



**TMUH HFC**

Taipei Medical University Hospital  
Heart Failure Center



## 從 A 到 Z 線上藥學論壇

# SGLT2i 於心衰竭從預防到治療的角色

2022/1/15

徐千彞醫師 Chien-Yi Hsu, M.D., Ph.D.

台北醫學大學附設醫院心臟內科 心臟衰竭組主任

國立陽明大學 臨床醫學研究所博士

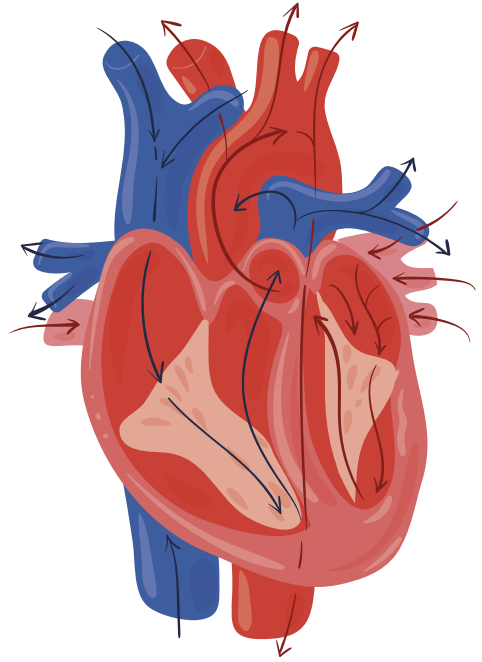
台北醫學大學 專任助理教授

台灣高血壓學會 理事 教育委員

台灣心肌梗塞學會 學術委員

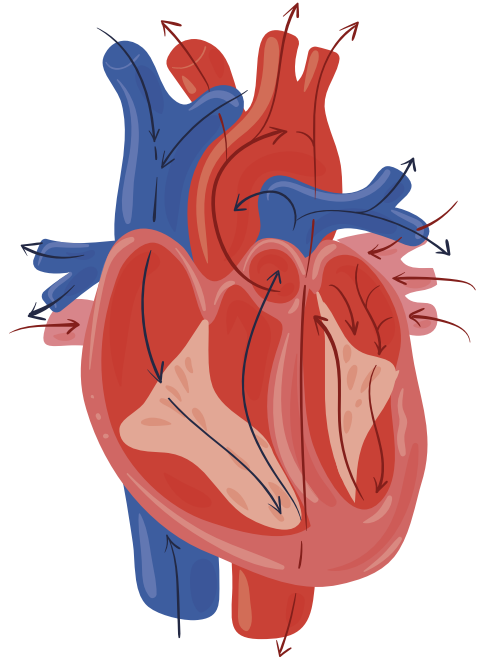


# Outline



- **The urgency and unmet needs of HF to patients**
- **Epoch-making treatment of HF with reducing mortality**
- **Timely prevention HF in T2D**
- **Conclusions**

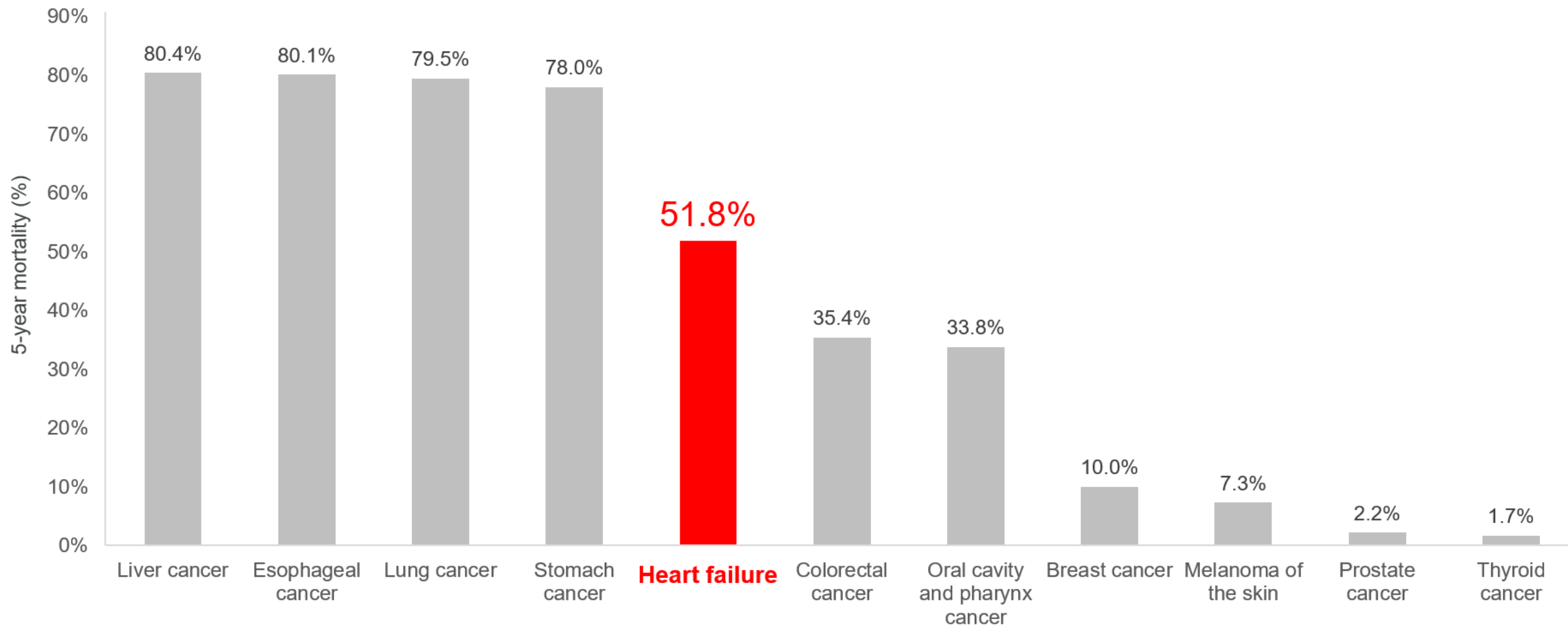
# Outline



- **The urgency and unmet needs of HF to patients**
- Epoch-making treatment of HF with reducing mortality
- Timely prevention HF in T2D
- Conclusions



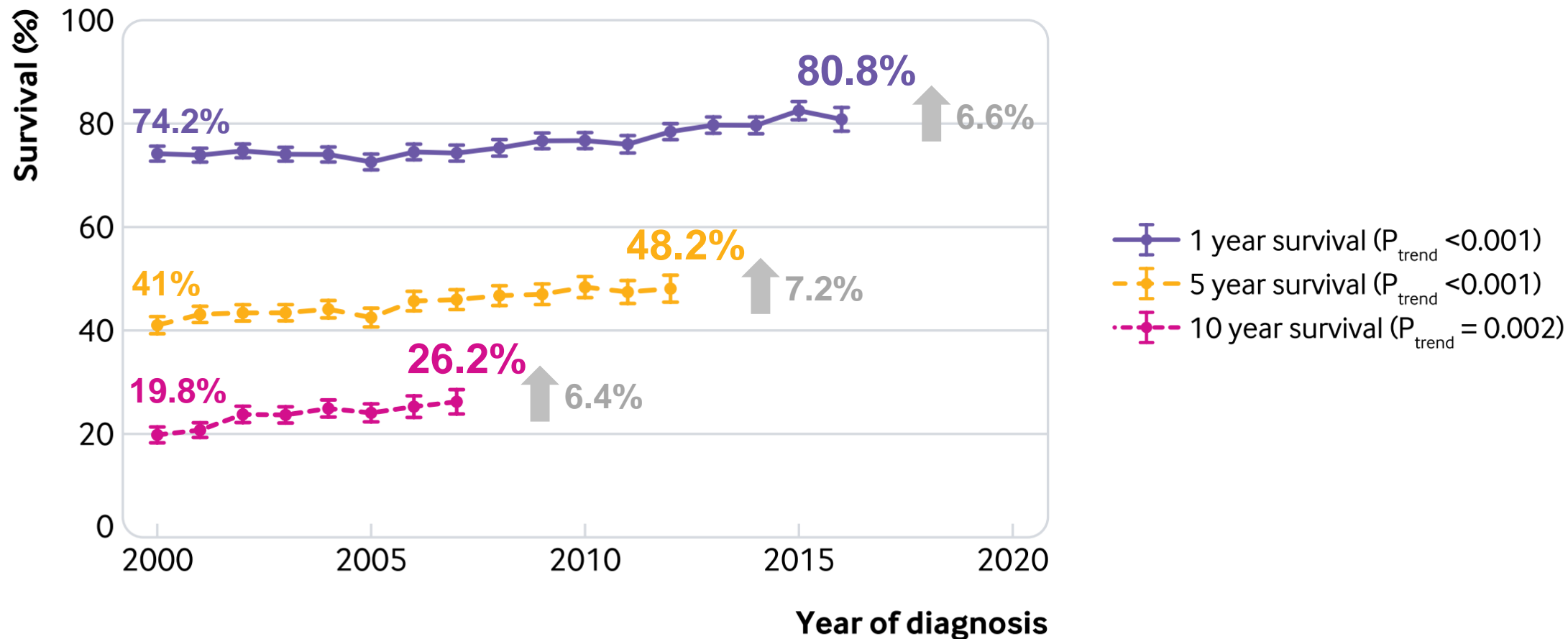
# 心衰竭比多數十大癌症5年死亡率還高



BMJ. 2019 Feb 13;364:l223.  
<https://seer.cancer.gov/statfacts/>



# 心衰竭**存活率**在過去15年有改善但仍有進步空間



Survival rates at one, five, and 10 years for people with heart failure by year of diagnosis



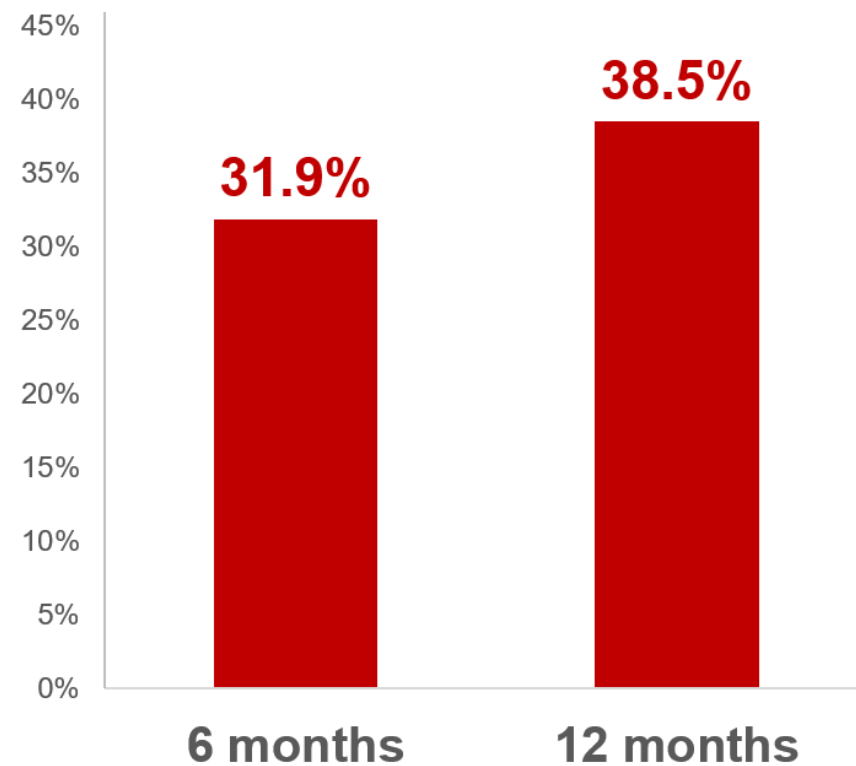
# 心衰竭住院病患的住院天數長、再住院比率高



Patients with hospitalization for HF in Taiwan

Re-hospitalization rates(%)

Hospitalization for HF	First year	Second year	Third year
Mean number of admission	1.6	1.6	1.5
<b>Mean length of stay (day)</b>	<b>20.6</b>	<b>22.7</b>	<b>20.1</b>
In-hospital mortality	13.9%	13.6%	13.2%



ESC Heart Fail. 2020 Sep 13. doi: 10.1002/ehf2.12892.

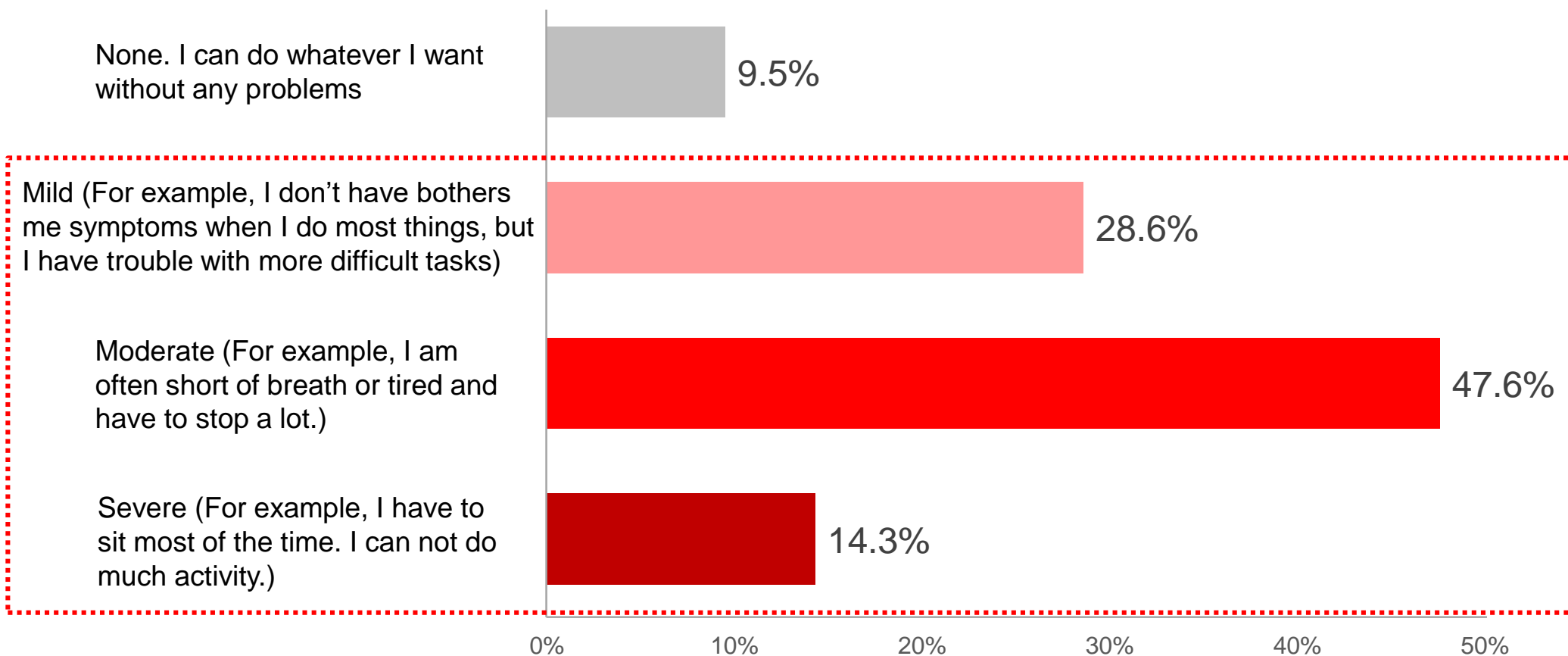
Acta Cardiol Sin 2017;33:127-138.



# 九成心衰竭病患受症狀或失能所苦

## Patient-Reported Severity of Heart Failure Symptoms or Disability

How would you describe your heart failure symptoms or disability?



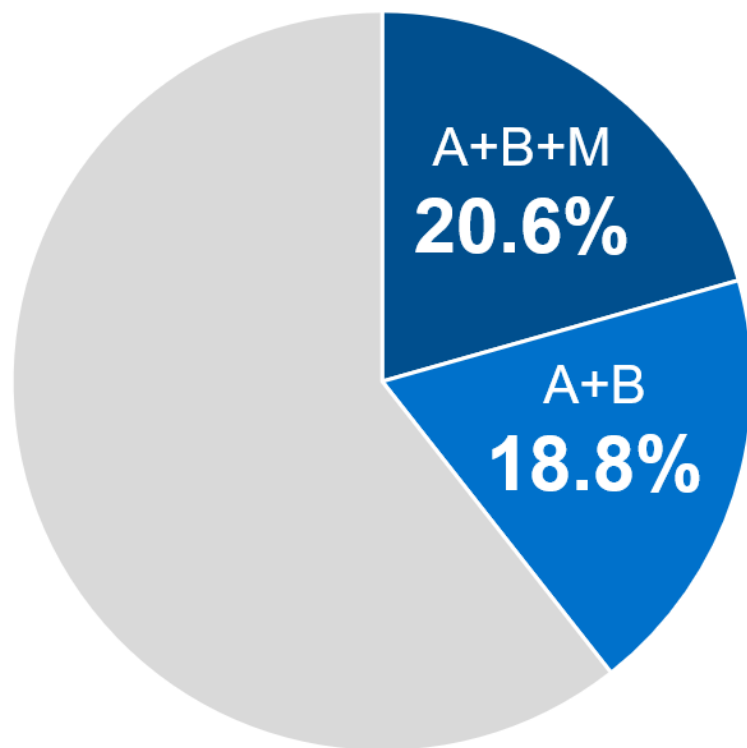
**90.5%**



# 僅4成病患使用RAASi + $\beta$ -blocker標準治療， 近3/4未達目標半劑量



**39.4%** HF patients with  
A+B(+M) therapy in Taiwan



Different types of guideline-directed medical therapy (GDMT) prescribed to the patients. A, renin-angiotensin system blockers; B, beta-blockers; M, mineralocorticoid receptor antagonists.

1. Acta Cardiol Sin 2017;33:127-138.
2. J Chin Med Assoc 2017; 80: 750-757.

Type and doses of guideline-recommended medications for the treat of heart failure

	At 12 months		
	Rate of use	Dose (mg/day)	≥50% of target dose
<b>RAS blockers</b>	<b>57.7%</b>		<b>24.3%</b>
ACEIs	16.9%		36.2%
Ramipril	44.2%	4.6 ± 4.4	36.1%
Captopril	15.3%	31.1 ± 20.8	12.0%
Enalapril	20.2%	12.3 ± 11.9	54.5%
Others	20.2%		
ARBs	40.8%		20.0%
Candesartan	32.9%	6.8 ± 5.2	10.0%
Valsartan	40.3%	112.4 ± 61.8	34.4%
Losartan	16.5%	40.5 ± 18.8	4.6%
Others	10.3%		
<b>Beta-blockers</b>	<b>66.2%</b>		<b>26.3%</b>
Bisoprolol	62.0%	2.7 ± 1.9	27.4%
Carvedilol	33.7%	15.0 ± 13.5	25.3%
Metoprolol	2.8%	48.6 ± 36.1	27.8%
<b>MRAs</b>	<b>40.8%</b>		<b>86.6%</b>
Spironolactone	99.5%	32.8 ± 29.3	86.6%
Eplerenone	0.5%	75.0 ± 35.4	100%

ACEI: Angiotensin-converting enzyme inhibitors.

