JBS 2 guidelines: A strategy to prevent CVD in diabetes

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Article points

1. The updated Joint British Societies' (JBS 2) guidelines propose practical, evidence-based guidance for the prevention of cardiovascular disease in people with and without diabetes.
2. An integrated approach to diabetes care which addresses all risk factors for all complications is needed, otherwise management becomes fragmented.
3. An intensive, multifactorial, target-driven management regimen can halve cardiovascular events.

Key words

- Cardiovascular risk
- Multifactorial intervention
- Alphabet Strategy
- Screening

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The recently published Joint British Societies' (JBS 2) guidelines on prevention of cardiovascular disease in clinical practice (British Cardiac Society et al, 2005) propose a consistent multidisciplinary approach to the management of individuals with established cardiovascular disease and those at high risk of developing it. The latter group includes, in particular, people with diabetes. In this article, the authors examine in more detail the issues touched upon in the commentary by two of them in the previous issue of the journal (Morrissey and Patel, 2006).

It is almost a truism that diabetes is a 'coronary heart disease equivalent': the risk of a person with diabetes experiencing a first heart attack is very similar to that of an individual without diabetes who has already had an attack having another one (Haffner et al, 1998). The Joint British Societies' (JBS 2) guidelines on prevention of cardiovascular disease in clinical practice (British Cardiac Society et al, 2005) aim to be both evidence based and easy to implement in everyday clinical practice.

They will be of particular interest to practitioners in primary care, where the majority of diabetes management takes place. Most of the interventions advised will be initiated in primary care. Even when they are commenced in secondary care – for example, on discharge from hospital – primary care teams will be responsible for follow-up and monitoring.

Integrated diabetes management

Two decades ago diabetes care was concerned primarily with management of glycaemia. It is now universally recognised that we need an integrated approach which addresses all risk factors for both microvascular and macrovascular complications, and which manages those complications effectively when they do occur. The impact of good glycaemic control on macrovascular disease is relatively small: its benefit is evident mainly in the prevention of microvascular complications (United Kingdom Prospective Diabetes Study [UKPDS] Group, 1998b). However, it is premature accelerated cardiovascular disease which shortens the lives of people with diabetes.

Diabetes care is complex, involves a wide range of professionals working across healthcare boundaries and is of limited effectiveness without the active involvement of the user. Cardiovascular disease prevention must be integrated with all other aspects of management, otherwise care becomes fragmented by focusing on specific complications rather than the person with diabetes as a whole.

The Alphabet Strategy, which was developed at the George Eliot Hospital, combines all dimensions of diabetes care into a single multidisciplinary user-centred approach and is endorsed by the JBS 2 guidelines. The strategy is a mnemonic-based template designed to ensure that all elements of management are delivered in a systematic, coherent and timely fashion (Morrissey et al, 2005). These elements are listed in *Table 1*. This approach delivers in everyday practice results comparable to those in clinical trials (Jaiveer et al, 2003).

Statins for everyone?

The most effective single intervention to reduce cardiovascular risk in individuals with diabetes is lipid lowering with a statin. A retrospective study of people attending our secondary care diabetes clinic showed that no less than 85–90% of the improvement in their coronary heart disease risk (calculated using the UKPDS Risk Engine) could be attributed to this one simple measure (Lee et al, 2004).

Jarvis (2006) chronicled the progressive downward trend in cholesterol targets over the past 8 years. American Diabetes Association (ADA; 2006) guidelines now recommend a target low-density lipoprotein (LDL)-cholesterol of less than 2.6 mmol/l. However, they also suggest statin therapy in all individuals with diabetes older than 40 years to reduce LDL-cholesterol by 30–40%, irrespective of baseline lipid profile.

Two recent large-scale clinical trials have fundamentally altered the landscape with regard to statin treatment in diabetes: the Heart Protection Study (HPS; HPS Collaborative Group, 2002) and the Collaborative AtoRvastatin Diabetes Study (CARDS; Colhoun et al, 2004).

