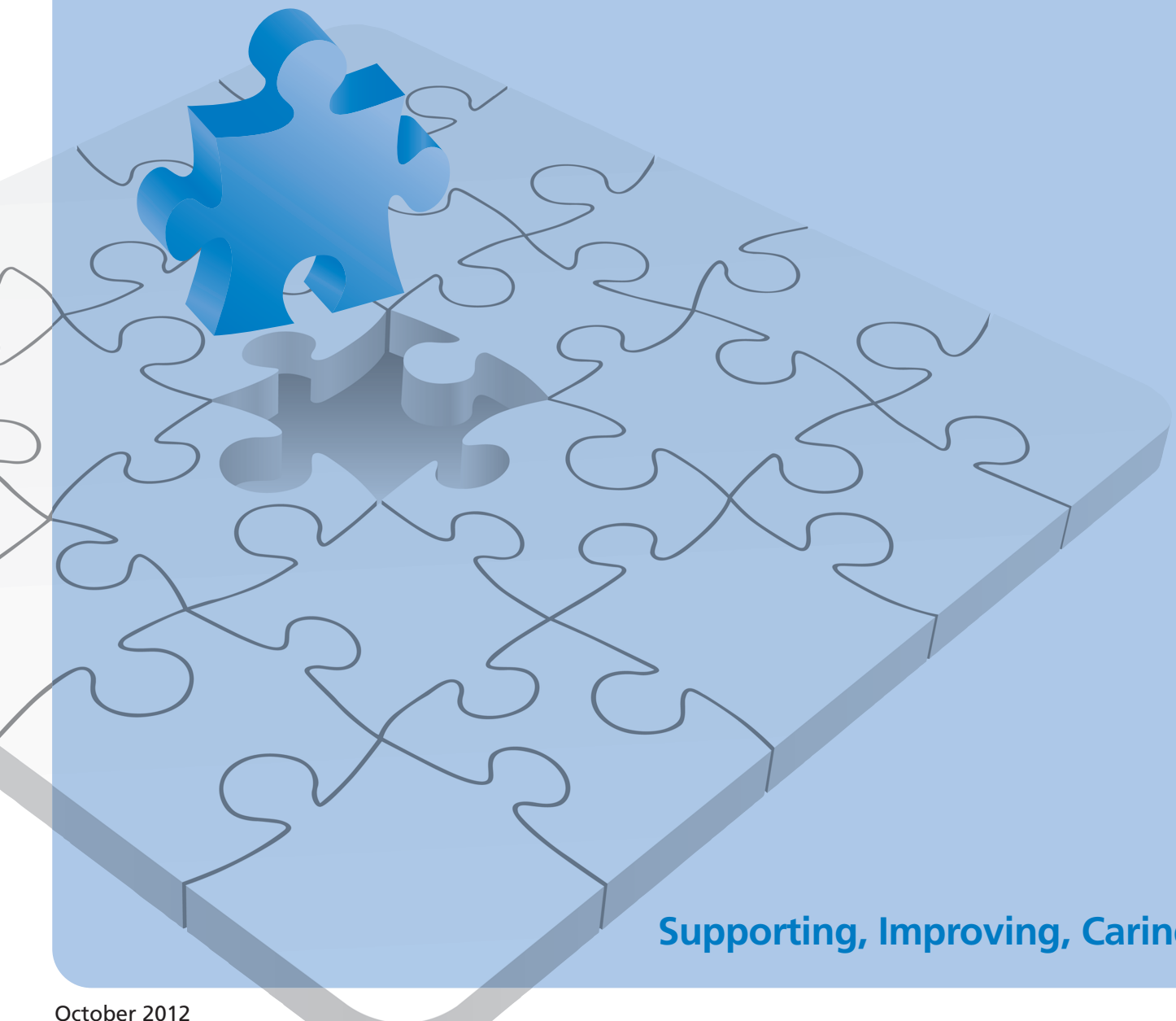
NHS

Diabetes

Optimal prescribing of glucose lowering therapy for patients with type 2 diabetes



Supporting, Improving, Caring

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Background

Diabetes is a chronic disease affecting millions of people in the UK, with nearly 41 million prescriptions for drugs used to treat diabetes issued in primary care in 2011/2 in England alone (1). In recent years the emergence of large primary care research databases has created an opportunity to address research questions in extremely large collections of data from a routine clinical setting. We used the General Practice Research Database (GPRD) and data from previously published trials to study questions of relevance to people with type 2 diabetes and their general practitioners, such as the effect of the most widely prescribed drugs and the prevalence of prescriptions for blood glucose monitoring.

