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

CONFLICTES D'INTERÈS

- 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

OBJECTIUS

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

CAS CLINIC

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.

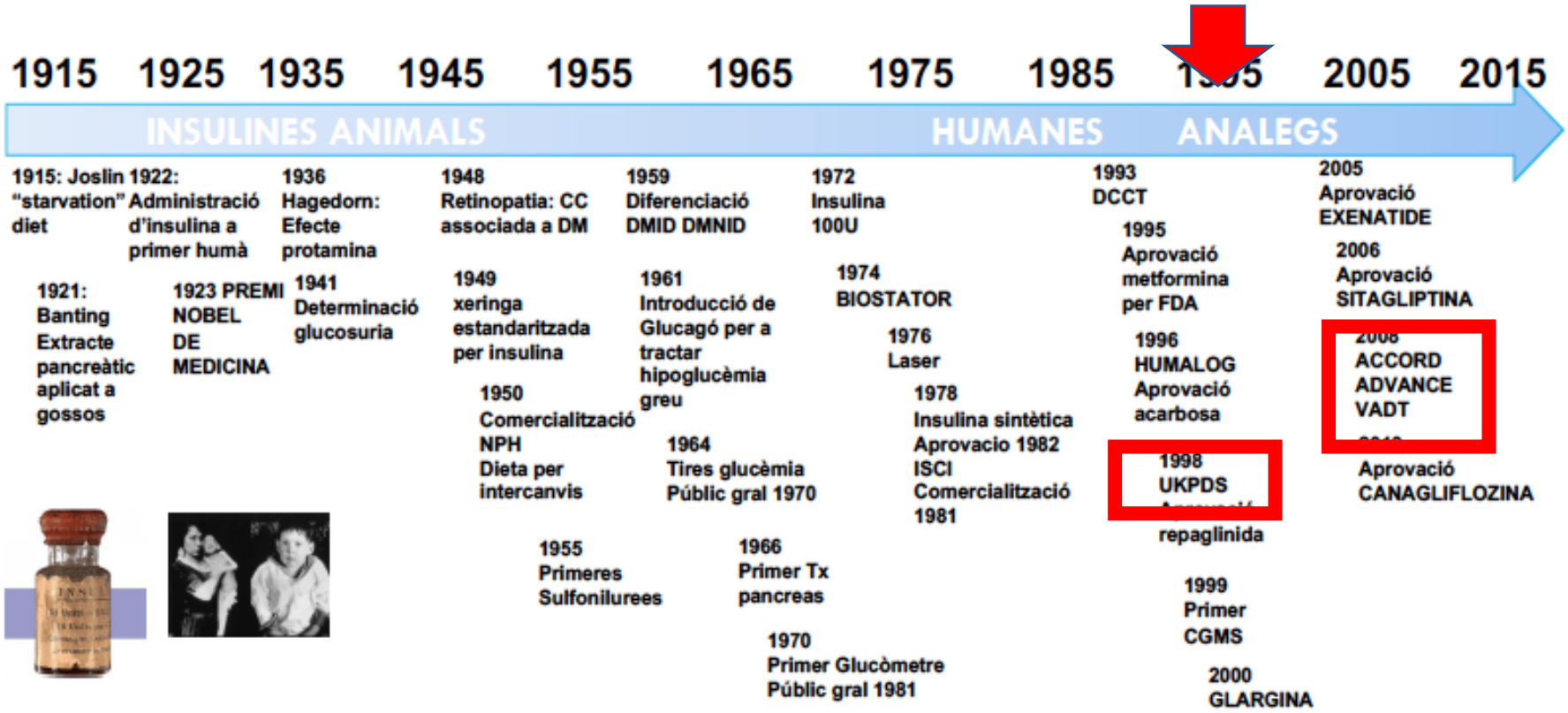
Ingressa per IAM.

Indicaries inici de glucosúric en aquest pacient?

