

## COMMENTS AND RESPONSES

## Patient Self-Management of Oral Anticoagulation

**TO THE EDITOR:** The design of the study by Menéndez-Jándula and colleagues on patient self-management of oral anticoagulant therapy (1) has some important limitations. The authors compared monthly conventional management of anticoagulant therapy with weekly self-management and reported no significant difference in unadjusted percentages of end-range international normalized ratios (INRs). However, this is an unfair comparison.

In my office, prothrombin times are checked every 2 weeks and then weekly if the dose has to be adjusted. Patients who do not require frequent dose adjustments can have this interval increased to 3 or 4 weeks. It would seem more reasonable for Menéndez-Jándula and colleagues to have compared conventional and self-management approaches using the same interval between tests. Furthermore, in my experience, portable INR monitors are not as accurate or as consistent as those used in the laboratory in my hospital. If the real therapeutic range is wider when portable monitors are used, more INR measurements would be within the therapeutic range. In Menéndez-Jándula and colleagues' study, were the INR measurements obtained from the portable monitors repeated in the office so the true accuracy and consistency of the portable monitors could be determined?

Given these 2 limitations, I do not feel that self-management of poor anticoagulant therapy is ready for prime time.

Finally, if the U.S. Food and Drug Administration would get around to approving a nonwarfarin anticoagulant, such as the thrombin inhibitor ximelagatran, self-management would probably become a moot point.

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## Reference

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**IN RESPONSE:** The main purpose of our study was to evaluate the reliability of self-management (with all of its theoretical advantages, including ease for weekly testing at home) in comparison with the actual management of anticoagulant therapy in Spanish clinics. In most Spanish clinics, the number of patients each clinic sees makes weekly monitoring almost impossible. For example, in our clinic, we monitor more than 6000 patients each month. Maybe the ideal design of our study would have included the same interval between tests in both arms, but in our opinion the results would not have been applicable to real-life practice.

In contrast to Dr. Wheeler's experience, our results were accurate and consistent using the portable monitor (CoaguChek S, Roche Diagnostics, Mannheim, Germany) in a previous pilot study. We compared the INR results of 150 patients obtained simultaneously with the portable coagulometer and through our laboratory (KC 10 coagulometer, Amelung, Lemgo, Germany). The correlation coefficient

was 0.95 (unpublished data). This excellent agreement between the use of CoaguChek devices and standard laboratory coagulometers has been reported elsewhere (1). In our trial, we found the mean percentage of in-range INRs ( $\pm$  SD) to be statistically significantly higher in the self-management group ( $58.6\% \pm 14.3\%$ ) than in the conventional management group ( $55.6\% \pm 19.6\%$ ), although we considered this difference irrelevant from a clinical point of view. Of course, the intended INR target ranges were the same width in both comparison groups.

We believe that the most important result from our study relates to the safety of self-management, not the efficacy of testing (which was at least as good in the self-management group as in the conventional group). We observed an impressive reduction (70%) in major complications and in minor hemorrhages in the self-management group, as well as a trend toward reduced mortality. For these reasons, we agree with Beyth (2) that a patient-professional partnership in long-term anticoagulation can reduce the incidence of very serious related complications and that this model of care requires a shift in focus and resources by health care systems and providers.

The new thrombin inhibitor ximelagatran is a very promising drug, with clinical outcomes similar to those seen with conventionally managed warfarin (3). It would be interesting to compare the use of ximelagatran with patient self-management using warfarin in appropriate clinical trials, considering that self-management by trained patients taking warfarin can result in severe complications in 1% or less of patient-years (4).

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## Commercial Weight Loss Programs

**TO THE EDITOR:** While I applaud Drs. Tsai and Wadden's call for more outcome data from weight loss programs (1), I was mystified by their conclusion. Because of the narrow criteria Tsai and Wadden imposed, several recent studies from Health Management Resources were not included. While randomized, controlled trials are one type of study, other available data should not be ignored. Ongoing data from treatment programs should be considered valid since a natural

“control” group exists in overweight, nondieting Americans (people, on average, are gaining  $\geq 0.45$  kg [ $\geq 1$  lb] yearly) (2). Furthermore, the authors call for “naturalistic studies” that follow a large cohort to determine the percentage of persons who complete various phases of treatment, as well as the amount of weight lost. When offered such data from Health Management Resources from dozens of major medical centers, the authors refused to consider it.

