CAMFiC
societat catalana de medicina familiar i comunitària

Generalitat de Catalunya
Departament de Salut

CatSalut
Servei Català de la Salut

XVII JORNADES D'ACTUALITZACIÓ TERAPÈUTICA 2017

Novetats terapèutiques: Canvien la pràctica clínica?

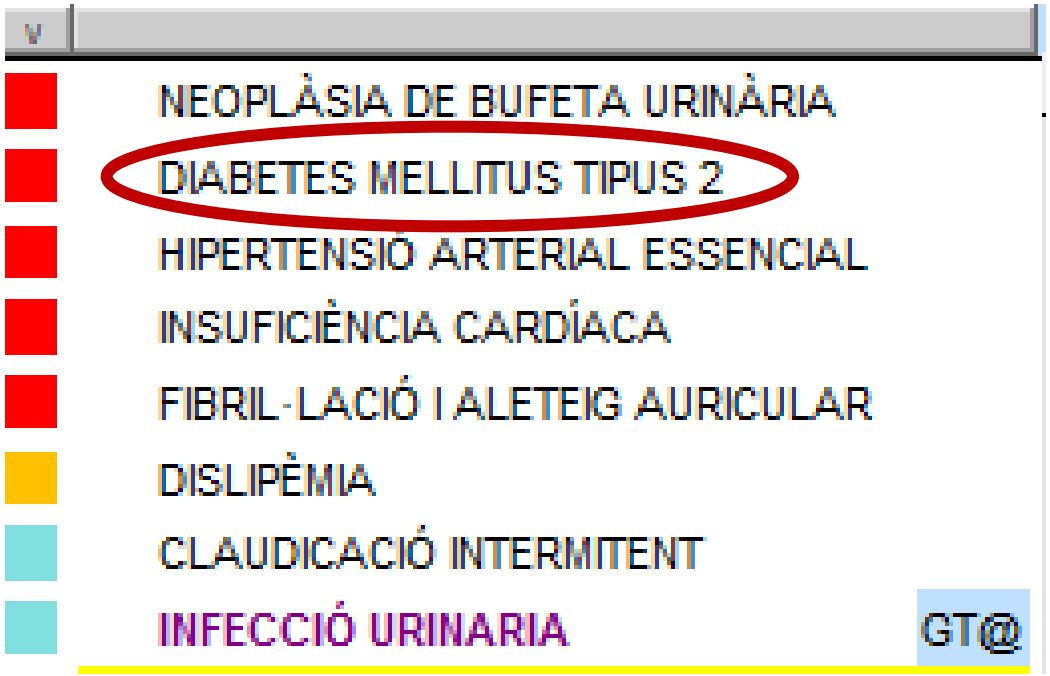
Laura Diego[1], Àngels Pellicer[2] ,Amelia Troncoso[3], Noemí Villén[3]

1. Centre d' Informació de Medicaments de Catalunya
2. Direcció d'Atenció Primària Girona. ICS
3.. Àmbit d'Atenció Primària Barcelona Ciutat. ICS

Juny-Octubre 2017

Arnau, 69 anys

Hba1c 7,5%



Medicament	Principi Actiu	Posologia	Durada
BISOPROLOL COR SANDOZ 2,5MG 28 COMPRIMIDOS RECUBIERTOS PELICULA EFG	BISOPROLOL HEMIFUMARAT	1 x 24 h.	Indefinida
ESPIRONOLACTONA ALTER 25MG 50COMP RECUB EFG	ESPIRONOLACTONA	1 x 24 h.	Indefinida
METFORMINA ALMUS 850MG 50 COMPRIMIDOS RECUBIERTOS PELICULA EFG	METFORMINA	1 x 12 h.	Indefinida
OMEPRAZOL ALMUS 20MG 56 CAPSULAS DURAS GASTRORRESISTENTES EFG	OMEPRAZOL	1 x 24 h.	Indefinida
PRAVASTATINA VIR 20 MG 28 COMPRIMIDOS EFG	PRAVASTATINA SODICA	1 x 24 h.	Indefinida
RAMIPRIL/HIDROCLOROTIAZIDA TECNIGEN 5/25MG 28 COMPRIMIDOS EFG	RAMIPRIL +DIURÈTIC	1 x 24 h.	Indefinida
SINTROM 4MG 20 COMPRIMIDOS	ACENOCUMAROL	1 x 24 h.	Indefinida

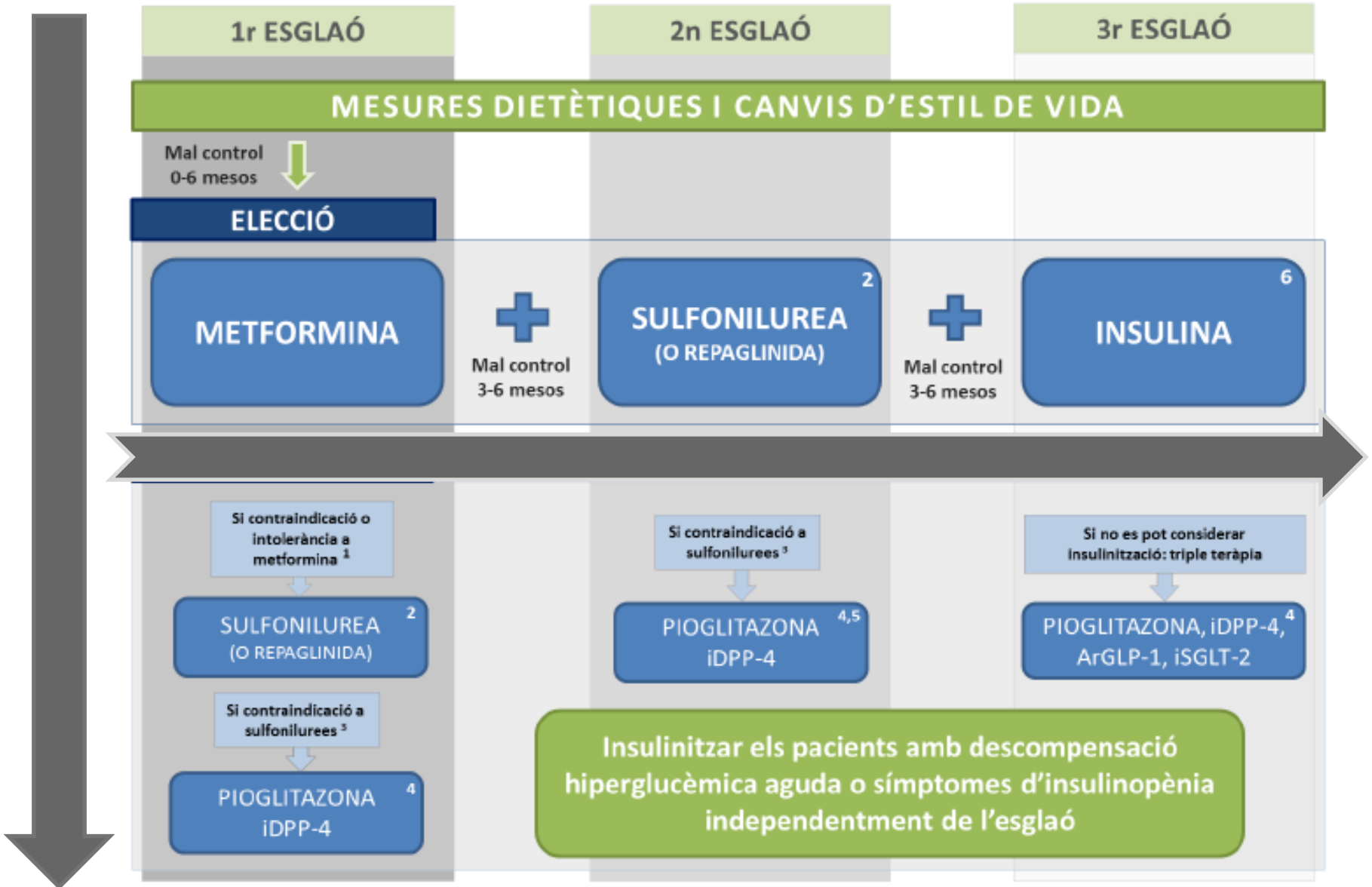
Novetats terapèutiques:
Diabetis Mellitus

PAUTES
D'HARMONITZACIÓ
FARMACTERAPÈUTICA
PHF-APC*

N. 1/2017

Pautes per a l'harmonització del tractament farmacològic de la diabetis mellitus tipus 2

Algorisme del tractament farmacològic hipoglucemiant



Metformina

↓ morbimortalitat **NNT15**

↓ HbA1c **1-2%**

2a línia

o

1a intensificació tractament

Alogliptina

Sitagliptina

Dapagliflozina

Linagliptina

Sulfonilurees

Canagliflozina

Saxagliptina

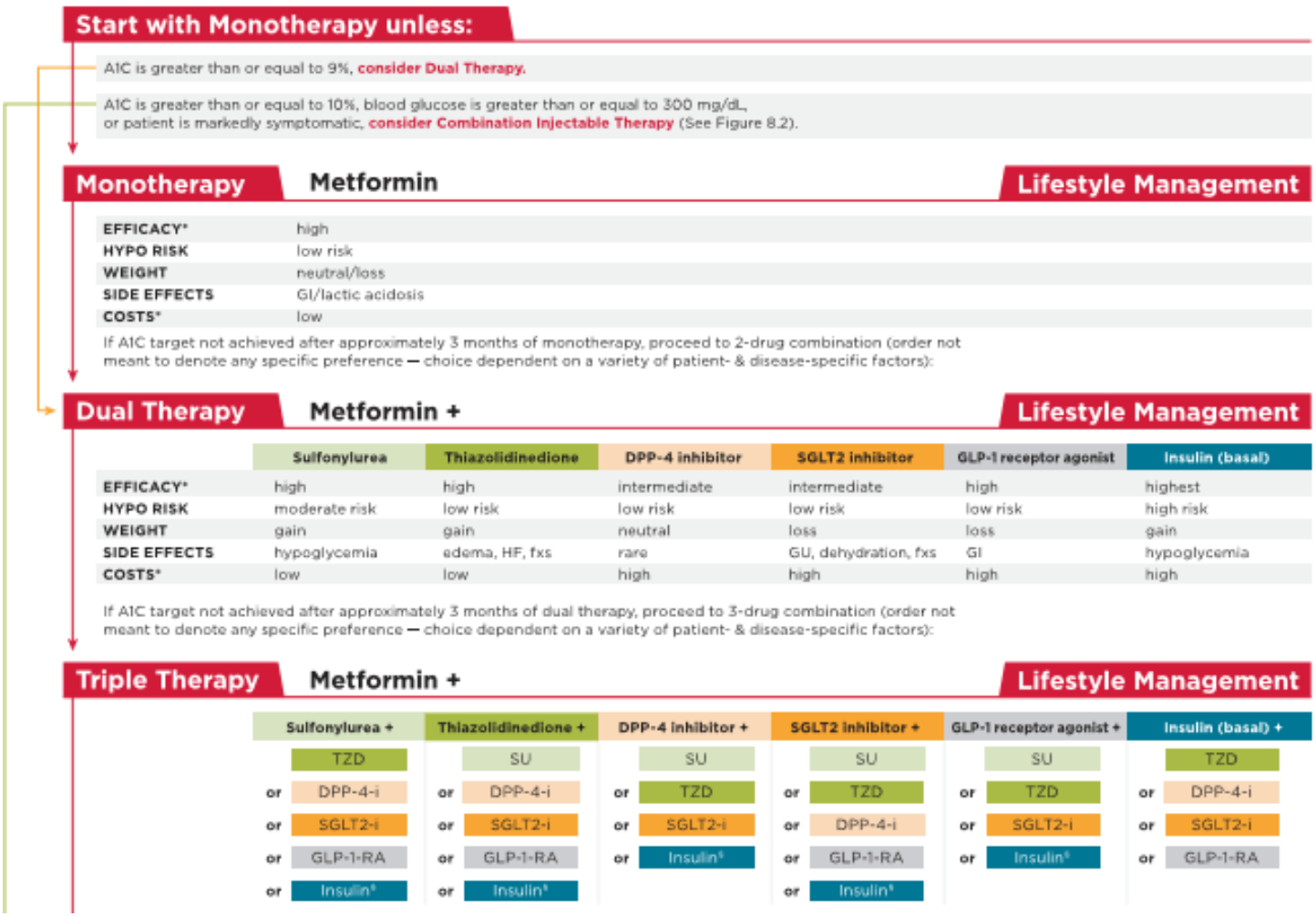
Vildagliptina

Empagliflozina

Glucosúric?

Sulfonilurea?

ADA 2017 Position Stament



Diabetes Care 2017;40(Suppl. 1):S1–S2 | DOI: 10.2337/dc17-S001

ADA 2017 Position Stament

	Sulfonylurea
EFFICACY*	high
HYPO RISK	moderate risk
WEIGHT	gain
SIDE EFFECTS	hypoglycemia
COSTS*	low

Diabetes Care 2017;40(Suppl. 1):S1–S2 | DOI: 10.2337/dc17-S001


Què en sabem de
les hipoglicèmies?

Endocrinol Nutr. 2016;63(Espec Cong):29

ELSEVIER DOYMA

Endocrinología y Nutrición

INCIDENCIA DE HIPOGLUCEMIAS GRAVES EN PACIENTES CON DIABETES MELLITUS TIPO 2 EN TRATAMIENTO CON SULFONILUREAS

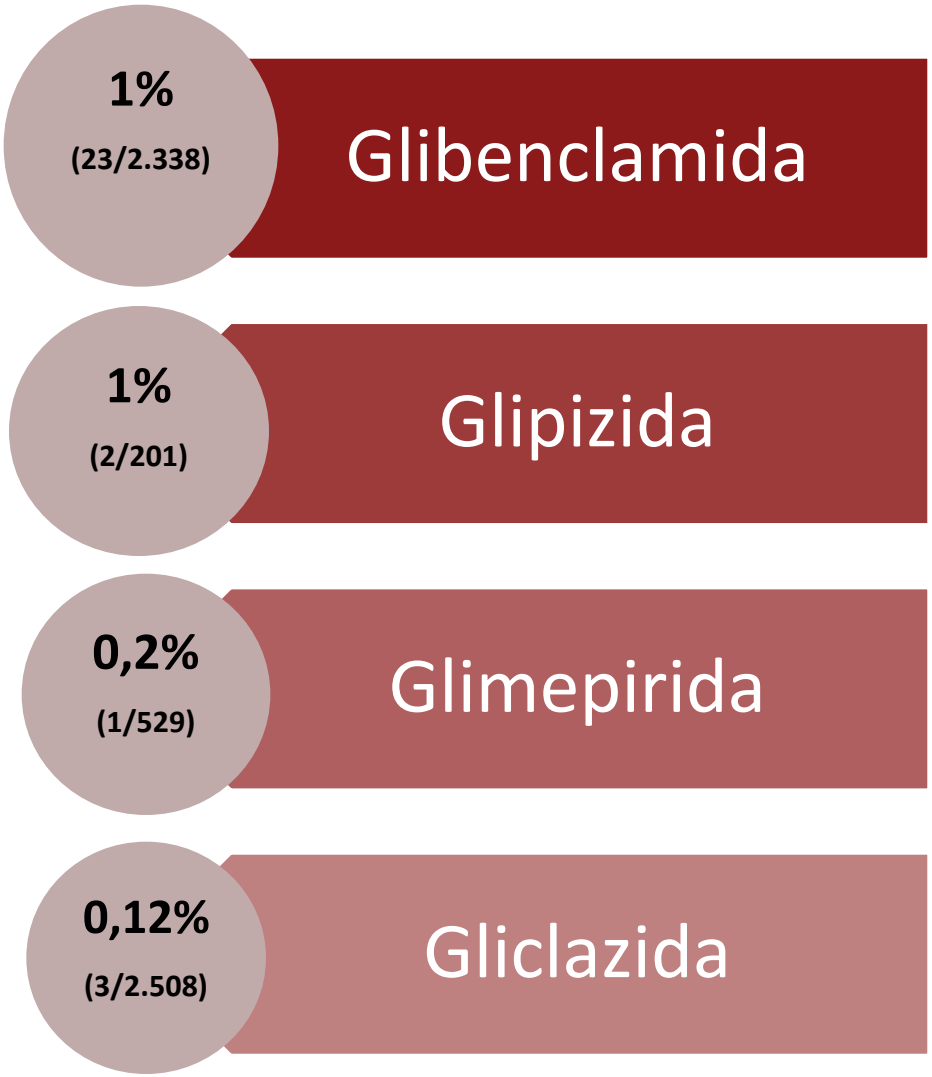
N. Ascoeta, A. Bujosa, J. Puig de Dou, J. Flores Le Roux, E. Climent Biescas, L. Gortazar de la Rica y S. Ballesta Purroy

Hospital del Mar, Barcelona.

Any 2012, Àrea influència Hospital del Mar

18.653	5.576	29
Pacients amb DM2	Sulfonilurees	Hipoglucèmies

Tots els principis actius igual?



Incidència global de hipoglucèmies greus:
0,54% (30/5.576)

Quines característiques tenien els pacients amb hipoglicèmia?

76,4 anys (±8,7)

HbA1c 7,14% (±1,4)

Depèn-dencia (31%)

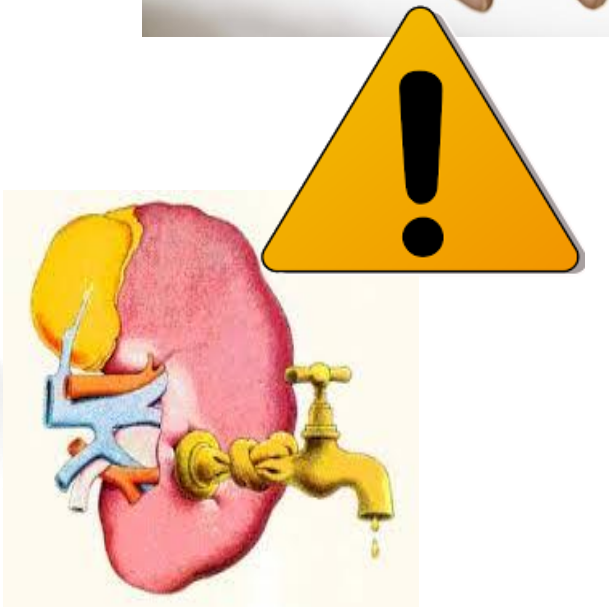
Deterio-rament cognitiu (13,8%)

IRC (27,6%)

Un 60% dels pacients tenia una HbA1c < 7

El principal desencadenant va ser la disminució de la ingesta (37%)

Podem fer quelcom per disminuir el risc d'hipoglucèmies de les sulfonilurees?



