



臨床試驗常用統計分析方法

SAS統計軟體操作 (2)

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Clinical Trial Phases

	Preclinical		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5-6.5		1-1.5	2	3-3.5		1.5-2.5	15 Total	
Test Population	Laboratory and Animal Studies		20-80 healthy volunteers	100-300 patient volunteers	1,000-3,000 patient volunteers				
Purpose	Assess safety and biological activity	File IND with FDA	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions for long term use	File NDA with FDA	Review process / approval		Additional post-marketing testing
Success Rate	5,000 compounds evaluated			5 enter clinical trials			1 approved		

Types of Clinical Trial data

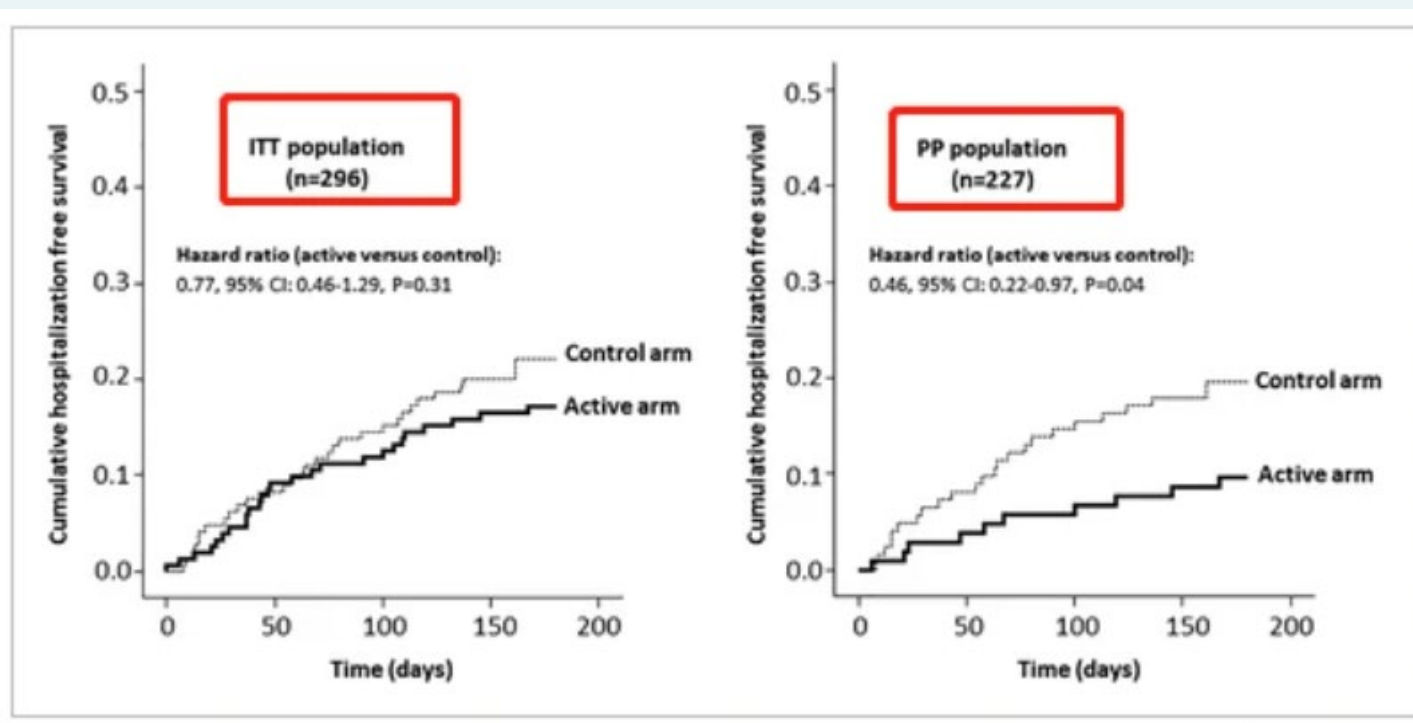
- Demographic Data
 - Age, Sex, Race, Country
- Pharmacokinetic Data
 - AUC, T-half, Cmax, Tmax
- Exposure Data
 - Study Drug
 - Other than Study Drug
 - Substance Use

C max: 最高血中濃度
T half: 到達血漿一半濃度
T max: 到達血漿最高濃度

Types of Clinical Trial data

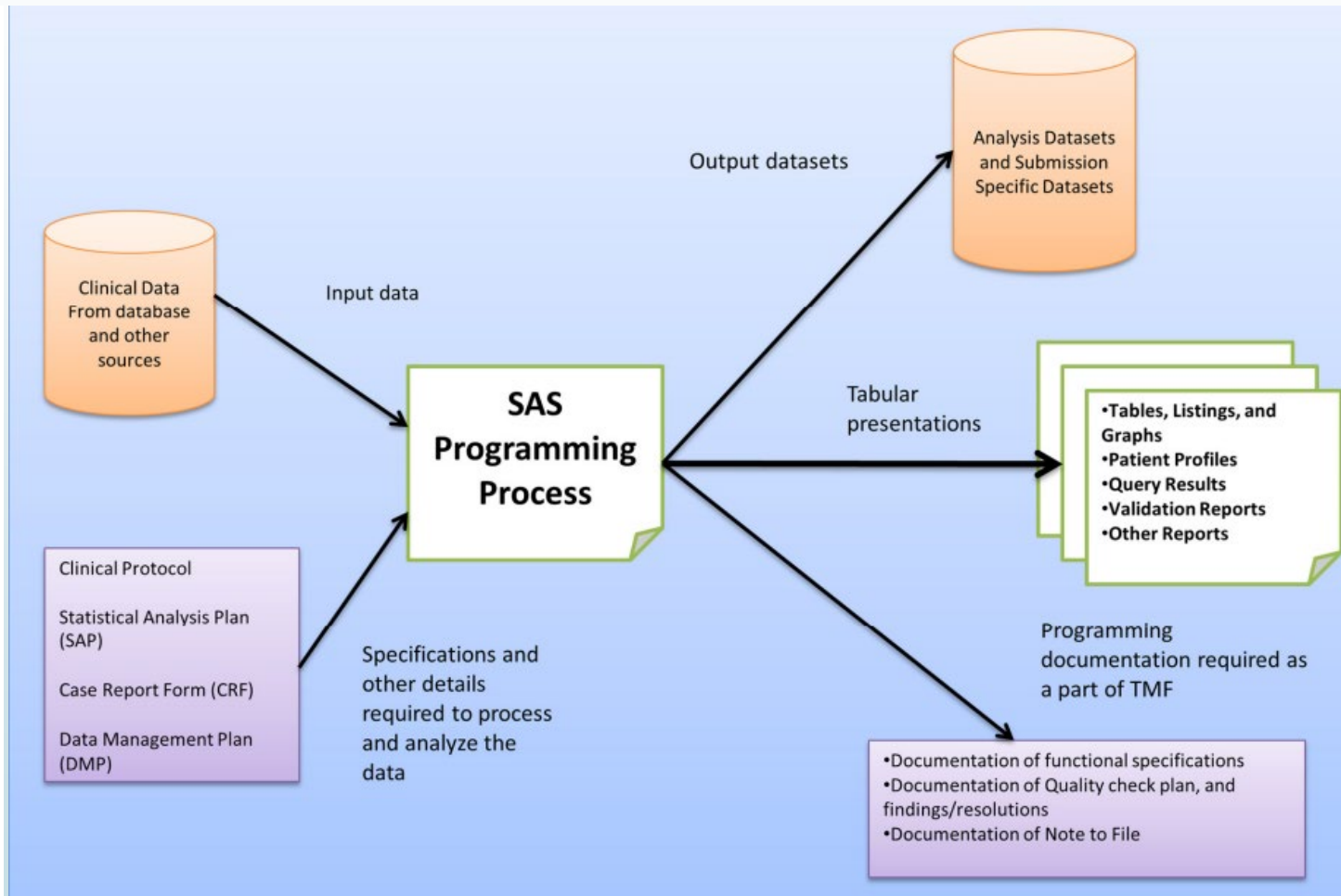
- Safety Data
 - Adverse Events, Laboratory, Vital Signs, Electrocardiogram, Physical Examination and Others
- Efficacy Data
 - Depends on Therapeutic Area
 - Cancer - Tumor size, Survival
- Other Data
 - Deviations, Milestones

分析族群	偏誤 (bias) 風險
意向分析 (ITT) 所有被隨機分派的受試者，根據分派結果分析	-
根據治療分析 (AT) 根據接受的治療分析	容易有干擾因子 (如同時影響配合度與結果的因子)
符合計畫書分析 (PP) 符合計畫書規定才納入分析 (排除不符計畫書，例如配合度差)	選擇性偏誤



