

The Starting Dose of Levothyroxine in Primary Hypothyroidism Treatment

A Prospective, Randomized, Double-blind Trial

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Background: The treatment of hypothyroidism with levothyroxine is effective and simple; however, recommendations for the starting dose vary considerably. To our knowledge, the levothyroxine starting dose has never been studied prospectively.

Methods: We conducted a prospective, randomized, double-blind trial that compared a full starting levothyroxine dose of 1.6 µg/kg with a low starting dose of 25 µg (increased every 4 weeks) in patients with newly diagnosed cardiac asymptomatic hypothyroidism. Safety was studied by documenting cardiac symptoms and events, and efficacy was studied by monitoring thyrotropin and free thyroxine levels and by assessing improvement of signs and symptoms and quality of life.

Results: Seventy-five consecutive patients were enrolled, of whom 50 underwent randomization. At baseline, the severity of hypothyroidism and age were com-

parable in the full-dose (n=25) vs the low-dose group (n=25): thyrotropin, 61 vs 48 mIU/L; free thyroxine, 0.56 vs 0.64 ng/dL (7.2 vs 8.2 pmol/L); and age, 47 vs 47 years. No cardiac complaints or events were documented during treatment or at bicycle ergometry at baseline, 12 weeks, or 24 weeks. Euthyroidism was reached in the full-dose vs the low-dose group in 13 vs 1 (4 weeks), 19 vs 3 (8 weeks), 19 vs 9 (12 weeks), 20 vs 14 (16 weeks), 20 vs 18 (20 weeks), and 21 vs 20 (24 weeks) patients ($P=.005$). However, signs and symptoms of hypothyroidism and quality of life improved at a comparable rate.

Conclusion: A full starting dose of levothyroxine in cardiac asymptomatic patients with primary hypothyroidism is safe and may be more convenient and cost-effective than a low starting dose regimen.

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P RIMARY HYPOTHYROIDISM IS A common disorder, most prevalent in women and most often caused by autoimmune thyroiditis. Overt hypothyroidism can present with classic symptoms of fatigue, weight gain, cold intolerance, and constipation. Fatigue, one of the major complaints, together with depression,¹ neuromuscular signs and symptoms,² and diastolic dysfunction³ can all lead

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to an impaired quality of life in patients with hypothyroidism. Furthermore, abnormalities of lipid metabolism, hyperhomocysteinemia, and arterial hypertension occur with increased frequency in hypothyroidism^{4,5} and are associated with an increased risk of premature atherosclerotic vascular disease.^{6,7}

Although the treatment of hypothyroidism with levothyroxine, one of the

most commonly prescribed drugs, seems effective and simple, recommendations for the starting dose of levothyroxine vary considerably: from 50 µg to a full replacement dose of 1.6 or 1.7 µg/kg in healthy adult patients younger than 65 years and from 25 to 50 µg/d in older patients and patients with known ischemic heart disease.⁸⁻¹³ The safety and efficacy of different initial doses of levothyroxine have, to our knowledge, never been studied prospectively. Moreover, in daily practice, many physicians still promote the dogma of "start low and go slow" irrespective of age or patient. This dogma is based on the association of hypothyroidism with ischemic heart disease.^{14,15} Interestingly, and in contradiction to this dogma, high doses of levothyroxine have been given to patients with myxedema coma, a patient group in whom a high prevalence of cardiac ischemia would be expected, without untoward effects.¹⁶ However, when levothyroxine was combined with triiodothyronine (T_3) in the treatment of such

severely ill patients, fatal outcome has been reported.⁹ Several case series and retrospective studies, dating back 4 to 6 decades, have shown considerable variability in the cardiac responses of patients with hypothyroidism to thyroid hormone therapy, ranging from precipitating acute coronary syndromes in patients without previous cardiac symptoms^{14,17} to controlling or even abolishing preexisting angina.^{17,18} These studies can be criticized for being retrospective, cross-sectional, or uncontrolled; for having small numbers of patients; or for using desiccated thyroid preparations that contain differing and therefore unpredictable amounts of both levothyroxine and T₃. Levothyroxine is converted into T₃ by type 1 deiodinase in the liver.¹⁹ The evidence for local deiodination of total thyroxine (T₄) in the human heart by type 2 deiodinase^{20,21} and the increased expression of type 2 deiodinase in the mouse heart during hypothyroidism²² could indicate mechanisms of adaptation in case of low or high serum levels of T₄.

