Association of British Clinical Diabetologists

Bristol meeting

A Year in Endocrinology 2023 - 2024 - what did we learn?

Karim Meeran
Imperial College
5th September 2024

Endocrinology 2023-2024
What have we learned?

- Guidelines: NICE on AI published last week, August 2024.
- Prednisolone versus hydrocortisone for AI June 2023
- Endocrine Society and ESE guideline on steroid induced AI
- Cortisol and synacthen tests (Newcastle August 2024)
- Crinecerfont for Congenital Adrenal Hyperplasia NEJM June 2024
- Atumelnant for ACTH dependant Cushings
- Levolio study EJE Dec 2023:
- Non-Blind studies all find that T3 with T4 is magic
- Blind studies all fail to find this: placebo effect is very potent

Adrenal insufficiency: identification and management

NICE guideline [NG243] Published: 28 August 2024

Guidance

Download guidance (PDF)

Next

Recommendations

thebmj

BMJ 2014;349:g4843 doi: 10.1136/bmj.g4843 (Published 30 July 2014)

No evidence of difference between prednisolone and hydrocortisone

EDITORIALS

Glucocorticoid replacement

Pending further studies of new agents, the old treatments are still the best

Anjali Amin *clinical research fellow*, Amir H Sam *senior lecturer in endocrinology*, Karim Meeran *professor of endocrinology*

Imperial Centre for Endocrinology, Imperial College London, UK

Steroids are among the most commonly prescribed drugs. Synthetic glucocorticoids such as prednisolone and

conventional doses of hydrocortisone. This was unsurprising, however, as the doses of hydrocortisone were not comparable:

Endocrine CONNECTIONS

A Sharma *et al.* | 12:8 | e230097

RESEARCH

26th July 2023

Optimising prednisolone or prednisone replacement in adrenal insufficiency

Angelica Sharma[1,2,*], **Katharine Lazarus**[1,2,*], **Deborah Papadopoulou**[1,2], **Hemanth Prabhudev**[2], **Tricia Tan**[1,2,3], **Karim Meeran**[1,2] and **Sirazum Choudhury**[1,2,3]

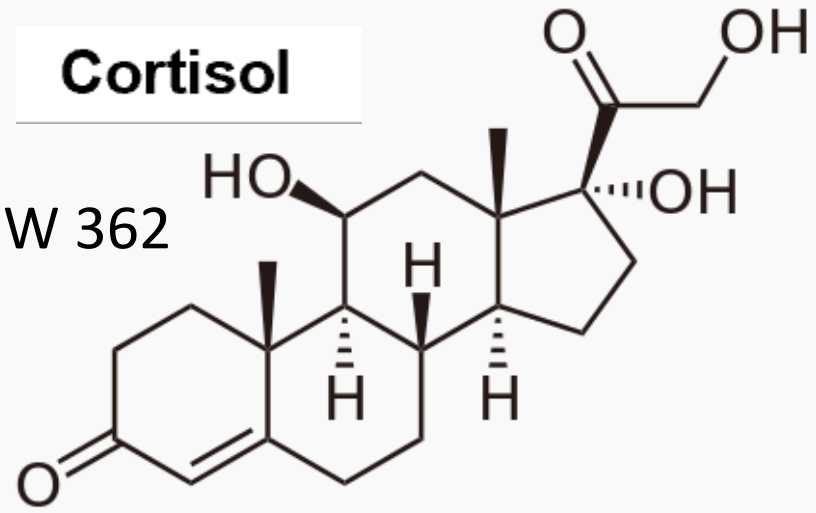
[1]Division of Diabetes, Endocrinology and Metabolism, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK
[2]Department of Endocrinology, Imperial College Healthcare NHS Trust, London, UK
[3]Department of Clinical Biochemistry, North West London Pathology, London, UK

Correspondence should be addressed to S Choudhury: s.choudhury@imperial.ac.uk

*(A Sharma and K Lazarus contributed equally to this work)

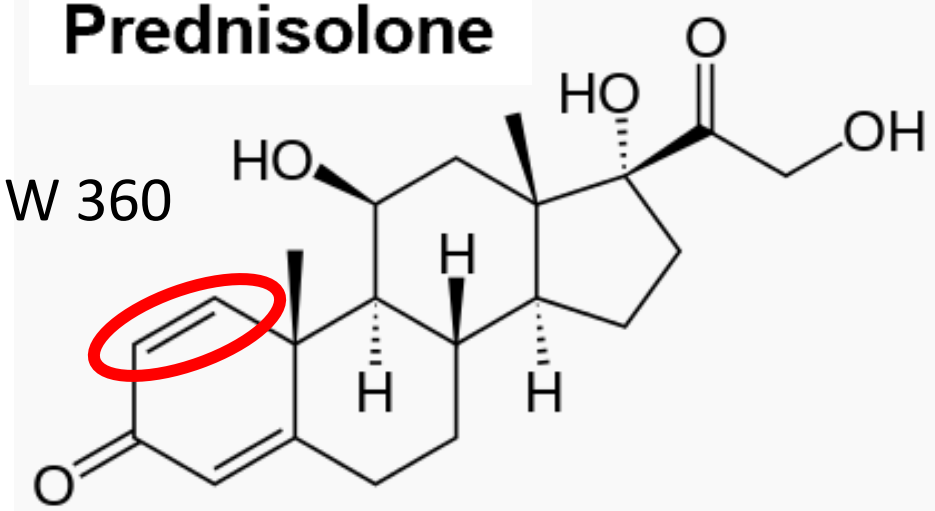
Cortisol

MW 362



Prednisolone

MW 360



Prednisolone has a longer half life and is more potent than cortisol
2.3x binding affinity than cortisol

Replacement dose 3-4mg ONCE daily

Prednisolone Replacement Therapy Mimics the Circadian Rhythm More Closely Than Other Glucocorticoids

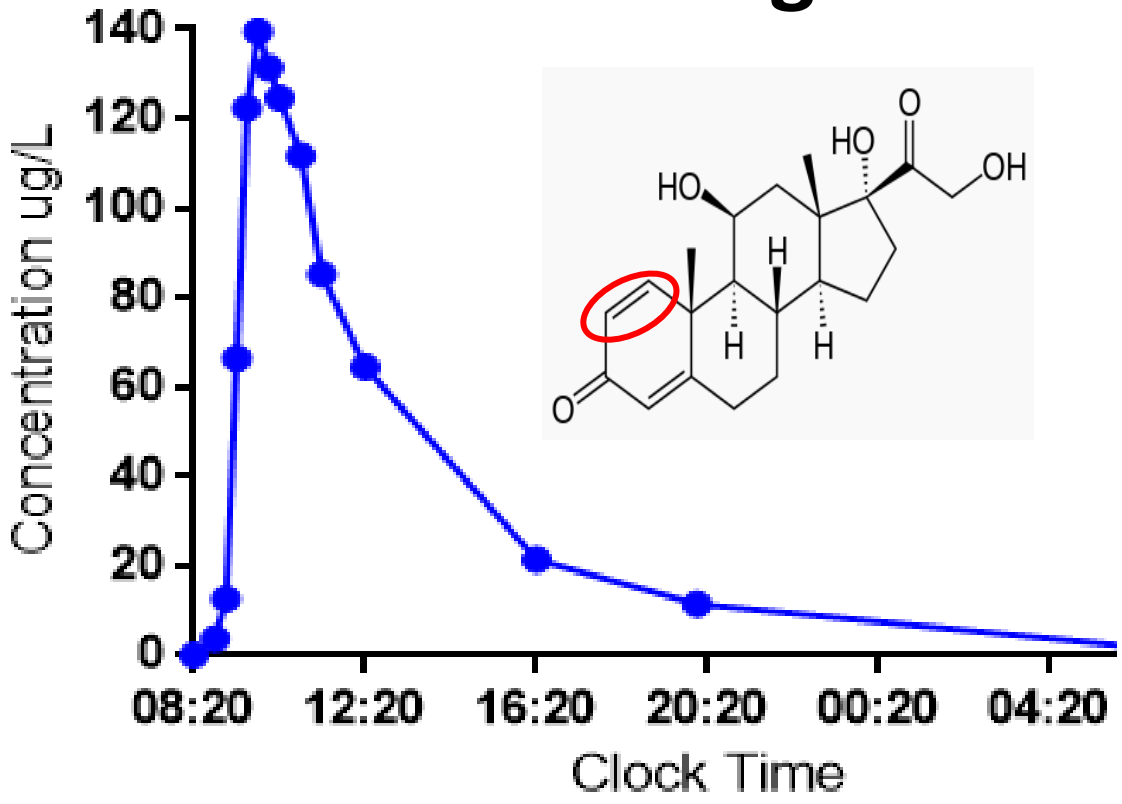
Journal of Applied Laboratory Medicine | 152–161 September 2016

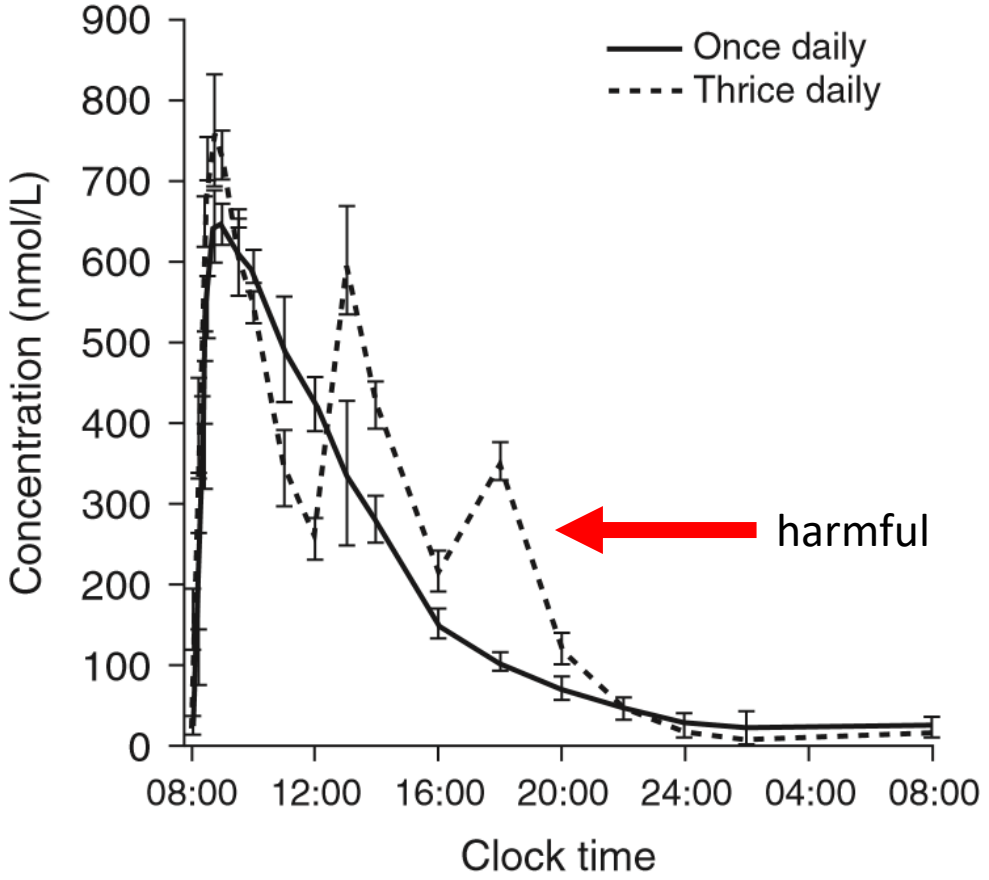
Emma L. Williams,[1] Sirazum Choudhury,[1] Tricia Tan,[2] and Karim Meeran[2,3]*

Background: This study examined the pharmacokinetic profile of prednisolone.
Methods: Using a newly developed ultra-performance liquid chromatography MS/MS method, prednisolone profiles in healthy volunteers and patients with adrenal insufficiency already treated with prednisolone were prospectively analyzed in a tertiary center.
Results: Twelve prednisolone day curves were analyzed. Six patients with secondary adrenal insufficiency provided 7 curves and 3 healthy volunteers provided 5 curves, 1 of which was with the prednisolone administered in divided doses. The mean prednisolone dose required for adequate replacement in hypoadrenal patients was 3.86 mg. The overall mean maximal serum concentration (C_{max}) was 114.0 μg/L and was achieved at an average time to maximal concentration (T_{max}) of 1.43 h. Total glucocorticoid exposure was represented by the mean area under the curve to 24 h (AUC_{0-24h}), which was 518.2 μg|·|h/L. Splitting the dose substantially increased the total glucocorticoid exposure.
Conclusions: The pharmacokinetic profile of prednisolone is similar to the published profile of dual-release hydrocortisone. Once-daily prednisolone can thus be used as a replacement for hydrocortisone. Further studies need to be carried out to accurately calculate an equivalent replacement dose. Prednisolone levels are a useful adjunct to dose adjustment when low doses are being used for replacement.

Prednisolone has the right half life for OD…

3mg





Rapidly absorbed with half life suitable for once daily administration

Pituitary (2022) 25:393–403
https://doi.org/10.1007/s11102-022-01218-y

Glucocorticoid Withdrawal Syndrome following treatment of endogenous Cushing Syndrome

Xin He[1] · James W. Findling[2,3] · Richard J. Auchus[1,4,5]

Accepted: 15 March 2022 / Published online: 26 April 2022

Abstract

Purpose: Literature regarding endogenous Cushing syndrome (CS) largely focuses on the challenges of diagnosis, subtyping, and treatment. The enigmatic phenomenon of glucocorticoid withdrawal syndrome (GWS), due to rapid reduction in cortisol exposure following treatment of CS, is less commonly discussed but also difficult to manage. We highlight the clinical approach to navigating patients from GWS and adrenal insufficiency to full hypothalamic-pituitary-adrenal (HPA) axis recovery.

Methods: We review the literature on the pathogenesis of GWS and its clinical presentation. We provide strategies for glucocorticoid dosing and tapering, HPA axis testing, as well as pharmacotherapy and ancillary treatments for GWS symptom

Glucocorticoid withdrawal syndrome (GWS)

- The enigmatic phenomenon of glucocorticoid withdrawal syndrome (GWS), due to rapid reduction in cortisol exposure following treatment of CS, is difficult to manage.

- (eg from 7mg to 6mg prednisolone, you get aches and pains)

- Awareness of GWS by treating physicians and patient education are essential. GWS is not the same as AI but it makes it difficult to wean

Imperial Centre *for* Endocrinology

Prednisolone withdrawal

Practically-speaking how do I reduce my prednisolone when my vasculitis is in remission? ***Printable version of table pdf*.**

If your rheumatologist wants to stop your prednisolone, either because you are in remission, or because you have had a newer treatment for your vasculitis, you have a choice. You can either stay on a small replacement dose forever (just over 3mg) or you can deliberately cut the dose so that the adrenal glands slowly awaken but risk feeling a bit tired and under the weather for a while. Almost all vasculitis patient's adrenal glands will recover if the dose is cut by 0.5mg every month. This is hard work for patients because for most of that time, you have to run on less glucocorticoid that you need in order to wake up the adrenal. This is the reason that some of you might choose to stay on 3mg daily even if your vasculitis is in remission.

Cutting from 3mg to nothing can take 6 months, and some people can do this more quickly than others. It depends of course on how long you have had prednisolone, but many authors suggest cutting by half a milligram per month.

Patients with no adrenal glands need approximately 3mg (varies from 2-5mg) prednisolone as there is no hope of the adrenal gland waking up. Details can be found here on http://www.imperialendo.com/prednisolone and http://dx.doi.org/10.1530/EC-17-0257.

I really want to get my prednisolone dose below 3mg, how do I do this?

The other way to reduce prednisolone below 3mg is to take 3mg on some days and 2mg on others. If you take 2mg for one day and 3mg for 6 days, and then slowly increase the number of days that you take 2mg for. It will in fact take 7 weeks to go from 3mg to 2mg. This should slowly help your adrenal gland to recover.

protocol

Week	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
0	5	5	5	5	5	5	5
1	5	4	5	4	5	4	5
2	4	4	4	4	4	4	4
3	4	3	4	3	4	3	4
4	3	3	3	3	3	3	3
5	3	3	3	2	3	3	3
6	3	2	3	3	2	3	3
7	3	2	3	2	3	2	3
8	2	3	2	3	2	3	2
9	2	3	2	2	3	2	2
10	2	2	2	3	2	2	2
11	2	2	2	2	2	2	2
12	2	2	2	1	2	2	2
13	2	1	2	2	1	2	2
14	2	1	2	1	2	1	2
15	1	2	1	2	1	2	1
16	1	2	1	1	2	1	1
17	1	1	1	2	1	1	1
18	1	1	1	1	1	1	1
19	1	1	1	0	1	1	1
20	1	0	1	1	0	1	1
21	1	0	1	0	1	0	1
22	0	1	0	1	0	1	0
23	0	1	0	0	1	0	0
24	0	0	0	1	0	0	0

Adrenal insufficiency: identification and management

NICE guideline [NG243] Published: 28 August 2024

Guidance

Download guidance (PDF)

Next

Recommendations

Physiological equivalent doses

The physiological equivalent dose is the dose of glucocorticoid that is equivalent to the amount that a healthy adrenal gland would normally produce:

- For people aged 16 years and over this is a total daily dose of hydrocortisone 15 mg, prednisolone 3 mg, or dexamethasone 0.5 mg.

1.9.4 Do not routinely change from prednisolone to hydrocortisone to manage dose tapering below a physiological equivalent dose.

1.9.5 Tell people who are tapering glucocorticoid doses below a physiological equivalent dose:

- to expect temporary symptoms, including fatigue, reduction in appetite and low mood

Glucocorticoid dose-tapering regimens

1.9.1 For people who have been taking glucocorticoids to treat an underlying condition

- reduce glucocorticoids to a daily physiological equivalent dose,

Decisions to taper dosages of glucocorticoid should be made by the clinical team who initiated the treatment.

1.9.2 For people who have been taking glucocorticoids for more than 12 weeks and no longer need them, after reducing to a daily physiological equivalent dose, consider stopping treatment using a slower dose-tapering regimen than in recommendation 1.9.1. For people taking prednisolone, once the daily dose is 3 mg, consider following the Imperial Centre for Endocrinology prednisolone withdrawal regimen.

Imperial Centre *for* Endocrinology

Prednisolone withdrawal

Practically-speaking how do I reduce my prednisolone when my vasculitis is in remission? ***Printable version of table pdf*.**

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What about patients on glucocorticoids for rheumatological problems (eg: GCA)

- Guidelines: steroid withdrawal
- Don’t do any tests
- Don’t involve endocrinologists

Diagnostic accuracy of morning serum cortisol concentration in confirming recovery of the hypothalamic-pituitary-adrenal axis in patients on chronic glucocorticoid therapy

Ella Sharma[1] | Joe Berry[2] | Bridget Griffiths[2] | Alice Lorenzi[2] | Ben Thompson[2] | Chris Boot[3] | Yaasir Mamoojee[1]

[1]Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

[2]Department of Rheumatology, Freemen Hospital, Newcastle upon Tyne, UK

[3]Department of Blood Sciences, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Correspondence
Yaasir Mamoojee, Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, UK.
Email: y.mamoojee@nhs.net

Clin Endocrinol (Oxf). 2024 Aug;101(2):140-141.

