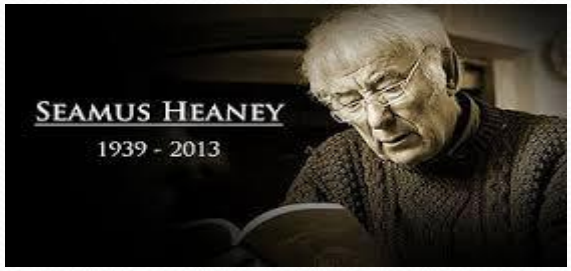
Thyroid update

ABCD

Karen Mullan MD FRCP

May 2017

Welcome




Dr. U. Graham

What's new?

- NEJM- Randomized Controlled Trials @3
  - 1. March: Subclinical hypothyroidism and isolated hypothyroxaemia in pregnancy
  - 2. April: Subclinical hypothyroidism in older persons
  - 3. May :Teprotumumab for Thyroid associated ophthalmopathy

- 4. Chernobyl disaster 30 year anniversary

  Children affected @ time are now age 30-48 years

  Migration across Europe in last 13 years

What's old

Environmental stress and thyrotoxicosis 1974

- Therapeutic auditing before and during civil unrest showed no change in incidence
    - DR Hadden, DG McDevitt The Lancet 07/09/1974: 577-578

Part 1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 2, 2017 VOL. 376 NO. 9

Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy

B.M. Casey, E.A. Thom, A.M. Peaceman, M.W. Varner, Y. Sorokin, D.G. Hirtz, U.M. Reddy, R.J. Wapner, J.M. Thorp, Jr., G. Saade, A.T.N. Tita, D.J. Rouse, B. Sibai, J.D. Iams, B.M. Mercer, J. Tolosa, S.N. Caritis, and J.P. VanDorsten, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

Study rationale and design

- Subclinical hypothyroidism /(hypothyroxinaemia) linked to adverse obstetric outcomes and with low childhood IQ

- Two separate trials- double blind placebo controlled with levothyroxine
  - Subclinical hypoth: fT4 n (11-24 pmol/l),TSH ≥ 4 mU/l
  - Hypothyroxinaemia: low fT4 (<11), n TSH (0.08-3.99)
- Monthly thyroid function tests and adjustments
- Children -annual development and behavioural testing
- Primary outcome was IQ score at age 5 (or age 3 if 5 yr data missing) or death at <3 years

