ADOPT: Good for sulfonylureas?

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Duality of interest: PDH has provided consultation advice on behalf of Newcastle University to manufacturers of sulfonylureas, PPAR-γ agonists, gliptins, endocannabinoid receptor blockers, and metformin. He is involved in major sponsored clinical trials of some of these medications.
This article complements a paper from Kahn and Zinman which reviews the importance of ADOPT to PPAR-γ agonists. In that context this article does not seek to be a balanced view of the relative merits of sulfonylureas, metformin and thiazolidinediones.

The ADOPT study was conceived in the hope that the seemingly inexorable decline in islet B-cell function described with metformin, sulfonylureas and insulin in the UK Prospective Diabetes Study (UKPDS) might be stopped or inhibited to a major degree by PPAR-γ agonists, in particular rosiglitazone (1,2). It was already well recognized that the rapid early efficacy of sulfonylureas in lowering glucose was not retained to 12 months, and that metformin and thiazolidinediones had slow onset of action over months, so the design of the study necessarily had to enable decline of measures of blood glucose control to be assessed for a considerable period from 1 year onwards. However the extent (degree and time) to which this early efficacy of the sulfonylureas in protecting against hyperglycaemia would persist was not accurately known. The study also provided a good opportunity to compare durability of effect of the three classes of drug directly in the context some shorter-term studies published since (3).

Metformin is currently well established as first line therapy in people with Type 2 diabetes, usually after lifestyle measures fail to achieve HbA1c levels of <6.5 %, although some consensus (as opposed to evidence-based) guidelines have suggested initiation immediately from diagnosis (4,5). This review will not challenge those ideas, although the evidence is not as strong as sometimes assumed. The exceptions to first line metformin use are where metformin is contraindicated, perhaps where someone is not overweight, and where presentation glucose levels are high and the rapid effect of a sulfonylurea is needed. In situations where metformin is contraindicated, or as second line add-on therapy to metformin when target levels are no longer met, the alternative choice to a sulfonylurea would be a thiazolidinedione or possibly a gliptin (it is assumed insulin would not usually be the preference of a person with diabetes at this stage) (4,5). ADOPT was not a combination
therapy study, but a host of studies in recent years, where glucose-lowering drugs were compared in monotherapy or in various combinations, suggest that outcomes are not different except for the exacerbation of hypoglycaemia. Accordingly in this review it will be assumed that the findings of a monotherapy study (ADOPT) can be extended to the more usual role of sulfonylureas and thiazolidinediones in combination with metformin.

A valid review of ADOPT and other longer term studies of oral glucose-lowering drugs (OGLDs) is hampered by three major issues. Firstly, both the reader of the papers and the author of this review have only access to averaged data. This can disguise the true nature of the changes occurring in individual people particularly were rescue therapies are introduced and/or data are censored at some point in deterioration of glucose control (Figure 1). Secondly very high drop out rates from studies as in ADOPT are of concern, particularly where the major outcome variable might cause dropout through dissatisfaction (as in studies of blood glucose control and body weight); no amount of data snooping can provide absolute reassurance of hidden biases. Thirdly data on changes in of islet B-cell function may be problematic where an insulin secretagogue (including sulfonylureas) is being used, and with HOMA analysis once glucose control has deteriorated with time (6).

**Criteria of a successful glucose-lowering medication**

The primary purpose of ADOPT was not to answer the question as to whether any of the three medications was better overall than the others, but rather specifically to address the issue of durability of blood glucose control in the longer-term. In their analysis, the authors have not for example addressed the question of which medication gave the best control over 1, 2, 3 and 4 years. Clinically however the issue of success at varying intervals is the critical one – health in chronic disease is not judged by health outcomes at any one time (and ultimately everyone is dead), but rather by quality of life over periods of years. Furthermore the EDIC trial outcomes (in people with Type 1 diabetes) remind us that early and tight blood glucose control can effectively delay the point at which a cardiovascular event occurs (7);
that study and the epidemiological analysis of the UKPDS suggest that a useful period of
good blood glucose control in preventing a cardiovascular event (an improvement in HbA\textsubscript{1c} of
\textgreater{}1.0 %) is as short as 2 years, and would be proportionately shorter for larger improvements
(7,8).

