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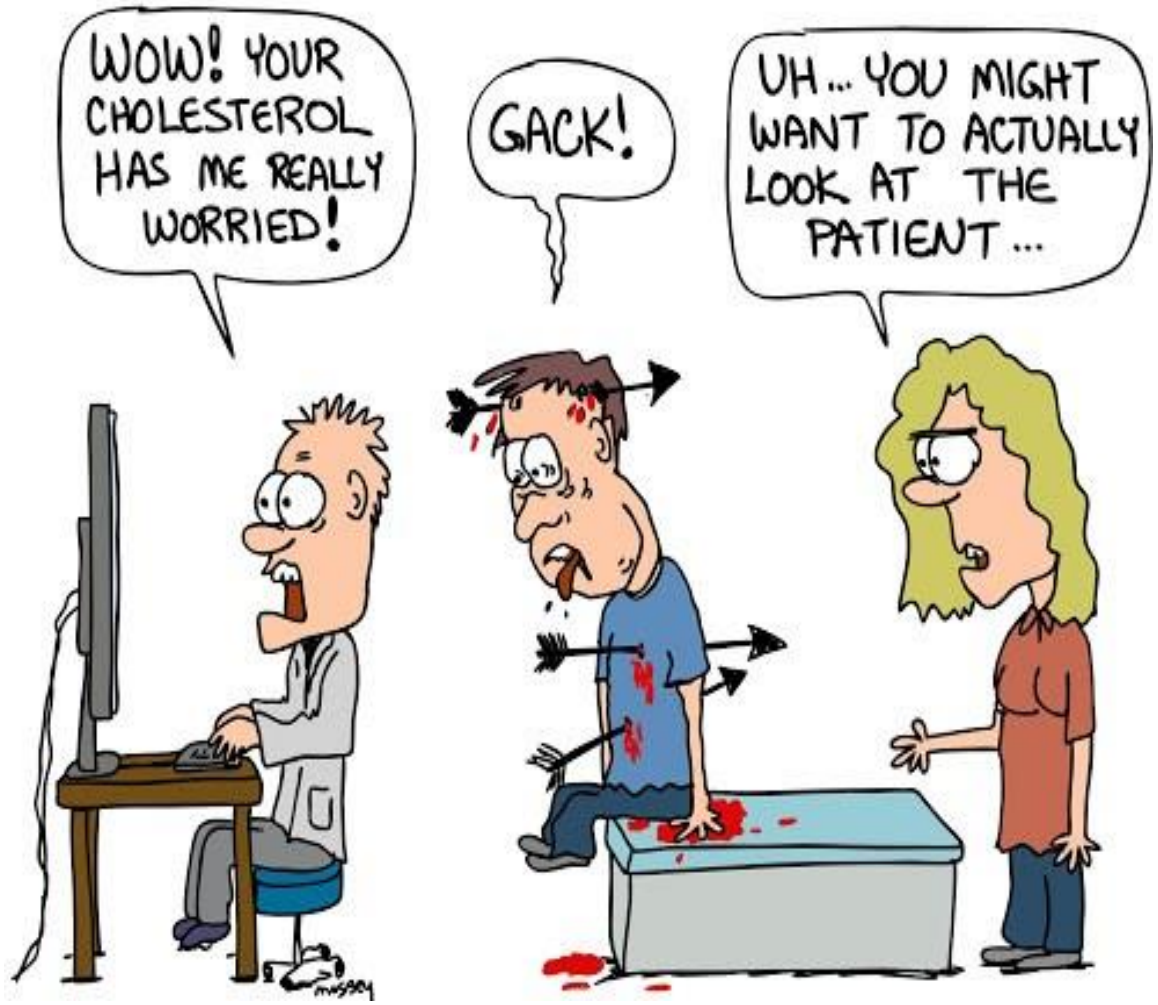
- Endocrine and Diabetes physician R&R hormone clinic clinic Jabalpur Madhya Pradesh
- Community board member American Association of Clinical Endocrinolog
- ECP Council American College Of Physician India Chapter
- Recipient of Eugene T Davidson Public Service Award 2022 by American Association of Clinical Endocrinology
- President of Asia Pacific Society for Endocrine Research APSER
- Editorial board member Journal of Endocrinology and Metabolism
- He is an editorial board member of MSD research
- Received Dr Hedgevar rising star award from IMA centenary conference
- Received diabetes india award in 2019
- Received research excellence award in 2020 for his study on hypogonadism

GNOSIS AND TREATMENTS OF THYROID

Management of Subclinical Thyroid Dysfunction

MANAGING PATIENTS

- Includes a holistic and overall clinical assessment and not just reacting to numbers.
- The biochemistry is a guide and not a binary treatment decision aid.



TSH REFERENCE RANGE

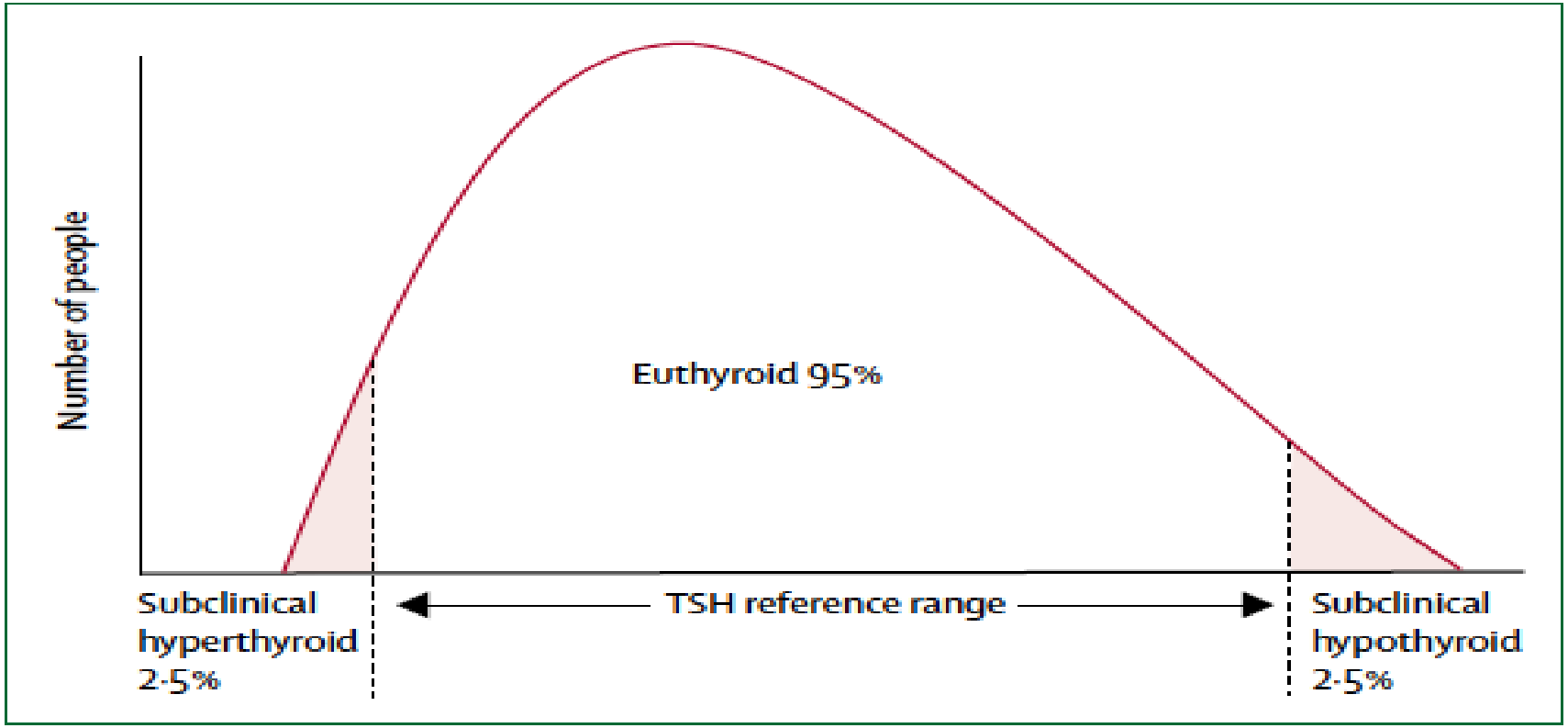


Figure 1: **Distribution of serum TSH in apparently euthyroid individuals**
With the 95% reference interval definition, 5% of individuals will fall outside of the euthyroid range. The hatched area represents the subclinical thyroid disease range, assuming thyroid hormone levels are within the normal range.
TSH=thyroid-stimulating hormone.

