SEE KAHN AND ZINMAN (P. 1672)

Counterpoint: A Diabetes Outcome Progression Trial (ADOPT): Good for Sulfonylureas?

A Diabetes Outcome Progression Trial (ADOPT) 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 peroxisome proliferator–activated receptor-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 hyperglycemia would persist was not accurately known. The study also provided a good opportunity to compare durability of effect of the three classes of drugs directly in the context of some shorter-term studies since published (3).

Metformin is currently well established as first-line therapy in people with type 2 diabetes, usually after lifestyle measures fail to achieve A1C levels <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, suggesting that outcomes are not different except for the exacerbation of hypoglycemia. 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 is hampered by three major issues. First, both the readers of the papers and the authors of this review only have access to averaged data. This can disguise the true nature of the changes occurring in individuals, particularly where rescue therapies are introduced and/or data are censored at some point in deterioration of glucose control (Fig. 1). Second, very high dropout 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 over hidden biases. Third, data on changes in islet B-cell function may be problematic where an insulin secretagogue (including sulfonylureas) is used and with homeostasis model assessment analysis once glucose control has deteriorated with time (6).

Criteria for successful glucose-lowering medication

The primary purpose of ADOPT was not to answer the question as to whether either of the three medications was better overall than the others, but rather to address specifically 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 dies), but rather by quality of life over periods of years. Furthermore, the EDIC (Epidemiology of Diabetes Interventions and Complications) Study outcomes (in individuals 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 A1C ≥1.0%) is as short as 2 years and would be proportionately shorter for larger improvements (7,8).

Balancing improved overall blood glucose control is an issue that might worsen health or perceived well-being. The familiar health issues that 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 hypoglycemia with the sulfonylureas, concerns arising from the DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) Trial regarding noncardiac failure cardiovascular outcomes and osteoporotic effects (9,10) of rosiglitazone. Regarding well-being, the issues that arise again include fluid retention (edema) and hypoglycemia but, in addition, body weight gain. The last may also have add-on health consequences outside the metabolic area through nonlinear exacerbation of such conditions as knee osteoarthrosis and sleep apnea, 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 that have approved reimbursement, and in some countries where patent laws are not applied. Even where insurance or reimbursement is available, health care resources are not unlimited, and it behooves funders in the interest of the populations they serve to determine where a medication is properly positioned on the

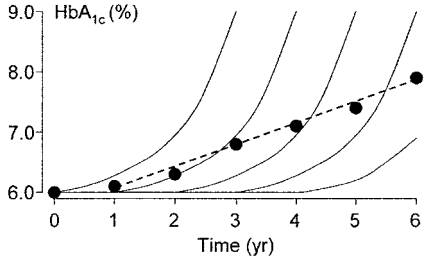

Figure 1—*Diagram to show how very nonlinear deterioration in individual blood glucose control with censoring on starting insulin (solid lines, five patients) can produce an apparently linear average decline (dashed line). Many other nonlinear examples can produce linear averages.*

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 of hyperglycemia (avoidance of A1C >6.5%)? *2*) How significant are the direct side effects of the therapies, and in particular hypoglycemia and fluid retention, to both other health risks and current quality of life? *3*) How does ADOPT impact on 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 affect 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 A1C is a lagging measure. Nevertheless, comparison of the fasting plasma glucose and A1C results would suggest that the effect of the sulfonylurea was nearly instantaneous, as the latter has already fallen markedly by 2 months, a fall two to three 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 of 2–12 months, the intercept with the metformin line occurring at the end of 1 year and only at 18 months with rosiglitazone (Fig. 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 individuals, as judged by the mean A1C and a criterion of <6.5%. However, the data suggest that these agents lower A1C by ~0.5% from the kind of baseline levels reported in the ADOPT study, a result almost exactly consistent with 18-month data with these groups of medications in the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) Study (11). As an approximation, it is then possible, with reservations, to use the ADOPT paper's data on time to failure at an A1C of 7.0% for glibenclamide alone as if it was used in combination with metformin with a failure criterion of ≥6.5%. This shows that on average the sulfonylurea would be successful in the ADOPT population for up to 2.75 years, a useful duration of effect clinically. Using the ADOPT authors' secondary criterion of success in maintaining fasting plasma glucose at <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 hypoglycemia for sulfonylureas, fluid retention and cardiac failure for the thiazolidinediones, and other cardiovascular safety for both. This review is not concerned with the thiazolidinediones, 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 concerns over an adverse non–cardiac failure cardiovascular profile raised in the DREAM study has been ameliorated (9).