OPEN ACCESS Freely available online

PLOS ONE

Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials

Gijs W. D. Landman[1]*, Geertruide H. de Bock[2], Kornelis J. J. van Hateren[1], Peter R. van Dijk[1], Klaas H. Groenier[3], Rijk O. B. Gans[4], Sebastiaan T. Houweling[1], Henk J. G. Bilo[1,4,5], Nanne Kleefstra[1]

1 Diabetes Centre Zwolle, Zwolle, The Netherlands, 2 Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands, 3 Department of General Practice, University Medical Centre Groningen, Groningen, The Netherlands, 4 Department Internal Medicine, University Medical Centre Groningen, Groningen, The Netherlands, 5 Department of Internal Medicine, Isala Clinics, Zwolle, The Netherlands

Conclusions: The methodological quality of randomized trials comparing gliclazide to other oral glucose lowering agents was poor and effect estimates on weight were limited by publication bias. The number of severe hypoglycemic episodes was extremely low, and gliclazide appears at least equally effective compared to other glucose lowering agents. None of the trials were designed for evaluating cardiovascular outcomes, which warrants attention in future randomized trials.

Landman GWD, de Bock GH, van Hateren KJJ, van Dijk PR, Groenier KH, et al. (2014) Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials. PLoS ONE 9(2): e82880. doi:10.1371/journal.pone.0082880

Diabetes Care Volume 40, May 2017

Modern Sulfonylureas: Dangerous or Wrongly Accused?

Matthew C. Riddle

Diabetes Care 2017;40:629–631 | DOI: 10.2337/dci17-0003

If new evidence supports a not guilty verdict, the modern sulfonylureas should regain respect and continue to be an important option for controlling glucose.

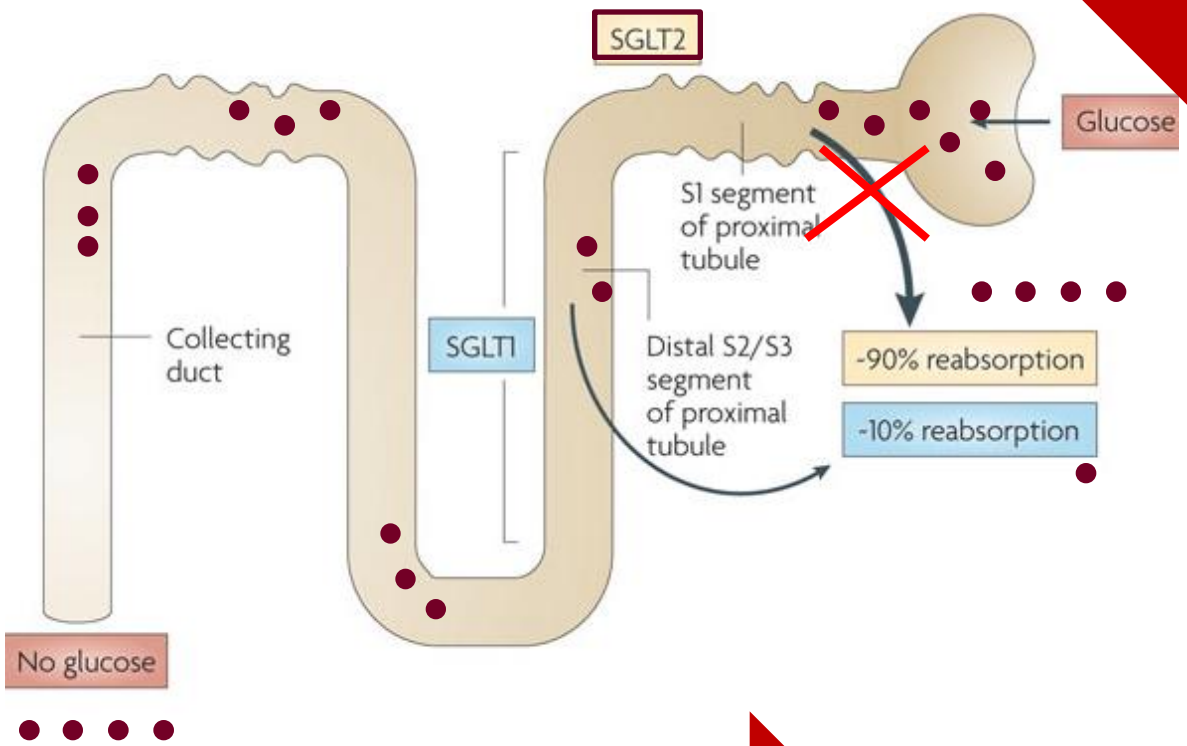
I si deixem triar als pacients?

Glucosúric?

i-SGLT-2 o “gliflozines”

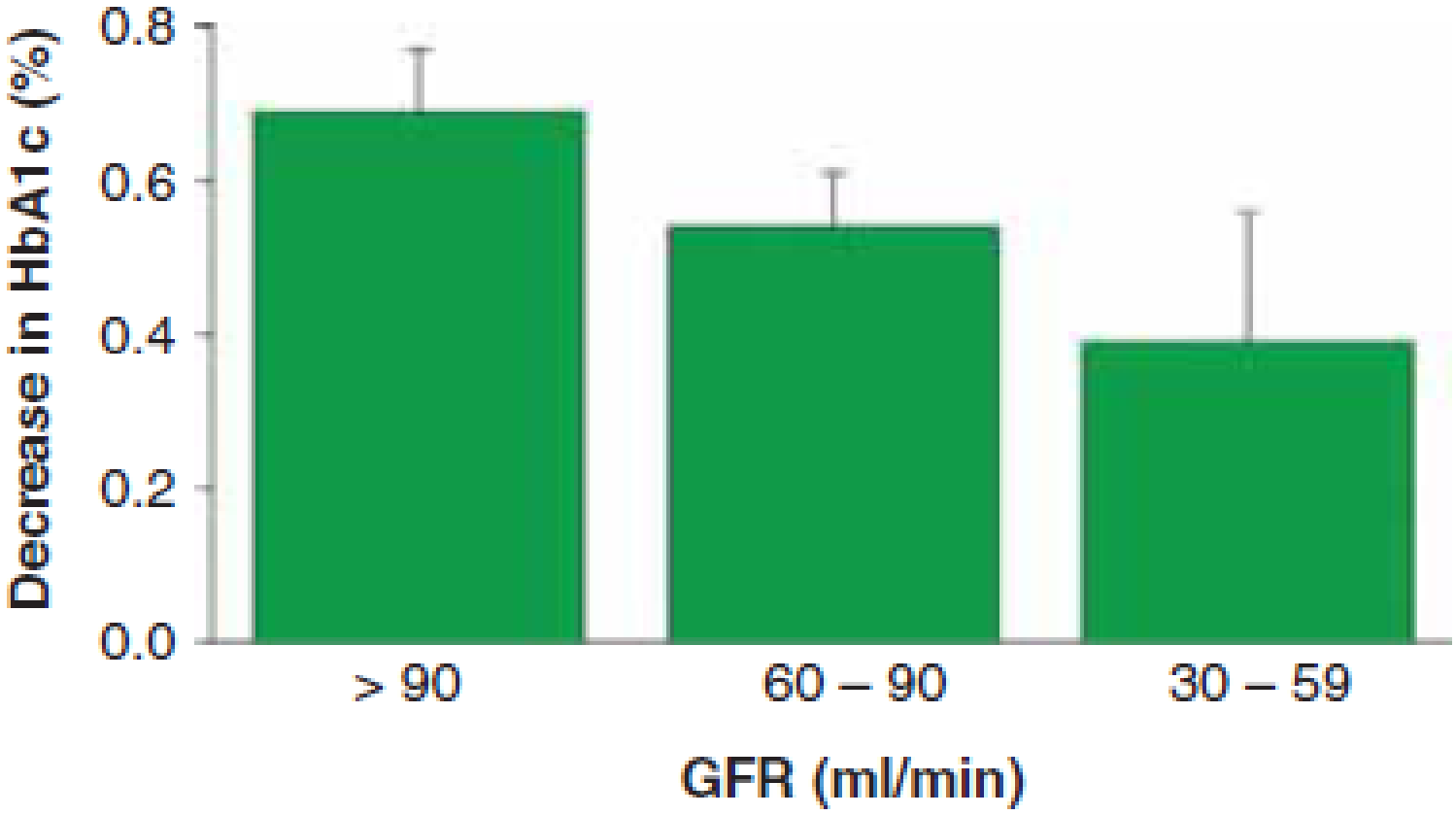
Dapagliflozina
Canagliflozina
Empagliflozina

Inhibició del SGLT-2



Glucosùria → **Diüresis osmòtica**

iSGLT-2: *Funció renal*



Control funció renal abans i al menys un cop a l'any

No iniciar tractament en FG <60

Abdul-Ghani MA.. Expert Opin. Pharmacother; 2013

i-SGLT2: *Llums i ombres*

⇩ PAS 2,6 - 6,1 mm Hg

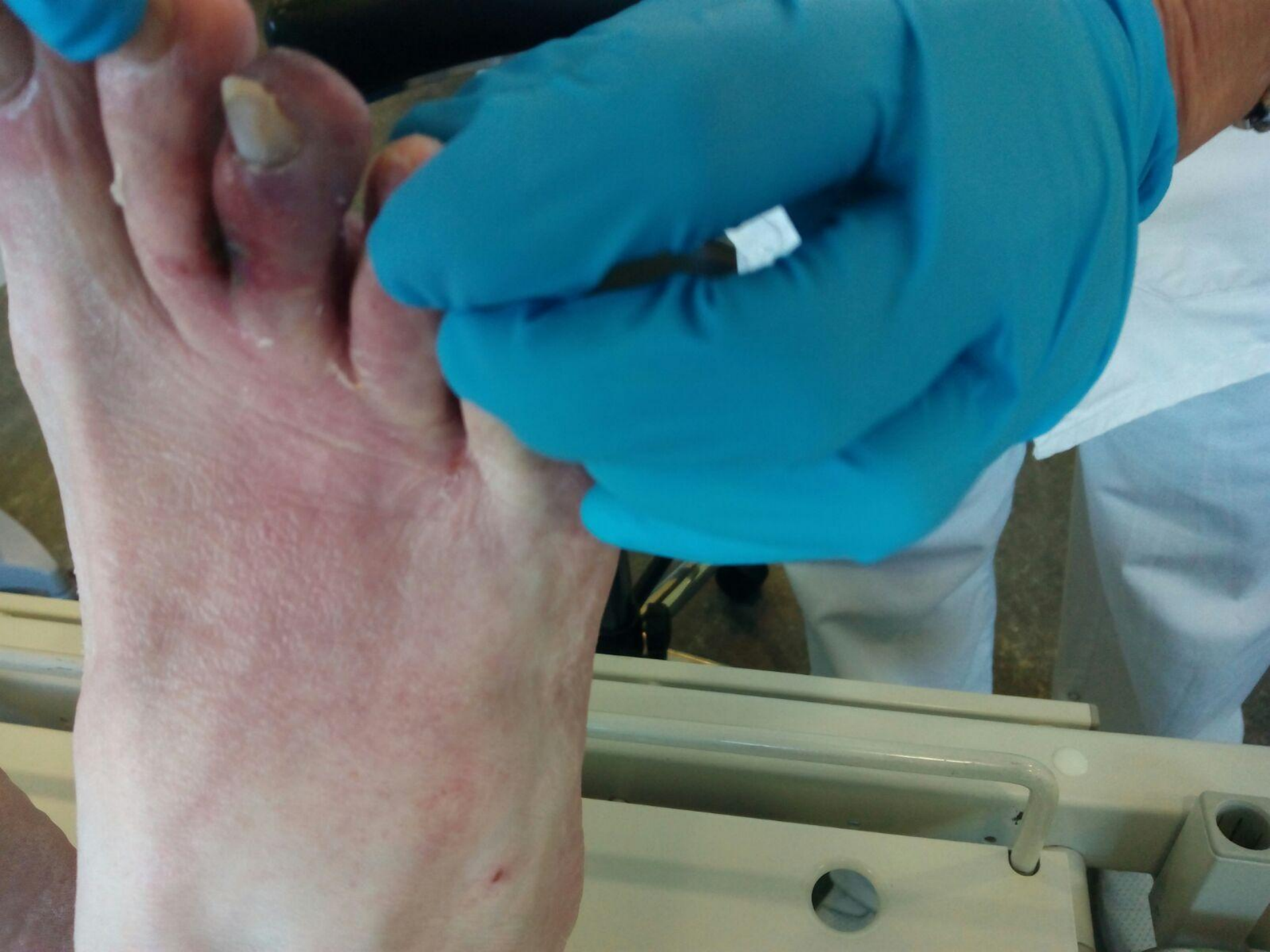
⇩ Hba1C 0,5-0,8%

⇩ 2-3 kg

⇧Infeccions Genitourinàries
NNH:5

⇧ cetoacidosis

⇧Fractures
NNH:286



i-SGLT2: *Llums i ombres*

⇩ PAS 2,6 - 6,1 mm Hg

⇩ Hba1C 0,5-0,8%

⇩ 2-3 kg

⇩ RCV ?

Cal FG>60

⇧Infeccions Genitourinàries
NNH:5

⇧Amputacions
NNH: 345

⇧ cetoacidosis

⇧Fractures
NNH:286

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

N Engl J Med 2007;356:2457-71.


4 mg
28

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

METHODS

The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

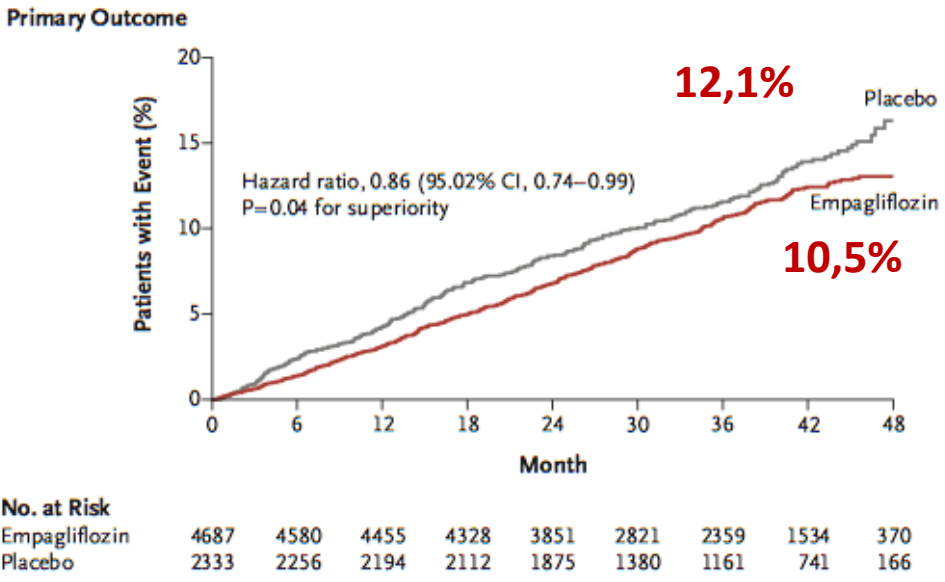
The mean age of the participants was 63.3 years, 35.8% were women, the mean duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). Although on the basis of the prespecified hypothesis testing sequence the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). Adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.


Empagliflozina
i canagliflozina
per a tothom!!


Ens ho mirem bé?

EMPA-REG OUTCOME

Seguretat CV empagliflozina



Reducció d'esdeveniments

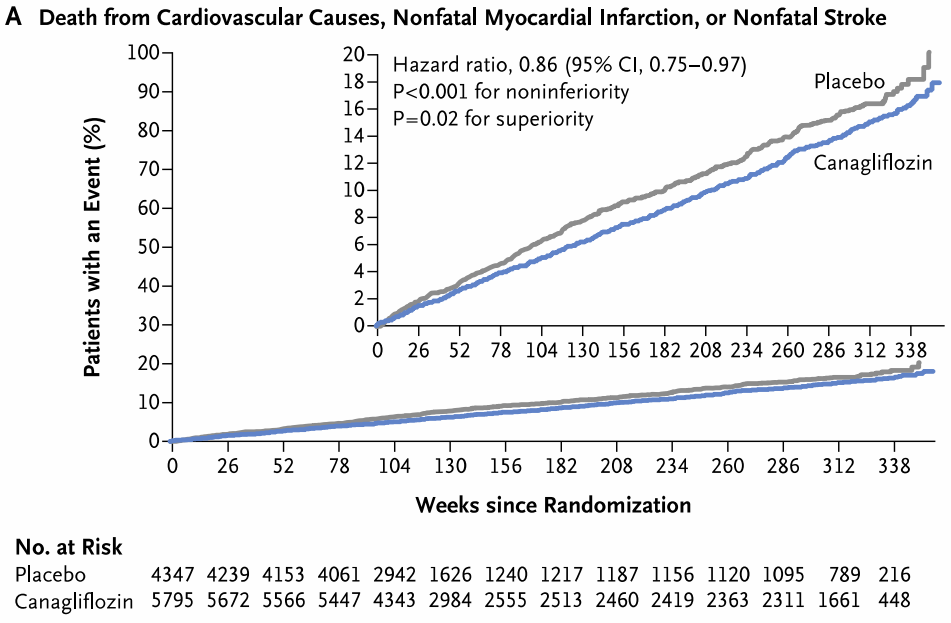
*(**mortalitat cv**, IM, ictus)*

NNT=62 als 3,1 anys

(31 a 2.152)

CANVAS:

Seguretat CV canagliflozina



Reducció d'esdeveniments

*(**mortalitat cv**, IM, ictus)*

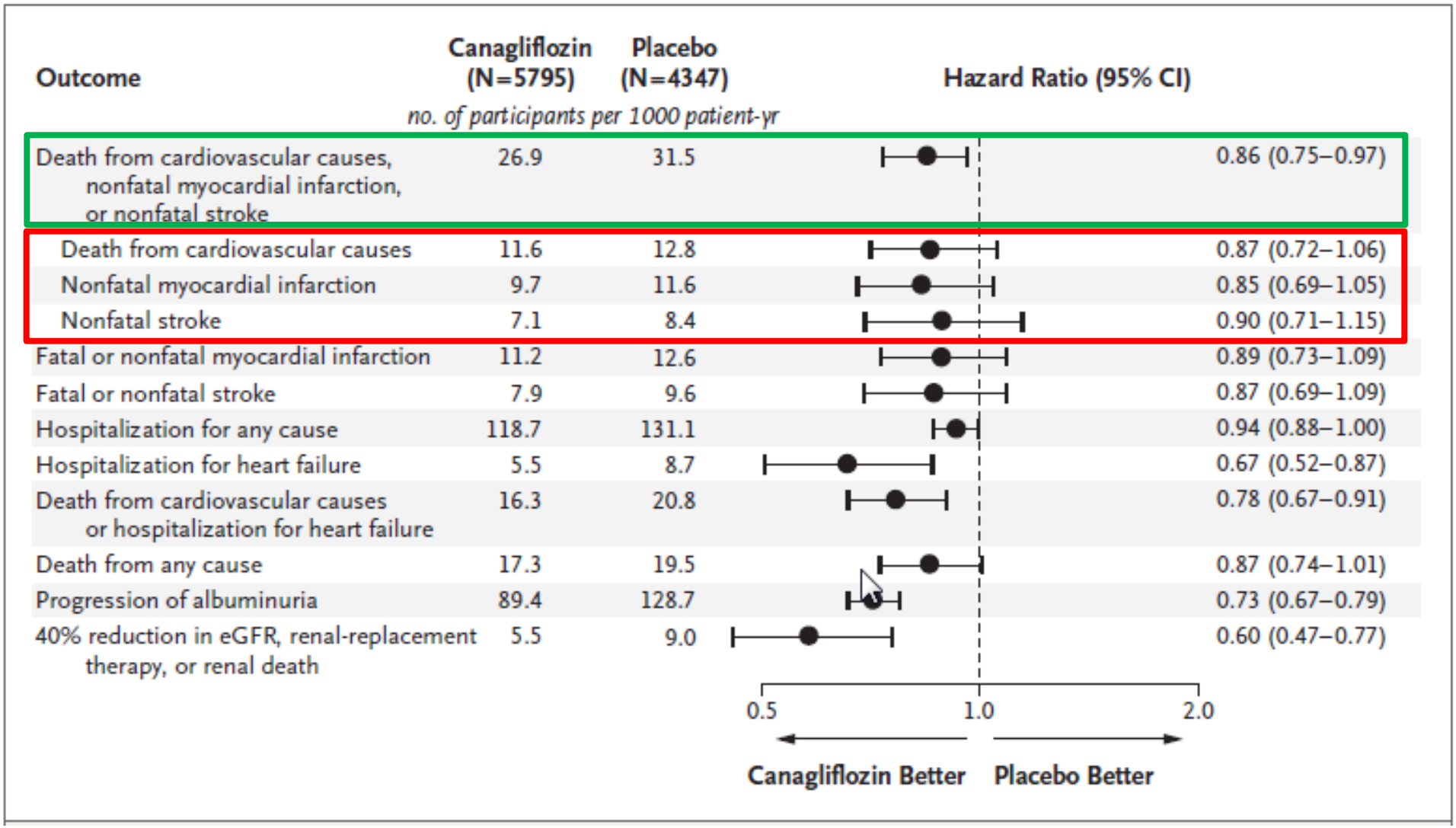
NNT=218 als 3,6 anys

	EMPAREG	CANVAS
Variable principal	Mortalitat CV + IAM no fatal + AVC no mortal	
Principi actiu	Empagliflozina	Canagliflozina
Pacients	7.020	10.142
RCV	PS	PP+PS
Promig durada (anys)	2,6	3,6
HR (IC 95%)	0,86 (0,74-0,99)	0,86 (0,75-0,97)
NNT	62 (31-2152)	218
RRA %	1,6	4,6

EMPA-REG

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

CANVAS


Outcome
Canagliflozin (N=5795)
Placebo (N=4347)
Hazard Ratio (95% CI)
no. of participants per 1000 patient-yr
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke 26.9 31.5 0.86 (0.75–0.97)
Death from cardiovascular causes 11.6 12.8 0.87 (0.72–1.06)
Nonfatal myocardial infarction 9.7 11.6 0.85 (0.69–1.05)
Nonfatal stroke 7.1 8.4 0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction 11.2 12.6 0.89 (0.73–1.09)
Fatal or nonfatal stroke 7.9 9.6 0.87 (0.69–1.09)
Hospitalization for any cause 118.7 131.1 0.94 (0.88–1.00)
Hospitalization for heart failure 5.5 8.7 0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure 16.3 20.8 0.78 (0.67–0.91)
Death from any cause 17.3 19.5 0.87 (0.74–1.01)
Progression of albuminuria 89.4 128.7 0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death 5.5 9.0 0.60 (0.47–0.77)
0.5
1.0
2.0
Canagliflozin Better
Placebo Better

Reflexió general d'elevada importància

Open Access Research

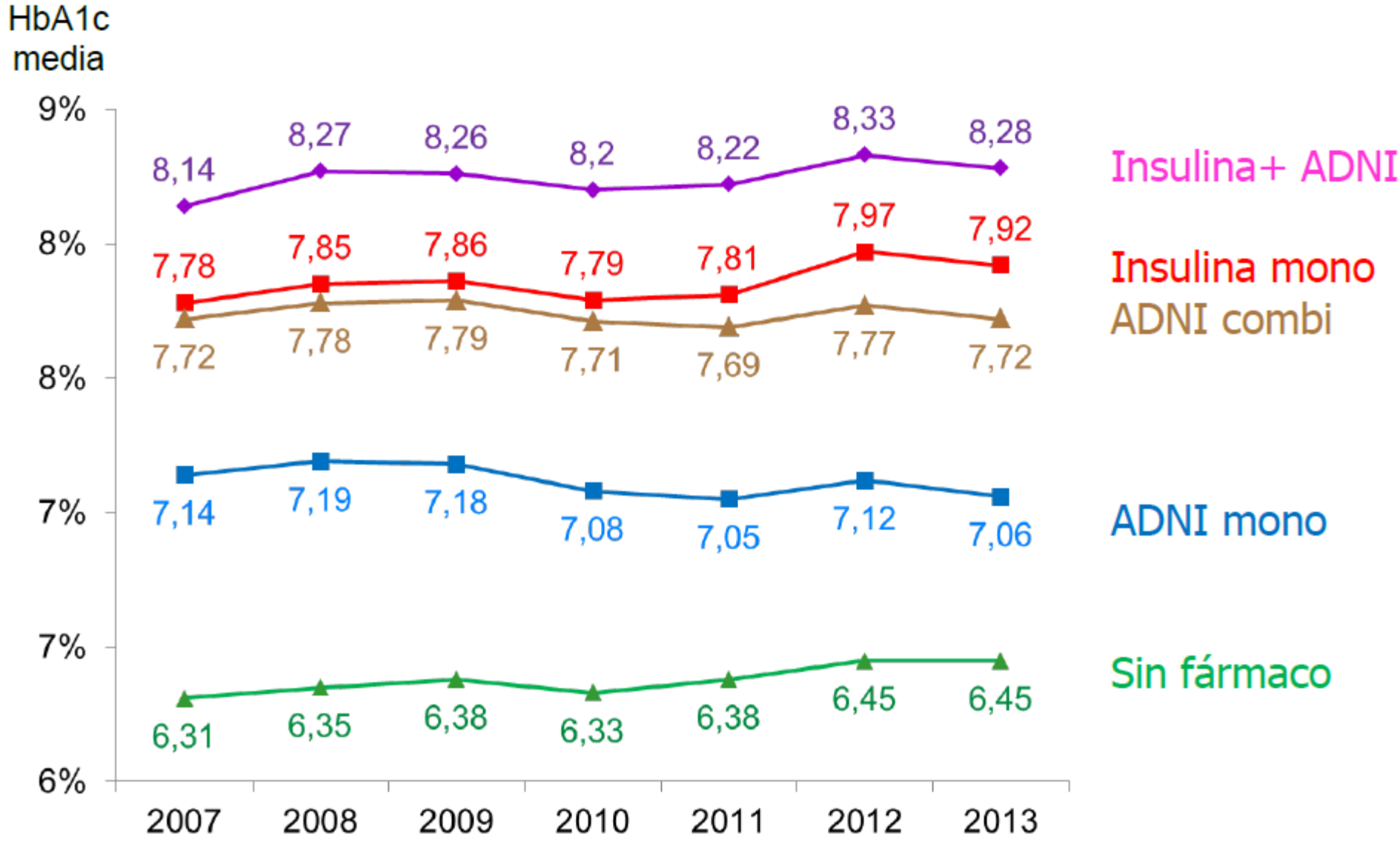
BMJ Open

Glycaemic control and antidiabetic treatment trends in primary care centres in patients with type 2 diabetes mellitus during 2007–2013 in Catalonia: a population-based study

Manel Mata-Cases,[1,2,3] Josep Franch-Nadal,[1,2,4] Jordi Real,[1,5] Dídac Mauricio[1,2,6]

BMJ Open 2016;6: e012463

Control HbA1c pràcticament constant

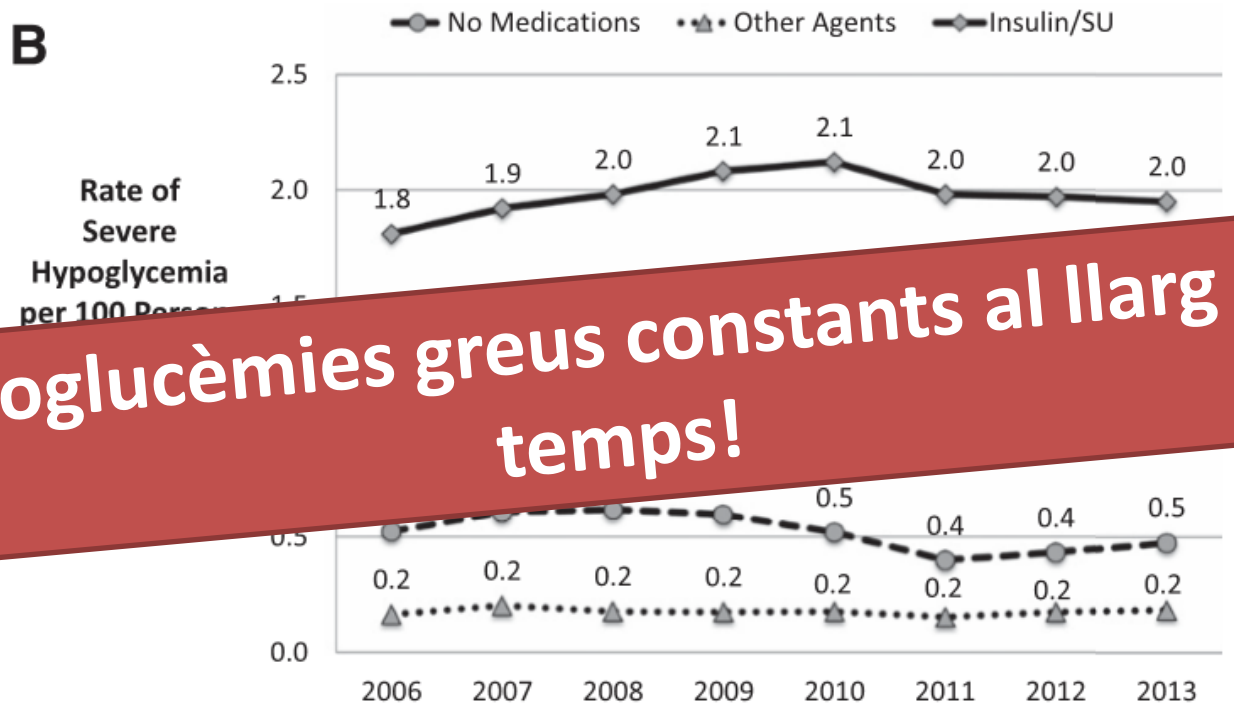


BMJ Open 2016;6: e012463

Trends in Drug Utilization, Glycemic Control, and Rates of Severe Hypoglycemia, 2006–2013

Kasia J. Lipska,[1] Xiaoxi Yao,[2,3] Jeph Herrin,[4] Rozalina G. McCoy,[2,3,5] Joseph S. Ross,[6,7] Michael A. Steinman,[8] Silvio E. Inzucchi,[1] Thomas M. Gill,[9] Harlan M. Krumholz,[4,7] and Nilay D. Shah[2,3,10]

DOI: 10.2337/dc16-0985



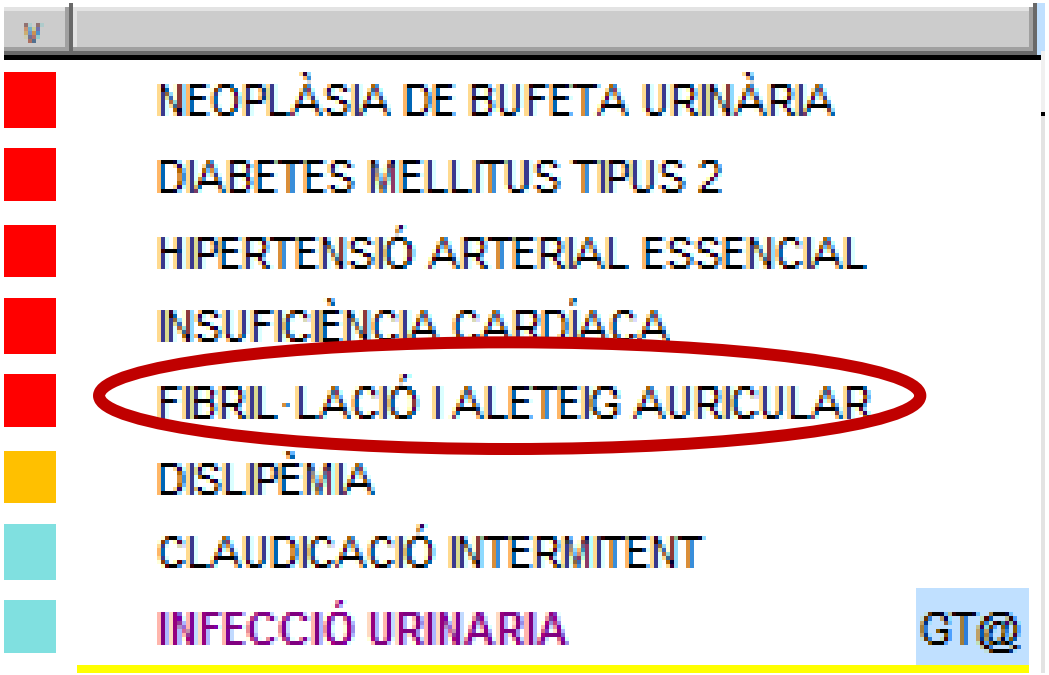
Hipoglucèmies greus constants al llarg del temps!

Figure 3—Age- and sex-standardized rate of severe hypoglycemia resulting in hospital admission, observation stay, or emergency department visit per 100 person-years, 2006–2013. *A*: Patients with T2DM who filled at least one glucose-lowering agent. *B*: Patients with T2DM who filled insulin or insulin secretagogues (diamonds), other glucose-lowering agents (triangles), and no glucose-lowering agents (circles). SU, sulfonylurea.


Time for CHANGE

Medicament	Principi Actiu	Posologia
BISOPROLOL COR SANDOZ 2,5MG 28 COMPRIMIDOS RECUBIERTOS PELICULA EFG	BISOPROLOL HEMIFUMARAT	1 x 24 h.
DIAMICRON 30MG 60 COMPRIMIDOSDE LIBERACION MODIFICADA	GLICLAZIDA	1 x 24 h.
ESPIRONOLACTONA ALTER 25MG 50COMP RECUB EFG	ESPIRONOLACTONA	1 x 24 h.
METFORMINA ALMUS 850MG 50 COMPRIMIDOS RECUBIERTOS PELICULA EFG	METFORMINA	1 x 12 h.
OMEPRAZOL ALMUS 20MG 56 CAPSULAS DURAS GASTRORRESISTENTES EFG	OMEPRAZOL	1 x 24 h.
PRAVASTATINA VIR 20 MG 28 COMPRIMIDOS EFG	PRAVASTATINA SODICA	1 x 24 h.
RAMIPRIL/HIDROCLOROTIAZIDA TECNIGEN 5/25MG 28 COMPRIMIDOS EFG	RAMIPRIL +DIURÈTIC	1 x 24 h.
SINTROM 4MG 20 COMPRIMIDOS	ACENOCUMAROL	1 x 24 h.

Arnau, 69 anys



Medicament	Principi Actiu	Posologia	Durada
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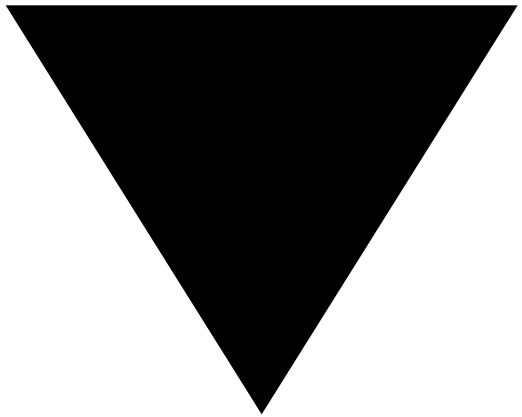
SINTROM 4MG 20 COMPRIMIDOS	ACENOCUMAROL	1 x 24 h.	Indefinida

NACO o DACO



Estudis de vida real

Aspectes de maneig pràctic

Nou principi actiu

4t NACO comercialitzat

Inhibidor del factor Xa

Dosi: 60 mg/dia

30 mg/dia:
FG: 15 - 50
Pes <60 Kg
Ciclosporina
Dronedarona
Eritromicina
Ketoconazol

Eficàcia similar a warfarina

Menys hemorràgies??

