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ELS ESTUDIS DE SEGURETAT CARDIOVASCULAR SGLT-2: LLUMS I OMBRES

Conflictes d'Interés

- Participació com a IC o IP en assajos clínics:
  - Seguretat CCV (EXSCEL, CAROLINA)
  - Insulines (NovoNordisk, Sanofi)
- Ajuda per a Assistència a congressos:
  - Menarini
  - Novo-Nordisk
- Ajuda per a Formació Continuada:
  - Menarini

Cas clínic

Pacient de 77 anys d'edat amb DM2 des de fa 10 anys.

Controlat amb metformina HbA1c 7,6%. IMC 28.

Fumador, DLP i HTA.

FG 56, Albuminúria 350mg/d, no altres CC de la DM.

Ingressa per IAM.

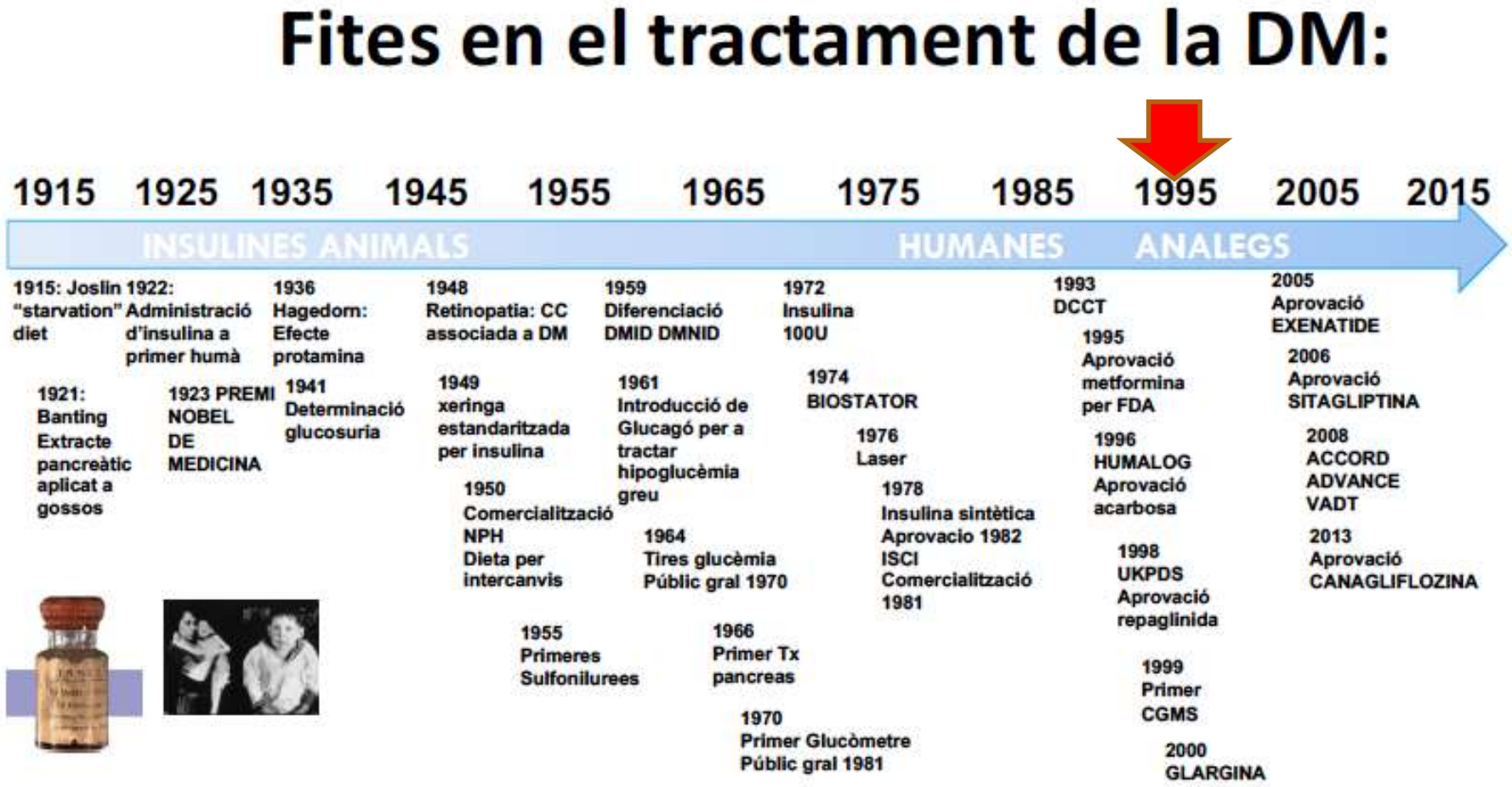
Indicaries un glucosúric en aquest pacient?

1. Sí, és el que diuen les guies clíniques i els estudis de seguretat CCV.
2. No, no penso que estiguin indicats.
3. No ho sé

