

Update on Management of Thyroid and Testosterone

Discussing common controversies and
uncertainties.

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Disclosures



There is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Objectives

Review the management of subclinical hypothyroidism, particularly for elderly patients or those with heart disease risk factors.

Review the use of thyroid hormone for patients with benign thyroid nodules.

Review the long-term management of patients with history of differentiated thyroid cancer.

Review recent safety data on testosterone replacement for men with hypogonadism.

Case Vignettes

Case #1

77 year-old woman presenting for discussion of fatigue / lack of energy. She reports recent forgetfulness and difficulty concentrating / “brain fog.”

PMH: HTN, hyperlipidemia

Meds: atenolol, pravastatin

Exam: BMI 29, BP 142/89, p62
moderate high-freq hand tremor

Labs: TSH 5.2 [0.45-4.5], Free T4 1.1 [0.8-1.4]

Question

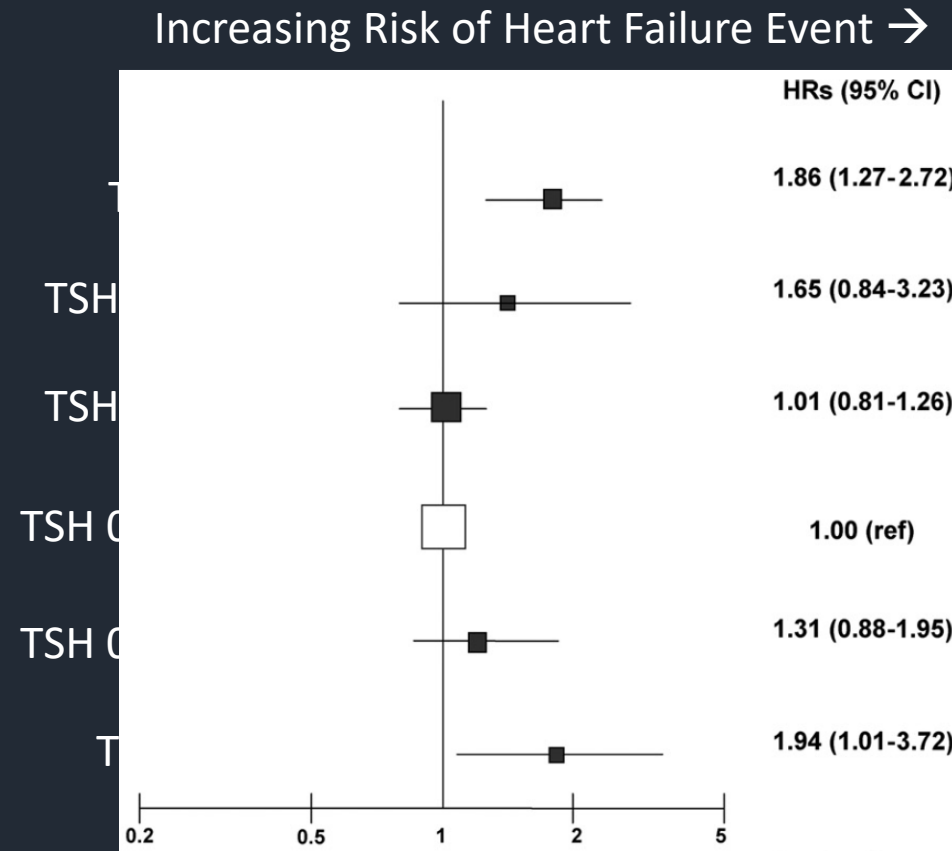
Adding levothyroxine 100mcg daily would be expected to...

- A. Mitigate the higher risk of heart failure seen in patients with elevated TSH.
- B. Lower risk of mortality, MI, or CV death.
- C. Improve BP and lipid profile.
- D. Improve fatigue.
- E. Improve memory / cognitive function.
- F. Reduce weight and BMI.
- G. More than one of the above.
- H. Normalize TSH, but nothing else.

Risk of CHF is not increased in mild Subclinical Hypothyroidism

Design: Pooled analysis of 6 prospective cohort studies of CHF events.

Patients: 25390 participants spanning 216,248 pt-years in USA and Europe.



Meta Analysis of Levothyroxine for Subclinical Hypothyroidism

LIPIDS

Modest improvement in:

- Total Cholesterol (p=0.02)
- Triglycerides (p=0.01)
- LDLc (p=0.007)

Plaque formation

Higher CIMT in patients with subclinical hypothyroidism vs. euthyroid controls

Modest Improvement in CIMT following levothyroxine in patients with subclinical hypothyroidism.

All-Cause Mortality benefit with Levothyroxine treatment?

Design: Retrospective cohort study in Denmark.

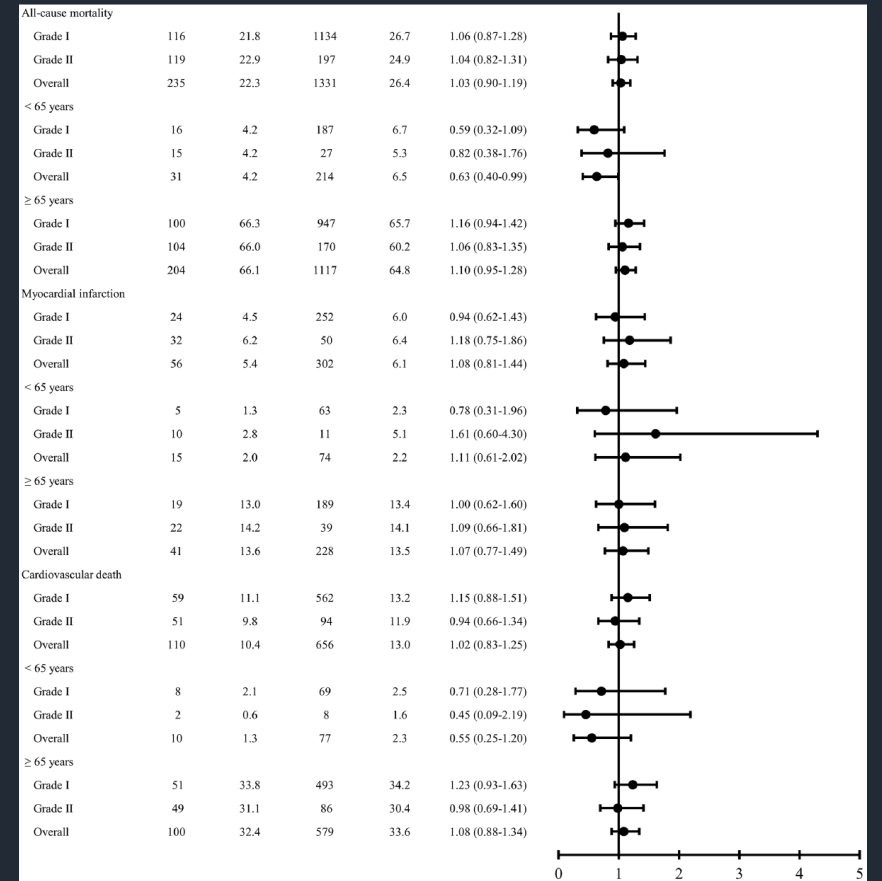
Patients: 12000 patients with subclinical hypothyroidism

Comparison: pharmacy fills for levothyroxine. 5y follow-up.

Outcomes: NO benefit on MI, Cardiovascular Death, or mortality for pts >65 years old.

Patients younger than 65 had slightly lower all-cause mortality.

