. | D |
| R164 | Members of care teams managing adults with Type 1 diabetes in institutions, such as nursing homes, residential homes and prisons, should follow the recommendations in this section.  | D |

### *Management during acute arterial events*

- |      |  |   |
|------|--|---|
| R165 | Optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, should be provided to all adults with Type 1 diabetes with threatened or actual myocardial infarction or stroke. Critical care and emergency departments should have a protocol for such management. | D |
|------|--|---|

## 13.4 Associated illness

### ▷ Rationale

Type 1 diabetes is an auto-immune disease associated with genes which modulate the immune response. Other auto-immune diseases are similarly associated, and manifestation of some of them can be sub-clinical while interacting with aspects of food absorption or metabolism.

### ▷ Evidence statements

#### *Latent pernicious anaemia*

Using a microbiological method to measure cobalamin concentration, one study from Australia<sup>309</sup> found reduced cobalamin concentration in six out of 371 people with Type 1 diabetes. Four of the patients showed no clinical signs of pernicious anaemia, the fifth was mildly anaemic and the sixth patient was not available for further testing. This medium-sized study with methodological limitations gave a prevalence of latent pernicious anaemia of 11 per 1000 in people with Type 1 diabetes (III).

#### *Prevalence of coeliac disease*

Using immunoglobulin A (IgA) class anti-endomysial antibodies (EmAb) detected by immunofluorescence (test) and histological confirmation of coeliac disease by small intestinal biopsy partial or total villous atrophy, a medium-sized study<sup>310</sup> showed in an unselected sample at an outpatients clinic that the prevalence of coeliac disease in the sampled population was 6.4% and that EmA were highly predictive of the presence of coeliac disease on biopsy (DS).

A larger study,<sup>311</sup> but with potential methodological limitations, found that in a two-step screening process of anti-gliadin antibodies (GA) detected by enzyme-linked immunosorbent assay (ELISA) assay and IgA class EmAb detected by immunofluorescence, the predictive value of GA was moderate, with a high false-positive rate for IgA-GA. Prevalence of coeliac disease in Type 1 diabetes to be up to 2.6% and that after 30 years diabetes duration, the prevalence of coeliac disease was >6%. The study also found that EmAb were highly predictive of the presence of coeliac disease on biopsy (DS).

The frequency of coeliac disease-specific serologic markers and the prevalence of coeliac disease in families of patients with Type 1 diabetes were evaluated in a medium-sized study<sup>312</sup> using a two-step screening process. The screening programme included circulating islet cell antibodies (ICA), anti-glutamic acid decarboxylase antibodies and GA, and then IgA class EmAb detected by immunofluorescence. This study found the prevalence of biopsy-proven coeliac disease to be 1.3% among patients with Type 1 diabetes and zero among controls, or family. Of screening assays, only EmAb were highly predictive of the presence of coeliac disease (DS).

Another diagnostic study using IgA class EmAb<sup>313</sup> compared people with Type 1 diabetes with adults with coeliac disease as true positives (as determined by intestinal biopsy) and controls (healthy and diseased) as true negatives (as determined by intestinal biopsy). The prevalence of biopsy-proven coeliac disease among adults with Type 1 diabetes was 3.13%. This study showed IgA class EmAb had high specificity in detecting coeliac disease in people with Type 1 diabetes (DS).

*Red cell distribution width*

Using red cell distribution width (RDW) as a screening test against EmAb and diagnostic duodenal biopsy as reference tests for coeliac disease one very small, methodologically-limited study<sup>314</sup> demonstrated the poor specificity of RDW in predicting coeliac disease in people with Type 1 diabetes. Given the potential methodological limitations, this evidence was not used to support any recommendations in this area (DS).

## ▷ Health economic evidence

The health economic searches found no relevant papers for the treatment of those with Type 1 diabetes suffering from concurrent disease.

## ▷ Consideration

While auto-immune conditions are probably more common in people with Type 1 diabetes than in the general population, the group did not feel that this should lead to any formal system of surveillance for the development of such conditions.

**RECOMMENDATIONS**

- R166** In adults with Type 1 diabetes of low body mass index or with unexplained weight loss, markers of coeliac disease should be assessed. **DS**
- R167** Healthcare professionals should be alert to the possibility of development of other auto-immune disease in adults with Type 1 diabetes (including Addison's disease, pernicious anaemia and thyroid disorders). **D**

**13.5 Psychological problems**

## ▷ Rationale

The management demands of insulin therapy, the risks of late complications of diabetes, and the problems of hypoglycaemia and social discrimination, can place significant emotional stress on people with Type 1 diabetes. This might precipitate or exacerbate psychological difficulties present for other reasons. Additionally, the stresses might in themselves be expected to interfere with a person's ability to self-manage their diabetes.

