Material suplementario

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Material suplementario 1. Lista de chequeo PRISMA (10)(10).

Sección y tema	Artículo #	Elemento de la lista de verificación	Página
TÍTULO			
Título	1	Identifique el informe como una revisión sistemática.	1
ABSTRACTO			
Abstracto	2	Consulte la lista de verificación de resúmenes de PRISMA 2020.	-
INTRODUCCIÓN			
Razón fundamental	3	Describa la justificación de la revisión en el contexto del conocimiento existente.	2
Objetivos	4	Proporcione una declaración explícita de los objetivos o preguntas que aborda la revisión.	2
MÉTODOS			
Criterios de elegibilidad	5	Especifique los criterios de inclusión y exclusión para la revisión y cómo se agruparon los estudios para las síntesis.	3
Fuentes de información	6	Especifique todas las bases de datos, registros, sitios web, organizaciones, listas de referencias y otras fuentes consultadas para identificar estudios. Indique la fecha de la última consulta o búsqueda de cada fuente.	3
Estrategia de búsqueda	7	Presentar las estrategias de búsqueda completas para todas las bases de datos, registros y sitios web, incluidos los filtros y límites utilizados.	3
Proceso de selección	8	Especifique los métodos utilizados para decidir si un estudio cumplió con los criterios de inclusión de la revisión, incluido cuántos revisores examinaron cada registro y cada informe recuperado, si trabajaron de forma independiente y, si corresponde, detalles de las herramientas de automatización utilizadas en el proceso.	3
Proceso de recopilación de datos	9	Especifique los métodos utilizados para recopilar datos de los informes, incluido cuántos revisores recopilaron datos de cada informe, si trabajaron de forma independiente, cualquier proceso para obtener o confirmar datos de los investigadores del estudio y, si corresponde, detalles de las herramientas de automatización utilizadas en el proceso.	3
Lista de los datos	10a	Enumere y defina todos los resultados para los que se buscaron datos. Especifique si se buscaron todos los resultados compatibles con cada dominio de resultados en cada estudio (p. ej., para todas las medidas, puntos temporales y análisis) y, de no ser así, los métodos utilizados para decidir qué resultados recopilar.	3,4
	10b	Enumere y defina todas las demás variables para las que se solicitaron datos (p. ej., características de los participantes y de la intervención, fuentes de financiación). Describa las suposiciones realizadas sobre la información faltante o poco clara.	3,4
Evaluación del riesgo de sesgo del estudio	11	Especifique los métodos utilizados para evaluar el riesgo de sesgo en los estudios incluidos, incluidos los detalles de las herramientas utilizadas, cuántos revisores evaluaron cada estudio y si trabajaron de forma independiente y, si corresponde, detalles de las herramientas de automatización utilizadas en el proceso.	6
Medidas de efecto	12	Especifique para cada resultado las medidas de efecto (por ejemplo, razón de riesgos, diferencia de medias) utilizadas en la síntesis o presentación de los resultados.	4,5
Métodos de síntesis	13a	Describa los procesos utilizados para decidir qué estudios eran elegibles para cada síntesis (por ejemplo, tabular las características de la intervención del estudio y compararlas con los grupos planificados para cada síntesis (ítem n.° 5)).	4
	13b	Describa cualquier método requerido para preparar los datos para su presentación o síntesis, como el manejo de estadísticas de resumen faltantes o la conversión de datos.	4
	13c	Describa cualquier método utilizado para tabular o mostrar visualmente los resultados de estudios y síntesis individuales.	4
	13d	Describa los métodos utilizados para sintetizar los resultados y justifique su elección. Si se realizó un metanálisis, describa los modelos, los métodos para identificar la presencia y el grado de heterogeneidad estadística, y los programas informáticos utilizados.	4
	13.ª edición	Describa cualquier método utilizado para explorar posibles causas de heterogeneidad entre los resultados del estudio (por ejemplo, análisis de subgrupos, metarregresión).	4,5
	13f	Describa cualquier análisis de sensibilidad realizado para evaluar la solidez de los resultados sintetizados.	5
Evaluación del sesgo de notificación	14	Describa cualquier método utilizado para evaluar el riesgo de sesgo debido a la falta de resultados en una síntesis (que surge de sesgos en los informes).	6
Evaluación de certeza	15	Describa cualquier método utilizado para evaluar la certeza (o confianza) en el conjunto de evidencia de un resultado.	5
RESULTADOS			
Selección de estudios	16a	Describa los resultados del proceso de búsqueda y selección, desde el número de registros identificados en la búsqueda hasta el número de estudios incluidos en la revisión, idealmente utilizando un diagrama de flujo.	5,6
	16b	Cite estudios que parezcan cumplir los criterios de inclusión, pero que fueron excluidos, y explique por qué fueron excluidos.	5,6
Características del estudio	17	Cite cada estudio incluido y presente sus características.	5,6
Riesgo de sesgo en los estudios	18	Presentar evaluaciones del riesgo de sesgo para cada estudio incluido.	6

Resultados de estudios individuales	19	Para todos los resultados, presente, para cada estudio: (a) estadísticas de resumen para cada grupo (cuando corresponda) y (b) una estimación del efecto y su precisión (por ejemplo, intervalo de confianza/credibilidad), idealmente utilizando tablas o gráficos estructurados.	5-8
Resultados de las síntesis	20a	Para cada síntesis, resuma brevemente las características y el riesgo de sesgo entre los estudios contribuyentes.	5-8
	20b	Presente los resultados de todas las síntesis estadísticas realizadas. Si se realizó un metanálisis, presente para cada uno la estimación resumida y su precisión (p. ej., intervalo de confianza/credibilidad) y las medidas de heterogeneidad estadística. Si se comparan grupos, describa la dirección del efecto.	5-8
	20 centavos	Presentar los resultados de todas las investigaciones sobre las posibles causas de la heterogeneidad entre los resultados de los estudios.	5-8
	20d	Presentar los resultados de todos los análisis de sensibilidad realizados para evaluar la robustez de los resultados sintetizados.	8
Sesgos en los informes	21	Presentar evaluaciones del riesgo de sesgo debido a resultados faltantes (derivados de sesgos de informe) para cada síntesis evaluada.	6
Certeza de la evidencia	22	Presentar evaluaciones de certeza (o confianza) en el conjunto de evidencia para cada resultado evaluado.	8
DISCUSIÓN			
Discusión	23a	Proporcionar una interpretación general de los resultados en el contexto de otra evidencia.	8-9
	23b	Discuta cualquier limitación de la evidencia incluida en la revisión.	8-9
	23c	Discuta cualquier limitación de los procesos de revisión utilizados.	8-9
	23d	Analice las implicaciones de los resultados para la práctica, la política y la investigación futura.	8-9
OTRA INFORMACIÓN			
Registro y protocolo	24a	Proporcionar información de registro para la revisión, incluido el nombre del registro y el número de registro, o indicar que la revisión no fue registrada.	2
	24b	Indique dónde se puede acceder al protocolo de revisión o indique que no se preparó un protocolo.	2
	24c	Describa y explique cualquier modificación a la información proporcionada en el registro o en el protocolo.	-
Apoyo	25	Describa las fuentes de apoyo financiero o no financiero para la revisión y el papel de los financiadores o patrocinadores en la revisión.	-
Intereses en competencia	26	Declarar cualquier interés en competencia de los autores de la revisión.	-
Disponibilidad de datos, códigos y otros materiales	27	Informe cuáles de los siguientes están disponibles públicamente y dónde se pueden encontrar: formularios de recopilación de datos de plantilla; datos extraídos de los estudios incluidos; datos utilizados para todos los análisis; código analítico; cualquier otro material utilizado en la revisión.	-

