Review: β-blockers for hypertension increase risk for new-onset diabetes compared with nondiuretic antihypertensive agents

Bangalore S, Parkar S, Grossman E, Messerli FH. **A meta-analysis of 94 492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus.** Am J Cardiol. 2007;100:1254-62.

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

QUESTION

In patients with hypertension, do β-blockers increase risk for new-onset diabetes?

METHODS

Data sources: MEDLINE, PubMed, and EMBASE/Excerpta Medica (to March 2007).

Study selection and assessment: Randomized controlled trials (RCTs) that were published in English in peer-reviewed journals, compared β-blockers with placebo or other antihypertensive agents as first-line therapy for hypertension, and reported incidence of new-onset diabetes at ≥ 1 year. 12 RCTs (n = 94 492, mean age 50 to 76 y, 33% to 100% men) met the selection criteria: 2 RCTs (n = 16 372) compared β-blockers with placebo, 5 RCTs (n = 17 860) compared β-blockers with thiazide diuretics, and 7 RCTs (n = 65 765) compared β-blockers (with or without diuretics) with nondiuretic antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or calcium-channel blockers). Median duration of follow-up was 5 years.

Outcomes: New-onset diabetes (variably defined), death, myocardial infarction (MI), and stroke.

MAIN RESULTS

Risk for new-onset diabetes was increased with β-blockers compared with ACE inhibitors, ARBs, and calcium-channel blockers; risk did not differ from placebo or diuretics (Table). Compared with nondiuretic agents, risk for new-onset diabetes was increased with β-blockers plus diuretics (relative risk [RR] 1.11, 95% CI 1.01 to 1.22, 3 RCTs) or β-blockers alone (RR 1.30, CI 1.22 to 1.39, 4 RCTs). β-blocker groups did not differ from all comparison groups combined for death (RR 1.04, CI 1.00 to 1.09) or MI (RR 1.02, CI 0.92 to 1.12); β-blockers were associated with increased risk for stroke (RR 1.15, CI 1.01 to 1.30).

CONCLUSION

In patients with hypertension, first-line therapy with β-blockers is associated with increased risk for new-onset diabetes but does not affect risk for death or myocardial infarction compared with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium-channel blockers.

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Risk for new-onset diabetes with β-blockers vs placebo or other antihypertensive agents at median 5 years*

Comparison agent	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		β-blockers	Comparison agent		
ACE inhibitor or ARB	4 (23 156)	7.6%	6.2%	23% (6 to 42)	71 (39 to 269)
Calcium-channel blocker	5 (44 975)	8.0%	6.6%	21% (7 to 36)	73 (43 to 217)
Placebo	2 (16 372)	1.6%	1.1%	44% (–31 to 200)	Not significant
				RRR (CI)	NNT
Diuretic	5 (17 860)	2.1%	2.7%	21% (–41 to 55)	Not significant

*ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; other abbreviations defined in Glossary. Weighted event rates, RRI, RRR, NNH, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

Because physicians prescribe a particular drug, rather than a drug class, for individual patients, the relevance of the meta-analysis by Bangalore and colleagues to clinical practice is unclear. Any analysis of β-adrenergic receptor antagonists is unavoidably confounded by their considerable variability in antagonist activity at β_1-, β_2-, and β_3-receptors; intrinsic agonist activity; membrane-stabilizing activity; and lipid solubility. The metaregression used in this review does not seem to have been adjusted for this important potential source of heterogeneity. The authors also excluded some important trials for reasons that seem arbitrary. Further, they did not describe how they adjusted for multiple comparisons in calculating statistical significance.

One large RCT found that captopril and atenolol were similarly effective in reducing the incidence of diabetic complications (1). Thiazide diuretics also have some adverse metabolic effects, yet another large RCT found that chlorthalidone, amlodipine, and lisinopril were similarly effective in reducing the combined rate of fatal or nonfatal MI, and that doxazosin, the drug with favorable metabolic effects, was inferior to the other 3 drugs (2).

Although antihypertensive drugs vary in their potential adverse effects, physicians will best serve their patients if they base prescribing decisions on evidence of outcomes that are meaningful to patients and not on surrogate markers of uncertain significance. Adverse drug event research provides information essential to recognizing or avoiding drug toxicity. Physicians would be well-advised to monitor patients on thiazides or β-blockers for hyperglycemia, those on amlodipine for edema, and those on ACE inhibitors for angioedema and modify antihypertensive therapy accordingly.

Patients with a combination of hypertension, hyperglycemia, abdominal obesity, elevated triglycerides, and reduced high-density lipoprotein cholesterol may have the metabolic syndrome and may benefit from weight loss and increased physical activity. However, concern about adverse metabolic effects should not dissuade physicians from using diuretics or β-blockers as antihypertensive agents.

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References

1. **UK Prospective Diabetes Study Group.** Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ. 1998;317:713-20.
2. **The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group.** Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97.