It is difficult to see how the authors reached the conclusion that Weight Watchers was the most successful program, especially since they acknowledge that Health Management Resources’ weight losses are greater than 20% of initial weight (22.5 to 27 kg [50 to 60 lb]). By Tsai and Wadden’s own analysis, participants in Weight Watchers were keeping off 3.2% of initial body weight at 2 years while Health Management Resources participants were keeping off 15.2% (2.9 vs. 13.7 kg [6.4 vs. 30.4 lb] for a 90-kg [200-lb] person). For people needing to lose weight and decrease their medical risk factors (for example, diabetes, heart disease, and hypertension), a loss of 2.7 kg (6 lb) is barely sufficient. Research clearly shows that greater weight loss leads to greater changes in medical risk factors (3).

Tsai and Wadden also made a grave error in their cost analysis. Since the Health Management Resources program includes the cost of meal replacements, the only fair way to compare it with other programs is to include the ongoing, normal cost of food. Once that cost is added (approximately \$58 for in-home meals [4] and \$48 for outside eating per week [5]), the “real cost” for Weight Watchers rises to approximately \$100 per week—more than food costs in any Health Management Resources treatment program, with less weight loss. In fact, 1 study found that food costs were actually lower in programs that provide meal replacements (6).

Health Management Resources has pioneered a research-based weight management program for over 20 years. Our data indicate that patients in our program are eating more than 35 servings of fruits and vegetables and doing more than 2000 kcal of exercise per week, while using meal replacements to lower caloric intake. It is a shame that Tsai and Wadden have given the impression that this is not successful, cost-effective, healthy weight loss.

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**Potential Financial Conflicts of Interest:** *Employment* (Health Management Resources).

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6. Hart K, Greenwood H, Truby H. Pound for pound? Comparing the costs incurred by subjects following four commercially available weight loss programmes. *J Hum Nutr Diet.* 2003;16:365.

**IN RESPONSE:** Dr. Gotthelf cites our call for naturalistic studies to determine the effectiveness of weight loss programs and states that she offered such data, which we declined. We outlined very specific criteria for original research to be included in our review, one of which was that the data had to be published in a journal. We applaud Health Management Resources for collecting further data from observational studies and encourage the company to submit these findings for peer review.

Dr. Gotthelf states that we concluded that Weight Watchers was the most successful program. We did not state this, but rather concluded that Weight Watchers was the most rigorously tested program. We agree that a 15% loss of initial weight, as found in 1 Health Management Resources study, is more clinically significant than a 3% loss. However, most persons treated in medically supervised programs do not maintain a loss of 15% of initial weight at 2 to 3 years. In one of Health Management Resources’ naturalistic studies, patients lost 19.2% of initial weight in 20 weeks but maintained a loss of only 7.3% at 3.4 years. This follow-up evaluation did not include 42% of the original sample, and the findings were not adjusted (using a baseline-carried-forward analysis) to account for the dropouts (1). Randomized comparisons of very-low-calorie diet regimens (as used in the Health Management Resources studies) and low-calorie diets (providing 1200 to 1500 kcal/d) have shown no difference in long-term weight losses (2), principally because of greater weight regain with the former approach.

Finally, Dr. Gotthelf states that we incorrectly estimated costs by including the price of meal replacements for medically supervised programs but not for programs that do not require meals to be purchased. This is a valid point. Our goal was to estimate the actual out-of-pocket costs associated with participating in each program. Clearly, participants must continue to purchase food when dieting. Some may spend approximately \$80 per week on food, comparable with the costs of Health Management Resources’ meal plan. Others, however, may spend substantially less. In reviewing Dr. Gotthelf’s cited sources, we believe she has overestimated the usual costs of food.

In general, the programs we reviewed, including Health Management Resources, are among the better options available to patients who wish to lose weight. Many are members of the Partnership for Healthy Weight Management and provide appropriate information to potential clients (3). Our intention was not to disparage the important service provided by these programs, but rather to review the available evidence and to encourage publication of further research.

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## Aggressive Treatment of High-Density Lipoprotein Cholesterol

**TO THE EDITOR:** Whitney and colleagues (1) provide an interesting glimpse into the agents that elevate high-density lipoprotein (HDL) cholesterol levels in the prestatin era. The combination of a fibrate, niacin, and a bile-acid sequestrant increased plasma HDL levels by 37%. This was associated with a beneficial impact on atherosclerotic burden and a combination of clinical end points. Careful follow-up resulted in effective adherence to both dietary modification and consumption of pharmacologic agents that have traditionally been associated with high intolerance rates.