ARB: Angiotensin receptor blockers.

MRA: Mineralocorticoid receptor antagonist.

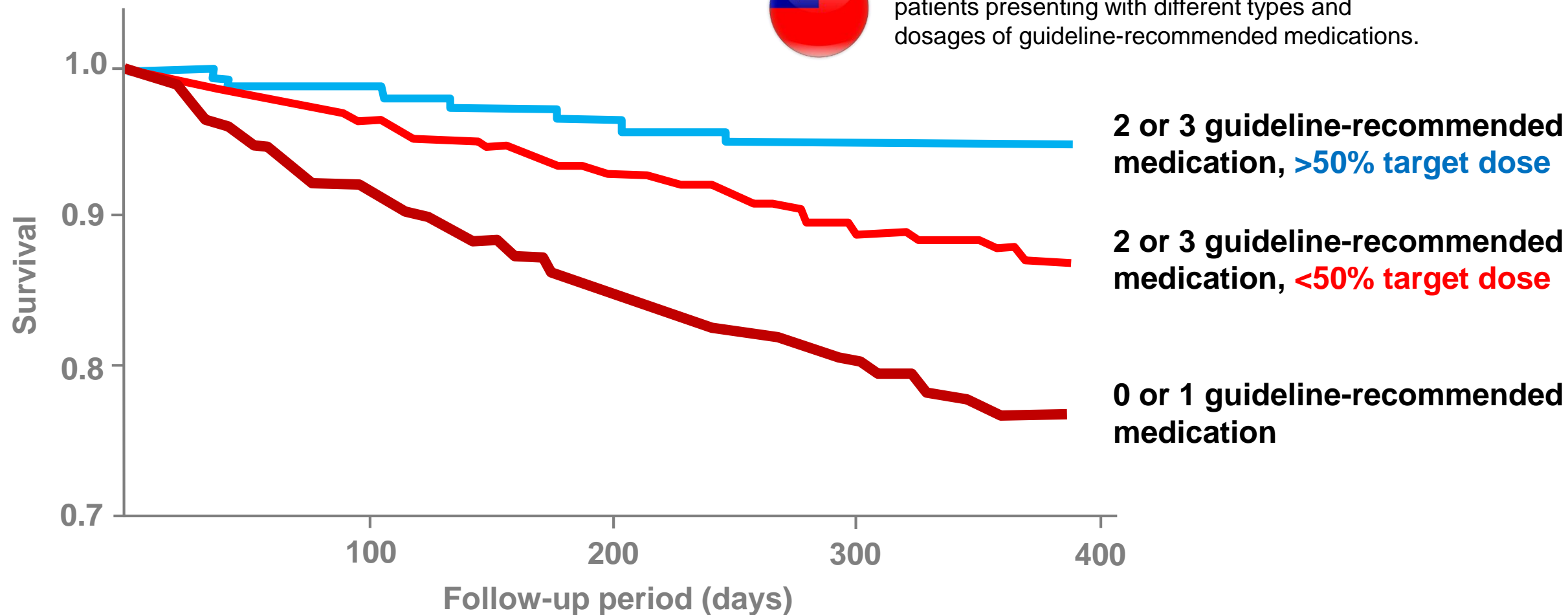
RAS: Renin-angiotensin system.



# 使用藥物種類不足及劑量不夠的HF病患存活率較低



Kaplan e Meier survival curves in the registry patients presenting with different types and dosages of guideline-recommended medications.





心衰竭治療藥物的副作用如**低血壓**、**高血鉀**  
可能是造成用藥不足的原因



**30.8%**

HF patients had

**Hypotension**

in the first year after diagnosis of HF

SBP $\leq$ 90 mmHg

BMJ Open. 2019 Jul 11;9(7):e028750.



**11.3%**

HF patients developed

**Hyperkalemia**

K<sup>+</sup> $\geq$ 5.5 mmol/L

MRAs or RAASi increase the risk of hyperkalemia

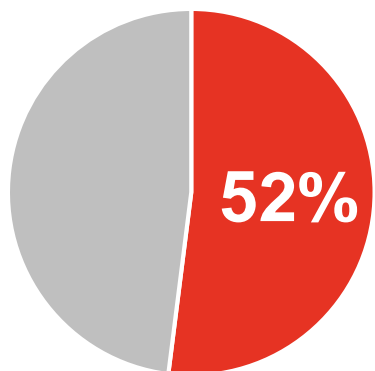
J Am Coll Cardiol. 2016 Oct 4;68(14):1575-89.



# 心衰竭治療的急迫性與困境

## High Mortality

### 5-year mortality<sup>1</sup>



Higher than colorectal cancer, oral cavity and pharynx cancer, breast cancer, melanoma of the skin, prostate cancer, thyroid cancer<sup>2</sup>

## Long length and high rehospitalization rate



~20 day

of mean length of heart failure hospitalization<sup>3</sup>

32%

of rehospitalization rates in 6 months<sup>4</sup>

## Still Symptomatic



91%

HF patients reported symptoms or disability<sup>5</sup>

## Insufficient optimal therapy

Only 39%

HF patients treated with 2 combined therapy recommended by HF guideline<sup>4</sup>



Only 24%

HF patients treated with  $\geq 50\%$  of target dose of RAASi<sup>6</sup>



31% HF patients had hypotension in the first year after diagnosis of HF<sup>7</sup>



11% HF patients developed Hyperkalemia<sup>8</sup>

1. BMJ. 2019 Feb 13;364:l223.

2. <https://seer.cancer.gov/statfacts/>

3. ESC Heart Fail. 2020 Sep 13.

4. Acta Cardiol Sin 2017;33:127-138.

5. JACC Heart Fail. 2020;8:429-440.

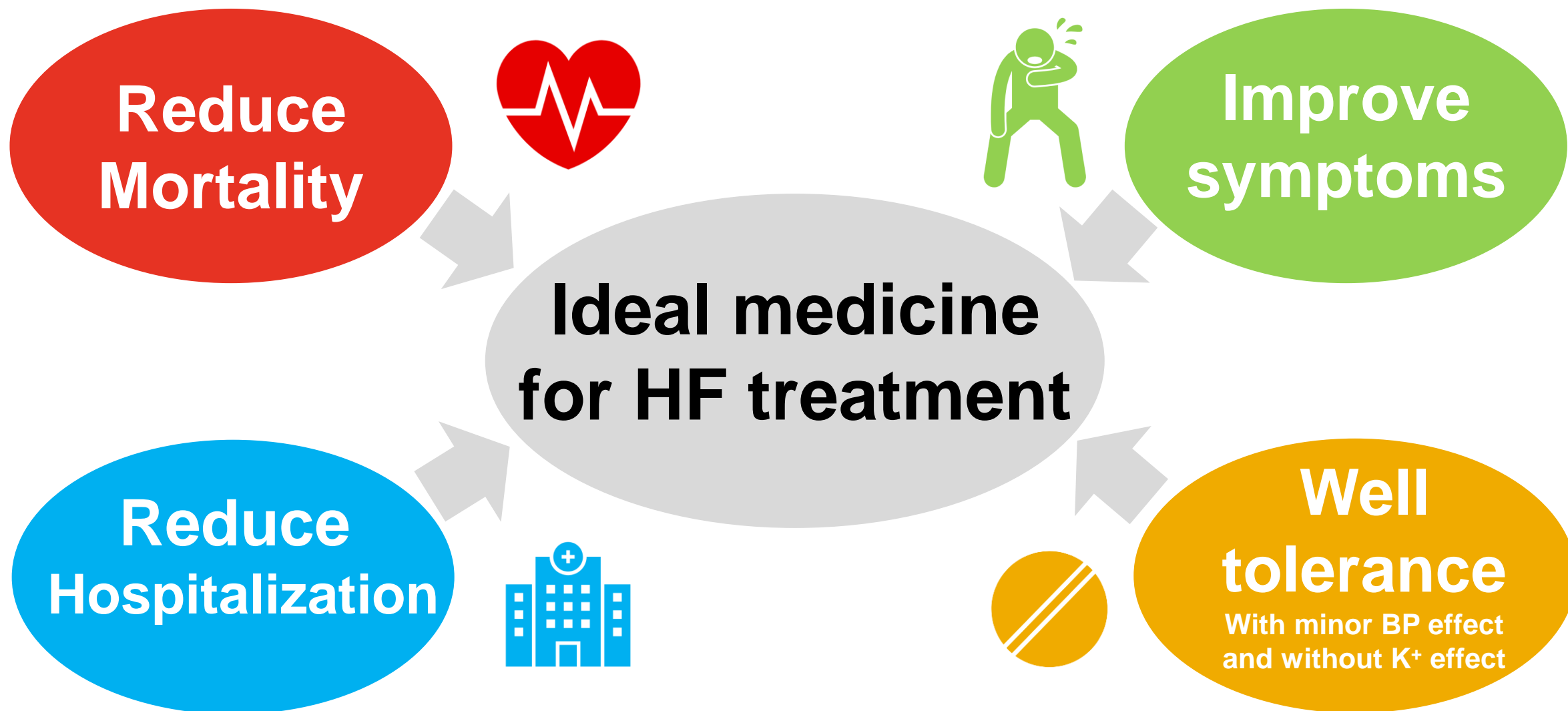
6. J Chin Med Assoc 2017; 80: 750-757.

7. BMJ Open. 2019 Jul 11;9(7):e028750.

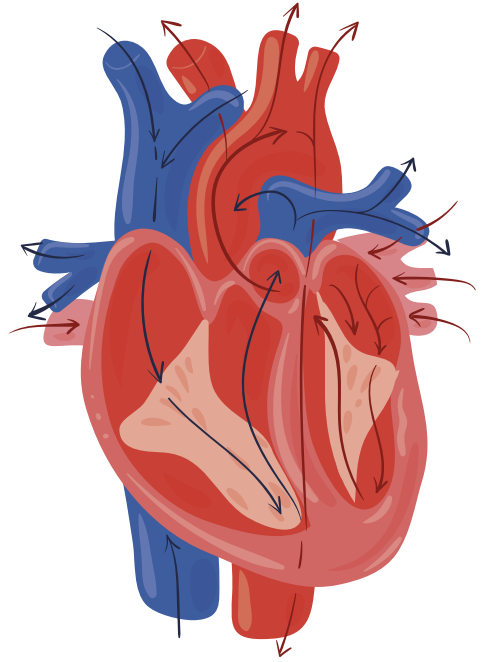
8. J Am Coll Cardiol. 2016 Oct 4;68(14):1575-89.



# 理想的心衰竭治療用藥



# Outline

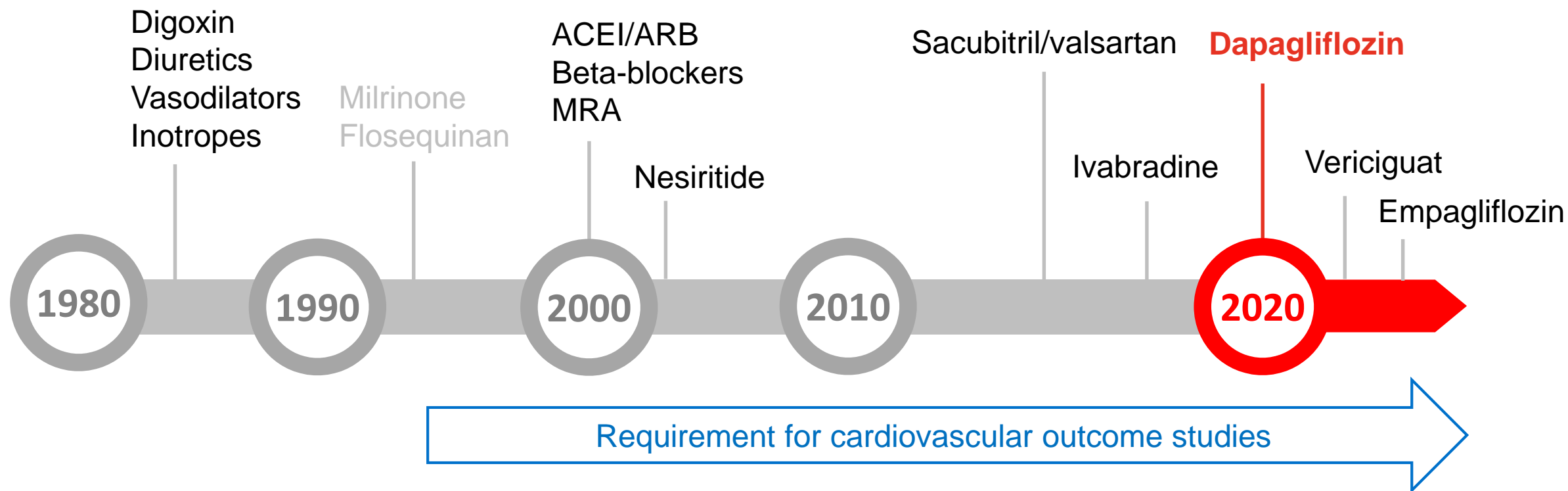


- The urgency and unmet needs of HF to patients
- **Epoch-making treatment of HF with reducing mortality**
- Timely prevention HF in T2D
- Conclusions



# 心衰竭治療新契機: **SGLT-2i**

## The History of Heart Failure Medicine

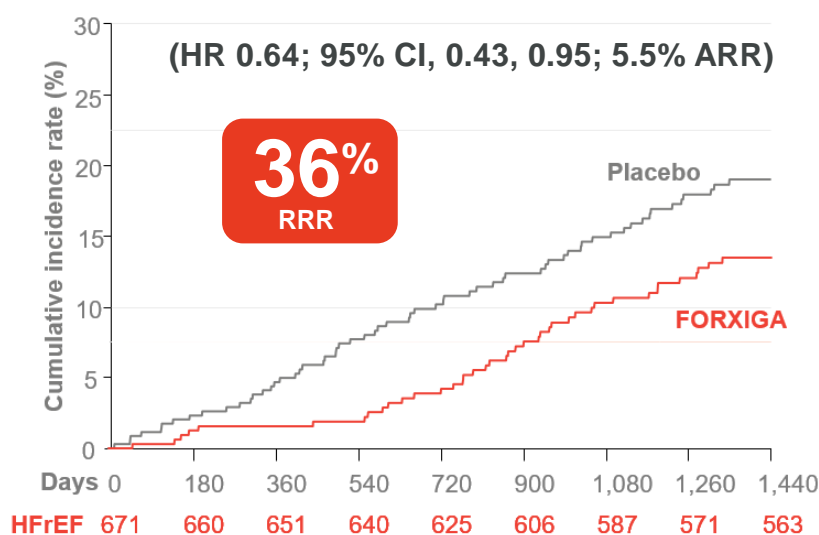


1. JACC Heart Fail. 2020 Jun;8(6):429-440.

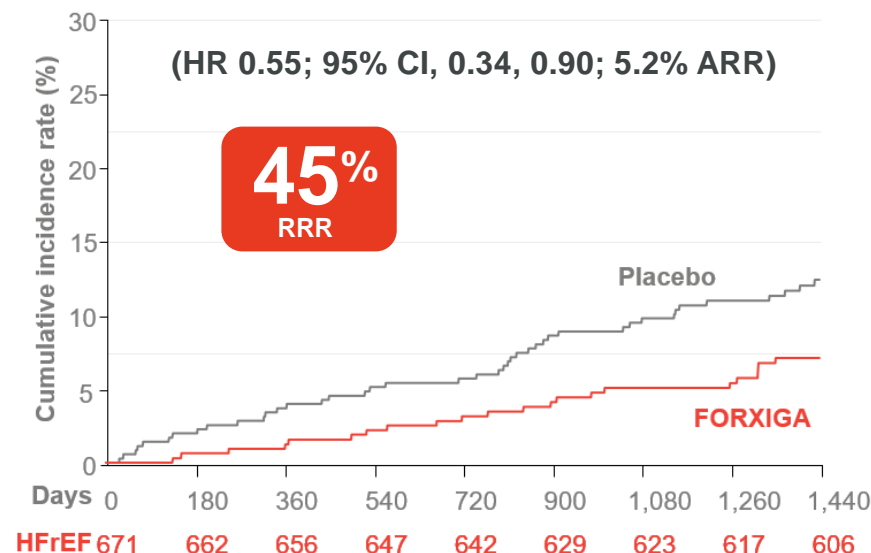
2. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure>

