Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

2016/8/23 Journal Club

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臨床現況

- 降血糖藥物分為biguanides、sulfonylurea、meglitinides、thiazolidinedione、α-glucosidase inhibitors、dipeptidyl peptidase-4 (DPP-4) inhibitors與第1型類昇糖素胜肽 (GLP-1 analog)、sodium-glucose cotransporter-2 (SGLT2) inhibitors與胰島素。

- 在降低心血管疾病的風險上，僅有metformin的證據較明確。新一代的降血糖藥物如：DPP-4 inhibitors、GLP-1 analog、SGLT2 inhibitors在一些研究上顯示出可能具有心血管的保護效果，然而目前並未有足夠的研究可以證實。

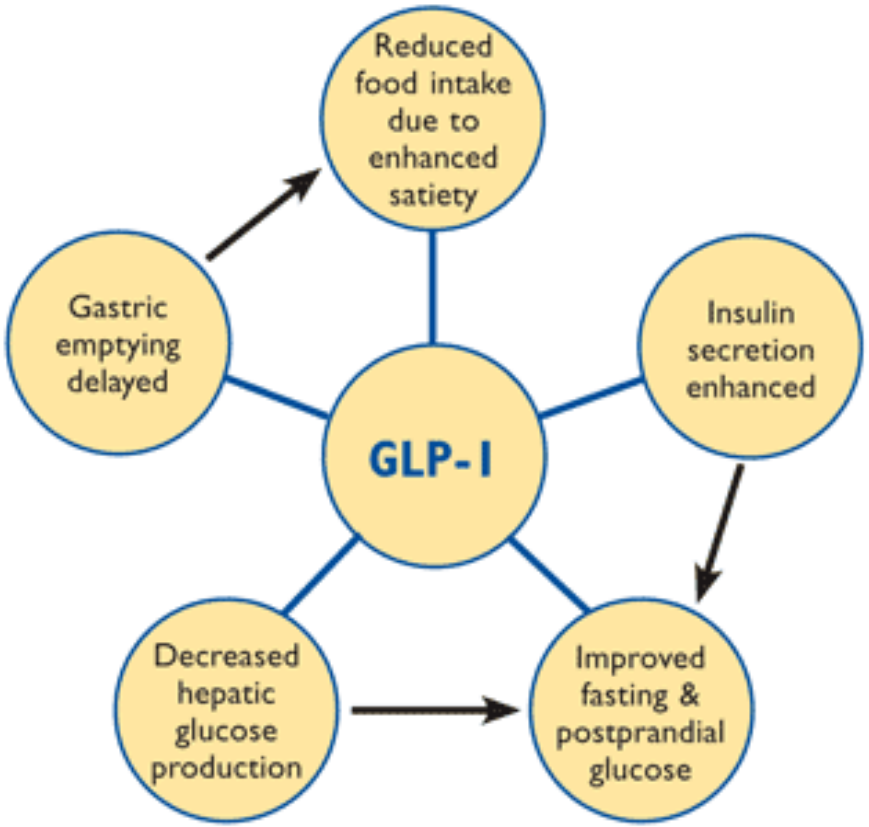
Liraglutide

- **機轉**：葡萄糖依賴性(glucose-dependent)的增加胰島素分泌、減少糖質新生和延遲胃排空
- **適應症**：第 2 型糖尿病。當患者已接受 metformin 或 sulphonylurea 單一治療至最大可忍受劑量仍未達理想血糖控制時，與 metformin 或 SU 併用；或當患者已接受 metformin 加上 SU 或metformin 加上 thiazolidinedione 兩種藥物治療仍未達理想血糖控制時，與 metformin 加上SU或 metformin 加上 TZD 併用。

Liraglutide

- **機轉**：

Figure 3. Mechanism of Action of GLP-1



GLP-1: glucagon-like peptide-1. Source: Reference 32.