Material suplementario 2. Estrategias de búsqueda

Característica	Reporte
Tipo de búsqueda	Actualización
Base de datos	MEDLINE
Plataforma	PubMed
Fecha de búsqueda	22-02-2022
Rango de fecha de búsqueda	01-07-2019 hasta 20-02-2022
Restricciones de lenguaje	Inglés
Otros límites	Ninguno
Estrategia de búsqueda	1. (Copd [tiab] OR chronic obstructive pulmonary disease [tiab] OR chronic bronchitis [tiab] OR emphysema [tiab] OR COAD [tiab] OR chronic obstructive airway disease [tiab] OR "Pulmonary Disease, Chronic Obstructive"[Mesh]) (113,398) 2. (Triple* [tiab] OR LABA/LAMA/ICS [tiab] OR LAMA/LABA/ICS [tiab] OR ICS/LABA/LAMA [tiab] OR ICS/LAMA/LABA [tiab] OR LAMA/ICS/LABA [tiab] OR LABA/ICS/LAMA [tiab] OR "LABA + LAMA + ICS" [tiab] OR "LAMA + LABA + ICS" [tiab] OR "ICS + LABA + LAMA" [tiab] OR "ICS + LAMA + LABA" [tiab] OR "Inhaled corticosteroids/long-acting β2 agonists/long-acting muscarinic antagonists" [tiab] OR "Long-acting β2 agonists/long-acting muscarinic antagonists/inhaled corticosteroids" [tiab] OR "Long-acting muscarinic antagonists/long-acting β2 agonists/inhaled corticosteroids" [tiab] OR "Inhaled corticosteroids/long-acting muscarinic antagonists/long-acting β2 agonists" [tiab] OR "Long-acting β2 agonists/inhaled corticosteroids/long-acting muscarinic antagonists" [tiab] OR "Long-acting muscarinic antagonists/inhaled corticosteroids/long-acting β2 agonists" [tiab]) (128,89) 3. (Fluticasonfuroate/vilanterol/umeclidinium [tiab] OR beclometasone/formoterol/glycopyrronium [tiab] OR fluticasone furoate/umeclidinium/vilanterol [tiab] OR Trelegy [tiab] OR Ellipta [tiab]) (183) 4. ("Adrenergic beta-2 Receptor Agonists"[Mesh] OR "Adrenergic beta-2 Receptor Agonists" [Pharmacological Action] OR LABA [tiab] OR LABAs [tiab] OR long-acting β2-agonist* [tiab] OR long-acting beta2-adrenergic receptor agonist* [tiab]) (21,801) 5. ("Formoterol Fumarate"[Mesh] OR Formoterol [tiab] OR Perforomist [tiab] OR Arformoterol [tiab] OR Brovana [tiab]) (2,791) 6. ("Indacaterol" [Supplementary Concept] OR Indacaterol [tiab] OR Arcapta [tiab] OR Onbrez [tiab]) (548) 7. ("Olodaterol" [Supplementary Concept] OR Olodaterol [tiab] OR Striverdi [tiab] OR "BI-1744 CL" [tiab])(246) 8. ("Salmeterol Xinafoate"[Mesh] OR Salmeterol [tiab] OR Serevent [tiab]) (3,124) 9. ("Vilanterol" [Supplementary Concept] OR Vilanterol [tiab] OR "GW 642444" [tiab]) (453) 10. (#4 OR #5 OR #6 OR #7 OR #8 OR #9)(23,136) 11. ("Muscarinic Antagonists" [Pharmacological Action] OR "Muscarinic Antagonists"[Mesh] OR Long-acting muscarinic antagonist* [tiab] OR LAMA [tiab] OR LAMAs [tiab]) (57,967) 12. ("Aclidinium bromide" [Supplementary Concept] OR Aclidinium [tiab] OR Tudorza [tiab] OR Genuair [tiab]) (263) 13. ("Glycopyrrolate"[Mesh] OR Glycopyrrolate [tiab] OR Glycopyrronium [tiab] OR Seebri [tiab] OR NVA237 [tiab] OR NVA-237 [tiab] OR Breezhaler [tiab])(1,867) 14. ("Tiotropium Bromide"[Mesh] OR Tiotropium [tiab] OR Spiriva [tiab]) (1,951) 15. ("GSK573719" [Supplementary Concept] OR Umeclidinium [tiab] OR Incruse [tiab] OR Ellipta [tiab]) (392) 16. (#11 OR #12 OR #13 OR #14 OR #15) (60,15) 17. ("Adrenal Cortex Hormones" [Mesh] OR "Adrenal Cortex Hormones" [Pharmacological Action] OR Inhaled steroid* [tiab] OR Inhaled corticosteroid* [tiab] OR ICS [tiab] OR ICSs [tiab]) (310,547) 18. ("Beclomethasone" [Mesh] OR Beclomethasone [tiab] OR Beclovent [tiab] OR Vanceril [tiab] OR QVAR [tiab] OR Ventolair [tiab] OR Beclocort [tiab]) (3,937) 19. ("Budesonide" [Mesh] OR Budesonide [tiab] OR Pulmicort [tiab] OR Spirocort [tiab] OR Entocort [tiab]) (6,829) 20. ("Flunisolide" [Supplementary Concept] OR Flunisolide [tiab] OR Aerobid [tiab] OR Aerospan [tiab] OR RS-3999 [tiab]) (381) 21. ("Fluticasone" [Mesh] OR Fluticasone [tiab] OR Flovent [tiab]) (4,909) 22. ("Mometasone Furoate"[Mesh] OR Mometasone [tiab]) (1,268) 23. ("Ciclesonide" [Supplementary Concept] OR Ciclesonide [tiab] OR Alvesco [tiab]) (445) 24. (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23) (318,274) 25. (#10 AND #16 AND #24) (1,178) 26. (long-acting β2-agonist plus long-acting muscarinic antagonist [tiab] OR long-acting muscarinic antagonist plus long-acting β2-agonist [tiab] OR LABA/LAMA [tiab] OR LAMA/LABA [tiab] OR long-acting β2-agonist/long-acting muscarinic antagonist [tiab] OR long-acting muscarinic antagonist/long-acting β2-agonist [tiab]) (399) 27. (umeclidinium/vilanterol [tiab] OR umeclidinium-vilanterol [tiab] OR UMEC/VI [tiab] OR vilanterol/umeclidinium [tiab] OR vilanterol-umeclidinium [tiab] OR VI/UMEC [tiab] OR Anoro [tiab]) (181) 28. ("QVA149" [Supplementary Concept] OR "indacaterol-glycopyrronium combination" [Supplementary Concept] OR glycopyrronium/indacaterol [tiab] OR glycopyrronium-indacaterol [tiab] OR indacaterol/glycopyrronium [tiab] OR indacaterol-glycopyrronium [tiab] OR IND/GLY [tiab] OR GLY/IND [tiab]) (173)

	29. ("tiotropium-olodaterol" [Supplementary Concept] OR tiotropium/olodaterol [tiab] OR tiotropium-olodaterol [tiab] OR TIO/OLO [tiab] OR olodaterol/tiotropium [tiab] OR olodaterol-tiotropium [tiab] OR OLO/TIO [tiab] OR Respimat [tiab]) (420) 30. (#26 OR #27 OR #28 OR #29) (996) 31. (#30 AND #24) (477) 32. (Long-acting β2-agonist plus inhaled corticosteroid [tiab] OR inhaled corticosteroid plus long-acting β2-agonist [tiab] OR LABA/ICS [tiab] OR ICSA/LABA [tiab] OR long-acting β2-agonist/inhaled corticosteroid [tiab] OR inhaled corticosteroid/long-acting β2-agonist [tiab]) (580) 33. ("Fluticasone-Salmeterol Drug Combination"[Mesh] OR Fluticasone/Salmeterol [tiab] OR Fluticasone-Salmeterol [tiab] OR Salmeterol/Fluticasone [tiab] OR Salmeterol-Fluticasone [tiab] OR FP/S [tiab] OR S/FP [tiab] OR Advair [tiab]) (1,016) 34. ("Budesonide, Formoterol Fumarate Drug Combination" [mesh] OR Budesonide/Formoterol [tiab] OR Formoterol/Budesonide [tiab] OR Budesonide-Formoterol [tiab] OR Formoterol-Budesonide [tiab] OR BD/FF [tiab] OR FF/BD [tiab] OR Symbicort [tiab]) (821) 35. ("fluticasone furoate-vilanterol trifenatate" [Supplementary Concept] OR fluticasone furoate/vilanterol [tiab] OR fluticasone furoate-vilanterol [tiab] OR FF/VI [tiab] OR vilanterol/fluticasone furoate [tiab] OR vilanterol-fluticasone furoate [tiab] OR VI/FF [tiab]) (258) 36. ("Mometasone Furoate, Formoterol Fumarate Drug Combination" [mesh] OR Mometasone/Formoterol [tiab] OR Mometasone-Formoterol [tiab] OR MF/F [tiab] OR Formoterol/Mometasone [tiab] OR Formoterol-Mometasone [tiab] OR F/MF [tiab]) (86) 37. (#32 OR #33 OR #34 OR #35 OR #36) (2,319) 38. (#37 AND #16) (524) 39. #1 AND (#2 OR #3 OR #25 OR #31 OR #38) (1,3) 40. (animals[mh] NOT humans[mh]) (4,960,809) 41. #39 NOT #40 (1,292) 42. (comment[pt] OR editorial[pt] OR letter[pt] OR in vitro techniques[mh] OR case reports[pt] OR case report[ti] OR news[pt] OR "Introductory Journal Article" [Publication Type] OR "Ephemera" [Publication Type] OR "Newspaper Article" [Publication Type] OR "Congresses" [Publication Type] OR comment [ti]) (4,954,335) 43. #41 NOT #42 (1,172) 44. ("2019/07/01"[Date - Create]: "2022"[Date - Create]) (3,869,794) 45. English[Language] (28,939,239) 46. #43 AND #44 AND #45 (360)
Referencias identificadas	360
Característica	Reporte
Tipo de búsqueda	Actualización
Base de datos	EMBASE
Plataforma	Elsevier
Fecha de búsqueda	22-02-2022
Rango de fecha de búsqueda	01-07-2019 hasta 22-02-2022
Restricciones de lenguaje	Inglés
Otros límites	Ninguno
Estrategia de búsqueda	1. 'chronic obstructive lung disease'/exp OR 'chronic obstructive lung disease' OR copd:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti OR 'chronic bronchitis':ab,ti OR emphysema:ab,ti OR coad:ab,ti OR 'chronic obstructive airway disease':ab,ti (216528) 2. triple*:ab,ti OR 'laba/lama/ics':ab,ti OR 'lama/laba/ics':ab,ti OR 'ics/laba/lama':ab,ti OR 'ics/lama/laba':ab,ti OR 'lama/ics/laba':ab,ti OR 'laba/ics/lama':ab,ti OR ((laba NEAR/1 lama NEAR/1 ics):ab,ti) OR ((lama NEAR/1 laba NEAR/1 ics):ab,ti) OR ((ics NEAR/1 laba NEAR/1 lama):ab,ti) OR ((ics NEAR/1 lama NEAR/1 laba):ab,ti) OR 'inhaled corticosteroids/long-acting β2 agonists/long-acting muscarinic antagonists':ab,ti OR 'long-acting β2 agonists/long-acting muscarinic antagonists/inhaled corticosteroids':ab,ti OR 'long-acting muscarinic antagonists/long-acting β2 agonists/inhaled corticosteroids':ab,ti OR 'inhaled corticosteroids/long-acting muscarinic antagonists/long-acting β2 agonists':ab,ti OR 'long-actingβ2 agonists/inhaled corticosteroids/long-acting muscarinic antagonists':ab,ti OR 'long-acting muscarinic antagonists/inhaled corticosteroids/long-acting β2 agonists':ab,ti (168470) 3. 'fluticasonfuroate/vilanterol/umeclidinium':ab,ti OR 'beclometasone/formoterol/glycopyrronium':ab,ti OR 'fluticasone furoate/umeclidinium/vilanterol':ab,ti OR trelegy:ab,ti OR ellipta:ab,ti (400) 4. 'beta 2 adrenergic receptor stimulating agent' OR laba:ab,ti OR labas:ab,ti OR 'long-acting β2-agonist*':ab,ti OR 'long-acting beta2-adrenergic receptor agonist*':ab,ti (19348) 5. 'formoterol fumarate' OR formoterol:ab,ti OR perforomist:ab,ti OR arformoterol:ab,ti OR brovana:ab,ti (5589) 6. indacaterol:ab,ti OR arcapta:ab,ti OR onbrez:ab,ti (1129) 7. olodaterol:ab,ti OR striverdi:ab,ti OR 'bi-1744 cl':ab,ti (518) 8. 'salmeterol xinafoate':ab,ti OR salmeterol:ab,ti OR serevent:ab,ti (4352)

