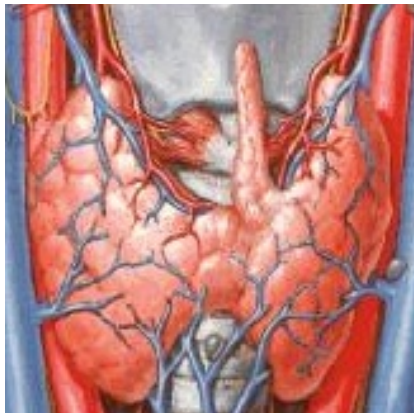
Roma,
9-11 novembre 2012

1^{0} CORSO NAZIONALE DI AGGIORNAMENTO AME
Roma 9-11 Novembre 2012

- **IPOTIROIDISMO E TERAPIA SOSTITUTIVA**
- **Sola T_4 o terapia in associazione?**

Fabrizio Monaco e Giorgio Napolitano
Sezione di Endocrinologia e Nefrologia
Università' "G. d'Annunzio" Chieti-Pescara

Produzione giornaliera degli ormoni tiroidei



Circolo ematico

T_4 ~ 80 μg* (100%)

T_4 ~80 μg

T_3 ~ 24 μg (80%)

T_3 ~ 6 μg* (20%)

T_3 ~30 μg

*Rapporto molare T_4:T_3 prodotte dalla tiroide = 14:1

British Medical Journal, 1970, **2**, 270–271

Combined Thyroxine and Triiodothyronine for Thyroid Replacement Therapy

SELWYN TAYLOR,* M.D., M.CH., F.R.C.S. ; M. KAPUR,† M.B., B.S., F.R.C.S. ; ROSS ADIE,‡ M.B., B.S., F.R.C.S.

It may be the experience of many clinicians, as it has been ours, that a very small group of patients with hypothyroidism are not entirely well on thyroxine replacement alone. It is particularly for these that we have found the T4/T3 tablet of value.

Controlled Clinical Trial of Combined Triiodothyronine and Thyroxine in the Treatment of Hypothyroidism

R. N. SMITH,* M.D., B.SC., M.R.C.P.ED. ; S. A. TAYLOR† ; J. C. MASSEY,‡ B.SC.

British Medical Journal, 1970, 4, 145-148

Numbers of patients recordings side effects during treatment		
Symptoms & signs	**T_3/T_4 Tablets**	**T_4 Tablets**
Palpitations	10 (7)	1 (0)
Irritability and nervousness	6 (6)	0
Dizziness	5 (4)	2 (0)
Tremor	4 (4)	0
Perspiration	3 (2)	1 (0)
Breathless	3 (2)	0
Loss of appetite	3 (3)	1 (0)
Headache	3 (1)	1 (0)
Indigestion	2 (2)	3 (0)
Oedema	1 (0)	0

*Numbers in parentheses indicate the N. of patients who rejected the tablets.

Controlled Clinical Trial of Combined Triiodothyronine and Thyroxine in the Treatment of Hypothyroidism

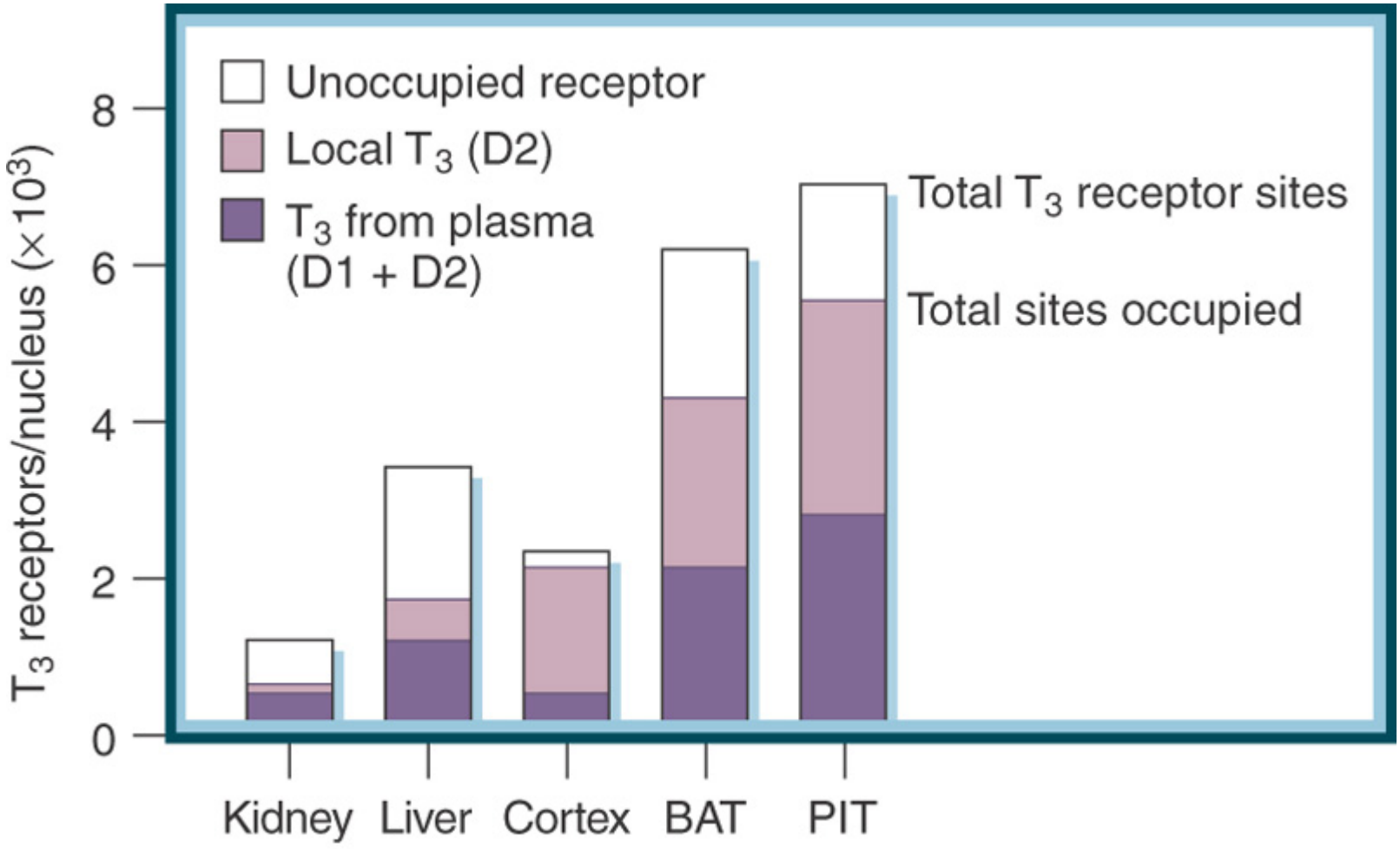
R. N. SMITH,* M.D., B.SC., M.R.C.P.ED. ; S. A. TAYLOR† ; J. C. MASSEY,‡ B.SC.

British Medical Journal, 1970, 4, 145-148

The shortcomings of combined therapy deduced from this study suggest that thyroxine has overall advantages for thyroid replacement therapy.

- **Studi sperimentali condotti nella seconda meta' degli anni '90 sui ratti, hanno rinnovato l'interesse sulla terapia combinata T_4/T_3**

ORIGINE DELLA T_3 INTRACELLULARE NEI DIVERSI TESSUTI DI RATTO



Williams' Textbook of Endocrinology 2012

Escobar-Morreale HF et al, Endocrinology 137: 2490-2502, 1996

Variazioni (rispetto ai controlli) dei livelli di T_4, T_3 nel plasma e nei tessuti in ratti tiroidectomizzati trattati con sola L-T_4 o L-T_4+L-T_3

	0.90 μg T_4					
	No T_3			0.15 μg T_3		
	T_4	T_3	TSH	T_4	T_3	TSH
Plasma	=	↓	↑	=	=	=[a]
Cerebral cortex	=	=	[a]	=	=	[a]
Pituitary	=	↓		=	=	
Cerebellum	=	↓		=	=	[a]
BAT	=	↓		=	=	
Liver	=	↓		=	=	[a]
Kidney	=	↓		=	=	[a]
Lung	=	↓		=	=	[a]
Heart	=	↓		=	=	[a]
Spleen	=	↓		=	=	
Muscle	=	↓		=	=	[a]
Adrenal	=	=	[a]	=	=	[a]
Ovary	=	↓		=	=	

……..the most effective treatment in restoring euthyroidism in thyroidectomized rats has been 0.9 μg T_4, plus 0.15 μg T_3/100 g BW/day, in which T_4, and T_3 are in a 5.0:1 molar ratio, similar to that present in the normal thyroidal secretion of the rat……

Escobar-Morreale HF et al, *Only the Combined Treatment with Thyroxine and Triiodothyronine Ensures Euthyroidism in All Tissues of the Thyroidectomized Rat,* **Endocrinology** 137: 2490-2502, 1996

Escobar-Morreale HF et al, *Only the Combined Treatment with Thyroxine and Triiodothyronine Ensures Euthyroidism in All Tissues of the Thyroidectomized Rat,* **Endocrinology** 137: 2490-2502, 1996

Combined replacement therapy with T_4 and T_3, (in proportions similar to those secreted by the normal rat thyroid) completely restored euthyroidism in thyroidectomized rats at much lower doses of T_4, than those needed to normalize T_3, in most tissues when T_4 alone was used.

If pertinent to man, these results might well justify a change in the current therapy for hypothyroidism.

EFFECTS OF THYROXINE AS COMPARED WITH THYROXINE PLUS TRIIODOTHYRONINE IN PATIENTS WITH HYPOTHYROIDISM

ROBERTAS BUNEVIČIUS, M.D., PH.D., GINTAUTAS KAŽANAVIČIUS, M.D., PH.D., RIMAS ŽALINKEVIČIUS, M.D., AND ARTHUR J. PRANGE, JR., M.D.

N Engl J Med 1999, 340: 424-429

- **Studio randomizzato, doppio cieco, incrociato, su 33 pazienti (16: terapia sostitutiva, 17: terapia soppressiva).**
- **I pazienti erano in terapia con L-T_4 da 73 ± 72 mesi: dose media 175±53 μg/die (range 100-300 μg/die).**
- **Terapia combinata per 5 settimane: sostituzione di una dose fissa di L-T_4 (50 μg/die) con una dose fissa di L-T_3 (12,5 μg/die) con un rapporto T_4:T_3 variabile da 4:1 a 20:1.**

TABLE 3. PSYCHOMETRIC FINDINGS AT THE END OF EACH TREATMENT PERIOD.*

TEST OR SCALE	AFTER THYROXINE (N=33)	AFTER THYROXINE PLUS TRIIODOTHYRONINE (N=33)	P VALUE†	NORMAL VALUE
Cognitive performance				
Digit Symbol Test				
Pairs recalled correctly	5.5±2.3	6.3±2.1	0.04	>6
Time (sec)	58±15	56±16	0.07	—
Raw score	48±12	47±12	0.76	>43
Digit Span Test				
Backward recall of digits	5.5±1.6	6.0±1.3	0.05	>5
Forward recall of digits	6.9±1.9	6.9±1.8	0.99	>5
Visual Scanning Test				
Time (sec)	75±23	71±25	0.15	<120
Total correct	58±2	59±2	0.53	>56
Errors	1.7±1.8	1.5±2.1	0.58	<3
Mood scores				
Beck Depression Inventory	9.8±7.7	7.9±5.3	0.10	<11
Spielberger State–Trait Anxiety Inventory	44±11	45±8	0.38	<50
Profile of Mood States				
Global score	33±28	24±24	0.01	—
Fatigue–inertia	9.3±4.3	7.2±3.9	0.001	<18
Depression–dejection	13.4±9.5	10.5±8.9	0.01	<26
Anger–hostility	9.1±7.3	7.3±5.2	0.04	<17
Confusion–bewilderment	5.3±4.5	4.3±3.5	0.13	<17
Tension–anxiety	8.5±5.3	7.7±5.4	0.23	<21
Vigor–activity	12.4±4.6	13.0±3.7	0.39	>9

Bunevicius R et al, N Engl J Med 1999, 340: 424-429

TABLE 4. RESULTS ON VISUAL-ANALOGUE SCALES AT THE END OF EACH TREATMENT PERIOD.*

SCALE	AFTER THYROXINE (N=33)	AFTER THYROXINE PLUS TRIIODOTHYRONINE (N=33)	P VALUE†
Mood			
Sad	40±24	26±19	<0.001
Confused	34±24	23±20	<0.001
Fearful	30±29	20±22	0.001
Irritable	39±28	27±22	0.002
Tense	42±29	28±23	0.007
Angry	32±28	25±20	0.02
Tired	49±26	39±28	0.04
Agitated	39±30	34±26	0.18
Physical symptoms			
Feel cold	37±27	23±24	0.004
Blurred vision	30±29	22±27	0.01
Nauseated	22±23	13±17	0.02
Sleepy	39±29	29±27	0.09
Light-headed	35±26	31±28	0.22
Drowsy	36±27	31±25	0.29
Feel hot	24±21	25±27	0.80

