LE MALATTIE
DELLA TIROIDE
(DALLA DIAGNOSI ALLA TERAPIA)

Focus sui percorsi aziendali

A cura del Gruppo tiroide ASL AL
Coordinatore: Dr. S. Singarelli

3° edizione

21 maggio e 18 giugno 2011

Sede: Centro " Il Caimano"
Via Maggiorini Ferraris 5
….
Acqui Terme

Ipotiroidismo subclinico: trattare o non trattare?

..*una relazione di 'minoranza'*

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Ipotiroidismo Subclinico (IS)

la definizione, l'epidemiologia

diagnosi non clinica:

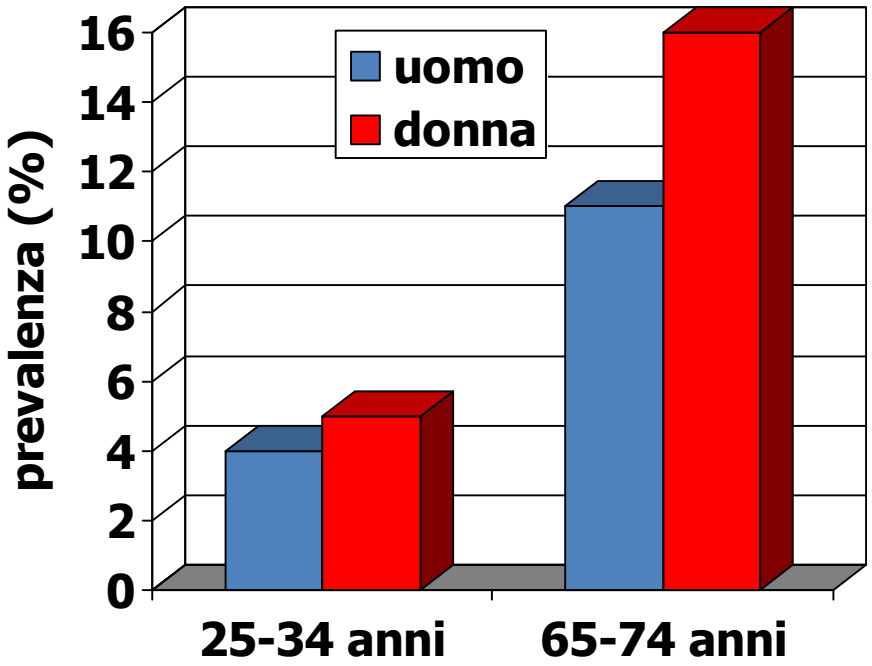
Valori normali di ormoni tiroidei circolanti

TSH sierico aumentato:

> 4.5 µU/ml

(> 3.5µU/ml ?)

- **Molto frequente: prevalenza nella popolazione adulta USA ca.9% (Colorado Study 2000)**
- **il 75% ha TSH sotto 10 µU/ml**



The Colorado thyroid disease prevance study
Canaris et al. Arch Int Med 2000

Spesso scoperto incidentalmente o per sintomatologia non specifica

IS – Quando trattare?

la base non è indecisa

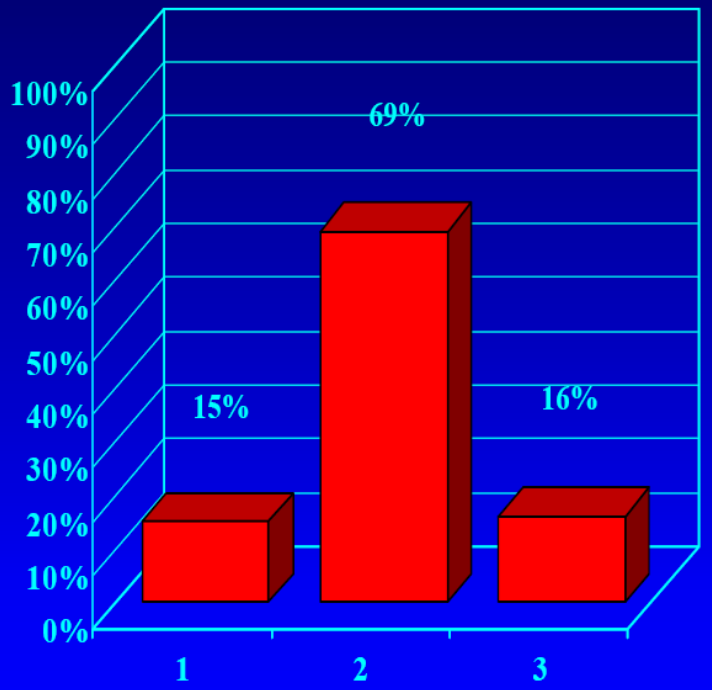
A.M.E.

Congresso Nazionale

Pescara 2005

Nella vostra pratica clinica quanti pazienti con ipotiroidismo subclinico mettete in terapia con tiroxina?

1 .La minoranza
2. La maggioranza
3. Circa metà



IS: case finding

quale paziente?

Certamente (o quasi)
da trattare

- Pz. sintomatico

  (veramente sintomatico!)
  - Astenia, facile affaticabilità
  - Depressione
  - Ipercolesterolemia resistente alla dieta
- Pz. asintomatico → Screening?

Table 3 - *Symptoms present in the study population.*

	Euthyroid Subjects (%) (n= 954)	Subclinical hypothyroidism (%) (n= 57)
Memory reduction	9.6	20.8*
Nervousness	11.4	18.8
Weight gain	10.0	16.7
Constipation	14.4	20.8
Lethargy	9.6	10.4
Anorexia	1.0	2.1
Dyspnea	1.8	2.1
Sensation of cold	6.2	6.3
Hair loss	8.9	8.3
Weakness	6.9	4.2
Others	0.2	0.2
At least one symptom	39.9	58.0**

*$p<0.05$; **$p<0.02$

Rivolta et al. J Endocrinol Invest 1999, 22:693

Screening?

Molte società scientifiche lo consigliano:

- *AMERICAN THYROID ASSOCIATION*

  Tutti gli adulti dai 35 anni ogni 5 anni in assenza di sintomi o di fattori di rischio, in caso contrario con frequenze maggiori
- *AMERICAN COLLEGE OF PHYSICIAN*

  Tutte le donne dopo i 50 anni (Am College of Physician)
- *AMERICAN ACADEMY OF FAMILY PHYSICIAN*

  Uomini e donne dopo i 60 anni (Am Accademy di Family Physician)

- *CANADIAN TASK FORCE*

  Mantenere una alta sorveglianza clinica e un alto indice di sospetto nelle donne in menopausa e entro 6 settimane dopo il parto

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

U.S. Preventive Services Task Force (USPSTF) 2004

An independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services.

CLINICAL GUIDELINES

Screening for Subclinical Thyroid Dysfunction in Nonpregnant Adults: A Summary of the Evidence for the U.S. Preventive Services Task Force

Mark Helfand, MD, MPH

Background: Subclinical thyroid dysfunction is a risk factor for developing symptomatic thyroid disease. Advocates of screening argue that early treatment can prevent serious morbidity in individuals who are found to have laboratory evidence of subclinical thyroid dysfunction.

