THERAPEUTICS

Ramipril did not reduce incident diabetes in patients with impaired glycemic control

Bosch J, Yusuf S, Gerstein HC, et al. **Effect of ramipril on the incidence of diabetes.** N Engl J Med. 2006;355:1-12.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Endocrinology ★★★★★★☆

QUESTION

In patients with impaired fasting glucose or impaired glucose tolerance at low risk for cardiovascular (CV) events, does ramipril reduce risk for diabetes?

METHODS

Design: Randomized placebo-controlled trial (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication [DREAM]).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, data collectors, and outcome assessors).*

Follow-up period: Median 3 years.

Setting: 191 centers in 21 countries.

Patients: 5269 patients ≥ 30 years of age (mean age 55 y, 59% women) who had impaired fasting plasma glucose (≥ 110 mg/dL [6.1 mmol/L] but < 126 mg/dL [7.0 mmol/L]) or impaired glucose tolerance (plasma glucose level ≥ 140 mg/dL [7.8 mmol/L] but < 200 mg/dL [11.1 mmol/L] 2 h after oral glucose load). Exclusion criteria were history of diabetes (except gestational diabetes), CV disease, or intolerance to angiotensin-converting enzyme inhibitors or thiazolidinediones.

Intervention: Ramipril, 5 mg/d for 2 months, then 10 mg/d for 10 months, and 15 mg/d after 1 year (n = 2623), or matching placebo (n = 2646).

Outcomes: Composite endpoint of newly diagnosed diabetes or death. Secondary outcomes included a composite endpoint of CV events (myocardial infarction, stroke, CV death, heart failure, revascularization, newly diagnosed angina with evidence of ischemia, or ventricular arrhythmia requiring resuscitation) and regression to normoglycemia (fasting plasma glucose level < 110 mg/dL [6.1 mmol/L] and 2-h post-load glucose level < 140 mg/dL [7.8 mmol/L]). The study had 90% power to detect > 22% risk reduction in the ramipril group.

Patient follow-up: 98% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for the primary or secondary composite endpoints (Table). More patients regressed to normoglycemia in the ramipril group than did those in the placebo group (Table).

CONCLUSION

In patients with impaired fasting glucose or impaired glucose tolerance at low risk for cardiovascular events, ramipril did not reduce diabetes or death.

Sources of funding: Canadian Institutes of Health Research; Sanofi-Avenits; GlaxoSmithKline; King Pharmaceuticals.

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*See Glossary.

Ramipril vs placebo in patients with impaired fasting glucose or glucose tolerance at median 3 years†

Outcomes	Ramipril	Placebo	RRR (95% CI)	NNT (CI)
Composite endpoint‡	18.1%	19.5%	8.1% (–2.7 to 17)	Not significant
			RBI (CI)	
Regression to normoglycemia	42.5%	38.2%	12% (5.4 to 20)	22 (14 to 49)
			RRI (CI)	NNH
Composite cardiovascular endpoint§	2.6%	2.4%	7.9% (–24 to 51)	Not significant

†Abbreviations defined in Glossary; RRR, RBI, RRI, NNT, NNH, and CI calculated from control event rates and hazard ratios in article.
‡Diabetes (17.1% vs 18.5%) or death (1.2% vs 1.2%).
§Myocardial infarction (0.5% vs 0.4%), stroke (0.2% vs 0.3%), cardiovascular death (0.5% vs 0.4%), heart failure (0.5% vs 0.2%), revascularization (1.0% vs 1.3%), newly diagnosed angina (0.9% vs 0.8%), or ventricular arrhythmia requiring resuscitation (0% vs 0%).

COMMENTARY

Difficulties in implementing intensive lifestyle changes have fueled enthusiasm for pharmacological interventions to prevent diabetes. ACE inhibitors and ARBs have small beneficial effects on glucose metabolism, presumably by inhibiting the renin-angiotensin system. The DREAM trial by Bosch and colleagues and the review by McCall and colleagues present apparently contradictory inferences. The systematic review and meta-analysis of 13 RCTs of ACE inhibitors and ARBs in patients with hypertension or CV disease showed a significant reduction in the incidence of diabetes (as a secondary or post hoc outcome in each trial). The methodologically rigorous DREAM trial investigated the prevention of diabetes and showed that taking ramipril for 3 years did not reduce the incidence of diabetes in patients with impaired fasting glucose or impaired glucose tolerance. There was, however, an increased regression to normoglycemia in patients taking ramipril. Why do these results differ and which should clinicians trust more: a large RCT (n > 5000) or a meta-analysis based on large trials (n > 67 000)?