The former compared the effect of simvastatin 40 mg against placebo in over 20 000 high-risk individuals, including a large number who were at risk simply because of having diabetes. In the treatment group, major vascular events were reduced by 24%. Importantly, people with diabetes benefited to the same extent as individuals who had previously had a myocardial infarction. Furthermore, benefit was independent of baseline lipid profile: those with an LDL-cholesterol less than 3 mmol/l gained the same benefit as those above 3.5 mmol/l.

CARDS was smaller than the HPS, with slightly fewer that 3000 participants, but all had type 2 diabetes as well as one other cardiovascular risk factor. Treatment with atorvastatin 10 mg reduced coronary events by 36% and stroke by 48% compared with placebo. Because of the dramatic reduction in stroke the trial was terminated early. As in the HPS, benefit was irrespective of baseline lipid profile except, intriguingly, in people with low triglyceride levels, who benefited less.

A mere 5 years ago, the Scottish Intercollegiate Guidelines Network recommended lipid lowering in diabetes when calculated 10-year cardiovascular risk exceeded 30% (SIGN, 2001). The JBS 2 guidelines eschew any mention of either risk calculation or a target for LDL-cholesterol; nor do the guidelines seek to distinguish between type 1 and type 2 diabetes. The JBS 2 authors concur with the ADA (2006) that all those with diabetes, type 1 or type 2, aged over 40 years should receive statin therapy. They also spell out in detail which high-risk individuals under the age of 40 years should be treated. The recommendations are summarised in *Table 2*. They fall short of suggesting that literally everybody with diabetes should be prescribed a statin. However, the evidence suggests that the overwhelming majority will benefit.

Low high-density lipoprotein-cholesterol and raised serum triglyceride levels are risk factors for cardiovascular disease and it is disappointing that studies show little benefit from agents which improve them, in particular fibrates and nicotinic acid. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,

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2. The best evidence for blood pressure lowering in type 2 diabetes is still that from the United Kingdom Propsective Diabetes Study.
3. Probably what matters most is that the blood pressure is lowered, not how it is lowered.

Table 1. The Alphabet Strategy.

A	dvice (diet, weight loss, smoking cessation, exercise)
B	lood pressure lowering
C	holesterol lowering
D	iabetes control
E	ye examination
F	eet examination
G	uardian drugs (such as aspirin, angiotensin-converting enzyme inhibitors and statins)

testing fenofibrate against placebo, showed a non-significant reduction in events, although extensive co-prescription of statins was a confounding factor (Keech et al, 2005). The therapeutic role of lipid-lowering agents other than statins remains uncertain.

Blood pressure: The lower the better

The JBS 2 guidelines propose, for individuals with diabetes, the daunting blood pressure target of less than 130/80 mmHg, which is considerably lower than the new General Medical Service Quality and Outcomes Framework (QOF) indicator of 145/85 mmHg (Kenny, 2006). However, the QOF is designed to provide financial incentives for improved performance, not necessarily to reflect evidence-based best practice.

The JBS 2 authors admit this will be difficult to achieve, especially in older people, and that it 'is not based on extensive clinical trial evidence.' However, they offer two persuasive justifications.

- Trial data show that the greater the blood pressure lowering the greater the benefit, and observational data show no blood pressure threshold below which risk declines no further.
- Blood pressure lowering is the most important factor in the prevention of diabetic nephropathy and end-stage renal failure.

The best evidence for blood pressure lowering in type 2 diabetes is still that from the UKPDS (UKPDS Group, 1998c). Participants were randomised to either intensive blood pressure-lowering therapy, which achieved 144/82 mmHg, or less intensive therapy, which achieved 154/87 mmHg. In the former group, microvascular end points, heart failure, stroke and death were reduced by 30–40%. There were also 21% fewer myocardial infarctions in the former group, which is encouraging, although the reduction was not statistically significant.