Purpose: This article focuses on whether it is useful to order a thyroid function test for patients who have no history of thyroid disease and have few or no signs or symptoms of thyroid dysfunction.

Data Sources: A MEDLINE search, supplemented by searches of EMBASE and the Cochrane Library, reference lists, and a local database of thyroid-related articles.

Study Selection: Controlled treatment studies that used thyroid-stimulating hormone (TSH) levels as an inclusion criterion and reported quality of life, symptoms, or lipid level outcomes were selected. Observational studies of the prevalence, progression, and consequences of subclinical thyroid dysfunction were also reviewed.

Data Extraction: The quality of each trial was assessed by using preset criteria, and information about setting, patients, interventions, and outcomes was abstracted.

Data Synthesis: The prevalence of unsuspected thyroid disease is lowest in men and highest in older women. Evidence regarding the efficacy of treatment in patients found by screening to have subclinical thyroid dysfunction is inconclusive. No trials of treatment of subclinical hyperthyroidism have been done. Several small, randomized trials of treatment of subclinical hypothyroidism have been done, but the results are inconclusive except in patients who have a history of treatment of Graves disease, a subgroup that is not a target of screening in the general population. Data on the adverse effects of broader use of L-thyroxine are sparse.

Conclusion: It is uncertain whether treatment will improve quality of life in otherwise healthy patients who have abnormal TSH levels and normal free thyroxine levels.

Ann Intern Med. 2004;140:128-141. www.annals.org
For author affiliation, see end of text.
See related article on pp 125-127.

Hyperthyroidism and hypothyroidism are common conditions that have lifelong effects on health (1, 2). About 5% of U.S. adults report having thyroid disease or taking thyroid medication (1, 2). Consequences of untreated hyperthyroidism include atrial fibrillation, congestive heart failure, osteoporosis, and neuropsychiatric disorders. Hypothyroidism causes symptoms that reduce functional status and quality of life (3). Subclinical thyroid dysfunction, which can be diagnosed by thyroid function tests before symptoms and complications occur, is viewed as a risk factor for hyperthyroidism and hypothyroidism complications. The goal of screening is to identify and treat patients with subclinical thyroid dysfunction before they develop these complications (4–6).

The term *subclinical hyperthyroidism* describes conditions characterized by a low thyroid-stimulating hormone (TSH) level and normal levels of circulating thyroid hormones (thyroxine and triiodothyronine). Subclinical hyperthyroidism has the same causes as overt hyperthyroidism. These include excessive doses of L-thyroxine, Graves disease, multinodular goiter, and solitary thyroid nodule. Most studies of the course of subclinical hyperthyroidism concern patients whose history, physical examination, ultrasonogram, or thyroid scan suggests one of these causes. There are relatively few studies of patients who are found on screening to have an undetectable TSH level, normal free thyroxine (T_4) level, and normal free triiodothyronine (T_3) level and negative results on thyroid evaluation, although this is the largest group to be identified in a screening program. The prevalence of subclinical hyperthyroidism is about 1% (95% CI, 0.4% to 1.7%) in men older than 60 years of age and 1.5% (CI, 0.8% to 2.5%) in women older than 60 years of age (7).

The terms *subclinical hypothyroidism* and *mild thyroid failure* refer to patients who have an elevated TSH level and a normal free T_4 level (**Table 1**) (6). Subclinical hypothyroidism is common, especially in older women (1, 2, 7–16). In an analysis of the Third National Health and Nutrition Examination Survey (NHANES III), a population-based survey of 17 353 people at least 12 years of age representing the U.S. population, the prevalence of subclinical hypothyroidism was 5.8% among white, non-Hispanic women; 1.2% among black, non-Hispanic women; and 5.3% among Mexican-American women (1). The prevalence of subclinical hypothyroidism was 3.4% among white men, 1.8% among black men, and 2.4% among Mexican-American men. In the Whickham survey, a large, good-quality, population-based study with 20-year follow-up, prevalence was 4% to 5% among women age 18 to 44 years, 8% to 10% among women age 45 to 74 years, and 17.4% among women older than age 75 years (17). The prevalence was 1% to 3% among men age 18 to 65 years and 6.2% among men older than age 65 years.

In this paper, I address whether the primary care physician should screen for thyroid function in patients seen in general medical practice who have no specific indication for thyroid testing and who come to the physician for other reasons. I focus on whether screening should be aimed at

The USPSTF found fair evidence that the thyroid-stimulating hormone (TSH) test can detect subclinical thyroid disease in people without symptoms of thyroid dysfunction but ***poor evidence that treatment improves clinically important outcomes in adults with screen-detected thyroid disease****.*

Ann Intern Med. 2004;140:125-127

Ann Intern Med. 2004;140:128-141

IS: lo screening dichiarato

IS: lo screening non dichiarato

quale paziente?

- Faccio un ‘check up’ ogni anno
- La mia mamma/zia/nonna/sorella/gatta aveva “la tiroide”
- Non riesco più a dimagrire anche se non mangio tanto
- Ho visto alla televisione…
- Ho smesso di fumare e così ho pensato di fare tutti gli esami..

- .. almeno il 30% non sa per quale motivo ha fatto quell’accertamento

Ipotiroidismo Subclinico

che cosa curiamo?

Alterazione biochimica

=

Stato patologico per cui è indicato il trattamento

Alterazione biochimica

Alterazione della qualità/durata di vita

Il trattamento ripristina il "*benessere*"

Il *beneficio* del trattamento supera gli eventuali effetti collaterali

Stato patologico per cui è indicato il trattamento

La condizione è *irreversibile* ?

Ipotiroidismo Subclinico

le domande

1. L'I.S. è reversibile?
2. Qual'è la variabilità e l'attendibilità del TSH?
3. C'è un associazione tra IS e CVD o mortalità? – l'IS è un fattore di rischio riconosciuto per CVD?
4. Il trattamento con l-tiroxina sostitutivo è efficace?
5. Il trattamento sostitutivo è innocuo?

2

Ipotiroidismo Subclinico:
variabilità e attendibilità del TSH

IS: il ‘range’ di normalità

variabilità e attendibilità del TSH

- Eterogenità spiccata nella glicosilazione
  - Variabilità del dosaggio del 30-40%
- 65% del valore è geneticamente determinato
- Condizioni parafisiologiche di variazione
  - Deficit di sonno
  - Stress
  - Attività fisica
  - Apporto iodico acuto
- Codizioni patologiche e iatrogeniche
  - Malattie non tiroidee
  - Farmaci: metoclopramide, sulpiride, cortisonici, analoghi somatostatina
- **Il TSH predice scarsamente i livelli di T4 tissutali**

Brabant G. et al. European Journal of Endocrinology 2006,154:633–637

3

C’è un’associazione tra mortalità CV e Ipotiroidismo Subclinico?

C’è un’associazione tra CVD e IS?

