Ipotiroidismo e Scompenso Cardiaco

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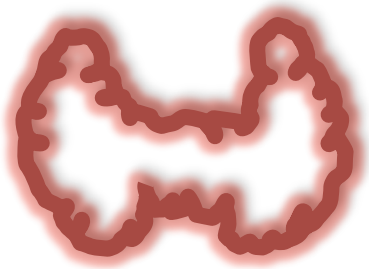


Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

NESSUNO

Ipotiroidismo e Scompenso Cardiaco

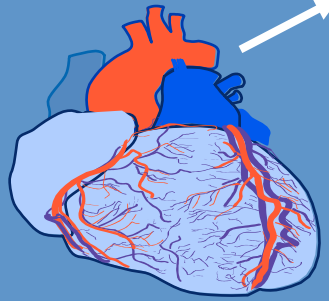
Agenda

- Ipotiroidismo e Scompenso Cardiaco: due malattie frequenti
- Effetti della carenza di ormoni tiroidei sul cuore
- EBM: ipotiroidismo e insorgenza e progressione dello scompenso cardiaco
- Low T3 syndrome nello scompenso cardiaco
- Effetto della terapia sostitutiva

Ipotiroidismo e Scompenso Cardiaco: due malattie frequenti

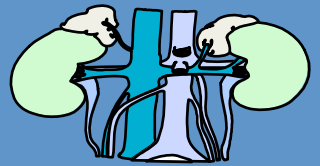
- Scompenso Cardiaco:
  - prevalenza 1-2%
  - Incidenza 5-10/1000/anno
- Ipotiroidismo:
  - Prevalenza 1.4-1.9% nelle donne – 1% nei maschi
  - 4-10% per l'ipotiroidismo subclinico

- Cardiopatia ischemica
- Valvulopatie
- Miocardiopatie
- Ipertensione grave non controllata



Portata cardiaca ↓

Perfusione renale ↓



Attivazione neuro-ormonale

↑Renina, angiotensina II

Attivazione SNS

Aldosterone

Apoptosi, flogosi, ipertrofia, fibrosi

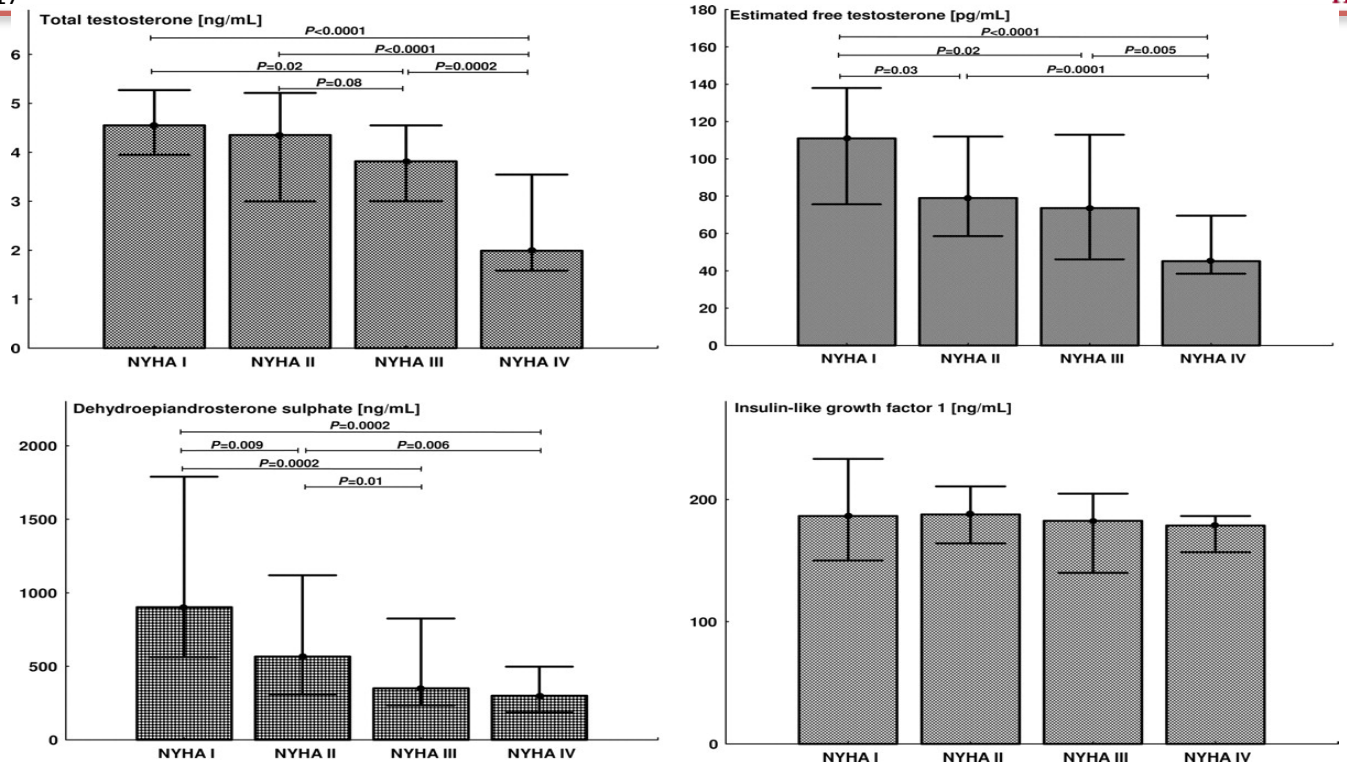
Vasocostrizione

Ritenzione idro-salina

Funz. Ventricolare ↓

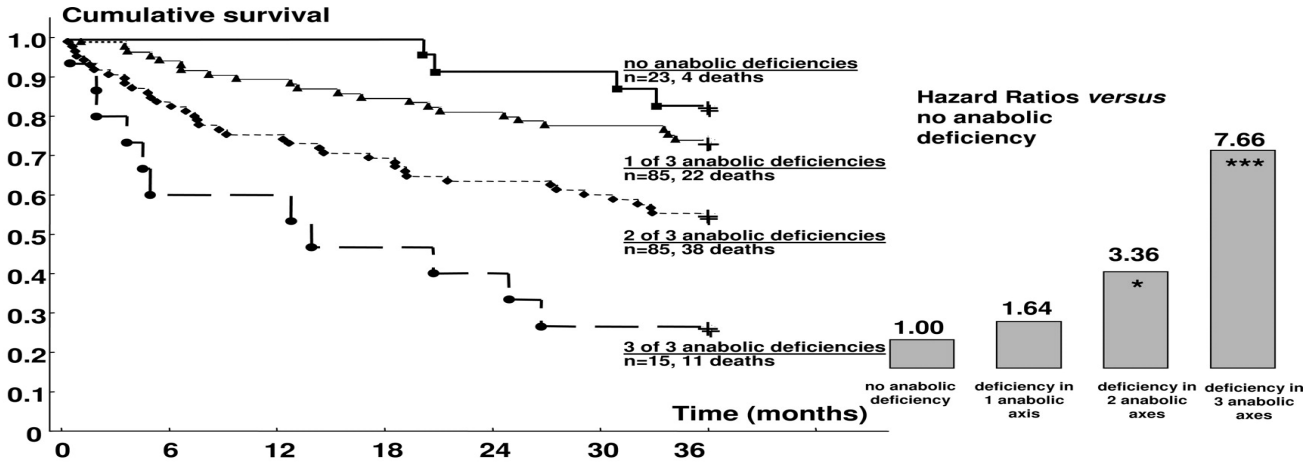
Aumento del pre-carico, incremento del consumo di ossigeno

Serum levels of anabolic hormones (medians with lower and upper quartiles) in men with CHF by NYHA class.



Ewa A. Jankowska et al. Anabolic Deficiency in Men With Chronic Heart Failure Circulation. 2006;114:1829-1837

Graded relationship between the number of impaired anabolic endocrine axes and survival in men with CHF. Kaplan-Meier survival plot and HRs are shown. *P<0.05 and ***P<0.001 vs men with no anabolic deficiency.



Men with no anabolic deficiency				
At risk	23	23	21	19
Deaths	–	0	2	4
Men with deficiency in 1 anabolic axis				
At risk	85	76	69	63
Deaths	–	9	16	22
Men with deficiency in 2 anabolic axes				
At risk	85	64	54	47
Deaths	–	21	31	38
Men with deficiency in 3 anabolic axes				
At risk	15	9	6	4
Deaths	–	6	9	11

Ewa A. Jankowska et al. Circulation. 2006;114:1829-1837

Contents lists available at ScienceDirect

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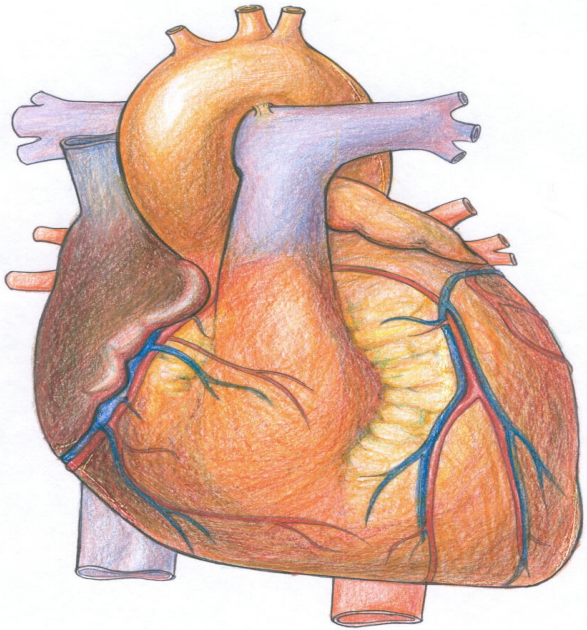
Letter to the Editor

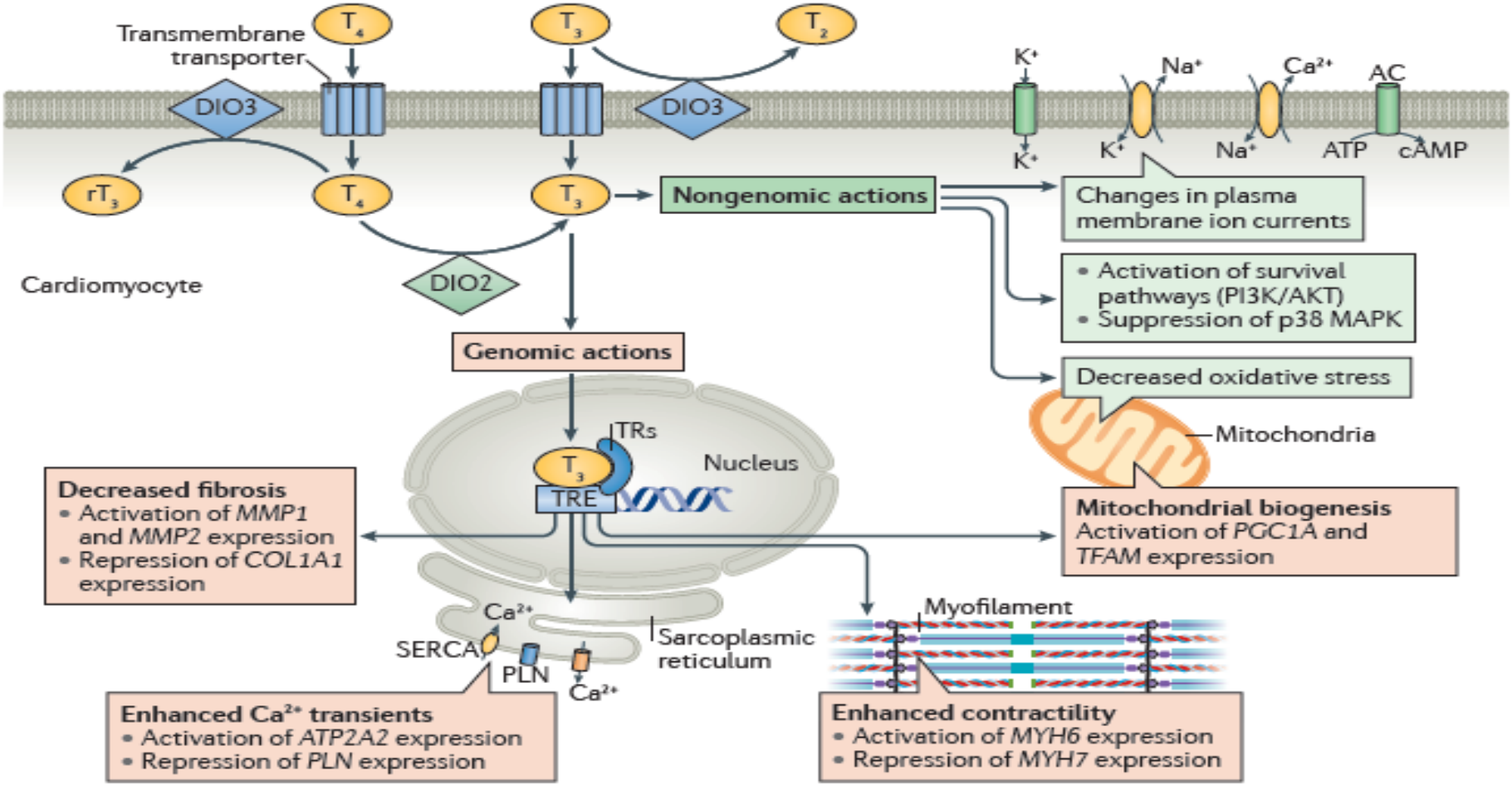
Multiple hormone deficiencies in chronic heart failure

Michele Arcopinto [a], Andrea Salzano [b], Eduardo Bossone [c], Francesco Ferrara [c], Emanuele Bobbio [b], Domenico Sirico [b], Olga Vriz [d], Carlo De Vincentiis [a], Margherita Matarazzo [b], Lavinia Saldamarco [b], Francesco Saccà [e], Raffaele Napoli [b], Massimo Iacoviello [f], Vincenzo Triggiani [g], Andrea M. Isidori [h], Carlo Vigorito [b], Jorgen Isgaard [i,1], Antonio Cittadini [b,*,1]