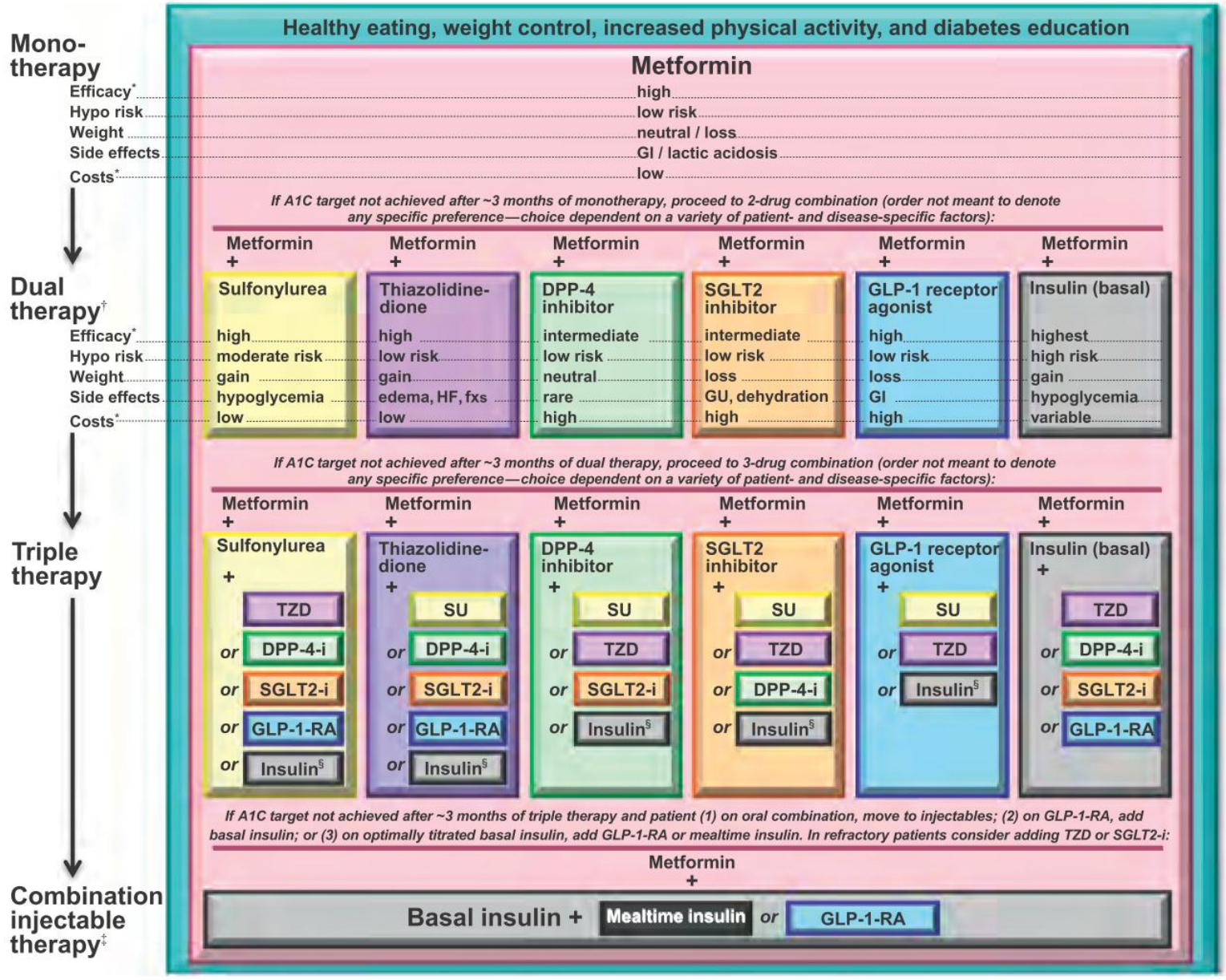
Liraglutide

- **劑量、用法**：以皮下注射方式注射在腹壁、大腿或上臂，Victoza ®起始劑量為每日 0.6 mg，使用一星期 (使用 0.6 mg 作為起始劑量是為了要減少在調整劑量過程中所造成的腸胃不適症狀，該劑量無法有效控制血糖)。給予每日 0.6 mg 一星期後，劑量應增加為每日 1.2 mg。如果 1.2 mg 劑量並沒有達到理想的血糖控制時，可增加劑量為 1.8 mg。
- **健保給付規定**：

  1.限用於已接受過最大耐受劑量的metformin 及/或 sulfonylurea 類藥物仍無法理想控制血糖之第二型糖尿病患者。

  2.本藥品不得與 insulin、DPP-4抑制劑、SGLT-2抑制劑等藥物併用。

2016 American Diabetes Association Guideline

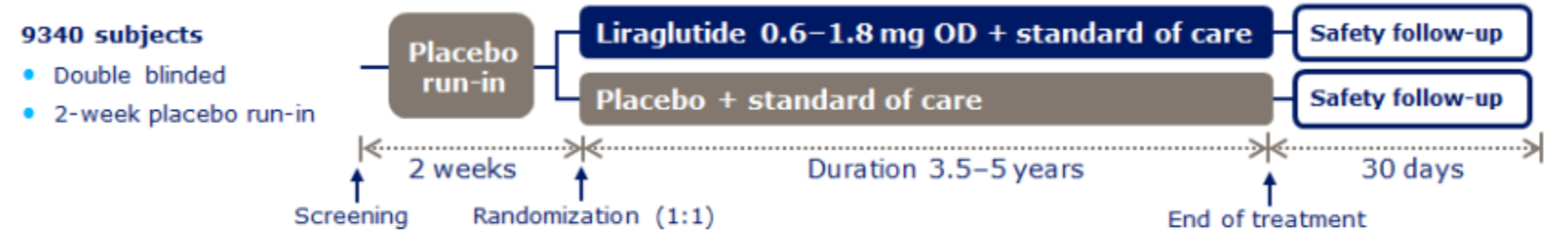


步驟 1：研究探討的問題為何？

評讀文獻	Marso SP, Daniels GH, Brown-Frandsen K, et al. **Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.** *N Engl J Med.* 2016 Jul 28;375(4):311-22.
研究問題 Problem	The cardiovascular effect of liraglutide, when added to standard care in patients with type 2 diabetes, remains unknown.
介入措施 Intervention	**Liraglutide**
比較 Comparison	**Placebo**
結果 Outcomes	Time from randomization to first occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke.

Study Design

Figure S1. Study design.



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
  or
- Age ≥60 years and risk factors for CV disease

Primary objective

To assess the effect of treatment with liraglutide compared with placebo on the incidence of CV events in adults with T2DM that are at high risk for CV events

Primary endpoint

- Time from randomization to first occurrence of a composite CV outcome (CV death, non-fatal MI, or non-fatal stroke)

Key secondary endpoints

- Time from randomization to first occurrence of an expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, revascularization, unstable angina or hosp. for heart failure)
- Time from randomization to all cause death
- Time from randomization to each individual component of the expanded composite CV outcome

步驟 2：研究的品質有多好(內在效度)？

招募(Recruitment)-受試者是否具有代表性？

最好的狀況是？
我們是否知道病人族群為何(收案場所、納入／排除條件)？在理想情況下，納入本研究之受試者應具有連續性(有時為隨機取樣)，了解符合收案條件的對象且簽署同意書。

6.2 Inclusion Criteria

1. Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the subject)

