Contents

Type 1 Diabetes

Diabetes is a group of disorders with a number of features in common, of which raised blood sugar is the most evident. This guideline is concerned only with type 1 diabetes, a condition that aetiologically is a pure hormone-deficiency disease. However, because hormone replacement with insulin therapy is sub-optimal, acute and long-term complications are endemic despite the implementation of lifestyle and other disease management measures.

Topic CG15AdultS15

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 ov er 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.

The group recognised the very considerable difficulties in reaching conclusions from the ev idence 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 ty pical of the metabolic syndrome and known to be predictors of high arterial risk in people w ith Type 2 diabetes and indeed non-diabetic po pulations. A further group of people will co mbine 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. Ac co r dingly 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 recog nised 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.

Arterial risk factors should be assessed annually Arterial risk factors should be assessed annually, and the assessment should include:

- albumin excretion rate
- smoking
- blood glucose control
- blood pressure
- full lipid profile (including HDL and LDL cholesterol and triglycerides)
- age
- family history of arterial disease (CVD)
- abdominal adiposity. ’

Evidence Statement CG15AdultES153

The Scottish intercollegiate guidelines 174 identify specific risk factors for arterial disease as cigarette smoking, dyslipidaemia, hypertension, hyperglycaemia, obesity and micro- albuminuria

(Linden 2011)

Evidence Statement CG15AdultES154

The guideline 174 re ports on non-randomised studies showing that smoking is an independent arterial risk factor in people with diabetes. Additional observational studies reported dyslip- idaemia. 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 re duction of LDL cholesterol represents a 36% reduction in risk of arterial disease

(Linden 2011)

Evidence Statement CG15AdultES155

Two controlled but not randomised studies reported within the guideline 174 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: 1218) reduction in risk of arterial death over 10 years

(Linden 2011)

Evidence Statement CG15AdultES156

The link between glycaemia and arterial morbidity and mortality was also reported in two studies reviewed in the SIGN guidelines. 174 In o ne study each 1% reduction in HbA 1c was associated with a 21% (95% CI: 1527) reduction in the risk of diabetes-related death and a 14% reduction for myocardial infarction over 10 years

(Linden 2011)

Evidence Statement CG15AdultES157

Ev idence for the other risk factors is sparse. In the SIGN guidelines, 174 no studies were identified for linking obesity as an indepen dent risk factor in established diabetes. One observational study reported microalbuminuria as an independent marker associated with doubling in arterial risk, however, there is ins ufficient evidence to determine whether reducing albumin excretion rate specifically reduces arterial morbidity or mortality

(Linden 2011)

Evidence Statement CG15AdultES158

A meta-analysis 175 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 w ith percentage of women. Duration of diabetes and mean HbA 1c we re 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

(Kanters et al. 1999)

Evidence Statement CG15AdultES159

One systematic review 176 e xamined 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

(Pignone et al. 2001)

Evidence Statement CG15AdultES160

Ev idence within this systematic review 176 for HDL cholesterol showed a higher analytical (6%) and biological (7.5%) variation than total cholesterol, however, two or three values were re quired 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

(Pignone et al. 2001)

Evidence Statement CG15AdultES161

A dditional studies within this systematic review 176 co nsidered 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)

(Pignone et al. 2001)

Evidence Statement CG15AdultES162

Also considered in this systematic review 176 was the comparable accuracy of total and HDL c holesterol 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 re vi ew 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

(Pignone et al. 2001)

Evidence Statement CG15AdultES163

Other studies included in this review 176 assessing characteristics of the screening tests showed that non-fasting total cholesterol alone is the easiest to perform for the patient and provider. T otal: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

(Pignone et al. 2001)

Evidence Statement CG15AdultES164

There was no evidence from this systematic review 176 to inform the question of appropriate frequency of screening. National guidelines reco mmend a five-year interval for people with previous normal results and more freque nt screening in those with borderline values

(Pignone et al. 2001)

Evidence Statement CG15AdultES165

One study 177 co mparing the Sheffield tables to the computer-calculated Framingham equation re v ealed 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 tab les 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

(Bayly et al. 1999)

Evidence Statement CG15AdultES166

A nother evaluation 178 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, w ith a slightly better positive predictive value than the original version (80% vs 71%). The Joint Br itish tables have good specificity (99%), but lo w 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 = 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%, r espectively). 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 = 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 = 10% level of risk, specificity deteriorates to 58%. The Joint Eu ro pean 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

(Bayly et al. 1999)

Evidence Statement CG15AdultES167

A further study from the same investigators 179 assessed the PROCAM program against that of the Framingham equation. Only 56% of the study populat ion were eligible for evaluation with PROCAM. This evaluation also systematically underestimates risk in comparison with the Fr amingham equation at low levels of absolute risk but overestimates at higher risk levels

(Game and Jones 2001)

Evidence Statement CG15AdultES168

The sensitivity and specificity of various risk pr ediction tables and charts was also investigated in one comparative study. 180 Co mpared 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- y ear arterial disease risk threshold specificity is significantly lower than the Sheffield tables. The Eu ro pean 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

(A. F. Jones 2001)

Topic CG15AdultS16

Prevention of arterial risk in people with Type 1 diabetes, through attention to blood glucose co ntrol (insulin therapy, patient education, nutrit ion, 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 re duce the risk of arterial events. The current section therefore deals with these approaches as applied to people with Type 1 diabetes.

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 Ty pe 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.

advice on smoking cessation 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. ’

Evidence Statement CG15AdultES169

The Scottish intercollegiate guidelines 174 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

(Linden 2011)

Evidence Statement CG15AdultES170

SIGN guidelines on lipids 181 and the prevention of ischaemic heart disease detail studies targeted at people with Type 2 diabetes. However, secondary prevention trials of lipids reported 77 Feature Women Men Blood pressure average (mmHg) >135/80 >135/80 Waist circumference (m) (use 0.10m lower >0.90 >1.00 figures for people of South Asian extraction) Serum HDL cholesterol (mmol/l) <1.2 <1.0 Serum triglycerides (mmol/l) >1.8 >1.8 Raised albumin exrection 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. Table 4 Features of the metabolic syndrome suggesting high arterial risk in people

with Type 1 diabetes 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

(J. Miller 2002)

Evidence Statement CG15AdultES171

The SIGN guidelines 174 re port 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 re duction in recurrent coronary events but numbers of people with diabetes in this study were to o 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

(Linden 2011)

Evidence Statement CG15AdultES172

Three randomised controlled trials 182184 re ported on the positive effect of pravastatin on arterial outcomes in people with diabetes. One study 182 re ported 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

(Rustemeijer et al. 1997)

(Raskin et al. 1995)

(Goldberg et al. 1998)

Evidence Statement CG15AdultES173

Similar results were seen in the further two trials. One study 183 reported re ductions in LDL c holesterol 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 184 was in a majority of sulfonylurea treated people with Type 2 diabetes, and pravastatin reduced t otal

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 w ith diabetes. Results were similar to those in people without diabetes, and were unaffected by adjustment for age and sex

(Raskin et al. 1995)

(Goldberg et al. 1998)

Evidence Statement CG15AdultES174

The SIGN management of arterial disease in diabetes guidelines 174 cite results from the Scandinavian Simvastan study, which contained 204 people with diabetes (of a study population of 4,444), and demonstrated that cholesterol-lowering therapy was highly effective co mpared with placebo in those undergoing revascularisation procedures, especially in those w ith diabetes (risk reduction 55% v s 32% in non-diabetes)

