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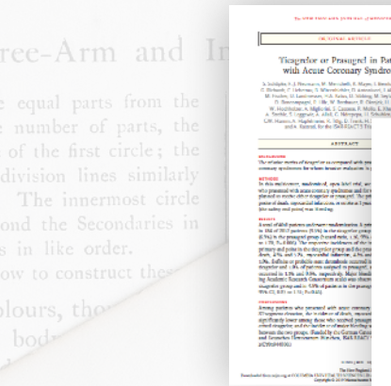
SESIÓN DE ACTUALIZACIÓN
MARTES 29 DE OCTUBRE DE 2019

SESIÓN CLÍNICA
Servicio de Medicina Interna
Consorcio Hospital General Universitario Valencia

Dr. Javier Pitarch Fabregat | R4 Medicina Interna
Dr. David Rodrigo Domínguez | R1 Medicina Interna

Índice

17 artículos



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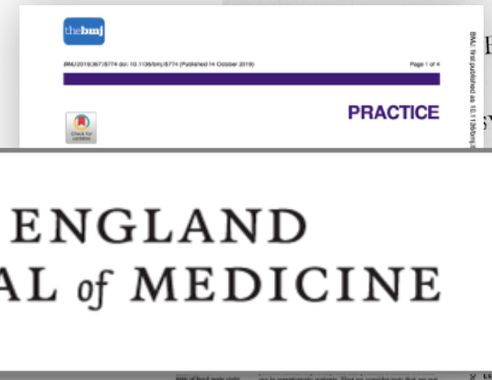

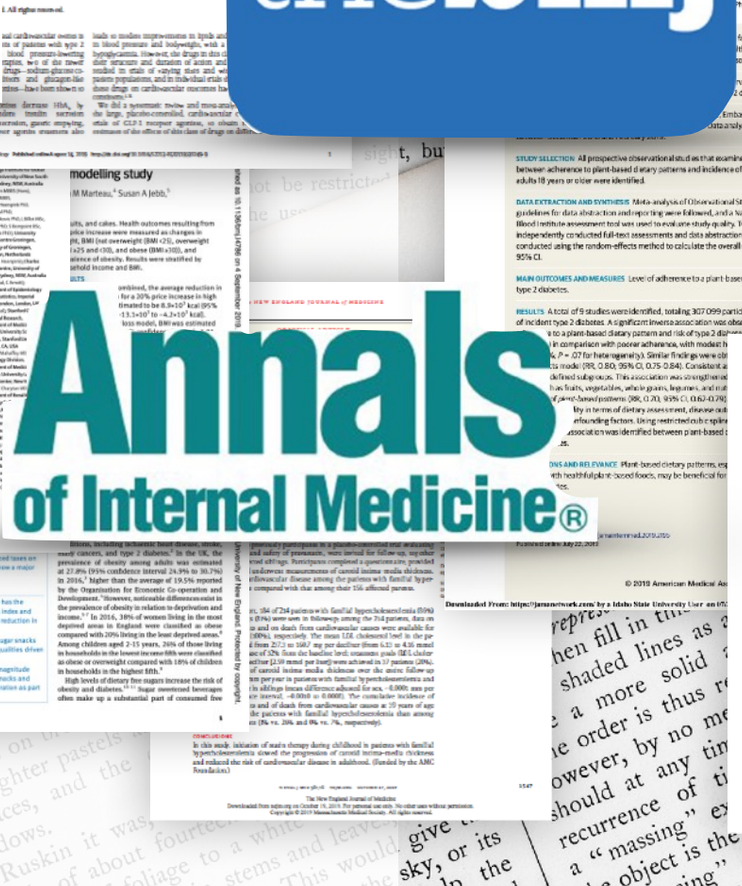

Índice

17 artículos

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

S. Schüpke, F.-J. Neumann, M. Menichelli, K. Mayer, I. Bernlochner, J. Wöhrle, G. Richardt, C. Liebetrau, B. Witzenbichler, D. Antoniucci, I. Akin, L. Bott-Flügel, M. Fischer, U. Landmesser, H.A. Katus, D. Sibbing, M. Seyfarth, M. Janisch, D. Boncompagni, R. Hilz, W. Rottbauer, R. Okrojek, H. Möllmann, W. Hochholzer, A. Migliorini, S. Cassese, P. Mollo, E. Xhepa, S. Kufner, A. Strehle, S. Leggewie, A. Allali, G. Ndrepepa, H. Schühlen, D.J. Angiolillo, C.W. Hamm, A. Hapfelmeier, R. Tölg, D. Trenk, H. Schunkert, K.-L. Laugwitz, and A. Kastrati, for the ISAR-REACT 5 Trial Investigators*

ABSTRACT

BACKGROUND

The relative merits of ticagrelor as compared with prasugrel in patients with acute coronary syndromes for whom invasive evaluation is planned are uncertain.

METHODS

In this multicenter, randomized, open-label trial, we randomly assigned patients who presented with acute coronary syndromes and for whom invasive evaluation was planned to receive either ticagrelor or prasugrel. The primary end point was the composite of death, myocardial infarction, or stroke at 1 year. A major secondary end point (the safety end point) was bleeding.

RESULTS

A total of 4018 patients underwent randomization. A primary-end point event occurred in 184 of 2012 patients (9.3%) in the ticagrelor group and in 137 of 2006 patients (6.9%) in the prasugrel group (hazard ratio, 1.36; 95% confidence interval [CI], 1.09 to 1.70; P=0.006). The respective incidences of the individual components of the primary end point in the ticagrelor group and the prasugrel group were as follows: death, 4.5% and 3.7%; myocardial infarction, 4.8% and 3.0%; and stroke, 1.1% and 1.0%. Definite or probable stent thrombosis occurred in 1.3% of patients assigned to ticagrelor and 1.0% of patients assigned to prasugrel, and definite stent thrombosis occurred in 1.1% and 0.6%, respectively. Major bleeding (as defined by the Bleeding Academic Research Consortium scale) was observed in 5.4% of patients in the ticagrelor group and in 4.8% of patients in the prasugrel group (hazard ratio, 1.12; 95% CI, 0.83 to 1.51; P=0.46).

CONCLUSIONS

Among patients who presented with acute coronary syndromes with or without ST-segment elevation, the incidence of death, myocardial infarction, or stroke was significantly lower among those who received prasugrel than among those who received ticagrelor, and the incidence of major bleeding was not significantly different between the two groups. (Funded by the German Center for Cardiovascular Research

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Schüpke at Deutsches Herzzentrum, Lazarettstr. 36, 80636 Munich, Germany, or at schuepke@dhm.mhn.de.

*A list of the centers and investigators participating in the ISAR-REACT 5 trial is provided in the Supplementary Appendix, available at NEJM.org.

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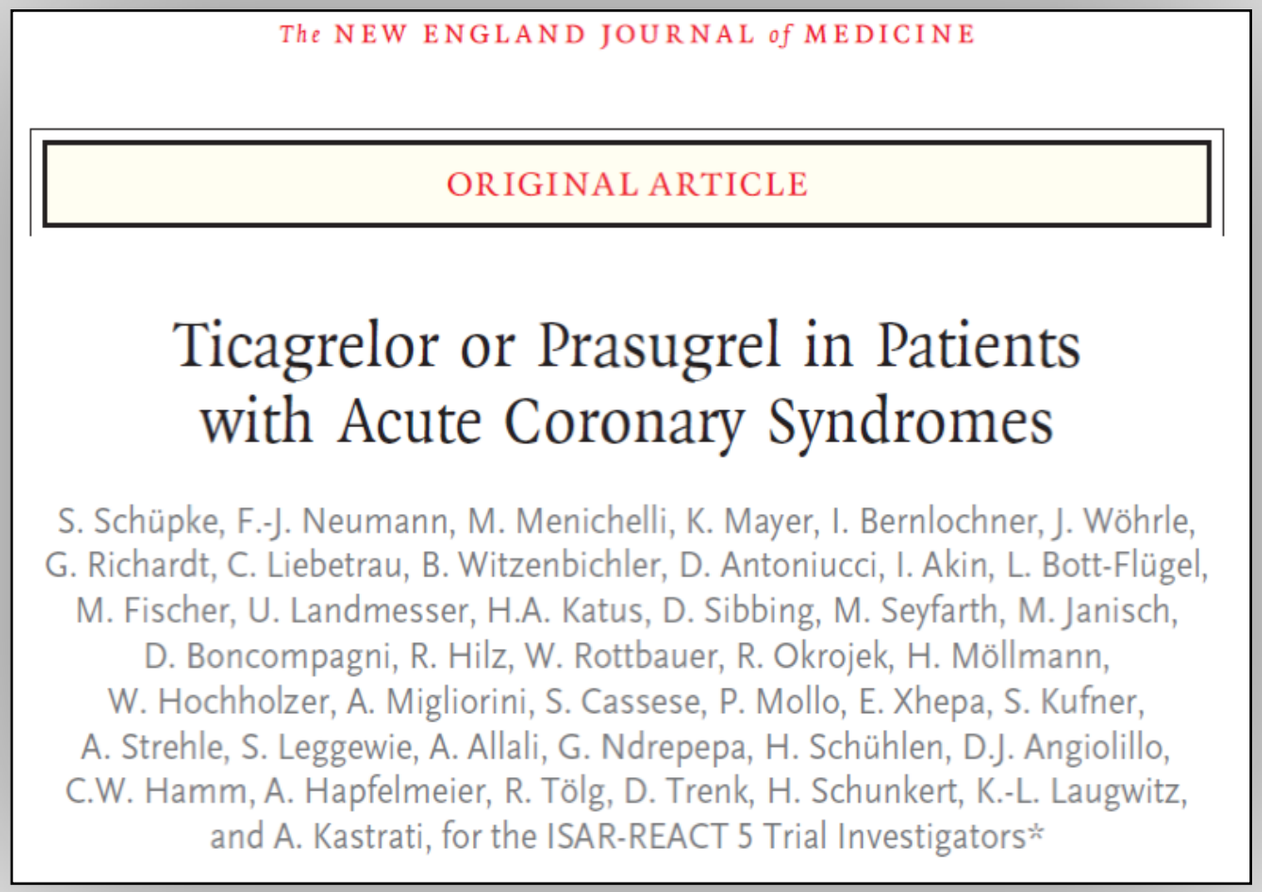

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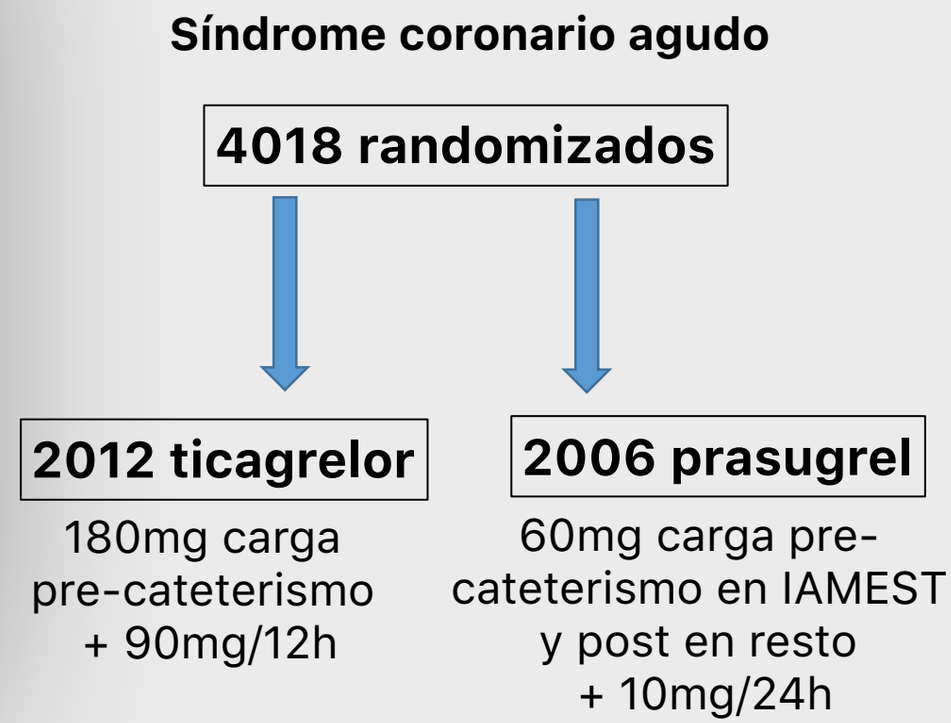

- Ensayo clínico fase 4 multicéntrico, randomizado y abierto
- Comparar la eficacia y la seguridad del tratamiento con **ticagrelor vs prasugrel en pacientes con síndrome coronario agudo** (IAMEST, IAMSEST, AI) que iban a ser sometidos a cateterismo.

- **End point primario: muerte + IAM + ictus en el primer año**
- **End point secundario**: sangrado en un año (tipo 3, 4 o 5 BARC); muerte o infarto o ictus en el primer año; trombosis del stent en el primer año

Resultados

	Ticagrelor (2012)	Prasugrel (2006)	Hazard ratio (95% IC)	p
End point primario	184 (9,3%)	137 (6,9%)	1,3 (1,09-1,70)	0,006
Muerte	90 (4,5%)	73 (3,7%)	1,23 (0,91-1,68)	
Infarto	96 (4,8%)	60 (3,0%)	1,63 (1,18-2,25)	
Ictus	22 (1,1%)	19 (1,0%)	1,17 (0,63-2,15)	
Trombosis stent	26 (1,3%)	20 (1,0%)	1,30 (0,72-2,33)	
Sangrado BARC 3, 4 o 5	95/1989 (5,4%)	80/1773 (4,8%)	1,12 (0,83-1,51)	P=0,46

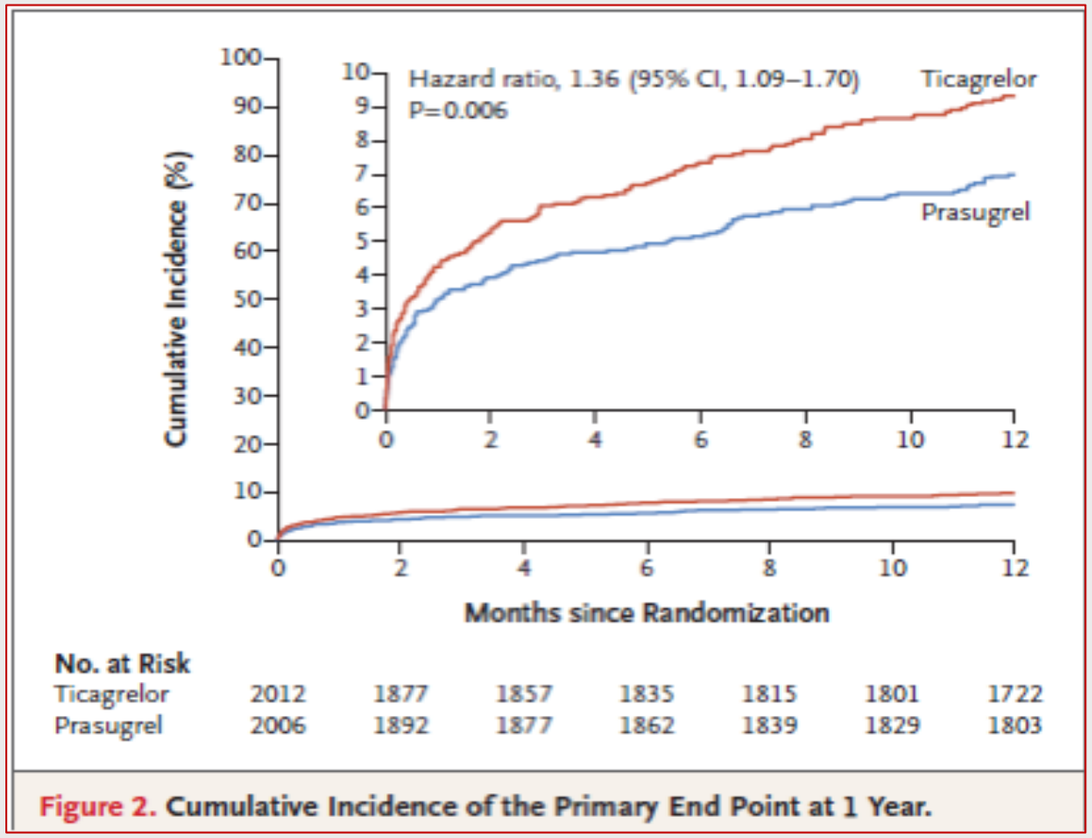

Figure 2. Cumulative Incidence of the Primary End Point at 1 Year.

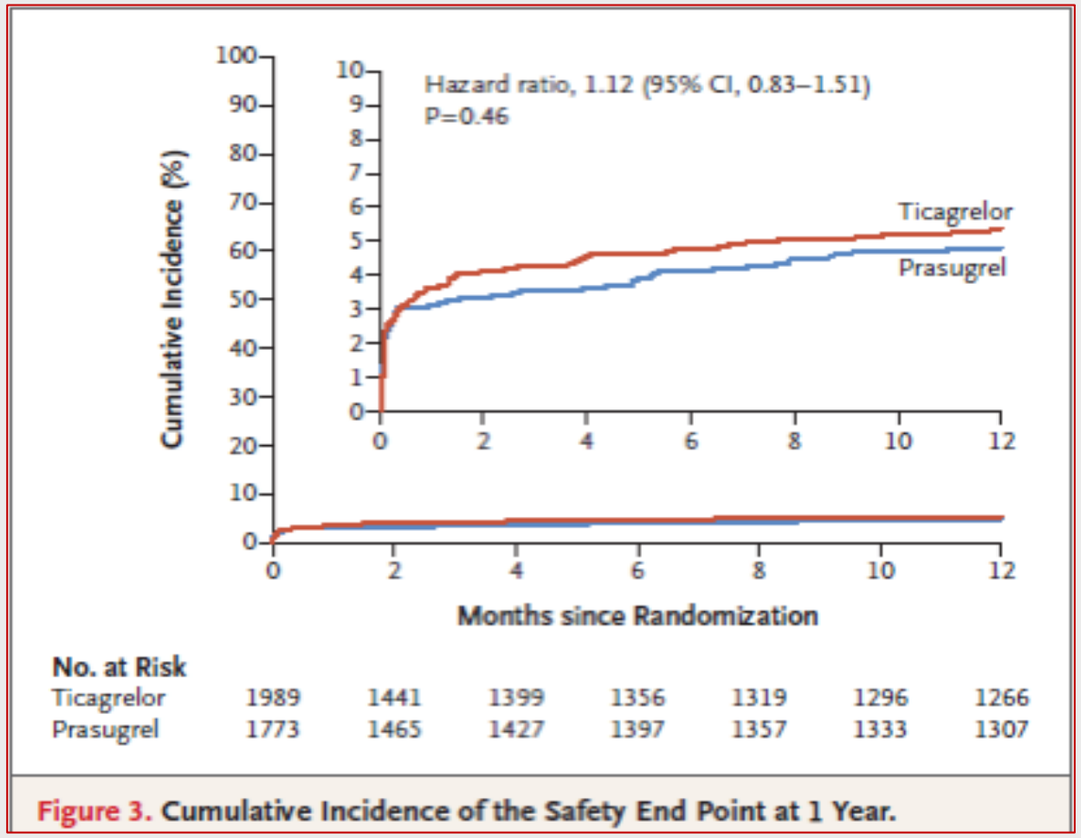

Figure 3. Cumulative Incidence of the Safety End Point at 1 Year.

Conclusiones

- La incidencia del end point combinado de muerte + IAM + ictus fue significativamente menor en los pacientes tratados con prasugrel respecto a los tratados con ticagrelor.
- La incidencia de sangrado mayor fue similar en ambos grupos.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

R. Mehran, U. Baber, S.K. Sharma, D.J. Cohen, D.J. Angiolillo, C. Briguori, J.Y. Cha, T. Collier, G. Dangas, D. Dudek, V. Džavlk, J. Escaned, R. Gil, P. Gurbel, C.W. Hamm, T. Henry, K. Huber, A. Kastrati, U. Kaul, R. Kornowski, M. Krucoff, V. Kunadian, S.O. Marx, S.R. Mehta, D. Moliterno, E.M. Ohman, K. Oldroyd, G. Sardella, S. Sartori, R. Shlofmitz, P.G. Steg, G. Weisz, B. Witzenbichler, Y. Han, S. Pocock, and C.M. Gibson

ABSTRACT

BACKGROUND

Monotherapy with a $P2Y_{12}$ inhibitor after a minimum period of dual antiplatelet therapy is an emerging approach to reduce the risk of bleeding after percutaneous coronary intervention (PCI).

METHODS

In a double-blind trial, we examined the effect of ticagrelor alone as compared with ticagrelor plus aspirin with regard to clinically relevant bleeding among patients who were at high risk for bleeding or an ischemic event and had undergone PCI. After 3 months of treatment with ticagrelor plus aspirin, patients who had not had a major bleeding event or ischemic event continued to take ticagrelor and were randomly assigned to receive aspirin or placebo for 1 year. The primary end point was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. We also evaluated the composite end point of death from any cause, nonfatal myocardial infarction, or nonfatal stroke, using a noninferiority hypothesis with an absolute margin of 1.6 percentage points.

RESULTS

We enrolled 9006 patients, and 7119 underwent randomization after 3 months. Between randomization and 1 year, the incidence of the primary end point was 4.0% among patients randomly assigned to receive ticagrelor plus placebo and 7.1% among patients assigned to receive ticagrelor plus aspirin (hazard ratio, 0.56; 95% confidence interval [CI], 0.45 to 0.68; P<0.001). The difference in risk between the groups was similar for BARC type 3 or 5 bleeding (incidence, 1.0% among patients receiving ticagrelor plus placebo and 2.0% among patients receiving ticagrelor plus aspirin; hazard ratio, 0.49; 99% CI, 0.33 to 0.74). The incidence of death from any cause, nonfatal myocardial infarction, or nonfatal stroke was 3.9% in both groups (difference, −0.06 percentage points; 99% CI, −0.97 to 0.84; hazard ratio, 0.99; 99% CI, 0.78 to 1.25; P<0.001 for noninferiority).

CONCLUSIONS

Among high-risk patients who underwent PCI and completed 3 months of dual antiplatelet therapy, ticagrelor monotherapy was associated with a lower incidence

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mehran at the Icahn School of Medicine at Mount Sinai, 1 Gustav L. Levy Place, Box 1030, New York, NY 10029, or at roxana.mehran@mountsinai.org.

Drs. Mehran and Baber contributed equally to this article.

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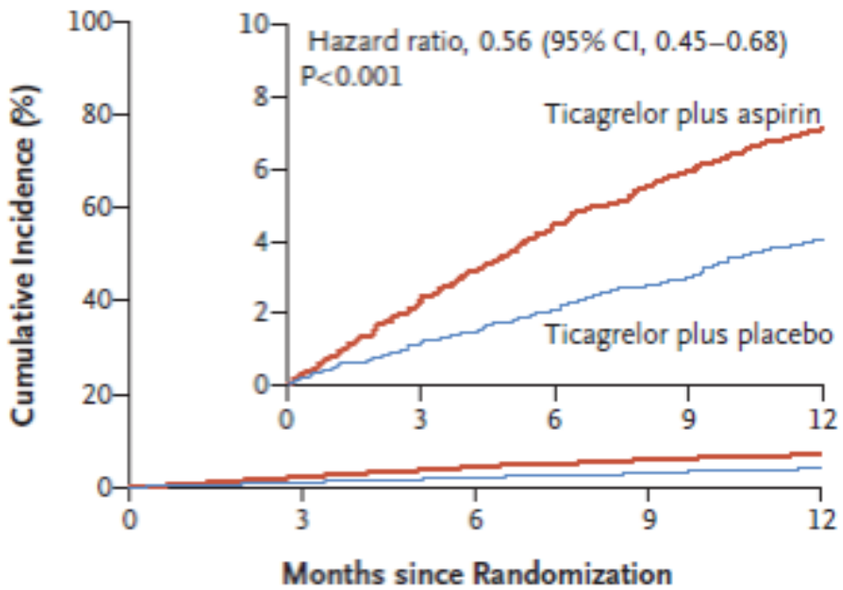
ORIGINAL ARTICLE

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

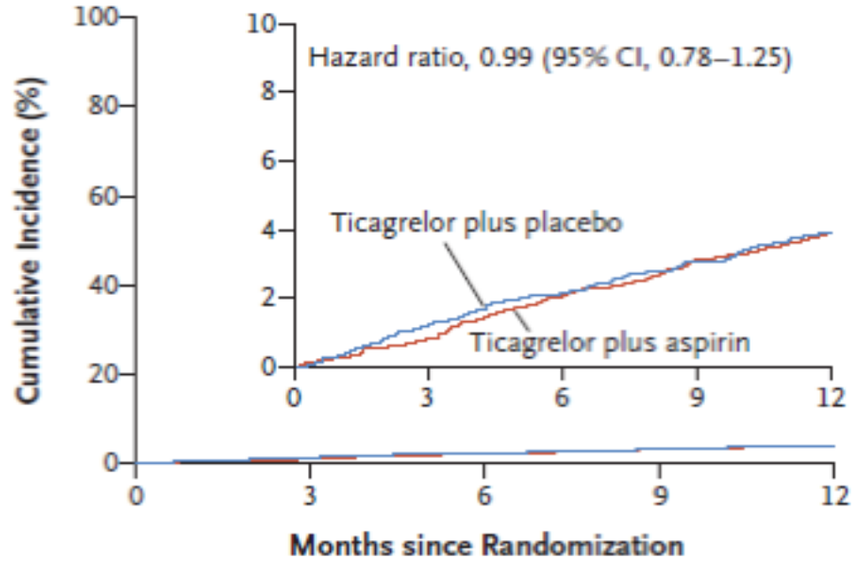
R. Mehran, U. Baber, S.K. Sharma, D.J. Cohen, D.J. Angiolillo, C. Briguori, J.Y. Cha, T. Collier, G. Dangas, D. Dudek, V. Džavík, J. Escaned, R. Gil, P. Gurbel, C.W. Hamm, T. Henry, K. Huber, A. Kastrati, U. Kaul, R. Kornowski, M. Krucoff, V. Kunadian, S.O. Marx, S.R. Mehta, D. Moliterno, E.M. Ohman, K. Oldroyd, G. Sardella, S. Sartori, R. Shlofmitz, P.G. Steg, G. Weisz, B. Witzenbichler, Y. Han, S. Pocock, and C.M. Gibson

- Ensayo clínico controlado, randomizado
- Pacientes en tratamiento con doble antiagregación (AAS + ticagrelor) tras un cateterismo (no IAMEST ni anticoagulación) con al menos una característica clínica y angiográfica de riesgo elevado de eventos trombóticos o de sangrado.
- **End point primario**: sangrado en el primer año
- **End point secundarios**: muerte, infarto o ictus en el primer año.



No. at Risk					
Ticagrelor plus aspirin	3564	3454	3357	3277	3213
Ticagrelor plus placebo	3555	3474	3424	3366	3321

Figure 2. Kaplan–Meier Estimates of the Incidence of BARC Type 2, 3, or 5 Bleeding 1 Year after Randomization (Intention-to-Treat Population).



No. at Risk					
Ticagrelor plus aspirin	3515	3466	3415	3361	3320
Ticagrelor plus placebo	3524	3457	3412	3365	3330

Figure 3. Kaplan–Meier Estimates of the Incidence of Death from Any Cause, Nonfatal Myocardial Infarction, or Nonfatal Stroke 1 Year after Randomization (Per-Protocol Population).

- La riesgo de sagrado mayor fue mayor en el grupo de ticagrelor + AAS respecto al grupo de ticagrelor + placebo, sin aumento de tasas de muerte, infarto, ictus o trombosis del stent.
- Ticagrelor en monoterapia puede ser una estrategia útil de antiagregación para disminuir la tasa de sangrados, manteniendo el beneficio isquémico en pacientes que se hayan sometido a ateterismo con alto riesgo de isquemia y sangrado.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor in Patients with Stable Coronary Disease and Diabetes

P.G. Steg, D.L. Bhatt, T. Simon, K. Fox, S.R. Mehta, R.A. Harrington, C. Held, M. Andersson, A. Himmelmann, W. Ridderstråle, M. Leonsson-Zachrisson, Y. Liu, G. Opolski, D. Zateyshchikov, J. Ge, J.C. Nicolau, R. Corbalán, J.H. Cornel, P. Widimský, and L.A. Leiter, for the THEMIS Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Patients with stable coronary artery disease and diabetes mellitus who have not had a myocardial infarction or stroke are at high risk for cardiovascular events. Whether adding ticagrelor to aspirin improves outcomes in this population is unclear.

METHODS

In this randomized, double-blind trial, we assigned patients who were 50 years of age or older and who had stable coronary artery disease and type 2 diabetes mellitus to receive either ticagrelor plus aspirin or placebo plus aspirin. Patients with previous myocardial infarction or stroke were excluded. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. The primary safety outcome was major bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria.

RESULTS

A total of 19,220 patients underwent randomization. The median follow-up was 39.9 months. Permanent treatment discontinuation was more frequent with ticagrelor than placebo (34.5% vs. 25.4%). The incidence of ischemic cardiovascular events (the primary efficacy outcome) was lower in the ticagrelor group than in the placebo group (7.7% vs. 8.5%; hazard ratio, 0.90; 95% confidence interval [CI], 0.81 to 0.99; P=0.04), whereas the incidence of TIMI major bleeding was higher (2.2% vs. 1.0%; hazard ratio, 2.32; 95% CI, 1.82 to 2.94; P<0.001), as was the incidence of intracranial hemorrhage (0.7% vs. 0.5%; hazard ratio, 1.71; 95% CI, 1.18 to 2.48; P=0.005). There was no significant difference in the incidence of fatal bleeding (0.2% vs. 0.1%; hazard ratio, 1.90; 95% CI, 0.87 to 4.15; P=0.11). The incidence of an exploratory composite outcome of irreversible harm (death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial hemorrhage) was similar in the ticagrelor group and the placebo group (10.1% vs. 10.8%; hazard ratio, 0.93; 95% CI, 0.86 to 1.02).

CONCLUSIONS

In patients with stable coronary artery disease and diabetes without a history of myocardial infarction or stroke, those who received ticagrelor plus aspirin had a lower incidence of ischemic cardiovascular events but a higher incidence of major

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Steg at the Department of Cardiology, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France, or at gabriel.steg@aphp.fr; or to Dr. Bhatt at Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, 75 Francis St., Boston, MA 02115, or at dlbhattmd@post.harvard.edu.

*A list of THEMIS investigators and committee members is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Steg and Bhatt contributed equally to this article.

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ORIGINAL ARTICLE

Ticagrelor in Patients with Stable Coronary Disease and Diabetes

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- Ensayo clínico controlado, randomizado, doble ciego
- Pacientes con diabetes y enfermedad coronaria estable (stent, estenosis en coronariografía 50%, bypass), sin historia de infarto o ictus.
- AAS + placebo vs AAS + ticagrelor
- **End point primario eficacia**: muerte, infarto o ictus en el primer año
- **End point primario seguridad**: sangrado mayor.

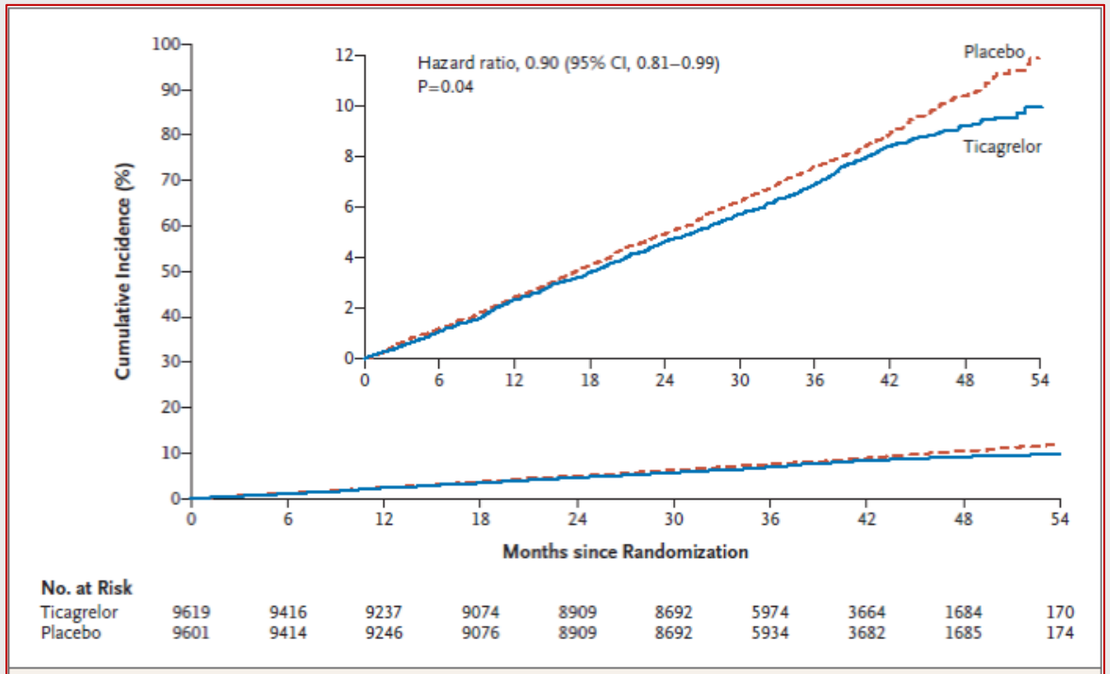

Figure 1. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.

