SUBCLINICAL THYROID DYSFUNCTION

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SUBCLINICAL THYROID DYSFUNCTION

1. Definitions and conceptual problems
   - reference ranges
   - intra-individual variation
   - continuous risk

2. Subclinical hypothyroidism

3. Subclinical hyperthyroidism

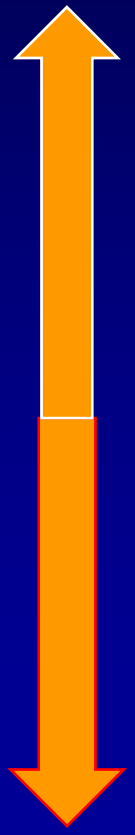
SUBCLINICAL THYROID DYSFUNCTION DEFINITIONS

Subclinical hypothyroidism
= increased serum TSH but normal serum FT4

Subclinical hyperthyroidism
= decreased serum TSH but normal serum FT4 and FT3

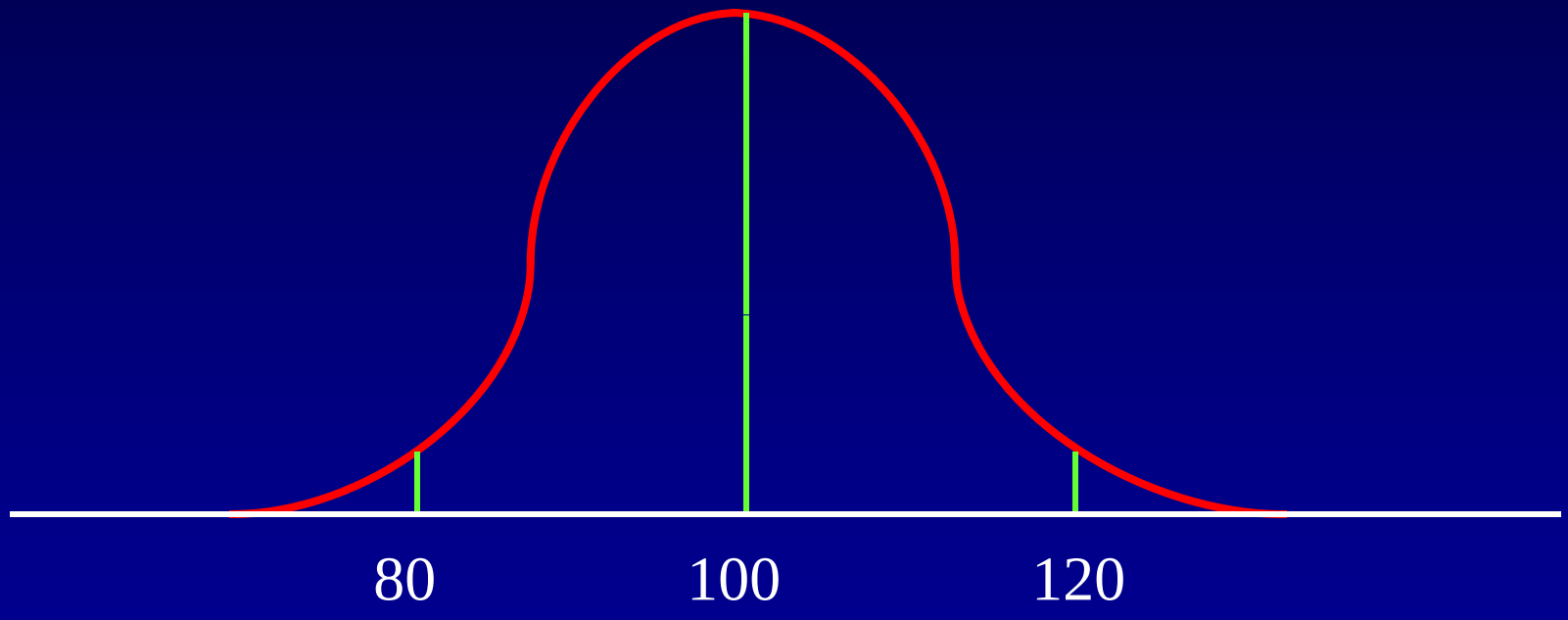
TRANSITIONS FROM EUTHYROIDISM TO HYPOTHYROIDISM OR HYPERTHYROIDISM

	Serum TSH	Serum FT4	Serum FT3
Overt hyperthyroidism	↓	↑	↑
T3-toxicosis	↓	N	↑
Subclinical hyperthyroidism	↓	N	N
Euthyroidism	N	N	N
Subclinical hypothyroidism	↑	N	N
Mild hypothyroidism	↑	↓	N
Overt hypothyroidism	↑	↓	↓



N = normal, ↓=decreased, ↑ = increased

WHAT IS NORMAL?
THAT WHAT IS NOT ABNORMAL



intelligence quotient

NORMAL VALUES

"The normal range has a vague but comforting role in laboratory medicine. It looms on the horizon of our consciousness, perfectly symmetrical like a Mount Fujijama, somewhat misty in its meanings, yet gratefully revered and acknowledged. Far from being pure and simple, however, like a cherised illusion of childhood, on close examination it proves to be maddeningly complex and is indeed one of the most stubborn and difficult problems limiting the usefulness of clinical laboratory data"

Benson 1972

TSH REFERENCE RANGE DERIVED FROM A POPULATION-BASED USA SURVEY (NHANES III)

	n	TSH mU/l median	TSH mU/l P2.5-P97.5
1. total population ≥ 12 yr	17.353	1.49	0.33-5.80
↓ excluded: people reporting thyroid disease, goiter, thyroid medication			
2. disease-free population	16.533	1.49	0.44-5.52
↓ excluded: pregnancy, lithium, sex steroids, thyroid antibodies, biochemical hyper/hypothyroidism			
3. reference population	13.344	**1.39**	**0.45-4.12**

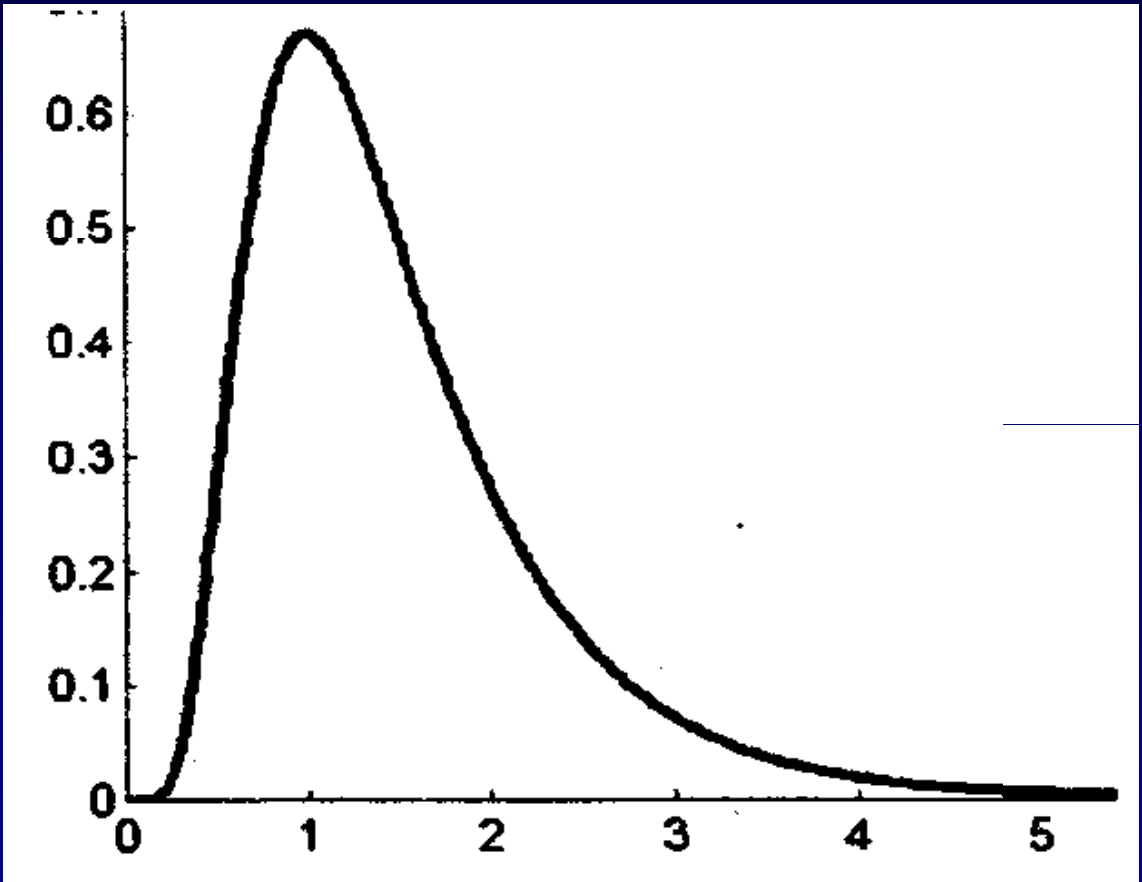
Hollowell et al., JCEM 2002

TSH REFERENCE RANGE BY AGE IN THE REFERENCE POPULATION OF THE NHANES III SURVEY

AGE GROUP	TSH mU/l	
	median	P2.5-P97.5
12-19 yr	1.35	0.46-4.07
20-29 yr	1.26	0.40-3.56
30-39 yr	1.29	0.42-3.69
40-49 yr	1.40	0.50-3.82
50-59 yr	1.50	0.52-4.03
60-69 yr	1.67	0.49-4.33
70-79 yr	1.76	0.45-5.90
≥80 yr	1.90	0.33-7.50

POPULATION-BASED TSH REFERENCE VALUES

SKEWED AT THE UPPER END



TSH mU/L

- no normal distribution of serum TSH
- >95% had TSH <2.5 mU/l in reference population of NHANES III

COMPONENTS OF VARIANCE OF THYROID FUNCTION TESTS

ANALYTE	COEFFICIENT OF VARIATION (%)		
	ANALYTICAL	INTRA-INDIVIDUAL	INTER-INDIVIDUAL
T4	4.4	5.1	10.2
FT4	5.9	9.5	12.1
T3	8.7	10.4	20.4
FT3	7.6	7.9	22.5
TSH	7.5	16.2	31.7