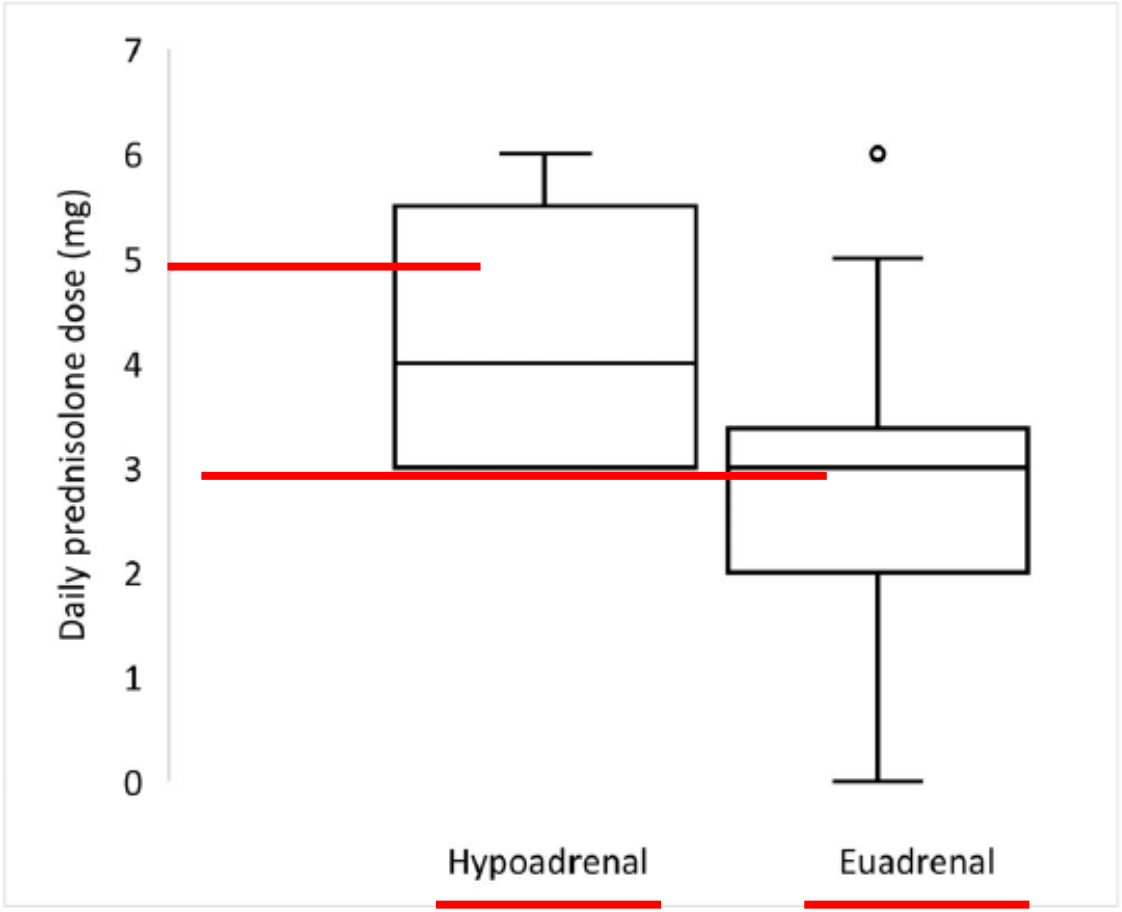

FIGURE 1 Box and whisker plot illustrating the distribution of daily prednisolone doses at time of SST in hypoadrenal and euadrenal patients on long-term CGT. CGT, chronic glucocorticoid therapy; SST, synacthen stimulation test.

daily prednisolone dose of ≤3 mg is reached. This is consistent with a recent study demonstrating that a once-daily prednisolone dose of 2–4 mg is more physiological based on achieving serum prednisolone concentrations within therapeutic target ranges in patients with AI.[6] It is assumed by many that prednisolone 5 mg once daily is not a suppressive dose and, indeed in many countries, the lowest strength tablet available is 5 mg. Therefore, in the absence of intercurrent acute illnesses, patients experiencing presumed hypoadrenal symptoms on a supra-therapeutic daily prednisolone dose of >4 mg may be considered to have steroid withdrawal symptoms. As such avoiding biochemical assessment to evaluate the integrity of the HPA axis in such patients but slowing down the rate of glucocorticoid tapering instead would be a clinically sound strategy.

In summary, we have validated an early serum cortisol concentration of >237 nmol/L (>8.6 μg/dL) as a safe and useful screening test with 100% specificity for predicting recovery of HPA axis in patients on long-term CGT on tapering regimes (although it should be noted that morning serum cortisol screening cutoff thresholds may vary depending on the assay utilised for cortisol

Clin Endocrinol (Oxf). 2024 Aug;101(2):140-141.

immunoassay had a specificity of 100% for predicting a normal SST, and morning cortisol ≤83 nmol/L (≤3 μg/dL) was 100% sensitive for AI.[5] It is worth noting that a minority of patients were prescribed CGT for non-endocrine conditions in the latter cohort.

Our data validates a morning serum cortisol concentration of >237 nmol/L (>8.6 μg/dL), on the Cortisol-II assay by Roche Diagnostics, with 100% specificity at predicting recovery of HPA axis in patients on tapering doses of CGT. This offers a more rapid, convenient and cost-effective screening method for patients requiring biochemical assessment of the HPA axis with the potential for significant resource savings without any adverse impact on patient safety. In most centres, the treatment of GCA involves prednisolone reduction very successfully, without the involvement of endocrinologists, for example, by reducing the dose over a few weeks from 60 to 10 mg, and then reducing the dose by 1 mg per month. The involvement of endocrinologists potentially limits the ability of the rheumatologists to wean the patient off prednisolone independently and should therefore not be the norm. Our observation further empowers the rheumatologists to wean patients off prednisolone safely, thus reversing the trend of endocrinology involvement.

Our data further suggest that assessment of the HPA axis, if desired during tapering doses of CGT, should be considered once a

REFERENCES

1. Burmester GR, Buttgereit F, Bernasconi C, et al. Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. *Lancet*. 2020;396(10246):267-276.
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6. Sharma A, Lazarus K, Papadopoulou D, et al. Optimising prednisolone or prednisone replacement in adrenal insufficiency. *Endocr Connect*. 2023;12(8):e230097.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Clin Endocrinol (Oxf). 2024 Aug;101(2):140-141.

NEJM Journal Watch

GUIDELINE WATCH | GENERAL MEDICINE, AMBULATORY MEDICINE, HOSPITAL MEDICINE

INFORMING PRACTICE

July 18, 2024

Glucocorticoid-Induced Adrenal Insufficiency: A New Guideline

Allan S. Brett, MD, reviewing Beuschlein F et al. Eur J Endocrinol 2024 May

This document provides a comprehensive overview, with specific recommendations for tapering steroid therapy.

Sponsoring Organizations: European Society of Endocrinology and Endocrine Society

Background

Clinicians vary considerably in their approach to patients with glucocorticoid-induced adrenal insufficiency.

European Journal of Endocrinology, 2024, **190**, G25–G51
https://doi.org/10.1093/ejendo/lvae029
Advance access publication 8 May 2024

Clinical Practice Guideline

European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and therapy of glucocorticoid-induced adrenal insufficiency

Felix Beuschlein,[1,2,3,*†] Tobias Else,[4,†] Irina Bancos,[5,6] Stefanie Hahner,[7] Oksana Hamidi,[8] Leonie van Hulsteijn,[9,10] Eystein S. Husebye,[11,12] Niki Karavitaki,[13,14,15] Alessandro Prete,[13,14,16] Anand Vaidya,[17] Christine Yedinak,[18] and Olaf M. Dekkers[10,19,20]

▾ 1.1 General recommendations for glucocorticoid therapy of non-endocrine conditions and recommendations regarding patient education

› R 1.1 We recommend that, in general, patients on, or tapering off glucocorticoids for non-endocrine conditions do not need to be evaluated by an endocrinology specialist.

- Routine dynamic testing (e.g., adrenocorticotropic hormone stimulation) is discouraged; the authors recommend it only in selected instances of ongoing uncertainty about adrenal status.

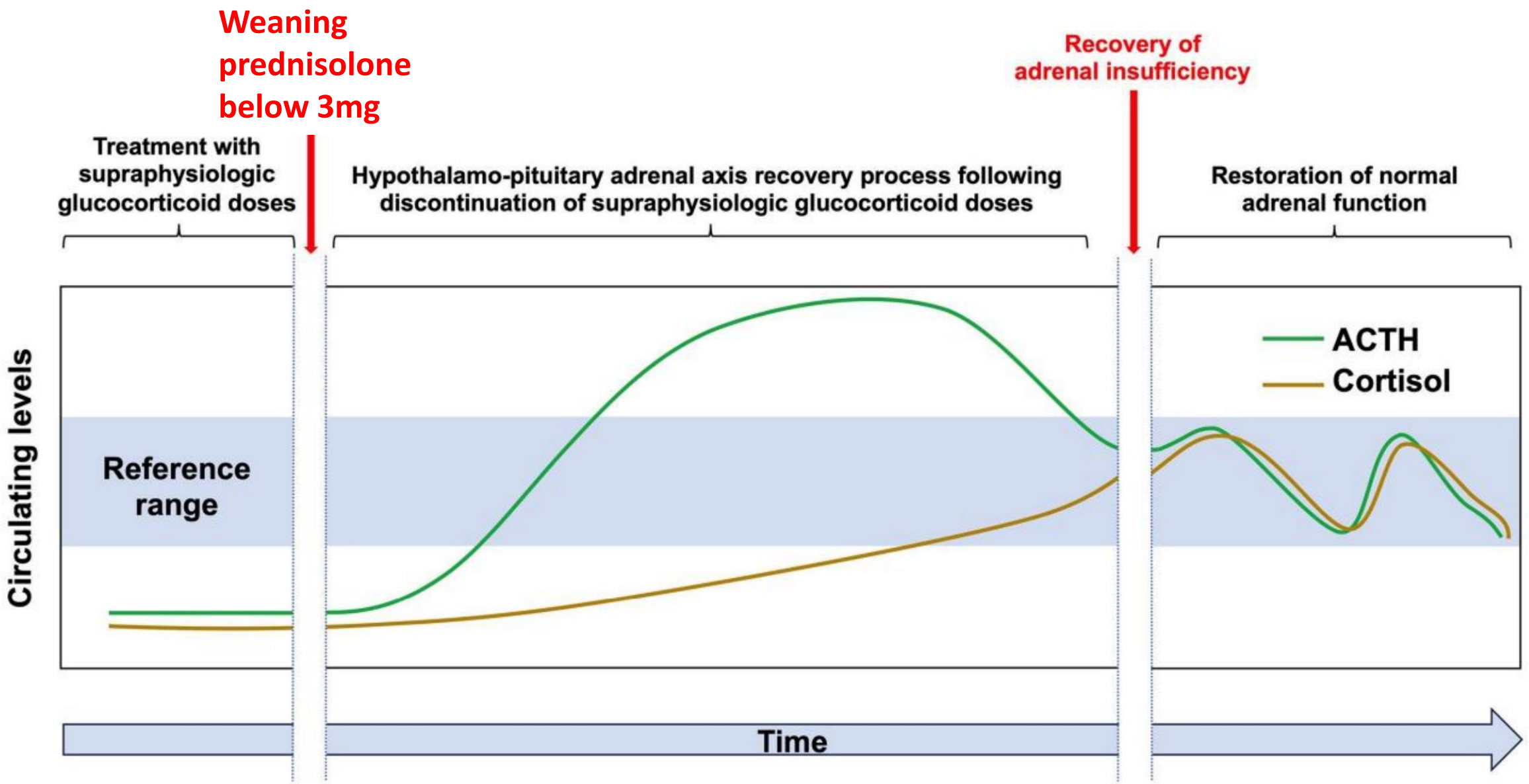


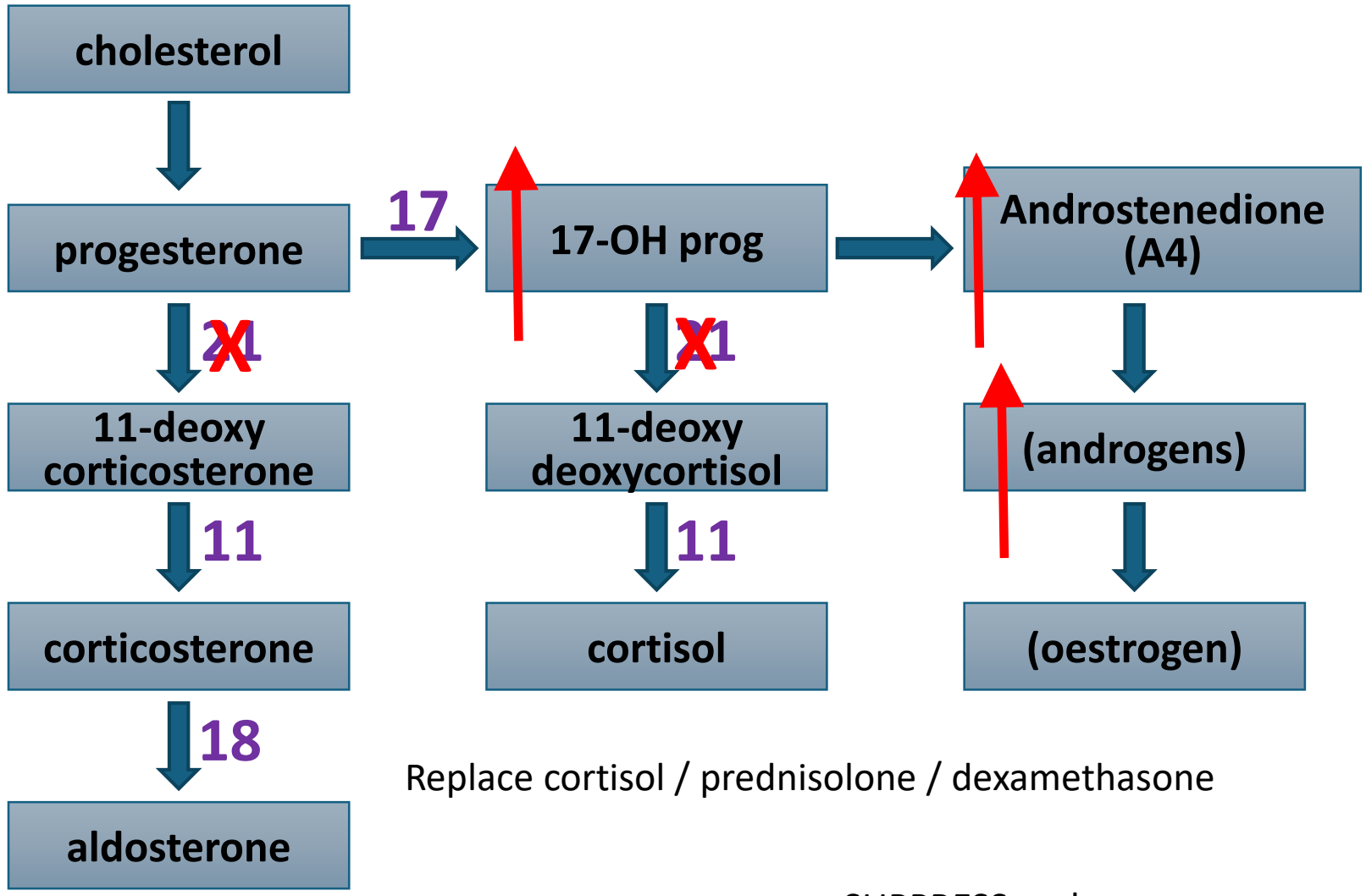
Figure 1: Schematic representation of HPA axis recovery following discontinuation of supraphysiologic glucocorticoid therapy (adapted from: Prete and Bancos 2021[53]).

Summary : what have we learned?

- Prednisolone 3mg daily is a replacement dose for most individuals who have no adrenal glands
- Steroid withdrawal syndrome results in people taking more steroid than they need
- Weaning below 3mg is easier if done slowly
- Patients who have steroid induced adrenal insufficiency also suffer from steroid withdrawal syndrome, but this is not an Addisonian crisis, and coming off steroids is best done without endocrinologist involvement

Congenital adrenal hyperplasia

21 hydroxylase deficiency

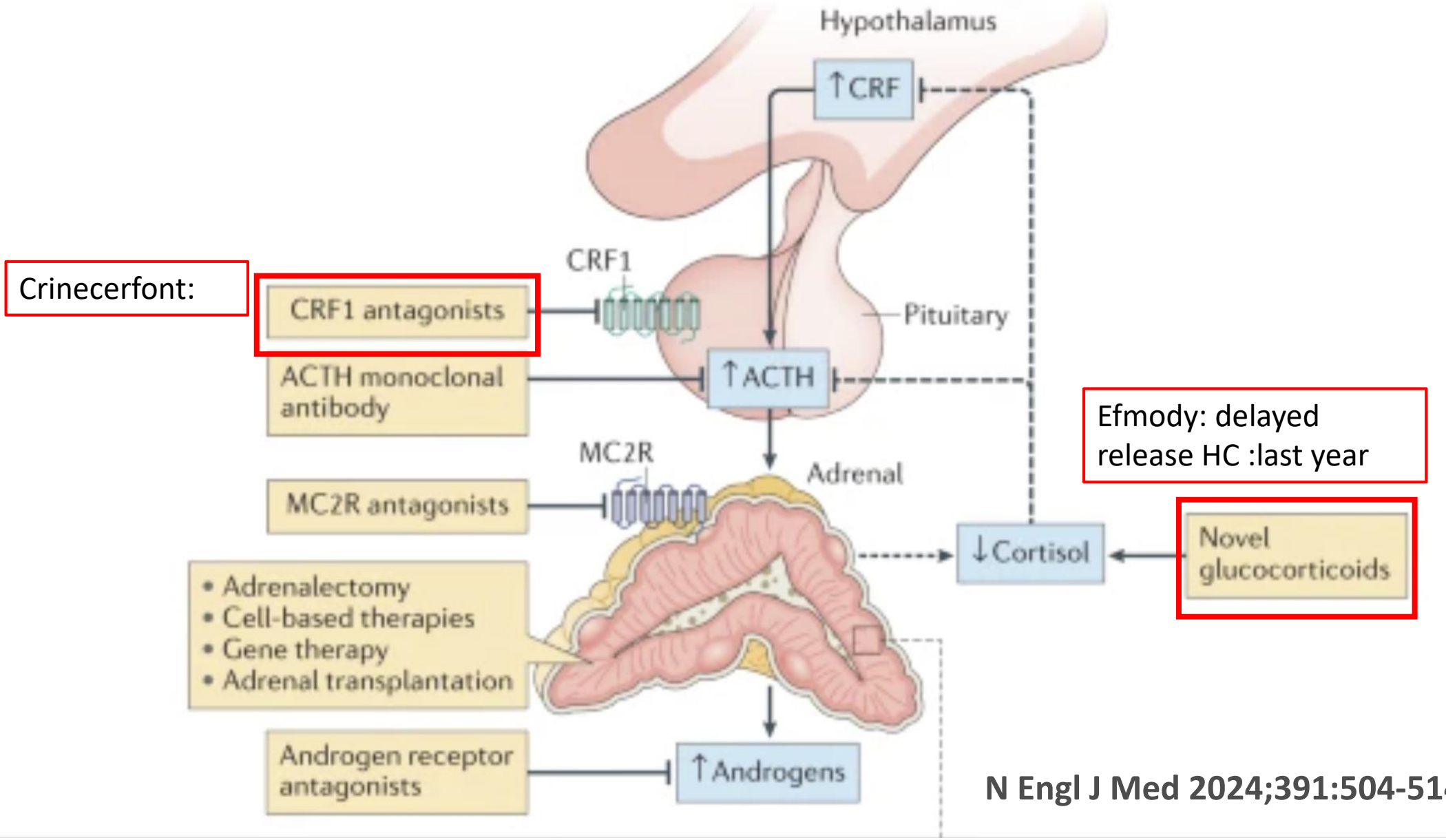


Replace cortisol / prednisolone / dexamethasone

SUPPRESS androgens

N Engl J Med 2024;391:504-514

Novel therapeutic approaches in classic CAH.