Jonklaas & Razvi, Lancet D&E 2019

TSH REFERENCE RANGE IS A MOVING TARGET

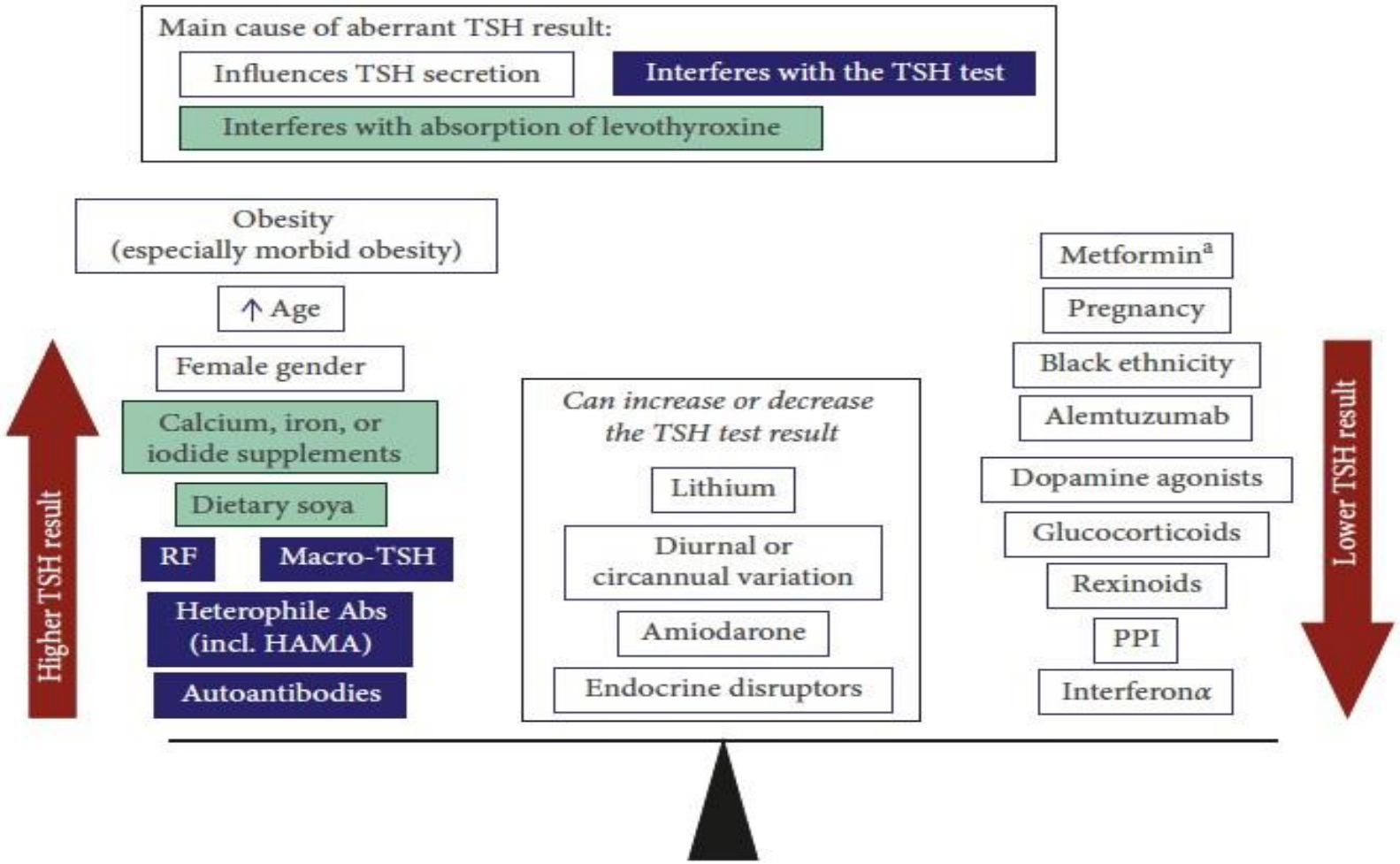


FIGURE 1: Overview of common factors that can produce an aberrant TSH test. [a]Metformin reduces serum TSH in people with overt or subclinical hypothyroidism and in euthyroid individuals with high normal baseline TSH levels (see refs [31] and [32]; see text for other references). HAMA: human anti-mouse antibody; RF: rheumatoid factor; TSH: thyrotropin.

Razvi et al, J Thyr Res 2019

DEBATE RE UPPER LIMIT OF TSH IS LONG-STANDING

CONTROVERSY IN CLINICAL ENDOCRINOLOGY

The Thyrotropin Reference Range Should Remain Unchanged

Martin I. Surks, Gayotri Goswami, and Gilbert H. Daniels

Division of Endocrinology and Metabolism, Department of Medicine (M.I.S., G.G.), and Department of Pathology (M.I.S.), Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York 10467; and Thyroid Unit and Department of Medicine, Massachusetts General Hospital and Harvard Medical School (G.H.D.), Boston, Massachusetts 02114

CONTROVERSY IN CLINICAL ENDOCRINOLOGY

The Evidence for a Narrower Thyrotropin Reference Range Is Compelling

Leonard Wartofsky and Richard A Dickey

Department of Medicine, Washington Hospital Center, Washington, D.C. 20010; Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814; and Georgetown University School of Medicine, Washington, D.C. 20006

JCEM 2005

AND CONTINUES

. . . . . .

Editorial Opinion

The Thyrotropin Reference Range Should Be Changed in Older Patients

Anne R. Cappola, MD, ScM

Cappola JAMA 2019

ASSOCIATIONS OF SUBCLINICAL THYROID DISEASE

SC Hypothyroidism

- Higher symptom burden and impaired QoL
- CV disease and heart failure
- Obesity
- Impaired cognition
- Worse pregnancy and foetal outcomes
- Progression to overt disease