Browning et al. 1986

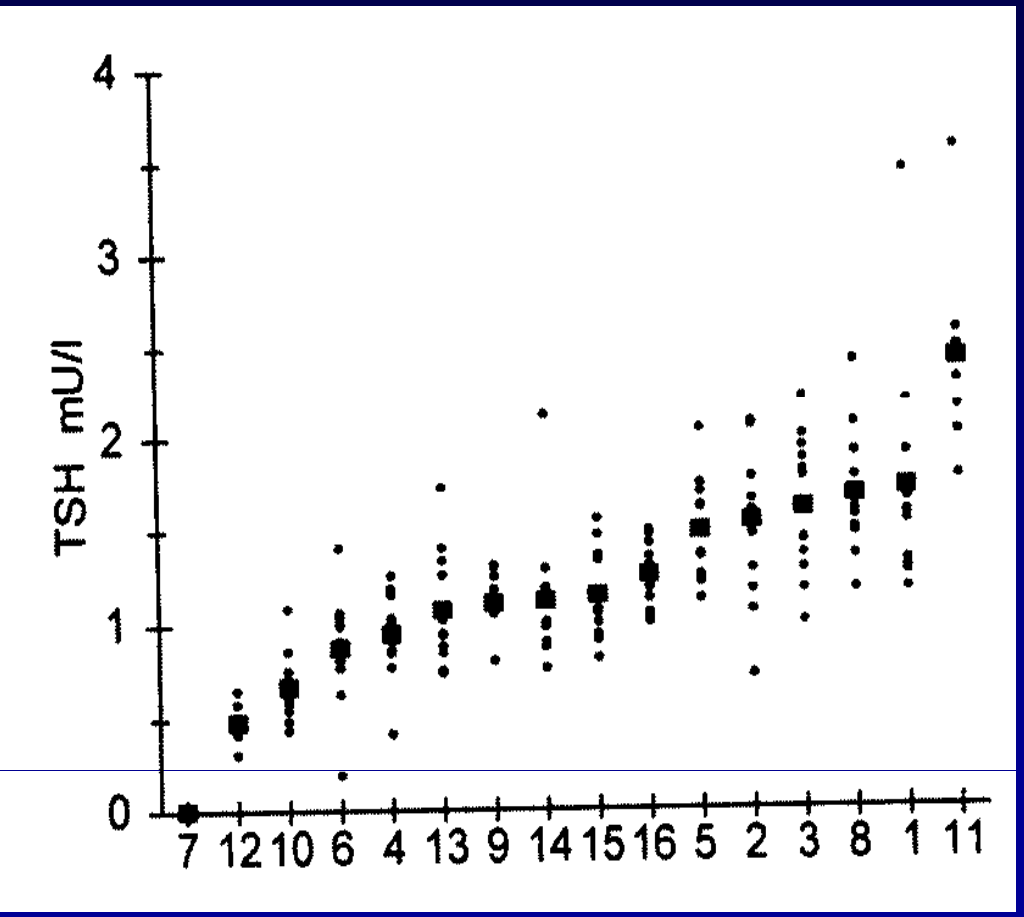
RELIABILITY OF REFERENCE RANGES

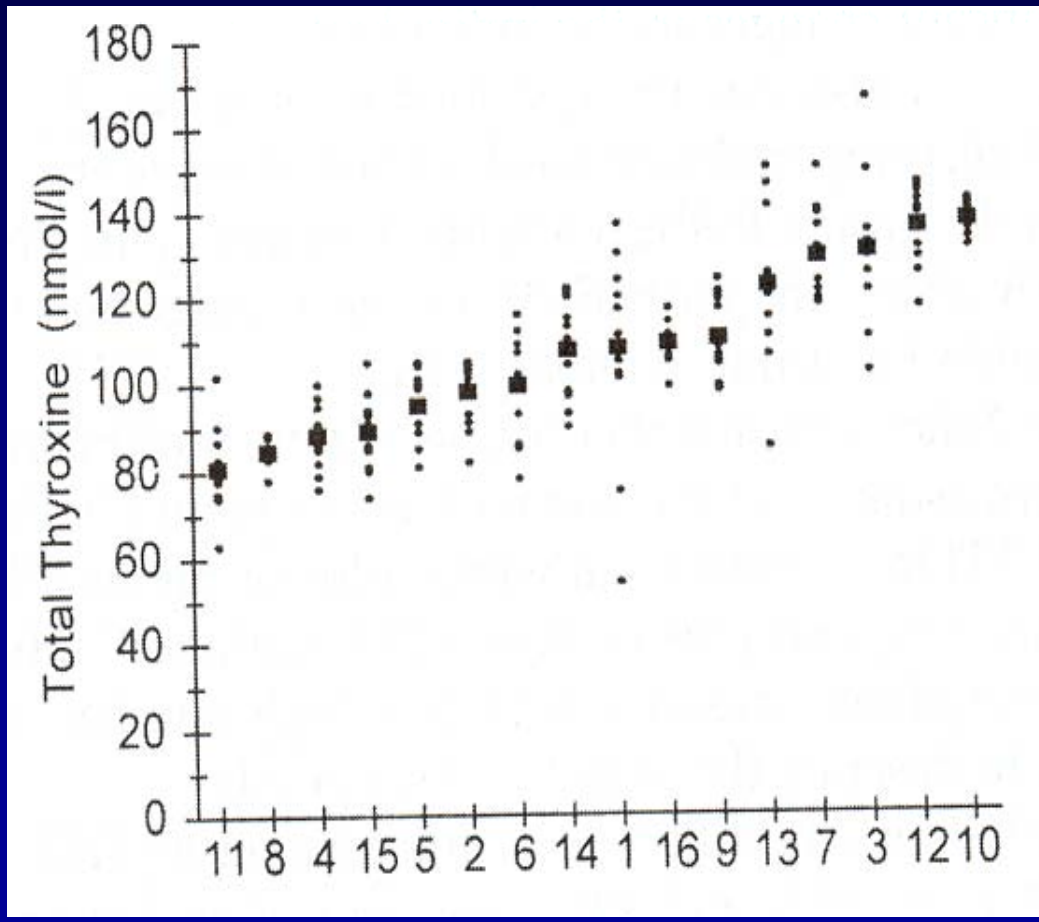
- Ratio of intra-individual to inter-individual variation

- Ratio <0.6 → population-based reference range is insensitive measure in majority of subjects
  Ratio >1.4 → population-based reference range works as intended

- Ratio is <0.6 for all thyroid function tests;
  Ratio for TSH is 0.36 (Nagayama 1993), 0.49 (Andersen 2002), 0.50 (Browning 1986)

