Evidence-based medicine. Part 6: Modern diabetes care

Tim Holt

Article points

1. Looking at the broad picture, a number of very basic principles have emerged that form the basis for modern diabetes management.
2. The principles relevant to primary care are summarised as a list of (hopefully) uncontroversial statements that are unlikely to change. This article looks at each in turn and asks: what is the evidence supporting this?
3. In most cases evolving policy will be based on a long-term appraisal of the risk:benefit ratio of novel interventions, initially suggested by serendipitous observations, supported by clinical trials, confirmed by meta-analysis, and followed up both by epidemiological surveillance and by qualitative study of their relevance to individuals.

Key words

- ACCORD
- ADVANCE
- UKPDS
- VADT

Tim Holt is Academic Clinical Lecturer at the Department of Primary Care, University of Oxford, Oxford.

The discovery of insulin was among the most important medical advances of the 20th century, and led to rapid adoption into clinical practice. Since then, a substantial evidence base has developed to support both clinical care and self-management of diabetes through modern pharmaceutical and health services research. Research methods have also developed over the same timescale, enabling the detection of more subtle benefits, and of adverse effects only evident over longer intervals. The last in a series about evidence-based medicine, this article identifies the key principles underlying the primary care management of diabetes and reviews some of the evidence that supports them.

Nineteenth century clinical practice lacked both effective treatments and robust evidence, and often did more harm than good (Wooten, 2007). The French lilac was reportedly used in medieval times to treat diabetes (Witters, 2001) and led to the modern drug metformin, but most other current antidiabetes agents arose in the 20th century (sulphonylureas, thiazolidinediones, glinides, acarbose). The incretin mimetics (glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) were licensed during the 2000s, but their development was rooted firmly in the basic science of preceding decades.

The discovery of insulin in the early 1920s (Tattersall, 2009) was followed by mass production of early formulations derived from animal sources and much later by the development of synthetic alternatives and of genetically engineered human insulins in the late 1970s. Later still, short- and long-acting insulin analogues were developed that are gradually displacing earlier regimens. The advantages of newer over older insulins do not apply universally to all patient groups and proved more difficult to establish than expected (Richter and Neises, 2005).

Other major 20th century advances included laser photocoagulation for diabetic retinopathy; improved anti-hypertensive agents including those with proteinuria-reducing effects; effective lipid-lowering agents; renal replacement therapy; HbA_{1c} measurement; and a proliferation of newer agents with at least short-term benefits in terms of blood glucose control.

As well as pharmaceutical advances, improved gadgetry, including compact devices for self-monitoring of blood glucose, disposable insulin pens, and tiny hypodermic needles, have made a huge difference to quality of life. Insulin pumps are a further

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1. The organisation of diabetes care has benefitted from 20th century inventions, such as electronic health records enabling audit and population-level chronic disease management.
2. The immediate benefit of insulin in the treatment of type 1 diabetes was obvious enough to make blinded trials both unnecessary and unethical, especially as the concept itself was in its infancy.
3. A number of controlled trials have randomised participants with impaired glucose tolerance to lifestyle interventions (aimed largely at nutritional management and physical activity) or to usual care.

advance that has changed the lives of many, and progress continues (although frustratingly slowly) towards islet-cell transplantation and automated blood glucose regulatory devices.

The organisation of diabetes care has also benefitted from 20th century inventions, such as electronic health records enabling audit and population-level chronic disease management. The World Health Organization, International Diabetes Federation, American Diabetes Association, and European Association for the Study of Diabetes have made the battle against diabetes a global endeavour, typified by the recent move towards worldwide standardisation of HbA_{1c} measurement (John et al, 2007).

Evidence-based medicine

The immediate benefit of insulin in the treatment of type 1 diabetes was obvious enough to make blinded trials both unnecessary and unethical, especially as the concept itself was in its infancy. In a setting echoing James Lind's original "trial" of citrus fruits for scurvy on the deck of a British frigate (Holt, 2011), Banting, Best and Collip worked their way through a hospital ward of Canadian children dying of ketoacidosis in 1922, injecting each in turn with the newly purified hormone. Before the last child had been treated, the first recipients were starting to respond. In contrast to the pattern more typical of modern pharmaceuticals, mass production of insulin occurred about a year after the first human was injected experimentally.