Deficit di OT e scompenso

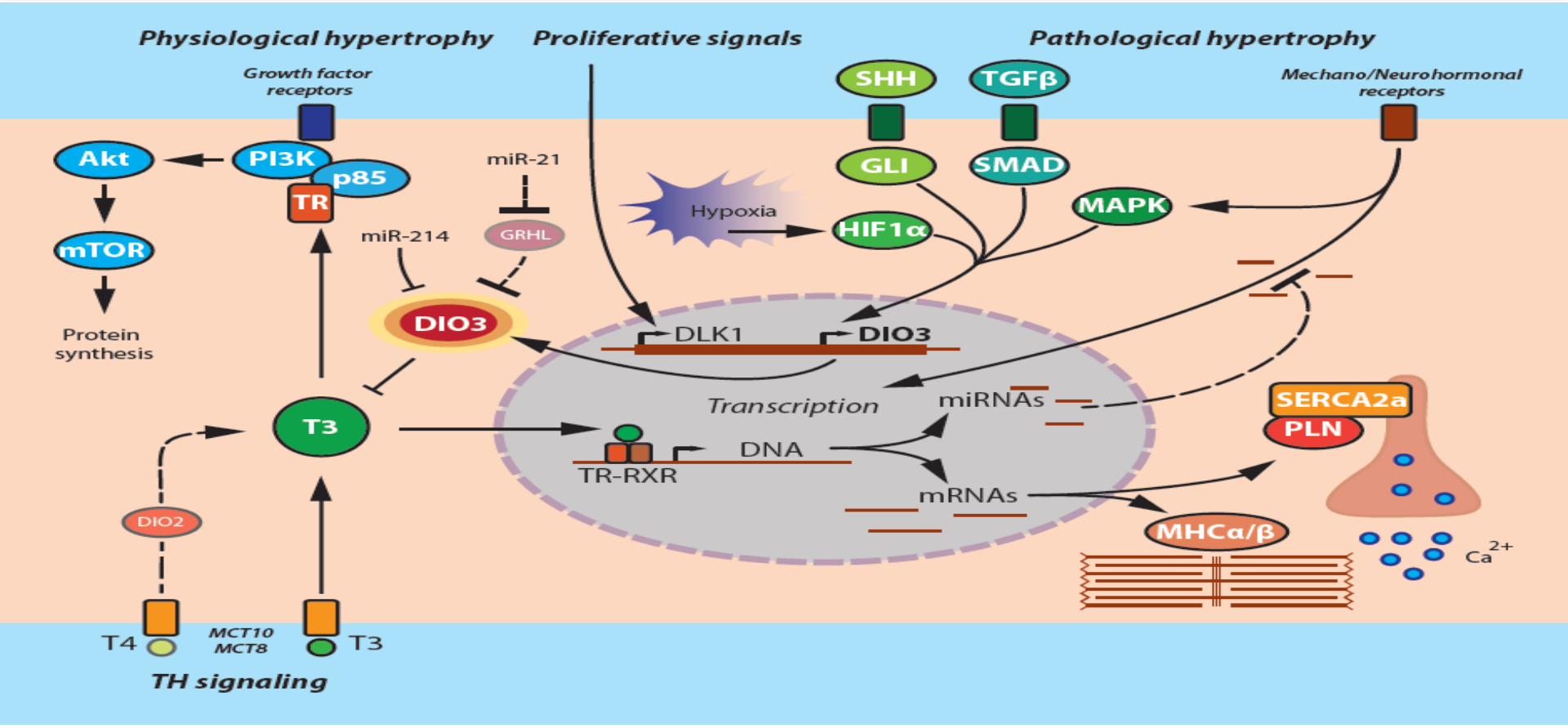
- Ipotiroidismo
- Ipotiroidismo subclinico
- Low T3 syndrome
- Amiodarone
- Alterazioni del TH-TR axis Signaling Pathway nello scompenso cardiaco





Jabbar A, et al Nat Rev Cardiol. 2017 Jan;14(1):39-55

Factors involved in the homeostasis and action of T3 in cardiomyocytes



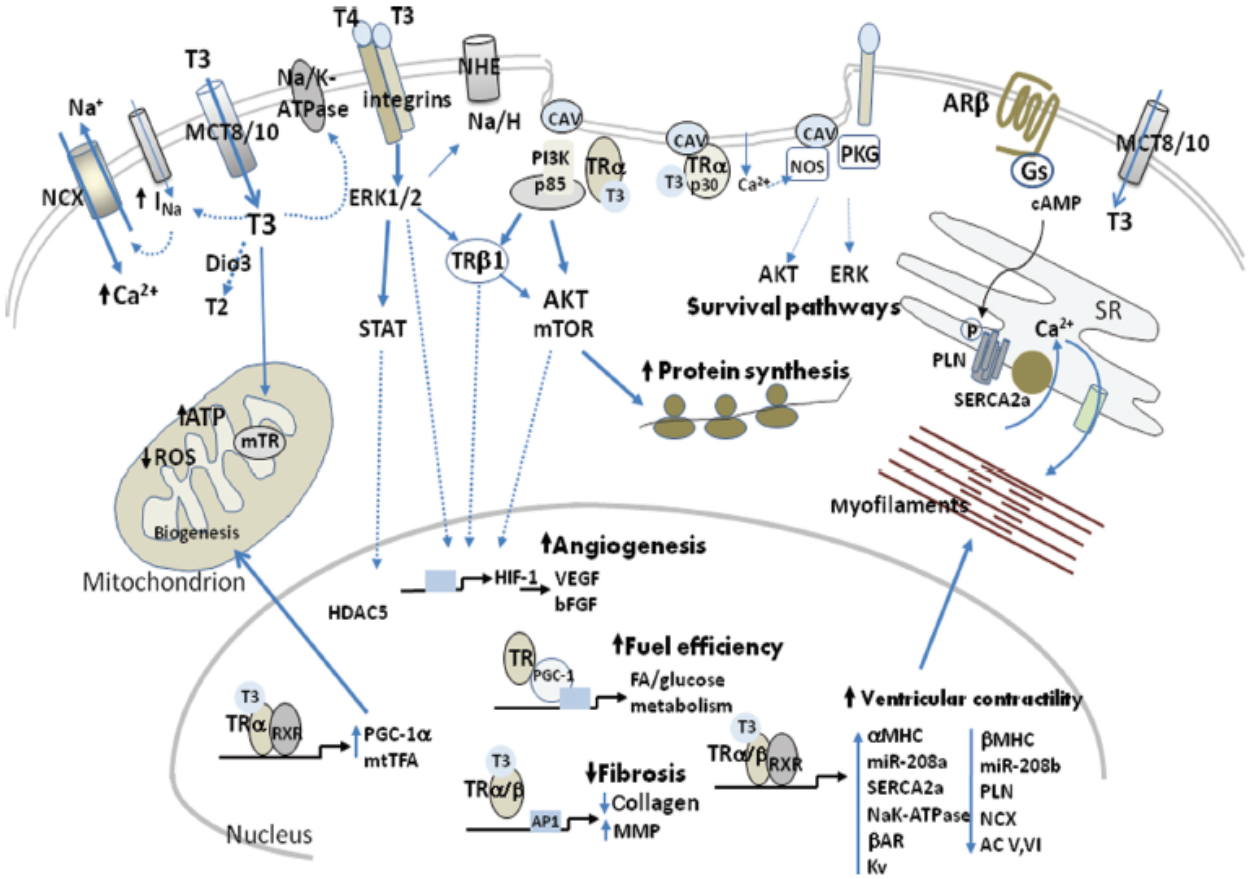


Figure 2 Actions of TH initiated at sites at the plasma membrane or cytosol and within the nucleus of myocytes, vascular smooth muscle, or endothelial cells or fibroblasts. Intracellular signaling cascades are activated by T3 or T4 binding to integrins or TRs localized to lipid-enriched membrane microdomains or unknown intracellular sites. T3-regulated genes are indicated showing effects that enhance cardiomyocyte contractility and calcium transients, decreased fibrosis, increased fuel efficiency, and mitochondrial biogenesis. Non-nuclear responses of T3 result in activation of survival pathways, physiologic hypertrophy, decreased oxidative stress, and changes in plasma membrane ion currents.

Thyroid Hormone and Cardioprotection
Anthony Martin Gerdes[1] and Kaie Ojamaa[2,3]
Comprehensive Physiology
Volume 6, July 2016

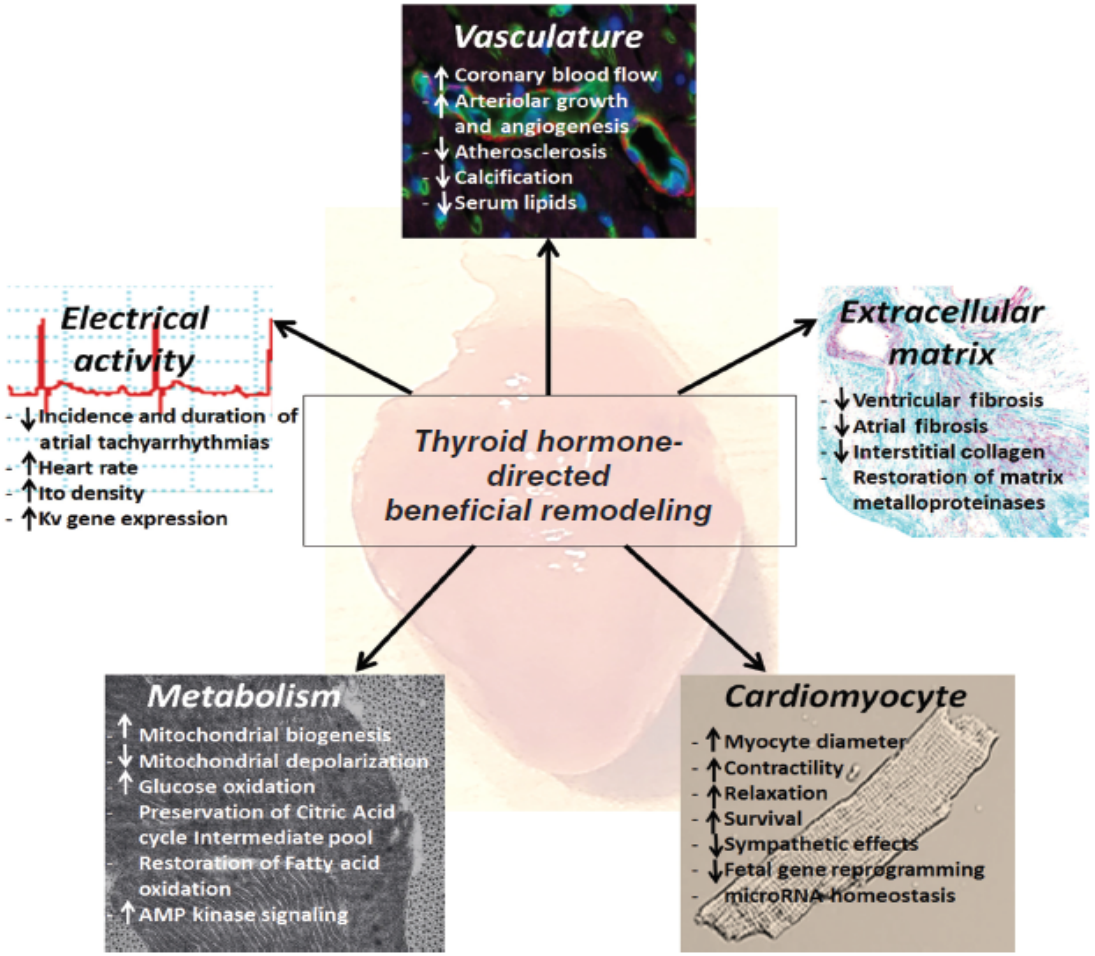


Figure 1 Summary of cardioprotective effects of thyroid hormones. Rajagopalan V, Gerdes AM. Role of thyroid hormones in ventricular remodeling. *Curr Heart Fail Rep* 12: 141-149, 2015. With permission from Springer.

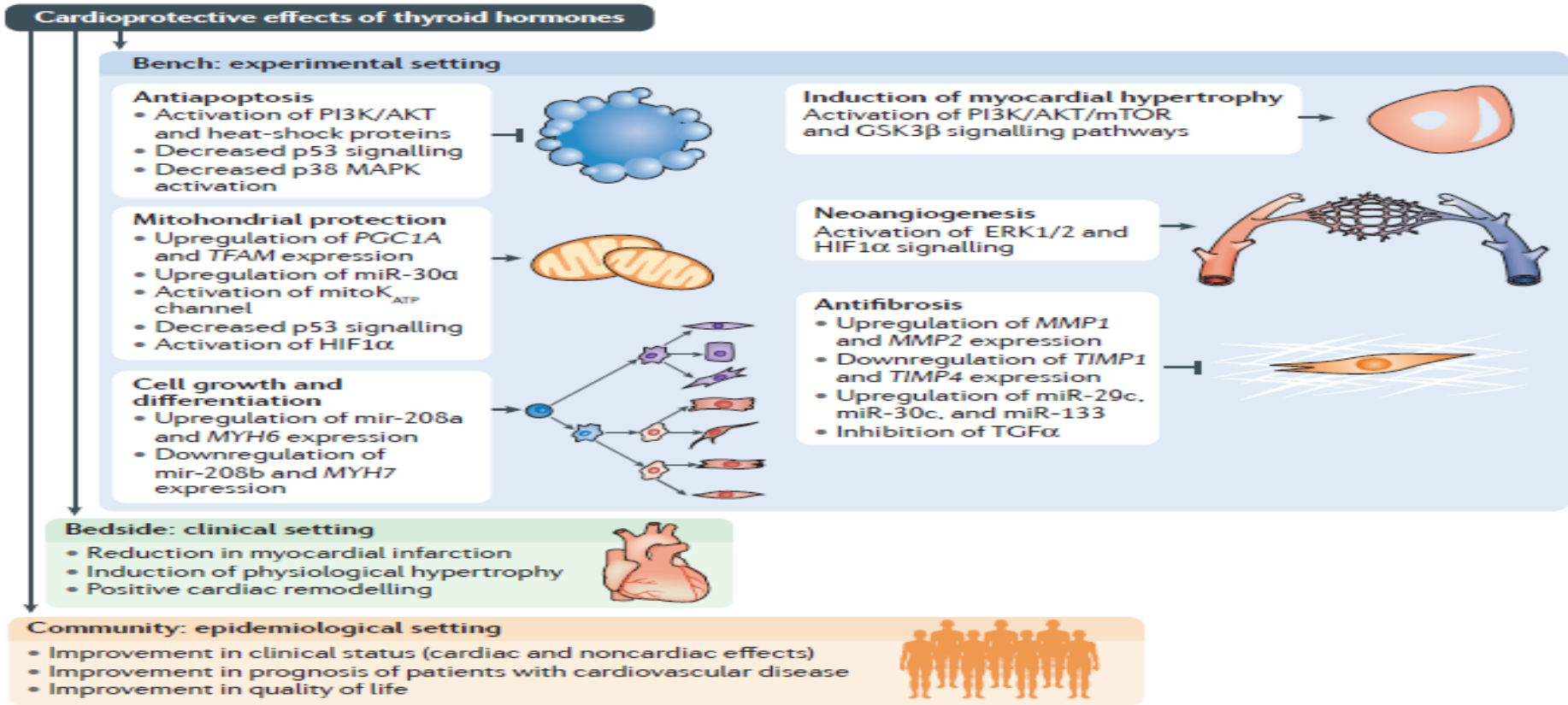


Figure 3 | **Thyroid hormones and cardioprotection.** Schematic representation of the translational potential of the cardioprotective effects of thyroid hormones, with examples of different mechanisms by which thyroid hormones are involved in cardioprotection (demonstrated in the experimental setting) and the potential effects of thyroid hormone replacement therapy for the management of patients with cardiovascular disease (both in the clinical and the epidemiological settings). AKT, serine/threonine-protein kinase; ERK1/2, extracellular signal-regulated kinases 1/2; GSK3β, glycogen synthase kinase 3β; HIF1α, hypoxia-inducible factor 1α; MAPK, mitogen-activated protein kinase; mir, microRNA; mitoK$_{ATP}$, mitochondrial ATP-sensitive potassium channel; mTOR, serine/threonine-protein kinase mTOR; PI3K, phosphatidylinositol 3-kinase; TGFα, transforming growth factor-α.

