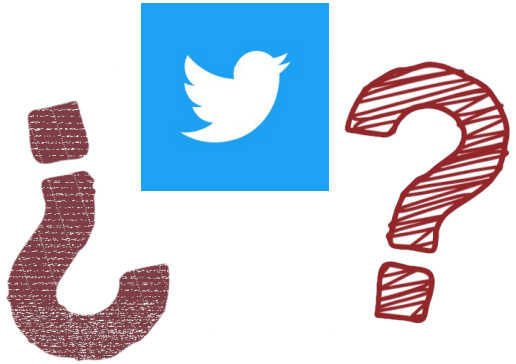
10 de Septiembre, 2019

¿Qué nos hemos perdido en verano?

Sesión Bibliográfica



Andrea Catalán Redón
R1 Medicina Interna

Fernando Alonso Ecenarro
R3 Medicina Interna

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1. Insuficiencia cardíaca y Fibrilación auricular
2. Diabetes mellitus / Factores de riesgo cardiovascular
3. Patología neurológica
4. Patología infecciosa
5. Y además…
6. Conclusiones

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2019	Dyslipidaemias
2019	Acute Pulmonary Embolism
2019	Supraventricular Tachycardia
2019	Chronic Coronary Syndromes

View more

1. Insuficiencia cardíaca

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees

- **MyM:** Ensayo clínico, aleatorizado, doble ciego. FEVI ≥ 45%, BNP elevado y daño estructural. 4822 pacientes. Novartis.
  - 97/103 mg sacubitril-valsartán x2 veces al día.
  - 160 mg de valsartán x 2 veces al día.
  - PO: hospitalizaciones por IC y muertes de causa cardíaca.
- **R:**
  - **894** eventos en 526 pacientes. Sac-vals.
  - **1009** eventos en 557 pacientes. Vals.
  - **RR 0,87 IC 95% (0.75-1.01) p=0.06.**
  - **Incidencia de muerte cardiovascular 8,5% en SV y 8,9% V. (HR 0,95; IC 0,79-1.16).**
  - **Hospitalizaciones por insuficiencia cardíaca 690 en SV y 797 V. (RR 0.85; IC 0.72-1.00).**
- **C:** Sacubitril – valsartán no disminuye el número total de hospitalizaciones por insuficiencia cardíaca ni las muertes de causa cardiovascular entre los pacientes con insuficiencia cardíaca con FEVI ≥ 45%.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

Table 2. Primary and Secondary Outcomes.*

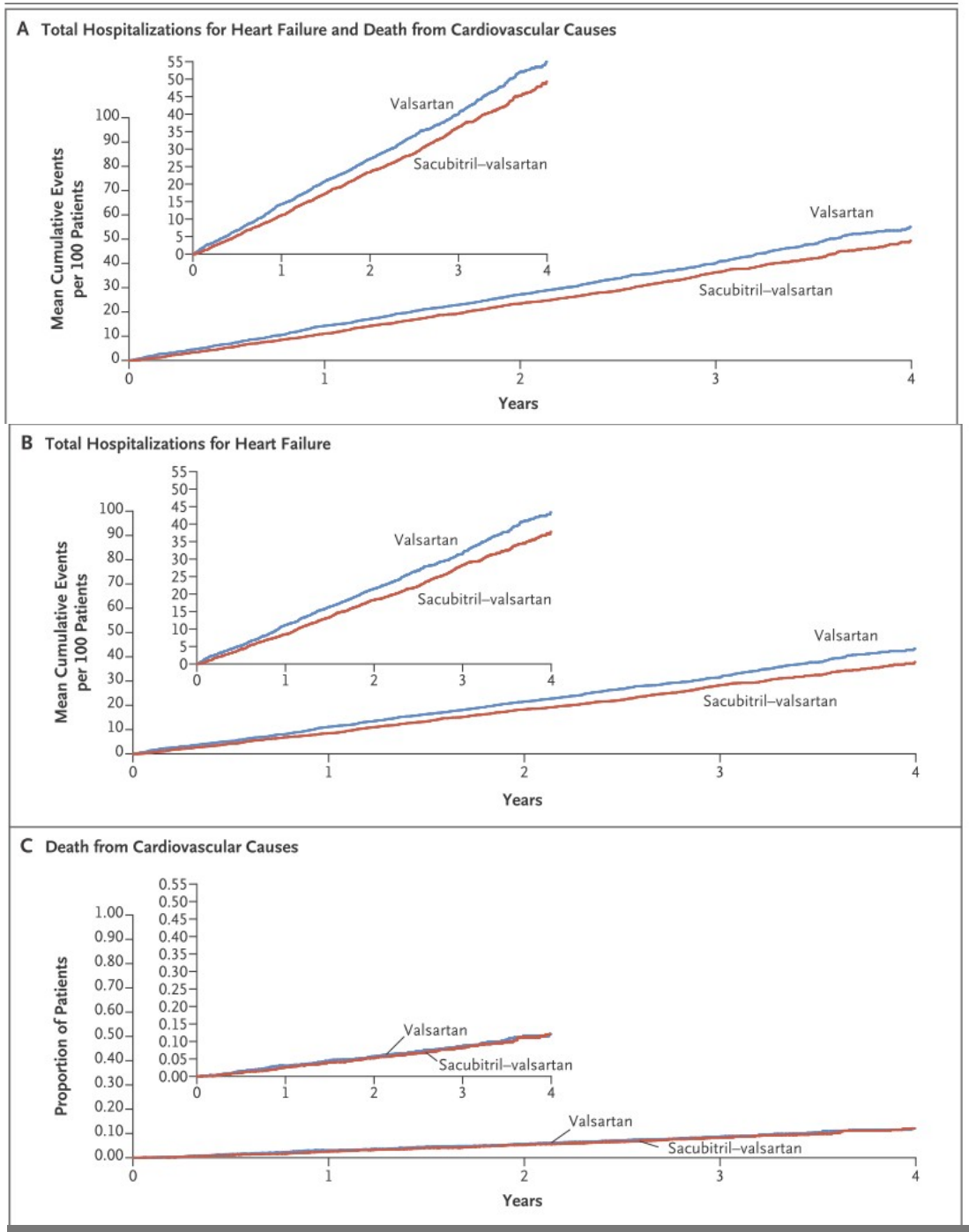
Outcome	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)
Secondary outcomes			
Change in NYHA class from baseline to 8 mo — no./total no. (%)			OR, 1.45 (1.13–1.86)
Improved	347/2316 (15.0)	289/2302 (12.6)	
Unchanged	1767/2316 (76.3)	1792/2302 (77.8)	
Worsened	202/2316 (8.7)	221/2302 (9.6)	
Change in KCCQ clinical summary score at 8 mo‡	−1.6±0.4	−2.6±0.4	Difference, 1.0 (0.0–2.1)
Renal composite outcome — no. (%)§	33 (1.4)	64 (2.7)	HR, 0.50 (0.33–0.77)
Death from any cause — no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84–1.13)

* Plus–minus values are means ±SD. Confidence intervals for secondary and exploratory efficacy outcomes have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. HR denotes hazard ratio, OR odds ratio, and RR rate ratio.

† Total hospitalizations for heart failure included first and recurrent events. The primary analysis was based on the model of Lin et al.,[13] and the composite outcome was adjudicated.

‡ Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations.

§ The renal composite outcome was defined as death from renal failure, end-stage renal disease, or a decrease in the estimated glomerular filtration rate of 50% or more from baseline.



ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–21
doi:10.1093/eurheartj/ehz641

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

Why new diagnostic recommendations for heart failure with preserved ejection fraction?

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–21
doi:10.1093/eurheartj/ehz641

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI ≥ 149/122 g/m² (m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (m/w) or RWT > 0,42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

