Thyroid Disease in Cardiovascular Patients

Stuart R. Chipkin, MD
Research Professor,
School of Public Health and Health Sciences
University of Massachusetts

Disclosure

Stuart R. Chipkin, MD

— Nothing to disclose

Brief Description of Thyroid Tests

- **TSH- pituitary hormone reflects thyroid status**
  - Affected by pituitary status, pressors, steroids, dilantin and other medications
  - Single best measure of STEADY STATE thyroid status
  - Generally should wait 2-3 months in-between tests
- **T4- larger pool of hormone released from thyroid**
  - Carried by binding proteins
  - fT4 represents“free” hormone but is not a direct measure
  - Total T4 = free + protein-bound
  - Converted in peripheral tissues to T3

Brief Description of Thyroid Tests

- **TSH- pituitary hormone reflects thyroid status**
- **T4- larger pool of hormone released from thyroid**
- **T3- smaller pool of more active hormone**
  - More variable serum levels
  - Rarely is made in excess of T4 (T3 toxicosis)
- **Thyroid peroxidase Antibodies (TPO- Ab)**
  - Antibody against enzyme in gland
  - Often positive in autoimmune thyroid disease
- **Thyroglobulin Antibodies(TG-Ab)**
  - Antibody against protein made in gland
  - Often positive in autoimmune thyroid disease

Brief Description of Thyroid Tests

- **TSH- pituitary hormone reflects thyroid status**
- **T4- larger pool of hormone released from thyroid**
- **T3- smaller pool of more active hormone**
- **Thyroid peroxidase Antibodies (TPO- Ab)**
- **Thyroglobulin Antibodies(TG-Ab)**
- **Thyrotropin Receptor Antibodies (TrAb)**
  - Antibodies which stimulate TSH receptor on thyroid cells
  - Often positive in Graves' Disease
- **Thyroid Uptake and Scan**
  - Measures percent uptake of tracer amount of I-131
  - High if endogenous production (Graves)
  - Low in inflammatory states (thyroiditis)

Case # 1

71 year old woman with palpitations.

- Holter, ETT, echocardiogram all benign.
- Follow-up, labs: TSH = 0.05 mIU/ml (range is 0.5-4.0).
- No complaints of weight loss, heat intolerance, tremor, nervousness, new anxiety, loose bowels. No family history of thyroid disease

Examination: pulse=72; BP=128/84; BMI=27.4 kg/m^2

- No lid lag or stare. No goiter. No bruits.
- Lungs: clear; Heart: S1 S2 normal.
- Extremities: no edema, good pulses
- Reflexes normal; No tremor.

71 y.o. woman with palpitations, benign cardiac work-up and TSH of 0.07. Examination normal

Repeat TSH=0.03 mIU/ml and free T4= 1.3 ng/dl (range=0.5-1.5 ng/dl).

Would you recommend:

A) Radioiodine uptake and scan
B) Thyroid peroxidase antibodies
C) Thyroglobulin antibodies
D) Thyrotropin receptor antibodies
E) All of the above
F) Further cardiac diagnostic testing
G) No further testing

71 y.o. woman with palpitations
Examination normal and benign cardiac work-up with low TSH and normal T4.

- T3 is in normal range
- TPO antibodies are positive
- Radioactive iodine uptake is 22% (normal is up to 35%)

Your recommendation would be:

A) No further work-up
B) Repeat thyroid tests yearly
C) Treat with radioactive iodine
D) Treat with methimazole/PTU
E) Recommend surgery (thyroidectomy)
F) Treat with a beta-blocker

Subclinical Hyperthyroidism

- Prevalence of 0.7-12.4%
  - Higher frequency when using 0.4-0.5 vs. 0.1 mIU/L
  - More common in women than men
  - More common in elderly
  - 10-30% are patients taking thyroid hormone
- Progression to overt hyperthyroidism= 1-5% per year
  - More often in elderly
  - More often with lower TSH values

Cardiovascular Consequences Subclinical Hyperthyroidism

- Impaired exercise capacity
  - Reduced tolerance, maximal VO_{2max} and anaerobic threshold
  - Reduction in peak workload
  - Reduction in ejection fraction during exercise
- Increased heart rate
- Increased left ventricular mass
  - Impaired left ventricular diastolic filling
- Increased risk for atrial arrhythmias

Aras D et al. Int J Cardiol 99:59–64, 2005
Biondi B et al. Cardiologia 44:443–449, 1999
Shargorodsky M et al. Thyroid 16:381–386, 2006
Biondi B et al. JCEM; 81:4224–4228, 1996
Mercuro G et al. JCEM 85:159–164, 2000

Atrial arrhythmias

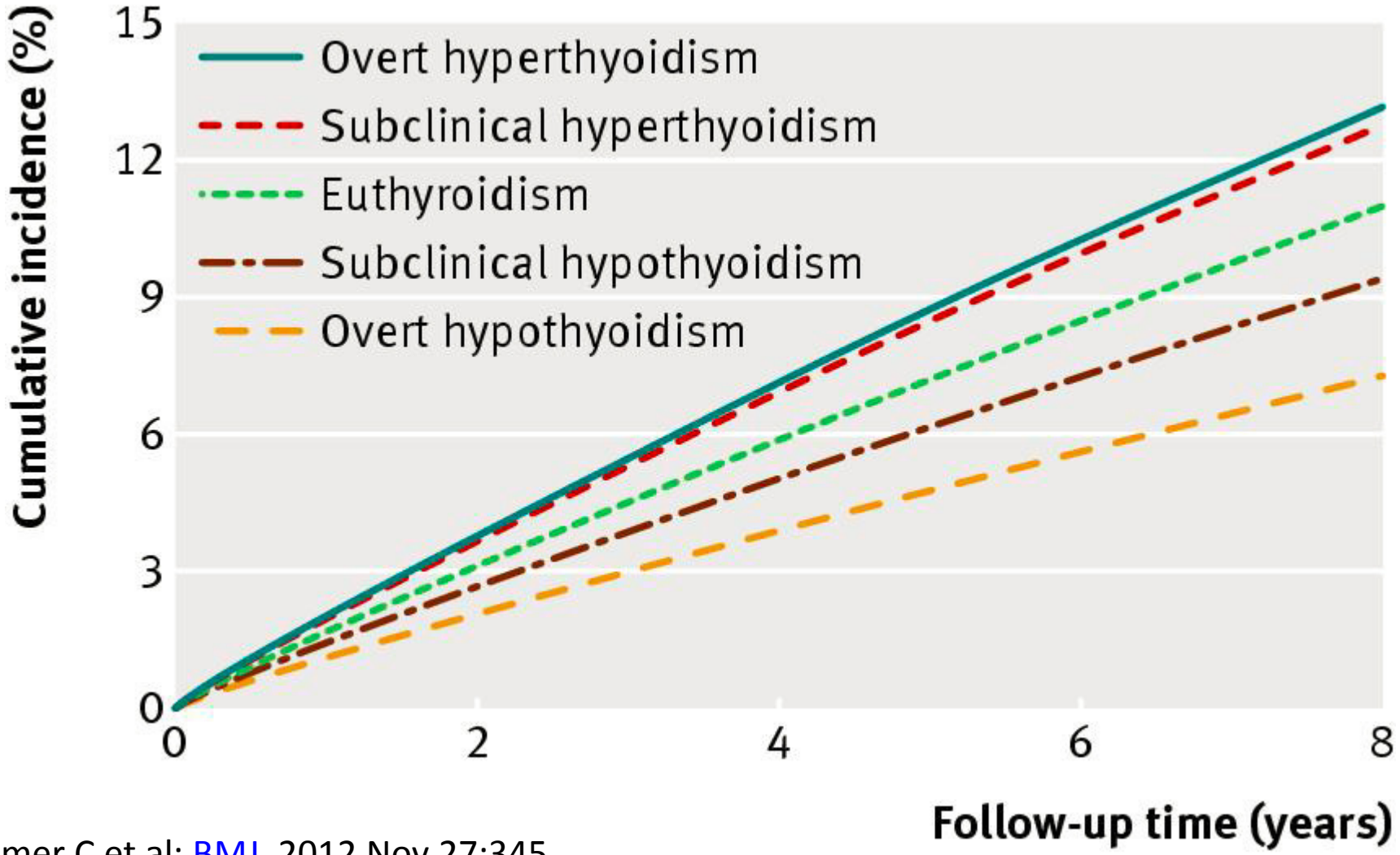
- Risk for atrial fibrillation (2-3 fold higher)
  - Frequency
    - Normal thyroid function= 2.3%
    - Overt hyperthyroidism= 13.8%
    - Subclinical hyperthyroidism= 12.7%
  - Risk factors:
    - Higher maximum P wave duration
    - Increased P wave dispersion
- Re-entrant atrioventricular nodal tachycardia
  - Short P-R interval