1. Sí, es el que diuen les guies clíniques i els estudis de seguretat CCV.
2. No, no penso que estigui indicat.
3. No ho tinc clar

CONTEXTUALITZACIÓ

Fites en el tractament de la DM:



CONTEXTUALITZACIÓ

Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a *Diabetes Care* Editors' Expert Forum

William T. Cefalu,[1] Sanjay Kaul,[2] Hertzel C. Gerstein,[3] Rury R. Holman,[4] Bernard Zinman,[5] Jay S. Skyler,[6] Jennifer B. Green,[7] John B. Buse,[8] Silvio E. Inzucchi,[9] Lawrence A. Leiter,[10] Itamar Raz,[11] Julio Rosenstock,[12] and Matthew C. Riddle[13]

Diabetes Care 2018;41:14–31 | https://doi.org/10.2337/dci17-0057

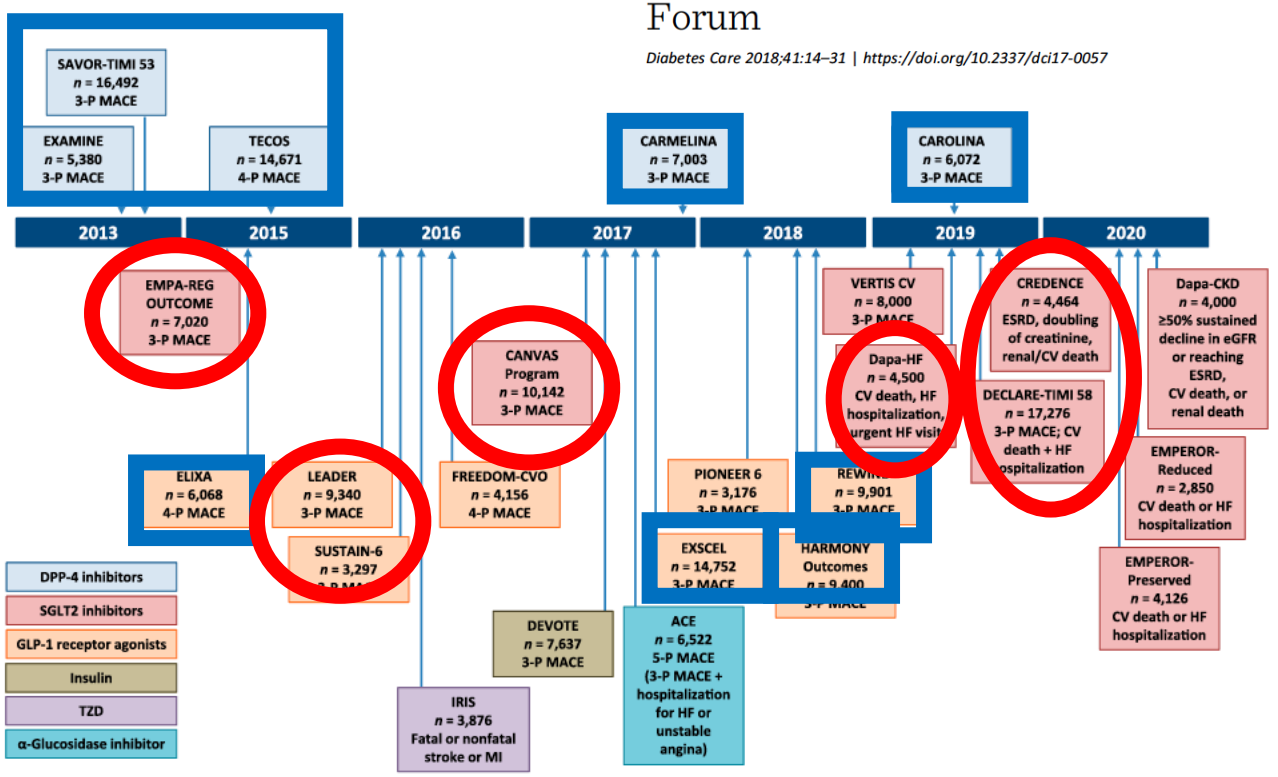


Figure 1—Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point. DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; ESRD, end-stage renal disease; HARMONY Outcomes, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; PIONEER 6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

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

Són RCT doble cecs.
S'han fet per a complir requeriment de la FDA
S'han publicat en revistes d'alt factor d'impacte.
Estan finançats per la industria
El comparador sol ser placebo
Molts tenen un disseny de no inferioritat

ESTUDIS 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.

