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Should We Treat for Subclinical Hypothyroidism?

Grand Rounds Discussion From Beth Israel Deaconess Medical Center

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In May 2015, the U.S. Preventive Services Task Force issued a guideline on screening for thyroid disease that included a systematic evidence review and an update of its 2004 recommendations. The review assessed the effect of treating screen-detected subclinical thyroid dysfunction on health outcomes. It found adequate evidence that treating subclinical hypothyroidism does not provide clinically meaningful improvements in blood pressure, body mass index, bone mineral density, lipid levels, or quality-of-life measures. The review also concluded that evidence was inadequate to determine whether screening for thyroid dysfunction reduced cardiovascular disease or related morbidity and mortality. In separate guidelines, the American Association of Clinical Endocrinologists and American Thyroid Association advocated aggressive case-finding and recommended screening persons with certain clinical conditions or characteristics rather than the general population. These societies argue that subclinical hypothyroidism adversely affects cardiovascular outcomes and thus merits case-finding. Here, 2 experts discuss their perspectives on whether treating subclinical hypothyroidism reduces morbidity and mortality, whether there are harms of treatment, and how they would balance the benefits and harms of treatment both in general and for a specific patient.

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Ms. C is a 60-year-old woman. In 2001, when she reported constipation, thyroid-stimulating hormone (TSH) level was 2.5 uIU/L; in 2003, when she reported fatigue, it was 3.5 uIU/L. Both are in the normal range (0.27 to 4.2 uIU/L). A repeated TSH measurement in 2012, when she reported increased sweating and a family history of "thyroid problems," was slightly elevated (5.8 uIU/L). In 2013, she reported fatigue; her TSH level was similar (5.9 uIU/L) to the 2012 measurement, and her free thyroxine (T_4) was normal (0.93 ng/dL). Given the stability of her TSH level, treatment was not initiated. Recently, she reported weight gain, intermittent constipation, and persistent fatigue.

Her history is noteworthy for hyperlipidemia treated with atorvastatin, 10 mg daily, and cervical radiculitis.

She is married and is the primary caregiver for her husband. She does not smoke or drink alcohol. Two of her three sisters receive thyroid medication.

At a recent periodic health examination, blood pressure was 136/79 mm Hg and heart rate was 77 beats/min. Her weight had increased by 9 pounds, to 156 pounds (body mass index, 29.6 kg/m^2). Her thyroid examination was normal. A repeated TSH measurement was 6.5 uIU/ML and free T_4 was 1.0 ng/dL. She and her primary care physician wonder whether she should begin thyroid replacement therapy.

About Beyond the Guidelines

Beyond the Guidelines is an educational feature based on recent guidelines. Each considers a patient who "falls between the cracks" of available evidence and for whom the optimal clinical course in unclear. Presented at Beth Israel Deaconess Medical Center (BIDMC) Grand Rounds, each conference reviews the background evidence and 2 experts then discuss the patient and field audience questions. Videos of the patient and conference, the slide presentation, and a CME/MOC activity accompany each article. For more information, visit www.annals.org/GrandRounds.

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MS. C'S STORY

About 2 years ago, my doctor noticed that I had a problem with my thyroid. Initially, I didn't notice too much. It's only recently, in the last 6 months, that I've put on about 10 pounds, which is unusual for me, in spite of going to the gym every day. I'm more fatigued than I used to be, and constipation has become a slight problem that wasn't there before. I'm not sure whether it's the thyroid and whether I'm trying to relate everything to it right now or if I'm just getting old.

I called all my sisters to check with them, and to my surprise I found that 2 of them are on thyroid medication. I didn't ask them what, but my eldest sister has been on it for the past 4 years. She said that she doesn't know whether she is getting better or not. They just take a blood test every 6 months, and they see the numbers go up and go down and they tweak it.

My doctor and I haven't spoken about medication yet. I have been thinking, because after I found out, I went to study what this does. Putting on weight has been bothering me a lot. I would like to take the medication so that I don't keep gaining weight. The others I am not particularly concerned about. I know my doctor is going to say, if it's good for me she is going to give it to me. If she was to put me on medication, I'll probably ask her what the side effects would be. For now, it's the medication that's the most important thing for me, whether I should be on the medication or not. That is my major concern right now.

See the **Patient Video** (available at www.annals.org) to view the patient telling her story.

