¿Qué nos hemos perdido en los **últimos meses**?

SESIÓN DE ACTUALIZACIÓN
MARTES 21 DE OCTUBRE DE 2021

SESIÓN CLÍNICA
Servicio de Medicina Interna
Consorcio Hospital General Universitario de Valencia

Dr. David Rodrigo Domínguez | R3 Medicina Interna
Dra. Victoria Lobo Antuña | R2 Medicina Interna

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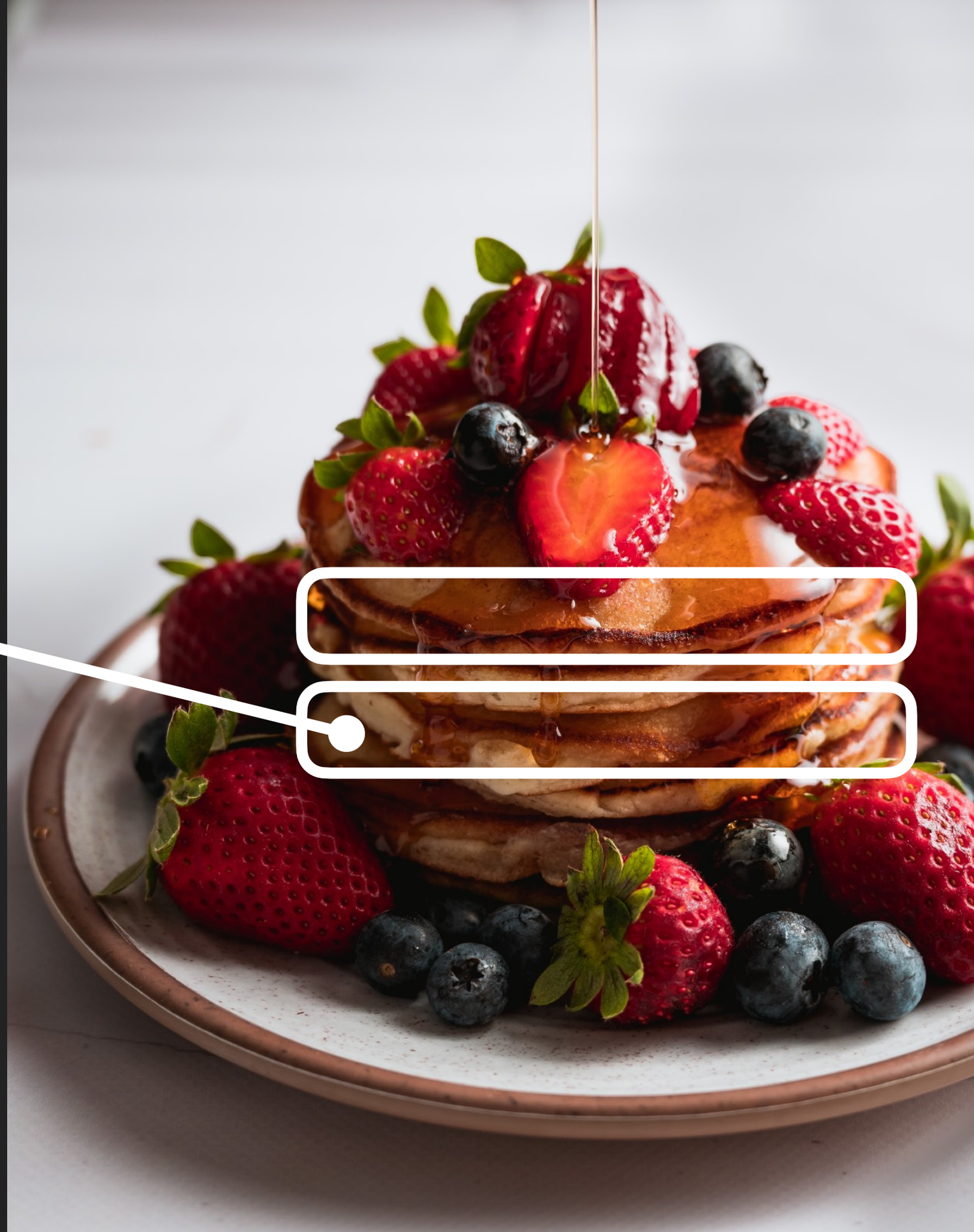

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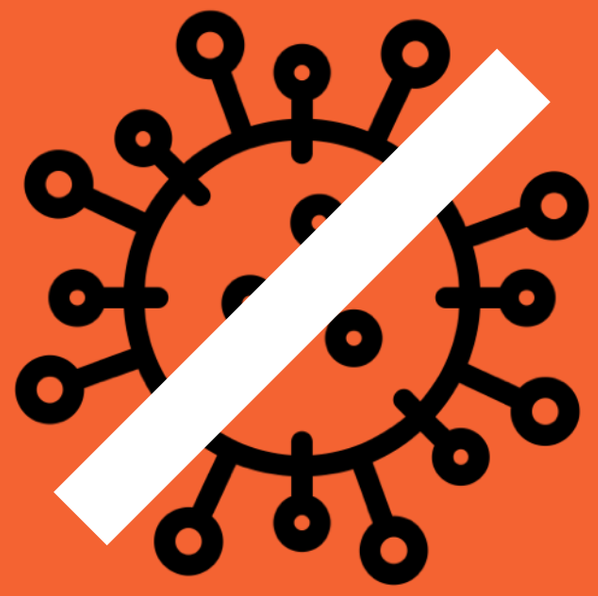

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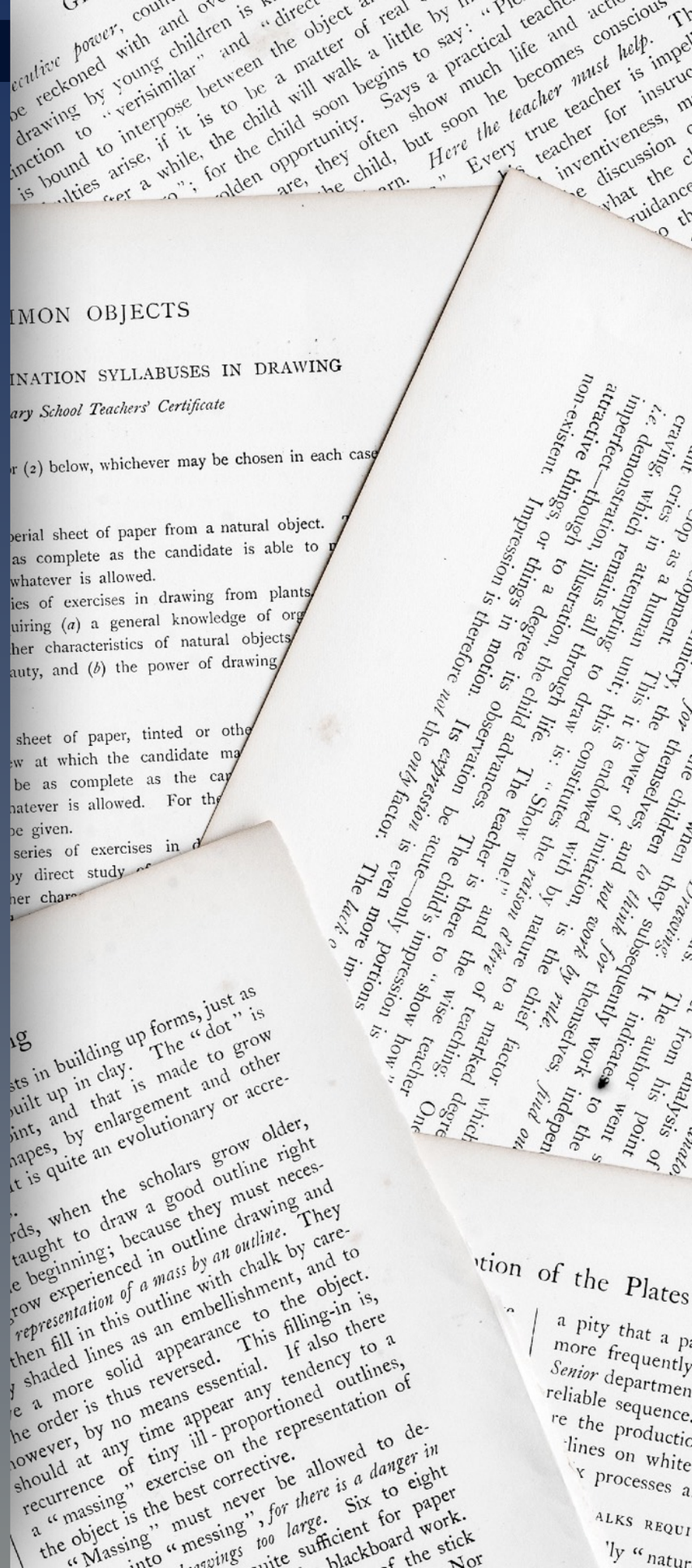
Artículos principales



ARTÍCULO PRINCIPAL

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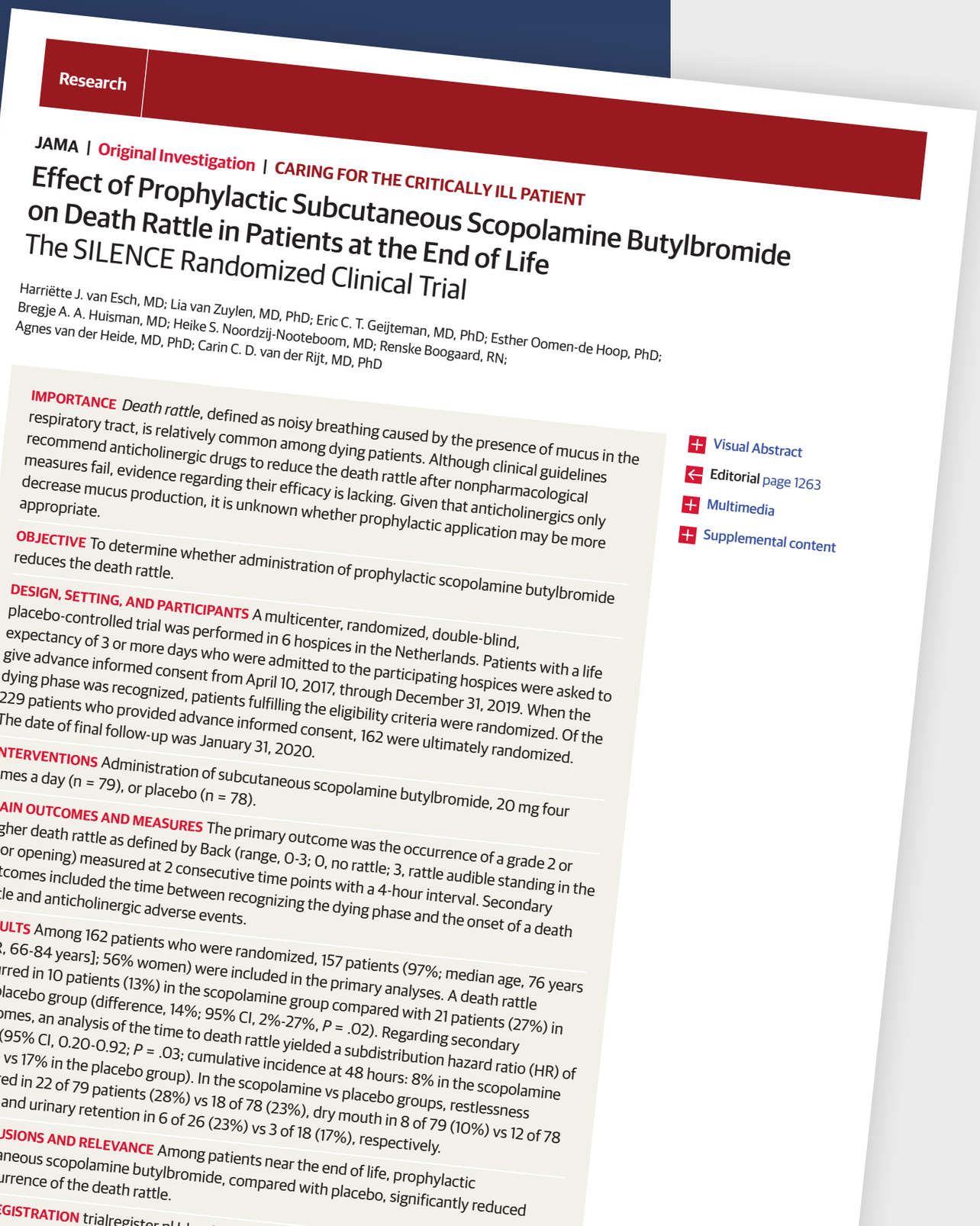

Research

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Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life
The SILENCE Randomized Clinical Trial

Harriëtte J. van Esch, MD; Lia van Zuylen, MD, PhD; Eric C. T. Geijteman, MD, PhD; Esther Oomen-de Hoop, PhD; Bregje A. A. Huisman, MD; Heike S. Noordzij-Nooteboom, MD; Renske Boogaard, RN; Agnes van der Heide, MD, PhD; Carin C. D. van der Rijt, MD, PhD

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CONCLUSIONS AND RELEVANCE Among patients near the end of life, prophylactic subcutaneous scopolamine butylbromide, compared with placebo, significantly reduced the occurrence of the death rattle.

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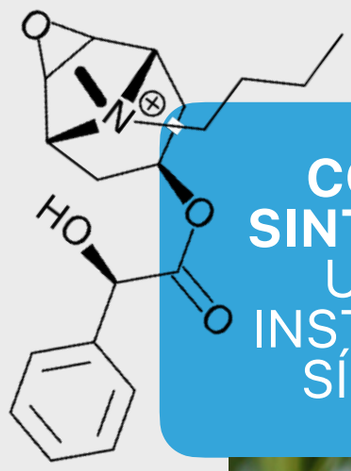
Background

- Frecuencia de los estertores (death rattle): 12%-92%
- Medidas:
  - No farmacológicas:
    - Físicas
    - Tranquilizar Familiares
  - Medidas Farmacológicas
- No evidencia



CONTROL SINTOMÁTICO UNA VEZ INSTAURADOS SÍNTOMAS

Likar R, Molnar M, Rupacher E. et al. A clinical study examining the efficacy of scopolaminehydrobromide in patients with death rattle (a randomized, double-blind, placebo-controlled study). Article in German. Zeitschrift fuer Palliativmedizin. 2002;3:15-19.

Heisler M, Hamilton G, Abbott A, Chengalaram A, Koceja T, Gerkin R. Randomized double-blind trial of sublingual atropine vs placebo for the management of death rattle.J Pain Symptom Manage. 2013;45(1):14-22.

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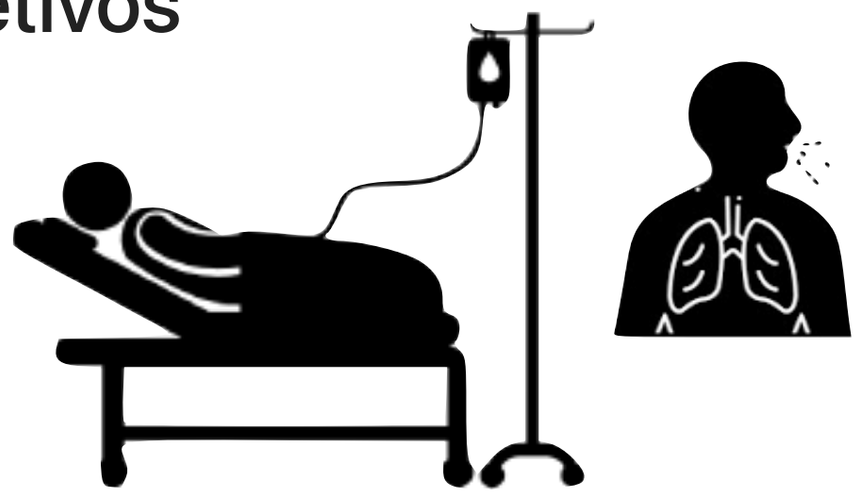
Objetivos



- **SILENCE** study → Determinar si el uso de escopolamina **profiláctica** reduce estertores

- Variables
  - Aparición **estertores grado ≥ 2**
  - 2as

    tiempo de aparición de estertores

    tiempo aparición efectos adversos

- *Exploratory end points*
  - tiempo entre fase de muerte y muerte
  - uso de sedantes y otros fármacos.

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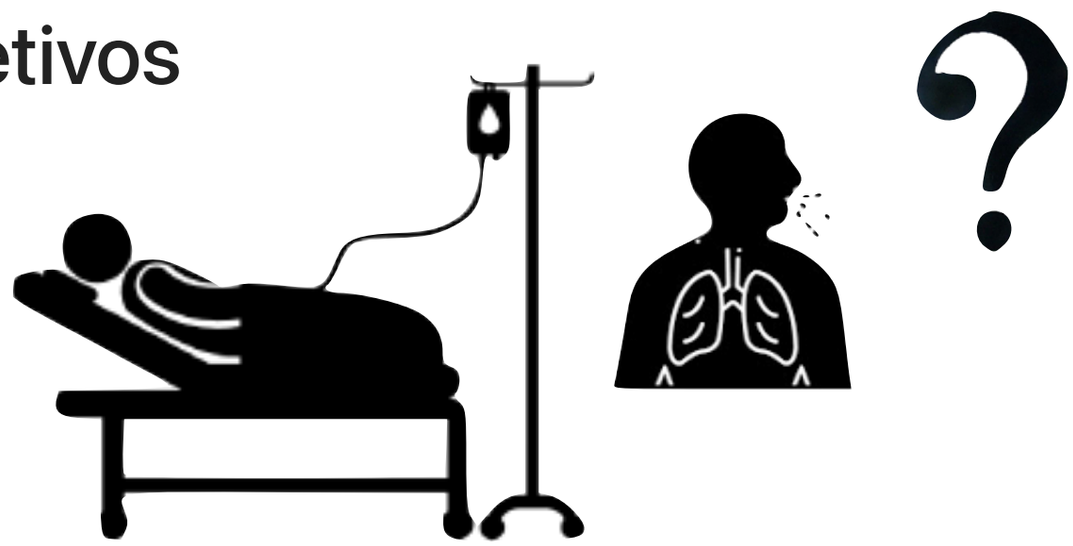

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Métodos

- Estudio **prospectivo**, multicéntrico, randomizado, doble ciego y controlado con placebo.
- Abril 2017 – Diciembre 2019
- **Criterios**:

✓ Esperanza de vida de al menos 3 días
✓ Ingreso en un hospicio hasta la muerte
✓ Capaz de comprender la información

✗ Traqueotomía o cánula traqueal
✗ Uso de anticolinérgicos sistémicos u octreotida
✗ Infección respiratoria activa.

