Minimizing Hypoglycemia While Maintaining Glycemic Control in Diabetes

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In an accompanying Perspectives article, Cryer (1) identifies a number of different areas where therapeutic interventions have the potential to reduce hypoglycemia without compromising glycemic control. Some approaches provide well-defined clinical benefits, a few offer dramatic reductions in hypoglycemia but remain out of reach for most people, and others, although promising, have yet to be properly evaluated (Table 1).

In this Perspectives article, I examine the evidence that underpins these interventions. It is beyond the scope of this article to review the data for each potential intervention in detail, but the reader is directed to the source where appropriate. The focus of this article is treatment of type 1 diabetes, as most of the specific potential therapies have been evaluated in this group, although included are comments in relation to recent trials of intensive therapy in type 2 diabetes.

PREVENTING ABSOLUTE OR RELATIVE INSULIN EXCESS

Education and skills training in self-management. Long before the benefits of tight glucose control had been established (2), the belief that insulin therapy should be designed to replace insulin "physiologically" had been advocated by a small number of enthusiastic clinicians. The advent of blood glucose monitoring in the late 1970s had a major impact, since background and meal-related insulin could be given separately and adjusted according to self-monitored blood glucose measurements. Participants were encouraged to eat freely, calculating their insulin dose according to their chosen amount of carbohydrate.

Integrating these components was a complex task, probably beyond that of many physicians, let alone patients. If this was to be undertaken every day, then patients needed to acquire the skill of flexible insulin self-management and apply it successfully. The therapeutic education approach was pioneered by Assal et al. (3), and Berger and Mühlhauser (4) went on to develop a residential training course (Insulin Treatment and Training program [ITTP]) evaluating the intervention in a series of studies, including randomized controlled trials. Their group highlighted the major differences between rates of severe hypoglycemia in different centers in the Diabetes Control and Complications Trial (DCCT) and suggested that these might have reflected a failure to train patients to undertake intensive self-management safely (5).

Their data, which involve a large evaluated roll-out, suggest that it is possible to improve and sustain glycemic control, comparable with the DCCT findings using conventional insulin while reducing rates of severe hypoglycemia (Fig. 1) (6,7). Different definitions of hypoglycemia prevent a detailed comparison between these and other studies, but their principle argument that no one should embark on intensive insulin therapy and aim for tight glucose targets without acquiring appropriate self-management skills is compelling. Even in countries where such training is fairly established (7,8), relatively few adults with type 1 diabetes appear to have undertaken validated courses in intensive insulin self-management.

Other programs have been developed to train patients specifically to recognize both high and low glucose values, although most interest has centered around the ability of patients to identify impending hypoglycemia. Blood glucose awareness training, developed by Cox et al. (9) at the University of Virginia, seeks to train patients with type 1 diabetes to improve estimation of their blood glucose based on recognition of external cues and the known pathophysiological changes associated with autonomic and neuroglycopenic responses to hypoglycemia. Participants also receive feedback on their glucose estimations. The approach shares several features with the ITTP training of the Düsseldorf group and has also been extensively evaluated. Trials led by the investigators have demonstrated prevention of a blunted counterregulatory response during intensification of insulin therapy (10) and an improved ability to estimate blood glucose that is maintained over some years with fewer severe hypoglycemic events (11).

In summary, there is a reasonable body of evidence demonstrating that high-quality skills training in insulin self-management involving accredited educators leads to improved glycemic control without increasing severe hypoglycemia. Specific programs appear particularly beneficial to those with hypoglycemic problems.

Improved insulin delivery in routine care. The limitations of subcutaneous insulin delivery have been well recognized ever since its discovery. The intermittent injection of insulin into subcutaneous tissue produces insulin profiles that, while able to control blood glucose sufficiently to relieve symptoms and prevent ketosis, are far from physiological. The advent of recombinant DNA technology in the 1980s prompted the pharmaceutical industry to engineer different structures of the insulin molecule to address the limitations of subcutaneous insulin delivery (12).

The tendency of insulin molecules of conventional animal structure to aggregate in crystalline solution delays its absorption. Transposing or substituting amino acids pro-

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TABLE 1
Approaches to reducing hypoglycemia in clinical practice

Preventing relative or absolute insulin excess
- Training in insulin self-management
- Blood glucose awareness training
- Insulin analogs
- Continuous subcutaneous insulin infusion
- Pancreas transplantation
- Islet-cell transplantation

Alerting patients to impending hypoglycemia
- Hypoglycemia alarms utilizing continuous glucose monitoring technology

Restoring symptoms of awareness of hypoglycemia
- Hypoglycemia unawareness reversal programs

Augmenting glucose counterregulation
- Indirect
- K_{ATP} channel openers
- Modafanil
- Diazoxide
- SSRIs
- Direct
- Alaninine
- Terbutaline

duces insulins with less tendency to self-aggregate (13). The molecules remain monomeric at high concentration, and their more rapid absorption results in a more physiological insulin profile. Yet the clinical advantages of quick-acting insulin analogs over conventional insulin have generally been modest in clinical trials, both in lowering A1C and reducing hypoglycemia, and some have concluded that they offer little additional benefit (14). Nevertheless, there is reasonable evidence reporting reduced nocturnal hypoglycemic risk when using rapid-acting insulin analogs in those with well-controlled type 1 diabetes (15,16), an outcome not included in the recent Cochrane review (14).