CONTEXT, EVIDENCE, AND GUIDELINES

Subclinical hypothyroidism is defined as TSH levels above 4.5 uIU/L with normal T_4 levels. About 5% of women and 3% of men in the United States have subclinical hypothyroidism (1), and approximately 33% to 55% of them will develop overt hypothyroidism over a period of 10 to 20 years (2–4). Previous work has suggested that subclinical hypothyroidism is associated with increased risk for coronary heart disease mortality (5, 6) and may be a risk factor for congestive heart failure (5). It is unclear whether treatment of subclinical hypothyroidism reduces risk for these adverse health outcomes.

In 2011, the Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ) published "Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism" (6). It found no evidence that treating subclinical hypothyroidism improved quality of life, blood pressure, or body mass index. Findings regarding lipids were less clear, and the reviewers concluded that treatment of subclinical hypothyroidism might result in a 5% improvement in lipid measurements. The AHRQ concluded that it was unclear whether screening and early treatment for thyroid disease are better than not screening or watchful waiting when TSH levels are mildly elevated.

In May 2015, the U.S. Preventive Services Task Force (USPSTF) updated its 2004 recommendation on screening for thyroid disease (7). The review examined the effect of treating screen-detected subclinical thyroid dysfunction on health outcomes (8). It found no evidence that treating subclinical hypothyroidism improved blood pressure, body mass index, quality of life, or cognitive function. Across 8 eligible studies, the difference between treatment and no treatment was minimal for mean total cholesterol levels (−28 to 0 mg/dL) and for mean low-density lipoprotein cholesterol levels (−22 to 2 mg/dL) (9).

Only 1 study has examined treatment of subclinical hypothyroidism and risk for subsequent cardiac events. In persons aged 40 to 70 years, treatment was associated with reduced risk for fatal or nonfatal ischemic heart disease events (4.2% vs. 6.6%; hazard ratio, 0.61 [95% CI, 0.39 to 0.95]). No statistically significant association between treatment and cardiovascular outcomes was found in persons older than 70 years (10).

The USPSTF review found inadequate evidence on the harms of treating subclinical thyroid dysfunction. Older data suggest that overtreatment is common and could lead to increased risk for osteoporosis, reduced cardiac output, and ventricular hypertrophy (11). Other potential harms include psychological effects of labeling, frequent false-positive results, and overdiagnosis and overtreatment (7). The USPSTF concluded that current evidence is insufficient to determine the balance of benefits and harms of screening for thyroid dysfunction (7).

In separate guidelines, the American Association of Clinical Endocrinologists (AACE) and American Thyroid Association (ATA) recommended aggressive case-finding only for patients with certain clinical conditions or characteristics (12, 13). These include a family history of thyroid disease, history of neck irradiation or thyroid surgery, dyslipidemia, atrial fibrillation, unexplained weight loss, hyperprolactinemia, certain autoimmune disorders, and use of medications that can cause thyroid dysfunction. In 2015, Hennessey and colleagues (14) reiterated these recommendations, concluding that this approach identifies persons who are most likely to have thyroid disease; to experience clinical consequences, including cardiovascular disease; and to benefit from treatment (14).

CLINICAL QUESTIONS

To structure a debate between our 2 discussants, we mutually agreed on the following key questions to consider when applying this guideline to clinical practice and to Ms. C in particular:

Question 1: Does treatment of subclinical hypothyroidism reduce morbidity and mortality?

Question 2: What are the harms of treatment?

Question 3: Balancing the benefits and harms, when would you recommend treatment, in general and for Ms. C in particular?

DISCUSSION

A Viewpoint in Favor of Treatment (Pamela Hartzband, MD)

Question 1: Does treatment of subclinical hypothyroidism reduce morbidity and mortality?

The USPSTF concluded that evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant asymptomatic adults (7). I agree.

However, today we are considering the case of Ms. C. She has a strongly positive family history of thyroid disease, has elevated cholesterol, and presents with symptoms compatible with hypothyroidism. She fits best into the group of patients for whom aggressive case-finding is advocated by AACE and ATA guidelines (12, 14). There is an evidence base suggesting that patients like Ms. C may benefit with respect to both morbidity and mortality.

Thyroid-stimulating hormone is a sensitive indicator of primary hypothyroidism. With intact pituitary function, a small decrease in free T_4 results in an inverse and more dramatic rise in TSH, allowing the diagnosis of subtle degrees of hypothyroidism. Although the normal range for TSH and free T_4 in a population is broad, for each individual TSH and free T_4 remain in a more narrow range, an individual set point. A gradual increase in TSH over time, as seen in Ms. C, is significant and suggests early thyroid failure (15).

