The updated Alphabet Strategy: Facilitating the implementation of NICE guidelines

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Article points

1. The "Alphabet Strategy" was created locally after primary care teams attached to the authors' secondary care centre felt that a single one-page guideline was needed, that could also be used to educate people with diabetes.
2. The strategy is a condensed but simple mnemonic approach based on the "seven most important aspects" of highly effective diabetes care.

Key words

- Alphabet Strategy
- NICE guidelines
- Type 2 diabetes

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The excess premature vascular disease morbidity and mortality associated with diabetes is well recognised (Huxley et al, 2006). Numerous single risk factor intervention trials and the recently published multifactorial intensified therapy trial provide abundant evidence that an intensified approach to the management of type 2 diabetes is clearly superior to the conventional treatment (Gaede et al, 2008). In 2008 NICE published guidance on the management of type 2 diabetes that replaced earlier guidelines from 2002. It is a comprehensive 280 page document with a quick reference guide that is likely to be the document more widely read. The guideline has been recently updated to consider the newer agents for blood glucose lowering. In this article the authors discuss their locally adapted updated "Alphabet Strategy" as a handy reference guide for primary care teams.

Worldwide, the number of people with type 2 diabetes is expected to have doubled by 2030 (Wild et al, 2004). The exact current prevalence of type 2 diabetes in the UK is unknown, and will vary with factors such as mix of ethnic groups and degree of social deprivation.

Global prevalence estimates for diabetes vary from around 3.5% to 5.0%, and a total of 1.71 million people in the 20- to 79-year-old age group have diabetes, of whom it is conventional to assume 85% have type 2 diabetes (International Diabetes Federation, 2006). This number does not take into account people with undiagnosed type 2 diabetes. The NHS spends around 5% of its budget or close to £10 million a day treating diabetes and its effects, and this is expected to rise to 10% by 2011 (Williams et al, 2002; Wild et al, 2004).

Fifty per cent of people with type 2 diabetes have evidence of complications at the time of diagnosis. It is estimated that type 2 diabetes "ages" the vasculature by 15 years and life expectancy is reduced on average by up to 10 years, with cardiovascular disease being the primary cause of death in this group (Perusicová, 2001; Laing et al, 2003; Booth et al, 2006).

With the increasing prevalence of diabetes, there will inevitably be an increase in deaths from cardiovascular disease, as well as an

increase in other complications associated with the condition. The human and economic costs of this epidemic are enormous and there is always a need for practical guidelines to improve the quality of diabetes care.

The Alphabet Strategy

The Alphabet Strategy was created locally after primary care teams attached to the authors' secondary care centre felt that a single, one-page guideline was needed, that could also be used to educate people with diabetes (*Figure 1*). The strategy is a condensed but simple mnemonic approach based on the "seven most important aspects" of highly effective diabetes care (Patel and Morrissey, 2002):

- Advice.
- Blood pressure.
- Cholesterol.
- Diabetes (glycaemic control).
- Eye care.
- Foot care.
- Guardian drugs.

Teaching and implementation materials comprise: education posters; an individualised care plan; a specifically designed diabetes passport including information relating to diabetes knowledge and individualised agreed targets; a diabetes presentation leaflet; one-page guides as well as a comprehensive 100-page guide; an evidence-based computer program with immediate access to results of landmark studies in diabetes; an audit tool; and an expert patient programme that provides lay-led, group-based support for people to self-manage their diabetes.

A: Advice

The first of the key priorities for implementing the new NICE guidelines is to "offer structured education to every person and/or their carer at and around the diagnosis with annual reinforcement and review" (National Collaborating Centre for Chronic Conditions [NCCCC], 2008).

Lifestyle is critically important in the prevention and management of type 2 diabetes, and diet and exercise are the most important part of lifestyle modification. Smoking cessation and reducing alcohol intake advice are essential and should be reinforced at every annual review.

