Update in Endocrinologia Clinica
Tiroide e scompenso cardiaco

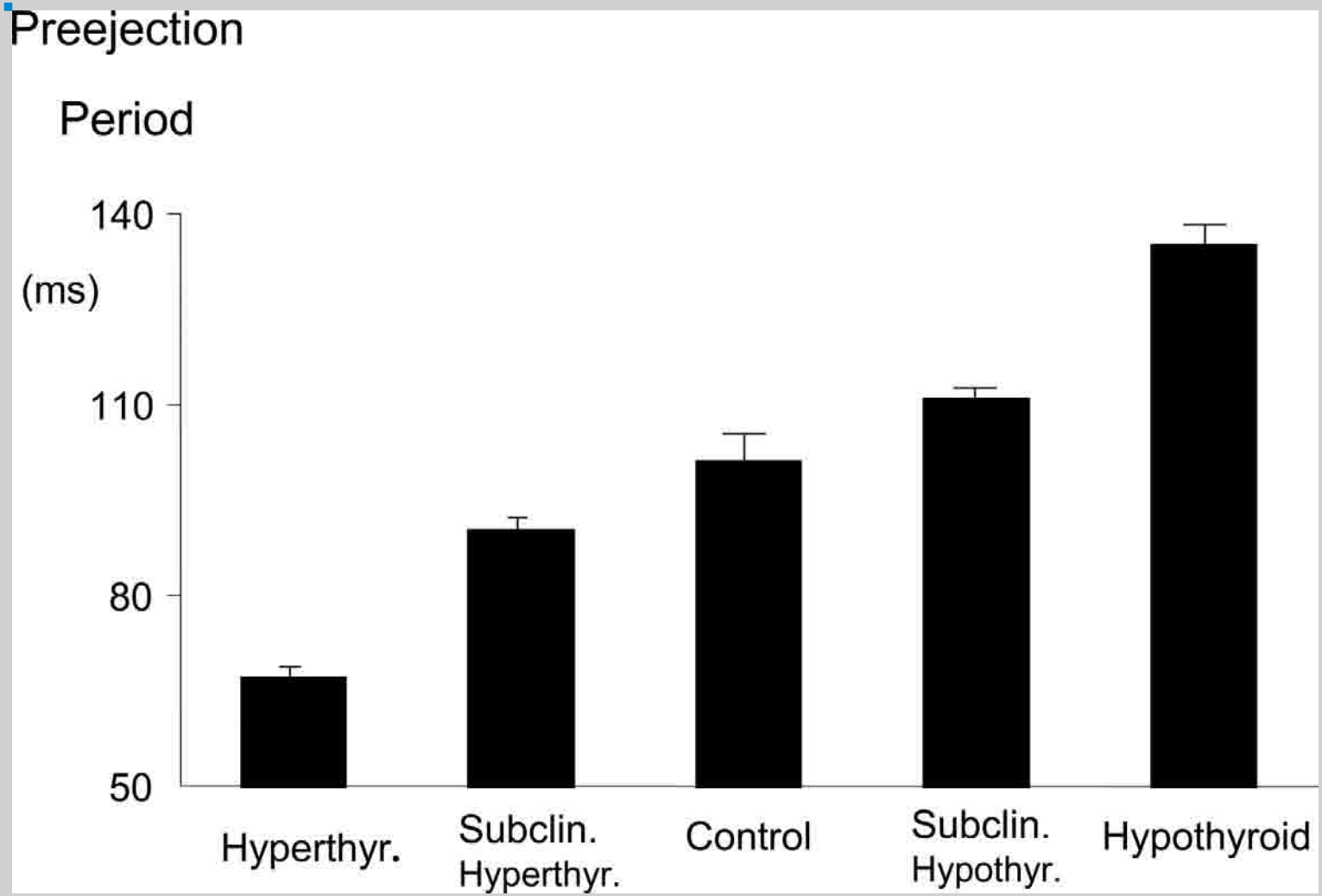
Bari,
7-10 novembre 2013

DISFUNZIONE TIROIDEA E SCOMPENSO CARDIACO: IL PUNTO DI VISTA DELL'ENDOCRINOLOGO

Fabio Monzani
Dipartimento di Medicina Clinica e Sperimentale
Università di Pisa

Effect of thyroid hormones on cardiac contractility

Bari,
7-10 novembre 2013



Kahaly et al. Endocr Rev, 2005

Isovolumic relaxation time, a measure of diastolic function, and thyroid status

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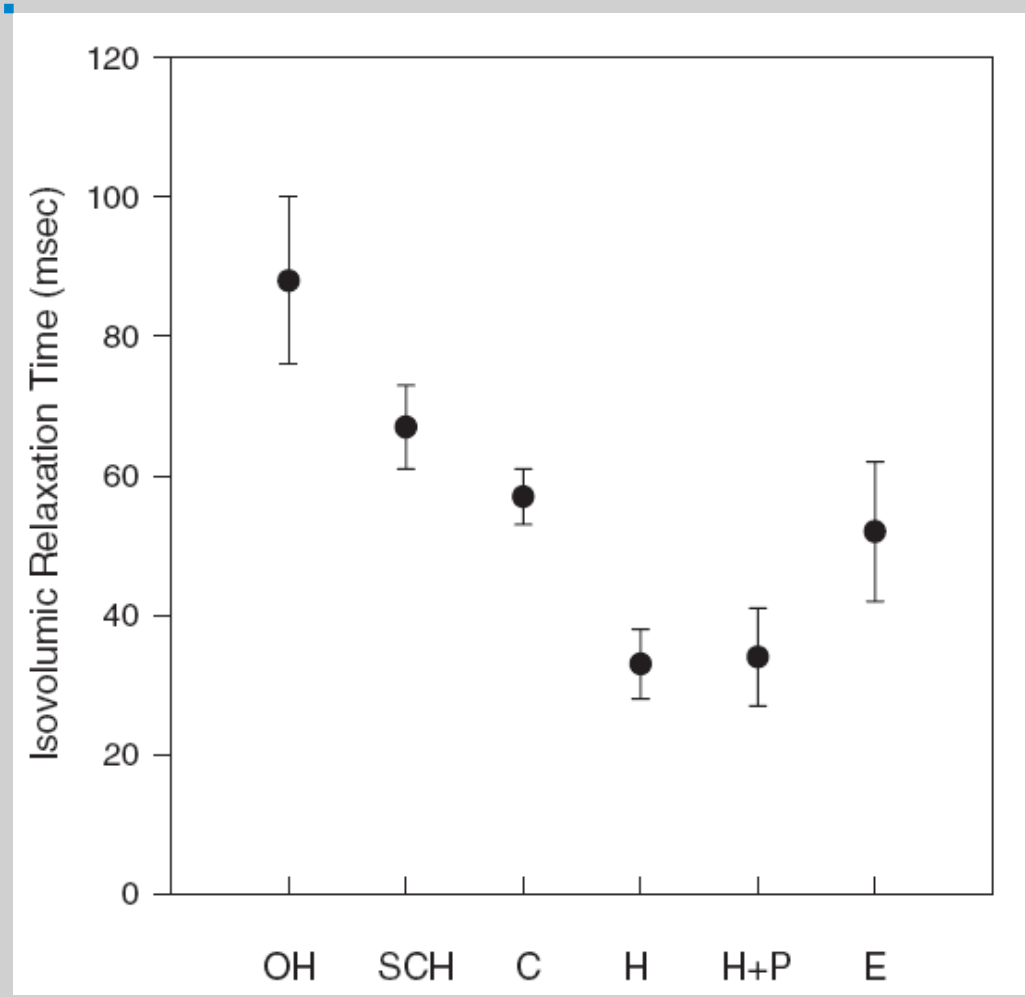

OH: overt hypothyroidism; SCH: subclinical hypothyroidism; C: controls; H: hyperthyroidism; H P: hyperthyroidism plus propranolol; E: hyperthyroidism after euthyroidism restoration

Klein et al. Circulation 2007

Systemic vascular resistance in normotensive patients with different degrees of thyroid dysfunction

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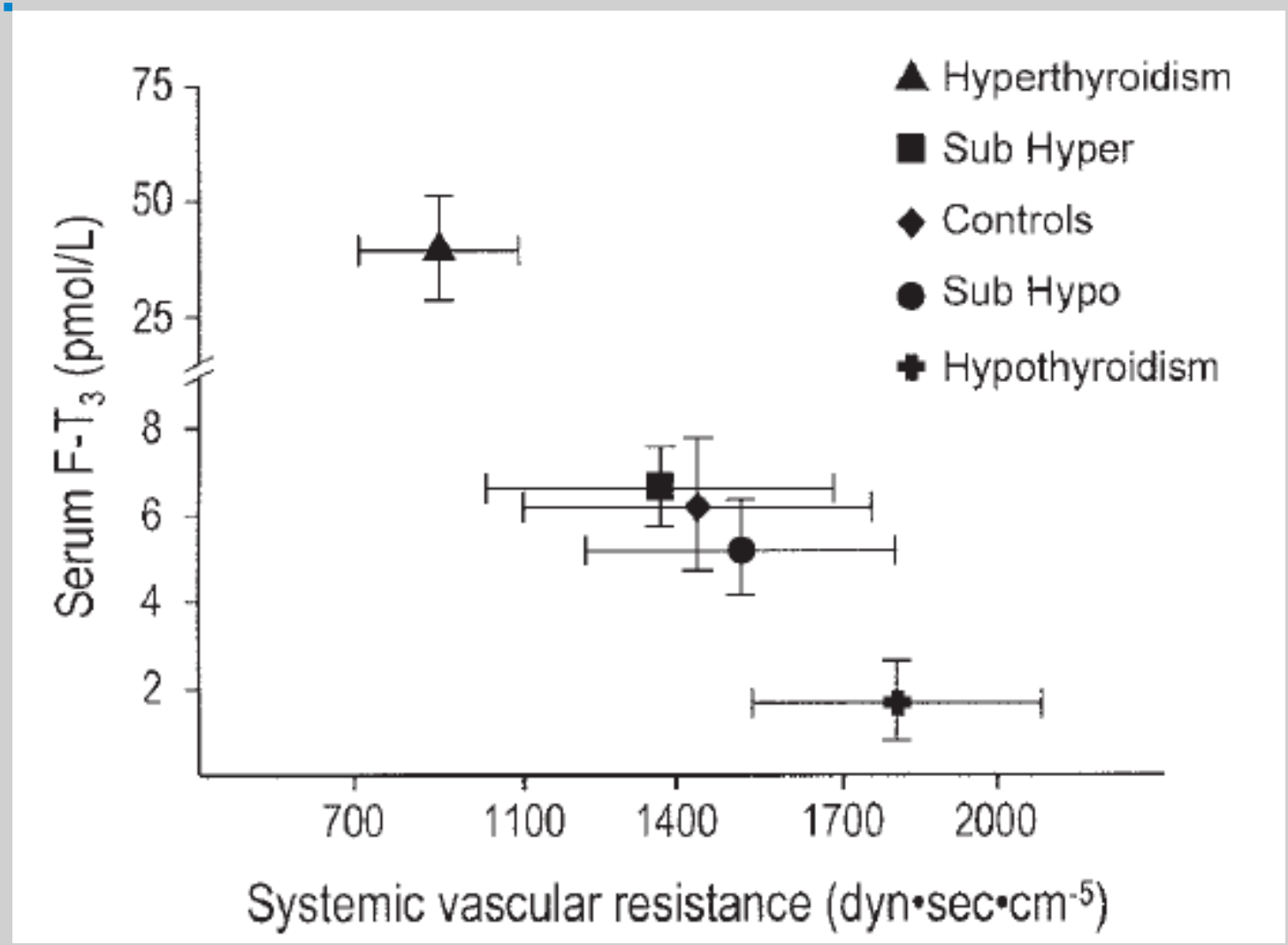