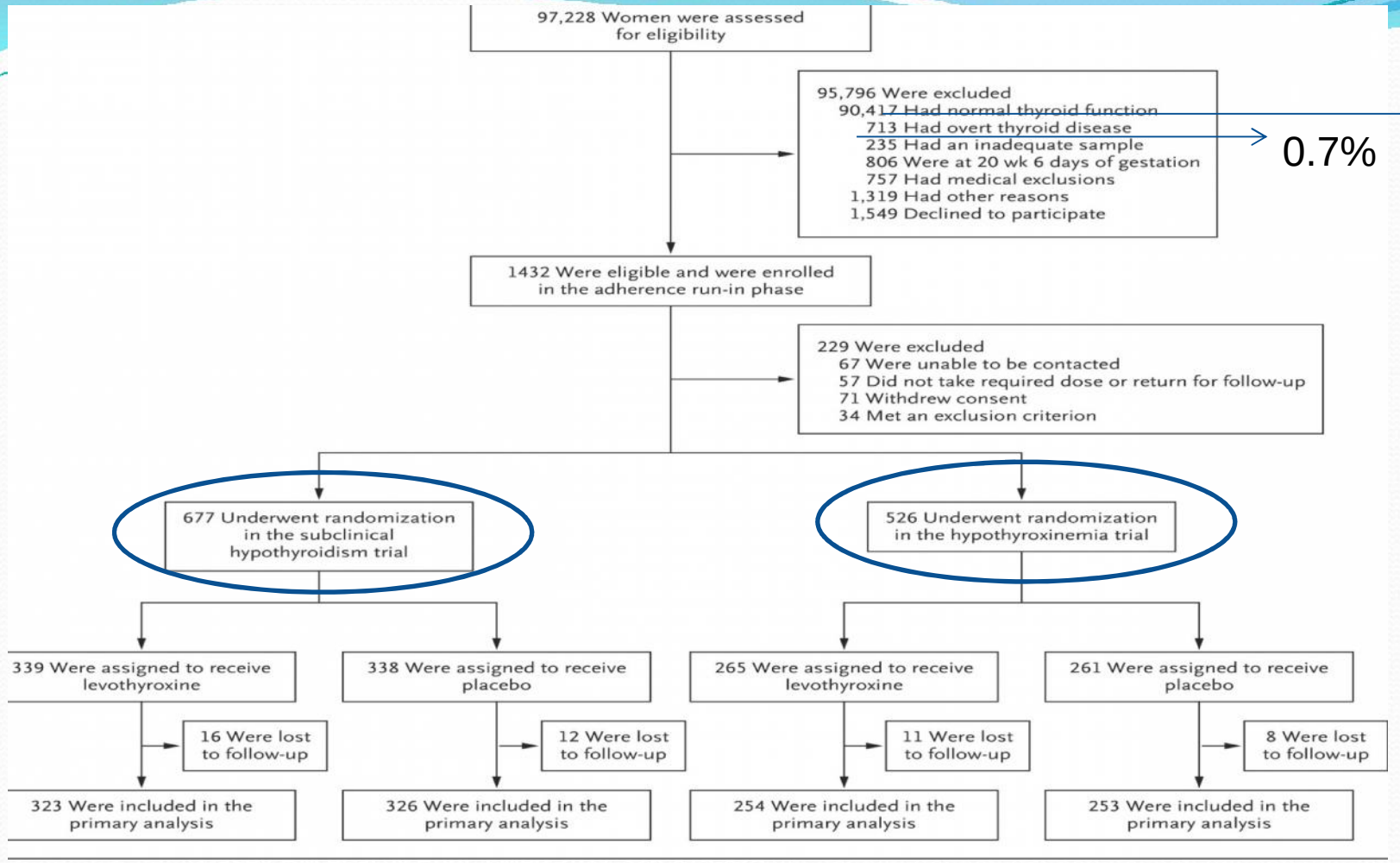

97,228 Women were assessed for eligibility
95,796 Were excluded
90,417 Had normal thyroid function
713 Had overt thyroid disease
235 Had an inadequate sample
806 Were at 20 wk 6 days of gestation
757 Had medical exclusions
1,319 Had other reasons
1,549 Declined to participate
93%
0.7%
1432 Were eligible and were enrolled in the adherence run-in phase
229 Were excluded
67 Were unable to be contacted
57 Did not take required dose or return for follow-up
71 Withdrew consent
34 Met an exclusion criterion
677 Underwent randomization in the subclinical hypothyroidism trial
526 Underwent randomization in the hypothyroxinemia trial
339 Were assigned to receive levothyroxine
338 Were assigned to receive placebo
265 Were assigned to receive levothyroxine
261 Were assigned to receive placebo
16 Were lost to follow-up
12 Were lost to follow-up
11 Were lost to follow-up
8 Were lost to follow-up
323 Were included in the primary analysis
326 Were included in the primary analysis
254 Were included in the primary analysis
253 Were included in the primary analysis

Table 1. Maternal Characteristics at Baseline.*

Characteristic	Subclinical Hypothyroidism		Hypothyroxinemia	
	Levothyroxine (N = 339)	Placebo (N = 338)	Levothyroxine (N = 265)	Placebo (N = 261)
Age — yr	27.7±5.7	27.3±5.7	27.8±5.7	28.0±5.8
Race or ethnic group — no. (%)†				
Black	27 (8)	25 (7)	61 (23)	65 (25)
Hispanic	195 (58)	185 (55)	131 (49)	125 (48)
White	109 (32)	117 (35)	69 (26)	69 (26)
Other	8 (2)	11 (3)	4 (2)	2 (1)
Body-mass index‡	28.1±6.4	28.2±6.4	30.3±6.4	30.2±7.1
Nulliparous — no. (%)	124 (37)	134 (40)	69 (26)	64 (25)
Baseline thyrotropin — mU/liter				
Median	4.5	4.3	1.5	1.4
95% CI	4.4–4.7	4.2–4.5	1.4–1.6	1.3–1.5
Baseline free thyroxine — ng/dl§				
Median	13.0 1.01	13.1 1.02	0.83 10.7	0.83
95% CI	1.00–1.02	1.01–1.04	0.82–0.83	0.82–0.83
Urinary iodine — μg/liter¶				
Median	199	196	185	191
95% CI	184–238	172–229	167–219	164–208
No. of weeks of gestation at randomization	16.6±3.0	16.7±3.0	18.0±2.8	17.7±2.9

Table 3. Developmental and Behavioral Outcomes in Offspring of Mothers with Subclinical Hypothyroidism.*

Outcome	Levothyroxine		Placebo		Difference (95% CI)†	P Value
	No. of Children	Median Value (95% CI)	No. of Children	Median Value (95% CI)		
Primary outcome‡	323	97 (94 to 99)	326	94 (92 to 96)	0 (−3 to 2)	0.71
Bayley-III score§						
At 12 mo						
Cognitive	311	100 (95 to 100)	315	100 (95 to 100)	0 (0 to 0)	0.63
Motor	312	97 (97 to 97)	314	97 (97 to 97)	0 (0 to 3)	0.83
Language	309	94 (94 to 97)	312	94 (94 to 97)	0 (0 to 3)	0.48
At 24 mo						
Cognitive	308	90 (90 to 90)	302	90 (90 to 90)	0 (0 to 0)	0.59

Table 4. Developmental and Behavioral Outcomes in Offspring of Mothers with Hypothyroxinemia.*

Outcome	Levothyroxine		Placebo		Difference (95% CI)†	P Value
	No. of Children	Median Value (95% CI)	No. of Children	Median Value (95% CI)		
Primary outcome	254	94 (91 to 95)	253	91 (89 to 93)	−1 (−4 to 1)	0.30
Bayley-III score						
At 12 mo						
Cognitive	247	100 (100 to 100)	238	100 (100 to 100)	0 (0 to 0)	0.89
Motor	246	97 (94 to 97)	236	97 (94 to 97)	0 (0 to 3)	0.54
Language	246	94 (91 to 94)	237	94 (91 to 97)	0 (−3 to 3)	0.92
At 24 mo						
Cognitive	235	90 (85 to 90)	235	90 (85 to 90)	0 (0 to 0)	0.70

