Rational treatment and monitoring in type 2 diabetes

Implications for pharmacists

Type 2 diabetes is common, on the increase, and its management consumes a significant amount of health care resources. On the one hand there is unmet need, and on the other, current spend may not be achieving the greatest possible health gain nor be good use of scarce resources. Managing blood glucose is part of the overall management of type 2 diabetes, but arguably not the most important part.[1] Self-monitoring of blood glucose (SMBG) is common in type 2 diabetes and the testing strips are expensive. A new study adds to the evidence base showing that routine SMBG in non-insulin users is not appropriate.[3]

Glitazones are an option to lower blood glucose levels. However, they have been linked with increased risk of heart failure and fractures (in women). A new meta-analysis suggests that rosiglitazone may also increase the risk of myocardial infarction.[4] Peter Burrill looks at the evidence for routine SMBG and glitazone use in type 2 diabetes.

FIRST PAPER[3]

Farmer A, Wade A, Goyder E, Yudkin P, French D, Craven A, Holman R, Kinmonth A-L, Neil A. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial (DiGEM). *BMJ* published online 25 June 2007.
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Context

Large trials of the management of patients with type 1 diabetes have incorporated self-monitoring of blood glucose (SMBG) as an essential part of self-management and it is accepted practice. There is some evidence that self-monitoring for insulin treated patients with type 2 diabetes can be beneficial, but optimisation of its use may be possible. A systematic review, by Welschen and colleagues, did not find that SMBG in people with type 2 diabetes not using insulin improved glucose control by a clinically relevant degree.[2] Blood glucose monitoring is expensive and a large amount of scarce NHS resource is used up each year providing the strips. Consensus guidelines have based recommendations for SMBG on a theoretical potential to better self-manage glycaemic control. This UK study tested whether SMBG, with or without instruction in incorporating findings into self-care, compared with standardised usual care can improve glycaemic control in patients with non-insulin treated diabetes.

The research[3]

The DiGEM study[3] was a four-year open, randomised, three arm, parallel group trial with sequential recruitment of patients from general practices in Oxfordshire and South Yorkshire.

Primary outcome measure

The primary aim was to determine whether HbA1c levels at 12 months were significantly different between patients with non-insulin treated type 2 diabetes receiving one of three allocated interventions. These were:

- standardised usual care with measurement of HbA1c levels by health professionals every three months (control group)
- use of a blood glucose meter (3 times daily on 2 days each week), with advice for participants to contact their doctor for interpretation of results, in addition to usual care (less intensive self-monitoring group)
- use of a blood glucose meter with training in self-interpretation and application of the results to diet, physical activity, and drug adherence (more intensive self-monitoring group). Participants were encouraged to experiment with the frequency of monitoring.

Secondary outcomes

Secondary outcomes were blood pressure, weight, total cholesterol level, ratio of total cholesterol to high density lipoprotein cholesterol (HDL-C) and body mass index (BMI). Patients in each arm of the trial received feedback on glycaemic control, which was used to explore success of goals and to set new ones. The patient's doctor was notified of all HbA1c results and asked to consider changes in drugs in line with the NICE diabetes guidelines for all patients. The doctor was also notified if blood glucose readings were consistently greater than 15mmol/l.

The trial was properly powered, appropriately randomised with concealed allocation, and with an intention-to-treat analysis. It was not funded by the pharmaceutical industry.

Key findings

Baseline personal and clinical characteristics were well balanced between the groups. The median (interquartile) duration of diabetes was 3.0 years (1.8–6.4 years), mean (±SD) age was 65.7 (±10.2) years, and mean (±SD) level of haemoglobin A1c was 7.5% (±1.1). Only 57 (12.6%) patients were lost to follow-up, which did not differ between groups.

At 12 months no difference was found in HbA1c levels between the groups after adjustment for baseline HbA1c levels (p=0.12). There was no evidence of difference in levels between groups over the period of follow-up (p=0.38). No differences were found in the secondary outcomes except for a small difference in total cholesterol levels between the three groups (p=0.01). The mean difference in change in total cholesterol levels from baseline to 12 months between the control group and less intensive intervention group (not adjusted for baseline) was -0.06.mmol/l (-0.26 to 0.14) and between the control group and more intensive intervention group was -0.23 (-0.43 to -0.04).