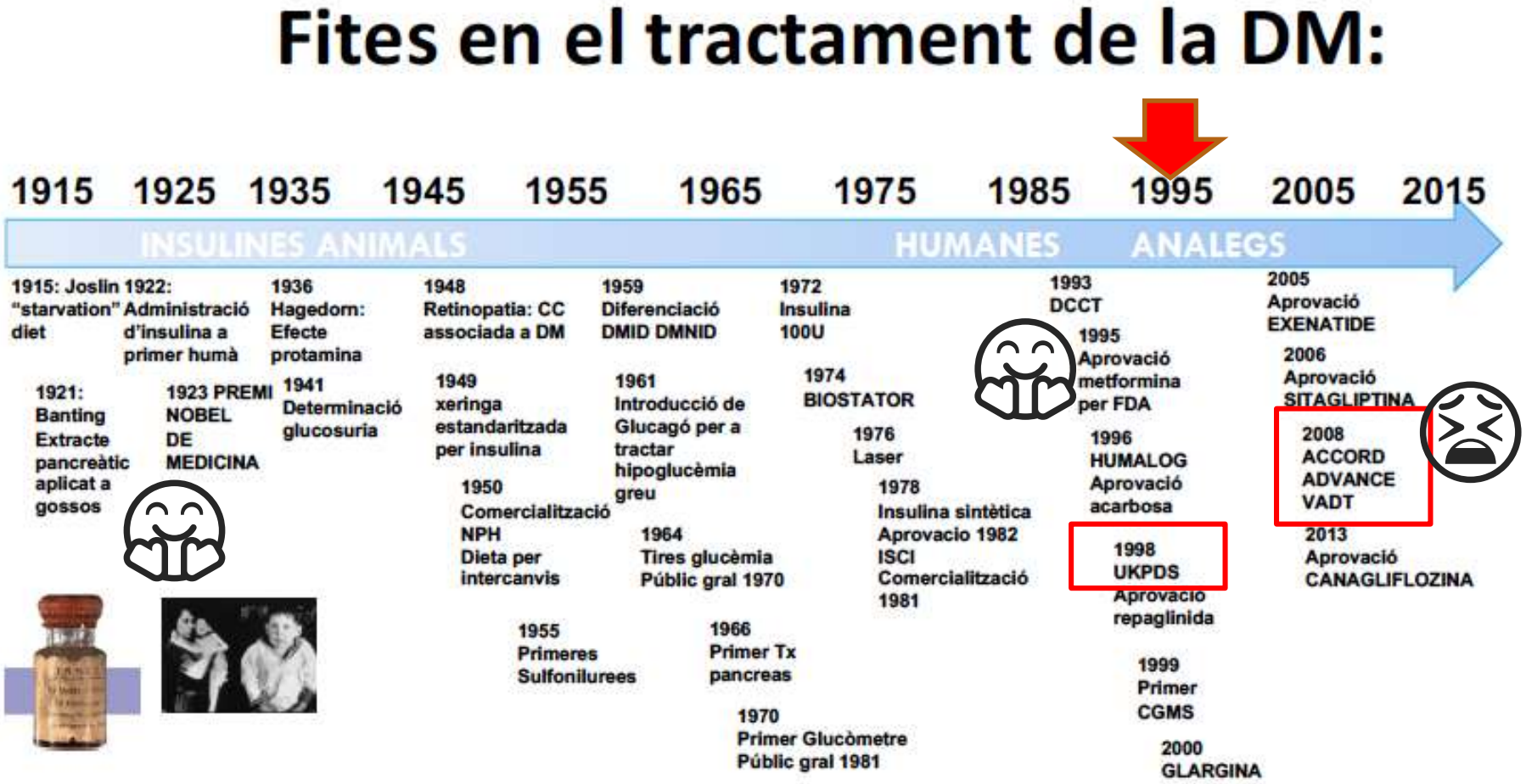
Objectius

- Contextualització dels CVOSafety Trials
- Punts crítics dels CVOSafety Trials
- Interpretació dels CVOSafety Trials

Contextualització



Contextualització



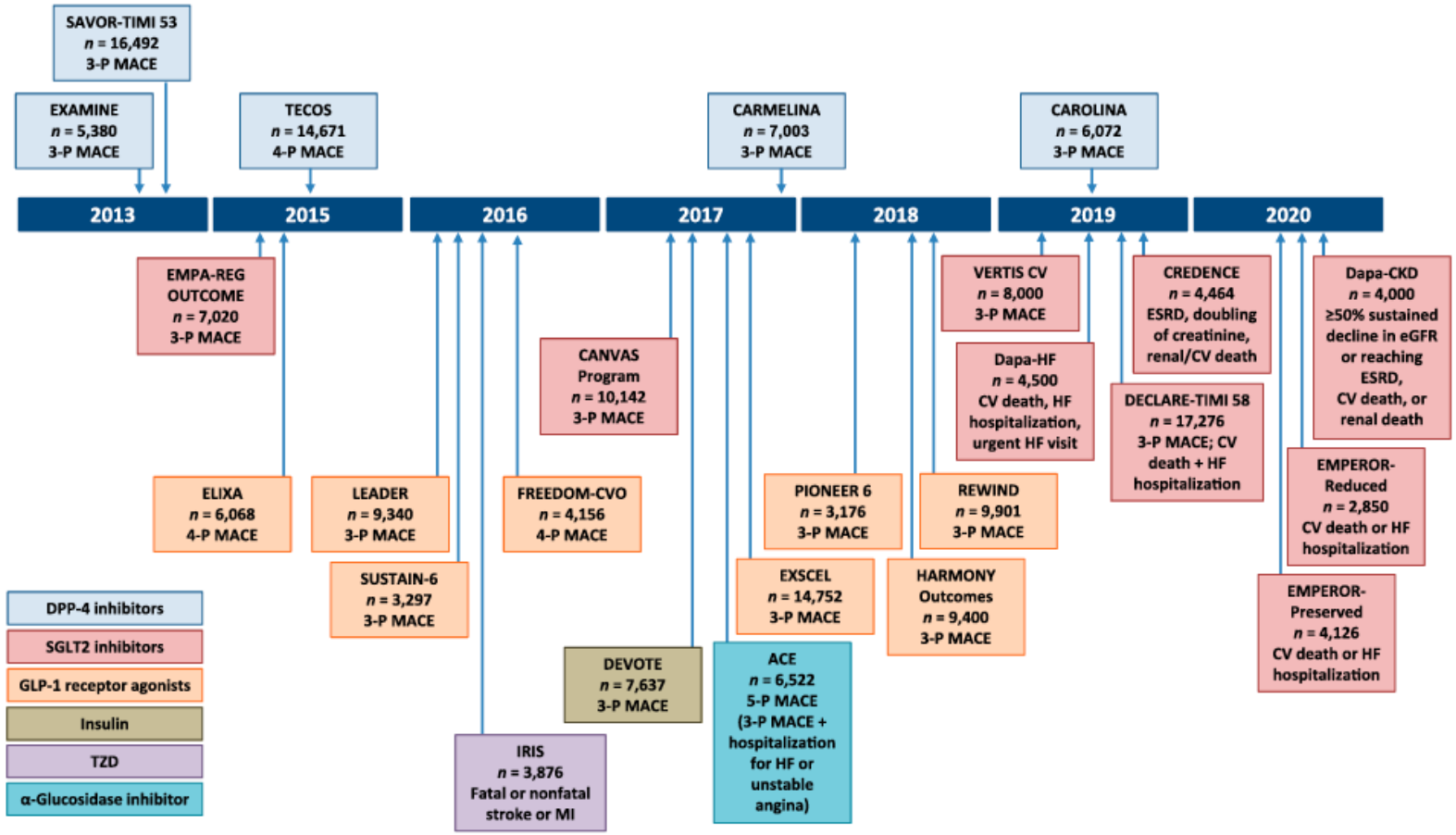
CVO-Safety Trials a la DM-2

- Requeriment de FDA
  - 2006: MA rosiglitazona increment risc isquèmia miocàrdica
  - 2008: FDA requereix que els nous fàrmacs HHOO tinguin una avaluació de riscos CCV:
    - Incloure pacients amb perfil d'alt risc i edat avançada
    - Prou temps de seguiment

Guidance for Industry –Diabetes Mellitus-Evaluatinc Cardiovascular Risk in New Antidiabetic Therapies to treat Type 2 Diabetes U.S Department of Health and Human Services Food and Drug Administration Center for Drueg Evaluationa and Research (CDER) December 2008