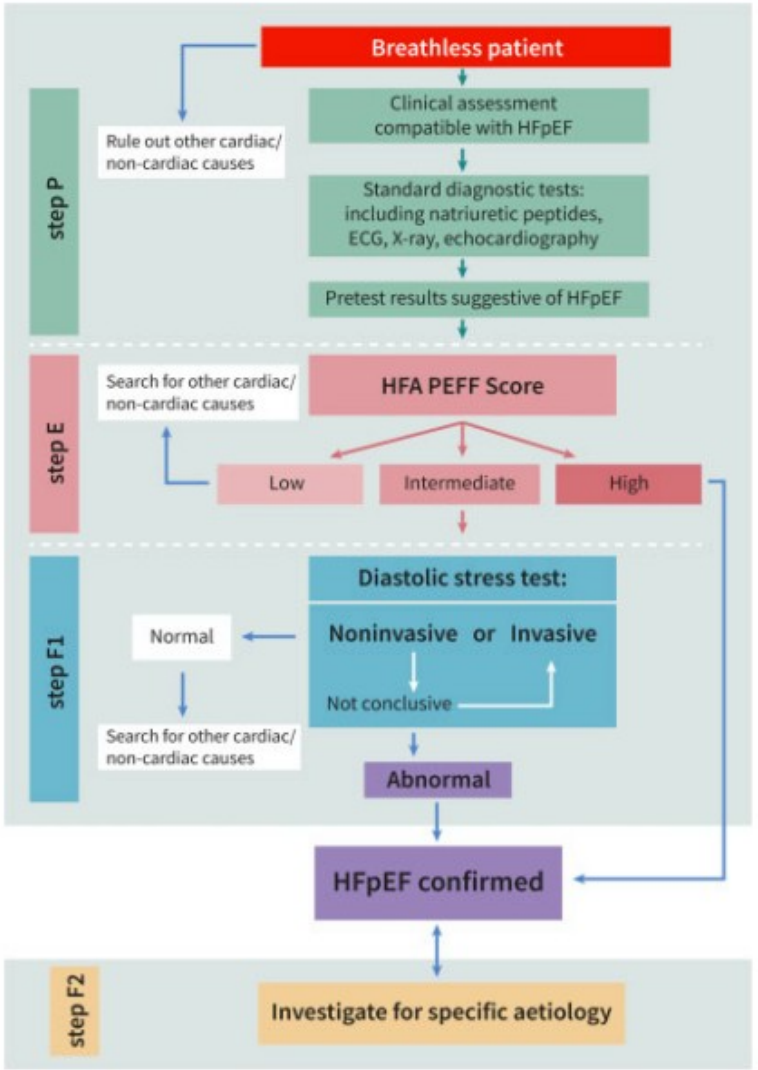


Figure 2 Flowchart of the HFA-PEFF diagnostic algorithm. Step P

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 74, NO. 5, 2019

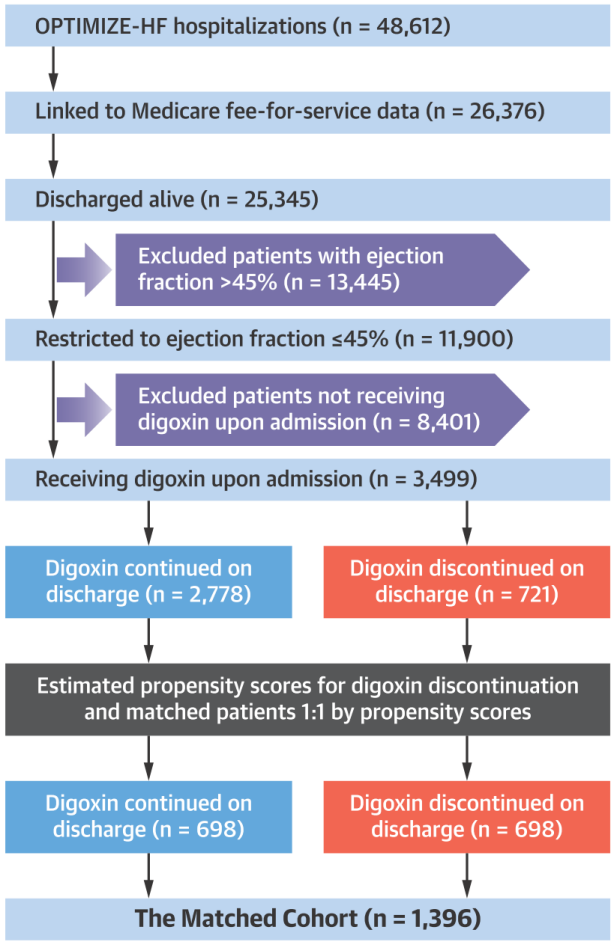
Digoxin Discontinuation and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction

Awais Malik, MD,[a,b] Ravi Masson, MD,[a,b] Steven Singh, MD,[a,b] Wen-Chih Wu, MD,[c,d] Milton Packer, MD,[e] Bertram Pitt, MD,[f] Finn Waagstein, MD, PHD,[g] Charity J. Morgan, PHD,[a,h] Richard M. Allman, MD,[h,i] Gregg C. Fonarow, MD,[j] Ali Ahmed, MD, MPH[a,b,i]

- **O:** Evaluar los efectos de la retirada de digoxina en los pacientes tras el ingreso a pesar de tratamiento correcto según guías clínicas.
- **MyM:** Estudio observacional. OPTIMIZE HF. 2003-2004. FEVI ≤ 45%. 11.900. 698 pacientes en cada brazo.
- **R:** 4 años tras el alta la retirada de digoxina se asocia con un mayor riesgo de reingreso por insuficiencia cardíaca (1.05-1.39) p=0,007.

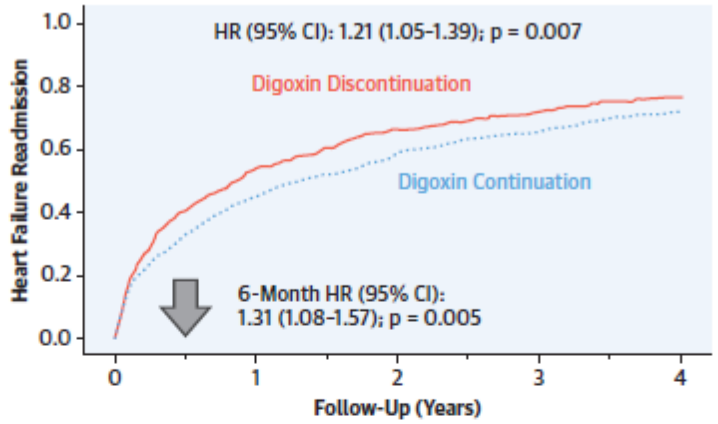
C: Entre los pacientes mayores de 80 años con FEVI ≤ 45% y que reciben tratamiento actualizado según guías clínicas, la retirada de digoxina al alta se asocia con peores resultados.

FIGURE 1 Assembly of the Study Cohort

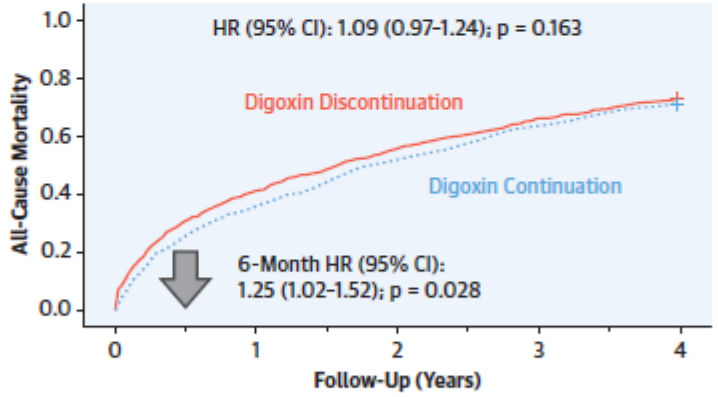


Flow chart displaying assembly of a matched cohort of patients with heart failure with reduced ejection fraction, by discontinuation of digoxin therapy. OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure registry.

CENTRAL ILLUSTRATION Kaplan-Meier Plots for Outcomes by Digoxin Discontinuation



Number at risk					
Digoxin Discontinuation	698	223	134	94	74
Digoxin Continuation	698	283	180	129	91



Number at risk					
Digoxin Discontinuation	698	411	308	236	188
Digoxin Continuation	698	447	336	254	200

Malik, A. et al. J Am Coll Cardiol. 2019;74(5):617-27.

This study assessed the relationship of discontinuation of pre-admission digoxin therapy with heart failure readmission **(top)** and all-cause mortality **(bottom)** in 698 pairs of propensity score-matched patients with heart failure with reduced ejection fraction. During 4 years of follow-up, digoxin discontinuation was associated with a significantly higher risk of heart failure readmission but not of all-cause mortality, compared with patients whose digoxin therapy was continued. During the first 6 months of follow-up, digoxin discontinuation was associated with a significantly higher risk of both outcomes. CI = confidence interval; HR = hazard ratio.

FIGURE 2 Forest Plots for Subgroup Analyses of Combined Outcome by Digoxin Discontinuation

	Total Patients (N = 1,396)	Digoxin Discontinuation No (n = 698)	Yes (n = 698)	Hazard Ratio (95% CI)	P value Effect	Interaction
Age						
<80 years (n = 878)	366/435 (84)	384/443 (87)		1.15 (0.99 - 1.32)	0.063	0.276
≥80 years (n = 518)	241/263 (92)	240/255 (94)		1.31 (1.10 - 1.57)	0.003	
Sex						
Male (n = 830)	361/411 (88)	374/419 (89)		1.19 (1.03 - 1.38)	0.018	0.940
Female (n = 566)	246/287 (86)	250/279 (90)		1.20 (1.01 - 1.43)	0.043	
Race						
Non-African American (n = 1,209)	536/614 (87)	529/595 (89)		1.18 (1.05 - 1.33)	0.007	0.612
African American (n = 187)	71/84 (85)	95/103 (92)		1.28 (0.94 - 1.74)	0.120	
Systolic Blood Pressure						
<120 mm Hg (n = 495)	229/255 (90)	224/240 (93)		1.27 (1.05 - 1.52)	0.012	0.466
≥120 mm Hg (n = 901)	378/443 (85)	400/458 (87)		1.18 (1.03 - 1.36)	0.020	
Heart Rate						
<70 beats/min (n = 439)	185/219 (84)	191/220 (87)		1.17 (0.95 - 1.43)	0.139	0.695
≥70 beats/min (n = 957)	422/479 (88)	433/478 (91)		1.21 (1.06 - 1.39)	0.005	
Coronary Artery Disease						
No (n = 518)	222/258 (86)	229/260 (88)		1.16 (0.96 - 1.39)	0.118	0.728
Yes (n = 878)	385/440 (88)	395/438 (90)		1.22 (1.06 - 1.40)	0.007	
Diabetes Mellitus						
No (n = 802)	339/396 (86)	355/406 (87)		1.17 (1.01 - 1.36)	0.042	0.679
Yes (n = 594)	268/302 (89)	269/292 (92)		1.24 (1.05 - 1.47)	0.012	
Atrial Fibrillation						
No (n = 769)	331/385 (86)	340/384 (89)		1.25 (1.08 - 1.46)	0.004	0.359
Yes (n = 627)	276/313 (88)	284/314 (90)		1.12 (0.95 - 1.33)	0.169	
Glomerular Filtration Rate						
≥45 ml/min/1.73 m^2 (n = 744)	316/383 (83)	307/361 (85)		1.16 (0.99 - 1.36)	0.065	0.626
<45 ml/min/1.73 m^2 (n = 652)	291/315 (92)	317/337 (94)		1.22 (1.04 - 1.43)	0.016	
Ejection Fraction						
≥25% (n = 922)	403/470 (86)	401/452 (89)		1.21 (1.05 - 1.39)	0.007	0.768
<25% (n = 474)	204/228 (89)	223/246 (91)		1.16 (0.96 - 1.40)	0.138	
ACE Inhibitor/ARB on Discharge						
Yes (n = 878)	379/449 (84)	381/429 (89)		1.23 (1.07 - 1.42)	0.005	0.539
No (n = 518)	228/249 (92)	243/269 (90)		1.13 (0.94 - 1.35)	0.184	
Beta-Blocker on Discharge						
Yes (n = 901)	397/457 (87)	393/444 (89)		1.11 (0.96 - 1.27)	0.161	0.044
No (n = 495)	210/241 (87)	231/254 (91)		1.38 (1.14 - 1.66)	0.001	
Overall (N = 1,396)	607/698 (87)	624/698 (89)		1.20 (1.07 - 1.34)	0.002	

In all subgroups analyzed, the association between digoxin discontinuation and the combined endpoint of heart failure readmission or all-cause mortality was homogeneous, except by beta-blocker use at hospital discharge. Note: Results of subgroup analyses need to be interpreted with caution because they may be false positive due to multiple comparisons and false negative due to inadequate power. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CI = confidence interval.