Biondi B et al. JCEM 85:4701–4705, 2003 Auer JA et al. Am Heart J 142:838–842, 2001
Tsuji H et al. Circulation 94:2850–2855, 1996 Sawin CT, et al. NEJM; 331:1249–1252, 1994

Subclinical Hyperthyroidism and Cardiovascular Risk

Study	Sample size	TSH mIU/L	Age (years)	Follow-up (years)	Outcome
Sawin (1994)	248/1424	0.1-0.4 <0.1	>60	10	No increased mortality ↑ A. fib (RR=1.6 and 3.1)
Parle (2001)	71/1191	<0.5	>60	10	– Mortality
Auer (2001)	613/23,638	<0.4	>45	13	↑ A. fib (5x)
Gussekloo (2004)	17/599	<0.3	85-89	4	↑ CV mortality
Walsh (2005)	39/2108	0.1-0.4 <0.1	51 ± 15	20	No increased mortality
Van den Beld (2005)	44/403	<0.4	73-94	4	TSH not related to mortality fT4 correlated with mortality
Cappola (2006)	47/3233	0.1-0.4 <0.1	74 ± 7	13	No increased CV death; ↑ A. fib
Selmer (2012)	435/6276	0.1-0.2 <0.1	48.9	10	RR= 1.16 RR= 1.41

Atrial Fibrillation in Danish Community



Selmer C et al; BMJ. 2012 Nov 27;345

Quality of Evidence- Subclinical Hyperthyroidism

	Strength of Association		Benefits of Treatment	
Clinical Condition	**TSH= 0.1-0.45**	**TSH < 0.1**	**TSH= 0.1-0.45**	**TSH < 0.1**
Progression to Overt Hyper	Insufficient	Good	None	None
Adverse Cardiac Endpoints (not A Fib)	Fair (data did not distinguish TSH ranges)		None	None
Atrial Fibrillation	Insufficient	Good	None	None
Cardiac Dysfunction	Insufficient	Fair	Insufficient (data did not distinguish TSH ranges)	
Systemic Hyperthyroid & Neuropsych Sx	Insufficient	Insufficient	None	Insufficient
Reduced Bone Density	None	Fair (post-menopausal)	None	Fair
Fractures	None	Insufficient	None	None

Surks MI, et al; JAMA 291:228-238, 2004

71 y.o. woman with palpitations, benign cardiac work-up and TSH of 0.05 mIU/ml and normal T4. Examination normal

- T3 is in normal range
- TPO antibodies are positive
- Radioactive iodine uptake is 22% (normal is up to 35%)

With this new information, now your recommendation would be:

A) No further work-up
B) Repeat thyroid tests yearly
C) Treat with radioactive iodine
D) Treat with methimazole/PTU
E) Recommend surgery for thyroidectomy
F) Treat with a beta-blocker

Alternative case

- Same as before- Woman with palpitations, benign cardiac work-up, normal examination but now:
- Age is now 45
- TSH= 0.3 mIU/L (free T4 and thyroid scan/uptake are still normal)
- Your recommendation would be:

A) No further work-up
B) Repeat thyroid tests every 6-12 months
C) Treat with radioactive iodine
D) Treat with methimazole/PTU
E) Recommend surgery for thyroidectomy
F) Treat with a beta-blocker

Recommendations: Subclinical Hyperthyroidism

	TSH < 0.1	TSH = 0.1-0.4
AGE OVER 65	TREAT DEFINITIVELY - RADIOACTIVE IODINE - ANTI-THYROID MEDS - SURGERY	TREAT - IF PRESENCE OF CV RISK
AGE UNDER 65	TREAT - IF SYMPTOMS OR CV RISK	MONITOR

European Thyroid Association
Eur Thyroid J. 2015 Sep; 4(3): 149–163.

Case # 2

- 60 year old woman is referred to you for treatment of lipids
- PCP noted hyperlipidemia and she is strongly against taking statin medications.
  - History hypertension on HCTZ. Non-smoker. Father had a CABG (age 62) and mother has HTN and high cholesterol.
  - Patient is trying to exercise more since being told of high cholesterol. Walks 30 minutes per day, three times per week (about 2 miles). Has also made some dietary changes (increasing dietary fiber).
- No excess fatigue, no recent weight gain (steady 15-20 lbs increase since going through menopause), no constipation, no excess dry skin, no cold intolerance. Some difficulty concentrating- attributes to post-menopause.
- No complaints of chest/arm/jaw pain or pressure. No SOB or edema. No symptoms of claudication or TIA.

60 y.o. woman, HTN (HCTZ), non-smoker, peri-menopausal weight gain, trouble concentrating

- Examination: Pulse=80, BP=138/88. BMI=29.5 kg/m^2. Eye movements intact. No carotid bruits or JVD. Mildly enlarged thyroid. Lungs: clear. Heart: S1 S2 with 2/6 systolic murmur. Abdomen: benign and no pedal edema. Reflexes intact (not hung-up).
- Laboratory studies:
  - Electrolytes normal (K=4.0, BUN/creat=18/0.8).
  - LFT's normal.
  - Total cholesterol=230 mg/dl; Triglycerides=165 mg/dl; HDL=48 mg/dl; LDL= 149 mg/dl.
  - TSH= 9 mU/ml (range=0.5-4.0 mU/ml).
  - Free T4= 0.7 (range=0.5-1.54 ng/dl).

How many of you have:

- Dry skin
- Poor memory
- Slow thinking
- Muscle weakness or cramping
- Fatigue
- Cold intolerance
- Puffy eyes
- Constipation
- Hoarseness

A) None of these

B) One of these

C) Two of these

D) Three or more of these

Subclinical Hypothyroidism

- Using a list of symptoms:
  - Dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramping, cold intolerance, puffy eyes, constipation, hoarseness
  - Euthyroid: 12.1%
  - Overt hypothyroid: 16.6%
  - "Mild" hypothyroidism: 13.8% ($p<0.05$ vs. euthyroid)
- Change in symptoms increased the likelihood of thyroid disease
- Community survey of woman
  - Subclinical hypothyroidism not associated with decrease in well-being or quality of life.

