Global Summaries

In Focus
Management of Type 1 Diabetes Mellitus

Glycaemic Management of Type 2 Diabetes

Reducing Cardiovascular Risk in Type 2 Diabetes Mellitus

Continuing Medical Education
Care of the Patient on Long-term Oral Glucocorticoids

Management of Plantar Fasciitis Evolving

In Focus: Diabetes

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CONTENTS

453-468 Continuing Medical Education

453 Care of the Patient on Long-term Oral Glucocorticoids
Shannon McCarthy, Mark Kotowicz

461 Management of Plantar Fasciitis Evolving
Brett R Fink

Coming Next...

* In Focus *

Acute Coronary Syndrome

• Ischaemic Heart Disease: Stable Angina
• Management of ST-Elevation Myocardial Infarction
• Ischaemic Heart Disease: Management of Non-ST-Elevation Acute Coronary Syndrome

and more!
**IL-6 receptor pathways and coronary disease**

Coronary disease is associated with chronic inflammation, but whether the association is causal is not known. Genetic mutations associated with increased biomarkers of inflammation have not been associated with increased coronary risk, making a direct causal link less likely. Now, two meta-analyses of studies of a mutation (Asp358Ala) in the interleukin 6 (IL-6) receptor gene (IL6R) have suggested that there may be a causal relationship between coronary disease and IL6R-related pathways.

One meta-analysis included 82 studies of Asp358Ala, coronary risk factors, and inflammation biomarkers in 125,222 subjects. The frequency of the mutation was also studied in 51,441 patients with coronary disease and 136,226 controls. The minor allele frequency of Asp358Ala was also studied in 51,441 patients with coronary disease and IL6R-related pathways. One meta-analysis included 82 studies of Asp358Ala, coronary risk factors, and inflammation biomarkers in 125,222 subjects. The frequency of the mutation was also studied in 51,441 patients with coronary disease and 136,226 controls. The minor allele frequency of Asp358Ala was 39% among people without coronary disease. It did not affect lipid levels, blood pressure, adiposity, blood sugar levels, or smoking rates. It did, however, increase IL6R and IL-6 levels and reduce levels of C-reactive-protein and fibrinogen, suggesting a block between production of IL-6 and downstream markers. There was a 3.4% reduction in coronary risk for every copy of 358Ala inherited.

The other meta-analysis included 40 studies (133,449 subjects) and confirmed that Asp358Ala was associated with increased levels of IL-6, and reduced levels of C-reactive-protein and fibrinogen, effects similar to those of the IL-6-blocking antibody, tocilizumab, used to treat rheumatoid arthritis. Possession of a single allele of an Asp358Ala-related single nucleotide polymorphism reduced the risk of coronary disease significantly by 5% in a large study of coronary disease patients and controls.

These results suggest that 358Ala reduces the systemic inflammatory response and also reduces coronary risk, thus supporting the hypothesis that chronic inflammation promotes coronary disease. Modulation of IL6R pathways might prevent coronary disease, but the effects on conventional risk factors might be difficult to predict.

**DERMATOLOGY**

Brodalumab for psoriasis

T-cell production of interleukin 17 is important in the pathogenesis of psoriasis. Brodalumab is a human monoclonal antibody against interleukin 17RA, one of the six cytokines of the interleukin 17 cytokine family. A multicentre, international study has shown that brodalumab is effective treatment for chronic plaque psoriasis over a 12-week period. The study included 198 patients with a score of at least 12 on the Psoriasis Area and Severity Index score (possible range, 0–72; higher scores indicating more severe disease) and at least 10% of body surface area affected. Randomization was to subcutaneous brodalumab or placebo. Brodalumab was given at doses of 70, 140, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 or 280 mg on day 1 and at weeks 4 and 8. At week 12, the improvement in PASI score was 45% with the 70-mg dose, 85.9% (140 mg), 86.3% (210 mg), 76.0% (280 mg), and 16% (placebo). An improvement of at least 75% was seen in 77% at the 140-mg dose and in 82% of the 210-mg group. An improvement of at least 90% was seen in 72% and 75% of these groups, respectively. No patient in the placebo group achieved these degrees of improvement. On the static physician’s global assessment at week 12, clear or minimal disease was recorded in 26%, 85%, 80%, and 69% of patients with increasing brodalumab doses and in 3% with placebo. Two patients, both in the 210-mg group, developed grade 3 neutropenia. The most common adverse events with brodalumab were nasopharyngitis (8%), upper respiratory tract infection (8%) and injection-site erythema (6%), all of which occurred at similar rates in the placebo group.

Brodalumab was effective treatment for psoriasis over a 12-week period.

Ixekizumab for psoriasis

Izekizumab is a humanized monoclonal antibody against interleukin 17. A 16-week, multicentre trial has shown it to be effective against psoriasis. A total of 142 patients with chronic, moderate-to-severe plaque psoriasis were randomized to subcutaneous ixekizumab or placebo at 0, 2, 4, 8, 12, and 16 weeks. Ixekizumab was given at doses of 10, 25, 75, or 150 mg. At 12 weeks, the proportions achieving a reduction in Psoriasis Area and Severity Index (PASI) score of at least 75% were 29% (10 mg dose), 77% (25 mg), 83% (75 mg), 82% (150 mg), and 8% (placebo); a significant improvement on placebo for all except the lowest dose of ixekizumab. For a reduction, in PASI score of at least 90%,
the corresponding figures were 18%, 50%, 59%, and 71% with increasing doses of ixekizumab and 0% with placebo; and for a 100% reduction, they were 0%, 17%, 38%, and 39% with ixekizumab and 0% with placebo. The proportions with clear or minimal disease on the static physician’s global assessment score were 25%, 70%, 72%, and 71% (ixekizumab), and 8% (placebo).

Ixekizumab was effective against psoriasis in a 16-week trial.


Topical ingenol mebutate for actinic keratoses

Actinic keratoses are common in light-skinned people and are premalignant. Treatment may be applied to lesions (cryosurgery) or to the whole area of affected skin (field therapy). Field therapy treatments include imiquimod, fluorouracil, diclofenac, and photodynamic therapy, and they often need to be applied for weeks or months. Ingenol mebutate is a pleiotropic effector that kills cells and promotes immune responses mediated through activation of protein kinase C delta, including neutrophil-mediated oxidative burst and clearance of tumours. Four multicentre US studies reported together have shown that 2 to 3 days of topical field therapy with ingenol mebutate gel is effective treatment for actinic keratoses.

In two trials, patients had lesions of the face or scalp, and in the other two the lesions were of the trunk or extremities. Patients were at least 18 years old and had four to eight typical lesions within a 25-cm² field of skin. They were randomized to apply either ingenol mebutate gel 0.015% or placebo (vehicle) gel to a 25-cm² contiguous field once daily for 3 days in the face or scalp lesions studies and 2 days in the trunk and extremities lesions studies. Complete clearance at 57 days was achieved in 42.2% (ingenol mebutate) vs 3.7% (placebo) in the face and scalp trials and in 34.1% vs 4.7% in the trunk and extremities trials. Local skin reactions peaked at days 3 to 8 and returned to baseline levels by day 29. Adverse events were usually mild to moderate and resolved without sequelae.

Ingenol mebutate gel applied for 2 or 3 days as topical field therapy may be effective for actinic keratoses.


DPP-4 inhibitors for type 2 diabetes

Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) reduce the breakdown of incretin hormones, mainly glucagon-like peptide 1 (GLP-1), tending to correct glucose homeostasis without increasing body weight. Their role in the treatment of type 2 diabetes remains uncertain. The authors of a systematic review and meta-analysis have suggested that they may be used as second-line treatment after metformin.

The meta-analysis included 27 reports of 19 studies (13,881 patients) with randomization to a DPP-4 inhibitor or another antidiabetic drug. DPP-4 inhibitor monotherapy, compared with metformin monotherapy, was associated with a lesser decrease in glycated haemoglobin A1c levels. As a second-line treatment DPP-4 inhibitors were similarly effective to pioglitazone, slightly less effective than sulfonylureas, and inferior to GLP-1 agonists. The risk of hypoglycaemia was less with DPP-4 inhibitors than with sulfonylureas when combined with metformin.

DPP-4 inhibitors could be used as added treatment when metformin is not completely successful. Guidelines all recommend starting treatment with metformin. When extra treatment is needed, US and European guidelines recommend adding insulin, a sulfonylurea, or a glitazone. UK (National Institute for Clinical Excellence) guidelines suggest a sulfonylurea, followed by insulin as a third-line option, with a DPP-4 inhibitor as a second-line option for patients at high risk of hypoglycaemia or intolerant of a sulfonylurea, or as third-line for patients who do not accept insulin. Studies of DPP-4 inhibitors with clinical end points are in progress.


White rice and diabetes

Many studies have examined the relationship between intake of white rice and risk of type 2 diabetes, but the findings have varied. Asian populations eat far more white rice than Western populations. A systematic review and meta-analysis has been reported.

The meta-analysis included data from seven cohorts: three Asian (Chinese and Japanese) and four Western (US and Australian). Baseline consumption of white rice averaged three to four servings a week in Asian populations and one to two servings a week in Western populations. In
the Asian cohorts, those who ate the most white rice had a 55% increase in risk of type 2 diabetes compared with those who ate the least. In the Western cohorts, the corresponding increase in risk was 12%. Using pooled data from both populations, each increase in intake of one serving per day increased the relative risk of type 2 diabetes by 11%.

It is concluded that high intake of white rice is associated with increased risk of type 2 diabetes, and this increase is more marked in Asian populations.


**GENERAL MEDICINE**

**Inpatient harms in developing countries**

Harm to patients in hospital that results from misguided health care is well documented in developed countries. Now, a report from eight developing or transitional countries has shown a similar incidence of adverse events.

The study was based on a convenience sample of 28 hospitals in Egypt, Jordan, Kenya, Morocco, Tunisia, South Africa, Sudan, and Yemen. A total of 15,548 randomly selected patient records were reviewed, and 8.2% showed at least one adverse event (range, 2.5% to 18.4% in different countries). Mortality from these adverse events was 30%, and 83% of the adverse events were considered preventable. About one-third (34%) of the events were due to therapeutic errors in non-complex clinical situations. Inadequate staff training or supervision or non-adherence to policies or protocols accounted for most adverse events.

The rate of health-care-derived adverse events in these countries was similar to those reported from developed countries, but they were more often preventable and the consequences were more serious.


**NEUROLOGY**

**Tenecteplase versus alteplase for acute ischaemic stroke**

Alteplase, a recombinant tissue plasminogen activator, is effective thrombolytic treatment for acute ischaemic stroke, but reperfusion with this treatment is often incomplete and delayed. Tenecteplase is a genetically engineered mutant tissue plasminogen activator that may have advantages over alteplase and is apparently effective for stroke at lower doses than for myocardial infarction. Now, a study in Australia has shown better results with tenecteplase than with alteplase in highly selected patients.

Patients who had a perfusion lesion of at least 20% greater than the infarct core on computed tomographic perfusion imaging at baseline and an associated vessel occlusion on computed tomographic angiography were selected. Using these criteria, 75 of 2,768 patients were enrolled within 6 hours of onset of stroke symptoms. They were randomized to intravenous alteplase 0.9 mg/kg, tenecteplase 0.1 mg/kg, or tenecteplase 0.25 mg/kg. Tenecteplase was given as a bolus, and alteplase as 10% of the dose by bolus, with the remaining 90% infused over the next hour. At 24 hours, the tenecteplase groups showed significantly greater reperfusion on perfusion-weighted magnetic resonance imaging and significantly greater clinical improvement on the National Institute of Health Stroke Scale. There were no significant differences between the groups in intracranial bleeding or other adverse effects. At 90 days, there was no serious disability in 72% (tenecteplase) vs 40% (alteplase). The 0.25 mg/kg dose of tenecteplase gave better results than the 0.1 mg/kg dose.

For these selected patients, tenecteplase was associated with better outcomes than alteplase.


**PSYCHIATRY**

**Lithium toxicity**

Lithium is effective in the treatment of bipolar disorder, providing protection against both depression and mania, but there are concerns about potential toxicity, in particular its effects on the kidneys and risk of teratogenicity. Present guidelines suggest avoiding lithium in pregnancy, but the degree of risk is unknown, as is the extent of renal toxicity. A systematic review and meta-analysis has clarified some issues.

The analysis included 385 studies, including 22 randomized, controlled trials, 197 case-control, uncontrolled cohort, or cross-sectional studies, and 166 case reports. Overall, lithium reduced glomerular filtration rate by 6.22 mL/min and urinary concentrating ability by 15% of normal maximum. The risk of chronic renal failure was low, with 0.5% of patients needing renal replacement therapy. The risk of hypothyroidism was increased almost sixfold. There was also an increased risk...
Lithium treatment increases the risks of hypothyroidism and hyperparathyroidism. The risk of end-stage renal failure is low, but urinary concentrating ability may be impaired, leading to clinical nephrogenic diabetes insipidus. The risk of teratogenicity is uncertain, but there was no significant increase in congenital malformations in this study. Serum calcium levels should be checked before and during treatment. Lancet editorialists conclude that these data confirm that, on balance, lithium is the treatment of choice for bipolar disorder.


CDC Recommends Two-Pronged Pneumococcal Vaccine Strategy For Immunocompromised Adults

The Pneumococcal Working Group of the US Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) recently recommended a combined pneumonia vaccination strategy integrating two types of vaccines for immunocompromised adults to protect against disease.

According to the recommendation, the 13-valent pneumococcal conjugate vaccine (PCV13), which protects against 13 serotypes of Streptococcus pneumoniae, may be integrated prior to or at specific points during the 23-valent polysaccharide vaccine (PPSV23) schedule already recommended for this group of patients.

The working group indicated that PCV13 may be given in vaccine-naive adults aged 19 or older with immunocompromising conditions such as human immunodeficiency virus, with functional or anatomic asplenia, cerebrospinal fluid leaks or cochlear implants, followed by a dose of PPSV23 after a minimum of 8 weeks.

The current recommendation for PPSV23 in immunocompromised adults is one dose followed by a second after 5 years and a booster again after age 65 but after at least 5 years following the last dose.

In an adult vaccinated with PPSV23, PCV13 may not be given until 1 year after the last dose of PPSV23 and additional PPSV23 may be given after at least 8 weeks following PCV13 administration.

This sequence allows antibodies resulting from the PCV13 vaccine that are non-inferior or superior to those created by PPSV23 vaccine to proliferate, as well as maintains appropriate immunogenicity.

PCV13 was originally recommended for all children under age 5. The vaccine was shown to have non-inferior immunogenicity compared with PPSV23 and was licensed for use among adults over 50 years in 2011.

There is a high burden of pneumococcal disease among immunocompromised adults. Combining PCV13 with PPSV23 would allow broader serotype protection.

The ACIP is currently awaiting a report on the indirect effects from PCV13 use in children, expected in 2013.

Treating type 1 diabetes requires regular exogenous insulin to prevent the ill effects of too much blood glucose and avoid the long-term complications of diabetes. Type 2 diabetes occurs as a chronic complex condition associated with hyperglycaemia and long-term end organ damage. New therapeutic agents may help reduce the risk of diabetic complications, particularly cardiovascular events.
Management of Type 1 Diabetes Mellitus

Michael Conall Dennedy, MD; Sean F Dinneen, MD, FRCPI, FACP

Treatment of type 1 diabetes mellitus involves the administration of exogenous insulin to avoid diabetic ketoacidosis, maintain glycaemic control and prevent the long-term complications associated with diabetes. Insulin therapy in type 1 diabetes presents a challenge to both the patient and the health-care professional.