Kidney & Blood Pressure Research

Kidney Blood Press Res
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Review Article

Diuretic Resistance in Cardio-Nephrology: Role of Pharmacokinetics, Hypochloremia, and Kidney Remodeling

Cristina Masella[a] Davide Viggiano[b, c] Ida Molfino[a] Miriam Zacchia[a] Giovanna Capolongo[a] Pietro Anastasio[a] Mariadelina Simeoni[d]

[a]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [b]BIOGEM Research Institute, Ariano Irpino, Italy; [c]Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy; [d]Department of Medical and Surgery Sciences, "Magna Graecia" University, Catanzaro, Italy

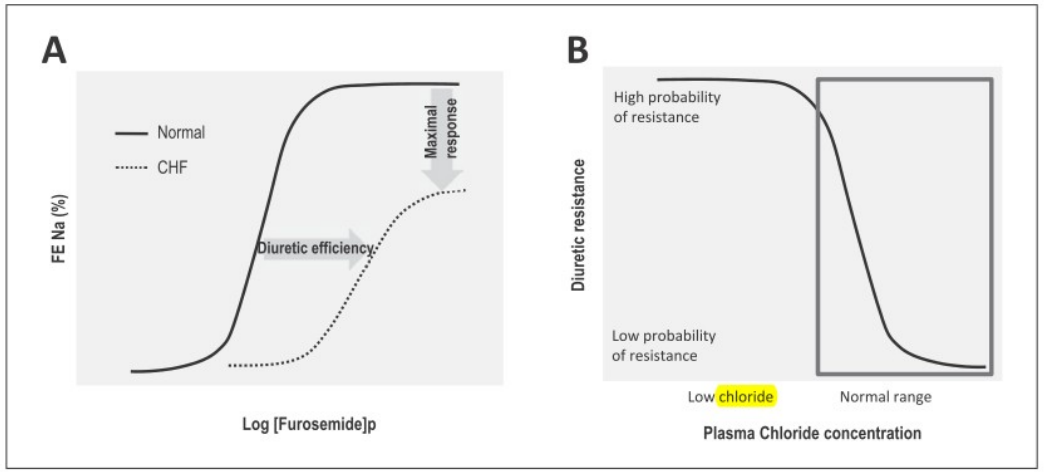


Fig. 1. A Changes of urinary sodium excretion fraction in response to furosemide administration. A shift of the dose-response curve is evident in CHF patients. **B** Relationship between serum chloride and the probability of developing diuretic resistance (redrawn from Hanberg et al. [22]).

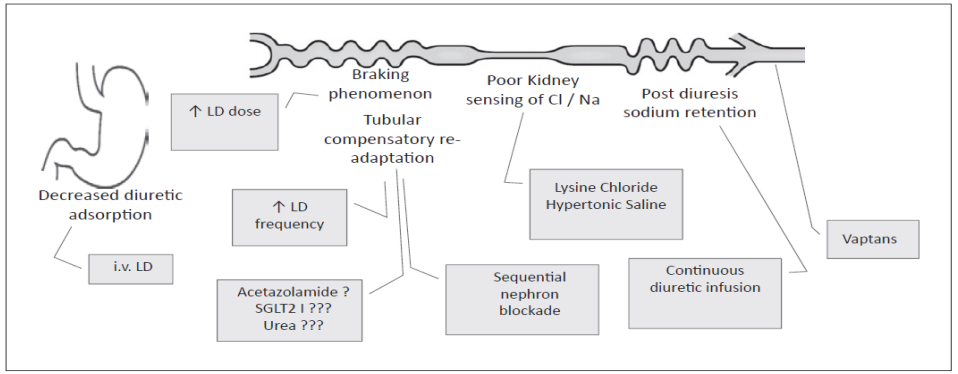


Fig. 3. Pathways involved in diuretic resistance and the therapeutic options (gray boxes) aimed at overcoming these mechanisms. LD, loop diuretics.

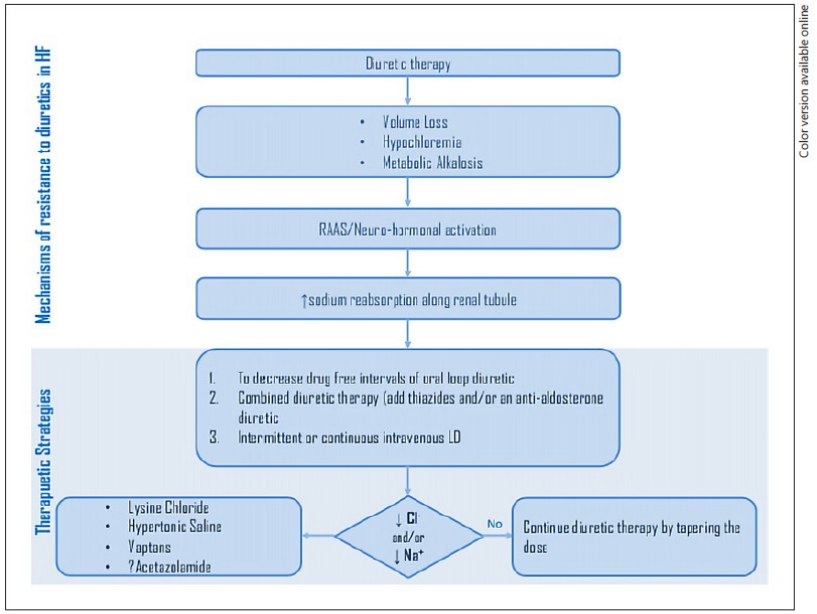


Fig. 4. Therapeutic algorithm to treat diuretic resistance.

2. Diabetes mellitus / Factores de riesgo cardiovascular

ESC European Society of Cardiology
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1432

STUDY DESIGN

Check for updates

A trial to evaluate the effect of the sodium–glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF)

John J.V. McMurray[1*], David L. DeMets[2], Silvio E. Inzucchi[3], Lars Køber[4], Mikhail N. Kosiborod[5], Anna M. Langkilde[6], Felipe A. Martinez[7], Olof Bengtsson[6], Piotr Ponikowski[8], Marc S. Sabatine[9], Mikaela Sjöstrand[6], Scott D. Solomon[10], on behalf of the DAPA-HF Committees and Investigators

Dapagliflozin reduces death and hospitalisation in patients with heart failure

DAPA-HF trial presented in a Hot Line Session today at ESC Congress 2019 together with WCC

01 Sep 2019

2. Diabetes mellitus / Factores de riesgo cardiovascular

Dapagliflozin reduces death and hospitalisation in patients with heart failure

DAPA-HF trial presented in a Hot Line Session today at ESC Congress 2019 together with WCC

01 Sep 2019

- **MyM:** Ensayo clínico, aleatorizado, doble ciego. 4.744 pacientes con IC FEVI deprimida. 20 países. Objetivo primario hospitalización por insuficiencia cardíaca/visita que requiera terapia iv o muerte de causa cardiovascular.
  - Dapaglifozina 10 mg 1 vez al día.
  - Placebo.
- **R:** Mediana de seguimiento de 18.2 meses el primary outcome ocurre en 386/2372 pacientes (16,3%) en el grupo de dapaglifozina y 502/2371 pacientes (21,2%) en el grupo de placebo. HR 0.74 IC 95% (0,65-0,85) p<0.00001.

> He concluded: "The trial shows that dapagliflozin reduces death and hospitalisation, and improves health-related quality of life, in patients with heart failure and reduced ejection fraction, with and without diabetes. The clinical implications are potentially huge - few drugs achieve these results in heart failure and dapagliflozin does even when added to excellent standard therapy."

2. Diabetes mellitus / Factores de riesgo cardiovascular

The NEW ENGLAND JOURNAL of MEDICINE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., et al., fc the PIONEER 6 Investigators*

- **MyM:** ensayo aleatorizado, doble ciego,. Variable: tiempo hasta aparición ECV importante.
- **R:** 3183 pacientes. Semaglutida: 3.8% ECV. Placebo 4.8% ECV. Semaglutida EA: gastrointestinales
- **C:** el perfil de riesgo CV dela semaglutida oral **no fue inferior** al del placebo.