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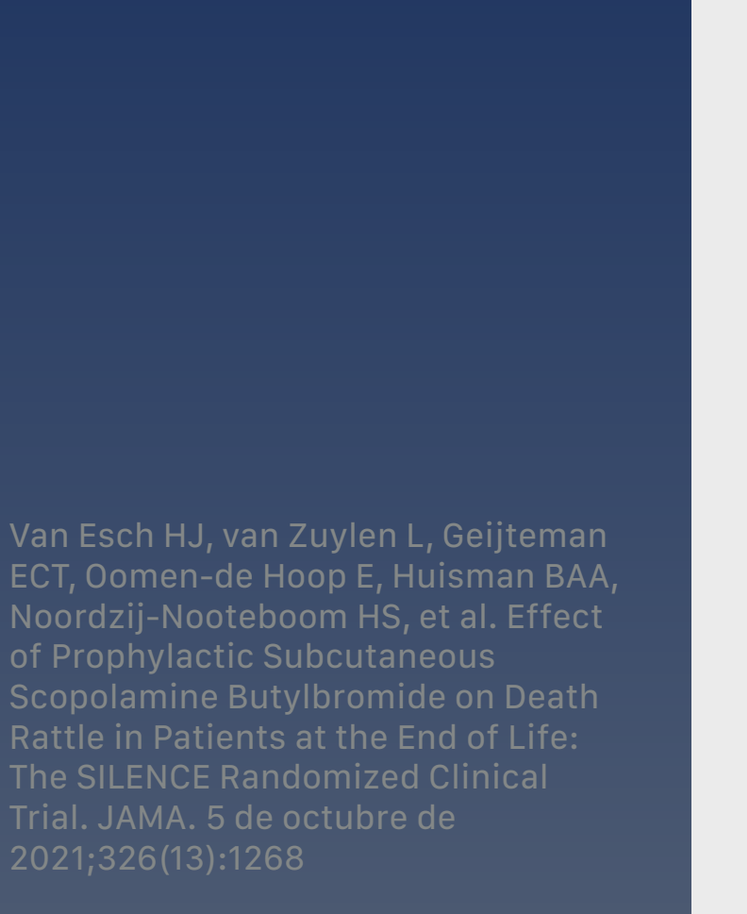

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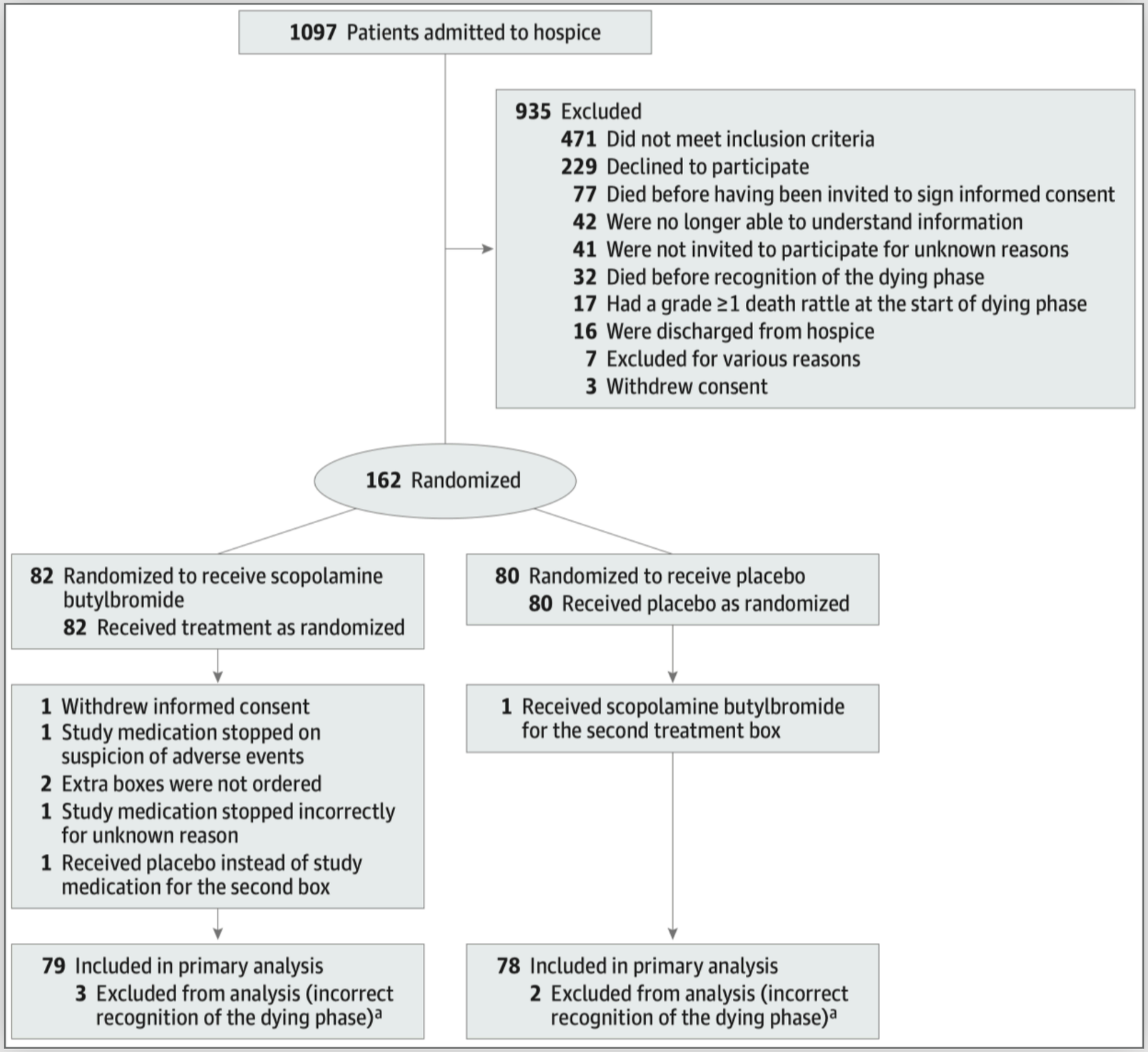


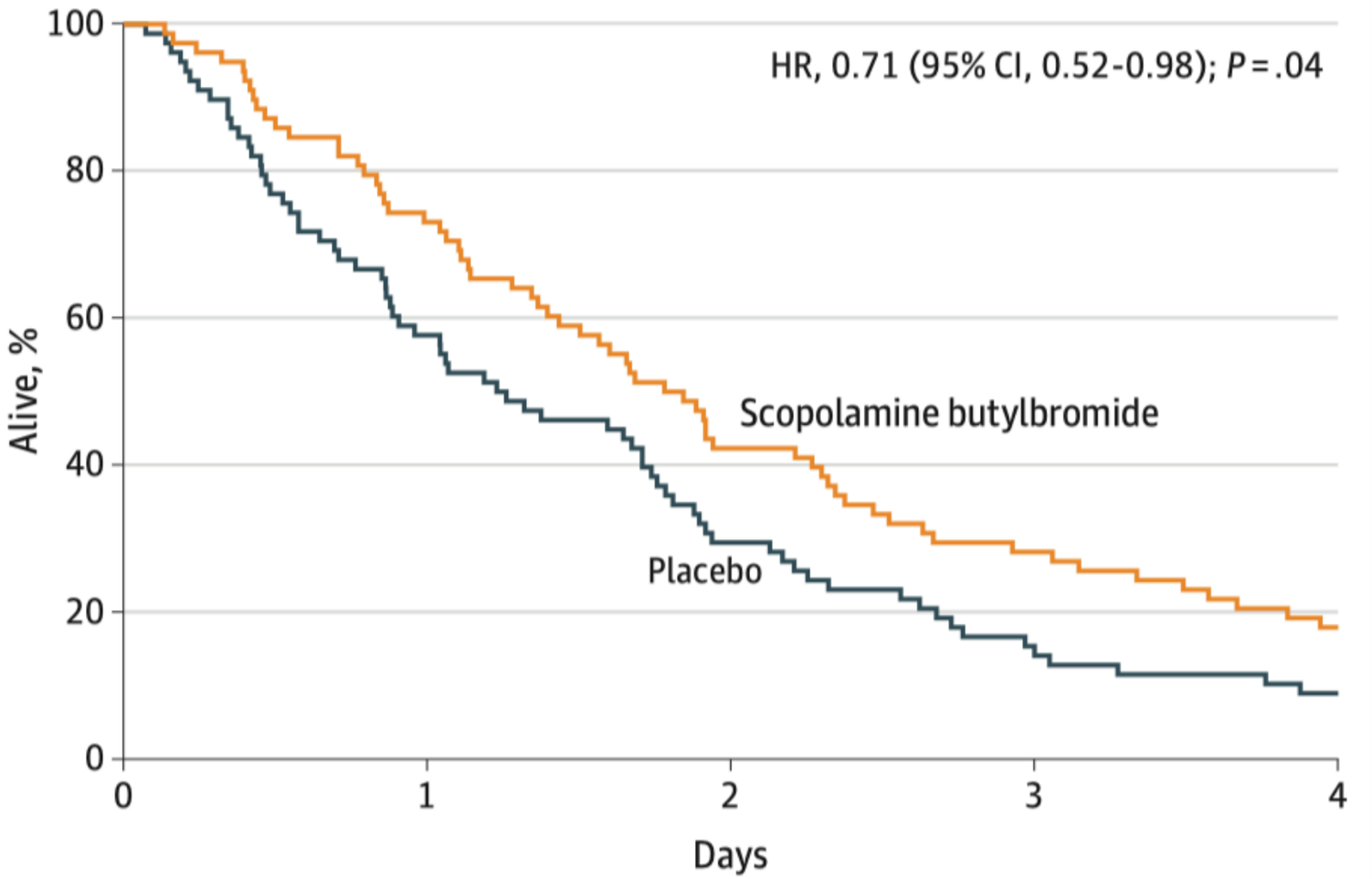
Resultados

Table 2. Summary of the Primary, Secondary, and Exploratory Outcomes in the Study of Scopolamine Butylbromide for Death Rattle

	No. (%)		Differences between percentages (95% CI), %[a]	*P* value	Cumulative occurrence at 48 h[b]			
	Scopolamine butylbromide (n = 79)	Placebo (n = 78)			Scopolamine butylbromide, %	Placebo, %	Sudistribution HR (95% CI)[c]	*P* value
Primary outcome								
Death rattle grade ≥2								
2 Time points	10 (13)	21 (27)	14 (2 to 27)	.02				
1 Time point not followed by improvement[d]	15 (19)	29 (37)	18 (4 to 32)	.01				
Secondary outcomes								
Time from the recognition of the dying phase to death rattle								
2 Time points					8	17	0.44 (0.20 to 0.92)	.03
1 Time point without improvement[d]					8	22	0.41 (0.22 to 0.78)	.006
Adverse events								
Restlessness								
CPD[e]	22 (28)	18 (23)	-5 (-18 to 9)		23	19	1.25 (0.67 to 2.32)	.48
VICS[f]	7 (9)	7 (9)	0 (-9 to 9)		7	7	0.99 (0.35 to 2.81)	.98
Dry mouth[g]	8 (10)	12 (15)	5 (-5 to 16)		8	12	0.65 (0.27 to 1.57)	.34
Urinary retention[h]	6/26 (23)	3/18 (17)	-6 (-30 to 17)		20	15	1.45 (0.37 to 5.69)	.60

Resultados

Figure 3. Time Until Death



No. at risk				
Placebo				
78	45	23	12	7
Scopolamine butylbromide				
78	57	33	22	14

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Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life
The SILENCE Randomized Clinical Trial

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Visual Abstract
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Multimedia
Supplemental content

IMPORTANCE *Death rattle*, defined as noisy breathing caused by the presence of mucus in the respiratory tract, is relatively common among dying patients. Although clinical guidelines recommend anticholinergic drugs to reduce the death rattle after nonpharmacological measures fail, evidence regarding their efficacy is lacking. Given that anticholinergics only decrease mucus production, it is unknown whether prophylactic application may be more appropriate.

OBJECTIVE To determine whether administration of prophylactic scopolamine butylbromide reduces the death rattle.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, randomized, double-blind, placebo-controlled trial was performed in 6 hospices in the Netherlands. Patients with a life expectancy of 3 or more days who were admitted to the participating hospices were asked to give advance informed consent from April 10, 2017, through December 31, 2019. When the dying phase was recognized, patients fulfilling the eligibility criteria were randomized. Of the 229 patients who provided advance informed consent, 162 were ultimately randomized. The date of final follow-up was January 31, 2020.

INTERVENTIONS Administration of subcutaneous scopolamine butylbromide, 20 mg four times a day (n = 79), or placebo (n = 78).

MAIN OUTCOMES AND MEASURES The primary outcome was the occurrence of a grade 2 or higher death rattle as defined by Back (range, 0-3; 0, no rattle; 3, rattle audible standing in the door opening) measured at 2 consecutive time points with a 4-hour interval. Secondary outcomes included the time between recognizing the dying phase and the onset of a death rattle and anticholinergic adverse events.

RESULTS Among 162 patients who were randomized, 157 patients (97%; median age, 76 years [IQR, 66-84 years]; 56% women) were included in the primary analyses. A death rattle occurred in 10 patients (13%) in the scopolamine group compared with 21 patients (27%) in the placebo group (difference, 14%; 95% CI, 2%-27%, $P = .02$). Regarding secondary outcomes, an analysis of the time to death rattle yielded a subdistribution hazard ratio (HR) of 0.44 (95% CI, 0.20-0.92; $P = .03$; cumulative incidence at 48 hours: 8% in the scopolamine group vs 17% in the placebo group). In the scopolamine vs placebo groups, restlessness occurred in 22 of 79 patients (28%) vs 18 of 78 (23%), dry mouth in
(15%), and urinary retention in 6 of

Conclusiones

1. **Reducción significativa** de estertores
2. **No aumento de efectos adversos**
3. **Duración de proceso de fallecimiento mayor**

- Limitaciones del estudio:
  - Baja participación en el estudio por limitaciones inclusión
  - Placebo con mayor % de patología respiratoria → *post hoc analysis*
  - Exclusión infecciones respiratorias
  - Administración subcutánea no siempre es posible

ARTÍCULO PRINCIPAL

Buetti N, Abbas M, Pittet D, de Kraker MEA, Teixeira D, Chraiti M-N, et al. Comparison of Routine Replacement With Clinically Indicated Replacement of Peripheral Intravenous Catheters. JAMA Intern Med [Internet]. 17 de septiembre de 2021 [citado 13 de octubre de 2021]; Disponible en: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2784458

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Corresponding Author: Niccolò Buetti, MD, MSc, Infection Control Program and

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Background

RECAMBIO DE CATÉTERES VENOSOS PERIFÉRICOS

¿INDICACIÓN CLÍNICA O RUTINARIAMENTE?

NO EXISTE UNA RECOMENDACIÓN FORMAL

US Centers for Disease Control and Prevention. CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections. Updated 2017.

Webster J, Osborne S, Rickard CM, Marsh N. Clinically-indicated replacement versus routine replacement of peripheral venous catheters. Cochrane Database Syst Rev. 2019;1:CD007798

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Objetivos

- Investigar la incidencia de infecciones sanguíneas asociadas a catéter venoso periférico tras cambiar la política de recambio rutinario cada 96 horas a recambio clínicamente indicado.

- Infección sanguínea asociada a cateter venoso periférico
  - Inserción → 48h tras retirada
  - Hemocultivo positivo = cultivo punta de catéter
  - Resolución sintomática tras retirada sin otro foco infeccioso

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Métodos

ESTUDIO DE COHORTES

Hospital Universitario de Ginebra

1 Enero 2016 → 29 Febrero 2020

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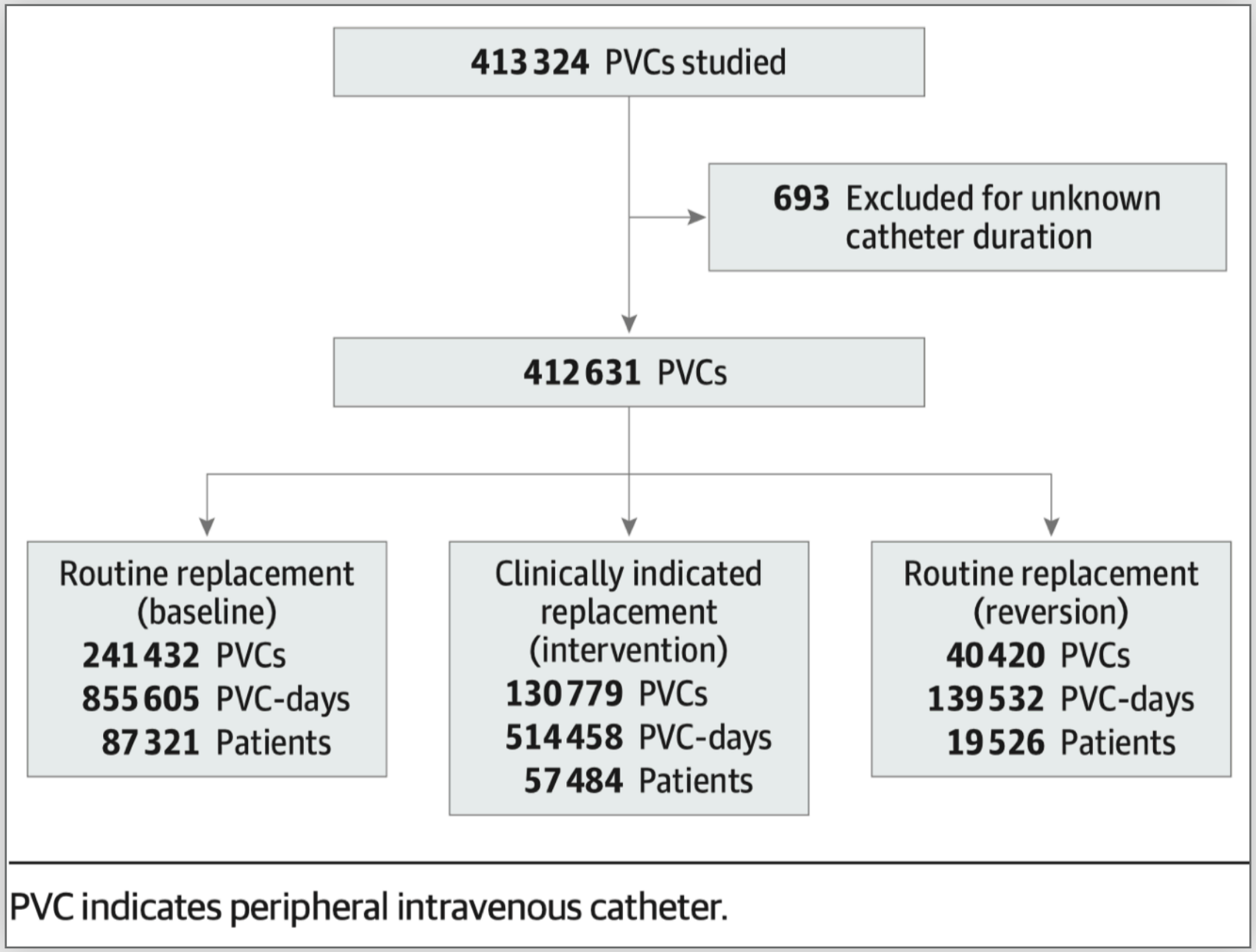
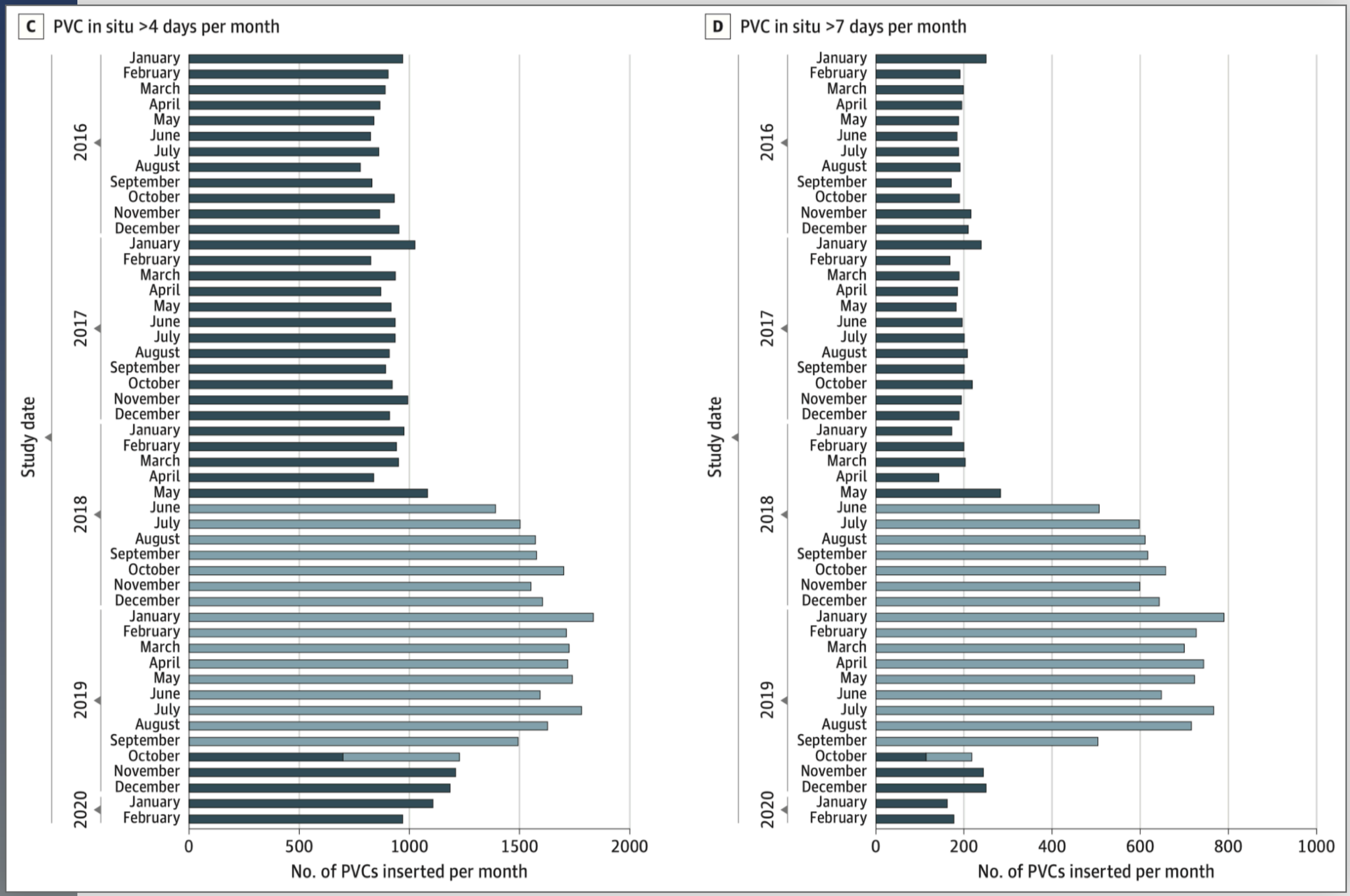


