

25<sup>th</sup> Annual Scientific AACE Clinical Congress

## Thyroid Function and Aging Thyroid Disorders in "Oldsters"; it's Ups and Downs

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## Disclosures

- No disclosures



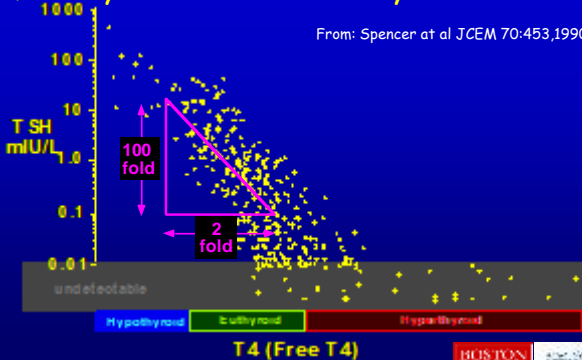
## Overview: Thyroid Function and Aging

- TSH rises with aging
- Extreme longevity and elevated TSH may not be bad
- Abnormal TSH levels can normalize in the elderly
  - If subclinical disease and clinically stable, DO NOT TREAT, REPEAT TFT
- What to do with an elderly patient and a LOW TSH
- What to do with an elderly patient and a HIGH TSH



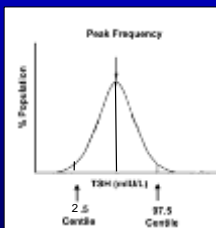
## TSH - Free T4 Relationships in Ambulatory Patients with Stable Thyroid Status

From: Spencer et al JCEM 70:453,1990



## In order to understand the changes in TSH with aging.....

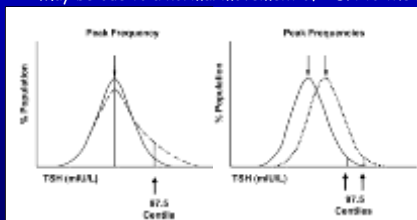
### What is a normal TSH?



- Mean  $\pm$  2 S.D. = middle 95% of the values
- 2.5% of normal values are labeled as TOO LOW
- 2.5% of normal values are labeled as TOO HIGH

## Theoretic TSH Distribution

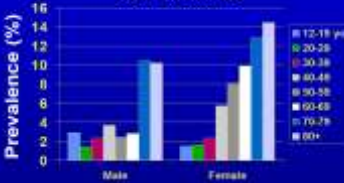
- NORMAL RANGE
  - Mean  $\pm$  2 SD (2.5 - 97.5% percentile)
- TSH are skewed to the higher TSH
  - Attributed to occult hypothyroidism
  - May be due to a normal movement of TSH to the right with aging



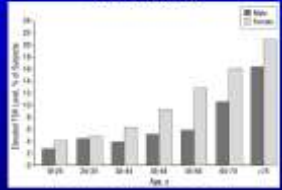
Theoretical TSH distribution curves for thyroid disease-free subjects

# Rising TSH by Age in Cross-sectional Studies

NHANES III (1988-1994)  
TSH > 4.5 uU/mL

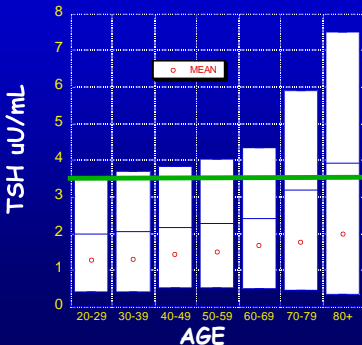


COLORADO DISEASE PREVALENCE  
TSH > 5.1 uU/mL



## NHANES III

Normal Range (2.5 - 97.5 Centile) by Decade



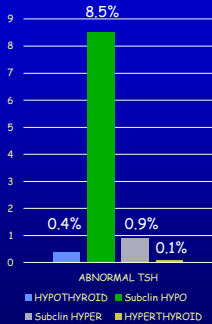
- The lower TSH limit stay relatively constant with age
- The MEAN rises with age
- The upper limit of normal rises with age
  - A "natural" rise of TSH with age? (survival benefit?)
  - Is there a progression to atrophic hypothyroidism with age that is included in normal
- Should be USED a BMD for the normal range in