Introduction

Failure of insulin secretion by pancreatic β cells underlies type 1 diabetes mellitus. The main management goal is to deliver subcutaneous exogenous insulin replacement therapy, so as to achieve near-normal glucose concentrations. Additional goals are to prevent the potentially fatal complication of diabetic ketoacidosis while also avoiding hypoglycaemia. Insulin replacement therapy requires regular monitoring of capillary glucose concentrations and must take into consideration energy intake (carbohydrate), energy expenditure, and the influence of environmental stressors and 'counter-regulatory' hormones on glycaemic control.

Patient adherence with a frequently difficult and inconvenient treatment regimen is often variable. More than 80 years after the discovery of insulin, true physiological replacement of insulin remains an elusive goal. This chapter focuses on the mechanisms of insulin replacement therapy and on the goal of patient-centred self-management of type 1 diabetes mellitus. Consideration will also be given to future directions for achieving glycaemic control and halting disease pro-
gression in individuals with type 1 diabetes.

Why Treat Type 1 Diabetes?

There are three arguments that can be used to justify insulin therapy in patients with type 1 diabetes.

• Without insulin therapy, patients with type 1 diabetes develop profound hyperglycaemia leading to ketosis, ketoacidosis, coma and death. Insulin therapy is therefore a life-saving intervention, and easy for patients, family members and health-care providers to accept.

• Insulin alleviates the unpleasant symptoms associated with hyperglycaemia, making the patient feel better. When plasma glucose is persistently above the renal threshold (about 10 mmol/L), glycosuria leads to osmotic diuresis, and the classical triad of polydipsia, polyuria and weight loss ensues. The weight loss associated with insulin deficiency results partly from loss of calories (in the form of glucose) in the urine and partly from a catabolic state associated with insulin deficiency. Insulin replacement, in this context, is aimed at achieving plasma glucose concentrations below the renal threshold and again is easy for patients to accept.

• The third justification for insulin replacement therapy is to avoid the microvascular complications associated with long-term hyperglycaemia. This is more difficult to achieve and harder for patients to accept. Until the publication of the results of the Diabetes Control and Complications Trial (DCCT), this reason for treating type 1 diabetes was assumed rather than based on evidence. The landmark findings of the DCCT showed clinically significant reductions in the development and/or progression of retinopathy, nephropathy and neuropathy in patients randomized to the intensive control arm of the trial. The study proved that near-normal plasma glucose concentrations reduce the risk of developing microvascular complications. Recently, long-term follow-up of the DCCT cohort showed fewer macrovascular events in the intensively treated patients. One way of interpreting the DCCT results is to infer that therapy aimed at avoiding symptoms (as in the conventionally treated group) is insufficient to prevent adverse outcomes over the lifetime of patients with the disease.

The DCCT was an efficacy study – the setting in which the intervention was evaluated was optimized to increase the likelihood of a good outcome. For example, patients in the intensive arm of the trial were seen as often as monthly, and had weekly telephone contact with members of the study team, including diabetes nurse educators, dietitians and psychologists. The challenge for most doctors is to translate the results of the DCCT into the ‘real world’, with its constraints on resources and time. The first step should be to engage the patient in the challenge. As discussed below, the work involved in achieving and maintaining near-normal plasma glucose over a lifetime is enormous. At a minimum, it involves daily attention to lifestyle (diet and exercise), and monitoring of plasma glucose and insulin dosing.

Patients with newly diagnosed type 1 diabetes can now anticipate a long life, but it is important to recognize that this is achieved at a price. The price of intensive control may be acceptable to many patients if they are given the tools and skills to achieve this. For those who fail to appreciate or achieve the benefits of good glycaemic control, the role of the diabetes care team is to help find the best degree of control that is acceptable to the patient (in terms of quality of life). The third justification for insulin therapy (avoidance of complications) is undoubtedly the greatest management challenge.
Management Tools for Type 1 Diabetes Mellitus

Types of Insulin Replacement Therapy
The broad principles of insulin therapy are to mimic, as closely as possible, physiological insulin release from the pancreas. This is most often attempted through a multiple daily injection (MDI) programme (Figure 1a). MDI involves preprandial administration of short-acting ‘bolus’ insulin and once- or twice-daily administration of long- or intermediate-acting ‘basal’ insulin. Bolus insulin controls postprandial glucose excursions while basal insulin regulates hepatic glucose output. A mixture of basal and bolus insulin as a fixed-dose mixed insulin preparation can be used as an alternative to the MDI programme (Figure 1b). Current regimens are far from physiological because insulin is delivered to the peripheral circulation rather than the portal circulation, and exogenous insulin concentrations are adjusted crudely and not on a minute-to-minute basis as occurs in vivo.

Human insulin: synthetic human insulin, manufactured using recombinant DNA techniques, has largely replaced animal insulin over the past two decades. Human insulin is less immunogenic than animal insulin. ‘Short-acting’ human insulin (human soluble insulin injection) has an onset of action of 20–40 minutes and a duration of action up to 6 hours. Therefore, this insulin should be administered 15–20 minutes in advance of carbohydrate intake. Intermediate-acting human insulins (insulin isophane suspension, insulin zinc suspension) are absorbed variably, and rather than producing a ‘peakless’ pharmacokinetic profile, desirable for a basal insulin, they have a peak of action after 4–10 hours. Their duration of action falls short of 24 hours and requires that these insulins are administered twice daily. The pharmacokinetic properties of intermediate-acting insulins contribute to nocturnal hypoglycaemia and may limit their efficacy when used as basal insulin.

Insulin analogues: insulin analogues were introduced in the 1990s and have been described as ‘designer insulins’. Fast-acting insulins such as lispro, aspart and glulisine were designed to act faster than conventional soluble human insulin. When compared with human insulins in clinical trials, analogues dem-
onstrate the benefits of a marginal reduction in hypoglycaemic episodes, particularly at night, and also improved patient convenience. Likewise, long-acting analogues, such as glargine and detemir, were designed to have a longer and more predictable profile of action than the conventional insulin isophane suspension or insulin zinc suspension.

Analogue insulins are now the most common insulins used in clinical practice in many countries. Short-acting insulin analogues (aspart, glulisine, lispro) are less likely to form stable hexameric compounds in the subcutaneous tissues following injection. Instead, they form smaller dimeric compounds or remain as monomers that are more rapidly absorbed upon administration, usually within 15 minutes of subcutaneous injection, with a peak at 30–90 minutes and a duration of action of 3–4 hours. Using these preparations can lead to more reliable control of postprandial glucose excursions. In spite of this improvement in postprandial glucose, little or no glycated haemoglobin A1c (HbA1c) reduction is observed. The main benefit of short-acting insulin analogues when compared with their short-acting human insulin counterparts is the reduced risk of severe hypoglycaemia (by up to 30%).

Long-acting analogues are structurally altered to have lower pH (glargine) or to complex with large molecules, such as albumin (detemir), which prolongs their duration of action by producing a slow-release, subcutaneous ‘depot’ upon administration. Insulin detemir also dissociates slowly from bound albumin in the plasma to prolong its action. Both insulins are described as ‘peakless’ as they produce a minimal peak of action significantly lower than that of the traditional intermediate-acting human insulins.

Both currently available long-acting insulin analogues can act for close to 24 hours at higher doses, and this makes them suitable for once-daily injection. However, they demonstrate dose dependency of duration of action and may require twice-daily administration at lower doses. Clinical trials comparing long-acting insulin analogues with their human, intermediate-acting counterparts show that they significantly reduce hypoglycaemic episodes, particularly nocturnal hypoglycaemia, while showing equivalence of glycaemic control. There is also evidence that less weight gain is observed with some long-acting insulin analogues when compared with human insulin isophane suspension.

Premixed insulins: fixed-ratio premixed insulins are mixtures of intermediate- and short-acting, human or analogue insulins (70% human isophane suspension/30% human insulin injection; 50% human isophane suspension/50% human insulin injection; 75% insulin lispro protamine suspension/25% insulin lispro injection; 70% insulin aspart protamine suspension/30% insulin aspart injection). A premixed insulin regimen usually involves twice-daily administration (Figure 1b). The convenience offered by the requirement for fewer daily injections is offset by the rigid dietary pattern necessary to achieve DCCT glycaemic targets with this regimen, which, in fact, offers little flexibility of daily routine. Premixed insulin may be injected with bolus insulin as part of an MDI regimen to control postprandial glucose excursions. However, this regimen offers little in the way of improved glycaemic control and does so at the cost of more frequent episodes of hypoglycaemia. Premixed insulins in type 1 diabetes mellitus are used more commonly in the paediatric
population, with a switch to MDI programme usually occurring in adolescence or young adulthood.

**Devices for Insulin Administration**

**Insulin pens**: syringe and vial as a method of insulin delivery are rarely used outside of the hospital setting. The usual method of delivery for subcutaneous insulin in the UK, Ireland and Europe involves use of pen devices. These devices are provided by the majority of insulin-producing pharmaceutical companies and allow easy ‘dial-up’ of the insulin dose and convenient, accurate injection with minimal discomfort using fine gauge needles. A clicking sound upon dial-up, indicating each unit of insulin primed, also assists those who are visually impaired. Many companies provide a device that hides the needle, assisting those with needle phobia and facilitating easier administration in the younger paediatric population.

**Insulin pumps and continuous subcutaneous insulin infusion (CSII)**: insulin pump devices (Figure 2) have become smaller and increasingly more sophisticated in their functionality. The improvement in insulin kinetics since the development of short-acting insulin analogues has also facilitated the broader use of this system. Insulin is delivered through a cannula placed subcutaneously and replaced with a 72-hour frequency. A continuous basal rate is programmed into the pump and additional boluses of insulin can be administered ‘at the push of a button’ pre-meals. ‘Smart pumps’ have a more sophisticated computer incorporated into the insulin pump. These facilitate administration of ‘correction’ boluses based on high glucose-sensor readings entered into the pump computer. They can also calculate and administer an appropriate insulin bolus when an estimation of the quantity of carbohydrate consumed is entered into the pump computer, the so-called ‘bolus wizard’. CSII allows basal insulin infusions to be calculated according to patterns of fasting glucose, which allows a flexibility of control not provided by the pharmacokinetic profile of long-acting or intermediate-acting insulins. The use of continuous glucose monitoring (CGM) systems (see below), which are now often combined within the pump device, may allow even more accurate calculation of basal insulin rates. The delivery of CSII through insulin pumps has been extensively investigated in the paediatric and young adult population. Repeated trials, although carried out on small numbers, and recent meta-analysis show a benefit of this modality compared with MDI, demonstrating reductions in both HbA1c (~0.5%) and clinically relevant hypoglycaemia, without an increase in body mass index. An international consensus statement on appropriate use of CSII in children and adolescents has established certain criteria for insulin pump usage. A summary of these is presented in Table 1.

**Glucose Monitoring**

Central to achieving target glycaemia and avoiding hypoglycaemia in type 1 diabetes is the requirement for the patient to be able to monitor blood glucose concentration. Small, accurate glucose monitoring devices provide fast measurement of capillary glucose using a droplet of blood obtained by finger-prick using a lancet. Measurements can be taken pre- or postprandially throughout the day, and required insulin doses can be calculated or adjusted, albeit retrospectively, by the patient. This system is now the standard of care. However, patient adherence can be variable as a result of the discomfort caused by the required, repetitive finger-pricking.
CGM Systems

This system, through which a subcutaneous, glucose oxidase-coated sensor measures interstitial fluid glucose concentrations and converts them to a plasma glucose estimate, provides a promising modality for future management of type 1 diabetes. A plot of plasma glucose concentrations over a 24-hour period is produced and can enable insulin adjustment to identify episodes of hyper- or hypoglycaemia that may not have been identified using conventional capillary glucose monitoring (Figure 3). The use of early CGM allowed retrospective interrogation of devices only. Newer devices facilitate ‘real-time’ glucose measurements and incorporate alarms to alert the user when hypoglycaemia occurs. More recently, real-time CGM and CSII technologies have been combined in a single device, and this exciting technology may represent a step towards an ‘artificial pancreas’. However, despite advances, this technology is in its infancy, and its current role in the management of type 1 diabetes is unclear. Currently available devices are less accurate during episodes of hypoglycaemia. One large prospective trial has shown an improvement in HbA1c of 0.5% in patients with type 1 diabetes aged ≥ 25 years and fewer episodes of hypoglycaemia overall, when subjects using real-time CGM were compared with subjects who self-monitored at least four times daily. However, subjects in these trials found the use of subcutaneous CGM glucose sensors uncomfortable and used them less frequently over the duration of the trial period. More extensive trials that incorporate intensive patient education are required before its routine introduction.

Hypoglycaemia

Hypoglycaemia is the major, rate-limiting step in achieving and maintaining tight glycaemic control in patients with type 1 diabetes.

Diabetes Self-management

Optimal self-management is the cornerstone of good diabetes care. Of the 8,760 hours in each year, a person with type 1 diabetes is likely to spend, at most, 46 in face-to-face contact with a health-care professional. The remaining time (which amounts to 99.9% of the year) involves the patient managing the disease and making day-to-day decisions for themselves.

Initial Diabetes Education

Initial diabetes education following diagnosis of the condition is often referred to as ‘survival skills’ training. It focuses on the knowledge and skills needed to avoid symptomatic hyperglycaemia and hypoglycaemia. It typically comprises:

- general facts about diabetes and the need for insulin
- the mechanics of self-monitoring of blood glucose and insulin self-administration
- recognition and treatment of hypoglycaemic episodes
- a general overview of the role of diet and exercise in treating diabetes.

This education often requires reinforcement once the patient has come to terms with the diagnosis. Even in patients who have had diabetes for many years, it is often worthwhile reviewing this basic knowledge.

Management of diabetes during intercurrent illness poses problems for many patients, and the following principles must be taught and constantly reinforced. Patients should:

- never stop insulin completely, even if they are unable to eat or are nauseated and vomiting
- monitor blood sugar more fre-
Figure 3. Glucose sensor data

Glucose sensor data

Non-diabetic individual

Day 1

Day 2

Day 3

Individual with type 1 diabetes

Day 1

Day 2

Day 3

Continuous glucose monitoring system data illustrate the striking contrast between the healthy β cell and the absent β cell replaced by exogenous insulin injections.

Graphs generated following the use of a continuous glucose monitoring system (CGMS) over 3 days. The upper graphs represent the glucose excursions from an individual without type 1 diabetes, in whom the β cell is intact. The lower graphs are taken from an individual with type 1 diabetes in whom β cell function is absent. In spite of exogenous insulin administration, there are significant postprandial glucose excursions and episodes of overnight hypoglycaemia evident from these tracings.
frequently and monitor for ketonuria on sick days
• know how to adjust their insulin doses for hyperglycaemia and for ketonuria
• avoid dehydration by drinking plenty of fluids
• know how and when to seek help from the health-care team.

Determining Management Targets
After starting an appropriate insulin programme, the next step in self-management is to decide on treatment targets. These vary, depending on clinical parameters including the age of the patient, the presence of co-morbidity, the willingness and/or ability of the patient to participate in self-management, and the skills and attitude of the health-care team in supporting a self-management approach. When agreeing targets, it is essential to assess (in all patients) the degree of hypoglycaemic awareness and (in women of childbearing age) the patient’s plans for future conception.

• In most patients, a preprandial blood glucose of 4–6 mmol/L and a bedtime value of 6–8 mmol/L are appropriate targets. A 2-hour postprandial target of less than 10 mmol/L is reasonable, although monitoring at this time is not always recommended.

• In patients with severe hypoglycaemia (arbitrarily defined as the occurrence of one or more episodes of hypoglycaemia requiring the assistance of another person for treatment), increasing the preprandial target to 6–8 mmol/L and the bedtime target to 8–10 mmol/L should be considered.

• Women who are pregnant or planning pregnancy should aim for less than 5 mmol/L pre prandial and less than 8 mmol/L 2 hours post prandial.

