Emerging evidence and guidance in diabetes care in 2012

Colin Kenny

The year 2012 was another interesting one for research in primary diabetes care. New guidance relevant to patient care was published and should impact on practices over the next 12 months. In addition, several well-developed clinical trials reported data, although few had really dramatic outcomes. This article reviews these developments and more from the year.

Article points

1. The year 2012 was another interesting one for research in primary diabetes care.
2. New guidance relevant to patient care was published and should impact on practices over the next 12 months.
3. Several well-developed clinical trials reported data, although few had really dramatic outcomes.

Key words

- Evidence
- Guidelines

This article reviews new evidence and guidelines that emerged in primary care diabetes in 2012.

Emerging evidence

Education interventions

A Health Technology Assessment suggested that, in people with impaired glucose tolerance, dietary change to ensure weight loss, coupled with physical activity, is clinically effective and cost-effective in reducing progression to diabetes (Gillett et al, 2012). The ADDITION-Cambridge study Group examined 20 184 individuals at high risk of prevalent undiagnosed diabetes in east England drawn from primary care settings (Simmons et al, 2012). They concluded that screening for type 2 diabetes in patients at increased risk was not associated with a reduction in all-cause, cardiovascular, or diabetes-related mortality within 10 years. Given this evidence, practices may want to reflect on the utility of screening for diabetes.

The investigators in the DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed) programme for people with newly diagnosed type 2 diabetes published 3-year follow-up data this year (Khunti et al, 2012b). This trial was based in primary care settings but unfortunately, in keeping with their reported 1-year data (Davies et al, 2008), there were no differences in biomedical or lifestyle outcomes compared with controls at 3 years, although some illness beliefs demonstrated improvements.

The GIANT (General Practitioner Implementation in Asia of Normoglycaemic Targets) study, which was based in primary care, this time in the Asia-Pacific region, published results around the same time as DESMOND (Reutens et al, 2012). People with type 2 diabetes were cluster-randomised to be educated on regional diabetes management guidelines or continue with standard care (Reutens et al, 2012). This structured GP education programme did not improve HbA_{1c} in patients with type 2 diabetes.

Finally, the Look AHEAD (Action for Health in Diabetes) study – a trial comparing an intensive lifestyle-intervention programme aimed at achieving and maintaining weight loss and fitness in people with type 2 diabetes and improving cardiovascular outcomes – was stopped for futility as the investigators

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Page points

1. Emerging evidence on the potential hazard of sulphonylureas runs contrary to the Quality, Innovation, Productivity and Prevention (QIPP) agenda encouraging practices in England to use them second line in a significant percentage of patients.
2. A systematic review and meta-analysis of dipeptidyl peptidase-4 (DPP-4) inhibitors concluded that in people with type 2 diabetes who do not achieve glycaemic targets with metformin alone, DPP-4 inhibitors can lower HbA_{1c}, in a similar way to sulphonylureas or pioglitazone, but with neutral effects on body weight.
3. On 14 November, the Bristol-Myers Squibb/ AstraZeneca alliance achieved a product licence for their drug dapagliflozin, which is a competitive, reversible inhibitor of sodium–glucose co-transporter 2 (SGLT2) in the proximal convoluted tubule.

did not foresee successful cardiovascular outcomes (http://www.theheart.org/article/1458351.do [accessed 03.12.12]).

The UK Government seems intent on a "shift-left" agenda, with a much greater emphasis on prevention of illnesses, particularly diabetes. None of the data published this year suggest that early interventions, such as education, improve long-term outcomes, particularly cardiovascular mortality.

Oral antidiabetes medicines

During the year, two large meta-analyses tried to answer the question: after metformin what is the next drug of choice? A retrospective cohort study using data from the UK-based General Practice Research Database examined the data on what to use after failure of metformin monotherapy (Morgan et al, 2012). Metformin plus pioglitazone was associated with significantly better all-cause mortality than metformin alone. Mean HbA_{1c} level improved between baseline and 12 months for all regimens other than sulphonylurea monotherapy. The combination of metformin plus pioglitazone appears to provide superior clinical outcomes compared with the most commonly used regimen, metformin plus sulphonylurea.

Another retrospective cohort study of the use of the sulphonylureas glibenclamide and glipizide compared with metformin for initial treatment of diabetes found an increased hazard of cardiovascular disease events or death associated with both sulphonylureas (Roumie et al, 2012).

Unfortunately this narrative on the potential hazard of sulphonylureas runs contrary to the Quality, Innovation, Productivity and Prevention (QIPP) agenda encouraging practices in England to use them second line in a significant percentage of patients.

DPP-4 inhibitors

A systematic review and meta-analysis of dipeptidyl peptidase-4 (DPP-4) inhibitors published in the *British Medical Journal* this year concluded that in people with type 2 diabetes who do not achieve glycaemic targets with metformin alone, DPP-4 inhibitors can lower HbA_{1c}, in a similar way to sulphonylureas or pioglitazone, but with neutral effects on body weight (Karagiannis et al, 2012). The reviewers did point to increased unit cost and uncertainty about long-term safety, owing to the relatively limited time for which the agents have been available.

SGLT2s

On 14 November, the Bristol-Myers Squibb/ AstraZeneca alliance achieved a product licence for their drug dapagliflozin, which is a competitive, reversible inhibitor of sodium–glucose co-transporter 2 (SGLT2) in the proximal convoluted tubule. It reduces glucose reabsorption by the kidneys and increases urinary glucose excretion. It is licensed as monotherapy – when diet and exercise alone do not provide adequate glycaemic control, in patients for whom the use of metformin is considered inappropriate owing to intolerance – and in combination with other glucose-lowering medications including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. This is a potentially important emerging class of drugs and more agents in the class are expected to achieve licenses in 2013.