A balance to improved overall blood glucose control are issues which might worsen health, or worsen perceived well-being. The familiar health issues which affect sulfonylureas and thiazolidinediones are putative worsening of cardiovascular outcomes (possible adverse cardiac effects on one hand, and exacerbation of cardiac failure from fluid retention on the other), and of hypoglycaemia with the sulfonylureas, together with the concerns arising from the DREAM study in regard of non-cardiac failure CV outcomes for rosiglitazone, and of osteoporotic effects (9,10). In regard of well-being the issues which arise again include fluid retention (oedema) and hypoglycaemia, but in addition body weight gain. The last may also have add-on health consequences outside the metabolic area through non-linear exacerbation of such conditions as knee osteoarthrosis and sleep apnoea, with significant impact on future quality of life.

Assessment of the success of a medication can only be made in the context of its cost-effectiveness. Newer medications, such as thiazolidinediones, are only easily available to the well insured, those in some socialist medical systems which have approved them for reimbursement, and in some countries where patent laws are not applied. Even where insurance or reimbursement are available, health care resources are not unlimited, and it behoves funders in the interest of the populations they serve to determine where a medication is properly positioned on the patient-care pathway. That issue will therefore also be addressed in this article.

In comparing glucose-lowering therapies the following questions can then be set:

1. Over time courses of 1, 2, 3, and 4 years how do sulfonylureas match up to thiazolidinediones (and metformin) in terms of amelioration hyperglycaemia (avoidance of HbA\textsubscript{1c} >6.5 %)?
2. How significant are the direct side effects of the therapies, and in particular hypoglycaemia and fluid retention, both to other health risk and current quality of life?
3. How does ADOPT impact on the concerns over cardiovascular safety of sulfonylureas (and thiazolidinediones)?
4. Of what importance are issues of weight gain, and how does the large quantitative difference between sulfonylureas and thiazolidinediones make a difference to patient choice?
5. What is the balance of cost impact and cost effectiveness issues?

Judgement on the medications

Glucose-lowering efficacy

In ADOPT blood glucose control was considerably better with the sulfonylurea than with metformin or rosiglitazone over the first 2 months of therapy, although the effect is difficult to quantify accurately as the first published data point is at 2 months, and HbA\text{1c} is a lagging measure. Nevertheless comparison of the FPG and HbA\text{1c} results would suggest that the effect of the sulfonylurea was nearly instantaneous, as the latter has already fallen markedly by 2 months, a fall 2-3 times greater than for the other medications (2).

This change is echoed over the first year (Table 1). Indeed the average blood glucose control was better with the sulfonylurea in the period 2-12 months, the intercept with the metformin line occurring at the end of 1 yr and only at 18 months with rosiglitazone (Figure 2). Notably, overall glucose control really only began to diverge between the three groups at 3 years, and in years 2 and 3 differed little between the three treatments. Accordingly average glucose control over the first 3 years was almost exactly the same for the three therapies (Table 1), with a possible slight advantage to the sulfonylureas.

None of the three therapies proved satisfactory as monotherapy in the majority of people, as judged by the mean HbA\text{1c} and a criterion of \(<6.5\%\). However the data suggest that these
agents lower HbA$_{1c}$ by around 0.5 % from the kind of baseline levels reported in the ADOPT study, a result almost exactly consistent with 18-month data from data with these groups of medications in the RECORD study (11). As an approximation it is then possible, with reservations, to use the ADOPT paper’s data on time to failure at an HbA$_{1c}$ of 7.0 % for glibenclamide alone as if it was used in combination with metformin with a failure criterion of $\geq$6.5%. This shows that on average the sulfonylurea would be successful in the ADOPT population to 2.75 years, a useful duration of effect clinically. Using the ADOPT authors secondary criterion of success in maintaining fasting plasma glucose to $<7.8$ mmol/l (140 mg/dl) as monotherapy, glibenclamide was successful at 4 years in 67 % of patients, a useful result, and far in excess of the success rates for medications in many areas of medicine.