Monitoring HbA1c for prescribing decisions

Diabetes is a progressive disease, and optimal management to maintain good glycaemic control in an individual with diabetes changes over time (2). Guidelines recommend regular monitoring of HbA1c to identify the need for changes in management, but diverge on the frequency at which HbA1c should be monitored. For example, NICE guidelines recommend monitoring "at 6-monthly intervals once ... stable" (3), while the Quality Outcomes Framework incentivises approximately annual monitoring (4). Work in other clinical areas such as hypertension, dyslipidaemia and HIV has shown that over-frequent monitoring may be counter-productive (5-7) and, further, that in some chronic conditions even annual monitoring may be over-frequent. Decision making about changes in management depend on being able to detect a clinically important change in a measurement from background variation (or noise). We have sought to apply similar methods to provide an evidence base for the intervals at which HbA1c should be monitored, to inform optimal glycaemic management as part of the overall care package for type 2 diabetes.

We used data from the Diabetes Glycaemic Education and Monitoring (DiGEM) study (8) to assess different sources of variation in HbA1c in people with type 2 diabetes: between-person variation, within-measurement (i.e. laboratory) variation, changes over time in an individual, and the variation between people in the time trends. We then used statistical modelling to estimate, from the trends and variations, the likely rates of positive and negative tests for HbA1c greater than 58.5 mmol/mol*. The paper by Oke et al. (9) gives more detail on these methods, on the estimates given below and the statistical uncertainty around them.

In the DiGEM cohort, the average change in HbA1c was 0.2% per month†. The rate of change varied between individuals, with a standard deviation of 0.7% per month†. The combined coefficient of variation (CV) for the biological and biochemical variation in individual HbA1c results was 4.4%.

* At the time the analysis was carried out, HbA1c units were percentages. For the purposes of this report, results have been converted to mmol/mol.

† Percentages in this section refer to relative change, not old units of HbA1c.

Table 1. The rate of positive tests, for HbA1c>58.5 mmol/mol*, per 1,000 patients, at a future test in a 6-monthly or annual monitoring programme.

	Next test is after 6 months		Next test is after 12 months	
	Positive tests per 1,000 patients	False positive tests per 1,000 patients (% of positive tests)	Positive tests per 1,000 patients	False positive tests per 1,000 patients (% of positive tests)
Current HbA1c is 56 mmol/mol	405	114 (28%)	479	76 (16%)
54 mmol/mol	283	112 (40%)	385	78 (20%)
52 mmol/mol	180	94 (52%)	296	74 (25%)
50 mmol/mol	103	66 (64%)	215	67 (31%)
48 mmol/mol	52	39 (76%)	147	54 (37%)

From these results we estimated the proportion of follow-up tests that would be positive (observed HbA1c above 58.5 mmol/mol) and, of these, the proportion that would be false positive (attributable to the within-measurement variation in HbA1c rather than the within-patient trend): see Table 1 above. For example, in patients whose HbA1c is currently 56 mmol/mol, with 6-monthly monitoring the rate of positive tests would be 405 per 1,000 patients, and of these, 28% would be false positive tests (Table 1, top row). For the same patients, with 12-monthly monitoring the rate of positive tests would be 479 per 1,000 patients, of which 16% would be false positive. As shown in the Table, with 6-monthly monitoring in some patient groups the majority of positive tests are false positive. With annual monitoring false positive tests are less frequent. We also find that, with either monitoring scheme, false negative results are relatively rare: more detail including estimates of the statistical uncertainty surrounding the results can be found in our published paper (9). The rate of change of HbA1c varies between patients, but it is typically quite slow: the average rate of change reported here corresponds to an increase of 1.2% over 6 months (note that this is a relative change, such as from 50 mmol/mol to 50.6 mmol/mol over 6 months, not old HbA1c units). As a result, for many people with diabetes, 6-monthly monitoring is more likely to yield a false-positive test – attributable to the within-measurement variability of HbA1c – than a true-positive test, attributable to the change over time in glycaemic control. Annual monitoring gives more time for a meaningful change to occur in HbA1c.