# DECLARE次分析：T2D併有HFrEF病患使用FORXIGA 觀察到降低心衰竭住院、心血管死亡、全因性死亡風險

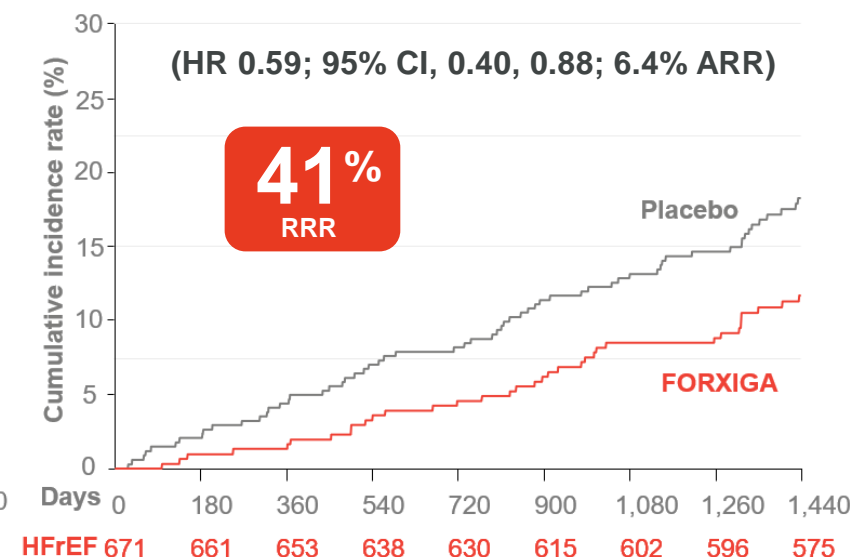
## hHF



## CV death

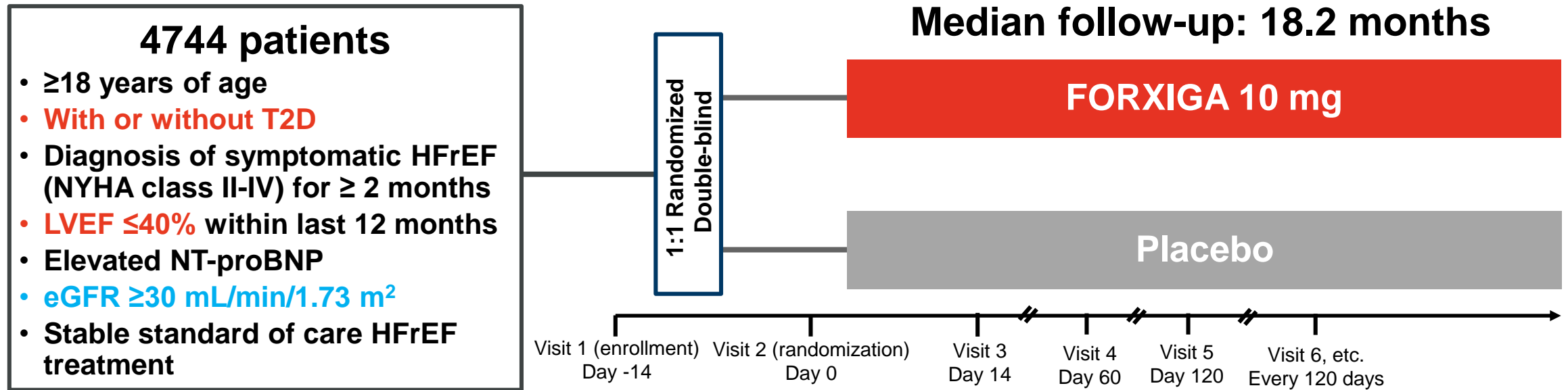


## All cause mortality



# FORXIGA 是否可以治療HFrEF?

# 研究設計：收納4744位心衰竭患者，標準治療加上 **FORXIGA** (起始、維持劑量皆為 10 mg)或placebo



## Primary Endpoint

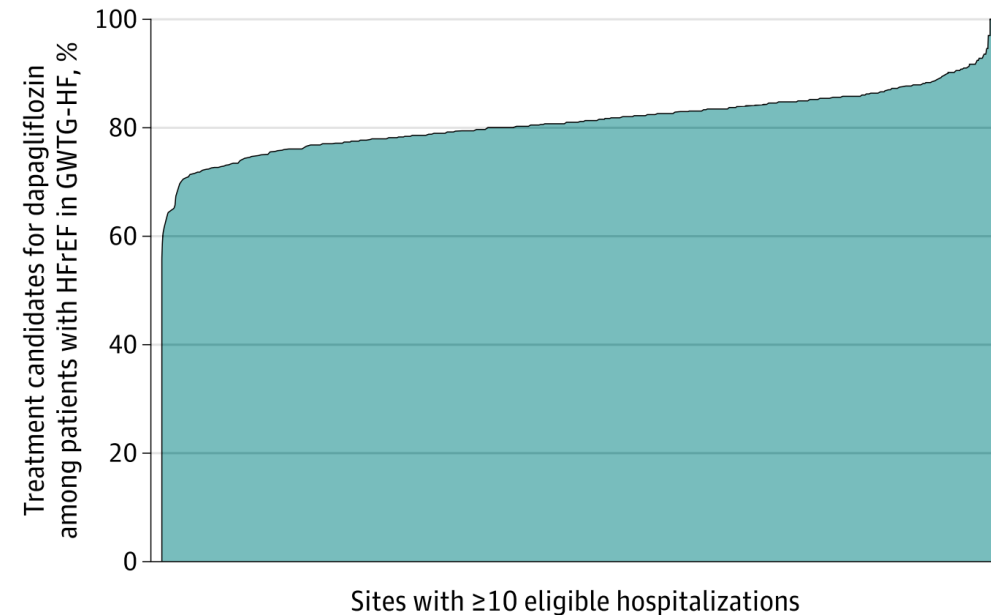
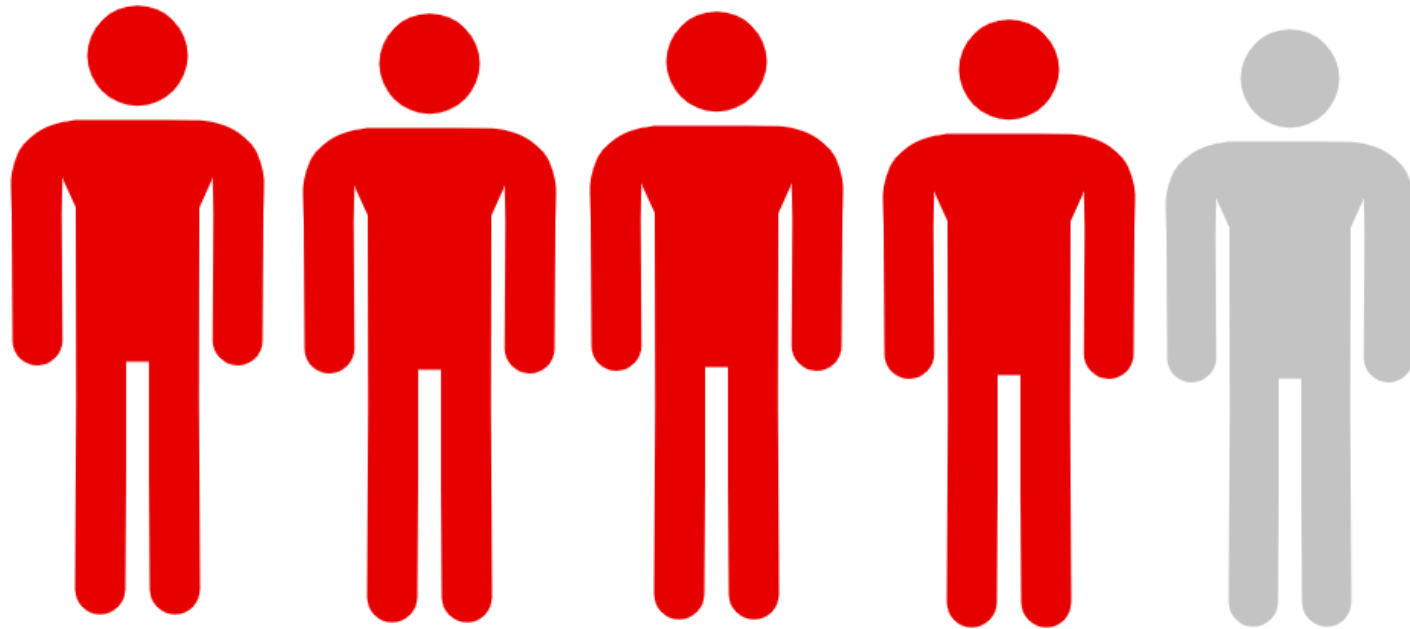
- Time to first occurrence of any of the components of the composite: **CV death or hHF or an urgent HF visit**



141 patients are enrolled

# 收納條件 符合現實臨床81% 的HFrEF病患

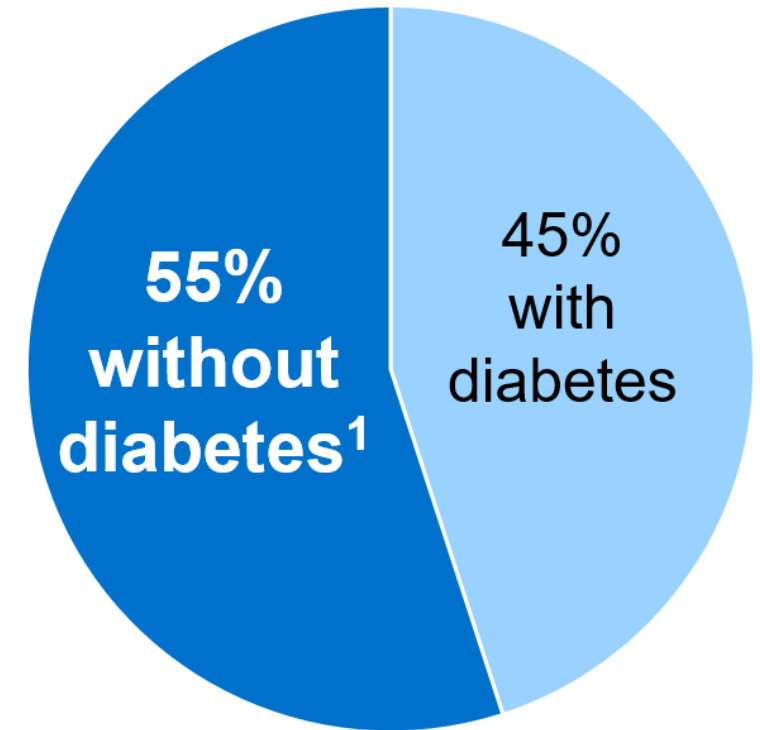
臨床上每5位HFrEF即有4位符合DAPA-HF收納條件



Among 154,714 patients with HFrEF, 125,497 (**81.1%**) would be candidates for initiation of dapagliflozin

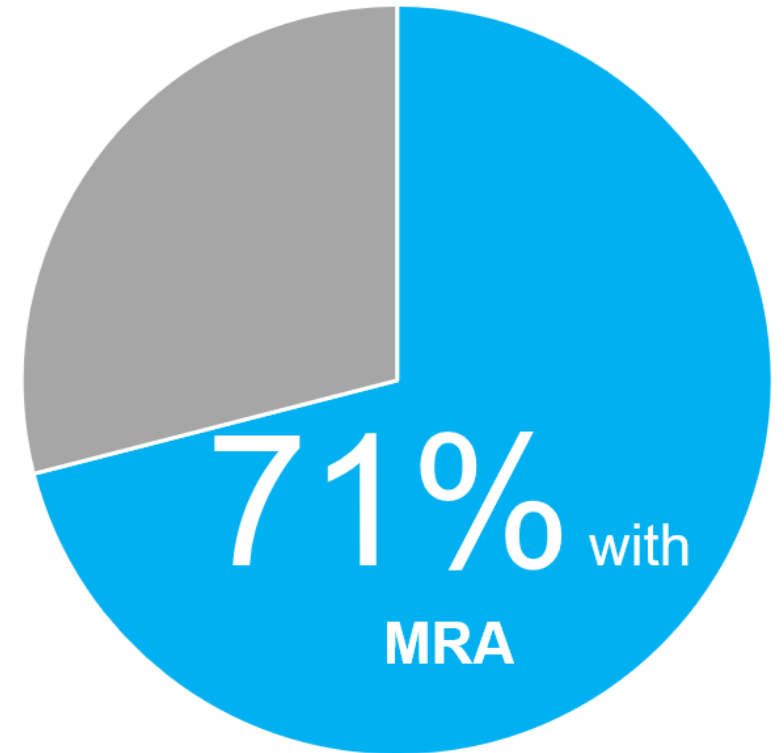
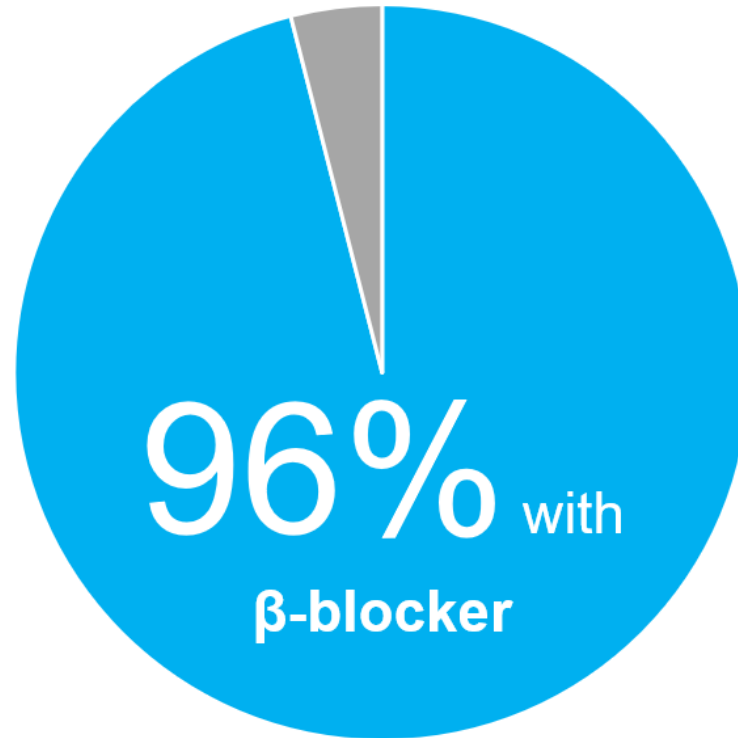
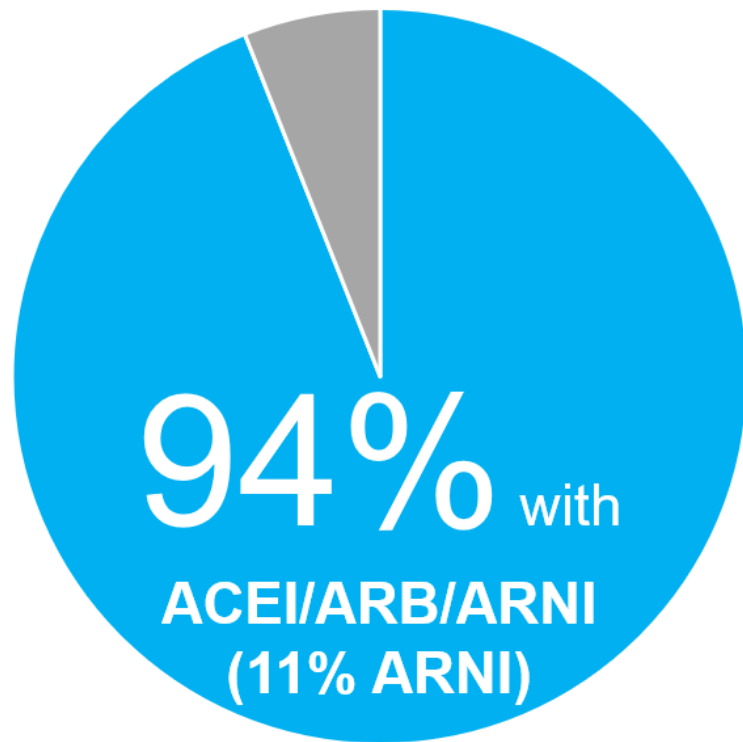
# 收納病患包含糖尿病45%、非糖尿病55%

Characteristic	DAPA 10 mg (n=2373)	Placebo (n=2371)
Mean age, yr	66.2 ± 11.0	66.5 ± 10.8
Systolic blood pressure, mmHg	122.0 ± 16.3	121.6 ± 16.3
Estimated GFR, mL/min/1.73m <sup>2</sup>	66.0 ± 19.6	65.5 ± 19.3
Estimated GFR <60 mL/min/1.73m <sup>2</sup> (%)	40.6%	40.7%
NYHA functional classification, n (%)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Left ventricular ejection fraction, %	31.2 ± 6.7	30.9 ± 6.9
Median NT-proBNP (IQR), pg/mL	1428 (857,2655)	1446 (857,2641)
Principal cause of heart failure (%)		
Ischemic	55.5%	57.3%
Non-ischemic	36.1%	35.0%
Unknown	8.4%	7.7%



**56%** HF patients without diabetes in Taiwan

# 收錄已接受標準治療的HF病患



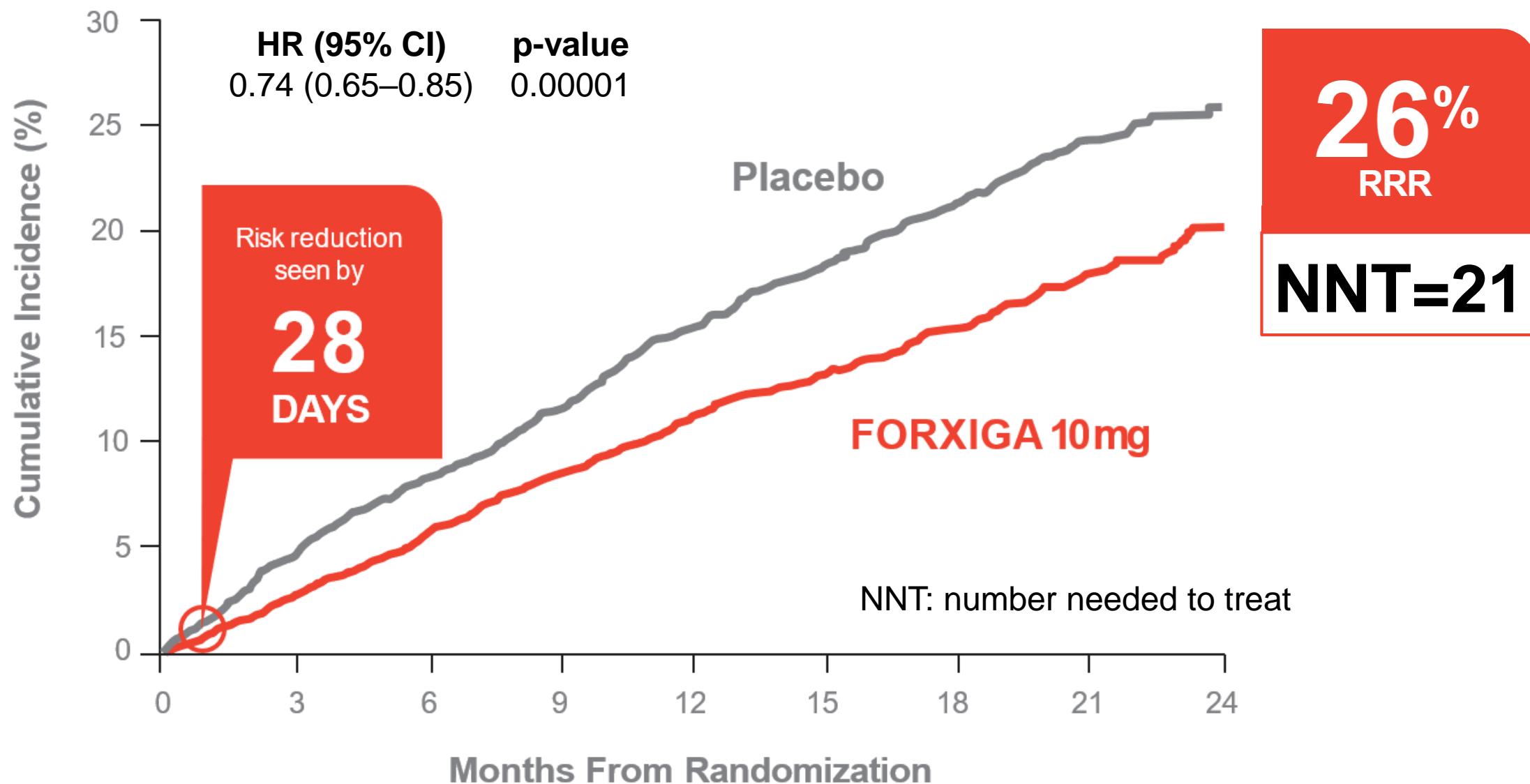
93% with diuretic, 19% with digitalis, 26% with ICD, 7% with CRT

MRA: mineralocorticoid receptor antagonist, ICD: implantable cardioverter defibrillator, CRT: cardiac resynchronization therapy

Eur J Heart Fail. 2019 Nov;21(11):1402-1411.

N Engl J Med. 2019;381:1995-2008.