(Linden 2011)

Evidence Statement CG15AdultES175

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 185 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 186 also reported a significant reduction in the plasma concentrations of total c holesterol, LDL cholesterol and apolipoprotein B after 12 weeks simvastatin treatment, wh ereas no changes were observed after placebo treatment

(Sweany 1995)

(Hommel et al. 1992)

Evidence Statement CG15AdultES176

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

(Winocour et al. 1990)

Evidence Statement CG15AdultES177

The SIGN guidelines 174 re port 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

(Linden 2011)

Evidence Statement CG15AdultES178

The North of England guidelines 188 on aspirin for the secondary prophylaxis of vascular disease in primary care reported a pooled risk ratio by combining he meta-analysis of the Antiplatelet Co llaborative 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 r aised vascular risk. Few studies were found containing comparisons of aspirin and alternative antiplatelet agents to enable comparison of their relative effectiveness

[@1994]

Evidence Statement CG15AdultES179

Fo r evidence relating specifically to people with diabetes the North of England guidelines 188 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 differen ce (by random effects model) of a 0.3% re duction 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 ex periencing 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 r isk, indicates that patients with diabetes alongside other indications of vascular risk are likely to benefit from routine aspirin therapy

[@1994]

Evidence Statement CG15AdultES180

Am erican Diabetes Association guidelines 76 indicate that meta-analysis and large-scale co llaborative 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 Tr ialists Group reported in the ADA guidelines 76 showed a trend toward increased risk re ductions with doses of aspirin = 325 mg/day, but the difference was not statistically significant. An estimated 3812 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

[@2003]

Evidence Statement CG15AdultES181

The ADA guidelines 76 also reported on the HOT study, which showed a reduction in arterial ev ents following aspirin therapy compared to placebo of 15% and a 36% reduction in my ocardial infarction. This study also showed that fatal bleeding including intracerebral bleeding were equal in aspirin and control groups, whereas non-fatal minor bleeding episodes we re 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

[@2003]

Evidence Statement CG15AdultES182

The ADA guidelines 76 also addressed the safety of aspirin use and reported several prospective r andomised studies in which a trend for an increase in haemorrhagic stroke followed aspirin therapy, although this has not reached statistical significance

[@2003]

Evidence Statement CG15AdultES183

Co ntraindications reported 76 include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding and c linically active hepatic disease

[@2003]

Evidence Statement CG15AdultES184

Re lative risk of MI reported by the ETDRS group 189 in which roughly 48% of men and women w ith diabetes had a history of arterial disease was lowered significantly in the first five years in those randomised to aspirin therapy

[@1992]

Evidence Statement CG15AdultES185

In the management of people with diabetes and new or established vascular disease, the SIGN guidelines 174 re fer to a meta-analysis of platelet inhibitor therapy demonstrating a 31% re duction in non-fatal reinfarction, a 42% reduction in non-fatal stroke and a 13% reduction in arterial mortality

(Linden 2011)

Evidence Statement CG15AdultES186

One meta-analysis 190 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 re co mmendations in this area

(Roffi, Chew, and Mukherjee 2002)

Evidence Statement CG15AdultES187

Also reported in the SIGN guideline 174 is a sub-study analysis of a large RCT demonstrating that addition of clopidogrel to aspirin over 312 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

(Linden 2011)

Evidence Statement CG15AdultES188

The ADA guidelines 76 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)

[@2003]

Evidence Statement CG15AdultES189

One randomised controlled study reviewed in the ADA guideline 76 showed that thrombolytic therapy reduced mortality after acute MI in subjects with diabetes by = 42% with no increase in r isk 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 co ntraindications for thrombolysis in patients with diabetes are the same as those without

[@2003]

Evidence Statement CG15AdultES190

The SIGN guideline 174 re ports 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 = 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 r isk to a greater absolute extent

(Linden 2011)

Evidence Statement CG15AdultES191

Three large trials (AIRE, SAVE and TRACE studies) 174 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

(Linden 2011)

Evidence Statement CG15AdultES192

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 191 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

[@2000]

Evidence Statement CG15AdultES193

Other results from the HOPE study 192 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 tr eatment with vitamin E and placebo. No differences were observed in the frequency of outcomes in people with diabetes in the two treatment groups

(Lonn et al. 2003)

Evidence Statement CG15AdultES194

SIGN guidelines 174 state that clinical presentation of stroke in people with diabetes is similar to that in people without diabetes. There is little eviden ce 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

(Linden 2011)

Evidence Statement CG15AdultES195

W hilst 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. 35052 An economic analysis 350 of simvastatin using the 4S trial data suggests that it would provide cost-effective mortality re duction in the UK amongst a similar population. A second cost-effectiveness paper 351 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. 352

(Grover et al. 2000)

(Grover et al. 2001)

Topic CG15AdultS1

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.

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. The25 role of symptoms and of HbA1c estimation were seen as useful but only supportive, as both lack absolute specificity.

Confirming diabetes 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 HbA1c ’

Evidence Statement CG15AdultES1

Diagnosis, in regard of types of diabetes, is generally not addressed by the WHO report.8 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)

(K. Alberti and Zimmet 1998)

Evidence Statement CG16AdultES2

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.

Topic CG15AdultS2

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, selfmonitoring, 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.

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 UKs 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.

Multidisciplinary teams provide advice 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. ’

Evidence Statement CG15AdultES10

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 study37 suggests improved blood glucose control, while another non-randomised study suggests improved survival (presumably mainly in people with Type 2 diabetes)

(Day, Metcalfe, and Johnson 1992)

Evidence Statement CG15AdultES11

Although papers were ascertained addressing these areas,3844 the papers were descriptive with no useful analysis of patient-related outcomes

(Bridgford and Davis 2001)

(T. M. Davis and Bridgford 2001)

(R. Engelbrecht et al. 1994)

(R. Engelbrecht et al. 1996)

(R. Engelbrecht et al. 1996)

(Rolf Engelbrecht, Ingenerf, and Reiner 2006)

(Gupta, Singla, and Kalra 2014)

Evidence Statement CG15AdultES12

A number of descriptive papers were identified,4548 suggesting such approaches can be feasible and have utility, but not demonstrating comparative advantage to traditional approaches

(Chiarelli et al. 1998)

(C. Gorman et al. 1996)

(Kucher et al. 1990)

(S. A. Smith et al. 1998)

Evidence Statement CG15AdultES13

However when such records were used to send judgemental letters to people with diabetes,49 randomising sites of care, intermediate outcomes were significantly improved (probably mainly in people with Type 2 diabetes)

(Chaudhry et al. 2007)

Evidence Statement CG15AdultES14

A number of approaches to medical care without direct patient contact are described in the literature. One RCT of a telecare system for insulin50 provided equivalent control at reduced cost, while another study12 using nurses resulted in improved blood glucose control

(EVANS 2000)

(Biermann et al. 2002)

Evidence Statement CG15AdultES15

In more rural and remote situations telemedicine can similarly provide apparent time and cost savings where images of foot problems51 and eye photographs52 need to be reviewed by specialists

(McGill, Constantino, and Yue 2000)

(Cummings et al. 2001)

Evidence Statement CG15AdultES16

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.5355 Reduced length of inpatient stay is consistently reported. One study suggests improved glucose control.55 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

(Levetan et al. 1995)

(Levetan et al. 1995)

(Koproski, Pretto, and Poretsky 1997)

Evidence Statement CG15AdultES17

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

Evidence Statement CG15AdultES18

Two potentially useful papers consider the type of treatment facility used to deliver care to those with Type 1 diabetes.334,335 One German study334 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 study335 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 study297 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.

