Timely Treatment for High-Risk Patient with T2DM for Cardio-Renal Complication

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Preventing Complications

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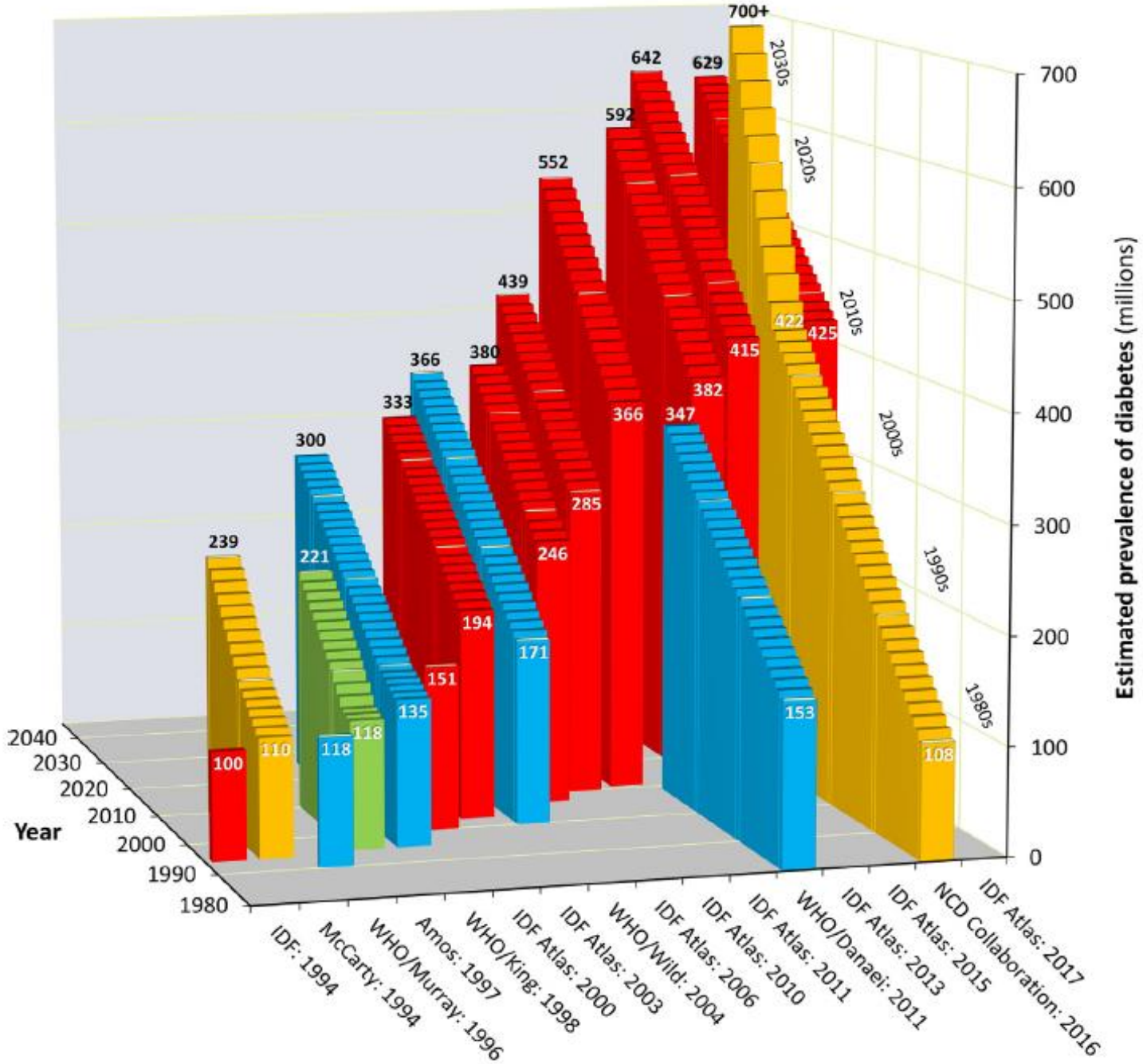
Outline

- Deterioration of renal & cardio function in diabetic patients
- New strategy for diabetes management with renal & cardiac complication consideration
- Conclusion



Wang CY, Neil D, Home P. Diabetes Res Clin Pract 2018. pii: S0168-8227(17)31877-6. doi: 10.1016/j.diabres.2018.06.007

從 2000 年到 2014 年
糖尿病人數約增加 2.6 倍

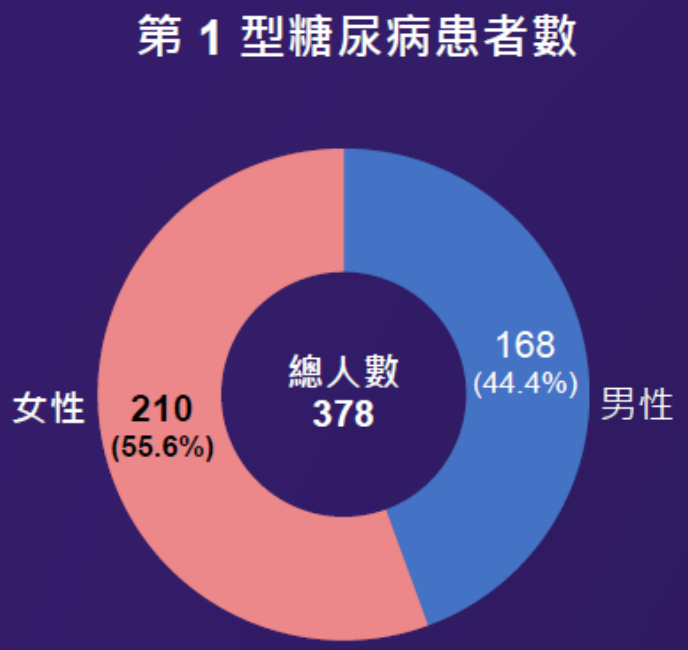
Table 1A Population with diabetes mellitus and prevalence of diabetes mellitus in Taiwan from 2005 to 2014.

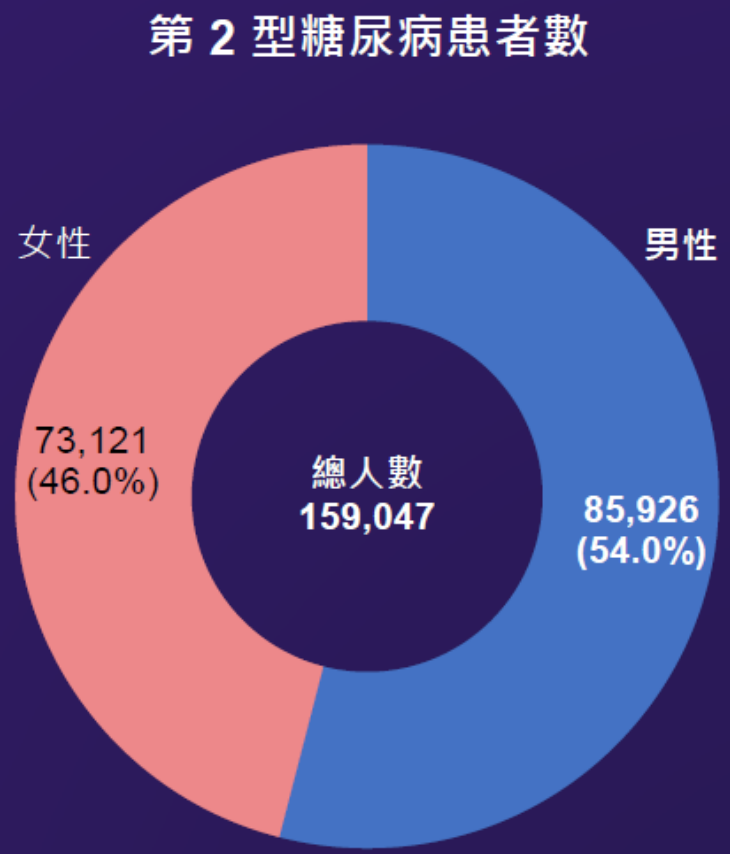
Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	P value
Residents (10^4)	2277.0	2287.7	2295.8	2303.7	2312.0	2316.2	2322.5	2331.6	2337.4	2343.4	<0.001
Total DM (10^4)	132.6	141.2	150.5	159.9	170.0	179.9	189.8	199.9	210.3	220.1	<0.001
Women (10^4)	65.4	69.4	73.9	78.3	83.0	87.7	92.5	97.4	102.3	106.9	<0.001
Men (10^4)	67.3	71.8	76.6	81.6	86.9	92.1	97.3	102.6	108.0	113.1	<0.001
Residents (10^4), 20–79 y/o	1648.6	1665.1	1680.6	1699.1	1715.3	1732.5	1747.6	1762.9	1778.7	1793.5	<0.001
Prevalence (%), 20–79 y/o	7.15	7.45	7.71	8.04	8.41	8.76	9.10	9.49	9.81	10.10	<0.001
Standardized Prevalence (%)	4.57	4.76	4.93	5.13	5.37	5.59	5.81	6.06	6.26	6.45	<0.001
Residents (10^4), 0–19 y/o	584.9	575.4	565.1	551.1	539.6	523.2	511.4	502.7	490.4	479.5	<0.001
Prevalence (%), 0–19 y/o	0.08	0.09	0.10	0.10	0.11	0.12	0.12	0.13	0.13	0.14	<0.001
Standardized Prevalence (%)	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.05	0.05	<0.001
Aged DM (%), ≧65 y/o[a]	48.9	48.9	49.0	49.0	48.5	48.3	48.6	48.9	49.5	50.3	0.134
Women (%)[b]	53.0	53.4	53.8	54.0	53.8	53.8	54.1	54.6	55.4	56.3	<0.001
Men (%)[b]	44.8	44.5	44.4	44.2	43.5	43.1	43.2	43.5	44.0	44.6	0.272
Prevalence of DM in the aged population (%)[c]	29.64	30.60	31.80	33.01	33.98	35.43	36.92	38.17	39.16	39.93	<0.001
Prevalence in women (%)[c]	31.55	32.40	33.50	34.52	35.41	36.73	38.06	39.14	39.98	40.56	<0.001
Prevalence in men (%)[c]	27.70	28.74	30.01	31.39	32.44	34.00	35.65	37.07	38.22	39.21	<0.001

[a] Numerator is population with DM who are aged ≧65 years, and denominator is total population with DM.
[b] Numerator is aged women (men) with DM, and denominator is total population of women (men) with DM.
[c] Numerator is women and/or men with DM aged ≧65 years, and denominator is total population of women and/or men aged ≧65 years.

Journal of the Formosan Medical Association (2019) 118, S66eS73

臺灣每年新發生糖尿病患者數約 16 萬人
且絕大多數為第 2 型糖尿病

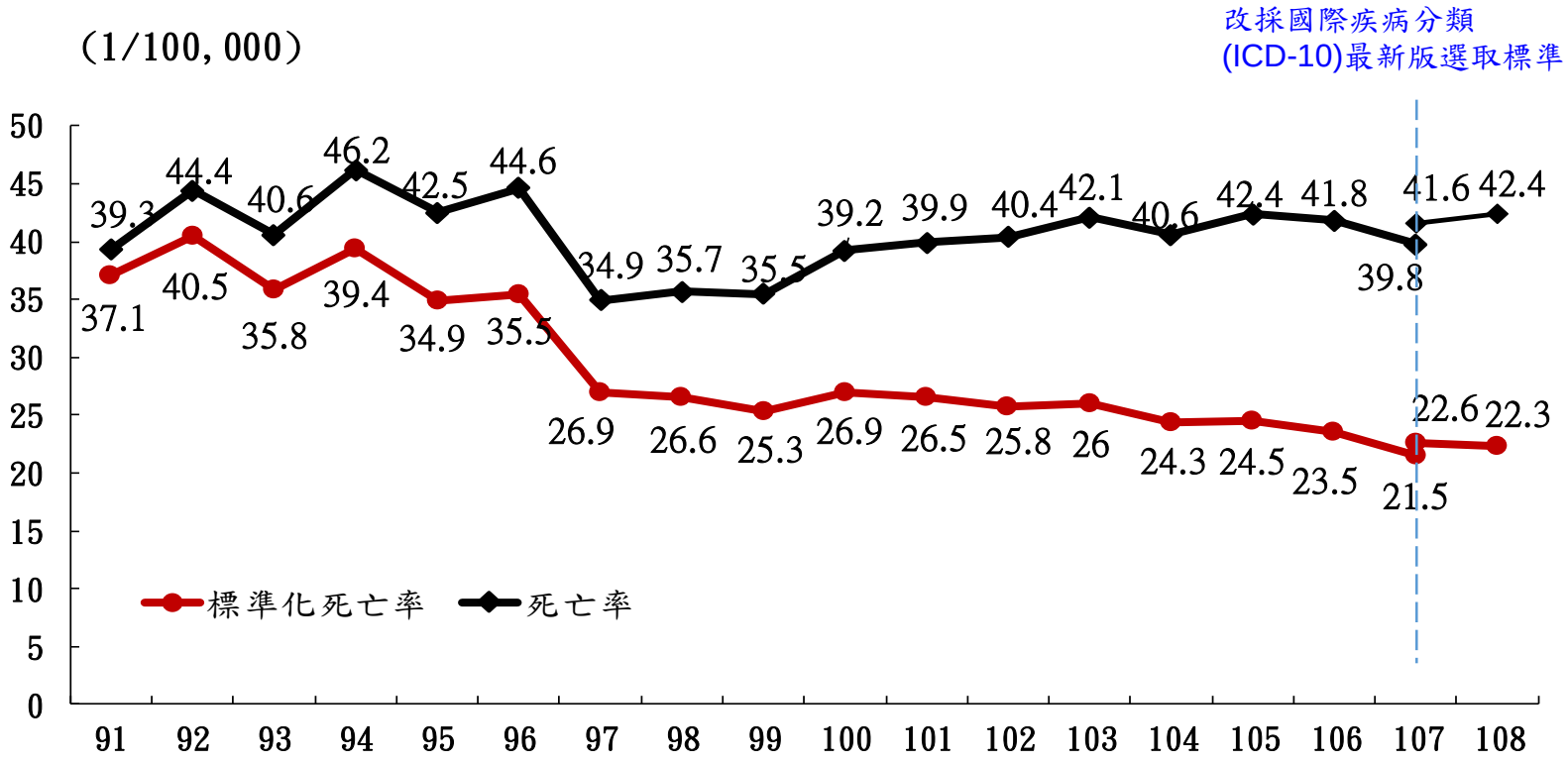




新發生第 2 型糖尿病患者數遠比第 1 型糖尿病患者多。
其中，第 1 型糖尿病以女性居多，第 2 型糖尿病則以男性為多。

Journal of the Formosan Medical Association (2019) 118, S66eS73

台灣糖尿病標準化死亡比率逐漸下降



備註：1.標準化死亡率係依世界衛生組織(WHO)編布之2000年世界標準人口年齡結構調整計算。
2.資料來源為行政院衛生署統計室（97年 以ICD-10統計）
3.108年起死因統計改採國際疾病分類(ICD-10)最新版選取標準，並以相同標準計算107年資料。

資料提供：國民健康署

臺灣第 2 型糖尿病的死亡人數逐年上升

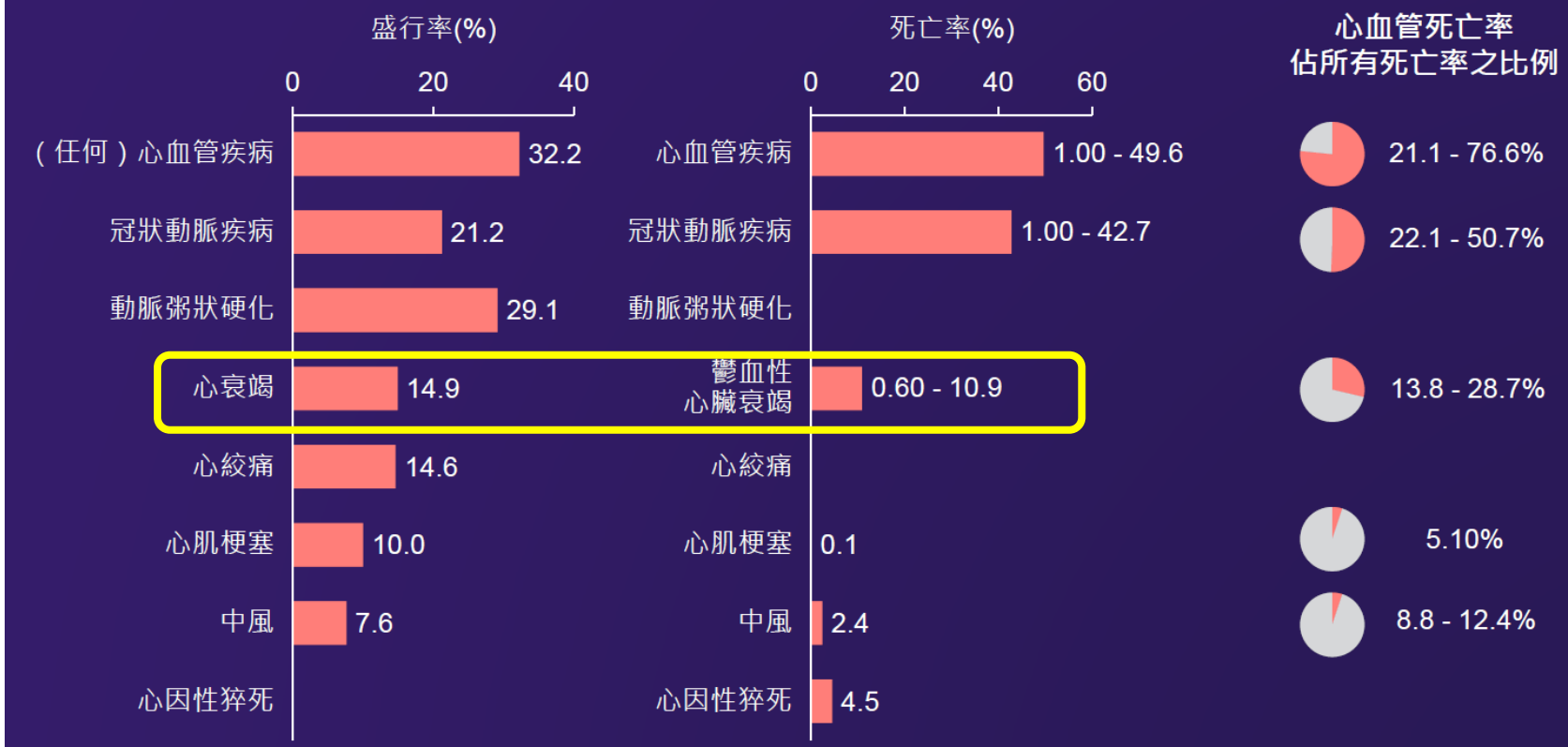
1. Data on several pre-specified causes of death were analyzed, including the top five causes of death in Taiwan in 2017, which were malignancy, **heart diseases**, pneumonia, cerebrovascular diseases and diabetes.
2. Besides, since renal diseases are important complications of diabetes, and the incidence as well as the prevalence of **renal diseases** have increased continuously, renal diseases were also selected as a cause of death to be analyzed.
3. These main causes of death were classified using ICD-9-CM or ICD-10-CM, and were as follows: 1) diabetes: 250 or E0eE14; 2) malignancies: 140e208 or C00eC97; 3) heart diseases: 390e392, 393e398, 410e414, 420e429, I01, I02, I05eI09, I20eI25, I27, and I30eI52; 4) cerebrovascular disease: 430e438 or I60eI69; 5) pneumonia: 480e486, 487, or J12eJ18; and 6) renal disease: 580e589, N00eN07, N17eN19.

死亡人數的增加應為糖尿病總人口增加的結果。

Journal of the Formosan Medical Association (2019) 118, S83eS89

糖尿病引起的大血管併發症是導致死亡的主因

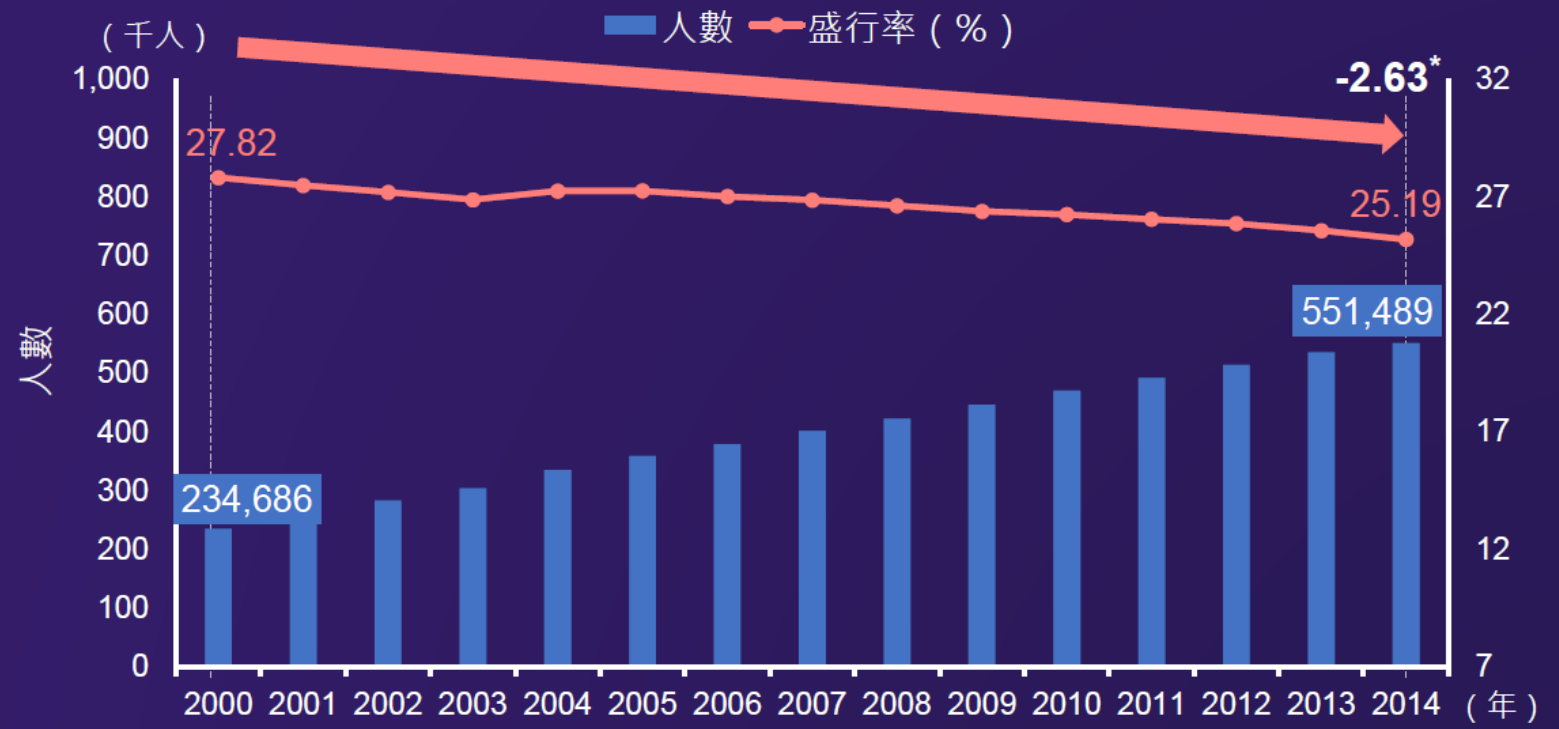
第 2 型糖尿病相關心血管併發症之盛行率與死亡率



Einarson TR, et al. Cardiovasc Diabetol. 2018 Jun 8; 17(1):83.