Most reviews report a period of 4 to 6 months before normalization of plasma thyrotropin and free thyroxine (FT₄) levels is attained.⁸⁻¹² A more rapid normalization could be of great benefit to patients with hypothyroidism regarding the reduction of cardiac risk factors, improvement of quality of life, and being less cumbersome for regular visits to the clinics. However, the efficacy and safety of different initial doses of levothyroxine have surprisingly never been studied prospectively in patients with primary hypothyroidism. This prompted us to compare a full initiating treatment dose of levothyroxine (1.6 µg/kg)²³ with the classic approach of "start low and go slow" in a prospective, randomized, double-blind study. The aim of the study was to prove that restoration of plasma thyrotropin and FT₄ levels within the normal reference range can be performed with a straightforward high-dose regimen without any increased risk of major adverse cardiac events.

METHODS

STUDY PARTICIPANTS

All patients with hypothyroidism who presented to our hospital between September 1999 and August 2002 were screened for inclusion. Of these patients, only those with first diagnosed, untreated primary autoimmune hypothyroidism (serum thyrotropin level >4.2 mIU/L and FT₄ level <0.78 ng/dL [<10 pmol/L]) were included. Patients with a history of cardiac disease or those taking cardiac medication, such as β -blockers, were excluded. Informed consent was obtained from each patient.

TREATMENT

Patients were randomly assigned to either a high starting levothyroxine dose of 1.6 µg/kg or a low dose of 25 µg. Randomization was stratified according to serum thyrotropin level below or above 50 mIU/L. During treatment, the levothyroxine dosage of each patient was initially adjusted with increments of 25 µg every 4 weeks and from 24 weeks onward every 12 weeks according to serum thyrotropin and FT₄ levels, with serum thyrotropin and FT₄ levels within the normal reference range (euthyroidism) as a target of treatment. The medication was prepared in liquid form²⁴ in 8 different strengths (25-200 µg/mL)

to have a constant volume of medication for each patient at every moment. The liquid formulation of levothyroxine was stable; the quality after 1 year was unchanged. Two-milliliter syringes were supplied to the patients, and the dose in 1 mL ranged from 25 to 200 µg of levothyroxine. Each patient took a volume of 1 mL/d. Levothyroxine medication was taken at bedtime, and no other medication was taken at the same time. The study protocol was approved by the local ethical committee.

ASSAYS

Serum thyrotropin levels (reference range, 0.4-4.2 mIU/L), T₃ levels (reference range, 84.42-162.34 ng/dL [1.3-2.5 nmol/L]), and FT₄ levels (reference range, 0.78-1.79 ng/dL [10-23 pmol/L]) were determined by a chemiluminescent enzyme immunoassay (ACS 180; Bayer Diagnostics, Tarrytown, NY). Total cholesterol (reference range, 96.7-251.3 mg/dL [2.5-6.5 mmol/L]), cholesterol subfractions (high-density lipoprotein cholesterol; reference range, 38.7-69.6 mg/dL [1.0-1.8 mmol/L]; low-density lipoprotein cholesterol; reference range, 58.0-174.0 mg/dL [1.5-4.5 mmol/L]; and triglycerides; reference range, 0.0-177.2 mg/dL [0.0-2.0 mmol/L]), creatine phosphokinase (reference range, 11-200 U/L), and creatinine (reference range, 0.45-0.90 mg/dL [40-80 µmol/L] in women and 0.51-1.02 mg/dL [45-90 µmol/L] in men) were measured with a Hitachi 911 analyzer (Tokyo, Japan). Homocysteine (reference range, <2.03 mg/L [<15 µmol/L]) was measured by high-performance liquid chromatography.

