Early Insulin: An Important Therapeutic Strategy

The issue of when and how to initiate insulin in type 2 diabetes is one that has engendered much debate (1). Some recent evidence may aid in this discussion.

First, the desirable glycemic targets are largely agreed upon, with only a few minor disagreements (2,3). Data from the U.K. Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) have demonstrated a strong correlation between glycemic burden and microvascular complications in both type 1 and type 2 diabetes, with no evidence of a threshold below which complications do not occur.

Further, the follow-up analysis of the DCCT, the EDIC (Epidemiology of Diabetes Interventions and Complications), has shown a "legacy effect" of improved glycemic control persisting for at least 5 years in the previously intensively treated group, even after some rise in HbA_{1c} (4). This increases the urgency to achieve and maintain good control as early as possible. Therefore, many authors on this subject agree that the target HbA_{1c} should be "as close to normal as possible while minimizing the risks of treatment" (3). Herein lies the rub or debate regarding the later caveat. That is, what is the risk and burden of treatment in terms of economic, mental, and physical aspects? Analysis of the quality of life for subjects in the intensively treated groups, in both the UKPDS and DCCT, showed no adverse effects on quality of life.

What of the risk of hypoglycemia?
This was clearly the major problem in the intensively treated group of type 1 diabetic patients in the DCCT, with an increased risk nearly threefold for serious hypoglycemia. Many have noted that this study was conducted without the use of analog insulins, which were not available at the time of this study. The hypoglycemia burden is less clear in the UKPDS, as there was no self-monitoring or verification of blood glucose for most episodes. There seems to be general agreement in the current literature that the risk of se-

vere hypoglycemia is substantially lower in type 2 than in type 1 diabetes, even in those intensively treated with insulin to comparable glycemic targets (5).

The natural history of β-cell function, once diabetes is established, has been amply demonstrated by the UKPDS (6). It is hoped that the inexorable decline seen in β-cell function will not occur to the same extent with thiazolidinedione treatment. Further, newer agents (e.g., glucagon-like peptide agonists/analogs or DPP [dipeptidylpeptidase] IV inhibitors) may be able to preserve β-cell function. However, proof of this awaits completion of randomized trials now underway. Therefore, for the present, it is safest to assume that most patients will eventually require adjunctive insulin to reach currently recommended A1c goals of <6.5–7.0%. The addition of basal insulin for patients not at goal on two or three oral antidiabetic medications is often the simplest way to initiate insulin therapy titrating to achieve a fasting plasma glucose of 100 mg/dl. This has been shown in a randomized multicenter trial to bring A1c below 7% in a majority of type 2 patients not controlled on metformin plus sulfonylurea, with a minimal risk of hypoglycemia (7).

At present there is little evidence to suggest that one form of glucose-lowering therapy is more effective than another in terms of lowering complications. The exception to this was metformin monotherapy in obese patients in the UKPDS who had significantly less cardiovascular morbidity compared with equivalent glucose-controlled patients treated with sulfonylurea or insulin (8). Therefore, probably any drug sequence that achieves and maintains A1c <6.5–7% is acceptable. However, we also learned from the UKPDS that monotherapy is unlikely to achieve or maintain control for very long. Therefore, earlier use of combination therapy, even as initial therapy, will facilitate reaching goal and relieving glucotoxicity, which likely plays some role in declining β-cell function. Since any single oral therapy is unlikely to lower reduce

A1c >1.5–2.0%, it is logical to consider initial combination therapy for patients presenting with an A1c ≥8.0–9.0%. The key here is moving along the treatment algorithm promptly when control has not been achieved. There is evidence that the trigger for intensifying therapy for many practitioners is a fasting plasma glucose level >180 mg/dl or an A1c >10% (9). Unless this paradigm is changed, it is likely that we and our patients will remain perpetually "behind the curve" and suffering the known consequences of hyperglycemia.