Casey BM et al. N Engl J Med 2017;376:811-820

Table 2. Pregnancy and Neonatal Outcomes.*

Outcome	Subclinical Hypothyroidism			Hypothyroxinemia		
	Levothyroxine (N=339)	Placebo (N=338)	P Value	Levothyroxine (N=263)	Placebo (N=261)	P Value
Maternal						
Week of gestation at delivery	39.1±2.5	38.9±3.1	0.57	39.0±2.4	38.8±3.1	0.46
Preterm birth — no. (%)						
At <34 wk	9 (3)	10 (3)	0.81	10 (4)	7 (3)	0.47
At <37 wk	31 (9)	37 (11)	0.44	31 (12)	20 (8)	0.11
Placental abruption — no. (%)	1 (<1)	5 (1)	0.12	3 (1)	2 (1)	1.00
Gestational hypertension — no. (%)	33 (10)	36 (11)	0.69	20 (8)	24 (9)	0.51
Preeclampsia — no. (%)	22 (6)	20 (6)	0.76	9 (3)	11 (4)	0.64
Gestational diabetes — no. (%)	25 (7)	22 (7)	0.66	21 (8)	24 (9)	0.62
Fetal or neonatal†						
Stillbirth or miscarriage — no. (%)	4 (1)	7 (2)	0.36	2 (1)	5 (2)	0.28
Neonatal death — no. (%)	0	1 (<1)	0.50	1 (<1)	1 (<1)	1.00

NEJM editorial

"Subclinical hypothyroidism and hypothyroxinemia in pregnancy- still no answers"

- Four randomized studies : effect of T4 2010-20 17
  - Positive 2010: T4 Rx improved composite preg outcomes (Negro et al JCEM)
    - In subset with TSH>2.5 and Ab+ in secondary analysis
  - Negative 2012:Controlled Antenatal Thyroid Screening (Lazarus et al NEJM)

    No benefit re obstetric outcomes or cognitive function @3.5 years in both SCH and hypothyroxinaemia

    Antibodies not checked; late start to Rx; 24% offspring lost to FU
  - Positive 2017: T4 Rx associated with lower rate preterm delivery in Ab+ (Nazapour et al EJE)
  - Negative: current study-weakness : late initiation of Rx –mean 17 weeks (foetal thyroid functional at 16-20 weeks)

NEJM editorial- "Still no answers"

"We continue to endorse the ATA guideline since the early initiation of low dose thyroxine for subclinical hypothyroidism may be of benefit, is inexpensive and is unlikely to be harmful"

Table 1. American Thyroid Association Recommendations for the Management of Subclinical Hypothyroidism and Hypothyroxinemia in Pregnancy.*

Laboratory Data	Levothyroxine Therapy	Recommendation Strength	Evidence Quality
Anti-TPO–positive and thyrotropin level > pregnancy-specific reference range	Yes	Strong	Moderate
Anti-TPO–negative and thyrotropin level >10 mU/liter	Yes	Strong	Low
Anti-TPO–positive and thyrotropin level >2.5 mU/liter and < upper limit of the reference range	Consider	Weak	Moderate
Anti-TPO–negative and thyrotropin level > upper limit of the reference range and <10 mU/liter	Consider	Weak	Low
Isolated maternal hypothyroxinemia†	No	Weak	Low

Part 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

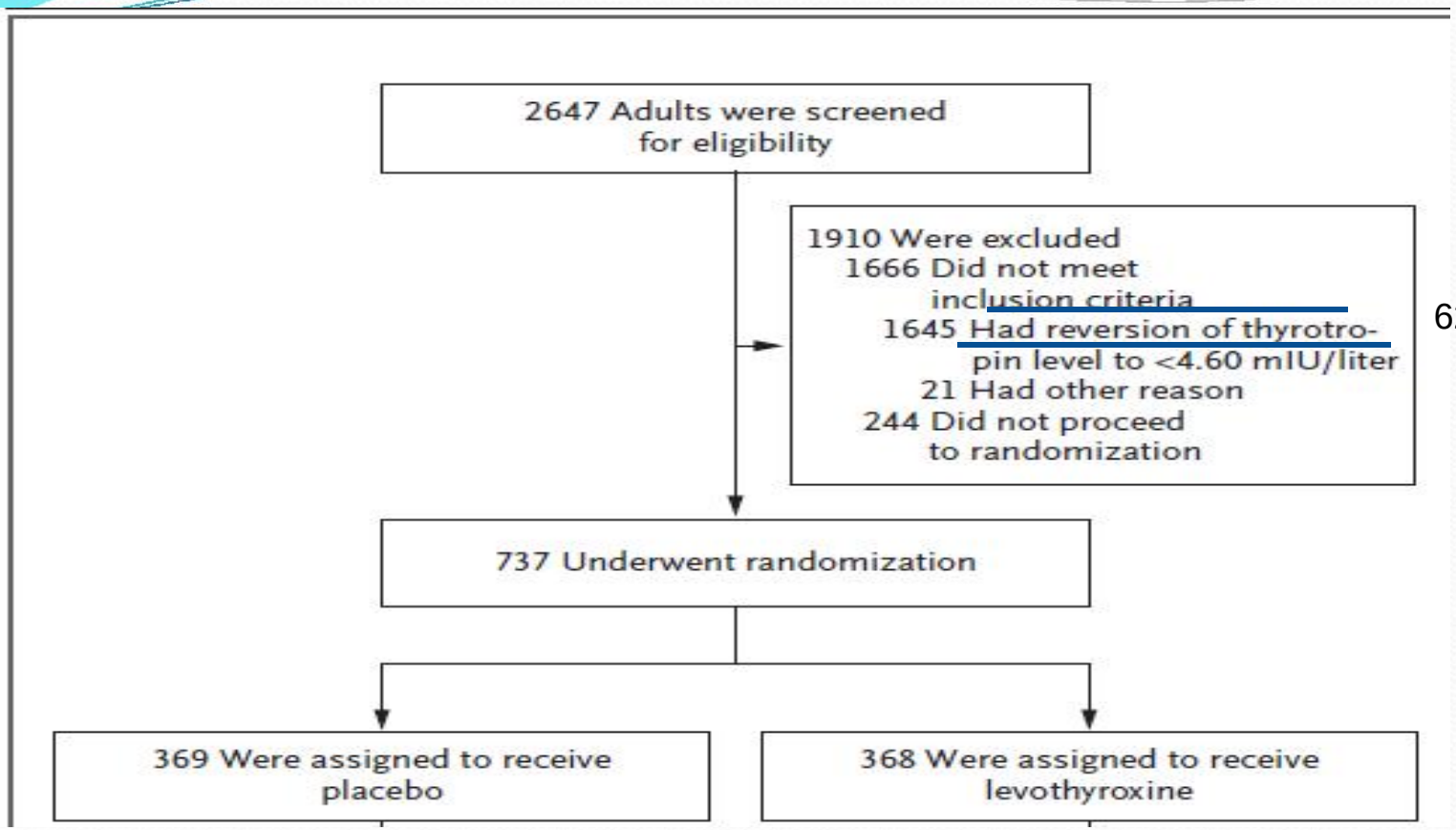
Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism

D.J. Stott, N. Rodondi, P.M. Kearney, I. Ford, R.G.J. Westendorp, S.P. Mooijaart, N. Sattar, C.E. Aubert, D. Aujesky, D.C. Bauer, C. Baumgartner, M.R. Blum, J.P. Browne, S. Byrne, T.-H. Collet, O.M. Dekkers, W.P.J. den Elzen, R.S. Du Puy, G. Ellis, M. Feller, C. Floriani, K. Hendry, C. Hurley, J.W. Jukema, S. Kean, M. Kelly, D. Krebs, P. Langhorne, G. McCarthy, V. McCarthy, A. McConnachie, M. McDade, M. Messow, A. O'Flynn, D. O'Riordan, R.K.E. Poortvliet, T.J Quinn, A. Russell, C. Sinnott, J.W.A. Smit, H.A. Van Dorland, K.A. Walsh, E.K. Walsh, T. Watt, R. Wilson, and J. Gussekloo, for the TRUST Study Group*

03/04/2017

Study design

- Double blind randomised placebo-controlled , parallel group trial
- 737 adults at least 65 years old
- Persistent subclinical hypothyroidism
  - TSH 4.6-19.99 mIU/l; fT4 within normal range
  - Levothyroxine start dose 50mcg/day (25 if body wt <50kg or coronary artery disease)
- Primary outcomes- at 1 year
  - Hypothyroid symptoms score (0-100)
  - Tiredness score on thyroid related QOL questionnaire (0-100)

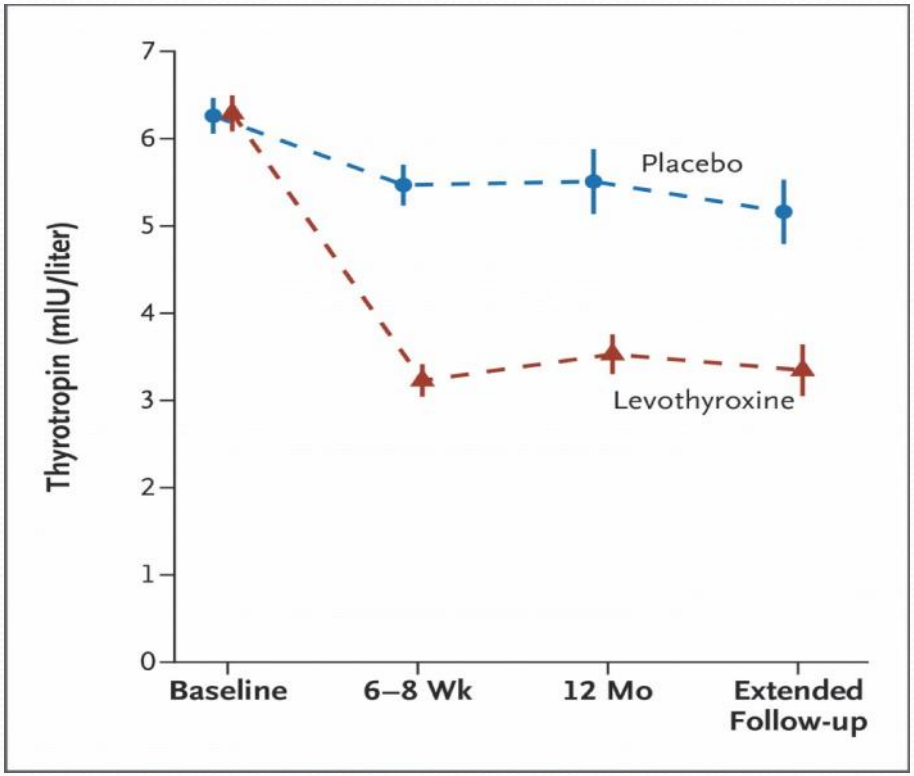

2647 Adults were screened for eligibility
1910 Were excluded
1666 Did not meet inclusion criteria
1645 Had reversion of thyrotropin level to <4.60 mIU/liter
21 Had other reason
244 Did not proceed to randomization
737 Underwent randomization
369 Were assigned to receive placebo
368 Were assigned to receive levothyroxine