	9. vilanterol:ab,ti OR 'gw 642444':ab,ti (879) 10. #4 OR #5 OR #6 OR #7 OR #8 OR #9 (26324) 11. 'muscarinic receptor blocking agent' OR 'long-acting muscarinic antagonist*':ab,ti OR lama:ab,ti OR lamas:ab,ti (12759) 12. aclidinium:ab,ti OR tudorza:ab,ti OR genuair:ab,ti (522) 13. 'glycopyrronium' OR glycopyrrolate:ab,ti OR glycopyrronium:ab,ti OR seebri:ab,ti OR nva237:ab,ti OR 'nva 237':ab,ti OR breezhaler:ab,ti (8480) 14. 'tiotropium bromide' OR tiotropium:ab,ti OR spiriva:ab,ti (6942) 15. gsk573719:ab,ti OR umeclidinium:ab,ti OR incruse:ab,ti OR ellipta:ab,ti (753) 16. #11 OR #12 OR #13 OR #14 OR #15 (25820) 17. 'corticosteroid' OR 'inhaled steroid*':ab,ti OR 'inhaled corticosteroid*':ab,ti OR ics:ab,ti OR icss:ab,ti (352606) 18. 'beclomethasone dipropionate' OR beclomethasone:ab,ti OR beclovent:ab,ti OR vanceril:ab,ti OR qvar:ab,ti OR ventolair:ab,ti OR beclocort:ab,ti (9845) 19. 'budesonide' OR budesonide:ab,ti OR pulmicort:ab,ti OR spirocort:ab,ti OR entocort:ab,ti (25506) 20. 'fluocinolone acetonide' OR flunisolide:ab,ti OR aerobid:ab,ti OR aerospan:ab,ti OR 'rs 3999':ab,ti (3953) 21. 'fluticasone' OR fluticasone:ab,ti OR flovent:ab,ti (20114) 22. 'mometasone furoate' OR mometasone:ab,ti (5849) 23. ciclesonide:ab,ti OR alvesco:ab,ti (650) 24. #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 (381196) 25. #10 AND #16 AND #24 (4246) 26. 'long-acting β2-agonist plus long-acting muscarinic antagonist':ab,ti OR 'long-acting muscarinic antagonist plus long-acting β2-agonist':ab,ti OR 'laba/lama':ab,ti OR 'lama/laba':ab,ti OR 'long-acting β2-agonist/long-acting muscarinic antagonist':ab,ti OR 'long-acting muscarinic antagonist/long-acting β2-agonist':ab,ti (951) 27. 'umeclidinium/vilanterol':ab,ti OR 'umeclidinium-vilanterol':ab,ti OR 'umec/vi':ab,ti OR 'vilanterol/umeclidinium':ab,ti OR 'vilanterol-umeclidinium':ab,ti OR 'vi/umec':ab,ti OR anoro:ab,ti (427) 28. qva149:ab,ti OR 'indacaterol-glycopyrronium combination':ab,ti OR 'glycopyrronium/indacaterol':ab,ti OR 'glycopyrronium-indacaterol':ab,ti OR 'indacaterol/glycopyrronium':ab,ti OR 'indacaterol glycopyrronium':ab,ti OR 'ind/gly':ab,ti OR 'gly/ind':ab,ti (516) 29. 'tiotropium/olodaterol':ab,ti OR 'tiotropium-olodaterol':ab,ti OR 'tio/olo':ab,ti OR 'olodaterol/tiotropium':ab,ti OR 'olodaterol-tiotropium':ab,ti OR 'olo/tio':ab,ti OR 'respimat':ab,ti (966) 30. #26 OR #27 OR #28 OR #29 (2471) 31. #24 AND #30 (1509) 32. 'long-acting β2-agonist plus inhaled corticosteroid':ab,ti OR 'inhaled corticosteroid plus long-acting β2-agonist':ab,ti OR 'laba/ics':ab,ti OR 'icsa/laba':ab,ti OR 'long-acting β2-agonist/inhaled corticosteroid':ab,ti OR 'inhaled corticosteroid/long-acting β2-agonist':ab,ti (614) 33. 'fluticasone propionate plus salmeterol' OR 'fluticasone/salmeterol':ab,ti OR 'fluticasone-salmeterol':ab,ti OR 'salmeterol/fluticasone':ab,ti OR 'salmeterol-fluticasone':ab,ti OR 'fp/s':ab,ti OR 's/fp':ab,ti OR advair:ab,ti (4670) 34. 'budesonide plus formoterol' OR 'budesonide/formoterol':ab,ti OR 'formoterol/budesonide':ab,ti OR 'budesonide-formoterol':ab,ti OR 'formoterol-budesonide':ab,ti OR 'bd/ff':ab,ti OR 'ff/bd':ab,ti OR symbicort:ab,ti (3375) 35. 'fluticasone furoate-vilanterol trifenatate':ab,ti OR 'fluticasone furoate/vilanterol':ab,ti OR 'fluticasone furoate-vilanterol':ab,ti OR 'ff/vi':ab,ti OR 'vilanterol/fluticasone furoate':ab,ti OR 'vilanterol-fluticasone furoate':ab,ti OR 'vi/ff':ab,ti (417) 36. 'formoterol fumarate plus mometasone furoate' OR 'mometasone/formoterol':ab,ti OR 'mometasone-formoterol':ab,ti OR 'mf/f':ab,ti OR 'formoterol/mometasone':ab,ti OR 'formoterol-mometasone':ab,ti OR 'f/mf':ab,ti (792) 37. #32 OR #33 OR #34 OR #35 OR #36 (8123) 38. #16 AND #37 (2219) 39. #1 AND (#2 OR #3 OR #25 OR #31 OR #38) (4558) 40. animals:ti,ab,lnk,kw,tn,tt,df,mn,dn NOT humans:ti,ab,lnk,kw,tn,tt,df,mn,dn (809494) 41. #39 NOT #40 (4553) 42. ((comment:it OR editorial:it OR letter:it OR 'in vitro techniques':kw OR case) AND reports:it OR case) AND report:tt OR news:it OR 'introductory journal article':it OR ephemera:it OR 'newspaper article':it OR congresses:it OR comment:tt (6896) 43. #41 NOT #42 (4553) 44. #41 NOT #42 AND [english]/lim AND [01-07-2019]/sd NOT [22-02-2022]/sd (1253) 45. #44 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) (621)
Referencias identificadas	621
Característica	Reporte
Tipo de búsqueda	Actualización
Base de datos	CENTRAL
Plataforma	OVID