How long should one give a treatment regimen before concluding that it is not sufficient and must be supplemented?
Here, also, I believe, there is a lack of general understanding of the dose response and time to maximal effect of some treatment regimens. Education in this area is likely to result in significant dividends. For example, we now know that the maximal effect of a sulfonylurea occurs with 5–10 mg glyburide or glypizide per day and 4–8 mg glimeperide per day (10). As with most antihypertensive drugs, the dose-response curve is not linear but heavily "front-loaded" toward lower doses, such that perhaps 80% of the effect is seen with half-maximal doses. For metformin monotherapy, dose-response studies suggest that 1,500–2,000 mg/day produced maximal glucose lowering. For the thiozolidenediones, data suggest that maximal glucose lowering will occur with 8 mg rosiglitazone or 45 mg pioglitazone.

Next, how quickly should the next agent be added?
For sulfonylureas, the majority for the effect may be seen within a few days to a week. Therefore, one could begin with 2.5–5.0 mg glyburide or glypizide or 1–2 mg glimeperide and titrate up at weekly intervals based on self-monitoring records reaching maximal doses within 2–4 weeks. Metformin is similarly rapid acting, with titration more commonly limited by the need to achieve gastrointestinal tolerance. It can be titrated at 4- to

7-day intervals, reaching maximal doses within 3–4 weeks. Therefore, there is little reason to wait longer than a month with both of these agents before concluding that they are not sufficient to manage the patient's hyperglycemia.

The thiazolidenediones are clearly different in this regard, requiring 2–4 weeks for onset of glucose lowering and 3–4 months for maximal effect. However, some effect should be evident within 1 month, and the patient should be within "striking distance" of the target (i.e., <8.0–8.5%) to continue this course. If not, I suggest that insulin should be initiated. My preference, as stated above, is usually for initiating basal insulin and titrating to a target fasting plasma glucose of 100 mg/dl. In this setting, one can begin with a low dose (e.g., 10–15 units), increasing once or twice weekly until the target is reached. Some patients may be better served by the use of a short-acting insulin analog before the largest meal in order to mitigate postprandial hyperglycemia. I have found that once the first injection has been given and the patient sees that there is a therapy that will control hyperglycemia, it is not difficult to persuade most patients to continue the therapy. Of course, continuing adjustment will be required to safely maintain control. I believe that in order to lower the A1c national average, a major mission of diabetes professionals should be to carry the message of prompt, effective control, including earlier introduction of insulin by primary care physicians. Experience to date suggests that this is not likely to happen otherwise.

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References
1. Bell DSH: Insulin as initial therapy for type 2 diabetes is not in the patient's best interest. *Endocr Pract* 10:208–212, 2004
2. American Diabetes Association: Standards of medical care in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1): S15–S35, 2004
3. American Association of Clinical Endocrinologists: The American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: the AACE system of intensive diabetes self-management: 2002 update. *Endocr Pract* 8 (Suppl. 1):40–82, 2002
4. DCCT/EDIC Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 342:381–389, 2000
5. Cryer P: Hypoglycemia: the limiting factor in the glycaemic treatment of type 1 and type 2 diabetes (Review). *Diabetologia* 45:937–948, 2002
6. Holman RR: The Treat-to-Target Trial: randomized addition of glargine or human NPH to oral therapy of type 2 diabetes. *Diabetes Res & Clin Prac* 40 (Suppl.): S21–S25, 1998
7. Riddle MC, Rosenstock J, Gerich J, the Insulin Glargine 4002 Study Investigators: The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26:3080–3086, 2003
8. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
9. Brown JP, Nichols GA, Perry A: The burden of treatment failure in type 2 diabetes. *Diabetes Care* 27:1535–1540, 2004
10. Abraira C, Henderson WG, Colwell JA, Nuttall FQ, Comstock JP, Emanuele NV, Levin SR, Sawin CT, Silbert CK: Response to intensive therapy steps and glipizide dose on combination with insulin in type 2 diabetes. *Diabetes Care* 21:574–579, 1998