Other pharmacological advances in diabetes have been problematic from a risk:benefit perspective. A number of drug therapies (for example, phenformin, troglitazone, rosiglitazone, rimonabant) have been withdrawn from use due to safety concerns, and even the approach to dietary management has undergone significant revisions. Diabetes is a good example in which the short-term benefits of drug therapy detectable in single randomised controlled trials have been outweighed by longer-term harms made evident either by observational evidence or by meta-analysis of many such trials.

Reflecting on this history, we might ask: what evidence can we be confident in for today's clinical practice? Looking at the broad picture, a number of very basic principles have emerged that form the basis for modern diabetes management. Those relevant to primary care are summarised in *Box 1* as a list of (hopefully) uncontroversial statements that are unlikely to change. This article looks at each in turn and asks: what is the evidence supporting this?

1. It is possible to prevent the onset of type 2 diabetes in those at risk using lifestyle interventions

A number of controlled trials have randomised participants with impaired glucose tolerance to lifestyle interventions (aimed largely at nutritional management and physical activity) or to usual care. These include the US Diabetes Prevention Program, which reduced the risk of developing diabetes by 58% compared with standard advice (Knowler et al, 2002), and the Finnish Diabetes Prevention Study (Lindström et al, 2003). The evidence was summarised in a meta-analysis published in 2007 (Gillies et al, 2007) and suggests a pooled hazard ratio for all diet and exercise intervention studies of 0.49 [95% confidence interval, 0.4–0.59].

2. Early intervention is better than later intervention in the prevention of complications

This is a broad principle whose evidence comes from many sources. The prevalence of retinopathy was reported in the Wisconsin Epidemiologic Studies of the 1970s and 1980s (Klein et al, 1984a; 1984b). These described the natural history of the condition and its pattern of risk factors, which included severity and duration of hyperglycaemia. The UKPDS (UK Prospective Diabetes Study) was a large randomised controlled trial of newly diagnosed people with type 2 diabetes that not only confirmed the high prevalence of established complications at diagnosis, but was also able

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1. The DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed) programme was found to improve weight, odds of not smoking, and illness belief scores, but not HbA_{1c}.
2. Much work has been done to develop structured education programmes and improve their impact on clinical and psychological outcomes and on quality of life.
3. The UK Prospective Diabetes Study provided evidence that metformin reduces risk of macrovascular disease beyond its glucose lowering effect.

to measure the impact of control of glycaemia on outcomes. Retinopathy of some degree was evident in 39% of men and 35% of women recruited to this study (Kohner et al, 1998) and more severe changes were not uncommon (8% of men and 4% of women). This, and other trials, confirmed the impact on progression for this and other microvascular complications, as well as on macrovascular risk through modification of other factors, so the importance of early intervention was clear. Much later, the longer term benefit of early control of several risk factors at once became evident and is discussed later in this article.

3. Structured education improves person-centred outcomes

Much work has been done to develop structured education programmes and improve their impact on clinical and psychological outcomes and on quality of life (Loveman et al, 2008). For type 2 diabetes, the Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) programme (Davies et al, 2008) was found to improve weight, odds of not smoking, and illness belief scores, but not HbA_{1c}. For type 1 diabetes, the Dose Adjustment for Normal Eating (DAFNE) programme involved a carbohydrate counting and insulin dose titration programme with dietary freedom, and improved HbA_{1c} level at 6 months as well as quality of life, without increasing risk of severe hypoglycaemia (DAFNE Study Group, 2002).

4. Metformin reduces both glycaemia and also the risk of myocardial infarction

Metformin belongs to a group of drugs called biguanides. The original biguanide was phenformin, which was found to cause lactic acidosis particularly in people with renal impairment, and was withdrawn in 1978. Metformin carries a much lower risk of this, but care is still needed and it should be avoided in people with a glomerular filtration rate (GFR) of <30 mL/min/1.73m^2.