臺灣第 2 型糖尿病
併發心血管疾病的盛行率逐年下降

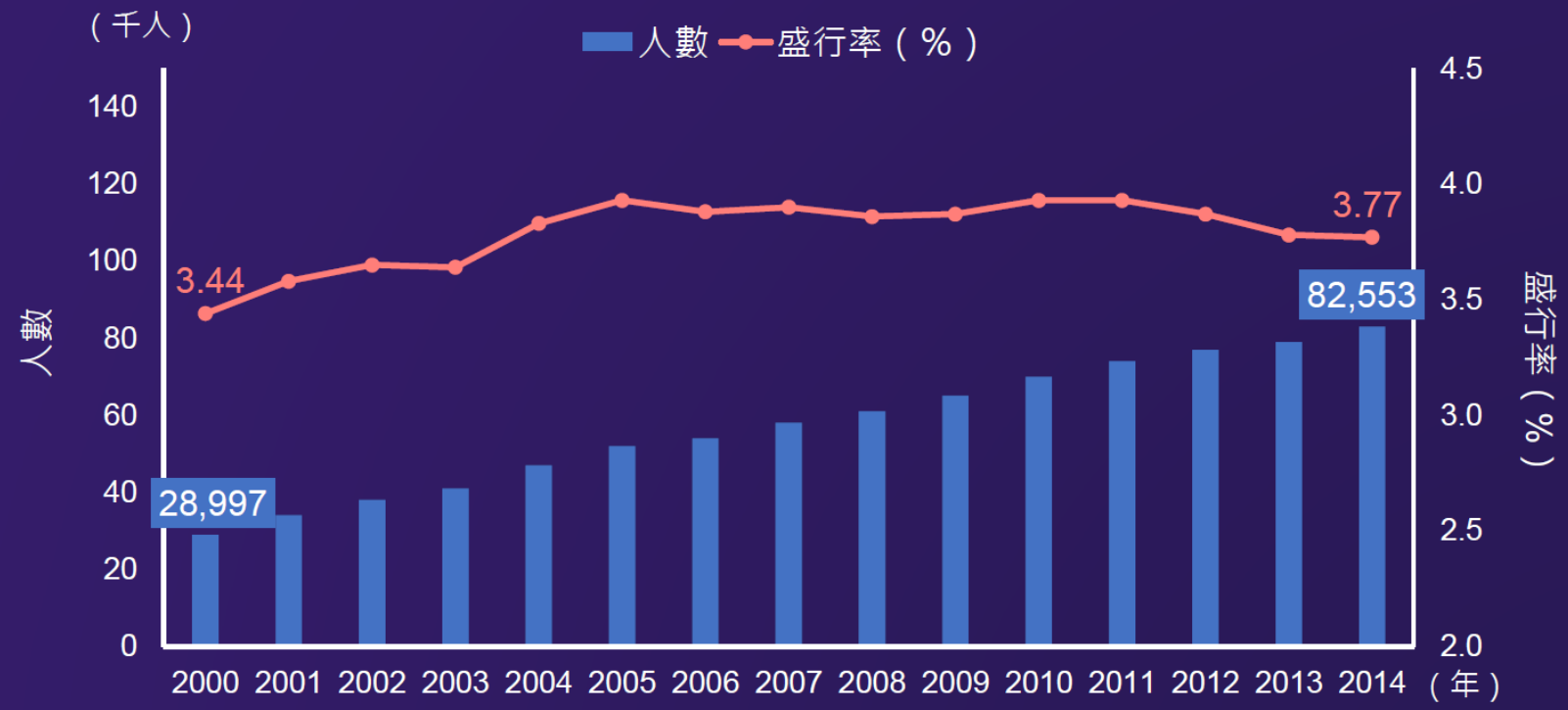
第 2 型糖尿病併發心血管疾病的患者人數與盛行率



*盛行率下降趨勢 $p < 0.001$

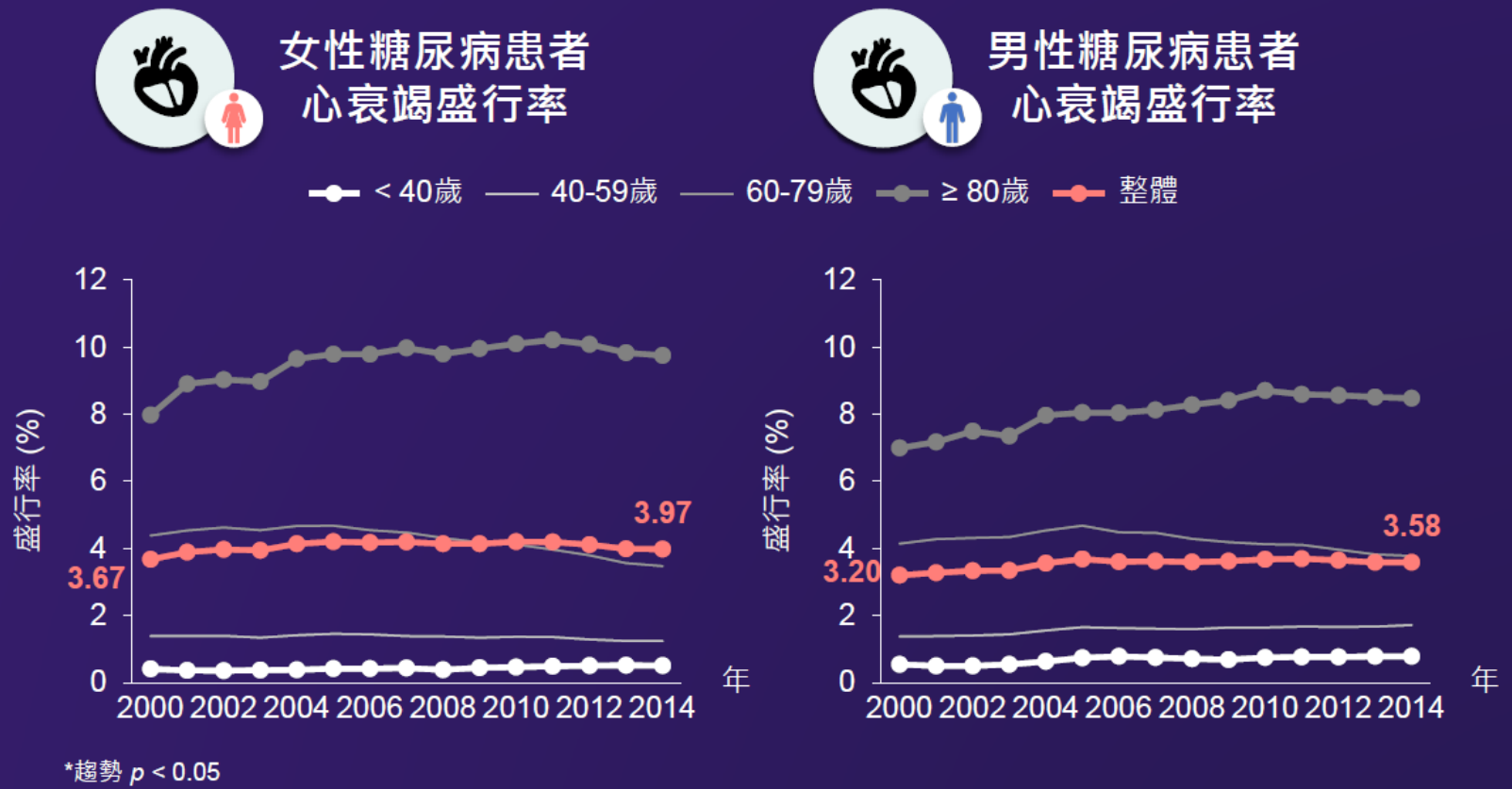
臺灣第 2 型糖尿病
併發心衰竭的盛行率呈上升趨勢

第 2 型糖尿病併發心衰竭的患者人數與盛行率



盛行率上升趨勢 $p = 0.011$

不論性別，< 40 歲與 ≥ 80 歲族群心衰竭盛行率皆呈上升趨勢



糖尿病患者年齡越大，心衰竭的盛行率越高；
不論性別，< 40 歲與 ≥ 80 歲這兩個族群的盛行率都呈上升趨勢。

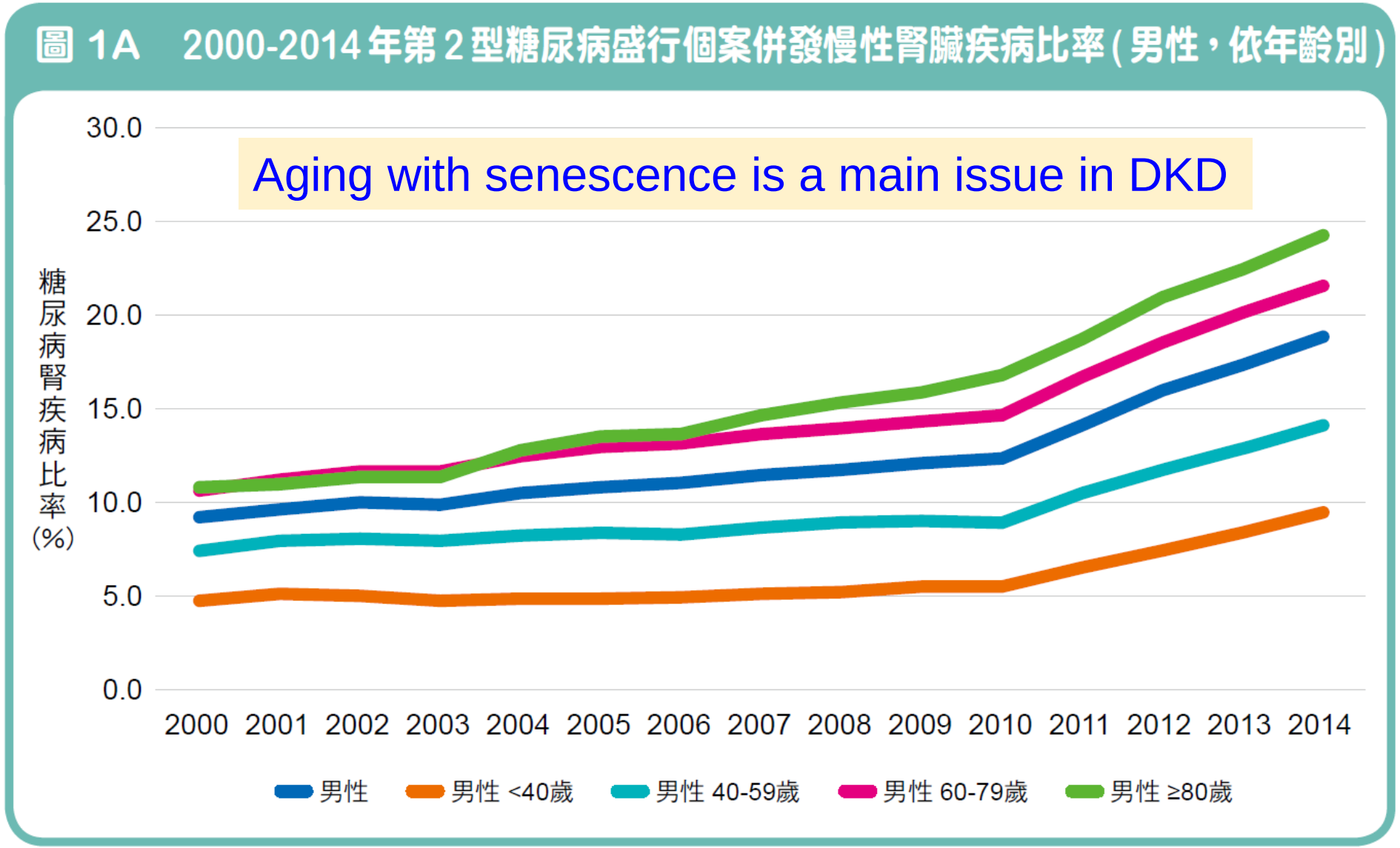
DKD in Taiwan ~ 2000 to 2014

表 5　2000-2014 年第 2 型糖尿病盛行個案併發慢性腎臟疾病之情況

	T2DM 盛行個案 (10^5)	糖尿病慢性腎臟疾病 (N)	糖尿病慢性腎臟疾病 (%)	透析 (N)	透析 (%)	腎臟移植 (N)	腎臟移植 (%)
2000	8.44	77,388	9.17	10,601	1.26	188	0.02
2001	9.44	90,599	9.60	12,353	1.31	281	0.03
2002	10.41	102,360	9.84	14,468	1.39	388	0.04
2003	11.32	110,332	9.75	16,572	1.46	431	0.04
2004	12.31	126,163	10.25	18,663	1.52	562	0.05
2005	13.19	138,184	10.48	21,029	1.59	722	0.05
2006	14.04	146,411	10.43	23,194	1.65	970	0.07
2007	14.96	162,372	10.85	25,553	1.71	1,095	0.07
2008	15.90	177,553	11.17	28,133	1.77	1,281	0.08
2009	16.90	192,095	11.37	30,831	1.82	1,394	0.08
2010	17.89	206,748	11.56	33,475	1.87	1,498	0.08
2011	18.88	251,807	13.34	35,568	1.88	1,652	0.09
2012	19.89	299,881	15.08	37,894	1.91	1,768	0.09
2013	20.92	344,626	16.47	40,026	1.91	1,890	0.09
2014	21.89	392,414	17.92	41,864	1.91	2,048	0.09
P for trend	-	-	<0.001	-	<0.001	-	<0.001

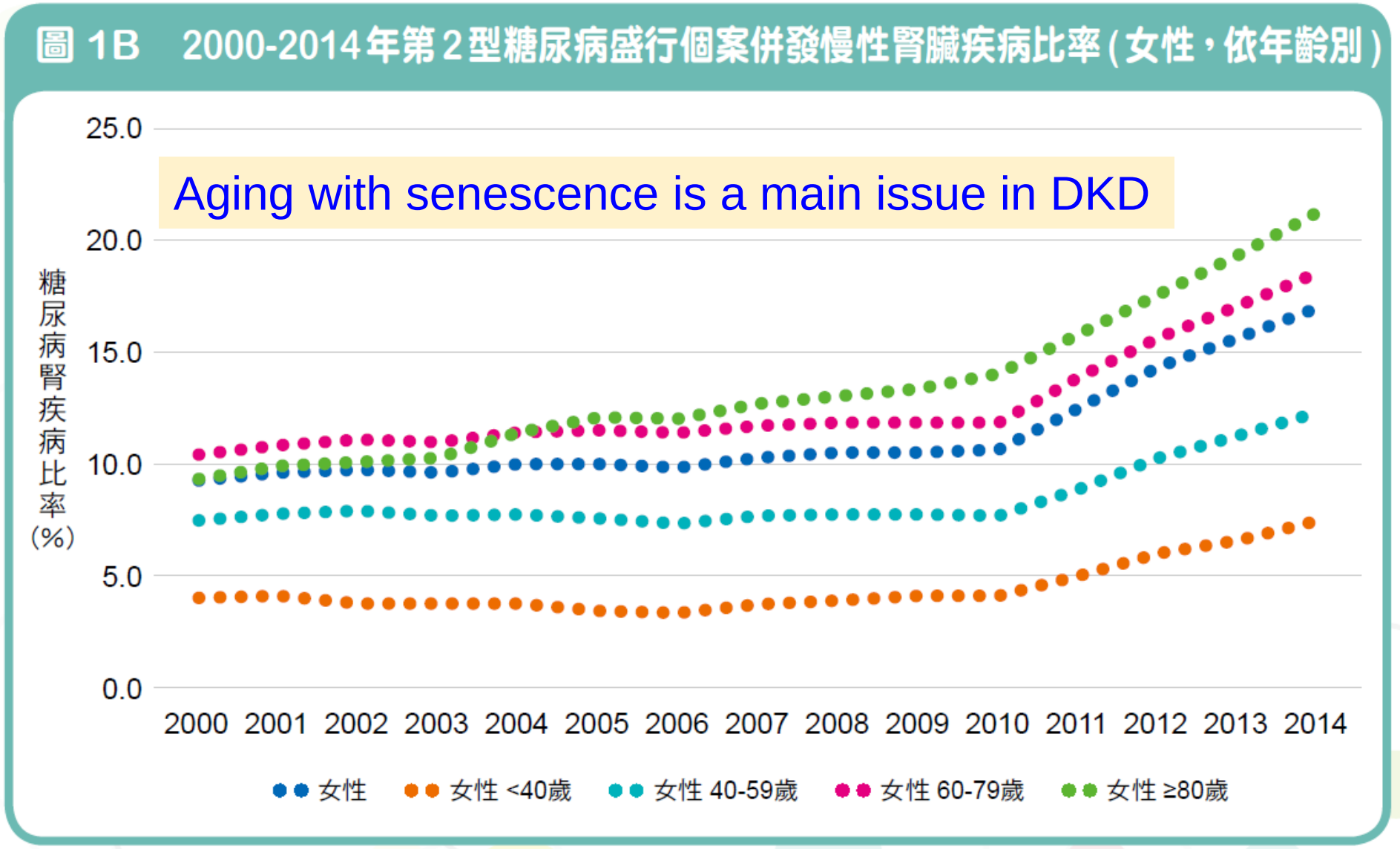
2019 Atlas of Diabetes Mellitus in Taiwan