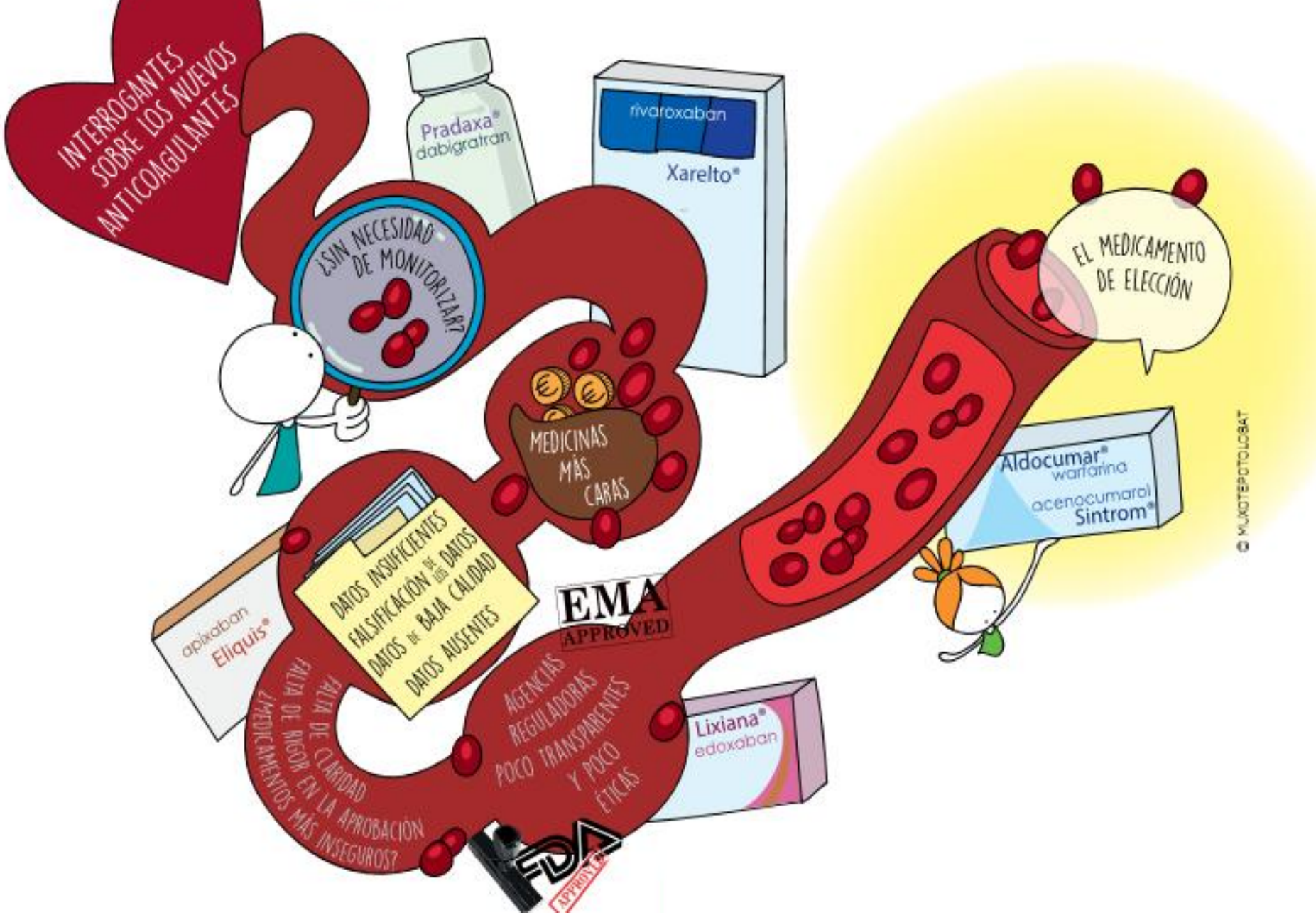
Indicat en ACxFA

No en prevenció de TEV en prótesis

No finançat: tractament TVP i TEP

NOTHING NEW

Estudis de vida real



BIT Navarra. 2016 vol 24, núm 1
www.bit.navarra.es

- Marketing: no necessitat de controls analítics
- Realitat:
  - Gran variabilitat interindividual
  - Monitorar redueix les complicacions greus sense afectar l'eficàcia
  - Concentració plasmàtica del fàrmac: es coneixen els llindars de seguretat!!
  - Dabigatran de 40ng/mL – 200ng/ML es més segur

thebmj

BMJ 2016;354:i5131 doi: 10.1136/bmj.i5131 (Published 28 September 2016)

FEATURE

INVESTIGATION

Manufacturer failed to disclose faulty device in rivaroxaban trial

An investigation by The BMJ finds that companies were aware of concerns about a faulty device in a regulatory trial and reveals data that suggests participants were put at unnecessary risk. **Deborah Cohen** reports

Deborah Cohen *associate editor, The BMJ, London, UK*

NON-INTERVENTIONAL STUDY REPORT

Title	**Apixaban drug utilization study in stroke prevention in atrial fibrillation (SPAF)**
Protocol number	B0661076
AEMPS Code	PFI-API-2016-01
Version identifier of the final study report	**1.0**
Date of last version of the final study report	**8 March 2017**

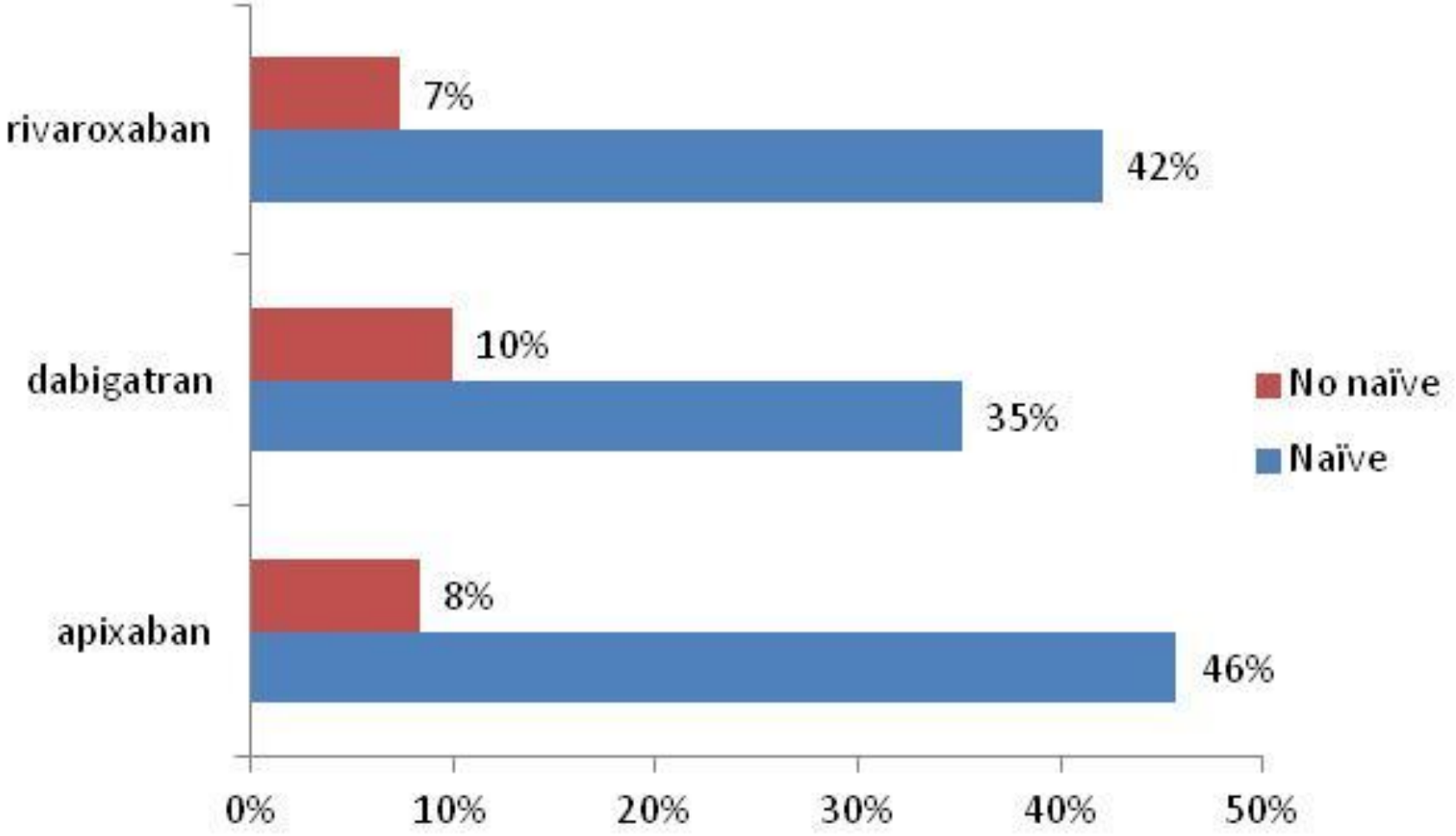
4.1 Study design

This DUS is a retrospective, observational, cohort study. DOAC and VKA users have been identified in the primary health care database SIDIAP (Information System for the Improvement of Research in Primary Care) in Catalonia, Spain.

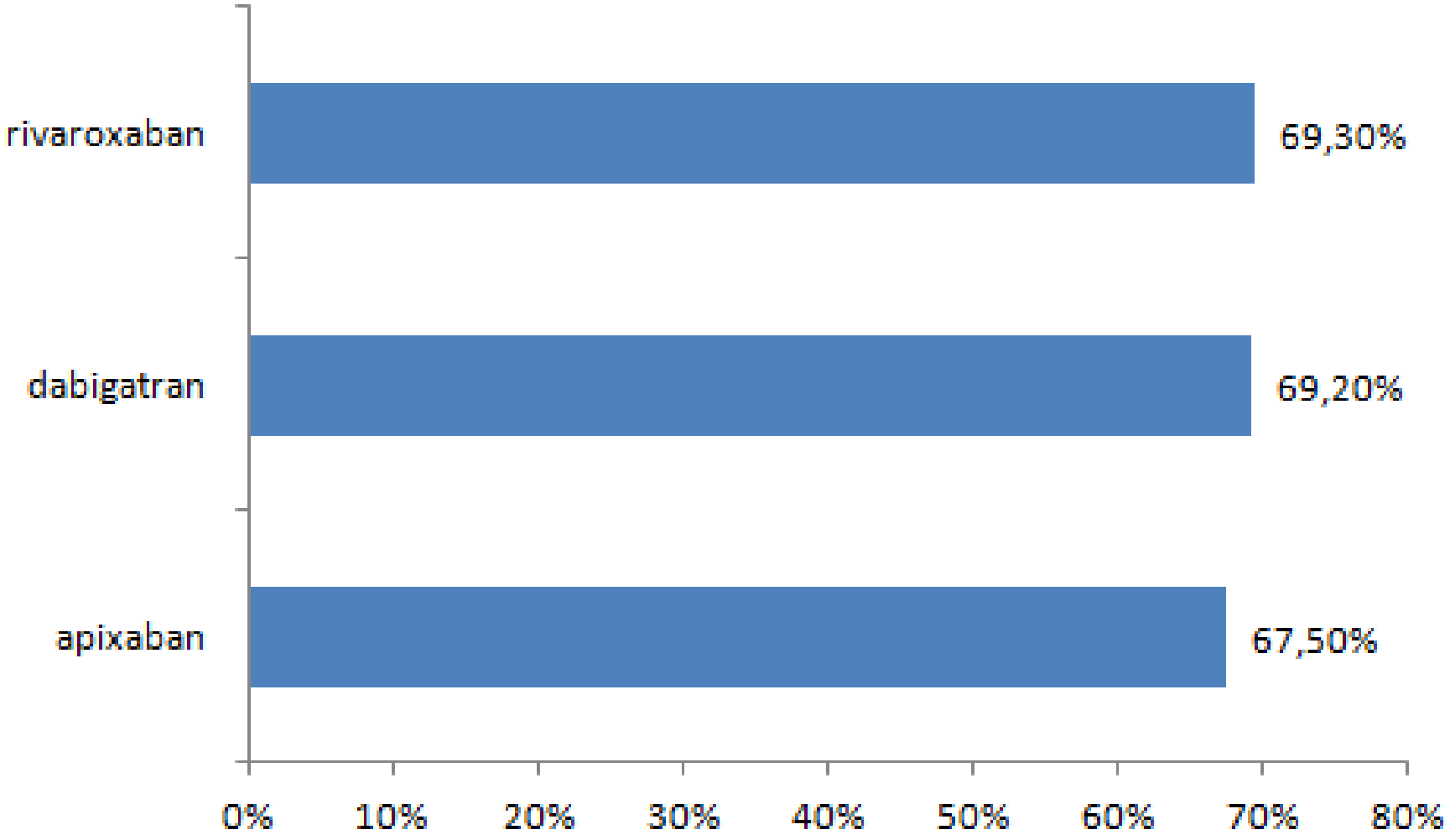
Agost 2013 to December 2014

http://www.encepp.eu/encepp/openAttachment/studyResult/18160

Entre un 35-42% dels pacients “Naive” NO recullen el NACO durant primer mes



I a l'any?


rivaroxaban
69,30%
dabigatran
69,20%
apixaban
67,50%
0%
10%
20%
30%
40%
50%
60%
70%
80%

a. USA Today. http://www.usatoday.com/news/health/2007-03-28-taking-medicine_N.htm

Es prescriu la dosis adequada?

Un 15,5% dels pacients pren la dosi de 5mg i hauria de prendre la de 2,5 mg

Un 27,9% dels pacients pren la dosi de 2,5mg i hauria de prendre la de 5 mg

JAMA Internal Medicine | Original Investigation

Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Ya-Hui Hsueh, PhD; Rima Izem, PhD; Mary Ross Southworth, PharmD; Yuqin Wei, MS; Jiemin Liao, MA; Margie R. Goulding, PhD; Katrina Mott, MHS; Yoganand Chillarige, MPA; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

CONCLUSIONS: El tractament amb rivaroxaban 20mg/dia es va associar amb un increment estadìsticament significatiu de les HIC i sagnat major extracraneal, incloent sagnat major gastrointestinal, comparat amb dabigatran 150mg/12h.

JAMAInternMed.2016;176(11):1662-1671.doi:10.1001/jamainternmed.2016.5954
PublishedonlineOctober3,2016.CorrectedonOctober17,2016.

Estudis de vida real

Aspectes de maneig pràctic

Nou principi actiu

Europace (2015) 17, 1467–1507

Europace
doi:10.1093/europace/euv309

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Advisors:, Azhar Ahmad, M.D. (Boehringer Ingelheim Pharma), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim Pharma), Susanne Hess, M.D. (Bayer Healthcare Pharmaceuticals), Markus Müller, M.D., Ph.D. (Pfizer Pharma), Felix Münzel, Ph.D. (Daiichi-Sankyo Europe), Markus Schwertfeger, M.D. (Daiichi-Sankyo Europe), Martin Van Eickels, M.D. (Bayer Healthcare Pharmaceuticals), and Isabelle Richard-Lordereau, M.D. (Bristol Myers Squibb/Pfizer)

Document reviewers:, Gregory Y.H. Lip, (Reviewer Coordinator; UK), Chern-En Chiang, (Taiwan), Jonathan Piccini, (USA), Tatjana Potpara, (Serbia), Laurent Fauchier, (France), Deirdre Lane, (UK), Alvaro Avezum, (Brazil), Torben Bjerregaard Larsen, (Denmark), Guiseppe Boriani, (Italy), Vanessa Roldan-Schilling, (Spain), Bulent Gorenek, (Turkey), and Irene Savelieva, (UK, on behalf of EP-Europace)

[1]Department of Cardiology – Arrhythmology, Hasselt University and Heart Center, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium; [2]Department of Cardiovascular Sciences, University of Leuven, Belgium; [3]Department of Cardiology, Amphia Ziekenhuis, Breda, Netherlands; [4]Department of Cardiology, Klinikum Oldenburg, Oldenburg, Germany; [5]Department of Neurology, University Hospital Essen, University Duisburg-Essen, Germany; [6]Department of Neurology, Ruprecht Karls Universität, Heidelberg, Germany; [7]Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [8]Clinical Cardiology, St George's University, London, UK; [9]University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK; and [10]Department of Cardiology and Angiology, University of Münster, Germany

The current manuscript is an update of the original Practical Guide, published in June 2013[Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, *et al.* European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;15:625–51; Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, *et al.* EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013;34:2094–106]. Non-vitamin K antagonist oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial fibrillation (AF). Both physicians and patients have to learn how to use these drugs effectively and safely in clinical practice. Many unresolved questions on how to optimally use these drugs in specific clinical situations remain. The European Heart Rhythm Association set out to coordinate a unified way of informing physicians on the use of the different NOACs. A writing group defined what needs to be considered as 'non-valvular AF' and listed 15 topics of concrete clinical scenarios for which practical answers were formulated, based on available evidence. The 15 topics are (i) practical start-up and follow-up scheme for patients on NOACs; (ii) how to measure the anticoagulant effect of

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- Interaccions
- Switching
- Adherència
- Errors dosificació
- IRC
- Intervencions quirúrgiques
- Sagnats
- …

Europace (2015) 17, 1467–1507

Què fer davant una IQ programada?

Risc de sagnat de l'IQ?

Principi actiu?

Funció renal?

Table 11 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of one to three teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)
Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
Non-coronary angiography (for coronary angiography and ACS: see 'Patient with atrial fibrillation and coronary artery disease' section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with major bleeding risk (i.e. frequent and/or with high impact)
Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with major bleeding risk AND increased thrombo-embolic risk[a]
Complex left-sided ablation (PVI; some VT ablations)

Europace (2015) 17, 1467–1507

No cal teràpia pont amb heparines!!

Table 3 **Last intake of drug before elective surgical intervention**

	Dabigatran		Apixaban–Edoxaban–Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl <15 mL/min	No official indication for use			
	There is no need for pre-operative bridging with LMWH/UFH			

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clinical impact.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

European Heart Journal Advance Access published June 14, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw058

Interaccions

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[$] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect[$] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SmPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[$$] (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[251]	No data yet	No effect	No effect[252]
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[238]	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	Up to minus 50%
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[247]

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[SmPC]	minus 35%	Up to minus 50%
Other factors:					
Age ≥ 80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	
Weight ≤ 60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Europace (2015) 17, 1467–1507

Antídots

Antidote	Data available for	Ex vivo	Animal	Phase 1 & 2 trials*	Phase 3	References	ClinicalTrials.gov numbers
andexanet alpha, PRT064445	apixaban	+	+	+#	+	21,25,27,29#	NCT02207725 NCT02220725 NCT02329327
	betrixaban	+	+	+	+	21,25	
	rivaroxaban	+	+	+	+	21,23,24,26	
	edoxaban	n.d.	n.d.	+	+	27	
	fondaparinux	+	+	n.d.	+	21	
	enoxaparin	+	+	+	+	21,25	
idarucizumab	dabigatran	+	+	+	+	32–39	NCT02028780 NCT02104947
modified thrombin (γT -S195A-IIa)	dabigatran	+	+	n.d.	n.d.	22	
aripazine (PER977)	apixaban	+	+	n.d.	n.d.	48,49,50,51	NCT02206100 NCT02205905 NCT01826266 NCT02207257 NCT02206087
	rivaroxaban	+	+	n.d.	n.d.	23,48,50,51	
	edoxaban	+	+	+	n.d.	49,50,51,52	
	enoxaparin	+	+	n.d.	n.d.	49,50	
	dabigatran	+	+	n.d.	n.d.	48,51	
	heparin	n.d.	n.d.	planned	n.d.	n.d.	

*as these antidotes are all tested in volunteers in whom real bleeding studies are not possible, the differentiation between phase 1 and 2 studies is difficult. # this trial is named phase 3 trial but it enrolls elderly volunteers and measures surrogate markers and not the efficacy of the antidote in patients with acute bleeding or acute invasive interventions. n.d.: no data available; planned: study does not recruit patients; +: completed or ongoing studies.

