## Evidence Based Medicine(EBM)

# Critical Appraisal for Randomized Controlled Trial

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實證醫學組

# *實證醫學的五個步驟

1) Ask an answerable question〔問可以回答的問題〕
2) Search for the best evidences〔搜尋最佳證據〕
3) Critically appraise those evidences〔嚴格的文獻評讀〕
4) Apply to the patient〔臨床應用〕
5) Evaluate our performance〔評估與稽核以上步驟〕

# *Critical Appraisal Tools

* Critical Appraisal Skills Programme(CASP) --- from Oxford Centre for Triple Value Healthcare
* Critical Appraisal Tools from CEBM(Centre for Evidence-Based Medicine) (University of Oxford)
* Critical Appraisal Tools from Joanna Briggs Institute
* Critical Appraisal Tools from Duke University
* ……

## CASP Appraisal Checklists

**(click to download either a version to print and handfill, or a version to fill in electronically)**

### Print

(print a paper version to fill in by hand, then file away for future reference)

**CASP Systematic Review Checklist** PDF

**CASP Qualitative Checklist** PDF

### Edit electronically

(save the file to your computer first, complete your appraisal and then save with the name of the paper)

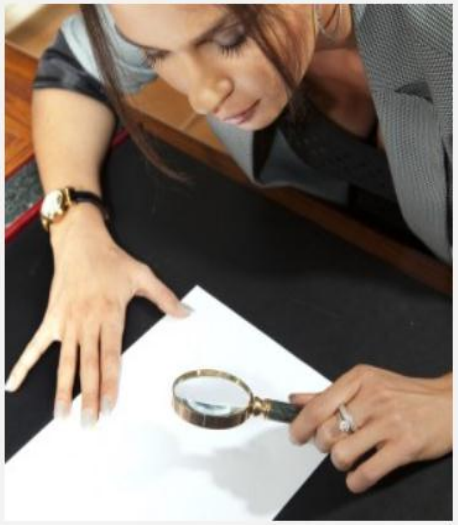
**CASP Systematic Review Checklist** PDF

**CASP Qualitative Checklist** PDF

# Critical Appraisal tools

Critical appraisal is the systematic evaluation of clinical research papers in order to establish:

1. Does this study address a clearly focused question?
2. Did the study use valid methods to address this question?
3. Are the valid results of this study important?
4. Are these valid, important results applicable to my patient or population?



If the answer to any of these questions is "no", you can save yourself the trouble of reading the rest of it.

This section contains useful tools and downloads for the critical

**What's on**

**Intro to Synthesising Qualitative Research**

***02 July 2019***

Systematic reviews of qualitative literature are increasingly common in health care and other disciplines. Join us for this one day introduction.

**EBMLive**

# Critical Appraisal Tools



## Critical Appraisal Tool Downloads

| | | |
|---|---|---|
| Checklist for Case Control Studies | PDF (268 KB) | DOC (52 KB) |
| Checklist for Case Reports | PDF (263 KB) | DOC (51 KB) |
| Checklist for Case Series | PDF (279 KB) | DOC (67 KB) |
| Checklist for Cohort Studies | PDF (272 KB) | DOC (54 KB) |
| Checklist for Diagnostic Test Accuracy Studies | PDF (271 KB) | DOC (57 KB) |
| Checklist for Economic Evaluations | PDF (201 KB) | DOC (60 KB) |
| Checklist for Prevalence Studies | PDF (274 KB) | DOC (55 KB) |
| Checklist for Quasi-Experimental Studies (non-randomized experimental studies) | PDF (269 KB) | DOC (56 KB) |

CASP
Critical Appraisal Skills Programme

www.casp-uk.net
info@casp-uk.net
Summertown Pavilion, Middle Way Oxford OX2 7LG

**CASP Checklist:** 11 questions to help you make sense of a **Randomised Controlled Trial**

**How to use this appraisal tool:** Three broad issues need to be considered when appraising a trial:

- Are the results of the study valid? (Section A)
- What are the results? (Section B)

→ **Critically appraisal**

- Will the results help locally? (Section C) → **Apply to patient**

The 11 questions on the following pages are designed to help you think about these issues systematically. The first three questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

## Section A: Are the results of the trial valid?

1. Did the trial address a clearly focused issue?

| | |
|---|---|
| Yes | |
| Can't Tell | |
| No | |

*此研究是否問了一個清楚明確的問題？

**是否文有對題？**

**看標題及摘要**，以PICO (patient, intervention, comparison, outcome)的方式思考，或是**找文章前言的最後一兩段**，會寫到這篇研究最主要的目的。

# 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

## ABSTRACT

### BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

### METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

Empagliflozin has been associated with an increase in levels of both low-density lipoprotein (LDL)[14] and high-density lipoprotein (HDL) cholesterol.[13-16] The most common side effects of empagliflozin are urinary tract infection and genital infection.[12]

In the EMPA-REG OUTCOME trial, we examined the effects of empagliflozin, as compared with placebo, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care.

## METHODS

### STUDY OVERSIGHT

The trial was designed and overseen by a steering committee that included academic investigators and employees of Boehringer Ingelheim. The

and revised by all the auth
assistance, which was pai
Ingelheim, was provided b
Group.

### STUDY DESIGN

As described previously,[23] th
double-blind, placebo-contr
the effect of once-daily emp
of either 10 mg or 25 mg
cardiovascular events in ad
betes at high cardiovascula
ground of standard care. Pa
590 sites in 42 countries.
until an adjudicated primar
occurred in at least 691 pat

### STUDY PATIENTS

Eligible patients with type 2

2. Was the assignment of patients to treatments randomised?

| | |
|---|---|
| Yes | |
| Can't Tell | |
| No | |

*此研究是否適當的隨機分派病患？

Randomization ?
Allocation concealment ?

***找研究方法 (Methods)的部分**，或以關鍵字搜尋“random”，來看此研究隨機分派的方法是否有說明並且適當。

# *Randomization

*隨機分派。

*讓組與組之間的基本特徵相近，目的是要控制可能的影響因子 (confounding factor)。

*Centralised computer randomisation is ideal and often used in multi-centred trials.

# *Allocation Concealment

*分派隱匿。

*分派受試者的過程中採取保密措施，無法得知下一位受試者將會被分派到哪一組。

*降低分派偏誤 (allocation bias)。

# *Examples of no allocation concealment

- *Holding translucent envelopes up to bright light to reveal upcoming assignment.
- *Opening unsealed assignment envelopes.
- *The whole randomization list is emailed to the study personnel in advance.
- *Asking a central randomization center for the next several assignments all at once.

n side effects of
nfection and geni-

E trial, we exam-
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2 diabetes at high
who were receiv-

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er Ingelheim. The
funding the trial.
independent aca-

Group.

## STUDY DESIGN

As described previously,[23] this was a randomized, double-blind, placebo-controlled trial to assess the effect of once-daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against a background of standard care. Patients were treated at 590 sites in 42 countries. The trial continued until an adjudicated primary outcome event had occurred in at least 691 patients.

## STUDY PATIENTS

Eligible patients with type 2 diabetes were adults (≥18 years of age) with a body-mass index (the weight in kilograms divided by the square of the

## STUDY PROCEDURES

Eligible patients underwent a 2-week, open-label, placebo run-in period in which background glucose-lowering therapy was unchanged. Patients meeting the inclusion criteria were then randomly assigned in a 1:1:1 ratio to receive either 10 mg or 25 mg of empagliflozin or placebo once daily. Randomization was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system and was stratified according to the glycated hemoglobin level at screening (<8.5% or ≥8.5%), body-mass index at randomization (<30 or ≥30), renal function at screening (eGFR, 30 to 59 ml, 60 to 89 ml, or ≥90 ml per minute per 1.73 $m^2$), and geographic region (North America [plus Australia and New Zealand], Latin America, Europe, Africa, or Asia).

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## STATISTICAL A

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obesity, and family history of premature CVD. Exclusion criteria have previously been reported (13).

## Randomization and Intervention

From October 2003 to June 2009, 7447 suitable candidates were enrolled in the trial. The study nurse from each recruiting center randomly assigned each participant to the corresponding intervention group following computer-generated random numbers for allocation contained in sealed envelopes, which were centrally prepared for each center by the coordinating unit. Four strata of randomization were built by sex and age (cutoff, 70 years) but not by baseline diabetes status. The primary care physicians did not participate in the randomization process. The study nurses were independent of the nursing staff of the primary care health centers. Therefore, they were not involved in the usual clinical care of participants, and their exclusive role was to collect data for the trial. Given the

3. Were all of the patients who entered the trial properly accounted for at its conclusion?

Yes

Can't Tell

No

*是否所有的病患都有納入結果中去分析？

Intention-To-Treat (ITT) or per-protocol (PP) analyses ?

How long is the follow-up ?

