Holistic Care for the Patients with Cardiovascular Diseases

Adapt 2018 Diabetes Guidelines Into Clinical Practice

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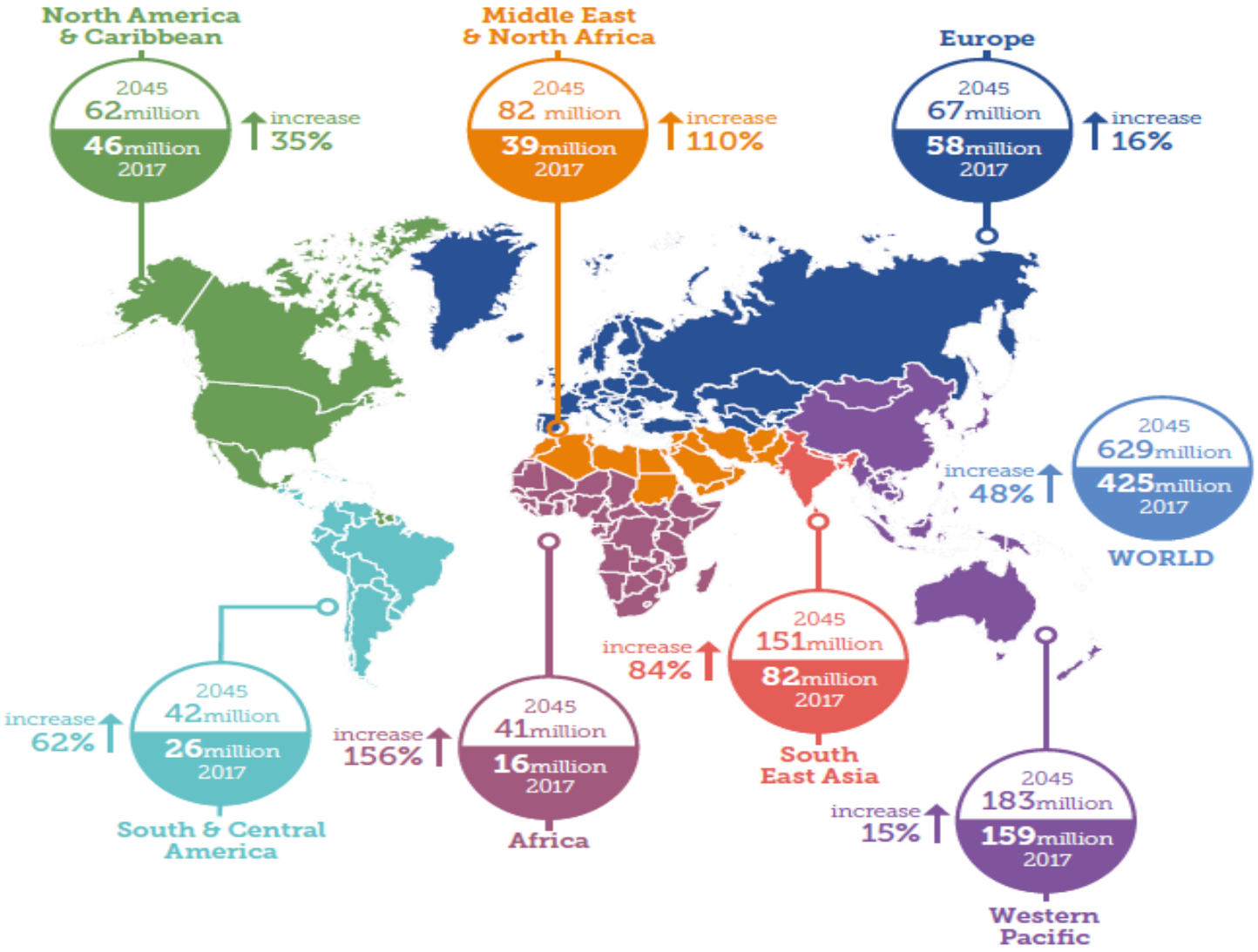
Diabetes: A global emergency

Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)

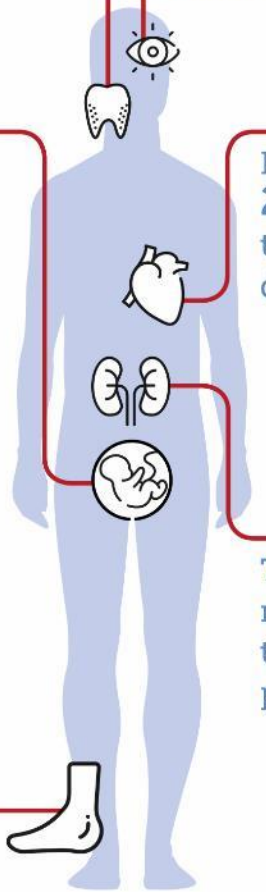


International Diabetes Federation

Diabetes Complications

People with diabetes are at **higher risk** of developing periodontal disease

Diabetic retinopathy affects over **one-third** of all people with diabetes and is the leading cause of vision loss in working-age adults



Pregnant woman with diabetes or at high risk for GDM should manage their glycaemia throughout their pregnancy to avoid lond-term consequences for themselves and their children, and **trasgenerational effects** (higher risk of obesity, diabetes, hypertension and kidney disease in the offspring)

People with diabetes are **2 to 3 times** more likely to have cardiovascular disease (CVD)

The prevalence of end-stage renal disease (ESRD) is up to **10 times higher** in people with diabetes

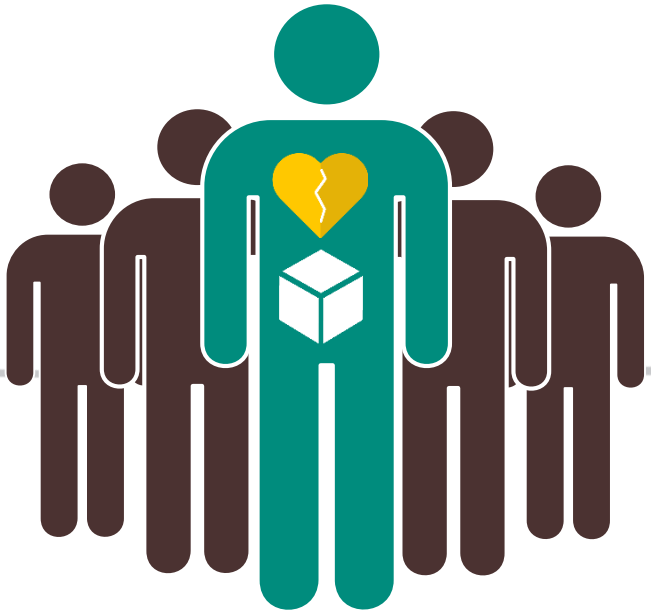
Every **30 seconds** a lower limb or part of a lower limb is lost to amputation somewhere in the world as a consequence of diabetes

International Diabetes Federation

1 in 5 Adults With Type 2 Diabetes or CV Disease had both conditions [a]

1 in **5** adults with type 2 diabetes had CV disease[1,b]

Type 2 diabetes mean (SD) age: 58 (11) years[2]



1 in **5** adults with CV disease had type 2 diabetes[2,c]

CV disease mean (SD) age: 61 (13) years[2,]

[a]CV disease includes myocardial infarct, angina, heart failure, stroke, other ischemic disease, arrhythmias, cardiac arrest, atherosclerosis, peripheral vascular disease, arterial thrombosis and embolism, cardiomyopathy, endocarditis, pericarditis, myocarditis, rheumatic heart disease and fever, conduction disorders, other unspecified CV disease conditions.

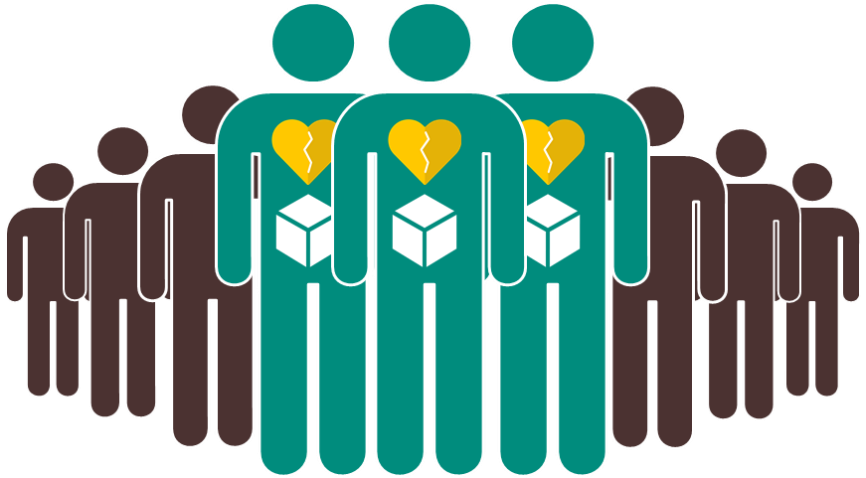
[b]Retrospective database analysis of 778,344 patients with type 2 diabetes; 17.8% had comorbid CV disease.

[c]Retrospective database analysis of 691,934 patients with CV disease; 20% had comorbid type 2 diabetes.

1. Sander S, et al. Poster presented at: 2016 American Academy of Managed Care Nexus; October 3-6, 2016; National Harbor, MD.
2. Data on File. Boehringer Ingelheim Pharmaceuticals, Inc.

Taiwan: More than 33% T2D patients have CVD[1]

In **Taiwan**



More than **1** in **3** adults with type 2 diabetes had CV disease[1].

Journal of the Formosan Medical Association (2012) 111, 625–636

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Prevalence of hypertension and dyslipidemia and their associations with micro- and macrovascular diseases in patients with diabetes in Taiwan: An analysis of nationwide data for 2000–2009

Li-Nien Tseng [a,b,i], Yao-Hsien Tseng [a,i], Yi-Der Jiang [c], Chia-Hsuin Chang [c,d], Ching-Hu Chung [e], Boniface J. Lin [f], Lee-Ming Chuang [c,d], Tong-Yuan Tai [g,**], Wayne H.-H. Sheu [a,b,h,*]

Table 3 Number of cases and prevalence of cardiovascular disease in individuals with diabetes by gender and age in Taiwan, 2000–2009.

				Year										*P* for trend
				2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	
F	Age group	<40	Number	1,680	1,515	1,521	1,467	1,506	1,509	1,422	1,644	1,539	1,536	
			Prevalence	8.87%	9.91%	9.00%	8.60%	8.15%	8.11%	7.34%	8.01%	7.25%	7.51%	0.001
		40–65	Number	58,212	58,668	60,549	62,709	66,525	67,416	68,535	71,700	73,536	71,922	
			Prevalence	32.51%	31.36%	30.33%	29.80%	29.44%	28.64%	27.87%	27.55%	26.77%	26.27%	<0.001
		>65	Number	85,482	90,249	96,987	101,721	110,274	117,081	121,656	127,974	134,256	135,327	
			Prevalence	51.67%	50.55%	49.76%	48.64%	48.43%	47.90%	46.80%	45.86%	44.86%	44.00%	<0.001
	Total		Number	145,374	150,432	159,057	165,897	178,305	186,006	191,613	201,318	209,331	208,785	
			Prevalence	40.00%	39.49%	38.66%	38.00%	37.77%	37.32%	36.48%	35.96%	35.17%	34.70%	<0.001
M	Age group	<40	Number	2,292	2,262	2,508	2,571	2,853	3,024	3,087	3,243	3,435	3,441	
			Prevalence	10.38%	10.60%	10.76%	10.47%	10.64%	10.83%	10.58%	10.63%	10.69%	11.12%	0.045
		40–65	Number	50,016	52,644	56,826	60,519	68,148	72,132	76,425	81,486	86,724	89,142	
			Prevalence	27.97%	27.21%	26.56%	26.10%	26.56%	26.42%	26.41%	26.14%	25.79%	25.99%	0.003
		>65	Number	71,694	74,187	79,023	82,440	88,251	93,597	96,765	101,985	106,767	107,397	
			Prevalence	50.60%	49.17%	48.33%	47.44%	46.93%	46.76%	45.80%	45.13%	44.25%	43.47%	<0.001
	Total		Number	124,002	129,093	138,357	145,530	159,252	168,753	176,277	186,714	196,926	199,980	
			Prevalence	36.20%	35.30%	34.53%	33.83%	33.78%	33.67%	33.27%	32.86%	32.30%	32.20%	<0.001
All CVD in DM				269,613	279,798	297,750	311,805	337,926	354,765	367,890	388,032	406,257	408,765	
% CVD in DM				38.14%	37.42%	36.60%	35.90%	35.76%	35.49%	34.87%	34.40%	33.72%	33.43%	<0.001

CVD = cardiovascular disease.

1. L.-N. Tseng et al. Journal of the Formosan Medical Association (2012) 111, 625e636

“CV disease is the No.1 cause of death worldwide in patients with T2D”

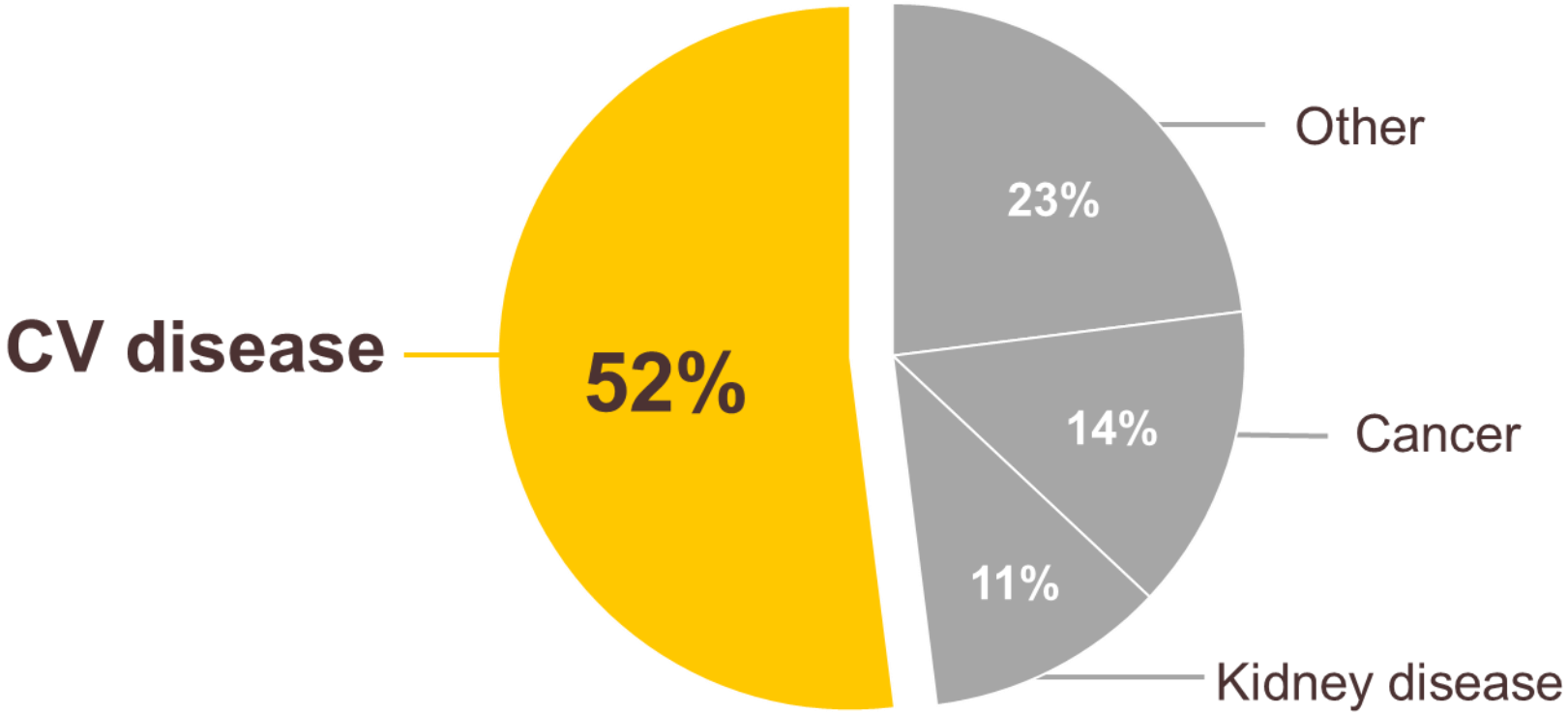
- Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes[1]

1. Morrish NJ *et al. Diabetologia* 2001;44 Suppl 2:S14

CV disease is the No.1 cause of death worldwide in patients with T2D[1]

Cause of death in patients with T2D[2]

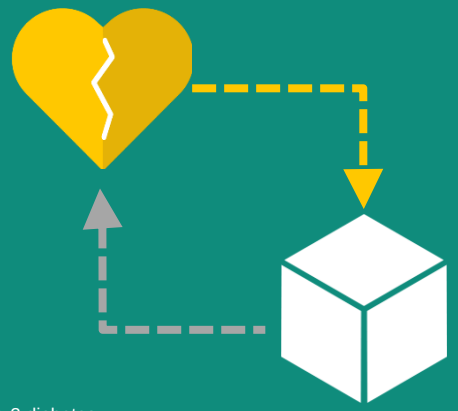
Mean follow-up was 9.4 years for men and 9.8 years for women; N=709