Biondi & Klein, Endocrine 2004

EPIDEMIOLOGIA DELL'IPERTIROIDISMO

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Età	Conclamato (%)	Subclinico (%)
<65 anni (n=255)	2	2
>65 anni (n=916)	1.6*	7.8

*1-2% aree iodio-sufficienti; 7-8% aree a carenza iodica

Biondi Cooper Endocrine Reviews 2008; *Ceresini G et al JACS 2009*

Subclinical Thyroid Disease

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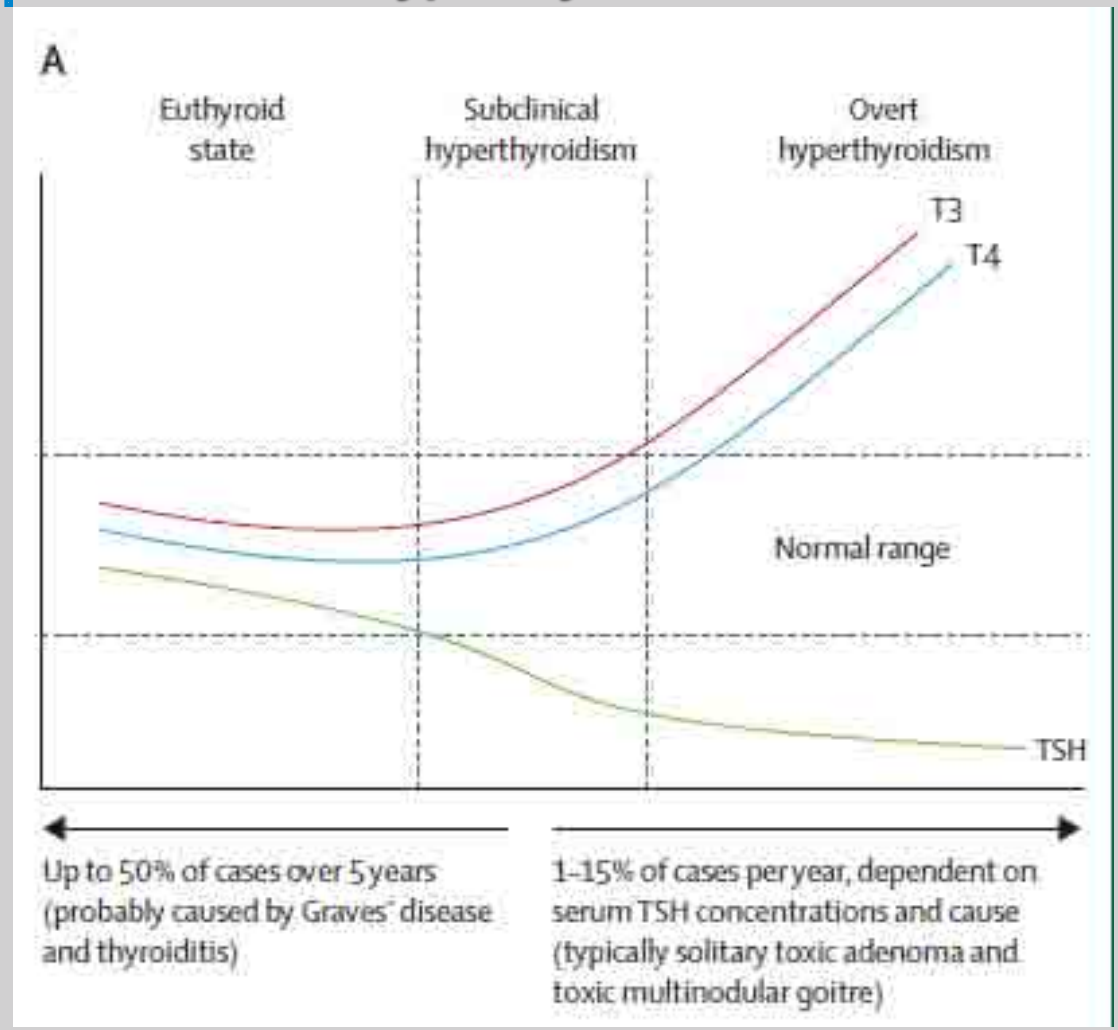
Development and progression or regression of subclinical hyperthyroidism



Cooper & Biondi Lancet 2012

Prevalence of Elevated Serum TSH by Decade of Age and Gender

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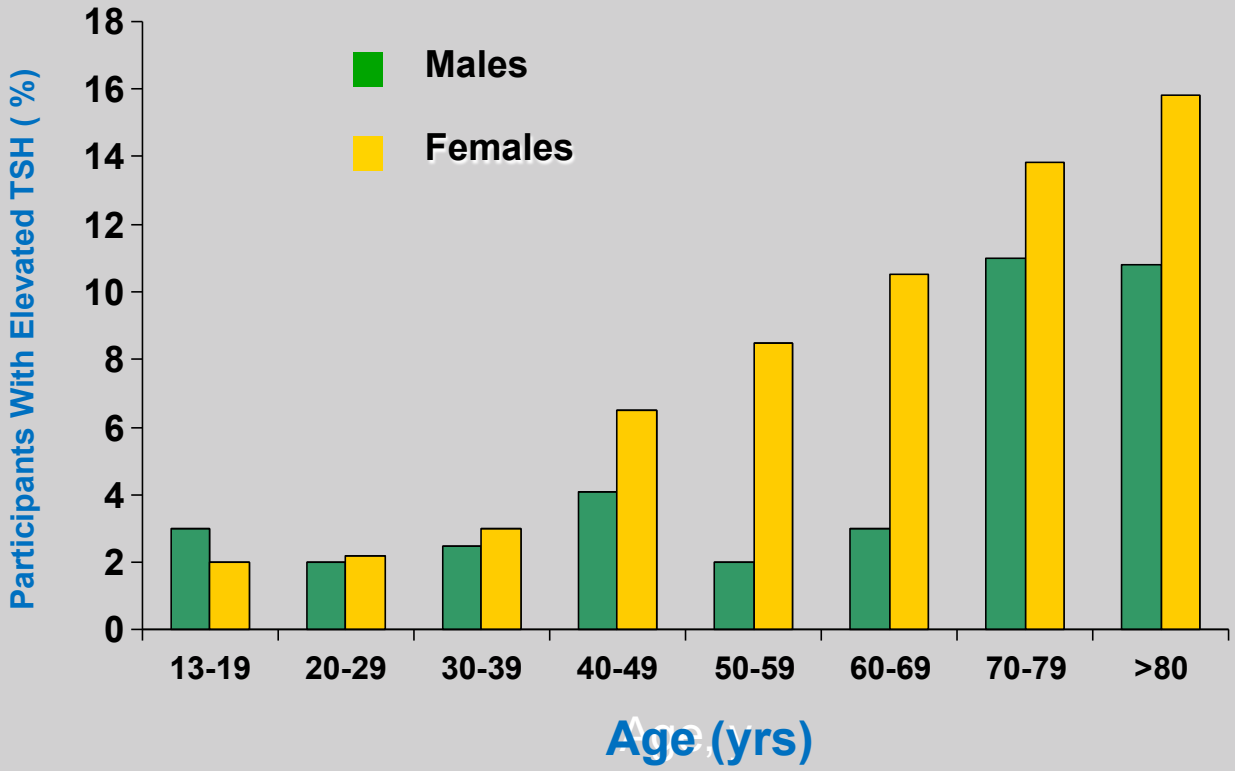
NHANES III Study (N=17 353)



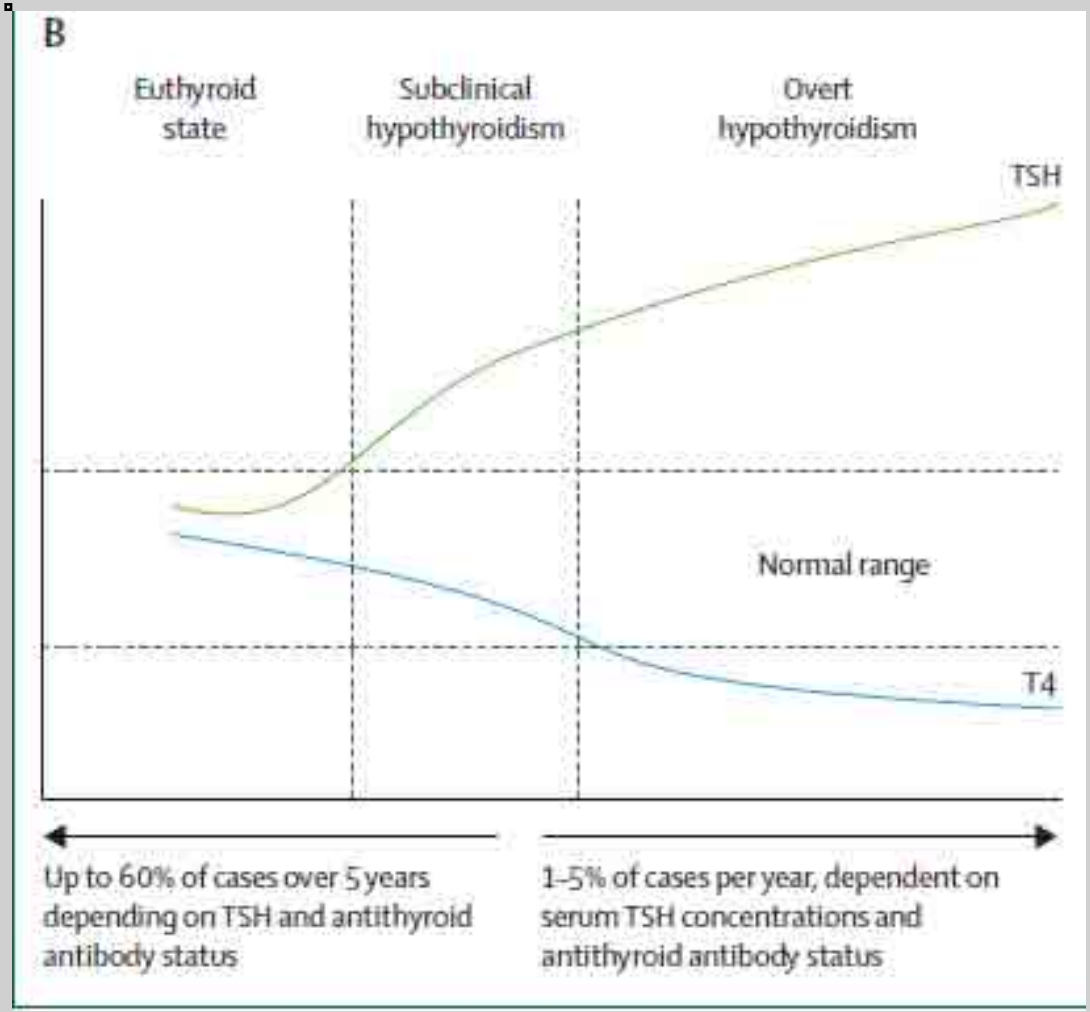
- Up to 40 years of age, prevalence is relatively low and similar between males and females
- Between 40 and 70 years of age, a higher percentage of female patients have elevated TSH levels
- At >70 years of age, prevalence is high and similar between males and females