Even after subtraction of cardiac failure events, numerically there were fewer cardiovascular disease 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 three, two, and two 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 outcomes that were not part of the study design. Nevertheless, the data do strongly suggest that long-held theoretical concerns about adverse effects of sulfonylureas,

Table 1—*Blood glucose control with glibenclamide (glyburide) compared with metformin and rosiglitazone in the ADOPT study (ref. 2)*

	Glibenclamide	Metformin	Rosiglitazone
Mean A1C (%)*			
Year 1†	6.5	6.7	6.8
Year 2	6.8	6.7	6.8
Year 3	7.0	6.9	6.8
Years 1–3†	6.7	6.8	6.8
A1C <7.0%			
At 4 years (% patients)	26	36	40
Time to ≥7.0% (years)	2.75	3.75	4.75
FPG			
<10.0 mmol/l (180 mg/dl)			
At 3 years (% patients)	84	92	93
At 4 years (% patients)	78	88	90
<7.8 mmol/l (140 mg/dl)			
At 4 years (% patients)	67	76	85

Baseline A1C was 7.4% in all groups and FPG 8.4 mmol/l (151–152 mg/dl). *Data is read from graphs and is thus subject to small errors. †Excludes the baseline measurement and thus glucose control over 0–2 months, when it is considerably better with the sulfonylurea. FPG, fasting plasma glucose.

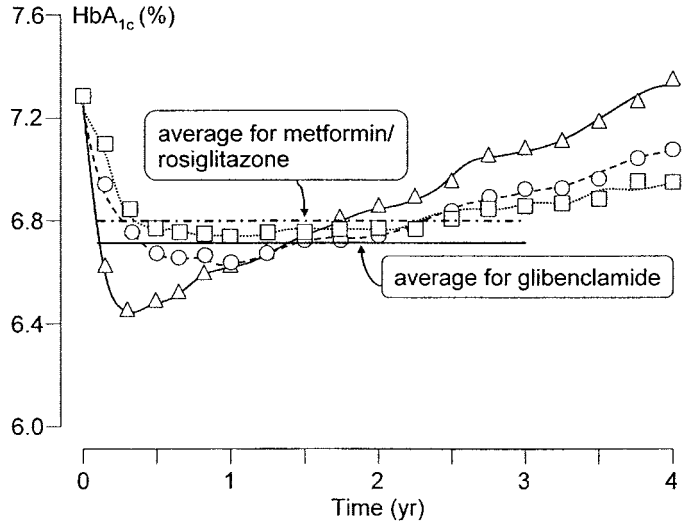

Figure 2—*Time course of A1C in ADOPT redrawn to show average blood glucose control over the first 3 years (ref. 2). Data from 4 years onward is omitted as invalid (only 55% falling to 20% of randomized participants continuing).* △*, glibenclamide;* ○*, metformin;* □*, rosiglitazone.*

and in particular glibenclamide, on prevention of ischemic preconditioning in cardiac muscle are unwarranted (12).

The issue of hypoglycemia with sulfonylureas is important and in some people can have a significant impact on quality of life through employment, recreation, or even falls and coma, particularly in the infirm elderly (13). In the general diabetic population treated with these medications, it is not such an issue, as evidenced for example by the UKPDS (1). Unfortunately, the hypoglycemia data available from the ADOPT study are of very poor quality and small in quantity. Thus hypoglycemia was not confirmed by a plasma glucose measurement as is usual in insulin studies, so that a prevalence rate (patients affected) of ~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 hypoglycemic 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 hypoglycemia 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 are difficult to come by, but the incidence of events is probably 2–10 times higher than with other sulfonylureas (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 hypoglycemia rate of ~0.5% patients per year (1). The impression then is that ADOPT does not worsen our impression that hypoglycemia is a problem in only 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 with other sulfonylureas because of its hypoglycemic tendency around lunchtime in individuals with good blood glucose control. Initial weight gain appears (graphically) to be 2.5 kg in ~1 year, not inconsistent with the average improvement of 0.8% in A1C 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 homeostasis model assessment 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 for up 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 was 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 acknowledgment of the reality that the real costs of diabetes come from failures of preventative medicine, that is, when complications develop. The second is the expanding prevalence of diabetes, driven by overeating and underactivity, together with increased life expectancy through better application of those preventative measures and the longer survival of people developing diabetes at a younger age (16). However, 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 antiplatelet 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 regarding hypoglyce-

mia (12). Put another way, over 3 years the glucose-lowering effect may be identical to a thiazolidinedione, but the cost–to–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 centered on the order of use of therapies as second or third line.

Conclusions

ADOPT presents 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 diagnosis if glucose-control targets are to be met.

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