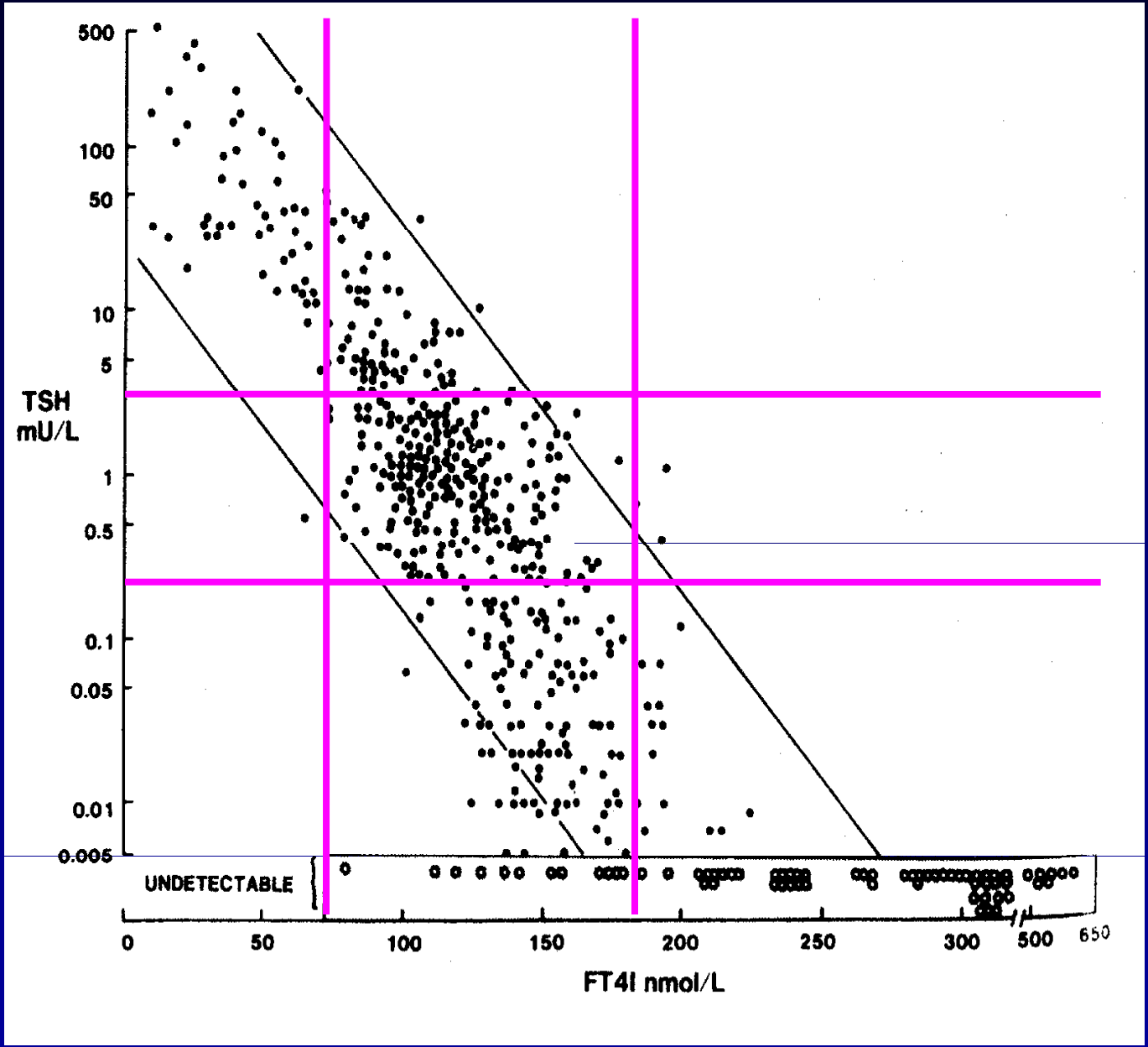
NARROW INTRA-INDIVIDUAL VARIATIONS IN SERUM TSH AND T4 IN 16 NORMAL SUBJECTS





Andersen et al. JCEM 2002

LOG-LINEAR RELATIONSHIP BETWEEN SERUM TSH AND FT4



Spencer et al., JCEM 1990

SUBCLINICAL HYPOTHYROIDISM

PATIENT A

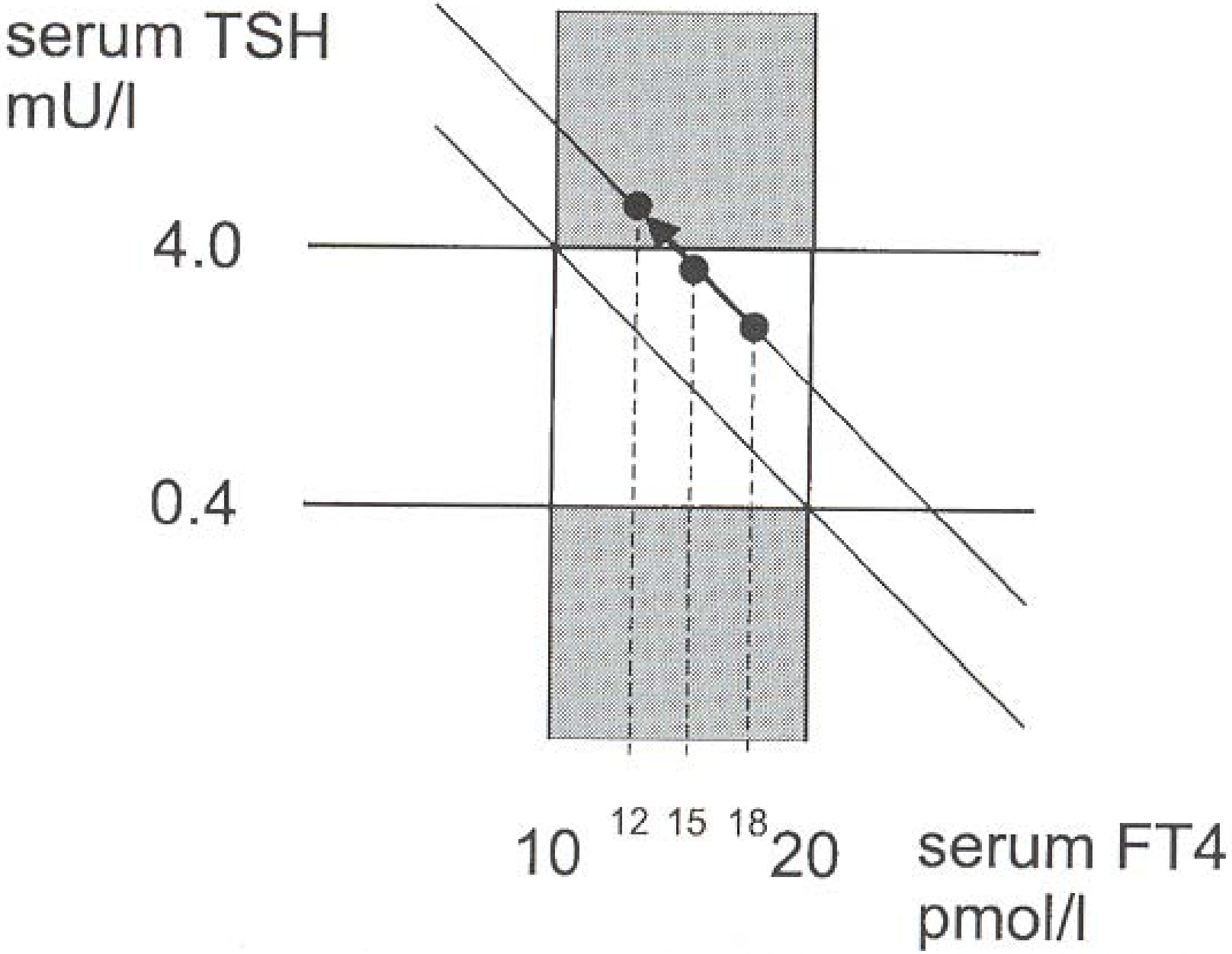
TSH 10 mU/l
FT4 12 pmol/l

no complaints

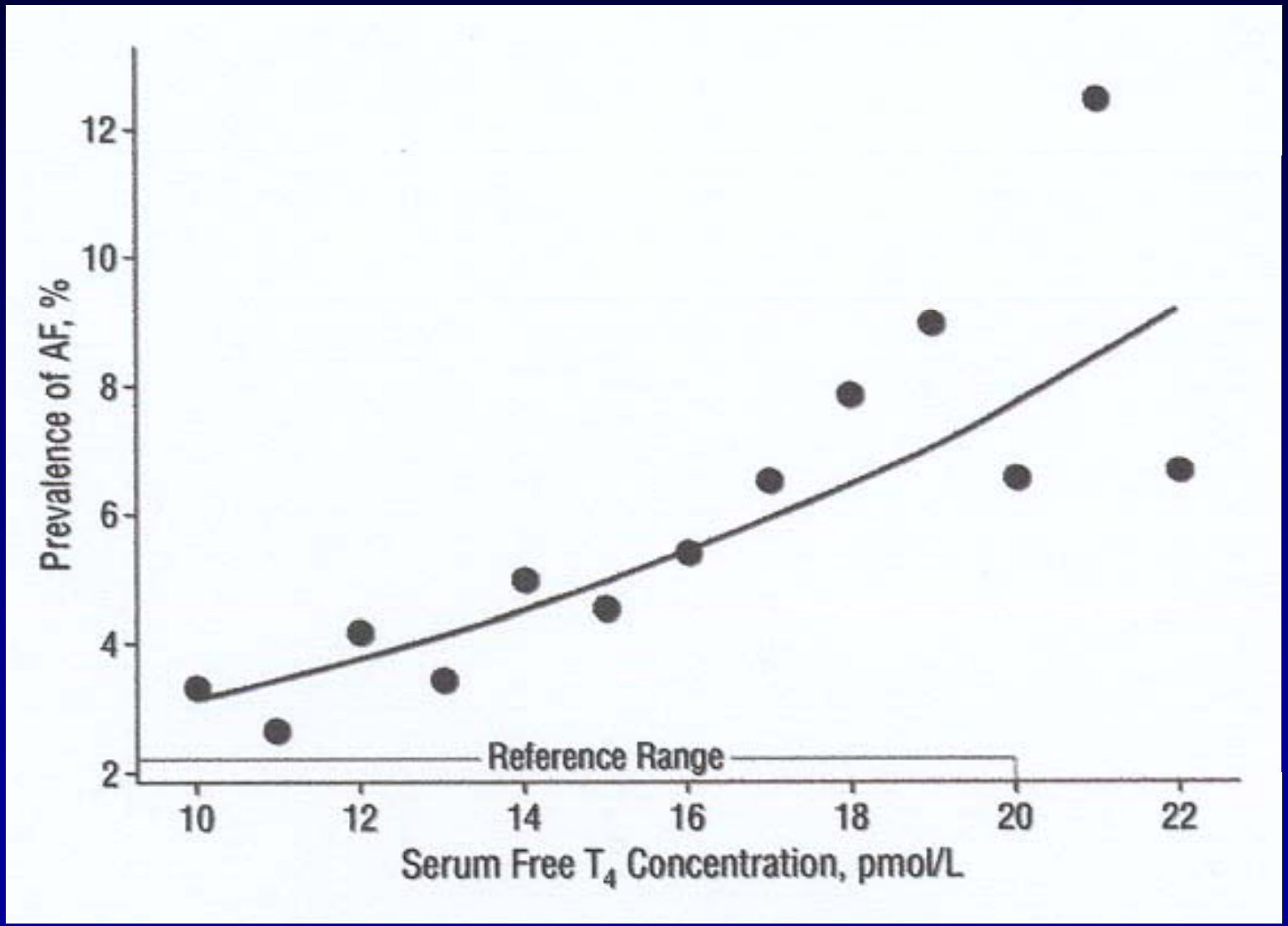
PATIENT B

TSH 10 mU/l
FT4 12 pmol/l

complaints,
disappearing on T4 treatment

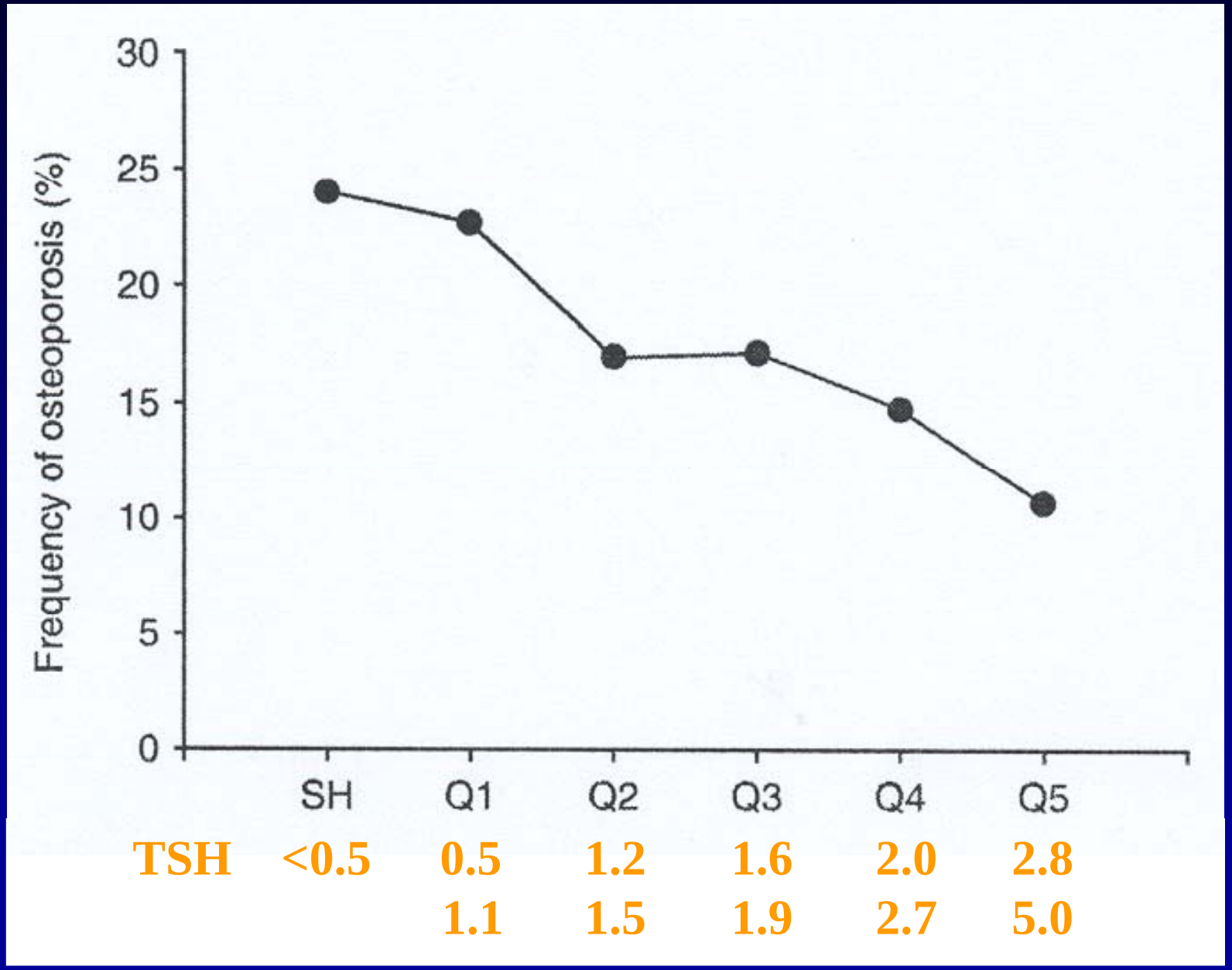

serum TSH
mU/l
4.0
0.4
10
12
15
18
20
serum FT4
pmol/l

FT4 WITHIN THE REFERENCE RANGE AS A RISK OF ATRIAL FIBRILLATION IN SUBJECTS >65 YR



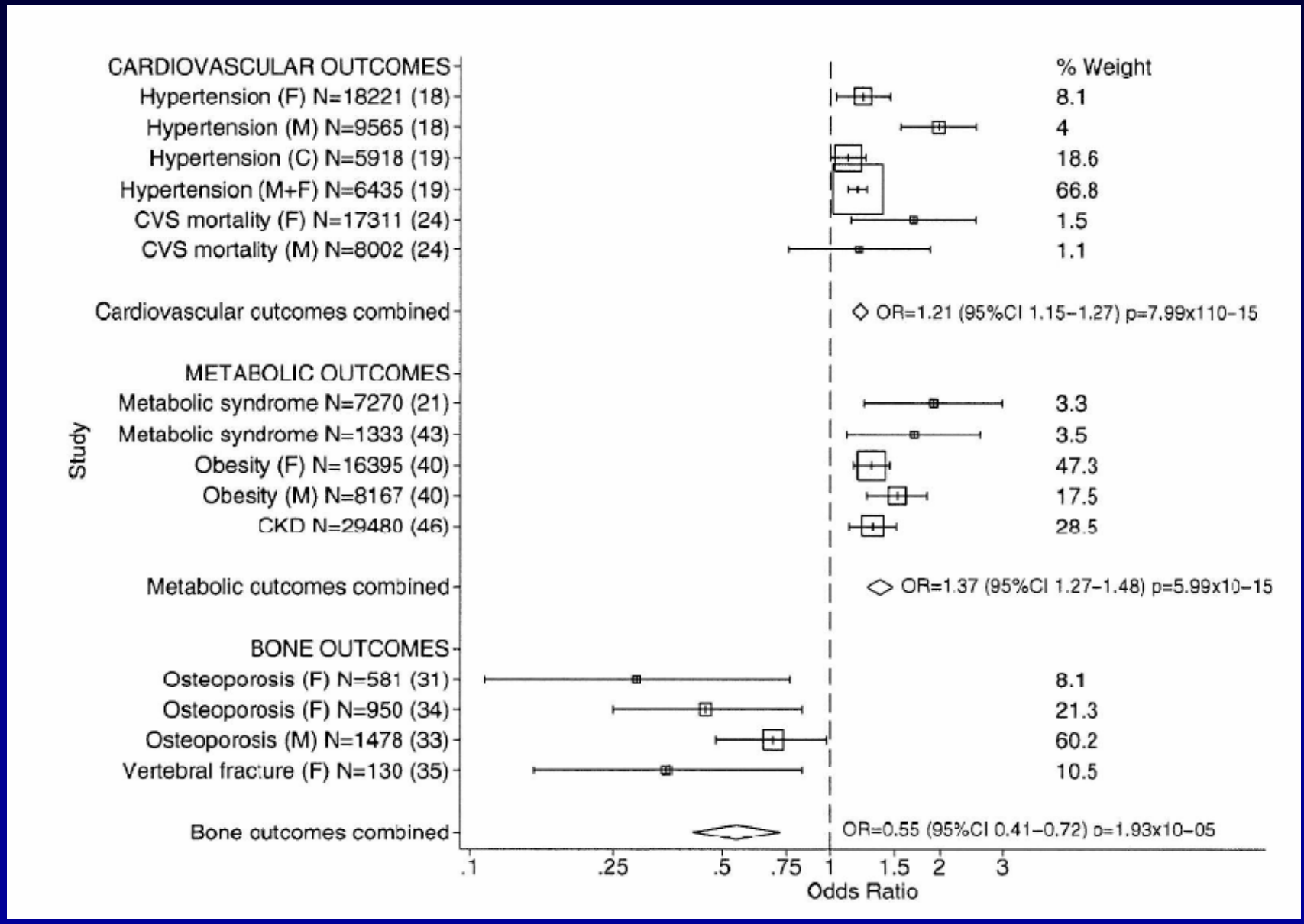
Gammage et al., Arch Int Med 2007

