

## CORRESPONDENCE

## Letters to the Editor

## Osteoporosis Is a Major Confounder in Observational Studies Investigating Bisphosphonate Therapy in Aortic Stenosis

We read the paper “Do Bisphosphonates Slow the Progression of Aortic Stenosis” by Aksoy et al. (1) with great interest. Given the central role that calcification plays in the progression of aortic stenosis, the question as to whether bisphosphonates might favorably modify this disease process is an important one.

In their large retrospective study, the researchers found that there was no difference in aortic stenosis progression between women who were taking and not taking bisphosphonate therapy after a median follow-up of 1.6 years. This lack of effect persisted even after sophisticated propensity matching; however, we believe that this analysis did not correct for one potentially important confounder.

The link between osteoporosis and increased vascular calcification, the so-called calcification paradox, is well established, and the researchers themselves previously extended this principle to aortic valve calcification (2–4). We therefore believe that the presence of osteoporosis in those prescribed bisphosphonate therapy may have had a significant incremental effect on aortic stenosis progression. As such, the lack of difference between the groups could be interpreted as a sign that bisphosphonates were in fact successful in normalizing disease progression in these patients.

In our opinion, it is unlikely that observational studies will be able to disentangle the effects of bisphosphonates and osteoporosis on aortic stenosis. The true impact of these drugs will only become clear within the setting of a randomized controlled trial.

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## REFERENCES

1. Aksoy O, Cam A, Goel SS, et al. Do bisphosphonates slow the progression of aortic stenosis? *J Am Coll Cardiol* 2012;59:1452–9.
2. Aksoy Y, Yagmur C, Tekin GO, et al. Aortic valve calcification: association with bone mineral density and cardiovascular risk factors. *Coron Artery Dis* 2005;16:379–83.
3. Persy V, D'Haese P. Vascular calcification and bone disease: the calcification paradox. *Trends Mol Med* 2009;15:405–16.

4. Raggi P, Giachelli C, Bellasi A. Interaction of vascular and bone disease in patients with normal renal function and patients undergoing dialysis. *Nat Clin Pract Cardiovasc Med* 2007;4:26–33.

## Reply

We thank the correspondents for their interesting comment on our recent paper (1). We would like to point out, however, that none of the authors of the present paper have been associated with the papers that they referenced. The calcification paradox whereby vascular calcification is more prevalent in those with reduced bone density or increased bone turnover has been well described. Increased valvular calcification has also been described in patients with osteoporosis, but specific data on whether osteoporosis accelerates aortic stenosis progression has not to our knowledge been reported. Additionally, we have no way of knowing whether the elderly women in our study who did not receive bisphosphonates had some degree of osteoporosis. The fact that many were receiving vitamin D and calcium supplementation suggests that a proportion at least were considered at risk for osteoporosis. The correspondents' contention that bisphosphonates in our study may have normalized an acceleration of aortic stenosis associated with osteoporosis is therefore interesting but still hypothetical. We agree with the correspondents and stated in our conclusions to the paper that prospective clinical trials of specific bisphosphonates will be needed to fully answer the question of the impact of this class of drugs on aortic stenosis progression.

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## REFERENCE

1. Aksoy O, Cam A, Goel SS, et al. Do bisphosphonates slow the progression of aortic stenosis? *J Am Coll Cardiol* 2012;59:1452–9.

## Challenging Interpretation of Elevated Cardiac Troponin T in a Complex Case With Rhabdomyolysis

We read with interest the correspondence letter by Sribhen et al. (1) referring to the article “Diseased skeletal muscle: a noncar-