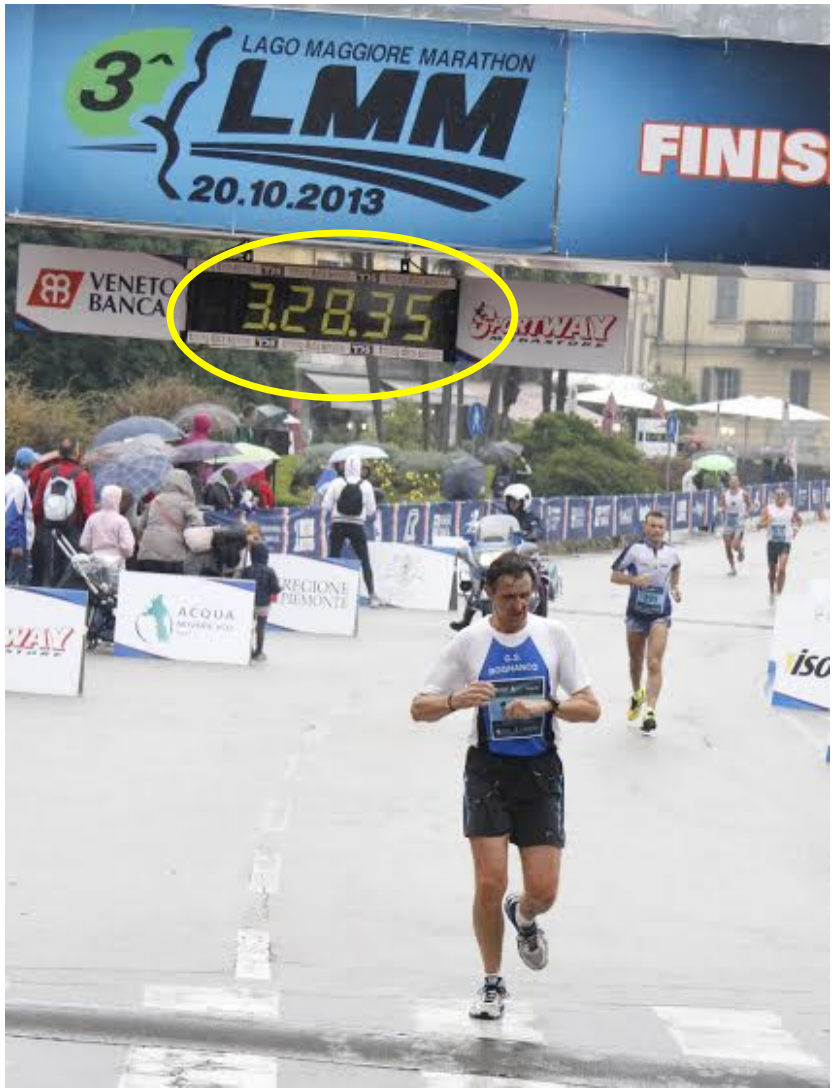
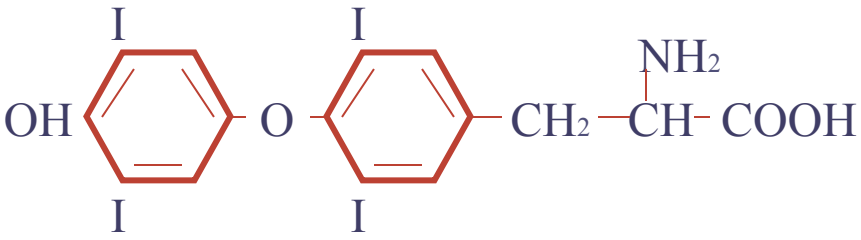
Fibrillazione Atriale & Tiroide

G. Saglietti
Diabetologia ed Endocrinologia A.S.L. VCO (VB)

Il motivo dell'invito…

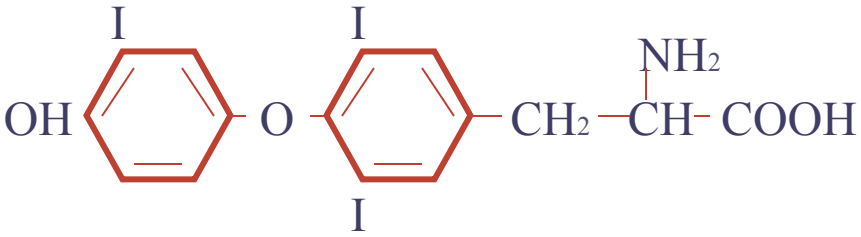


Gli ormoni tiroidei



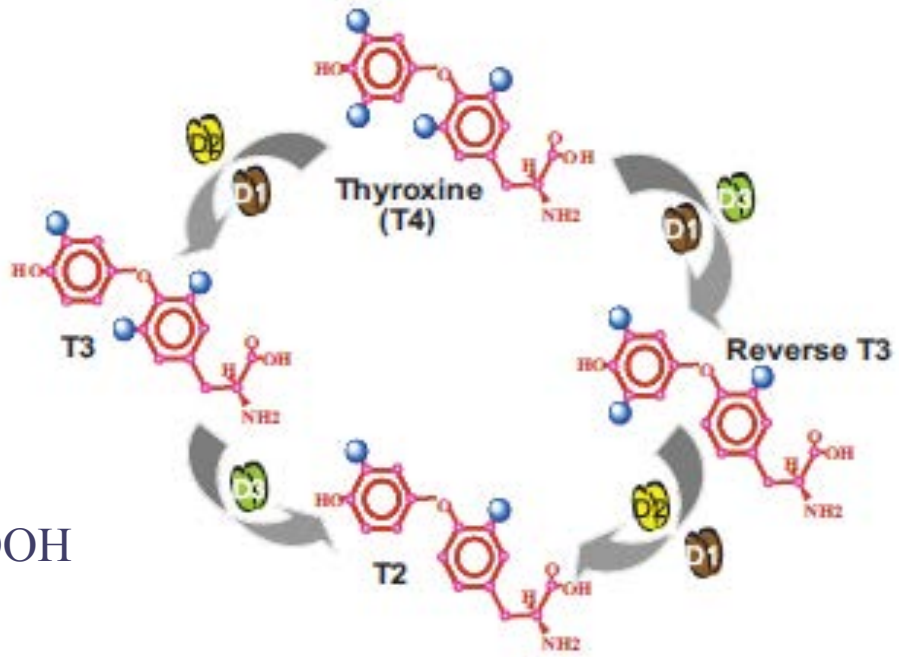
Tetraiodotironina (T4)

Concentrazione (nmol/l): 103
Produzione tiroidea (%): 100
Emivita (giorni): 7

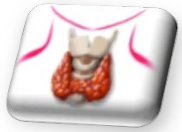


Triiodotironina (T3)

Concentrazione (nmol/l): 2
Produzione tiroidea (%): 20
Emivita (giorni): 1



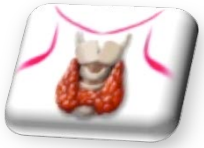
Classificazione dell' ipertiroidismo



Werner & Ingbars The Thyroid – LIPPINCOTT WILLIAMS & WILKINS 2000

Ipertiroidismo		Tireotossicosi	
M. di Basedow	70-85%	Tiroidite silente	5 – 25%
Adenoma tossico	3 – 30%	Tiroidite subacuta	
Gozzo tossico multinodulare	5 – 15%	Ormone esogeno	
Ipersecrezione di TSH	Rara	Tiroiditi farmaco-indotte	
Tumori trofoblastici	Rari	Tiroidite da raggi	
Struma ovarii	Raro		

Segni e sintomi di ipertiroidismo



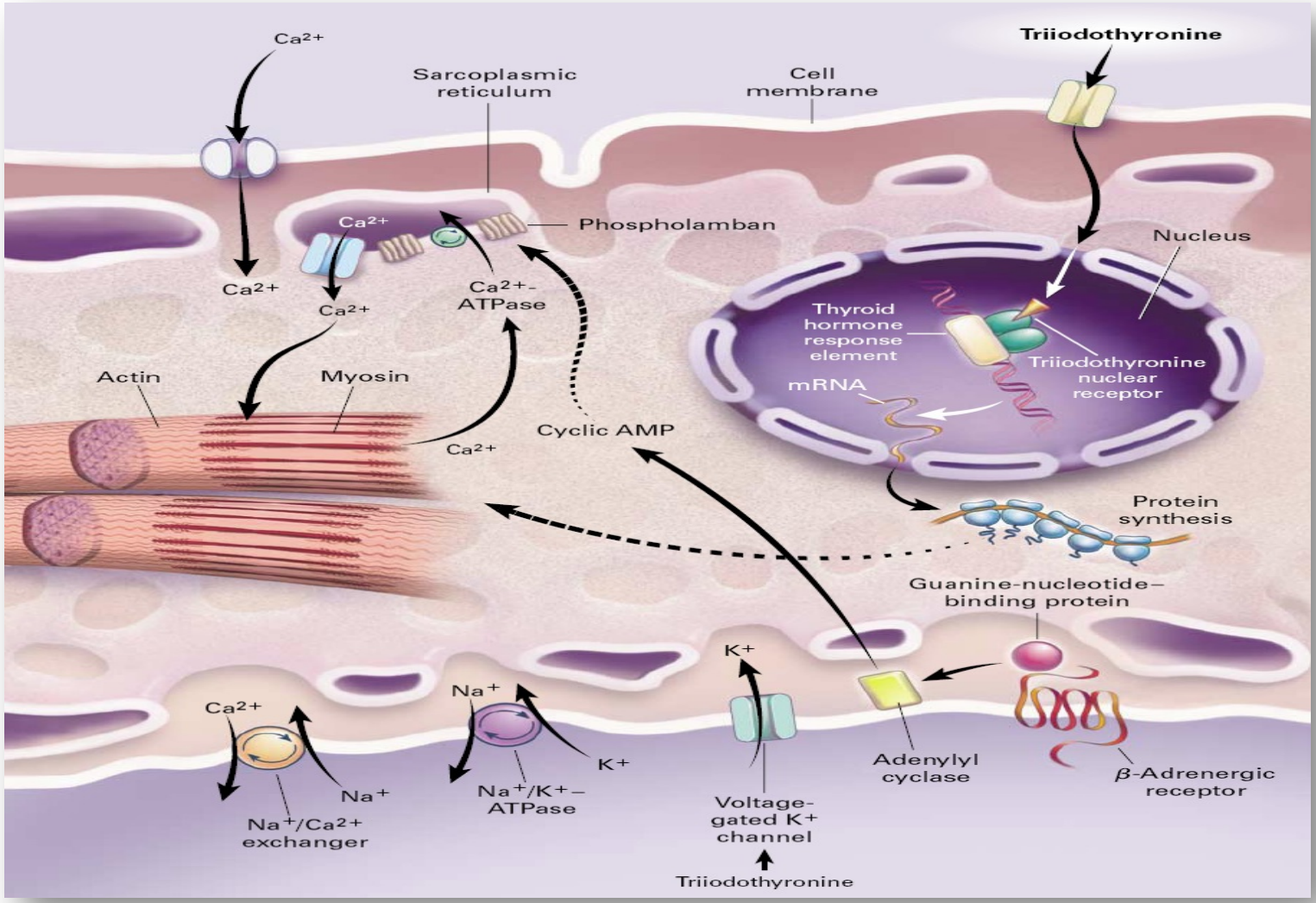
AACE Endocrine Practice Vol 8 n° 6 Nov/Dic 2002

- Nervosismo/irritabilità
- Tachicardia
- Intolleranza al caldo
- Perdita di peso
- Diarrea
- Dermopatia
- Esoftalmo
- Dispnea
- Alterazioni mestruali
- Ridotta fertilità
- Turbe mentali
- Turbe del sonno
- Fatica
- Gozzo