Crinecerfont:

Efmody: delayed release HC :last year

N Engl J Med 2024;391:504-514

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia

R.J. Auchus, O. Hamidi, R. Pivonello, I. Bancos, G. Russo, S.F. Witchel, A.M. Isidori, P. Rodien, U. Srirangalingam, F.W. Kiefer, H. Falhammar, D.P. Merke, N. Reisch, K. Sarafoglou, G.B. Cutler, Jr., J. Sturgeon, E. Roberts, V.H. Lin, J.L. Chan, and R.H. Farber, for the CAHtalyst Adult Trial Investigators*

ABSTRACT

BACKGROUND

Adrenal insufficiency in patients with classic 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) is treated with glucocorticoid replacement therapy. Control of adrenal-derived androgen excess usually requires supraphysiologic glucocorticoid dosing, which predisposes patients to glucocorticoid-related complications. Crinecerfont, an oral corticotropin-releasing factor type 1 receptor antagonist, lowered androstenedione levels in phase 2 trials involving patients with CAH.

METHODS

In this phase 3 trial, we randomly assigned adults with CAH in a 2:1 ratio to receive crinecerfont or placebo for 24 weeks. Glucocorticoid treatment was maintained at a stable level for 4 weeks to evaluate androstenedione values, followed by glucocorticoid dose reduction and optimization over 20 weeks to achieve the lowest glucocorticoid dose that maintained androstenedione control (≤120% of the baseline value or within the reference range). The primary efficacy end point was the percent change in the daily glucocorticoid dose from baseline to week 24 with maintenance of androstenedione control.

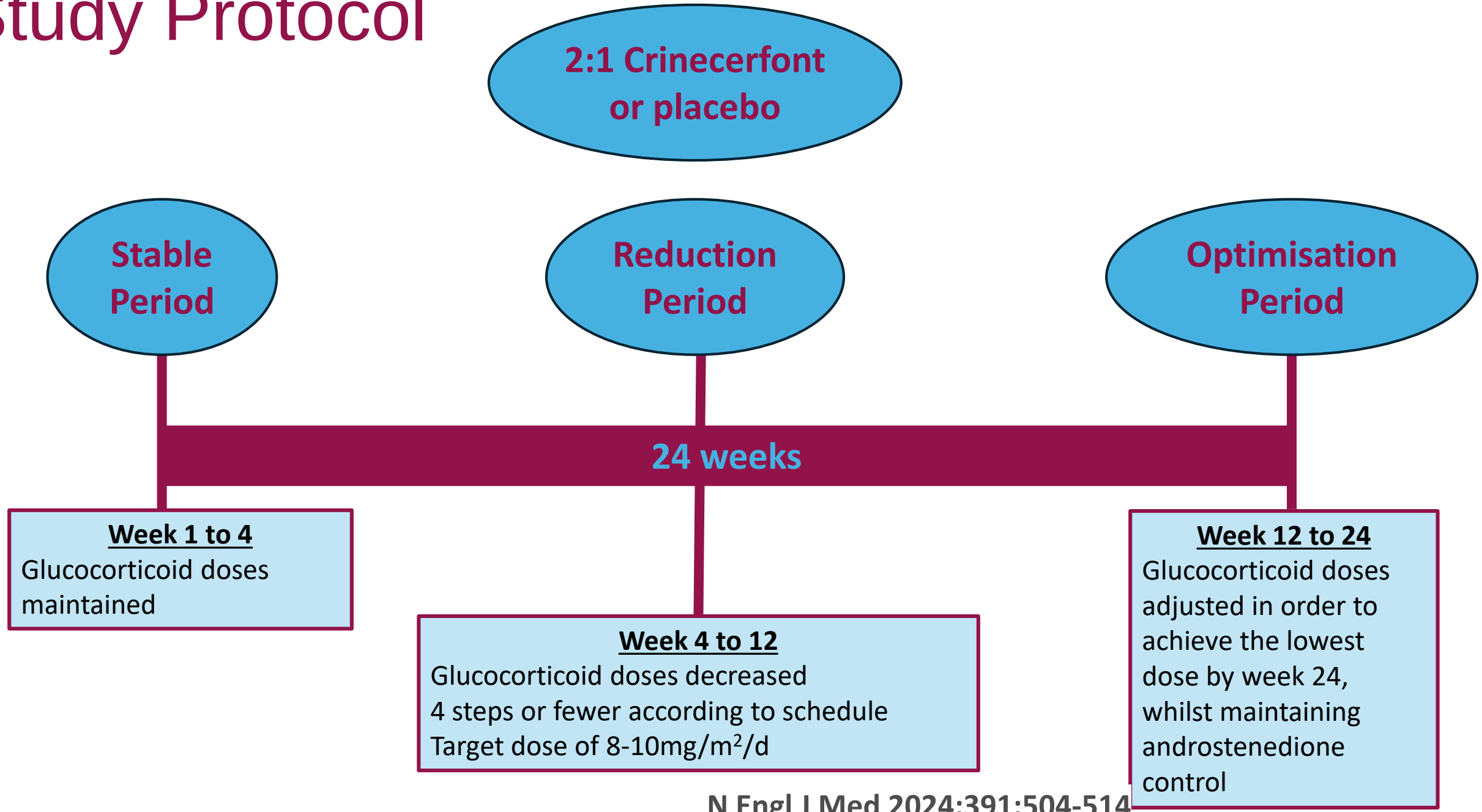
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Auchus can be contacted at rauchus@med.umich.edu or at the Departments of Pharmacology and Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan Medical School, 5560A MSRB II, 1150 W. Medical Center Dr., Ann Arbor, MI 48109.

*The investigators in the CAHtalyst trial are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on June 1, 2024, at NEJM.org.

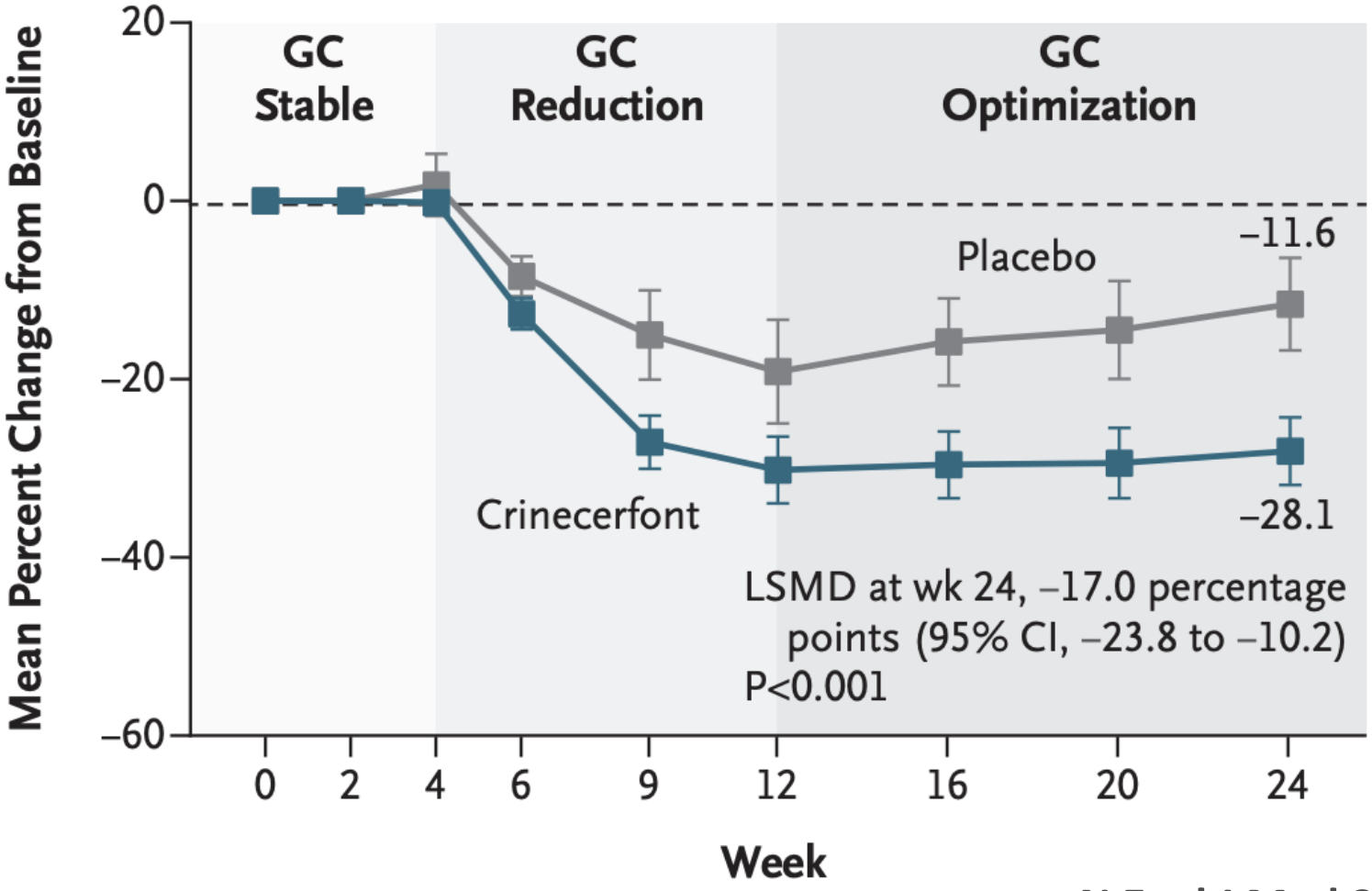
N Engl J Med 2024;391:504-514

Study Protocol



N Engl J Med 2024;391:504-514

Percent Change in Glucocorticoid Dose with Maintenance of Androstenedione Control



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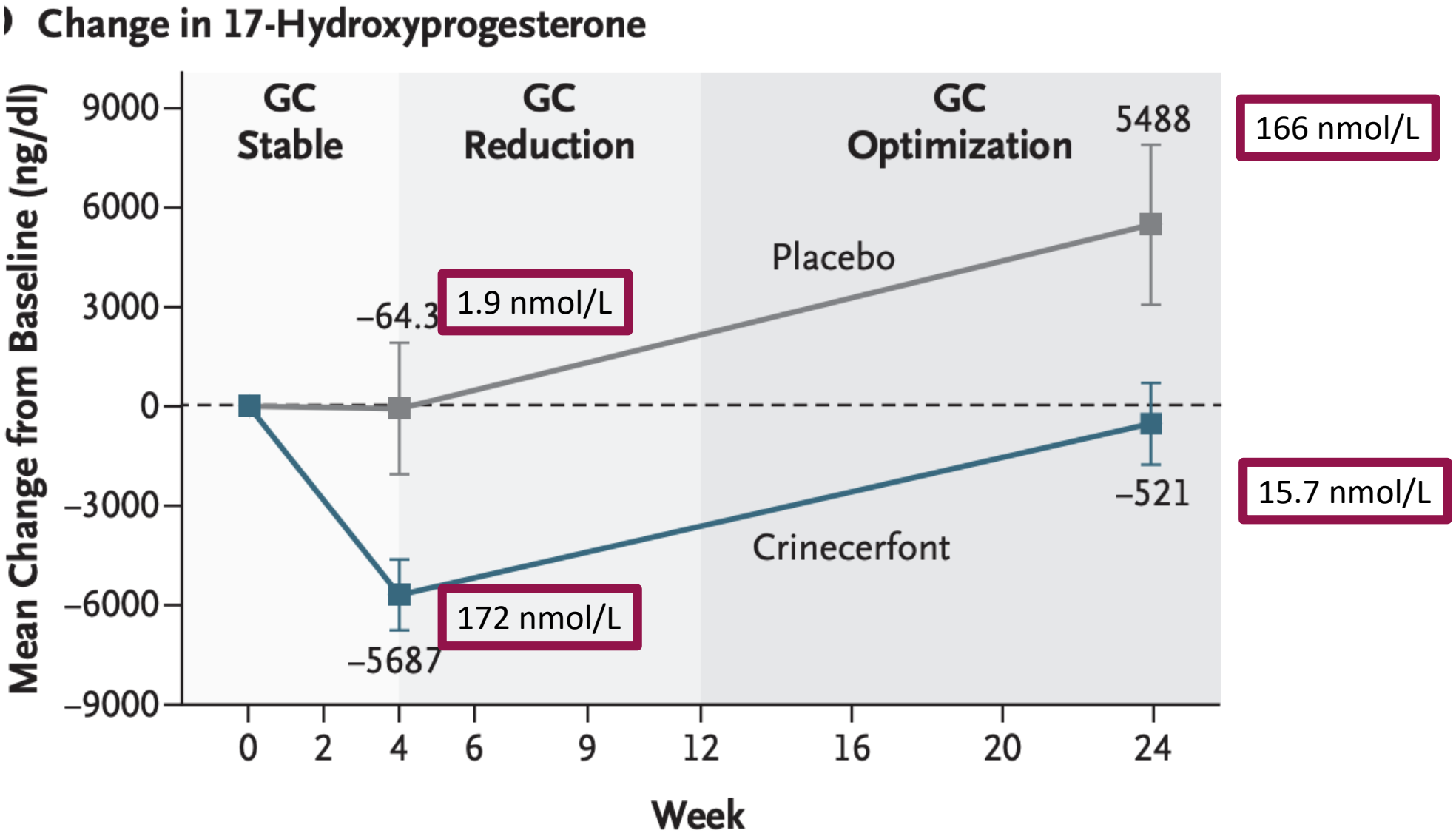


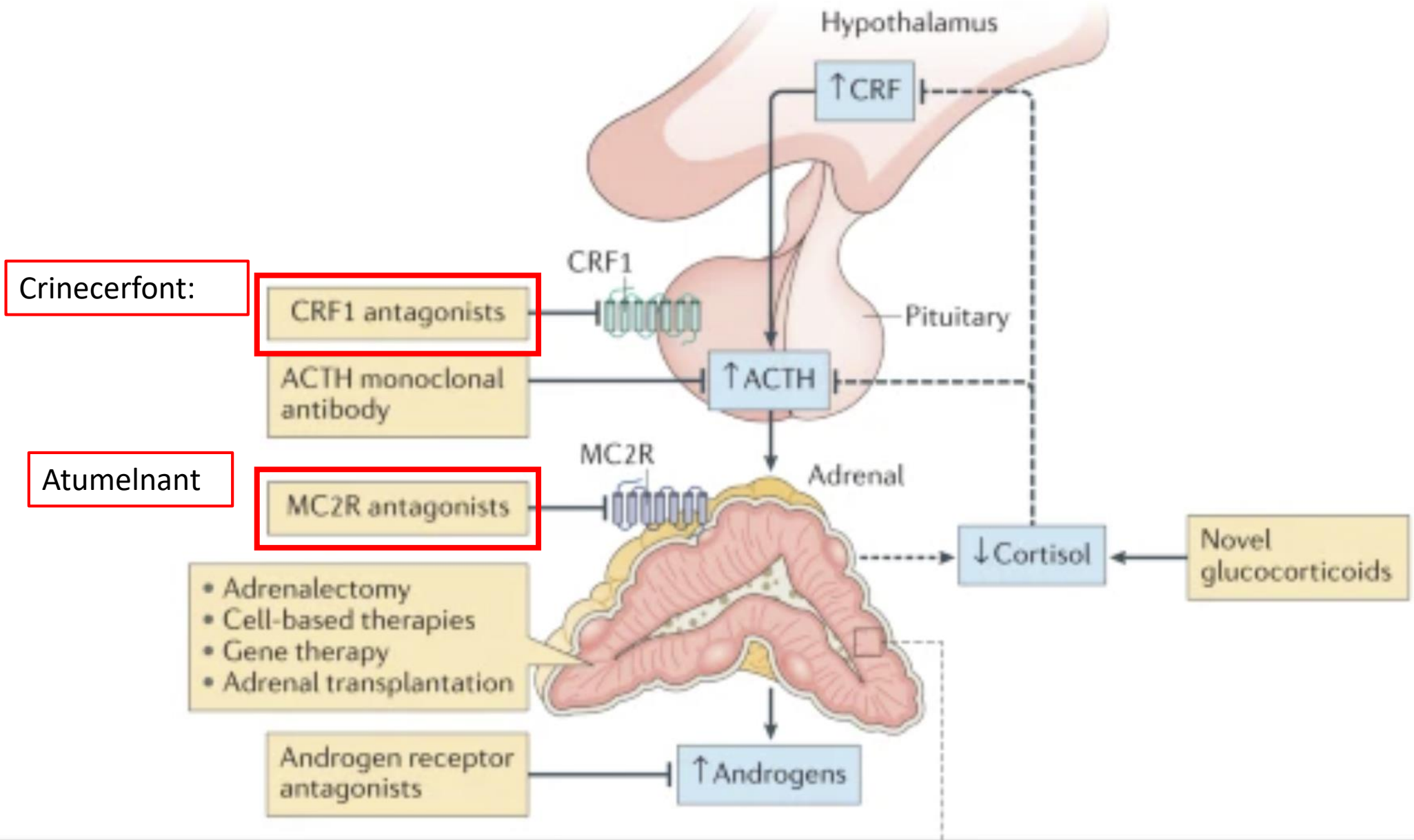
N Engl J Med 2024;391:504-514

Summary

- Crinecerfont therapy allowed a reduction in the glucocorticoid dose and maintenance of A4 control in 63% of patients, as compared to 18% of patients in the placebo group

N Engl J Med 2024;391:504-514

Novel therapeutic approaches in classic CAH. and Cushings disease



Crinecerfont:

Atumelnant

Atumelnant (CRN04894) Induces Rapid and Sustained Reductions in Serum and Urine Cortisol in Patients With ACTH-Dependent Cushing Syndrome During a Phase 1b/2a, Single Center, 10-Day, Inpatient, Open-Label Study

Henrik Elenius[1]; Raven McGlotten[1]; Casey Moore[1]; Alejandro Ayala[2]; Yang Wu[2]; Peter J. Trainer[2]; R. Scott Struthers[2]; Alan Krasner[2]; Stephen F. Betz[2]; Lynnette K. Nieman[1]

[1]Section on Translational Endocrinology, NIDDK, NIH, Bethesda, MD, USA; [2]Crinetics Pharmaceuticals, Inc., San Diego, CA, USA

MON-680

INTRODUCTION

- Available medical therapies for Cushing syndrome are not optimal, with variable efficacy, delays to target cortisol, and significant adverse reactions
- Atumelnant (CRN04894) is a potent, once-daily, oral, nonpeptide, first-in-class competitive and selective melanocortin type 2 receptor antagonist
  - Blocks ACTH-mediated G-protein activation and signaling at the adrenal cortex
  - Being developed for the treatment of ACTH-dependent Cushing syndrome (ADCS) and classic congenital adrenal hyperplasia
- We report preliminary data from the first-in-disease, dose-finding study of atumelnant in patients with ADCS (NCT05804669)

METHODS

- Inpatient participants with active ADCS: 24h urine free cortisol (UFC) >1.3× upper limit of normal (ULN), ACTH >10 pg/mL
- Atumelnant 80 mg administered orally, once daily at 08.00 for 10 days (D1-10) followed by a 4-day washout
- Efficacy endpoints included changes in UFC (ULN 45 µg/d), and pre-dose AM serum cortisol and AM plasma ACTH (ULN 46 pg/mL)
- Daily questionnaires assessed adverse events (AEs) and signs and symptoms of adrenal insufficiency (AI) and ADCS

RESULTS: PARTICIPANTS AND EFFICACY

- All 5 participants (4 men; 4 Cushing disease, 1 ectopic ACTH; median age, 47 years [range, 34-55]) completed the study