Hollowell et al. JCEM 2002

Subclinical Thyroid Disease

Bari,
7-10 novembre 2013

Development and progression or regression of subclinical hypothyroidism



Cooper & Biondi Lancet 2012

TSH distribution by age groups

disease-free populations

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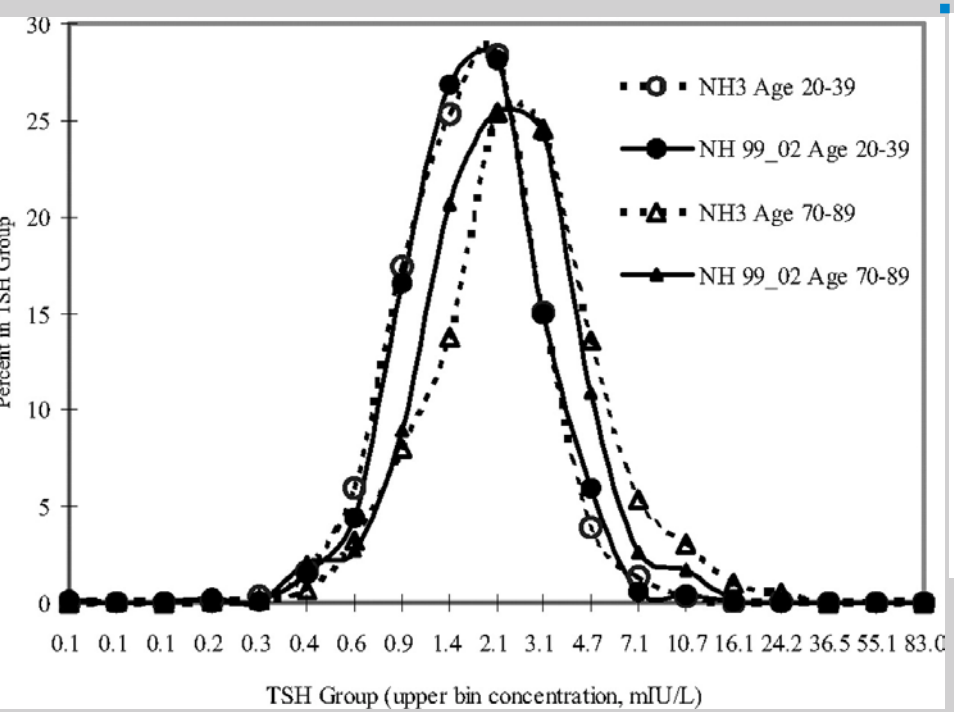

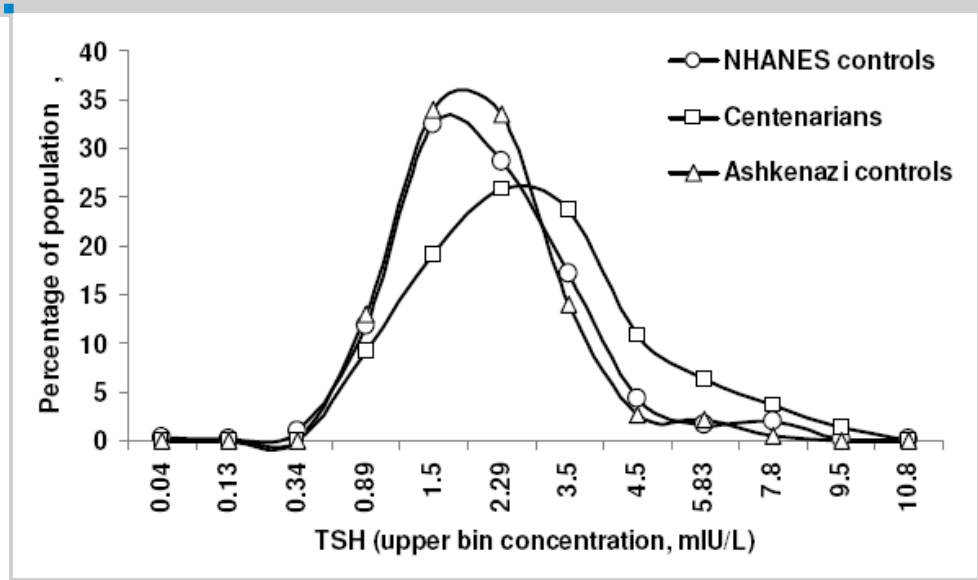

NHANES III (1988-1994) and NHANES 1999-2002

236 Ashkenazi Jewish centenarians living independently, median age: 97.7 yrs
188 younger unrelated Ashkenazi Jews (controls), median age: 71.0 yrs
605 NHANES controls, age range 60-79 yrs

Surks et al. JCEM 2007; Atzmon et al. JCEM 2009

Heart failure and thyroid dysfunction (Hyperthyroidism)

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High-output HF in hyperthyroidism

Congestive circulation may occur with increased cardiac output in the absence of underlying heart disease due to the effects of:

- Persistent tachycardia
- Increased cardiac preload
- Reduced systemic vascular resistance
- Elevated ventricular filling pressure
- Increased pulmonary arterial pressure

Low-output HF in hyperthyroidism

HF with low cardiac output may occur especially in elderly patients and in patients with underlying heart disease due to the effects of:

- Increased cardiac preload
- Impaired left ventricular filling
- Loss of atrial contribution to atrial fibrillation
- Rapid ventricular rate
- Increased systemic vascular resistance
- Decreased contractile reserve

Biondi B. Eur J Endocrinol 2012

Heart failure and thyroid dysfunction (Hypothyroidism)

Bari,
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HF may occur in patients with overt hypothyroidism and in elderly patients with subclinical hypothyroidism with TSH > 10 mU/l due to the effects of:

- Bradycardia
- Impaired systolic function
- Impaired left ventricular diastolic filling
- Increased systemic vascular resistance
- Diastolic hypertension
- Increased arterial stiffness
- Endothelial dysfunction

Biondi B. Eur J Endocrinol 2012

Concurrent effect of ageing and hypothyroidism on heart and vasculature

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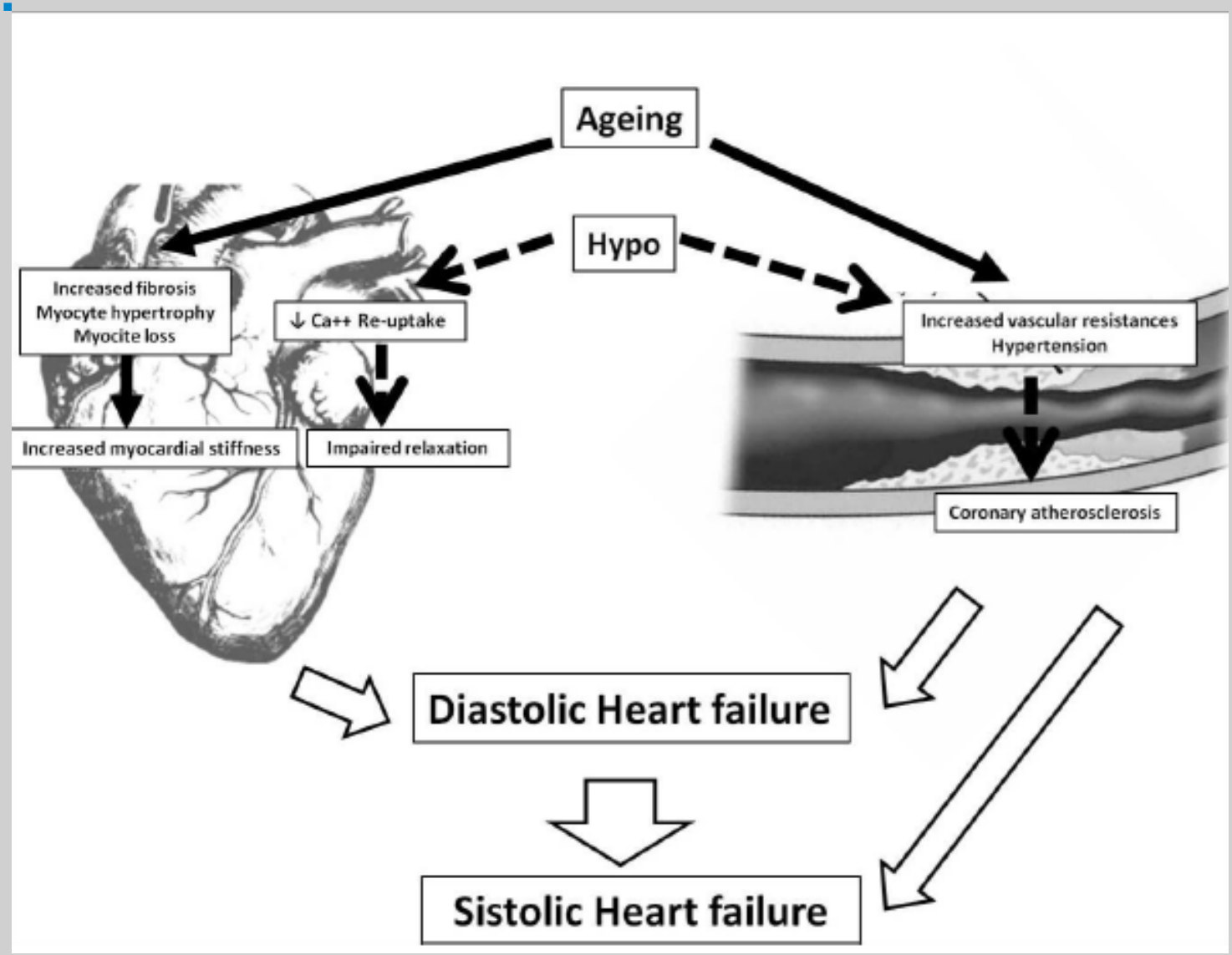