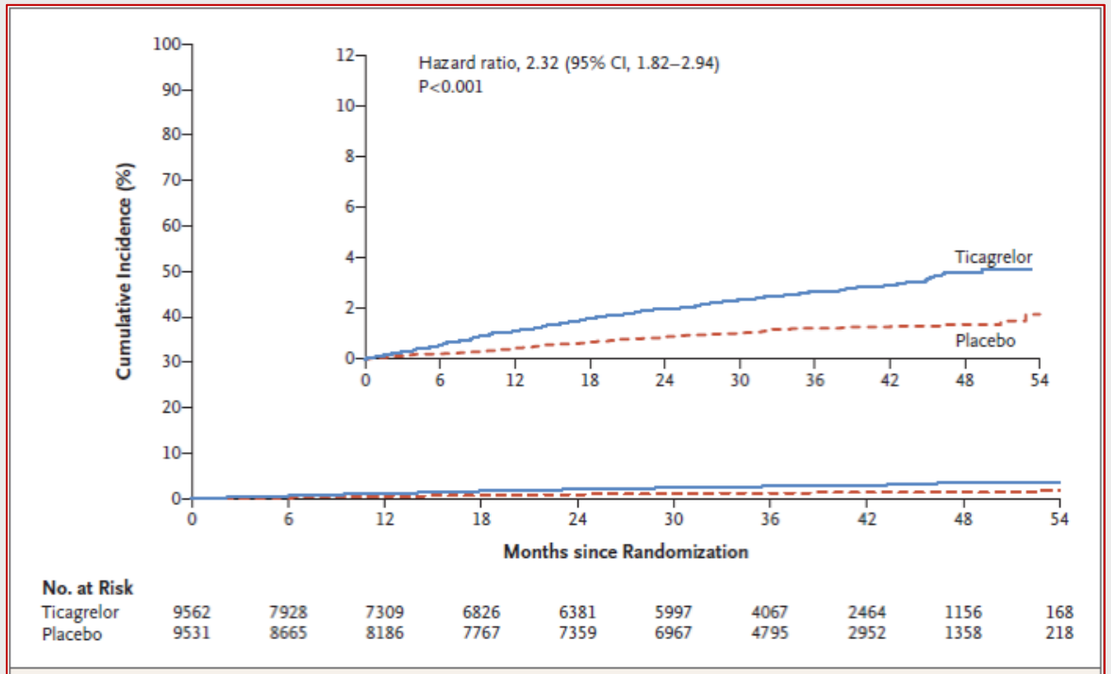

Figure 2. Kaplan–Meier Analysis of the Primary Safety Outcome.

- Menor riesgo de infarto (HR 0,71-0,98) e ictus (HR 0,64-0,99) en el grupo con AAS+tiagrelor vs AAS+placebo, sin diferencias de mortalidad. NNT=138
- Mayor riesgo de sangrado mayor (incluyendo hemorragia intracraneal) en el grupo con AAS+ticagrelor vs AAS+placebo (HR 1,82-2,94). NNH=93
- La doble antiagregación con ticagrelor no presenta una ratio riesgo-beneficio favorable en la población de este estudio.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

RESULTS

Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. McMurray at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl., Glasgow G12 8TA, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

*A complete list of DAPA-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 19, 2019, at NEJM.org.

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Contexto

McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019:1–13. doi:10.1056/nejmoa1911303.

The NEW ENGLAND JOURNAL of MEDICINE

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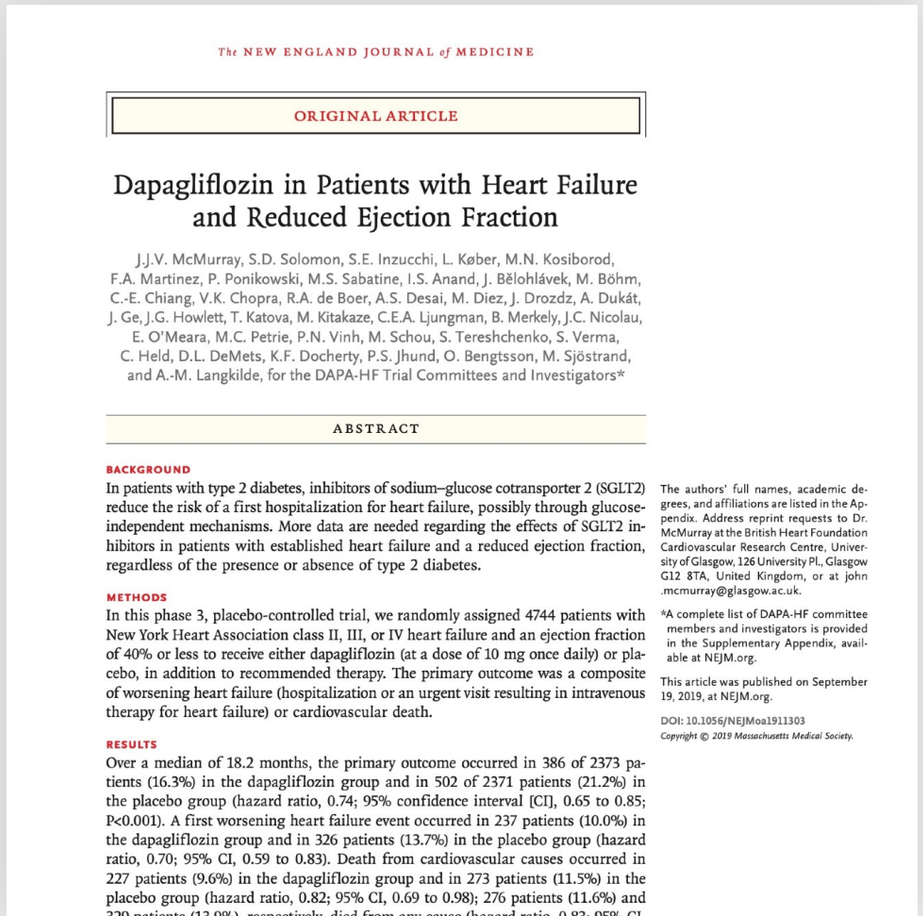

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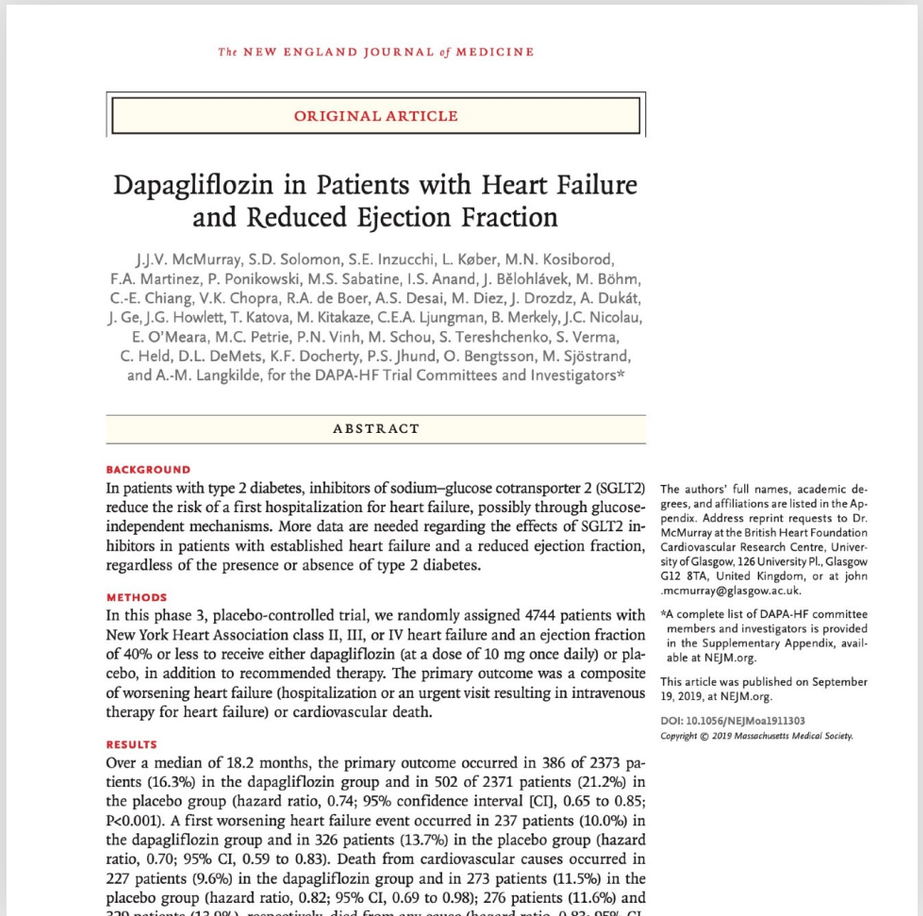

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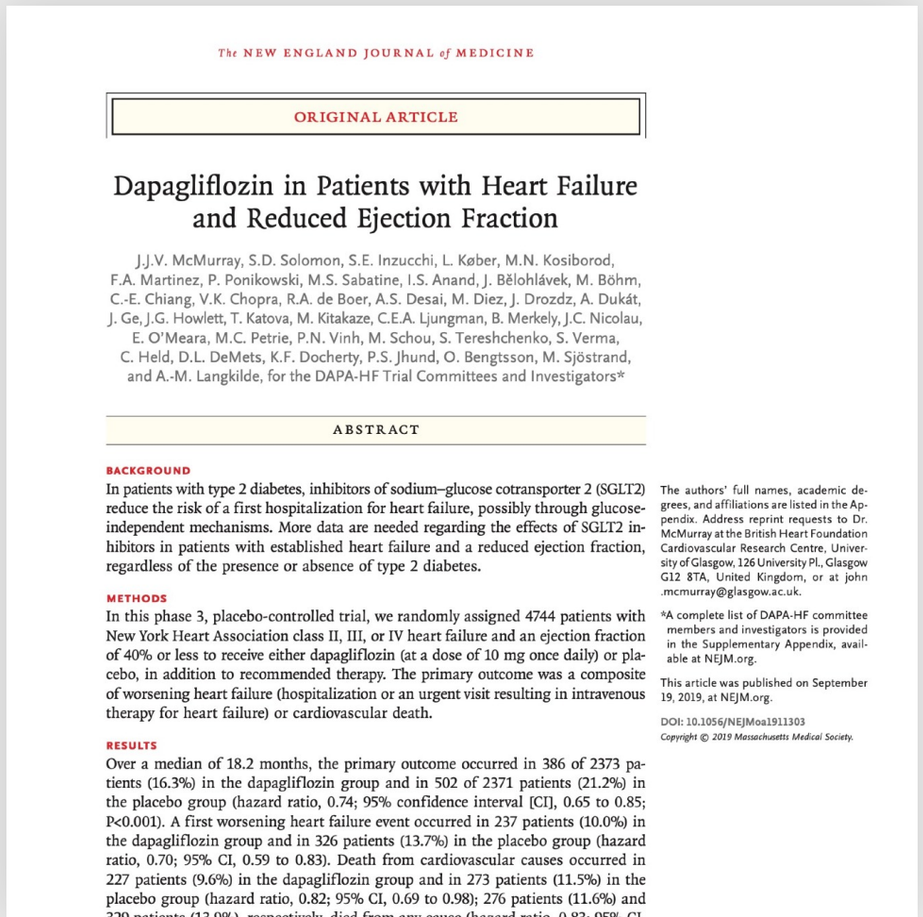

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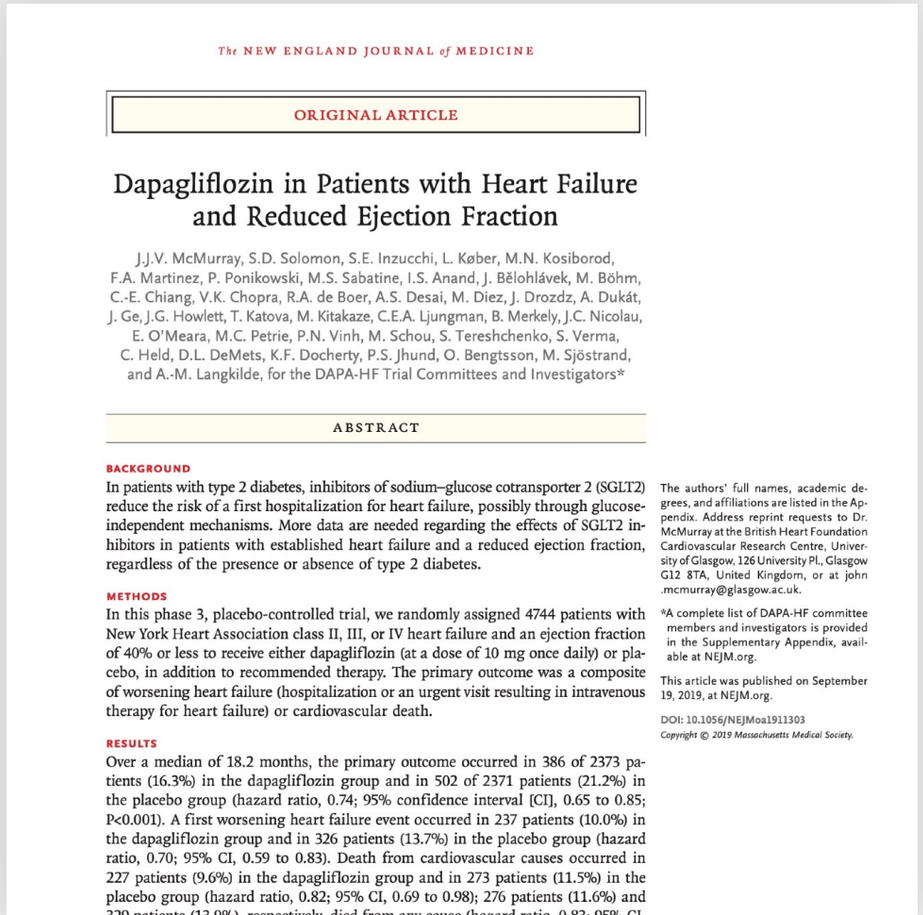

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Métodos

- **Ensayo clínico** fase 3 aleatorizado y controlado con **placebo.**

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J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

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Métodos

- **Ensayo clínico** fase 3 aleatorizado y controlado con **placebo**

- **Objetivo** primario (compuesto):

Empeoramiento de IC (**hospitalización** o una visita **urgente** que resultara en terapia intravenosa para IC)

OR

Muerte de **causa CV**

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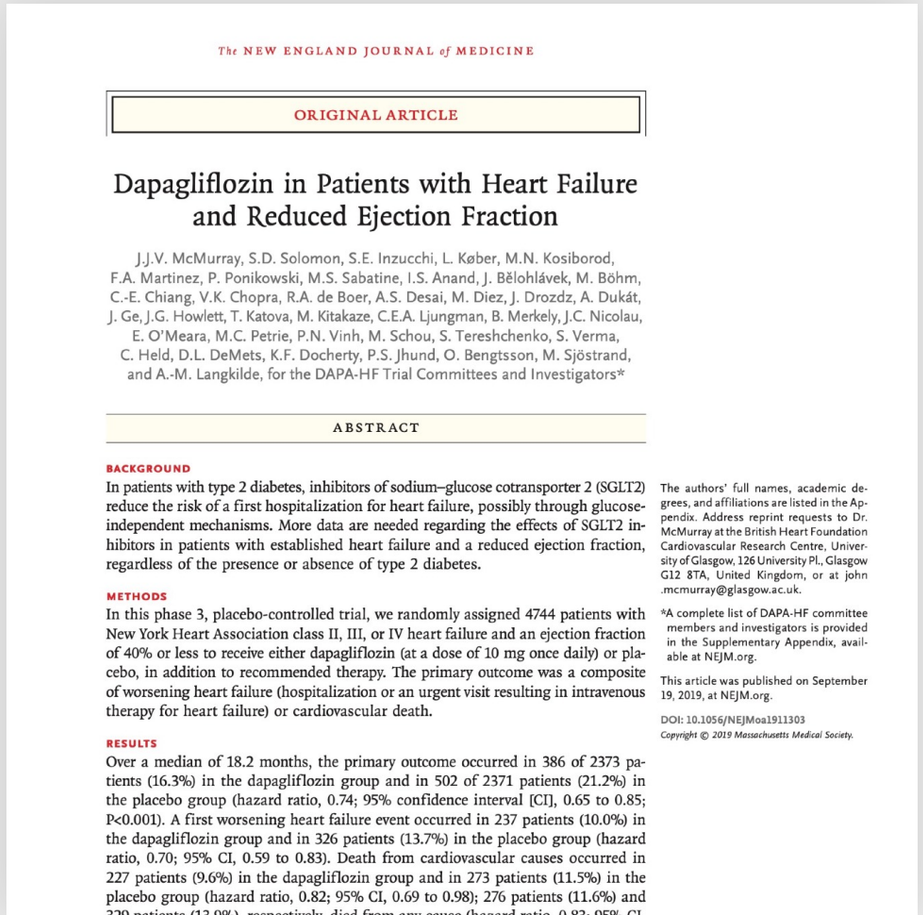

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Criterios de inclusión

- Edad ≥ 18 años
- FEVI **≤ 40%**
- **Síntomas** de clase **II, III o IV** de la New York Heart Association (NYHA)
- NT-proBNP de:
  - **≥ 600** pg/ml
  - ≥400 pg/ml si habían sido hospitalizados por insuficiencia cardíaca en los 12 meses anteriores.
  - ≥ 900 pg/ml independientemente de sus antecedentes de hospitalización a los pacientes con FA o flutter.
- **Terapia óptima estándar** farmacológica y/o con dispositivos para la IC y la DM2.

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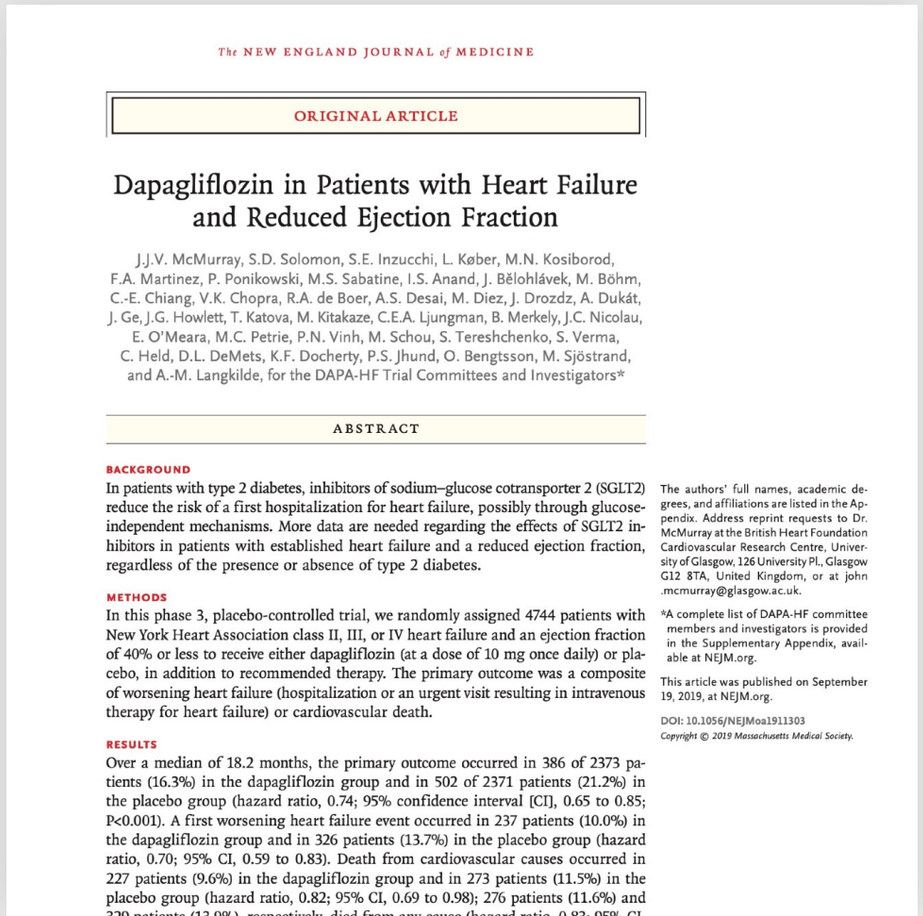

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Criterios de exclusión

- **Efectos adversos** inaceptables de iSGLT2
- DM tipo **1**
- PA**S < 95** mmHg o hipotensión
- **Filtrado** Glomerular **< 30** ml/min/1,73m²

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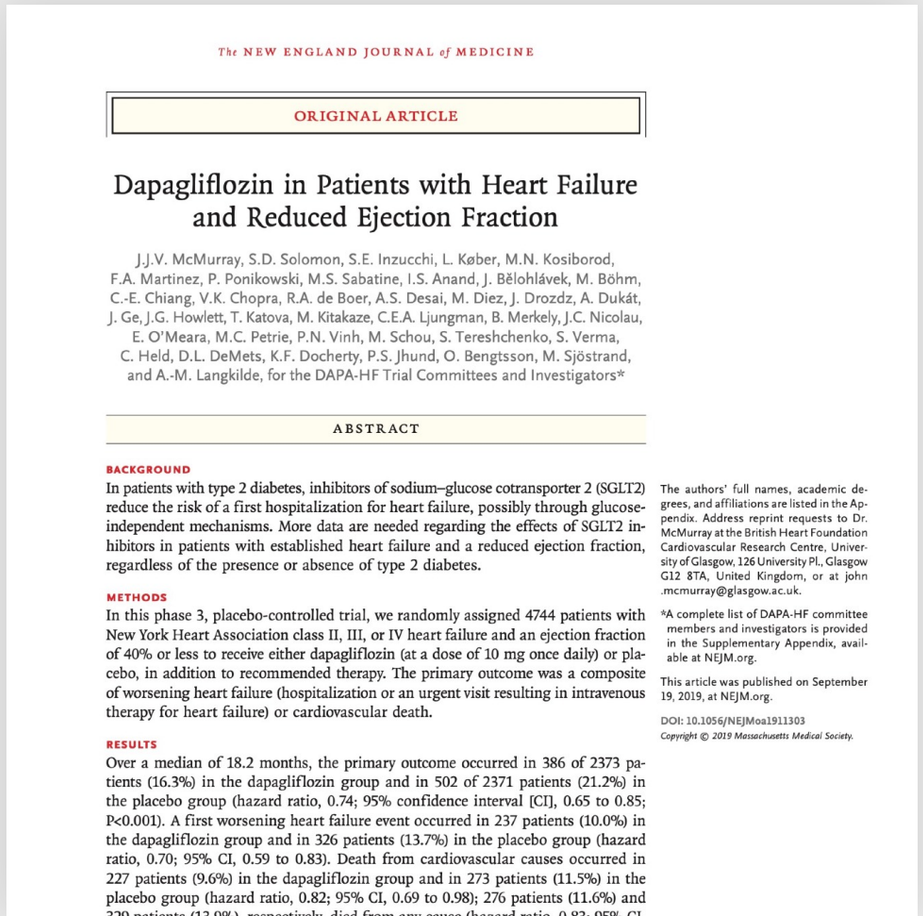

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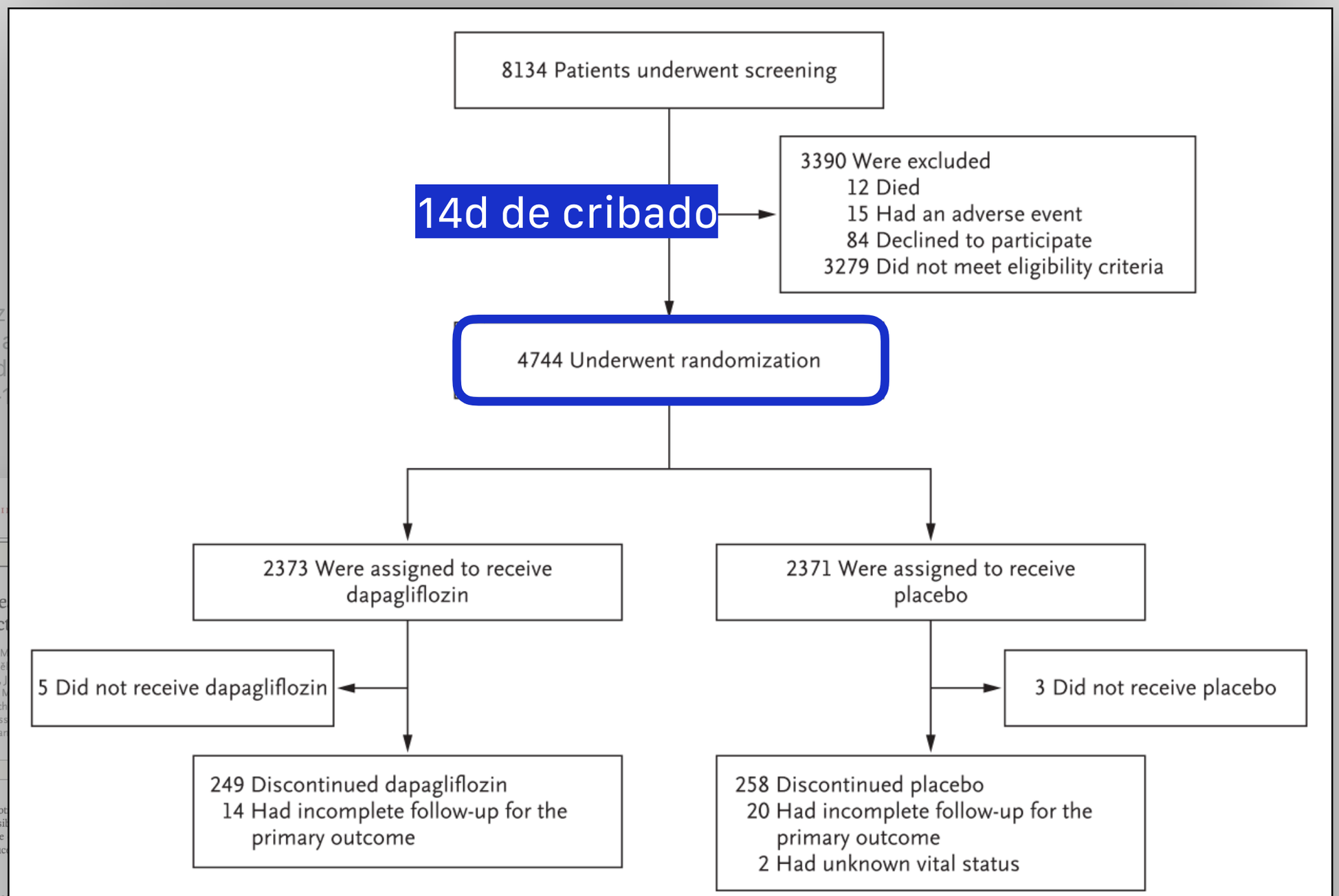

Figure 1. Enrollment and Follow-up.

All the patients who underwent randomization were included in the primary analysis. Patients who did not receive a dose of either dapagliflozin or placebo were excluded from the safety analysis.

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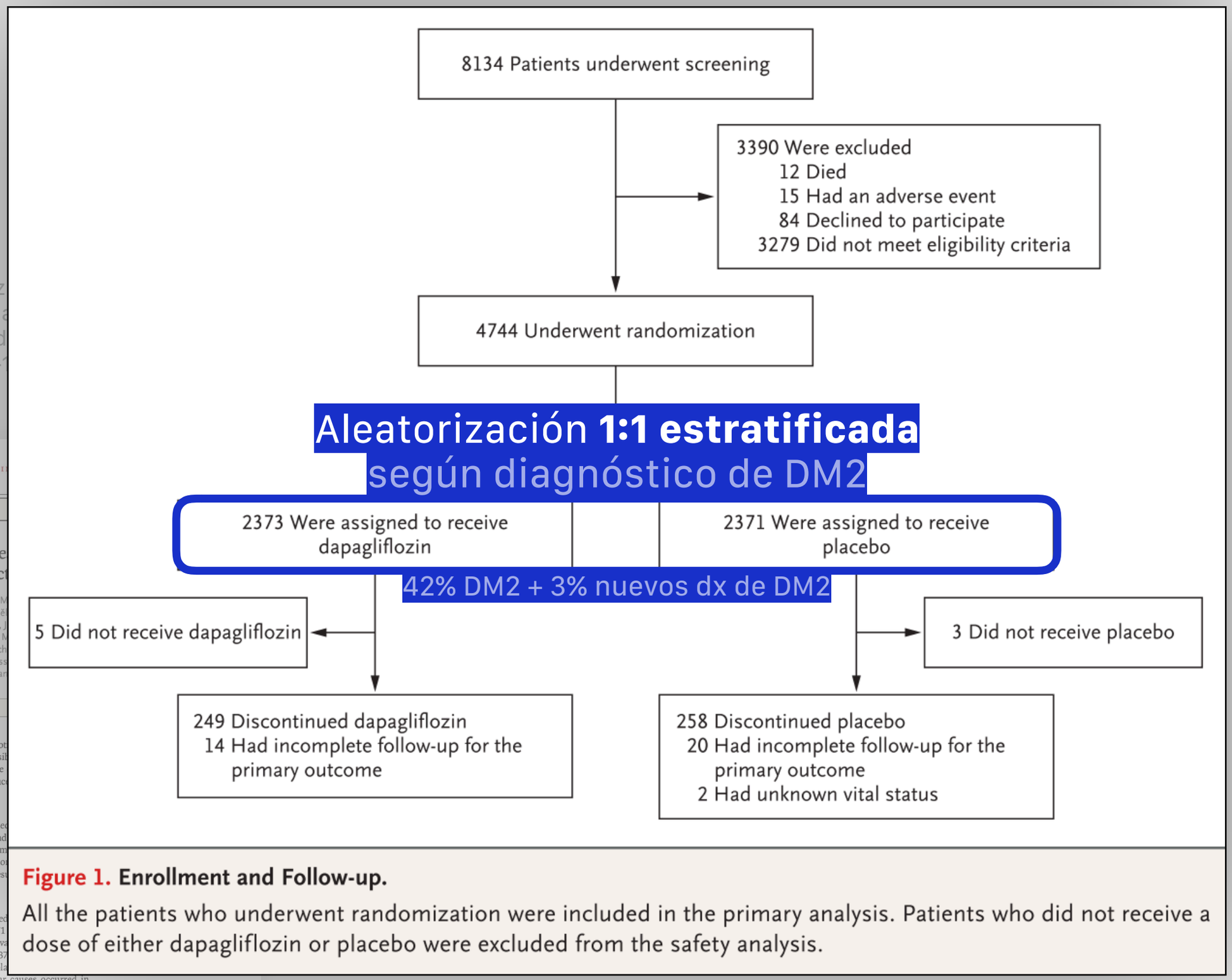

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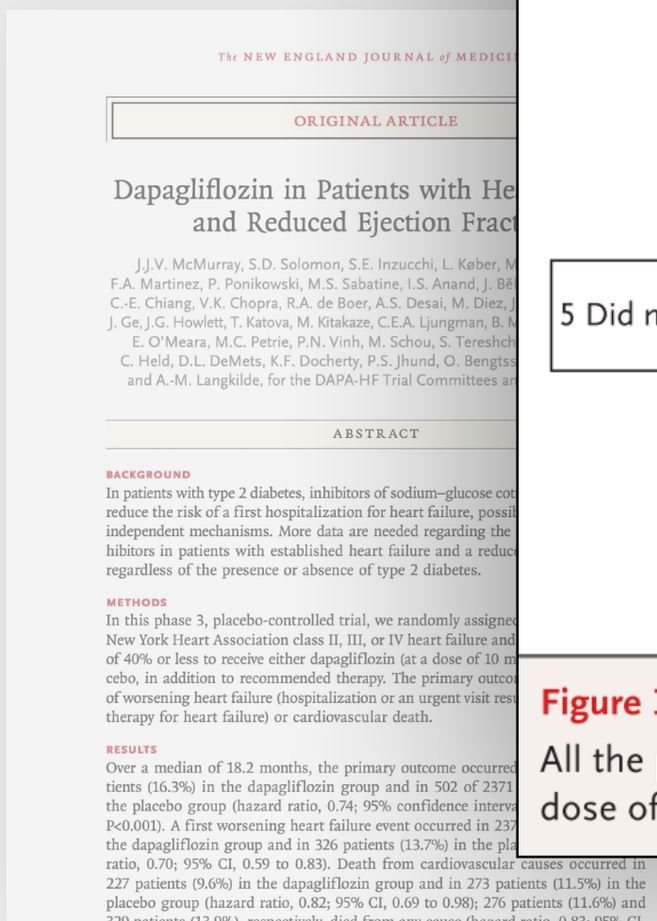

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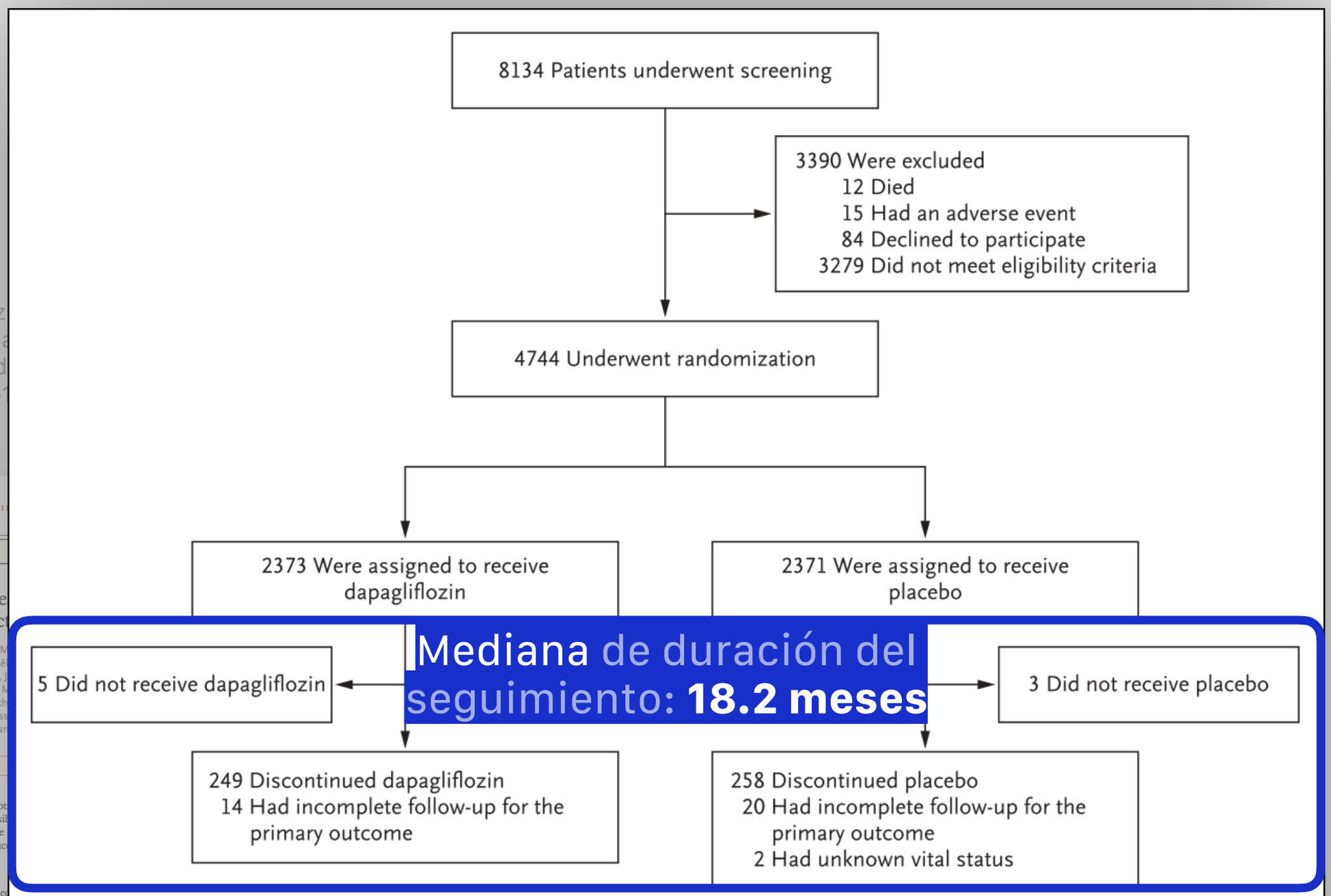