The jury is still out whether newer antihypertensive agents, in particular angiontensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, have advantages over older ones, although there is now a suspicion that the use of beta-blockers should be restricted to those with established coronary heart disease (Beevers, 2005). Beta-blockers can also 'interfere with metabolic and autonomic responses to hypoglycaemia' (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006) and thus mask the warning signs for hypoglycaemic episodes.

The evidence for renin–angiotensin system blockade is best in terms of nephroprotection. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT; ALLHAT Collaborative Research Group, 2002) detected no significant differences in cardiovascular outcomes between treatment regimens based on chlorthalidone, amlodipine or lisinopril.

Few people will respond adequately to monotherapy (Brown et al, 2003) and we believe that it makes clinical sense to start with an ACE inhibitor or a diuretic, and then add in the other agent, followed by a calcium-channel blocker if needed. Probably what matters most is that the blood pressure is lowered, not how it is lowered.

Aim for normal glucose

The Diabetes Control and Complications Trial (DCCT; DCCT Research Group, 1993) first made us aware of the importance of good glycaemic control in the prevention of microvascular complications in type 1 diabetes, and the UKPDS (UKPDS Group, 1998b) confirmed the same for type 2. In the UKPDS, hyperglycaemia was also a cardiovascular risk factor: every 1% increase in HbA_{1c} was associated with 14% more deaths, 14% more myocardial infarctions and 12% more strokes (Stratton et al, 2000). However, the effect of treatment was not large. The intensively treated group, who achieved an HbA_{1c} of 7.0%, had 16% fewer myocardial infarctions than the conventionally treated group, who achieved an HbA_{1c} of 7.9%, but the reduction in myocardial infarctions failed to reach statistical significance.

The DCCT was not powered to detect a beneficial effect on cardiovascular disease over its original 10-year duration; nor was it designed to be. However, follow-up of the participants several years later revealed a 57% reduction in the risk of non-fatal myocardial infarction, stroke or cardiovascular death in the previously intensively treated group (Nathan et al, 2005).

Table 2. Indications for statin treatment in diabetes in the updated Joint British Societies' (JBS 2) guidelines (British Cardiac Society et al, 2005).

1 All those aged ≥40 years with either type 1 or type 2 diabetes.

2 People aged 18–39 years with either type 1 or type 2 diabetes and at least one of the following:
- retinopathy of greater than background severity
- nephropathy, including microalbuminuria alone
- poor glycaemic control (HbA_{1c} >9%)
- elevated blood pressure requiring antihypertensive therapy
- serum total cholesterol >6.0 mmol/l
- features of the metabolic syndrome
- family history of premature cardiovascular disease in a first-degree relative.

Since good glycaemic control definitely prevents microvascular complications and may prevent cardiovascular events, the only acceptable target is normoglycaemia. Unfortunately, in many of the people with diabetes we see, we will fail; and even the revised QOF indicator of HbA_{1c} less than 7.5% (Kenny, 2006) can be daunting, especially in those with diabetes of long duration and people on insulin treatment. However, it is necessary that we do everything we can.

As with blood pressure, probably what matters most is that blood glucose is brought within the normal range, not how that is done. However, the JBS 2 authors remind us that a retrospective analysis of the UKPDS showed better outcomes in overweight people treated with metformin (UKPDS Group, 1998a). This drug lowers glucose equally effectively in those of normal weight, it is cheap, and, provided the contraindications are observed, it is safe. Consequently, it is the drug of choice in type 2 diabetes when lifestyle modifications are no longer sufficient.

There are interesting suggestions that glitazones may have a beneficial effect on macrovascular disease. The only large-scale outcome trial to date, the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), demonstrated a relatively small but significant benefit, but at the cost of an increase in heart failure (Dormandy et al, 2005).

Benefits of aspirin

Although the use of low-dose aspirin is widely advocated, the evidence for its benefit in primary prevention in individuals with diabetes is limited. Hopefully, the issue will be resolved by A Study of Cardiovascular Events iN Diabetes (ASCEND; http://www.ctsu.ox.ac.uk/ascend/index.htm [accessed 16.06.06]), which will compare aspirin and omega-3 fatty acids, both in combination and individually, with placebo in primary prevention in 10 000 people with diabetes.

