



## Tiroide e scompenso cardiaco



Bari 08 Novembre 2013

## 12° Congresso Nazionale AME

Associazione Medici Endocrinologi

## 6th Joint Meeting with AACE

American Association of Clinical Endocrinologists

## Update in Endocrinologia Clinica

Disfunzione tiroidea e scompenso cardiaco: il punto di vista del cardiologo

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7-10 novembre 2013

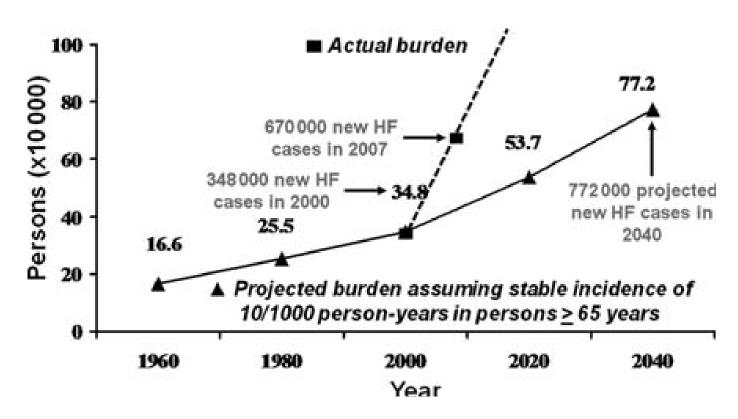
Bari, Sheraton Nicolaus Hotel & Conference Center





### Epidemiologia dell'insufficienza cardiaca

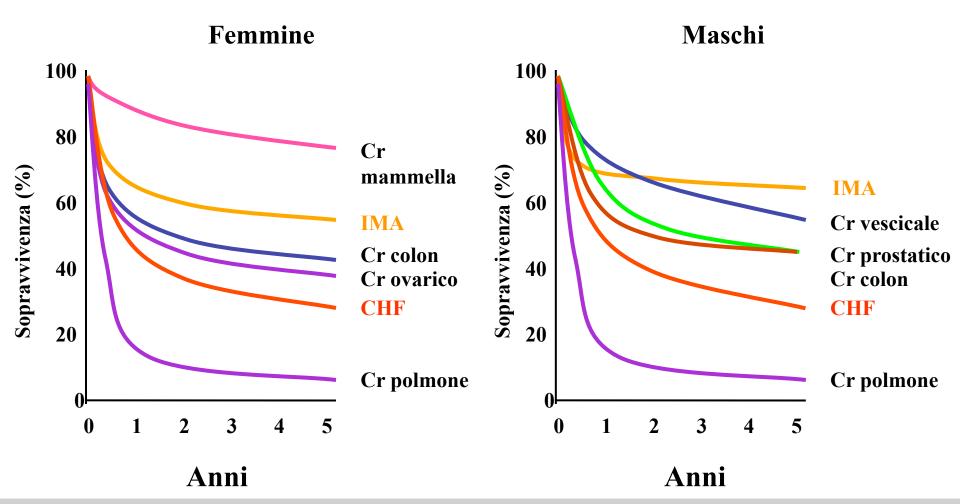
### Proiezione relativa agli USA







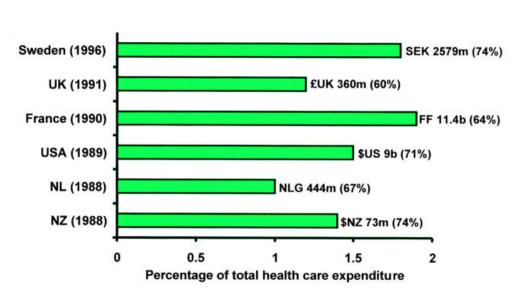
### Sopravvivenza dei pazienti con scompenso cardiaco



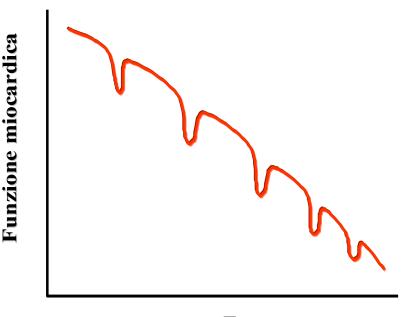




### Costi di gestione ed ospedalizzazioni



McMurray JJ et alEur Heart J 1998;19:P9-16.

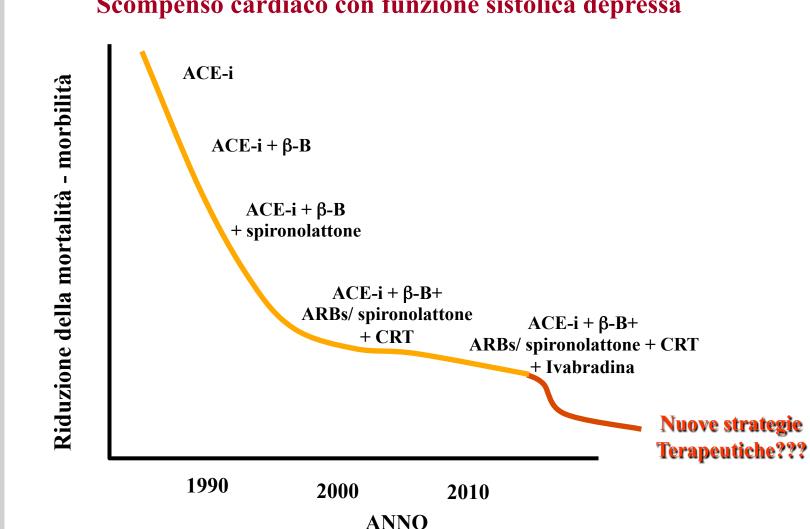


Tempo







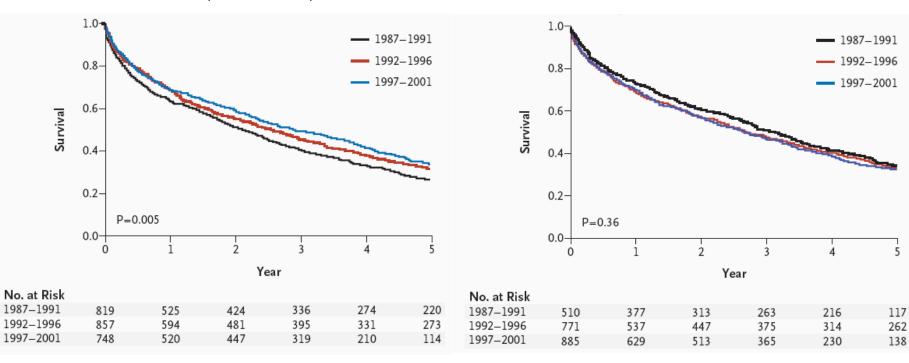






# Funzione sistolica ridotta (HFREF)

# Funzione sistolica preservata (HFPEF)\*



<sup>\*</sup>Rappresentano almeno il 50% dei pazienti con scompenso cardiaco. Sono di età più avanzata, più frequentemente di sesso femminile, ipertesi e fibrillanti, affetti da multiple comorbilità