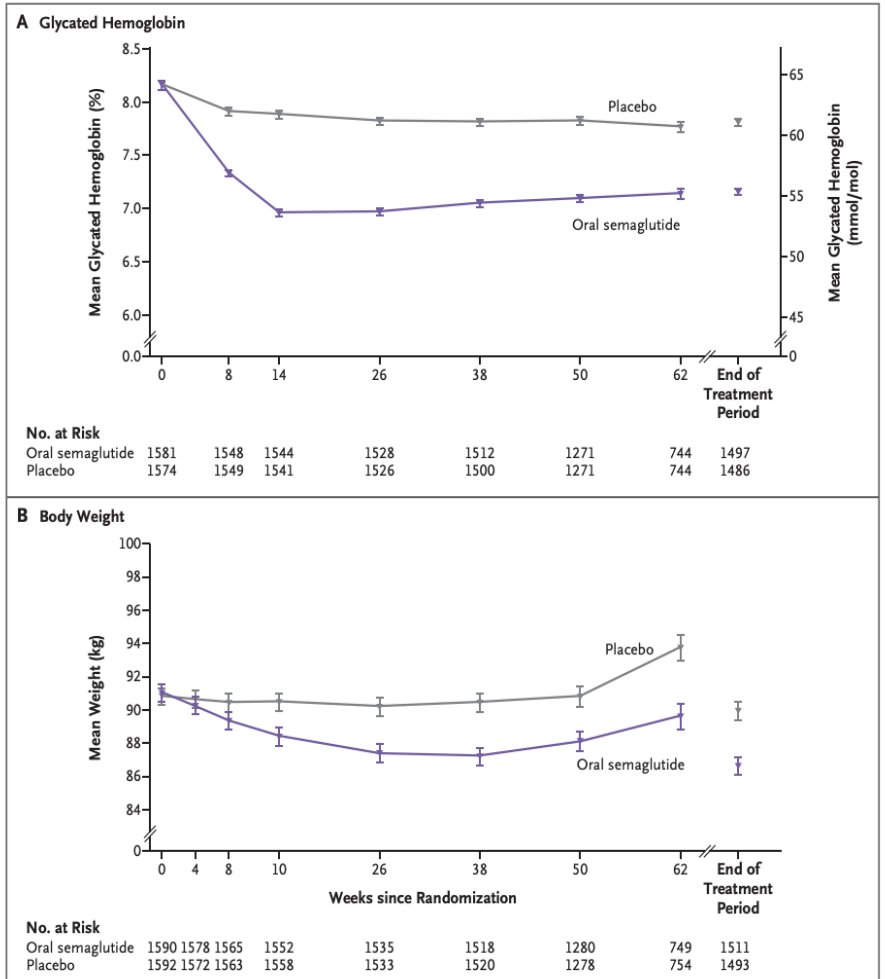


Figure 2. Efficacy Outcomes (In-Trial Observation Period).
The curves show the observed change from baseline in the glycated hemoglobin level (Panel A) and body weight (Panel B). Data are for the full analysis set during the in-trial observation period, which was from randomization to the last visit (end of treatment). The end of treatment occurred when the required number of first major adverse cardiovascular events was exceeded. The individual patients' in-trial observation period ranged from 2 to 87 weeks, with a median duration of 69 weeks. I bars indicate standard errors.

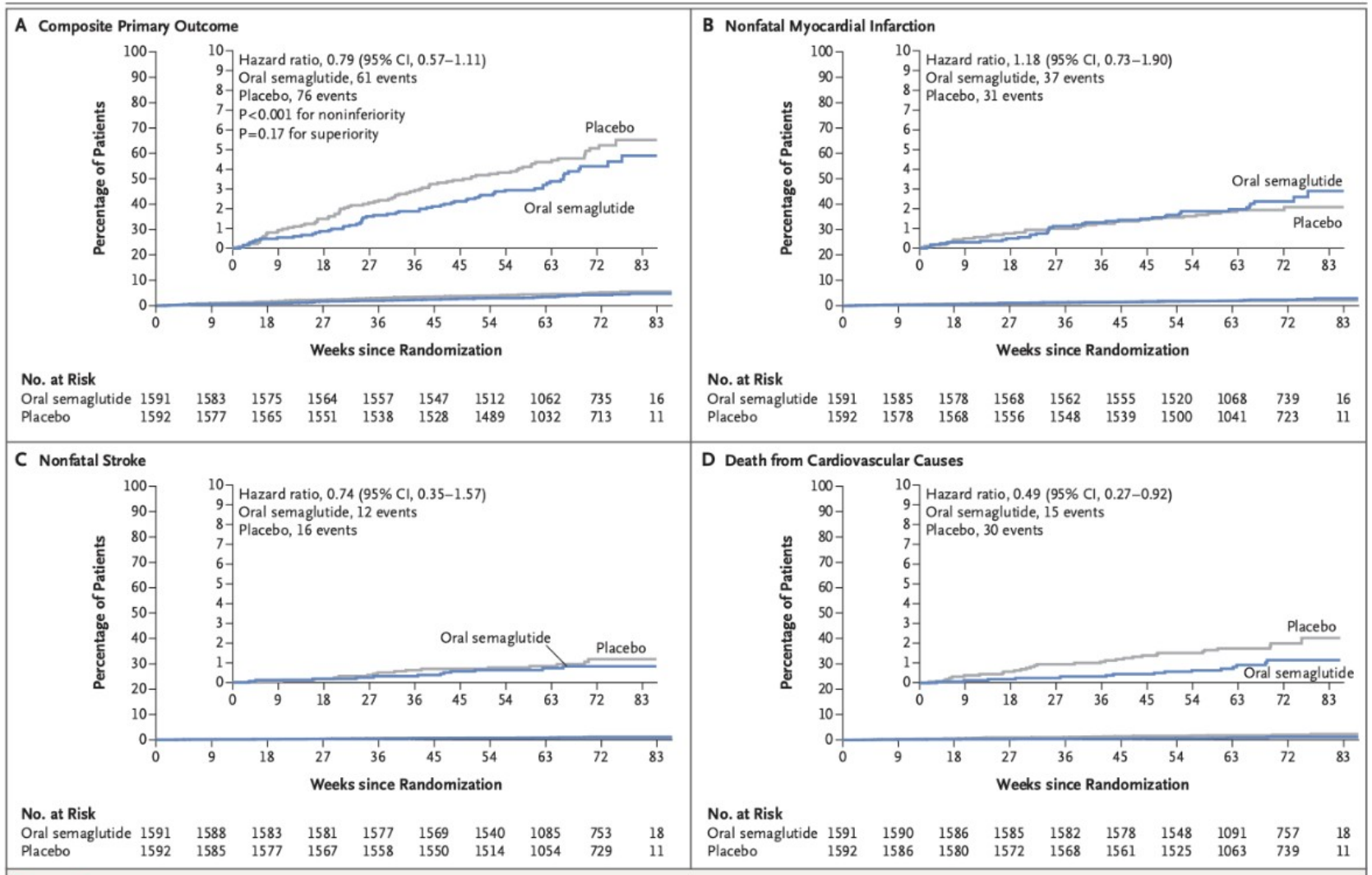


Figure 1. Cardiovascular Outcomes.

Shown are cumulative-incidence plots for the primary outcome (first major adverse cardiovascular events, representing a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). Cumulative-incidence estimates are based on time from randomization to first event confirmed by the event-adjudication committee, with death from noncardiovascular causes (Panels A and D) or death from any cause modeled as competing risks. Data for patients were censored at the end of the in-trial observation period (from randomization to the final follow-up visit). Deaths from cardiovascular causes included deaths for which the cause was undetermined. The analysis for confirmation of noninferiority was controlled for multiple comparisons; P values and confidence intervals for other analyses have not been adjusted for multiple comparisons. The insets show the same data on an expanded y axis. CI denotes confidence interval.

2. Diabetes mellitus / Factores de riesgo cardiovascular

Vitamin D Supplementation and Prevention of Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

Anastassios G. Pittas, M.D., Bess Dawson-Hughes, M.D., Patricia Sheehan, R.N., M.P.H., M.S., James H. Ware, Ph.D., et al., for the D2d Research Group*

- **MyM:** ensayo clínico aleatorizado, doble ciego, controlado con placebo
- **R:** 2423 pacientes prediabéticos. La razón de riesgo para la vitamina D en comparación con el placebo fue de 0,88 (intervalo de confianza del 95%, 0,75 a 1,04; P = 0,12).
- **C:** la suplementación con vit D no disminuye la incidencia de desarrollar diabetes tipo 2 en pacientes de alto riesgo.

