

# Subclinical Hypothyroidism

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- Disclosure - I am on the Speaker's Bureau for Abbott. I have limited my presentation to evidence that is supported by peer-reviewed studies and will provide a balanced view of available therapeutic options, where applicable.

# ~~Subclinical Hypothyroidism~~

- SH can also be defined by an elevated TSH with normal levels of  $T_4$ , Free  $T_4$ , and  $T_3$ .
- This later definition does not mention the presence or absence of symptoms.

# Subclinical Hypothyroidism

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- Affects 5 – 10% of the general population
- Affects 10% of the elderly population
- More common in females

## Confounding Factors

Patients with SCH have higher BMI, increased frequency of hyperlipidemia, diabetes and hypertension compared to euthyroid patients.

# Case Presentation

34 year old woman with complains of fatigue, dry skin, hair loss, constipation and cold intolerance. TSH = 4.0.

Trial of treatment or not?

# Screening For Thyroid Disease

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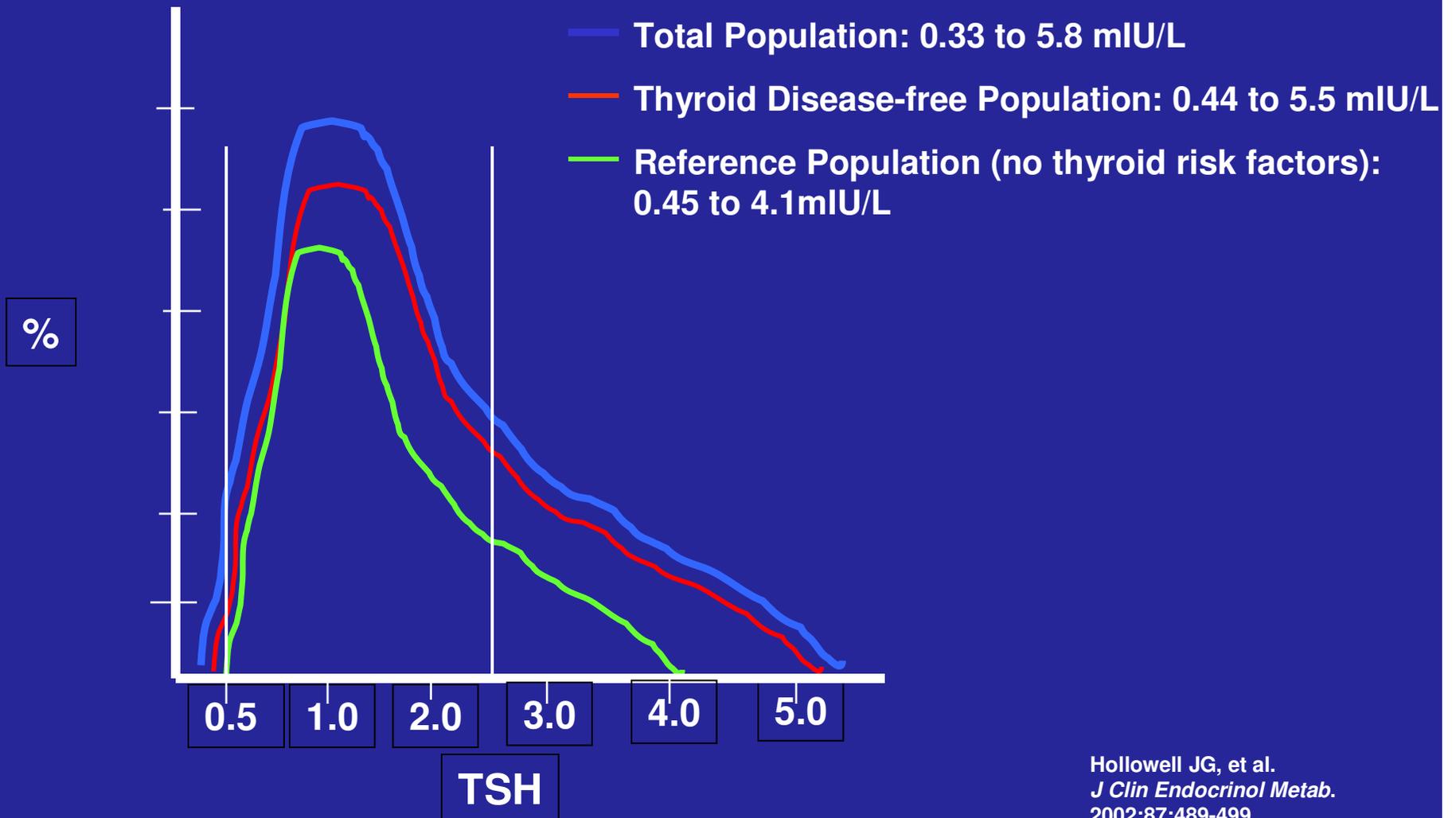
**Normal TSH = normal thyroid function**

**Low TSH = Hyperthyroidism.**

**High TSH = Primary Hypothyroidism**

- **When the TSH is abnormal, follow with a serum Free T4 for confirmation.**

# NHANES III: TSH Normal Range



# Recommended TSH Normals

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- Most labs .4 – 4.5
- AACE .3 – 3.0
- NACB .5 – 2.0

# **Routine TSH Screening Recommendations**

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- **American Academy of Family Physicians – patients over age 60 or with risk factors**
- **American Thyroid Association – all patients over 35 every 5 years**
- **AACE – women before or during first trimester of pregnancy**
- **American College of Physicians – women over 50**

# What Group of Patients Should Always Be Treated For Subclinical Hypothyroidism?

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- Neonates
- Teenagers who have not closed their epiphyses
- Pregnant women
- Elderly patients over the age of 70

# Thyroid Medication in Pregnancy

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- 85% of women with thyroid dysfunction require a substantial increase in their usual dose
- Dose requirements often increase 30 – 50%
- Median time of dose increase is 6 – 8 weeks and plateaus at 16 – 20 weeks

# **Pregnancy Outcomes – Subclinical Hypothyroidism**

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- **Increase pre-eclampsia**
- **Increase placental abruption**
- **Increase pre-term delivery**
- **Low birth weight**
- **Questionable effect on IQ**
- **Increase respiratory distress**

# Miscarriage Rate with Subclinical Hypothyroidism

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- TSH .4 – 2.5 vs 2.6 – 4.0

Twice the miscarriage rate!!

