American Family Physician
A peer reviewed journal of the American Academy of Family Physicians

April 1, 2007 Table of Contents

FPIN's Clinical Inquiries

Glycemic Control in Patients with Type 2 Diabetes

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Clinical Question

What is the most effective oral monotherapy for glycemic control in patients with type 2 diabetes?

Evidence-Based Answer

There is no clearly superior oral agent for glycemic control in patients with type 2 diabetes. (Strength of Recommendation [SOR]: C)

Metformin (Glucophage) has shown additional benefit when compared with other treatments (including insulin) for diabetes-related outcomes and all-cause mortality and should be considered the agent of choice for initial monotherapy, particularly in obese patients. (SOR: A)

Evidence Summary

A systematic review of 63 randomized controlled trials (RCTs) compared A1C reductions among the five classes of oral agents.1 The studies met the following criteria: study period of at least three months, enrollment of at least 10 subjects, and reported A1C reduction. Two groups of trials-monotherapy head-to-head studies (23 trials) and monotherapy versus placebo studies (31 trials)-were compared. A1C reductions were similar among studies with comparable numbers of subjects and lengths of follow-up (Table 11). Head-to-head trials comparing two or more drugs also showed similar effectiveness for reducing A1C.1

Table 1. Clinical Trials of Monotherapy for Glycemic Control in Patients with Type 2 Diabetes

Medication class (number of trials)	Study length	Number of subjects	Ranges of A1C reductions (%)
Sulfonylurea (4)	12 weeks to 10 years	204 to 3,867	0.9 to 2.5
Alpha glucosidase inhibitor	16 weeks to 2	40 to 495	0.4 to 1.3

(12)	years		
Metformin (7)	11 weeks to 10.7 years	27 to 753	0.8 to 3.0
Meglitinide (4)	12 to 24 weeks	93 to 701	0.6 to 1.7
Thiazolidinedione (4)	24 to 26 weeks	402 to 959	1.1 to 1.6

Information from Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA 2002;287:360-72.

The United Kingdom Prospective Diabetes Study included 4,075 newly diagnosed patients with type 2 diabetes who had A1C levels of 7.5 to 10.7 percent.2 After three months of diet therapy, subjects were randomized to four groups: insulin, sulfonylurea, metformin, or continued diet therapy. Only 50 percent of the patients in any group had A1C levels of less than 7 percent after three years, and only 25 percent had levels of less than 7 percent after nine years.2

Glycemic control is not the ultimate goal of diabetes treatment; the focus should be on which medications best reduce morbidity and mortality. A Cochrane review that included 29 trials and 5,259 participants looked at intensive glucose control with metformin.3 Metformin showed greater benefits for all-cause mortality (P = .03) and diabetes-related outcomes (P = .009) when compared with sulfonylurea, placebo, diet, thiazolidinedione, insulin, meglitinides, and glucosidase inhibitors.3

A systematic review of alpha-glucosidase inhibitors found no clear evidence that they reduce morbidity or mortality.4

Recommendations from Others

The American Diabetes Association recommends that patients with type 2 diabetes maintain an A1C of less than 7 percent. They do not recommend any specific medications for therapy.5

The Institute for Clinical Systems Improvement reports that the single best choice for oral therapy for type 2 diabetes has not been determined.6 The guideline also states that the United Kingdom Prospective Diabetes Study provides strong evidence that metformin in monotherapy may offer advantages for obese patients with type 2 diabetes with respect to morbidity and mortality. The guideline aconsiders sulfonylurea a good choice for monotherapy because it is relatively inexpensive and generally well tolerated.6

Clinical Commentary

Oral therapy for diabetes has long been an issue of "This is how I was trained" for physicians. Early on, sulfonylureas were the only choice. When metformin arrived on the scene in the 1990s, it brought more choice, and with the introduction of thiazolidinediones, meglitinides, and glucosidase inhibitors, the situation is even less clear. Achieving glucose and A1C goals remains one of the aims of diabetic therapy, but the bottom line should be reduction in morbidity and mortality.

Monotherapy with metformin is therefore appealing for several reasons: (1) it is generally well tolerated and its side effects are usually easy to manage; (2) the risk of hypoglycemia is minimal; and (3) it has direct effects on insulin resistance. With evidence of benefit in total morbidity and mortality over other oral antidiabetic agents, metformin seems a good choice for monotherapy when a single agent is effective.

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Author disclosure: Nothing to disclose.

Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/levels_of_evidence.asp).

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