Bunevicius R et al, N Engl J Med 1999, 340: 424-429

TABLE 2. BIOCHEMICAL AND PHYSIOLOGIC VALUES AT THE END OF EACH TREATMENT PERIOD.*

VALUE†	AFTER THYROXINE (N=33)	AFTER THYROXINE PLUS TRIIODOTHYRONINE (N=33)	P VALUE‡	NORMAL RANGE
Serum thyrotropin (μU/ml)	0.8±2.5	0.5±1.1	0.56	0.3–5.0
No. of patients with undetectable serum thyrotropin (<0.05 μU/ml)	7	5	—	—
Serum free thyroxine (ng/dl)	2.3±0.7	1.8±0.6	<0.001	0.7–2.1
Serum total thyroxine (μg/dl)	15.2±3.8	11.3±3.3	<0.001	4–11
Serum total triiodothyronine (ng/dl)	87±38	117±42	<0.001	75–175
Serum triglycerides (mg/dl)	129±54	132±55	0.76	47–228
Serum cholesterol (mg/dl)	219±46	217±43	0.66	152–268
Serum sex hormone–binding globulin (μg/dl)	2.6±1.3	3.1±1.5	0.007	0.4–3.5
Pulse rate at rest (beats/min)	69±11	72±12	0.04	—
Blood pressure while seated (mm Hg)				
Systolic	130±21	124±18	0.18	—
Diastolic	79±12	77±14	0.52	—

Bunevicius R et al, N Engl J Med 1999, 340: 424-429

Combined Thyroxine/Liothyronine Treatment Does Not Improve Well-Being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomized Controlled Trial in Patients with Primary Hypothyroidism

JOHN P. WALSH, LAUREN SHIELS, EE MUN LIM, CHOTOO I. BHAGAT, LYNLEY C. WARD, BRONWYN G. A. STUCKEY, SATVINDER S. DHALIWAL, GERARD T. CHEW, MINOTI C. BHAGAT, AND ANDREA J. CUSSONS

J Clin Endocrinol Metab 88: 4543–4550, 2003

- **Studio randomizzato, doppio cieco, incrociato, su 110 pazienti in terapia sostitutiva.**
- **I pazienti erano in terapia con L-T_4 da 8 ± 8,3 anni: dose media 136±36 μg/die.**
- **Terapia combinata per 10 settimane: sostituzione di una dose fissa di L-T_4 (50 μg/die) con una dose fissa di L-T_3 (10 μg/die) con un rapporto T_4:T_3 variabile da 5:1 a 15:1.**

SELF-ADMINISTERED QUESTIONNAIRES

Questionnaire	T_4 Alone	Combined T_3/T_4	
Short Form 36 (SF-36)	NO SIGNIFICANT DIFFERENCE		
General Health Questionnaire 28 (GHQ-28) *			
Total	18.3 ± 1	21.2 ± 1	p<0.033
Social dysfunction	6.7 ± 0.3	7.7 ± 0.3	p<0.028
Thyroid symptom questionnaire (TSQ) *			
Anxiety	24.9 ± 1.8	30.7 ± 1.8	p<0.026
Sickness/nausea	12.8 ± 1.6	17.4 ± 1.6	p<0.049
Others questions	NO SIGNIFICANT DIFFERENCE		

* Higher scores indicate worse psychological wellbeing

Walsh JP R et al, J Clin Endocrinol Metab 2003, 88: 4543

TABLE 3. Cognitive function test scores (mean ± SEM) for all subjects at the end of each treatment

	Thyroxine alone	Combined thyroxine/T_3	*P* value
Symbol digit modalities test	56.2 ± 0.3	56.4 ± 0.4	0.72
Trail making test			
Part A (s)	24.7 ± 0.4	25.5 ± 0.4	0.18
Part B (s)	61.4 ± 1.5	61.9 ± 1.5	0.80
Digit span test			
Forward	8.5 ± 0.1	8.5 ± 0.1	0.99
Backward	7.0 ± 0.1	6.9 ± 0.1	0.74

Walsh JP R et al, J Clin Endocrinol Metab 2003, 88: 4543

SIGNIFICANT CHANGES IN CLINICAL AND BIOCHEMICAL PARAMETERS

Parameters	T_4 Alone	Combined T_3/T_4	
Pulse rate (beats/min)	68.8 ± 0.5	67.3 ± 0.5	p<0.001
Zulewski score	3.5 ± 0.1	3.9 ± 0.1	p<0.001
Serum TSH (mU/L)	1.5 ± 0.2	3.1 ± 0.2	p<0.001
Serum FT_4 (pmol/L)	15.6 ± 0.2	11.4 ± 0.2	p<0.001
Serum SHBG (nmol/L)	49.4 ± 1.0	45.5 ± 1.0	p<0.01
Plasma Cholesterol (nmol/L)	5.1 ± 0.04	5.2 ± 0.04	p<0.015

Walsh JP R et al, J Clin Endocrinol Metab 2003, 88: 4543

SINOSSI DEI PRINCIPALI STUDI EFFETTUATI DAL 2003 AL 2005

Autore	N. paz.	Studio	$T_4 \rightarrow T_3$ $T_4 : T_3$	Efficacia terapia combinata
Clyde 2003	44	Randomizzato controllato	50μg →15μg 5,4:1	NO
Sawka 2003	40	Randomizzato controllato	50%→12,5μg 3–5:1	NO
Siegmund 2004	36	Randomizzato incrociato	5%→T_3* 19:1	NO
Rodriguez 2005	30	Randomizzato incrociato	50μg →10μg 7:1	NO
Escobar-Morreale 2005	28	Randomizzato incrociato	25μg →3μg 15:1	NO
Saravanan 2005	697	Randomizzato controllato	50μg →10μg 7,7:1	NO
Appelhof 2005	141	Randomizzato controllato	25μg →T_3** 10:1 o 5:1	NO

$T_4 \rightarrow T_3$ = dose di T_4 rimpiazzata da T_3; $T_4:T_3$ rapporto tra le dosi (in peso)

*dose variabile di T_3 in sostituzione del 5% della dose di T_4

**dose variabile di T_3 per ottenere un $T_4:T_3$ di 10:1 o 5:1

The Journal of Clinical Endocrinology & Metabolism 91(7):2592–2599

Thyroxine-Triiodothyronine Combination Therapy *Versus* Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials

Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman, and Leonard Leibovici

"No difference was found in the effectiveness of combination vs. monotherapy in any of the following symptoms: bodily pain, depression, anxiety, fatigue, quality of life, body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high density lipoprotein. Adverse events did not differ between regimens."

The Journal of Clinical Endocrinology & Metabolism 91(7):2592–2599

Thyroxine-Triiodothyronine Combination Therapy *Versus* Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials

Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman, and Leonard Leibovici

"Given the conclusive evidence, **monotherapy with T_4 should remain the standard treatment for hypothyroidism.** It is doubtful whether further trials evaluating combination therapy are needed because the chances that the accumulated evidence will change are low."

European Journal of Endocrinology (2009) **161** 895–902

Effect of combination therapy with thyroxine (T_4) and 3,5,3′-triiodothyronine versus T_4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study

Birte Nygaard, Ebbe Winther Jensen, Jan Kvetny[1], Anne Jarløv[2] and Jens Faber

- Studio randomizzato, doppio cieco, incrociato, su 59 pazienti con ipotiroidismo primario autoimmune.

- I pazienti erano in terapia con L-T_4 da almeno 6 mesi: dose media 129±29 μg/die.

- Terapia combinata per 12 settimane: sostituzione di una dose fissa di L-T_4 (50 μg/die) con una dose fissa di L-T_3 (20 μg/die) con un rapporto T_4/T_3 variabile da 2,5:1 a 8:1 (media= 4:1).

Table 1 Changes in scores of quality of life (QOL) and psychological well-being

	On T_4 mono-therapy	On T_4/T_3 combinatior therapy	T_4 treatment versus T_3/T_4 combination therapy (*P* value)
BDI	7.6+0.8	5.7+0.7	**0.01***
General health	66+2.9	72+2.6	**0.02***
Social functioning	85+2.6	90+1.8	**0.07**
Mental health	76+2.0	80+1.7	**0.04**
Vitality	59+3.1	65+2.7	**0.02***
Somatisation	0.77+0.08	0.68+0.09	**0.12**
Interpersonal sensitivity	0.53+0.07	0.43+0.06	**0.12**
Depression	0.75+0.09	0.57+0.08	**0.01***
Anxiety	0.49+0.06	0.35+0.06	**0.01***
GSI	0.56+0.06	0.45+0.06	**0.01***
PST	1.42+0.05	1.29+0.07	**0.02***
Calculated significance level (FDR thresholds (14))*			**0.032**

Nygaard B et al, Eur J Endocrinol 2009, 161: 895-902

Table 4. Preference of patients in RCTs comparing T4 monotherapy with T4+T3 combination therapy in cross-over or parallel study designs

Author	n	Preference T4 monotherapy	Preference none	Preference T4+T3 therapy	p value
Crossover studies					
Walsh et al. [41]	100	46	18	36	0.32
Nygaard et al. [5]	59	9	21	29	0.002
Bunevicius et al. [44]	33	2	11	20	0.001
Escobar-Morreale et al. [46]	26	2	6	18*	0.015
Bunevicius et al. [48]	10	2	2	6	–
Total	228 (100%)	61 (27%)	58 (25%)	109 (48%)	
Parallel study					
Appelhof et al. [40]	140	14/48(29%)		43/92(47%)	0.024

* Including 6 patients who preferred the combination of 87.5 μg L-T4 + 7.5 μg L-T3 for a final 8-week add-on regimen that was not randomized.

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T_4 + L-T_3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T_4 + L-T_3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

Recommendations

- **There is insufficient evidence that L-T_4 + L-T_3 combination therapy serves the hypothyroid patient better than T_4 monotherapy.**

- ***It is recommended that L-T_4 monotherapy remains the standard treatment of hypothyroidism.***

ETA Guidelines, Eur Thyroid J 2012;1:55–71

Could It Be that Trials Comparing L-T_4+L-T_3 Combination Therapy and L-T_4 Monotherapy Have Not Targeted the Right Population?

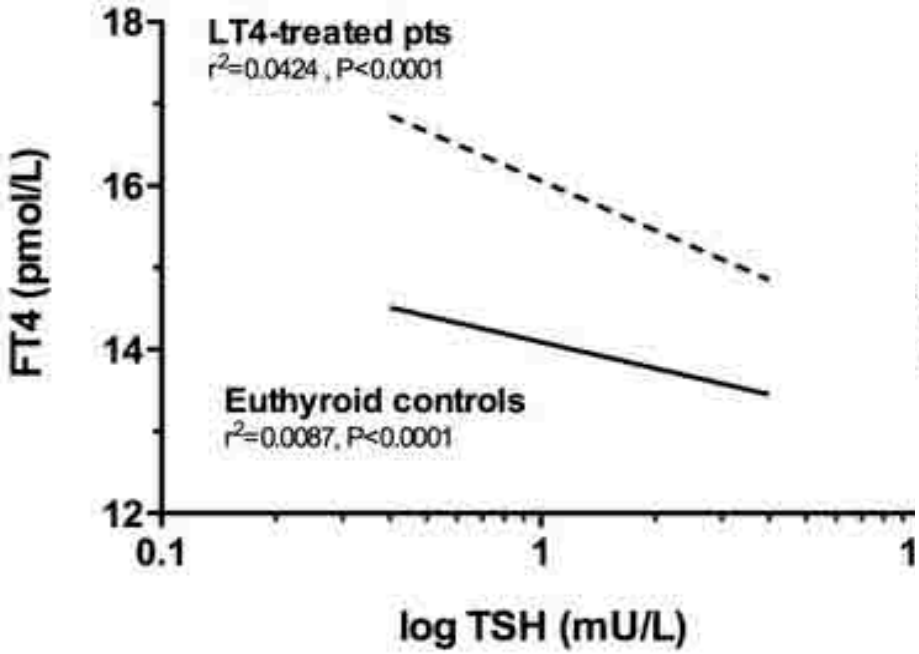
Who Could Benefit from Combination Therapy?