Fecha de búsqueda	21-02-2022
Rango de fecha de búsqueda	2019 hasta 2022
Restricciones de lenguaje	Inglés
Otros límites	Ninguno
Estrategia de búsqueda	1. (Copd or "chronic obstructive pulmonary disease" or "chronic bronchitis" or emphysema or COAD or "chronic obstructive airway disease").tw. or Pulmonary Disease, Chronic Obstructive/ (23680) 2. (Triple* or "LABA/LAMA/ICS" or "LAMA/LABA/ICS" or "ICS/LABA/LAMA" or "ICS/LAMA/LABA" or "LAMA/ICS/LABA" or "LABA/ICS/LAMA" or (LABA adj LAMA adj ICS) or (LAMA adj LABA adj ICS) or (ICS adj LABA adj LAMA) or (ICS adj LAMA adj LABA) or "Inhaled corticosteroids/long-acting β2 agonists/long-acting muscarinic antagonists" or "Long-acting β2 agonists/long-acting muscarinic antagonists/inhaled corticosteroids" or "Long-acting muscarinic antagonists/long-acting β2 agonists/inhaled corticosteroids" or "Inhaled corticosteroids/long-acting muscarinic antagonists/long-acting β2 agonists" OR "Long-actingβ2 agonists/inhaled corticosteroids/long-acting muscarinic antagonists" OR "Long-acting muscarinic antagonists/inhaled corticosteroids/long-acting β2 agonists").tw. (14222) 3. ("Fluticasonfuroate/vilanterol/umeclidinium" or "beclometasone/formoterol/glycopyrronium" or "fluticasone furoate/umeclidinium/vilanterol" or Trelegy or Ellipta).tw. (297) 4. Adrenergic beta-2 Receptor Agonists/ or Adrenergic beta-2 Receptor Agonists/ or (LABA or LABAs or "long-acting β2-agonist*" or "long-acting beta2-adrenergic receptor agonist*").tw. (2084) 5. Formoterol Fumarate/ or (Formoterol or Perforomist or Arformoterol or Brovana).tw. (3393) 6. (Indacaterol or Arcapta or Onbrez).tw. (817) 7. (Olodaterol or Striverdi or "BI-1744 CL").tw. (395) 8. ("Salmeterol Xinafoate" or Salmeterol or Serevent).tw. (3192) 9. (Vilanterol or "GW 642444").tw. (714) 10. or/4-9 (8406) 11. Muscarinic Antagonists/ or ("Long-acting muscarinic antagonist*" or LAMA or LAMAs).tw. (1800) 12. (Aclidinium or Tudorza or Genuair).tw. (351) 13. Glycopyrrolate/ or (Glycopyrrolate or GlycopyrroniumOR Seebri or NVA237 or NVA-237 or Breezhaler).tw. (1308) 14. Tiotropium Bromide/ or (Tiotropium or Spiriva).tw. (2411) 15. (GSK573719 or Umeclidinium or Incruse or Ellipta).tw. (616) 16. or/11-15 (5294) 17. Adrenal Cortex Hormones/ or ("Inhaled steroid*" or "Inhaled corticosteroid*" or ICS or ICSs).tw. (9466) 18. Beclomethasone/ or (Beclomethasone or Beclovent or Vanceril or QVAR or Ventolair or Beclocort).tw. (2341) 19. Budesonide/ or (Budesonide or Pulmicort or Spirocort or Entocort).tw. (4896) 20. Fluocinolone Acetonide/ or (Flunisolide or Aerobid or Aerospan or RS-3999).tw. (450) 21. Fluticasone/ or (Fluticasone or Flovent).tw. (5572) 22. Mometasone Furoate/ or Mometasone.tw. (1311) 23. (Ciclesonide or Alvesco).tw. (524) 24. or/17-23 (19236) 25. 10 and 16 and 24 (1161) 26. ("long-acting β2-agonist plus long-acting muscarinic antagonist" or "long-acting muscarinic antagonist plus long-acting β2-agonist" or "LABA/LAMA" or "LAMA/LABA" or "long-acting β2-agonist/long-acting muscarinic antagonist" or "long-acting muscarinic antagonist/long-acting β2-agonist").tw. (339) 27. ("umeclidinium/vilanterol" or "umeclidinium-vilanterol" or "UMEC/VI" or "vilanterol/umeclidinium" or "vilanterol-umeclidinium" or "VI/UMEC" or Anoro).tw. (323) 28. (QVA149 or "indacaterol-glycopyrronium combination" or "glycopyrronium/indacaterol" or "glycopyrronium-indacaterol" or "indacaterol/glycopyrronium" or indacaterol-glycopyrronium or "IND/GLY" or "GLY/IND").tw. (484) 29. ("tiotropium-olodaterol" or "tiotropium/olodaterolOR tiotropium-olodaterol" or "TIO/OLO" or "olodaterol/tiotropium" or "olodaterol-tiotropium" or "OLO/TIO" or "Respimat").tw. (793) 30. or/26-29 (1739) 31. 30 and 24 (802) 32. ("long-acting β2-agonist plus inhaled corticosteroid" or "inhaled corticosteroid plus long-acting β2-agonist" or "LABA/ICS" or "ICSA/LABA" or "long-acting β2-agonist/inhaled corticosteroid" or "inhaled corticosteroid/long-acting β2-agonist").tw. (211) 33. Fluticasone-Salmeterol Drug Combination/ or ("Fluticasone/Salmeterol" or "Fluticasone-Salmeterol" or "Salmeterol/Fluticasone" or "Salmeterol-Fluticasone" or "FP/S" or "S/FP" or Advair).tw. (1334) 34. Budesonide, Formoterol Fumarate Drug Combination/ or ("Budesonide/Formoterol" or "Formoterol/Budesonide" or "Budesonide-Formoterol" or "Formoterol-Budesonide" or "BD/FF" or "FF/BD" or Symbicort).tw. (1355) 35. ("fluticasone furoate-vilanterol trifenatate" or "fluticasone furoate/vilanterol" or "fluticasone furoate-vilanterol" or "FF/VI" or "vilanterol/fluticasone furoate" or "vilanterol-fluticasone furoate" or "VI/FF").tw. (401) 36. Mometasone Furoate, Formoterol Fumarate Drug Combination/ or ("Mometasone/Formoterol" or "Mometasone-Formoterol" or "MF/F" or "Formoterol/Mometasone" or "Formoterol-Mometasone" or "F/MF").tw. (138) 37. or/32-36 (3170)

	38. 37 and 16 (615) 39. 1 and (2 or 3 or 25 or 31 or 38) (1129) 40. (animals not humans).mp. (2592) 41. 39 not 40 (1129) 42. (comment or editorial or letter).pt. or "in vitro techniques".hw. or case reports.pt. or case report.ti. or news.pt. or "Introductory Journal Article".pt. or "Ephemera".pt. or "Newspaper Article".pt. or "Congresses".pt. or comment.ti. (13341) 43. 41 not 42 (1124) 44. limit 43 to english language (793) 45. limit 44 to yr="2019 -Current" (232)
Referencias identificadas	232

Resumen:

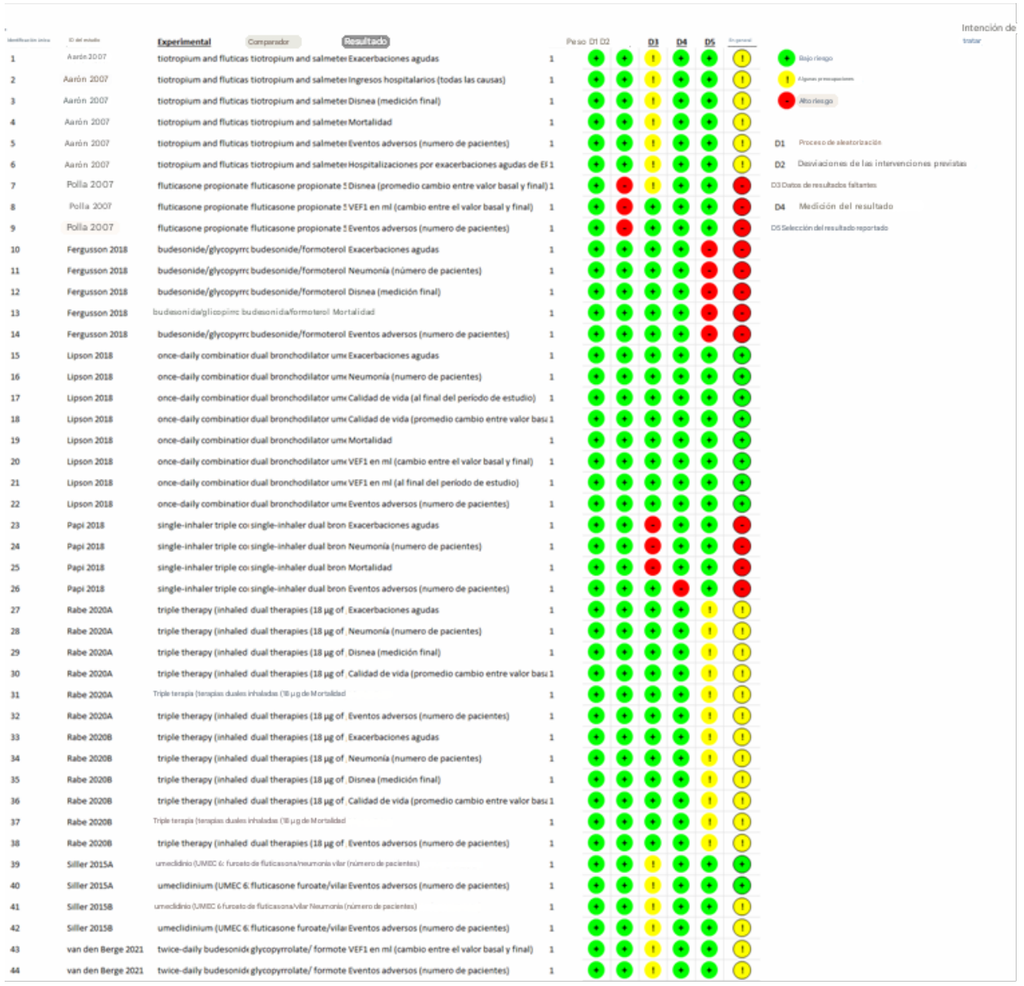
Base de datos	Referencias identificadas
MEDLINE - PubMed	360
EMBASE - Elsevier	621
CENTRAL - OVID	232

Material suplementario 3. Criterios de inclusión para los reportes de ensayos clínicos

Tipo de evidencia	Revisión sistemática de ensayos clínicos, controlados, aleatorizados.
Población	Se incluyeron estudios en pacientes adultos mayores de 18 años con diagnóstico de EPOC estable sintomático, con disnea persistente y/o intolerancia al ejercicio.
Tiempo	Estudios publicados entre julio de 2019 y febrero de 2022
Intervención	**Triple terapia con CSI/LABA/LAMA (combinaciones a dosis fija o combinaciones abiertas)** ***Combinaciones fijas (1 dispositivo)*** Fluticasona/umeclidinio/vilanterol Beclometasona/formoterol/glicopirronio Budesonida/glicopirronio/formoterol ***Combinaciones abiertas (>1 dispositivo)*** Budesonida/glicopirronio/formoterol Fluticasona/salmeterol/tiotropio Budesonida/formoterol/tiotropio Fluticasona/umeclidinio/vilanterol
Comparaciones	**Terapia dual LABA/LAMA** Umeclidinio/vilanterol Indacaterol/glicopirronio Tiotropio/olodaterol Formoterol/aclidinio Formoterol/glicopirronio Salmeterol/tiotropio
Desenlaces	**Críticos** Mortalidad[a] Exacerbaciones agudas[a] Frecuencia de neumonías[a] Hospitalizaciones/Admisiones (todas las causas) [a] Disnea (cambio en escala MMRC, BORG, TDI) [b] Actividad física (capacidad de ejercicio, caminata 6 minutos) [b] Calidad de vida relacionada con la salud evaluada a través del cuestionario respiratorio Saint George) [b] FEV1 [b] Eventos adversos emergentes del tratamiento[a] **Evaluación de desenlaces** Se evaluaron los siguientes desenlaces: - Mortalidad: tasa ajustada de mortalidad - Exacerbaciones agudas: tasa ajustada de exacerbaciones moderadas y severas por paciente-año - Neumonía: frecuencia en eventos de neumonías por cualquier causa - Hospitalización: ingresos hospitalarios por exacerbaciones y por todas las causas - Actividad física: capacidad de ejercicio evaluada por caminata 6 minutos - Disnea: medido por el Índice Transicional de Disnea, MMRC (Modified Medical Research Council Dyspnea Scale) - Calidad de vida relacionada con la salud (CVRS): medido por el cuestionario respiratorio Saint George - Volumen espiratorio forzado en el primer segundo (FEV1) o el cambio desde el inicio - Eventos adversos: eventos adversos emergentes del tratamiento.