L’ipertiroidismo: effetti cardiaci

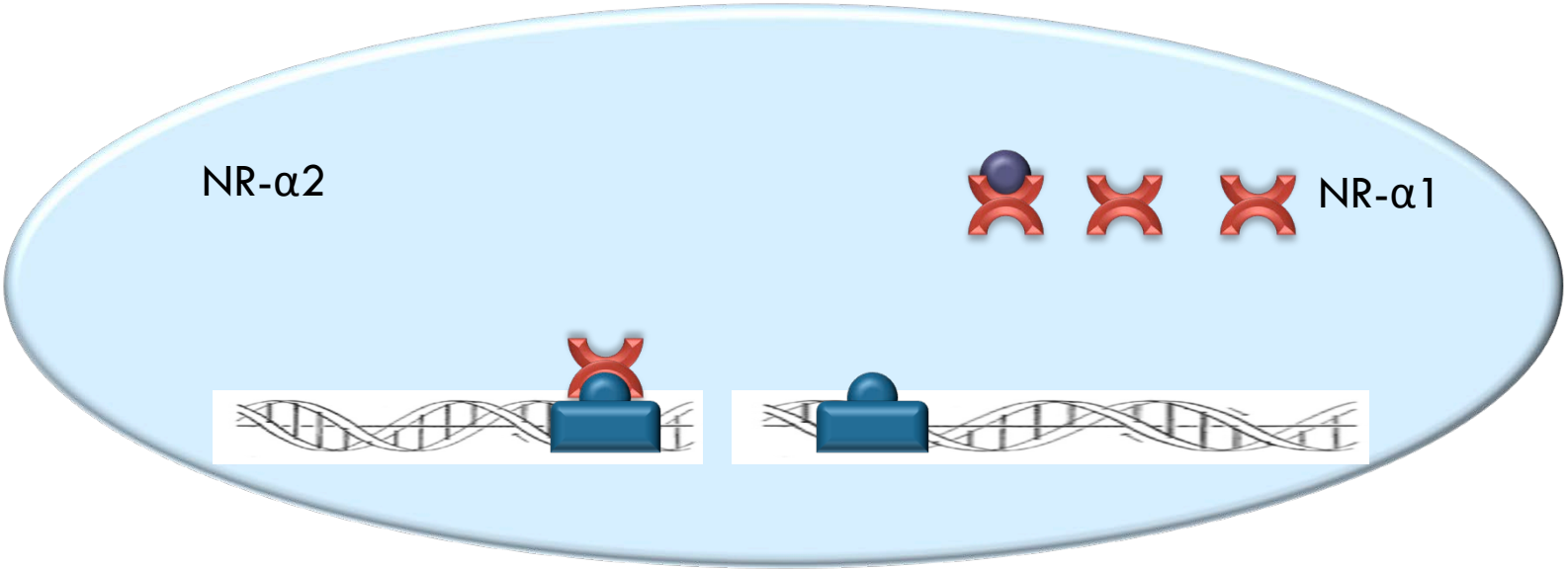
Effetti cardiaci degli ormoni tiroidei

Klein I et Al.: NEJM, 344 N° 7; 2001



Effetti "genomici" di T3

S. Fazio et Al. Recent Prog Horm Res, 2004



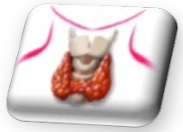
TRANSCRIPTIONAL REPRESSION

B-isoform of myosin heavy chain
Phospholamban
Nuclear receptor α-1
Adenyl-ciclase types V e VI
Na/Ca exchanger

TRANSCRIPTIONAL SYNTHESIS

α-isoform of myosin heavy chain
Sarcoplasmic reticulum Calcium ATPase
B1 adrenergic receptor
Guanine-nucleotide-regulatory protein
Na/K ATPase
Voltage-gated K channels

Effetti degli ormoni tiroidei sul cuore

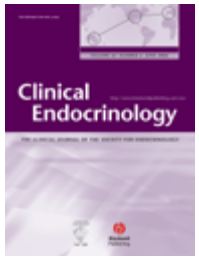


Kahaly G and Dillman WH: ENDOCR REW 2005 26:704-728

Gene	Transcription	TRE	mRNA	Protein	Activity
Myocytes—myofibrils					
MHC α	↑	Yes	↑↑↑	↑↑↑	Speed contraction ↑
MHC β	↓	Yes	↓↓↓	↓↓↓	Speed contraction ↓
C-actin	N/D	N/D	↑↑↑	N/D	Thin filament contractile protein
S-actin	N/D	N/D	↑↑↑	N/D	Thin filament contractile protein
Troponin I	N/D	N/D	↑↑↑	N/D	Thin filament regulatory protein
Myocytes—sarcoplasmic reticulum					
SERCA 2	↑	Yes	↑↑↑	↑↑↑	Ca sequestration ↑
Phospholamban	N/D	N/D	↓T3/↓Tx	N/D	SERCA 2 inhibition
Ryanodine channel	N/D	N/D	↑↑↑	N/D	Ca Efflux ↑
Myocytes—sarcolemma					
NaK ATPase					
α1			↑Tx→E	↑Tx→E	Na Efflux ↑
α2			↑Tx→E	↑Tx→E	
β			↑Tx→E	↑Tx→E	
βi Receptor	↑	N/D	↑↑	↑↑	Adrenergic ↑
Gi α	N/D	N/D	↓↓	↓↓	Adrenergic ↓
Gi β	N/D	N/D	↓↓	↓↓	Adrenergic ↓
Gs	N/D	N/D	N/D	↑	Adrenergic ↑

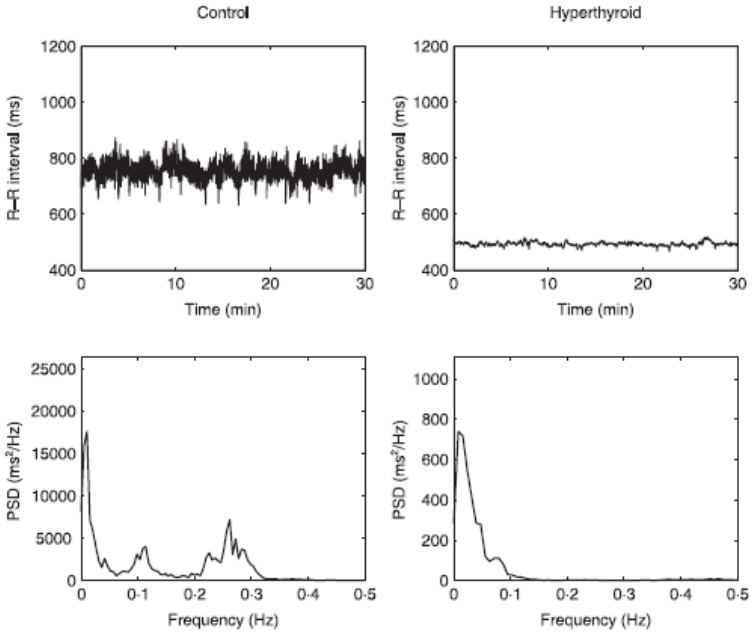
↑, An increase of parameter after TH administration; ↓, a decrease in the hypothyroid state; N/D, not determined; E, extranuclear effect.

Ipertiroidismo e sistema simpatico



Hyperthyroidism is characterized by both increased sympathetic and decreased vagal modulation of heart rate: evidence from spectral analysis of heart rate variability

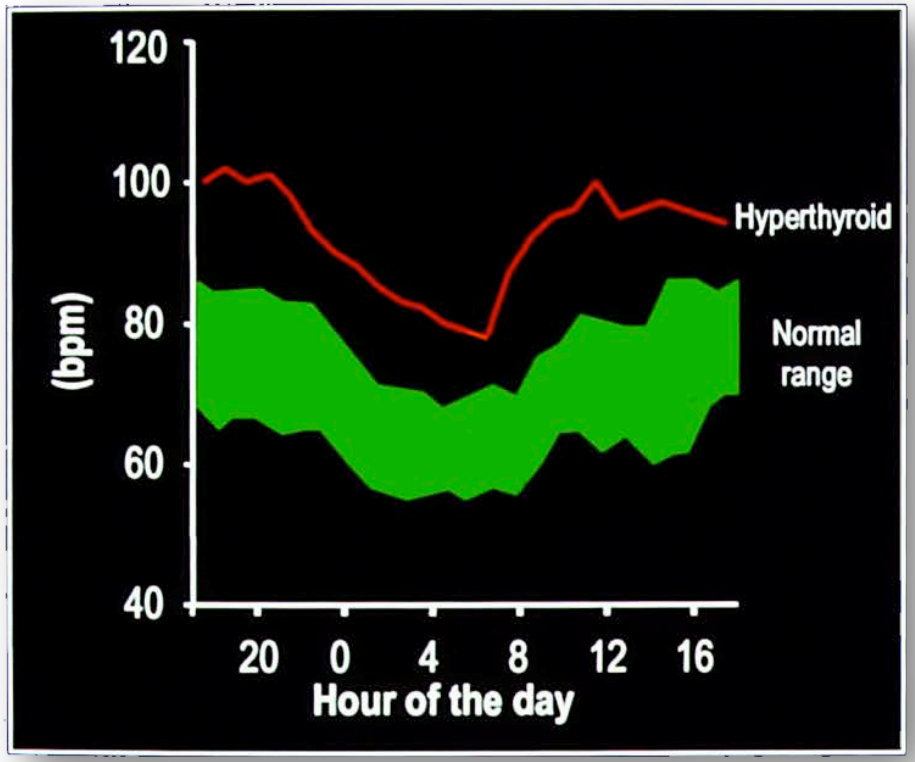
Jin-Long Chen*†, Hung-Wen Chiu‡, Yin-Jiun Tseng†§ and Woei-Chyn Chu†¶

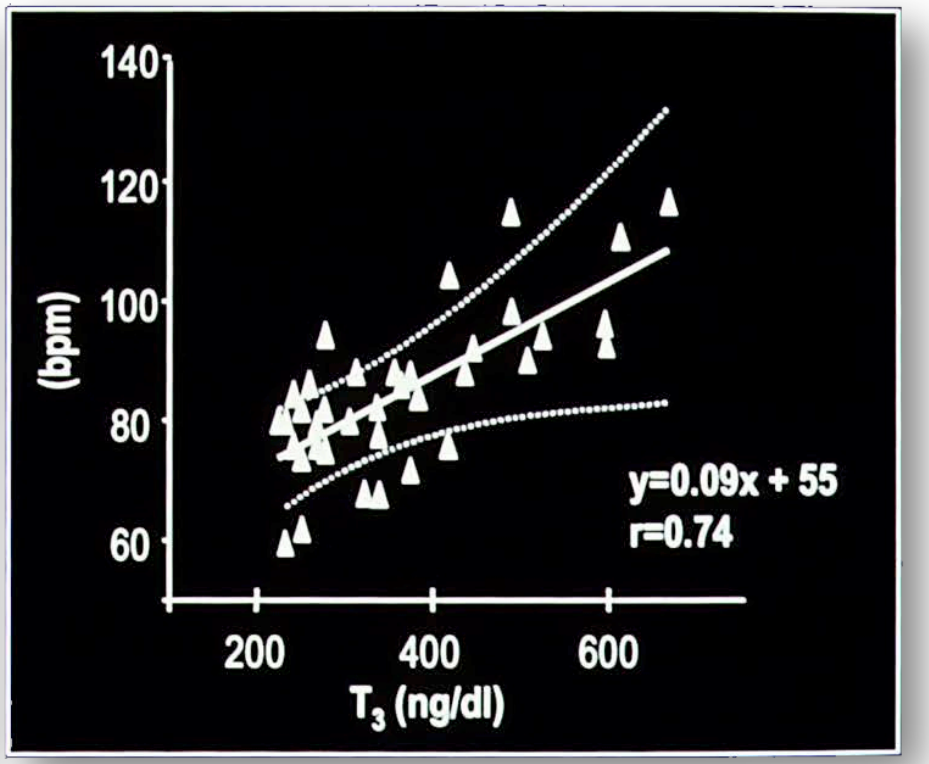


Based on the spectral analysis of HRV, our results suggest that hyperthyroidism is in a sympathovagal imbalanced state, which is associated with both increased sympathetic and decreased vagal modulation of the heart rate. These autonomic dysfunctions could be restored to normal after correction of the hyperthyroidism.