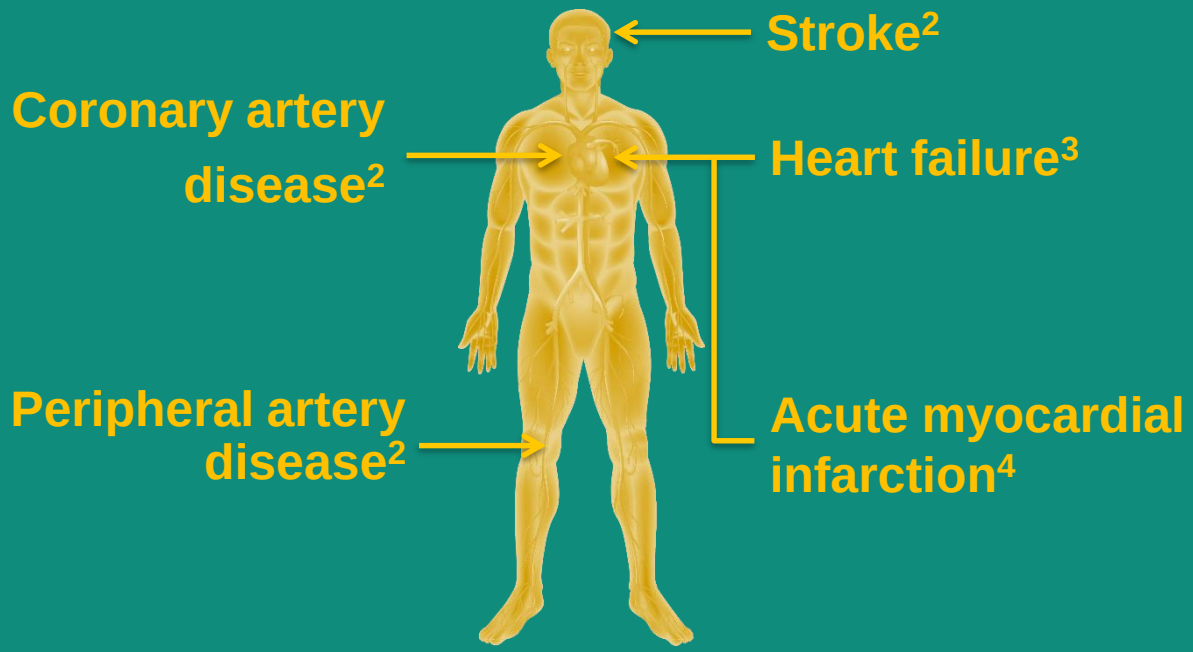
CV, cardiovascular; T2D, type 2 diabetes

1. International Diabetes Federation. IDF Diabetes Atlas. 7th edn. 2015. www.idf.org/diabetesatlas (accessed June 2017);
2. Morrish NJ *et al. Diabetologia* 2001;44 Suppl 2:S14

CV disease is an inevitable complication and No.1 cause of death in T2D



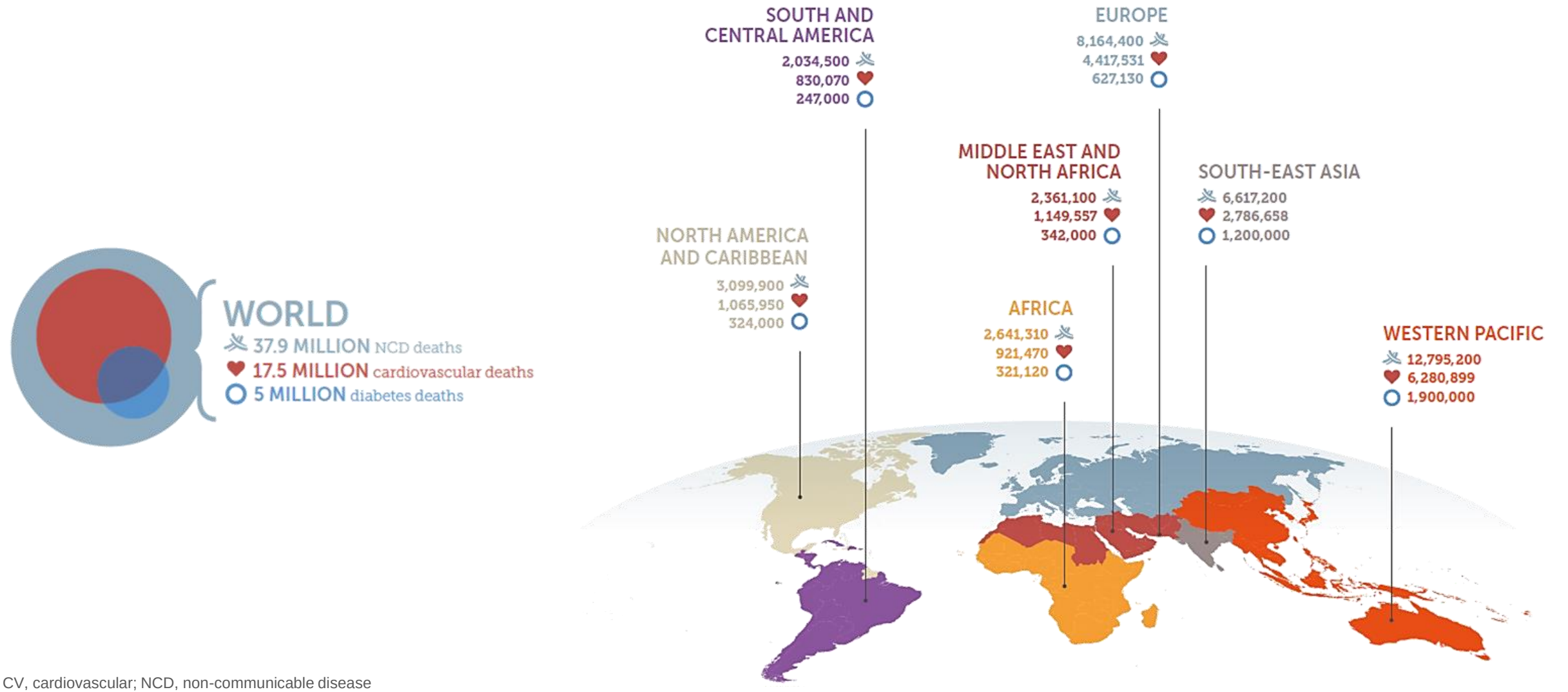
Complex and multifactorial pathophysiological pathways in T2D are responsible for CV disease[1]



CV, cardiovascular; T2D, type 2 diabetes

1. Dokken BB. *Diabetes Spectrum* 2008;21:160;
2. World Health Organization. Types of cardiovascular disease. 2015. Available at: www.who.int/cardiovascular_diseases/en/cvd_atlas_01_types.pdf?ua=1 ;
3. American Heart Association. What is cardiovascular disease? 2014. Available at: www.heart.org/HEARTORG/Caregiver/Resources/WhatisCardiovascularDisease/WhatisCardiovascularDisease_UCM_301852_Article.jsp ;
4. Thygesen K *et al. Eur Heart J* 2012;33:2551 (all websites accessed March 2017)

Western Pacific countries have the highest mortality rates due to diabetes and CV disease in the world



CV, cardiovascular; NCD, non-communicable disease

Diabetes and Cardiovascular Disease. International Disease Federation 2016. Available at: http://www.idf.org/sites/default/files/CVD_in_diabetes_report.pdf (accessed April 2017)

Diabetic correlated CV Death in Taiwan, 2008 - 2016

In Taiwan

The number of patients with T2D dying from CV disease is still increasing as the main causes in past 10 years[1].

97年多重死因分析-節錄[1]

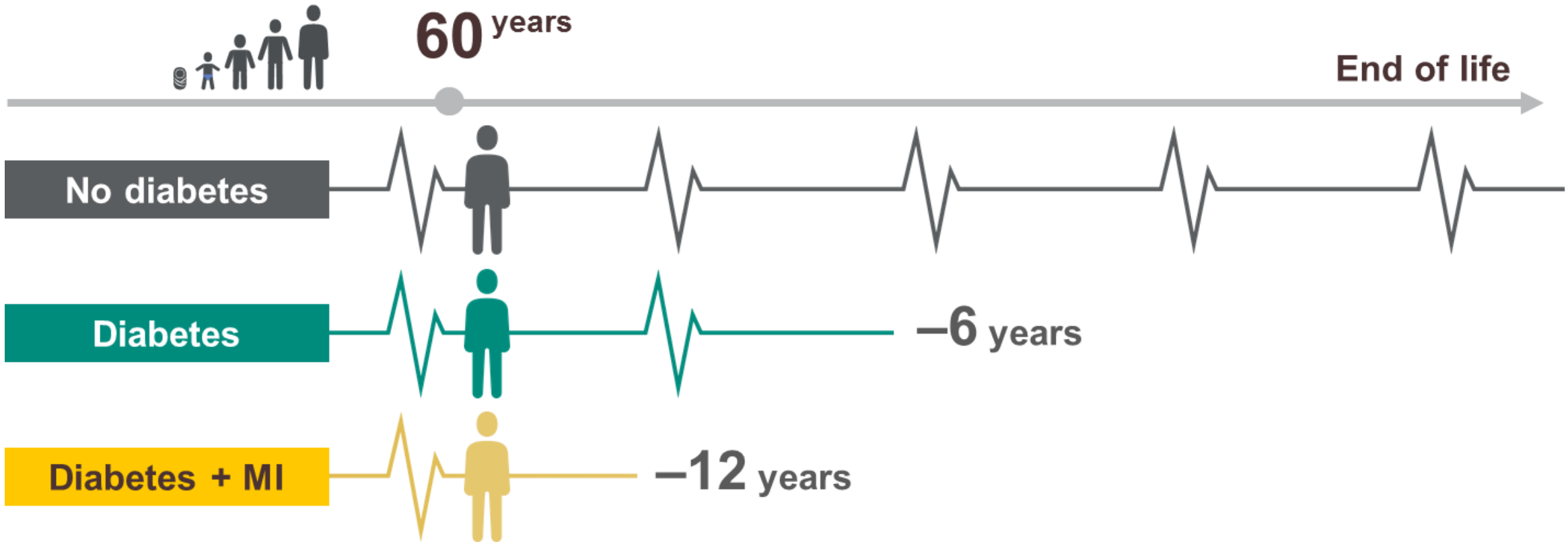
死亡原因	死亡人數	提及死因		
		心臟疾病（高血壓性疾病除外）	腦血管疾病	高血壓性疾病
	人	%	%	%
糖尿病	8,036	36.7	19.9	30.2

105年多重死因分析-節錄[1]

死亡原因	死亡人數	提及死因		
		心臟疾病（高血壓性疾病除外）	腦血管疾病	高血壓性疾病
	人	%	%	%
糖尿病	9,960	38.5	18.0	37.8

1. 國民健康署多重死因分析 97~105

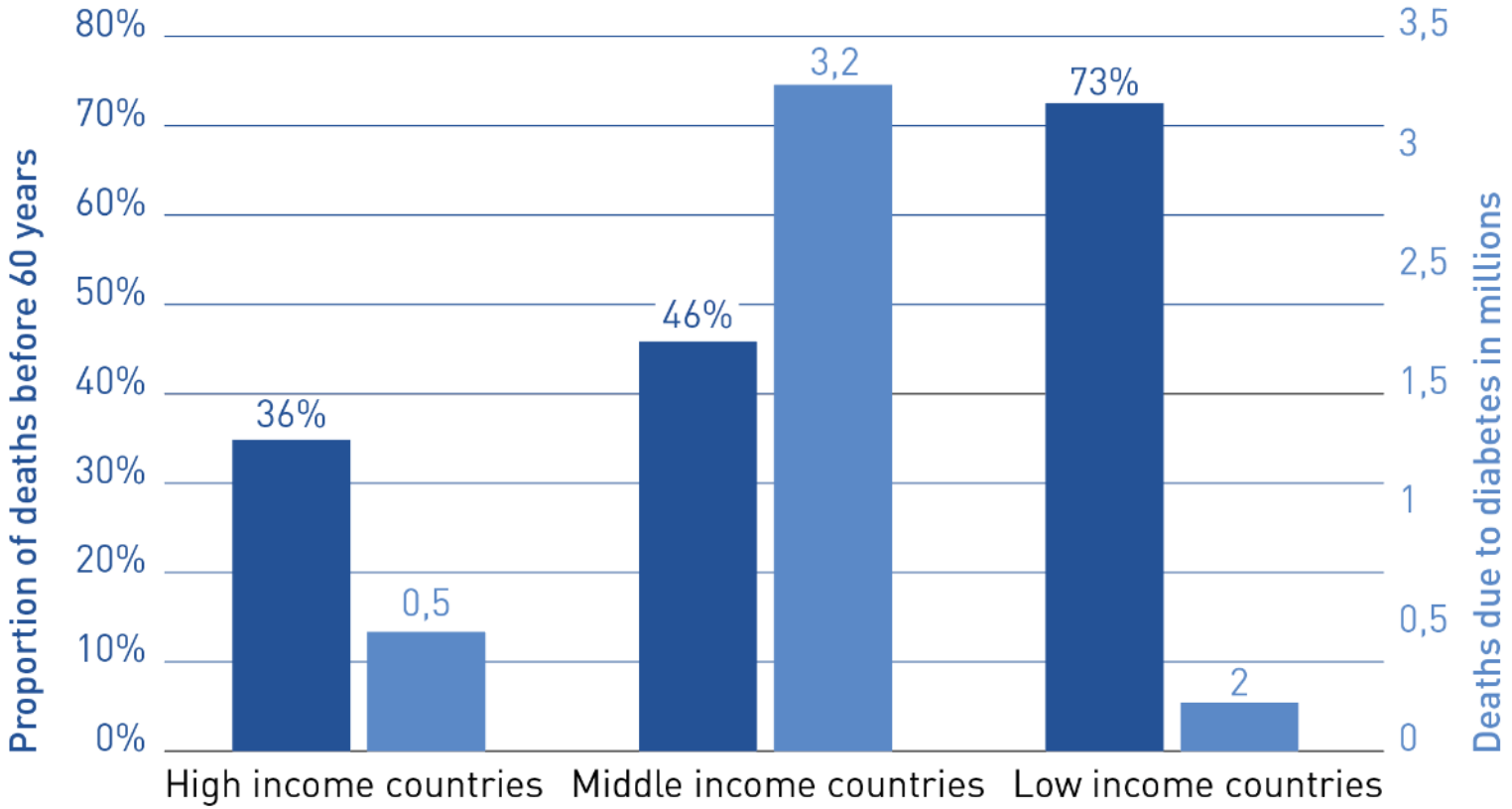
Life expectancy is significantly decreased in patients with T2D and established CV disease*



In this case, CV disease is represented by MI or stroke. *Male, 60 years of age with history of MI or stroke
CV, cardiovascular; MI, myocardial infarction; T2D, type 2 diabetes
The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52

Mortality

Deaths attributable to diabetes by age (20-79 years)



"Half of the 4 million people who die from diabetes are under the age of 60"

International Diabetes Federation

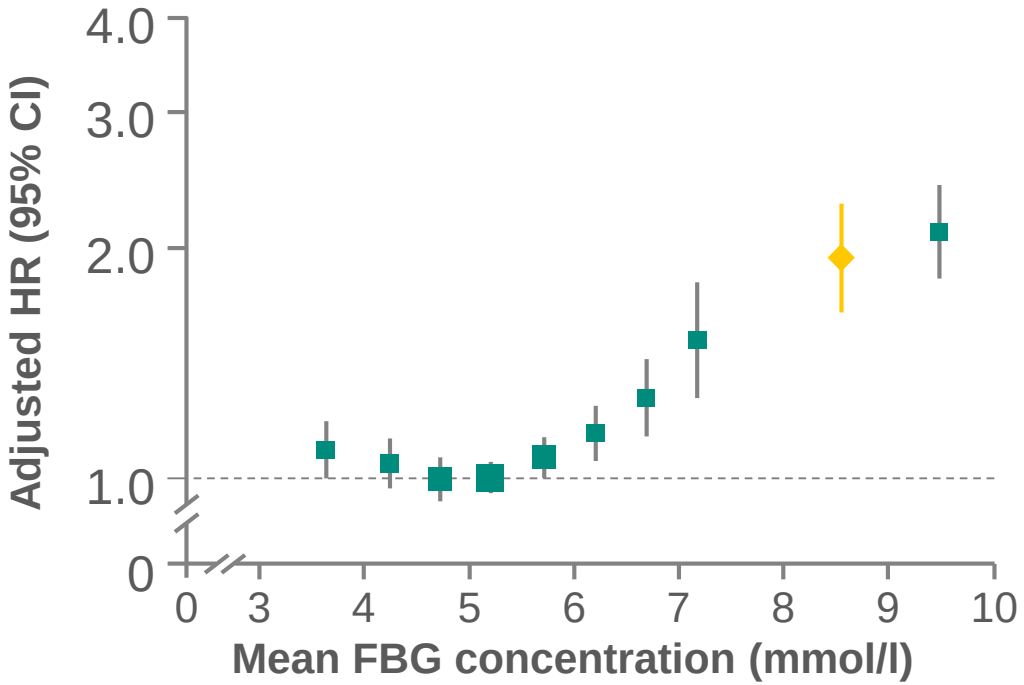
“T2D is a significant risk factor for CV disease”

- World Heart Federation. Diabetes[1]

1. World Heart Federation. Diabetes. 2016. Available at: www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/diabetes (accessed March 2017)