These results were obtained by statistical modelling based on observational data. Although randomised trials are often regarded as the best source of evidence, in practice monitoring and diagnostic problems require infeasibly large trials, even by modern standards (10). We did not have a 'gold standard' with which to consider which HbA1c tests in the DiGEM study were 'true positive' or 'false positive'; instead we have used modelling methods to infer the proportion of such tests that would be true or false positive, based on the variability and rate of change. For full details of standard errors, confidence intervals, and sensitivity analyses for our results, see our published paper (9), but in brief, our models serve to quantify the high rate of erroneous tests that would be expected, given that the rate of change of HbA1c is low compared with the within-measurement CV. Although the biological variability of HbA1c is relatively stable (compared with albumin:creatinine ratio, for example), all such measures are subject to both biological and assay variability, and our estimates are similar to those from other studies (11, 12).

* At the time the analysis was carried out, HbA1c units were percentages. For the purposes of this report, results have been converted to mmol/mol.

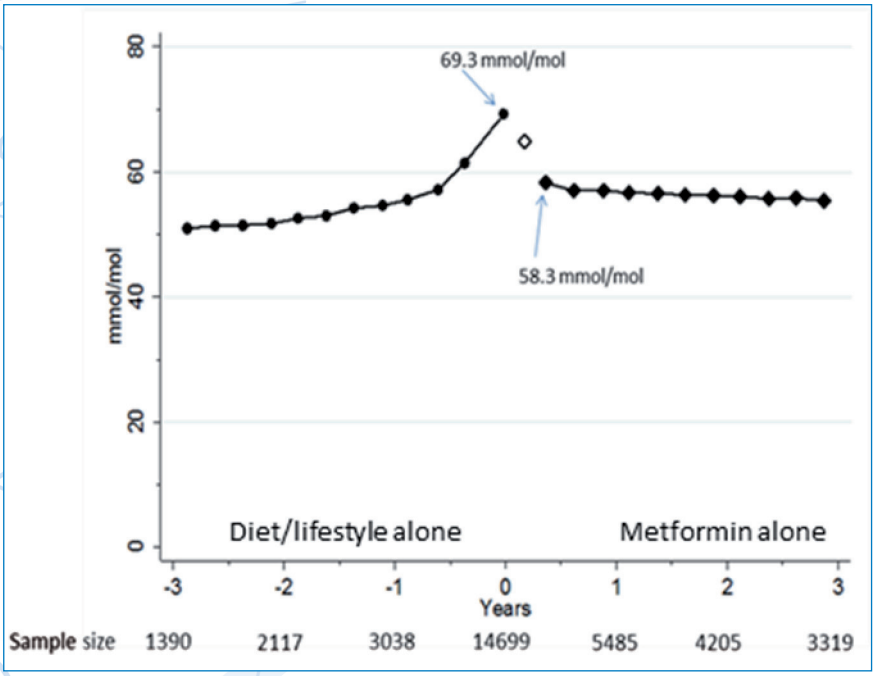
In summary, 6-monthly testing of HbA1c may be over-frequent for many patients. Annual testing would give lower rates of false-positive tests. In the context of the wider project, false-positive tests correspond to the potential for prescribing decisions, such as a dose increase or an additional medication, being made in response to a chance finding rather than a true change.

Monotherapy and combination therapy in UK general practice

We investigated the HbA1c-lowering effects of metformin and sulfonylureas in routine general practice in the UK. To do this we obtained data from the General Practice Research Database on 100,000 people with type 2 diabetes in UK general practice between 1989 and 2011. We plotted their HbA1c measurements before and after initiation of monotherapy with metformin or gliclazide, and before and after initiation of combination therapy with both metformin and gliclazide.

Figure 1 shows the mean HbA1c values at each quarter before and after initiation of metformin monotherapy in a cohort of 14,699 patients taking no prior glucose lowering treatments. The x-axis measures time to or from the last HbA1c measurement before first prescription of metformin. Thus the left part of the graph (solid circles) shows mean HbA1c while managed by diet and lifestyle alone, and the right part of the graph (solid diamonds) shows mean HbA1c while treated with metformin monotherapy. (The hollow diamond represents the mean of any HbA1c measurements taken less than three months from the first metformin prescription.)

Figure 1. HbA1c measured before and after initiation of metformin.



These results were presented (13) at the 48th annual meeting of the European Association for the Study of Diabetes in Berlin, 2012, and we can obtain similar figures for sulfonylurea monotherapy and oral combination therapy. However, this graphical method does not allow for changing doses of metformin, or for statistical artefacts created by the artificially defined 'time 0'. Randomised trial data comparing fixed metformin doses to placebo would overcome these limitations, and so we conducted a systematic review of randomised trials as described below.