Frequenza cardiaca nell' ipertiroidismo conclamato

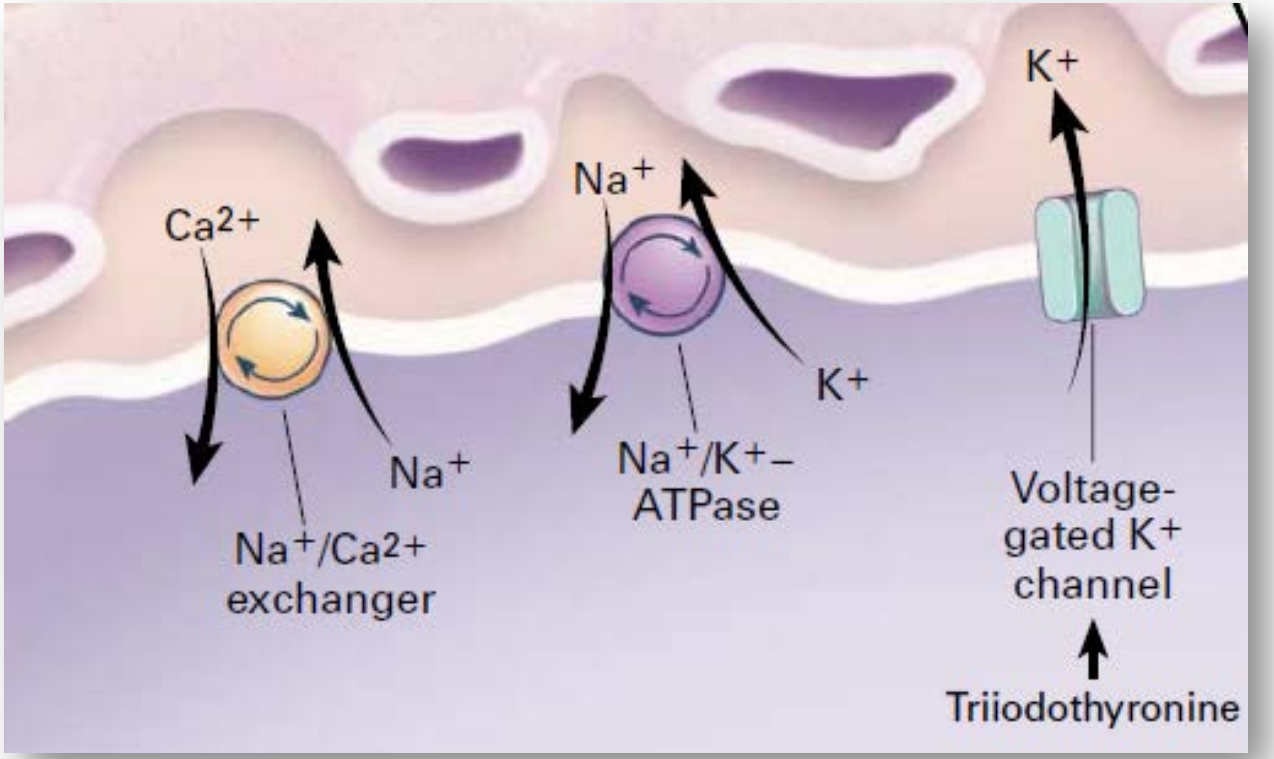
Olshausen KV et Al.: AM J CARDIOL, 1989





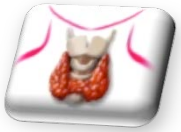
Effetti "non genomici" di T3

Klein I et Al.: NEJM, 344 N° 7; 2001



Modulazione delle performances dei canali del SODIO, POTASSIO e CALCIO
Aumento dell' INOTROPISMO e del CRONOTROPISMO

Effetti degli ormoni tiroidei sul cuore



Kahaly G and Dillman WH: ENDOCRI REW 2005 26:704-728

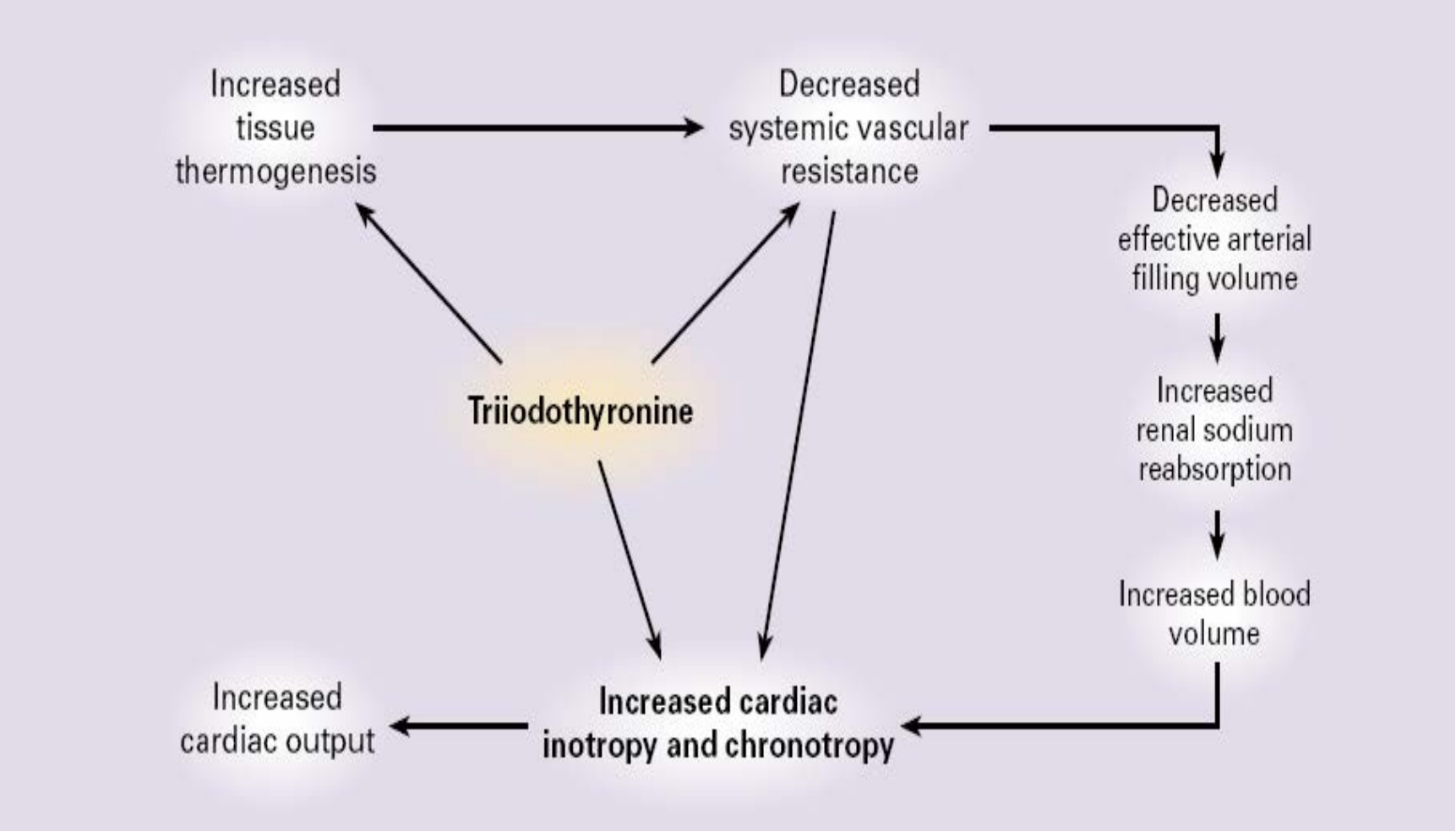
Physical examination	Hemodynamic changes	ECG/x-ray/ultrasound
Hyperthyroidism		
Tachycardia at rest	↑ Cardiac output	↓ QT interval
↑ Pulse amplitude	↑ Myocardial contractility	↓ PR interval
Systolic murmur	↑ Systolic/diastolic function	ST segment elevation
Mitral valve prolapse	↑ Systolic blood pressure	Atrial fibrillation
↑ First heart sound	↑ Blood volume	Wolff-Parkinson White Syndr
Possible third heart sound	↑ Venous resistance	↓ Contraction times
Ankle swelling	↓ Arterial resistance	Cardiac hypertrophy
Unspecific symptoms (palpitations, shortness of breath, chest pain)	↓ Diastolic blood pressure	Heart block
Means-Learman "scratch"	↓↓ Circulation time	

