



RECOMENDACIÓN TRATAMIENTO

INFORME DE BÚSQUEDA Y SÍNTESIS DE EVIDENCIA DE EFECTOS DESEABLES E INDESEABLES Guía de Práctica Clínica de Hipotiroidismo en personas de 15 años y más

A. PREGUNTA CLÍNICA

En adultos con hipotiroidismo subclínico ¿Se debe “tratar con levotiroxina” en comparación a “no tratar”?

Análisis y definición de los componentes de la pregunta en formato PICO

Población: Adultos con hipotiroidismo subclínico.

Intervención: Levotiroxina.

Comparación: No tratar.

Desenlace (outcome): Mortalidad, eventos cardiovasculares, calidad de vida, efectos adversos, síntomas relacionados a la tiroides, síntomas depresivos.

A. MÉTODOS

Se realizó una búsqueda general de revisiones sistemáticas sobre hipotiroidismo (ver Anexo 1: estrategia de búsqueda). Las bases de datos utilizadas fueron: Cochrane database of systematic reviews (CDSR); Database of Abstracts of Reviews of Effectiveness (DARE); HTA Database; PubMed; LILACS; CINAHL; PsycINFO; EMBASE; EPPI-Centre Evidence Library; 3ie Systematic Reviews and Policy Briefs Campbell Library; Clinical Evidence; SUPPORT Summaries; WHO institutional Repository for information Sharing; NICE public health guidelines and systematic reviews; ACP Journal Club; Evidencias en Pediatría; y The JBI Database of Systematic Reviews and Implementation Reports. No se aplicaron restricciones en base al idioma o estado de publicación. Dos revisores de manera independiente realizaron la selección de los títulos y los resúmenes, la evaluación del texto completo y la extracción de datos. Un investigador o clínico experimentado resolvió cualquier discrepancia entre los distintos revisores. Finalmente, se seleccionaron las revisiones sistemáticas (y los estudios incluidos en éstas) correspondientes a la temática y se clasificaron en función de las preguntas a las que daban respuesta.

Los resultados se encuentran alojados en la plataforma Living Overview of the Evidence (L-OVE), sistema que permite la actualización periódica de la evidencia.

B. RESULTADOS

Resumen de la evidencia identificada

Se buscaron revisiones sistemáticas que presentaran un análisis de estudios en pacientes adultos (excluyendo mujeres embarazadas o que estén intentando embarazarse) [abordados en otra pregunta GES] con hipotiroidismo subclínico en los cuales se realizó tratamiento con levotiroxina en

comparación con no realizarlo. Se identificaron 17 revisiones sistemáticas que incluyeron 78 estudios primarios, de los cuales 33 corresponden a ensayos aleatorizados. Para más detalle ver “*Matriz de evidencia*”¹, en el siguiente enlace: [Levotiroxina en adultos con hipotiroidismo subclínico \(mujeres embarazadas o que están intentando embarazarse\)](#).

Tabla 1: Resumen de la evidencia identificada

Revisión sistemática	17 [1-17]
Estudios primarios	33 ensayos [18-50], 45 estudios observacionales [51-95]

Selección de la evidencia

Se realizó un análisis de la matriz de evidencia, identificándose que todos las revisiones sistemáticas son relevantes, ya que abordan los componentes de la pregunta priorizada por el panel. Sin embargo, cinco ensayos fueron excluidos debido a que no cumplen con los criterios especificados: dos incluyeron exclusivamente a pacientes con nefropatía diabética e hipotiroidismo subclínico [22, 31], uno incluyó pacientes con niveles de TSH normales [43] y dos ensayos no compararon contra el no tratamiento [25, 35].

Finalmente, de los 28 ensayos identificados, sólo nueve reportaron información asociada a los desenlaces críticos priorizados por el panel [27-29,34,40,41,44,45,47].