Population based & cohort studies

Associazione

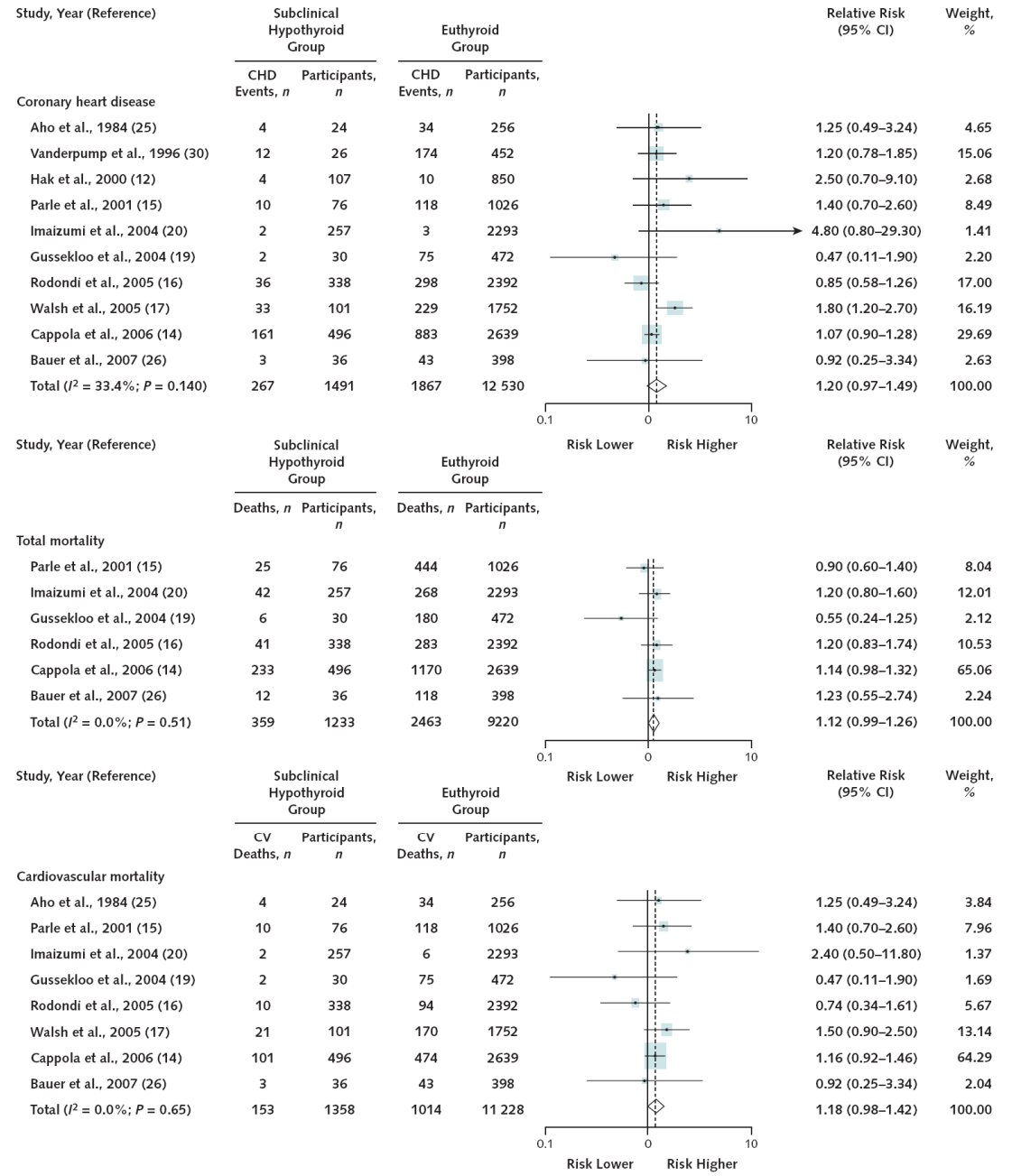
- Bastenie PA, Lancet 1977 (n=649)
- Hak AE, Ann Intern Med 2000 (n=1149)
- Imaizumi M, J Clin Endocrinol Metab 2004 (n=2856)
- Walsh JP, Arch Intern Med 2005 (n=2108)

NON associazione

- Tunbridge WM, Clin Endocrinol 1977 (n=2779)
- Vanderpump MP, Thyroid 1996 (n=1877)
- Parle JV, Lancet 2001 (n=1191)
- Cappola, JAMA 2006 (n=3233)
- Rodondi N, Arch Intern Med. 2005 (n=2730)

C'è un'associazione tra mortalità CV e IS?

Meta-analysis: Subclinical Thyroid Dysfunction and the Risk for Coronary Heart Disease and Mortality
Nicolas Ochs et al.
Ann Intern Med. 2008;148:832-845.



Study, Year (Reference)	Subclinical Hypothyroid Group: CHD Events, *n*	Subclinical Hypothyroid Group: Participants, *n*	Euthyroid Group: CHD Events, *n*	Euthyroid Group: Participants, *n*	Relative Risk (95% CI)	Weight, %
Coronary heart disease						
Aho et al., 1984 (25)	4	24	34	256	1.25 (0.49–3.24)	4.65
Vanderpump et al., 1996 (30)	12	26	174	452	1.20 (0.78–1.85)	15.06
Hak et al., 2000 (12)	4	107	10	850	2.50 (0.70–9.10)	2.68
Parle et al., 2001 (15)	10	76	118	1026	1.40 (0.70–2.60)	8.49
Imaizumi et al., 2004 (20)	2	257	3	2293	4.80 (0.80–29.30)	1.41
Gussekloo et al., 2004 (19)	2	30	75	472	0.47 (0.11–1.90)	2.20
Rodondi et al., 2005 (16)	36	338	298	2392	0.85 (0.58–1.26)	17.00
Walsh et al., 2005 (17)	33	101	229	1752	1.80 (1.20–2.70)	16.19
Cappola et al., 2006 (14)	161	496	883	2639	1.07 (0.90–1.28)	29.69
Bauer et al., 2007 (26)	3	36	43	398	0.92 (0.25–3.34)	2.63
Total (I^2 = 33.4%; P = 0.140)	267	1491	1867	12 530	1.20 (0.97–1.49)	100.00

0.1 0 10
Risk Lower Risk Higher

Study, Year (Reference)	Subclinical Hypothyroid Group: Deaths, *n*	Subclinical Hypothyroid Group: Participants, *n*	Euthyroid Group: Deaths, *n*	Euthyroid Group: Participants, *n*	Relative Risk (95% CI)	Weight, %
Total mortality						
Parle et al., 2001 (15)	25	76	444	1026	0.90 (0.60–1.40)	8.04
Imaizumi et al., 2004 (20)	42	257	268	2293	1.20 (0.80–1.60)	12.01
Gussekloo et al., 2004 (19)	6	30	180	472	0.55 (0.24–1.25)	2.12
Rodondi et al., 2005 (16)	41	338	283	2392	1.20 (0.83–1.74)	10.53
Cappola et al., 2006 (14)	233	496	1170	2639	1.14 (0.98–1.32)	65.06
Bauer et al., 2007 (26)	12	36	118	398	1.23 (0.55–2.74)	2.24
Total (I^2 = 0.0%; P = 0.51)	359	1233	2463	9220	1.12 (0.99–1.26)	100.00