CVO-Safety Trials a la DM-2

- Requeriment de FDA



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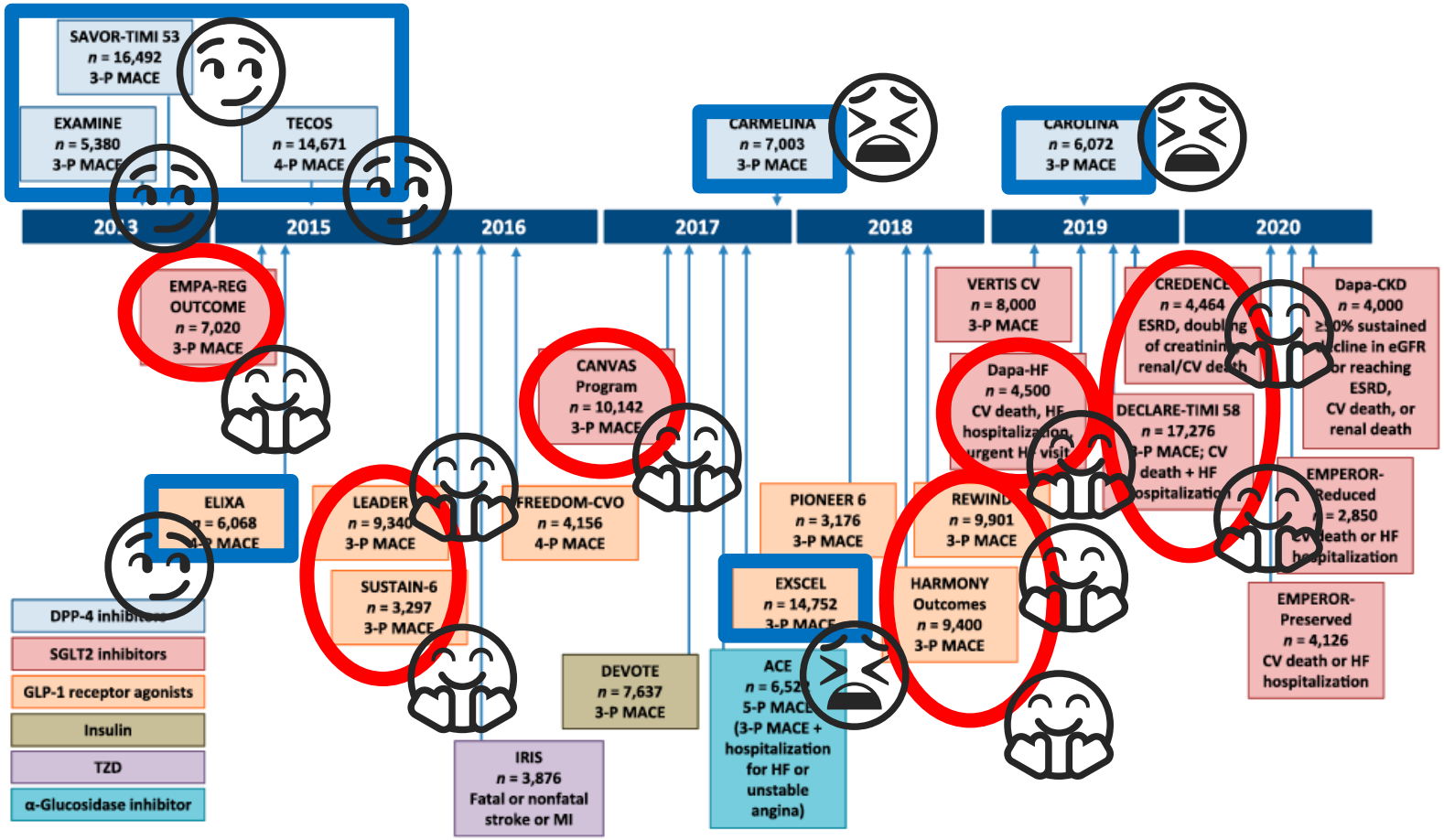
CVO-Safety Trials a la DM-2

- Requeriment de FDA



Guidance for Industry –Diabetes Mellitus-Evaluatinc Cardiovascular Risk in New Antidiabetic Therapies to treat Type 2 Diabetes U.S Department of Health and Human Services Food and Drug Administration Center for Drueg Evaluationa and Research (CDER) December 2008

CVO-Safety Trials a la DM-2,
Què tenen en comú la major part d'aquests estudis?

Són assajos clínics (RCT)
S'han publicat en revistes d'alt factor d'impacte
Estan finançats per la industria
Molts tenen un disseny de no inferioritat
El comparador sol ser placebo

Assajos clínics de no inferioritat … són importants?

- Cada vegada més freqüents

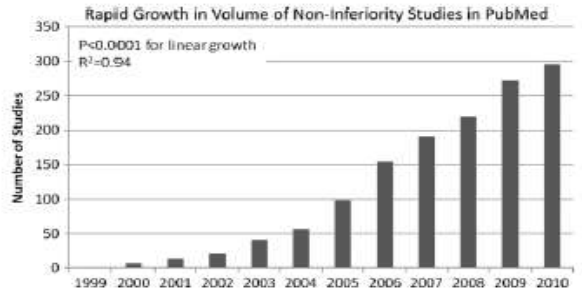


Figure 1. Number of noninferiority studies reported in PubMed by year. Entries were identified by searching for the terms "non-inferior," "non-inferiority," "noninferior," or "noninferiority." Entries were filtered to include only those classified as clinical trials or randomized controlled trials. Data were fit with a linear model using year as the continuous predictor variable.

Clin. Cardiol. 35, 9, 523–525 (2012)

Assajos clínics de no inferioritat … són importants?

- Cada vegada més freqüents
- Antibioteràpia, malalties cardiovasculars

Oncologia, Endocrinologia entre els camps més freqüents

- Els estudis de no inferioritat són un xic peculiars.

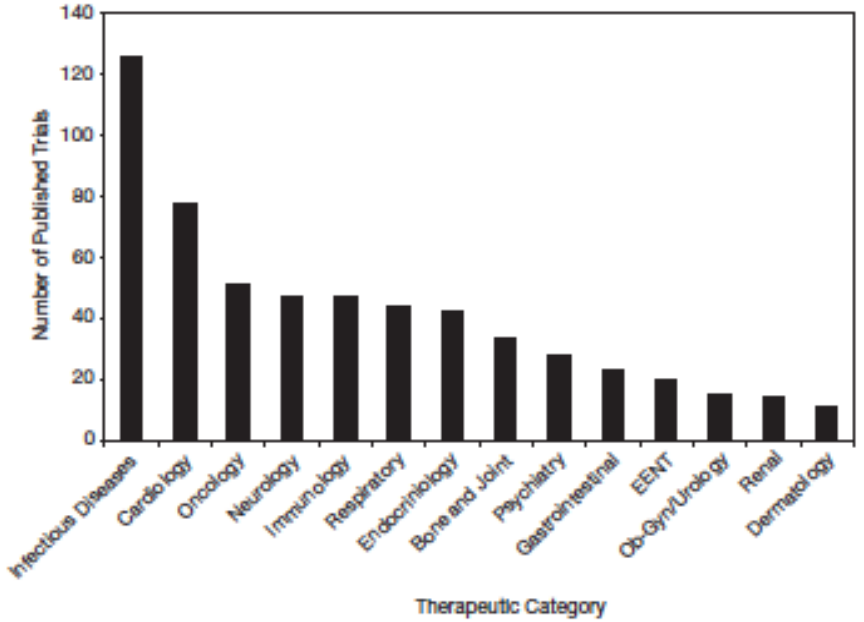


Figure 3. Numbers of published noninferiority trials by therapeutic category. EENT = eye, ears, nose, and throat; Ob-Gyn = obstetrics and gynecology.

(Pharmacotherapy 2011;31(9):833–839)

Assajos clínics de no inferioritat … sabem?

Assajos clínics de no inferioritat. La base.

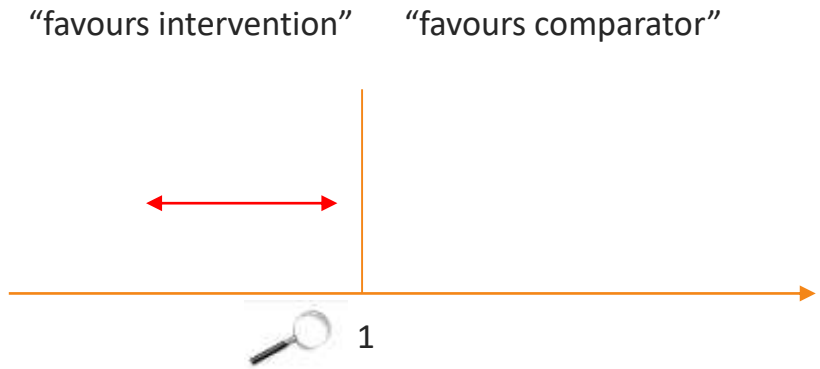
1. Quan están justificats?

