Should I stay or should I lower? What are the harms of biochemical overtreatment of hypothyroidism?

Bottom line (25th October 2012):

The group agreed that it appears safe to treat patients to a low TSH (0.04-0.4) if they are stable, however as harms seem to emerge when TSH is suppressed (<0.04) then more careful discussion and counselling with these patients is required.

Questions	Evidence
What is the risk of osteoporosis and/or fractures with biochemical overtreatment?	**Comparing patients (n = 1180) taking levothyroxine with general population there is no difference in fracture rate. Among patients taking levothyroxine there is no difference between those with normal TSH and those with suppressed TSH in terms of fractures although there is a trend towards an increased risk of fracture in those who were ≥65yr (Leese 1992)** **No difference in BMD of forearm between postmenopausal women in control vs hypothyroid (n = 78) groups (Grant 1993)** **High (>0.4) and suppressed (≤0.03) TSH risk factors for admission/death associated with osteoporotic fracture. Treatment resulting in low (0.04-0.4) but not suppressed TSH not associated with increased risk ((n = 17,684) Flynn 2010)**
What is the risk of cardiovascular disease, in particular, arrhythmia with biochemical overtreatment?	**Comparing patients (n = 1180) taking levothyroxine with general population there is increased risk of IHD in those <65yr. Among patients taking levothyroxine there is no difference between those with normal TSH and those with suppressed TSH in terms of IHD (Leese 1992)** **High (>0.4) and suppressed (≤0.03) TSH risk factors for admission/death associated with CVD and dysrhythmia but treatment resulting in low (0.04-0.4) but not suppressed TSH not associated with increased risk ((n = 17,684) Flynn 2010)**
What are the benefits of biochemical overtreatment?	**Nil evidence**
Is a normal level of TSH a good measure to use to reduce morbidity and mortality in a patient taking levothyroxine?	**High (>0.4) and suppressed (≤0.03) TSH risk factors for admission/death associated with CVD, dysrhythmia and osteoporotic fracture but treatment resulting in low (0.04-0.4) but not suppressed TSH not associated with increased risk and often preferred by patients ((n = 17,684) Flynn 2010)**

Context:

This clinical question was based on the following typical situation:

Mrs Jones, a 47 year old mother of two and an accountant attends to discuss her recent thyroid function results and is otherwise well. For the third time in a row, her TSH has been suppressed to 0.03 while her T4 is 19. Medication: 150mcg levothyroxine, denies missing any doses. You suggest to reduce her levothyroxine dose as you are concerned about the future risk of osteoporosis and arrhythmias with chronic overmedication. Mrs Jones tells you that she has previously tried reducing her dose on the advice of another colleague and she felt tired and lethargic so she went back to her usual dose. She cannot afford to be feeling less than top form as she has many pressures both at home and work. You close the consultation agreeing that she remain on same dose of levothyroxine and will recheck her TFT in another year. On one hand you are left feeling that you have been patient centred. On the other hand, you feel that you have not been able to inform Mrs Jones fully of the risks and benefits of keeping at the same dose or reducing levothyroxine. You are left wondering...

a) What is the risk of osteoporosis and/or fractures with biochemical overtreatment?

b) What is the risk of cardiovascular disease, in particular, arrhythmia with biochemical overtreatment?

c) What are the benefits of biochemical overtreatment?

d) Thus...is a normal level of TSH a good measure to use to reduce morbidity and mortality in a patient taking levothyroxine?

Inclusion/exclusion:

Excluding: pregnancy and 6 months post-partum, central hypothyroidism

PICO:

POPULATION: Male and female adults >18yr old taking levothyroxine for primary hypothyroidism

INTERVENTION: T4 dose adjusted to keep TSH in reference range

COMPARATOR: T4 dose adjusted to within its reference range but with suppressed TSH