DKD in Taiwan ~ 2000 to 2014



2019 Atlas of Diabetes Mellitus in Taiwan

DKD in Taiwan ~ 2000 to 2014



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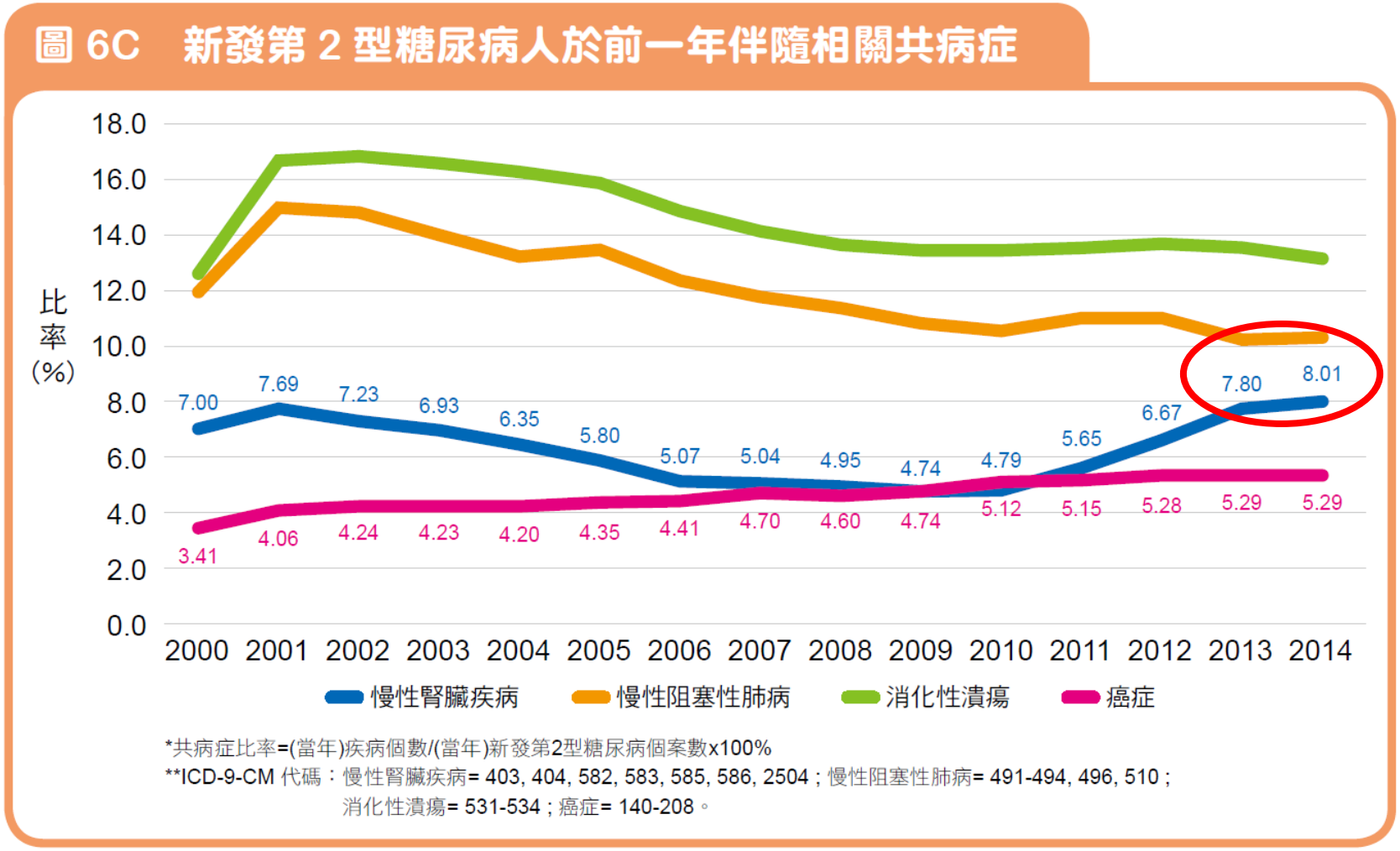
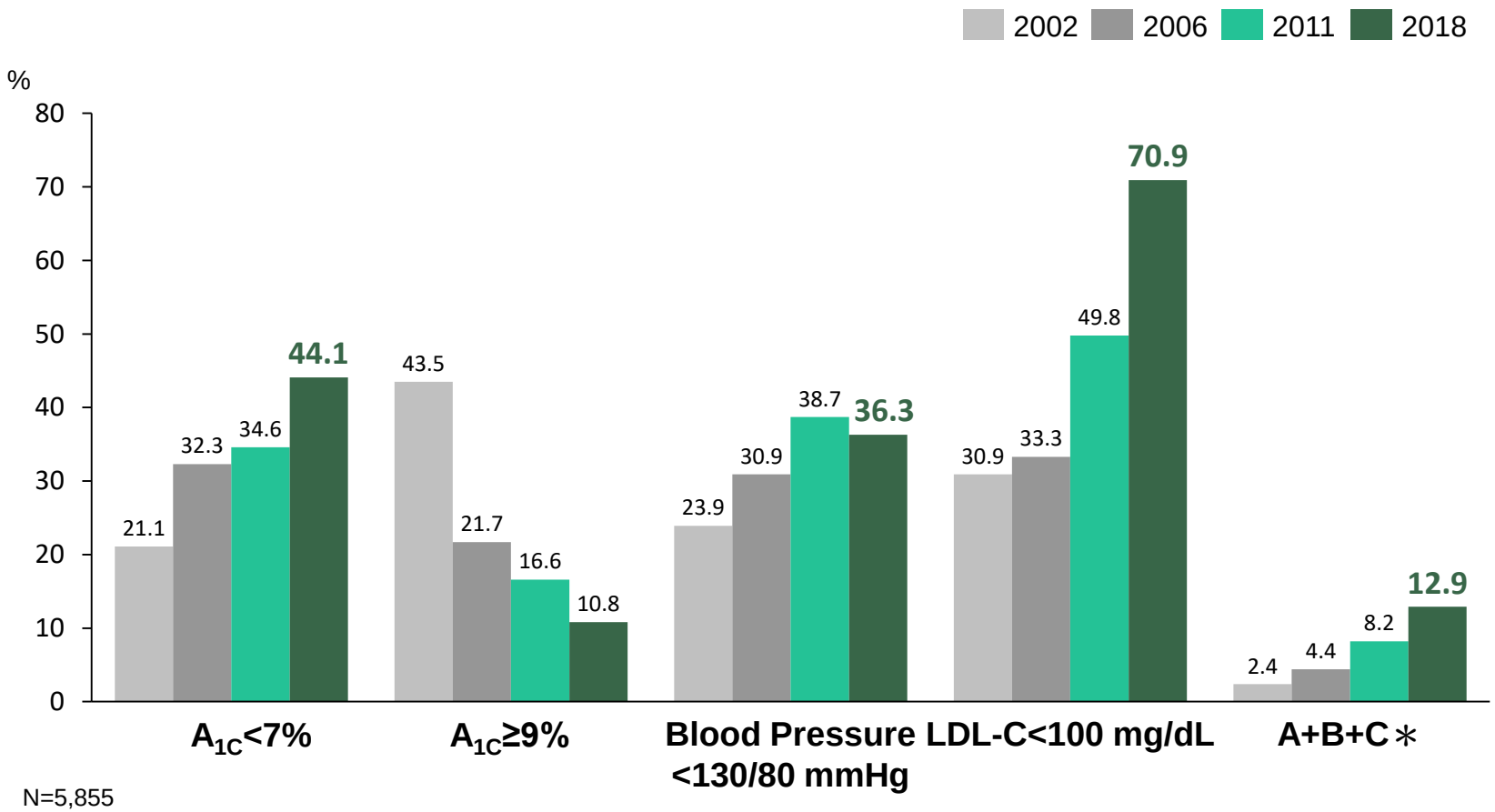
DKD in Taiwan ~ 2000 to 2014



2019 Atlas of Diabetes Mellitus in Taiwan

台灣糖尿病健康促進機構之品管調查研究

三高控制狀況 －TADE 2002/2006/2011/2018 調查



N=5,855

*A：A_{1C} <7%、B：BP<130/80 mmHg、C：LDL-C<100 mg/dL

2020; In writing and submission

Glucose Control and Vascular Outcomes in Type 2 Diabetes: Is the Picture Clear?

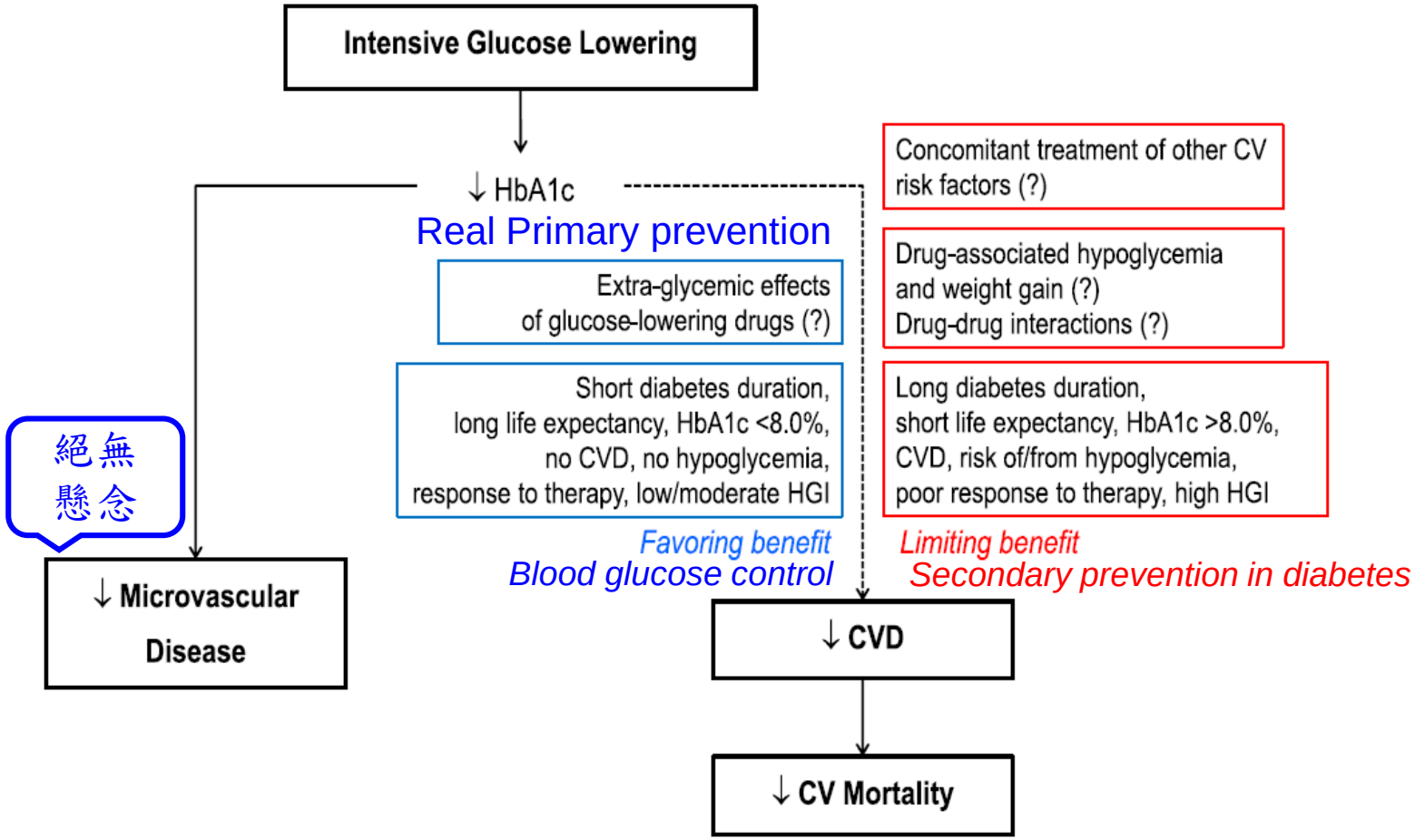


Figure 1—Relationship between intensive glucose control and vascular complications in T2D. CV, cardiovascular.

Francesco Giorgino, Philip D. Home, and Jaakko Tuomilehto. Diabetes Care 2016;39(Suppl. 2):S187–S195

Oral based therapy versus Insulin in All Cause Mortality

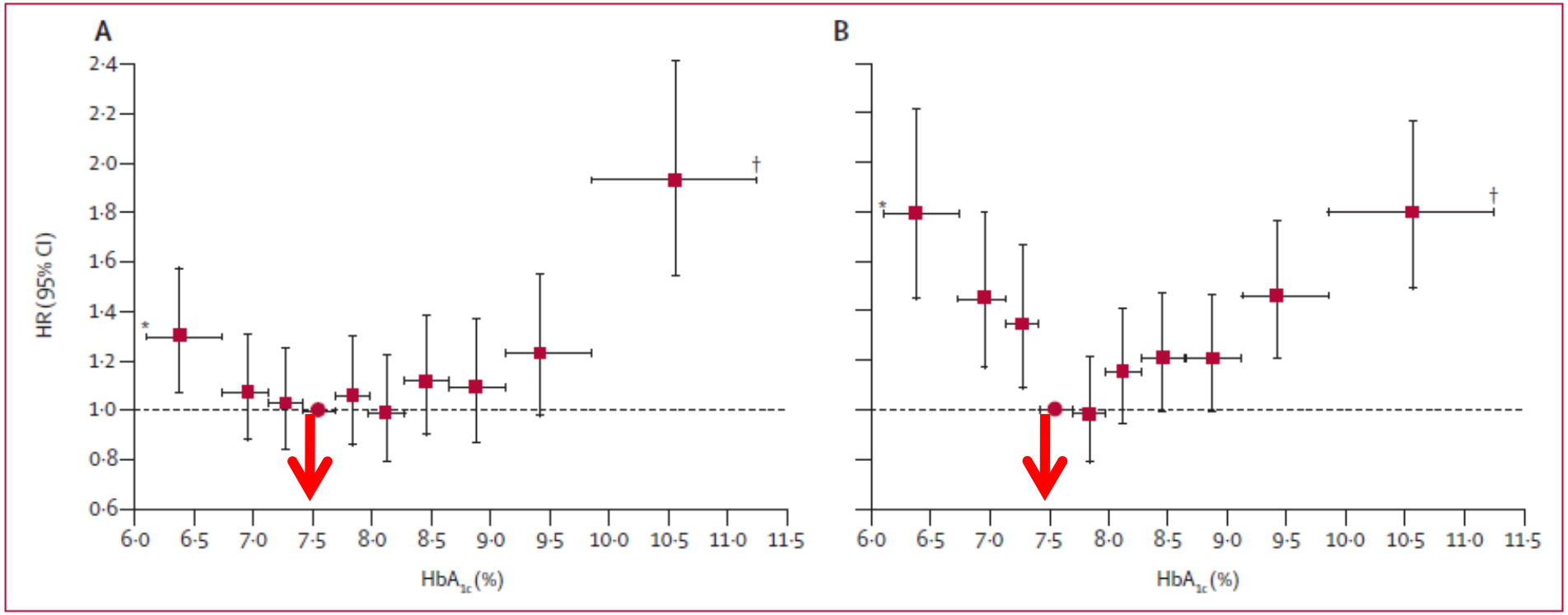


Figure 1: **Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies**
Cox proportional hazards models were used, with the HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

Currie CJ, et al. Lancet 2010;375:481-489

Table 9—*Correlation of A1C with average glucose*

A1C (%)	Mean plasma glucose mg/dl	Mean plasma glucose mmol/l
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92 (49). A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dl or mmol/l, is available at http://professional.diabetes.org/eAG.

A1c 6.5% ~ 140 mg/dl

A1c 7.5% ~ 168.5 mg/dl

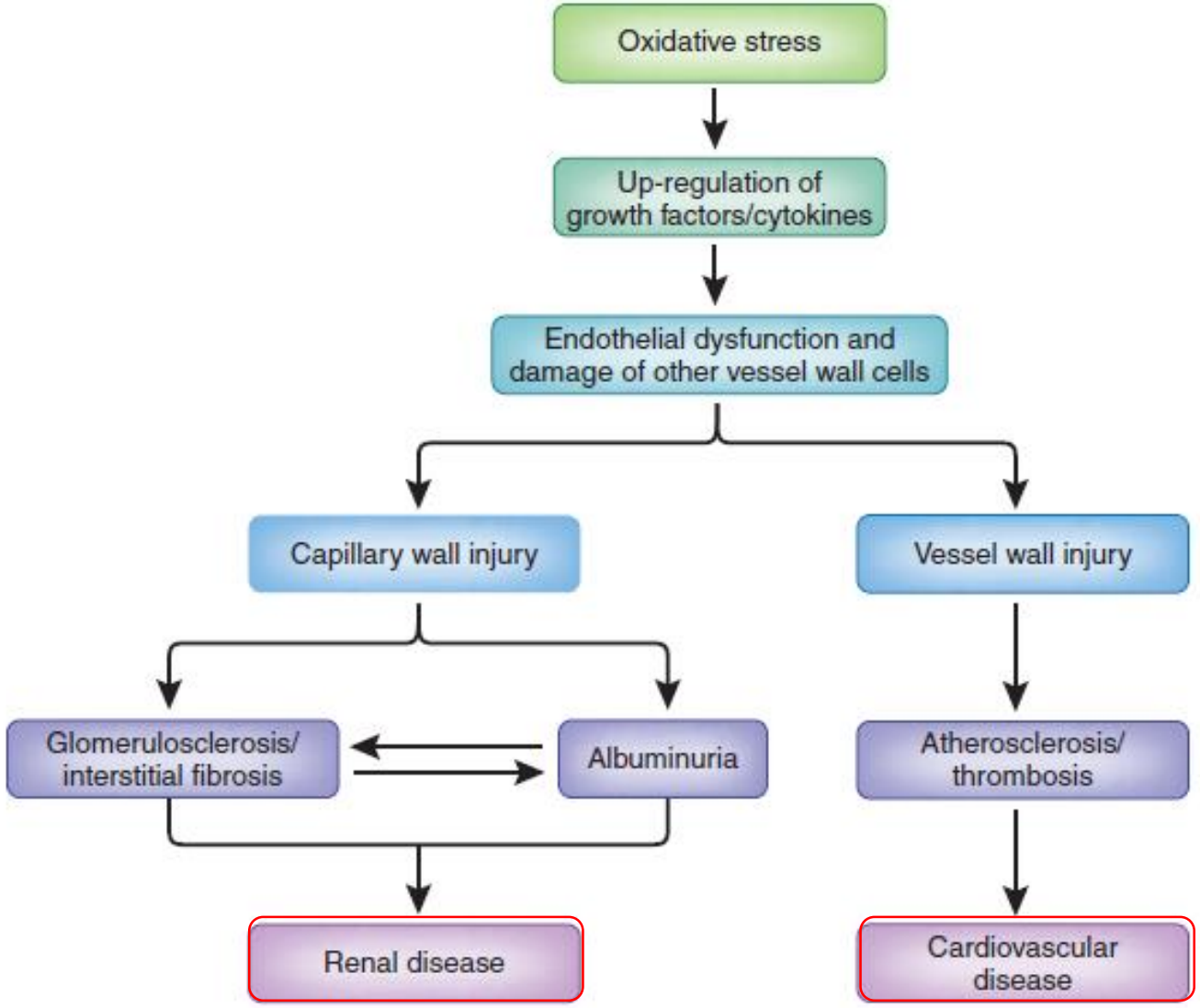
OHA: 6.9~9.4%
151.2 ~ 223.2 mg/dl

Insulin: 7.5~8.9%
168.5 ~ 209.1 mg/dl

All: 7.5~8.1%
168.5 ~ 185.9 mg/dl

American Diabetes Association Diabetes Care 2010;33:S11

Putative pathophysiologic mechanism between Albuminuria and Cardiovascular Disease



Karalliedde k, et al. J Am Soc Nephrol 21: 2020–2027, 2010

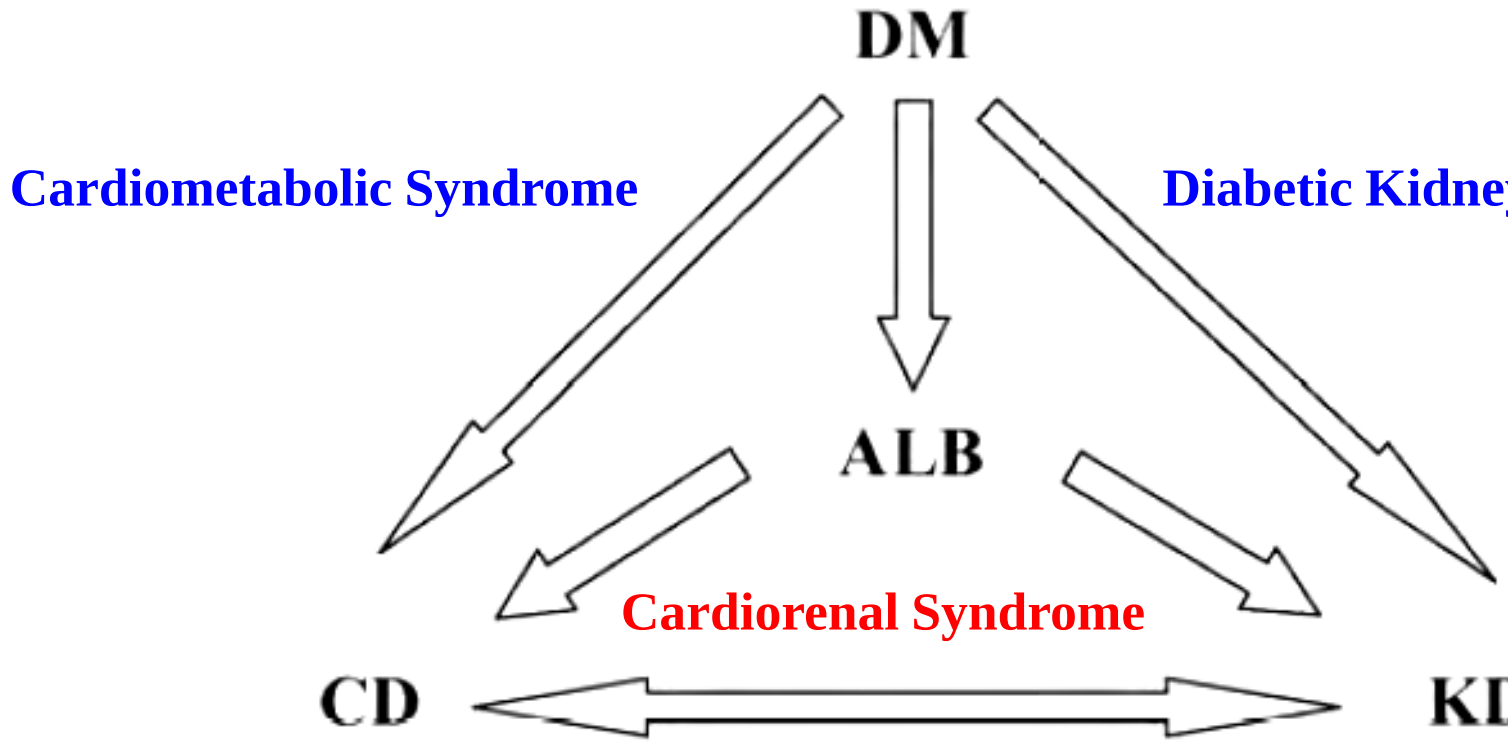


Fig. 1 – The dual effect of diabetes on both heart and kidney with the bi-directionality of signaling between the two organs (DM, diabetes mellitus; ALB, albuminuria; CD, cardiac dysfunction; KD, kidney dysfunction).

