Effects of Antihypertensive Drugs on Bones

Wiens M, Etminan M, Gill SS, Takkouche B. Effects of antihypertensive drug treatments on fracture outcomes: a meta-analysis of observational studies. J Intern Med 2006;260:350–62.

Study Overview

Objective. To examine the effect of antihypertensive drugs (ie, angiotensin-converting enzyme [ACE] inhibitors, diuretics, β blockers, calcium channel blockers [CCBs], and α blockers) on fracture risk in older adults.

Design. A meta-analysis of observational studies.

Data sources. The MEDLINE, EMBASE, LILACS, and ISI Proceedings databases were searched for studies that presented original data from case-control or cohort studies; explicitly defined the exposure of interest as ACE inhibitors, diuretics, β blockers, CCBs, or α blockers; presented relative risks (RRs) or odds ratios and 95% confidence intervals (CIs) or had data for these to be calculated; and had fracture as a clearly defined outcome. Of 1742 studies identified, 54 (40 case-control and 14 cohort) were included for analysis.

Main outcome measures. The primary outcome was a pooled estimate result on the risk of fracture from use of ACE inhibitors, diuretics, β blockers, CCBs, or α blockers. Secondary outcomes included risk of fracture stratified by medication, prolonged use of medication, age, sex, and study quality.

Main results. Of 54 studies, 38 involved diuretics (25 for thiazide diuretics, 11 for nonthiazide diuretics). The pooled RR of any fracture was 0.86 (95% CI, 0.81–0.92) with the use of thiazide diuretics and 1.19 (95% CI, 0.91–1.57) with the use of nonthiazide diuretics. There were 8 β-blocker studies, which demonstrated a statistically significantly decreased risk of fracture (RR, 0.86 [95% CI, 0.70–0.98]). There was 1 ACE inhibitor study, which showed significant protection against fracture (RR, 0.81 [95% CI, 0.73–0.89]). Use of α blockers (2 studies) or CCBs (1 study) had no significant impact on fracture risk.

Conclusion. Thiazide diuretics and β blockers appeared to lower the risk of fractures in older adults. Data from randomized controlled studies are needed before thiazide diuretics and β blockers can be recommended for fracture prevention in older adults.

Commentary

Meta-analyses are useful for a number of reasons. By combining small studies, meta-analyses increase the likelihood of uncovering statistically significant findings. They can also increase precision and better estimate a treatment's effect. Finally, meta-analyses can be used to resolve controversies in the existing literature. The current literature on the association of antihypertensive drug treatment and the risk of fracture is mixed. Although some studies have demonstrated that antihypertensive drugs may protect against fracture risk [1], others have shown that these drugs have no effect [2] or may actually increase risk of fracture [3]. This study by Wiens et al is the first meta-analysis to examine the relationship between antihypertensive drugs and fracture risk since 1995 and to investigate antihypertensive drug classes besides diuretics.

While statistically powerful, meta-analyses can be misleading if applied across studies whose data should not be combined. Studies usually have different medication doses, study populations, and treatment durations, and because of these differing variables it is sometimes difficult to determine how best to summarize results. Studies can be pooled if they report on similar questions answered in similar ways, but even this approach may not take into account the quality of each study. Assessment of study quality for articles used in meta-analyses is immportant in order to minimize the impact of low-quality studies on the results. Wiens et al created their own quality scale to measure methodologic quality of each included cohort or case-control study. While this tool attempted to control for misclassification bias, it did little to ensure that selection bias and confounders were addressed. This is an important limitation of this study and was acknowledged by the investigators. A more comprehensive quality assessment tool that examined the presence of each of these biases would have been more useful and might have explained some of the observed statistical heterogeneity.

Applications for Clinical Practice

Several classes of antihypertensive medications are significantly associated with reduced risk of fracture, with diuretics being the most studied class. It is interesting that a

protective association was observed for 2 other classes of antihypertensives—β blockers and ACE inhibitors—but not for α blockers or CCBs. While the mechanism of fracture risk protection is understandable for thiazide diuretics (a hypocalciuric and bone mineral density–sparing effect), the mechanism for other classes of antihypertensives is not yet understood. The choice of antihypertensive drugs should be guided by other clinical factors, not the risk of bone fractures. Future randomized trials of antihypertensive agents should attempt to quantify the risk of fractures in addition to other prespecified secondary outcomes.

—Review by Jackie Aperi, MA, New York University School of Medicine, and Nirav R. Shah, MD, MPH

References

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