# Triple Therapy

## Definitions, application, and treating to target

In this issue of *Diabetes Care*, Strowig, Avilés-Santa, and Raskin (1) evaluated the glycemic response to "triple therapy" in a small number of patients. Their study of triple therapy involved adding metformin to type 2 diabetic patients receiving >30 units of insulin plus troglitazone or adding troglitazone to similar patients receiving >30 units of insulin plus metformin. The added oral antidiabetes medications were titrated upward over 1 month to maximal doses and the patients followed for another 3 months without further changes in their doses. Insulin doses were not allowed to be increased but could be decreased in response to hypoglycemia. Although these patients were well controlled at baseline, their control improved even further with this triple therapy. A1C levels in patients in whom troglitazone was added fell from 7.0 ± 0.8% (mean ± SD) at baseline to 6.1 ± 0.4%. Corresponding changes in A1C levels in the group receiving metformin as the third medication were 6.2 ± 0.8 to 5.8 ± 0.6%.

There is no agreement on what constitutes triple therapy. The term has been used to describe oral medications from three classes of antidiabetes drugs, as well as various insulin regimens (mixed-split, basal-bolus, preprandial lispro) in combination with two oral medications (1–3). Although triple therapy has not been used to describe it, probably the most common combination is bedtime NPH (or glargine) insulin plus two oral medications. I would propose that we modify the term triple therapy in patients taking three medications to "triple oral therapy" or "triple therapy with insulin," depending on what the patient is taking. The specific components can then be added, e.g., triple oral therapy (metformin, glyburide, pioglitazone), triple therapy with insulin (bedtime glargine, glipizide, rosiglitazone), etc. If one wanted to be more specific, the doses of each could be placed next to the drug.

Regardless of terminology, one must put triple therapy in the therapeutic perspective. There is no one right way to treat type 2 diabetes. The goal is to achieve evidence-based targets. For a glycemic outcome, the American Diabetes Association's goal is an A1C level <7%. This is based on the results of five studies in several thousand diabetic patients carried out over 6–9 years relating the average A1C level to the development and progression of the microvascular complications of diabetes (4–8). All five demonstrated that if the average A1C level was <1% above the upper limit of normal (ULN) for the assay used (e.g., <7% for the assay used in the Diabetes Control and Complications Trial [DCCT], in which the ULN was 6.0%), there was virtually no development or progression of diabetic retinopathy or nephropathy. If the average A1C levels were between 1 and 2% above the ULN (7–8% in a DCCT-standardized assay), there was a slight increase in the development and progression of these complications. Average values >2% above the ULN (>8% in a DCCT-standardized assay) were associated with much higher risks for the microvascular complications. Thus, lower goal values, e.g., <6.5%, are not evidence based, and the harm of increased hypoglycemia (4) would not seem balanced by any additional benefit.

Many studies have compared various therapeutic approaches in type 2 diabetic patients at specific points in the course of their disease progression, e.g., failing monotherapy, failing dual oral therapy. There have been no studies, and indeed there probably never will be, directly comparing different therapeutic approaches along the progressive continuum of type 2 diabetes. However, two studies (9,10), utilizing very similar therapeutic approaches that were driven by algorithms, demonstrated glycemic outcomes just slightly above the A1C target level of 7% after 1 year. That these results were achieved in poorly educated, minority populations strongly suggests that similar outcomes are attainable in general. Therapy was progressively increased from diet/exercise in asymptomatic patients to monotherapy with metformin or a sulfonylurea agent, and to dual oral therapy with both of these. An important factor in their success was the imperative to raise the doses of metformin or the sulfonylurea agent every 2 weeks until either the American Diabetes Association's fasting plasma glucose goal was achieved or the maximal dose was reached, at which time the other medication was added. In this manner, patients did not remain out of control for long periods of time. Before glitazones became available, the next step was to add bedtime NPH insulin. If the cost of glitazones is a factor, this still remains an attractive option. In our institution (9), glitazones have been added to the formulary to be used for either triple oral therapy (metformin, glipizide or glyburide, glitazone) (11) (or if patients take >80 units insulin/day and remain in poor control). If triple oral therapy fails, bedtime insulin is substituted for the glitazone.

Since triple oral therapy (metformin ≥2,000 mg/day, glyburide 20 mg/day, pioglitazone 45 mg/day) was as effective as triple therapy with insulin (metformin ≥2,000 mg/day, glyburide 20 mg/day, bedtime NPH) (12), cost and lifestyle considerations may be the deciding factors when dual therapy fails. Of course, the bottom line is to treat to target, regardless of how one gets there. The approach described above is a cost-effective way to do just that.

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