***找 Methods 中的 Statistical Analysis 及 Results 的部分。** (在PDF中用 intention-to-treat 關鍵字找)

# *Intention-to-treat(ITT) analysis

*所謂的 intention-to-treat，應該具備以下條件:

(1) 無論是否接受介入，都應該維持隨機分派後的狀態
(2) 應該評估所有受試者的預後
(3) 所有接受隨機分派的受試者都應該納入分析

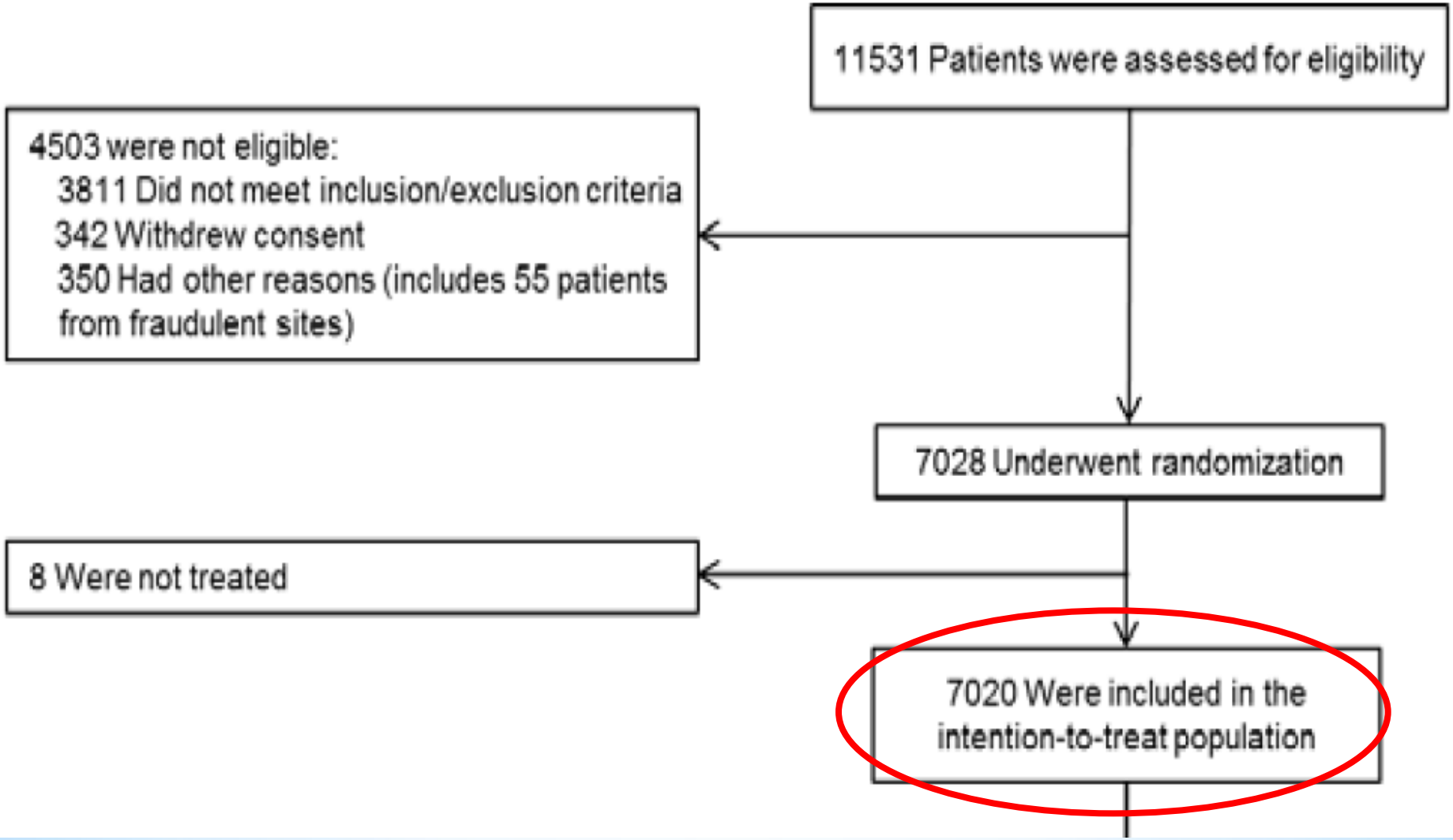
# *Per protocol (PP) analysis

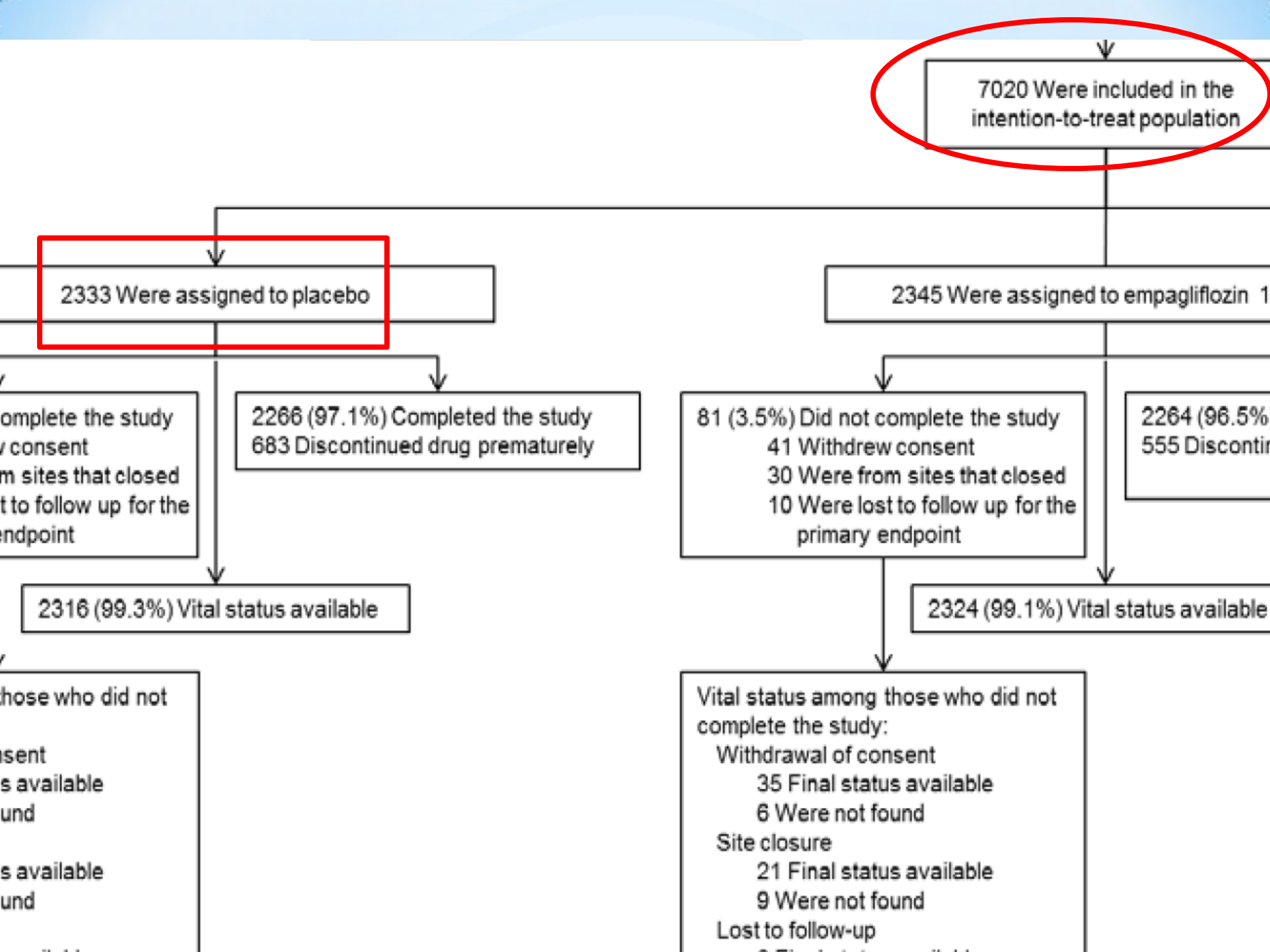
*所謂的 Per Protocol，依字面上的意思，就是按照計劃書接受分派的治療

*Per Protocol analysis 即是按照計劃書乖乖接受治療的受試者才納入分析

numbers of patients at risk, cumulative-incidence plots have been truncated at 48 months. We calculated the number of patients who would need to be treated to prevent one death on the basis of the exponential distribution.