2. Men or women with type 2 diabetes

- Prior cardiovascular disease cohort: age ≥50 and ≥1 of the following criteria:
  a) prior myocardial infarction
  b) prior stroke or prior transient ischaemic attack (TIA)
  c) prior coronary, carotid or peripheral arterial revascularisation
  d) >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries
  e) history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes
  f) asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo
  g) chronic heart failure NYHA class II-III
  h) chronic renal failure, defined as glomerular filtration rate < 60 mL/min/1.73m^2 per Modification of Diet in Renal Disease (MDRD) or < 60 mL/min per Cockroft-Gault formula

OR

- No Prior cardiovascular disease group: Age ≥60 y and ≥1 of the following criteria:
  a) microalbuminuria or proteinuria
  b) hypertension and left ventricular hypertrophy by ECG or imaging
  c) left ventricular systolic or diastolic dysfunction by imaging
  d) ankle/brachial index <0.9

4. Anti-diabetic drug naïve or treated with one or more oral anti-diabetic drugs or treated with human NPH insulin or long-acting insulin analogue, alone or in combination with OAD(s)

5. $HbA_{1c} \geq 7.0\%$ at screening

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6.3 Exclusion Criteria

1. Type 1 diabetes
2. Use of a GLP-1 receptor agonist (exenatide, liraglutide or other) or pramlintide or any DPP-4 inhibitor within the 3 months prior to screening
3. Use of insulin other than human NPH insulin or long-acting insulin analogue within 3 months prior to screening. Short-term use of other insulin during this period in connection with intercurrent illness is allowed, at Investigators discretion
4. Acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent acute complications of diabetes (e.g., diabetes ketoacidosis) in the previous 3 months
5. An acute coronary or cerebrovascular event in the previous 14 days
6. Currently planned coronary, carotid or peripheral artery revascularisation
7. Chronic heart failure NYHA class IV
8. Current continuous renal replacement therapy
9. Estimated glomerular filtration rate (eGFR) (as per MDRD) < 30 mL/min/1.73m^2 at screening. The criterion is applicable after a target number of 220 subjects with eGFR < 30 mL/min are randomised (see section 6.4)
10. End stage liver disease, defined as the presence of acute or chronic liver disease and recent history of one or more of the following: ascites, encephalopathy, variceal bleeding, bilirubin ≥ 2.0 mg/dL, albumin level ≤ 3.5 g/dL, prothrombin time ≥ 4 seconds prolonged, international normalised ratio (INR) ≥1.7 or prior liver transplant
11. A prior solid organ transplant or awaiting solid organ transplant

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12. Malignant neoplasm requiring chemotherapy, surgery, radiation or palliative therapy in the previous 5 years. Patients with intraepithelial squamos cell carcinoma of the skin (Bowen's disease) treated with topical 5FU and subjects with basal cell skin cancer are allowed to enter the trial

13. Family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC)

14. Personal history of non-familial medullary thyroid carcinoma

評讀結果：
■是□否□不清楚

步驟 2：研究的品質有多好(內在效度)？

分派(Allocation)-分派方式是否隨機且具隱匿性？

最好的狀況是？
最理想的方式是以中央電腦進行隨機分配，此方式常用於多中心試驗，而較小型的試驗可由獨立人員(如醫院藥師)「監督」隨機分配的過程。

10.1 Randomisation

A randomisation session will be carried out for all subjects by using the IV/WRS.

Subjects meeting all inclusion/exclusion criteria will be randomised in a 1:1 manner to receive a double-blind, once daily dose of maximum 1.8 mg of liraglutide, or equivalent placebo as an add-on to their SOC treatment.

Subjects will be started on 0.6 mg of liraglutide or the equivalence of placebo. Dose escalation will proceed to 1.2 mg after 1 week followed by dose escalation to 1.8 mg after one week. Dose increase period can be extended based on subject's tolerance to the trial product. Further, the dose can be reduced at any time in the trial if required by the subject's tolerance to the trial product.

評讀結果：
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步驟 2：研究的品質有多好(內在效度)？

...每個組別，在研究開始時的情況是否相同？

最好的狀況是？
若隨機分配順利，各組研究對象的條件應是相近、可互相比較的。每組研究對象的基本條件越相近越好。應有指標可確認各組研究
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(如 p值)。

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Table S2. Baseline characteristics.

	Liraglutide (N=4,668)	Placebo (N=4,672)
Male sex	3011 (64.5)	2992 (64.0)
Age, years	64.2 ±7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic region		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30.0)	1446 (31.0)
Asia	360 (7.7)	351 (7.5)
Rest of the world	1268 (27.2)	1218 (26.1)
Glycated hemoglobin, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ± 21.2	91.6 ± 20.8
Systolic blood pressure, mm Hg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mm Hg	77.2 ± 10.3	77.0 ± 10.1
Heart failure[a]	835 (17.9)	832 (17.8)
Established CVD (age ≥50)	3831 (82.1)	3767 (80.6)
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or transient ischemic attack	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD[b]	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia[c]	1241 (26.6)	1231 (26.3)
Heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease[d]	1185 (25.4)	1122 (24.0)
CVD risk factors (age ≥60)	837 (17.9)	905 (19.4)
Microalbuminuria or proteinuria	501 (10.7)	558 (11.9)
Hypertension and left ventricular hypertrophy	248 (5.3)	251 (5.4)
Left ventricular systolic or diastolic dysfunction	203 (4.3)	191 (4.1)
Ankle-brachial index <0.9	110 (2.4)	116 (2.5)
Renal function		
Normal (eGFR ≥90)	1620 (34.7)	1655 (35.4)
Mild impairment (eGFR 60–89)	1932 (41.4)	1975 (42.3)
Moderate impairment (eGFR 30–59)	999 (21.4)	935 (20.0)
Severe impairment (eGFR <30)	117 (2.5)	107 (2.3)

There were no statistically significant differences. Continuous variables were tested using a Wilcoxon