Increasing Risk of Event →



For patients >65 years old, Consider treatment at TSH >7.0

		Thyrotropin level, mU/L	Patients <65 years	Patients ≥65 years
		0.4-4.4	Normal thyrotropin reference range	
Subclinical hypothyroidism	Grade 1	4.5-6.9	<ul style="list-style-type: none"> • Measure thyroid peroxidase (TPO) antibodies • Annual follow-up thyrotropin measurement of asymptomatic patients • Consider treatment with levothyroxine (LT₄) in patients with <ul style="list-style-type: none"> Multiple symptoms of hypothyroidism Positive TPO antibodies Progressively increasing thyrotropin levels A plan for pregnancy Goiter 	Treatment is not recommended
		7.0-9.9	Treat with LT ₄ to reduce risk of fatal stroke and coronary heart disease (CHD) mortality ^a	Consider treatment with LT ₄ to reduce risk of CHD mortality ^a
	Grade 2	≥10.0	Treat with LT ₄ to reduce risk of progression to overt hypothyroidism, heart failure, CHD events, and CHD mortality ^a	

Question

Adding levothyroxine 100mcg daily would be expected to...

- A. ~~Mitigate the higher risk of heart failure seen in patients with elevated TSH.~~
- B. ~~Lower risk of mortality, MI, or CV death.~~
- C. Improve ~~BP~~ and lipid profile.
- D. Improve fatigue.
- E. Improve memory / cognitive function.
- F. Reduce weight and BMI.
- G. Adding levothyroxine would have multiple benefits (above).
- H. Normalize TSH, but worsen the tremor.

Case #1

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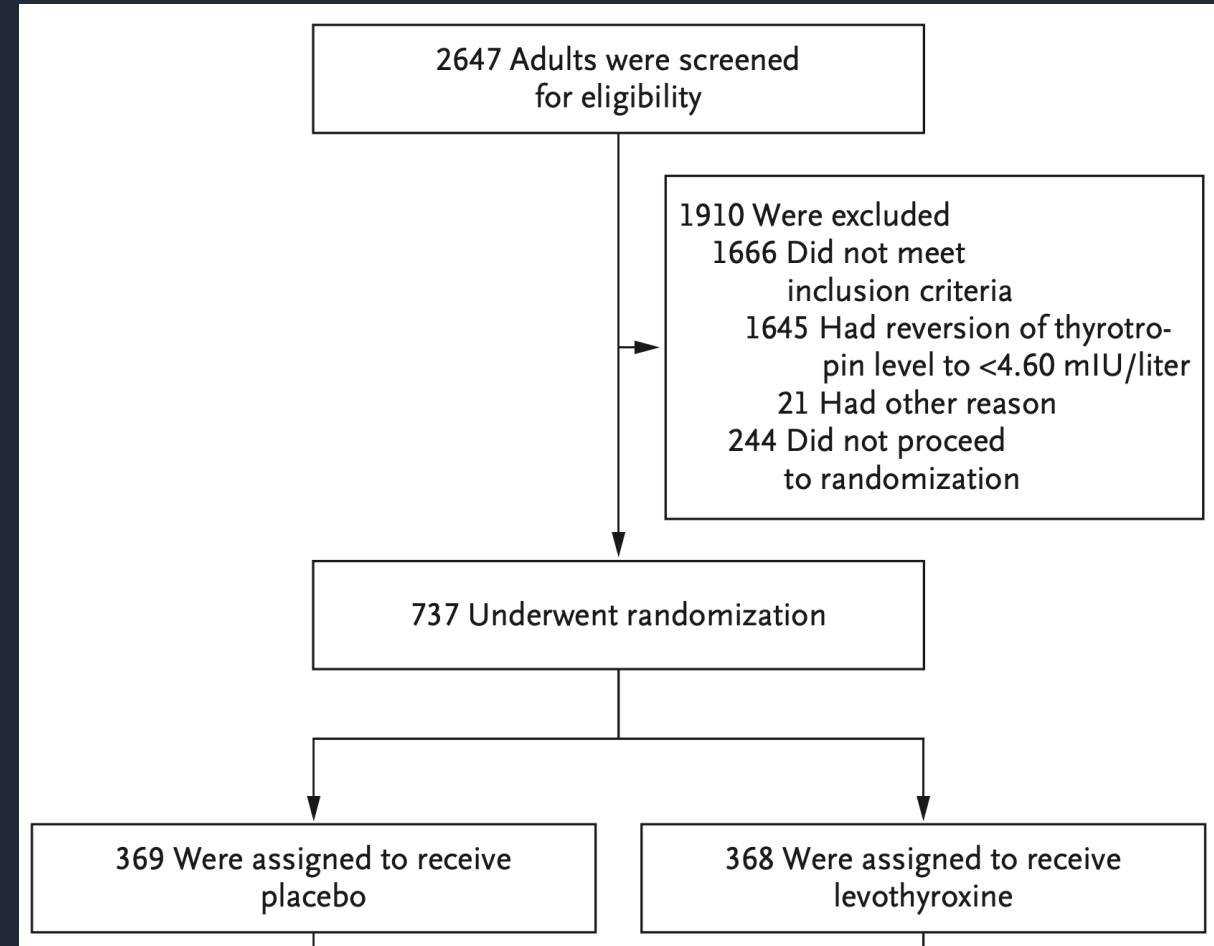
RCT of Levothyroxine for Subclinical Hypothyroidism

Patients: 737 adults >65 years old with subclinical hypothyroidism

Intervention: Levothyroxine vs. placebo (treating providers blinded to TSH)

Comparison: Symptom scores, multiple secondary outcomes.

Follow-up: 1yr and beyond



RCT of Levothyroxine for Subclinical Hypothyroidism

NO BENEFIT on:

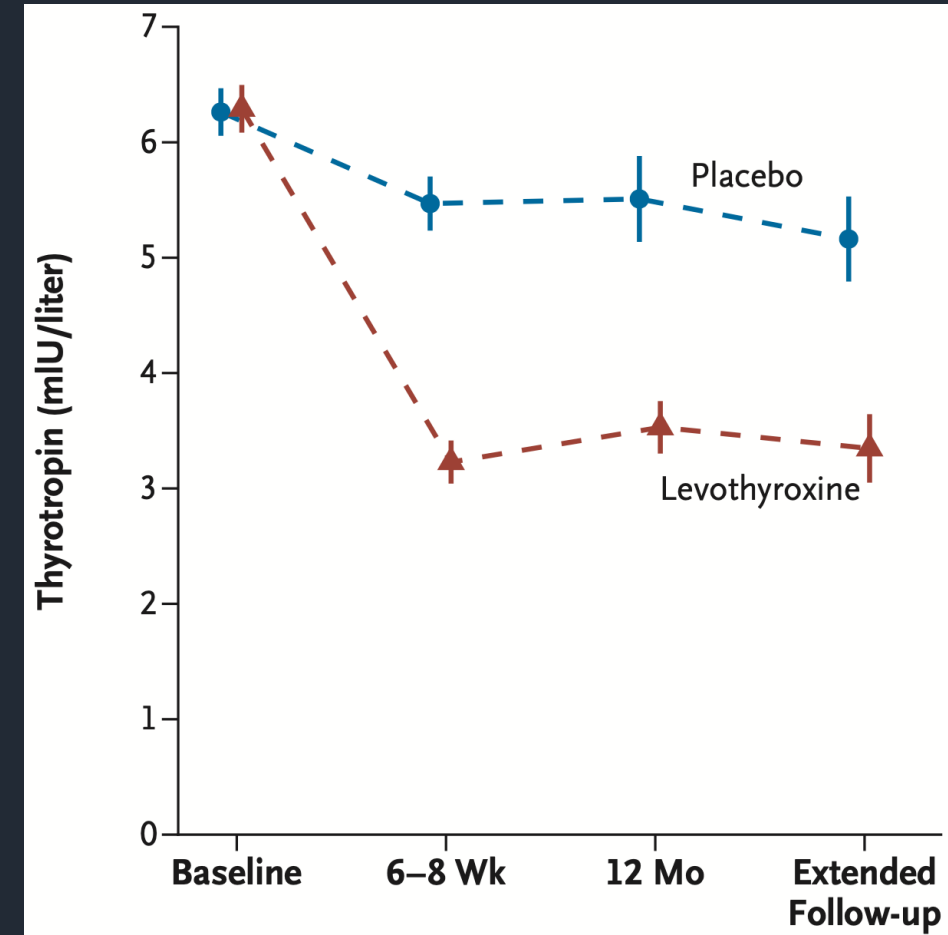
Hypothyroid symptom score,
Tiredness score

Weight, BMI, waist circumference, BP

Barthel, iADL score

Under-powered to assess CV risks.