62% reverted

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Placebo Group (N=369)	Levothyroxine Group (N=368)
Age — yr		
Mean	74.8±6.8	74.0±5.8
Range	65.1–93.4	65.2–93.0
Female sex — no. (%)	198 (53.7)	198 (53.8)
White race — no. (%)†	362 (98.1)	362 (98.4)
Standard housing — no. (%)‡	356 (96.5)	358 (97.3)
Previous medical conditions and clinical descriptors — no./total no. (%)		
Ischemic heart disease§	50/369 (13.6)	50/368 (13.6)
Atrial fibrillation	44/368 (12.0)	45/364 (12.4)
Hypertension	183/366 (50.0)	192/368 (52.2)
Diabetes mellitus	54/368 (14.7)	63/368 (17.1)
Osteoporosis	47/367 (12.8)	41/364 (11.3)
Current smoking	33/369 (8.9)	29/368 (7.9)
Median no. of concomitant medicines (IQR)	4 (2–6)	4 (2–6)
Median Mini–Mental State Examination score (IQR)¶	29 (28–30)	29 (27–30)
Weight <50 kg — no. (%)	5 (1.4)	5 (1.4)
Laboratory results		
Thyrotropin — mIU/liter	6.38±2.01	6.41±2.01
Median (IQR)	5.76 (5.10–6.94)	5.73 (5.12–6.83)
Range	4.60–17.60	4.60–17.60
Free thyroxine — pmol/liter‖	13.3±1.9	13.4±2.1
Outcome measures**		
Hypothyroid Symptoms score	16.9±17.9	17.5±18.8
Tiredness score	25.5±20.3	25.9±20.6

NEJM



P<0.001

NEJM 03/04/2017

Table 2. Outcomes at 12 Months and Extended Follow-up.*

Variable	Baseline		At 12 Mo				At Extended Follow-up Visit†			
	Placebo (N=369)	Levothyroxine (N=368)	Placebo (N=320)	Levothyroxine (N=318)	Difference (95% CI)	P Value	Placebo (N=187)	Levothyroxine (N=194)	Difference (95% CI)	P Value
Thyrotropin — mIU/liter	6.38±2.01	6.41±2.01	5.48±2.48	3.63±2.11	−1.92 (−2.24 to −1.59)	<0.001	5.28±2.50	3.47±2.08	−1.88 (−2.32 to −1.45)	<0.001
Median (IQR)	5.76 (5.10 to 6.94)	5.70 (5.12 to 6.83)	4.90 (3.91 to 6.46)	3.16 (2.45 to 4.22)	—	—	4.94 (3.78 to 6.26)	3.00 (2.26 to 4.16)	—	—
Primary outcomes‡										
Hypothyroid Symptoms score	16.9±17.9	17.5±18.8	16.7±17.5	16.6±16.9	0.0 (−2.0 to 2.1)	0.99	15.2±15.9	17.9±9.1	1.0 (−1.9 to 3.9)	0.50
Tiredness score	25.5±20.3	25.9±20.6	28.6±19.5	28.7±20.2	0.4 (−2.1 to 2.9)	0.77	31.9±22.1	30.2±20.5	−3.5 (−7.0 to 0.0)	0.05

Table 3. Clinical Outcomes and Adverse Events.*

Variable	All Patients (N=737)	Placebo Group (N=369)	Levothyroxine Group (N=368)	Hazard Ratio (95% CI)
Clinical outcome				
Fatal or nonfatal cardiovascular event — no. (%)	38 (5.2)	20 (5.4)	18 (4.9)	0.89 (0.47–1.69)
Cardiovascular death — no. (%)	3 (0.4)	1 (0.3)	2 (0.5)	—
Death from any cause — no. (%)	15 (2.0)	5 (1.4)	10 (2.7)	1.91 (0.65–5.60)
Serious adverse event				
No. of patients with ≥1 serious adverse event	181 (24.6)	103 (27.9)	78 (21.2)	0.94 (0.88–1.00)†
No. of events	343	201	142	—
Adverse event of special interest				
New-onset atrial fibrillation — no. (%)	24 (3.3)	13 (3.5)	11 (3.0)	0.80 (0.35–1.80)
Heart failure — no. (%)	9 (1.2)	6 (1.6)	3 (0.8)	—
Fracture — no. (%)	17 (2.3)	8 (2.2)	9 (2.4)	1.06 (0.41–2.76)
New diagnosis of osteoporosis — no. (%)	7 (0.9)	4 (1.1)	3 (0.8)	—
Withdrawal				
Permanent discontinuation of trial regimen — no. (%)	160 (21.7)	79 (21.4)	81 (22.0)	1.06 (0.78–1.44)
Withdrawal from follow-up — no. (%)	41 (5.6)	22 (6.0)	19 (5.2)	0.84 (0.46–1.56)

Strengths

- Powered sufficiently
  - 80% power to detect a change with T4 vs placebo of
    - 3.0 points on hypothyroid symptom score and
    - 4.1 points on tiredness score
  - used validated measures of thyroid specific QOL
  - shown previously to be sensitive to change

Potential weaknesses

- Not powered to detect cv effects
- Thyroid antibodies not measured
- Treatment not aggressive enough to see an effect
  - ?target TSH 2.5 mIU/l– European Thyroid Association guidelines2013
- Cohort
  - Very few had TSH >10 mIU/l
    - ?would this subgroup benefit more
  - Low symptomatic scores at baseline
    - ?would more symptomatic patients benefit

Conclusions

- No differences in mean change at 1 year in Hypothyroid symptom score or the tiredness score
- No beneficial effects of levothyroxine on secondary outcome measures
- No significant excess of serious adverse events (prespecified as being of special interest)

- Levothyroxine no apparent benefit in older persons with sublinical hypothyroidism