CLINICAL SCORE AND QUESTIONNAIRES

A clinical score of hypothyroidism²⁵ was completed on each visit (every 4 weeks during the first 24 weeks of treatment and every 12 weeks thereafter) by a blinded physician (A.B.). The 12 symptoms and signs included dry skin, hoarseness, paresthesia, diminished sweating, constipation, impaired hearing, weight gain, delayed ankle reflex, cold skin, slow movements, periorbital puffiness, and coarse skin. The symptoms and signs were quantified as 1 point, meaning present, or 0 points, meaning absent. Two questionnaires were obtained at 0, 12, 24, and 48 weeks. This interval of 12 weeks was chosen to minimize recall bias. The first questionnaire assessed 10 symptoms of hypothyroidism: lack of energy, dry skin, constipation, aches and pains, cold intolerance, poor memory, depression, weight gain, tiredness after waking up, and feeling down.²⁶ Patients scored these symptoms as 1, indicating not present; 2, hardly present; 3, present; or 4, severely present. The second questionnaire was a general quality-of-life questionnaire (the RAND 36-Item Health Survey questionnaire²⁷) that concerned 8 scales: physical functioning, social functioning, role limitations (physical problems), role limitations (emotional problems), mental health, vitality, pain, and general health perception. Scores per scale ranged from 0 to 100, the highest score indicating the best state of health.

CARDIAC ASSESSMENTS

At every visit, body weight and continuous pulse rate and blood pressure in the resting state were measured by a research nurse, and an electrocardiogram (ECG) was acquired. All 12-lead ECGs were analyzed by 1 cardiologist and scored according to previously published criteria.²⁸

At baseline, dobutamine stress echocardiography was performed as previously described^{29,30} and analyzed by 2 experienced independent and blinded cardiologists. Myocardial ischemia was defined as the development of new or worsening of preexisting wall motion abnormalities in at least 2 segments of the left ventricle.

Table 1. Baseline Characteristics of the Included and Excluded Patients

Characteristic	Included Full-Dose Group	Included Low-Dose Group	P Value (Full vs Low)	Excluded	P Value (Included vs Excluded)
Patients, No. (F/M)	25 (17/8)	25 (22/3)		25 (21/4)	
Age, mean \pm SD (range), y	47 \pm 18 (25-86)	47 \pm 16 (22-74)	.8	62 \pm 20 (21-92)	<.001
BMI, mean \pm SD	29 \pm 6	28 \pm 4	.6	29 \pm 6	.8
Heart rate, mean \pm SD, beats/min	67 \pm 11	66 \pm 11	.9	70 \pm 11	.7
Systolic blood pressure, mean \pm SD, mm Hg	133 \pm 18	127 \pm 15	.4	142 \pm 40	.4
Diastolic blood pressure, mean \pm SD, mm Hg	83 \pm 10	78 \pm 13	.3	81 \pm 19	.3
Thyrotropin, median (range), mIU/L	61 (14-797)	48 (11-262)	.2	43 (16-289)	.03
FT ₄ , mean \pm SD, ng/dL	0.56 \pm 0.25	0.64 \pm 0.19	.2	0.57 \pm 0.19	.3
T ₃ , mean \pm SD, ng/dL	97.4 \pm 39.0	116.9 \pm 39.0	.1	97.4 \pm 39.0	.4
Total cholesterol, mean \pm SD, mg/dL	228.2 \pm 58.0	220.4 \pm 65.7	.7	235.9 \pm 61.9	.6
HDL-C, mean \pm SD, mg/dL	54.1 \pm 15.5	54.1 \pm 11.6	.9	58.0 \pm 11.6	.9
LDL-C, mean \pm SD, mg/dL	150.8 \pm 50.3	139.2 \pm 61.9	.4	143.1 \pm 50.3	.7
Triglycerides, mean \pm SD, mg/dL	124.0 \pm 79.7	141.7 \pm 79.7	.5	159.5 \pm 79.7	.5
Creatine kinase, median \pm SD, U/L	153	115	.1	113	.9
Creatinine, mean \pm SD, mg/dL	0.95 \pm 0.25	0.97 \pm 0.26	.6	1.04 \pm 0.33	.6
Homocysteine, mean \pm SD, mg/L	1.45 \pm 0.69	1.46 \pm 0.66	.7	NA	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); FT₄, free thyroxine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not available; T₃, total triiodothyronine.