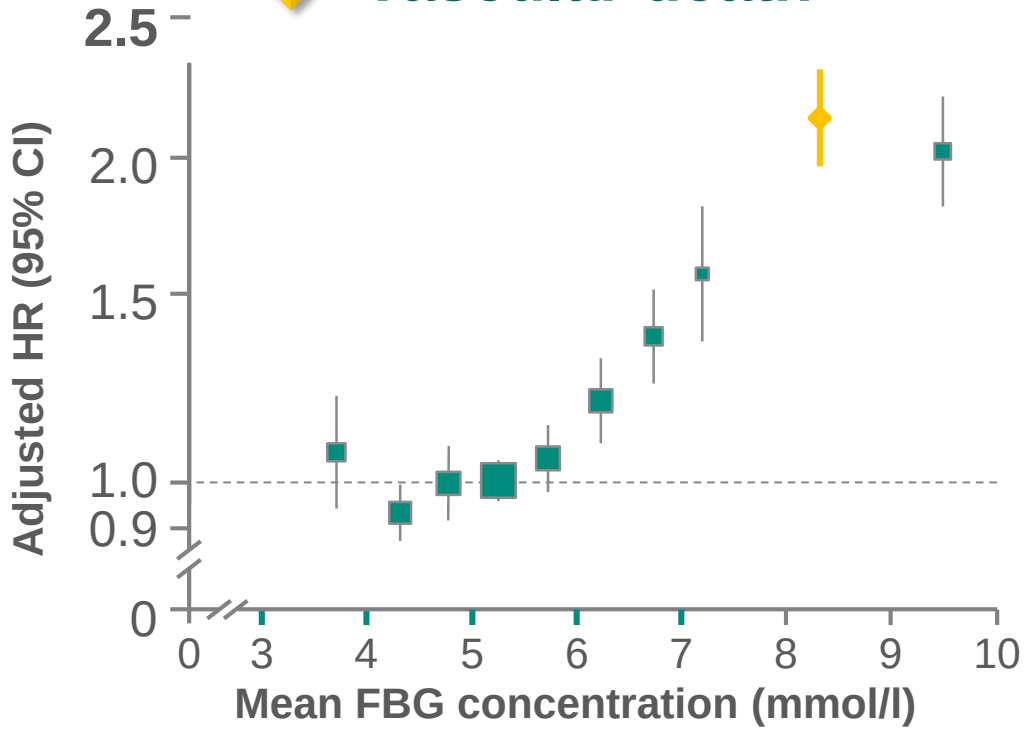
Risk of adverse CV outcomes increases with rising blood glucose levels

Coronary heart disease[1]



Analysis of 279,290 individuals in 102 studies

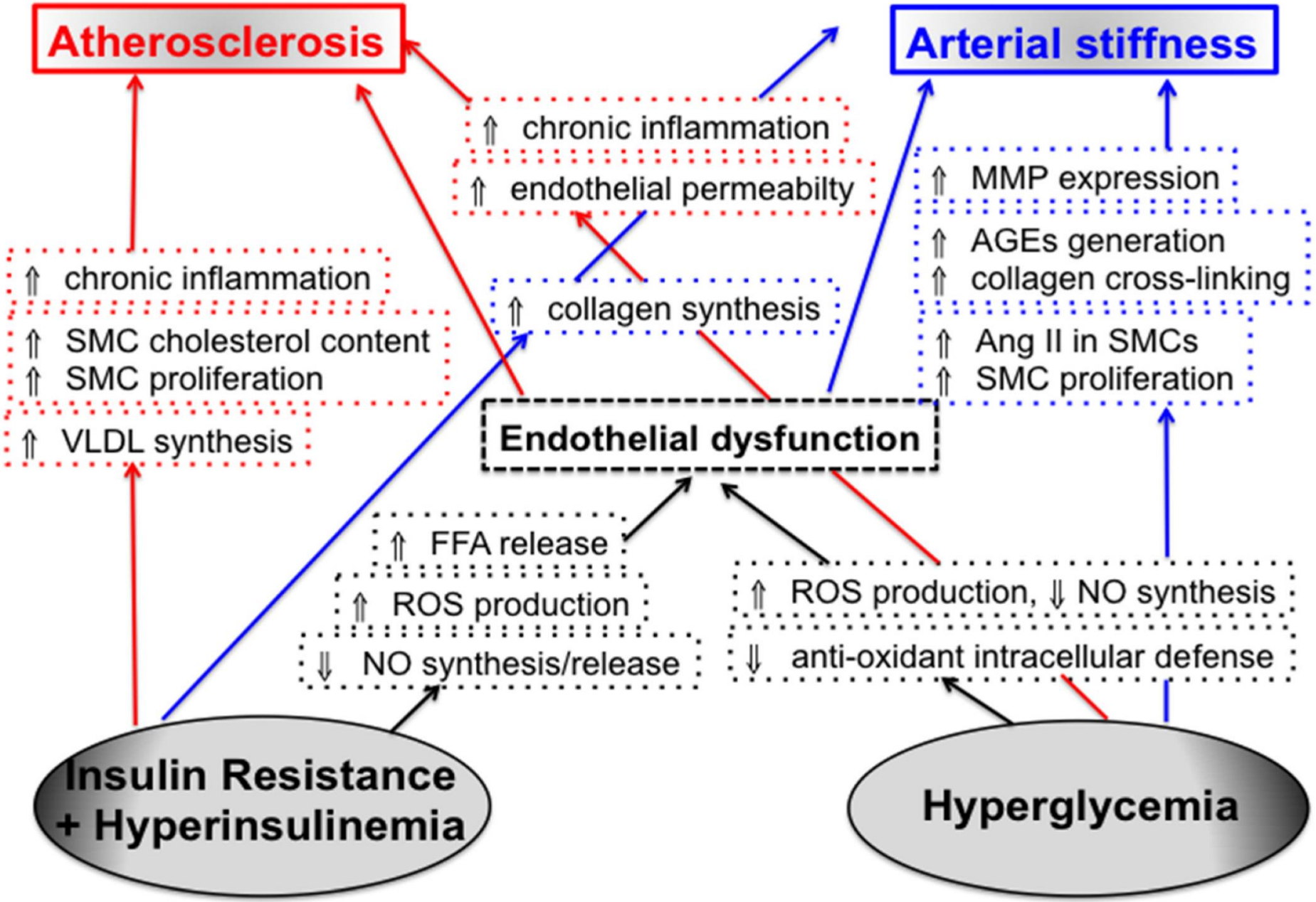
Vascular death[2]



Analysis of 16,211 deaths in 50 studies

CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; HR, hazard ratio

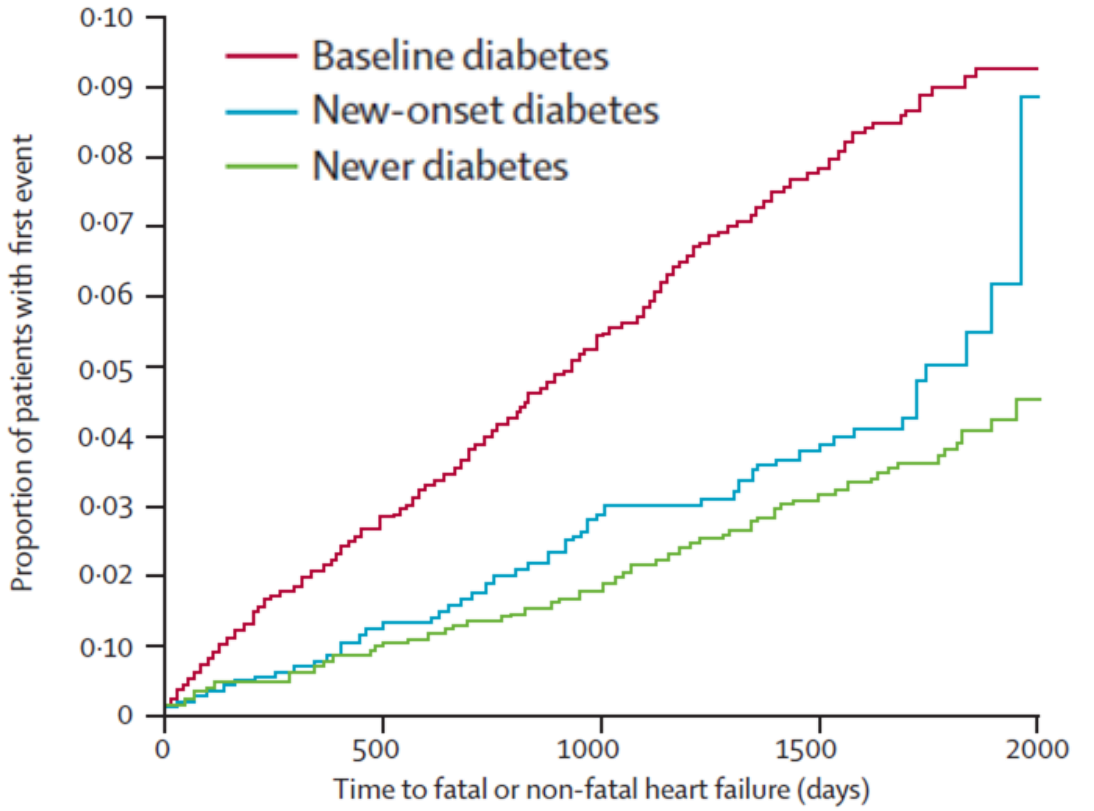
1. Sarwar N *et al. Lancet* 2010;375:2215; 2. Seshasai SRK *et al. N Engl J Med* 2011;364:829



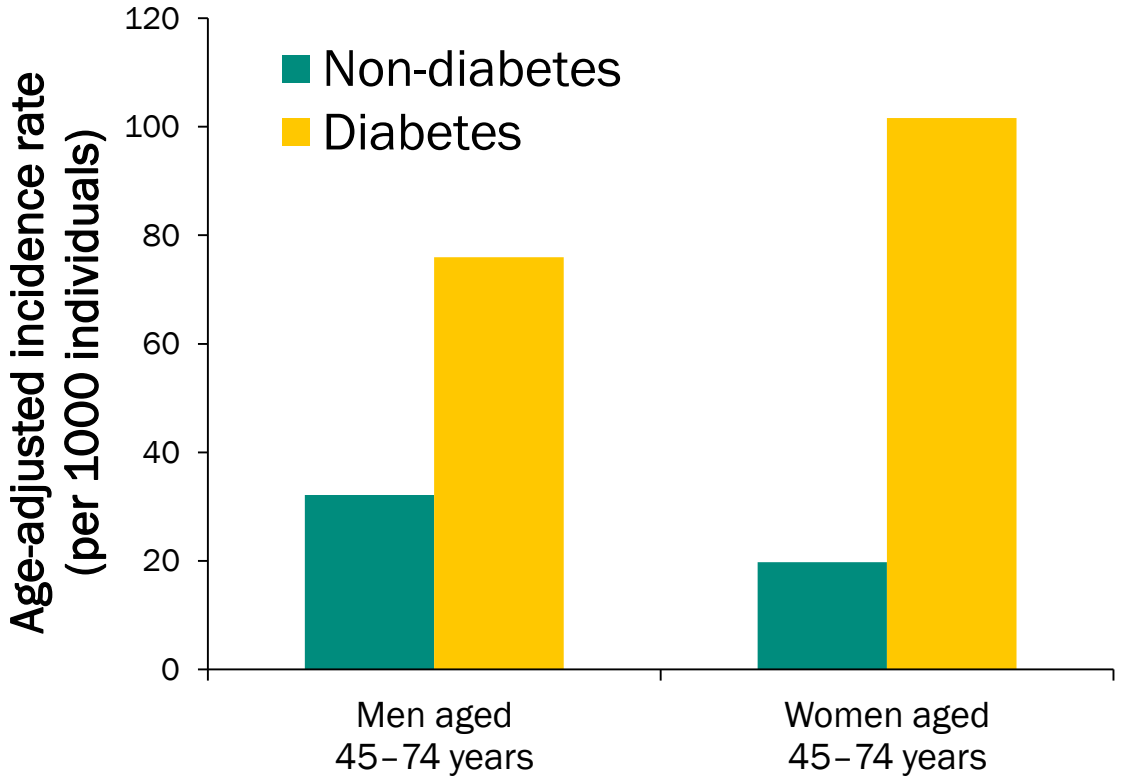
Kozakova M *et al. Int. J. Environ. Res. Public Health* 2016; 13(2): 201

Diabetes accelerates the onset and increases the risk of HF

Cumulative risk of HF by diabetes status in the VALUE trial (n=5,250)*[2]



People with diabetes have a 2 to 5 fold higher risk of developing HF[3]

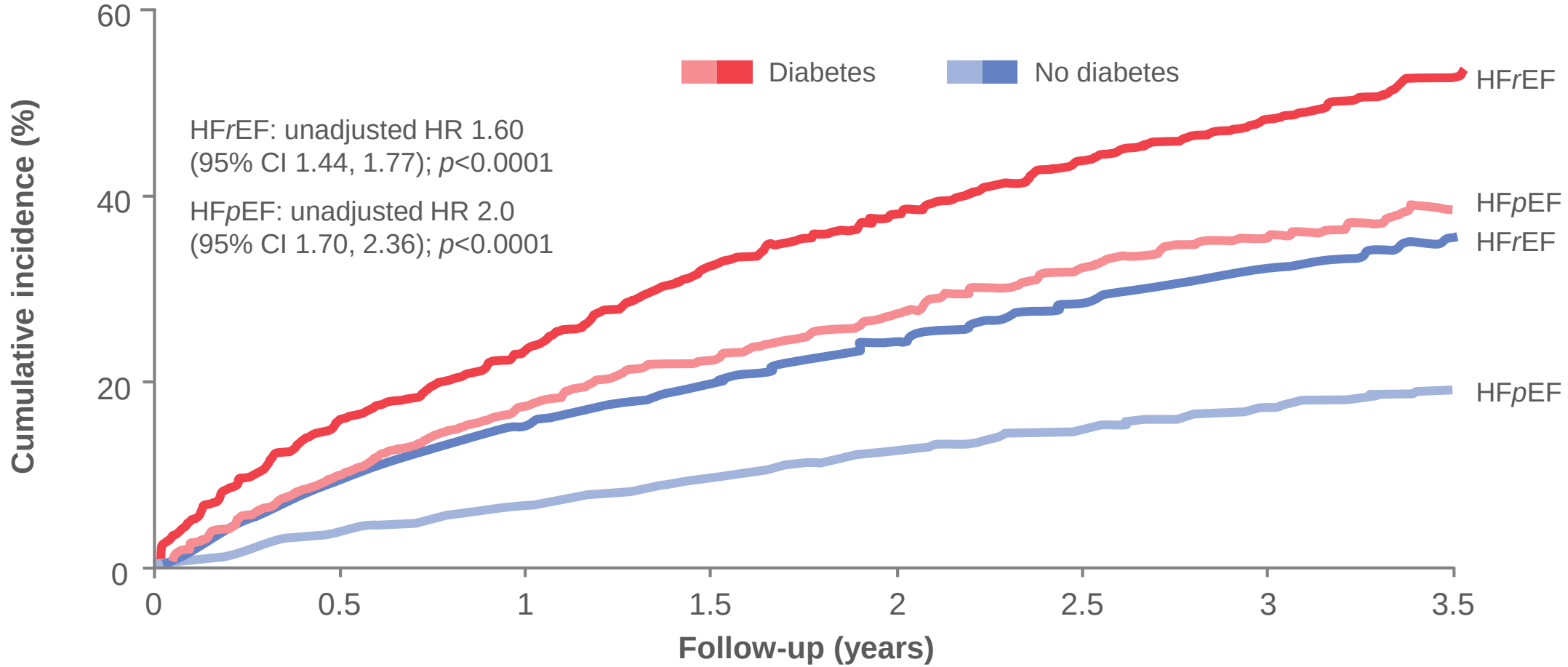


* Sample consisted of individuals with hypertension and CV disease or with high CV disease risk; amlodipine and valsartan combined ; HF, heart failure

1. Hess K, et al. *Eur Heart J Suppl*. 2012;14(Suppl B):B4-B13; 2. McMurray JJV *et al. Lancet Diabetes Endocrinol* 2014;2:843 ; 3, Kannel WB *et al. Am J Cardiol* 1974;34:29

Patients with diabetes and HF have a worse prognosis than patients with HF alone

CV death or HHF in patients with or without diabetes



*HRs refer to the risk of CV death or HHF in patients with diabetes versus non-diabetes

MacDonald MR *et al. Eur Heart J* 2008;29:1377

T2D established with CVD should be faced

European Society of Cardiology[1]

*Patients with '**diabetes, and at least one other CV risk factor** or target organ damage, should be considered to be at **very high risk**…*

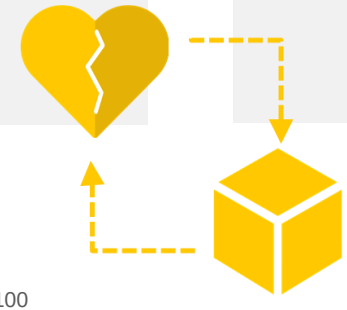
***…Most other people with diabetes** […] **are categorised as high risk**…*

*…High risk persons […] may be candidates for **drug treatment.**'*

Canadian Diabetes Association[2]

'Diabetes promotes both the development and adverse impact of CV disease risk factors...