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

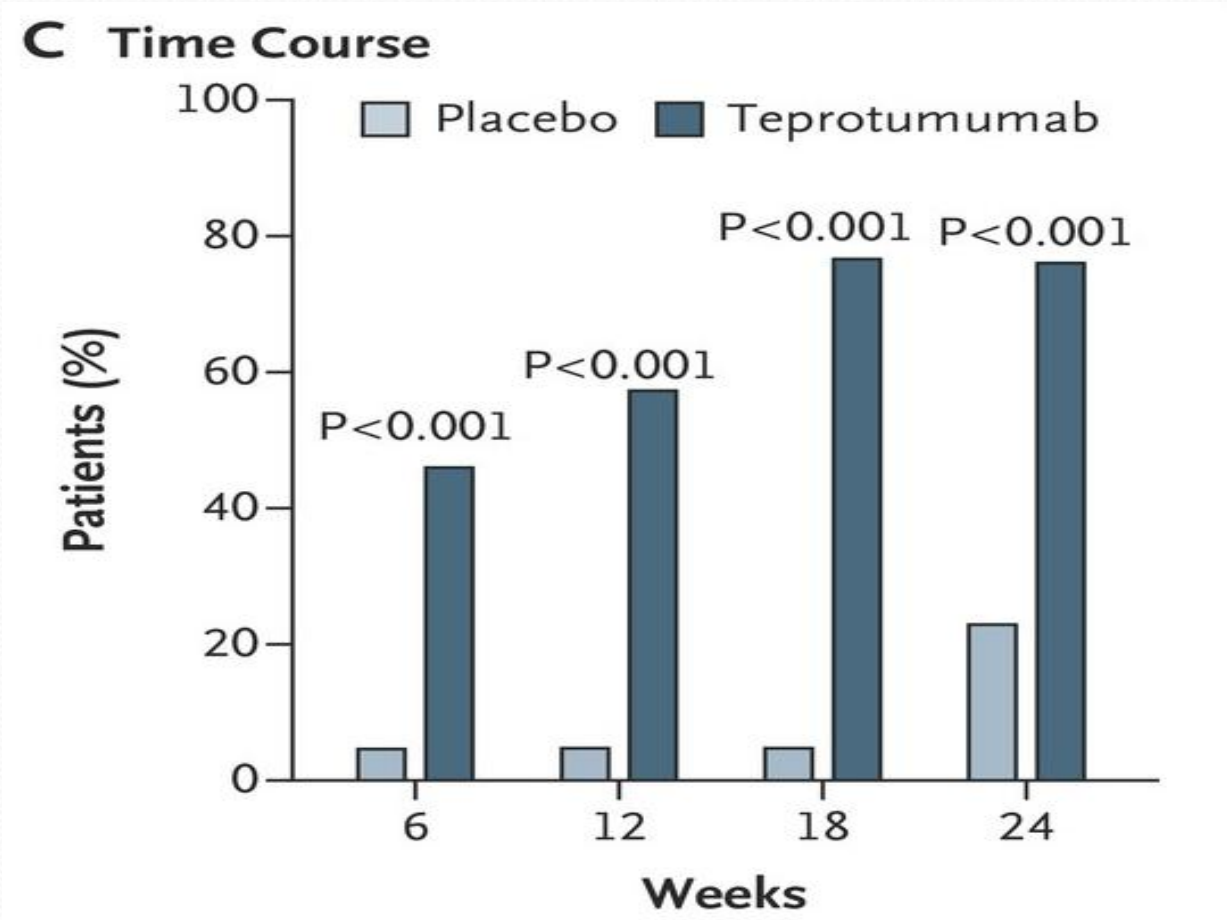
Teprotumumab for Thyroid-Associated Ophthalmopathy

Terry J. Smith, M.D., George J. Kahaly, M.D., Ph.D., Daniel G. Ezra, M.D., James C. Fleming, M.D., Roger A. Dailey, M.D., Rosa A. Tang, M.D., Gerald J. Harris, M.D., Alessandro Antonelli, M.D., Mario Salvi, M.D., Robert A. Goldberg, M.D., James W. Gigantelli, M.D., Steven M. Couch, M.D., Erin M. Shriver, M.D., Brent R. Hayek, M.D., Eric M. Hink, M.D., Richard M. Woodward, Ph.D., Kathleen Gabriel, R.N., Guido Magni, M.D., Ph.D., and Raymond S. Douglas, M.D., Ph.D.