We performed the primary analysis using a modified intention-to-treat approach among patients who had received at least one dose of a study drug. Data for patients who did not have an event were censored on the last day they were known to be free of the outcome. Secondary


11531 Patients were assessed for eligibility
4503 were not eligible:
3811 Did not meet inclusion/exclusion criteria
342 Withdrew consent
350 Had other reasons (includes 55 patients from fraudulent sites)
7028 Underwent randomization
8 Were not treated
7020 Were included in the intention-to-treat population


7020 Were included in the intention-to-treat population
2333 Were assigned to placebo
2345 Were assigned to empagliflozin
omplete the study
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m sites that closed
t to follow up for the
ndpoint
2266 (97.1%) Completed the study
683 Discontinued drug prematurely
81 (3.5%) Did not complete the study
41 Withdrew consent
30 Were from sites that closed
10 Were lost to follow up for the primary endpoint
2264 (96.5%
555 Discontin
2316 (99.3%) Vital status available
2324 (99.1%) Vital status available
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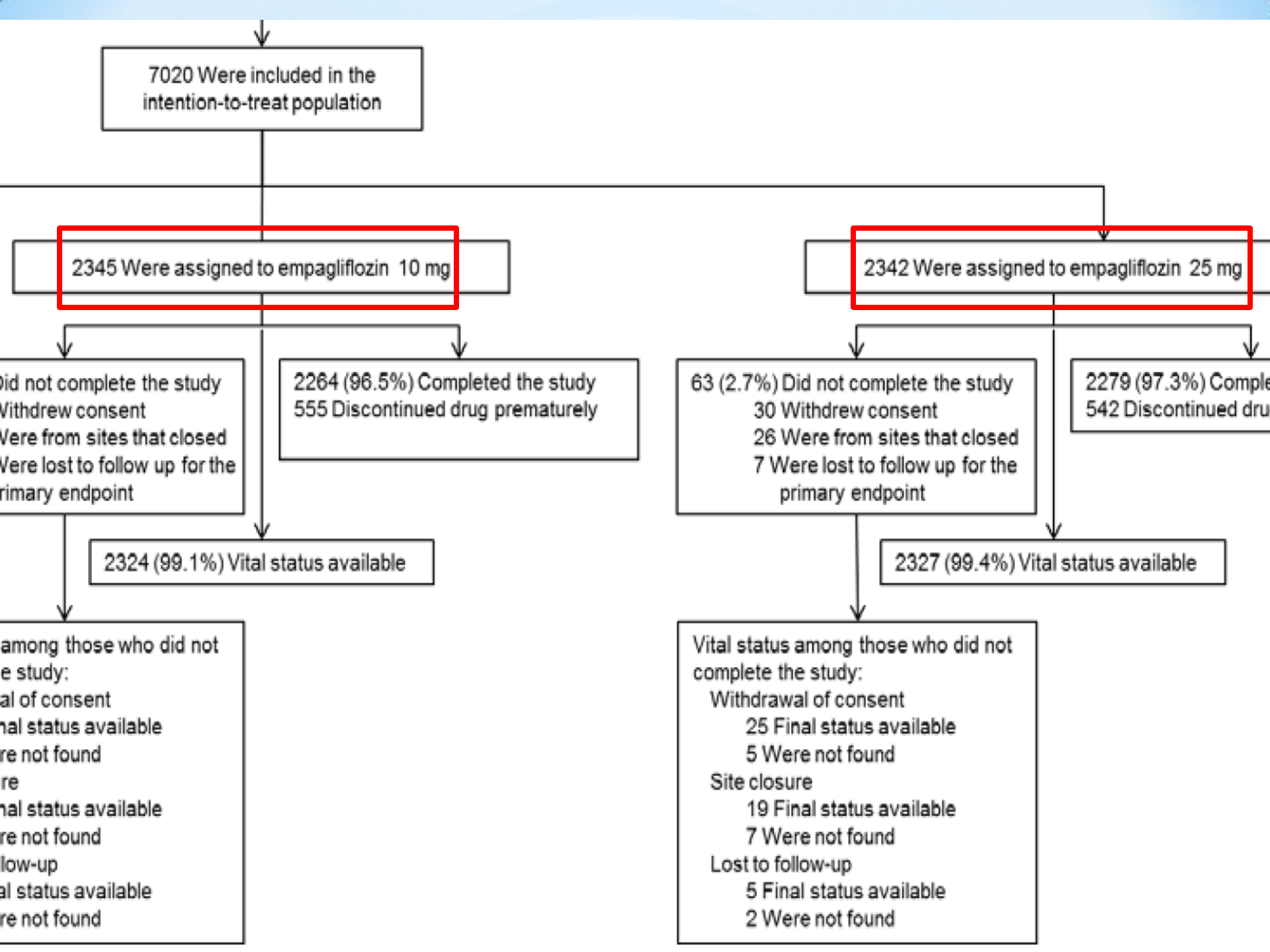
und
Vital status among those who did not complete the study:
Withdrawal of consent
35 Final status available
6 Were not found
Site closure
21 Final status available
9 Were not found
Lost to follow-up


7020 Were included in the intention-to-treat population
2345 Were assigned to empagliflozin 10 mg
2342 Were assigned to empagliflozin 25 mg
id not complete the study
Withdrew consent
Were from sites that closed
Were lost to follow up for the rimary endpoint
2264 (96.5%) Completed the study
555 Discontinued drug prematurely
63 (2.7%) Did not complete the study
30 Withdrew consent
26 Were from sites that closed
7 Were lost to follow up for the primary endpoint
2279 (97.3%) Comple
542 Discontinued dru
2324 (99.1%) Vital status available
2327 (99.4%) Vital status available
among those who did not e study:
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al status available
re not found
Vital status among those who did not complete the study:
Withdrawal of consent
25 Final status available
5 Were not found
Site closure
19 Final status available
7 Were not found
Lost to follow-up
5 Final status available
2 Were not found

| | | |
|---|---|---|
| | Total: 7020 | |
| Placebo: 2333 | Empagliflozin 10mg: 2345 | Empagliflozin 25mg: 2342 |
| | Empagliflozin 10mg + 25mg: 2345 + 2342 = 4687 | |

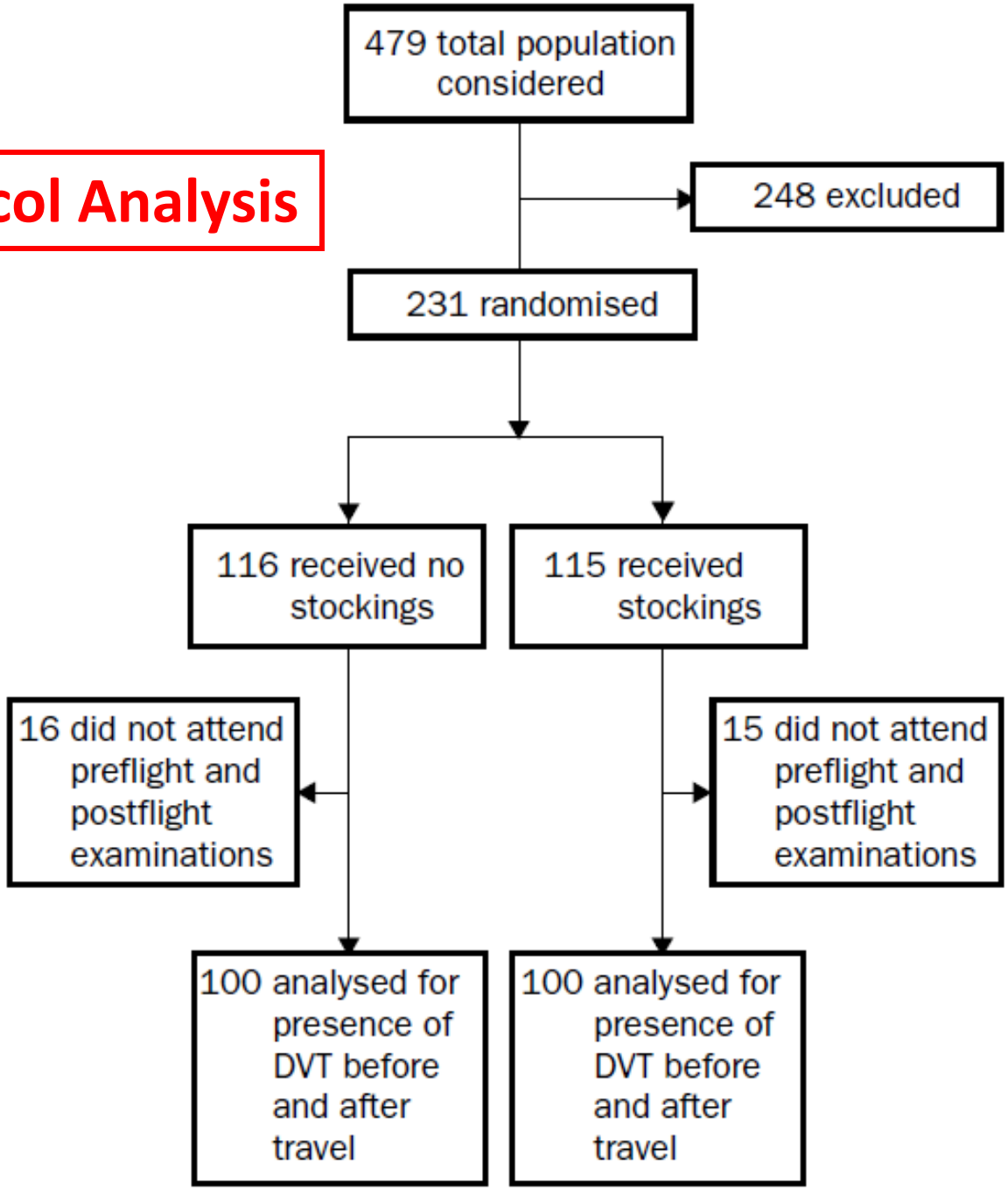
**Table 1. Primary and Secondary Cardiovascular Outcomes.**