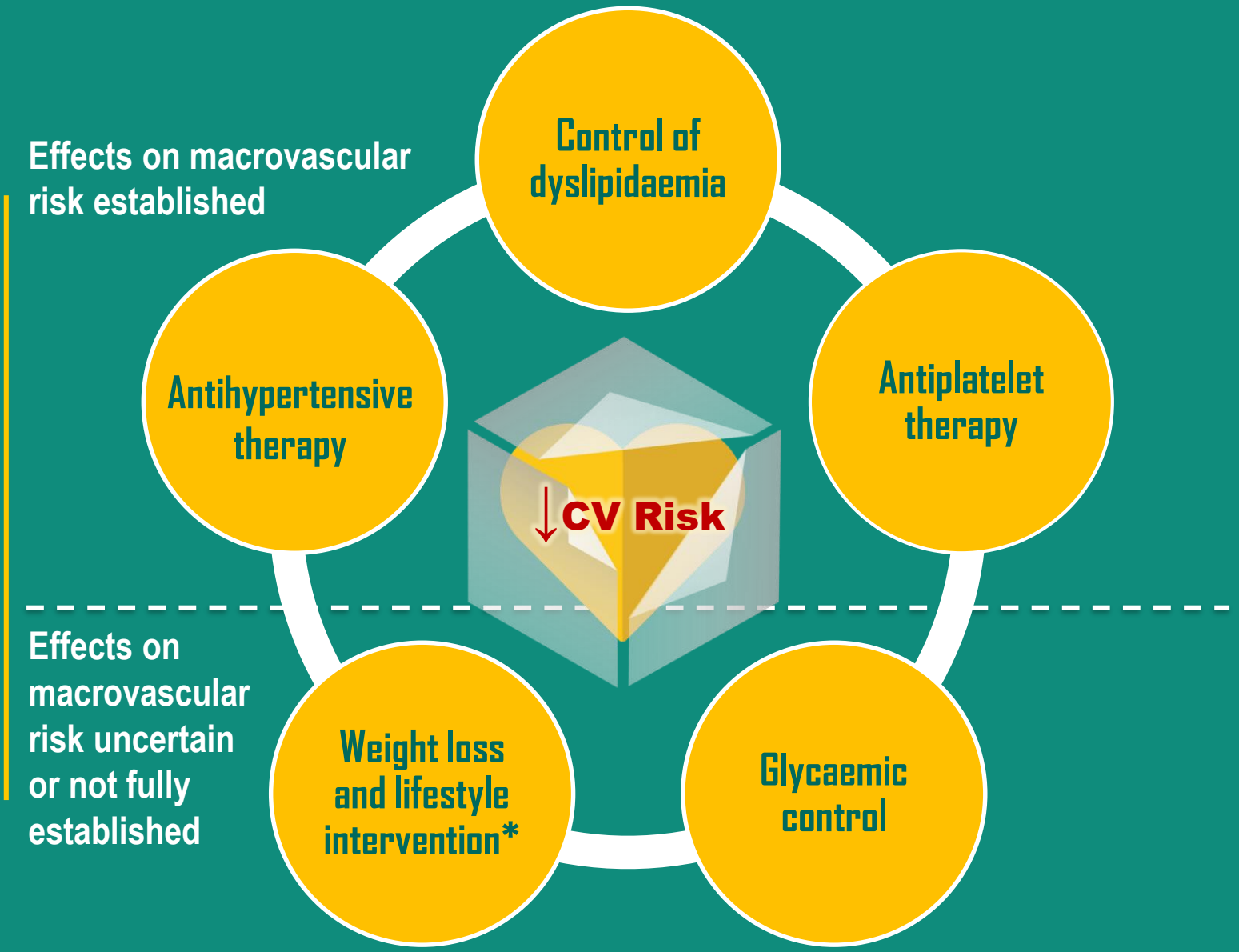
*…**All adults with diabetes require** chronic disease care strategies that include […] for many individuals, **pharmacological vascular protection**…'*



CV, cardiovascular; T2D, type 2 diabetes

1. Piepoli MF *et al. Eur Heart J* 2016;37:2315; 2. Canadian Diabetes Association. *Can J Diabetes* 2013;37:S100

Management of CV risk factors in T2D

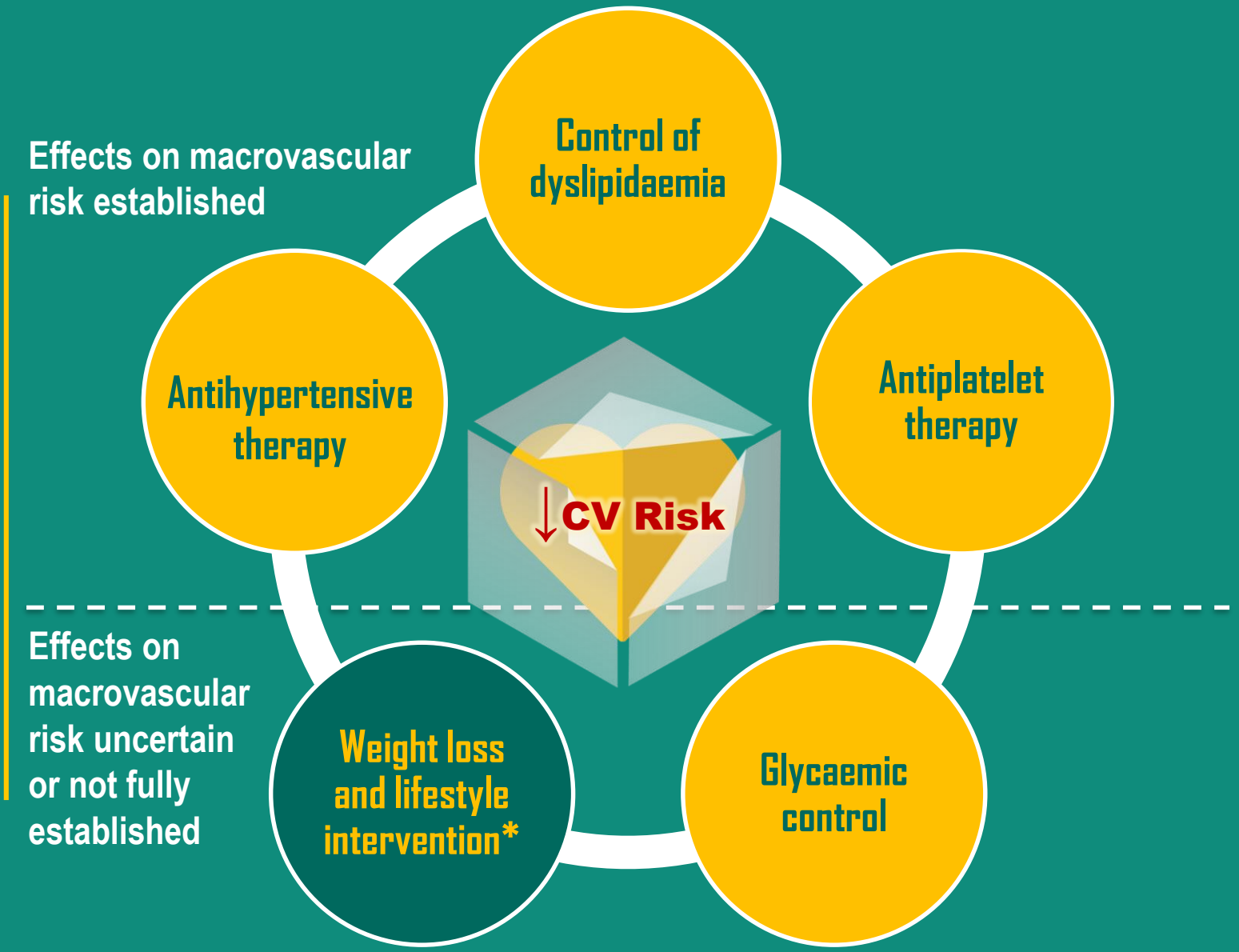


*Includes smoking cessation.

Anonymous. Eur Heart J 2013;34:3035–87.

Management of CV risk factors in T2D

Weight loss and lifestyle intervention



*Includes smoking cessation.

Anonymous. Eur Heart J 2013;34:3035–87.

Life style Interventions and their impacts on CV risk[1]

LOOK AHEAD

Duration:

2001 Aug ~ 2012 Sep
(Follow-up : average 9.6 years)

Patients:

5,145 obese T2D patients

Intensive life style control

V.S

Control

LOOK AHEAD study, 2013[1]

Lifestyle Intervention in T2D

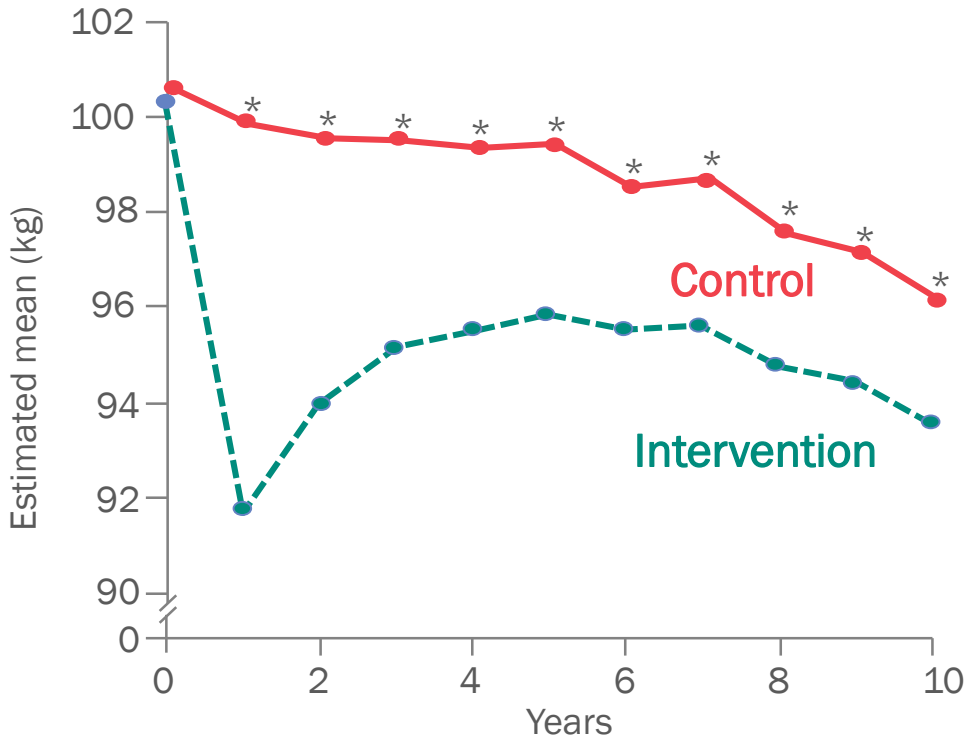
HbA_{1c}	Improved	Blood Pressure	Improved
Physical Fitness	Improved	Lipid Profiles	Improved
Waist Circumference	Improved	Cardiovascular Death	Neutral
Body Weight	Improved	All-cause Death	Neutral

Cardiovascular Risk Factors

1. Look AHEAD Research Group. *N Engl J Med* 2013;369:145–54.

Intensive lifestyle intervention, focused on weight loss, did not improve CV risk in T2D in the long term

Weight Loss



Main effect: -4 (95% CI: -5 to -3) * p < 0.001

Major CV Events*

No. at risk						
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

*Endpoint: Composite of CV death, non-fatal MI, non-fatal stroke and hospitalisation for angina.

Look AHEAD Research Group. N Engl J Med 2013;369:145–54.

Management of CV risk factors in T2D

Glycaemic Control

*Includes smoking cessation.

Anonymous. Eur Heart J 2013;34:3035–87.

Does Intensive glycaemic control help : Learning from UKPDS

UKPDS

United Kingdom Prospective Diabetes Study

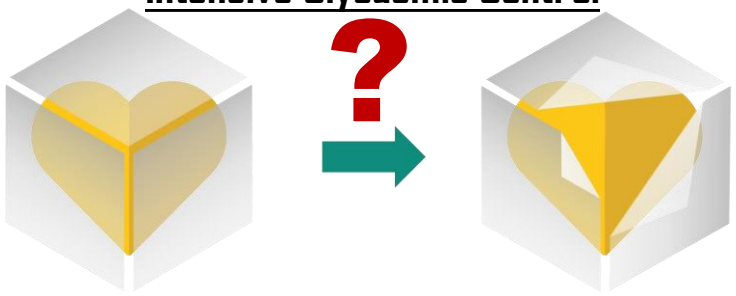
Duration:

1977-1997 (The pre-statin era)

Patients:

5,012 New diagnosis T2D

Intensive Glycaemic Control



Randomization

Conventional glycemic control

- The target fasting glucose was less than 270 mg/dl.
- With the intention of keeping asymptomatic.

Intensive glycemic control

- The target fasting glucose was 108 mg/dl.
- When diet failed to achieve these targets, patients were randomized to SUs, insulin or metformin (in obese patients only).
- When single treatments failed, combinations were used.

*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.
UKPDS 33. Lancet 1998;352:837–53.

UKPDS: Intensive glycaemic control reduced microvascular but not macrovascular outcomes

UKPDS

United Kingdom Prospective Diabetes Study

Duration:

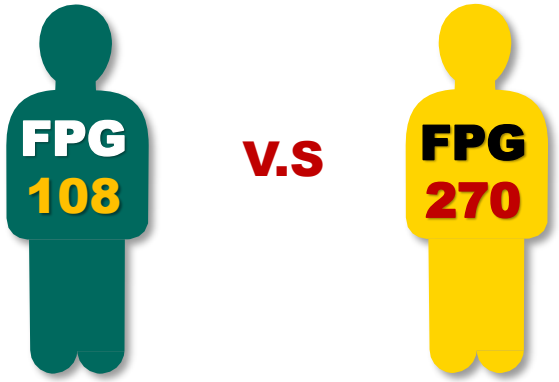
1977-1997 (The pre-statin era)

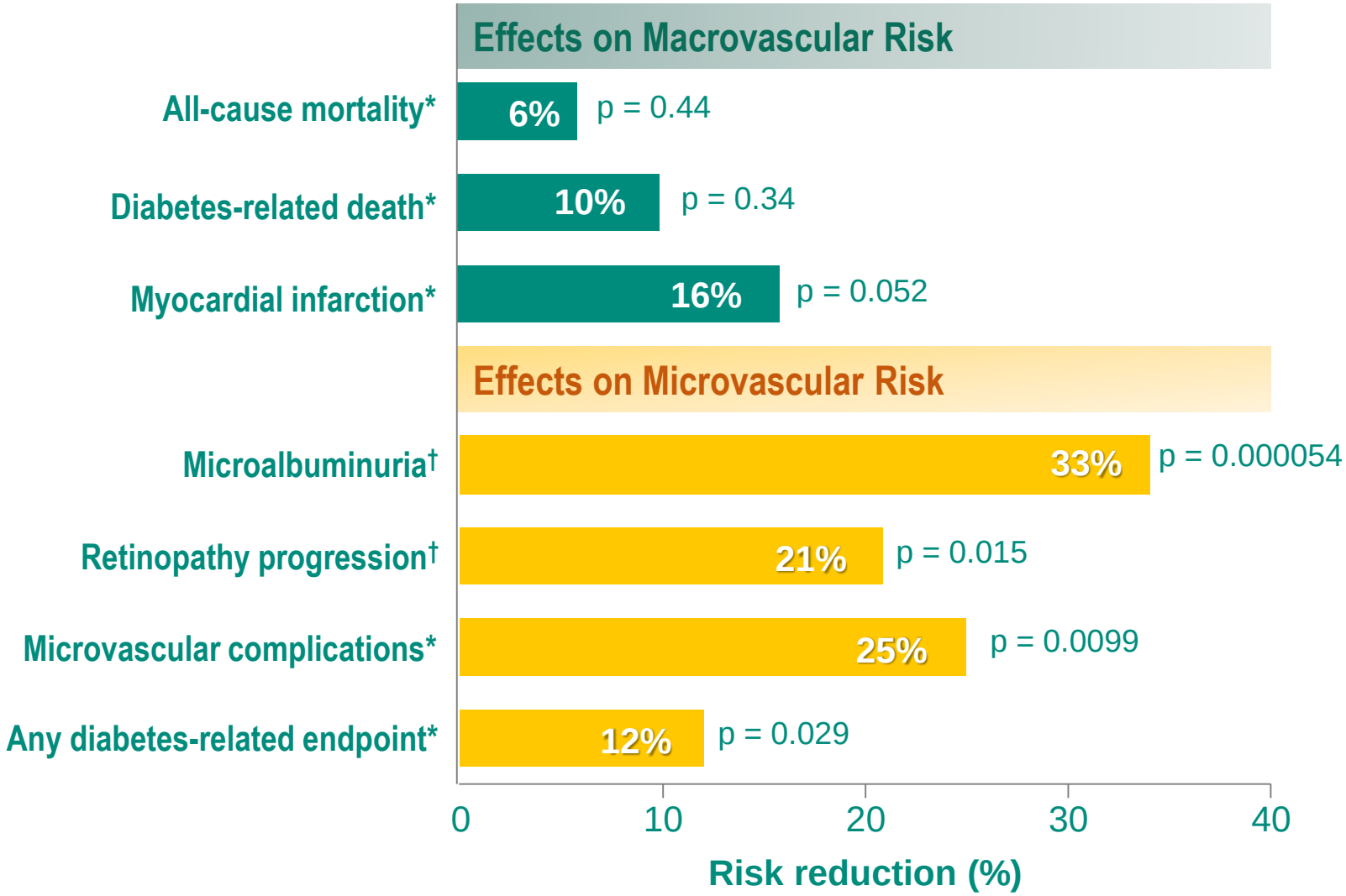
Patients:

5,012 New diagnosis T2D

Intensive glycemic control

Conventional glycemic control





*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.
UKPDS 33. Lancet 1998;352:837–53.

UKPDS: Long-term follow-up revealed significant reduction in MI associated with previous intensive glycaemic control

UKPDS

10 years follow up

Duration:

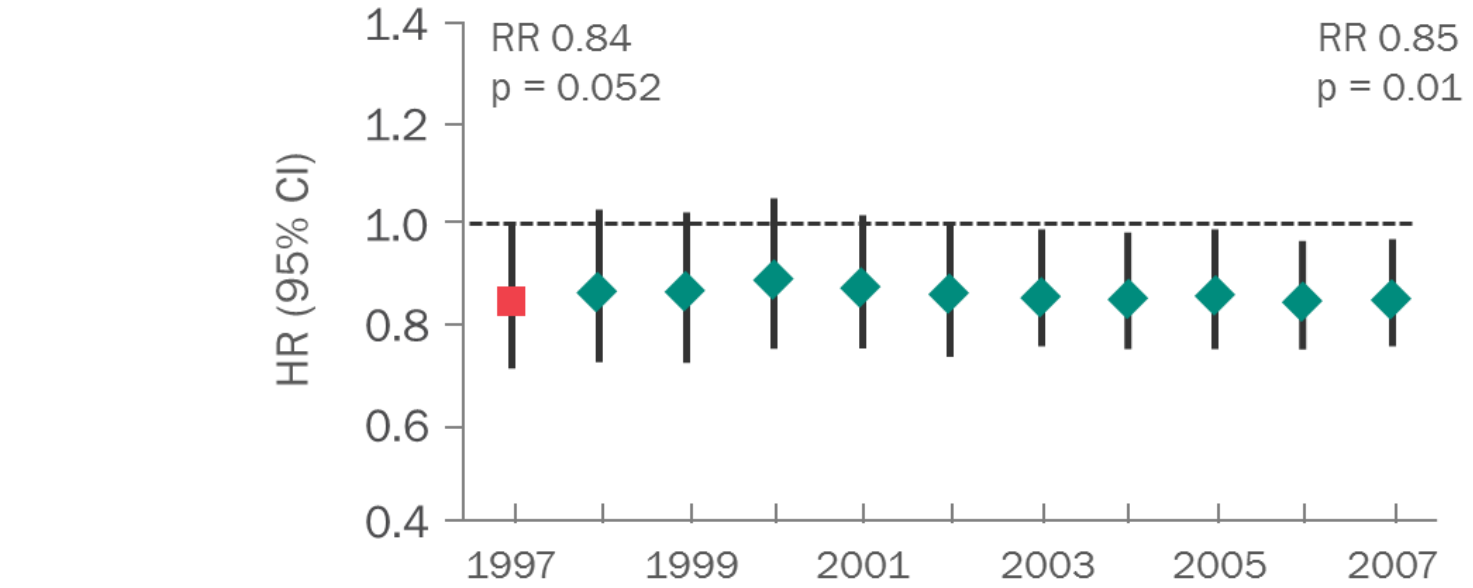
1997 – 2007

Patients:

3,277 attended annual UKPDS

Intensive glycemic control		Conventional glycemic control
FPG 108	v.s	FPG 270

10 years follow-up of Fatal or non-fatal MI with Intensive treatment: The Legacy Effect



No. of events						
Conventional therapy	186	212	239	271	296	319
Sulphonylurea–insulin	387	450	513	573	636	678

- Overall values at the end of the study in 1997
- Annual values during the 10-year post-trial monitoring period

Holman et al. N Engl J Med 2008;359:1577–89.