Randomised clinical trials have shown that progression to diabetes can be prevented or postponed by lifestyle intervention. In the Finnish Diabetes Prevention Study, intensive lifestyle intervention (involving 5% weight reduction per year and moderate exercise of 30 minutes per day) reduced diabetes risk by 58% compared with the control group (Lindström et al, 2003). These results have been reproduced by the Diabetes Prevention Program, in which lifestyle intervention was superior to metformin treatment (Knowler et al, 2002). This type of intervention is a feasible option to prevent and improve type 2 diabetes and should be implemented in the primary healthcare system.

In a study of the DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed) programme, structured group education that involved 6 hours of education delivered by two trained healthcare professionals, was tested. The enhanced education programme resulted in a statistically significant improvement in weight loss (P=0.027), smoking cessation (P=0.033), illness belief scores (P=0.001) and depression (P=0.032), despite little or no effect on HbA_{1c} levels over a 12-month period (Davies et al, 2008). For an education programme to be effective it should take into consideration any cultural, religious or language issues. The Alphabet Strategy has been used in a diverse range of settings and in people of varying age and ethnicity to good effect.

Page points

1. The 10-year follow-up results of the UKPDS show that the benefits seen in people originally assigned to tight blood pressure control, except for peripheral vascular disease, were not sustained once the differences in blood pressure, seen early in the trial, were lost.
2. This contrasts with the continuing benefit of earlier improved glucose control seen during the same follow-up period.
3. The most common form of dyslipidaemia in diabetes is mixed hypercholesteraemia with elevated triglycerides and low HDL cholesterol.
4. Dyslipidaemia is an important contributor to the increased cardiovascular risk associated with type 2 diabetes.

B: Blood pressure

Elevated blood pressure greatly increases the already elevated cardiovascular risk in people with type 2 diabetes (Williams, 2003). People with high blood pressure may require a combination of drugs to achieve the recommended blood pressure targets, with many requiring three or more.

In the UKPDS (UK Prospective Diabetes Study [UKPDS Study Group 1998a]), intensive antihypertensive therapy (a blood pressure target of 144/88 mmHg versus the conventional target of 154/87 mmHg) significantly reduced the risk of stroke by 44% and death by 32% (predominantly cardiovascular disease). Reducing blood pressure slows the progression of retinopathy, albuminuria and nephropathy (Estacio et al, 2000). Further cardiovascular benefit would be expected if blood pressure could be lowered to an optimal target of less than 130/80 mmHg in people with existing microvascular or macrovascular complications. It is usually possible to reduce blood pressure to optimal levels safely by using multiple therapies (Poulter et al, 2005). The evidence for the renin-angiotensin system blockade, especially for nephroprotection and cardiovascular protection, supports the use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-2 receptor blocker (A2RB) as first-line treatment for hypertension in people with diabetes (Heart Outcomes Prevention Evaluation Study Investigators, 2000).

In a substudy of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, the mean blood pressure in the intervention group was 135/75 mmHg, the incidence of combined microvascular and macrovascular events was reduced by 18% and there was a 21% reduction in the development or worsening of nephropathy or microalbuminuria (Patel et al, 2007). ADVANCE added some support for the use of a diuretic as second-line therapy in people with diabetes in addition to an ACE or an A2RB.

Other medications will be required to achieve blood pressure targets in most people with diabetes, and calcium channel blockers, alpha-blockers, beta-blockers or spironolactone are all suitable therapies to consider. Potassium level should be monitored regularly in cases where spironolactone is added to ACE or A2RB.

The 10-year follow-up results of the UKPDS (Holman et al, 2008a) show that the benefits seen in people originally assigned to tight blood pressure control, except for peripheral vascular disease, were not sustained once the differences in blood pressure, seen early in the trial, were lost. This contrasts with the continuing benefit of earlier improved glucose control seen during the same follow-up period (Holman et al, 2008b). These results indicate that a sustained control of blood pressure is essential for continuing cardiovascular benefits. The target should be <140/80 mmHg generally, and <130/80 mmHg in the presence of microvascular or macrovascular complications.