Pasqualetti et al. Endocrine, Metabolic & Immune Disorders - Drug Targets, 2013

Prognostic *impact of subclinical* thyroid dysfunction in heart failure

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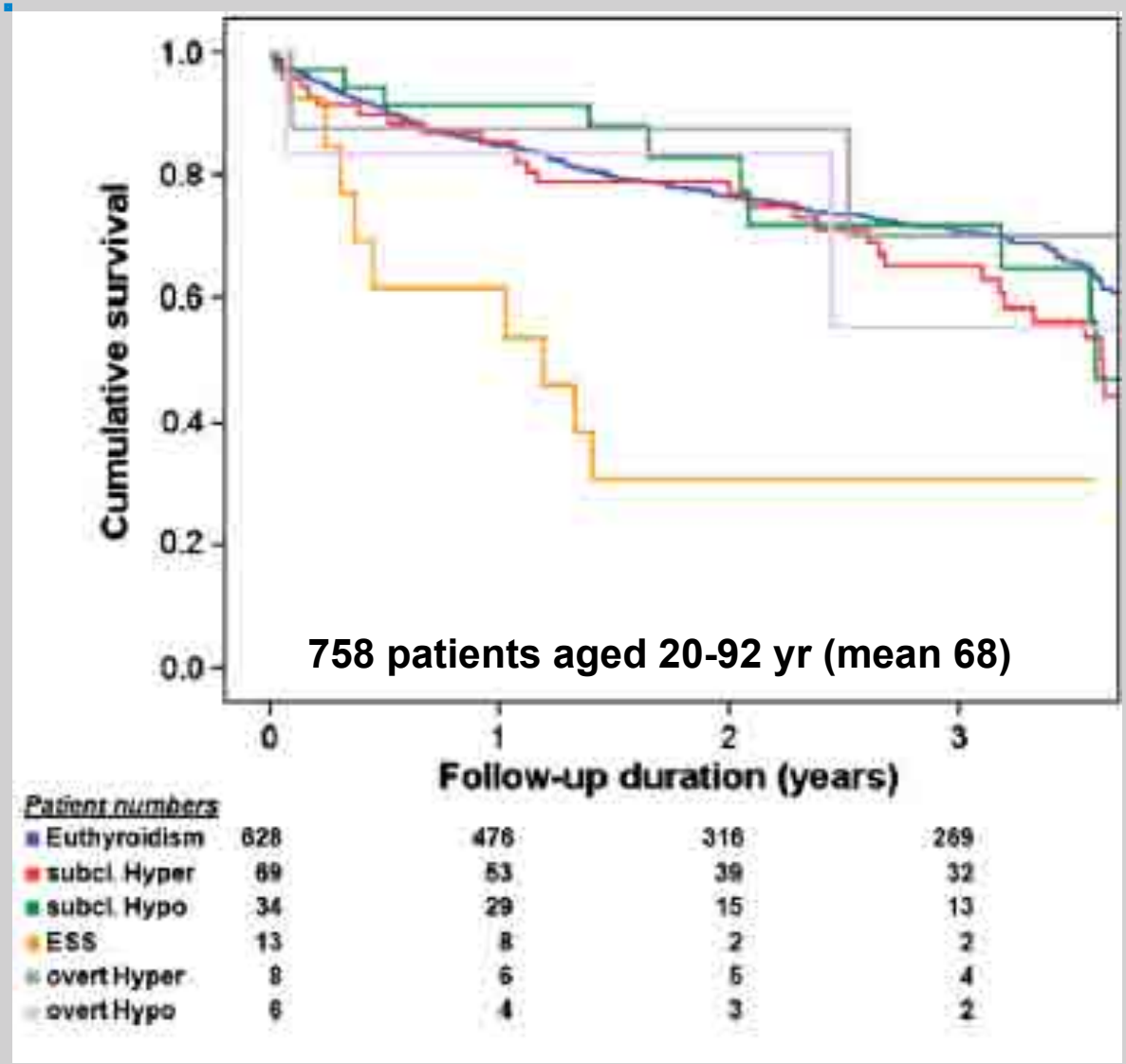

This study suggests no relevant prognostic role of subclinical thyroid dysfunction in patients with moderate and severe heart failure thus, there is no need for specific treatment

At follow-up subclinical thyroid dysfunction (9.1% subhyper - 4.5 sHT) had normalized spontaneously in 77% of patients.

Frey A. International Journal of Cardiology 2013

Subclinical Thyroid Dysfunction and the Risk of HF in Older Persons at High CV Risk

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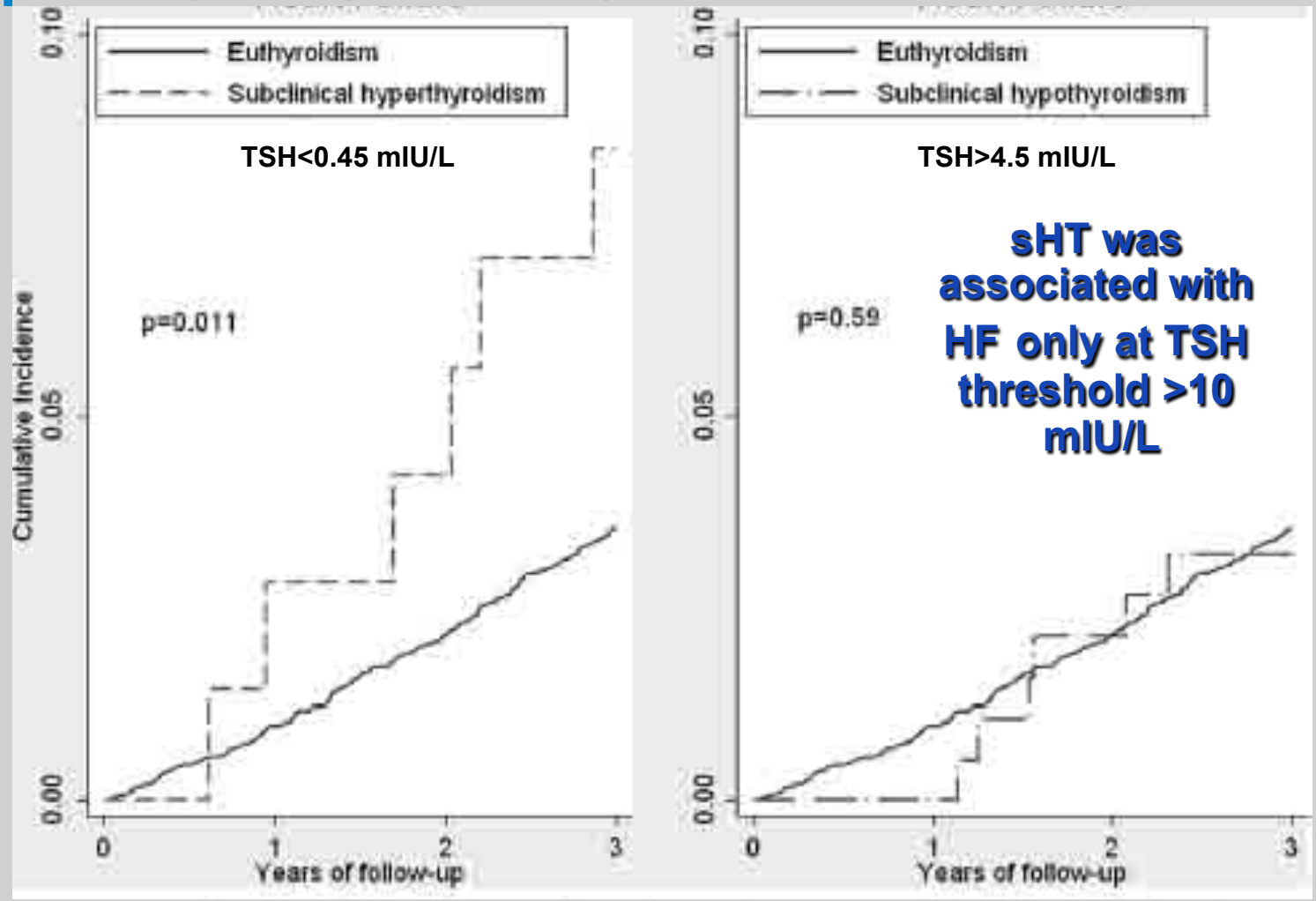
Cumulative incidence of HF hospitalization with respect to subclinical thyroid dysfunction (5316 patients, aged 70-82 yr)