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes

Study[1]	Baseline HbA_{1c} Control vs intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS	9%→ 7.9% vs 7%	Newly diagnosed	↓	↓	↔	↓ *MI only*	↔	↓
ACCORD[1–3]	8.3%→ 7.5% vs 6.4%	10.0	↓*		↔		↑	
ADVANCE	7.5 %→ 7.3% vs 6.5%	8.0	↓	↔**	↔	↔	↔	↔
VADT	9.4 %→ 8.4% vs 6.9%	11.5	↓	?	↔	↓	↔	↔

Long-term follow-up[1,4,5]

↓ = decreased

↔ = neutral

↑ = increased

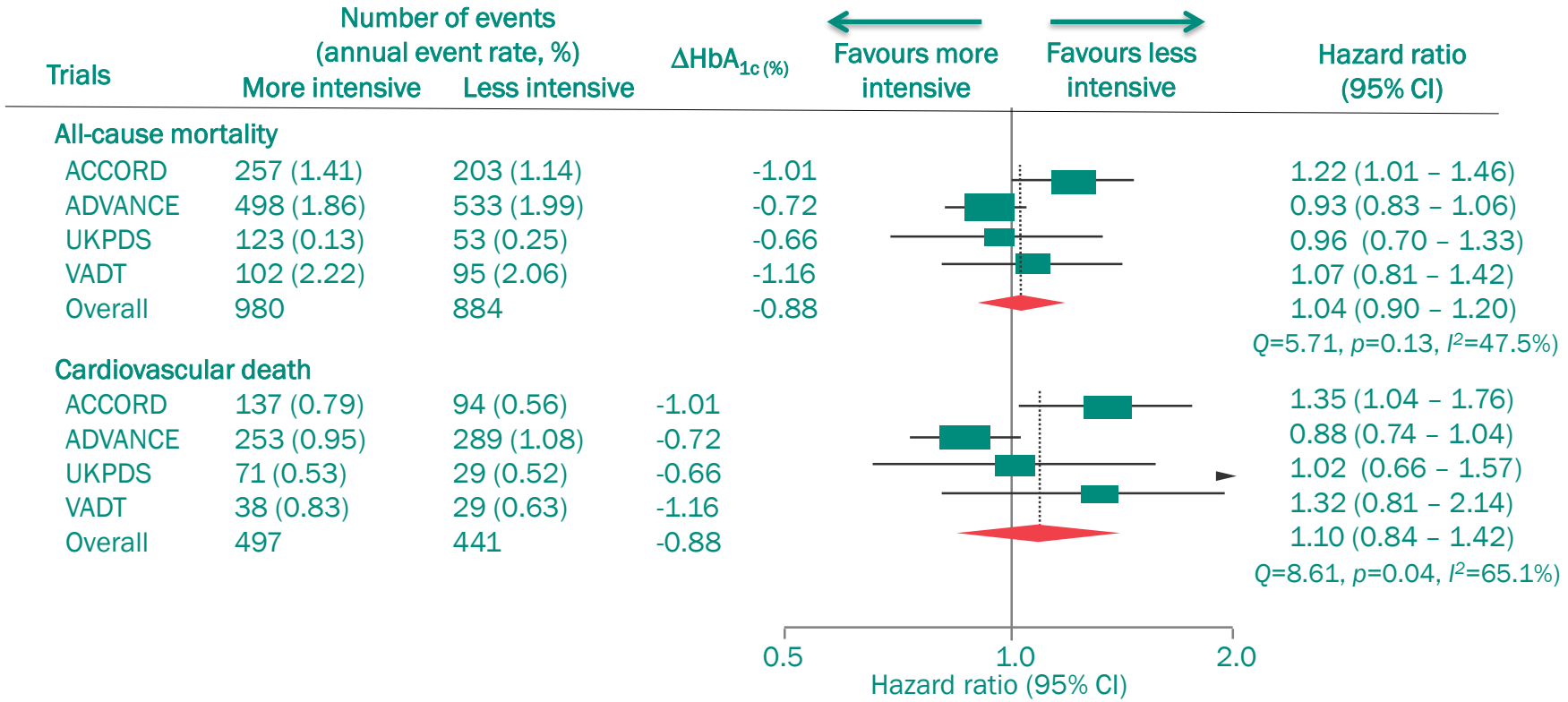
*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria2,3

**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)5

1. Table adapted from Bergenstal et al. Am J Med 2010;123:374.e9–e18. 2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8.
3. Ismail-Beigi et al. Lancet 2010;376:419–30. 4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT). 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

No evidence from prospective trials that more intensive glycaemic control reduces mortality

Meta-analysis including 27,049 participants and 2370 major vascular events

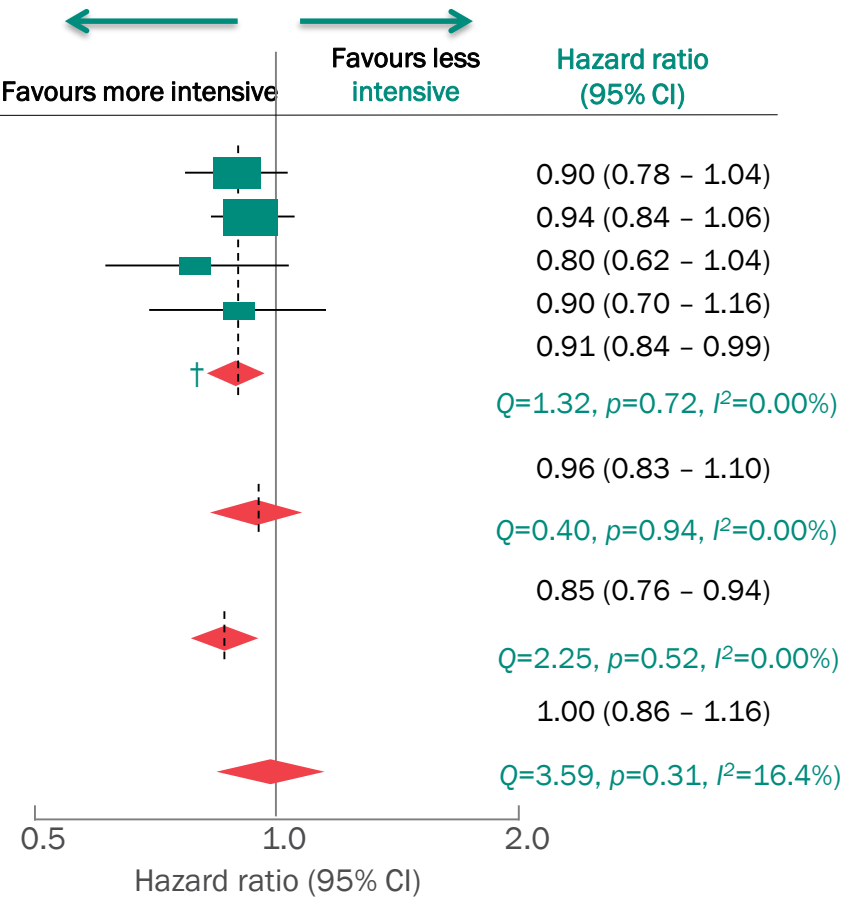


Turnbull et al. Diabetologia 2009;52:2288–98.

Meta-analysis shows modest benefit of intensive glycaemic control on macrovascular risk

Meta-analysis including 27,049 participants and 2370 major vascular events

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA_{1c} (%)	Hazard ratio (95% CI)
Major cardiovascular events*				
ACCORD	352 (2.11)	371 (2.29)	-1.01	0.90 (0.78 – 1.04)
ADVANCE	557 (2.15)	590 (2.28)	-0.72	0.94 (0.84 – 1.06)
UKPDS	169 (1.30)	87 (1.60)	-0.66	0.80 (0.62 – 1.04)
VADT	116 (2.68)	128 (2.98)	-1.16	0.90 (0.70 – 1.16)
Overall	1194	1176	-0.88	0.91 (0.84 – 0.99)
				Q=1.32, p=0.72, I^2=0.00%)
Stroke				
Overall	378	370	-0.88	0.96 (0.83 – 1.10)
				Q=0.40, p=0.94, I^2=0.00%)
Myocardial infarction				
Overall	730	745	-0.88	0.85 (0.76 – 0.94)
				Q=2.25, p=0.52, I^2=0.00%)
Hospitalised/fatal heart failure				
Overall	459	446	-0.88	1.00 (0.86 – 1.16)
				Q=3.59, p=0.31, I^2=16.4%)

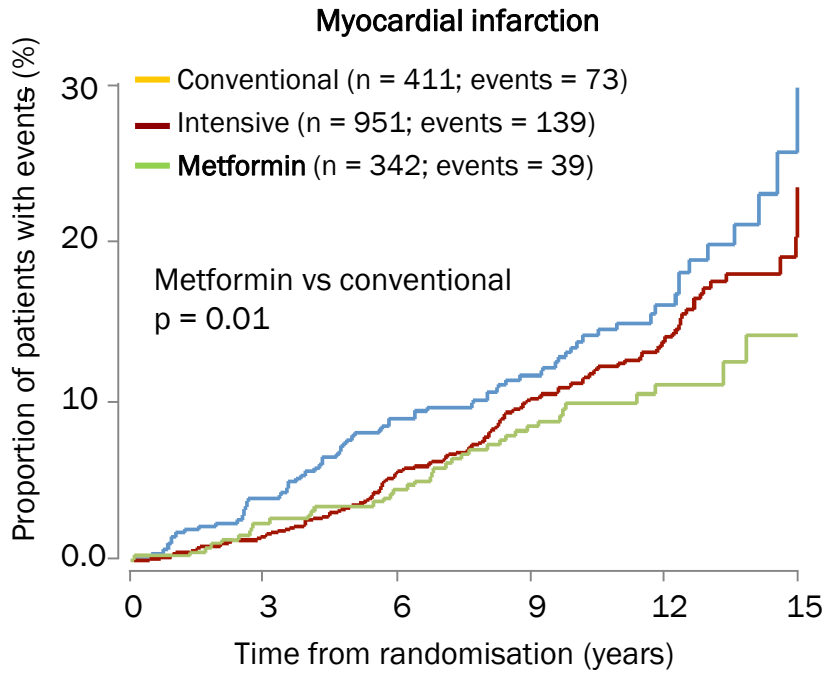


*Major CV events = CV death or non-fatal stroke or non-fatal MI.
†Diamonds incorporate point estimate (vertical dashed line) and encompass 95% CI of overall effect for each outcome.
Turnbull et al. Diabetologia 2009;52:2288–98.

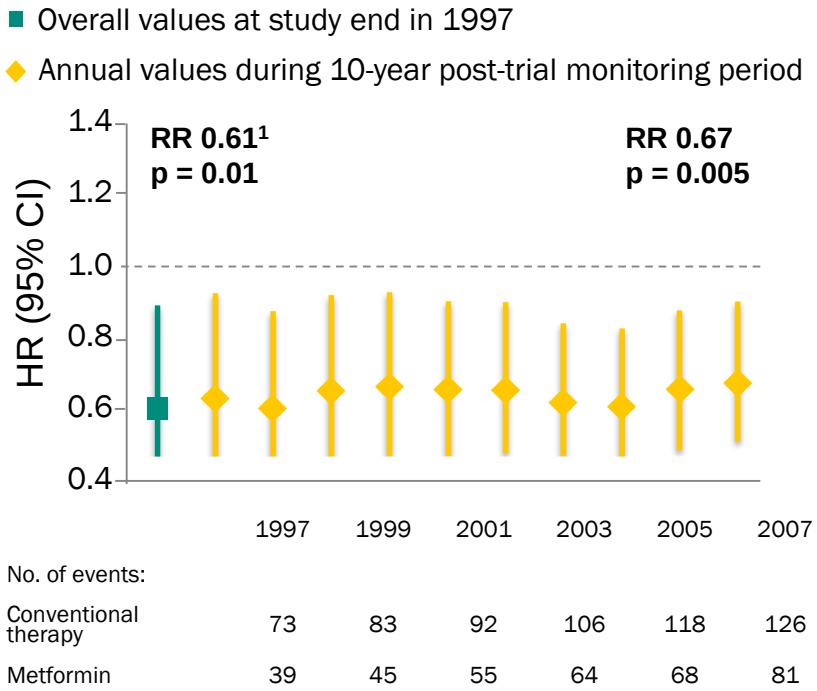
Starts from Metformin…

UKPDS 34 provides some evidence for beneficial CV effects of metformin in overweight patients

Risk of MI is 39% lower with metformin vs conventional therapy in obese patients[1,2]



Significant reduction in MI maintained over 10 years' follow-up[3]



No. of events:						
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

1. UKPDS 34. Lancet 1998;352:854–65. 2. http://www.medicines.org.uk/emc/medicine/23244/SPC. 3. Holman et al. N Engl J Med 2008;359:1577–89.

Then inspired from CV safety issues

Adverse CV events led the FDA to require demonstration of CV safety for new glucose-lowering drugs

1961 — UGDP study: tolbutamide discontinued due to increased CV mortality vs other treatment groups[1]

2005 — Muraglitazar found to potentially increase CV risk during FDA assessment[2]

- Sponsor withdrew application[1]

2007 — Rosiglitazone associated with increased risk for MI and CV-related death[3]

- Withdrawn in the EU[1]
- Use restricted in US[1]*

*In 2013, FDA panel voted to reduce safety restrictions on rosiglitazone[7]

2008 — ACCORD study: intensive glucose lowering was associated with increased all-cause mortality[4]
HR 1.22 (95% CI: 1.01–1.46); p = 0.04

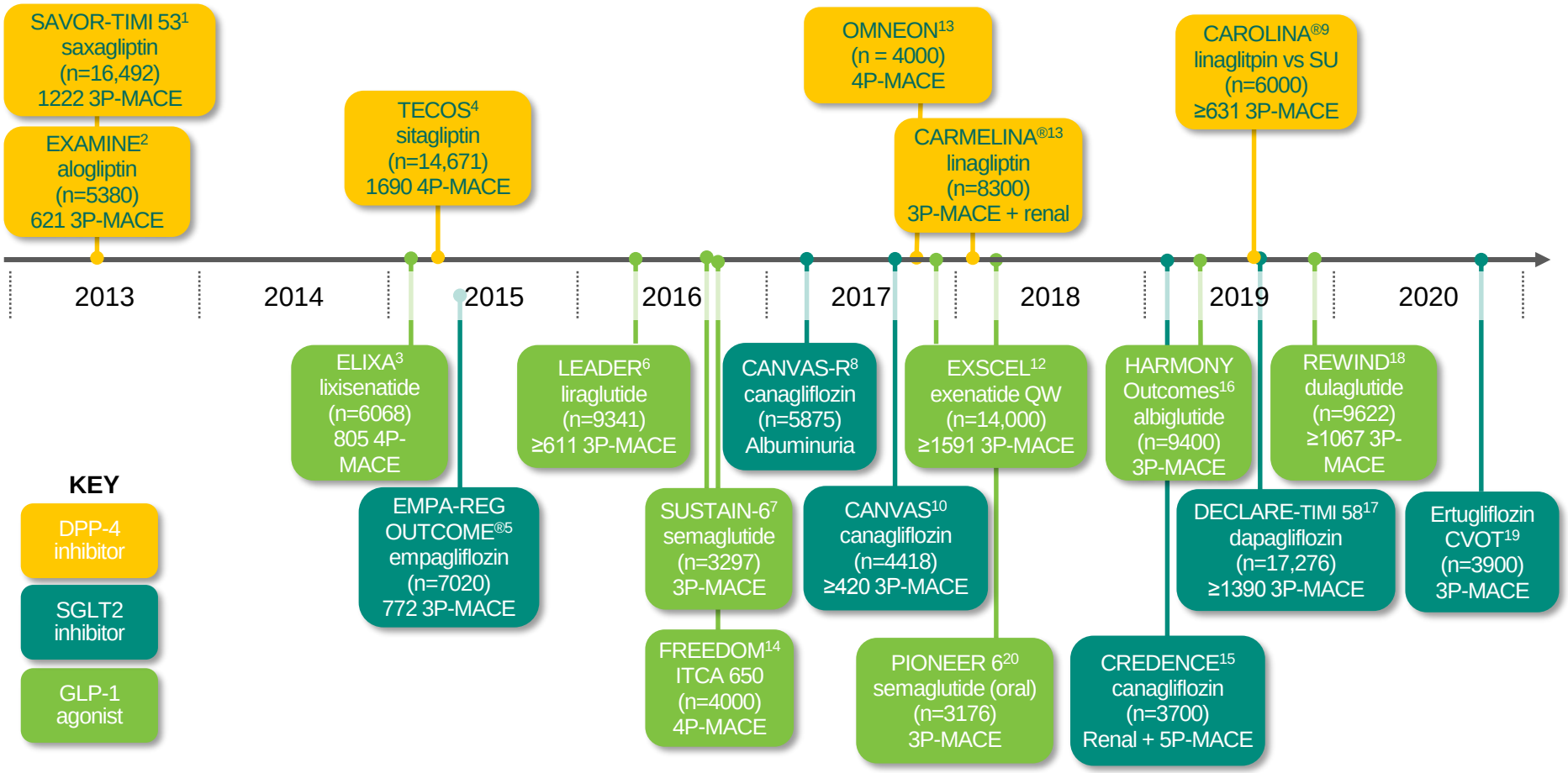
2008 — **New FDA requirements[5]**

2012 — **New EMA requirements[6]**

New diabetes drugs should demonstrate CV safety with meta-analysis and a CVOT

1. Nissen. Ann Intern Med 2012;157:671–2. 2. Nissen et al. JAMA 2005;294:2581–6. 3. Nissen et al. N Engl J Med 2007;356:2457–71. 4. ACCORD Study Group. N Engl J Med 2008;358:2545–59.
5. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/%20guidances/ucm071627.pdf
6. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf
7. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm376683.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