# FORXIGA減少26% 心衰竭惡化及心血管死亡 (NNT=21), 28天即顯著改善

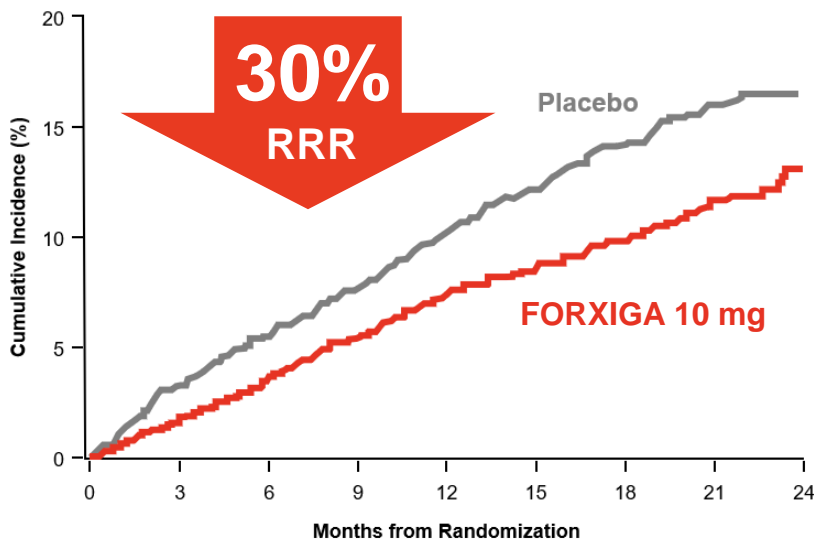


# FORXIGA 唯一 SGLT-2i 針對 HFrEF

## 顯著減少心衰竭惡化、心血管死亡、總死亡

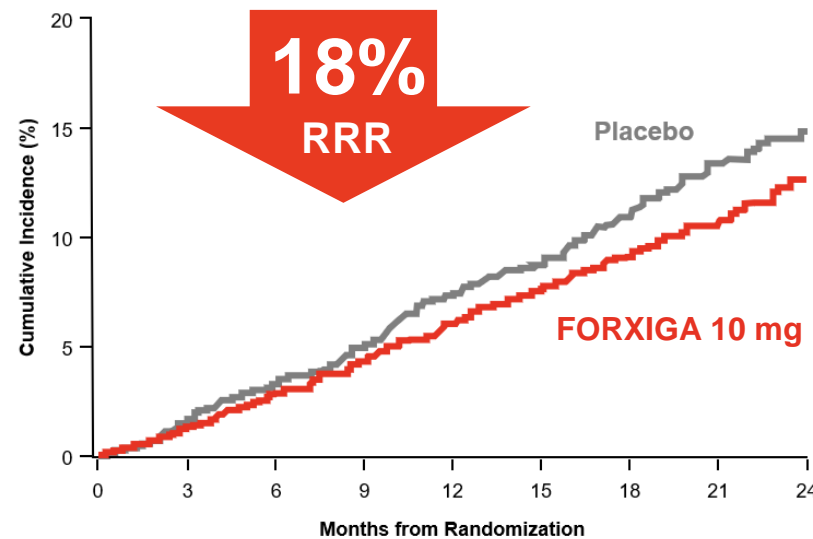
### Worsening HF Event\*

HR 0.70 (0.59-0.83);  $p=0.00003$



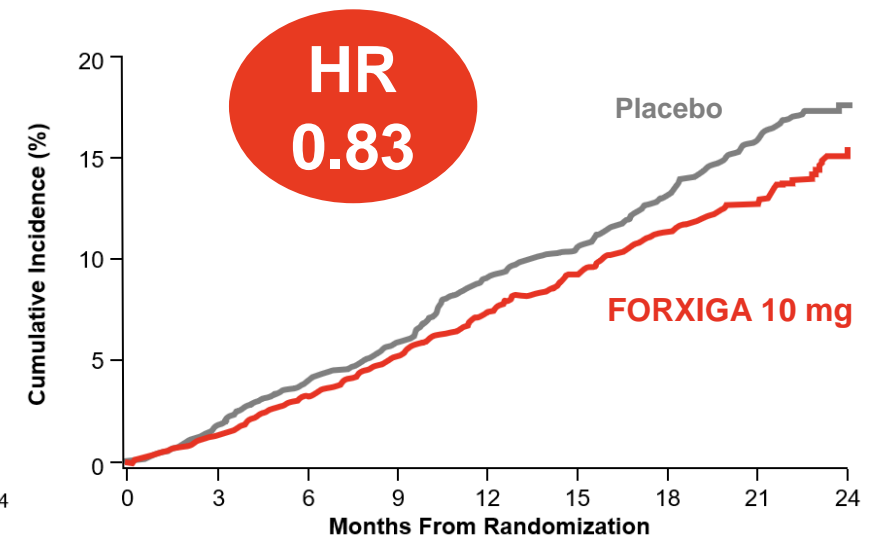
### CV Death

HR 0.82 (0.69-0.98);  $p=0.029$

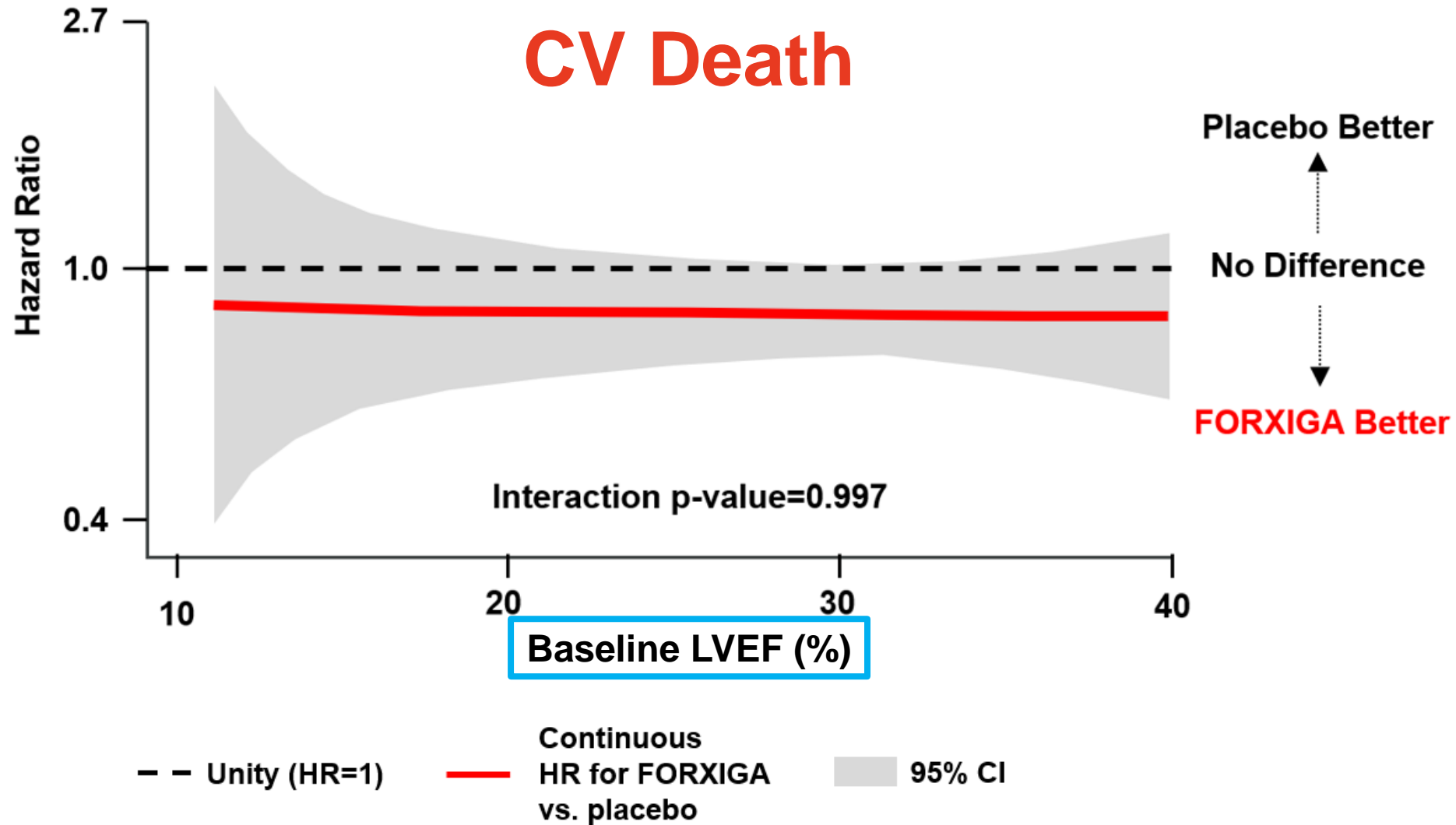


### All-cause Death

HR 0.83 (0.71-0.97);  $p=0.022^{\#}$

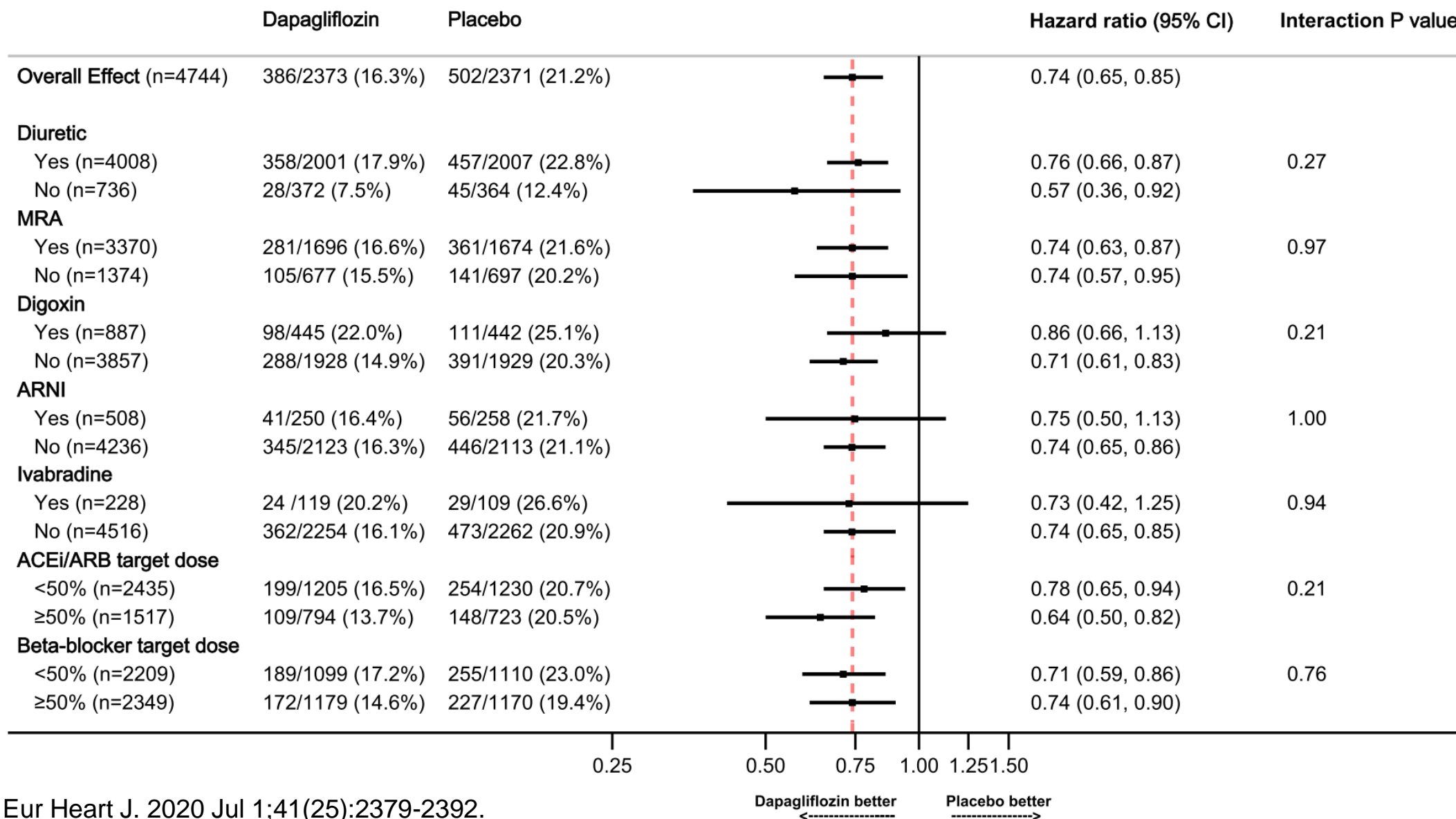


# FORXIGA降低 心血管死亡 不受LVEF影響



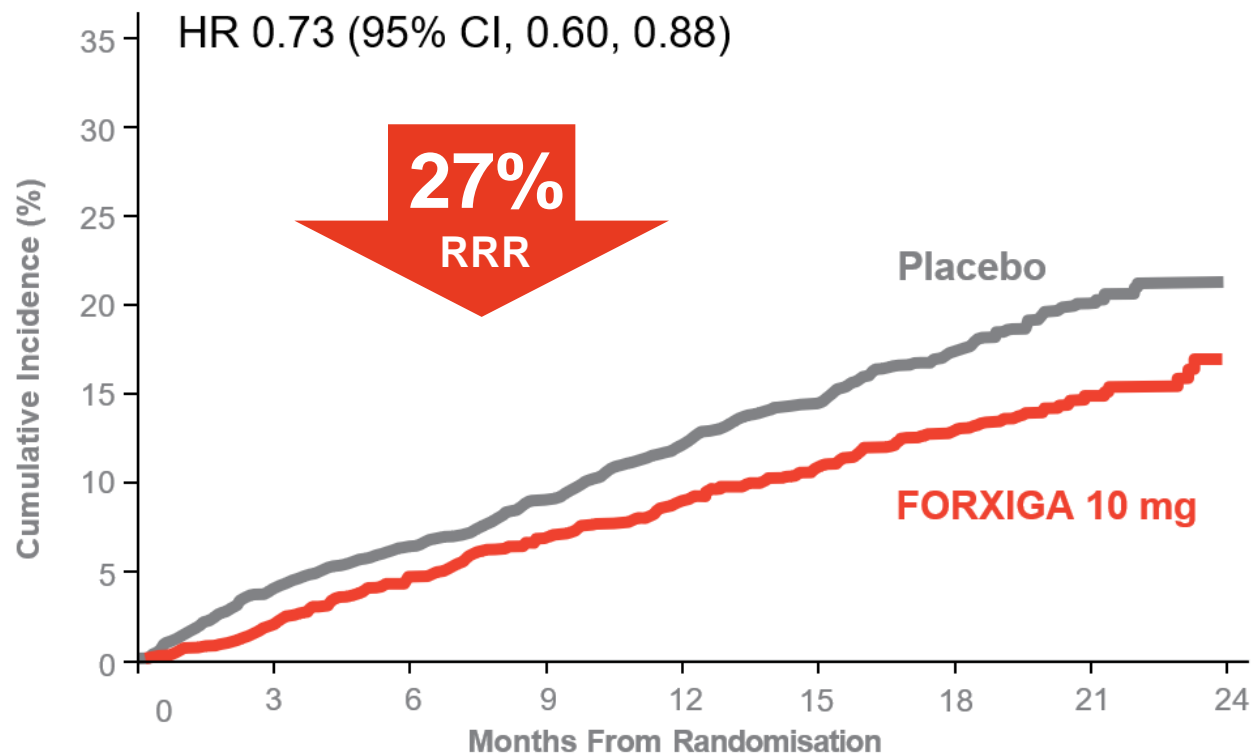
# FORXIGA降低 心衰竭惡化及心血管死亡

## 不受其他HF治療藥物影響

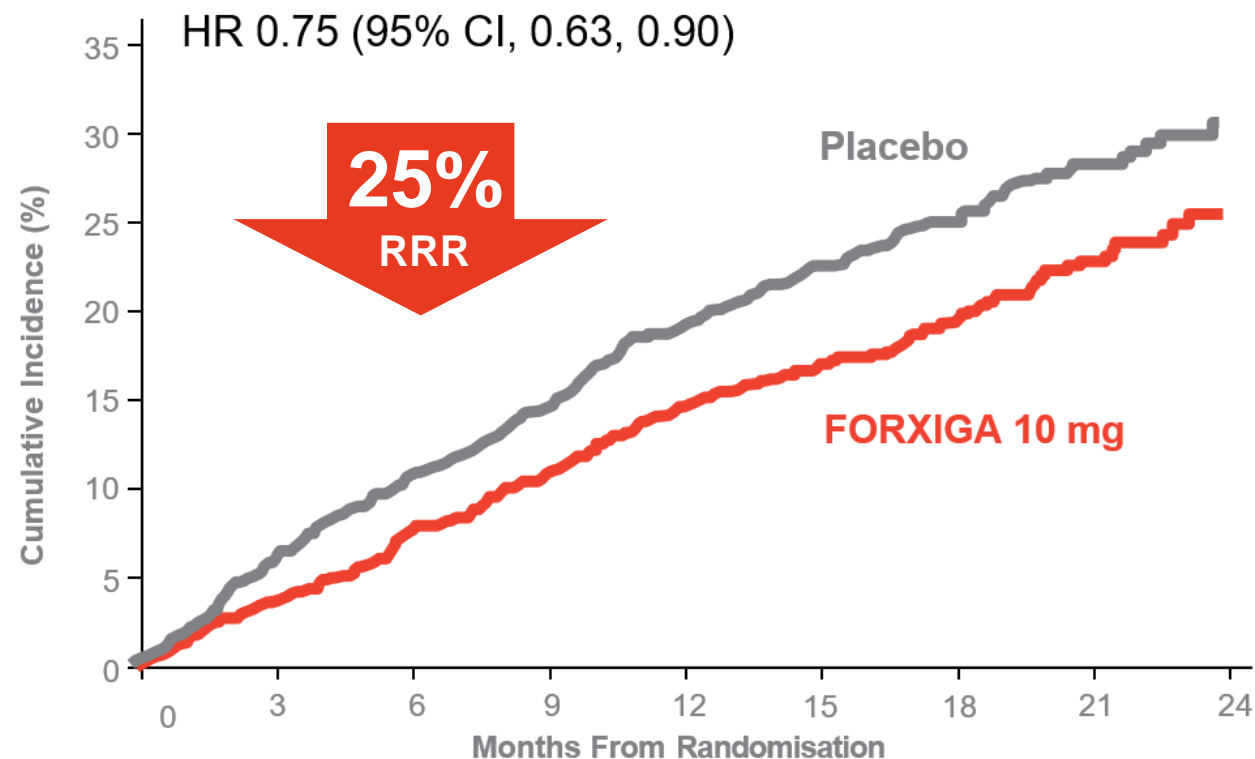


# 有/無糖尿病HF患者使用FORXIGA 皆能降低心衰竭惡化及心血管死亡

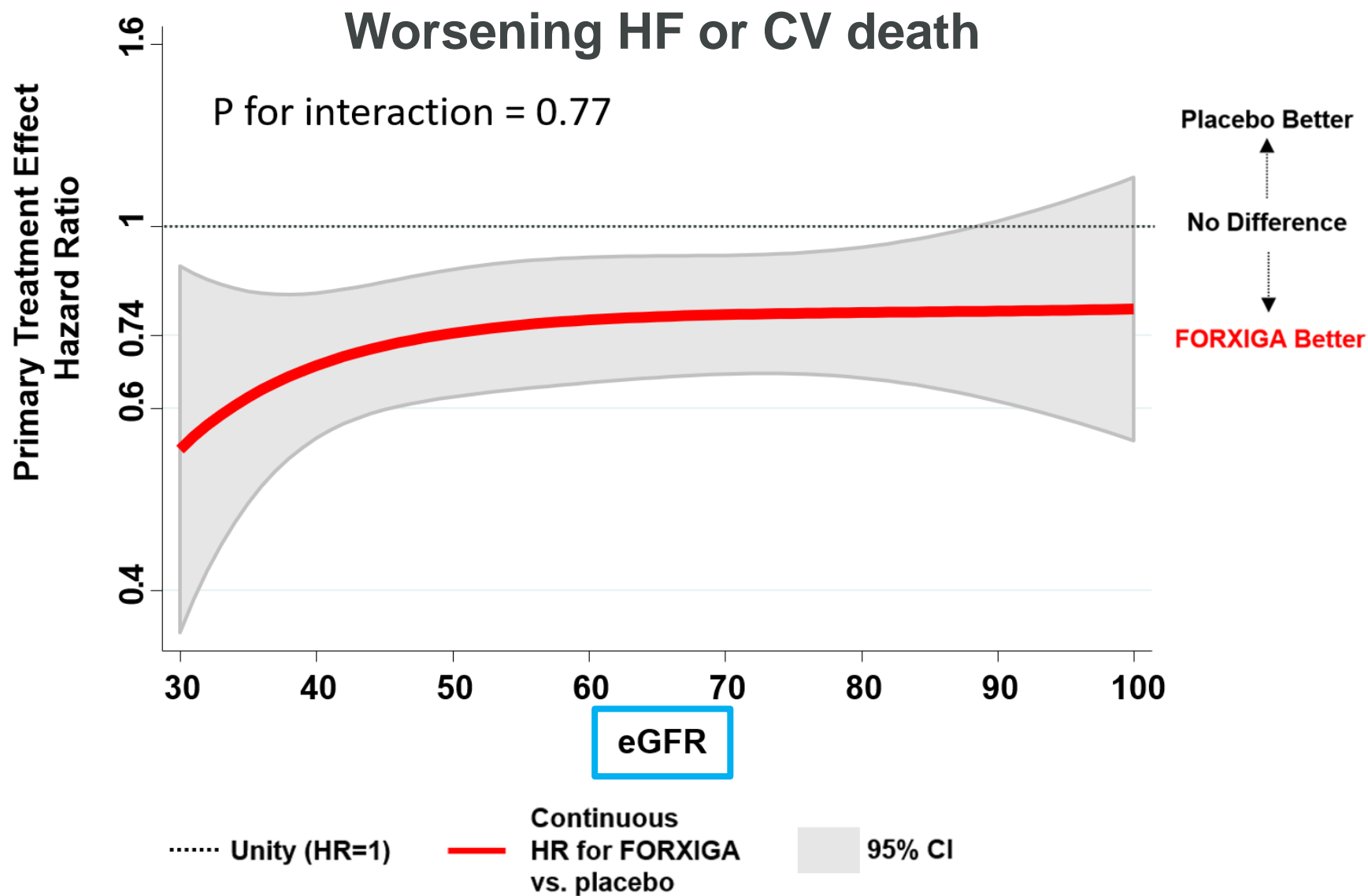
Patients **without T2D** (n = 2605)



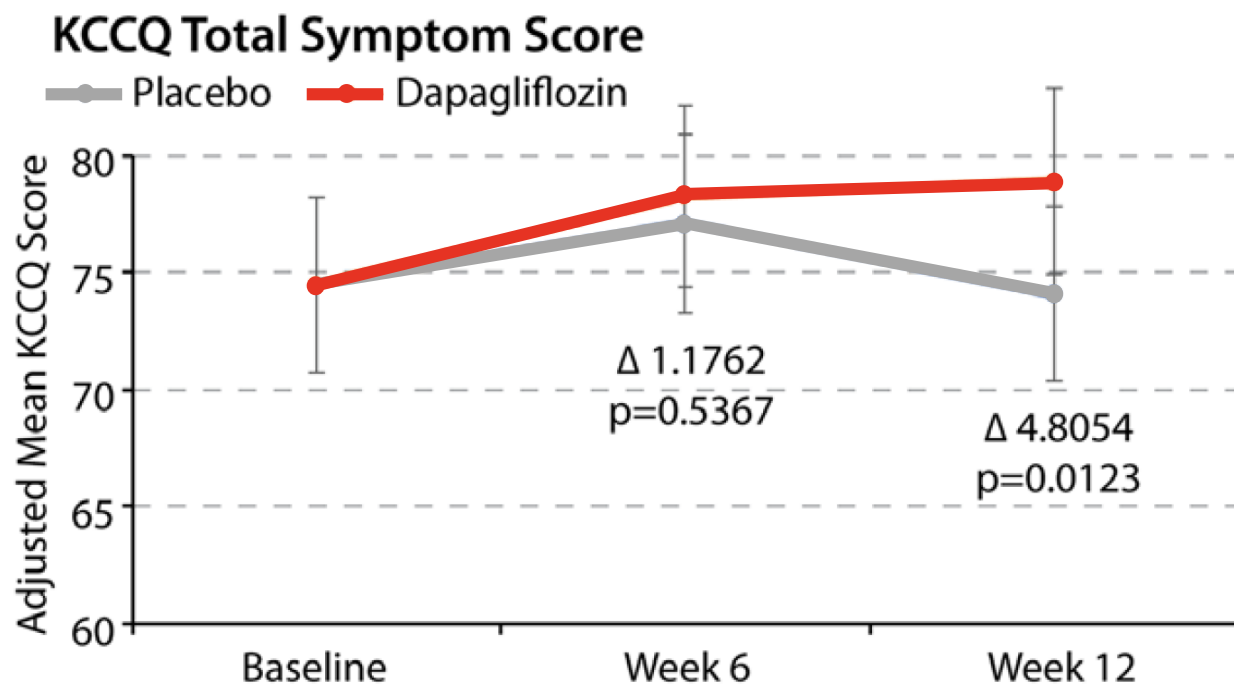
Patients with **T2D** (n = 2139)



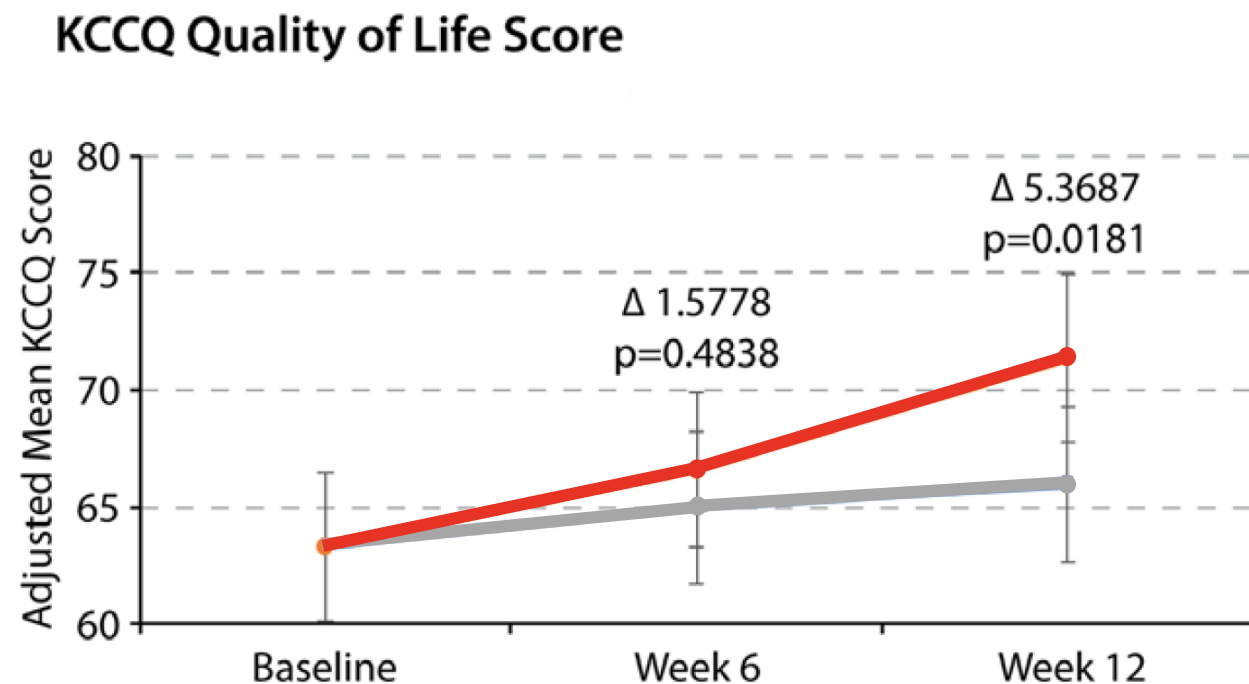
# FORXIGA降低心衰竭惡化及心血管死亡不受eGFR影響



# FORXIGA有效改善心衰竭病患**症狀**和**生活品質**



KCCQ Symptom Score quantifies the frequency and burden of clinical symptoms in heart failure, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea and patients' edema/swelling. An total symptom score is included subscale scores for both frequency and severity.