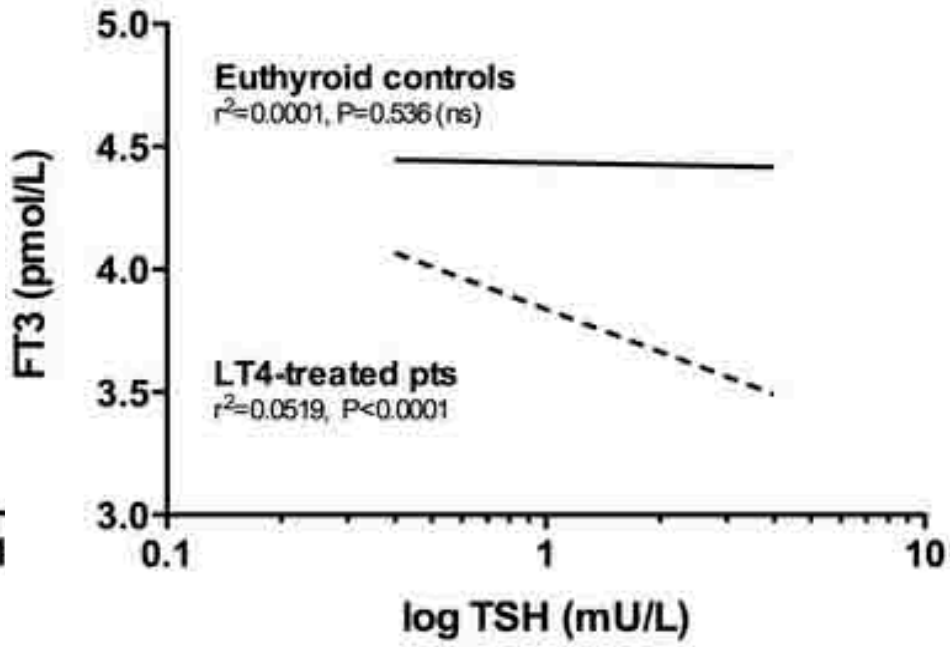
…no differences were observed in cognitive function, mood, psychological symptoms, quality of life, or thyroid disease-related symptoms in the majority of these studies

2) Thyroidectomized patients or patients submitted to radioiodine activities resulting in a lack of sufficient endogenous thyroid function and absence of residual thyroidal T3 production;

Biondi B, Wartofsky L. J Clin Endocrinol Metab, 2012, 97:2256–2271.

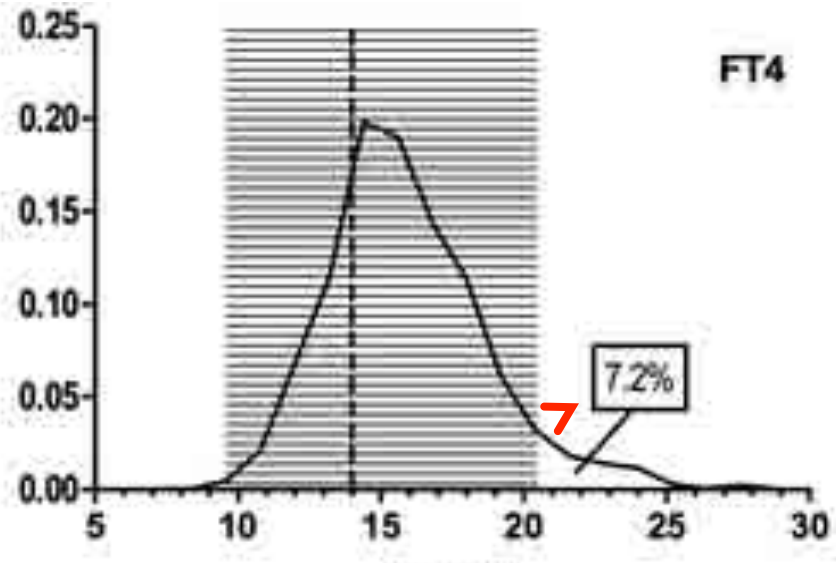
Correlation between TSH and free thyroid hormones in euthyroid controls and in athyreotic patients.

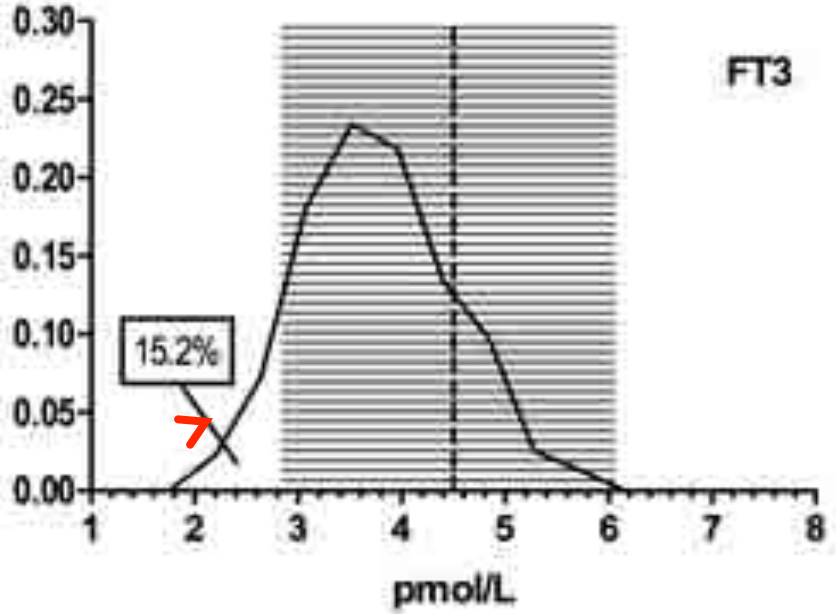




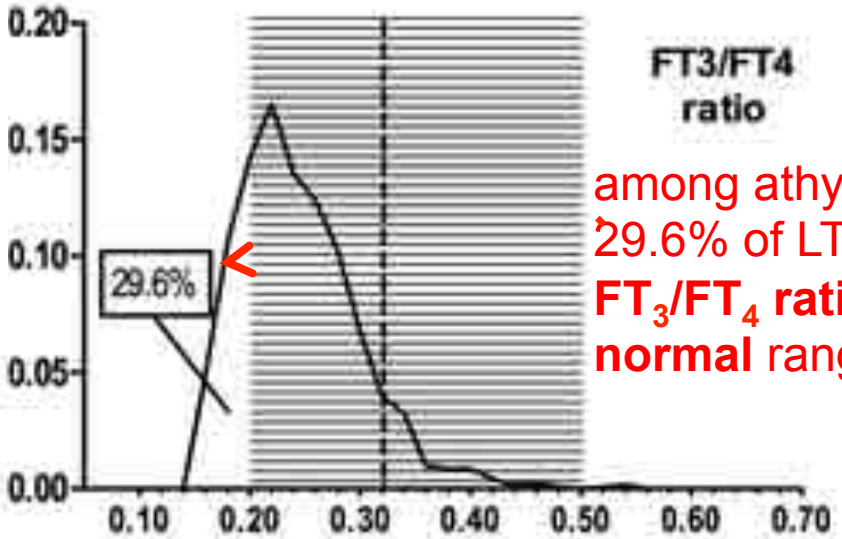
Gullo D et al PLoS ONE 2011, 6: e22552.

FT_4, FT_3 AND FT_3/FT_4 RATIO FREQUENCY DISTRIBUTION IN ATHYREOTIC PATIENTS TREATED WITH L-T_4





Among athyreotic patients despite normal TSH
7.2% had FT4 higher than normal range
And **15.2%** had **FT3 levels lower** than the normal range



among athyreotic patients 29.6% of LT_4 treated Pts had **FT_3/FT_4 ratios lower han normal** range

Gullo D et al PLoS ONE 2011, 6: e22552.

Conclusions

Gullo D et al PLoS ONE 2011, 6: e22552.

Athyreotic patients have a highly heterogeneous T_3 production capacity from orally administered levothyroxine.

More than 20% of these patients, despite normal TSH levels, do not maintain FT_3 or FT_4 values in the reference range, reflecting the inadequacy of peripheral deiodination to compensate for the absent T_3 secretion.

A more physiological treatment than L-Thyroxine monotherapy may be required in some hypothyroid patients

TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodo-thyronine levels in patients who have undergone total thyroidectomy

- The mean serum TSH of a normal population is 1.4 to 1.6 mU/L, with the range from 0.4 to 3 or 4 mU/L.

- In athyreotic Pts treated mono T_4, FT_3 levels are equal to those before operation only if serum TSH is between 0.03 and 0.3 mU/L.

- This stresses that the adequacy of thyroxine treatment is different if it is based on serum TSH or on peripheral parameters of thyroid hormones.

Ito M, Miyauchi et Al.Eur J Endocrinol, June 18, 2012

Who Could Benefit from Combination Therapy?

…no differences were observed in cognitive function, mood, psychological symptoms, quality of life, or thyroid disease-related symptoms in the majority of these studies

higher serum T4 levels are necessary in thyroidectomized patients to obtain normal serum T3 concentrations and thereby compensate for the absence of the 20% fraction of circulating T3 normally directly secreted by the thyroid

3) patients with certain D2 polymorphisms (the enzyme responsible for T3 tissue availability) who tend to have a preference for combination T4/T3 replacement therapy;

Biondi B, Wartofsky L. J Clin Endocrinol Metab, 2012, 97:2256–2271.

The three deiodinase enzymes [deiodinase type 1 (D1), D2, and D3] play a vital role in maintaining euthyroidism both at a serum and local tissue level.

- D1 and D2 are activating enzymes and convert T_4 to T_3 by outer ring deiodination.

- D1 is found in liver, kidney, thyroid, and pituitary in humans, and D2 in skeletal muscle, central nervous system, pituitary, thyroid, heart, and brown adipose tissue.

- Predictions based on isolated cell deiodinase activity and reported tissue activities in humans suggest that both are responsible for maintaining serum levels of T_3, although D2 predominates in hypothyroidism and D1 in hyperthyroidism .

- D3 inactivates thyroid hormones by inner ring deiodination, converting T_3 to T_2 and T_4 to rT_3.

Common Variation in the *DIO2* Gene Predicts Baseline Psychological Well-Being and Response to Combination Thyroxine Plus Triiodothyronine Therapy in Hypothyroid Patients

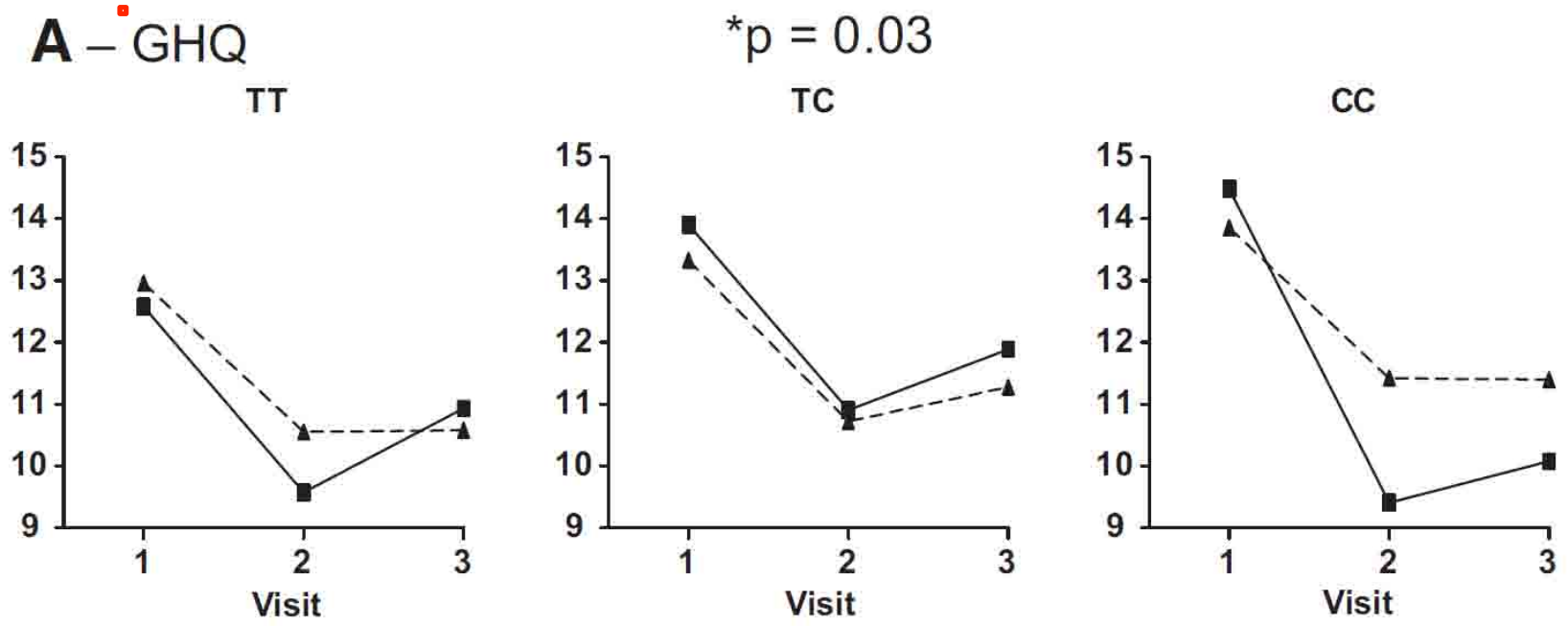
Vijay Panicker, Ponnusamy Saravanan, Bijay Vaidya, Jonathan Evans, Andrew T. Hattersley, Timothy M. Frayling, and Colin M. Dayan

