To the Editor:

The recent publication by Page, et. al. highlights an important collection of agents that may cause or exacerbate heart failure (HF).[1] The short section on Complementary and Alternative Medicines (CAM) was especially important, given their high U.S. prevalence of use and poor reporting to clinicians. Unfortunately, the section contained some misrepresentations of the available data and overstatements of the potential for harm.

The authors cite the 2007 National Health Interview Survey (NHIS) CAM supplement, which reported 38% of U.S. adults use CAM therapies. That statistic was based on use of any CAM therapy, such as acupuncture, massage, or yoga, which is not relevant to the potential danger of using natural products (NP) for heart failure. Furthermore, it is striking that the authors did not cite the more recent 2012 NHIS results.

Page and colleagues list 3 important measures for clinicians, one of which is to avoid ephedra-like products. However, ephedra has been banned in the U.S. since 2004, making this measure largely irrelevant.[2] Their tables (Tables 7-9) also contain both irrelevant and inaccurate information. For example, tetrandrine (a quinolone alkaloid) and gossypol (a phenol derivative) are neither CAM products nor commercially available for patient use; aconite (*Aconitum spp.*) and lily-of-the-valley (*Convallaria majalis*) are not commonly available, prescribed, or used NPs (Table 9); hawthorn does not interact with digoxin (Table 7), which was demonstrated in a well done human clinical trial.[3] Although the hawthorn trial was noted in the Natural Medicines database that Page, et. al. cited as their primary source of CAM interaction information, instead the authors reported a 'significant interaction' based on another reference from the same database, which itself cited a different publication that, in turn cited two textbooks, but no clinical trials, as their source for the purported interaction.

In yet another example, black cohosh (*Cimicifuga racemosa*), was listed as having 'significant interactions' with ACE-I/ARBs and β-blockers. To support these interactions the authors again cite a tertiary source, which cited a single study that reported black cohosh caused a 7% reduction in CYP2D6 in healthy human volunteers. However, the authors of the black cohosh publication noted that the result '*while statistically significant, may not be clinically relevant*.'[4] Not cited by Page, et. al. was a second human clinical trial looking at CYP2D6, which concluded black cohosh '*exerted no significant effects on CYP2D6 activity*.'[5] Presumably, Page, et. al. listed a potential interaction with β-blockers also based on purported effects on CYP2D6. However, even if black cohosh were a perpetrator agent via CYP2D6, this would not be a class effect since not all β-blockers are metabolized by CYP2D6. Lastly, class activity against ACE-I or ARBs was not substantiated by their referenced source.

The above are a few examples of the inaccuracies and poorly reported information in the CAM section. Subsequently, we recommend the section be re-reviewed by experts in clinical pharmacology and the use of natural products, and future publications on CAM therapies should include authors with expertise in these areas.

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2. FDA Issues Regulation Prohibiting Sale of Dietary Supplements Containing Ephedrine Alkaloids and Reiterates Its Advice That Consumers Stop Using These Products. *FDA News Release* 2004; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108242.htm.
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4. Gurley B, Gardner S, Hubbard M, et al. *In vivo* effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clinical Pharmacology & Therapeutics.* 2005;77(5):415-426.
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Reply:

We thank Dr. Asher et al for their interest in our Clinical Science Statement and for their critical comments regarding the section on Complementary and Alternative Medicines (CAM). Drs. Asher and Hawke assert the CAM section includes both irrelevant and inaccurate information. We disagree with their opinion that the inclusion of ephedra-like products is irrelevant. Caution against using these products in patients with HF is one of only three declarative statements regarding CAM in the 2010 Heart Failure Society of America (HFSA) Guidelines, indicating its importance and certainty for harm in the minds of experts.[1] While it is banned in the US, it is available in other countries, which is an important source of this journal's readership. They further contend four other CAM therapies were irrelevant for inclusion due to lack of commercial availability or uncommon usage. However, no reference was provided to substantiate these claims. In the US, there is online availability of these products from recognizable suppliers such as Walgreens and Amazon. In addition, these products may be compounded and sold at local herbal apothocaries, which we have observed in our own practices. Furthermore, the 2010 state-of-the-art article by Tachjian et al includes all five therapies deemed irrelevant by Asher and Hawke, further suggesting their relevance for inclusion.[2]

Drs. Asher and Hawke provide three examples of what they feel are inaccuracies about CAM therapies and interactions with commonly used HF medications. All three are from a table in which we indicated the presence (or absence) of significant interaction (Table 7). Based on their review, it appears they take issue with our simplification of what are actually complex interactions with varying clinical significance to CAM specialists and researchers in this field. Admittedly, when one strives for simplicity, as we did with this table, details are lost. Our challenge, as authors of this broad topic with limited space allocation, was to create a fairly comprehensive and accessible guide, with the stated modest goal to highlight concerns with CAM.

To populate the tables, we relied primarily on the expertise that maintains the Natural Medicine Comprehensive Database. This evidence-based database is continuously updated, and the more than twenty-five researchers, writers and editors apply a consistent and well-described method of interaction determination.[3] Specifically regarding the criticism by Asher and Hawke of the black cohosh and ACEI/ARB interaction, we refer them to the evidenced-based systematic review by Ulbricht and Windsor.[4] Due to theoretical hypotensive effects, "black cohosh should be used cautiously with other hypotensive agents." While these reports were in animal models, they state that "increased peripheral blood flow has been associated with black cohosh administration." We appreciate Asher and Hawke for pointing out this 2014 article was not included within our references.

Finally, we disagree with Asher and Hawke with regards to a re-reivew by natural product experts. The overall intent of this section was to provide practical, easy-to-follow information for practitioners caring for patients with HF. Our working group believes this small section adequately promotes awareness of potential deleterious effects of alternative therapies. As Asher and Hawke mention, this was only a small portion of our entire Statement, and thus could not address all CAM. We also agree with the response by Tachijan et al to Dr. Asher's similar criticisms of their state-of the art-article in which they recomend "a thoughtful evaluation of issues related to the use of herbal products in patients with cardiovascular (and other chronic) conditions".[2,5,6]

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