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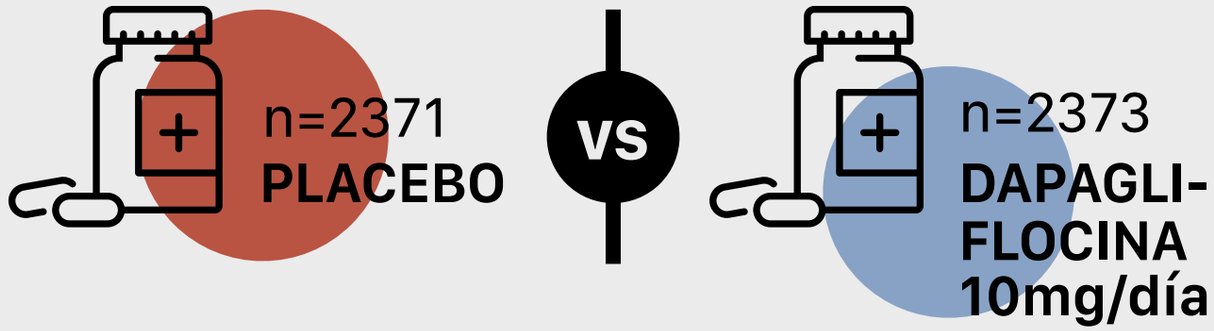

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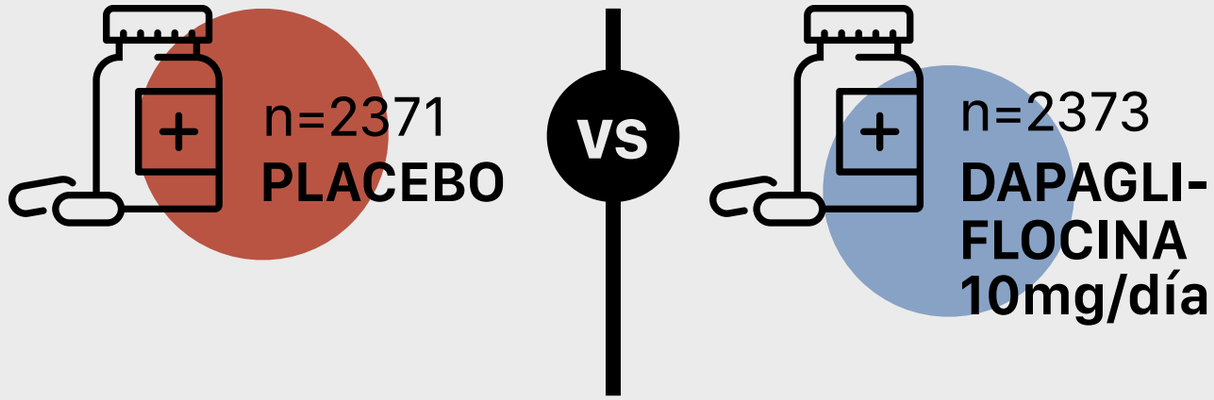

↓ IC

OR

Muerte de causa CV

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ABSTRACT

BACKGROUND

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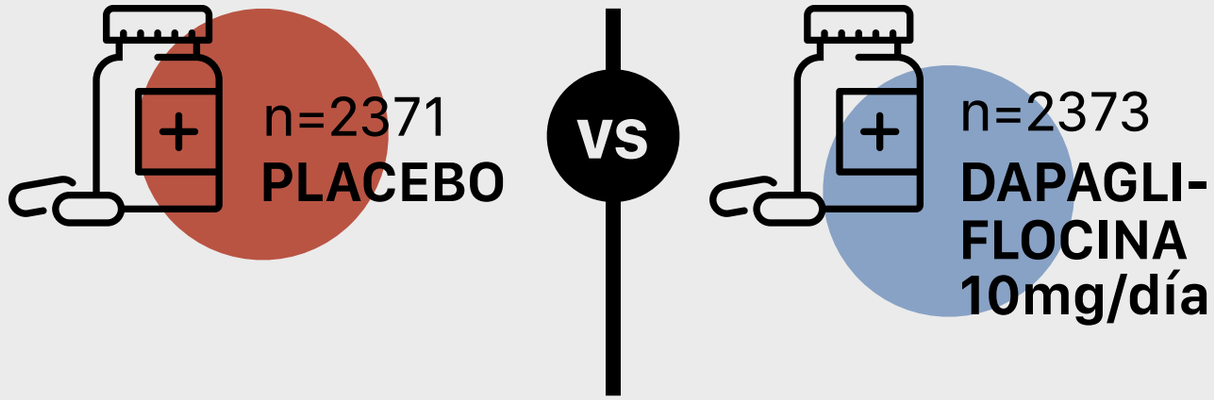
Resultados



15.6 eventos/ 100p-año

↓ IC

OR

Muerte de causa CV

11.6 eventos/ 100p-año

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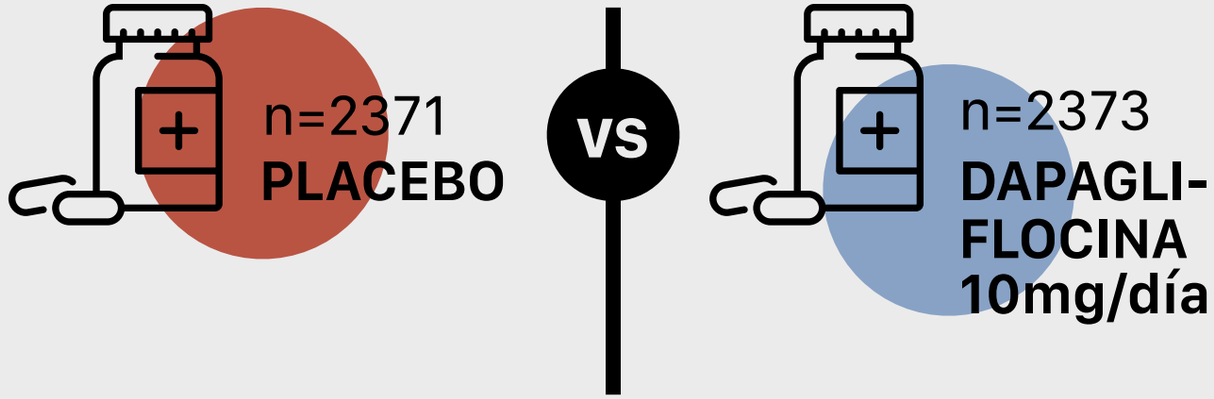

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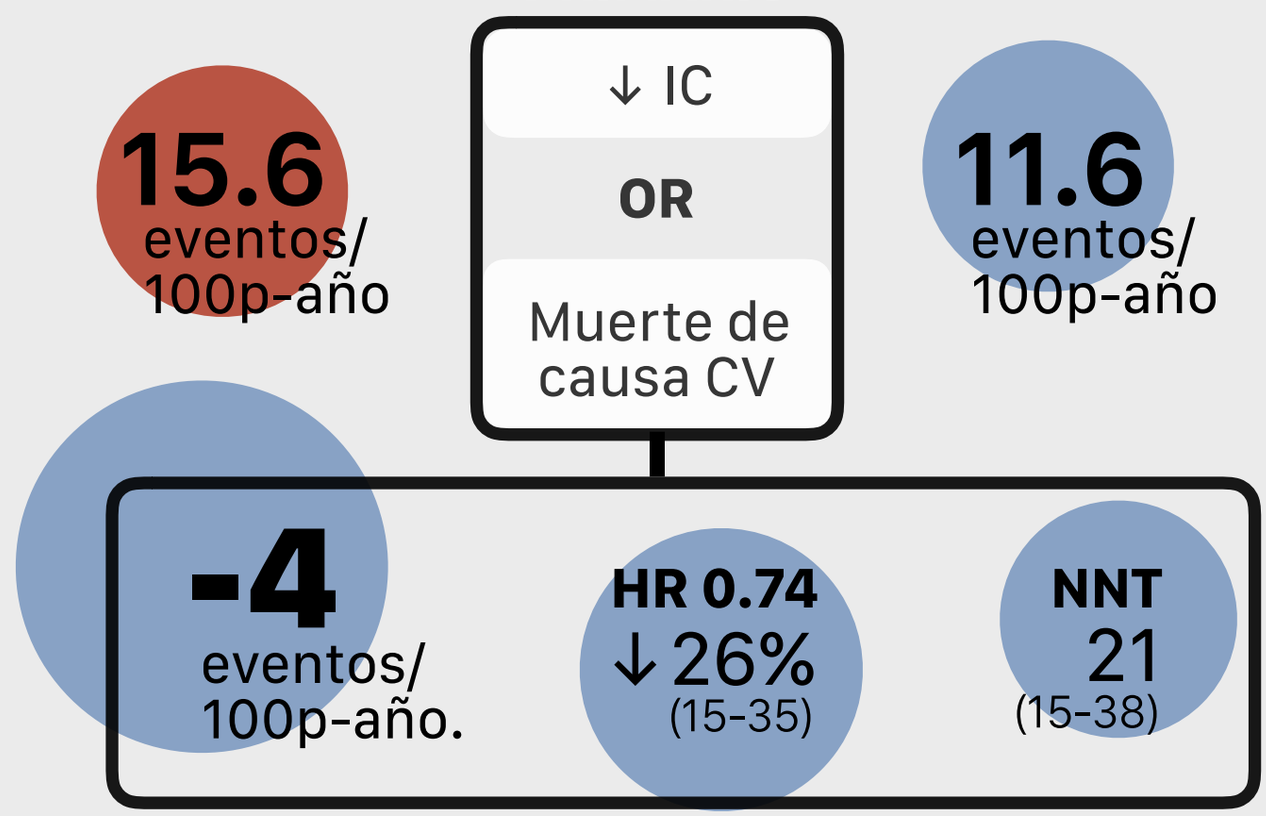

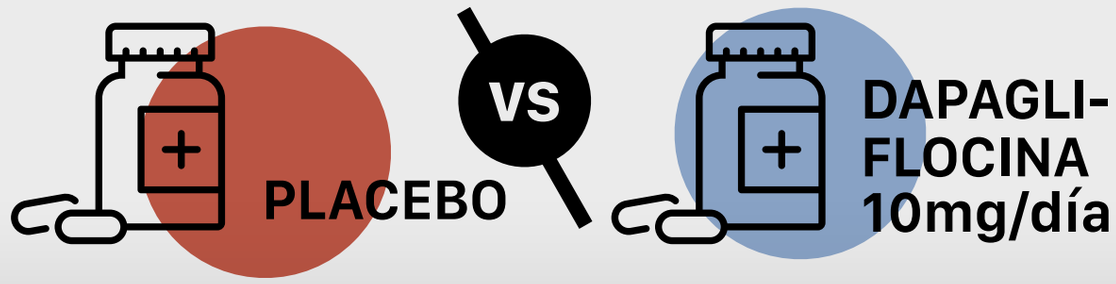

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Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo§	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001
Worsening renal function — no. (%)¶	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	NA
Death from any cause — no. (%)	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)	NA

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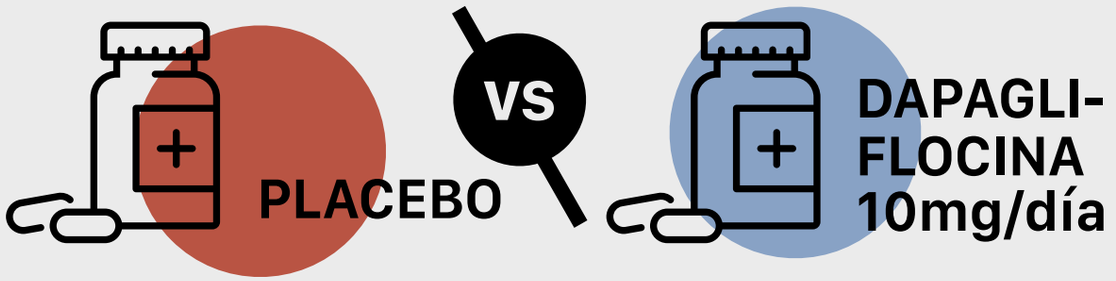

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Ningún exceso de RAM reseñable.

Safety outcomes‖						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	0.79
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	—	—	0.40
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	—	—	0.36
Fracture	49/2368 (2.1)		50/2368 (2.1)	—	—	1.00
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	—	—	1.00
Major hypoglycemia**	4/2368 (0.2)	—	4/2368 (0.2)	—	—	NA
Diabetic ketoacidosis††	3/2368 (0.1)	—	0	—	—	NA
Fournier's gangrene	0	—	1/2368 (<0.1)	—	—	NA

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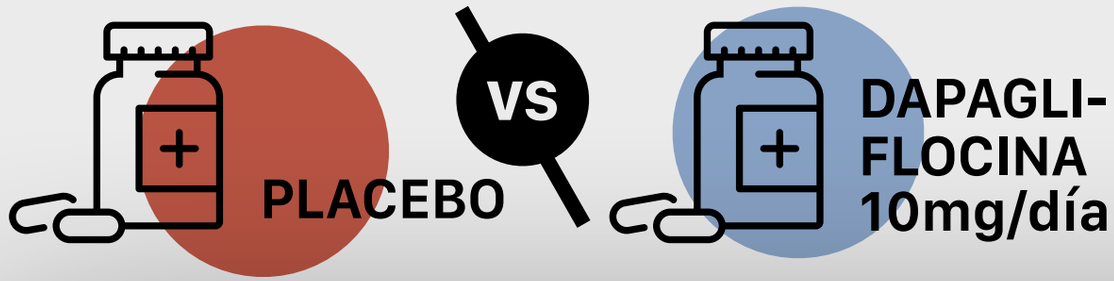

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Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Age			
≤65 yr	162/1032	196/998	0.78 (0.63–0.96)
>65 yr	224/1341	306/1373	0.72 (0.60–0.85)
Sex			
Male	307/1809	406/1826	0.73 (0.63–0.85)
Female	79/564	96/545	0.79 (0.59–1.06)
Race			
White	275/1662	348/1671	0.78 (0.66–0.91)
Black	26/122	32/104	0.62 (0.37–1.04)
Asian	78/552	118/564	0.64 (0.48–0.86)
Other	7/37	4/32	
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)

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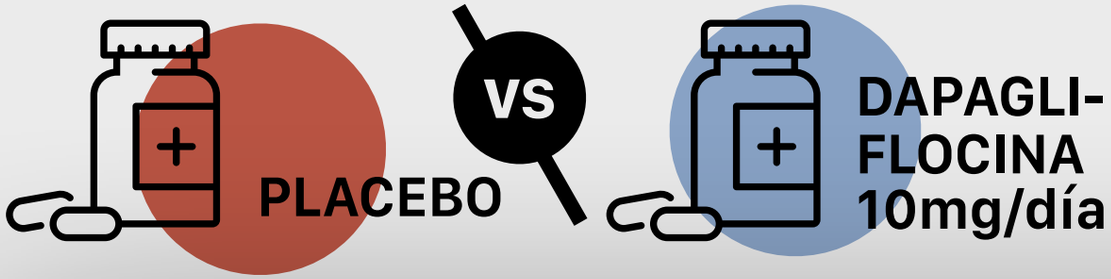

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Cardiovascular Researc
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in the Supplementary
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19, 2019, at NEJM.org

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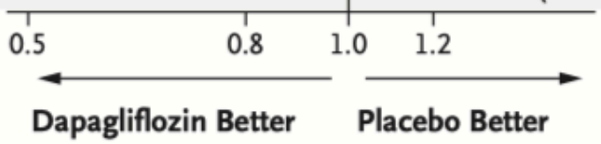
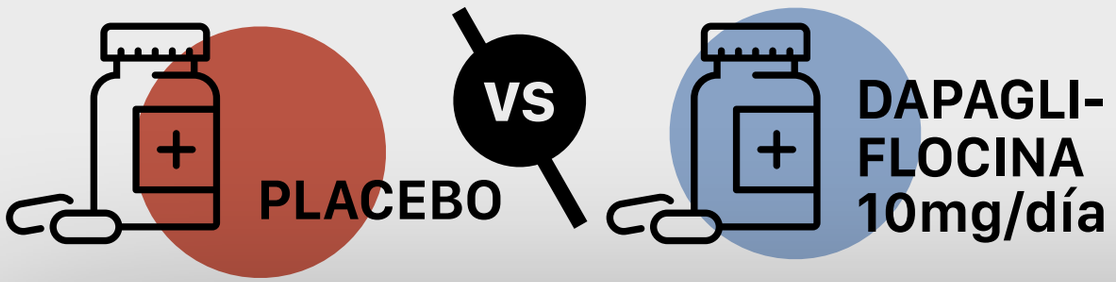
NYHA class				
II	190/1606	289/1597		0.63 (0.52–0.75)
III or IV ✕	196/767	213/774		0.90 (0.74–1.09)
LVEF				
≤Median	222/1230	307/1239		0.70 (0.59–0.84)
>Median	164/1143	195/1132		0.81 (0.65–0.99)
NT-proBNP				
≤Median	100/1193	155/1179		0.63 (0.49–0.80)
>Median	286/1179	347/1191		0.79 (0.68–0.92)
Hospitalization for heart failure				
Yes	195/1124	279/1127		0.67 (0.56–0.80)
No	191/1249	223/1244		0.84 (0.69–1.01)
MRA at baseline				
Yes	281/1696	361/1674		0.74 (0.63–0.87)
No	105/677	141/697		0.74 (0.57–0.95)
Type 2 diabetes at baseline				
Yes =	215/1075	271/1064		0.75 (0.63–0.90)
No =	171/1298	231/1307		0.73 (0.60–0.88)
Atrial fibrillation or flutter on enrollment ECG				
Yes ✕	109/569	126/559		0.82 (0.63–1.06)
No	277/1804	376/1812		0.72 (0.61–0.84)
Main cause of heart failure				
Ischemic	223/1316	289/1358		0.77 (0.65–0.92)
Nonischemic or unknown	163/1057	213/1013		0.71 (0.58–0.87)
Body-mass index				
<30	259/1537	320/1533		0.78 (0.66–0.92)
≥30	127/834	182/838		0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m²)				
<60	191/962	254/964		0.72 (0.59–0.86)
≥60	195/1410	248/1406		0.76 (0.63–0.92)





Resultados

Un análisis de subgrupos post hoc que incluyó a pacientes que tomaban **sacubitril-valsartán** al inicio del estudio, el cociente de riesgos para la comparación de dapagliflozina y placebo para la medida de resultado primaria fue de 0,75 (IC del 95%: **0,50 a 1,13**), en comparación con 0,74 (IC del 95%: 0,65 a 0,86) entre los que no tomaban sacubitril-valsartán.

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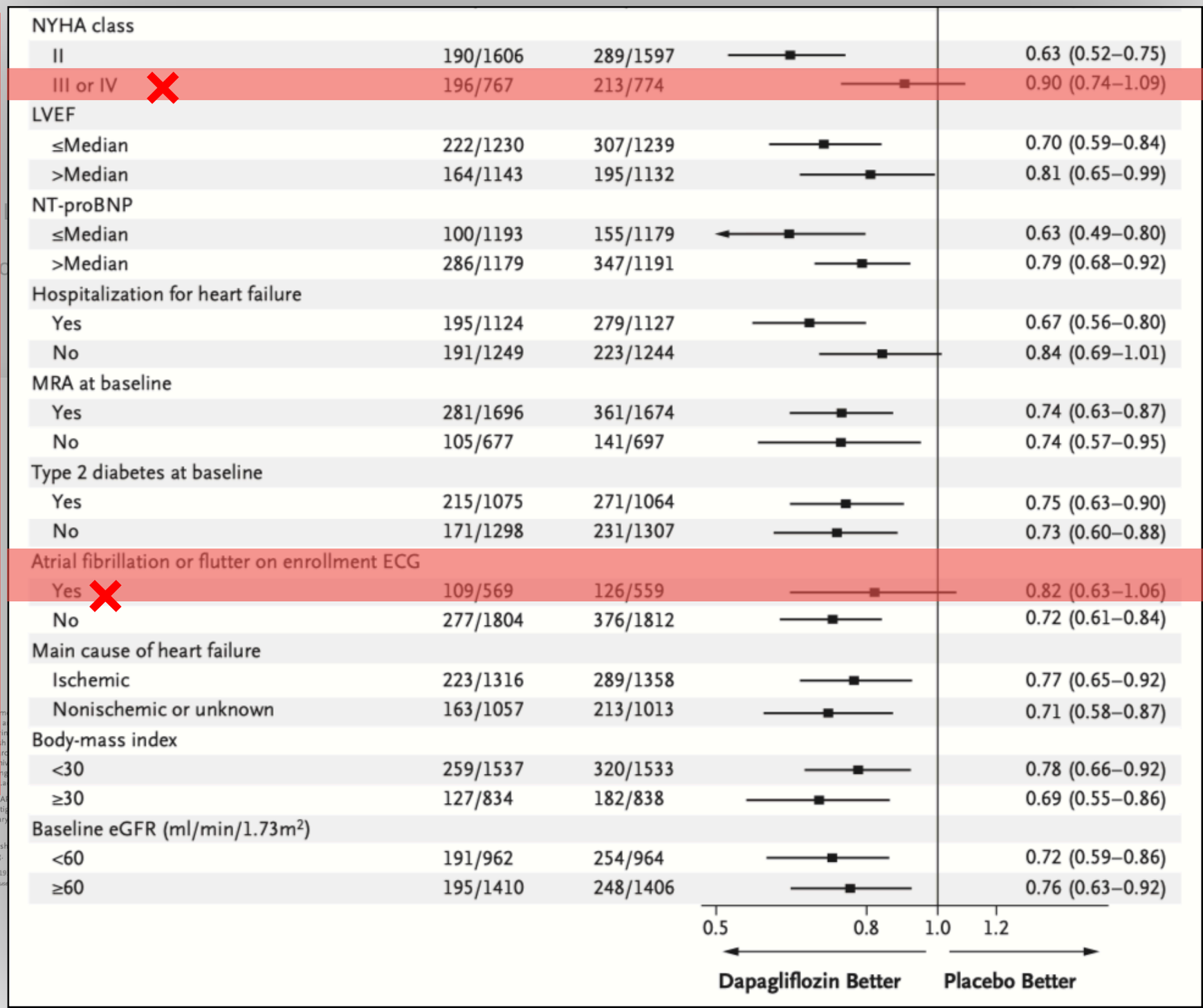

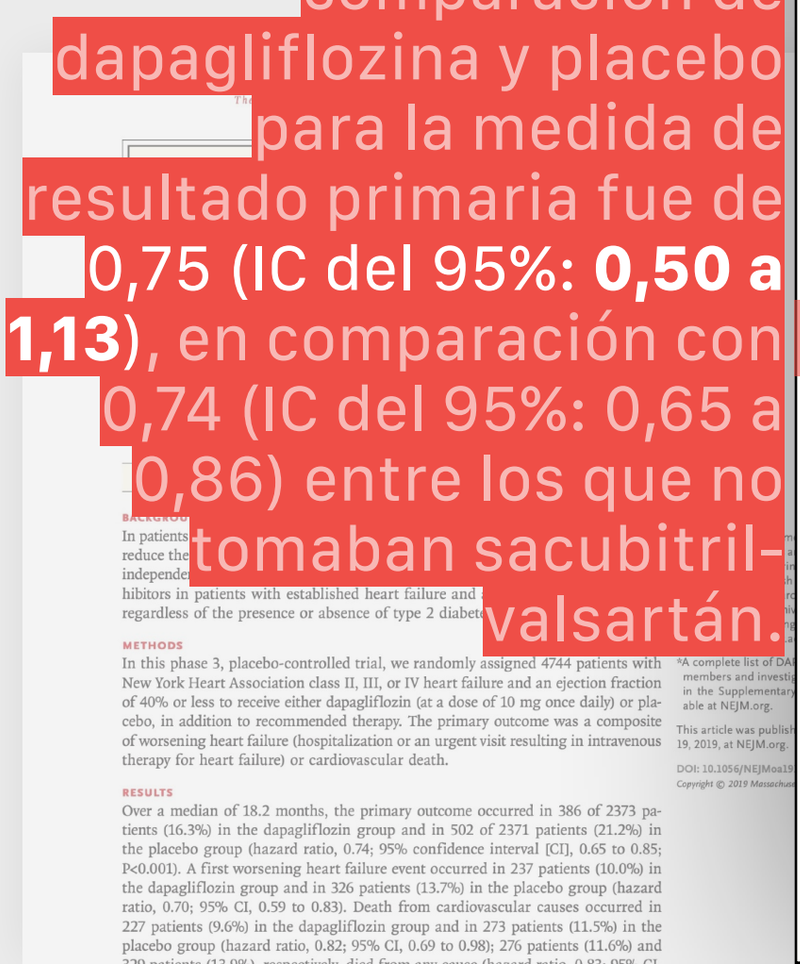

BACKGROUND
In patients
reduce the
independe
hibitors in patients with established heart failure and
regardless of the presence or absence of type 2 diabet

METHODS
In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

RESULTS
Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and

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Conclusión del **DAPA-HF**

En pacientes con **FEVI↓** (con o sin DM2) hubo mejoría **sintomática** (KCCQ) y el riesgo de...

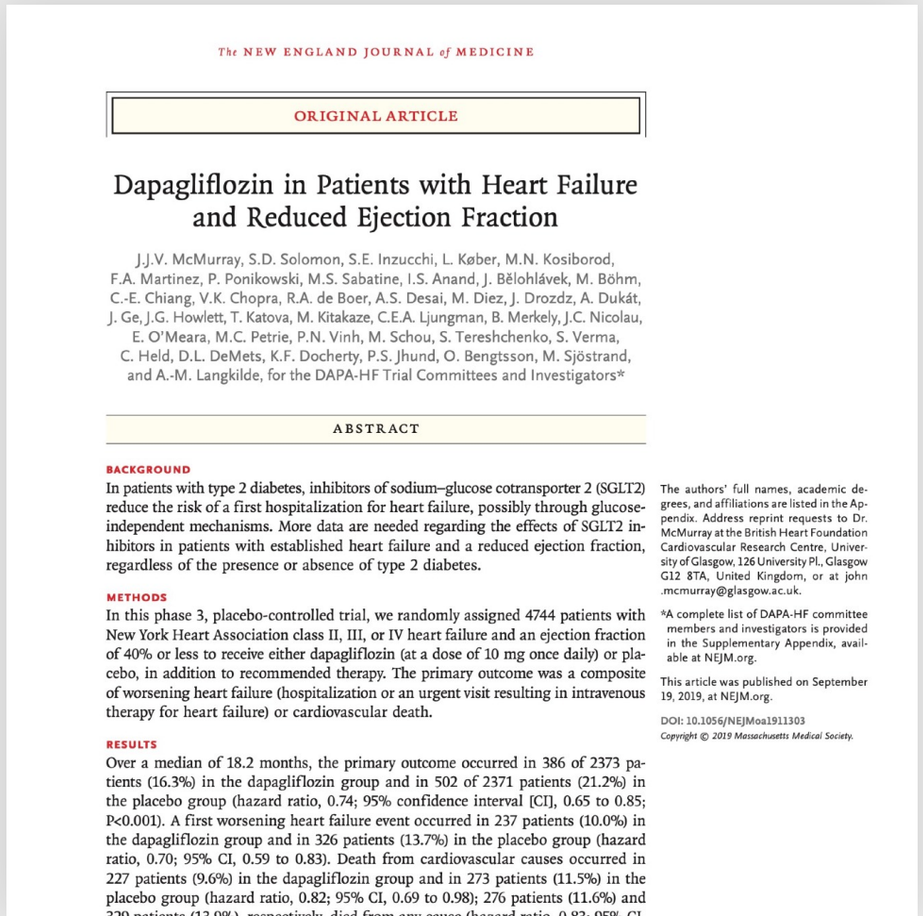
- **empeoramiento de IC** (hospitalización, visitas a urgencias)

o de

- **muerte CV**

...fue **menor** entre los que recibieron **dapagliflozina** que entre los que recibieron placebo.

McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019:1–13. doi:10.1056/nejmoa1911303.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

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The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. McMurray at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl., Glasgow G12 8TA, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

*A complete list of DAPA-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

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Background The effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors on kidney failure, particularly the need for dialysis or transplantation or death due to kidney disease, is uncertain. Additionally, previous studies have been underpowered to robustly assess heterogeneity of effects on kidney outcomes by different levels of estimated glomerular filtration rate (eGFR) and albuminuria. We aimed to do a systematic review and meta-analysis to assess the effects of SGLT2 inhibitors on major kidney outcomes in patients with type 2 diabetes and to determine the consistency of effect size across trials and different levels of eGFR and albuminuria.

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The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia (B L Neuen MBBS (Hons), T Young MBBS, Prof H J L Heerspink PhD, Prof B Neal PhD, Prof V Perkovic PhD, L Billot MSc, C Arnott PhD, S Bompoint BSc, M J Jardine PhD); **University Medical Centre Groningen, University of Groningen, Groningen, Netherlands** (Prof H J L Heerspink); **Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia** (Prof B Neal, C Arnott); **Department of Epidemiology and Biostatistics, Imperial College London, London, UK** (Prof B Neal); **Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford University, Stanford, CA, USA** (Prof K W Mahaffey MD); **Nephrology Division, Department of Medicine, New York University Langone Medical Center, New York, NY, USA** (D M Charytan MD); **Department of Renal Medicine, University College London, London, UK** (Prof D C Wheeler MD); **Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia** (C Arnott); **Division of Nephrology, University of British Columbia, Vancouver, BC, Canada** (Prof A Levin MD)

Introduction

About 2·6 million people are estimated to have received dialysis or undergone kidney transplantation for kidney failure in 2010, and this number is projected to more than double by 2030.[1] In many countries, more than half

Treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been shown to prevent major adverse kidney outcomes in people with diabetes, and these drugs are recommended by clinical practice guidelines for the

Métodos

- **Revisión sistemática y meta-análisis** de los ensayos aleatorios, controlados, de los inhibidores de los SGLT2 en personas con diabetes tipo 2.
- De los 2085 registros identificados, **4 estudios** cumplieron con los criterios de inclusión, evaluando 3 inhibidores del SGLT2:
  - **empagliflozina** (EMPA-REG OUTCOME),
  - **canagliflozina** (CANVAS y CREDENCE), y
  - **dapagliflozina** (DECLARE-TIMI 58).
- Total de 38 723 participantes

Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;2:1–10. doi:10.1016/s2213-8587(19)30256-6

Articles

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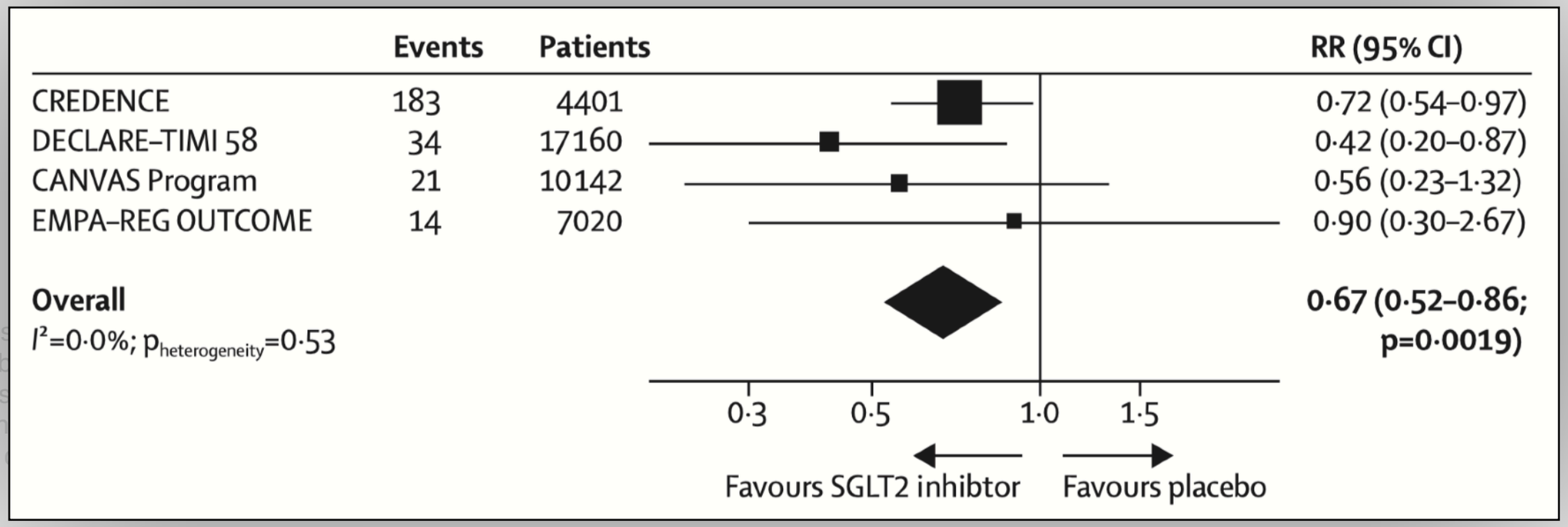
Resultados



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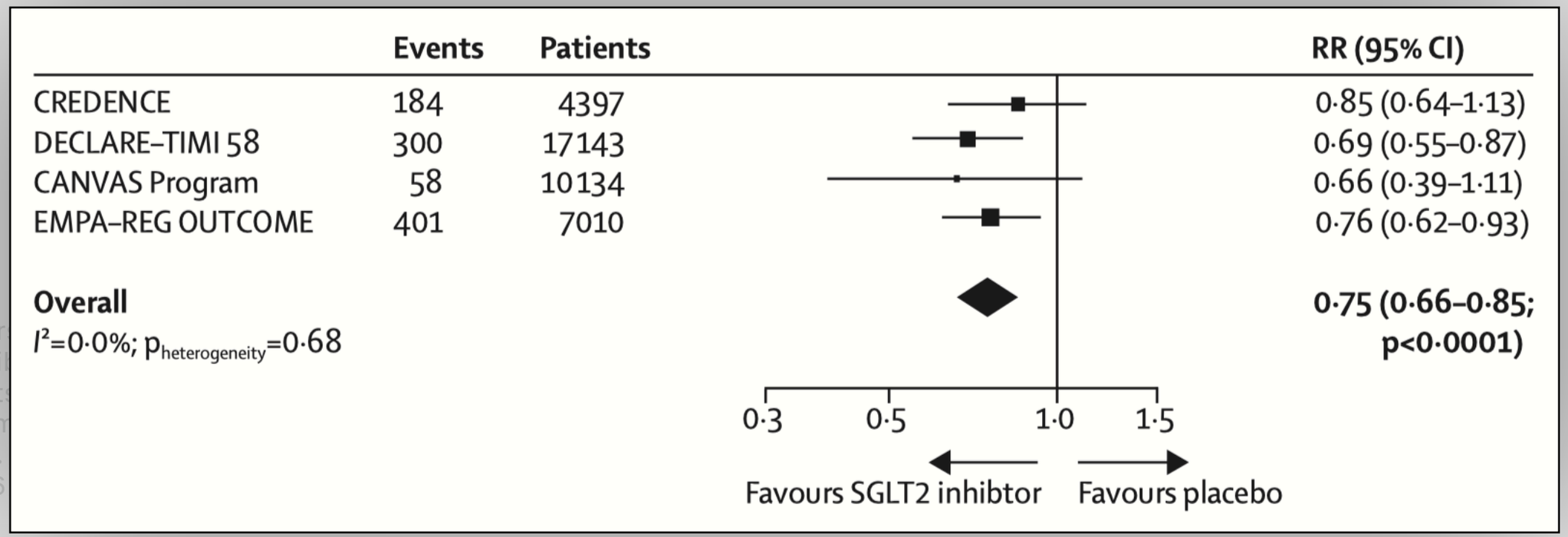
↓33% (14-48) en comparación con placebo.

