In Reply We agree with Drs Redington and Caldarone that many animal and human studies have shown that a single or few (<5) short episodes of remote ischemic preconditioning (typically 5 minutes of limb ischemia followed by 5 minutes of reperfusion) are protective for many organs (including the heart, brain, and kidney) with few reported adverse effects.

However, few studies have examined the long-term effects of repeated episodes of remote ischemic preconditioning, and this is what we referred to in our Editorial that the effects of multiple episodes of remote ischemic preconditioning, which patients may be exposed to if remote ischemic preconditioning is widely used, are unclear.

For example, the study by Meng et al1 used remote ischemic preconditioning twice daily during 300 consecutive days to reduce stroke, but did not examine molecular mechanisms of brain protection or cardiovascular adverse effects. Similarly, a study by Shaked et al2 that used intermittent cycles of remote ischemic preconditioning as adjunctive therapy for treatment of diabetic foot ulcers did not examine cardiovascular effects.

Redington appeared to agree with our point of view as the coauthor of a review article,3 which cautioned that “hyperconditioning (ie, an as-yet undefined, excessive number of conditioning episodes) may be deleterious.” Another recent review article by Whittaker and Przyklenk4 suggested that in addition to tachyphylaxis (ie, increased tolerance to the effect of an intervention), repeated episodes of limb ischemia may have unfavorable consequences for collagen and systemic effects mediated via matrix metalloproteinases.

The authors concluded that the benefits of protection against ischemia may be found at low doses (ie, low number and duration of preconditioning episodes), but these benefits may be lost and adverse effects may occur (collagen damage) at high doses.

In addition, remote ischemic preconditioning may have limited utility for cardioprotection in 2 large populations (elderly patients and those with diabetes) at high risk for cardiovascular diseases,5 and may be associated with higher risk for atrial fibrillation, even when used at the conventional dose (5-minute episodes of ischemia/reperfusion repeated 5 times) before coronary artery bypass graft surgery.6

Therefore, even though we share the enthusiasm of Redington and Caldarone for the promise of remote ischemic preconditioning for organ protection, investigators in the field should examine potential long-term harmful effects to various organs, including the heart, particularly when hyperconditioning is used.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


To the Editor We wish to retract the article “Effect of Ramipril on Walking Times and Quality of Life Among Patients With Peripheral Artery Disease and Intermittent Claudication: A Randomized Controlled Trial,” published in the February 6, 2013, issue of JAMA.1 A recent internal subanalysis of these data revealed anomalies, which triggered an investigation and an admission of fabricated results by Anna A. Ahimastos, PhD, who is both the first and corresponding author and was responsible for data collection and integrity for the article. No other coauthors were involved in this misrepresentation. In particular, the data collected at the Townsville and Brisbane sites remain valid. Given the current indications for ramipril, we do not believe that patients have been adversely affected.

All authors recognize the seriousness of this issue and apologize unreservedly to the editors, reviewers, and readers of JAMA. A system of good clinical practice was in place; however, clinical governance and audit procedures will be reviewed and strengthened to minimize the chance of possible recurrence of such behavior. We are also in the process of examining other studies for which Dr Ahimastos had oversight of data collection and integrity.

We sincerely regret that this study has been compromised. We feel deeply disappointed and let down by this
situation and are committed to rapidly correcting the public record and implementing practices to prevent recurrence.

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CORRECTION
Clarification of the Number of References and Studies Used in Review: In the Review entitled “Nonalcoholic Fatty Liver Disease: A Systematic Review” published in the June 9, 2015, issue of JAMA,1 the number of references was correct; however, the numbers for the individual study categories were incorrect. In the “Evidence Review” section of the abstract, the last sentence should be “A total of 88 references were selected, including 14 randomized clinical trials, 19 cohort or case-control studies, 1 population-based study, 2 practice guidelines, 7 meta-analyses, 43 classified as other, and 2 webpages.” In the “Literature Search” section, first full paragraph, the last sentence should be “For NAFLD and cirrhosis, there were 3396 identified, 163 clinical studies reviewed, and 31 referenced; mortality, 537 identified, 163 clinical studies reviewed, and 11 referenced; biomarkers, 1171 identified, 73 clinical studies reviewed, and 31 referenced; and treatment, 3107 identified, 223 clinical studies reviewed, and 33 referenced.” The following new sentence will become the last sentence of this paragraph: “The same study often appeared in more than 1 search.” In the next paragraph of this section, the last sentence should be “Overall, 14 randomized clinical trials, 19 cohort or case-control studies, 1 population-based study, 7 meta-analyses, 2 practice guidelines, and 43 classified as other were used for this analysis (additional details appear in the efigure in the Supplement).” In addition, in Figure 1, the word “is” has been added 3 times to the legend to improve readability. In Figure 3, the abbreviation “AFRI” has been changed to “ARFI” in the figure itself and in the legend. In the eFigure, the numbers of studies for 2 boxes in the last row of the figure were changed and the following sentence was added as a figure legend: “The same study often appeared in more than 1 search.” This article was corrected online.


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