The reported effect on plaque burden should be interpreted with caution. Atherosclerotic extent was measured by coronary angiography, using a global estimate of severity and qualitative assessment. This result should be viewed in the context of previous reports showing that infusion of reconstituted HDL promoted rapid atherosclerotic regression, as assessed by intravascular ultrasonography, a more accurate measure of plaque burden (2). Furthermore, when patients who did not proceed to follow-up angiography were included in the analysis, it was assumed that there was no change in their plaque burden. This is in contrast to the stated assumption that standard medical care during this period would be associated with a 2% progression in angiographic stenosis. This assumption should be applied to the analysis.

It is premature to dismiss the concept that these agents had no impact on inflammation. Although fibrinogen levels were not altered, C-reactive protein level was not reported. It is likely that the beneficial effects of fibrate therapy result, in part, from the anti-inflammatory sequelae of fibrates' interaction with peroxisome proliferator-activated receptor- $\alpha$  (3).

Strategies to increase plasma HDL cholesterol levels are of immense interest. It remains unclear whether quantity or quality of HDL is more important. Ultimately, we need to consider that any therapeutic options developed to promote HDL will need to be tested in the setting of statin therapy.

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**IN RESPONSE:** We appreciate Dr. Nicholls's comments and agree that the agents studied in the Armed Forces Regression Study (AFREGS), particularly niacin, have not traditionally been well tolerated. With newer formulations of niacin and proper patient instruction, adherence has been much improved (1). Until newer agents have undergone more rigorous study and review, niacin remains the single most effective agent to increase HDL cholesterol level. Whether its well-established clinical benefits are derived from changes in quantity or quality of HDL or low-density lipoprotein cholesterol remains controversial, and unfortunately lipoprotein subtyping was not performed in the AFREGS population.

Although fibrinogen levels did not change with therapy, such a small study cannot exclude modulation of inflammation by study drugs. We examined fibrinogen and leukocyte count in several subsets of patients in AFREGS and could not find evidence of any greater benefit in patients with increased inflammation, or evidence that therapy significantly altered levels of fibrinogen or leukocytes.

In terms of assessing atherosclerotic burden, we agree with Dr. Nicholls that intravascular ultrasonography is a tremendous advance and provides significantly better plaque characterization than angiography (2). It unfortunately remains slightly more invasive, is time-consuming, and is not widely available. It is also important to note that despite the limits of angiography, the AFREGS results and the results of other quantitative coronary angiography studies do not dramatically differ in magnitude from those of recent studies using intravascular ultrasonography (3). In particular, in the REVERSAL (REVERSal of Atherosclerosis with Lipitor) study, a 1.4% difference in percentage of obstructive volume was seen between high- and moderate-dose statins (4). When the suggested 2% progression of atherosclerosis in patients not receiving final angiography in AFREGS is used, the difference in progression between treatment groups remains approximately 2% (0.6% reduction with combination therapy compared with a 1.5% progression in patients receiving placebo), with even stronger statistical significance.

The use of combination therapy without a statin, despite our favorable results, cannot be generally recommended for the secondary prevention of cardiovascular disease. The proven benefit of statins in the reduction of clinical events, including myocardial infarction, stroke, and death, is too significant to totally disregard. Guidelines mainly recommend targeted HDL treatment if goal levels are not achieved with diet, lifestyle, and statins (5). For primary prevention, however, the data are less clear, and further studies will be necessary to establish the most effective treatment strategy.

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### Cognitive Psychology of Missed Diagnoses

**TO THE EDITOR:** I thank Dr. Redelmeier for his recent article on the cognitive psychology of missed diagnoses (1). I hope it will prove useful in my own clinical practice as well as in the teaching of clinical skills to medical students and residents. Regarding the framing pitfall, perhaps another clinical maxim to consider would be, "Never choose a frame too small for the picture." In my own experience, it seems that framing is often the act of narrowing a diagnosis through choice of words, the utility of which needs to be weighed against the danger of prematurely eliminating alternative explanations. In this sense, framing appears to be closely linked to premature closure. Regarding the underlying rationales for each type of cognitive error, the article mentioned the ability to "produce the desired results with a minimum of delay, cost, and anxiety." In addition, one would think that our perceived need as physicians to appear omniscient, or at least highly self-confident, may often underlie common cognitive errors in arriving at a diagnosis. Expressing confidence in our diagnosis to the patient may be thought to be helpful in healing the patient or at least in increasing patient satisfaction with the visit, although evidence seems to be scanty for both of these options (2). The extent to which these concerns might underlie some of the common cognitive errors in diagnosis seems to await further research.