OBJETIVO COMPUESTO:

- **Diálisis**
- OR
- **Trasplante**
- OR
- **Muerte** de **causa renal**

Resultados



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The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia (B L Neuen MBBS (Hons), T Young MBBS, Prof H J L Heerspink PhD, Prof B Neal PhD, Prof V Perkovic PhD, L Billot MSc, C Arnott PhD, S Bompoint BSc, M J Jardine PhD); University Medical Centre Groningen, University of Groningen, Groningen, Netherlands (Prof H J L Heerspink); Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia (Prof B Neal, C Arnott); Department of Epidemiology and Biostatistics, Imperial College London, London, UK (Prof B Neal); Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford University, Stanford, CA, USA (Prof K W Mahaffey MD); Nephrology Division, Department of Medicine, New York University Langone Medical Center, New York, NY, USA (D M Charytan MD);

Insuficiencia Renal Aguda

↓25%
(15-34)
en comparación con placebo.

Resultados

	Events	Patients	RR (95% CI)
Dialysis, transplantation, or death due to kidney disease	252	38723	0·67 (0·52–0·86)
ESKD	335	38723	0·65 (0·53–0·81)
Substantial loss of kidney function, ESKD, or death due to kidney disease	967	38671	0·58 (0·51–0·66)
Substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease	2323	38676	0·71 (0·63–0·82)
Acute kidney injury	943	38684	0·75 (0·66–0·85)

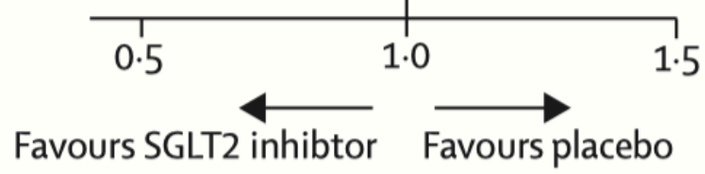

Figure 4: **Summary of the effects of SGLT2 inhibition on major kidney outcomes**
ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

Renoprotección en *todo* el espectro de filtrados hasta **30** ml/min/1.73m2

Neuen BL, Young T, Heerspi
Billot L, et al. SGLT2 inhibito
kidney failure in patients wi
systematic review and meta
Endocrinol 2019;2:1–10. doi
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SGLT2 inhibitors for the prevention
patients with type 2 diabetes: a syst
meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laur
David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

Summary
Background The effects of sodium-glucose co-transporter-2 (SGLT2) i
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trials of SGLT2 inhibitors that reported effects on major kidney outco
MEDLINE and Embase from database inception to June 14, 2019, to
a composite of dialysis, transplantation, or death due to kidney disea
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registered with PROSPERO (CRD42019131774).

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disease, 335 developed end-stage kidney disease, and 943 had acute
reduced the risk of dialysis, transplantation, or death due to kidney disease (RR 0·67, 95% CI 0·52–0·86, p=0·0019),
an effect consistent across studies (I^2=0%, $p_{heterogeneity}$=0·53). SGLT2 inhibitors also reduced end-stage kidney disease
(0·65, 0·53–0·81, p<0·0001), and acute kidney injury (0·75, 0·66–0·85, p<0·0001), with consistent benefits across
studies. Although we identified some evidence that the proportional effect of SGLT2 inhibitors might attenuate with
declining kidney function (p_{trend}=0·073), there was clear, separate evidence of benefit for all eGFR subgroups, including
for participants with a baseline eGFR 30–45 mL/min per 1·73 m² (RR 0·70, 95% CI 0·54–0·91, p=0·0080).
Renoprotection was also consistent across studies irrespective of baseline albuminuria (p_{trend}=0·66) and use of RAS
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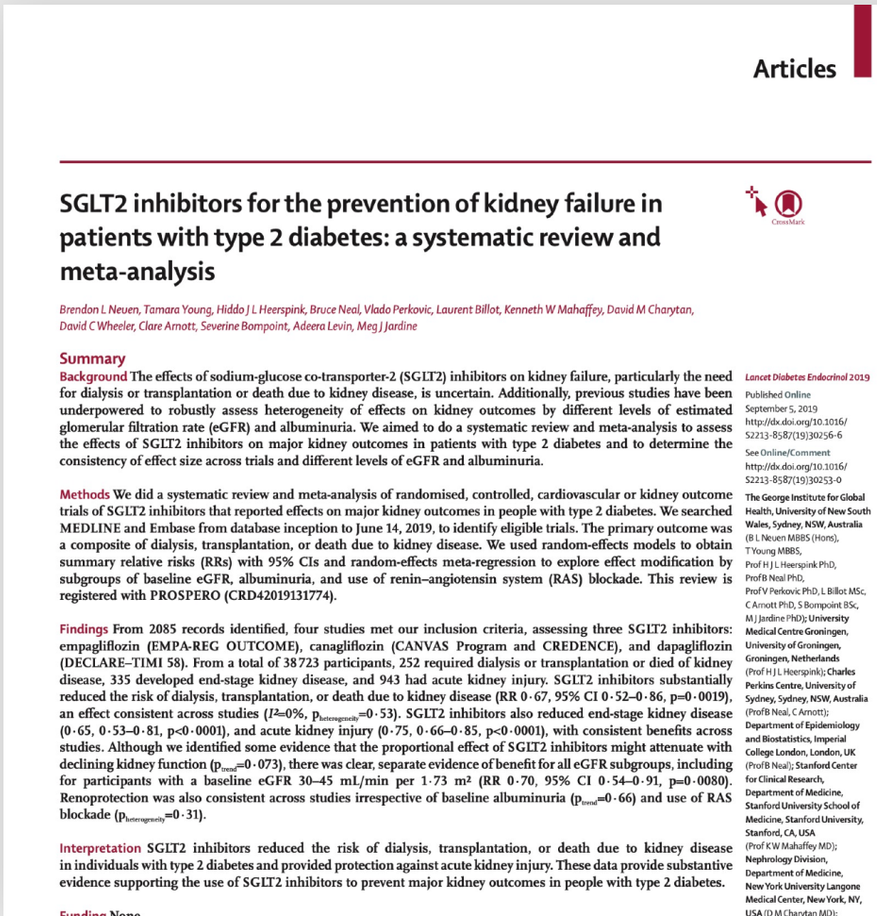
Interpretation SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney disease
in individuals with type 2 diabetes and provided protection against acute kidney injury. These data provide substantive
evidence supporting the use of SGLT2 inhibitors to prevent major kidney outcomes in people with type 2 diabetes.

Perkins Centre, University of Sydney, Sydney, NSW, Australia (Prof B Neal, C Arnott); Department of Epidemiology and Biostatistics, Imperial College London, London, UK (Prof B Neal); Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford University, Stanford, CA, USA (Prof K W Mahaffey MD); Nephrology Division, Department of Medicine, New York University Langone Medical Center, New York, NY, USA (D M Charytan MD);

1º **caída** temprana del FG, pero luego **protección** contra la disminución de la función renal.

Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;2:1–10. doi:10.1016/s2213-8587(19)30256-6



Articles

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

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Discusión: mecanismos propuestos

- Corrección de la hemodinámica glomerular aberrante inducida por la hiperglucemia, que provoca la pérdida progresiva de nefronas:
  Constricción arteriolar *aferente*
  ↓ Presión intraglomerular
- ↑ oxigenación del riñón
  ↓ requerimientos de energía tubular,
  ↓ FRA
- efectos metabólicos y antiinflamatorios
- efectos ↓ de la albuminuria
- función endotelial glomerular

Por su parte, los bloqueadores de RAA actúan con aumento de la vasodilatación arterial *eferente*.

Discusión: áreas de incertidumbre de los iSGLT2

- ¿Efecto en FG<30?
- ¿Efectividad comparativa con aGLP1?
- Próximos ensayos con objetivos renales:
  - DAPA-CKD,
  - EMPA-KIDNEY,
  - SCORED (sotagliflocina, en FG de hasta 20)

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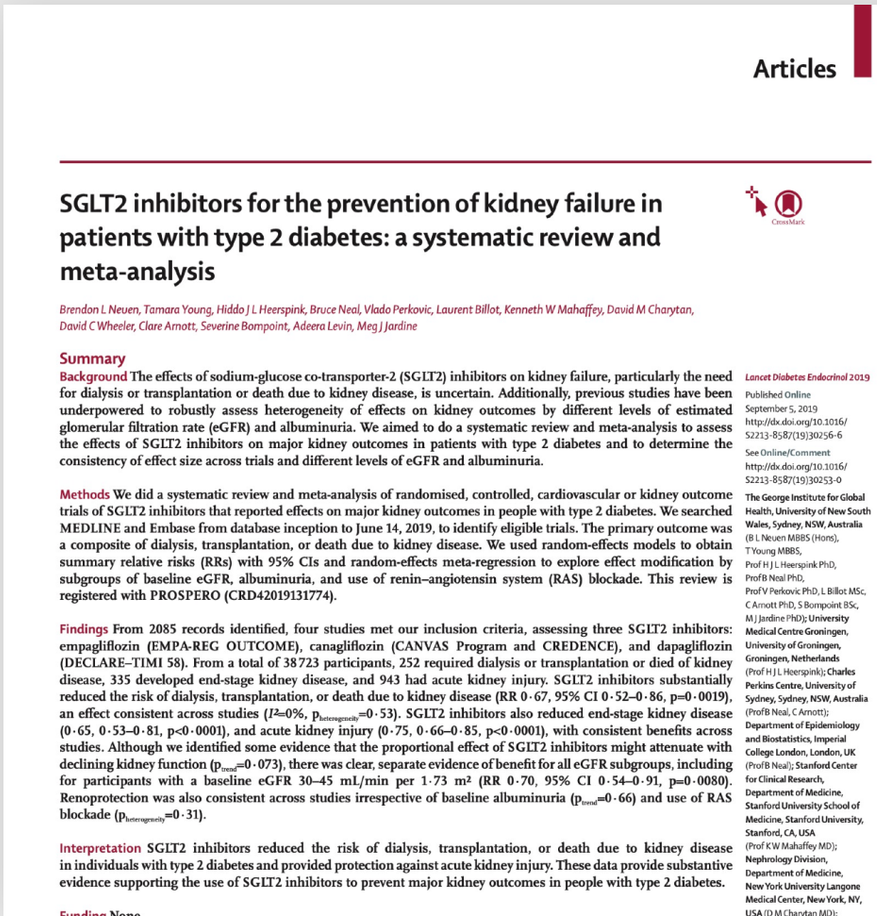

Articles

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Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial

Ildiko Lingvay, Andrei-Mircea Catarig, Juan P Frias, Harish Kumar, Nanna L Lausvig, Carel W le Roux, Desirée Thielke, Adie Viljoen, Rory J McCrimmon

Summary

Background Existing guidelines for management of type 2 diabetes recommend a patient-centred approach to guide the choice of pharmacological agents. Although glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter-2 (SGLT2) inhibitors are increasingly used as second-line agents, direct comparisons between these treatments are insufficient. In the SUSTAIN 8 trial, we compared the efficacy and safety of semaglutide (a GLP-1 receptor agonist) with canagliflozin (an SGLT2 inhibitor) in patients with type 2 diabetes.

Methods This was a double-blind, parallel-group, phase 3b, randomised controlled trial done at 111 centres in 11 countries. Eligible patients were at least 18 years old and had uncontrolled type 2 diabetes (HbA_{1c} 7·0–10·5% [53–91 mmol/mol]) on stable daily metformin therapy. Patients were randomly assigned (1:1) by use of an interactive web response system to subcutaneous semaglutide 1·0 mg once weekly or oral canagliflozin 300 mg once daily. The primary endpoint was change from baseline in HbA_{1c}, and the confirmatory secondary endpoint was change from baseline in bodyweight, both at week 52. The primary analysis population included all randomly assigned patients, using on-treatment data collected before initiation of rescue medication. The safety analysis was done on a population that included all patients exposed to at least one dose of trial product. The trial was powered for HbA_{1c} and bodyweight superiority under reasonable assumptions. This trial is registered with ClinicalTrials.gov, NCT03136484.

Findings Between March 15, 2017, and Nov 16, 2018, 788 patients were randomly assigned to semaglutide 1·0 mg (394 patients) or canagliflozin 300 mg (394 patients). 739 patients completed the trial (367 in the semaglutide group and 372 in the canagliflozin group). From overall baseline mean, patients receiving semaglutide had significantly greater reductions in HbA_{1c} and bodyweight than those receiving canagliflozin (HbA_{1c} estimated treatment difference [ETD] –0·49 percentage points, 95% CI –0·65 to –0·33; –5·34 mmol/mol, 95% CI –7·10 to –3·57; p<0·0001; and bodyweight ETD –1·06 kg, 95% CI –1·76 to –0·36; p=0·0029). Gastrointestinal disorders, most commonly nausea, were the most frequently reported adverse events with semaglutide, occurring in 184 (47%) of 392 patients; whereas infections and infestations (defined using the Medical Dictionary for Regulatory Activities, version 21.0), most commonly urinary tract infections, occurred more frequently with canagliflozin, in 136 (35%) of 394 patients. Premature treatment discontinuation because of adverse events occurred in 38 (10%) of 392 patients with semaglutide and in 20 (5%) of 394 patients with canagliflozin. One fatal adverse event confirmed unlikely to be caused by treatment occurred in the semaglutide group.

Interpretation Once-weekly semaglutide 1·0 mg was superior to daily canagliflozin 300 mg in reducing HbA_{1c} and bodyweight in patients with type 2 diabetes uncontrolled on metformin therapy. These outcomes might guide treatment intensification choices.

Funding Novo Nordisk.

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Department of Internal Medicine/Endocrinology, Department of Clinical Sciences, UT Southwestern Medical Center, University of Texas, Dallas, TX, USA (Prof I Lingvay MD); **Novo Nordisk, Søborg, Denmark** (A-M Catarig MD, N L Lausvig MSc, D Thielke MD); **National Research Institute, Los Angeles, CA, USA** (J P Frias MD); **Centre for Endocrinology and Diabetes, Amrita Hospital, Kochi, India** (H Kumar MRCP); **Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland** (Prof C W le Roux MD); **Borthwick Diabetes Research Centre, Stevenage, UK** (A Viljoen MBChB); **and School of Medicine, University of Dundee, Dundee, UK** (Prof R J McCrimmon MBChB)

Correspondence to:
Prof Ildiko Lingvay, Department of Internal Medicine/Endocrinology, Department of Clinical Sciences, UT Southwestern Medical Center, Dallas, TX 75390-9302, USA
ildiko.lingvay@UTSouthwestern.edu

Introduction

Existing guidelines for the comprehensive management of type 2 diabetes recommend a patient-centred approach

co-transporter-2 (SGLT2)[5] inhibitors are preferred add-on treatment options for patients with cardiovascular disease and poorly controlled HbA_{1c} after first-line

Lingvay I, Catarig A-M, Frias JP, Kumar H, Lausvig NL, le Roux CW, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol 2019;8587:1–11. doi: 10.1016/s2213-8587(19)30311-0.

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Correspondence to: Prof Ildiko Lingvay, Department of Internal Medicine/Endocrinology,

Métodos

- Ensayo clínico fase 3b, controlado, aleatorizado paralelo, doble ciego, realizado en 111 centros de 11 países.
- Pacientes con **DM2 no controlada** (HbA 1c 7.0-10.5% [53-91 mmol/mol]) en terapia diaria estable con **metformina**.
- **Objetivo** (medido en la semana 52):
  - Objetivo primario: **↓HbA1c**
  - Objetivo secundario: **peso** corporal

⚠️ Ojo!

Novo Nordisk (semaglutide) diseñó el estudio, monitoreó los centros, la recolección de datos, el análisis de datos, la interpretación de los mismos, y proporcionó un redactor médico como apoyo editorial.

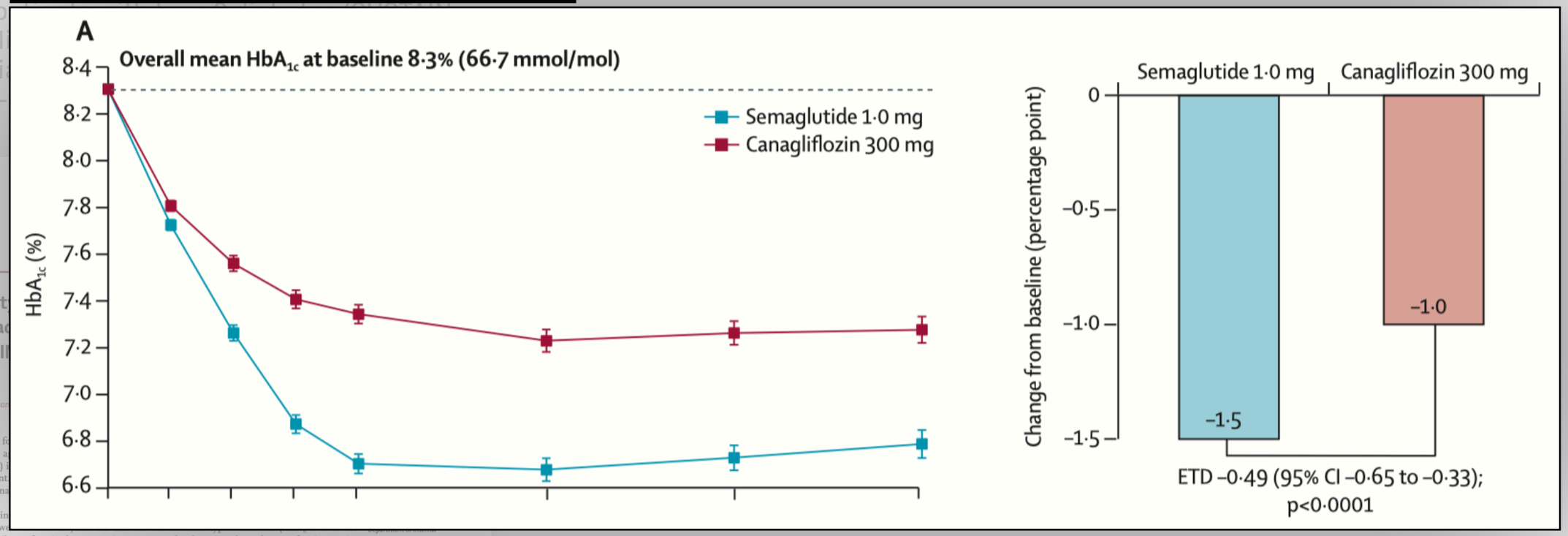
Resultados

MEJOR
n=394
SEMA-GLUTIDE
1mg/w sc.

>

n=394
CANAGLI-FLOCINA
300mg/día

HEMOGLOBINA GLICOSILADA



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Efficacy and safet… canagliflozin as a… diabetes (SUSTAI… controlled trial

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Background Existing guidelines fo… the choice of pharmacological a… glucose cotransporter-2 (SGLT2) i… these treatments are insufficient… GLP-1 receptor agonist) with cana…

Methods This was a double-blin… 11 countries. Eligible patients w… [53–91 mmol/mol]) on stable daily metformin therapy. Patients were randomly assigned (1:1) by use of an interactive web response system to subcutaneous semaglutide 1·0 mg once weekly or oral canagliflozin 300 mg once daily. The primary endpoint was change from baseline in HbA_{1c}, and the confirmatory secondary endpoint was change from baseline in bodyweight, both at week 52. The primary analysis population included all randomly assigned patients, using on-treatment data collected before initiation of rescue medication. The safety analysis was done on a population that included all patients exposed to at least one dose of trial product. The trial was powered for HbA_{1c} and bodyweight superiority under reasonable assumptions. This trial is registered with ClinicalTrials.gov, NCT03136484.

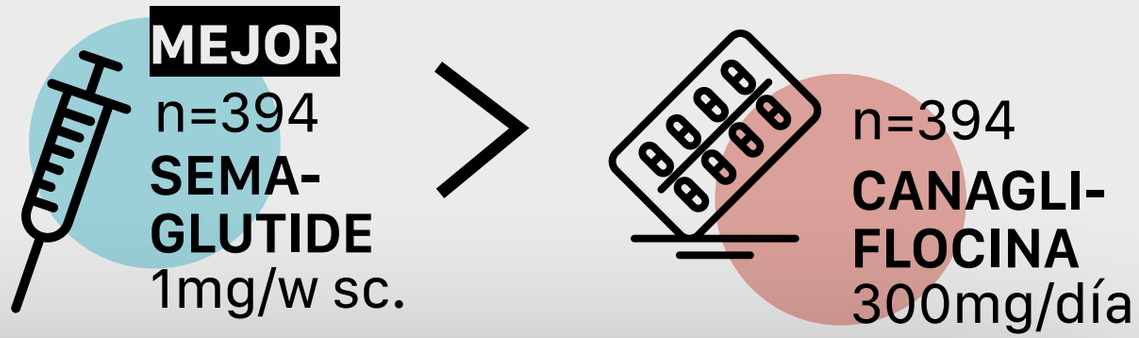
Findings Between March 15, 2017, and Nov 16, 2018, 788 patients were randomly assigned to semaglutide 1·0 mg (394 patients) or canagliflozin 300 mg (394 patients). 739 patients completed the trial (367 in the semaglutide group and 372 in the canagliflozin group). From overall baseline mean, patients receiving semaglutide had significantly greater reductions in HbA_{1c} and bodyweight than those receiving canagliflozin (HbA_{1c} estimated treatment difference [ETD] −0·49 percentage points, 95% CI −0·65 to −0·33; −5·34 mmol/mol, 95% CI −7·10 to −3·57; p<0·0001; and bodyweight ETD −1·06 kg, 95% CI −1·76 to −0·36; p=0·0029). Gastrointestinal disorders, most commonly nausea, were the most frequently reported adverse events with semaglutide, occurring in 184 (47%) of 392 patients; whereas infections and infestations (defined using the Medical Dictionary for Regulatory Activities, version 21.0), most commonly urinary tract infections, occurred more frequently with canagliflozin, in 136 (35%) of 394 patients. Premature treatment discontinuation because of adverse events occurred in 38 (10%) of 392 patients with semaglutide and in 20 (5%) of 394 patients with canagliflozin. One fatal adverse event confirmed unlikely to be caused by treatment occurred in the semaglutide group.

Interpretation Once-weekly semaglutide 1·0 mg was superior to daily canagliflozin 300 mg in reducing HbA_{1c} and bodyweight in patients with type 2 diabetes uncontrolled on metformin therapy. These outcomes might guide treatment intensification choices.

Medicine/Endocrinology, Department of Clinical Sciences, UT Southwestern Medical Center, University of Texas, Dallas, TX, USA (Prof I Lingvay MD); Novo Nordisk, Søborg, Denmark (A-M Catarig MD, N L Lausvig MSc, D Thielke MD); National Research Institute, Los Angeles, CA, USA (J P Frias MD); Centre for Endocrinology and Diabetes, Amrita Hospital, Kochi, India (H Kumar MRCP); Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland (Prof C W le Roux MD); Borthwick Diabetes Research Centre, Stevenage, UK (A Viljoen MBChB); and School of Medicine, University of Dundee, Dundee, UK (Prof R J McCrimmon MBChB)

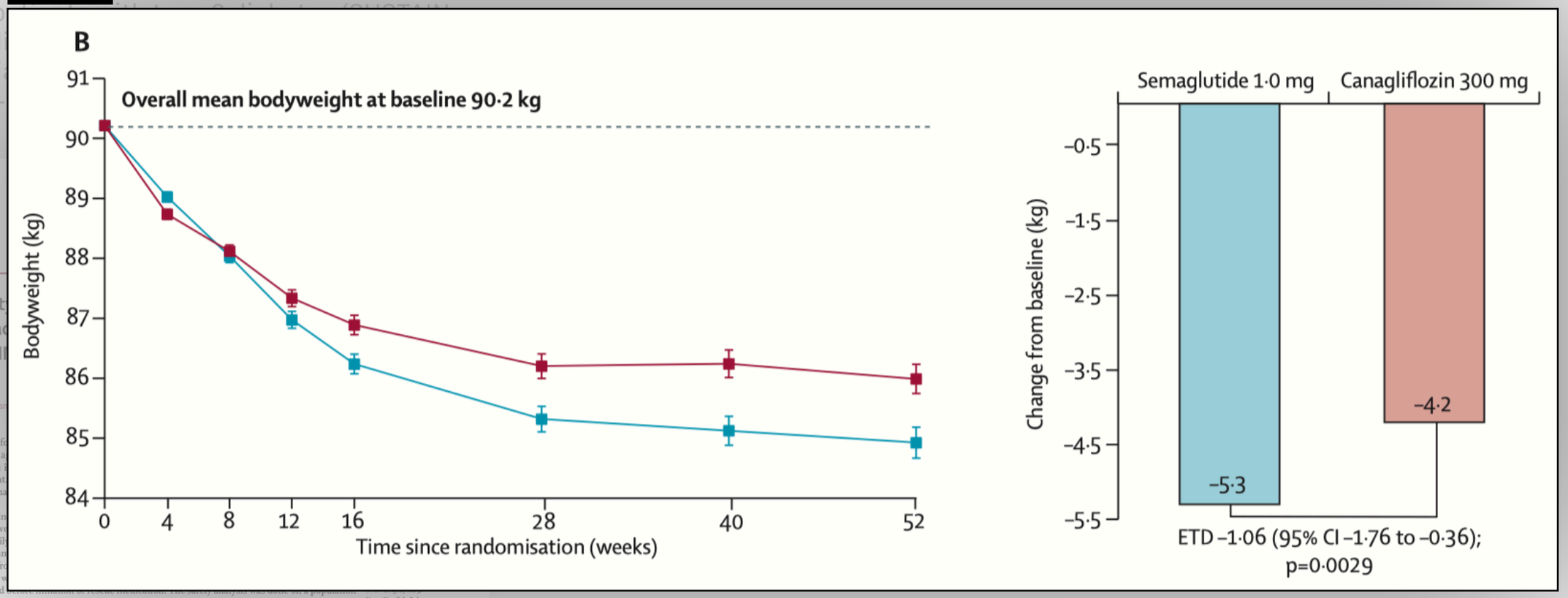
Correspondence to: Prof Ildiko Lingvay, Department of Internal Medicine/Endocrinology,

Resultados



Lingvay I, Catarig A-M, Frias JP, Kumar H, Lausvig NL, le Roux CW, et al. Efficacy and safety of once-weekly semaglutide v canagliflozin as add-on to metformin in p 8): a double-bl trial. Lancet Di 10.1016/s2213-

PESO



×2 pacientes lograron una **pérdida de peso de al menos un 10%** con semaglutida que aquellos con canagliflozina después de 1 año de tratamiento.

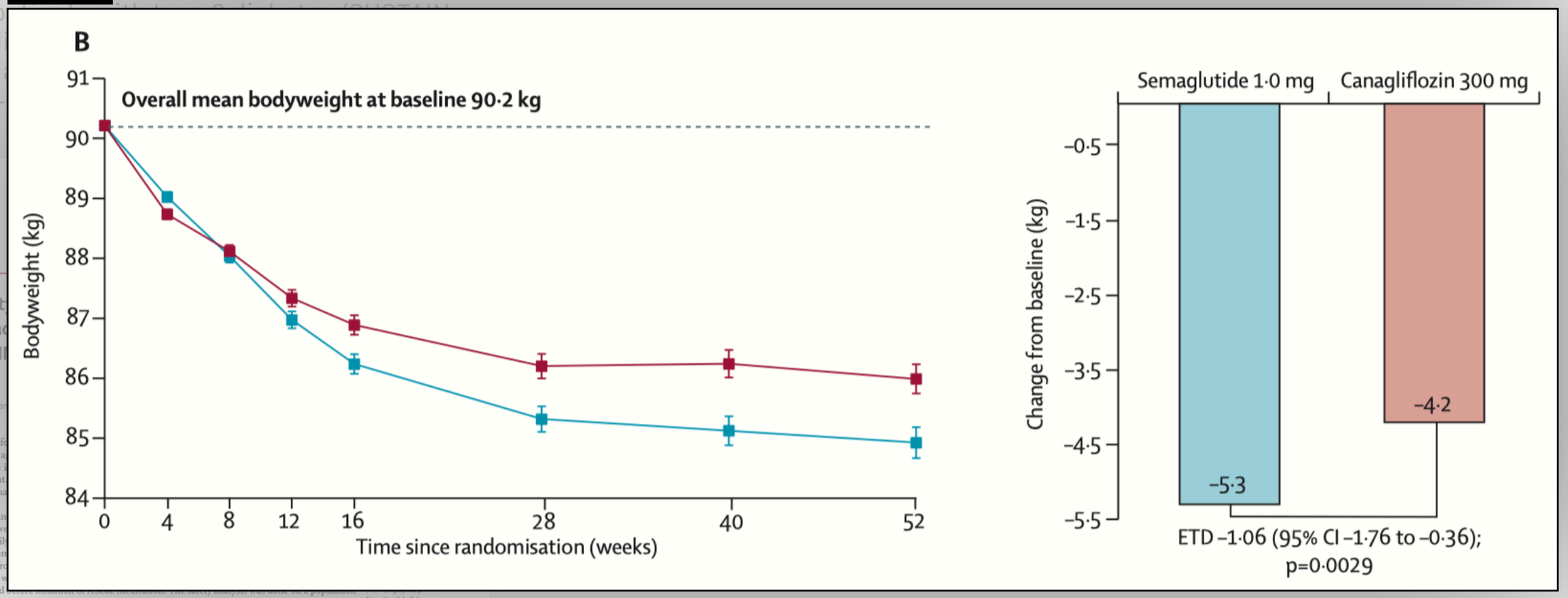
Resultados

MEJOR
n=394
SEMA-GLUTIDE
1mg/w sc.

>

n=394
CANAGLI-FLOCINA
300mg/día

PESO



Un análisis post-hoc encontró que el **7%** de los pacientes eran **superrespondedores**, logrando al menos un 15% de pérdida de peso.

Lingvay I, Catarig A-M, Frias JP, Kumar H, Lausvig NL, le Roux CW, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7(11):834–44. doi: 10.1016/s2213-8587(19)30311-0

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Check for updates

Trends in incidence of total or type 2 diabetes: systematic review

Dianna J Magliano,[1,2] Rakibul M Islam,[1,2] Elizabeth L M Barr,[1] Edward W Gregg,[3,4] Meda E Pavkov,[3] Jessica L Harding,[3] Maryam Tabesh,[1,2] Digsu N Koye,[1,2] Jonathan E Shaw,[1,2]

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[4]School of Public Health, Epidemiology and Biostatistics, Imperial College London, London, UK

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D J Magliano
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Cite this as: *BMJ* 2019;366:l5003
http://dx.doi.org/10.1136/bmj.l5003

Accepted: 16 July 2019

ABSTRACT

OBJECTIVE

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DESIGN

Systematic review of studies reporting trends of diabetes incidence in adults from 1980 to 2017 according to PRISMA guidelines.

DATA SOURCES

Medline, Embase, CINAHL, and reference lists of relevant publications.

ELIGIBILITY CRITERIA

Studies of open population based cohorts, diabetes registries, and administrative and health insurance databases on secular trends in the incidence of total diabetes or type 2 diabetes in adults were included. Poisson regression was used to model data by age group and year.

RESULTS

Among the 22 833 screened abstracts, 47 studies were included, providing data on 121 separate sex specific or ethnicity specific populations; 42 (89%) of the included studies reported on diagnosed diabetes. In 1960-89, 36% (8/22) of the populations studied had increasing trends in incidence of diabetes, 55% (12/22) had stable trends, and 9% (2/22) had decreasing trends. In 1990-2005, diabetes incidence increased in 66% (33/50) of populations, was stable in 32% (16/50), and decreased in 2% (1/50). In 2006-14, increasing trends were reported in only 33% (11/33) of populations, whereas 30% (10/33) and 36% (12/33) had stable or declining incidence, respectively.

CONCLUSIONS

The incidence of clinically diagnosed diabetes has continued to rise in only a minority of populations studied since 2006, with over a third of populations having a fall in incidence in this time period. Preventive strategies could have contributed to the fall in diabetes incidence in recent years. Data are limited in low and middle income countries, where trends in diabetes incidence could be different.

SYSTEMATIC REVIEW REGISTRATION

Prospero CRD42018092287.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Monitoring of the diabetes epidemic has mainly focused on reporting diabetes prevalence, which continues to rise; however, increasing prevalence is partly driven by improved medical treatment and declining mortality

Studies on diabetes incidence are scarce, but among those that exist, some report a fall or stabilisation of diabetes incidence;

Whether the proportion of studies reporting falling incidence has changed over time is not known

WHAT THIS STUDY ADDS

This systematic review of published data reporting diabetes incidence trends over time shows that in most countries with available data, incidence of diabetes (mainly diagnosed diabetes) increased from the 1990s to the mid-2000s, and has been stable or falling since

Preventive strategies and public health education and awareness campaigns

Introduction

Over the past few decades, the prevalence of diabetes in developed and developing countries has risen substantially, making diabetes a key health priority globally.[1] Examination of trends in total burden of diabetes is an essential part of the monitoring of this health priority area, but, to date, it has consisted primarily of studies looking at diabetes prevalence.[1-5] Prevalence estimates suggest that the diabetes burden is still rising in most countries, and this is often interpreted as evidence of increasing risk in the population. However, selective incidence studies[6 7] and some accompanying risk factor data[8] suggest otherwise. Prevalence can be a crude and misleading metric of the trajectory of an epidemic, because increasing prevalence of a disease might be due to either increasing incidence or to improved survival. Furthermore, prevalence cannot be reliably used to study the effects of changes in population risk factors, because their effects are detected earlier with incidence trends than with prevalence trends, and incidence is not affected by changes in survival.