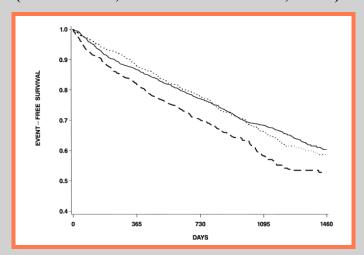


# Scompenso cardiaco: rilevanza epidemiologica delle comorbilità

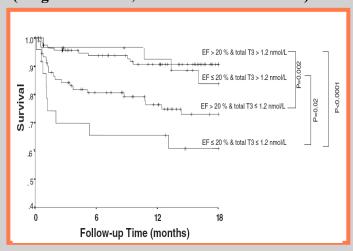


**Diabete** 

(Dries DL et al, J Am Coll Cardiol 2001;38:421)

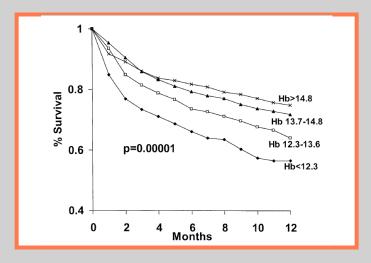


LT3
(Pingitore A et al., Am J Med 2005:118:132)



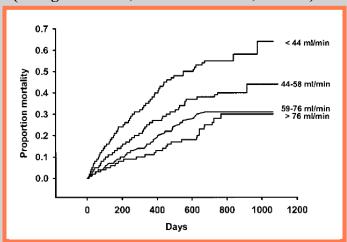
Anemia

(Horwich TP et al, J Am Coll Cardiol 2002;39:1780)



**GFR** 

(Hillege HL et al., Circulation 2000;103:203)





# Disfunzione tiroidea e scompenso cardiaco: il punto di vista del cardiologo



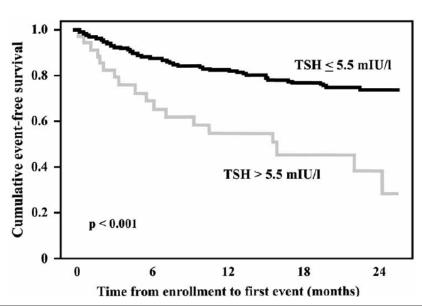
### Quesiti frequenti dei cardiologi

- Ipotiroidismo e Low T3 syndrome: quale impatto prognostico?
- Approccio terapeutico alla ridotta funzione tiroidea
- Low T3 syndrome marcatore o mediatore di prognosi
- Ipertiroidismo e scompenso cardiaco
- Problematiche legate all' ipo- ed ipertiroidismo indotti da amiodarone





### Ipotiroidismo subclinico



	Multivariate C	Cox Regression			
	HR (95% CI)				
TSH(mIU/l)	1.10 (1.05-1.14)	<0.001			
fT3 (ng/dl)	0.73 (0.42-1.27)	0.27			
fT4 (pg/ml)	0.88 (0.37-2.11)	0.78			
fT3/fT4	0.89 (0.61-1.29)	0.53			





+	Coordinating center		No events	No participants	Median age	Women	Sub Hypo	Sub Hyper	Person-years
-	Cardiovascular Health	n study	831	3064	71	60%	16.2%	1.4%	34,531
10000	Health, Aging and Bo	dy Composition st	udy 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	;	ı		Hazard F	Ratios (95%	CI)
10.0	-19.9	40	223				1.86	(1.27-2.72)	<b>1</b>
7.0-9	9.9	54	422	_	-	_	1.65	(0.84-3.23)	P for trend < 0.01
4.5-6	5.9	156	1420		⊩		1.01	(0.81-1.26)	
	-4.49 hyroid)	1762	22,265				<b>1</b> (r	eference)	
0.10	-0.44	41	494	-	-		1.31	(0.88-1.95)	P for trend
< 0.1	10	16	154		-	_	1.94	(1.01-3.72)	0.047