Table 2. TH and TH Analog DITPA Treatment in Patients With HF

Author/ Year	Study Design	Population	Patients, n	Age*, y	NYHA	LVEF, %	Main Findings	Heart Rate	Side Effects
Moruzzi et al,[85] 1994	Randomized (1:1)						VR (dobutamine est), ↑ CO utamine test), consumption, ↑ exercise nce, ↑ resting LVEF	Unchanged	No
Moruzzi et al,[91] 1996							↑ Cardiac	Unchanged	No
								anged	No
								nged	No
								nged	No
Pi et 2008									No
Goldman et al,[94] 2009	Rand placel								tolerated, ht loss, ue, GI complaints

NYHA indicate cardiac index; U volume; NT-pro- pro-brain natriuretic peptide; T, Treated; P, Placebo; GI, gastrointestinal; m2bs, m2 body surface; and OS, oral administration.
*Age reported as range, mean, or mean+SD.

GUIDELINES FOR THE TREATMENT OF HYPOTHYROIDISM

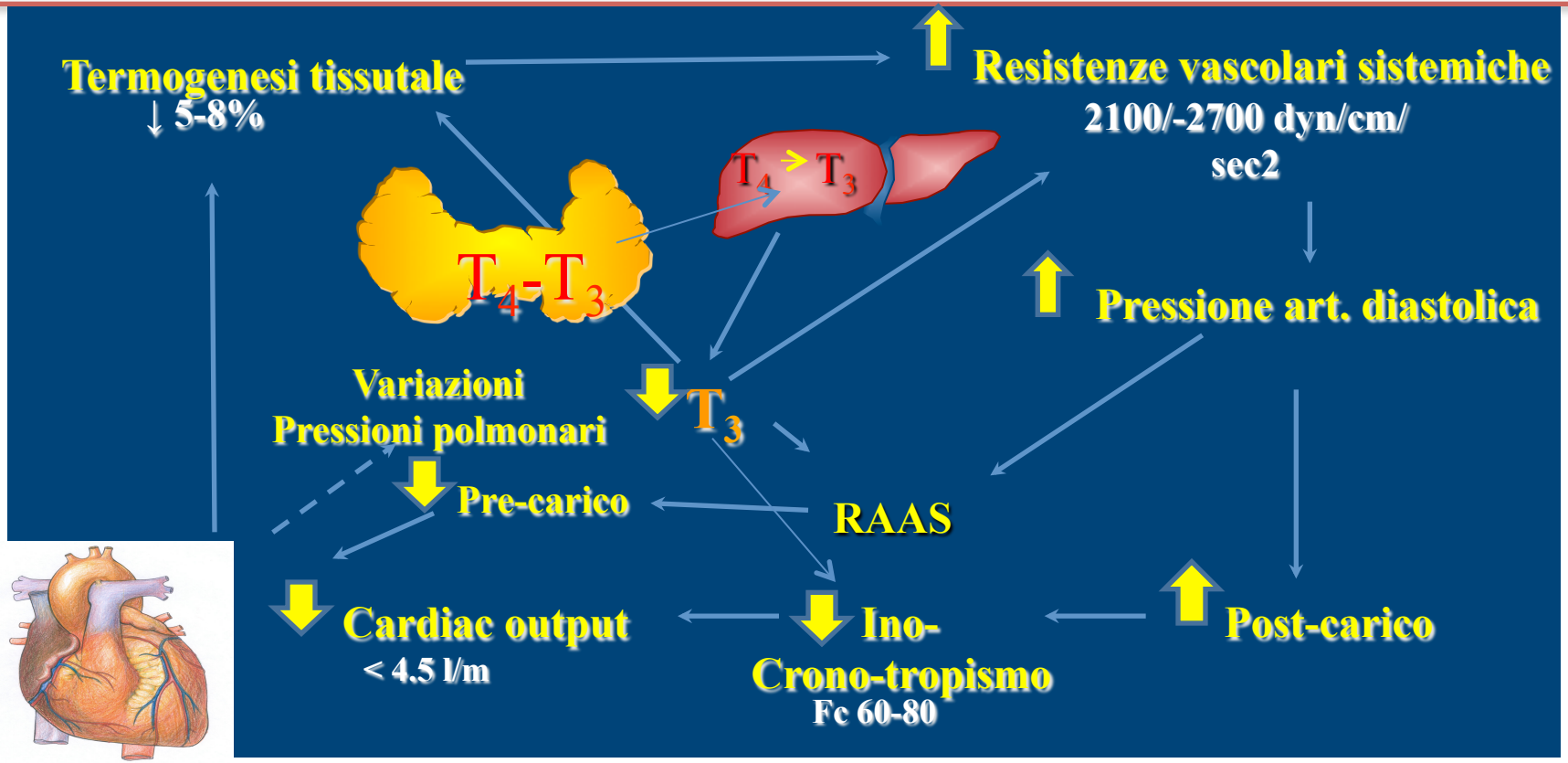
Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement

[1,2,4]Jonklaas, J., [1,3,5]Bianco, A.C., [2,6]Bauer, A.J., [2,7]Burman, K.D., [2,8]Cappola, A.R., [3,9]Celi, F.S., [2,10]Cooper, D.S., [3,5]Kim, B.W., [3,11]Peeters, R.P., [2,12]Rosenthal, M.S., [2,13]Sawka, A.M.

Thyroid hormone analogs and euthyroid patients

23	Should thyroid hormone analog therapy be used in euthyroid individuals with non-hypothyroid-related medical conditions (such as dyslipidemia) based on current evidence?
Strong Rec, Low Q	Although pre-clinical data suggest that the concept of thyromimetic use for treatment of non-hypothyroid-related medical conditions may be promising, we recommend against the use of such drugs outside of the research setting, due to concerns about the lack of clear benefit or excessive side effects, of currently available preparations.
22c	In hospitalized adult patients with cardiac dysfunction, such as advanced heart failure, and low serum triiodothyronine concentrations, should thyroid hormone replacement be instituted with liothyronine?
Weak Rec, Mod Q	We recommend against the routine use of liothyronine as a form of therapy for hospitalized patients with heart failure and low serum triiodothyronine concentrations given the mixed data from short-term trials, the hypothetical risks, and pending further randomized trials confirming benefit and safety.

Modificazioni emodinamiche nell'ipotiroidismo



Modificata da Klein I, Danzi S, Circulation 2007; 16:1725-35

B. Biondi / Best Practice & Research Clinical Endocrinology & Metabolism 26 (2012) 431–446

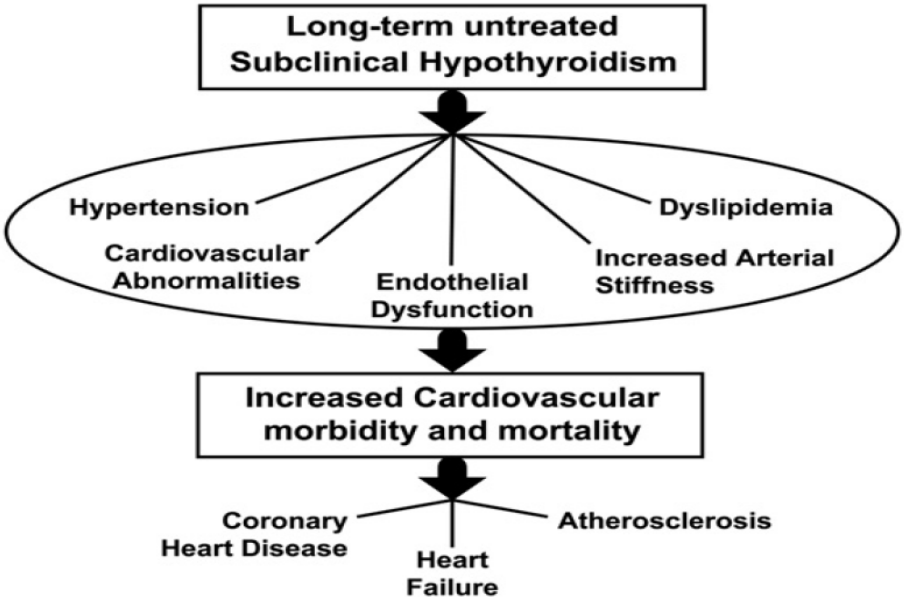


Fig. 1. Cardiovascular risk in patients with long-term untreated subclinical hypothyroidism.

Long-term cardiovascular consequences of persistent mild thyroid hormone deficiency

- Cardiac morphology and function:
  - Depressed systolic function at rest
  - LV diastolic dysfunction at rest and during exercise
  - Impaired LV systolic function on exercise
- Vascular abnormalities:
  - Increased SVR
  - Increased prevalence of diastolic hypertension
  - Increased arterial stiffness
  - Endothelial dysfunction
  - Increased carotid artery intima-media thickness