Outcome (median, range)	Day 1	Day 11
UFC (µg/d)	252 (99-293)	24 (3.9-51)
AM cortisol (µg/dL)	14 (10.7-18.1)	1.4 (1.0-4.7)
AM ACTH (pg/mL)	52.1 (33-1088)	78 (48.8-4045)

- Each participant developed biochemical evidence of AI (AM cortisol <5 µg/dL) after median 2 doses (range, 1-10), commenced physiologic hydrocortisone (HC) add-back, and completed 10 days of atumelnant
- All participants had biochemical disease control (normal UFC and AM cortisol <5 µg/dL) by day 11, while receiving HC replacement, despite increase in ACTH
- HC was stopped (median day 13; range, 12-18) when AM cortisol was ≥7 µg/dL

Cortisol and ACTH Changes During Atumelnant Treatment

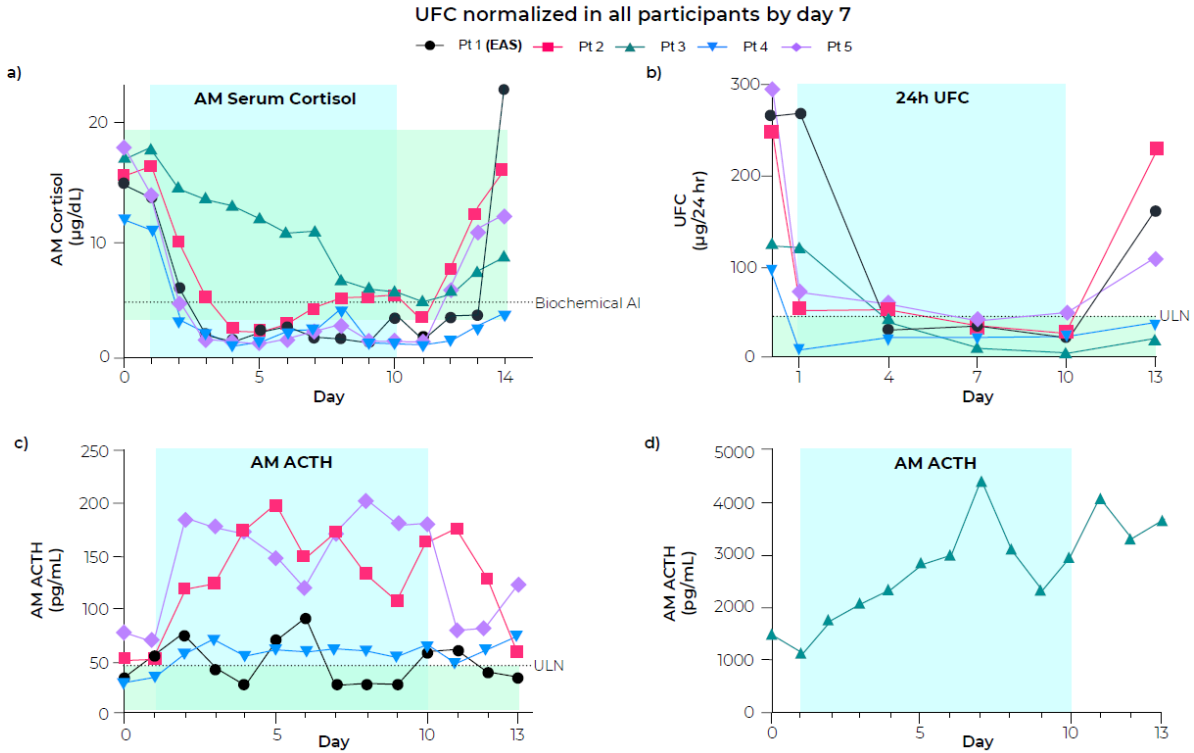


Figure. Cortisol and ACTH levels for each patient (Pt) during atumelnant therapy. Hydrocortisone was given when AM cortisol fell to <5 µg/dL and stopped when cortisol was ≥7 µg/dL. The dotted line represents adrenal insufficiency (cortisol <5 µg/dL) in a), and the ULN in b) and c). In b) day shown for UFC is start of 24h collection. Blue areas indicate treatment days, green areas mark the RR.

- Pt 3, with a slower reduction of serum cortisol, had a markedly higher baseline ACTH
- No loss of efficacy or clinical sequelae related to compensatory rises in ACTH caused by cortisol lowering. No change in ACTH seen in participant with ectopic ACTH syndrome

RESULTS: IMPROVEMENT IN CS SYMPTOMS

- Improvement in Cushing symptoms/signs: insomnia (4/4 pts), trouble concentrating (4/5), anxiety (3/4), tiredness (3/4), hypertension (3/5), brain fog (3/5), bloating (2/4)
- Resolution of neutrophilia (3/3), leukocytosis (2/2), low testosterone (3/4)

RESULTS: ADVERSE EVENTS

- New headache + anorexia and/or nausea (4/5 pts). Most side effects improved with HC add-back
- Serious adverse events included AI (expected and reported per protocol) and one non-treatment related transient GI bleed on day 29
- Two participants had transient, minor elevations in serum creatinine (<1.2 × ULN). Two participants had small increases in ALT (<1.5 × ULN). Notably both had preexisting steatosis

CONCLUSIONS

- The first 5 patients with ADCS to receive once-daily, oral atumelnant experienced rapid lowering of serum and urine cortisol, leading to adrenal insufficiency and improvement or resolution of some signs and symptoms of ADCS
- The observed compensatory increase in ACTH was not associated with loss of efficacy or clinical sequelae
- Atumelnant was generally well-tolerated
- This ongoing study will explore further the relationship between atumelnant dose, including lower doses, and therapeutic response

ACKNOWLEDGMENTS

NIH National Institute of Diabetes and Digestive and Kidney Diseases

This work was supported by the NIDDK intramural program.

Crinetics Pharmaceuticals

A joint Clinical Trial Agreement with Crinetics Pharmaceutical, Inc., supports this work.

ENDO 2024 • June 1-4, 2024 • Boston, MA

Atumelnant (CRN04894) Induces Rapid and Sustained Reductions in Serum and Urine Cortisol in Patients With ACTH-Dependent Cushing Syndrome During a Phase 1b/2a, Single Center, 10-Day, Inpatient, Open-Label Study

Henrik Elenius[1]; Raven McGlotten[1]; Casey Moore[1]; Alejandro Ayala[2]; Yang Wu[2]; Peter J. Trainer[2]; R. Scott Struthers[2]; Alan Krasner[2]; Stephen F. Betz[2]; Lynnette K. Nieman[1]

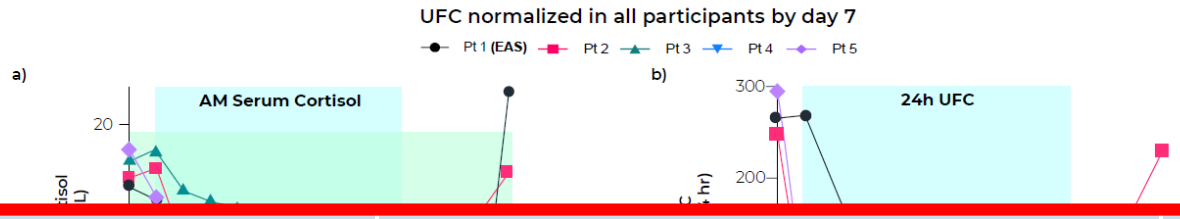
[1]Section on Translational Endocrinology, NIDDK, NIH, Bethesda, MD, USA; [2]Crinetics Pharmaceuticals, Inc., San Diego, CA, USA

MON-680

INTRODUCTION

- Available medical therapies for Cushing syndrome are not optimal, with variable efficacy, delays to target cortisol, and significant adverse reactions
- Atumelnant (CRN04894) is a potent, once-daily, oral, nonpeptide, first-in-class competitive and selective melanocortin type 2 receptor antagonist
  - Blocks ACTH-mediated G-protein activation and signaling at the adrenal cortex
  - Being developed for the treatment of ACTH-dependent Cushing syndrome (ADCS) and classic congenital adrenal hyperplasia
- We report preliminary data from the first-in-disease, dose-finding study of atumelnant in patients with ADCS (NCT05804669)

Cortisol and ACTH Changes During Atumelnant Treatment



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- Resolution of neutrophilia (3/3), leukocytosis (2/2), low testosterone (3/4)

RESULTS: ADVERSE EVENTS

- New headache + anorexia and/or nausea (4/5 pts). Most side effects improved with HC add-back
- Serious adverse events included AI (expected and reported per protocol)

- Each participant developed biochemical evidence of AI (AM cortisol <5 µg/dL) after median 2 doses (range, 1-10), commenced physiologic hydrocortisone (HC) add-back, and completed 10 days of atumelnant
- All participants had biochemical disease control (normal UFC and AM cortisol <5 µg/dL) by day 11, while receiving HC replacement, despite increase in ACTH

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European Journal Endocrinol 2024 190;12-22

Original Research

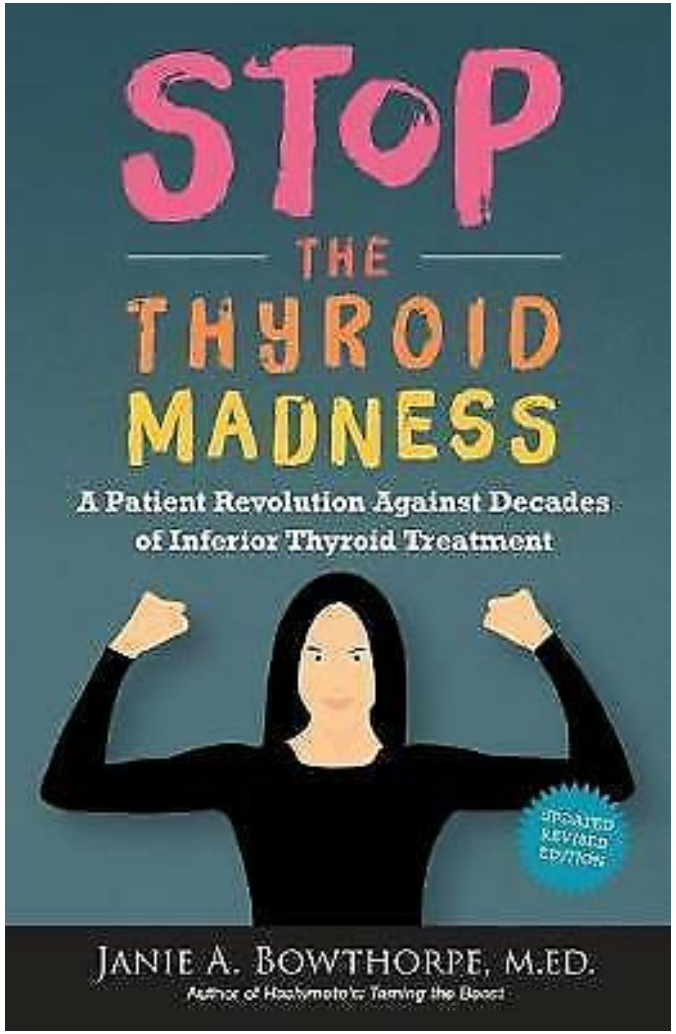
Randomized double-blind placebo-controlled trial on levothyroxine and liothyronine combination therapy in totally thyroidectomized subjects: the LEVOLIO study

Giulia Brigante,[1,2,*] Daniele Santi,[1,2] Gisella Boselli,[1] Gianluca Margiotta,[1] Rossella Corleto,[1] Maria Laura Monzani,[1,2] Andrea Craparo,[1] Michela Locaso,[1] Samantha Sperduti,[1,3] Neena Roy,[1] Livio Casarini,[1,3] Tommaso Trenti,[4] Simonetta Tagliavini,[4] Maria Cristina De Santis,[4] Laura Roli,[4] Vincenzo Rochira,[1,2] and Manuela Simoni[1,2,3]

[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, 41124 Modena, Italy
[2]Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, 41126 Modena, Italy
[3]Center for Genomic Research, University of Modena and Reggio Emilia, 41126 Modena, Italy
[4]Department of Laboratory Medicine and Anatomy Pathology, Azienda USL Modena, 41126 Modena, Italy

*Corresponding author: Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; Unit of Endocrinology, OCSAE, Via P. Gardini 1355, 41126 Modena, Italy. Email: giulia.brigante@unimore.it

The Problem: from thyroid patients :



- The problem is your doctor
- They only spend an hour in their medical course learning about the thyroid
- They don’t know any better
- It is a shame that we have to fight to get what our bodies need

Weak guidelines

ATA and ETA : LT4 therapy of choice in hypothyroidism; do not support combined use due to insufficient evidence from controlled trials, and lack of long term LT3 safety data; and unavailability of LT3 formulations that mirror natural physiology

BTA: L-T4/L-T3 combination therapy in patients with hypothyroidism should not be used routinely.

Consider as an **experimental approach** if persistent complaints despite TSH in ref range

Open and **balanced discussion** of benefits, likely risks of over-replacement and lack of long-term safety data

Discontinue if no improvement after 3 months

Aim of Levolio

- To evaluate the effect of combination therapy with **LT4 + LT3** on peripheral tissues, **as reflected by sex hormone binding globulin (SHBG) levels**, in totally thyroidectomized patients without residual thyroid function

- Achieved by partially replacing LT4 with customized twice-daily doses of LT3 (respecting circadian rhythm and the physiological T3/T4 ratio)

- Changes in **other tissue markers** and **quality of life**
- DIO2- rs225014 and MCT10-rs17606253 genetic variant effects

European Journal Endocrinol 2024 190;12-22

Why these genes?

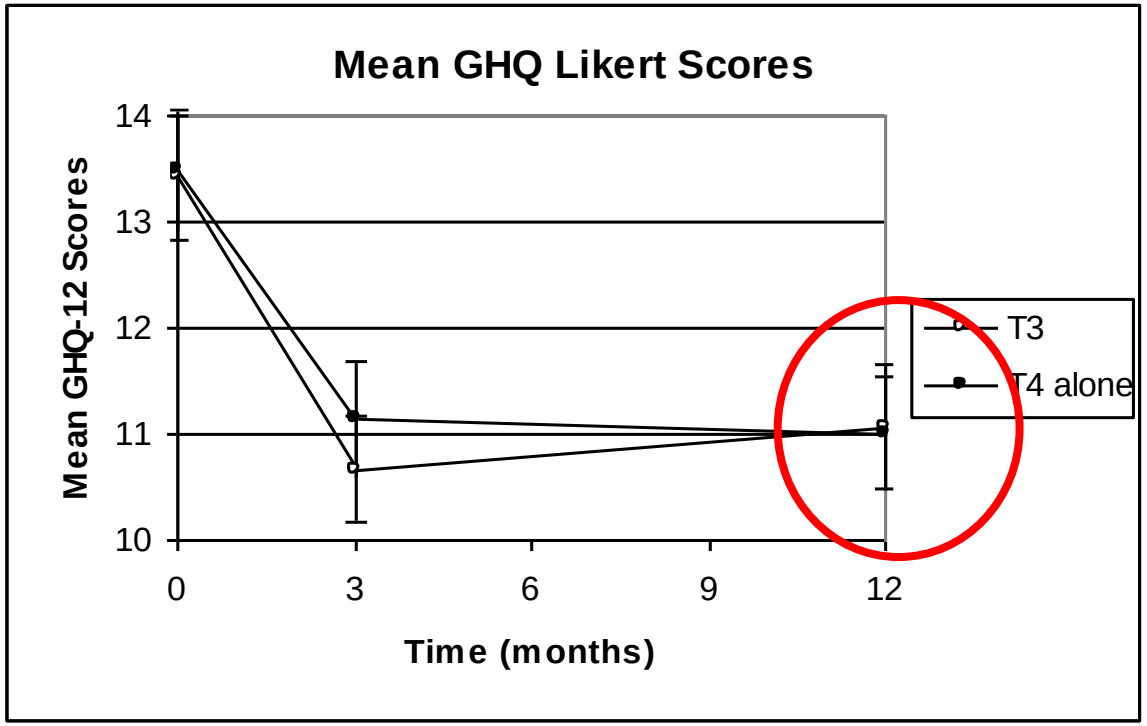
Previous studies on T3 from 2005 (!)

- Watts study (Weston Area T4T3 study) (2005)
- N=697
- Reduced their thyroxine dose by 50mcg

- Added a capsule of either 50mcg thyroxine
- 10mcg liothyronine (blind and randomised)
- Measured general health (GHQ 12) score – 0 to 36 (36=very tired)

Everybody benefits, even those only on T4…

WATTS study – T4 vs T4/T3 n=697



- 10 ug T3 substituted for 50ug T4
- Note persistent placebo effect

Saravanan et al 2005

Partial Substitution of Thyroxine (T_4) with Tri-Iodothyronine in Patients on T_4 Replacement Therapy: Results of a Large Community-Based Randomized Controlled Trial

Ponnusamy Saravanan, Dawn J. Simmons, Rosemary Greenwood, Tim J. Peters, and Colin M. Dayan

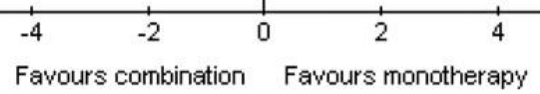
Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology (P.S., D.J.S., C.M.D.) and Academic Unit of Primary Health Care, Department of Community-Based Medicine (T.J.P.), University of Bristol, Bristol BS1 3NY, United Kingdom; and Research and Development Support Unit (R.G.), Bristol Royal Infirmary, Bristol BS2 8HW, United Kingdom

Conflicting results have recently been published about the benefits of combined T_4 and T_3 in treating hypothyroid patients. However, these studies may have been underpowered to detect differences in psychological well-being specifically related to T_4 replacement. We conducted a large, double-blind, randomized controlled trial of partial substitution of 50 μg T_4 by 10 μg T_3 *vs.* the original dose of T_4 in 697 hypothyroid patients. Thyroid function showed a rise in TSH (132%), a fall in free T_4 (35%, $P < 0.001$), and unchanged basal free T_3 levels ($P = 0.92$). At 3 months, there was a large (39%) placebo effect improvement in psychiatric caseness defined by the General Health Questionnaire (GHQ) 12 score in the control group compared with baseline, and this was sustained at 12 months. Differences *vs.* the intervention (T_3) group were more modest with improvements in GHQ caseness (odds ratio, 0.61; 95% confidence interval, 0.42, 0.90; $P = 0.01$) and Hospital Anxiety and Depression questionnaire-anxiety scores at 3 months ($P < 0.03$) but not GHQ Likert scores, Hospital Anxiety and Depression questionnaire-depression, thyroid symptoms, or visual analog scales of mood and the initial differences were lost at 12 months. These results may be consistent with a subgroup of patients showing transient improvement after partial substitution with T_3 but do not provide conclusive evidence of specific benefit from partial substitution of T_4 by T_3 in patients on T_4 replacement. They also emphasize the large and sustained placebo effect that can follow changes in thyroid hormone administration. (*J Clin Endocrinol Metab* 90: 805–812, 2005)

2005: T3=£4/month T4=£1

No benefit….meta-analysis

Study or sub-category	Combination therapy N	Combination therapy Mean (SD)	Monotherapy N	Monotherapy Mean (SD)	Weight %	SMD (random) 95% CI	Quality
01 Non-crossover design							
Appelhof 2005	45	24.00(9.10)	45	25.20(10.00)	10.31	-0.12 [-0.54, 0.29]	A
Clyde 2003	17	4.65(5.61)	17	3.82(4.10)	7.32	0.16 [-0.51, 0.84]	A
Sawka 2003	20	0.69(0.64)	19	0.56(0.58)	7.77	0.21 [-0.42, 0.84]	A
Levitt 2005	17	5.40(3.10)	14	5.20(2.70)	6.98	0.07 [-0.64, 0.77]	D
Saravanan 2005	324	4.26(2.41)	328	4.54(2.39)	13.10	-0.12 [-0.27, 0.04]	D
Subtotal (95% CI)	423		423		45.49	-0.08 [-0.22, 0.05]	
Test for heterogeneity: Chi² = 1.73, df = 4 (P = 0.78), I² = 0%							
Test for overall effect: Z = 1.23 (P = 0.22)							
02 Crossover design							
Bunevicius 1999	33	7.90(5.30)	33	9.80(7.70)	9.43	-0.28 [-0.77, 0.20]	A
Bunevicius 2002	10	3.30(3.50)	10	5.20(5.10)	5.45	-0.42 [-1.30, 0.47]	A
Escobar-M. 2005	26	23.90(29.40)	26	23.80(28.80)	8.74	0.00 [-0.54, 0.55]	A
Walsh 2003	101	37.60(1.70)	101	36.10(1.70)	11.80	0.88 [0.59, 1.17]	A
Siegmund 2004	23	5.50(5.70)	23	6.90(6.70)	8.32	-0.22 [-0.80, 0.36]	B
Rodriguez 2005	301	10.40(7.50)	30	8.40(7.60)	10.77	0.27 [-0.11, 0.64]	D
Subtotal (95% CI)	494		223		54.51	0.09 [-0.37, 0.55]	
Test for heterogeneity: Chi² = 27.69, df = 5 (P < 0.0001), I² = 81.9%							
Test for overall effect: Z = 0.39 (P = 0.70)							
Total (95% CI)	917		646		100.00	0.07 [-0.20, 0.34]	
Test for heterogeneity: Chi² = 42.11, df = 10 (P < 0.00001), I² = 76.3%							
Test for overall effect: Z = 0.51 (P = 0.61)							



Grozinsky-Glasberg, S. et al. J Clin Endocrinol Metab 2006;91:2592-2599

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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

Endocrine Institute (S.G.-G.) and Department of Medicine E (A.F., L.L.), Rabin Medical Center, and Geha Mental Health Center (E.N., A.W.), Petah-Tiqva 49100, Israel; and Sackler Faculty of Medicine (E.N., A.W., L.L.), Tel-Aviv University, Ramat-Aviv, Tel-Aviv 69978, Israel

Context: In some patients symptoms of hypothyroidism persist despite therapy with T_4.