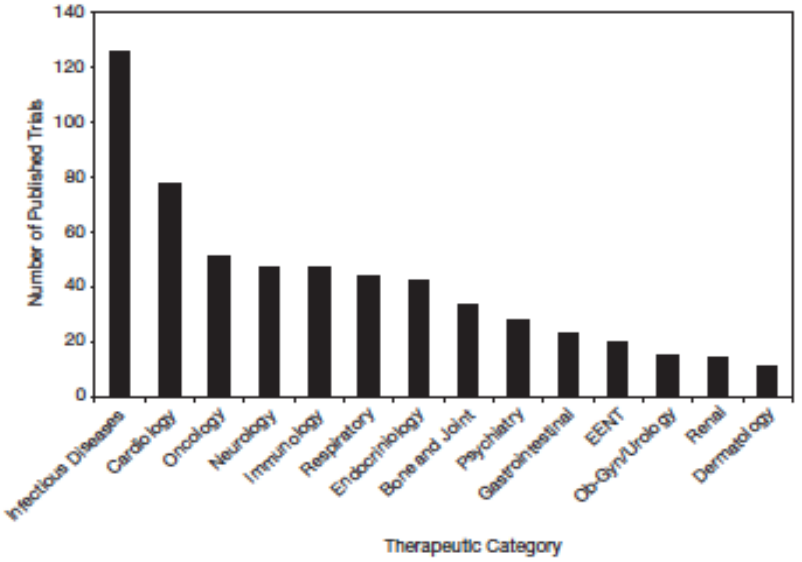


Figure 3. Numbers of published noninferiority trials by therapeutic category. EENT = eye, ears, nose, and throat; Ob-Gyn = obstetrics and gynecology.

(Pharmacotherapy 2011;31(9):833–839)

ESTUDIS 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*

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

CrossMark

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

10.1136/ebmed-2017-110685

Abstract

haemoglobin, the Food and Drug Administration (FDA)

▸ 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

Assajos clínics de no inferioritat. La base.
4. L'anàlisi per protocol és crític

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.	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? Es el que demana la FDA per a demostrar seguretat CCV er 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

XXX CONGRESO DE LA SOCIEDAD ESPAÑOLA DE DIABETES
CENTRO DE CONVENCIONES DEL HOTEL BARCELÓ RENACIMIENTO
Sevilla 24-26 Abril 2019 www.sedsevilla2019.com

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

Wifredo Ricart 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 **T**rials) 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 ítems) 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.

		EMPAGLIFLOZIN	CANAGLIFLOZIN	DAPAGLIFLOZIN	LIRAGLUTIDE	SEMAGLUTIDE	LIXISENATIDE	EXENATIDE	ALBIGLUTIDE	SAXAGLIPTIN	ALOGLIPTIN	SITAGLITPIN	LINAGLIPTIN	% 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													42
	% adherencia	46	36	46	46	46	18	27	27	27	81	27	46	

Extension of 2010 CONSORT checklist; Rojo: 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.

- 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?

- 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?

- Is the hypothesis clearly stated?

En realitat, cal anar a l'apartat d'anàlisi estadística per a trobar que es tracta d'estudis de no inferio *ANTI-CONSORT* de no inferioritat no s'esmenta enlloc del paper.

- 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?

- 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?

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

- 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?

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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.

