

## EDITORIAL COMMENT

# Where's the "Label" for Beet Juice

## The Value of the Food and Drug Administration\*



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Olympic marathon runners and college football stars chug-a-lug beet juice for a performance boost. This humble edible is now an international superstar with top billing in pricey juices. This juice is proposed to work wonders by increasing levels of artery-relaxing nitric oxide (NO). Relaxed arteries, the ads blast, mean increased blood flow, and that means better athletic (and don't forget sexual) performance. Some studies suggest beet juice could give elite competitors the edge at the finish line (1).

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The paper by Eggebeen et al. (2) in this issue of *JACC: Heart Failure* extends the observations with scientific rigor to examine whether this second processing pathway for NO benefits patients with heart failure and preserved ejection fraction (HFpEF). Orally ingested inorganic nitrate absorbed across your upper intestine is concentrated from your blood into your salivary glands. It is then secreted into your mouth, where it contacts bacteria that reduce inorganic nitrate ( $\text{NO}_3^-$ ) to nitrite ( $\text{NO}_2^-$ ). On swallowing your saliva, the nitrite enters your circulation, where it meets mammalian nitrite reductases that convert it to NO, resulting in vasodilation. These reductases are even more active in low oxygen and acidotic environments, which makes this pathway even more attractive for patients with HFpEF (3,4). It is as if Eggebeen et al. decided to give inorganic nitrate as a

drug but without regulatory hurdles, and in a way you could prescribe easily. But the "label" of a drug approved for marketing by the U.S. Food and Drug Administration (FDA) provides information so we know it is effective for specific conditions, and we know how to prescribe it safely. I think we need the equivalent for lifestyle and functional foods. That lack is true of many lifestyle interventions.

For example, although data from many studies indicate doing any physical activity (that does not involve unusual injury risk) reduces development of chronic diseases and disability and increases longevity (5,6), we only know by implication the minimal physical activity for maximal prevention from any chronic disease; we know even less about the optimal dose requirement (least effort for maximal benefit) for treating or reversing such diseases as diabetes, memory dysfunction, obesity, or heart failure of any origin. Nor do we have data on sex differences in doses of physical activity for preventing or treating diseases, or how even aspirin or tomatoes interact with exercise.

And with physical activity, we may have the most data. We do not know (at least, I cannot find reliable consistent results) the dose of meditation to recommend (2 vs. 6 vs. 20 min) or the type of stress-managing process that consistently delivers maximum results for minimal dose or time commitment, or how that differs between stressors or from person to person. Food choices such as beet juice may be most difficult to study. But rigorous study is what is needed, because logic is frequently flawed by not fully understanding the mechanisms of disease and well-being, as recently evidenced by data on salt in heart failure, whose proscription appears in doubt when logic has been challenged by science (7).

The question asked about beet juice in this equivalent to an early phase 2 clinical study is whether a single dose versus a week of the same dose alters

\*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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exercise capacity, symptoms, and biochemical measurements in patients with HFpEF (4). We learn that a week of beet juice is effective, and the effect correlates with reduction of blood pressure (BP). Would a higher dose benefit more, or a low dose given longer not induce tachyphylaxis, as evident from organic nitrates? Furthermore, how does beet juice interact with weight loss induced by calorie restriction and exercise, which work by a different mechanism to improve exercise capacity in HFpEF (8)?

And why use beet juice versus a pill of, say, potassium nitrate? The elevation of plasma  $\text{NO}_2^-$  and cGMP concentration after  $\text{KNO}_3$  is associated with reductions in BP that closely match those achieved after similar doses of dietary nitrate (9). The reduction in BP of  $\text{NO}_3^-$  supplementation was dose dependent in the range between 4 and 24 mmol irrespective of formulation (dietary or supplementation) (10) and was sustained for at least 24 h (11).

Studies with foods may be even more difficult than those with a supplement or drug. Ensuring uniformity of the food is difficult, because consistent storage and preparation of food are needed. In addition, food-food and food-drug interactions need evaluation. For example, the way nitrates are thought to work involves symbiotic bacteria in the mouth (see above). Alteration of bacteria by mouthwashes or by antibiotic drugs in food adds inconsistency to effect. In previous studies, changes in plasma  $\text{NO}_2^-$  levels and reductions in BP were abolished if subjects used an antibacterial mouth wash or refrained from swallowing their saliva, thereby interrupting the entero-salivary circulation and preventing the rise in plasma  $\text{NO}_2^-$  levels (3), so these were exclusion criteria in this study. But do you question your patients about mouthwash use and saliva swallowing? I haven't, till now.

Because of drug-food, variations in food content, and interactions among other activities and foods and even salivary, these studies and especially their application to clinical practice without a package insert are difficult. But Eggebeen et al. (2) overcame these obstacles: the beet juice was uniform, and levels of nitrates and nitrite indicate success at achieving changes in the active and placebo groups that differed significantly.

Another issue is concern with the safety of current nitrate consumption. The average daily intake of nitrate from regular food sources (predominantly vegetables) is 1.5 to 2 mmol; the acceptable upper daily intake as set by the World Health Organization is about 4.2 mmol for a 70-kg person because of concerns about methemoglobinemia and carcinogenesis (12). These concerns appear to have been allayed over the years. The average daily intake in the active treatment group

was 6.4 mmol (2), without evidence of methemoglobinemia. Some researchers suspect that artery-relaxing nitrates are a big reason for the BP-lowering prowess of the DASH diet (13). Patients predisposed to oxalate renal stones may need to avoid certain high-nitrate vegetables that also contain oxalate, such as spinach and beetroot (12). Another worry about beet juice is that it may raise blood sugar levels too quickly. You can ask patients to sip the juice over the entire day. Remember to recommend your patients decrease calories in the rest of their diet, because obesity contributes to symptoms in HFpEF.

On the basis of this and prior studies, can you recommend beet juice for individual trial in HFpEF patients? Yes, some would say: there is little downside and potentially substantial benefit; after all, it is an "n of 1" trial. The risk of cancer and other issues with side effects probably do not matter for people whose life expectancy is <10 years. Although more study can help, we can prescribe this to our patients easily; just warn them about beet-colored poop and beeturia. These advocates of keeping the same process as for evaluating lifestyle treatments (haphazard, without a systematic exploration of benefits, risks, and doses) would say that asking for the same rigor in studies of lifestyle choices and functional foods as in medication studies wastes money and time. Others would say we need an FDA approach for functional foods. We really do not know the optimal dose of inorganic nitrates or timing and interactions. [A tomato-beet soup-based calorie-restricted diet with thrice-weekly exercise might reduce rehospitalizations in HFpEF patients (2,8,14)].

The safety margin from overdoing beet juice may be as narrow as for many drugs. We know some body builders and sprinters and some octogenarians with exertional dyspnea who will say if one bottle of beet juice makes them finish stronger or feel better, then 10 or 20 bottles will make them finish in record times and feel 20 years younger.

Maybe we need a clearinghouse at the National Institutes of Health or the FDA that indicates what studies are needed to fill knowledge gaps about lifestyle treatments and that fosters sponsorship of such studies. After all, diet and diet choices are not even in the present guidelines for treatment of HFpEF (14). We need confidence concerning what, and what dose of, each of the basic lifestyle treatments we can prescribe to whom, and what side effects to assay.

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**KEY WORDS** exercise, heart failure with preserved ejection fraction, nitrate, nitric oxide, nitrite