0.1 0 10
Risk Lower Risk Higher

Study, Year (Reference)	Subclinical Hypothyroid Group: CV Deaths, *n*	Subclinical Hypothyroid Group: Participants, *n*	Euthyroid Group: CV Deaths, *n*	Euthyroid Group: Participants, *n*	Relative Risk (95% CI)	Weight, %
Cardiovascular mortality						
Aho et al., 1984 (25)	4	24	34	256	1.25 (0.49–3.24)	3.84
Parle et al., 2001 (15)	10	76	118	1026	1.40 (0.70–2.60)	7.96
Imaizumi et al., 2004 (20)	2	257	6	2293	2.40 (0.50–11.80)	1.37
Gussekloo et al., 2004 (19)	2	30	75	472	0.47 (0.11–1.90)	1.69
Rodondi et al., 2005 (16)	10	338	94	2392	0.74 (0.34–1.61)	5.67
Walsh et al., 2005 (17)	21	101	170	1752	1.50 (0.90–2.50)	13.14
Cappola et al., 2006 (14)	101	496	474	2639	1.16 (0.92–1.46)	64.29
Bauer et al., 2007 (26)	3	36	43	398	0.92 (0.25–3.34)	2.04
Total (I^2 = 0.0%; P = 0.65)	153	1358	1014	11 228	1.18 (0.98–1.42)	100.00

0.1 0 10
Risk Lower Risk Higher

The diamonds represent relative risks and the horizontal lines represent 95% CIs of the effect of subclinical hypothyroidism. CHD = coronary heart disease; CV = cardiovascular.

JAMA
2004, **292**
2591-2599

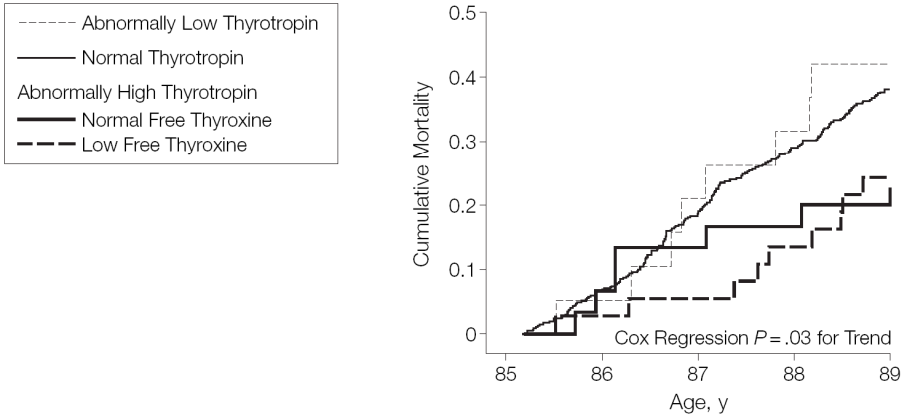
Thyroid Status, Disability and Cognitive Function, and Survival in Old Age

Jacobijn Gussekloo, MD, PhD
Eric van Exel, MD, PhD
Anton J. M. de Craen, PhD
Arend E. Meinders, MD, PhD
Marijke Frölich, PhD
Rudi G. J. Westendorp, MD, PhD

Design, Setting, and Participants
A prospective, observational, population-based follow-up study within the Leiden 85-Plus Study of 87% of a 2-year birth cohort (1912-1914) in the municipality of Leiden, the Netherlands. A total of 599 participants were followed up from age 85 years through age 89 years (mean [SD] follow-up, 3.7 [1.4] years).

Results Plasma levels of thyrotropin and free thyroxine were not associated with disability in daily life, depressive symptoms, and cognitive impairment at baseline or during follow-up. Increasing levels of thyrotropin were associated with a lower mortality rate that remained after adjustments were made for baseline disability and health status. The hazard ratio (HR) for mortality per SD increase of 2.71 mIU/L of thyrotropin was 0.77 (95% confidence interval [CI], 0.63-0.94; *P*=.009). The HR for mortality per SD increase of 0.21 ng/dL (2.67 pmol/L) of free thyroxine increased 1.16-fold (95% CI, 1.04-1.30; *P*=.009)

Figure 2. Cumulative Mortality of Participants Based on Clinical Stratification of Thyroid Status



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

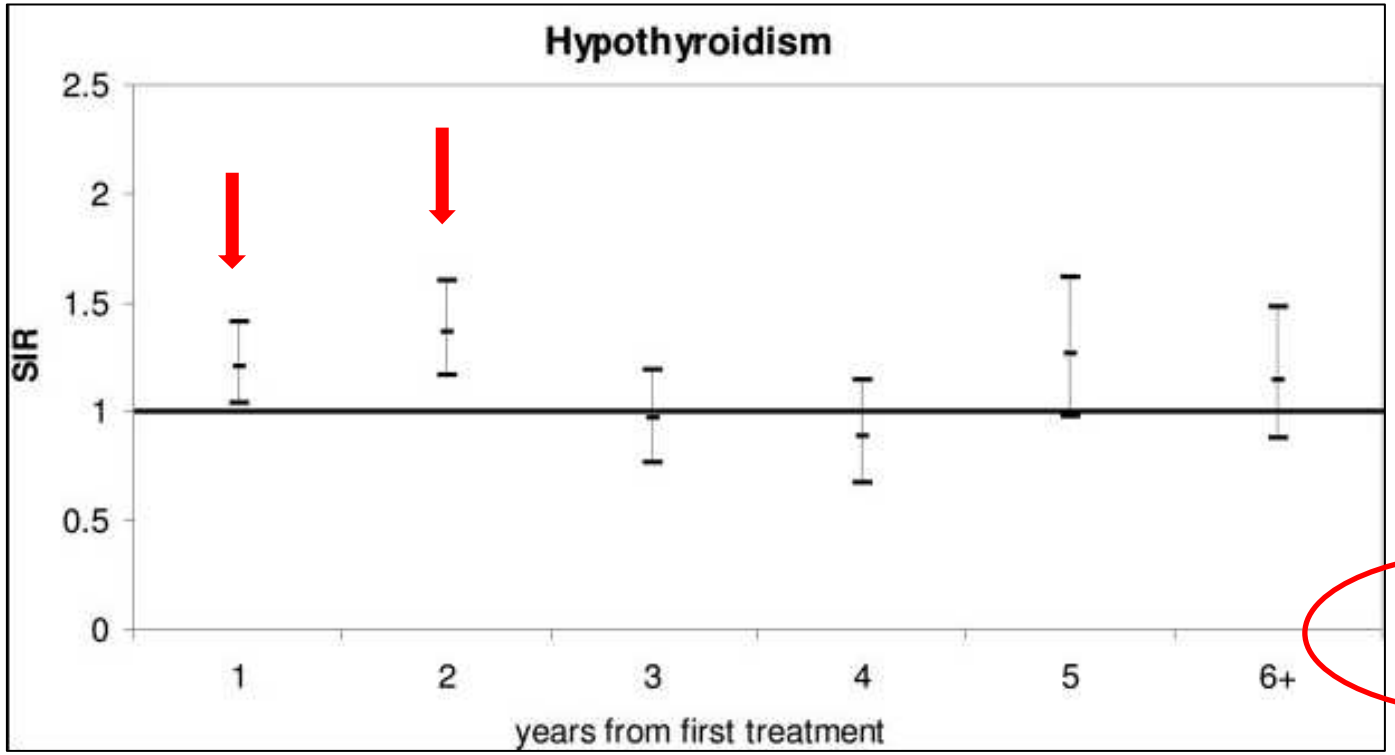
Plasma thyrotropin levels below 0.3 mIU/L were considered to be abnormally low; levels above 4.8 mIU/L were considered to be abnormally high. Plasma free thyroxine levels below 1.01 ng/dL (13 pmol/L) were considered to be abnormally low; levels between 1.01 and 1.79 ng/dL (13 and 23 pmol/L) were considered to be normal.