C: Cholesterol

The most common form of dyslipidaemia in diabetes is mixed hypercholesteraemia with elevated triglycerides and low HDL cholesterol. Dyslipidaemia is an important contributor to the increased cardiovascular risk associated with type 2 diabetes. The primary role of treatment is to lower cholesterol to <4 mmol/L and lower the LDL cholesterol to a target of <2 mmol/L; the statin is the drug class of choice. The secondary target is to manage the triglycerides and lower HDL in most cases with the addition of a fibrate. Several trials of statins have shown significant reductions in cardiovascular events in people with diabetes (Pyorälä et al, 1997). This treatment effect was independent of baseline cholesterol.

The CARDS (Collaborative Atorvastatin Diabetes Study) looked at people with type 2 diabetes and one risk factor (microalbuminuria, hypertension, smoker or retinopathy). In participants treated with a statin, acute coronary events were reduced by 36% and stroke by 48% (Griebenow, 2005).

There is strong evidence that intensive cholesterol-lowering with atorvastatin (at a dose of 80 mg) is superior in reducing major cardiovascular events in people with diabetes and established ischaemic heart disease (Ridker et al, 2005). Initiating treatment with simvastatin at 40 mg would be appropriate; increasing the dose,

changing to a more potent statin or adding ezetimibe would be the next step to achieve cholesterol targets.

All people with type 2 diabetes over the age of 40 years (<40 years of age if they have other cardiovascular risk factors) should be offered a statin unless the cardiovascular risk from non-hyperglycaemia related factors is low at which point, further assessment is required (NCCCC, 2008). Statins have a relatively modest efficacy in raising levels of HDL cholesterol or lowering triglyceride levels. In a recent survey in the USA more than 50% of men and over 70% of women with diabetes had a persistently low HDL cholesterol level (<1.0 mmol/L) and over 50% of all patients had triglyceride >1.7 mmol/L (Jacobs et al, 2005). Data from randomised controlled trials also support a role for fibrates in reducing cardiovascular risk in people with diabetes (Keech et al, 2005), although the extent of evidence is less than for the statins. Fibrate should be considered if the person with diabetes is at high risk of cardiovascular disease and triglyceride levels are >2.3 mmol/L despite statin therapy (NCCCC, 2008).

D: Diabetes

Glycaemia is related to the risk of developing cardiovascular disease, and numerous randomised controlled trials have shown that good glycaemic control can reduce the risk of developing microvascular and macrovascular complications in people with type 2 diabetes. In the UKPDS, participants with an average HbA_{1c} of 7.0% (53 mmol/mol; comprising the intensive treatment group) had considerably fewer microvascular complications than the conventional treatment group with HbA_{1c} levels of 7.9% (63 mmol/mol) (UKPDS Group, 1998b). The authors of the study have also shown that good glycaemic control reduces the risk of peripheral vascular disease with a favourable trend for a lower risk of myocardial infarction (Stratton et al, 2000).

In the ADVANCE study, a reduction in HbA_{1c} levels from 7.5% (58 mmol/mol) to 6.5% (48 mmol/mol) was associated with further reduction in renal outcome and no adverse effect on macrovascular events or mortality (ADVANCE Collaborative Group et al, 2008). This was in contrast to the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study published earlier which showed increased mortality in the intensive glycaemic control group (ACCORD Study Group et al, 2008).

The increased mortality observed in the intensive therapy group in the ACCORD study might be related to the adverse cardiovascular effects of hypoglycaemia when striving for a normal target HbA_{1c} level. A possible explanation of why ADVANCE showed no benefit of blood glucose control on cardiovascular outcomes is that a 5-year follow-up is not long

enough to pick up the slow-acting effects of glucose-lowering on cardiovascular disease, or the blood glucose control was too late and could not "stop the moving train".