# Hypothyroidism & Thyrotoxicosis

## Prevalence in Cross-section Studies

COLORADO HEALTH STUDY  
24,337 subjects  
TSH Normal Range 0.3-5.1

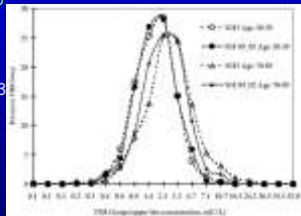
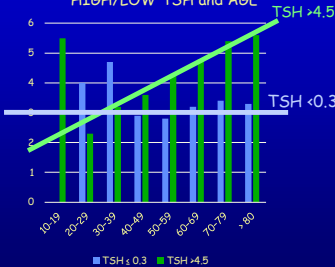


Hollowell JG, et al. *J Clin Endocrinol Metab.* 2002;87:489-499. Canaris GJ, et al. *Arch Int Med.* 2000;160:526-534



# Cross-sectional Population Study: Age-related Changes in TFT

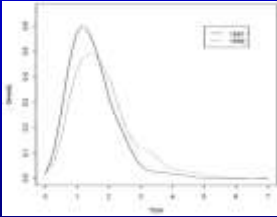
HIGH/LOW TSH and AGE



Hollowell JCEM 2002; 87:489-499; Surks JCEM 2007;92:4575-4582;



## Longitudinal Study Also Show Age-related Rise in TSH



- 908 without thyroid disease
  - Mean age 62 years
  - 13 year follow-up
- Mean TSH increased 1.4901.81 mIU/L
  - Most marked in the elderly
  - 0.08 mIU/L increased each decade
- Mean Free T4 unchanged
- Is this rise physiologic or pathologic?

Bremner JCEM 2012;97:1554-1562



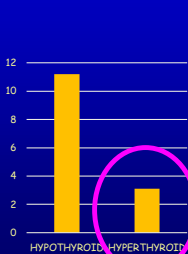
## Hyperthyroidism in the Elderly



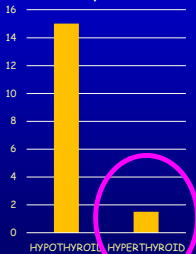
# Thyroid Dysfunction and Age

Prevalence in Cross-section Studies

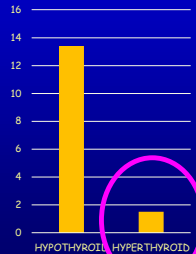
Israeli: 1744 Subjects  
> 65 years



US CV Study  
3233 Subjects  
> 65 years



UK: 3594 Subjects  
> 65 years



Hollowell JG, et al. *J Clin Endocrinol Metab.* 2002;87:489-499; *Parle cin Endocrinol*  
1991;31:77-81



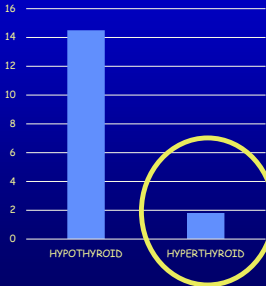
## Risk of Subclinical Hyperthyroidism

- Progression to overt disease
- Risk of death
- Risk of atrial fibrillation and other cardiovascular disease
- Risk of osteoporosis

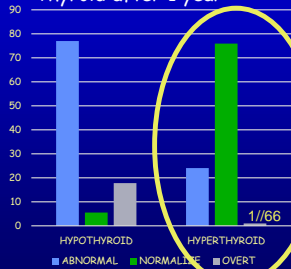


## Longitudinal Community Practice Retrospective Cross-sectional Study

1210 Subjects > 60 years



73 hypo- and 66 hyper-  
Thyroid after 1 year



Parle Clin Endocrinolo 1991;34:77-84

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## Longitudinal, Prospective Subclinical Hyperthyroid

