XXV REUNIÓN

INSUFICIENCIA CARDIACA Y FIBRILACIÓN AURICULAR

4 y 5 mayo 2023 | Palacio de Congresos Girona

#25ICyFA

SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

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SEMI Grupo de Insuficiencia Cardiaca y Fibrilación Auricular

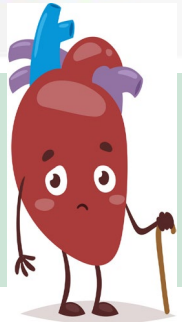
CARA A CARA:
ANTICOAGULAR INSUFICIENCIA CARDIACA EN RITMO SINUSAL

NO

Alejandra Gullón Ojesto MD, PhD
Servicio de Medicina Interna
Hospital Universitario de La Princesa (Madrid)

El espectro de los pacientes con IC es muy amplio

EPIDEMIOLOGIA DE LOS ICTUS en PACIENTES CON IC



- Los pacientes con IC tienen **un riesgo 2-5 veces superior de ictus**. La prevalencia de ictus isquémico en pacientes con IC crónica es mucho mayor que en población general (8-11% vs 1%).
- La IC no sólo **incrementa** la incidencia de ictus, sino también su **mortalidad y morbilidad** en comparación de los pacientes sin IC (mortalidad de 2-4 veces superior).
- La gravedad de la IC **(NYHA)** es el predictor más relevante de ictus y también de su mortalidad en pacientes con IC.
- La **presencia de FA en pacientes con ictus e IC varía entre 20-51%** según las cohortes y características.
  - En pacientes con FA el riesgo de ictus isquémico fue similar entre los pacientes con IC con FEp o FEr (ACTIVE-W trial)

- En **pacientes SIN FA:**
  - La **severidad de la IC (NYHA) y la disminución de la FEVI** son los principales factores de riesgo de ictus.
  - El **riesgo de ictus es 1,5-2,1 veces superior** que en pacientes en RS sin IC.

Scherbakov N. ESC Hear Fail 2015;2(01):1–4
Barkhudaryan A.J Clin Med. 2021 Mar 9;10(5):1146
Rivas A. Thromb Haemost . 2022 Jun;122(6):871-878

LA ANTICOAGULACIÓN NO ES EFICAZ CONTRA TODOS LOS MECANISMOS ETIOLÓGICOS DEL ICTUS EN EL PACIENTE CON IC

ETIOPATOGENIA DE LOS ICTUS en PACIENTES CON IC

- ✓ Formación de trombos (Afib)
- ✓ Alteración contractilidad VI (± AI)
- ✓ Mecanismos de activación de coagulación: inflamación, citokinas…
- ✓ Disfunción endotelial
- ✓ Activación del SRAA (ICFEr)
- ✓ Reducción del flujo cerebral => lesiones de pequeño vaso

20-30%

Ictus cardioembólicos
(FA, disfx sistólica, miocardiopatía dilatada, valvulares…)

Ictus aterotrombóticos y lacunares
(enfermedad coronaria, HTA…)