TSH WITHIN THE REFERENCE RANGE AS A RISK OF OSTEOPOROSIS IN HEALTHY POSTMENOPAUSAL WOMEN



Kim et al., Clin Endocrinol 2006

ADVERSE OUTCOMES OF HIGHER TSH LEVELS WITHIN THE REFERENCE RANGE



Taylor et al. JCEM 2013; 98: 3562

SUBCLINICAL HYPO/HYPERTHYROIDISM

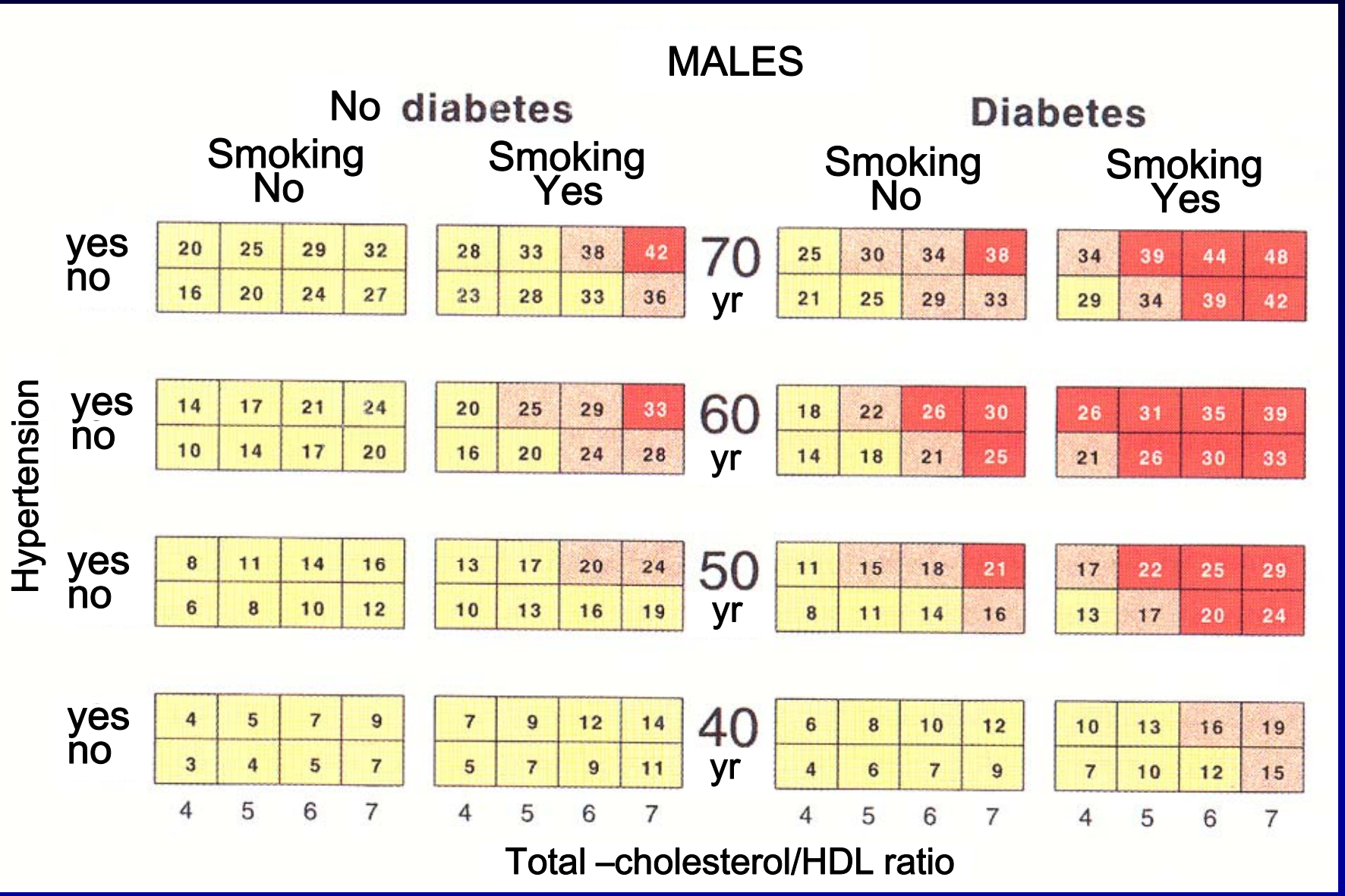
1. Subclinical hypo/hyperthyroidism is a misnomer:
   - clinical signs and symptoms may or may not be present
   - defined by biochemical criteria: TSH (but not FT4 or FT3) outside reference range

2. Reference ranges have clear limitations

3. Associated risks also observed for values within reference range

4. Utility of treatment at a particular TSH level may depend on other risk factors (like age, sex, smoking, blood pressure, lipids, diabetes)
   - indication for treatment by risk charts?