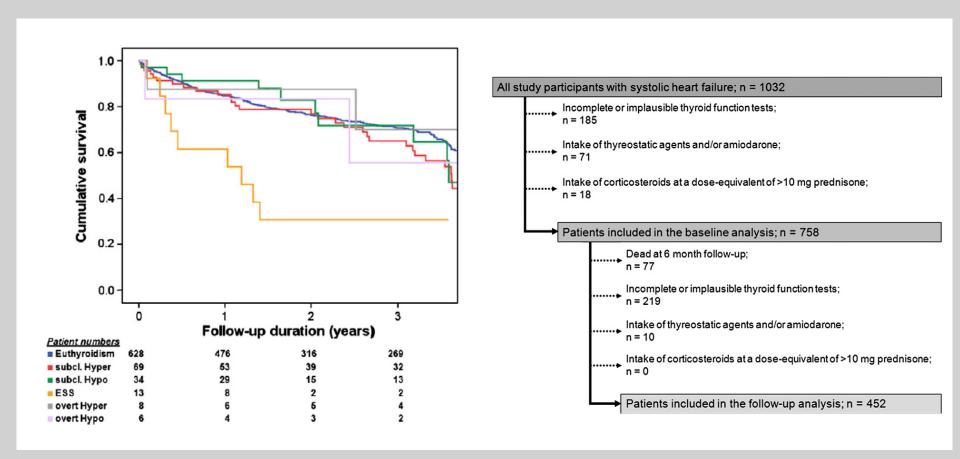
0.2

P value for quadratic pattern < 0.01





### Pazienti ospedalizzati per scompenso cardiaco







## Pazienti ospedalizzati per scompenso cardiaco

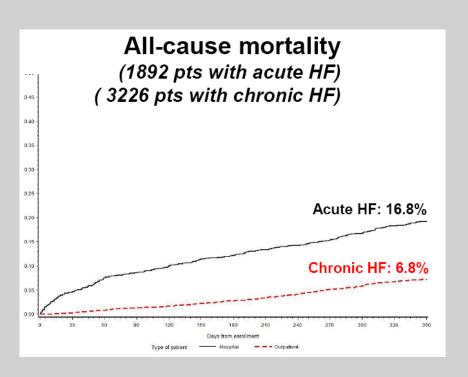
	Euthyroidism (n = 628)	Euthyroid sick syndrome ( $n=13$ )	Subclinical hyperthyroidism (n=69)	Subclinical hypothyroidism $(n=34)$
Age [years]	67 (13)	75 (10)*	72 (9)*	62 (12)*
Diagnosis of heart failure known				
<1 year	253 (40)	4 (31)	25 (36)	20 (59)
1-5 years	126 (20)	1 (7)	18 (26)	3 (9)
>5 years	249 (40)	8 (62)	26 (38)	11 (32)
NYHA functional class				
I	18 (3)	0 (0)	1 (2)	0 (0)
II	344 (55)	5 (42)	33 (48)	19 (58)
III	244 (39)	7 (58)	30 (43)	12 (36)
IV	19 (3)	0 (0)	5 (7)	2 (6)
Comorbidities†				
Atrial fibrillation	174 (28)	4 (33)	26 (38)	6 (18)
Peripheral vascular disease	67 (11)	1 (0,8)	9 (13)	4 (12)
Hypertension	483 (77)	9 (75)	54 (78)	22 (67)
Diabetes mellitus	213 (34)	7 (58)	30 (44)	8 (24)
Dyslipidemia	362 (58)	3 (23)*	38 (55)	21 (62)
COPD	108 (17)	4 (33)	12 (17)	3 (1)
Anemia	186 (30)	8 (67)*	25 (36)	10 (30)
Renal dysfunction	275 (44)	9 (75)*	30 (44)	12 (36)
Uncured malignancy	67 (11)	3 (25)	14 (20)	3 (1)
Current heart failure medication				
ACEi and/or ARB	570 (91)	8 (62)*	63 (91)	27 (79)
Beta blocker	526 (84)	9 (75)	58 (84)	29 (88)
Spironolactone or eplerenone	266 (43)	3 (25)	23 (33)	14 (42)
Diuretics (loop or thiazides)	541 (86)	12 (92)	62 (90)	25 (74)
Statin	296 (47)	3 (25)	35 (51)	20 (61)

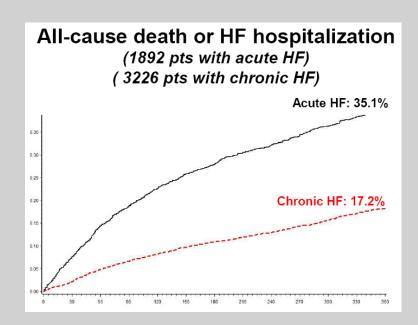




### Impatto prognostico ospedalizzazione scompenso cardiaco

### The Heart Failure Pilot survey: 1-year follow-up







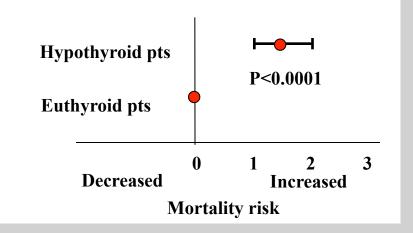


### **SCD-HeFT**

Baseline Thyroid Group				Overall Thyroid Group		
Baseline Characteristic	Hyperthyroid at Baseline n = 20 (0.9%)	Euthyroid at Baseline n = 1,930 (86.7%)	Hypothyroid at Baseline n = 275 (12.4%)	Hyperthyroid (Baseline + New Onset) n = 109 (4.9%)	Euthyroid (at All Times) n = 1,500 (67.4%)	Hypothyroid (Baseline + New Onset) n = 616 (27.7%)
Age (yrs)	56.8 ± 14.7	59.2 ± 11.8	61.7 ± 12.0*	$\textbf{54.5} \pm \textbf{12.0}\dagger$	59.1 ± 11.7	61.5 $\pm$ 11.8 $\dagger$
Age >60 yrs	40% (8)	49% (947)	60% (166)*	32% (35)†	48% (723)	59% (363)†
Women	35% (7)	22% (417)	41% (113)*	22% (24)	20% (296)	35% (217)†
Nonwhite race	25% (5)	24% (454)	18% (50)*	26% (28)	25% (377)	17% (104)†
NYHA class III	20% (4)	29% (551)	32% (88)	27% (29)	29% (428)	30% (186)
Ischemic HF etiology	40% (8)	52% (996)	51% (140)	42% (46)	52% (776)	52% (322)
Ejection fraction (%)	$\textbf{23.1} \pm \textbf{6.4}$	$\textbf{23.9} \pm \textbf{6.8}$	$\textbf{24.7} \pm \textbf{6.9}$	$\textbf{24.2}\pm\textbf{6.2}$	$\textbf{23.9}\pm\textbf{6.9}$	$\textbf{24.2}\pm\textbf{6.8}$
6-min walk distance (ft)	1,080.4 $\pm$ 396.6	$\textbf{1,122.2} \pm \textbf{398.5}$	$\textbf{1,091.0}\pm\textbf{409.3}$	$\textbf{1,140.2} \pm \textbf{395.1}$	1,126.6 $\pm$ 405.5	$\textbf{1,093.3} \pm \textbf{385.8} \dagger$

Values are mean  $\pm$  SD or % (n). Comparisons are with the euthyroid group within each classification, using Wilcoxon rank sum tests for continuous variables and likelihood ratio chi-square tests for categorical variables. \*p < 0.05 for baseline group comparisons. †p < 0.05 for overall group comparisons.

HF = heart failure; NYHA = New York Heart Association.