Autoimmune hypothyroidism, the most common cause of primary hypothyroidism in the United States, is a progressive disorder. In the earliest stage, thyroid antibodies may be positive but TSH is normal. Over time TSH rises; T_4 is initially normal but eventually becomes low. The rise in TSH associated with hypothyroidism is a continuum without a precise cutoff where subclinical disease becomes overt (16). In women, the progression from subclinical to overt hypothyroidism occurs at a rate of 2.6% per year; if antithyroid peroxidase antibodies are present, the rate increases to 4.3% (3). Still, it may take many years to develop overt hypothyroidism. At what point should we consider treatment?

In reviewing the evidence for benefit of treatment, there are not only conflicting data but also conflicting interpretation of the same data by different experts. With regard to lipids, the National Cholesterol Education Program recommends testing for hypothyroidism in patients with elevated cholesterol (16). If a mildly elevated TSH is found, should the patient be treated with levothyroxine? This question is directly relevant to Ms. C. Although a relationship between dyslipidemia and overt hypothyroidism is clear, there is controversy with respect to subclinical disease. Studies of the effect of levothyroxine treatment on lipid levels and other intermediate markers of cardiac risk in subclinical hypothyroidism are conflicting with both positive and negative studies of variable quality (17). Discordant results may be due in part to inclusion of participants with TSH levels as low as 3.0 and as high as 15. Further, several lipid studies called negative in the AHRQ evidence review were termed positive by other experts (18–20).

Subclinical hypothyroidism has been associated with increased risk for cardiovascular morbidity and mortality in some prospective population-based studies but not others (17, 18). The most compelling data come from a large retrospective cohort study in the United Kingdom. In that study, there was a decrease in ischemic cardiovascular events and mortality when adults younger than 70 years with TSH levels ranging from 5 to 10 were treated with levothyroxine. The effect of treatment with levothyroxine was similar in magnitude to that seen in studies of statin therapy for primary prevention of cardiovascular disease. This benefit was not seen in subjects older than 70 years (10, 21). Randomized, controlled trials (RCTs) are needed for a definitive answer.

Overt hypothyroidism is associated with well-described symptoms and physical findings, and improvement follows treatment with levothyroxine. The extent to which patients experience hypothyroid symptoms is related not only to the degree of hypothyroidism but also to the duration (21). Further, symptoms are quite variable, so aggregate data may not apply to the individual. Let's consider Ms. C. In the video interview, she reports several nonspecific symptoms suggestive of hypothyroidism: fatigue, constipation, scalp hair loss, weight gain. Her TSH is elevated. Is there a role for a therapeutic trial of levothyroxine?

Although relief of symptoms is often the primary goal of our patients, there is a paucity of evidence showing symptomatic improvement with treatment of subclinical hypothyroidism. A Swiss study showed improvement in 2 symptom scores (Billewicz and Zulewski scores) with treatment, but only in patients with a pretreatment TSH greater than 12 (20). Another study of subclinical hypothyroidism also noted improvement in symptoms with treatment in patients with a mean TSH of 11 (22). In both studies, patients had known thyroid disease (treated Graves or Hashimoto thyroiditis).

Question 2: What are the harms of treatment?

There is remarkably limited evidence for harms related to the treatment of subclinical hypothyroidism (8). However, there is speculation that patients might develop hyperthyroidism from excessive doses of levothyroxine. Although studies show that both overtreatment and undertreatment of hypothyroidism are common in clinical practice (23), this is avoidable by initiating treatment of subclinical hypothyroidism with low-dose levothyroxine (25 to 50 mcg), as suggested in the AACE/ATA guidelines, and careful monitoring (12). When population screening is considered, the cost of treatment is critical. With regard to individual patients like Ms. C, treatment is inexpensive as levothyroxine is available at low cost.

The psychological effect of labeling a patient with a diagnosis of hypothyroidism is a potential concern. However, in the context of shared decision making, it's important to fully inform patients like Ms. C of all test

results and treatment options. In our attempt to avoid psychological effects of labeling, we risk reverting to medical paternalism. Most patients are capable of understanding expert controversy and making a considered decision (24).