(Rose et al. 2000)

[@1994]

(M. Davies et al. 2001)

Evidence Statement CG15AdultES4

A nurse specialist approach has been justified by a number of before-and-after studies and case series with such input1317

(Hearnshaw et al. 2001)

(Batista et al. 2010)

(Larsson et al. 1995)

(Brink, Miller, and Moltz)

(Yokoyama et al. 2001)

Evidence Statement CG15AdultES5

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 study18 (it is unclear whether that study is randomised) showing less foot ulceration

(Dargis et al. 1999)

Evidence Statement CG15AdultES6

A number of historically-controlled or descriptive studies support this approach, mainly reporting on patient preference outcomes15,1921

(Larsson et al. 1995)

(D. Cox et al. 1995)

(APELQVIST et al. 1994)

(Frykberg 1997)

Evidence Statement CG15AdultES7

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

(Riazi et al. 2000)

[@1992]

Evidence Statement CG15AdultES8

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 Federations European guideline recommends integration of these activities into one patient visit.24 Annual review is also the basis of many quality control structures proposed for diabetes care,25 including (implicitly) that of the UK Audit Commission

[@1998]

(Grabert, Schweiggert, and Holl 2002)

Evidence Statement CG15AdultES9

A series of descriptive papers appear to demonstrate the feasibility of establishing populationbased and clinic-based diabetes registers, with varying densities of information.2636 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

(Azzopardi et al. 1995)

(S. D. Burnett, Woolf, and Yudkin 1992)

(Shirley D. Burnett, Press, and Yudkin 1993)

(**???**)

(Comino et al. 2013)

(Howitt and Cheales 1993)

(Kelly, Bilous, and Murray 1998)

(R. W. Taylor et al. 2010)

(D. Edelman 2001)

(Kopelman, Michell, and Sanderson 1995)

(Vaughan et al. 1996)

Evidence Statement CG17AdultES3

The Diabetes Control and Complications Trial (DCCT),9 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 review10 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 RCT11 of the impact of structured team care as compared to usual care showed improved satisfaction and blood glucose control at six months. An RCT12 of the use of diabetes specialist nurses to adjust insulin doses over the telephone showed improved blood glucose control.

Topic CG15AdultS3

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 byhealthcare team, family and friends). Informal interpersonal variables, such as social resources and support, have been found to be associated with better diabetes self-management,56 7 family environment,58 60 and marital interaction.61 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.

•

Support groups 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. ’

Evidence Statement CG15AdultES19

The Diabetes Attitudes, Wishes and Needs (DAWN) questionnaire study 62 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

[@2002]

Evidence Statement CG15AdultES20

There are still significant numbers of people emerging from the confirmation of a diagnosis who are underinformed and unsupported. 63 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 64

[@2008]

(Greenwood 2003)

Evidence Statement CG15AdultES21

R esearch evaluating the effectiveness of support groups for patients and carers, across n umerous conditions and groups (not necessarily diabetes), has shown specific benefits including:

- psychological and emotional benefits 65 including lower pain perception and improved ability to cope with stress 63,667
- reduction of carers burdens and stresses 689
- improvement in quality of life 7071
- improved self-care through health promotion strategies which have been helpful in smoking cessation and management of chronic conditions 723
- improved access to health service provision 74
- reduced isolation, overcoming depression and loss of self-esteem 64
- better understanding of conditions, symptoms and healthcare systems through education and information. 67

(Jessup 2001)

(Knight, Lutzky, and Macofsky-Urban 1993)

(R. W. Toseland et al. 1992)

(M. S. Labrecque, Peak, and Toseland 1992)

(Ostwald et al. 1999)

(Hanestad and Albrektsen 1993)

(Maxwell, Hunt, and Bush 1992)

(Fisher et al. 1998)

(Morris 1998)

(Tomlinson 1992)

Evidence Statement CG15AdultES22

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: 67a

- diet
- insulin

- medicines other than insulin
- new diagnosis
- travel.

Topic CG15AdultS5

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 w ith 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. Ac co r dingly patient education is a true corner stone 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.

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 manage- ment 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 inap propriateness of the classical clinical trial model when just one feature of an integrated pac kage 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) c ould not be ignored. Such information suggested that educational interventions were likely to be c ost-effective, but it was impossible to make compar ative judgements of different education models, a conclusion seemingly also reached by the NICE Appraisal Committee on the basis of a re port from the University of Southamptons health technology assessment unit. Is sues 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 groups experience of these in practice, served to guide recommendations broadly in line with those of Diabetes UK and the International Diabetes Federation (Europe).

Structured diabetes education 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.
'

Evidence Statement CG15AdultES23

There were no trials located in newly-diagnosed people with Type 1 diabetes specifically, or co ncerned with the initial content of educatio n. The American Diabetes Association (ADA) guidelines 76 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

[@2003]

Evidence Statement CG15AdultES24

One small randomised controlled trial 77 co mparing the efficacy of classroom teaching of diabetes skills, compared to individualised learning, found that classroom teaching led to a gr eater 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

(Street et al. 1993)

Evidence Statement CG15AdultES25

One randomised controlled study compared two interactive computer schemes to reinforce an educational video. The first gave additional f eedback and information on the correct answers, the second only the correct answers. 78 Pe ople 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 use r ratings for the two software packages, but the people in the additional feedback group had a better diabetes knowledge at baseline, so the re sults may be biased by this confounding factor

(RICCOMINI 2002)

Evidence Statement CG15AdultES26

An update of the US standards for diabetes self-management education79 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.

- 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 chroniccomplications 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 individuals assessment, education plan,intervention, evaluation and follow-up in the permanent confidential education record.

(Mensing et al. 2000)

Evidence Statement CG15AdultES27

Within an overall review of patient education models for diabetes (not type-specific) one health technology assessment80 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 ter ms of reduced HbA 1c levels. In another study, an intensive five-day training course was found to be effective in reducing HbA 1c levels. In one study there was no difference in blood gl ucose control with education compared to usual care, while there were no between-group co mparisons 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 neuro pathy 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 directl y attributable to the education aspect of the intervention.