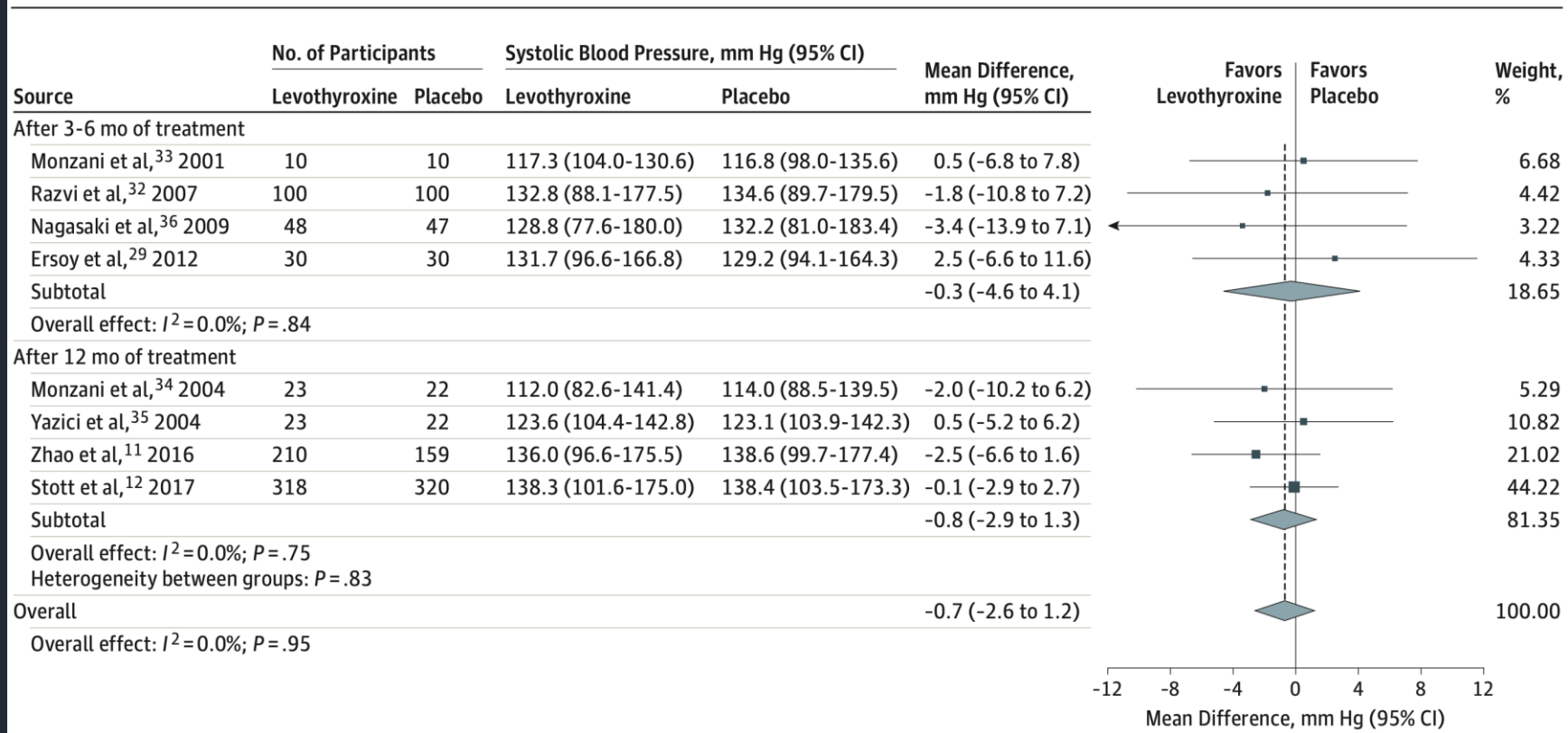
Deaths in treatment group 2.7%,
placebo group 1.4%



Meta Analysis of Levothyroxine for Subclinical Hypothyroidism

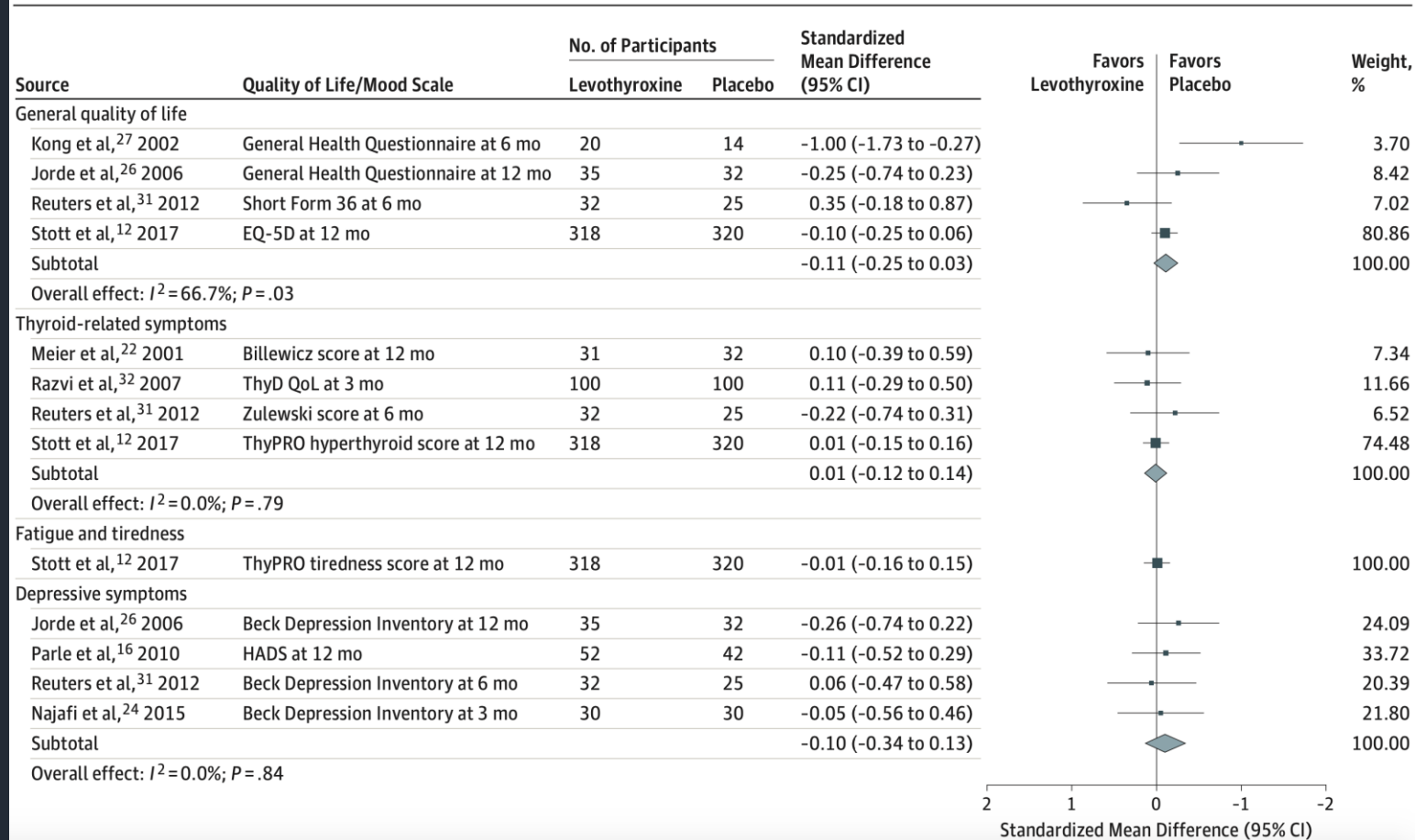
Systolic BP

Figure 3. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Systolic Blood Pressure