Question 3: Balancing the benefits and harms, when would you recommend treatment, in general and for Ms. C in particular?

I would consider offering Ms. C a trial of levothyroxine. Based on family history, she is at increased risk for thyroid disease and was appropriately tested by measuring TSH (12). After finding an elevated TSH, I would measure antithyroid peroxidase antibodies, which would most likely be positive in her case and might affect her treatment decision. Based on available evidence, levothyroxine treatment could reduce her cholesterol and risk for heart disease. She might be able to reduce or even discontinue her statin. Her symptoms might improve, although there is little evidence for that. There is no evidence base suggesting harm if she is treated with low-dose levothyroxine and carefully monitored. I believe that for Ms. C the potential for benefit outweighs potential risk. If she does not feel better and if cholesterol is not improved, then levothyroxine could be stopped until her TSH rises further. But in the end, the decision is up to Ms. C, as she is the one who will enjoy the benefits but also assume the risks (24).

A Viewpoint Against Treatment (Carol K. Bates, MD)

Question 1: Does treatment of subclinical hypothyroidism reduce morbidity and mortality?

The first question is whether this is a reliable result given the known diurnal variation in TSH. In paired samples of 20 patients, the mean value when measured between 8 and 9 a.m. was 5.83 but was 3.79 when measured between 2 and 4 p.m. (25). Our patient's abnormal TSH values were all drawn between 9 a.m. and noon; her TSH might have been normal if measured in the afternoon.

Much of the treatment debate focuses on the relationship between subclinical hypothyroidism and heart disease. While there is an association among congestive heart failure, coronary artery disease, and subclinical hypothyroidism, our patient's TSH is only mildly increased. In a recent meta-analysis including more than 25 000 patients, the hazard ratio for a TSH of 4.5 to 6.9 was 1.0 (range, 0.86 to 1.18) for a cardiac event and 1.09 (range, 0.91 to 1.30) for cardiac death (26).

Some have argued that subclinical hypothyroidism be treated to lower cholesterol levels. Ms. C started a statin in 2003 when her TSH was 3.5 and thus euthyroid. Any efforts to lower cholesterol might be done by adjusting her statin dose rather than adding levothyroxine.

Ms. C's TSH was measured because of symptoms associated with hypothyroidism. And yet, the cardinal symptoms of hypothyroidism are also common in euthyroid patients. In 1 population-based study of more than 25 000 patients with hypothyroidism in Colorado, an increase in dry skin, the most prevalent symptom, was present in 28% of those with TSH greater than 5.1 but also in about 25% of those with normal TSH. Focusing on Ms. C, fatigue was present in 18% with abnormal TSH and about 15% when normal; constipation in 8% with abnormal TSH versus about 6% when normal (23). It is therefore tempting but potentially incorrect to attribute Ms. C's symptoms to her thyroid.

Ms. C is primarily motivated to consider treatment to promote weight loss. Unfortunately, there is no evidence that patients with a TSH of 5 to 10 will lose weight with treatment (8). The recent USPSTF review summarized the results of 6 studies that reported change in body mass index in RCTs of replacement therapy. Weight change ranged from an increase of 1 kg/m^2 in 32 patients treated for 1 year to a maximum loss of 1 kg/m^2.

Ms. C is understandably concerned, because several of her siblings are on thyroid medication. We know that a family history of thyroid disease is a risk factor, but we do not know the degree of thyroid dysfunction in the treated family members nor whether their treatment has been helpful. Patients are increasingly being treated for borderline hypothyroidism, and Ms. C's family members may fall in that category (8).

Question 2: What are the harms of treatment?

It is seemingly simple just to replace a physiologic hormone. Since most of us are doing targeted screening for symptoms, it is tempting to see if symptoms improve with treatment. What's the harm?

There are no other medicines where dosing is so finely tuned—with 12 doses, with gradations of 12 mcg between 75 and 125 mcg, the most common dose range. This is necessary because thyroid hormone has a narrow therapeutic range, analogous to warfarin (27). Furthermore, thyroid hormone has a half-life of 7 days, such that errors in dosing have a durable effect beyond that day. Poor adherence can increase TSH, prompting dose increases that could later trigger hyperthyroidism if adherence improves (28, 29).