SI conversion factors: To convert FT₄ to picomoles per liter, multiply by 12.87; T₃ to nanomoles per liter, multiply by 0.0154; cholesterol components to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; creatinine to micromoles per liter, multiply by 88.4; homocysteine to micromoles per liter, multiply by 7.397.

A bicycle ergometer (Lode, Groningen, the Netherlands) was used for the bicycle ergometry, which was performed as previously described.³⁰ During exercise, continuous ECG monitoring was performed. Ischemia was defined as an ST depression of 0.1 mV or more, according to the criteria described by Roelandt et al.³¹ Bicycle ergometry was also used to assess exercise tolerance. Therefore, at the start of ergometry, a target performance was assessed for each patient, depending on height, age, and sex, according to general accepted criteria. Exercise tolerance was determined by dividing the maximum achieved workload per patient by his or her target performance. An exercise performance of less than 80% was considered insufficient. Bicycle ergometry was performed at baseline and repeated at 12 and 24 weeks.

STATISTICAL ANALYSIS

All analyses were performed according to the intention-to-treat approach, although no crossovers occurred after randomization. Data are expressed as mean \pm SD. Statistical comparisons (differences between full and low starting dose groups) were performed by means of a 2-group unpaired Wilcoxon rank sum test. An unpaired Kruskal-Wallis analysis of variance with repeated measures was performed to detect differences over time. $P < .05$ was considered statistically significant.

RESULTS

STUDY POPULATION

Seventy-five consecutive patients with primary hypothyroidism were screened for inclusion, of whom 50 underwent randomization, 25 patients to the high-dose group (thyrotropin < 50 mIU/L: $n = 11$; thyrotropin > 50 mIU/L: $n = 14$) and 25 patients to the low-dose group (thyrotropin < 50 mIU/L: $n = 14$; thyrotropin > 50 mIU/L: $n = 11$). Twenty-five patients were excluded because of a history of cardiac disease (myocardial infarction: $n = 4$; angina pec-

toris: $n = 5$), medication for long-standing hypertension ($n = 5$), unwillingness to participate in the study ($n = 6$), hypothyroidism due to postpartum thyroiditis ($n = 2$), pregnancy ($n = 1$), myxedema (pre)coma ($n = 1$), or unwillingness to follow the study protocol ($n = 1$).

Baseline characteristics of the included and excluded patients are given in **Table 1**. None of the patients had minimal hypothyroidism with a thyrotropin level less than 10 mIU/L. The echocardiogram at rest showed normal wall motions in all patients. None of the patients had silent ischemia. During both dobutamine stress testing and exercise testing, none of the patients complained of angina pectoris. Dobutamine stress echocardiography did not demonstrate wall motion abnormalities signifying myocardial ischemia.

LEVOTHYROXINE DOSAGE

The levothyroxine dose in the full-dose group was increased slightly from a mean of 128 μg (1.6 $\mu\text{g/kg}$) at baseline to a mean of 139 μg (1.7 $\mu\text{g/kg}$) at 48 weeks; in the low-dose group, the dose was increased until 16 weeks of treatment, after which it remained unchanged, with a mean of 110 μg (1.5 $\mu\text{g/kg}$) (**Figure 1**; full-dose vs low-dose group; $P = .04$).