SAS在臨床試驗的重要性

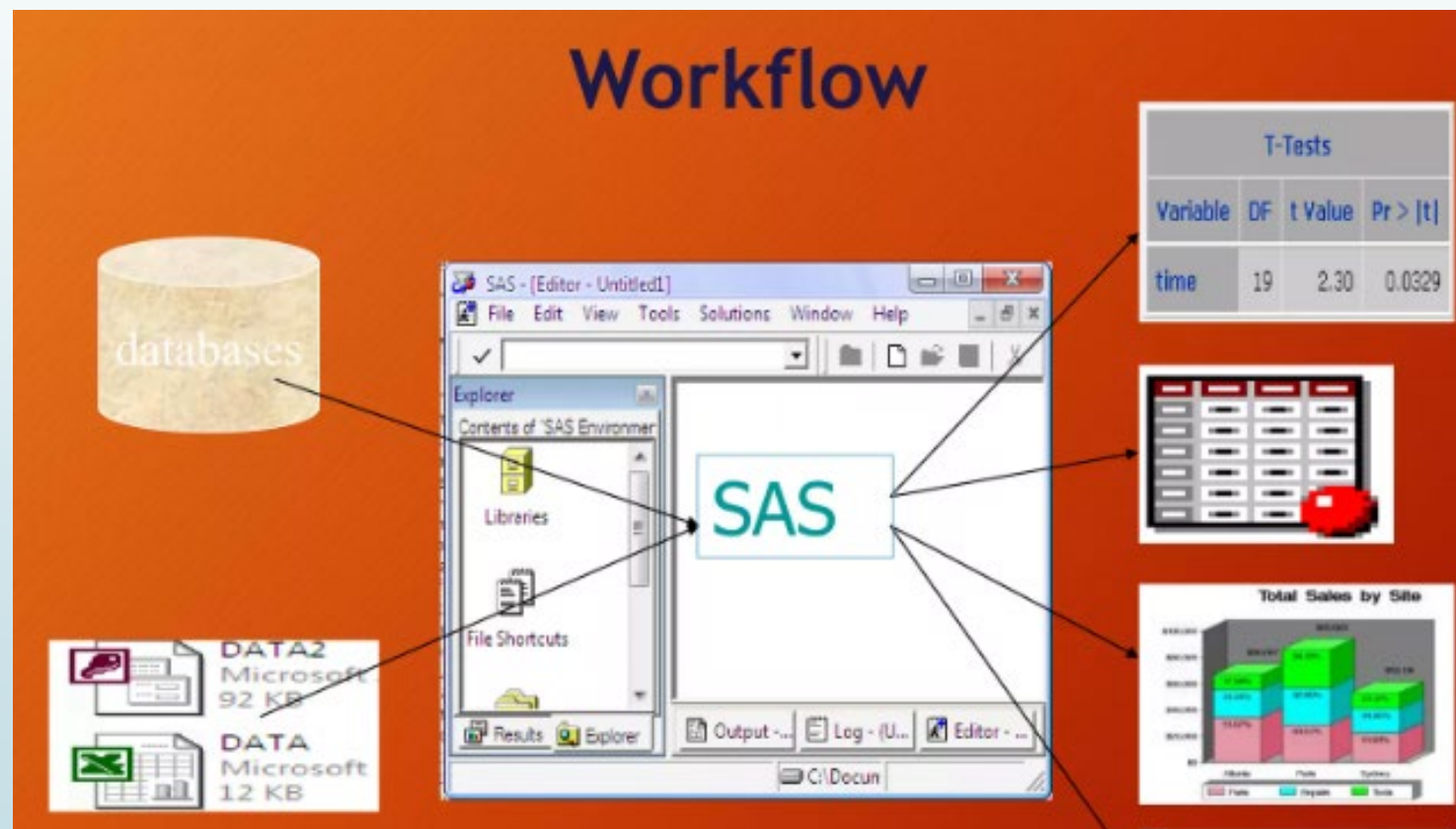
- **數據管理：**臨床試驗需要收集大量數據，包括受試者基本信息、治療方案、生命體徵、實驗室數據等等。SAS可以幫助研究人員有效地管理這些數據
- **數據分析：**豐富的統計分析功能，如描述性統計分析、存活分析、多變量分析、幫助研究人員從數據中提取有價值的信息，評估新藥的安全性和有效性
- **數據視覺化呈現：**將數據以圖表、表格等形式呈現，使數據更加直觀和易於理解，幫助研究人員發現數據中的規律和趨勢



Clinical Trial Data Management using SAS

- Clinical Trial Data Management using SAS mostly for the following purposes:

- **Analyzing Data**



Analyzing Data

Descriptive Statistics

- Organise
- Summarise
- Simplify
- Describe and present data

Inferential Statistics

- Generalise from samples to populations
- Hypothesis testing
- Make predictions

Five types of statistical analysis

Descriptive

What are the characteristics of the respondents?

Inferential

What are the characteristics of the population?

Differences

Are two or more groups the same or different?

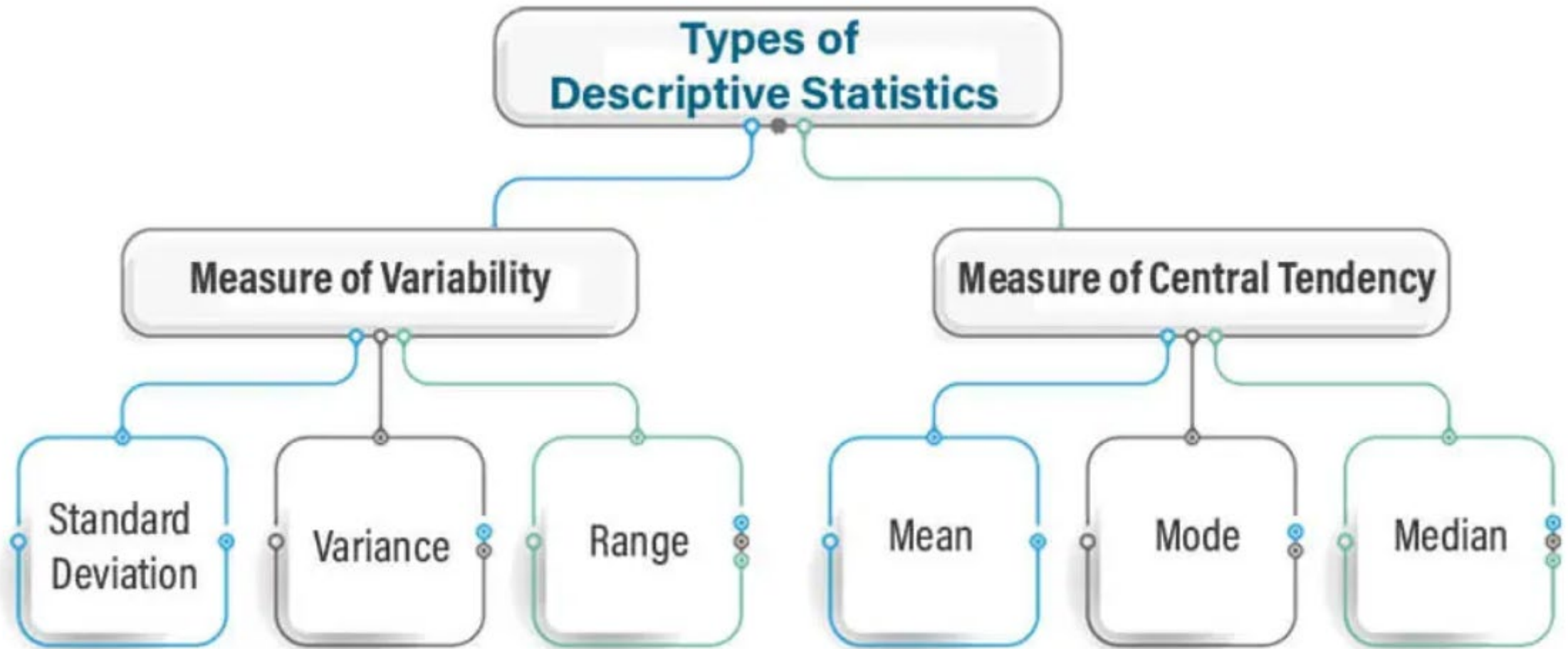
Associative

Are two or more variables related in a systematic way?

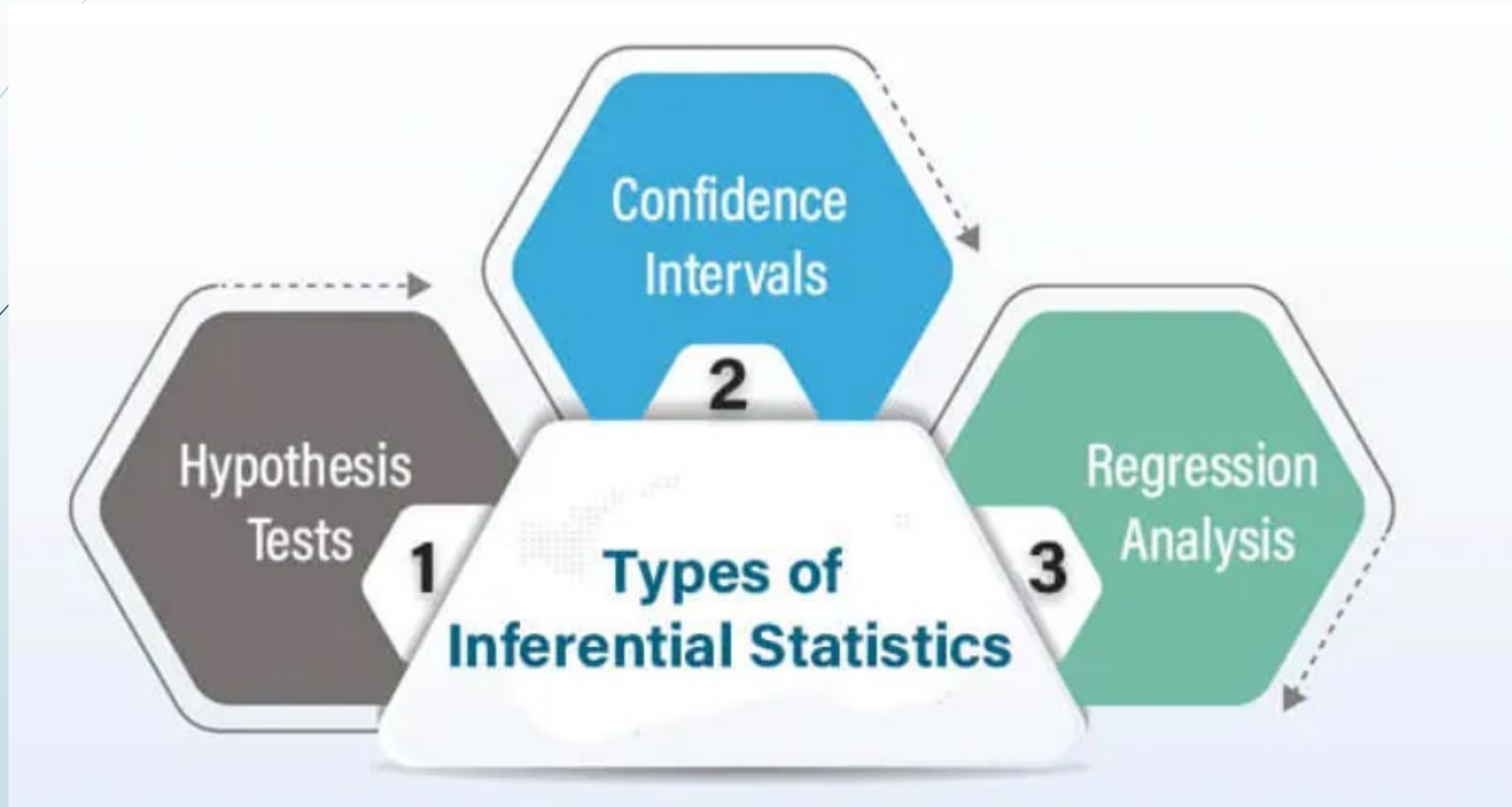
Predictive

Can we predict one variable if we know one or more other variables?