The other main pharmacokinetic limitation of conventional insulin delivery has also been addressed. Human NPH insulin exhibits considerable inter- and intra-individual variability in part due to the necessity of resuspension before injection. This, plus a pronounced peak of action around 6–8 h after injection, contributes to the risk of nocturnal hypoglycemia. Insulin manufacturers have tried to solve these problems in ingenious ways. Insulin glargine

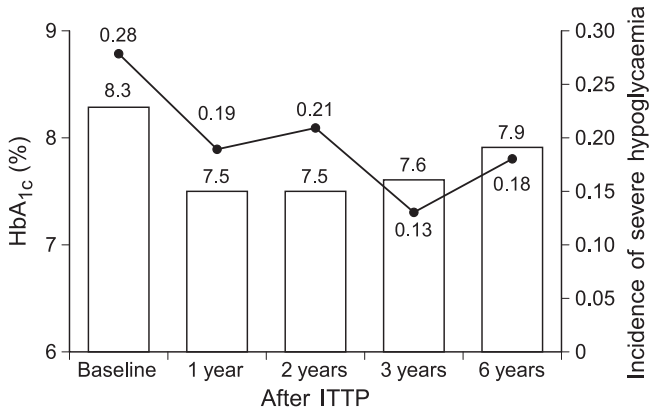

FIG. 1. A1C and incidence of severe hypoglycemia (per patient per preceding year) at baseline and at follow-up examinations in patients with diabetes duration >1 year at entry following delivery of an ITTP (N = 538). Severe hypoglycemia was defined as a self-reported episode of hypoglycemia necessitating treatment with intravenous glucose or glucagon injection. (Reproduced with permission from reference 6.)

(Lantus), a diarginyl insulin analog, is a soluble insulin at an acid pH and crystallizes in the more alkaline subcutaneous environment (13). Insulin detemir (Levemir) has been constructed by adding a myristoyl fatty acid side chain at the COOH-terminus of the B-chain, which causes the insulin to bind to albumin (13). Both insulins have a more prolonged action than NPH, and a reduced peak, and provide a more physiological free insulin profile with the potential to lower rates of hypoglycemia. Yet, as with rapid-acting insulin analogs, the major pharmacokinetic differences compared with NPH insulin are not in general reflected in the clinical trial data.

Benefits of long-acting insulin analogs have been modest in both types of diabetes with little if any difference in glycemic control and only slight reductions in hypoglycemia, mostly at night (17). The combination of both long- and short-acting insulin analogs leads to significant albeit minor reductions in both A1C and hypoglycemia in adults with type 1 diabetes (18,19).

A major difficulty in interpreting the mountain of data regarding insulin treatment is that the limitation of its delivery is just one of many factors determining glycemic control and the risk of hypoglycemia. Thus, regulatory clinical trials may underestimate the potential benefit because they rarely recruit highly motivated individuals who are expert at self-managing their diabetes and can best utilize the pharmacokinetic advantages. Regulatory trials may also favor conventional insulins because clinical experience with the newer insulins is often necessary to establish the most effective combination and timing of injection. However, because asymptomatic nocturnal hypoglycemia may contribute to the generation of hypoglycemia unawareness (20), such insulins should be offered to those skilled in insulin self-management who are experiencing hypoglycemic problems.

Continuous subcutaneous insulin infusion. The limitations of long-acting insulins have driven the increasing use of continuous subcutaneous insulin infusion (CSII) as a realistic treatment option for many, at least in wealthy countries. The approach is now used by over 20% of individuals with type 1 diabetes in the U.S. (21). CSII is the most effective generally available method of insulin delivery, although subcutaneous administration plus the continued need for frequent adjustments of infusion rates according to intermittent self-monitoring of blood glucose is hardly physiological. The need to justify reimbursement of the increase in costs has resulted in a substantial number of trials and systematic reviews. The most recent reviews that include trials involving more modern devices report decreases in A1C of ~0.6–0.4% with no increase in hypoglycemia, but the advantages were confined to adults with type 1 diabetes (22,23). In addition, there were insufficient data to establish benefit in children and no advantage of CSII in type 2 diabetes. Few groups have undertaken a formal meta-analysis of hypoglycemic outcomes due to different definitions and potential bias due to lack of blinding when judging end points.