Setting of treatment targets should take into account both the overall clinical setting and the patient’s capabilities and understanding. In some patients (eg, those with a terminal illness), avoidance of symptomatic hyperglycaemia or hypoglycaemia may be an appropriate aim. In all cases, establishment of targets should be discussed with the patient early in the development of the self-management education programme.

Life-long Learning
After initial education, the patient is now ready to embark on what should be a programme of life-long learning in how to master his or her diabetes. Proper self-management education requires commitment on the part of both patient and health-care team. Patients differ in their willingness to engage in mastering their disease, and their commitment to self-management may vary over time. Self-management education cannot be delivered in the course of a single outpatient clinic visit. Different teaching strategies are available and may be suited to individual patients; ideally, several strategies (eg, one-to-one teaching, group education, self-study) should be available.

The main components of a comprehensive self-management skills training programme are outlined in Table 2. The aim is to provide patients with the knowledge and skills they need to manage their lives with their disease. This concept of ‘therapeutic patient education’ has been outlined in a World Health Organization document and also applies to other chronic diseases. Systems for delivering care are often focused more on acute than chronic illness; it is easier to transfer a patient with severe hypoglycaemia to the emergency department than to educate him or her on how to prevent future episodes from occurring.

Structured education programmes have, in recent years, become a recognized means of delivering high-
quality education to individuals with diabetes. They are characterized by a curriculum (updated at intervals), by educators trained in the delivery of the curriculum, by peer review and quality assurance of the delivery of the education, and by ongoing audit of programme outcomes. The Dose Adjustment for Normal Eating programme is a leading example of this approach applied to individuals with type 1 diabetes.

**Nutrition**

The aim of nutritional education is to help patients learn how their calorie intake influences day-to-day fluctuations in blood glucose, and how to use this knowledge to establish a meal plan appropriate to their management aims.

An emphasis on distribution of carbohydrate calories (‘carbohydrate exchanges’) throughout the day was a common dietary educational tool. Modern variations on this approach include use of the glycaemic index, in which foods are ranked on the basis of their glycaemic effect compared with a standard food. A similar approach (carbohydrate counting) has become popular in patients on basal–bolus insulin regimens or CSII pump therapy. This method requires an understanding of the number of grams of carbohydrate ingested and the likely impact on the glucose response to that meal. The popularity of this approach is partly related to the ‘free diet’ that it encourages compared with its more restrictive forerunners.

**Difficult Aspects of Type 1 Diabetes Management**

**Patient Adherence and Recurrent Diabetic Ketoacidosis**

Recurrent diabetic ketoacidosis often results from insulin omission. However, understanding the reasons for non-adherence in any single patient requires careful interaction with the patient. It is important to develop a good relationship between the patient and the multidisciplinary diabetes team. Consultation with a specialist psychologist may be required to tease out the psychosocial issues underlying insulin non-adherence and recurrent diabetic ketoacidosis.

**Exercise**

In non-diabetic individuals, exercise is associated with increased insulin sensitivity, reduced insulin secretion, and increased counter-regulatory hormone secretion. The latter two responses offset any decrease in plasma glucose that might result from increased

![Table 2. Self-management education programme](image-url)
insulin sensitivity; the net result is that plasma glucose concentrations are maintained within the normal range. Individuals with type 1 diabetes must decide for themselves how to adjust their insulin doses for planned exercise. Education on exercise in diabetes aims to enable patients to plan activity and understand their individual response. If this is accomplished, exercise can be a useful tool in achieving good glycaemic control.

Unplanned exercise in a patient with type 1 diabetes results in increased counter-regulatory hormone secretion; because β cells are unable to alter the amount of circulating insulin, the plasma glucose response to exercise depends entirely on the prevailing amount of exogenous insulin. If this is excessive, hypoglycaemia can result; if it is insufficient, hyperglycaemia can occur.

Patients must learn what their ‘comfort zone’ is for a given degree of exercise; for example, vigorous physical activity (eg, 45 minutes of competitive squash) may be ‘safe’ at a pre-exercise plasma glucose level of 10 mmol/L but may lead to hyperglycaemia at 6 mmol/L. Patients must also understand that exercise can sometimes raise blood glucose (generally when pre-exercise plasma glucose is > 15 mmol/L).24

Additional considerations include:
• delayed hypoglycaemia (several hours after cessation of exercise), related to replenishment of glycogen stores in the exercised muscles
• the need to avoid injection into exercised limbs; increased subcutaneous blood flow increases insulin absorption,
• the importance of planning exercise, reducing preprandial insulin bolus with the last meal prior to exercise and/or carrying snacks to treat hypoglycaemia.

Non-insulin Modes of Therapy

Amylin Analogues (eg, Pramlintide)

Pramlintide is a synthetic analogue of amylin, a polypeptide hormone, co-secreted with insulin from pancreatic β cells.25 This agent is licensed for use in the US but not yet in Europe. It is injected preprandially in addition to insulin and has shown modest improvements in postprandial hyperglycaemia with 20–30% decrease of insulin dose.26 Treatment of type 1 diabetes with pramlintide is associated with fewer hypoglycaemic episodes and significant weight loss. Its use is limited by troublesome and often persistent nausea. Any potential benefit of introducing this therapy to a patient with type 1 diabetes must be weighed against the burden of additional injections as this drug is administered subcutaneously.

Pancreatic and Islet Transplantation

Whole-organ pancreatic transplantation for the treatment of type 1 diabetes has largely been reserved for those undergoing renal transplantation for end-stage diabetic nephropathy. While normalization of glycaemic control is achieved following successful transplantation, this mode of therapy carries the risk of pancreatic graft rejection and the consequent burden of pharmacological immunosuppression.27 In spite of immunosuppression, recurrence of type 1 diabetes mellitus can occur in some transplant recipients due to persistent autoimmunity.28

Islet cell transplantation provides a promising treatment option for type 1 diabetes. β Cells isolated from a donor pancreas are injected into the portal venous system where they then lodge within liver sinusoids. These β cells remain glucose-sensitive and secrete insulin into the portal system, in the same way as occurs in the physiological situation.29 Variable graft survival is observed following islet transplantation, resulting in an effort to produce a standardized methodology for this technique internationally.30,31 In a recent international trial of the ‘Edmonton protocol’, 36 individuals were enrolled, 21 achieved insulin independence and adequate glycaemic control at some point during the trial, but 16 of these required exogenous insulin 2 years post transplantation.31 Variable β-cell yield using this isolation technique requires harvest from more than one pancreas to provide sufficient tissue for successful transplantation. Concern has also been expressed regarding the potential for the development of portal hypertension as a consequence of sinusoidal occlusion by grafted β cells. Nonetheless, with the future promise of engineered β cells using stem cell differentiation methods, this technique of cell delivery/transplantation may provide a successful long-term treatment of glycaemia in type 1 diabetes.

Immunotherapy

Pancreatic β-cell preservation using immune suppression or immune tolerance has been disappointing. When used as secondary prevention of type 1 diabetes, ciclosporin and anti-CD3 antibodies reduce the required insulin dose and prolong β-cell survival, as assessed by fasting and stimulated serum C-peptide concentrations.32 However, both of these treatment modalities have unacceptable side-effect profiles, particularly given the age of the target population. Glutamic acid decarboxylase–alum immunization, in an attempt to promote immune tolerance in subjects with diagnosed type 1 diabetes, did not significantly reduce the requirement for insulin or improve fasting serum C-peptide concentrations.
concentrations. The use of these therapies requires more research before their introduction as mainstream approaches to the prevention of type 1 diabetes mellitus.

Declaration of Interests
None.

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Type 2 diabetes mellitus (T2DM) is a chronic complex condition associated with hyperglycaemia and long-term end-organ damage. This long-term end-organ damage due to exposure to hyperglycaemia leads to increased risk of cardiovascular disease and excess mortality. Apart from glycaemic management, it is essential to target various other contributors, including weight, smoking, blood pressure and lipids, effectively. Pharmacological and non-pharmacological management aimed to improve glycaemic control in patients with T2DM is an ever-evolving and challenging field. Over the last few years, interesting information has emerged from clinical research about targets and aim of anti-hyperglycaemic therapy. Various newer therapeutic agents are available as well as being developed to target completely new and different pathophysiological aspects of hyperglycaemia in T2DM. New information is gained about existing formulations and combinations. Some agents directly or indirectly aimed to help glycaemic control have been withdrawn due to safety, efficacy and financial concerns. In this brief review, we take the opportunity to summarize this field and examine current aspects of glycaemic management of T2DM.
Clinical Excellence (NICE) undertook a comprehensive review of current evidence and issued national guidelines for the management of type 2 diabetes; a further supplement was provided in May 2009 which focused on the newer anti-hyperglycaemic agents.\textsuperscript{4,5} The field of anti-hyperglycaemic therapy is rapidly evolving. Following new concerns regarding the safety of existing oral agents, the last few years have seen the introduction of new oral as well as injectable agents, the availability of various combination therapies, and the withdrawal of some agents on grounds of safety. There is an impressive array of new therapies on the horizon that could transform treatment of T2DM in the future, and in this brief review we present a summary of the current position.

**Patient Education and New Approaches to Self-management**

Patient empowerment and supported self-care are pivotal in the management of any chronic condition. However, NICE, in their first review about education models for type 1 and type 2 diabetes, could not recommend a specific programme for patients with T2DM.\textsuperscript{5} A number of other reviews of this area highlighted the shortage of high-quality research in this area. During their recent review, NICE identified 14 studies in total about structured education in T2DM; however, only three studies were UK-based.\textsuperscript{4}

The DESMOND Collaborative Project (Diabetes Education Self-Management Ongoing Newly Diagnosed) is set out to develop an evidence-based structured education and self-management programme for people with T2DM. DESMOND is built on a clearly stated philosophy and explicit principles of care that are used to develop the individual’s understanding of diabetes, the specific monitoring and goal-setting skills necessary for effective self-management, and the confidence necessary to take charge of their own diabetes.

Following a successful pilot study of the intervention, a fully randomized control trial was designed with improved glycaemic control (HbA\textsubscript{1c}) at 1 year as the primary outcome.\textsuperscript{7} In this randomized control trial, 824 adults with T2DM recruited from 207 general practices were randomized to receive intervention with structured education or usual care. The intervention was a curriculum-based group education programme delivered by trained healthcare professionals in 2 half days/1 full day that was quality assured. HbA\textsubscript{1c} was lower in the intervention arm (−1.49\% vs −1.21\%), but this was non-significant after adjusting for baseline and cluster. The intervention group had a significantly greater weight loss (2.98 vs 1.86 kg; \(P = 0.027\)) along with a greater change in illness belief scores (\(P < 0.001\)) and a lower depression scores (\(P < 0.05\)). The odds ratio in relation to giving up smoking was 3.56 in the intervention group (95\% CI, 1.11–11.45; \(P = 0.033\)) at the end of 12 months.\textsuperscript{8} As a result, the 10-year modelled cardiovascular risks were significantly lower in the intervention arm. Data from programmes in people with established diabetes have also demonstrated significant biomedical and psychosocial benefits.\textsuperscript{8,10} Structured education programmes fulfilling nationally agreed criteria outlined in the report from Patient Education Working Group should be offered to all people with T2DM from diagnosis.\textsuperscript{11}

### Dietary and Lifestyle Interventions

Dietary modification and lifestyle intervention remain the initial mainstays of treatment of T2DM. Because most patients with T2DM are overweight and have features of metabolic syndrome, weight reduction reduces insulin resistance and improves other cardiovascular risk factors. Early and continued involvement of a dietitian with an interest in diabetes is important. It should be noted that dietary and lifestyle management are key components of the structured education programme referred to above.

### General Aims of Dietary Intervention

Energy intake and expenditure balance should be adjusted to achieve a body mass index of 20–25 kg/m\(^2\). In clinical practice, however, realistic and individual targets should be set for weight loss. With an exercise programme, weight loss of 1–2 kg/month can be achieved by reducing the caloric intake below that required for weight maintenance by at least 500 kcal/day.

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**Table 1. Effects of 1% reduction in updated mean HbA\textsubscript{1c} on complications of type 2 diabetes**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related complication</td>
<td>21%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14%</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>37%</td>
</tr>
<tr>
<td>Death due to diabetes</td>
<td>21%</td>
</tr>
</tbody>
</table>

Benefits of Exercise

Regular physical activity increases muscle-related energy expenditure, improves insulin sensitivity, reduces blood pressure, and improves lipid profile. Exercise improves glycaemic control in T2DM. Generally, any form of exercise with duration of 30 minutes is recommended to aid weight loss when accompanied by an appropriate diet. However, whereas a recent study confirmed that 30 minutes of moderate-intensity exercise on most days was associated with a reduction in blood pressure and serum concentrations of total cholesterol and triglyceride, 60–75 minutes was required to reduce weight, waist circumference, fasting glucose and low-density lipoprotein cholesterol, increase high-density lipoprotein (HDL), and reduce overall 10-year cardiovascular risk.\(^1\)\(^2\)

Oral Anti-hyperglycaemic Agents (OAAs)

The Need for OAAs in T2DM

Key metabolic defects characterizing type 2 diabetes are β-cell dysfunction and insulin resistance.\(^1\)\(^3\) β-Cell dysfunction is progressive and leads to an increase in HbA\(_{1c}\), necessitating management with higher-dose oral anti-hyperglycaemic agents (OAAs), combinations of OAAs and, often, insulin therapy. In the UKPDS, about 50% of patients required combination therapy 3 years into the study, and 75% by 9 years.\(^1\)\(^4\)

Targets of Therapy

Current NICE guidance suggests that HbA\(_{1c}\) targets should be individualized and patients encouraged to achieve agreed HbA\(_{1c}\) targets. Insulin therapy is recommended if HbA\(_{1c}\) remains above 7.5% despite use of appropriate and tolerated OAAs\(^5\) (Figure 1). Aggressive glycaemic therapy to achieve HbA\(_{1c}\) below 6.5% should be avoided in patients with longer duration of diabetes and in presence of cardiovascular disease. Recent evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study suggests that an HbA\(_{1c}\) below 6.5% is achievable with intensive therapy, but this strategy is associated with increased risk of hypoglycaemia and mortality in patients with existing cardiovascular disease.\(^1\)\(^5\) Increased cardiovascular mortality in ACCORD study was thought to be due to various factors including longer diabetes duration of participants, extent of pre-existing cardiovascular disease and rapid decline in HbA\(_{1c}\) in the intensively treated patients.\(^1\)\(^6\)

Post hoc analysis of this data suggests that this risk is higher in patients with poor baseline glycaemic control and in patients who do not show improvement in HbA\(_{1c}\) despite the intensification of anti-hyperglycaemic therapy. In this subgroup of patients, attention should be directed towards patient education and adherence to treatment rather than intensifying glycaemic therapy further.\(^1\)\(^7\),\(^1\)\(^8\)

Metformin

Since the 1950s, the biguanides have been the mainstay of OAA treatment, 

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**Figure 1. Blood glucose-lowering therapy**

<table>
<thead>
<tr>
<th>HbA(_{1c}) &gt; 7.5%</th>
<th>HbA(_{1c}) &gt; 6.5%</th>
<th>HbA(_{1c}) ≤ 6.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add third agent:</td>
<td>Add DPP-4 inhibitor</td>
<td>Commence metformin with active dose nitration</td>
</tr>
<tr>
<td>Metformin + SU + Insulin</td>
<td>Add glitazones</td>
<td>HbA(_{1c}) more than 6.5% after lifestyle and dietary modifications</td>
</tr>
</tbody>
</table>

but metformin is the only biguanide currently used in clinical practice. Its mechanism of action is unclear but probably involves reducing hepatic glucose production and increasing peripheral glucose uptake and thereby reducing insulin resistance. Metformin also has cardioprotective benefits, as shown in UKPDS and other major studies. It is the first-line agent in overweight patients. The starting dose is 500 mg administered once daily with meals, increasing the dose gradually to the maximal tolerated dose or total daily dose of 2–3 g administered in two to three divided doses. Metformin is also available in strength of 850 mg which can be prescribed three times a day. It can be given as monotherapy or in combination with almost any other glucose-lowering agent.

