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### Paper:

Stephens, J. (2018). Subclinical Hyperthyroidism. *New England Journal of Medicine*, 379(15), 1483-1486.  
<http://dx.doi.org/10.1056/NEJMc1809627>

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venous systems in 46.8% of cases in the EVRA trial.<sup>1</sup> A previous trial showed that foam sclerotherapy for truncal incompetence resulted in a lower occlusion rate (51%) at 1 year than did endovenous laser ablation (97%), with up to 54% of patients requiring additional treatment by 5 years.<sup>4</sup> We propose that if thermal ablation had been used exclusively in the trial by Gohel et al., the healing rates may have been even higher in the intervention groups.<sup>4,5</sup>

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1811147

**THE AUTHORS REPLY:** We agree that the concept of comparing endovenous interventions with compression alone would be interesting. However, considering the evidence of the benefits of compression with respect to leg ulcer healing, we be-

lieved that it may be regarded as unethical not to offer compression to patients. The study was therefore designed to show whether there was a benefit of early intervention in terms of healing, in light of the fact that the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study clearly showed that recurrence rates were lower with compression plus surgical intervention than with compression alone.<sup>1</sup>

We acknowledge that ablation of the truncal vein by thermal ablation may result in a higher long-term occlusion rate than ablation by other means.<sup>2</sup> However, a number of randomized studies have shown good results with respect to the use of foam treatment to enhance leg-ulcer healing.<sup>3,4</sup> There is also a need to evaluate the potential benefit of foam sclerotherapy applied to the small veins in the base of the leg ulcer in terms of ulcer healing.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1811147

## Subclinical Hyperthyroidism

**TO THE EDITOR:** In their Clinical Practice article, Biondi and Cooper (June 21 issue)<sup>1</sup> state that Graves' disease is a common cause of endogenous subclinical hyperthyroidism, accounting for 40% of cases in populations with adequate iodine

intake. The authors cite a review article<sup>2</sup> that references original articles reporting a prevalence of Graves' disease that is much lower than 40% (<10%) among patients with subclinical hyperthyroidism.<sup>3</sup> Indeed, although one study showed

that 4 of 10 patients with a fully suppressed thyrotropin level did have underlying Graves' disease, of the 20 patients who had a persistently partially suppressed thyrotropin level, only 1 (5%) had underlying Graves' disease.<sup>4</sup>

Graves' disease is implicated in a small but clinically significant proportion of patients with subclinical hyperthyroidism who have a fully suppressed thyrotropin level.<sup>2,4</sup> However, only a minority of patients with a partially suppressed thyrotropin level have underlying Graves' disease, and these patients are more likely to have underlying multinodular goiter or toxic adenoma than patients with a fully suppressed thyrotropin level.<sup>4,5</sup>

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1809627

**TO THE EDITOR:** Mortality is increased among patients with hyperthyroidism, independent of the thyrotropin level<sup>1</sup> and phenotype.<sup>2</sup> In their article on subclinical hyperthyroidism, Biondi and Cooper advocate treating a 65-year-old woman with mild subclinical hyperthyroidism (thyrotropin level, 0.2 mU per liter) and some clinically aggravating factors. We think that this recommendation can be extended far beyond their suggestions.

In population-based, observational studies based on Danish databases and involving more

than 230,000 patients (mean follow-up, 7 years), we have found an excess mortality of 36% (95% confidence interval [CI], 16 to 60) among patients with untreated subclinical hyperthyroidism.<sup>3</sup> In patients who received treatment and were followed over a similar period, no excess mortality was shown. In patients who received treatment for hypothyroidism, every 6-month period of overtreatment (thyrotropin level <0.3 mU per liter) was associated with an excess mortality of 18% (95% CI, 15 to 21).<sup>4</sup> Overall, this rate was independent of other preexisting conditions, sex, and whether the patient was younger than 65 years of age or 65 years or older.

These data provide strong support for treatment of all patients with verified subclinical hyperthyroidism, whether endogenous or exogenous. They also underscore the necessity of maintaining a normal thyrotropin level in patients during follow-up.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1809627

**TO THE EDITOR:** An important consideration that is missing from the differential diagnosis of Biondi and Cooper is laboratory interference. Spurious values of thyroid-function tests caused by interference with laboratory assays have been reported in relation to patient antibodies,<sup>1</sup> paraproteins in multiple myeloma,<sup>2</sup> and most importantly, supra-physiologic levels of biotin.

Biotin interferes with many common immunoassays.<sup>3</sup> However, the manner in which biotin affects thyroid-function tests is particularly alarming, since it produces a biochemical picture consistent with Graves' disease.<sup>4</sup>

The Recommended Dietary Allowance of biotin, which is also labeled as vitamin H, vitamin B<sub>7</sub>, and coenzyme R, is 300  $\mu$ g daily, but it is available commercially in doses of up to 100,000  $\mu$ g. Patients may not report biotin use, and often they are unaware of its common presence in products for hair and nail care.