- 117 female subjects > 60 years old
  - Subclinical hyperthyroidism (low measurable TSH, normal Free T4)
  - 15 normalized (presumed euthyroid sick syndrome)
    - 13 without autoimmune or nodular disease)
  - Median F/UP 41 months
  - Median age 68 years
  - REST OF SUBJECTS HAD THYROID DISEASE
    - 89% nodular goiter & 11% diffuse uptake

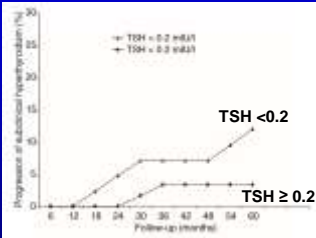
Rosaro Clin Endocrinol 2010; 72:685-688

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## Longitudinal, Prospective Subclinical Hypothyroid



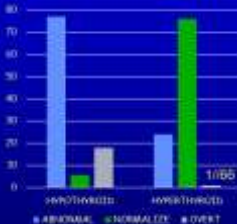
- 89% of subclinical hyperthyroidism due to nodular goiter
- 1/3 spontaneous normalization
- 3% progressed to overt hyperthyroidism

- F/UP median 41 months
  - 0% became hypothyroid
  - 3% progressed to overt hyperthyroidism
  - 33% normalization of TSH
  - 60% persistent subclinical hyperthyroidism
    - 5.6% developed afib or CHF
- 1 predictor of progression:
  - Initial TSH < 0.2 (12%) vs ≥ 0.2 (3.3%) P<0.05
- All progression occurred in nodular goiter

Rosaro Clin Endocrinol 2010; 72:685-688



## Additional Data that Subclinical Hyperthyroidism Rarely Progresses to Overt Disease

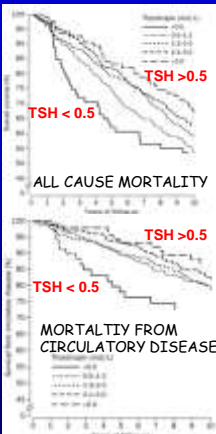


- Parle demonstrated in 1/66 in patients >60 years with TSH < 0.5 mIU/L progressed after 10 years
- Sawin 1/168 patients with initial TSH 0.1 - 0.4 mIU/L progressed to over hyperthyroidism
- REC

Parle Clin Endocrinol 1991;34:77-84; Sawin Arch Intern Med 1991;151:165



## Hyperthyroidism in Elderly and Increased Risk of Death

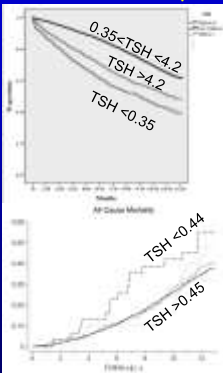


- 1191 subject >60 years old in longitudinal 10 yr cohort study
- Poorest overall survival with suppressed TSH
  - No difference between <0.1 and 0.1-0.49 mIU/L
- Increased mortality from circulatory disease with suppressed TSH

Parle Lancet 2001;358:861-5



## Mortality with Subclinical Hyperthyroidism



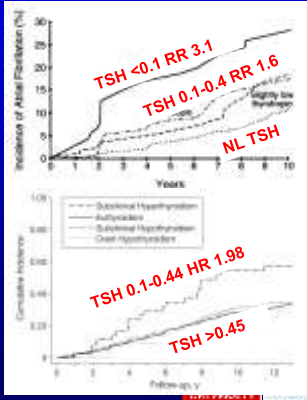
- Israel study of 17,440 in health care system > 60 years
  - Increased risk of mortality after multivariate analysis subclinical hyperthyroidism HR1.95
- US CV study of 3,233 >65 yrs
  - Well controlled study
  - Few overt hyperthyroid in study
  - After multivariate analysis there was no increased risk of death from
    - All causes 1.08 95% CI (0.72-1.62)
    - CVD HR 1.07 95% CI (0.9-1.28)