臨床試驗 常見統計方法



臨床試驗 常見統計方法





Europace (2014) **16**, 174–181
doi:10.1093/europace/eut293

CLINICAL RESEARCH

Atrial fibrillation

Effect of dronedarone on clinical end points in patients with atrial fibrillation and coronary heart disease: insights from the **ATHENA** trial

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Table I Baseline characteristics of patients with and without coronary heart disease^a

	CHD		No CHD	
	Placebo (n = 737)	Dronedarone (n = 668)	Placebo (n = 1590)	Dronedarone (n = 1633)
Mean age, years (SD)	73.5 (8.2)	73.1 (7.7)	70.8 (9.3)	70.9 (9.3)
Male gender	485 (65.8%)	419 (62.7%)	804 (50.6%)	751 (46%)
Hypertension	639 (86.7%)	593 (88.8%)	1357 (85.3%)	1406 (86.1%)
Hypercholesterolemia	436 (59.2%)	416 (62.3%)	566 (35.6%)	618 (37.8%)
Diabetes mellitus	199 (27.0%)	166 (24.9%)	264 (16.6%)	316 (19.4%)
Chronic renal failure	38 (5.2%)	40 (6.0%)	45 (2.8%)	45 (2.8%)
Congestive heart failure	287 (38.9%)	261 (39.1%)	406 (25.5%)	411 (25.2%)
NYHA class III	67 (9.1%)	58 (8.7%)	42 (2.6%)	33 (2.0%)
LVEF <35%	58/723 (8.0%)	52/658 (7.9%)	29/1558 (1.9%)	40/1605 (2.5%)
Oral anticoagulant	436 (59.2%)	414 (62.0%)	948 (59.6%)	989 (60.6%)
Low dose of aspirin (≤ 365 mg)	413 (56.0%)	390 (58.4%)	606 (38.1%)	628 (38.5%)
Beta-blocking agents ^b	559 (75.8%)	534 (79.9%)	1082 (68.1%)	1094 (67.0%)
ARB or ACE inhibitor	551 (74.8%)	495 (74.1%)	1051 (66.1%)	1119 (68.5%)
Statins ^c	453 (1.5%)	429 (64.2%)	461 (29.0%)	449 (27.5%)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

^aData are numbers (%) unless otherwise specified.

^bNot including sotalol.

^cStatins are defined as 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.

Mean (Std)

N (%)



Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus

Diabetes Care 2019;42:1067–1074 | <https://doi.org/10.2337/dc19-0093>



*Thea Anine Strøm Halden,¹
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Laavanyaah Rajakumar,¹ Ida Robertsen,²
Jan Brox,³ Jens Bollerslev,^{4,5}
Anders Hartmann,¹ Anders Åsberg,^{1,2} and
Trond Jenssen^{1,4}*

Table 1—Baseline characteristics presented as median (absolute range) or number of patients (%)

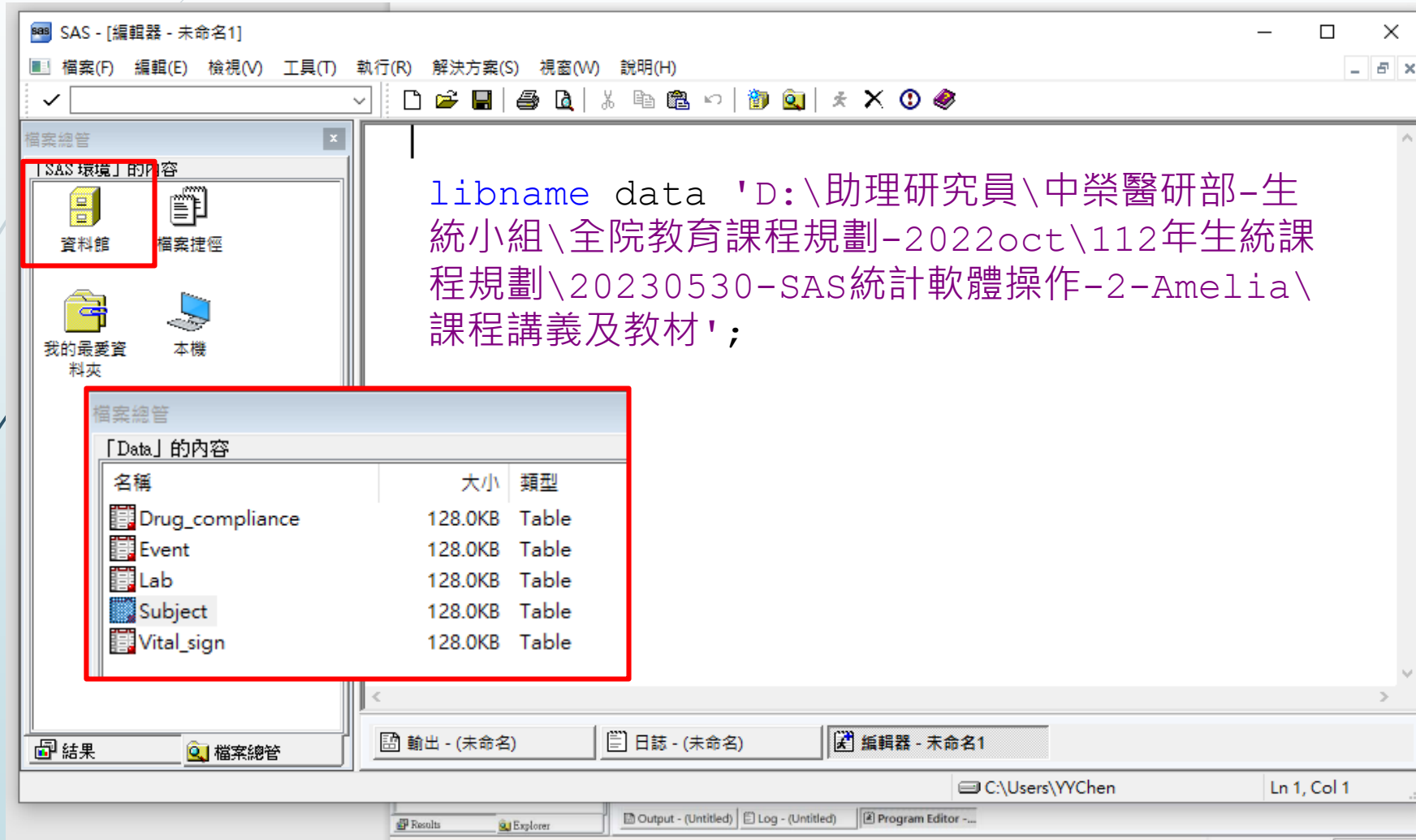
	Empagliflozin, <i>n</i> = 22	Placebo, <i>n</i> = 22
Sex (male/female), <i>n</i>	17/5	17/5
Age (years)	63 (31, 72)	59 (21, 75)
Time since transplantation (years)	3 (1, 16)	3 (1, 15)
BMI (kg/m ²)	28.8 (24.7, 39.3)	27.5 (22.4, 45.8)
WHR (cm)	1.01 (0.82, 1.25)	0.98 (0.80, 1.11)
Systolic blood pressure (mmHg)	143 (111, 176)	140 (100, 163)
Diastolic blood pressure (mmHg)	79 (63, 94)	82 (55, 94)
HbA _{1c} (%)	6.9 (6.5, 8.2)	6.8 (6.1, 7.2)
HbA _{1c} (mmol/mol)	52 (38, 83)	51 (40, 73)
FPG (mmol/L)	8.0 (5.0, 13.1)	7.3 (4.5, 12.5)
eGFR (mL/min/1.73 m ²)	66 (41, 83)	59 (44, 82)
LDL (mmol/L)	2.8 (1.2, 4.2)	2.8 (2.0, 3.8)
Triglycerides (mmol/L)	1.8 (1.1, 3.2)	2.2 (1.1, 5.6)
Smoking, <i>n</i>		
Smoker	4 (18.2)	0 (0.00)
Ex-smoker	13 (59.1)	11 (50.0)
Never smoked	5 (22.7)	11 (50.0)

Median (IQR)

N (%)

SAS 9.4 起始畫面

設定SAS永久檔位置



libname data 'D:\助理研究員\中榮醫研部-生
統小組\全院教育課程規劃-2022oct\112年生統課
程規劃\20230530-SAS統計軟體操作-2-Amelia\
課程講義及教材';

名稱	大小	類型
Drug_compliance	128.0KB	Table
Event	128.0KB	Table
Lab	128.0KB	Table
Subject	128.0KB	Table
Vital_sign	128.0KB	Table

利用SAS進行常態性檢定資料分佈：

```
/*Normality Test*/  
data lab; set data.final;  
if visit=1; keep Group age SBP AST Creatinine; run;  
  
proc univariate data=lab normal ;  
var sbp;  
class group; run;
```