Meta Analysis of Levothyroxine for Subclinical Hypothyroidism

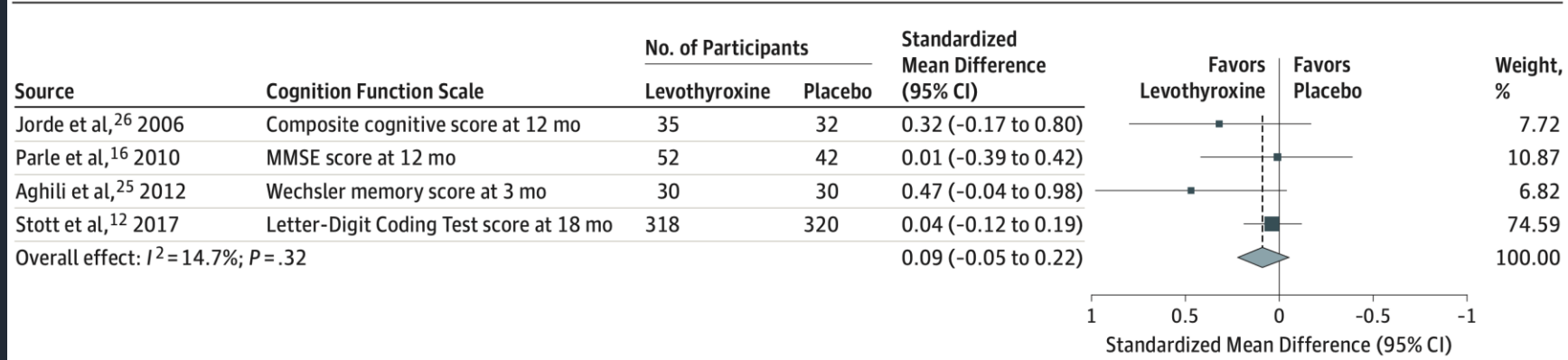
Figure 1. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Quality-of-Life and Mood-Related Outcomes



Meta Analysis of Levothyroxine for Subclinical Hypothyroidism

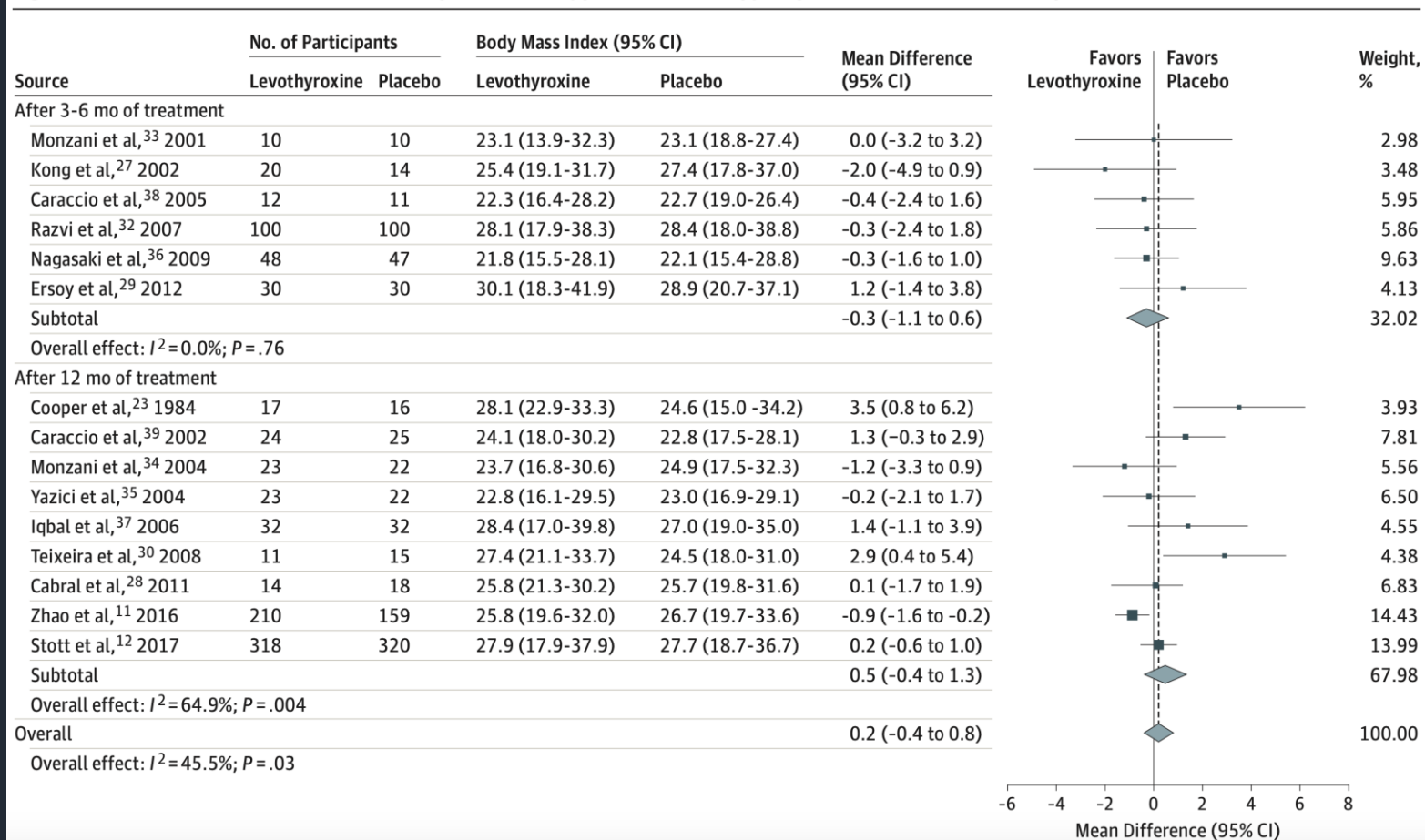
Cognition

Figure 2. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Cognitive Function



Meta Analysis of Levothyroxine for Subclinical Hypothyroidism

Figure 4. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Body Mass Index



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Case #2

55 y/o woman returning for assessment of a thyroid nodule, that you had discovered on attentive physical exam 1 month ago. Imaging confirmed a 3.5cm solid nodule on right lobe, which was benign by fine-needle aspiration.

She denies dysphagia, hoarseness, dyspnea, choking sensation, or pain.

PMH: none

Exam: Wt 80kg, BMI 29, BP 112/63, p82

Labs: TSH 2.0 [0.45-4.5], FT4 1.1 [0.8-1.4]