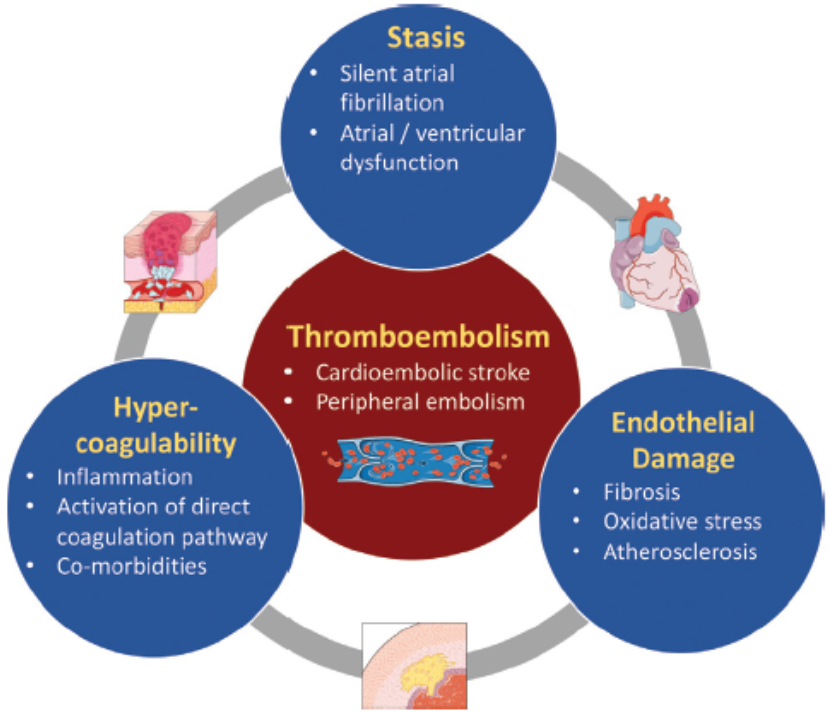


Fig. 1 Thrombosis formation and specific heart failure-related components that pertain to Virchow's triad.

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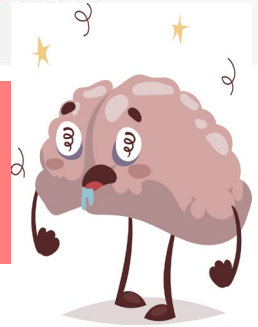
Barkhudaryan A.J Clin Med. 2021 Mar 9;10(5):1146 // Rivas A. Thromb Haemost . 2022 Jun;122(6):871-878.

ICTUS en PACIENTES CON IC en RITMO SINUSAL



ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599–3726
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

12.5 Stroke

HF and stroke frequently coexist because of an overlap of shared risk factors and subsequent mechanisms.[519,634] A higher risk of stroke is present also in HF patients in SR.[39,426,635–637] AF confers an additional risk and patients with HF and AF have a five-fold increased risk compared to the control population.[519,634,638]

As a temporal trend, the incidence of stroke is higher in the first 30 days after HF diagnosis or an episode of HF decompensation and decreases in the first 6 months following the acute event.[637,639] Patients with stroke and HF have higher mortality, more severe neurological deficits and longer hospital stays than those without HF.[637,640] Similarly, patients with HF and stroke have a higher mortality than patients without stroke.[640] In COMMANDER-HF, 47.5% of strokes were either disabling, 16.5%, or fatal, 31%.[637]

Patients with HF and concomitant AF, including paroxysmal AF, have a CHA_2DS_2-VASc score of at least 1 and have therefore an indication to anticoagulation. The indication to antithrombotic strategies in patients with HF and SR is controversial. In the Warfarin and Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, warfarin reduced ischaemic stroke as compared with aspirin, but increased major haemorrhages and did not influence the primary endpoint of ischaemic stroke, intracerebral haemorrhage, or death.[641] Meta-analyses confirm an increased risk of bleeding outweighing ischaemic stroke prevention in placebo-controlled trials in patients with HFrEF and SR.[642] In COMMANDER-HF, rivaroxaban 2.5 mg b.i.d. did not improve the composite outcome of all-cause mortality, MI or stroke, nor did it favourably influence HF-related deaths or HF hospitalizations.[579] There are no data to support a routine strategy of anticoagulation in patients with HFrEF in SR who do not have history of paroxysmal AF. However, low-dose rivaroxaban may be considered in patients with concomitant CCS or peripheral artery disease, a high risk of stroke and no major haemorrhagic risk