The UKPDS provided evidence that metformin reduces risk of macrovascular disease beyond its blood glucose-lowering effect (UKPDS Group, 1998a). *Figure 1* shows the hazard ratios for myocardial infarction in this study for the insulin/sulphonylurea group and the metformin group, both compared with "conventional" (lifestyle) therapy. Despite the fact that the metformin arm participants achieved less effective glycaemic control, and were more obese, the hazard ratio for myocardial infarction was more significant. This suggests a protective effect for this drug that goes beyond blood glucose lowering, and is part of the basis for encouraging its early use at diagnosis, even in those with only mild hyperglycaemia.

Box 1. Key evidence-based principles of diabetes management in primary care.

- It is possible to prevent the onset of diabetes in those at risk using lifestyle interventions.
- Early intervention is better than later intervention in the treatment of complications.
- Structured education improves person-centred outcomes.
- Metformin reduces both glycaemia and also the risk of myocardial infarction.
- Good glycaemic control improves microvascular outcomes including retinopathy and nephropathy.
- Lipid-lowering improves macrovascular risk, including that of myocardial infarction, stroke and cardiovascular death.
- Blood pressure control improves both micro- and macrovascular outcomes.
- Renin–angiotensin system-blockers reduce progression of nephropathy in people with all levels of albuminuria.
- There is an enduring benefit of multifactorial risk factor control if started early on in the course of diabetes.
- "Tight" glycaemic control (low glycaemic targets in people with established diabetes) does not improve clinical outcomes compared with standard care in type 2 diabetes.
- Screening for retinopathy linked to early intervention can prevent visual loss.
- Foot screening programmes linked to early intervention can reduce amputation rates.

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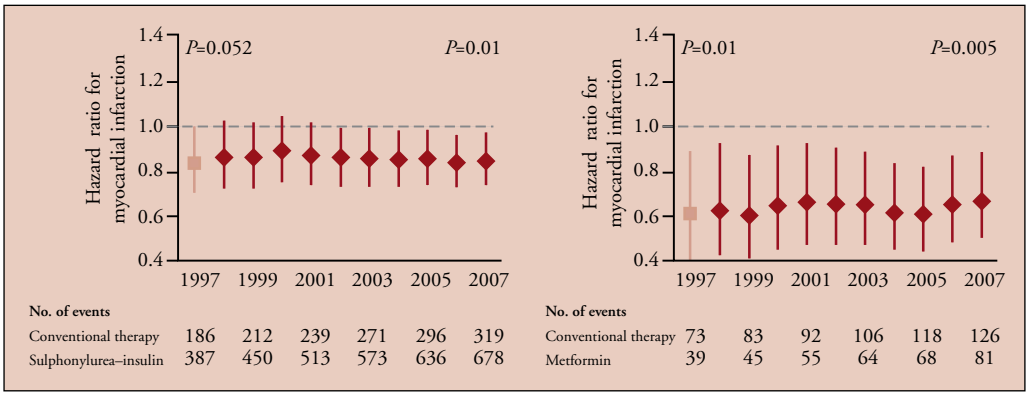
1. The early 1990s was a time of controversy over the use of lipid-lowering drugs, and the UK Prospective Diabetes Study (UKPDS) did not address the benefits of lipid lowering.
2. The benefit of lipid-lowering was confirmed definitively through the Collaborative Atorvastatin Diabetes Study, which had to be stopped early due to a risk reduction of 37% for major cardiovascular events in the arm receiving 10 mg atorvastatin compared with placebo.
3. Evidence for the benefit of blood pressure control in type 2 diabetes came originally from the UKPDS and since then, the focus of interest has moved to the question of whether specific drug classes have beneficial effects above that of blood pressure lowering.

Figure 1. Follow-up of participants of the UKPDS after completion of the trial in 1997. Despite better glycaemic control in the sulphonylurea–insulin group, the metformin group achieved a much more significant reduction in risk of myocardial infarction. This benefit was sustained in both treatment groups for the following decade (Holman et al, 2008). Reproduced with permission from the Massachusetts Medical Society.