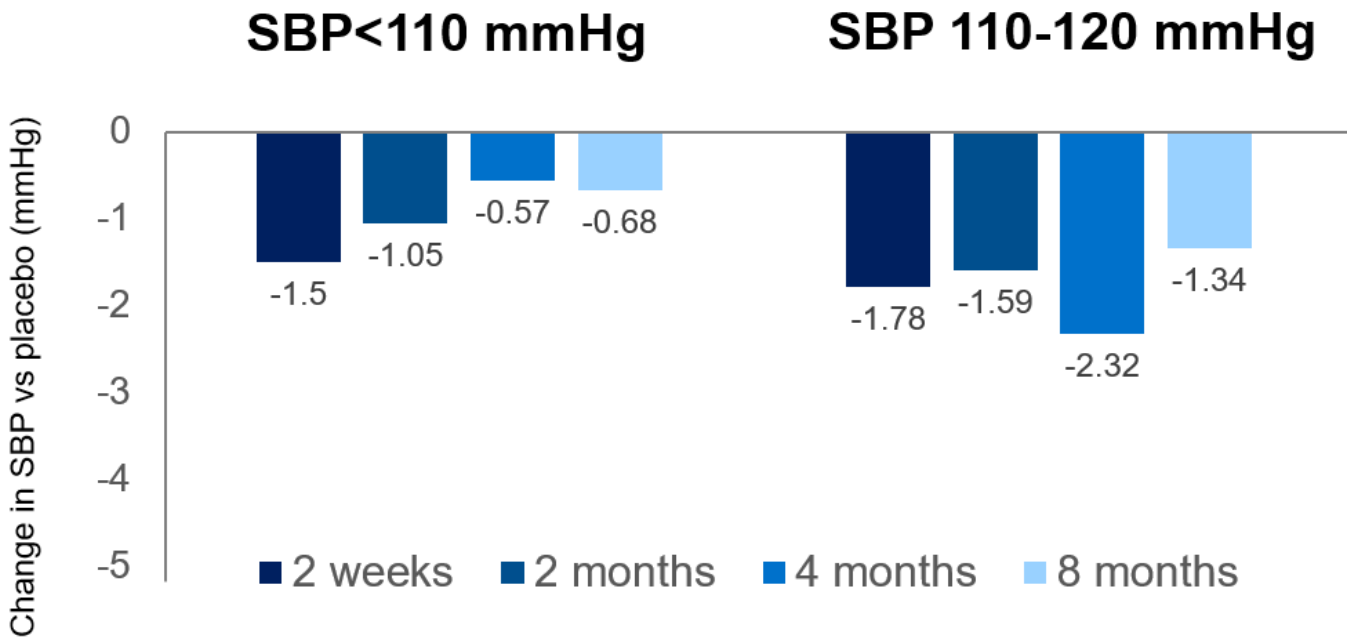
KCCQ Quality of Life Score is designed to reflect patients' assessment of their quality of life, given the current status of their heart failure.

KCCQ scores are transformed to a range of 0 to 100, in which **higher scores reflect better health status**

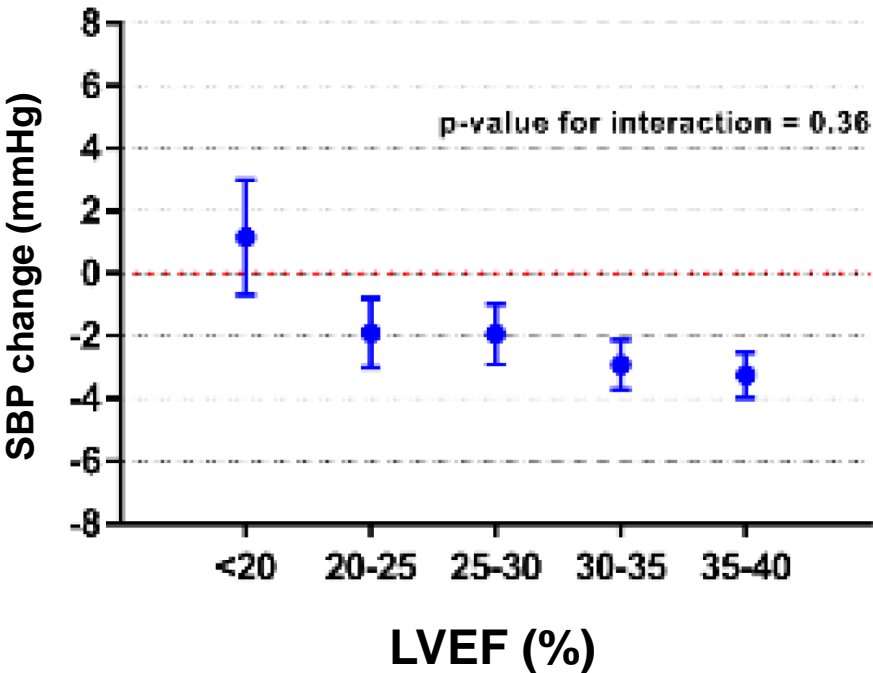
KCCQ: Kansas City Cardiomyopathy Questionnaire;  
Circulation. 2019 Oct 29;140(18):1463-1476.

# FORXIGA對 不同基值SBP、LVEF 心衰竭病患的**血壓**影響

**SBP** change with FORXIGA, according to baseline SBP

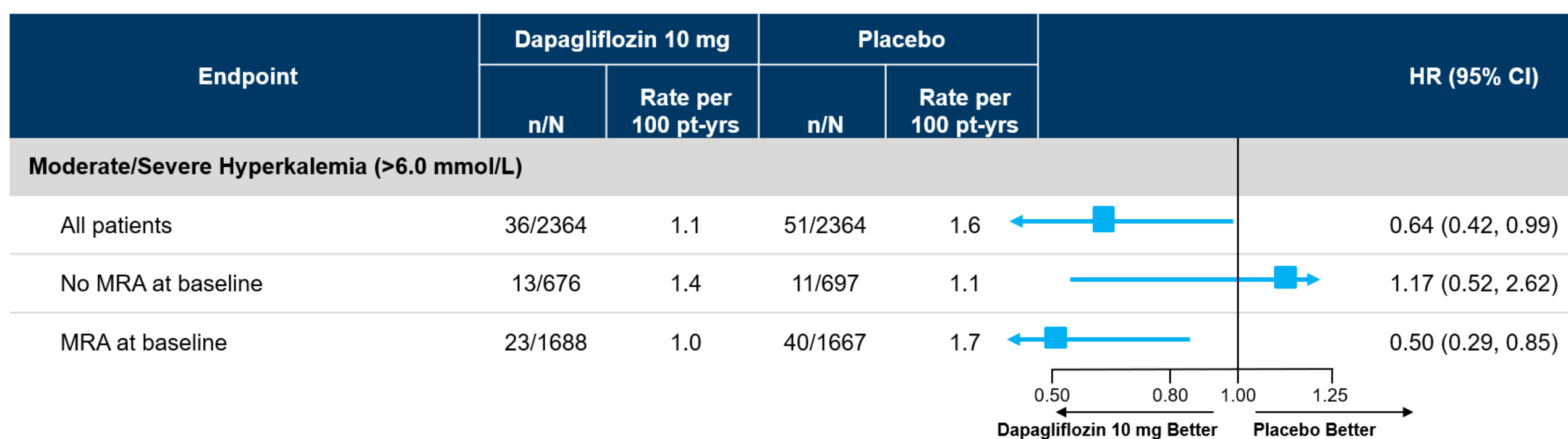


Placebo-corrected **SBP** change after 2 weeks with FORXIGA, according to baseline LVEF



# FORXIGA 不會 增加高血鉀風險

HF patients with FORXIGA had lower risk of severe hyperkalemia vs. placebo in DAPA-HF

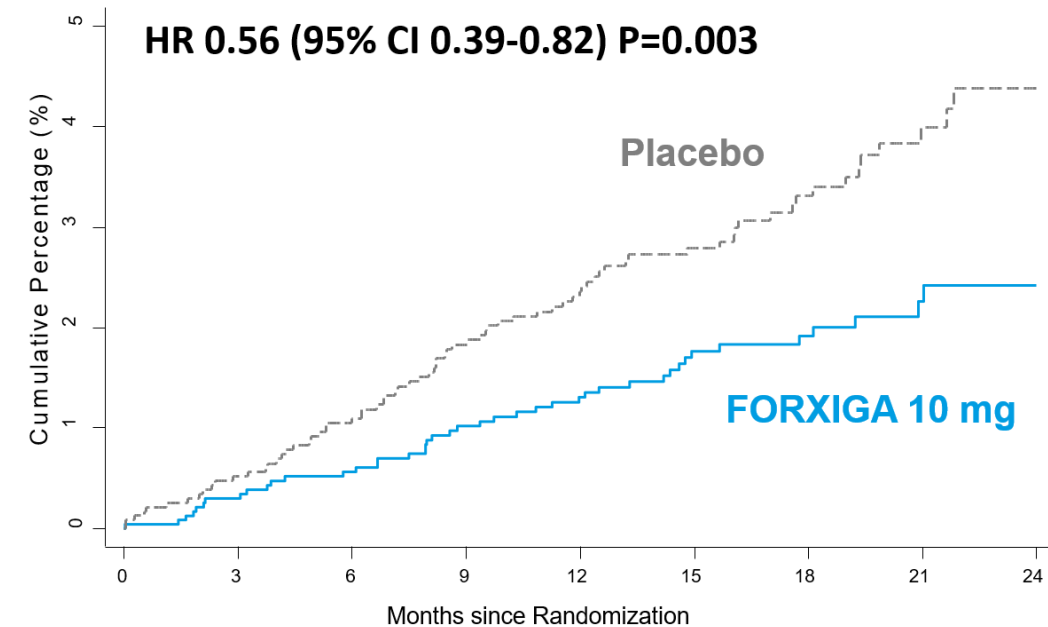


- MRA: mineralocorticoid receptor antagonists
- European Heart Journal, Volume 41, Issue Supplement\_2, November 2020, ehaa946.0939, <https://doi.org/10.1093/ehjci/ehaa946.0939>