| 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 |

**Table 2. Adverse Events.***

| Event | Placebo (N = 2333) | Empagliflozin, 10 mg (N = 2345) | Empagliflozin, 25 mg (N = 2342) | Pooled Empagliflozin (N = 4687) |
|---|---|---|---|---|
| | *number of patients (percent)* | | | |
| Any adverse event | 2139 (91.7) | 2112 (90.1) | 2118 (90.4) | 4230 (90.2)† |
| Severe adverse event | 592 (25.4) | 536 (22.9) | 564 (24.1) | 1100 (23.5)‡ |
| Serious adverse event | | | | |
| Any | 988 (42.3) | 876 (37.4) | 913 (39.0) | 1789 (38.2)† |
| Death | 119 (5.1) | 97 (4.1) | 79 (3.4) | 176 (3.8)§ |
| Adverse event leading to discontinuation of a study drug | 453 (19.4) | 416 (17.7) | 397 (17.0) | 813 (17.3)§ |
| Confirmed hypoglycemic adverse event¶ | | | | |
| Any | 650 (27.9) | 656 (28.0) | 647 (27.6) | 1303 (27.8) |
| Requiring assistance | 36 (1.5) | 33 (1.4) | 30 (1.3) | 63 (1.3) |
| Event consistent with urinary tract infection‖ | 423 (18.1) | 426 (18.2) | 416 (17.8) | 842 (18.0) |
| Male patients | 158 (9.4) | 180 (10.9) | 170 (10.1) | 350 (10.5) |
| Female patients | 265 (40.6) | 246 (35.5) | 246 (37.3) | 492 (36.4)‡ |
| Complicated urinary tract infection** | 41 (1.8) | 34 (1.4) | 48 (2.0) | 82 (1.7) |
| Event consistent with genital infection†† | 42 (1.8) | 153 (6.5) | 148 (6.3) | 301 (6.4)† |

# Per Protocol Analysis



# *Follow Up

*How long is the follow-up ?

*How complete is the follow-up ?

# *How long is the follow-up ?

## Study 要做多久才夠 ?

*Infection control:  3 to 4 weeks

*Diabetes control:  6 months

*Risk of cardiovascular disease: 5-6 years ?

*Risk of cancer:  > 10 years ?

*“轉骨丹” 或 “當大人” 的療效: ?

# *How complete is the follow-up ?

*Drop out rate: should be at least **< 20%** (If few patients have the outcome of interest, then even small losses to follow-up can bias the results.)

*The number and reason for loss to follow-up ?

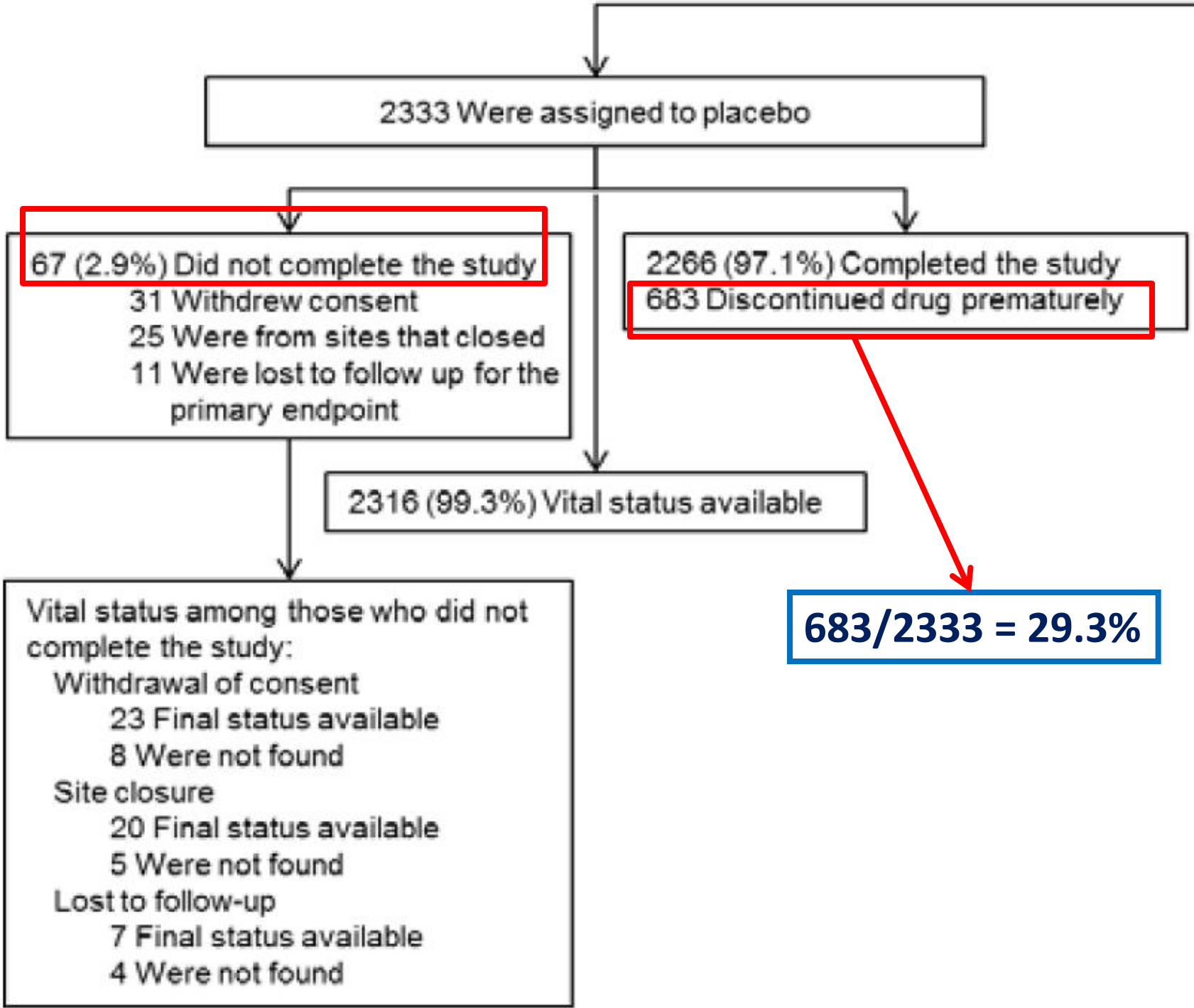
*Is the drop out rate in both groups (control and experiment) equal ?