## ▷ Evidence statements

*Depressed mood and glycaemic control*

A small cohort study examining depressed mood as a factor in glycaemic control in Type 1 diabetes<sup>315</sup> found a strong positive correlation between mood and glycaemic control. As the depression scores for this sample were mainly in the normal range, the results of this study indicate that mood, rather than clinical depression *per se*, is associated with significant differences in glycaemic control (IIa).

A medium-sized cohort study<sup>316</sup> examined depression and its effect on reporting diabetes symptoms in Type 1 diabetes. The study found that seven of nine symptoms attributed to diabetes (hyperglycaemic symptoms, hypoglycaemic symptoms and non-specific symptoms of poor control) were associated with depression whereas only one of nine symptoms attributed to diabetes was related to HbA<sub>1c</sub> (IIa).

A meta-analysis of cross-sectional studies<sup>317</sup> examined whether depression is associated with glycaemic control. A weak correlation was found between depression and glycaemic control. However, the study has certain potential issues with the methodology used. No systematic quality appraisal has been given for those studies included in the meta-analysis. Effect size estimates may be unstable due to the small number of studies and the small sample sizes of some studies (III).

#### *Injection anxiety and glycaemic control*

One medium-sized cohort study<sup>318</sup> examined ‘fear of blood and injury’ and its association with glycaemic control in Type 1 diabetes. The study shows that Type 1 diabetes adults with poorer glycaemic control perform fewer blood glucose measurements per day. The relationship between poor glycaemic control and fewer blood glucose measurements is mediated by fear of blood and injury (IIa).

Another medium-sized cohort study<sup>319</sup> examined injection anxiety in Type 1 and Type 2 diabetes. The study found a significant negative correlation between injection anxiety and the number of insulin injections. However, no significant difference was found in the degree of glycaemic control between diabetes patients with high vs low anxiety scores. The results of this study are not analysed separately for people with Type 1 and Type 2 diabetes (III).

One meta-analysis<sup>320</sup> examined whether or not anxiety is associated with poor glycaemic control in adults with Type 1 and Type 2 diabetes. The studies that were limited to Type 1 diabetes found a weak correlation between anxiety and glycaemic control. However, the study has some possible methodological limitations which may have introduced bias into analysis. No systematic quality appraisal has been given for those studies included in the meta-analysis. Effect size estimates may be unstable due to the small number of studies and the small sample sizes of some studies (III).

#### *Prevalence of depression in Type 1 diabetes*

One recent meta-analysis of prevalence studies examining the prevalence of depression in Type 1 diabetes<sup>321</sup> found a significantly higher prevalence of depression in Type 1 diabetes (21.7%) than in non-diabetes control subjects (8.6%). Potential methodological factors inherent to the study may limit the validity of the results derived from the meta-analysis (III).

One retrospective cross-sectional case-control study<sup>322</sup> examined the prevalence of antidepressant use in Type 1 diabetes compared to age- and sex-matched controls. The study found a significantly higher proportion of Type 1 diabetes patients (12.8%) had received a prescription for antidepressants in the past twelve months compared to controls (7.4%). The data for this study was derived from a localised computerised database of 28 GP practices so caution needs to be taken when generalising these results to other geographical areas (III).

*Management of depression*

A medium-sized prospective 12-month follow-up study in Type 1 diabetes<sup>323</sup> evaluated whether a blood glucose awareness training programme (BGAT-2) would improve mood. No significant improvement in mood was detected in baseline scores at six and 12 months. This is attributed to baseline scores being within the normal limits. When subjects who feel within the range of mild depression were examined separately, these individuals did demonstrate a significant reduction in baseline scores at six and 12 months (Ib).

A small randomised controlled trial<sup>324</sup> evaluated the efficacy of nortriptyline for depression and poor glycaemic control in a mixed (Type 1 and Type 2) diabetes population with poor glycaemic control. The study found that the nortriptyline group were significantly less depressed after eight weeks than the placebo-treated patients. Of the nortriptyline-treated patients, 57% successfully remitted compared to 35.7% of the placebo-treated patients. No significant difference in response rate was found between Type 1 and Type 2 diabetes. Furthermore, in the sample as a whole (Type 1 and Type 2) there was a non-significant trend towards worsened glycaemic control, both in patients who received nortriptyline and those who received placebo (Ib).