Insulin

Data from SOLVE (the Study of Once Daily Levemir) were published this year (Khunti et al, 2012a). The study was based in primary care throughout Europe, with several practices in the UK involved, and examined how insulin detemir was used. The aim was to examine the timing of this insulin's initiation in routine clinical practice, especially in relation to glycaemic control and use of oral antidiabetes drugs. The study found that, despite well-documented benefits of timely glycaemic control and consensus guidelines encouraging earlier use of insulin, considerable clinical inertia exists

with respect to initiating appropriate insulin therapy in people with type 2 diabetes. Regional differences throughout Europe exist in the timing of insulin initiation and in the use of oral antidiabetes agents, with the UK faring poorly compared with other European nations, often initiating insulin at a much higher level of HbA_{1c}.

The ORIGIN (Outcome Reduction with Initial Glargine Intervention) study, which examined long-term use of insulin glargine, also published results this year (ORIGIN Trial Investigators et al, 2012). The ORIGIN study assessed the effects of treatment with insulin glargine versus standard care on cardiovascular outcomes. There was a median follow-up of more than 6 years. Key findings were that insulin glargine had no increased risk in cancer incidence, a low rate of severe hypoglycaemia, and no increased cardiovascular risk.

Complementary and alternative medicines

A large Cochrane database analysis published this year concluded that there is insufficient evidence to support the use of cinnamon for type 1 or type 2 diabetes. The reviewers suggested that there might be benefit in further trials exploring factors that include health-related quality of life, diabetes complications and costs (Leach and Kumar, 2012).

Surgery

This year the *New England Journal of Medicine* reported on two approaches to surgery in people with diabetes. First, in the context of bariatric surgery in obese people with uncontrolled type 2 diabetes, 12 months of medical therapy plus bariatric surgery achieved target glycaemic control in significantly more patients than medical therapy alone (Schauer et al, 2012). Another study examined patients with diabetes and advanced coronary artery disease and yielded results suggesting that coronary artery bypass grafting was superior to percutaneous coronary intervention as it significantly reduced rates of death and myocardial infarction (Farkouh et al, 2012).

New guidance for 2012

HbA_{1c}

The utility of HbA_{1c} in diagnosing diabetes was reflected on during the year as practices became accustomed to using an HbA_{1c} of 48 mmol/mol (6.5%) as the cut-point to diagnose symptomatic individuals with diabetes. A UK expert advisory body, convened by the Department of Health, outlined how the World Health Organization's recommendations should be implemented (John et al, 2012). The report provided guidance about the use of the new test and detailed advice on management, particularly emphasising when not to rely on the test, including in younger patients, in those with serious undercurrent illness, and when the clinical situation is rapidly evolving.

New EASD/ADA guidance on prescribing in type 2 diabetes

Emerging data on new and existing agents have led the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) to publish a joint position statement on prescribing in type 2 diabetes (Inzucchi et al, 2012). They take a pragmatic approach, suggesting that unless there are prevalent contraindications, metformin is the optimal first-line drug. After metformin, there are limited data to guide choice. They conclude that combination therapy with an additional one or two oral or injectable agents is reasonable, aiming to minimise side effects where possible. This guidance conflicts with both contemporary NICE and SIGN guidelines, which are much more proscriptive.

Diabetes prevention guidance

Prevention studies have demonstrated a reduction in the development of diabetes of more than 50% in individuals at high risk of the condition who undertook an intensive lifestyle change programme, and by lower amounts in those treated with metformin or

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1. In July 2012, NICE published its guideline on identifying high-risk individuals and the components of quality-assured, evidence-based lifestyle change programmes that could be implemented across the UK to achieve future reductions in type 2 diabetes.
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other drug therapies (NICE, 2012). In July 2012, NICE published its guideline that makes recommendations for how such high-risk individuals may be identified, and the components of quality-assured, evidence-based lifestyle change programmes that could be implemented across the UK to achieve future reductions in type 2 diabetes (NICE, 2012).

A two-step process for the identification was recommended. In stage 1, either a practice-based search or individual questionnaires would be used to identify those who may be at risk. Those identified at risk would then have a blood test (either fasting plasma glucose or HbA_{1c}), which would divide them into those with potential diabetes, those at high risk who would qualify for the lifestyle change programme and those who are at moderate risk and would receive brief intervention. Individuals aged 40–74 years would be assessed during the NHS Health Checks, while those aged 25–39 from high-risk ethnic groups would also be offered assessment.

The challenge will be for public health and commissioning groups to design, develop, implement and evaluate the effectiveness of these intensive lifestyle programmes in a bid to halt the diabetes epidemic in the UK.

Guidance on driving and diabetes

In recent years, changes imposed by the EU to the Group 1 (cars and motorcycles) licence rules for those on insulin have meant that they have become stricter than those previously applied in the UK, particularly concerning hypoglycaemia. Conversely, the regulations governing the licensing of drivers on insulin wishing to drive Group 2 (large goods vehicles and passenger-carrying vehicles) became less strict as the UK relaxed its legislation to come in line with Europe, although people with type 1 diabetes seeking Group 2 licences are still strictly regulated.

This year, further tweaks have been made to the guidance for drivers with diabetes and updated guidance has been published (Driver and Vehicle Licensing Agency, 2012). ■

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