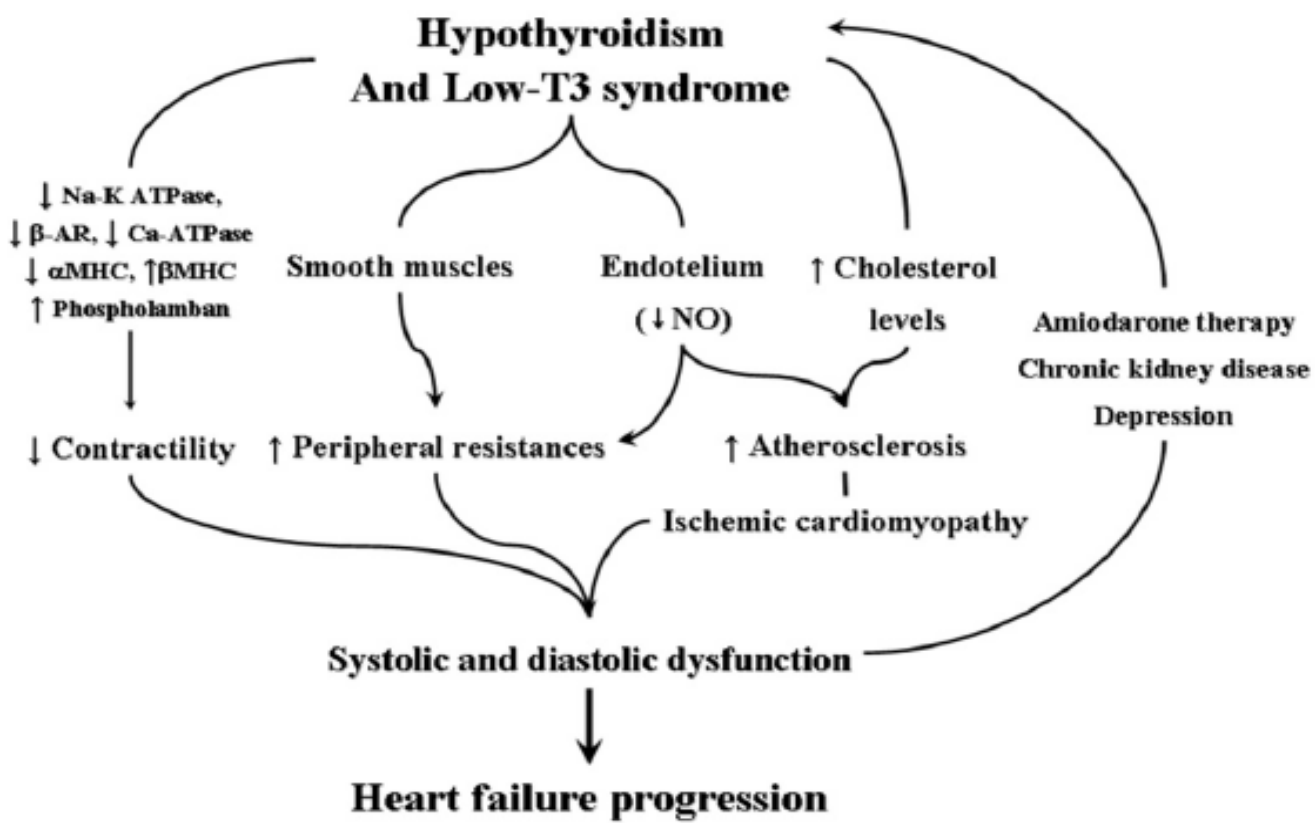


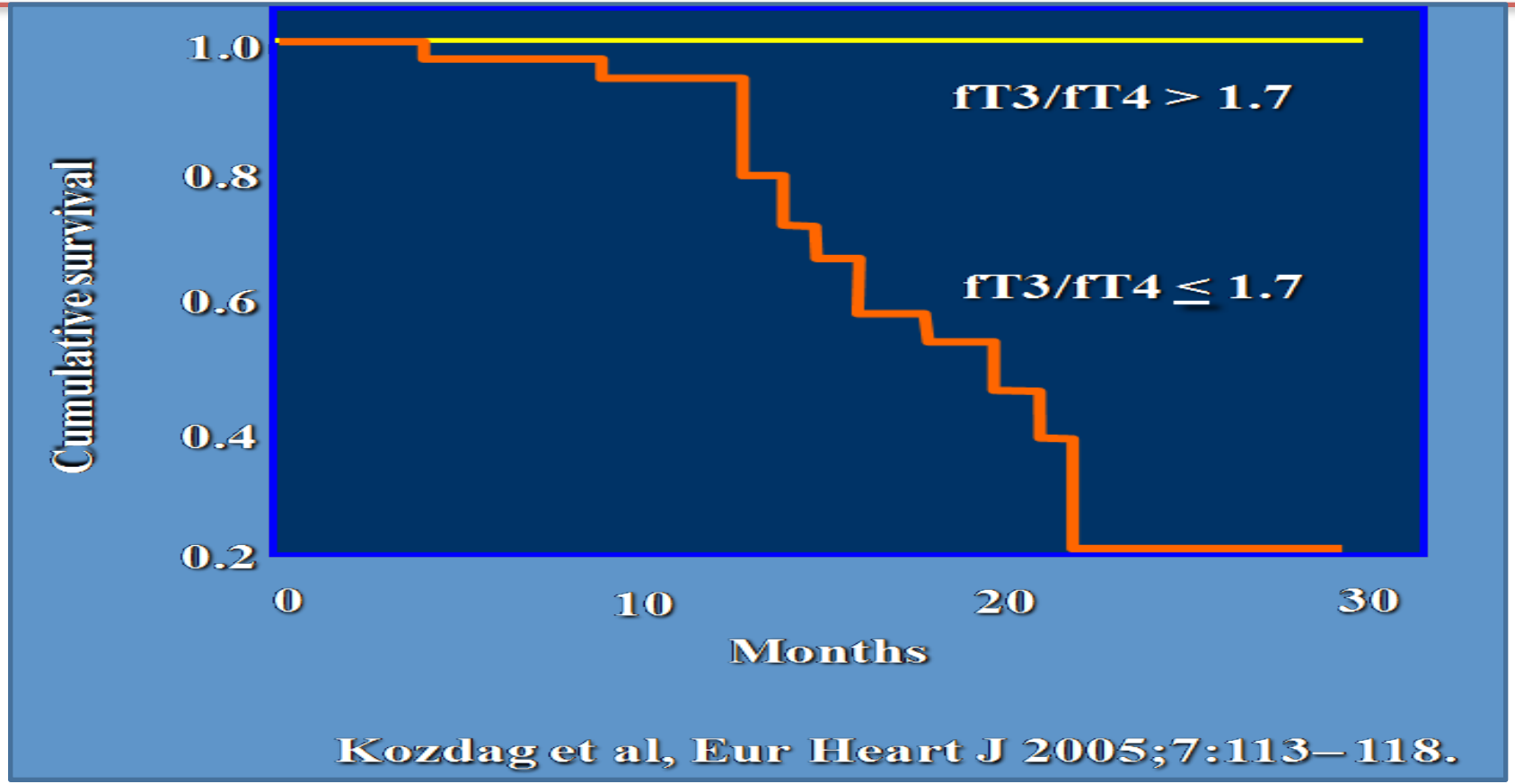
Fig. (1). Main mechanisms by which hypothyroidism can lead to systolic and diastolic dysfunction and, as a consequence, to heart failure progression. The potential influence of chronic heart failure on the possible onset of thyroid dysfunction is also represented.
AR: Adrenergic receptor; MHC: myosin heavy chain; NO: nitric oxide; T3: triiodothyronine.

Triggiani V and Iacoviello M Endocrine, Metabolic & Immune Disorders – Drug Targets, 2013.13:22-37

Table 1. Studies evaluating the prognostic role of Thyroid Hormones deficiency in heart failure patients.

First Author (Year)	Clinical Setting	Number of Patients	Thyroid Function Evaluation	End-points (Mean Follow-up)	Results
Hamilton *et al.* (1990) [66]	Hospitalized patients with chronic advanced heart failure (ischemic and non ischemic cardiomyopathy)	84	fT3, reverse T3, fT4, TSH	• Death or heart transplantation (Follow-up: 7.3± 6.6 months)	Low fT3/reverse T3 ratio associated with poor ventricular function and worse short term prognosis
Opasich *et al.* (1996) [67]	Patients admitted to Heart Failure Unit for assessment of cardiac transplantation	199	T3, T4, fT3, fT4, TSH	• All-cause mortality	Association of total T3 to all cause mortality
Pingitore *et al.* (2005) [68]	Patients admitted with diagnosis of ischemic and non ischemic cardiomyopathy	281	T3, T4, fT3, fT4, TSH	• All-cause and cardiac mortality (Follow-up: 12± 7 months)	Independent association of total T3 and fT3 to all cause mortality
Kodzag *et al.* (2005) [70]	Patients with diagnosis of ischemic and non ischemic cardiomyopathy admitted for congestive heart failure	111	fT3, fT4, fT3/fT4, TSH	• Composite end-point: cardiac death, cardiac transplantation and DC-shock due to ventricular fibrillation (Follow-up: 12± 8 months)	Independent association of fT3/fT4 ratio, but not of the other thyroid hormones, with the events
Iacoviello *et al.* (2008) [61]	Outpatients with diagnosis of CHF (with diagnosis of ischemic and non ischemic cardiomyopathy) in stable clinical conditions and conventional therapy	338	fT4, fT3, TSH	• Composite end-point: death due to heart failure worsening, cardiac trans-plantation and hospitalization due to acute decompensated heart failure (Follow-up: 15± 8 months)	Independent association of TSH serum levels with heart failure progression
Passino *et al.* (2009) [69]	In- or Outpatients with systolic heart failure (ischemic and non ischemic cardiomyopathy)	442	fT3, fT4, TSH	• All-cause and cardiac mortality (Follow-up: median 36 months)	Independent association of fT3 to all cause and cardiac mortality
Triggiani *et al.* (2012) [71]	Outpatients with diagnosis of CHF (with diagnosis of ischemic and non ischemic cardiomyopathy) in stable clinical conditions and conventional therapy	422	Hypothyroidism at the enrolment or during follow-up	• Composite end-point: death due to heart failure worsening, cardiac trans-plantation and hospitalization due to acute decompensated heart failure (Follow-up: 28± 13 months)	The diagnosis of hypothyroidism at the enrolment as well as its occurrence during follow-up were associated to events

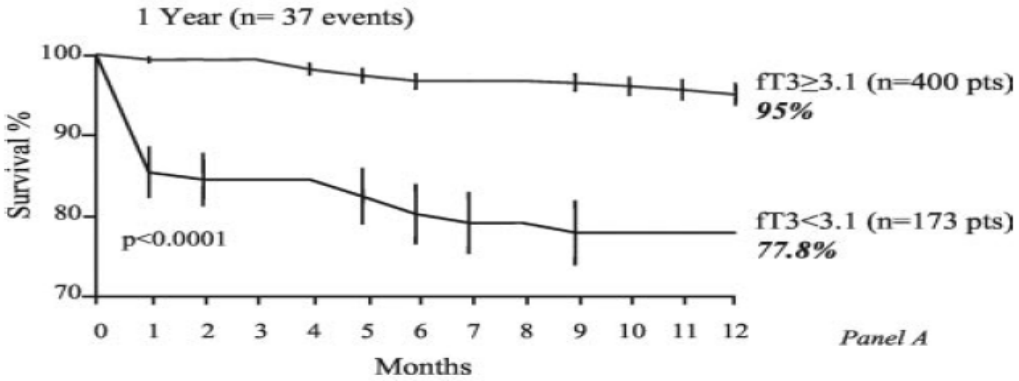
Abbreviations: CHF: chronic heart failure; fT3: free triiodothyronine; fT4: free thyroxine; T3: triiodothyronine; T4: thyroxine; TSH: thyrotropin.


Cumulative survival
1.0
0.8
0.6
0.4
0.2
0
10
20
30
Months
fT3/fT4 > 1.7
fT3/fT4 ≤ 1.7
Kozdag et al, Eur Heart J 2005;7:113–118.

Low-T3 Syndrome

A Strong Prognostic Predictor of Death in Patients With Heart Disease

Giorgio Iervasi, MD; Alessandro Pingitore, MD, PhD; Patrizia Landi, BSc; Mauro Raciti, BSc; Andrea Ripoli, PhD; Maria Scarlattini, BSc; Antonio L'Abbate, MD; Luigi Donato, MD



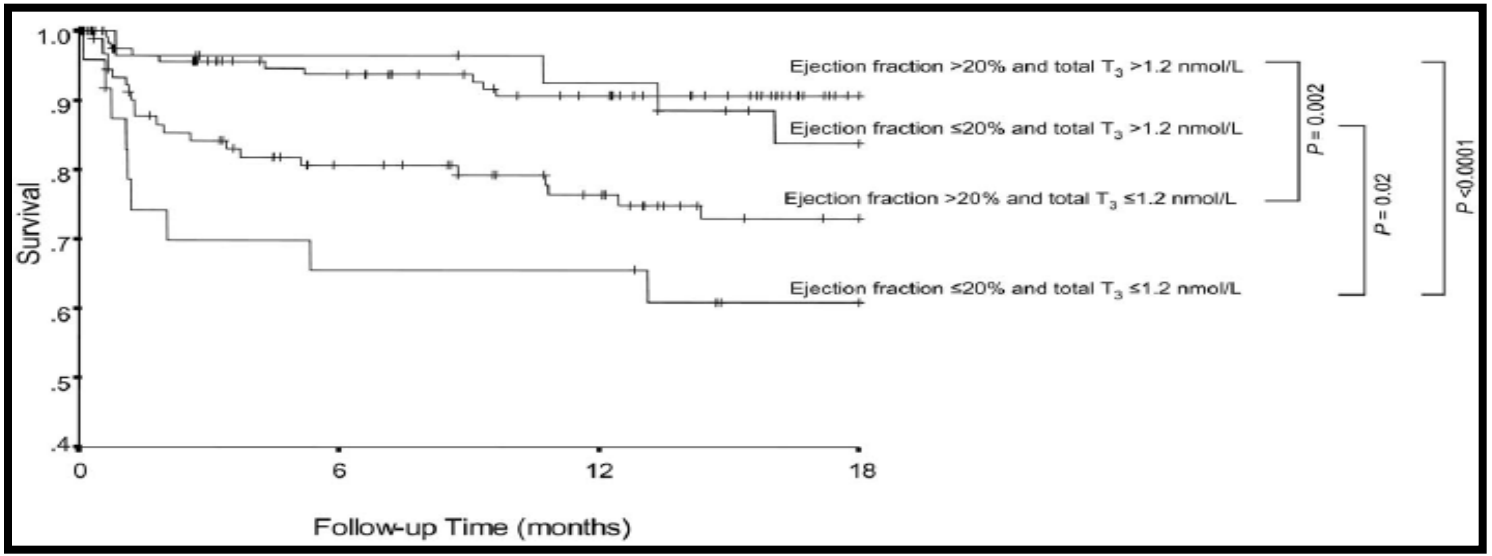
Circulation 2003;107;708-713

TABLE 3. Multivariate Analysis of Predictors of 1-Year Mortality

Variables	Hazard Ratio	Standard Error	95% CI	*P*
Cumulative death				
fT3	3.582	0.2784	2.0755 to 6.1815	0.0001
Age	1.051	0.0173	1.0154 to 1.0866	0.005
LVEF	1.037	0.0119	1.0132 to 1.0616	0.006
Dyslipidemia*	2.955	0.4460	1.2331 to 7.0841	0.023
Cardiac death				
FT3	2.359	0.3742	1.1329 to 4.9122	0.016
Age	1.047	0.0243	0.9984 to 1.0982	0.040
LVEF	1.069	0.0178	1.0329 to 1.1075	0.0001
Dyslipidemia*	4.236	0.5922	1.3272 to 13.5246	0.04

*Dichotomized variable.

Low T3 syndrome and ejection fraction as predictors of mortality



A low T3 level is a better predictor of all-cause and cardiovascular mortality than is an abnormal left ventricular ejection fraction

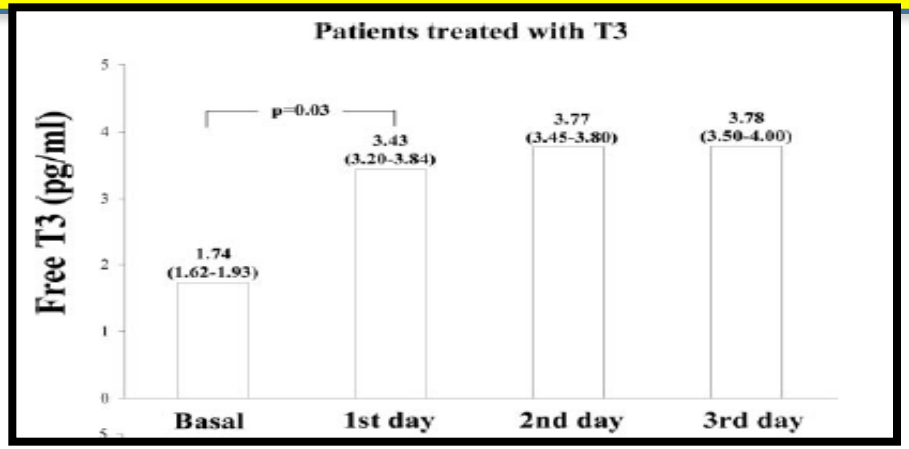
Pingitore et al. Am J Med 2005

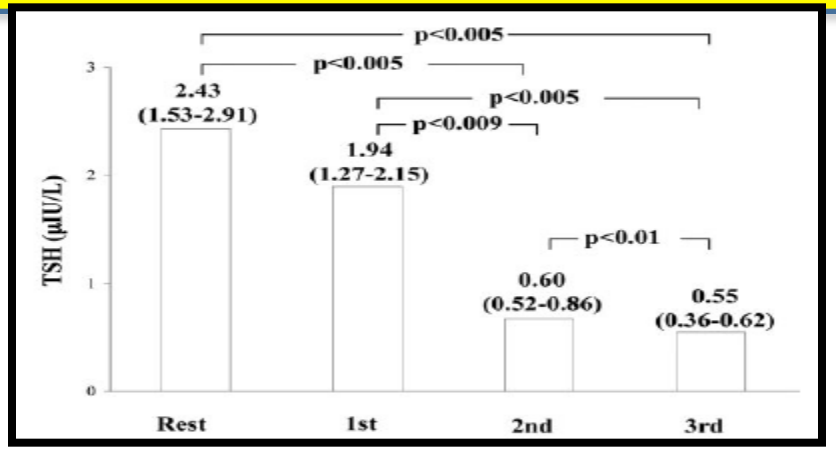
Meta-analysis of the prognostic role of NTIS in cardiovascular diseases.