Escala de clasificación de disnea BORG; EPOC: enfermedad pulmonar obstructiva crónica; CSI: corticoesteroide inhalado; LABA: beta 2 de acción larga; LAMA: antimuscarínico de acción larga; MMRC: Modified Medical Research Council Dyspnea Scale TDI: transitional dyspnea index; FEV1: volumen espiratorio forzado en 1 segundo; CVRS : Calidad de vida relacionada con la salud
[a.] Desenlace dicotómico; [b.] Desenlace continuo

Material suplementario 4. Evaluación de riesgo de sesgo por desenlace entre los ECA que compararon triple terapia vs terapia dual en pacientes con EPOC



	ID del estudio	Experimental	Comparador	Resultado		Peso	D1	D2	D3	D4	D5	En general
1	Aarón 2007	tiotropium and fluticas tiotropium and salmeter		Exacerbaciones agudas	1		+	+	!	+	+	!
2	Aarón 2007	tiotropium and fluticas tiotropium and salmeter		Ingresos hospitalarios (todas las causas)	1		+	+	!	+	+	!
3	Aarón 2007	tiotropium and fluticas tiotropium and salmeter		Disnea (medición final)	1		+	+	!	+	+	!
4	Aarón 2007	tiotropium and fluticas tiotropium and salmeter		Mortalidad	1		+	+	!	+	+	!
5	Aarón 2007	tiotropium and fluticas tiotropium and salmeter		Eventos adversos (numero de pacientes)	1		+	+	!	+	+	!
6	Aarón 2007	tiotropium and fluticas tiotropium and salmeter		Hospitalizaciones por exacerbaciones agudas de EI	1		+	+	!	+	+	!
7	Polla 2007	fluticasone propionate fluticasone propionate !		Disnea (promedio cambio entre valor basal y final)	1		+	-	!	+	+	-
8	Polla 2007	fluticasone propionate fluticasone propionate !		VEF1 en ml (cambio entre el valor basal y final)	1		+	-	+	+	+	-
9	Polla 2007	fluticasone propionate fluticasone propionate !		Eventos adversos (numero de pacientes)	1		+	-	+	+	+	-
10	Fergusson 2018	budesonide/glycopyrrc budesonide/formoterol		Exacerbaciones agudas	1		+	+	+	+	-	-
11	Fergusson 2018	budesonide/glycopyrrc budesonide/formoterol		Neumonía (número de pacientes)	1		+	+	+	+	-	-
12	Fergusson 2018	budesonide/glycopyrrc budesonide/formoterol		Disnea (medición final)	1		+	+	+	+	-	-
13	Fergusson 2018	budesonida/glicopirrc budesonida/formoterol		Mortalidad	1		+	+	+	+	-	-
14	Fergusson 2018	budesonide/glycopyrrc budesonide/formoterol		Eventos adversos (numero de pacientes)	1		+	+	+	+	-	-
15	Lipson 2018	once-daily combinatior dual bronchodilator umc		Exacerbaciones agudas	1		+	+	+	+	+	+
16	Lipson 2018	once-daily combinatior dual bronchodilator umc		Neumonía (numero de pacientes)	1		+	+	+	+	+	+
17	Lipson 2018	once-daily combinatior dual bronchodilator umc		Calidad de vida (al final del periodo de estudio)	1		+	+	+	+	+	+
18	Lipson 2018	once-daily combinatior dual bronchodilator umc		Calidad de vida (promedio cambio entre valor basa	1		+	+	+	+	+	+
19	Lipson 2018	once-daily combinatior dual bronchodilator umc		Mortalidad	1		+	+	+	+	+	+
20	Lipson 2018	once-daily combinatior dual bronchodilator umc		VEF1 en ml (cambio entre el valor basal y final)	1		+	+	+	+	+	+
21	Lipson 2018	once-daily combinatior dual bronchodilator umc		VEF1 en ml (al final del periodo de estudio)	1		+	+	+	+	+	+
22	Lipson 2018	once-daily combinatior dual bronchodilator umc		Eventos adversos (numero de pacientes)	1		+	+	+	+	+	+
23	Papi 2018	single-inhaler triple co:	single-inhaler dual bron	Exacerbaciones agudas	1		+	+	-	+	+	-
24	Papi 2018	single-inhaler triple co:	single-inhaler dual bron	Neumonía (numero de pacientes)	1		+	+	-	+	+	-
25	Papi 2018	single-inhaler triple co:	single-inhaler dual bron	Mortalidad	1		+	+	-	+	+	-
26	Papi 2018	single-inhaler triple co:	single-inhaler dual bron	Eventos adversos (numero de pacientes)	1		+	+	+	-	+	-
27	Rabe 2020A	triple therapy (inhaled	dual therapies (18 µg of	Exacerbaciones agudas	1		+	+	+	+	!	!
28	Rabe 2020A	triple therapy (inhaled	dual therapies (18 µg of	Neumonía (numero de pacientes)	1		+	+	+	+	!	!
29	Rabe 2020A	triple therapy (inhaled	dual therapies (18 µg of	Disnea (medición final)	1		+	+	+	+	!	!
30	Rabe 2020A	triple therapy (inhaled	dual therapies (18 µg of	Calidad de vida (promedio cambio entre valor basa	1		+	+	+	+	!	!
31	Rabe 2020A	Triple terapia (terapias duales inhaladas (18 µg de		Mortalidad	1		+	+	+	+	!	!
32	Rabe 2020A	triple therapy (inhaled	dual therapies (18 µg of	Eventos adversos (numero de pacientes)	1		+	+	+	+	!	!
33	Rabe 2020B	triple therapy (inhaled	dual therapies (18 µg of	Exacerbaciones agudas	1		+	+	+	+	!	!
34	Rabe 2020B	triple therapy (inhaled	dual therapies (18 µg of	Neumonía (numero de pacientes)	1		+	+	+	+	!	!
35	Rabe 2020B	triple therapy (inhaled	dual therapies (18 µg of	Disnea (medición final)	1		+	+	+	+	!	!
36	Rabe 2020B	triple therapy (inhaled	dual therapies (18 µg of	Calidad de vida (promedio cambio entre valor basa	1		+	+	+	+	!	!
37	Rabe 2020B	Triple terapia (terapias duales inhaladas (18 µg de		Mortalidad	1		+	+	+	+	!	!
38	Rabe 2020B	triple therapy (inhaled	dual therapies (18 µg of	Eventos adversos (numero de pacientes)	1		+	+	+	+	!	!
39	Siller 2015A	umeclidinio (UMEC 6	furoato de fluticasona/	neumonía vilar (número de pacientes)	1		+	+	!	+	+	+
40	Siller 2015A	umeclidinium (UMEC 6	fluticasone furoate/vilar	Eventos adversos (numero de pacientes)	1		+	+	!	+	+	+
41	Siller 2015B	umeclidinio (UMEC 6	furoato de fluticasona/	Vilar Neumonía (número de pacientes)	1		+	+	!	+	+	!
42	Siller 2015B	umeclidinium (UMEC 6	fluticasone furoate/vilar	Eventos adversos (numero de pacientes)	1		+	+	!	+	+	!
43	van den Berge 2021	twice-daily budesonide	glycopyrrolate/ formote	VEF1 en ml (cambio entre el valor basal y final)	1		+	+	!	+	+	!
44	van den Berge 2021	twice-daily budesonide	glycopyrrolate/ formote	Eventos adversos (numero de pacientes)	1		+	+	!	+	+	!

Intención de tratar

+ Bajo riesgo
! Algunas preocupaciones
- Alto riesgo

D1 Proceso de aleatorización
D2 Desviaciones de las intervenciones previstas
D3 Datos de resultados faltantes
D4 Medición del resultado
D5 Selección del resultado reportado

Material suplementario 5. Otros hallazgos reportados en los ensayos clínicos incluidos

Figura 1. Ensayo clínico que compararon triple terapia con terapia dual para reducción de hospitalizaciones por todas las causas

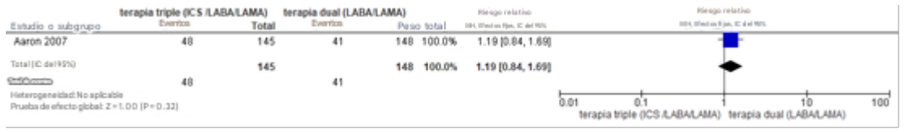


Figura 2. Ensayo clínico que compararó triple terapia con terapia dual para reducción de disnea como el cambio promedio entre valor basal y final

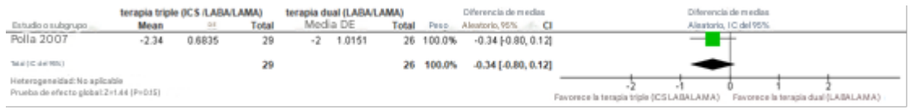


Figura 3. Ensayo clínico que comparó triple terapia con terapia dual para mejoría de la calidad de vida medido como el valor promedio al final del período de estudio

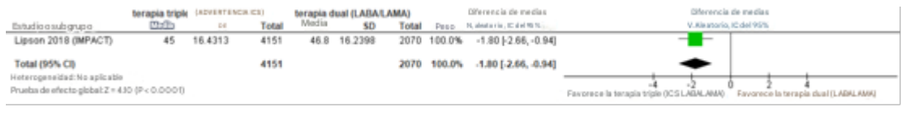
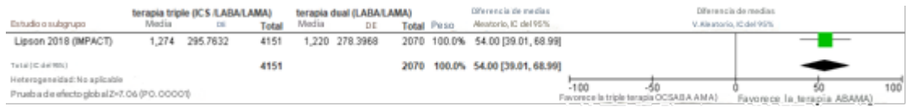


Figura 4. Ensayo clínico que comparó triple terapia con terapia dual para mejoría del FEV1 al final del período de estudio



Material suplementario 6. Análisis de subgrupos

Figura 1. Análisis de subgrupos para el desenlace exacerbaciones agudas, comparando terapia abierta vs fija