A small randomised controlled trial<sup>325</sup> evaluated the antidepressant efficacy of fluoxetine in diabetic patients (mixed population type sample) with major depressive disorder. At the conclusion of the eight-week treatment period, a significant reduction in symptoms of depression was found in the fluoxetine-treated group compared to the placebo group. However, no significant difference in the improvement of glycaemic control was found between patients who received fluoxetine and those who received placebo (Ib).

A small random two-group parallel comparison with a pre-test and nine and 15 months follow-up study<sup>326</sup> compared the effects of a standard intensive treatment, patient education and distress reduction programme, with a standard treatment and patient education. Outcomes examined were psychological variables and metabolic control. At nine months follow-up, depression improved significantly in the intensive treatment group compared to the standard treatment group. No significant difference was found in metabolic control between the two groups. At 15 months follow-up, improvement in depression faded and metabolic control was worsened (Ib).

*Management of anxiety in Type 1 diabetes*

A small double-blind randomised controlled trial in a mixed (Type 1 and Type 2) diabetes population<sup>327</sup> examined the effects of alprazolam on glucose regulation in anxious and non-anxious patients with poor glycaemic control. Patients treated with alprazolam had a significantly greater reduction in GHb levels than those receiving placebo, regardless of anxiety. Both alprazolam and placebo similarly improved anxiety among anxious patients. Results were not analysed separately for Type 1 and Type 2 diabetes (Ib).

## ▷ Consideration

It was felt that, whether or not depression and other psychological illness was more common in people with Type 1 diabetes, the literature being inconclusive, the interaction with self-

management demanded professional alertness to such problems. A degree of competence in managing these problems at least matching that of an experienced general practitioner is clearly desirable.

## RECOMMENDATIONS

- |             |   |          |
|-------------|---|----------|
| <b>R168</b> | Members of professional teams providing care or advice to adults with Type 1 diabetes should be alert to the development or presence of clinical or sub-clinical depression and/or anxiety, in particular where someone reports or appears to be having difficulties with self-management.  | <b>B</b> |
| <b>R169</b> | Diabetes professionals should ensure they have appropriate skills in the detection and basic management of non-severe psychological disorders in people from different cultural backgrounds. They should be familiar with appropriate counselling techniques and appropriate drug therapy, while arranging prompt referral to specialists of those people in whom psychological difficulties continue to interfere significantly with well-being or diabetes self-management. | <b>D</b> |
| <b>R170</b> | Special management techniques or treatment for non-severe psychological illness should not commonly be used, except where diabetes-related arterial complications give rise to special precautions over drug therapy.   | <b>D</b> |

### 13.6 Eating disorders

#### ▷ Rationale

Due to the inadequacies of subcutaneous insulin therapy, dietary self-management is an inevitable consequence of the optimal self-care of Type 1 diabetes. Eating disorders are not uncommon in the general population, while Type 1 diabetes is most commonly diagnosed at an age (12–20) when consciousness of own body image is high. Accordingly, eating disorders are seen in people with Type 1 diabetes, and will interfere with self-management.

A review of the management of eating disorders is outside the scope of this guideline. A systematic search of the literature was, however, undertaken to review the types and relevant prevalence of eating disorders, and whether any specific issues of management had been identified in the Type 1 diabetes population.

#### ▷ Evidence statements

Many papers on eating disorders in diabetes include people with Type 2 diabetes. Extrapolation to Type 1 diabetes from such populations is not safe. Assessment of eating disorders can be by interview (specific, low prevalence) or questionnaire (non-specific, high prevalence), and may or may not include manipulation of insulin dosage (dose omission or reduction). Accordingly published prevalence and odds ratio *vs* matched populations vary. Furthermore there may be cultural variations depending on attitudes to obesity and peer pressure. People with diabetes often are in continued contact with professional care teams, and the input of those teams might be expected to have influence on behavioural disorders (IV).

A follow-up study using interview methods in a clinic population<sup>328</sup> found no eating disorders at all. Nevertheless a proportion of young people did use insulin dose manipulation to control weight, and appeared to have worse outcomes (markers of late complications of diabetes) as a result (III).

A group in Toronto published a series of papers over the last decade, including a non-systematic review.<sup>329–30</sup> They note the odds ratio for eating disorders in young people compared to non-diabetic controls is around 2.0, with an excess prevalence of 2%–5%. The principal disorders described are bulimia nervosa and insulin dose manipulation, the conditions tend to be chronic even under care, and diabetes outcomes relatively poor compared to peers (III).

A review,<sup>331</sup> described as a meta-analysis of prevalence studies, concurred with these figures for bulimia and dose manipulation, and could not find evidence of increased prevalence of anorexia nervosa (III).