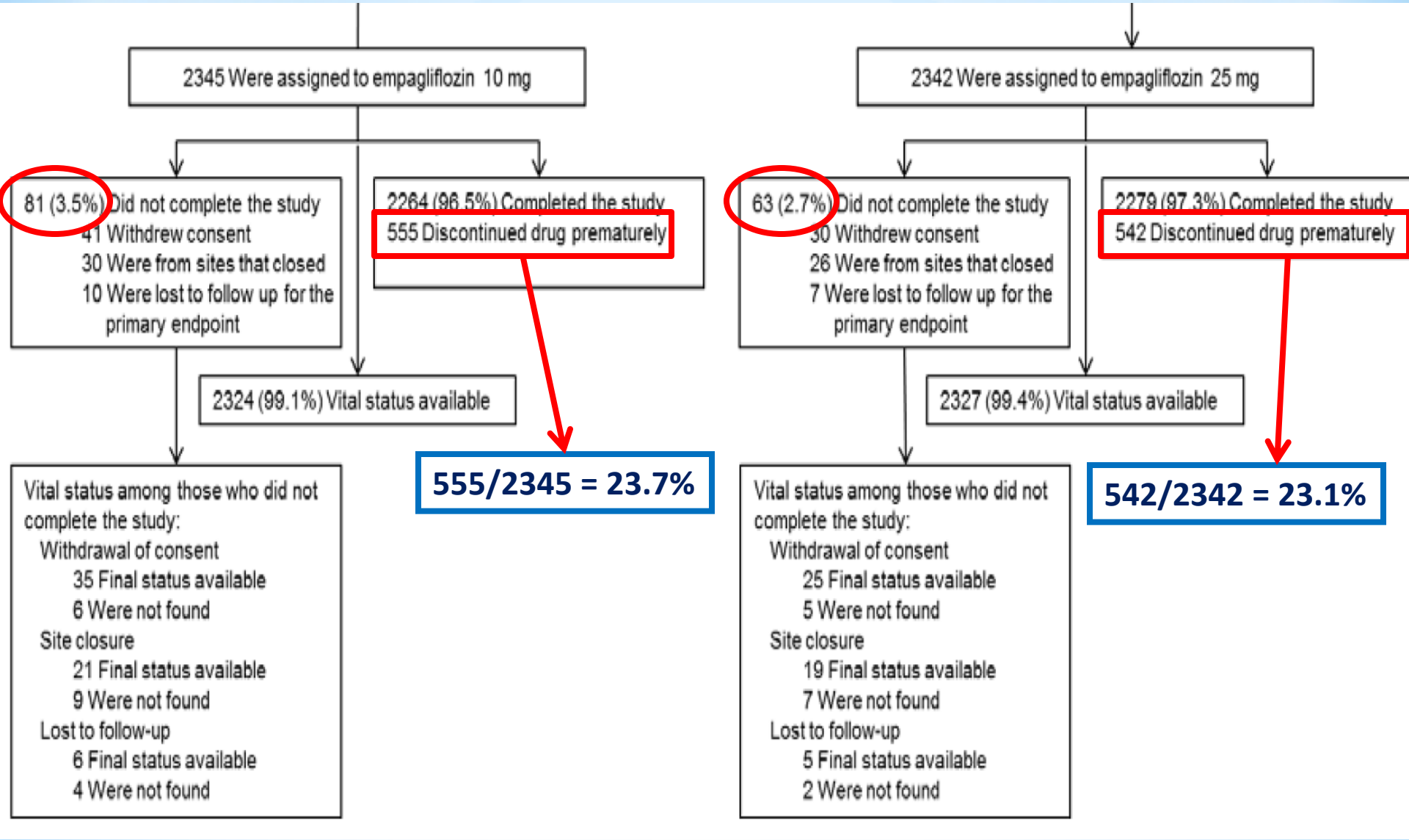
# RESULTS

## STUDY PATIENTS

A total of 7028 patients underwent randomization from September 2010 through April 2013. Of these patients, 7020 were treated and included in the primary analysis (Fig. S1 in Section G in the Supplementary Appendix). Reasons for premature discontinuation are provided in Table S1 in Section H in the Supplementary Appendix. Overall, 97.0% of patients completed the study, with 25.4% of patients prematurely discontinuing a study drug. Final vital status was available for 99.2% of patients.

At baseline, demographic and clinical characteristics were well balanced between the placebo


2333 Were assigned to placebo
67 (2.9%) Did not complete the study
31 Withdrew consent
25 Were from sites that closed
11 Were lost to follow up for the primary endpoint
2266 (97.1%) Completed the study
683 Discontinued drug prematurely
2316 (99.3%) Vital status available
Vital status among those who did not complete the study:
Withdrawal of consent
23 Final status available
8 Were not found
Site closure
20 Final status available
5 Were not found
Lost to follow-up
7 Final status available
4 Were not found
683/2333 = 29.3%


2345 Were assigned to empagliflozin 10 mg
81 (3.5%) Did not complete the study
41 Withdrew consent
30 Were from sites that closed
10 Were lost to follow up for the primary endpoint
2264 (96.5%) Completed the study
555 Discontinued drug prematurely
2324 (99.1%) Vital status available
555/2345 = 23.7%
Vital status among those who did not complete the study:
Withdrawal of consent
35 Final status available
6 Were not found
Site closure
21 Final status available
9 Were not found
Lost to follow-up
6 Final status available
4 Were not found
2342 Were assigned to empagliflozin 25 mg
63 (2.7%) Did not complete the study
30 Withdrew consent
26 Were from sites that closed
7 Were lost to follow up for the primary endpoint
2279 (97.3%) Completed the study
542 Discontinued drug prematurely
2327 (99.4%) Vital status available
542/2342 = 23.1%
Vital status among those who did not complete the study:
Withdrawal of consent
25 Final status available
5 Were not found
Site closure
19 Final status available
7 Were not found
Lost to follow-up
5 Final status available
2 Were not found

## Section H. Reasons for premature discontinuation from study medication

Table S1. Reasons for premature discontinuation from study medication

| | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg | Pooled empagliflozin |
|---|---|---|---|---|
| | no. (%) | | | |
| Treated | 2333 (100.0) | 2345 (100.0) | 2342 (100.0) | 4687 (100.0) |
| Prematurely discontinued from trial medication | 683 (29.3) | 555 (23.7) | 542 (23.1) | 1097 (23.4) |
| Adverse event | 303 (13.0) | 267 (11.4) | 273 (11.7) | 540 (11.5) |
| Refusal to continue, not due to adverse event | 172 (7.4) | 118 (5.0) | 122 (5.2) | 240 (5.1) |
| Non-compliant with protocol | 15 (0.6) | 15 (0.6) | 12 (0.5) | 27 (0.6) |
| Lost to follow up | 15 (0.6) | 9 (0.4) | 6 (0.3) | 15 (0.3) |
| Lack of efficacy* | 11 (0.5) | 1 (<0.1) | 0 | 1 (<0.1) |
| Other | 162 (6.9) | 142 (6.1) | 125 (5.3) | 267 (5.7) |
| Missing | 5 (0.2) | 3 (0.1) | 4 (0.2) | 7 (0.1) |

*Hyperglycemia above the protocol-defined level despite intensification or addition of glucose-lowering therapy.

## Section J. Treatment and observation times

Table S3. Treatment and observation times

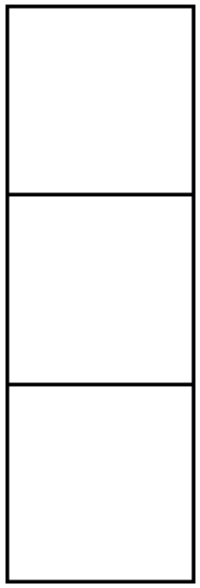
| | **Placebo (N = 2333)** | **Pooled empagliflozin (N = 4687)** |
|---|---|---|
| Treatment – years | | |
| Median (interquartile range) | 2.6 (1.8–3.4) | 2.6 (2.0–3.4) |
| Mean | 2.5 | 2.6 |
| Observation – years | | |
| Median (interquartile range) | 3.1 (2.2–3.5) | 3.2 (2.2–3.6) |
| Mean | 2.9 | 3.0 |

4. Were patients, health workers and study personnel 'blind' to treatment?

Yes

Can't Tell

No



*病患、醫療照護者、分析數據人員是否都是「盲性的」？

*看 **Methods 的 study design** 敘述，是否有使用適當的 match placebo 或 sham therapy 來讓病患或醫療照護者無法分辨。

# *Blinding

*單盲 (Single - blinded) --- 病人(受試者) 不知道自己被分派到的研究組別

*雙盲 (Double - blinded) --- 病人與研究人員或醫師都不知道病人的分派組別

*三盲 (Triple-blinded) --- 病人、醫療照護者、分析數據人員都不知道病人的分派組別

*非盲 (Unblinded or Open label) --- 所有人都知道病人被分派到的研究組別

*If the outcome is objective (eg., death) then blinding is less critical.

## STUDY DESIGN

As described previously,[23] this was a randomized, double-blind, placebo-controlled trial to assess the effect of once-daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against a background of standard care. Patients were treated at 590 sites in 42 countries. The trial continued until an adjudicated primary outcome event had occurred in at least 691 patients.

## STUDY PROCEDURES

Eligible patients underwent a 2-week, open-label, placebo run-in period in which background glucose-lowering therapy was unchanged. Patients meeting the inclusion criteria were then randomly assigned in a 1:1:1 ratio to receive either 10 mg or 25 mg of empagliflozin or placebo once daily. Randomization was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system and was stratified according to the glycated hemoglobin level at screening (<8.5% or ≥8.5%), body-

## STUDY OUTCOMES

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina. Definitions of the major clinical outcomes are provided in Section E in the Supplementary Appendix.

Safety was assessed on the basis of adverse

5. Were the groups similar at the start of the trial

| | |
|---|---|
| Yes | |
| Can't Tell | |
| No | |

*隨機分派後的兩組病患基本特質是否相似？

*找 Result 的第一段描述，和Table 1: Characteristics of Patients。Table 1如果沒秀P值，一般來說都是沒有達到統計學上的差異，可以用 Result的第一段描述來確認。

*Consider about confounding factors that might affect the outcome, such as age, sex, social class …

ing a study drug. Final vital status was available for 99.2% of patients.