Metformin and HbA1c: systematic review

A previous review (14) addressed the effects on HbA1c of inhibitors of dipeptidylpeptidase type 4 (DPP-4), thiazolidinediones ('glitazones'), and a glucagon-like peptide-1 (GLP-1) analogue, but did not include older medications, such as metformin and sulfonylureas. We conducted a review of metformin, currently the first-line oral glucose lowering therapy recommended for maintenance of glycaemic control in people with type 2 diabetes.

We searched databases of medical publications (MEDLINE, EMBASE) and clinical trials (Cochrane Library) for randomized trials, at least 12 weeks in duration, of metformin in people with diabetes. Monotherapy trials (metformin versus placebo or usual care), oral combination therapy trials (metformin plus another oral glucose lowering therapy versus the other oral glucose lowering therapy alone), and insulin combination therapy trials (metformin plus insulin versus insulin alone) were all considered eligible for inclusion. We also collected data from trials that had more than one metformin arm, to assess whether HbA1c lowering is dose related.

In 19 trials of metformin monotherapy, the average reduction in HbA1c after allocation to treatment was 12 mmol/mol* more in patients allocated to metformin than in patients allocated to placebo/usual care. In 16 trials of oral combination therapy, the average reduction in HbA1c was 11 mmol/mol more in patients allocated to metformin in addition to another oral glucose lowering therapy than in patients allocated to the other oral therapy alone. All of these trials were conducted in people with type 2 diabetes. In 7 studies comparing different doses of metformin, the reduction in HbA1c was on average 3 mmol/mol greater in the higher dose arm than the lower dose arm, for a typical dose difference of about 1000mg.

In 9 trials of metformin in combination with insulin therapy in people with type 2 diabetes, the reduction in HbA1c was 9 mmol/mol more in people allocated to metformin than in those allocated to insulin alone. We also found four trials studying metformin in type 1 diabetes, but these were in general small and subject to particular limitations. The limitations of these studies and of our analyses, the uncertainty surrounding our estimates, and limited analyses of adverse events can be found in our published paper (15).

Our results confirm that HbA1c is lowered by metformin, by about 9 to 12 mmol/mol. This is at the lower range of previously published estimates (16, 17) but similar to the best estimates of effects of newer agents (14). We have also found evidence that higher doses of metformin have a modest additional effect compared to lower doses.

* The trials studied reported HbA1c in old (%) units. Results have been converted to mmol/mol for the purposes of this report.

Sulfonylureas and HbA1c: systematic review

Following the metformin review, we have conducted a similar review of sulfonylurea trials. At the 48th Annual meeting of the European Association for the Study of Diabetes in Berlin, 2012, we reported that sulfonylureas reduced HbA1c by about 18 mmol/mol compared with placebo, or by about 6 mmol/mol when used in combination with insulin, but we could find no evidence that the effect was greater with higher doses (18). A manuscript reporting these results is in preparation.

Prescriptions for blood glucose monitoring in type 2 diabetes: trends and prevalence

The work described above addresses the relationship between prescribing decisions and HbA1c monitoring, but we have also used data from the GPRD to assess the prevalence of self-monitoring among people with type 2 diabetes in the UK. In 2011, 37% of people with type 2 diabetes had at least one prescription for blood glucose monitoring supplies and 29% had more than one prescription. The median number of prescriptions for blood glucose monitoring was 3, with quartiles 1 and 7. A report assessing how blood glucose monitoring varies by mode of diabetes treatment is in preparation.

Discussion and conclusions

These findings provide a valuable insight that may guide our expectations about response when starting glucose lowering medication. They provide us with information about average response and variation around that. In addition, the response will be affected by adherence to medication and lifestyle factors.

Six-monthly monitoring of HbA1c, as recommended by NICE Guidelines, may be over-frequent. Annual monitoring is likely to result in fewer unnecessary treatment changes.

The HbA1c lowering effects of metformin and sulfonylureas are at least comparable to those reported for newer, more expensive oral glucose lowering therapies.

Higher doses of metformin are more effective at lowering HbA1c than lower doses, but the difference between doses is small compared to the main effect of metformin. For sulfonylureas we find no evidence for a greater effect at higher doses.

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