Grossman Am J Med 2016; 129, 423-430;  
Cappola JAMA 2006;29:1033



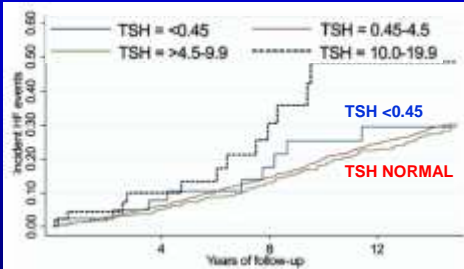
## Subclinical Hyperthyroidism and Atrial Fibrillation

- Framingham Heart Study, 1048 subjects >60 years
  - Prospective 10 yr longitudinal study
  - Atrial fibrillation
    - 16% Slightly LOW TSH 0.1-0.4 mIU/L (RR 1.6)
    - 28% LOW TSH <0.1 mIU/L (RR 3.1)
- US Cardiovascular Study, 3233 subjects >65 years
  - Prospective 13 yr longitudinal study
  - Atrial fibrillation
    - Increased with TSH 0.1-0.4 HR 1.98 (1.29-3.03)



Sawin NEJM 1994;331:1249-52 Cappola JAMA 2006;295:1033

## Subclinical Hyperthyroidism and CHF



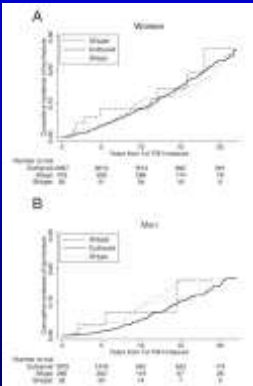
- 3044 in US Cardiovascular Longitudinal Study
  - 1.4% subclinical hyperthyroidism
  - No increased risk of CHF or EKG changes

Rodondi J Am Coll Cardiol 2008;52:1152-9



## Bone Health and Subclinical Hyperthyroidism

- US Cardiovascular study with 4926 subjects >65 years
  - Cross-sectional analysis of 1317 who had BMD and median f/up 12 yrs
  - No significant association of subclinical HYPERTHYROIDISM or HYPOTHYROIDISM with BMD or fracture in men or women

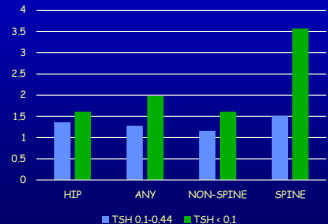
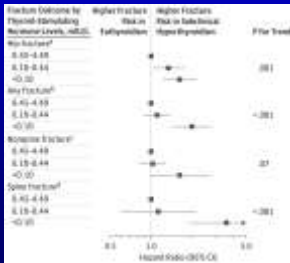


Garrin JCEM. 2014;99:2657-64



## Meta-analysis Fracture and Hyperthyroidism

- 13 prospective studies with 70,298
  - Median age 64 with F/U 12.1 yrs
  - Hyperthyroidism associated with increased risk of hip and other fractures especially TSH <0.1



Blum JAMA 2015;313:2055



## SUMMARY: Risk of Subclinical Hyperthyroidism

- Prevalence 1.5-2% in > 65 years
  - Etiology usually nodular goiter
- Progression to overt disease
  - 20-70% normalize without treatment
  - 1-3% progresses to hyperthyroidism
    - More likely with very low TSH
    - More likely with nodular thyroid disease
- Risk of death - conflicting data but yes
- Risk of atrial fibrillation -yes 2-3 x risk
- Risk of osteoporosis
  - Hyperthyroidism associated with increased risk of hip and other fractures especially TSH <0.1



