Drugs for diabetes: part 9 prescribing for patients with cardiac disease

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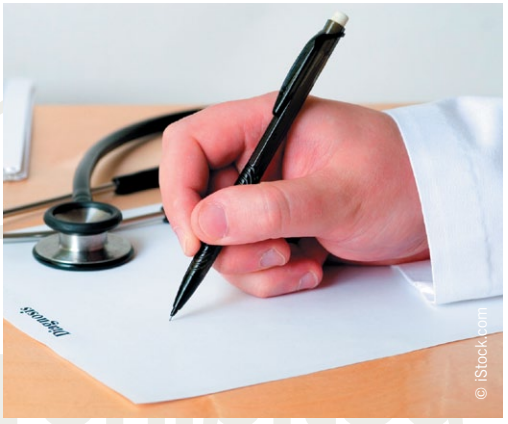
Up to one-third of patients with heart disease have diabetes. Cardiological status should be considered when deciding on treatment for diabetes. Patients with stable coronary disease can be treated with metformin, sulphonylureas or pioglitazone. Following an acute coronary syndrome, intensive insulin therapy with multi-dose insulin has been shown to reduce mortality, and longer-term treatment with pioglitazone may reduce recurrent events. There is little trial information for glycaemia control in patients with chronic heart failure, and metformin and insulin are both frequently used. Dipeptidylpeptidase-4 (DPP-4) inhibitors are new oral antidiabetic drugs, which are weight neutral, and the injected glucagon-like peptide-1 (GLP-1) receptor agonists reduce weight. Long-term outcome studies are awaited to see if they have cardiovascular advantages in any particular group of patients.

Introduction

The incidence of diabetes is rising rapidly and patients with diabetes have a significantly increased risk of developing cardiovascular disease. The approach to the treatment of hyperglycaemia in patients with type 2 diabetes is evolving with the introduction of new medications. Intensive glycaemic control is desirable to limit microvascular complications,[1] but, in those with established diabetes, aggressive blood-glucose lowering may be detrimental.[2] The oral antidiabetic drug, rosiglitazone, has recently been removed from the European market due to its perceived lack of cardiovascular safety. In 2008, the Food and Drug Administration (FDA) issued recommendations that all new drugs for diabetes should provide data regarding cardiovascular safety, in addition to glycaemic control, prior to approval. It is important to consider both the impact on glycaemic control and cardiovascular risk when prescribing drugs for diabetes.



Stable coronary heart disease

The approach to diabetes management in patients with stable, established coronary heart disease is similar to those with no cardiac history. The cardiovascular risk associated with diabetes means that use of statins and angiotensin-converting enzyme (ACE) inhibitors is standard above the age of 40 years (**table 1**). When considering glycaemic control, a glycosylated haemoglobin (HbA_{1c}) target of 7% or 53 mmol/mol is generally accepted in the UK.[3]

Type 1 diabetes

Type 1 diabetes requires exogenous insulin treatment and metformin is used in some cases as an insulin-sensitising agent. Insulin can be delivered as a twice-daily fixed mixture or with multiple-daily injections (MDI) of basal and prandial insulin or even as a continuous subcutaneous insulin infusion (CSII). The newer insulin analogues allow people with type 1 diabetes improved glycaemic control with less hypoglycaemia but have not shown prognostic benefit in type 2 diabetes.[4]

The Diabetes Control and Complications Trial (DCCT) examined the impact of intensive glycaemic control in patients with type 1 diabetes for less than 10 years on microvascular and macrovascular events over an average of 6.5 years, compared with standard care.[1] The Epidemiology of Diabetes Interventions and Complications (EDIC) trial followed this group for a further 10 years. The intensive group had a 42% reduction in any cardiovascular event and a 57% reduction in nonfatal myocardial infarction (MI), stroke or

Table 1. Considerations in the management of diabetes according to cardiovascular status

	No known vascular disease	Stable CHD	ACS and myocardial infarction	Chronic heart failure
Glycaemia	Intensive treatment with metformin, sulphonylurea or pioglitazone	Intensive treatment, consider treatment with pioglitazone	Intensive treatment with multi-dose insulin, pioglitazone	Metformin, insulin
Cholesterol	Simvastatin 40 mg or atorvastatin 10 mg	Consider atorvastatin 80 mg	Atorvastatin 80 mg	Consider omega-3-acid ethyl esters capsules
Blood pressure	ACE inhibitor, calcium channel blocker or diuretic	Beta blocker or calcium channel blocker for symptom control	Beta blocker for prognosis	Beta blocker for prognosis
RAS inhibition (ACE inhibitor or ARB)	For blood pressure or microalbuminuria	ACE inhibitor or ARB for prognosis	ACE inhibitor for prognosis	ACE inhibitor or ARB for prognosis
Antiplatelet drugs	None	Aspirin (or clopidogrel)	Aspirin plus clopidogrel	
Other drugs		Ivabradine	Eplerenone	Ivabradine, eplerenone

Key: ACS = acute coronary syndrome; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CHD = coronary heart disease; RAS = renin-angiotensin system

cardiovascular death.[5] These benefits were retained despite returning to standard care after DCCT and have been referred to as 'metabolic memory' or 'legacy effect'.