Effetti cronotropi

Effetti inotropi

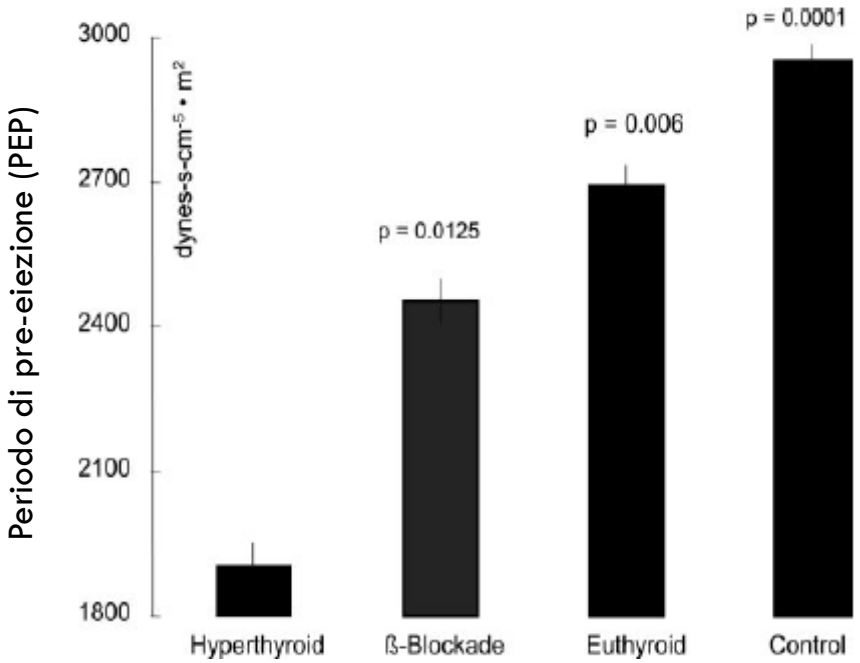
Effetti cardiaci dell' ipertiroidismo

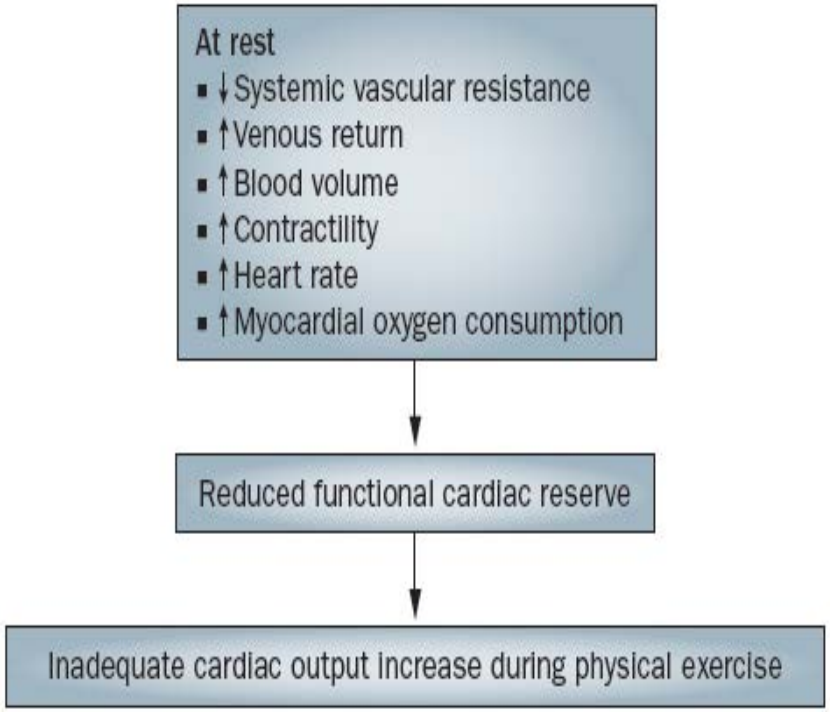
Klein I et Al.: NEJM, 344 N° 7; 2001



Fattori responsabili di ridotta riserva cardiaca

Kahaly G and Dillman WH: ENDOCRI REW 2005 26:704-728

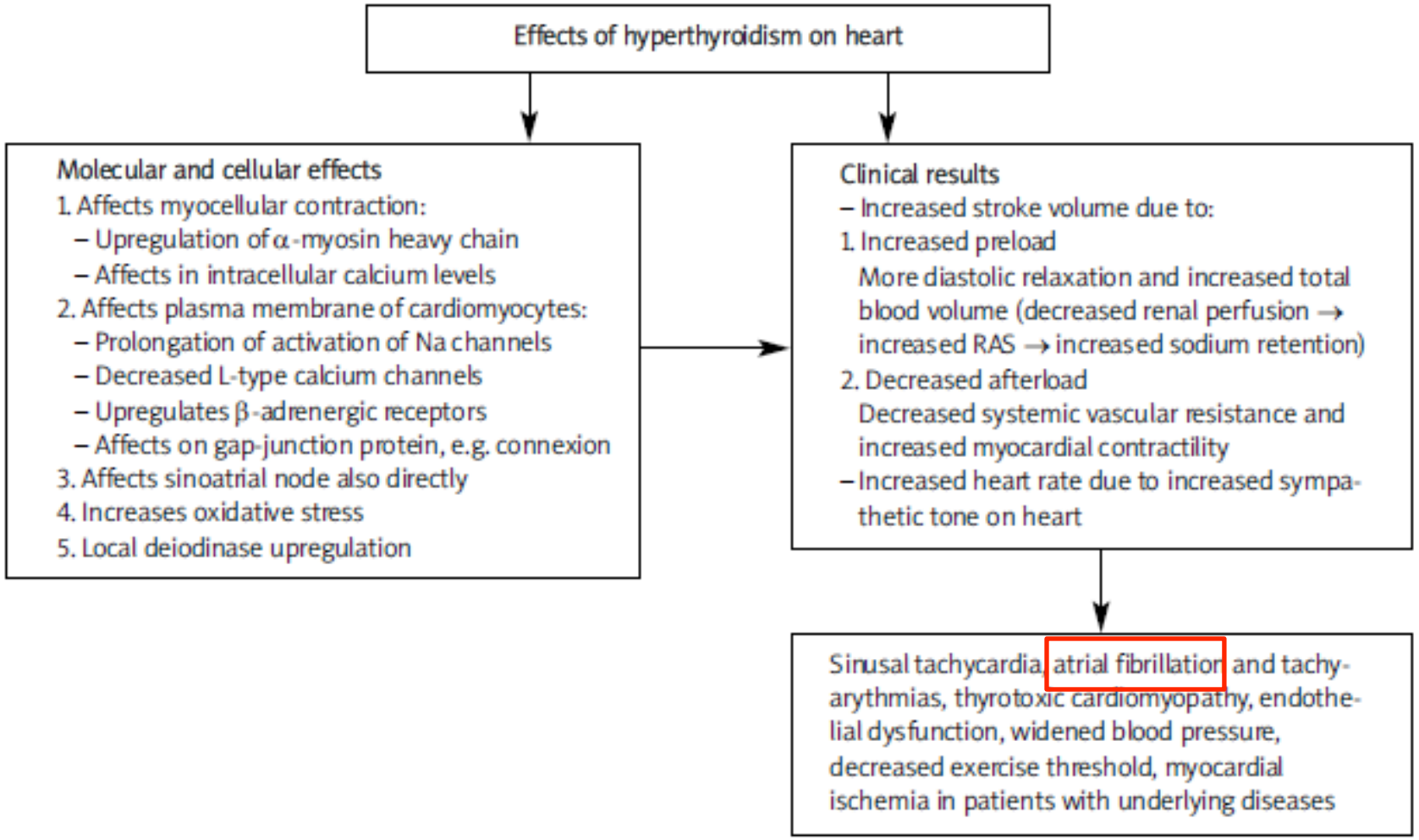




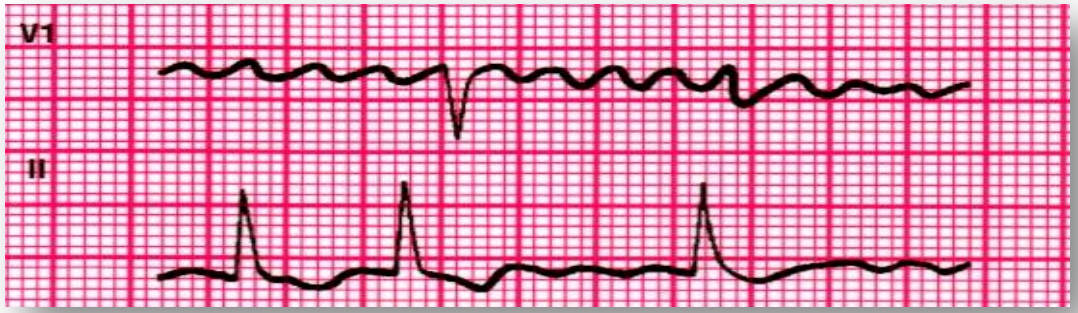
Biondi B, Kahaly GJ:NAT REV ENDOCRINOL 6,431-443,2010

Effetti dell'ipertiroidismo sul cuore

Ertek S, Cicero AF: ARCH MED SCI 2013;9,5:944-952

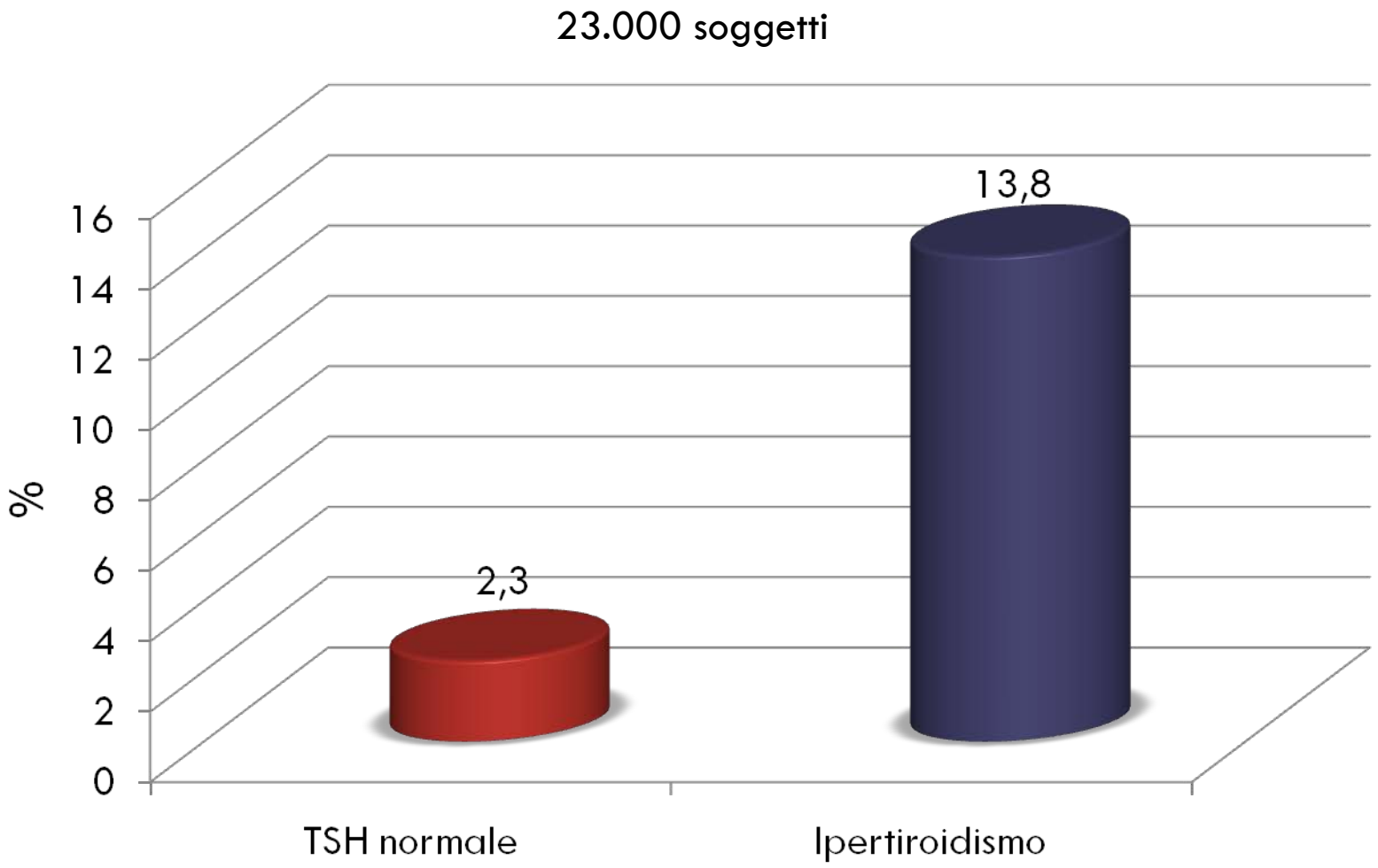


Ipertiroidismo e fibrillazione atriale



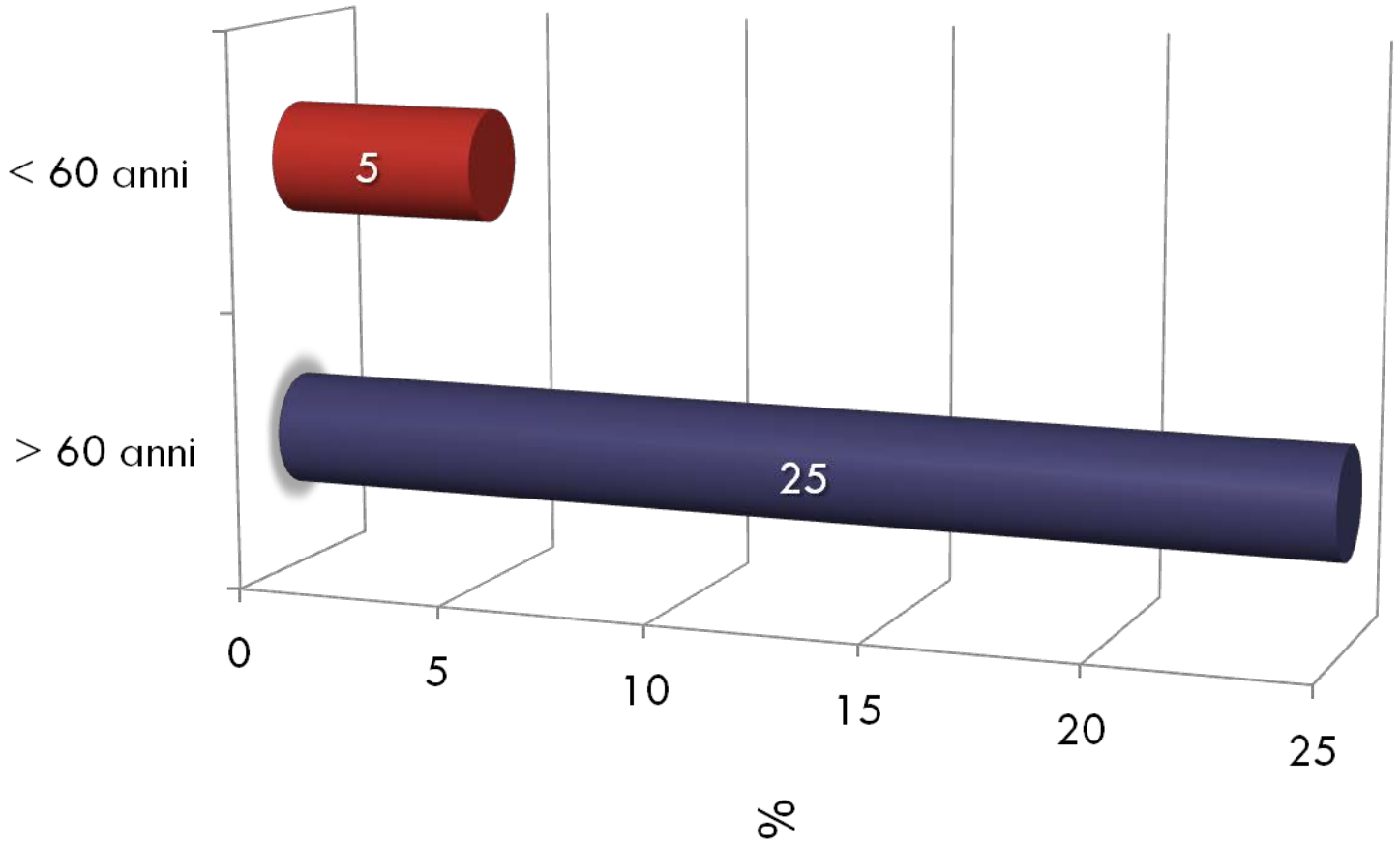
Prevalenza di F.A.