SAS 系統

UNIVARIATE 程序
變數: SBP (SBP)
Group = 2

Mean (std)

動差			
N	34	總和權重	34
平均值	130.558824	總和觀測	4439
標準差	18.6664359	變異數	348.435829
偏態	0.42712288	峰度	0.42294941
未校正平方和	591049	校正平方和	11498.3824
變異係數	14.2973377	標準誤差平均值	3.20126734

基本統計量值

位置		變異性	
平均值	130.5588	標準差	18.66644
中位數	129.5000	變異數	348.43583
眾數	119.0000	全距	86.00000
		內四分位距	21.00000

分位數 (定義 5)

層級	分位數
100% 最大值	180.0
99%	180.0
95%	164.0
90%	154.0
75% Q3	140.0
50% 中位數	129.5
25% Q1	119.0
10%	107.0
5%	101.0
1%	94.0
0% 最小值	94.0

Median (IQR)

常態性檢定

檢定	統計值		p 值	
Shapiro-Wilk	W	0.981536	Pr < W	0.8198
Kolmogorov-Smirnov	D	0.100622	Pr > D	>0.1500
Cramer-von Mises	W-Sq	0.046868	Pr > W-Sq	>0.2500
Anderson-Darling	A-Sq	0.26081	Pr > A-Sq	>0.2500

常態性檢定 → 符合常態分佈 $P > 0.05$

Kolmogorov-Smirnov (K-S) 檢定：樣本數50個以上

Shapiro-Wilk (S-W) 檢定：樣本數50個以下

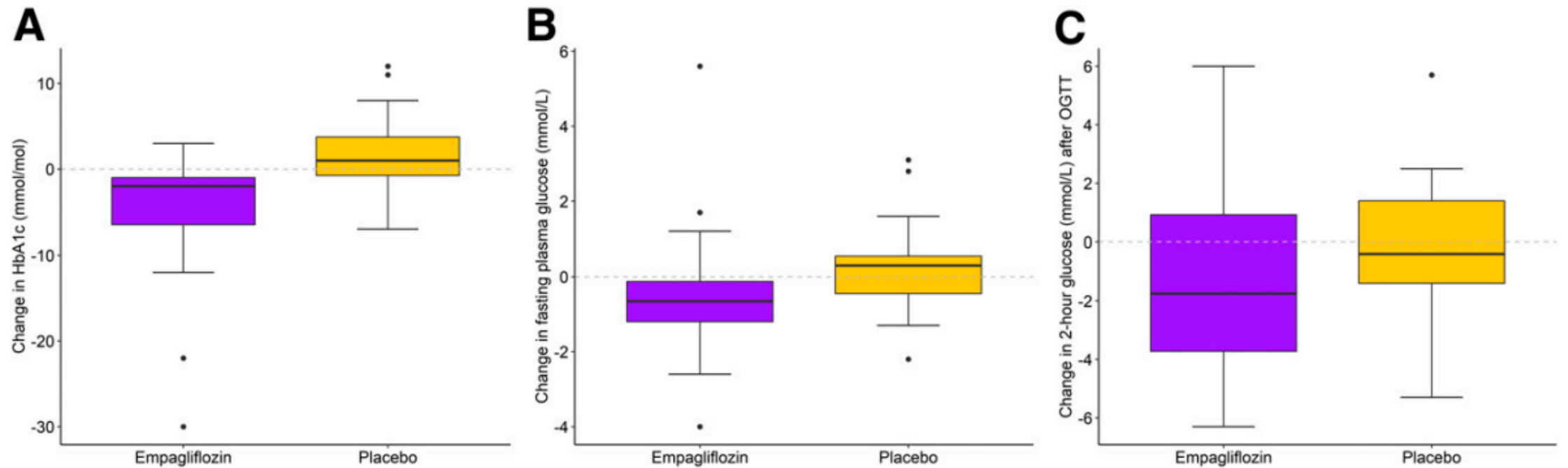
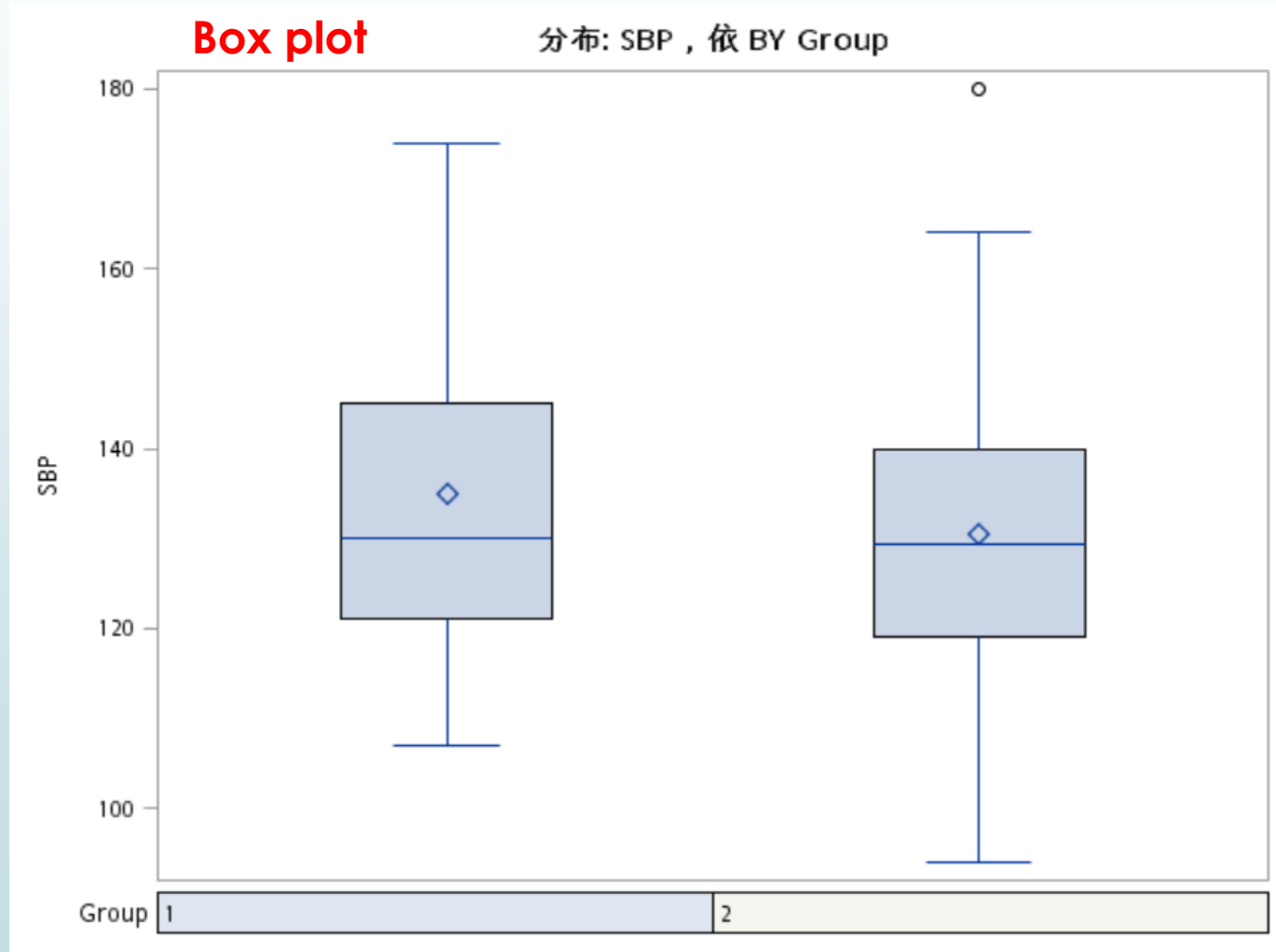


Figure 1—Median (IQR) change from baseline to week 24 in HbA_{1c} ($P = 0.018$) (A), FPG ($P = 0.27$) (B), and 2-h glucose after an OGTT ($P = 1$) (C) in the two intervention groups.