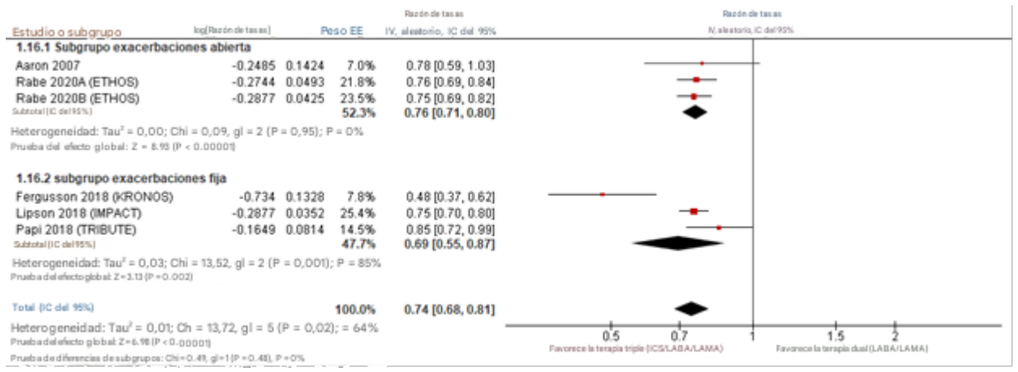


Figura 2. Análisis de subgrupos para el desenlace mortalidad, comparando terapia abierta vs fija

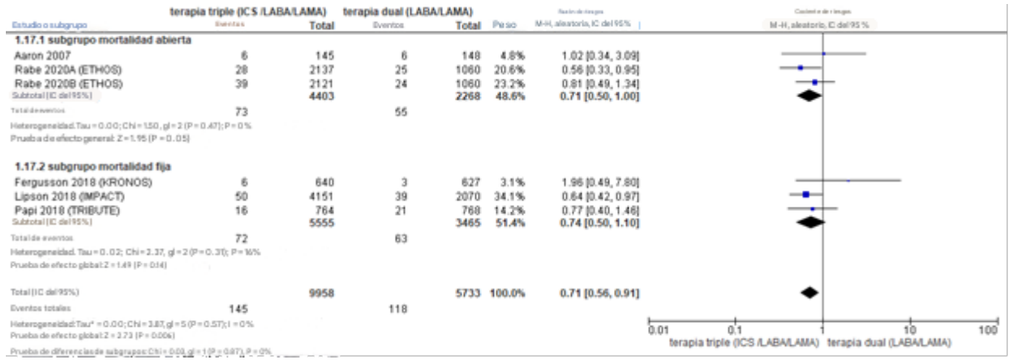


Figura 3. Análisis de subgrupos para el desenlace neumonía comparando terapia abierta vs fija

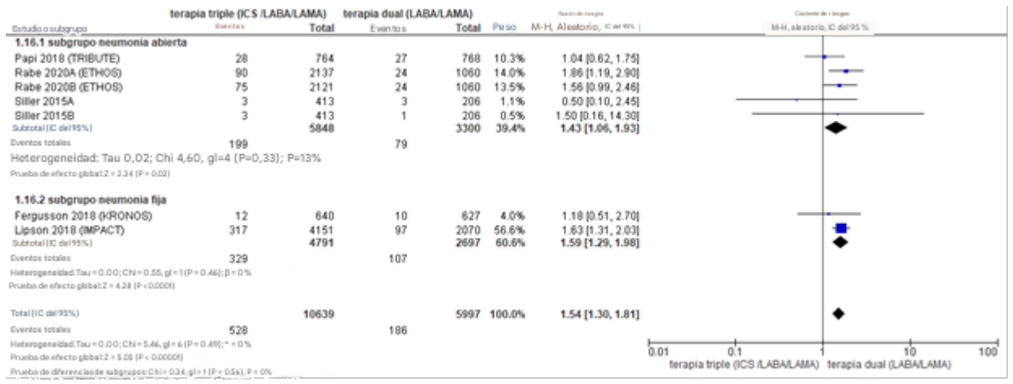
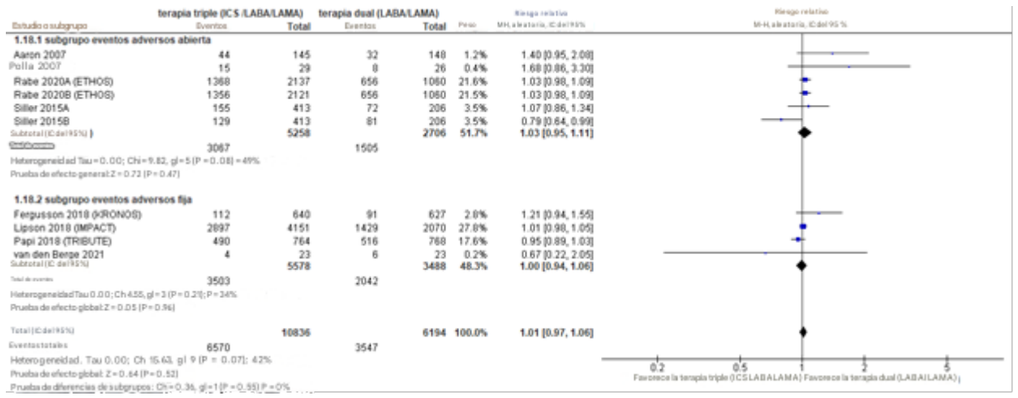


Figura 4. Análisis de subgrupos para el desenlace eventos adversos, comparando terapia abierta vs fija



Material suplementario 7. Análisis de la validez del análisis por subgrupos usando el instrumento ICEMAN (en inglés, instrumento no disponible en español)

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) in meta-analyses of randomized controlled trials

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN)

in meta-analyses of randomized controlled trials *Version 1.0* ***EXACERBACIONES SUBGRUPO TERAPIA ABIERTA VS FIJA***

Quick instructions

- Synonyms for effect modification include subgroup effect, interaction, and moderation
- The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier
- Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
- Completely unclear goes under probably reduced credibility
- It is helpful to provide a supporting comment or quotation under each question
- Whether an effect modification is patient-important is not part of the credibility assessment
- The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s): -

If available, protocol reference(s): -

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up):

exacerbaciones

State a single effect measure of interest (e.g., relative or absolute risk difference): rate ratio

State a single potential effect modifier of interest (e.g., age or comorbidity): terapia abierta vs fija

Was the potential effect modifier measured before or at randomization? [**X**] yes, continue [ ] no, stop here

and refer to manual for further instructions

Credibility assessment

1: Is the analysis of effect modification based on comparison within rather than between trials?

[**X**] Completely between [ ] Mostly between or unclear [ ] Mostly within [ ] Completely within

Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.

Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information

Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information

All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g., meta-analysis of interactions

Comment:

2: For within-trial comparisons, is the effect modification similar from trial to trial? [**X**] Not applicable: no or one within-RCT comparison

[ ] Definitely not similar

Effect modification reported for two or more trials and clearly different directions

[ ] Probably not similar or unclear

Effect modification not reported for individual trials or too imprecise to tell

[ ] Mostly similar

Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude

[ ] Definitely similar

Effect modification reported for two or more trials, similar in direction, only some differences in magnitude

Comment:

3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison

[ ] Very small

1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression

[**X**] Rather small or unclear

3-4 in smallest subgroup; 6-10 in continuous meta-regression

[ ] Rather large

5-9 in smallest subgroup; 11 to 15 in continuous meta-regression

[ ] Large

10 or more in smallest subgroup; more than 15 in continuous meta-regression

Comment:

4: Was the direction of effect modification correctly hypothesized a priori?

[ ] Definitely no

Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible

[ ] Probably no or unclear

Vague hypothesis or hypothesized direction unclear

[ ] Probably yes

No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification

[**X**] Definitely yes

Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale

Comment:

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[ ] Chance a very likely explanation

[ ] Chance a likely explanation or unclear

[ ] Chance may not explain

[**X**] Chance an unlikely explanation

Interaction or meta-regression p-value >0.05

Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable

Interaction or meta-regression p-value ≤0.01 and >0.005

Interaction or meta-regression p-value ≤0.005

Comment:

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no

Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis

[ ] Probably no or unclear

No mention of number or 4-10 effect modifiers tested and number not considered in analysis

[ ] Probably yes

No protocol available but unequivocal statement of 3 or fewer effect modifiers tested

[**X**] Definitely yes

Protocol available and 3 or fewer effect modifiers tested or number considered in analysis

Comment:

7: Did the authors use a random effects model?

[ ] Definitely no

Fixed (or common) effect or fixed effects model explicitly stated

[ ] Probably no or unclear

Probably fixed effect(s) model

[ ] Probably yes

Probably random (or mixed) effects

[**X**] Definitely yes

Random (or mixed) effects explicitly stated

Comment:

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [**X**] not applicable: not continuous

[ ] Definitely no

Analysis based on exploratory cut point(s), e.g., picking cut point associated with highest interaction p-value

[ ] Probably no or unclear

Analysis based on cut point(s) of unclear origin

[ ] Probably yes

Analysis based on pre-specified cut point(s), e.g., suggested by prior RCT

[ ] Definitely yes

Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship

Comment:

---

9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) [**X**] not applicable

[ ] Yes, probably decrease

[ ] Yes, probably increase

Comment:

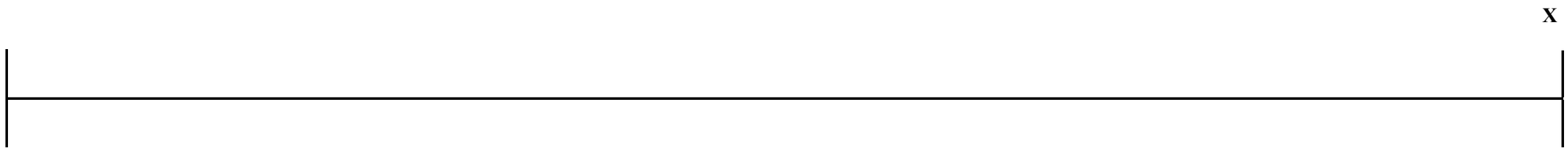
10: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably decrease credibility or unclear à very low