Ronco C. Contrib Nephrol. 2010;164:33–38

Cardio-Renal Syndrome

- No commonly accepted definition
- Term originated from other areas (e.g. Hepato-renal Syndrome)
- General term used to define heart-kidney pathological Interactions
- It describes the initiation and progression of renal insufficiency (RI) secondary to heart failure(HF)
- It should include the damage/dysfunction induced to one of the two organs by an acute or chronic dysfunction of the other organ (Bi-directionality)

Adapted from Claudio Ronco, MD, Italy

Ronco C. Contrib Nephrol. 2010;164:33–38

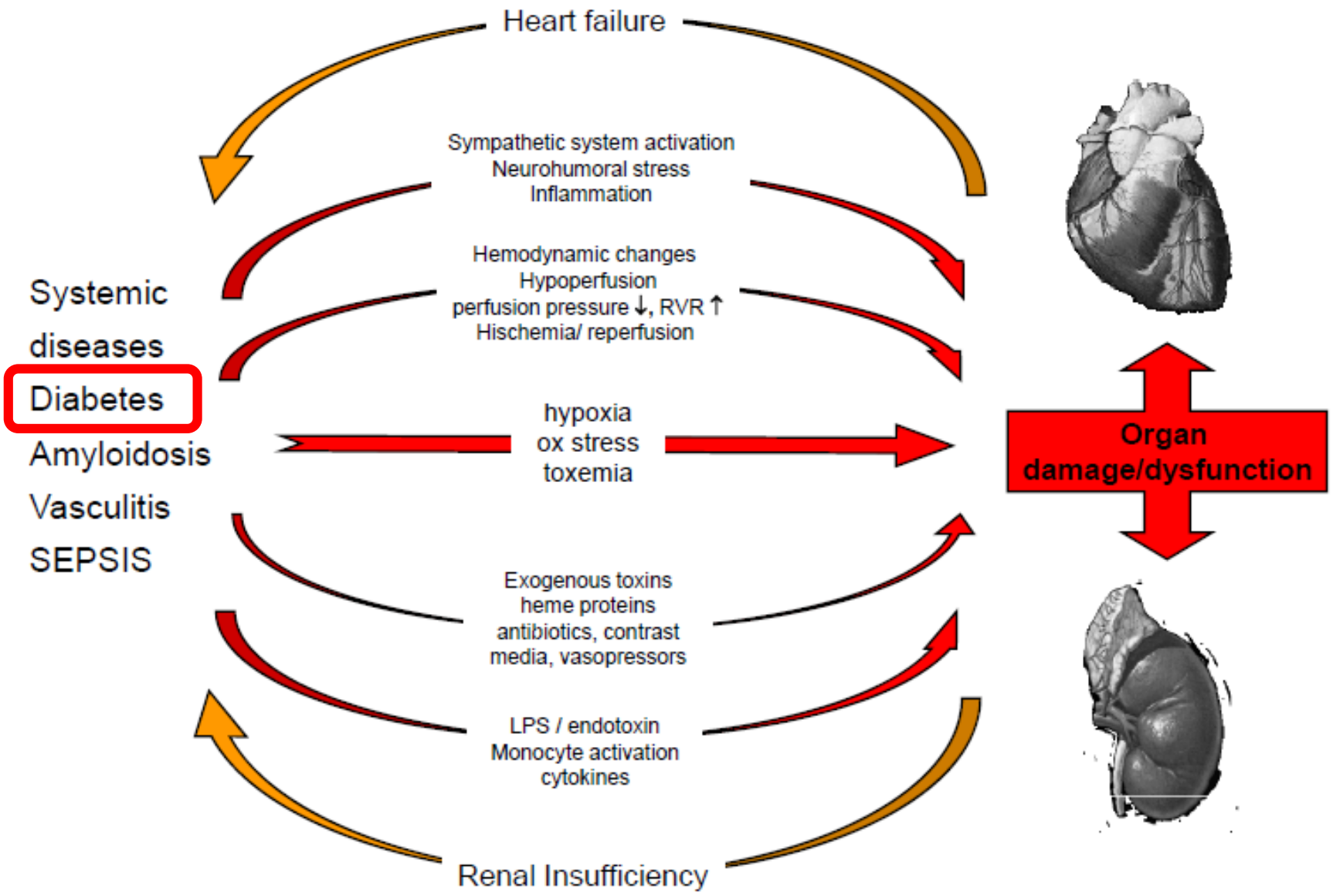
Cardiorenal syndrome classification

Table 1. Definition and classification of the CRS

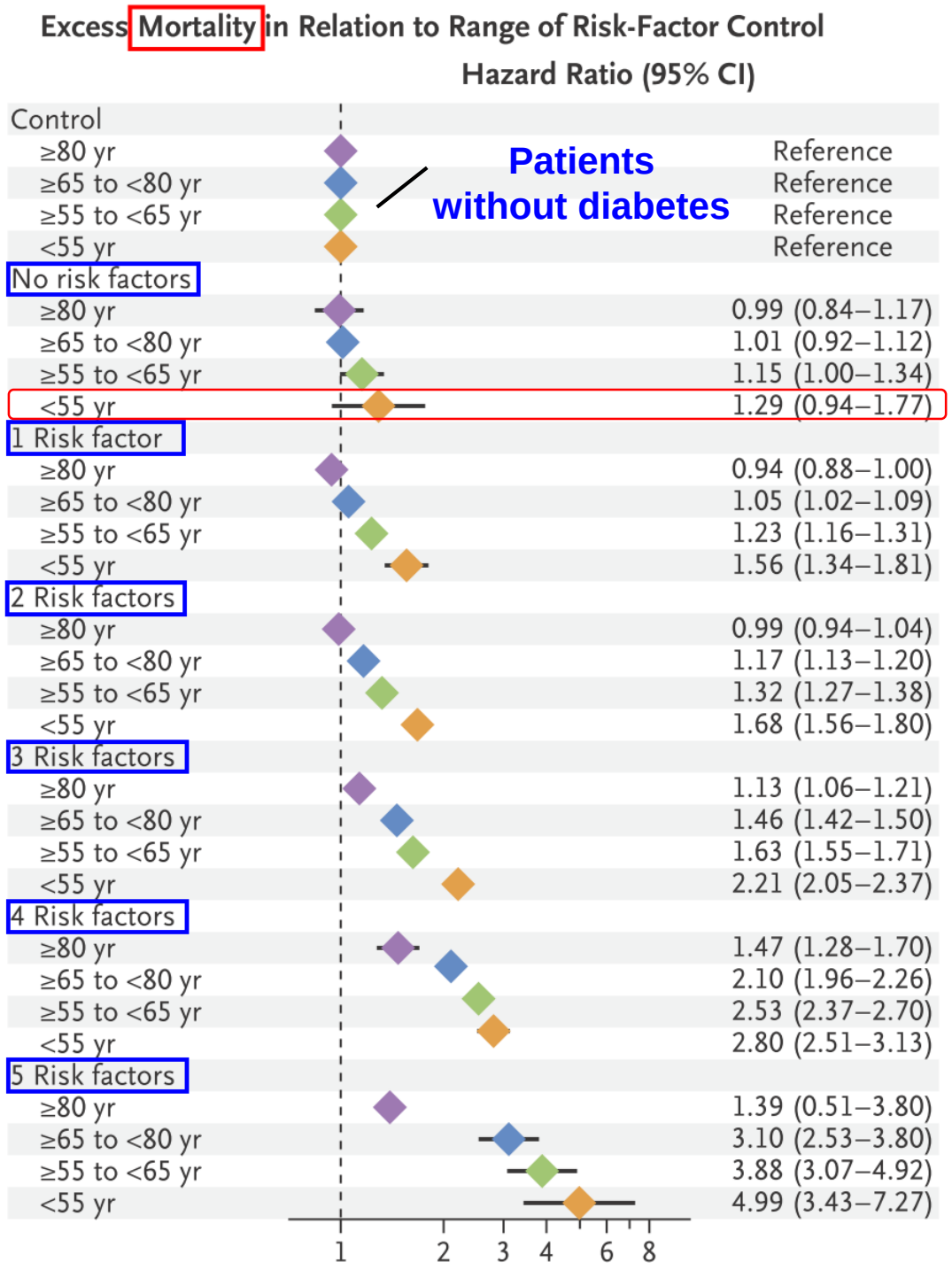
CRS general definition: Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other
Acute CRS (Type 1) Acute worsening of cardiac function leading to renal dysfunction
Chronic CRS (Type 2) Chronic abnormalities in cardiac function leading to renal dysfunction
Acute Renocardiac Syndrome (Type 3) Acute worsening of renal function causing cardiac dysfunction
Chronic Renocardiac Syndrome (Type 4) Chronic abnormalities in renal function leading to cardiac disease
Secondary CRS (Type 5) Systemic conditions causing simultaneous dysfunction of the heart and kidney

Ronco C. Contrib Nephrol. 2010;164:33–38

Cardiorenal syndrome Type 5



Ronco C, et al. J Am Coll Cardiol 2008;52:1527–39

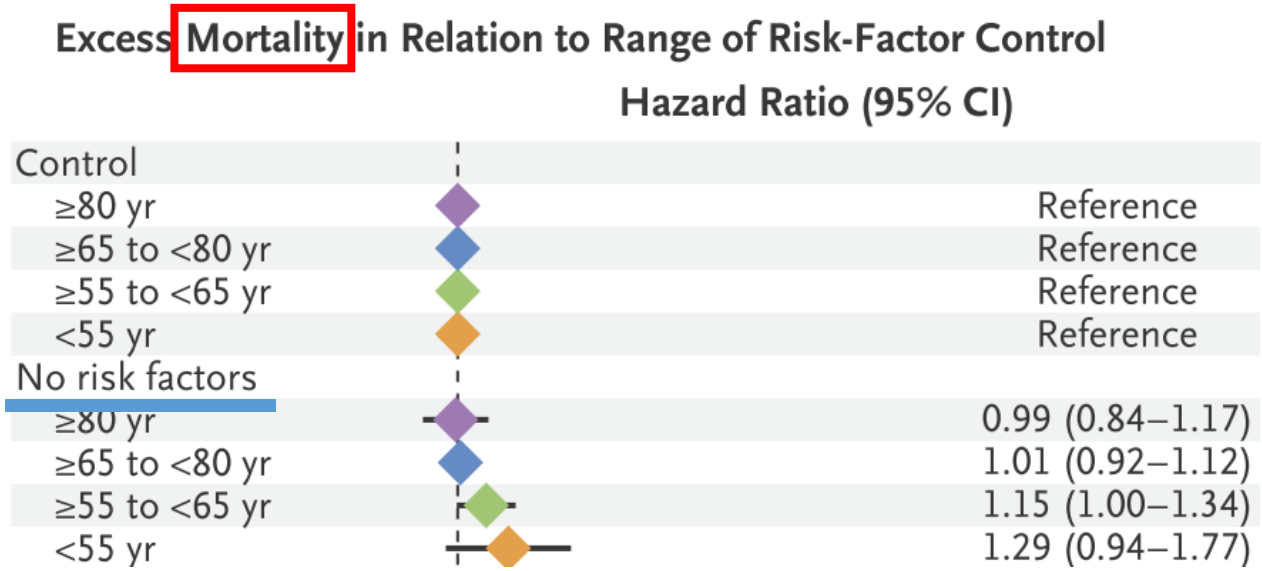


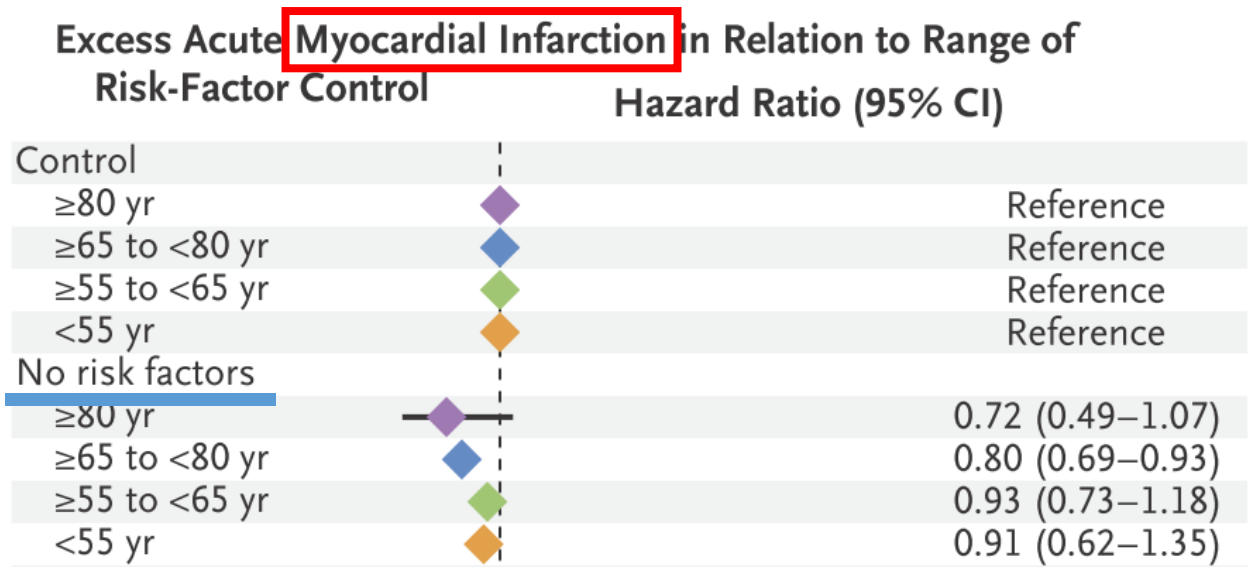
****Patients with more risk factors within target ranges are associated with lower risk of mortality****

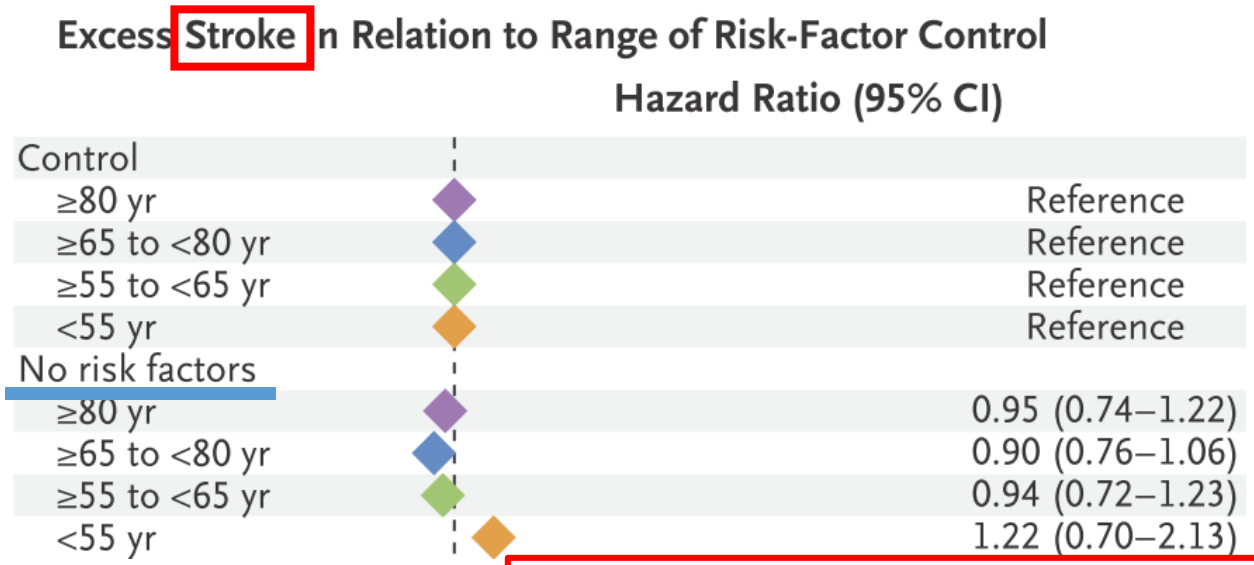
Five risk factors:

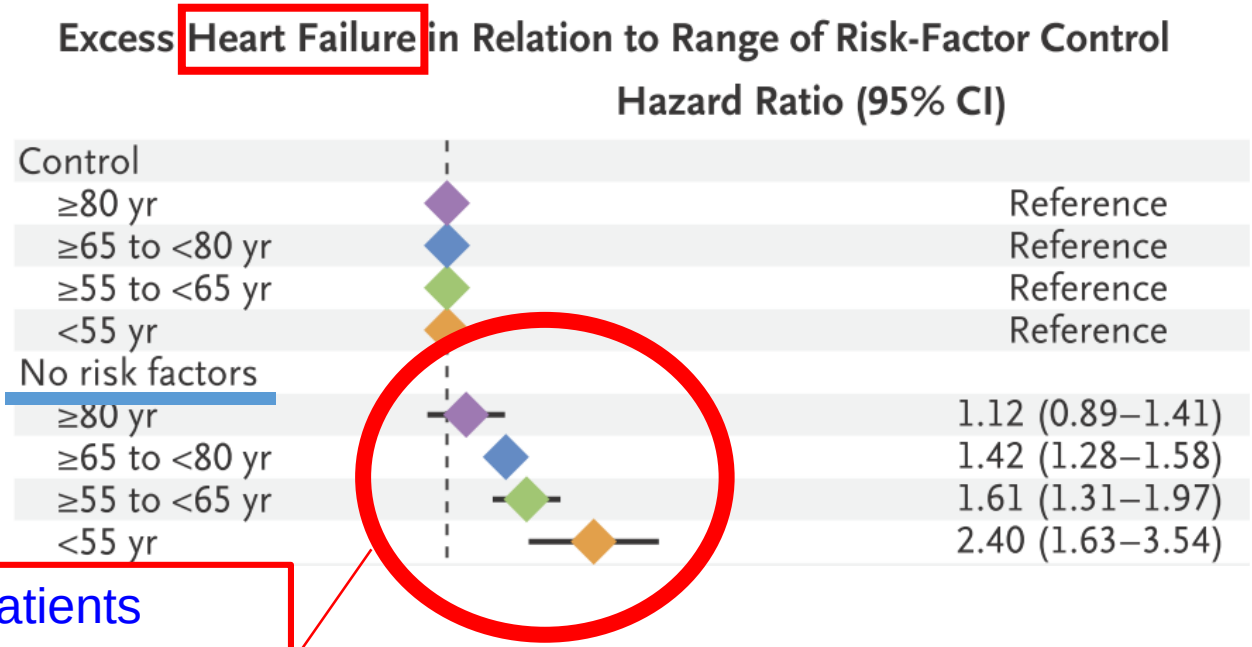
1. Elevated A1c (≥7.0%)
2. Elevated LDL (≥2.5 mmol; 97 mg/dl)
3. Elevated BP (≥140/80 mm Hg)
4. Albuminuria (presence of microalbuminuria or macroalbuminuria)
5. Smoking (current smoker)

Rawshani A et al. N Engl J Med. 2018 Aug 16;379(7):633-644.









Heart Failure revealed higher in patients with 5 risk factors but controlled within target ranges, particularly in younger patients.

Rawshani A et al. N Engl J Med. 2018 Aug 16;379(7):633-644.

Epidemiology and Outcomes in Combined Cardiorenal Disease: The Scope of the Problem

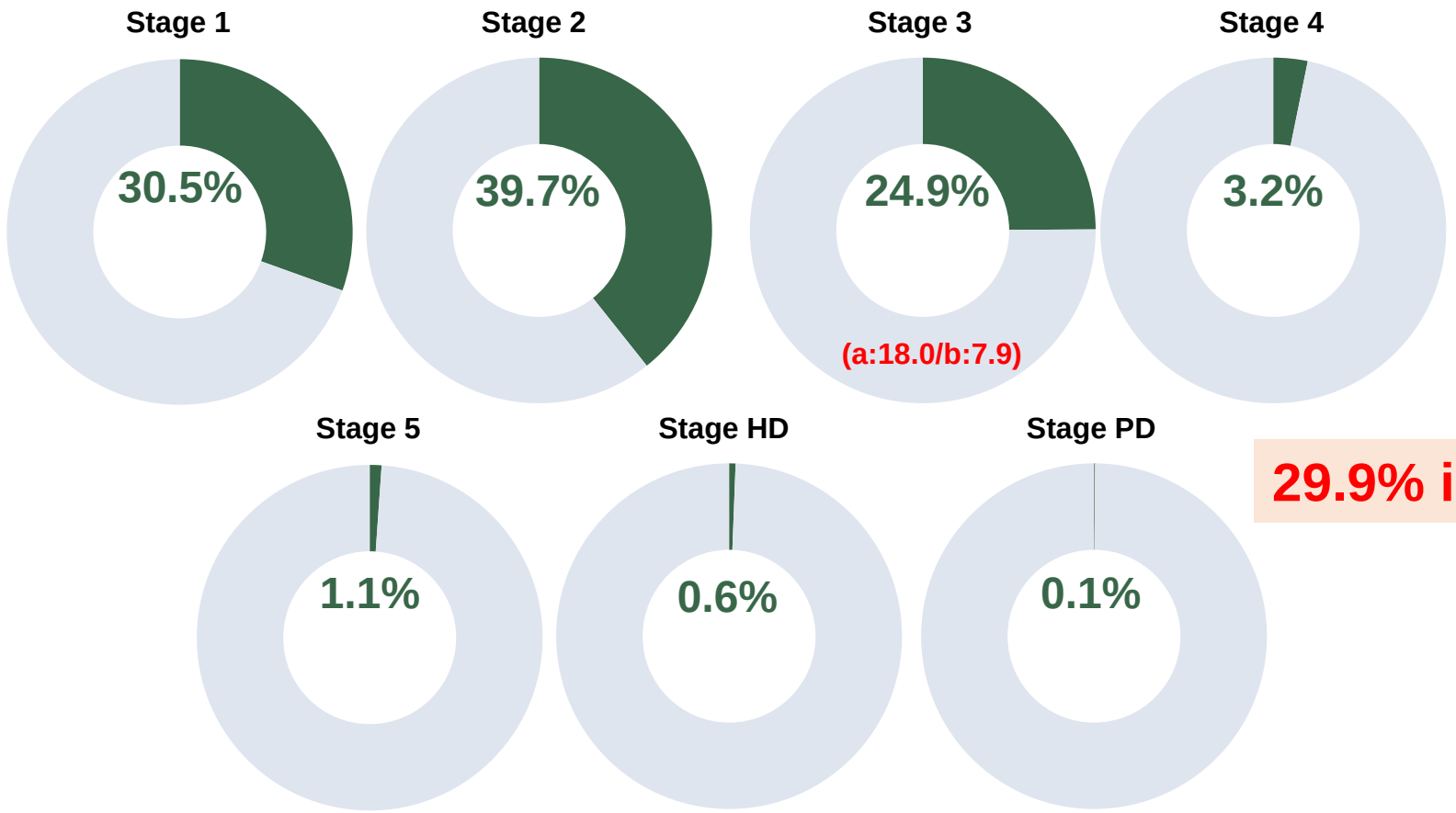
Prevalence of Renal Disease in Patients With HF

In the Acute Decompensated Heart Failure National Registry (ADHERE) 1) ≥105 000 individuals admitted for acute decompensated HF, 30% had a history of renal insufficiency, 21% had serum creatinine concentrations >2.0 mg/dL, and 9% had creatinine concentrations >3.0 mg/dL.[3] McAlister et al[4] found th 2) only 17% of 754 outpatients with HF had creatinine clearances >90 mL/min. In their cohort, 39% with New York Heart Association (NYHA) class IV symptoms and 31% with NYHA class III symptoms had creatinine clearance <30 mL/min. These numbers are striking when one considers the complexity of treating volume overload in those with coexistent renal disease and that there are >1 million hospital admissions for decompensated HF in the United States annually.