J Clin Endocrinol Metab 2009, 94: 1623-1629

TABLE 3. Genotype of rs225014 and all psychological parameters at baseline

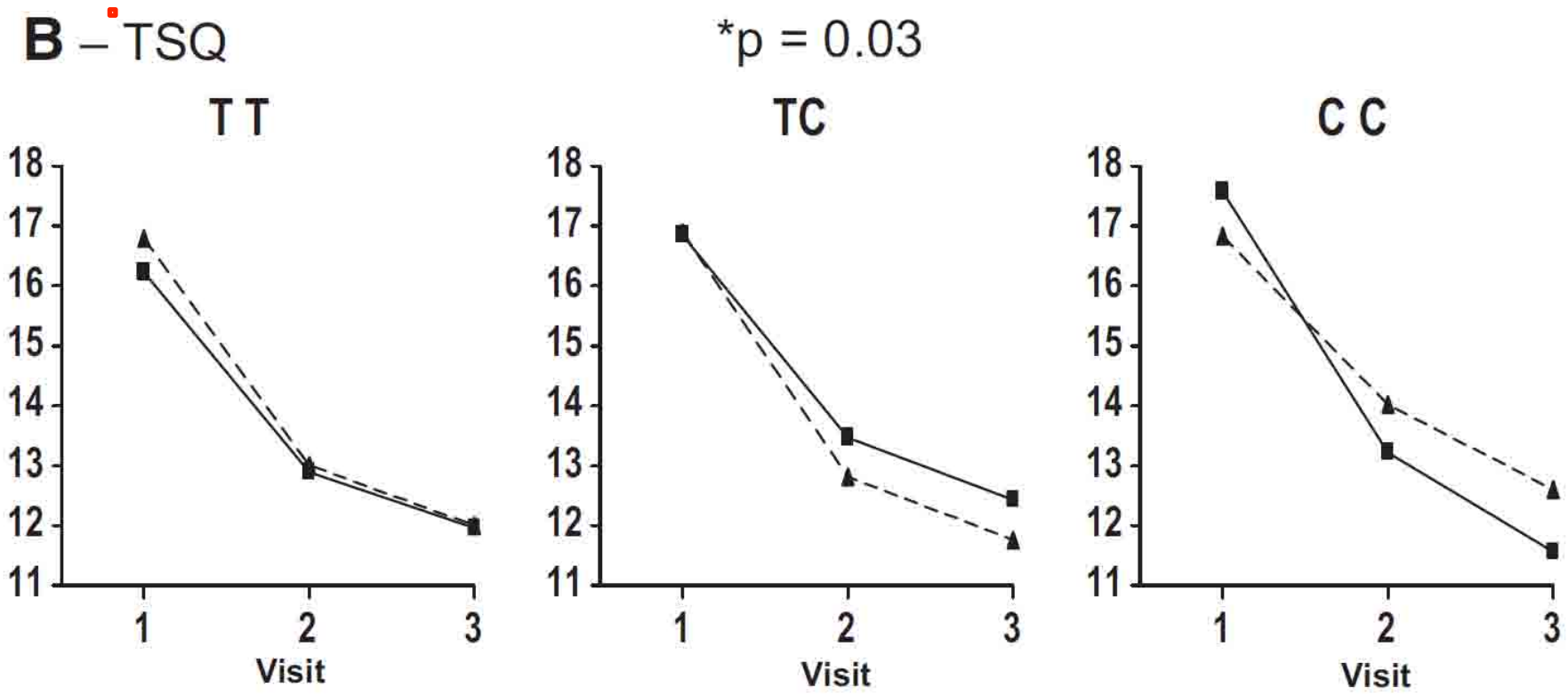
	Common homozygous (TT)		Heterozygous (TC)		Minor homozygous (CC)		
	n	Mean (95% CI) or percent of cases	n	Mean (95% CI) or percent of cases	n	Mean (95% CI) or percent of cases	*P*
GHQ Likert score	223	12.8 (12.2, 13.4)	236	13.6 (13.0, 14.3)	87	14.1 (12.8, 15.5)	0.02
GHQ case	217	39.2%	235	43.8%	86	46.5%	0.20
HAD-D case	223	13.0%	236	20.8%	87	24.1%	0.01
HAD-A case	223	40.4%	236	46.6%	87	48.3%	0.14
TSQ Likert score	216	16.5 (15.9, 17.1)	231	16.9 (16.3, 17.4)	83	17.2 (16.2, 18.1)	0.23
TSQ case	216	62.0%	231	62.3%	83	66.3%	0.56

RISPOSTA ALLA TERAPIA DEI PAZIENTI CON DIVERSO GENOTIPO rs225014 (TT; TC; CC)



Panicker V et al, J Clin Endocrinol Metab 2009, 94: 1623-1629

RISPOSTA ALLA TERAPIA DEI PAZIENTI CON DIVERSO GENOTIPO rs225014 (TT; TC; CC)



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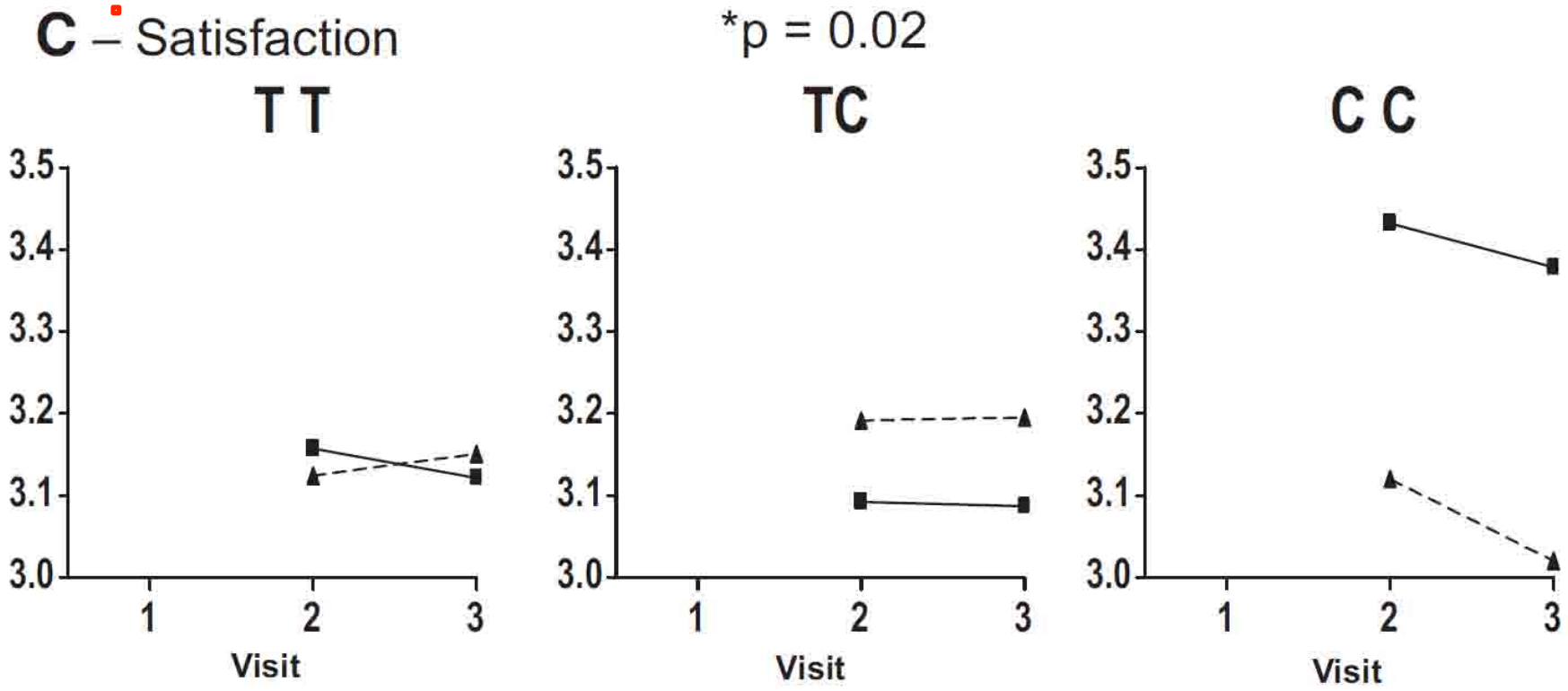
RISPOSTA ALLA TERAPIA DEI PAZIENTI CON DIVERSO GENOTIPO rs225014 (TT; TC; CC)



Panicker V et al, J Clin Endocrinol Metab 2009, 94: 1623-1629

Results: The rarer CC genotype of the rs225014 single-nucleotide polymorphisms (SNPs) in the deiodinase 2 gene (DIO2) was present in 16% of the study population…..
This polymorphism had no impact on circulating thyroid hormone levels.

CONCLUSIONS:

Our results require replication but suggest that commonly inherited variation in the DIO2 gene is associated with impaired baseline psychological well-being on T_4 and enhanced response to combination T_4/T_3 therapy, but did not affect serum thyroid hormone levels.

Panicker V et al, J Clin Endocrinol Metab 2009, 94: 1623-1629

Who Could Benefit from Combination Therapy?

…no differences were observed in cognitive function, mood, psychological symptoms, quality of life, or thyroid disease-related symptoms in the majority of these studies

higher serum T4 levels are necessary in thyroidectomized patients to obtain normal serum T3 concentrations and thereby compensate for the absence of the 20% fraction of circulating T3 normally directly secreted by the thyroid

….there may be a small number of patients with a D2 polymorphism that could benefit from combination therapy… Prospective trials will be necessary to further evaluate the neuropsychiatric response to combined T4/T3 treatment *vs.* monotherapy with L-T4 in patients with the Thr92Ala polymorphism.

4) depressed hypothyroid patients who might benefit from the antidepressant effect of liothyronine.

Biondi B, Wartofsky L. J Clin Endocrinol Metab, 2012, 97:2256–2271.

Does a Combination Regimen of Thyroxine (T4) and 3,5,3-Triiodothyronine Improve Depressive Symptoms Better Than T4 Alone in Patients with Hypothyroidism? Results of a Double-Blind, Randomized, Controlled Trial

In conclusion, our data do not support the routine use of T3 in addition to T4 to maintain euthyroidism in hypothyroid patients who are receiving stable doses of levothyroxine hormone, but who complain of depressive symptoms.

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…T3 in combination with tricyclic antidepressants compared with placebo in euthyroid patients with resistant depression. .. Double-blind placebo-controlled studies are needed to investigate the potential beneficial effects of combined T3 and T4 treatment

Patients who must not receive combination therapy

- **The offspring of mothers with serum T4 levels in the lowest 10th percentile of the reference range at the end of the first trimester have been reported to have subnormal intellectual development even if TSH levels are normal**

- **Based on these findings, desiccated thyroid and L-thyroxine/L-triiodothyronine combinations, which cause lowering of serum T4 levels, should not be used during pregnancy.**
  Furthermore, patients being treated with these preparations should be switched to L-thyroxine when planning to conceive and at the very latest when found to be pregnant.