利用SAS進行常態性檢定資料分佈：

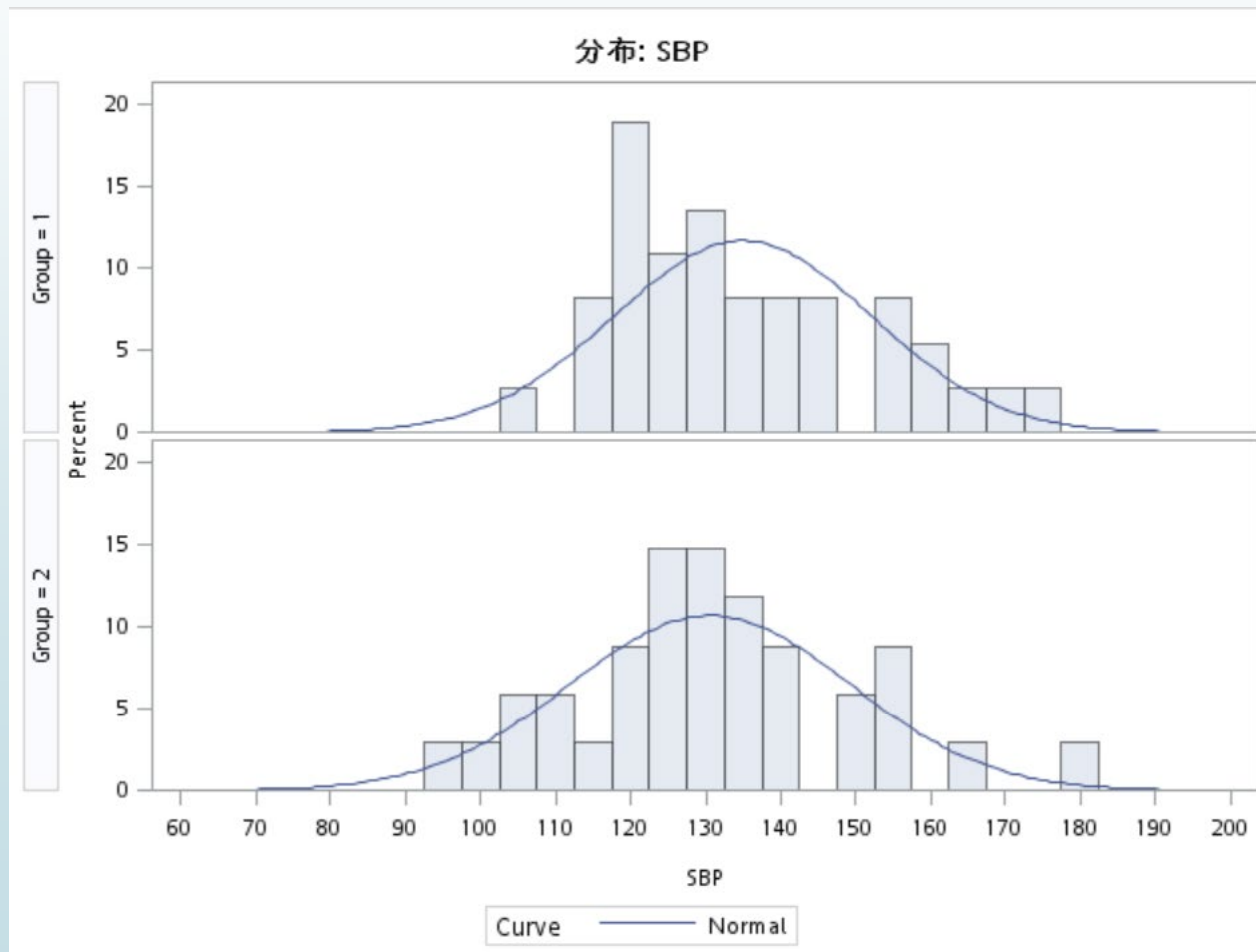
```
proc sort data=lab; by group;  
proc univariate data=lab normal plot;  
var sbp;  
by group; run;
```



利用SAS進行常態性檢定資料分佈：

```
proc univariate data=lab ;  
title histogram;  
histogram sbp / midpoint = 60 to 200 by 5 Normal;  
class group; run;
```

Histogram



Analyzing Data using SAS

長資料格式：data.final

► 利用 SAS 進行 描述性統計分析：連續型變數

```
PROC MEANS DATA=data.final
MAXDEC=2  N  MEAN  STD  MEDIAN Q1 Q3
/*MEDIAN Q1 Q3  MIN MAX  N VAR SKEWNESS KURTOSIS T PROBT CLM /*CLM 樣本信賴區間*/;
VAR  SBP DBP Creatinine  AST ALT  ;
CLASS  visit  ;
/*BY  Group  ; */ RUN;
```

Visit	觀測值數目	變數	標籤	N	平均值	標準差	中位數	下四分位數	上四分位數
1	76	SBP	SBP	76	132.80	17.30	130.00	121.50	140.00
		DBP	DBP	76	80.20	11.26	79.00	73.50	89.00
		Creatinine	Creatinine	75	1.05	0.32	0.99	0.86	1.15
		AST	AST	76	22.71	10.44	20.00	17.00	23.00
		ALT	ALT	76	24.86	20.70	20.00	15.00	25.50
2	73	SBP	SBP	73	132.77	17.84	130.00	121.00	140.00
		DBP	DBP	73	79.85	11.58	79.00	73.00	89.00
		Creatinine	Creatinine	0	.	.	.	.	.
		AST	AST	0	.	.	.	.	.
		ALT	ALT	0	.	.	.	.	.
3	71	SBP	SBP	71	128.68	15.69	127.00	120.00	138.00
		DBP	DBP	71	77.55	10.45	78.00	70.00	86.00
		Creatinine	Creatinine	71	1.03	0.29	1.00	0.87	1.18
		AST	AST	71	22.15	9.33	20.00	17.00	23.00
		ALT	ALT	71	23.28	16.33	20.00	15.00	26.00

Visit	觀測值數目	變數	標籤	N	平均值	標準差	中位數	下四分位數	上四分位數
4	71	SBP	SBP	69	125.58	16.29	125.00	114.00	135.00
		DBP	DBP	69	78.03	14.18	76.00	70.00	82.00
		Creatinine	Creatinine	0	.	.	.	.	.
		AST	AST	0	.	.	.	.	.
		ALT	ALT	0	.	.	.	.	.
5	71	SBP	SBP	64	128.08	14.53	130.00	119.50	138.50
		DBP	DBP	64	77.83	11.09	79.00	68.50	85.50
		Creatinine	Creatinine	0	.	.	.	.	.
		AST	AST	0	.	.	.	.	.
		ALT	ALT	0	.	.	.	.	.
6	71	SBP	SBP	71	128.90	15.30	128.00	119.00	138.00
		DBP	DBP	71	77.32	9.99	79.00	70.00	85.00
		Creatinine	Creatinine	68	1.03	0.28	1.00	0.89	1.12
		AST	AST	68	21.10	7.72	20.00	17.00	23.00
		ALT	ALT	68	21.54	10.77	19.00	15.00	27.00

Analyzing Data using SAS

利用 SAS 進行 推論性統計分析：Student's t test

```
/*Student's t test*/  
data lab; set data.final;  
if visit=1; keep Group SBP gender; run;
```

```
PROC TTEST DATA=lab ;  
CLASS group; VAR SBP ; RUN;
```

TTEST 程序

變數: SBP (SBP)

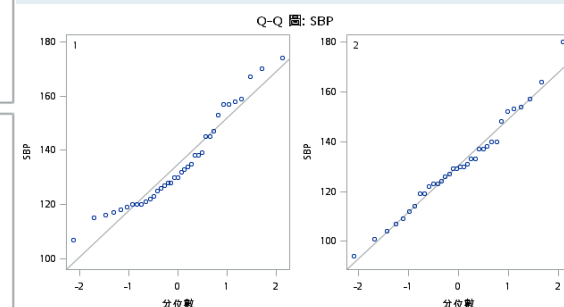
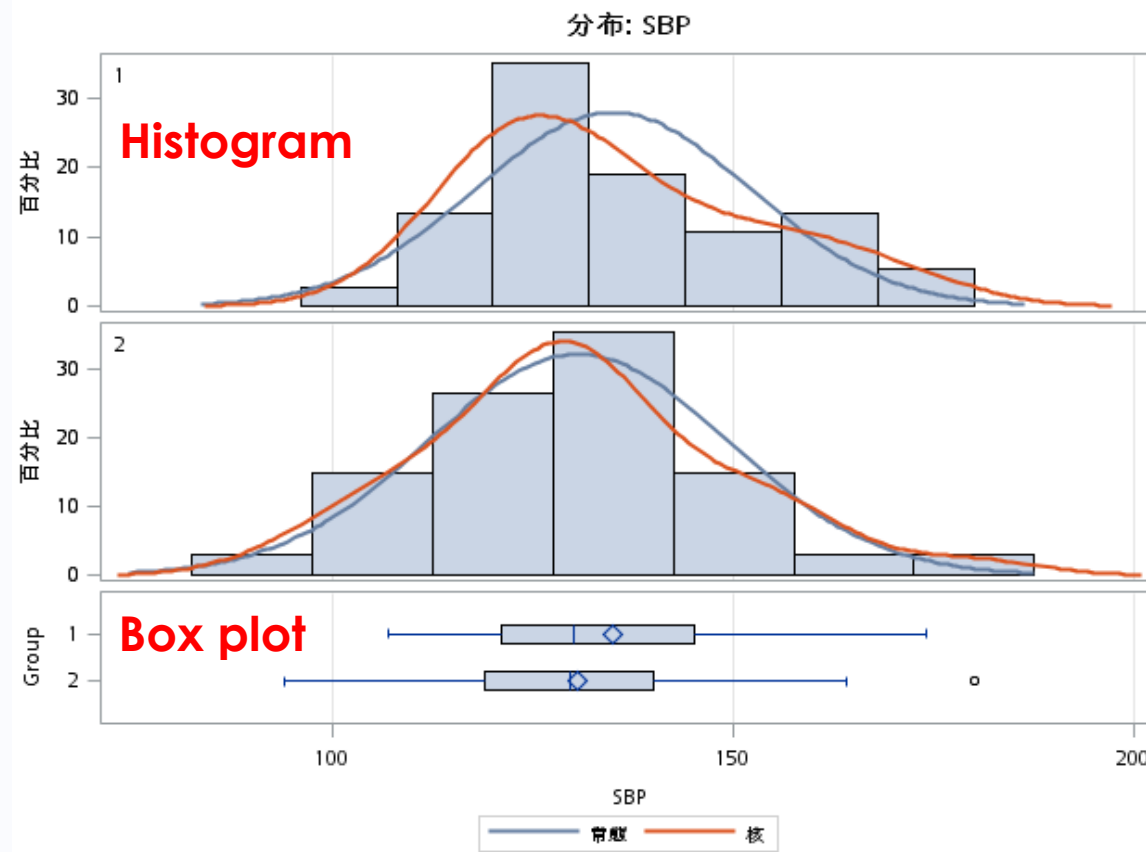
Group	N	平均值	標準差	標準誤差	最小值	最大值
1	37	134.9	17.1188	2.8143	107.0	174.0
2	34	130.6	18.6664	3.2013	94.0000	180.0
Diff (1-2)		4.3871	17.8757	4.2467		

Group	方法	平均值	95% CL 平均值	標準差	95% CL 標準差
1		134.9	129.2 140.7	17.1188	13.9212 22.2366
2		130.6	124.0 137.1	18.6664	15.0559 24.5702
Diff (1-2)	集區	4.3871	-4.0848 12.8591	17.8757	15.3269 21.4491
Diff (1-2)	Satterthwaite	4.3871	-4.1207 12.8949		