REAL WORLD EVIDENCE

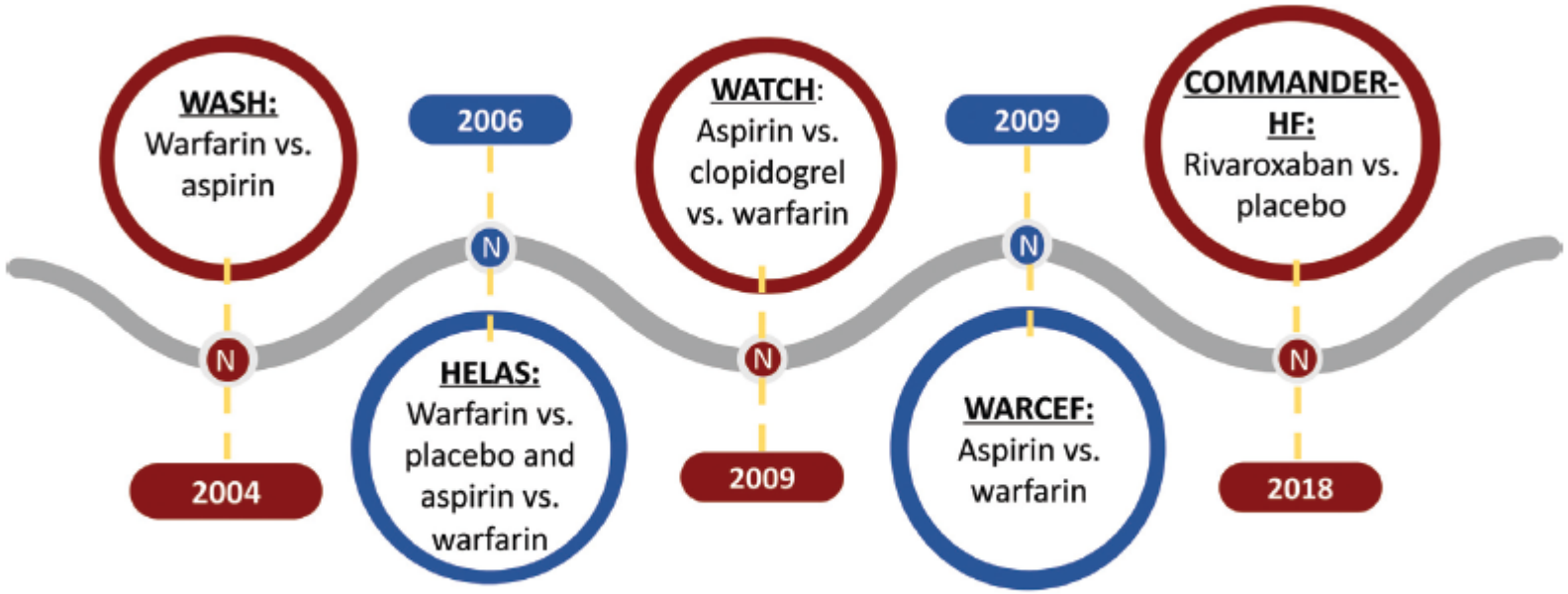
Acute Ischemic Stroke, Depressed Left Ventricular Ejection Fraction, and Sinus Rhythm: Prevalence and Practice Patterns

Stroke. 2022;53:1883–1891. DOI: 10.1161/STROKEAHA.121.036706

- Estudio retrospectivo de 4 centros hospitalarios en EEUU
- N: **14338 pacientes hospitalizados** por ictus isquémico agudo entre 2002-2018

- ✓ La prevalencia de **ictus isquémico agudo en pacientes con IC con FEr (<40%) en RS fue de un 5%** (4,1-6%)
- ✓ De los 534 pacientes dados de alta:
  - 38% anticoagulados
  - 55% antiagregantes sólo
  - 7% sin tto antitrombótico
- ✓ El centro de trabajo y la severidad al ingreso (NIHSS) fueron los predictores independientes de uso de anticoagulantes.

ENSAYOS CLINICOS DE ANTICOAGULACION EN PACIENTES CON IC en RITMO SINUSAL



N = neutral treatment effect on primary outcome

Fig. 2 Timeline of landmark randomized clinical trials assessing anticoagulation in patients with heart failure in sinus rhythm.