One small randomised controlled trial of a group psycho-education programme to improve sub-clinical disordered eating in women with Type 1 diabetes<sup>332</sup> found no significant differences between the intervention and control (standard care) in outcomes of metabolic control with both groups showing improvements from baseline. There was also no significant difference in concordance with diabetes treatment or eating disorder symptomology at six weeks (Ib).

A position statement of the American Dietetic Association and the Dietitians of Canada<sup>333</sup> found evidence that the prevalence of eating disorders among young adult women with Type 1 diabetes to be about 5% to 11%. It is suggested that dietetic professionals have a vital role in the management of diabetes as they have an understanding of the health issues that affect women with diabetes (IV).

#### ▷ Consideration

The group felt that the evidence on the whole suggested that eating disorders were more prevalent in people with Type 1 diabetes, and particularly in young adults. Insulin dose manipulation of calorie loss accounted for much of this, and perhaps the long-term follow-up study's results were influenced by the benefits of the good long-term support offered. Experience of eating disorders in clinical practice was that in the context of insulin therapy they can have serious short- and long-term impacts, sometimes fatal.

## RECOMMENDATIONS

- |      |  |   |
|------|--|---|
| R171 | Members of multidisciplinary professional teams should be alert to the possibility of bulimia nervosa, anorexia nervosa and insulin dose manipulation in adults with Type 1 diabetes with:                                       | C |
|      | <ul style="list-style-type: none"> <li>● over-concern with body shape and weight</li> <li>● low body mass index</li> <li>● poor overall blood glucose control.</li> </ul>  |   |
| R172 | The risk of morbidity from the complications of poor metabolic control suggests that consideration should be given to early (and occasionally urgent) referral of adults with Type 1 diabetes to local eating disorder services. | D |

- R173** Provision for high-quality professional team support at regular intervals with regard to counselling about lifestyle issues and particularly nutritional behaviour should be made for all adults with Type 1 diabetes from the time of diagnosis (see section 6.1, 'Education programmes for adults with Type 1 diabetes' and 6.3, 'Dietary management'). **D**

# 14 Areas for future research

## Priority areas

- ❑ Comparative studies of education models from the time of diagnosis of Type 1 diabetes.
- ❑ Use of well-being and treatment satisfaction assessment tools to enhance the patient-professional interface and make care more directed to the agenda of adults with Type 1 diabetes, while improving biomedical outcomes.
- ❑ A study of multiple interventions to reduce arterial and microvascular risk in adults with Type 1 diabetes identified as being at high risk of development or progression of the late complications.
- ❑ Long-term assessment of recall systems allowing longer intervals between complication/risk factor detection visits according to assessed risk.
- ❑ Trials of regimens and duration of traditional antibiotic therapies in adults with neuropathic foot ulceration.
- ❑ Studies of the effectiveness of quality assurance systems in the surveillance of late complications.

## Other areas

- ❑ Cognitive behavioural therapy for adults with very poor glucose control without obvious organic cause.
- ❑ Development of assessment interviews and questionnaires designed for eating disorders in adults with Type 1 diabetes.
- ❑ Epidemiological studies of trends in the incidence of late complications in defined populations of adults with Type 1 diabetes.
- ❑ Role of lipid-lowering drugs in the prevention of arterial disease in adults with Type 1 diabetes, and studies of markers of higher risk.
- ❑ Models of care for the primary prevention of foot ulceration in adults with Type 1 diabetes.
- ❑ Studies of the economics of the combined and fragmented annual review system.
- ❑ Studies of skill substitution for the initial assessment of diabetes eye photographs in diabetes eye screening.
- ❑ Studies of different methods of day-to-day and meal-to-meal adjustment of insulin doses using defined insulin regimens and appropriate educational packages.
- ❑ Trials of combined renin-angiotensin system blockers in progressive diabetic nephropathy
- ❑ Studies of the optimal use of the new rapid-acting and extended-acting insulins.
- ❑ Approaches to the management of hypoglycaemia unawareness using the new insulins.
- ❑ Assessment of the economic burden of Type 1 diabetes in defined populations.
- ❑ Assessment of the reliability and patient acceptability of self-monitoring of blood glucose in the context of specific regimens.
- ❑ Comparative studies of alternate site and traditional site self-glucose monitoring including patient satisfaction measures.

- ❑ Studies of the role of continuous glucose monitoring systems.
- ❑ Means of surveillance for, and treatment of, sexual dysfunction in women with Type 1 diabetes.
- ❑ Trials of different insulin regimens for people with poor glycaemic control despite apparently optimal education and self-care.
- ❑ Robust studies of the efficacy of the oral glucose-lowering agents, metformin and insulin sensitisers.
- ❑ Development of a useful arterial risk equation specifically for adults with Type 1 diabetes.