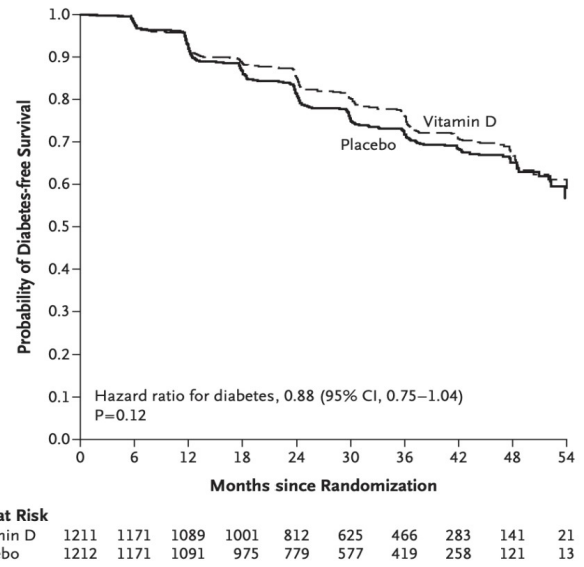
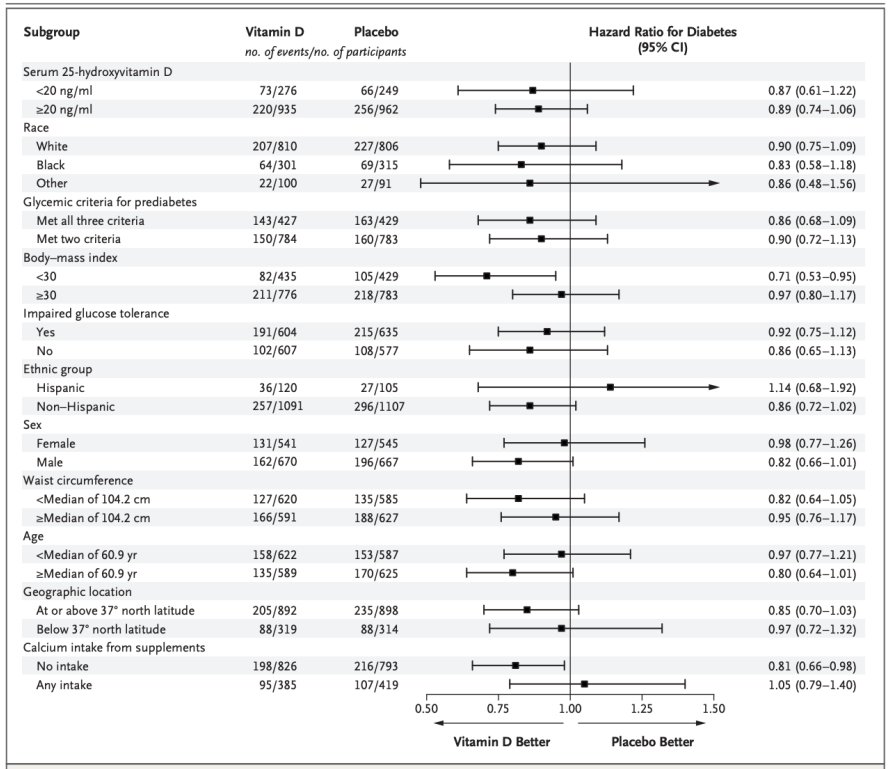


Figure 2. Kaplan–Meier Curves for Survival Free from Diabetes among Adults at Risk for Type 2 Diabetes.
The hazard ratio for new-onset diabetes between the vitamin D group and the placebo group is derived from Cox regression, with stratification according to trial site, body-mass index, and race.



Subgroup	Vitamin D (no. of events/no. of participants)	Placebo (no. of events/no. of participants)	Hazard Ratio for Diabetes (95% CI)
Serum 25-hydroxyvitamin D			
<20 ng/ml	73/276	66/249	0.87 (0.61–1.22)
≥20 ng/ml	220/935	256/962	0.89 (0.74–1.06)
Race			
White	207/810	227/806	0.90 (0.75–1.09)
Black	64/301	69/315	0.83 (0.58–1.18)
Other	22/100	27/91	0.86 (0.48–1.56)
Glycemic criteria for prediabetes			
Met all three criteria	143/427	163/429	0.86 (0.68–1.09)
Met two criteria	150/784	160/783	0.90 (0.72–1.13)
Body–mass index			
<30	82/435	105/429	0.71 (0.53–0.95)
≥30	211/776	218/783	0.97 (0.80–1.17)
Impaired glucose tolerance			
Yes	191/604	215/635	0.92 (0.75–1.12)
No	102/607	108/577	0.86 (0.65–1.13)
Ethnic group			
Hispanic	36/120	27/105	1.14 (0.68–1.92)
Non–Hispanic	257/1091	296/1107	0.86 (0.72–1.02)
Sex			
Female	131/541	127/545	0.98 (0.77–1.26)
Male	162/670	196/667	0.82 (0.66–1.01)
Waist circumference			
<Median of 104.2 cm	127/620	135/585	0.82 (0.64–1.05)
≥Median of 104.2 cm	166/591	188/627	0.95 (0.76–1.17)
Age			
<Median of 60.9 yr	158/622	153/587	0.97 (0.77–1.21)
≥Median of 60.9 yr	135/589	170/625	0.80 (0.64–1.01)
Geographic location			
At or above 37° north latitude	205/892	235/898	0.85 (0.70–1.03)
Below 37° north latitude	88/319	88/314	0.97 (0.72–1.32)
Calcium intake from supplements			
No intake	198/826	216/793	0.81 (0.66–0.98)
Any intake	95/385	107/419	1.05 (0.79–1.40)

Figure 3. Prespecified Subgroup Analyses.
Participants met at least two of three glycemic criteria for prediabetes: fasting plasma glucose level, 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter); plasma glucose level 2 hours after a 75-g oral glucose load, 140 to 199 mg per deciliter (7.8 to 11.0 mmol per liter) (impaired glucose tolerance); and glycated hemoglobin level, 5.7 to 6.4% (39 to 47 mmol per mole). To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.

3. Enfermedades neurológicas

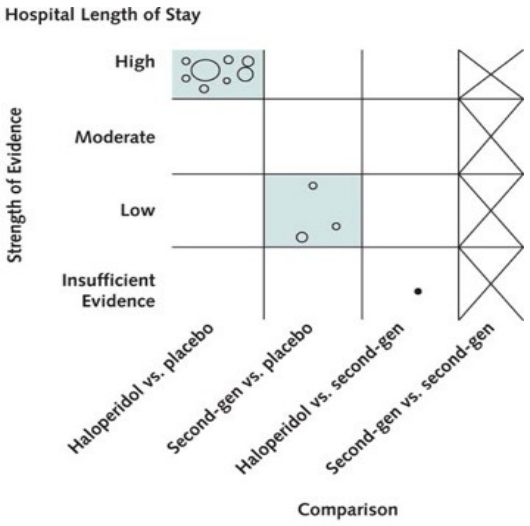
Annals of Internal Medicine®

Antipsychotics for Preventing Delirium in Hospitalized Adults: A Systematic Review FREE

Esther S. Oh, MD, PhD; Dale M. Needham, MD, PhD; Roozbeh Nikooie, MD; Lisa M. Wilson, ScM; Allen Zhang, BS; Karen A. Robi
*Karin J. Neufeld, MD, MPH **

Comparison	Studies, n (N)
Delirium incidence	
Haloperidol vs. placebo*	9 (3412)
Second-generation vs. placebo†‡	3 (627)
Mortality	
Haloperidol vs. placebo†	8 (3023)

Comparison	Studies, n (N)	Study Po
Cardiac effects		
Haloperidol vs. placebo	6 (2653)	At risk for
Haloperidol vs. placebo	7 (2721)	At risk for
Neurologic effects		
Haloperidol vs. placebo	8 (3276)	At risk for
Haloperidol vs. placebo	4 (2069)	Critically i
Sedation		
Haloperidol vs. placebo	4 (881)	At risk for



- **MyM:** metaanálisis de 14 ECA.
- **R:** 14 ECA con 4281 pacientes. 10 variables.
- C: la evidencia actual no respalda el uso rutinario de haloperidol o antipsicóticos de 2ª generación para la prevención. Evidencia limitada sobre la disminución de la incidencia por los antipsicóticos de segunda generación.

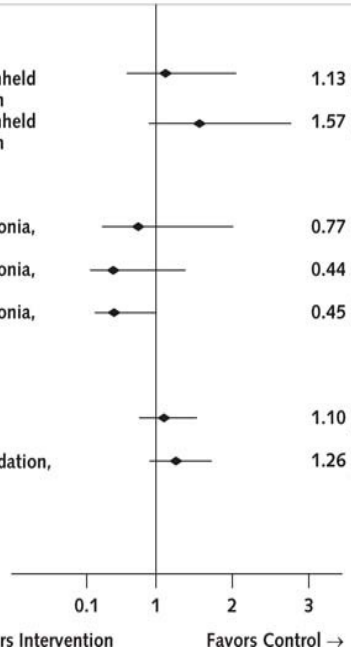
3. Enfermedades neurológicas

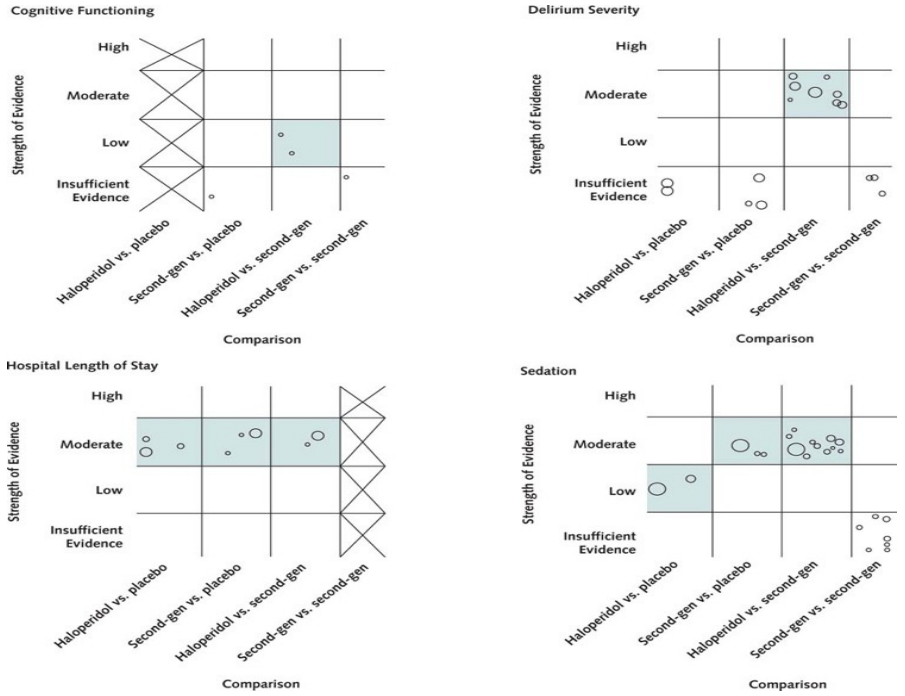
Annals of Internal Medicine®

Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review FREE

*Roozbeh Nikooie, MD; Karin J. Neufeld, MD, MPH; Esther S. Oh, MD, PhD; Lisa M. Wilson, ScM; Allen Zhang, BS; Karen A. Robinson, PhD *; Dale M. Needham, MD, PhD **