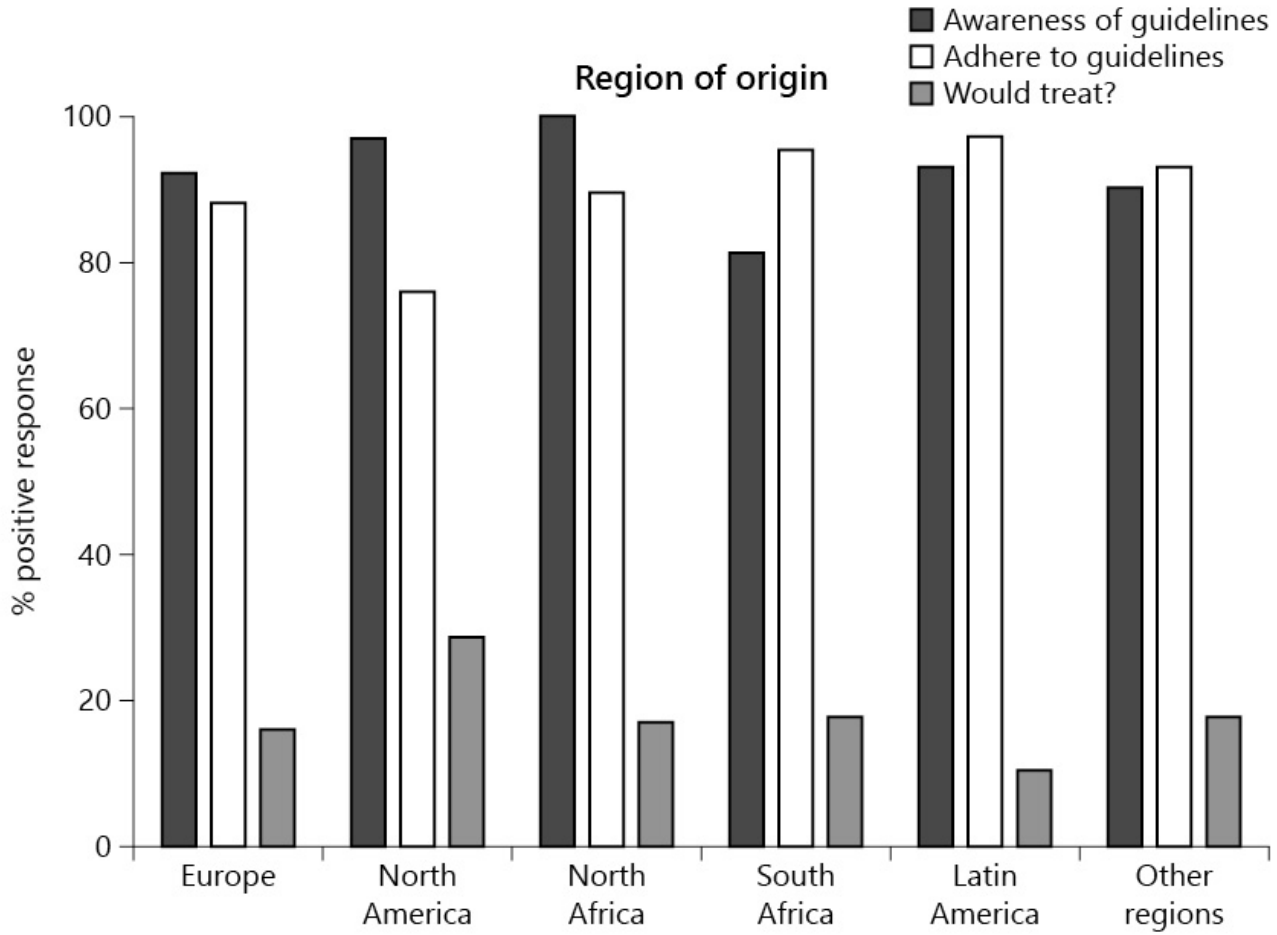
SC Hyperthyroidism

- AF
- Osteoporosis
- Dementia
- CV disease
- Progression to overt disease

80-YR OLD MAN WITH MILDLY RAISED SERUM TSH

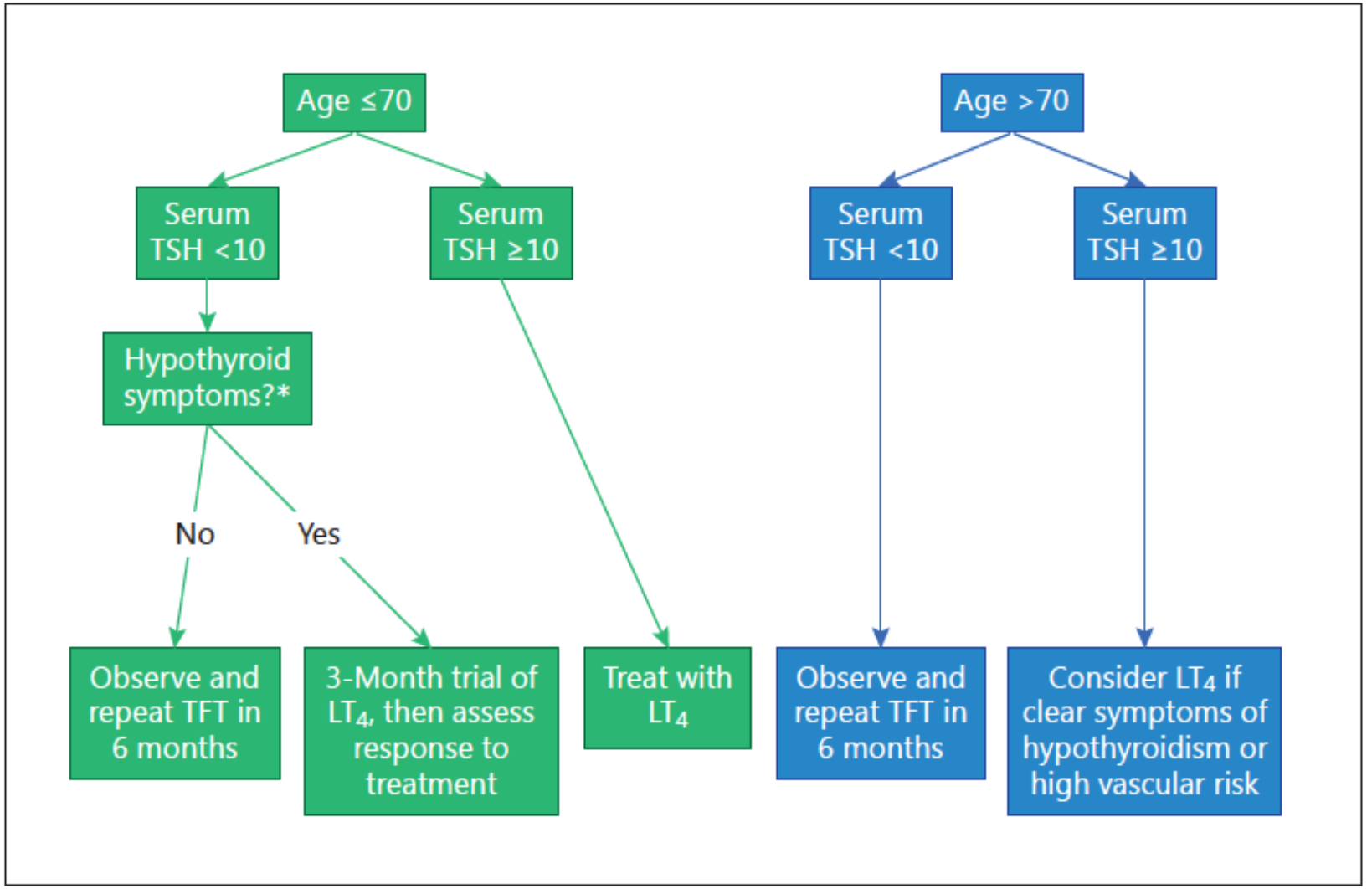
- 80-year-old gentleman with sustained subclinical hypothyroidism with serum TSH levels of **6.5** and **6.8** (reference range 0.4–4.5 mIU/L) and FT4 **14.0** and **13.5** (reference range 10–22 pmol/L) on 2 separate occasions and who was experiencing **tiredness.**
- The question is whether he should be treated with LT4 to improve his symptoms?

RESPONSE FROM ENDOCRINOLOGISTS ACROSS VARIOUS PARTS OF THE WORLD

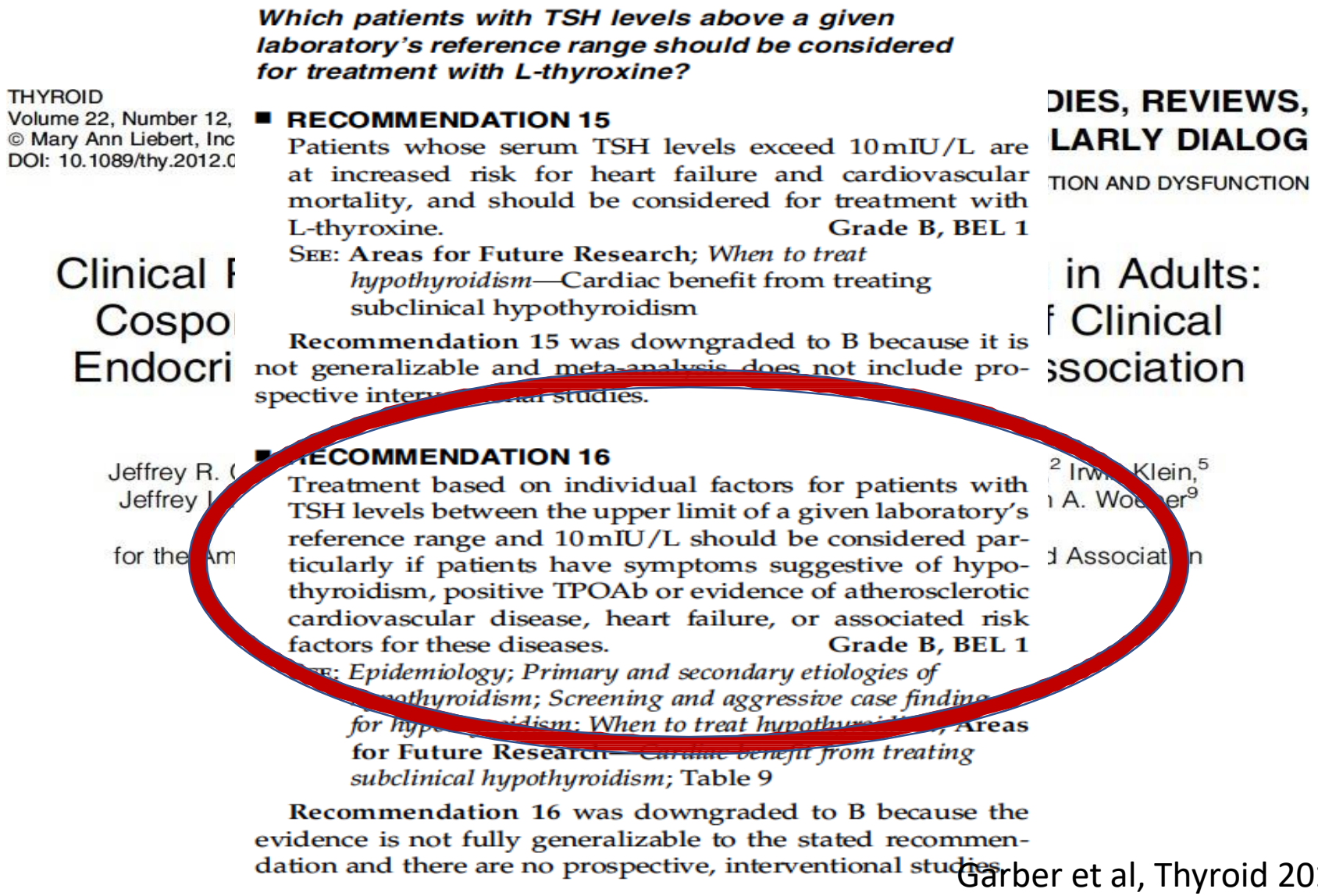


Razvi et al, Eur Thyroid Journal (in press)

ETA GUIDELINES FOR SCH



ATA/AACE SCH GUIDELINES 2012 GARBER



Which patients with TSH levels above a given laboratory's reference range should be considered for treatment with L-thyroxine?