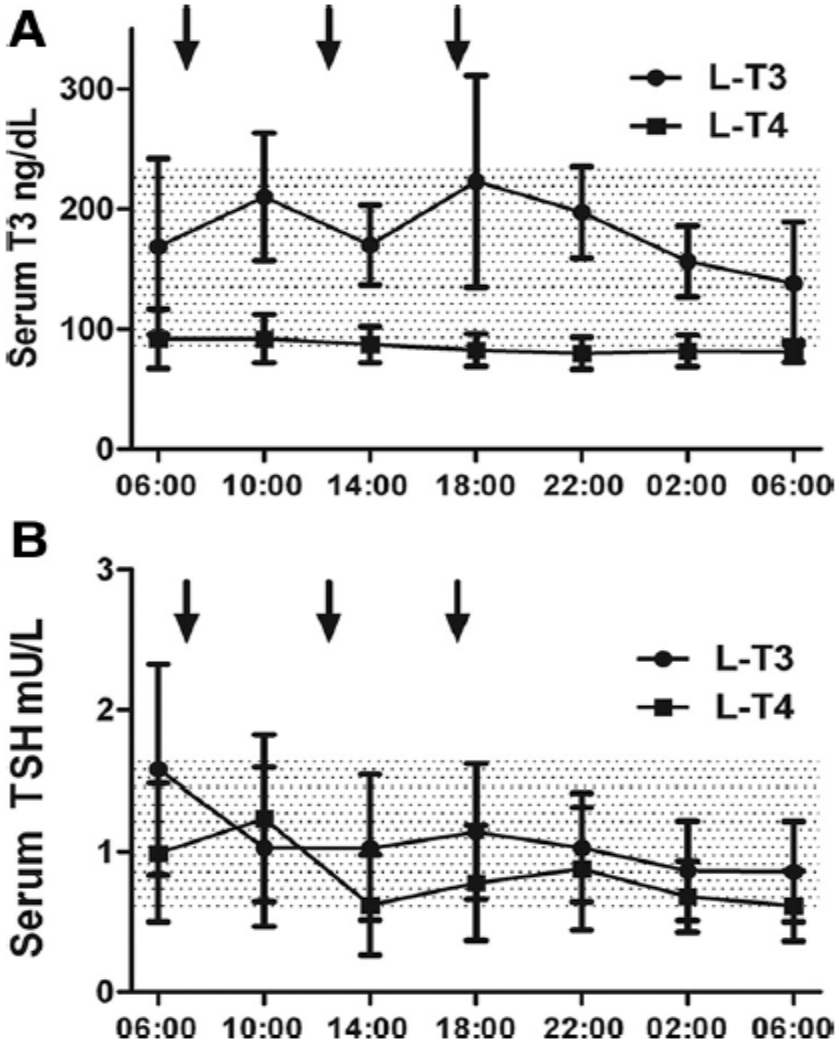
Garber JR, AACE, ATA guidelines for hypothyroidism, Thyroid 2012, 22

CONCLUSIONE 1
Mono T_4 vs combined therapy (T_4+T_3)

- **La maggior parte degli studi non evidenzia finora un vantaggio della terapia combinata T_4/T_3 rispetto alla monoterapia con T_4.**

- **Sono inoltre necessari ulteriori studi che utilizzino preparazioni a lento rilascio di T_3 con un ottimale rapporto T_3:T_4.**

Liothyronine *Versus* Levothyroxine



Celi FS, J Clin Endocrinol Metab, 2011, 96:3466–3474

Conclusione. 2.
Mono T_4 vs combined therapy (T_4+T_3)

- As **a clinician** I consider the small difference in serum T_3 levels as clinically insignificant and therefore **I routinely use L-thyroxine as the sole treatment for hypothyroidism**.
- **In a few** patients not satisfied with the treatment, rarely **I may add** 12.5 μg of T_3.

A.G Burger Clinical Thyroidology, 2012, 24

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

Start combination therapy in an L-T4/L-T3 dose ratio between 13: 1 and 20: 1 by weight

(L-T4 once daily, and the daily L-T3 dose in two doses)

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- L-T_4: its long half-life of 1 week is advantageous allowing one daily dose and it generates stable T_3 levels by conversion of T_4 into T_3 in peripheral tissues. In contrast, the half-life of T_3 is short (about 1 day), and treatment with L-T_3 would require several doses per day with wide variation in serum T_3 levels along the 24-hour period.
- Elevated serum T_3 concentrations may occur during
- the absorption of L-T_3 which can be associated with
- symptoms of tachycardia and nervousness.

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

many practising physicians have the experience that some of their hypothyroid patients have persistent complaints, despite adequate treatment with L-T4 as evident from normalization of TSH, free T4 and T3 concentrations. The creation of special interest groups like that of ‘Hypo but not Happy’

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- **Table 1.** Possible causes of persistent complaints in L-T_4-treated hypothyroid patients
- I. Nonspecific causes: related to the chronic nature of the disease
- II. Specific causes: related to thyroid disease and thyroid hormone replacement
- 1. Associated autoimmune diseases
- 2. Thyroid autoimmunity per se
- 3. Inadequacy of L-T_4 dose
- 4. Inadequacy of L-T_4 treatment modality

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- **Table 3.** Ratios of serum FT4 to FT3 concentrations (both in pmol/l) in L-T4-treated hypothyroid patients at baseline, and after completing study medication with either T4 or T4+T3

Author	Baseline	T4mono	T4+T3combination
Saravanan et al.	5.5	5.5	3.9
Walsh et al.	4.5	4.2	3.3
Sawka et al.	3.9	4.0	2.2
Escobar-Morreale et al.	4.1	4.1	3.4
Siegmund et al.	4.3	4.6	4.0
Mean FT4:FT3 ratio	4.3	4.5	3.4

Table 5. Relation between polymorphism rs2235544 in *DIO1* and thyroid function in hypothyroid patients on L-T4 replacement (derived from Panicker et al. [57], with modifications)

Genotype	AA	AC	CC	p value for trend
FT4, pmol/l	21.7	21.1	20.4	0.007
FT3, pmol/l	3.75	3.88	3.91	0.092
FT4/FT3 ratio	5.79	5.44	5.22	0.001
TSH, mU/l	0.9	0.65	0.67	NS

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- Recommendations
- (1) In L-T4-treated hypothyroid patients with normal serum TSH values, psychological distress, impaired wellbeing and cognitive disturbances occur more often than in controls (1/+00).
- (2) Data suggest that 5–10% of L-T4-treated hypothyroid patients with normal serum TSH have persistent symptoms which
- (3) Suggested explanations for persistent symptoms in L-T4-treated hypothyroid patients despite normalization of serum TSH, include: awareness of a chronic disease, presence of associated autoimmune diseases, thyroid autoimmunity
- per se (independent of thyroid function),and inadequacy of L-T4 treatment to restore physiological T4 and T3 concentrations in serum and tissues (2/+00).

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- no difference in the effectiveness of combination versus monotherapy in any of the following items:
- bodily pain (standardized mean difference SMD 0.00, 95% CI –0.34, 0.35), depression (SMD 0.07, 95% CI –0.20, 0.34), anxiety (SMD 0.00, 95% CI –0.12, 0.11), fatigue (SMD –0.12, 95% CI –0.33, 0.09), quality of life (SMD 0.03, 95% CI –0.09, 0.15), body weight, total serum cholesterol, triglycerides, low-density lipoprotein, and highdensity lipoprotein. Adverse events did not differ between
- regimens (RR 1.19, 95% CI 0.63, 2.24). The authors of the meta-analysis concluded: ‘It is doubtful whether further trials evaluating combination therapy are needed because the chances that the accumulated evidence will change are low’.

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- Recommendations
- (4) There is insufficient evidence that L-T4 + L-T3
- combination therapy serves the hypothyroid patient better than T4 monotherapy (1/++0).
- (5) It is recommended that L-T4 monotherapy remains the standard treatment of hypothyroidism (1/+++).

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

Recommendations

(6) Limited data suggest that psychological well-being and preference for L-T4 + L-T3 combination therapy may be influenced by polymorphisms in thyroid hormone pathway genes, specifically in thyroid hormone transporters and deiodinases (2/+00).

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- Recommendations
- (7) It is suggested that L-T4 + L-T3 combination therapy might be considered as an experimental approach in compliant L-T4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range, provided they have previously given support to deal with the chronic nature of their disease and associated autoimmune diseases have been ruled out (2/+00).
- (8) T4+T3 combination therapy is not recommended
- in pregnant women and in patients with cardiac arrhythmias (2/+00).
- (9) It is suggested that L-T4 + L-T3 combination therapy is discontinued if no improvement is experienced after 3 months (2/++0).

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- Recommendations
- (10) It is suggested that L-T4 + L-T3 combination treatment should be started in a L-T4/L-T3 dose ratio between 13: 1 and 20: 1 by weight (2/+00).
- (11) Whereas L-T4 can be given once daily, the daily
- L-T3 dose should be divided (if possible) in two doses (one before breakfast and the largest one before sleeping)
- (2/+00).

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- Recommendations
- (12) As the currently available L-T4 + L-T3 combination preparations contain a L-T4/L-T3 dose ratio lower than 13: 1, it is recommended to use separate L-T4 and L-T3 tablets in L-T4 + L-T3 combination therapy (1/+00).
- (13) It is recommended that L-T4 + L-T3 combination therapy should be monitored by thyroid function tests in blood samples withdrawn before morning medication 2012 ETA Guidelines Eur Thyroid J 2012;1:55–71 69 has been taken, aiming at normal serum TSH, free T4, free T3 and free T4/free T3 ratio (1/++0).
- (14) If dose adjustment of L-T4 + L-T3 combinationtherapy is necessary to achieve a normal serum TSH, free T4, free T3 and free T4/free T3 ratio, it is suggested the dose of just one of the components is changed, preferably of L-T3 (2/+00).
- (15) It is suggested that treatment of hypothyroidism by the combination of L-T4 and L-T3 should be supervised by accredited internists/endocrinologists (2/++0).

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

- Recommendations
- (16) Suggestions for future research are:
- (a) prospective studies in hypothyroid patients starting L-T4 therapy, comparing baseline characteristics between those who will and those who will not be satisfied with the outcome of L-T4 monotherapy;
- (b) trials investigating the L-T4/L-T3 dose ratio that best approximates the serum FT4/FT3 concentration ratios in healthy subjects;
- (c) randomized clinical trials comparing L-T4 + L-T3 combination therapy and L-T4 monotherapy in hypothyroid patients who are carriers of polymorphisms in thyroid hormone transporters and deiodinases;
- (d) studies with a slow-release preparation of L-T3;
- (e) prospective studies assessing the long-term efficacy
- and safety of L-T4 + L-T3 combination therapy (2/+00).

Mono T_4 vs combined therapy (T_4+T_3)

- The mean serum TSH of a normal population is 1.4 to 1.6 mU/L, with the range varying from 0.4 to 3 or 4.

- With thyroxine treatment, all available T_3 has to be generated by conversion from T_4, while in normal subjects approximately 10 to 20% of T_3 is provided by thyroidal secretion.

- In the pituitary there is an active local conversion of T_4 to T_3 and circulating T_3 plays a minor role in governing TSH secretion. This raises the question of whether using serum TSH as the only monitor of adequate thyroid substitution is a fully adequate procedure.

- FT_3 levels are equal those before operation only if serum TSH is between 0.03 and 0.3 mU/L. The clinical significance of this difference is difficult to appreciate since the informative value of clinical testing of well-being is limited. This stresses that the definition of adequacy of thyroxine treatment is different if it is based on serum TSH or on peripheral thyroid hormones.

- *Ito M, Miyauchi et Al, Should We Treat Patients with Hypothyroidism with T4 and T3 Instead of T4 Alone? Clinical Thyroidology, 2012, 24,*

Mono T4 vs combined therapy (T4+T3)

- There is a small but significant imbalance between the circulating hormones and TSH levels.

- T_4 is considered a pro-hormone, yet it has some direct effects, such as the inactivation of deiodinase type 2. Therefore, if the aim is to achieve a perfect substitution, then a combination treatment of T_4 and T_3 may be necessary.

- As for the science, as a clinician I consider this small difference in serum T_3 levels as clinically insignificant and therefore to routinely use levothyroxine as the sole treatment for hypothyroidism. Some patients are not satisfied with the treatment; rarely, I may add 12.5 μg of triiodothyronine.

Thyroid hormones physiology

Thyroxine (T_4) is produced exclusively by the thyroid gland; its daily production rate is about **80-100 μg** at an average body surface area of 1.79 m^2 (56.2 μg/day/m^2).