Nanchen D J Clin Endocrionol Metab 2012

Incident Heart Failure Events

The Cardiovascular Health Study: *3044 adults >65 yrs of age*

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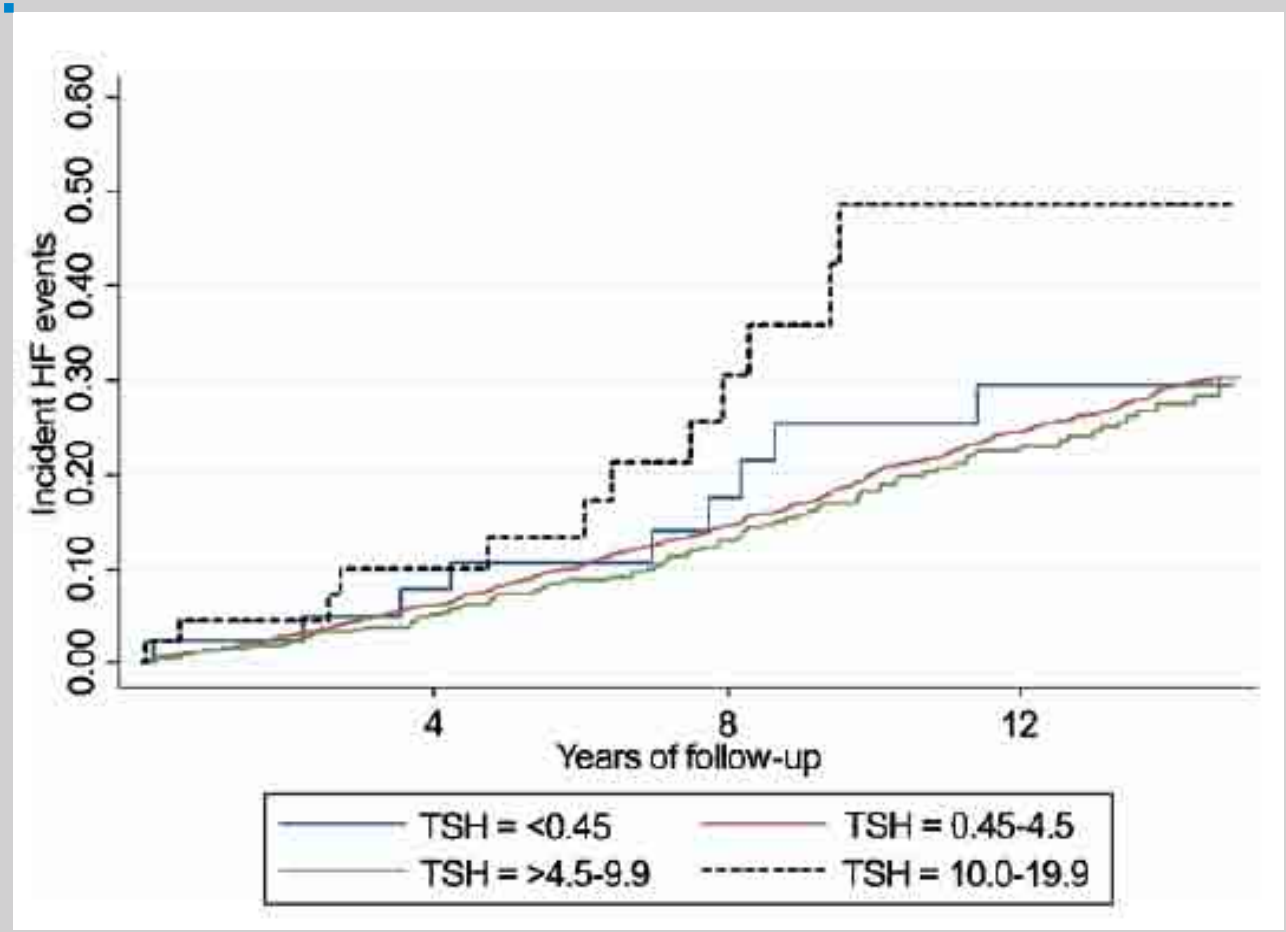

Participants with TSH 10.0 to 19.9 mU/l who were untreated by LT4 replacement had a greater incidence of HF events compared with euthyroid participants (41.7 vs. 22.9 x 1,000 person-years, p=0.01)

Rodondi et al. JACC 2008

Subclinical Thyroid Dysfunction and the Risk of HF in Older Persons at High CV Risk

Bari,
7-10 novembre 2013

Cardiovascular morbidities by subclinical thyroid status at baseline

	Subclinical hyperthyroidism				Subclinical hypothyroidism		
	TSH < 0.1 mIU/liter (n = 28)	TSH = 0.1–0.44 mIU/liter (n = 43)	Overall, TSH < 0.45 mIU/liter (n = 71)	Euthyroidism, TSH = 0.45–4.49 mIU/liter (n = 5046)	Overall, TSH ≥4.5 mIU/liter (n = 199)	TSH = 4.5–10 mIU/liter (n = 161)	TSH >10 mIU/liter (n = 38)
Heart failure hospitalization							
No. of events	4	3	7	194	6	2	4
Incidence rate[b]	45.7[a]	21.6	30.9[a]	12.1	9.7	4.0	32.9[a]
Age- and sex-adjusted HR (95% CI)	4.61[a] (1.71–12.47)	1.97 (0.63–6.17)	2.93[a] (1.37–6.24)	1.00	0.87 (0.38–1.96)	0.36 (0.09–1.44)	3.01[a] (1.12–8.11)
Multivariate adjusted HR (95% CI)[c]	4.78[a] (1.76–13.04)	2.29 (0.73–7.20)	3.27[a] (1.52–7.02)	1.00	0.80 (0.36–1.82)	0.35 (0.09–1.42)	2.28 (0.84–6.23)
Atrial fibrillation							
No. of events	1	2	3	478	16	11	5
Incidence rate[b]	11.6	14.2	13.2	30.5	26.1	22.3	41.0
Age- and sex-adjusted HR (95% CI)	0.46 (0.64–3.25)	0.51 (0.13–2.05)	0.49 (0.16–1.53)	1.00	0.93 (0.57–1.54)	0.80 (0.44–1.46)	1.47 (0.61–3.55)
Multivariate adjusted HR (95% CI)[c]	0.50 (0.07–3.55)	0.55 (0.14–2.20)	0.53 (0.17–1.65)	1.00	0.90 (0.55–1.48)	0.77 (0.42–1.41)	1.43 (0.59–3.46)
CVD[d]							
No. of events	3	4	7	852	32	23	9
Incidence rate[b]	34.0	29.3	31.1	55.8	54.9	48.8	80.9
Age- and sex-adjusted HR (95% CI)	0.71 (0.23–2.20)	0.58 (0.22–1.56)	0.63 (0.30–1.33)	1.00	1.06 (0.74–1.51)	0.94 (0.62–1.43)	1.56 (0.81–3.01)
Multivariate adjusted HR (95% CI)[c]	0.66 (0.21–2.06)	0.62 (0.23–1.66)	0.64 (0.30–1.34)	1.00	1.00 (0.71–1.43)	0.89 (0.59–1.35)	1.48 (0.78–2.87)
Coronary heart disease[e]							
No. of events	3	3	6	564	15	11	4
Incidence rate[b]	34.0	21.7	26.5	35.9	24.6	22.5	33.0
Age- and sex-adjusted HR (95% CI)	1.12 (0.36–3.48)	0.67 (0.22–2.09)	0.84 (0.37–1.88)	1.00	0.75 (0.45–1.25)	0.68 (0.38–1.24)	1.00 (0.38–2.68)
Multivariate adjusted HR (95% CI)[c]	1.10 (0.35–3.44)	0.72 (0.23–2.25)	0.87 (0.39–1.96)	1.00	0.70 (0.42–1.18)	0.66 (0.36–1.19)	0.89 (0.33–2.38)

Older people at high CV risk with low or very high TSH appear at increased risk of incident HF

Nanchen D J Clin Endocrionol Metab 2012

Subclinical Hypothyroidism and Heart Failure Risk in Older People

Bari,
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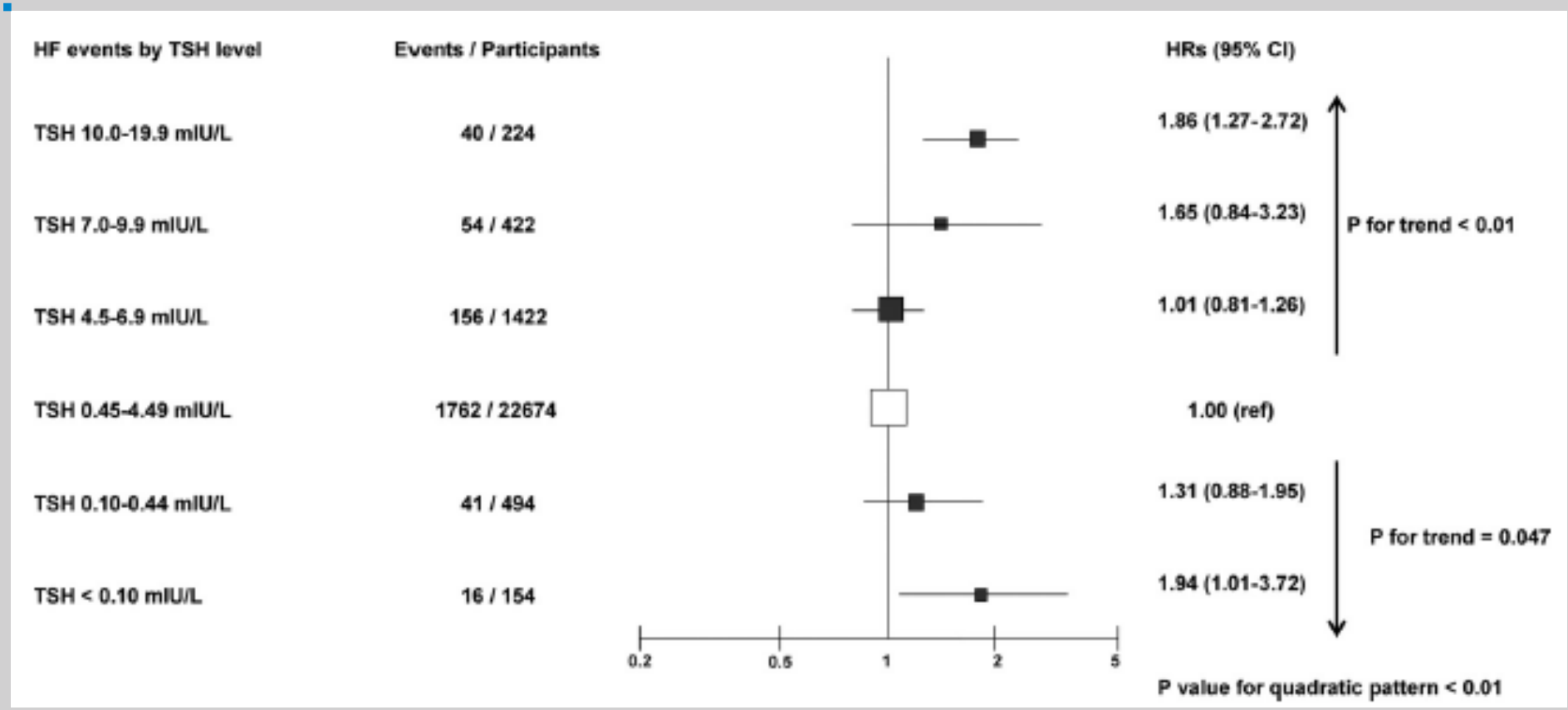
Most representative prospective clinical studies on the risk of HF events in older patients with or without sHT

Study	# of Subjects (sHT)	TSH* (mIU/L)	Age° (years)	Follow-up (years)	Setting	HF Events
Rodondi et al. [88]	3021 (495)	>4.5	64-100	12.3	Community dwelling	Increased risk for TSH>10.0
Rodondi et al. [94]	2680 (335)	>4.5	69-81	7.1	Community dwelling	Increased risk for TSH>7.0
Hyland et al. [95]	4863 (679)	>4.5	74 (5.9)	10.0	Community dwelling	No increased risk at all
Iacoviello et al. [89]	328 (39)	>5.5	66 (21-92)	1.1	Outpatients with HF	Increased risk at all
Nanchen et al. [90]	5516 (444)	>4.5	75 (69-83)	3.3	Community dwelling	Increased risk for TSH>10.0

Subclinical Thyroid Dysfunction and the Risk of HF Events: data analysis from 6 prospective studies

Bari,
7-10 novembre 2013

Risks of heart failure events were increased with both higher and lower TSH levels, particularly for TSH >10 and <0.10 mIU/L



Gencer B. Circulation 2012

Is Subclinical Hypothyroidism a CV Risk Factor in the Elderly?