5. Good glycaemic control improves microvascular outcomes including retinopathy and nephropathy

Microvascular disease is associated with both duration of diabetes and severity of hyperglycaemia. The retinopathy findings mentioned above at diagnosis in the UKPDS were positively correlated with baseline fasting blood glucose levels. This finding suggested that glycaemic control would be likely to reduce microvascular outcomes. The evidence came not only for people with type 2 diabetes from UKPDS (UKPDS Group, 1998a; 1998b), but also for people with type 1 diabetes in the DCCT (Diabetes Control and Complications Trial; DCCT Research Group, 1993). These classic studies encouraged good control of blood glucose in both types of diabetes. However, as discussed later, these benefits may be outweighed if blood glucose levels are taken too low.

6. Lipid lowering improves macrovascular risk in type 2 diabetes

The early 1990s was a time of controversy over the use of lipid-lowering drugs (Davey Smith and Pekkanen, 1992), and the UKPDS did not address the benefits of lipid lowering. However, by the end of this decade the benefits were becoming clearer, and a subgroup analysis in the Heart Protection Study suggested significant benefit in diabetes (Collins et al, 2003). This was confirmed definitively through the CARDS (Collaborative Atorvastatin Diabetes Study), which had to be stopped early due to a risk reduction of 37% for major cardiovascular events in the arm receiving 10 mg atorvastatin compared with placebo (Colhoun et al, 2004).

7. Blood pressure control improves both micro- and macrovascular outcomes

Evidence for the benefit of blood pressure control in type 2 diabetes came originally from the UKPDS (UKPDS Group, 1998c) and since then, the focus of interest has moved to the question of whether specific drug classes have beneficial effects above that of blood pressure lowering.

Three important large trials involved participants both with and without diabetes. The HOPE (Heart Outcomes Prevention Evaluation) study compared the angiotensin-converting enzyme (ACE) inhibitor ramipril with placebo (in addition to usual anti-hypertensive care in both arms) and found significant reductions in cardiovascular events and death in the ramipril arm despite only a small difference in blood pressure (Yusef et al, 2000). However, the interpretation of this finding remains controversial. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) compared ACE inhibitors, calcium channel blockers and thiazide diuretics (ALLHAT Officers and Coordinators for the ALLHAT

Collaborative Research Group et al, 2002). The results confirmed that thiazides, despite being theoretically diabetogenic, improve outcomes in people with hypertension both with and without diabetes. However, ASCOT–BPLA (Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) compared an amlodipine–perindopril regimen with an atenolol–thiazide regimen and was stopped early after reporting favourable outcomes in the former arm, and an increased incidence of diabetes in the latter (Dahlöf et al, 2005). An impact of this study was to question the position of beta-blockers in the treatment of hypertension, and resulted in changes to the standard hypertension treatment algorithm in the UK.

8. RAS-blockers reduce progression of nephropathy in people with all levels of albuminuria

An overall conclusion of anti-hypertensive trials – summarised in the NICE Clinical Guideline 66 (National Collaborating Centre for Chronic Conditions [NCCCC], 2008) – was that it is largely through blood pressure reduction that benefit occurs, irrespective of drug class, unless the person has evidence of diabetic nephropathy, including any degree of albuminuria, in which case blockade of the renin–angiotensin system (RAS) confers additional benefit. RAS-blockers (ACE inhibitors and angiotensin-2 receptor blockers [AR2Bs]) have a proteinuria-reducing effect, and have been shown to reduce progression of renal failure in people with albuminuria (Strippoli et al, 2005). There is also evidence that ACE inhibitors can prevent the onset of microalbuminuria, although more research is needed (Strippoli et al, 2006), and it has proven difficult to isolate the specific reno-protective effects of RAS-blockade from the blood pressure lowering benefits (Casas et al, 2005). However ACE inhibitors are now recommended as first choice for all hypertensive people with type 2 diabetes (NCCCC, 2008), and should also be offered to normotensive people with microalbumin or higher degrees of albuminuria.