Circulation. 2010;121:2592-2600

The 4th Quality Survey (2018) of Diabetes Control by TADE in Taiwan Diabetes Health Promotion Institute

併發症－CKD (N=5,855)



29.9% in Stage 3-5

2020; In writing and submission

NADKD (normoalbuminuric diabetic kidney disease)

- 大型世代研究指出eGFR ＜ 60 mL/min/1.73m2 的第2 型糖尿病病人中，有高達50 % 以上之病人UACR 是正常，被稱為正常白蛋白尿糖尿病腎臟疾病（normoalbuminuric diabetic kidney disease，NADKD)。

- 隨著糖尿病盛行率的增加，NADKD 病人也越來越多，國外及我國研究均指出NADKD 病人之心血管疾病與死亡率較正常GFR 且正常UACR 病人顯著增加；但較白蛋白尿且GFR ＜ 60 mL/min/1.73m2 之病人為低。eGFR 小於60 mL/min/1.73m2 且併有白蛋白尿之糖尿病病人還是比NADKD 病人容易進入ESRD 或腎臟功能惡化。

1. Penno G, Solini A, Orsi E, et al. Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study. Diabetologia 2018;
2. Chen C, Wang C, Hu C, et al. Normoalbuminuric diabetic kidney disease. Frontiers of medicine. 2017;11:310-318
3. Shimizu M, Furuichi K, Yokoyama H, et al. Kidney lesions in diabetic patients with normoalbuminuric renal insufficiency. Clinical and experimental nephrology 2014;18:305-312

2019 台灣糖尿病腎臟疾病臨床照護指引

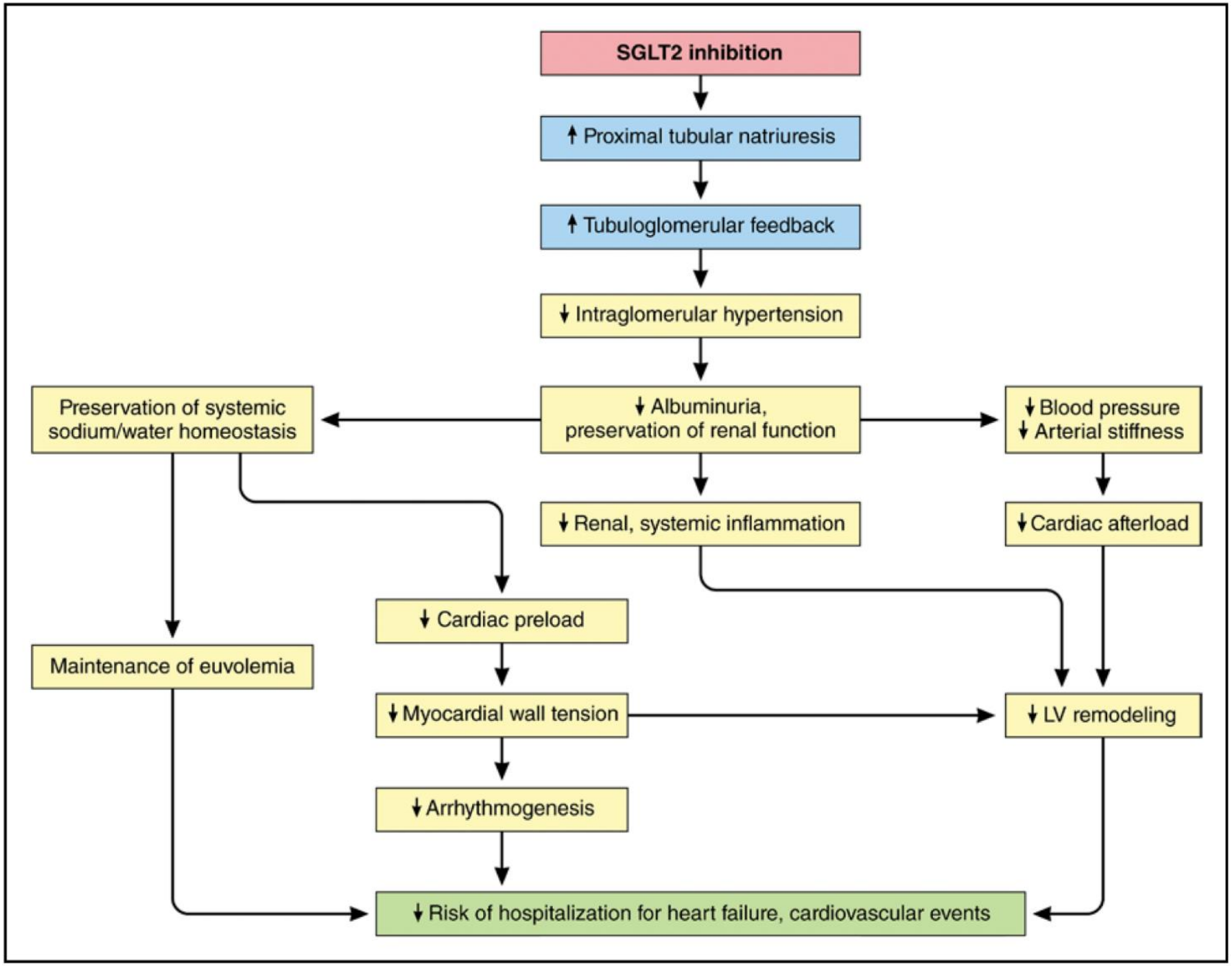


Figure 7. The renal-cardio hypothesis for cardiovascular protection with SGLT2 inhibition: a nephrocentric perspective.
LV indicates left ventricular; and SGLT2, sodium-glucose cotransporter-2.

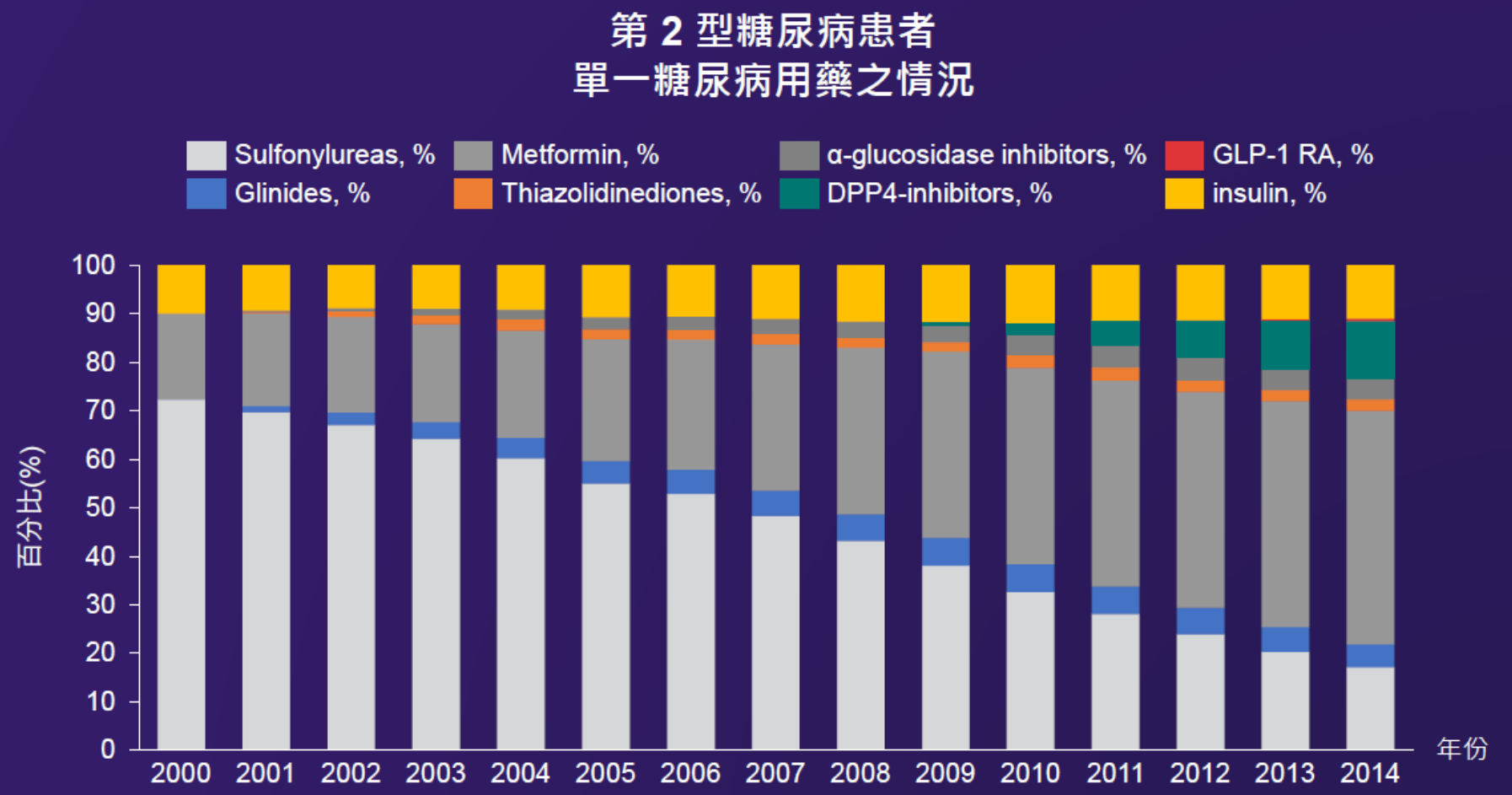
Circulation

Cherney DZ et al. Circulation. 2016 Sep 6;134(10):752-72.

Outline

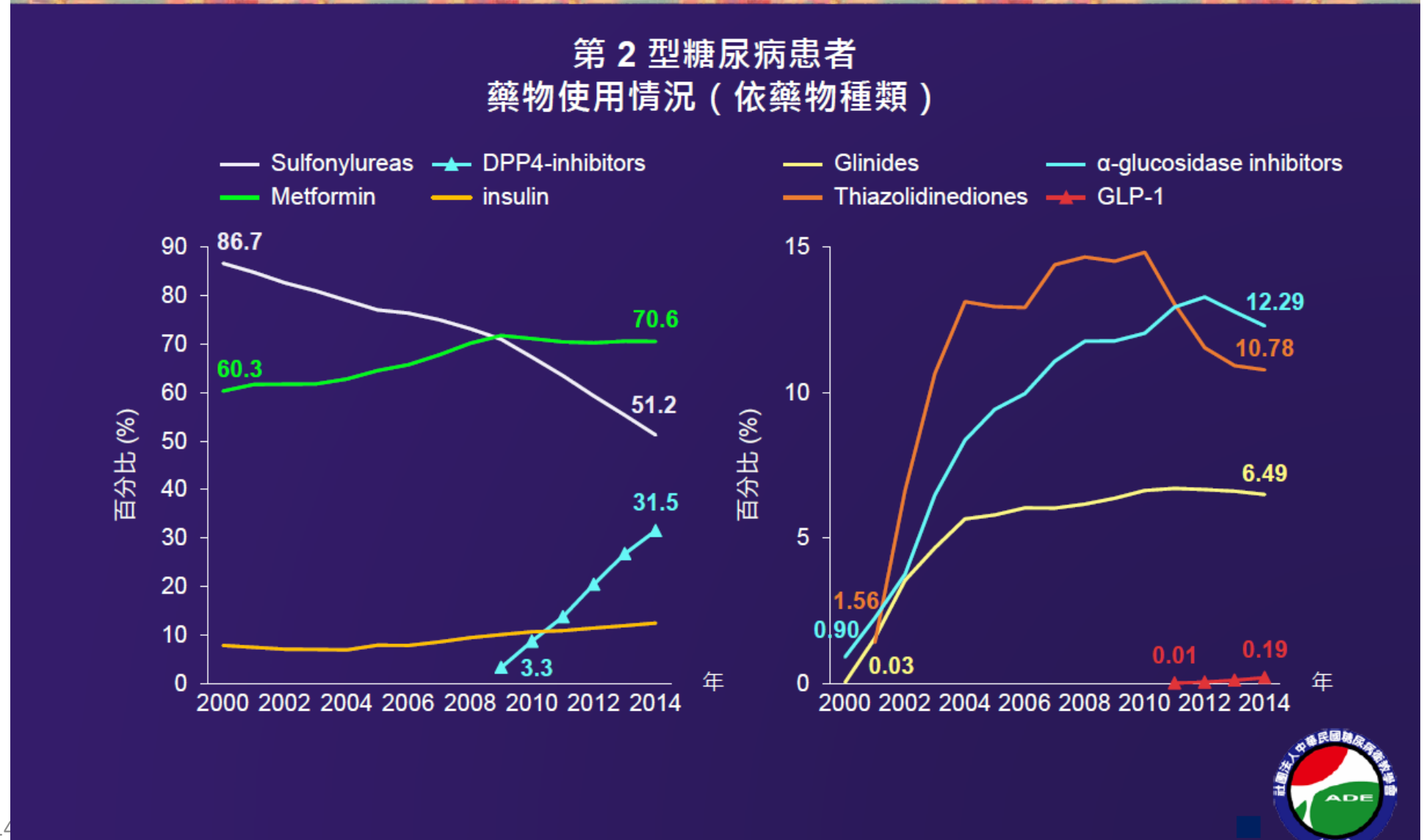
- Deterioration of renal & cardio function in diabetic patients
- New strategy for diabetes management with renal & cardiac complication consideration
- Conclusion

單一使用 Metformin 或 DPP-4 Inhibitors 治療的趨勢增加



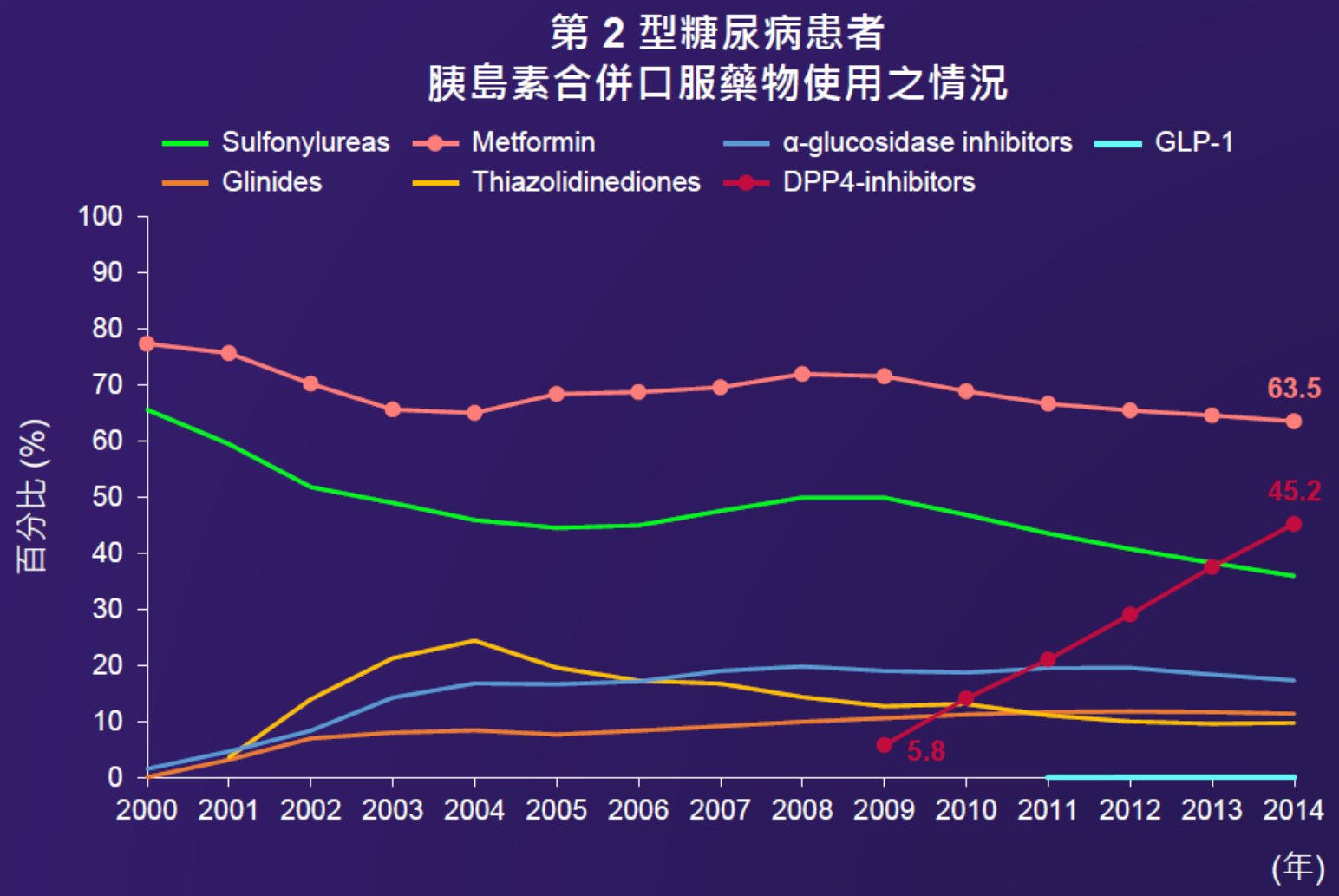
Journal of the Formosan Medical Association (2019) 118, S74eS82

DPP-4 inhibitors 與 GLP-1 agonists 的使用量遞增



Journal of the Formosan Medical Association (2019) 118, S74eS82

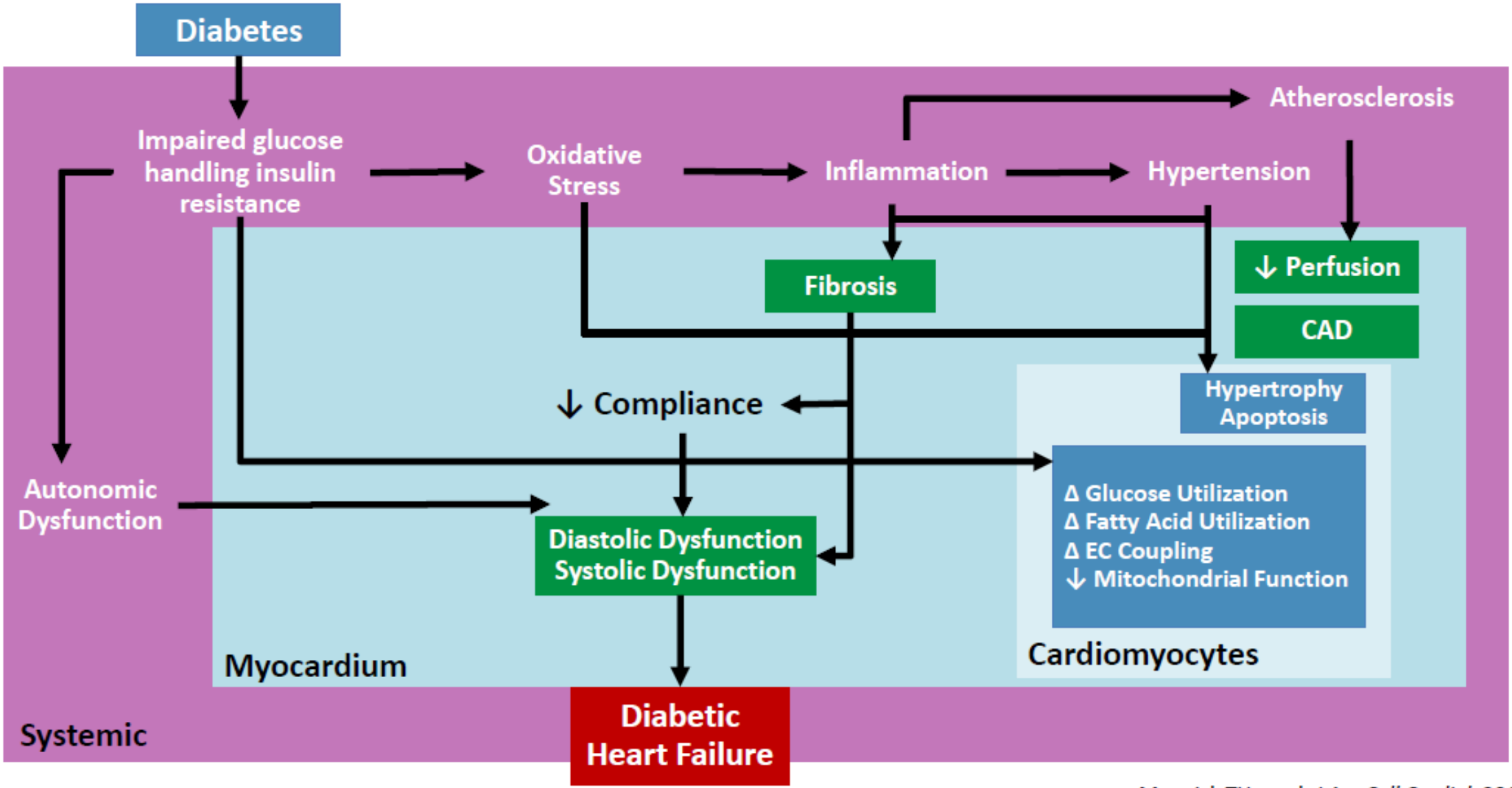
胰島素併用 Metformin 比例仍為最高，DPP-4 inhibitors 則迅速增加



Journal of the Formosan Medical Association (2019) 118, S74eS82

Diabetic Heart Failure

Interactions of Systemic, Myocardial, and Cellular Manifestations



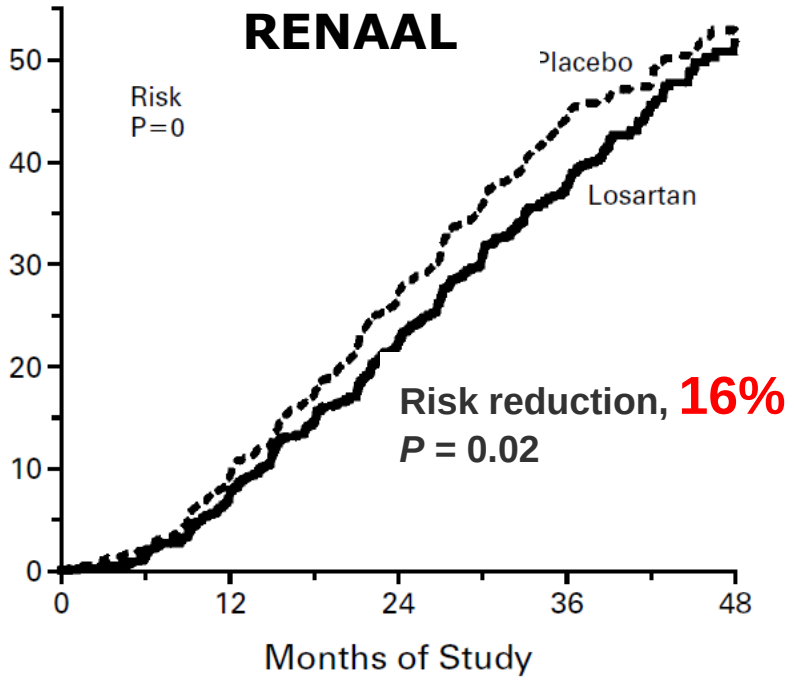
Marwick TH, et al. *J Am Coll Cardiol.* 2018.