Incidence measures the proportion of people who develop diabetes over a period of time among the population at risk. It is the appropriate measure of population risk, and a valuable way of assessing whether public health campaigns for diabetes prevention are succeeding. While prevalence can rise simply because mortality falls, incidence of diagnosed diabetes is affected only by the risk of the population and the amount of screening undertaken. Changes in prevalence might be an inadequate guide to the effects of prevention activities, and could lead to the inappropriate rejection of effective interventions. It is

BMJ: first published as 10.1136/bmj.l5003 on 11 September 2019. Downloaded from http://www.bmj.com/ on 26 September 2019 at University of New England. Prot

Contexto

- El seguimiento de la epidemia de diabetes se ha centrado principalmente en informar sobre la **prevalencia de diabetes**, **que sigue aumentando**; sin embargo, el aumento de la prevalencia se debe en parte a la **mejora del tratamiento médico** y a la **disminución de la mortalidad**.
- **Revisión sistemática** de los estudios que informan sobre las tendencias de la incidencia de diabetes en adultos entre 1980 y 2017, de acuerdo con las directrices de **PRISMA**.

Magliano DJ, Islam RM, Barr ELM, Gregg EW, Pavkov ME, Harding JL, et al. Trends in incidence of total or type 2 diabetes: Systematic review. BMJ 2019;366:1–12. doi: 10.1136/bmj.l5003

RESEARCH

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Trends in incidence of total or type 2 diabetes: systematic review

Check for updates

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CONCLUSIONS
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Prospero CRD42018092287.

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Whether the proportion of studies reporting falling incidence has changed over

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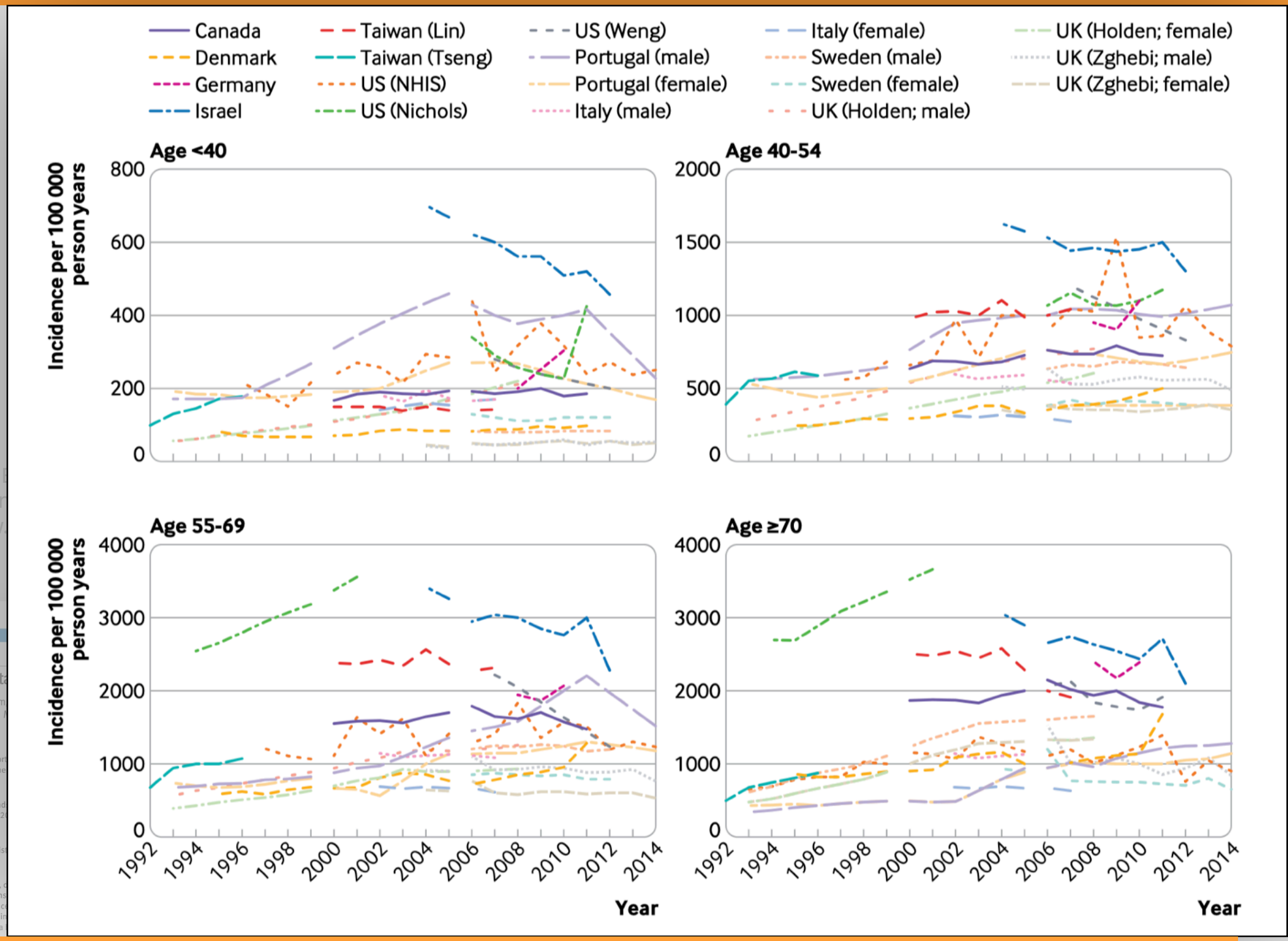

En la mayoría de los países con datos disponibles, la incidencia de la diabetes **aumentó desde los años 90** hasta mediados de la década de 2000, y se ha mantenido **estable o ha descendido** desde entonces.

Magliano DJ, Islam RM, Barr E
Harding JL, et al. Trends in in
diabetes: Systematic review.
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Trends in incidence of tota

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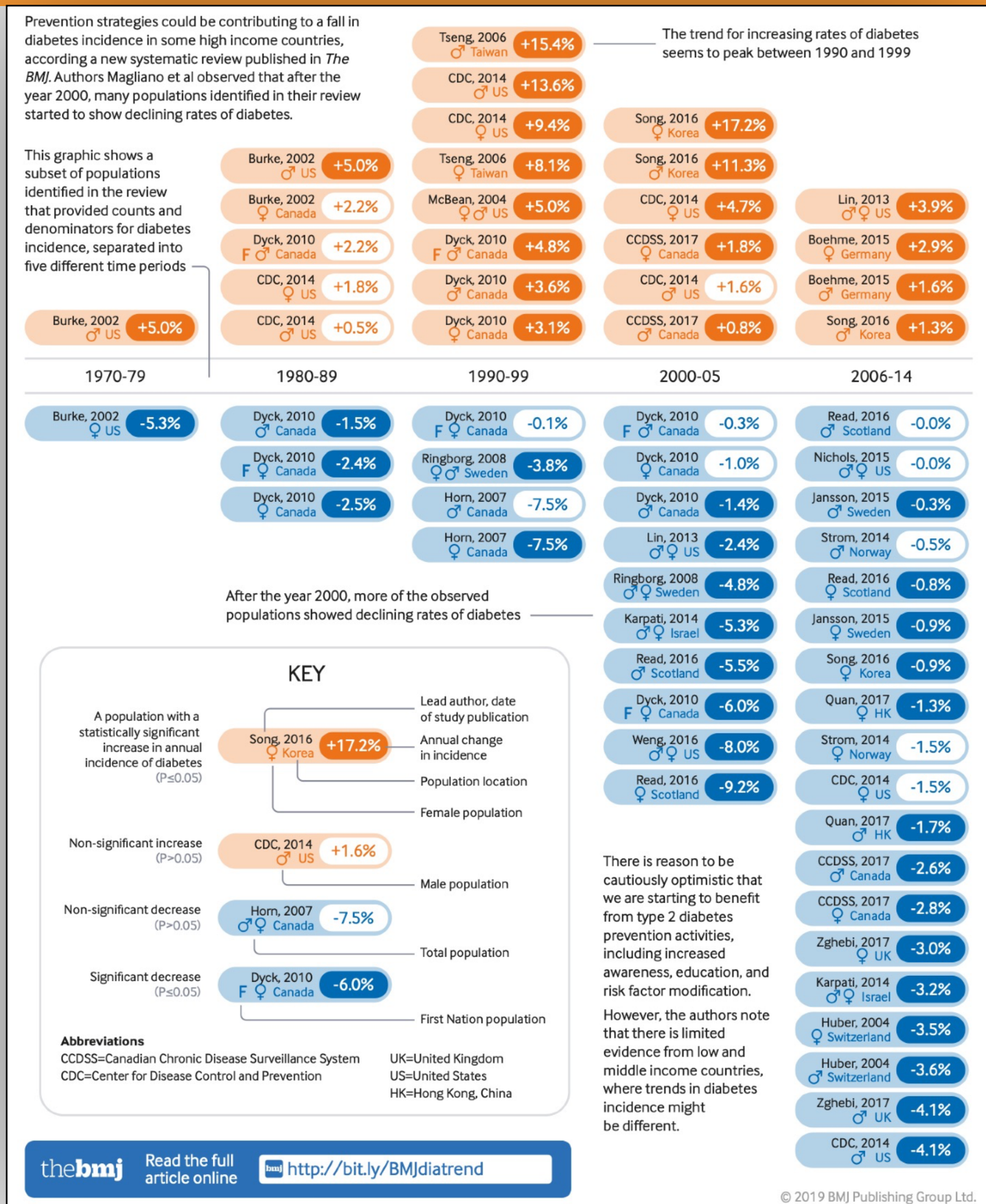

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RESEARCH

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Research

JAMA Internal Medicine | Original Investigation

Association Between Plant-Based Dietary Patterns and Risk of Type 2 Diabetes
A Systematic Review and Meta-analysis

Frank Qian, MPH; Gang Liu, PhD; Frank B. Hu, MD, PhD; Shilpa N. Bhupathiraju, PhD; Qi Sun, MD, ScD

IMPORTANCE Accumulating epidemiologic evidence has suggested favorable associations between plant-based dietary patterns and risk of type 2 diabetes, although there is a lack of a quantitative summary of evidence substantiating this important association.

OBJECTIVE To quantitatively synthesize available prospective observational evidence on the association between plant-based dietary patterns and risk of type 2 diabetes.

DATA SOURCES A systematic search of PubMed and MEDLINE, Embase, Web of Science, and reference lists through February 15, 2019, was conducted. Data analysis was conducted between December 2018 and February 2019.

STUDY SELECTION All prospective observational studies that examined the association between adherence to plant-based dietary patterns and incidence of type 2 diabetes among adults 18 years or older were identified.

DATA EXTRACTION AND SYNTHESIS Meta-analysis of Observational Studies in Epidemiology guidelines for data abstraction and reporting were followed, and a National Heart, Lung, and Blood Institute assessment tool was used to evaluate study quality. Two authors independently conducted full-text assessments and data abstraction. Meta-analysis was conducted using the random-effects method to calculate the overall relative risk (RR) and 95% CI.

MAIN OUTCOMES AND MEASURES Level of adherence to a plant-based diet and incidence of type 2 diabetes.

RESULTS A total of 9 studies were identified, totaling 307 099 participants with 23 544 cases of incident type 2 diabetes. A significant inverse association was observed between higher adherence to a plant-based dietary pattern and risk of type 2 diabetes (RR, 0.77; 95% CI, 0.71-0.84) in comparison with poorer adherence, with modest heterogeneity across studies (I^2 = 44.5%; P = .07 for heterogeneity). Similar findings were obtained when using the fixed-effects model (RR, 0.80; 95% CI, 0.75-0.84). Consistent associations were observed across predefined subgroups. This association was strengthened when healthy plant-based foods, such as fruits, vegetables, whole grains, legumes, and nuts, were included in the definition of *plant-based patterns* (RR, 0.70; 95% CI, 0.62-0.79). Most studies were deemed to have good quality in terms of dietary assessment, disease outcomes, and statistical adjustment for confounding factors. Using restricted cubic splines, a significant inverse linear dose-response association was identified between plant-based dietary indices and risk of type 2 diabetes.

CONCLUSIONS AND RELEVANCE Plant-based dietary patterns, especially when they are enriched with healthful plant-based foods, may be beneficial for the primary prevention of type 2 diabetes.

Supplemental content

Author Affiliations: Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Qian, Liu, Hu, Bhupathiraju, Sun); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Hu); Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Hu, Bhupathiraju, Sun).

Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association Between Plant-Based Dietary Patterns and Risk of Type 2 Diabetes. JAMA Intern Med 2019;179:1335. doi:10.1001/jamainternmed.2019.2195

¿Cuál es el papel de los **patrones dietéticos** veganos o vegetarianos en la **prevención** primaria de la **diabetes tipo 2** entre los adultos?

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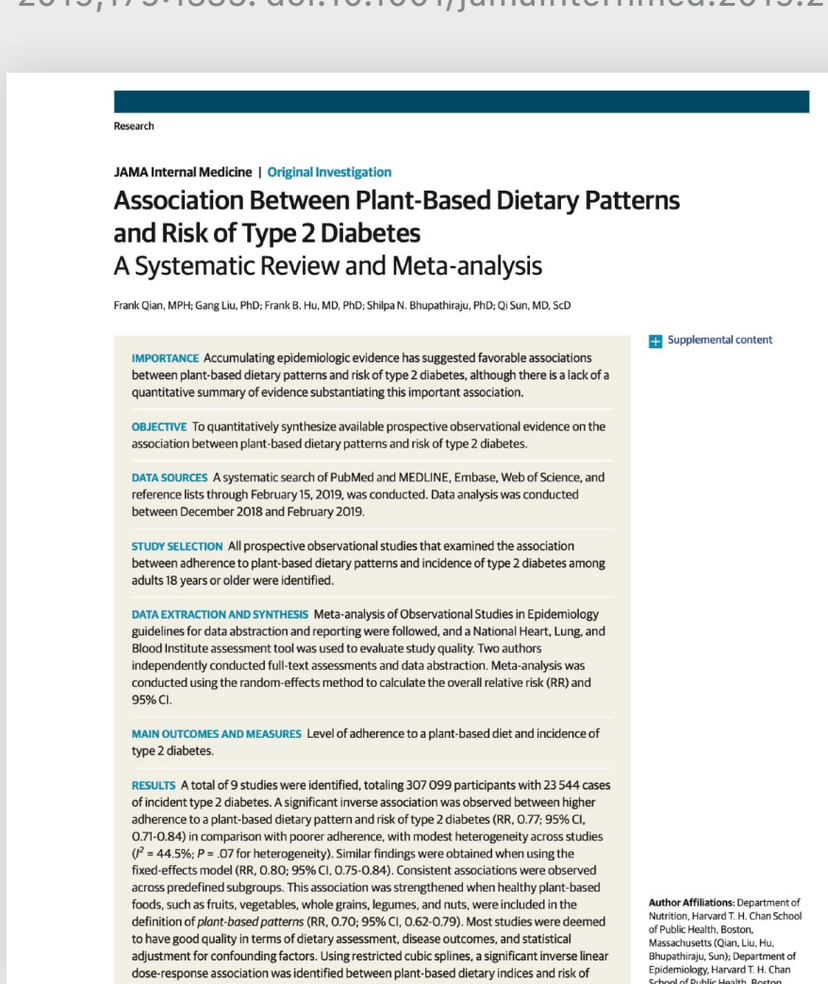

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Association Between Plant-Based Dietary Patterns and Risk of Type 2 Diabetes
A Systematic Review and Meta-analysis

Frank Qian, MPH; Gang Liu, PhD; Frank B. Hu, MD, PhD; Shilpa N. Bhupathiraju, PhD; Qi Sun, MD, ScD

Supplemental content

IMPORTANCE Accumulating epidemiologic evidence has suggested favorable associations between plant-based dietary patterns and risk of type 2 diabetes, although there is a lack of a quantitative summary of evidence substantiating this important association.

OBJECTIVE To quantitatively synthesize available prospective observational evidence on the association between plant-based dietary patterns and risk of type 2 diabetes.

DATA SOURCES A systematic search of PubMed and MEDLINE, Embase, Web of Science, and reference lists through February 15, 2019, was conducted. Data analysis was conducted between December 2018 and February 2019.

STUDY SELECTION All prospective observational studies that examined the association between adherence to plant-based dietary patterns and incidence of type 2 diabetes among adults 18 years or older were identified.

DATA EXTRACTION AND SYNTHESIS Meta-analysis of Observational Studies in Epidemiology guidelines for data abstraction and reporting were followed, and a National Heart, Lung, and Blood Institute assessment tool was used to evaluate study quality. Two authors independently conducted full-text assessments and data abstraction. Meta-analysis was conducted using the random-effects method to calculate the overall relative risk (RR) and 95% CI.

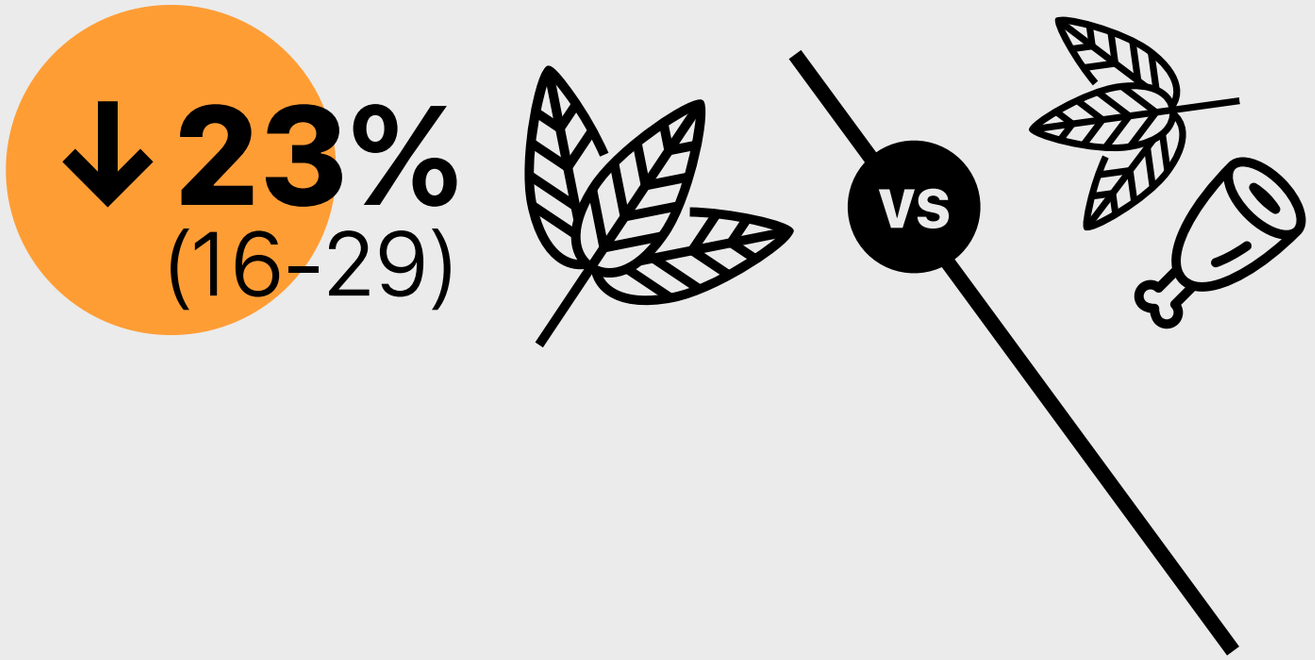
MAIN OUTCOMES AND MEASURES Level of adherence to a plant-based diet and incidence of type 2 diabetes.

RESULTS A total of 9 studies were identified, totaling 307 099 participants with 23 544 cases of incident type 2 diabetes. A significant inverse association was observed between higher adherence to a plant-based dietary pattern and risk of type 2 diabetes (RR, 0.77; 95% CI, 0.71-0.84) in comparison with poorer adherence, with modest heterogeneity across studies (I^2 = 44.5%; P = .07 for heterogeneity). Similar findings were obtained when using the fixed-effects model (RR, 0.80; 95% CI, 0.75-0.84). Consistent associations were observed across predefined subgroups. This association was strengthened when healthy plant-based foods, such as fruits, vegetables, whole grains, legumes, and nuts, were included in the definition of *plant-based patterns* (RR, 0.70; 95% CI, 0.62-0.79). Most studies were deemed to have good quality in terms of dietary assessment, disease outcomes, and statistical adjustment for confounding factors. Using restricted cubic splines, a significant inverse linear dose-response association was identified between plant-based dietary indices and risk of

Author Affiliations: Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Qian, Liu, Hu, Bhupathiraju, Sun); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston

307 099 participantes, con 23 544 casos de DM2.

La adherencia a los patrones dietéticos basados en plantas se asoció **inversamente** con el **riesgo de DM2**.



Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association Between Plant-Based Dietary Patterns and Risk of Type 2 Diabetes. JAMA Intern Med 2019;179:1335. doi:10.1001/jamainternmed.2019.2195

Research

JAMA Internal Medicine | Original Investigation

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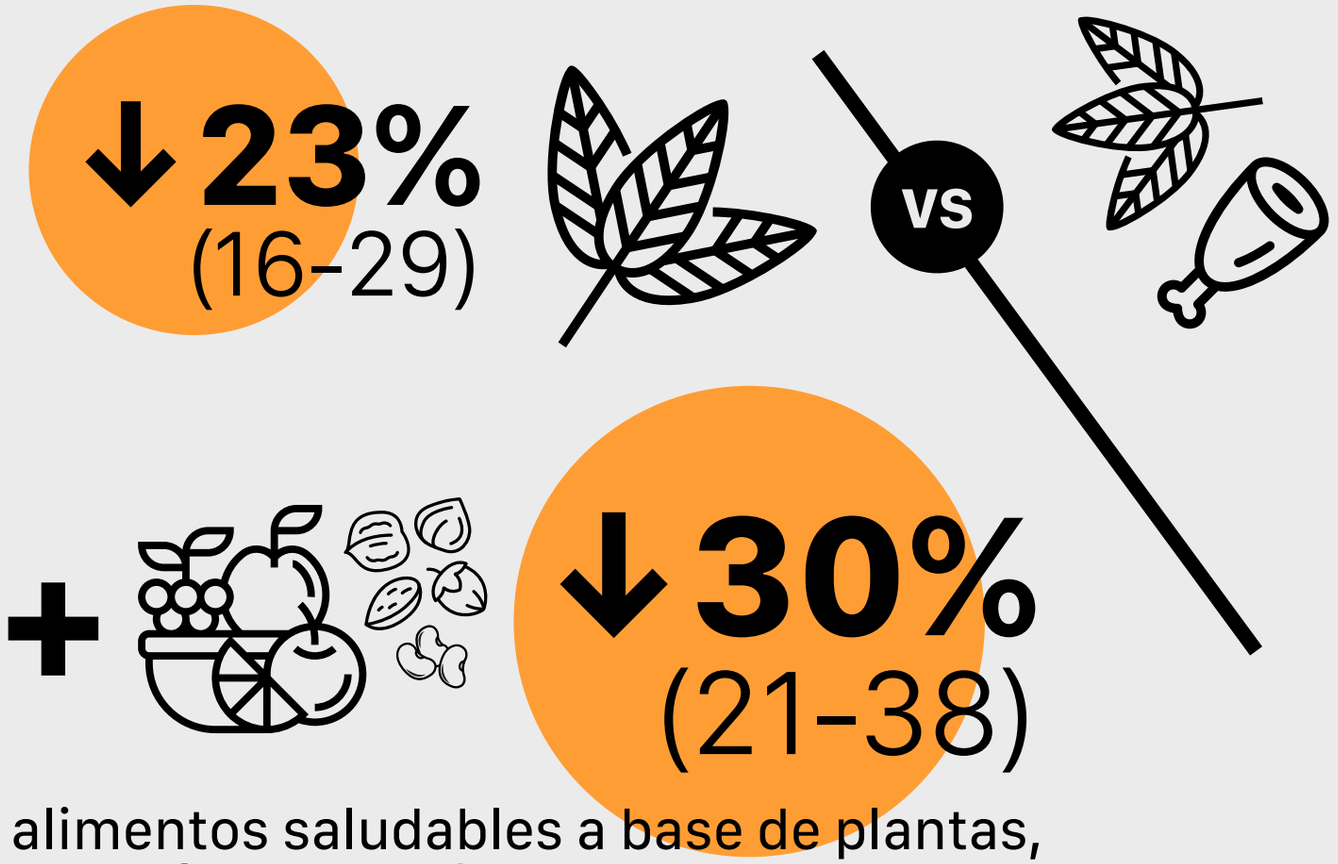

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Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long term health outcomes in patients with hypothyroidism: longitudinal study

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Accepted: 9 July 2019

ABSTRACT

OBJECTIVE

To explore whether thyroid stimulating hormone (TSH) concentration in patients with a diagnosis of hypothyroidism is associated with increased all cause mortality and a higher risk of cardiovascular disease and fractures.

DESIGN

Retrospective cohort study.

SETTING

The Health Improvement Network (THIN), a database of electronic patient records from UK primary care.

PARTICIPANTS

Adult patients with incident hypothyroidism from 1 January 1995 to 31 December 2017.

EXPOSURE

TSH concentration in patients with hypothyroidism.

MAIN OUTCOME MEASURES

Ischaemic heart disease, heart failure, stroke/transient ischaemic attack, atrial fibrillation, any fractures, fragility fractures, and mortality. Longitudinal TSH measurements from diagnosis to outcomes, study end, or loss to follow-up were collected. An extended Cox proportional hazards model with TSH considered as a time varying covariate was fitted for each outcome.

RESULTS

162 369 patients with hypothyroidism and 863 072 TSH measurements were included in the analysis. Compared with the reference TSH category (2-2.5 mIU/L), risk of ischaemic heart disease and heart failure increased at high TSH concentrations (>10 mIU/L) (hazard ratio 1.18 (95% confidence interval 1.02 to 1.38; P=0.03) and 1.42 (1.21 to 1.67; P<0.001), respectively). A protective effect for heart failure was seen at low TSH concentrations (hazard ratio 0.79 (0.64 to 0.99; P=0.04) for TSH <0.1 mIU/L and 0.76 (0.62 to 0.92; P=0.006) for 0.1-0.4 mIU/L). Increased mortality was observed in both the lowest and highest TSH categories (hazard ratio 1.18 (1.08 to 1.28; P<0.001), 1.29 (1.22 to 1.36; P<0.001), and 2.21 (2.07 to 2.36; P<0.001) for TSH <0.1 mIU/L, 4-10 mIU/L, and >10 mIU/L. An increase in the risk of fragility fractures was observed in patients in the highest TSH category (>10 mIU/L) (hazard ratio 1.15 (1.01 to 1.31; P=0.03)).

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Hypothyroidism is highly prevalent and can substantially affect patients' wellbeing

No specific optimal target for thyroid stimulating hormone (TSH) concentration exists in the context of thyroid hormone replacement

Whether variation in TSH concentration within normal limits may significantly affect patients' outcomes remains unclear

WHAT THIS STUDY ADDS

No clinically meaningful difference in the pattern of long term health outcomes (mortality, cardiovascular disease, fractures) was seen when TSH concentrations were within recommended normal limits

Compared with the reference TSH category (2-2.5 mIU/L), risk of ischaemic heart disease, heart failure, and fragility fractures was increased at high TSH

Introduction

Hypothyroidism is a highly prevalent global health problem that can substantially affect patients' wellbeing.[1] Lifelong treatment with thyroid hormone (replacement therapy) is needed when the diagnosis of persistent thyroid hormone deficiency is confirmed; consequently, levothyroxine is one of the most commonly prescribed drugs in Western countries,[2 3] and this is likely to increase further in the foreseeable future.[4]

Long term adverse health outcomes in patients with thyroid dysfunction and treatment targets to optimise these outcomes, generally monitored by serial

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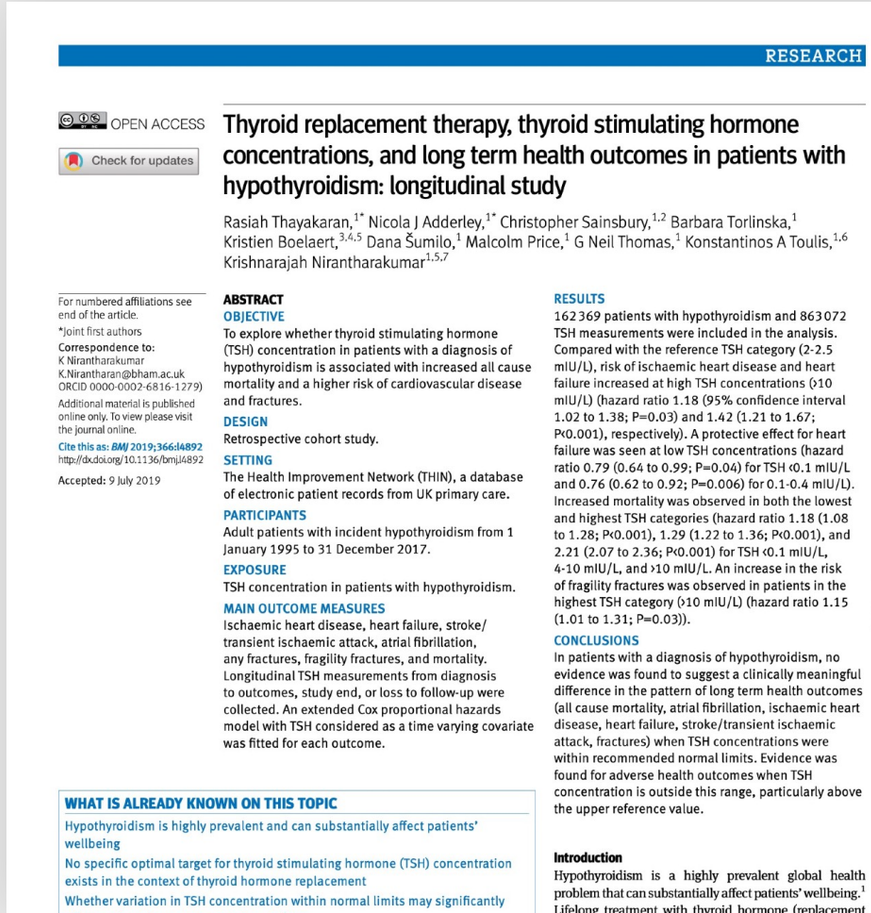
Cohortes retrospectivo con 162.369 pacientes con hipotiroidismo y 863.072 mediciones de TSH.