Resultados


C
PVC in situ >4 days per month
D
PVC in situ >7 days per month
Study date
2016
2017
2018
2019
2020
January
February
March
April
May
June
July
August
September
October
November
December
0
500
1000
1500
2000
No. of PVCs inserted per month
0
200
400
600
800
1000
No. of PVCs inserted per month

Resultados

Table. Characteristics of the Study Population by Study Period[a]

Characteristic	Baseline	Intervention	Reversion	*P* value
Sex[b]				
Female	47 114 (54.0)	31 259 (54.4)	10 555 (54.1)	.28
Male	40 207 (46.0)	26 225 (45.6)	8971 (45.9)	
Age, median (IQR)[b]	51 (33-71)	52 (33-72)	55 (35-74)	<.001
ICU admission	7120 (2.9)	2782 (2.1)	732 (1.8)	<.001
No. of catheters per patient, median (IQR)[c]	1 (1-2)	1 (1-2)	1 (1-2)	<.001
Dwell time, d				
>4	26 372 (10.9)	26 656 (20.4)	5170 (12.8)	<.001
>7	5745 (2.4)	10656 (8.1)	947 (2.3)	<.001
Insertion site				
Forearm	130 877 (54.2)	50 584 (38.7)	15 276 (37.8)	<.001
Arm	6930 (2.9)	2105 (1.6)	675 (1.7)	
Elbow	12 247 (5.1)	21 508 (16.4)	7530 (18.6)	
Hand	69 615 (28.8)	30 930 (23.7)	9141 (22.6)	
Other	6018 (2.5)	2636 (2.0)	771 (1.9)	
Wrist	15 745 (6.5)	23 016 (17.6)	7027 (17.4)	
Operator				
Out-of-hospital	18 909 (7.8)	10 573 (8.1)	2786 (6.9)	<.001
In-hospital	222 523 (92.2)	120 206 (91.9)	37 634 (93.1)	
PVC-BSI	11 (<0.1)	46 (<0.1)	4 (<0.1)	<.001

Infecciones asociadas a catéter:

Baseline: 11

intervention: 46

Reversion: 4

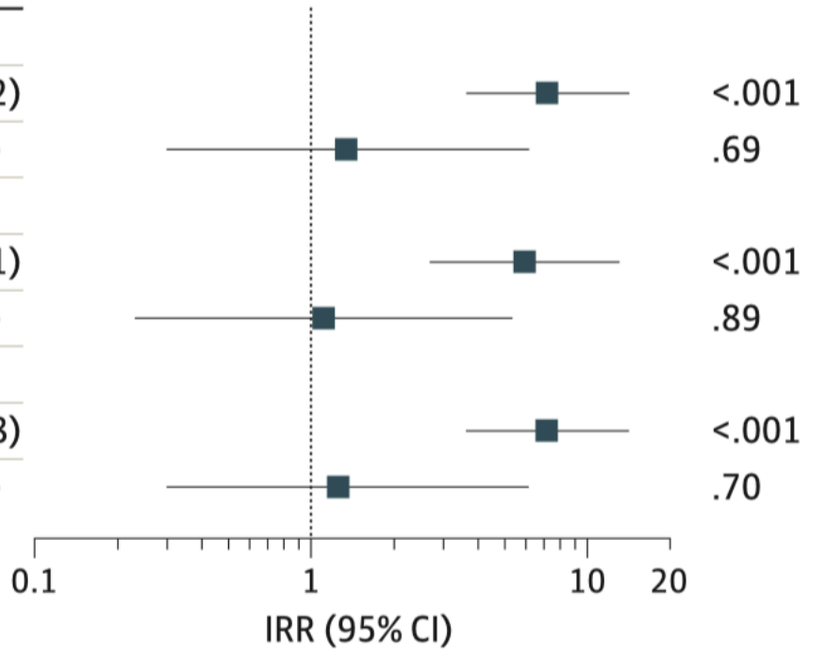
≤ 4 DÍAS → 12

> 4 DÍAS → 49

Resultados

Figure 4. Incidence Rate Ratios (IRRs) of Peripheral Venous Catheter–Associated Bloodstream Infections During the Intervention and Reversion Periods

Source	IRR (95% CI)	*P* value
Main analysis		
Intervention period (clinically indicated replacement)	7.20 (3.65-14.22)	<.001
Reversion period (routine replacement)	1.35 (0.30-6.17)	.69
Sensitivity analysis excluding 2016		
Intervention period (clinically indicated replacement)	5.94 (2.69-13.11)	<.001
Reversion period (routine replacement)	1.12 (0.23-5.37)	.89
Sensitivity analysis excluding children		
Intervention period (clinically indicated replacement)	7.18 (3.64-14.18)	<.001
Reversion period (routine replacement)	1.35 (0.30-6.15)	.70



The baseline period (routine replacement) served as the reference.

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Supplemental content

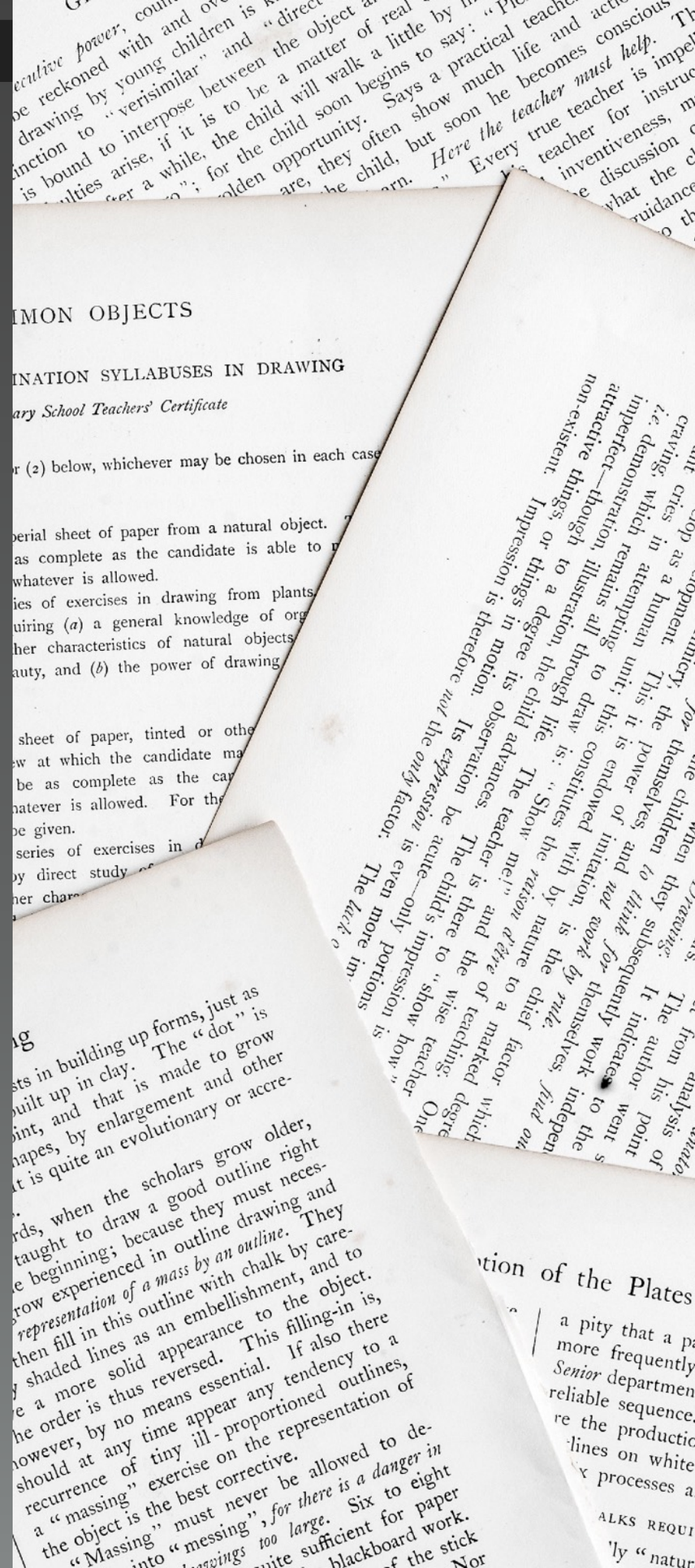
Author Affiliations: Infection Control Program and World Health Organization Collaborating Centre on Patient Safety, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland (Buetti, Abbas, Pittet, de Kraker, Teixeira, Chraiti, Sauvan, Sauser, Harbarth, Zingg); Unité Mixte de Recherche (*UMR*) *1137, Infection, Antimicrobials, Modelling, Evolution (IAME), INSERM, Université* de Paris, Paris,

Conclusiones

1. El recambio bajo indicación clínica parece asociarse a un mayor riesgo de infecciones sanguíneas asociadas a catéter comparado con el recambio rutinario.
2. Infección asociada a CVP es un evento raro pero relevante.

- Limitaciones del estudio:
  - Es un estudio observacional
  - Zonas de inserción cambiaron en los intervalos de tiempo
  - Periodo de reversión corto

Microrresúmenes



MICRORRESUMEN

Es mejor añadir **metronizazol** a la enfermedad pélvica inflamatoria

Wiesenfeld HC, Meyn LA, Darville T, Macio IS, Hillier SL. A Randomized Controlled Trial of Ceftriaxone and Doxycycline, With or Without Metronidazole, for the Treatment of Acute Pelvic Inflammatory Disease. Clin Infect Dis. 2021 Apr 8;72(7):1181-1189. doi: 10.1093/cid/ciaa101. PMID: 32052831; PMCID: PMC8028096.

- Ensayo de 233 mujeres con EPI leve a moderada que fueron tratadas con ceftriaxona y doxiciclina y asignadas aleatoriamente a recibir adicionalmente **metronidazol 500 mg dos veces al día** o placebo **durante 14 días**.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

A Randomized Controlled Trial of Ceftriaxone and Doxycycline, With or Without Metronidazole, for the Treatment of Acute Pelvic Inflammatory Disease

Harold C. Wiesenfeld,[1,2] Leslie A. Meyn,[1,2] Toni Darville,[3] Ingrid S. Macio,[2] and Sharon L. Hillier[1,2]

[1]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, [2]Magee-Womens Research Institute, Pittsburgh, Pennsylvania, USA, and [3]Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

(See the Editorial Commentary by Mitchell on pages 1190–91.)

Background. Anaerobic organisms are important pathogens in acute pelvic inflammatory disease (PID). The currently recommended PID regimen of a single dose of ceftriaxone and doxycycline for 14 days has limited anaerobic activity. The need for broader anaerobic coverage is unknown and concerns have been raised about metronidazole tolerability.

Methods. We conducted a randomized, double-blind, placebo-controlled trial comparing ceftriaxone 250 mg intramuscular single dose and doxycycline for 14 days, with or without 14 days of metronidazole in women with acute PID. The primary outcome was clinical improvement at 3 days following enrollment. Additional outcomes at 30 days following treatment were the presence of anaerobic organisms in the endometrium, clinical cure (absence of fever and reduction in tenderness), adherence, and tolerability.

Results. We enrolled 233 women (116 to metronidazole and 117 to placebo). Clinical improvement at 3 days was similar between the 2 groups. At 30 days following treatment, anaerobic organisms were less frequently recovered from the endometrium in women treated with metronidazole than placebo (8% vs 21%, $P < .05$) and cervical *Mycoplasma genitalium* was reduced (4% vs 14%, $P < .05$). Pelvic tenderness was also less common among women receiving metronidazole (9% vs 20%, $P < .05$). Adverse events and adherence were similar in each treatment group.

Conclusions. In women treated for acute PID, the addition of metronidazole to ceftriaxone and doxycycline was well tolerated and resulted in reduced endometrial anaerobes, decreased *M. genitalium*, and reduced pelvic tenderness compared to ceftriaxone and doxycycline. Metronidazole should be routinely added to ceftriaxone and doxycycline for the treatment of women with acute PID.

Clinical Trials Registration. NCT01160640.

Keywords. pelvic inflammatory disease; anaerobes; metronidazole.

Pelvic inflammatory disease (PID) results from ascension of microorganisms from the vagina or endocervix to the endometrium and fallopian tubes. Organisms recognized to cause PID and its sequelae include *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Mycoplasma genitalium* has been associated with endometritis but its association with infertility is less certain [1]. Facultative and anaerobic microbes associated with vaginal dysbiosis have been associated with endometrial and tubal infections and are recovered from the upper genital tract at higher

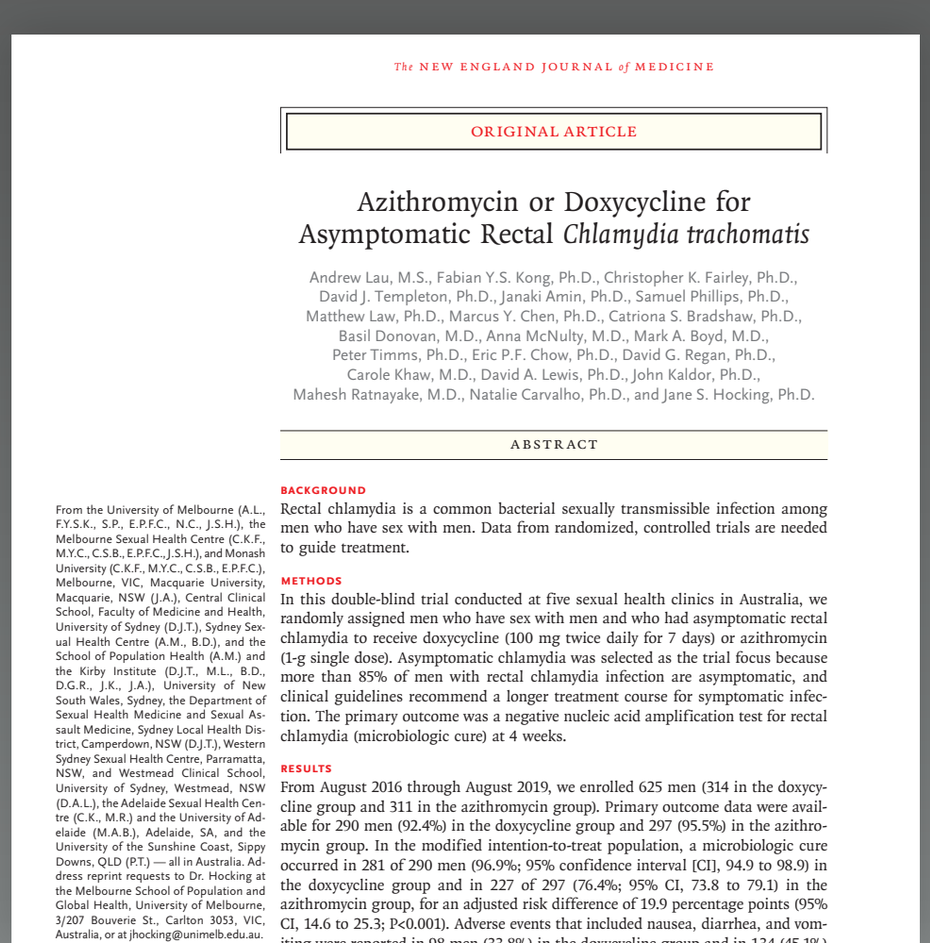
of PID [5]. This regimen is effective against *N. gonorrhoeae* and *C. trachomatis*, but has limited activity against anaerobic organisms. Despite the frequent recovery of anaerobic organisms in women with acute PID, the need for antimicrobial therapy with broader anaerobic coverage is unknown. This uncertainty is reflected in the CDC guidelines that list metronidazole as an optional addition to ceftriaxone and doxycycline, while the European guidelines recommend the addition of metronidazole [6]. However, a recent systematic review and meta-analysis of

- A los 30 días:
  - ✓ una **menor tasa de molestias pélvicas (9 vs 20%)**
  - ✓ una tendencia no significativa hacia una mayor tasa de curación (96 vs 90%).