9. There is enduring benefit of multifactorial vascular risk factor control started early in the course of diabetes

After the benefits of blood pressure, glycaemic and lipid control became evident in the 1990s, the question arose over whether a multifactorial "package" of intervention would confer additional benefit, combining pharmacological therapies with lifestyle manoeuvres. The STENO-2 study (Gaede et al, 2008) is particularly well known for confirming not only the effectiveness of

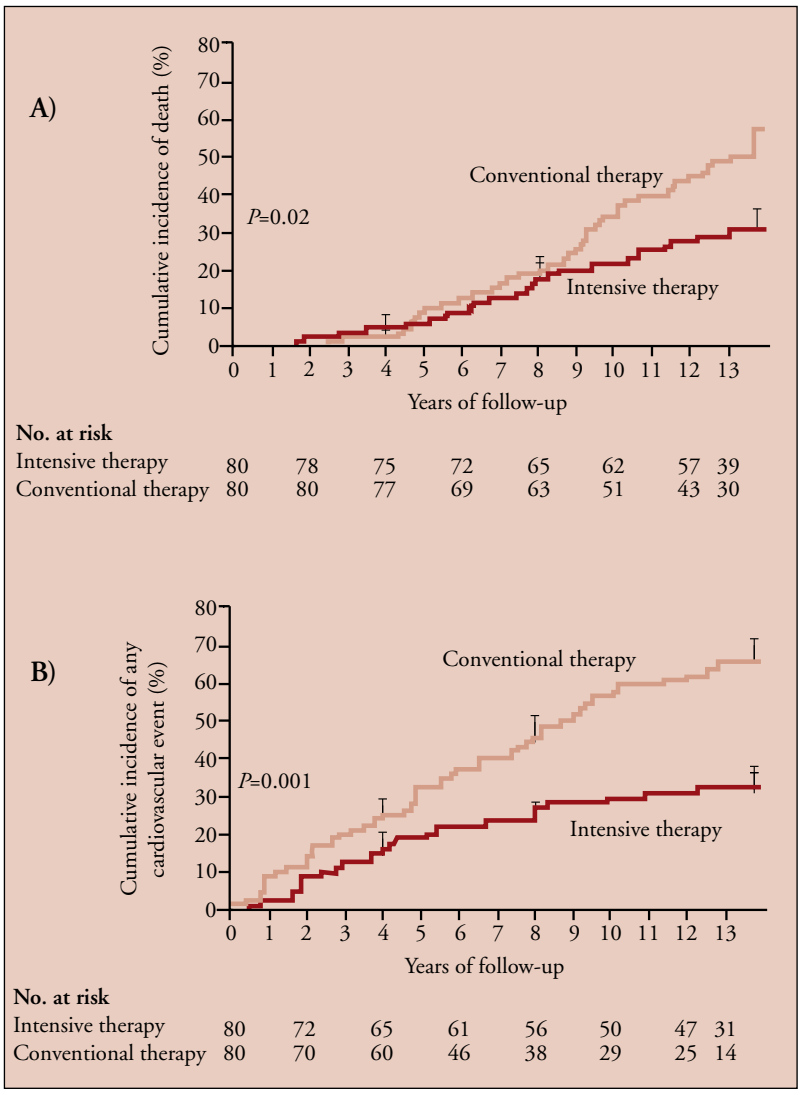


Figure 2. Cumulative incidence of (A) death and (B) any cardiovascular event in the STENO-2 trial. The mean treatment period ended after 7.8 years, but follow-up demonstrates the continuing benefit of the multifactorial intervention on outcomes (Gaede et al, 2008). Reproduced with permission from the Massachusetts Medical Society.

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1. The success of glycaemic control on microvascular disease was evident in the UK Prospective Diabetes Study (UKPDS). However, effects on macrovascular disease were less clear.
2. There was a need to determine: whether the benefits of tight glycaemic control outweighed the risks; whether the benefits (and risks) would increase with the lower targets achievable with newer hypoglycaemic agents; and whether the achievement of "tight" control was appropriate in people with more established diabetes and at risk of cardiovascular events, in contrast to the newly-diagnosed participants of UKPDS.
3. The ability of "tight" (rather than just "good") glycaemic control to reduce macrovascular risk was still unclear, and three trials were designed to investigate it: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial).

the multifactorial approach but also the enduring benefit when such a package is delivered successfully. *Figure 2* demonstrates that outcomes continued to diverge in the two trial arm populations for a further 5.5 years after the 7.8-year trial follow-up was completed. We would usually expect the lines to converge as risk factor control becomes more similar between the post-trial populations. This reinforces the phenomenon also evident in *Figure 1*, where the UKPDS macrovascular benefits were maintained for a full 10 years after the trial ended (Holman et al, 2008). This is now referred to as the "legacy effect" and strengthens the case both for early intervention and early detection of type 2 diabetes.