Evidence Statement CG15AdultES28

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 care81

(I. Weerdt et al. 1991)

Evidence Statement CG15AdultES29

A medium-sized randomised controlled trial 82 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 1c levels were reduced compared with normal clinical care in people w ith Type 1 diabetes. However, age differences between the control and intervention groups at baseline mean that this study is possibly methodologically limited

(Lennon et al. 1990)

Evidence Statement CG15AdultES30

A nother moderate-sized systematic review of eight trials encompassing over 3,000 patients with either Type 1 or Type 2 diabetes, 83 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 re vi ew found that an intensive educational inter ve ntion 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. Au thors of the review noted methodological limitations of the included studies, and outcome re porting times varied between individual trials

(Valk, Kriegsman, and Assendelft 2002)

Evidence Statement CG15AdultES31

Ev aluation, in a large systematic review, 84 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 glycated 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 c hildren or adolescents showed a significant decrease in GHb after DSME, and a borderline 6 Education programmes and self-care 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

(NORRIS et al. 2002)

Evidence Statement CG15AdultES32

A small randomised controlled trial 12 in people with Type 1 diabetes found that an intervention wh ereby patients received regular telephone contact with a diabetes nurse to alter insulin re g imen decreased HbA 1c ov er six months compared to usual care. This difference was not found to be affected by age, sex or type of diabetes

(EVANS 2000)

Evidence Statement CG15AdultES33

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, 85 w hich 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 w ould not form a rigorous basis for recommending such an approach

(P. M. Jones 1990)

Evidence Statement CG15AdultES34

A similar intervention among adolescents (mean age 18 years) in India enrolled in a prospective r andomised trial, 86 w ith 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 pe ople 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

(Sudhir, Kumaraiah, and Munichoodappa 2003)

Evidence Statement CG15AdultES35

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 co mpared 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 87

(Korhonen et al. 1983)

Evidence Statement CG15AdultES36

There were no significant differences in adherence to glucose self-monitoring or in blood gl ucose 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 Type 1 diabetes in adults: national

clinical guideline for diagnosis and management tr ial. 88 The trial included a population of people with Type 1 diabetes who had had the co ndition 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 re ce iv ing 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

(W. A. Davis, Bruce, and Davis 2007)

Evidence Statement CG15AdultES37

A ssessing the cost-effectiveness of patient education is complicated by the fact that patient education is rarely assessed in isolation. Recent NICE guidance 338 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. 339,340 Of these, only one 339 included Type 1 diabetes patients, and this established cost-effectiveness ratios for altering food habits.

(Bryant et al. 2007)

(Glasgow et al. 1997)

(R. M. Kaplan et al. 1987)

Topic CG15AdultS6

In sulin therapy has to be adjusted with lifesty le, 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 w ould be to the advantage of any person using insulin therapy. Potential should exist here to assist with diabetes self-education, dose optimisat ion, reassurance over hypoglycaemia and helping professionals give optimum advice on insulin regimens.

Self-monitoring does not, in itself, appear to improve blood glucose control. However, the gr oup 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 re vi ew is agreed as necessary and normal practice. Different individuals are noted to use this te c hnology 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.

Self-monitoring of blood glucose levels 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. ’

Evidence Statement CG15AdultES38

Pa pe rs contained within a systematic review 89 suggest that the evidence on issues of observer tr aining, interdevice variability, the effects of long-term use and patient acceptability have not been adequately addressed

(Coster et al. 2000)

Evidence Statement CG15AdultES39

One study within the systematic review 89 co mparing 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 re sults when no test had been performed. These findings were confirmed in another reviewed study of 14 people who recorded lower blood gl ucose values in logbook records than meter memories

(Coster et al. 2000)

Evidence Statement CG15AdultES40

Reported within the systematic review, one trial 89 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

(Coster et al. 2000)

Evidence Statement CG15AdultES41

Pa tient factors (as described below) were shown to have an impact (both positive and negative) on the reliability of monitoring in five studies. 89 Re liability can be improved through proper training of patients, and was shown in sub-group analysis to be equally as good in older pe ople, and people with visual impairments (on co ndition 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

(Coster et al. 2000)

Evidence Statement CG15AdultES42

Four trials contained within a systematic review 89 failed to show with sufficient power a demonstrated effect of SMBG on blood glucose control

(Coster et al. 2000)

Evidence Statement CG15AdultES43

Two trials comparing urine and blood testing showed no clinical difference in the two tests89

(Coster et al. 2000)

Evidence Statement CG15AdultES44

A systematic review 89 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

(Coster et al. 2000)

Evidence Statement CG15AdultES45

One methodologically-limited crossover study 90 co mparing blood glucose meters with visual t est 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

(E. Brown et al. 1986)

Evidence Statement CG15AdultES46

One methodologically-limited comparative study 91 showed that fructosamine self-test results co rr elated 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

(S. V. Edelman, Callahan, and Deeb 2000)

Evidence Statement CG15AdultES47

A further methodologically-limited diagnostic study 92 in people with Type 2 diabetes showed self-testing of fructosamine to be comparable in accuracy to laboratory fructosamine and GHb values

(Cefalu et al. 1999)

Evidence Statement CG15AdultES48

One trial with 25 patients 93 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

(Gordon, Semple, and Paterson 1991)

Evidence Statement CG15AdultES49

A study of the preferences of 18 patients within a systematic review 89 reported a pr eference for t esting four times daily twice weekly, or four times daily once a week, compared to twice daily ev ery day of the week

(Coster et al. 2000)

Evidence Statement CG15AdultES50

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 89

(Coster et al. 2000)

Evidence Statement CG15AdultES51

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 89 identifies one paper considering the cost-effectiveness of blood or urine glucose monitoring against conventional dietary control amongst those with Type 1 diabetes. 341 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

(Coster et al. 2000)

(Starostina et al. 1994)

Topic CG15AdultS7

The imperfect nature of insulin replacement the ra py , 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 ex cursions are to be appropriately minimised. Fu r thermore, 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.

The group was impressed by the systematic approach to nutritional recommendations published by the ADA, 76 and the consistency of that approach with the new recommendations from Diabetes UK. 107 Co nsideration 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 diabet es had particularly addressed the relevance of one programme for mealtime insulin dose ad justment (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 appraisals 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 ex cursions and arterial risk

Offer nutritional information at time of diagnosis Nutritional information sensitive to personal needs and culture should be offered from the time of diagnosis of Type 1 diabetes. ’

Evidence Statement CG15AdultES52

F our small randomised controlled trials 9497 we re identified examining different diet regimens in people with Type 1 diabetes. One randomised controlled study 94 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 1c , cholesterol, body weight and insulin dose were not affected

(R. Giacco et al. 2000)

(HANSEN et al. 1999)

(Chantelau and Wichmann 1992)

(McCulloch et al. 1985)

Evidence Statement CG15AdultES53

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 97 was seen at 12 months to improve HbA 1c

(McCulloch et al. 1985)

Evidence Statement CG15AdultES54

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

(Chantelau and Wichmann 1992)

Evidence Statement CG15AdultES55

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. 95 Outcomes of urinary sodium ex cretion, blood pressure, BMI and HbA 1c we re not significantly different between the diets

(HANSEN et al. 1999)

Evidence Statement CG15AdultES56

Canadian clinical practice guidelines 98 re co mmend 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

(Lau 2007)

Evidence Statement CG15AdultES57

A medium-sized randomised controlled trial 99 of a five-day outpatient programme to enable patients to replace insulin by matching it to desired carbohydrate intake amongst adults with Ty pe 1 diabetes found that the intervention improved HbA 1c com pared 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

(D. S. Group 2002)

Evidence Statement CG15AdultES58

A similar small trial 96 in which intensified insulin plus simplified diet was compared to co nv entional therapy and diet found HbA 1c to be significantly reduced, although there was no differences between the study groups for outcomes of body weight, BMI, cholesterol or triglyce rides

(Chantelau and Wichmann 1992)

Evidence Statement CG15AdultES59

A large cohort study 100 comparing degree of liberalisation of diet away from a specific co ntrolled diet after a treatment and teaching programme with estimation of carbohydrate intake and subsequent insulin self-adjustme nt found that there was no significant relationship between BMI and degree of diet liberalisation. In addition there was no relationship with HbA1c 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 gl ucose more than three times a day

(MÃHAUSER et al. 1995)

Evidence Statement CG15AdultES60

The recent evidence-based guidelines for nutrition principles developed by the ADA, 76 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

[@2003]

Evidence Statement CG15AdultES61

The recent NICE Technology Appraisal 101 into patient education models (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.