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**IN RESPONSE:** Dr. Derauf provides some insightful feedback in a kindly manner. His introduction of another maxim is particularly welcome, as are his remarks about the role of confidence in medicine. In moderation, confidence is necessary because facing trouble requires courage, the stakes in medical care are high, and clinicians do not want to act capriciously. Taken to extremes, however, any self-deception is a source of fallibility. A valid rationale is what distinguishes confidence from self-deception.

Psychology research also shows that people sometimes are overly dependent on rationale. In one study (1), students were offered an attractive vacation following a tough examination. By random assignment, one third were told they had passed the examination; in this case, most accepted the offer (presumably as a reward). One third were told they had failed; in this case, most still accepted the offer (presumably as a consolation). The final third were told the examination results were delayed; in this case, most declined the offer. Apparently, the lack of a rationale dissuaded some students from accepting a vacation that was otherwise attractive regardless of circumstance. The general pattern is that even minor decisions require the presence of a rationale.

Biology is complex, and patient presentations are uncertain; hence, a clinician may seek or construct all sorts of rationales. Once a rationale is obtained, such clinicians tend to lack the circumspection of dispassionate reviewers. As Dr. Derauf mentions, self-deception underpins a basic vulnerability to framing effects and a failure to intercept errors. As Dr. Derauf also emphasizes, self-deception is sometimes reinforced by the patient. Alas, self-deception is a resource many of us have in abundance.

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### CLINICAL OBSERVATION

#### A New Concept of Unopposed $\beta$ -Adrenergic Overstimulation in a Patient with Pheochromocytoma

**TO THE EDITOR:** *Background:* The concept of unopposed  $\beta$ -adrenergic overstimulation during selective  $\alpha$ -adrenergic blockade in patients with pheochromocytoma is well recognized (1–4). We present a case that suggests the existence of an opposite phenomenon: a syndrome of unopposed  $\beta$ -adrenergic overstimulation.

*Case Report:* A 46-year-old woman with multiple endocrine neoplasia type 2A was admitted to the endocrine ward of the National Institutes of Health Warren Grant Magnuson Clinical Center. On a previous admission, she had reported progressive spells of headaches,

**Table 1. Epinephrine, Norepinephrine, Metanephrine, and Normetanephrine Levels**

Variable	Value in Patient	Normal Range
<b>Plasma level, pmol/L</b>		
Epinephrine	393	22–453
Norepinephrine	3741	473–2943
Metanephrine	1453	61–310
Normetanephrine	5179	98–612
<b>Urine level</b>		
Epinephrine, nmol/24 h	115	0–109
Norepinephrine, nmol/24 h	662	89–473
Metanephrine, $\mu$ mol/24 h	10	0.15–0.91
Normetanephrine, $\mu$ mol/24 h	21	0.65–2.5

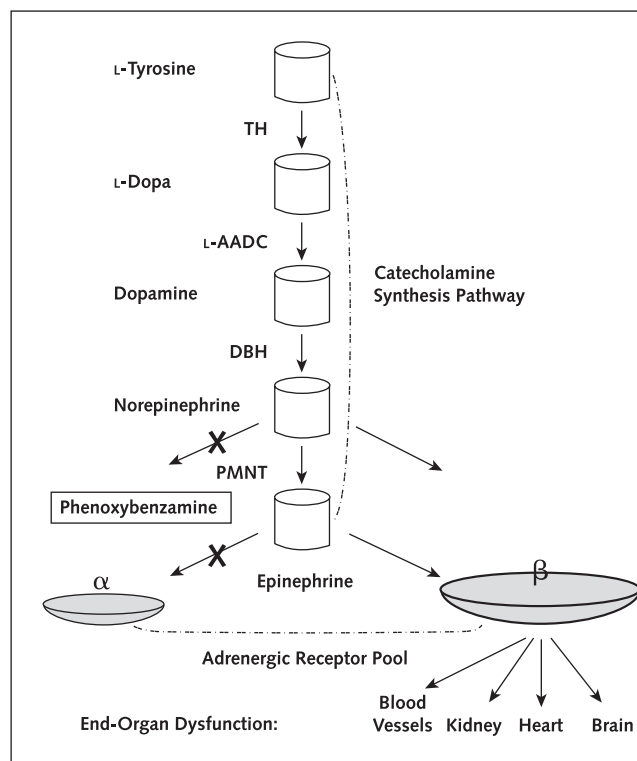
paleness, and palpitations and was found to have bilateral adrenal pheochromocytomas (right side, 4.7 × 3.1 cm; left side, 2.0 × 1.5 cm) with significantly elevated catecholamine and metanephrine levels (Table 1). The patient had extensive cervical and mediastinal adenopathy from metastatic medullary thyroid cancer and serum calcitonin levels greater than 30 000 pg/mL. Oral furosemide (20 mg/d) had been added to her long-term medications 35 days before the current admission in an attempt to improve chronic peripheral edema, but no significant changes in urine output, weight, vital signs, or edema were observed.

