

Controlling the effectiveness of digoxin

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intake or plasma levels of lutein in our study, although this could be undertaken.

A number of epidemiologic studies have now demonstrated an association between dietary intake or plasma levels of antioxidant vitamins and the risk of atherosclerotic vascular disease. However, large-scale randomized trials to test further for a causal relationship between antioxidant intake and ischemic heart disease have provided conflicting results (2). Although there is plausible biological evidence to suggest antioxidants may prevent the early stages of atherogenesis, it is unknown as to whether they alter the later processes that produce clinical events. To determine the role of antioxidant vitamins in atherosclerosis, it may be more appropriate to examine the relationship between dietary intake or plasma levels of these vitamins and measures of early atherosclerosis rather than clinical cardiovascular events (3).

Although we remain very interested in investigating antioxidant defenses against lipid peroxidation and novel risk factors for atherosclerosis, we would support the concept that this essential ongoing research should not distract us from efforts to implement more proven preventive strategies (4).

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Controlling the Effectiveness of Digoxin

In a recent issue of the *Journal*, Adams, et al. (1) correctly stated that: "Patients taking digoxin did significantly better than those not taking the drug, but the serum concentration did not correlate with outcome." Nevertheless, they concluded: "These results support the possibility that a lower therapeutic goal for serum digoxin concentration is warranted in patients with heart failure."

This conclusion is flawed because in individual patients the concentration of digoxin in the serum does not accurately represent the amount of digoxin in the tissues where it works. The digoxin in the serum is only a tiny fraction of the total amount of digoxin in the body. The total amount of digoxin in the body is easy to calculate from the doses administered, and it does correlate with outcome (2-4). Guiding dosage this way allowed high doses of digoxin (15 to 19 $\mu\text{g}/\text{kg}$ of lean body weight) to be given to

patients after cardiac operations, and the patients recovered rapidly (5,6).

Because serum digoxin concentrations poorly guide dosage and results, contradictions between serum levels and results have been seen by many doctors. Low serum concentrations of digoxin appeared in patients who received therapeutic benefits. In contrast, high serum concentrations of 2.5 ng/ml have been seen in patients who had no signs or symptoms of toxicity.

Dr. Jelliffe published a method for calculating the milligrams of digoxin needed to produce a specific peak total body load of digoxin and to engender a desired therapeutic result (2-4). A safe, effective amount of peak total body digoxin to treat heart failure is 8 to 10 $\mu\text{g}/\text{kg}$ of lean body weight. This program is used at the University of Southern California/Los Angeles County Medical Center and at several other hospitals.

Studying the effects of digoxin requires knowing the total amount of digoxin in the body, which controls the amount of digoxin in the tissues where digoxin works.

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REPLY

We appreciate Dr. Krohn's interest and comments concerning our analysis. We believe our conclusions as stated in the study are correct. While it is true that the serum digoxin concentration (SDC) is significantly higher than the tissue concentration during the distributive phase of digoxin dosing (6 to 12 h), both the SDC and the amount of drug in the body decline in parallel and are directly related 12 to 24 h post-dose (1). This is the rationale for the recommendation to always draw the SDC as a trough concentration—that is, 24 h after the dose (2). This was mandated in both the PROVED and RADIANCE protocols.

We agree with Dr. Krohn's statement that total body stores of digoxin are easy to calculate. Unfortunately, we are unable to do this for each individual patient in these studies. However, the dosing guidelines cited by Dr. Krohn are incorporated into the dosing table that is currently included in the Lanoxin package

insert (2). A similar strategy was used in the PROVED, RADIANCE, and DIG studies, which produced mean SDCs in the range of 0.9 to 1.2 ng/ml. We also agree that the current therapeutic range for digoxin (0.8 to 2.0 ng/ml) is poorly defined and is based primarily on toxicity—not efficacy. As Dr. Krohn states, some patients may have high concentrations (>2.0 ng/ml) without evidence of toxicity, whereas others may have relatively low concentrations and demonstrate efficacy, a point we are attempting to make with our study. However, it is clear that, in general, the higher the concentration, the greater the risk for toxicity. Our analysis, within the limitations indicated, finds no evidence for a relationship between serum concentration and efficacy. Patients who continued digoxin, including those with a low SDC, did better than those who had it withdrawn. Because lower SDCs appear to be effective, toxicity can be minimized with a low dose of digoxin while preserving clinical benefit.

