What is the role of combination therapy (insulin plus oral medication) in type 2 diabetes?

Staci Eskesen, MD, Gary Kelsberg, MD
Valley Family Medicine Residency, Renton, Wash

Kristin Hitchcock, MSI
Department of Family Medicine, University of Chicago

EVIDENCE-BASED ANSWER

Combination therapy using insulin plus metformin (Glucophage), a sulfonylurea, or both produces glycemic control comparable with using insulin alone, but there is less weight gain when metformin is used (strength of recommendation [SOR]: **B**, based on systematic review of randomized controlled trials [RCTs] with some heterogeneity). Combination therapy using insulin and pioglitazone (Actos) reduces glycosylated hemoglobin (HbA_{1c}) more than either insulin alone or adding pioglitazone to a sulfonylurea, but results in more weight gain (SOR: **A**, based on RCT). Using insulin glargine (Lantus) in combination therapy produces fewer nocturnal hypoglycemic events than using neutral protamine Hagedorn (NPH) insulin, while producing equivalent HbA_{1c} reduction (SOR: **B**, based on RCT).

When the HbA_{1c} is high (above 9.0% to 9.5%) on 1 or 2 oral agents, beginning combination therapy is more effective than adding another oral agent (SOR: **B**, based on subpopulation analysis in RCTs).

CLINICAL COMMENTARY

Educate patients from the time of diagnosis that insulin is not a failure

Combination therapy for patients with type 2 diabetes is a safe and effective stepping stone between oral therapy and insulin therapy. Unfortunately, significant barriers remain to getting insulin started when oral agents alone are insufficient. Patients often do not understand the common need for insulin therapy as type 2 diabetes advances, and some physicians continue to use the threat of insulin as a punitive incentive to promote patient compliance. It is little wonder that many patients perceive a physician's eventual recommendation for insulin therapy as a personal failure. Patients are also concerned about the discomfort, inconvenience, and risk of insulin injections. Physicians should focus on educating their patients from the time of diagnosis that insulin is not a failure, but just another tool that will help them achieve their blood sugar goals.

Vincent Lo, MD
San Joaquin General Hospital, French Camp, Calif

Evidence summary

A systematic review evaluated beginning combination therapy (adding insulin to oral medication) compared with switching to insulin alone in patients with type 2 diabetes mellitus with inadequate glycemic control on oral medication.[1] Twenty RCTs studied a total of 1811

FAST TRACK

When HbA_{1c} is high, beginning combination therapy is more effective than adding another oral agent

patients; glycemic control was the primary outcome measure. Oral medication comprised either sulfonylureas (75%), metformin (4%), or both (21%). Individual studies used different insulin dosing schedules and statistical measures. However, overall, combination therapy provided glucose control comparable with insulin alone. In only 1 small, low-quality study did insulin plus metformin reduce HbA_{1c} more than other combination therapy regimens or insulin alone. Ten studies reported a trend toward less weight gain with combination therapy that included metformin. Fourteen studies found the same incidence of hypoglycemic episodes in combination therapy and insulin alone.

Three later RCTs of overweight patients with inadequate control on oral agents (HbA_{1c} >7% on a sulfonylurea, metformin, or both) also compared beginning combination therapy with switching to insulin alone (with 70/30 or NPH insulin twice daily). In one study with 64 patients followed for 12 months, HbA_{1c} fell by 0.14% less (nonsignificant) in the combination therapy group (bedtime NPH plus sulfonylurea and metformin) than in the insulin alone group (70/30 twice daily).[2] The combination therapy group gained significantly less weight than the insulin-alone group (1.3 kg vs 4.2 kg; *P*=.01).

In the second study of 261 patients, the combination therapy group (glimepiride [Amaryl] plus bedtime NPH) had a significantly higher HbA_{1c} after 9 months than 2 groups using insulin alone (twice daily 70/30, and twice daily NPH insulin) (8.9% vs 8.3% and 8.4%).[3] Mean weight gain was similar in all 3 groups but only a minority of patients reached a target HbA_{1c} of 6.5%. In the final study of only 16 patients, HbA1c after 6 months improved significantly and equally in both groups (baseline: 8.3%, combination therapy final: 6.8%; insulin alone final: 7.0%). However, the combination therapy group gained significantly less weight.[4]

An open-label RCT with 341 patients who were inadequately controlled on metformin compared beginning combination therapy (biphasic insulin aspart 30/70 [Novolog Mix 70/30] and metformin) with switching to insulin alone (biphasic insulin aspart 30/70).[5] A third group added a second oral medication (sulfonylurea and metformin). After 16 weeks, patients taking combination therapy had a significantly lower HbA_{1c} than those on insulin alone (treatment difference 0.39%, *P*=.007).