Objective: The objective of the study was to compare the effectiveness of T_4-T_3 combination *vs.* T_4 monotherapy for the treatment of clinical hypothyroidism in adults.

Data Sources: PubMed, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched in September 2005. References of all included trials were scanned for additional studies. We put no restrictions on language, year of publication, or publication status.

Study Selection: All randomized trials that compared the effectiveness of T_4-T_3 combination *vs.* T_4 monotherapy for the treatment of clinical hypothyroidism in adults were included.

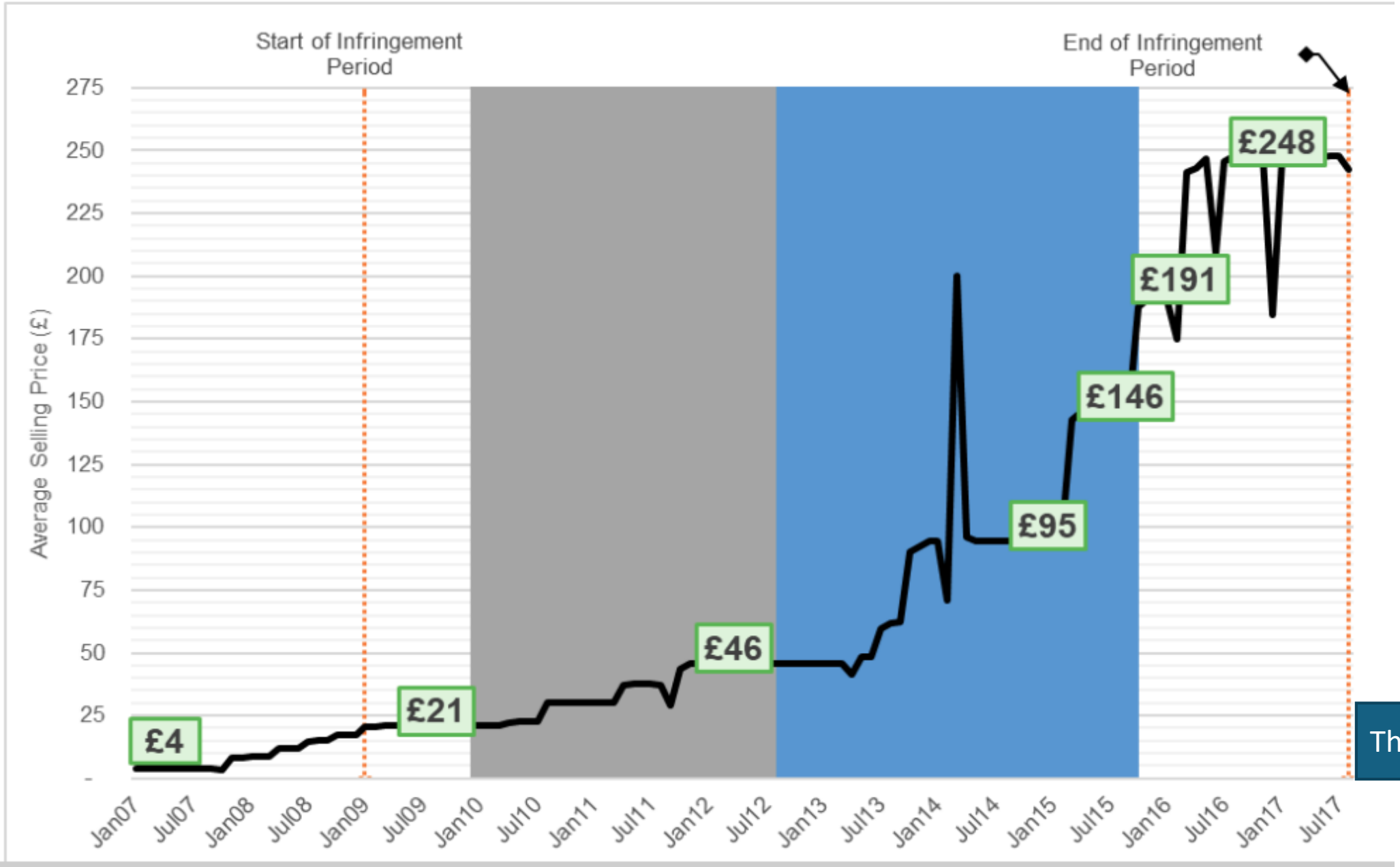
Data Extraction: The data were extracted by two independent reviewers.

Data Synthesis: We included 11 studies, in which 1216 patients were randomized. No difference was found in the effectiveness of combination *vs.* monotherapy in any of the following symptoms: bodily pain [standardized mean difference (SMD) 0.00, 95% confidence interval (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, triglyceride levels, low-density lipoprotein, and high-density lipoprotein. Adverse events did not differ between regimens.

Conclusions: T_4 monotherapy should remain the treatment of choice for clinical hypothyroidism. (***J Clin Endocrinol Metab* 91: 2592–2599, 2006**)

2006: T3=£4/month T4=£1

Figure 1.1: Advanz's monthly ASP for Liothyronine Tablets (January 2007 – July 2017)



Thyroxine £1.50

January 2020

North Central London
Joint Formulary Committee

Oral liothyronine in Primary Hypothyroidism: Position Statement

New patients

Prescribers in primary care should not initiate liothyronine (T3) for adults, children and young people.

Consultant NHS Endocrinologists may offer liothyronine in rare situations for patients who meet national criteria. There is no obligation for endocrinologists to offer liothyronine owing to the limited evidence of benefit over levothyroxine (T4) monotherapy and uncertainty over long-term safety.

GPs should only take on prescribing of liothyronine where the treatment is recommended by a consultant NHS Endocrinologist, after a successful trial has been carried out. GPs should not take on prescribing for patients initiated on liothyronine in private clinics, abroad, or via other self-funded routes.

Existing patients

All patients prescribed liothyronine, either alone or in combination with levothyroxine, should be reviewed by a consultant NHS Endocrinologist with consideration given to switching to levothyroxine monotherapy where clinically appropriate.

This position statement does not apply to liothyronine as an adjuvant to radioactive iodine.

Endocrine Care

A Common Variation in Deiodinase 1 Gene *DIO1* Is Associated with the Relative Levels of Free Thyroxine and Triiodothyronine

Vijay Panicker, Christie Cluett, Beverley Shields, Anna Murray, Kirstie S. Parnell, John R. B. Perry, Michael N. Weedon, Andrew Singleton, Dena Hernandez, Jonathan Evans, Claire Durant, Luigi Ferrucci, David Melzer, Ponnusamy Saravanan, Theo J. Visser, Graziano Ceresini, Andrew T. Hattersley, Bijay Vaidya, Colin M. Dayan, and Timothy M. Frayling

Henry Wellcome Laboratories for Integrative Neurosciences and Endocrinology (V.P., P.S., C.M.D.) and Academic Unit of Psychiatry (J.E., C.D.), University of Bristol, Bristol BS1 3NY, United Kingdom; Faculty of Medicine, Dentistry, and Health Sciences (V.P.), University of Western Australia, Perth 6009, Australia; Genetics of Complex Traits (V.P., C.C., B.S., A.M., K.S.P., J.R.B.P., M.N.W., D.M., A.T.H., T.M.F.), Institute of Biomedical and Clinical Science, Peninsula Medical School, Exeter EX1 2LU, United Kingdom; Molecular Genetics Unit (A.S., D.H.) and Longitudinal Studies Section (L.F.), Clinical Research Branch, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892; Clinical Sciences Research Unit (P.S.), University of Warwick, Warwick CV2 2DX United Kingdom; Department of Internal Medicine (T.J.V.), Erasmus University Medical Centre, 3015 GD Rotterdam, The Netherlands; Department of Internal Medicine and Biomedical Sciences (G.C.), Section of Geriatrics, University of Parma, 43100 Parma, Italy; and Department of Endocrinology (B.V.), Royal Devon and Exeter Hospital, Exeter EX2 5DW, United Kingdom

2008

Introduction: Genetic factors influence circulating thyroid hormone levels, but the common gene variants involved have not been conclusively identified. The genes encoding the iodothyronine deiodinases are good candidates because they alter the balance of thyroid hormones. We aimed to thoroughly examine the role of common variation across the three deiodinase genes in relation to thyroid hormones.

TABLE 2. The fT_3/fT_4 ratio by genotype in WATTs cohort

	TT Common homozygous		TC Heterozygous		CC Minor homozygous		*P* for trend	
SNP	Mean fT_3/fT_4 (95% CI)	n	Mean fT_3/fT_4 (95% CI)	n	Mean fT_3/fT_4 (95% CI)	n	Unadjusted	Adjusted[a]
DIO1								
rs11206237	0.187 (0.183, 0.192)	399	0.187 (0.180, 0.195)	130	0.192 (0.177, 0.207)	16	0.82	0.96
rs11206244	0.193 (0.187, 0.199)	239	0.186 (0.181, 0.192)	238	0.175 (0.166, 0.185)	69	0.005	0.004
rs2235544	0.177 (0.171, 0.184)	143	0.189 (0.184, 0.195)	288	0.196 (0.187, 0.205)	111	0.001	0.001
rs2268181	0.187 (0.182, 0.192)	387	0.189 (0.182, 0.196)	140	0.192 (0.178, 0.205)	19	0.63	0.88
rs2294511	0.192 (0.186, 0.197)	240	0.185 (0.179, 0.190)	248	0.183 (0.171, 0.195)	56	0.08	0.08
rs2294512	0.186 (0.180, 0.191)	252	0.186 (0.180, 0.191)	245	0.205 (0.190, 0.220)	50	0.06	0.02
rs4926616	0.189 (0.183, 0.194)	245	0.188 (0.182, 0.194)	236	0.186 (0.174, 0.197)	56	0.67	0.68
rs731828	0.185 (0.179, 0.191)	183	0.189 (0.183, 0.194)	278	0.190 (0.179, 0.201)	84	0.32	0.19
rs7527713	0.187 (0.182, 0.192)	362	0.189 (0.182, 0.196)	157	0.184 (0.170, 0.198)	26	0.96	0.75
DIO2								
rs225011	0.184 (0.177, 0.190)	172	0.189 (0.183, 0.195)	264	0.190 (0.182, 0.198)	107	0.22	0.24
rs225014	0.186 (0.180, 0.192)	223	0.187 (0.181, 0.193)	236	0.193 (0.184, 0.203)	87	0.25	0.28
rs225015	0.187 (0.181, 0.193)	237	0.187 (0.181, 0.193)	236	0.193 (0.183, 0.204)	71	0.42	0.46
DIO3								
rs17716499	0.191 (0.185, 0.196)	202	0.184 (0.178, 0.189)	248	0.193 (0.183, 0.202)	95	0.89	0.97
rs7150269	0.191 (0.184, 0.197)	169	0.186 (0.180, 0.192)	254	0.187 (0.179, 0.196)	121	0.48	0.50
rs8011440	0.190 (0.184, 0.195)	215	0.186 (0.180, 0.192)	246	0.188 (0.178, 0.199)	85	0.65	0.54
rs945006	0.187 (0.183, 0.192)	438	0.187 (0.178, 0.196)	92	0.200 (0.156, 0.243)	10	0.69	0.55

CI, Confidence interval.

[a] Adjusted for age and sex.

Endocrine Care

A Common Variation in Deiodinase 1 Gene *DIO1* Is Associated with the Relative Levels of Free Thyroxine and Triiodothyronine

Vijay Panicker, Christie Cluett, Beverley Shields, Anna Murray, Kirstie S. Parnell, John R. B. Perry, Michael N. Weedon, Andrew Singleton, Dena Hernandez, Jonathan Evans, Claire Durant, Luigi Ferrucci, David Melzer, Ponnusamy Saravanan, Theo J. Visser, Graziano Ceresini, Andrew T. Hattersley, Bijay Vaidya, Colin M. Dayan, and Timothy M. Frayling

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2008

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ORIGINAL ARTICLE

Endocrine Care

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

Methods: We analyzed common variants in the three deiodinase genes *vs.* baseline psychological morbidity and response to T_4/T_3 in 552 subjects on T_4 from the Weston Area T_4 T_3 Study (WATTS). Primary outcome was improvement in psychological well-being assessed by the General Health Questionnaire 12 (GHQ-12).

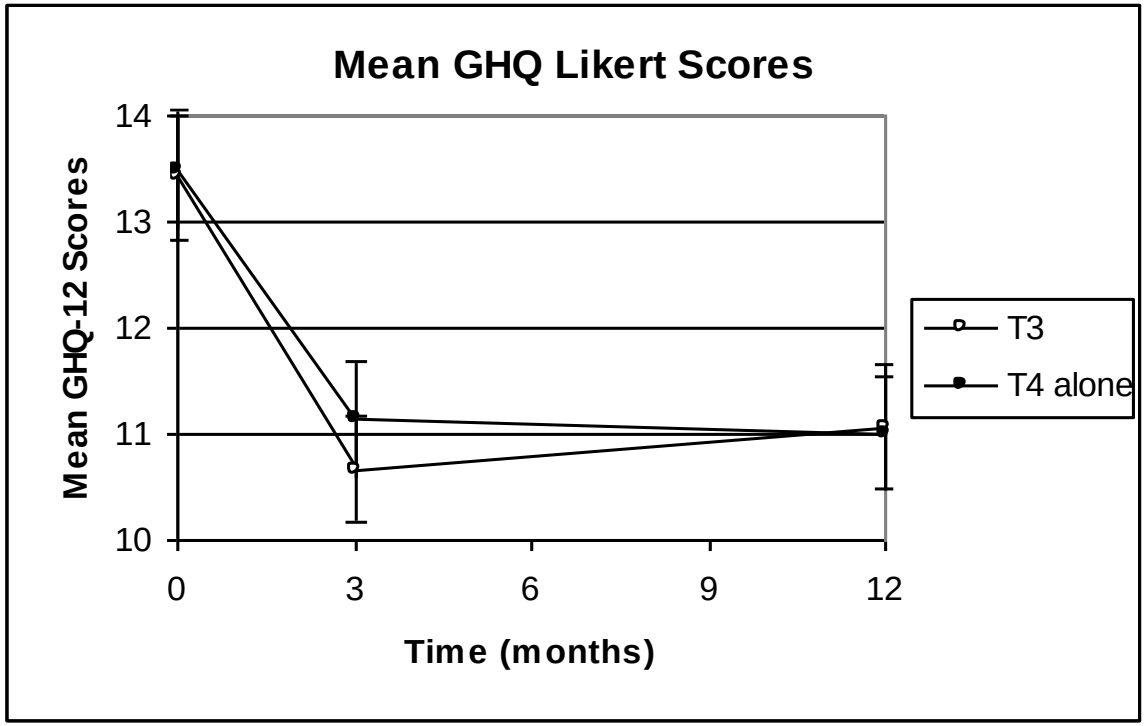
Results: The rarer CC genotype of the rs225014 polymorphism in the deiodinase 2 gene (*DIO2*) was present in 16% of the study population and was associated with worse baseline GHQ scores in patients on T_4 (CC *vs.* TT genotype: 14.1 *vs.* 12.8, $P = 0.03$). In addition, this genotype showed greater improvement on T_4/T_3 therapy compared with T_4 only by 2.3 GHQ points at 3 months and 1.4 at 12 months ($P = 0.03$ for repeated measures ANOVA). 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 both 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. (***J Clin Endocrinol Metab* 94: 1623–1629, 2009**)

2009

Everybody benefits…

WATTS study – T4 vs T4/T3 n=697



- 10 ug T3 substituted for 50ug T4
- Note persistent placebo effect

Saravanan et al 2005

TABLE 2. Relationship between genotype and GHQ-12 scores at baseline in all studied SNPs

	TT Common homozygous		TC Heterozygous		CC Minor homozygous		
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	*P*
DIO1							
rs11206237	399	13.4 (12.9, 13.9)	130	13.5 (12.6, 14.4)	16	11.7 (9.5, 13.9)	0.56
rs11206244	239	13.2 (12.5, 13.8)	238	13.6 (12.9, 14.3)	69	13.2 (12.1, 14.2)	0.70
rs2235544	143	13.6 (12.8, 14.4)	288	13.4 (12.8, 14.0)	111	13.1 (12.2, 14.1)	0.50
rs2268181	387	13.4 (12.9, 14.0)	140	13.3 (12.5, 14.2)	19	11.9 (10.0, 13.9)	0.37
rs2294511	240	13.2 (12.6, 13.8)	248	13.6 (12.9, 14.3)	56	13.2 (11.9, 14.5)	0.71
rs2294512	252	13.7 (13.1, 14.4)	245	13.0 (12.3, 13.7)	50	13.2 (11.8, 14.6)	0.18
rs4926616	245	13.2 (12.5, 13.8)	236	13.7 (13.0, 14.4)	56	13.1 (11.7, 14.5)	0.63
rs731828	183	13.4 (12.7, 14.1)	278	13.2 (12.6, 13.8)	84	13.8 (12.7, 14.9)	0.70
rs7527713	362	13.5 (12.9, 14.0)	157	13.1 (12.3, 13.9)	26	13.0 (11.1, 15.0)	0.46
DIO2							
rs225011	172	12.6 (11.9, 13.3)	264	13.7 (13.1, 14.3)	107	13.7 (12.5, 14.9)	0.06
rs225014	**223**	**12.8 (12.2, 13.4)**	**236**	**13.6 (13.0, 14.3)**	**87**	**14.1 (12.8, 15.5)**	**0.02**
rs225015	**237**	**12.9 (12.3, 13.5)**	**236**	**13.6 (12.9, 14.3)**	**71**	**14.3 (12.8, 15.8)**	**0.03**
DIO3							
rs17716499	202	12.9 (12.3, 13.6)	248	13.6 (12.9, 14.3)	95	13.7 (12.7, 14.6)	0.19
rs7150269	121	13.6 (12.6, 14.5)	254	13.4 (12.8, 14.1)	169	13.1 (12.4, 13.8)	0.44
rs8011440	215	13.1 (12.5, 13.8)	246	13.5 (12.8, 14.2)	85	13.4 (12.3, 14.5)	0.51
rs945006	438	13.4 (12.9, 13.8)	92	13.4 (12.3, 14.4)	10	13.4 (9.7, 17.1)	0.98

Bold values indicate $P < 0.05$. CI, Confidence interval.