RESEARCH

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PARTICIPANTS
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EXPOSURE
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RESULTS
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El riesgo de **cardiopatía isquémica**, **IC** y **fracturas de fragilidad** aumentó con TSH >10 mIU/L

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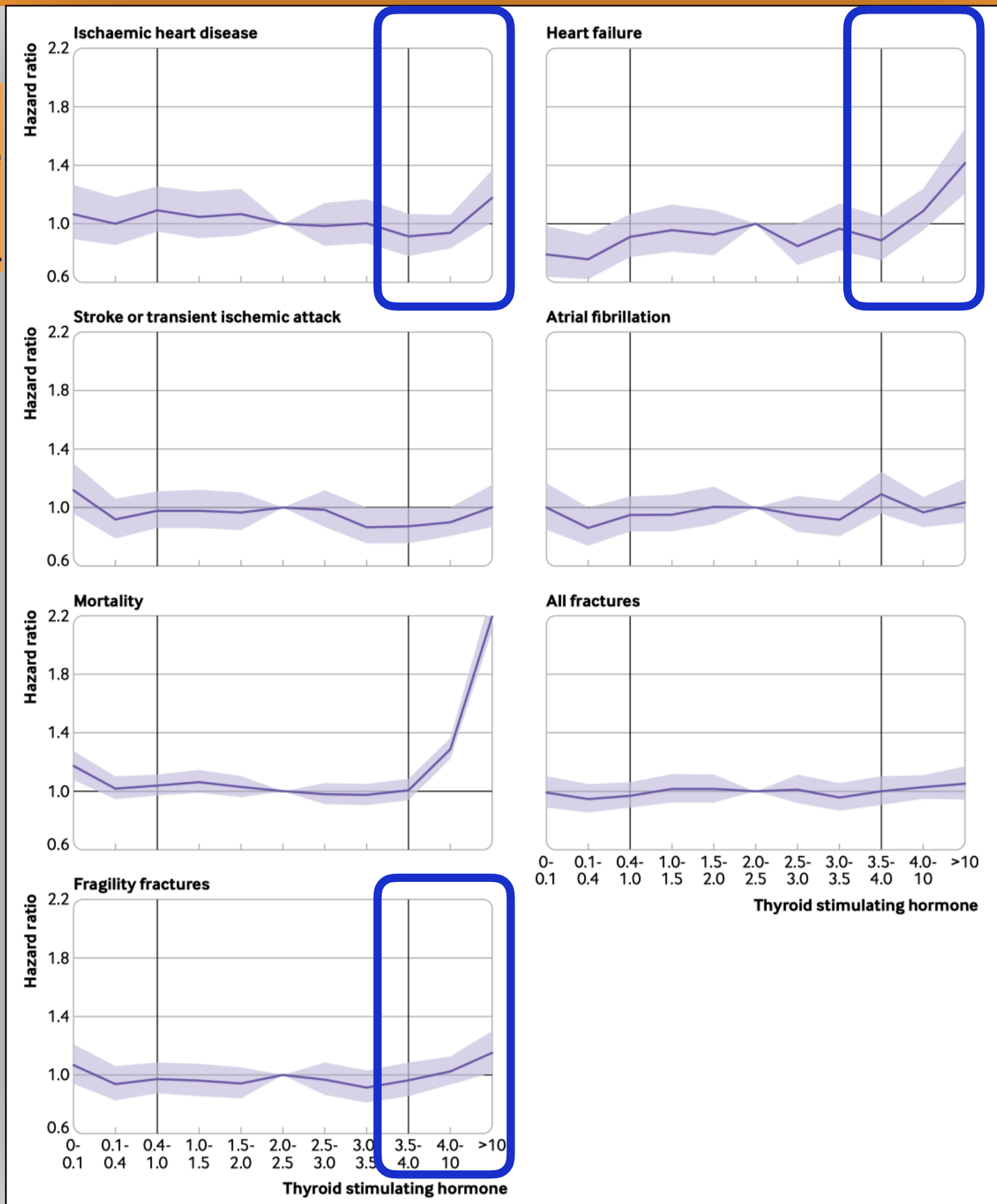

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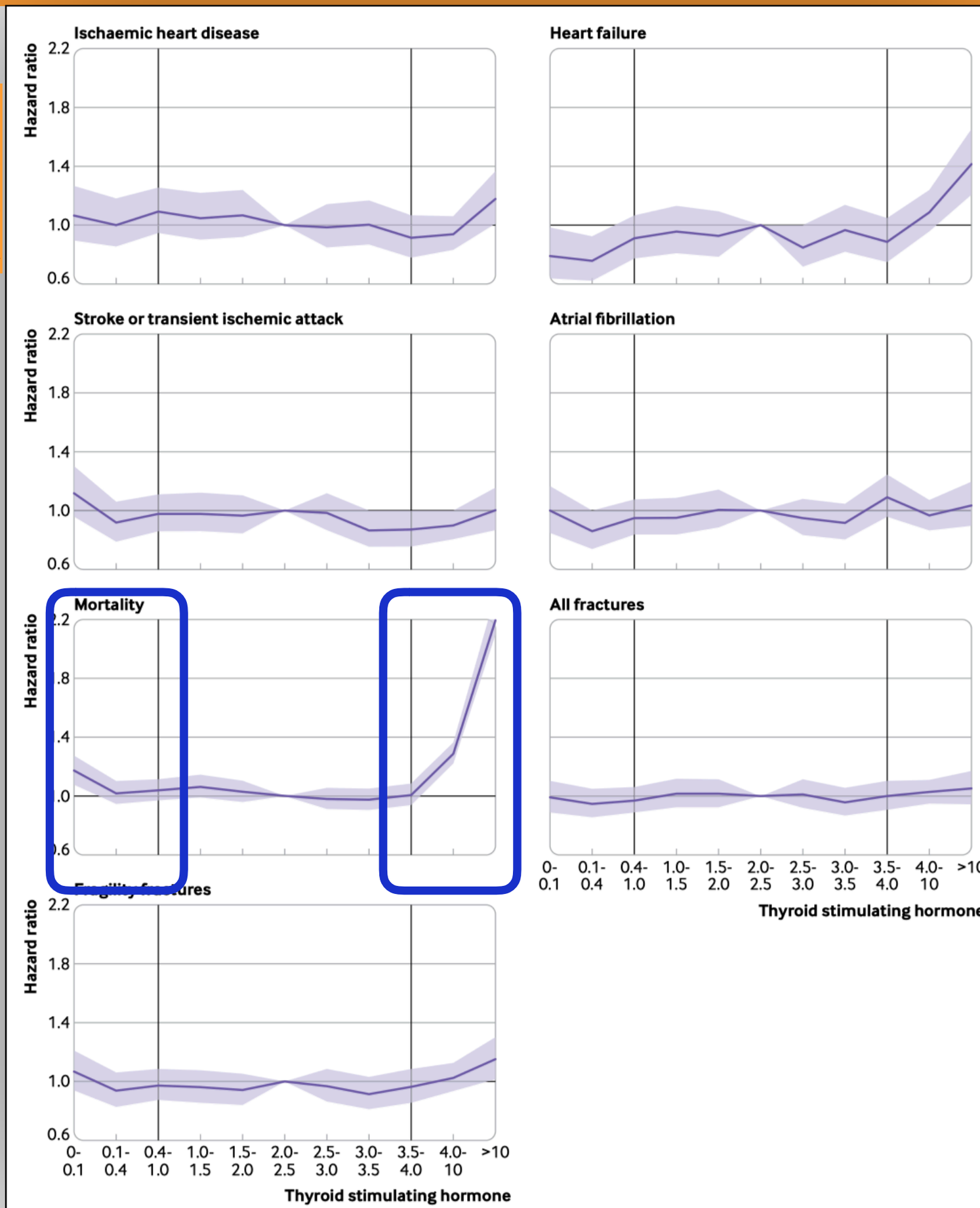

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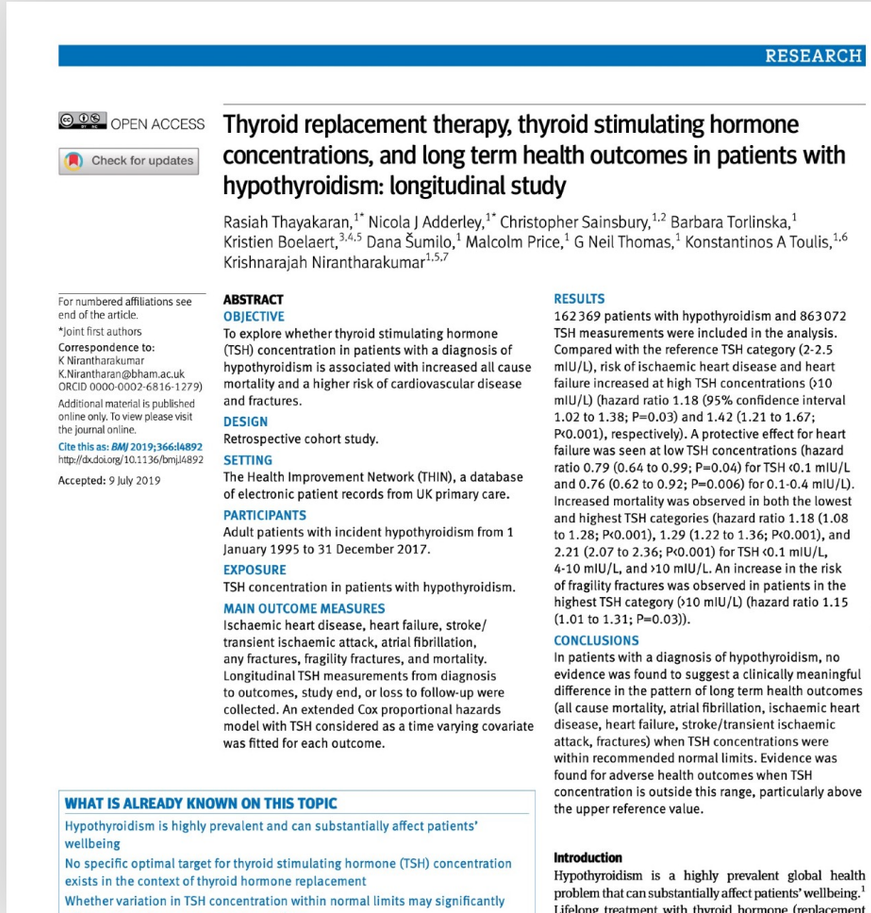

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Retrospective cohort study.

SETTING
The Health Improvement Network (THIN), a database of electronic patient records from UK primary care.

PARTICIPANTS
Adult patients with incident hypothyroidism from 1 January 1995 to 31 December 2017.

EXPOSURE
TSH concentration in patients with hypothyroidism.

MAIN OUTCOME MEASURES
Ischaemic heart disease, heart failure, stroke/transient ischaemic attack, atrial fibrillation, any fractures, fragility fractures, and mortality. Longitudinal TSH measurements from diagnosis to outcomes, study end, or loss to follow-up were collected. An extended Cox proportional hazards model with TSH considered as a time varying covariate was fitted for each outcome.

RESULTS
162 369 patients with hypothyroidism and 863 072 TSH measurements were included in the analysis. Compared with the reference TSH category (2-2.5 mIU/L), risk of ischaemic heart disease and heart failure increased at high TSH concentrations (>10 mIU/L) (hazard ratio 1.18 (95% confidence interval 1.02 to 1.38; P=0.03) and 1.42 (1.21 to 1.67; P<0.001), respectively). A protective effect for heart failure was seen at low TSH concentrations (hazard ratio 0.79 (0.64 to 0.99; P=0.04) for TSH <0.1 mIU/L and 0.76 (0.62 to 0.92; P=0.006) for 0.1-0.4 mIU/L). Increased mortality was observed in both the lowest and highest TSH categories (hazard ratio 1.18 (1.08 to 1.28; P<0.001), 1.29 (1.22 to 1.36; P<0.001), and 2.21 (2.07 to 2.36; P<0.001) for TSH <0.1 mIU/L, 4-10 mIU/L, and >10 mIU/L. An increase in the risk of fragility fractures was observed in patients in the highest TSH category (>10 mIU/L) (hazard ratio 1.15 (1.01 to 1.31; P=0.03)).

CONCLUSIONS
In patients with a diagnosis of hypothyroidism, no evidence was found to suggest a clinically meaningful difference in the pattern of long term health outcomes (all cause mortality, atrial fibrillation, ischaemic heart disease, heart failure, stroke/transient ischaemic attack, fractures) when TSH concentrations were within recommended normal limits. Evidence was found for adverse health outcomes when TSH concentration is outside this range, particularly above the upper reference value.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hypothyroidism is highly prevalent and can substantially affect patients' wellbeing

No specific optimal target for thyroid stimulating hormone (TSH) concentration exists in the context of thyroid hormone replacement

Whether variation in TSH concentration within normal limits may significantly

Introduction

Hypothyroidism is a highly prevalent global health problem that can substantially affect patients' wellbeing.[1] Lifelong treatment with thyroid hormone (replacement

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En pacientes con un diagnóstico de **hipotiroidismo con [TSH] dentro de los límites normales** recomendados **no se encontraron diferencias** clínicamente significativas en el patrón de resultados de salud a largo plazo:

- mortalidad por todas las causas,
- fibrilación auricular,
- cardiopatía isquémica,
- insuficiencia cardíaca,
- accidente cerebrovascular/ ataque isquémico transitorio,
- fracturas

thebmj

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PRACTICE

RATIONAL TESTING

Blood markers for cancer

Jessica Watson *NIHR doctoral research fellow*[1], Luke Mounce *research fellow*[2], Sarah ER Bailey *research fellow*[2], Sharon L Cooper *patient contributor*[2], Willie Hamilton *professor of primary care diagnostics*[2]

[1]Centre for Academic Primary Care, Bristol Medical School, University of Bristol, Bristol, UK; [2]University of Exeter, Exeter, UK

What you need to know

- "Triage" blood tests in primary care, such as haemoglobin, platelets, serum calcium level, liver function tests, and inflammatory markers such as C reactive protein and erythrocyte sedimentation rate may provide "clues" to cancer in patients with non-specific symptoms
- Triage tests do not have the performance characteristics of rule-out tests
- Evidence supports the use of only a small number of specific cancer markers, such as CA125 and PSA, in primary care

A 61 year old man with a one month history of back pain visits his general practitioner (GP). He has hypertension, has never smoked, and reports fatigue for several months. The pain is keeping him awake at night. He has not lost weight. Clinical examination is normal. The differential diagnosis for this patient is wide, including potential malignant causes such as pancreatic, myeloma, and prostate cancer or metastatic disease.

Cancer can be difficult to identifymany of the common symptoms are non-specific and low risk, and even the most well known "alarm" symptoms have relatively low positive predictive values (PPVs) for underlying malignancy[1]; for example, weight loss has a PPV for underlying malignancy of only 0-3.3%,[2] while rectal bleeding has a PPV of 2.2-15.8%.[3] Cancer markers used in hospital settings, when applied to low risk primary care patients, have low positive predictive values and high false positive rates.[4] Identifying patients whose non-specific symptoms may be caused by cancer, rather than benign disease, is therefore a challenge for primary care physicians.

While formal diagnosis usually happens in secondary care, the often by referral.[5] Those with estimated risk <3% may receive an initial panel of primary care investigations, or triage testing, to stratify risk. Triage tests can provide clues to help identify patients for referral, and crucially can point towards the site of an underlying malignancy. This is particularly useful when the patient's vague symptoms could be caused by several different cancer types, and can guide decision making on any need for further investigation.

This article discusses blood tests to detect or stratify risk for possible cancer in primary care and presents evidence for their use in symptomatic patients. First we consider tests that are not specific for any one type of cancer but which may help primary care providers stratify risk of malignancy. Then we discuss specific markers for certain types of cancer. Blood tests that might be used for screening asymptomatic patients, tests for less common malignancies (eg, gastrin, prolactin) or for monitoring patients with known malignancies, are beyond the scope of this article.

Search strategy

In August 2019 we replicated the search strategy used by NICE in its most recent guidance, NG12, restricted to papers published after 2014 (2011 for ovary) as the NICE searches had been performed before that date. LM, SB, and WH worked in pairs to assess candidate abstracts for blood tests used in primary care, and extracted full texts for relevant hits, supplemented by a large personal library of existing references.

What is the next investigation?

Non-specific blood tests or clues for cancer

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thebmj Visual summary

Predictive values of diagnostic blood tests as non-specific cancer markers, based on primary care studies or reviews

Types of blood tests and results

Patient groups

Some patients may be in multiple groups

Darker lines and boxes represent features with ≥1% positive predictive value

Positive predictive value
95% confidence interval
Evidence type
Number of included: participants, studies, cases, controls

Cancers associated

Approximate 1 year background risk of cancer type for women and men

HAEMOGLOBIN

Anaemia

- All patients → 1.1% (0.7-1.8%) Meta-analysis, 6 studies, 3 375 342 participants
- Adults → 0.3-1.4% Systematic review, 11 studies
- Women ≥55 → 0.2% (0.1-0.2%) Case-control, 3149 cases, 14 091 controls
- Patients ≥60 → 0.9% (0.5-1.6%) Meta-analysis, 6 studies, 3 375 342 participants

PLATELETS

Thrombocytosis

- Patients ≥55 → 1.6% (0.8-3.1%) Case-control, 21 GP practices
- Patients ≥60 → 0.1% (0.1-0.1%) Case-control, 2732 cases, 9537 controls
- Patients ≥40 → 5.9% (2.2-12.0%) Meta-analysis, 10 studies, 89 550 participants

Thrombocytopaenia

- Women ≥55 → 0.3% (0.2-0.3%) Case-control, 3149 cases, 14 091 controls
- Patients ≥60 → 0.5% (0.4-0.5%) Case-control, 7471 cases, 32 877 controls

FASTING PLASMA GLUCOSE (HBA1C)

Raised blood glucose

- Women ≥55 → 0.1% (0.09-0.11%) Case-control, 3635 cases, 16 459 controls
- Patients ≥60 → 0.1% (0.1-0.2%) Case-control, 2732 cases, 9537 controls

New onset diabetes

- Patients ≥60 → 0.16% Case-control, 3635 cases, 16 459 controls
- Patients ≥60 → 0.2% (0.2-0.2%) Case-control, 3635 cases, 16 459 controls

INFLAMMATORY MARKERS

Raised inflammatory markers

- All patients → 0.16% (0.15-0.17%) Case-control, 3635 cases, 16 459 controls
- Patients ≥60 → 4.1-12.9% Systematic review, 8 studies, 3 438 363 participants
- Adults → 0.2% (0.1-0.2%) Case-control, 2703 cases, 12 157 controls

LIVER FUNCTION TESTS

Jaundice

- Patients ≥40 → 0.08% (0.08-0.09%) Case-control, 2703 cases, 12 157 controls

Abnormal liver function

- All patients → 0.3% (0.2-0.3%) Case-control, 2703 cases, 12 157 controls
- Patients ≥60 → 0.17% (0.16-0.19%) Case-control, 2703 cases, 12 157 controls

Low albumin (<35g/L)

- Patients ≥60 → 0.2% (0.18-0.22%) Case-control, 2703 cases, 12 157 controls
- Older population (median age 84) → 0.7% (0.5-1.0%) Case-control, 2703 cases, 12 157 controls

RENAL FUNCTION

Raised creatinine

- All patients → 0.1% (0.1-0.2%) Case-control, 4915 cases, 21 718 controls
- Patients ≥60 → 0.3-1.4% Systematic review, 11 studies, 3 451 675 participants
- Patients ≥60 → 0.1% (0.12-0.14%) Case-control, 4915 cases, 21 718 controls

SERUM CALCIUM

Raised calcium (>2.6 mmol/L)

- Patients ≥60 → 0.2% (0.17-0.23%) Case-control, 4915 cases, 21 718 controls
- Patients ≥40 → ♂ 11.6% (11.0-12.3%) ♀ 6.2% (5.9-6.5%) Cohort study, 40 000 participants
- Patients ≥60 → 3.5% (3.4-3.7%) Cohort study, 155 646 participants
- Patients ≥60 → ♂ 11.5% (11.1-11.9%) ♀ 4.1% (3.9-4.4%) Cohort study, 54 267 participants
- Patients ≥40 → 28.4% (26.7-30.0%) Cohort study, 100 122 participants

WHITE CELL COUNT

Leucopenia

- Patients ≥60 → 0.3% (0.25-0.30%) Case-control, 4362 cases, 19 468 controls
- Patients ≥60 → 0.2% (0.22-0.25%) Case-control, 4362 cases, 19 468 controls

Leucocytosis

- Patients ≥60 → 0.3% (0.26-0.34%) Case-control, 4362 cases, 19 468 controls
- Patients ≥60 → 0.1% (0.12-0.14%) Case-control, 4362 cases, 19 468 controls

Cancers associated

- Stomach ♀ 0.01% ♂ 0.02%
- Oesophageal ♀ 0.02% ♂ 0.04%
- Renal ♀ 0.02% ♂ 0.04%
- Colorectal ♀ 0.10% ♂ 0.18%
- Lung ♀ 0.12% ♂ 0.14%
- Oesophagogastric ♀ 0.03% ♂ 0.07%
- Pancreatic ♀ 0.03% ♂ 0.03%
- Endometrial ♀ 0.06%
- Myeloma ♀ 0.01% ♂ 0.02%
- Bladder ♀ 0.02% ♂ 0.05%
- All ♀ 0.9% ♂ 1.0%
- Non-Hodgkin lymphoma ♀ 0.04% ♂ 0.05%

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NG PLASMA
SE (HBA1C)

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New onset diabetes

omen
≥55

Patients
≥60

INFLAMMATORY MARKERS

Raised inflammatory markers

All patients

Patients
≥60

Adults

LIVER FUNCTION TESTS

Jaundice

Patients
≥40

Abnormal liver function

All patients

Patients
≥60

Low albumin (<35g/L)

Older population (median age 84)

RENAL FUNCTION

Raised creatinine

Patients
≥60

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Patients
≥60

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0.16%
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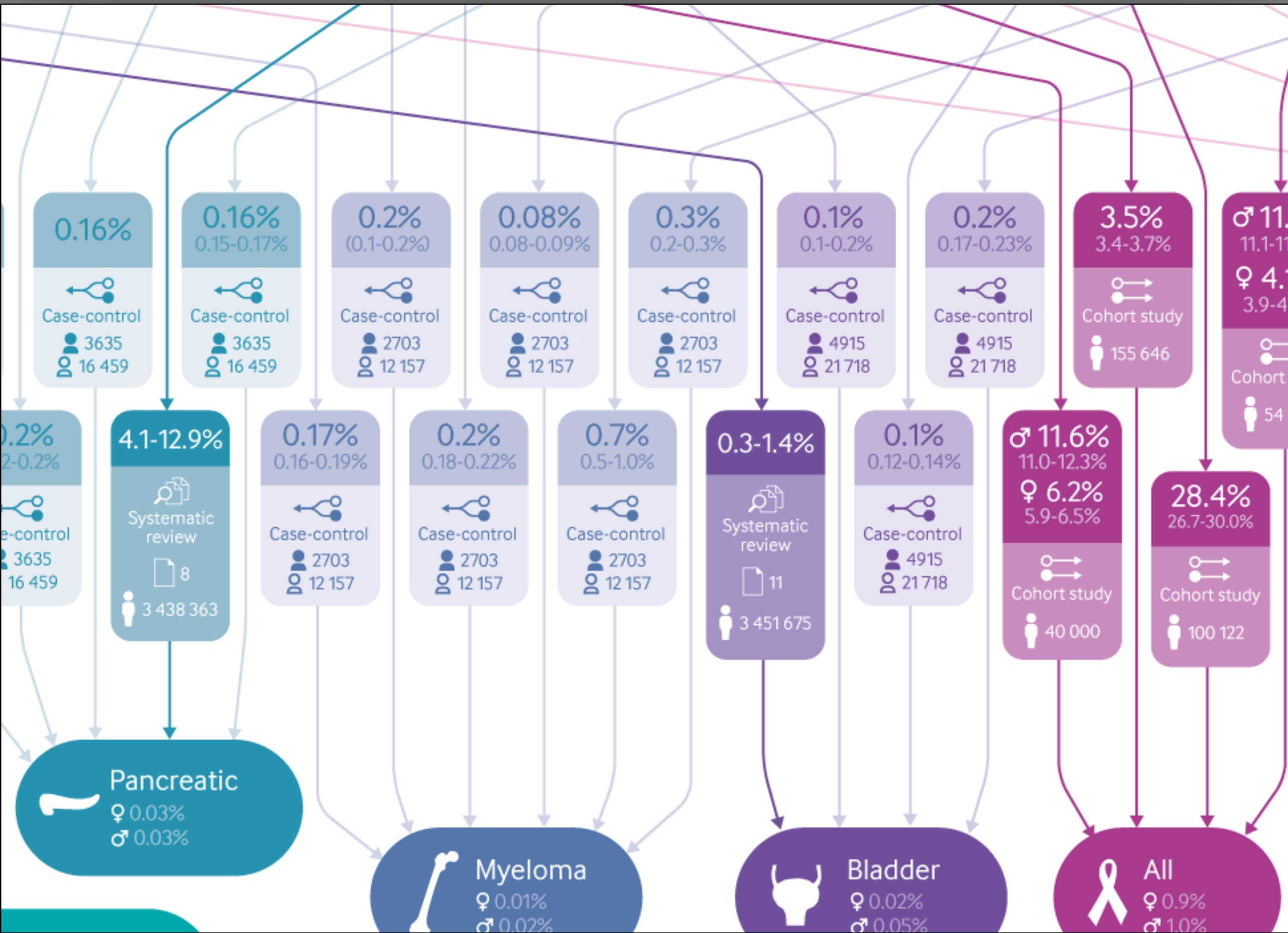
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Cohort study
40 000
28.4%
26.7-30.0%
Cohort study
100 122
Pancreatic
♀ 0.03%
♂ 0.03%
Myeloma
♀ 0.01%
♂ 0.02%
Bladder
♀ 0.02%
♂ 0.05%
All
♀ 0.9%
♂ 1.0%

RESEARCH

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Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study

Tammy Y N Tong,[1] Paul N Appleby,[1] Kathryn E Bradbury,[1] Aurora Perez-Cornago,[1] Ruth C Travis,[1] Robert Clarke,[2] Timothy J Key[1]

[1]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Oxford OX3 7LF, UK

[2]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Big Data Institute, University of Oxford, Oxford, UK

Correspondence to: T Y N Tong
tammy.tong@ndph.ox.ac.uk
(or @tammy_tong on Twitter
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Accepted: 10 July 2019

ABSTRACT

OBJECTIVE

To examine the associations of vegetarianism with risks of ischaemic heart disease and stroke.

DESIGN

Prospective cohort study.

SETTING

The EPIC-Oxford study, a cohort in the United Kingdom with a large proportion of non-meat eaters, recruited across the country between 1993 and 2001.

PARTICIPANTS

48 188 participants with no history of ischaemic heart disease, stroke, or angina (or cardiovascular disease) were classified into three distinct diet groups: meat eaters (participants who consumed meat, regardless of whether they consumed fish, dairy, or eggs; n=24 428), fish eaters (consumed fish but no meat; n=7506), and vegetarians including vegans (n=16 254), based on dietary information collected at baseline, and subsequently around 2010 (n=28 364).

MAIN OUTCOME MEASURES

Incident cases of ischaemic heart disease and stroke (including ischaemic and haemorrhagic types) identified through record linkage until 2016.

RESULTS

Over 18.1 years of follow-up, 2820 cases of ischaemic heart disease and 1072 cases of total stroke (519 ischaemic stroke and 300 haemorrhagic stroke) were recorded. After adjusting for sociodemographic and lifestyle confounders, fish eaters and vegetarians had 13% (hazard ratio 0.87, 95% confidence interval 0.77 to 0.99) and 22% (0.78, 0.70 to 0.87) lower rates of ischaemic heart disease than meat eaters, respectively (P<0.001 for heterogeneity). This difference was equivalent to 10 fewer cases of ischaemic heart disease (95% confidence interval 6.7 to 13.1 fewer) in vegetarians than in meat eaters per 1000 population over 10 years. The associations for ischaemic heart disease were partly attenuated after adjustment for self reported high blood cholesterol, high blood pressure, diabetes, and body mass index (hazard ratio 0.90, 95% confidence interval 0.81 to 1.00 in vegetarians with all adjustments). By contrast, vegetarians had 20% higher rates of total stroke (hazard ratio 1.20, 95% confidence interval 1.02 to 1.40) than meat eaters, equivalent to three more cases of total stroke (95% confidence interval 0.8 to 5.4 more) per 1000 population over 10 years, mostly due to a higher rate of haemorrhagic stroke. The associations for stroke did not attenuate after further adjustment of disease risk factors.

CONCLUSIONS

In this prospective cohort in the UK, fish eaters and vegetarians had lower rates of ischaemic heart disease than meat eaters, although vegetarians had higher rates of haemorrhagic and total stroke.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Vegetarian and vegan diets have become increasingly popular in recent years, but the potential benefits and hazards of these diets are not fully understood

Previous studies of two diet groups have reported that vegetarians have lower risks of ischaemic heart disease than non-vegetarians

However, no evidence has been reported of a difference in the risk of mortality from stroke, possibly because of limited available data and lack of available evidence on stroke subtypes

WHAT THIS STUDY ADDS

This study showed that fish eaters and vegetarians (including vegans) had lower

Introduction

Vegetarian and vegan diets have become increasingly popular in recent years, partly due to perceived health benefits, as well as concerns about the environment and animal welfare.[1] In the United Kingdom, both the representative National Diet and Nutrition Survey 2008-12 and a 2016 Ipsos MORI survey estimated about 1.7 million vegetarians and vegans living in the country.[2 3] Evidence suggests that vegetarians might have different disease risks compared with non-vegetarians,[4] but data from large scale prospective studies are limited, because few studies have recruited sufficient numbers of vegetarian participants.

For ischaemic heart disease, some but not all previous studies reported significantly lower risks of mortality from ischaemic heart disease in vegetarians than in non-vegetarians.[5-7] In terms of incidence, the only previous study (the European Prospective Investigation into Cancer (EPIC)-Oxford) reported that vegetarians had a lower risk of ischaemic heart disease

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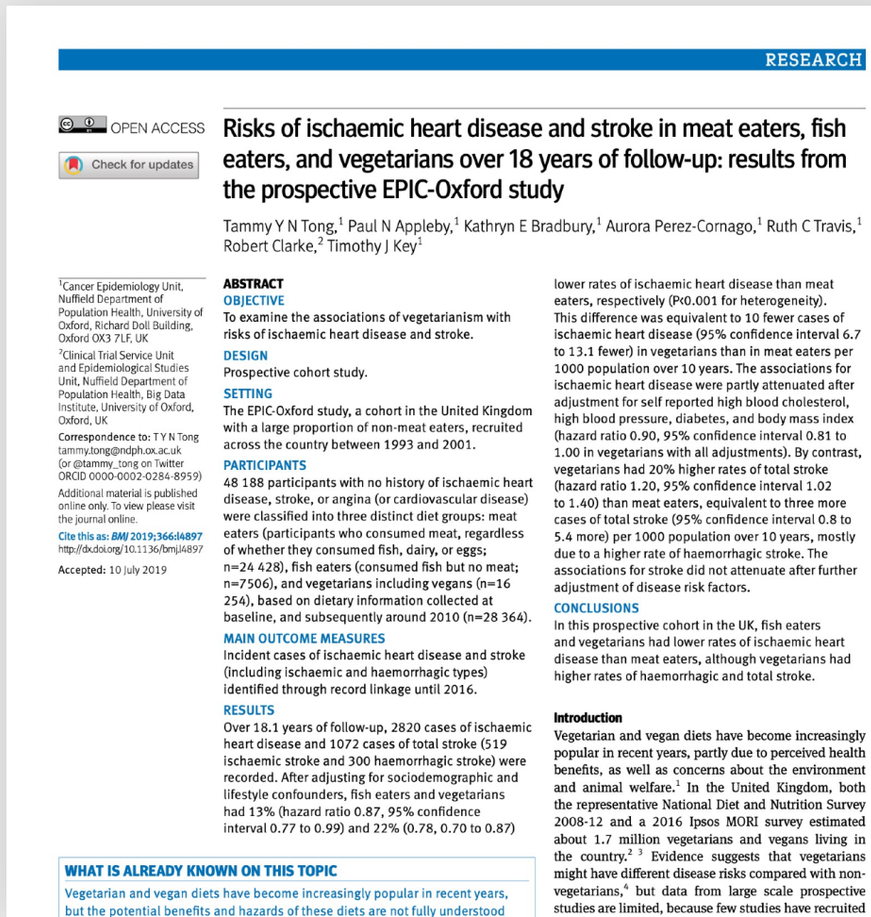
Cohortes prospectivo con más de **18 años** de seguimiento y **48.188 participantes sin antecedentes** de cardiopatía isquémica, accidente cerebrovascular o angina (o enfermedad cardiovascular).

Ajustando por confusores de estilo de vida y sociodemográficos.

Tong TYN, Appleby PN, Bradbury KE, Perez-Cornago A, Travis RC, Clarke R, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. Bmj 2019:l4897. doi:10.1136/bmj.l4897.



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n = 16254
vegetarianos
y veganos

n = 7506
consumidores
de **pescado**
(consumieron
pescado pero
no carne)

n = 24 428
consumidores
de **carne**
(independiente
mente de si
consumieron
pescado,
lácteos o
huevos)

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In this prospective cohort in the UK, fish eaters and vegetarians had lower rates of ischaemic heart disease than meat eaters, although vegetarians had higher rates of haemorrhagic and total stroke.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Vegetarian and vegan diets have become increasingly popular in recent years, but the potential benefits and hazards of these diets are not fully understood

Introduction

Vegetarian and vegan diets have become increasingly popular in recent years, partly due to perceived health benefits, as well as concerns about the environment and animal welfare.[1] In the United Kingdom, both the representative National Diet and Nutrition Survey 2008-12 and a 2016 Ipsos MORI survey estimated about 1.7 million vegetarians and vegans living in the country.[2 3] Evidence suggests that vegetarians might have different disease risks compared with non-vegetarians,[4] but data from large scale prospective studies are limited, because few studies have recruited

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Tong TYN, Appleby PN, Bradbury KE, Perez-Cornago A, Travis RC, Clarke R, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. Bmj 2019:l4897. doi:10.1136/bmj.l4897.

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Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study

Tammy Y N Tong,[1] Paul N Appleby,[1] Kathryn E Bradbury,[1] Aurora Perez-Cornago,[1] Ruth C Travis,[1] Robert Clarke,[2] Timothy J Key[1]

[1]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Oxford OX3 7LF, UK
[2]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Big Data Institute, University of Oxford, Oxford, UK

Correspondence to: T Y N Tong
tammy.tong@ndph.ox.ac.uk
(or @tammy_tong on Twitter
ORCID 0000-0002-0284-8959)

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Accepted: 10 July 2019

ABSTRACT

OBJECTIVE
To examine the associations of vegetarianism with risks of ischaemic heart disease and stroke.

DESIGN
Prospective cohort study.

SETTING
The EPIC-Oxford study, a cohort in the United Kingdom with a large proportion of non-meat eaters, recruited across the country between 1993 and 2001.

PARTICIPANTS
48 188 participants with no history of ischaemic heart disease, stroke, or angina (or cardiovascular disease) were classified into three distinct diet groups: meat eaters (participants who consumed meat, regardless of whether they consumed fish, dairy, or eggs; n=24 428), fish eaters (consumed fish but no meat; n=7506), and vegetarians including vegans (n=16 254), based on dietary information collected at baseline, and subsequently around 2010 (n=28 364).

MAIN OUTCOME MEASURES
Incident cases of ischaemic heart disease and stroke (including ischaemic and haemorrhagic types) identified through record linkage until 2016.

RESULTS
Over 18.1 years of follow-up, 2820 cases of ischaemic heart disease and 1072 cases of total stroke (519 ischaemic stroke and 300 haemorrhagic stroke) were recorded. After adjusting for sociodemographic and lifestyle confounders, fish eaters and vegetarians had 13% (hazard ratio 0.87, 95% confidence interval 0.77 to 0.99) and 22% (0.78, 0.70 to 0.87) lower rates of ischaemic heart disease than meat eaters, respectively (P<0.001 for heterogeneity). This difference was equivalent to 10 fewer cases of ischaemic heart disease (95% confidence interval 6.7 to 13.1 fewer) in vegetarians than in meat eaters per 1000 population over 10 years. The associations for ischaemic heart disease were partly attenuated after adjustment for self reported high blood cholesterol, high blood pressure, diabetes, and body mass index (hazard ratio 0.90, 95% confidence interval 0.81 to 1.00 in vegetarians with all adjustments). By contrast, vegetarians had 20% higher rates of total stroke (hazard ratio 1.20, 95% confidence interval 1.02 to 1.40) than meat eaters, equivalent to three more cases of total stroke (95% confidence interval 0.8 to 5.4 more) per 1000 population over 10 years, mostly due to a higher rate of haemorrhagic stroke. The associations for stroke did not attenuate after further adjustment of disease risk factors.