The 10-year post-trial follow-up of newly diagnosed people with type 2 diabetes randomised in the UKPDS (Holman, 2008b) demonstrated a continued reduction in microvascular risk (24%) and emergent risk reductions for myocardial infarction (15%) and death from any cause (13%), despite an early loss of glycaemic differences, now termed the "legacy effect". A continued benefit after metformin therapy was evident during the 10-year post-trial follow-up among overweight people (33% risk reduction for myocardial infarction and 27% for death from any cause). This crucial information creates strong arguments in favour of early intense optimisation of blood glucose.

Metformin should still be the first-line oral agent for obese people with type 2 diabetes if HbA_{1c} levels remain above 6.5% (48 mmol/mol) after lifestyle modification. Metformin use was associated with cardiovascular benefit (UKPDS Group, 1998c) and it should be increased gradually to the maximal tolerated dose. Stop metformin if creatinine levels are >150 µmol/L or if GFR <30 mL/min. Second-line agents include sulphonylureas, and then insulin therapy as third-line. Treatment should be tailored to the needs of the individual and a rapid-acting insulin secretagogue could be an option in people with an erratic lifestyle. DPP-4 inhibitors were included in the recently published NICE guidelines (NICE, 2009) as a possible third-line therapy, after metformin and sulphonylurea, or as a second-line therapy after metformin if a sulphonylurea is contraindicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences. They are also suggested as second-line add-on to a sulphonylurea if metformin is contraindicated or not tolerated. DPP-4 inhibitors will be particularly useful in people with weight gain or cardiac failure.

Recommendations regarding thiazolinediones (TZDs) have been recently updated, and they are considered as possible second- or third-line agents (NICE, 2009) being particularly useful in people with marked insulin resistance. NICE has stated that when prescribing a TZD, the most up-to-date advice from regulatory authorities regarding cost and safety issues should be taken into account. NICE has specifically recommended pioglitazone if a TZD is used with insulin treatment. TZDs should not be used in people with heart failure or at high risk of fracture and people should be warned about possible fluid retention.

Exenatide, a glucagon-like peptide-1 receptor agonist, has been recommended for people with diabetes and a high BMI (≥35 kg/m^2), who have specific psychological, biochemical or medical problems associated with a high body weight and an HbA_{1c} level ≥7.5% (≥58 mmol/mol) after a trial of metformin and a sulphonylurea (NICE, 2009). People with a lower BMI may be considered for exenatide therapy if insulin would have significant occupational implications or if weight loss would benefit other significant obesity related comorbidities. It should only be continued in cases of maintained beneficial response (1 percentage point [10.9 mmol/mol] reduction of HbA_{1c} and 3% weight reduction within 6 months) (NICE, 2009).

E: Eye care

Diabetic retinopathy is the most common diabetic eye disease and is the leading cause of blindness in the working-age population in the UK (Younis et al, 2003). There are often no symptoms in the early stages of the disease, therefore retinal screening should be carried out annually, ideally using a digital retinal photography programme to detect early changes. Visual acuity testing should be done routinely as part of an eye surveillance programme.

Urgent referral to an ophthalmologist is mandatory if there are features of maculopathy, preproliferative retinopathy or an unexplained drop in visual acuity. People should have an emergency review by an ophthalmologist in cases of sudden loss of vision, retinal detachment, pre-retinal vitreous haemorrhage or rubeosis iridis (NCCCC, 2008). Good glycaemic, blood pressure and cholesterol control is key to prevent development or worsening of diabetic retinopathy (UKPDS Group, 1998b; Estacio et al, 2000).

Page points

1. Second-line agents include sulphonylureas, and then insulin therapy as third-line.
2. Metformin should still be the first-line oral agent for obese people with type 2 diabetes if HbA_{1c} levels remain above 6.5% (48 mmol/mol) after lifestyle modification.
3. Diabetic retinopathy is the most common diabetic eye disease and is the leading cause of blindness in the working-age population in the UK.
4. Urgent referral to an ophthalmologist is mandatory if there are features of maculopathy, preproliferative retinopathy or an unexplained drop in visual acuity.

