Published in final edited form as:

JAMA Intern Med. 2017 January 01; 177(1): 77–78. doi:10.1001/jamainternmed.2016.7040.

Dodging Complexity: Cardiovascular Medications and Fractures

Cathleen S. Colón-Emeric, MD, MHS and Richard Lee, MD, MHS

Duke University School of Medicine and the Durham VA Geriatric Research Education and Clinical Center

The American Computer Scientist Alan Perlis wrote, “Fools ignore complexity. Pragmatists suffer it. Some can avoid it. Geniuses remove it.(1)” Geriatricians (a pragmatic bunch) will tell you that the relationships between medications and geriatric syndromes such as osteoporotic fractures are inherently complex and often involve trade-offs between benefits in one system and harms in another. Patients with low bone density and/or fractures have a higher risk of cardiovascular disease and vice versa; common pathophysiologic pathways have been postulated. Medications used to treat cardiovascular disease including beta blockers, angiotensin system blocking medications, calcium channel blockers, and thiazide diuretics have been hypothesized to affect bone metabolism, both positively and negatively. (2) These same medications may increase falls through changes in blood pressure, heart rate, and (in the case of ACE inhibitors) muscle metabolism; fall risk may vary by class. One in ten falls results in an osteoporotic fracture. Given the high prevalence of low bone density (55%) and cardiovascular disease (>70%) in people over age 65 years, it would be foolish to ignore the complex interaction between cardiovascular medications and osteoporotic fractures.

Fortunately, choosing a first line antihypertensive drug may be one situation where we can largely avoid it. In this issue of *JAMA-Internal Medicine*, Puttnam and colleagues report a secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Their analysis described the risk of hip and pelvic fractures in a large number of patients with mild-moderate hypertension and other cardiovascular risk factors who were randomized to a thiazide (chlorthalidone), angiotensin-converting enzyme inhibitor (Lisinopril), or calcium channel blocker (amlodipine) as first line treatment for hypertension. Medicare and Veterans Affairs records were used to identify hip and pelvic fractures during the study (average 4.9 years) and for an additional 4 years after the study concluded. They found a significant 21% lower hazard of hip and pelvic fractures during the trial period for chlorthalidone users compared to amlodipine or lisinopril users; comparisons between chlorthalidone and the other agents individually showed similar magnitude reductions but a statistically significance only between chlorthalidone and lisinopril (relative risk reduction 25%). The use of beta blockers in ALLHAT was not randomized and was a second line treatment, limiting conclusions about this important class. While the diminished hip and pelvic fracture risk with thiazides was attenuated after the trial ended and subjects were no longer constrained in their choice of medication, a trend to decreased risk remained suggesting a continued effect. The findings largely confirm prior observational studies

showing a decreased risk of hip and other fractures with thiazides in a dose and duration dependent manner. However, these studies were never adequately able to exclude the possibility of unmeasured confounders accounting for the differential fracture rates, especially concomitant cardiovascular disease and fall risk factors. The large sample size and randomized, blinded nature of ALLHAT greatly mitigate these concerns because such confounders are likely to be balanced between the groups. This is good news for those of us wanting to avoid complexity, because thiazides are also a preferred class for the first line treatment of hypertension based on lower rates of cardiovascular events observed in ALLHAT and other trials, as described in American Heart Association/American College of Cardiology and Joint National Committee 8 guidelines. It appears that a preferred agent for cardiovascular prevention is also a preferred agent for fracture prevention.