步驟 2：研究的品質有多好(內在效度)？

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最好的狀況是？
若隨機分配順利，各組研究對象的條件應是相近、可互相比較的。每組研究對象的基本條件越相近越好。應有指標可確認各組研究對象之間的差異是否達到統計上顯著的差異(如 p值)。

	Baseline		
	Liraglutide (N=4668)	Placebo (N=4672)	p-value
Cardiovascular medication			
Antihypertensive therapy	4322 (92.6)	4299 (92.0)	0.30
Beta blockers	2649 (56.7)	2524 (54.0)	0.008
Calcium channel blockers	1531 (32.8)	1477 (31.6)	0.22
ACE inhibitors	2412 (51.7)	2349 (50.3)	0.18
ARBs	1486 (31.8)	1484 (31.8)	0.94
Others	468 (10.0)	452 (9.7)	0.57
Diuretics	1950 (41.8)	1949 (41.7)	0.96
Loop diuretics	823 (17.6)	833 (17.8)	0.80
Thiazides	826 (17.7)	787 (16.8)	0.28
Thiazide-like diuretics	325 (7.0)	355 (7.6)	0.24
Aldosterone antagonists	254 (5.4)	250 (5.4)	0.85
Lipid-lowering drugs	3554 (76.1)	3511 (75.1)	0.27
Statins	3395 (72.7)	3334 (71.4)	0.14
Ezetimibe	163 (3.5)	166 (3.6)	0.87
Others	492 (10.5)	510 (10.9)	0.56
Platelet aggregation inhibitors	3203 (68.6)	3119 (66.8)	0.06

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評讀結果：
■是□否□不清楚

	Baseline		
	Liraglutide (N=4668)	Placebo (N=4672)	p-value
Acetylsalicylic acid	2975 (63.7)	2899 (62.1)	0.09
Clopidogrel, ticlopidine, prasugrel, ticagrelor	718 (15.4)	743 (15.9)	0.49
Other anti-thrombotic drugs	309 (6.6)	314 (6.7)	0.84
Antihyperglycemic medication			
Metformin	3537 (75.8)	3599 (77.0)	0.15
Sulfonylureas	2362 (50.6)	2359 (50.5)	0.92
Alpha-glucosidase inhibitors	137 (2.9)	122 (2.6)	0.34
Thiazolidinediones	294 (6.3)	279 (6.0)	0.51
DPP-4 inhibitors	4 (<0.1)	2 (<0.1)	0.41
GLP-1RAs	0	1 (<0.1)	0.32
SGLT-2 inhibitors	N/A	N/A	N/A
Glinides	177 (3.8)	171 (3.7)	0.74
Others	0	1 (<0.1)	0.32
Insulin treatment	2035 (43.6)	2124 (45.5)	0.07
Premix	483 (10.3)	471 (10.1)	0.67
Short-acting	112 (2.4)	98 (2.1)	0.33
Intermediate-acting	643 (13.8)	679 (14.5)	0.29
Long-acting	1098 (23.5)	1122 (24.0)	0.58
Other insulins	59 (1.3)	48 (1.0)	0.28
No insulin treatment	2633 (56.4)	2548 (54.5)	0.07

步驟 2：研究的品質有多好(內在效度)？

維持(Maintenance)-各組是否給予相同的治療？

最好的狀況是？
各研究組別之間，除了對病人的介入之外，其餘的治療應完全相同(即為了執行本研究所增加的治療、檢驗或評估應相同)。

	Introduced during trial		
	Liraglutide (N=4668)	Placebo (N=4672)	p-value
Cardiovascular medication			
Antihypertensive therapy	160 (3.4)	163 (3.5)	0.87
Beta blockers	69 (1.5)	66 (1.4)	0.79
Calcium channel blockers	34 (0.7)	29 (0.6)	0.53
ACE inhibitors	81 (1.7)	93 (2.0)	0.36
ARBs	51 (1.1)	65 (1.4)	0.19
Others	11 (0.2)	13 (0.3)	0.68
Diuretics	516 (11.1)	647 (13.8)	<.001
Loop diuretics	304 (6.5)	382 (8.2)	<.01
Thiazides	170 (3.6)	236 (5.1)	<.001
Thiazide-like diuretics	73 (1.6)	93 (2.0)	0.12
Aldosterone antagonists	117 (2.5)	95 (2.0)	0.13
Lipid-lowering drugs	417 (8.9)	481 (10.3)	0.026
Statins	379 (8.1)	450 (9.6)	0.010
Ezetimibe	17 (0.4)	16 (0.3)	0.86
Others	62 (1.3)	64 (1.4)	0.86
Platelet aggregation inhibitors	375 (8.0)	427 (9.1)	0.06

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	Introduced during trial		
	Liraglutide (N=4668)	Placebo (N=4672)	p-value
Acetylsalicylic acid	335 (7.2)	369 (7.9)	0.19
Clopidogrel, ticlopidine, prasugrel, ticagrelor	104 (2.2)	124 (2.7)	0.18
Other anti-thrombotic drugs	235 (5.0)	275 (5.9)	0.07
Antihyperglycemic medication			
Metformin	250 (5.4)	301 (6.4)	0.026
Sulfonylureas	353 (7.6)	505 (10.8)	<.001
Alpha-glucosidase inhibitors	83 (1.8)	147 (3.1)	<.001
Thiazolidinediones	99 (2.1)	160 (3.4)	<.001
DPP-4 inhibitors	149 (3.2)	170 (3.6)	0.24
GLP-1RAs	87 (1.9)	139 (3.0)	<.001
SGLT-2 inhibitors	100 (2.1)	130 (2.8)	0.046
Glinides	85 (1.8)	137 (2.9)	<.001
Others	0	1 (<0.1)	0.32
Insulin treatment	1336 (28.6)	2018 (43.2)	<.001
Premix	683 (14.6)	1067 (22.8)	<.001
Short-acting	641 (13.7)	984 (21.1)	<.001
Intermediate-acting	687 (14.7)	998 (21.4)	<.001
Long-acting	747 (16.0)	1153 (24.7)	<.001
Other insulins	226 (4.8)	321 (6.9)	<.001
No insulin treatment	1832 (39.2)	1343 (28.7)	<.001