At baseline, demographic and clinical characteristics were well balanced between the placebo group and the empagliflozin group (Table S2 in Section I in the Supplementary Appendix). According to the inclusion criteria, more than 99% of patients had established cardiovascular disease, and patients were well treated with respect to the use of lipid-lowering therapy and antihypertensive medications at baseline. The median duration of

Table S2. Baseline characteristics

| Characteristic* | Placebo (N = 2333) | Empagliflozin 10 mg (N = 2345) | Empagliflozin 25 mg (N = 2342) | Pooled empagliflozin (N = 4687) |
|---|---|---|---|---|
| Age – years | 63.2 ± 8.8 | 63.0 ± 8.6) | 63.2 ± 8.6) | 63.1 ± 8.6 |
| Male – no. (%) | 1680 (72.0) | 1653 (70.5) | 1683 (71.9) | 3336 (71.2) |
| Race – no. (%) | | | | |
| White | 1678 (71.9) | 1707 (72.8) | 1696 (72.4) | 3403 (72.6) |
| Asian | 511 (21.9) | 505 (21.5) | 501 (21.4) | 1006 (21.5) |
| Black/African-American | 120 (5.1) | 119 (5.1) | 118 (5.0) | 237 (5.1) |
| Other/Missing | 24 (1.0) | 14 (0.6) | 27 (1.2) | 41 (0.9) |
| Ethnicity – no. (%) | | | | |
| Not Hispanic or Latino | 1912 (82.0) | 1909 (81.4) | 1926 (82.2) | 3835 (81.8) |
| Hispanic or Latino | 418 (17.9) | 432 (18.4) | 415 (17.7) | 847 (18.1) |
| Missing | 3 (0.1) | 4 (0.2) | 1 (<0.1) | 5 (0.1) |
| Region – no. (%) | | | | |
| Europe | 959 (41.1) | 966 (41.2) | 960 (41.0) | 1926 (41.1) |
| North America (plus Australia and New Zealand) | 462 (19.8) | 466 (19.9) | 466 (19.9) | 932 (19.9) |
| Asia | 450 (19.3) | 447 (19.1) | 450 (19.2) | 897 (19.1) |
| Latin America | 360 (15.4) | 359 (15.3) | 362 (15.5) | 721 (15.4) |
| Africa | 102 (4.4) | 107 (4.6) | 104 (4.4) | 211 (4.5) |
| Weight – kg | 86.6 ± 19.1 | 85.9 ± 18.8 | 86.5 ± 19.0 | 86.2 ± 18.9 |
| Body mass index – $kg/m^2$† | 30.7 ± 5.2 | 30.6 ± 5.2 | 30.6 ± 5.3 | 30.6 ± 5.3 |
| CV risk factor – no. (%) | 2307 (98.9) | 2333 (99.5) | 2324 (99.2) | 4657 (99.4) |
| Coronary artery disease | 1763 (75.6) | 1782 (76.0) | 1763 (75.3) | 3545 (75.6) |
| Multi-vessel coronary artery disease | 1100 (47.1) | 1078 (46.0) | 1101 (47.0) | 2179 (46.5) |
| History of myocardial infarction | 1083 (46.4) | 1107 (47.2) | 1083 (46.2) | 2190 (46.7) |
| Coronary artery bypass graft | 563 (24.1) | 594 (25.3) | 581 (24.8) | 1175 (25.1) |
| History of stroke‡ | 553 (23.7) | 535 (22.8) | 549 (23.4) | 1084 (23.1) |
| Peripheral artery disease | 479 (20.5) | 465 (19.8) | 517 (22.1) | 982 (21.0) |
| Single vessel coronary artery disease‡ | 238 (10.2) | 258 (11.0) | 240 (10.2) | 498 (10.6) |
| Cardiac failure§ | 244 (10.5) | 240 (10.2) | 222 (9.5) | 462 (9.9) |
| Glycated hemoglobin – %¶ | 8.08 ± 0.84 | 8.07 ± 0.86 | 8.06 ± 0.84 | 8.07 ± 0.85 |
| Time since diagnosis of type 2 diabetes – no. (%) | | | | |

6. Aside from the experimental intervention, were the groups treated equally?

Yes

Can't Tell

No

*除了研究介入的差別，兩組間其他的治療是否相等？

*看 Methods 中的 treatment 或 study procedures 部分的描述，看是否有提到允許其他治療或追加治療，並思考會不會影響結果。也要看 Results 中實地執行的情況。

*若 blinding 做得好，基本上應該不會有治療不平等的問題。

Africa, or Asia).

Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization, although intensification was permitted if the patient had a confirmed fasting glucose level of more than 240 mg per deciliter (>13.3 mmol per liter). In cases of medical necessity, dose reduction or discontinuation of background medication could occur. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines. Throughout the trial, investigators were encouraged to treat other cardiovascular risk factors (including dyslipidemia and hypertension) to achieve the best available standard of care according to local guidelines. Patients were instructed to attend the clinic at prespecified times, which

## CARDIOVASCULAR RISK FACTORS

Over the course of the study, empagliflozin, as compared with placebo, was associated with small reductions in weight, waist circumference, uric acid level, and systolic and diastolic blood pressure with no increase in heart rate and small increases in both LDL and HDL cholesterol (Fig. S3 in Section P in the Supplementary Appendix). A higher percentage of patients in the placebo group received additional glucose-lowering medications (including sulfonylurea and insulin), antihypertensive medications (including diuretics), and anticoagulants during the trial, with no between-group difference in the receipt of lipid-lowering drugs (Tables S11 and S12 in Section Q in the Supplementary Appendix).

## Section Q. Glucose-lowering and cardiovascular medications introduced post-baseline

Table S11. Glucose-lowering medications introduced post-baseline

| | Placebo (N = 2333) | Empagliflozin (N = 4687) |
|---|---|---|
| | no. (%) | |
| Any glucose-lowering therapy | 736 (31.5) | 914 (19.5) |
| Insulin | 268 (11.5) | 273 (5.8) |
| Dipeptidyl peptidase-4 inhibitor | 193 (8.3) | 263 (5.6) |
| Sulfonylurea | 164 (7.0) | 176 (3.8) |
| Metformin | 112 (4.8) | 172 (3.7) |
| Thiazolidinedione | 68 (2.9) | 56 (1.2) |
| Glucagon-like peptide-1 agonist | 57 (2.4) | 65 (1.4) |

Data are from patients treated with ≥1 dose of study drug.

Table S12. Cardiovascular medications introduced post-baseline

| | Placebo (N = 2333) | Empagliflozin (N = 4687) |
|---|---|---|
| | no. (%) | |
| Anti-hypertensive therapy | 1106 (47.4) | 1903 (40.6) |
| Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers | 640 (27.4) | 1108 (23.6) |
| Diuretics | 530 (22.7) | 760 (16.2) |
| Beta blockers | 420 (18.0) | 745 (15.9) |
| Calcium channel blockers | 427 (18.3) | 592 (12.6) |
| Mineralocorticoid receptor antagonists | 110 (4.7) | 135 (2.9) |
| Renin inhibitors | 6 (0.3) | 8 (0.2) |
| Other | 138 (5.9) | 234 (5.0) |
| Lipid-lowering drugs | 643 (27.6) | 1245 (26.6) |
| Statins | 529 (22.7) | 1040 (22.2) |
| Fibrates | 118 (5.1) | 188 (4.0) |
| Ezetimibe | 44 (1.9) | 87 (1.9) |
| Niacin | 12 (0.5) | 23 (0.5) |
| Other | 64 (2.7) | 92 (2.0) |
| Anticoagulants | 623 (26.7) | 1179 (25.2) |
| Acetylsalicylic acid | 402 (17.2) | 736 (15.7) |
| Clopidogrel | 112 (4.8) | 224 (4.8) |
| Vitamin K antagonists | 89 (3.8) | 136 (2.9) |

Data are from patients treated with ≥1 dose of study drug.

## Section B: What are the results?

### 7. How large was the treatment effect?

*治療效果有多大？

*What outcomes were measured ?

*What results were found for each outcome ?

*Is it statistically significant ?  P value ?

*Calculate the number needed to treat (NNT).

# *Number needed to treat(NNT)

- **SAMPLE CALCULATIONS**

| **Occurrence of diabetic neuropathy at 5 years among insulin-dependent diabetics in the DCCT trial** | | **Relative risk reduction (RRR)** | **Absolute risk reduction (ARR)** | **Number needed to treat (NNT)** |
|---|---|---|---|---|
| Usual insulin regimen control event rate (CER) | Intensive insulin regimen experimental event rate (EER) | $\frac{CER - EER}{CER}$ | CER-EER | 1/ARR |
| 9.6% | 2.8% | $\frac{9.6\% - 2.8\%}{9.6\%} = 71\%$ | 9.6% - 2.8% = 6.8% | 1/6.8% = 15 patients **(1/0.068=14.7)** |
| | | **95% CI *⇒** | 4.4% to 9.2% | 11 to 23 |

*For clinical trial: NNT = 1/ARR

*NNT --- 小數點無條件進位。

# *Number needed to treat(NNT) or Number needed to harm(NNH)

*統計上無意義的話就不必算 NNT或 NNH了。

*For clinical trial:

NNT = 1/ARR (absolute risk reduction)

NNH = 1/ARI (absolute risk increase)

*NNT —— 小數點無條件進位

*NNH —— 小數點無條件捨棄

# *3-30 Rule of EBM

*Absolute risk reduction (ARR) > 3% (not < 2%)

*Relative risk reduction (RRR) > 30% (not < 20%)

*NNT < 30 (not > 50)

Enrique Sánchez-Delgado
Medical Director Clínica Sánchez-Incer; Bosques Altamira
Managua, Nicaragua
Making evidence easy for general practitioners: Rule 3-30
Letter to editor for: Why general practitioners do not implement evidence: qualitative study. BMJ 2001;323:1100

**Table 1. Primary and Secondary Cardiovascular Outcomes.**

| 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 |

**Table 1.** Primary and Secondary Cardiovascular Outcomes.

| 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† |

*Relative risk reduction (RRR) = ?

*Absolute risk reduction (ARR) = ?