C’è un’associazione tra mortalità CV e IS?

Mortality and Vascular Outcomes in Patients Treated for Thyroid Dysfunction

R. W. V. Flynn, T. M. MacDonald, R. T. Jung, A. D. Morris, and G. P. Leese

J Clin Endocrinol Metab 91: 2159–2164, 2006



Conclusions:
We found no increase in all-cause mortality in subjects with treated thyroid disease. However, there was increased risk of cardiovascular morbidity in patients with treated primary hypothyroidism and dysrhythmias in treated hyperthyroidism.

4

Il trattamento sostitutivo del Ipotiroidismo Subclinico con l-tiroxina è efficace?

Il trattamento sostitutivo è efficace?

TABLE 1. CARDIOVASCULAR ABNORMALITIES IN MILD THYROID HORMONE DEFICIENCY

Left ventricular diastolic dysfunction at rest and during exercise
Impaired left ventricular systolic function on exercise
Increased systemic vascular resistance
Increased prevalence of diastolic hypertension
Increased arterial stiffness
Endothelial dysfunction

TABLE 2. EFFECTS OF REPLACEMENT THERAPY WITH LEVOTHYROXINE ON CARDIOVASCULAR PARAMETERS IN MILD HYPOTHYROIDISM

Improved systolic function
Improved diastolic function at rest and during exercise
Improved cardiac preload
Improved endothelial function
Reduction in systemic vascular resistance
Improved arterial stiffness
Improved diastolic blood pressure

THYROID
Volume 17, Number 7, 2007

DOI: 10.1089/thy.2007.0158

Cardiovascular Effects of Mild Hypothyroidism

Bernadette Biondi

Based on the data available, it appears that L-T4 replacement should be considered in patients with mild hypothyroidism in presence of associated cardiovascular risk factors in the attempt to reverse these negative prognostic factors and improve the cardiovascular risk.

	Endpoints	No. casi
Biondi B, J Clin Endocrinol Metab. 1999;84:2064-7	Funzione cardiaca	33 casi
Caraccio N, J Clin Endocrinol Metab. 2002;87:1533-38	Lipidi	49 pz e 33 controlli
Caraccio N, J Clin Endocrinol Metab. 2005;90:4057-62	Risposta all'esercizio	23 pz e 10 controlli
Christ-Crain, Atherosclerosis 2003;166:379-86	CRP, Homocyst	63 pazienti
Cooper DS, Ann Intern Med. 1984;101:18-24.	Sintomi	33 pazienti
Jaeschke R, J Gen Intern Med. 1996;11:744-49.	Sintomi	37 pazienti
Jensovsky J, Cas Lek Cesk. 2000;139:313-16.	Sintomi	20 donne
Jensovsky J, Endocr Regul. 2002;36:115-22.	Sintomi	31 pz, 29 controlli
Kong WM, Am J Med. 2002;112:348-54.	Sintomi	40 donne
Meier C, J Clin Endocrinol Metab. 2001;86:4860-4866.	Lipidi	66 donne
Monzani F, J Clin Endocrinol Metab. 2001;86:1110-1115.	Lipidi	20 pz e 26 controlli
Monzani F, J Clin Endocrinol Metab. 2004;89:2099-106.	IMT	45 pazienti
Nystrom E, Clin Endocrinol (Oxf). 1988;29:63-75.	Sintomi	20 donne
Pollock MA, BMJ. 2001;20;323:891-95.	Sintomi	25 pz 19 controlli
Yazici M, Int J Cardiol. 2004;95:135-43.	Funzione cardiaca	45 pz 29 controlli

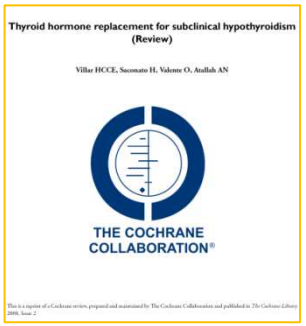
Il trattamento sostitutivo è efficace? : RCTs

Il trt è efficace

Il trt non è efficace

IS: efficacia del trattamento

Cochrane Coll – Sistematic Review



Villar et al. The Cochrane Library 2008, Issue 2

Main results

Twelve trials of 6 to 14 months duration involving 350 people were included. Eleven trials investigated levothyroxine replacement with placebo, one study compared levothyroxine replacement with no treatment. We did not identify any trial that assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood and quality of life with no statistically significant improvement.

One study showed a statistically significant improvement in **cognitive function**. Six

Authors' conclusions

In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.

IS: il trattamento sostitutivo è efficace?

Studi su assetto lipidico

Consensus Conference ATA-AACE-ES 2002

Table 7.8: Response to LT4 Treatment Stratified by TSH levels

					% Response to Therapy in Patients with Shypo			
Reference	**Design**	**Subjects (N)**		**Subgroups Baseline TSH values**	**TC**	**LDL**	**HDL**	**TG**
		Placebo	**Shypo**					
Meier et al. 2001	RCT	32	31	<12 mU/L >12mUI/L	0 -6*	0 -10**	0 0	0 0
Efstathiadou et al. 2001	Clinical Trial (uncontrolled)		37 18	TSH<10 mU/L TSH>10 mU/L	-4 -8**	-5 -9*	-5* -12**	-1 0
Michalopolou et al. 1998	Clinical Trial (uncontrolled)		**Group A** TC/TG: 35 LDL/HDL: 18 **Group B:** TC/TG: 35 LDL/HDL: 18 **Group C** TC/TG: 35 LDL/HDL: 18 **Group D** TC/TG: 35 LDL/HDL: 18	**Group A:** Low normal TSH **Group B:** Low normal TSH **Group C** High normal TSH **Group D** High TSH	-3 -1 0 -8**	-4 -4 -2 -13**	-5 +5 0 0	-2 -10* 0 -4
Miura et al. 1994	Clinical Trial (uncontrolled)		**Group 1** =15 **Group 2** =19	**Group 1** TSH<10 mU/L **Group 2** TSH> 10 mU/L	-2 -8**	-4 -18**	-6 -4	-18 +22
Diekman et al. 1995	Retrospective Follow-Up		21	**Group 1:** 5.0-9.9 mU/L **Group 2:** 10.0-39.3 mU/L **Group 3:** ≥ 40 mU/L	**Group 1**: -4 **Group 2**: -12* **Group 3** -34*	**Group 1** -7 **Group 2** -13* **Group 3** -41*	**Group 1** +6 **Group 2** -13** **Group 3** -9	**Group 1** -4 **Group 2** -4 **Group 3** -5

*: Significant change in levels after treatment, $p<0.05$
**: Significant change in levels after treatment, $p<0.01$

Il trattamento sostitutivo è efficace?