步驟 2：研究的品質有多好(內在效度)？

…是否有足夠的追蹤(Follow up)？

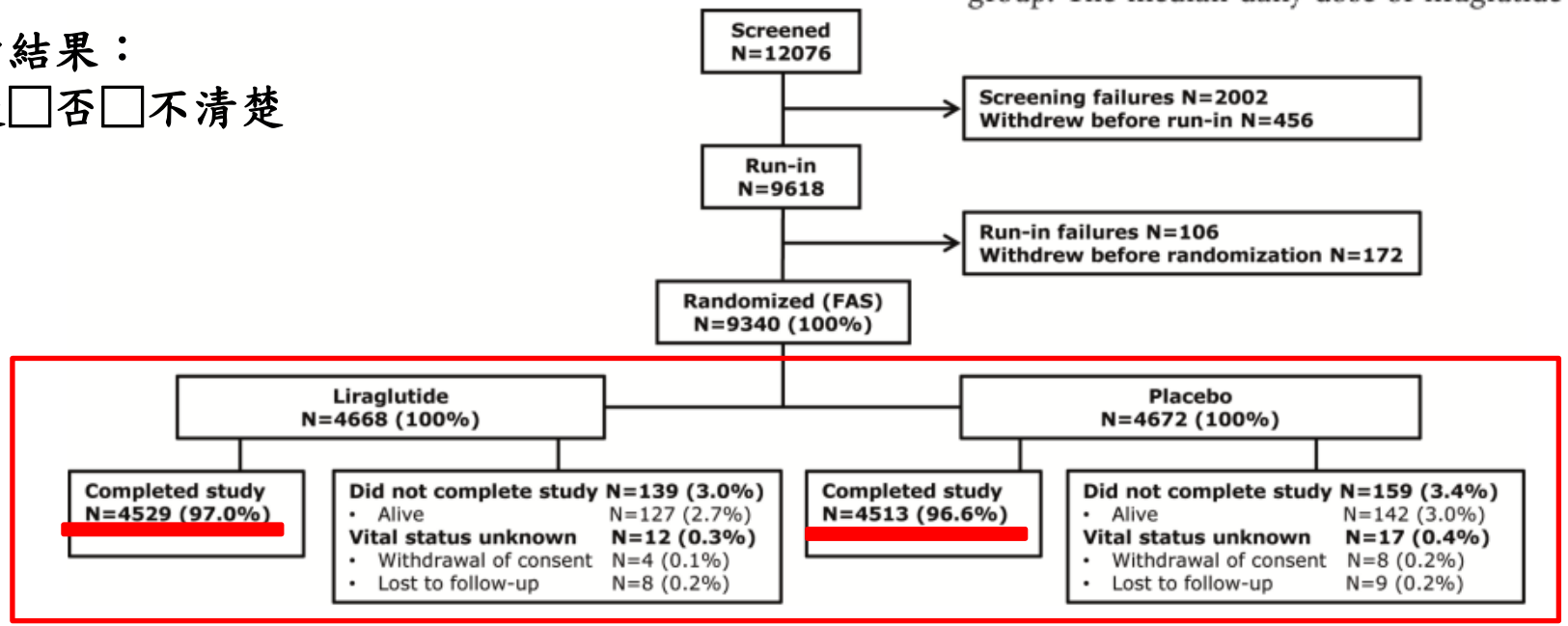
最好的狀況是？
研究中流失(無法繼續追蹤)的病人，最好少於 20%。病人應依照隨機分配的組別進行統計分析(即「治療意向分析法」Intention –to-treat , ITT analysis)。

Table 18–1 Sample size calculations

	PLAN						
	1	2	3	4	5	6	7
Event rate placebo/liraglutide (%/year)	1.8/1.8	1.4/1.4	1.0/1.0	1.8/1.8	1.8/1.7	1.4/1.3	1.7/1.8
Drop-out (%)	10	10	10	15	10	10	10
Expected number of events	611	611	611	611	594	462	594
N total	8754	11162	15496	9008	8754	8754	8754
Power	90%	90%	90%	90%	97.3%	95.1%	68.6%

come. The median time of exposure to liraglutide or placebo was 3.5 years. The mean percentage of time that patients received the trial regimen was 84% for liraglutide and 83% for placebo. The median follow-up was 3.8 years in each group. The median daily dose of liraglutide was

Figure S2. Study subject disposition.



評讀結果：
■是□否□不清楚

步驟 2：研究的品質有多好(內在效度)？

評估(Measurement)-受試者與評估者是否對治療方式及評估目的維持盲法(blind)？

最好的狀況是？
在客觀(objective) 結果(如：死亡)方面，盲法的重要性較低，但在主觀結果 (如：症狀或功能)方面，評估者維持盲法非常重要。

Trial Product(s):

Novo Nordisk A/S will supply the following trial products:

- Liraglutide 6.0 mg/mL, 3 mL pen-injector for sc injection
- Placebo, 3 mL pen-injector for sc injection

評讀結果：

■是□否□不清楚

All components of the cardiovascular and microvascular endpoints will be adjudicated by an independent Adjudication Committee in a blinded manner. Definitions and diagnostic criteria for these will be developed by the Committee and contained in the Committee operations manual, the dose indicator lines up with the relevant dose. There will be one pen type with a 3-step scale including 0.6, 1.2 and 1.8 mg. This pen-type is to be used throughout the trial. Liraglutide or placebo is administered once daily by subcutaneous injection, either in the abdomen, thigh or upper arm.