CKD is classified based on: · Cause (C) · GFR (G) · Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m²) Description and range	G1	Normal or high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

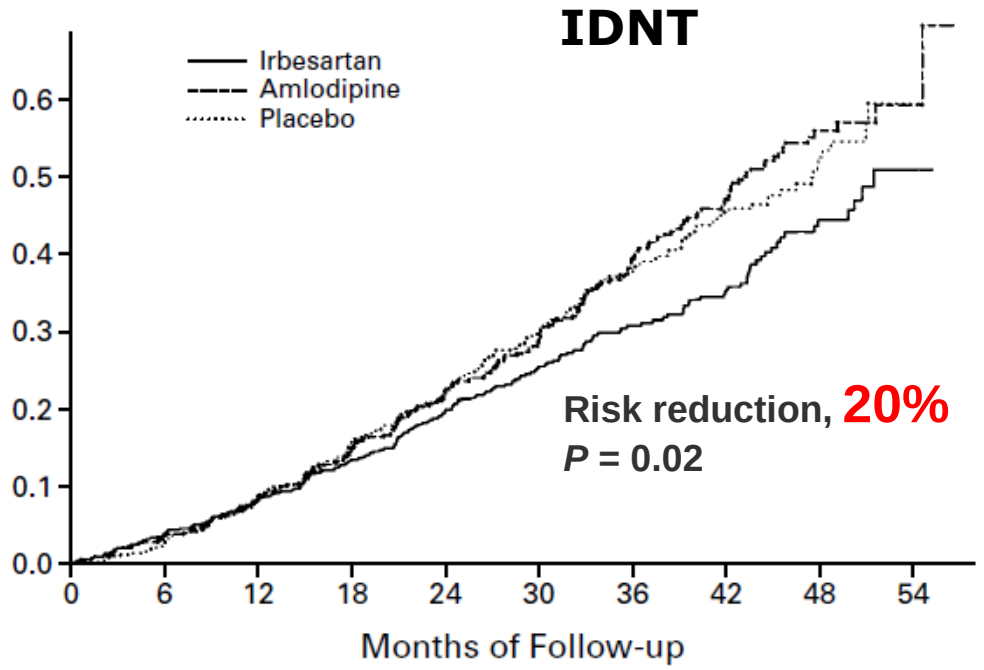
Figure 11.1—Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to nephrology according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state as well as the likelihood of impacting a change in management for any individual patient must be taken into account. "Refer" indicates that nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. Reprinted with permission from Vassalotti et al. (188).

Figure 11.1—Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to nephrology according to glomerular filtration rate (GFR) and albuminuria.

Composite Endpoints:
Doubling of serum creatinine, ESKD, or Death



1513 patients with **T2D and nephropathy** were randomized to take losartan (50 to 100 mg once daily) vs. placebo with mean follow-up 3.4 years



1715 **hypertensive patients with nephropathy due to type 2 diabetes** to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo with mean follow-up 2.6 years

The NEW ENGLAND JOURNAL of MEDICINE

ARB: angiotensin receptor blocker, ESKD: end-stage kidney disease

1. N Engl J Med. 2001;345(12):861-869. 2. N Eng J Med. 2001;345(12):851-860.

Renoprotective effects in various anti-diabetic Medications

Table 2 | Possible cardiorenal mechanistic interactions between SGLT2 inhibitors and DPP4 inhibitors

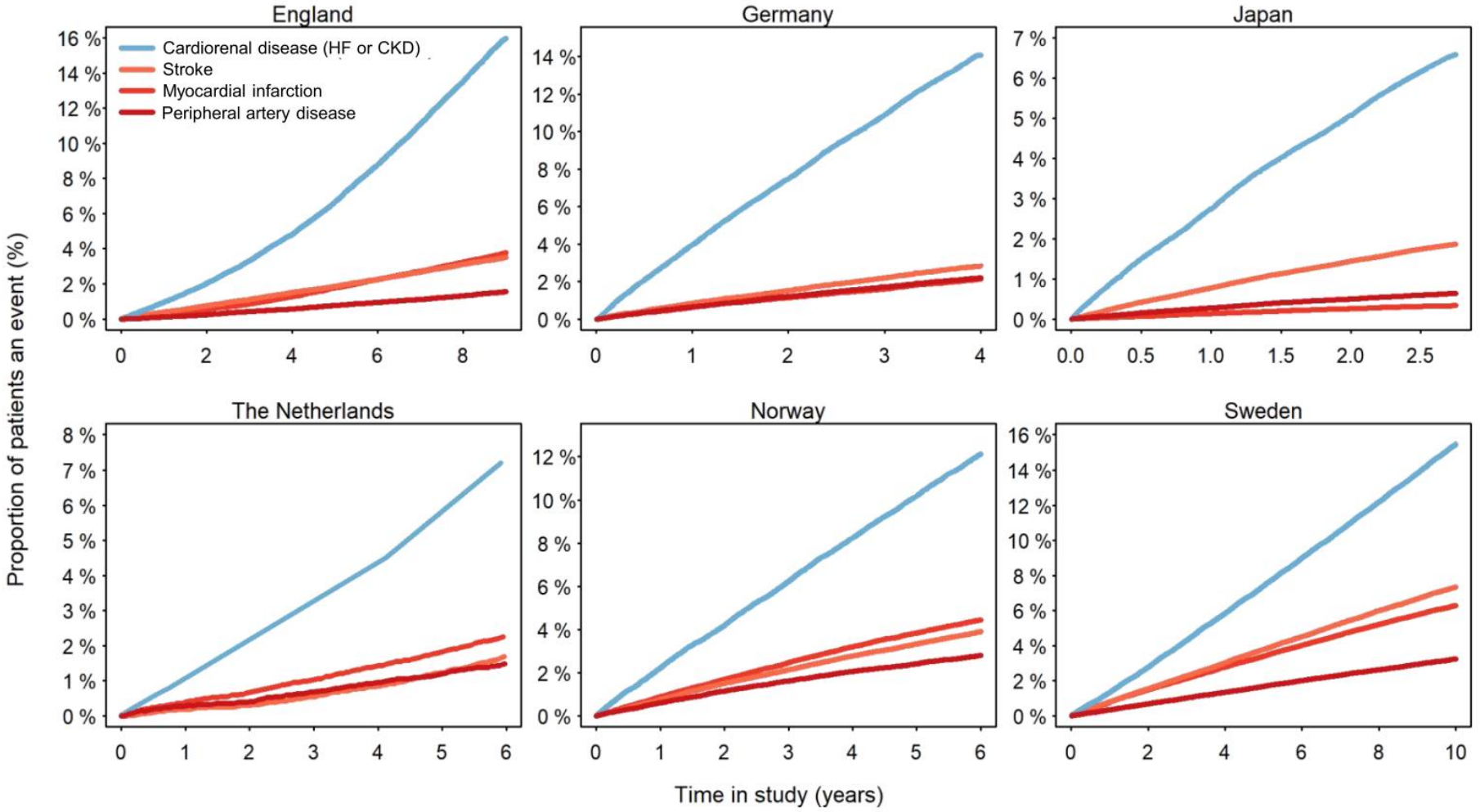
	SGLT2 inhibition	DPP4 inhibition	GLP1-RA	Anticipated impact of combination SGLT2 inhibitor-DPP4 inhibitor therapy	Anticipated impact of Combination SGLT2 inhibitor-GLP1 RA therapy
Renal parameters					
Renal hemodynamics	↓Glomerular hypertension	↔	↔	↓Glomerular hypertension	↓Glomerular hypertension
Albuminuria	↓30%–50%	↓10%–20%	↓20%–30%	↓↓	↓↓
Inflammation	↓MCP-1, IL-6, NF-κB, ROS	↓Inflammation, ROS	↓Inflammation, ROS	↓↓	↓↓
Natriuresis	↑Proximal natriuresis (FENa+)	↑Distal natriuresis (FENa+)	↑Proximal natriuresis (FENa+)	↑↑	↑↑
Blood pressure	↓4–6 mm Hg	↔	↔/↓	↓	↓↓
Cardiovascular events					
Ischemic events	↔/↓	↔/↑	↓	↔/↓	↓/↓↓
Heart failure	↓/↓	↔/↑	↔	↓/↓	↓/↓↓
Metabolic parameters					
HbA1c[a]	↓	↓	↓	↓↓	↓↓
Weight	↓	↔	↓	↓	↓↓

DPP-4, dipeptidyl-peptidase-4; FENa+, fractional excretion of sodium; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor κB; ROS, reactive oxygen species; SGLT2, sodium glucose cotransport-2.

[a]The addition of SGLT2 inhibition to DPP4 inhibition has been shown to reduce HbA1c.[140]

Heerspink, etal. Kidney International (2018) 94, 26–39

6個國家~77萬未有心腎併發症的T2D病患追蹤4.5年結果: CKD(36%)、HF(24%)為最常見的第一個共病症



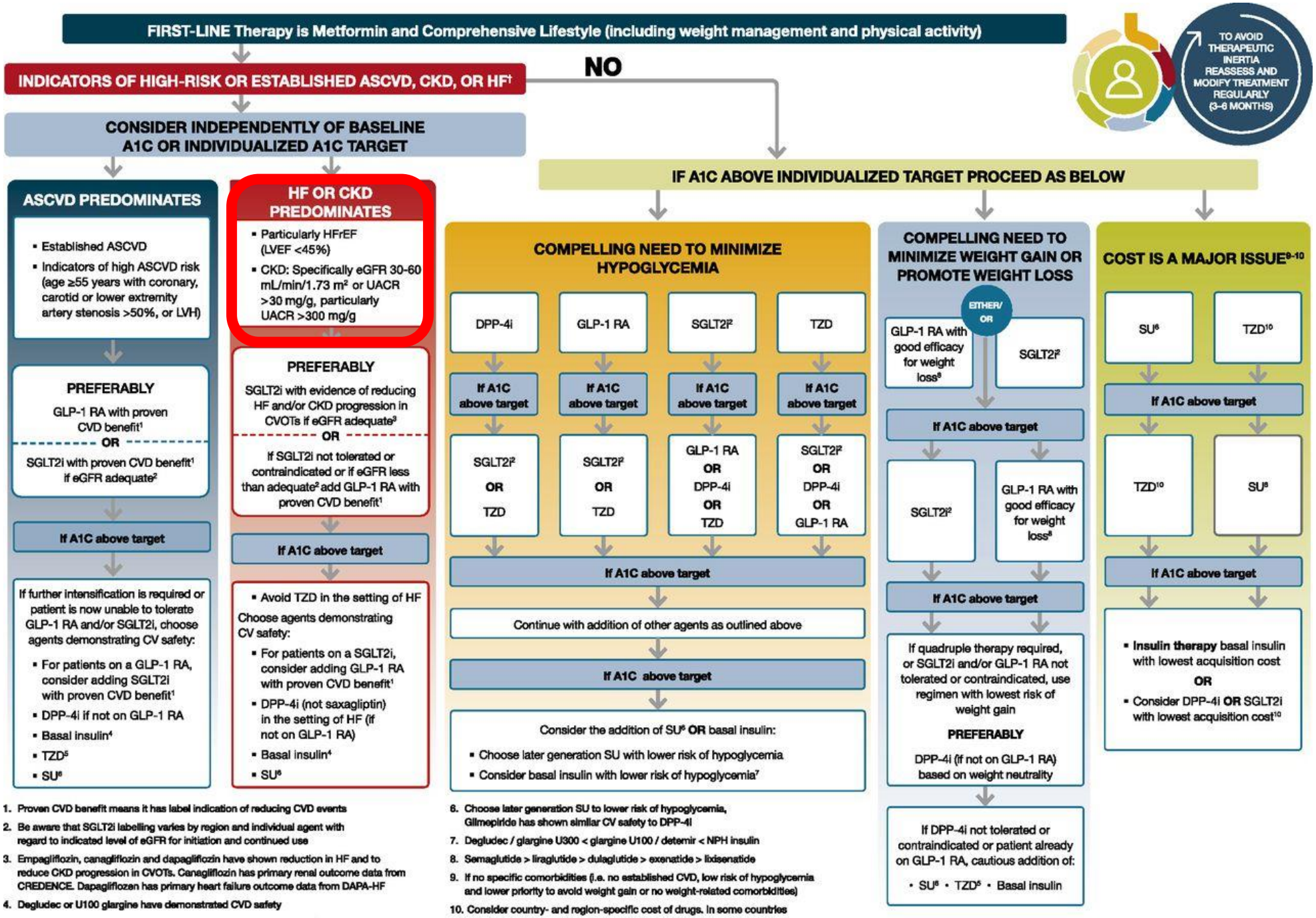
137,081 (18%) developed a first CVRD manifestation, represented by **CKD** (**36%**), **HF** (**24%**), stroke (16%), MI (14%) and PAD (10%).

CVRD: cardiovascular- and renal disease; Diabetes Obes Metab. 2020 May 3. doi: 10.1111/dom.14074.

Domains of Cardiorenal Prevention

- Neurohormonal
- Cardiac and renal hemodynamic
- Na and volume regulation (narrow optimal levels)
- Organ ischemia
- Inflammatory
- Oxidative injury
- Maladaptions of other systems
  - Hematological
  - Hepatic
  - Immune
  - Bone and mineral disorder

Ronco C, et al. J Am Coll Cardiol 2008;52:1527–39)



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Glucose-lowering Medication in Type 2 Diabetes: Overall Approach

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020*. *Diabetes Care* 2020;43(Suppl. 1):S98-S110

SGLT2i: CVOT Summary

	EMPA-REG[1]	CANVAS program[2]	DECLARE[3]
Medication	Empa	Cana	Dapa
Study type	RCT	RCT	RCT
Patients	7,020	10,143	17,160
History of CVD, %	100	66	40.6
Follow-up, year	3.1	3.9 (6.0/2.5)	4.5
Primary MACE Outcome, %	**-14***	**-14***	-7
CV Death, %	**-38***	-13	-2
Nonfatal MI, %	-13	-15	-11
Nonfatal Stroke, %	24	-10	1
Primary HHF or CV death Outcome, %	-	-	**-17***
All-Cause Mortality, %	**-31***	-13	7
Hospitalization for HF, %	**-35***	**-33***	**-27***

*significant

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 2. Bruce Neal et al. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1611925.; 3. S.D. Wiviott SD, et al. . N Engl J Med. 2018 Nov 10.

SGLT-2i大型臨床試驗的系統性回顧及統合分析：>80%病患已使用ACEI or ARB

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

THE LANCET Diabetes & Endocrinology

DECLARE TIMI-58 | EMPA-REG OUTCOME® | CANVAS Program | CREDENCE

- A systematic review and meta-analysis of randomized, controlled, cardiovascular or kidney outcome trials of SGLT2 inhibitors that reported effects on major kidney outcomes
  - 4 studies and 38,723 participants: empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS Program and CREDENCE), and dapagliflozin (DECLARE-TIMI 58)

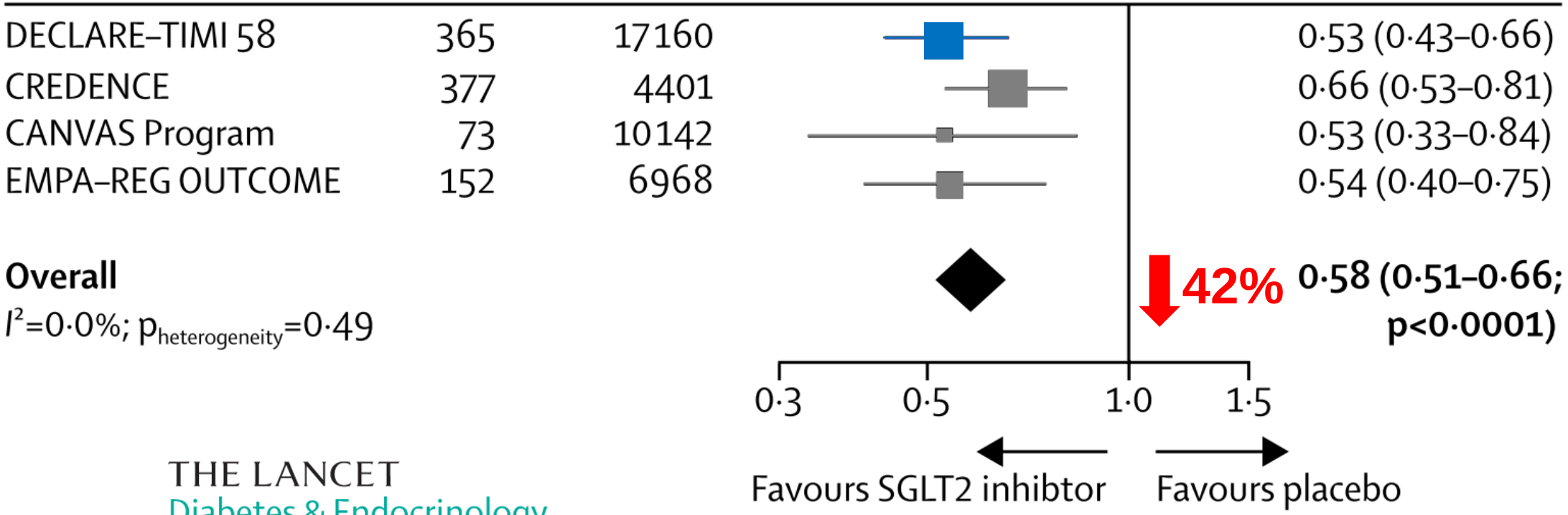
	DECLARE–TIMI 58	CREDENCE	CANVAS Program	EMPA-REG
Baseline use of RAS blockade	81.3%	99.9%	80.0%	80.7%
Hypertension	89.4%	96.8%	90.0%	95.2%

1. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854. 2. Diabetes Obes Metab. 2018 May;20(5):1102-1110. 3. N Engl J Med. 2019 Jun 13;380(24):2295-2306. 4. N Engl J Med. 2017 Aug 17;377(7):644-657. 5. N Engl J Med. 2015 Nov 26;373(22):2117-28.