■ **RECOMMENDATION 15**

Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine. **Grade B, BEL 1**

SEE: **Areas for Future Research**; *When to treat hypothyroidism*—Cardiac benefit from treating subclinical hypothyroidism

Recommendation 15 was downgraded to B because it is not generalizable and meta-analysis does not include prospective interventional studies.

■ **RECOMMENDATION 16**

Treatment based on individual factors for patients with TSH levels between the upper limit of a given laboratory's reference range and 10 mIU/L should be considered particularly if patients have symptoms suggestive of hypothyroidism, positive TPOAb or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases. **Grade B, BEL 1**

SEE: *Epidemiology*; *Primary and secondary etiologies of hypothyroidism*; *Screening and aggressive case finding for hypothyroidism*; *When to treat hypothyroidism*; **Areas for Future Research**—*Cardiac benefit from treating subclinical hypothyroidism*; Table 9

Recommendation 16 was downgraded to B because the evidence is not fully generalizable to the stated recommendation and there are no prospective, interventional studies.

Garber et al, Thyroid 2012

LT4 PRESCRIBING IN USA AND UK

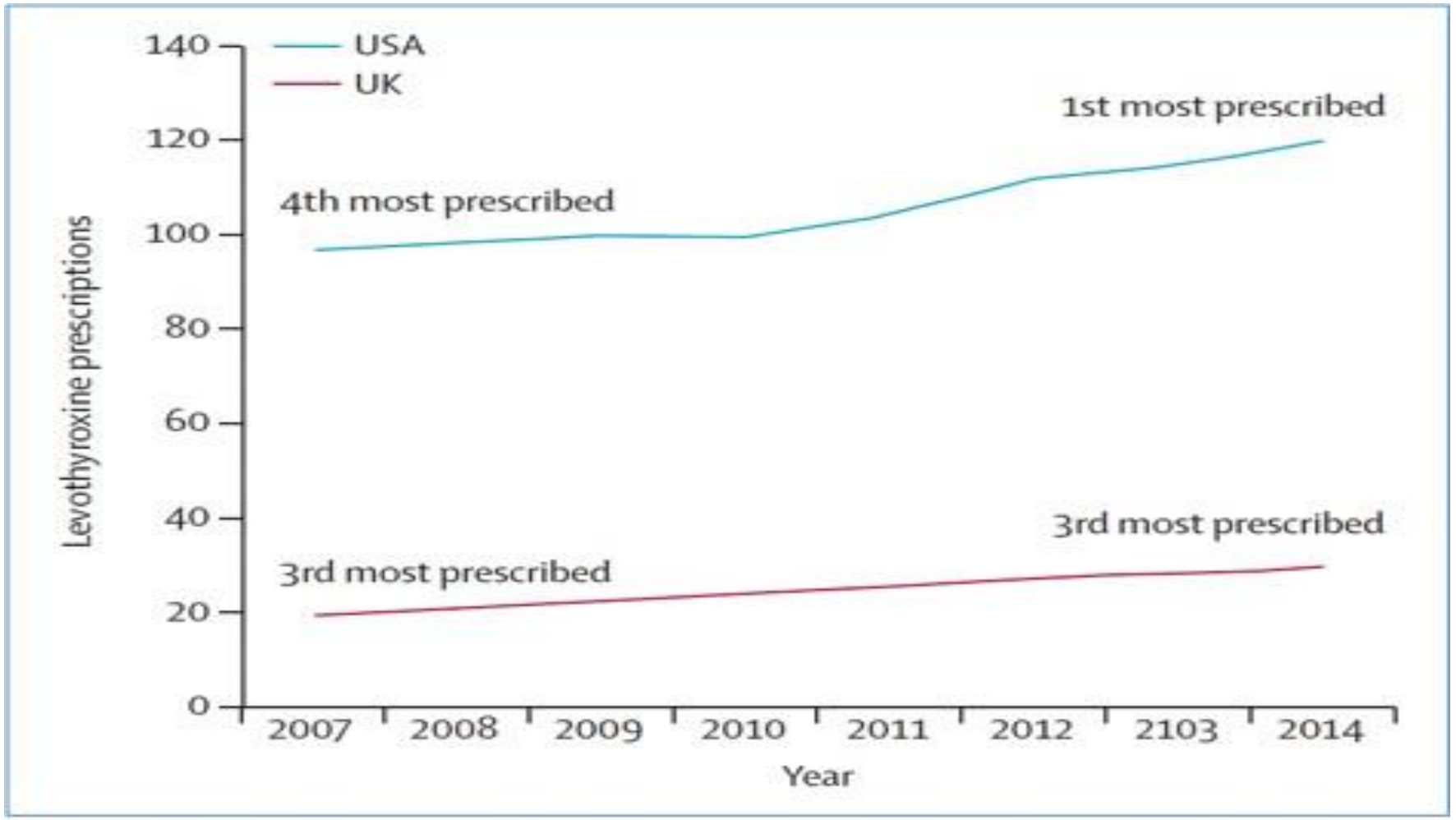


Figure: **Levothyroxine prescriptions from 2007 to 2014 in the USA and the UK**

Rodriguez-Guitterezz et al, Lancet Diabetes Endocrinol 2016

RCT IN 80 YR OLD SCH

JAMA | Original Inv

Association
and Thyroid
Aged 80 Yea

yroidism

Simon P. Mooijaart, MD, P
Nicolas Rodondi, MD, MA
Rosalinde K. E. Poortvliet
Robin P. Peeters, MD, PhD
Tinh-Hai Collet, MD; Torq
Johannes W. A. Smit, MD

PhD;
, MD;

Key Points

Question Among adults aged 80 years and older with subclinical hypothyroidism, what is the association between treatment with levothyroxine and thyroid-related symptoms?

Findings In this pooled analysis of data from 2 randomized clinical trials that included 251 participants aged 80 years and older, treatment with levothyroxine, compared with placebo, was not significantly associated with improvement in thyroid-related patient-reported quality of life outcome scores (range, 0-100; higher scores indicate worse quality of life; minimal clinically important difference, 9) for hypothyroid symptoms (adjusted between-group difference, 1.3) or tiredness (adjusted between-group difference, 0.1).

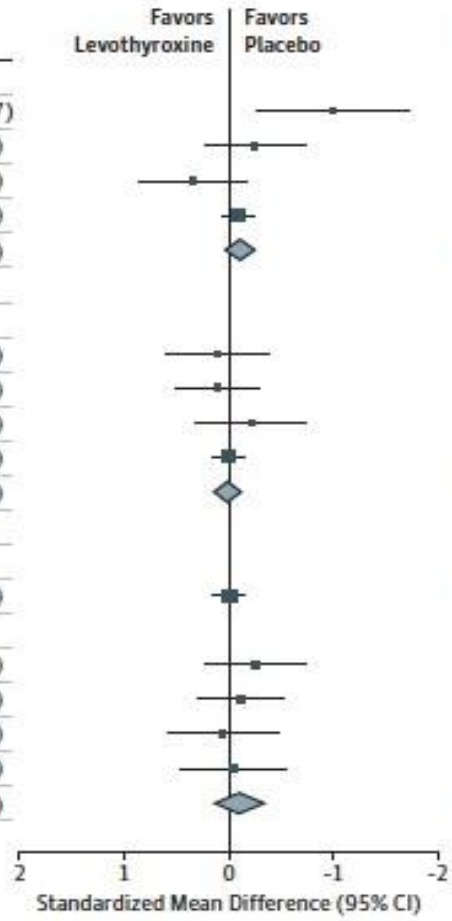
Meaning These findings do not support routine treatment with levothyroxine for subclinical hypothyroidism in adults aged 80 years and older.