Canaris GJ et al; J Gen Intern Med 12:544–550, 1997
Bell RJ, et al; Clin Endocrinol 66:548–556, 2007

Impact of Hypothyroidism on Heart
(Similar changes in Subclinical Hypothyroidism)

- Increased systemic vascular resistance
- Diastolic dysfunction
- Reduced systolic function
- Decreased cardiac preload
- Related changes
  - Increased arterial stiffness
  - Endothelial dysfunction
  - Altered coaguability
  - Increased levels of C-reactive protein

Vascular Changes in Subclinical Hypothyroidism

- Elevated cholesterol and LDL cholesterol
- Increased Apolipoprotein B (Apo B)
- Increased intima-media thickness (carotid)
- No differences in myocardial function compared with euthyroid controls at baseline
  - No changes after dobutamine stress

Owen PJD, et al. J Clin Endocrinol Metab 9:2126–2132, 2006
Monzani F,. J Clin Endocrinol Metab 89:2099–2106, 2004

Conflicting Data on Lipid Changes in Subclinical Hypothyroidism

- Whickham Survey and NHANES III- no relationships
- Healthy Aging and Body Composition Study:
  - TSH >5.5 mIU/L associated with 10 mg/dl increase in total cholesterol
- Middle Age Population
  - For every increase in TSH of 1 mIU/L, rise of:
  - 3.5 mg/dl total cholesterol in women
  - 6.2 mg/dl rise in total cholesterol in men
- Among older women with TSH > 5.5 mIU/L,
  - LDL was 13% higher
  - HDL was 12% higher
  - LDL:HDL was 29% higher

TunbridgeWM,et al. Clin Endocrinol (Oxf) 7:495–508, 1977
Hueston WJ and PearsonWS. Ann Fam Med 2:351–355, 2004
Kanaya AM, et al. Arch Intern Med, 162:773–779, 2002
Bindels AJ, et al. Clin Endocrinol, 50:217–220 1999

Effect of Replacing Thyroid Hormone on Lipid Status

- Overall, conflicting results
  - Most studies: no impact in subclinical hypothyroid
  - Few studies: small decrease in LDL (if elevated at baseline)
  - More likely to see decrease in LDL with higher baseline TSH value

Meier C, et al. J Clin Endocrinol Metab 86:4860–4866, 2001
Razvi S, et al. J Clin Endocrinol Metab 92:1715–1723, 2007

Replacing Thyroid Hormone on Heart and Vascular System

- Decrease in SVR (not all studies)
- Decrease in mean arterial pressure
- Endothelial dependent vasodilation
- Decreased carotid intima-media thickness

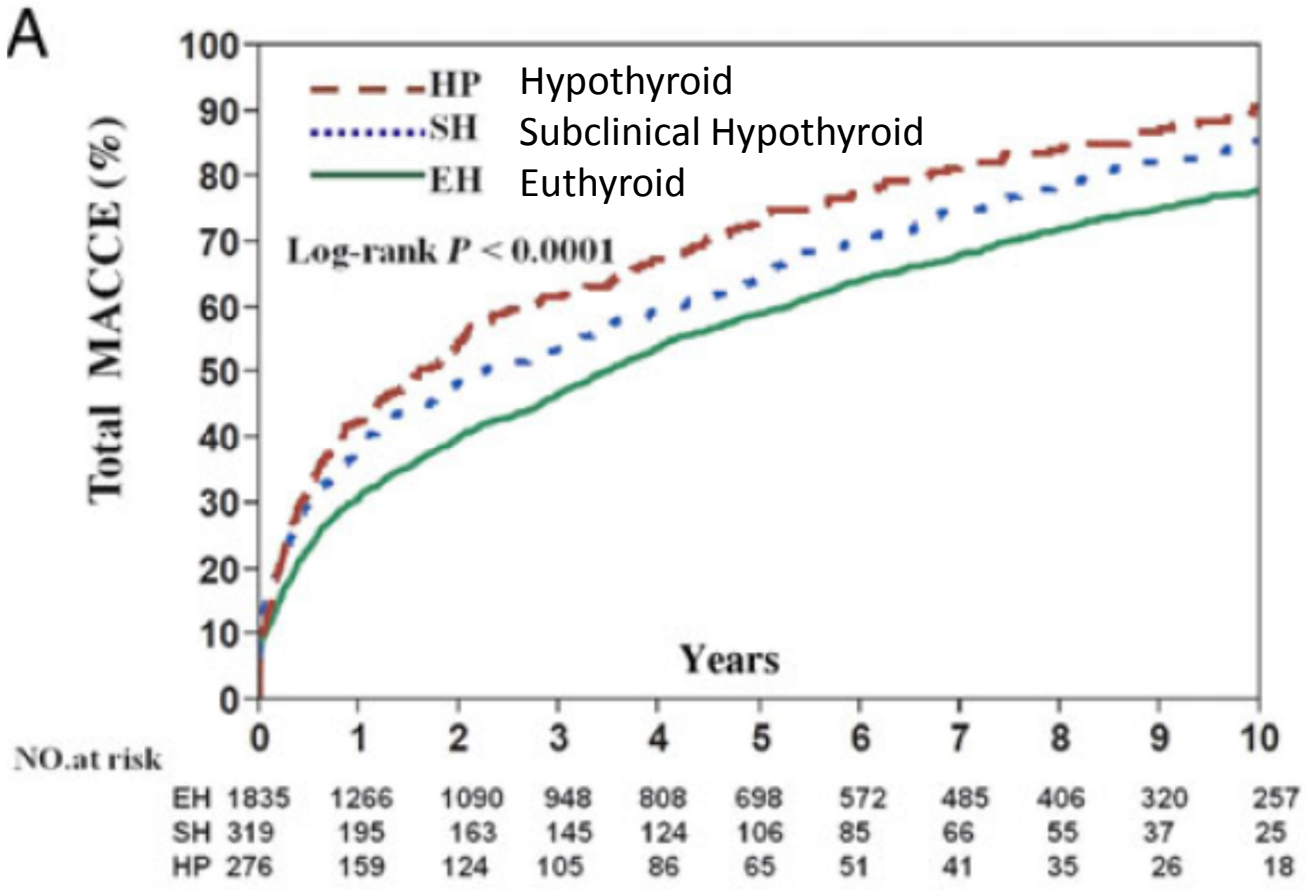
Monzani F, et al. J Clin Endocrinol Metab 86:1110–1115, 2001
Yazici M, et al. Int J Cardiol 95:135–143, 2004
Monzani F,. J Clin Endocrinol Metab 89:2099–2106, 2004
Razvi S, et al. J Clin Endocrinol Metab 92:1715–1723, 2007

Other CV Risk Factors and Subclinical Hypothyroidism

- Lp(a) not related to TSH (unless over 12 mIU/L)
  - No change with T4 treatment
- Homocysteine not related to TSH
  - No change with T4 treatment
- Coagulation parameters inconsistent
  - More consistent in overt hypothyroidism
- C-reactive protein higher in subclinical TSH hypo
  - Predicted CV disease in men under age 50 (OR=3.4)
  - Not different in NHANES III
  - No change with T4 treatment