S'assumeix que l'eficàcia de la nova intervenció pot ser quelcom inferior a la del **comparador de referència** a canvi de millor posologia, preu, tolerabilitat…

Ho: la **nova intervenció "A"** **és significativament pitjor** que el **comparador de referència** per un marge acceptable "δ".
El marge d'acceptabilitat (tolerancia) "δ" ha de tenir justificació clínica.

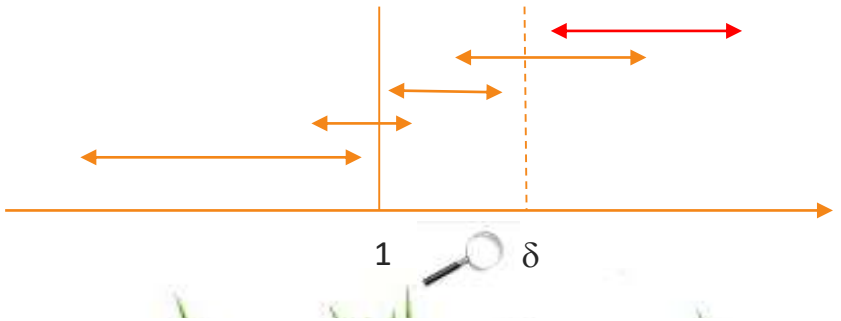
H0: SUPERIORITY eA=eC	TRUTH	
	H0 DOES NOT CORRESPOND TO TRUTH	H0 CORRESPONDS TO TRUTH
REJECT H0	*TRUE POSITIVE Intervenció efectiva*	*FALSE POSITIVE (α ERROR)*
NOT REJECT H0	*FALSE NEGATIVE (β ERROR)*	*TRUE NEGATIVE*

H0: NON-INFERIORITY eA<eC	TRUTH	
	H0 DOES NOT CORRESPOND TO TRUTH	H0 CORRESPONDS TO TRUTH
REJECT H0	*TRUE POSITIVE: Intervenció no inferior*	*FALSE POSITIVE (α ERROR)*
NOT REJECT H0	*FALSE NEGATIVE (β ERROR)*	*TRUE NEGATIVE Intervenció inferior*



Estudi superioritat: Potència (focus) centrat en detectar diferències entre intervenció i comparador

Estudi no inferioritat: Potència (focus) centrat en detectar si intervenció és inferior o no a comparador



Assajos clínics de no inferioritat. La base.
2. Importància de δ

El valor δ determina la mida de la mostra en els estudis de no-inferioritat.

Com més laxe el límit δ, menys esdeveniments calen per a demostrar no inferioritat.

Ha de tenir una justificació clínica.

Perspective

Reflections on using non-inferiority randomised placebo controlled trials in assessing cardiovascular safety of new agents for treatment of type 2 diabetes

Denise Campbell-Scherer

http://dx.doi.org/10.1136/ebmed-2016-110652

Evid Based Med April 2017 | volume 22 | number 2 |

Table 1 Estimation of the cardiovascular events required to fall below the FDA target cut-off in the design of a cardiovascular safety non-inferiority trial as a function of the expected true HR of the intervention (for 90% power)[8]

True HR	Upper HR boundary	<1.8	<1.3
0.70		48	110
0.75		55	139
0.80		64	179
0.85		75	233
0.90		88	311
0.95		103	428
1.0		122	611
1.05		145	921
1.1		174	1507

Non-inferiority margin.
FDA, Food and Drug Administration.

En el cas dels CVOSafety trials:

Des de 2008 la FDA exigeix als nous fàrmacs per la DM de presentar resultats de seguretat CCV en pacients d'alt risc CCV i amb un temps de seguiment perllongat.

En fàrmacs comercialitzats l'IC 95% del HR d'esdeveniments CCV (MACE) no pot superar el δ 1,3.

En el cas dels fàrmacs no comercialitzats l'IC del HR d'esdeveniments CCV (MACE) en comparació amb el comparador (Placebo) no pot superar el δ 1,8.

Guidance for Industry –Diabetes Mellitus-Evaluatinc Cardiovascular Risk in New Antidiabetic Therapies to treat Type 2 Diabetes U.S Department of Health and Human Services Food and Drug Administration Center for Drueg Evaluationa and Research (CDER) December 2008

”IN OTHER WORDS”…

Els nous fàrmacs han de demostrar que no augmenten el risc de patir esdeveniments cardiovasculars per sobre d’un 30% ó 80% del que ho faria el comparador (sovint placebo) en funció de si el fàrmac està o no comercialitzat.

Assajos clínics de no inferioritat. La base.
3. Intervenció i control s'han d'administrar en condicions òptimes de comparació


START

Assajos clínics de no inferioritat. La base.

4. L'anàlisi per protocol és crític per a aceptar la hipòtesi de no inferioritat

ANÀLISI	Els pacients s'analitzen	Estimació de magnitud d'efecte d'intervenció	Quan s'ha de fer
Intenció de Tractar	En funció de grup d'aleatorització	Relativitza efecte intervenció.	ESTUDIS DE SUPERIORITAT
Per Protocol	En funció del tractament que han seguit realment.	Assegura que l'efecte és degut a la intervenció estudiada i no a altres factors	ESTUDIS DE NO INFERIORITAT

Manca d'adherencia!! Augment falsos positius (falsos no inferiors)

THE JOURNAL OF FAMILY PRACTICE

ONLINE EXCLUSIVE

7 questions to ask when evaluating a noninferiority trial

While most physicians are accustomed to evaluating randomized placebo-controlled studies, many are less familiar with the purpose and takeaway of noninferiority trials. Here's help.

Anne Mounsey, MD; Anthony J. Viera, MD, MPH; Rosalie Dominik, DrPH
Department of Family Medicine, University of North Carolina at Chapel Hill (Drs. Mounsey and Viera); Department of Biostatistics, Gillings School of Global Public Health (Dr. Dominik)

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1. Is a noninferiority trial appropriate?	• Is the primary objective to evaluate whether a new treatment is noninferior to, or no worse than, a standard treatment? • Has the efficacy of the standard treatment been previously established? • Are the known or expected advantages of the new treatment described?
2. Is the noninferiority margin based on clinical judgment and statistical reasoning?	• Does the choice of margin reflect both the severity of the disease and the uncertainty in the estimate of the efficacy of the standard treatment?
3. Are the hypothesis and statistical analysis formulated correctly?	• Is the hypothesis clearly stated? • Is the null hypothesis that the outcome for the standard treatment is better than the outcome for the new treatment by some prespecified margin?
4. Is the sample size appropriate and justified?	• Was the sample size appropriately planned? • What assumptions about the outcomes for the treatment groups were used for sample size calculations, and were they clinically reasonable assumptions?
5. Is the noninferiority trial as similar as possible to the trial(s) comparing the standard treatment with placebo?	• Are the inclusion/exclusion criteria, dosing, method of assessing the outcome, and duration of follow-up nearly identical to the trial(s) that established efficacy of the standard treatment?
6. Is a per protocol analysis reported in the results?	• If the results are given for intention-to-treat analysis, are they also given for per protocol analysis?
7. Are the overall design and execution of the trial high quality?	• Were appropriate methods for allocation concealment and blinding used? • Was the follow-up rate high? • Were the groups similar at baseline and subject to the same care?