INDICATION FOR STATIN TREATMENT BASED ON ABSOLUTE RISK (%) TO DEVELOP ISCHEMIC HEART DISEASE IN THE NEXT 10 YEARS



SUBCLINICAL THYROID DYSFUNCTION

1. Definitions and conceptual problems

2. Subclinical hypothyroidism
   - prevalence and natural history
   - associations
   - management

3. Subclinical hyperthyroidism

PREVALENCE AND NATURAL HISTORY OF SUBCLINICAL HYPOTHYROIDISM

1. PREVALENCE
   - 5-10% in the general population
   - higher in women than in men, increases with advancing age

2. NATURAL HISTORY
   - Cardiovascular Health Study of subjects ≥ 65 yr - after 2 yr:
   - 35% spontaneous normalization of TSH

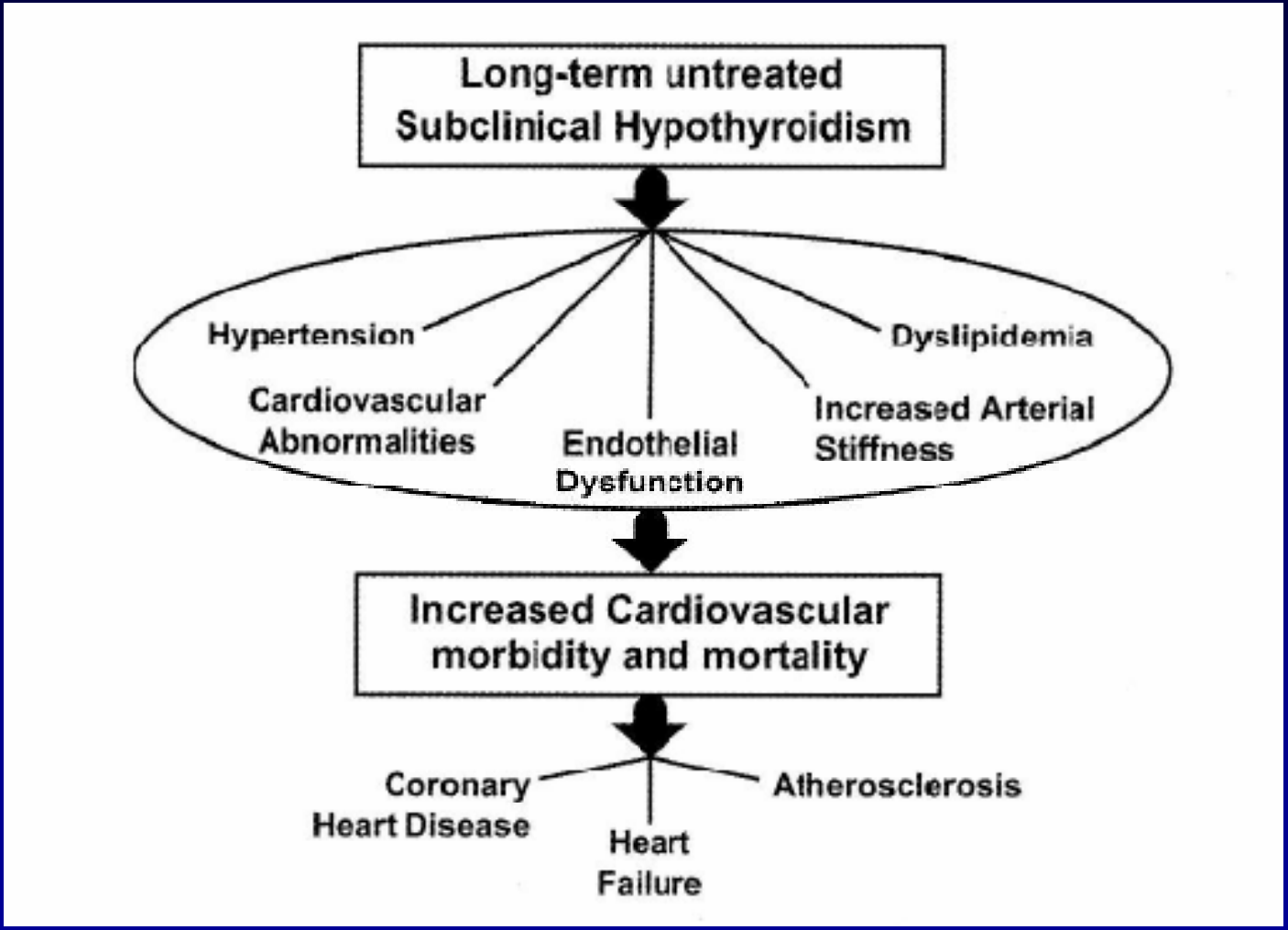
     TSH 4.5-6.9 mU/L 46% TPO-Ab negative 48%

     TSH 7.0-9.9 mU/L 15% TPO-Ab positive 15%

     TSH ≥ 10 mU/L 7%
   - 56% persistent subclinical hypothyroidism
   - 2% progression to overt hypothyroidism predominantly TSH ≥ 10 mU/L

Somwaru et al. JCEM 2012; 97: 1962

POTENTIAL CARDIOVASCULAR RISK OF LONG-TERM SUBCLINICAL HYPOTHYROIDISM



Biondi et al. BPRCEM 2012; 26: 431

SUBCLINICAL HYPOTHYROIDISM AND RISK OF ADVERSE HEALTH OUTCOMES

1. Adverse health outcomes
   - cardiovascular, bones, metabolism, mental health

2. Cross-sectional association studies → prevalence of outcomes
   Longitudinal association studies → incidence of outcomes

3. Large discrepancies in outcomes between individual studies
   - absent and present (positive or negative) associations are described
   - many confounders, too small sample size

4. Association may not necessarily imply causation
   - but causal relationship often likely in view of dose-response relationship with TSH and biologic plausibility

5. Progress by pooling studies: meta-analyses

SUBCLINCAL HYPOTHYROIDISM AND RISK OF ISCHEMIC HEART DISEASE : EFFECT OF AGE

15 studies with 2531 subclinical hypothyroid and 26491 euthroid subjexts

	Odds ratio Subclinical hypo <65 yr	**Odds ratio Subclinical hypo ≥65 yr**
Prevalence IHD	1.57 (1.19 – 2.06) P<0.001	1.01 (0.87 – 1.18) NS
Incidence IHD	1.68 (1.27 – 2.23) P<0.001	1.02 (0.85 – 1.22) NS
Mortality IHD	1.37 (1.04 – 1.79) P=0.02	0.85 (0.56 – 1.29) NS

Razvi et al. JCEM 2008; 93: 2998

SUBCLINICAL HYPOTHYROIDISM AND RISK OF CORONARY HEART DISEASE (CHD) – ROLE OF TSH

individual data analysis of 55287 participants from 11 cohorts with 542494 person-years of follow-up

	Hazard ratio TSH 4.5-6.9 mU/L	Hazard ratio TSH 7.0-9.9 mU/L	Hazard ratio TSH 10-19.9 mU/L	P for trend
CHD events	1.00 (0.86 – 1.18)	1.17 (0.96 – 1.43)	1.89 (1.28 – 2.80)	<0.001
CHD mortality	1.09 (0.91 – 1.30)	1.42 (1.03 – 1.95)	1.58 (1.10 – 2.27)	0.005

Hazard ratio's adjusted for age and sex; HR 1.0 (reference) TSH 0.45-4.49 mU/L)

Rodondi et al. JAMA 2010; 304: 1365

SUBCLINICAL HYPOTHYROIDISM AND RISK OF CORONARY HEART DISEASE - ROLE OF TPO-Ab

individual data analysis of 38274 participants from 6 cohorts with 460333 person-years of follow-up

	Hazard ratio TPO-Ab positive	Hazard ratio TPO-Ab negative	P-value
CHD events	1.16 (0.87 – 1.56)	1.26 (1.02 – 1.56)	NS
CHD mortality	1.15 (0.87 – 1.53)	1.26 (1.01 – 1.58)	NS

Hazard ratio's adjust for age and sex; HR 1.0 (reference) TSH 0.45-4.49 mU/L

Collet et al. JCEM 2014; 99: 3353

SUBCLINICAL HYPOTHYROIDISM AND RISK OF HEART FAILURE – ROLE OF TSH

individual data analysis of 25390 participants from 6 cohorts with 216248 person-years of follow-up

	Hazard ratio TSH 4.5-6.9 mU/l	Hazard ratio TSH 7.0-9.9 mU/L	Hazard ratio TSH 10-19.9 mU/L	P for trend
Heart failure	1.01 (0.81 – 1.26)	1.65 (0.84 – 3.23)	1.86 (1.27 – 2.72)	<0.01

Hazard ratio's adjusted for age and sex; HR 1.0 (reference) TSH 0.45- 4.49 mU/L

Gencer et al. Circulation 2012; 126: 1040

EXOGENOUS SUBCLINICAL HYPOTHYROIDISM AND RISK OF ADVERSE HEALTH OUTCOMES

Population-based study of all patients taking L-T4 in Tayside, Scotland

Category		Prevalence	Hazard ratio (95% CI)
Normal TSH	0.4-4.0 mU/L	61.7%	Reference 1.0
High TSH	> 4.0 mU/L	11.2%	1.83 (1.41-2.37) fractures 1.80 (1.33-2.44) dysrhythmias 1.95 (1.73-2.21) cardiovascular diseases