The most common adverse effects are gastrointestinal and include diarrhoea, nausea, vomiting, and flatulence; about 10% of patients discontinue its use because of these effects. Tolerability may be improved by using a smaller initial dose, gradual dose titrations, taking the drug with meals, and using extended-release preparations. The dosage should be reviewed if the estimated glomerular filtration rate (eGFR) is less than 45 mL/min or serum creatinine is > 130 mmol/L. Metformin should also be avoided in clinical or laboratory evidence of liver dysfunction and in patients with unstable or acute congestive heart failure due to the rare possibility of lactic acidosis. It should be discontinued temporarily in the event of sepsis, dehydration and use of contrast materials, and during peri-operative and in the immediate post-coronary event periods.

**Sulphonylureas**

The sulphonylureas (eg, gliclazide, glimepiride) are insulin secretagogues that bind to a membrane receptor of the pancreatic β cell, promoting closure of ATP-dependent potassium channels. They are licensed for monotherapy or in combination with other OAs except meglitinides. They are effective in reducing fasting plasma glucose and in reducing HbA1c by about 1.5–2.0%, but are associated with weight gain and increased risk of hypoglycaemia. Gliclazide is commenced at a dosage of 40–80 mg given once or twice a day and increased to maximum of 160 mg twice a day. Gliclazide MR is a modified-release preparation given once a day at the starting dose of 30 mg/day (equivalent to 80 mg of standard release gliclazide). Glimepiride is taken once a day up to a maximum dosage of 4 mg/day, which can be increased to 6 mg/day in exceptional patients. In prospective UK hypoglycaemic study, 7% of patients on sulphonylurea experienced at least one severe hypoglycaemic episode over 9–12 months. These episodes can be prolonged and potentially dangerous with long-acting sulphonylurea such as glibenclamide. Predisposing factors for the development of hypoglycaemia are age, liver, renal and cognitive impairment, and other interacting medications such as listed in British National Formulary Appendix 1. Patients presenting with hypoglycaemia secondary to sulphonylurea use should be hospitalized and their blood glucose monitored for 24–48 hours; this is particularly important in older patients with renal impairment.

**Prandial Glucose Regulators (Meglitinides)**

Prandial glucose regulators have been developed to target early-phase insulin secretion, which is one of the earliest pathophysiological manifestations of T2DM. Repaglinide and nateglinide are currently available rapid-acting insulin secretagogues with a fast onset and short duration of action. Meglitinides act on a different β-cell membrane receptor from sulphonylureas, but also promote closure of ATP-dependent potassium channels. Meglitinides are licensed for use as monotherapy, as an add-on to metformin when the latter alone is insufficient for glycaemic control, and in combination with insulin. Flexible dosing is possible, suitable for shift-workers and individuals with a flexible lifestyle, although multiple doses must be taken. Repaglinide is started at a dose of 0.5 mg taken 15 minutes before meals and adjusted to a maximum of 16 mg/day or a maximum single dose of 4 mg. Nateglinide is started at 60 mg taken three times daily with meals and adjusted to a maximum of 180 mg
three times daily. Meglitinides are more expensive than sulphonylureas.

**Thiazolidinediones**

Thiazolidinediones are insulin sensitizers and act primarily by activating the peroxisome proliferator-activated receptor (PPAR) γ present in liver, skeletal muscles and adipose tissue. This activation enhances the effects of endogenous insulin on target organs reducing insulin resistance. Rosiglitazone and pioglitazone are currently available glitazones shown to reduce HbA1c by up to 1.5%. They do not generally cause hypoglycaemia. One meta-analysis involving 42 studies concluded that rosiglitazone was associated with a significant increase in the risk of myocardial infarction and a borderline significant finding for death from cardiovascular causes. An unplanned interim analysis of Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD) study was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes. More importantly, this analysis did not provide any reassurance regarding the safety of rosiglitazone in respect of the risk of myocardial infarction. The European Medicines Evaluation Agency issued a warning to prescribers to avoid rosiglitazone in patients with ischaemic heart disease. A meta-analysis of studies involving pioglitazone suggested significantly lower risks of myocardial infarction, stroke or death. These agents are associated with fewer hypoglycaemic episodes than they occur with sulphonylureas, but lead to increased peripheral oedema, weight gain and an increased risk of distal fractures, especially in postmenopausal women. Recommended doses are pioglitazone, 15–45 mg once daily, and rosiglitazone, 4–8 mg taken in one or two divided doses.

Thiazolidinediones have been licensed for use as monotherapy and in combination with metformin, sulphonylurea and with insulin. NICE recommends their use in addition to a first-line agent (either metformin or sulphonylurea) if another second-line agent (sulphonylurea or metformin respectively) is poorly tolerated or contraindicated. Thiazolidinediones are recommended as third-line agents in addition to metformin and sulphonylurea for patients in whom insulin therapy is unacceptable. Pioglitazone can be combined with insulin, but the combined use is associated with significant weight gain.

**Insulin Therapy**

In the UKPDS, more than 50% of patients required additional insulin therapy by 6 years; this was largely attributed to the fact that β-cell function worsened from about 53% at diagnosis to about 28% after 6 years of follow-up. The issue of insulin therapy should be discussed when HbA1c is increasing and consistently more than 7.5%, and maximal tolerated oral therapy and lifestyle changes are in place. General indications are shown in Table 2. The topic should be approached sensitively, the decision to start insulin made in partnership with the patient, and the choice of regimen tailored to the individual’s needs. The patient should agree with the decision and understand the benefits of insulin and the implications of its use. Access to appropriate dietary and lifestyle advice is essential.

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**Table 2. General indications for insulin and early insulin use in type 2 diabetes**

- All previous attempts to achieve desired target (lifestyle measures, maximal oral therapy) have failed
- Persistent failure to achieve optimal HbA1c
- Symptomatic patient (weight loss, lethargy)
- Steroid-induced diabetes
- Gestational diabetes; women with type 2 diabetes who become pregnant or are planning pregnancy
- Post-acute myocardial infarction
- Intolerance to oral agents
- More suited to patient’s lifestyle
- Acute neuropathy (eg, proximal amyotrophy)

In the following clinical scenarios, insulin is considered early

- Newly diagnosed patients with random plasma glucose > 11.1 mmol/L presenting with myocardial infarction, severe intercurrent illness (eg, sepsis), ketonaemia/ketonuria or hyperosmolar non-ketotic state
- Patients with fasting plasma glucose > 15 mmol/L and/or random glucose > 24 mmol/L who are increasingly symptomatic
Potential Barriers to Insulin Therapy
The main barriers to insulin therapy are hypoglycaemia, weight gain and fear of injections. Occupational factors may also be a barrier (e.g., in heavy goods vehicle drivers). Generally, patients taking insulin gain weight mainly because of improved glycaemic control. To limit this, one should determine the patient’s appropriate weight and discuss the fact that additional ‘snacks’ are not automatically required; they should be tailored to the individual’s needs and the type of insulin regimen.

Insulins
Porcine and bovine insulins were the very first insulin preparations available before the advent of human and analogue insulins. They now account for only about 7% of insulin prescriptions in the UK and are predominantly used in patients with type 1 diabetes. All insulin formulations are now produced at a concentration of 100 units/mL. For individual patients requiring high doses, insulin can be produced on a named-patient basis at a concentration of 500 units/mL (human regular insulin injection). The rate of insulin absorption differs between sites, being fastest in the abdomen and slowest in the thigh and buttocks. The site of insulin injection should be varied to prevent lipohypertrophy.

Types of Insulin and Their Actions (Figure 2)
Short-acting and rapid-acting insulins
– soluble human insulin comprises unmodified insulin in solution at neutral pH. It should be injected 20 or 30 minutes before a meal so that the peak of blood insulin corresponds with the blood glucose increase. Insulin analogues developed through recombinant DNA technology are insulin molecules, the structure of which has been altered to gain some advantage over standard human insulin. Insulin lispro, insulin aspart and glulisine are currently available rapid-acting analogues. Compared with soluble human insulin, they:

**Figure 2. Types of insulin and their actions**
• are more rapidly absorbed
• show less variability in their absorption rate
• can be injected immediately before food
• limit the postprandial glucose increase more effectively
• incur less risk of nocturnal hypoglycaemia.

Intermediate-acting and long-acting insulins – longer-acting insulins include insulin isophane suspension, insulin zinc suspension, human insulin extended zinc suspension, and long-acting basal analogue insulin (insulin detemir and insulin glargine).

• Insulin glargine precipitates in the subcutaneous tissue and also forms hexamers, which delay absorption and result in a prolonged duration of action.25
• The prolonged action of insulin detemir is a consequence of strong self-association of detemir molecules at the injection site, and albumin binding via the extra fatty acid side-chain. The rate of absorption is limited by the low concentrations of insulin detemir available for diffusion through tissues and across capillary walls.26

These insulins have the advantage of greater predictability, potentially less weight gain, and a lower risk of hypoglycaemia, particularly at night.27,28

Mixed insulins – various premixed or ‘biphasic’ insulins are available and can be given twice daily. A 30% short-acting/70% insulin isophane suspension mixture is the most common formulation used. New mixtures of the rapid-acting analogues with insulin isophane suspension have been produced that are taken immediately before a meal and may therefore offer greater flexibility; better postprandial control has been reported, but these insulin formulations are more expensive.

**Insulin Regimens in T2DM (Table 3)**

An appropriate insulin regimen is usually required to address both basal (fasting and preprandial) plasma glucose and prandial, post-meal excursions. Basal hyperglycaemia is addressed by isophane (medium-acting) insulin given twice daily or one of the long-acting analogues, glargine and detemir. Post-meal glucose excursions (prandial) can be targeted using short-acting insulins, alone or as mixed insulin. A reasonable starting dose of insulin is 10 units twice a day for twice-daily mixtures and 10–12 units once a day for once-daily insulin isophane suspension and insulin analogues. The Treating to Target in Type 2 Diabetes (4-T) study was designed to compare three types of insulin regimens (basal, prandial or biphasic) in addition to OAA in patients with T2DM. Whilst the risk of hypoglycaemia and weight gain was greater in patients using biphasic or prandial insulins, by 3 years the majority of patients required a ‘complex’ insulin regimen. This study supports the initiation of basal insulin first, followed by intensification with a basal–prandial regimen.29

**Incretin-based Therapy**

An oral glucose load stimulates increased insulin release from pancreatic β cells, whereas a glucose load administered intravenously has an isoglycaemic effect. This is known as the incretin effect.30 Two main gut hormones – glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) – are released from intestinal cells in response to food. These hormones are called ‘incretins’. GLP-1 is a potent incretin and has variety of favourable metabolic effects.
Compared with the insulin released from pancreatic β cells stimulated in an oral glucose load, an intravenous glucose load results in an isoglycaemic effect, known as the incretin effect. It inhibits glucagon secretion, delays gastric emptying and reduces food intake leading to weight loss. It has also shown to increase β-cell proliferation. Since its release is glucose-dependent, it is unlikely to be associated with hypoglycaemia.31

The discovery of these favourable effects of GLP-1 led to the development of new therapeutic agents targeted to mimic or augment the action of this important molecule. Unfortunately, the half-life of endogenous GLP-1 is about 2 minutes, as it is rapidly degraded by enzyme dipeptidyl peptidase 4 (DPP-4). Incretin-based therapy is broadly divided into two groups. The agents targeted towards inhibition of DPP-4 enzyme, leading to increased activity of endogenous GLP-1, are called DPP-4 inhibitors (incretin enhancers) and are taken orally. Agents that are analogous to GLP-1 but partially resistant to degradation by endogenous DPP-4 are called GLP-1 agonists (incretin mimetics) and are administered as subcutaneous injections.

**DPP-4 Inhibitors**

Sitagliptin, vildagliptin and saxagliptin are currently licensed for the treatment of type 2 diabetes in the UK. NICE recommends their use in addition to a first-line agent (either metformin or sulphonylurea) when sulphonylurea use is contraindicated owing to the risk of hypoglycaemia or metformin is poorly tolerated. Sitagliptin is recommended as a third-line agent in addition to metformin and sulphonylurea for patients in whom insulin therapy is unacceptable (Figure 1).5

DPP-4 inhibitors may be preferred to a thiazolidinedione if the latter is contraindicated or has led to weight gain or peripheral oedema.5

Sitagliptin is licensed for use along with metformin and/or sulphonylurea and the dose is 100 mg once a day taken orally. Vildagliptin is given in a dosage of 50 mg twice daily in combination with metformin, thiazolidinedione or 50 mg once daily with concurrent sulphonylurea therapy. Saxagliptin is given in a dosage of 5 mg once a day taken orally. These agents should be avoided in patients with eGFR < 50 mL/min. Generally, these agents are tolerated well with occasional gastrointestinal and other adverse effects. Liver function should be monitored before treatment and every 3 months for the first year (and periodically during vildagliptin therapy) owing to the rare incidence of liver toxicity. DPP-4 inhibitors are generally weight neutral and less likely to be associated with hypoglycaemia than sulphonylureas. The risk of hypoglycaemia is increased in patients taking a concomitant sulphonylurea, the dose of which should be reduced if necessary.

**GLP-1 Agonists/Incretin Mimetics**

An alternative approach for incretin-based therapy is the use of GLP-1 analogues that mimic the effect of GLP-1 but are resistant to degradation by DPP-4. Exenatide and liraglutide are the two compounds in this class and are administered subcutaneously. Exenatide is the first incretin mimic licensed to be used in patients with T2DM. It shares 53% amino acid identity with endogenous GLP-1. It is currently licensed to be used as monotherapy or in combination with metformin and/or a sulphonylurea. The initial dosage is 5 μg twice daily, increased to a maximum dose of 10 μg twice daily after 1 month if tolerated. Exenatide should be used with caution when eGFR is between 30 and 50 mL/min and should be avoided if eGFR is below 30 mL/min. Improvement in glycaemic control can be sustained.
over a period of 3 years with continued exenatide therapy. 32

Recently, liraglutide, a once-daily preparation with 97% amino acid sequence identity with endogenous GLP-1 has been licensed for the use in patients with T2DM. Its prolonged long half-life results from formation of heptamers at the injection site, leading to slow absorption and reversible binding with albumin; this results in delayed renal clearance as well as degradation by DDP-4 enzyme, and this drug requires only once a day administration. It is licensed for use along with metformin and or sulphonylurea. It is available in 0.6 mg, 1.2 mg and 1.8 mg by subcutaneous injections. Currently, there is less experience for use of liraglutide in patients with eGFR less than 60 mL/min.

NICE recommends use of exenatide in addition to metformin and/or sulphonylurea in patients with body mass index > 35 kg/m² whose glycaemic control is inadequate (HbA1c > 7.5%). It should be continued only if HbA1c is reduced by 1% and weight loss of 3% is achieved at 6 months. 5 NICE is currently looking at the use of liraglutide. Indications for use of liraglutide are fairly similar to that of exenatide; head-to-head trials show that the two drugs have similar effects on weight, but liraglutide treatment leads to greater HbA1c reductions and less persistent nausea. 33 The adverse effects of GLP-1 agonists are related to their gastrointestinal actions and include nausea, vomiting and occasional abdominal pain.

In comparison to orally available DPP-4 inhibitors, GLP-1 agonists are associated with more weight loss and greater reduction in HbA1c. 34

Recently Discontinued Agents

Rimonabant, an endocannabinoid receptor blocker that was used as a weight loss medication for patients with T2DM, had to be withdrawn because of an increased risk of depression associated with its use. Another weight loss drug, sibutramine, was recently withdrawn because its use led to increased risks of non-fatal heart attacks and stroke. The inhaled insulin formulation was withdrawn for financial reasons in view of poor patient and physician acceptance. It had several drawbacks apart from its high cost, including its bulkiness as an inhalation device, unpredictable dosing and long-term safety concerns.