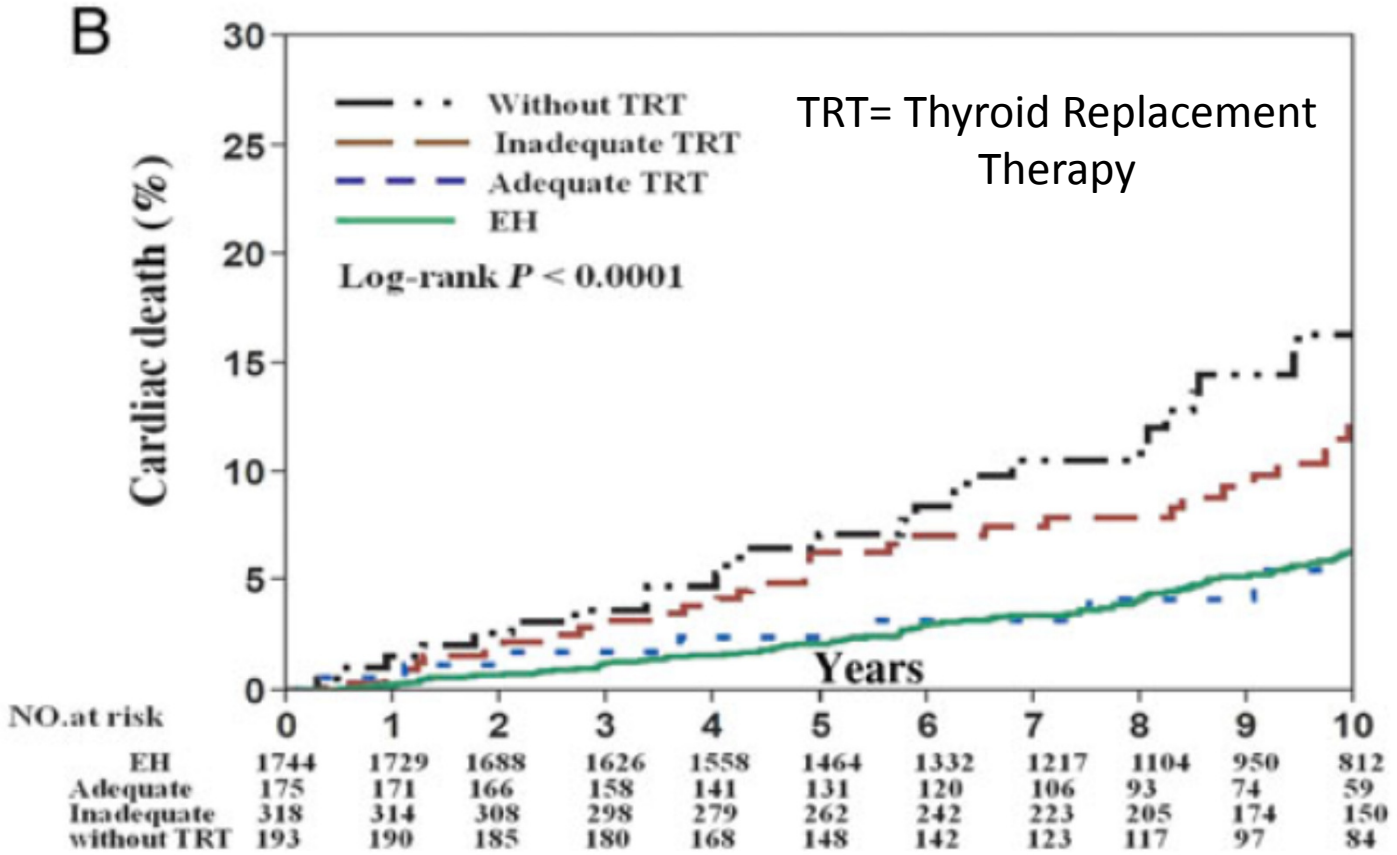
Kvetny J et al. Clin Endocrinol 61:232–238, 2004
Hueston WJ, et al. Clin Endocrinol (Oxf) 63:582–587, 2005
Monzani F,. J Clin Endocrinol Metab 89:2099–2106, 2004

Impact of Thyroid Status on Adverse CV Events in Patients Undergoing Percutaneous Intervention



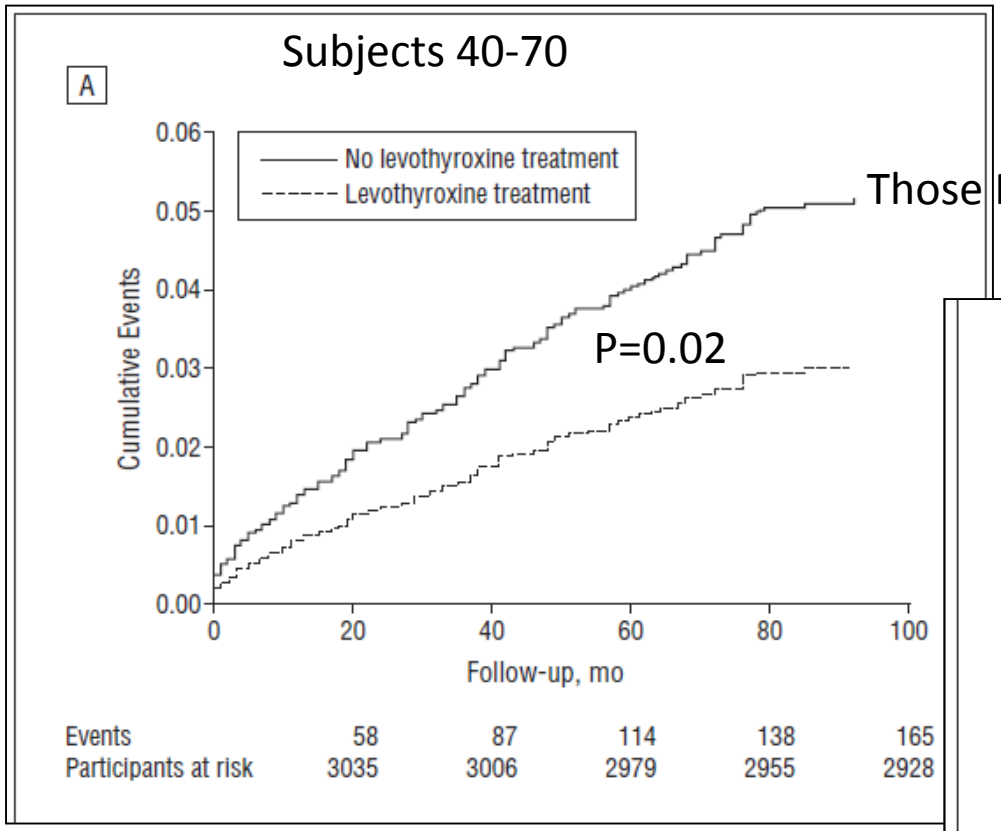
Zhang et al; European Heart Journal (2016) 37, 2055–2065

Impact of Thyroid Replacement: Patients Undergoing Percutaneous CV Intervention

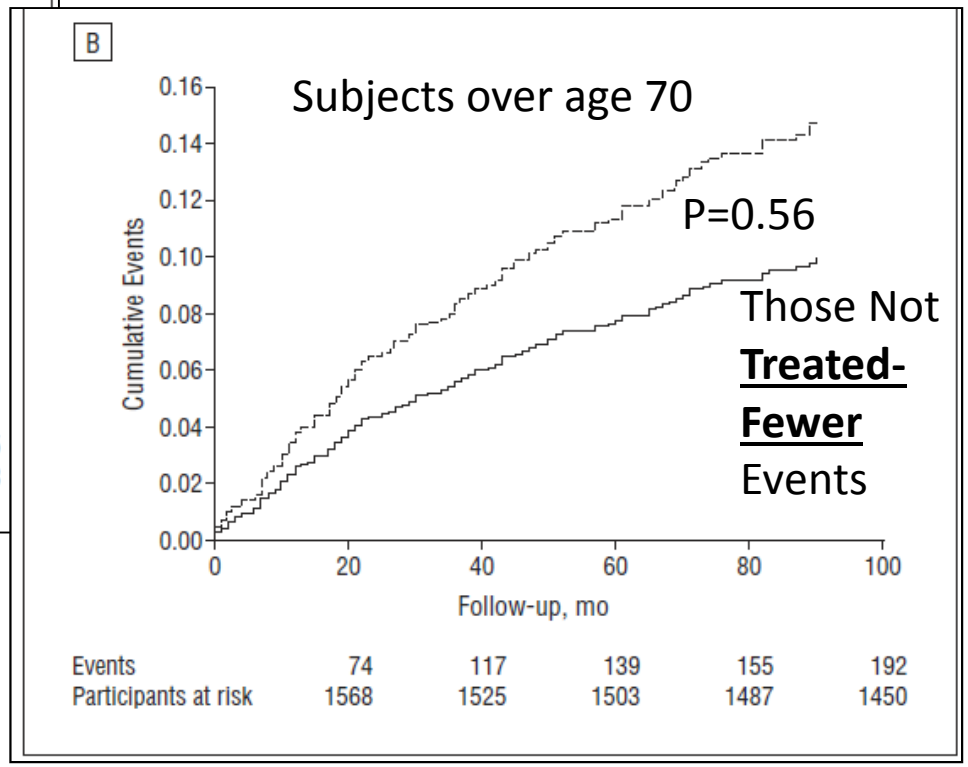


Zhang et al; European Heart Journal (2016) 37, 2055–2065

Observational Study of Treating Subclinical Hypothyroidism on Ischemic Heart Disease



Those Not Treated→ **More** events



Those Not **Treated-Fewer** Events

Razvi S et al; *Arch Intern Med.* 2012;172(10):811-817

Impact of Treating Subclinical Hypothyroidism on Ischemic Heart Disease

Age Group, y	Patients, No. (%)		Events, No. (%)		HR[a] (95% CI)
	Treated	Untreated	Treated	Untreated	
40-50	433	384	8 (1.8)	9 (2.3)	0.86 (0.09-18.92)
51-60	642	576	24 (3.7)	29 (5.0)	0.43 (0.16-1.15)
61-70	560	498	22 (3.9)	43 (8.6)	0.41 (0.17-0.97)
71-80	504	454	48 (9.5)	29 (6.4)	1.06 (0.62-1.70)
81-90	268	296	35 (13.1)	28 (9.5)	1.36 (0.57-3.20)
91-107	51	66	4 (7.8)	5 (7.6)	1.67 (0.09-31.4)

[a]Data adjusted for sex, BMI , socioeconomic deprivation score, total cholesterol level, index TSH, smoking status, systolic and diastolic BP, diabetes status, and levothyroxine use.