After randomisation, treatment with liraglutide or placebo will be double-blind throughout the trial.

Liraglutide will be available at a concentration of 6.0 mg/mL and supplied in a 3 mL disposable pen-injector. Placebo is supplied in an identical disposable pen-injector.

Subjects will be started on 0.6 mg of liraglutide or the equivalence of placebo. Dose escalation of liraglutide or corresponding placebo will proceed to 1.2 mg after one week followed by dose escalation to 1.8 mg after one week. Dose increase period can be extended based on subject's

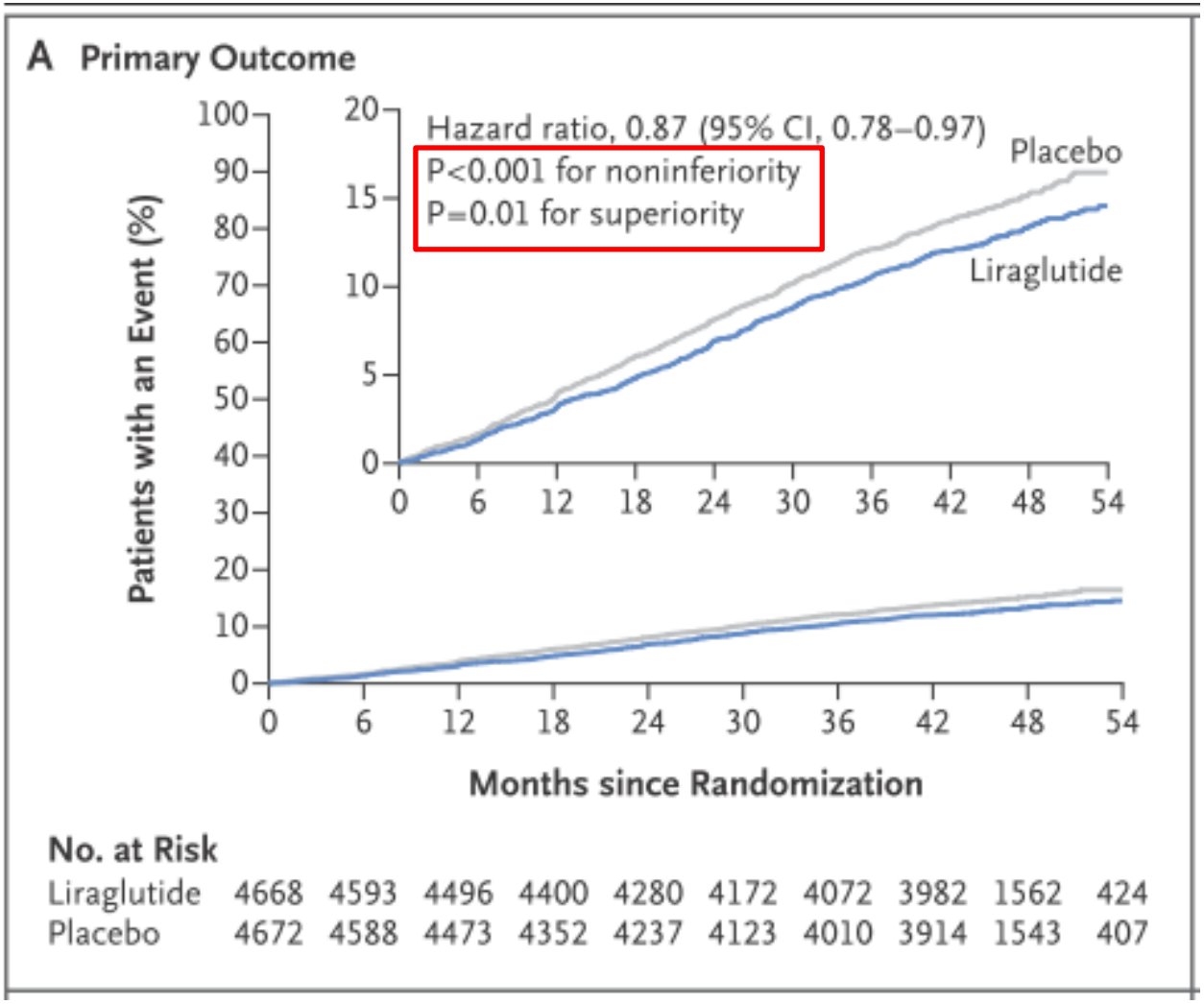
研究結果

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

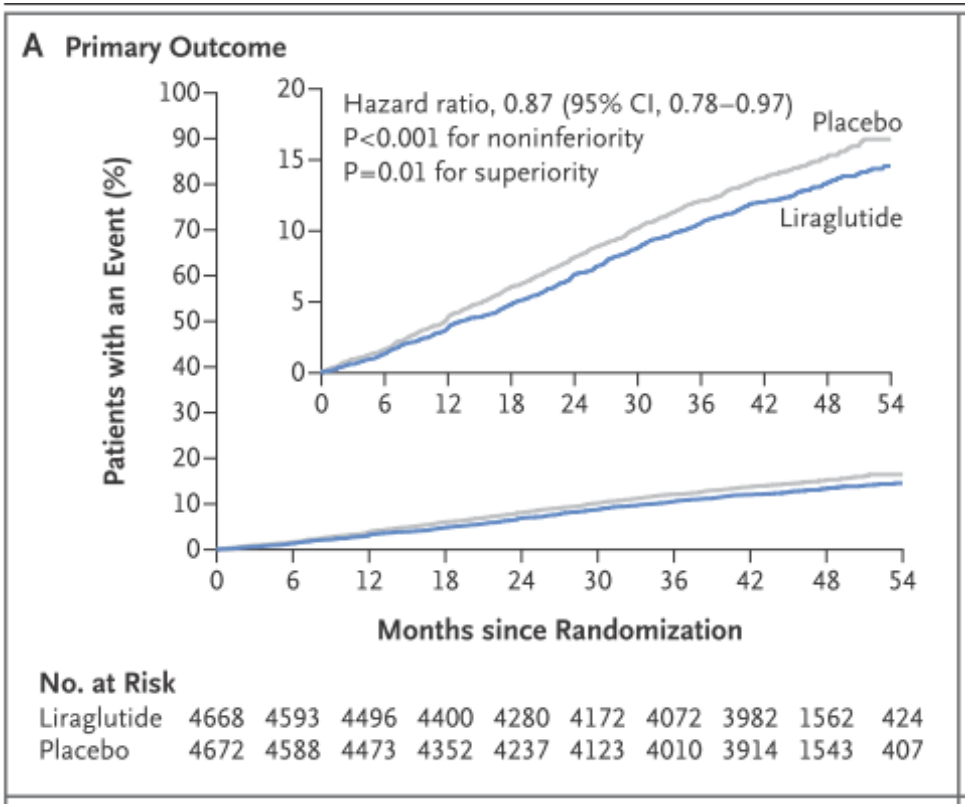
* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (181 patients in the liraglutide group vs. 227 in the placebo group), nonfatal (including silent) myocardial infarction (275 vs. 304), or nonfatal stroke (152 vs. 163). The P value is for superiority.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure.
§ This analysis was not prespecified.

研究結果


A Primary Outcome
Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4593 4496 4400 4280 4172 4072 3982 1562 424
Placebo 4672 4588 4473 4352 4237 4123 4010 3914 1543 407

步驟 3：研究結果的意義為何？

這個研究結果是否可能隨機(巧合)發生？



p值，當p值<0.05，代表成立虛無假設的機率小於5%，不容易隨機(巧合)發生

Results-內在效度

招募(Recruitment)-受試者是否具有代表性？	是
分派(Allocation)-分派方式是否隨機且具隱匿性？	是
…每個組別，在研究開始時的情況是否相同？	是
維持(Maintenance)-各組是否給予相同的治療？	否
…是否有足夠的追蹤(Follow up)？	是
評估(Measurement)-受試者與評估者是否對治療方式及評估目的維持盲法(blind)？	是