10. "Tight" glycaemic control does not improve clinical outcomes compared with standard care in established type 2 diabetes

The success of glycaemic control on microvascular disease was evident in the UKPDS as discussed above. However, as *Figure 1* shows, effects on macrovascular disease were less clear and the myocardial infarction hazard ratio for the sulphonylurea–insulin group compared with conventional therapy group fell just short of statistical significance at the trial completion (P=0.052). The UKPDS also confirmed that the benefits came at a price – increased hypoglycaemia and weight gain in those treated with these drugs.

There was, therefore, a need to determine: whether the benefits outweighed these risks; whether the benefits (and risks) would increase with the lower targets achievable with newer hypoglycaemic agents; and whether the achievement of "tight" control was appropriate in people with more established diabetes and at risk of cardiovascular events, in contrast to the newly-diagnosed participants of UKPDS.

While end-stage renal failure is an important emerging issue for all healthcare systems, and diabetic retinopathy remains the most common cause of blindness in working-age people in the Western world, the main preventable threat to older populations is from macrovascular disease. The ability of "tight" (rather than just "good") glycaemic control to reduce risk of this was still unclear, and three trials were designed to investigate it: ACCORD (Action to Control Cardiovascular Risk in Diabetes; ACCORD Study Group et al, 2008), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation; ADVANCE Collaborative Group et al, 2008) and VADT (Veterans Affairs Diabetes Trial; Duckworth et al, 2009).

The ACCORD trial randomised participants to a tight control arm aiming for a target HbA_{1c} of ≤6.0% (≤42 mmol/mol) or a more standard approach. A median level of 6.4% (46 mmol/mol) was achieved in the intensive arm (compared with 7.5% [58 mmol/mol] in the standard treatment arm), using multiple therapies including insulin if needed. In contrast to the relatively poor target achievement of UKPDS (conducted at a time of more limited treatment options) (Turner et al, 1999), this difference was maintained for a median follow-up time of 3.4 years. At this point, the trial was stopped. This was necessary because the all-cause mortality in the intensive arm was higher than for standard care (annual mortality 14.1 per 1000 versus 11.4 per 1000). The cause of the increased mortality was unclear, and appeared to be higher in those aiming for a low HbA_{1c} level but not achieving it.

ADVANCE compared groups randomised to either gliclazide MR (modified release) (plus other treatments if needed, aiming for an HbA_{1c} level of ≤6.5% [≤48 mmol/mol]) versus any non-gliclazide therapy and a target based on local guidelines in the various international centres. While the trial's composite primary endpoint of all microvascular and major cardiovascular events was significantly reduced, this was largely due to a substantial reduction in albuminuria development, with no significant reduction in macrovascular outcomes.

In the VADT, a difference in HbA_{1c} of 6.9% (52 mmol/mol) versus 8.5% (69 mmol/mol) was achieved between the intensive versus standard trial arms, respectively. No significant

improvement in macrovascular disease was reported, but there was a suggestion of benefit if therapy was started early in the course of disease. The details of these trials and the interesting implications for policy are discussed in a USA position statement published in 2009 (Skyler et al, 2009). A more recent systematic review has confirmed that all-cause mortality, cardiovascular deaths, and other clinical end-points are not reduced by "tight" rather than standard glycaemic control in type 2 diabetes (Boussageon et al, 2011). This should not stop us aiming for the standard control targets that are clearly beneficial, particularly when part of a multifactorial intervention package started early in the course of diabetes, as discussed above.