CV safety trials are being conducted for each compound within the newer classes



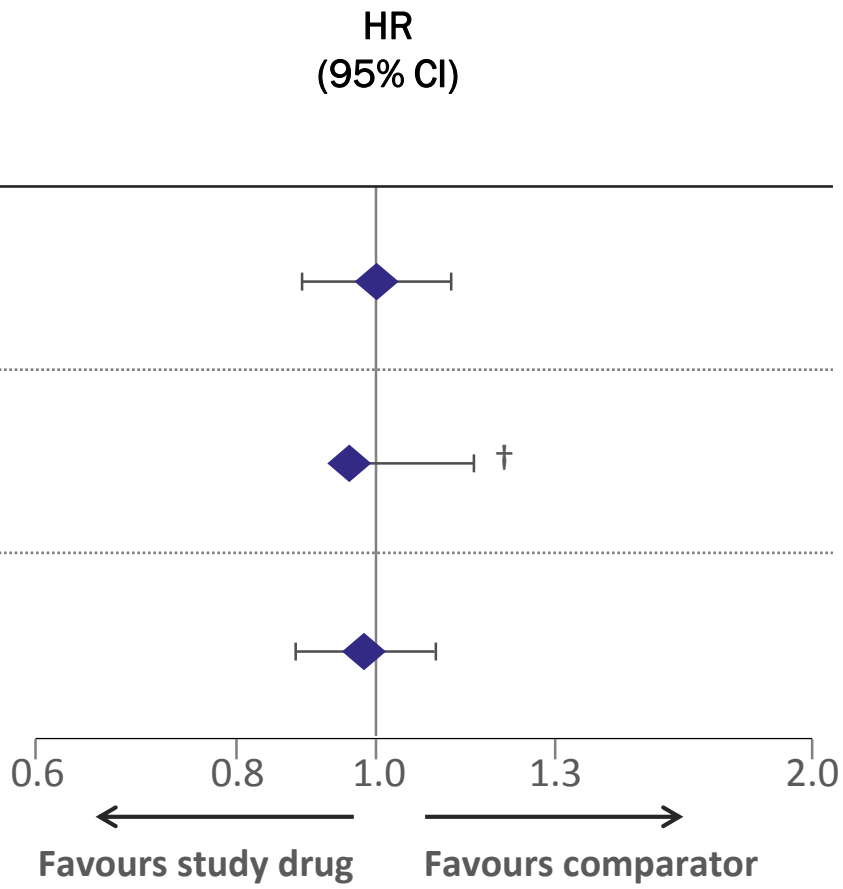
Trial disclosure dates for non-published trials from clinicaltrials.gov

3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 4-point major adverse cardiovascular events; 5P-MACE, 5-point major adverse cardiovascular events; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2

Adapted from Johansen OE. World J Diabetes 2015;6:1092 (references 1–19 expanded in slide notes)

No DPP4 inhibitor has been shown to reduce major adverse CV events in T2D patients[1-3]

	Number of patients with events (event rate, number of events/ 100 person-years)	
	Placebo + usual care	Study drug + usual care
SAVOR-TIMI 53[1] (Saxagliptin)	609 (3.7)	613 (3.7)
EXAMINE[2] (Alogliptin)	316 (11.8%)*	305 (11.3%)*
TECOS[3] (Sitagliptin)	851 (4.17)	839 (4.06)



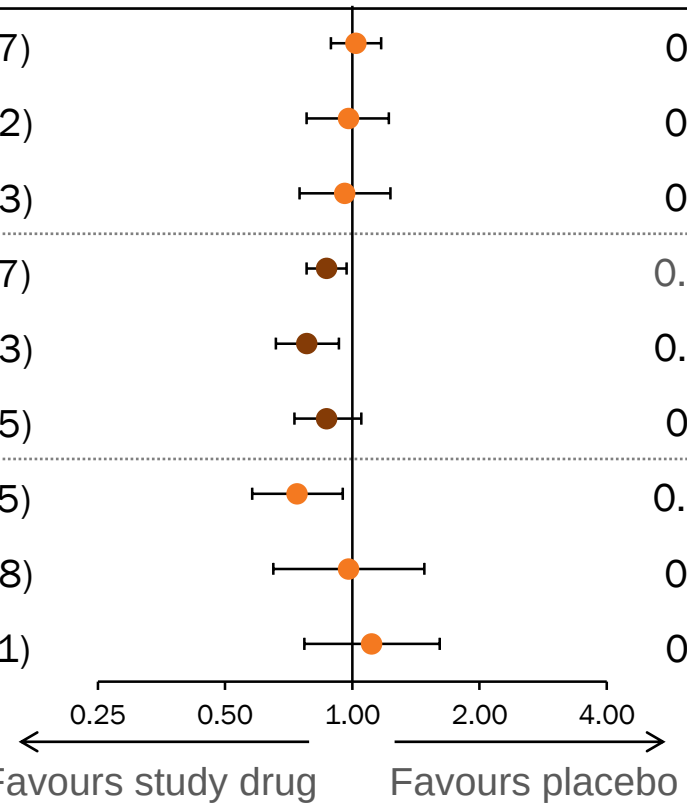
*Total event rate, %; †Upper boundary of 1-sided repeated CI

1. Scirica BM et al. N Engl J Med 2013;369:1317; 2. White WB et al. N Engl J Med 2013;369:1327; 3. Green JB et al. N Engl J Med 2015;373;232

Direct comparison of trials is not valid due to differences in study design, populations and methodology

CVOTs have revealed different CV effects of GLP-1 RA

Trial	Primary outcome	Patients with event/n treated n/N (%) Placebo + usual care	Study drug + usual care	HR (95% CI)	*p*-value
ELIXA[1] (Lixisenatide)	4P-MACE	399/3034 (13.2)	406/3034 (13.4)	1.02 (0.89, 1.17)	0.81
	CV death	158/3034 (5.2)	156/3034 (5.1)	0.98 (0.78, 1.22)	0.85
	HHF	127/3034 (4.2)	122/3034 (4.0)	0.96 (0.75, 1.23)	0.75
LEADER®[2] (Liraglutide)	3P-MACE	694/4672 (14.9)	608/4668 (13.0)	0.87 (0.78, 0.97)	0.01*
	CV death	278/4672 (6.0)	219/4668 (4.7)	0.78 (0.66, 0.93)	0.007
	HHF	248/4672 (5.3)	218/4668 (4.7)	0.87 (0.73, 1.05)	0.11
SUSTAIN-6®[3] (Semaglutide)	3P-MACE	146/1649 (8.9)	108/1648 (6.6)	0.74 (0.58, 0.95)	0.02*
	CV death	46/1649 (2.8)	44/1648 (2.7)	0.98 (0.65, 1.48)	0.92
	HHF	54/1648 (3.3)	59/1648 (3.6)	1.11 (0.77, 1.61)	0.12



**p*-value for superiority.

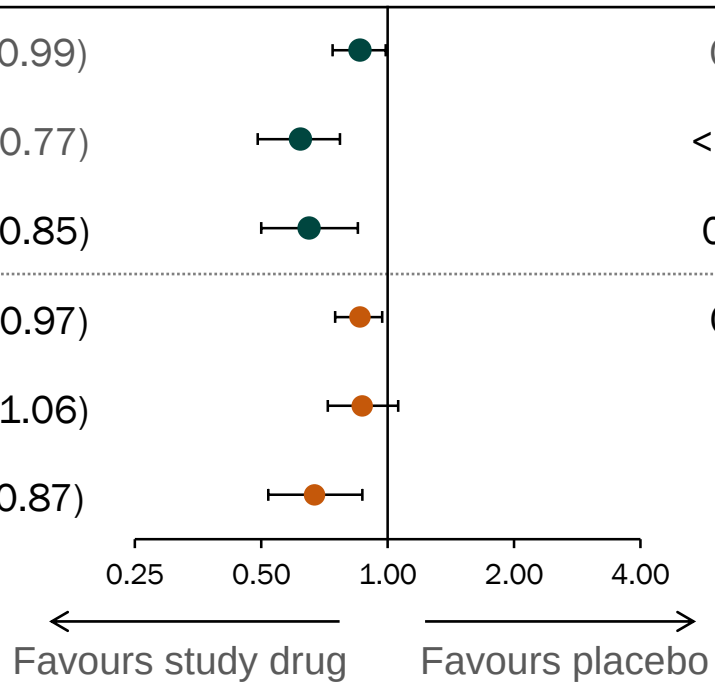
3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; GLP-1, glucagon-like peptide – 1;HHF, hospitalisation for heart failure

1. Pfeffer MA *et al. N Engl J Med* 2015;373:2247; 2. Marso SP *et al. N Eng J Med* 2016;375:311; 3. Marso SP *et al. N Eng J Med* 2016;375:1834

Direct comparison of trials is not valid due to differences in study design, populations and methodology

Both SGLT2 inhibitor CVOTs have reported CV benefits, however, in different extend of clinical endpoints.

Trial	Primary outcome	Patients with event/n treated n/N (%) Placebo + usual care	Study drug + usual care	HR (95% CI)	*p*-value
EMPA-REG OUTCOME®[1] (Empagliflozin)	3P-MACE	282/2333 (12.1)	490/4687 (10.5)	0.86 (0.74, 0.99)	0.04*
	CV death	137/2333 (5.9)	172/4687 (3.7)	0.62 (0.49, 0.77)	<0.001†
	HHF	95/2333 (4.1)	126/4687 (2.7)	0.65 (0.50, 0.85)	0.002†
CANVAS®[2] (Canagliflozin)	3P-MACE	426/4347 (9.8)	585/5795 (10.1)	0.86 (0.75, 0.97)	0.02*
	CV death	185/4347 (4.3)	268/5795 (4.6)	0.87 (0.72, 1.06)	-
	HHF	120/4347 (2.8)	123/5795 (2.1)	0.67 (0.52, 0.87)	-



*p-value for superiority. †nominal *p*-value
3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HHF, hospitalisation for heart failure; SGLT2, sodium-glucose transporter 2
1. Zinman B *et al. N Engl J Med* 2015:373:2117; 2. Neal B *et al. N Engl J Med* 2017; doi:10.1056/NEJMoa1611925

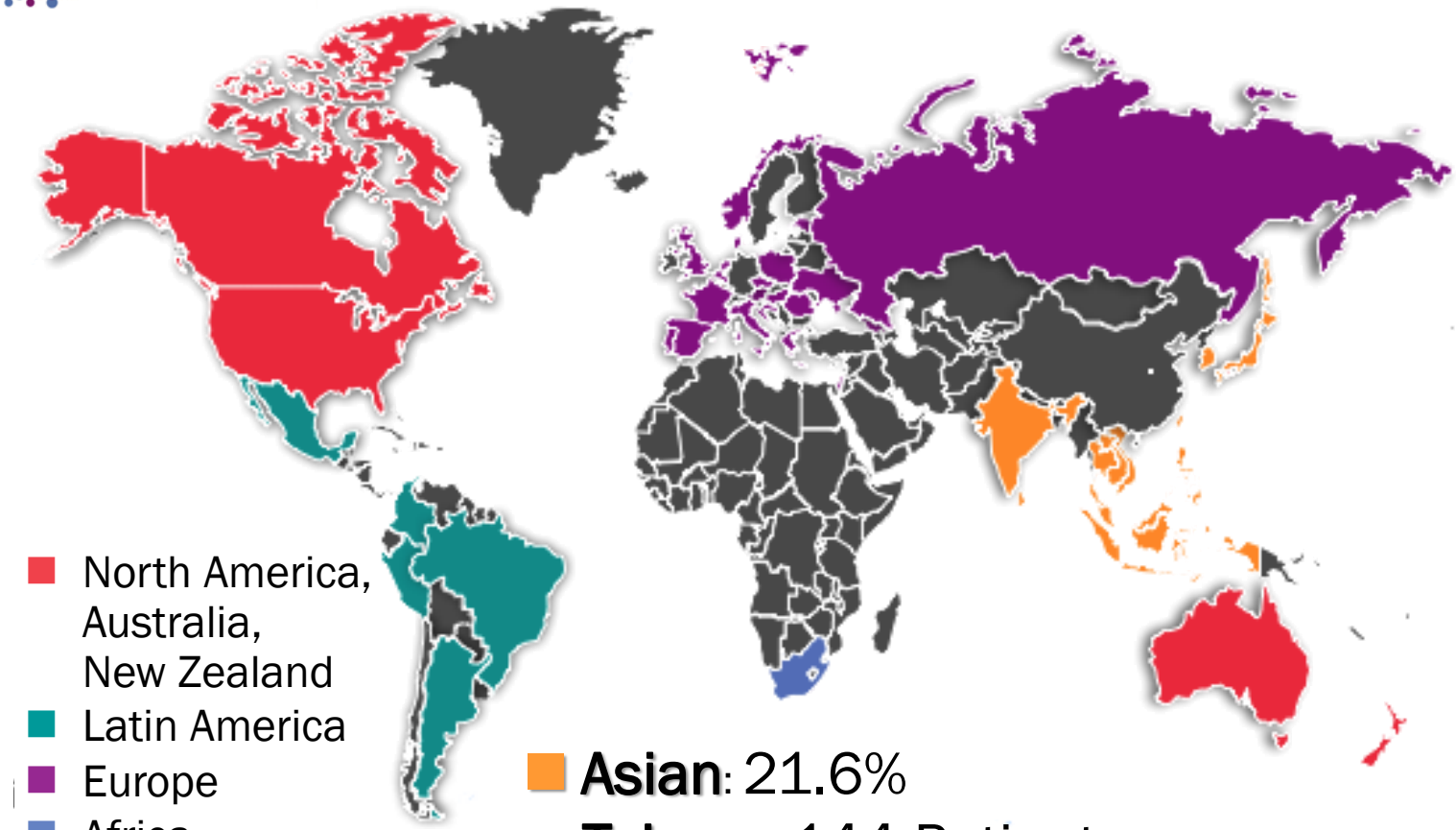
Direct comparison of trials is not valid due to differences in study design, populations and methodology

Jardiance® and EMPA-REG OUTCOME®, was the first to provide insight into CV benefits of a glucose-lowering agent

Jardiance & EMPA-REG OUTCOME® revealed a new era in the management of T2D

EMPA-REG OUTCOME® was a large randomized, double-blind, placebo-controlled CV outcomes trial[1]

EMPA-REG OUTCOME®

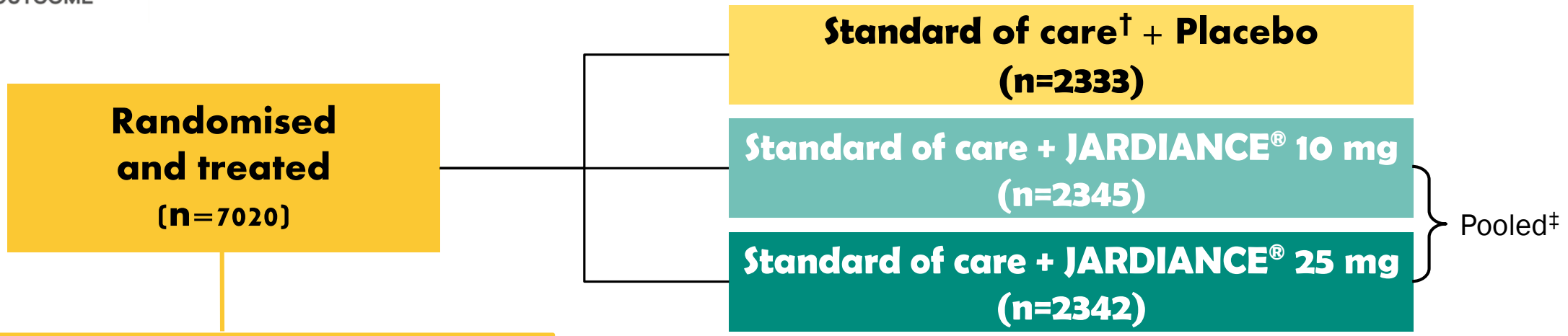


- Over 7,000 patients
- 42 countries, 590 sites
- Asian: 21.6%
- Taiwan: 144 patients

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28.

Patients received JARDIANCE® or placebo on top of standard of care for CV and T2D management[1]

EMPA-REG OUTCOME®



- Adults with T2D
- Established CV disease (CAD, PAD, MI or stroke)
- HbA_{1c} 7-10%
- eGFR >30 mL/min/1.73m$^{2\#}$

- **Glucose-lowering therapy was to remain unchanged for the first 12 weeks**
- **The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event**

†Standard of care included antihypertensives, lipid-lowering agents, anticoagulants and glucose-lowering therapies.[1]

‡Data from both doses of JARDIANCE® were pooled for statistical analysis versus placebo.