## Renal Safety

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Renal AE, n (%)	153 (6.5)	170 (7.2)	0.36
Renal Serious AE, n (%)	38 (1.6)	65 (2.7)	0.009
Renal AE leading to discontinuation, n (%)	8 (0.3)	9 (0.4)	1.0
Serious AKI as reported by investigator, n (%)	23 (1.0)	46 (1.9)	0.007

## Doubling of serum creatinine\*



# FORXIGA 安全性與安慰劑相當

## T2D

Event, %	FORXIGA (n = 1073)	Placebo (n = 1063)
Any serious AE	41.7	48.3
AE leading to treatment discontinuation	4.0	5.4
<b>AE of interest</b>		
Volume depletion	7.8	7.8
Kidney AE	8.5	8.7
Fracture	2.1	2.4
Amputation	1.1	0.8
Major hypoglycaemia	0.4	0.4
Diabetic ketoacidosis	0.3	0

## No T2D

FORXIGA (n = 1295)	Placebo (n = 1305)	Interaction <i>P</i> -value
34.6	36.9	0.16
5.3	4.5	0.09
7.3	6.1	0.40
4.8	6.0	0.36
2.1	1.9	0.58
0.1	0.2	0.24
0	0	NA
0	0	NA

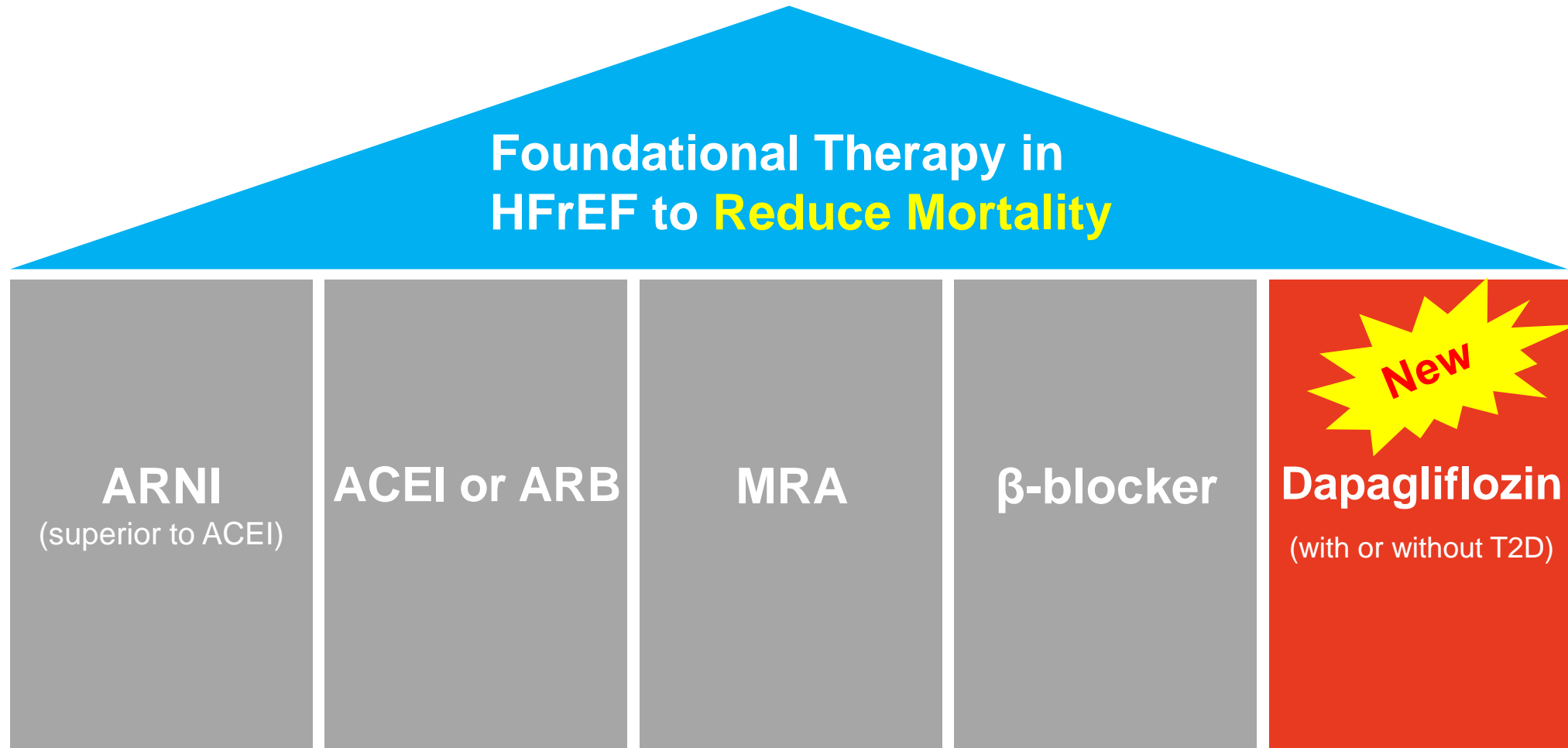
# 近十年發表的心衰竭試驗結果

Trial (N; median follow-up month)	Drug	健保價 (daily cost)	Background Rx.	CV death/HHF HR (95%CI)	HHF HR (95%CI)	CV death HR (95%CI)	All-cause mortality HR (95%CI)
<b>EMPHASIS-HF</b> (N=2737; 21 months)	Eplerenone 50 mg QD vs placebo	\$28.2 (50 mg once day)	ACEI/ARB 94% BB 87% MRA n/a	<b>0.66</b> (0.56–0.78)	<b>0.61</b> (0.50–0.75)	<b>0.77</b> (0.62–0.96)	<b>0.78</b> (0.64–0.95)
<b>SHIFT</b> (N=6558; 22.9 months)	Ivabradine 7.5 mg BID vs placebo	\$47.6 (7.5 mg twice daily)	ACEI/ARB 93% BB 90% MRA 60%	<b>0.82</b> (0.75–0.90)	<b>0.74</b> (0.66–0.83)	0.91 (0.80–1.03)	0.90 (0.80–1.02)
<b>PARADIGM-HF</b> (N=8399; 27 months)	Sacubitril/valsartan 200 mg BID vs Enalapril	\$118 (200 mg twice daily)	ACEI/ARB 100% BB 93% MRA 56%	<b>0.80</b> (0.73–0.87)	<b>0.79</b> (0.71–0.89)	<b>0.80</b> (0.71–0.89)	<b>0.84</b> (0.76–0.93)
<b>DAPA-HF</b> (N=4744; 18.2 months)	Dapagliflozin 10 mg QD vs placebo	\$ 28.6 (10 mg once daily)	ACEI/ARB/ARNI 94% BB 96% MRA 71%	<b>0.75</b> (0.65–0.85)	<b>0.70</b> (0.59–0.83)	<b>0.82</b> (0.69–0.98)	<b>0.83</b> (0.71–0.97)
<b>EMPEROR-reduced</b> (N=3730; 16 months)	Empagliflozin 10 mg QD vs placebo	\$ 30.3 (10 mg once daily)	ACEI/ARB/ARNI 89% BB 95% MRA 71%	<b>0.75</b> (0.65–0.86)	<b>0.69</b> (0.59–0.81)	0.92 (0.75–1.12)	0.92 (0.77–1.10)
<b>VICTORIA</b> (N=5050; 10.8 months)	Vericiguat 10 mg QD vs placebo	none	ACEI/ARB/ARNI 88% BB 93% MRA 70%	<b>0.90</b> (0.82–0.98)	0.90 (0.81–1.00)	0.93 (0.81–1.06)	0.95 (0.84–1.07)
<b>GALACTIC-HF</b> (N=8256; 21.8 months)	Omecamtiv Mecarbil vs placebo	none	ACEI/ARB/ARNI 87% BB 94% MRA 78%	<b>0.92</b> (0.86–0.99)	0.95 (0.87–1.03)	1.01 (0.92–1.11)	1.00 (0.92–1.09)

1. N Engl J Med. 2011 Jan 6;364(1):11-21. 2. Lancet. 2010 Sep 11;376(9744):875-85. 3. N Engl J Med. 2014 Sep 11;371(11):993-1004. 4. N Engl J Med. 2019 Nov 21;381(21):1995-2008. 5. N Engl J Med. 2020 Oct 8;383(15):1413-1424. 6. N Engl J Med. 2020 May 14;382(20):1883-1893. 7. N Engl J Med 2021; 384:105-116.

# "DAPA-HF ushers in a new paradigm in the treatment of HF"

- Eugene Braunwald



# FORXIGA 抗衰救命心選擇



福適佳 膜衣錠 5 毫克、10 毫克

Forxiga Film-coated Tablets 5 mg, 10 mg

本藥須由醫師處方使用

5 毫克 衛部藥輸字第 026475 號

10 毫克 衛部藥輸字第 026476 號

## 1 適應症

### 1.1 第二型糖尿病

- 血糖控制：配合飲食和運動，以改善第二型糖尿病成人病人的血糖控制。
- 預防心血管事件：用於具第二型糖尿病且已有心血管疾病(CVD)或多重心血管風險因子的成人病人時，可降低心衰竭住院的風險。
- 預防腎臟病：降低慢性腎臟病(CKD)新發生或惡化的風險。

### 1.2 心衰竭

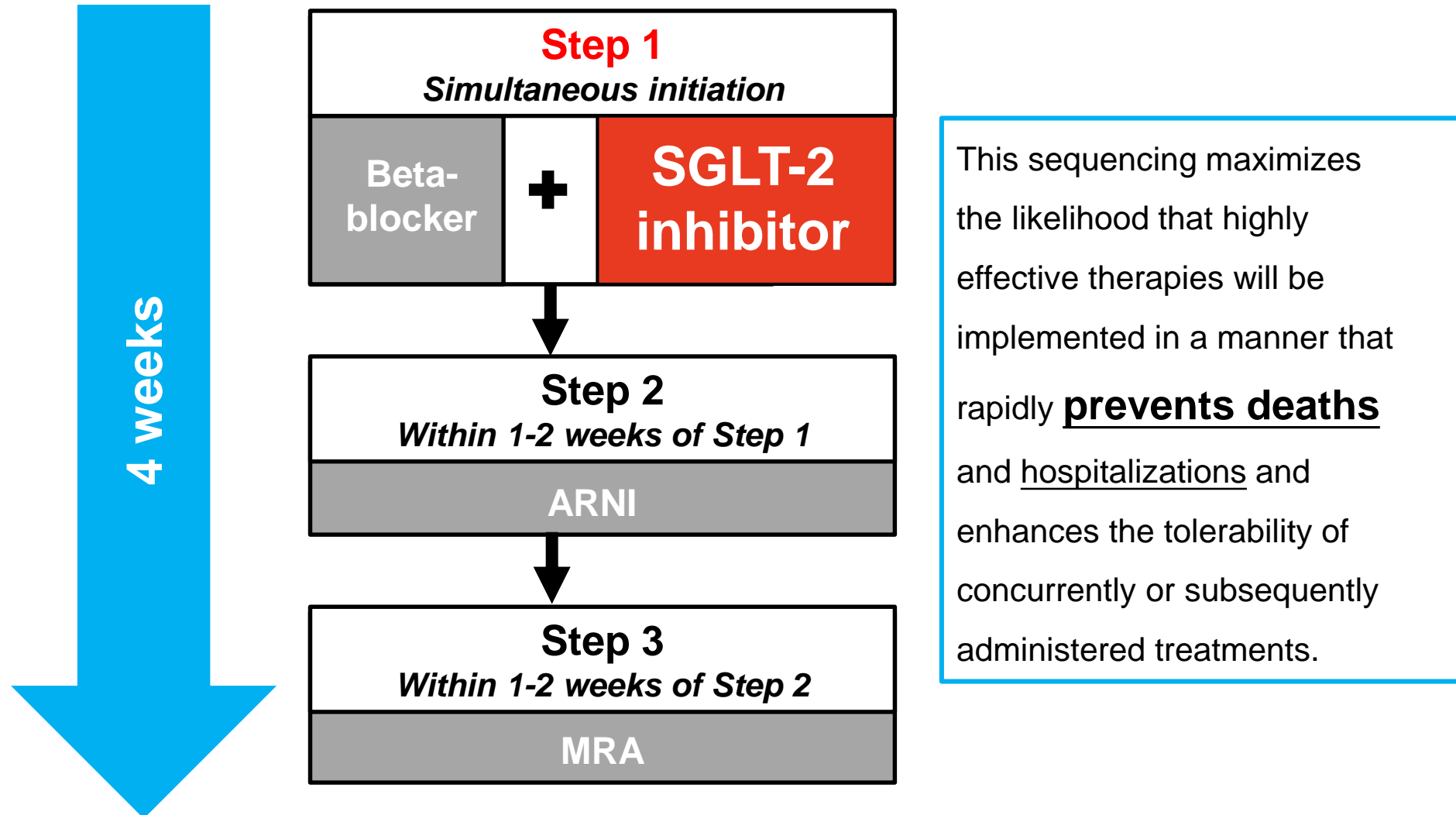
用於心衰竭(NYHA 分類第二至四級) 且心室射出分率降低( $\leq 40\%$ )的成人病人時，可降低心血管死亡和心衰竭住院的風險。

### 1.3 慢性腎臟病

用於治療有惡化風險之慢性腎臟病的成人病人時，可降低持續性腎絲球過濾率(eGFR)下降、末期腎病(ESKD)、心衰竭住院和心血管死亡的風險。

Approved

# 國際心衰竭專家提出治療新序列：四週內加上能減少死亡的藥物



This sequencing maximizes the likelihood that highly effective therapies will be implemented in a manner that rapidly **prevents deaths** and hospitalizations and enhances the tolerability of concurrently or subsequently administered treatments.

SGLT-2: Sodium-Glucose Cotransporter 2, ARNI: angiotensin-receptor neprilysin inhibitor, MRA: mineralocorticoid receptor antagonist  
The proposed algorithm represents one possibility of many and can be individualized to specific circumstances.  
John J.V. McMurray, Milton Packer. Circulation . 2021 Mar 2;143(9):875-877.

及時使用FORXIGA提供全面心臟保護

# HFrEF Treatment

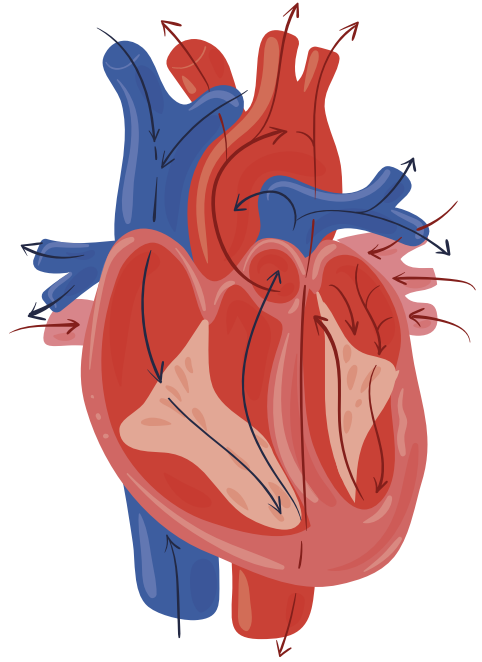
心衰竭病患使用於 $\text{eGFR} \geq 25$ ，持續用至透析前

ACEI, ARB or ARNI



**FORXIGA 10 mg**

# Outline

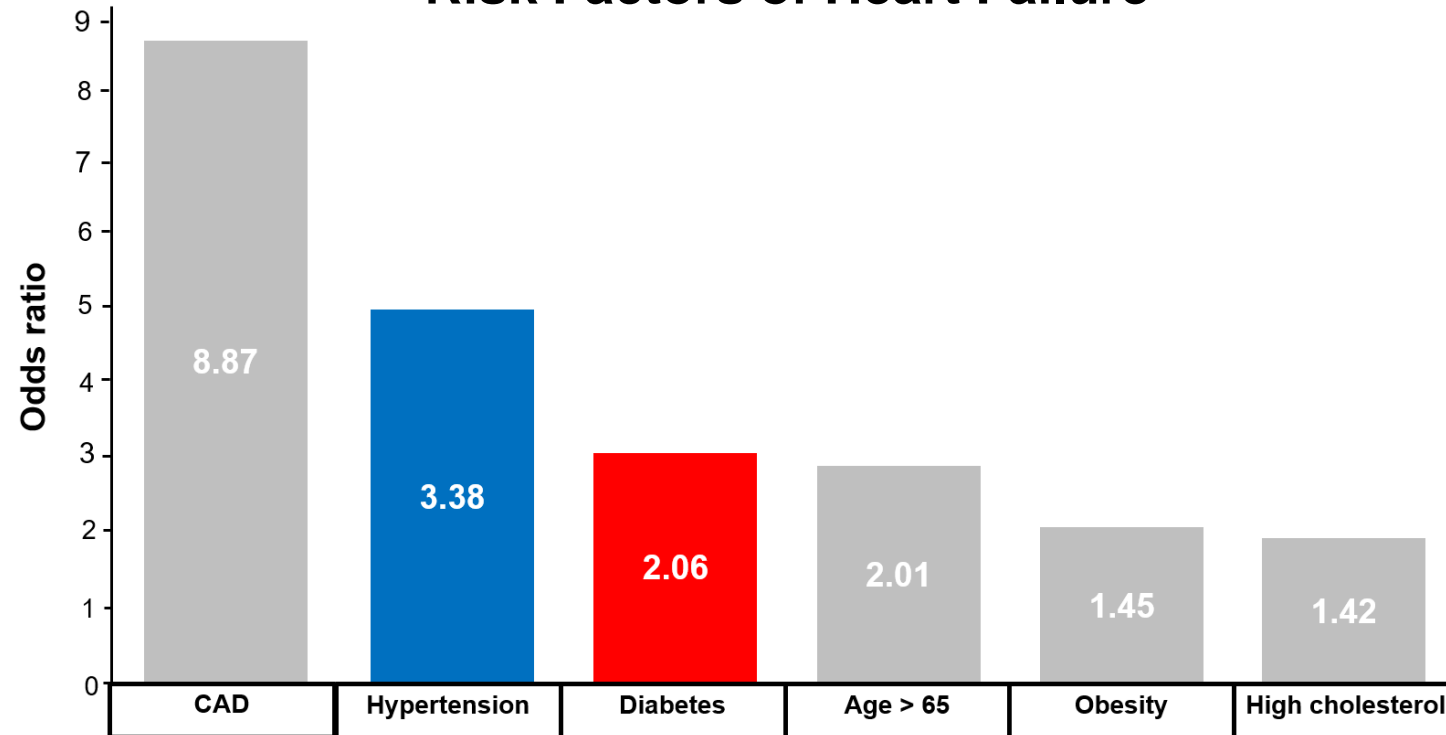


- The urgency and unmet needs of HF to patients
- Epoch-making treatment of HF with reducing mortality
- **Timely prevention HF in T2D**
- Conclusions