Auer J et Al.: AM HEART J 142: 838-42, 2001



F.A. negli ipertiroidei in rapporto all' età

Agner T et al.: DAN MED BULL 1984: 31; 157-159



Ipertiroidismo e rischio di F.A. o flutter

Frost L et Al.: ARCH INTERN MED 164:2004

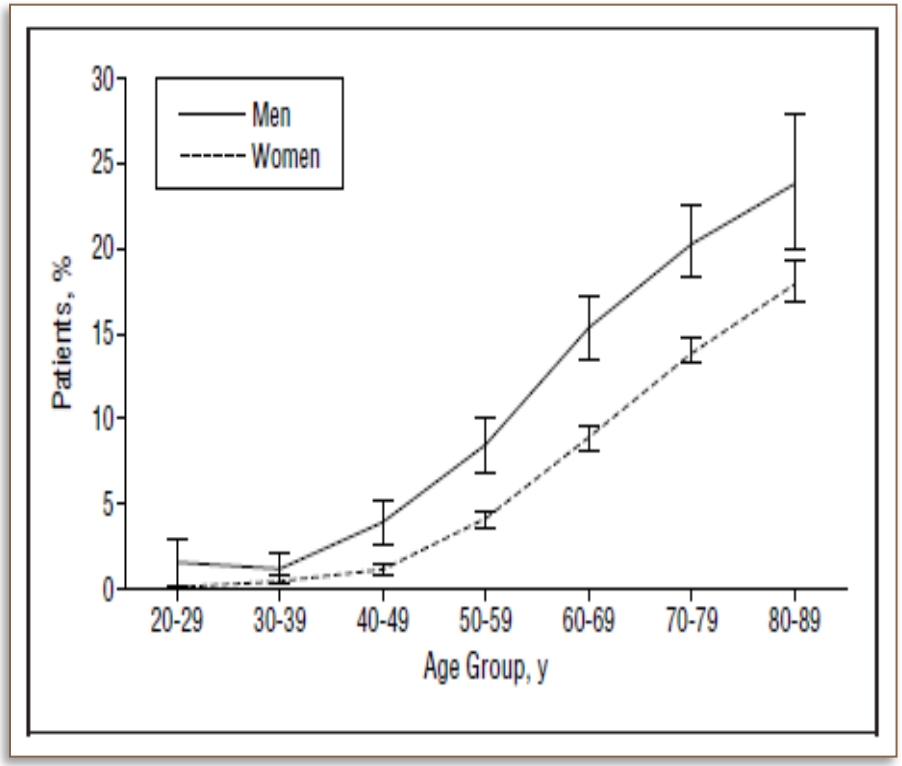
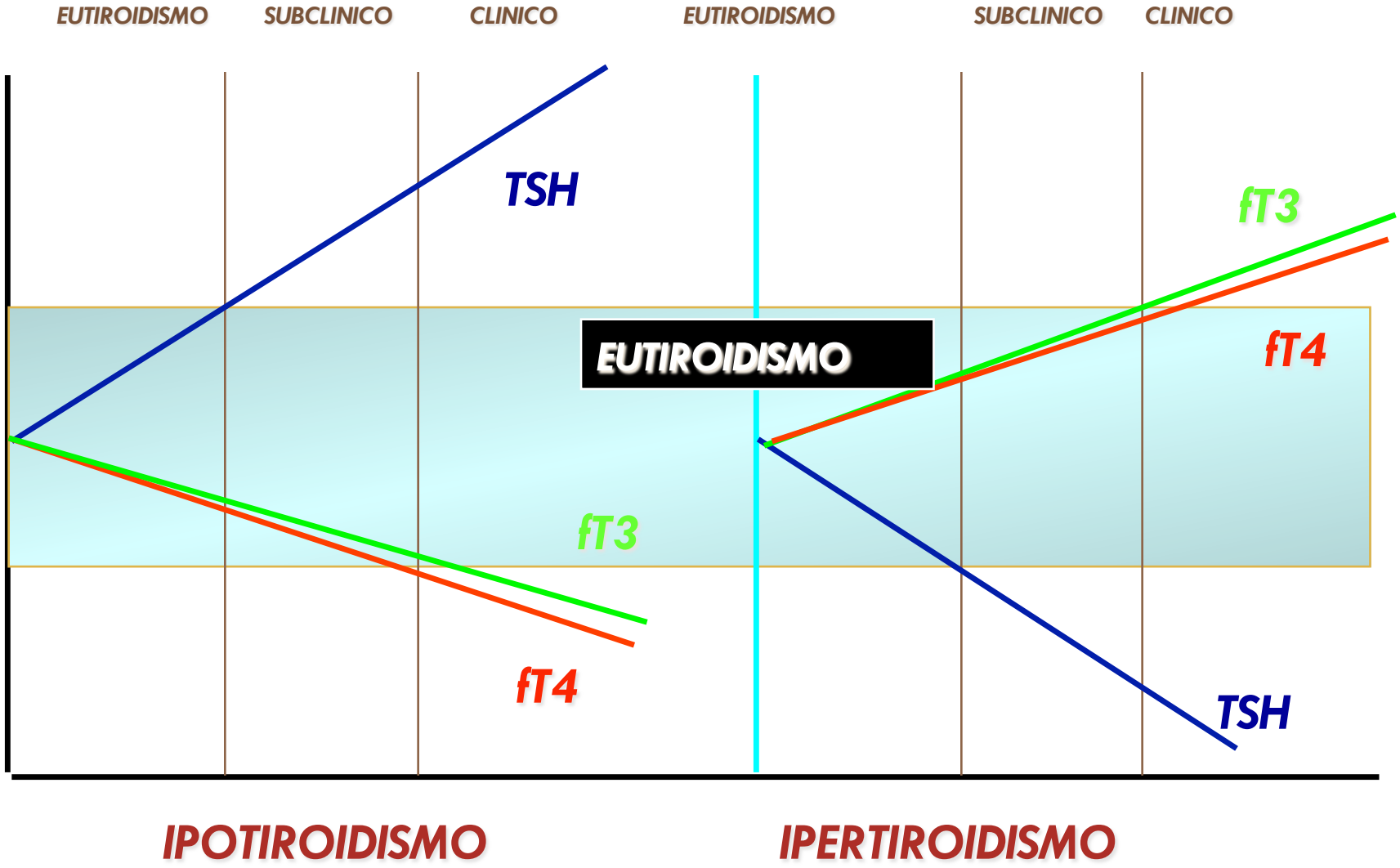


Table 3. Risk Factors for Atrial Fibrillation Among 40628 Patients With Hyperthyroidism in Denmark (January 1, 1980–December 31, 1999)

Characteristic	Adjusted OR (95% CI)*
Men (reference, women)	1.7 (1.6-1.9)
Age at diagnosis of hyperthyroidism (risk per 10-y increment)	1.7 (1.7-1.8)
Medical condition before or at diagnosis of hyperthyroidism†	
Hypertension	0.9 (0.8-1.0)
Diabetes	0.9 (0.8-1.1)
Ischemic heart disease	1.3 (1.2-1.4)
Congestive heart failure	2.8 (2.6-3.1)
Aortic and/or mitral valve disease	1.9 (1.5-2.4)

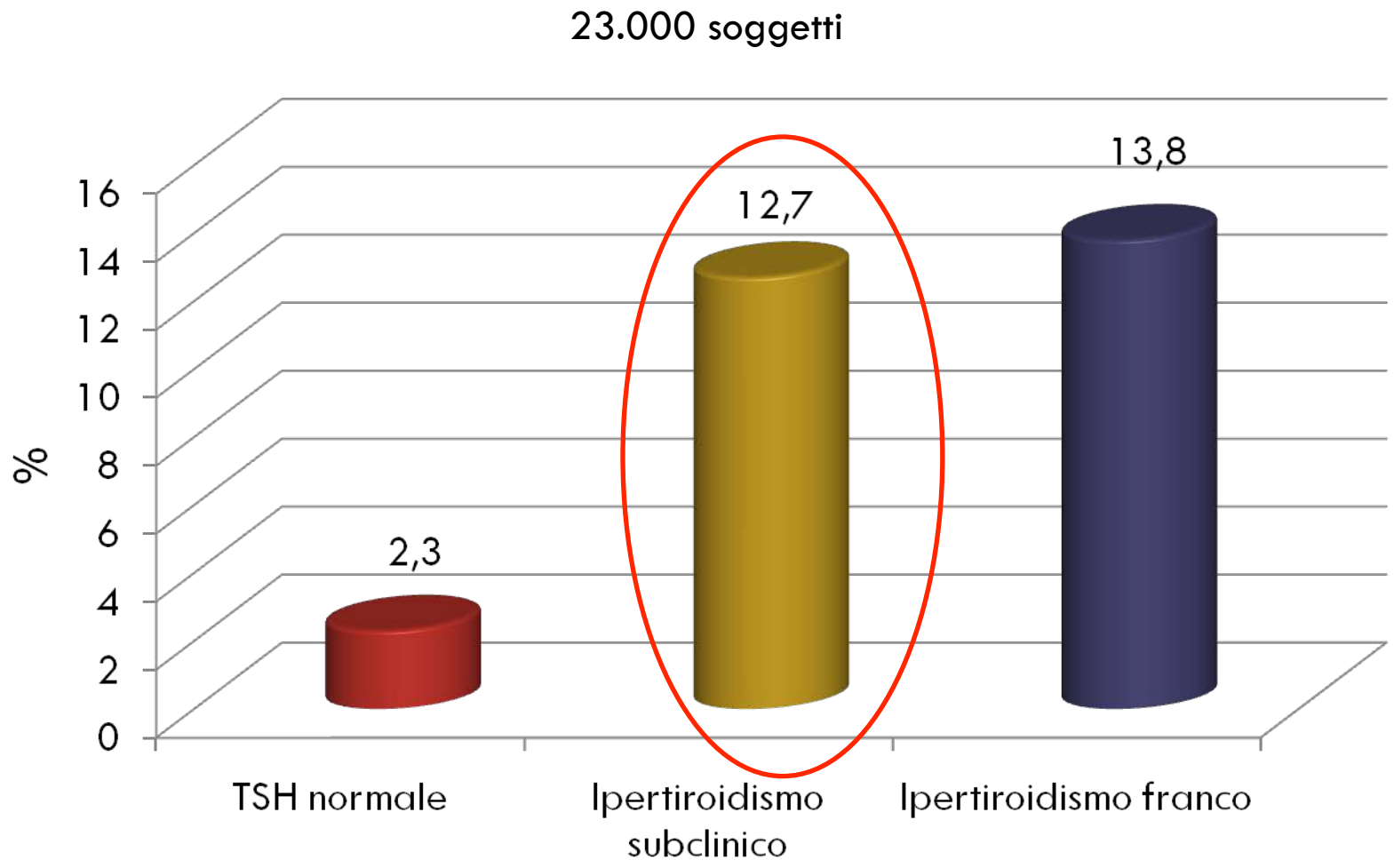
Prevalenza= 8,3%
M= 12,1% - F=7,6%

Relazione TSH/ormoni tiroidei



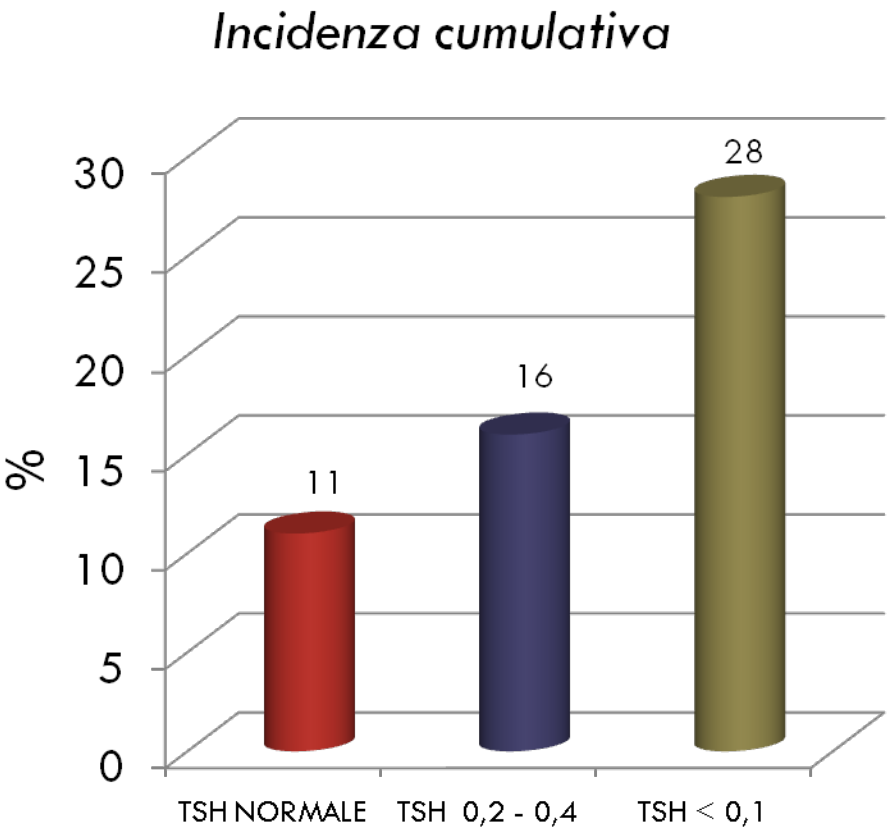
Prevalenza di F.A.