Razvi S et al; *Arch Intern Med.* 2012;172(10):811-817

US Preventive Task Force

Screening and treatment of subclinical hypothyroidism

- **No improvement in:**
  - Quality of life,
  - Cognitive function,
  - Blood pressure, or body mass index.
- **Potential beneficial effects on:**
  - Lipid levels, but effects not statistically significant and of uncertain clinical significance

Rugge JB et al; Ann Intern Med. 2015;162:35-45

60 y.o. woman, HTN (HCTZ), non-smoker
peri-menopausal weight gain, trouble concentrating
TSH=9 (high) and fT4=0.7 (low-normal)
(remember- she hates statins)

You would recommend:

A) Start statin therapy
B) Start resin therapy
C) Start statin therapy and thyroid hormone
D) Start levothyroxine
E) Increase exercise and repeat labs in 8-12 weeks
F) Start iodine supplements

Quality of Evidence- Treating Subclinical Hypothyoidism

	Strength of Association		Benefits of Treatment
Clinical Condition	TSH= 4.5-10	TSH > 10	
Progression to Overt Hypothyroidism	Good	Good	
Adverse Cardiac Endpoints	Insufficient	Insufficient	
Elevated total/LDL Cholesterol	Insufficient	Fair	
Cardiac Dysfunction	Data did not distinguish TSH		
Systemic Hypothyroid Sx	None	Insufficient	
Neuropsych Sx	None	Insufficient	

Await results from TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism)

- 3,000 older subjects over 5 year period (started Feb 2013)

Based on Surks MI, et al; JAMA 291:228-238, 2004
Also *Arch Intern Med*;172(10):811-817, 2012

Thank you and Safe Travel.

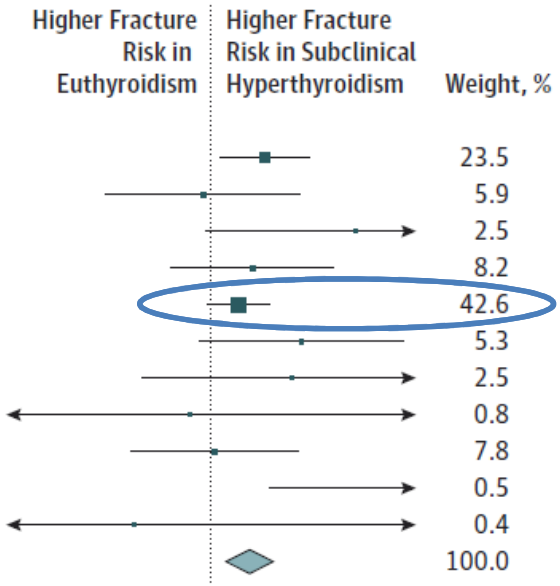
Questions?

Subclinical Hyperthyroidism Conflicting results on overall mortality

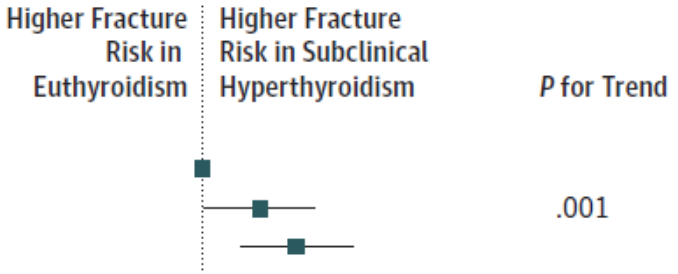
- All-cause and cardiovascular mortality were higher in a group of individuals with SH(serum TSH<0.5mU/L) aged ≥ 60 years at 1, 2, and 5 years of follow-up, but not after 10 years of follow-up (271).
- Another study- increase in mortality over 4 years of follow-up among persons aged ≥ 85 years (267),
- Third study, individuals with SH and concomitant heart disease had an increase in cardiovascular and all-cause mortality (272).
- But two other longitudinal population-based studies reported no increase in overall mortality in persons with SH (255,273).
- Two recent meta-analyses
  - All-cause mortality risk in SH progressively increases with age (274), which might explain the conflicting reports.
  - No statistically significant increase in mortality in SH (275)

Subclincial Hyperthyroidism – Risk of Fracture by Meta-analysis

Fracture Outcome by Study	Euthyroidism		Subclinical Hyperthyroidism		Hazard Ratio (95% CI)
	No. With Fracture	Total No. of Participants	No. With Fracture	Total No. of Participants	
Hip fracture					
Cardiovascular Health Study[8]	378	2853	34	159	1.52 (1.07-2.17)
Health, Aging, and Body Composition Study[37]	171	2347	7	82	0.94 (0.44-2.00)
Osteoporotic Fractures in Men Study (MrOS)[7]	51	1411	3	30	3.09 (0.96-9.94)
EPIC-Norfolk Study[38]	189	11986	10	360	1.38 (0.73-2.61)
HUNT Study[39]	1507	31377	70	945	1.24 (0.98-1.58)
Invecchiare in Chianti Study (InCHIANTI)[21]	45	1066	7	87	2.03 (0.91-4.52)
Leiden 85-Plus Study[40]	34	456	3	23	1.89 (0.58-6.15)
Osteoporosis and Ultrasound Study (OPUS)[41]	6	1172	1	212	0.85 (0.10-7.06)
Rotterdam Study[42]	106	1611	10	120	1.03 (0.54-1.99)
Sheffield Study[6]	3	285	1	11	21.43 (1.59-289)
Busselton Health Study[19]	44	1907	0	53	0.55 (0.03-9.20)
Overall ($\tau^2 = 0.01$)	2534	56471	146	2082	1.36 (1.13-1.64)