Annals of Internal Medicine

Screening for Thyroid Disease

An Update

Mark Helfand and Craig C. Redfern

15 July 1998 | Volume 129 Issue 2 | Pages 144-158

- **In summary, L-thyroxine treatment may reduce the serum cholesterol level by 6-8% in selected patients who have both a TSH level of 10 mU/L and an elevated total cholesterol level (>or = to 6.2 mmol/L, 240 mg/dl).**
- **How much would a reduction in total cholesterol level of 0.4 to 0.6 mmol/L (15-23 mg/dl, 6% to 8%) decrease the incidence of cardiovascular disease?**
- **In a 60-year-old woman with a pretreatment total cholesterol level of 6.5 mmol/L (250 mg/dl) and no other risk factors, a reduction of 0.6 mmol/L (8%) would decrease the risk for developing ischemic heart disease from 10% to 9%.**
- ***Una donna di 65 anni italiana con un colesterolo di 6.5 mmol/L (250 mg/dl) senza altri fattori di rischio CV, ha un rischio stimato del 3.2% (ISS – Progetto Cuore). Una riduzione di 23 mg/dl del colesterolo (0.6 mmol/L; 8%) porterebbe il rischio al 2.9%.***
- ***NNT x 10 anni = 1/(0,031-0,029) = 1/0,002 = 500***
- ***Per ogni anno di trattamento l'NNT per prevenire un caso di cardiopatia ischemica sarebbe 5000 per una riduzione del colesterolo di 0.6 mmol/L (8%).***

5

Il trattamento sostitutivo del Ipotiroidismo Subclinico con l-tiroxina è innocuo?

Thyrotoxicosis factitia

Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism

C. T. Sawin, A. Geller, M. M. Kaplan, P. Bacharach, P. W. Wilson and J. M. Hershman
Arch Intern Med. 1991;151:165-8

We studied a large population (n = 2575) of unselected ambulatory persons older than **60 years** to determine the prevalence of a low serum thyroid-stimulating hormone (TSH) level, ie, of **less than 0.1 mU/L** using a sensitive assay, a level suggestive of hyperthyroidism in younger adults. **One hundred one persons (3.9%) had a low serum TSH level. About half of them (51/101) were taking thyroid hormone.**
...

The Colorado Thyroid Disease Prevalence Study

Canaris GJ, Manowitz NR, Mayor G, Ridgway EC.

Arch Intern Med 2000, 160:526-34

... Of the group who reported taking thyroid medication, nearly 40% had an abnormal serum TSH level. **More than one fifth had TSH level that was suppressed** below normal.... Interestingly, 92% of the people taking thyroid medications had seen a health care provider in the previous year....

Table 2. Prevalence of Thyroid Abnormalities

Thyroid Status*	No. of Subjects (%)
Total subjects	(N = 25 862)
Euthyroid	22 842 (88.3)
Hypothyroid	114 (0.4)
Subclinical hypothyroid	2336 (9.0)
Hyperthyroid	35 (0.1)
Subclinical hyperthyroid	535 (2.1)
Subjects taking thyroid medication	(n = 1525)
Euthyroid	916 (60.1)
Hypothyroid	11 (0.7)
Subclinical hypothyroid	269 (17.6)
Hyperthyroid	13 (0.9)
Subclinical hyperthyroid	316 (20.7)

Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment.

Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Br J Gen Pract 1993, 43:107-9

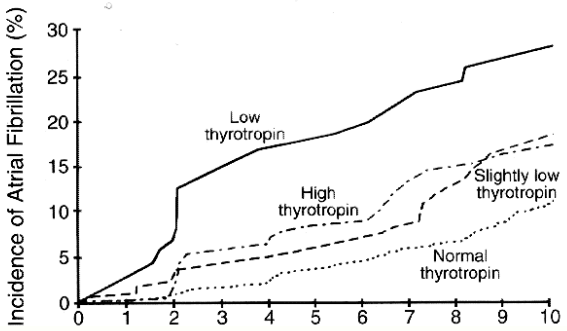
... in the United Kingdom and to **examine the frequency of abnormal serum thyroid stimulating hormone concentrations in those prescribed thyroxine for hypothyroidism...** Of **18,944 patients registered, 146 (0.8%) were being prescribed thyroxine**; 134 of these had primary hypothyroidism and the remainder had other thyroid or pituitary diseases prior to treatment. **Of the 97 patients with primary hypothyroidism who agreed to have their thyroid stimulating hormone level measured, abnormal serum levels were found in 48%, high levels in 27% and low levels in 21%..**

The NEW ENGLAND JOURNAL of MEDICINE
Volume 331:1249-1252 November 10, 1994 Number 19

Low Serum Thyrotropin Concentrations as a Risk Factor for Atrial Fibrillation in Older Persons

Clark T. Sawin, Andrew Geller, Philip A. Wolf, Albert J. Belanger, Errol Baker, Pamela Bacharach, Peter Wilson, Emelia J. Benjamin, and Ralph B. D'Agostino

- **Data from the Framingham Study.**
- **Among people 60 years of age or older, a low serum thyrotropin concentration is associated with a threefold higher risk that atrial fibrillation will develop in the subsequent decade.**
- **one excess case of atrial fibrillation may occur for every 114 patients treated with doses of L-thyroxine sufficient to suppress TSH**



Serum Thyrotropin Value	No. at Risk	Sex (M/F)	No. with AF	Rate of AF (per 1000 Person-Years)*	P Value†
Low (≤0.1 mU/liter)	61	8/53	13	28	0.005
Slightly low (>0.1 to 0.4 mU/liter)	187	84/103	23	16	0.11
Normal (>0.4 to 5.0 mU/liter)	1576	680/896	133	11	—
High (>5.0 mU/liter)	183	42/141	23	15	0.08
All subjects	2007	814/1193	192	12	—

*The age-adjusted incidence per 1000 person-years of follow-up.

†For the comparison with the rate in the group with the normal serum thyrotropin values.

Il trattamento dell'IS è innocuo?

il rischio di fibrillazione atriale

Supponiamo di avere 100 pazienti trattati con tiroxina; di questi 20 hanno TSH inibito (come da studi di popolazione), supponiamo 19 tra 0,1 e 0,4 e 1 sotto 0,1.