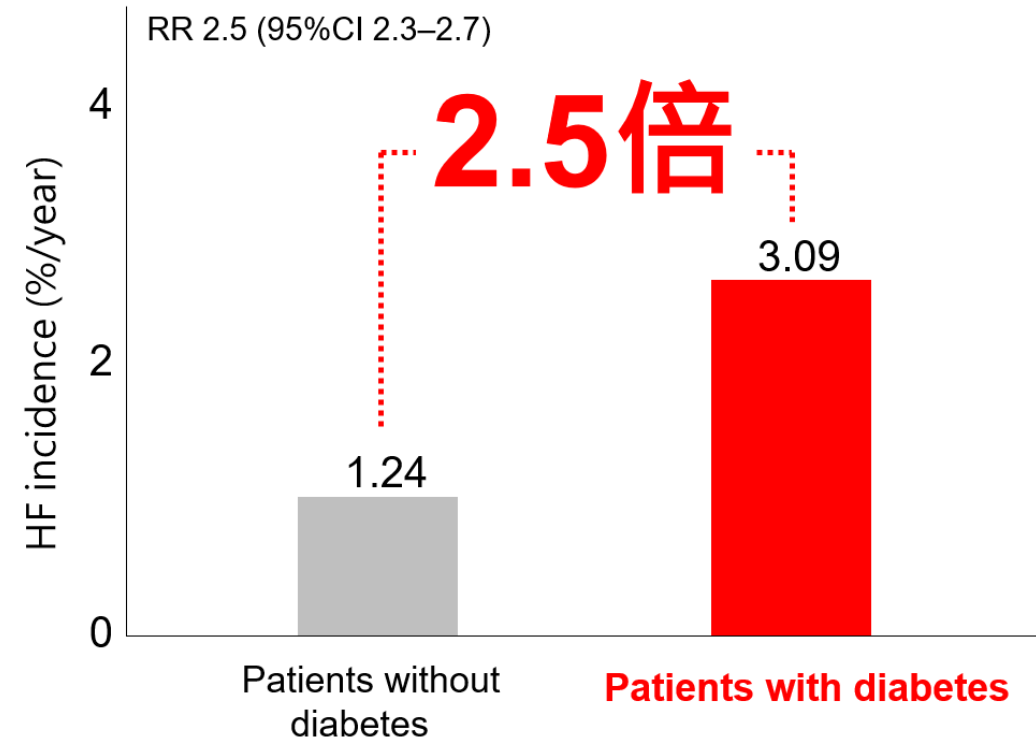
# 糖尿病是除CAD、高血壓外，導致心衰竭的重要風險因子

## 糖尿病增加約**2.5倍**罹患心衰竭風險

Risk Factors of Heart Failure<sup>1</sup>



Diabetes increased risk of Heart Failure<sup>2</sup>



1. J Community Hosp Intern Med Perspect. 2017 Mar 31;7(1):15-20.

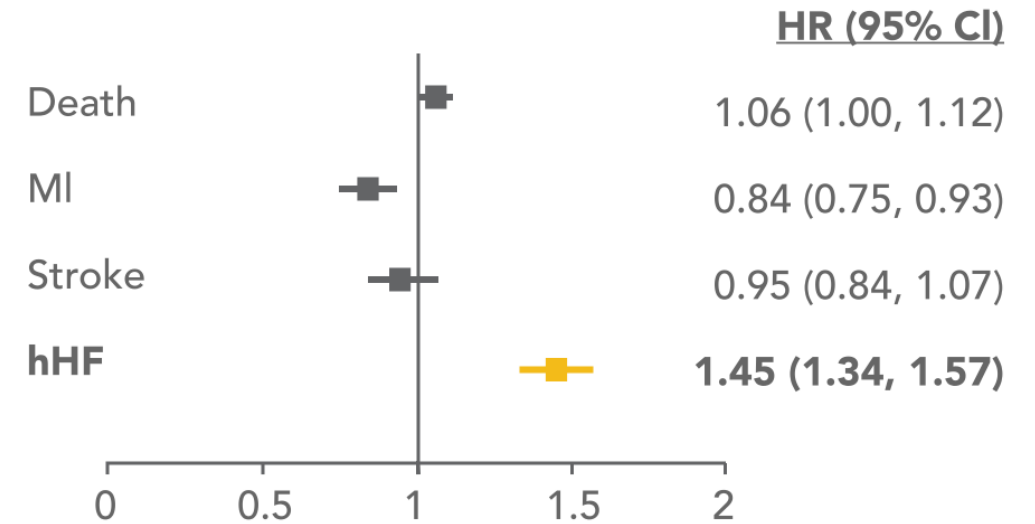
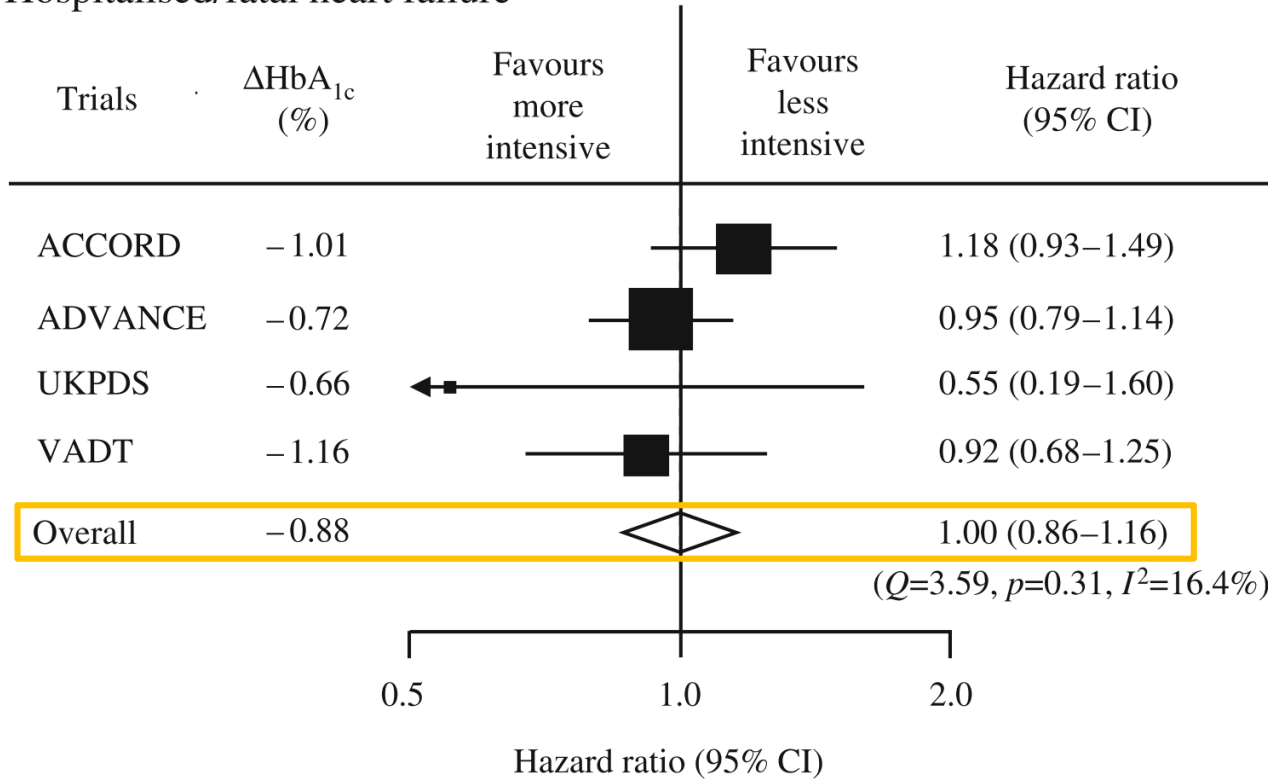
2. Diabetes Care. 2004 Aug;27(8):1879-84.

# 控制三高無法有效降低HF風險

糖尿病患降低A1c無法減少HF風險

糖尿病患控制好三高，HF風險仍增加

Hospitalised/fatal heart failure



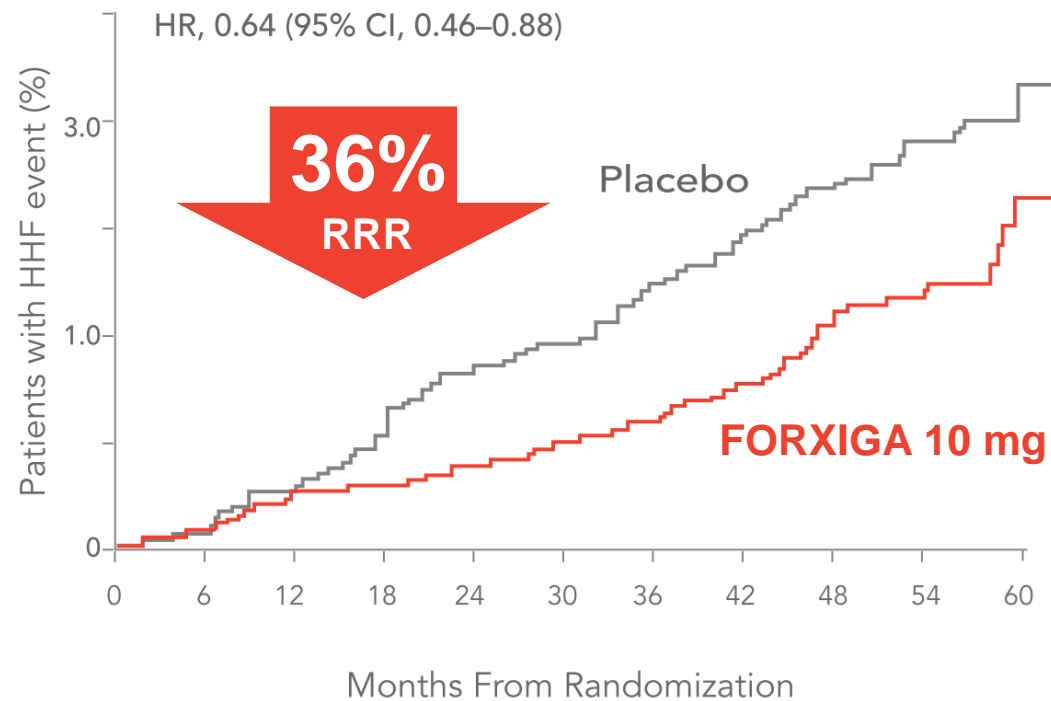
The risk of heart failure was consistently higher among T2D patients who had 5 risk factors within target range (**A1c**<7.0%, LDL<2.5 mmol; 97 mg/dl, **BP**<140/80 mmHg, albuminuria, current smoking) compared to patients without diabetes

MI: myocardial infarction, hHF: hospitalization for heart failure

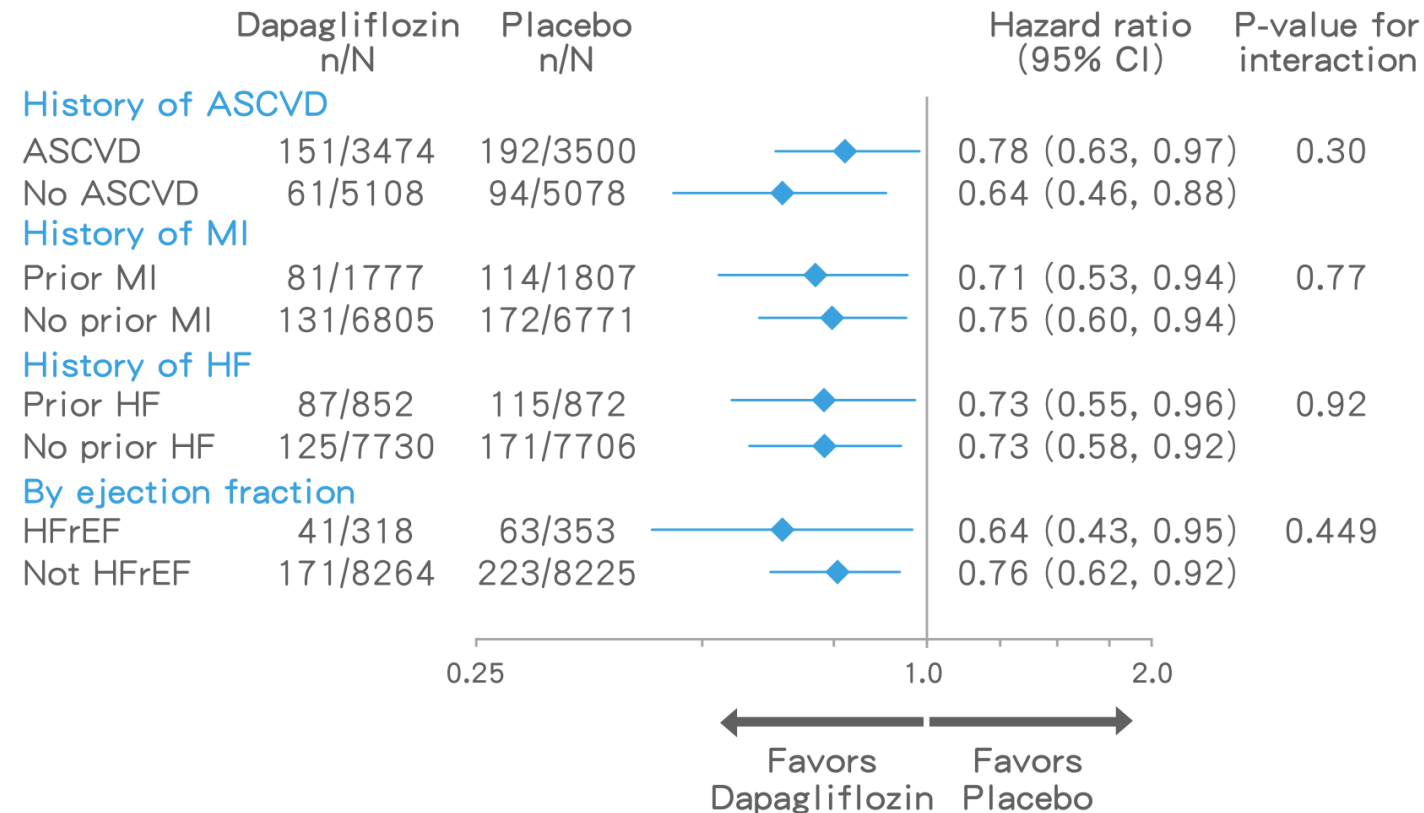
1. Diabetologia. 2009 Nov;52(11):2288-98.
2. N Engl J Med. 2018 Aug 16;379(7):633-644.

# 糖尿病患者使用FORXIGA有效預防心衰竭住院

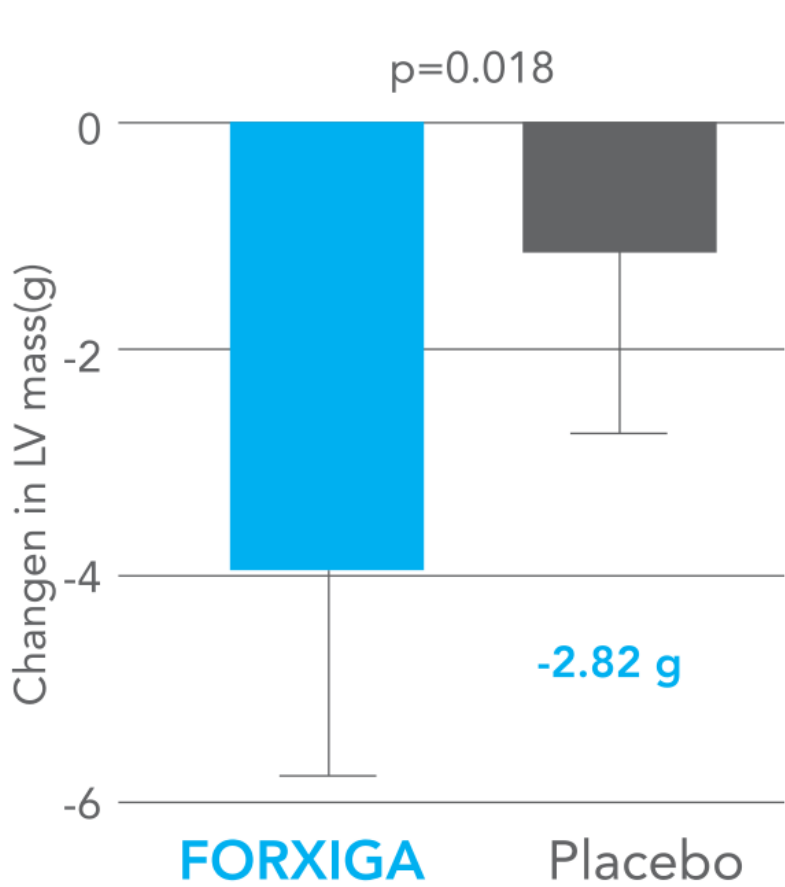
## Hospitalization for heart failure in T2D patients with **multiple risk factors** (subgroup analysis of DECLARE)