Type 2 diabetes

For patients with type 2 diabetes, treatment requires more consideration due to the increasing choice of medications available and the recent conflicting evidence regarding intensity of diabetes control. Additionally, there is now significant focus on cardiovascular risk management as well as glycaemic control (**table 1**).

The UK Prospective Diabetes Study (UKPDS) and its 10-year follow-up showed that early intensive glycaemic control, this time in type 2 diabetes, would also lead to later cardiovascular benefit or 'legacy effect' despite relaxation of HbA_{1c} target outside of the study.[6] Patients with coronary heart disease were excluded from the UKPDS at baseline, but on follow-up MI was the most common cause of death.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial set out to assess whether intensive glycaemic control in patients with established type 2 diabetes, cardiovascular disease, or high cardiovascular risk would provide cardiovascular benefit. ACCORD was terminated prematurely due to increased mortality in the intensive control group.[2] This trial has resulted in considerable debate because of this unexpected outcome. In drawing conclusions there are a few points to consider: there was widespread use of the thiazolidinedione rosiglitazone, which is no longer available on the European market due to cardiovascular risk, the intensive group were very aggressively treated and HbA_{1c} lowered over a short time period with a target of 6% or 42 mmol/mol, and the people within the intensive group who had higher mortality were those who did not achieve target.[7] Another large trial assessing intensive glycaemic control in a similar group of patients, the Action in Diabetes and Vascular disease: preterAx and diamicroN mr Controlled Evaluation (ADVANCE) trial, demonstrated benefit with intensive control on a composite microvascular and macrovascular end point.[8] In this trial, the target HbA_{1c} was 6.5% or 48 mmol/mol and the time allowed to achieve this was more relaxed. This approach may be more acceptable for patients with greater than 10 years of type 2 diabetes.

Management of type 2 diabetes must be holistic and includes education, lifestyle intervention and medication. There are now several newer antidiabetic drugs available, in addition to the well-established metformin, sulphonylureas and insulin. The newer agents include oral dipeptidylpeptidase-4 (DPP-4) inhibitors and injected glucagon-like peptide-1 (GLP-1) agonists.

Metformin is the first-choice medication in type 2 diabetes.[9] It improves glycaemic control by increasing insulin sensitivity and reducing gluconeogenesis in the liver.[10] Data from the UKPDS showed metformin to have similar effect on glycaemia to sulphonylurea and insulin, but it had a greater risk reduction for diabetes-related death and MI in overweight subjects.

Sulphonylureas, which stimulate pancreatic insulin secretion, and insulin are associated with hypoglycaemia and weight gain, both are side effects that can increase cardiac stress in diabetes.[4,11] In UKPDS, the sulphonylurea gliclazide was found to have a non-significant risk reduction for MI. Insulin is reserved for third-line treatment in type 2 diabetes and when introduced should be a once-daily long-acting dose.

Glitazones

In 2010, rosiglitazone lost its European recommendation and the FDA significantly restricted its use in the USA. This was in response to data from a large meta-analysis which found that rosiglitazone was associated with a significant increase in MI.[12] There are some conflicting data available as the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial found an increased risk of heart failure

with rosiglitazone but not an association with cardiovascular death, and the trial was inconclusive regarding MI.[13]

Pioglitazone, the other thiazolidinedione, acts on peroxisome proliferator-activated receptor-gamma (PPARγ) receptors to increase insulin sensitivity;[14] it has had somewhat more favourable cardiovascular outcomes. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) sought to show cardiovascular benefit from pioglitazone. It did not meet its primary end point, but a main secondary end point of all-cause mortality, stroke, and MI was significantly reduced and subgroup analysis found benefit in high-risk patients who had previous MI.[15,16] A common side effect of pioglitazone is fluid retention, and this may cause heart failure in those at risk, subgroup analysis did not show any associated increase in mortality.[17]

The FDA mandated a trial comparing rosiglitazone and pioglitazone on cardiovascular outcomes. The Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial had just started recruiting patients when it was stopped prematurely by the FDA: 16,000 patients were to be randomised using a 3 x 2 design (the other part of the study comparing Vitamin D and placebo). Only 1,332 subjects were in the study when it was terminated by the FDA because of ongoing concerns about the cardiovascular safety of rosiglitazone, so no conclusions can be made either about rosiglitazone compared with pioglitazone, or about possible benefits of vitamin D on cardiovascular outcomes in patients with diabetes.