Flynn et al. JCEM 2010; 95: 186

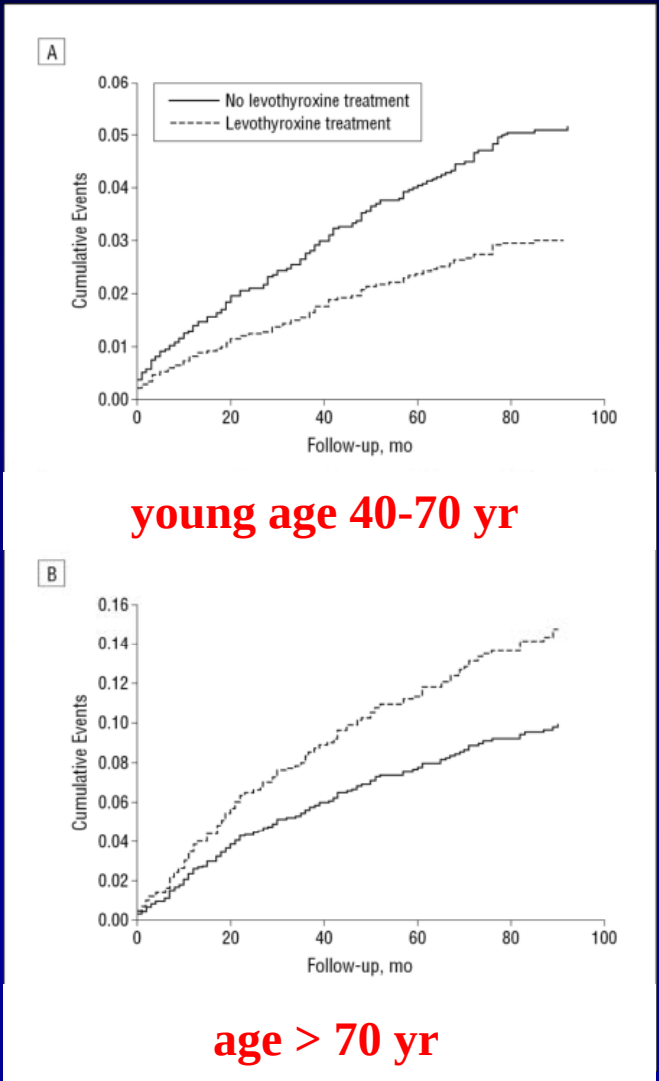
BENEFIT OF T4 TREATMENT OF SUBCLINICAL HYPOTHYROIDISM: A META-ANALYSIS

- 12 randomized clinical trials comparing T4 with placebo or nothing
  350 subjects, duration 6-14 months

- no improvement of survival or cardiovascular morbidity
- no improvement of quality-of-life or symptoms
- some improvement of lipids and left ventricular function

Cochrane Database Syst Rev 2007

EFFECT OF L-T4 TREATMENT OF SUBCLINICAL HYPOTHYROIDISM ON INCIDENT ISCHEMIC HEART DISEASE (IHD) - EFFECT OF AGE



young age 40-70 yr

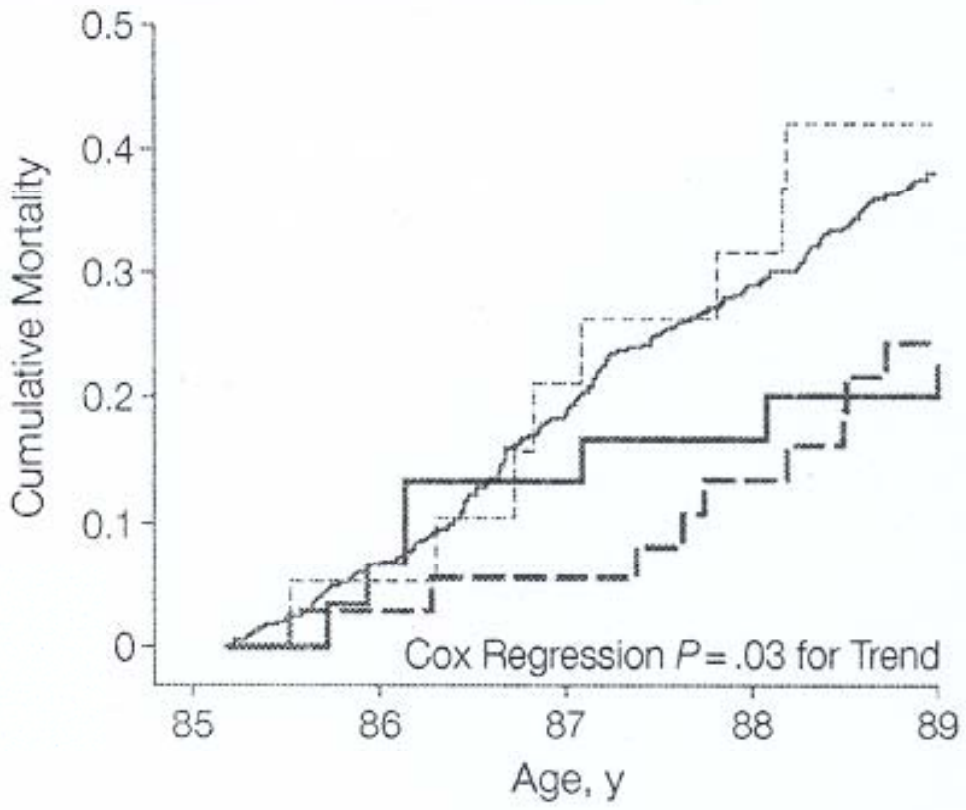
age > 70 yr

GP reseach database UK 2001-2009
Subclinical hypo TSH 5-10 mU/L

	Young age 40-70 yr	Old age >70 yr
On L-T4	52.8%	49.9%
Incident IHD untreated	6.6%	10.7%
Incident IHD treated	4.2%	12.7%
Hazard ratio (95% CI)	0.61 (0.39 – 0.95)	0.99 (0.59 – 1.33)

Ravzi et al. Arch Int Med 2012; 172: 811

CUMULATIVE MORTALITY IN THE LEIDEN 85-PLUS STUDY



Abnormally Low Thyrotropin	19	18	15	13	11
Normal Thyrotropin	472	441	385	335	287
Abnormally High Thyrotropin					
Normal Free Thyroxine	30	28	26	25	23
Low Free Thyroxine	37	36	35	32	28

Gussekloo et al. JAMA 2004; 292: 2591-2599

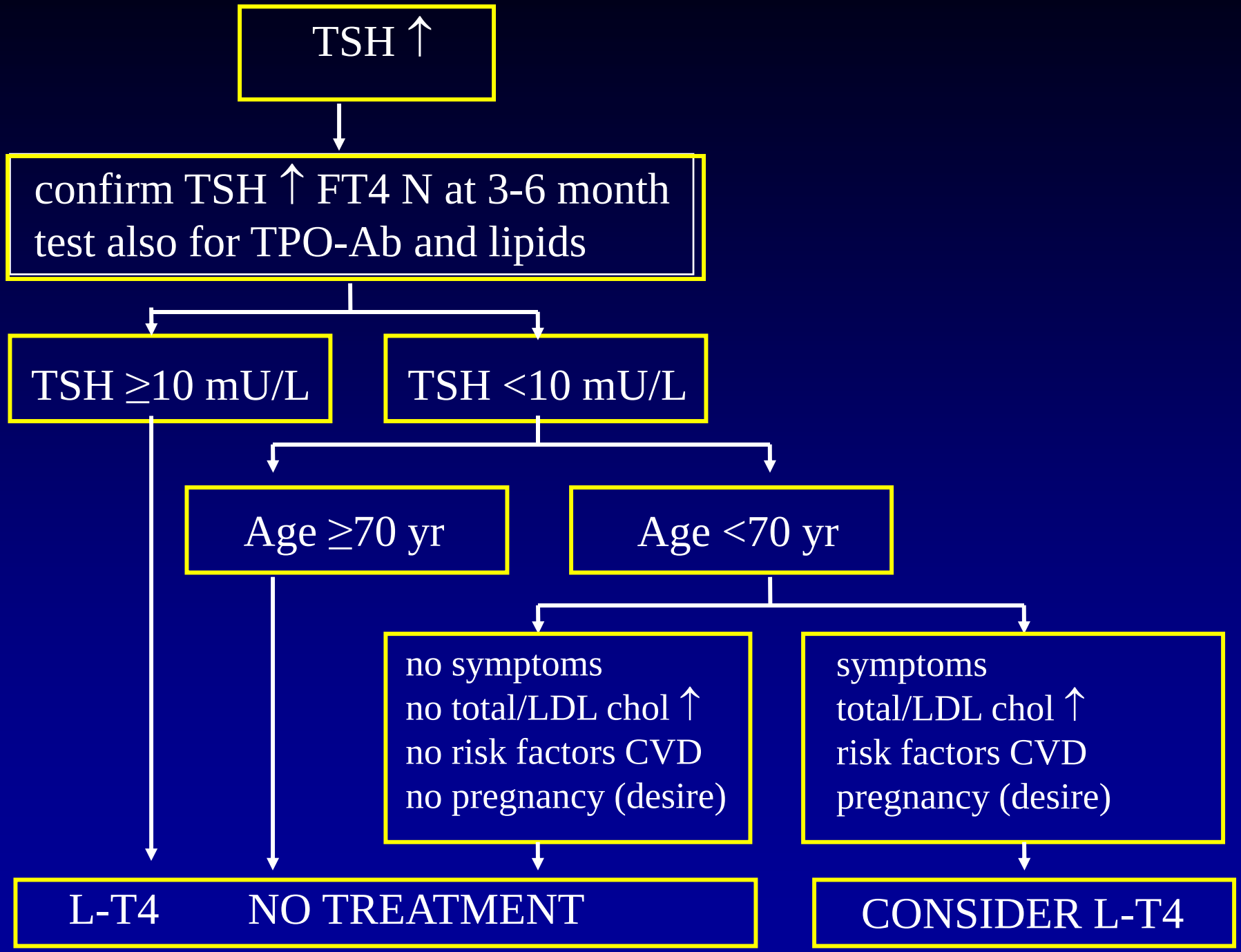
DIFFERENTIAL DIAGNOSIS OF ELEVATED TSH BUT NORMAL FT4

THYROID DISEASE

- chronic autoimmune thyroiditis
- thyroidectomy, 131I therapy
- inappropriate dosage of antithyroid drugs