1. Is a noninferiority trial appropriate?

- Is the primary objective to evaluate whether a new treatment is noninferior to, or no worse than, a standard treatment?
- Has the efficacy of the standard treatment been previously established?
- Are the known or expected advantages of the new treatment described?

2. Is the noninferiority margin based on clinical judgment and statistical reasoning?

- Does the choice of margin reflect both the severity of the disease and the uncertainty in the estimate of the efficacy of the standard treatment?

Es el que demana la FDA per a demostrar seguretat CCV

3. Are the hypothesis and statistical analysis formulated correctly?

- Is the hypothesis clearly stated?
- Is the null hypothesis that the outcome for the standard treatment is better than the outcome for the new treatment by some prespecified margin?

XXX CONGRESO DE LA SOCIEDAD ESPAÑOLA DE DIABETES
CENTRO DE CONVENCIONES DEL HOTEL BARCELÓ RENACIMIENTO
Sevilla 24-26 Abril 2019

¿SE RESPETAN LAS NORMAS CONSORT EN LAS PUBLICACIONES DE LOS ESTUDIOS DE SEGURIDAD CARDIOVASCULAR? LAS FORMAS TAMBIÉN IMPORTAN

Wilfredo Risart Engel, Mariona Esteve Serra, Rebeca Barahona San Millan, Mercè Fernández Balsells
Unidad de Endocrinología y Nutrición. Hospital Josep Trueta de Girona
Hospital Universitari de Girona Doctor Josep Trueta

Introducción: Las publicaciones de alto factor de impacto exigen a los autores de los estudios randomizados adherencia a las recomendaciones CONSORT (**Con**solidated **S**tandards **o**f **R**eporting Trials) cuyo objetivo es facilitar la exposición completa y transparente de los estudios y ayudar a su interpretación y evaluación crítica.

Material y métodos: Se seleccionaron los Cardiovascular Outcome Trials de fármacos antidiabéticos en pacientes con DM2, publicados desde 2008 hasta finales del 2018.

Se utilizó el checklist CONSORT que hace referencia a los estudios aleatorizados (25 items) y la extensión para los estudios de no-inferioridad (11 items) publicadas en 2010.

Para cada ítem del checklist se tuvo en cuenta si la información estaba contenida en el artículo (SÍ) o si no aparecía (NO).

Objetivo: Valorar el grado de adherencia con las guías CONSORT de las publicaciones de los estudios de seguridad cardiovascular (CVOtrials) en diabetes mellitus tipo 2 (DM2).

Resultados: Análisis de 12 Cardiovascular Outcome Trials (n=3 inhibidores SGLT-2, n=5 análogos de la GLP-1 y n=4 inhibidores de la DPPIV). Todos resultaron ser de no-inferioridad. Todos se publicaron con posterioridad a las guías CONSORT. En ninguna de las publicaciones se identificaba en el título que se tratara de un ensayo randomizado de no-inferioridad. Globalmente, la adherencia con cada ítem se recoge en la tabla adjunta.

		% adherencia
1	Identification as a noninferiority randomized trial in the title	0
2a	Justification of noninferiority design	17
2b	Rationale for choice of the noninferiority margin	8
4a	Participants in the noninferiority trial similar to those in any trial(s) that established efficacy of the reference treatment	8
5	Reference treatment in the noninferiority trial identical to that in any trial(s) that established efficacy	17
6a	Specify the noninferiority outcome(s) and whether hypotheses for main and secondary outcome(s) are noninferiority or superiority	25
7a	Sample size calculated using a noninferiority criterion	83
7b	Outcome(s) related to noninferiority hypothesis	58
12a	1- or 2-sided confidence interval	92
17a	Figure showing confidence intervals and the noninferiority	83
22	Interpret results in relation to the noninferiority hypothesis, if a superiority conclusion is drawn, provide justification for switching	92
	% adherencia	46

Extension of 2010 CONSORT checklist; Roja: Ausente; Verde: Presente

Conclusiones: Paradójicamente, aunque la totalidad de los CVO Trials en DM2 están publicados en revistas adheridas a las normas de publicación CONSORT, la mayoría de ítems que deberían constar en referencia al diseño de no-inferioridad no están correctamente referenciados. Más allá del aspecto meramente formal, la falta de adherencia con las recomendaciones CONSORT dificulta el análisis crítico de estas publicaciones, entorpeciendo la evaluación de la calidad de los estudios.

En realitat, cal anar a l'apartat d'anàlisi estadística per a trobar que es tracta d'estudis de no inferioritat. La hipòtesi inicial de no inferioritat no s'esmenta enlloc del paper.

ANTI-CONSORT

4. Is the sample size appropriate and justified?

- Was the sample size appropriately planned?
- What assumptions about the outcomes for the treatment groups were used for sample size calculations, and were they clinically reasonable assumptions?

El nombre d'esdeveniments calculat en base al marge de no inferioritat δ es molt inferior al que seria necessari si els estudis s'haguessin planificat d'entrada com a estudis de superioritat.

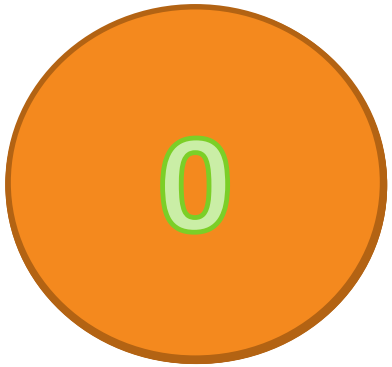
Assajos clínics de no inferioritat. Un petit joc

TRIAL Calculated Number of events for primary Hypothesis testing (non-inferiority and superiority)	Results reported: HR of primary outcome, p values for non-inferiority and superiority NNT (95% IC) Calculadora epidemiológica OST FLCritica (Servicio Vasco de Evaluación de Tecnologías Sanitarias)	*I si la mida de la mostra s'hagués calculat per a demostrar superioritat d'entrada?*
EMPAREG, 2015 691events (2:1) 7028 patients (3,1 years)	EMPA 490/4687 (10,5%) VS PLACEBO 282/2333 (12,1%) HR, 0.86; 95.02% confidence interval, 0.74 to 0.99; P = 0.04 for superiority NNT 31-2152 (point estimate 61) durant 3,1 anys per a evitar un 3p MACE	2080 para beta 0.1, p bilateral 0.05, 2:1 x3
CANVAS, 2017 688 events 10142 patients (3,6 years)	CANA 426/4347 (9,8%) VS PLACEBO 585/5795 (10,1%) HR 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P = 0.02 for superiority NNT no calculable Segons calculadora epidemiològica les dades corresponen a RR 0,97 (0,86-1,09) ***IN FACT: APPENDIX REPORTS P 0,5980 WHEN RISKS ARE REPORTED	1848 para beta 0.1, p bilateral 0.05, 2:1 x3
DECLARE-TIMI 58, 2018 1390 events 17160 patients (4,2 years)	3pMACE: DAPA 756/8582 (8,8%) vs PLACEBO 803/8578 (9,4%) HR 0,83; 95% confidence interval [CI] 0,93 to 1,03; p=0,17 CV death or Hospitalization for Hfailure: No differences in CV death: CV death: DAPA 205/8582 VS PLACEBO 210/8578 Hfailure: DAPA 212/8582 (2,5%) vs PLACEBO 286/8578 (3,3%) HR 0,73 (0,61-0,85) NNT 73-276 (point estimate 115) durant 4,2 years per a evitar 1 ingrés hospitalari per insuficiència cardíaca	--- --- --- X1,5 681 para beta 0,1, p bilateral 0,05, 1:1 Aquesta xifra multiplica per 1,4 els ingressos per ICC reportats en l'estudi.