Question

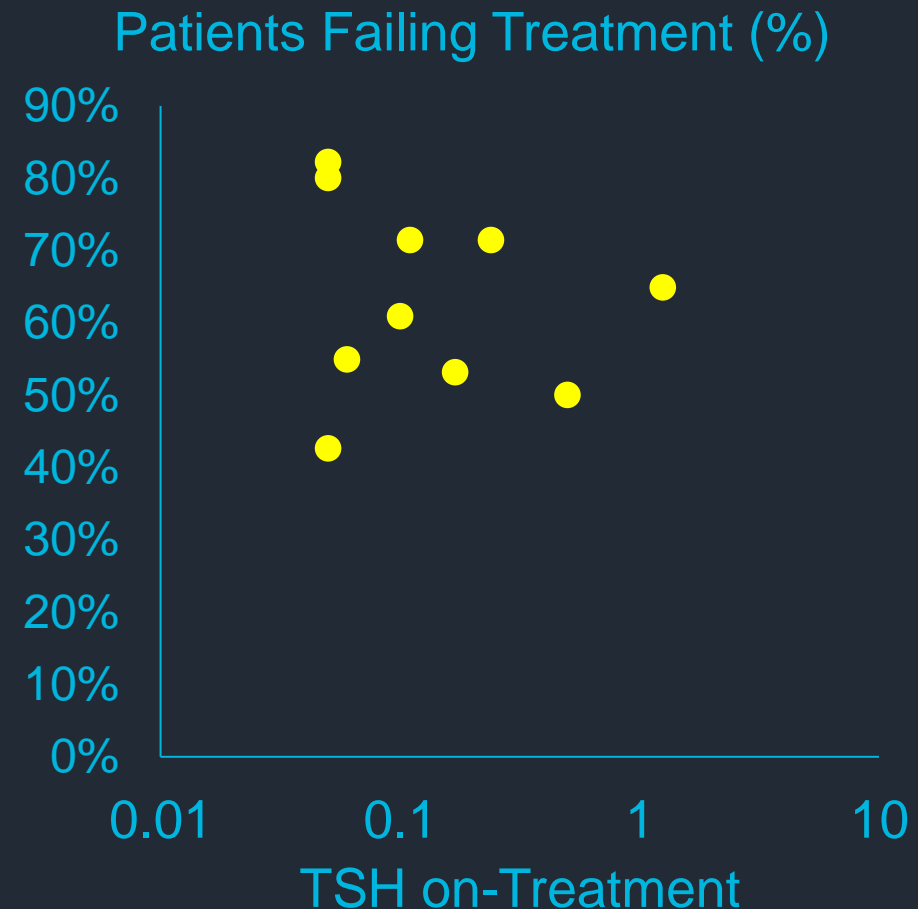
Adding levothyroxine 100mcg daily would be expected to...

- A. Reduce risk that the nodule will progress to thyroid cancer.
- B. Shrink the nodule.
- C. Improve overall quality of life.
- D. None of the above.

Meta Analysis of 10 Studies: Low likelihood of success

Meta Analysis of 10 trials of levothyroxine for patients with benign thyroid nodules.

Goal of treatment was reduction in nodule size: generally 5-15% reduction after 6-18 months treatment.



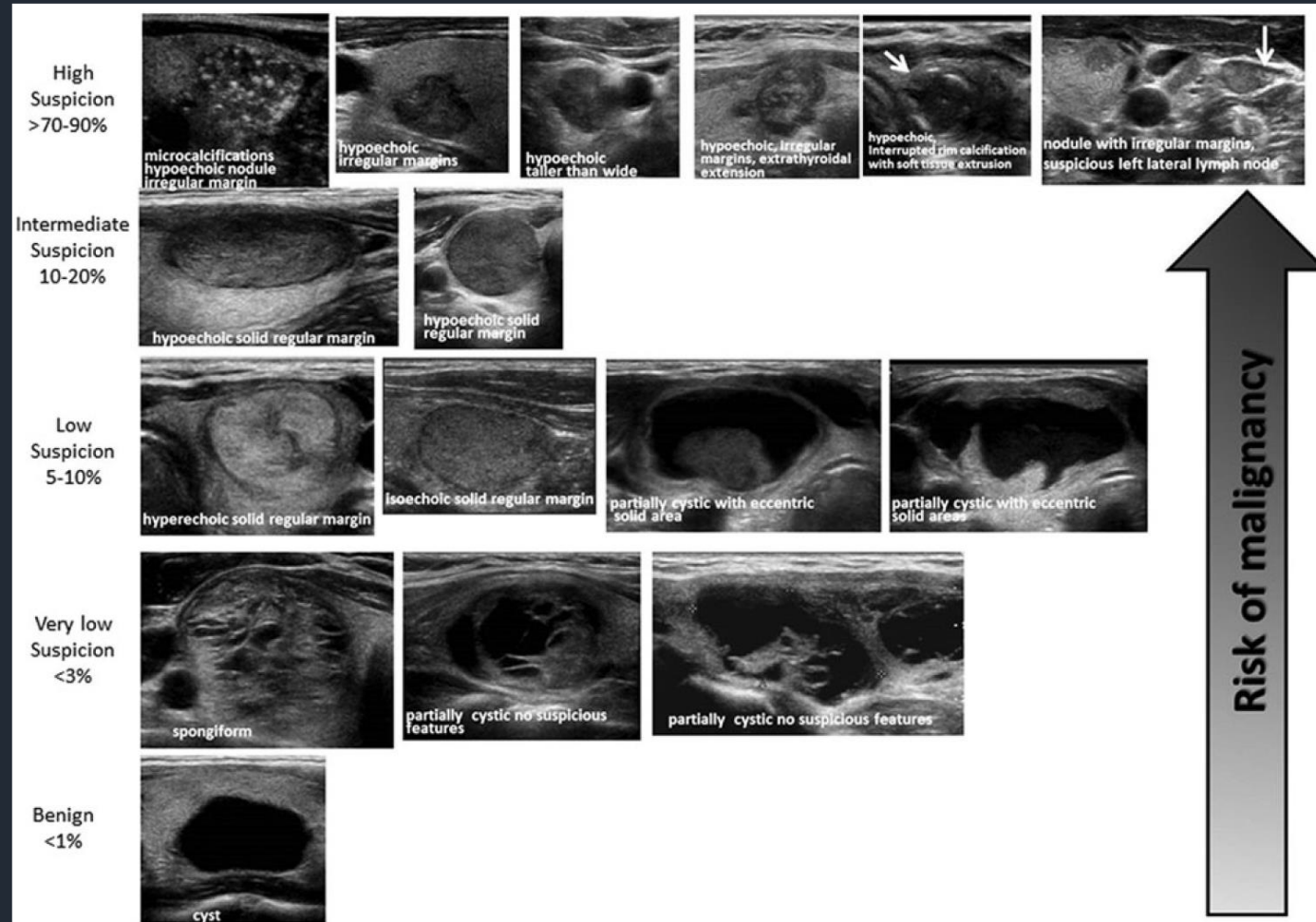
American Thyroid Association Guidelines: No levothyroxine

“Routine TSH suppression therapy for benign thyroid nodules in iodine sufficient populations is not recommended.

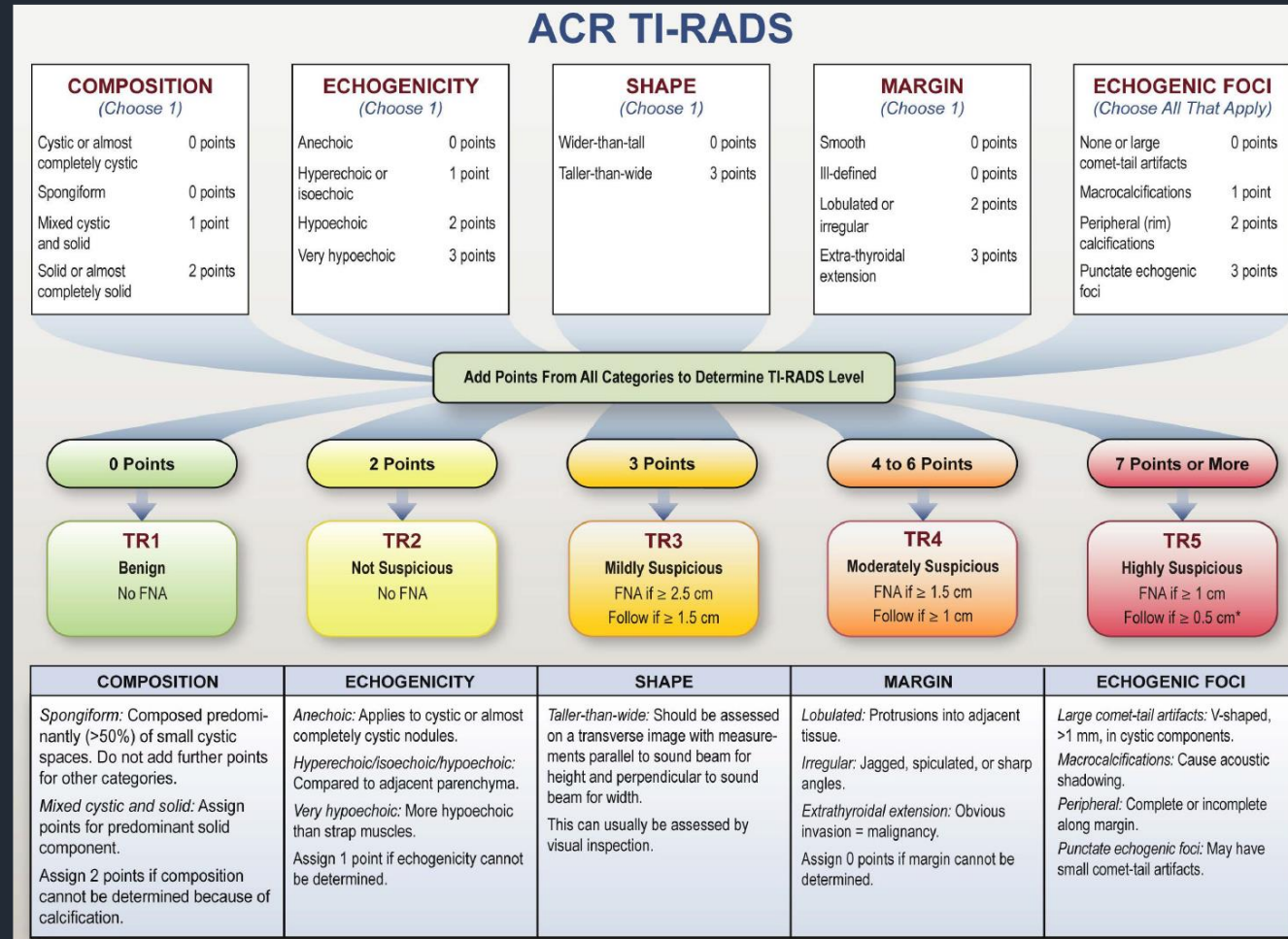
Though modest responses to therapy can be detected, the potential harm outweighs benefit for most patients.”