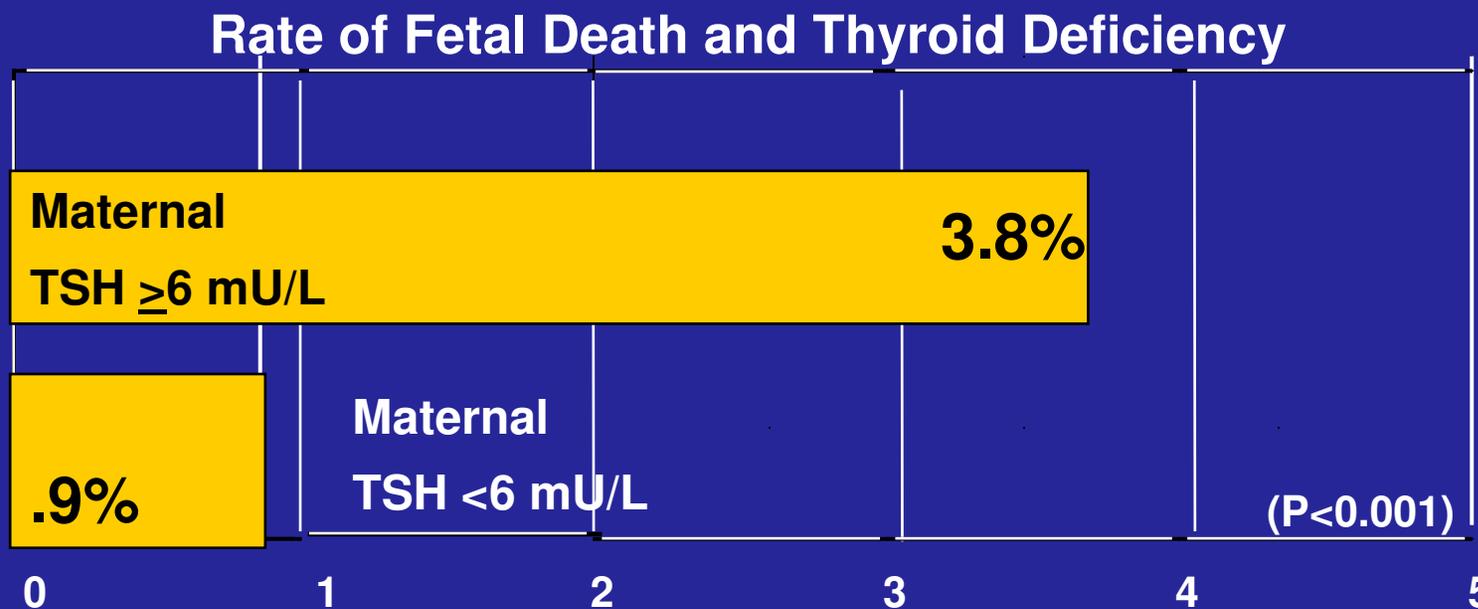
Goal: First trimester TSH <2.5  
Second and third trimester TSH <3.0

Increase miscarriage rate with  
positive thyroid antibodies

# Consequences of Mild Hypothyroidism

## Fetal Death

- TSH  $\geq 6$  mU/L in 2.2% of mothers with singleton pregnancies (n=9,403)
- Fetal death rate 4x greater with high TSH
- Other pregnancy complications were equivalent



# Example:

- 85 y.o. woman who lives by herself. She had recently lost her husband. She was tired, somnolent and forgetful. No goiter.
- TSH screen: 7.8 mU/L ( n: 0.4-5 )
- Free T4: 1.0 ng/dL ( n: 0.8-1.8)
- Treatment?

# 85 Year Old Woman

- **Treat with thyroxine**
- **Treat with Armour thyroid**
- **Do not treat**
- **Refer to endocrinology**

# Subclinical Hypothyroidism

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- She was given 50 mcg of Levothyroxine daily.

# Subclinical Hypothyroidism

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- The patient was admitted 6 weeks later with severe dyspnea. She was in A-Fib and congestive heart failure.
- Serum TSH < 0.01 mU/L (n: 0.4-5)
- Serum free T4 high at 2.3 ng/dL (0.8-1.8)

# Subclinical Hypothyroidism

- **Three months later on no thyroid hormone: TSH: 2.3 uU/ml, normal**  
**Free T4: 1.3 ng/dL, normal**

# Subclinical Hypothyroidism

- **10% of the population in the sixth decade have subclinical hypothyroidism.**

## **Of Those:**

- **5% per year progress to overt hypothyroidism**
- **In 20-50%, the TSH returns to normal**
- **The rest stay the same**

# **Should we have an age adjusted TSH?**

**Some data support a TSH of 7.0 in healthy elderly population.**

## Why Treat Subclinical Hypothyroidism?

High proportion of individuals with SCH are treated with thyroxine for subjective effect on hypothyroid symptoms.

<u>SCH</u>	<u>Getting Old</u>
1. Tired	Yes
2. Weight gain	Yes
3. Myalgias	Yes
4. Muscle cramps	Yes
5. Constipation	Yes
6. Poor nails/hair	Yes
7. Hair loss	Yes
8. Depression/cognitive decline	Yes

Perceived amelioration of CV risk factors including hyperlipidemia.

# **GPRD – World's Largest Data Base 2001 - 2009**

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- **Age greater than 40**
- **TSH 5 – 10**
- **Normal free T-4**
- **Excluded patients with cerebrovascular or IHD**
- **Age 40 – 70 or over 70**
- **Thyroxine vs placebo**

## GPRD Findings

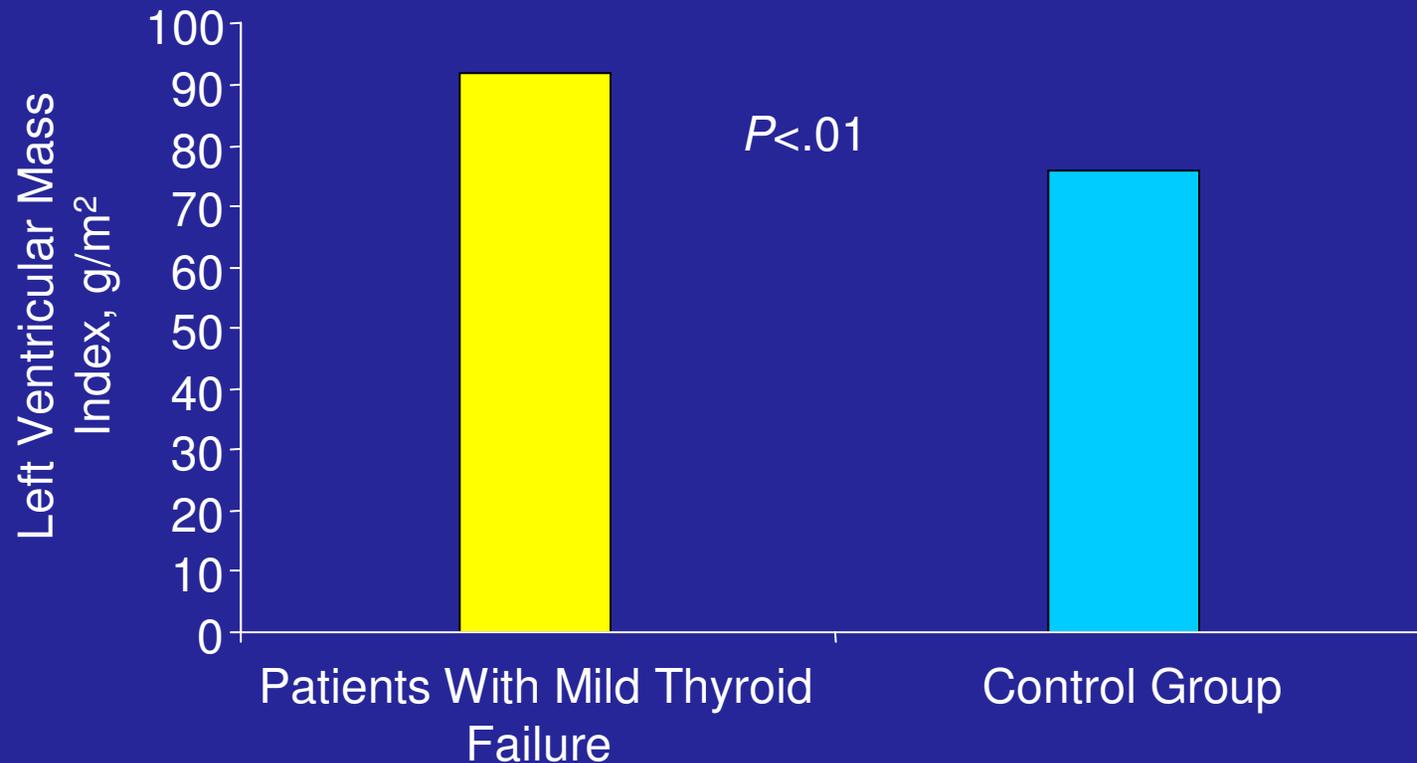
- **38.4% of untreated patients reverted to a euthyroid state**
- **2.5% developed subclinical hyperthyroidism**
- **1.3% became overtly hypothyroid**