Idarucizumab (Praxbind®)

Antídot específic per a dabigatran

1.700€

Idarucizumab (Praxbind®)

< 12 h

+

Cirurgia emergent que no es pugui demorar més de 8 hores.
i TTPa 1'5 vegades superior al normal

o

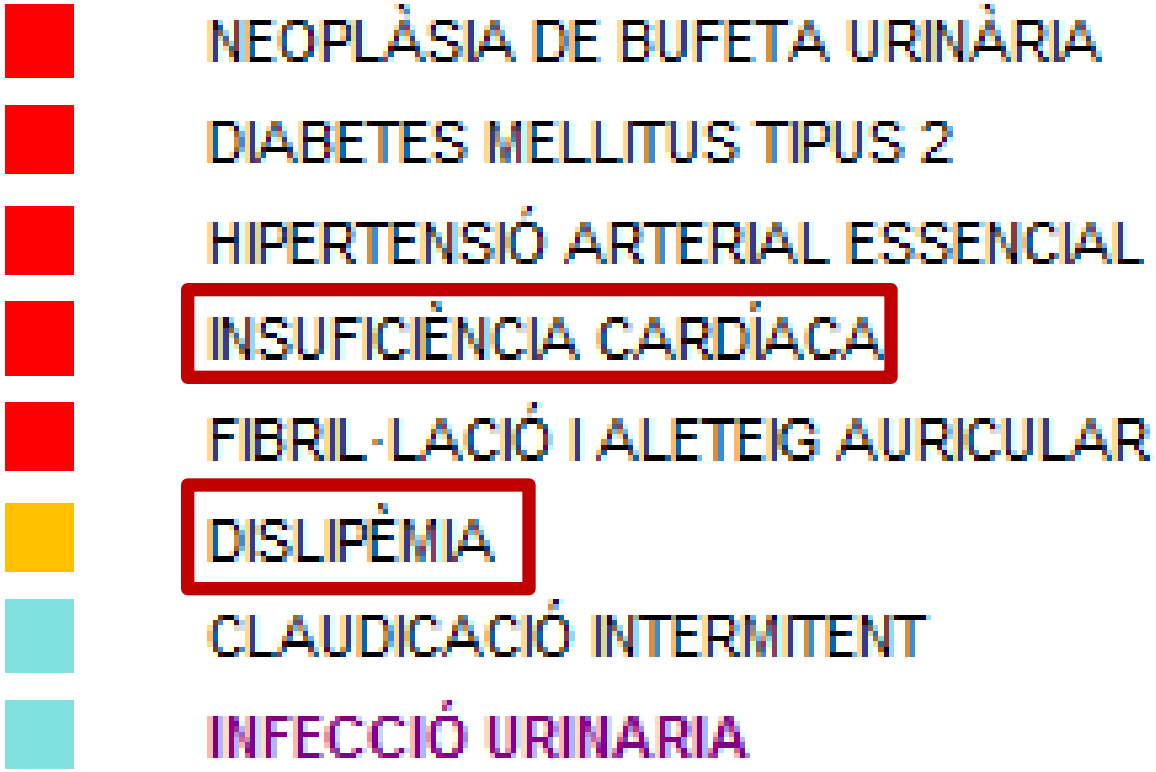
Hemorràgia amb risc vital que no hagi respòst a les mesures de reanimació inicials.

Idarucizumab (Praxbind®)

- Resultats d'eficàcia i seguretat
  - 3 estudis fase I: voluntaris sans
  - 1 estudi fase III: anàlisi intermèdia d'un estudi obert, no controlat (REVERSE-AD) (n=123).
- Eficàcia quantificada mediant proves de coagulació.
- Es desconeix la seva contribució a la reducció de la morbimortalitat.


Time for CHANGE

Medicament	Principi Actiu	Posologia	Durada
BISOPROLOL COR SANDOZ 2,5MG 28 COMPRIMIDOS RECUBIERTOS PELICULA EFG	BISOPROLOL HEMIFUMARAT	1 x 24 h.	Indefinida
DIAMICRON 30MG 60 COMPRIMIDOSDE LIBERACION MODIFICADA	GLICLAZIDA	1 x 24 h.	Indefinida
ESPIRONOLACTONA ALTER 25MG 50COMP RECUB EFG	ESPIRONOLACTONA	1 x 24 h.	Indefinida
METFORMINA ALMUS 850MG 50 COMPRIMIDOS RECUBIERTOS PELICULA EFG	METFORMINA	1 x 12 h.	Indefinida
OMEPRAZOL ALMUS 20MG 56 CAPSULAS DURAS GASTRORRESISTENTES EFG	OMEPRAZOL	1 x 24 h.	Indefinida
PRAVASTATINA VIR 20 MG 28 COMPRIMIDOS EFG	PRAVASTATINA SODICA	1 x 24 h.	Indefinida
RAMIPRIL/HIDROCLOROTIAZIDA TECNIGEN 5/25MG 28 COMPRIMIDOS EFG	RAMIPRIL +DIURÈTIC	1 x 24 h.	Indefinida
SINTROM 4MG 20 COMPRIMIDOS	ACENOCUMAROL	1 x 24 h.	Indefinida


NEOPLÀSIA DE BUFETA URINÀRIA
DIABETES MELLITUS TIPUS 2
HIPERTENSIÓ ARTERIAL ESSENCIAL
INSUFICIÈNCIA CARDÍACA
FIBRIL·LACIÓ I ALETEIG AURICULAR
DISLIPÈMIA
CLAUDICACIÓ INTERMITENT
INFECCIÓ URINARIA

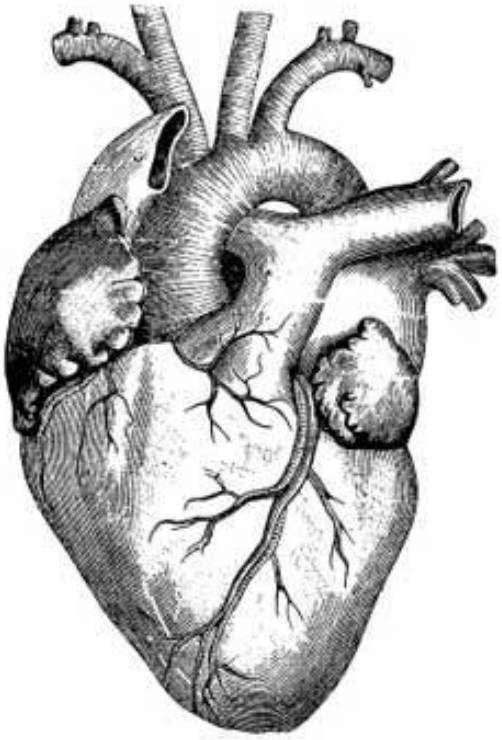
1 de cada 3 nous medicaments aprovats presenta problemes de seguretat

JAMA. 2017;317(18):1854-1863

Seguretat dels nous medicaments

- 222 medicaments a EEUU 2000-10
- 4,2 anys en aparèixer reaccions
- 3 retirades de medicaments
- Medicaments més implicats
  - Salut mental
  - **Aprovats *fast track***
  - **Biològics**

JAMA. 2017;317(18):1854-1863

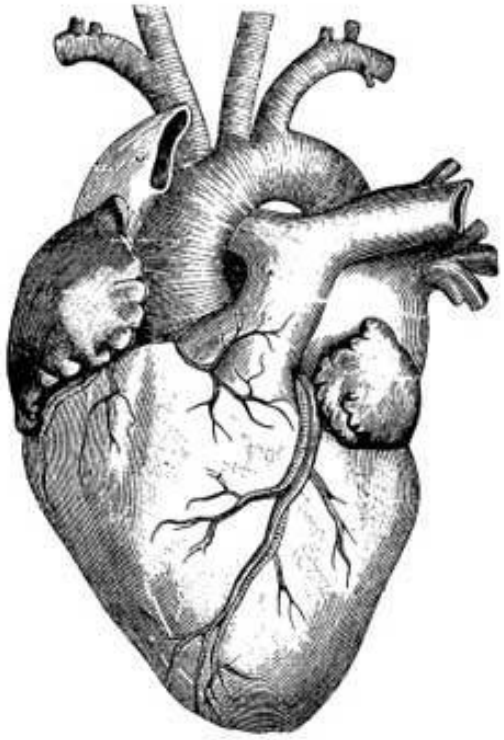


Insuficiència cardíaca crònica

ARNi: Sacubitril-Valsartan

Hipolipemiants

iPCSK9: Alirocumab i evolocumab



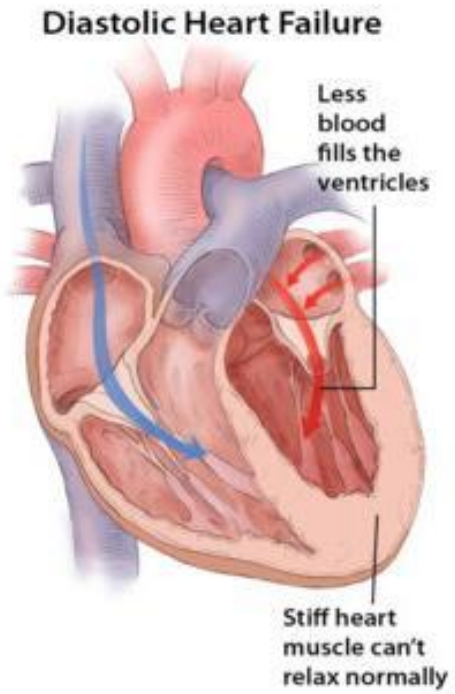
Insuficiència cardíaca crònica

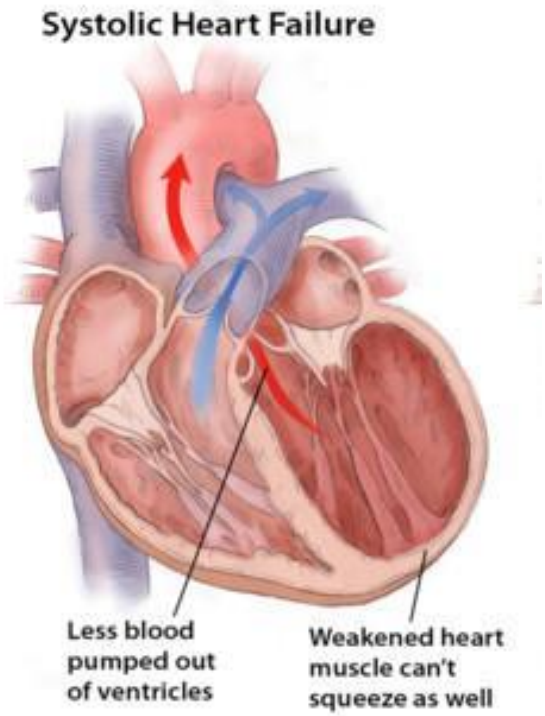
ARNi: Sacubitril-Valsartan

Hipolipemiants

iPSCK9: Alirocumab i evolocumab

Tractament de la ICC





IC diastòlica

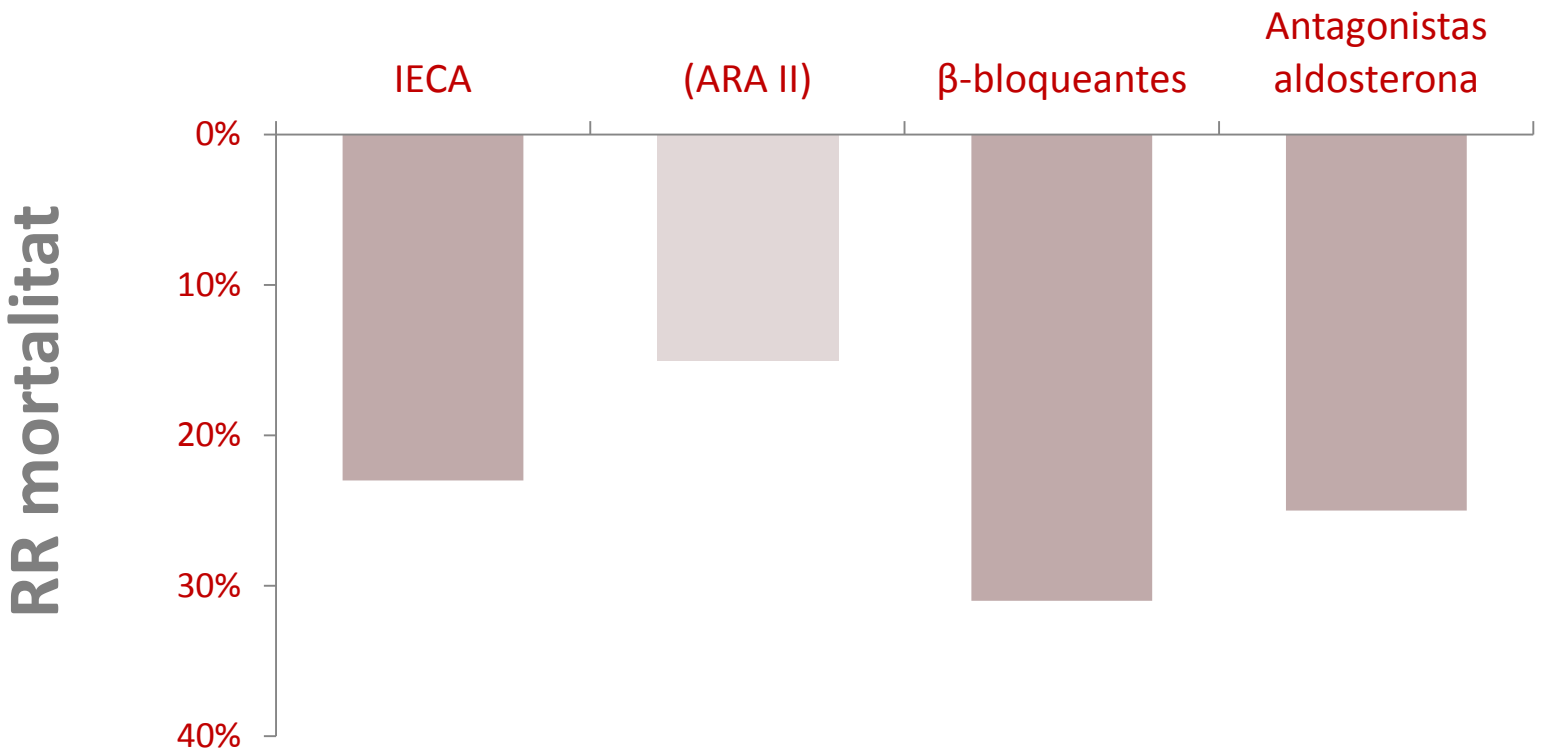
FEVI preservada

NO hi ha evidència ↓ mortalitat amb cap tractament

IC sistòlica

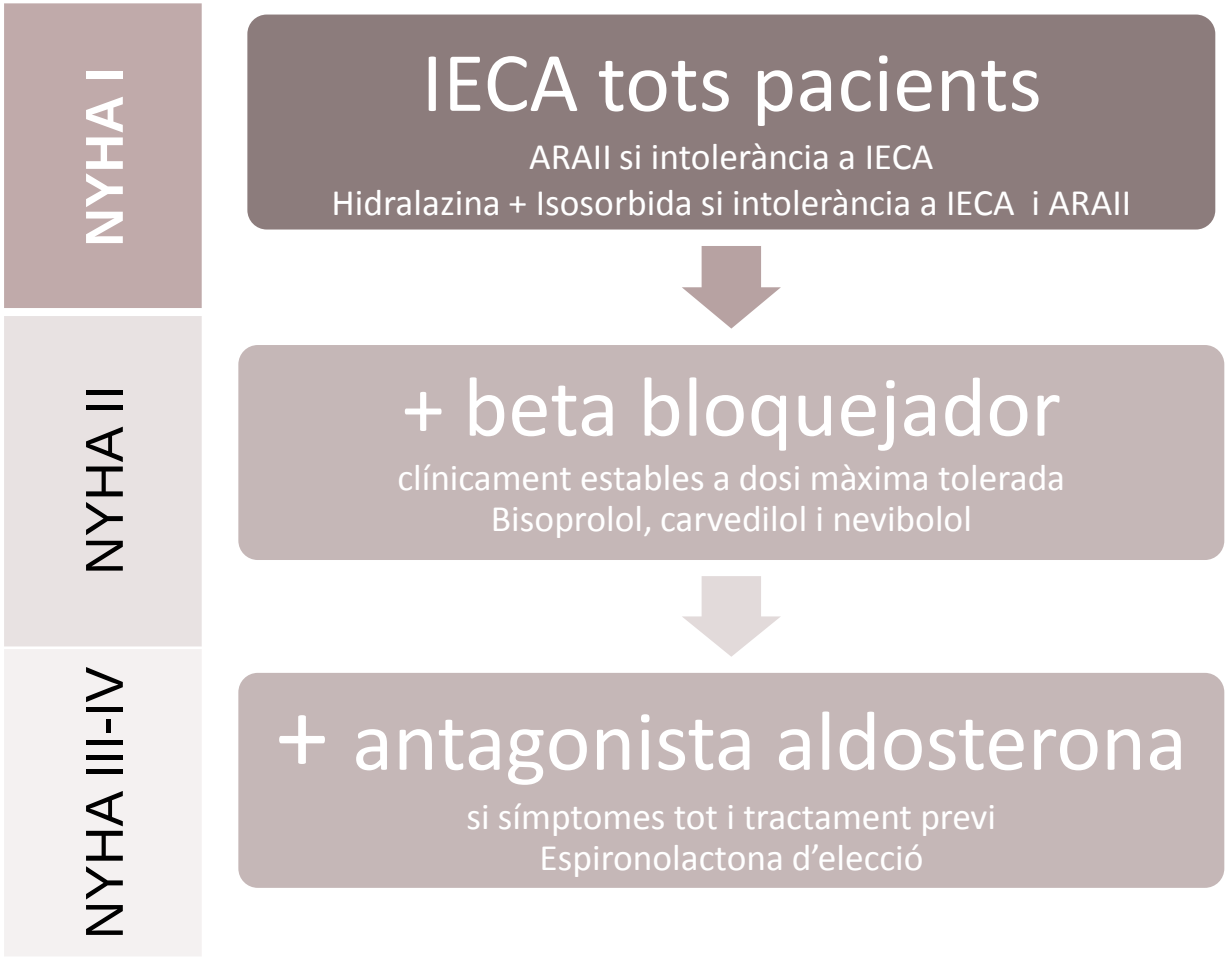
FEVI <40% o reduïda

Reducció mortalitat en IC-FEr



Font: UpToDate 2016

Tractament de la IC-FEr



+ diürètic

Si congestió i retenció hidrosalina

1ª causa ingrès >65 anys i 50% mortalitat als 5 anys

Pautes per l'harmonització del tractament farmacològic de la ICC. 2013

Sacubitril-Valsartan (Entresto®)

Indicació

- Tractament de la IC FEVI reduida

Dosi

- Iniciar amb dosi 100mg/bd i a les 2-4 setmanes pujar a la dosi màxima.

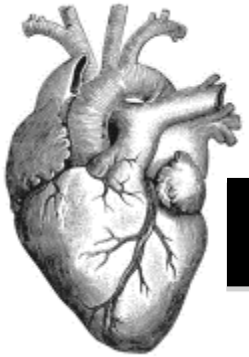
Equivalència

- Valsartan en Entresto + biodisponible que valsartan en monoteràpia
  - 97/**103mg** = 160mg
  - 49/**51mg** = 80 mg
  - 24/**26mg** = 40mg

Resposta beneficiosa

Pèptids Natriurètics

Sistema PN



Sistema RAA

Resposta fisiopatològica

Angiotensina II

Mecanisme dual SPN-RAAS

Ne[illegible]isina **Sacubitril**

Fragments inactius

Valsartan

Receptor AT_1

Vasodilatació
↑Natriurèsi
↑ Diurèsis

Vasoconstricció
↑ Retenció Na+
↑ fibrosi
↑ hipertròfia vent.