Incretin-based therapies

The DPP-4 inhibitors and GLP-1 receptor agonists are both classes of drug working on the incretin system, which amplifies insulin secretion in response to oral carbohydrate intake.[18,19] They are attractive treatment options for type 2 diabetes given that they have low risk of hypoglycaemia, similar effect on HbA_{1c} and do not cause weight gain.

DPP-4 inhibitors, such as sitagliptin, vildagliptin and saxagliptin, were found to non-significantly reduce cardiovascular events in a recent meta-analysis.[20] Several large randomised-controlled trials of cardiovascular safety are ongoing, including one designed to show non-inferiority of sitagliptin versus placebo and one to show superiority of saxagliptin over placebo.

GLP-1 receptor agonists, such as exenatide and liraglutide, require subcutaneous injection and commonly cause weight loss. Additional potential cardiovascular benefits exist as they have been shown to reduce blood pressure independently of weight loss, and may have other direct effects upon the cardiovascular system.[21,22]

Acute coronary syndromes

The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study was a trial of intensive insulin following acute MI in patients with diabetes, which found a prognostic benefit of acute insulin-glucose infusion followed by at least three months of subcutaneous insulin.[23] DIGAMI-2 was set up to establish whether the benefit came from the acute intravenous insulin or the three months of intensive subcutaneous insulin by having three trial groups. Unfortunately, no significant difference was demonstrated between the patients receiving routine management, those with acute insulin or those with three months of intensive insulin treatment, but trial numbers were small and by the end most of the patients in each group were on the same intensity of treatment.[24]

Recent National Institute for Health and Clinical Excellence (NICE) guidance has been published on the management of hyperglycaemia in acute coronary syndrome.[25] Hyperglycaemia is common in patients who do not have a diagnosis of diabetes and is a risk factor for future development of diabetes. NICE advise that hyperglycaemia should be avoided with blood glucose target of less than 11 mmol/L for the 48-hour period following an acute event. The method for this glycaemic control is patient dependent, but a dose-adjusted insulin infusion should be considered with regular blood glucose monitoring and avoidance of hypoglycaemia.

Following the first 48 hours of care, the choice of antidiabetic drugs will depend on the clinical picture and pre-existing diabetes control. Patients with type 1 diabetes and poor control may have increased interest in intensifying their insulin, perhaps from twice-daily mixed insulin to multiple-daily injections with the option of carbohydrate counting. There will be a group of patients with type 2 diabetes who require insulin following acute coronary syndrome to achieve glycaemic control, but many will go back to their usual regimen.

NICE advises that patients with hyperglycaemia but no known diabetes should have HbA_{1c} checked as an inpatient, then a fasting glucose following discharge (more than four days after event). Lifestyle advice should be given and warning about future risk of diabetes, which should be screened for annually.

Patients known to have diabetes will require a review of their medication. For those on metformin there is concern regarding the potential risk of lactic acidosis when given at times of tissue hypoxia, but there is no conclusive evidence to suggest metformin should not be used following MI.[26] If metformin is the sole agent, it is also important to consider the glycaemic impact of removal peri-angiography when the contrast load in combination with metformin may potentially lead to renal impairment and lactic acidosis.

Other medications used in type 2 diabetes may require adjustment. Gliclazide and other sulphonylureas have not been associated with either increased or decreased mortality post-MI.[27] Pioglitazone may reduce rates of recurrent MI but may also precipitate cardiac failure.[16,17] There are no available data regarding GLP-1 agonists and DPP-4 inhibitors in patients following acute coronary syndromes.

Chronic heart failure

People with diabetes have a higher incidence of chronic heart failure and are more likely to develop heart failure at a younger age.[28] Poor glycaemic control, blood pressure and obesity are modifiable factors that contribute to risk of cardiovascular disease. It may be opportune to consider glycaemic control when managing patients with heart failure, many of whom will have co-existent renal failure.