# **Depression, Anxiety and Cognitive Function and Subclinical Hypo and Hyperthyroidism**

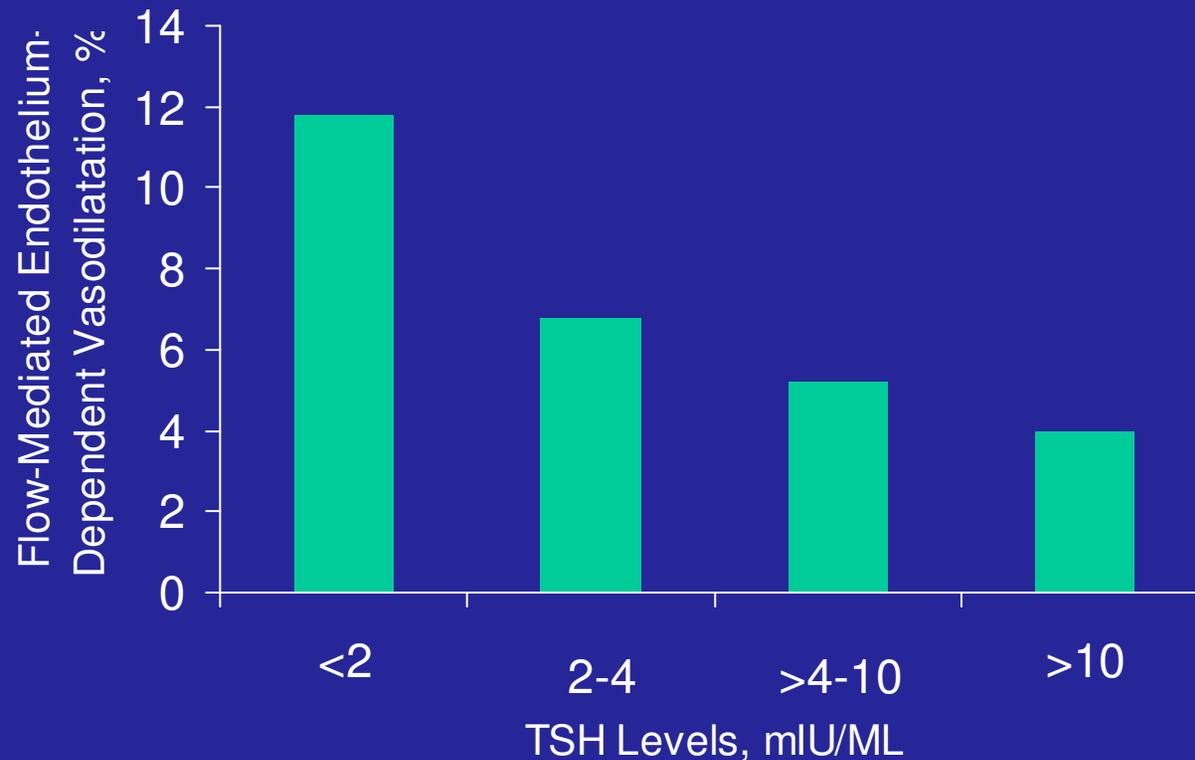
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- **5,868 patients age 65 – 98**
- **No increased depression with subclinical hypothyroidism**
- **No increased anxiety with subclinical hypothyroidism**
- **No decreased cognitive function**

# Increased Left Ventricular Mass With Mild Thyroid Failure



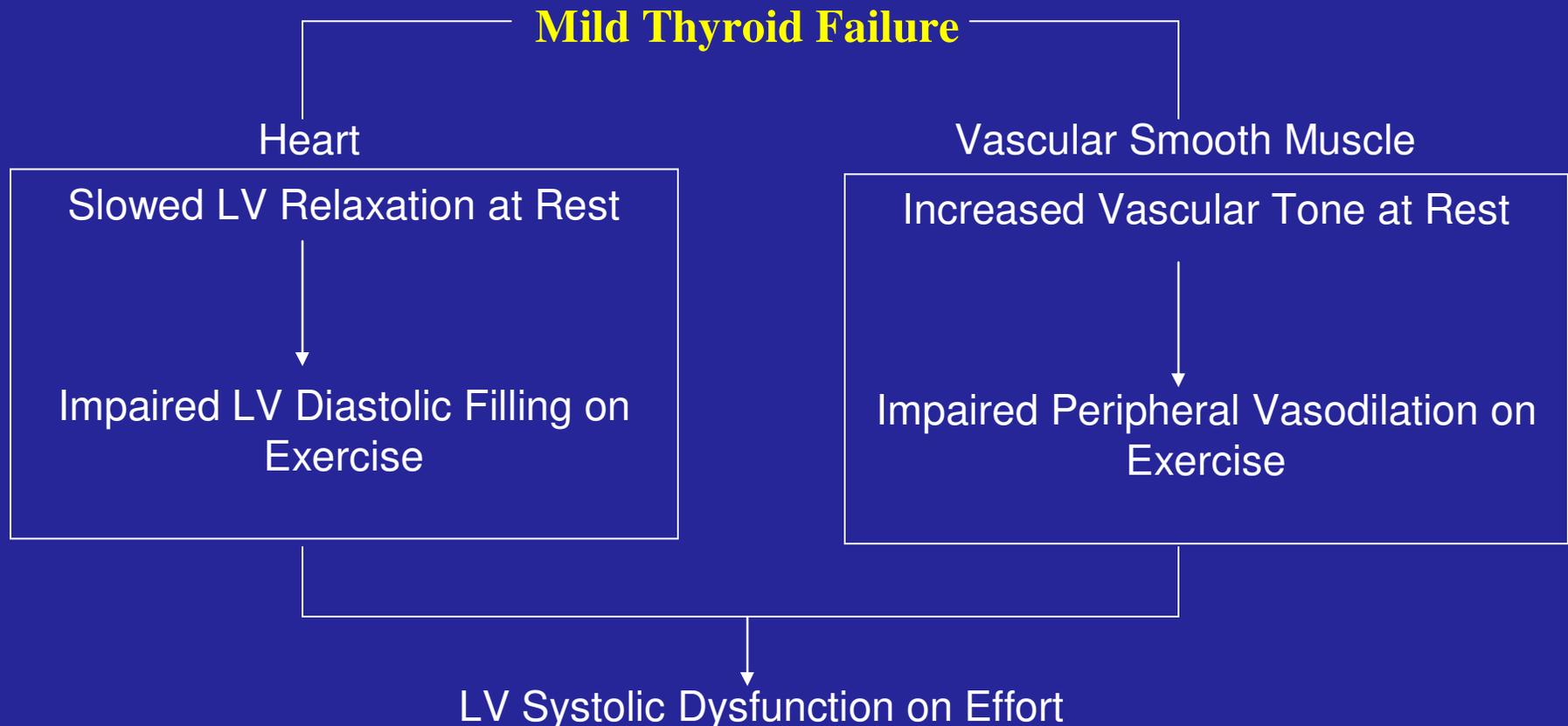
# Endothelial Function in Patients With Mild Thyroid Failure and CAD Risk