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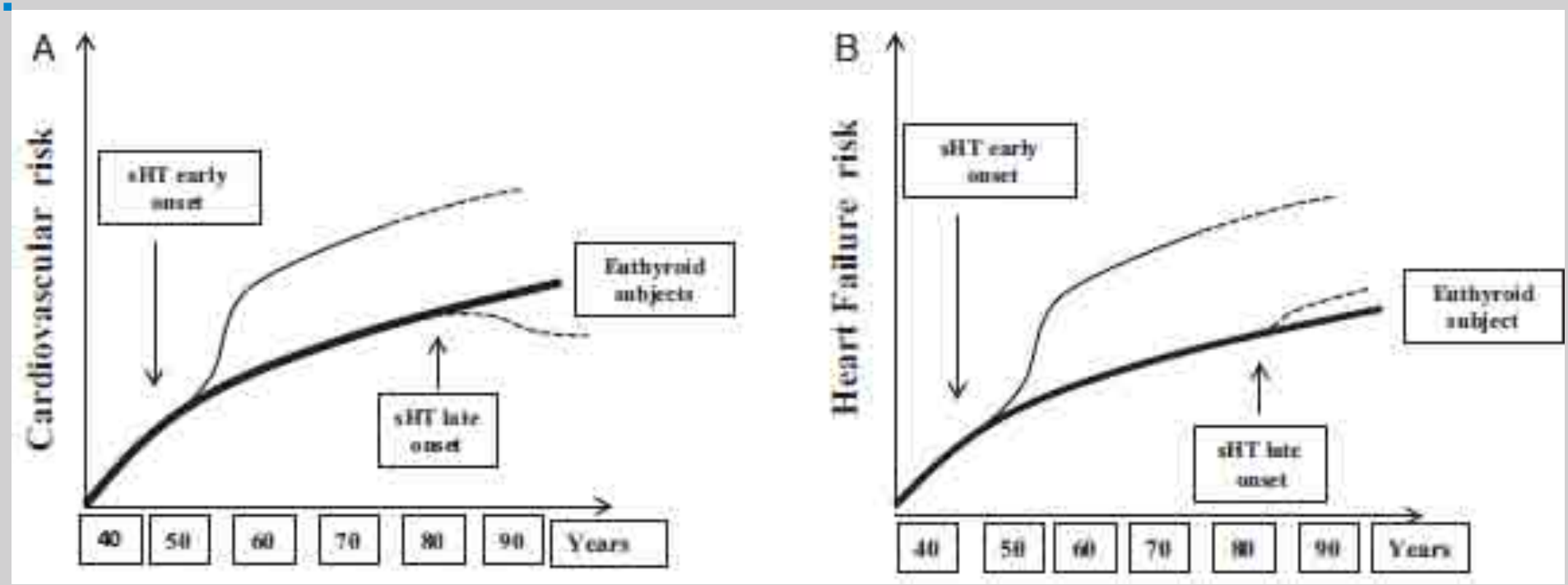
Graphical representation of global CV or HF risk over time in euthyroid subjects (bold line) and in patients with early (aged<60 y) or late onset (aged>80 y) sHT (fine line) as derived from the best scientific evidence. Dotted lines refer to uncertain area or unexplored classes of patients



Pasqualetti G et al JCEM 2013

Mild hypothyroidism and mitochondrial dysfunction: effect of disease duration

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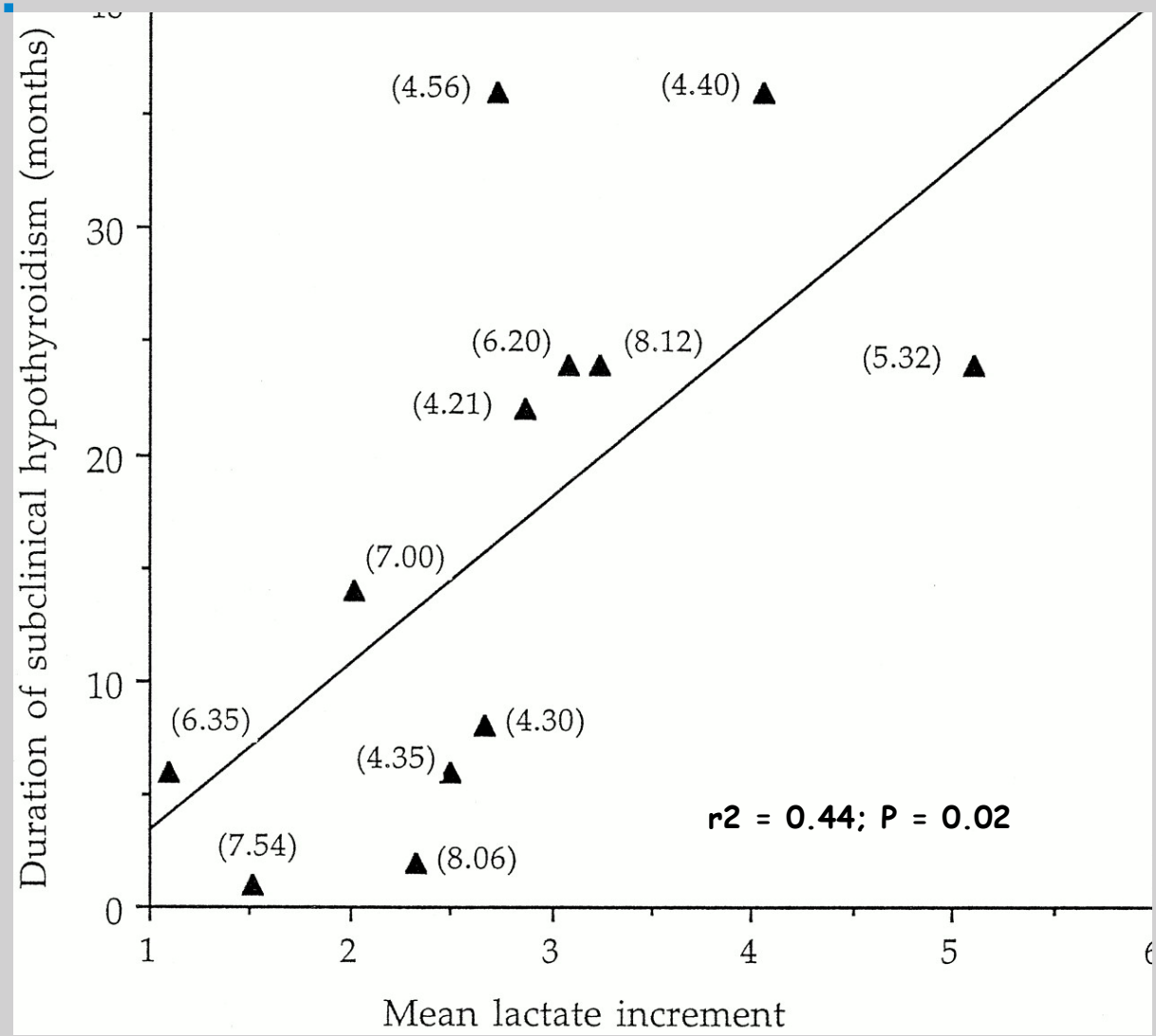

Monzani et al. J Clin Endocrinol Metab 1997

All-cause mortality in patients with subclinical hyperthyroidism: a meta-analysis

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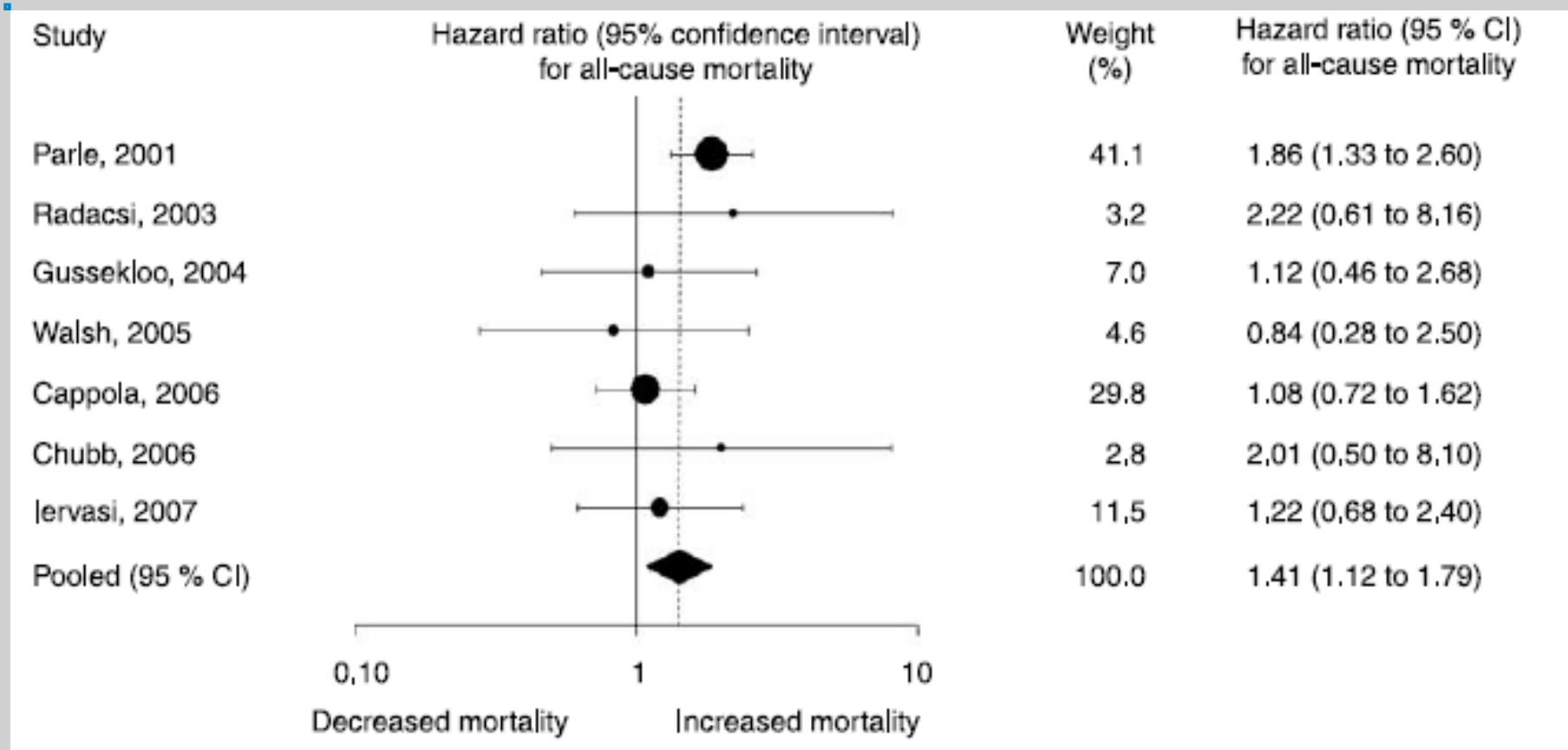