11. Screening for retinopathy linked to early intervention can prevent visual loss

The benefits of early intervention for diabetic retinopathy became evident during the trials of photocoagulation during the 1970s (Early Treatment Diabetic Retinopathy Study Research Group, 1985). The success of this treatment has reduced the anxiety of people living with longstanding diabetes and must count as one of the major advances in diabetes care since the discovery of insulin. However, this research question is slightly different from that of the effectiveness of population screening. It would not now be considered ethical to conduct a trial of screening versus no screening but its justification has been made on modelling grounds for the overall population with diabetes (Singer et al, 1992; Fong et al, 2004). However, the cost-effectiveness of different screening intervals is quite dependent on the risk of short-term visual loss, which differs between subgroups of the overall population with diabetes (Vijan et al, 2000). So the case for screening is robust, even though the appropriate screening interval in the various subgroups might be arguable.

12. Foot screening programmes linked to early intervention can reduce amputation rates

While the need to act urgently in the face of threatening or established ulceration is unambiguous, the effectiveness and cost-effectiveness of regular foot screening by a clinician (as with the retinopathy screening question above) is less clear because it depends on the background risk of the population. The conclusion of much research on this question is that routine screening of the whole population with diabetes is only effective if linked to robust referral mechanisms to provide the early intervention when complications become evident (Singh et al, 2005).

In UK primary care, the QOF rewards us for screening feet, but acting on our findings is not measured under this system and the majority of our patients in primary care are at low short-term risk. Only if our screening assessments are linked to clear referral pathways can the benefits of primary care foot screening be realised. General practice teams are in a crucial position to maximise these benefits through early intervention, but it is the specialist podiatrists and surgeons that actually make the difference to ultimate disability, and access to their expertise should be seen as part of the screening programme.

Conclusions

The major research findings supporting modern primary care management of diabetes started with the discovery of insulin in the early 1920s. The benefits of this were so immediately obvious that confirmatory research trials were deemed unnecessary. Other discoveries have required subtle statistical techniques applied to large study datasets and in the process have led to the early termination of several resource-intensive trials and to the withdrawal of therapies in the post-licensing phase.

There are many evidence-based issues more relevant to secondary care and these have not been covered in this article. The benefits of revascularisation for foot ulcer healing, the impact of specific ophthalmological procedures on retinal outcomes, and the options for intervention in the later stages of renal failure are just a few examples. As primary care clinicians we need to think about our own role in the overall process of care, and to understand the evolving evidence base that supports it.

Page points

1. The benefits of early intervention for diabetic retinopathy became evident during the trials of photocoagulation during the 1970s.
2. The success of photocoagulation has reduced the anxiety of people living with longstanding diabetes and must count as one of the major advances in diabetes care since the discovery of insulin.
3. While the need to act urgently in the face of threatening or established ulceration is unambiguous, the effectiveness and cost-effectiveness of regular foot screening by a clinician, is less clear because it depends on the background risk of the population.

"In most cases evolving policy will be based on a long-term appraisal of the risk:benefit ratio of novel interventions, initially suggested by serendipitous observations, supported by clinical trials, confirmed by meta-analysis, and followed up both by epidemiological surveillance and by qualitative study of their relevance to individuals."

Even more questions are unresolved but close to being answered. Will the newer agents (GLP-1 receptor agonists, DPP-4 inhibitors) reduce cardiovascular events in the longer term? Is low-dose aspirin of overall benefit in people with diabetes but no history of cardiovascular disease? How can we make structured type 2 education programmes more effective at impacting on hard clinical outcomes? What is the role of bariatric surgery in the prevention and treatment of type 2 diabetes?