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	--- --- --- 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. x1,5

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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

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Blinding

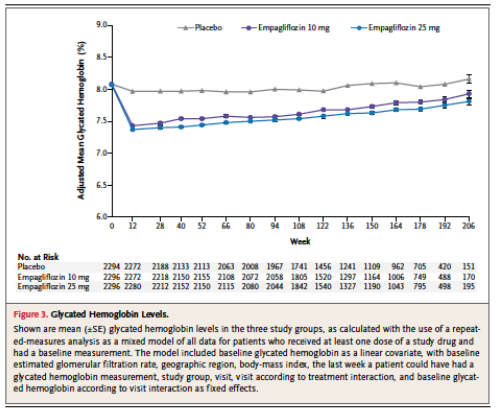
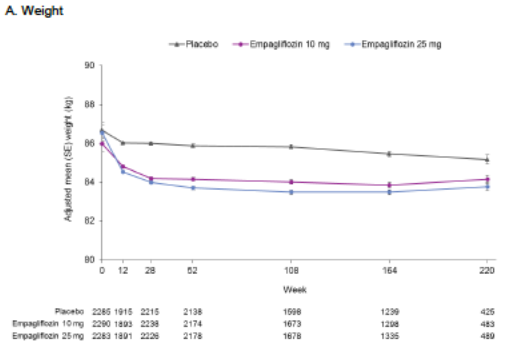
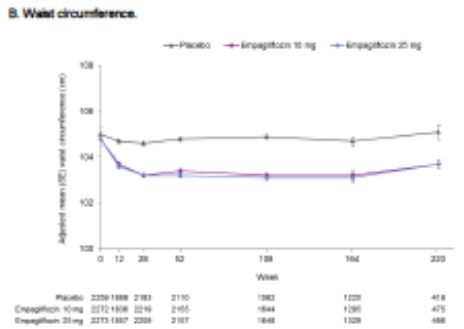
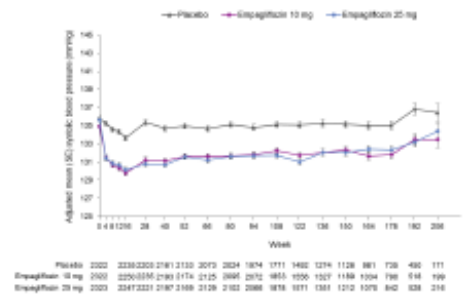


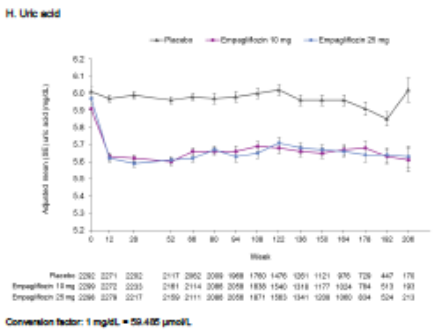
Figure 3. Glycated Hemoglobin Levels.

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.









Conversion factor: 1 mg/dL = 59.485 μmol/L

Similarity of care: Standard DM2 treatment implementing local guidelines

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	8,1
Control		8,16		8,25		7,9
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.

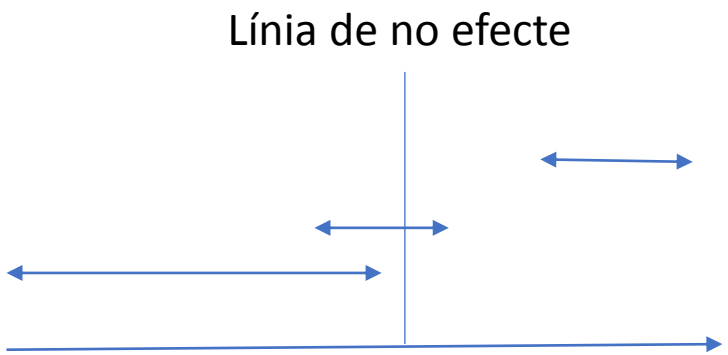
There are no special emergency procedures to be followed.