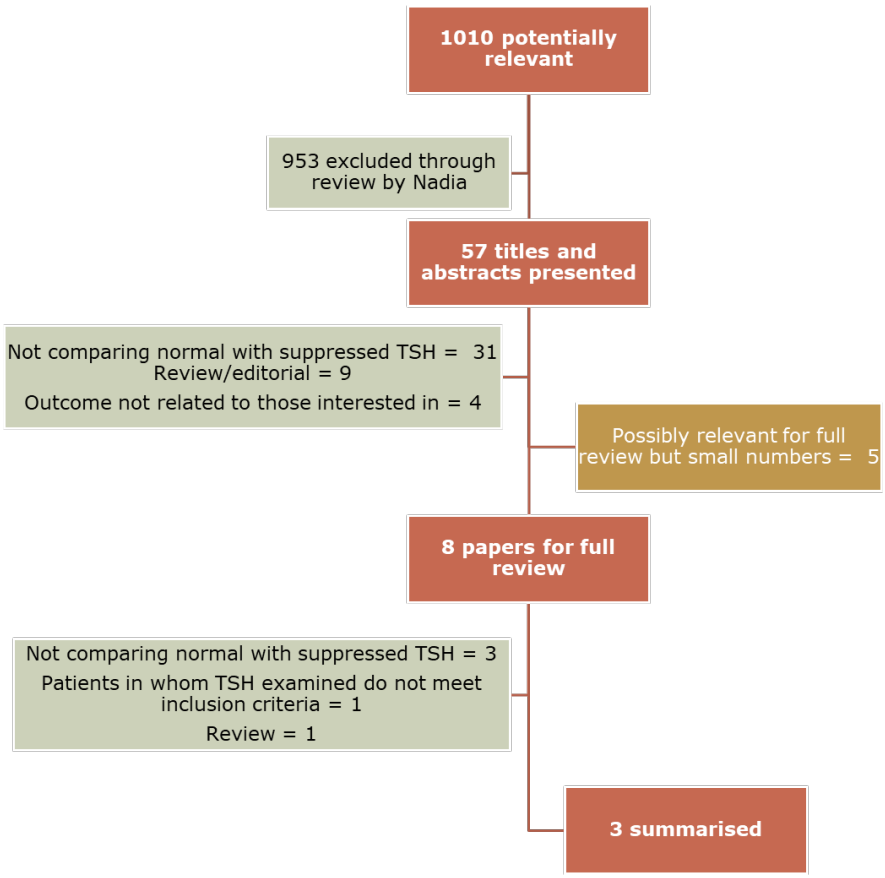
OUTCOME: Harm – arrhythmia, osteoporosis, mortality. Benefits – “clinical wellbeing”(asymptomatic euthyroidism), reduced CVD risk

Evidence sources:

A literature review was undertaken:

1	exp Hypothyroidism/	**27041**
2	hypothyroid*.ti,ab.	23941
3	myx?edema.ti,ab.	2117
4	or/1-3	35072
5	levothyroxine.ti,ab.	1682
6	Thyroxine/	32099
7	(thyroxin* or l-thyroxine).ti,ab.	23599
8	or/5-7	39750
9	Osteoporosis/	32601
10	osteoporo*.ti,ab.	43265
11	Bone Density/	36799
12	(bone adj densit*).ti,ab.	11404
13	fracture*.ti,ab.	147053

14	exp Arrhythmias, Cardiac/	**155007**
15	arrhythmia*.ti,ab.	55821
16	(adverse adj (effect* or event*)).ti,ab.	139093
17	harm*.ti,ab.	74096
18	cardio*.ti,ab.	432202
19	quality of life/	102772
20	(quality adj2 life).ti,ab.	117475
21	(wellbeing or (well adj being)).ti,ab.	36078
22	exp Mortality/	255657
23	mortality.ti,ab.	384460
24	death.ti,ab.	397264
25	or/9-24	1841429
26	4 and 8 and 25	1010



Primary evidence examined:

- Leese GP, Jung RT, Guthrie C, Waugh N, Browning MC. Morbidity in patients on L-thyroxine: a comparison of those with normal TSH to those with a suppressed TSH. Clinical Endocrinology 1992; 37(6):500-3
- Grant DJ, McMurdo ME, Mole PA, Paterson CR, Davies RR. Suppressed TSH levels secondary to thyroxine replacement therapy are not associated with osteoporosis. Clinical Endocrinology 1993; 39(5):529-33
- Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. **Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy**. J Clin Endocrinol Metab 2010; 95(1):186-93

Impact:

I have stopped bringing in patients for appointments if their TSH is only mildly supressed, especially if this has been the case for a long time (Salaried GP)