Glycaemic Management in Elderly Patients With T2DM

Half of all people with diabetes in the UK are over the age of 65 and a quarter are over 75. 35 The management of glycaemia in elderly patients can be complex and must be individualized for the patient. Patients who have life expectancy long enough to obtain the benefits of long-term intensive diabetes management, and who are active and have good cognitive function, should be supported with continual education and care to maintain skills in order to achieve glycaemic goals similar to those that apply in younger adults with diabetes.

However, elderly patients often have coexisting illnesses, including complications secondary to diabetes, other long-term conditions, poor functional and cognitive status, and reliance on others for management of their diabetes. To reduce undue risks, these factors need consideration whilst individualizing management plans. These patients often have renal impairment precluding the use of metformin. The sulphonylurea group of drugs can be considered as alternatives or in addition to metformin, but particular care should be exercised to prevent hypoglycaemia. Worsening renal function, poor oral intake and imbalance between medication-food timings are important causes of hypoglycaemia in any patient taking a sulphonylurea or insulin, but these episodes are more likely to happen in elderly patients. Patients and carers should therefore be educated appropriately about the recognition and treatment of hypoglycaemia. Long-acting sulphonylureas, such as glibenclamide, should be avoided in elderly patients with a high risk of hypoglycaemia.

DPP-4 inhibitors could theoretically be a useful option in addition to metformin in selected patients at risk of hypoglycaemia. However, currently available DPP-4 inhibitors are not licensed for use if eGFR is below 50 mL/min and there are few trial data in elderly subjects. Thiazolidinediones should be used cautiously in patients at high risk of bone loss or fractures.

In selected patients, insulin
treatment may be the safest option in view of other co-morbidities and intolerance of oral agents. Selection of the insulin regimen, doses and injection device should take into consideration the limiting factors, such as poor coordination, and visual and/or variable cognitive functions. Patients using a disposable insulin injection device, which has a large easy-to-read dial, large push button for injection and audible clicks for each unit injected, were less likely to need help with insulin administration than people using traditional vials/syringes. Human isophane insulin and detemir can be administered using the disposable insulin injection device.

For older people relying on others to administer their insulin, once-daily long-acting insulin analogues (eg, glargine, detemir) are preferred. These patients should have individualized care plans aimed at avoiding symptomatic hypo- or hyperglycaemia.

The Future

- **Other incretin-based agents**: there are about 10 more agents targeting the DDP-4 enzyme currently in various stages of development. A long-acting once-weekly formulation of exenatide (exenatide long-acting release) has been developed and has been submitted for approval by the Food and Drug Administration. In clinical trials, it is well tolerated and associated with greater HbA1c reduction (1.9% vs 1.5%) than twice-daily exenatide over 30-week period. Recently, these patients completed 52 weeks therapy with exenatide long-acting release and an improvement in glycaemic control was sustained during this extended period. It was used in a 2-mg once-weekly preparation in clinical trials. Taspoglutide and albiglutide, two other human GLP-1 agonists intended for weekly or less frequent administration, are also on the horizon.

- **SGLT2 inhibitors**: sodium-glucose co-transporter 2 (SGLT2), present in proximal renal tubules and plays a major role in reabsorbing glucose from the tubular fluid. Inhibition of this co-transporter leads to calorie loss by increasing urinary glucose. As a result, glycemic control is improved without risk of weight gain or hypoglycaemia as this approach is insulin-independent. Increased glycosuria leads to increased diuresis and urogenital infections. The SGLT2 inhibitor, dapagliflozin, is currently undergoing phase III clinical trials. Sergliflozin and remogliflozin are amongst the other SGLT2 inhibitors in development.

- **Dual PPAR-α and PPAR-γ agonists**: agents activating both PPAR-α receptors, improving dyslipidaemia, and PPAR-γ receptors, reducing insulin resistance, are also on the horizon. One of these agents, aleglitazar, has been shown to improve HbA1c by 0.36–1.35% in a dose-dependent manner during a placebo-controlled trial over 16 weeks. Phase III trials and longer preclinical studies are needed to confirm the safety of these agents.

- **Glucokinase activators**: molecules that activate the glucokinase enzyme present in hepatic cells and pancreatic β cells, leading to increased glycogen synthesis and glucose release. This effect has proved beneficial in reducing plasma glucose in animal models and the role of these drugs in humans is currently being tested.

- **Glucagon receptor antagonists**: glucagon is secreted by pancreatic α cells and plays a vital role to maintain glucose homeostasis. It prevents hypoglycaemia and counteracts the effects of insulin by stimulating hepatic glucose synthesis and mobilization. In patients with T2DM, glucagon/insulin ratio is increased, leading to glucogenesis and glycogenolysis. Experimental studies have shown a state of hyperglucagonemia in patients with T2DM and suppression of this excess glucagon levels or activity resulted in improvement of glycemic control. One such agent, Bay 27-9955, has been shown to reduce the glucagon-induced hyperglycaemia in adults. There are various peptide- and non-peptide-based glucagon receptor antagonists currently being tested in animals and humans.

Declaration of Interests

Professor Melanie Davies has acted as consultant, advisory board member and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Servier, BMS and Roche. She has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp & Dohme, GlaxoSmithKline and Servier.

References


Reducing Cardiovascular Risk in Type 2 Diabetes Mellitus

David Preiss, MRCP; DipRCPath; Naveed Sattar, PhD, FRCPath, FRCP

The last decade has seen a paradigm shift in our understanding of the best mechanisms to lower cardiovascular risk in patients with type 2 diabetes. In the past, considerable emphasis was placed on reduction of plasma glucose as a key mechanism to lowering cardiovascular risk, and there were misplaced perceptions of benefit from aspirin in all patients. There is now overwhelming evidence that lowering cholesterol with statin therapy and lowering blood pressure with antihypertensive agents, at least to a systolic value of 130 mm Hg, are the keys to success in achieving such benefits.

Introduction

Morbidity and mortality in patients with type 2 diabetes are higher than in those without diabetes, and this elevation in risk is especially marked in those with concomitant microalbuminuria or a history of cardiovascular events. Major modifiable cardiovascular risk factors in type 2 diabetes include smoking, dyslipidaemia, hypertension and, potentially, hyperglycaemia. Consequently, there have been numerous large randomized trials investigating the effect on cardiovascular outcomes and death of agents that lower serum lipids, blood pressure or plasma glucose. In addition, anti-platelet agents have been tested in primary and secondary prevention trials in diabetes. In this article, we will examine the relevant findings in these four key areas with particular focus on meta-analyses of randomized controlled trials.
Lipid-lowering Therapy

Whereas most large trials of lipid-lowering agents have included mainly non-diabetic participants, many of these trials have included sufficient numbers of patients with type 2 diabetes for the data to be combined statistically in meta-analyses. There have also been a small number of important trials conducted specifically in diabetic participants. Of the agents investigated, statins and fibrates have been examined far more thoroughly than other agents. Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, act by reducing cholesterol synthesis. The major effect of this inhibition is to increase low-density lipoprotein (LDL) cholesterol uptake by the liver with a resultant fall in circulating LDL cholesterol. The mechanism of action of fibrates is not fully understood, but they help to correct hypertriglyceridaemia and low high-density lipoprotein (HDL) cholesterol, both of which are features of insulin resistance.

Statin Therapy

The beneficial effect of statin therapy on cardiovascular outcomes in type 2 diabetes has resembled those found in non-diabetic individuals. The four published statin trials with the biggest populations of patients with diabetes have been the Heart Protection Study, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm, and the Collaborative Atorvastatin Diabetes Study. Of these, only the Collaborative Atorvastatin Diabetes Study was conducted specifically in patients with diabetes whereas the others included both diabetic and non-diabetic patients. In the Cholesterol Treatment Trialists’ meta-analysis of outcomes in over 18,000 diabetic patients from all relevant statin trials, including the four noted above,1 a 1 mmol/L reduction in LDL cholesterol reduced the combined end point of coronary heart disease (CHD) death and non-fatal myocardial infarction (MI) by 22% (hazard ratio [HR], 0.78; 99% confidence interval [CI], 0.69–0.87), cardiovascular disease (CVD) events by 21% (HR, 0.79; 99% CI, 0.72–0.86), vascular death by 13% (HR, 0.87; 99% CI, 0.76–1.00) and all-cause death by 9% (HR, 0.91; 99% CI, 0.82–1.01) with no effect on non-vascular deaths. Similarly, coronary revascularization was reduced by 25% and stroke by 21%. Results are summarized in Figure 1. Relative benefits were similar in patients with and without pre-existing vascular disease and in those with and without a history of hypertension. Furthermore, benefits were similar in men and women, in various body mass index categories, and in smokers and non-smokers. Accordingly, it is important to appreciate that the benefits of statin therapy are greater in absolute terms in those who are already at higher risk of cardiovascular events. For example, using data from the Cholesterol Treatment Trialists’ meta-analysis, lowering LDL cholesterol by 1 mmol/L in 1,000 patients with diabetes and existing baseline CVD (ie, secondary prevention) over 5 years would reduce the number of major vascular events by 57, while treatment in patients with diabetes free of CVD at baseline (primary prevention) would only lead to 36 fewer events. Of note, it was recently demonstrated that statin therapy slightly elevates the risk of developing diabetes.2 It is not known whether statin therapy has any detrimental effect on glycaemic control in those with established diabetes or on the intensity of therapy needed to maintain a certain level of glycaemic control.

Fibrates

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,3 published in 2005, provided the first large-scale evidence for the effect of fibrate therapy in type 2 diabetes. This placebo-controlled study evaluated fenofibrate in 9,795 patients over 5 years. Whilst the primary end point (non-fatal MI and CHD death combined) was non-significantly reduced by 11% (HR, 0.89 [0.75–1.05]), when examined separately this was composed of a significant reduction in non-fatal MI of 24% (HR, 0.76 [0.62–0.94]) but a non-significant increase in CHD death of 19% (HR, 1.19 [0.90–1.57]). Furthermore, all-cause mortality was also slightly higher in the fenofibrate recipients (HR, 1.11 [0.95–1.29]). This finding of slightly higher mortality has been noted before in other fibrate trials in mixed populations. While statin use may have partially clouded analysis of the FIELD results, it appears that fenofibrate therapy is associated with, at best, a weak protective effect on non-fatal MI only. In subsequently published FIELD results, the investigators have reported reductions in microvascular complications, such as retinopathy requiring laser treatment, and amputation.3,5 Whether fibrate therapy will provide benefit in these microvascular areas remains controversial, however, and further research is needed. In early 2010, the complex, double two-by-two factorial design, Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which is also referred to in subsequent sections of this article, provided data regarding combination lipid-lowering therapy.6 In ACCORD, 5,518 patients were randomized to either fenofibrate
or placebo, added to ongoing simvastatin therapy. As in FIELD, results again showed no clear benefit of fibrate therapy. In ACCORD, the primary combined outcome of non-fatal MI, non-fatal stroke or CVD death was not significantly lowered (HR, 0.92 [0.79–1.08]) and results for total mortality were similar.

**Other Agents**

Other agents (ezetimibe, omega-3 fatty acids, nicotinic acid, bile acid sequestrants, etc) have been less well studied in patients with diabetes. However, it should be noted that nicotinic acid, the mechanism of action of which is incompletely understood but which has a moderate (~15–20%) HDL cholesterol increasing effect, has been noted to cause a significant deterio-

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**Figure 1. Benefits of statin therapy per 1 mmol/L reduction in low-density lipoprotein cholesterol in patients with and without diabetes (from the Cholesterol Treatment Trialists’ meta-analysis)**

<table>
<thead>
<tr>
<th>Major vascular event and prior diabetes</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate ratio (confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major coronary event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>776 (8.3%)</td>
<td>979 (10.5%)</td>
<td>0.78 (0.69–0.87)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2,561 (7.2%)</td>
<td>3,441 (9.6%)</td>
<td>0.77 (0.73–0.81)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3,337 (7.4%)</td>
<td>4,420 (9.8%)</td>
<td>0.77 (0.74–0.80)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup:</td>
<td>$\chi^2_1=0.1; p=0.8$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coronary revascularization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>591 (5.2%)</td>
<td>627 (6.7%)</td>
<td>0.75 (0.64–0.88)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2,129 (6.0%)</td>
<td>2,807 (7.9%)</td>
<td>0.76 (0.72–0.81)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>2,620 (5.8%)</td>
<td>3,434 (7.6%)</td>
<td>0.76 (0.73–0.80)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup:</td>
<td>$\chi^2_1=0.1; p=0.8$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>407 (4.4%)</td>
<td>501 (5.4%)</td>
<td>0.79 (0.67–0.93)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>933 (2.7%)</td>
<td>1,116 (3.2%)</td>
<td>0.84 (0.76–0.93)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1,340 (3.0%)</td>
<td>1,617 (3.7%)</td>
<td>0.83 (0.77–0.88)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup:</td>
<td>$\chi^2_1=0.8; p=0.4$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major vascular event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1,465 (15.6%)</td>
<td>1,782 (19.2%)</td>
<td>0.79 (0.72–0.86)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>4,889 (13.7%)</td>
<td>6,212 (17.4%)</td>
<td>0.79 (0.76–0.86)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6,354 (14.1%)</td>
<td>7,994 (17.8%)</td>
<td>0.79 (0.77–0.81)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup:</td>
<td>$\chi^2_1=0.8; p=0.4$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ration in glycaemic control in diabetes. This is usually manageable with appropriate adjustment of glucose-lowering therapy. The results of an ongoing end point trial of niacin (combined with an agent to reduce facial flushing) in 20,000 patients with vascular disease, of whom 7,000 will also have diabetes, are eagerly awaited, and should become available in 2013.

**Glucose-lowering Therapy**

The effect of intensive glucose lowering on clinical events in type 2 diabetes is currently a hotly debated issue. Clear conclusions are complicated by the fact that the relevant trials have studied differing populations, have used different agents and combinations of agents, and have pursued glucose lowering in the intensive treatment arm with varying degrees of vigour. To date, four major end point trials have compared the effects of intensive glucose lowering with standard diabetes care. The trials are the landmark United Kingdom Prospective Diabetes Study (UKPDS)\(^7\) and three trials published in the *New England Journal of Medicine* in the last 2 years, namely ACCORD,\(^8\) the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial\(^9\) and the somewhat smaller Veterans Affairs Diabetes Trial (VADT).\(^10\)

**Recent Trials and Meta-analyses**

Details of the relevant trials are listed in Table 1. Individually, the trials produced few significant results with the noteworthy exception of ACCORD, which was terminated early following the unexpected findings in the interim analysis of more deaths and CVD deaths in the intensively treated arm. The results of the four trials have been combined in recent meta-analyses in the hope of obtaining further insights into the potential value of intensive therapy.\(^11,12\) In one of these meta-analyses, data from the four trials indicated that MI and major CVD events were indeed reduced by intensive glucose control. However, subgroup analysis showed that whereas intensive glucose lowering was effective in lowering major CVD events in those with no known vascular disease, there was no similar effect in those with established vascular disease. In the second meta-analysis, another trial (Prospective Pioglitazone Clinical Trial in Macrovascular Events [PROactive]) was added to the four trials mentioned above. Whilst not strictly designed to compare differential glycaemic control, PROactive compared pioglitazone therapy to placebo with the inevitable result that the placebo arm endured worse glycaemic control during follow-up. The results of this second meta-analysis were much the same as in the first, showing significant reductions in total MI and non-fatal MI (Figure 2). However, there was no apparent effect on all-cause mortality in either meta-analysis. The increases in total and CVD deaths in ACCORD and the trend towards an increase in CVD death in VADT have prompted concerns about the safety of intensive glucose lowering and the appropriateness of pursuing tight glucose control, particularly in older patients with diabetes.

