What is the best medical therapy for new-onset type 2 diabetes?

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EVIDENCE-BASED ANSWER

Sulfonylureas, metformin, thiazolidinediones, and non-sulfonylurea secretagogues differ little in their ability to decrease glycosylated hemoglobin (HbA_{1c}) levels when used as initial monotherapy for diabetes mellitus type 2 (strength of recommendation [SOR]: **A**, based on systematic reviews); α-glucosidase inhibitors may also be as effective (SOR: **B**, based on systematic reviews with inconsistent results). Metformin is generally indicated in obese patients because it improves all-cause mortality and diabetes related outcomes (SOR: **B**, based on a single high-quality randomized controlled trial [RCT]). Insulin is generally not recommended as an initial agent (SOR: **C**, expert opinion). ❑

EVIDENCE SUMMARY

Oral agents are commonly prescribed for patients with diabetes mellitus type 2 when diet and exercise fail. Options for initiating therapy include sulfonylureas, metformin (Glucophage), α-glucosidase inhibitors, thiazolidinediones, and non-sulfonylurea secretagogues (repaglinide [Prandin] and nateglinide [Starlix]).

A systematic review with 31 placebo-controlled randomized trials (total n=12,185 patients) evaluated changes in HbA_{1c} with monotherapy using 5 different classes of oral agents (TABLE).(1) Except for the a-glucosidase inhibitor acarbose (Precose), which was less effective, all agents typically reduced HbA_{1c} by 1% to 2%. However, in an additional 19 out of 23 randomized head-to-head studies (total n=5396) included in the same systematic review, all classes showed equal efficacy.

Head-to-head studies are difficult to compare since hypoglycemic medications may reach peak effects at different times. An RCT compared glimepiride (Amaryl), pioglitazone (Actos), and metformin over 12 months of use by 114 patients with diabetes.(3) There was no difference among the groups in overall HbA_{1c} reduction. However, glimepiride decreased HbA_{1c} rapidly over 1 month and reached a nadir at 4 months. Pioglitazone did not reduce HbA_{1c} until 6 months and reached its nadir at 7 to 9 months. Metformin produced an intermediate response.

A meta-analysis of head to head studies involving a-glucosidase inhibitors included 8 trials comparing acarbose with sulfonylureas. In pooled results, sulfonylureas trended towards greater HbA_{1c} reduction but did not reach significance (additional HbA_{1c} decrease 0.4%; 95% confidence interval [CI], 0%–0.8%).(4)

A meta-analysis of head-to-head studies involving metformin showed equal efficacy compared with injected insulin (2 trials, 811 participants), α-glucosidase inhibitors (2 trials, 223 participants), and non-sulfonylurea secretagogues (2 trials, 413 participants).(5) In 12 trials with 2067 patients, metformin decreased HbA_{1c} more than sulfonylureas did (standardized mean difference [SMD] −0.14; 95% CI, −0.28 to −0.01). In 3 trials with 246 patients, metformin also produced greater HbA_{1c} decreases than thiazolidinediones (SMD +0.28; 95% CI, +0.52 to +0.03). In the United Kingdom Prospective Diabetes Study (UKPDS), metformin improved diabetes-related outcomes and all-cause mortality in obese patients (relative risk of mortality=0.73; 95% CI, 0.55–0.97; *P*=.03; number needed to treat [NNT]=19).(6)

Table. Oral medications as monotherapy in type 2 diabetes mellitus (1,2)

Class	Dosing Interval	Typical HBA_{1C} Reduction	Cost* per Month†	Contraindications/Cautions
Sulfonylureas	1x daily	1.4%–1.8%	$	DKA, caution in hepatic or renal disease
Metformin	1–2x daily	1.1%–2.0%	$$	Congestive heart failure, acute or chronic metabolic acidosis, Cr ?1.5 male, Cr ?1.4 female, COPD, severe hepatic disease, alcoholism. Use caution in the elderly.
α-glucosidase inhibitors	3x daily	0.6%–1.0%	$$$	Cr ?2.0, abnormal baseline liver function tests, inflammatory bowel disease
Thiazolidinediones	1–2x daily	1.5%–1.6%	$$$–$$$$	Class III to IV heart failure, baseline ALT >2.5
Non-sulfonylurea secretagogues	3x daily	1.8%–1.9%	$$–$$$	Caution with liver disease

* The "typical" range excludes the studies with the highest and lowest measured effects.
† $ = $0 to $25; $$ = $25 to $60; $$$ = $60 to $120; $$$$ = $120 to $180.
DKA, diabetic ketoacidosis; Cr, chromium; COPD, chronic obstructive pulmonary disease; ALT, alanine transaminease.

A systematic review with 22 RCTs (total n=7370), ranging in length from 12 weeks to 3 years, compared 2 oral agents with a single oral agent or placebo. (1) Combinations of oral agents produced statistically significant additional improvement in HbA_{1c} in 21 of 22 studies. The magnitude of this effect across the studies was on the order of a 1% change in HbA_{1c}, although the data were not subject to a formal meta-analysis.

Inhaled insulin may expand the list of initial therapies for type 2 diabetes. A 12-week manufacturer-sponsored RCT with 134 patients (mean HbA_{1c}=9.5) compared inhaled insulin with rosiglitazone (Avandia). (7) More patients using inhaled insulin achieved an HbA_{1c} <8.0 (82.7% vs 58.2%; *P*=.0003); however, inhaled insulin produced more adverse effects, including cough and hypoglycemia. ❑

CLINICAL COMMENTARY

Consider the advantages of each class to best meet your patient's goals

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Lifestyle modification is the cornerstone of initial treatment of type 2 diabetes. However, in clinical practice, medications (monotherapy or combination therapy) are often started along with diet and exercise recommendations. Physicians and patients should clearly understand the treatment goals before initiating therapy. Multiple factors often influence treatment goals, such as presence or absence of symptoms, age-related risks from potential hypoglycemia, degree of hyperglycemia, presence of morbidities (renal insufficiency, heart failure, obesity), cost of the medication, as well as patient or physician preferences. Despite their comparable efficacy in the reduction of HbA_{1c} level, each class of oral hypoglycemic medication has a different mechanism of action and adverse side-effect profile. Therefore, physicians must consider the advantages and disadvantages of each class to choose a medication regimen that best meets their patient's individual treatment goals. ❑

FAST TRACK

Metformin improved diabetes-related outcomes and all-cause mortality in obese patients

RECOMMENDATIONS FROM OTHERS

The International Diabetes Federation (IDF) recommends metformin as the initial oral agent unless contraindicated. (8) A sulfonylurea is an acceptable alternative in patients who are not overweight. The IDF states that insulin should be added when oral agents fail.

FAST TRACK

Patients on inhaled insulin achieved an HbA_{1c} of less than 8, but also had more adverse effects

The Institute for Clinical Systems Improvement (ICSI) says that the "single best choice drug for oral agent therapy for type 2 diabetes has not been determined" and must be chosen in the context of age, weight, and other comorbidities. (9) The ICSI suggests metformin as an appropriate first agent for obese patients and recommends sulfonylureas or metformin as monotherapy for others because they are both economical and well tolerated. The American Diabetes Association does not specifically recommend a best initial agent or combination of agents for type 2 diabetes. (10) ❑

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