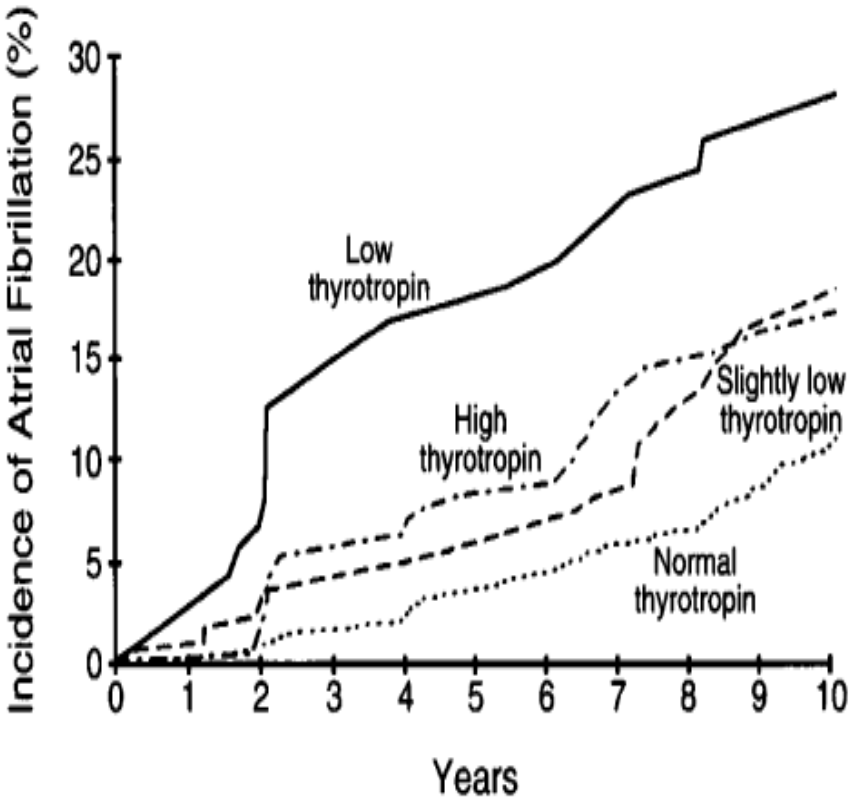
Auer J et Al.: AM HEART J 142: 838-42, 2001



Correlazione TSH/F.A. (Framingham n°2007)

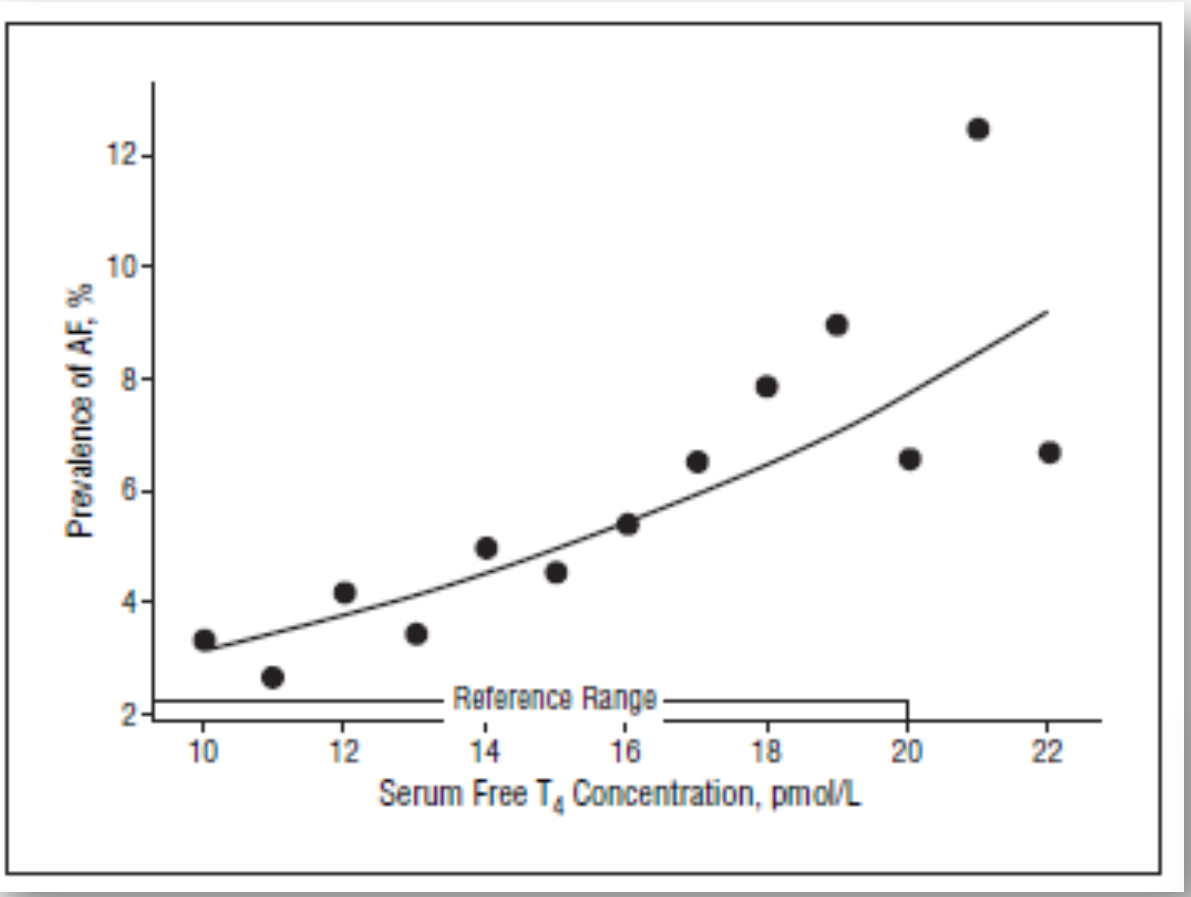
Sawin CT et Al.: NEJM 1994; 331:124952





Relazione FT4/F.A.

Gammage MD et Al.: ARCH INTERN MED 167, 2007



Conclusions: The biochemical finding of subclinical hyperthyroidism is associated with AF on resting electrocardiogram. Even in euthyroid subjects with normal serum TSH levels, serum free T_4 concentration is independently associated with AF.

Ipertiroidismo e infiammazione

Table 1. Baseline characteristics.

	HT- SR Group (n = 35)	HT-AF Group (n = 30)	Control Group (n = 35)	P Value
Clinical findings				
Age, yr(s)	55 ± 11	57 ± 9	56 ± 13	0.74
Male	10 (28.6)	15 (50)	13 (37.1)	0.2
Diabetes mellitus	6 (17.1)	2 (6.7)	3 (8.6)	0.3
Hypertension	12 (34.3)	14 (46.7)	11 (31.4)	0.4
Smoking	6 (17.1)	11 (36.7)	7 (20)	0.14
TNG/TMNG	21(60)/14(40)	19(63.3)/11(33.7)	-	0.8
Medications				
ACEI or ARB	10 (28.6)	8 (28.6)	7 (20)	0.68
β-blocker	1 (2.9)	1 (3.3)	-	0.57
Diuretics	5 (14.3)	1 (3.3)	-	0.1
Calcium channel blocker	4 (11.4)	8 (26.7)	5 (14.3)	0.23
Statin	5(14.3)	2 (6.7)	3 (8.6)	0.56
Echocardiographic findings				
Left atrial diameter (mm)	37 ± 5.3	42 ± 3	35.3 ± 2.3	< 0.001[a]
Left ventricular mass (g)	179.2 ± 27.9	200.1 ± 35.6	183.5 ± 32.3	0.038[b]
Left ventricular diastolic dysfunction	3 (8.6)	4 (13.3)	4 (11.4)	0.8
Laboratory findings				
Hs-CRP (mg/L)	0.36 ± 0.36	0.64 ± 0.56	0.27 ± 0.22	< 0.0013[c]
Free T3 (pg/mL)	4.6 ± 1.75	6.0 ± 3.45	3.08 ± 0.51	< 0.001[d]
Free T4 (ng/dL)	1.88 ± 0.7	3.0 ± 1.62	1.18 ± 0.23	< 0.001[e]
Free TSH (μIU/mL)	0.03 ±0.05	0.04 ± 0.05	1.9 ± 1.9	< 0.001[f]

Ipertiroidismo e rischio di stroke

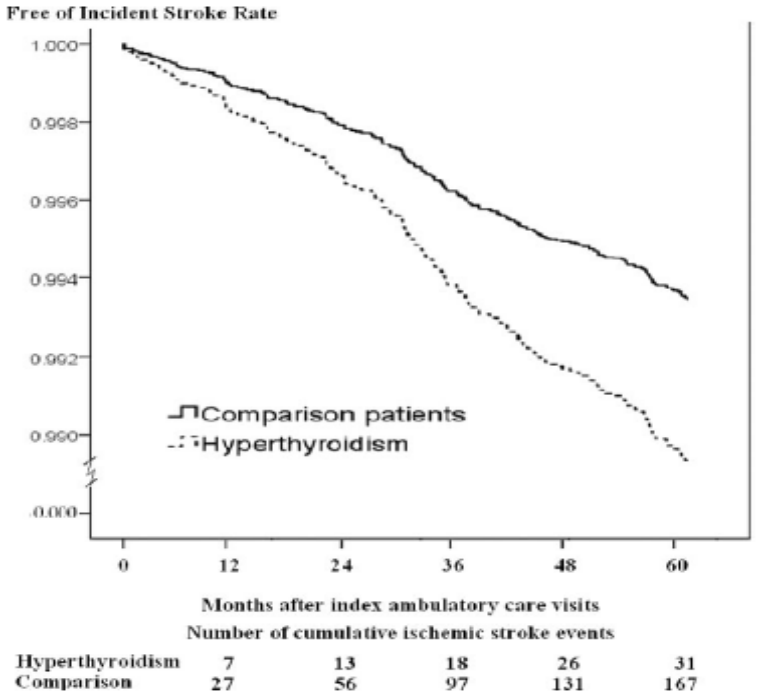
Sheu JJ et Al.: STROKE.2010;41:961-966

Table 2. Crude and Adjusted Hazard Ratios for Stroke Among the Sample Patients During the 5-Year Follow-Up Period Starting From the Index Ambulatory Care Visit (n=28 584)

Presence of Ischemic Stroke	Total Sample		Comparison		Hyperthyroidism	
	N	%	N	%	N	%
5-year follow-up period						
Yes	198	0.7	167	0.7	31	1.0
No	28,386	99.3	25,241	99.3	3,145	99.0
Crude HR (95% CI)	…		1.00		1.49† (1.01–2.19)	
Adjusted* hazard ratio (95% CI)	…		1.00		1.44† (1.02–2.12)	

*Adjustments are made for patient's age, gender, hypertension, diabetes, atrial fibrillation, coronary heart disease, hyperlipidemia, use of antiarrhythmics, monthly income, urbanization level, and geographical region.

†$P<0.05$.



Conclusions: *our study shows an association between hyperthyroidism and the risk of subsequent ischemic stroke in young adults…our results indicate a need for thyroid function testing and detection of hyperthyroidism in surveys to identify the etiology of ischemic stroke in young people*

FA in ipertiroidismo e rischio embolico

Review

Embolic Risk in Atrial Fibrillation that Arises from Hyperthyroidism

Review of the Medical Literature

Elie Traube, MD
Neil L. Coplan, MD, FACC

Atrial fibrillation, the most common cardiac complication of hyperthyroidism, occurs in an estimated 10% to 25% of overtly hyperthyroid patients. The prevalence of atrial fibrillation increases with age in the general population and in thyrotoxic patients. Other risk factors for atrial fibrillation in thyrotoxic patients include male sex, ischemic or valvular heart disease, and congestive heart failure. The incidence of arterial embolism or stroke in thyrotoxic atrial fibrillation is less clear. There are many reports of arterial thromboembolism associated with hyperthyroidism, including cases of young adults without coexisting risk factors other than thyrotoxic atrial fibrillation.

The use of anticoagulative agents to prevent thromboembolic sequelae of thyrotoxic atrial fibrillation is controversial: national organizations provide conflicting recommendations in their practice guidelines. Herein, we review the medical literature and examine the evidence behind the recommendations in order to determine the best approach to thromboembolic prophylaxis in patients who have atrial fibrillation that is associated with hyperthyroidism. ***(Tex Heart Inst J 2011;38(3):225-8)***

"…the most evidence-based study did not find that the trend toward increase embolic risk was a statistically significant independent risk factor when other known risk factors were considered…Given the lack of clear evidence, the ACC/AHA classification of thyrotoxicosis as a moderate thromboembolic risk factor seems to be reasonable, and the recommendation to initiate anticoagulation when there are no controindication appear to be warranted"

New-Onset Atrial Fibrillation Is a Predictor of Subsequent Hyperthyroidism: A Nationwide Cohort Study

Christian Selmer[1]*, Morten Lock Hansen[1], Jonas Bjerring Olesen[1], Charlotte Mérie[1], Jesper Lindhardsen[1], Anne-Marie Schjerning Olsen[1], Jesper Clausager Madsen[4], Ulla Schmidt[3], Jens Faber[3], Peter Riis Hansen[1], Ole Dyg Pedersen[2], Christian Torp-Pedersen[1], Gunnar Hilmar Gislason[1]

1 Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark, 2 Department of Cardiology, Roskilde University Hospital, Roskilde, Denmark, 3 Department of Endocrinology, Herlev University Hospital, Herlev, Denmark, 4 Copenhagen General Practitioners Laboratory, Copenhagen, Denmark