Do these results mean that patients treated with other cardiovascular medications for appropriate clinical situations are being placed at higher risk for fracture (e.g., ACE inhibitors for concomitant heart failure or kidney disease; beta blockers or calcium channel blockers for rate control in atrial fibrillation)? Probably not. The ALLHAT study did not include a placebo control group, so the present study is unable to address whether these agents increase fracture risk over no treatment. However, a nationwide case-control study in Denmark comparing users of beta blockers, ACE inhibitors, and calcium channel blockers suggested a 6–9% lower fracture risk for each group relative to non-users that was similar across classes.(3) In a systematic review of medications and fall risk, 9 studies examining cardiovascular medications showed no increased risk while only 3 showed a modest increased risk of falls; moreover the positive studies included second and third line treatments such as nitrates, hydralazine, and alpha blockers known to cause orthostasis.(4) These and other similar studies suggest that first and second line cardiovascular medicines are likely not a substantial contributor to falls and fractures when used appropriately, while thiazides likely have a small beneficial impact on bone through their anti-calciuric and other metabolic bone effects.

There are some important caveats to these conclusions. Several epidemiological studies have demonstrated an association between the initiation of cardiovascular medications and short term fall and fracture risk. Initiation of antihypertensives including thiazides was associated with 2-fold increased risk of injurious falls in the first 14 days across medication classes.(5) This underscores the importance of close initial monitoring for hypotension, orthostasis, and bradycardia after initiation (or dose change) of cardiovascular medications. In another large observational study, the risk of hip fracture was elevated for 1–2 weeks following loop or thiazide diuretics initiation in older women, while no such transient increase in risk was seen for ACE inhibitors.(6) These findings may be related to risk of hyponatremia or urinary urgency; thiazides are the most common cause of hyponatremia requiring hospitalization, and bathrooms are one of the most common sites for falls. Finally, patient priorities and preferences cannot be ignored. When asked to prioritize avoidance of cardiovascular outcomes, fall-related injuries, and medication symptoms in a discreet choice task, about half of older adults prioritize preventing falls and medication effects, while the other half prioritize preventing cardiovascular events.(7) Thus, while the choice of thiazide as first line therapy for hypertension over other agents might be relatively straightforward based on its two-fold benefit on cardiovascular disease and bone, some complexity remains. We need to

ensure that treatment is consistent with patient goals and preferences, and we need to monitor patients carefully, especially during the first several weeks of treatment.

Is the dual benefit of thiazides a happy coincidence, or related to a common underlying mechanism of action in vascular tissue and bone? The science here is thin, and additional studies examining the overlap between cardiovascular disease and metabolic bone disease may help us develop other pleiotropic agents with a beneficial impact on both systems. While we have avoided complexity in the case of choosing antihypertensive medications, we have yet to reach genius-level understanding that explains the complex interactions between bone, vascular disease, and the drugs that treat them.

References

1. Perlis AJ. Special Feature: Epigrams on programming. *J SIGPLAN Not.* 1982; 17(9):7–13. [PubMed: 6176706]
2. Ghosh M, Majumdar SR. Antihypertensive medications, bone mineral density, and fractures: a review of old cardiac drugs that provides new insights into osteoporosis. *Endocrine.* 2014; 46(3): 397–405. [PubMed: 24504763]
3. Rejnmark L, Vestergaard P, Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: a nationwide case-control study. *Journal of Hypertension.* 2006; 24(3):581–9. [PubMed: 16467662]
4. Hartikainen S, Lönnroos E, Louhivuori K. Medication as a Risk Factor for Falls: Critical Systematic Review. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2007; 62(10):1172–81.
5. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of falls on initiation of antihypertensive drugs in the elderly. *Osteoporosis International.* 2013; 24(10):2649–57. [PubMed: 23612794]
6. Berry SD, Zhu Y, Choi H, Kiel DP, Zhang Y. Diuretic initiation and the acute risk of hip fracture. *Osteoporosis International.* 2013; 24(2):689–95. [PubMed: 22790610]
7. Tinetti ME, McAvay GJ, Fried TR, Allore HG, Salmon JC, Foody JM, et al. Health Outcome Priorities Among Competing Cardiovascular, Fall Injury, and Medication-Related Symptom Outcomes. *Journal of the American Geriatrics Society.* 2008; 56(8):1409–16. [PubMed: 18662210]