Concerns about the use of metformin in heart failure exist due to the potential to develop lactic acidosis in hypoperfused states, and it is common practice to discontinue metformin during episodes of acute heart failure. There are no randomised-controlled trials looking at metformin in heart failure, but observational data suggest a decrease in mortality and lower heart failure re-admission rates when compared with placebo.[29] In a retrospective cohort study of

more than 5,000 people starting medication for diabetes, high-dose sulphonylurea was found to produce a higher risk of developing heart failure than metformin or low-dose sulphonylurea.[30]

Thiazolidinediones are the main class of diabetes drug to be avoided in patients with cardiac failure due to side effects including fluid retention.[14] A meta-analysis of thiazolidinediones found a relative risk of 1.72 for heart failure with greater risk associated with rosiglitazone than pioglitazone.[31] Pioglitazone is associated with increased symptomatic heart failure, but, interestingly, not an increase in mortality.[17]

GLP-1 agonists have some promising data from animal studies suggesting an ability to improve left ventricular function. The addition of modest blood-pressure-lowering effects potentially elevates the desirability of these agents over insulin as an injectable therapy, although more studies are required.

Despite its associated weight gain, there is no direct evidence of insulin worsening heart failure in the majority of patients. Data from studies using acute insulin in cardiac patients such as DIGAMI, DIGAMI-2 and the Hyperglycaemia: Intensive Insulin Infusion in Infarction (HI-5) trial show either no increase in heart failure or a reduction in heart failure.[23,24,32] Insulin is also likely to be used in type 2 diabetes in the presence of severe insulin resistance, which itself is associated with left ventricular dysfunction.[33] There are a few case reports of individuals who had marked sodium and water retention when starting insulin therapy, but this is very rare.

Conclusion

Cardiovascular disease is arguably the most important complication of diabetes and is an important outcome in clinical trials as new drugs for diabetes must now prove their cardiovascular safety prior to approval. Many of the well-established diabetes medications do not have the benefit of strong cardiovascular safety data, rather they demonstrate the ability to control diabetes with the surrogate glycaemic marker HbA_{1c}. Recent large trials assessing the impact of glycaemic control on cardiovascular risk highlight the importance of individualised care and addressing other modifiable cardiovascular risk factors in order to gain long-term benefit

Conflict of interest

MF has served on advisory boards for AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Serono, MSD, Novartis, Novo Nordisk, Roche, Sanofi Aventis and Takeda. GAMcK has served on advisory boards for Boehringer Ingelheim and Eli Lilly. AW: none declared

Key messages

- Patients with diabetes and stable coronary disease should be treated to a target HbA1c of 7.0% (53 mmol/mol) avoiding hypoglycaemia and weight gain; pioglitazone may be useful but causes weight gain. Longer-term safety data for incretin-based therapies is awaited
- Following acute coronary syndromes, patients should be treated with intravenous insulin followed by multi-dose subcutaneous insulin for at least three months
- Glycaemic control in patients with diabetes and chronic heart failure requires further investigation; metformin can be used in stable patients

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BOOK REVIEW

Book review

Ultrasound in clinical diagnosis. From pioneering developments in Lund to global application in medicine

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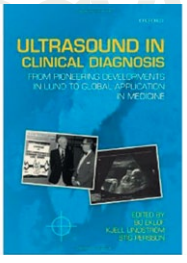

Ultrasound, like X-ray, has penetrated almost all fields of clinical medicine as a valuable diagnostic tool. Attempts have even been made to use it for therapeutic purposes. Although the history of the development of medical ultrasound has been relatively short, the application of ultrasound in clinical practice is irreplaceable by any other existing technology. Not only is it a feasible technique for the medical profession to use in any field they choose, it is also harmless to patients.

Understanding the history of ultrasound in medicine helps those who are interested in comprehending its practical significance and the potential for future development. The publication of this book is timely as most pioneers in this technique still have a fresh memory and can fill our knowledge gaps in this most commonly used diagnostic technique.

This book is the result of a collective effort by 25 contributors who are enthusiasts and practitioners in the field. It covers, in detail, the germination of medical ultrasound and the painstaking early experiments. It takes readers through cardiology, neurology, obstetrics and gynaecology, vascular disease, ophthalmology and otorhinolaryngology. It also includes the relation of ultrasound with radiology, new technology in ultrasound, and industrial developments. There are many photographs and illustrations, some of which are of real historical significance and have inspired generations of scientists and clinicians in the field. A drawback, however, is there is much repetition and overlap in content, which can be inevitable in a book with multi-authorship.

Overall, this is a valuable book for those who are interested in ultrasound, either in its clinical application or in further development of its potential. It can also serve as interesting and educational reading material for medical trainees, medical students and the wider audience.

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