Adherence to thyroid hormone therapy is not easy. Because food affects absorption, it should be taken an hour before breakfast. One randomized study with a crossover design compared the outcomes of dosing 30 minutes before breakfast on an empty stomach to immediately before bedtime in 90 patients. The TSH was 1.25 mIU/L lower with bedtime dosing, reflecting impaired absorption associated with breakfast 30 minutes after dosing (30). In 1 small study, coffee reduced thyroid hormone absorption when consumed within an hour of thyroid hormone dosing (31). Should we be asking people to change their morning habits to treat an abnormal test result that may not be meaningful?

Thyroid hormone places additional burdens on patient's time and finances, given the need to retest frequently. Because the therapeutic range is narrow and formulations can vary in potency by as much as 10%, it

is recommended that patients have TSH measured 6 weeks after any dose change, including a change in the drug's manufacturer (21). Since TSH measurement can cost $95 per test and free T_4 $146 per test (Horowitz G. Personal communication.), and given that high copays for testing are becoming increasingly common, this can result in substantial expense for both the patient and the health care system (32).

Over- and undertreatment with thyroid hormone replacement are common. In a community-based study of 339 patients older than 65 years on thyroid hormone replacement, 37.5% were overtreated and 16.4% were undertreated (33). The consequences of overtreatment can be serious, contributing to bone loss and resulting in atrial fibrillation. In a study analyzing 14 years of data in hypothyroid patients, 6-month periods of overtreatment were associated with an increased risk for hip and major osteoporotic fracture (34). In a 10-year population study of more than 2000 patients aged 60 years or older, a low TSH increased the risk for atrial fibrillation (35).

Finally, there is harm in medicalizing a normal condition. The upper range of TSH is arbitrarily set based on population data rather than a determination that those with a higher TSH are more likely to have symptoms or develop an associated comorbidity (8). Asking patients to return repeatedly for blood tests and to take a medication on a daily basis with particular constraints will likely make patients worry that they have a significant medical problem. One study concluded that knowledge of hypothyroidism is associated with a decreased quality of life in comparison with untreated hypothyroidism (36).

Question 3: Balancing the benefits and harms, when would you recommend treatment, in general and for Ms. C in particular?

So what does this mean for Ms. C? First, I would try to mitigate any decrease in quality of life associated with the knowledge that her TSH is abnormal. Second, while she could opt to be treated, she should understand that she has no risk for heart disease at her degree of thyroid dysfunction and that her goal of weight loss and symptom relief likely won't occur. If she were to embark on treatment, I would suggest monitoring her weight and symptoms. While many authorities would recommend treatment at a calculated full replacement dose, my experience suggests that this risks overtreatment, and I would recommend starting at 25 to 50 mcg. If her symptoms did not improve, I would suggest that she stop treatment and continue periodic testing of her TSH with reflex free T_4 testing. If free T_4 were to fall below normal or TSH were greater than 10, I would recommend treatment. If not treated, I would suggest periodic surveillance of TSH at otherwise-scheduled visits or if she had symptoms that could indicate that thyroid levels may have substantially changed.

SUMMARY

Ms. C and her primary care physician wonder whether she should be treated for subclinical hypothyroidism. Our experts disagree. Dr. Hartzband reasons that Ms. C's gradual increase in TSH levels over the years indicates that she truly has subclinical hypothyroidism and will progress to overt hypothyroidism over time. She believes that Ms. C would benefit from treatment given that she has hyperlipidemia and that treatment might enable her to stop taking atorvastatin and reduce her risk for cardiovascular morbidity and mortality. She agrees with Dr. Bates that symptom relief, our patient's primary goal, may not occur. Finally, she does not think that there is an evidence base for harm in treatment using low-dose levothyroxine with careful monitoring and suggests that providers not be afraid to initiate therapy for fear of overtreatment. She would leave the final decision to Ms. C but would offer a trial of low-dose levothyroxine and would cease treatment if Ms. C obtained no benefit.

In contrast, Dr. Bates believes that Ms. C is unlikely to obtain symptomatic benefit from treatment with thyroid replacement. Furthermore, she found no data suggesting that thyroid replacement confers additional benefit in a patient already receiving a statin. Lastly, Dr. Bates' review of the data suggests that Ms. C is not at increased risk for a cardiac event or death based on her very mildly increased TSH levels.