PLOS ONE | www.plosone.org February 2013 | Volume 8 | Issue 2 | e57893

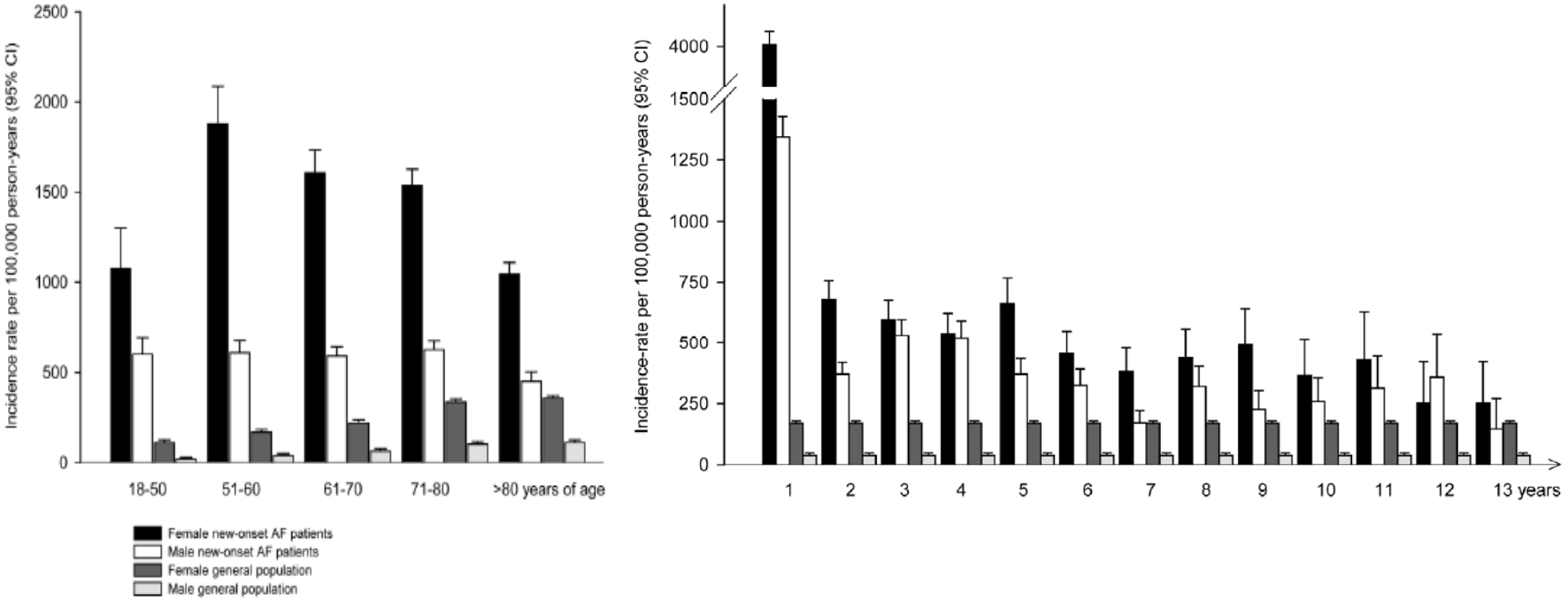


Figure 2. Development of hyperthyroidism in patients with new-onset atrial fibrillation and in the general population stratified by sex and age groups. Incidence rates per 100,000 person-years (95% confidence intervals). AF, Atrial Fibrillation; CI, Confidence Interval.
doi:10.1371/journal.pone.0057893.g002

La terapia

Risposta alla terapia tireostatica

- Il ripristino del R.S. in risposta alla terapia tireostatica è più probabile nei pazienti giovani, con F.A. di recente insorgenza ed in quelli con bassa P.A.S. Il ripristino dell'eutiroidismo con tireostatici risulta in una conversione a R.S. entro 6 – 12 settimane in più del 50% dei pazienti con F.A. di recente insorgenza

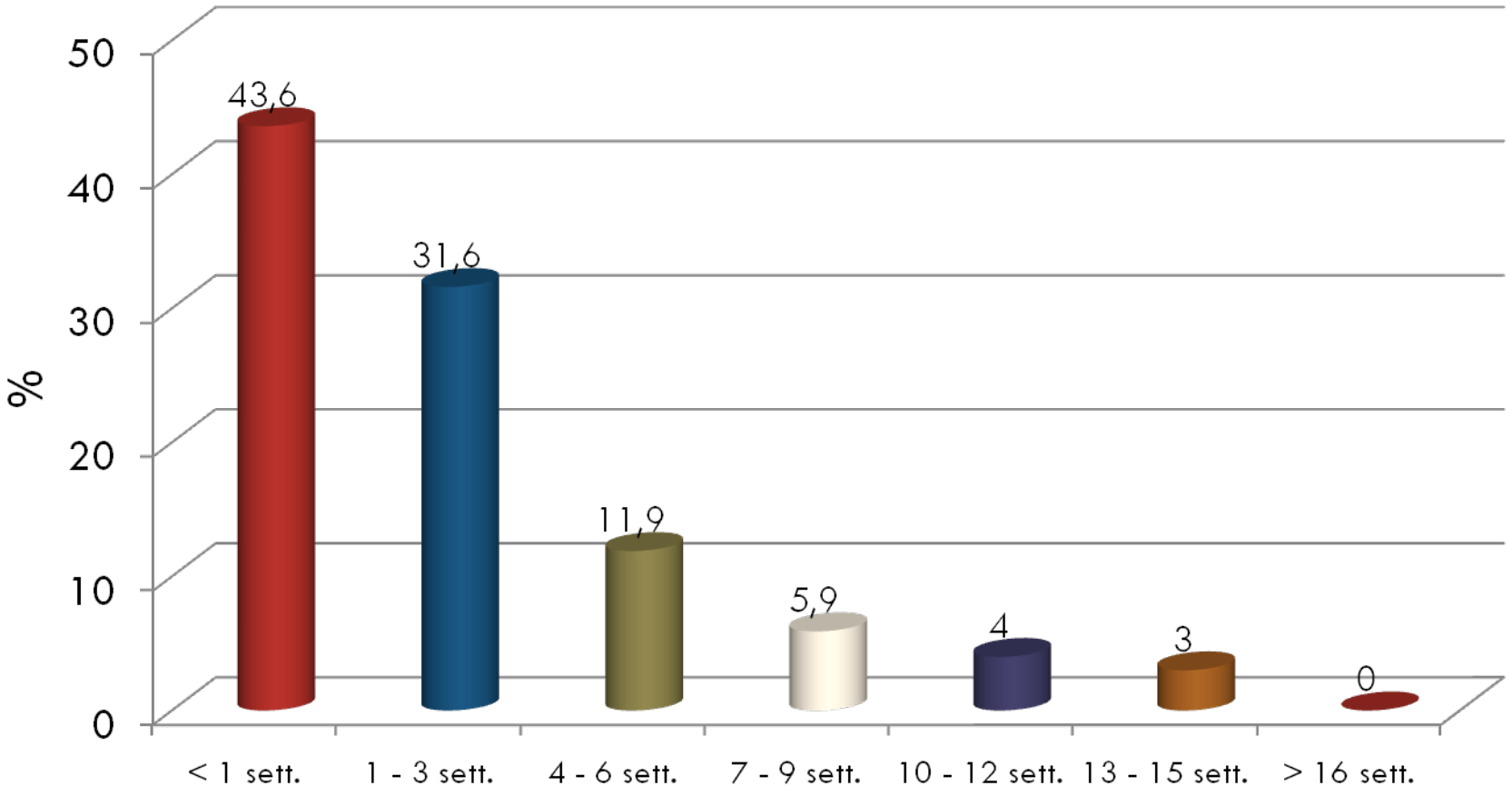
- I maggiori determinanti del ripristino del R.S. sono la durata dell'F.A., l'età del paziente e la presenza di cardiopatia concomitante

- Pazienti > 60 anni con cardiopatia e con F.A da più di un anno, frequentemente non ripristinano il R.S. con la risoluzione dell'ipertiroidismo

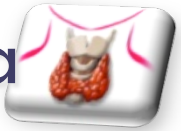
- La F.A. che persiste per 4 mesi o più dopo il controllo dell'ipertiroidismo, raramente ritorna al R.S. senza cardioversione

Intervallo tra ripristino dell'eutiroidismo e ritorno spontaneo a ritmo sinusale

Nakazawa HK et Al. AM J MED 1982, 72:903-906



Effetti cardiovascolari della terapia tireostatica



Sgarbi JA et Al.: JCEM 2003, 88(4):1672-1677

TABLE 3. Electrocardiography 24-h monitoring (Holter) in controls and in patients with subclinical hyperthyroidism (SCH), before and 6 months after achieving stabilized euthyroidism by antithyroid treatment

	Controls (n = 10)	P^a	SCH before therapy (n = 10)	P^b	SCH after therapy[d] (n = 10)	P^c
Heart rate (beats/min)	73.5 (56–80)	0.04	81.5 (70–94)	0.008	73.5 (56–89)	0.73
Total 24-h heart rate (beats/24 h)	96,132 (74,929–109,251)	0.1	104,658 (76,449–134,806)	0.004	91,802 (68,437–123,255)	0.79
Atrial premature beats (beats/24 h)	2.5 (0–64)	0.001	86.5 (3–286)	0.002	10.5 (0–34)	0.76
Ventricular premature beats (beats/24 h)	0.0 (0–9)	0.009	8.0 (0–67)	0.003	0.0 (0–9)	0.96

Results are expressed as median (range). $P < 0.05$ was considered significant.
[a] Controls *vs.* SCH patients before treatment by the Mann-Whitney *U* test.
[b] SCH patients before *vs.* after treatment by Wilcoxon signed-rank test.
[c] SCH patients after treatment *vs.* controls by the Mann-Whitney *U* test.
[d] Six months after reaching the euthyroidism.

Six months after reaching the euthyroidism, these heart rhytm abnormalities significantly improved or disappeared, suggesting that an earlier antithyroid therapy might avoid the potential progression to more complexarrhytmias…

Risposta alla terapia tireostatica

- Farmaci antiaritmici dovrebbero essere somministrati dopo la cardioversione per evitare recidiva di F.A.

- I pazienti ipertiroidei hanno un' aumentata sensibilità all' anticoagulante orale per aumentata clearance dei fattori della coagulazione

- Quindi agli ipertiroidei dovrebbero essere somministrate dosi ridotte di A.O.

- Per il controllo della tachicardia usare β-bloccanti (il propranololo – INDERAL® - riduce la conversione di T4 a T3)

Terapia dell'ipertiroidismo subclinico

Tireotossicosi subclinica endogena

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Terapia dell'ipertiroidismo subclinico

Il trattamento dell'ipertiroidismo subclinico **deve essere considerato in presenza di:**

- **Valori persistentemente indosabili di TSH**
- **Presenza di sintomi persistenti di iperattività adrenergica**
- **Elevato rischio cardiovascolare o di osteoporosi**
- **Anziani con TSH basso o indosabile**