Comparison	Studies, *n* (*N*)	Study Population	Outcome	Pooled Meta-analysis*	Pooled RR (95% CI)†
Cardiac effects					
Haloperidol vs. placebo	3 (808)	Critically ill patients	QTc prolonged >500 ms or withheld drug owing to QTc prolongation		1.13 (0.62–2.05)
Second-generation‡ vs. placebo	3 (703)	Critically ill patients	QTc prolonged >500 ms or withheld drug owing to QTc prolongation		1.57 (0.90–2.76)
Neurologic effects					
Haloperidol vs. placebo	3 (808)	Critically ill patients	Extrapyramidal symptoms, dystonia, akathisia		0.77 (0.29–2.01)
Second-generation‡ vs. placebo	3 (709)	Inpatients with or without critical illness	Extrapyramidal symptoms, dystonia, akathisia		0.44 (0.14–1.39)
Second-generation§ vs. haloperidol	6 (869)	Inpatients with or without critical illness	Extrapyramidal symptoms, dystonia, akathisia		0.45 (0.20–1.01)
Sedation					
Haloperidol vs. placebo	3 (644)	Inpatients with or without critical illness	Somnolence, oversedation		1.10 (0.78–1.53)
Second-generationII vs. haloperidol	6 (872)	Inpatients with or without critical illness	Sleepiness, excessive/severe sedation, hypersomnia, oversedation		1.26 (0.92–1.72)





- **MyM:** metaanálisis, 16 ECA y 10 estudios observacionales.
- **R:** ECA -> 1768 pacientes, EO -> 3839
- **C:** el tratamiento del SCA con antipsicóticos no mejora los resultados.

4. Enfermedades infecciosas

Annals of Internal Medicine®

ORIGINAL RESEARCH | 6 AUGUST 2019

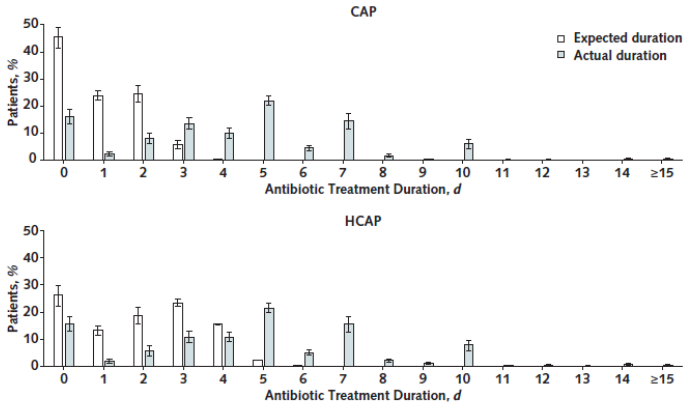
Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia: A Multihospital Cohort Study

Valerie M. Vaughn, MD, MSc; Scott A. Flanders, MD; Ashley Snyder, MS; Anna Conlon, PhD; Mary A.M. Rogers, PhD, MS; Anurag N. Malani, MD; Elizabeth McLaughlin, MS, RN; Sarah Bloemers, MPH; Arjun Srinivasan, MD; Jerod Nagel, PharmD, BCPS; Scott Kaatz, DO; Danielle Osterholzer, MD; Rama Thyagarajan, MD; Lama Hsaiky, PharmD, BCPS; Vineet Chopra, MD, MSc; Tejal N. Gandhi, MD

- **MyM:** Estudio cohorte retrospectivo.
- **R:** 6481 médicos de AP con neumonía. El 67.8% recibieron un exceso de terapia antibiótica.

  C: Los pacientes hospitalizados con neumonía reciben un exceso de tratamiento antibiótico. Se ha asociado a un aumento de los efectos adversos.

Figure 3. Expected vs. actual antibiotic treatment duration after discharge for hospitalized patients with CAP (*top*) and HCAP (*bottom*) (n = 6481).



Although CAP and HCAP have different distributions of expected treatment durations after discharge, patients with CAP and those with HCAP were treated similarly at discharge, which may explain why those with CAP were more likely to have an excess duration. Expected durations after discharge were calculated on the basis of classification of pneumonia (CAP vs. HCAP), time to clinical stability (defined as being afebrile [temperature <37.9 °C] for ≥48 h and having ≤1 vital sign abnormality), and treatment duration during hospitalization. Actual treatment duration after discharge was the duration prescribed at discharge. Error bars represent 95% CIs. CAP = community-acquired pneumonia; HCAP = health care–associated pneumonia.

Table 3. Association of Excess Antibiotic Treatment Duration With 30-Day Adverse Outcomes (n = 6481)*

Outcomes at 30 Days	Appropriate Duration (n = 2090), n (%)†	Excess Duration (n = 4391), n (%)‡	Unadjusted OR per Excess Day (95% CI)§	Unadjusted P Value§	Adjusted OR per Excess Day (95% CI)§	Adjusted P Value§
Mortality‖	40 (1.9)	88 (2.0)	0.99 (0.94–1.03)	0.52	1.01 (0.97–1.05)	0.60
Readmission‖	294 (14.1)	497 (11.3)	0.99 (0.96–1.02)	0.48	1.00 (0.98–1.03)	0.92
Emergency department visit‖	238 (11.4)	480 (10.9)	0.97 (0.94–1.00)	0.021	0.98 (0.95–1.01)	0.166
Antibiotic-associated adverse event¶	72 (3.4)	210 (4.8)	1.04 (1.01–1.07)	0.012	1.03 (1.00–1.06)	0.038
Clostridioides difficile infection**	11 (0.5)	22 (0.5)	0.92 (0.81–1.05)	0.21	0.93 (0.81–1.07)	0.30
Provider-documented††‡‡	43 (2.1)	87 (2.0)	1.00 (0.94–1.05)	0.86	0.99 (0.94–1.05)	0.85
Patient-reported††§§	26/1132 (2.3)	114/2460 (4.6)	1.05 (1.02–1.08)	<0.001	1.05 (1.02–1.08)	0.001
Composite adverse outcome‖	499 (23.9)	897 (20.4)	0.98 (0.96–1.00)	0.078	0.99 (0.97–1.01)	0.40

OR = odds ratio.

4. Enfermedades infecciosas

EDITORIAL

Annals of Internal Medicine

Duration of Antibiotic Therapy: Shorter Is Better

- Más de 45 ensayos clínicos aleatorios y 2 metaanálisis comparaban ciclos cortos vs ciclos largos de tratamiento ATB.
  - **NAC: 3 a 5 días** de tratamiento es al menos tan efectivo como 7-14 días
  - **Nosocomial: 8 días** igual de efectivos como 15 días

- **E. observacional de Vaughn:** 6500 pacientes con NAC entre 2017 y 2018.
- 2/3 excedieron la duración → **tto oral al alta.** **Ciclos largos**: no aumentan supervivencia, ni disminuyen los reingresos o las visitas a urgencias. Además, por cada día de tratamiento ATB en exceso se aumenta un 5% el nº de EA.
- Aumento de las tasas de resistencia.

4. Enfermedades infecciosas

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Risk Factors and Outcomes Associated With Treatment of Asymptomatic Bacteriuria in Hospitalized Patients

Lindsay A. Petty, MD; Valerie M. Vaughn, MD, MSc; Scott A. Flanders, MD; Anurag N. Malani, MD; Anna Conlon, PhD; Keith S. Kaye, MD, MPH; Rama Thyagarajan, MD; Danielle Osterholzer, MD; Daniel Nielsen, MS; Gregory A. Eschenauer, PharmD; Sarah Bloemers, MPH; Elizabeth McLaughlin, BSN, MS; Tejal N. Gandhi, MD

Table 3. Multivariable Model of Patient Factors Associated With Treatment of Asymptomatic Bacteriuria (N = 2773)

Variable	No.	Odds Ratio (95% CI)[a]	*P* Value[b]
Patient characteristics			
Age (per 10-y increase)		1.10 (1.02-1.18)	.01
Dementia	560	1.57 (1.15-2.13)	.004
Incontinence	593	1.81 (1.36-2.41)	<.001
Acutely altered mental status	470	1.93 (1.23-3.04)	.004
Laboratory tests			
Urine culture with *Escherichia coli*	1372	1.42 (1.12-1.79)	.003
Peripheral leukocytosis[c]	967	1.55 (1.21-2.00)	<.001
Bacteriuria ≥100 000 CFU	2211	2.30 (1.83-2.91)	<.001
Positive urinalysis[d]	2486	2.83 (2.05-3.93)	<.001

- **O:** Evaluar los factores asociados al tratamiento de bacteriuria asintomática en pacientes hospitalizados.
- **MyM:** Estudio de cohortes retrospectivo (Enero 2016-Febrero 2018). 46 hospitales participantes. Michigan.
  - **Bacteriuria asintomática**: Cultivo positivo sin evidencia de signos de infección atribuibles a ITU (tb sedimento).
- **R: 2733** pacientes. 78,2% mujeres. 82,7% tratados con antibióticos durante 7 días.
  - **Factores asociados:** edad avanzada (OR 1.10; IC 1.02-1.18), demencia (OR 1.57; IC 1.15-2.13), alteración aguda del estado mental (OR 1.93; IC 1.23-3.04), incontinencia urinaria (OR 1.81; IC 1.36-2.41), leucocitosis (OR 1.55; IC 1.21-2.0), leucocituria/nitritos positivos (OR 2.83; IC 2.05-3.93) y > 10.000 UFC (OR 2.33; IC 1.83-2.91).
  - **Mayor tiempo de hospitalización** después del test urinario (RR 1.37 IC 1.28-1.47)