In the meantime, the best evidence is from the Hypertension Optimal Treatment (HOT) trial (Hansson et al, 1998). This investigated both aggressive blood pressure lowering and aspirin use in almost 19 000 individuals with hypertension. The latter reduced myocardial infarction by 36% with no effect on stroke. Eight per cent of participants in the study had diabetes; in this sub-group, aggressive blood pressure lowering (diastolic blood pressure 80 mmHg, compared with 90 mmHg) reduced major cardiovascular events by half.

Current ADA guidelines (2006) recommend aspirin in people aged over 40 years and in those aged 30–40 years with additional cardiovascular risk factors. The JBS 2 guidelines take a slightly more cautious approach, suggesting its use in individuals with established macrovascular disease, in those aged over 50 years, in those with long-standing diabetes, and – in the light of the HOT trial – in those with treated hypertension (see *Table 3*). As with lipid-lowering therapy, the guidelines see no need to make a distinction between type 1 and type 2 diabetes.

Provided the contraindications are observed, low-dose aspirin is reasonably safe: in the HOT trial it produced twice as many bleeds as placebo but no increase in fatal bleeds.

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3. Although the use of low-dose aspirin is widely advocated, the evidence for its benefit in primary prevention in individuals with diabetes is limited.

Table 3. Indications for low-dose aspirin treatment in diabetes in the updated Joint British Societies' (JBS 2) guidelines (British Cardiac Society et al, 2005).

1 People with established macrovascular disease.

2 People aged ≥50 years.

3 People aged <50 years who either:
- have had diabetes for >10 years *or*
- require treatment for hypertension.

Lessons from Steno-2

The message so far is that statin treatment reduces macrovascular events, glycaemic control reduces microvascular events, and blood pressure lowering reduces both. The question is: what is the aggregate benefit if all these interventions are delivered together? The answer is provided by the landmark Steno-2 study (Gaede et al, 2003).

In this trial, 160 people with type 2 diabetes and microalbuminuria were randomised to conventional treatment, according to Danish national guidelines, or intensive treatment with lifestyle modification and pharmacological interventions. The latter targeted hyperglycaemia, hypertension, dyslipidaemia, microalbuminuria and prevention of cardiovascular disease with aspirin. The targets were very similar to those advocated by the JBS 2 guidelines (*Table 4*) and the Alphabet Strategy.

Over the average 7.8 years of follow-up, it was found that intensive, multifactorial, target-driven intervention resulted in significant improvements in HbA_{1c}, blood pressure, serum cholesterol and triglyceride levels, and urine albumin excretion. There were 85 cardiovascular events in 35 of 80 participants (44%) in the conventional therapy group but only 33 events in 19 of 80 participants (24%) in the intensive therapy group. Non-fatal myocardial infarction was reduced by 70%, non-fatal stroke by 85% and amputations by 50%.

This was not a comparison of good versus poor diabetes care: management of the conventionally treated group was in no way sub-standard. Raising the standard from very good to excellent doubles the benefit to people with diabetes (Gaede et al, 2003).

Screening for dysglycaemia

One possible reason for the rather disappointing results of trials like PROactive is that the intervention was simply too late to be of much benefit. In that trial, all participants

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3. One possible reason for the rather disappointing results of trials like PROactive is that the intervention was simply too late to be of much benefit.

Table 4. A comparison of Steno-2 recommendations (Gaede et al, 2003) with the updated Joint British Societies' (JBS 2) guidelines (British Cardiac Society et al, 2005).