MICRORRESUMEN

Doxiciclina es superior a azitromicina en la infección rectal asintomática por clamidia en HSH

Lau A, Kong FYS, Fairley CK, Templeton DJ, Amin J, Phillips S, et al. Azithromycin or Doxycycline for Asymptomatic Rectal Chlamydia trachomatis. N Engl J Med. 24 de junio de 2021;384(25):2418-27.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*

Andrew Lau, M.S., Fabian Y.S. Kong, Ph.D., Christopher K. Fairley, Ph.D., David J. Templeton, Ph.D., Janaki Amin, Ph.D., Samuel Phillips, Ph.D., Matthew Law, Ph.D., Marcus Y. Chen, Ph.D., Catriona S. Bradshaw, Ph.D., Basil Donovan, M.D., Anna McNulty, M.D., Mark A. Boyd, M.D., Peter Timms, Ph.D., Eric P.F. Chow, Ph.D., David G. Regan, Ph.D., Carole Khaw, M.D., David A. Lewis, Ph.D., John Kaldor, Ph.D., Mahesh Ratnayake, M.D., Natalie Carvalho, Ph.D., and Jane S. Hocking, Ph.D.

ABSTRACT

BACKGROUND

Rectal chlamydia is a common bacterial sexually transmissible infection among men who have sex with men. Data from randomized, controlled trials are needed to guide treatment.

METHODS

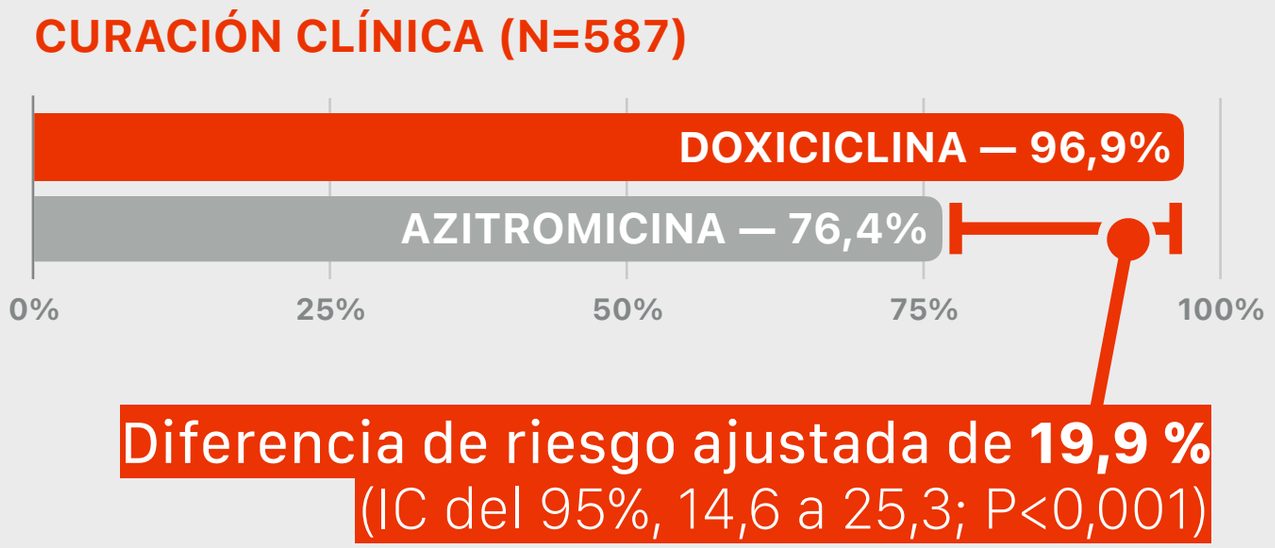
In this double-blind trial conducted at five sexual health clinics in Australia, we randomly assigned men who have sex with men and who had asymptomatic rectal chlamydia to receive doxycycline (100 mg twice daily for 7 days) or azithromycin (1-g single dose). Asymptomatic chlamydia was selected as the trial focus because more than 85% of men with rectal chlamydia infection are asymptomatic, and clinical guidelines recommend a longer treatment course for symptomatic infection. The primary outcome was a negative nucleic acid amplification test for rectal chlamydia (microbiologic cure) at 4 weeks.

RESULTS

From August 2016 through August 2019, we enrolled 625 men (314 in the doxycycline group and 311 in the azithromycin group). Primary outcome data were available for 290 men (92.4%) in the doxycycline group and 297 (95.5%) in the azithromycin group. In the modified intention-to-treat population, a microbiologic cure occurred in 281 of 290 men (96.9%; 95% confidence interval [CI], 94.9 to 98.9) in the doxycycline group and in 227 of 297 (76.4%; 95% CI, 73.8 to 79.1) in the azithromycin group, for an adjusted risk difference of 19.9 percentage points (95% CI, 14.6 to 25.3; P<0.001). Adverse events that included nausea, diarrhea, and vomiting were reported in 98 men (32.8%) in the doxycycline group and in 134 (45.1%)

From the University of Melbourne (A.L., F.Y.S.K., S.P., E.P.F.C., N.C., J.S.H.), the Melbourne Sexual Health Centre (C.K.F., M.Y.C., C.S.B., E.P.F.C., J.S.H.), and Monash University (C.K.F., M.Y.C., C.S.B., E.P.F.C.), Melbourne, VIC, Macquarie University, Macquarie, NSW (J.A.), Central Clinical School, Faculty of Medicine and Health, University of Sydney (D.J.T.), Sydney Sexual Health Centre (A.M., B.D.), and the School of Population Health (A.M.) and the Kirby Institute (D.J.T., M.L., B.D., D.G.R., J.K., J.A.), University of New South Wales, Sydney, the Department of Sexual Health Medicine and Sexual Assault Medicine, Sydney Local Health District, Camperdown, NSW (D.J.T.), Western Sydney Sexual Health Centre, Parramatta, NSW, and Westmead Clinical School, University of Sydney, Westmead, NSW (D.A.L.), the Adelaide Sexual Health Centre (C.K., M.R.) and the University of Adelaide (M.A.B.), Adelaide, SA, and the University of the Sunshine Coast, Sippy Downs, QLD (P.T.) — all in Australia. Address reprint requests to Dr. Hocking at the Melbourne School of Population and Global Health, University of Melbourne, 3/207 Bouverie St., Carlton 3053, VIC, Australia, or at jhocking@unimelb.edu.au.

- Respuesta clínica: PCR negativa de clamidia rectal a las 4 semanas.
- **Una pauta de 7 días de doxiciclina (100mg cada 12h) fue superior a una dosis única de azitromicina 1g** en el tratamiento de la infección rectal por clamidia entre los hombres que tienen relaciones sexuales con hombres.



MICRORRESUMEN

La antibioterapia **diferida** es segura y **eficaz** para la mayoría de infecciones respiratorias

Stuart B, Hounkpatin H, Becque T, Yao G, Zhu S, Alonso-Coello P, et al. Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis. BMJ. 28 de abril de 2021;n808

- **Revisión sistemática** y **metaanálisis** de datos de pacientes individuales procedentes de...
  - 9 ensayos controlados aleatorios y
  - 4 estudios observacionales
- 55 682 pacientes en total

RESEARCH

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Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis

Beth Stuart,[1] Hilda Hounkpatin,[1] Taeko Becque,[1] Guiqing Yao,[2] Shihua Zhu,[1] Pablo Alonso-Coello,[3] Attila Altiner,[4] Bruce Arroll,[5] Dankmar Böhning,[6] Jennifer Bostock,[7] Heiner C Bucher,[8] Jennifer Chao,[9] Mariam de la Poza,[10] Nick Francis,[1] David Gillespie,[11] Alastair D Hay,[12] Timothy Kenealy,[5] Christin Löffler,[4] David P McCormick,[13] Gemma Mas-Dalmau,[14] Laura Muñoz,[15] Kirsty Samuel,[16] Michael Moore,[1] Paul Little[1]

For numbered affiliations see end of the article.

Correspondence to: B Stuart Academic Unit of Primary Care, Population Sciences and Medical Education, Faculty of Medicine, University of Southampton, Southampton SO16 5ST, UK bls1@soton.ac.uk (ORCID 0000-0001-5432-7437)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;372:n808 http://dx.doi.org/10.1136/bmj.n808

Accepted: 15 March 2021

ABSTRACT

OBJECTIVE

To assess the overall effect of delayed antibiotic prescribing on average symptom severity for patients with respiratory tract infections in the community, and to identify any factors modifying this effect.

DESIGN

Systematic review and individual patient data meta-analysis.

DATA SOURCES

Cochrane Central Register of Controlled Trials, Ovid Medline, Ovid Embase, EBSCO CINAHL Plus, and Web of Science.

ELIGIBILITY CRITERIA FOR STUDY SELECTION

Randomised controlled trials and observational cohort studies in a community setting that allowed comparison between delayed versus no antibiotic prescribing, and delayed versus immediate antibiotic prescribing.

MAIN OUTCOME MEASURES

The primary outcome was the average symptom severity two to four days after the initial consultation measured on a seven item scale (ranging from normal to as bad as could be). Secondary outcomes were duration of illness after the initial consultation, complications resulting in admission to hospital or death, reconsultation with the same or worsening illness, and patient satisfaction rated on a Likert scale.

RESULTS

Data were obtained from nine randomised controlled trials and four observational studies, totalling 55 682 patients. No difference was found in follow-up symptom severity (seven point scale) for delayed versus immediate antibiotics (adjusted mean difference −0.003, 95% confidence interval −0.12 to 0.11) or delayed versus no antibiotics (0.02, −0.11 to 0.15). Symptom duration was slightly longer in those given delayed versus immediate antibiotics (11.4 *v* 10.9 days), but was similar for delayed versus no antibiotics. Complications resulting in hospital admission or death were lower with delayed versus no antibiotics (odds ratio 0.62, 95% confidence interval 0.30 to 1.27) and delayed versus immediate antibiotics (0.78, 0.53 to 1.13). A significant reduction in reconsultation rates (odds ratio 0.72, 95% confidence interval 0.60 to 0.87) and an increase in patient satisfaction (adjusted mean difference 0.09, 0.06 to 0.11) were observed in delayed versus no antibiotics. The effect of delayed versus immediate antibiotics and delayed versus no antibiotics was not modified by previous duration of illness, fever, comorbidity, or severity of symptoms. Children younger than 5 years had a slightly higher follow-up symptom severity with delayed antibiotics than with immediate antibiotics (adjusted mean difference 0.10, 95% confidence interval 0.03 to 0.18), but no increased severity was found in the older age group.

CONCLUSIONS

Delayed antibiotic prescribing is a safe and effective strategy for most patients, including those in higher risk subgroups. Delayed prescribing was associated

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No and age of participants*	Condition	Intervention and comparison group	Type of delay	S
716; 25.3 (17.0)	Sore throat	None, immediate, delayed	Prescription to be filled if symptoms did not start to settle after 3 days	+
315; 5.0 (2.8)	Acute otitis media	None, immediate, delayed	Prescription collected after 72 hours if child still not improving	+
129; 25.6 (23.0)	Common cold	Immediate, delayed	Prescription to be filled after 3 days if symptoms fail to improve	–
223; 2.7 (2.7)	Acute otitis media	None, delayed	No antibiotics unless returning with acute ear symptoms within 30 days	+
807; 39 (20.8)	Lower respiratory tract infection	None, immediate, delayed	Prescription to be filled if symptoms not resolved after 4 days	+
232; 5.1 (2.4)	Acute otitis media	None, delayed	Advised to fill prescription if symptoms did not resolve in 2-3 days	–
889; 31.0 (21.2)	Acute respiratory tract infection	None, delayed	Four types: recontact, postdated, collection, patient led	+
405; 44.9 (16.6)	Acute respiratory tract infection	None, immediate, delayed	Collection or patient led if symptoms did not start to improve after a few days	+
437; 6.3 (3.1)	Acute respiratory tract infection	None, immediate, delayed	Collection or patient led if symptoms did not start to improve after a few days	+
2690; 47.8 (16.3)	Cough or lower respiratory tract infection	None, immediate, delayed	Advised to fill if symptoms did not start to improve after 2-7 days	+
12 626; 34.0 (14.6)	Sore throat	None, immediate, delayed	Patient led	+
28 856; 51.7 (17.9)	Acute lower respiratory tract infection	None, immediate, delayed	Advised to fill if symptoms did not start to improve; median advised delay=3 days	–
8320; 3.9 (3.7)	Acute cough and respiratory tract infection	None, immediate, delayed	Advised to fill if symptoms did not start to improve; median advised delay=3 days	+
unavailable				
114; 7.5 (2.6); 7.8 (2.3)	Sore throat	Immediate, delayed	No detail	+
113; NR	Sore throat	Immediate, delayed	No detail	+
229; 7.8 (0.23); 8.3 (0.24)	Sore throat	Immediate, delayed	No detail	+
191; 41.6	Cough	Immediate, delayed	Patient to pick up prescription after 1 week of delay	–
283; 3.2	Acute otitis media	Immediate, delayed	No detail	–
194; 5	Acute otitis media	Immediate, delayed	To be filled only if symptoms did not improve within 2 days	–
1672; 4.8	Acute otitis media	Immediate, delayed	No detail	–
144; NR	Acute otitis media	Immediate, delayed	To be filled only if symptoms did not improve within 2 days	–
120; 47.6 (16.3); 48 (17.8)	Acute cough or sore throat	Immediate, delayed	No detail	–

RESEARCH

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Beth Stuart,[1] Hilda Hounkpatin,[1] Taeko Becque,[1] Guiqing Yao,[2] Shihua Zhu,[1] Pablo Alonso-Coello,[3] Attila Altiner,[4] Bruce Arroll,[5] Dankmar Böhning,[6] Jennifer Bostock,[7] Heiner C Bucher,[8] Jennifer Chao,[9] Mariam de la Poza,[10] Nick Francis,[1] David Gillespie,[11] Alastair D Hay,[12] Timothy Kenealy,[5] Christin Löffler,[4] David P McCormick,[13] Gemma Mas-Dalmau,[14] Laura Muñoz,[15] Kirsty Samuel,[16] Michael Moore,[1] Paul Little[1]

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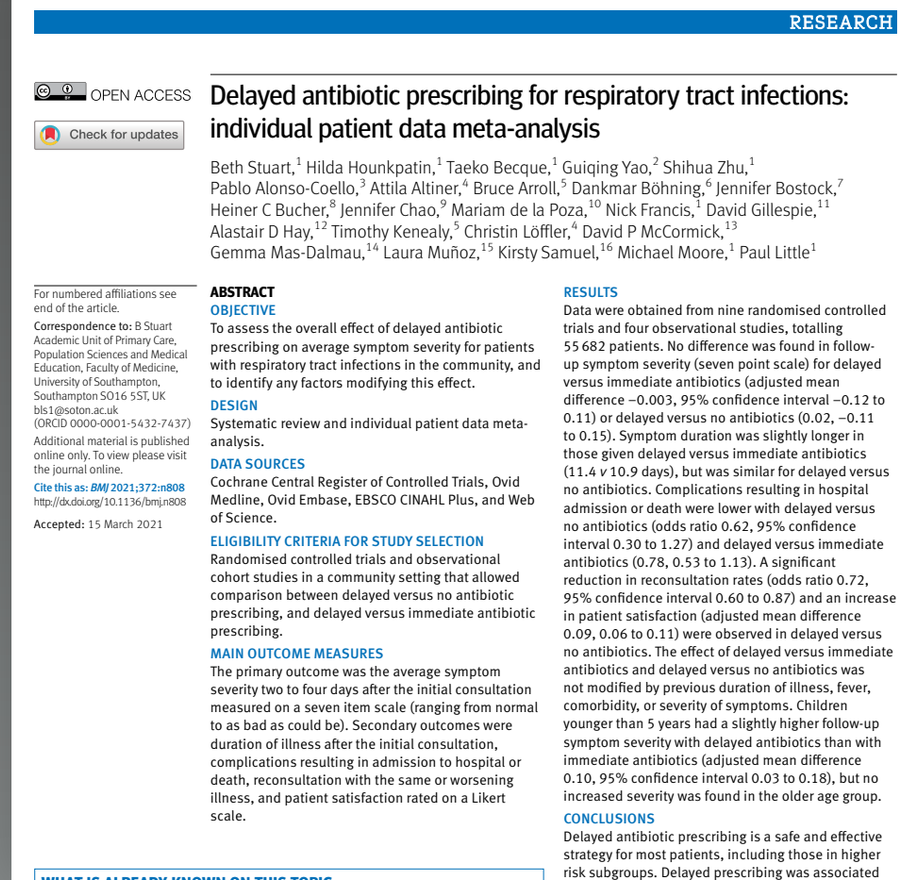

RESEARCH

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- Sin diferencias en la **gravedad de los síntomas**.
- **12 horas más de duración de síntomas** en los que recibieron antibióticos diferidos frente a inmediatos.
- Las complicaciones con **ingresos o muertes fueron menores con los antibióticos diferidos**...

  frente a los no administrados ↓38% (OR 0,30–1,27),

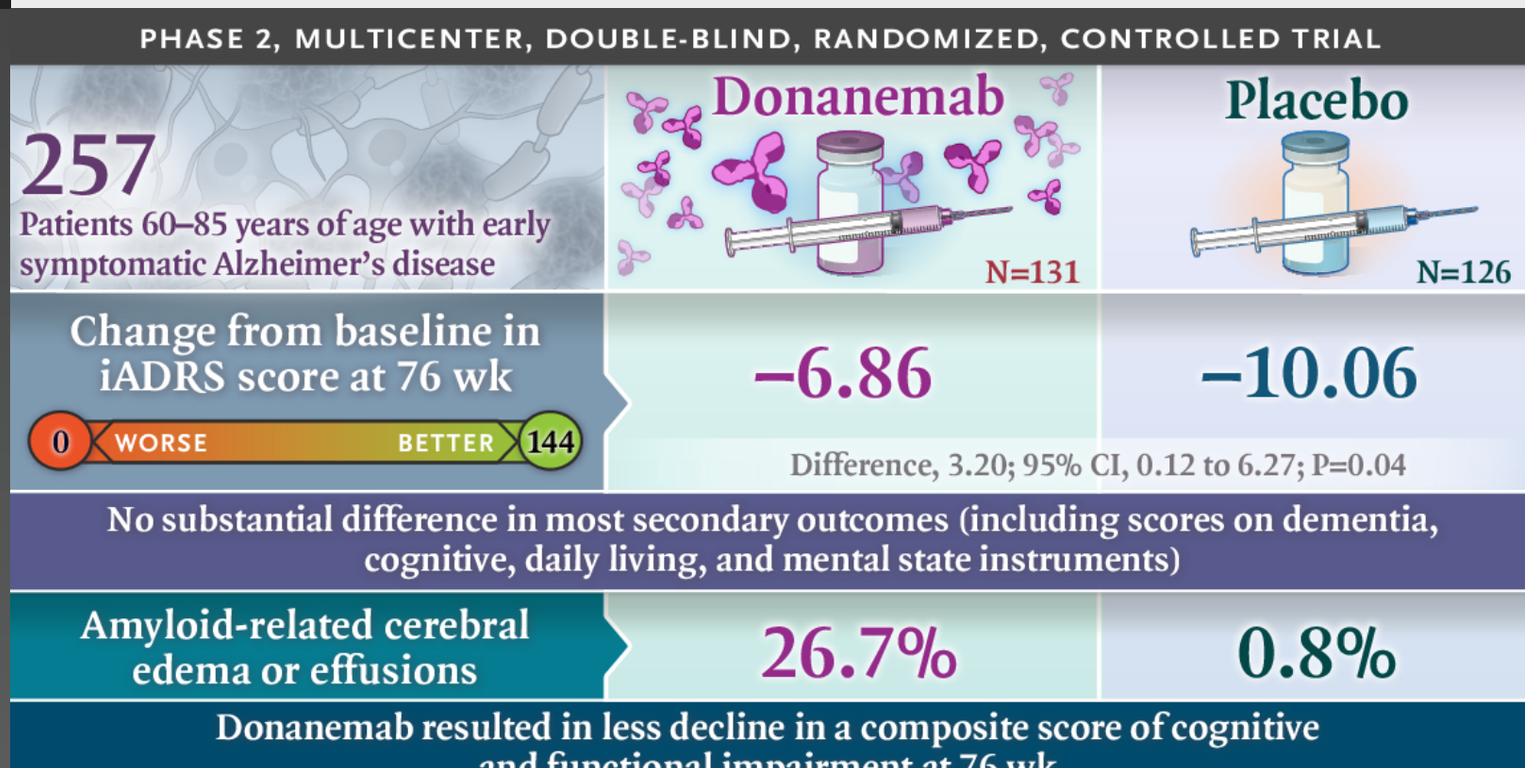
  frente a los inmediatos ↓22% (OR 0,53–1,13).