In addition, Dr. Bates has serious concerns about potential harms of treatment, including the risk for overtreatment leading to atrial fibrillation and osteoporosis, inherent dosing challenges, and the burden and cost of care. She is particularly concerned about the harm of medicalizing a condition that may not require treatment, especially when even knowledge of hypothyroidism is associated with decreased quality of life. Given her assessment of a lack of benefit and potential for harm, Dr. Bates would not recommend treatment. However, if Ms. C wanted to proceed with treatment, Dr. Bates concurs with Dr. Hartzband that it should start with low-dose levothyroxine to avoid overtreatment and to monitor for improvement. Both discussants agree that this option can be challenging because even when a treatment trial provides no clear benefit, some patients may be reluctant to stop it.

Both discussants also agree that research needs and gaps are significant and need to be addressed. These include determining the effect of treatment of subclinical thyroid dysfunction on cardiac outcomes, evaluating the harms of screening and treatment for thyroid dysfunction, clarifying the criteria for defining abnormal thyroid function, and identifying a biologic effect whose measurement would identify the persons most likely to benefit. While we await further data, both our discussants concur with shared decision-making so that Ms. C makes a fully informed decision.

A transcript of the audience question-and-answer period is available in the **Appendix** (available at www.annals.org). To view the entire **conference video**,

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including the question-and-answer session, go to www.annals.org.

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Appendix: Questions and Comments

Dr. Smetana: So, Dr. Hartzband, I was struck by data that Carol presented on the frequency of potential hypothyroid symptoms in the general population. My guess is actually if we surveyed our audience, that even more than 15% of us would endorse fatigue. And I wondered, does that sort of make the whole issue of aggressive case-finding flawed—if identifying patients who would benefit from testing and treatment based on symptoms might capture patients with symptoms no more often than in euthyroid patients?

Dr. Hartzband: Well, I think it's certainly true that fatigue, constipation, and weight gain are very common symptoms that one sees in clinical practice. In fact, I can't remember the last patient who came in to see me who didn't have at least one of those symptoms. On the other hand, having multiple symptoms and recent-onset symptoms does seem to have some predictive value. So I think you need to take the entire picture in hand when you're thinking about this and not pursue mild symptoms if they don't seem important. Somebody who's had fatigue for 10 years, maybe not.

Dr. Smetana: And Carol, one follow-up question for you. The data regarding a potential reduction in cardiovascular events in treatment in younger individuals, does that change your view at all in terms of screening and treating younger patients?

Dr. Bates: It has not changed my view. I should acknowledge that I do engage in aggressive case-finding, but then I struggle with the realities of what to do. I have treated many patients with subclinical hypothyroidism, but moving forward I think I will treat fewer of them. I wouldn't screen patients who are younger simply for this reason. Since the prevalence of hypothyroidism increases with age, we're going to be targeting those patients who are less likely to benefit.

Dr. Smetana: Let's move on to the audience's questions. We have about 10 minutes. Raise your hand if you'd like to ask a question, Risa and I will come around with the microphones. Please introduce yourself first. Dr. Zeidel?

Dr. Mark Zeidel: Mark Zeidel, chair of the Department. One of the problems here seems to be that we have hormonal levels and then we have biological effect. We really don't have a decent measure of the biological effect, which I think Dr. Hartzband was mentioning. There are different set points, and different people may achieve biological effect at different hormone levels. Is there anything on the horizon that will allow us to identify who is achieving appropriate biological effect with thyroid hormone, and who might not be? Because if we could stratify patients that way, I suspect we would find benefit. We would find the patients who would benefit from therapy and separate those from the ones who don't, and that would clarify a lot of what these studies are about. So is there anything on the horizon? I guess I'm asking Pam, as the person who does thyroid disease.

Dr. Hartzband: It's a very good question, and one of the interesting things that has been recently found is that there are polymorphisms in the deiodinase genes that may account for differences in clinical symptoms; this is an active area of clinical research.