Laboratories should report not only whether assays are vulnerable, but also the expected pattern. In order to avoid unnecessary testing, referrals, or treatment, I think clinicians should recommend that patients abstain from biotin supplements for 48 to 72 hours before a blood sample is obtained, or longer in patients who are taking megadoses of biotin or who have impaired renal function.

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The views expressed in this letter are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of Defense, or the U.S. government.

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1809627

**THE AUTHORS REPLY:** Williams et al. take issue with the fact that we stated that 40% of patients with subclinical hyperthyroidism have Graves' disease, with the remainder having toxic multinodular goiter or a solitary autonomously functioning thyroid nodule. Although precise percentages of each diagnosis are difficult to glean from the literature, we agree with Williams et al. that Graves' disease occurs in a distinct minority of patients, especially in those with mild subclinical

hyperthyroidism, in whom serum thyrotropin levels are not fully suppressed.

Hegedüs et al. cite their own study showing higher mortality among patients with untreated subclinical hyperthyroidism than among those who receive treatment.<sup>1</sup> We did not include this study in our article because of the paradoxical nature of their findings. In their population, mortality among patients with untreated overt hyperthyroidism (hazard ratio, 1.03; 95% CI, 0.88 to 1.20) was the same as that observed among patients with treated overt hyperthyroidism (hazard ratio, 1.03; 95% CI, 0.93 to 1.15), and these rates of death were not different from those in the euthyroid control population. Because of space limitations, we were not able to describe their article fully. We cannot agree with their recommendation, which is based solely on observational data, to treat all patients with subclinical hyperthyroidism. We stand by published clinical practice guidelines that advocate individualized treatment decisions based on the level of serum thyrotropin, patient age, and coexisting conditions.

Haddad appropriately points out that ingestion of biotin can cause falsely low serum thyrotropin levels in immunoassays using streptavidin-biotin systems. In addition to affecting serum thyrotropin levels, artifactual values for free thyroxine, triiodothyronine (T<sub>3</sub>), free T<sub>3</sub>, prolactin, N-terminal pro-brain natriuretic peptide, and 25-hydroxyvitamin D may be observed.<sup>2</sup> Since clinicians do not usually know the assay system being used in clinical chemical laboratory tests, patients should avoid biotin ingestion before undergoing routine laboratory testing. Furthermore, as was pointed out by Haddad, there are a host of other causes of spurious findings in thyroid-function tests,<sup>3</sup> so results require clinical correlation and should never be interpreted in isolation.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix

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DOI: 10.1056/NEJMc1809627

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## CORRECTIONS

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease (N Engl J Med 2016;374:2032-2043). The disclosure statement for Dr. Lonn (p. 2042) should have read, "Dr. Lonn reports receiving fees for serving on advisory boards from Amgen, Sanofi, Novartis, and Servier, lecture fees from Amgen and Sanofi, and grant support through her institution from Bayer, GlaxoSmithKline, Merck/Schering-Plough, Eli Lilly, and Cadila Pharmaceuticals," rather than "Dr. Lonn reports receiving fees for serving on advisory boards from Amgen, Sanofi, Novartis, Cadila Pharmaceuticals, and Servier, lecture fees from Amgen and Sanofi, and grant support through her institution from Bayer, GlaxoSmithKline, Merck/Schering-Plough, and Eli Lilly." The article is correct and the disclosure forms have been updated at NEJM.org.

Effects of Testosterone Treatment in Older Men (N Engl J Med 2016;374:611-624). Corrections made in the trial database revealed errors in several numbers reported in the text and tables. In the first sentence of the Physical Function Trial subsection of Results (p. 615), the parenthetical "(mean difference, 4.09 m; P=0.28)" should have read, "(mean difference, 4.15 m; P=0.25)." In the second sentence, the parenthetical "(odds ratio, 1.76; P=0.003)" should have read, "(odds ratio, 1.77; P=0.003)." In the "Men enrolled in Physical Function Trial" section of Table 2 (p. 618), in the Testosterone row below "6-Min walking distance," the value in the Month 9 column should have been 5.5±50.3, rather than 5.3±50.3. In the same row, in the Treatment Effect column, the values should have been 4.15 (−2.95 to 11.24), rather than 4.09 (−3.00 to 11.18), and the P value on the far right should have been 0.25, rather than 0.28. In the "All Testosterone Trials participants" section of the table, in the Testosterone row below "Increase of ≥50 m in 6-min walk test," the values in the Treatment Effect column should have been 1.77 (1.21 to 2.58), rather than 1.76 (1.21 to 2.57). In the same section of the table, in the rows below "6-Min walking distance" (p. 619), the Month 3 value for Testosterone should have been 10.0±45.1, rather than 10.9±45.1, and the Month 3 value for Placebo should have been 1.5±41.9, rather than 1.6±41.9. The article is correct at NEJM.org.

