

Trials That Matter: Rosiglitazone, Ramipril, and the Prevention of Type 2 Diabetes

Despite the growing number of options for treating type 2 diabetes, clinicians wanting to prevent the disease in high-risk patients have few good choices. Lifestyle changes that lead to weight loss can prevent diabetes (1, 2) but are difficult to adopt and maintain (3). Drugs used to treat diabetes are often expensive, and testing has only recently begun on their efficacy as primary preventive agents. Two large trials in 2002 showed that metformin (1) and acarbose (4) effectively prevent diabetes in participants with impaired glucose tolerance, but neither drug has been approved by the U.S. Food and Drug Administration (FDA) for prevention and their use has not become part of routine practice.

Thiazolidinediones and angiotensin-converting enzyme inhibitors are also potential candidates for primary diabetes prevention. Troglitazone showed early promise in clinical trials (5, 6), but further testing was preempted by the drug's withdrawal from the market. Secondary analyses of large trials of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers for treating cardiovascular disease raised the possibility that the effects of these drugs might protect against diabetes (7–9). The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial was designed to determine if ramipril and rosiglitazone could fulfill the promise of type 2 diabetes prevention suggested by the earlier studies (10, 11).

WHAT DID THIS LANDMARK TRIAL SHOW?

The trial investigators randomly assigned 5269 patients with impaired fasting glucose (plasma glucose level >6.1 mmol/L [>110 mg/dL] but <7.0 mmol/L [<126 mg/dL]), impaired glucose tolerance (plasma glucose level ≥ 7.8 mmol/L [≥ 140 mg/dL] but <11.1 mmol/L [<200 mg/dL] 2 hours after an oral glucose load), or both to receive ramipril (5 mg daily increased to 10 mg after 2 months and to 15 mg after 1 year), rosiglitazone (4 mg daily increased to 8 mg after 2 months), both, or placebo. The participants were evaluated at months 2, 6, and 12, and once a year thereafter, for the composite outcome of death or diabetes (primary outcome) and for regression to normal glucose levels (secondary outcome).

Participants were middle-aged (mean age, 54.7 years) and overweight (mean body mass index, 31 kg/m²). After a median follow-up of 3 years (range, 2.5 to 4.7 years), the researchers detected a significant reduction in the primary outcome among participants taking rosiglitazone (11.6% rosiglitazone vs. 26% placebo; hazard ratio, 0.40 [95% CI, 0.35 to 0.46]; $P < 0.001$) but not in those taking ramipril (17.1% ramipril vs. 18.5% placebo; hazard ratio, 0.91 [CI, 0.80 to 1.03]; $P = 0.150$). The difference in primary out-

come among trial groups was entirely attributable to a reduction in newly diagnosed diabetes in the rosiglitazone group and was evident across multiple subgroups, including those defined by age, race, sex, weight, and body mass index. More patients taking rosiglitazone regressed to normal glucose levels (38.6% rosiglitazone vs. 20.5% placebo; hazard ratio, 1.83 [CI, 1.65 to 2.04]; $P < 0.001$). Taking both rosiglitazone and ramipril had no apparent benefit.

Although both medications were generally safe and had a low frequency of severe adverse events, rosiglitazone was associated with a significantly higher prevalence of peripheral edema (6.8% vs. 4.9% [$P = 0.003$] at the final study visit) and a 2.2-kg higher body mass. More important, rosiglitazone appeared to lead to an increased frequency of heart failure (14 [0.5%] patients taking rosiglitazone vs. 2 [0.1%] patients taking placebo; hazard ratio, 7.03 [CI, 1.60 to 30.9]; $P = 0.01$) (10).

HOW DOES THIS TRIAL ADVANCE WHAT WE KNOW?

The DREAM trial provides additional evidence that overweight, middle-aged persons with glucose intolerance have a high risk for diabetes (25% over 3 years in the placebo group). It lays to rest the hope that angiotensin-converting enzyme inhibitors might prevent progression and clarifies the role of thiazolidinediones in the debate over whether and how best to prevent or at least delay the disease (5, 6). That debate now centers around the relative efficacy, safety, cost, likelihood of adherence, and persistence of effect of the 4 interventions that have been directly evaluated in diabetes prevention trials: lifestyle changes, metformin, acarbose, and rosiglitazone (Table [1, 2, 4, 10, 12]).

No one questions that lifestyle changes are the intervention of choice to prevent or delay type 2 diabetes in at-risk patients. No other intervention has a larger preventive effect. Lifestyle changes are also the safest intervention and have other health benefits. It is important to note that a long-term follow-up study of patients randomly assigned to a 4-year lifestyle intervention has demonstrated that the beneficial effects of lifestyle intervention on diabetes development last for up to 7 years (13).