Dr. James Hennessey: I am Jim Hennessy; you saw one of my publications there. Thank you very much for using it. I just wanted to give some background. We wrote that piece not to treat an individual patient, and I certainly appreciate that and I shared that earlier, but rather to point out the difficulties in trying to interpret the USPSTF conclusion. The conclusion seemed to be saying to us, and to many of you, "Thyroid function testing? Don't bother." In other words, don't get this ball rolling in the first place. Our major objections were many of the things that you pointed out. The evidence is poor, and a lot of the problem with the poor evidence was that the USPSTF would rate a study as being fair or good, but when we read the study we thought it was terrible because of defects in the methods. When you conclude that there is no impact of treatment based upon a defective study design—wait a minute! Does that really mean that there is no impact of treatment? The other major problem with this, and especially in the cardiovascular realm, is the interesting finding that younger patients actually seem to respond to treatment versus older patients, and that the cutoff point for TSH in the majority of studies is too low. Because, as we would like to put forward here, we should use an age-adjusted TSH. So an 85-year-old with a TSH of 7 is probably normal and not subclinically hypothyroid, versus a 30-year-old with a TSH of 4 is probably abnormal. So that's one point to be made, but most of the cardiovascular studies included either a single TSH or a confirmed TSH greater than 3.5, or 4 or 5. So many of the patients who were included and didn't show any improvement didn't have thyroid disease. It's difficult to show an effect of thyroid hormone when you don't have thyroid disease. I have a whole list here of things that I agree with Dr. Bates on, and I certainly really appreciated Dr. Hartzband's discussion. Dr. Smetana, when we think about it, does this undercut aggressive case-finding? No. I think it makes the point for aggressive case-finding. Because when patients have these multiple symptoms, we are not going to offer them thyroid hormone as we might have 30 or 40 years ago, just based on those symptoms, because we're going to rule out thyroid disease. And as I pointed out to Dr. Burns,

then it's up to the general internist to find out really what is going on.

Dr. Bates: We didn't talk about the age-adjusted TSH range, but just as a caution, our lab reports a single normal range and doesn't factor in an age-adjusted range. So be cautious in older patients with mild TSH elevations.

Dr. Jacqueline Wolf: A lot of patients have constipation, depression, and also everything else that you have up there. So they come into my office saying, "I'm sure I'm hypothyroid," with weight gain and constipation. They would rather know whether they are hypothyroid than adjust their diet, exercise, and do the things that we all know are much more difficult than taking thyroid medication. So given that, what would you say to people who you are pretty sure don't have thyroid disease but absolutely want to be tested? Generally, I think that knowing for sure that they do or don't have hypothyroidism helps them have a better quality of life. What would you say to testing all of those people, which increases your cost?

Dr. Hartzband: Well, I think, as Dr. Hennessey said, most of those people are going to have a normal TSH level, so it can be helpful. You test, you say, "This could be hypothyroidism, but it isn't." But then if the TSH is elevated, you have to consider whether treatment is appropriate.

Dr. Bates: I would agree. I think it's really hard not to test a patient in that scenario. I think they are potentially less motivated to make the changes that you would want them to make because they may be so completely focused on the possibility that they are hypothyroid.

Dr. Wolf: And I will also make the comment that a number of my patients vary their thyroid medicines to try to get diarrhea and lose weight. Could you comment on that?

Dr. Hartzband: I actually don't think I've seen that. I think that patients who take thyroid hormone are in general very compliant with their medication because they are afraid that they'll gain weight if they don't take it, or they just won't feel well, but to deliberately induce diarrhea to lose weight—I haven't seen it.

Dr. Bates: I have one patient who thought more of a good thing is a better thing and wasn't intentionally trying to lose weight. She just assumed that more was better. I will say that, in my own practice, the amount of variability in patients remaining in the therapeutic range is horrible, and may relate to inadequate histories on my part in ascertaining how adherent they are with their medication in the weeks prior. I do very carefully try to sort that out whenever I get a high TSH that's outside of the target range before boosting the dose. Some of the variations may relate to poor absorption, but because the notion of delaying breakfast and coffee for an hour is so abhorrent to me, I have a hard time suggesting that my patients do that.

Dr. Thomas Delbanco: One of the pearls that I grew up with from my thyroid gurus is that it's very nice to be hypothyroid, because you may live longer, and you should wait until someone is really myxedematous, and then treat them and then they'll have a new lease on life. Any sense to that?

Dr. Hartzband: Well, there are data on elderly patients who are mildly hypothyroid, and there does appear to be an increase in longevity. If you look at TSH levels in patients who are in their 90s (I had a nice slide of that, but no time to include it), you can see an extension of the normal range—a sort of a peak on the high side with TSH levels that are quite high. So thinking about treating elderly patients is a whole different topic that we didn't address today. High TSHs may not only be normal, but be good in that population. But for a 30- or 40- or even a 60-year-old, like our patient, I would say no—that it would better to be treated if you're hypothyroid.