	Steno-2	JBS 2
Advice (diet, weight loss, smoking cessation, exercise)	Standard	Standard
Blood pressure lowering	<130/80 mmHg*	<140/80 mmHg (optimal <130/80 mmHg)
Cholesterol lowering (total)	<4.5 mmol/l	<4.0 mmol/l
Diabetes control (HbA_{1c})	<6.5%	≤6.5%
Eye examination	Annually	Annually
Feet examination	Annually	Annually
Guardian drugs (such as aspirin, angiotensin-converting enzyme inhibitors and statins)	All	Most

**This was tightened during the trial from an initial target of 140/85 mmHg*

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1. The 'prediabetic' states of impaired glucose tolerance (IGT) and impaired fasting glucose increase the risk not only of diabetes but also of cardiovascular disease.
2. Randomised controlled trials have shown the benefit of lifestyle and pharmaceutical interventions in IGT to postpone or even prevent diabetes.
3. The relationship between glycaemia and cardiovascular risk extends well below the diabetes threshold.

had established macrovascular disease and over 40% had a history of diabetes of 10 years or more. Indeed, delaying intervention until diabetes is actually diagnosed results in many lost opportunities. In the UKPDS, 50% of participants showed evidence of complications at the time of diagnosis of type 2 diabetes (UKPDS Group, 1990).

The 'prediabetic' states of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) increase the risk not only of diabetes but also of cardiovascular disease. Randomised controlled trials have shown the benefit of lifestyle and pharmaceutical interventions in IGT to postpone or even prevent diabetes. The Diabetes Prevention Program (Knowler et al, 2002) demonstrated reductions in the development of diabetes of 58% by lifestyle change and 31% by metformin. The benefit of combining the two is not yet known.

The notion of an incremental, step-wise progression from 'normal' glucose tolerance through IGT to diabetes is itself misleading. The relationship between glycaemia and cardiovascular risk extends well below the diabetes threshold. All-cause, cardiovascular and coronary heart disease mortalities rise with HbA_{1c}, with the lowest rates being seen in individuals with an HbA_{1c} less than 5% (Khaw et al, 2001). Glycaemia in the healthy population, like blood pressure and cholesterol, appears to be continuously related to cardiovascular risk (Coutinho et al, 1999).

Simply waiting for individuals to present with diabetes is not an acceptable strategy. The most accurate instrument to detect dysglycaemia is the oral glucose tolerance test (OGTT), but routine use of this is not practicable. People who definitely should have an OGTT are those admitted to the coronary care unit: previously undiagnosed diabetes and IGT are extremely common in those with acute myocardial infarction (Norhammar et al, 2002).

For those without diagnosed cardiovascular disease, the JBS 2 guidelines propose a pragmatic approach. The JBS 2 authors suggest that all adults aged over 40 years should have random (non-fasting) blood glucose measured