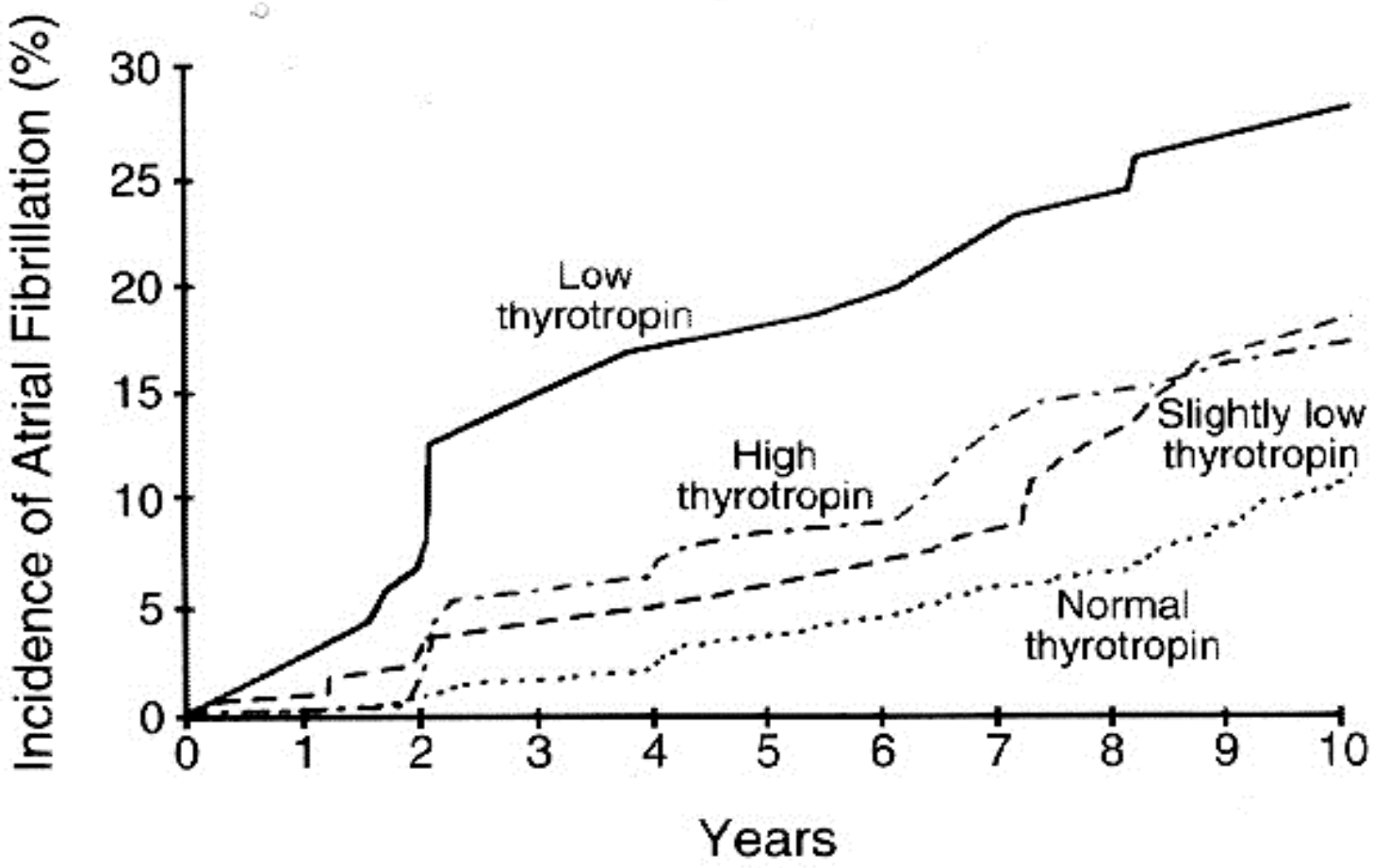


Fracture Outcome by Thyroid-Stimulating Hormone Levels, mIU/L	Euthyroidism		Subclinical Hyperthyroidism		Hazard Ratio (95% CI)
	No. With Fracture	Total No. of Participants	No. With Fracture	Total No. of Participants	
Hip fracture[a]					
0.45-4.49	2534	56471			1 [Reference]
0.10-0.44			99	1568	1.34 (1.01-1.77)
<0.10			47	510	1.61 (1.21-2.15)



Blum MR et al; JAMA. 2015; 313:2055-2065

Cumulative Atrial Fibrillation (≥60 years old) Based on Baseline Serum TSH Values



Sawin CT et al. N Engl J Med 1994;331:1249-1252.

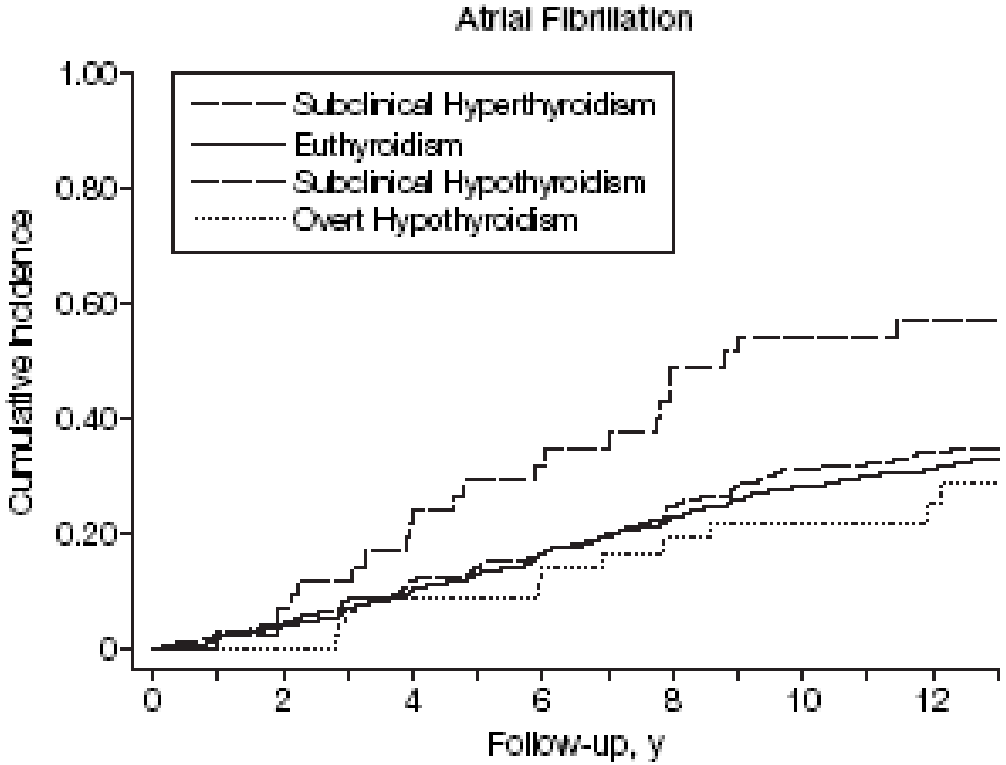
TABLE 8. SUBCLINICAL HYPERTHYROIDISM: WHEN TO TREAT

Factor	*TSH (<0.1 mU/L)*	*TSH (0.1–0.5 mU/L)*[a]
Age > 65	Yes	Consider treating
Age < 65 with comorbidities		
Heart disease	Yes	Consider treating
Osteoporosis	Yes	No
Menopausal	Consider treating	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Age < 65, asymptomatic	Consider treating	No

[a]Where 0.5 mU/L is the lower limit of the normal range.