La frequenza/anno attesa di FA è:

- nel caso con TSH inibito è 2,8%/anno
- nei 19 con TSH tra 0.4 e 0.1 µU/ml è 1,6%/anno
- negli 80 rimanenti con TSH di norma è 1,1%/anno

Il rischio totale di FA nei miei 100 pazienti è 1,227
(0,19*1.6+0,01*2.8+0.8*1.1)
Eccedenza del rischio 1,212-1,1=0,112)

Calcolo del NNH/anno (0,112:100=1:x) = 893

Cioè per ogni 893 IS trattati per 1 anno devo aspettarmi un caso di FA in più rispetto all'atteso

Consensus Conference ATA-AACE-ES 2002

13 Esperti:

8 tiroidologi + 5 altri componenti:

cardiologia

epidemiologia

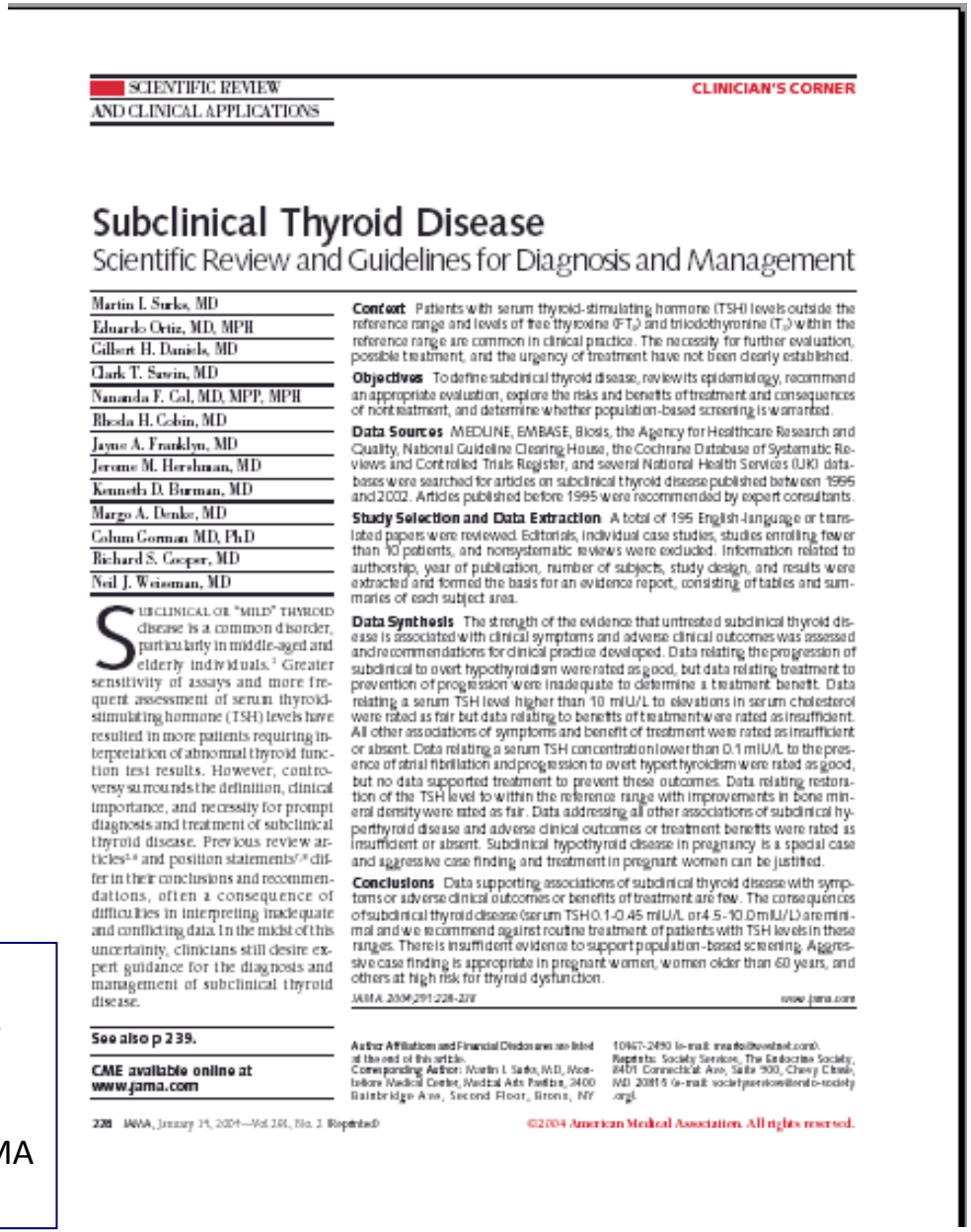
medicina generale

nutrizione

statistica

EBM

Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ
2004 Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291:228–238



SCIENTIFIC REVIEW AND CLINICAL APPLICATIONS

CLINICIAN'S CORNER

Subclinical Thyroid Disease

Scientific Review and Guidelines for Diagnosis and Management

Martin I. Surks, MD
Eduardo Ortiz, MD, MPH
Gilbert H. Daniels, MD
Clark T. Sawin, MD
Nananda F. Col, MD, MPP, MPH
Rhoda H. Cobin, MD
Jayne A. Franklyn, MD
Jerome M. Hershman, MD
Kenneth D. Burman, MD
Margo A. Denke, MD
Colum Gorman MD, PhD
Richard S. Cooper, MD
Neil J. Weissman, MD

Context Patients with serum thyroid-stimulating hormone (TSH) levels outside the reference range and levels of free thyroxine (FT_4) and triiodothyronine (T_3) within the reference range are common in clinical practice. The necessity for further evaluation, possible treatment, and the urgency of treatment have not been clearly established.

Objectives To define subclinical thyroid disease, review its epidemiology, recommend an appropriate evaluation, explore the risks and benefits of treatment and consequences of nontreatment, and determine whether population-based screening is warranted.

Data Sources MEDLINE, EMBASE, Biosis, the Agency for Healthcare Research and Quality, National Guideline Clearing House, the Cochrane Database of Systematic Reviews and Controlled Trials Register, and several National Health Services (UK) databases were searched for articles on subclinical thyroid disease published between 1995 and 2002. Articles published before 1995 were recommended by expert consultants.

Study Selection and Data Extraction A total of 195 English-language or translated papers were reviewed. Editorials, individual case studies, studies enrolling fewer than 10 patients, and nonsystematic reviews were excluded. Information related to authorship, year of publication, number of subjects, study design, and results were extracted and formed the basis for an evidence report, consisting of tables and summaries of each subject area.

Data Synthesis The strength of the evidence that untreated subclinical thyroid disease is associated with clinical symptoms and adverse clinical outcomes was assessed and recommendations for clinical practice developed. Data relating the progression of subclinical to overt hypothyroidism were rated as good, but data relating treatment to prevention of progression were inadequate to determine a treatment benefit. Data relating a serum TSH level higher than 10 mIU/L to elevations in serum cholesterol were rated as fair but data relating to benefits of treatment were rated as insufficient. All other associations of symptoms and benefit of treatment were rated as insufficient or absent. Data relating a serum TSH concentration lower than 0.1 mIU/L to the presence of atrial fibrillation and progression to overt hyperthyroidism were rated as good, but no data supported treatment to prevent these outcomes. Data relating restoration of the TSH level to within the reference range with improvements in bone mineral density were rated as fair. Data addressing all other associations of subclinical hyperthyroid disease and adverse clinical outcomes or treatment benefits were rated as insufficient or absent. Subclinical hypothyroid disease in pregnancy is a special case and aggressive case finding and treatment in pregnant women can be justified.

Conclusions Data supporting associations of subclinical thyroid disease with symptoms or adverse clinical outcomes or benefits of treatment are few. The consequences of subclinical thyroid disease (serum TSH 0.1-0.45 mIU/L or 4.5-10.0 mIU/L) are minimal and we recommend against routine treatment of patients with TSH levels in these ranges. There is insufficient evidence to support population-based screening. Aggressive case finding is appropriate in pregnant women, women older than 60 years, and others at high risk for thyroid dysfunction.

JAMA. 2004;291:228-238 www.jama.com

See also p 239.