Analyses	No. of studies	HR(95% CI)	P value	I^2
All-cause mortality				
All studies	19	2.49(2.04–3.03)	<0.001	52.6%
Adjusted estimates	11	2.52(1.87–3.40)	<0.001	59.8%
Strict diagnostic criteria of NTIS	13	2.78(2.04–3.80)	<0.001	64.5%
Strict diagnostic criteria with adjustment	10	2.44(1.80–3.32)	<0.001	60.6%
Excluding thyroid hormone replacement	15	2.56(2.07–3.17)	<0.001	52.3%
Heart failure	9	2.58(2.08–3.18)	<0.001	16.5%
CAD	2	1.81(1.09–3.03)	0.023	0%
AMI	3	3.66(1.49–9.01)	0.005	74.1%
Heart failure with adjustment	5	3.89(2.54–5.95)	<0.001	0%
CAD with adjustment	2	1.81(1.09–3.03)	0.023	0%
Cardiac mortality				
All studies	9	2.29(1.91–2.74)	<0.001	0%
Adjusted estimates	5	2.06(1.58–2.69)	<0.001	0.8%
Strict diagnostic criteria of NTIS	6	2.16(1.75–2.67)	<0.001	0%
Strict diagnostic criteria with adjustment	4	1.93(1.46–2.56)	<0.001	0%
Excluding thyroid hormone replacement	7	2.15(1.75–2.64)	<0.001	0%
Heart failure	5	2.55(1.96–3.31)	<0.001	0%
CAD	2	1.76(1.21–2.55)	0.003	4.3%
Heart failure with adjustment	2	3.03(1.73–5.32)	<0.001	0%
CAD with adjustment	2	1.76(1.21–2.55)	0.003	4.3%
MACE				
All studies	9	1.75(1.42–2.16)	<0.001	64.7%
Adjusted estimates	4	1.73(1.32–2.26)	<0.001	27.6%
Strict diagnostic criteria of NTIS	8	1.73(1.39–2.16)	<0.001	68.6%
Strict diagnostic criteria with adjustment	4	1.73(1.32–2.26)	<0.001	27.6%
Excluding thyroid hormone replacement	6	1.76(1.24–2.50)	0.001	73.5%
Heart failure	2	1.71(0.71–4.13)	0.233	88.0%
CAD	2	1.60(1.15–2.22)	0.005	55.6%
AMI	2	1.75(0.99–3.09)	0.053	50.4%
Heart failure with adjustment	1	2.14(1.00–4.57)	0.050	NA
CAD with adjustment	2	1.60(1.15–2.22)	0.005	55.6%
AMI with adjustment	1	2.83(1.16–6.89)	0.022	NA

(HR: hazard ratio; 95% CI, 95% confidence interval; CAD, coronary artery disease; AMI, acute myocardial infarction; NA, not available.)

Acute Effects of T3 Replacement in Patients with CHF and Low-T3 Syndrome





Parameters	Patients treated with L-T_3			Patients treated with placebo	
	Before L-T_3	After L-T_3	*P* value before L-T_3 *vs.* after L-T_3	Basal	*P* value before L-T_3 *vs.* basal
LV EDV (ml/m^2 bs)	133 (114–158)	142 (132–161)	0.02	130 (117–153)	ns
LV ESV (ml/m^2 bs)	103 (84–127)	108 (89–124)	ns	91 (86–115)	ns
LV SV (ml/m^2 bs)	35 (28–39)	40 (34–44)	0.01	36 (29–48)	ns
CO (liter/min)	4.1 (3.3–5.4)	4.8 (3.4–5.4)	ns	4.7 (4.0–5.3)	ns
CI (liter/m^2 bs × min)	2.2 (1.7–2.8)	2.5 (1.9–2.7)	ns	2.5 (2.1–2.9)	ns
LV EF (%)	25 (18–32)	28 (22–32)	ns	27 (23–41)	ns
SVR (dyne/sec × cm)	2.07 (1.92–3.13)	2.10 (1.87–2.48)	ns	2.03 (1.86–2.36)	ns
Elastance	1.36 (0.93–1.63)	1.27 (0.91–1.36)	ns	1.32 (0.97–2.14)	ns
External cardiac work (ml × mm Hg × bpm)	201,226 (161,084–3,002,307)	226,519 (169,276–266,388)	ns	253,950 (190,929–306,180)	ns
Internal cardiac work (ml × bpm × mm Hg/2)	401,849 (348,910–534,505)	396,885 (343,080–473,613)	ns	360,260 (314,153–440,763)	ns
Total cardiac work	626,859 (492,291–787,522)	592,085 (540,060–756,684)	ns	599,945 (538,645–748,639)	ns

Data are expressed as median (25th and 75th percentiles). bpm, Beats per minute; CI, cardiac index.

Pingitore et al.
JCEM 2008

ITALIAN CHAPTER

Acute Effects of Triiodothyronine (T_3) Replacement Therapy in Patients with Chronic Heart Failure and Low-T_3 Syndrome: A Randomized, Placebo-Controlled Study

Alessandro Pingitore, Elena Galli, Andrea Barison, Annalisa Iervasi, Maria Scarlattini, Daniele Nucci, Antonio L'Abbate, Rita Mariotti, and Giorgio Iervasi

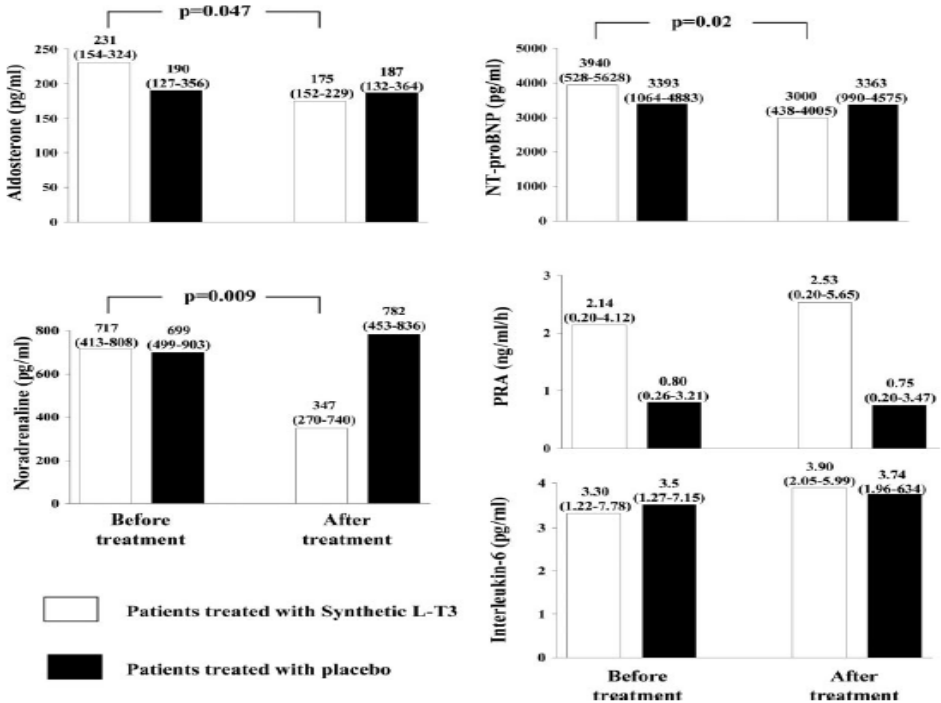


FIG. 4. Aldosterone, noradrenaline, NT-proBNP, PRA, and IL-6 levels in patients treated with L-T_3 and in patients treated with placebo.

J. Clin. Endocrinol. Metab. 2008 93:1351-1358

GUIDELINES FOR THE TREATMENT OF HYPOTHYROIDISM

Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement

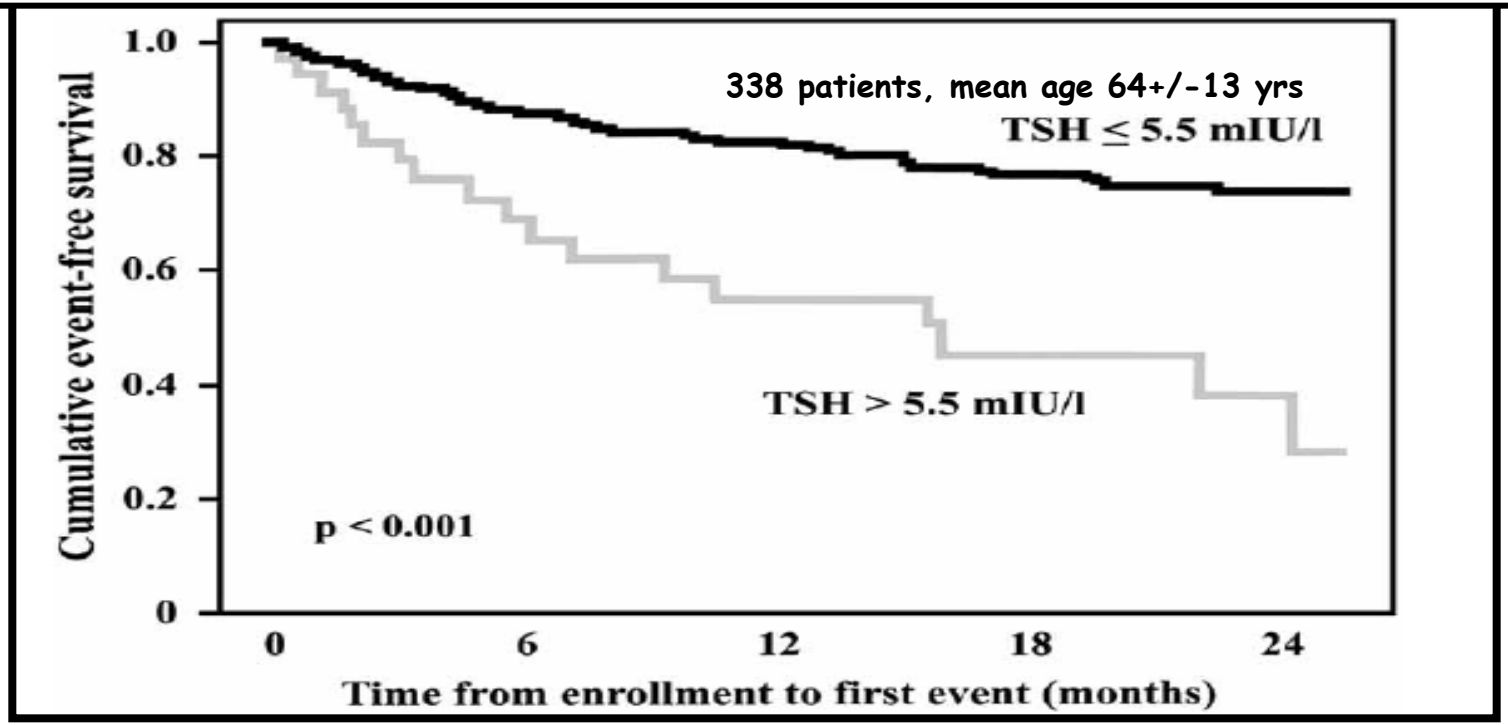
[1,2,4]Jonklaas, J., [1,3,5]Bianco, A.C., [2,6]Bauer, A.J., [2,7]Burman, K.D., [2,8]Cappola, A.R., [3,9]Celi, F.S., [2,10]Cooper, D.S., [3,5]Kim, B.W., [3,11]Peeters, R.P., [2,12]Rosenthal, M.S., [2,13]Sawka, A.M.