Page points

1. Diabetic foot ulcers account for 50–75% of non-traumatic lower extremity amputation. Peripheral neuropathy and peripheral vascular disease are risk factors for the development of a foot ulcer.
2. Cardiovascular protective drugs including aspirin, statins, an ACE-inhibitor or an A2RB should be considered in almost all people with type 2 diabetes unless contraindicated.
3. The targets for most people with type 2 diabetes who are taking aspirin and statins, with a blood pressure at or below 130/80 mmHg and an HbA_{1c} level <7.5% (58 mmol/mol) have been incorporated into the NICE guidance; therefore mortality reduction from cardiovascular disease similar to the levels seen in the Steno 2 study may be expected in the UK population with diabetes.
4. The NICE guideline offers the opportunity for systems of diabetes care to commission high quality patient-centered care based on education, both for healthcare professionals and for people with diabetes and intensive treatment.

F: Foot care

Diabetic foot ulcers account for 50–75% of non traumatic lower extremity amputation (Holzer et al, 1998). Peripheral neuropathy and peripheral vascular disease are risk factors for the development of a foot ulcer.

People with diabetes should be educated about foot care and how to avoid ulceration. Annual review by a practice nurse or podiatrist is essential. Examination of the feet should include peripheral pulses and 10-g monofilament testing. If there is any evidence of a neuropathic or ischaemic area of the foot, referral to a podiatrist is essential as there is a high risk of ulceration (NICE, 2004). People with a foot ulcer should be urgently referred to a specialised foot clinic and any suspicion of infection should prompt treatment with antibiotics.

G: Guardian drugs

Cardiovascular protective drugs, including aspirin, statins, ACE-inhibitors or A2RBs, should be considered in almost all people with type 2 diabetes unless contraindicated. In individuals intolerant of aspirin, clopidogrel use would be appropriate as an alternative.

The multifactorial polypharmacy advised in the authors' Alphabet Strategy is similar to the approach advocated in the Steno-2 study (Gaede et al, 2008). In this study 160 participants with type 2 diabetes and persistent microalbuminuria were randomly assigned to receive either intensive therapy or conventional therapy. The intensive therapy in the initial 7.8 years follow-up resulted in 50% reduction in vascular complications, during the total follow-up of 13.3 years the mortality rate was 30% for the intensive therapy group compared with 50% for the conventional group. The intensive multifactorial intervention in the Steno-2 study significantly reduced the risk of cardiovascular disease by 53%, stroke by 85%, amputations by 50%, nephropathy by 61%, retinopathy by 58% and autonomic neuropathy by 67% compared with conventional care (Gaede et al, 2008).

The current NICE guideline advocates a multifactorial polypharmacy approach to the management of type 2 diabetes, with many people likely to be receiving aspirin, statin therapy, antihypertensive agents and glucose-lowering medication aimed at reaching HbA_{1c} targets. As such, mortality reduction from cardiovascular disease similar to the levels seen in the Steno-2 study may be expected in the UK population with diabetes.

Conclusion

NICE guidelines offer the opportunity for systems of diabetes care to commission high-quality patient-centered care based on education, both for healthcare professionals and for people with diabetes. The key "Darzi" visions of the NHS next stage review (care being fair, safe, effective and personalised) (Department of Health, 2008) should remain key principles in creating excellence in diabetes care. The Alphabet Strategy has previously shown that its use can achieve standards of care similar to UKPDS and Steno-2 intensive cohorts (Patel and Morrissey, 2002).