Mooijaart et al, JAMA 2019

META-ANALYSIS OF RCTS FOR QOL

Figure 1. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Quality-of-Life and Mood-Related Outcomes

Source	Quality of Life/Mood Scale	No. of Participants		Standardized Mean Difference (95% CI)	Weight, %
		Levothyroxine	Placebo		
General quality of life					
Kong et al,[27] 2002	General Health Questionnaire at 6 mo	20	14	-1.00 (-1.73 to -0.27)	3.70
Jorde et al,[26] 2006	General Health Questionnaire at 12 mo	35	32	-0.25 (-0.74 to 0.23)	8.42
Reuters et al,[31] 2012	Short Form 36 at 6 mo	32	25	0.35 (-0.18 to 0.87)	7.02
Stott et al,[12] 2017	EQ-5D at 12 mo	318	320	-0.10 (-0.25 to 0.06)	80.86
Subtotal				-0.11 (-0.25 to 0.03)	100.00
Overall effect: I^2 = 66.7%; P = .03					
Thyroid-related symptoms					
Meier et al,[22] 2001	Billewicz score at 12 mo	31	32	0.10 (-0.39 to 0.59)	7.34
Razvi et al,[32] 2007	ThyD QoL at 3 mo	100	100	0.11 (-0.29 to 0.50)	11.66
Reuters et al,[31] 2012	Zulewski score at 6 mo	32	25	-0.22 (-0.74 to 0.31)	6.52
Stott et al,[12] 2017	ThyPRO hyperthyroid score at 12 mo	318	320	0.01 (-0.15 to 0.16)	74.48
Subtotal				0.01 (-0.12 to 0.14)	100.00
Overall effect: I^2 = 0.0%; P = .79					
Fatigue and tiredness					
Stott et al,[12] 2017	ThyPRO tiredness score at 12 mo	318	320	-0.01 (-0.16 to 0.15)	100.00
Depressive symptoms					
Jorde et al,[26] 2006	Beck Depression Inventory at 12 mo	35	32	-0.26 (-0.74 to 0.22)	24.09
Parle et al,[16] 2010	HADS at 12 mo	52	42	-0.11 (-0.52 to 0.29)	33.72
Reuters et al,[31] 2012	Beck Depression Inventory at 6 mo	32	25	0.06 (-0.47 to 0.58)	20.39
Najafi et al,[24] 2015	Beck Depression Inventory at 3 mo	30	30	-0.05 (-0.56 to 0.46)	21.80
Subtotal				-0.10 (-0.34 to 0.13)	100.00
Overall effect: I^2 = 0.0%; P = .84					



Feller M et al, JAMA 2018

RCT IN HIGH CARDIAC RISK WITH SCH

Research

JAMA | Original Inv

Effect of Lev
With Subclir
A Randomize

Avais Jabbar, MD; Lorna
Honey Thomas, MD; Jehi
Deborah D. Stocken, PhD

Key Points

Question Does levothyroxine treatment improve left ventricular function in patients with subclinical hypothyroidism presenting with acute myocardial infarction?

Findings In this randomized clinical trial that included 95 participants with subclinical hypothyroidism and acute myocardial infarction, treatment with levothyroxine, compared with placebo, did not significantly improve left ventricular ejection fraction after 52 weeks (mean left ventricular ejection fraction, 53.8% vs 56.1%, respectively).

Meaning These findings do not support treatment of subclinical hypothyroidism in patients with acute myocardial infarction.

Jabbar et al, JAMA 2020

NATURAL COURSE OF TSH LEVELS

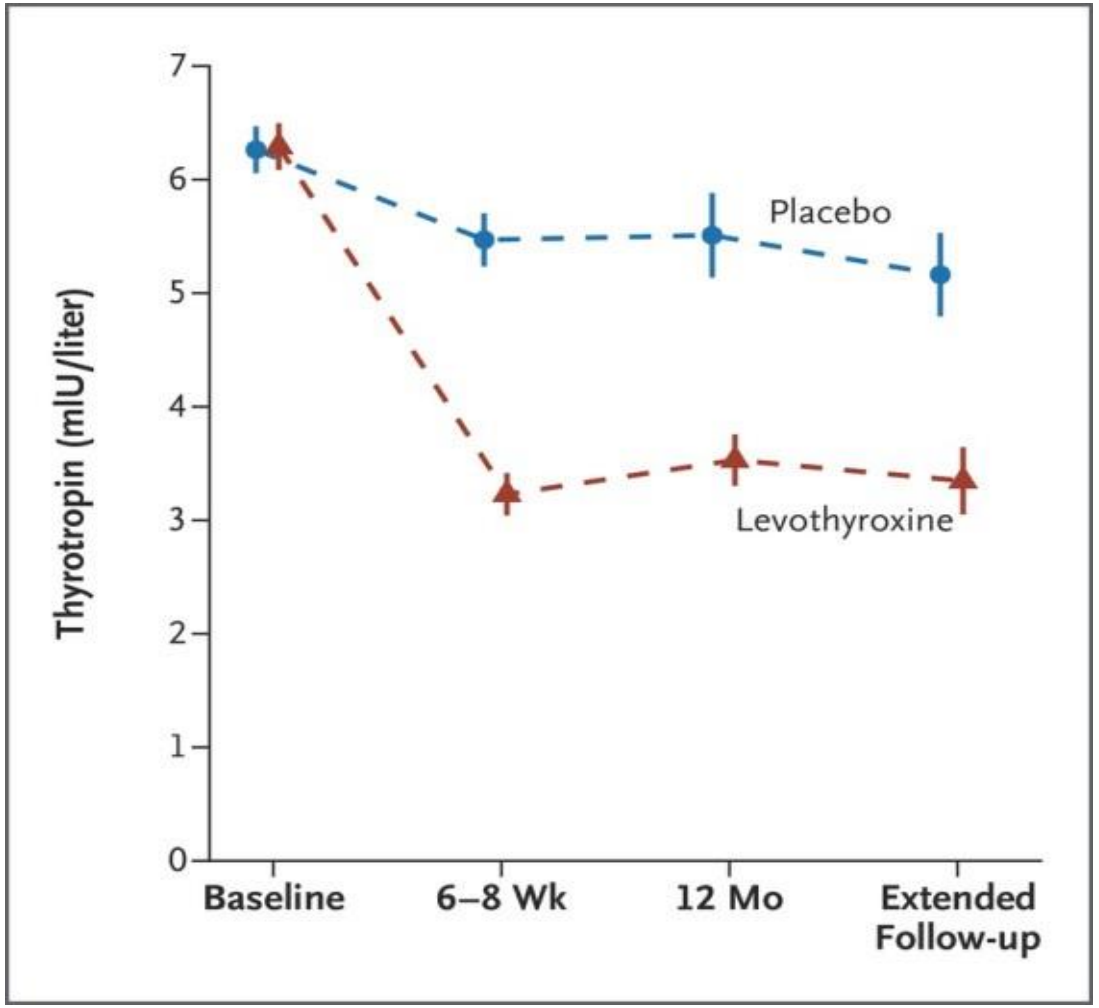


Table 3. Post Hoc Analysis of Thyroid Function and Dose of Levothyroxine During the Course of the Study

	Mean (SD)					
	Visit 1 (baseline)	Visit 2 (4 wk)	Visit 3 (8 wk)	Visit 4 (12 wk)	Visit 5 (24 wk)	Visit 6 (52 wk)
Levothyroxine group						
Thyrotropin, median (IQR), mU/L	5.8 (5.0-7.1)	2.6 (1.8-3.5)	1.8 (1.4-2.3)	2.2 (1.6-2.9)	1.8 (1.4-2.3)	1.8 (1.3-2.2)
FT_4, ng/dL	1.14 (0.16)					1.34 (0.21)
FT_3, pg/mL	2.99 (0.52)					3.06 (0.39)
Dose of levothyroxine, median (IQR), µg/d		25 (25-25)	50 (25-50)	50 (25-68.8)	50 (25-75)	50 (50-75)
Placebo group						
Thyrotropin, median (IQR), mU/L	5.7 (4.7-7.3)	3.4 (2.8-4.2)	3.8 (3.0-4.9)	3.9 (3.3-4.7)	3.8 (3.0-4.9)	3.2 (2.7-4.2)
FT_4, ng/dL	1.13 (0.19)					1.13 (0.16)
FT_3, pg/mL	2.86 (0.52)					3.12 (0.39)

Abbreviations: FT_4, free thyroxine; FT_3, free triiodothyronine; IQR, interquartile range.

SI conversion factors: To convert FT_4 to pmol/L, multiply by 12.87; and FT_3 to pmol/L, multiply by 1.54.

TABLE 3. Thyroid function over time

	Baseline		6 months			12 months		
Group	TSH [median, (IQR), range]	Free T_4 [median, (IQR), range]	TSH [median, (IQR), range]	Free T_4 [median, (IQR), range]	Proportion in euthyroid range	TSH [median, (IQR), range]	Free T_4 [median, (IQR), range]	Proportion in euthyroid range
T_4	6.6 (6–8.5), 5.6–28.9	12.9 (11.7–13.7), 9.4–16.8	4.0 (2.7–4.6), 0.8–20.6	15.4 (14.9–17.4), 9.5–19.4	82.2%	3.7 (2.8–4.9), 0.2–6.9	16.2 (14.2–17.3), 12.8–24.8	84.4%
Placebo	6.65 (5.9–8.3), 5.6–20.5	12.45 (11.4–13.2), 9.6–16.7	6.4 (5.0–8.5), 1.2–19.0	12.5 (11.2–14.2), 9.6–21.1	34.5%	5.45 (3.9–9.2), 0.9–17.3	12.85 (11.4–14.4), 9.7–22.2	50.0%