Flow-mediated vasodilatation is impaired in patients with mild thyroid failure, which could contribute to the development of CAD.

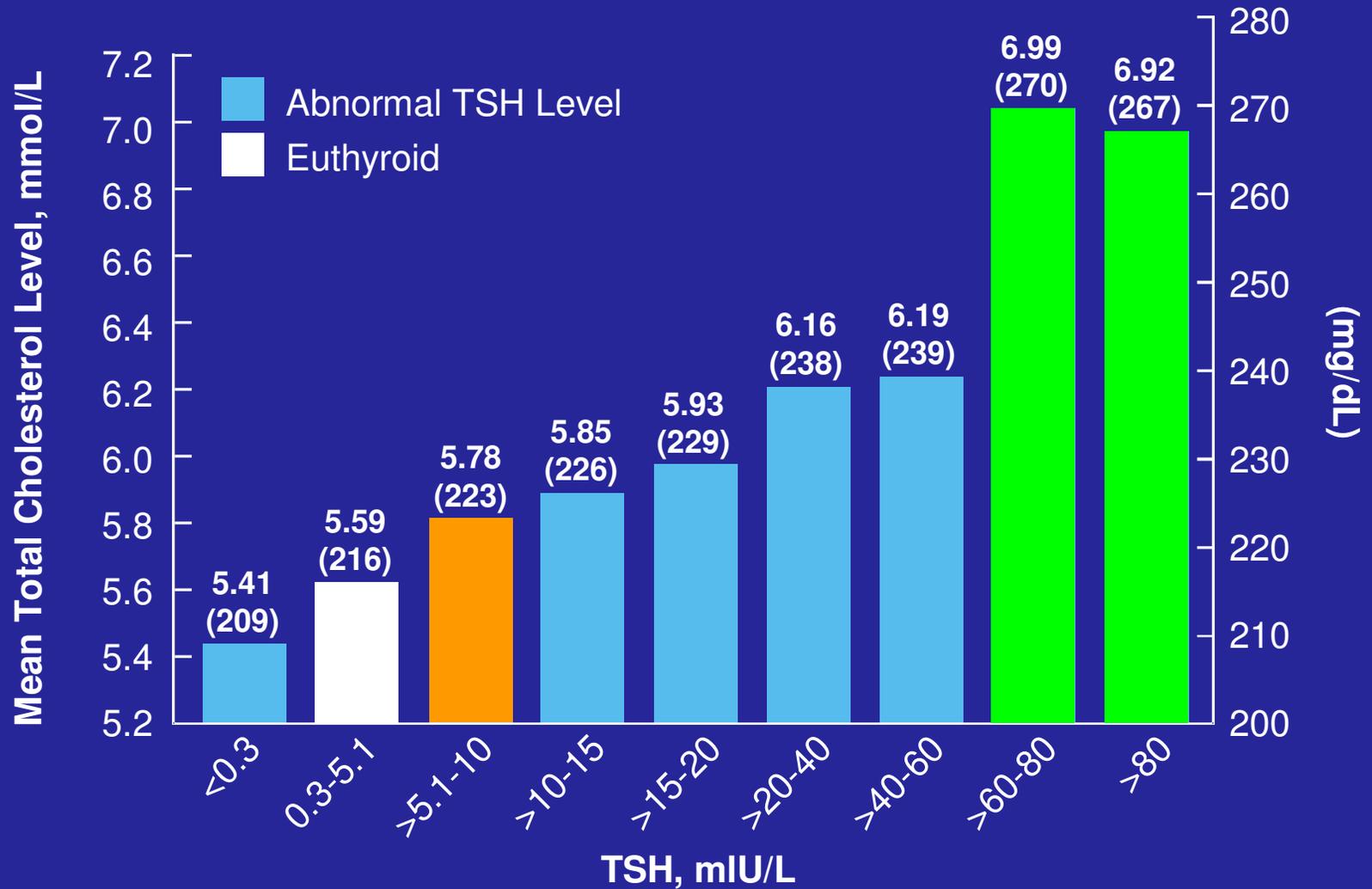
# Slowed Left Ventricular Relaxation in Mild Thyroid Failure

Cardiovascular Abnormalities Leading to LV Dysfunction on Effort in Mild Thyroid Failure

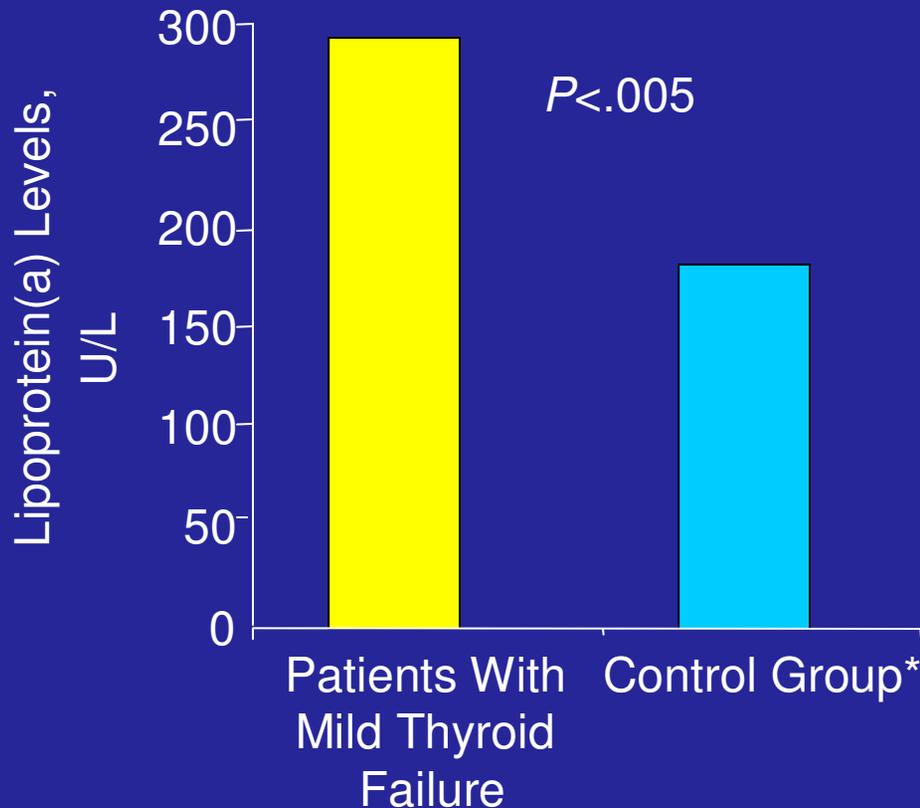


# Consequences of Hypothyroidism

## Cholesterol - Mild & Overt



# Elevated Lipoprotein(a) Levels Increase CAD Risk



- Elevated lipoprotein(a) levels are associated with an increased risk of CAD development and MI occurrence
- Patients with mild thyroid failure have higher lipoprotein(a) levels, which increases their risk of CAD