Bahn RS et al; THYROID; 21 (6): 593-641, 2011

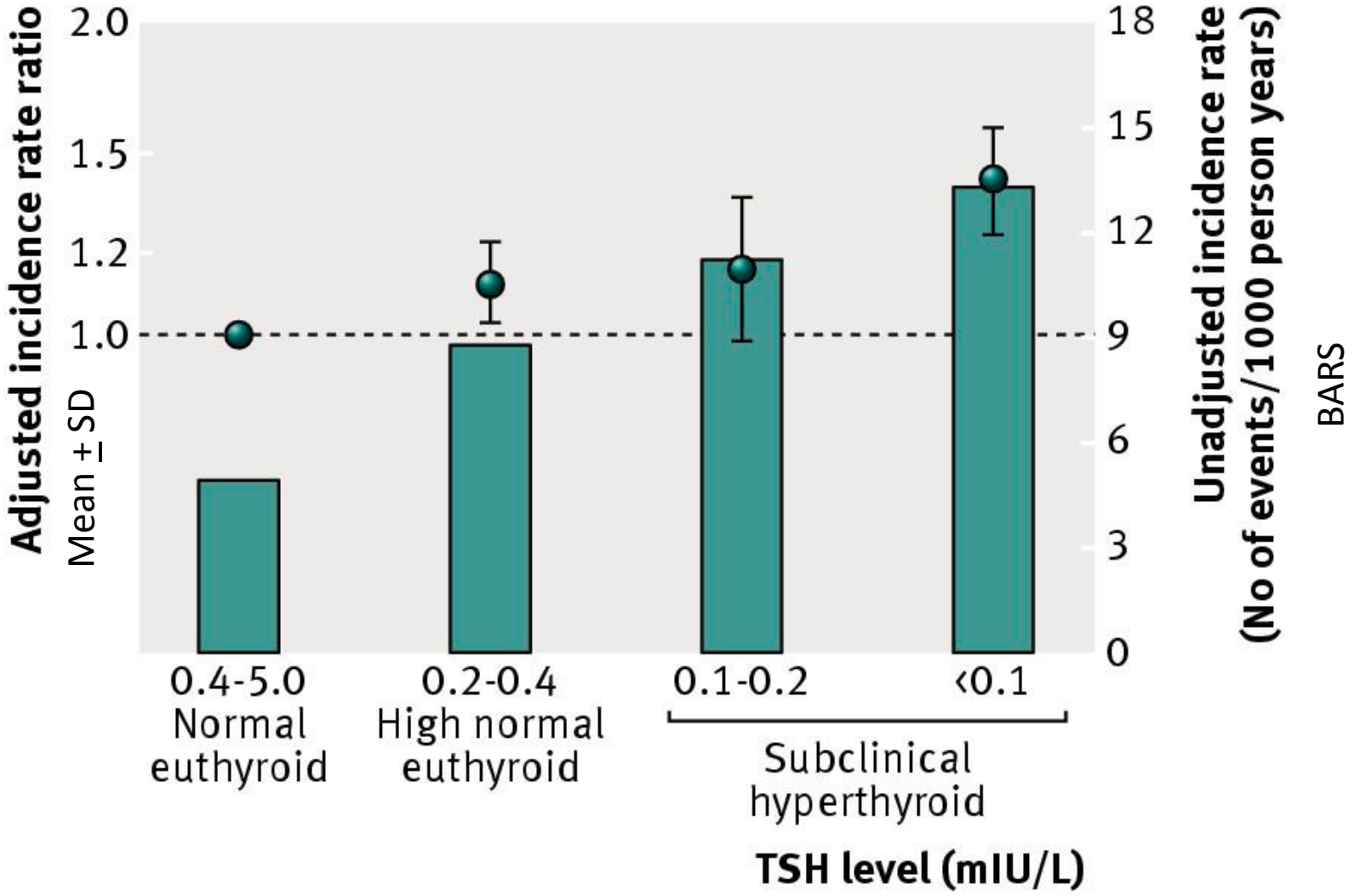
Risk for Atrial Fibrillation Among Elderly Patients with Thyroid Disease



No. at Risk							
Subclinical Hyperthyroidism	47	41	31	27	19	17	14
Euthyroidism	2502	2336	2093	1823	1576	1342	1150
Subclinical Hypothyroidism	472	440	393	348	293	243	208
Overt Hypothyroidism	49	47	40	35	32	29	22

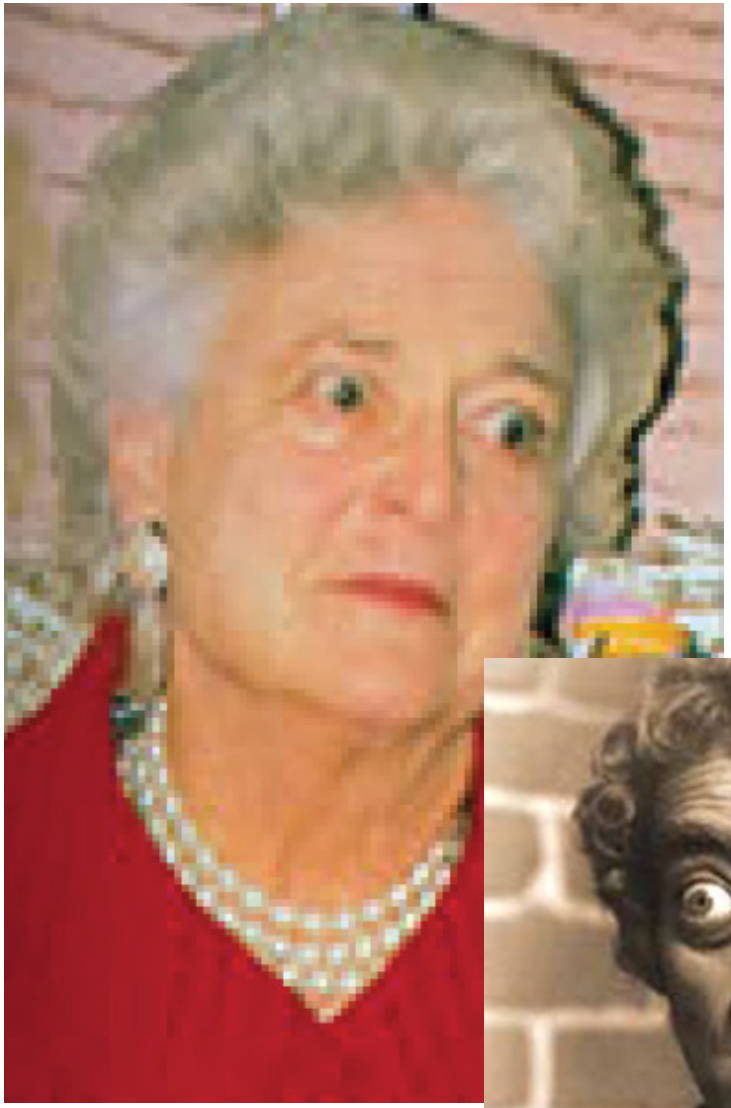
Cappola AR et al; JAMA 295: 1033-1041, 2006