NO THYROID DISEASE

- assay interference by heterophilic antibodies
- euthyroid sick syndrome (recovery phase)
- impaired renal function
- adrenal insufficiency
- TSHoma, RTH


TSH ↑
confirm TSH ↑ FT4 N at 3-6 month
test also for TPO-Ab and lipids
TSH ≥10 mU/L
TSH <10 mU/L
Age ≥70 yr
Age <70 yr
no symptoms
no total/LDL chol ↑
no risk factors CVD
no pregnancy (desire)
symptoms
total/LDL chol ↑
risk factors CVD
pregnancy (desire)
L-T4
NO TREATMENT
CONSIDER L-T4

SUBCLINICAL THYROID DYSFUNCTION

1. Definitions and conceptual problems

2. Subclinical hypothyroidism

3. Subclinical hyperthyroidism
   - prevalence and natural history
   - associations
   - management

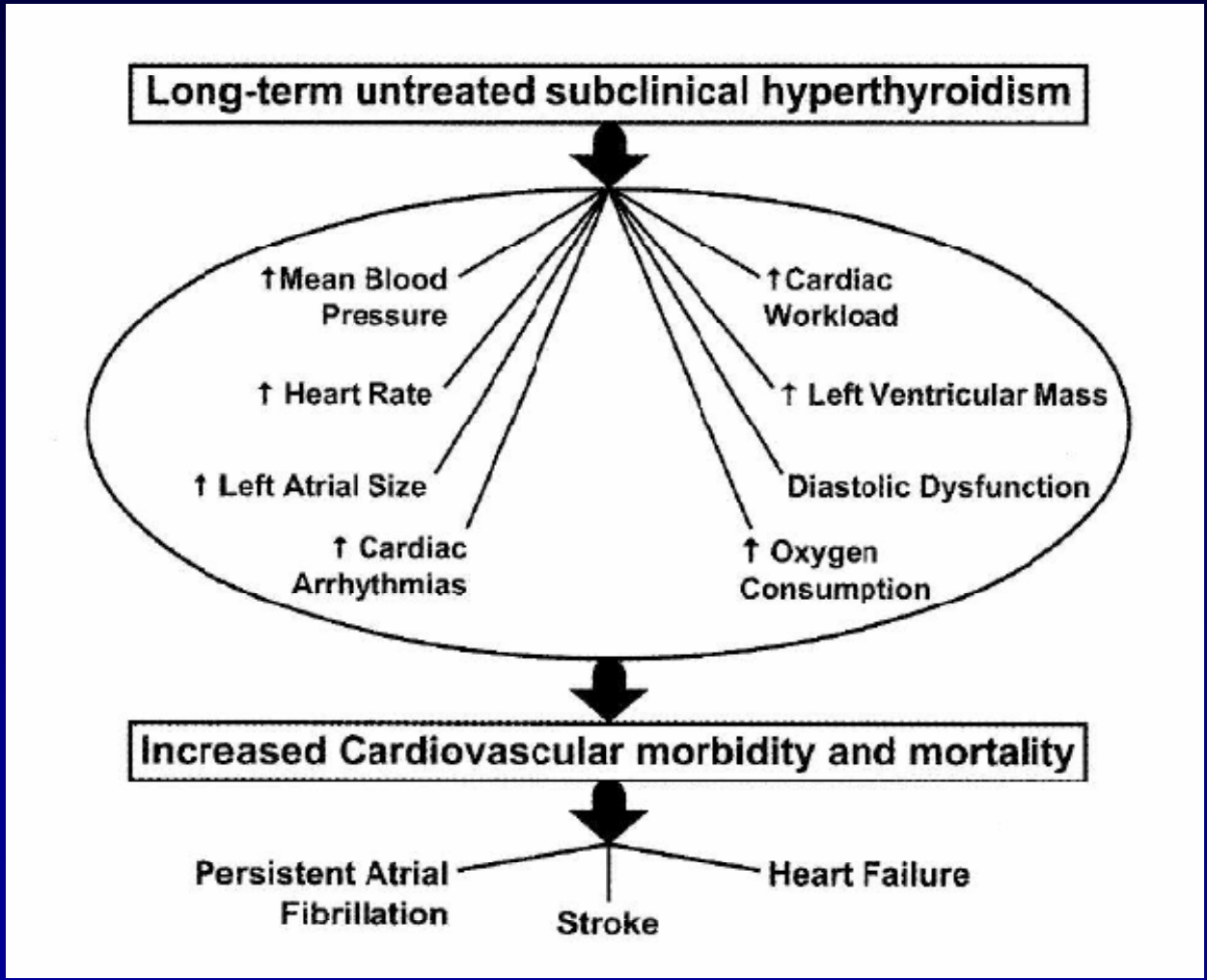
PREVALENCE AND NATURAL HISTORY OF SUBCLINICAL HYPERTHYROIDISM

1. PREVALENCE
   - 0.7 - 3.2% in the general population
   - higher in women than in men, increases with advancing age

2. NATURAL HISTORY
   - 24% spontaneous normalization of TSH at 3.5 yr
     TSH 0.1-0.4 mU/L 35% at 7 yr
     TSH <0.1 mU/L rarely
   - 73% persistence of subclinical hyperthyroidism at 3.5 yr
     63% at 7 yr
   - 3% progression to overt hypothyroidism at 3.5 yr
     TSH 0.1-0.4 mU/L rarely 0.5-0.7% at 7 yr
     TSH <0.1 mU/L 26% at 5 yr (9% Graves' disease, 21% multinodular goiter, 61% autonomous nodule)

Rosario CE 2010; 72: 685; Schouten et al. CE 2011; 74: 257; Vadiveloo JCEM 2011; 96: E1