Overall, combination therapy and 2 oral medications reduced HbA_{1c} by the same amount, but combination therapy reduced HbA_{1c} more in a subpopulation of patients with HbA_{1c} >9.0% at baseline (treatment difference 0.46%, *P*=.027). The group on insulin alone weighed significantly more (4.6 kg, *P*<.001) at the end of the trial than the group taking 2 oral medications.

An open-label RCT of 756 patients with inadequate glycemic control (HbA_{1c} >7.5%, mean 8.6%) on either 1 or 2 oral agents (70% taking both metformin and a sulfonylurea) compared combination therapy using bedtime insulin glargine with combination therapy using morning NPH.[6] Each group titrated insulin doses to achieve a target fasting glucose ≤100. By 24 weeks, both groups had equivalently reduced HbA_{1c} (mean HbA_{1c}=6.96% with glargine, and 6.97% with NPH; *P*=NS), but fewer patients experienced nocturnal hypoglycemia with glargine than with NPH (33.2% vs 26.7%, *P*<.05).

Another open-label RCT evaluated 281 patients with at least 3 months of inadequate glycemic control (HbA_{1c}= 7.4%–14.7%) on a sulfonylurea.[7] Patients were randomized to a) switching to a combination of biphasic insulin aspart 30/70 plus pioglitazone, b) adding pioglitazone to the sulfonylurea, or c) switching to insulin alone (biphasic insulin aspart 30/70). After 18 weeks, insulin plus pioglitazone reduced HbA_{1c} significantly more than either glyburide

plus pioglitazone (*P*=.005) or insulin alone (*P*=.005). However, the insulin plus pioglitazone group had the most weight gain (mean 4 kg, similar to other pioglitazone trials). There were no major hypoglycemic events.

Another open-label RCT evaluated 217 patients inadequately controlled (HbA_{1c}=7.5%–11%) on a 2-drug oral regimen (metformin and a sulfonylurea, each drug dosed at ≥50% of the recommended maximum), randomized to add either insulin glargine or rosiglitazone (Avandia).[8] Both groups reduced HbA_{1c} equivalently after 24 weeks (–1.7% for glargine vs –1.5% for rosiglitazone). However, in patients with a baseline HbA_{1c} >9.5%, adding insulin glargine reduced HbA_{1c} significantly more than rosiglitazone.

Recommendations by others

A comparative analysis of guidelines on diabetes from 13 different countries (including the US) found general agreement in the recommendation to add a second oral agent to maximum doses of an initial agent in patients with poor glycemic control.[9] However, no consensus was reached on the value or indications of combination therapy with oral agents and insulin.

The European Diabetes Policy Group recommends adding a second oral agent when the maximum dose of a single agent is reached, and using triple therapy when targets are not reached on maximum tolerated doses of 2 agents. Continued therapy with oral agents is advised when initiating insulin.[10]

FAST TRACK

Ten studies reported a trend toward less weight gain with combination therapy that included metformin

REFERENCES

1. Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2004;(4):CD003418.
2. Goudswaard AN, Stolk RP, Zuithoff P, de Valk HW, Rutten GE. Starting insulin in type 2 diabetes: continue oral hypoglycemic agents? A randomized trial in primary care. *J Fam Pract* 2004; 53:393-399.
3. Stehouwer MHA, DeVries JH, Lumeij JA, et al. Combined bedtime insulin-daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: effects on HbA1c and hypoglycemia rate-a randomized trial . *Diabetes Metab Res Rev* 2003; 19:148-152.
4. Olsson PO, Lindstrom T. Combination-therapy with bedtime NPH insulin and sulphonylureas gives similar glycaemic control but lower weight gain than insulin twice daily in patients with type 2 diabetes. *Diabetes Metab* 2002; 28(4 Pt 1):272-277.
5. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. *Diabetes Obes Metab* 2006; 8:39-48.
7. Riddle MC, Rosenstock J, Gerich J, and 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* 2003; 26:3080-3086.
7. Raz I, Stranks S, Filipczak R, et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: an 18 week, randomized, open-label study. *Clin Ther* 2005; 27:1432-1443.
8. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients. *Diabetes Care* 2006; 29:554-559.
9. Burgers JS, Grol R, Klazinga NS, et al. Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. *Diabetes Care* 2002; 25:1933-1939.
10. European Diabetes Policy Group 1999. A desktop guide to Type 2 diabetes mellitus. *Diabet Med* 1999; 16:716-730.