with lower doses. This is not unusual because 5 mg of atorvastatin and 10 mg of simvastatin (doses that are 50% lower than recommended initially by package inserts) reduce LDL cholesterol levels by 28% to 30% on average, which is enough for many patients with mild-to-moderate LDL cholesterol elevations (2,3). Indeed, dose-related adverse effects, such as myalgia and gastrointestinal discomfort, are major reasons why 50% of patients quit statin treatment within months of starting (4,5), and the incidence of liver enzyme elevations and liver toxicities are known to increase directly with the statin dosage (6,7). Thus, statin doses must be gauged to individual response and tolerance.

Moreover, that the majority of patients in the Frolkis study did not achieve expected LDL cholesterol reductions reflects a failure of the system, not of the drugs. Many of the patients required upward adjustments in their statin dosages but did not receive them. In everyday practice, clinicians must recognize that the projected LDL cholesterol reductions in package inserts are based on statistical means from studies, and that even in these studies individual responses vary considerably (8,9). Similar and even greater variability is seen with everyday patients. The key is for physicians to anticipate this variability and to adjust statin doses according to each patient's response. This often means an upward adjustment of dosage. In the 38% of patients who, because of genetic variations in metabolic enzyme functioning or other factors, have greater than expected reductions in LDL cholesterol levels, downward adjustments in dosage may sometimes be necessary to reduce dose-related adverse effects and maintain adherence.

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The Reply:

We appreciate Dr. Cohen's comments, but take issue with some of his conclusions and assertions. First, we disagree that it is "well known that . . . treatment outcomes in everyday medical practice can vary greatly from those in controlled clinical studies." In fact, that was the central purpose of our study. We are concerned that clinicians will uncritically adopt the treatment guidelines provided in package inserts, which have been derived from the ideal conditions of a randomized study. The disparity in our own clinical outcomes relative to those projections motivated our analysis.

Second, we are confused by Dr. Cohen's statement that the fact that a substantial proportion of our patients (38%) achieved low-density lipoprotein (LDL) cholesterol reductions that were greater than predicted by package insert parameters "explains" those patients "who cannot tolerate standard initial statin doses." We reported no data on tolerance or intolerance, and our results cannot address whether these patients would have achieved their individual target LDL cholesterol levels at lower doses.

Third, the studies that Dr. Cohen cites in support of his statement that "dose-related adverse effects, such as myalgia and gastrointestinal discomfort, are major reasons why 50% of patients quit statin treatment within months of starting" used data derived from large administrative databases of elderly subjects with free or low-cost medication. There were no individual clinical data available, and no information, as stated by the authors, on adverse events.

However, we agree that "statin doses must be gauged to individual response and tolerance"—which is, of course, our practice. Our report was confined, for purposes of generalizability, to patients receiving standard doses of the most commonly used statins, but each drug and dose were selected on the basis of each patient's risk status and LDL cholesterol level. This is related to our next area of confusion: Dr. Cohen's assertion that many of our patients "required upward adjustments in their statin dosages, but did not receive them." Again, the data we reported were primarily for the first follow-up visit, with the goal of examining initial LDL cholesterol reduction. We did report on a fraction of patients at a second follow-up visit that maintained the same dose. Although this reveals that LDL-lowering outcomes for the prescribed dose are similar to that of the initial follow-up visit, the basis for subsequently increasing or decreasing doses (which we certainly hope we did appropriately), or whether patients eventually achieved their LDL cholesterol targets, cannot be evaluated from our report or the data provided. Dr. Cohen does, however, raise

an important point. There is considerable data to suggest that physicians do not titrate statin doses upward after the initial prescription, a likely contributor to the "treatment gap" between cholesterol-lowering guidelines and actual practice.

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RIGHT HEART FAILURE AND HYPERTHYROIDISM: A NEGLECTED PRESENTATION

To the Editor:

Heart failure is a rare manifestation of thyrotoxicosis in previously healthy patients (1). Predominantly right-sided heart failure in hyperthyroidism is even more uncommon. We describe 2 such patients and discuss the mechanism.

The first patient was a previously healthy 47-year-old woman who presented with shortness of breath and leg swelling. She was tachypneic and mildly tremulous, with a temperature of 38.5°C, an irregular heart rate of 136 beats per minute, and blood pressure of 127/70 mm Hg. Jugular venous distension, moderate ascites, and 4+ pedal edema were prominent. Thyroid gland was diffusely enlarged, without lid lag or exophthalmos. Cardiac examination revealed an apical 2/6 systolic murmur, no third heart sounds, and bibasilar rales. Electrocardiography showed atrial fibrillation. A chest radiograph showed mild pulmonary congestion and cardiomegaly. Laboratory results included a thyrotropin level <0.005 μIU/mL, a free thyroxine level of 2.5 ng/mL, and a total triiodothyronine level of 432 ng/dL. Uptake of I_{131} was 42% (2 hours) and 62% (24 hours). Workup for pulmonary emboli or infectious diseases was negative, pulmonary function tests were normal, and autoantibodies were not found. Echocardiography revealed normal left ventricular (LV) function, mild mitral regurgitation, and pulmonary hypertension (45 mm Hg) with tricuspid regurgitation. Symptoms resolved rapidly with furosemide, propranolol, and propylthiouracil, and the patient was discharged. However, noncompliance with the medications resulted in relapse of thyrotoxicosis and right heart failure, which resolved with reinstitution of therapy. The patient remains well.

The second patient was a 42-year-old woman admitted for anasarca that developed over several weeks. Ten years ago, she was diagnosed with Graves' disease and treated with propylthiouracil and propranolol. However, she remained in atrial fibrillation and dependent on both drugs. Radioactive iodine was refused. Two months before admission, she stopped taking her medications. Shortly afterward she had progressive swelling of the legs and abdomen, and weight gain. She was afebrile, with a blood pressure of 170/100 mm Hg and an irregular heart rate of 150

Table. Characteristics of Patients with Graves' Disease and Right-Sided Heart Failure

Patient Age/Sex	Clinical Presentation	Pretreatment PAP* (PVR†)	Outcome	Post-treatment PAP* (PVR†)	Reference
47/F	Severe right heart failure	45 mm Hg	Rapid resolution	Not done	Current report
42/F	Anasarca	60 mm Hg	Complete resolution	22 mm Hg	Current report
47/M	Anasarca	45/18 mm Hg (78 dyne · sec · cm^{-5})	Rapid resolution	Not done	3
62/F	Anasarca	Not done	Tricuspid regurgitation resolved	Not done	4
59/F	Anasarca	50 mm Hg	Complete resolution of right heart failure	Not done	4
32/M	Edema, severe tricuspid regurgitation	27 mm Hg	Edema and tricuspid regurgitation resolved	Not done	5
54/M	Ankle edema, distended neck veins	56 mm Hg	Complete resolution	35 mm Hg	6
46/F	Peripheral edema	53 mm Hg (256 dyne · sec · cm^{-5})	Complete resolution	15 mm Hg (80 dyne · sec · cm^{-5})	7

* Systolic PAP obtained by transthoracic echocardiogram except in 2 patients (references 3 and 7) in whom systolic and diastolic pulmonary pressures were obtained by cardiac catheterization.
† PVR obtained by cardiac catheterization.
F = female; M = male; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.