Observational studies report greater reductions in A1C and severe hypoglycemia but are inevitably prone to bias because only those who experience benefit are likely to continue using the approach. Furthermore, the use of CSII is a complex intervention involving not only the pump but also instruction in carbohydrate counting and insulin adjustment within a structured training program. Thus, part of the benefit of pump therapy may relate to the training that accompanies it. Few trials have apparently

controlled for the training element, and reported decreases in rates of severe hypoglycemia are similar to those reported for self-management training using multiple injections.

Nevertheless, it seems clear that, for highly motivated individuals with the ability to self-manage their diabetes effectively, modern CSII technology can improve glycemic control without increasing hypoglycemia. If acceptable to the patient, it should also be part of a package for patients experiencing problems with hypoglycemia.

Preventing insulin excess for the few, implantable pumps and pancreas and islet transplantation. There are a number of interventions reported to have major effects in reducing hypoglycemia. The use of implantable pumps housed within the subcutaneous tissue of the abdominal wall and insulin delivered into the peritoneum have been pioneered by a group in France. Clinical experience is relatively limited at around 350 patient-years, but the investigators have reported major reductions in severe hypoglycemia, impressive A1C concentrations, and improved quality of life (24). Evaluation of such therapy is largely based on observational studies, although some randomized trials have been undertaken. Catheter blockage is a continuing problem, and after over 15 years of experience the approach has not entered mainstream clinical care. It would not appear to be a realistic treatment option for most adults with diabetes in the foreseeable future.

The limitations of current insulin delivery are emphasized by the dramatic effect that pancreas transplantation has in curing the problems of hypoglycemia. Whole pancreas transplantation leads to insulin independence in the short and medium term and the resolution of hypoglycemia unawareness at the expense of considerable perioperative morbidity and occasional mortality. The results of whole pancreas transplantation have improved in recent years, with 80% graft survival at 5 years, and it is now approved as a treatment for severe hypoglycemic instability (25).

Islet cell transplantation is less invasive but results in less preservation of insulin secretion; a recent report from specialist North American centers indicates that under 10% of recipients are insulin free at 2 years (26). Nevertheless, around 70% of individuals had detectable C-peptide, of whom none were experiencing previous difficulties with hypoglycemia unawareness.

Both treatments are accompanied by the hazards of prolonged immunosuppression with increased risks of infection and malignancy. Add to this the current shortage of donor tissue, and it is clear that, although this treatment has moved from an experimental to a clinical treatment in some countries and cures even severe hypoglycemia unawareness, it is not an option for most individuals with type 1 diabetes, either now or in the medium to long term. Nevertheless, pancreas or islet transplantation should be considered for patients with profound problems with hypoglycemia in those areas where it is available and when other treatments have failed.

ALERTING PATIENTS TO IMPENDING HYPOGLYCEMIA

Continuous glucose monitoring. Continuous glucose monitoring technology has now been available for over 10 years, and each year sees further development and refinement; devices now on the market can provide readings in real time and are able to alert patients to a falling glucose level. Early studies highlighted the ability of devices to identify unsuspected nocturnal hypoglycemia (27), but reports of hypoglycemia in nondiabetic individuals and disparate values registered by two similar devices attached simultaneously to the same person led to a reappraisal of their ability to identify hypoglycemia reliably (28). The problems are not purely technological (29). Even if the equipment records glucose concentrations quickly and accurately, measurements will inevitably differ due to *1*) the need for calibration with blood glucose, since failure to calibrate under steady-state conditions introduces error, and *2*) the physiological differences between values measured in subcutaneous tissue (interstitial glucose) and blood glucose. Thus, "real time" devices may be of more use when providing information about the change in glucose rather than absolute values. Continuous glucose monitoring can identify unsuspected low glucose values, particularly at night, which might contribute to the generation of hypoglycemia unawareness. Yet, this cannot overcome the difficulty of adjusting imperfect insulin delivery systems in an attempt to prevent insulin excess.

The real immediate potential lies in their use as a hypoglycemia alarm, yet years after the first introduction of such devices, few individuals with type 1 diabetes are using them regularly. There will always be a tradeoff between sensitivity and specificity, but at present specificity is insufficient (30), perhaps in part due to differences between interstitial and blood glucose (29). The need to replace sensors at relatively short intervals, the greater accuracy in the high rather than the low glucose range, and the difficulty in arousing patients from sleep during nocturnal hypoglycemic episodes emphasize the hurdles still to be overcome. An independent group recently concluded that none of the current devices performed reliably enough to be recommended as hypoglycemia alarms (31).