## Recommendation for Evaluation and Treatment of Suppressed TSH in the Elderly

- If low TSH, repeat with FT4, total T3, TPOab (TSI) and thyroid US in 3 months
- If TSH 0.1-0.4 mIU/L
  - Observation if TSH 0.1-0.4, normal US, negative thyroid Ab, normal HR, normal BMD, no CV or skeletal risk factors
    - Check TSH, FT4, total T3 every 6-12 mo
  - Graves disease: Treat with ATD (MMI 5-10 mg/d) if **cardiovascular disease or risk factors**
  - Nodular goiter: Treat with RAI if **cardiovascular disease or risk factors** (consider normalize TSH first with ATD)
    - If cannot comply with radiation restrictions - longterm ATD



## Recommendation for Evaluation and Treatment of Suppressed TSH in the Elderly

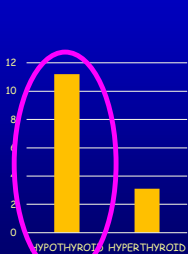
- If TSH < 0.1 mIU/L
  - Graves disease
    - Treat with ATD, RAI or surgery
  - Toxic nodular goiter
    - RAI or surgery
    - Surgery if large goiter or compressive symptoms

## Hypothyroidism in the Elderly

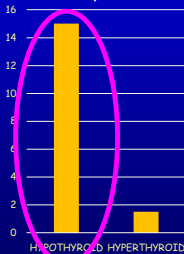
# Thyroid Dysfunction and Age

Prevalence in Cross-section Studies

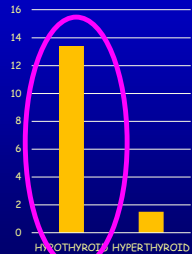
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Hollowell JG, et al. *J Clin Endocrinol Metab.* 2002;87:489-499; Parle Clin Endocrinol 1991;31:77-81



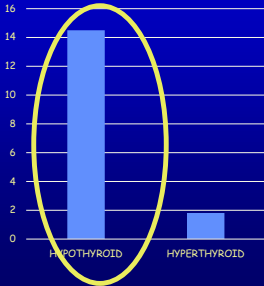
## Risk of Subclinical Hypothyroidism

- Survival advantage of high TSH?
- Progression to overt disease
- Risk of death

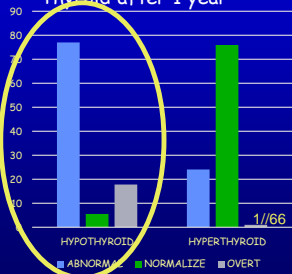


## Longitudinal Community Practice Retrospective Cross-sectional Study

1210 Subjects > 60 years



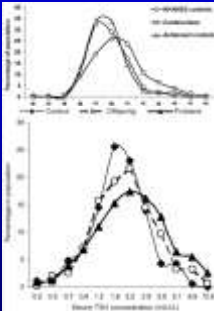
73 hypo- and 66 hyper-  
Thyroid after 1 year



Parle Clin Endocrinolo 1991;34:77-84



## Elevated TSH: Survival Advantage? Centenarian Study



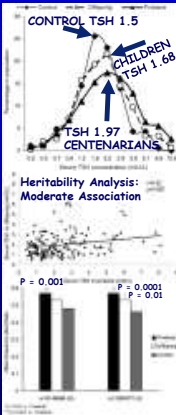
- 232 Ashkenazi Jewish centenarians (166 females, median age, 97.8 yr; and 66 males, median age 97.6 yr)
- Control groups:
  - 188 younger unrelated Ashkenazi Jews (females, median age:69.7 yr; males, median age: 72.3 yr)
  - NHANES 1998-2002 60-79 years
- TSH higher in the centenarians [1.97 (0.42-7.15) mIU/liter] compared with the Ashkenazi controls [1.55 (0.46-4.55) mIU/liter] (median, 2.5 and 97.5 centiles) ( $P < 0.001$ ).
- The percentage of subjects with TSH greater than 2.5 mIU/liter was 15.4% in the controls and 35.2% in the centenarians