JARDIANCE® can be used be used down to an eGFR of 45 mL/min/1.73m^2.

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28.

In addition to T2D, all patients had established CV disease[1]

EMPA-REG OUTCOME®

Patient characteristics

63	57%	30.6	105
Age (years)	Pt with T2D duration >10 years	BMI (kg/m^2)	Waist circumference (cm)

T2D Patients 99% with any CV Disease*

76%	47%	23%	10%	21%
Coronary artery disease	History of MI	History of stroke	Heart failure	Peripheral artery disease

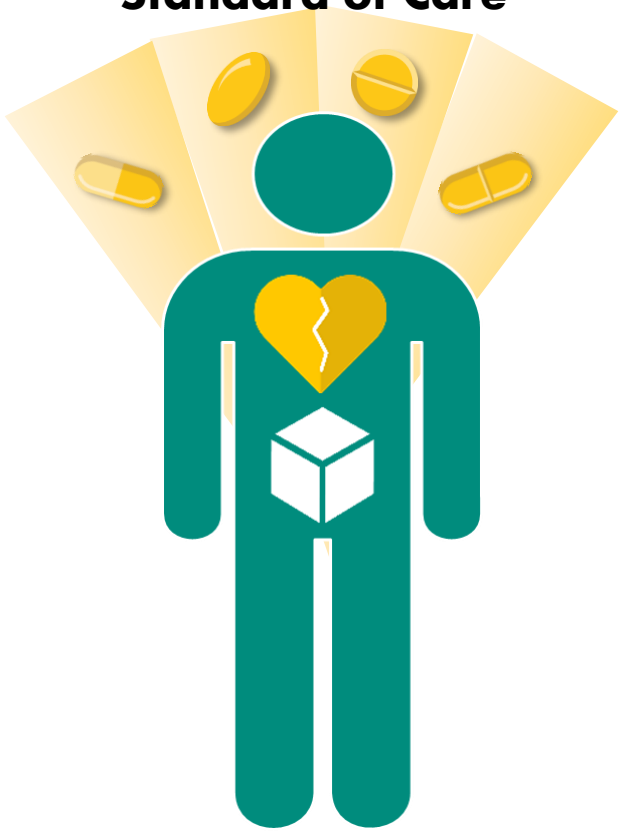
Data are mean or %. BMI, body mass index; Data are from patients treated with ≥1 dose of study drug
*Established CV disease; †Placebo, n=2332; ‡Based on narrow standardised MedDRA query 'cardiac failure'
CV, cardiovascular; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28.

JARDIANCE® Patients Received Standard of Care for CV Disease and Type 2 Diabetes

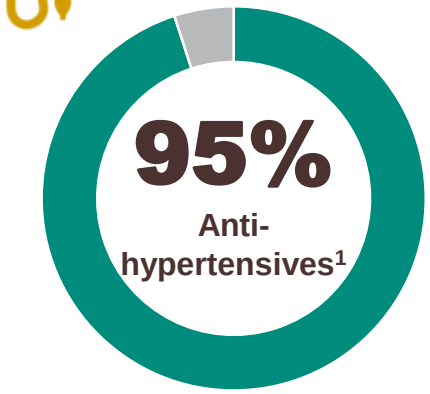
EMPA-REG OUTCOME®

Standard of Care



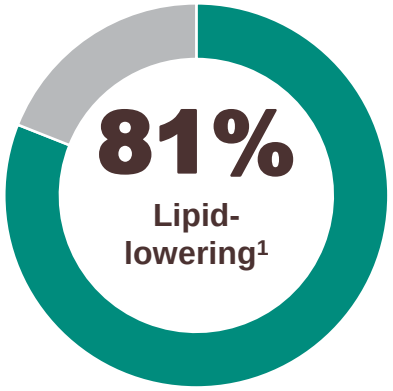
Patients receiving therapy at baseline

Blood pressure management



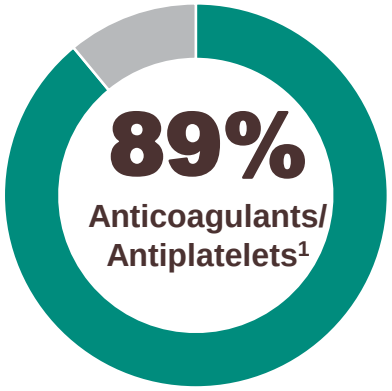
ACEi/ARBs	81%
Beta-blockers	65%
Diuretics	43%
Ca-channel blockers	33%

Lipid management



Statins	77%
Fibrates	9%
Ezetimibe	4%
Niacin	2%
Other	8%

Antiplatelet Therapy



ASA	83%
Clopidogrel	11%
Vitamin K antagonists	6%

Glycaemic management

Metformin	74%
Insulin	48%
Sulphonylurea	43%
DPP-4 inhibitors	11%
TZDs	4%
GLP-1 RA	3%

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; TZD, thiazolidinedione

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Zinman B *et al. Cardiovasc Diabetol* 2014;13:102

JARDIANCE®:
The only oral T2D agent approved to reduce the risk of CV death

EMPA-REG OUTCOME®

In patients with T2D and established CV disease (CAD, PAD, MI or stroke) vs placebo on top of standard of care[1,2]

38% relative risk reduction in CV death vs placebo on top of standard of care[1]

HR=0.62; P<0.001

- Primary endpoint met superiority vs placebo. Primary endpoint was composite of CV death, non-fatal MI and non-fatal stroke (HR=0.86; P=0.04)

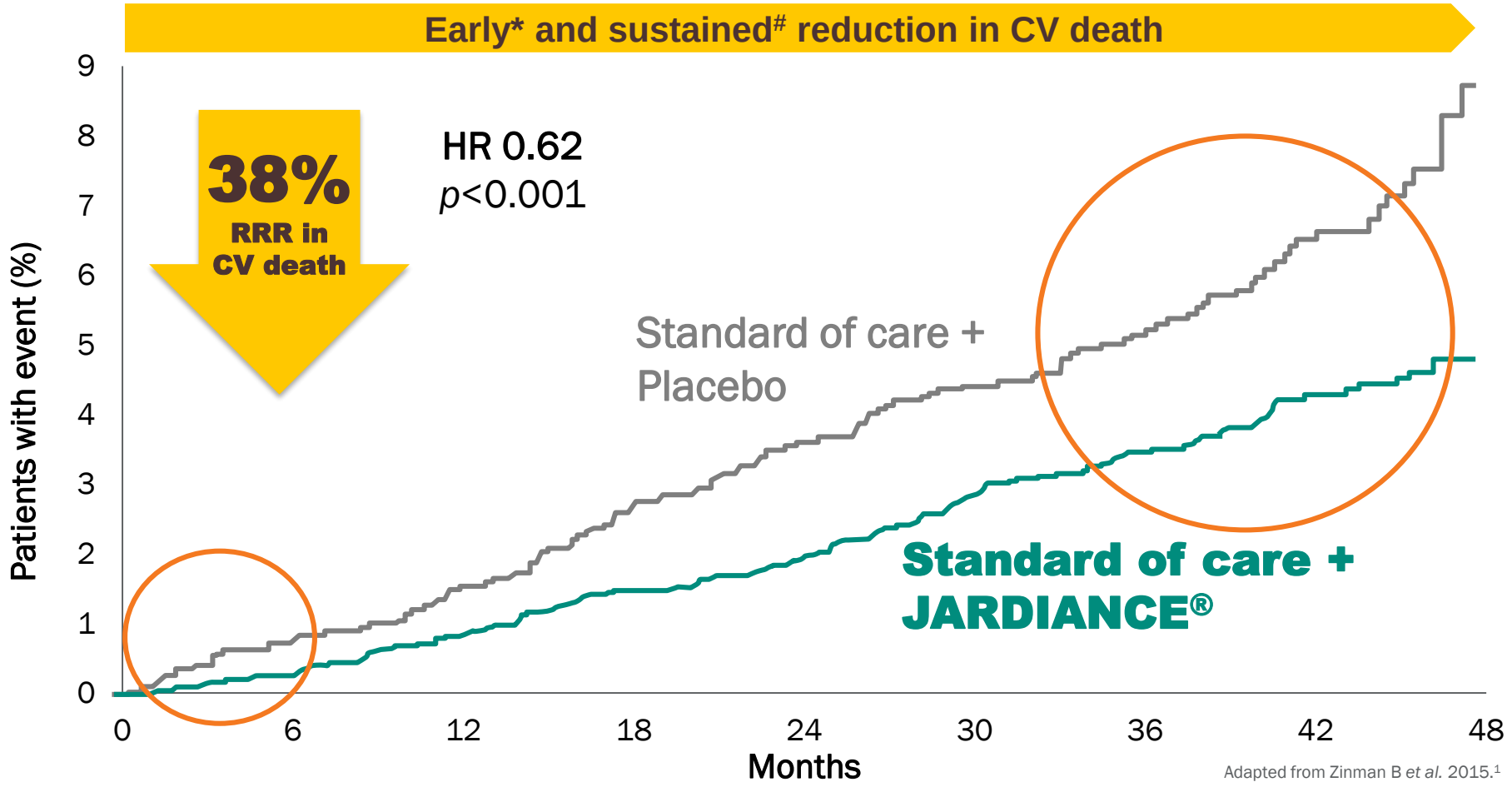
Standard of care included antihypertensives, lipid-lowering agents, anticoagulants and glucose-lowering therapies.[1]
The absolute risk for CV death was 5.9% in patients receiving standard of care plus placebo and was reduced to 3.7% in patients receiving standard of care plus JARDIANCE® (p<0.001).[1]

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28. 2. JARDIANCE® Approved Product Information.

CV death

JARDIANCE® reduced the relative risk of CV death by 38%

vs placebo on top of standard of care in patients with T2D and established CV disease (CAD, PAD, MI or stroke)[1]



Adapted from Zinman B *et al.* 2015.[1]

Results achieved on top of standard of care

- Antihypertensive
- Lipid lowering agents
- Anticoagulants
- Glucose lowering agents

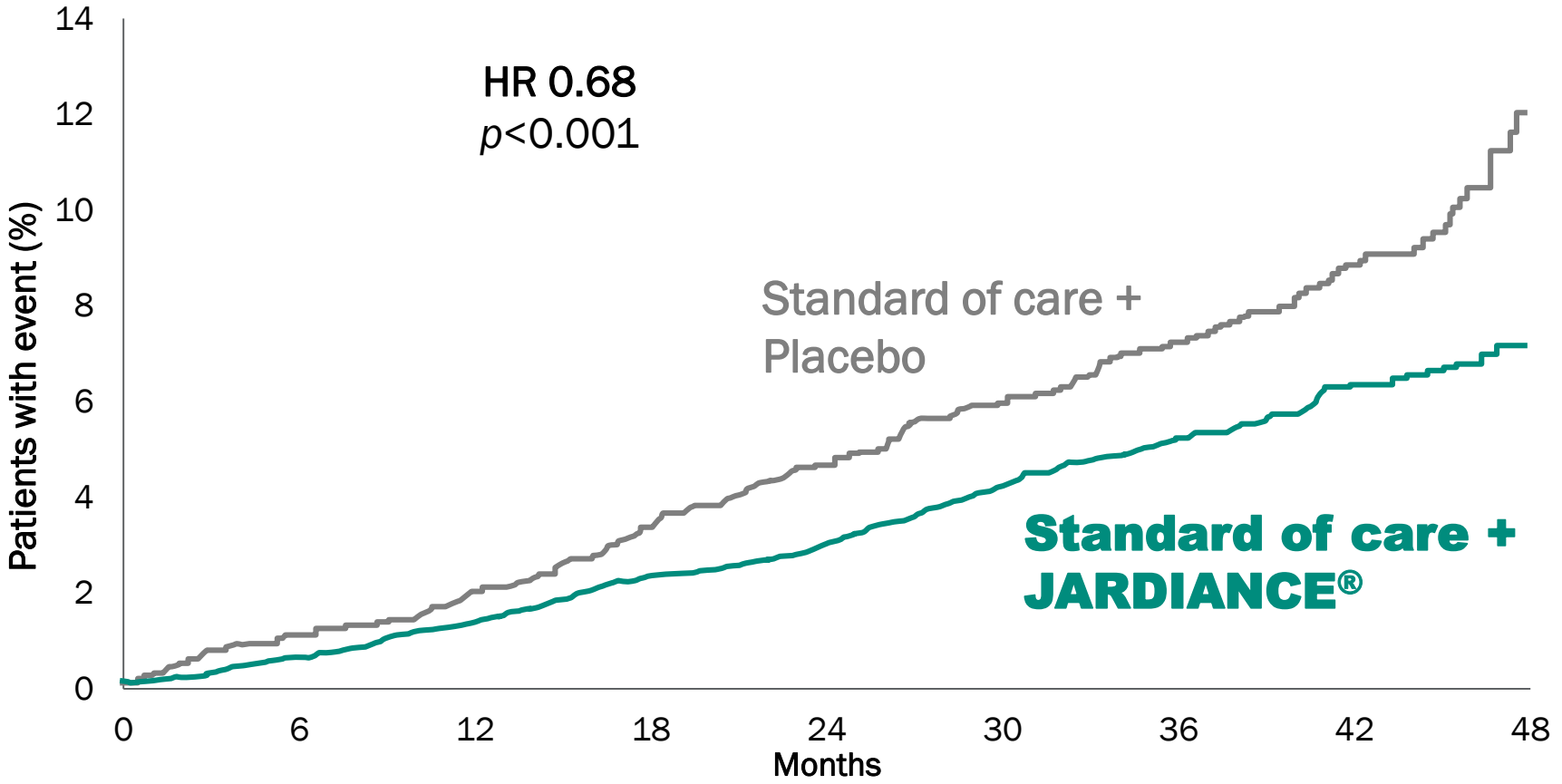
EMPA-REG OUTCOME®

*Within 6 months from start. #Up to 48 months from start.
CV death was a pre-specified secondary endpoint. Cumulative incidence function. HR, hazard ratio
The absolute risk for CV death was 5.9% in patients receiving standard of care plus placebo and was reduced to 3.7% in patients receiving standard of care plus JARDIANCE® (p<0.001).[1]

1. Zinman B *et al. N Engl J Med* 2015;373:2117-28.

EMPA-REG OUTCOME : All-cause mortality

vs placebo on top of standard of care in patients with T2D and established CV disease (CAD, PAD, MI or stroke)[1]



Results achieved on top of standard of care

- Antihypertensive
- Lipid lowering agents
- Anticoagulants
- Glucose lowering agents

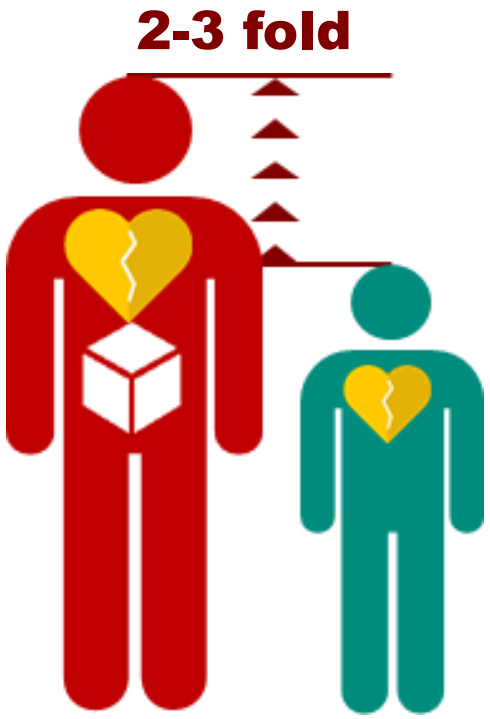
*Within 6 months from start. #Up to 48 months from start.
All cause mortality was a pre-specified secondary endpoint. Kaplan-Meier estimate. HR, hazard ratio
The absolute risk for all-cause mortality was 8.3% in patients receiving standard of care plus placebo and was reduced to 5.7% in patients receiving standard of care plus JARDIANCE® (p<0.001).[1]

1. Zinman B *et al. N Engl J Med* 2015;373:2117-28.

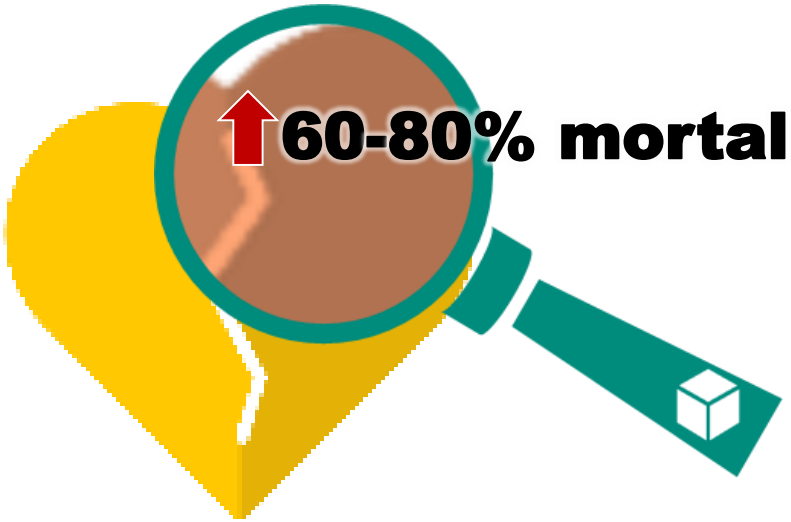
EMPA-REG OUTCOME®

JARDIANCE® is not indicated to reduce all-cause mortality

People with T2D are at increased risk of heart failure[1-3]



People with diabetes have a 2- to 3-fold higher risk of developing HF[1]