Observational studies have reported reductions in severe hypoglycemia, but in the absence of a control group it is unclear whether this reduction was entirely due to the provision of the device. Randomized controlled trials have generally shown modest advantages in surrogate end points, such as the time spent in the normoglycemic range (29). Whether this translates into a reduced risk of severe hypoglycemia is unclear, as most studies are underpowered due to insufficient numbers of patients. A recent systematic review found that the use of continuous monitoring did not reduce A1C, but there was a suggestion that episodes of nocturnal hypoglycemia were reduced (32). Unfortunately, the heterogeneity of the studies, largely due to different definitions of hypoglycemia, made it impossible to increase statistical power by pooling the data. It is important that investigators agree to a common definition of hypoglycemia in order to allow meta-analyses to analyze future trials.

In the absence of a reliable alarm, as Wolpert (33) has highlighted, the potential of continuous glucose monitoring to reduce hypoglycemia will depend upon the ability of patients to combine the information obtained with the proper adjustments to insulin and eating habits. This requires an active interest in self-management as well as a good working knowledge of the effects of insulin. As with other therapeutic advances assessed in this review, the failure to establish much effect on hypoglycemia may be because the expert application of these practical skills is limited to relatively few patients.

Closed-loop systems. In view of the limitations described above, the development of a closed loop system in which continuous glucose monitoring is combined with the use of a pump controlled by an external computer has major attractions. It would obviate the need for input from the patient apart from filling the insulin reservoir and replacing the sensor and its attachment. The potential for such a device is clearly huge, although the expense will limit uptake even within the developed world.

A detailed review of recent approaches to closed-loop systems is available elsewhere (34). Most of the current work focuses on devices that incorporate both subcutaneous glucose sensing and insulin delivery. The limitations of subcutaneous insulin administration are less important when blood glucose flux is relatively low and challenged during eating or exercise. Thus, much effort is focused on overnight glucose control. Some promising early data are emerging, and investment in the field is now considerable, but closed loop devices remain research tools. The development of a practical reliable device, even for those with hypoglycemic problems, remains years away.

RESTORING SYMPTOMS

Programs reversing hypoglycemia unawareness. The observation that repeated episodes of short-duration mild hypoglycemia impair sympathoadrenal and symptomatic response to subsequent episodes and contribute to hypoglycemia-associated autonomic failure suggests that defects are functional rather than structural. The implication that such impairment might therefore be reversible has been established by different groups in experimental settings (35–37). What is more relevant is how such approaches work in clinical practice. The essential component reported by three studies was the avoidance of all hypoglycemic episodes for a few weeks. This required a labor-intensive approach with frequent, often daily, contact between professional and patient and blood glucose monitoring and insulin adjustment to prevent episodes, particularly at night (Table 2). In these relatively short-term studies, there was no significant deterioration in glycemic control, although A1C increased in all three. It is not clear whether reversal of unawareness can be achieved in all patients or if such benefits are sustainable. For those who regain symptomatic awareness there is the challenging task of maintaining reasonable glycemic control while avoiding relapse due to further hypoglycemic episodes.

One center has retested four of six patients with unawareness 3 years after their reversal program (38). Relatively tight glycemic control had been maintained, repeated hypoglycemia had generally been avoided, and symptomatic responses to experimental hypoglycemia, while lower than those measured at the end of the original study, were higher than at baseline. However, these are small numbers. It is noteworthy that no center appears to have published their long-term clinical experience of managing this problem, and such reports would be of considerable value. Anecdotally, it is our experience, as well as the experience of others, that some individuals find it impossible to alter their glucose targets and continue to be subject to severe hypoglycemic episodes. The fact that severe problems with hypoglycemia and unawareness have emerged as the main clinical indication for whole pancreas and islet transplantation also suggests that hypoglycemia reversal programs are limited in the degree and duration of benefit.

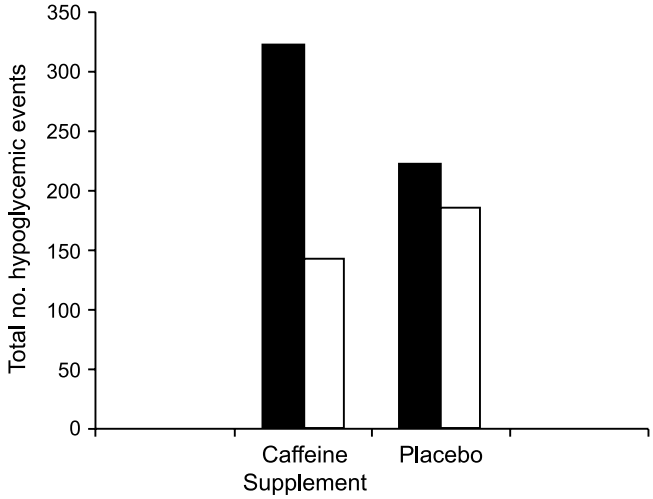

FIG. 2. Total number of hypoglycemic events in 34 individuals with type 1 diabetes over 3 months. □, biochemical (P = NS); ■, symptomatic (P < 0.03, caffeine vs. placebo). (Reproduced with permission from reference 40.)