According to presurgical protocol, metyrosine, 250 mg 4 times daily, and phenoxybenzamine, 10 mg twice daily, were started 5 days before readmission. Within 48 hours, the patient developed progressively worsening symptoms of severe diffuse peripheral edema, shortness of breath, low urine output, and somnolence that required urgent hospitalization. Medications at admission also included acetaminophen–oxycodone for chronic pain; fentanyl patch, 100 mg/h; furosemide, 20 mg/d; and L-thyroxine, 150  $\mu$ g/d. On physical examination, the patient was somnolent but able to be roused, severely and diffusely edematous, and hypotensive and tachycardic. However, she had clear lungs, distant heart sound, and nontender abdomen with normal bowel sounds. Thirty-five days before admission, at admission, and at day 6 after admission, the patient's weight was 80.4 kg, 94.6 kg, and 85.6 kg; her blood pressure was 116/64 mm Hg, 94/54 mm Hg, and 132/70 mm Hg; and her approximate heart rate was 90 beats/min, 110 beats/min, and 80 beats/min, respectively.

Electrocardiography and chest radiography did not show acute processes. Metyrosine and furosemide were withdrawn immediately, phenoxybenzamine dose was decreased to 5 mg twice daily, and propranolol was started at 5 mg twice daily. The patient responded rapidly: Within 24 hours, heart rate decreased and blood pressure increased, and within 48 hours, urine output increased, weight decreased, and edema and somnolence significantly and progressively improved. On day 6, the patient underwent uncomplicated partial bilateral adrenalectomy. She continued to improve and was discharged home shortly thereafter.

**Discussion:** Clinicians should consider unopposed hyper- $\beta$ -adrenergic stimulation in patients with pheochromocytoma. In cases of catecholamine excess, selective  $\beta$ -adrenergic blockade will shift all available amounts of catecholamines to the  $\beta$ -adrenergic receptor compartment, enabling selective  $\beta$ -adrenergic overstimulation concurrently with  $\beta$ -adrenergic blockade. In contrast to unopposed  $\alpha$ -adrenergic stimulation (as in the case of selective  $\alpha$ -blockade), where the main clinical picture is one of severe peripheral vasoconstriction,

**Figure. Suggested pathogenesis of unopposed  $\alpha$ -blockade-induced  $\beta$ -adrenergic overstimulation.**



DBH = dopamine  $\beta$ -hydroxylase; L-AADC = L-amino acid decarboxylase; L-dopa = L-3, 4-dihydroxyphenylalanine; PMNT = phenylethanolamine-*N*-methyltransferase; TH = tyrosine hydroxylase.

tion, unopposed  $\beta$ -adrenergic blockade will show opposite features. It somewhat resembles thyrotoxicosis with sepsis: hyperdynamic low-output cardiac state and decreased peripheral vascular resistance. This model is summarized in the Figure and is associated with the clinical consequences seen in our patient (Table 2). If untreated, this condition would progress to further diastolic dysfunction and frank congestive heart failure with hypotension and organ hypoperfusion.

To our knowledge, this phenomenon has never been described before in patients with pheochromocytoma. We believe that unopposed  $\beta$ -adrenergic overstimulation is often underdiagnosed in its

**Table 2. Characteristics of the Syndrome of Unopposed  $\beta$ -Adrenergic Overactivity (Organ System and Sign or Symptom)**

<b>Cardiac</b>	Tachycardia Diastolic dysfunction Diffuse edema
<b>Vascular</b>	Peripheral vasodilation Hypotension
<b>Cerebral</b>	Hypoperfusion (somnolence)
<b>Renal</b>	Hypoperfusion (oliguria)

more common milder forms, while in more severe forms patients are usually treated with both  $\alpha$ -blockers and  $\beta$ -blockers. This syndrome is more likely to be mild because of the preferential desensitization of  $\beta$ -adrenergic receptors compared with their  $\alpha$ -adrenergic counterparts in states of catecholamine excess, as seen in patients with pheochromocytoma (5, 6). Thus, patients with less pronounced desensitization of  $\beta$ -adrenergic receptors may present with the symptoms described here. Such patients should be started on  $\beta$ -blockade, which should be tapered to alleviate clinical symptoms.

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**Potential Financial Conflicts of Interest:** None disclosed.

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