Atzmon JCEM 2009;94:1251-1254; Atzmon JCEM 2009;94:4768-75





## Genetic Inheritability of Elevated TSH and Extreme Longevity



- 232 Ashkenazi Jewish centenarians (n = 232; median age, 97 yr) (MEDIAN TSH 1.97)
- Control groups:
  - Their offspring (n = 366; median age, 69 yr, MEDIAN TSH 1.68)
  - Age-matched controls without familial longevity (n = 163; median age, 70 yr, MEDIAN TSH 1.50)
- Offspring had higher median serum TSH, compared to controls with estimated heritability of 0.3 (P = 0.004).
- Allele frequency of two SNPs in the promoter/enhancer region of TSHR gene but NOT TSHbeta gene associated with increased serum TSH

Atzmon JCEM 2009;94:4768-75

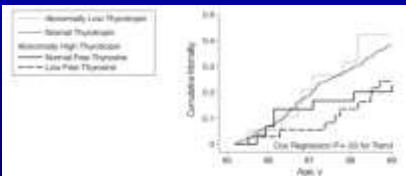
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## Lower Mortality in Oldest Old with High TSH

Leiden 85 Plus Study 599 subjects 85-89 yrs

- The oldest old, elderly individuals high TSH do not experience adverse effects and may have a prolonged life span
- Risk of mortality of high TSH 0.76 (p 0.005) vs normal TSH.



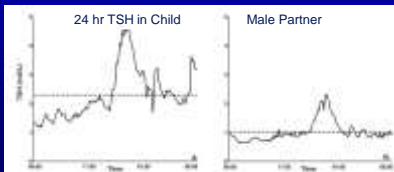
Gusseklou et al. AMA. 2004;292(21):2591-2599. doi:10.1001/jama.292.21.2591

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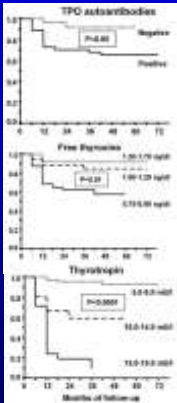


## Higher TSH Secretion in Children of Nonagenarians than Partners

- 38 children of nonagenarians of the Leden Longevity Study
  - Compared with partners, offspring displayed higher mean & basal TSH secretion



Jansen et al JCEM DOI: <http://dx.doi.org.ezproxy.bu.edu/10.1210/jc.2015-2624>



## Natural History Mild Hypothyroidism:

- 107 patients followed for 72 months with subclinical hypothyroidism (elevated TSH, normal Free T4)
  - Mean age 62 years from outpatient Endo clinic
  - 26% required T4 RX
- Overt hypothyroidism associated if baseline:
  - + TPO Ab
  - Free T4 < 1
  - Extent of TSH elevation
    - > 10 (~40%)
    - >15 (~90%)
- Low risk of overt hypothyroidism if TSH 5-10
  - Recommend biochemical monitoring

Diez & Iglesias JCEM 2004;89:4890-7



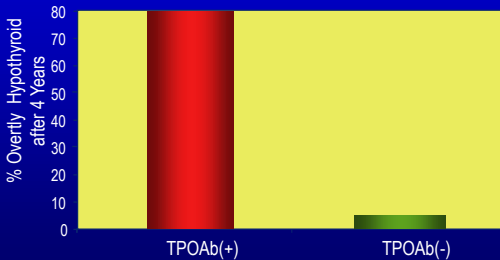
## Progression to Overt Hypothyroidism in CV Study

- Large population cohort followed for 4 years
  - 3992 >65 years
  - 12.8% subclinical hypothyroid
  - 0.61% overt hypothyroidism
- Overt hypothyroidism associated if baseline:
  - TSH >10
  - Not associated with age or TPO ab status
- Low risk of overt hypothyroidism if TSH 5-10
  - Recommend biochemical monitoring

Somwaru JCEM 2012;97:1962



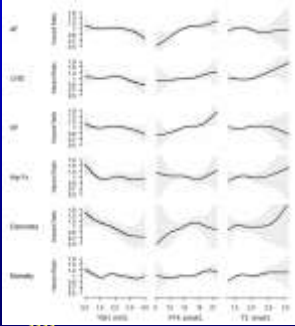
## Subclinical Hypothyroidism Progression in the Elderly



Rosenthal, et al. JAMA. 1987; 258:209.