Daily production rate of triiodothyronine (T_3) for a body surface area of 1.79 m^2 is about **29 μg** (16 μg/day/m^2): 20% (**6 μg**, or 3.3 μg/day/m^2) is secreted by the thyroid gland, and 80% (23 μg, or 12.7 μg/day/m^2) is generated in extrathyroidal tissues by 5’-deiodination of T_4

Wiersinga et Al 2012 ETA Guidelines: *The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism* Eur Thyroid J 2012;1:55–71

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TABLE 3. Cognitive function test scores (mean ± SEM) for all subjects at the end of each treatment

	Thyroxine alone	Combined thyroxine/T_3	*P* value
Symbol digit modalities test	56.2 ± 0.3	56.4 ± 0.4	0.72
Trail making test			
Part A (s)	24.7 ± 0.4	25.5 ± 0.4	0.18
Part B (s)	61.4 ± 1.5	61.9 ± 1.5	0.80
Digit span test			
Forward	8.5 ± 0.1	8.5 ± 0.1	0.99
Backward	7.0 ± 0.1	6.9 ± 0.1	0.74

Walsh JP R et al, J Clin Endocrinol Metab 2003, 88: 4543

Thyroid hormones physiology

- T_4: daily production rate is about 100 μg at an average body surface area of 1.79 m^2
- T_3: daily production rate is about 29 μg

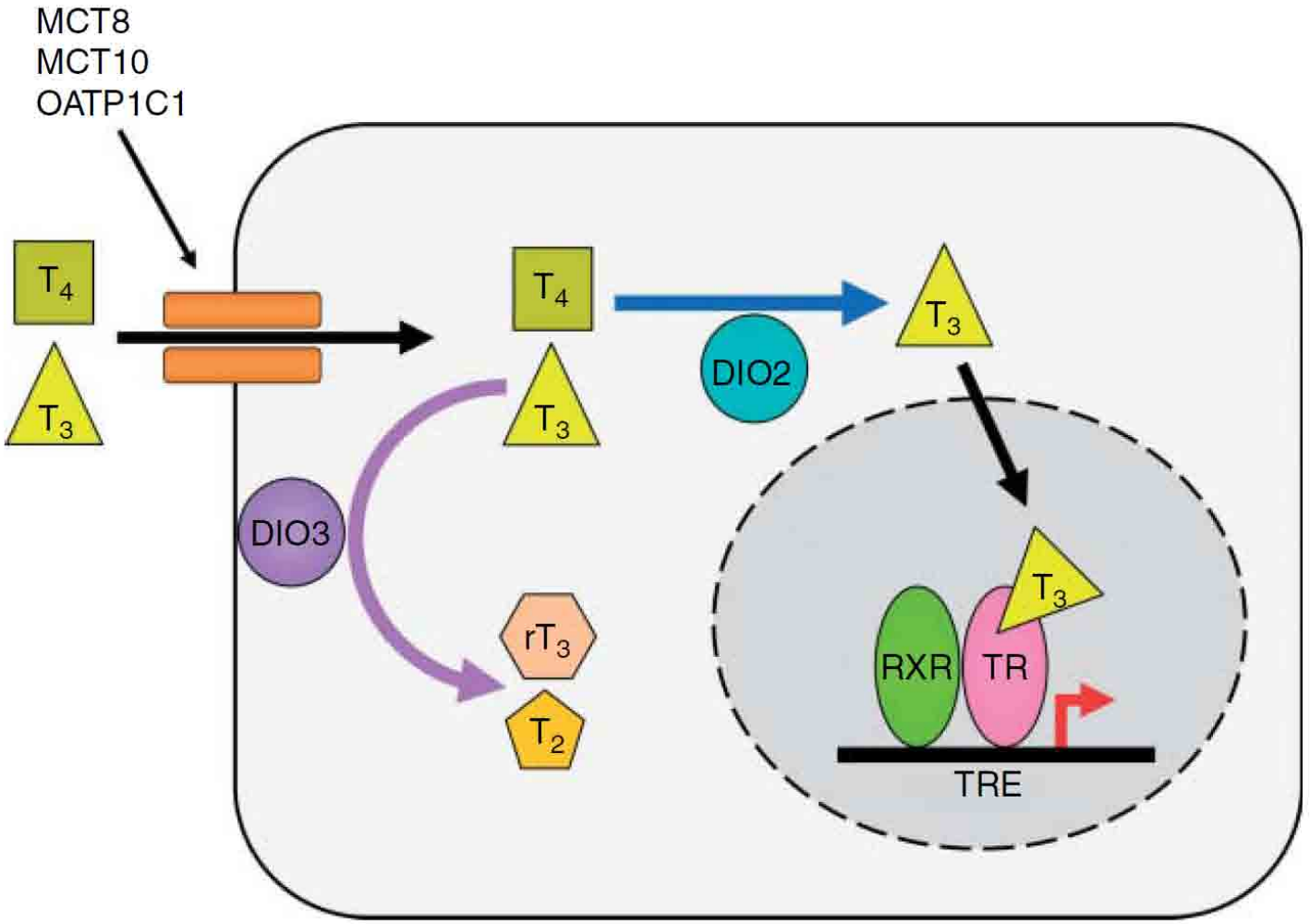
- Thus T_3 : 20% (6 μg) is secreted by the thyroid gland, and 80% (23 μg) is generated in extrathyroidal tissues by 5'-deiodination of T_4.

TABLE 2. BIOCHEMICAL AND PHYSIOLOGIC VALUES AT THE END OF EACH TREATMENT PERIOD.*

VALUE†	AFTER THYROXINE (N=33)	AFTER THYROXINE PLUS TRIIODOTHYRONINE (N=33)	P VALUE‡	NORMAL RANGE
Serum thyrotropin (μU/ml)	0.8±2.5	0.5±1.1	0.56	0.3–5.0
No. of patients with undetectable serum thyrotropin (<0.05 μU/ml)	7	5	—	—
Serum free thyroxine (ng/dl)	2.3±0.7	1.8±0.6	<0.001	0.7–2.1
Serum total thyroxine (μg/dl)	15.2±3.8	11.3±3.3	<0.001	4–11
Serum total triiodothyronine (ng/dl)	87±38	117±42	<0.001	75–175
Serum triglycerides (mg/dl)	129±54	132±55	0.76	47–228
Serum cholesterol (mg/dl)	219±46	217±43	0.66	152–268
Serum sex hormone–binding globulin (μg/dl)	2.6±1.3	3.1±1.5	0.007	0.4–3.5
Pulse rate at rest (beats/min)	69±11	72±12	0.04	—
Blood pressure while seated (mm Hg)				
Systolic	130±21	124±18	0.18	—
Diastolic	79±12	77±14	0.52	—
Sensory threshold (V)				
4th Finger	7.5±2.6	7.4±2.4	0.87	6–10
4th Toe	9.4±3.0	9.3±2.9	0.89	8–12
Achilles reflex relaxation half-time (msec)	282±22	286±28	0.28	240–320

Bunevicius R et al, N Engl J Med 1999, 340: 424-429

ORIGINE DELLA T_3 INTRACELLULARE



Williams GR et al, J Endocrinol 2011, 209: 261-272

SIGNIFICANT CHANGES IN CLINICAL AND BIOCHEMICAL PARAMETERS

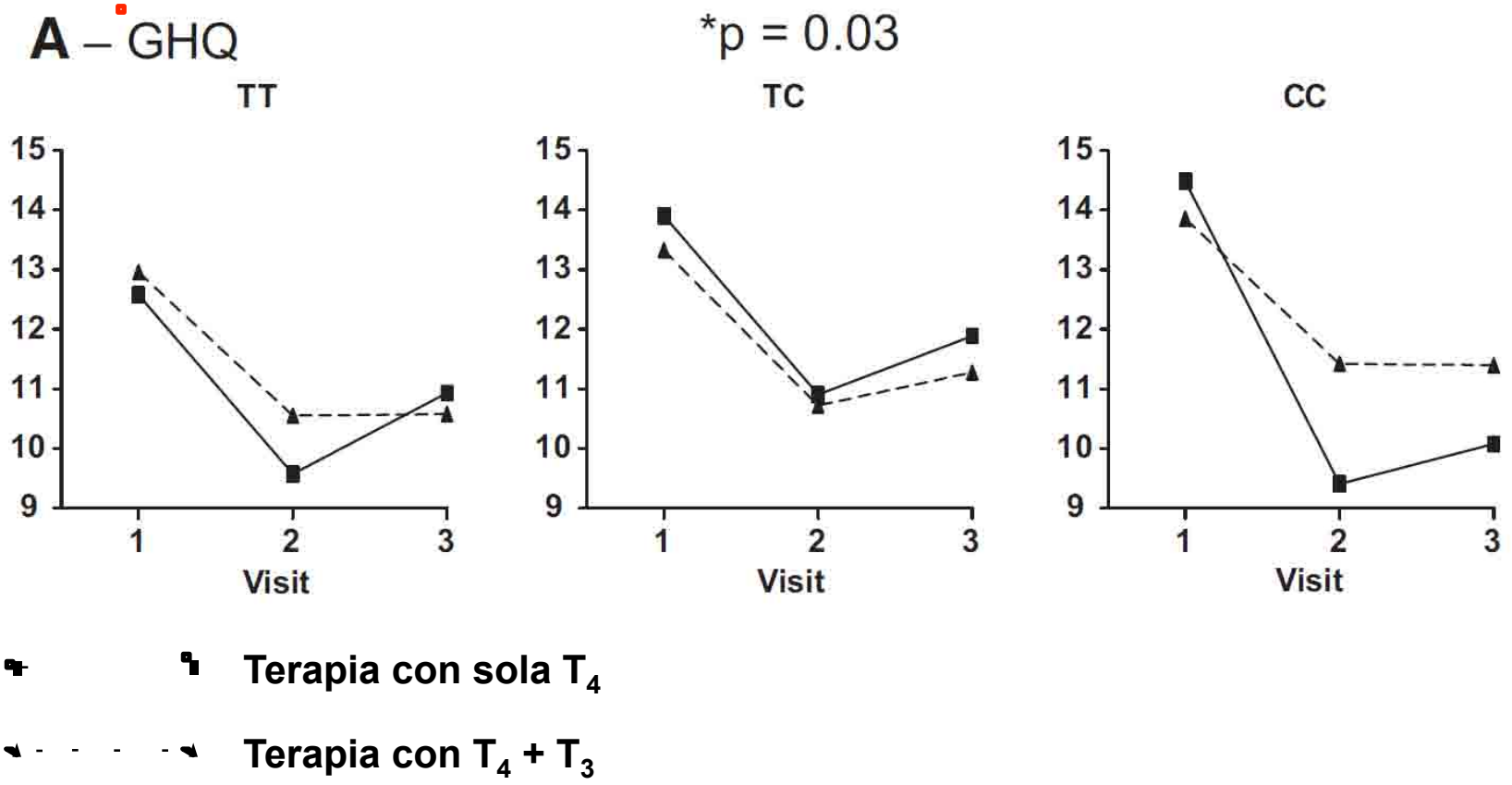
Parameters	T_4 Alone	Combined T_3/T_4	
Pulse rate (beats/min)	68.8 ± 0.5	67.3 ± 0.5	p<0.001
Zulewski score	3.5 ± 0.1	3.9 ± 0.1	p<0.001
Serum TSH (mU/L)	1.5 ± 0.2	3.1 ± 0.2	p<0.001
Serum FT_4 (pmol/L)	15.6 ± 0.2	11.4 ± 0.2	p<0.001
Serum SHBG (nmol/L)	49.4 ± 1.0	45.5 ± 1.0	p<0.01
Plasma Cholesterol (nmol/L)	5.1 ± 0.04	5.2 ± 0.04	p<0.015

Walsh JP R et al, J Clin Endocrinol Metab 2003, 88: 4543

RISPOSTA ALLA TERAPIA DEI PAZIENTI CON DIVERSO GENOTIPO rs225014

(TT common homozygous ; TC heterozygous; CC minor homozygous)