### Pazienti ospedalizzati

	Patients with SE (n=16)	Patients without SE (n=95)	p
Free-T3 (pg/ml)	$2.14 \pm 0.78$	$2.67 \pm 0.68$	0.02
Free-T4 (ng/dl)	$1.80 \pm 0.78$	$1.44 \pm 0.50$	NS
TSH	$1.41 \pm 0.77$	$1.41\pm1.4$	NS
f-T3/f-T4 ratio (10 <sup>-1</sup> )	$1.31 \pm 0.37$	$2.01\pm0.72$	< 0.001

### Pazienti ospedalizzati

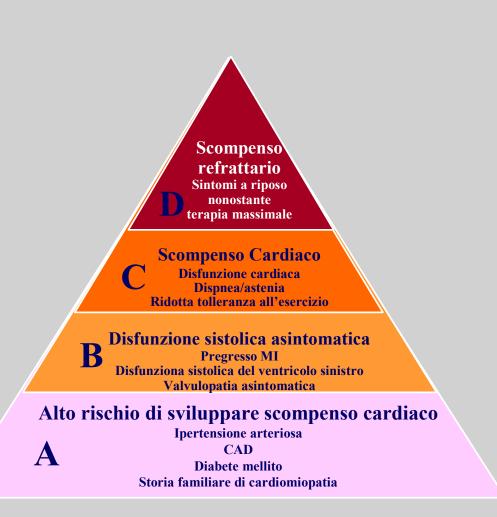
	Died during follow-up (n = 64)	Survived throughout follow-up (n = 217)	P value
TSH (mIU/L) Total T <sub>3</sub> (nmol/L)* Total T <sub>4</sub> (nmol/L)* Free T <sub>3</sub> (pmol/L)* Free T <sub>4</sub> (pmol/L)*	2.3 ± 2.6	1.9 ± 2.2	0.28
	1.0 ± 0.4	1.3 ± 0.3	<0.001
	104 ± 35	127 ± 67	0.10
	3.2 ± 1.4	3.7 ± 1.0	0.01
	18.2 ± 5.3	18.1 ± 5.0	0.83

Baseline characteristics of the study grou	ıp
Medications on admission	
Digitalis	61 (55%)
ACE-I/ARB	44 (40%)
Diuretics	37 (33%)
Spironolactone	6 (5%)
β-Blockers	11 (10%)
Aspirin	92 (83%)

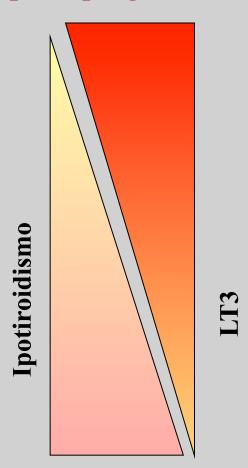
	Died during follow-up (n = 64)	Survived throughout follow-up (n = 217)	P value
Beta-blocker use	17 (27)	21 (33)	0.45
Amiodarone use	20 (31)	85 (39)	0.31
ACE inhibitor use	22 (34)	104 (48)	0.07







### **Impatto prognostico\***





# Disfunzione tiroidea e scompenso cardiaco: il punto di vista del cardiologo



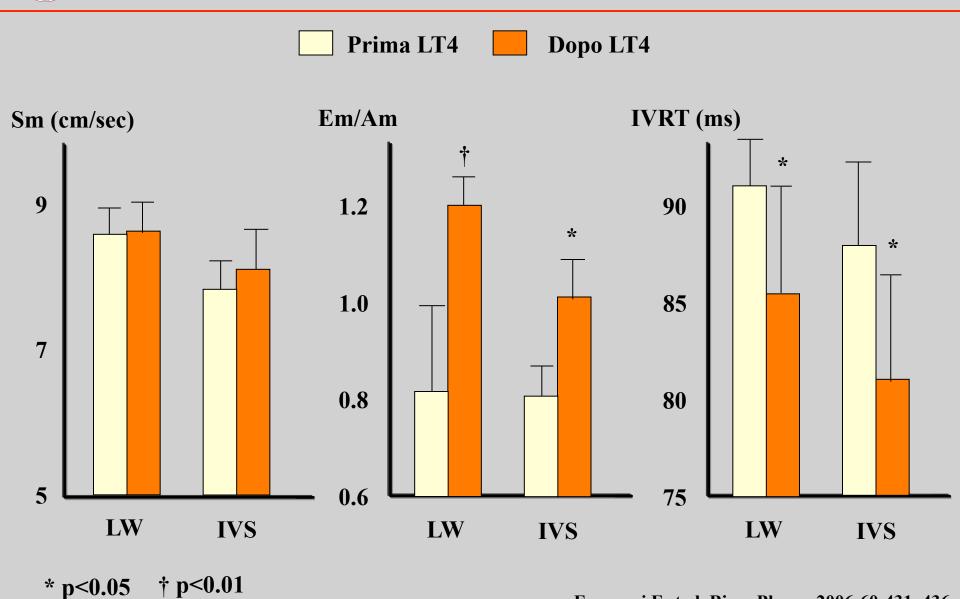
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- Approccio terapeutico alla ridotta funzione tiroidea
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- Ipertiroidismo e scompenso cardiaco
- Problematiche legate all' ipo- ed ipertiroidismo indotti da amiodarone



# Ipotiroidismo e scompenso cardiaco: quando iniziare la terapia sostitutiva





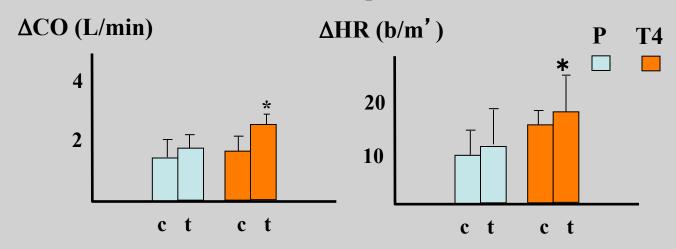
Franzoni F et al. Biom Pharm 2006;60:431–436



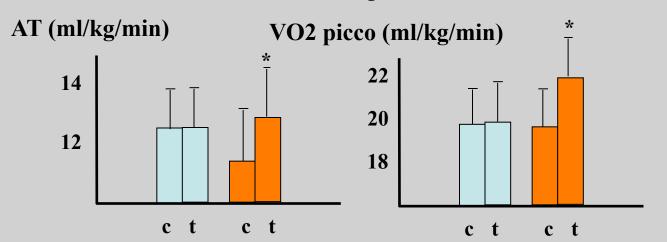
# Ipotiroidismo e scompenso cardiaco: quando iniziare la terapia sostitutiva