CME available online at www.jama.com

Author Affiliations and Financial Disclosures are listed at the end of this article.
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Reprints: Society Services, The Endocrine Society, 8401 Connecticut Ave, Suite 900, Chevy Chase, MD 20815 (e-mail: societyservices@endo-society.org).

Consensus Conference ATA-AACE-ES 2002

http://endo-society.org/education/evidence-report.cfm

Due condizioni distinte:

- TSH tra 4,5 e 10 µU/ml (75% dei casi)
- TSH > 10 µU/ml

Table 1. Quality of Evidence on the Strength of Association and Risks/Benefits of Treatment of Subclinical Hypothyroidism

	Strength of Association		Benefits of Treatment	
Clinical Condition	Serum TSH 4.5-10 mIU/L	Serum TSH >10 mIU/L	Serum TSH 4.5-10 mIU/L	Serum TSH >10 mIU/L
Progression to overt hypothyroidism	Good	Good	*	*
Adverse cardiac end points	Insufficient	Insufficient	No evidence	No evidence
Elevations in serum total and LDL cholesterol	Insufficient	Fair	Insufficient	Insufficient
Cardiac dysfunction	†	Insufficient	Insufficient	Insufficient
Systemic hypothyroid symptoms	None	Insufficient	Insufficient	Insufficient
Neuropsychiatric symptoms	None	Insufficient	Insufficient	Insufficient

Abbreviations: LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.
*Thyroid hormone therapy normalizes serum TSH at any TSH concentration. Overt hypothyroidism occurs earlier in untreated patients with serum TSH >10 mIU/L than in those with serum TSH between 4.5 and 10 mIU/L.
†Data did not distinguish between serum TSH concentrations between 4.5 and 10 mIU/L and >10 mIU/L.

JAMA, 2004; 291:228-238

Consensus Conference ATA-AACE-ES 2002 recommends against routine treatment of subclinical hypothyroididsm

SCIENTIFIC REVIEW
AND CLINICAL APPLICATIONS

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JAMA. 2004;291:228-238

www.jama.com

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

Lack of evidence of benefit… not evidence for lack or benefit!

0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(1):581–585

doi: 10.1210/jc.2004-1231

CONSENSUS STATEMENT: Subclinical Thyroid Dysfunction: A Joint Statement on Management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society

Hossein Gharib, R. Michael Tuttle, H. Jack Baskin, Lisa H. Fish, Peter A. Singer, and Michael T. McDermott

Mayo Clinic College of Medicine (H.G.), Rochester, Minnesota 55905; Memorial Sloan-Kettering Cancer Center (R.M.T.), New York, New York 10003; Florida Thyroid & Endocrine Clinic (H.J.B.), Orlando, Florida 32804; Park-Nicollet Clinic (L.H.F.), Minneapolis, Minnesota 55404; University of Southern California School of Medicine (P.A.S.), Los Angeles, California 90033; and University of Colorado Health Sciences Center (M.T.M.), Denver, Colorado 80262

… Our reasons for disagreement on these issues are centered on the consensus conference participants' heavy, if not exclusive, reliance on EBM methodology to substantiate these negative recommendations. Their negative recommendations are inappropriate, in our opinion, because they are based primarily on a lack of evidence for benefit rather than on evidence for a lack of benefit.

Ipotiroidismo subclinico

THYROID
Volume 17, Number 4, 2007

DOI: 10.1089/thy.2006.0286

In My View

Aspects of Treatment of Subclinical Hypothyroidism

John H. Lazarus, M.A., M.D., FRCP, FACE, FRCOG

Patient A:

- 45-year-old female
- complaining of lethargy
- free T_4 12.3 nmol/L, TSH 9.8 mU/L
- positive TPOAb
- total cholesterol (TC) 6.2 mmol/L

Patient B:

- 54-year-old female
- complaining of depression and weight gain
- free T_4 14.8 nmol/L, TSH 6.8 mU/L
- negative TPOAb
- TC 6.0 mmol/L

This author suggests that T4 treatment should be given to Patient A. The TSH level of 6.8 in Patient B is clearly outside the reference range, and some expert thyroidologists would consider levothyroxine therapy at this TSH level; my personal practice would be to not treat

.. If TSH is elevated and TPOAb are positive one should lean towards treatment rather than against. Treatment in this situation would definitely prevent the onset of hypothyroidism in these patients. If TPOAb are negative and the TSH is<10 then treatment should only be given if symptoms are evident.
If symptoms are not evident, careful follow-up probably at 6-month intervals is to be recommended.

Ipotiroidismo subclinico

- Molto frequente (quasi il 10% della popolazione; ¾ TSH<10)
- Trattare:
  - quando il TSH è maggiore di 10 µU/ml (è verosimile che esista un'evoluzione probabile verso l'ipotiroidismo franco sopp. se AbTPO > 200)
  - una sintomatologia
  - gravidanza
  - gozzo?
- Se **TSH < 10 µU/ml:**
  - non certo un incremento del rischio cardiovascolare.
  - forse nel soggetto molto anziano è un fattore protettivo
  - i potenziali danni del trattamento equivalgono ai potenziali benefici
- Lo **screening** dell'ipotiroidismo subclinico **non è indicato**
- Con TSH tra limite superiore del range di normalità e 10 µU/ml **il trattamento di routine non è indicato**

Ma la terapia costa così poco…

Tavola 10. Primi trenta principi attivi per consumo territoriale^ di classe A-SSN: confronto fra i primi 9 mesi del periodo 2005-2010

ATC	Principio attivo	DDD/1000 ab die	%	Rango 2010	Rango 2009	Rango 2008	Rango 2007	Rango 2006	Rango 2005
C	ramipril	50,7	5,3	1	1	1	1	2	2
B	acido acetilsalicilico	43,8	4,6	2	2	2	2	1	1
C	amlodipina	27,7	2,9	3	3	3	3	3	3
C	furosemide	22,0	2,3	4	4	4	4	6	6
A	lansoprazolo	20,9	2,2	5	5	5	8	30	55
H	levotiroxina	18,8	2,0	6	6	7	7	7	7
C	atorvastatina	17,9	1,9	7	9	9	11	11	12
A	metformina	16,4	1,7	8	10	10	12	13	16
A	omeprazolo	16,1	1,7	9	11	22	39	14	11
C	enalapril	15,5	1,6	10	7	6	5	5	5
C	nitroglicerina	14,9	1,6	11	8	8	6	4	4
C	rosuvastatina	14,0	1,5	12	14	17	19	29	54
C	simvastatina	13,3	1,4	13	12	14	15	16	14
C	valsartan	12,9	1,3	14	17	18	16	18	20

DDD = defined daily dose

IS – quanto costa il trattamento?

- La prevalenza del'IS nel sesso femminile è di circa l'8%
- In Italia ci sono 25.500.000 donne adulte
- L'8% (2.295.000 circa) sono ipotiroidee subcliniche

Supponiamo di trattarne il 70% cioè 1.606.500:

Il costo dell'eutirox 75 è di 2.74 € a confezione; il fabbisogno annuale individuale di eutirox è di 7.3 confezioni; Il costo annuale individuale della terapia con l-tiroxina è di circa 20 €

- Il trattamento delle donne italiane con IS costerebbe ca. 32.130.000 €/anno

Un percorso regionale per le tireopatie

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