22c	**In hospitalized adult patients with cardiac dysfunction, such as advanced heart failure, and low serum triiodothyronine concentrations, should thyroid hormone replacement be instituted with liothyronine?**
Weak Rec, Mod Q	**We recommend against the routine use of liothyronine as a form of therapy for hospitalized patients with heart failure and low serum triiodothyronine concentrations given the mixed data from short-term trials, the hypothetical risks, and pending further randomized trials confirming benefit and safety.**

Prognostic Role of Sub-Clinical Hypothyroidism in Chronic Heart Failure Outpatients

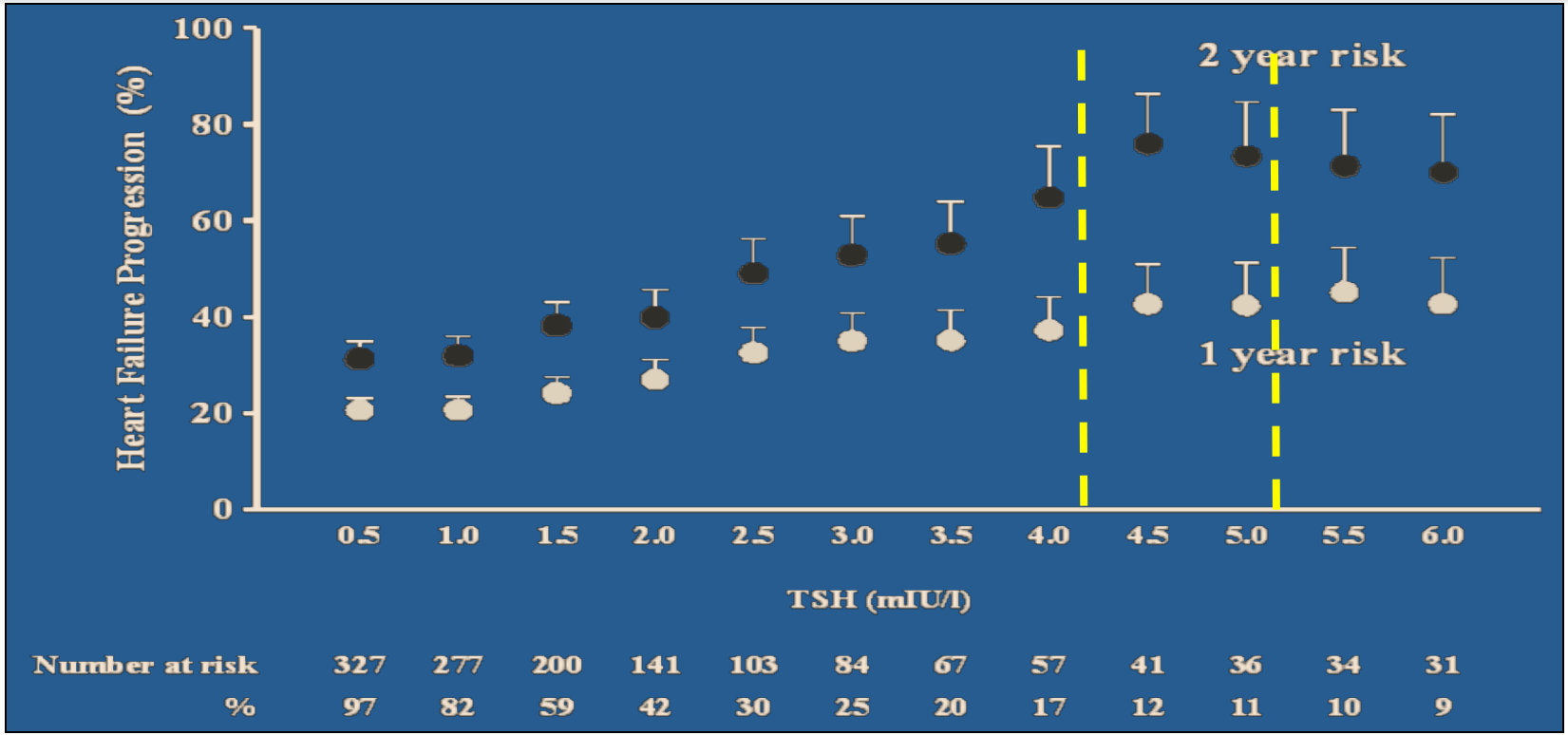
M. Iacoviello[1,*], P. Guida[1], E. Guastamacchia[2], V. Triggiani[2], C. Forleo[1], R. Catanzaro[1], M. Cicala[1], M. Basile[1], S. Sorrentino[1] and S. Favale[1]

Current Pharmaceutical Design 2008;14:2686-92



Kaplan-Meier survival curves of patients with and without hypothyroidism

HR: 3.44 (2.05-5.76) at univariate, and 2.03 (1.16-3.55) at multivariate regression analysis



Iacoviello M et al, Curr Pharm Des. 2008;14:2686-92

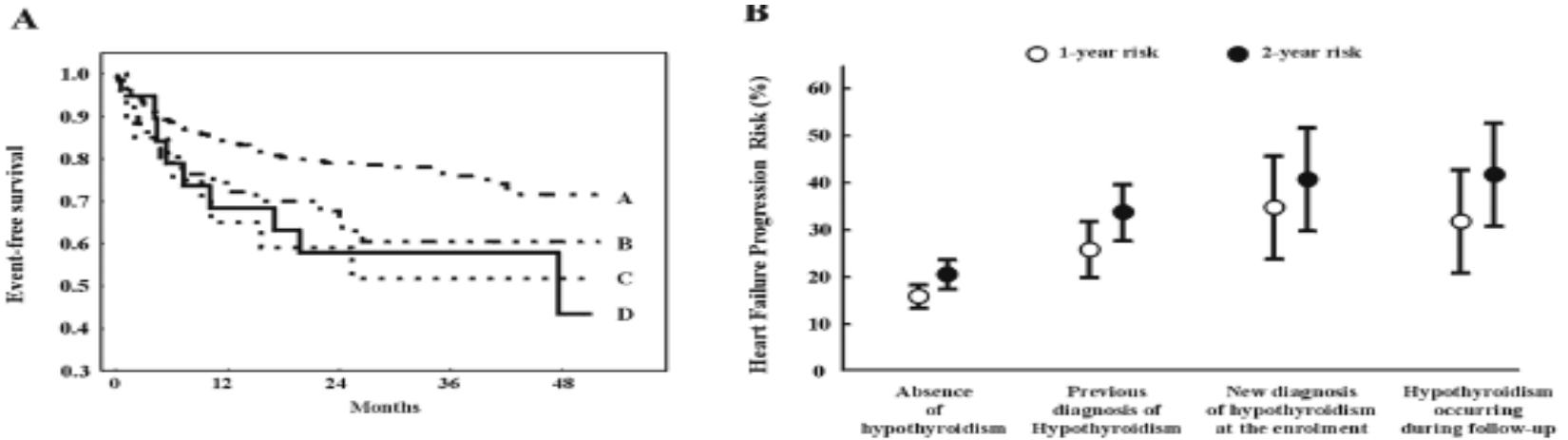
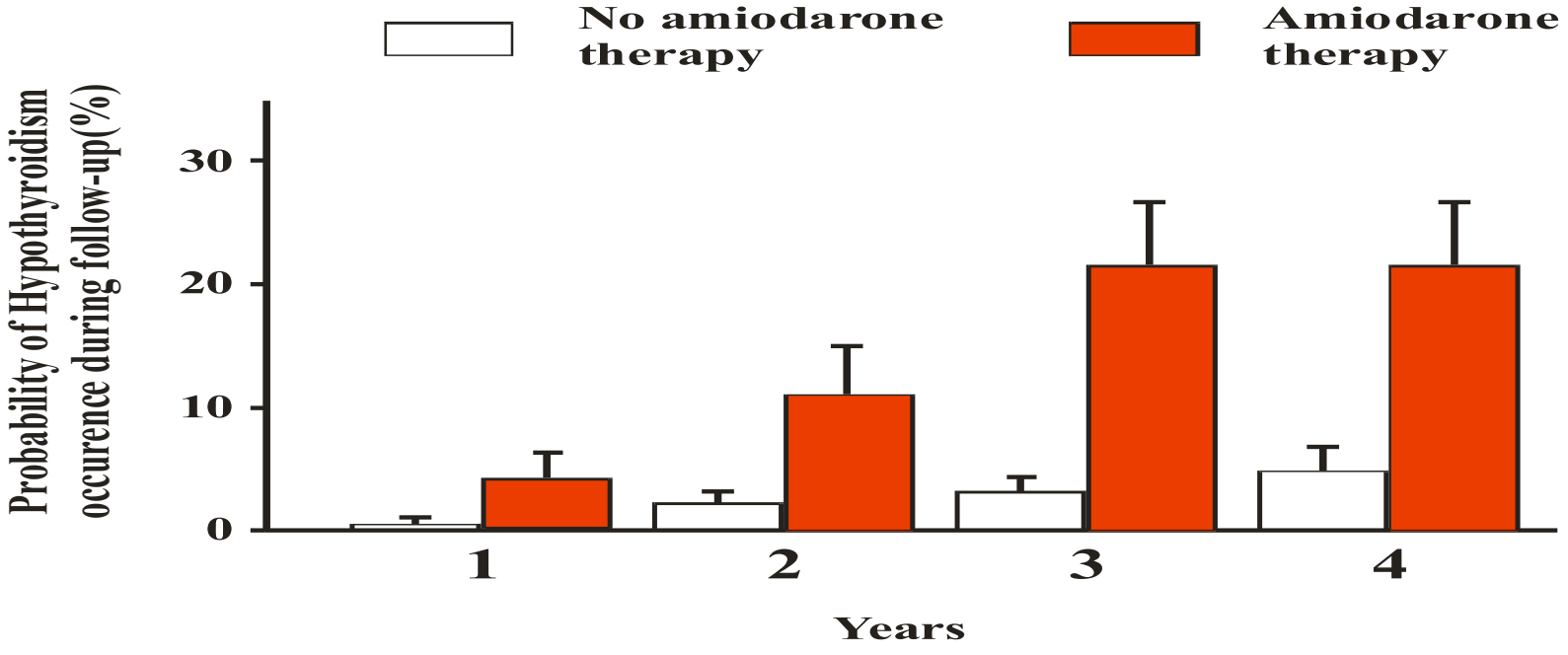


Fig. (2). Results of the study of Triggiani *et al.* [68] enrolling outpatients with diagnosis of chronic heart failure in stable clinical conditions. In panel **A**, Kaplan-Meier curves relative to composite end-point reflecting heart failure progression (hospitalization for acute decompensated heart failure, heart transplantation or death due to heart failure worsening) in patients in euthyroid status at the enrolment and during follow-up (group A), previous diagnosis of hypothyroidism (group B), new diagnosis of hypothyroidism at the enrolment (group C) and occurrence of hypothyroidism during follow-up (group D). In panel **B**, the probability of 1-year and 2-year occurrence of heart failure progression in different subgroups estimated on the basis of Kaplan-Meier analysis.

Triggiani, V.; Iacoviello, M.; Monzani, F.; Puzzovivo, A.; Guida, P.; Forleo, C.; Ciccone, M.M.; Catanzaro, R.; Tafaro, E.; Licchelli, B.; Giagulli, V.A.; Guastamacchia, E. and Favale, S. (2012) Incidence and prevalence of hypothyroidism in patients affected by chronic heart failure: role of amiodarone. *Endocr. Metab. Immun. Disord. Drug Targets,* **12**, 86-94.



Overall prevalence of hypothyroidism at the first evaluation: 17% .

Incidence rate: 26/1000/year

Triggiani, V.; Iacoviello, M.; Monzani, F.; Puzzovivo, A.; Guida, P.; Forleo, C.; Ciccone, M.M.; Catanzaro, R.; Tafaro, E.; Licchelli, B.; Giagulli, V.A.; Guastamacchia, E. and Favale, S. (2012) Incidence and prevalence of hypothyroidism in patients affected by chronic heart failure: role of amiodarone. *Endocr. Metab. Immun. Disord. Drug Targets*, **12**, 86-94.

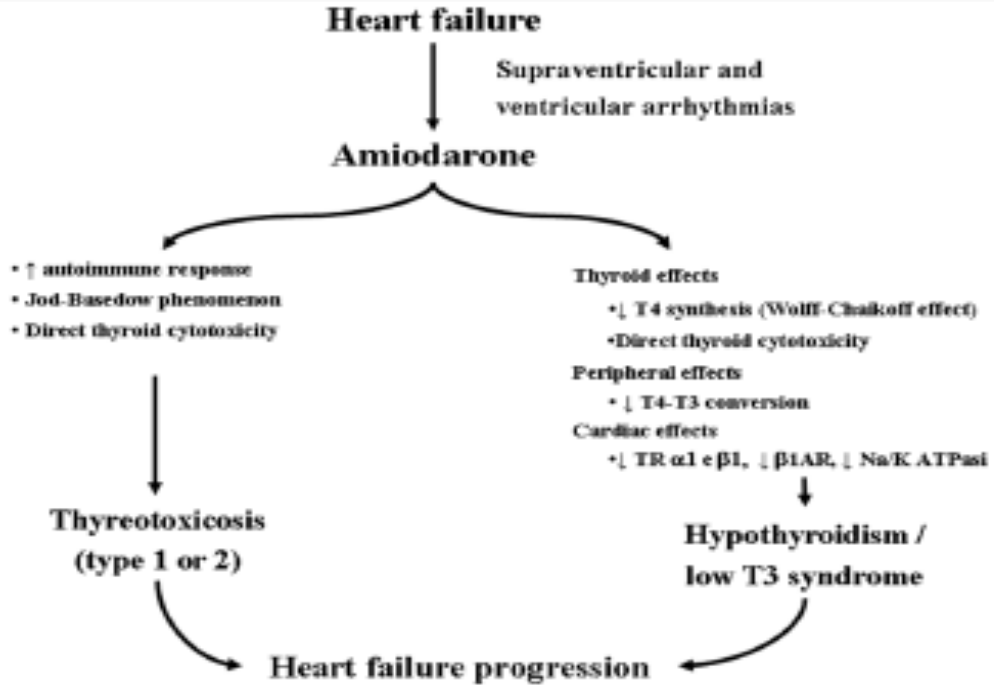


Fig. (3). Main mechanisms by which amiodarone can induce hyper- or hypothyroidism thus favouring heart failure progression. AR: Adrenergic receptor; T3: triiodothyronine. T4: thyroxine. TR: thyroid receptor.