Everybody benefits…

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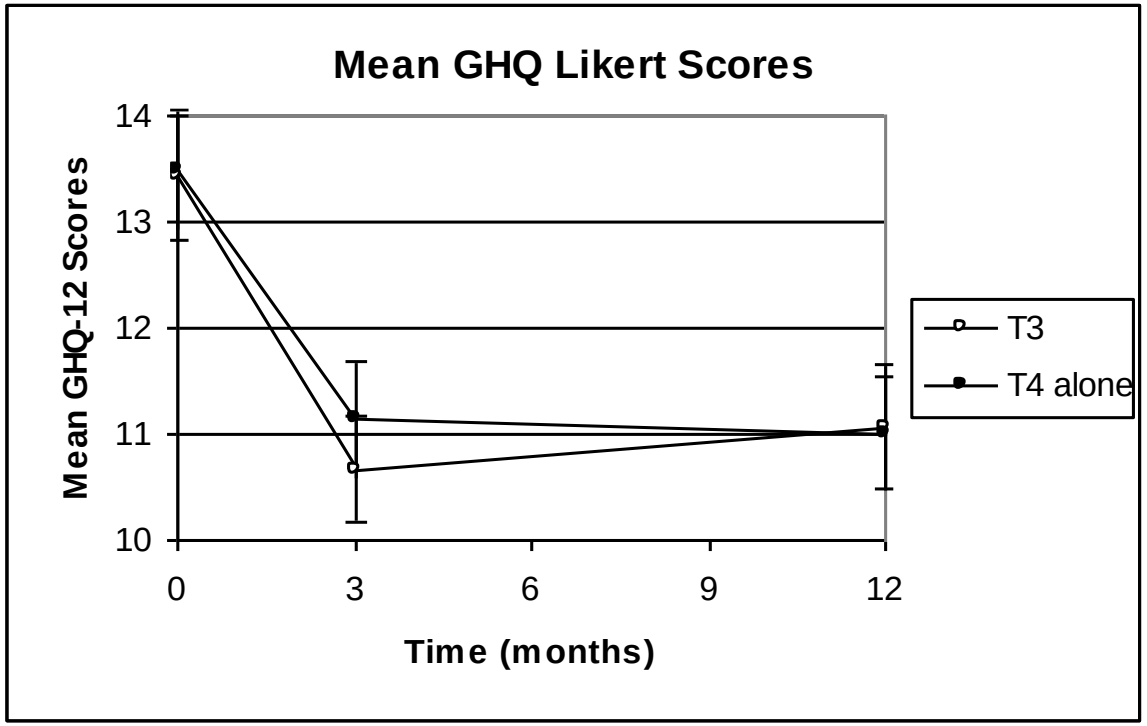

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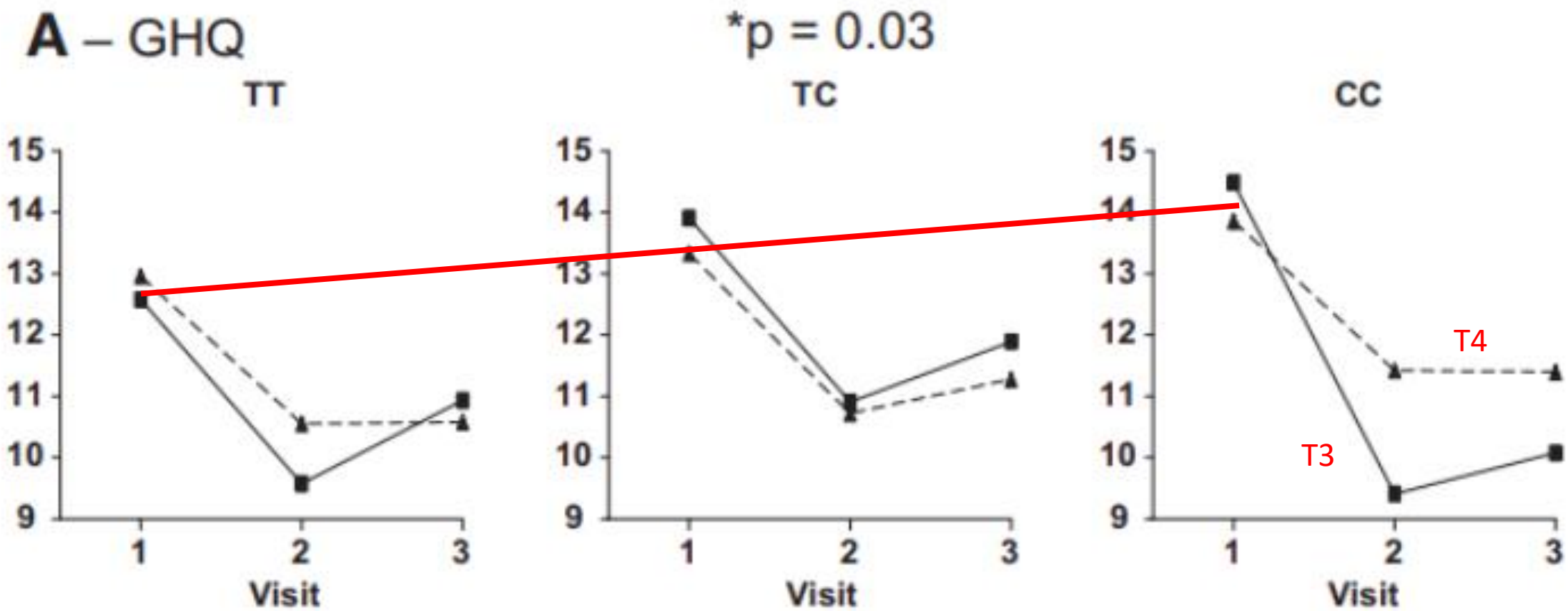
J Clin Endocrinol Metab, May 2009, 94(5):1623–1629



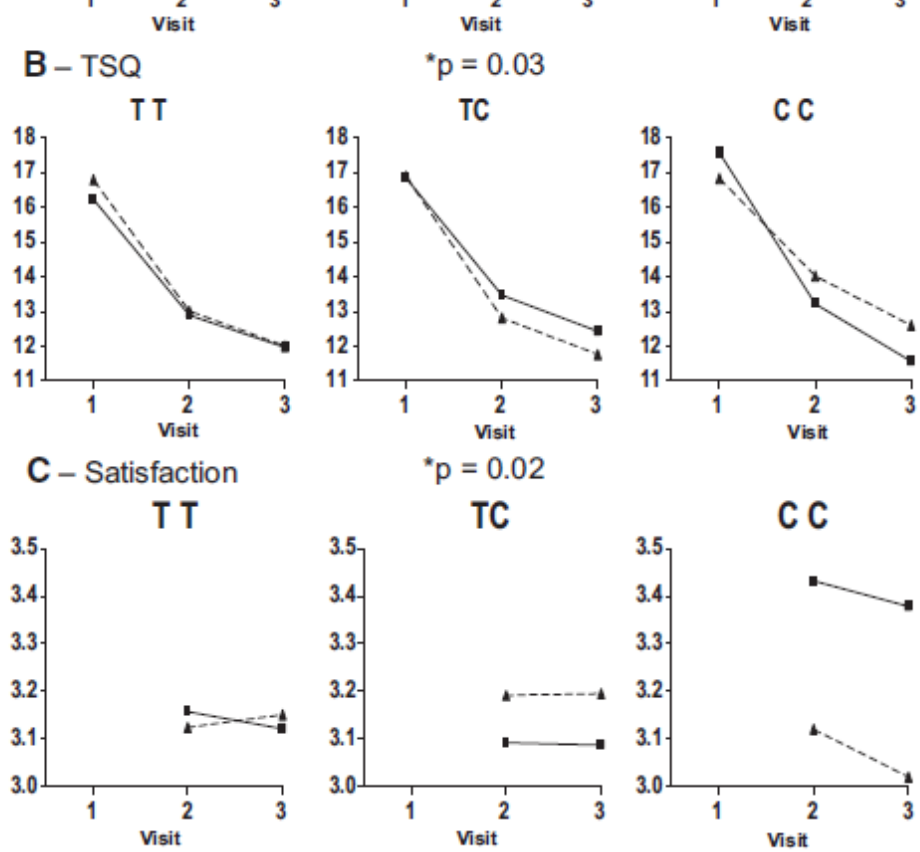


FIG. 1. Response to therapy by genotype rs225014 as measured by GHQ (A), TSQ (B), and satisfaction score (C). *Squares* and *continuous line*, T_4/T_3 group; *triangles* and *dashed line*, T_4-only group. *P* values reflect the significance of an effect of the CC genotype on difference in scores by treatment arm using repeated-measures ANOVA. *, $P < 0.05$. There was a significant effect of the interaction between the CC genotype and treatment arm at follow-up (visits 2 and 3) on GHQ scores, TSQ scores, and satisfaction. There are no baseline (visit 1) scores for satisfaction with therapy (C) because this was not assessed at baseline. For GHQ and TSQ scores, higher scores indicate worse well-being, whereas for satisfaction higher scores indicate more satisfied.

effect was suggested by the graphs (Fig. 1) and has been proposed previously (29). For satisfaction score, no baseline score was adjusted for because there was no baseline assessment. No correction was made for multiple testing because, despite being the largest study to date, it is still underpowered to detect all but very large differential gene-treatment effects. Instead, we have chosen to report the *P* values and associations, which should be considered suggestive, and have qualified our findings by stating clearly that the results need replicating as a risk of type I statistical error exists. Analyses were performed on Stata version 9.0 (www.stata.com) and SPSS version 14.0 (www.spss.com).

all of those from *DIO1* and *DIO3* did not show any association. Because the two D2 SNPs that had showed an association, rs225014 and rs225015, are in strong linkage disequilibrium with an r^2 of 0.88 in this population, and rs225014 is also in linkage disequilibrium with the third SNP studied in this gene, rs225011 (r^2 of 0.59), further analysis is shown on rs225014 alone. In this SNP the possible base combinations of thymine (T) and cytosine (C) are TT, TC and CC. For GHQ-12, each C allele of rs225014 was associated with an average increase of 0.71 GHQ points (worse well-being, *P* for the trend = 0.02) with a difference between the CC and TT alleles of 1.3 points.

Table 3 shows the relationship between rs225014 genotype and baseline psychological well-being for other parameters measured in WATTS. The scores for GHQ-12 from Table 2 are included for comparison. An association with HAD-D (depression) caseness in the same direction as GHQ was seen ($P = 0.01$). Each C allele was associated with a 49% increase in odds of being a HAD-D case ($P = 0.01$) and as a result caseness was almost twice as great in subjects homozygous for the CC genotype as in subjects with the TT genotype (24 *vs.* 13%). No significant differences were seen in the other psychological scores, although all the scores appeared to increase in the same direction across the genotypes (Table 3), with the TT genotype having the lowest score and TC intermediate and CC the worst score. We published previously that rs225014 did not have any detectable effect on baseline thyroid function in this cohort, and hence, this effect appears to be independent of serum thyroid hormone levels (30).

Genotype and response to therapy

Results of repeated-measures ANOVA for response to treatment by genotype and treatment arm for rs225014 are shown in

repeated-measures ANOVA. *, $P < 0.05$. There was a significant effect of the interaction between the CC genotype and treatment arm at follow-up (visits 2 and 3) on GHQ scores, TSQ scores, and satisfaction. There are no baseline (visit 1) scores for satisfaction with therapy (C) because this was not assessed at baseline. For GHQ and TSQ scores, higher scores indicate worse well-being, whereas for satisfaction highe scores indicate more satisfied.

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Fig. 1. *P* values

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

Methods: We analyzed common variants in the three deiodinase genes *vs.* baseline psychological morbidity and response to T_4/T_3 in 552 subjects on T_4 from the Weston Area T_4 T_3 Study (WATTS). Primary outcome was improvement in psychological well-being assessed by the General Health Questionnaire 12 (GHQ-12).

Results: The rarer CC genotype of the rs225014 polymorphism in the deiodinase 2 gene (*DIO2*) was present in 16% of the study population and was associated with worse baseline GHQ scores in patients on T_4 (CC *vs.* TT genotype: 14.1 *vs.* 12.8, $P = 0.03$). In addition, this genotype showed greater improvement on T_4/T_3 therapy compared with T_4 only by 2.3 GHQ points at 3 months and 1.4 at 12 months ($P = 0.03$ for repeated measures ANOVA). 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 both 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. (***J Clin Endocrinol Metab* 94: 1623–1629, 2009**)

exon 3 of the D2 gene resulting in a Thr92Ala substitution

Deiodinase 2 (DIO2) expert genetic test proves insightful

The Deiodinase 2 (DIO2) gene was researched in 2009 and the results were published in a paper titled *Common Variation in the DIO2 Gene Predicts Baseline Psychological Well-Being and Response to Combination Thyroxine plus Triiodothyronine Therapy in Hypothyroid Patients.*[1]

Firstly, you need to know that everyone inherits two copies of each gene, one from their mother and one from their father.

To explain this paper briefly, the Deiodinase 2 gene activates triiodothyronine (T3) and the researchers found that a tiny change in this gene could mean that although the body gets enough T3, the brain doesn't.

The patients on this study were given levothyroxine (T4) only for a set period and then combination treatment of both levothyroxine and liothyronine (synthetic T3). The patients who had normal genes did not feel any different on T4/T3 combination treatment. However, those who had one variant gene (inherited from one of their parents) felt better on the combination treatment and those with two variant genes (inherited from both parents) felt better still.

This means that there is a possibility that patients who are on levothyroxine alone, still have symptoms and have the variant Deiodinase 2 gene may improve with the addition of liothyronine .

Because this gene causes a deficiency of T3 within the cells, the usual thyroid hormone function tests will not show up a problem. This means that your TSH, FT4 and FT3 blood tests will look normal.

The study concluded:

European Journal of Endocrinology, 2024, **190**, 12–22
https://doi.org/10.1093/ejendo/lvad172

European Journal Endocrinol 2024 190;12-22

Original Research

Randomized double-blind placebo-controlled trial on levothyroxine and liothyronine combination therapy in totally thyroidectomized subjects: the LEVOLIO study

Giulia Brigante,[1,2,*] Daniele Santi,[1,2] Gisella Boselli,[1] Gianluca Margiotta,[1] Rossella Corleto,[1] Maria Laura Monzani,[1,2] Andrea Craparo,[1] Michela Locaso,[1] Samantha Sperduti,[1,3] Neena Roy,[1] Livio Casarini,[1,3] Tommaso Trenti,[4] Simonetta Tagliavini,[4] Maria Cristina De Santis,[4] Laura Roli,[4] Vincenzo Rochira,[1,2] and Manuela Simoni[1,2,3]

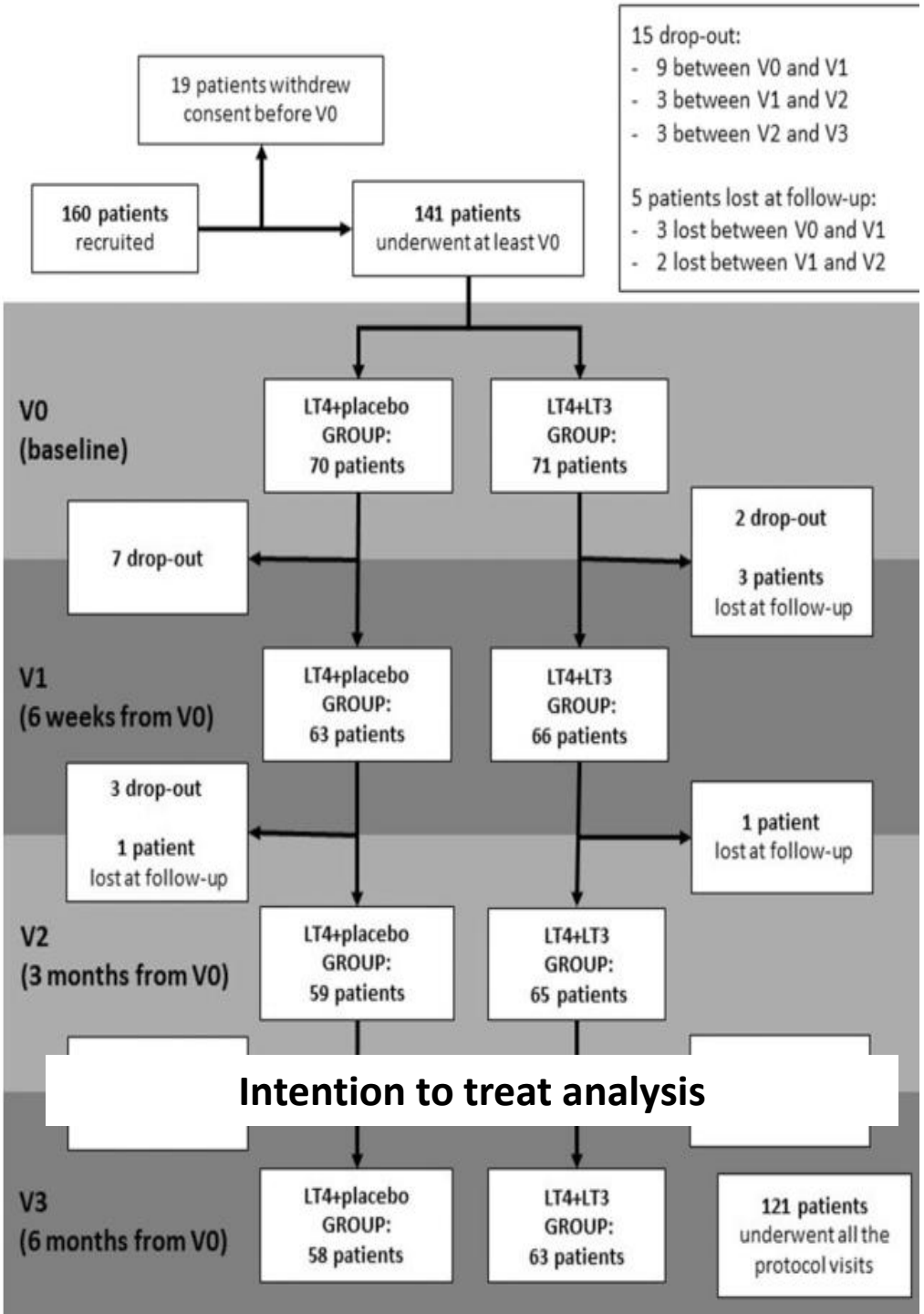
[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, 41124 Modena, Italy
[2]Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, 41126 Modena, Italy
[3]Center for Genomic Research, University of Modena and Reggio Emilia, 41126 Modena, Italy
[4]Department of Laboratory Medicine and Anatomy Pathology, Azienda USL Modena, 41126 Modena, Italy

*Corresponding author: Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; Unit of Endocrinology, OCSAE, Via P. Gardini 1355, 41126 Modena, Italy. Email: giulia.brigante@unimore.it