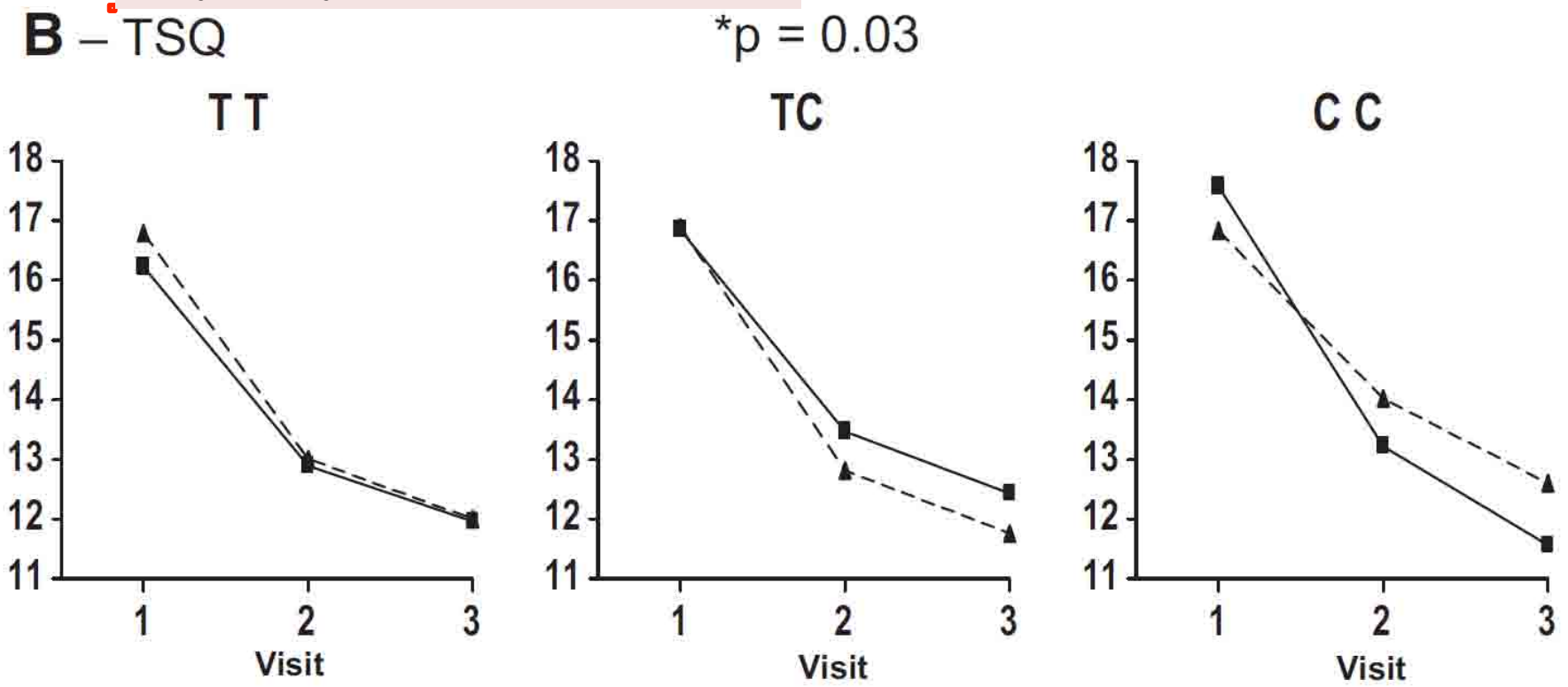
T= Thymine C= cytosine



Panicker V et al, A Common Variation in Deiodinase 1 Gene *DIO1 Is* Associated with the Relative Levels of Free Thyroxine and TriiodothyronineJ Clin Endocrinol Metab 93: 3075–3081, 2008)

RISPOSTA ALLA TERAPIA DEI PAZIENTI CON DIVERSO GENOTIPO rs225014 (TT; TC; CC)

Thyroid symptoms Questionnaire



Panicker V et al, A Common Variation in Deiodinase 1 Gene *DIO1 Is* Associated with the Relative Levels of Free Thyroxine and TriiodothyronineJ Clin Endocrinol Metab 93: 3075–3081, 2008*)*

Controlled Clinical Trial of Combined Triiodothyronine and Thyroxine in the Treatment of Hypothyroidism

R. N. SMITH,* M.D., B.SC., M.R.C.P.ED. ; S. A. TAYLOR† ; J. C. MASSEY,‡ B.SC.

British Medical Journal, 1970, 4, 145-148

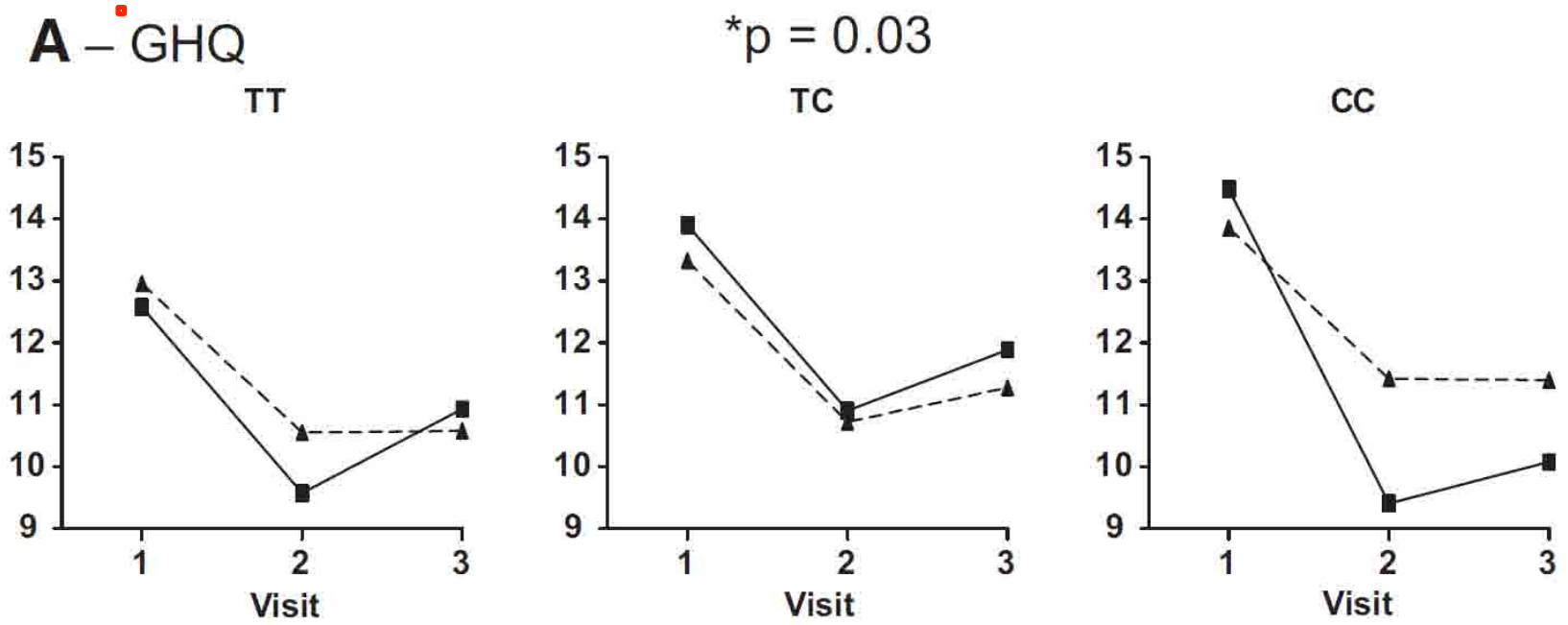
Numbers of patients recordings side effects during treatment

Symptoms & signs	T_3/T_4 Tablets	T_4 Tablets
Palpitations	10 (7)	1 (0)
Irritability and nervousness	6 (6)	0
Dizziness	5 (4)	2 (0)
Tremor	4 (4)	0
Perspiration	3 (2)	1 (0)
Breathless	3 (2)	0
Loss of appetite	3 (3)	1 (0)
Headache	3 (1)	1 (0)
Indigestion	2 (2)	3 (0)
Oedema	1 (0)	0

*Numbers in parentheses indicate the N. of patients who rejected the tablets.

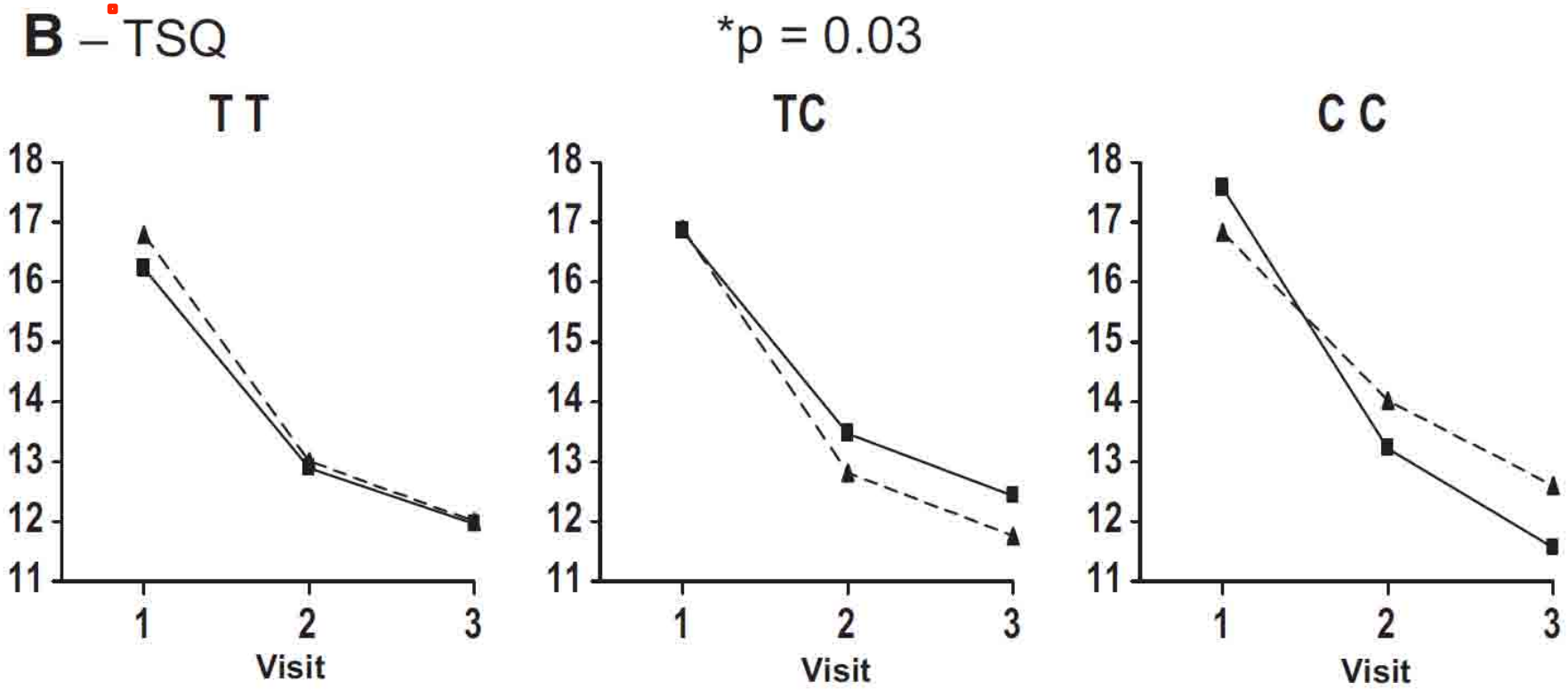
RISPOSTA ALLA TERAPIA DEI PAZIENTI CON DIVERSO GENOTIPO rs225014 (TT; TC; CC)

T= Thymine C= cytosine



Panicker V et al, *Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients.* J Clin Endocrinol Metab 2009, 94: 1623-1629

RISPOSTA ALLA TERAPIA DEI PAZIENTI CON DIVERSO GENOTIPO rs225014 (TT; TC; CC)



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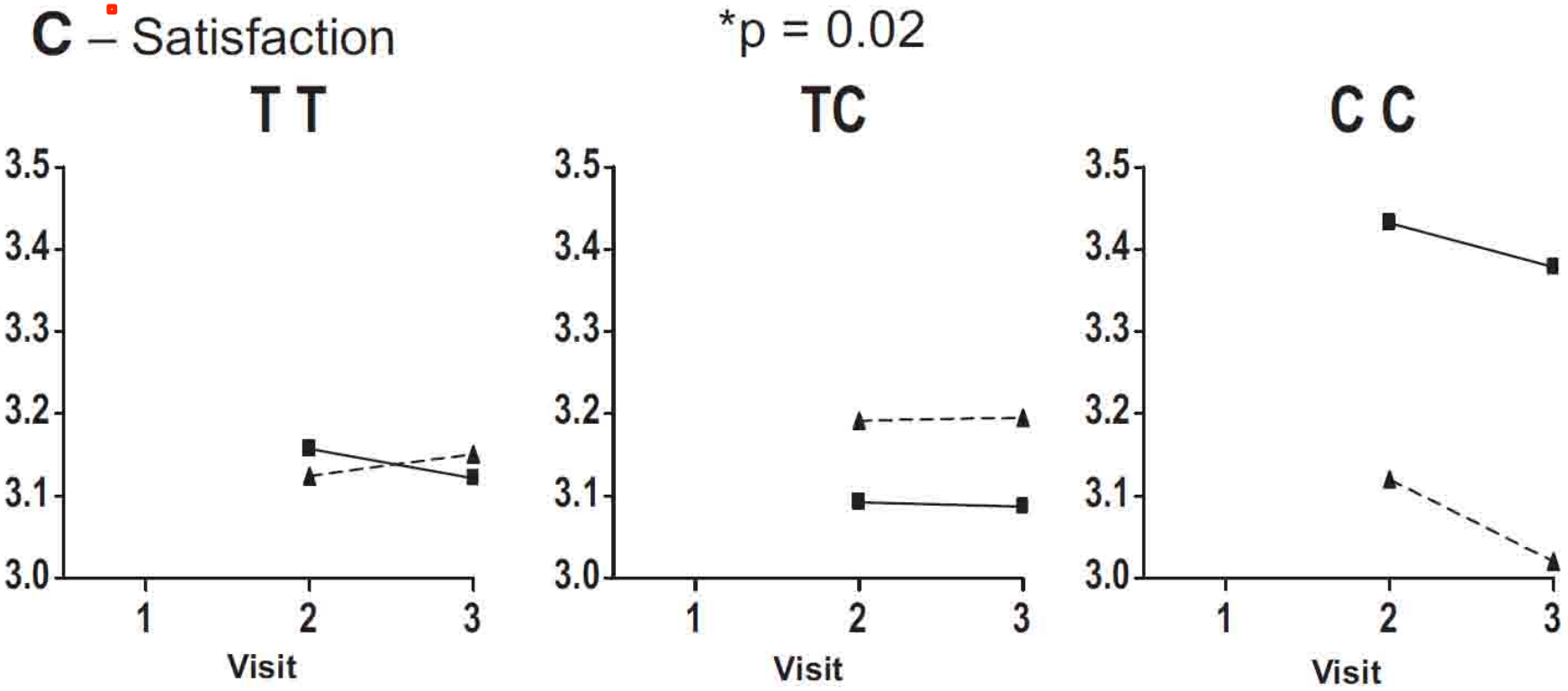
T= Thymine C= cytosine



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Mono T_4 vs combined therapy (T_4+T_3)

- The mean serum TSH of a normal population is 1.4 to 1.6 mU/L, with the range varying from 0.4 to 3 or 4 mU/L.