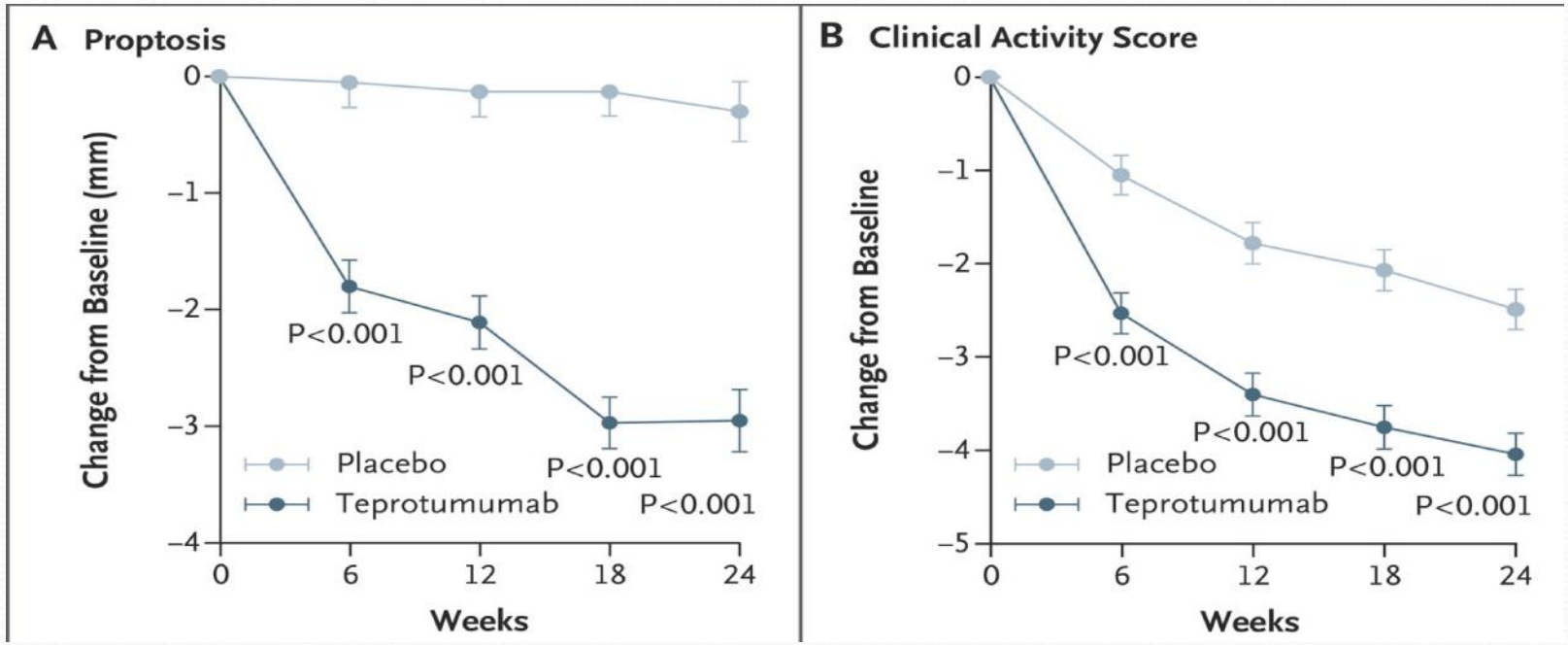
May 4th 2017

Design Study

- Multicentre double blind randomized placebo controlled trial
- Determine the efficacy and safety of teprotumumab
  - Human monoclonal antibody inhibitor of IGF-I receptor
  - 88 patients with active mod-severe ophthalopathy
  - Iv infusion every 3 weeks@8 times (6 months)
  - 1^0 endpoints- at 24 weeks:
    - ≥2 point reduction in Clinical Activity Score
    - ≥2mm reduction of proptosis



69% MAB vs 20% placebo had a response



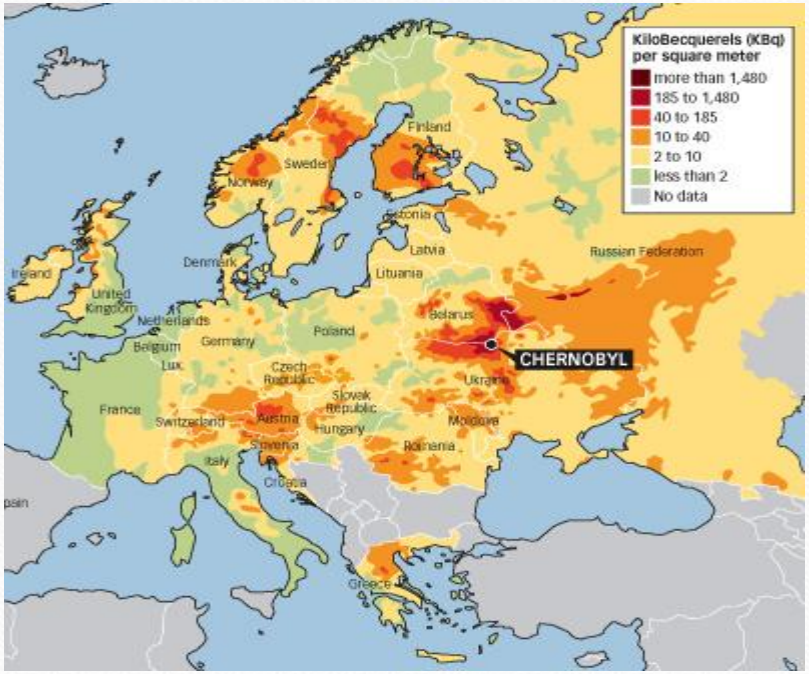
Only drug related adverse event was hyperglycaemia in patients for diabetes

Conclusion

- Teprotumumab was more effective than placebo in reducing proptosis and the clinical activity score
- Subjective diplopia and GO-QOL scores significantly improved in a clinically meaningful way
- Results similar order of magnitude to that reported after decompression surgery

Part 4

Chernobyl 30 year anniversary

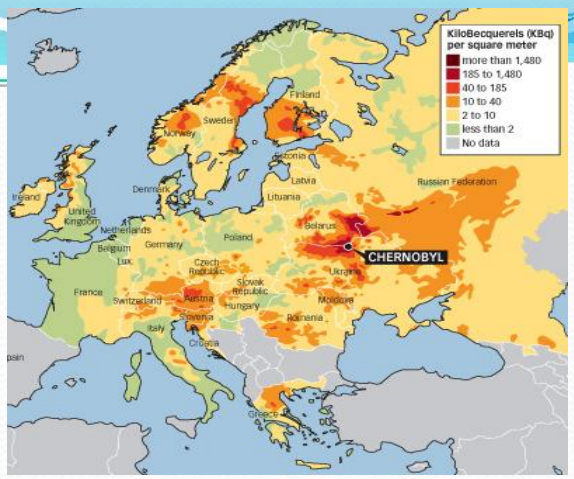


- April 1986
- Children @ time now age 30-48 years
- Working age population
- Clinic- expectation of surveillance program