No difference was found between the groups in the proportions of patients prescribed an increase in hypoglycaemic drugs between baseline and 12 months. Also no differences were found in statin prescribing. The difference in total cholesterol levels is unlikely to be clinically significant and did not result in increased use of statins.

This appears to have been a robust study, performed in general practices in England, which has implications for local guidelines. The participants were representative of well-controlled, non-insulin treated patients with type 2 diabetes living in the community who are the target group for the current recommendations of up to twice daily self-monitoring and testing after meals.

No significant improvement in glycaemic control was found after 12 months in patients with non-insulin treated type 2 diabetes using self-monitoring of blood glucose levels when compared to those not self-monitoring. No evidence was found of a significantly different impact of self-monitoring on glycaemic control when comparing subgroups of patients defined by duration of diabetes, therapy, diabetes-related complications, and EQ-5D score (a measure of health-related quality of life). Also no evidence was found that more intensive compared with less intensive monitoring led to differences in glycaemic control. As the authors comment: 'Despite an intervention based on standards of best clinical practice and underpinned by appropriate psychological theory, we found no convincing evidence of an effect on glycaemic control'.[3]

The authors conclude: 'Routine self-monitoring of blood glucose for patients with reasonably well controlled non-insulin treated type 2 diabetes seems to offer, at best, small advantages; is not well accepted; and the cost, effort, and time involved in the procedures may be better directed to supporting other health-related behaviours. Current guidelines for the use of self-monitoring of blood glucose among patients with reasonably well controlled non-insulin treated type 2 diabetes should be reviewed.'[3]

All our interventions should be effective, cost-effective and affordable. Current evidence suggests that the routine use of SMBG in non-insulin treated diabetes does not meet these criteria.

SECOND PAPER[4]

Nissen SE, Wolski K. Effect of rosiglitazone and the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356:** 2457–71.

Context

The goal of the treatment of type 2 diabetes is to decrease cardiovascular disease — the largest cause of death in these patients. Glitazones have already been shown to increase the risk of hospitalisations for heart failure. A new study now suggests that rosiglitazone is associated with an increased risk of MI.[4]

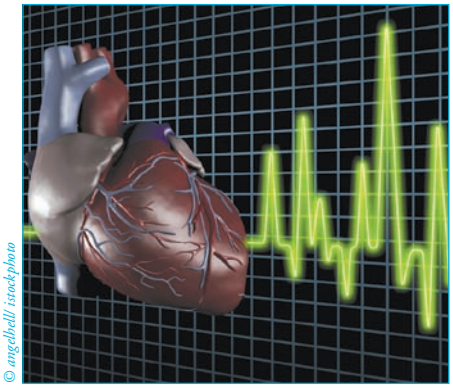
The research[4]

The authors of this meta-analysis have pooled data from 42 trials to determine if use of the drug increases the risk of MI or cardiovascular death. Since the studies were not specifically designed to evaluate cardiac outcomes, most did not describe how cardiac endpoints were determined. Most studies were between 24 and 52 weeks duration, with a typical dosage range for rosiglitazone of 4 to 8 mg/day. The average age of patients was 56 years and more than half were men; the mean HbA1c was 8.2%.

Key findings

The results showed a significant increase in the likelihood of MI (odds ratio, OR, 1.43, 95% CI 1.03 to 1.98, p=0.03) and a non-significant increase in the risk of death from cardiovascular causes (OR 1.64, 95% CI 0.98 to 2.74, p=0.06) in patients taking rosiglitazone compared with the control group. The absolute increase in risk of MI was small. On the other hand, the studies were short and most excluded patients with pre-existing heart disease, which explains the small total number of cardiovascular events in both groups. Results were similar whether the control group took placebo or an active comparator, suggesting that the increased risk of MI found in the rosiglitazone group was not a function of the protective effects of active comparator drugs.

The authors of the meta-analysis conclude: 'Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers



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should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.'[4]

The authors, in their discussion, admit that the results are based on a relatively small number of events, resulting in odds ratios that could be affected by small changes in the classification of events, but they add that the findings are worrisome because of the high incidence of cardiovascular events in people with diabetes. One potential contributing factor may be the adverse effect of rosiglitazone on serum lipids. They call for urgent comprehensive evaluations to clarify the cardiovascular risks of rosiglitazone.