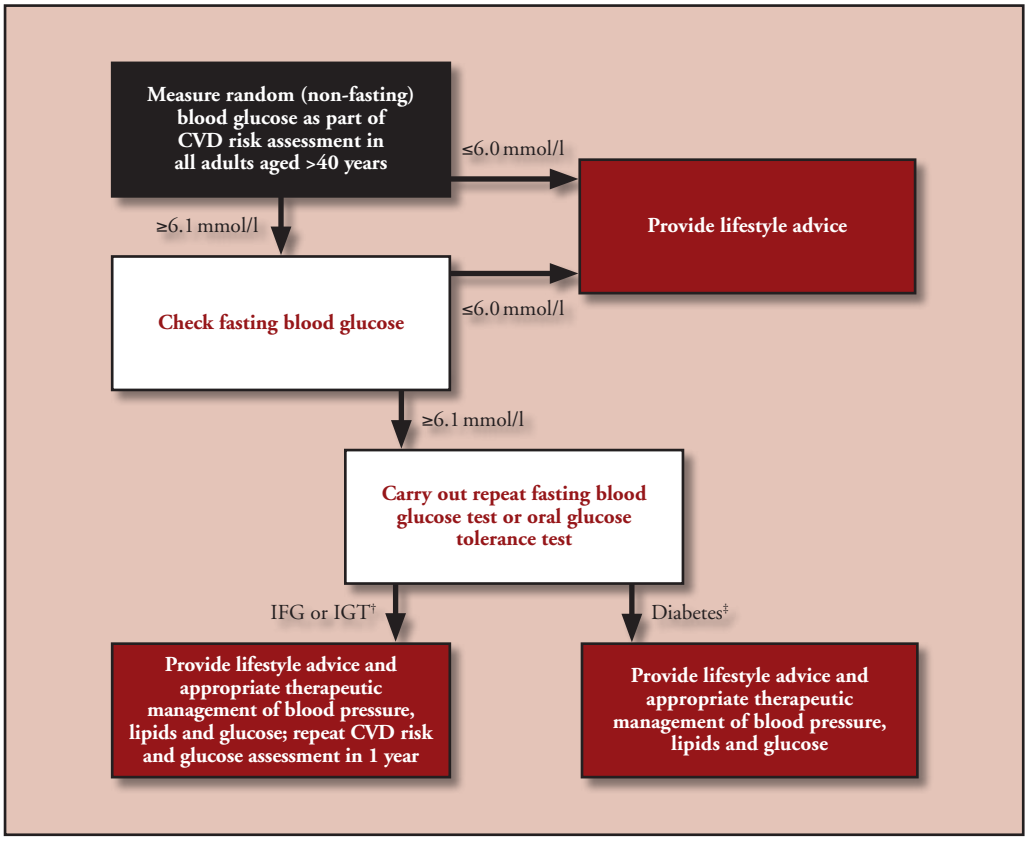

Figure 1. The recommended algorithm for dysglycaemia screening in the JBS 2 guidelines (adapted from British Cardiac Society et al, 2005). †Impaired fasting glucose (IFG) diagnosed from fasting blood glucose ≥6.1 mmol/l and <7.0 mmol/l; impaired glucose tolerance (IGT) diagnosed from oral glucose tolerance test 2-hour glucose ≥7.8 mmol/l and ≤11.0 mmol/l. ‡Diabetes diagnosed from fasting blood glucose ≥7.0 mmol/l or oral glucose tolerance test 2-hour glucose ≥11.1 mmol/l. CVD, cardiovascular disease.

as part of a cardiovascular risk assessment in primary care. Those found to be at low risk and with a glucose of 6 mmol/l or less should be reassessed in 5 years. However, if the random blood glucose is 6.1 mmol/l or more then further testing should be undertaken with a view to the detection of IFG, IGT or diabetes. At-risk individuals can be offered lifestyle and pharmaceutical interventions to achieve risk factor targets including those for glycaemia. The recommended algorithm in the JBS 2 guidelines is shown in *Figure 1*.

Conclusion

The first targets for primary care teams may well be the indicators in the QOF. However, the evidence casts doubt on some of these: in particular, the indicator for a total cholesterol level of 5 mmol/l or less appears distinctly lax. In this area, the JBS 2 guidelines, in fact, simplify the decision whether to start treatment by focusing on the clinical situation rather than on biochemical targets or calculated cardiovascular risk. The blood pressure and HbA_{1c} targets advocated by JBS 2 are also far more demanding than the indicators in the QOF. Meeting these will be formidable tasks but the evidence for benefit is now incontrovertible and the therapeutic options are improving.

The biggest challenge of all, we feel, will be the early detection of dysglycaemia. Fortunately this fits well into the health promotion strategies already widely undertaken in primary care. At least in the short term, the workload and resource implications will be considerable. But rising to this challenge will be greatly rewarded by the prevention of many cardiovascular events and deaths consequent upon diabetes. ■

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1. The first targets for primary care teams may well be the indicators in the Quality and Outcomes Framework.
2. Blood pressure lowering and glycaemic control remain formidable tasks but the evidence for benefit is now incontrovertible and the therapeutic options are improving.
3. The biggest challenge of all, the authors feel, will be the early detection of dysglycaemia.