Omapatrilato
(inhibidor ECA+NEP) No comercialitzado per risc d'**angioedema**

The NEW ENGLAND JOURNAL of MEDICINE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Sc... D.,

PARADIGM-HF

BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed

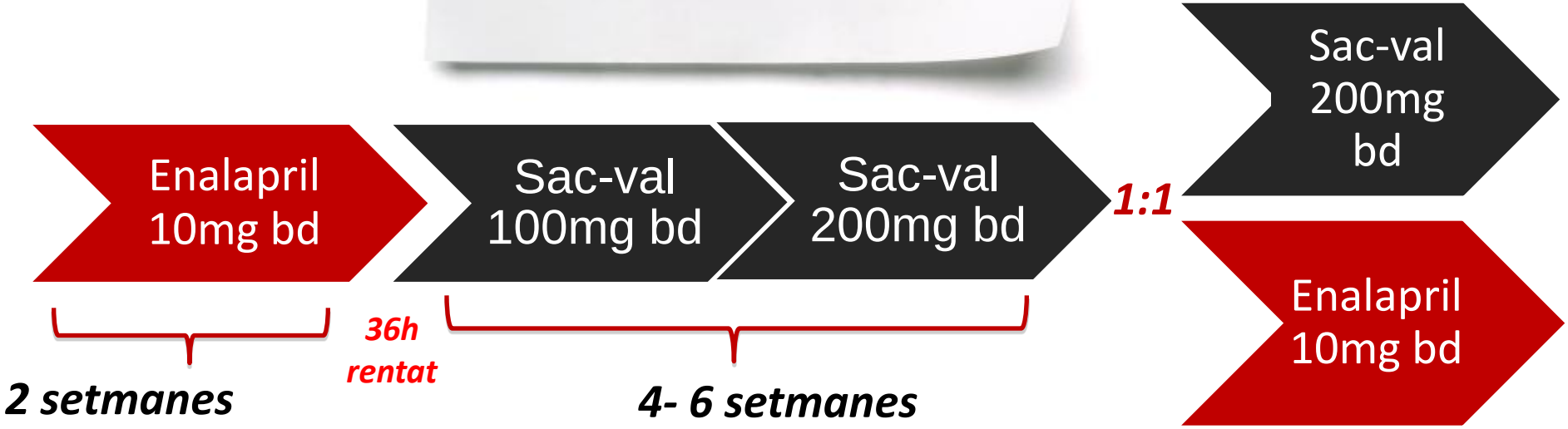
From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceutical, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg,

Disseny PARADIGM-HF

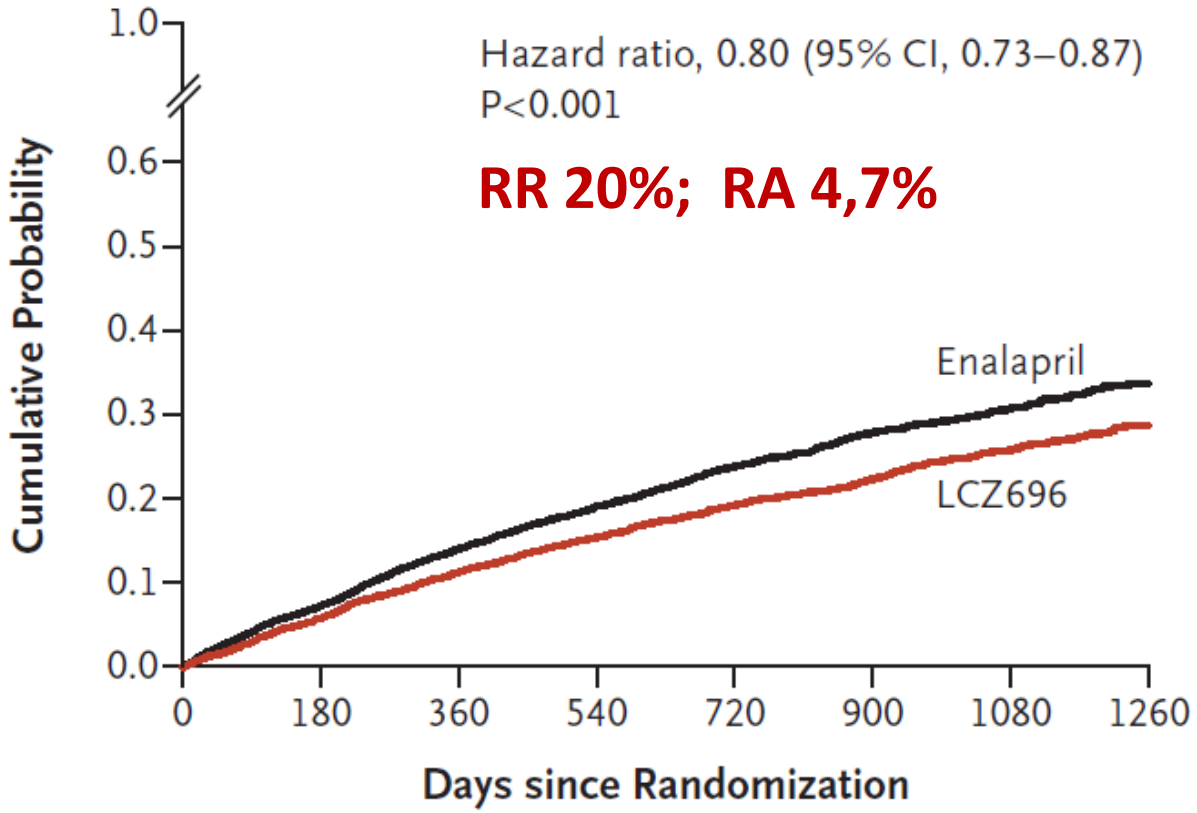
Run-in

20% *abandonament,* ***12%*** *x RA*

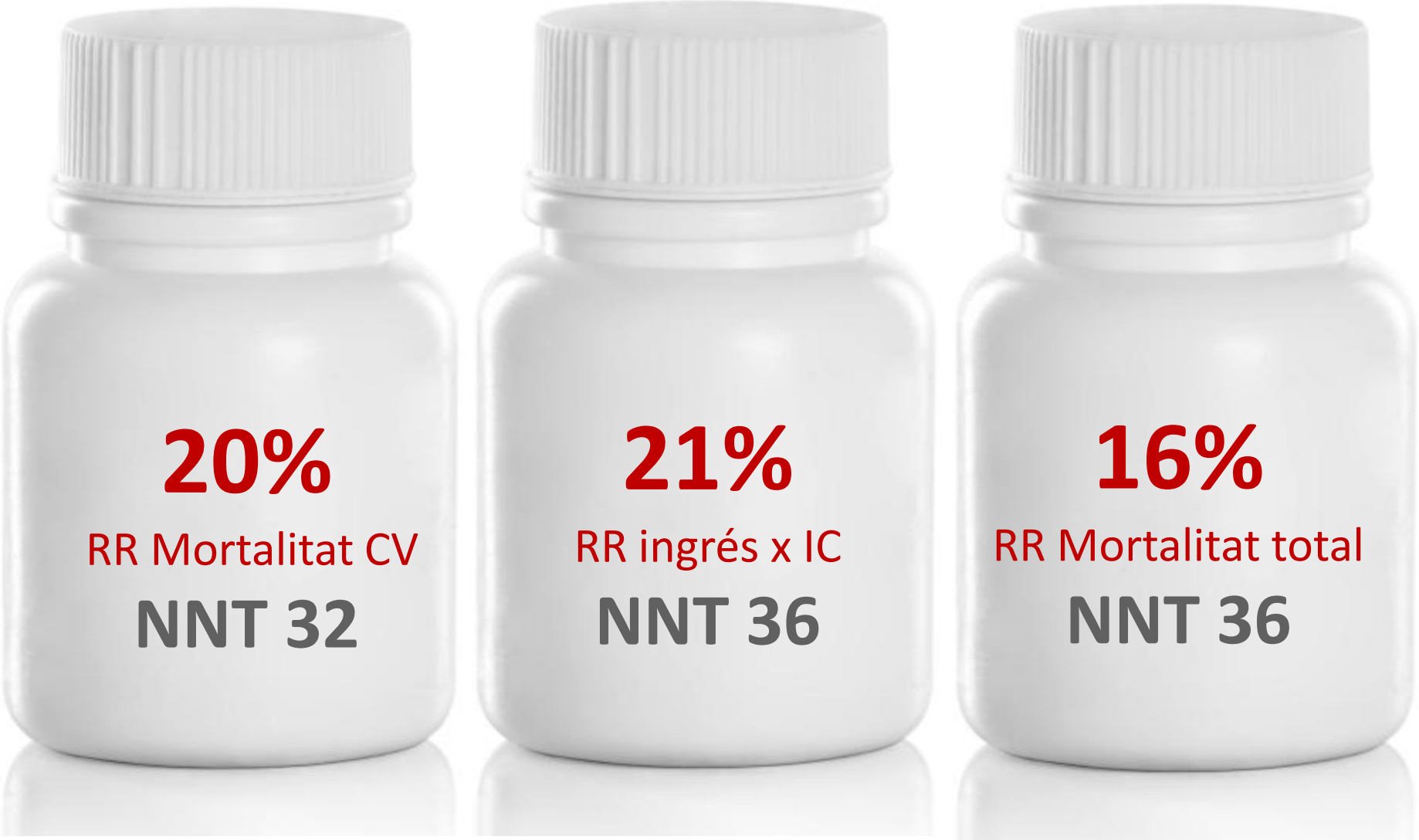
selecció *població*



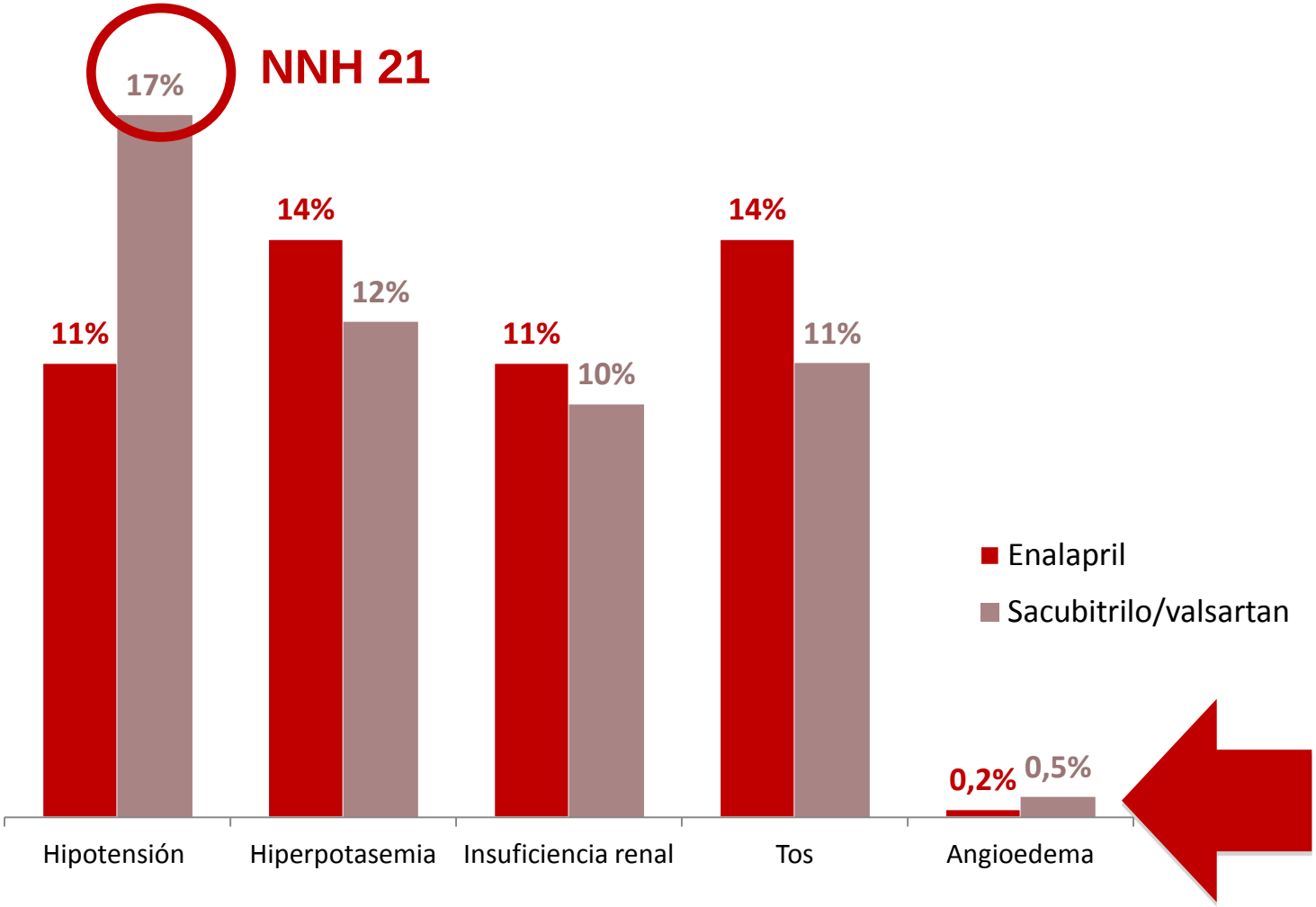
Resultats d'eficàcia



NNT 21 *per evitar una mort CV o ingrés per IC (27 meses)*


20%
RR Mortalitat CV
NNT 32
21%
RR ingrés x IC
NNT 36
16%
RR Mortalitat total
NNT 36

Seguretat

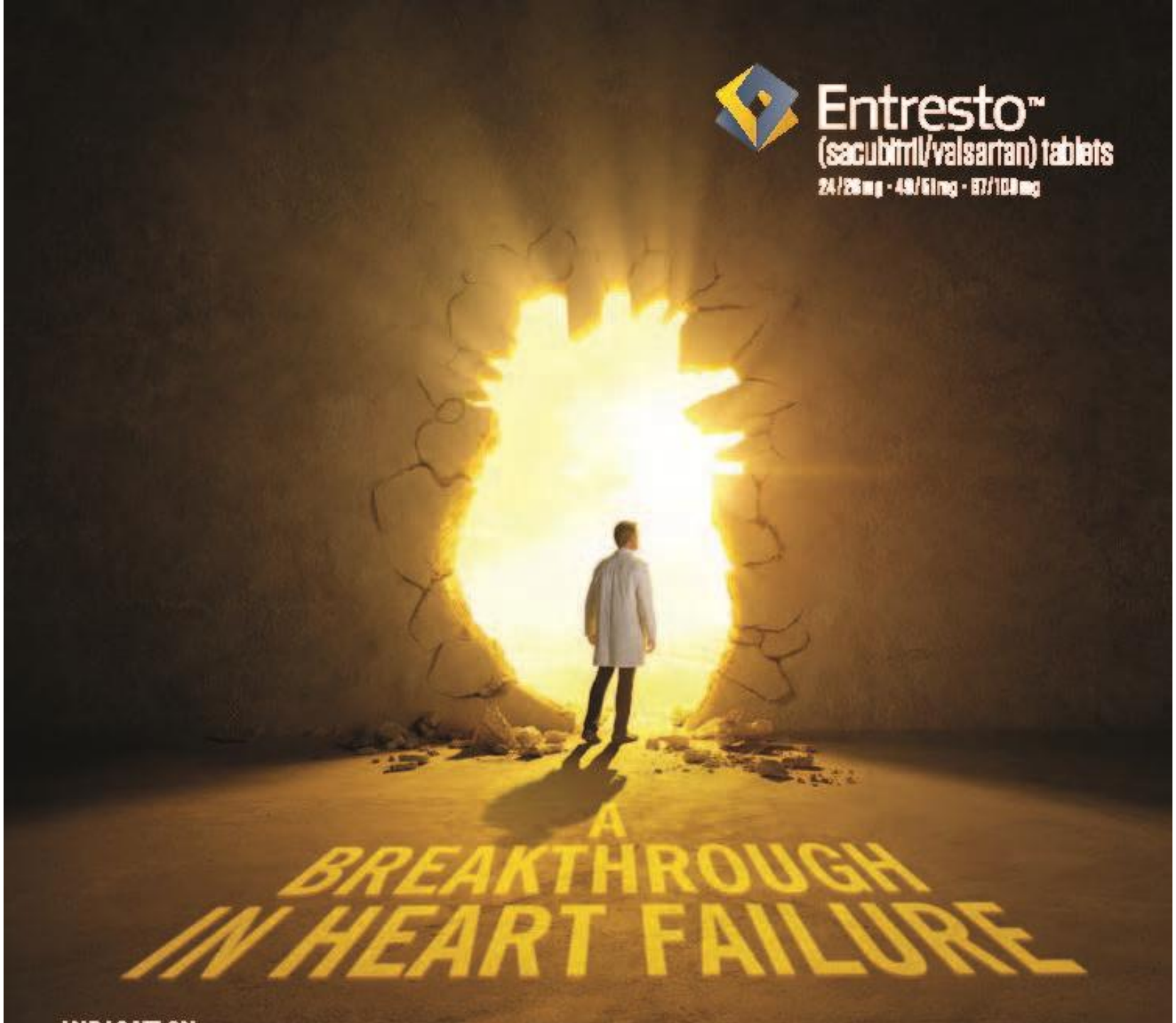

NNH 21
17%
14%
12%
11%
11%
10%
14%
11%
0,2%
0,5%
Enalapril
Sacubitrilo/valsartan
Hipotensión
Hiperpotasemia
Insuficiencia renal
Tos
Angioedema