The meta-analysis by McCall and colleagues showed a 20% relative risk reduction (95% CI 16 to 24) in the incidence of diabetes, similar to previous meta-analyses of 10 (1) and 12 (2) RCTs. Some methodological issues merit attention. First and foremost, reporting bias may affect these reviews. This occurs when the likelihood of publication of research depends on the direction of the results (i.e., when secondary or exploratory analyses of RCTs conducted with a different primary purpose do not get published because they failed to show a significant effect of ACE inhibitors or ARBs on the incidence of diabetes). If the reviewers did not contact authors of all ACE inhibitor and ARB trials for data on the effect of ACE inhibitor and ARBs on the incidence of diabetes, then reporting bias may affect their reviews. For example, these reviews did not include the ACE inhibitor trials AIRE (3) and TRACE (4), which did not report diabetes as an outcome. Therefore, because of reporting bias, systematic reviews of published analyses may overestimate the true effect of the interventions. Other shortcomings of this review include: no analyses of the methodological quality of individual included studies, no assessment of heterogeneity between studies, and no description of pooling procedures.

(continued on page 11)

Review: ACE inhibitors and angiotensin-receptor blockers reduce diabetes in hypertension and other CV risk factors

McCall KL, Craddock D, Edwards K. **Effect of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers on the rate of new-onset diabetes mellitus: a review and pooled analysis.** Pharmacotherapy. 2006;26:1297-306.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Endocrinology ★★★★★★☆

QUESTION

In patients with hypertension or other cardiovascular risk factors, can angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) reduce new-onset diabetes mellitus?

METHODS

Data sources: MEDLINE (January 1966 to October 2005).

Study selection and assessment: Randomized controlled trials (RCTs) that compared ACE inhibitors or ARBs as the primary intervention with a control group that did not receive an ACE inhibitor or ARB and reported the rate of new-onset diabetes. 13 RCTs (n = 67 271; age range 22 to 89 y; mean follow-up 4 y, range 1 to 6 y) met the selection criteria.

Outcomes: New-onset diabetes.

MAIN RESULTS

Meta-analyses showed that patients receiving ACE inhibitors or ARBs had lower incidences of diabetes than those receiving a control (β-blocker or thiazide, atenolol or hydrochlorothiazide, dihydropyridine calcium-channel blockers, amlodipine, chlorthalidone, or placebo) (Table).

CONCLUSION

Angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers reduce new-onset diabetes mellitus in patients with hypertension or other cardiovascular risk factors.

Source of funding: Not stated.

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Prevention of new-onset diabetes with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) vs control in patients with hypertension or other cardiovascular risk factors at mean 4 years*

Number of trials (n)	Comparisons	Weighted event rates	RRR (95% CI)	NNT (CI)
13 (67 271)	ACE inhibitor or ARB vs control†	7.2% vs 9.0%	20% (16 to 24)	56 (47 to 70)
6 (20 891)	ACE inhibitor or ARB vs placebo	6.1% vs 7.9%	23% (15 to 31)	55 (41 to 85)
6 (32 429)	ACE inhibitor or ARB vs-β blocker or thiazide	6.0% vs 7.8%	23% (17 to 29)	56 (45 to 76)
3 (17 384)	ACE inhibitor or ARB vs dihydropyridine CCB	10% vs 13%	18% (11 to 24)	45 (34 to 73)

*CCB = calcium-channel blocker. Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from control event rates and relative risks in article.

†Control = β-blocker or thiazide, atenolol or hydrochlorothiazide, dihydropyridine CCB, amlodipine, chlorthalidone, or placebo.

COMMENTARY *(continued from page 10)*

The DREAM trial yielded results that were less sanguine but not entirely incompatible with the results of the systematic review. The duration of follow-up was brief (curves for the incidence of diabetes in each group began to separate as the trial drew to a close) and the resulting CI was wide, meaning that the results did not exclude the possibility of some benefit of ramipril in preventing diabetes.

Ultimately, is delaying the diagnosis of diabetes desirable enough to begin prescribing a medication to patients at risk, or should clinicians demand evidence that earlier introduction (i.e., before the diagnosis) is indeed associated with improved health outcomes, especially for CV events? In the DREAM trial, CV events were not significantly reduced when ACE inhibitors were given to patients at very low risk for these events.

Except in rare cases where patients with diabetes develop hypoglycemia when they start using ACE inhibitors, it remains doubtful whether ACE inhibitors or ARBs significantly improve glucose metabolism. While improvement in glucose tolerance may be an added benefit for patients who take ACE inhibitors for other indications, especially hypertension, these drugs cannot be recommended solely with the intention of preventing type 2 diabetes. 2 large RCTs with ARBs are currently underway, which may shed more light on this issue (5, 6).

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