- Two or more responses definitely decrease credibility à maximum usually low even if all other responses satisfy credibility criteria
- One response definitely decreases credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably decrease credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably decrease credibility à high very likely

Place a mark on the continuous line (or type “x” in editable version)



Very low credibility	**Low credibility**	**Moderate credibility**	**High credibility**
Very likely no effect modification Use overall effect for each subgroup	Likely no effect modification Use overall effect for each subgroup but note remaining uncertainty	Likely effect modification Use separate effects for each subgroup but note remaining uncertainty	Very likely effect modification Use separate effects for each subgroup

Comment:

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN)

in meta-analyses of randomized controlled trials *Version 1.0* ***NEUMONÍA SUBGRUPO TERAPIA ABIERTA VS FIJA***

Quick instructions

- Synonyms for effect modification include subgroup effect, interaction, and moderation
- The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier
- Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
- Completely unclear goes under probably reduced credibility
- It is helpful to provide a supporting comment or quotation under each question
- Whether an effect modification is patient-important is not part of the credibility assessment
- The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s): -

If available, protocol reference(s): -

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up): neumonía

State a single effect measure of interest (e.g., relative or absolute risk difference): risk ratio

State a single potential effect modifier of interest (e.g., age or comorbidity): terapia abierta vs fija

Was the potential effect modifier measured before or at randomization? [**X**] yes, continue [ ] no, stop here and refer to manual for further instructions

Credibility assessment

1: Is the analysis of effect modification based on comparison within rather than between trials?

[**X** Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.	*Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information*	*Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information*	*All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g., meta-analysis of interactions*

Comment:

2: For within-trial comparisons, is the effect modification similar from trial to trial? [**X**] Not applicable: no or one within-RCT comparison

[ ] Definitely not similar	[ ] Probably not similar or unclear	[ ] Mostly similar	[ ] Definitely similar
Effect modification reported for two or more trials and clearly different directions	*Effect modification not reported for individual trials or too imprecise to tell*	*Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude*	*Effect modification reported for two or more trials, similar in direction, only some differences in magnitude*

Comment:

3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison

[ ] Very small	[**X**] Rather small or unclear	[ ] Rather large	[ ] Large
1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression	*3-4 in smallest subgroup; 6-10 in continuous meta-regression*	*5-9 in smallest subgroup; 11 to 15 in continuous meta-regression*	*10 or more in smallest subgroup; more than 15 in continuous meta-regression*

Comment:

4: Was the direction of effect modification correctly hypothesized a priori?

[ ] Definitely no

Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible

[ ] Probably no or unclear

Vague hypothesis or hypothesized direction unclear

[ ] Probably yes

No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification

[**X**] Definitely yes

Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale

Comment:

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[ ] Chance a very likely explanation

Interaction or meta-regression p-value >0.05

[ ] Chance a likely explanation or unclear

Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable

[ ] Chance may not explain

Interaction or meta-regression p-value ≤0.01 and >0.005

[**X**] Chance an unlikely explanation

Interaction or meta-regression p-value ≤0.005

Comment:

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no

Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis

[ ] Probably no or unclear

No mention of number or 4-10 effect modifiers tested and number not considered in analysis

[ ] Probably yes

No protocol available but unequivocal statement of 3 or fewer effect modifiers tested

[**X**] Definitely yes

Protocol available and 3 or fewer effect modifiers tested or number considered in analysis

Comment:

7: Did the authors use a random effects model?

[ ] Definitely no

Fixed (or common) effect or fixed effects model explicitly stated

[ ] Probably no or unclear

Probably fixed effect(s) model

[ ] Probably yes

Probably random (or mixed) effects

[**X**] Definitely yes

Random (or mixed) effects explicitly stated

Comment:

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [**X**] not applicable: not continuous

[ ] Definitely no

Analysis based on exploratory cut point(s), e.g., picking cut point associated with highest interaction p-value

[ ] Probably no or unclear

Analysis based on cut point(s) of unclear origin

[ ] Probably yes

Analysis based on pre-specified cut point(s), e.g., suggested by prior RCT

[ ] Definitely yes

Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship

Comment:

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9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) [**X**] not applicable

[ ] Yes, probably decrease [ ] Yes, probably increase

Comment:

10: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably decrease credibility or unclear à very low
- Two or more responses definitely decrease credibility à maximum usually low even if all other responses satisfy credibility criteria
- One response definitely decreases credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably decrease credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably decrease credibility à high very likely

Place a mark on the continuous line (or type “x” in editable version)

		X	
Very low credibility	**Low credibility**	**Moderate credibility**	**High credibility**
Very likely no effect modification Use overall effect for each subgroup	Likely no effect modification Use overall effect for each subgroup but note remaining uncertainty	Likely effect modification Use separate effects for each subgroup but note remaining uncertainty	Very likely effect modification Use separate effects for each subgroup

Comment:

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN)

in meta-analyses of randomized controlled trials *Version 1.0* ***MORTALIDAD SUBGRUPO TERAPIA ABIERTA VS FIJA***

Quick instructions

- Synonyms for effect modification include subgroup effect, interaction, and moderation
- The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier
- Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
- Completely unclear goes under probably reduced credibility
- It is helpful to provide a supporting comment or quotation under each question
- Whether an effect modification is patient-important is not part of the credibility assessment
- The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s): -

If available, protocol reference(s): -

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up):

mortalidad

State a single effect measure of interest (e.g., relative or absolute risk difference): risk ratio

State a single potential effect modifier of interest (e.g., age or comorbidity): terapia abierta vs fija

Was the potential effect modifier measured before or at randomization? [**X** yes, continue [ ] no, stop here

and refer to manual for further instructions

Credibility assessment

1: Is the analysis of effect modification based on comparison within rather than between trials?

[**X**] Completely between [ ] Mostly between or unclear [ ] Mostly within [ ] Completely within

Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.

Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information

Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information

All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g., meta-analysis of interactions

Comment:

2: For within-trial comparisons, is the effect modification similar from trial to trial? [**X**] Not applicable: no or one within-RCT comparison

[ ] Definitely not similar

Effect modification reported for two or more trials and clearly different directions

[ ] Probably not similar or unclear

Effect modification not reported for individual trials or too imprecise to tell

[ ] Mostly similar

Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude

[ ] Definitely similar

Effect modification reported for two or more trials, similar in direction, only some differences in magnitude

Comment:

3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison

[ ] Very small

1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression

[**X**] Rather small or unclear

3-4 in smallest subgroup; 6-10 in continuous meta-regression

[ ] Rather large

5-9 in smallest subgroup; 11 to 15 in continuous meta-regression

[ ] Large

10 or more in smallest subgroup; more than 15 in continuous meta-regression

Comment:

4: Was the direction of effect modification correctly hypothesized a priori?

[ ] Definitely no

Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible

[ ] Probably no or unclear

Vague hypothesis or hypothesized direction unclear

[ ] Probably yes

No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification

[**X**] Definitely yes

Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale

Comment:

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[ ] Chance a very likely explanation

Interaction or meta-regression p-value >0.05

[ ] Chance a likely explanation or unclear

Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable

[**X**] Chance may not explain

Interaction or meta-regression p-value ≤0.01 and >0.005

[ ] Chance an unlikely explanation

Interaction or meta-regression p-value ≤0.005

Comment:

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no

Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis

[ ] Probably no or unclear

No mention of number or 4-10 effect modifiers tested and number not considered in analysis

[ ] Probably yes

No protocol available but unequivocal statement of 3 or fewer effect modifiers tested

[**X**] Definitely yes

Protocol available and 3 or fewer effect modifiers tested or number considered in analysis

Comment:

7: Did the authors use a random effects model?

[ ] Definitely no

Fixed (or common) effect or fixed effects model explicitly stated

[ ] Probably no or unclear

Probably fixed effect(s) model

[ ] Probably yes

Probably random (or mixed) effects

[**X**] Definitely yes

Random (or mixed) effects explicitly stated

Comment:

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [**X**] not applicable: not continuous

[ ] Definitely no

Analysis based on exploratory cut point(s), e.g., picking cut point associated with highest interaction p-value

[ ] Probably no or unclear

Analysis based on cut point(s) of unclear origin

[ ] Probably yes

Analysis based on pre-specified cut point(s), e.g., suggested by prior RCT

[ ] Definitely yes

Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship

Comment:

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9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) [**X**] not applicable

[ ] Yes, probably decrease

[ ] Yes, probably increase

Comment:

10: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably decrease credibility or unclear à very low
- Two or more responses definitely decrease credibility à maximum usually low even if all other responses satisfy credibility criteria
- One response definitely decreases credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably decrease credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably decrease credibility à high very likely

Place a mark on the continuous line (or type “x” in editable version)

		X	
Very low credibility	**Low credibility**	**Moderate credibility**	**High credibility**
Very likely no effect modification Use overall effect for each subgroup	Likely no effect modification Use overall effect for each subgroup but note remaining uncertainty	Likely effect modification Use separate effects for each subgroup but note remaining uncertainty	Very likely effect modification Use separate effects for each subgroup

Comment:

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN)

in meta-analyses of randomized controlled trials *Version 1.0* ***EVENTOS ADVERSOS SUBGRUPO TERAPIA ABIERTA VS FIJA***

Quick instructions

- Synonyms for effect modification include subgroup effect, interaction, and moderation
- The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier
- Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
- Completely unclear goes under probably reduced credibility
- It is helpful to provide a supporting comment or quotation under each question

- Whether an effect modification is patient-important is not part of the credibility assessment
- The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s): -

If available, protocol reference(s): -

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up): eventos adversos

State a single effect measure of interest (e.g., relative or absolute risk difference): risk ratio

State a single potential effect modifier of interest (e.g., age or comorbidity): terapia abierta vs fija

Was the potential effect modifier measured before or at randomization? [**X**] yes, continue [ ] no, stop here and refer to manual for further instructions

Credibility assessment

1: Is the analysis of effect modification based on comparison within rather than between trials?