A coherent explanation for these important findings has yet to be found. Of note, the reader should be

<table>
<thead>
<tr>
<th>Trials</th>
<th>N</th>
<th>Age</th>
<th>Baseline HbA(_1c) (%)</th>
<th>Glycaemic control aims</th>
<th>Mean difference (%) in HbA(_1c) in trial</th>
<th>Effect of intensive therapy on death</th>
<th>Effect of intensive therapy on CVD death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Standard Intensive</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>UKPDS</td>
<td>3,867</td>
<td>53</td>
<td>7.1</td>
<td>Best achievable with diet</td>
<td>−0.66</td>
<td>0.96 (0.70–1.33)</td>
<td>1.02 (0.66–1.57)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>11,140</td>
<td>66</td>
<td>7.5</td>
<td>HbA(_1c) &gt; 6.5%</td>
<td>−0.72</td>
<td>0.93 (0.83–1.06)</td>
<td>0.88 (0.74–1.04)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>10,251</td>
<td>62</td>
<td>8.3</td>
<td>HbA(_1c) &lt; 6%</td>
<td>−1.01</td>
<td>1.22 (1.01–1.46)</td>
<td>1.35 (1.04–1.76)</td>
</tr>
<tr>
<td>VADT</td>
<td>1,791</td>
<td>60</td>
<td>9.4</td>
<td>Standard care</td>
<td>−1.16</td>
<td>1.07 (0.81–1.42)</td>
<td>1.32 (0.81–2.14)</td>
</tr>
</tbody>
</table>

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; CI = confidence interval; CVD = cardiovascular disease; HbA\(_1c\) = glycaated haemoglobin A\(_1c\); HR = hazard ratio; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.
aware that in ACCORD, glycated haemoglobin A1c (HbA1c) was reduced more aggressively and quickly than in the other trials, and that ACCORD and VADT achieved the greatest differences in HbA1c between treatment arms. Also, as might have been expected, there were more cases of hypoglycaemia in intensively treated patients, which may have influenced outcomes.

Finally, it should be recognized that newer classes of glucose-lowering drugs have appeared in recent years and several ongoing trials will help to determine whether targeting the glucagon-like peptide 1 axis, directly or indirectly, is a better approach to lowering vascular risk in diabetes. Until such studies report, metformin remains the first agent of choice for most patients, given its proven vascular benefit, demonstrated in UKPDS.

**Antihypertensive Agents**

Blood pressure is a major determinant of incident vascular events in individuals with type 2 diabetes. The benefits of blood pressure-lowering therapy are now well established, but unanswered questions remain. First, clinical trial data have not provided a treatment threshold to serve as a target. Second, whilst angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists have become established as first-choice agents for blood pressure-lowering in diabetes because of their ability to reduce the development and progression of albuminuria, a surrogate marker of diabetic renal disease, there is little evidence to show that these agents reduce the all-important progression to end-stage renal failure.13 Third, a recent paper suggested that variation in blood pressure may also be an important factor determining future CVD risk. This unconfirmed observation suggests that agents which lead to more stable, though not necessarily lower, blood pressure values may achieve better reduction in CVD risk.14

**Recent Trials and Meta-analyses**

A 2005 meta-analysis15 showed that ACEi reduce CVD events, CVD death and total mortality compared with placebo and that effects of calcium channel blockers (CCB) are broadly the same as ACEi when compared with placebo, although the results were largely non-significant perhaps because of the smaller numbers studied. The same study showed that more intensive blood pressure lowering also lowers CVD events. In direct comparisons of ACEi, CCB and other agents (β-blockers and diuretics), no agent was statistically superior in reducing CVD events, CVD death or death. The blood pressure-lowering part of the

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**Figure 2. Effects of intensive glucose control compared with standard glycaemic control on coronary heart disease events in diabetes**

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS</td>
<td>3,071/1,549</td>
<td>426/259</td>
<td>8.6%</td>
</tr>
<tr>
<td>PROactive</td>
<td>2,605/2,633</td>
<td>164/202</td>
<td>20.2%</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5,571/5,569</td>
<td>310/337</td>
<td>36.5%</td>
</tr>
<tr>
<td>VADT</td>
<td>892/899</td>
<td>77/90</td>
<td>9.0%</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5,128/5,123</td>
<td>205/248</td>
<td>25.7%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>17,267/15,773</strong></td>
<td><strong>1,182/1,136</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

ALLHAT trial also showed no difference in outcomes between CCB, diuretic and ACEi. In 2007, the ADVANCE trial reported that combination therapy with perindopril and indapamide, compared with placebo, resulted in a reduction in blood pressure of 5.6/2.2 mm Hg with significant reductions in all-cause death and CVD death but a non-significant reduction in CVD events.16

Clinicians are often advised to lower blood pressure in patients with type 2 diabetes to below systolic 130 mm Hg. However, until release of ACCORD’s blood pressure-lowering results,17 trials had not specifically examined this recommendation or managed to achieve this level of blood pressure. ACCORD examined whether lowering systolic blood pressure below 120 mm Hg is preferable to the easier target of 140 mm Hg, using various antihypertensive agents. In the trial, the two arms achieved blood pressure results of 119 mmHg and 134 mm Hg. Against expectations, the composite primary end point of non-fatal MI and stroke plus CVD death was not reduced and neither was total mortality.

**Antiplatelet Agents**

Antiplatelet therapy is of proven value in the secondary prevention of CVD. This is also the case for patients with type 2 diabetes. The best early evidence comes from a 1994 meta-analysis of antiplatelet therapy (mostly aspirin) compared with control in high-risk patients (defined as those with unstable angina, MI, stroke or transient ischaemic attack).18 Here, it was shown that antiplatelet therapy reduced CVD events significantly by 38 events per 1,000 patients treated, a similar reduction to that found in those without diabetes; benefit was similar in men and women.

Recent data have challenged the value of using antiplatelet therapy for primary prevention of CVD in type 2 diabetes. A recent meta-analysis incor-
In focus

Practice points

- Statin therapy remains the best and only effective lipid-modifying agent in type 2 diabetes.
- Fibrates, used as monotherapy or in combination therapy, have not been shown to provide cardiovascular benefit during trials conducted in patients with type 2 diabetes.
- The true effect of intensive glucose lowering cannot be conclusively quantified, but available trial results suggest a slight reduction in cardiovascular disease (CVD) events.
- Recent trial findings have led to the speculative but sensible recommendations that intensive glucose lowering is more appropriate in younger patients and those with a recent diagnosis of type 2 diabetes, but less appropriate in older patients and those with existing CVD.
- Whatever the CVD effects of intensive glucose lowering, even if beneficial, they are considerably smaller than can be achieved with statin therapy or blood pressure-lowering therapy (Figure 3).
- Lowering systolic blood pressure in the majority of type 2 diabetes patients to around 130 mm Hg appears beneficial. However, there is currently little proven benefit in pursuing targets lower than this.
- The actual lowering of blood pressure appears to be the critical aspect in reducing CVD risk rather than the method or agent used to lower blood pressure.
- The angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist class of agents reduces development and progression of albuminuria. However, evidence of reduction in progression to end-stage renal failure remains weak at present.
- The case for secondary prevention of CVD with aspirin is strong.
- Any small benefit from treating patients with type 2 diabetes but no history of CVD with aspirin is probably matched by the increase in episodes of bleeding. Current evidence argues against using aspirin in all patients with type 2 diabetes.

porating six placebo-controlled trials of aspirin, in 10,117 diabetic participants with no history of CVD, found a borderline reduction in major CVD events but no change in CVD mortality and total mortality.\(^1\) Interestingly, MIs were significantly reduced in men (by 43%) but not in women, suggesting a possible gender interaction. As expected, episodes of any bleeding and gastrointestinal bleeding were approximately twice as common among those taking aspirin. These findings resemble those found in unselected trial populations that have also concluded that whereas aspirin is definitely valuable for secondary prevention, it is of uncertain net value for primary prevention owing to the trade-off between reduced CVD risk and increased bleeding.\(^2\) This work also demonstrated that in a primary prevention population risk factors that increase the risk of CVD generally increase the risk of bleeding.

These observations are currently being extended in two large trials. ASCEND is recruiting 10,000 diabetic patients with no CVD and randomizing to either aspirin 100 mg daily or placebo. ACCEPT-D is recruiting 5,170 patients in order to investigate the effect of aspirin or placebo in diabetic patients with no history of CVD who are already being treated with simvastatin 20 mg daily.

Declaration of Interests

None.

References


A complete list of references can be obtained upon request from the editor.


About the Authors

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Medical Progress September 2012
Dear Editor,

Re: Oral Anticoagulation in Atrial Fibrillation: A Look at ROCKET-AF, RE-LY and Warfarin Use

Following the article on ‘Oral Anticoagulation in Atrial Fibrillation: A Look at ROCKET-AF, RE-LY and Warfarin Use’, I would like to express my concerns regarding the misinterpretation of the RE-LY clinical study and other issues with regard to the comparison of RE-LY and ROCKET-AF clinical trials.

1. Establishing non-inferiority and superiority
   a. Before comparing with warfarin, the efficacy of warfarin must be ensured, which is normally expressed as time in therapeutic range (TTR). TTR should be over 60%, as several major studies have showed. Mean TTR values were only 55% for ROCKET-AF and 64% for RE-LY. This information was not mentioned in the article.
   b. Both ROCKET-AF and RE-LY were designed to test for non-inferiority against warfarin, but in both cases the authors pre-specified that in case of a demonstrated non-inferiority, then they would need to test for superiority. In RE-LY, it is based on intent-to-treat (ITT) population; in ROCKET-AF, it was for a sub-group of the ITT population.

      The difference in conclusion between per-protocol (PP), as-treated population (superiority) and ITT population in ROCKET-AF (non-inferiority) were caused not only by different population sizes (n = 6,958 vs n = 7,081) but also by the huge difference in the follow-up period (590 days vs 707 days). Moreover, based on the European Union and US statistical principles, ITT analysis should be normally used for superiority test and to avoid over-optimistic estimates. PP analysis is normally only used for non-inferiority conclusion. Therefore, superiority conclusion should not be drawn from the PP-as-treated population as the authors did.

   It is also mentioned in the conclusion for ROCKET-AF that in patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. In Table 2 on primary end point of stroke or systemic embolism, of the ROCKET AF article, details are given explaining the difference between the ITT population (7,081 patients in the rivaroxaban group, 7,090 in the warfarin group), where superiority was not demonstrated, and the safety, as-treated population (7,061 patients in the rivaroxaban, 7,082 patients in the warfarin group), where superiority was statistically significant. The difference between the two populations represents 20 patients (0.28%) in the rivaroxaban group and eight patients (0.11%) in the warfarin group.

   In summary, the results of the ROCKET-AF trial clearly conclude non-inferiority with warfarin because the authors applied the agreed statistical consensus that superiority has to be based on ITT population. The RE-LY results demonstrated superiority of dabigatran over well-controlled warfarin. Subsequent publications have also shown a significant lower incidence of life-threatening bleeding and intracranial bleeding with dabigatran 150 mg versus warfarin.

   The recognized highest value of the ITT population is based on the risk to bias the results with a selection of any subgroup. The analysis of subgroups has, of course, a scientific value, for a wider understanding of the results, but they cannot hide or reverse the main findings.

   Therefore, we do not agree with the statement made in the article.

2. Discontinuation rates reported in the RE-LY trial

   As different clinical studies have different study designs and follow-up times, discontinuation rates may differ. The discontinuation rates reported in the RE-LY trial are as follows:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Discontinuation rate year 1</th>
<th>Discontinuation rate year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>10.20%</td>
<td>1.60%</td>
</tr>
<tr>
<td>Dabigatran 110 mg, twice a day</td>
<td>14.50%</td>
<td>20.70%</td>
</tr>
<tr>
<td>Dabigatran 150 mg, twice a day</td>
<td>15.50%</td>
<td>21.20%</td>
</tr>
</tbody>
</table>

3. No direct comparison should be made between RE-LY and ROCKET-AF

   There have been no direct comparisons between direct thrombin inhibitors and factor X inhibitors or any analyses
to conclude which compound is better than the other.

Based on all the points above, we do not agree with the overall conclusion made in the above-mentioned article.

It is important to fully understand the design, methods and findings of a clinical study to come to a conclusion. Misinterpretation of clinical study findings may distort the original meaning of the authors and lead to inaccurate information provided to health-care professionals.

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**References**

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**Reply**

I would like to thank Dr Ling Hui for her comments. As stated in my article,¹ the RE-LY² and ROCKET-AF³ studies were not head-to-head studies, thus we cannot compare these two studies as light to light or apple to apple, as the study designs, study populations and the efficacy and safety analyses were all different.

The issue on time in therapeutic range (TTR) was addressed clearly in the online Table 5 of the ROCKET-AF Supplementary Appendix.⁴ In ROCKET-AF, the TTR was calculated from all international normalized ratio (INR) values during the study period and for 7 days after warfarin interruptions, whereas for RE-LY the TTR was calculated differently. Furthermore, the effect of rivaroxaban did not differ across quartiles of the duration of time that INR values were within the therapeutic range according to study centre (P = 0.74 for interaction). Thus, the efficacy of rivaroxaban as compared with warfarin was as favourable in centres with the best INR control as in those with poorer control.

I agree with Dr Ling Hui that in the per-protocol, as-treated population, rivaroxaban was non-inferior to warfarin; and in the intention-to-treat population, rivaroxaban was superior to warfarin while patients were on treatment (as indicated in Table 2 of my article¹ and also stated in Table 2 of the ROCKET AF article³).

It was written in the conclusion of my article that rivaroxaban was superior in a per-protocol setting – this is incorrect and was either due to a typographical error or oversight of the author, and the author would like to apologize for this error. What was meant was that rivaroxaban was superior to warfarin while patient was on treatment, as stated in Table 2 of the original paper.

The difference between these results reflect the fact that among patients who discontinued therapy before the conclusion of the trial, no significant difference in outcomes would have been anticipated.

In addition, this is a double-blind, double-dummy study, and at the end of the trial there was difficulty in transitioning to open-label therapy in patients on rivaroxaban. Events occurring at the end of the study, therefore, were related to difficulties in achieving the transition from blinded trial therapy to open-label use of a vitamin K antagonist when the patient had previously been assigned to the rivaroxaban group, since presumably many patients who had previously been assigned to the warfarin group would have already had therapeutic INR levels.

In response to the discontinuation rates reported in the RE-LY trial, the table as provided by Dr Ling is self-explanatory.

Concerning your point that no direct comparison should be made between the RE-LY and ROCKET-AF studies, I have not made any statement to conclude that rivaroxaban is a better compound than dabigatran.

At the end of the day, we have to tailor our treatment to what we think is best for our patient. It is up to the individual clinician to decide which of the newer agents is the most appropriate for his or her patient.

**References**

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Care of the Patient on Long-term Oral Glucocorticoids

Shannon McCarthy, MBBS (Hons), BMedSci, GradCertTertTeach; Mark Kotowicz, MBBS, FRACP

Prolonged oral glucocorticoid therapy is particularly prevalent in older adults, and these patients are vulnerable to the varied complications of this treatment. Care must be taken to use the lowest possible dose and the shortest duration of therapy.

Use of oral glucocorticoid therapy is widespread in our community for the treatment of inflammatory and autoimmune conditions, but is complicated by the significant side effects of these drugs. Although the most common indication for oral glucocorticoid therapy is respiratory disease, especially chronic obstructive pulmonary disease, rheumatological diseases are the leading indication for prolonged therapy (see the box on this page).