- **Reconsultas** ↓28% (OR 0,60–0,87) y **↑ satisfacción** del paciente VS ausencia de antibióticos.
- El efecto de los antibióticos diferidos **no se modificó** por la duración previa de la enfermedad, la fiebre, la comorbilidad o la gravedad de los síntomas. Los niños menores de 5 años tuvieron mayor gravedad de los síntomas, pero no los de mayor edad.

MICRORRESUMEN

Donanemab (ac. anti-amiloide β) apenas reduce el declive cognitivo y funcional tras año y medio en alzheimer

Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, et al. Donanemab in Early Alzheimer's Disease. N Engl J Med. 6 de mayo de 2021;384(18):1691-704



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2021 VOL. 384 NO. 18

Donanemab in Early Alzheimer's Disease

Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway, M.D., and Daniel M. Skovronsky, M.D., Ph.D.

ABSTRACT

BACKGROUND

A hallmark of Alzheimer's disease is the accumulation of amyloid-β (Aβ) peptide. Donanemab, an antibody that targets a modified form of deposited Aβ, is being investigated for the treatment of early Alzheimer's disease.

METHODS

We conducted a phase 2 trial of donanemab in patients with early symptomatic Alzheimer's disease who had tau and amyloid deposition on positron-emission tomography (PET). Patients were randomly assigned in a 1:1 ratio to receive donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo intravenously every 4 weeks for up to 72 weeks. The primary outcome was the change from baseline in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; range, 0 to 144, with lower scores indicating greater cognitive and functional impairment) at 76 weeks. Secondary outcomes included the change in scores on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB), the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog$_{13}$), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL), and the Mini–Mental State Examination (MMSE), as well as the change in the amyloid and tau burden on PET.

RESULTS

A total of 257 patients were enrolled; 131 were assigned to receive donanemab and 126 to receive placebo. The baseline iADRS score was 106 in both groups. The change from baseline in the iADRS score at 76 weeks was −6.86 with donanemab and −10.06 with placebo (difference, 3.20; 95% confidence interval, 0.12 to 6.27;

From Eli Lilly (M.A.M., A.C.L., C.D.E., A.M.W., P.A.A., S.W.A., S.S., J.S., J.R.S., M.B., D.M.S.) and the Departments of Neurology, of Radiology and Imaging Sciences, and of Medical and Molecular Genetics and the Indiana Alzheimer Disease Center, Indiana University School of Medicine (L.G.A.) — both in Indianapolis; and the Departments of Psychiatry and Human Behavior and of Neurology, Butler Hospital, Warren Alpert Medical School of Brown University, Providence, RI (S.P.S.). Address reprint requests to Dr. Mintun at Eli Lilly, Lilly Corporate Center, Indianapolis, IN 46285, or at mintun@lilly.com.

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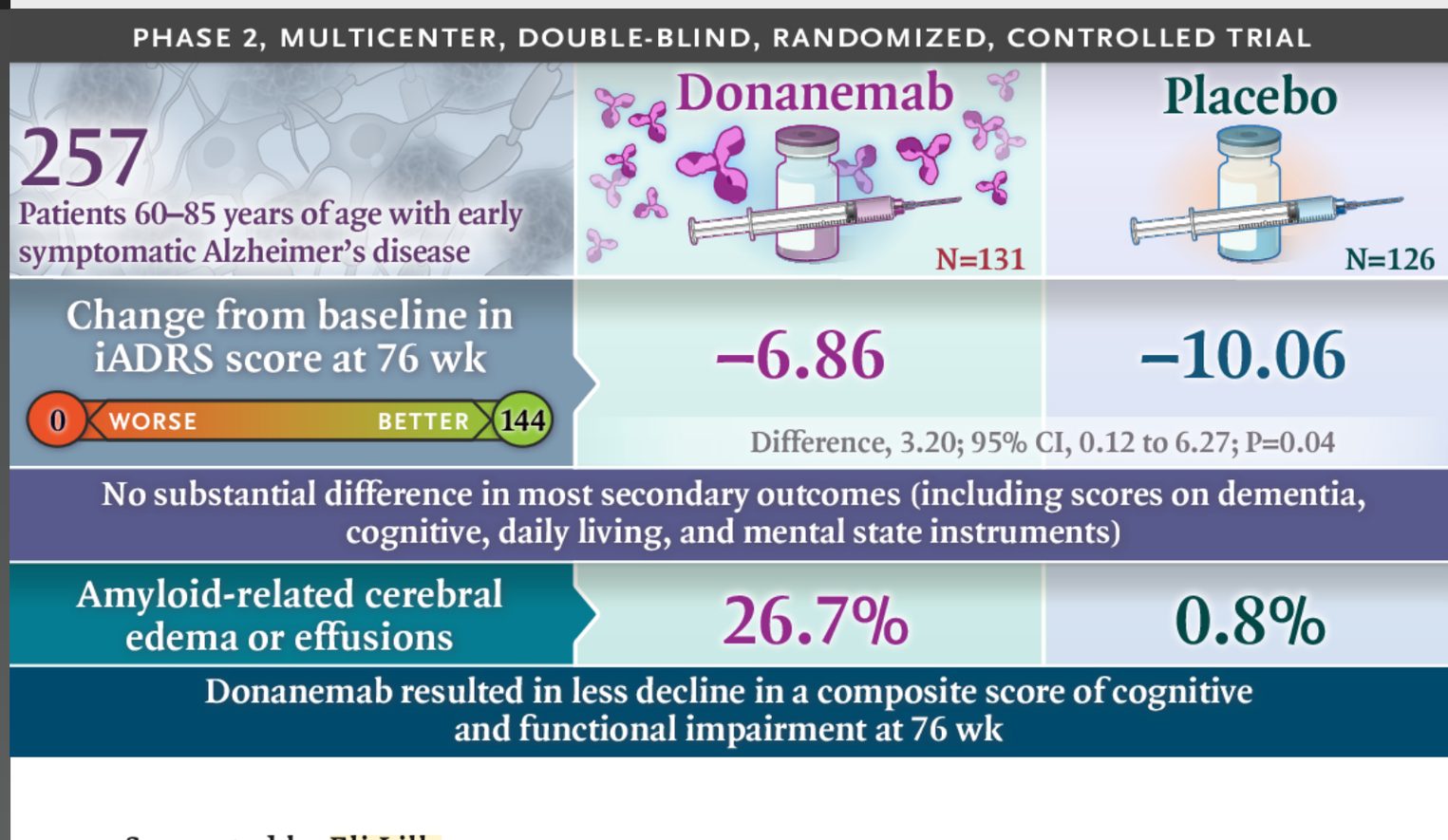
N Engl J Med 2021;384:1691-704.
DOI: 10.1056/NEJMoa2100708

MICRORRESUMEN

Donanemab (ac. anti-amiloide β) apenas reduce el declive cognitivo y funcional tras año y medio en alzheimer

Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, et al. Donanemab in Early Alzheimer's Disease. N Engl J Med. 6 de mayo de 2021;384(18):1691-704



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2021 VOL. 384 NO. 18

Donanemab in Early Alzheimer's Disease

Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway, M.D., and Daniel M. Skovronsky, M.D., Ph.D.

ABSTRACT

BACKGROUND

A hallmark of Alzheimer's disease is the accumulation of amyloid-β (Aβ) peptide. Donanemab, an antibody that targets a modified form of deposited Aβ, is being investigated for the treatment of early Alzheimer's disease.

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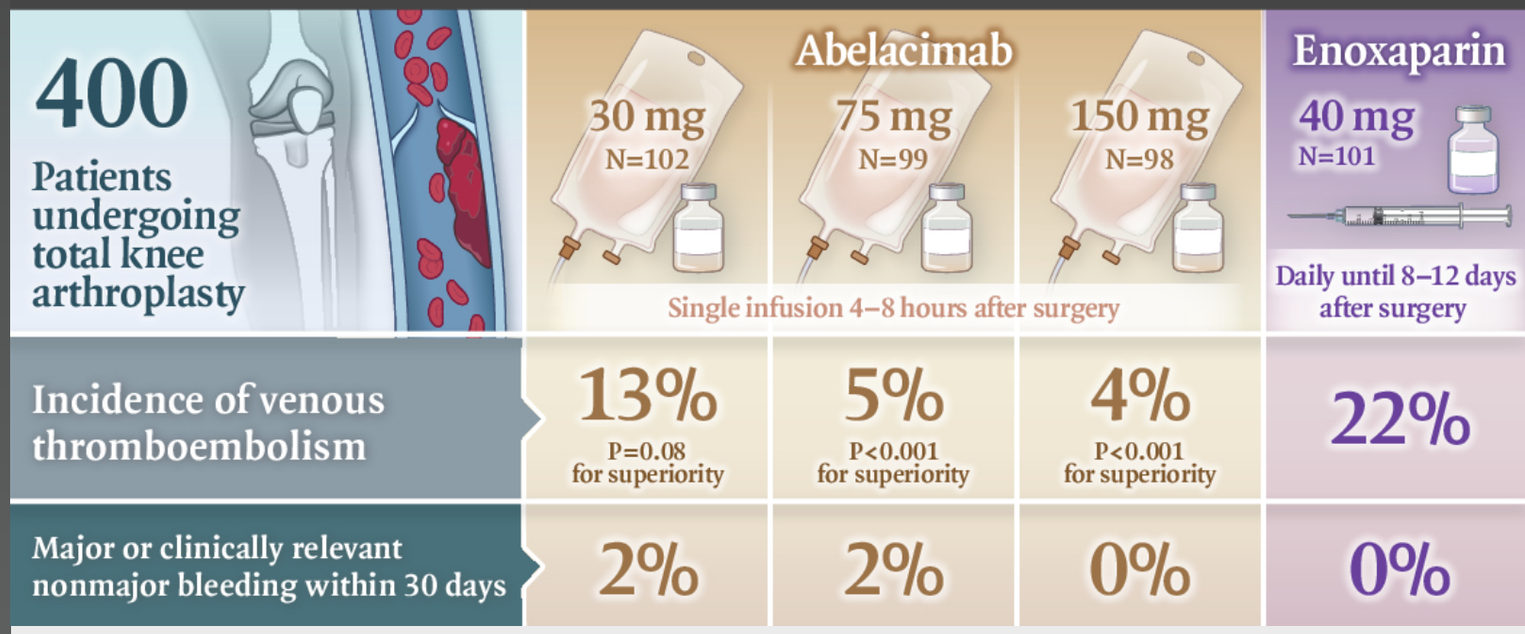
Supported by Eli Lilly.

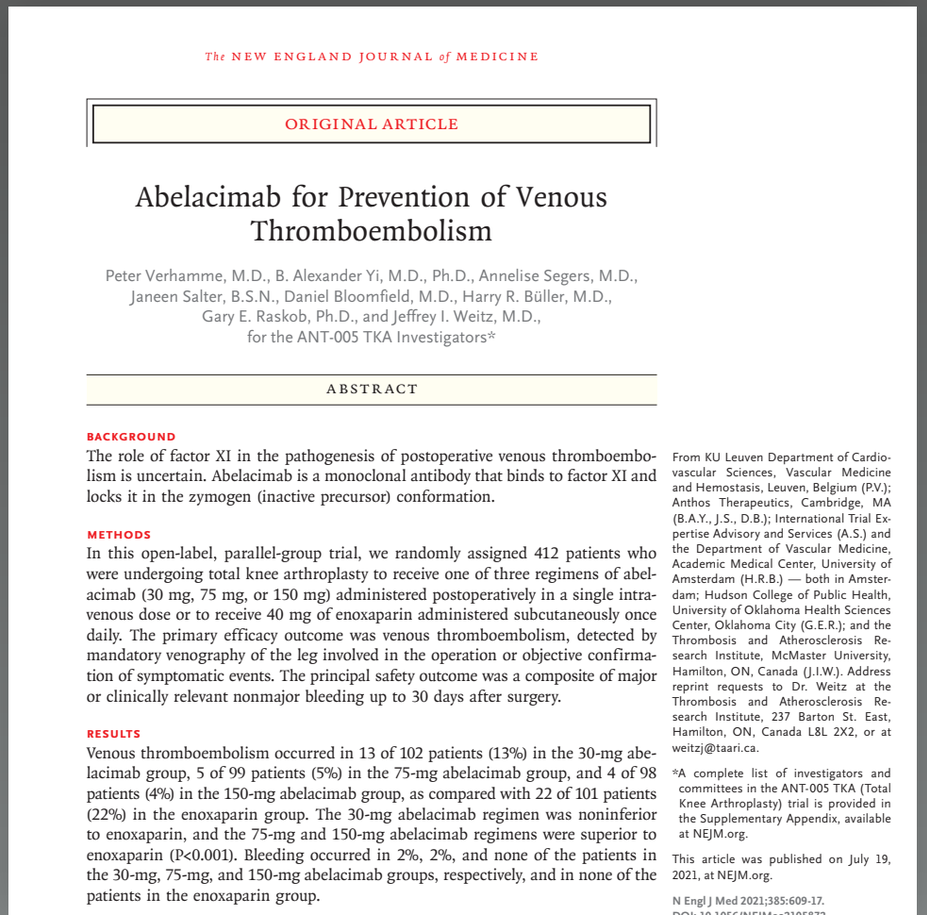
Dr. Mintun reports being employed by and owning shares in Eli Lilly and being employed by Avid Radiopharmaceuticals; Dr. Lo, being employed by and owning stocks and shares in Eli Lilly; Dr. Duggan Evans, being employed by and owning stocks in Eli Lilly; Dr. Wessels, being employed by and owning shares in Eli Lilly; Dr. Ardayfio, being employed by and owning stocks in Eli Lilly; Dr. Andersen, being employed by and owning shares in Eli Lilly; Dr. Shcherbinin, being employed by and owning stocks in Eli Lilly; Dr. Sparks, being employed by and owning stocks in Eli Lilly; Dr. Sims, being employed by and owning stocks in Eli Lilly; Dr. Brys, being employed by and owning stocks in Eli Lilly; Dr. Apostolova, receiving donated supplies from Avid Radiopharmaceuticals, grant support and research support from Roche Diagnostics, research support from Life Molecular Imaging, and consulting fees from Biogen and Two Labs and serving on a data and safety monitoring board for IQVIA; Dr. Salloway, receiving grant support and consulting fees from Biogen, Eisai, Eli Lilly, Genentech, and Roche and consulting fees and travel support from Avid Radiopharmaceuticals; and Dr. Skovronsky, being employed by and owning shares in

MICRORRESUMEN

Abelacimab (anti-factor XI) **reduce el riesgo de TVP tras artroplastia de rodilla**

Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, Büller HR, et al. Abelacimab for Prevention of Venous Thromboembolism. N Engl J Med. 12 de agosto de 2021;385(7):609-17.





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abelacimab for Prevention of Venous Thromboembolism

Peter Verhamme, M.D., B. Alexander Yi, M.D., Ph.D., Annelise Segers, M.D., Janeen Salter, B.S.N., Daniel Bloomfield, M.D., Harry R. Büller, M.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the ANT-005 TKA Investigators*

ABSTRACT

BACKGROUND
The role of factor XI in the pathogenesis of postoperative venous thromboembolism is uncertain. Abelacimab is a monoclonal antibody that binds to factor XI and locks it in the zymogen (inactive precursor) conformation.

METHODS
In this open-label, parallel-group trial, we randomly assigned 412 patients who were undergoing total knee arthroplasty to receive one of three regimens of abelacimab (30 mg, 75 mg, or 150 mg) administered postoperatively in a single intravenous dose or to receive 40 mg of enoxaparin administered subcutaneously once daily. The primary efficacy outcome was venous thromboembolism, detected by mandatory venography of the leg involved in the operation or objective confirmation of symptomatic events. The principal safety outcome was a composite of major or clinically relevant nonmajor bleeding up to 30 days after surgery.

RESULTS
Venous thromboembolism occurred in 13 of 102 patients (13%) in the 30-mg abelacimab group, 5 of 99 patients (5%) in the 75-mg abelacimab group, and 4 of 98 patients (4%) in the 150-mg abelacimab group, as compared with 22 of 101 patients (22%) in the enoxaparin group. The 30-mg abelacimab regimen was noninferior to enoxaparin, and the 75-mg and 150-mg abelacimab regimens were superior to enoxaparin (P<0.001). Bleeding occurred in 2%, 2%, and none of the patients in the 30-mg, 75-mg, and 150-mg abelacimab groups, respectively, and in none of the patients in the enoxaparin group.

From KU Leuven Department of Cardiovascular Sciences, Vascular Medicine and Hemostasis, Leuven, Belgium (P.V.); Anthos Therapeutics, Cambridge, MA (B.A.Y., J.S., D.B.); International Trial Expertise Advisory and Services (A.S.) and the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam (H.R.B.) — both in Amsterdam; Hudson College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City (G.E.R.); and the Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada (J.I.W.). Address reprint requests to Dr. Weitz at the Thrombosis and Atherosclerosis Research Institute, 237 Barton St. East, Hamilton, ON, Canada L8L 2X2, or at weitzj@taari.ca.

*A complete list of investigators and committees in the ANT-005 TKA (Total Knee Arthroplasty) trial is provided in the Supplementary Appendix, available at NEJM.org.

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N Engl J Med 2021;385:609-17.