SPECIFIC THERAPIES TO PREVENT OR REDUCE HYPOGLYCEMIA BY AUGMENTING COUNTERREGULATION

Caffeine/theophylline. The adenosine antagonists caffeine and theophylline are probably the most studied of potential therapeutic agents to reverse or prevent hypoglycemia unawareness. The potential of caffeine was suggested by a study that reported increased catecholamines and symptoms during experimental hypoglycemia (39). Based on this and other studies, the authors undertook a 3-month clinical trial in patients with type 1 diabetes and demonstrated an increased number of symptomatic episodes, although there was no difference in asymptomatic or severe episodes (Fig. 2) (40). A more recent study involving relatively small numbers has reported reduced duration of nocturnal hypoglycemia (41) as measured by continuous glucose monitoring.

Theophylline has also been evaluated as a treatment for hypoglycemia unawareness. Patients were recruited to a study in which theophylline was given as an intravenous infusion during a slow-fall hypoglycemic clamp (42). The rise in cerebral blood flow was prevented, and the threshold for the increase in symptoms and epinephrine shifted to a higher level, although there was no increase in glucagon concentrations. The same group then studied the effect of oral theophylline over 2 weeks and again demonstrated increases in symptoms (although not epinephrine) during experimental hypoglycemia (43).

While these results are of interest, the crucial question is whether these agents protect patients from severe episodes during clinical treatment. In no study were patients treated for an amount of time sufficient to assess the effect on hypoglycemia unawareness or rates of severe hypoglycemia. This is of particular relevance to these agents because they reduce cerebral blood flow. While this might

TABLE 2
Characteristics of hypoglycemia reversal programs

- Prevention of all hypoglycemic episodes for 3–6 weeks while keeping glycemic control unaltered
- Frequent monitoring of blood glucose (especially at night)
- Insulin dose and type adjustments
- Labor-intensive process for patient and clinician
- Lengthy process (often taking months)

contribute to a more pronounced symptomatic response, increased vulnerability to severe episodes may in fact be an unwanted consequence.

Modafanil. The evidence that ATP-sensitive K^+ channels (K_{ATP} channels) modulate hypothalamic sensing of hypoglycemia (44) and deficient counterregulation (45), perhaps through effects on γ-aminobutyric acid (GABA) (46), presents other therapeutic targets. Modafanil, an agent used in narcolepsy, reduces GABA activity most likely through effects on K^+ channels (47). The hypothesis that inhibition of GABAminergic neurones might augment the sympathoadrenal response has been tested in nondiabetic subjects who received a moderate dose of modafanil or placebo immediately before a slow-fall glucose clamp (48). There was a modest increase in adrenergic symptoms and protection of cognitive function but no effect on epinephrine levels. The authors concluded that modafanil was worthy of further investigation, but apparently neither they nor anyone else has since studied patients with diabetes or hypoglycemia unawareness.

The same group has also investigated drugs that modify K_{ATP} channels, namely gliburide (a channel closer) and diazoxide (a channel opener) (49). Immediate delivery of either agent to nondiabetic subjects before experimental hypoglycemia had no effect on counterregulatory responses, although those treated with gliburide showed some preservation of cognitive function compared with those treated with diazoxide and those given placebo. A further study where diazoxide was administered immediately before experimental hypoglycemia also had no effect on sympathoadrenal responses (50). These human data contradict the positive effect of K^+ channel openers on the hypoglycemic sympathoadrenal response observed in rodents for reasons that are as yet unclear. Thus, clinical potential remains uncertain and needs further investigation.

Selective serotonin reuptake inhibitors. The use of selective serotonin reuptake inhibitors (SSRIs) to augment the counterregulatory response has also been explored (51). Early reports actually associated these drugs with hypoglycemia, but the authors reasoned that blocking serotonin uptake might increase sympathetic outflow. They demonstrated increased sympathoadrenal responses and cortisol concentrations during experimental hypoglycemia in nondiabetic subjects, but symptoms were unaltered. These observations now need confirming in diabetic subjects and those with unawareness.

Boosting glucose counterregulation. A number of human studies in experimental settings have measured the potential of pharmacological activation of counterregulatory mechanisms to boost blood glucose levels and therefore reduce the risk of hypoglycemia, particularly at night. Alanine may restore deficient glucagon responses in individuals with type 1 diabetes at least in part (52). Nocturnal hypoglycemia can be prevented by oral terbutaline given at bedtime in contrast to the relative ineffectiveness of bedtime snacks but at the expense of a higher fasting glucose concentration (53). The authors commented that finding a dose that could reliably prevent nocturnal hypoglycemia without raising fasting glucose concentrations is challenging (54).