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ALLHAT Collaborative Research Group (2002) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Journal of the American Medical Association* **288**(23): 2981–97

American Diabetes Association (2006) Standards of medical care in diabetes – 2006. *Diabetes Care* **29**(Suppl 1): S4–42

Beevers DG (2005) The end of beta blockers for uncomplicated hypertension? *Lancet* **366**(9496): 1510–2

British Cardiac Society, British Hypertension Society, Diabetes UK et al (2005) JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* **91**(Suppl 5): v1–52

British Medical Association, Royal Pharmaceutical Society of Great Britain (BMA, RPSGB; 2006) 2.4 Beta-adrenoceptor blocking drugs. In: *British National Formulary*. BMA and RPSGB, London. Available at http://www.bnf.org/bnf/bnf/51/2455.htm (accessed 16.06.2006)

Brown MJ, Cruickshank JK, Dominiczak AF et al (2003) Better blood pressure control: how to combine drugs. *Journal of Human Hypertension* **17**(2): 81–6

Colhoun HM, Betteridge DJ, Durrington PN et al (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* **364**(9435): 685–96

Coutinho M, Gerstein HC, Wang Y, Yusuf S (1999) The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* **22**(2): 233–40

Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* **329**(14): 977–86

Dormandy JA, Charbonnel B, Eckland DJ et al (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**(9493): 1279–89

Gaede P, Vedel P, Larsen N et al (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New England Journal of Medicine* **348**(5): 383–93

Haffner SM, Lehto S, Ronnemaa T et al (1998) Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England Journal of Medicine* **339**(4): 229–34

Hansson L, Zanchetti A, Carruthers SG et al (1998) Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* **351**(9118): 1755–62

Heart Protection Study Collaborative Group (2002) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* **360**(9326): 7–22

Jaiveer P, Saraswathy J, Lee JD et al (2003) The Alphabet strategy – a tool to achieve clinical trial standards in routine practice? *British Journal of Diabetes & Vascular Disease* **3**(6): 410–3

Jarvis S (2006) NICE guidance on statins: Implications for primary care. *Diabetes and Primary Care* **8**(1): 10–8

Keech A, Simes RJ, Barter P et al (2005) Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* **366**(9500): 1849–61

Kenny C (2006) How changes to the QOF will affect diabetes care. *Diabetes and Primary Care* **8**(1): 22–30

Khaw KT, Wareham N, Luben R et al (2001) Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). *British Medical Journal* **322**(7277): 15–20

Knowler WC, Barrett-Connor E, Fowler SE et al (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine* **346**(6): 393–403

Lee JD, Morrissey JR, Patel V (2004) Recalculation of cardiovascular risk score as a surrogate marker of change in clinical care of diabetes patients: the Alphabet POEM project (Practice Of Evidence-based Medicine). *Current Medical Research and Opinion* **20**(5): 765–72

Morrissey J, Patel V (2006) JBS 2: Promoting a consistent approach to CVD. *Diabetes and Primary Care* **8**(1): 9

Morrissey J, Shaikh S, Patel V (2005) The Alphabet Strategy: a systematic approach to diabetes management. *Clinician in Management* **13**(2): 83–6

Nathan DM, Cleary PA, Backlund JY et al (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New England Journal of Medicine* **353**(25): 2643–53

Norhammar A, Tenerz A, Nilsson G et al (2002) Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* **359**(9324): 2140–4

Scottish Intercollegiate Guidelines Network (SIGN; 2001) *Management of diabetes. SIGN Publication No. 55.* Royal College of Physicians, Edinburgh

Stratton IM, Adler AI, Neil HA et al (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *British Medical Journal* **321**(7258): 405–12

UK Prospective Diabetes Study (UKPDS) Group (1990) UK Prospective Diabetes Study 6. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Research* **13**(1): 1–11

UKPDS Group (1998a) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**(9131): 854–65

UKPDS Group (1998b) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**(9131): 837–53

UKPDS Group (1998c) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *British Medical Journal* **317**(7160): 703–13