No iniciar en pacients amb

- PAS < 100mmHg
- FG < 30ml/min/m^2
- K+ > 5,4 mmol/l

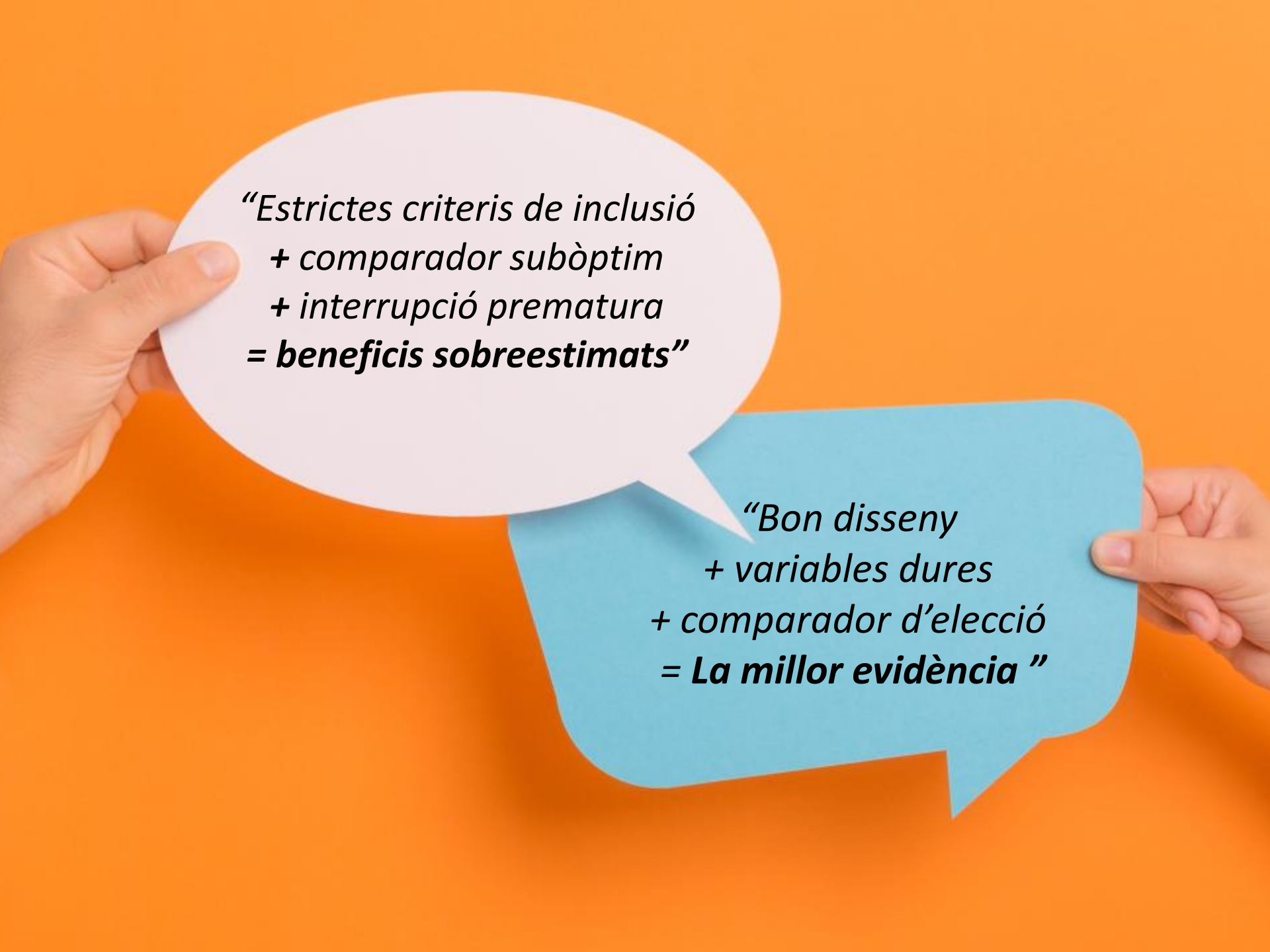
•Per evitar risc d'angioedema

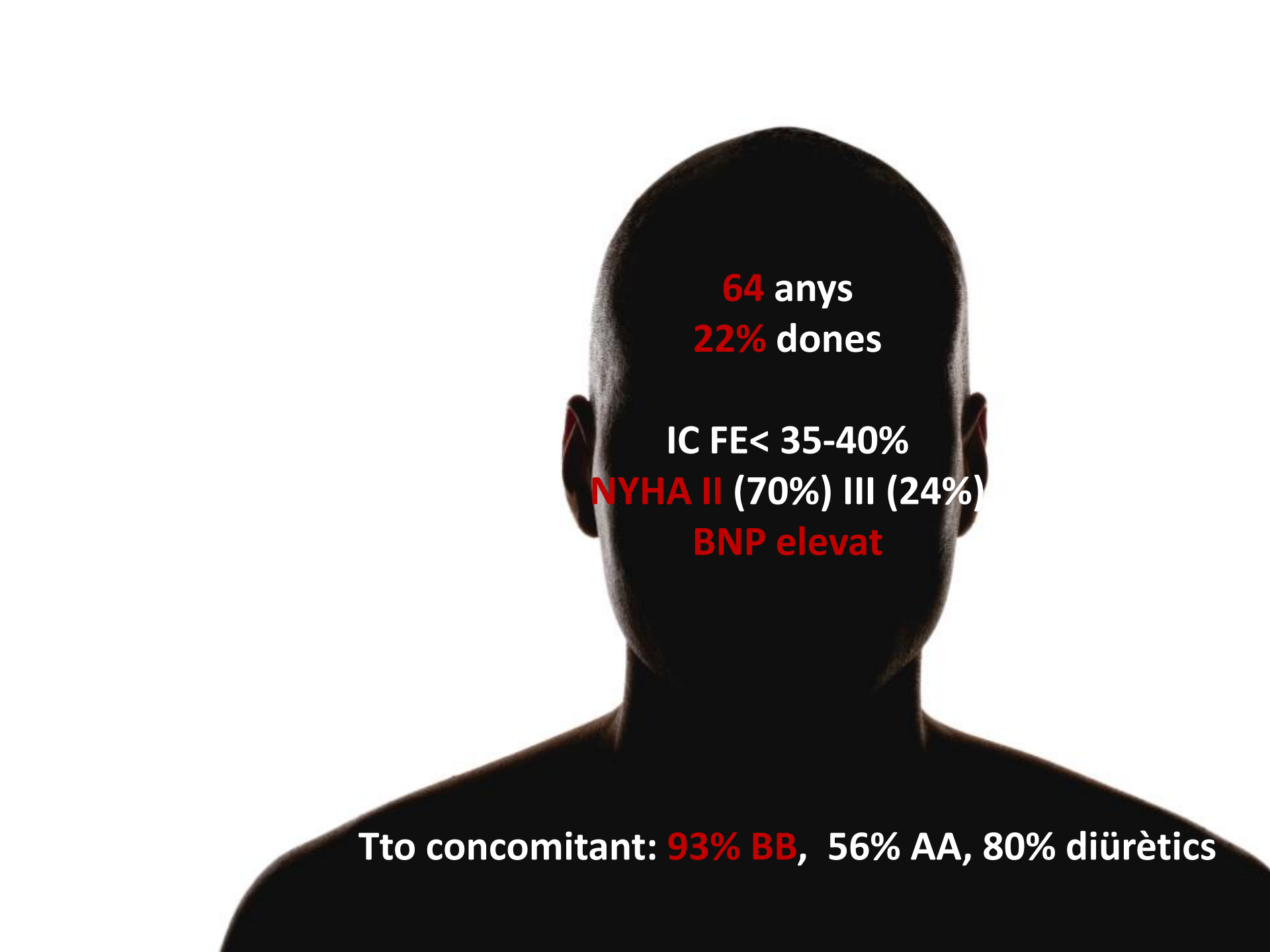
- NO associar a IECA
- Respectar **36h rentat**
- Contraindicat si antecedents d'angioedema


Entresto™
(sacubitril/valsartan) tablets
24/26 mg · 49/51 mg · 97/103 mg
A
BREAKTHROUGH
IN HEART FAILURE

Canvi de PARADIGMa

¿Realitat o il·lusió?


“Estrictes criteris de inclusió
***+** comparador subòptim*
***+** interrupció prematura*
= beneficis sobreestimats”
“Bon disseny
+ variables dures
+ comparador d’elecció
= La millor evidència ”


64 anys
22% dones
IC FE< 35-40%
NYHA II (70%) III (24%)
BNP elevat
Tto concomitant: 93% BB, 56% AA, 80% diürètics

Incerteses

- Població: NYHA I i IV o edat > 75 anys
- Tractament inicial
- Tolerabilitat i incidència real d'efectes adversos
- Risc teòric de deteriorament cognitiu (↑ β-amiloide)

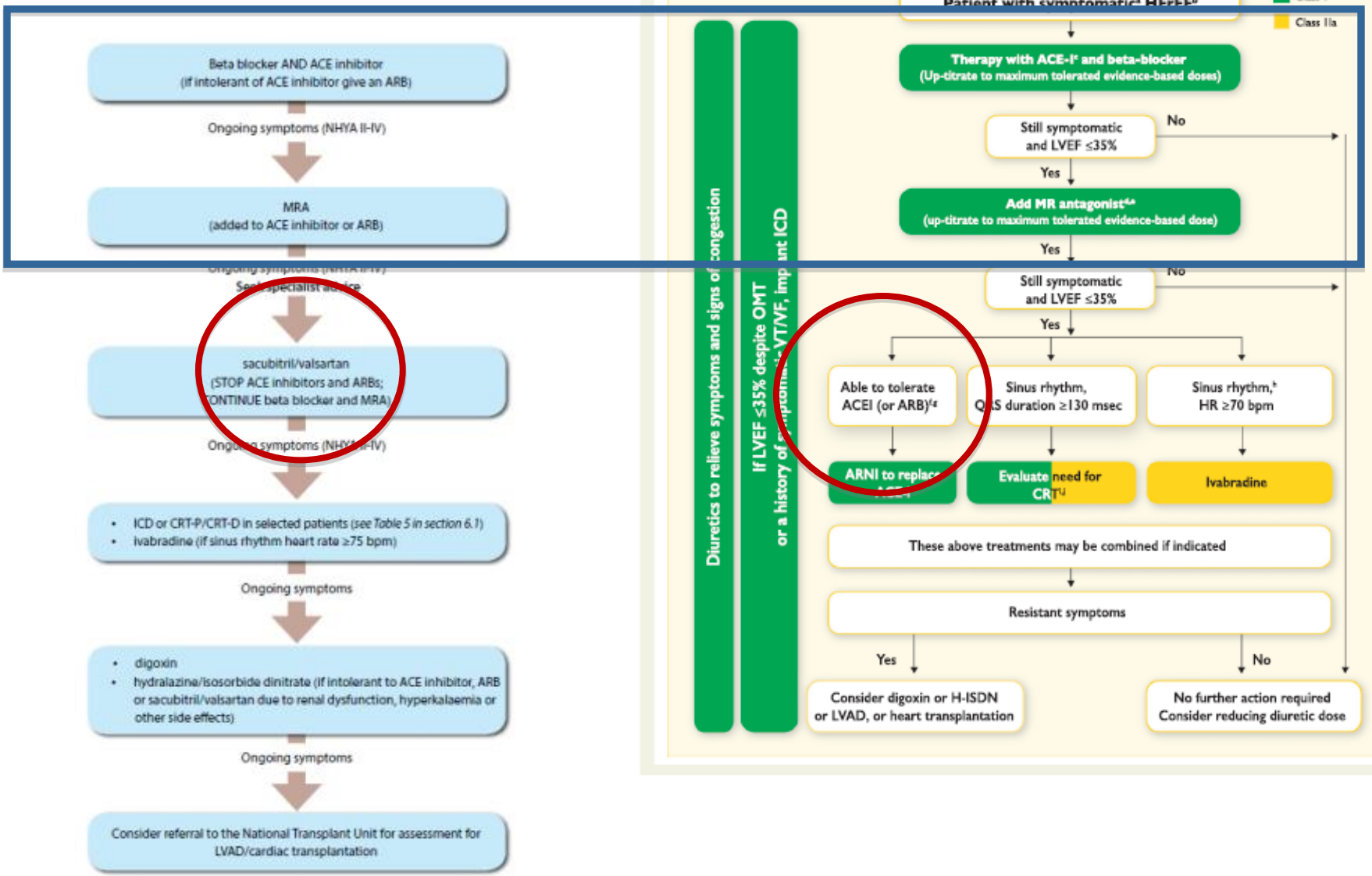
Pacients candidats a Catalunya

	Classe Funcional	Fracció Ejecció	Lloc en la Terapèutica	Altres
NICE	NYHA II-IV	FEVI < 35%	**Alternativa a IECA/ARAII si** •Símptomes •Dosi òptima IECA + BB + AA durant 4 setmanes	Inicio tractament **especialista en IC**
CADTH	NYHA II-III	FEVI< 40%	**Alternativa a IECA (ARAII) si** •Símptomes •Dosi òptima IECA + BB + AA durant 4 setmanes	**BNP** >150pg/L
GENESIS	NYHA II-III	FEVI< 35%	**Alternativa IECA/ARAII si** •Símptomes •Dosi òptima i IECA (o ARAII) estable durant 4 setmanes	
agencia española de medicamentos y productos sanitarios	NYHA II-III	FEVI< 35%	**Alternativa IECA/ARAII si** • Símptomes • Dosis òptima i estable IECA (ARAII) + BB+ AA	**BNP, NT-proBNP elevats**

Alternativa a IECA (o ARAII) si:

- FEVI<35%
- NYHA II-III
- Pèptids elevats
- Simptomàtics
- Tractament optimitzat amb IECA + BB + AA

GPC SIGN



GPC ESC

1. **No hi ha canvi de PARADIGMa**
2. Sacubitril-valsartan per pacients que compleixen criteris **PARADIGM-HF**
3. **Estudis en marxa**
   - ICFE preservada
   - Tractament inicial
4. Des de **l'atenció primària és essencial**
   - Precaució: angioedema i hipotensió
   - Monitoritzar: PA, K^+ i funció renal

NEOPLÀSIA DE BUFETA URINÀRIA

DIABETES MELLITUS TIPUS 2

HIPERTENSIÓ ARTERIAL ESSENCIAL

INSUFICIÈNCIA CARDÍACA

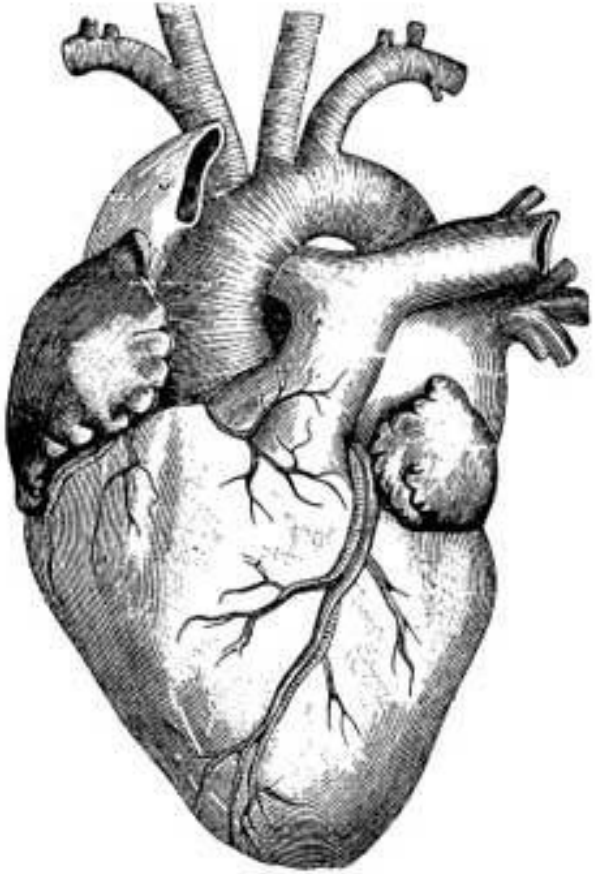
FIBRIL·LACIÓ ALETEIG AURICULAR

DISLIPÈMIA

CLAUDICACIÓ INTERMITENT

INFECCIÓ URINARIA

Medicament	Principi Actiu	Posologia	Durada
BISOPROLOL COR SANDOZ 2,5MG 28 COMPRIMIDOS RECUBIERTOS PELICULA EFG	BISOPROLOL HEMIFUMARAT	1 x 24 h.	Indefinida
ESPIRONOLACTONA ALTER 25MG 50COMP RECUB EFG	ESPIRONOLACTONA	1 x 24 h.	Indefinida
METFORMINA ALMUS 850MG 50 COMPRIMIDOS RECUBIERTOS PELICULA EFG	METFORMINA	1 x 12 h.	Indefinida
OMEPRAZOL ALMUS 20MG 56 CAPSULAS DURAS GASTRORRESISTENTES EFG	OMEPRAZOL	1 x 24 h.	Indefinida
PRAVASTATINA VIR 20 MG 28 COMPRIMIDOS EFG	PRAVASTATINA SODICA	1 x 24 h.	Indefinida
RAMIPRIL/HIDROCLOROTIAZIDA TECNIGEN 5/25MG 28 COMPRIMIDOS EFG	RAMIPRIL +DIURÈTIC	1 x 24 h.	Indefinida
SINTROM 4MG 20 COMPRIMIDOS	ACENOCUMAROL	1 x 24 h.	Indefinida



Insuficiència cardíaca crònica

ARNi: Sacubitril-Valsartan

Hipolipemiants

iPCSK9: Alirocumab i evolocumab

“Amb la explotació i aplicació dels descobriment recents, la malaltia coronaria podria desaparèixer com problema de salut publica al començament del SXXI”

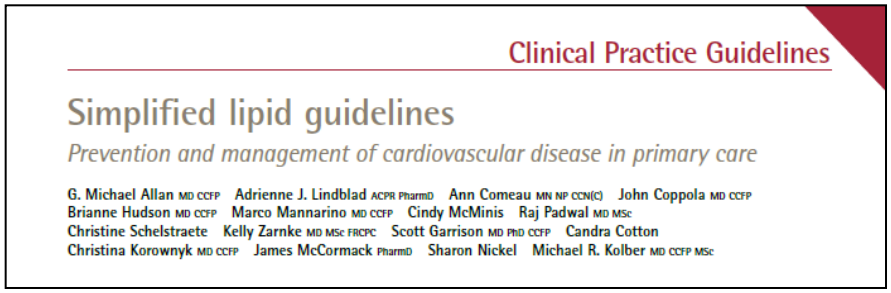
Goldstein & Brown
Premi Nobel Medicina 1985

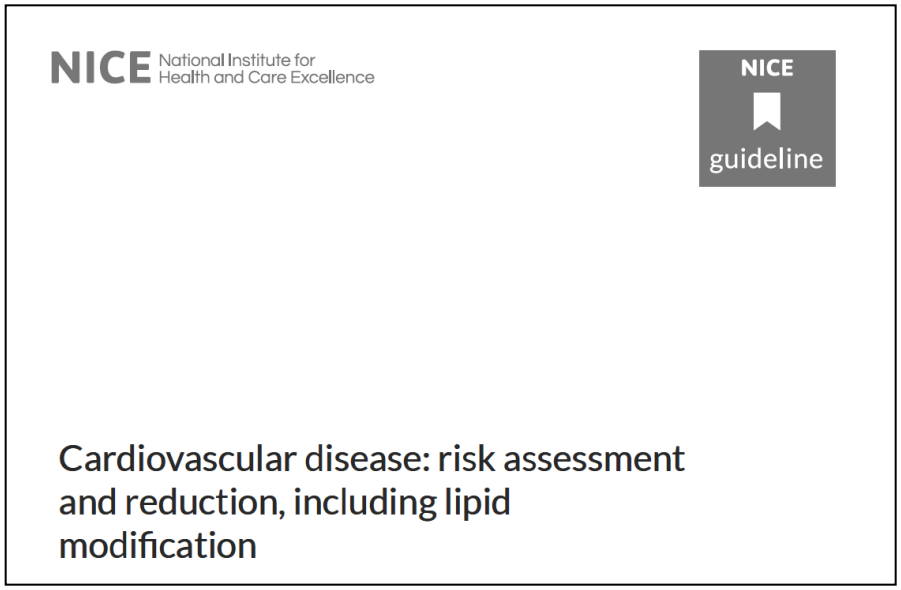
c-LDL com a factor de RCV

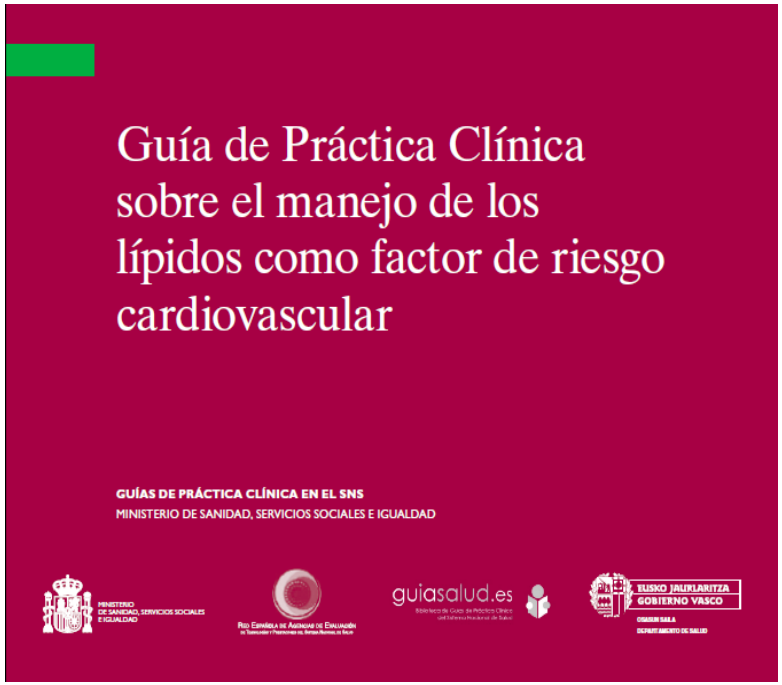
- Correlació c-LDL↑ i malalties CV
- Estatines redueixen esdeveniments