**Therapy side effects**

The main side effects to be considered are hypoglycaemia for sulfonylureas, fluid retention and cardiac failure (CHF) for the thiazolidinedione, and other cardiovascular safety for both. This review is not concerned with the thiazolidinedione, but since the drugs do compete for a role in second line therapy (and increasingly also with the gliptins), it should be noted that the issues of fluid retention, use of loop diuretics (which carry morbidity) and bone changes with that class of drugs are confirmed by ADOPT as real, while the sceptre of an adverse non-CHF cardiovascular profile raised in the DREAM study has been ameliorated (9).

Even after subtraction of CHF events, numerically there were less CVD events in ADOPT in the glibenclamide group than in the metformin and rosiglitazone groups, namely 32, 40, and 39 patients affected respectively. Figures for myocardial infarction are 18, 27 and 23 patients respectively, with 3, 2, and 2 fatalities; data on stroke and peripheral arterial disease were unremarkable. It should be noted that these data should be interpreted as safety data and not subject to forms of statistical analysis, which would be unsafe given the low statistical power for in outcomes which were not part of the study design. Nevertheless the data does strongly suggest that long-held theoretical concerns about adverse effects of
sulfonylureas, and in particular glibenclamide, on prevention of ischaemic preconditioning in cardiac muscle are unwarranted (12).

The issue of hypoglycaemia with sulfonylureas is an important one, and in some people can have significant impact on quality of life through employment, recreation, or even falls and coma particularly in the infirm elderly (13). In the general diabetes population treated with these medications it is not such an issue, as evidenced for example by the UKPDS (1). Unfortunately the hypoglycaemia data available from the ADOPT study is very poor quality, and small in quantity. Thus hypoglycaemia was not confirmed by a plasma glucose measurement as is usual in insulin studies, so that a prevalence rate (patients affected) of around 10-12 % was recorded even for people on rosiglitazone or metformin monotherapy. Subtraction of this figure suggests that perhaps 28 % of people on glibenclamide might have had hypoglycaemic symptoms, and just 0.6 % an investigator-defined serious event, at some time during the 5 years of the study. It is not possible from the data given to calculate the event rate (episodes per year), or the number of people with a recurrent problem.

Glibenclamide is easily the most notorious member of its class as far as hypoglycaemia is concerned, not just in clinical practice but also in terms of national serious adverse event reporting, particularly in association with renal disease (12,14). Indeed this is one reason it is often chosen as a comparator in oral therapy drug trials, the other being its continued widespread usage globally. Data on the extent of this problem is difficult to come by, but the incidence of events is probably 2-10 times higher than with other sulphonylureas (12). In the 2-year pioglitazone-gliclazide study gliclazide seems to have been associated with 10-13 % of patients having an event in 2 years (n=952 exposed), with no mention of events giving rise to serious health problems (3). The UKPDS used only the two drugs with the worst reputation in this field (glibenclamide and chlorpropamide) finding a serious hypoglycaemia rate of around 0.5 % of patients per year (1). The impression then is that ADOPT does not worsen our impression that hypoglycaemia is a problem in only in a minority of people using
sulfonylureas, and that careful choice of agent and self-monitoring are important in avoiding the issue in routine clinical practice.

Weight gain

The body weight trajectory in participants randomized to glibenclamide in ADOPT is reassuring (unlike that for the thiazolidinedione) and cannot really be called a side effect. Again it must be noted that stimulation of appetite is a particular problem with glibenclamide compared to other sulfonylureas, due to its hypoglycaemic tendency around lunch-time in people in good blood glucose control. Initial weight gain appears (graphically) to be 2.5 kg in around 1 year, not inconsistent with the average improvement of 0.8 % in HbA$_1c$, and entirely consistent with amelioration of urinary glycosuria and a >10 % reduction in blood glucose concentration driven glucose metabolism (15). Thereafter body weight fell slowly over the rest of the study, consistent with the slow deterioration of blood glucose control and secular trends of weight with age in the general population. This was true despite stimulation of endogenous insulin secretion, which by HOMA analysis was nearly normalized by glibenclamide at 6 months (this assumes equivalence between the ADOPT and Oxford insulin assays) and remained above baseline and numerically higher than for the other medications out to 4 years.

This weight change would not then be expected to have any adverse metabolic effect. Little confirmatory information is available from the study itself, though overall insulin sensitivity seems to have improved with glibenclamide during the study. Data on lipids are not available through the study, but at 4 years serum LDL cholesterol concentration was not different from metformin, though HDL cholesterol marginally (3 %) lower.