Finally, Dr. Krohn notes the high doses of digoxin used for the acute management of supraventricular arrhythmias postoperatively, whereas our analysis focuses on the outpatient management of patients with chronic heart failure. We would suggest that, for a number of reasons (age, left ventricular function, renal function, etc.), these may be two totally different patient populations. Their handling of digoxin, requirement of higher SDC, and ability to tolerate a higher SDC may differ as well. Perhaps the most important point is that the SDC should not serve as the sole marker for efficacy or toxicity but should be taken into consideration along with the patient's clinical information. The dose and SDC should always be individualized for any given patient.

Optimal dosing remains a vital but relatively poorly studied aspect of cardiovascular therapeutics. We believe our work provides useful data concerning dosing of digoxin, a medication that remains among the most commonly prescribed worldwide for heart failure.

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Long-Term Outcome in Patients With Apical Hypertrophic Cardiomyopathy

We read with interest the study by Eriksson et al. (1), which described the long-term outcome in patients with apical hypertrophic cardiomyopathy (A-HCM). The characteristic hallmarks of A-HCM as originally described (2) included the presence of giant negative T waves and a spade-like configuration at end-diastole on left ventriculography. Only 47% of their patients had giant negative T waves at baseline. Other forms of so-called A-HCM

such as that described by Maron et al. (3) relate to cases with apical distribution of septal hypertrophy with mid-ventricular constriction rather than the typical concentric apical hypertrophy of the Japanese form. They offer a very different clinical presentation, electrocardiogram, morphology, and prognosis (4,5).

As described initially in Japan, A-HCM is also found in non-Japanese patients (4-6) provided one adheres to the original criteria (2). In a longitudinal study fulfilling the exact "Japanese" criteria of A-HCM, patients were followed for 5 to 20 years (6). Sustained ventricular tachycardia in 18% and atrial fibrillation in another 18% of patients appeared as a very late complication. The T-wave negativity was reduced in 36% and loss of R-wave voltage was found in 27% of cases. Thus, patients may lose some of their electrocardiographic diagnostic characteristics and may develop life-threatening arrhythmias (6,7). One such patient with normal coronary arteries who had an automatic internal pacemaker defibrillator implanted for recurrent ventricular tachycardia developed an apical aneurysm with clot and has since died of severe pulmonary edema. Moreover, knowledge of the possibility of late aneurysmatic formation in A-HCM in the absence of coronary artery disease is mandatory to avoid the misdiagnosis of congenital defects in the form of Cantrell's syndrome (8,9).

In our study, reduction in T-wave negativity and R-wave voltage was not associated with myocardial infarction (MI) as reported by the investigators (1). In what percentage of their patients were these electrocardiographic changes associated with MI?

Lacking long-term studies and owing to the rarity of true A-HCM outside Japan, the prognosis has generally been considered benign based primarily on Japanese observations. However, considering recent Japanese experience (7) and our own (6) in addition to that of Eriksson et al. (1), in whose patients one-third did develop "unfavorable clinical events and potentially life-threatening complications, such as myocardial infarction, arrhythmia and stroke," all suggest that a complacent approach in this entity is unsafe. Close long-term follow-up is essential to reveal and manage in time potentially fatal complications, particularly in the elderly. Additional studies are needed to investigate further the genetic basis of A-HCM and to define risk-stratification strategies. In our opinion, A-HCM can no longer be viewed as a benign entity neither inside nor outside Japan.

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