Methods

- Longitudinal, prospective, double-blind, randomized, placebo-controlled study
- 3 years (From March 2017 to March 2020)
- 160 hypothyroid patients on LT4 therapy following **total thyroidectomy**
- Thyroxine dose reduced, and drops of either T3 or T4 were added back twice daily

European Journal Endocrinol 2024 190;12-22



6 months, 4 visits (baseline, 6 weeks, 3 months, 6 months)

Dosing:

- TDD LT4 reduced to 80%, 20% replaced by drops (either LT3 or LT4)

- Both groups: 80% LT4 in the morning as tablet
- [LT4+LT3]: 20% split into BD LT3 – am and pm
- [LT4+placebo]: 20% LT4 drops given in am, placebo drops in pm

- Blood tests and dose titration at each visit by one unblinded doctor who never met the patients

Genotyping- V1

- DIO2-rs225014 and MCT10-rs17606253 variants were genotyped at baseline

Titration- all visits

- TSH testsd at 8 am before Rx, Dose adjustments as required at V1 – V3
- (LT4 + LT3) : reduction/increase performed on the TTD LT4 (µg) corresponding to the sum of the thyroid hormones prescribed in the previous visit – case by case - new reduced/increased dosage was converted into doses of LT4 and LT3 following a pre-defined formula
- **Aim to maintain to maintain T4/T3 ratio between 13:1 and 20:1**

QoL assessment – V0, V2, V3

- The Italian version of the ThyPRO

Adherence

- Assessment of the daily compilation of the therapeutic scheme delivered to the patient
- Validated questionnaire Morisky Medication Adherence Scale

Results

- 121 patients [63 in the LT4 + LT3 and 58 in the LT4 + placebo group] underwent all visits

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Primary Outcome: changes in tissue markers of peripheral thyroid function

- **No significant differences** in tissue markers were observed between the [LT4 + LT3] and [LT4 + placebo] groups at the end of treatment

- SHBG was slightly higher in the [LT4 +LT3 group] (52.9 ± 25.8 nmol/L) compared to the [LT4+placebo] (48.9 ± 33.1 nmol/L) (ns)

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Secondary Outcomes: TFTs

	Visit 0 (baseline)		Visit 3 (6 months)		Comparison between groups at visit 3		
	LT4 + LT3 group ($n = 71$)	LT4 + placebo group ($n = 70$)	LT4 + LT3 ($n = 63$)	LT4 + placebo ($n = 58$)	Mean difference	*P*	95% CI
TSH (μIU/mL)	1.4 ± 1.5	1.1 ± 1.2	1.3 ± 2.7	2.6 ± 5.3	−1.3	.08	−2.8, 0.2
fT3 (pg/mL)	3.0 ± 0.3	3.0 ± 0.3	3.2 ± 0.5	2.9 ± 0.4	0.3	.002	0.1, 0.5
fT4 (pg/mL)	11.9 ± 2.2	11.7 ± 1.8	10.4 ± 2.2	11.3 ± 2.0	−0.9	.02	−1.7, −0.2
Total-CH (mg/dL)	206.5 ± 33.3	203.4 ± 48.0	210.0 ± 36.6	219.6 ± 44.7	−9.5	.21	−24.4, 5.3
HDL cholesterol (mg/dL)	52.1 ± 13.2	50.2 ± 13.4	54.9 ± 14.4	54.8 ± 14.0	0.1	.98	−4.7, 5.0
Triglycerides (mg/dL)	108.0 ± 67.2	105.2 ± 79.6	100.9 ± 70.8	110.0 ± 71.2	−9.1	.49	−35, 16.8
CTX (ng/dL)	9.6 ± 7.1	11.4 ± 8.7	12.3 ± 10.0	11.7 ± 10.1	0.5	.79	−3.2, 4.2
Osteocalcin (ng/mL)	17.3 ± 4.6	17.4 ± 4.7	18.3 ± 4.5	17.0 ± 4.9	1.3	.14	−0.4, 3.0
Bone alkaline phosphatase (μg/L)	11.3 ± 3.9	11.8 ± 3.6	11.7 ± 4.1	11.5 ± 3.6	0.1	.86	−1.3, 1.6

So TSH went up a bit (1.1 to 2.6) in those on placebo but not in those on T4 and T3
So you might expect those on T3 to feel “better”

European Journal Endocrinol 2024 190;12-22

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	Visit 0 (baseline)		Visit 3 (6 months)		Comparison between groups at visit 3		
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So T3 went down a bit (3.0 to 2.9) in those on placebo but up in those on T4 and T3(3.0 to 3.2)

So you might expect those on T3 to feel “better”

European Journal Endocrinol 2024 190;12-22

Secondary Outcomes: Changes in tissue markers of peripheral thyroid hormone action

	Visit 0 (baseline)		Visit 3 (6 months)		Comparison between groups at visit 3		
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Bone alkaline phosphatase (μg/L)	11.3 ± 3.9	11.8 ± 3.6	11.7 ± 4.1	11.5 ± 3.6	0.1	.86	−1.3, 1.6

No change in bone turnover

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fT3:fT4

At baseline:

- fT3/fT4 below physiological range (0.27-0.37) in both groups

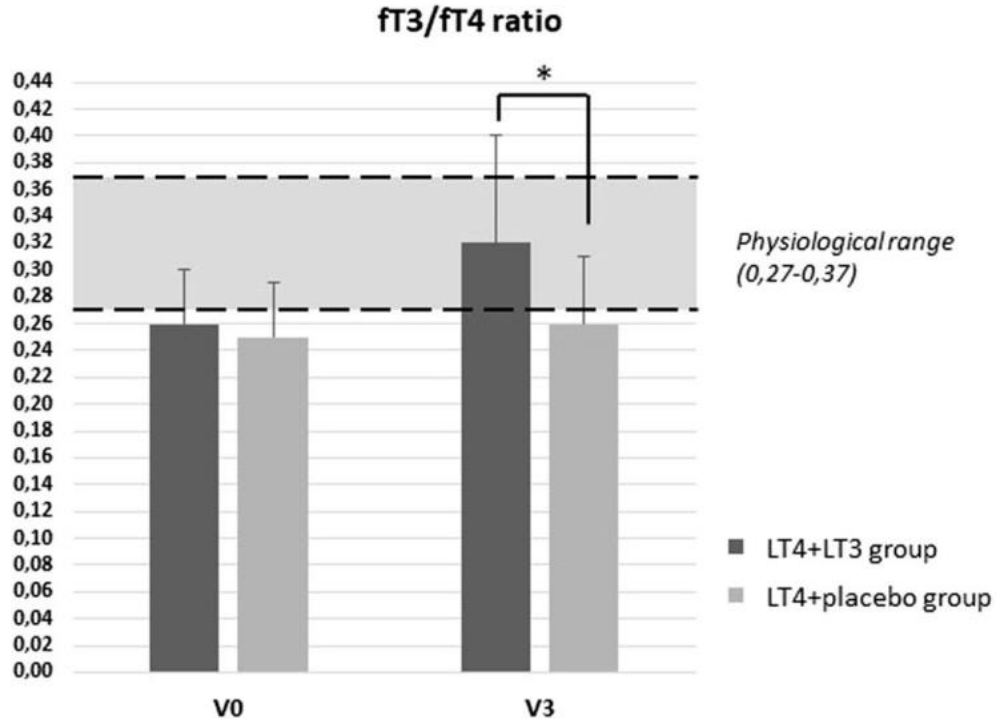
- suggests a suboptimal compensation under LT4 alone, despite mean normal TSH

End of treatment:

- [LT4+placebo]: fT3/fT4 remained low (0.26 ± 0.05)
- [LT4 + LT3]: normalized (0.32 ± 0.08]

P < .001

The physiological range of the fT3/fT4 ratio (in the presence of physiological TSH levels has been proposed in the consensus document on the evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism approved by the American Thyroid Association (ATA), British Thyroid Association (BTA), and European Thyroid Association (ETA)



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Changes in quality of life

- No significant differences in the totalized score in ThyPRO items between groups
- The same results were confirmed, performing separate analysis for males and females
- No significant correlations were found between the scores in any of these items and TSH, fT4, fT3, and fT3/fT4

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QoL and symptoms

No difference in anything

	Visit 0 (baseline)		Visit 3 (6 months)		Comparison between groups at visit 3		
	LT4 + LT3 group ($n = 71$)	LT4 + placebo group ($n = 70$)	LT4 + LT3 ($n = 63$)	LT4 + placebo ($n = 58$)	Mean difference	*P*	95% CI
ThyPRO questionnaire scores							
Goiter symptoms	9.5 ± 8.6	9.5 ± 11.3	8.3 ± 10.0	8.9 ± 9.8	−0.5	.78	−4.1, 3.1
Hyperthyroid symptoms	20.2 ± 17.0	20.7 ± 15.2	16.1 ± 12.2	18.5 ± 13.2	−2.4	.31	−7.1, 2.2
Hypothyroid symptoms	21.1 ± 18.1	20.6 ± 17.3	17.3 ± 17.5	17.8 ± 15.0	−0.4	.88	−6.4, 5.5
Eye symptoms	15.7 ± 15.1	11.9 ± 11.8	13.0 ± 13.6	12.2 ± 12.9	0.7	.76	−4.0, 5.6
Tiredness	17.9 ± 17.3	13.6 ± 13.4	14.8 ± 15.5	14.0 ± 14.7	0.8	.76	−4.7, 6.3
Cognitive problems	25.9 ± 22.2	21.7 ± 17.6	19.1 ± 15.2	18.6 ± 16.1	0.5	.85	−5.2, 6.2
Anxiety	26.4 ± 20.4	26.9 ± 19.4	17.3 ± 14.8	21.2 ± 19.9	−3.8	.23	−9.9, 2.2
Depressivity	30.8 ± 18.1	30.7 ± 17.0	24.7 ± 13.9	29.0 ± 20.1	−4.3	.18	−10.6, 1.9
Emotional susceptibility	31.8 ± 18.8	31.4 ± 16.3	25.1 ± 14.8	28.4 ± 17.9	−3.3	.29	−9.2, 2.9
Impaired social life	13.2 ± 16.8	11.8 ± 14.7	7.6 ± 11.5	9.2 ± 14.6	−1.6	.53	−6.8, 3.4
Impaired daily life	13.8 ± 17.6	10.2 ± 12.9	9.2 ± 10.6	11.8 ± 15.2	−2.6	.29	−7.9, 2.2
Impaired sex life	21.7 ± 27.7	21.1 ± 23.2	21.4 ± 25.2	21.1 ± 24.6	0.3	.93	−9.0, 9.7
Cosmetic complaints	18.2 ± 22.7	13.7 ± 16.3	11.6 ± 16.4	9.1 ± 12.2	2.5	.36	−2.8, 7.8
Overall impact	25.0 ± 24.6	17.2 ± 23.9	13.8 ± 20.5	12.7 ± 19.0	1.0	.77	−6.2, 8.4

European Journal Endocrinol 2024 190;12-22

LT4/LT3

- **The most frequent adverse effect was TSH reduction below the normal range,** despite the dose of combination therapy being meticulously calculated considering the physiological T4/T3 ratio as suggested by the ETA guidelines.

European Journal Endocrinol 2024 190;12-22

Preference: compared to baseline

- 56% preferred LT4+LT3
- 60% of patients preferred the LT4 + placebo group
- (P =0.58)

European Journal Endocrinol 2024 190;12-22

Influence of DIO2 and MCT10 SNPs on experimental treatment outcome

There were no significant genotype-related differences between the LT4 + LT3 group and the LT4 + placebo group for the studied outcomes

European Journal Endocrinol 2024 190;12-22

Summary

[LT4+LT3] Vs placebo:

- significant reduction of TSH
- significant increase of fT3 and fT3/fT4

No significant difference between groups:

- peripheral tissue markers of thyroid function
- QoL
- BMI

European Journal Endocrinol 2024 190;12-22

Conclusions

- **[LT4 + LT3] therapy** at a dose adapted according to TSH-level, with twice-daily LT3, is capable to restore the physiologic fT3/fT4 ratio

- No beneficial effect of combined therapy on **SHBG hepatic secretion and bone turnover markers** [proxy of the effect of thyroid hormones on liver and bone] nor QOL

- Patients did not prefer LT4 + LT3

- Neither preference nor therapeutic compensation is influenced by DIO2-rs225014 and MCT10-rs17606253

European Journal Endocrinol 2024 190;12-22

BTA guidelines need updating

ATA and ETA : LT4 therapy of choice in hypothyroidism; do not support combined use due to insufficient evidence from controlled trials, and lack of long term LT3 safety data; and unavailability of LT3 formulations that mirror natural physiology

BTA: L-T4/L-T3 combination therapy in patients with hypothyroidism should not be used routinely.

Consider as an **experimental approach** if persistent complaints despite TSH in ref range

Open and **balanced discussion** of benefits, likely risks of over-replacement and lack of long-term safety data

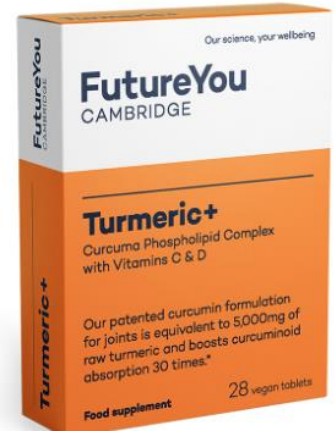
Discontinue if no improvement after 3 months

CCGs commissioned a T3 withdrawal clinic

- My experience: since 2017.
- Patients are mostly on:
- T4 daily 50mcg to 150mcg
- T3 daily 2.5mcg to 40mcg once, twice or thrice daily
- Armour thyroid
- Ashwaganda
- Turmeric
- Co-enzyme Q

offer

£38.50 (Nov 2022)



- Note that they are still tired despite being on T3 and measure it with a questionnaire

We have a duty to protect vulnerable patients

- From the use of expensive and potentially harmful (T3) placebos

- T3
- Vitamin D
- Multivitamins
- Ashwaganda
- Co-enzyme Q
- Turmeric

If you spend NHS resources on unproven treatments, someone else does not get a renal transplant

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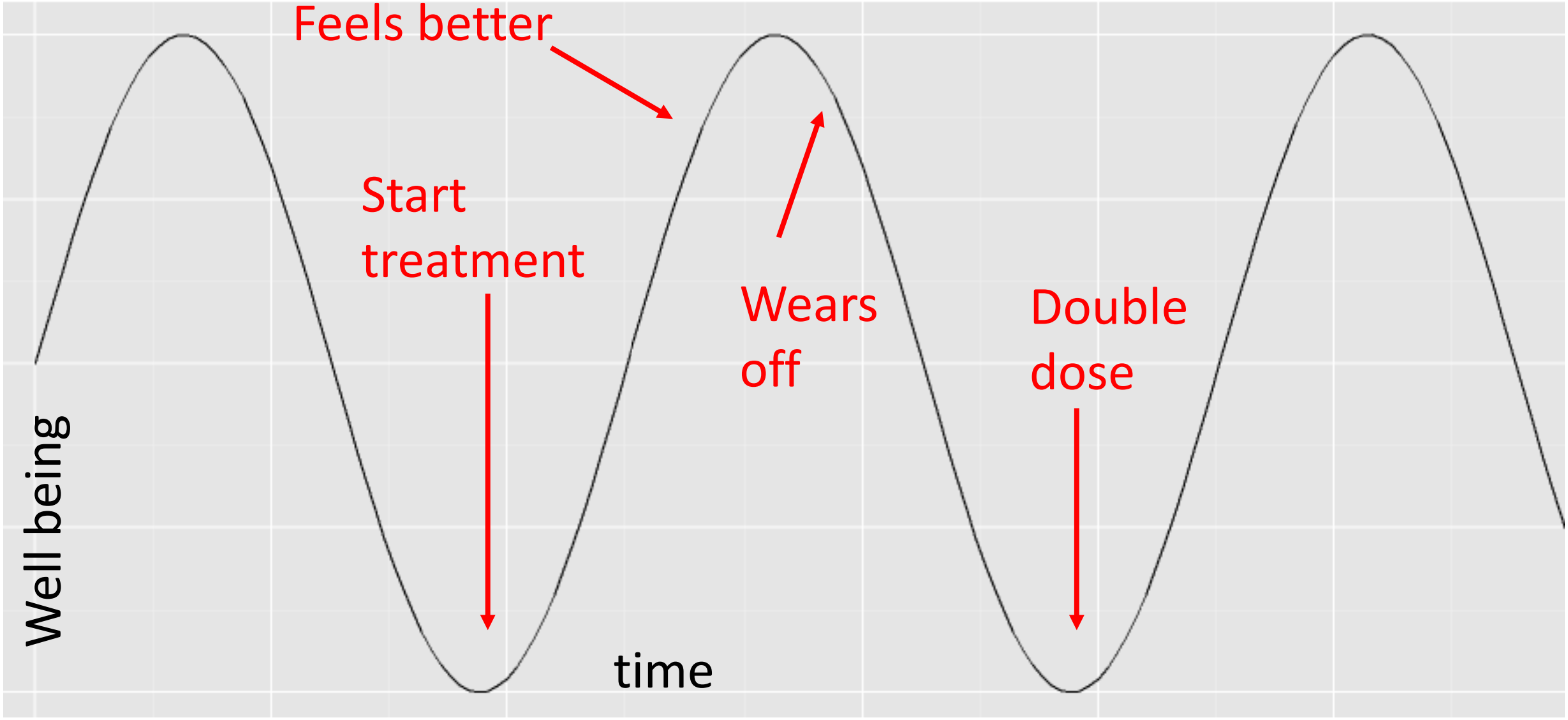
- Blind studies all fail to find this: placebo effect is very potent

Association of British Clinical Diabetologists

“trial of therapy” causes bias…



- “Trials of therapy” of liothyronine (and other complementary remedies) are subject to a large placebo effect and should not be used.