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:

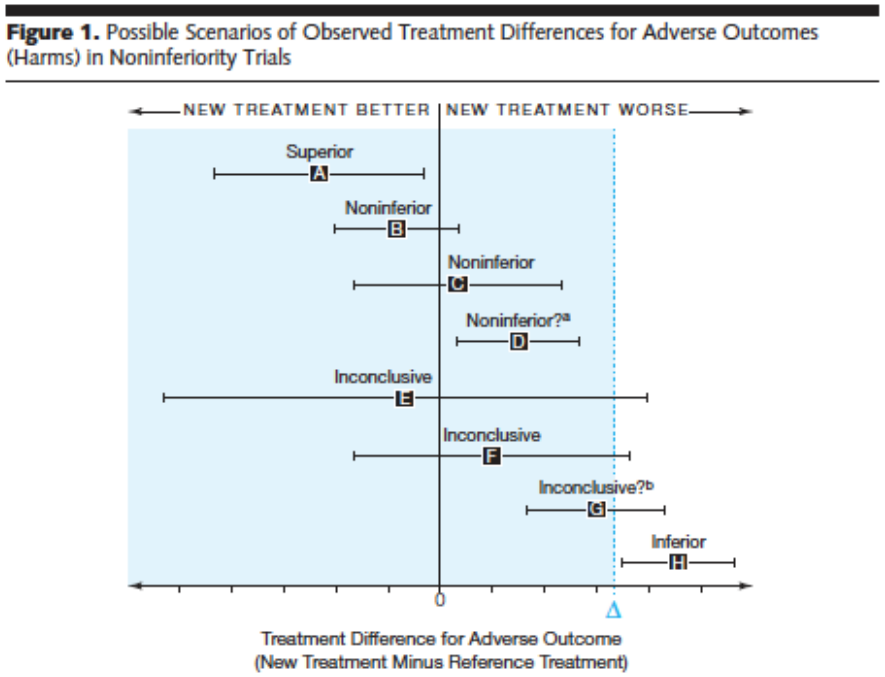


Figure 1. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials

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

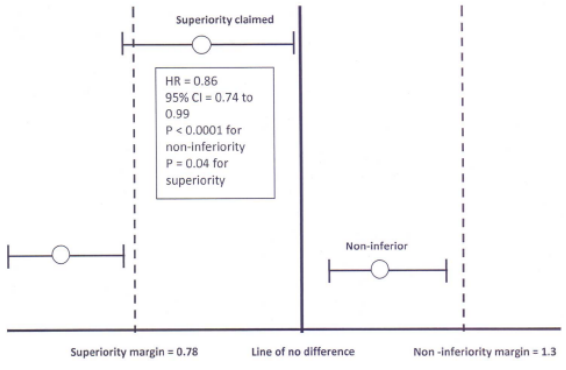
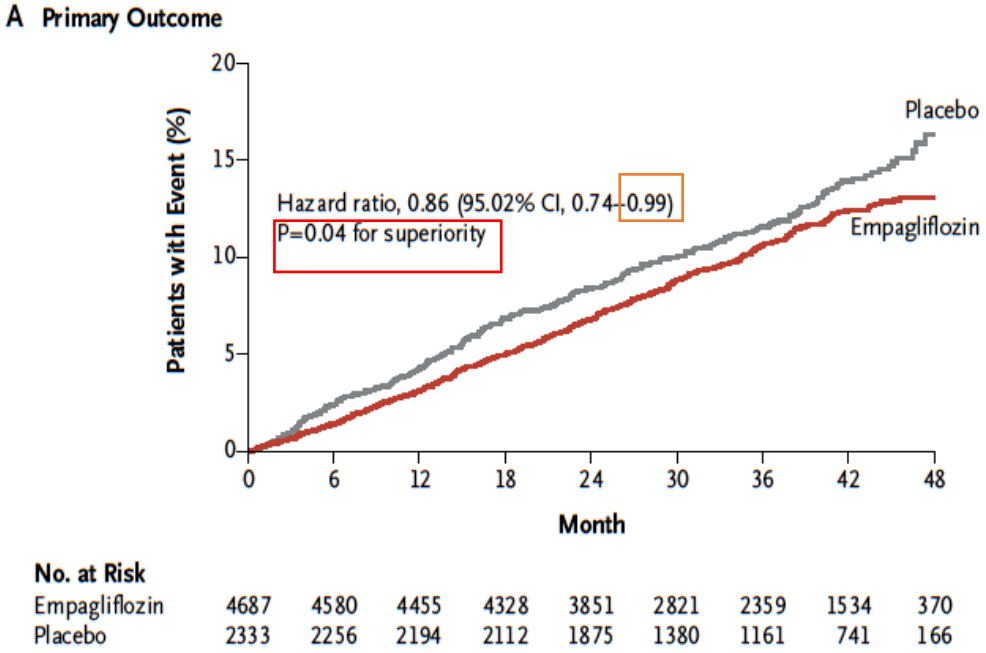
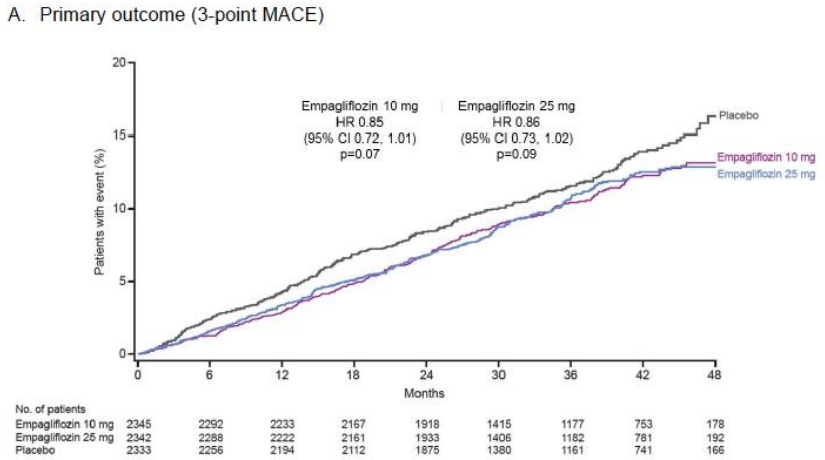
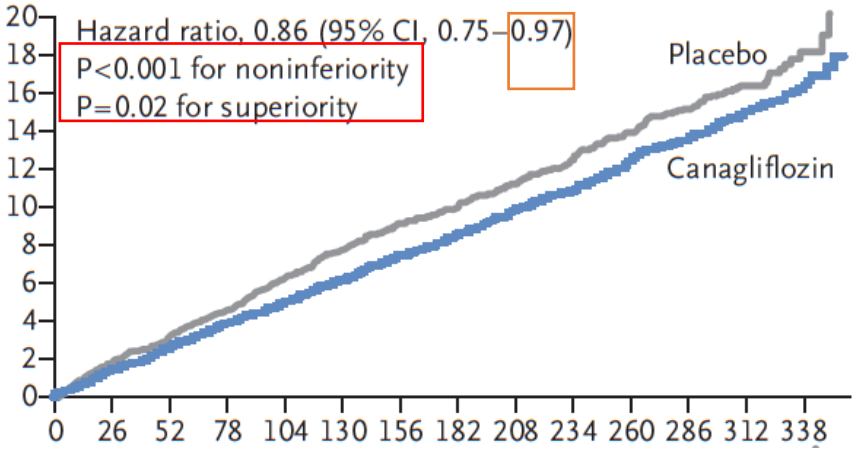


Figure 1 Superiority margin similar to the non-inferiority margin showing the erroneousness of claiming superiority. From the results of the primary composite outcome (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) in the Empagliflozin, Cardiovascular Outcomes, 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

Studies reporting superiority for primary outcome (MACE-3) Follow-up (years)
EMPAREG Empagliflozin, 10 Empagliflozin 25 Placebo
CANVAS/ Canagliflozin 100 Canaglifozin 300 Placebo CANVAS R Canagliflozin 100 to 300 Placebo

"Si un total de "(índice de fragilidad)" eventos del outcome analizado se pasaran del grupo comparador al grupo de intervención, se perdería la significación estadística para superioridad."