OUTCOMES

Laboratory Parameters

At 4 weeks, median serum thyrotropin level had normalized in the full-dose group (high-dose vs low-dose group: 4.2 vs 26.7 mIU/L; $P = .005$), whereas in the low-dose group, the median thyrotropin level normalized only at 16 weeks. A similar significant difference between the full-dose and low-dose groups with regard to the nor-

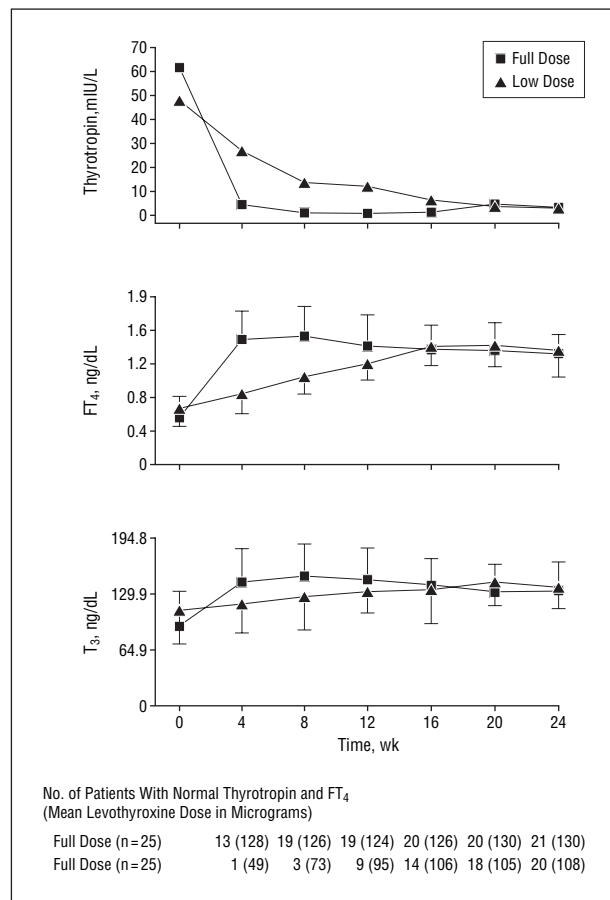


Figure 1. Thyroid parameters (median thyrotropin, mean free thyroxine [FT₄], and mean total triiodothyronine [T₃]) during treatment. Error bars indicate SD. $P < .01$ for the full-dose group vs low-dose group. To convert FT₄ to picomoles per liter, multiply by 12.87; T₃ to millimoles per liter, multiply by 0.0154.

malization of the mean FT₄ and T₃ plasma levels was observed (Figure 1).

Initially, total and low-density lipoprotein cholesterol levels decreased over time with no appreciable difference between the 2 groups; thereafter, no change occurred (**Figure 2**). Serum high-density lipoprotein cholesterol and triglyceride levels did not change over time. Serum homocysteine levels decreased in the full-dose group from 1.45 to 1.16 mg/L (10.7-8.6 μ mol/L) and in the low-dose group from 1.46-1.37 mg/L (10.8-10.1 μ mol/L) ($P = .2$). Median serum creatine kinase levels showed no significant change.

Clinical Score, Questionnaires, and Anthropometric Parameters

The clinical score and the symptoms of hypothyroidism decreased until 24 weeks of treatment at a comparable rate in both groups (**Figure 3**). The quality of life improved on all 8 scales for both groups (**Table 2**), with no significant difference between the full-dose and the low-dose groups. At baseline, the 2 groups differed for the role limits due to physical functioning. We performed a subgroup analysis concerning the responses in patients with a serum thyrotropin level greater than 50