Dr. Bates: I would just add that perhaps one of the most satisfying things that one does as an internist is to uncover overt severe hypothyroidism and treat it. I've had many satisfying encounters but many less-satisfying encounters in treating subclinical hypothyroidism.

Dr. Jerome Groopman: I was curious in terms of the evidence base for harm, distinguishing between the elderly and this patient, who's 60. Most of the data seemed related to hip fracture, osteoporosis, and atrial arrhythmias that were weighted with regard to the elderly, as opposed to her. Are there data on harms in her age group?

Dr. Bates: I don't know that there are clear data on overreplacement in this age group. I think anecdotally we have all seen it, but I don't know that there are good data.

Dr. Jeffrey Garber: Thank you both for those illuminating talks. Jim and I spent years on developing the guideline that you quoted, and the response was a little short-term. But what's interesting is that this is called "Beyond the Guidelines" and appropriately so, because there isn't a single guideline out there that discusses a brief clinical trial of a low-dose of levothyroxine, and both of you came to the same conclusions. Just 2 other editorial comments. One of the other reasons to do a clinical trial is that this patient, who became the sole caretaker of her husband, may have many other problems. And if you don't clear the air that it's not her thyroid, it's hard to drill down as a clinician or at least let the patient open up about the other things that may be going on. And lastly, you had cited the hormone replacement trial and that they might be parallel here. Not only don't we have a good RCT to address this, but it may well be that the discrepancy between treating

the younger and the older is that it's too late when they are older. If you let the subclinical hypothyroidism go untreated for decades, an insidious incipient progressive coronary disease may develop so that by the time you're in your 70s, it's too late–just like starting hormone replacement therapy in the mid-60s doesn't work.

Dr. Bates: I think it would be great if somebody did an RCT in this population, a larger RCT than the small studies that are being published to date.

Dr. Hartzband: I agree.

Dr. Leo Stolbeck: I was wondering, in terms of the variation in the TSH that you found in the morning versus the afternoon, what do you use as your criteria for someone you are treating, who you are reasonably certain is hypothyroid, in terms of changing the dose? I've seen the situation of patients being bounced up and down because there is a change of 1 in the TSH level. What are your criteria?

Dr. Hartzband: Personally, unless the TSH is way off, I usually make patients repeat the level in a month or two to look for the trend because TSH levels can vary up or down by several points on repeated determinations. That's my personal practice.

Dr. Bates: It's my practice as well. The conundrum is that this patient has a TSH of 6.5, which we might not necessarily act upon if we had a patient with overt hypothyroidism who had a TSH rise. So here we are considering treating somebody for a TSH that we might just watch in somebody who really absolutely needed thyroid hormone replacement therapy. It's really hard to look at numbers that are abnormal and not act on them. It's hard to have that conversation with patients, and it engenders worry. It's hard to sit on it, but that's probably the right thing to do. I certainly have had patients who have become over-replaced because I overreacted to a TSH value.

Dr. Hartzband: And I would add to that, that if we had somebody who had overt hypothyroidism with a TSH of 60 or 80, we wouldn't recommend treating them down to 9 or 8 or 6 and just leaving them there. That's the other side of the argument.

Dr. Eileen Reynolds: Thanks very much for your comments today; I think the number of questions and the discussion show how challenging patients like this can be. A number of audience questions and both of your comments suggest that a short-term trial of medication might be in order. But I would just like to reflect that getting a patient off levothyroxine is actually–I think–harder than getting them off a proton-pump inhibitor. I wonder if you can reflect on how successful either of you have been at convincing a patient to stop taking levothyroxine once they have been on it, because they become pretty committed to believing that they should take it.

Dr. Hartzband: That's a good point. I have had several patients where I didn't have very good documentation that they actually had hypothyroidism and they had been on therapy for 20 years. I have suggested to those who are what I would call medical minimalists, who don't really like to take medications, to come off it. And I've had a number of them agree. One woman very patiently waited the month to come in and get her TSH, and when I got the result back it was 60. So she really did have hypothyroidism. On the other hand, I think you are right–there are people who believe that every symptom is related to their thyroid, and they have minor variations in their TSH that they feel are incredibly significant. So definitely, I have had that experience, too.

Dr. Bates: I've had patients who, at the end of the day, haven't felt any different and have acknowledged it. In these patients, it's easy to stop the levothyroxine. I've also had patients who are convinced that very mild TSH abnormalities are causing severe symptoms, although I have some skepticism.