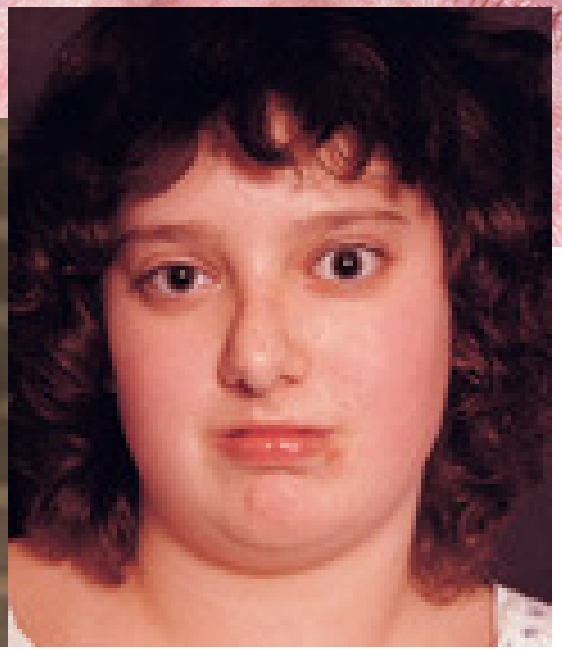
Rates of Atrial Fibrillation by TSH



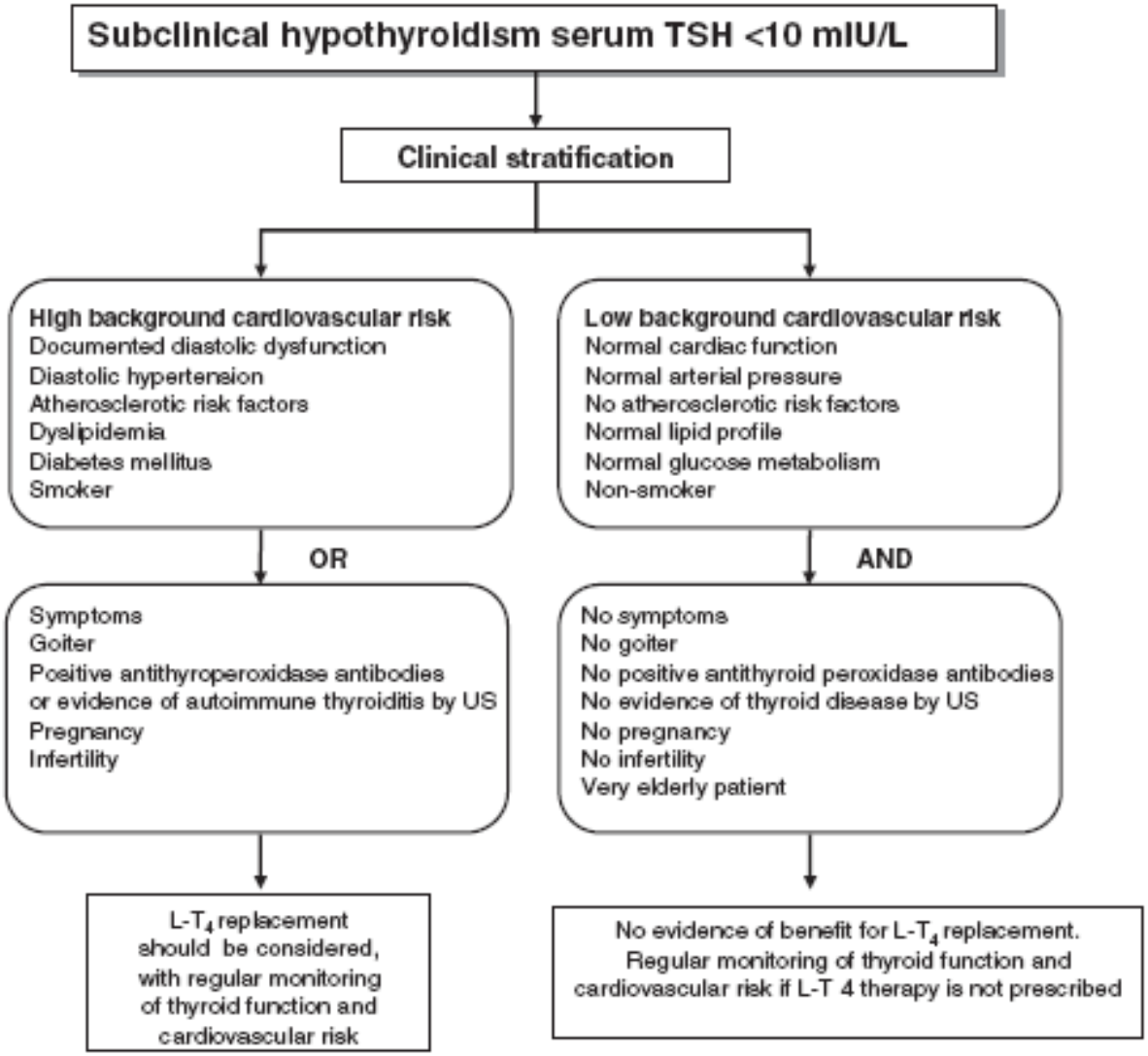
Selmer C et al; BMJ. 2012 Nov 27;345

Eye findings- Hyperthyroidism





One approach to Subclinical Hypothyroid Patient



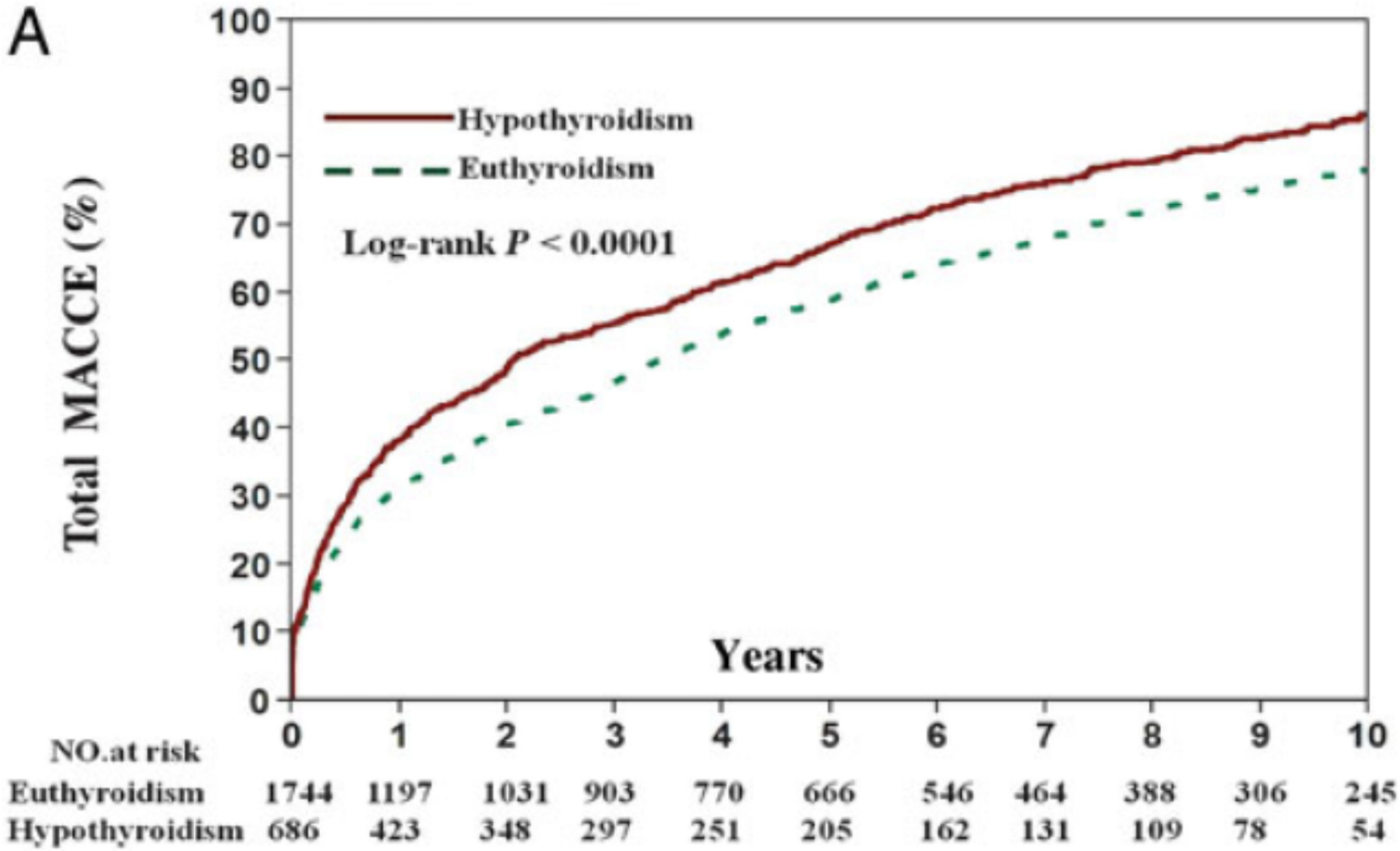
Endocrine Reviews, February 2008, 29(1):76–131

ALTERNATE CASE:
72 y.o. woman, HTN (HCTZ), non-smoker, peri-menopausal with weight gain and trouble concentrating
TSH=16 (high) and fT4=0.4 (low)
(remember- she hates statins)

You would recommend:

A) Start statin therapy
B) Start resin therapy
C) Start statin therapy and thyroid hormone
D) Start levothyroxine
E) Increase exercise and repeat labs in 8-12 weeks
F) Start thyroid extract (combination T4/T3 preparation)

Impact of High TSH on Percutaneous Coronary Intervention



Zhang et al; European Heart Journal (2016) 37, 2055–2065

Table 3 **Hazard ratios for major adverse cardiovascular and cerebral events in patients with hypothyroidism vs. euthyroidism**

Variable	Adjusted HR[a]	95% CI	*P*-value
MACCE	1.28	1.13–1.45	0.0001
Cardiac death	1.14	0.75–1.69	0.54
Myocardial infarction	1.25	1.01–1.53	0.037
Heart failure	1.46	1.13–1.88	0.004
Revascularization	1.26	1.10–1.43	0.0008
Stroke	1.62	1.04–2.49	0.04

[a]Adjusted for age, gender, diabetes, hypertension, dyslipidaemia, family of CAD, renal failure, current smoking, heart failure, history of MI, number of diseased vessels, stent type, aspirin, β-blockers, ACE inhibitors, and statins.

Zhang et al; European Heart Journal (2016) 37, 2055–2065