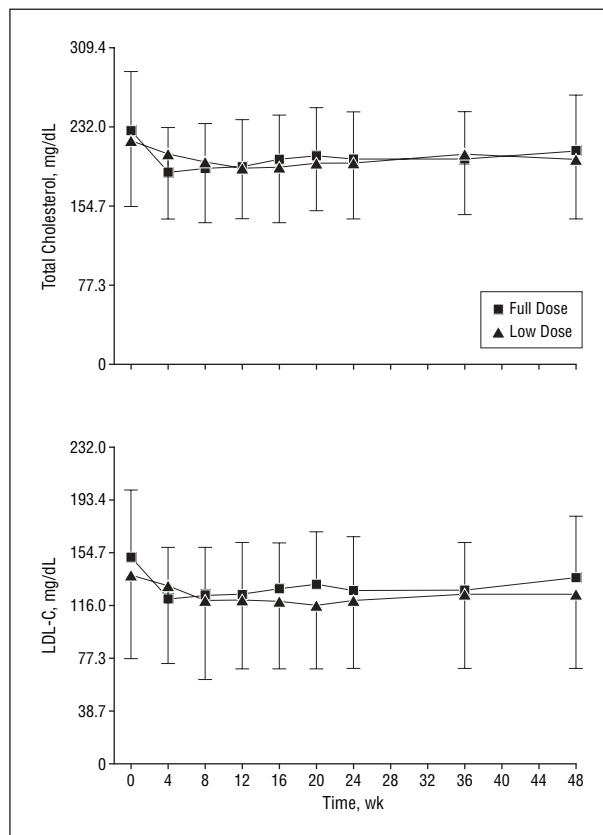


Figure 2. Mean total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels for the full-dose and low-dose groups during treatment. $P = .8$ and $P = .6$ for total cholesterol and LDL-C, respectively, for the full-dose group vs low-dose group. To convert total cholesterol and LDL-C to millimoles per liter, multiply by 0.0259.

mIU/L and in those with a serum thyrotropin level less than 50 mIU/L, but no difference in outcome was found. Body weight, heart rate, and blood pressure did not change in either group during treatment.

SAFETY

No palpitations, angina pectoris, or other cardiac events were documented in any of the patients during treatment. No interim dose adjustments because of adverse effects were necessary, and in none of the patients did we have to interrupt the study protocol. None of the patients had anginal complaints during bicycle ergometry at 12 and 24 weeks, and continuous ECG monitoring did not demonstrate ischemia or serious arrhythmias.

At baseline, sinus bradycardia was observed in 43% of patients in the full-dose group and 7% in the low-dose group. At 8 weeks, sinus bradycardia was observed in 17% and 25% of patients in the full-dose and low-dose groups, respectively. Prolongation of the QT interval corrected for heart rate (QTc > 0.43 milliseconds) was observed in 10% of patients in both groups at baseline. At 8 weeks, prolonged QTc interval was observed in 4% of patients in the full-dose group and 13% of patients in the low-dose group. Exercise performance improved in the full-dose group from 92% to 102% ($P < .001$) and remained unaltered in the low-dose group.

Since we did not observe any cardiac adverse events, we believe that it is safe to treat patients with hypothyroidism with a full replacement dose of levothyroxine (1.6 $\mu\text{g}/\text{kg}$) if they have no history of ischemic heart disease. Such a treatment strategy is more practical and convenient for the patients and will make outpatient control more cost-effective.

We excluded patients with a cardiac history from this study. Therefore, the findings of our study are possibly not applicable to patients with coronary artery disease. The patients who were excluded from our study were