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n = 16254
vegetarianos
y veganos

↓ **10** (22%)
(6.7-13.1)
casos/1000p en
10 años menos de
CARDIOPATÍA ISQUÉMICA

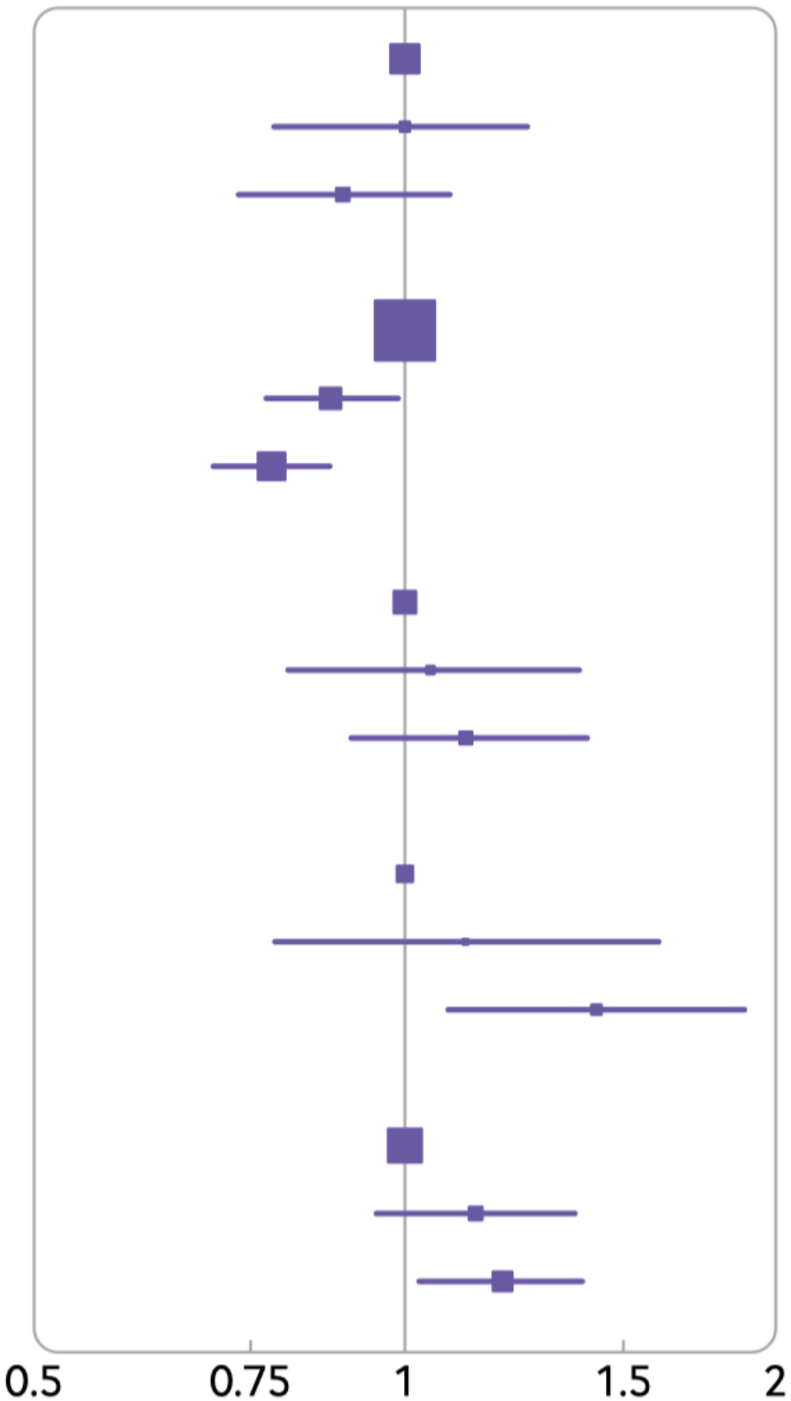
↑ **3** (20%)
(0.8-5.4)
casos/1000p en
10 años más de
ICTUS (hemorrágico sobre todo)

n = 7506
consumidores
de **pescado**
(consumieron
pescado pero
no carne)

↓13%
CARDIOPATÍA ISQUÉMICA

n = 24 428
consumidores
de **carne**
(independiente
mente de si
consumieron
pescado,
lácteos o
huevos)

Outcome and diet groups	Cases	Person years	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P heterogeneity
Acute myocardial infarction					
Meat eaters	559	438 001		Reference	
Fish eaters	84	132 168		1.00 (0.78 to 1.26)	
Vegetarians	145	278 800		0.89 (0.73 to 1.09)	0.51
Ischaemic heart disease					
Meat eaters	2026	429 125		Reference	
Fish eaters	298	130 816		0.87 (0.77 to 0.99)	
Vegetarians	496	276 938		0.78 (0.70 to 0.87)	<0.001
Ischaemic stroke					
Meat eaters	340	438 418		Reference	
Fish eaters	62	132 040		1.05 (0.80 to 1.39)	
Vegetarians	117	278 383		1.12 (0.90 to 1.41)	0.59
Haemorrhagic stroke					
Meat eaters	173	438 418		Reference	
Fish eaters	38	132 040		1.12 (0.78 to 1.61)	
Vegetarians	89	278 383		1.43 (1.08 to 1.90)	0.04
Total stroke					
Meat eaters	678	438 418		Reference	
Fish eaters	136	132 040		1.14 (0.94 to 1.38)	
Vegetarians	258	278 383		1.20 (1.02 to 1.40)	0.06



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Vegetarians ✗	89	278 383		1.43 (1.08 to 1.90)	0.04
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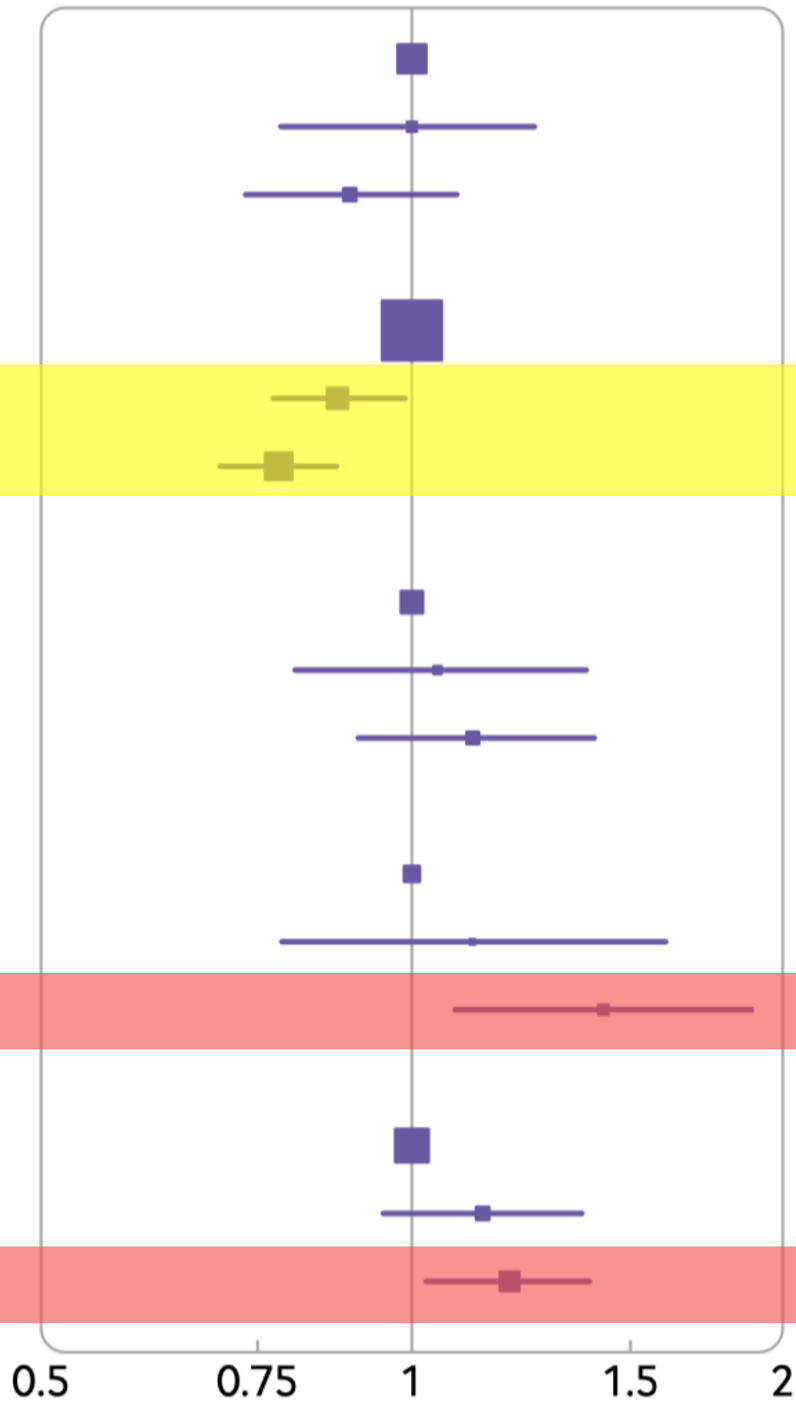

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Potential impact on prevalence of obesity in the UK of a 20% price increase in high sugar snacks: modelling study

Pauline F D Scheelbeek,[1,2] Laura Cornelsen,[3] Theresa M Marteau,[4] Susan A Jebb,[5] Richard D Smith[6]

For numbered affiliations see end of the article.

Correspondence to:
P F D Scheelbeek
pauline.scheelbeek@lshtm.ac.uk
(or @lshtm_planet on Twitter;
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Accepted: 17 July 2019

ABSTRACT

OBJECTIVE

To estimate the potential impact on body mass index (BMI) and prevalence of obesity of a 20% price increase in high sugar snacks.

DESIGN

Modelling study.

SETTING

General adult population of the United Kingdom.

PARTICIPANTS

36 324 households with data on product level household expenditure from UK Kantar FMCG (fast moving consumer goods) panel for January 2012 to December 2013. Data were used to estimate changes in energy (kcal, 1 kcal=4.18 kJ=0.00418 MJ) purchase associated with a 20% price increase in high sugar snacks. Data for 2544 adults from waves 5 to 8 of the National Diet and Nutrition Survey (2012-16) were used to estimate resulting changes in BMI and prevalence of obesity.

MAIN OUTCOME MEASURES

The effect on per person take home energy purchases of a 20% price increase for three categories of high sugar snacks: confectionery (including chocolate), biscuits, and cakes. Health outcomes resulting from the price increase were measured as changes in weight, BMI (not overweight (BMI <25), overweight (BMI ≥25 and <30), and obese (BMI ≥30)), and prevalence of obesity. Results were stratified by household income and BMI.

RESULTS

For income groups combined, the average reduction in energy consumption for a 20% price increase in high sugar snacks was estimated to be 8.9×10^3 kcal (95% confidence interval -13.1×10^3 to -4.2×10^3 kcal). Using a static weight loss model, BMI was estimated to decrease by 0.53 (95% confidence interval −1.01 to −0.06) on average across all categories and income groups. This change could reduce the UK prevalence of obesity by 2.7 percentage points (95% confidence interval −3.7 to −1.7 percentage points) after one year. The impact of a 20% price increase in high sugar snacks on energy purchase was largest in low income households classified as obese and smallest in high income households classified as not overweight.

CONCLUSIONS

Increasing the price of high sugar snacks by 20% could reduce energy intake, BMI, and prevalence of obesity. This finding was in a UK context and was double that modelled for a similar price increase in sugar sweetened beverages.

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Taxation strategies to lower sugar and energy intake have focused on sugar sweetened beverages; in the UK, high sugar snacks, such as confectionery, make a more substantial contribution to intakes of free sugars and energy than do sugar sweetened beverages

Encouraged by the large reformulation efforts of the food industry after the Soft Drink Industry Levy was introduced, Public Health England developed a voluntary sugar reduction and reformulation programme for snacks, showing modest results after the first year and highlighting the need for additional interventions to reduce sugar intake through high sugar snacks

Several countries, including Mexico, Finland, and Hungary introduced taxes on unhealthy foods, including high sugar snacks: early evaluations show a major reduction in the purchase of such foods

WHAT THIS STUDY ADDS

Our study suggests that a 20% price increase in high sugar snacks has the potential to reduce overall energy purchased among all body mass index and income groups in the UK, leading to an estimated population level reduction in obesity prevalence of 2.7 percentage points after the first year

The results of this study also suggest that price increases in high sugar snacks

Introduction

Over the past decades the prevalence of obesity has increased steeply, with rates tripling globally between 1975 and 2016. In 2016, about two billion adults (aged 18 or more) worldwide were overweight, of whom more than 650 million were classified as obese.[1] Obesity is a major risk factor for several chronic conditions, including ischaemic heart disease, stroke, many cancers, and type 2 diabetes.[2] In the UK, the prevalence of obesity among adults was estimated at 27.8% (95% confidence interval 24.9% to 30.7%) in 2016,[3] higher than the average of 19.5% reported by the Organisation for Economic Co-operation and Development.[4] However, noticeable differences exist in the prevalence of obesity in relation to deprivation and income.[5-7] In 2016, 38% of women living in the most deprived areas in England were classified as obese compared with 20% living in the least deprived areas.[8] Among children aged 2-15 years, 26% of those living

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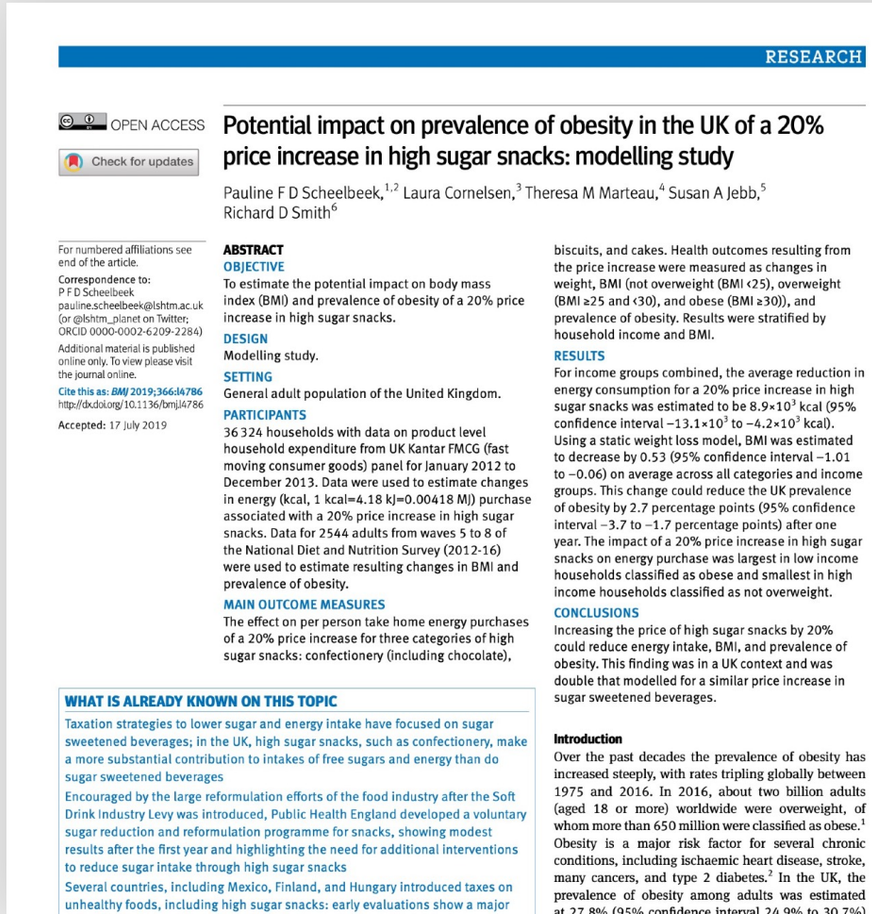
Contexto

- Las estrategias fiscales para reducir el consumo de azúcar y energía se han centrado en las **bebidas azucaradas**.
- En el Reino Unido los aperitivos con alto contenido de azúcar contribuyen de forma más sustancial a la ingesta de azúcares y energía libres que las bebidas azucaradas.
- **México, Finlandia y Hungría**, han introducido impuestos sobre alimentos no saludables como los aperitivos con alto contenido de azúcar y las primeras evaluaciones muestran una importante **reducción en la compra** de tales alimentos.

Scheelbeek PFD, Cornelsen L, Marteau TM, Jebb SA, Smith RD. Potential impact on prevalence of obesity in the UK of a 20% price increase in high sugar snacks: modelling study. Bmj 2019:l4786. doi:10.1136/bmj.l4786



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pauline.scheelbeek@lshtm.ac.uk
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The effect on per person take home energy purchases of a 20% price increase for three categories of high sugar snacks: confectionery (including chocolate), biscuits, and cakes. Health outcomes resulting from the price increase were measured as changes in weight, BMI (not overweight (BMI <25), overweight (BMI ≥25 and <30), and obese (BMI ≥30)), and prevalence of obesity. Results were stratified by household income and BMI.

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Estudio de modelización para **estimar** el impacto potencial sobre el índice de masa corporal (**IMC**) y la prevalencia de obesidad de un **aumento del 20% en el precio** de los snacks con alto contenido de azúcar.

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Resultados

↓IMC en 0,53 (IC95%: -1,01 a -0,06) promedio en todas las categorías y grupos de ingresos.

Este cambio podría reducir la prevalencia de la obesidad en UK en **2,7%** (intervalo de confianza del 95%: -3,7 a -1,7 puntos porcentuales) después de un año.

Tuvo **más impacto en los hogares de bajos ingresos y obesos** y menor impacto en hogares de altos ingresos normopeso.

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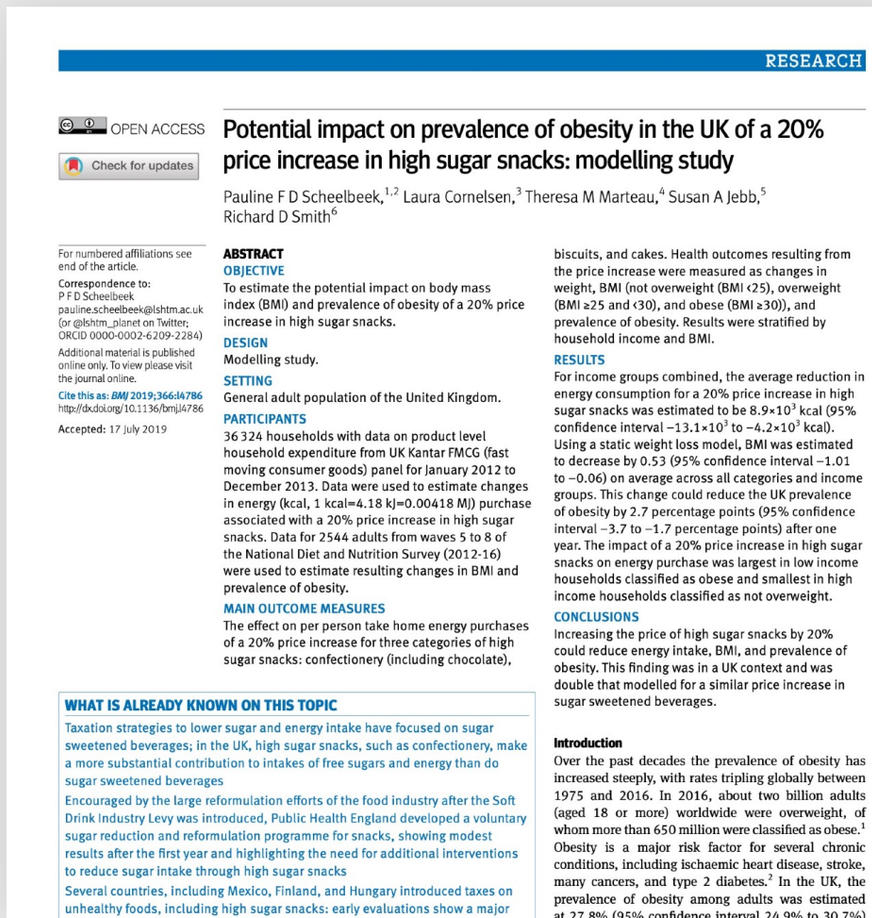

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The effect on per person take home energy purchases of a 20% price increase for three categories of high sugar snacks: confectionery (including chocolate), biscuits, and cakes. Health outcomes resulting from the price increase were measured as changes in weight, BMI (not overweight (BMI <25), overweight (BMI ≥25 and <30), and obese (BMI ≥30)), and prevalence of obesity. Results were stratified by household income and BMI.

RESULTS
For income groups combined, the average reduction in energy consumption for a 20% price increase in high sugar snacks was estimated to be 8.9×10^3 kcal (95% confidence interval -13.1×10^3 to -4.2×10^3 kcal). Using a static weight loss model, BMI was estimated to decrease by 0.53 (95% confidence interval −1.01 to −0.06) on average across all categories and income groups. This change could reduce the UK prevalence of obesity by 2.7 percentage points (95% confidence interval −3.7 to −1.7 percentage points) after one year. The impact of a 20% price increase in high sugar snacks on energy purchase was largest in low income households classified as obese and smallest in high income households classified as not overweight.

CONCLUSIONS
Increasing the price of high sugar snacks by 20% could reduce energy intake, BMI, and prevalence of obesity. This finding was in a UK context and was double that modelled for a similar price increase in sugar sweetened beverages.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Taxation strategies to lower sugar and energy intake have focused on sugar sweetened beverages; in the UK, high sugar snacks, such as confectionery, make a more substantial contribution to intakes of free sugars and energy than do sugar sweetened beverages

Encouraged by the large reformulation efforts of the food industry after the Soft Drink Industry Levy was introduced, Public Health England developed a voluntary sugar reduction and reformulation programme for snacks, showing modest results after the first year and highlighting the need for additional interventions to reduce sugar intake through high sugar snacks

Several countries, including Mexico, Finland, and Hungary introduced taxes on unhealthy foods, including high sugar snacks: early evaluations show a major

Introduction

Over the past decades the prevalence of obesity has increased steeply, with rates tripling globally between 1975 and 2016. In 2016, about two billion adults (aged 18 or more) worldwide were overweight, of whom more than 650 million were classified as obese.[1] Obesity is a major risk factor for several chronic conditions, including ischaemic heart disease, stroke, many cancers, and type 2 diabetes.[2] In the UK, the prevalence of obesity among adults was estimated at 27.8% (95% confidence interval 24.9% to 30.7%)

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Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults

Myriam Alexander,[1] A Katrina Loomis,[2] Johan van der Lei,[3] Talita Duarte-Salles,[4] Daniel Prieto-Alhambra,[5] David Ansell,[6,7] Alessandro Pasqua,[8] Francesco Lapi,[8] Peter Rijnbeek,[3] Mees Mosseveld,[3] Paul Avillach,[3,9] Peter Egger,[1] Nafeesa N Dhalwani,[10] Stuart Kendrick,[11] Carlos Cells-Morales,[12] Dawn M Waterworth,[13] William Alazawi,[14*] Naveed Sattar[12*]

For numbered affiliations see end of the article.

*Contributed equally

Correspondence to: N Sattar Naveed.sattar@glasgow.ac.uk (ORCID 0000-0002-1606-2597)

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ABSTRACT

OBJECTIVE

To estimate the risk of acute myocardial infarction (AMI) or stroke in adults with non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

DESIGN

Matched cohort study.

SETTING

Population based, electronic primary healthcare databases before 31 December 2015 from four European countries: Italy (n=1 542 672), Netherlands (n=2 225 925), Spain (n=5 488 397), and UK (n=12 695 046).

PARTICIPANTS

120 795 adults with a recorded diagnosis of NAFLD or NASH and no other liver diseases, matched at time of NAFLD diagnosis (index date) by age, sex, practice site, and visit, recorded at six months before or after the date of diagnosis, with up to 100 patients without NAFLD or NASH in the same database.

MAIN OUTCOME MEASURES

Primary outcome was incident fatal or non-fatal AMI and ischaemic or unspecified stroke. Hazard ratios were estimated using Cox models and pooled across databases by random effect meta-analyses.

RESULTS

120 795 patients with recorded NAFLD or NASH diagnoses were identified with mean follow-up 2.1-5.5 years. After adjustment for age and smoking the pooled hazard ratio for AMI was 1.17 (95% confidence interval 1.05 to 1.30; 1035 events in participants with NAFLD or NASH, 67 823 in matched controls). In a group with more complete data on risk factors (86 098 NAFLD and 4 664 988 matched controls), the hazard ratio for AMI after adjustment for systolic blood pressure, type 2 diabetes, total cholesterol level, statin use, and hypertension was 1.01 (0.91 to 1.12; 747 events in participants with NAFLD or NASH, 37 462 in matched controls). After adjustment for age and smoking status the pooled hazard ratio for stroke was 1.18 (1.11 to 1.24; 2187 events in participants with NAFLD or NASH, 134 001 in matched controls). In the group with more complete data on risk factors, the hazard ratio for stroke was 1.04 (0.99 to 1.09; 1666 events in participants with NAFLD, 83 882 in matched controls) after further adjustment for type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension.

CONCLUSIONS

The diagnosis of NAFLD in current routine care of 17.7 million patient appears not to be associated with AMI or stroke risk after adjustment for established cardiovascular risk factors. Cardiovascular risk assessment in adults with a diagnosis of NAFLD is important but should be done in the same way as for the general population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Non-alcoholic fatty liver disease (NAFLD) is associated with metabolic syndrome and other risk factors for acute myocardial infarction (AMI) or stroke

NAFLD is associated with increased risk of AMI and stroke and cardiovascular surrogate markers

Introduction

For several years, researchers have proposed that, in addition to being a marker of ectopic fat accumulation and diabetes risk (which is unambiguous), non-alcoholic fatty liver disease (NAFLD) might have important associations with cardiovascular outcomes.[1] The incidence of NAFLD has increased alongside that of obesity and diabetes worldwide, however its "impact" on complications from those conditions, including risk of cardiovascular disease, has not yet been established. In some ways this is not surprising because people with NAFLD often have abnormal glucose and lipid levels and are usually overweight or obese. Other mechanisms that could explain a possible association include increased oxidative stress, deranged adipokine profile, and hypercoagulability, which are more likely in people with NAFLD,[2] giving rise to risk of AMI or stroke beyond those of traditional risk factors. Studies have shown an increased prevalence of surrogate markers

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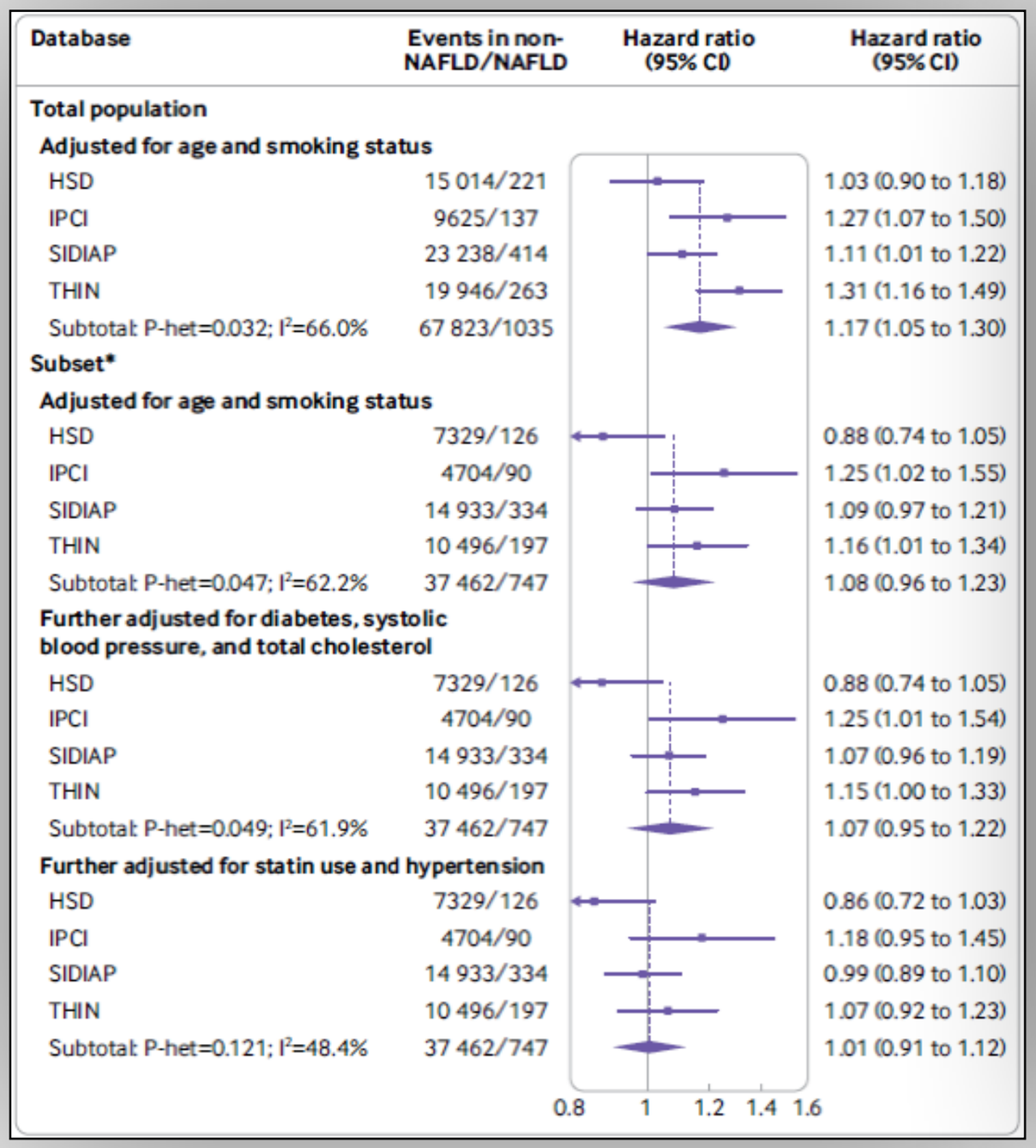
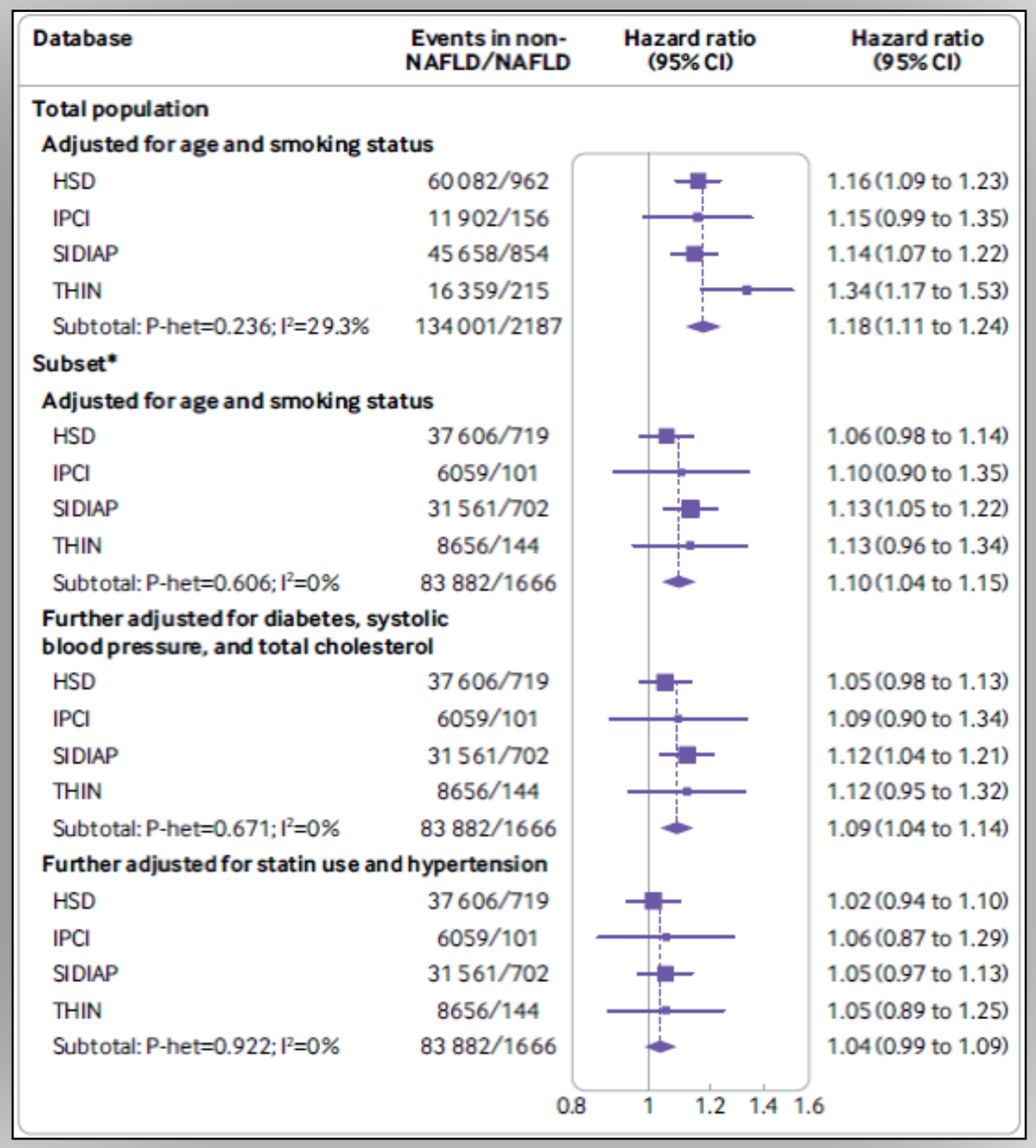
RESEARCH

Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults

Myriam Alexander,[1] A Katrina Loomis,[2] Johan van der Lei,[3] Talita Duarte-Salles,[4] Daniel Prieto-Alhambra,[5] David Ansell,[6,7] Alessandro Pasqua,[8] Francesco Lapi,[8] Peter Rijnbeek,[3] Mees Mosseveld,[3] Paul Avillach,[3,9] Peter Egger,[1] Nafeesa N Dhalwani,[10] Stuart Kendrick,[11] Carlos Celis-Morales,[12] Dawn M Waterworth,[13] William Alazawi,[14*] Naveed Sattar[12*]

- Estudio prospectivo con cohortes apareadas a partir de 4 bases de datos de pacientes de tención primaria con diagnóstico de esteatosis o esteatohepatitis no alcohólica. Muestra 120795 pacientes.
- Estratificación por edad, sexo, tabaquismo, diabetes, presión arterial, niveles de LDL y uso de estatinas.
- Determinar riesgo de infarto e ictus en pacientes con esteatosis y esteatohepatitis no alcohólica.





La presencia de esteatosis o esteatohepatitis no alcohólica no supone un aumento del riesgo cardiovascular por sí sola. Debe hacerse una valoración global del riesgo cardiovascular en estos pacientes.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D., D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D., Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.

ABSTRACT

BACKGROUND

Familial hypercholesterolemia is characterized by severely elevated low-density lipoprotein (LDL) cholesterol levels and premature cardiovascular disease. The short-term efficacy of statin therapy in children is well established, but longer follow-up studies evaluating changes in the risk of cardiovascular disease are scarce.

METHODS

We report a 20-year follow-up study of statin therapy in children. A total of 214 patients with familial hypercholesterolemia (genetically confirmed in 98% of the patients), who were previously participants in a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, were invited for follow-up, together with their 95 unaffected siblings. Participants completed a questionnaire, provided blood samples, and underwent measurements of carotid intima–media thickness. The incidence of cardiovascular disease among the patients with familial hypercholesterolemia was compared with that among their 156 affected parents.