SGLT-2i統合分析：在>80%已使用ACEI or ARB的糖尿病患，仍能下降42%腎臟事件風險

	DECLARE–TIMI 58	CREDENCE	CANVAS Program	EMPA-REG
Baseline use of RAS blockade	81.3%	99.9%	80.0%	80.7%

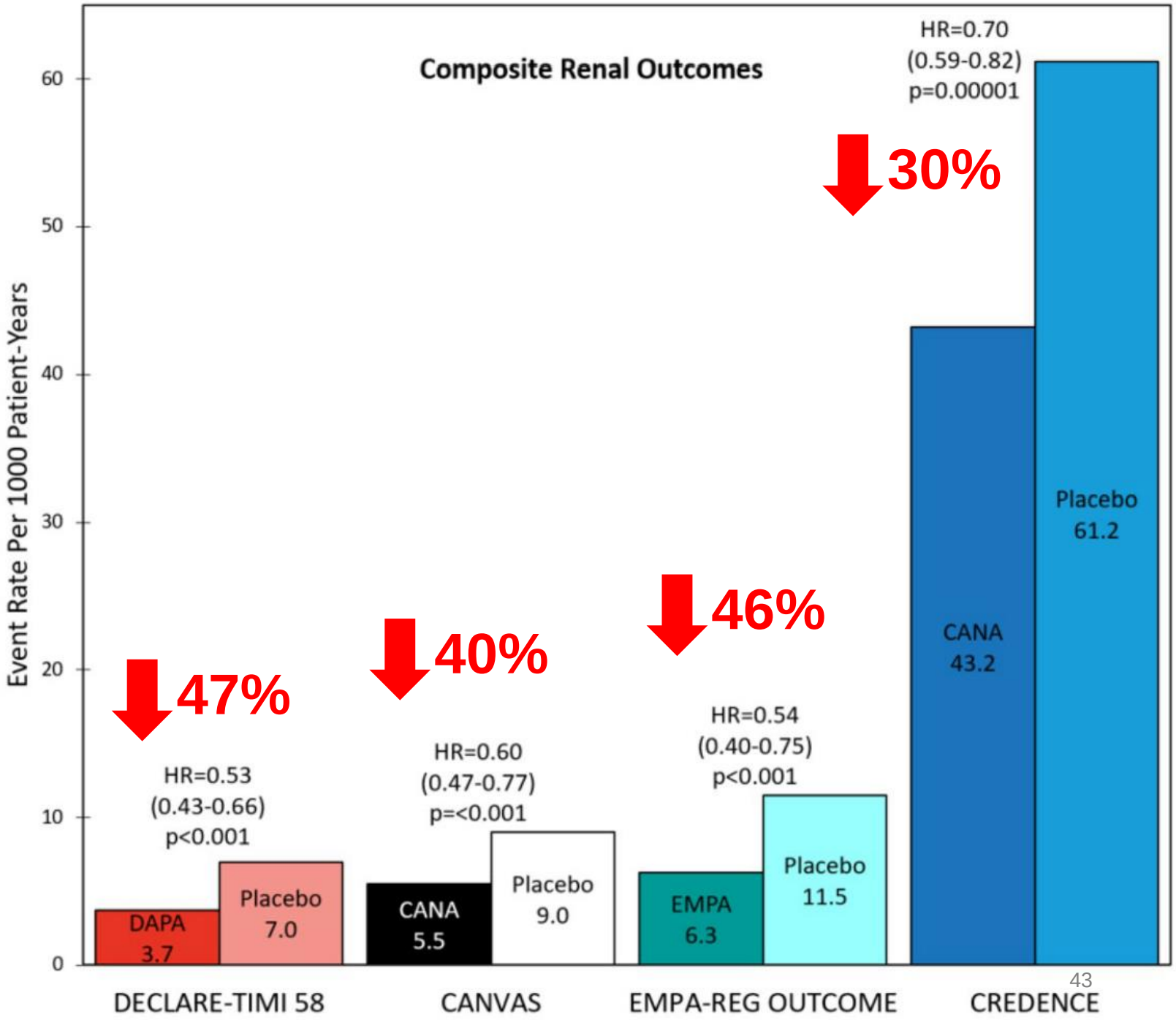
Substantial loss of kidney function, ESKD, or death due to kidney disease



THE LANCET
Diabetes & Endocrinology

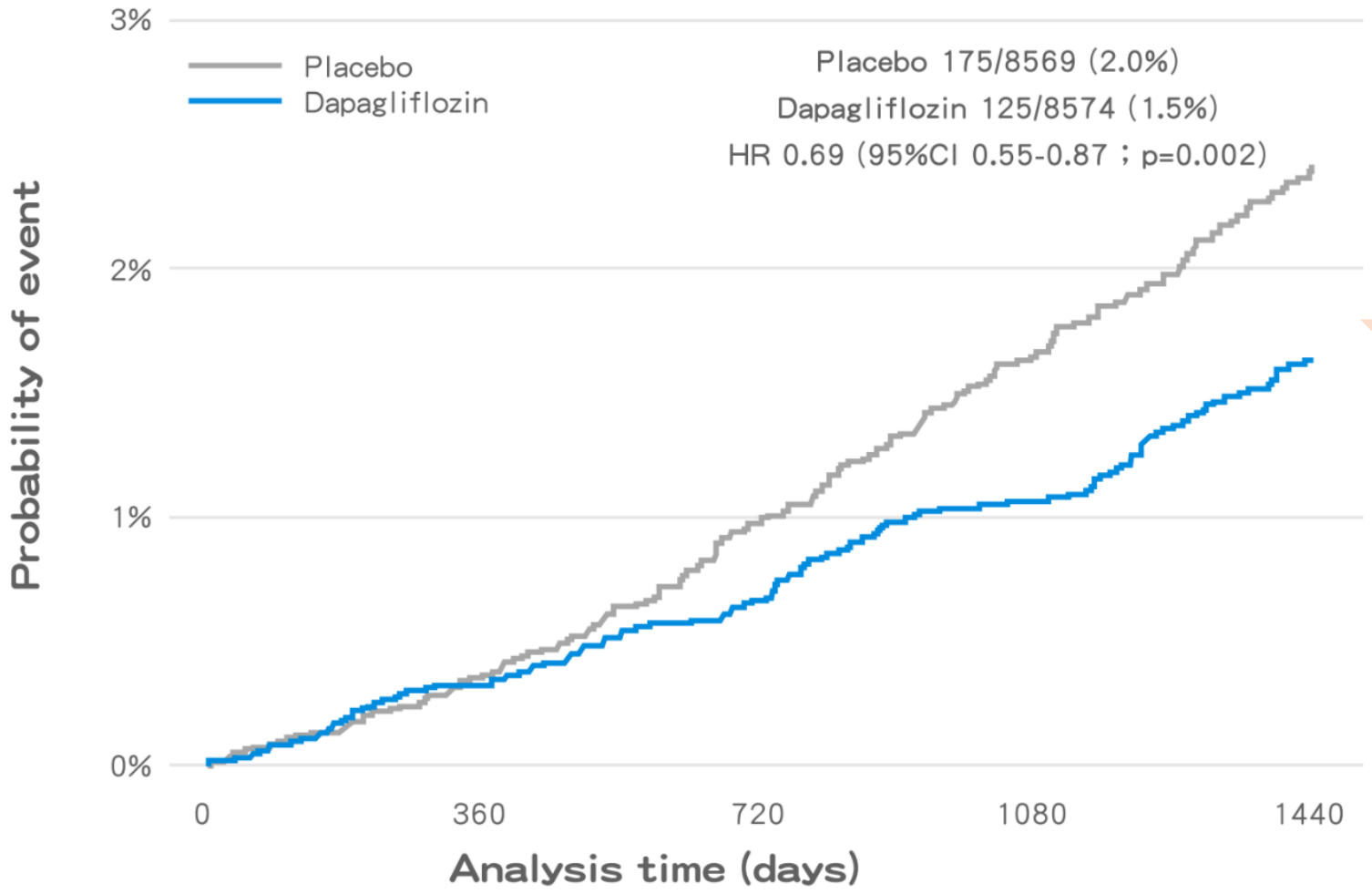
Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.

Composite renal outcome rates in SGLT-2i trials



Cardiovasc Diabetol. 2019 Aug 5;18(1):99.

DECLARE試驗：使用Dapagliflozin病患有較低AKI風險



31%

Number at risk:

Placebo	8569	7851	7175	6517	4135
Dapagliflozin	8574	7921	7355	6847	4417

Diabetes Obes Metab. 2020 Apr 2. doi: 10.1111/dom.14041.

CVD-REAL 3: kidney outcome of SGLT-2i in real-world practice

Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study

CVDREAL3
Kidney outcome

Hiddo J L Heerspink, Avraham Karasik, Marcus Thuresson, Cheli Melzer-Cohen, Gabriel Chodick, Kamlesh Khunti, John P H Wilding, Luis Alberto Garcia Rodriguez, Lucia Cea-Soriano, Shun Kohsaka, Antonio Nicolucci, Giuseppe Lucisano, Fang-Ju Lin, Chih-Yuan Wang, Eric Wittbrodt, Peter Fenici, Mikhail Kosiborod

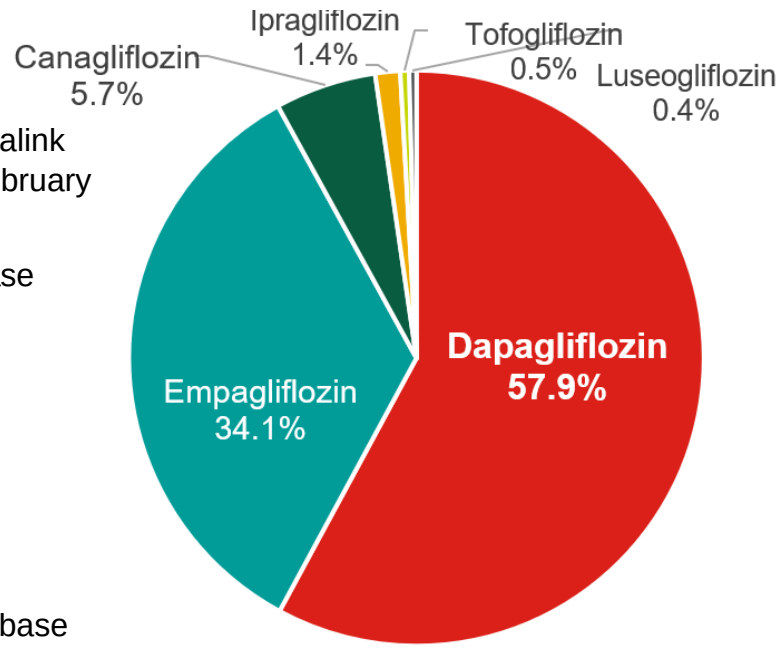
United Kingdom: Clinical Practice Research Datalink
First collection date: 2013 - February

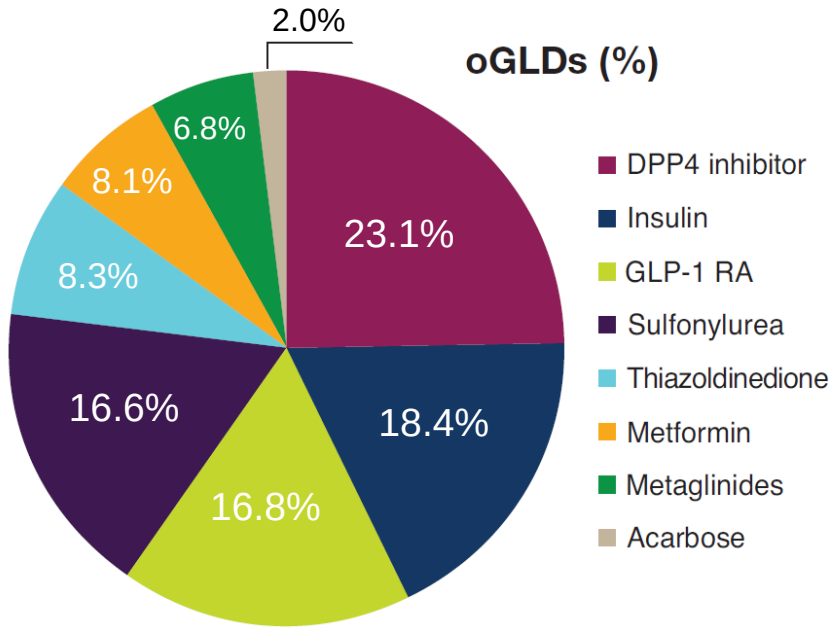
Japan: Medical Data Vision hospital-based database
First collection date: 2014 - April

Israel: Maccabi Healthcare Services database
First collection date: 2015 - April

Italy: Network of diabetes outpatient clinics
First collection date: 2015 - October

Taiwan: National Taiwan University Hospital Database
First collection date: 2016 - May





SGLT-2 inhibitors vs. oGLD (other glucose-lowering drugs)

Composition of total exposure time

Lancet Diabetes Endocrinol. Volume 8, Issue 1, January 2020, Pages 27-35

Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study

United Kingdom: Clinical Practice Research Datalink
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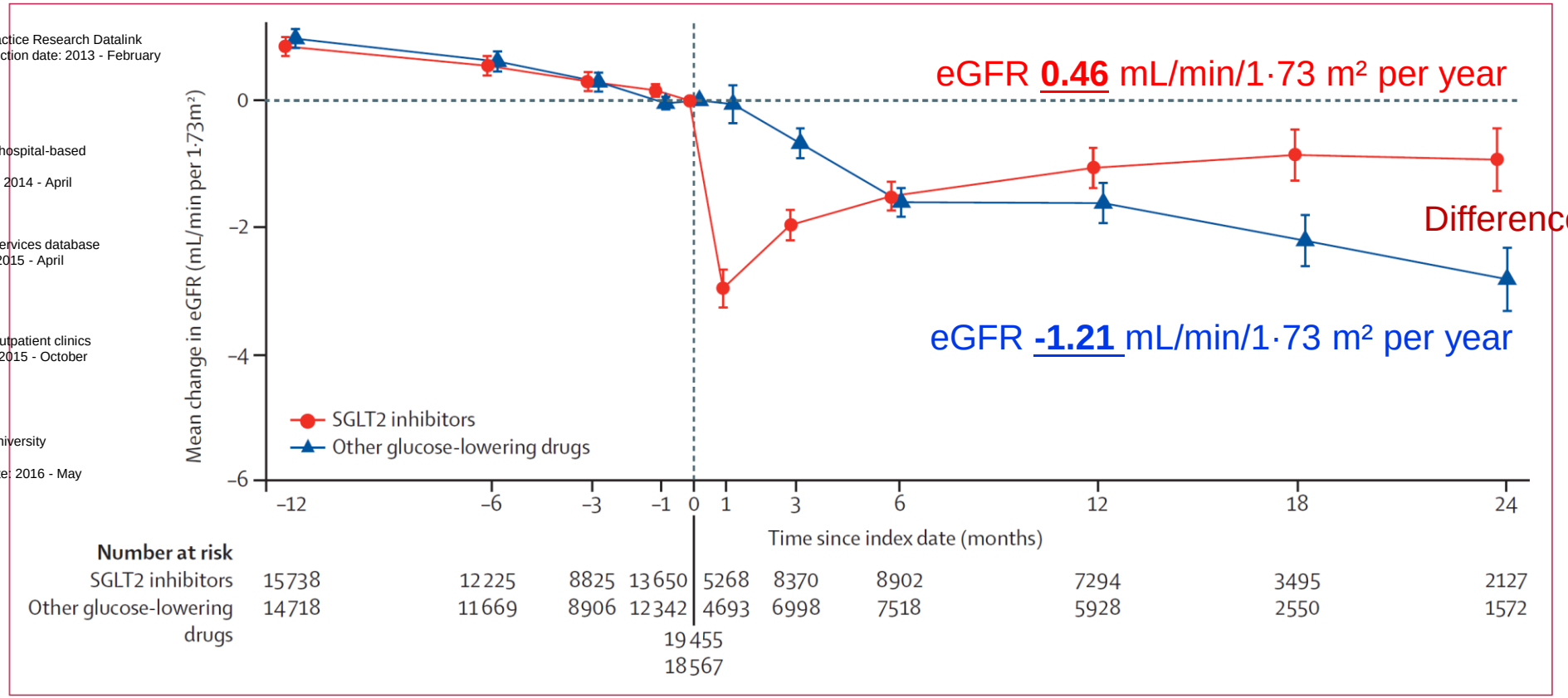
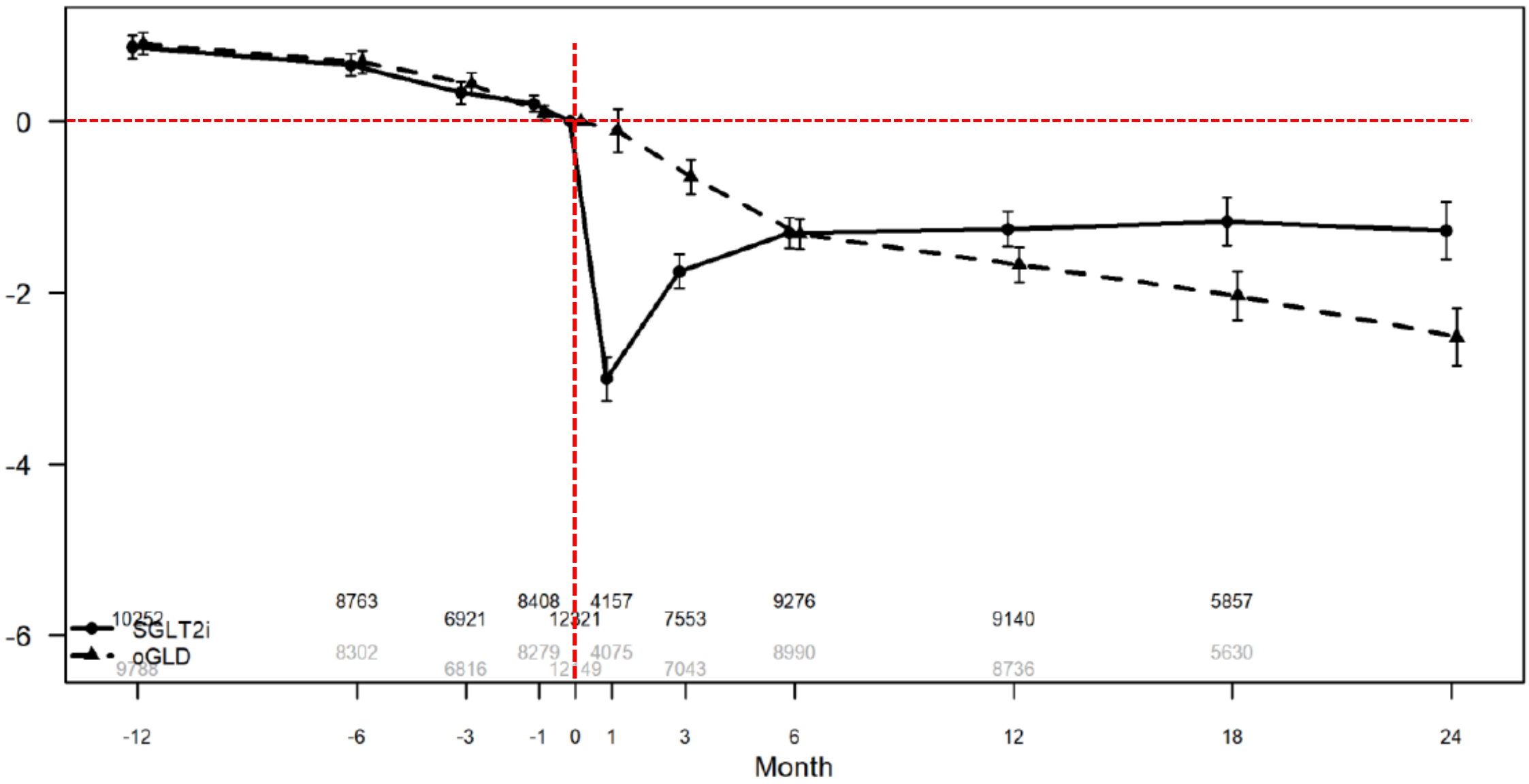
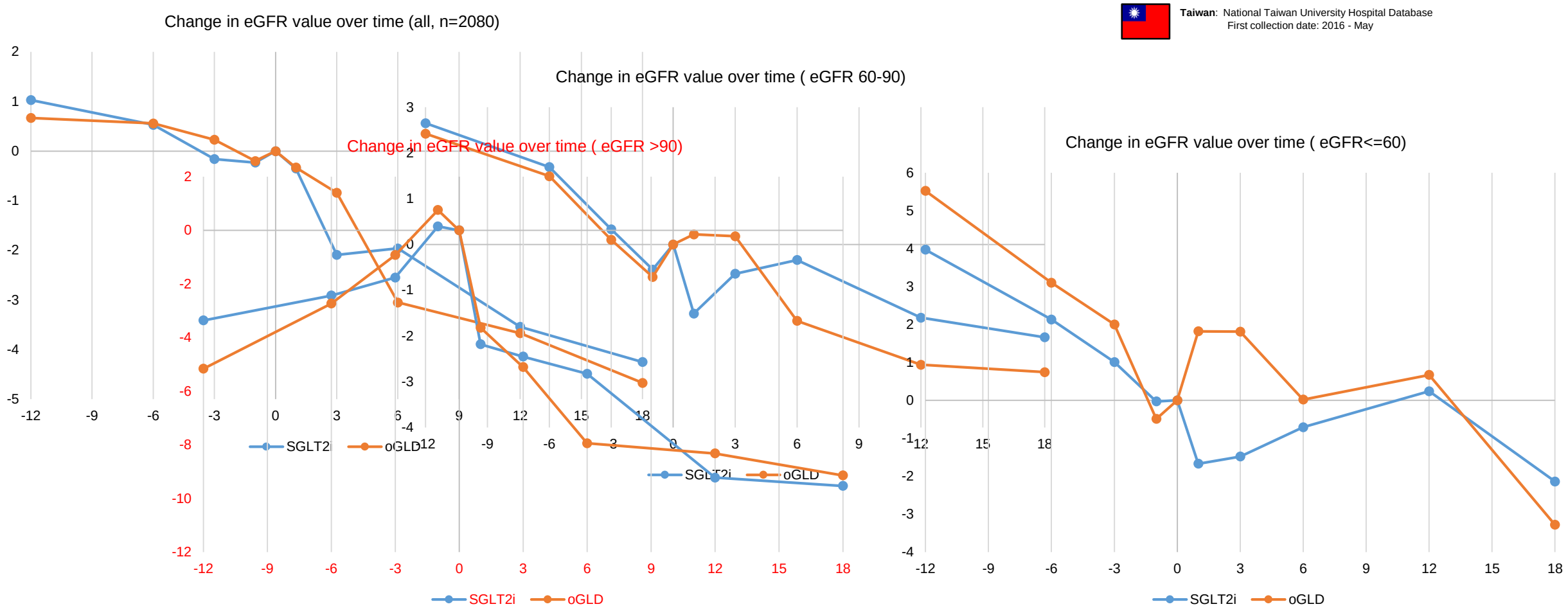


Figure 2: **Change in eGFR over time before and after initiation of SGLT2 inhibitors or other glucose-lowering drugs (on treatment)**
Error bars show 95% CI. Numbers below the graph refer to the number of patients at each timepoint. The eGFR slope calculation was calculated from baseline, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. As a result of the acute decrease in eGFR followed by a small increase in eGFR during the remainder of the follow-up, the overall eGFR slope was positive despite the change from baseline at the end of follow-up being negative. eGFR=estimated glomerular filtration rate. SGLT2=sodium-glucose co-transporter-2.