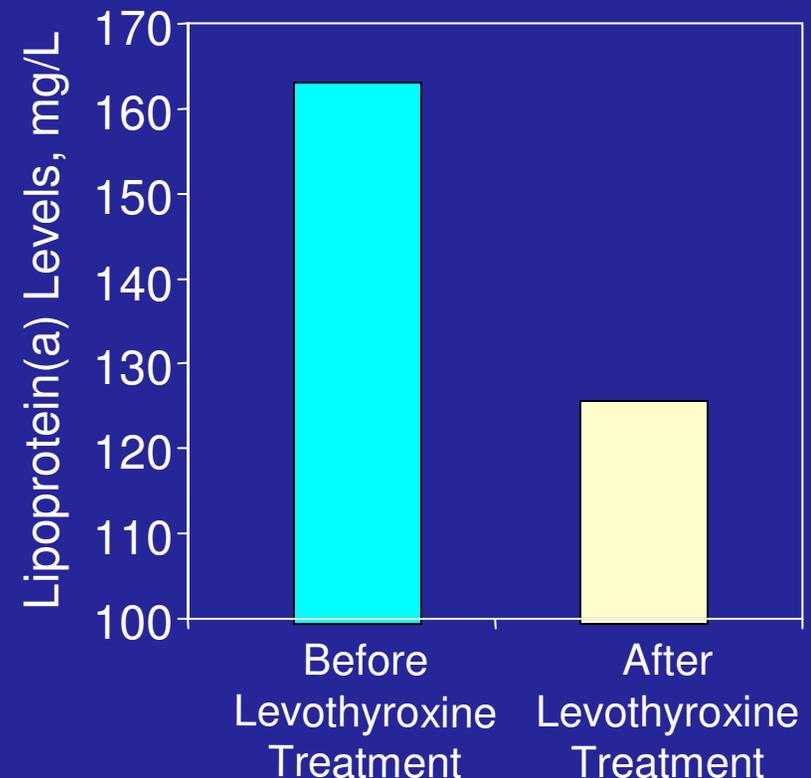
\*Control group consisted of age- and gender-matched healthy patients.

PROCAM. Lipoprotein(a) and cardiovascular risk.  
Available at: [http://www.chd-taskforce.de/pdf/sk\\_procam\\_03.pdf](http://www.chd-taskforce.de/pdf/sk_procam_03.pdf).

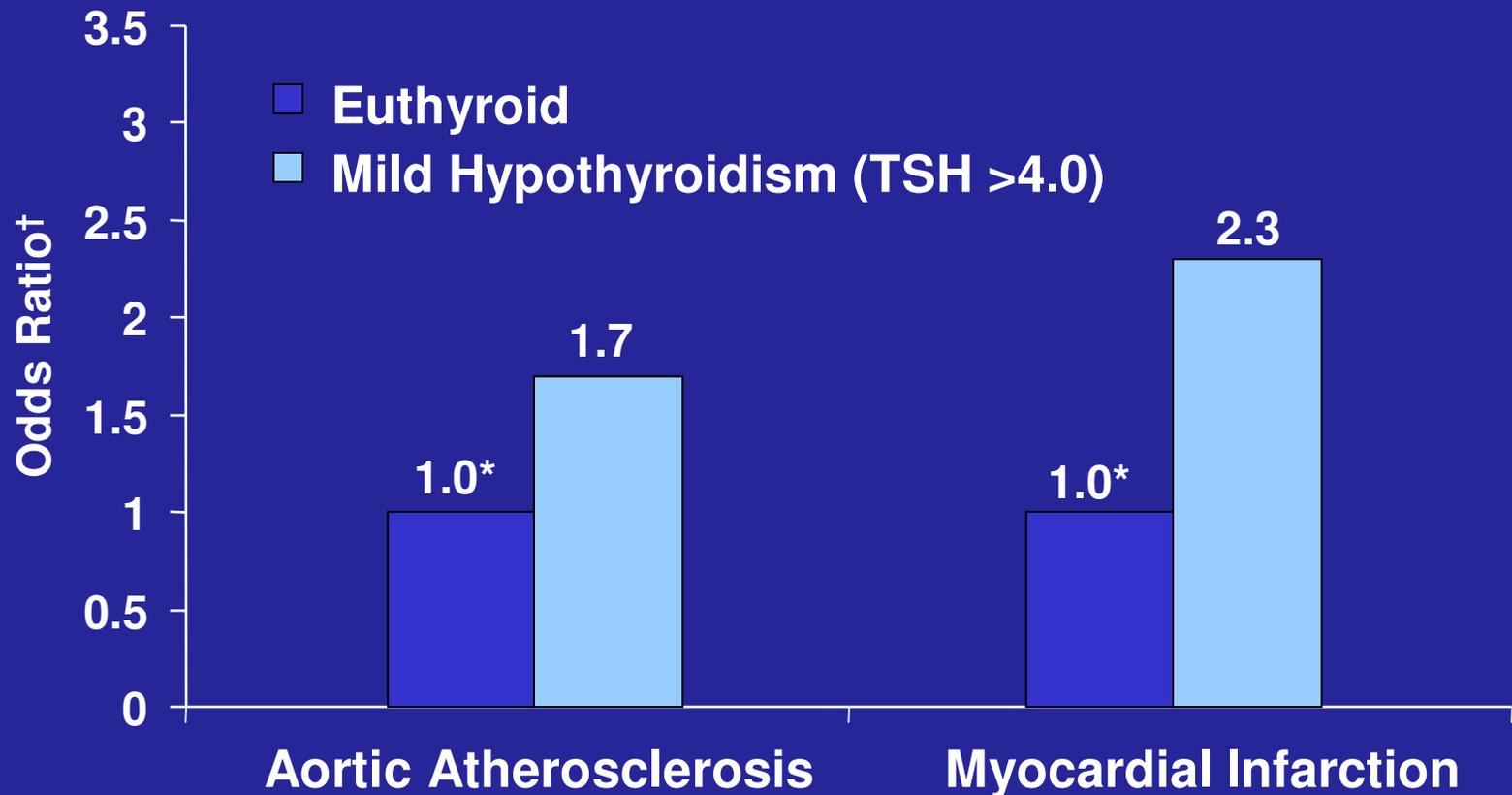
Accessed April 17, 2003.  
Kung AW, et al. *Clin Endocrinol*. 1995;43:445-449.