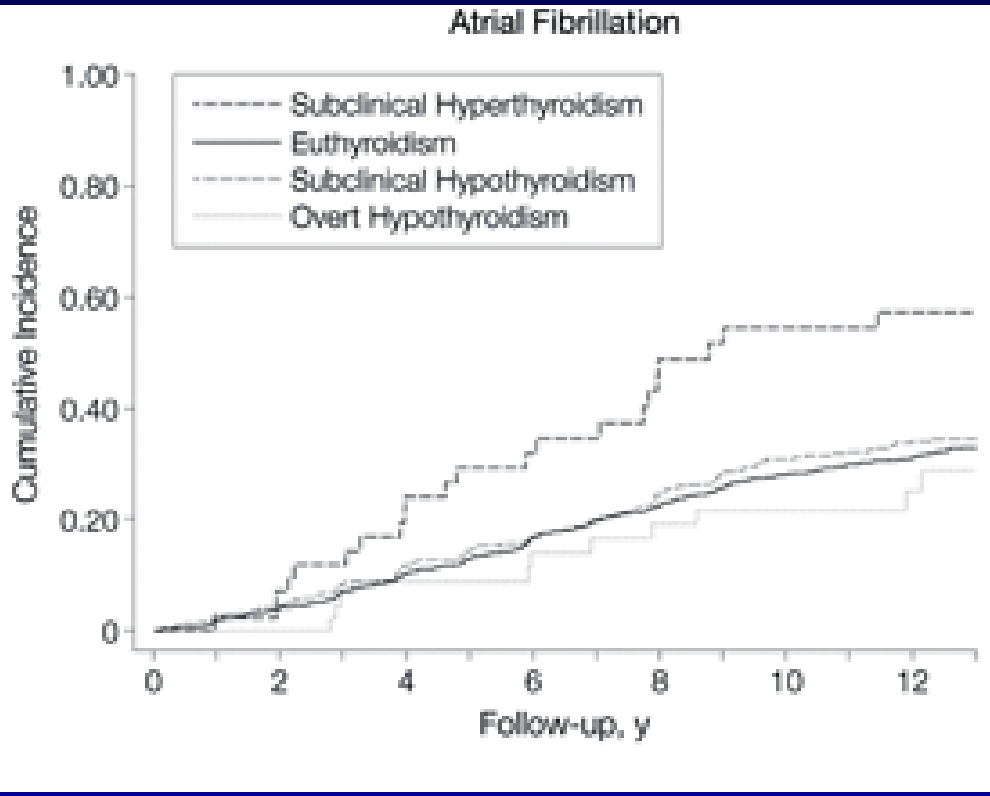
POTENTIAL CARDIOVASCULAR RISK OF LONG-TERM SUBCLINICAL HYPERTHYROIDISM

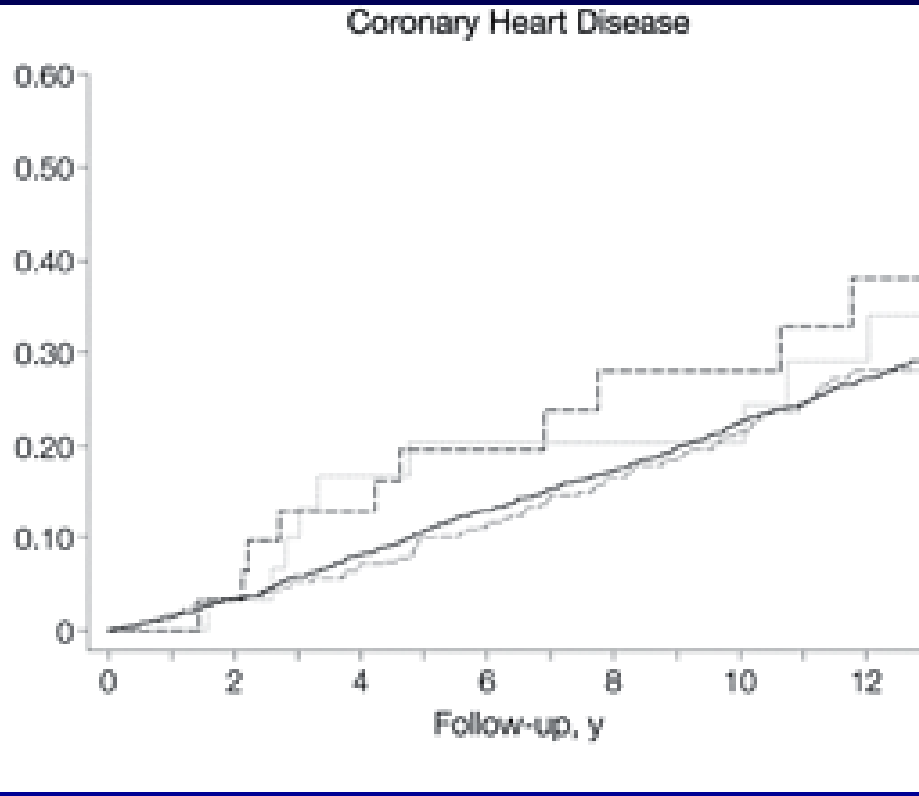


Biondi et al. BPRCEM 2012; 26: 431

SUBCLINICAL HYPERTHYROIDISM AND RISK OF ATRIAL FIBRILLATION

the US Cardiovascular Health Study in the 65+ population

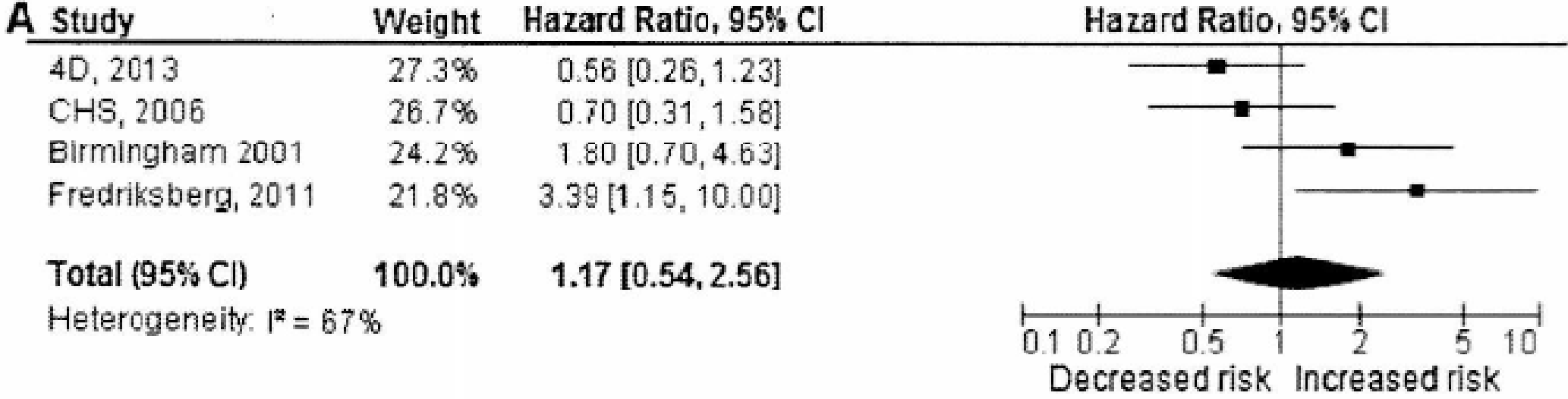




Cappola et al. JAMA 2006; 295: 1033

SUBCLINICAL HYPERTHYROIDISM AND RISK OF STROKE

11309 participants from 6 cohort studies with 665 stroke events



Chaker et al. Eur J Epidemiol 2014; 29: 791

SUBCLINICAL HYPERTHYROIDISM AND RISK OF HEART FAILURE – ROLE OF TSH

individual data analysis of 25390 participants from 6 cohorts with 216248 person-years of follow-up

	Hazard ratio TSH <0.1 mU/l	**Hazard ratio TSH 0.1-0.39 mU/L**	**P for trend**
Heart failure	1.94 (1.01 – 3.72)	1.31 (0.88 – 1.95)	0.047

Hazard ratio's adjusted for age and sex; HR 1.0 (reference) TSH 0.45- 4.49 mU/L

Gencer et al. Circulation 2012; 126: 1040

SUBCLINICAL HYPERTHYROIDISM AND RISK OF FRACTURES

50245 participants from 7 cohorts with 1966 hip and 3281 non-spine fractures

	Hazard ratio all subjects	**Hazard ratio exclusive subjects on L-T4**
Hip fractures	1.26 (0.96 – 1.65)	2.16 (0.87 – 5.37)
Non-spine fractures	1.16 (0.95 – 1.42)	1.43 (0.73 – 2.78)

Wirth et al. Ann Intern Med 2014; 161: 189

EXOGENOUS SUBCLINICAL HYPERTHYROIDISM AND RISK OF ADVERSE HEALTH OUTCOMES

Population-based study of all patients taking L-T4 in Tayside, Scotland

Category		Prevalence	Hazard ratio (95% CI)
Suppressed TSH	≤ 0.03 mU/L	6.1%	2.02 (1.55-2.62) fractures 1.60 (1.10-2.33) dysrhythmias 1.37 (1.10-1.60) cardiovascular diseases
Low TSH	0.04-0.4 mU/L	21.1%	1.13 (0.92-1.39) fractures 1.13 (0.88-1.47) dysrhythmias 1.10 (0.99-1.12) cardiovascular diseases
Normal TSH	0.4-4.0 mU/L	61.7%	Reference 1.0

Flynn et al. JCEM 2010; 95: 186

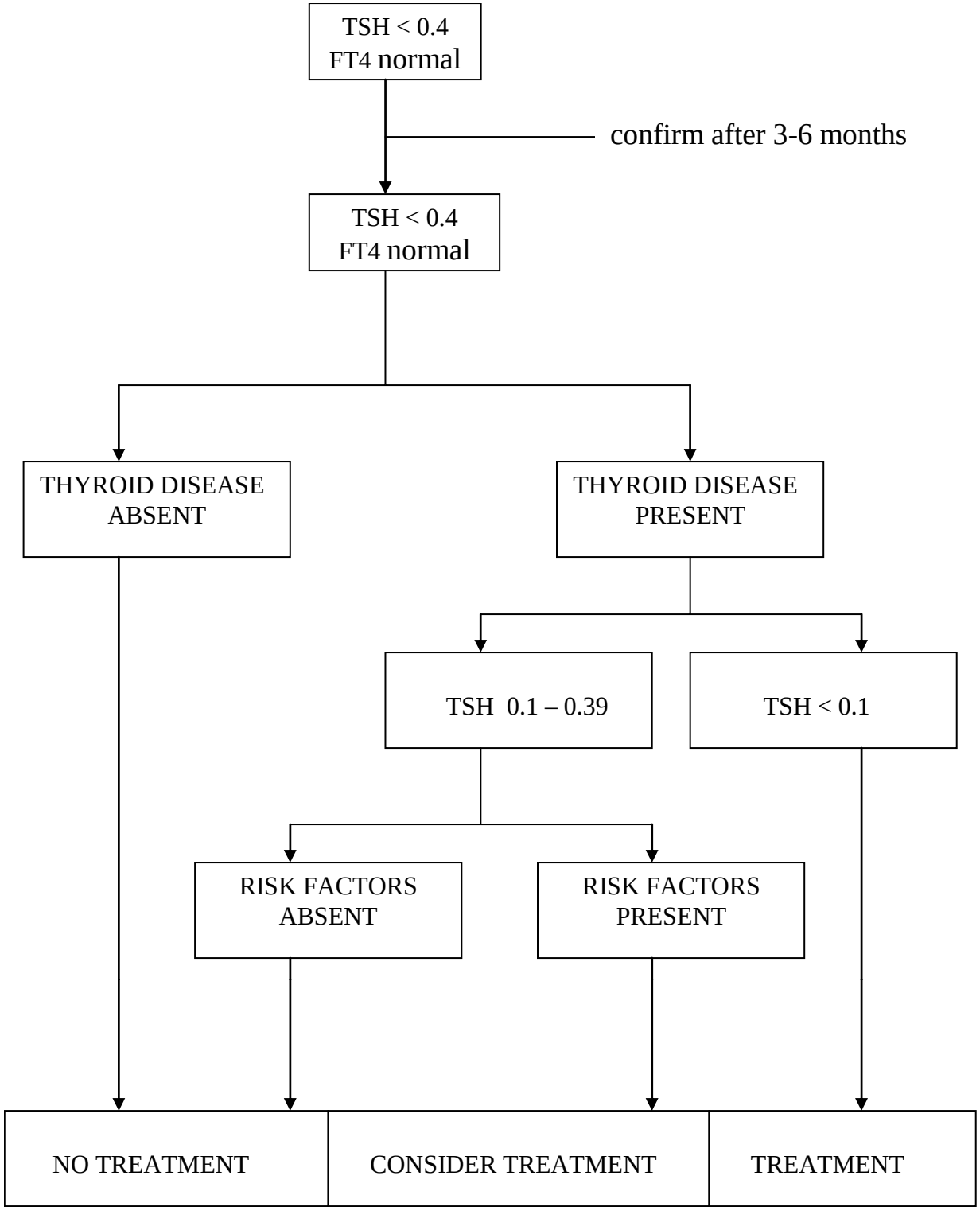
DIFFERENTIAL DIAGNOSIS OF DECREASED TSH BUT NORMAL FT4

THYROID DISEASE

- Graves' disease
- multinodular goiter
- autonomous thyroid nodule
- chronic lymphocytic thyroiditis
- excessive dosage of thyroxine

NO THYROID DISEASE

- pituitary disease
- dopaminergic drugs
- glucocorticoids (high doses)



RISK FACTORS

- **age >65 yr**
- **postmenopause**
- **osteoporosis**
- **cardiovascular risks**

SUBCLINICAL HYPO/HYPERTHYROIDISM
HOW TO END THE CONTROVERSY
TO TREAT OR NOT TO TREAT?

- Thyroid Studies Collaboration:
  - individual participant data from 55287 participants with 542494 person-years of follow-up from 11 international prospective cohorts
  - individual participant data analyses generally considered the highest level of nonrandomized evidence

- Randomized Clinical Trials
  - Thyoid hormone Replacement for Untreated older adults with Subclinical hypothyroidism Trial = TRUST
  - European Commission funded multicenter, double-blind, placebo-controlled randomized trial among 3000 adults age 65 and older with persistent subclinical hypothyroidism