### Variazioni emodinamiche dopo infusione di dobutamina



### Test cardiopolmonare

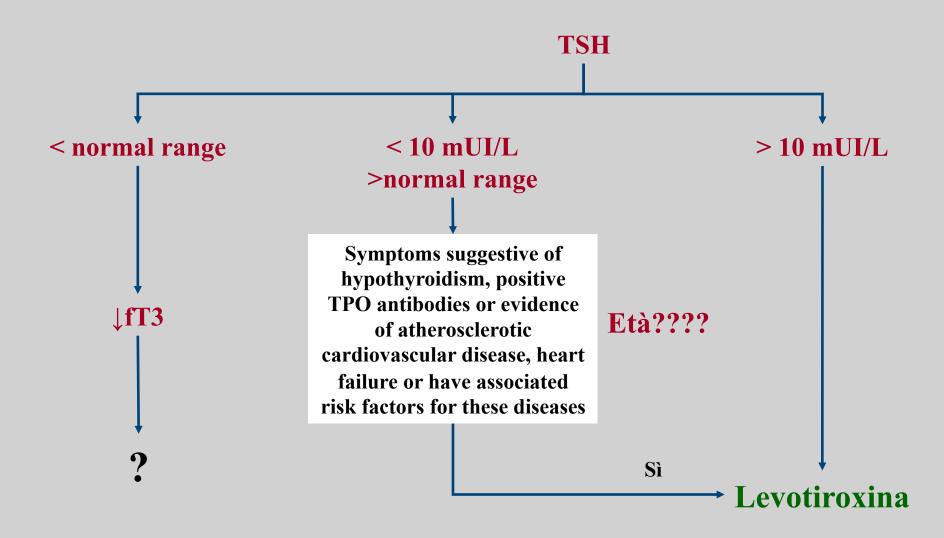


Moruzzi et al Am J med 1996; 101:461-7



# Ipotiroidismo e scompenso cardiaco: quando iniziare la terapia sostitutiva





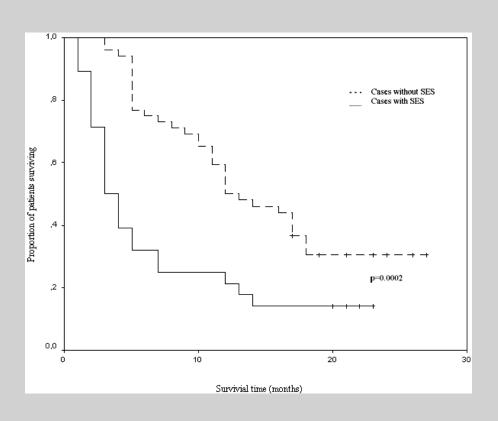
Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association



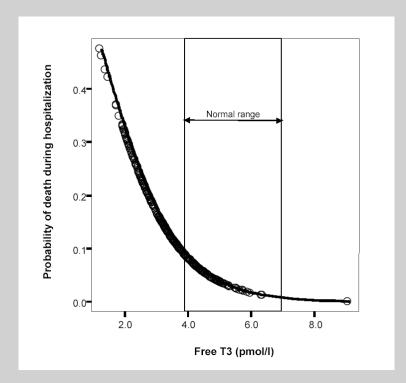
## Low T3 syndrome: marker o mediatore di prognosi?



## Pazienti con Cr. Polmonare a piccole cellule



## Pazienti dopo intervento chirurgico

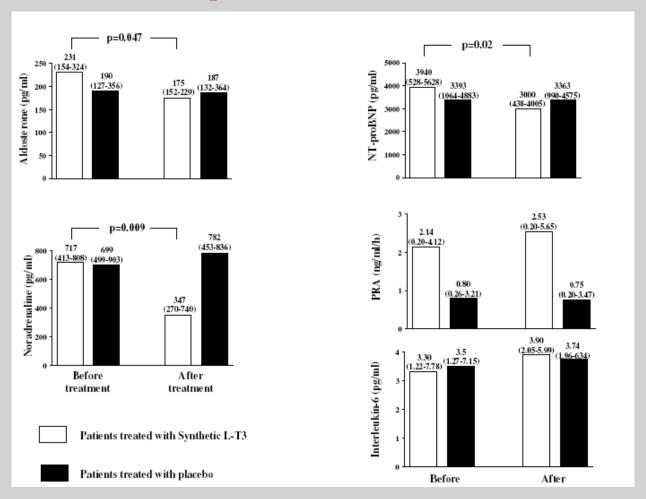




### Low T3 syndrome: marker o mediatore di prognosi?



### Terapia sostitutiva con L-T3





# Disfunzione tiroidea e scompenso cardiaco: il punto di vista del cardiologo



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## Ipertiroidismo e scompenso cardiaco

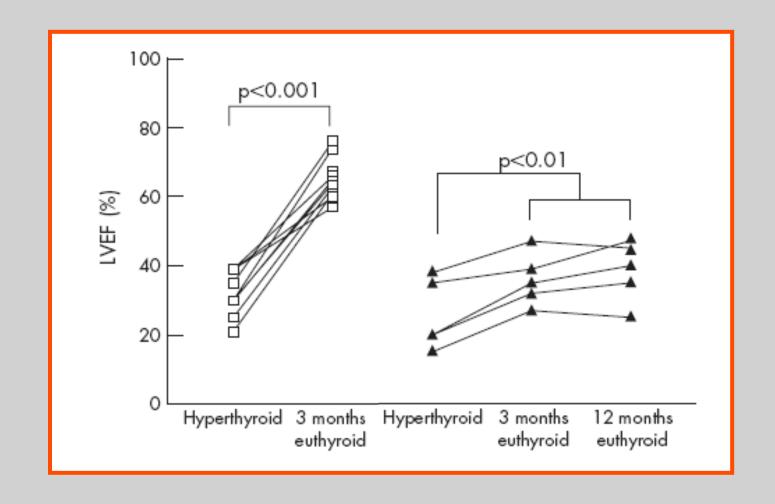


	All (n=591)	Without heart failure (n = 55				
Age, years Male Hypertension Diabetes mellitus Smoking history Free thyroxine, pmol/l	45 (1) 140 (24) 50 (9) 32 (5) 116 (20) 52 (1)	44 (1) 120 (22) 39 (7) 27 (5) 103 (18) 52 (1)		LV systolic of Absent (n = 18)	dysfunction Present (n = 16)	p Value
Aetiology of hyperthyroidism Graves' diseases Toxic multinodular goitre Others  Duration of symptoms of hyperthyroidism, months Atrial fibrillation at presentation Heart rate at presentation, bpm	362 (61) 226 (38) 3 (1) 35 (14) 82 (14) 110 (5)	346 (62) 208 (37) 3 (1) 32 (16) 50 (9) 100 (3)	Age, years Male Hypertension Diabetes mellitus Smoking history Free thyroxine, pmol/l Aetiology of hyperthyroidism	72 (3) 6 (33) 3 (17) 3 (17) 4 (22) 66 (12)	58 (4) 14 (88) 8 (50) 2 (13) 9 (56) 39 (4)	0.03 <0.01 0.07 1.0 0.07 0.04
Values are in n (%) or mean (SEM).			Graves' diseases Toxic multinodular goitre	11 (61) 7 (39)	5 (31) 11 (69)	0.10
			Duration of symptoms of hyperthyroidism, days Atrial fibrillation Heart rate, bpm LV end-diastolic dimension, cm LVEF	40 (25) 18 (100) 140 (5) 4.3 (0.1) 62 (2)	38 (16) 14 (88) 137 (9) 5.3 (0.2) 29 (2)	0.85 0.21 0.79 <0.01 <0.01