Todos ellos en IC con FE reducida

Table 1 Clinical trials evaluating outcomes of anticoagulation in patients with HF in SR

RCT (*N* of patients)	Study design	Population	Mean follow-up (mo)	Comparison group	Primary composite endpoint	Efficacy (results)	Safety outcome: major bleeding	Sex-based differences
WASH (2004) (*n* = 279)	Open label, multicenter Recruitment: 1994–1998	Clinical diagnosis of HF requiring diuretics and LVEF ≤35% Median age of 62 years	27	ASA 300 mg versus warfarin (target INR: 2.0–3.0) versus	Death, nonfatal MI, nonfatal stroke	Aspirin versus no ATT: HR: 1.16 (95% CI: 0.74–1.85) Warfarin versus no ATT: HR: 0.88 (95% CI: 0.54–1.43)	Warfarin 4%, aspirin 1% No ATT 0%	No analyses done
						composite outcome.		
WARCEF (2012) (*n* = 2,305)	Double-blind, double-dummy, multicenter Recruitment: 2002–2010	HF with LVEF ≤35% Median age of 61 and 80% male	42	Warfarin (target INR of 2.5–3.0) versus ASA 325 mg	Ischemic stroke, intracerebral hemorrhage, or death from any cause	Warfarin vs. ASA: HR: 0.93 (95% CI: 0.79–1.10) No significant difference in the primary composite outcome. Reduction in ischemic strokes seen with warfarin versus aspirin (HR: 0.52; 95% CI: 0.33–0.82)	Warfarin 1.78%/ patient-year ASA 0.87%/ patient-year	No analyses done
COMMANDER-HF (2018) (*n* = 5,022)	Double-blinded, placebo-controlled, multicenter Recruitment: 2013–2017	LVEF ≤ 40%, CAD, and recent decompensated HF Median age of 66 and 77% male	Event-driven	Rivaroxaban 2.5 mg versus placebo	Death from any cause, MI, or stroke	Rivaroxaban versus placebo: HR: 0.94 (95% CI: 0.84–1.05) No significant difference in primary composite outcome. Neurological Endpoint of Rivaroxaban versus placebo: HR: 0.68 (95% CI: 0.49–0.94, $p = 0.002$) Posthoc analysis examined primary neurological endpoint of all-cause stroke or TIA, 32% decrease with rivaroxaban.	Rivaroxaban versus placebo; HR: 0.80 (95% CI: 0.43–1.49, $p = 0.48$)	Males: rivaroxaban versus placebo, HR: 0.92 (95% CI: 0.81–1.04) Females: rivaroxaban versus placebo, HR: 1.05 (95% CI: 0.83–1.33)

A diferencia de los ensayos en FA en los que las variables principales evalúan riesgo de ictus en los ensayos de IC-RS las variables principales eran compuestas en incluían siempre la mortalidad por cualquier causa.

Rivas A. Thromb Haemost . 2022 Jun;122(6):871-878

Anticoagulation therapy in heart failure and sinus rhythm: a systematic review and meta-analysis

Simon A S Beggs,[1] Rasmus Rørth,[2] Roy S Gardner,[3] John J V McMurray[1]

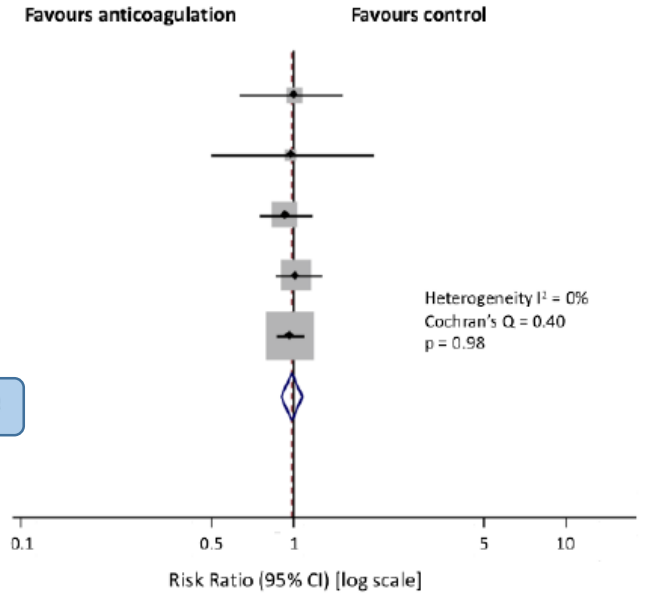
Beggs SAS, *et al*. *Heart* 2019;**105**:1325–1334. doi:10.1136/heartjnl-2018-314381