Table 4. Outcomes for Treatment vs No Treatment for Asymptomatic Bacteriuria (N = 2733)

Outcome[a]	No. (%) Antibiotics (n = 2259)	No. (%) No Antibiotics (n = 474)	Unadjusted Odds Ratio (95% CI)	Unadjusted *P* Value	Adjusted Odds Ratio (95% CI)	Adjusted *P* Value
30-d Postdischarge mortality[b]	63 (2.8)	11 (2.3)	1.22 (0.66-2.26)	.53	1.34 (0.72-2.49)	.35
30-d Postdischarge readmission[b]	362 (16.0)	66 (13.9)	1.16 (0.87-1.56)	.31	1.29 (0.92-1.81)	.14
30-d Postdischarge ED visit[b]	272 (12.0)	62 (13.1)	0.91 (0.70-1.18)	.48	0.90 (0.66-1.24)	.52
Discharge to post-acute care facility[b,c]	811 (35.9)	102 (21.5)	1.98 (1.58-2.48)	<.001	1.19 (0.90-1.57)	.22
Clostridioides difficile infection[d]	14 (0.6)	2 (0.4)	1.39 (0.41-4.68)	.59	0.88 (0.20-3.86)	.86
Duration of hospitalization, median (IQR), d[e]	4 (3-6)	3 (2-5)	1.37 (1.28-1.47)[f]	<.001	1.37 (1.28-1.47)[f]	<.001

Abbreviations: ED, emergency department; IQR, interquartile range.

[a] Outcomes were adjusted for patient variables found to be significant ($P < .05$) and associated with treatment in the bivariate and multivariate analysis.

[b] Mortality, readmissions, ED visits, and discharge to post-acute care facility were adjusted for age, Charlson Comorbidity Index score, hospitalization in 90 days preceding current admission, admission from nursing home, and insurance type.

[c] Long-term acute care hospital, skilled nursing facility, inpatient rehabilitation, and subacute rehabilitation.

[d] Infection occurring within 30 days of discharge was adjusted for age, history of antibiotic use and number of antibiotics in previous 90 days, admission from skilled nursing facility, prior hospitalization, proton-pump inhibitor use, immunosuppression, and Charlson Comorbidity Index score.

[e] From date of urine testing (either urine culture or urinalysis, whichever was performed first). Adjusted for age, sex, Charlson Comorbidity Index score, prior hospitalization, admission from nursing home, and insurance type.

[f] Relative risk given because because duration of hospitalization is a continuous variable.

- **C:** El tratamiento antibiótico no parece relacionarse con mejoría de resultados, sino con una mayor duración de la hospitalización.

5. Y además…

JIM Journal of Internal Medicine
Founded in 1863

Original Article

D-dimer levels and risk of recurrence following provoked venous thromboembolism: findings from the RIETE registry

O. Avnery, M. Martin, A. Bura-Riviere, G. Barillari, L. Mazzolai, I. Mahé, P.J. Marchena, P. Verhamme, M. Monreal, M.H. Ellis, for the RIETE Investigators

- **MyM:** Estudio observacional retrospectivo. Base RIETE.
- **R:** 1655 pacientes sin cáncer con TEV con factores de riesgo transitorios. 460 f. mayor y 1195 f. menores.
  - FR. mayor: niveles elevados de dímero d (n = 171) tuvieron una tasa de recurrencias **no significativamente** mayor (cociente de riesgos [HR]: 2,14; IC del 95%: 0,96 a 4,79)
  - FR. menores: niveles elevados de dímero d (n = 382) tuvieron una tasa más alta de recurrencias (HR: 2,34; IC del 95%: 1,51–3,63) que aquellos con niveles normales.
- **C:** Niveles elevados de dímero D asocian mayor riesgo de recurrencia en pacientes con f. de riesgo menores.

Table III. Rates of recurrent VTE or death in patients with raised vs. normal d-dimer levels after discontinuing treatment for VTE provoked by a transient risk factor.

	Raised d-dimers		Normal d-dimers		Hazard ratio (95% CI)	P value
	N	N per 100 patient-years	N	N per 100 patient-years		
Major transient risk factors, N	***171***		***289***			
Duration of therapy						
Mean days ± SD	484±499		565±594			0.133
Median days (IQR)	308 (78-858)		367 (91-892)			0.277
Outcomes,						
VTE overall	13	5.74 (3.19-9.57)	12	2.68 (1.45-4.56)	2.14 (0.96-4.79)	0.062
Deep vein thrombosis	7	3.09 (1.35-6.11)	7	1.57 (0.68-3.10)	1.97 (0.66-5.88)	0.215
Pulmonary embolism	6	2.65 (1.07-5.51)	5	1.12 (0.41-2.48)	2.37 (0.69-8.43)	0.167
Death	3	1.32 (0.34-3.60)	2	0.45 (0.07-1.48)	2.96 (0.44-24.9)	0.261
In patients with d-dimer levels measured ≤30 days after discontinuing therapy (N=129)						
VTE overall	2	3.04 (0.51-10.1)	4	3.42 (1.09-8.24)	0.89 (0.11-5.02)	0.929
Deep vein thrombosis	2	3.04 (0.51-10.1)	3	2.56 (0.65-6.97)	1.19 (0.14-7.98)	0.840
Pulmonary embolism	0	-	1	0.85 (0.04-4.21)	-	0.640
In patients with d-dimer levels measured >30 days after discontinuing therapy (N=331)						
VTE overall	11	6.84 (3.60-11.9)	8	2.42 (1.13-4.60)	2.82 (1.12-7.36)	0.027
Deep vein thrombosis	5	3.11 (1.14-6.89)	4	1.21 (0.38-2.92)	2.57 (0.65-10.7)	0.175
Pulmonary embolism	6	3.73 (1.51-7.76)	4	1.21 (0.38-2.92)	3.08 (0.84-12.4)	0.088
Minor transient risk factors, N	***382***		***813***			
Duration of therapy						
Mean days ± SD	530±519		515±536			0.650
Median days (IQR)	381 (99-868)		367 (79-829)			0.537
Outcomes,						
VTE overall	43	7.79 (5.71-10.4)	38	3.34 (2.39-4.53)	2.34 (1.51-3.63)	<0.001
Deep vein thrombosis	23	4.16 (2.70-6.15)	21	1.84 (1.17-2.77)	2.26 (1.24-4.12)	0.008
Pulmonary embolism	20	3.61 (2.27-5.48)	17	1.48 (0.89-2.33)	2.44 (1.27-4.72)	0.008
Death	13	2.36 (1.31-3.93)	9	0.79 (0.39-1.45)	2.98 (1.27-7.27)	0.012
In patients with d-dimer levels measured ≤30 days after discontinuing therapy (N=858)						
VTE overall	28	7.28 (4.93-10.4)	26	3.23 (2.16-4.67)	2.25 (1.31-3.87)	0.003
Deep vein thrombosis	16	4.15 (2.46-6.60)	14	1.74 (0.99-2.85)	2.39 (1.15-4.98)	0.019
Pulmonary embolism	12	3.11 (1.68-5.29)	12	1.49 (0.81-2.53)	2.09 (0.92-4.74)	0.077
In patients with d-dimer levels measured >30 days after discontinuing therapy (N=337)						
VTE overall	15	8.97 (5.21-14.5)	12	3.58 (1.94-6.09)	2.50 (1.16-5.48)	0.019
Deep vein thrombosis	7	4.19 (1.83-8.28)	7	2.09 (0.91-4.13)	2.00 (0.67-5.97)	0.206
Pulmonary embolism	8	4.78 (2.22-9.08)	5	1.47 (0.54-3.27)	3.24 (1.05-10.9)	0.041

Abbreviations: VTE, venous thromboembolism; SD, standard deviation; IQR, inter-quartile range; CI, confidence intervals.

Accepted Article

5. Y además…

Annals of Internal Medicine®

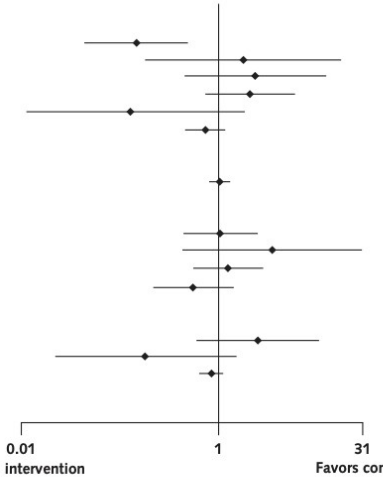
Benefits and Harms of Oral Anticoagulant Therapy in Chronic Kidney Disease

A Systematic Review and Meta-analysis

Jeffrey T. Ha, MBBS; Brendon L. Neuen, MBBS(Hons); Lap P. Cheng, MBBS; Min Jun, PhD; Tadashi Toyama, PhD; Martin P. Gallagher, PhD; Meg J. Jardine, PhD; Manish M. Sood, MD; Amit X. Garg, PhD; Suetonia C. Palmer, PhD; Patrick B. Mark, PhD; David C. Wheeler, MD; Vivekanand Jha, MD; Ben Freedman, PhD; David W. Johnson, PhD; Vlado Perkovic, PhD; and Sunil V. Badve, PhD

Figure 3. Treatment effects in trials involving participants with acute VTE on recurrent VTE or VTE-related death, all-cause death, and bleeding outcomes.