(Blinkhorn 2003)

Topic CG15AdultS8

Ma ny 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 re co mmended 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 Ty pe 1 diabetes.

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 co nsistent 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 ex ercise programme as part of a lifestyle improvement initiative. Some people will undertake significant exercise by choice and would benefit from support in so doing.

Advise that physical activity can reduce enhanced arterial risk Adults with Type 1 diabetes should be advised that physical activity can reduce their enhanced arterial risk in the medium and longer term. ’

Evidence Statement CG15AdultES62

One small randomised controlled trial 102 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 tr aining. There were no significant changes in outcomes of HbA 1c and plasma glucose. The study was not blinded due to the nature of the intervention

(LAAKSONEN et al. 2000)

Evidence Statement CG15AdultES63

A small cross-sectional study 103 ev aluating the effect of three months of individualised aerobic ex ercise in altering blood pressure and lipid profile found that HbA 1c , 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

(Ligtenberg 1999)

Evidence Statement CG15AdultES64

Another study with a similar intervention 102 found that four months of aerobic training provided no changes in terms of HbA 1c or total cholesterol, although there were benefits of ex ercise compared to control in terms of peak oxygen uptake

(LAAKSONEN et al. 2000)

Evidence Statement CG15AdultES65

A prospective non-randomised study 104 w ith 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 ex ercise. Also cholesterol decreased significantly, however there were no reported significant c hanges in fasting blood glucose, HbA 1c and microalbuminuria

(Lehmann et al. 1997)

Evidence Statement CG15AdultES66

A medium-sized randomised controlled trial 105 of intensive advice and lifestyle programme w ith specified diet and exercise prescriptions compared to conventional care found that HbA 1c decreased from baseline measurements significantly over six months in the control group but re mained 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

(Perry et al. 1997)

Evidence Statement CG15AdultES67

A small before and after study 106 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 w ith 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

(S. H. Schneider et al. 1992)

Evidence Statement CG15AdultES68

A non-randomised prospective controlled study 103 to assess whether exercise is related to better diabetes control was reviewed. There was no significant correlation between the exercise ex pe nditure and HbA 1c in all Type 1 diabetes patients, nor was there any relationship to the frequency of mild hypoglycaemic events

(Ligtenberg 1999)

Evidence Statement CG15AdultES69

The ADA 76 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

[@2003]

Topic CG15AdultS10

Ty pe 1 diabetes is for most of the time asymptomatic once effective therapy is instituted. However, it is generally understood that there is a re lationship 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.

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 1c is the only measure for which quantitative information linking glucose control to complications is av ailable, and then only when standardised to the assay used in the DCCT study. Near patient t esting was felt to be a core component of making optimal and relevant use of HbA 1c re sults. Co ntinuous glucose monitoring systems were considered to not yet have established their usefulness beyond problem-solving in the occasional person with recurrent blood glucose co ntrol problems at the same time of day.

Clinical monitoring of blood glucose levels Clinical monitoring of blood glucose levels by high precision DCCT-aligned methods of haemoglobin A 1c (HbA 1c) should be performed every two to six months depending on:

- achieved level of blood glucose control
- stability of blood glucose control
- change in insulin dose or regimen ’

Evidence Statement CG15AdultES70

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

(Coster et al. 2000)

Evidence Statement CG15AdultES71

Tw o studies in a systematic review 89 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

(Coster et al. 2000)

Evidence Statement CG15AdultES72

The same systematic review 89 re ported 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 re duction in morbidity

(Coster et al. 2000)

Evidence Statement CG15AdultES73

A Danish systematic review 108 re ported that HbA 1c values allowed clinicians to identify patients with poor glycaemic control, concluding that GHb is the most clinically appropriate t est of long-term glycaemia and should be used in routine management of Type 1 diabetes

(Larsen and Hørder 1989)

Evidence Statement CG15AdultES74

One study within a systematic review 89 recommended that no more than six GHb assays were necessary in a given year

(Coster et al. 2000)

Evidence Statement CG15AdultES75

ADA recommendations 76 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

[@2003]

Evidence Statement CG15AdultES76

One study within a systematic review 89 re ported 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

(Coster et al. 2000)

Evidence Statement CG15AdultES77

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

(Coster et al. 2000)

Evidence Statement CG15AdultES78

Two studies contained within a systematic review, 89 in patients with renal failure and elderly Ty pe 2 diabetes patients with liver cirrhosis and nephrotic syndrome, suggest the influence of ch ro nic conditions rather than metabolic control on fructosamine levels is the source of unreliability in test result. The systematic review co ncludes that more evidence is needed to r esolve these issues

(Coster et al. 2000)

Evidence Statement CG15AdultES79

One correlation study within a review 89 showed no significant correlation between HbA 1c and fructosamine results over a six month follow-up

(Coster et al. 2000)

Evidence Statement CG15AdultES80

ADA recommendations 76 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

[@2003]

Evidence Statement CG15AdultES81

A systematic review 89 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

(Coster et al. 2000)

Evidence Statement CG15AdultES82

A nother study found that fasting blood glucose level (FBG) and serum fructosamine are not as useful as HbA 1c for monitoring diabetic control, but are additional extras for assessing control ov er short and long periods 89

(Coster et al. 2000)

Evidence Statement CG15AdultES83

Three observational studies 109111 co mpared continuous glucose monitoring systems (CGMS) w ith 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

(Gross et al. 2000)

(Gross et al. 2000)

(Maran et al. 2002)

Evidence Statement CG15AdultES84

One study 111 re ported 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

(Maran et al. 2002)

Evidence Statement CG15AdultES85

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

(Bernstein, Jacobs, and Granata 2002)

Evidence Statement CG15AdultES86

In the same review, 112 questionnaires recording patient satisfaction of near patient testing co ncluded that the introduction of near patient testing for HbA 1c 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

(Bernstein, Jacobs, and Granata 2002)

Evidence Statement CG15AdultES87

W ithin the health technology assessment, 112 a retrospective cohort study showed that, after allowing for confounding factors, mean HbA 1c 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 1c level, further, prospective studies are required

(Bernstein, Jacobs, and Granata 2002)

Evidence Statement CG15AdultES88

A systematic review 89 re ported four studies on the effectiveness of benchtop analysers co mpared 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 1c , compared w ith high performance liquid chromatography (HPLC)

(Coster et al. 2000)

Evidence Statement CG15AdultES89

An HTA report 112 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 89 re co mmended further research into the cost-effectiveness of near patient t esting for diabetes, FBG and fructosamine testing. No other paper in the health economics searches specifically addressed the issue of clinical monitoring

(Bernstein, Jacobs, and Granata 2002)

(Coster et al. 2000)

Topic CG15AdultS11

The DCCT, and a number of smaller studies which are potentially underpowered, 113 suggest that more intensive management of people with Type 1 diabetes (by themselves, with advice) re duces 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 ch oose 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 1c 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.