## NOTICES

*Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received.*

## 2ND INTERNATIONAL SYMPOSIUM ON RESEARCH IN ACUPUNCTURE

The symposium will be held in Bologna, Italy, Oct. 20 and 21. Contact Alessandra Ricci at [segreteria@scuola.acupunctureresearch.eu](mailto:segreteria@scuola.acupunctureresearch.eu); or call (39) 340-9553985; or see <https://www.acupunctureresearch.eu/>.

## MEDICAL SPANISH AND CULTURAL COMPETENCY CONFERENCE

The conference will be held in La Paz, Mexico, Oct. 19–22; in San Francisco, Nov. 2–5; in San Diego, CA, Nov. 16–19; in Phoenix, AZ, Nov. 30–Dec. 3; and in Las Vegas, Dec. 7–10.

Contact Rios Associates, 3729 N. Bay Horse Loop, Tucson, AZ 85719; or call (520) 907-3318; or fax (480) 772-4889; or see <http://www.medspanish.org>.

## THOMAS L. PETTY ASPEN LUNG CONFERENCE

The 62nd Annual Meeting, entitled "Exploring New Therapeutic Pathways in Pulmonary Hypertension: Metabolism, Proliferation, and Personalized Medicine," will be held in Aspen, CO, June 5–8. Deadline for submission of abstracts is Feb. 14.

Contact Dr. Brian Graham, c/o Jeanne Cleary, Thomas L. Petty Aspen Lung Conference, P.O. Box 1622, Parker, CO 80134; or call (303) 358-2797; or e-mail [Jeanne.Cleary@ucdenver.edu](mailto:Jeanne.Cleary@ucdenver.edu); or see <http://www.aspenlungconference.org>.

## MAYO CLINIC SCOTTSDALE

The following courses will be offered in Scottsdale, AZ, unless otherwise indicated: "21st Annual Mayo Clinic Internal Medicine Update" (Oct. 25–28); "Mayo Clinic Pancreatic and Hepato-Biliary Cancer Symposium 2018" (Oct. 26 and 27); "Multidisciplinary Update in Breast Disease" (Nov. 8–10); "Mayo Clinic Cancer Center: Thoracic Oncology Update 2018" (Phoenix, AZ, Nov. 9 and 10); "Mayo Pathology Update 2019" (Phoenix, AZ, Jan. 24–26); "Practical Proton Therapy Seminar and Workshop" (Jan. 24–26); and "15th Annual Mayo Clinic Women's Health Update" (Feb. 28–March 2).

Contact Mayo School of Continuous Professional Development, Mayo Clinic, 13400 E. Shea Blvd., Scottsdale, AZ 85259; or call (480) 301-4580; or fax (480) 301-8323; or e-mail [mca.cme@mayo.edu](mailto:mca.cme@mayo.edu); or see <http://www.mayo.edu/cme>.

## MAYO CLINIC

The following courses will be offered in Rochester, MN, unless otherwise indicated: "92nd Annual Clinical Reviews 2018" (Oct. 22–24, Nov. 5–7); "Mayo Clinic Opioid Conference: Evidence, Clinical Considerations and Best Practice 2018" (Kohler, WI, Oct. 25 and 26); "Mayo Clinic Frontiers in Addiction Treatment 2018" (Nov. 2); "28th Annual Mayo Clinic Symposium on Sports Medicine 2018" (Nov. 9 and 10); "Symposium on Regenerative Medicine and Surgery" (Scottsdale, AZ, Nov. 29–Dec. 1); "2019 Mayo Clinic Advancements in Surgical & Medical Management of the Spine" (Kohala Coast, HI, Jan. 13–17); "16th Annual Mayo Clinic Hematology Review 2019" (Minneapolis, Jan. 19); "Psychiatry in Medical Settings 2019" (Sarasota, FL, Jan. 24–26); "31st Annual Selected Topics in Internal Medicine" (Waikoloa, Big Island, HI, Jan. 28–Feb. 1); "2019 Multiple Sclerosis and Autoimmune Neurology Update" (Phoenix, AZ, Feb. 8 and 9); "7th Annual Acute Care of the Complex Hospitalized Patient for NPs & PAs" (Scottsdale, AZ, Feb. 13–16); "Clinical Multidisciplinary Hematology & Oncology: the 16th Annual Review" (Scottsdale, AZ, Feb. 15–17); "Mayo Clinic Gastroenterology and Hepatology 2019" (Scottsdale, AZ, Feb. 21–24); and "Mayo Clinic Psychiatry Clinical Updates 2019" (Kohala Coast, HI, Feb. 26–March 1).

Contact the Mayo School of Continuous Professional Development, 200 First St. SW, Rochester, MN 55905; or call (800) 323-2688 or (507) 284-2509; or fax (507) 284-0532; or see <https://ce.mayo.edu>; or e-mail [cme@mayo.edu](mailto:cme@mayo.edu).