Estimador del efecto

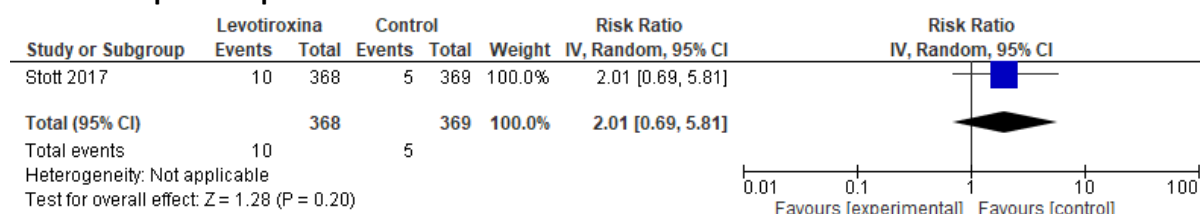
Al analizar la evidencia identificada, se concluyó que existen 2 de las revisiones sistemáticas [4, 15] que en conjunto:

1. Incluyen el total de los estudios posiblemente relevantes, considerando que según la metodología GRADE² los estudios observacionales no se deben incorporar al análisis cuando no incrementan la certeza de la evidencia ni aportan información adicional relevante.
2. Entregan un estimador agregado del efecto (metanálisis) para los desenlaces de interés.

Por lo que se decidió reutilizar su información para construir la tabla de resumen de resultados.

Metanálisis

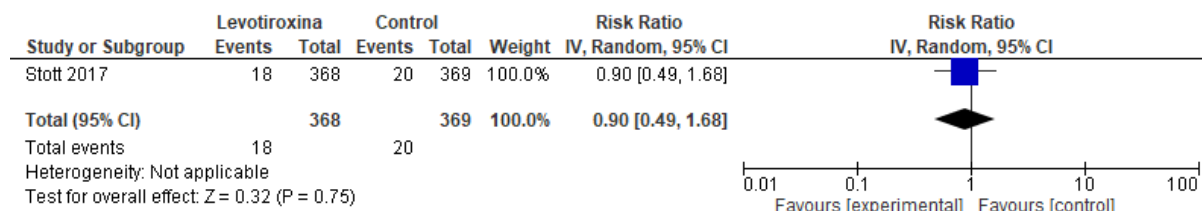
Mortalidad por cualquier causa



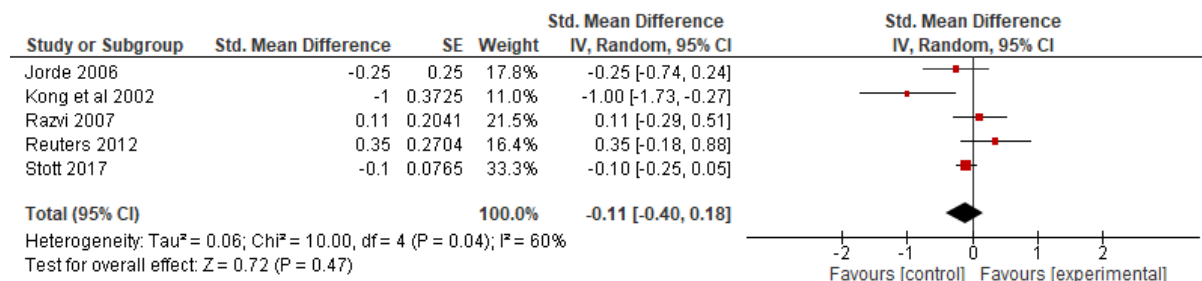
¹ **Matriz de Evidencia**, tabla dinámica que grafica el conjunto de evidencia existente para una pregunta (en este caso, la pregunta del presente informe). Las filas representan las revisiones sistemáticas y las columnas los estudios primarios que estas revisiones han identificado. Los recuadros en verde corresponden a los estudios incluidos en cada revisión. La matriz se actualiza periódicamente, incorporando nuevas revisiones sistemáticas pertinentes y los respectivos estudios primarios.

² Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PubMed PMID: 21247734

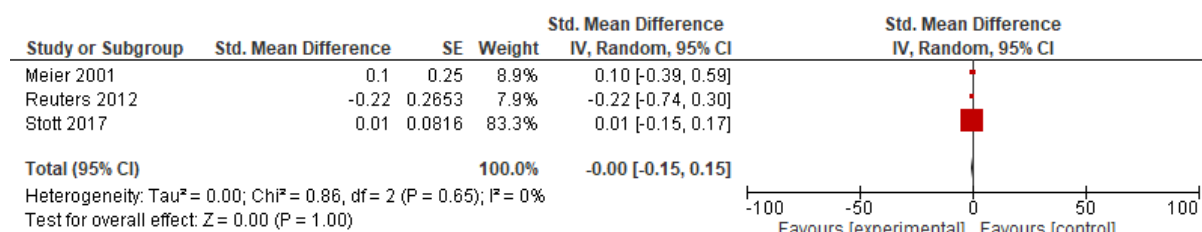
Eventos cardiovasculares



Calidad de vida



Síntomas relacionados a la tiroides



Síntomas depresivos

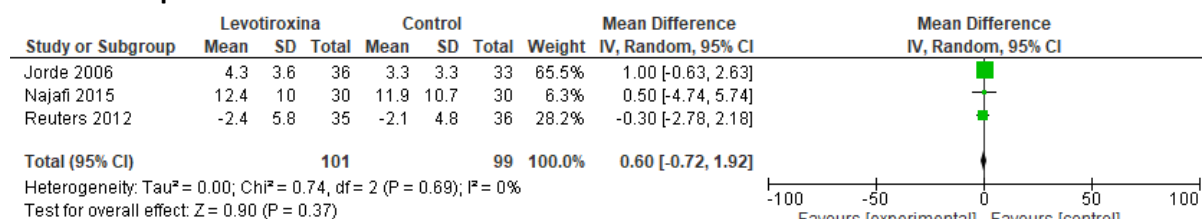
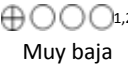




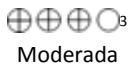


Tabla de Resumen de Resultados (Summary of Findings)

LEVOTIROXINA EN ADULTOS CON HIPOTIROIDISMO SUBCLÍNICO.						
Pacientes	Adultos con hipotiroidismo subclínico.					
Intervención	Levotiroxina.					
Comparación	No tratar.					
Desenlaces	Efecto relativo (IC 95%) -- Estudios/ pacientes	Efecto absoluto estimado*			Certeza de la evidencia (GRADE)	Mensajes clave en términos sencillos
		SIN levotiroxina	CON levotiroxina	Diferencia (IC 95%)		
Mortalidad por cualquier causa	RR 2,01 (0,69 a 5,81) -- 1 ensayo [47] /737 pacientes	14 por 1000	27 por 1000	Diferencia: 13 más (4 menos a 65 más)	 Muy baja	El tratamiento con levotiroxina en adultos con hipotiroidismo subclínico podría aumentar la mortalidad. Sin embargo, existe considerable incertidumbre dado que la certeza de la evidencia es muy baja.
Eventos cardiovasculares **	RR 0,90 (0,49 a 1,68) -- 1 ensayo [47] /737 pacientes	54 por 1000	49 por 1000	Diferencia: 5 menos (28 menos a 37 más)	 Muy baja	El tratamiento con levotiroxina en adultos con hipotiroidismo subclínico podría tener poco impacto en el desarrollo de eventos cardiovasculares. Sin embargo, existe considerable incertidumbre dado que la certeza de la evidencia es muy baja.
Calidad de vida*** (3 a 12 meses)	-- 5 ensayos [28, 29, 44, 45, 47] /896 pacientes	DME: 0,11 (Margen de error: 0,4 menor a 0,18 más)			 Baja	El tratamiento con levotiroxina en adultos con hipotiroidismo subclínico podría tener poco impacto en la calidad de vida.
Efectos adversos****	Sólo dos ensayos que incluyeron 57 pacientes reportaron efectos adversos [27,41]. Sin embargo, no se identificaron diferencias significativas entre los grupos: uno de ellos [41] reportó que 2 participantes pertenecientes al grupo de intervención tuvieron que abandonar el estudio por un empeoramiento de las palpitaciones y el otro ensayo [27] reportó 3 efectos adversos en el grupo de intervención y 2 en el grupo de control.				 Baja	El tratamiento con levotiroxina en adultos con hipotiroidismo subclínico podría tener un bajo riesgo de efectos adversos.
Síntomas relacionados a la tiroides*** (6 a 12 meses)	-- 3 ensayos [34,45,47] /874 pacientes	DME: 0 (Margen de error: 0,15 menor a 0,15 más)			 Baja	El tratamiento con levotiroxina en adultos con hipotiroidismo subclínico podría tener poco impacto en los síntomas relacionados a la tiroides.
Síntomas depresivos ***** (3 a 12 meses)	-- 3 ensayos [28,40,45] /200 pacientes	3,3 puntos	3,9 puntos	DM: 0,6 más (0,72 menos a 1,92 más)	 Moderada	El tratamiento con levotiroxina en adultos con hipotiroidismo subclínico probablemente tiene poco impacto en los síntomas depresivos.