## Ipertiroidismo e scompenso cardiaco

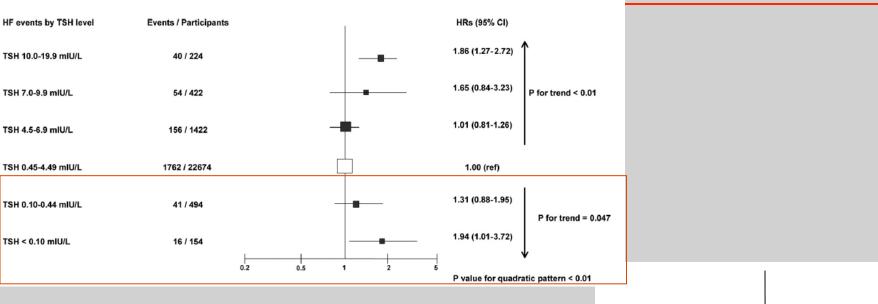




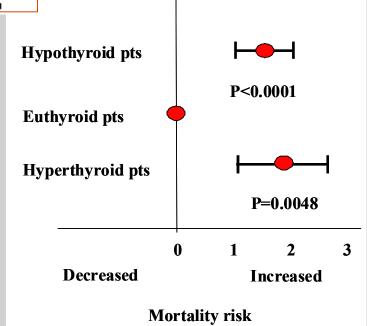


## Ipertiroidismo e scompenso cardiaco









Mitchell JE et al. JACC-HF 2013;1:48-55



# Disfunzione tiroidea e scompenso cardiaco: il punto di vista del cardiologo



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## Gestione delle aritmie nello scompenso cardiaco



Classe	Molecole	Meccanismo	Classe indica	nzione
Antiaritmici		d'azione	Aritmie sopraventricolari	Aritmie ventricolari
Class I				
Class Ia	Chinidina	$\downarrow I_{Na}, \downarrow I_{K}$	III	III
Class Ib	Mexiletina	$\downarrow$ I $_{ m Na}$	III	?
Class Ic	Propafenone, Flecainide	$\downarrow$ I <sub>Na</sub> , $\downarrow$ β-AR $\downarrow$ I <sub>Na</sub>	III	Ш
Class II	β-bloccanti	↓ β-AR	I	I
	Amiodarone	$\downarrow\!\mathbf{I_K}$	IIb	IIb
Class III	Dronedarone	$\downarrow$ I <sub>K</sub>	Ш	III
	Sotalolo	$\downarrow I_K$ , $\downarrow \beta$ -AR	?	?
Class IV	Verapamil, Diltiazem	$\downarrow$ I $_{\mathrm{Ca}}$	III	III
Other	Digoxin	↓Na/K ATPasi	I	III



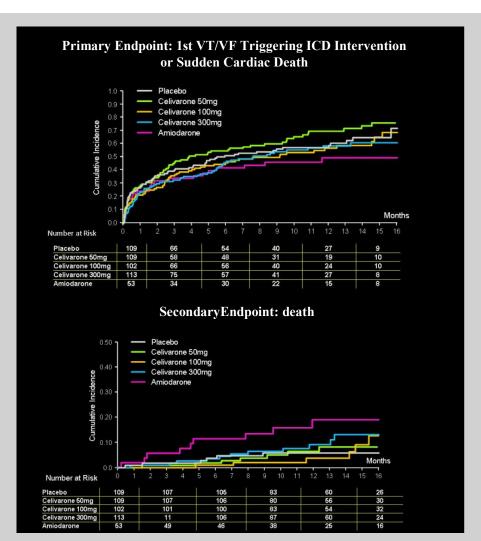
## Gestione delle aritmie nello scompenso cardiaco



## Dronedarone Studio ANDROMEDA

## Celivarone Studio ALPHEE

Aumentata mortalità nei pazienti scon scompenso cardiaco cronico, classe NYHA III-IV