# Levothyroxine Treatment Reduces Lipoprotein(a) Levels in Patients With Mild Thyroid Failure

- Lipoprotein(a) levels in patients with mild thyroid failure had a statistically significant ( $P < .001$ ) mean decrease after treatment with levothyroxine
- Levothyroxine therapy is effective in lowering lipoprotein(a) levels and had beneficial effects on lipid profiles



# Consequences of Mild Hypothyroidism Atherosclerosis



# **Cardiac Benefits of Thyroxine Treatment in SCH**

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**Decrease LDL**

**Decrease total cholesterol**

**Improve endothelial function**

**Decrease carotid intimal medial  
thickness**

**Improved left ventricular diastolic  
function**

# Subclinical Thyroid Disease – Risk of CHF

<u>TSH</u>	<u>Hazard Ratio</u>
• 7 – 9.9	1.01
• Over 10	1.86
• .1 - .4	1.31

# Subclinical Hypothyroidism – Cardiovascular Health Study

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- Retrospective, age over 65 years, 4863 patients
- TSH    4.5 - 6.9  
          7.0 - 9.9  
          10.0 - 19.9    > 679 patients
- No increase in CHD, CVD death or heart failure in any of the groups

# Subclinical Hypothyroidism – Cardiovascular Health Study

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# Subclinical Hypothyroidism

- Increase TSH with normal T4/T3
- 10% of elderly population
- Recent Meta-analysis confirms increased CV events in young to middle age adults
- We lack proof that treatment of SCH is efficacious

# **Subclinical Hypothyroidism – Development of Ischemic Heart Disease**

## Young Patients 40 - 70 years

- 68 of 1634 patients treated with thyroxine
- 97 of 1459 untreated patients

## Older Patients over 70 years

- 104 of 819 patients treated with thyroxine
- 88 of 823 untreated patients

# Subclinical Hypothyroidism- Development of Ischemic Heart Disease

## Patients age 40 - 70

39% decrease cardiovascular disease

64% decrease all-cause mortality

- 46% decrease circulatory disorders
- 41% decrease malignant neoplasms
- Non-significant 24% decrease A-fib