It is noteworthy that, as with other potential treatments described above, these small-scale studies that provide proof of principle have not been followed by larger trials, have not been adequately powered, and are of insufficient duration to measure differences in severe hypoglycemia. It is unclear whether this gap in the literature is related to a perception that therapies are ineffective, the difficulty in securing funding, or merely the logistics in running multicenter trials.

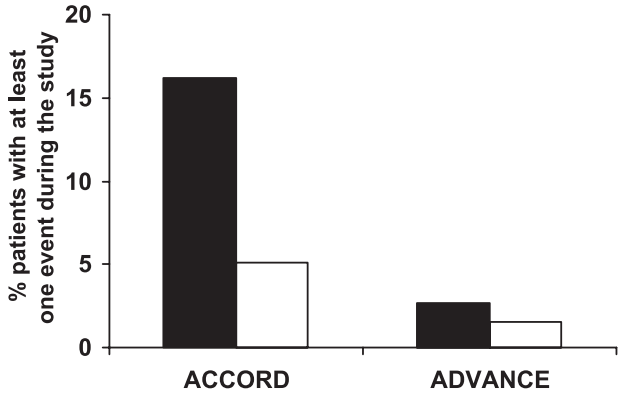

FIG. 3. Absolute rates of severe hypoglycemia (% of subjects affected during the trial) in the two glucose arms of the ACCORD and ADVANCE trials. ■, intensive control; □, standard control.

TYPE 2 DIABETES

It is beyond the scope of this review to evaluate specific treatments for type 2 diabetes. Montori et al. (55) have recently commented that there are few independently funded trials that have addressed the effects of glucose-lowering therapy using end points that are relevant to patients. However, some relevant observations can be drawn from the recent publication of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (56) and ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation) (57) trials, although more detailed information regarding hypoglycemia will emerge shortly. The ACCORD trial utilized an aggressive glucose control strategy with multiple oral agents and the early use of insulin, combining both overnight and preprandial insulin and aiming for an A1C of ≤6%. This produced considerable severe hypoglycemia, which may have contributed to the adverse outcomes. In contrast, a less aggressive approach targeting fasting glucose by the stepwise addition of oral agents and eventually overnight basal insulin produced much less severe hypoglycemia and weight gain with an A1C level of 6.5% (Fig. 3) (57).

CONCLUSIONS

The virtual elimination of severe hypoglycemia in the few patients receiving either islet or whole pancreas transplants demonstrates vividly the failure of current treatment to reproduce the physiology of the β-cell. As we approach 100 years of insulin therapy, many who strive for tight glycemic control are prevented from achieving these targets by the frequently troublesome and occasionally devastating side effect of hypoglycemia. Data from clinical trials indicate that insulin analogs, pumps, and continuous glucose monitoring have generally modest effects in reducing hypoglycemic risk: those who appear to gain most benefit are those actively and skillfully engaged in their own diabetes self-management. Reversal of hypoglycemia unawareness, at least in part, can be achieved within relatively short time periods and without major deterioration in glycemic control, although the long-term experience of individuals remains unclear.

Some of the pathological pathways emerging from animal studies have identified potential therapeutic targets, but early clinical trials have been unimpressive. It remains to be seen how useful animal models of hypoglycemia will be in identifying specific therapies to prevent or reverse hypoglycemia. Promising pilot work in human studies should be followed by adequately powered studies measuring severe hypoglycemia. It is also important that trials, including those sponsored by the pharmaceutical industry, use similar definitions of hypoglycemia.

The closed-loop device trials signal a potentially exciting advance, as would the availability of reliable hypoglycemia alarms, but the technology is currently inadequate for the task. In the short-term, it appears that high-quality educational/behavioral interventions offer the most cost-effective way of enabling less hypoglycemia without worsening glycemic control, particularly as successful graduates of such programs appear best placed to take advantage of technological advances.