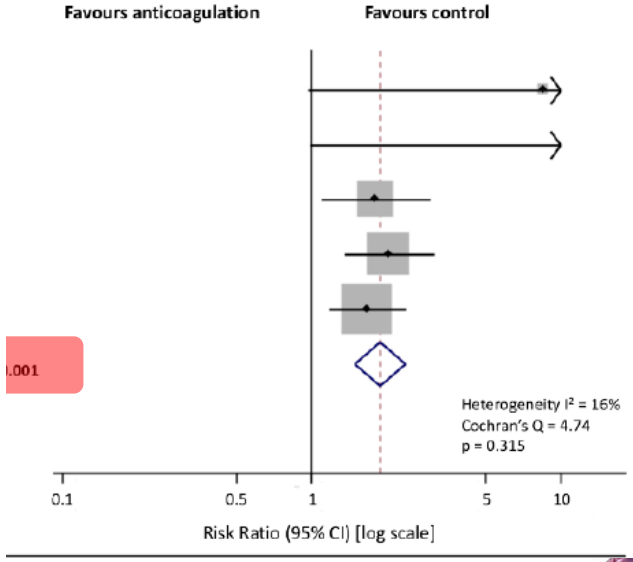
Study	Year of Publication	No. of Patients	Risk Ratio (95% CI)
WASH	2004	254	0.30 (0.02 – 5.81)
HELAS	2006	197	0.76 (0.13 – 4.46)
WATCH	2009	1587	0.57 (0.30 – 1.31)
WARCEF	2012	2305	0.61 (0.33 – 0.83)
COMMANDER	2018	5022	0.66 (0.47 – 0.95)
Combined		**9365**	0.63 (0.49 – 0.81) p =

ICTUS NO FATAL

Study	Year of Publication	No. of Patients	Risk Ratio (95% CI)
WASH	2004	254	1.01 (0.63 – 1.52)
HELAS	2006	197	0.99 (0.50 – 1.97)
WATCH	2009	1587	0.94 (0.75 – 1.18)
WARCEF	2012	2305	1.03 (0.86 – 1.27)
COMMANDER	2018	5022	0.98 (0.87 – 1.10)
Combined		**9365**	0.99 (0.90 – 1.08) p = 0.742

MORTALIDAD POR CUALQUIER CAUSA





HEMORRAGIA MAYOR

Net clinical benefit of antithrombotic therapy in patients with heart failure and sinus rhythm: A network meta-analysis from 5 clinical trials

Chi Zhang[a,1], Na Wang[b,1], Nan-Nan Shen[c], Ling-Cong Kong[d], Jie He[d], Yue Wu[e], Da Feng[f,*], Zhi-Chun Gu[a,*]

Thrombosis Research 190 (2020) 122–128

Table 3
Direct comparisons of treatments for the risk of clinical outcomes.

Treatment comparison	No. of studies	With rivaroxaban/warfarin therapy	With placebo/antiplatelet therapy	With placebo/antiplatelet therapy	RR	95%CI	I^2
Stroke							
Rivaroxaban vs placebo	1	51/2507(2.03%)	76/2515(3.02%)	127/5022(2.52%)	0.67	0.47–0.96	–
Warfarin vs placebo	2	2/172(1.16%)	3/138(2.17%)	5/310(1.61%)	0.56	0.09–3.618	0.00%
Warfarin vs antiplatelet agents	4	34/1854(1.83%)	83/2351(3.53%)	117/4205(2.78%)	0.49	0.33–0.73	0.00%
Major bleeding							
Rivaroxaban vs placebo	1	82/2507(3.27%)	50/2515(1.98%)	132/5022(2.62%)	1.64	1.16–2.33	–
Warfarin vs placebo	2	11/172(6.39%)	0/138(0%)	11/310(3.54%)	8.71	1.14–66.46	0.00%
Warfarin vs antiplatelet agents	4	111/1854(5.98%)	66/2351(2.81%)	177/4205(4.21%)	2.05	1.51–2.78	0.00%
All-cause death							
Rivaroxaban vs placebo	1	546/2507(21.78%)	556/2515(22.14%)	1102/5022(21.94%)	0.98	0.89–1.09	–
Warfarin vs placebo	2	33/172(19.19%)	25/138(18.12%)	58/310(18.71%)	1.18	0.74–1.89	0.00%
Warfarin vs antiplatelet agents	4	125/712(17.56%)	223/1188(18.77%)	348/1900(18.32%)	0.99	0.88–1.21	0.00%