(Strong recommendation, High-quality evidence)

American Thyroid Association Guidelines for Nodules



TI-RADS scoring system for Thyroid Nodules



Thyroid Nodules

Concluding Thoughts

Initial evaluation with TSH, Ultrasound

Suppressed TSH → obtain thyroid scan

Nonsuppressed TSH → ultrasound

Malignancy is treatable, easily ruled out.

Note family history, radiation exposure,
nodule size, sonographic characteristics

Radiologist should comment on FNA indication.

Hyperthyroidism from functioning nodule

Treatable medically or with radio-iodine

Treatment of local compressive symptoms

Careful attention to risks / benefits.

Case #3

65 y/o woman presents to establish care after recently relocating to the area. Medical history is notable for papillary thyroid cancer, diagnosed in her early 30s. She was treated with total thyroidectomy and I-131 ablation.

Since then, cancer follow-up has been spotty. Recently, she has felt no growth or adenopathy in the neck.

Case #3

PMH: Thyroid Cancer, postsurgical hypothyroidism

ROS: Hand tremor, poor sleep

Meds: Levothyroxine 150mcg daily

Exam: Wt 62kg, BMI 20, BP 112/63, p88

No palpable thyroid tissue. No LAD.

Moderate high-freq intention tremor.

Labs: TSH 0.1 [0.45-4.5], FT4 1.6 [0.8-1.4]

Question

Reducing levothyroxine to 100mcg daily would be expected to...

- A. Increase the risk of recurrent thyroid cancer.
- B. Cause weight gain.
- C. Mitigate the increased risk of cardiovascular death seen in patients like this.
- D. None of the above.

Assessing Disease Status in Differentiated Thyroid Cancer

Excellent Response: no clinical, biochemical, or structural evidence of disease

Biochemical Incomplete Response: abnormal Thyroglobulin or rising anti-Tg antibody levels in the absence of localizable disease.

Structural Incomplete Response: loco-regional disease or distant metastases

Indeterminate Response: nonspecific findings that cannot be confidently classified as either benign or malignant.

Long-Term Clinical Outcomes in Differentiated Thyroid Cancer

Category	Disease-Specific Death Rate	Recurrence Risk
Excellent Response	<1%	1-4%
Biochemical Incomplete Response	<1%	20% develop structural disease 50% improve to NED
Structural Incomplete Response	11% with local-regional disease 50% with distant mets	50-85% of patients will have persistent disease despite treatment
Indeterminate Response	<1%	10-20% develop structural disease

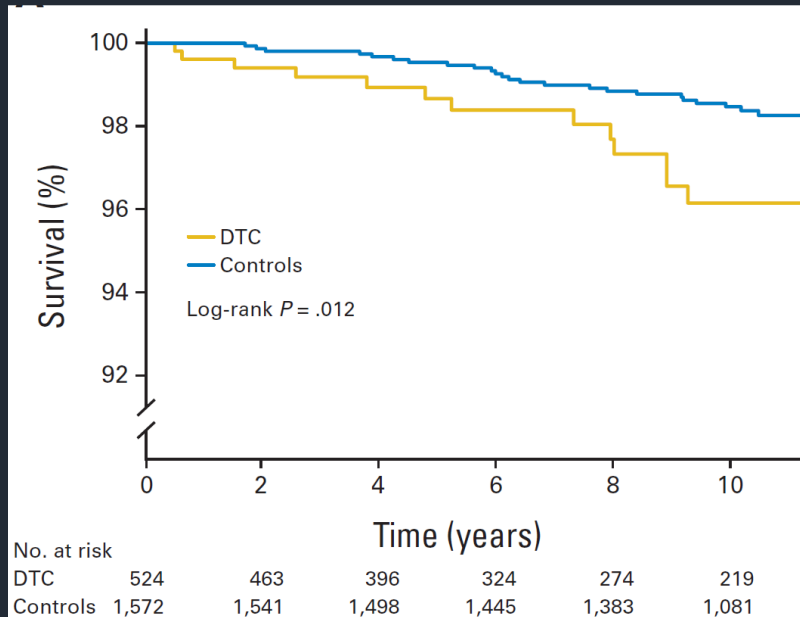
Risk-Based TSH Goals in Differentiated Thyroid Cancer

Increasing Risk of TSH Suppression	Excellent	Indeterminate	Biochemical Incomplete **	Structural Incomplete
No Known Risk				
Menopause				
Tachycardia				
Osteopenia				
Age > 60				
Osteoporosis				
Atrial Fibrillation				

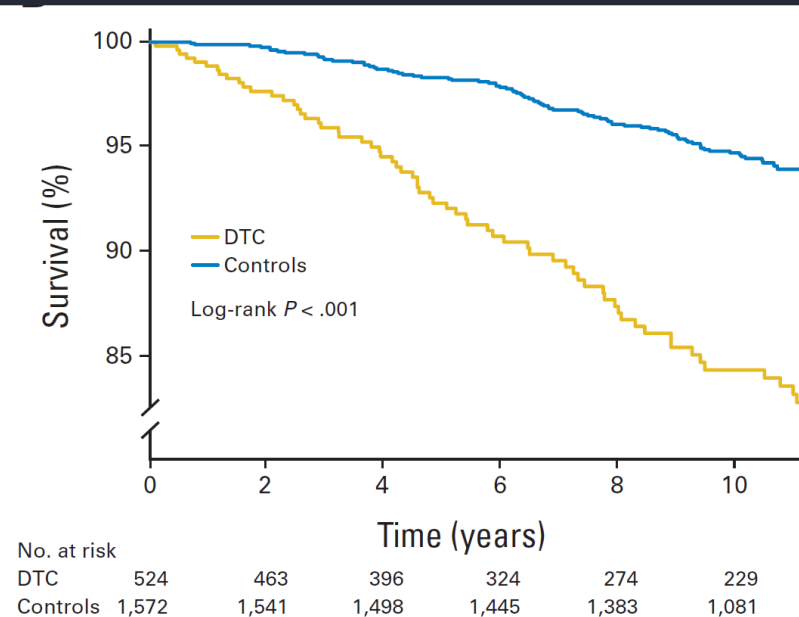
Moderate or Complete Suppression. TSH target <0.1 mU/L
Mild suppression. TSH target 0.1–0.5 mU/L*
No suppression. TSH target 0.5–2.0 mU/L*

Mortality in Thyroid Cancer Patients correlates with TSH.