REFERENCES

1. Cryer PE: The barrier of hypoglycemia in diabetes. *Diabetes* 57:3169–3176, 2008
2. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:683–689, 1993
3. Assal JP, Mühlhauser I, Pernet A, Gfeller R, Jorgens V, Berger M: Patient education as the basis for diabetes care in clinical practice and research. *Diabetologia* 28:602–613, 1985
4. Muhlhauser I, Berger M: Patient education: evaluation of a complex intervention. *Diabetologia* 45:1723–1733, 2002
5. Muhlhauser I, Berger M: Diabetes education and insulin therapy: when will they ever learn? *J Intern Med* 233:321–326, 1993
6. Bott S, Bott U, Berger M, Mühlhauser I: Intensified insulin therapy and the risk of severe hypoglycaemia. *Diabetologia* 40:926–932, 1997
7. Samann A, Muhlhauser I, Bender R, Kloos C, Muller UA: Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. *Diabetologia* 48:1965–1970, 2005
8. Plank J, Kohler G, Rakovac I, Semlitsch BM, Horvath K, Bock G, Kraly B, Pieber TR: Long-term evaluation of a structured outpatient education programme for intensified insulin therapy in patients with type 1 diabetes: a 12-year follow-up. *Diabetologia* 47:1370–1375, 2004
9. Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W: A multicenter evaluation of blood glucose awareness training-II. *Diabetes Care* 18:523–528, 1995
10. Kinsley BT, Weinger K, Bajaj M, Levy CJ, Simonson DC, Quigley M, Cox DJ, Jacobson AM: Blood glucose awareness training and epinephrine responses to hypoglycemia during intensive treatment in type 1 diabetes. *Diabetes Care* 22:1022–1028, 1999
11. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W: Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care* 24:637–642, 2001
12. Brange J, Ribel U, Hansen JF, Dodson G, Hansen MT, Havelund S, Melberg SG, Norris F, Norris K, Snel L, et al.: Monomeric insulins obtained by protein engineering and their medical implications. *Nature* 333:679–682, 1988
13. Owens DR, Zinman B, Bolli GB: Insulins today and beyond. *Lancet* 358:739–746, 2001
14. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev* CD003287, 2006
15. Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson-Jh Jr: Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. *Diabetes Care* 20:1827–1832, 1997
16. Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH, Windfeld K, Lindholm A: Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type 1 diabetes. *Diabet Med* 21:769–775, 2004
17. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A: Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* CD005613, 2007
18. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA: Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia* 47:622–629, 2004
19. Ashwell SG, Amiel SA, Bilous RW, Dashora U, Heller SR, Hepburn DA, Shutler SD, Stephens JW, Home PD: Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. *Diabet Med* 23:285–292, 2006
20. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J: Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes* 42:1233–1237, 1993
21. Pickup JC: Are insulin pumps underutilized in type 1 diabetes? Yes. *Diabetes Care* 29:1449–1452, 2006
22. Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N: Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technol Assess* 8:iii, 1–171, 2004
23. Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, Siebenhofer A: Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 51:941–951, 2008
24. Renard E, Schaepelynck-Belicar P: Implantable insulin pumps: a position statement about their clinical use. *Diabete Metab* 33:158–166, 2007
25. Meloche RM: Transplantation for the treatment of type 1 diabetes. *World J Gastroenterol* 13:6347–6355, 2007
26. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, Lakey JR: International trial of the Edmonton protocol for islet transplantation. *N Engl J Med* 355:1318–1330, 2006
27. Kaufman FR, Austin J, Neinstein A, Jeng L, Halvorson M, Devoe DJ, Pitukcheewanont P: Nocturnal hypoglycemia detected with the continuous glucose monitoring system in pediatric patients with type 1 diabetes. *J Pediatr* 141:625–630, 2002
28. McGowan K, Thomas W, Moran A: Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care* 25:1499–1503, 2002
29. Reach G: Continuous glucose monitoring and diabetes health outcomes: a critical appraisal. *Diabetes Technol Ther* 10:69–80, 2008
30. Wentholt IM, Hoekstra JB, Devries JH: Continuous glucose monitors: the long-awaited watch dogs? *Diabetes Technol Ther* 9:399–409, 2007
31. Mauras N, Beck RW, Ruedy KJ, Kollman C, Tamborlane WV, Chase HP, Buckingham BA, Tsalikian E, Weinzimer S, Booth AD, Xing D: Lack of accuracy of continuous glucose sensors in healthy, nondiabetic children: results of the Diabetes Res in Children Network (DirecNet) accuracy study. *J Pediatr* 144:770–775, 2004
32. Chetty VT, Almulla A, Odueyungbo A, Thabane L: The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in type I diabetic patients: a systematic review. *Diabetes Res Clin Pract* 81:79–87, 2008
33. Wolpert HA: The nuts and bolts of achieving end points with real-time continuous glucose monitoring. *Diabetes Care* 31 (Suppl. 2):S146–S149, 2008
34. Hovorka R: The future of continuous glucose monitoring: closed loop. *Curr Diabetes Rev* 4:269–279, 2008
35. Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F, Lepore M, Annibale B, Ciofetta M, Bottini P, Porcellti F, Scionti L, Santeusanio F, Brunetti P, Bolli GB: Meticulous prevention of hypoglycemia normalizes the glycemic thresholds of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 42:1683–1689, 1993
36. Cranston I, Lomas J, Maran A, Macdonald IA, Amiel SA: Restoration of hypoglycaemia unawareness in patients with long- duration insulin-dependent diabetes. *Lancet* 344:283–287, 1994
37. Dagogo-Jack SE, Rattarasarn C, Cryer PE: Reversal of hypoglycemia unawareness, but not counterregulation, in IDDM. *Diabetes* 43:1426–1434, 1994
38. Dagogo-Jack S, Fanelli CG, Cryer PE: Durable reversal of hypoglycemia unawareness in type 1 diabetes. *Diabetes Care* 22:866–867, 1999
39. Kerr D, Sherwin RS, Pavalkis F, Fayad PB, Sikorski L, Rife F, Tamborlane