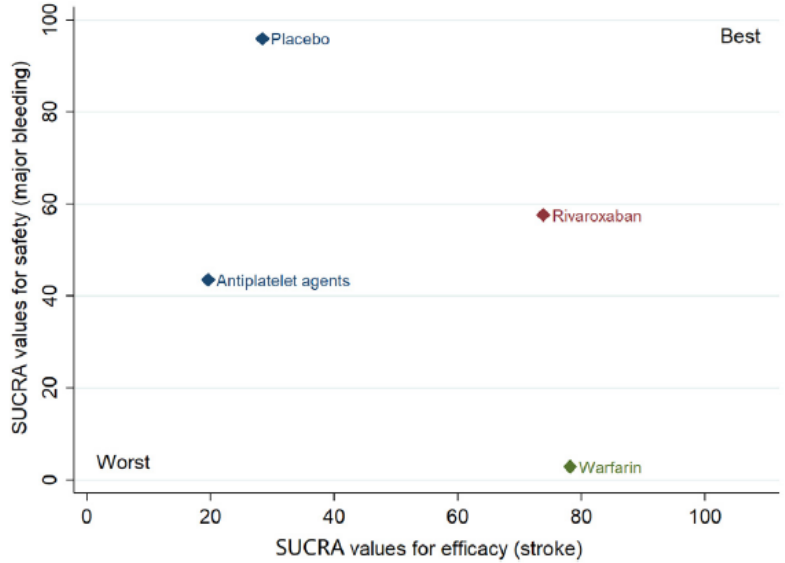


Fig. 3. Surface under the cumulative ranking (SUCRA) plot. Ranking of treatments expresses the probability associated to each one being the best with respect to efficacy (stroke) and safety (major bleeding). Treatments in the upper right corner are more effective and safer than the other treatments.

Efficacy and Safety of Oral Anticoagulants in Patients with Systolic Heart Failure in Sinus Rhythm: A Systematic Review and Meta-analysis of Randomized Controlled Trials and Cohort Studies

Marie H. Nygaard[1] Anne-Mette Hvas[2,3] Erik L. Grove[1,2]

TH Open 2020;4:e383–e392.

receiving OAC therapy had a lower risk of stroke than patients receiving antiplatelet therapy or no treatment/placebo. Conversely, an increased risk of major bleeding was seen based on the calculated ORs of all five RCTs. No benefit was found from OAC as regard to all-cause mortality and MI. The lack of benefit from OAC on all-cause mortality was supported by an additional meta-analysis of three cohort studies with a total of 22,282 patients.

Conclusion

The present study demonstrates a reduced risk of ischemic stroke among HF patients in sinus rhythm treated with OAC, but treatment with OAC also increases the risk of major bleeding. Thus, based on the results of the present meta-analysis supported by a sensitivity analysis, routine OAC treatment is not justified in patients with HF in sinus rhythm, unless indicated for other cardiovascular conditions. Future studies may be able to identify HF patients with an increased risk of stroke who based on, for example, risk scores or echocardiography findings are likely to benefit from anticoagulant treatment.

