LETTERS TO THE EDITOR

Reporting Associations Between Dietary Supplements and Adverse Events

To the Editor: The article by Gange et al., published in the April 2006 issue of Mayo Clinic Proceedings, purported to document an association between bitter orange peel extract and variant angina in a borderline-obese 57-year-old man. However, the authors’ identification of bitter orange as the offending ingredient must be considered speculative. It would be no more accurate to assume that any of the other 9 ingredients in the supplement, or the drugs or other supplements the patient was taking concomitantly, were the cause of the patient’s angina.

The authors posit a possible association between the product and the reported symptoms but also acknowledge the possibility that “the sentinel vasospasm event was due to chance and not from bitter orange ingestion.” Without further explanation, they then state that it was “more likely…that his first episodes of variant angina were due to consuming a dietary supplement….” The rationale for this focus on bitter orange was apparently related to the alkaloids in that ingredient. However, the references provided in the discussion of the physiological effects of these alkaloids do not substantiate the authors’ conclusion.

Although the reports by Hofstetter et al. and Zhao et al. may support the statement that “synephrine caused ventricular arrhythmias, increased cardiac output, and vasoconstriction” in animals, these studies measured effects after intravenous administration, and thus their results have limited relevance to orally consumed supplements. To support their position that “synephrine can induce hypertension in humans,” Gange et al. cited Hofstetter et al. and an article by Keogh and Baron that dealt specifically with abuse of sympathomimetics. The relationship between intentional abuse of stimulants and the possible effects of a product containing only about 3 mg of synephrine must be challenged. Dose comparison is also relevant to their citation of the report by Huang et al. who infused rats with synephrine at rates from 0.095 to 0.38 mg/kg per minute, which in a 70-kg man would be equivalent to at least double the dose contained in the supplement for every minute of this study. Although Chobanian et al. listed bitter orange as a “cause of resistant hypertension” in humans, they provided no reference for that assertion. These authors also identified obesity and excessive alcohol intake as causes of resistant hypertension, but Gange et al. did not draw the obvious link to their patient, whose body mass index (calculated as weight in kilograms divided by the square of height in meters) was recorded as 29.5 kg/m² and whose alcohol use was reported as “3 to 4 alcoholic beverages at night.” Finally, Blumenthal does not support the statement that Gange et al. attributed to that source.

Our organization has called for legislation to require marketers of dietary supplements to submit to the US Food and Drug Administration all serious adverse event reports that they receive. One of the obstacles we have encountered in advocating this policy is the industry’s concern that generation of such reports will lead to speculative cause-and-effect associations, such as that expressed by Gange et al. It is essential that health care professionals describe observed associations between dietary supplements and adverse events accurately and that any speculative conclusions are clearly identified as such.

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In reply: We appreciate Mr McGuffin’s interest in our case report. However, we disagree with his claim that the known cardiovascular effects seen with intravenous administration of synephrine would not be expected when the drug is taken orally. No matter the route of delivery, pharmacokinetics support similar physiological effects once a drug has reached steady-state concentrations. Because steady-state levels were likely present in our patient, the references mentioned are relevant. We acknowledge that the doses of synephrine used in some studies have been higher than those ingested by our patient. However, in our report, we highlighted the fact that CortiSlim also contains numerous other vasoactive compounds that might act synergistically with synephrine. Indeed, a recent small randomized, double-blind study showed that a multicomponent dietary supplement containing synephrine increases blood pressure and heart rate in healthy adult subjects.

We did not purport that the use of a bitter orange–containing supplement caused hypertension in our patient, and we
agree that the hypertension he experienced could be attributed to other underlying factors such as his alcohol intake and obesity. More importantly, we reported a case of variant angina that was associated with an element of myocardial necrosis as well as a potentially fatal cardiac arrhythmia. The patient’s presentation with heart block and inferior ST-segment elevations on electrocardiography is consistent with acute obstruction of the right coronary artery. However, angiography showed no atherosclerotic disease in this vessel. Thus, variant angina, thought to be exacerbated by the dietary supplement, was the trigger for the patient’s initial presenting symptoms.

As in any case report, we detailed a single clinical scenario. However, we believe that our report presents a tenable case for the association of variant angina with the ingestion of this dietary supplement. Dietary supplements containing bitter orange have already been linked to a number of deleterious cardiovascular effects. In addition, our patient’s presentation was temporally related to ingestion of the product, and his symptoms improved after its cessation. Furthermore, use of the validated Naranjo probability scale supports a possible causal relationship.

We strongly support Mr McGuffin’s plea for legislation that would require manufacturers of dietary supplements to submit adverse-event reports to the Food and Drug Administration. Unfortunately, due to a relative lack of regulations imposed on the production and distribution of herbal supplements, scientific data concerning the safety and efficacy of the ingredients found in CortiSlim and other dietary supplements are not readily available. In addition, the labeling of ingredients and their concentrations in dietary supplements is often inaccurate. As a result, incorrect assumptions could be made regarding the safety of “ephedra-free” supplements. Until more stringent regulations are imposed for assessing the safety of these compounds, we believe that clinical reports such as ours remain essential in identifying and alerting physicians and the general public to the potential dangers they might pose.