"Podemos estar 95% seguros de que habría que tratar entre "(margen inferior IC 95%)" y "(margen superior IC 95%)" pacientes con "(Criterios Inclusión)" durante "(tiempo de seguimiento)" años para evitar un evento CCV (muerte 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)

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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ELSEVIER

Journal of Clinical Epidemiology 67 (2014) 622–628

Journal of Clinical Epidemiology

The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index

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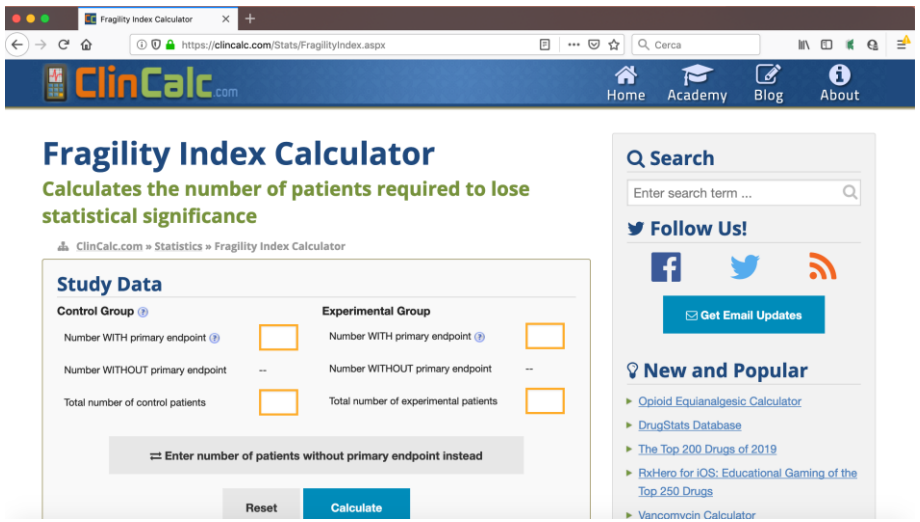

THE JOURNAL OF FAMILY PRACTICE

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
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peace
Love

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

ABSTRACT

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

METHODS

In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m² of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m²), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.

RESULTS

The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.

CONCLUSIONS

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South Wales Sydney, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at vperkovic@georgeinstitute.org.au.

*A complete list of the CREDENCE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 14, 2019, at NEJM.org.

DOI: 10.1056/NEJMoa1811744

Peculiaritats

PRIMARY OUTCOME:

Primary outcome:
The primary outcome was a composite of endstage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m2 sustained for at least 30 days according to central laboratory assessment), doubling of the serum creatinine level from baseline (average of randomization and prerandomization value) sustained for at least 30 days according to central laboratory assessment, or death from renal or cardiovascular disease.

STOPPED EARLY:

Randomized Trials Stopped Early for Benefit

A Systematic Review

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Christoph H. Eggert, MD
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Edward Mills, PhD
Gordon H. Guyatt, MD, MSc

Context Randomized clinical trials (RCTs) that stop earlier than planned because of apparent benefit often receive great attention and affect clinical practice. Their prevalence, the magnitude and plausibility of their treatment effects, and the extent to which they report information about how investigators decided to stop early are, however, unknown.

Objective To evaluate the epidemiology and reporting quality of RCTs involving interventions stopped early for benefit.

Data Sources Systematic review up to November 2004 of MEDLINE, EMBASE, Current Contents, and full-text journal content databases to identify RCTs stopped early for benefit.

Study Selection Randomized clinical trials of any intervention reported as having stopped early because of results favoring the intervention. There were no exclusion criteria.