  ↓c-LDL 40mg/dl: ↓ 22% morbimortalitat
- GPC recomanen tractar segons c-LDL

Canvi tendència en les GPC







Estatines d’elecció

Abandonament xifres de c-LDL per guiar el tractament

Nous hipolipemiants: *iPCSK9*

~~**Bococizumab**~~

Evolocumab
(Repatha)

Alirocumab
(Praluent)

Evolocumab i alirocumab

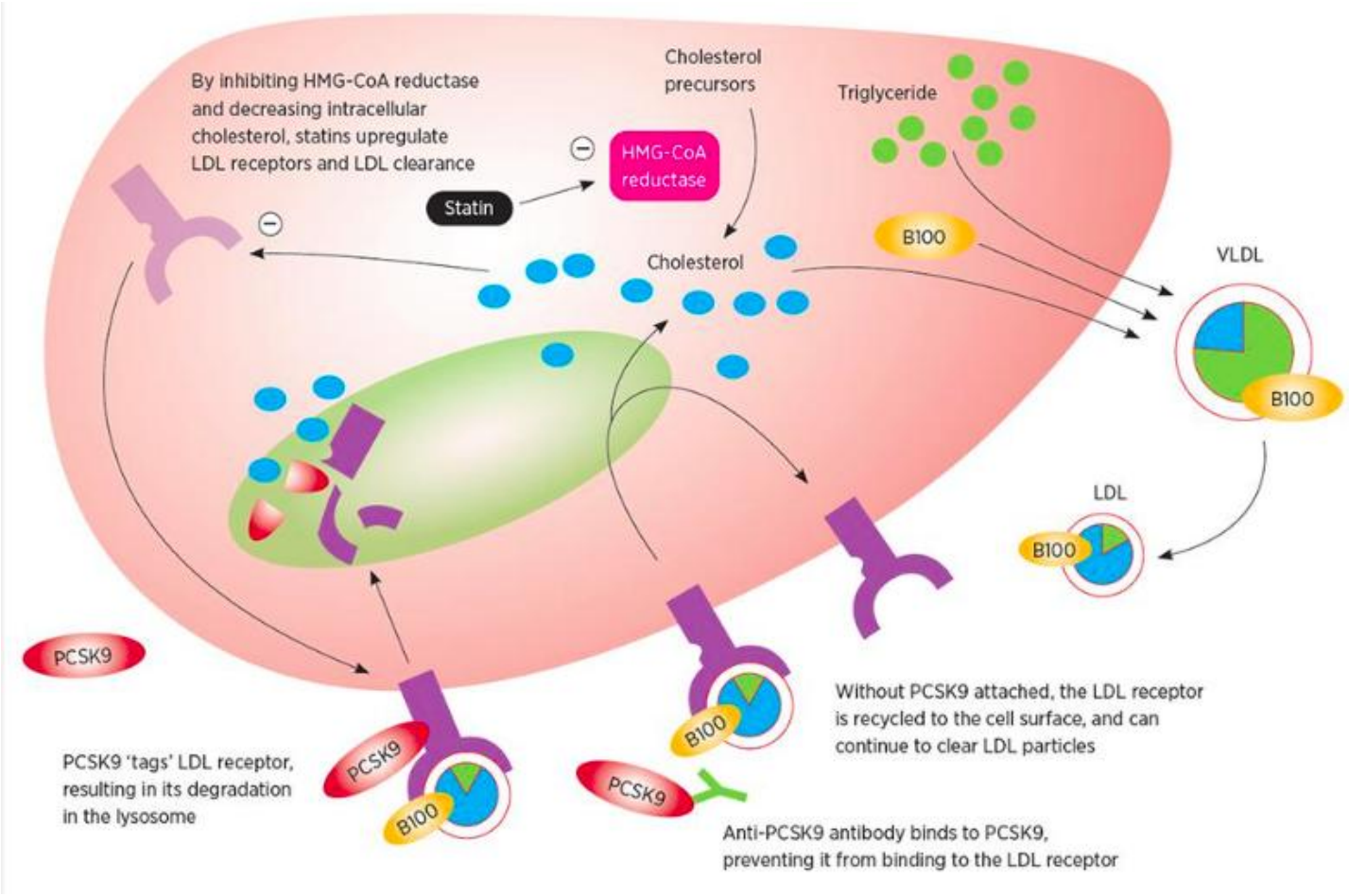
- **Indicació**

  Si no s'aconsegueix l'objectiu c-LDL

  - **Associat a estatines** en H. familiar/no familiar i dislipèmia mixta
  - **Monoteràpia** o amb altres hipolipemiants si intolerància a les estatines

- **iPCSK9** anticossos monoclonals humans
  - SC cada 2-4 setmanes
  - Alt cost
  - Dispensació ambulatòria hospitalària

iPCSK9: *Mecanisme d'acció*



iPCSK-9: *Eficàcia per l'autorització*

Població	Reducció c-LDL		
	Evolocumab		Alirocumab
	420mg/mes	140mg cada 2 setmanes	75-150mg cada 2 setmanes
HF homozigòtica	30%		indicació no aprovada
HF heterozigòtica	56%	61%	45%-61%
HP o dislipèmia mixta	50-59%	57-66%	38%-50%
Intolerància estatines	39%	56%	45%

Reducció del LDL-c 57%

Reducció del 36% vs. ezetimiba

Es consideren alternatives equivalentes

Lipinski et al. Eur Heart J. 2016

Modificada d'Australian Prescriber, 2016

iPCSK9*: Seguretat*

- **Ben tolerats a curt termini**
  - ✓ Reaccions lloc injecció
  - ✓ Infeccions: tracte respiratori, grip
  - ✓ Artralgia, lumbalgia, cefalea
- **Potencials riscos**
  - ✓ Immunogenicitat
  - ✓ Hipersensibilitat
  - ✓ Efectes adversos neurocognitus

Incerteses

- Es manté l'eficàcia a llarg termini?
- Efectes d'un c-LDL tan baix????
- Reduccions de c-LDL … i de la mortalitat?
  - Pendent resultats d'estudis FOURIER (evolocumab) i ODDISEY-OUTCOMES (alirocumab)

Pacients cadidats a iPCSK9 a Catalunya

Com a complement d'un estil de vida saludable (dieta, control de pes, exercici físic adequat i abandonament d'hàbits tòxics) en els següents pacients:

- **HFho (només evolocumab)**
- **HFhe, H no familiar o dislipèmia mixta**
  - ✓ Actuació intensiva sobre FR modificables
  - ✓ Tractament **optimitzat** min 8 setmanes
  - ✓ **Adherència 100%** (6 mesos previs)
  - ✓ **c-LDL > límits establerts**

Quins valors de c-LDL?

FACTORS DE RISC:
- Home > 40 anys; dona > 45 anys.
- Antecedents familiars de cardiopatia isquèmica precoç
- Lp(a) > 50 mg/dl
- HDL < 40 i TG > 200
- Hipertensió
- Tabaquisme
- FGe (MDRD) < 60 ml/min/1,74 m^2
- Síndrome metabòlica; obesitat; prediabetis.

	Prevenció Primària	Prevenció Secundària
HFhe	+ 1FR c-LDL **>160mg/dl**	+ malaltia vascular ateromatosa **C-LDL >100mg/dl**
	+ 2FR c-LDL **>130mg/dl**	
	+ DM c-LDL **>130 mg/dl**	
	+ aterosclerosi subclin. **c-LDL >130 mg/dl**	
	+ DM + 2 FR **c-LDL 100mg/dl**	
HnoF o Dislipèmia mixta	**No finançat**	MV ateromatosa **c-LDL >130mg/dl**
		MV ateromatosa + DM o 2FR **c-LDL >100mg/dl**
		Malaltia isquèmica greu o inestab **c-LDL >100mg/dl**

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Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

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Huei Wang, Ph.D., Thomas Liu,
and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ny C. Keech, M.D.,
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r S. Sever, Ph.D., F.R.C.P.,

ABSTRACT

BACKGROUND

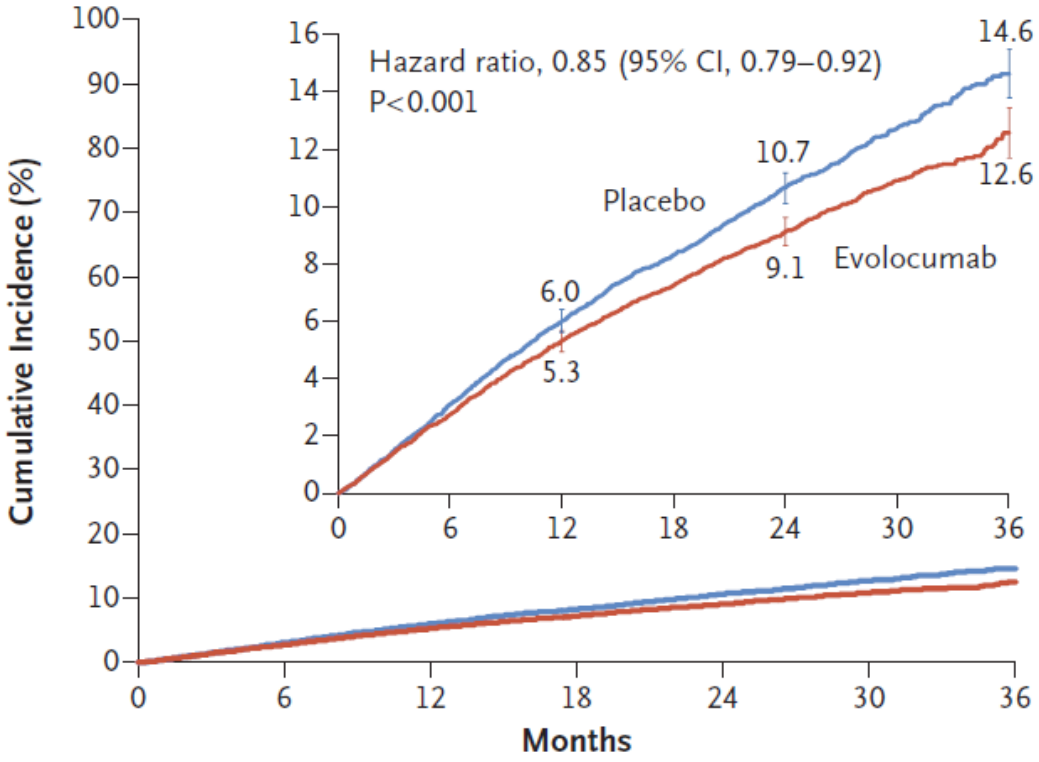
Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W., S.A.M., J.F.K.); Sydney Medical School, National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (A.C.K.); Amgen, Thousand Oaks, CA (N.H., H.W., T.L., S.M.W.); International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London (P.S.S.); and Oslo University Hospital, Ullevål and Medical Faculty, University of Oslo, Oslo (T.R.P.). Address reprint requests to Dr. Sabatine at the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 60 Fenwood Rd

Estudi FOURIER (*evolocumab*)



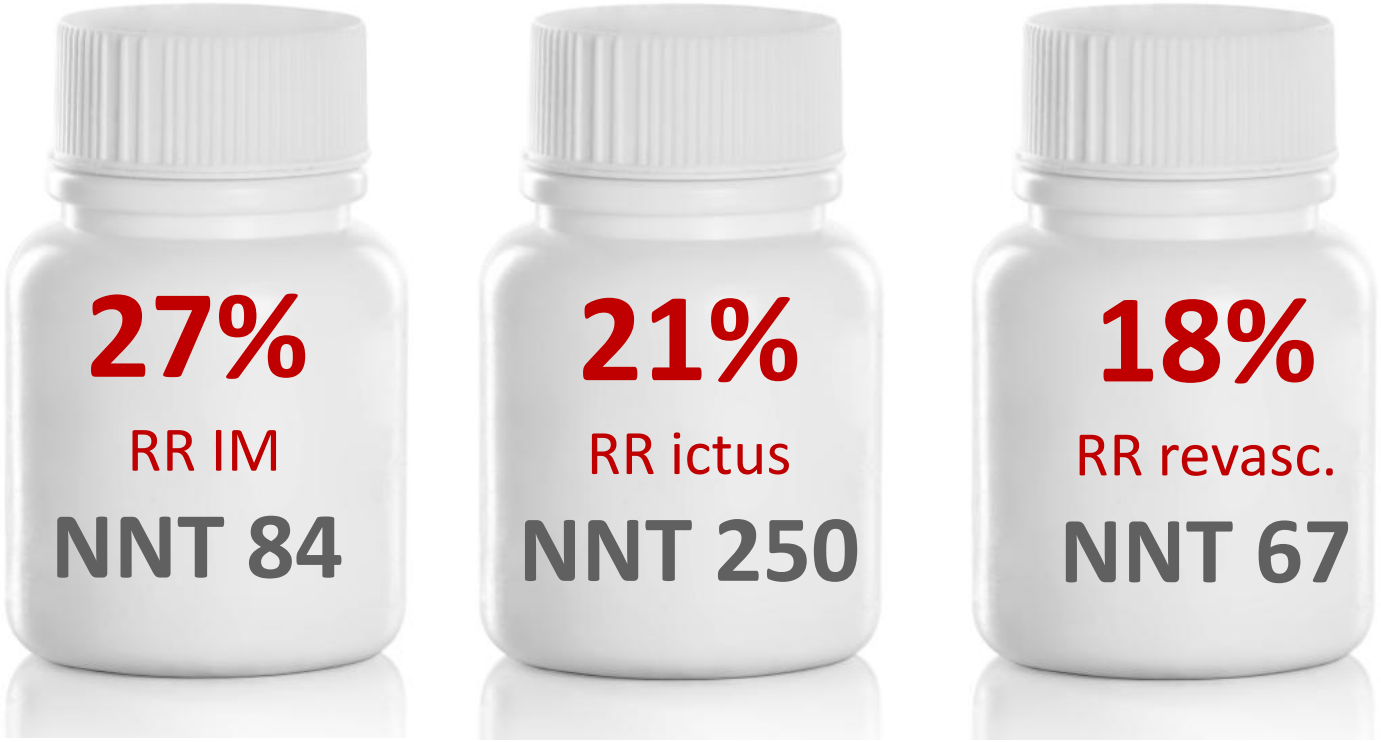
Reducció c-LDL 60%
92mg/dl a 30mg/dl

Sense problemes seguretat addicionals

RR 15% o RA 1,5%

NNT 74 per evitar un esdeveniment (mort CV, IM, ictus, hospitalització x angina o revascularització) **en 2 anys**

Resutats positius i... decepcionants



Sense diferències en la reducció de la mortalitat CV o mortalitat total

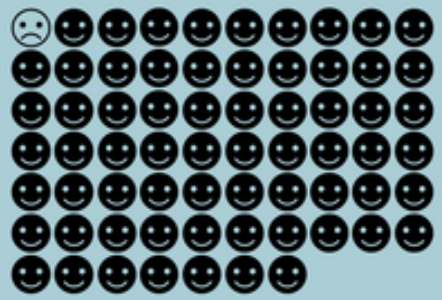
Reduces CV events

5.1% → 4.5%
(percent of patients/year)

Cost 5.570€/any

824.703€/any
to prevent 1 CV event

Does not reduce deaths



1.5% → 1.5%
(percent of patients/year)

Reflexió

Grans reduccions de c-LDL, reduccions d'esdeveniments modestes

- **Hem arribat al sostre del benefici?**
  - ODISSEY OUTCOME amb alirocumab
  - Inclisiran: inhibidor de la sintesi del PCSK9 per interferència ARN
- **Quan més baix millor?**
  - Hem de mirar més enllá del c-LDL
- **Valen el que costen?**

- NEOPLÀSIA DE BUFETA URINÀRIA
- DIABETES MELLITUS TIPUS 2
- HIPERTENSIÓ ARTERIAL ESSENCIAL
- INSUFICIÈNCIA CARDÍACA
- FIBRIL·LACIÓ I ALETEIG AURICULAR
- DISLIPÈMIA
- CLAUDICACIÓ INTERMITENT
- INFECCIÓ URINARIA

Medicament	Principi Actiu	Posologia	Durada
BISOPROLOL COR SANDOZ 2,5MG 28 COMPRIMIDOS RECUBIERTOS PELICULA EFG	BISOPROLOL HEMIFUMARAT	1 x 24 h.	Indefinida
DIAMICRON 30MG 60 COMPRIMIDOSDE LIBERACION MODIFICADA	GLICLAZIDA	1 x 24 h.	Indefinida
ESPIRONOLACTONA ALTER 25MG 50COMP RECUB EFG	ESPIRONOLACTONA	1 x 24 h.	Indefinida
METFORMINA ALMUS 850MG 50 COMPRIMIDOS RECUBIERTOS PELICULA EFG	METFORMINA	1 x 12 h.	Indefinida
OMEPRAZOL ALMUS 20MG 56 CAPSULAS DURAS GASTRORRESISTENTES EFG	OMEPRAZOL	1 x 24 h.	Indefinida
PRAVASTATINA VIR 20 MG 28 COMPRIMIDOS EFG	PRAVASTATINA SODICA	1 x 24 h.	Indefinida
RAMIPRIL/HIDROCLOROTIAZIDA TECNIGEN 5/25MG 28 COMPRIMIDOS EFG	RAMIPRIL +DIURÈTIC	1 x 24 h.	Indefinida
SINTROM 4MG 20 COMPRIMIDOS	ACENOCUMAROL	1 x 24 h.	Indefinida


Kahoot!

DEMAND EVIDENCE AND THINK CRITICALLY

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