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thiazide/atenolol had no increased CVD mortality (hazard ratio, 1.04) after 14.3 years of follow-up. In the Blood Pressure Lowering Treatment Trialist’s Collaboration prospective meta-analysis (>46,000 participants with >6000 CVD events and >2800 coronary heart disease events), no difference in CVD or coronary heart disease rates was noted between the angiotensin-converting enzyme inhibitor and diuretic/β-blocker groups.6

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In reply: We welcome the opportunity to address Dr Rashidi’s comments on our recent article. While it is true that we reviewed studies indicating that hypertensive patients taking thiazide diuretics are at greater risk for developing diabetes mellitus (DM) than when taking other selected antihypertensive agents, our article also explored the potential effects of several drug classes, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, diuretics, calcium channel blockers, α-blockers, and centrally acting agents. Furthermore, we do not dispute the fact that the thiazide diuretic chlorthalidone compared favorably to amlodipine and lisinopril in reducing the combined incidence of coronary heart disease, stroke, and heart failure in ALLHAT, underscoring the beneficial effect of blood pressure control on limiting CVD events.

Nevertheless, decreasing the risk of DM in hypertensive patients should be of concern to physicians, particularly when high risk patients face many years to decades with the disease. To this end, preventing the transition from impaired glucose tolerance (IGT) to DM is being explored in the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, in which more than 9000 patients with IGT will be monitored for at least 3 years to determine whether restoration of insulin response (nateglinide) or improved insulin sensitivity by angiotensin receptor blockade (valsartan) can prevent the transition from IGT to DM and whether the prevention of this transition affects the incidence of CVD. Likewise, in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study, 5269 patients with IGT are being randomized to ramipril or rosiglitazone vs placebo to determine the effect of these agents on reducing the progression of IGT to DM. These ongoing studies should help clarify the extent to which inhibitors of the renin-angiotensin system can reduce the incidence of new-onset DM in high-risk patients.

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Usefulness of Left Ventricular Ejection Fraction in Patients With Overt Heart Failure

To the Editor: The usefulness of left ventricular ejection fraction (LVEF) measurements, discussed by Kurtz et al in the July 2006 issue of Mayo Clinic Proceedings, may be overrated, at least in patients with clinically overt heart failure (HF). As shown in a recent comparative validation, clinically overt HF must be diagnosed on the basis of clinical criteria rather than echocardiographic criteria because only the former are applicable across the entire range of LVEFs. Furthermore, a subnormal LVEF can occur in the absence of clinically overt HF, just as clinically overt HF can occur in the presence of a normal LVEF. The usefulness of echocardiography is further undermined by the fact that its most widely used modality, 2-dimensional echocardiography, is itself of questionable reproducibility, being characterized not only by a multiplicity of methodologies but also by interobserver variability in the range of 9% to 21% and intraobserver variability of 6% to 13% in the absence of contrast imaging. Even with the benefit of subjective visual assessment of global left ventricular func-
tion (“eyeballing”), this modality is beset by interobserver variability of 8% to 17% and intraobserver variability of 11% to 13%. 

While it is undoubtedly true that subnormal LVEF in patients with subclinical HF can be an indication for angiotensin-converting enzyme inhibitor therapy, this treatment modality also confers benefits in the form of reduced rates of death from cardiovascular causes and a decreased incidence of myocardial infarction in high-risk patients with vascular disease or diabetes irrespective of LVEF or HF status. In patients with clinically overt HF, both those with an LVEF lower than 40% and those with an LVEF higher than 40% benefit from blockade of the renin-angiotensin-aldosterone system, although not to the same extent. Indeed, the most striking benefit from the use of angiotensin-converting enzyme inhibitors in patients with HF was reported in a trial in which subjects were enrolled not on the basis of subnormal LVEF but on the basis of clinical criteria for severe HF. Since that trial, we have come full circle in recognizing that once HF becomes clinically overt, all patients have a dismal prognosis regardless of LVEF.

Accordingly, rather than reverting to the mantra of equating left ventricular dysfunction solely with subnormal LVEF, we should acknowledge that in patients with clinically overt HF, there is an overlap between left ventricular dysfunction characterized by subnormal LVEF and left ventricular dysfunction coexisting with normal LVEF. In light of that acknowledgment, we should focus more on “fine-tuning” our clinical criteria for HF diagnosis.

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In reply: We appreciate Dr Jolobe’s interest in our recent article and understand his concerns about the variability of ejection fraction measurements and the appropriateness of their use for the diagnosis of HF. Although these points are indeed important, the purpose of our article was to review the measurement of ejection fraction, which is recommended by the clinical practice guidelines of the American Heart Association and American College of Cardiology. Nevertheless, we appreciate the opportunity to exchange views with one of our readers.

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CORRECTIONS

Incorrect numbers: In the article by Rule et al entitled “Limitations of Estimating Glomerular Filtration Rate From Serum Creatinine in the General Population,” published in the November 2006 issue of Mayo Clinic Proceedings (Mayo Clin Proc. 2006;81:1427-1434), an incorrect number appeared in Table 4 under the column heading “Healthy sample” and the row entry “Measured GFR-90th percentile.” The number 225 should be replaced by 115. An incorrect number appeared in the title of Table 6: “…Normal Range (25th to 97.5th Percentile)”… should be replaced by “…Normal Range (2.5th to 97.5th Percentile)”…