Comparison, by Outcome	Trials, *n*	Events/Participants, *n/N* Intervention	Events/Participants, *n/N* Control	RR (95% CI)	I^2, %	GRADE Certainty of Evidence
VTE or VTE-related death						
NOAC vs. placebo	2	3/298	18/245	0.14 (0.04–0.48)	0	Low
NOAC vs. LMWH	1	2/38	1/34	1.79 (0.17–18.87)	NA	Very low
VKA vs. LMWH	2	24/150	11/143	2.39 (0.44–12.96)	76	Very low
Any OAC vs. LMWH	3	26/188	12/177	2.10 (0.72–6.15)	51	Very low
NOAC vs. ASA	1	0/92	3/64	0.12 (0.01–1.87)	NA	Very low
NOAC vs. VKA	5	27/947	40/925	0.72 (0.44–1.17)	0	Low
All-cause death						
VKA vs. LMWH	2	66/144	61/137	1.01 (0.79–1.31)	0	Very low
Major bleeding						
VKA vs. LMWH	2	11/149	10/143	1.03 (0.43–2.51)	10	Very low
NOAC vs. LMWH	1	4/38	1/34	3.58 (0.42–30.48)	NA	Very low
Any OAC vs. LMWH	3	15/187	11/177	1.24 (0.54–2.88)	11	Very low
NOAC vs. VKA	3	14/610	27/598	0.54 (0.21–1.43)	51	Very low
Major or nonmajor clinically relevant bleeding						
NOAC vs. placebo	1	10/91	2/46	2.53 (0.58–11.06)	NA	Very low
NOAC vs. ASA	1	1/92	4/64	0.17 (0.02–1.52)	NA	Very low
NOAC vs. VKA	3	79/703	95/708	0.84 (0.63–1.11)	0	Low

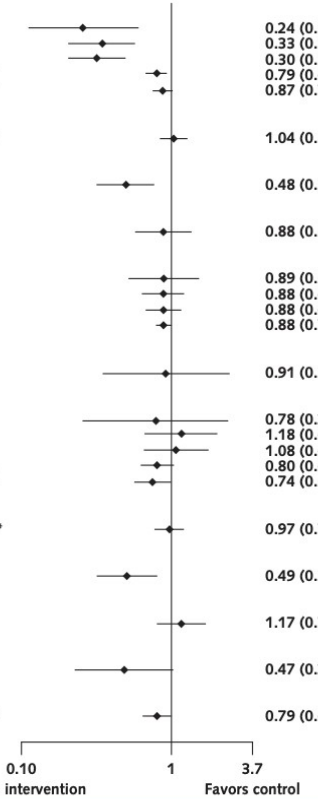


ASA = aspirin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; LMWH = low-molecular-weight heparin; NA = not applicable; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; RR = risk ratio; VKA = vitamin K antagonist; VTE = venous thromboembolism.

- **MyM:** Metaanálisis de 45 ensayos. Comparan R/B entre AVK y NACOS en pacientes con ERC estadio 3-5.
- **R:** 34.082 pacientes anticoagulados por diversos motivos.
  - FA: NACOs disminuyen el riesgos de accidente cerebrovascular o embolia sistémica (razón de riesgo [RR], 0,79 [IC del 95%, 0,66 a 0,93]) y accidente cerebrovascular hemorrágico (RR, 0,48 [IC, 0,30 a 0,76])
  - TEV recurrente o muerte por TVE: NACO resultados **inciertos** (RR, 0,72 [IC, 0,44 a 1,17])
  - En todos los ensayos: los NACO aparentemente **redujeron el riesgo de hemorragia mayor** en comparación a los AVK (RR, 0,75[IC, 0,56 a 1,01]
- **C:** Según estadio de ERC:
  - **Temprano**: NACO perfil riesgo-beneficio superior a los AVK.
  - **Avanzado**: no hay pruebas suficientes.

Figure 2. Treatment effects in trials involving participants with atrial fibrillation on stroke or systemic embolism, nonhemorrhagic stroke, hemorrhagic stroke, myocardial infarction, all-cause death, and bleeding outcomes.

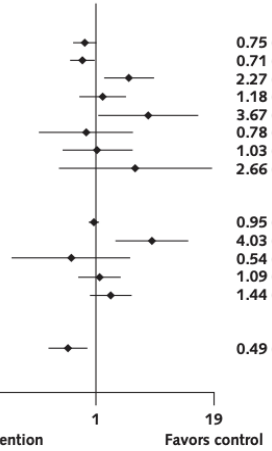
Comparison, by Outcome	Trials, *n*	Events/Participants, *n/N* Intervention	Events/Participants, *n/N* Control	RR (95%CI)	I^2, %	GRADE Certainty of Evidence
Stroke or systemic embolism						
VKA vs. ASA	1	6/267	23/249	0.24 (0.10–0.59)	NA	Very low
NOAC vs. ASA	1	17/857	51/840	0.33 (0.19–0.56)	NA	Very low
Any OAC vs. ASA	2	23/1124	74/1089	0.30 (0.19–0.48)	0	Moderate
High-dose NOAC vs. VKA	5	227/5735	283/5597	0.79 (0.66–0.93)	0	High
High- and low-dose NOAC vs. VKA	5	389/8265	283/5597	0.87 (0.74–1.02)	8	High
Nonhemorrhagic stroke						
High-dose NOAC vs. VKA	3	151/4362	144/4328	1.04 (0.83–1.30)	0	Moderate
Hemorrhagic stroke						
High-dose NOAC vs. VKA	3	27/4362	57/4328	0.48 (0.30–0.76)	0	Moderate
Myocardial infarction						
High-dose NOAC vs. VKA	1	34/1379	38/1361	0.88 (0.56–1.39)	NA	Very low
All-cause death						
VKA vs. ASA	1	21/267	22/249	0.89 (0.50–1.58)	NA	Very low
NOAC vs. ASA	1	59/857	66/840	0.88 (0.62–1.23)	NA	Very low
Any OAC vs. ASA	2	80/1124	88/1089	0.88 (0.66–1.18)	0	Low
High-dose NOAC vs. VKA	3	598/4113	664/4002	0.88 (0.78–0.99)	22	Moderate
Death or ischemic event after PCI/ACS						
High-dose NOAC vs. VKA	2	13/73*	8/72*	0.91 (0.33–2.56)	75	Very low
Major bleeding						
VKA vs. ASA	1	5/267	6/249	0.78 (0.24–2.51)	NA	Very low
NOAC vs. ASA	1	24/857	20/840	1.18 (0.65–2.11)	NA	Very low
Any OAC vs. ASA	2	29/1124	26/1089	1.08 (0.64–1.83)	0	Low
High-dose NOAC vs. VKA	5	402/5600	491/5473	0.80 (0.61–1.04)	75	Low
High- and low-dose NOAC vs. VKA	5	574/8121	491/5473	0.74 (0.55–1.00)	83	Low
Major or nonmajor clinically relevant bleeding						
High-dose NOAC vs. VKA	5	401/1792*	396/1762*	0.97 (0.76–1.23)	28	Low
Intracranial hemorrhage						
High-dose NOAC vs. VKA	3	41/4102	81/3954	0.49 (0.30–0.80)	36	Moderate
Gastrointestinal bleeding						
High-dose NOAC vs. VKA	1	51/1372	43/1356	1.17 (0.79–1.75)	NA	Very low
Fatal bleeding						
High-dose NOAC vs. VKA	1	9/1372	19/1356	0.47 (0.21–1.03)	NA	Very low
Minor bleeding						
High-dose NOAC vs. VKA	1	120/1372	150/1356	0.79 (0.63–0.99)	NA	Very low



ACS = acute coronary syndrome; ASA = aspirin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NA = not applicable; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; RR = risk ratio; VKA = vitamin K antagonist.
* The number of events was not reported in 1 trial; hence, generic inverse variance meta-analysis was performed.

Figure 4. Treatment effects in all trials combined on major bleeding, major or nonmajor clinically relevant bleeding, and intracranial hemorrhage.

Comparison, by Outcome	Trials, *n*	Events/Participants, *n/N* Intervention	Events/Participants, *n/N* Control	RR (95%CI)	I^2, %	GRADE Certainty of Evidence
Major bleeding						
High-dose NOAC vs. VKA	9	416/6215	518/6076	0.75 (0.56–1.01)	67	Low
High- and low-dose NOAC vs. VKA	9	588/8736	518/6076	0.71 (0.52–0.96)	76	Low
NOAC vs. placebo	4	126/4480	68/4230	2.27 (1.21–4.26)	50	Low
NOAC vs. ASA	1	24/857	20/840	1.18 (0.65–2.11)	NA	Very low
NOAC vs. LMWH	4	12/443	3/420	3.67 (1.05–12.89)	0	Very low
VKA vs. ASA	1	5/267	6/249	0.78 (0.24–2.51)	NA	Very low
VKA vs. LMWH	2	11/149	10/143	1.03 (0.43–2.51)	10	Very low
Low-intensity VKA vs. placebo	2	16/184	7/182	2.66 (0.39–18.19)	48	Very low
Major or nonmajor clinically relevant bleeding						
High-dose NOAC vs. VKA	8	480/2495*	491/2470*	0.95 (0.83–1.07)	4	Low
NOAC vs. placebo	3	48/397	5/177	4.03 (1.62–10.03)	0	Very low
NOAC vs. ASA	2	1/92*	4/64*	0.54 (0.12–2.36)	47	Very low
NOAC vs. LMWH	3	27/640	26/674	1.09 (0.64–1.85)	0	Very low
Low-intensity VKA vs. placebo	1	26/87	18/87	1.44 (0.86–2.44)	NA	Very low
Intracranial hemorrhage						
High-dose NOAC vs. VKA	3	41/4102	81/3954	0.49 (0.30–0.80)	36	Moderate



ASA = aspirin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; LMWH = low-molecular-weight heparin; NA = not applicable; NOAC = non-vitamin K oral anticoagulant; RR = risk ratio; VKA = vitamin K antagonist.
* The number of events was not reported in 1 trial; hence, generic inverse variance meta-analysis was performed.

6. Conclusiones