This article provides an easy-to-use summary based on the Alphabet Strategy and NICE guidelines for type 2 diabetes (NCCCC, 2008; NICE, 2009) that the authors hope will be of practical benefit to healthcare professionals in diabetes care. ■

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NICE Clinical Guidelines 2008: Locally Adapted Guideline
Diabetes Care: The Alphabet Strategy Approach

Advice:

- **Smoking cessation, physical activity, weight control (5–10% loss per year if overweight).**
- **Structured education:** especially self-management, beliefs, knowledge, skills – involve carers.
- **Regular follow-up with complete annual review.**
- **Diabetes prevention lifestyle targets:** weight reduction >5% if obese, fat intake <30% of energy intake, saturated fat <10% of energy intake, fibre >15g per 1000 calories, exercise 4 hours/week. Normal dietary NaCl.

Blood pressure: *Target <140/80 mmHg, < 130/80 mmHg if microvascular or macrovascular complications*

- **Step 1. A** (angiotensin converting enzyme-inhibitor or angiotensin receptor blocker), in African-Caribbean A + D (diuretic) or C (calcium channel blocker).
- **Step 2. A + (D or C).**
- **Step 3. A+D+C.**
- **Step 4.** Add alpha-blocker (doxazosin) or beta-blocker or potassium sparing diuretic (e.g. spironolactone).

Cholesterol: *Target total cholesterol ≤4 mmol/L or LDL cholesterol ≤2 mmol/L*

- **Aged over 40** – initiate simvastatin 40 mg, increase to 80 mg if target not met.
- **Aged under 40** – consider simvastatin 40 mg if cardiovascular risk factors.
- If target not achieved: rosuvastatin 10 mg (if 10% drop needed) otherwise consider ezetimibe 10 mg once-daily.
- If cardiovascular risk is high, consider adding fenofibrate to statin therapy if triglycerides > 2.3 mmol/L.

Diabetes control: *Target HbA_{1c} level ≤6.5% (≤48 mmol/mol) where realistic (otherwise <7.5% [<58 mmol/mol])*

- **Step 1.** Metformin 500 mg bd, to 500 mg tds to 850 mg tds. Metformin contraindicated if creatinine >150 µmol/L or eGFR <30 mL/min.
- **Step 2.** Add sulphonylurea eg: gliclazide 80 mg bd increasing to 160 mg bd. Gliptin (sitagliptin or vildagliptin) if significant hypoglycaemia risk.
- **Step 3.** Triple therapy with addition of gliptin (especially if weight gain or any coronary heart disease or congestive cardiac failure). Other option TZD (rosiglitazone or pioglitazone) or add insulin.
- **Insulin regimens locally:** Biphasic insulin aspart 30/70 bd, basal bolus regimen with insulin aspart and insulin glargine or insulin detemir.
- **Exenatide:** Consider if BMI >35 kg/m^2 or weight-gain specific important issue, HbA_{1c} >7.5% (>58 mmol/mol), instead of insulin or TZD. **NB: Metformin useful in obese people with type 1 diabetes.**

Eye screening:

- **Screening for and effective management of diabetic retinopathy**. Retinal screening should be carried out annually by a trained person, refer to ophthalmologist if necessary.

Feet screening:

- **Annual review.** Examination should include: pedal pulses, 10g monofilament testing. If neuropathic or ischaemic foot, referral to podiatry is essential as high risk of ulceration. If ulcers present, refer urgently to foot-at-risk clinic.

Guardian drugs:

- **Aspirin 75 mg once-daily:** all ≥50 years of age, <50 years if other cardiovascular risk factors or cardiovascular disease.
- **ACE inhibitor:** ramipril 10 mg once-daily or lisinopril 20 or 40 mg for most people

  or

  AR2B: (best evidence: losartan 100 mg once-daily, irbesartan 300 mg once-daily).
  - **NB: No statins or ACE-I or ARBs in pregnancy, 15% fetal malformation.**

Figure 1. The Alphabet Strategy 1-page reference guide. Readers should note that this guide was prepared prior to the latest NICE guidelines update (NICE, 2009) and that it outlines the authors' local approach to managing type 2 diabetes.