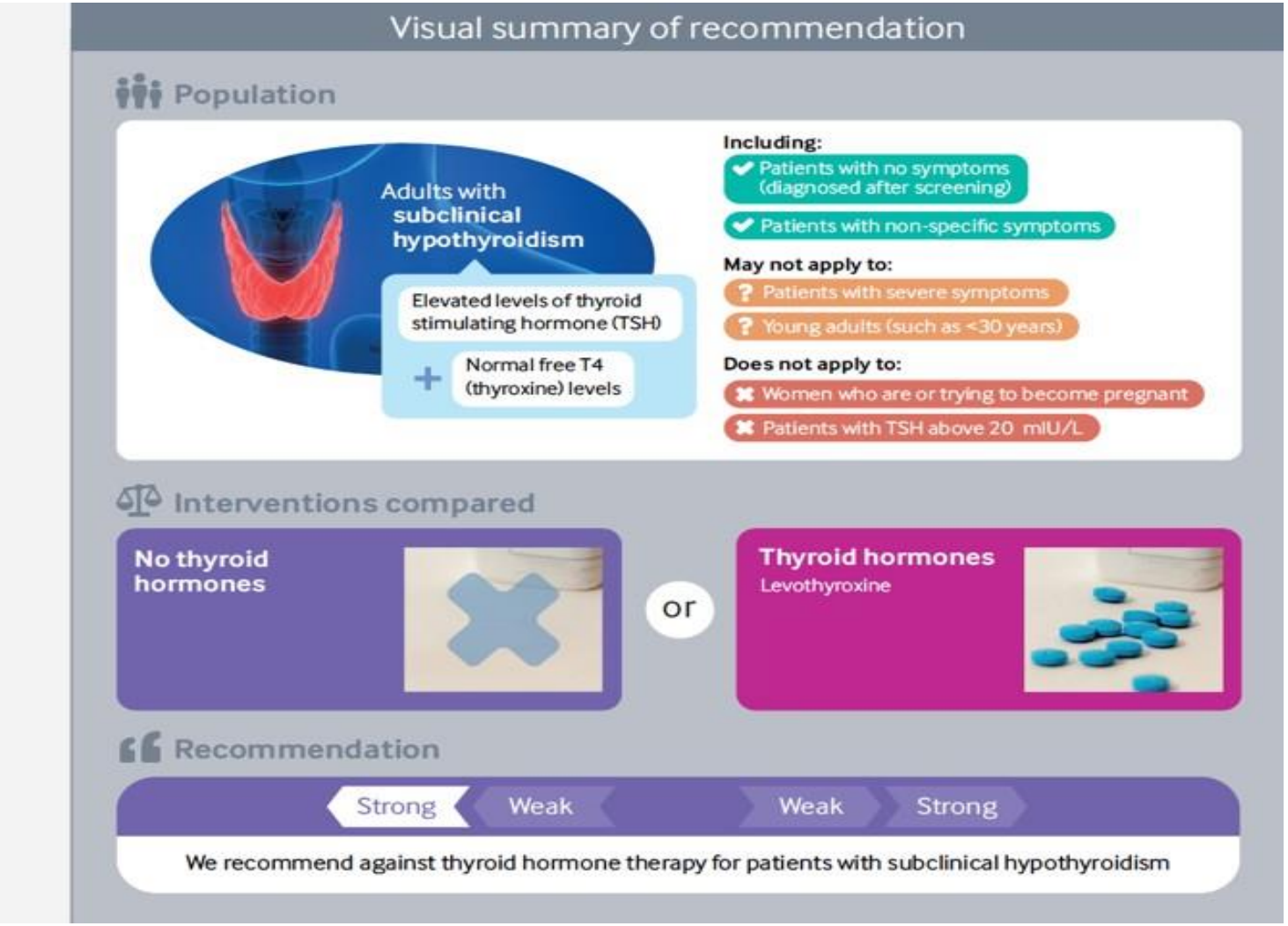
Significant difference in TSH level between the placebo and T_4 groups at both 6 and 12 months (Mann-Whitney *U* test $z = 5.1$, $P < 0.0001$; $z = 3.8$, $P = 0.0002$).

Stott D et al, TRUST trial. NEJM 2016

Jabbar A et al, ThyrAMI trial, JAMA 2020

Parle J, et al. BETS trial, JCEM 2010

RECENT CLINICAL PRACTICE GUIDELINE



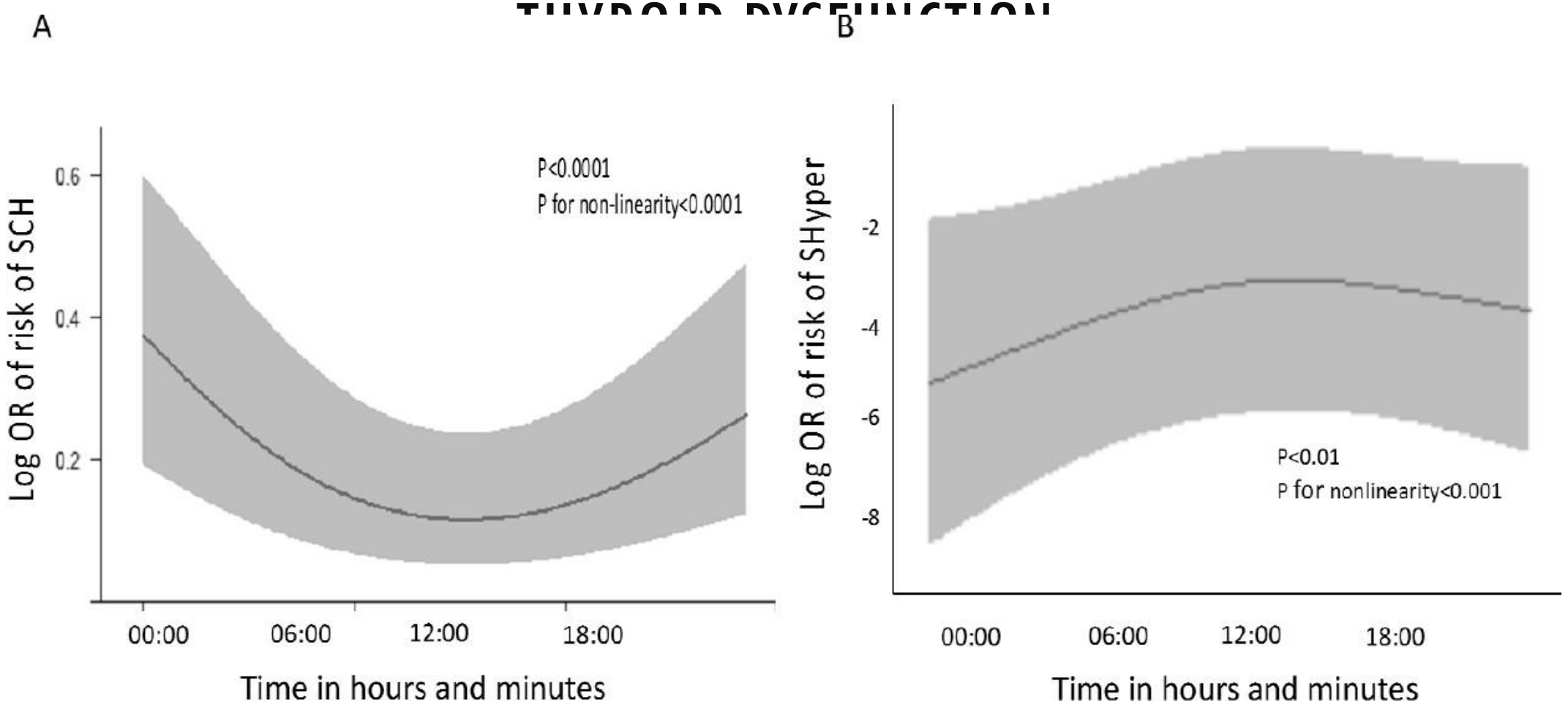
Bekkering G et al, BMJ 2019

SIMILARLY…

…..

- Obesity (TSH levels normalise after weight loss in 75-80% of mild SCH)
- Iodine intake (proportion of SCH increases with iodine intake)
- Sample timing (diurnal variation of TSH and