Triggiani V and Iacoviello M Endocrine, Metabolic & Immune Disorders – Drug Targets, 2013.13:22-37

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

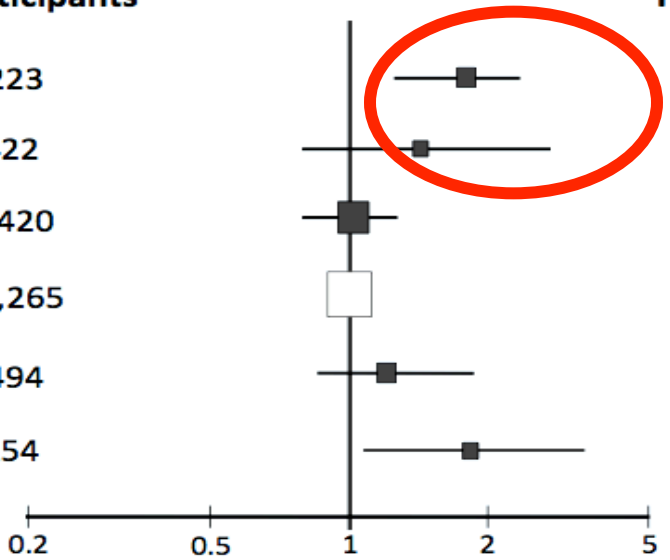
Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events: An Individual Participant Data Analysis from Six Prospective Cohorts

Baris Gencer, Tinh-Hai Collet, Vanessa Virgini, Douglas C. Bauer, Jacobijn Gussekloo, Anne R. Cappola, David Nanchen, Wendy P. J. den Elzen, Philippe Balmer, Robert N. Luben, Massimo Iacoviello, Vincenzo Triggiani, Jacques Cornuz, Anne B. Newman, Kay-Tee Khaw, J. Wouter Jukema, Rudi G. J. Westendorp, Eric Vittinghoff, Drahomir Aujesky and Nicolas Rodondi

Coordinating center	No events	No participants	Median age	Women	Sub Hypo	Sub Hyper	Person-years
Cardiovascular Health study	831	3064	71	60%	16.2%	1.4%	34,531
Health, Aging and Body Composition study	366	2762	74	51%	12.1%	3.0%	17,869
EPIC-Norfolk study	474	13,066	58	54%	5.5%	2.8%	143,694
Leiden 85-plus study	92	514	85	65%	6.8%	4.5%	1861
Bari study	77	335	66	23%	11.6%	2.1%	370
PROSPER	229	5649	75	51%	7.9%	2.3%	17,923
Overall	2069	25,390	70	53.8%	8.1%	2.6%	216,248

Hazard Ratios for Heart Failure (HF) Events according to Thyroid-Stimulating Hormone (TSH) levels

TSH level (mIU/L)	No events	No participants	Hazard Ratios (95% CI)
10.0-19.9	40	223	1.86 (1.27-2.72)
7.0-9.9	54	422	1.65 (0.84-3.23)
4.5-6.9	156	1420	1.01 (0.81-1.26)
0.45-4.49 (euthyroid)	1762	22,265	1 (reference)
0.10-0.44	41	494	1.31 (0.88-1.95)
< 0.10	16	154	1.94 (1.01-3.72)



P for trend < 0.01

P for trend 0.047

P value for quadratic pattern < 0.01

Circulation2012;126:1040-1049

European Journal of Heart Failure (2014) 16, 217–226
doi:10.1002/ejhf.42

The effect of thyroid function on clinical outcome in patients with heart failure

Shmuel Chen, Ayelet Shauer, Donna R. Zwas, Chaim Lotan, Andre Keren, and Israel Gotsman*

Heart Failure Center, Heart Institute, Hadassah University Hospital, Jerusalem, Israel

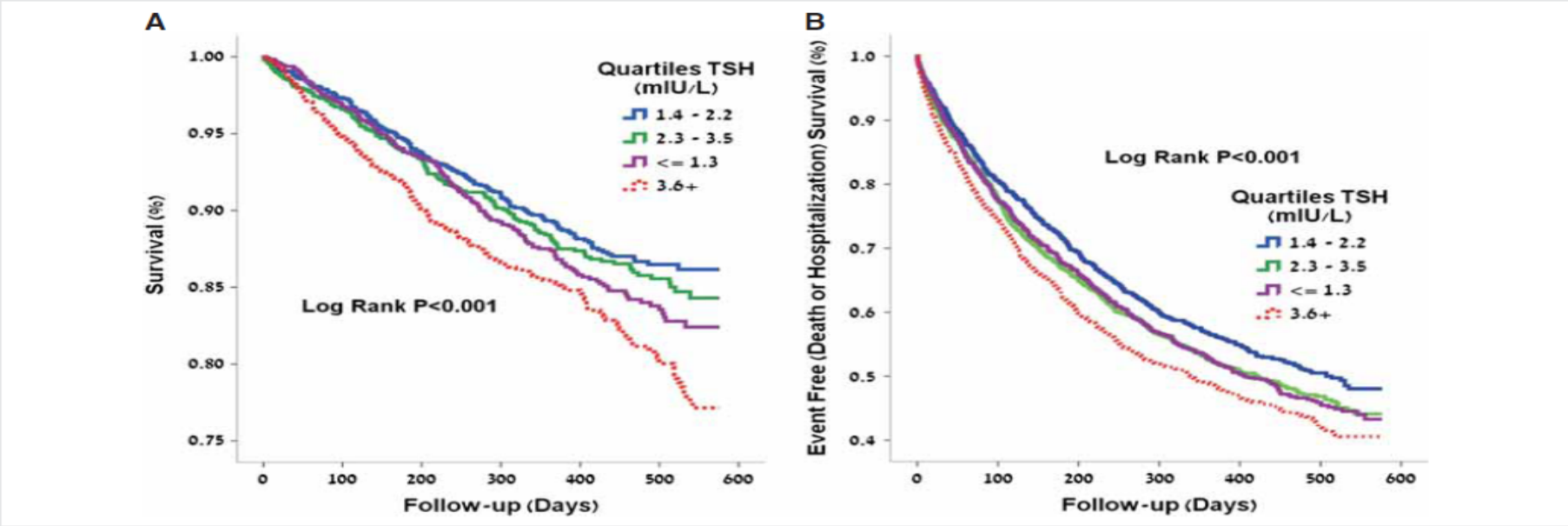


Figure 1 Kaplan–Meier clinical outcome survival analysis according to thyroid-stimulating hormone (TSH) quartiles. The survival rate was lowest in the highest TSH quartile. Survival rates (*A*) and event-free survival from cardiac hospitalization and death (*B*).

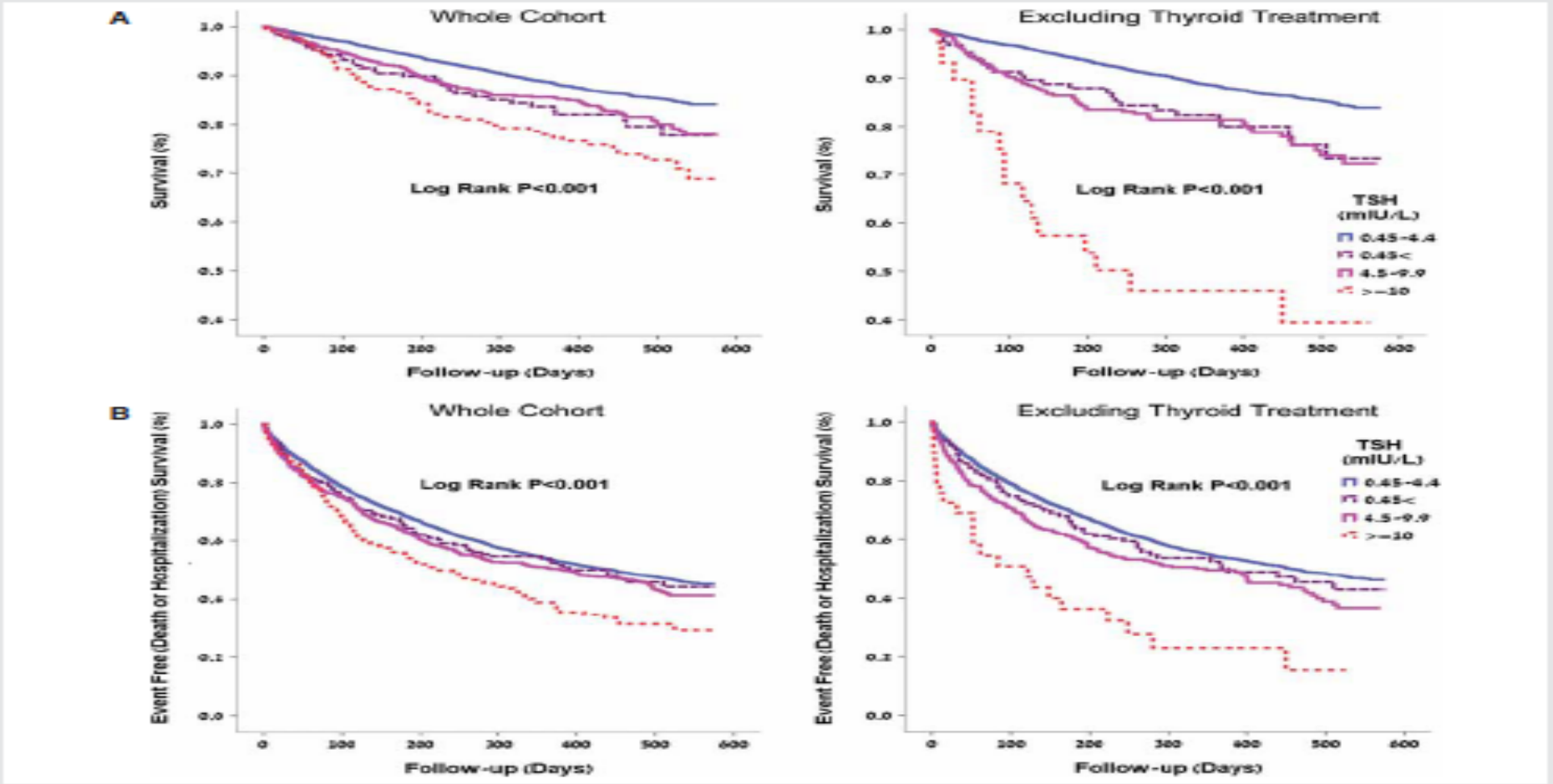


Figure 3 Kaplan–Meier clinical outcome survival analysis according to clinical cut-offs of thyroid-stimulating hormone (TSH) levels. Data presented in the whole cohort and in the cohort with exclusion of patients receiving thyroid treatment (levothyroxine and antithyroid medication). There was an increasing clinical event rate with increasing TSH levels and with low TSH levels. Survival rates (*A*) and event-free survival from cardiac hospitalization and death (*B*).

European Journal of Heart Failure (2014) 16, 217–226
doi:10.1002/ejhf.42

The effect of thyroid function on clinical outcome in patients with heart failure

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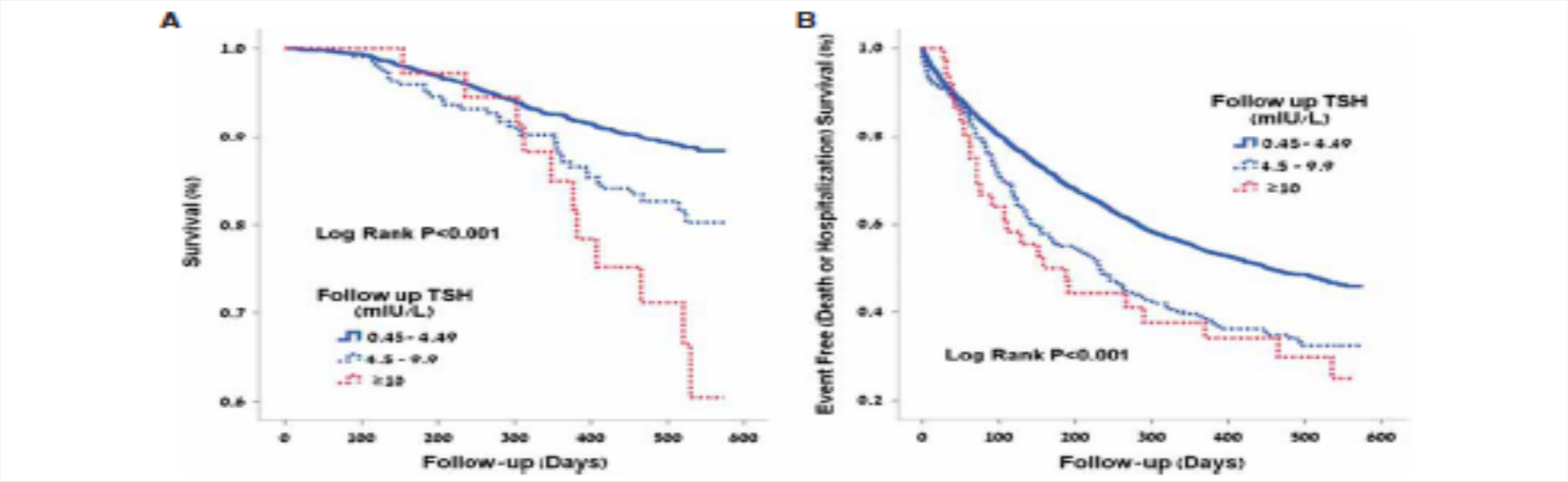

Figure 4 Kaplan–Meier clinical outcome survival analysis based on changes in thyroid-stimulating hormone (TSH) during follow up. Development of an increased TSH during follow-up in patients with normal baseline TSH was associated with a reduced survival rate (*A*) as well as reduced event-free survival from cardiac hospitalization and death (*B*). This was significant even with mildly elevated TSH (TSH between 4.5 and 10 mIU/L).

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Prognostic Role of Hypothyroidism in Heart Failure

A Meta-Analysis

Ning Ning, MM, Dengfeng Gao, MD, PhD, Vincenzo Triggiani, MD, Massimo Iacoviello, MD, PhD, Judith E. Mitchell, MD, Rui Ma, MM, Yan Zhang, MM, and Huijuan Kou, PhD

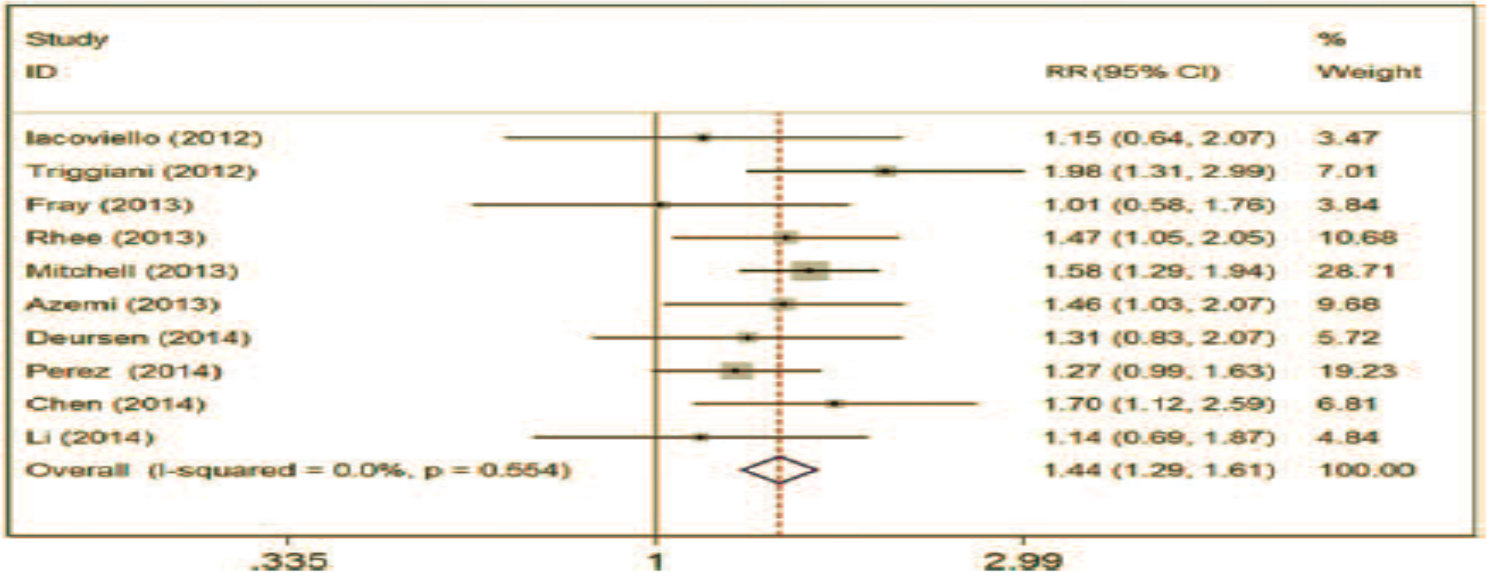

FIGURE 2. Forest plot of relative risk (RR) for hypothyroidism and all-cause mortality in patients with heart failure. Weights are from random-effects analysis.