In conclusion, the evidence base for modern diabetes care relies very much on mixed research methods, to ensure that we do more good than harm. Pharmaceutical companies are required to establish the cardiovascular safety of new hypoglycaemic agents through randomised controlled trials. But in most cases evolving policy will also be based on a long-term appraisal of the risk:benefit ratio of novel interventions, initially suggested by serendipitous observations, supported by clinical trials, confirmed by meta-analysis, and followed up both by epidemiological surveillance and by qualitative study of their relevance to individuals. ■

Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME et al (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**: 2545–59

ADVANCE Collaborative Group, Patel A, MacMahon S et al (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* **358**: 2560–72

ALLHAT Officers and Coordinators for the 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). *JAMA* **288**: 2981–97

Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M et al (2011) Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* **343**: d4169

Casas JP, Chua W, Loukogeorgakis S et al (2005) Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* **366**: 2026–33

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**: 685–96

Collins R, Armitage J, Parish S et al (2003) MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* **361**: 2005–16

DAFNE Study Group (2002) Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* **325**: 746

Dahlöf B, Sever PS, Poulter NR et al (2005) Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* **366**: 895–906

Davey Smith G, Pekkanen J (1992) Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* **304**: 431–4

Davies MJ, Heller S, Skinner TC et al (2008) Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* **336**: 491–5

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. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* **329**: 977–86

Duckworth W, Abraira C, Moritz T et al (2009) Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* **360**: 129–39

Early Treatment Diabetic Retinopathy Study Research Group (1985) Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* **103**: 1796–806

Fong DS, Aiello L, Gardner TW, King GL (2004) Retinopathy in diabetes. *Diabetes Care* **27**(Suppl 1): S84–7

Gaede P, Lund-Andersen H, Parving HH, Pedersen O (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* **358**: 580–91

Gillies CL, Abrams KR, Lambert PC et al (2007) Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* **334**: 299

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Holt T (2011) Evidence-based medicine. Part 2: Randomised controlled trials. *Diabetes & Primary Care* **13**: 82–7

John WG, Mosca A, Weykamp C, Goodall I (2007) HbA_{1c} standardisation: history, science and politics. *Clin Biochem Rev* **28**: 163–8

Klein R, Klein BE, Moss SE et al (1984a) The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* **102**: 520–6

Klein R, Klein BE, Moss SE et al (1984b) The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* **102**: 527–32

Knowler WC, Barrett-Connor E, Fowler SE et al (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* **346**: 393–403

Kohner EM, Aldington SJ, Stratton IM et al (1998) United Kingdom Prospective Diabetes Study, 30: diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. *Arch Ophthalmol* **116**: 297–303

Lindström J, Louheranta A, Mannelin M et al (2003) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* **26**: 3230–6

Loveman E, Frampton GK, Clegg AJ (2008) The clinical effectiveness of diabetes education models for type 2 diabetes: a systematic review. *Health Technol Assess* **12**: 1–116

National Collaborating Centre for Chronic Conditions (2008) *Type 2 Diabetes. National Clinical Guideline for Management in Primary and Secondary Care (Update).* Royal College of Physicians, London

Richter B, Neises G (2005) 'Human' insulin versus animal insulin in people with diabetes mellitus. *Cochrane Database Syst Rev* (1): CD003816

Singer DE, Nathan DM, Fogel HA, Schachat AP (1992) Screening for diabetic retinopathy. *Ann Intern Med* **116**: 660–71

Singh N, Armstrong DG, Lipsky BA (2005) Preventing foot ulcers in patients with diabetes. *JAMA* **293**: 217–28

Skyler JS, Bergenstal R, Bonow RO et al (2009) Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* **119**: 351–7

Strippoli GF, Craig M, Craig JC (2005) Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database Syst Rev* (4): CD004136

Strippoli GF, Bonifati C, Craig M et al (2006) Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev* (4): CD006257

Tattersall R (2009) *Diabetes: The Biography.* Oxford University Press, Oxford

Turner RC, Cull CA, Frighi V, Holman RR (1999) Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* **281**: 2005–12

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

UK Prospective Diabetes Study 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**: 837–53

UK Prospective Diabetes Study Group (1998c) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**: 703–13

Vijan S, Hofer TP, Hayward RA (2000) Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. *JAMA* **283**: 889–96

Witters LA (2001) The blooming of the French lilac. *J Clin Invest* **108**: 1105–7

Wooton D (2007) *Bad Medicine: Doctors Doing Harm Since Hippocrates.* Oxford University Press, Oxford

Yusuf S, Sleight P, Pogue J et al (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* **342**: 145–53