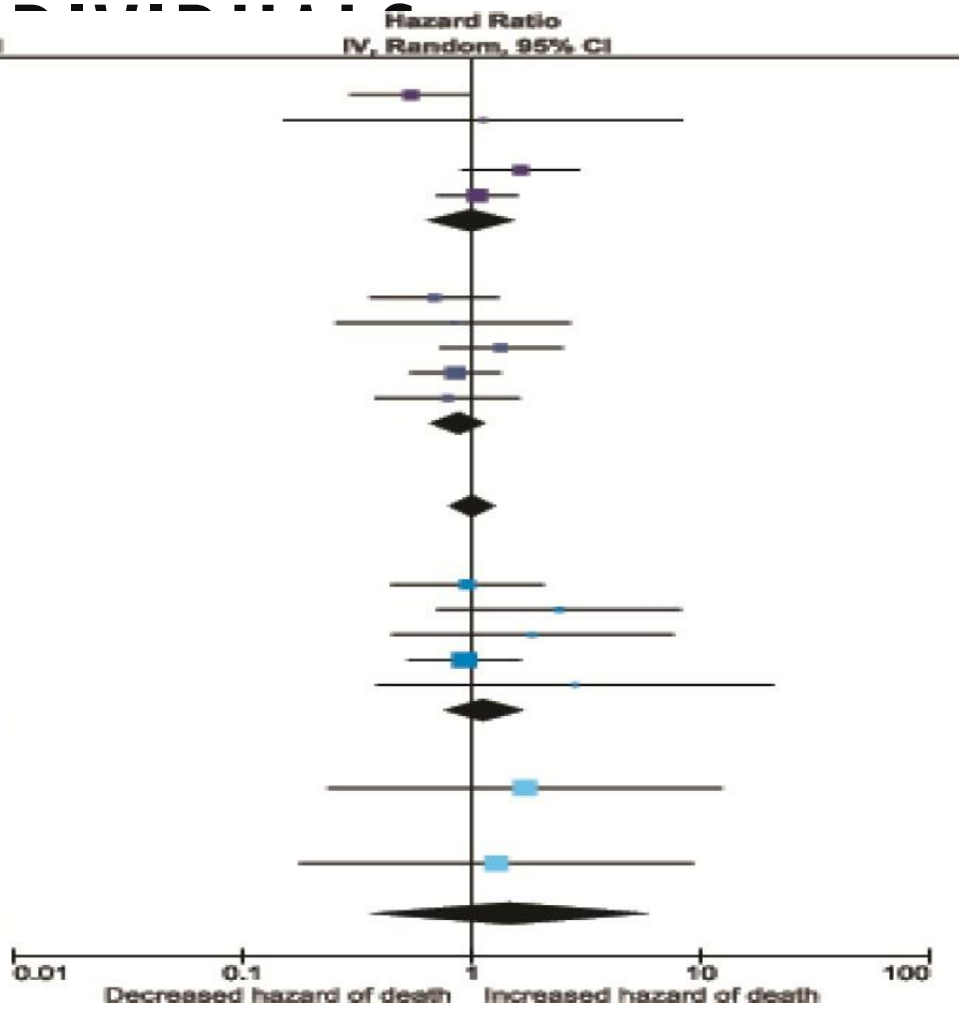
IMPACT OF SAMPLE TIMING ON DIAGNOSING SUBCLINICAL THYROID DYSFUNCTION



Razvi S et al, JCEM 2019

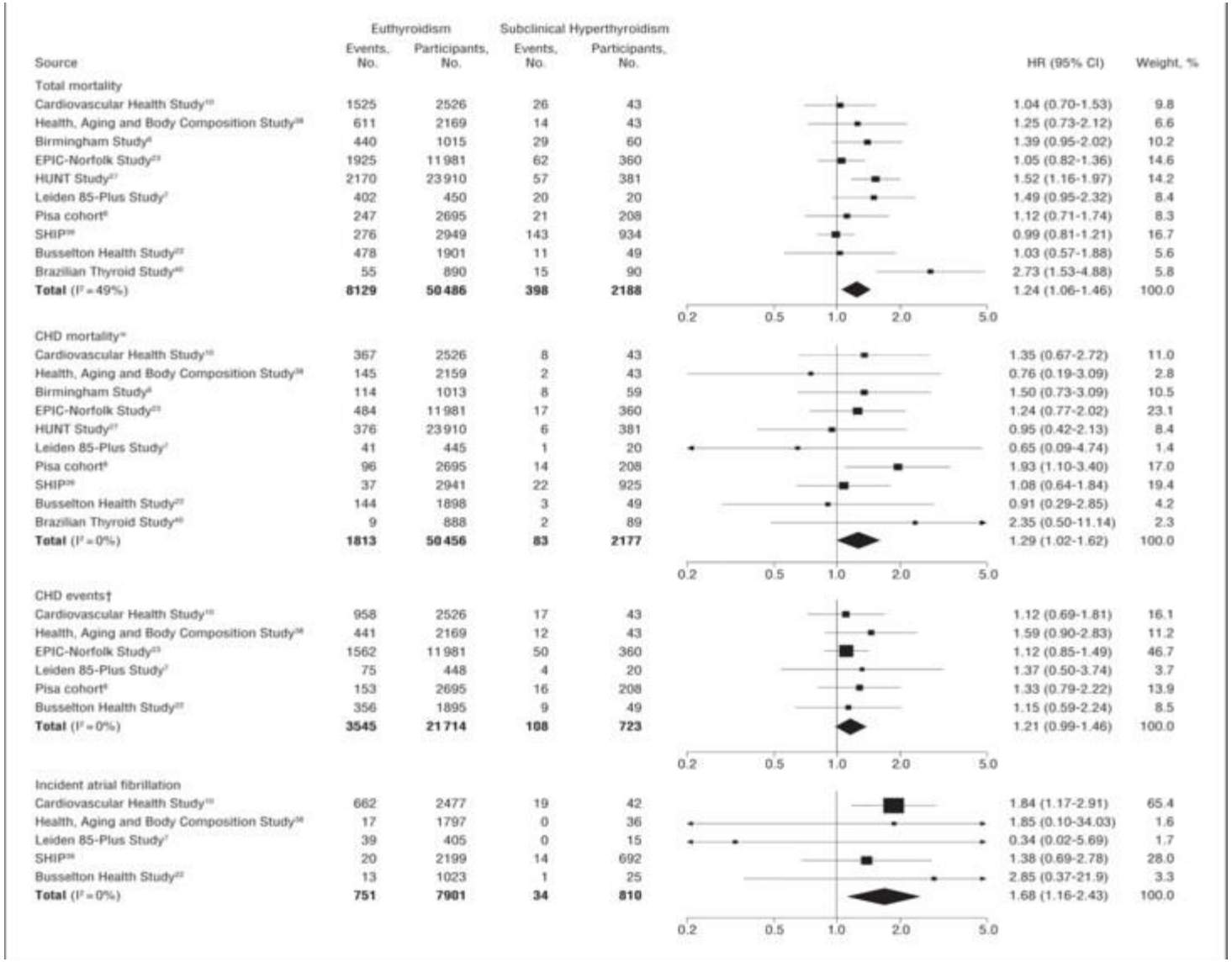
HYPERTHYROIDISM AND ALL-CAUSE MORTALITY IN

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Overt Hypothyroidism				
Leiden 85-plus study	-0.609	0.309	27.5%	0.54 [0.30, 1.00]
LiLacs-NZ - Māori	0.115	1.018	4.6%	1.12 [0.15, 8.25]
LiLacs-NZ - Non-Māori				
Newcastle 85+ study	0.491	0.295	28.8%	1.63 [0.92, 2.91]
TCS	0.057	0.2	39.1%	1.06 [0.72, 1.57]
Subtotal (95% CI)			100.0%	1.00 [0.64, 1.56]
Subclinical Hypothyroidism				
Leiden 85-plus study	-0.381	0.324	19.1%	0.68 [0.36, 1.29]
LiLacs-NZ - Māori	-0.189	0.595	5.7%	0.83 [0.26, 2.66]
LiLacs-NZ - Non-Māori	0.291	0.308	21.1%	1.34 [0.73, 2.45]
Newcastle 85+ study	-0.165	0.226	39.2%	0.85 [0.54, 1.32]
TCS	-0.247	0.366	14.9%	0.78 [0.38, 1.60]
Subtotal (95% CI)			100.0%	0.88 [0.67, 1.17]
Euthyroidism				
Subtotal (95% CI)				1.00 [ref.]
Subclinical Hyperthyroidism				
Leiden 85-plus study	-0.047	0.385	27.2%	0.95 [0.45, 2.03]
LiLacs-NZ - Māori	0.876	0.619	10.5%	2.40 [0.71, 8.08]
LiLacs-NZ - Non-Māori	0.608	0.716	7.9%	1.84 [0.45, 7.47]
Newcastle 85+ study	-0.077	0.283	50.4%	0.93 [0.53, 1.61]
TCS	1.039	1.01	4.0%	2.83 [0.39, 20.46]
Subtotal (95% CI)			100.0%	1.14 [0.77, 1.69]
Overt Hyperthyroidism				
Leiden 85-plus study	0.532	1.004	50.0%	1.70 [0.24, 12.18]
LiLacs-NZ - Māori				
LiLacs-NZ - Non-Māori				
Newcastle 85+ study	0.243	1.003	50.0%	1.28 [0.18, 9.11]
TCS				
Subtotal (95% CI)			100.0%	1.47 [0.37, 5.92]