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Prognostic Role of Hypothyroidism in Heart Failure

A Meta-Analysis

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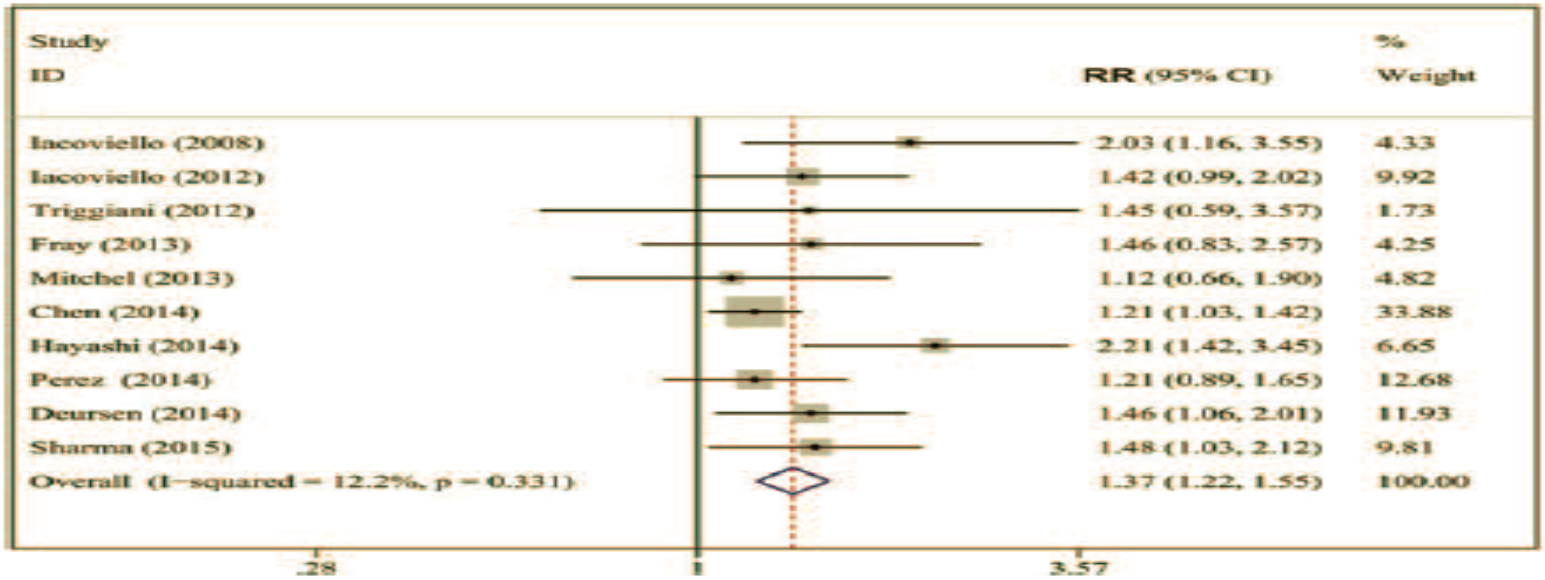

FIGURE 3. Forest plot of RR for hypothyroidism and cardiac death and/or hospitalization in patients with heart failure. Weights are from random-effects analysis.

Clinical setting	Results (ref.)
Prevalence and significance of abnormal TH metabolism in ischemic and non-ischemic congestive HF.	**The free T3 index/rT3 ratio was the only independent predictor of poor 6-week outcome** Hamilton MA, Stevenson LW, Luu M, Walden JA. Altered thyroid hormone metabolism in advanced heart failure. J Am Coll Cardiol. 1990;16:91–5.
Presence and pathophysiological implications of sick euthyroid syndrome in chronic HF patients.	**Alterations in cardiac index and ventricular filling pressures were more significant in sick euthyroid syndrome than those in non-sick euthyroid syndrome patients** Opasich C, Pacini F, Ambrosino N, Riccardi PG, Febo O, Ferrari R, et al. Sick euthyroid syndrome in patients with moderate to-severe chronic heart failure. Eur Heart J. 1996;17:1860–6..
T3 concentrations as an adjunct to clinical and functional parameters when estimating prognosis in patients with chronic HF.	**Low T3 levels are an independent predictor of mortality in patients with chronic HF** Pingitore A, Landi P, Taddei MC, Ripoli A, L' Abbate A, Iervasi G. Triiodothyronine levels for risk stratification of patients with chronic heart failure. Am J Med. 2005;118:132–6.
Correlations of TH levels with echocardiographic parameters and their associations with subsequent mortality in patients with dilated cardiomyopathy.	**A low FT3/FT4 ratio was associated with an increased risk of mortality** Kozdag G, Ural D, Vural A, Agacdiken A, Kahraman G, Sahin T, et al. Relation between free triiodothyronine/free thyroxine ratio, echocardiographic parameters and mortality in dilated cardiomyopathy. Eur J Heart Fail. 2005;7:113–8..

Low FT3 and high brain natriuretic peptide levels in patients with HFrEF and no thyroid disease.	**Patients with low FT3 and higher brain natriuretic peptide levels showed the highest risk of all-cause and cardiac death** Passino C, Pingitore A, Landi P, Fontana M, Zyw L, Clerico A, et al. Prognostic value of combined measurement of brain natriuretic peptide and triiodothyronine in heart failure. J Cardiac Fail. 2009;15:35–40..
Persistent subclinical hypothyroidism and risk of HF, based on TSH levels.	**No association was found between the various TSH levels and the risk of HF** Hyland KA, Arnold AM, Lee JS, Cappola AR. Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the cardiovascular health study. J Clin Endocrinol Metab. 2013;98(2):533–40..
Prevalence and incidence of hypothyroidism in a group of congestive HF outpatients in stable clinical conditions, with particular reference to the role of amiodarone therapy.	**The diagnosis of hypothyroidism at enrollment as well as its occurrence during follow-up was associated to events. Hypothyroidism, especially the subclinical form, frequently occurs in patients affected by congestive HF receiving amiodarone therapy** Triggiani V, Iacoviello M, Monzani F, Puzzovivo A, Guida P, Forleo C, et al. Incidence and prevalence of hypothyroidism in patients affected by chronic heart failure: role of amiodarone. Endocr Metab Immun Disord Drug Targets. 2012;12:86–94..
Individuals with HFrEF (ejection fraction ≤35%) with altered thyroid function levels and based on TSH levels.	**A TSH level <0.3 or >5.0 mIU/L was associated with increased relative risk of death around 85 and 58%, respectively** Mitchell JE, Hellkamp AS, Mark DB, Anderson J, Johnson GW, Poole JE, et al. Thyroid function in heart failure and impact on mortality. JACC Heart Fail. 2013;1(1):48–55..

Risk of developing congestive HF based on the TSH level.	**The risk of congestive HF was only present in patients aged 70–79 years old, when the TSH value was ≥7.0 mIU/L** Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med. 2005;165(21):2460–6..
Subclinical TD and risk of HF based on the TSH value.	**The risk of HF increased among individuals with TSH values ≥10.0 mIU/L, and in those with TSH values <0.10 mIU/L** Gencer B, …Iacoviello M, Triggiani V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Thyroid Studies Collaboration. Circulation. 2012;126(9):1040–9..
Prognostic role of thyroid function deficiency in patients with chronic HF.	**TSH levels even slightly above normal range are independently associated with a greater likelihood of HF progression** Iacoviello M, Guida P, Guastamacchia E, Triggiani V, Forleo C, Catanzaro R, et al. Prognostic role of sub-clinical hypothyroidism in chronic heart failure outpatients. Curr Pharm Des. 2008;14:2686–92..
Subclinical TD and risk of HF among participants with a known cardiovascular risk.	**The rate of HF was higher among the group with subclinical thyroid dysfunction** Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S, et al. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab. 2012;97(3):852–61.
Subclinical TD in adults ≥65 years old and incidence of HF.	**Individuals with TSH ≥ 10.0 mIU/L have a higher incidence of HF versus euthyroid participants** Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. the Cardiovascular Health study. J Am Coll Cardiol. 2008;52:1152–9..

Prognostic impact of euthyroidism, subclinical TD, and the "euthyroid sick syndrome" in patients with HFrEF.	**Those with "euthyroid sick syndrome" had a higher risk of death, as compared against normal thyroid function individuals** Frey A, Kroiss M, Berliner D, Seifert M, Allolio B, Güder G, et al. Prognostic impact of subclinical thyroid dysfunction in heart failure. Int J Cardiol. 2013;168(1):300–5.
Effect of TSH levels and clinical results in HF patients.	**The percentage survival was lower for individuals with TSH values of ≤1.3 or ≥3.6 mIU/L** Chen S, Shauer A, Zwas DR, Lotan C, Keren A, Gotsman I. The effect of thyroid function on clinical outcome in patients with heart failure. Eur J Heart Fail. 2014;16(2):217–26..
TSH levels in individuals with HFrEF and risk of cardiovascular death, hospitalization due to HF, and all-cause mortality.	**Participants with hypothyroidism experienced high cardiovascular and all-cause mortality rates, in addition to a high risk of hospital admission due to worsening of the HF** Perez AC, Jhund PS, Stott DJ, Gullestad L, Cleland JG, van Veldhuisen DJ, et al. Thyroid-stimulating hormone and clinical outcomes: the CORONA trial (controlled rosuvastatin multinational study in heart failure). JACC Heart Fail. 2014;2(1):35–40..
The prognostic role of hypothyroidism and risk of death and/or hospitalization of HF patients.	**Overt and subclinical hypothyroidism were associated with an increased risk of all-cause mortality, cardiac death, and/or hospitalization, particularly in patients >65 old** Ning N, Gao D, Triggiani V, Iacoviello M, Mitchell JE, Ma R, et al. Prognostic role of hypothyroidism in heart failure: a meta-analysis. Medicine (Baltimore). 2015;94(30):e1159. .

N Engl J Med. 2017 Jun 29;376(26):2534-2544. doi: 10.1056/NEJMoa1603825. Epub 2017 Apr 3.

Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism.

Stott DJ[1], Rodondi N[1], Kearney PM[1], Ford I[1], Westendorp RGJ[1], Mooijaart SP[1], Sattar N[1], Aubert CE[1], Aujesky D[1], Bauer DC[1], Baumgartner C[1], Blum MR[1], Browne JP[1], Byrne S[1], Collet TH[1], Dekkers OM[1], den Elzen WPJ[1], Du Puy RS[1], Ellis G[1], Feller M[1], Floriani C[1], Hendry K[1], Hurley C[1], Jukema JW[1], Kean S[1], Kelly M[1], Krebs D[1], Langhorne P[1], McCarthy G[1], McCarthy V[1], McConnachie A[1], McDade M[1], Messow M[1], O'Flynn A[1], O'Riordan D[1], Poortvliet RKE[1], Quinn TJ[1], Russell A[1], Sinnott C[1], Smit JWA[1], Van Dorland HA[1], Walsh KA[1], Walsh EK[1], Watt T[1], Wilson R[1], Gussekloo J[1]; TRUST Study Group.

Abstract

BACKGROUND:

The use of levothyroxine to treat subclinical hypothyroidism is controversial. We aimed to determine whether levothyroxine provided clinical benefits in older persons with this condition.

METHODS:

We conducted a double-blind, randomized, placebo-controlled, parallel-group trial involving 737 adults who were at least 65 years of age and who had persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter; free thyroxine level within the reference range). A total of 368 patients were assigned to receive levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease), with dose adjustment according to the thyrotropin level; 369 patients were assigned to receive placebo with mock dose adjustment. The two primary outcomes were the change in the Hypothyroid Symptoms score and Tiredness score on a thyroid-related quality-of-life questionnaire at 1 year (range of each scale is 0 to 100, with higher scores indicating more symptoms or tiredness, respectively; minimum clinically important difference, 9 points).

RESULTS:

The mean age of the patients was 74.4 years, and 396 patients (53.7%) were women. The mean (±SD) thyrotropin level was 6.40±2.01 mIU per liter at baseline; at 1 year, this level had decreased to 5.48 mIU per liter in the placebo group, as compared with 3.63 mIU per liter in the levothyroxine group (P<0.001), at a median dose of 50 µg. We found no differences in the mean change at 1 year in the Hypothyroid Symptoms score (0.2±15.3 in the placebo group and 0.2±14.4 in the levothyroxine group; between-group difference, 0.0; 95% confidence interval [CI], -2.0 to 2.1) or the Tiredness score (3.2±17.7 and 3.8±18.4, respectively; between-group difference, 0.4; 95% CI, -2.1 to 2.9). No beneficial effects of levothyroxine were seen on secondary-outcome measures. There was no significant excess of serious adverse events prespecified as being of special interest.

CONCLUSIONS:

Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism. (Funded by European Union FP7 and others; TRUST ClinicalTrials.gov number, NCT01660126 .).