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


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

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

**Methods**
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 years, 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**

<table>
<thead>
<tr>
<th>Comparison agent</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>RRI (95% CI)</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>4 (23,156)</td>
<td>7.6%</td>
<td>6.2%</td>
<td>23% (6 to 42)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>5 (44,975)</td>
<td>8.0%</td>
<td>6.6%</td>
<td>21% (7 to 36)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2 (16,372)</td>
<td>1.6%</td>
<td>1.1%</td>
<td>44% (−31 to 200)</td>
</tr>
<tr>
<td><strong>Comparison agent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>5 (17,860)</td>
<td>2.1%</td>
<td>2.7%</td>
<td>21% (−41 to 55)</td>
</tr>
</tbody>
</table>

*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 unavoidable confounded by their considerable variability in antagonist activity at β₁-, β₂-, and β₃-receptors; intrinsic agonist activity; membrane-stabilizing activity; and lipid solubility. The metagression 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 chlorothalidone, 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**