Older adults and the elderly have the highest usage of oral glucocorticoids and are vulnerable to myriad complications. Most complications are directly related to the dose and duration of therapy.

This article provides a structured approach to the prevention and management of the common and serious complications of oral glucocorticoid therapy.

Cardiovascular Risk

Many of the conditions requiring treatment with glucocorticoids are themselves risk factors for increased rates of cardiovascular events. However, glucocorticoid therapy compounds the risk of myocardial infarction, stroke, peripheral arterial disease and congestive cardiac failure. Glucocorticoids increase insulin resistance and stimulate a hyperinsulinaemic state. They also increase rates of synthesis of very low-density lipoproteins.

“Older adults and the elderly have the highest usage of oral glucocorticoids and are vulnerable to myriad complications”

Conditions that may require long-term glucocorticoid therapy

Rheumatological
- Rheumatoid arthritis
- Large- and small-vessel vasculitis
- Systemic lupus erythematosus
- Polymyalgia rheumatica
- Arthritis associated with inflammatory bowel disease
- Polymyositis and dermatomyositis
- Ankylosing spondylitis

Respiratory
- Chronic obstructive pulmonary disease
- Asthma
- Interstitial lung disease

Renal
- Nephrotic syndrome
- Glomerulonephritis

Haematological
- Immune thrombocytopenia
- Acquired haemolytic anaemia

Neurological
- Duchenne muscular dystrophy
- Myasthenia gravis
- Chronic demyelinating peripheral neuropathy

Oncological
- Cerebral tumours
- Chemotherapy

Post-transplantation
Patients on chronic treatment require assessment of cardiovascular risk factors at regular intervals. Although evidence is lacking that interventions to modify cardiovascular risk in glucocorticoid-treated patients do reduce risk, it would seem prudent to address these risk factors.

Osteoporosis

Glucocorticoid therapy is the most common cause of secondary osteoporosis (glucocorticoid-induced osteoporosis), but most patients on long-term glucocorticoid therapy are neither screened for osteoporosis nor treated. Both current and prior glucocorticoid use increase the risk of osteoporotic fracture beyond the attributable risk of bone mineral density differences alone. Even in patients with normal bone density, use of glucocorticoids increases the risk of vertebral fracture. However, discontinuation of glucocorticoid therapy results in a rapid reduction in fracture risk.

Glucocorticoids inhibit bone formation, decrease gastrointestinal absorption of calcium, increase renal calcium excretion, and may stimulate bone resorption. In addition, they suppress the pituitary gonadal axis, reducing sex steroid concentrations, particularly in postmenopausal women.

Treatment with calcium and vitamin D can prevent bone loss. Unless contraindicated, prophylactic bisphosphonate therapy should be considered in patients receiving prednisolone 7.5 mg or more per day (or equivalent) for more than 3 months. An antiresorptive therapy is indicated if patients on long-term glucocorticoid therapy suffer a fragility fracture.

Recent data suggest that use of the bone formation-stimulating agent, teriparatide, may be superior to bisphosphonate therapy in glucocorticoid-induced osteoporosis. Assessment of additional osteoporotic risk factors, and non-pharmacological measures such as exercise and smoking cessation, are also beneficial. Elderly patients should receive a comprehensive falls prevention strategy, as 20% of patients with a fractured neck of femur will die within 1 year and 20% will require permanent residential care.

Glucocorticoids are also the leading cause of avascular necrosis (AVN) of the femoral head, although the overall incidence of this complication is low. Patients on more than 20 mg/day of prednisolone (or equivalent) or those with Cushing’s syndrome are at the highest risk. AVN of the femoral head may be asymptomatic, or may manifest as groin pain, either on walking or at rest, and occasionally at night. A high index of suspicion is needed to diagnose this disorder in the early treatable stages, when X-rays are usually normal. Magnetic resonance imaging is the most sensitive test.

AVN of the femoral head may represent another indication for bisphosphonate therapy, with data indicating that these agents can preserve bone microarchitecture, permitting repopulation of the bony structure with bone cells. Compared with historical controls, patients with AVN who were treated for 3 years with oral alendronate had better
clinical function, lower rates of progression, and lower rates of total hip replacement after a mean follow up of 4 years.10

Glucose Metabolism

Glucocorticoids lead to deranged glucose metabolism by stimulating hepatic gluconeogenesis and inhibition of adipose tissue glucose uptake. Although development of diabetes with glucocorticoid therapy in a patient with previously normal glucose metabolism is uncommon, patients with diabetes are very sensitive to the effects of glucocorticoids. The longer the duration of the patient’s diabetes, the more exaggerated the hyperglycaemia when they take glucocorticoids.11

There are no trials and little evidence regarding the treatment of glucocorticoid-induced hyperglycaemia. Because glucocorticoids particularly affect postprandial glucose levels, rather than fasting levels, commencing acarbose, repaglinide or sulfonylureas is reasonable for patients with mild hyperglycaemia. For those with moderate to severe hyperglycaemia, insulin is required. Prandial insulin (short duration; rapid-onset or very rapid-onset) may be sufficient to maintain glycaemic control without additional basal insulin.

Gastrointestinal Risks

Although glucocorticoids are traditionally believed to be a risk factor for gastrointestinal ulceration, there is some emerging evidence that glucocorticoids may be gastroprotective. However, patients taking glucocorticoids who have gastrointestinal haemorrhages have higher mortality. The risk of gastrointestinal bleeding with the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids is up to 20 times that of age- and sex-matched controls.12 The risk of gastrointestinal ulceration and bleeding with glucocorticoids alone is lower than with NSAIDs alone, and prophylaxis with a proton pump inhibitor is not recommended unless the patient is also taking regular aspirin.

Patients taking glucocorticoids long-term also have higher rates of non-alcoholic fatty liver disease.13

Renal Complications

Glucocorticoid therapy causes hypertension and fluid retention. This is particularly pertinent in patients with pre-existing hypertension and/or cardiovascular risk factors, and in patients with cardiac failure. Kaliuresis also occurs, but clinically significant hypo-kalaemia is rare.

Immunity

Immunosuppression occurs at pharmacological doses of glucocorticoids. Various complex mechanisms contribute to immunosuppression, such as the decreased production of cytokines, impaired phagocyte adherence, eosinophil sequestration in tissues, and decreased circulating T cells.

Reactivation of latent tuberculosis and herpes zoster can occur, but routine screening for latent tuberculosis prior to glucocorticoid therapy is not advised. Influenza virus vaccine and pneumococcal vaccine remain immunogenic in patients taking glucocorticoids; these are both subunit vaccines. Patients taking doses greater than 20 mg/day prednisolone (or equivalent) should not receive live attenuated vaccines – that is, measles, mumps and rubella vaccine, varicella zoster vaccine, yellow fever vaccine and the oral polio vaccine (only used nowadays in regions with high incidences of polio).14

As with other patients who are heavily immunosuppressed (such as those with human immunodeficiency virus infection and those undergoing chemotherapy), patients on long-term
oral glucocorticoid treatment are at increased risk of malignancy, particularly non-melanoma skin cancer.15,16

Use in Pregnancy

Women of childbearing age taking glucocorticoids for prolonged periods should receive counselling regarding the issues of contraception and pregnancy. High-dose oral prednisolone (more than 1 to 2 mg/kg/day) in the first trimester is associated with increased rates of cleft lip and palate in the fetus. Other adverse effects in the infant, while rare, include masculinization of female infants, intrauterine growth restriction, neonatal cataracts, and adrenal suppression.

Women planning to conceive should have an oral glucose tolerance test prior to pregnancy, and this should be repeated after conception. They should also take calcium supplementation (to prevent osteopenia) and have regular blood pressure monitoring.

The use of dexamethasone is not recommended during pregnancy because, unlike hydrocortisone, prednisone, prednisolone and methylprednisolone, this drug crosses the placenta.17 Glucocorticoid requirements in women with adrenal suppression may or may not increase during pregnancy, and dosing should be tailored to the individual.18 If the hypothalamic–pituitary–adrenal (HPA) axis is suppressed, labouring women require 150 mg/day intravenous hydrocortisone in divided doses.19

Intercurrent Illness and Perioperative Management

Treatment with supraphysiological doses of glucocorticoids may lead to suppression of the HPA axis. Evening dosing, use of dexamethasone and doses equivalent to more than 5 mg/day prednisolone convey the highest risk of iatrogenic adrenal insufficiency, but suppression can occur even with low doses or short courses, and patients should be cautioned. A Medic Alert bracelet may be helpful.

To evaluate for adrenal insufficiency, the patient’s endogenous serum cortisol level may be measured in the early morning, prior to the daily corticosteroid dose. If the cortisol level is below 83 nmol/L, the patient has adrenal suppression; if it is above 550 nmol/L, adrenal function is intact. For patients with intermediate values, a short adrenocorticotropic hormone (ACTH) test (the Synacthen test) may be performed to diagnose adrenal insufficiency.20,21 If the patient fails to respond to exogenous ACTH (in the
form of the synthetic ACTH tetracosactrin), there is adrenal dysfunction. If the patient responds to tetracosactrin but subsequently fails to respond to exogenous corticotropin-releasing hormone, there is central HPA axis dysfunction.

When the HPA axis is suppressed, patients experiencing minor illness or undergoing minor surgery should double their usual glucocorticoid dose until recovery. Severe illness or major surgery requires 75 to 200 mg/day of intravenous hydrocortisone in divided doses.22,23

Other Adverse Effects
Prolonged therapy with oral glucocorticoids has a range of other adverse effects.

Dermatological Effects
Prolonged oral therapy with glucocorticoids can be associated with skin thinning, purpura, acne, hypertrichosis, and alopecia.

Ophthalmological Effects
Patients taking glucocorticoids are four times more likely to develop cataracts.24–27 This can contribute to visual deterioration and falls risk in the elderly. Patients also experience higher rates of glaucoma. Visual field testing using confrontation is not sensitive for detecting glaucoma, and regular fundoscopy by an experienced operator is recommended.

Myopathy
Corticosteroid myopathy rarely occurs at low doses.28 It usually manifests as leg weakness greater than arm weakness, and patients may complain of difficulty rising from a chair. Examination reveals proximal muscle weakness without pain or tenderness.

This complication can occur at any time during treatment. There are no proven preventative agents.

Neuropsychiatric Effects
Insomnia and euphoria are common in patients on prolonged oral glucocorticoid therapy, and depression, memory impairment, difficulty with concentration, akathisia and pseudotumour cerebri may occur. Glucocorticoid-induced psychosis is uncommon, and associated only with high doses. Behavioural changes and dementia can also occur. The phenomenon of steroid dementia may take up to a year to resolve after cessation of treatment.29

Drug Interactions
Glucocorticoids are metabolized in the liver and therefore may have effects on and be affected by other drugs that also have a hepatic metabolism, as discussed in the box on this page.

“Patients taking glucocorticoids are four times more likely to develop cataracts”

Drug Interactions

Cytochrome P450 2C19-related
Prednisolone induces cytochrome P450 2C19, which is involved in the metabolism of several important groups of drugs – including many proton pump inhibitors, antiepileptics and antidepressants. Prednisolone may, therefore, cause reduced efficacy of:
- lansoprazole, omeprazole, pantoprazole, rabeprazole
- diazepam, phenobarbitone, amitriptyline, citalopram
- cyclophosphamide
- indomethacin
- progesterone
- propranolol.

Cytochrome P450 3A-related
Prednisolone and other glucocorticoids are metabolized by cytochrome P450 enzymes of the CYP3A family (CYP3A4, CYP3A5, CYP3A7 and CYP3A43). Inhibition of these enzymes by diltiazem, protease inhibitors and itraconazole can exacerbate dose-related side effects of these glucocorticoids. Conversely, inducers of these CYP enzymes, such as rifampicin, can precipitate an adrenal crisis.

As mentioned earlier, there is an increased risk of gastric ulceration with the concomitant use of glucocorticoids and NSAIDs.

Conclusion
Prolonged oral glucocorticoid therapy is associated with significant side effects, and care should be taken that the lowest possible dose and the shortest duration of therapy are used. If complications occur, advice should be sought regarding the use of steroid-sparing agents instead. Some tips for GPs who are caring for patients taking oral glucocorticoids for prolonged periods are provided in the box on page 458.
Tips for GPs

Long-term oral glucocorticoid therapy is associated with significant side effects. Care must be taken to use the lowest possible dose and the shortest duration of therapy. Advice should be obtained regarding the use of steroid-sparing agents if complications occur. Particular endpoints are listed below.

• Regular assessment of cardiovascular risk factors – blood pressure, cholesterol, glycaemic control and smoking – is required. If a patient is taking regular aspirin, proton pump inhibitor prophylaxis against gastric ulceration is recommended.

• All patients should receive calcium with or without vitamin D as bone protection. Bisphosphonate therapy should be considered in patients taking more than 7.5 mg/day prednisolone (or equivalent) for 3 months.

• Patients should undergo yearly fundoscopy to screen for glaucoma and cataracts.

• Patients are at increasing risk of non-melanoma skin cancer and should follow the regular guidelines regarding sun protection.

• Neuropsychiatric side effects may occur.

• Patients are immunosuppressed and therefore; diseases such as tuberculosis and herpes zoster may reactivate. Patients taking more than 20 mg/day prednisolone (or equivalent) should not receive live vaccines.

• Patients should be educated regarding the dangers of sudden withdrawal of glucocorticoid therapy and about the management of intercurrent illness and preparation for travel.

• Expert advice in pregnant women.

Declaration of Interests

None.

References


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This continuing medical education service is brought to you by the Medical Progress Institute, an institute dedicated to CME learning. Read the article ‘Care of the Patient on Long-term Oral Glucocorticoids’ and answer the following questions. Answers are shown at the bottom of this page.

CME Article:
Care of the Patient on Long-term Oral Glucocorticoids

Please answer True or False to the questions below.

1. Older adults and the elderly have the highest usage of oral glucocorticoids.  
2. Glucocorticoids decrease insulin resistance.  
3. Glucocorticoid use increases the risk of osteoporotic fracture.  
4. Glucocorticoids inhibit bone formation, decrease gastrointestinal calcium absorption, and increase renal calcium excretion.  
5. Rheumatoid arthritis, chronic obstructive pulmonary disease and glomerulonephritis may require long-term glucocorticoids therapy.  
6. Glucocorticoids are the leading cause of avascular necrosis of the femoral head.  
7. Glucocorticoid therapy does not cause hypertension or fluid retention.  
8. Influenza virus vaccine and pneumococcal vaccine are no longer immunogenic in patients taking glucocorticoids.  
9. Patients on long-term oral glucocorticoids should always take calcium with or without vitamin D for bone protection.  
10. Patients taking glucocorticoids are twice as likely to develop cataracts.
Management of Plantar Fasciitis Evolving

Brett R Fink, MD

Initial treatment of patients with plantar fasciitis is based on an understanding of the functions of the plantar fascia and the methods for reducing stress applied to it. The differential diagnosis of heel pain may be narrowed by carefully identifying the area of tenderness. There is little scientific evidence to indicate that traditional approaches to treatment substantially improve patients’ long-term outcome, but spontaneous improvement and resolution are common. A rational approach to treatment begins with identifying the possible causes of connective tissue irritation. If specific problems can be identified, a strategy designed to correct these factors should be planned. Surgical release is indicated for severe plantar fascial pain after prolonged attempts at non-operative treatment. Many intriguing new approaches to treatment-resistant plantar fasciitis are under investigation.

Heel pain, including that caused by plantar fasciitis, is a common reason why patients seek evaluation from a doctor. The impairment that results from heel pain often is a nuisance, and the pain can be so exquisite and disabling that it interferes with the patient’s recreational, work, and social activities. Initial treatment may be instituted by a variety of doctors, including family physicians, internists, physiatrists, orthopaedists, and podiatrists.