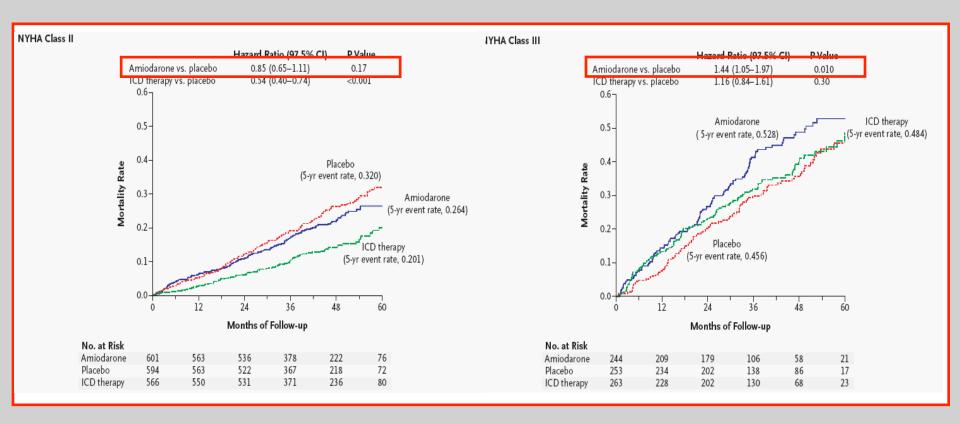




## **SCD-HeFT**

#### **Classe NYHA II**

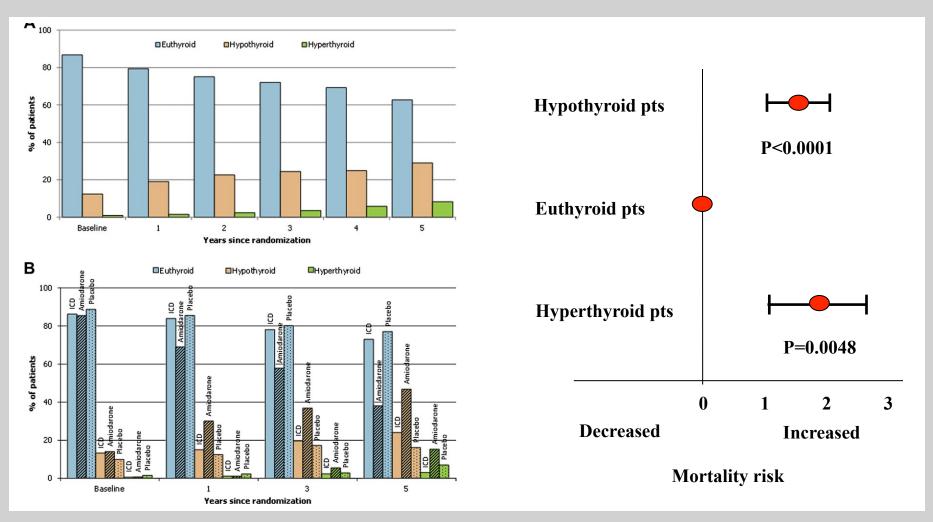
### Classe NYHA III







### **SCD-HeFT**





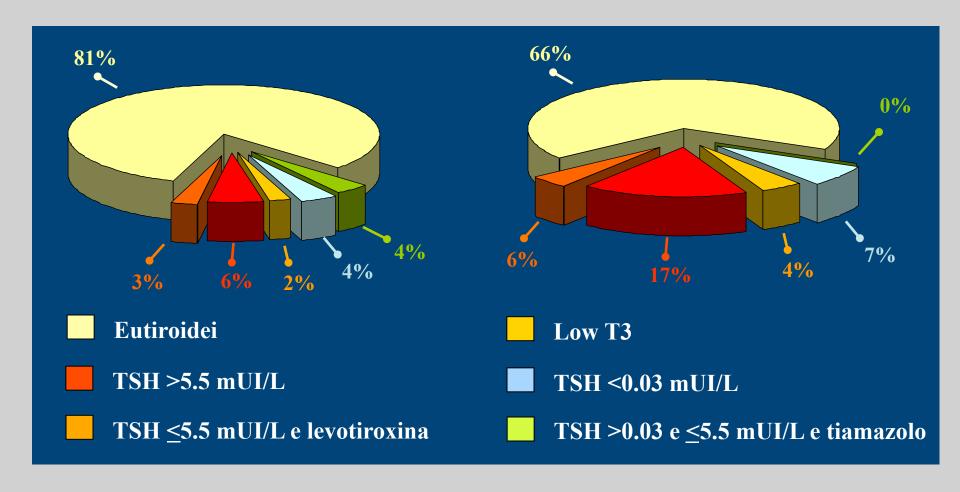


### Popolazione senza amiodarone

N: 222, NYHA 2.2±0.5, LVEF 34±9

### Popolazione con amiodarone

N: 116, NYHA 2.5±0.5†, LVEF 28±8†

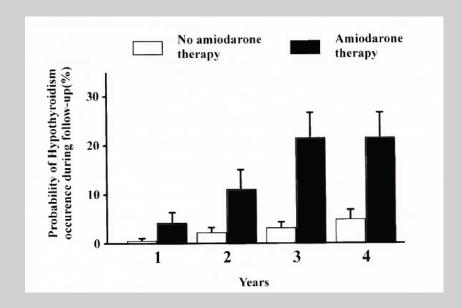


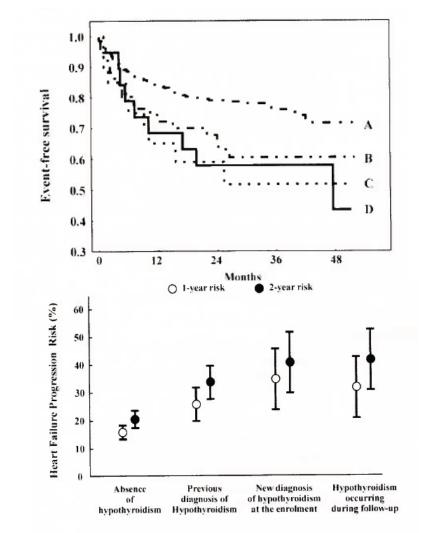






Bari.





A: Absence of hypothyroidism

B: Previous diagnosis of hypothyroidism

C: Diagnosis of hypothyroidism at the enrollment

D: Hypothyroidism during follow-up



p Value

0.54\* 0.04† 0.07† 0.23‡ 0.55‡



	Normal EF (n = 57)	Impaired EF (n :	= 26)
Duration of follow-up (months)	50 (19-78)	44 (16-78)	)
Primary composite end point (%)	28 (49)	19 (73)	
Death (%)	8 (14)	8 (31)	
Heart transplantation (%)	1 (2)	2 (8)	
Hospitalization for heart failure (%)	8 (14)	5 (19)	
Stroke (%)	2 (4)	3 (12)	Λ
Acute myocardial infarction (%)	2 (4)	1(4)	^
Hospitalization for arrhythmia management (%)	11 (19)	12 (46)	
Atrial fibrillation	5 (9)	2 (8)	
Ventricular fibrillation/tachycardia	2 (4)	8 (31)	0
Implantation of defibrillator device	1 (2)	6 (23)	=
Pacemaker implantation	4 (7)	3 (12)	ΪVΒ
Hospitalization for treatment complication	3 (5)	0	surviva

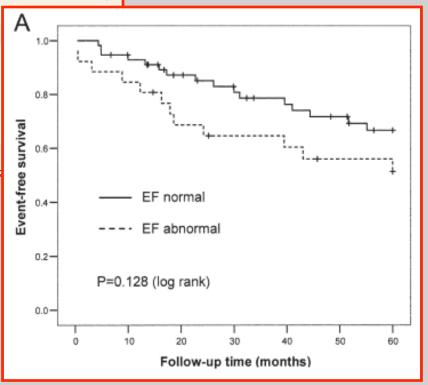






Table 1. Amiodarone Monitoring and Recommendations Monitoring System Baseline Follow-up Possible Adverse Effect Recommendation ECG (at baseline and Yearly Cardiac QT prolongation; torsade Reduce amiodarone dose during loading dose) or discontinue use de pointes Symptomatic sinoatrial Reduce amiodarone dose or conduction system or discontinue use impairment Dermatologic Physical examination As needed for Photosensitivity to UV light Avoid sunlight; use sunscreen signs/symptoms Blue-gray skin discolor Heduce amicoaron or discontinue use Endocrine Thyroid function tests Every 6 mo Hyperthyroidism Discontinue amiodarone; refer to endocrinologist Hypothyroidism Treat with levothyroxine upper limit of reference range or discontinue use Reduce amicde Neurologic Physical examination As needed for See "Evidence Syntnesis or discontinue use signs/symptoms Ophthalmologic Eve examination As needed for Corneal microdeposits Continue amiodarone signs/symptoms treatment Optic neuropathy Discontinue treatment Pulmonary Pulmonary function tests As needed for Pulmonary toxicity (cough, Discontinue amiodarone signs/symptoms fever, dyspnea) immediately; consider corticosteroid treatment Chest radiograph Yearly

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram.