Literature review-Chernobyl thyroid

- In last year >30 publications
- 880 publications in total
- 5 million exposed
- Registries and surveillance program – USS
  - Belarus 1.5m
  - Russia 760000
  - Ukraine 2.6m
- Children up to age 18

Risk



- Age
- Degree of exposure
- Iodine deficiency
- No good evidence of increase risk outside of described area of moderate/severe exposure ( )
- Gomel pop 0.5 million
  - 70 miles north
  - Children born 1986-1993
  - 244/251 developed thyroid cancer
- North Wales farms back in action since 2012

Statistics/modelling

- Cardis et al
- 2005: thyroid cancer attributable 6000
- Expected to grow- modelling:
- Lifetime thyroid cancers attributable 17000

Broad themes- learning

- WHO:Continued monitoring of those exposed as children for the forseeable
- Screen with USS but will increase absolute rate cancer
- Iodine sufficiency in population likely to be protective
- Public health measures must be swift
  - Containment
  - Stop consumption contaminated products- milk
  - Early admin stable iodine –KI-reduces up to 90% contamination of thyroid
    - (pregnant women and children <10 years the priority)

Literature review-Chernobyl thyroid

- **1.** Cahoon et al J Clin Endocrinol Metab. 2017 Mar 22

- Risk of any thyroid nodule increased with dose and younger age in Belarus.
  - Excess odds ratios per Gray (EOR/Gy)(95%CI)
  - neoplastic nodules was 3.82 (0.87, 15.52) and
  - Non-neoplastic nodule 0.32 (<0.03, 0.7)

Exposure mean after Chernobyl 0.6 Gy; max detected among children 33Gy

Literature review-Chernobyl thyroid

- **2. A 30 year surgical experience**
  - Michel et al Acta Chir Bel 2016

  - Persistent higher incidence of PTC among Belgian children <15 years vs >15 years at the time of the Chernobyl accident (19.5% of surgically resected lesions vs 8.1%) $p<0.001$

Literature review-Chernobyl thyroid

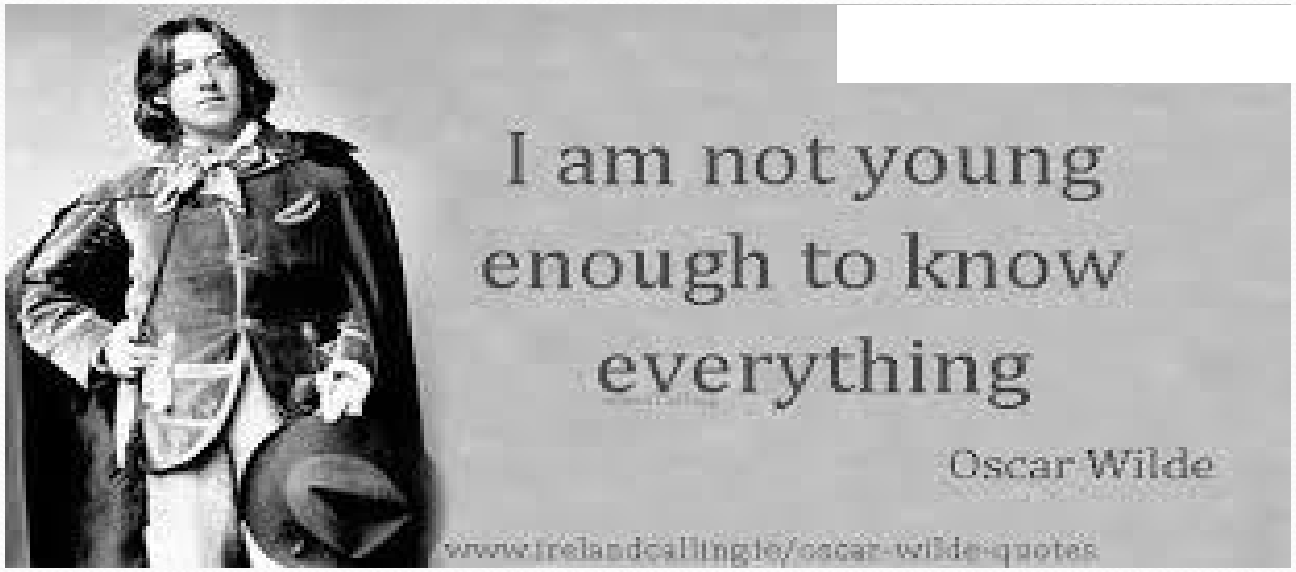
- 3. Handkiewicz-Junak D et al Eur J Nucl Med Mol Imaging. 2016

- Significant, but subtle, differences in gene expression (10)in the post-Chernobyl PTC are associated with previous low-dose radiation exposure - Gene signature

Conclusions

- Subclinical hypothyroidism in elderly- tide away from treatment
- Subclinical hypothyroidism/hypothyroxinaemia in pregnancy – jury out?
- Do we eventually have a monoclonal antibody therapy in endocrinology?
- Chernobyl 30 years on-lessons learned- not over yet

Questions?


I am not young enough to know everything
Oscar Wilde
www.irelandcalling.ie/oscar-wilde-quotes