[**X**] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.	*Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information*	*Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information*	*All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g., meta-analysis of interactions*

Comment:

2: For within-trial comparisons, is the effect modification similar from trial to trial? [**X**] Not applicable: no or one within-RCT comparison

[ ] Definitely not similar	[ ] Probably not similar or unclear	[ ] Mostly similar	[ ] Definitely similar
Effect modification reported for two or more trials and clearly different directions	*Effect modification not reported for individual trials or too imprecise to tell*	*Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude*	*Effect modification reported for two or more trials, similar in direction, only some differences in magnitude*

Comment:

3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison

[ ] Very small	[**X**] Rather small or unclear	[ ] Rather large	[ ] Large
1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression	*3-4 in smallest subgroup; 6-10 in continuous meta-regression*	*5-9 in smallest subgroup; 11 to 15 in continuous meta-regression*	*10 or more in smallest subgroup; more than 15 in continuous meta-regression*

Comment:

4: Was the direction of effect modification correctly hypothesized a priori?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes
Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	*Vague hypothesis or hypothesized direction unclear*	*No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification*	*Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale*

Comment:

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[ ] Chance a very likely explanation	[ ] Chance a likely explanation or unclear	[**X**] Chance may not explain	[ ] Chance an unlikely explanation
Interaction or meta-regression p-value >0.05	*Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable*	*Interaction or meta-regression p-value ≤0.01 and >0.005*	*Interaction or meta-regression p-value ≤0.005*

Comment:

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes
Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis	*No mention of number or 4-10 effect modifiers tested and number not considered in analysis*	*No protocol available but unequivocal statement of 3 or fewer effect modifiers tested*	*Protocol available and 3 or fewer effect modifiers tested or number considered in analysis*

Comment:

7: Did the authors use a random effects model?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes
Fixed (or common) effect or fixed effects model explicitly stated	*Probably fixed effect(s) model*	*Probably random (or mixed) effects*	*Random (or mixed) effects explicitly stated*

Comment:

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [**X**] not applicable: not continuous

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Analysis based on exploratory cut point(s), e.g., picking cut point associated with highest interaction p-value	*Analysis based on cut point(s) of unclear origin*	*Analysis based on pre-specified cut point(s), e.g., suggested by prior RCT*	*Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship*

Comment:

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9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) [**X**] not applicable

	[ ] Yes, probably decrease	[ ] Yes, probably increase	

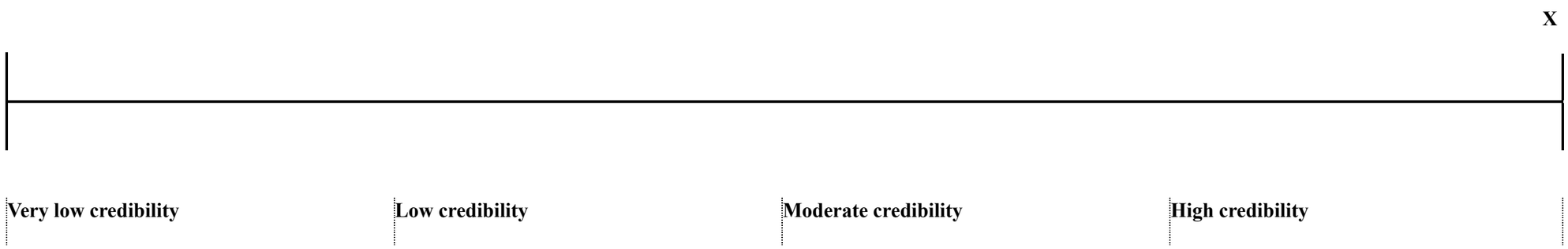
Comment:

10: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably decrease credibility or unclear à very low
- Two or more responses definitely decrease credibility à maximum usually low even if all other responses satisfy credibility criteria
- One response definitely decreases credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably decrease credibility à maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably decrease credibility à high very likely

Place a mark on the continuous line (or type “x” in editable version)



Use overall effect for each subgroup

Use overall effect for each subgroup but note remaining uncertainty

Use separate effects for each subgroup but note remaining uncertainty

Use separate effects for each subgroup

Comment:

Material suplementario 8. Análisis de sensibilidad.

Figura 1. Análisis de sensibilidad para el desenlace exacerbaciones entre estudios de alto riesgo vs bajo riesgo de sesgo

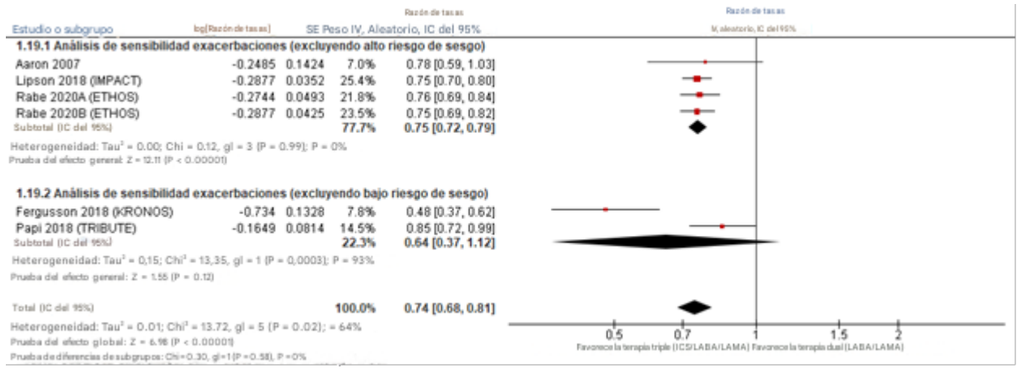


Figura 2. Análisis de sensibilidad para el desenlace neumonía entre estudios de alto riesgo vs bajo riesgo de sesgo

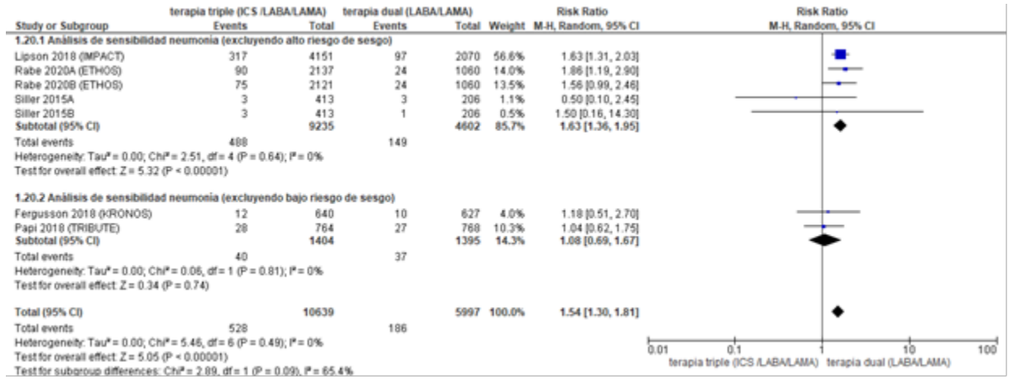


Figura 3. Análisis de sensibilidad para el desenlace mortalidad entre estudios de alto riesgo vs bajo riesgo de sesgo

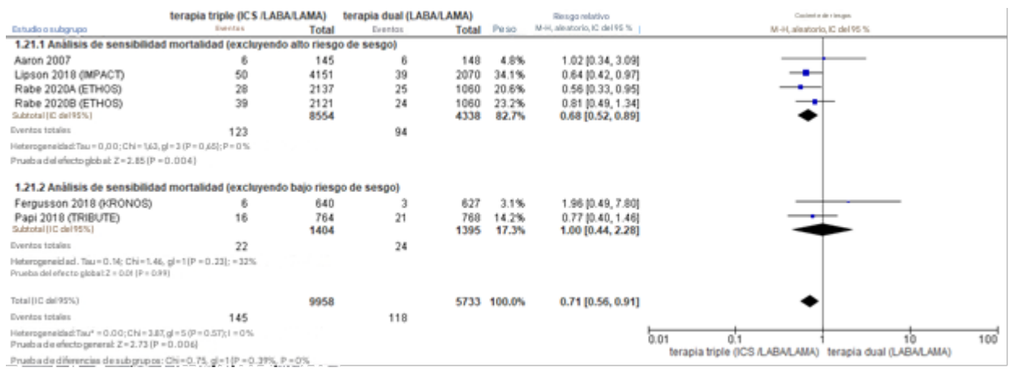
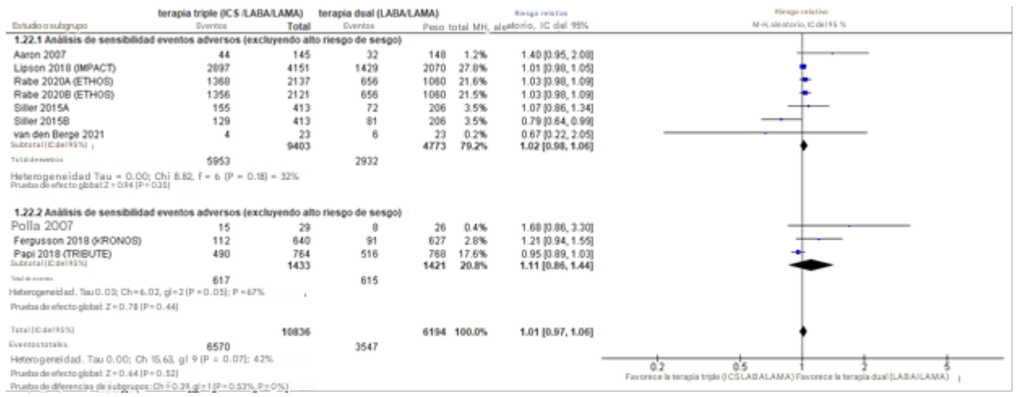


Figura 4. Análisis de sensibilidad para el desenlace eventos adversos entre estudios de alto riesgo vs bajo riesgo de sesgo



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