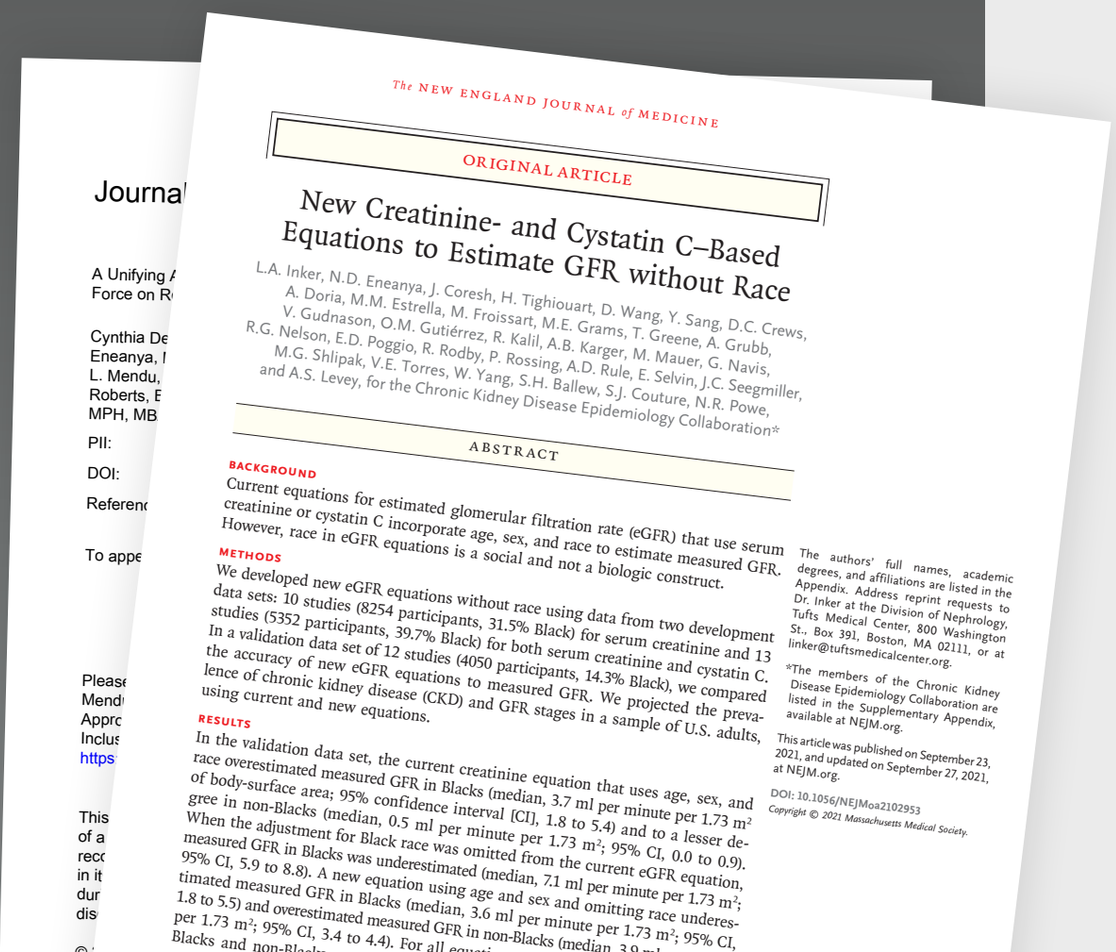
- Monoclonal totalmente humano que se une al **dominio catalítico del factor XI** y lo bloquea en la conformación zimógena (precursor inactivo), impidiendo así su activación por el factor XIIa o la trombina.

MICRORRESUMEN

Nueva estimación del FG sin incluir un factor **racial**

Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. American Journal of Kidney Diseases. septiembre de 2021;S0272638621008283.

Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. N Engl J Med. 23 de septiembre de 2021;NEJMoa2102953.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L.A. Inker, N.D. Eneanya, J. Coresh, H. Tighiouart, D. Wang, Y. Sang, D.C. Crews, A. Doria, M.M. Estrella, M. Froissart, M.E. Grams, T. Greene, A. Grubb, V. Gudnason, O.M. Gutiérrez, R. Kalil, A.B. Karger, M. Mauer, G. Navis, R.G. Nelson, E.D. Poggio, R. Rodby, P. Rossing, A.D. Rule, E. Selvin, J.C. Seegmiller, M.G. Shlipak, V.E. Torres, W. Yang, S.H. Ballew, S.J. Couture, N.R. Powe, and A.S. Levey, for the Chronic Kidney Disease Epidemiology Collaboration*

ABSTRACT

BACKGROUND

Current equations for estimated glomerular filtration rate (eGFR) that use serum creatinine or cystatin C incorporate age, sex, and race to estimate measured GFR. However, race in eGFR equations is a social and not a biologic construct.

METHODS

We developed new eGFR equations without race using data from two development data sets: 10 studies (8254 participants, 31.5% Black) for serum creatinine and 13 studies (5352 participants, 39.7% Black) for both serum creatinine and cystatin C. In a validation data set of 12 studies (4050 participants, 14.3% Black), we compared the accuracy of new eGFR equations to measured GFR. We projected the prevalence of chronic kidney disease (CKD) and GFR stages in a sample of U.S. adults, using current and new equations.

RESULTS

In the validation data set, the current creatinine equation that uses age, sex, and race overestimated measured GFR in Blacks (median, 3.7 ml per minute per 1.73 m^2 of body-surface area; 95% confidence interval [CI], 1.8 to 5.4) and to a lesser degree in non-Blacks (median, 0.5 ml per minute per 1.73 m^2; 95% CI, 0.0 to 0.9). When the adjustment for Black race was omitted from the current eGFR equation, measured GFR in Blacks was underestimated (median, 7.1 ml per minute per 1.73 m^2; 95% CI, 5.9 to 8.8). A new equation using age and sex and omitting race underestimated measured GFR in Blacks (median, 3.6 ml per minute per 1.73 m^2; 95% CI, 1.8 to 5.5) and overestimated measured GFR in non-Blacks (median, 3.9 ml per 1.73 m^2; 95% CI, 3.4 to 4.4). For all equations, Blacks and non-Blacks

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Inker at the Division of Nephrology, Tufts Medical Center, 800 Washington St., Box 391, Boston, MA 02111, or at linker@tuftsmedicalcenter.org.

*The members of the Chronic Kidney Disease Epidemiology Collaboration are listed in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2102953

- Anteriormente, la CKD-EPI utilizada para estimar la tasa de filtración glomerular **incluía un término para la raza** → para cualquier edad, sexo y creatinina sérica, un individuo negro tendría un FG estimado más alto.

- La Sociedad Americana de Nefrología y la Fundación Nacional del Riñón reevaluaron la inclusión de la raza en la estimación de la TFG y determinaron que **una nueva ecuación que no incluía la raza era suficientemente precisa para su uso clínico**. Sus posibles consecuencias adversas **no afectan desproporcionadamente a ningún grupo** y está disponible de inmediato para todos los laboratorios.

- Recomiendan uso mayor, rutinario y oportuno de la **cistatina C**, especialmente para confirmar la TFGe en adultos para la toma de decisiones clínicas.

MICRORRESUMEN

En la IRA hipoxémica en la UCI, un objetivo de oxigenación más bajo no aumenta supervivencia

Schjørring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. N Engl J Med. 8 de abril de 2021;384(14):1301-11

The NEW ENGLAND JOURNAL of MEDICINE

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Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure

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ABSTRACT

BACKGROUND

Patients with acute hypoxemic respiratory failure in the intensive care unit (ICU) are treated with supplemental oxygen, but the benefits and harms of different oxygenation targets are unclear. We hypothesized that using a lower target for partial pressure of arterial oxygen (Pao_2) would result in lower mortality than using a higher target.

METHODS

In this multicenter trial, we randomly assigned 2928 adult patients who had recently been admitted to the ICU (≤12 hours before randomization) and who were receiving at least 10 liters of oxygen per minute in an open system or had a fraction of inspired oxygen of at least 0.50 in a closed system to receive oxygen therapy targeting a Pao_2 of either 60 mm Hg (lower-oxygenation group) or 90 mm Hg (higher-oxygenation group) for a maximum of 90 days. The primary outcome was death within 90 days.

RESULTS

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Drs. Schjørring and Klitgaard contributed equally to this article.

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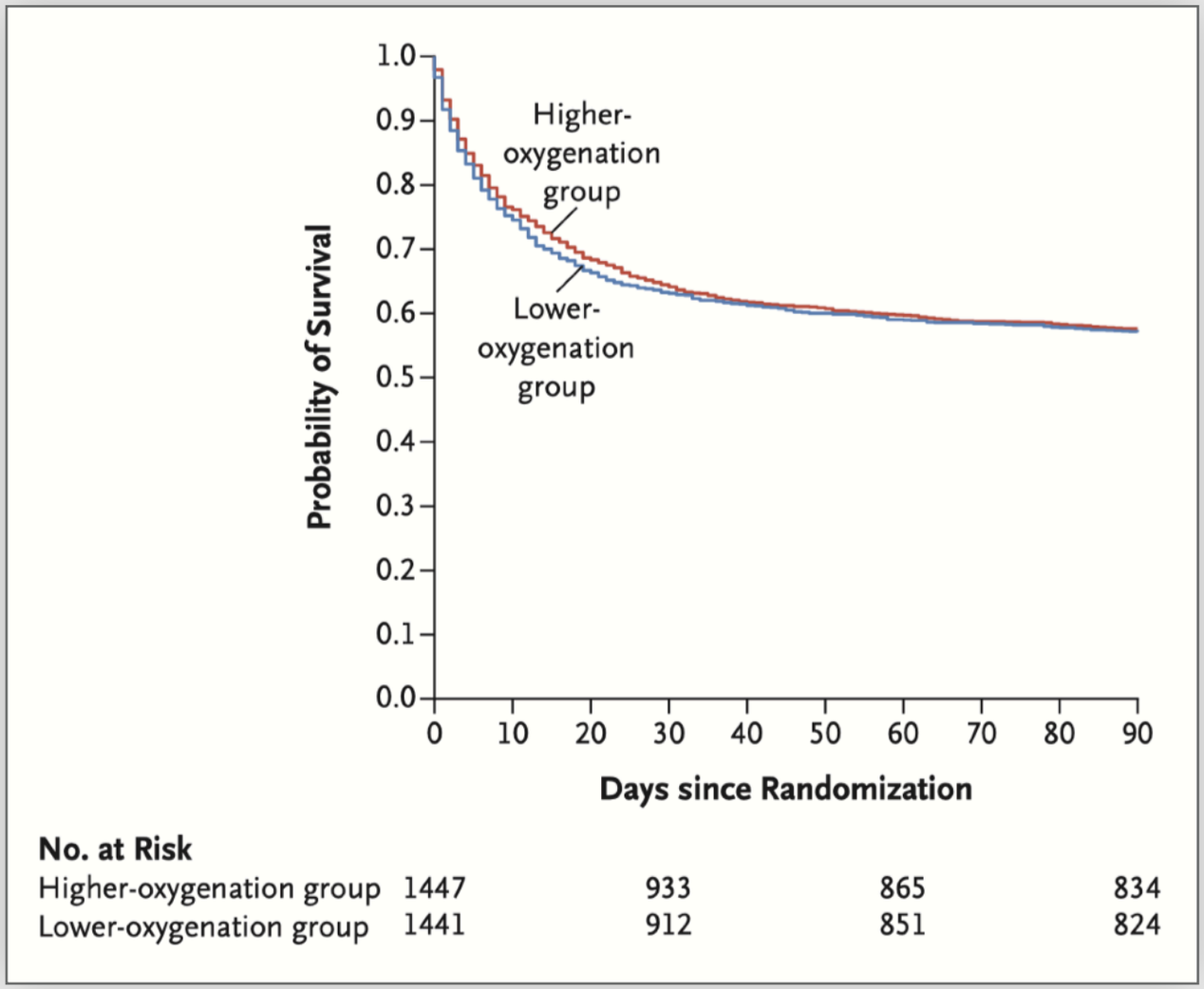
- Objetivo de **PaO_2 60** vs **90 mmHg** durante un máximo de 90 días

⊗ A los **90 días**, **no** mejora mortalidad (HR 1,04 IC 95% [0,93 a 1,16]), necesidad de UCI, días de vida tras el alta hospitalaria ni eventos adversos graves



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ORIGINAL ARTICLE

Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure

O.L. Schjørring, T.L. Klitgaard, A. Perner, J. Wetterslev, T. Lange, M. Siegemund, M. Bäcklund, F. Keus, J.H. Laake, M. Morgan, K.M. Thormar, S.A. Rosborg, J. Bisgaard, A.E.S. Erntgaard, A.-S.H. Lynnerup, R.L. Pedersen, E. Crescioli, T.C. Gielstrup, M.T. Behzadi, L.M. Poulsen, S. Estrup, J.P. Laigaard, C. Andersen, C.B. Mortensen, B.A. Brand, J. White, I.-L. Jarnvig, M.H. Møller, L. Quist, M.H. Bestle, M. Schønemann-Lund, M.K. Kamper, M. Hindborg, A. Hollinger, C.E. Gebhard, N. Zellweger, C.S. Meyhoff, M. Hjort, L.K. Bech, T. Grøfte, H. Bundgaard, L.H.M. Østergaard, M.A. Thyø, T. Hildebrandt, B. Uslu, C.G. Sølling, N. Møller-Nielsen, A.C. Brøchner, M. Borup, M. Okkonen, W. Dieperink, U.G. Pedersen, A.S. Andreasen, L. Buus, T.N. Aslam, R.R. Winding, J.C. Schefold, S.B. Thorup, S.A. Iversen, J. Engstrøm, M.-B.N. Kjær, and B.S. Rasmussen, for the HOT-ICU Investigators*

ABSTRACT

BACKGROUND

Patients with acute hypoxemic respiratory failure in the intensive care unit (ICU) are treated with supplemental oxygen, but the benefits and harms of different oxygenation targets are unclear. We hypothesized that using a lower target for partial pressure of arterial oxygen (Pao_2) would result in lower mortality than using a higher target.

METHODS

In this multicenter trial, we randomly assigned 2928 adult patients who had recently been admitted to the ICU (≤12 hours before randomization) and who were receiving at least 10 liters of oxygen per minute in an open system or had a fraction of inspired oxygen of at least 0.50 in a closed system to receive oxygen therapy targeting a Pao_2 of either 60 mm Hg (lower-oxygenation group) or 90 mm Hg (higher-oxygenation group) for a maximum of 90 days. The primary outcome was death within 90 days.

RESULTS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Rasmussen at the Department of Anesthesia and Intensive Care, Aalborg University Hospital, Hobrovej 18-21, DK-9000 Aalborg, Denmark, or at bodil.steen.rasmussen@rn.dk.

*A complete list of investigators in the HOT-ICU trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Schjørring and Klitgaard contributed equally to this article.

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N Engl J Med 2021;384:1301-11.

MICRORRESUMEN

El acamprosato es la única intervención en AP con suficiente evidencia para el **mantenimiento de la abstinencia alcohólica 1 año tras desintoxicación**

Cheng H-Y, McGuinness LA, Elbers RG, MacArthur GJ, Taylor A, McAleenan A, et al. Treatment interventions to maintain abstinence from alcohol in primary care: systematic review and network meta-analysis. BMJ. 25 de noviembre de 2020;m3934.

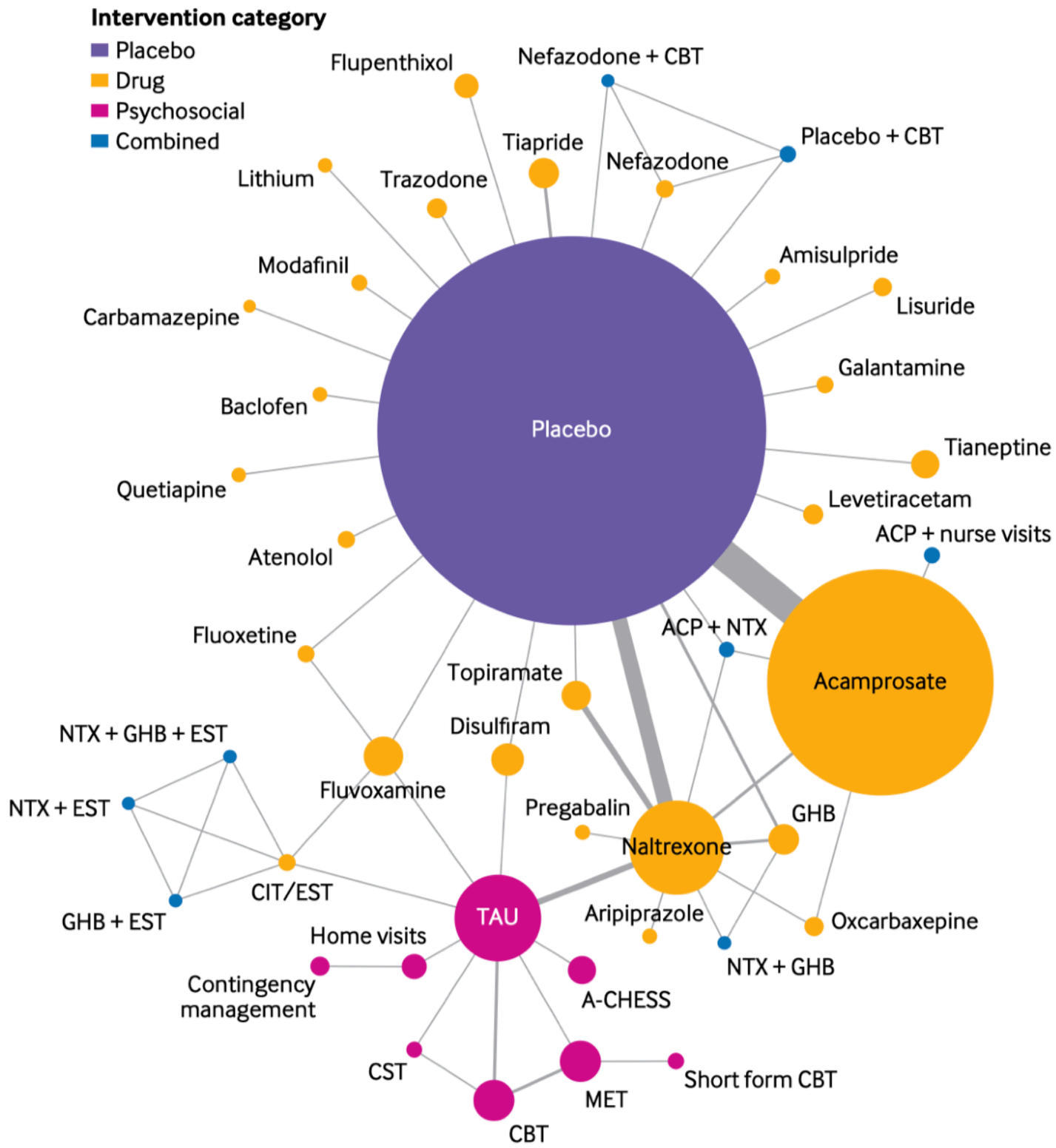

Fig 3 | Network plots for all cause dropouts in relation to treatment for alcohol dependency. Size of circles is proportional to number of randomised patients and width of lines is proportional to number of studies in each direct comparison. A-CHESS=Addiction-Comprehensive Health Enhancement Support System; ACP=acamprosate; CBT=cognitive behavioural therapy; CIT=citalopram; CST=coping skill training; GHB=sodium salt of gamma hydroxybutyric acid (sodium oxybate); MET=motivational enhancement therapy; NTX=naltrexone; TAU=treatment as usual

RESEARCH

Treatment interventions to maintain abstinence from alcohol in primary care: systematic review and network meta-analysis

Hung-Yuan Cheng,[1] Luke A McGuinness,[1] Roy G Elbers,[1] Georgina J MacArthur,[1] Abigail Taylor,[1] Alexandra McAleenan,[1] Sarah Dawson,[1] José A López-López,[1,2] Julian P T Higgins,[1,3,4] Sean Cowlishaw,[1,5] Anne Lingford-Hughes,[6] Matthew Hickman,[1,3,4] David Kessler[1,4,7]

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Cite this as: *BMJ* 2020;371:m3934 http://dx.doi.org/10.1136/bmj.m3934

Accepted: 21 September 2020

ABSTRACT

OBJECTIVE
To determine the most effective interventions in recently detoxified, alcohol dependent patients for implementation in primary care.

DESIGN
Systematic review and network meta-analysis.

DATA SOURCES
Medline, Embase, PsycINFO, Cochrane CENTRAL, ClinicalTrials.gov, and the World Health Organization's International Clinical Trials Registry Platform.