Du Puy et al, Thyroid 2020

META-ANALYSIS OF OBSERVATIONAL STUDIES IN SHYPER



Source	Euthyroidism Events, No.	Euthyroidism Participants, No.	Subclinical Hyperthyroidism Events, No.	Subclinical Hyperthyroidism Participants, No.	HR (95% CI)	Weight, %
Total mortality						
Cardiovascular Health Study[15]	1525	2526	26	43	1.04 (0.70-1.53)	9.8
Health, Aging and Body Composition Study[38]	611	2169	14	43	1.25 (0.73-2.12)	6.6
Birmingham Study[6]	440	1015	29	60	1.39 (0.95-2.02)	10.2
EPIC-Norfolk Study[23]	1925	11 981	62	360	1.05 (0.82-1.36)	14.6
HUNT Study[27]	2170	23 910	57	381	1.52 (1.16-1.97)	14.2
Leiden 85-Plus Study[7]	402	450	20	20	1.49 (0.95-2.32)	8.4
Pisa cohort[8]	247	2695	21	208	1.12 (0.71-1.74)	8.3
SHIP[39]	276	2949	143	934	0.99 (0.81-1.21)	16.7
Busselton Health Study[22]	478	1901	11	49	1.03 (0.57-1.88)	5.6
Brazilian Thyroid Study[40]	55	890	15	90	2.73 (1.53-4.88)	5.8
Total (I^2 = 49%)	**8129**	**50 486**	**398**	**2188**	1.24 (1.06-1.46)	100.0
CHD mortality*						
Cardiovascular Health Study[15]	367	2526	8	43	1.35 (0.67-2.72)	11.0
Health, Aging and Body Composition Study[38]	145	2159	2	43	0.76 (0.19-3.09)	2.8
Birmingham Study[6]	114	1013	8	59	1.50 (0.73-3.09)	10.5
EPIC-Norfolk Study[23]	484	11 981	17	360	1.24 (0.77-2.02)	23.1
HUNT Study[27]	376	23 910	6	381	0.95 (0.42-2.13)	8.4
Leiden 85-Plus Study[7]	41	445	1	20	0.65 (0.09-4.74)	1.4
Pisa cohort[8]	96	2695	14	208	1.93 (1.10-3.40)	17.0
SHIP[39]	37	2941	22	925	1.08 (0.64-1.84)	19.4
Busselton Health Study[22]	144	1898	3	49	0.91 (0.29-2.85)	4.2
Brazilian Thyroid Study[40]	9	888	2	89	2.35 (0.50-11.14)	2.3
Total (I^2 = 0%)	**1813**	**50 456**	**83**	**2177**	1.29 (1.02-1.62)	100.0
CHD events†						
Cardiovascular Health Study[15]	958	2526	17	43	1.12 (0.69-1.81)	16.1
Health, Aging and Body Composition Study[38]	441	2169	12	43	1.59 (0.90-2.83)	11.2
EPIC-Norfolk Study[23]	1562	11 981	50	360	1.12 (0.85-1.49)	46.7
Leiden 85-Plus Study[7]	75	448	4	20	1.37 (0.50-3.74)	3.7
Pisa cohort[8]	153	2695	16	208	1.33 (0.79-2.22)	13.9
Busselton Health Study[22]	356	1895	9	49	1.15 (0.59-2.24)	8.5
Total (I^2 = 0%)	**3545**	**21 714**	**108**	**723**	1.21 (0.99-1.46)	100.0
Incident atrial fibrillation						
Cardiovascular Health Study[15]	662	2477	19	42	1.84 (1.17-2.91)	65.4
Health, Aging and Body Composition Study[38]	17	1797	0	36	1.85 (0.10-34.03)	1.6
Leiden 85-Plus Study[7]	39	405	0	15	0.34 (0.02-5.69)	1.7
SHIP[39]	20	2199	14	692	1.38 (0.69-2.78)	28.0
Busselton Health Study[22]	13	1023	1	25	2.85 (0.37-21.9)	3.3
Total (I^2 = 0%)	**751**	**7901**	**34**	**810**	1.68 (1.16-2.43)	100.0

Collet et al, Arch Intern Med 2012

ATA GUIDELINES FOR MANAGEMENT OF SCHYPER

TSH persistently <0.1 mU/L, treatment is recommended in:

- >65 yrs
- Cardiac risk factors
- Heart disease
- Osteoporosis
- Post menopausal women not on oestrogens or bisphosphonates
- With symptoms

In younger patients (< 65 yrs), treatment should be considered if TSH is persistently < 0.1 mU/L

Ross et al, Thyroid 2016

SCHYPER GUIDELINES 2015

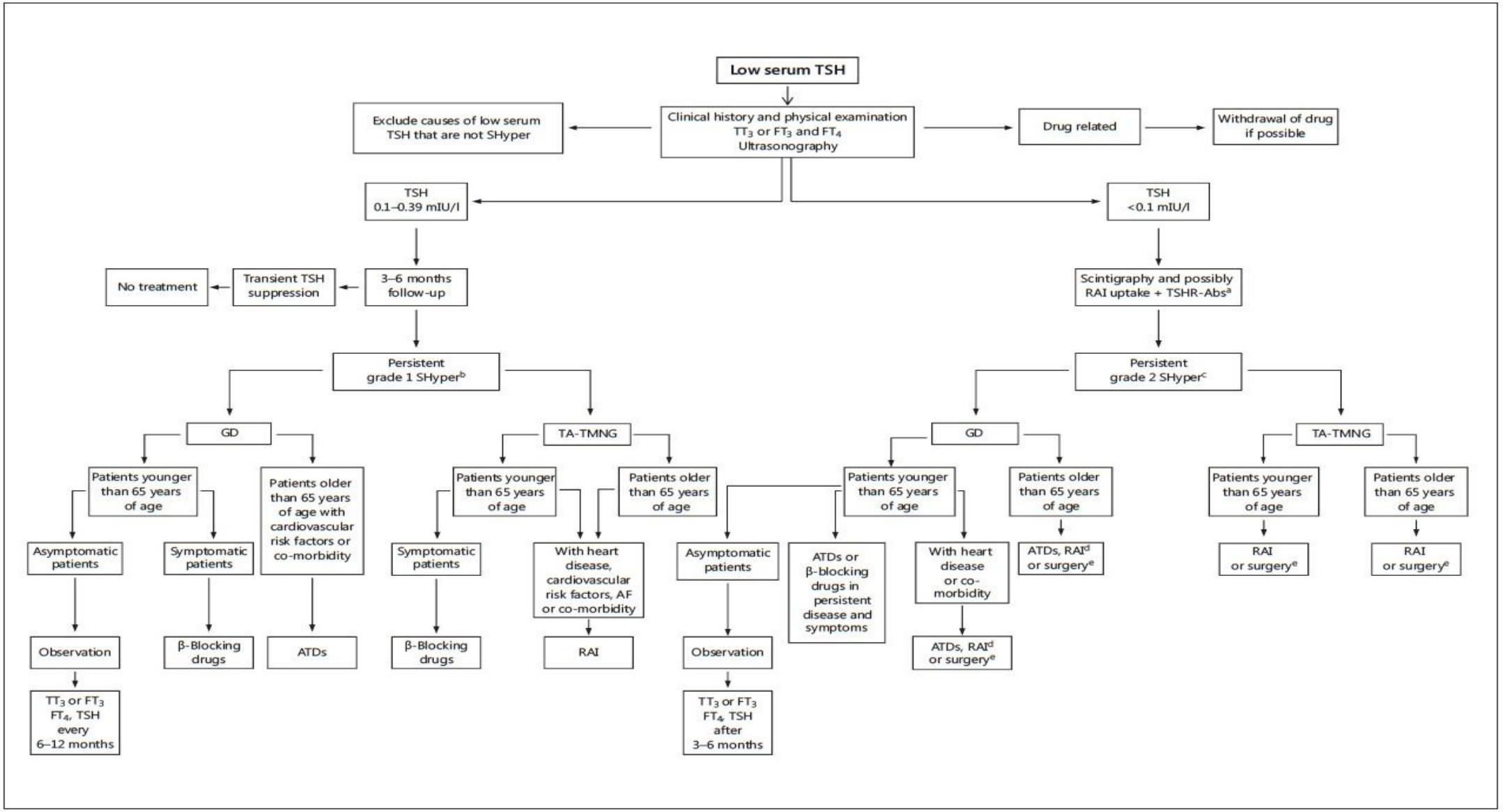


Fig. 1. Algorithm for the management of SHyper. [a] TSHR-Abs = TSH-receptor antibodies. [b] Grade 1 SHyper (TSH levels: 0.1–0.39 mIU/l). [c] Grade 2 SHyper (TSH levels <0.1 mIU/l). [d] RAI in patients with recurrences or if ATDs are not tolerated. [e] Surgery in patients with large goitre, symptoms of compression or thyroid malignancies.

WHO SHOULD BE TREATED?

Subclinical Hypothyroidism

- Younger people
- TSH >10 mU/L
- Pregnancy TSH> UL + TPOAb or TSH >10 mU/L

Subclinical Hyperthyroidism

- Undetectable TSH with additional risk factors for AF or osteoporosis

SUMMARY

- The associations between SCTD and various outcomes are not being confirmed as causal in most instances.
- A number of individual circumstances need to be considered (age, comorbidities, symptoms, iodine intake, time of sampling, etc.) and not just elevated TSH when managing these patients.
- High quality evidence is required to evaluate long-term outcomes to ensure safe and effective therapies are prescribed.