There must be a threshold for glucose control and the development of microvascular co mplications, or non-diabetic people would get complications. Indeed, this threshold must be we ll above the normal range as people with impaired glucose tolerance (IGT) do not (by definition) get microvascular complications. As people with IGT have HbA 1c levels of up to 7.0%, this by itself sets a lower limit of microvascular risk. The microvascular thresholds of HbA 1c 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%. Re co mmendations 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 Ty pe 2 diabetes go for HbA 1c 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 co nsider tighter targets for glucose control (if feasible) in people in these categories. Ho we ve r, 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 w ho 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 Ty pe 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 co ntrol and counter impressions of failure if targets are not attained.

Maintaining a DCCT-harmonised HbA 1c below 7.5% Adults with Type 1

diabetes should be advised that maintaining a DCCT-harmonised HbA 1c below 7.5% is likely to minimise their risk of developing diabetic eye, kidney or nerve damage in the longer term. '

Evidence Statement CG15AdultES100

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

(MCCANCE 1989)

Evidence Statement CG15AdultES101

Ne ither the Oslo nor Stockholm studies of control and complications in Type 1 diabetes 121 give useful data on targets and thresholds, beyond showing that people with lower levels on average do better

(Reichard, Nilsson, and Rosenqvist 1993)

Evidence Statement CG15AdultES102

A non-randomised controlled study 122 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 7.98.5% HbA 1c (the authors chose to centre on 8.1%)

(A. S. Krolewski et al. 1995)

Evidence Statement CG15AdultES103

A non-randomised controlled study 123 looked at how glycated Hb measurement related to OG TT re sults, performing a meta-analysis on 18 studies. Unfortunately most of these were published before any kind of GHb standardisation, rendering the results uninterpretable

(A. L. Peters 1996)

Evidence Statement CG15AdultES104

A further cohort study 124 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 co ntrol relationships were the same in Type 1 and Type 2 diabetes. The data presentations are strongly reminiscent of previous work, 122 w ith 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 1c somewhere above 7.4% (and below 9.1%)

(A. S. Krolewski et al. 1995)

[@1994]

Evidence Statement CG15AdultES105

Tw o non-randomised controlled studies 116,125 re port the relationship between HbA 1c and self- monitored pre- and post-prandial glucose levels. The reports are consistent and can be related to D CCT-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 gl ucose profiles between bedtime and pre-breakfast readings. These data give the most robust ev idence of the relationship between HbA 1c and the toxic glucose concentrations which actually cause the microvascular damage

(Rohlfing et al. 2002)

(Nathan et al. 1984)

Evidence Statement CG15AdultES90

In 1989, the European NIDDM Policy Group (Type 2 diabetes) suggested HbA 1 was good <8.5%, acceptable 8.59.5%, poor >9.5% (equivalent to HbA 1c of <6.9, 6.97.7, >7.7%). No ev idence 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 114

(K. G. M. M. Alberti and Gries 1988)

Evidence Statement CG15AdultES91

In 1993, the above guidelines were revised to HbA 1c <6.5%, 6.57.5%, 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- D CCT recommendations are not justified in the text 115

(E. D. P. Group 1999)

Evidence Statement CG15AdultES92

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 1c : adequate 6.27.5%, 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 115

(E. D. P. Group 1999)

Evidence Statement CG15AdultES93

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

(Boynton 1998)

Evidence Statement CG15AdultES94

The ADA has republished its recommendations yearly. 76 These choose a glycaemic goal of HbA 1c <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 1c of 7.0% equates to mean self-monitored plasma glucose of 9.5 mmol/l 116

[@2003]

(Rohlfing et al. 2002)

Evidence Statement CG15AdultES95

Ho we ve r in the same issue (January 2003), 76 the ADA notes in a chapter on Implications of the D CCT that the level of glucose control to be sought under ideal circumstances is an HbA 1c of around 7.2% (average glucose 8.6 mmol/l). This argument is based on that achieved in the D CCT, and is thus not theoretically justified

[@2003]

Evidence Statement CG15AdultES96

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 1c of about 7.7%

Evidence Statement CG15AdultES97

The DCCT data has never been satisfactorily analysed with a view to answering this question. A graph in the original main paper 117 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:

- 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

[@1993]

Evidence Statement CG15AdultES98

Fu r ther analysis was published in 1995. 118 Un fortunately, 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 r etinopathy progression in the intensively managed group did not increase with time with a mean HbA 1c of 8.0%, and increased little at this level in the conventionally managed group w ith time

[@1995]

Evidence Statement CG15AdultES99

R eanalysis of the published DCCT curve 118 suggests no worsening of retinopathy rates from normal levels until HbA 1c >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. 119 A similar level is found for r etinopathy of 2% per 100 patient years at an HbA 1c of 7.5% and of 1% per 100 patient years at a level of 6.5%

[@1995]

(Stratton et al. 2001)

Topic CG15AdultS12

Ty pe 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. Fu r thermore subcutaneous depot insulin preparations have, until recently, not come close to providing the physiological plasma insulin profiles occurring at mealtimes or in the inter- prandial basal state. A number of preparations of mealtime and extended-acting insulins are av ailable, and combining these to suit individual needs, while taking account of preferences for n umbers of injections, gives a variety of possib le insulin regimens of differing characteristics. W hile insulin deficiency is the hallmark of Type 1 diabetes, a few people retain some insulin secretion for a short time (and might therefo re benefit from insulin secretagogues). Some gl ucose-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.

It was noted that Type 1 diabetes is a hormone deficiency disease. The problems faced by people w ith the condition (injections, hypoglycaemia, hyperglycaemia, consequences of capricious co ntrol, late complications) were noted to be solely a function of the poor state of insulin re placement 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 befo re meals and human isophane (NPH) insulin for basal supply had become widespread, and that, the analogues aside, there was no evidence to ch allenge that conventional practice. Long-acting analogues, or rather insulin glargine, are co ve re d by NICE appraisal guidance, and this recommends their availability for use in people w ith Type 1 diabetes. Rapid-acting insulin analogues are supported by an evidence base for less hy poglycaemia at night and at some other times, reduced hyperglycaemic excursions after meals and small improvements in HbA

1c , suggesting that these too should have an increasing r ole 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 co mbination 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 1c 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 gl ucose 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 we re 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- * 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.

Access to insulin Adults with Type 1 diabetes should have access to the types (preparation and species) of insulin they find allow them optimal well-being. ’

Evidence Statement CG15AdultES106

In sulin with the molecular structure of human and animal insulins is currently available. Ev idence from the majority of studies 1268 re ports no significant differences in hypoglycaemic episodes and glycaemic control between the insulin of human and animal chemical structures

(Richter, Neises, and Bergerhoff 2002)

(George et al. 1997)

(Karlson and Agardh 1994)

Evidence Statement CG15AdultES107

Co nv entional two-dose insulin regimens may re sult in a high frequency of nocturnal hy poglycaemia. Intensified three-dose insulin regimens improve glycaemic control, but often do not improve morning blood glucose 129

(Egger et al. 1997)

Evidence Statement CG15AdultES108

Co ntinuous subcutaneous insulin infusion (CSII) improves nocturnal and morning glycaemic co ntrol compared with multiple daily injection (MDI) regimens. With multiple injection re g imens the morning injection must not be delaye d. Total and bolus insulin doses required are lower with CSII compared with MDI 130

(Haakens et al. 1989)

Evidence Statement CG15AdultES109

Mo r tality from acute metabolic causes (ketoacidosis) was reported as significantly increased w ith intensified treatment; odds ratio 7.20 (pumps) 1.13 (multiple daily injection). 129 The pump data is however based on early pump technologies