WV, During MJ: Effect of caffeine on the recognition of and responses to hypoglycemia in humans. *Ann Int Med* 119:799–804, 1993
40. Watson JM, Jenkins EJ, Hamilton P, Lunt MJ, Kerr D: Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 23:455–459, 2000
41. Richardson T, Thomas P, Ryder J, Kerr D: Influence of caffeine on frequency of hypoglycemia detected by continuous interstitial glucose monitoring system in patients with long-standing type 1 diabetes. *Diabetes Care* 28:1316–1320, 2005
42. de Galan BE, Tack CJ, Lenders JW, Pasman JW, Elving LD, Russel FG, Lutterman JA, Smits P: Theophylline improves hypoglycemia unawareness in type 1 diabetes. *Diabetes* 51:790–796, 2002
43. de Galan BE, Tack CJ, Lenders JW, Lutterman JA, Smits P: Effect of 2 weeks of theophylline on glucose counterregulation in patients with type 1 diabetes and unawareness of hypoglycemia. *Clin Pharmacol Ther* 74:77–84, 2003
44. Evans ML, McCrimmon RJ, Flanagan DE, Keshavarz T, Fan X, McNay EC, Jacob RJ, Sherwin RS: Hypothalamic ATP-sensitive K + channels play a key role in sensing hypoglycemia and triggering counterregulatory epinephrine and glucagon responses. *Diabetes* 53:2542–2551, 2004
45. McCrimmon RJ, Evans ML, Fan X, McNay EC, Chan O, Ding Y, Zhu W, Gram DX, Sherwin RS: Activation of ATP-sensitive K+ channels in the ventromedial hypothalamus amplifies counterregulatory hormone responses to hypoglycemia in normal and recurrently hypoglycemic rats. *Diabetes* 54:3169–3174, 2005
46. Chan O, Lawson M, Zhu W, Beverly JL, Sherwin RS: ATP-sensitive K(+) channels regulate the release of GABA in the ventromedial hypothalamus during hypoglycemia. *Diabetes* 56:1120–1126, 2007
47. Huang Q, Zhang L, Tang H, Wang L, Wang Y: Modafinil modulates GABA-activated currents in rat hippocampal pyramidal neurons. *Brain Res* 1208:74–78, 2008
48. Smith D, Pernet A, Rosenthal JM, Bingham EM, Reid H, Macdonald IA, Amiel SA: The effect of modafinil on counter-regulatory and cognitive responses to hypoglycaemia. *Diabetologia* 47:1704–1711, 2004
49. Bingham E, Hopkins D, Pernet A, Reid H, Macdonald IA, Amiel SA: The effects of KATP channel modulators on counterregulatory responses and cognitive function during acute controlled hypoglycaemia in healthy men: a pilot study. *Diabet Med* 20:231–237, 2003
50. Raju B, Cryer PE: Loss of the decrement in intraislet insulin plausibly explains loss of the glucagon response to hypoglycemia in insulin-deficient diabetes: documentation of the intraislet insulin hypothesis in humans. *Diabetes* 54:757–764, 2005
51. Briscoe VJ, Ertl AC, Tate DB, Dawling S, Davis SN: Effects of a selective serotonin reuptake inhibitor, fluoxetine, on counterregulatory responses to hypoglycemia in healthy individuals. *Diabetes* 57:2453–2460, 2008
52. Porcellati F, Pampanelli S, Rossetti P, Busciantella Ricci N, Marzotti S, Lucidi P, Santeusanio F, Bolli GB, Fanelli CG: Effect of the amino acid alanine on glucagon secretion in non-diabetic and type 1 diabetic subjects during hyperinsulinaemic euglycaemia, hypoglycaemia and post-hypoglycaemic hyperglycaemia. *Diabetologia* 50:422–430, 2007
53. Raju B, Arbelaez AM, Breckenridge SM, Cryer PE: Nocturnal hypoglycemia in type 1 diabetes: an assessment of preventive bedtime treatments. *J Clin Endocrinol Metab* 91:2087–2092, 2006
54. Saleh TY, Cryer PE: Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 20:1231–1236, 1997
55. Montori VM, Gandhi GY, Guyatt GH: Patient-important outcomes in diabetes: time for consensus. *Lancet* 370:1104–1106, 2007
56. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545–2559, 2008
57. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358:2560–2572, 2008