## Hospitalization for heart failure in different patient types with T2D



# FORXIGA顯著下降左心室肥大糖尿病患者的 LV mass



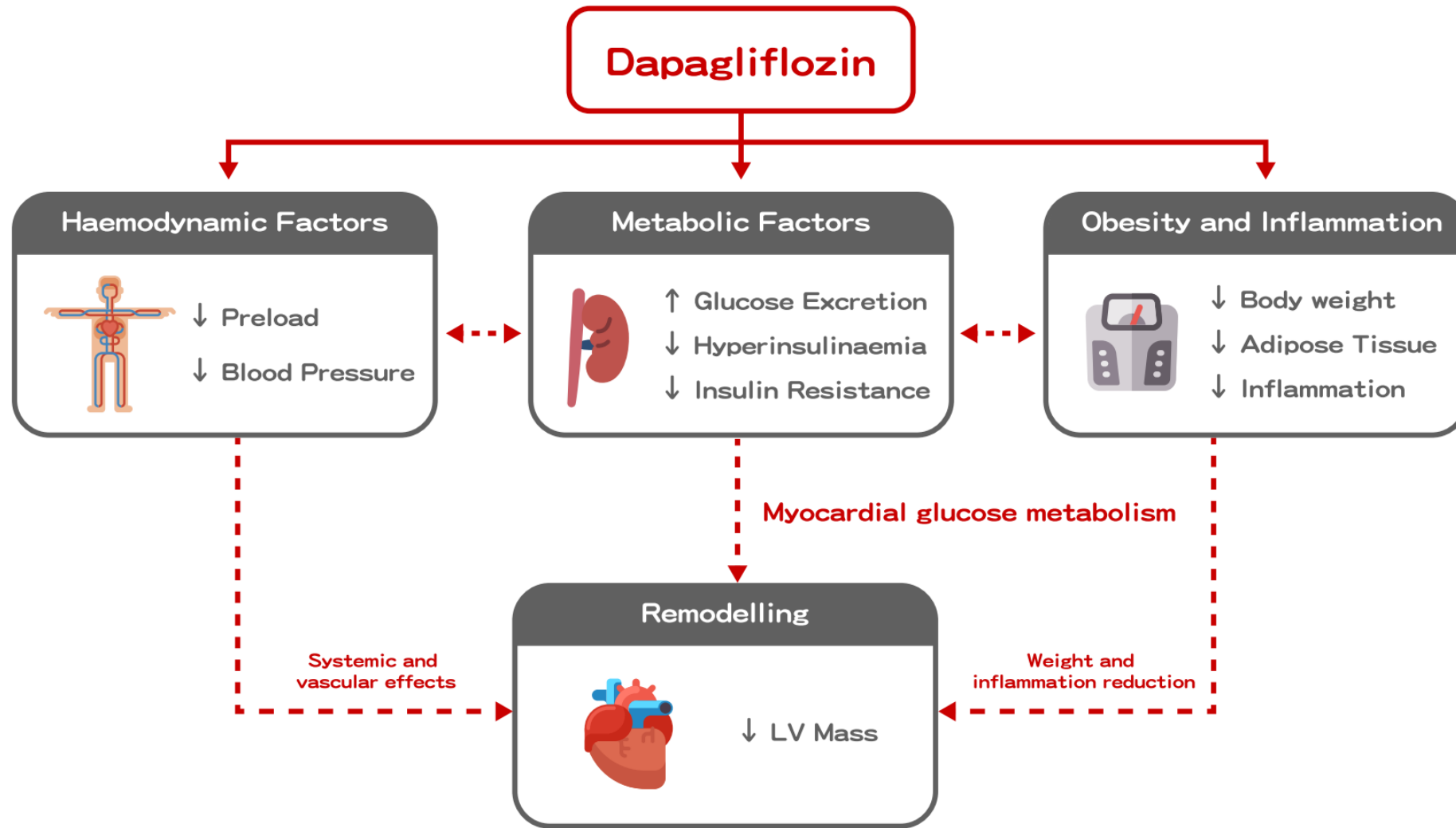
Variable change	FORXIGA vs Placebo Difference	P-value	達統計學差異
24 h SBP (mmHg)	-3.63	0.012	V
Nocturnal SBP (mmHg)	-4.38	0.017	V
Weight (kg)	-3.77	<0.001	V
BMI (kg/m <sup>2</sup> )	-1.35	<0.001	V
VAT volume (cm <sup>3</sup> )	-679.40	<0.001	V
SCAT volume (cm <sup>3</sup> )	-609.76	0.001	V
Hemoglobin (g/dL)	+0.95	<0.001	V
Hematocrit (%)	+2.90	<0.001	V
Fasting glucose (mg/dl)	-30.2	0.002	V
HbA1c (%)	-0.89	0.025	V
HOMA-IR	-2.56	0.017	V
hsCRP (ng/L)	-1296.04	0.049	V

**DAPA-LVH trial:** 66 T2D patients with LV hypertrophy are randomly assigned to receive dapagliflozin 10 mg once daily or placebo for 12 months. Primary endpoint: LV mass assessed by cardiac MRI

LV: left ventricular, MRI: magnetic resonance imaging, VAT: visceral adipose tissue, SCAT: subcutaneous adipose tissue, HOMA-IR: homeostatic model assessment of insulin resistance, hsCRP: high sensitive C-reactive protein.

# FORXIGA 減少 LV mass 的可能機轉：

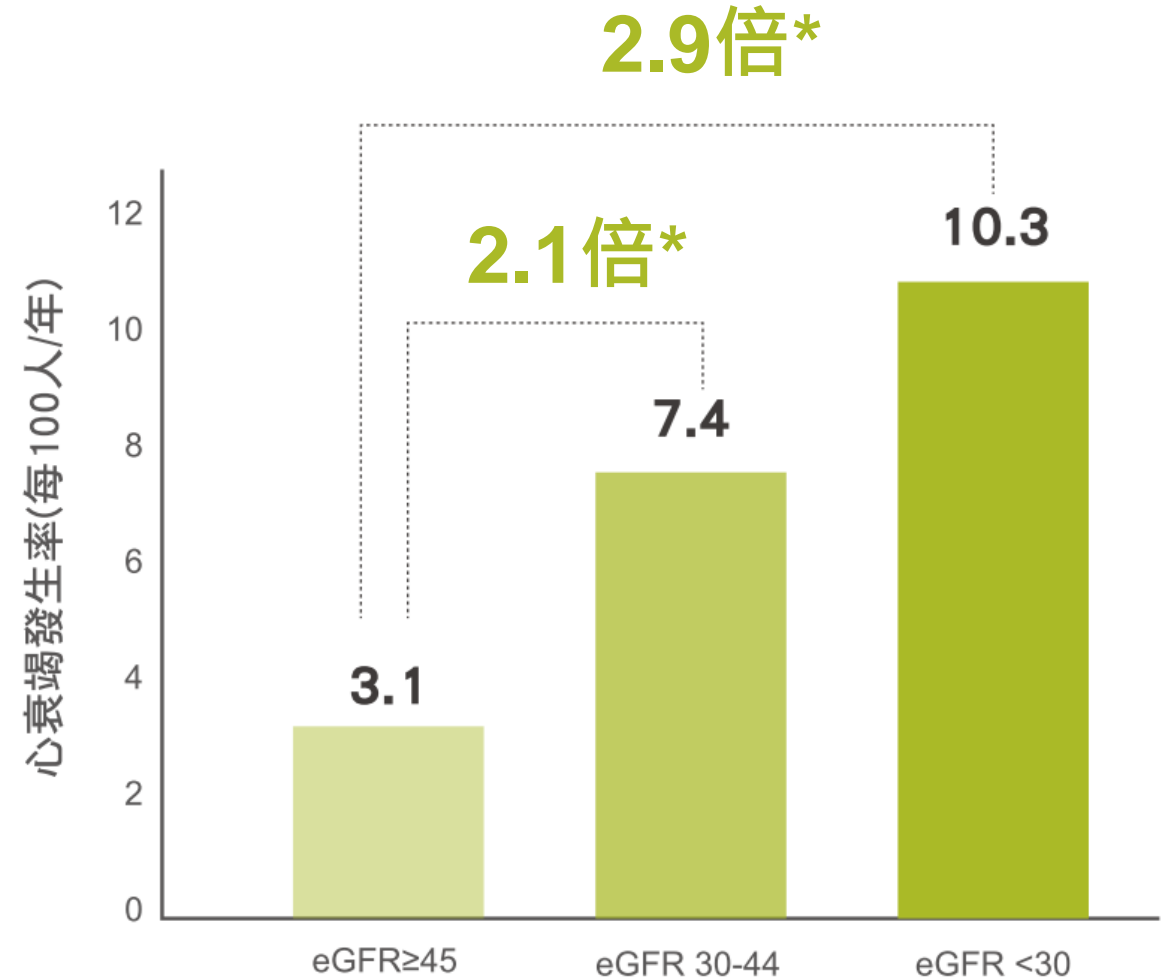
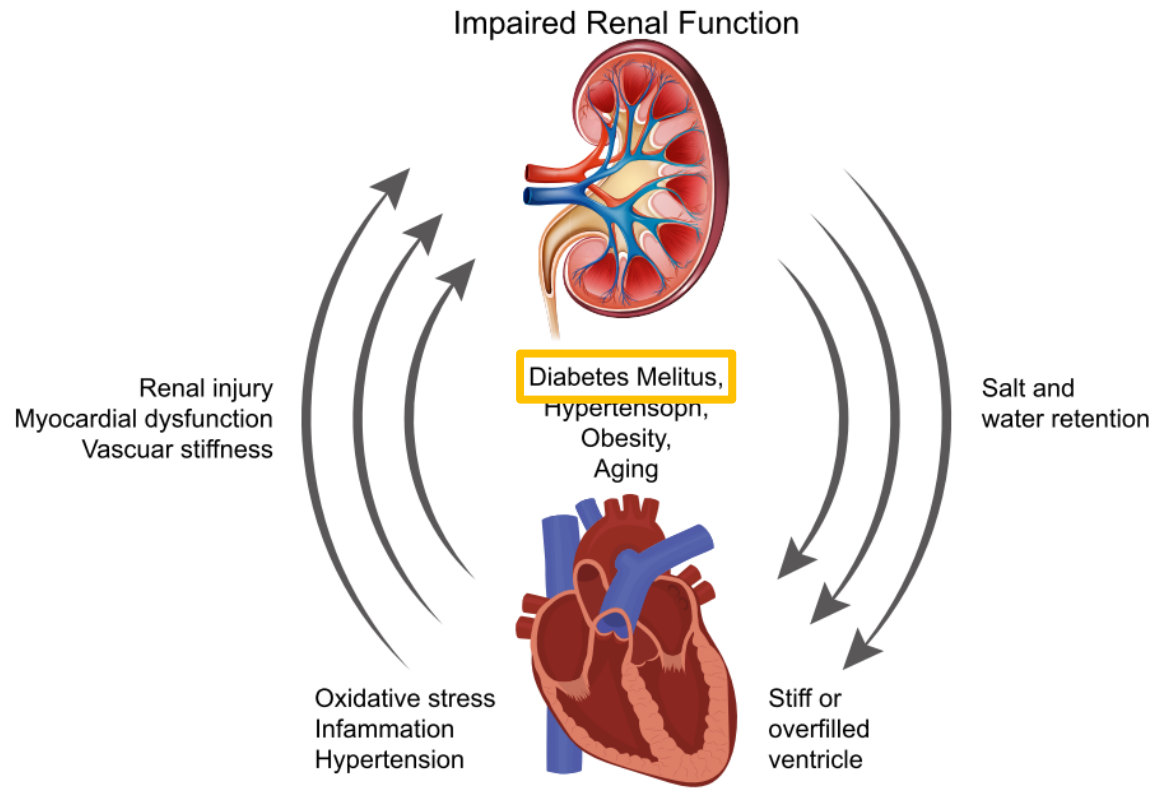
## 1.血液動力學因子 2.代謝因子 3.肥胖和發炎的改善



**Take home figure** Proposed mechanisms by which dapagliflozin regressed left ventricular mass.

# 糖尿病會導致心腎症候群；腎功能越差，心衰竭發生率越高

## Cardio-renal syndrome



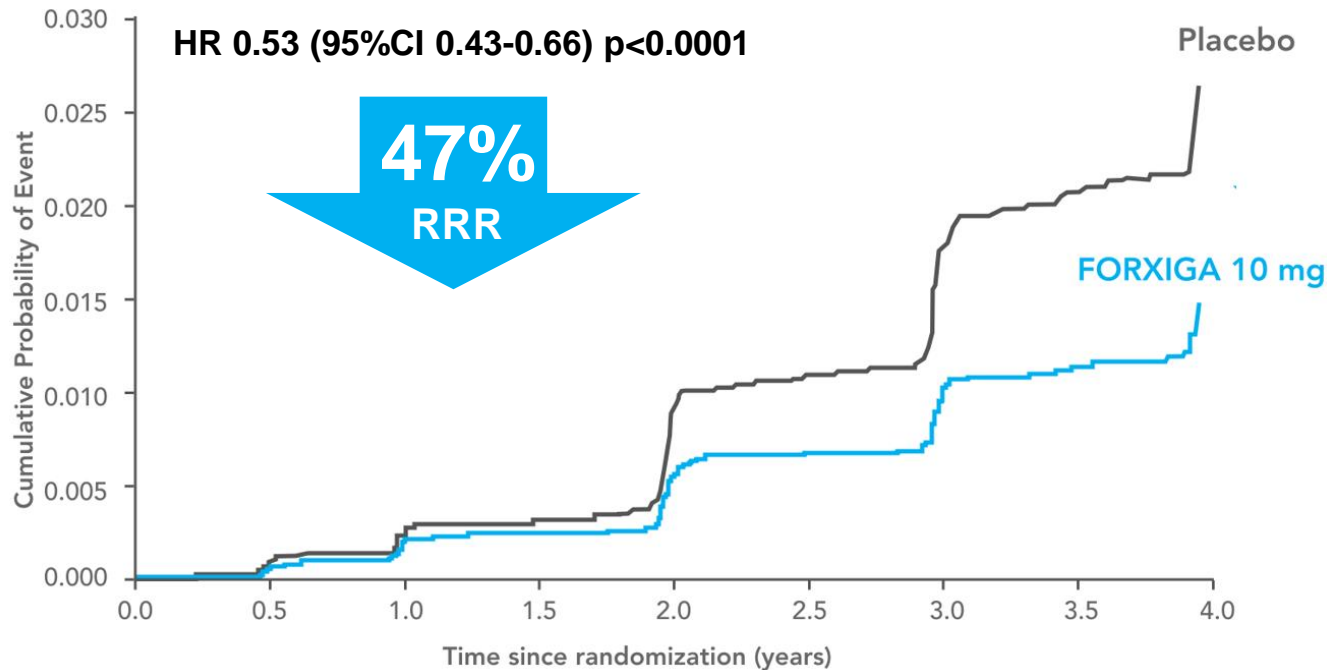
\*adjustment for demographic characteristics

1. Circulation. 2016 Aug 9;134(6):435-7.
2. J Am Coll Cardiol. 2019 Jun 4;73(21):2691-2700.

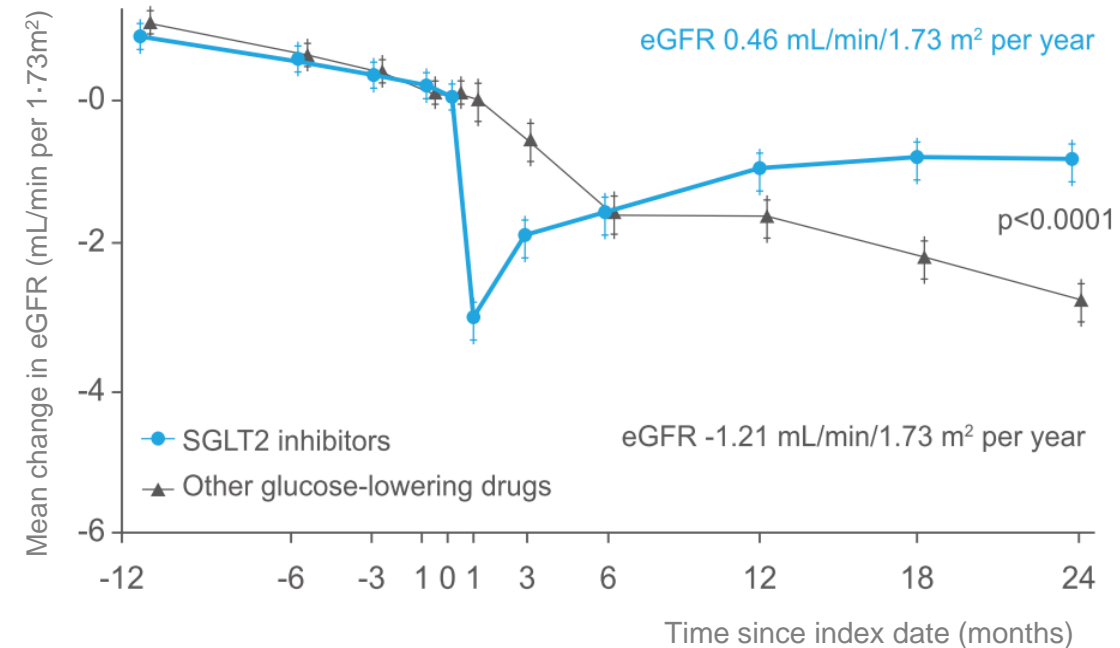
# 使用FORXIGA的糖尿病患，腎臟惡化風險較低



糖尿病患使用FORXIGA比起placebo，  
**47%**較低腎臟惡化風險



多國RWE: 糖尿病患使用SGLT-2i比  
其他降糖藥更能維持eGFR



The data is based upon Real World Evidence (RWE) data and is subject to potential confounding bias usually associated with observational research.

# FORXIGA唯一提供從預防到治療完整保護

T2D +  
Risk factors

## Prevention



唯一初級預防  
從腎護心

↓ **36% hHF**

Renal outcome HR 0.53 (0.43-0.66)

HFrEF

## Treatment



**DAPA-HF** 抗衰救命心選擇

唯一SGLT-2i顯著減少HFrEF死亡\*

↓ **26% CV death  
or worsening HF**

**NNT 21**

↓ **18% CV death**

# 及時使用FORXIGA提供全面心臟保護

T2D +  
Risk factors

## Prevention

HFrEF

## Treatment

糖尿病合併多重心血管風險因子

Metformin



心衰竭病患

ACEI, ARB or ARNI



**FORXIGA 10 mg**

# Conclusions

- 治療糖尿病

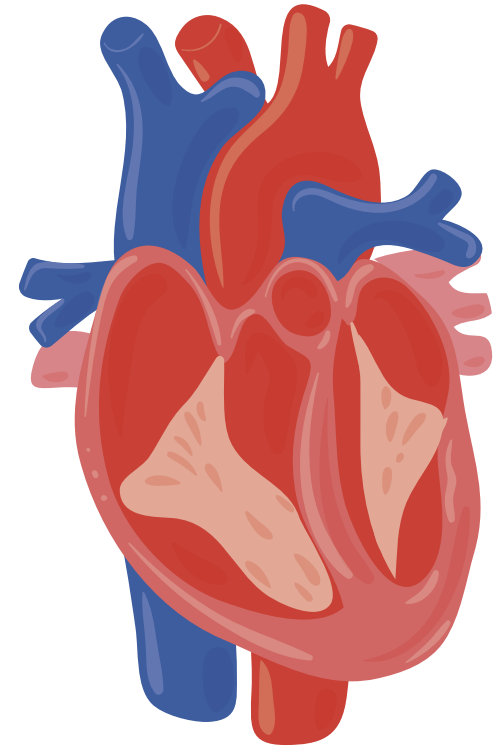
**FORXIGA 唯一預防心衰竭住院**

- 治療心衰竭

**FORXIGA 抗衰救命心選擇**

1. 減少心血管死亡或心衰竭惡化 (NNT=21)
2. 針對HFrEF患者, FORXIGA唯一SGLT-2i顯著減少心血管死亡\*
3. 針對非糖尿病療效一致，安全性與安慰劑相當

\*CV death, HR 0.82 (0.69-0.98), p=0.029 in DAPA-HF



# THANKS!

---

Do you have any questions?

北醫附醫 徐千彛醫師



[chienyihsu@tmu.edu.tw](mailto:chienyihsu@tmu.edu.tw)