(Egger et al. 1997)

Evidence Statement CG15AdultES110

S imilar glycaemic control results from either lente or isophane (NPH) insulin when used as basal insulin for multiple injection regimens toge ther with a short-acting insulin preparation before meals 131

(Tunbridge et al. 1989)

Evidence Statement CG15AdultES111

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 Ty pe 1 diabetes; 132 some studies in this review show significantly lower fasting blood glucose w ith insulin glargine than isophane (NPH) insulin and others suggest that people on insulin g largine may experience

fewer hypoglycaemic ev ents than people receiving once-daily isophane (NPH) insulin 132

(&NA 2008)

Evidence Statement CG15AdultES112

Ev idence from a large multicentred study suggests that people commonl y 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 hy poglycaemia suggests that this regimen does not give satisfactory post-prandial blood glucose contr ol in many patients 133

(L. Vignati, Anderson, and Iversen 1997)

Evidence Statement CG15AdultES113

Rapid acting insulin analogues allow injection close r to mealtimes due to their pharmacokinetic profile 1346

(F. S. Nielsen et al. 1995)

(Lindholm, McEwen, and Riis 1999)

(Sindaco et al. 1998)

Evidence Statement CG15AdultES114

A meta-analysis 137 and several open-label trials 133,138145 show that insulin lispro is more effective than unmodified (soluble) human insulin in improving post-prandial glucose co ntrol, without an increase in the rate of hypoglycaemic episodes

(L. Vignati, Anderson, and Iversen 1997)

(Davey et al. 1997)

(Lalli et al. 1999)

(J. H. Anderson et al. 1997)

(PfÃ¼tzner et al. 1996)

(Renner et al. 1999)

(Ebeling et al. 1997)

(Roach et al. 1999)

(U.K. Trial Group 2000)

(Roach et al. 1999)

Evidence Statement CG15AdultES115

Two studies 1467 show reduced frequency of nocturnal hypoglycaemia 148 with insulin lispro compared to unmodified (soluble) human insulin

(F. Holleman et al. 1997)

(Ahmed and Home 1998)

(B. L. Brunelle et al. 1998)

Evidence Statement CG15AdultES116

Two studies 1489 show reduced frequency of severe hypoglycaemia with insulin lispro co mpared to unmodified (soluble) human insulin

(B. L. Brunelle et al. 1998)

(Battista, Feeny, and Hodge 1995)

Evidence Statement CG15AdultES117

Pa tients perceive an improvement in their well-being and quality of life with rapid-acting insulin analogues due to flexibility of inject ion times and less frequent hypoglycaemic reactions 128,141,146

(Karlson and Agardh 1994)

(Renner et al. 1999)

(F. Holleman et al. 1997)

Evidence Statement CG15AdultES118

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

(L. Vignati, Anderson, and Iversen 1997)

(Davey et al. 1997)

(Battista, Feeny, and Hodge 1995)

Evidence Statement CG15AdultES119

Two multicentre randomised studies 14950 and one RCT 135 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

(Lindholm, McEwen, and Riis 1999)

(Battista, Feeny, and Hodge 1995)

(Home et al. 1998)

Evidence Statement CG15AdultES120

A before-and-after study has shown that a lower dose of mealtime insulin can be taken along w ith 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 142

(Ebeling et al. 1997)

Evidence Statement CG15AdultES121

Tw o randomised trials have shown that it is possible to replace mealtime unmodified (soluble) h uman insulin with insulin lispro or insulin aspart without detriment to glycaemic control if care is taken to replace basal insulin delivery more physiologically 1512

(Zinman et al. 1999)

(Hermansen et al. 2001)

Evidence Statement CG15AdultES122

A multi-arm randomised trial found that a dding a few units of isophane (NPH) insulin to insulin lispro at each meal, in combination with bedtime NPH insulin improves blood glucose co ncentrations compared to an unmodified (soluble) human insulin regimen in a multidose reg imen 136

(Sindaco et al. 1998)

Evidence Statement CG15AdultES123

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 ev ening split regimen reduced by more than 60% the risk of nocturnal hypoglycaemia; 1534 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

(Stades et al. 2002)

(Fanelli 2002)

Evidence Statement CG15AdultES124

Wh en 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 1c ; 130 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

(Haakens et al. 1989)

Evidence Statement CG15AdultES125

Fr equency of hypoglycaemic reactions was found to be similar on patient-mixed and premixed insulins. 143,155 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; 155 83% of people expressed a preference for premixed insulins throughout the trial

(Roach et al. 1999)

(Dunbar et al. 1994)

Evidence Statement CG15AdultES126

Fe w 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. 156 Po or 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 tr eatment goals and the ways in which these goals are to be attained as well as an explanation of the advantages and disadvantages

(Swinnen et al. 2009)

Evidence Statement CG15AdultES127

F our randomised controlled trials, two large parallel groups, 1578 and two small crossover designs 15960 we re 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 m ulticentred study 157 w ith variable doses titrated up to 300 mg three times a day for 24 weeks, found a significant reduction in HbA 1c levels with acarbose compared to placebo, and decreases in fasting and post-prandial glucose levels to two hours. There were no differences between gr oups for daily insulin dose or hypoglycaemic ev ents, although adverse events of abdominal pain, diarrhoea and flatulence were more common with acarbose. This led to more frequent tr eatment discontinuation in the acarbose group than the placebo group. A similar Italian tr ial 158 w ith up to 100 mg acarbose three times daily for 24 weeks found no difference in HbA 1c 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

(Hollander, Pi-Sunyer, and Coniff 1997)

(Riccardi et al. 1999)

(Viviani et al. 1988)

(Marena et al. 1991)

Evidence Statement CG15AdultES128

The two crossover trials with 100 mg acarbose three times a day over relatively short time periods did not assess requirement for wash ou t 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 1c w ith acarbose, 160 while the other found no significant differences between gr oups. 159 Po te ntial methodological limitations of these trials would not permit them to be used as an evidence base to inform recommendations in this area

(Viviani et al. 1988)

(Marena et al. 1991)

Evidence Statement CG15AdultES129

Tw o small randomised controlled trials investigat ed 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 gl yburide (orally) for 12 weeks compared to placebo after a 12-week open-label insulin stabilisation run-in period 161 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 le ve ls at any stage of the study. A randomised study without comparison between groups at baseline with 5 mg glyburide daily for 24 weeks co mpared to placebo 162 found no differences in plasma C-peptide levels between groups, nor difference in plasma glucose concentrations at any time point. Although HbA 1c levels were re ported 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 ev idence base to inform recommendations in this area

(Tzefos and Olin 2010)

(NATHAN 1988)

Evidence Statement CG15AdultES130

Co mparison 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 163 found mean blood glucose level, HbA 1c and blood glucose variability to be significantly lower w ith 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

(Burke, Hartog, and Waterfield 1984)

Evidence Statement CG15AdultES131

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. 164 Although glycated haemoglobin both fasting and one hour post-breakfast were found to be very similar in both gr oups, 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 ov erwhelming majority of people with Type 1 diabetes

(Fallucca, Sciullo, and Maldonato 1996)

Evidence Statement CG15AdultES132

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 Ty pe 1 diabetes (including reduced basal therapy) as compared to placebo over a period of six months. This was achieved without significant change to HbA 1c or increased incidence of hy poglycaemia

Evidence Statement CG15AdultES133

The health economic searches produced no studies giving guidance on appropriate insulin re g imens 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 132 re co mmended insulin glargine as a long-acting preparation for people with Type 1 diabet es alongside insulin NPH. The crucial issue for the c ost-effectiveness of insulin glargine is the amount of utility associated with reducing the fear of hypoglycaemia. Tw o cost-benefit studies were identified that considered the role of insulin lispro. 342,380 Ne ither 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 co mplexity 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, 3434,381 of which two attempted to form QALYs. The health utility values in each of the studies are poor: in one study 343 non-preference-based values are used; in another 381 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. Tw o models analysed intensive treatment in cost-per-life-year terms, and differed in their re sults. One study 343 produced a cost-per-life-year figure of US$28,661 at 1994 prices, whilst another 344 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 c ost analyses also suggest that the DCCT cost estimates may be overestimates. 3456 Few inferences can be drawn because these studies are limited but it appears likely that intensive tr

eatment, including intensive insulin regimens, will be cost-effective.