Association of Oral Anticoagulation With Stroke in Atrial Fibrillation or Heart Failure

A Comparative Meta-Analysis

Catriona Reddin, MB; Conor Judge, MB, BEng; Elaine Loughlin, MB; Robert Murphy, MB; Maria Costello, MB; Alberto Alvarez, PhD; John Ferguson, PhD; Andrew Smyth, PhD; Michelle Canavan, PhD; Martin J. O'Donnell, PhD

Stroke. 2021;52:3151–3162. DOI: 10.1161/STROKEAHA.120.033910

21 estudios: 15 (n=19332) en FA y 6 (n=9866) en ICFEr+RS

- ✓ La ACO se asoció **a reducción de ictus en ambos escenarios de forma similar**: OR 0,51 (0,42-0,63) para FA y OR 0,61 (0,47-0,79) para IC, pero **la RAR fue el doble en FA (2,55% vs 1,3%)** porque la incidencia de ictus en el grupo control fue mucho mayor en los ensayos de FA (7% vs 3,1%)
- ✓ La ACO se asoció de forma significativa a **incremento del sangrado mayor en los ensayos de IC** [OR 1,91 (1,52-2,42)] pero **no en los de FA** [OR 1,27 (0,74-2,18)]. No incremento de hemorragia fatal en ambos.
- ✓ La ACO **no se asoció a una reducción del riesgo de mortalidad total** tanto en FA [OR 0,89 (0,78-1)] como en IC [OR 0,99 (0,9-1,09)]. La mortalidad del grupo control en los ensayos de IC fue mucho mayor que en FA (19% vs 9,6%)

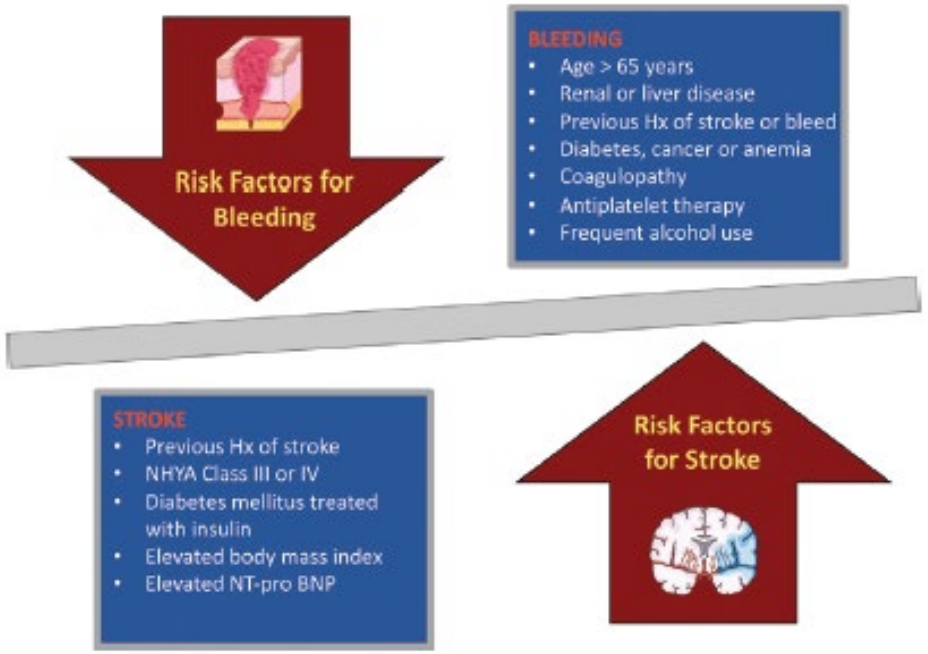
Thromb Haemost 2022;122:871–878.

Stroke and Thromboembolism in Patients with Heart Failure and Sinus Rhythm: A Matter of Risk Stratification?

Angelica Rivas[1] Mandy N. Lauw[2] Renate B. Schnabel[3,4] Mark Crowther[1] Harriette G. C. Van Spall[1,5,6,7]

La mortalidad en los pacientes con IC está condicionada por muchos otros aspectos y comorbilidades más allá del ictus.

➔ **Selección** de aquellos con verdaderamente mayor riesgo de ictus en los que el riesgo hemorrágico sea asumible.



Uso de ACO tiempo dependiente…

UTILIDAD DE LA ESCALA CHA2DS2-VASc

También útil en pacientes con IC y RS.

Puntuaciones ≥4 muy alto riesgo de ictus independientemente de si existe FA o no.

Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GYH. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. JAMA 2015;314 (10):1030–1038

UTILIDAD DE BIOMARCADORES /INDICADORES ECOCARDIOGRÁFICOS

UTILIDAD DE DETECCIÓN DE FA subclínica

Dispositivos, “wearable tech”, IA…

AHA/ASA GUIDELINE

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

2b	B-R	4. In patients with ischemic stroke or TIA in sinus rhythm with ischemic or nonischemic cardiomyopathy and reduced EF without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized.[524–528]

Stroke. 2021;52:e364–e467. DOI: 10.1161/STR.0000000000000375

Personalized Healthcare

CONCLUSIONES

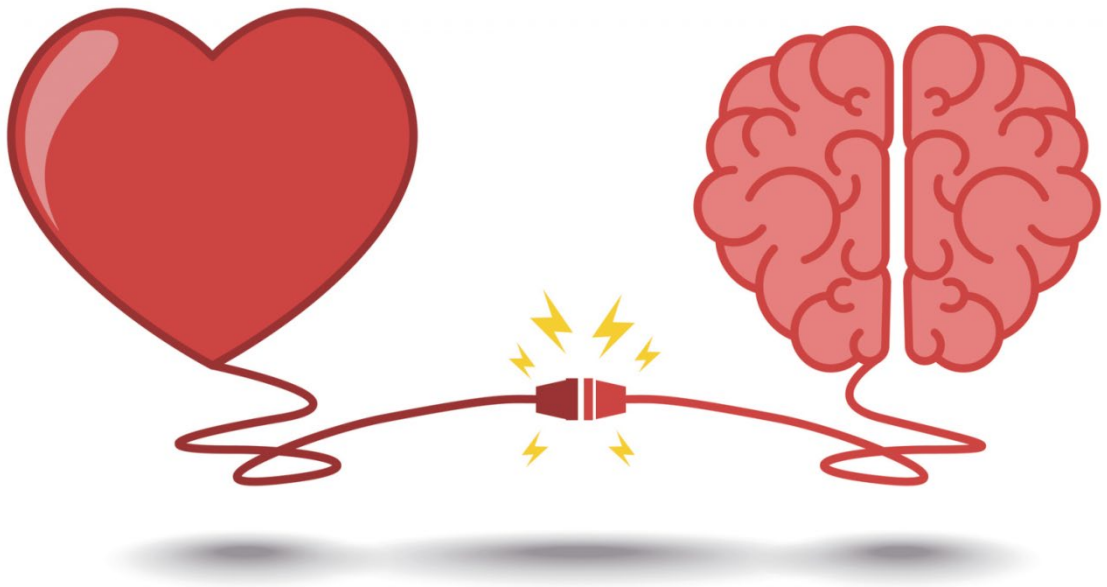
- ✓ El uso generalizado de AVK en pacientes con IC (FE r) en RS, a pesar de reducir el riesgo de ictus, tiene un **beneficio clínico neto DESFAVORABLE** por su aumento de complicaciones hemorrágicas en comparación con antiagregantes o placebo.

- ✓ El uso de **rivaroxaban en dosis bajas** (2,5mg cada 12h) además del tto habitual (incluida la AAG) en pacientes con IC (con FE r) y enfermedad arteriosclerótica establecida podría asociarse a un beneficio antitrombótico sin un incremento relevante del riesgo hemorrágico grave o fatal.

- ✓ La mayoría de las **causas de muerte de los pacientes con IC en RS** no son susceptibles de la reducción de riesgo con la anticoagulación.

- ✓ La **selección pormenorizada** del subgrupo de pacientes con muy elevado riesgo trombótico (AP de ictus previo, FA silente, primeros momentos tras diagnóstico agudo o descompensación, NYHA elevado…) y aceptable riesgo hemorrágico podría ser de utilidad para identificar a los candidatos al uso de anticoagulantes.

- ✓ Futuros estudios tendrán que discernir si la estrategia de uso de mini-dosis de ACOD (± AAG) o dosis plenas de ACOD podrían aportar un BCN y en qué escenarios.



MUCHAS GRACIAS POR LA ATENCIÓN