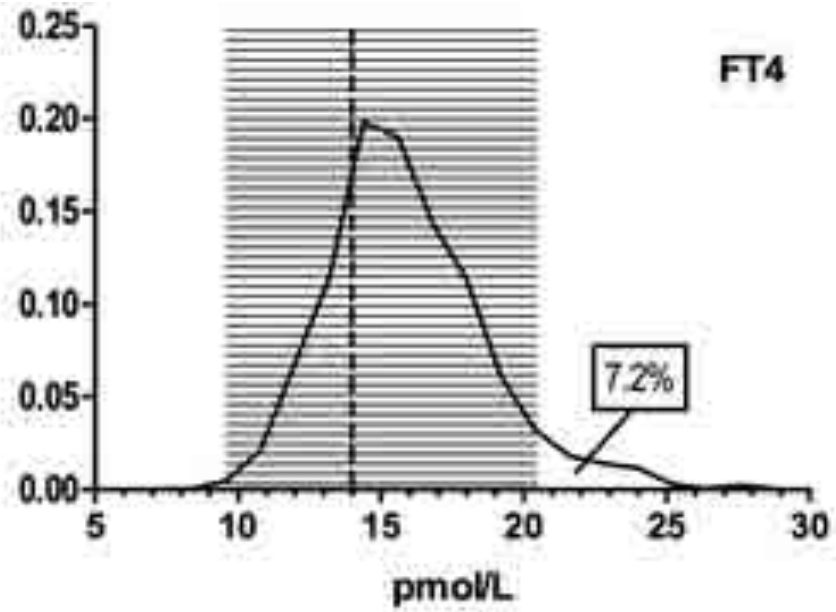
- With T_4 treatment, all available T_3 has to be generated by conversion from T_4, while in normal subjects approximately 10 to 20% of T_3 is provided by thyroid.

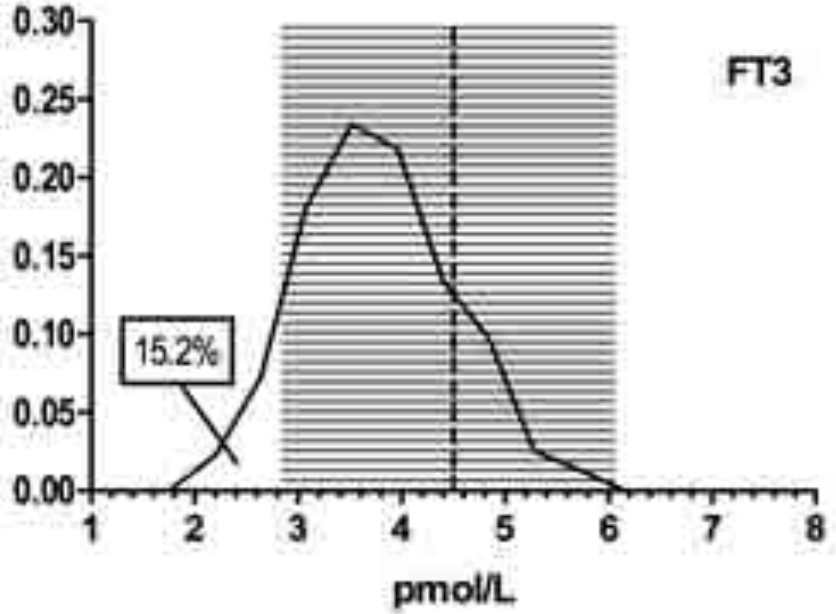
- *Ito M, Miyauchi et Al, Should We Treat Patients with Hypothyroidism with T_4 and T_3 Instead of T_4 Alone? Clinical Thyroidology, 2012, 24,*

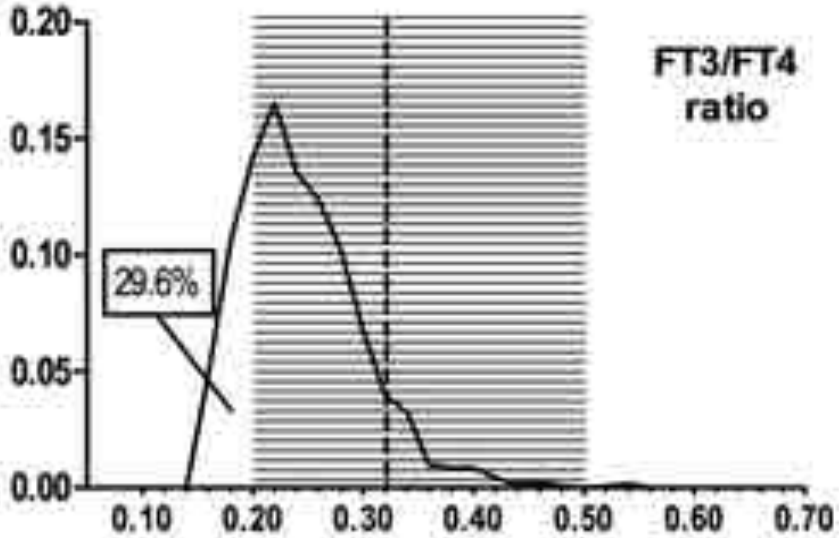
Conclusione. 2.
Mono T_4 vs combined therapy (T_4+T_3)

- There is a small but significant imbalance between the circulating FT_3 and FT_4 and TSH.
- T_4 is considered a pro-hormone, yet it has some direct effects, such as the inactivation of deiodinase type 2.
- Therefore, if the aim is to achieve a perfect substitution therapy, then a combination treatment of T_4 and T_3 may be necessary.
- As for the science, as **a clinician** I consider this small difference in serum T_3 levels as clinically insignificant and therefore **to routinely use levothyroxine as the sole treatment for hypothyroidism**. **In some** patients are not satisfied with the treatment rarely, **I may add** 12.5 μg of T_3.
- ***A.G Burger*** *Clinical Thyroidology, 2012, 24*

FT4, FT3 AND FT3/FT4 RATIO FREQUENCY DISTRIBUTION IN ATHYREOTIC PATIENTS TREATED WITH L-T4







Gullo D et al PLoS ONE 2011, 6: e22552.

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Combined Thyroxine/Liothyronine Treatment Does Not Improve Well-Being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomized Controlled Trial in Patients with Primary Hypothyroidism

JOHN P. WALSH, LAUREN SHIELS, EE MUN LIM, CHOTOO I. BHAGAT, LYNLEY C. WARD, BRONWYN G. A. STUCKEY, SATVINDER S. DHALIWAL, GERARD T. CHEW, MINOTI C. BHAGAT, AND ANDREA J. CUSSONS

J Clin Endocrinol Metab 88: 4543–4550, 2003

- **Studio randomizzato, doppio cieco, incrociato, su 110 pazienti in terapia sostitutiva.**
- **I pazienti erano in terapia con L-T_4 da 8 ± 8,3 anni: dose media 136±36 μg/die.**
- **Terapia combinata per 10 settimane: sostituzione di una dose fissa di L-T_4 (50 μg/die) con una dose fissa di L-T_3 (10 μg/die) con un rapporto T_4:T_3 variabile da 5:1 a 15:1.**

SINOSSI DEI PRINCIPALI STUDI EFFETTUATI DAL 2003 AL 2005

Autore	N. paz.	Studio	$T_4 \rightarrow T_3$ $T_4 : T_3$	Efficacia terapia combinata
Clyde 2003	44	Randomizzato controllato	50μg →15μg 5,4:1	NO
Sawka 2003	40	Randomizzato controllato	50%→12,5μg 3–5:1	NO
Siegmund 2004	36	Randomizzato incrociato	5%→T_3* 19:1	NO
Rodriguez 2005	30	Randomizzato incrociato	50μg →10μg 7:1	NO
Escobar-Morreale 2005	28	Randomizzato incrociato	25μg →3μg 15:1	NO
Saravanan 2005	697	Randomizzato controllato	50μg →10μg 7,7:1	NO
Appelhof 2005	141	Randomizzato controllato	25μg →T_3** 10:1 o 5:1	NO

$T_4 \rightarrow T_3$ = dose di T_4 rimpiazzata da T_3; $T_4:T_3$ rapporto tra le dosi (in peso)

*dose variabile di T_3 in sostituzione del 5% della dose di T_4

**dose variabile di T_3 per ottenere un $T_4:T_3$ di 10:1 o 5:1

The Journal of Clinical Endocrinology & Metabolism 91(7):2592–2599

Thyroxine-Triiodothyronine Combination Therapy *Versus* Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials

Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman, and Leonard Leibovici

"No difference was found in the effectiveness of combination vs. monotherapy in any of the following symptoms: bodily pain, depression, anxiety, fatigue, quality of life, body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high density lipoprotein. Adverse events did not differ between regimens."

The Journal of Clinical Endocrinology & Metabolism 91(7):2592–2599

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Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman, and Leonard Leibovici

"Given the conclusive evidence, **monotherapy with T_4 should remain the standard treatment for hypothyroidism.**
It is doubtful whether further trials evaluating combination therapy are needed because the chances that the accumulated evidence will change are low."

European Journal of Endocrinology (2009) **161** 895–902

Effect of combination therapy with thyroxine (T_4) and 3,5,3′-triiodothyronine versus T_4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study

Birte Nygaard, Ebbe Winther Jensen, Jan Kvetny[1], Anne Jarløv[2] and Jens Faber

- Studio randomizzato, doppio cieco, incrociato, su 59 pazienti con ipotiroidismo primario autoimmune.
- I pazienti erano in terapia con L-T_4 da almeno 6 mesi: dose media 129±29 μg/die.
- Terapia combinata per 12 settimane: sostituzione di una dose fissa di L-T_4 (50 μg/die) con una dose fissa di L-T_3 (20 μg/die) con un rapporto T_4:T_3 variabile da 2,5:1 a 8:1 (media= 4:1).

Who Could Benefit from Combination Therapy?

…no differences were observed in cognitive function, mood, psychological symptoms, quality of life, or thyroid disease-related symptoms in the majority of these studies

higher serum T4 levels are necessary in thyroidectomized patients to obtain normal serum T3 concentrations and thereby compensate for the absence of the 20% fraction of circulating T3 normally directly secreted by the thyroid

….there may be a small number of patients with a D2 polymorphism that could benefit from combination therapy… Prospective trials will be necessary to further evaluate the neuropsychiatric response to combined T4/T3 treatment *vs.* monotherapy with L-T4 in patients with the Thr92Ala polymorphism.

…T3 in combination with tricyclic antidepressants compared with placebo in euthyroid patients with resistant depression. .. Double-blind placebo-controlled studies are needed to investigate the potential beneficial effects of combined T3 and T4 treatment

1^0 CORSO NAZIONALE DI AGGIORNAMENTO AME

Roma 9-11 Novembre 2012

IPOTIROIDISMO E TERAPIA SOSTITUTIVA

Sola T_4 o terapia in associazione?

Fabrizio Monaco e Giorgio Napolitano
Sezione di Endocrinologia e Nefrologia
Università' "G. d'Annunzio" Chieti-Pescara

Conclusione. 2.
Mono T_4 vs combined therapy (T_4+T_3)

- As **a clinician** I consider the small difference in serum T_3 levels as clinically insignificant and therefore **I routinely use L-thyroxine as the sole treatment for hypothyroidism**.
- **In a few** patients not satisfied with the treatment, rarely **I may add** 12.5 μg of T_3.

- ***A.G Burger Clinical Thyroidology, 2012, 24***