Data Extraction Twelve reviewers working independently and in duplicate abstracted data on content area and type of intervention tested, reporting of funding, type of end point driving study termination, treatment effect, length of follow-up, estimated sample size and total sample studied, role of a data and safety monitoring board in stopping the study, number of interim analyses planned and conducted, and existence and type of monitoring methods, statistical boundaries, and adjustment procedures for interim analyses and early stopping.

Data Synthesis Of 143 RCTs stopped early for benefit, the majority (92) were published in 5 high-impact medical journals. Typically, these were industry-funded drug trials in cardiology, cancer, and human immunodeficiency virus/AIDS. The proportion of all RCTs published in high-impact journals that were stopped early for benefit increased from 0.5% in 1990-1994 to 1.2% in 2000-2004 ($P<.001$ for trend). On average, RCTs recruited 63% (SD, 25%) of the planned sample and stopped after a median of 13 (interquartile range [IQR], 3-25) months of follow-up, 1 interim analysis, and when a median of 66 (IQR, 23-195) patients had experienced the end point driving study termination (event). The median risk ratio among truncated RCTs was 0.53 (IQR, 0.28-0.66). One hundred thirty-five (94%) of the 143 RCTs did not report at least 1 of the following: the planned sample size (n=28), the interim analysis after which the trial was stopped (n=45), whether a stopping rule informed the decision (n=48), or an adjusted analysis accounting for interim monitoring and truncation (n=129). Trials with fewer events yielded greater treatment effects (odds ratio, 28; 95% confidence interval, 11-73).

Conclusions RCTs stopped early for benefit are becoming more common, often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small. These findings suggest clinicians should view the results of such trials with skepticism.

JAMA. 2005;294:2203-2209 www.jama.com

Els trials que s'aturen prematurament per benefici de la intervenció:

- *Inclouen 60% dels individus planejats en promig*
- *Sobrevaloren sistemàticament l'efecte de la intervenció sense cap factor de correcció/ Modulació*
- *No es reporten detalls de forma transparent*

ORIGINAL ARTICLE

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STOPPED EARLY:

HIERARCHICAL HYPOTHESIS:

The primary outcome was a composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 sustained for at least 30 days according to central laboratory assessment), doubling of the serum creatinine level from baseline (average of randomization and prerandomization value) sustained for at least 30 days according to central laboratory assessment, or death from renal or cardiovascular disease.

Secondary outcomes that were planned for sequential hierarchical testing were specified in the following order: first, a composite of cardiovascular death or hospitalization for heart failure; second, a composite of cardiovascular death, myocardial infarction, or stroke; third, hospitalization for heart failure; fourth, a composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death; fifth, cardiovascular death; sixth, death from any cause; and seventh, a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or for unstable angina. All other efficacy outcomes were exploratory.

HIPÓTESIS JERÁRQUICA,

QUÉ TENDRIA QUE PROBARSE PRIMERO?

LO MÁS FRECUENTE?

O LO MÁS IMPORTANTE?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

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

ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

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

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Peculiaritats

Estudi de superioritat

VARIABLE PRIMÀRIA:
Ingrés o consulta per IC que Requereixi de tt iv o
MACE-3

VARIABLE PRIMÀRIA:
Ingrés o consulta per IC que Requereixi de tt iv o
Mort Cardiovascular

VARIABLE PRIMÀRIA:
HR (95%IC) 0,74 (0,65 to 0,85)

- Descompensació IC

HR (95% IC) 0,70 (0,59-0,83)

- Cardiovascular Death

HR (95%IC) 0,82 (0,69-0,98)

ELSEVIER

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The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index

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HR (95%IC) 0,82 (0,69-0,98)

Follow-up 18 mesos	NNT (95%) IC	Fragility Index
Outcome primario		
Ingreso por ICC o necesidad de tto iv		
Muerte CCV		

- *Si 5 esdeveniments del grup dapa passessin al grup placebo es perdria la significació estadística.*
- *Aquest nombre és inferior al número de pacients perduts de seguiment*
- *Els resultats pel que fa el component mort CCV són poc robustos.*

https://clincalc.com/Stats/FragilityIndex.aspx