## Tireotossicosi indotta dall' amiodarone

	Tipo I	Tipo II
Gozzo / Ab antitiroidei	Spesso presente	Solitamente assente
Captazione Iodio radioattivo	Basso/normale/aumentato	Basso/soppresso
Livelli Il6	Lievemente aumentato	Marcatamente aumentato
Color Doppler tiroide	I-III	0
Risposta tionamidi	Sì	No
Risposta perclorato	Sì	No
Risposta cortisonici	Probailmente no	Sì
Conseguente ipotiroidismo	No	Possibile



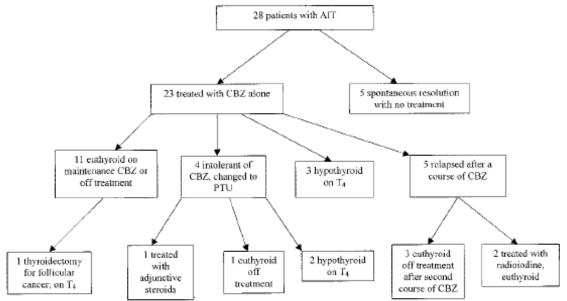


## Sospendere l'amiodarone?

### Successful Treatment of Amiodarone-Induced Thyrotoxicosis

Faizel Osman, MB, MRCP; Jayne A. Franklyn, MD, PhD, FRCP; Michael C. Sheppard, PhD, FRCP; Michael D. Gammage, MD, FRCP

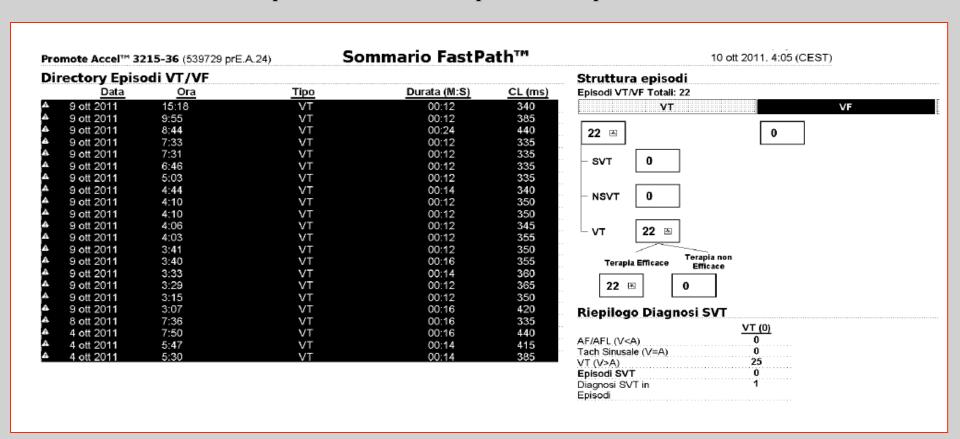
Conclusions—Continuing amiodarone has no adverse influence on response to treatment of AIT. First-line therapy with a thionamide alone is appropriate in iodine-replete areas, thus avoiding potential complications of other drugs. Differentiating between 2 possible types of AIT does not influence management or outcome. (Circulation, 2002;105: 1275-1277.)







Sig. B.F. 71 aa. 27.11.2013 Dimissione da ricovero ordinario per TV recidivanti ed ipertiroidismo iatrogeno in cardiomiopatia dilatativa non ischemica (FEVS 35-40%), già sottoposta ad ablazione di TV. Ecografia tiroidea compatibile con ipertiroidismo tipo 2. Terapia alla dimissione: Tapazole 1 compressa b.i.d.







Ricoveri	Data	FEVS	NT-proBNP	fT3	fT4	TSH	Tp/Procedure
Ingresso	14/09/2011	35-40%	884.3	6.66	3.61	<0.01	Sospende Amiodarone inizia Tapazole
Dimissione	27/09/2011	20 10,0	237.9				•
Ingresso Dimissione	17/10/2011 22/12/2011	35%	2443.1 1125.0	7.66	4.35	<0.01	Durante degenza raggiungimento eutiroidismo Insorgenza di ipotiroidismo
Ingresso	24/12/2011	30%	925.0	2.33	1.28	22.3	Riduzione
Dimissione	21/01/2012	30%	923.0	2.50	1.18	19.39	tapazole
Ingresso Dimissione	22/01/2012 04/02/2012	-	-	-	-	-	Ablazione TV
Ingresso Dimissione	17/02/2011 23/02/2011	27%	650.0	2.92	1.05	17.6	Ottimizzazione tp con sotalolo e mexiletina



# Disfunzione tiroidea e scompenso cardiaco: il punto di vista del cardiologo



### Conclusioni

- Le alterazioni della funzione tiroidea rappresentano sicuramente una condizione favorente l'insorgenza e la instabilizzazione dello scompenso cardiaco
- Al momento l'approccio terapeutico più favorevole per il trattamento sia dell'ipoche dell'ipertiroidismo non è basato su evidenze di studi clinici randomizzati
- Ciò è ancora più rilevante se si considera che l'amiodarone rimane un farmaco insostituibile per il trattamento delle aritmie in presenza di scompenso cardiaco e che tale farmaco è fortemente associato all'insorgenza di anomalie della funzione tiroidea
- Rimane infine irrisolto l'approccio alla sindrome del T3 basso che è sicuramente associato ad una prognosi infausta ma non è chiaro se sia marcatore o mediatore di prognosi





### **Special issue:**

## Relevance of Endocrine and Metabolic Disorders in Heart Failure: From Pathophysiology to Therapeutic Approach

Endocrine, Metabolic & Immune Disorders - Drug Targets, 2013, Vol. 13,

•http://benthamscience.com/contents.php?in=108119&m=March&y=2013&id=ZnJlZQ==

Grazie per l'attenzione!!!!!