6. Is a per protocol analysis reported in the results?

- If the results are given for intention-to-treat analysis, are they also given for per protocol analysis?

Teniu idea de quants pacients varen interrompre el tractament assignat en aquests estudis?



- EMPAREG:
  - 25%
- CANVAS/CANVAS-R:
  - 29%
- DECLARE-TIMI:
  - 21-25%

I POT SER AIXÒ RELLEVANT EN UN ESTUDI DE NO INFERIORITAT?

6. Is a per protocol analysis reported in the results?

- If the results are given for intention-to-treat analysis, are they also given for per protocol analysis?

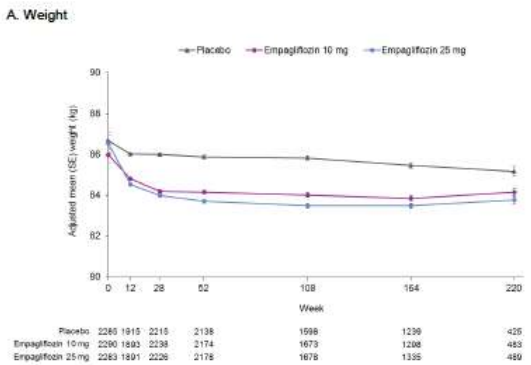
Els resultats es donen només per intenció de tractar o bé
ITT modificat, no es dona anàlisi per protocol, tot i baixa adherència

Anàlisi per protocol: HR 0,86 (0,75-1,00)
Saiz-Fernández LC, 2016. BIFT Navarra

7. Are the overall design and execution of the trial high quality?

- Were appropriate methods for allocation concealment and blinding used?
- Was the follow-up rate high?
- Were the groups similar at baseline and subject to the same care?

Blinding



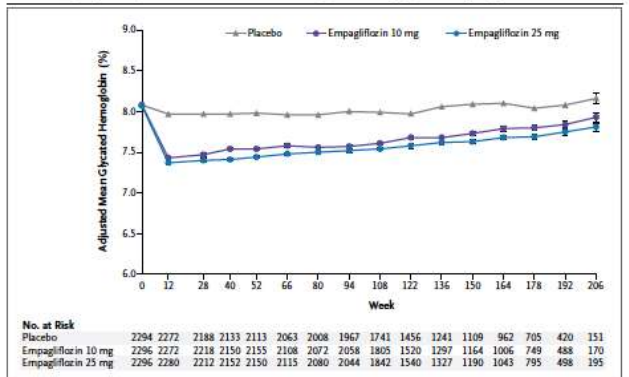
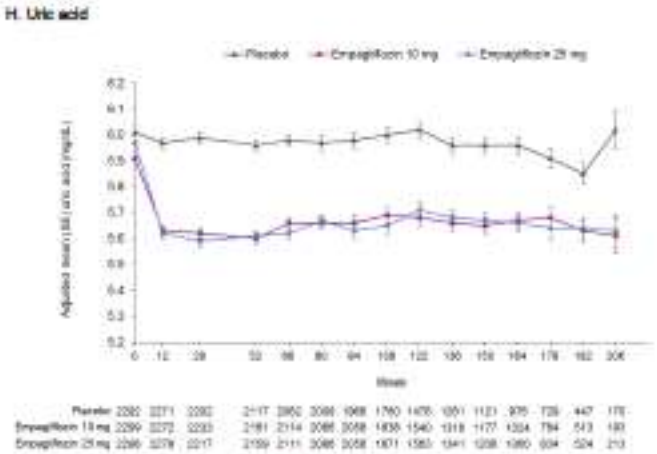
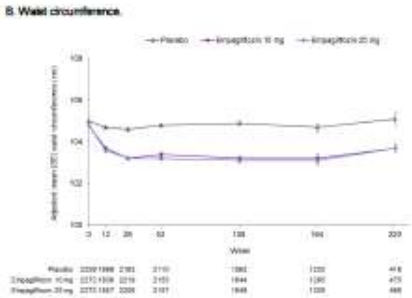
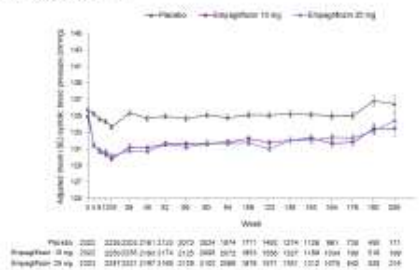


Figure 3. Glycated Hemoglobin Levels.

Shown are mean (±SE) glycated hemoglobin levels in the three study groups, as calculated with the use of a repeated-measures analysis as a mixed model of all data for patients who received at least one dose of a study drug and had a baseline measurement. The model included baseline glycated hemoglobin as a linear covariate, with baseline estimated glomerular filtration rate, geographic region, body-mass index, the last week a patient could have had a glycated hemoglobin measurement, study group, visit, visit according to treatment interaction, and baseline glycated hemoglobin according to visit interaction as fixed effects.







Similarity of care: “Standard DM2 treatment” implementing “local guidelines”

	EMPAREG		CANVAS		DECLARE-TIMI58	
HbA1c	INI	END	INI	END	INI	END
Intervenció	8,1	7,81	8,2 +/- 0,9	7,7	8,3 +/- 1,2	7,9
Control		8,16		8,25		8,1
TT stoppat	25%		29%		21-25%	

All patients participating in this trial will be treated in accordance to best standard of care in compliance with local guidelines and recommendations. On top of the treatment to achieve the above mentioned standards, two thirds of the subjects participating in this trial may derive a direct benefit from being treated with an active compound on top of their standard antidiabetic therapy. The patients will receive the investigational medication BI 10773 that has already demonstrated favorable HbA_{1c} and glucose changes at the tested doses. All the patients taking part in the trial may derive general medical benefit from careful and close monitoring by medical personnel during the study. Safety will be ensured by monitoring the subjects for AEs both clinically and by laboratory testing and by the home blood glucose monitoring. During the first 12 weeks **(for Portugal During all trial duration)** of the study, patients who are not adequately controlled as evidenced by a confirmed high FPG value (refer to Section 4.2.1) will receive rescue therapy to ensure their safety. After Visit 6 (12 weeks after randomization) the investigator will be allowed to add treatment to achieve best standard of care according to local guidelines **(for Portugal: and international guidelines). In the interest of this best standard of care, treatment changes should be considered based on the fasting plasma glucose and HbA_{1c} cut-off levels defined in Section 4.2.1.**

En l'EMPAREG, intensificació si
Entre setmanes 1-12
- Si glucèmia>240

Entre setmanes 12-28:
- Si glucèmia >200

Entre setmanes 28-final:
- Si glucèmia >180 o HbA1c>8%

4.2.1 Rescue medication, emergency procedures, and additional treatments

During the first 12 weeks after randomization (i.e., from Visits 3 to Visit 6), patients taking antidiabetic treatment should continue to take the antidiabetic treatment they were receiving before the Informed Consent signature as background therapy, the dose of which should remain unchanged if at all possible. Background medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations. After Visit 6 the background medication can remain unchanged or change partially or completely based on the investigators clinical judgment to achieve best care according to local guidelines. **For Japan, pioglitazone should not be used as background therapy.**

Rescue medication, for the treatment of hyperglycaemia, can be initiated during the initial double-blind treatment period of the trial (i.e., from Visits 3 to Visit 6) when patients are treatment naïve or on stable background treatment **(for Portugal Week 1 – 12 i.e. up to and including the result from Visit 6)** but only if the patient has a glucose level > 240 mg/dl (>13.3 mmol/l) **(for France: glucose level >200 mg/dl > 11.1 mmol/l)** after an overnight fast. This result for Fasting Plasma Glucose which can be obtained from the HBGM device should be confirmed, meaning that there is a minimum of two measurements, at least one of which should be performed after an overnight fast at the investigational site, and on a different day to the initial (overnight fast) measurement.