Lancet Diabetes Endocrinol 2020; 8: 27–35


0
-2
-4
-6
SGLT2i
oGLD
10252
8763
6921
8408
12321
4157
7553
9276
9140
5857
9788
8302
6816
8279
12149
4075
7043
8990
8736
5630
-12
-6
-3
-1
0
1
3
6
12
18
24
Month

How about subgroup analysis in Taiwan?



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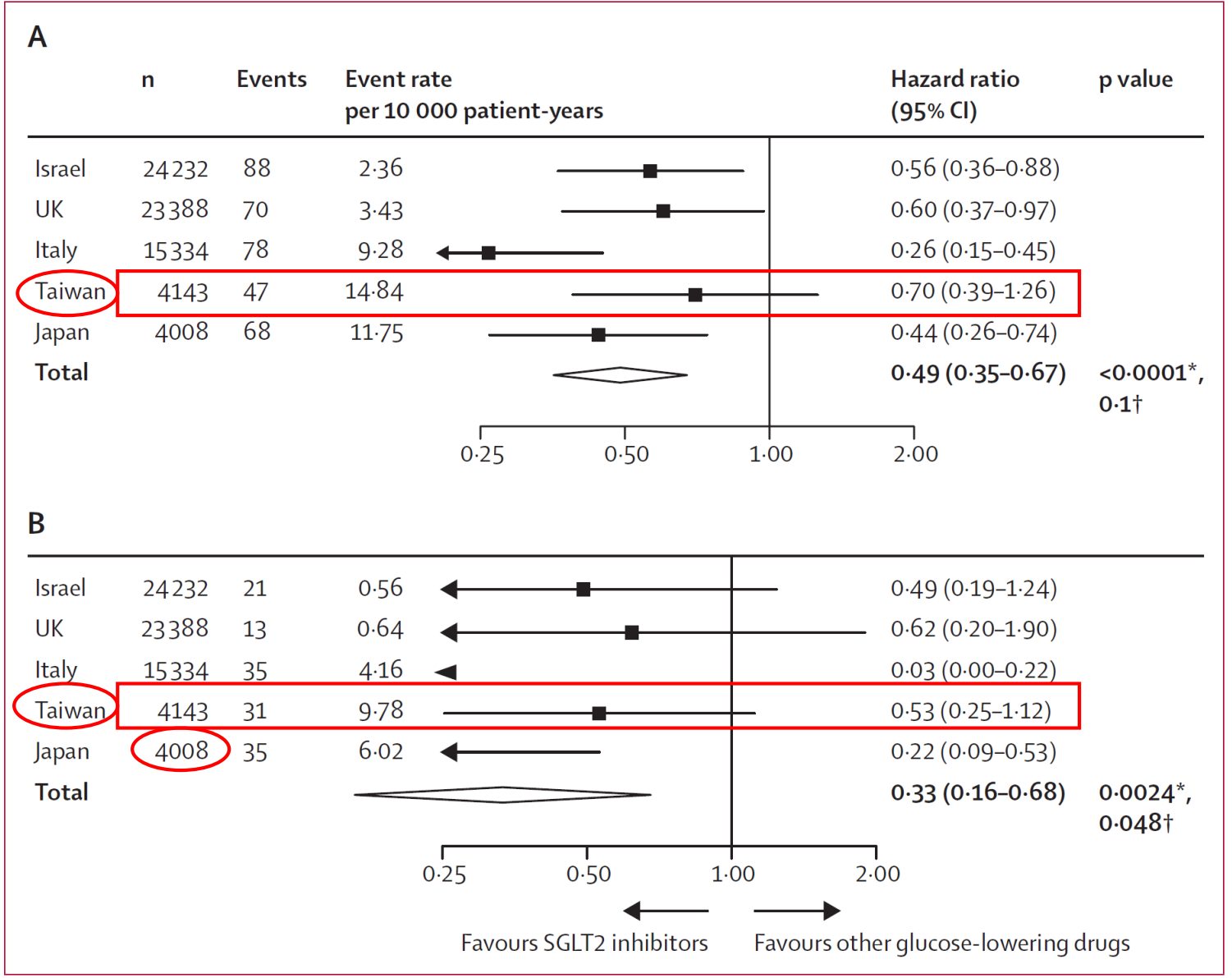
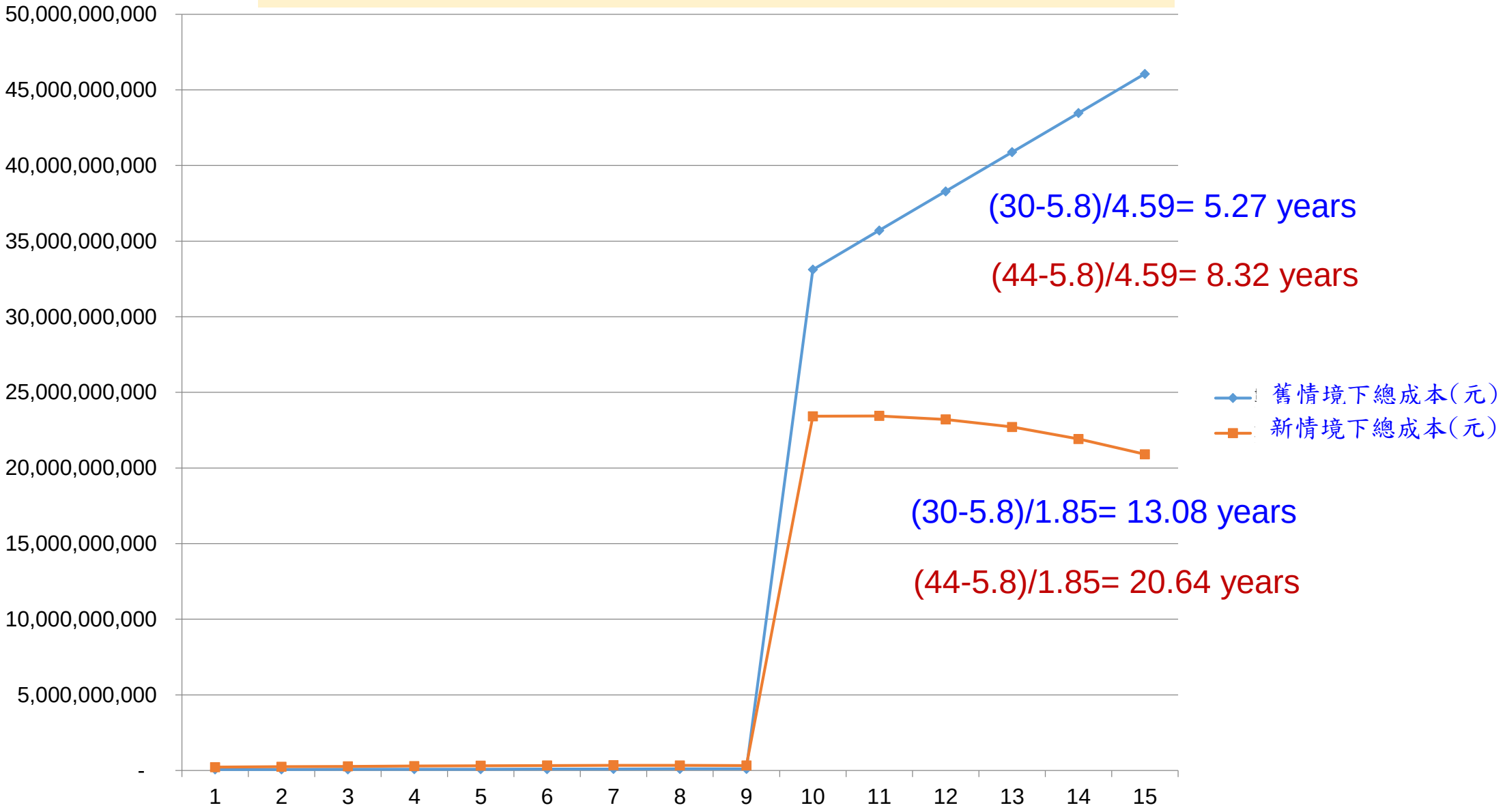


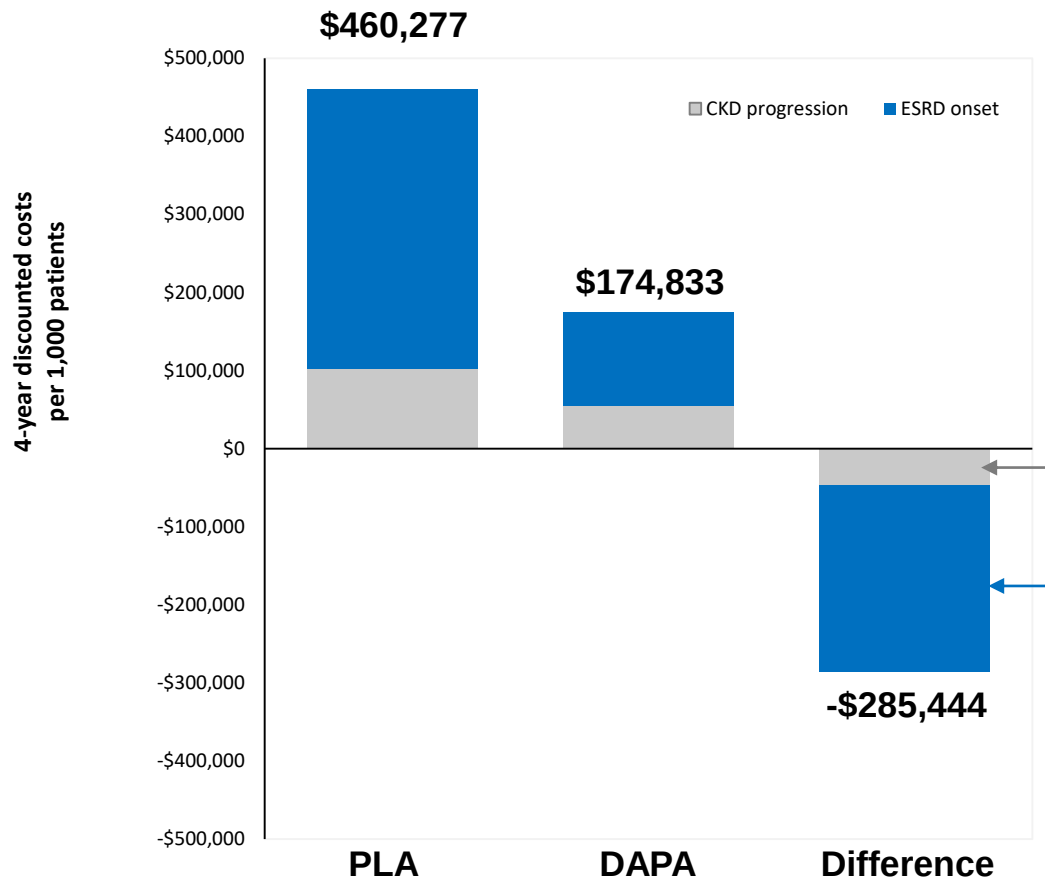
Figure 4: **Forest plots for the composite kidney outcome and ESKD (intention to treat)**
(A) Composite of 50% decline in estimated glomerular filtration rate or ESKD. (B) ESKD alone. ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. *p value for SGLT2 inhibitors compared with other glucose-lowering drugs. †$p_{heterogeneity}$.

Lancet Diabetes Endocrinol 2020; 8: 27–35

Pharmaco-economics in certain Scenarios



DECLARE renal outcomes藥物經濟學分析：可減少62% renal related cost



62% Renal related cost

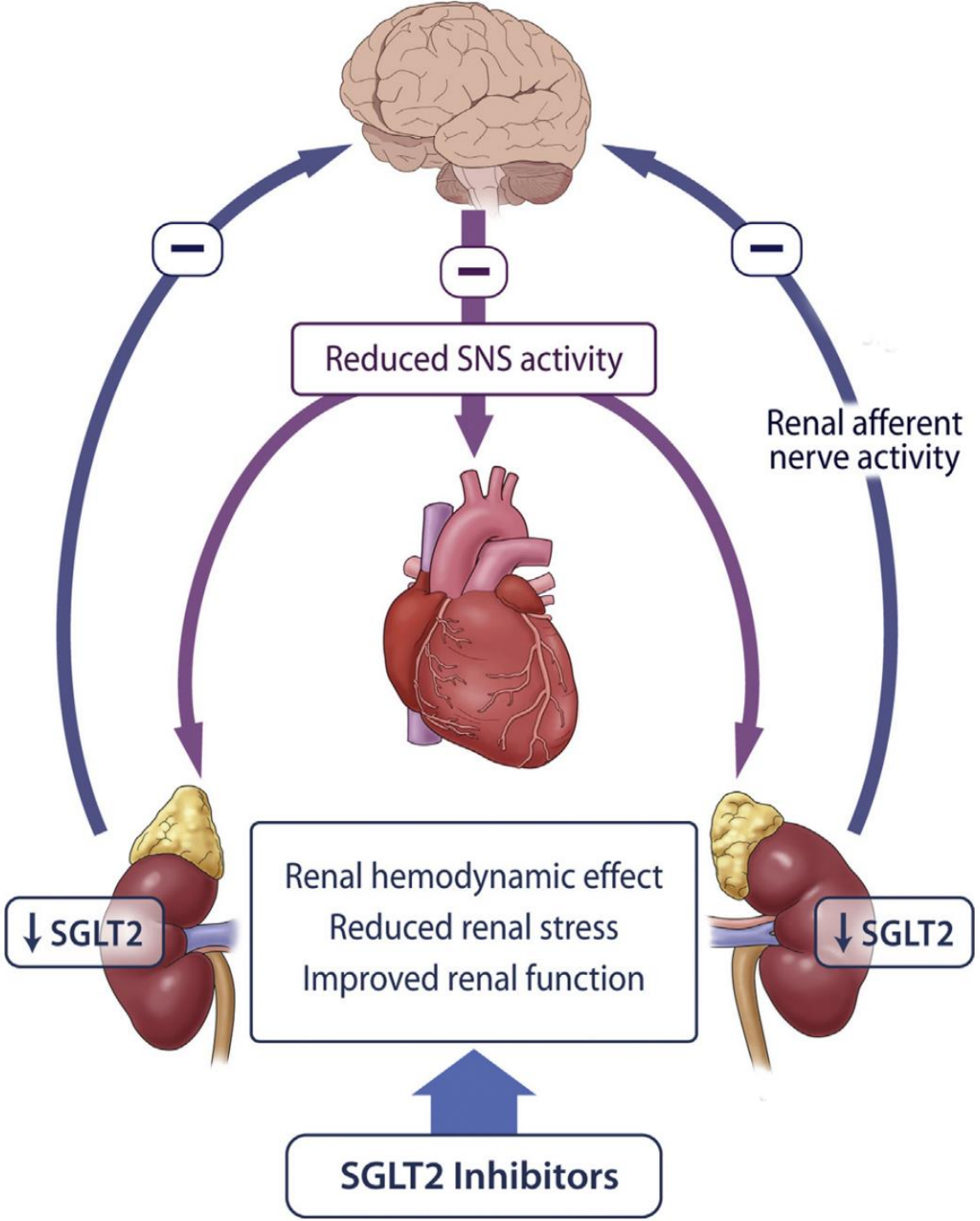
62% reduction overall

46% reduction in CKD progression costs

67% reduction in ESRD costs

1,126 days' requirement for renal replacement therapy avoided

Philip McEwan et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA 15-OR

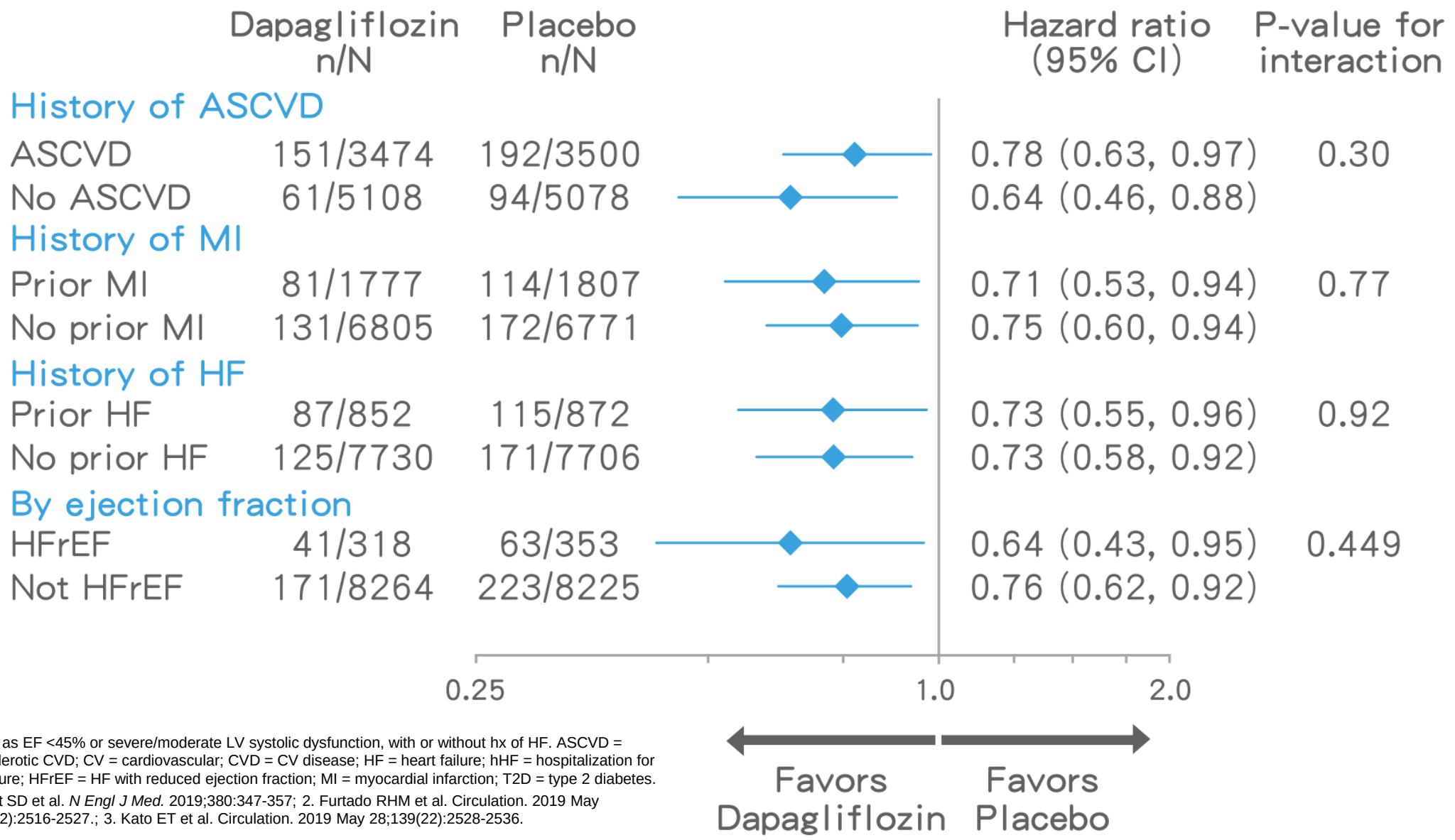


1. Sodium glucose cotransporter 2 (SGLT2) inhibitors, secondary to reducing renal stress, may reduce afferent renal sympathetic nervous system (SNS) activation.

2. A reduction in central SNS activation may serve as an important mechanism of heart failure protection and reduce renal SGLT2 expression.

JACC Basic Transl Sci. 2020 Feb 24;5(2):180-182.

Dapagliflozin在不同T2D病患一致有效預防心衰竭住院



[a]Defined as EF <45% or severe/moderate LV systolic dysfunction, with or without hx of HF. ASCVD = atherosclerotic CVD; CV = cardiovascular; CVD = CV disease; HF = heart failure; hHF = hospitalization for heart failure; HFrEF = HF with reduced ejection fraction; MI = myocardial infarction; T2D = type 2 diabetes.

1. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357; 2. Furtado RHM et al. Circulation. 2019 May 28;139(22):2516-2527.; 3. Kato ET et al. Circulation. 2019 May 28;139(22):2528-2536.

Outline

- Deterioration of renal & cardio function in diabetic patients
- New strategy for diabetes management with renal & cardiac complication consideration
- Conclusion

Take Home Message

- **Control of 5 risk factors including A1c, BP, LDL, albuminuria, smoking can lower risk of death, MI, stroke, but CKD/HF should be further clarified**

- **Concerns about the CV safety**
  - 4 DPP-4i all show neutral CV outcome, and VERIFY revealed the benefits of early combination
  - 4 of the 6 GLP-1 RA show positive CV outcome (LEADER, SUSTAIN-6, HARMONY, REWIND)
  - SGLT-2i show positive CV/HF outcome (EMPA-REG, CANVAS, DECLARE, CREDENCE, except VERTIS)

- **The latest guidelines recommend Efficacy together with CV benefits for T2DM management, however, we still need to remember the importance of glycemic control**

Take Home Message

- 2020 ADA guideline recommend:
  - SGLT-2i as first choice after metformin in patients with CKD independent of A1c
- 2019 ERA recommend T2D patients with CKD:
  - not on A1c target → use SGLT-2i
  - on A1c target → consider switch to SGLT-2i
- 2019 KDIGO guideline: SGLT-2i as first-line therapy for T2D patients with CKD
- 2019 DAROC, DAROC/TSN recommend:
  - SGLT-2i with lowering renal progression risk evidence

- SGLT-2i can also reduce HF risk; renal-cardio effect may serve an importance mechanism for heart protection

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Thanks very much for your listening!!

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