RESULTS

Of the original cohort, 184 of 214 patients with familial hypercholesterolemia (86%) and 77 of 95 siblings (81%) were seen in follow-up; among the 214 patients, data on cardiovascular events and on death from cardiovascular causes were available for 203 (95%) and 214 (100%), respectively. The mean LDL cholesterol level in the patients had decreased from 207.3 to 160.7 mg per deciliter (from 6.13 to 4.16 mmol per liter) — a decrease of 32% from the baseline level; treatment goals (LDL cholesterol <100 mg per deciliter [2.59 mmol per liter]) were achieved in 37 patients (20%). Mean progression of carotid intima–media thickness over the entire follow-up period was 0.0056 mm per year in patients with familial hypercholesterolemia and 0.0057 mm per year in siblings (mean difference adjusted for sex, −0.0001 mm per year; 95% confidence interval, −0.0010 to 0.0008). The cumulative incidence of cardiovascular events and of death from cardiovascular causes at 39 years of age was lower among the patients with familial hypercholesterolemia than among their affected parents (1% vs. 20% and 0% vs. 7%, respectively).

CONCLUSIONS

From the Departments of Pediatrics (I.K.L., A.W., D.M.K., J.W.G.), Clinical Epidemiology, Biostatistics, and Bioinformatics (I.K.L., M.H.H., B.A.H.), and Vascular Medicine (I.K.L., J.J.P.K.), Amsterdam University Medical Centers, Amsterdam, and Imagelaboratories and Cardiovascular, Erichem (E.G.) — both in the Netherlands. Address reprint requests to Dr. Kastelein at the Department of Vascular Medicine, Amsterdam University Medical Centers, Rm. F4-159.2, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at j.j.kastelein@amsterdamumc.nl.

Drs. Kastelein and Hutten contributed equally to this article.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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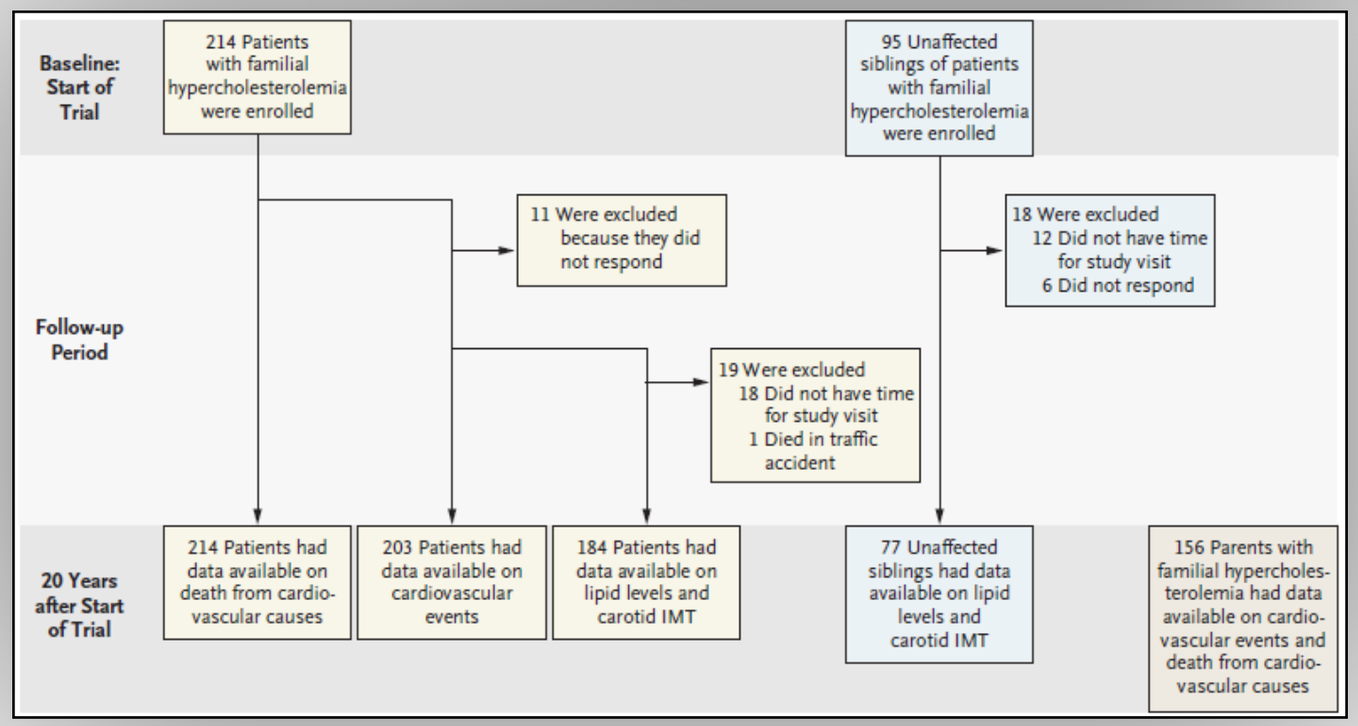
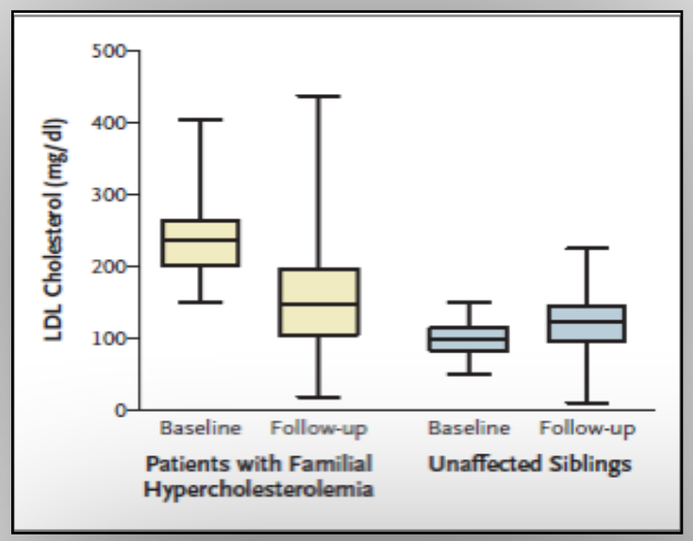
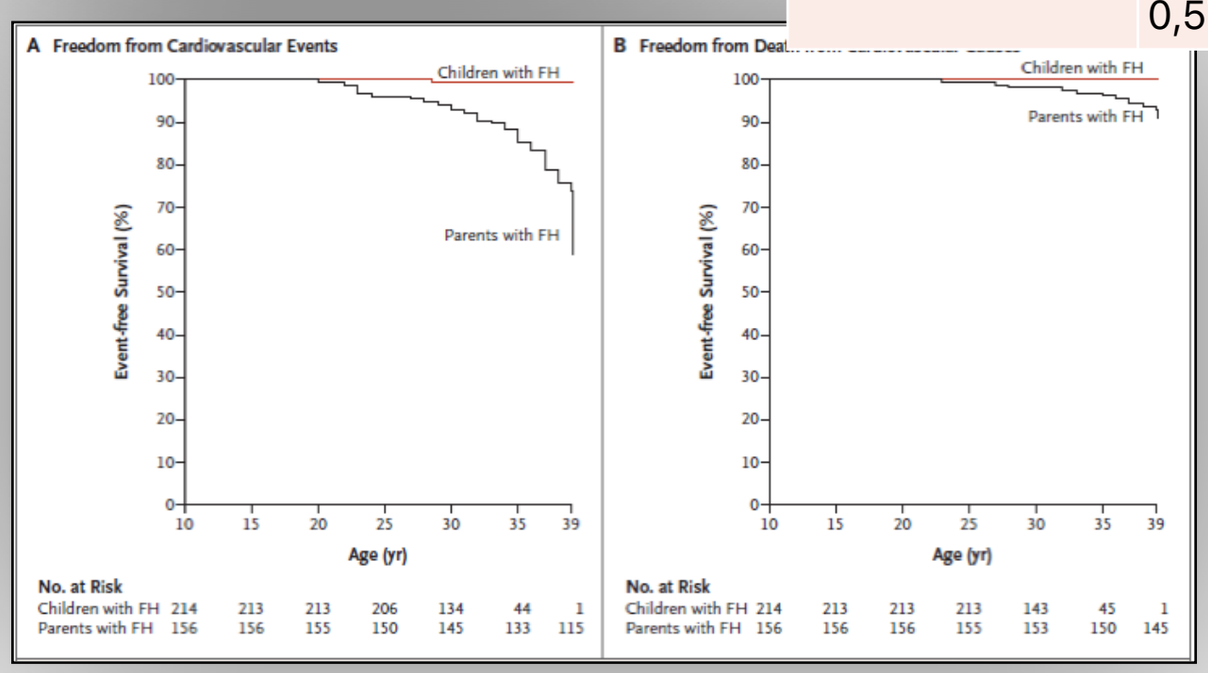
Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D., D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D., Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.



- Estudio observacional a 20 años sobre la base de ensayo clínico previo.
- Pacientes con hipercolesterolemia familiar, hermanos sanos y padres.
- Valoración de niveles de LDL, media de la íntima de la carótida y mortalidad cardiovascular (comparada con padres)



	H. familiar	Controles	Diferencia
Baseline	0.446 mm (95% CI, 0.439 a 0.453)	0.439 mm (95% CI, 0.430 a 0.449)	0.012 mm (95% CI, 0.002 a 0.021)
20 años	0.555 mm (95% CI, 0.542 a 0.567)	0.551 mm (95% CI, 0.531 a 0.570)	0.008 mm; (95% CI, −0.009 a 0.026)
LDL<100	0,532mm (95% CI, 0,508 a 0,556)	-	0,022mm; (95% CI, 0,003 a 0,047)
LDL>100	0,560mm (95% CI, 0,546 a 0,574)	-	



Conclusión:
La terapia con estatinas, en los pacientes con hipercolesterolemia familiar, iniciada en la infancia, enlentece el desarrollo de la placa de ateroma en la carótida y reduce el riesgo de enfermedad cardiovascular en la edad adulta.

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John J V McMurray

Summary

Background Glucagon-like peptide-1 (GLP-1) receptor agonists differ in their structure and duration of action and have been studied in trials of varying sizes and with different patient populations, with inconsistent effects on cardiovascular outcomes reported. We aimed to synthesise the available evidence by doing a systematic review and meta-analysis of cardiovascular outcome trials of these drugs.

Methods We searched MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials for eligible placebo-controlled trials reporting major adverse cardiovascular events (MACE; ie, cardiovascular death, stroke, or myocardial infarction) up to June 15, 2019. We did a meta-analysis using a random-effects model to estimate overall hazard ratios (HRs) for MACE, its components, death from any cause, hospital admission for heart failure, kidney outcomes, and key safety outcomes (severe hypoglycaemia, pancreatitis, and pancreatic cancer). We also examined MACE in several subgroups based on patient characteristics (history of cardiovascular disease, BMI, age, baseline HbA1c, and baseline estimated glomerular filtration rate), trial duration, treatment dosing interval, and structural homology.

Findings Of 27 publications screened, seven trials, with a combined total of 56 004 participants, were included: ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), Harmony Outcomes (albiglutide), REWIND (dulaglutide), and PIONEER 6 (oral semaglutide). Overall, GLP-1 receptor agonist treatment reduced MACE by 12% (HR 0·88, 95% CI 0·82–0·94; p<0·0001). There was no statistically significant heterogeneity across the subgroups examined. HRs were 0·88 (95% CI 0·81–0·96; p=0·003) for death from cardiovascular causes, 0·84 (0·76–0·93; p<0·0001) for fatal or non-fatal stroke, and 0·91 (0·84–1·00; p=0·043) for fatal or non-fatal myocardial infarction. GLP-1 receptor agonist treatment reduced all-cause mortality by 12% (0·88, 0·83–0·95; p=0·001), hospital admission for heart failure by 9% (0·91, 0·83–0·99; p=0·028), and a broad composite kidney outcome (development of new-onset macroalbuminuria, decline in estimated glomerular filtration rate [or increase in creatinine], progression to end-stage kidney disease, or death attributable to kidney causes) by 17% (0·83, 0·78–0·89; p<0·0001), mainly due to a reduction in urinary albumin excretion. There was no increase in risk of severe hypoglycaemia, pancreatitis, or pancreatic cancer.

Interpretation Treatment with GLP-1 receptor agonists has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with type 2 diabetes.

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BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK (S L Kristensen MD, R Rørth MD, P S Jhund MD, Prof N Sattar FMedSci, Prof M C Petrie MD, Prof J J V McMurray MD); Department of Cardiology, Herlev-Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark (S L Kristensen, R Rørth, Prof L Køber MD); Medical Research Council Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK (D Preiss PhD)

Correspondence to:
Prof John JV McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, UK
john.mcmurray@glasgow.ac.uk

Introduction

Prevention of non-fatal and fatal cardiovascular events is a key goal of the management of patients with type 2 diabetes.[1,2] In addition to blood pressure-lowering and cholesterol-lowering therapies, two of the newer classes of antihyperglycaemic drugs—sodium-glucose co-

leads to modest improvements in lipids and reductions in blood pressure and bodyweight, with a low risk of hypoglycaemia. However, the drugs in this class differ in their structure and duration of action and have been studied in trials of varying sizes and with different

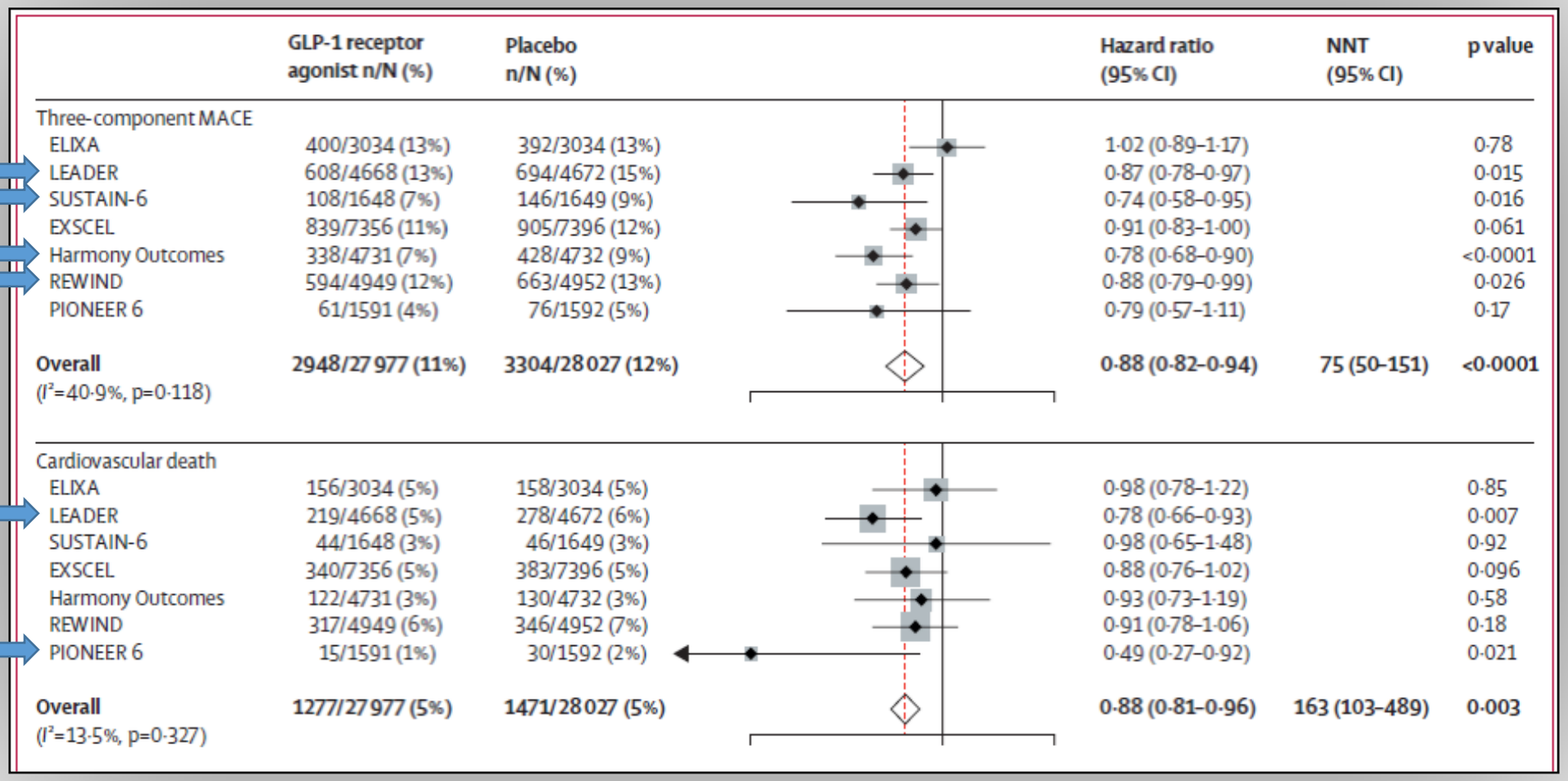
Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

- Revisión sistemática y metanálisis de ensayos controlados con placebo hasta el 15 de junio de 2019.
- Revisión 7 ensayos (56004 pacientes). ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), Harmony Outcomes (albiglutide), REWIND dulaglutide), y PIONEER 6 (semaglutide oral).
- Ensayos con end points primarios de seguridad cardiovascular (MACE: muerte, infarto, ictus); análisis de seguridad renal.
- End points de seguridad: hipoglucemia severa, retinopatía, pancreatitis y cáncer de páncreas.

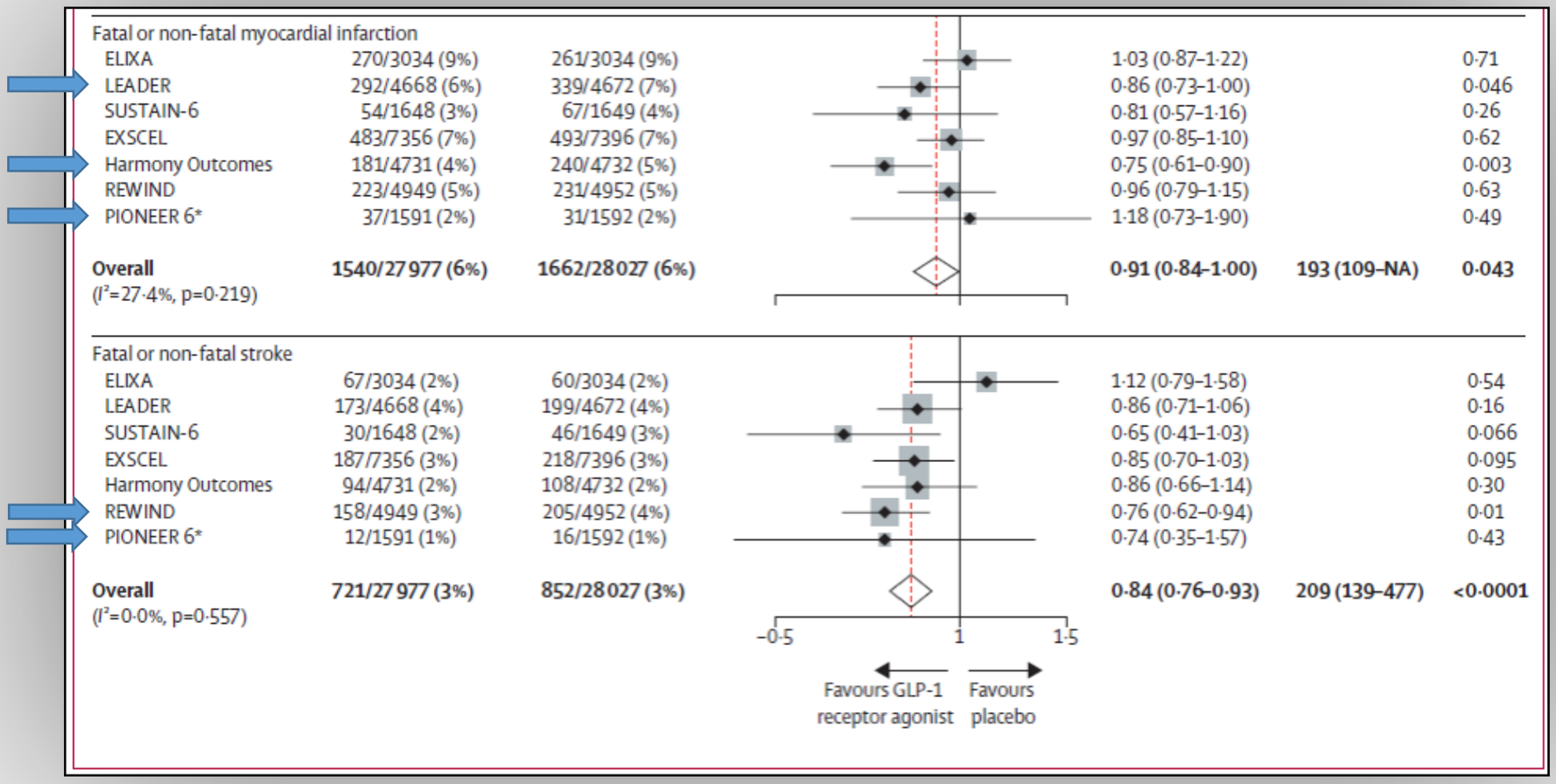
	ELIXA (n=6068)[7]	LEADER (n=9340)[8,14]	SUSTAIN-6 (n=3297)[9]	EXSCEL (n=14752)[11]	Harmony Outcomes (n=9463)[10]	REWIND (n=9901)[12,13]	PIONEER 6 (n=3183)[14]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide (oral)
Structural basis	Exendin-4	Human GLP-1	Human GLP-1	Exendin-4	Human GLP-1	Human GLP-1	Human GLP-1
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral
Dose	20 µg per day	1·8 mg per day	0·5 or 1 mg per week	2 mg per week	30 or 50 mg per week	1·5 mg per week	14 mg per day
Age (years)	60 (10)	64 (7)	65 (7)	62 (9)	64 (7)	66 (7)	66 (7)
Sex							
Men	4207 (69%)	6003 (64%)	2002 (61%)	9149 (62%)	6569 (69%)	5312 (54%)	2176 (68%)
Women	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)	2894 (31%)	4589 (46%)	1007 (32%)
Ethnic origin							
White	4576 (75%)	7238 (77%)	2736 (83%)	11175 (76%)	6583 (70%)	7498 (76%)	2300 (72%)
Other	1492 (25%)	2102 (23%)	561 (17%)	3577 (24%)	2880 (30%)	2403 (24%)	883 (28%)
BMI (kg/m^2)	30·1 (5·6)	32·5 (6·3)	32·8 (6·2)	32·7 (6·4)	32·3 (5·9)	32·3 (5·7)	32·3 (6·5)
Diabetes duration (years)	9·2 (8·2)	12·8 (8·0)	13·9 (8·1)	13·1 (8·3)	14·2 (8·8)	10·6 (7·2)	14·9 (8·5)
HbA_{1c} (%)	7·7 (1·3)	8·7 (1·6)	8·7 (1·5)	8·1 (1·0)	8·7 (1·5)	7·3 (1·1)	8·2 (1·6)
Established cardiovascular disease	6068 (100%)	7598 (81%)	2735 (83%)	10782 (73%)	9463 (100%)	3114 (31%)	2695 (85%)
History of heart failure	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	853 (9%)	388 (12%)
Systolic blood pressure (mm Hg)	129 (17)	136 (18)	136 (17)	135 (17)	135 (17)	137 (17)	136 (18)
eGFR (mL/min per 1·73 m^2)*	78 (21)	80 (NR)	80 (61–92)	77 (61–92)	79 (25)	75 (24)	74 (21)
Glucose-lowering drugs used							
Insulin	2374 (39%)	4169 (45%)	1913 (58%)	6838 (46%)	5597 (59%)	2363 (24%)	1930 (61%)
Biguanides	4021 (66%)	7144 (76%)	2414 (73%)	11295 (77%)	6969 (74%)	8037 (81%)	2463 (77%)
Sulfonylurea	2004 (33%)	4733 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	4552 (46%)	1027 (32%)
Thiazolidinedione	95 (2%)	575 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	118 (4%)
DPP-4 inhibitor	NA	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	88 (1%)	2 (<1%)
SGLT2 inhibitor	NA	NA	5 (<1%)	77 (1%)	575 (6%)	12 (<1%)	305 (10%)

Numerical data are mean (SD) or n (%), unless otherwise specified. GLP-1=glucagon-like peptide-1. eGFR=estimated glomerular filtration rate. NR=not reported. DPP-4=dipeptidyl peptidase-4. SGLT2=sodium-glucose co-transporter-2. *eGFR data are median (IQR) for SUSTAIN-6 and EXSCEL.

Table: **Baseline characteristics and use of glucose-lowering drugs across included trials**



- Reducción del 12% MACE (HR 0,88, 95% IC 0,82-0,94, p<0,0001). NNT 75 a los 3,2 años.
- Mayor duración de seguimiento en estudio LEADER vs ELIXA
- Reducción mortalidad cardiovascular (HR 0,88, 95% IC 0,81-0,96, p<0,0001).



- Reducción infarto fatal y no fatal (HR 0,91, 95% IC 0,84-1,00, p<0,043)
- Posible efecto antiarterioscerótico por el tiempo a la aparición de los efectos. ¿Sinergia con iSGLT2?
- Liraglutide y albiglutide, con tasas de reducción de insuficiencia cardíaca mayores.

- No heterogenicidad por el nivel basal de HbA1c
- No heterogenicidad por el intervalo de dosificación (diario vs semanal)
- No heterogenicidad por prevención primaria vs prevención secundaria
- Disminución de ingresos por insuficiencia cardíaca 9% (HR 0,91 IC95% 0,83-0,99; p=0,028; NNT 312). Posible relación con CI. Harmony (albiglutide) p<0,0001.
- Posible efecto de la homología al GLP1 humano (albiglutide, dulaglutide, liraglutide y semaglutide vs exenatide y lixisenatide) p=0,06.
- Mejoría de los resultados a nivel renal (macroalbuminria + empeoramiento de función renal) en un 17% (HR 0,83 IC95% 0,78-0,89, NNT 62) por reducción de albuminuria.
- No aumento de efectos secundarios (hipoglucemias graves, pancreatitis, cáncer de páncreas o tiroides)

Annals of Internal Medicine®

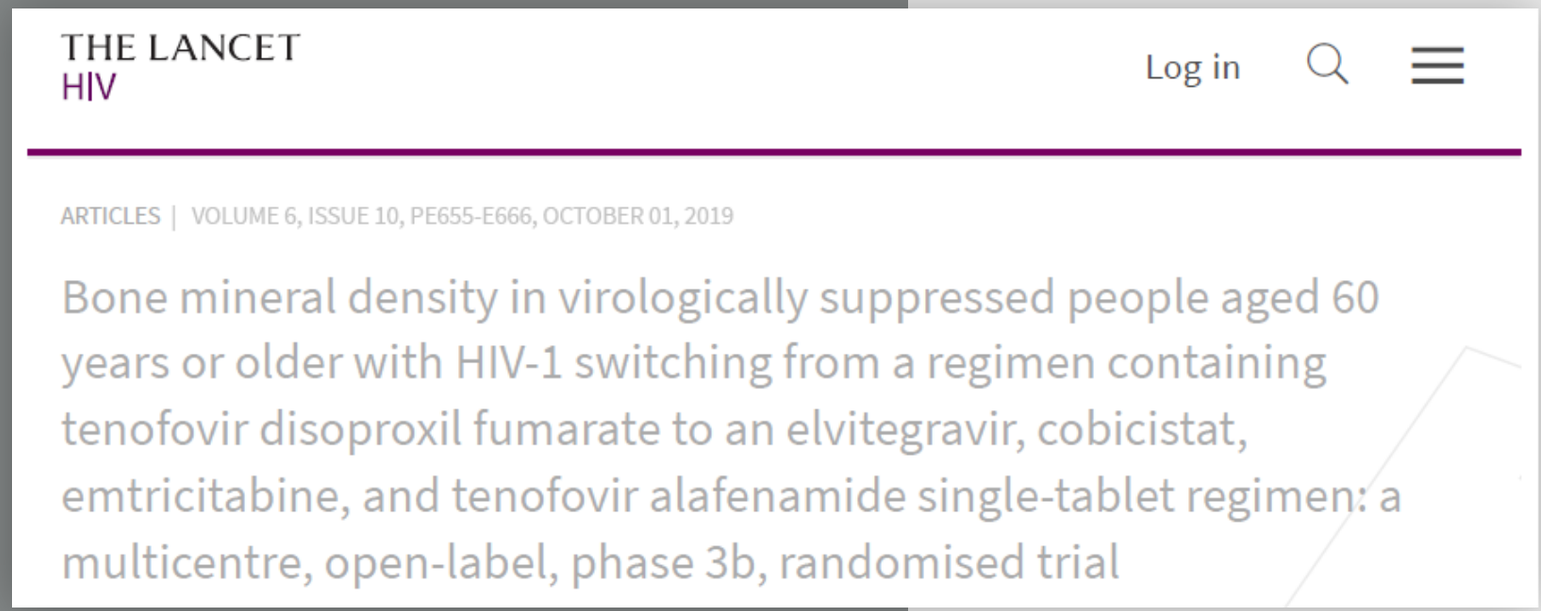
MENU

ORIGINAL RESEARCH | 15 OCTOBER 2019

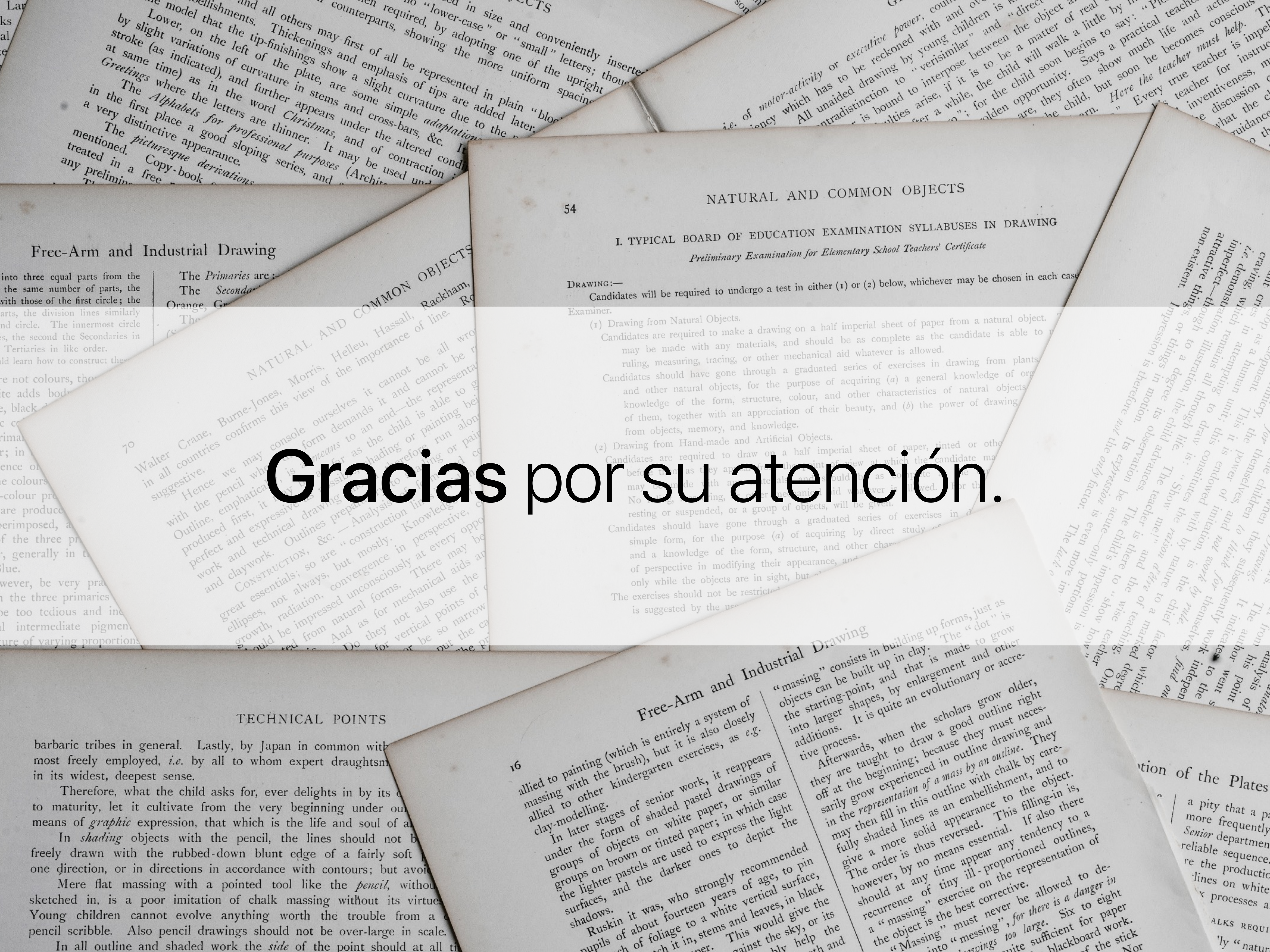
Blood Culture Results Before and After Antimicrobial Administration in Patients With Severe Manifestations of Sepsis: A Diagnostic Study

*Matthew P. Cheng, MD; Robert Stenstrom, MD, PhD; Katryn Paquette, MD; Sarah N. Stabler, PharmD; Murtaza Akhter, MD; Adam C. Davidson, MD; Marko Gavric, BSc; Alexander Lawandi, MD; Rehman Jinah, BSc; Zahid Saeed, MD; Koray Demir, MD; Kelly Huang, BSc; Amirali Mahpour, MD; Chris Shamatutu, BSc; Chelsea Caya, MSc; Jean-Marc Troquet, MD; Greg Clark, MD; Cedric P. Yansouni, MD; David Sweet, MD; for the FABLED Investigators **

- 325 pacientes con criterios de sepsis a los que se les extrajo hemocultivos antes y 120min después del inicio del tratamiento antibiótico.
- Positividad de hemocultivos pre-antibiótico 31,4% vs 19,4% hemocultivos post-antibiótico. IC95% 5,4%-18,6%; p<0,001.
- Sensibilidad del cultivo post-antibiótico 52,9% (IC95% 42,8%-62,9%)
- El inicio de la terapia antibiótica empírica previo a la extracción de hemocultivos reduce su sensibilidad.



- Estudio prospectivo, multicéntrico, randomizado, abierto con el objetivo de determinar el efecto del cambio de regímenes basados en tenofovir difumarato (TDF) a regímenes basados en tenofovir alafenamida (TAF) en pacientes VIH sobre la densidad mineral ósea.
- 167 randomizados 1:2 a mantener tratamiento con TDF vs cambio a regimen basado en TAF (Genvoya®). Determinación de DMO a las 48 semanas.
- **Resultados**:
  - **DMO columna**: +2,24% (ds3,27) TAF vs -0,10% (ds3,39) TDF; (2,43% [IC95% 1,34-3,52]; p<0,0001)
  - **DMO cadera**: +1,33% (ds2,20) TAF vs -0,73% (ds3,21) TDF; (2,04% [1,17-2,90]; p<0,0001)



Gracias por su atención.