*Number needed to treat (NNT) = ?

**Table 1. Primary and Secondary Cardiovascular Outcomes.**

| 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† |

*Relative risk reduction (RRR) = (12.1 – 10.5) /12.1

= 1.6/12.1 = 0.132 = 13.2%

*Absolute risk reduction (ARR) = 12.1 – 10.5 = 1.6%

*Number needed to treat (NNT) = 1/ARR = 1/0.016

= 62.5 = 63

Table 1. Primary and Secondary Cardiovascular Outcomes.

| Outcome | Placebo (N=2333) | | Empagliflozin (N=4687) | | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|
| 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 |

*Relative risk reduction (RRR) = (8.3 – 5.7) /8.3

= 2.6/8.3 = 0.313 = 31.3%

*Absolute risk reduction (ARR) = 8.3 – 5.7 = 2.6%

*Number needed to treat (NNT) = 1/ARR = 1/0.026

= 38.5 = 39

characteristics.

Notably, reductions in the risks of death from cardiovascular causes and from any cause occurred early in the trial, and these benefits continued throughout the study. The relative reduction of 32% in the risk of death from any cause in the pooled empagliflozin group means that 39 patients (41 in the 10-mg group and 38 in the 25-mg group) would need to be treated during a 3-year period to prevent one death, but these numbers cannot be extrapolated to patient populations with other clinical characteristics.

Even though investigators were encouraged to

8. How precise was the estimate of the treatment effect?

HINT: Consider

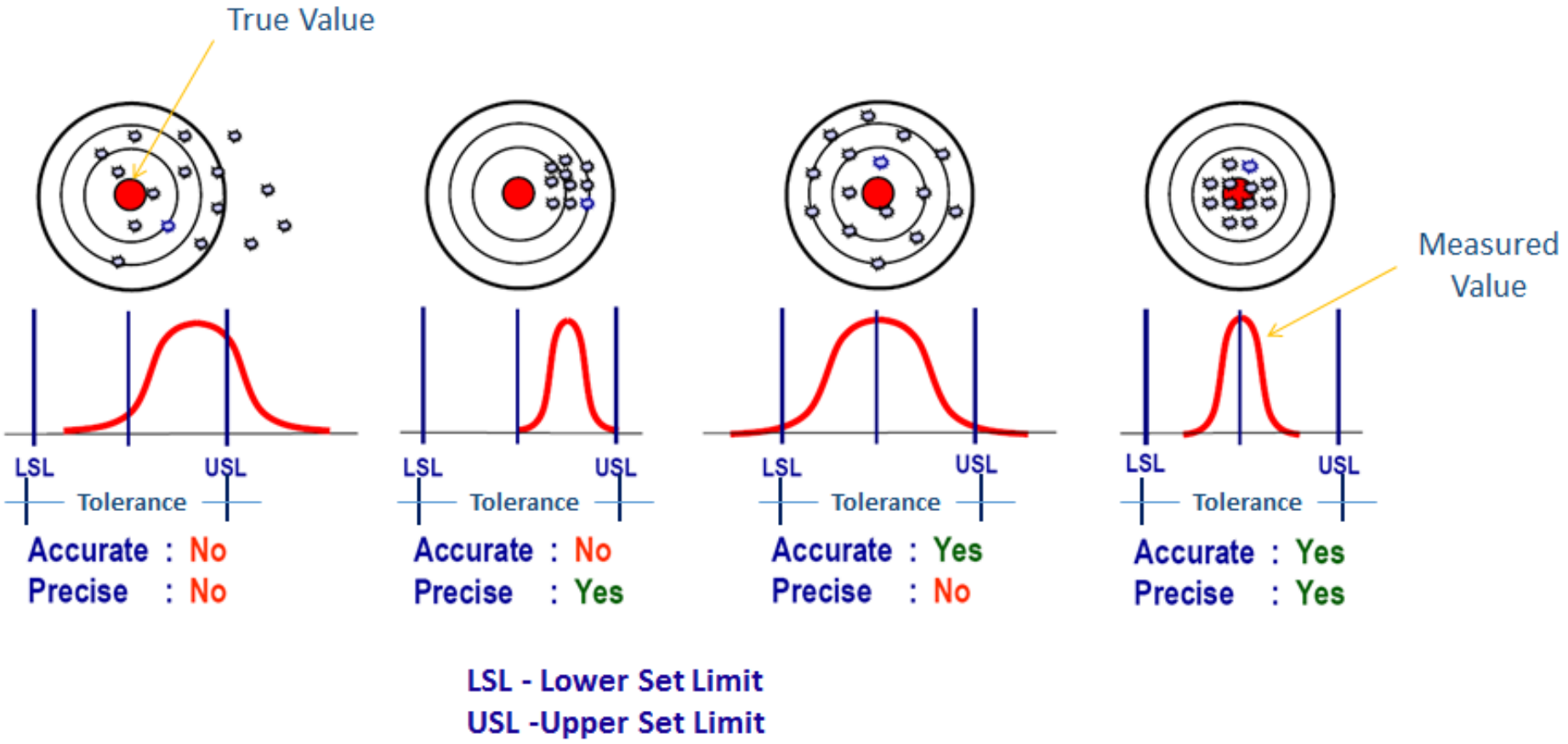
- what are the confidence limits

*治療效果的估計值有多精確？

*What is the confidence interval ?

*Narrow confidence interval is more precise.

# *Accuracy(準確) and Precision(精確)




*Accuracy is how close a measured value is to the actual (true) value.

*Precision is how close the measured values are to each other.

# *Accuracy(準確) and Precision(精確)

*假設明天下午的氣溫是 28°C

*我今天的氣象預測: 氣溫的 95% confidence interval 是:

1) 10°C – 24°C --- low accuracy, low precision
2) 20°C – 24°C --- low accuracy, high precision
3) 10°C – 38°C --- high accuracy, low precision
4) 26°C – 30°C --- high accuracy, high precision

# *Confidence Interval

*一般用 95% confidence interval, P < 0.05。允許5%的犯錯機會。結果若在 confidence interval 內，表示有統計學上的意義。

*Narrow confidence interval --- high precision

*95% confidence interval is more narrow than 99% confidence interval --- so the precision increase, but the accuracy decrease

*Confidence interval becomes narrower when the sample size increases.

# *Confidence Interval

*怎樣的 confidence interval 才算 narrow？ ---- 沒有標準答案，視情況而定。

*Risk ratio，odds ratio，hazard ratio等的 95% confidence interval 上下值差異能小於 0.25 一般來說會認為精確度很好，如果大於 0.5 可能就不是那麼精確，但要隨著研究題目、臨床問題而定，沒有一定的答案。

*研究結果若沒達到統計學上的差異，也可以看信賴區間是否夠窄，來看這樣"沒有差異"的結果，是否精確，有沒有可能只差一點、再增加一些樣本數而變成有顯著性的差異，還是已經是一個既定的結果。

**Table 1. Primary and Secondary Cardiovascular Outcomes.**

| 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† |

*Hazard ratio: 0.86 (0.74 – 0.99)，用 Empagliflozin 可減少14% primary outcome的風險。

*0.99 – 0.74 = 0.25 ---- 算 narrow confidence interval

*但要知道，減少的風險95%會落成 0.74 – 0.99 間，意即最好可減少26% primary outcome的風險，最差則只減少1% primary outcome的風險。

Table 1. Primary and Secondary Cardiovascular Outcomes.

| Outcome | Placebo (N=2333) | | Empagliflozin (N=4687) | | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|
| 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 |

* Hazard ratio: 0.68 (0.57 – 0.82)，用 Empagliflozin 可減少32% death from any cause 的風險。

* 0.82 – 0.57 = 0.25 ---- 算 narrow confidence interval

* 減少的風險95%會落成 0.57 – 0.82 間，意即最好可減少 43% death from any cause 的風險，最差也還能減少18% death from any cause 的風險。

# *實證醫學的五個步驟

1) Ask an answerable question〔問可以回答的問題〕
2) Search for the best evidences〔搜尋最佳證據〕
3) Critically appraise those evidences〔嚴格的文獻評讀〕
4) Apply to the patient〔臨床應用〕
5) Evaluate our performance〔評估與稽核以上步驟〕

Section C: Will the results help locally?