Results

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
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† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (181 patients in the liraglutide group vs. 227 in the placebo group), nonfatal (including silent) myocardial infarction (275 vs. 304), or nonfatal stroke (152 vs. 163). The P value is for superiority.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure.
§ This analysis was not prespecified.

Discussion

- NNT=66(Primary outcome)
- NNT=98(Death from any cause)

than did those in the placebo group. The number of patients who would need to be treated to prevent one event in 3 years was 66 in the analysis of the primary outcome and 98 in the analysis of death from any cause.[10] There has been con-

Discussion

- There has been concern about the risk of hospitalization for heart failure with various agents that have been used to treat diabetes mellitus, including DPP-4 inhibitors. In the present trial, there were fewer hospitalizations for heart failure among patients in the liraglutide group

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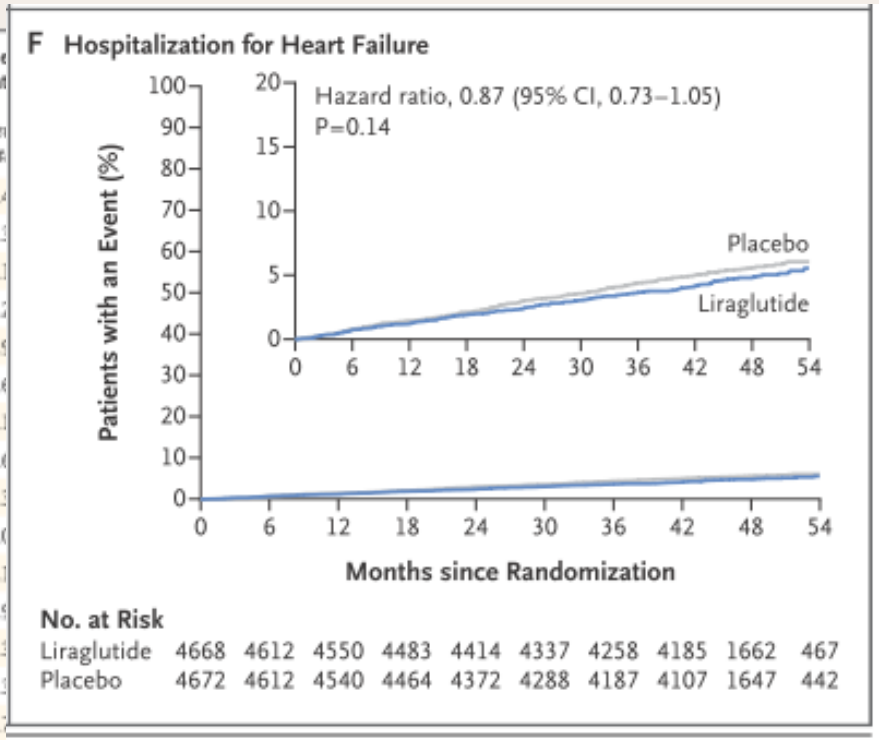

Discussion

at baseline and during the trial. There were fewer add-on therapies for diabetes medications, lipid-lowering medications, and diuretics in patients in the liraglutide group than in those in the placebo group. Subgroup analyses suggest a

Higher use of diuretics in placebo group,which may decrease the risk of heart failure ?