方法	變異數	自由度	t 值	Pr > t
集區	均等	69	1.03	0.3052
Satterthwaite	不均等	67.023	1.03	0.3071

變異數相等性

方法	分子自由度	分母自由度	F 值	Pr > F
Folded F	33	36	1.19	0.6104



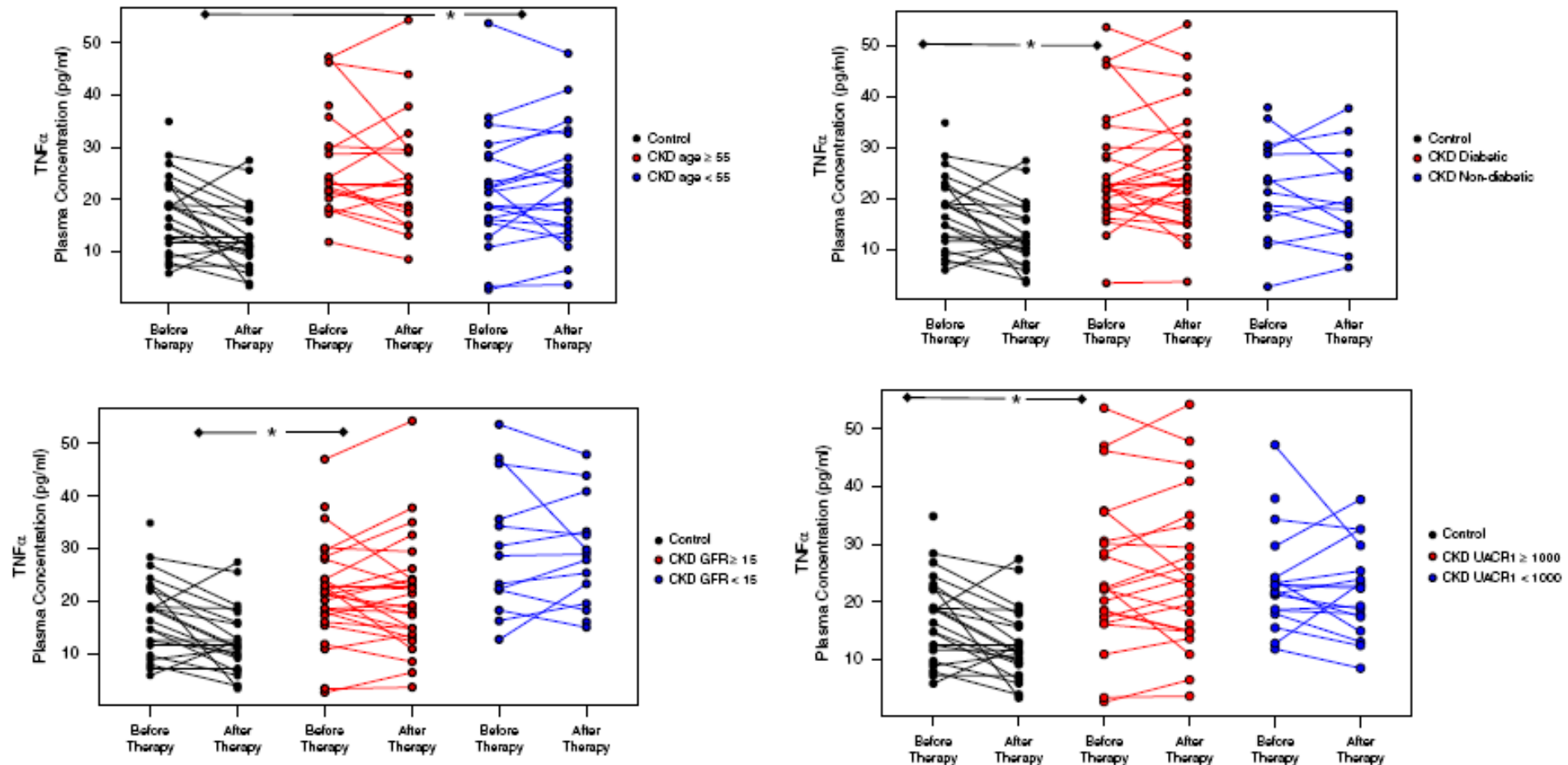


Figure 7. | Line graphs represent plasma TNF- α levels for each study participant before and after DAPT. Non-CKD controls (reference group) in each panel and participants with CKD stratified into two groups on the basis of (A) age < 55 years or ≥ 55 years, (B) presence of diabetes, (C) GFR < 15 ml/min per 1.73 m^2 or ≥ 15 ml/min per 1.73 m^2 , (D) albuminuria (UACR1) < 1000 mg/g or ≥ 1000 mg/g of creatinine. Generalized linear regression model P values with an asterisk represent significant differences when comparing mean change in TNF- α levels in a CKD subgroup with the reference group.]

Analyzing Data using SAS

➡ 利用 SAS 進行 推論性統計分析：Paired t test

```
/*Paired t test*/
```

短資料格式：data.vital_sign_m

```
PROC TTEST DATA= data.vital_sign_m ;
```

```
    PAIRED SBP1*SBP2; /*before : after 不  
同於兩組獨立樣本t檢定，此處以paired後面接著兩個變  
數，分別是前測與後側的數值，以星號連結*/
```

```
RUN;
```

SAS 系統

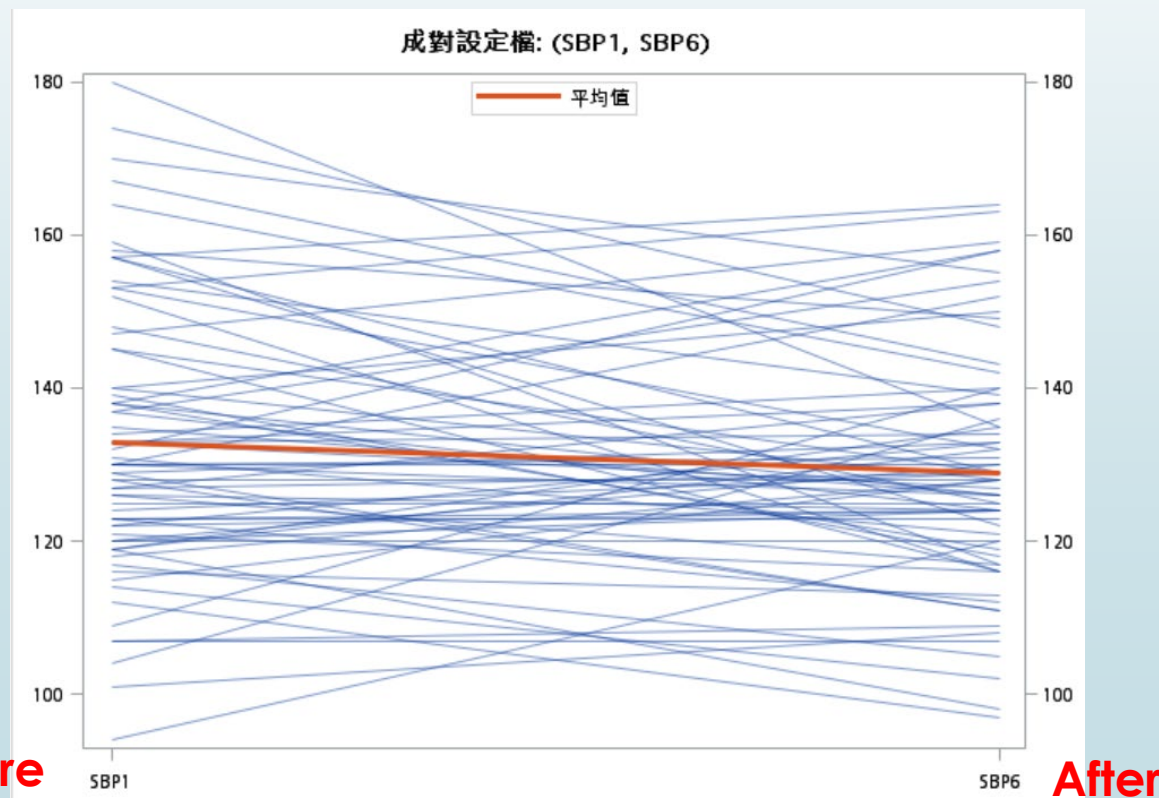
TTEST 程序

差異: SBP1 - SBP6

N	平均值	標準差	標準誤差	最小值	最大值
71	3.9437	16.7945	1.9931	-32.0000	45.0000

平均值	95% CL 平均值	標準差	95% CL 標準差
3.9437	-0.0315 7.9188	16.7945	14.4145 20.1231

自由度	t 值	Pr > t
70	1.98	0.0518



Analyzing Data using SAS

► 利用 SAS 進行 推論性統計分析：

類別型變數 + Chi-square test

```
/*類別型變數 + Chi-square test*/
```

```
data lab; set data.final;
```

```
if visit=1; keep Group SBP gender; run;
```

```
PROC FREQ data=lab;
```

```
table gender*group / chisq expected exact ; run;
```