The accompanying editorial to this paper recognises that the possibility that the findings were due to chance cannot be excluded.[5] The authors point out that the possibility of cardiovascular benefit associated with rosiglitazone seems remote and there are no data showing that rosiglitazone prevents microvascular disease. They conclude that the rationale for prescribing rosiglitazone at this time is unclear and call for regulatory action by the FDA.[5]

GlaxoSmithKline has responded by saying it strongly disagrees with the conclusions of the *New England Journal of Medicine* (*NEJM*) paper.[6] An unsigned editorial in the *Lancet* (2 June 2007)[7] urged waiting for further results from the RECORD study before acting on the *NEJM* papers. The *NEJM online Journal Watch Cardiology* Editor-in-Chief Harlan M. Krumholz commented on the *Lancet* editorial:[8] 'Why would you wait when Avandia has never been shown to avert events or save lives? And now that there is evidence of potential harm — and there are alternative meds — it seems to me that the pressure is on for the company to show that it is safe and effective.'[8]

The SPC for Avandia actually lists the adverse event of cardiac ischaemia as common (≥1/100, <1/10).[9]

An unplanned interim analysis of the RECORD study has been published on-line by the *NEJM* (5 June 2007).[10] The primary endpoint was hospitalisation or death from CV causes. RECORD is planned to run for 6 years and the mean follow-up of this analysis is 3.75 years.[10] The authors admit that it therefore has limited statistical power to detect treatment differences. At this moment in time there is no difference in the primary endpoint (HR 1.11 [CI 0.93 to 1.32])[10] but will this become statistically significant after 6 years? The Kaplan-Meier graphs show divergence of the lines with more primary events for rosiglitazone. There is already a doubling of the risk of heart failure with rosiglitazone (HR 2.15 [1.30 to 3.57]).[10] The three editorials accompanying this paper[11–13] all say that there is continued uncertainty about the cardiovascular safety of rosiglitazone.

An FDA alert advised that health care professionals should factor this new information into their individual treatment decisions for their patients.[14] The EMEA and MHRA have both advised that patients should not stop treatment with rosiglitazone but to discuss the medication with their doctor at their next routine appointment. No specifics are given about what the doctor should advise at this appointment.

Where does this leave us?

So what should we do? Considering all the available evidence I suggest that we should:

- maximise the use of metformin (using SR as appropriate) and avoid unnecessary use of glitazones,
- reiterate that glitazones should only be used according to the NICE guidance,
- if a glitazone is indicated, pioglitazone would appear to have a better risk/benefit ratio (and is cheaper) and should be the glitazone of choice.

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References

1. Burrill P. We must reassess our priorities and targets in type 2 diabetes. *Pharmacy in Practice* 2006; **16:** 72–8.
2. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. *Diabetes Care* 2005; 28: 1510–17.
3. Farmer A, Wade A, Goyder E, Yudkin P, French D, Craven A, Holman R, Kinmonth A-L, Neil A. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial (DiGEM). *BMJ* published online 25 June 2007. Doi:10.1136/bmj.39247.447431.BE
4. Nissen SE, Wolski K. Effect of rosiglitazone and the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356:** 2457–71.
5. Psaty BM, Furberg CD. Rosiglitazone and cardiovascular risk. *N Engl J Med* 2007; **356:** 2522-24.
6. GlaxoSmithKline response to *New England Journal of Medicine* editorials, available at: http://www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=1038.
7. Anon. Rosiglitazone: seeking a balanced perspective. *Lancet* 2007; **369:** 1834.
8. First Watch News article in which Krumholz commented on the *Lancet* editorial. *Lancet* urges 'more considered approach' to rosiglitazone controversy. Published in the e-journal *Physician's First Watch* 24 May 2007, available at: http://firstwatch.jwatch.org/cgi/content/full/2007/524/1
9. Avandia SPC. Available through http://emc.medicines.org.uk.
10. Home PD, Pocock SJ, Beck-Nielsen H *et al* for the RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes — an interim analysis. *N Engl J Med* 2007; **357:** 28–38.
11. Drazen JM, Morrissey S, Curfman GD. Rosiglitazone — continued uncertainty about safety. *N Engl J Med* 2007; **357:** 63–4.
12. Nathan DM. Rosiglitazone and cardiotoxicity — weighing the evidence. *N Engl J Med* 2007; **357:** 64–6.
13. Psaty BM, Furberg CD. The record on rosiglitazone and the risk of myocardial infarction. *N Engl J Med* 2007; **357:** 67–9.
14. FDA. Information for healthcare professionals. Rosiglitazone maleate. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazoneHCP.pdf