For Portugal: From Visit 6 (Week 12) onwards, the following cut-off levels for adjustments in the background medication and/or introduction of additional anti-diabetic medication are recommended:

- **Week 12 – 28 (i.e. from the day after Visit 6 onwards):**
  The patient has a glucose level > 200 mg/dl (> 11.1mmol/l) after an overnight fast.

- **Week 28 – end of trial (i.e. from the day after Visit 8 onwards):**
  The patient has a glucose level > 180 mg/dl (> 10.0mmol/l) and/or an HbA_{1c} > 8.0% after an overnight fast.

If the above criteria are met, the initiation of rescue medication is at the Investigator's discretion, based on the patient's current clinical condition (e.g., ongoing illness etc.), as well as the choice of rescue medication and its dosage dependent upon existing background medication. Rescue medication can also include up titration of background therapy. If insulin is part of the background therapy, changes by more than 10% of the total daily prescribed dose would be considered rescue therapy as well. Other SGLT-2 inhibitors **(for Japan: and pioglitazone)** (if available) must not be used as rescue medication. Regardless of the choice made, rescue medication should be taken in accordance with the local prescribing information of that respective medication, taking into account potential contraindications. A fasting plasma glucose and an HbA_{1c} sample should be taken before initiation of rescue therapy and sent to central lab for analysis. The HbA_{1c} sample is not required if a sample has been taken and sent to the central lab for analysis within the last 4 weeks.

In the case of symptomatic hypoglycaemia or severe hypoglycaemia appropriate adjustment of antidiabetic therapy, such as a dose reduction / discontinuation of ongoing rescue medication or existing background therapy can be initiated. Reduction or discontinuation of ongoing rescue medication should be considered before a reduction in the dose of existing background therapy.

Any rescue medication or any change in dose (i.e., dose reduction/increase) of antidiabetic medication (including background therapy) will be recorded in the source documents and on the appropriate pages of the eCRF.

Rescue medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

Any additional treatment, that does not qualify as a rescue medication, and is considered necessary for the patient's welfare may be given at the discretion of the Investigator. Exceptions to this are the restrictions described in Section 4.2.2.

There are no special emergency procedures to be followed.

7. Are the overall design and execution of the trial high quality?

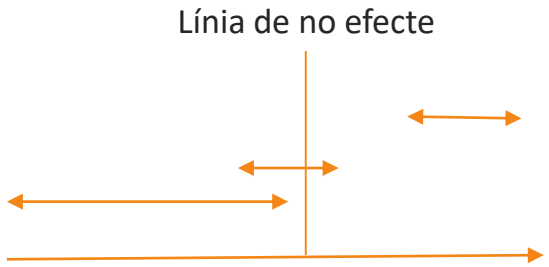
- Were appropriate methods for allocation concealment and blinding used?
- Was the follow-up rate high?
- Were the groups similar at baseline and subject to the same care?

Són estudis doble cec, pel seu disseny, però es podien identificar els pacients del grup d'intervenció i del grup control en base a paràmetres analítics de seguiment rutinari.

Les pérdues varen ser baixes però moltes suspensions de tractament

El tractament de la glucèmia va ser diferent:
Inèrcia+Intervenció vs Inèrcia+Placebo

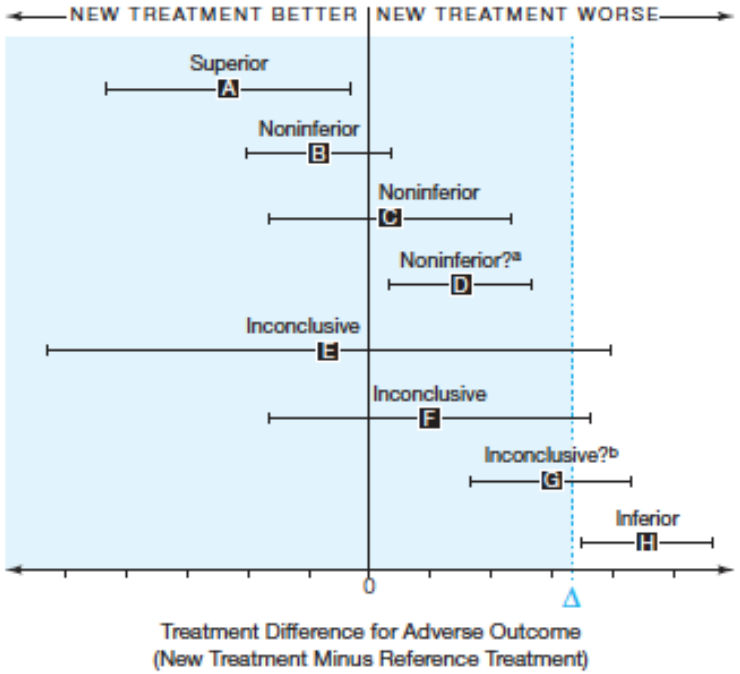
La importància dels intèrvals de confiança. Conceptes clau.



1. És el rang de valors que té un 95% de probabilitats d'incloure el valor real a la població a la qual pertany la mostra.
   - **Tots els valors dintre de l'intèrval de confiança tenen la mateixa probabilitat de correspondre al valor real de la població.**
2. Dóna informació de si les diferències trobades són estadísticament significatives i de la magnitud de les diferències.
   - Si inclou la línia de no efecte, l'efecte de la intervenció no és estadísticament diferent de l'efecte del control.
   - Com més ampli l'intèrval de confiança, més incertesa sobre l'efecte real de la intervenció.
   - L'amplitud de l'intèrval de confiança depen de la mida de la mostra, com més gran l'estudi generalment més petit l'intèrval de confiança i menys incertesa

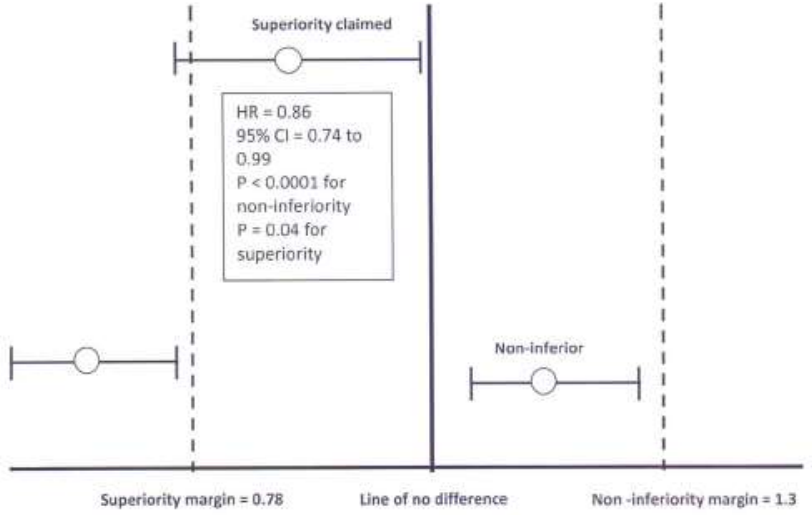
Possibles resultats d'un estudi de no-inferioritat:

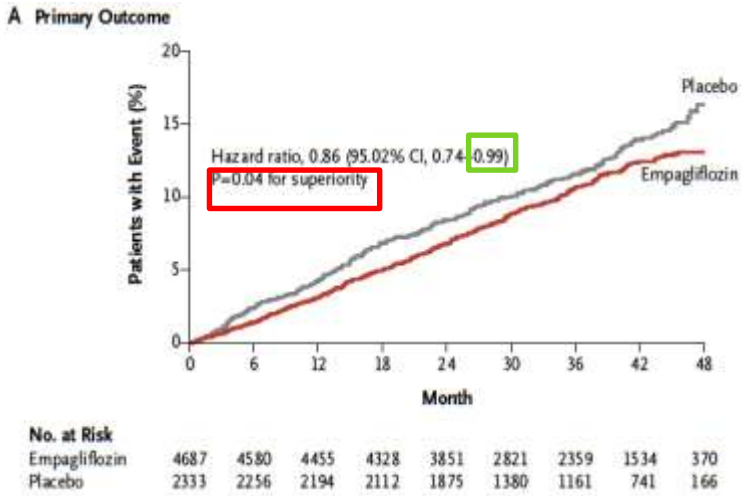
Figure 1. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



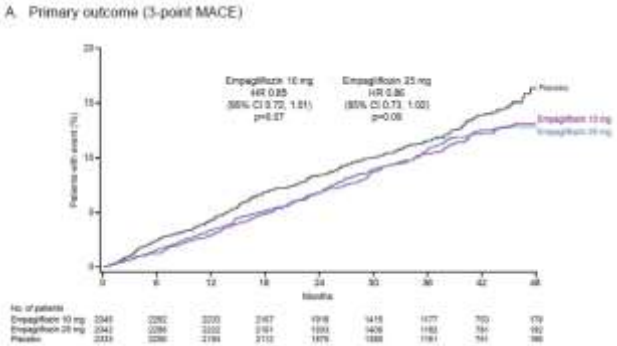
Estadísticament és correcte testar per la superioritat d'una intervenció si s'ha demostrat prèviament la no-inferioritat, altre tema és que les troballes siguin clínicament rellevants

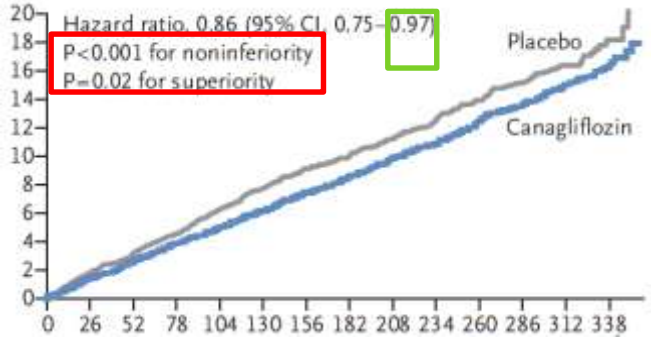
Figure 1 Superiority margin similar to the non-inferiority margin showing the erroneousness of claiming superiority. From the results of the primary composite outcome (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes study. The primary hypothesis was to show non-inferiority with a margin of 1.3. If superiority is to be claimed, the results should lie as shown in the far left of the figure.





La hipòtesi de superioritat es pot demostrar després d'haver demostrat no inferioritat, altre cosa es que sigui un resultat robust o rellevant





La resta de resultats fora dels outcomes primaris i secundaris són exploratoris i s'haurien de confirmar amb estudis adients

Què estem comprant amb els estudis de seguretat CCV que reporten superioritat?

TRIAL Calculated Number of events for primary Hypothesis testing (non-inferiority and superiority)	Results reported: HR of primary outcome, p values for non-inferiority and superiority NNT (95% IC) Calculadora epidemiológica OST FLCritica (Servicio Vasco de Evaluación de Tecnologías Sanitarias)
EMPAREG, 2015 691events (2:1) 7028 patients 3,1 years	EMPA 490/4687 (10,5%) VS PLACEBO 282/2333 (12,1%) HR, 0.86; 95% confidence interval, 0.74 to 0.99; P = 0.04 for superiority **NNT 31-2152 (point estimate 61) durant 3,1 anys per a evitar un 3p MACE**
CANVAS, 2017 688 events 10142 patients 3,6 years	CANA 426/4347 (9,8%) VS PLACEBO 585/5795 (10,1%) HR 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P = 0.02 for superiority **NNT no calculable Segons calculadora epidemiològica les dades corresponen a RR 0,97 (0,86-1,09)** ***IN FACT: APPENDIX REPORTS P 0,5980 WHEN RISKS ARE REPORTED
DECLARE-TIMI 58, 2018 1390 events 17160 patients 4,2 years	3pMACE: DAPA 756/8582 (8,8%) vs PLACEBO 803/8578 (9,4%) HR 0,83; 95% confidence interval [CI] 0,93 to 1,03; p=0,17 CV death or Hospitalization for Hfailure: No differences in CV death: CV death: DAPA 205/8582 VS PLACEBO 210/8578 Hfailure: DAPA 212/8582 (2,5%) vs PLACEBO 286/8578 (3,3%) HR 0,73 (0,61-0,85) **NNT 73-276 (point estimate 115) durant 4,2 years per a evitar 1 ingrés hospitalari per insuficiència cardíaca**

"Podems estar 95% segurs que caldria tratar entre "(marge inferior IC 95%)" y "(marge superior IC 95%)" pacients amb"(Criteris d'Inclusió)" durant "(temps de seguimint)" anys per tal d'evitar un esdeveniment CCV (mort o iam no mortal o ictus no mortal)"

CONCLUSIONS. CONTEXTUALITZACIÓ

- L'objectiu dels CVOSafety Trials és demostrar seguretat cardiovascular, no demostrar superioritat.

- La troballa de superioritat és sorprenent, màxim en fàrmacs de grups terapèutics diferents (arGLP1 i iSGLT2).

- La metodologia dels CVOSafety Trials és comuna: són estudis de no-inferioritat.

CONCLUSIONS. PUNTS CRÍTICS DE LA NO-INFERIORITAT

- Grup intervenció i grup control no competeixen en igualtat de condicions.

- L'anàlisi per protocol no és l'anàlisi primari dels estudis.
  - Pel percentatge elevat de pacients que suspenen tractament assignat probable que ITT i IPP puguin ser diferents (manca d'adherencia causa de falsos positius)

La superioritat només s'hauria d'avaluar si l'anàlisi per protocol demostra no inferioritat.

CONCLUSIONS. INTERPRETACIÓ DE LA NO-INFERIORITAT

- Fins i tot assumint que el salt de no inferioritat a superioritat fos adequat, els resultats de superioritat no són robustos i s'haurien de corroborar amb estudis dissenyats amb aquest objectiu.

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