- There is no genuine evidence of benefit of liothyronine

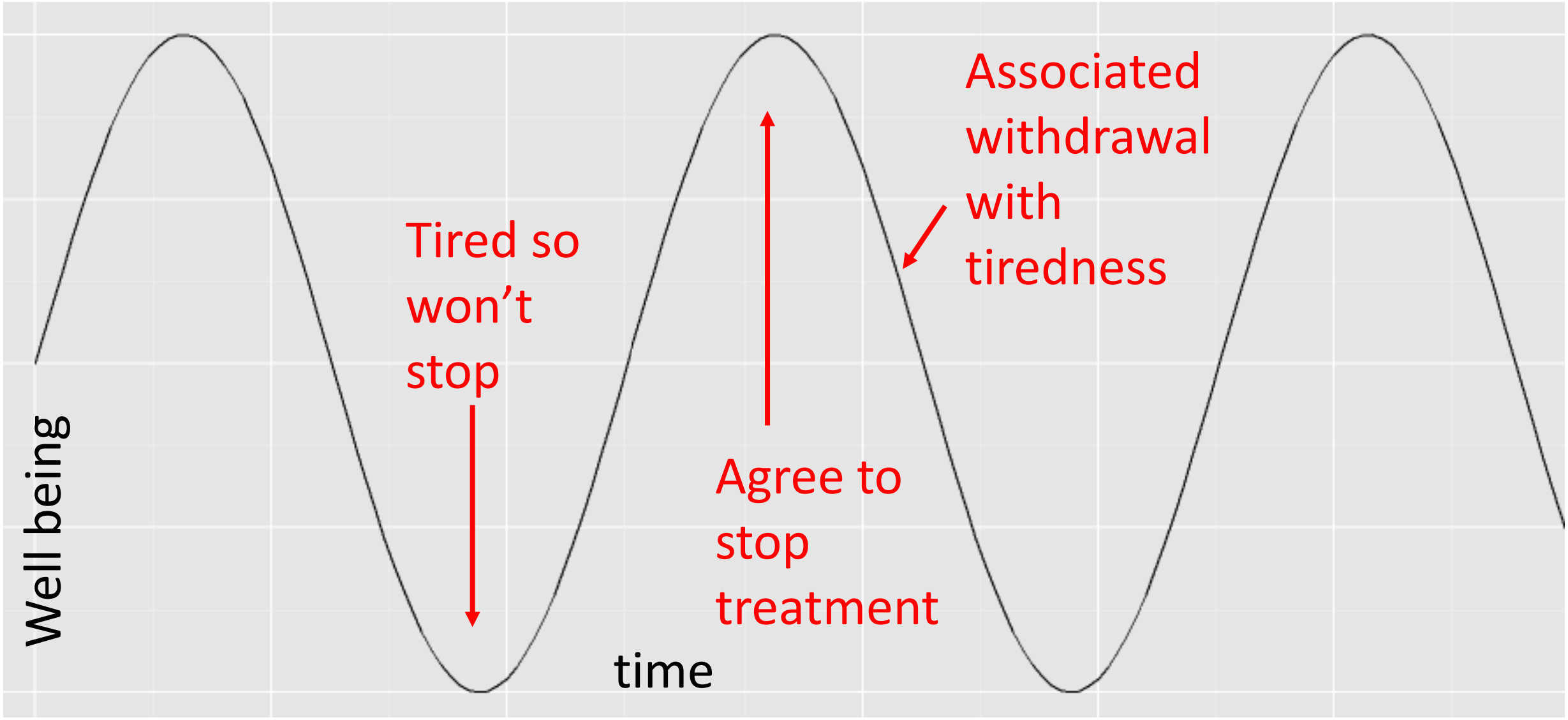
- “I have the gene doctor”: rs225014 SNP = Thr92Ala DIO2 gene:

No evidence of genetic variance in need for liothyronine

- Patients with tiredness and depression are vulnerable to being manipulated by private practitioners and websites they need to know that we are on their side

- We must maximise efficiency on drug spend and not use drugs that don’t work

Fear of stopping as they only stop when well…



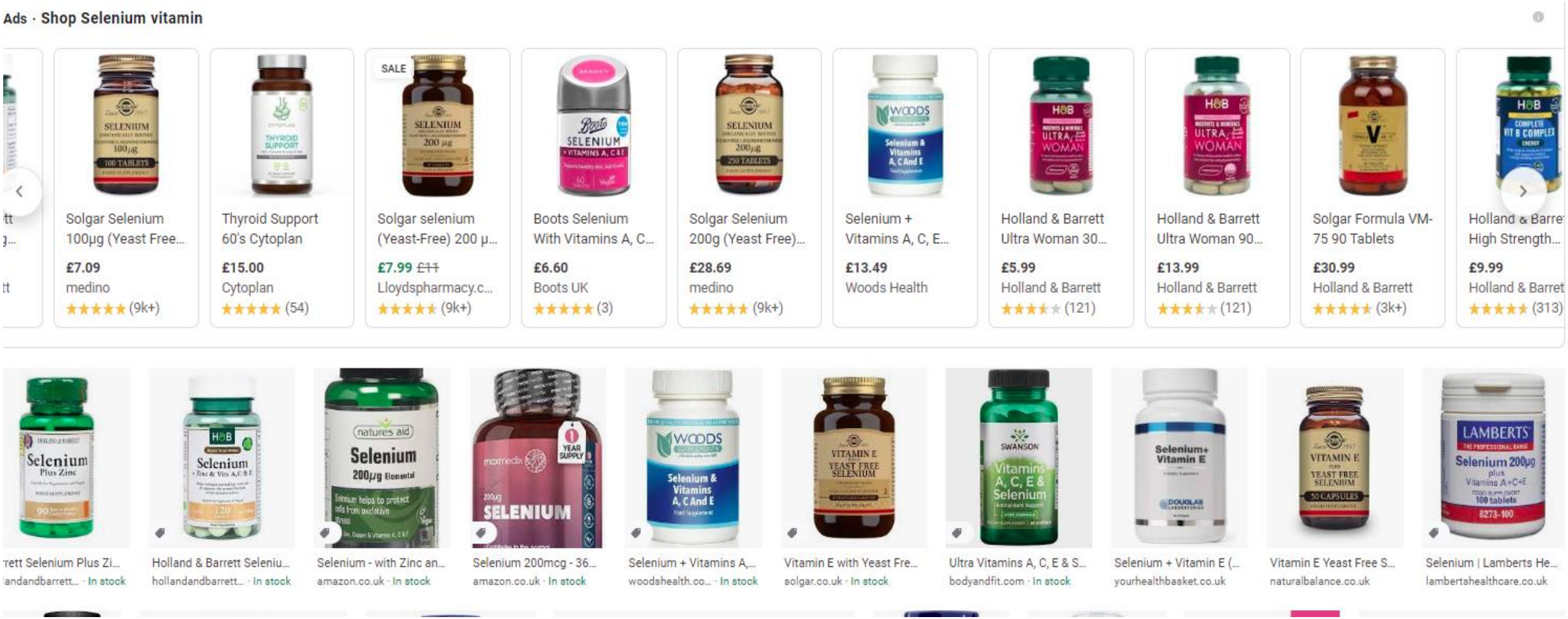
Chronic fatigue and “brain fog”

- Listen to the patient. Determine if they have had some form of psychological trauma in the past.
- Talking therapies?
- Many are already on placebos, co enzyme Q, Ashwaganda, Turmeric
- Nothing wrong with the placebo effect, but if you are paying for treatment, we need evidence of additional benefit on top of placebo.
- Look at history of hypothyroidism. Some have never been diagnosed with actual hypothyroidism, but started with a “trial of thyroxine”
- Even when on all these treatments, they remain tired but they are afraid to reduce any of them

Explain the risks of a suppressed TSH

- Long term risks osteoporosis and AF (many say they don’t care)
- Offer regular monitoring (e-mail clinic) as they come off T3
- Give them time to talk
- ? Blind trial: needs a fully on board patient
- Some need an alternative placebo, so find one that is cheap and harmless
- Ask them what they think might work.
- Suggest selenium

Selenium : another placebo?



Brazil nuts: a cheap source of selenium

Ads · Shop brazil nuts selenium

Duchy Organic Brazil Nuts

£3.75

Waitrose & Partn...

★★★★★ (4)

Holland & Barrett Flaked Brazil Nuts...

£3.99

Holland & Barrett

Waitrose Brazil Nuts

£4.75

Waitrose & Partn...

★★★★★ (71)

Waitrose Brazil Nuts

£2.75

Waitrose & Partn...

★★★★½ (41)

Holland & Barrett Whole Brazil Nuts...

£14.99

Holland & Barrett

★★★★½ (96)

Sainsbury's Brazil Nuts 100g

★★★½☆ Any 2 for £3.50 View all

PRICE LOCK*

Brazil Nuts

£1.45

£1.45 / 100g

ASDA Brazil

200g

Live Better

Live Better

£2.40

(£1.20/100g)

razil nuts: Health benefits, nutrition ...

nedicalnewstoday.com

7 Proven Health Benefits of Brazil Nuts

healthline.com

5 health benefits of Brazil nuts | BBC...

bbcgoodfood.com

Take 1 brazil nut per day as T3 being withdrawn...

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Published: 29 June 2021

Comparative Effectiveness of Levothyroxine, Desiccated Thyroid Extract, and Levothyroxine+Liothyronine in Hypothyroidism

Mohamed K.M. Shakir,[1,2] Daniel I. Brooks,[1] Elizabeth A. McAninch,[3] Tatiana L. Fonseca,[4] Vinh Q. Mai,[1,2] Antonio C. Bianco,[4] and Thanh D. Hoang[1,2]

[1]Walter Reed National Military Medical Center, Bethesda, MD 20889-5600, USA; [2]Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA; [3]Division of Endocrinology and Metabolism, Rush University Medical Center, Chicago, IL 60612, USA; and [4]Section of Adult and Pediatric Endocrinology, University of Chicago, Chicago, IL 60637, USA

Study design: double blind crossover

All 75 patients had all treatments in random order for 22 weeks each

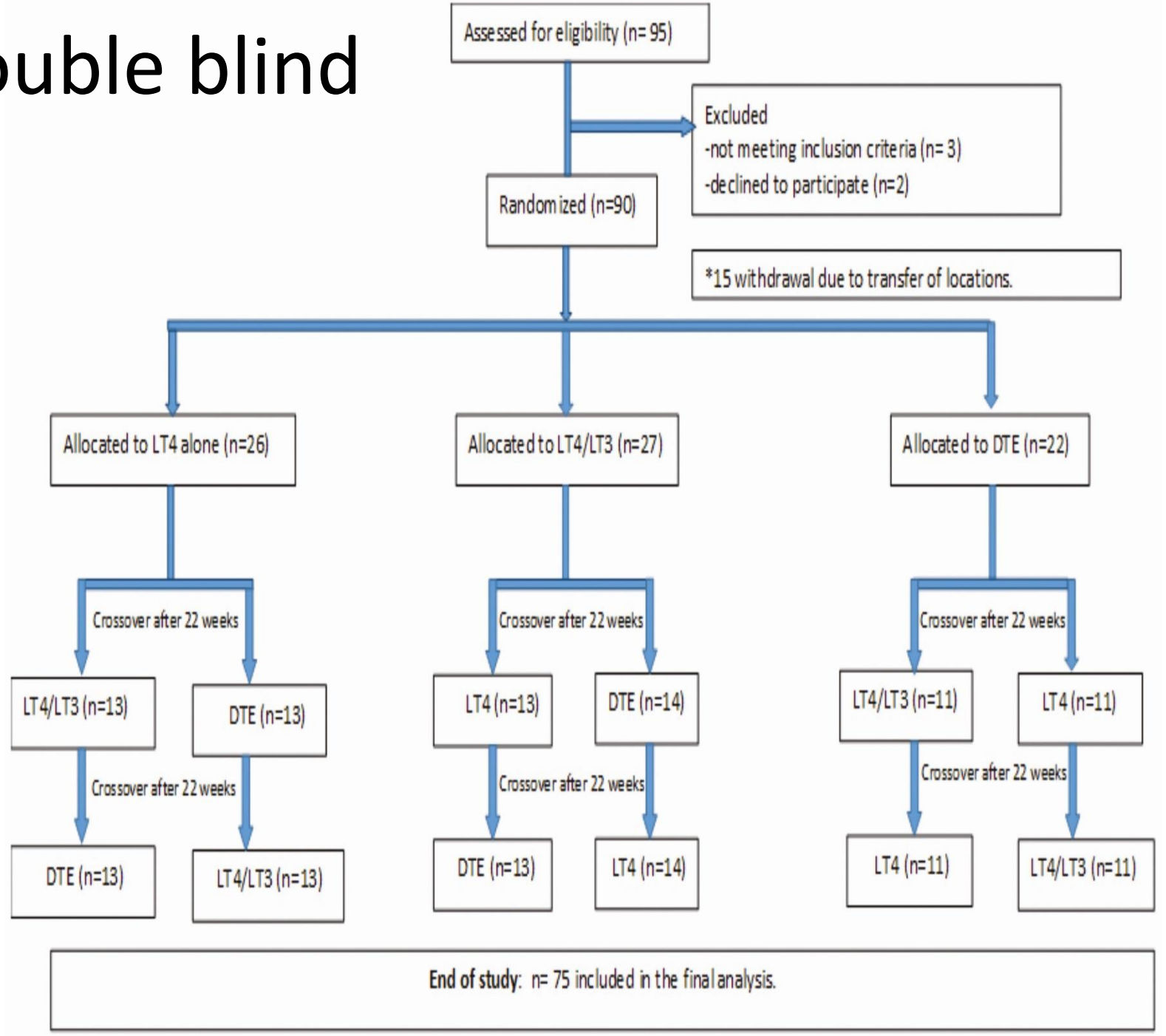


Table 4. Primary and secondary outcomes

Parameters	LT4 (N = 75)	DTE (N = 75)	LT4 + LT3 (N = 75)	*P* value
Primary outcomes				
Quality of life and cognition				
TSQ-36	15.9 (7.49)	14.5 (8.22)	14.9 (6.67)	0.357
GHQ-12	11.9 (5.13)	11.7 (6.16)	11.6 (4.83)	0.891
BDI	7.15 (7.11)	7.09 (8.55)	7.33 (7.67)	0.947
AMI	121 (12.8)	121 (14.7)	120 (14.0)	0.825
VMI	80.4 (12.1)	79.8 (8.06)	81.0 (11.3)	0.518
VWMI	116 (14.3)	115 (18.2)	117 (17.2)	0.461
IMI	99.7 (10.7)	97.9 (15.4)	98.0 (15.2)	0.537
DMI	101 (12.0)	101 (10.8)	100 (16.3)	0.827
Secondary outcomes				
Thyroid function tests				
T3 (60-181 ng/dL)	103 (22.1)	155 (48.7)	132 (33.2)	<0.001
T3 resin	28.1 (3.48)	25.8 (4.01)	26.6 (3.95)	<0.001
T3 reverse	20.6 (5.60)	14.4 (5.31)	16.7 (5.02)	<0.001
TSH	1.63 (1.28)	2.34 (1.48)	1.76 (1.13)	<0.001
Total T4	8.46 (2.14)	5.62 (1.38)	6.92 (1.62)	<0.001
Free T4	1.44 (0.358)	0.980 (0.673)	1.21 (0.532)	<0.001
Free T4 direct dialysis	1.30 (0.292)	0.828 (0.293)	1.06 (0.286)	<0.001
Total T4/T3 ratio	82.1(9.7)	36.2(2.8)	52.4 (4.9)	<0.001
Metabolism				
Weight (lbs)	181 (38.7)	180 (40.0)	178 (43.6)	0.278
Total cholesterol	195 (42.5)	196 (37.1)	195 (38.2)	0.85
LDL cholesterol	130 (35.3)	127 (33.6)	126 (35.8)	0.31
HDL cholesterol	59.7 (15.6)	60.5 (18.9)	60.4 (17.8)	0.773
Triglyceride	109 (74.8)	109 (65.7)	102 (63.5)	0.411
SHBG	72.3 (48.1)	69.5 (37.9)	75.0 (45.7)	0.08
Leptin	22.1 (17.9)	21.5 (17.7)	22.2 (18.6)	0.826

T3 no benefit in a blind study

- But what if you subanalyse those who are particularly tired when they were on T4 alone?

- And is there a link of that tiredness to DIO2 gene?

Table 8. Patients' characteristics presented after the group was broken down by TSQ-36 scores while on therapy with LT4 (L, M, or H)

Parameters	L 1-13 (N = 30)	M 14-21 (N = 25)	H 22-33 (N = 20)	*P* value
Age	49.8 (11.1)	49.7 (8.29)	51.0 (7.64)	0.877
Sex				
Female	24 (80.0%)	18 (72.0%)	16 (80.0%)	0.779
Male	6 (20.0%)	7 (28.0%)	4 (20.0%)	
Genotype_group.y				
Heterozygous	14 (46.7%)	15 (60.0%)	12 (60.0%)	0.679
Ala92-DIO2	3 (10.0%)	3 (12.0%)	3 (15.0%)	
Thr92-DIO2	13 (43.3%)	7 (28.0%)	5 (25.0%)	
Etiology				
Autoimmune	19 (63.3%)	16 (64.0%)	11 (55.0%)	0.795
Nonautoimmune	11 (36.7%)	9 (36.0%)	9 (45.0%)	
Preference				
LT4	12 (40.0%)	1 (4.0%)	2 (10.0%)	0.00892
DTE	9 (30.0%)	13 (52.0%)	7 (35.0%)	
LT4 + LT3	5 (16.7%)	8 (32.0%)	10 (50.0%)	
No preference	4 (13.3%)	3 (12.0%)	1 (5.0%)	
Preference for LT4				
Yes	12 (40.0%)	1 (4.0%)	2 (10.0%)	0.0017
No	18 (60.0%)	24 (96.0%)	18 (90.0%)	
TSH (0.27-4.68 mU/μL)	1.93 (1.31)	1.54 (1.23)	1.32 (1.24)	0.23
T4 (4.5-12 mcg/dL)	8.20 (2.36)	8.77 (1.34)	8.45 (2.60)	0.63
T3 (60-181 ng/dL)	102 (26.9)	103 (14.5)	105 (23.0)	0.896

However tired, no link to gene

We have a duty to protect vulnerable patients

- From the use of expensive and potentially harmful (T3) placebos

- T3
- Vitamin D
- Multivitamins
- Ashwaganda
- Co-enzyme Q
- Turmeric

If you spend NHS resources on unproven treatments, someone else does not get a renal transplant

Protocol to reduce DTE or T3…

Week	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
0	60	60	60	60	60	60	60
1	60	60	60	30	60	60	60
2	60	30	60	60	30	60	60
3	60	30	60	30	60	30	60
4	30	60	30	60	30	60	30
5	30	60	30	30	60	30	30
6	30	30	30	60	30	30	30
7	30	30	30	30	30	30	30
8	30	30	30	0	30	30	30
9	30	0	30	30	0	30	30
10	30	0	30	0	30	0	30
11	0	30	0	30	0	30	0
12	0	30	0	0	30	0	0
13	0	0	0	30	0	0	0
14	0	0	0	0	0	0	0

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 22 February 2022
doi: 10.3389/fendo.2022.816566

Effect of Liothyronine Treatment on Quality of Life in Female Hypothyroid Patients With Residual Symptoms on Levothyroxine Therapy: A Randomized Crossover Study

Not blind: Fatigue questionnaire in a Norwegian population

Daily T4 or tds T3

	Baseline (n = 59)	On LT4 (n = 49)		On LT3 (n = 48)		LT4 *vs.* LT3 (n = 47)	
	Score	Change from baseline	*P* value	Change from baseline	*P* value	Change from LT4 to LT3	*P* value
Physical fatigue	12.2 ± 3.9	-0.5 ± 4.7	0.438	-4.0 ± 6.2	<0.001	-3.2 ± 6.1	0.001
Mental fatigue	6.6 ± 2.4	-0.4 ± 2.4	0.203	-1.8 ± 2.9	<0.001	-1.2 ± 2.7	0.004
Total fatigue	18.9 ± 5.8	-1 ± 6.6	0.303	-5.8 ± 8.7	<0.001	-4.4 ± 8.3	0.001

Data are presented as mean ± SD. Combining the scores of physical and mental fatigues produce total fatigue, with a maximum score of 33. Higher scores imply higher levels of fatigue.

Significant placebo effect

- We identified the homozygous variant of the **D2-Thr92Ala**
- polymorphism in only 6.8% of our patients. **Paradoxically**, the only significant difference we found between the presence of D2-Thr92Ala polymorphism and a non-Thr92Ala polymorphism in the deiodinase 2 gene, was a **lower score in overall QoL on LT4 treatment, indicating improved QoL.** This result is in contrast to the hypothesis that this polymorphism may impair the effect of deiodinase 2 and reduce the conversion of T4 to T3 at the cellular level.

- Five patients on LT3 dropped out of the study due to side effects, which may indicate that some patients do not seem to tolerate LT3 monotherapy. Based on our results, the D2-Thr92Ala polymorphism was not associated with reduced thyroid-specific QoL or treatment effects.

frontiers in Endocrinology

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Predatory journal will publish any old rubbish…

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Not blind studies are misleading…

Summary

- No evidence of benefit of Liothyronine over thyroxine
- Profound and prolonged placebo effect

- Money spent on liothyronine could be used to fund the nurses wage increase. Every time you sign a prescription for T3, you condemn another nurse to a wage freeze
- Vulnerable patients are being taken advantage of.

- “Trials of therapy” are flawed.

- Slow weaning and an explanation of the placebo effect and the risks

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