## Thyroid dysfunction in the Elderly



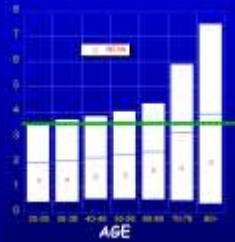
- 3996 participants in 2010
- Higher TSH was negatively associated (P .03) and higher FT4 was positively associated (P .007) with mortality
- Higher FT4 was associated with atrial fibrillation (P .001) and heart failure (P .004). Compared with the first quartile
- TSH in the fourth quartile had a 9.6 per 1000 person-year lower incidence of dementia (P .05)

## Subclinical Hypothyroidism and Cognitive Impairment

- Systematic review and meta-analysis
- 1,190 subjects >60 years in 15 studies
- No association with
  - Mini mental state exam (MMSE)
  - Executive function
  - Memory (random effects model)

## SUMMARY: Hypothyroidism and the Elderly

- TSH rises with age
  - Age specific normal range (2.5-97.5%) suggests that TSH elevation 4-7 may be a normal aging
    - True increase in hypothyroidism
    - Genetic survival advantage to higher TSH in the oldest old
- Prevalence hypothyroidism 11-15% of the elderly
  - Mostly subclinical
  - 15-20% progress to overt disease
  - <5% normalize TSH with time



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## Recommendation for Evaluation and Treatment of Elevated TSH in the Elderly

- TSH found on screening
  - Repeat with FT4 and TPO ab
- Progression to overt disease
  - Most likely if TSH >10
  - Free T4 < 1.0
  - Positive TPO antibody
- Subclinical disease is associated with subclinical hypothyroidism
  - LT4 therapy will reduce total and LDL cholesterol in subclinical hypothyroidism but rarely achieves goal levels

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## Recommendation for Evaluation and Treatment of Elevated TSH in the Elderly

- Most associated problems (CHD, CV mortality) only with TSH > 10
  - No interventional studies or randomized studies
- Treatment to normalize TSH is recommended after repeat TSH is > 10
- Persistently elevated TSH between 4.5-9.9
  - Younger patients 65-84 years should be considered for symptoms especially with + TPOAb or low FT4
  - Older patients > 85 years should be carefully followed without T4 therapy
    - TFT every 6 mo for 2 years, then annually

Pearce 2013 ETA Guideline: Management of Subclinical Hypothyroidism Eur Thyroid J 2013;2:215.



## Recommendation for Evaluation and Treatment of Elevated TSH in the Elderly

- LT4 therapy
  - Full dose in the elderly without CAD
    - Large studies suggest 50-100 mcg/day will normalize TSH in most subclinical hypothyroid patients
    - Randomized trial in elderly > 70 years with no heart disease
      - Lower doses with cardiac disease: 25-50mcg with increase by 25 mcg/day every 2-3 weeks.
    - Check TSH 2 months after adjustment
      - Goal is 0.5-2.5 mU/L but in > 70-75 TSH 1-5 is acceptable

Razvi. JCEM 2007;92:1715;Roos arch Intern Med 2005;165:1714



## SUMMARY

- A suppressed TSH occurs in about 3% of the elderly
  - 50-70% will normalize without treatment (if peripheral hormone levels normal)
  - Overt disease rarely progresses but the risk increased with  $TSH < 0.2$
  - Treatment depends on symptoms, CV and bone risks factors
- TSH rise with age due to development of thyroid failure but also perhaps because of survival advantage of the "oldest old"
  - Occurs primarily in females until  $>80$
  - Rarely normalizes
  - Progression with  $TSH > 10$  and + TPO ab
  - CV sequelae occur when  $TSH > 10$
  - Treatment :
    - TSH  $> 10$  in all
    - TSH 4.5-9.9:
      - Young elderly with symptoms, CV risk
      - Oldest old: careful observation without treatment



Thank you for your attention!  
QUESTIONS?