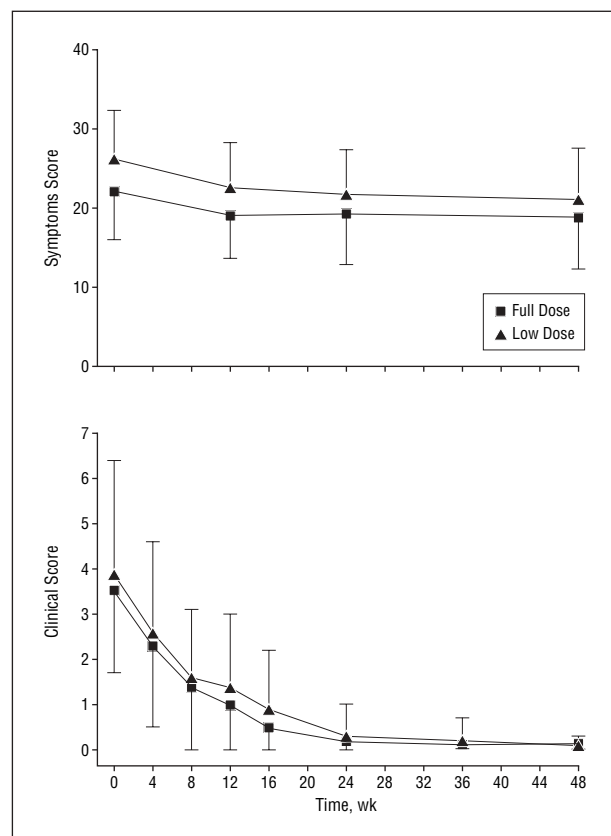


Figure 3. Mean symptoms and clinical scores for full-dose and low-dose groups during treatment. $P = .4$ and $P = .8$ for the symptoms score and clinical score, respectively, for the full-dose vs low-dose group.

older; hence, the mean age of included patients was relatively young. However, the included patients represented a wide age spectrum (range, 22-86 years; median age, 46 years). None of the included patients had asymptomatic cardiac ischemia demonstrated by dobutamine stress echocardiography or bicycle ergometry.³⁰ The prevalence of asymptomatic or silent coronary artery disease in patients with untreated primary hypothyroidism is unknown, but our findings suggest that it might be very low. Although bicycle ergometry may have limited sensitivity and specificity for detection of coronary artery disease (55%-70% and 85%-95%, respectively³²), with lowest sensitivity in young women, we also performed dobutamine stress echocardiography in our patients, which is the most specific noninvasive test for assessing coronary artery disease, with a sensitivity and specificity of 80% and 84%, respectively.²⁹

Our results show that when levothyroxine was given in a full replacement dose of 1.6 $\mu\text{g}/\text{kg}$, it took approximately 4 weeks for serum thyrotropin and FT_4 levels to normalize. This is more rapid than stated in most reports.⁸⁻¹² On the other hand, Spencer et al³³ showed that when levothyroxine was given in a single high dose of 2 mg intravenously, thyrotropin levels declined toward normal within 5 days. Several explanations exist for the observed buildup of a steady state in our patients. First, only approximately 75% of oral levothyroxine is absorbed.³⁴ Second, in patients with hypothyroidism, serum T_3 is derived from T_4 by deiodination; therefore, serum T_4 levels have to be higher than in patients without thyroid disease.²³ Third, the half-life of serum levothyroxine in patients with hypothyroidism is approximately 10 days; therefore, it takes approximately 5 to 6 weeks to reach steady-state T_4 levels.¹² At the end of the study, serum thyrotropin levels had not normalized in all patients. Inadequate treatment has been found to occur in a substantial percentage of patients treated for hypothyroidism.³⁵ The explanation in our patients could be suboptimal compliance and varying intestinal absorption of levothyroxine. The small but significant difference in final levothyroxine dose between the 2 groups is unexplained. A difference between the 2 randomized groups in compliance or intestinal absorption of levothyroxine seems improbable.

