

Review: Angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors have the lowest risk for diabetes

Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201-7.

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

QUESTION

In patients with hypertension or other cardiovascular risk factors, what are the relative odds of developing diabetes with long-term use of the various types of antihypertensive drugs?

METHODS

Data sources: MEDLINE, Cochrane Database of Systematic Reviews, PubMed, OvidWeb (to September 2006), and reference lists.

Study selection and assessment: Long-term randomized controlled trials (RCTs) of antihypertensive drugs that reported the number of new cases of diabetes among patients without diabetes at baseline. 22 RCTs (48 treatment groups, $n = 155\,961$) met the selection criteria, comparing various combinations of angiotensin-converting enzyme (ACE) inhibitors (8 RCTs), angiotensin-receptor blockers (ARBs) (5 RCTs), calcium-channel blockers (9 RCTs), β -blockers (9 RCTs), diuretics (8 RCTs), and placebo (9 RCTs).

Outcome: Proportion of patients who developed diabetes.

MAIN RESULTS

In the 22 trials, each drug type (including placebo) was directly compared with each of the other 5 drug types in ≥ 1 RCT, except no trial directly compared ACE inhibitors with ARBs. Using network meta-analysis to combine direct and indirect comparisons among the drug types, the risk for diabetes was lowest for ARBs then, in ascending order, ACE inhibitors, placebo, calcium-channel blockers, β -blockers, and diuretics (Table). Risk for diabetes did not differ between ARBs and ACE inhibitors, or between β -blockers and diuretics.

CONCLUSIONS

In patients with hypertension or other cardiovascular risk factors, the antihypertensive drugs associated with the lowest risk for diabetes with long-term use are angiotensin-receptor blockers and angiotensin-converting-enzyme inhibitors. The drugs associated with the highest risk are β -blockers and diuretics.

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Relative odds for incident diabetes with long-term antihypertensive drug use*

Types of drug	Number of trials (n)	Odds ratio (95% CI) compared with diuretics	Odds ratio (CI) compared with placebo
Angiotensin-receptor blockers	5 (14 185)	0.62 (0.51 to 0.77)	0.84 (0.70 to 1.00)
Angiotensin-converting enzyme inhibitors	8 (23 351)	0.67 (0.57 to 0.79)	0.90 (0.78 to 1.04)
Placebo	9 (24 767)	0.75 (0.63 to 0.89)	Referent
Calcium-channel blockers	9 (38 809)	0.79 (0.67 to 0.92)	1.05 (0.90 to 1.24)
β -blockers	9 (36 150)	0.93 (0.78 to 1.11)	1.25 (1.05 to 1.48)
Diuretics	8 (18 699)	Referent	1.34 (1.12 to 1.60)

*CI defined in Glossary. Corrected data provided by author.

COMMENTARY

The network meta-analysis by Elliott and Meyer quantifies the risk for incident diabetes associated with commonly prescribed antihypertensive drugs. These summary estimates should be viewed as associative and not causal, as they are predominantly based on data from secondary or post hoc analyses of RCTs.

There are several practical implications from this and other recently published evidence. First, as Elliott and Meyer note, the absolute increase in diabetes incidence associated with thiazide diuretics and β -blockers seems to be small. One should not avoid using such drugs in patients with compelling indications or who have not yet reached target blood pressure goals. Second, the clinical significance of thiazide-induced "diabetogenic" effects is uncertain, as the wealth of accumulated evidence to date shows equivalent reductions in major cardiovascular events, cardiovascular mortality, and overall mortality with thiazide diuretic-based regimens and other commonly used agents in patients with and without diabetes (1). Third, avoidance of hypokalemia may minimize any increase in blood glucose (2). Fourth, β -blockers are less efficacious than other agents in reducing stroke and, in the absence of compelling indications, are already not considered first-line agents, particularly in older patients (3). Finally, pending the results of ongoing studies, little *direct* evidence shows that ACE inhibitors or ARBs reduce

diabetes incidence and that this reduction is a true preventive effect (4).

Overall, proper blood pressure control is paramount, most patients require multiple drugs to achieve blood pressure targets, and many patients remain untreated or undertreated. One must be continuously mindful of these 3 important points when interpreting the results of studies in this field.

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