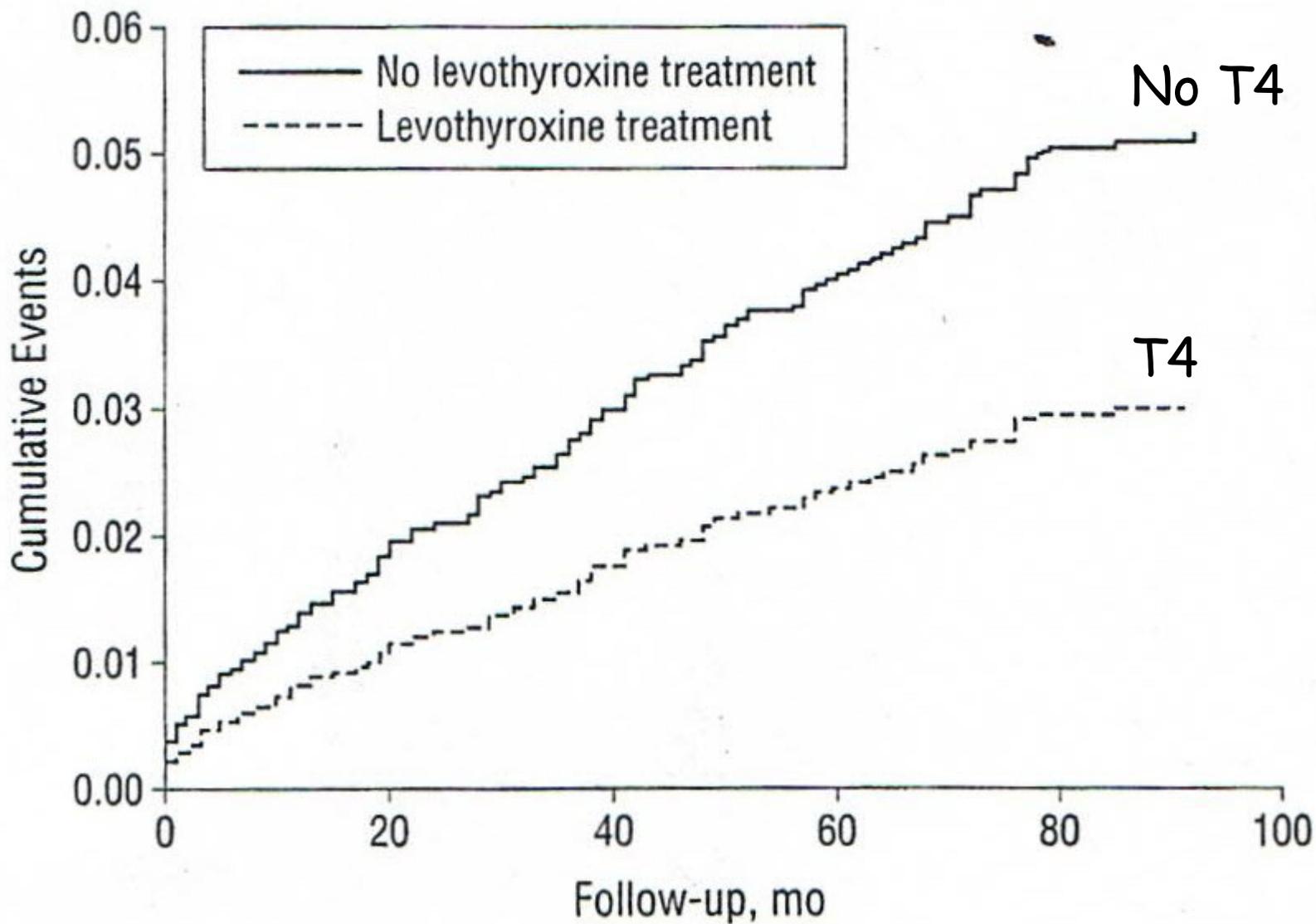
## Patients age over 70

No change IHD

No change all-cause mortality

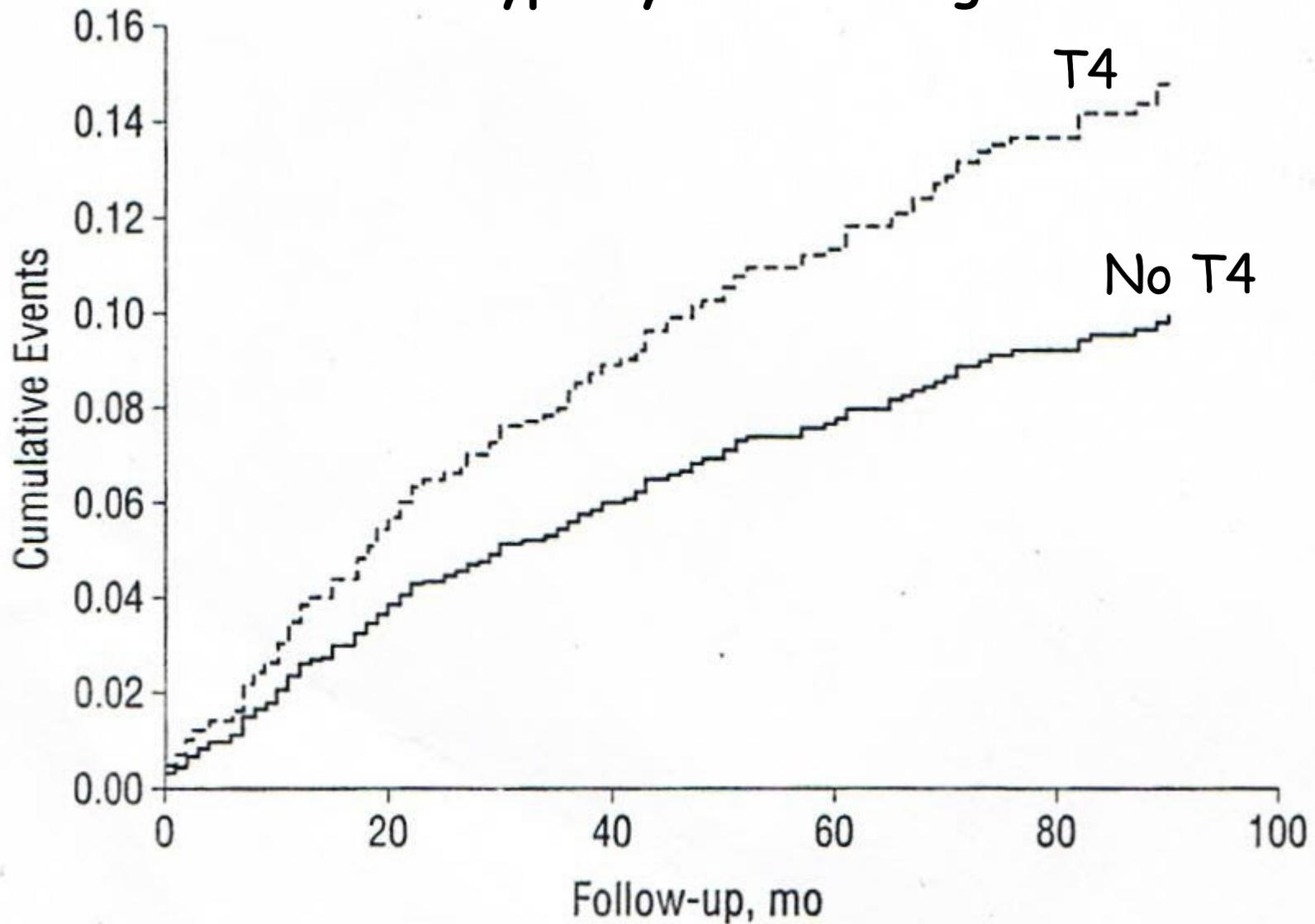
A

# Subclinical Hypothyroidism - Age Under 70



B

## Subclinical Hypothyroidism - Age Over 70



Events	74	117	139	155	192
Participants at risk	1568	1525	1503	1487	1450

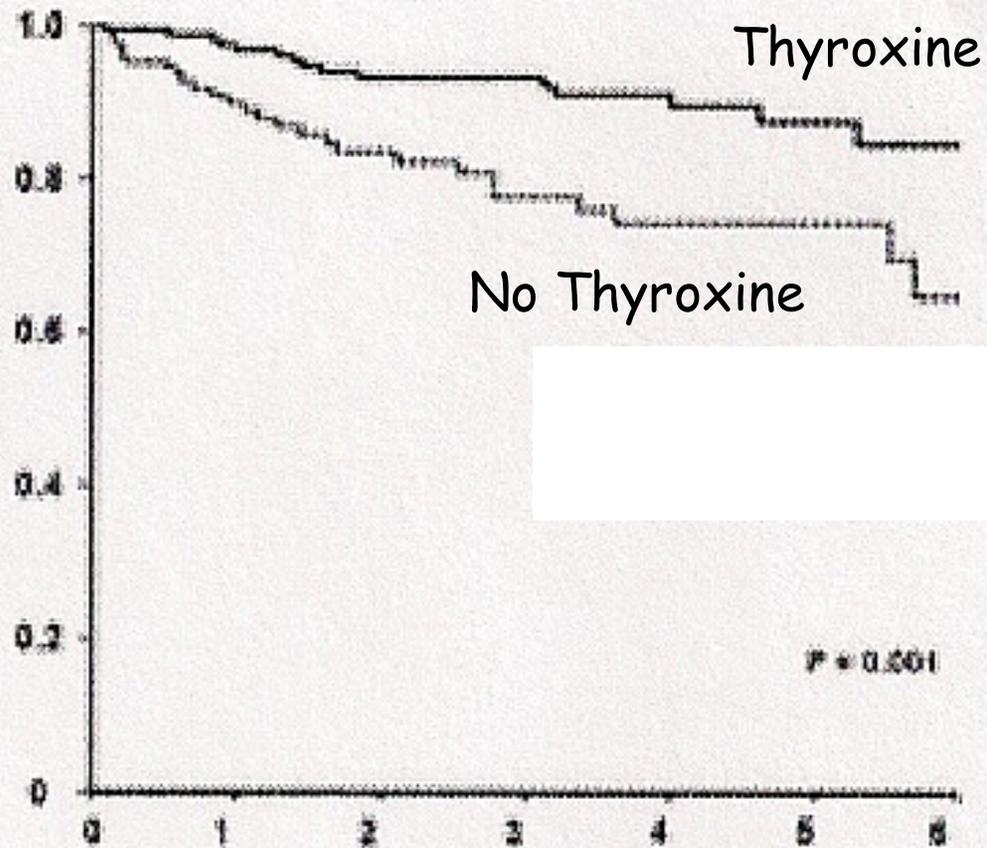
# Subclinical Hypothyroidism – Effects of Treatment on GFR

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- Decrease in GFR 50% or progression to ESRD
- 180 patients treated with thyroxine and 129 patients without thyroxine
- Follow-up 34 +/- 24 months