STUDY SELECTION
Randomised controlled trials comparing two or more interventions that could be used in primary care. The population was patients with alcohol dependency diagnosed by standardised clinical tools and who became detoxified within four weeks.

DATA EXTRACTION
Outcomes of interest were continuous abstinence from alcohol (effectiveness) and all cause dropouts (as a proxy for acceptability) at least 12 weeks after start of intervention.

RESULTS
64 trials (43 interventions) were included. The median probability of abstinence across placebo arms was 25%. Compared with placebo, the only intervention associated with increased probability of abstinence and moderate certainty evidence was acamprosate (odds ratio 1.86, 95% confidence interval 1.49 to 2.33, corresponding to an absolute probability of 38%). Of the 62 included trials that reported all cause dropouts, interventions associated with a reduced number of dropouts compared with placebo (probability 50%) and moderate certainty of evidence were acamprosate (0.73, 0.62 to 0.86; 42%), naltrexone (0.70, 0.50 to 0.98; 41%), and acamprosate-naltrexone (0.30, 0.13 to 0.67; 17%). Acamprosate was the only intervention associated with moderate confidence in the evidence of effectiveness and acceptability up to 12 months. It is uncertain whether other interventions can help maintain abstinence and reduce dropouts because of low confidence in the evidence.

CONCLUSIONS
Evidence is lacking for benefit from interventions that could be implemented in primary care settings for alcohol abstinence, other than for acamprosate. More evidence from high quality randomised controlled trials is needed, as are strategies using combined interventions (combinations of drug interventions or drug and psychosocial interventions) to improve treatment of alcohol dependency in primary care.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42016049779.

Introduction

In the United Kingdom, the morbidity and mortality burden from alcohol consumption remains high, with 7% of hospital admissions related to alcohol.[1] Liver disease is the third most common cause of premature death in the UK and the only major cause of death that is on the increase, with about two thirds of such deaths related to alcohol.[2] Alcohol related harm is estimated to cost the UK National Health Service £3.5bn ($4.5bn; €3.9bn) annually, with the total annual cost to the UK estimated at £21bn.[1,3]

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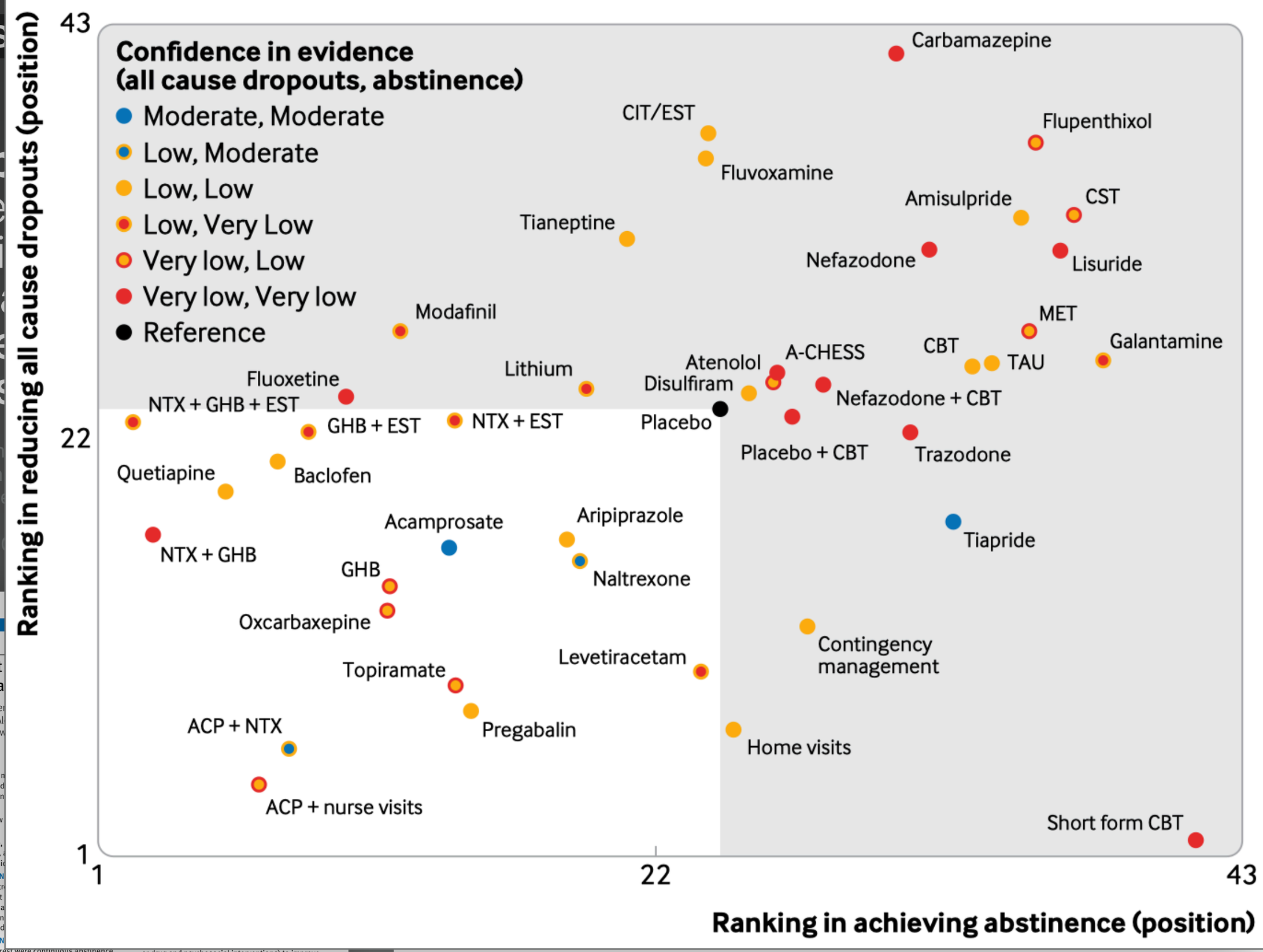

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Treatment
primary ca

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Alexandra McAl
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DESIGN
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Fig 4 | Clustered ranking plot by mean rank values from results of network meta-analyses of abstinence and all cause dropouts. Interventions are coloured according to the confidence of evidence by outline (abstinence) and fill (all cause dropout). The interventions in the white zone were ranked better than placebo based on both outcomes. A-CHESS=Addiction-Comprehensive Health Enhancement Support System; ACP=acamprosate; CBT=cognitive behavioural therapy; CIT=citalopram; EST=escitalopram; CST=coping skill training; GHB=sodium salt of gamma hydroxybutyric acid (sodium oxybate); MET=motivational enhancement therapy; NTX=naltrexone; TAU=treatment as usual

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2021 VOL. 385 NO. 12

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ABSTRACT

BACKGROUND

Salt substitutes with reduced sodium levels and increased potassium levels have been shown to lower blood pressure, but their effects on cardiovascular and safety outcomes are uncertain.

METHODS

We conducted an open-label, cluster-randomized trial involving persons from 600 villages in rural China. The participants had a history of stroke or were 60 years of age or older and had high blood pressure. The villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which the participants continued to use regular salt (100% sodium chloride). The primary outcome was stroke, the secondary outcomes were major adverse cardiovascular events and death from any cause, and the safety outcome was clinical hyperkalemia.

RESULTS

A total of 20,995 persons were enrolled in the trial. The mean age of the participants was 65.4 years, and 49.5% were female, 72.6% had a history of stroke, and 88.4% a history of hypertension. The mean duration of follow-up was 4.74 years. The rate of stroke was lower with the salt substitute than with regular salt (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; P=0.006), as were the rates of major cardiovascular events

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*Deceased.

Drs. Neal and Wu contributed equally to this article.

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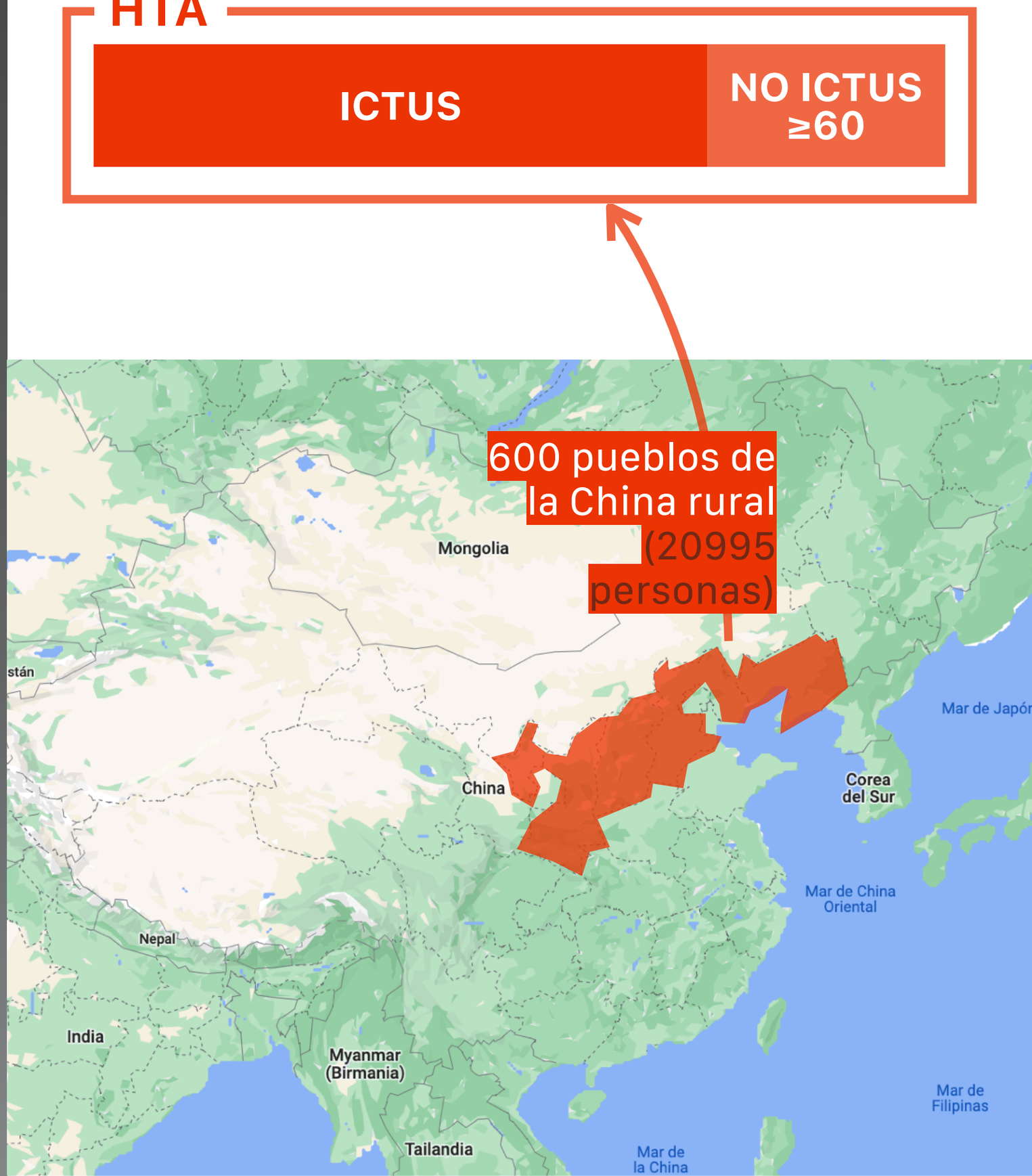

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Outcomes	Salt Substitute	Regular Salt	Rate Ratio	P Value
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Stroke	29.14	33.65	0.86 (0.77–0.96)	P=0.006
Major Adverse CV Events	49.09	56.29	0.87 (0.80–0.94)	P<0.001
Death from Any Cause	39.28	44.61	0.88 (0.82–0.95)	P<0.001
Hyperkalemia	3.35	3.30	1.04 (0.80–1.37)	P=0.76

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Death from Any Cause	39.28	44.61	0.88 (0.82–0.95)	P<0.001
Hyperkalemia	3.35	3.30	1.04 (0.80–1.37)	P=0.76

- ✓ Ictus ↓14%
- ✓ Eventos CV mayores ↓13%
- ✓ Muerte por cualquier causa ↓12%

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2021 VOL. 385 NO. 12

Effect of Salt Substitution on Cardiovascular Events and Death

B. Neal, Y. Wu, X. Feng, R. Zhang, Y. Zhang, J. Shi,* J. Zhang, M. Tian, L. Huang, Z. Li, Y. Yu, Y. Zhao, B. Zhou, J. Sun, Y. Liu, X. Yin, Z. Hao, J. Yu, K.-C. Li, X. Zhang, P. Duan, F. Wang, B. Ma, W. Shi, G.L. Di Tanna, S. Stepien, S. Shan, S.-A. Pearson, N. Li, L.L. Yan, D. Labarthe, and P. Elliott

ABSTRACT

BACKGROUND

Salt substitutes with reduced sodium levels and increased potassium levels have been shown to lower blood pressure, but their effects on cardiovascular and safety outcomes are uncertain.

METHODS

We conducted an open-label, cluster-randomized trial involving persons from 600 villages in rural China. The participants had a history of stroke or were 60 years of age or older and had high blood pressure. The villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which the participants continued to use regular salt (100% sodium chloride). The primary outcome was stroke, the secondary outcomes were major adverse cardiovascular events and death from any cause, and the safety outcome was clinical hyperkalemia.

RESULTS

A total of 20,995 persons were enrolled in the trial. The mean age of the participants was 65.4 years, and 49.5% were female, 72.6% had a history of stroke, and 88.4% a history of hypertension. The mean duration of follow-up was 4.74 years. The rate of stroke was lower with the salt substitute than with regular salt (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; P=0.006), as were the rates of major cardiovascular events

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wu at Peking University Clinical Research Center, Peking University, 38 Xueyuan Rd., Haidian District, Beijing, China, or at wuyf@bjmu.edu.cn, or to Dr. Tian at the George Institute for Global Health at Peking University Health Science Center, Rm. 052A, Unit 1, Tayuan Diplomatic Office Bldg., No. 14 Liangmahe Nan Lu, Chaoyang District, Beijing, China, or at mtian@georgeinstitute.org.cn.

*Deceased.

Drs. Neal and Wu contributed equally to this article.

This article was published on August 29, 2021, at NEJM.org.

N Engl J Med 2021;385:1067-77.
DOI: 10.1056/NEJMoa2105675

MICRORRESUMEN

Un **sustituto de la sal** reduce ictus, eventos cardiovasculares graves y **muerte por cualquier causa** en pacientes hipertensos (con ictus previo o ≥60 años)

Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, et al. Effect of Salt Substitution on Cardiovascular Events and Death. N Engl J Med. 16 de septiembre de 2021;385(12):1067-77

Outcomes	Salt Substitute	Regular Salt	Rate Ratio (95% CI)	P Value
	no. of events per 1000 person-yr			
Stroke	29.14	33.65	0.86 (0.77–0.96)	P=0.006
Major Adverse CV Events	49.09	56.29	0.87 (0.80–0.94)	P<0.001
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Hyperkalemia	3.35	3.30	1.04 (0.80–1.37)	P=0.76

- ✓ Ictus ↓14%
- ✓ Eventos CV mayores ↓13%
- ✓ **Muerte** por cualquier causa ↓12%
- ✓ Sin aumento de **hiperpotasemia**

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MÁS LECTURAS DE INTERÉS...

Pirfenidona en lCFpEF con fibrosis miocárdica reduce levemente el volumen extracelular miocárdico (-1,21%; lC del 95%, -2,12 a -0,31; p = 0,009) en un ensayo fase 2

Lewis GA, Dodd S, Clayton D, Bedson E, Eccleson H, Schelbert EB, et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. Nat Med. agosto de 2021;27(8):1477-82

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01452-0

Check for updates

Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial

Gavin A. Lewis[1,2], Susanna Dodd[3], Dannii Clayton[4], Emma Bedson[4], Helen Eccleson[4], Erik B. Schelbert[5,6,7], Josephine H. Naish[1], Beatriz Duran Jimenez[2], Simon G. Williams[2], Colin Cunnington[2], Fozia Zahir Ahmed[1,2], Anne Cooper[8], Rajavarma Viswesvaraiah[9], Stuart Russell[10], Theresa McDonagh[11], Paula R. Williamson[3] and Christopher A. Miller[1,2,12] ✉

In heart failure with preserved ejection fraction (HFpEF), the occurrence of myocardial fibrosis is associated with adverse outcome. Whether pirfenidone, an oral antifibrotic agent without hemodynamic effect, is efficacious and safe for the treatment of HFpEF is unknown. In this double-blind, phase 2 trial (NCT02932566), we enrolled patients with heart failure, an ejection fraction of 45% or higher and elevated levels of natriuretic peptides. Eligible patients underwent cardiovascular magnetic resonance and those with evidence of myocardial fibrosis, defined as a myocardial extracellular volume of 27% or greater, were randomly assigned to receive pirfenidone or placebo for 52 weeks. Forty-seven patients were randomized to each of the pirfenidone and placebo groups. The primary outcome was change in myocardial extracellular volume, from baseline to 52 weeks. In comparison to placebo, pirfenidone reduced myocardial extracellular volume (between-group difference, −1.21%; 95% confidence interval, −2.12 to −0.31; *P* = 0.009), meeting the predefined primary outcome. Twelve patients (26%) in the pirfenidone group and 14 patients (30%) in the placebo group experienced one or more serious adverse events. The most common adverse events in the pirfenidone group were nausea, insomnia and rash. In conclusion, among patients with HFpEF and myocardial fibrosis, administration of pirfenidone for 52 weeks reduced myocardial fibrosis. The favorable effects of pirfenidone in patients with HFpEF will need to be confirmed in future trials.

Heart failure with preserved ejection fraction (HFpEF) is common and is associated with high morbidity and mortality[1]. HFpEF involves a diverse range of pathophysiological mechanisms, and this heterogeneity may have contributed to the neutral findings of some phase 3 trials that have considered HFpEF as a single entity and taken a one-size-fits-all approach to its treatment[2]. By contrast, trials that have targeted specific biological mechanisms, such as the Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy (ATTR-ACT) trial, and the Rivaroxaban with or without Aspirin in Patients with Heart Failure and Chronic Coronary or Peripheral Artery Disease (COMPASS) trial, have shown benefit[3,4]. Predictive enrichment trial design means selecting patients who are more likely to respond to a given therapy on the basis of a biological mechanism or specific disease pathway[5,6].

novel approach to heart failure that involves specifically targeting the extracellular matrix, we identified patients with HFpEF and myocardial fibrosis, and tested whether pirfenidone would result in regression of myocardial fibrosis.

Results

Patients. From 7 March 2017 to 19 December 2018, 601 patients were screened at six sites in the United Kingdom. Of these, 136 had a baseline assessment. Twenty-nine patients were excluded for reasons of ineligibility, and 13 further patients were found to have extracellular volume (ECV) < 27% (median ECV 24.7%, interquartile range (IQR) 24.5–24.9), that is, below the threshold for entry. Ninety-four patients were randomly assigned to receive pirfenidone or placebo (Fig. 1). At the end of the trial, 12 patients had withdrawn from the study and two had died. No patient was lost to follow-up.

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CA125 elevado (≥ 35 U/mL) podría identificar a los pacientes que **se benefician de una hospitalización más prolongada para evitar reingresos por ICA a medio plazo**

Lorenzo M, Palau P, Llàcer P, Domínguez E, Ventura B, Núñez G, et al. Clinical utility of antigen carbohydrate 125 for planning the optimal length of stay in acute heart failure. European Journal of Internal Medicine. octubre de 2021;92:94-9.