CV Death



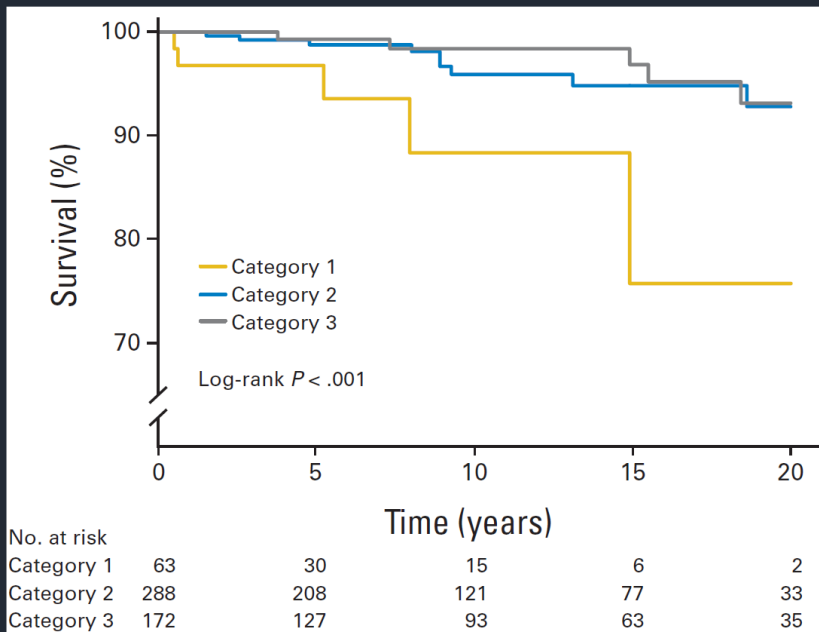
All Cause Mortality



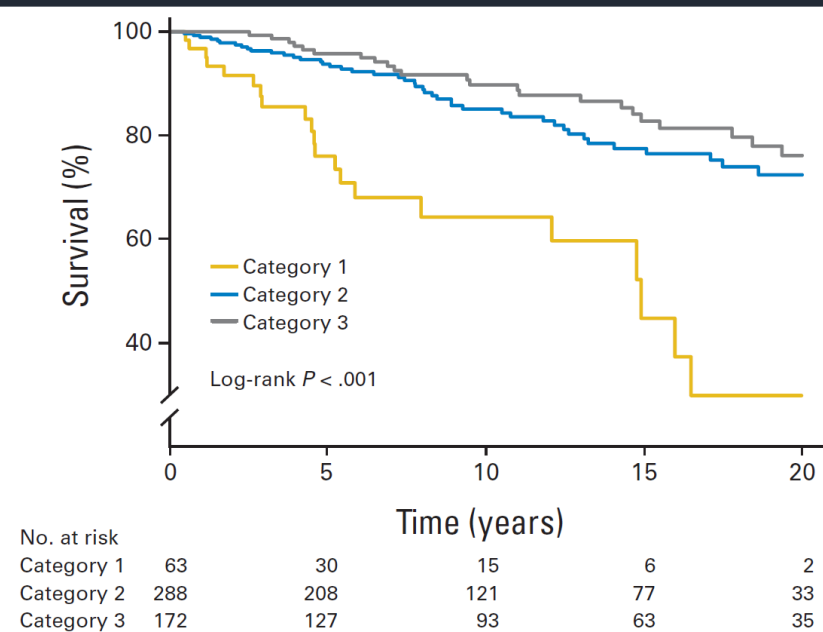
Differentiated Thyroid Cancer Patients
Age-Matched Controls

CV Mortality in Thyroid Cancer Patients correlates with TSH.

CV Death



All Cause Mortality



Category 1: mean TSH <0.02
 Category 2: mean TSH 0.02-0.2
 Category 3: mean TSH >0.2

Risk-Based TSH Goals in Differentiated Thyroid Cancer

Increasing Risk of TSH Suppression	Excellent	Indeterminate	Biochemical Incomplete **	Structural Incomplete
No Known Risk				
Menopause				
Tachycardia				
Osteopenia				
Age > 60				
Osteoporosis				
Atrial Fibrillation				

Moderate or Complete Suppression. TSH target <0.1 mU/L
Mild suppression. TSH target 0.1–0.5 mU/L*
No suppression. TSH target 0.5–2.0 mU/L*

Concerning Testosterone therapy for men

Case #4

65 y/o man presents for review of recent bone density tests after suffering a low-trauma fracture. One month earlier, he had slipped in the shower and fractured his humerus. During the repair, his orthopedic surgeon commented that his bones felt thin and weak.

For the last 2 years he has noted a reduction in libido, difficulty maintaining adequate erectile function.

Muscle mass / strength are modestly lower and he feels more deconditioned. Mood has been slightly more depressed.

Case #4

PMH: CAD (Angioplasty 5 years ago), Hypertension, Sleep Apnea, and Hyperlipidemia

FH: Father with CABG at age 50

ROS: Weight Gain

Meds: Lisinopril, Atorvastatin

Exam: Wt 92kg, BMI 28, BP 132/63, p88
Virilized. Modest temporal hairline recession.
Facial hair on jaw line and sideburn area.

Male musculature, not particularly bulky (endomorph).

Fatty enlargement of breasts bilaterally.

Mammary glands nickel-sized, concentric with areolae, nontender.

Testes 10cc bilaterally. Ovoid and firm with no masses.

Labs: Morning total testosterone 220 [240-950]

DEXA Scan: L-Spine T-score -2.4, Femoral Neck T-Score -2.8

Question

What advice is most appropriate given his history of cardiovascular disease?

- A. Prescribing testosterone is not recommended due to higher risk of heart attack and stroke
- B. Testosterone therapy would not increase cardiovascular risk and can be prescribed right away
- C. Before prescribing testosterone, the diagnosis of hypogonadism needs confirmation, and more information about safety is needed.
- D. Referral to online Men's Health clinic is most appropriate.

WHY is the diagnosis of hypogonadism so tricky?

- Testosterone levels fluctuate during the day / night cycle, vary with age and body mass
- Testosterone is a difficult substance to measure accurately
- Testosterone is 99% bound to SHBG, so changes in this protein level can falsely raise or lower the total testosterone without changing the biologically active testosterone levels.
- Controversy regarding risks and benefits of testosterone treatment in aging men with underlying illness.

Pearls and Pitfalls in the Diagnosis of Hypogonadism in Men

Clinical Manifestations

- **Specific Symptoms**
 - Loss of Libido
 - Erectile Dysfunction
 - Loss of muscle mass
 - Decreased body hair
- **Clinical Scenarios**
 - Anemia
 - Osteoporosis
 - Infertility
 - Gynecomastia (glandular)
 - Pituitary adenoma

Biochemical Testing

- **Reproducibility**
 - Consistently low morning levels
 - Tested at baseline health, fasting
- **Proper Assay**
 - LC/MS method recommended
 - AVOID “direct” free testosterone
- **Free Testosterone**
 - Obesity, Diabetes, Insulin Resistance, Glucocorticoids, Nephrotic Syndrome
 - SEND-OUT for Equilibrium Dialysis
 - AVOID “direct” free testosterone

Potential Underlying Causes of Hypogonadism in Men

Primary Hypogonadism Elevated FSH / LH

- **Chemical Injury**
 - Chemotherapy, toxins
- **Physical Injury (torsion)**
- **Infectious**
 - Mumps, HIV
- **Autoimmune**
- **Congenital / Genetic**
 - Klinefelter Syndrome (XXY)
 - Cryptorchidism