In cosmetic terms a weight gain of 2.5 kg in one year is a minor but significant problem, but stabilization of body weight over a period of 4 years subsequently is likely to be welcomed by many people with diabetes.

Costs and cost-effectiveness
Costs of diabetes care are coming into ever sharper focus at present driven by three issues. The first of these is the welcome acknowledgement of the reality that the real costs of diabetes come from failures of preventative medicine, that is when the complications develop. The second is the expanding prevalence of diabetes, driven by overeating and underactivity, together with increase life expectancy through better application of those preventative measures and the longer survival of people developing diabetes at a younger age (16). But the third issue is the increased costs of new technologies, notably medications and methods of giving them. To put this in perspective, in the uncomplicated patient, items such as insulin pumps, inhaled insulin, new oral agents, new anti-platelet drugs, and new lipid lowering drugs can easily double or triple the total costs (not just the drug costs) of diabetes care.

ADOPT is positive for sulfonylureas because the sister drugs of glibenclamide such as gliclazide and glipizide are widely available at generic prices, while having a better safety profile in regard of hypoglycaemia (12). Put another way, over 3 years the glucose-lowering effect may be identical to a thiazolidinedione, but the cost:glucose-lowering ratio is some six times or so better for the sulfonylurea. At present the comparative side effect profiles would not suggest that any added costs of therapy were higher for the sulfonylurea, and perhaps the reverse. The only thing that could change this analysis would be demonstration of a fundamental improvement in preservation of islet B-cells that could reduce the need for further (expensive) therapies later in the course of the disease, but meanwhile the argument is more around the order of use of the therapies second or third line.

**Conclusions**

ADOPT is good news for sulfonylureas. In the guise of glibenclamide they are found to be safe, very effective initially, and equally effective over 3 years to the competitor medications. Weight gain is moderate and physiological, and insulin sensitivity and islet B-cell function are not adversely affected. They remain inexpensive and highly cost-effective (17,18). But
combination therapy with metformin will be needed for most people within the first year of from diagnosis, if glucose-control targets are to be met.

References


Table 1. Blood glucose control with glibenclamide (glyburide) compared to metformin and rosiglitazone in the ADOPT study (1)

<table>
<thead>
<tr>
<th></th>
<th>glibenclamide</th>
<th>metformin</th>
<th>rosiglitazone</th>
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<tbody>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
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<td></td>
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<tr>
<td>mean in year 1 (%)</td>
<td>6.5</td>
<td>6.7</td>
<td>6.8</td>
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<td>mean in year 2 (%)</td>
<td>6.8</td>
<td>6.7</td>
<td>6.8</td>
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<tr>
<td>mean in year 3 (%)</td>
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<td>6.9</td>
<td>6.8</td>
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<tr>
<td>3-yr mean</td>
<td>6.7</td>
<td>6.8</td>
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**HbA1c <7.0 %**

- at 4 yr (% patients) 26 36 40
- time to ≥7.0 % (yr) 2.75 3.75 5.00

**FPG <10.0 mmol/l (180 mg/dl)**

- at 3 yr (% patients) 84 92 93
- at 4 yr (% patients) 78 88 90

**FPG <7.8 mmol/l (140 mg/dl)**

- at 4 yr (% patients) 67 76 85

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\(a\), this data is read from graphs, and is thus subject to small errors

\(b\), excludes the baseline measurement, and thus glucose control over 0-2 months when it is considerably better with the sulfonylurea

Baseline **HbA1c** was 7.4 % in all groups, and **FPG 8.4 mmol/l (151-152 mg/dl)**
Figure 1. Diagram to show how very non-linear deterioration in individual blood glucose control with censoring on starting insulin (solid lines, five patients) can produce an apparently linear average decline (dashed line). Many other non-linear examples can produce linear averages.
Figure 2. Time course of HbA1c in the ADOPT study redrawn to show average blood glucose control over the first 3 years (1). Data from 4 years onward is omitted as invalid (only 55-20% of randomized participants continuing). △, glibenclamide, ○, metformin, □, rosiglitazone.