IC 95%: Intervalo de confianza del 95%. | | RR: Riesgo relativo. | | DM: Diferencia de media. | | DME: Diferencia de media estandarizada.

GRADE: Grados de evidencia Grading of Recommendations Assessment, Development and Evaluation.

* El **riesgo/promedio SIN levotiroxina** está basado en el riesgo/promedio del grupo control en los estudios. El **riesgo/promedio CON levotiroxina** (y su intervalo de confianza) está calculado a partir del efecto relativo/diferencia de medias (y su intervalo de confianza).

** Incluye eventos cardiovasculares fatales y no fatales, tales como infarto agudo al miocardio, accidente cerebrovascular, amputaciones, revascularización por aterosclerosis vascular, entre otros.

*** La diferencia media estandarizada se utiliza cuando el desenlace ha sido medido en diferentes escalas, siendo difícil su interpretación clínica. Comúnmente se acepta que valores cercanos a 0,2 tendrían poca relevancia clínica, valores de 0,5 tendrían relevancia moderada (se reconoce clínicamente) y valores superiores a 0,8 tendrían relevancia alta.

**** Los efectos adversos observados fueron angina, fibrilación auricular, gota, palpitaciones y accidente cerebrovascular.

***** Evaluado con escala BDI (Beck Depression Inventory), que va de 0 a 63 puntos, donde mayor puntaje indica mayor presencia de síntomas depresivos.

¹ Se disminuyó dos niveles de certeza de la evidencia por tratarse de evidencia indirecta, ya que toda o la mayoría de la evidencia proviene de un ensayo que contempla una población de 74 años de edad promedio. El desenlace calidad de vida no fue penalizado debido a que este ensayo sólo aporta un 33% a la estimación del efecto.

² Se disminuyó un nivel de certeza de la evidencia por imprecisión, debido a que a cada extremo del intervalo de confianza se tomarían decisiones diferentes.

³ Se disminuyó un nivel de certeza de la evidencia por riesgo de sesgo, debido a que en la mayoría de los ensayos no estaba clara la generación ni el ocultamiento de la secuencia de aleatorización y se observaron limitaciones en el enmascaramiento de los participantes.

⁴ Se disminuyó un nivel de certeza de la evidencia por inconsistencia, debido a que se observó heterogeneidad significativa (I²= 60%).

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ANEXO 1: ESTRATEGIA DE BÚSQUEDA

- #1 hypothy*
 #2 hashimoto*
 #3 "autoimmune thyroiditis"
 #4 AIT
 #5 #1 OR #2 OR #3 OR #4
 #6 deficien*
 #7 insufficien*
 #8 replacement*
 #9 dysfunction*
 #10 #6 OR #7 OR #8 OR #9
 #11 thyroid*
 #12 #10 AND #11
 #13 #5 OR #12
 #14 subclinic*
 #15 "sub-clinical"
 #16 mild
 #17 #14 OR #15 OR #16
 #18 #13 AND #17
 #19 thyroxin*
 #20 tyroxin*
 #21 levothyroxin*
 #22 "L-thyroxin"
 #23 T4
 #24 "T-4"
 #25 LT4
 #26 "L-T4"
 #27 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
 #28 #18 AND #27