However, counseling a healthy lifestyle is clearly not working in practice. The twin epidemics of obesity and diabetes, and their downstream microvascular and cardiovascular consequences, have increased dramatically despite an environment in which lifestyle changes are encouraged and the benefits have been well-described. If lifestyle changes were adhered to in practice as well as they have been in clinical trials, the epidemics would not exist in the first place. Therefore, other measures are necessary to ad-

Table. Interventions to Prevent Type 2 Diabetes*

Variable	Intervention				
	Lifestyle		Metformin	Acarbose	Rosiglitazone
Trial (reference)	FDPS (2, 12)	DPP (1)	DPP (1)	STOP-NIDDM (4)	DREAM (10)
Mean follow-up, y	3.2	2.8	2.8	3.3	3.0
Patient characteristics					
Mean age, y	55.0	50.6	50.9	54	54.7
Body mass index, kg/m ²	31	33.9	33.9	31	31
Outcomes					
Weight change, kg†	-4.2	-5.6	-2.1	0.5	2.2
Relative reduction in occurrence of type 2 diabetes mellitus (95% CI), %	58 (30-70)‡	58 (48-66)§	31 (17-43)§	25 (10-37)‡	62 (56-67)‡
Adverse events	None	Musculoskeletal symptoms	GI symptoms	GI symptoms	Peripheral edema Weight gain Heart failure
Persistence of effect	Confirmed	Pending	Pending	No	Pending

* Enrollment criteria for all trials included impaired fasting glucose, impaired glucose tolerance, or both. DPP = Diabetes Prevention Program; DREAM = Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial; FDPS = Finnish Diabetes Prevention Study; GI = gastrointestinal; STOP-NIDDM = Study to Prevent Non-Insulin-Dependent Diabetes Mellitus.

† All estimates are mean weight change relative to within-group baseline except for rosiglitazone, which is mean weight change relative to placebo.

‡ Reduction in hazard (1.0 - hazard ratio); acarbose estimate adjusted for age, sex, and body mass index.

§ Absolute percentage difference (drug - placebo).

dress the diabetes epidemic currently manifesting as 1.5 million new cases of diabetes per year (14).

Are medications a reasonable “other measure”? If so, which should be used? The DREAM trial does not answer either question directly, but by defining the benefits and risks of rosiglitazone it clarifies the relative advantages and disadvantages of the 3 drugs studied in diabetes prevention trials.

Indirect comparisons of agents across trials are imperfect, but the trial data suggest that rosiglitazone is as efficacious as lifestyle changes and conveys about twice the relative risk reduction for diabetes of metformin or acarbose. However, this benefit comes at the cost of clinically significant fluid retention; weight gain; and, in some studies, heart failure. The risk for heart failure has been demonstrated in other recent large clinical trials of thiazolidinediones (12, 15) and of muraglitazar, an agent with actions like thiazolidinediones (16). Moreover, the advantage in efficacy of rosiglitazone over metformin is probably reduced in people with a body mass index of 35 kg/m² or higher, who experienced a 53% (CI, 36% to 65%) reduction in diabetes development with metformin (1), which is closer to the 60% reduction in hazard observed with rosiglitazone.

Adherence to once-daily rosiglitazone and twice-daily metformin was similar at 72% of participants in each trial. In contrast, adherence to acarbose was poor, with nearly 25% of participants withdrawing from the trial due to gastrointestinal adverse events.

Rosiglitazone is expensive (about 4 to 5 times the cost of metformin) (17), and the persistence of its preventive effect is unknown. The DREAM trial included a 3-month posttrial washout period to evaluate the incidence of new diabetes after discontinuation of rosiglitazone therapy, but

those data have not yet been reported. Investigators are also following the metformin trial population to determine whether people who continue to use the drug continue to have a lower risk for diabetes.

In summary, rosiglitazone is the most efficacious of the drugs, but is also expensive and possibly most harmful. Metformin is nearly as effective as rosiglitazone in the most obese patients, is safe and generally well-tolerated with high adherence, and is inexpensive relative to the other drug options. Acarbose, although it is safe, is less effective and is poorly tolerated by many people.

WHAT SHOULD CLINICIANS DO?

Clinicians should continue to counsel patients with impaired glucose tolerance or impaired fasting glucose on the benefits of lifestyle changes; specifically, physical activity and a low-calorie, low-fat diet targeted to achieve weight loss of at least 7% of initial body weight. An informal approach to achieving these goals is likely to be less effective than the more intensive interventions used in the clinical trials, which involve specific individualized instructions delivered and periodically reinforced by case managers and nutritionists.

For patients unable to adopt or maintain these lifestyle changes, rosiglitazone does not seem to be the answer. Preventive treatment needs to be safe, because many people who take it will not develop diabetes. It must also be more beneficial and cost-effective than delaying treatment until diabetes develops. On the basis of DREAM trial data, rosiglitazone does not meet these criteria, and clinicians should consider other available medications for use in individuals at high risk for diabetes.

Among those medications, metformin appears to be

most reasonable. Although no drug is currently FDA-approved for prevention, metformin's generally excellent efficacy and safety profile, its high level of acceptance, and its relatively low cost compared with other available agents suggest it has a role to play in preventing or delaying the onset of diabetes in people with documented impaired glucose tolerance and impaired fasting glucose who are younger (<60 years of age) and obese (body mass index >35 kg/m²).

More work is needed, however, to fully justify that impression. Although it seems logical to conclude that a shorter period of exposure to hyperglycemia and diabetes is beneficial, the long-term benefits and cost-effectiveness of early treatment with any drug, compared with waiting for diabetes to develop before beginning treatment, are yet unproven.

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Potential Financial Conflicts of Interest: *Honoraria:* D.M. Nathan (GlaxoSmithKline).

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Ann Intern Med. 2007;146:461-463.

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