HR for treatment = .28

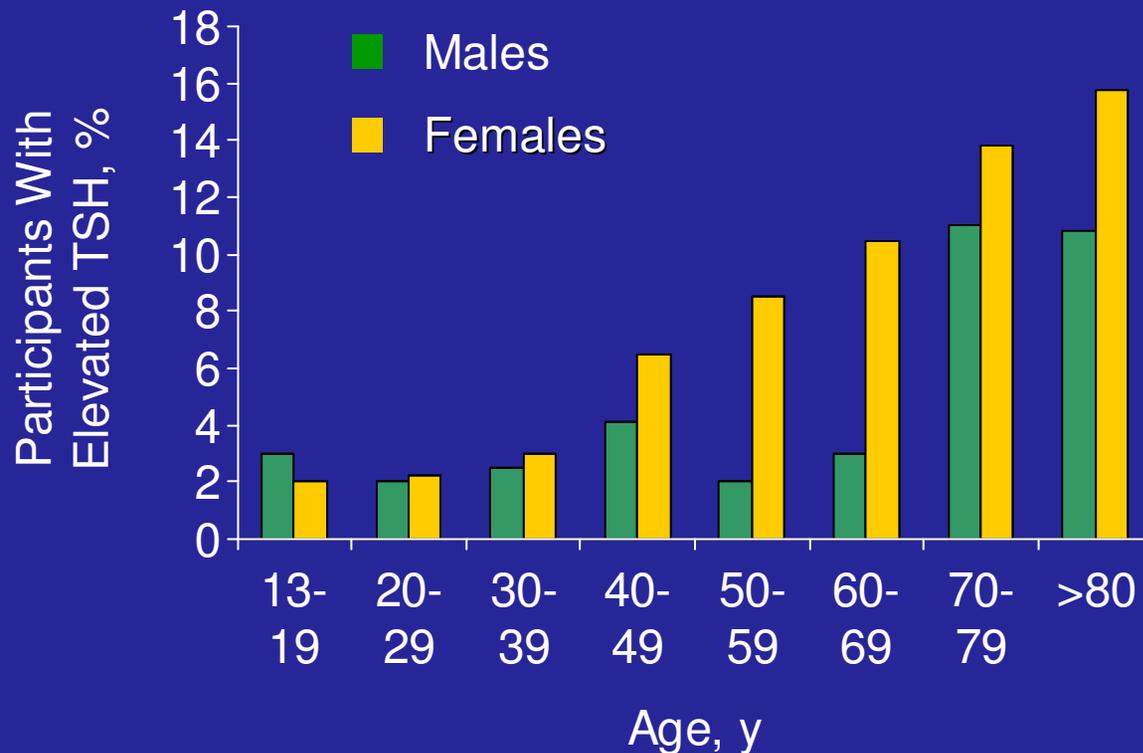
Renal event - free survival



Duration (years)

# Prevalence of Elevated Serum TSH by Decade of Age and Gender

NHANES III Study (N=17 353)



- At <40 years of age, prevalence is relatively low and similar between males and females
- At  $\geq 40$  years of age, a higher percentage of female patients have elevated TSH levels

# **Subclinical Hypothyroidism In The Elderly**

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- **May not have any adverse effects**
- **One study of a healthy population over 85 years showed SCH associated with increased longevity**

“One of the reasons that treating older patients with subclinical hypothyroidism might not help them is because there is nothing wrong with them in the first place.”

David Cooper, M. D.

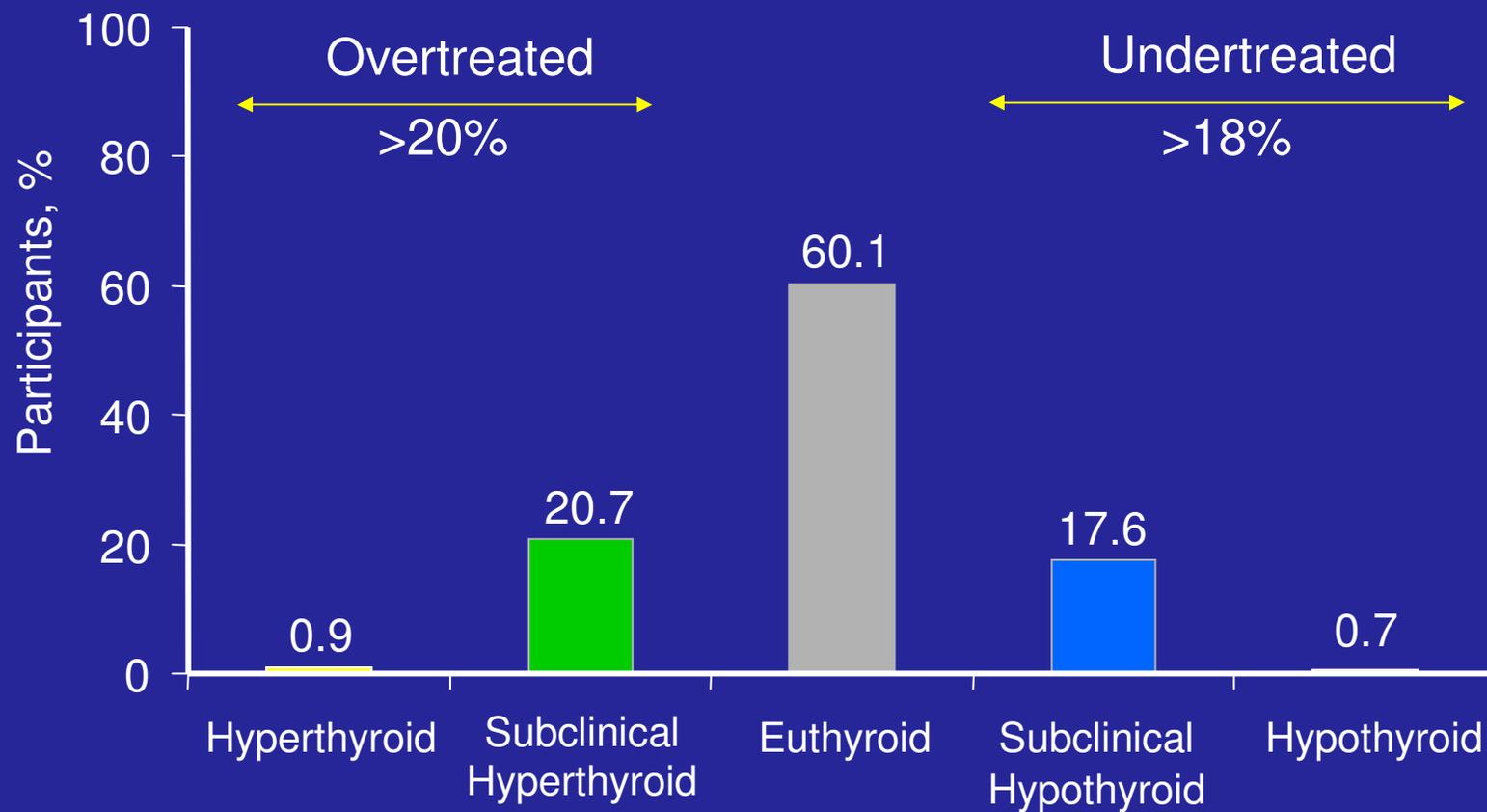
# What Percent of Patients on Thyroxine have a Suppressed TSH?

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- 15%
- 20%
- 40%
- 45%

# Thyroid Status of Treated Patients

## Colorado Thyroid Disease Prevalence Study



# Consequences of Subclinical Hypothyroidism

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- 3 – 20% will develop overt hypothyroidism
- Risk is especially high in those with a goiter or thyroid antibodies

Trust Trial... 3,000 Patients Over Age 65

Thyroid Hormone Replacement for  
Subclinical Hypothyroidism Trial

# Subclinical Hypothyroidism- Who To Treat?

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- TSH >10
- Positive thyroid antibodies
- Goiter
- Age <70 years
- Pregnant patients
- Renal insufficiency
- ? Children/ adolescents

## Example:

- **85 y.o. woman who lives by herself. She had recently lost her husband. She was tired, somnolent and forgetful. No goiter.**
- **TSH screen: 7.8 mU/L ( n: 0.4-5 )**
- **Free T4: 1.0 ng/dL ( n: 0.8-1.8)**
- **Treatment?**

?????Questions?????