Secondary Hypogonadism Normal or Low FSH / LH

- **Anatomic Lesions of Pituitary**
 - Adenomas, cysts
- **Endocrine Disorders**
 - Cushing's Syndrome
 - Hyperprolactinemia
- **Suppression of Gonadotrophs**
 - Opiate analgesics
 - Long-term corticosteroids
 - Acute medical illness (transient)

Potential Benefits and Harms of Testosterone Replacement in Men

Beneficial Effects

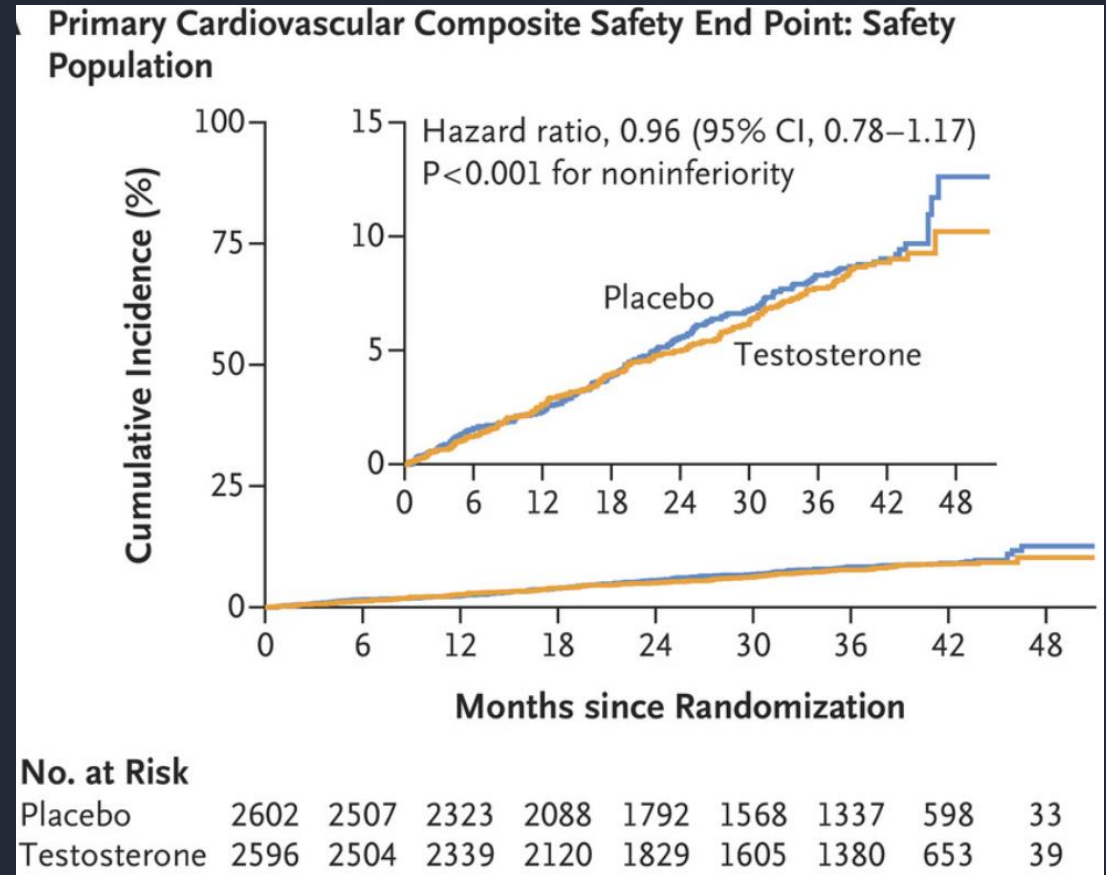
- **Significant Improvement**
 - Bone density
 - Anemia
- **Moderate Improvement**
 - Sexual function
 - Mood
- **Questionable Improvement**
 - Executive function
 - Cognition
 - Fitness (6-minute walk test)

Potential Harms

- **Prostate**
 - AVOID in patients with palpable prostate nodule or PSA >4
- **Erythrocytosis**
 - Hct >52%
- **Decreased HDLc**
- **Sleep Apnea**
- **Higher risk of CV events?**

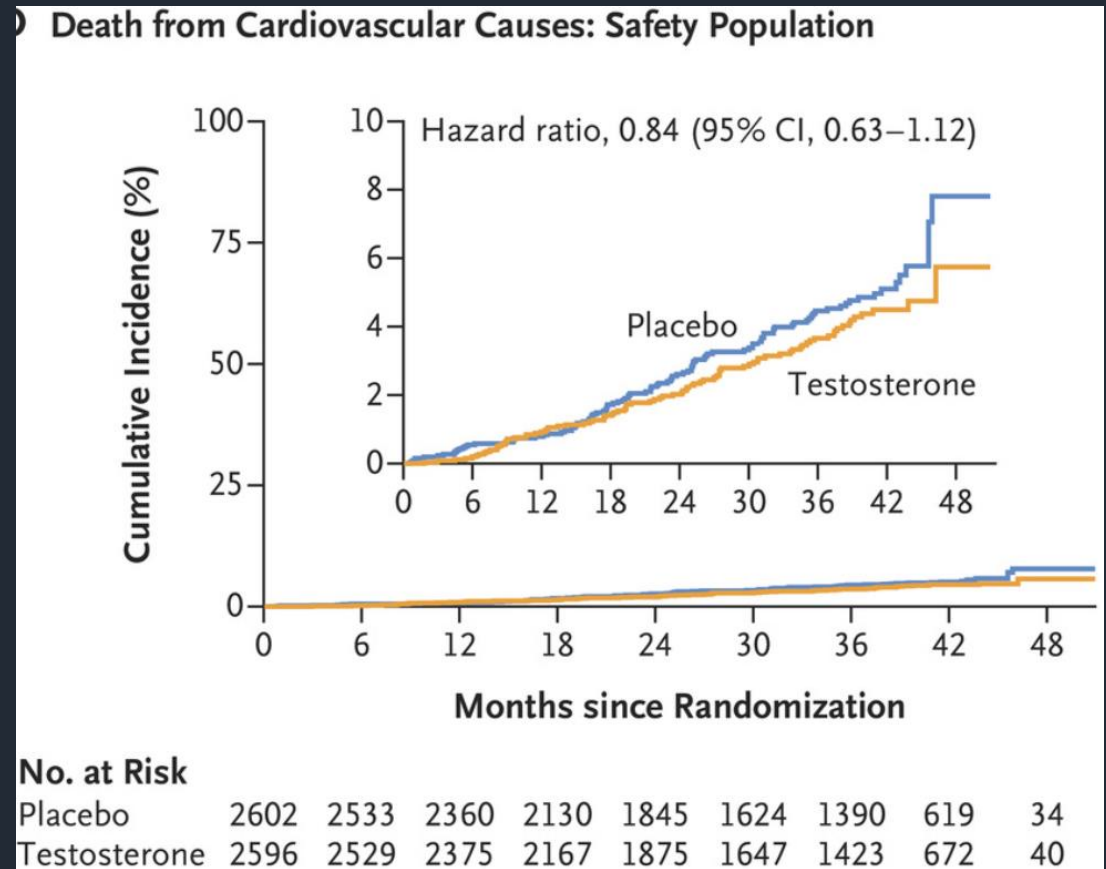
Randomized Trial Examining Cardiovascular Outcomes in TRT

- Randomized, double-blind, placebo-controlled trial of 5,246 men with pre-existing CAD or multiple risk factors and total testosterone <300
- Transdermal testosterone gel adjusted to on-treatment level of 350-750.
- Primary outcome: cardiovascular death or MACE.



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- Randomized, double-blind, placebo-controlled trial of 5,246 men with pre-existing CAD or multiple risk factors and total testosterone <300
- Transdermal testosterone gel adjusted to on-treatment level of 350-750.
- Primary outcome: **NO INCREASE** in cardiovascular death or major adverse cardiovascular events.



Acknowledgments

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