Plantar fasciitis is a common and painful heel disorder. Initial treatment is centred on an understanding of the important functions of the plantar fascia and the methods for reducing the stress that is applied to it with daily activities. Exciting new treatment methods are on the horizon. In many cases, however, the high-grade scientific evaluation that is necessary for widespread application of these methods is not yet available. In this article, I provide an update on the latest approaches to the diagnosis and management of plantar fasciitis.

Diagnosis

The Mechanics of the Arch

Arch mechanics are centred on the plantar fascia.1 The architecture of the midfoot bones has no inherent stability. Pressure applied to the forefoot in the absence of connective tissue support leads to shearing and displacement of the joints. The intrinsic plantar ligaments closely line the inferior surface of the midfoot (Figure 1). Although the integrity of the intrinsic ligaments is crucial to the posture of the arch, these ligaments do not have sufficient leverage or size to stabilize the midfoot against the magnitude of body weight.

Hicks2 described the windlass model of arch stability. The plantar fascia inserts onto the forefoot into the plantar plates of the metatarso-phalangeal joints and by extension into the base of the proximal phalanx of each toe. This causes the plantar fascia to tighten when the toes are dorsiflexed. The tightness accentuates and stiffens the arch at the end of the step (Figure 2). Because the first metatarsal head is the largest in diameter, the plantar fascia attached to the hallux tightens more; thus, the arch is more accentuated on the medial foot, causing the foot to invert.

When combined with the force of forefoot pressure, the tension within
Structures important in supporting the arch of the foot include the plantar fascia, the intrinsic musculature and ligaments, and the bony architecture. The intrinsic plantar ligaments closely line the inferior surface of the midfoot. Although the integrity of the intrinsic ligaments is crucial to the posture of the arch, these ligaments do not have sufficient leverage or size to stabilize the midfoot against the magnitude of body weight alone. In plantar fasciitis, the most common site of pain is the origin of the plantar fascia at the medial tubercle of the calcaneus.
the plantar fascia redirects the force along the axis of the bones. This redirection reduces shear stresses across the foot that would otherwise lead to stress fractures and premature arthritis in the midfoot.

This function is shared by the foot’s intrinsic muscles, which, like the plantar fascia, stabilize the arch by linking the heel to the toes. One study that evaluated arch function demonstrated a 3.2-mm drop in the height of the navicular from the floor when the intrinsic muscles were paralyzed in vivo. The health and conditioning of these muscles may be a factor responsible for the development of arch pathology and plantar fasciitis that is not well recognized.

**Differential Diagnosis**

Although plantar fasciitis is the predominant source of heel pain, a few of the less common reasons for heel pain also should be kept in mind (Table). The differential diagnosis of heel pain may be narrowed by carefully identifying the area of tenderness. Tenderness with stress fractures of the calcaneus usually is palpable circumferentially around the tuberosity of the calcaneus.

Pain resulting from neuritis of branches of the posterior tibial nerve occurs medially and along the superior border of the intrinsic musculature or along the posteromedial aspect of the ankle. A percussion sign may elicit pain that radiates into the sensory distribution of the nerve, the plantar forefoot, or the heel.

Connective tissue damage in the plantar fascia usually is located somewhat discretely at the insertion of this structure along the anterior and medial aspect of the weight-bearing portion of the heel. The tenderness also may be appreciated at the central or lateral portion of the heel. In some cases, it may extend distally along the medial band into the longitudinal arch.

The diagnostic value of plain radiographs of the heel has been questioned. In practice, these studies rarely change treatment decisions. However, the use of radiographs in the management of musculoskeletal disorders has become so routine that some discussion with the patient about their appropriate use may be necessary to explain their omission. If the pain is not improving progressively or if invasive treatment is planned, radiographs certainly should be obtained to rule out extremely rare abnormalities that may alter the treatment plan, although the finding of a heel spur provides little help in selecting the best management of this disorder.

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**Figure 2.**

a. The windlass mechanism of arch stability as described by Hicks is shown in a simplified representation of the bony arch and the plantar fascia. b. Dorsiflexion of the hallux tightens the plantar fascia, which stiffens and accentuates the height of the arch.

“The diagnostic value of plain radiographs of the heel has been questioned”
More advanced radiographic studies, such as magnetic resonance imaging, computed tomography, ultrasonography, and nuclear medicine, are rarely necessary, and their use should be confined to cases in which there is confusion in the diagnosis. For example, fibromyalgia syndrome is common in patients who present with heel pain, possibly making the physical examination results less reliable. Although surgery may be helpful for patients with fibromyalgia syndrome, a more aggressive radiological evaluation may be prudent in the selection of patients for surgical treatment.

**Causes**

Deterioration of the plantar fascia occurs for many reasons. Connective tissue deterioration is associated with many systemic factors that alter microcirculation within tissue, such as the patient’s age, arteriosclerosis, lipid abnormalities, tobacco abuse, and diabetes mellitus. Rheumatoid arthritis, ankylosing spondylitis, and other seronegative arthropathies can be associated with plantar fasciitis and other enthesopathies.

Some predisposing factors relate to the biomechanical environment of the ligament. Mechanical overload of the plantar fascia has been suspected to play a significant role in the development of plantar fasciitis. Several studies have identified associations of plantar fasciitis with obesity and poor ankle flexibility; both of these factors would be expected to add to the mechanical load of the forefoot.

The plantar fascia also may be damaged by direct impact on the heel through gait or repetitive trauma to or overloading of the front of the foot through gait abnormalities, posture, and other tendon contractures (e.g., hamstring tendon contractures). Damage to other supporting structures that assist in arch stabilization may increase the stress on the plantar fascia; this may include injuries to the posterior tibial tendon or intrinsic plantar ligaments, resulting in acquired flatfoot deformity, or ‘fallen arches’, and instability caused by midfoot arthritis. The intrinsic musculature may be compromised in many ways, including weakness resulting from compressive or peripheral neuropathy and deconditioning because of the patient’s age or the use of overprotective footwear or arch supports.

**Treatment**

**Conservative Approaches**

There is little scientific evidence to indicate that traditional approaches to treatment substantially improve patients’ long-term outcome. The natural history of plantar fasciitis is unknown. Nearly all accepted conservative therapies yield a high success rate. As a result, large study sizes are necessary to identify statistically significant differences in effectiveness.

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**Table. Differential diagnosis for heel pain**

<table>
<thead>
<tr>
<th>Soft tissue</th>
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<tbody>
<tr>
<td>• Achilles tendinitis</td>
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<tr>
<td>• Fat pad atrophy</td>
</tr>
<tr>
<td>• Plantar fascia rupture</td>
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<tr>
<td>• Plantar fasciitis</td>
</tr>
<tr>
<td>• Plantar fibromatosis</td>
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<tr>
<td>• Posterior tibial tendinitis</td>
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<tr>
<td>• Spring ligament injury</td>
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<table>
<thead>
<tr>
<th>Skeletal</th>
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<tbody>
<tr>
<td>• Arthritis/instability of midfoot/joints</td>
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<tr>
<td>• Bone contusion</td>
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<td>• Calcaneal stress fracture</td>
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<table>
<thead>
<tr>
<th>Neurological</th>
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</thead>
<tbody>
<tr>
<td>• Charcot/neuropathic arthropathy</td>
</tr>
<tr>
<td>• Entrapment of Baxter nerve</td>
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<tr>
<td>• Medial calcaneal nerve injury</td>
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<tr>
<td>• Peripheral neuropathy</td>
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<tr>
<td>• Tarsal tunnel syndrome</td>
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<table>
<thead>
<tr>
<th>Other diagnoses</th>
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</thead>
<tbody>
<tr>
<td>• Neoplasms</td>
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**Plantar fasciitis**

Non-steroidal anti-inflammatory drugs are prescribed frequently for plantar fasciitis.
However, studies of this size and quality are rare in clinical medicine.

A rational approach to management of plantar fasciitis begins with identification of the possible causes of the connective tissue irritation. If specific problems can be identified, a strategy designed to correct these factors should be planned.

If the discomfort from the plantar fasciitis is not severe, a good starting point is a programme that includes weight loss, simple stretching exercises, and mechanical protection of the plantar fascia. Casting has been shown to be highly effective for severe pain. Although immobilization leads to deconditioning of the musculature and mechanical weakening of the plantar fascia, it seems to help resolve severe, acute pain.

Exercise therapy is an effective approach. Hamstring and Achilles contractures have been associated with the development of plantar fasciitis, and stretching programmes have been a mainstay of treatment. Most programmes focus on improving the flexibility of these muscles. Stretches that concentrate on the plantar fascia seem to increase the effectiveness of standard stretching programmes over the short term.

Conditioning exercises for the foot help relieve stress on the plantar fascia by strengthening supporting structures. Although deep tissue massage techniques are used frequently, they have not been proved to be effective. Therapeutic ultrasound and other modalities have not been shown to be useful.

There has been a lot of experience with braces that maintain the ankle in a neutral or slightly dorsiflexed position at night, and several prospective trials have shown improvement with their use over several weeks. However, patients often do not tolerate these braces well while sleeping, especially in cases in which there is bilateral involvement.

Non-steroidal anti-inflammatory drugs are prescribed frequently for plantar fasciitis. Although they are effective as a pain medication, they do little to accelerate recovery from plantar fasciitis. Pathology studies of surgical specimens show degeneration, fragmentation, and revascularization but little evidence of acute or long-term inflammatory changes.

Corticosteroid injections are effective for relieving acute pain in patients with plantar fasciitis. Corticosteroids work by modulating the production of inflammatory and anti-inflammatory proteins within the cell. The long-term effect of these injections on plantar fascia is less well understood, and no or incomplete relief often is seen several days or weeks after the procedure. The injections are associated with rupture of the plantar fascia and atrophy of the fat pad of the heel and, thus, should be used judiciously.

Rocker-soled shoes reduce pressure on the forefoot and often help reduce plantar fascial pain. However, this comes at the expense of increased ankle motion, shoe weight, and instability. Arch supports are another effective method of treatment, but no clear increase in satisfaction is demonstrated with custom arch supports compared with less expensive prefabricated inserts. Whether these types of footwear changes are helpful preventive measures in otherwise healthy feet is uncertain.

“A rational approach to management of plantar fasciitis begins with identification of the possible causes of the connective tissue irritation”
Surgery
Surgical release of the plantar fascia is indicated for severe plantar fascial pain after prolonged attempts at non-operative treatment have been made. Usually, a portion (one-third to one-half) of the fascia is cut. The American Orthopedic Foot and Ankle Society and the American College of Foot and Ankle Surgeons have recommended 6 months of non-operative management before this step is considered. The connective tissue may be released endoscopically (using a fiberoptic scope) or through an open approach. The ultimate results are comparable. In patients who have undergone excessive (more than 50%) fasciotomy, results have been poor. The progressive loss of the windlass effect may lead to a risk of midfoot pain and stress fractures in these patients.

Investigational Treatments
Many intriguing new approaches to treatment-resistant plantar fasciitis are under investigation. Although their effectiveness is questionable, many physicians are incorporating them into their practices. Because traditional treatment is time-tested and cost-efficient, evidence of clear superiority of these newer techniques is necessary before they should be accepted as mainstream treatments.

The machine used for managing musculoskeletal disorders with extracorporeal shock wave therapy (ESWT)—the application of high-intensity pulses of ultrasonic energy—was modified from designs that were used successfully to break up kidney stones. The US Food and Drug Administration approved ESWT in 2000 for the treatment of patients with plantar fasciitis who did not improve with conservative therapy. The initial results of controlled studies indicated that such treatment is moderately effective and has few adverse effects, although it did require general or local anaesthesia.

A later, well-publicized study disputed the findings of a beneficial effect with this treatment. Criticism of this report included patient selection (many of the subjects had pain for a brief period) and the low-energy technique used. Many well-controlled, blinded, randomized studies have since reported encouraging results. The results achieved with this procedure probably vary greatly with the device used and the amount of energy delivered. Interest in this treatment seems to be waning.

Botulism toxin injection has been used frequently for cosmetic purposes and in the management of neuromuscular disorders. Such injection also has been used off-label for musculoskeletal disorders, including lateral epicondylitis, low back pain, and plantar fasciitis. Injection into the plantar fascia has been shown to provide significant pain relief. Whether the mechanism of the pain relief involves paralysis of the irritated intrinsic muscles near the heel or a direct analgesic effect is not clear. Because the studies evaluating botulism toxin injection have been small and uncontrolled, endorsement awaits validation from larger, higher-quality investigations.

The use of autograft whole-blood injections has fallen out of favour, but currently there is considerable interest in the use of platelet-rich plasma (PRP) in the management of a wide variety of musculoskeletal complaints. This preparation is separated from whole blood after it has been centrifuged. The buffy coat layer, which contains the platelets, is isolated from the serum and red blood cells. However, there have been no good published studies to support the use of PRP.

Despite the lack of clear proven...
indications for PRP, its use in the community seems to be increasing. Some of the demand may be fueled by reports of high-profile athletes with various musculoskeletal injuries having received successful treatment with PRP. This treatment can be quite expensive and often is not covered by insurances. Although no published studies are available in peer-reviewed journals supporting the use of PRP in plantar fasciitis, one placebo-controlled study showed no significant effect in patients with Achilles tendinopathy.19

With radiofrequency microtenotomy—the perforation of tissue with a radiofrequency probe during surgical, percutaneous, or endoscopic exposure—the mechanical disruption is less than with that of the use of plantar fasciotomy. This may reduce the possibility of midfoot pain, or ‘lateral column syndrome’, which complicates plantar fasciotomy postoperatively. Although radiofrequency microtenotomy has been available on the market for more than 10 years, the literature currently evaluating it consists of only small case series.

Studies comparing the results of this procedure with those of more conventional surgical fasciotomy procedures are necessary before it can be recommended as an alternative. None are currently available.

Large, Well-controlled Trials Needed

Although plantar fasciitis may lead to considerable and prolonged pain in a few cases, it often improves spontaneously. Therefore, large, well-controlled trials are necessary before new therapies should be adopted as standard practice. Although many promising treatments for plantar fasciitis are on the horizon, widespread use of these modalities should be reserved to controlled clinical trials until their usefulness is proved definitively.

References


About the Author

Dr Fink is an orthopaedic surgeon who specializes in foot and ankle surgery at the Indiana Orthopedic Center in Indianapolis, USA.
This continuing medical education service is brought to you by the Medical Progress Institute, an institute dedicated to CME learning. Read the article ‘Management of Plantar Fasciitis Evolving’ and answer the following questions. Answers are shown at the bottom of this page.

**CME Article:**

**Management of Plantar Fasciitis Evolving**

Please answer True or False to the questions below.

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<tbody>
<tr>
<td>1. Arch pain is a common complaint among patients with plantar fasciitis.</td>
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<td>2. Obesity and poor ankle flexibility are associated with plantar fasciitis.</td>
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<td>3. Vigorous massage has been shown to be effective for severe pain in patients with plantar fasciitis.</td>
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<td>4. Deep tissue massage techniques, although used frequently, have not been proven effective.</td>
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<tr>
<td>5. Non-steroidal anti-inflammatory drugs are effective for heel pain, but do little to hasten recovery from plantar fasciitis.</td>
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<td>6. Corticosteroid injections are effective for relieving stress fractures in patients with this heel disorder.</td>
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<td>7. Rocker-soled shoes increase pressure on the forefoot and often increase plantar fascial pain.</td>
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<td>8. Twelve months of non-operative management is recommended before surgery can be considered in patients with plantar fasciitis.</td>
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<td>9. Extracorporeal shock wave therapy is approved for use in patients with plantar fasciitis who do not respond to conservative therapy.</td>
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<tr>
<td>10. Previous studies do not support the use of platelet-rich plasma for the treatment of various musculoskeletal injuries.</td>
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