Topic CG15AdultS13

As a large protein, insulin cannot be taken orally (it is digested) and is only absorbed across mu c ous 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.

In sulin 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 w ould have to give injections. The desirability and often cost-effectiveness of this was noted. In jection 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 w ith 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 Me dicines and Healthcare Products Regulatory Agency (MHRA, formerly the Medical Devices Ag ency) in the bulletin DB2000(04). Consequently, the guideline cannot make such a re co mmendation. Other common sense issues included provision for sharps disposal, and ch eck on the condition of injection sites annually or if blood glucose control problems worsen.

access to insulin injection delivery device 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.
’

Evidence Statement CG15AdultES134

NICE guidance 165 co ncluded 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 practi c e, patients who go on to pumps are carefully selected, and to a large degree self-select ed. 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

(Al-Mrayat 2009)

Evidence Statement CG15AdultES135

One randomised trial 166 of medium sample size compared a multiple injection regimen from a pen injector with conventional treatment with twice-daily syringe injection. No significant differ- ences were seen in GHb values, blood glucose values or hypoglycaemic episodes. Patient satisfac- tion 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

(D. P. Murray et al. 1988)

Evidence Statement CG15AdultES136

One randomised crossover trial 167 co mpared 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 gl ucose 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 we re re co rd ed between injections at either site following injections containing both isophane (NPH) and unmodified (soluble) insulin

(Bantle, Neal, and Frankamp 1993)

Evidence Statement CG15AdultES137

One prospective study 168 co mparing the absorption of insulin injected superficially and deep subcutaneously at the fat-muscle boundary showed no significant difference between the two te c hniques. A sub-group of 10 participants showed no difference in overall serum free insulin or plasma glucose values following superficial and deep subcutaneous injection

(Meijer et al. 1990)

Evidence Statement CG15AdultES138

One study 169 re ported benefits associated with injection through clothing, compared with co nv entional injection practice with skin preparat ion over a 20-week trial period. This study had some methodological limitations

(Fleming et al. 1997)

Evidence Statement CG15AdultES139

The health economic searches produced three published papers 3479 co nsidering the use of insulin pens. None of the three papers compare their benefits (patient satisfaction, or improved HbA 1c) against their costs.

(Graff and McClanahan 1998)

(HÃ¶rnquist et al. 1995)

(HÃ¶rnquist et al. 1990)

Topic CG15AdultS14

Hy poglycaemia is, for most people using insulin therapy, an inevitable consequence of the erratic absorption of insulin from subcutaneous tissue after depot injection or infusion, c oupled 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 ch oice 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.

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 re co mmendations, and secondarily under education and lifestyle issues. The group noted issues re lated 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 co ntext, and not simply attributed to lifestyle problems secondary to insulin therapy. Hy poglycaemia 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 re co mmendations on insulin therapy and clinical monitoring addressed other aspects of such management). No useful hard evidence was available for cognitive decline occurring in people w ith 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 re co g nised 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 gl ucagon, it was agreed that the best means of detecting this was by absence of a response to gl ucagon 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.

management of hypoglycaemic symptoms 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. '

Evidence Statement CG15AdultES140

Canadian clinical practice guidelines 98 re ported 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

(Lau 2007)

Evidence Statement CG15AdultES141

One study within the Canadian guidelines 98 re ported 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

(Lau 2007)

Evidence Statement CG15AdultES142

A bedtime snack may be needed to avoid nocturnal hypoglycaemia. Two studies from a systematic review 98 showed prepared cornstarch snack bars have some benefit in overnight re duction of hypoglycaemia, but the number of events were not significantly reduced

(Lau 2007)

Evidence Statement CG15AdultES143

Canadian clinical practice guidelines 98 re port one paper on the link between incidence of prior hy poglycaemic episodes and worsening in the defect of the hormonal responses to hy poglycaemia, leading to a reduction in the self-detection of hypoglycaemia. Eight papers re port the benefits of strict avoidance

of hypoglycaemia in improving recognition of severe hy poglycaemia or the responses of counter-regulatory hormones

(Lau 2007)

Evidence Statement CG15AdultES144

A randomised controlled study 170 co mpared blood glucose awareness training (BGAT) with no tr aining 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 hy poglycaemia following BGAT, compared with controls, although BGAT does lead to a better detection of low blood glucose levels in people starting intensive diabetes management

(Kinsley et al. 1999)

Evidence Statement CG15AdultES145

An observational study 171 co mpared blood glucose sensitivity and prediction accuracy in inpatients before and after blood glucose awareness training, showed no additional effect on the improvement of HbA 1c . The decrease in HbA 1c was not however accompanied by a change in the accuracy of blood glucose estimation or sensitivit y of recognition of low blood glucose levels

(Fritsche et al. 1998)

Evidence Statement CG15AdultES146

Canadian clinical practice guidelines 98 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

(Lau 2007)

Evidence Statement CG15AdultES147

Evidence on the impact of hypoglycaemia on cognitive function is not clear. Two prospective studies reported within the Canadian guidelines 98 did not find association between intensive diabetes management and cognitive function.

However, six retrospective studies found subjects w ith recurrent hypoglycaemia performed more poorly in a range of intellectual tests

(Lau 2007)

Evidence Statement CG15AdultES148

Tw o randomised studies compared the use of glucagon and dextrose in the treatment of severe hy poglycaemia. One study 172 co mpared intramuscular administration of 1 mg glucagon with 50 ml 50% IV dextrose in people with hypoglycaemic coma. A second study 173 co mpared intravenous administration of 1 mg glucagon vs 50 ml 50% dextrose in people with hypo- gl yc aemic coma. Both studies showed a significantly slower recovery to a normal level of co nsciousness in the glucagon treated group

(A. W. Patrick et al. 1990)

(A. Collier et al. 1987)

Evidence Statement CG15AdultES149

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

Evidence Statement CG15AdultES150

No co rr elation was seen between time taken to recovery of consciousness and initial plasma gl ucose concentration or duration of hypoglycaemia in either of the studies. Side effects were similar among the treatment groups

Evidence Statement CG15AdultES151

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

Evidence Statement CG15AdultES152

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

Topic CG15AdultS9

C ultural 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.

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. Insome areas there was overlap with social/deprivation issues. The groups recommendations address cultural/religious issues in the appropriate sections of this guideline, emphasising the primacy of the individual in this regard.

Manage as an individual 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 ’

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