	Introduced during trial		
	Liraglutide (N=4668)	Placebo (N=4672)	p-value
Cardiovascular medication			
Antihypertensive therapy	160 (3.4)	163 (3.5)	0.87
Beta blockers	69 (1.5)	66 (1.4)	0.79
Calcium channel blockers	34 (0.7)	29 (0.6)	0.53
ACE inhibitors	81 (1.7)	93 (2.0)	0.36
ARBs	51 (1.1)	65 (1.4)	0.19
Others	11 (0.2)	13 (0.3)	0.68
Diuretics	516 (11.1)	647 (13.8)	<.001
Loop diuretics	304 (6.5)	382 (8.2)	<.01
Thiazides	170 (3.6)	236 (5.1)	<.001
Thiazide-like diuretics	73 (1.6)	93 (2.0)	0.12
Aldosterone antagonists	117 (2.5)	95 (2.0)	0.13
Lipid-lowering drugs	417 (8.9)	481 (10.3)	0.026
Statins	379 (8.1)	450 (9.6)	0.010
Ezetimibe	17 (0.4)	16 (0.3)	0.86
Others	62 (1.3)	64 (1.4)	0.86
Platelet aggregation inhibitors	375 (8.0)	427 (9.1)	0.06

Discussion

at baseline and during the trial. There were fewer add-on therapies for diabetes medications, lipid-lowering medications, and diuretics in patients in the liraglutide group than in those in the placebo group. Subgroup analyses suggest a

Higher use of SU and TZD in placebo group,which are known to be associated with cardiovascular adverse event,may influence the result of non-inferioroty ?

	Introduced during trial		
	Liraglutide (N=4668)	Placebo (N=4672)	p-value
Acetylsalicylic acid	335 (7.2)	369 (7.9)	0.19
Clopidogrel, ticlopidine, prasugrel, ticagrelor	104 (2.2)	124 (2.7)	0.18
~~Other anti-thrombotic drugs~~	~~235 (5.0)~~	~~275 (5.9)~~	~~0.07~~
Antihyperglycemic medication			
Metformin	250 (5.4)	301 (6.4)	0.026
Sulfonylureas	353 (7.6)	505 (10.8)	<.001
Alpha-glucosidase inhibitors	83 (1.8)	147 (3.1)	<.001
Thiazolidinediones	99 (2.1)	160 (3.4)	<.001
DPP-4 inhibitors	149 (3.2)	170 (3.6)	0.24
GLP-1RAs	87 (1.9)	139 (3.0)	<.001
SGLT-2 inhibitors	100 (2.1)	130 (2.8)	0.046
Glinides	85 (1.8)	137 (2.9)	<.001
Others	0	1 (<0.1)	0.32
Insulin treatment	1336 (28.6)	2018 (43.2)	<.001
Premix	683 (14.6)	1067 (22.8)	<.001
Short-acting	641 (13.7)	984 (21.1)	<.001
Intermediate-acting	687 (14.7)	998 (21.4)	<.001
Long-acting	747 (16.0)	1153 (24.7)	<.001
Other insulins	226 (4.8)	321 (6.9)	<.001
No insulin treatment	1832 (39.2)	1343 (28.7)	<.001

Side effect

Table 2. Selected Adverse Events Reported during the Trial.*

Event	Liraglutide (N=4668)	Placebo (N=4672)	P Value
	no. of patients (%)		
Adverse event			
Any adverse event	2909 (62.3)	2839 (60.8)	0.12
Serious adverse event	2320 (49.7)	2354 (50.4)	0.51
Confirmed hypoglycemia†	2039 (43.7)	2130 (45.6)	0.06
Severe adverse event	1502 (32.2)	1533 (32.8)	0.51
Hypothyroidism	44 (0.9)	33 (0.7)	0.21
Hyperthyroidism	13 (0.3)	8 (0.2)	0.27
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Diarrhea	27 (0.6)	5 (0.1)	<0.001
Increased lipase level‡	15 (0.3)	11 (0.2)	0.43
Abdominal pain	11 (0.2)	3 (0.1)	0.03
Decreased appetite	11 (0.2)	2 (<0.1)	0.01
Abdominal discomfort	10 (0.2)	0	0.002
Pancreatitis or neoplasm§			
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

Limitation

- A limitation of our trial is that patients were **followed for only 3.5 to 5.0 years**, so the safety and efficacy data are restricted to that time period.
- because our trial recruited a population of patients who were at high risk for cardiovascular events and who had a baseline glycated hemoglobin level of 7% or more, the **observed benefits and risks may not apply to patients at lower risk**

Conclusion

CONCLUSIONS

In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.)

- 在此篇文獻中， Victoza於primary outcome方面確實與Placebo group有顯著差異性，但分項來看(first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke的發生率)， Victoza與Placebo並無顯著差異性，表示仍有許多數據待揭露。
- 相較於此篇文獻無提供CHF相關的死亡率及發生率，EMPA-REG OUTCOME study明確顯示出Empagliflozin(SGLT2-inhibitor)在CHF方面的benefit，這也可以提供我們另一臨床使用上的參考

Conclusion

	Victoza® (Liraglutide)	**Jardiance®** (Empagliflozin)	**Forxiga®** (Dapagliflozin)
價格	$1778	$32.3(25mg、10mg價格相同)	$30.2
途徑	皮下注射	口服	口服

- ongoing trials of SGLT2 inhibitors
  - canagliflozin (Canagliflozin Cardiovascular Assessment Study [CANVAS]; ClinicalTrials.gov number, NCT01032629)
  - dapagliflozin (DECLARE–TIMI58, NCT01730534).

EMPA-REG OUTCOME study

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.

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
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

如果病人使用metformin控制血糖，效果不錯，但想自費試試新藥，是否會建議?
(紅：不建議；黃：可再評估；綠：建議)

THANKS FOR YOUR ATTENTION