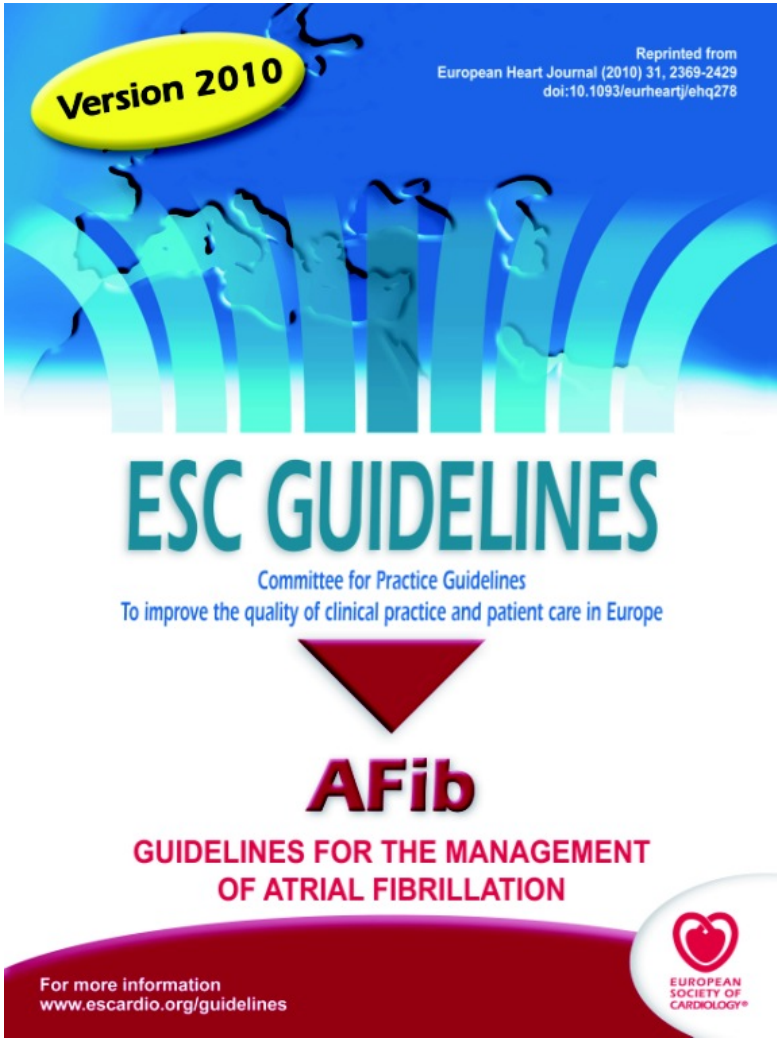
TABLE 8. SUBCLINICAL HYPERTHYROIDISM: WHEN TO TREAT

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

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

Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists 2010

Le linee guida

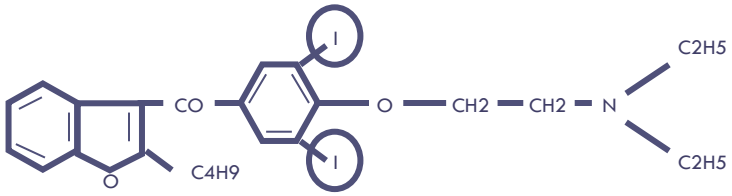


Recommendations for AF in hyperthyroidism

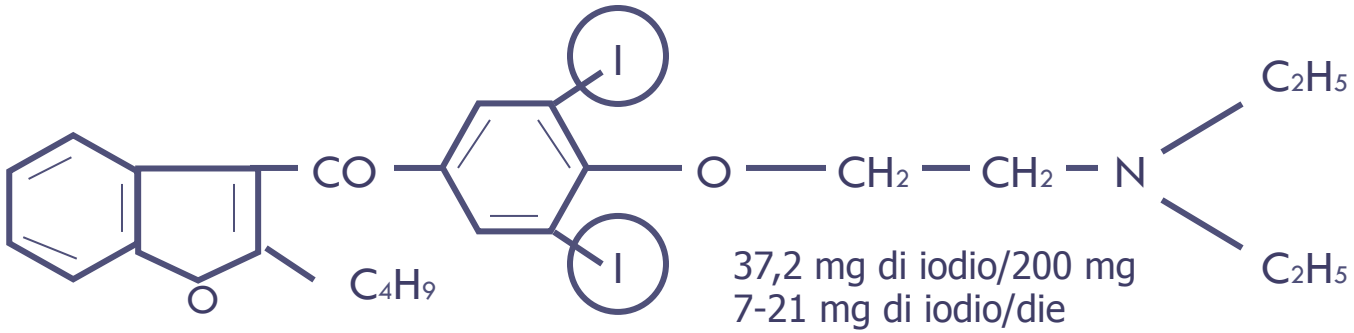
Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with active thyroid disease, antithrombotic therapy is recommended based on the presence of other stroke risk factors.	I	C	
Administration of a β-blocker is recommended to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated.	I	C	
When a β-blocker cannot be used, administration of a non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with AF and thyrotoxicosis.	I	C	
If a rhythm control strategy is desirable, it is necessary to normalize thyroid function prior to cardioversion, as otherwise the risk of relapse remains high.	I	C	
Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.	I	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
AF = atrial fibrillation.

Amiodarone e tiroide



L' Amiodarone



37,2 mg di iodio/200 mg
7-21 mg di iodio/die
Fabbisogno: 150-200 ug/die

Emivita dell'Amiodarone: 100 giorni
Le riserve del farmaco possono persistere 9 mesi dopo la sospensione

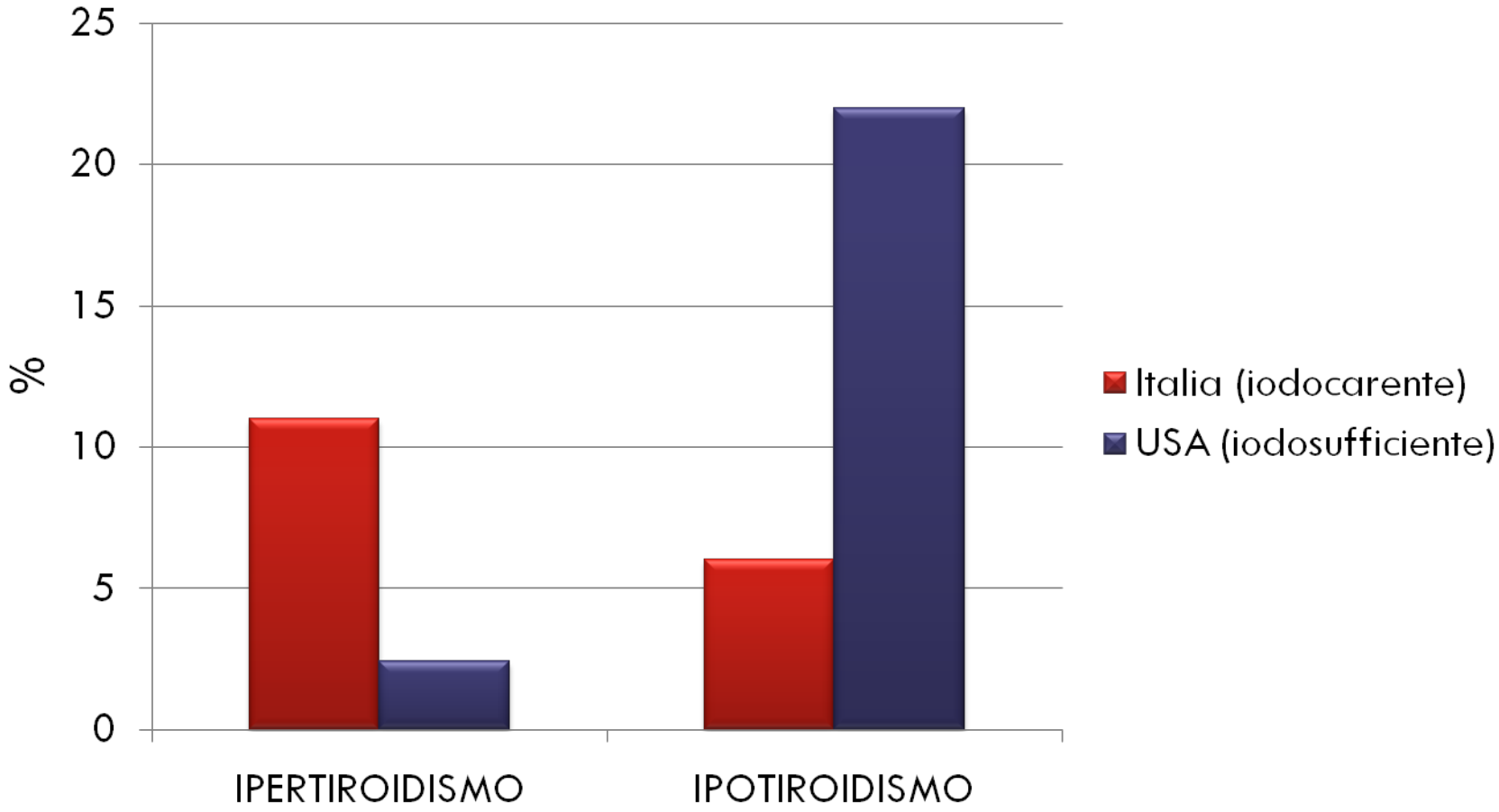
Effetti dell'amiodarone sulla tiroide

Martino E et Al.: ENDOCR REV 2001, 22:240-54

Effetti intrinseci del farmaco	Effetti iodio-indotti
Blocco dell'ingresso dell'ormone tiroideo nelle cellule	Impossibilità a sfuggire all'effetto "Wolff – Chaikoff"
Inibizione delle desiodasi tipo 1 e tipo 5	Potenziamento dell'immunità anti-tiroidea
Riduzione del legame della T3 ai recettori	Sintesi ormonale non controllata (effetto "Jod-Basedow")
Citotossicità diretta	

Ormone	Effetti acuti (< 3 mesi)	Effetti cronici (> 3 mesi)
FT4	↑ 50%	Rimane ↑ 120 – 40% rispetto basale
FT3	↓ 15 – 20% (rimane nel range)	↓ 20%, rimane in range
rT3	↑ > 200%	Rimane ↑ >150%
TSH	↑ 20 – 50% (effetto transitorio)	Normale

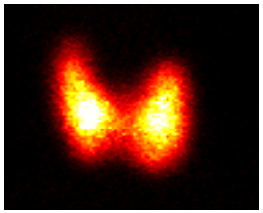
Incidenza di disfunzione tiroidea nei pazienti trattati cronicamente con Amiodarone



AIT tipo 1

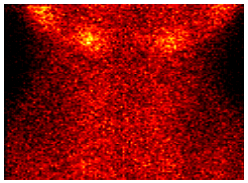
- Ipertiroidismo iodio-indotto che si presenta in pazienti con sottostante patologia tiroidea

- In tali pazienti con struma multinodulare o Basedow l'esposizione acuta allo iodio scatena una improvvisa ipersecrezione ormonale



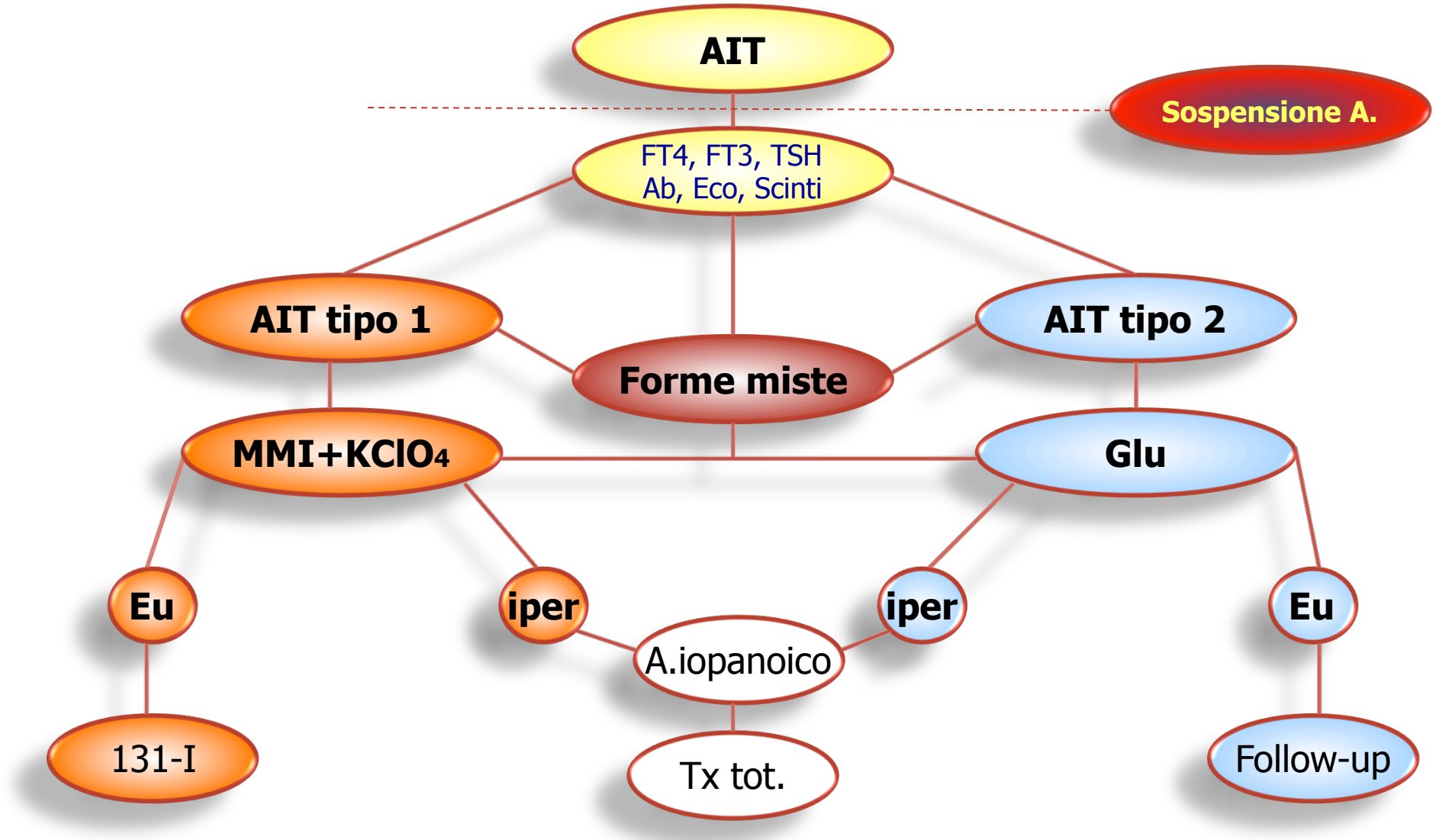
AIT tipo 2

- Succede in tiroidi apparentemente normali ed è causato da una tiroidite distruttiva indotta dal farmaco o da suoi metaboliti
- Causa dismissione di ormone preformato
- La fase citotossica è talora seguita da lieve ipotiroidismo



Flow-chart terapeutica dell' AIT

Bogazzi A et Al.: L' ENDOCRINOLOGO 5; 1-2, 2004



Grazie per l'attenzione