In the reviews on treatment of hypothyroidism, most authors state that the period of normalization of the clini-

Table 2. Quality-of-Life Scores During Treatment in 8 Categories From the RAND 36-Item Health Survey Questionnaires*

Score	Full-Dose Group by Week				Low-Dose Group by Week				P Value (Full vs Low Dose)
	0	12	24	48	0	12	24	48	
Physical functioning	63	73	73	72	63	66	68	69	.5
Role limits due to physical functioning	54	67	68	69	21	40	54	60	.03
Social functioning	62	69	75	79	52	63	71	67	.2
Emotional well-being	42	51	57	51	38	44	47	50	.3
Role limits due to emotional well-being	60	67	65	71	45	64	71	62	.7
Pain	58	73	71	69	63	67	61	64	.5
Energy	56	68	66	60	56	61	60	61	.7
General health	45	52	55	51	46	47	53	50	.6

*Scores ranged from 0 to 100.

cal scores, symptoms, and quality of life is approximately 3 to 6 months.^{9,36} However, the effects of treatment of hypothyroidism on quality of life have been systematically studied only in patients with subclinical hypothyroidism.³⁷ These studies showed conflicting results and included patients with a variety of causes of hypothyroidism, and methods were not always clearly described. For these reasons, these studies could not be compared with the results of our study. The absence of a more rapid normalization of the clinical scores, symptoms, and quality of life in the high starting dose group is not well understood. It might be that plasma T₄ levels do not correspond to tissue T₄ levels, as has been shown in rat models,³⁸ and that most tissues need a longer time for recovery from long-lasting hypothyroidism. Alternatively, the fact that we did not observe a difference in the rate of improvement in the 2 groups could be explained by adaptations of the metabolism of thyroid hormones in states of hypothyroidism. The local production of T₃ from T₄ by type 2 iodothyronine deiodinase, particularly in the brain, is increased during hypothyroidism, whereas the degradation of T₃ by type 3 iodothyronine deiodinase is reduced, thus prolonging the residence time of T₃.³⁹ However, we might also have missed a more rapid normalization because the questionnaires were not repeated until 12 weeks of therapy.

Our study supports the recommendation of a full replacement starting dose of levothyroxine of 1.6 µg/kg in healthy adult patients younger than 65 years.⁹ Moreover, our study also provides evidence that it is safe to treat patients older than 65 years with hypothyroidism with a full replacement dose of levothyroxine if they have no history of ischemic heart disease. We believe that by adopting such a policy, the need for frequent biochemical and clinical monitoring implicit in the "start low and go slow" alternative is obviated. It will further enhance compliance and make outpatient control more cost-effective and convenient for the patients. Our study results apply only to patients without suspected silent ischemia. Therefore, it is not known what the starting dose should be in patients with hypothyroidism who have cardiac disease, but it seems prudent to start at a lower dose.

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Correction

Errors in Data. In the Original Investigation by Russell et al titled "Effects of Prehypertension on Admissions and Deaths: A Simulation," published in the October 25, 2004, issue of the ARCHIVES (2004;164:2119-2124), an inadvertent error occurred in how the exercise and alcohol consumption variables were handled in the simulation model used to calculate the impact of prehypertension and residual hypertension. This resulted in data errors in Table 2 and Table 3 on page 2122 and subsequent errors wherever these data were cited in the abstract and the text. In addition, the column headings in Table 3 should have read "Change," as these were absolute changes, not percentage changes. Even though the main finding of the study was essentially unchanged, correcting the data errors completely would have required publication of an extensive correction, including republication of correct data points in the abstract and throughout the text, along with republication of the corrected tables. To present the findings as clearly as possible, the entire corrected article now appears on the ARCHIVES Web site in the October 25 issue (available at <http://archinte.ama-assn.org/cgi/content/full/164/19/2119>), replacing the incorrect version.

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Correction

Errors in Figure and Text. In the Original Investigation by Roos et al titled "The Starting Dose of Levothyroxine in Primary Hypothyroidism Treatment," published in the August 8/22 issue of the ARCHIVES (2005; 165:1714-1720), there were errors in Figure 1 and in the text. In Figure 1, the lower row on the bottom should have read "Low Dose" instead of "Full Dose." In the second paragraph of the "Safety" subsection, the first sentence should have read "At baseline, sinus bradycardia was observed in 40% of patients in the full-dose group and 28% in the low-dose group."