9. Can the results be applied to the local population, or in your context?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider whether
- the patients covered by the trial are similar enough to the patients to whom you will apply this
- how they differ

## *此研究是否可應用到你的病患？

我們的病患與研究中的病患是否不同？

我們是否有這種藥或設備？

治療的方法是否與我們的病患相似？

# *我們的病患與研究中的病患是否不同？

*我們的病患是否符合納入條件(including criteria)，而沒有在排除條件(excluding criteria) 之中？

*從研究樣本的人口學和臨床特徵的描述中，比較我們的病人和文獻中的病人是否相似。

*性別、年齡、體重、種族、疾病特徵

Table S2. Baseline characteristics

| Characteristic* | Placebo (N = 2333) | Empagliflozin 10 mg (N = 2345) | Empagliflozin 25 mg (N = 2342) | Pooled empagliflozin (N = 4687) |
|---|---|---|---|---|
| Age – years | 63.2 ± 8.8 | 63.0 ± 8.6) | 63.2 ± 8.6) | 63.1 ± 8.6 |
| Male – no. (%) | 1680 (72.0) | 1653 (70.5) | 1683 (71.9) | 3336 (71.2) |
| Race – no. (%) | | | | |
| White | 1678 (71.9) | 1707 (72.8) | 1696 (72.4) | 3403 (72.6) |
| Asian | 511 (21.9) | 505 (21.5) | 501 (21.4) | 1006 (21.5) |
| Black/African-American | 120 (5.1) | 119 (5.1) | 118 (5.0) | 237 (5.1) |
| Other/Missing | 24 (1.0) | 14 (0.6) | 27 (1.2) | 41 (0.9) |
| Ethnicity – no. (%) | | | | |
| Not Hispanic or Latino | 1912 (82.0) | 1909 (81.4) | 1926 (82.2) | 3835 (81.8) |
| Hispanic or Latino | 418 (17.9) | 432 (18.4) | 415 (17.7) | 847 (18.1) |
| Missing | 3 (0.1) | 4 (0.2) | 1 (<0.1) | 5 (0.1) |
| Region – no. (%) | | | | |
| Europe | 959 (41.1) | 966 (41.2) | 960 (41.0) | 1926 (41.1) |
| North America (plus Australia and New Zealand) | 462 (19.8) | 466 (19.9) | 466 (19.9) | 932 (19.9) |
| Asia | 450 (19.3) | 447 (19.1) | 450 (19.2) | 897 (19.1) |
| Latin America | 360 (15.4) | 359 (15.3) | 362 (15.5) | 721 (15.4) |
| Africa | 102 (4.4) | 107 (4.6) | 104 (4.4) | 211 (4.5) |
| Weight – kg | 86.6 ± 19.1 | 85.9 ± 18.8 | 86.5 ± 19.0 | 86.2 ± 18.9 |
| Body mass index – $kg/m^2$† | 30.7 ± 5.2 | 30.6 ± 5.2 | 30.6 ± 5.3 | 30.6 ± 5.3 |
| CV risk factor – no. (%) | 2307 (98.9) | 2333 (99.5) | 2324 (99.2) | 4657 (99.4) |
| Coronary artery disease | 1763 (75.6) | 1782 (76.0) | 1763 (75.3) | 3545 (75.6) |
| Multi-vessel coronary artery disease | 1100 (47.1) | 1078 (46.0) | 1101 (47.0) | 2179 (46.5) |
| History of myocardial infarction | 1083 (46.4) | 1107 (47.2) | 1083 (46.2) | 2190 (46.7) |
| Coronary artery bypass graft | 563 (24.1) | 594 (25.3) | 581 (24.8) | 1175 (25.1) |
| History of stroke‡ | 553 (23.7) | 535 (22.8) | 549 (23.4) | 1084 (23.1) |
| Peripheral artery disease | 479 (20.5) | 465 (19.8) | 517 (22.1) | 982 (21.0) |
| Single vessel coronary artery disease‡ | 238 (10.2) | 258 (11.0) | 240 (10.2) | 498 (10.6) |
| Cardiac failure§ | 244 (10.5) | 240 (10.2) | 222 (9.5) | 462 (9.9) |
| Glycated hemoglobin – %¶ | 8.08 ± 0.84 | 8.07 ± 0.86 | 8.06 ± 0.84 | 8.07 ± 0.85 |
| Time since diagnosis of type 2 diabetes – no. (%) | | | | |

# *我們是否有這種藥或設備?

*進口？

*國內生產？

*品質如何？

# *治療的方法是否與我們的病患相似?

- *從方法(Method)中去看研究所用的藥物，在品項、劑量、與給藥間隔是否與我們的病患相似。

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## STUDY DESIGN

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As described previously,[23] this was a randomized, double-blind, placebo-controlled trial to assess the effect of once-daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against a background of standard care. Patients were treated at 590 sites in 42 countries. The trial continued until an adjudicated primary outcome event had occurred in at least 691 patients.

teer-

10. Were all clinically important outcomes considered?

Yes ☐

Can't Tell ☐

No ☐

HINT: Consider whether

- there is other information you would like to have seen
- if not, does this affect the decision

***是否所有重要的臨床結果都被考量到？**

*這題是要我們去思考，這篇研究是否有呈現我們最想要看的臨床重要結果？

*會不會血糖下降，死亡率反而上升？ 會不會死亡率下降，但中風臥床的比率反而上升？

**Table 1. Primary and Secondary Cardiovascular Outcomes.**

| 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 |

11. Are the benefits worth the harms and costs?

| | |
|---|---|
| Yes | |
| Can't Tell | |
| No | |

HINT: Consider

- even if this is not addressed by the trial, what do **you** think?

*這些好處隨之而來的傷害和花費是否值得？

What is the adverse effect ?

What is the cost ?

| Event | Placebo (N = 2333) | Empagliflozin, 10 mg (N = 2345) | Empagliflozin, 25 mg (N = 2342) | Pooled Empagliflozin (N = 4687) |
|---|---|---|---|---|
| | *number of patients (percent)* | | | |
| Any adverse event | 2139 (91.7) | 2112 (90.1) | 2118 (90.4) | 4230 (90.2)† |
| Severe adverse event | 592 (25.4) | 536 (22.9) | 564 (24.1) | 1100 (23.5)‡ |
| Serious adverse event | | | | |
| Any | 988 (42.3) | 876 (37.4) | 913 (39.0) | 1789 (38.2)† |
| Death | 119 (5.1) | 97 (4.1) | 79 (3.4) | 176 (3.8)§ |
| Adverse event leading to discontinuation of a study drug | 453 (19.4) | 416 (17.7) | 397 (17.0) | 813 (17.3)§ |
| Confirmed hypoglycemic adverse event¶ | | | | |
| Any | 650 (27.9) | 656 (28.0) | 647 (27.6) | 1303 (27.8) |
| Requiring assistance | 36 (1.5) | 33 (1.4) | 30 (1.3) | 63 (1.3) |
| Event consistent with urinary tract infection‖ | 423 (18.1) | 426 (18.2) | 416 (17.8) | 842 (18.0) |
| Male patients | 158 (9.4) | 180 (10.9) | 170 (10.1) | 350 (10.5) |
| Female patients | 265 (40.6) | 246 (35.5) | 246 (37.3) | 492 (36.4)‡ |
| Complicated urinary tract infection** | 41 (1.8) | 34 (1.4) | 48 (2.0) | 82 (1.7) |
| Event consistent with genital infection†† | 42 (1.8) | 153 (6.5) | 148 (6.3) | 301 (6.4)† |
| Male patients | 25 (1.5) | 89 (5.4) | 77 (4.6) | 166 (5.0)† |
| Female patients | 17 (2.6) | 64 (9.2) | 71 (10.8) | 135 (10.0)† |
| Event consistent with volume depletion‡‡ | 115 (4.9) | 115 (4.9) | 124 (5.3) | 239 (5.1) |
| Acute renal failure§§ | 155 (6.6) | 121 (5.2) | 125 (5.3) | 246 (5.2)§ |

**Table 2. Adverse Events.***

| Event | Placebo (N = 2333) | Empagliflozin, 10 mg (N = 2345) | Empagliflozin, 25 mg (N = 2342) | Pooled Empagliflozin (N = 4687) |
|---|---|---|---|---|
| | *number of patients (percent)* | | | |
| Event consistent with genital infection†† | 42 (1.8) | 153 (6.5) | 148 (6.3) | 301 (6.4)† |
| Male patients | 25 (1.5) | 89 (5.4) | 77 (4.6) | 166 (5.0)† |
| Female patients | 17 (2.6) | 64 (9.2) | 71 (10.8) | 135 (10.0)† |
| Event consistent with volume depletion†† | 115 (4.9) | 115 (4.9) | 124 (5.3) | 239 (5.1) |

*Adverse effect of genital infection in female:

Absolute risk increase (ARI): 10.0% - 2.6% = 7.4%

Number needed to harm (NNT) = 1/ARI = 1/0.074

= 13.5 = **13**

# *Benefit and Harm

*For diabetic adult patient (mean age of 63) with high risk of CV disease, treat with Empagliflozin for 3 years period:

*Number needed to treat (NNT) for death for any cause : **39**

*Number needed to harm (NNH) for female for genital infection: **13**

# *成本效益

*費用

*這藥健保有給付嗎？

*病人經濟狀況是否負擔得起？

*COPE --- Cost Of Preventing an Event

*COPE = NNT × Time × Cost

# *Cost Of Prevention an Event (COPE)

- *For diabetic adult patient (mean age of 63) with high risk of CV disease, treat with Empagliflozin for 3 years period:
- *Number needed to treat (NNT) for death for any cause： 39
- *Empagliflozin 25mg 健保價一顆30.7元
- ***COPE = NNT × Time × Cost**
- *COPE = 39 x 3 x 365 x 30.7 = 1,311,043元

# *Thank You