Haentjens et al. Eur J Endocrinol 2008

Excess mortality from all causes after the diagnosis of subclinical hyperthyroidism

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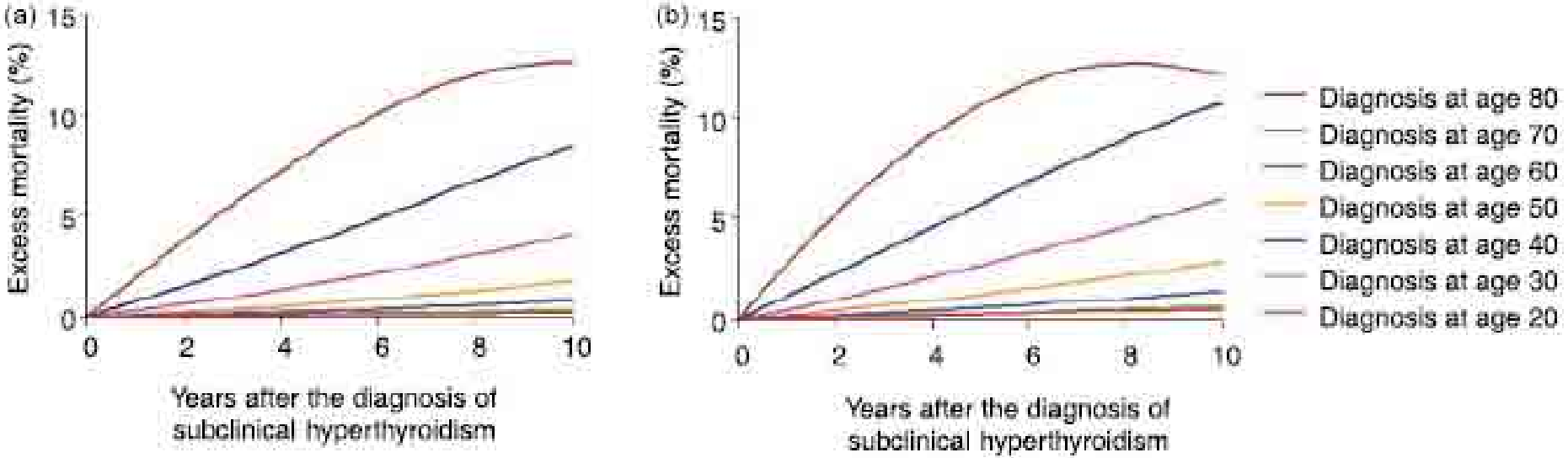
Role of the Age

Women

Men



From aggregated data reported in original cohort studies and life-tables

Haentjens et al. Eur J Endocrinol 2008

Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality
A meta-analysis

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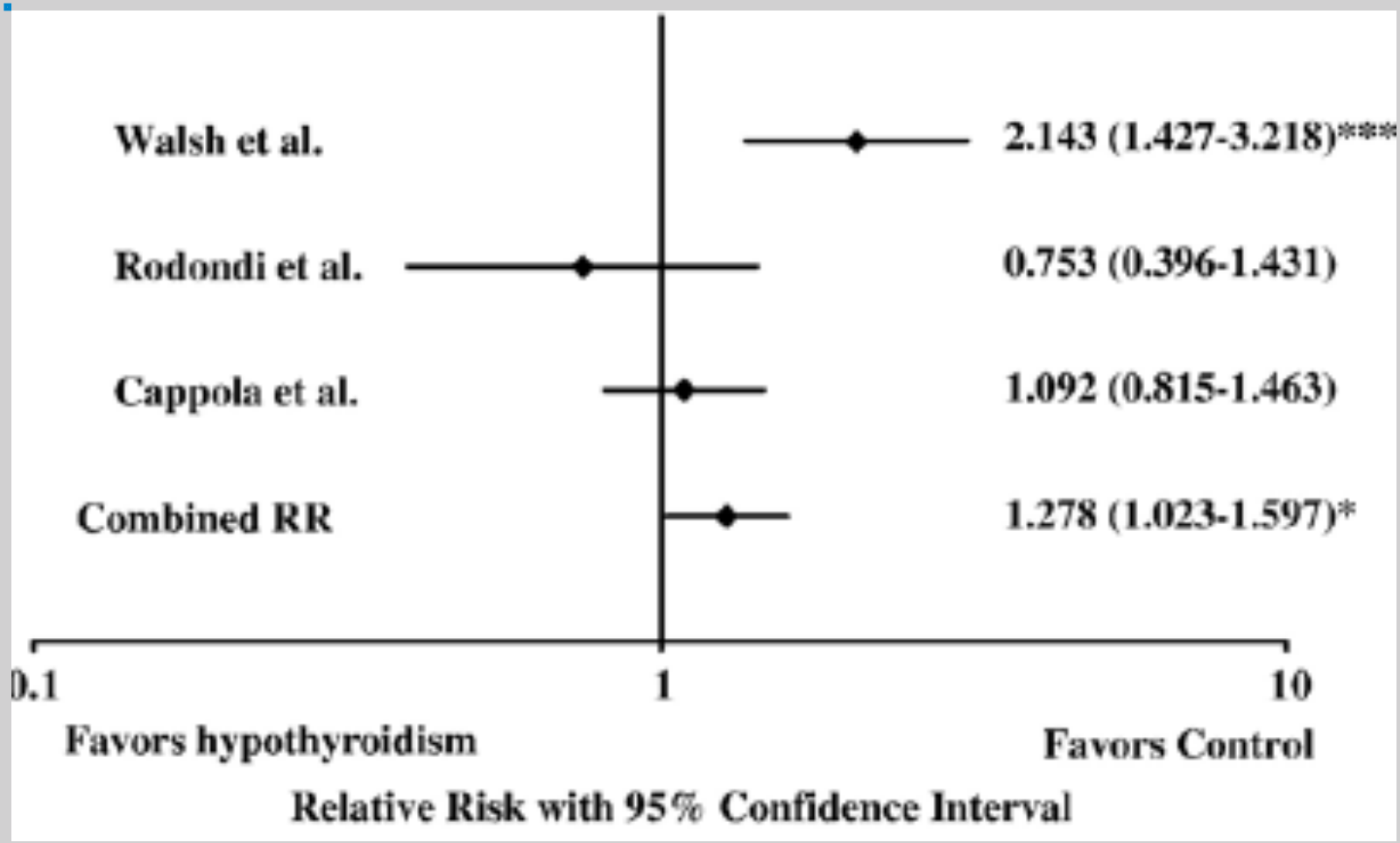
Relative Risk of CV Mortality in Subclinical Hypothyroidism



Singh S. et al International Journal of Cardiology 2008

Subclinical Hypothyroidism and Survival: The Effects of Heart Failure and Race

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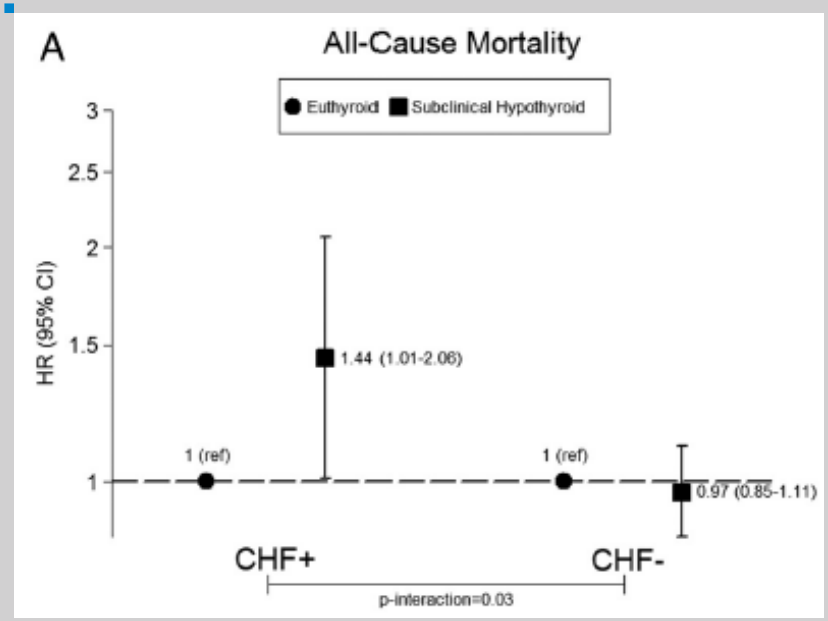
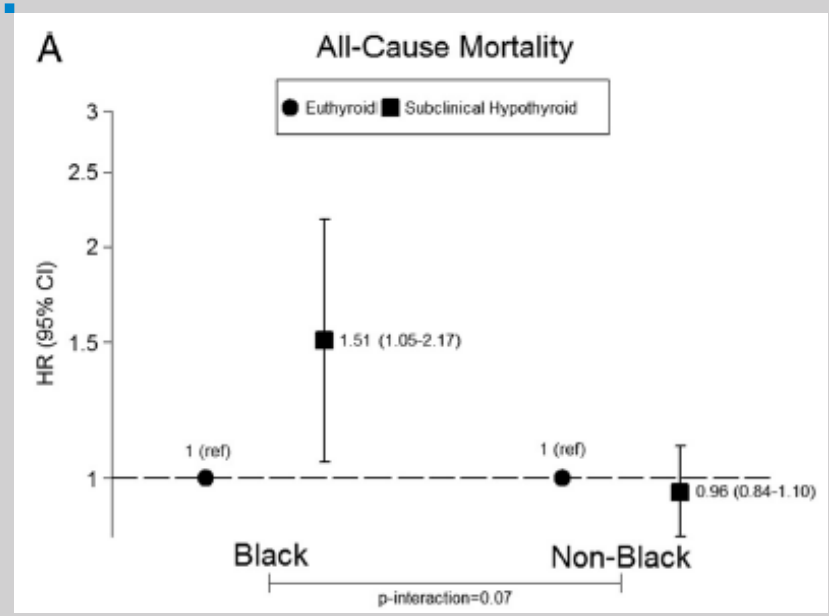
Retrospective study on 14879 participants from the NHANES III survey (1988 -1994)