SAS 系統

FREQ 程序

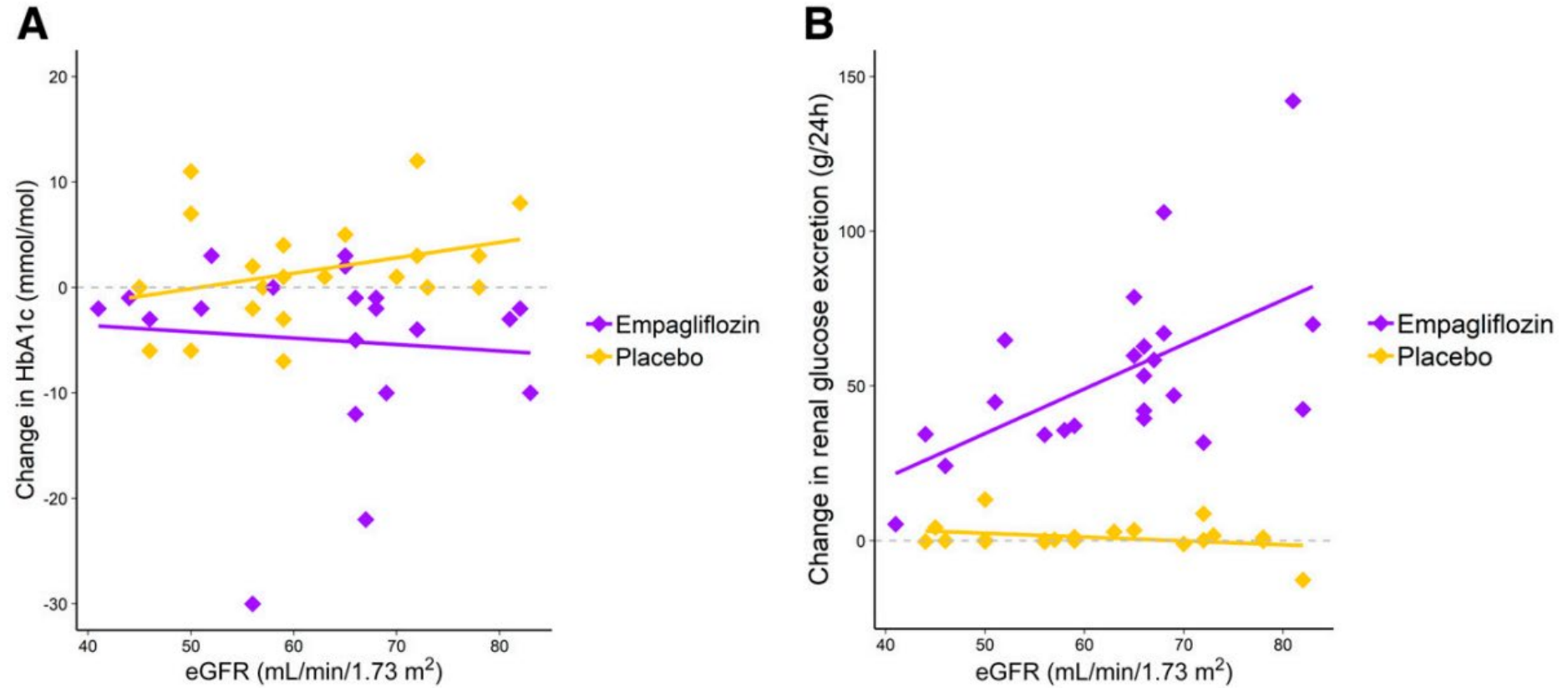
次數 預期 百分比 列百分比 欄百分比	Table of Gender by Group			
	Gender(Gender)	Group(Group)		總計
		1	2	
	0	7	8	15
		7.8169	7.1831	21.13
		9.86	11.27	
		46.67	53.33	
		18.92	23.53	
	1	30	26	56
		29.183	26.817	78.87
		42.25	36.62	
		53.57	46.43	
		81.08	76.47	
	總計	37	34	71
		52.11	47.89	100.00
次數遺漏 = 5				

表格 Group-Gender*s 的統計值

統計值	自由度	值	機率
卡方	1	0.2260	0.6345
概度比卡方	1	0.2259	0.6346
連續性調整卡方	1	0.0340	0.8537
Mantel-Haenszel 卡方	1	0.2228	0.6369
Phi 係數		-0.0564	
列聯係數		0.0563	
Cramer V		-0.0564	

Fisher 精準檢定

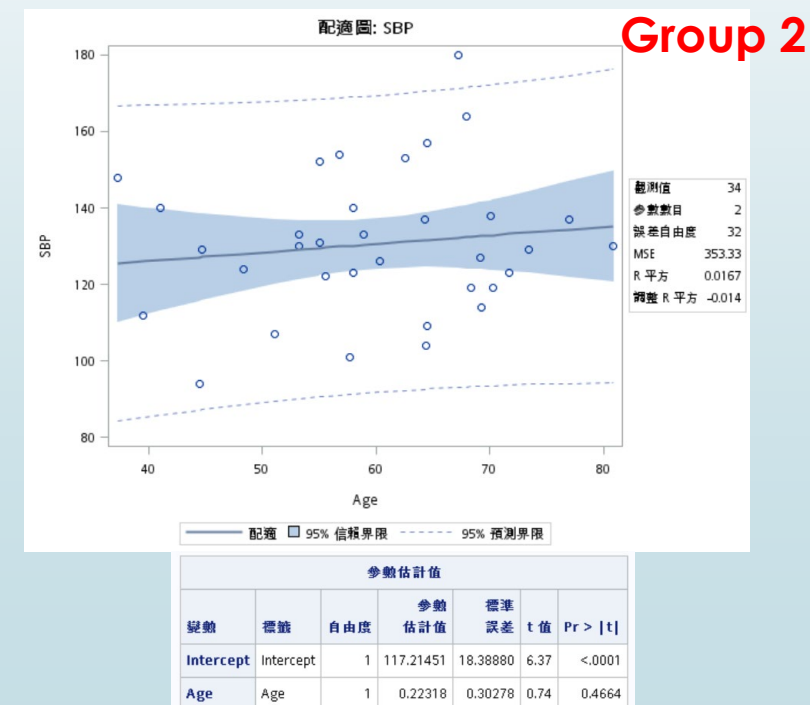
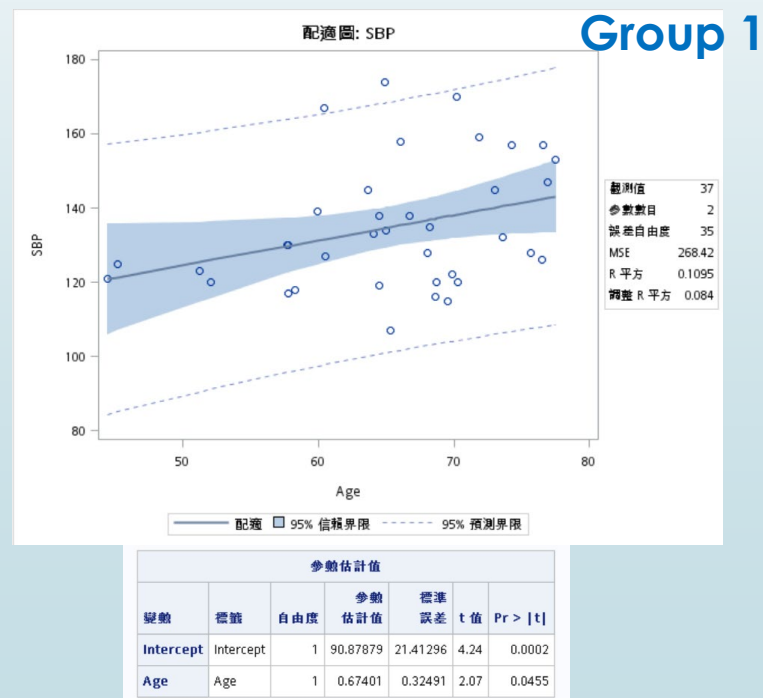
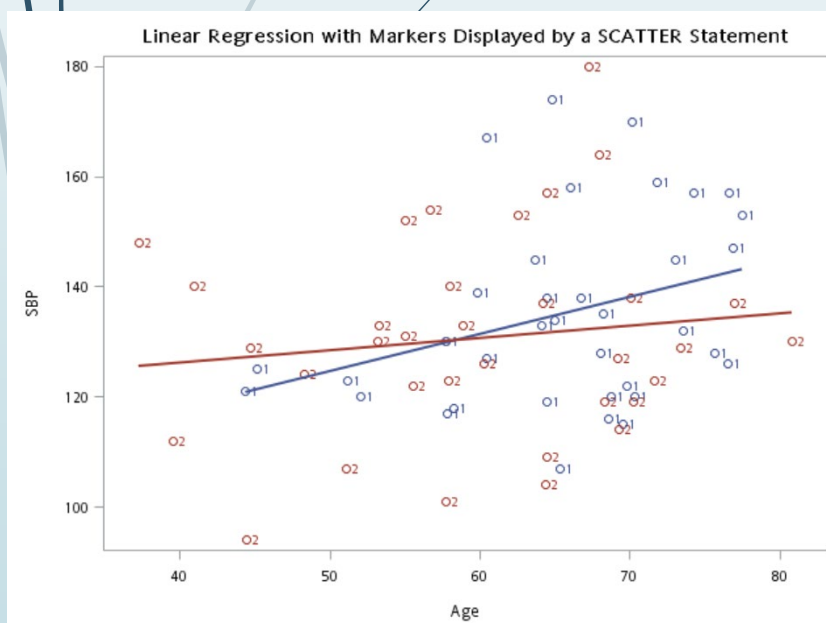
儲存格 (1,1) 次數 (F)	7
左邊 Pr <= F	0.4262
右邊 Pr >= F	0.7782
表格機率 (P)	0.2044
雙邊 Pr <= P	0.7729



Analyzing Data using SAS

► 利用 SAS 進行 推論性統計分析：
Linear regression

```
/*Linear regression*/  
proc sort data=lab; by group /*descending*/; run;  
proc sgplot data=lab noautolegend;  
  title 'Linear Regression with Markers Displayed by a SCATTER Statement';  
  scatter y=SBP x=age / group=group markerchar=group;  
  reg y=SBP x=age / group=group ; run;  
  
proc reg data =lab ; Model sbp = age ; by group; run;
```



Analyzing Data using SAS

- 利用 SAS 進行 推論性統計分析：重複測量
Generalized estimating equations (GEE)