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Original article

Clinical utility of antigen carbohydrate 125 for planning the optimal length of stay in acute heart failure

Miguel Lorenzo[a,1], Patricia Palau[a,1], Pau Llàcer[b], Eloy Domínguez[c], Bruno Ventura[c], Gonzalo Núñez[a], Gema Miñana[a,d], Javier Solsona[c], Enrique Santas[a], Rafael De La Espriella[a], Vicent Bodí[a,d], Eduardo Núñez[a], Juan Sanchis[a,d], Antoni Bayés-Genís[d,e], Julio Núñez[a,d,*]

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[b] Servicio de Medicina Interna. Hospital Universitario Ramón y Cajal. Madrid, Spain
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ARTICLE INFO

Keywords
CA125
length of stay
acute heart failure

ABSTRACT

Background: The optimal length of stay (LOS) in patients hospitalized for acute heart failure (AHF) remains controversial. Plasma antigen carbohydrate 125 (CA125) has emerged as a reliable proxy of congestion. We aimed to evaluate whether there is a differential impact of LOS on the risk of 6-month AHF readmission across CA125 levels.
Methods: This is a retrospective study that included 1,387 patients discharged for AHF in two third-level centers. CA125 was measured 48±24 h after admission. The association between CA125 and LOS with the risk of subsequent AHF readmission at 6 months was analyzed by Cox regression analysis accounting for death as a competing event.
Results: The median (IQR) age of the sample was 78 (69–83) years, 625 (41.1%) patients were women, and 832 (60%) exhibited preserved left ventricular ejection fraction. The median LOS and CA125 were 6 (4–9) days and 36 (17–83) U/mL, respectively. A total of 707 (51%) patients displayed high CA125 levels (≥35 U/mL). At 6 months, 87 deaths (6,3%) and 304 AHF readmissions (21,9%) were registered, respectively. A multivariate analysis revealed a differential effect of LOS on 6-month AHF readmission across CA125 levels (p-value for interaction=0.010). In those with CA125<35 U/mL, LOS≥7 days did not modify the risk (HR:1.31; 95% CI: 0.92-1.87, p=0.131). Conversely, in those with CA125≥35 U/mL, LOS≥7 days was associated with a lower risk of AHF readmission (HR:0.70; 95% CI: 0.51-0.98, p=0.036).
Conclusions: In patients with AHF, high CA125 levels may identify those patients that benefit from a more prolonged hospitalization in terms of reducing the risk of mid-term AHF readmissions.

Introduction

expenditures [2,3]. Thus, healthcare providers' initiatives have traditionally focused on decreasing LOS [4]. Nevertheless, a too short LOS

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Dejar de fumar, pero **no reducir el consumo** se asoció con un menor riesgo de ictus e IM

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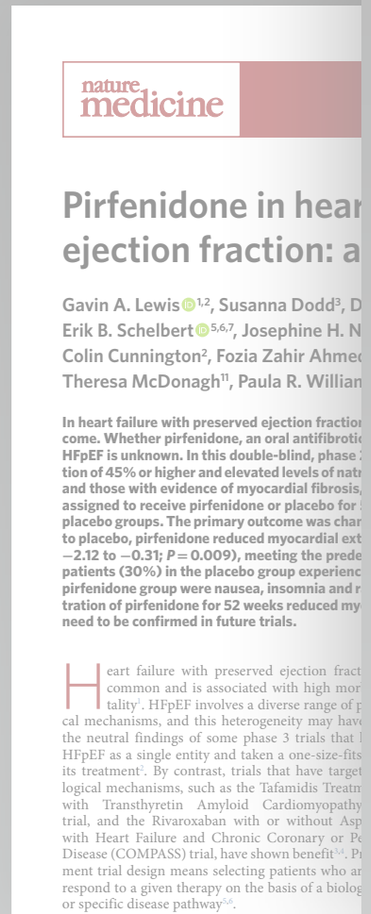
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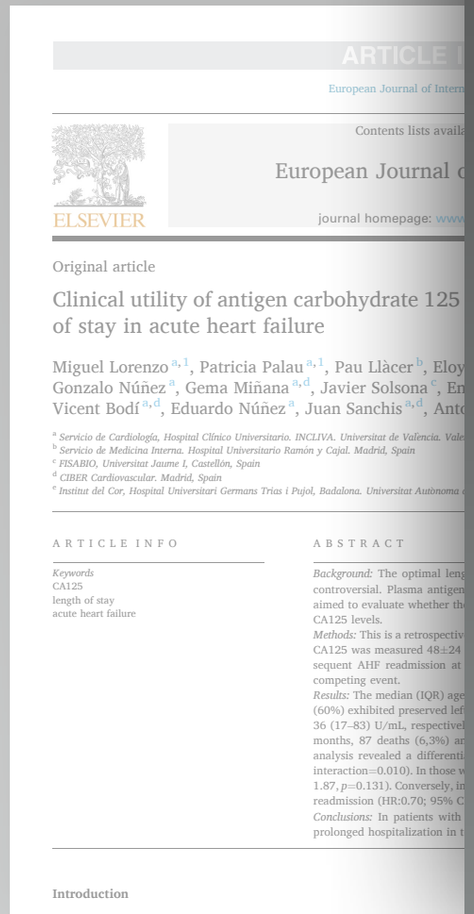
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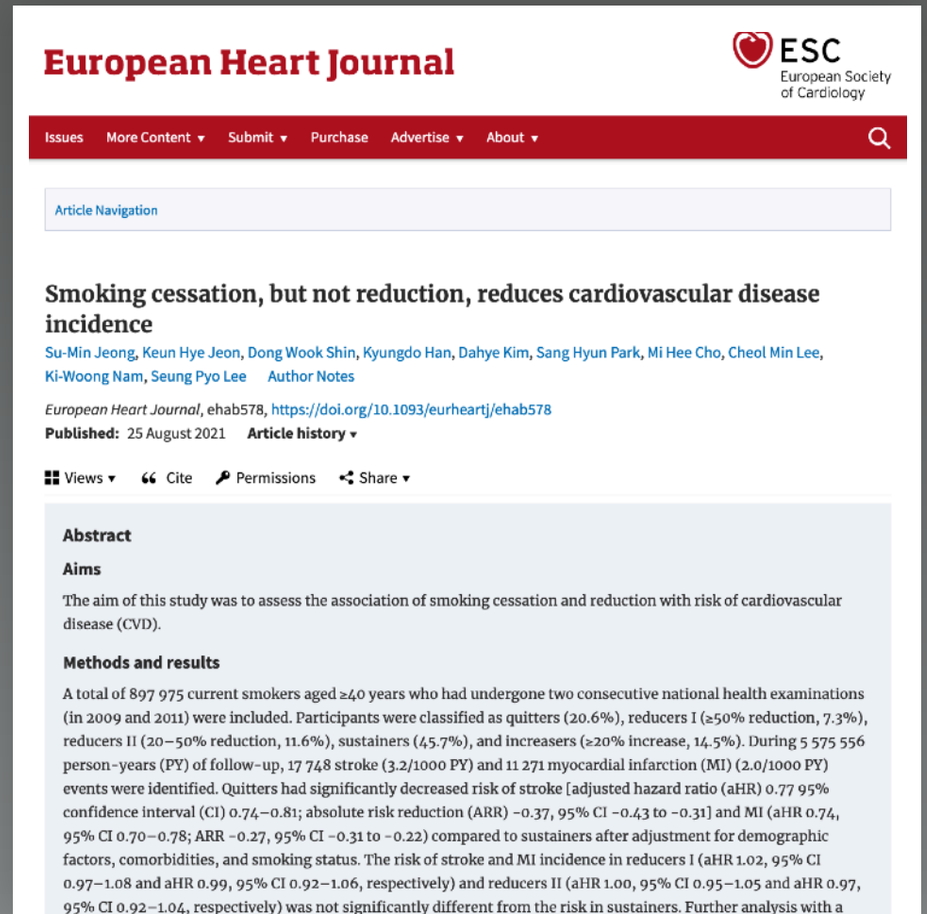
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Smoking cessation, but not reduction, reduces cardiovascular disease incidence

Su-Min Jeong, Keun Hye Jeon, Dong Wook Shin, Kyungdo Han, Dahye Kim, Sang Hyun Park, Mi Hee Cho, Cheol Min Lee, Ki-Woong Nam, Seung Pyo Lee Author Notes

European Heart Journal, ehab578, https://doi.org/10.1093/eurheartj/ehab578
Published: 25 August 2021 **Article history**

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Abstract

Aims

The aim of this study was to assess the association of smoking cessation and reduction with risk of cardiovascular disease (CVD).

Methods and results

A total of 897 975 current smokers aged ≥40 years who had undergone two consecutive national health examinations (in 2009 and 2011) were included. Participants were classified as quitters (20.6%), reducers I (≥50% reduction, 7.3%), reducers II (20–50% reduction, 11.6%), sustainers (45.7%), and increasers (≥20% increase, 14.5%). During 5 575 556 person-years (PY) of follow-up, 17 748 stroke (3.2/1000 PY) and 11 271 myocardial infarction (MI) (2.0/1000 PY) events were identified. Quitters had significantly decreased risk of stroke [adjusted hazard ratio (aHR) 0.77 95% confidence interval (CI) 0.74–0.81; absolute risk reduction (ARR) −0.37, 95% CI −0.43 to −0.31] and MI (aHR 0.74, 95% CI 0.70–0.78; ARR −0.27, 95% CI −0.31 to −0.22) compared to sustainers after adjustment for demographic factors, comorbidities, and smoking status. The risk of stroke and MI incidence in reducers I (aHR 1.02, 95% CI 0.97–1.08 and aHR 0.99, 95% CI 0.92–1.06, respectively) and reducers II (aHR 1.00, 95% CI 0.95–1.05 and aHR 0.97, 95% CI 0.92–1.04, respectively) was not significantly different from the risk in sustainers. Further analysis with a

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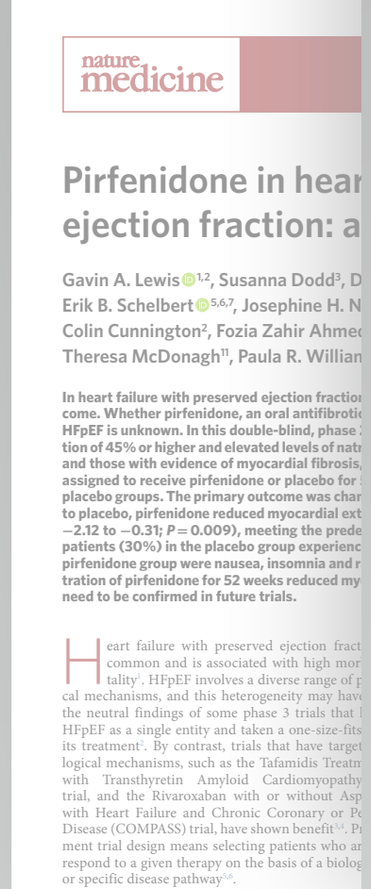
En mayores hipertensos, el objetivo de **PAS < 130** mmHg reduce eventos cardiovasculares más que el objetivo de 130-150 mm Hg

Zhang W, Zhang S, Deng Y, Wu S, Ren J, Sun G, et al. Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. N Engl J Med. 30 de septiembre de 2021;385(14):1268-79.



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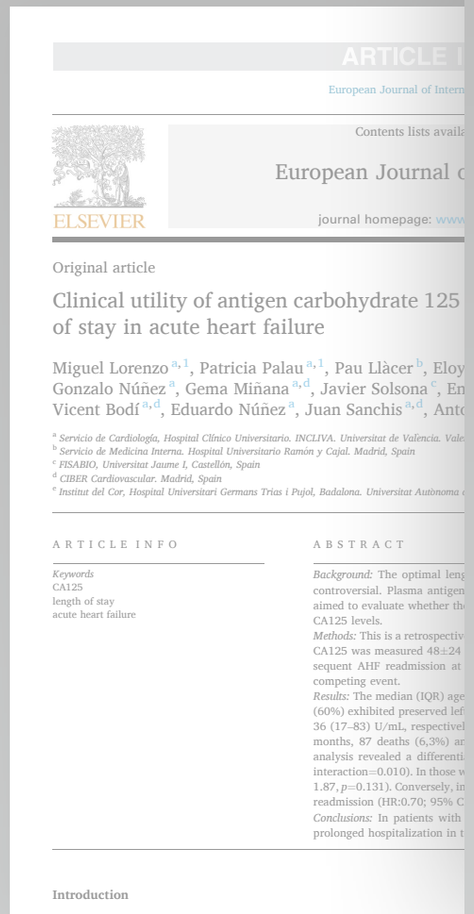

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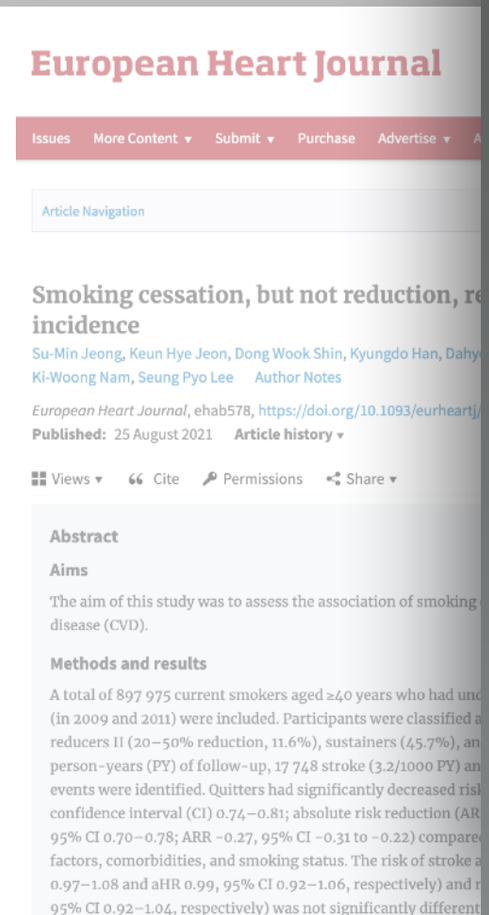
months, 87 deaths (6,3%) ar
analysis revealed a differenti
interaction=0.010). In those w
1.87, p=0.131). Conversely, in
readmission (HR:0.70; 95% C
Conclusions: In patients with
prolonged hospitalization in t

Introduction



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Smoking cessation, but not reduction, re
incidence

Su-Min Jeong, Keun Hye Jeon, Dong Wook Shin, Kyungdo Han, Dahy
Ki-Woong Nam, Seung Pyo Lee Author Notes

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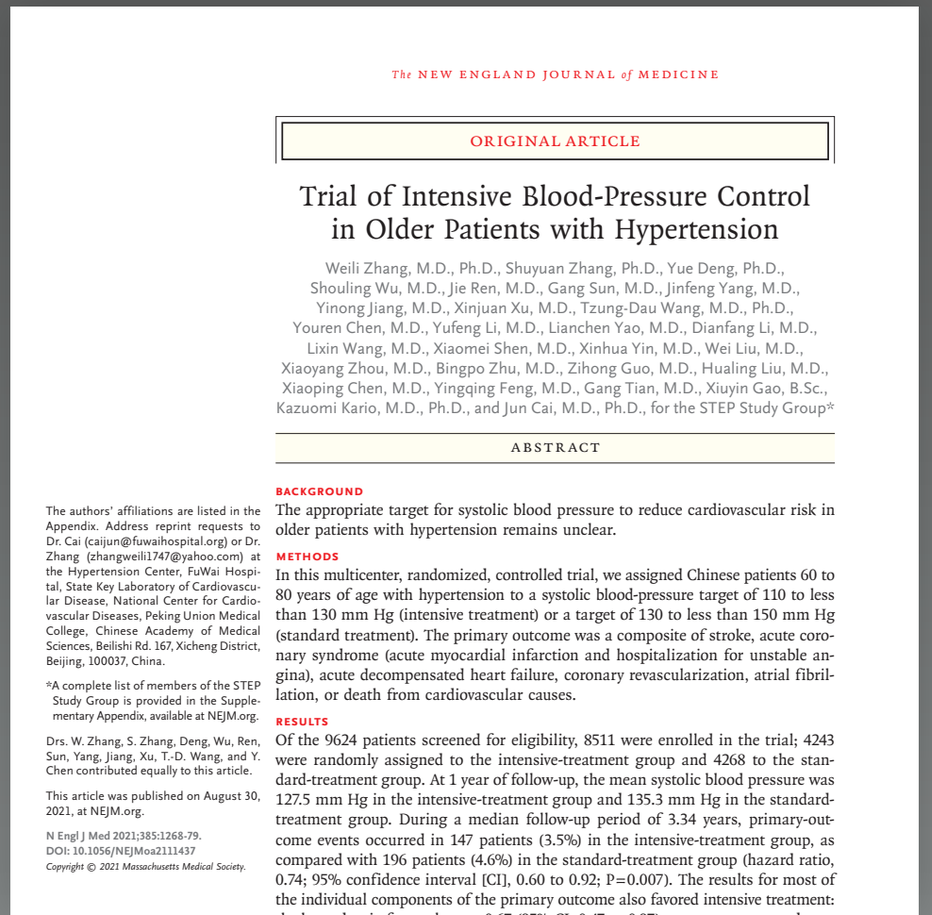
Abstract

Aims

The aim of this study was to assess the association of smoking
disease (CVD).

Methods and results

A total of 897 975 current smokers aged ≥40 years who had unc
(in 2009 and 2011) were included. Participants were classified a
reducers II (20–50% reduction, 11.6%), sustainers (45.7%), an
person-years (PY) of follow-up, 17 748 stroke (3.2/1000 PY) an
events were identified. Quitters had significantly decreased risk
confidence interval (CI) 0.74–0.81; absolute risk reduction (AR
95% CI 0.70–0.78; ARR −0.27, 95% CI −0.31 to −0.22) compare
factors, comorbidities, and smoking status. The risk of stroke a
0.97–1.08 and aHR 0.99, 95% CI 0.92–1.06, respectively) and r
95% CI 0.92–1.04, respectively) was not significantly different



The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

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*A complete list of members of the STEP Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. W. Zhang, S. Zhang, Deng, Wu, Ren, Sun, Yang, Jiang, Xu, T.-D. Wang, and Y. Chen contributed equally to this article.

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ABSTRACT

BACKGROUND
The appropriate target for systolic blood pressure to reduce cardiovascular risk in older patients with hypertension remains unclear.

METHODS
In this multicenter, randomized, controlled trial, we assigned Chinese patients 60 to 80 years of age with hypertension to a systolic blood-pressure target of 110 to less than 130 mm Hg (intensive treatment) or a target of 130 to less than 150 mm Hg (standard treatment). The primary outcome was a composite of stroke, acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

RESULTS
Of the 9624 patients screened for eligibility, 8511 were enrolled in the trial; 4243 were randomly assigned to the intensive-treatment group and 4268 to the standard-treatment group. At 1 year of follow-up, the mean systolic blood pressure was 127.5 mm Hg in the intensive-treatment group and 135.3 mm Hg in the standard-treatment group. During a median follow-up period of 3.34 years, primary-outcome events occurred in 147 patients (3.5%) in the intensive-treatment group, as compared with 196 patients (4.6%) in the standard-treatment group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.92; P=0.007). The results for most of the individual components of the primary outcome also favored intensive treatment:

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