CV Mortality Within Strata Defined by CHF Status and Race

	Subclinical Hypothyroidism (TSH/TT_4-Based Definition)			Hypothyroidism Overall		
	HR (95% CI)		*P* Interaction for CHF	HR (95% CI)		*P* Interaction for CHF
	CHF Present	CHF Absent		CHF present	CHF Absent	
Black	2.03 (0.35–11.68)	1.98 (1.14–3.44)	.09	1.25 (0.23–6.68)	2.06 (1.20–3.51)	.05
Non-Black	1.39 (0.87–2.23)	0.87 (0.70–1.07)	.01	1.53 (0.98–2.40)	0.86 (0.70–1.06)	.01
P interaction for race	>.9	.01		.4	.004	

Rhee CM et al J Clin Endocrinol Metab 2013

HF &Thyroid Dysfunction

Bari,
7-10 novembre 2013

Clinical practice suggestions for the prevention and treatment of HF in patients with thyroid dysfunction

1. Thyroid function tests are indicated in patients receiving amiodarone and when thyroid dysfunction is considered a possible or concomitant cause of congestive HF, atrial fibrillation, pulmonary hypertension, dilated cardiomyopathy or coronary heart disease (e.g. patients without pre-existing cardiac disease or other identifiable causes of these disorders)
2. Correction of thyroid dysfunction should be the first procedure in patients with HF
3. Definitive treatment should be performed to recover cardiac function in patients with hyperthyroidism
4. Doppler echocardiography is mandatory to assess cardiac function, pulmonary pressure, valve disease and pleural or pericardial effusion in symptomatic patients
5. Prompt, effective treatment of cardiac manifestations should be initiated in patients with thyroid dysfunction to improve cardiac hemodynamics
6. Hospitalization is required to treat HF in patients with pre-existing left ventricular dysfunction or when HF does not improve upon restoration of euthyroidism

Biondi B. Eur J Endocrinol 2012

Is Subclinical Hypothyroidism a CV Risk Factor in the Elderly?

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- The decision to treat old sHT patients should derive from a specific evaluation of the possible thyroid dysfunction causes, pre-existent CV risk, the presence of HF, comorbidity, or frailty as well as the actual level of serum TSH
- Moderately old patients (<70–75 y) could be considered clinically similar to the adult population, albeit with a higher optimal TSH target value (around 2–3 mIU/L), whereas the oldest old subjects (>80–85 y) should be carefully followed with a wait and see strategy, generally avoiding hormonal treatment.
- Treatment must be individualized, gradual, and closely monitored once any underlying coexisting morbidity or pharmacological interference has been excluded

Pasqualetti et al JCEM 2013

2013 ETA Guideline: Management of Subclinical Hypothyroidism

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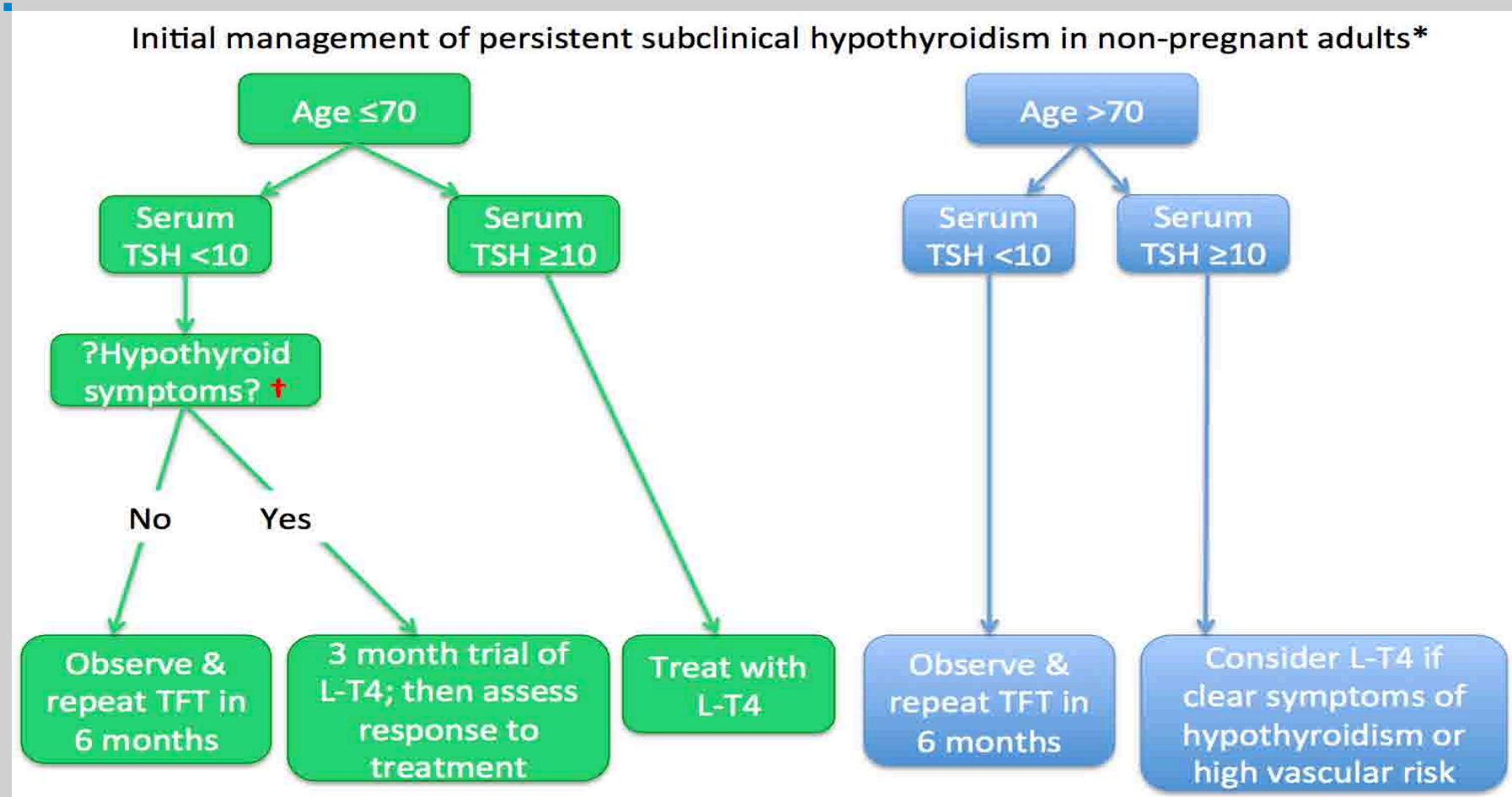

*Persistent subclinical hypothyroidism describes patients with elevated serum TSH and within reference range serum FT4 on two occasions separated by at least 3 months. This algorithm is meant as a guide and clinicians are expected to use their discretion and judgment in interpreting the age threshold around 70 years.

†Depending on circumstances, individuals with goitre, dyslipidaemia and diabetes may also be considered for treatment, along with those with a plan for pregnancy in the near future

Pierce S et al. European Thyroid Journal 2013 (in press)

Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the ATA and American Association of Clinical Endocrinologists

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Clinical Condition	Strength of Association: Serum TSH 0.1-0.45 mIU/L	Strength of Association: Serum TSH <0.1 mIU/L	Benefits of Treatment: Serum TSH 0.1-0.45 mIU/L	Benefits of Treatment: Serum TSH <0.1 mIU/L
Progression to overt hyperthyroidism	Insufficient	Good	None	None
Adverse cardiac end points apart from atrial fibrillation	Fair	*	None	None
Atrial fibrillation	Insufficient	Good	None	None
Cardiac dysfunction	Insufficient	Fair	*	Insufficient
Systemic hyperthyroid and neuropsychiatric symptoms	Insufficient	Insufficient	None	Insufficient
Reduced bone mineral density	None	Fair†	None	Fair
Fractures	None	Insufficient	None	None

Subclinical Hyperthyroidism: When to Treat

Factor	*TSH (<0.1 mU/L)*	*TSH (0.1–0.5 mU/L)*
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

Surks MI et al JAMA 2004; Bhan RS et al Thyroid 2011

Take Home Messages

Bari,
7-10 novembre 2013

- The effects of subtle thyroid dysfunction may be different in different age ranges
- Age-specific reference ranges for serum TSH should be considered in order to establish a diagnosis of sHT in older people
- Individuals with subclinical hyperthyroidism demonstrate a 41% increase in relative all causes mortality as compared to euthyroid subjects
- The absolute excess mortality after diagnosis depends on age, with a remarkable increase from 60 yrs onward
- Individuals with subclinical hyperthyroidism should be treated, particularly those with serum TSH <0.1 mU/L

Take Home Messages (1)

Bari,
7-10 novembre 2013

- sHT should be considered in 2 categories according to the elevation in serum TSH level: mildly increased TSH levels (4.0–10.0 mIU/l), and more severely increased TSH value (>10 mIU/l)

- The main studies supports a role for sHT as a risk factor for HF events, especially in older people with serum TSH>10 mIU/l

- Replacement therapy with LT4 is recommended for patients with serum TSH>10 mIU/l. A higher optimal TSH target value (around 3-4 mIU/l) should be used in older people (>70 yr)

- In symptomatic young patients with serum TSH <10mU/l, a trial of levothyroxine replacement therapy should be considered.

- The oldest old subjects (>80-85 years) with serum TSH ≤10 mU/l should be carefully followed with a wait and see strategy, generally avoiding hormonal treatment

Un ringraziamento particolare a tutti coloro che hanno collaborato con me, contribuendo alla realizzazione di questa presentazione

Bari,
7-10 novembre 2013

Grazie per l'attenzione

Geriatrix