長資料格式：data.final

```
proc sort data= data.final ; by screening_no visit; run;

/*GEE: Repeated measure*/
proc genmod data= data.final ;
  class screening_no group (ref=first) gender (ref=first)
  visit (ref=first) / param=ref;
  model SBP = group age gender / dist = normal link = log ;
/*link=logit dist=binomial; dist = normal link = log ; dist =
poisson link = log offset = o COVB*/
repeated subject=screening_no (visit) ; run;
```

已收斂演算法。

GEE 模型資訊	
相關結構	獨立
主題效果	Screening_no(Visit) (433 層級)
群集數	433
含有遺漏值的群集	16
相關矩陣維度	1
最大群集大小	1
最小群集大小	0

GEE 參數估計值的分析

經驗標準誤差估計值						
參數		估計值	標準誤差	95% 信賴界限		Z Pr > Z
Intercept		4.6678	0.0425	4.5845	4.7512	109.79 <.0001
Group	2	0.0047	0.0124	-0.0196	0.0290	0.38 0.7038
Age		0.0028	0.0006	0.0017	0.0040	4.79 <.0001
Gender	1	0.0203	0.0154	-0.0099	0.0504	1.32 0.1881

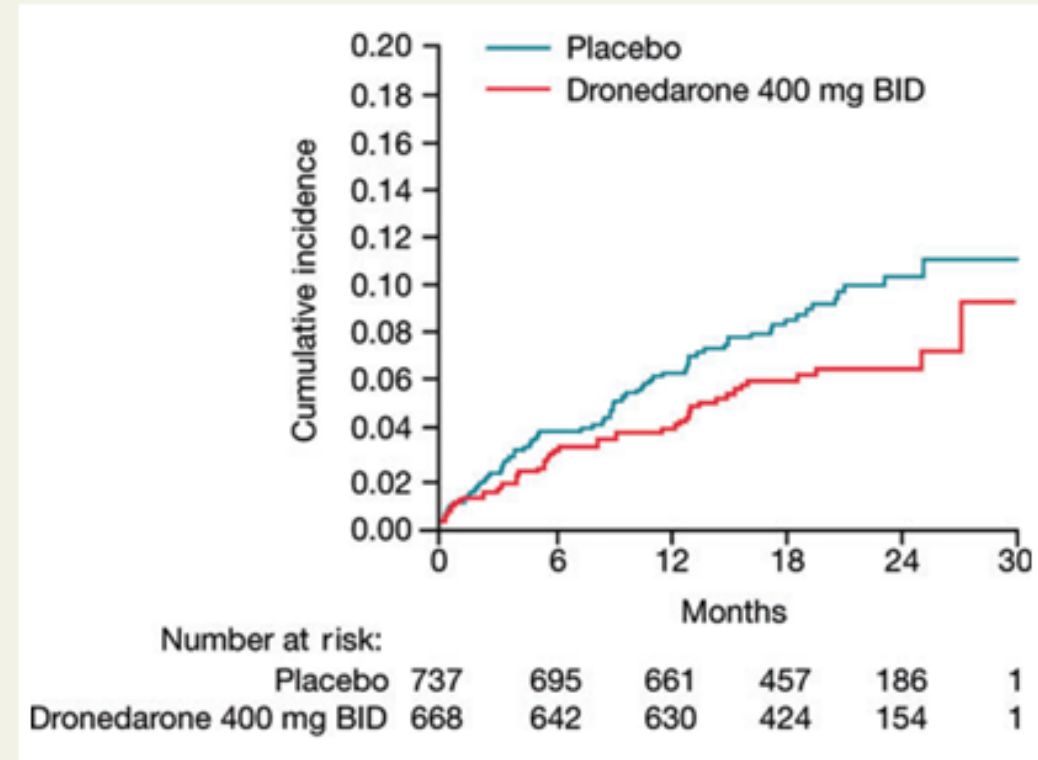


Figure 2 Cumulative risk of the occurrence of first acute coronary syndrome in patients with coronary heart disease. BID, twice daily.

Analyzing Data using SAS

► 利用 SAS 進行 推論性統計：存活分析

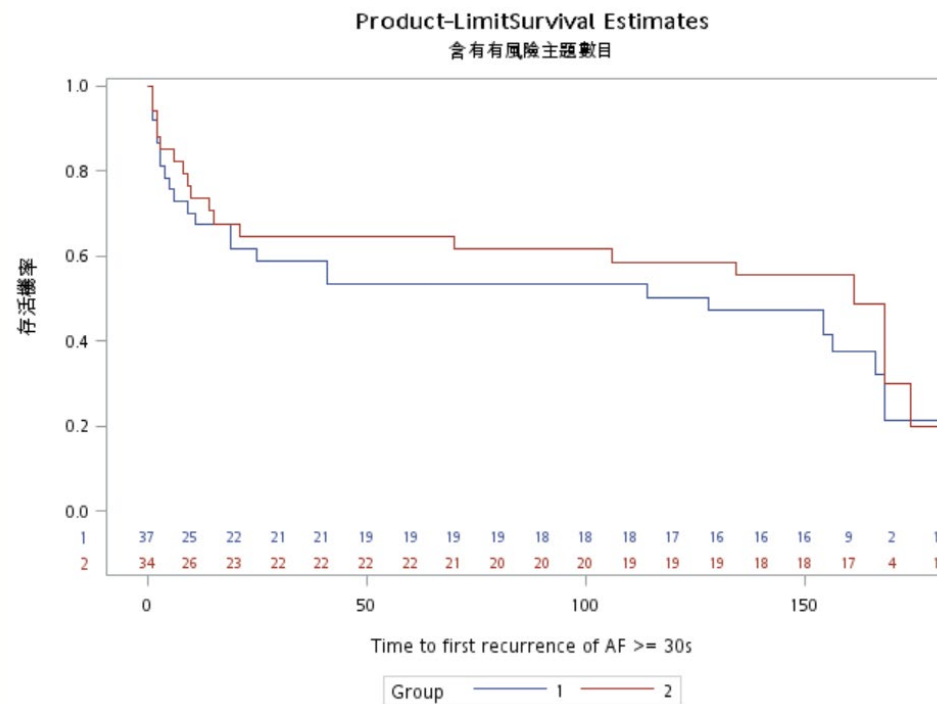
Kaplan-Meier Survival Curves

```
/*KM plots*/  
PROC LIFETEST DATA= data.itt6 METHOD=KM NOTABLE  
PLOTS=SURVIVAL (ATRISK=0 TO 180 BY 10 NOCENSOR /*CB 95%CI*/);  
/*KM/PL意思相同; (SURVIVAL) / (S) 意思相同*/  
    TIME Time_first_rec* First_AF_recurrence (0);  
    STRATA group ; /*diagage (65,75); age切65↓, 65-75, 75↑; */  
/* by age65; */  
RUN;
```

分層相等性的檢定

檢定	卡方	自由度	Pr > 卡方
對數排名	0.5519	1	0.4576
Wilcoxon	0.8589	1	0.3540
-2Log(LR)	0.2575	1	0.6119

Event-free survival rate



Europace (2014) **16**, 174–181
doi:10.1093/europace/eut293

Table 2 Comparison of the effect of dronedarone among patients with and without coronary heart disease

Outcome	CHD	Placebo, n/N (%)	Dronedarone, n/N (%)	HR for dronedarone (95% CI)	P value ^a
First cardiovascular hospitalization or death from any cause	Yes	350/737 (47.49)	252/668 (37.72)	0.733 (0.62–0.86)	0.535
	No	567/1590 (35.66)	482/1663 (29.52)	0.782 (0.69–0.88)	
Cardiovascular death	Yes	47/737 (6.38)	26/668 (3.89)	0.602 (0.37–0.97)	0.350
	No	47/1590 (2.96)	39/1663 (2.39)	0.814 (0.53–1.24)	
First ACS	Yes	67/737 (9.09)	42/668 (6.29)	0.671 (0.46–0.99)	0.429
	No	29/1590 (1.82)	26/1633 (1.59)	0.876 (0.52–1.49)	
First stroke, ACS or cardiovascular death	Yes	116/737 (15.74)	67/668 (10.03)	0.615 (0.46–0.83)	0.272
	No	101/1590 (6.35)	81/1633 (4.96)	0.778 (0.58–1.04)	

ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval.

^aP value of interaction between CHD status and treatment based on Cox regression model.

Analyzing Data using SAS

- 利用 SAS 進行 推論性統計：存活分析
Cox proportional hazard model

```
/*Cox regression*/  
PROC PHREG DATA=data.itt6 ;  
class gender (ref=first ) group (ref="2") htn (ref=first ) dm(ref=first )  
hyperlipidemia (ref=first ) cad (ref=first ) cva (ref=first) hf (ref=first) ;  
/*by age65;*/  
MODEL Time_first_rec* First_AF_recurrence (0) =group age gender htn/ RISKLIMITS;  
RUN;
```

最大概度估計值的分析										
參數		自由度	參數 估計值	標準 誤差	卡方	Pr > ChiSq	危險 比	95% 危險比信賴界限		標籤
Group	1	1	0.26032	0.31998	0.6619	0.4159	1.297	0.693	2.429	Group 1
Age		1	-0.00476	0.01606	0.0878	0.7670	0.995	0.964	1.027	Age
Gender	1	1	-0.13546	0.35660	0.1443	0.7040	0.873	0.434	1.757	Gender 1
HTN	1	1	-0.01737	0.30505	0.0032	0.9546	0.983	0.541	1.787	HTN 1

Descriptive Statistics



Descriptive statistics is achieved with the help of tables, graphs, etc.

Inferential Statistics



Inferential statistics is achieved by probability.

Descriptive Statistics



The goal of descriptive statistics is to describe and summarize the data.

Inferential Statistics



The goal of inferential statistics is to test and make predictions.

Descriptive Statistics



The algorithm of descriptive statistics is mean, mode, and median.

Inferential Statistics



The algorithm of inferential statistics is ANOVA and regression.



Thank you for listening