Heart Failure x Diabetes

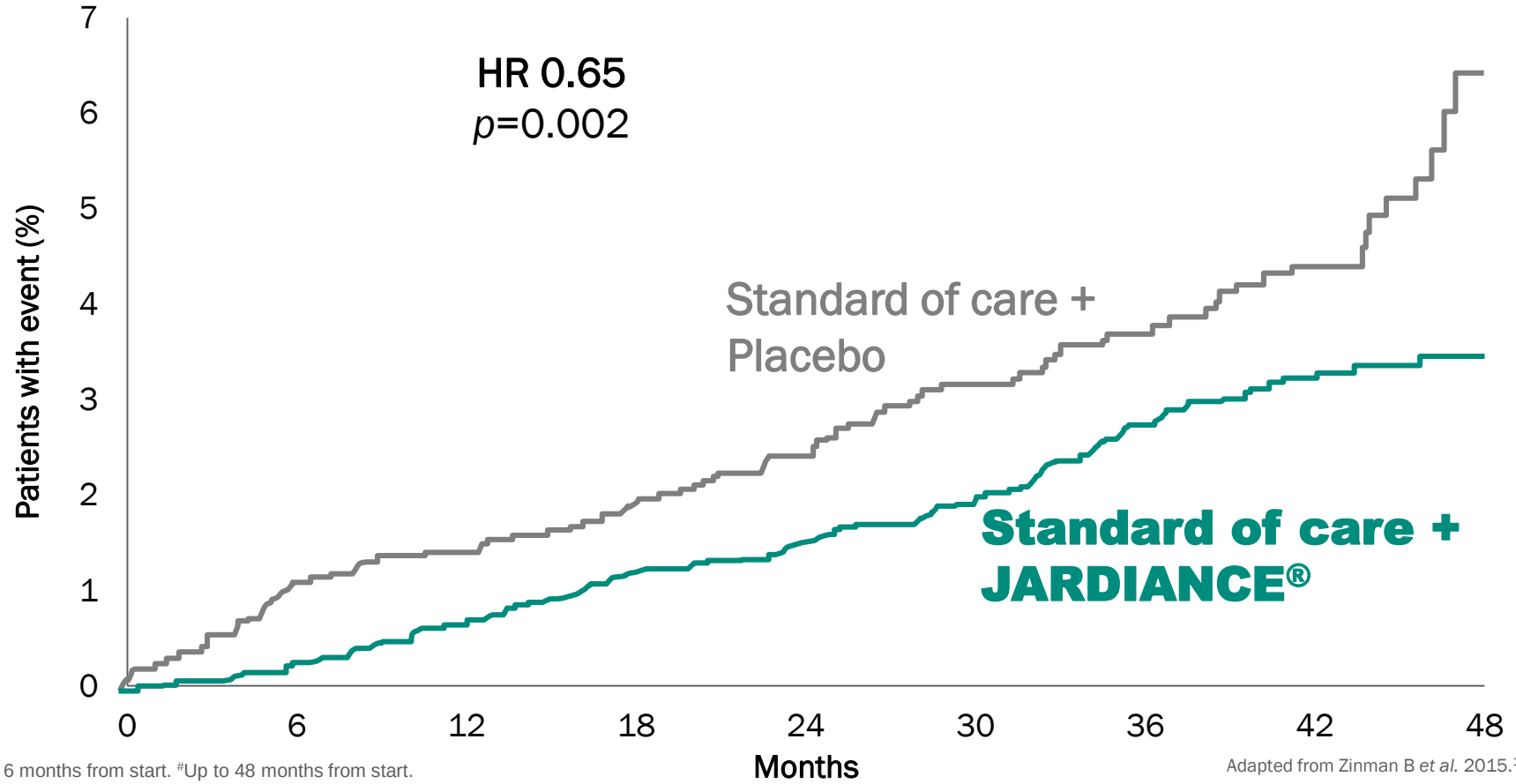
Diabetes confers a 60–80% greater probability of all-cause and CV death in those with established HF[2]*

*Based on data from two clinical studies. HF, heart failure

1. Gilbert RE and Krum H. *Lancet* 2015;385:2107–17. 2. Amaral N and Okonko DO. *Diab Vasc Dis Res* 2015;12:239–48. 3. Cubbon RM *et al*. *Diab Vasc Dis Res* 2013;10:330–6.

EMPA-REG OUTCOME : Hospitalization of Heart Failure

vs placebo on top of standard of care in patients with T2D and established CV disease (CAD, PAD, MI or stroke)[1]



Adapted from Zinman B *et al.* 2015.[1]

Results achieved on top of standard of care

- Antihypertensive
- Lipid lowering agents
- Anticoagulants
- Glucose lowering agents

*Within 6 months from start. #Up to 48 months from start.

Hospitalisation for heart failure was a pre-specified secondary endpoint. Cumulative incidence function. HR, hazard ratio

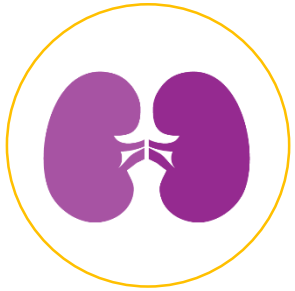
The absolute risk for hospitalisation for heart failure was 4.1% in patients receiving standard of care plus placebo and was reduced to 2.7% in patients receiving standard of care plus JARDIANCE® (p<0.002).[1]

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28.

EMPA-REG OUTCOME®

What has Jardiance done after added on to standard of care in patients with T2D x CVD ?

Relative risk reduction:

3P-MACE	CV death	All-cause mortality	HHF	Incident or worsening nephropathy
				
↓14%	**↓38%**	**HR 0.68** *p*<0.001	**HR 0.65** *p=0.002*	**HR 0.61** *p*<0.001

3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure; T2D, type 2 diabetes

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. N Engl J Med* 2016;375:323

Number needed to treat (NNT) to save 1 life

4S[1]

Simvastatin[1]
for 5.4 years

30

In high CV risk
5% diabetes,
26% hypertension

HOPE[2]

Ramipril[2]
for 5 years

56

In high CV risk
38% diabetes,
46% hypertension

EMPA-REG OUTCOME®[3]
JARDIANCE®[3]

for 3.1 years

39

T2D with established CV disease (CAD, PAD, MI or stroke) on top of standard of care

92% hypertension

Pre-ACEi/ARB era

> 80% ACEi/ARB

Pre-statin era

<29% statin

> 75% statin

1994 — 2000 — Now

Standard of care included antihypertensive, lipid-lowering agents, anticoagulants and glucose-lowering therapies.[3] ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers,

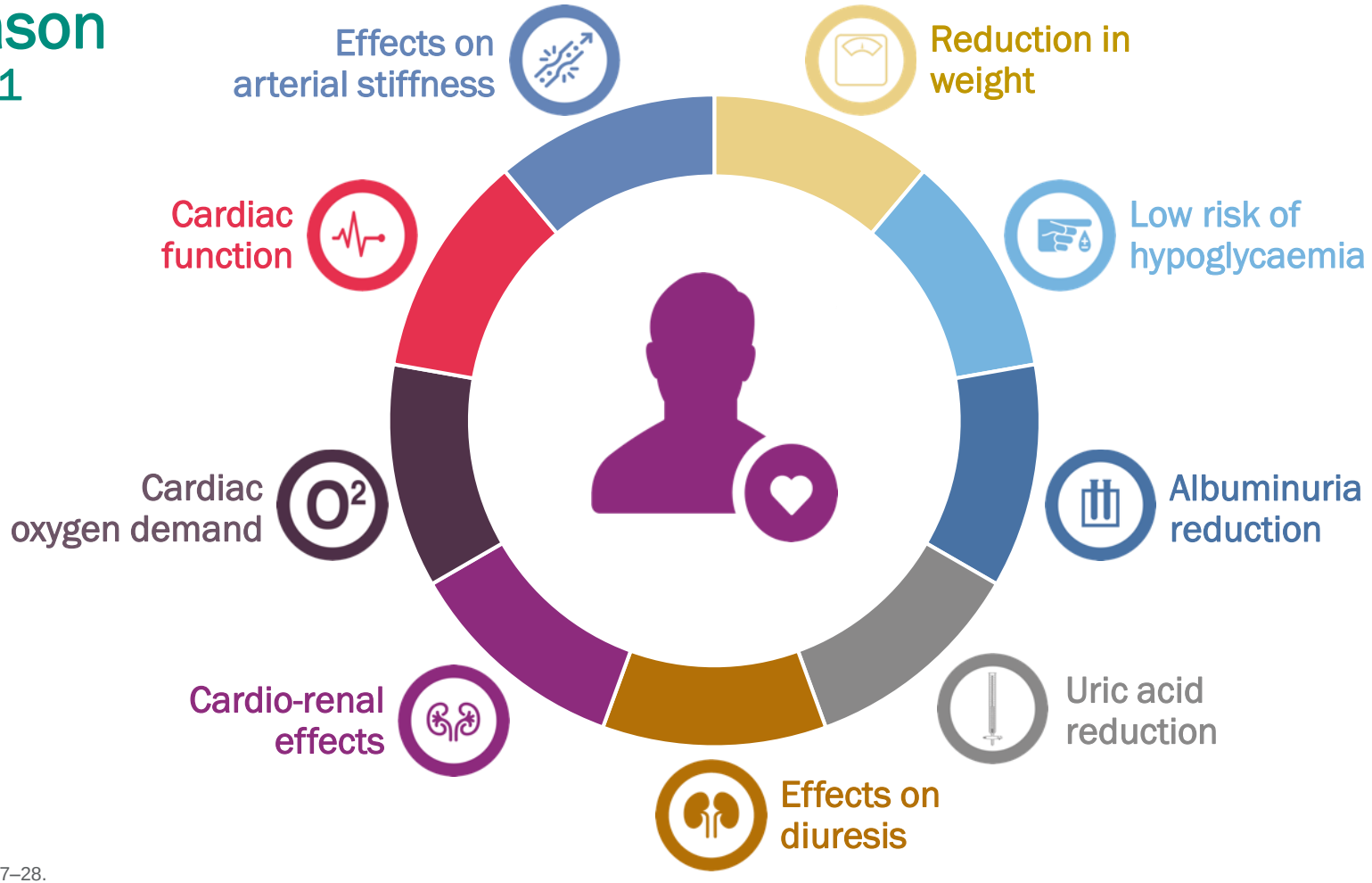
1. 4S investigators. *Lancet* 1994;344:1383-89. 2. HOPE investigators, *N Engl J Med* 2000;342:145-53. 3. Zinman B *et al. N Engl J Med* 2015;373:2117-28.

What may explain the CV and renal benefits of Jardiance® ?

The **Heart** of Diabetes

These results are not explained by HbA_{1c} reduction alone[1]

The exact reason is unknown...[1]

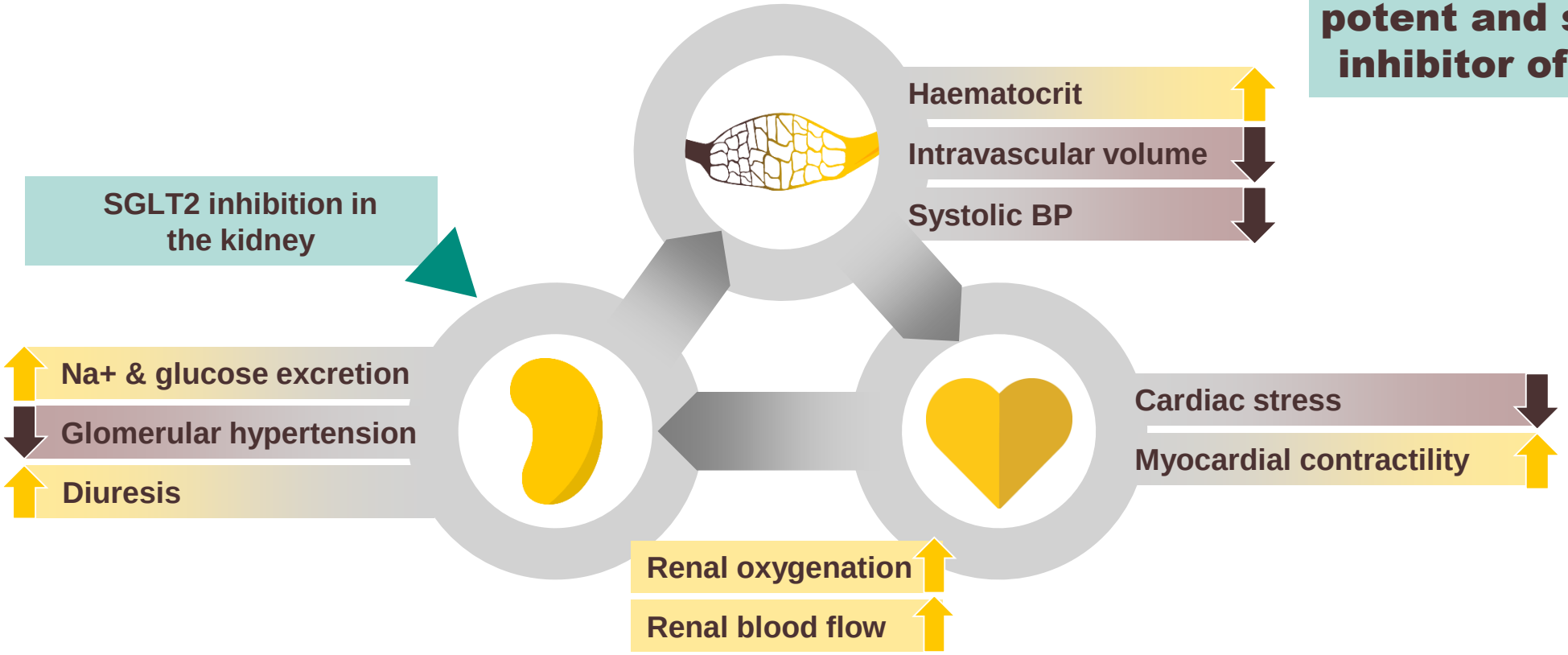


1. Zinman B *et al. N Engl J Med* 2015; 373:2117–28.

The mechanisms that explain the CV benefits of Jardiance® are likely to be multifactorial

Jardiance® modulates several factors related to CV risk[1]

Jardiance® is a reversible, highly potent and selective inhibitor of SGLT2[2]

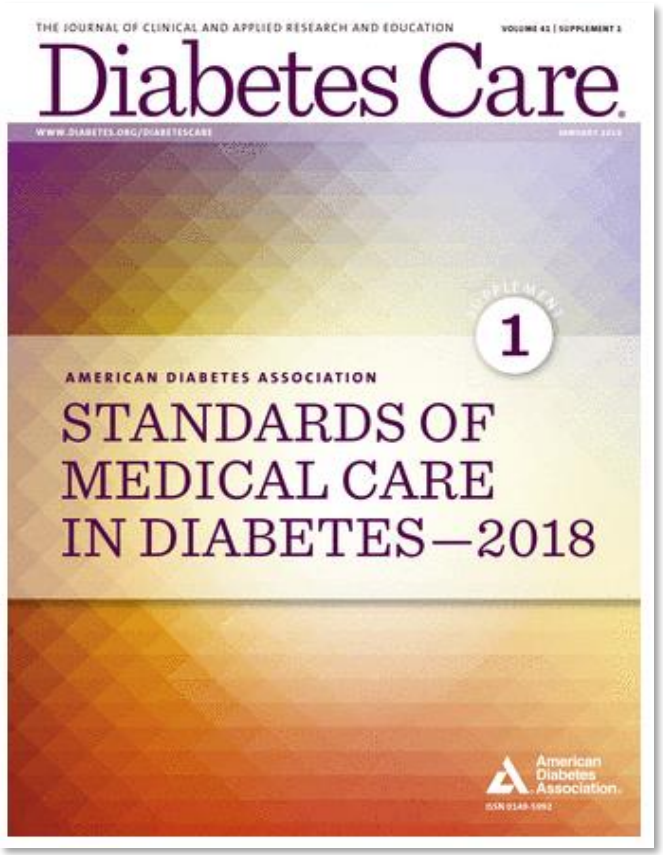


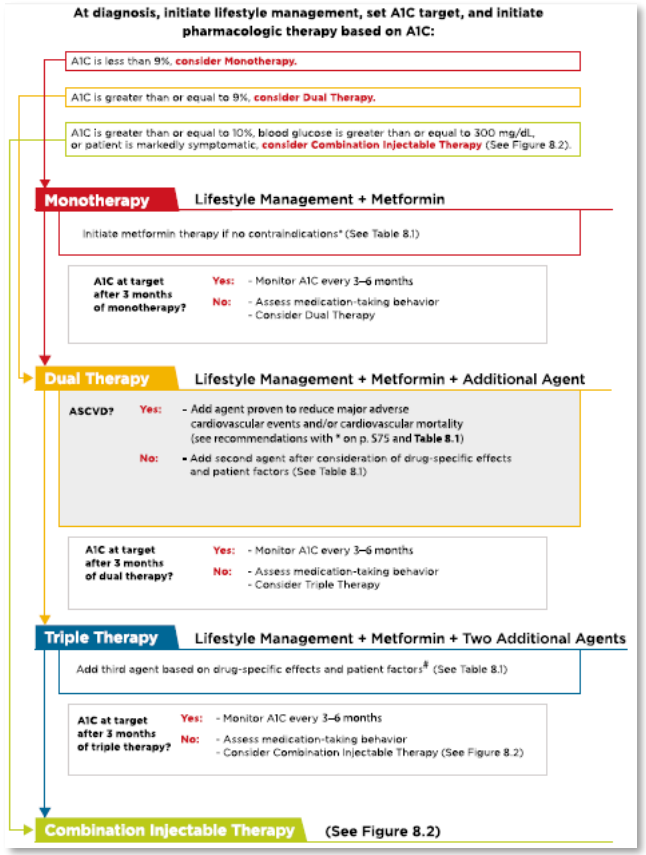
BP, blood pressure; CV, cardiovascular;
SGLT2, sodium-glucose co-transporter-2

1. Sattar N *et al. Diabetologia* 2016;59:1333;
2. Boehringer Ingelheim Jardiance® (empagliflozin). Prescribing Information. 2016

8. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008





ADA 2018 : Standard of Medical Care in T2DM

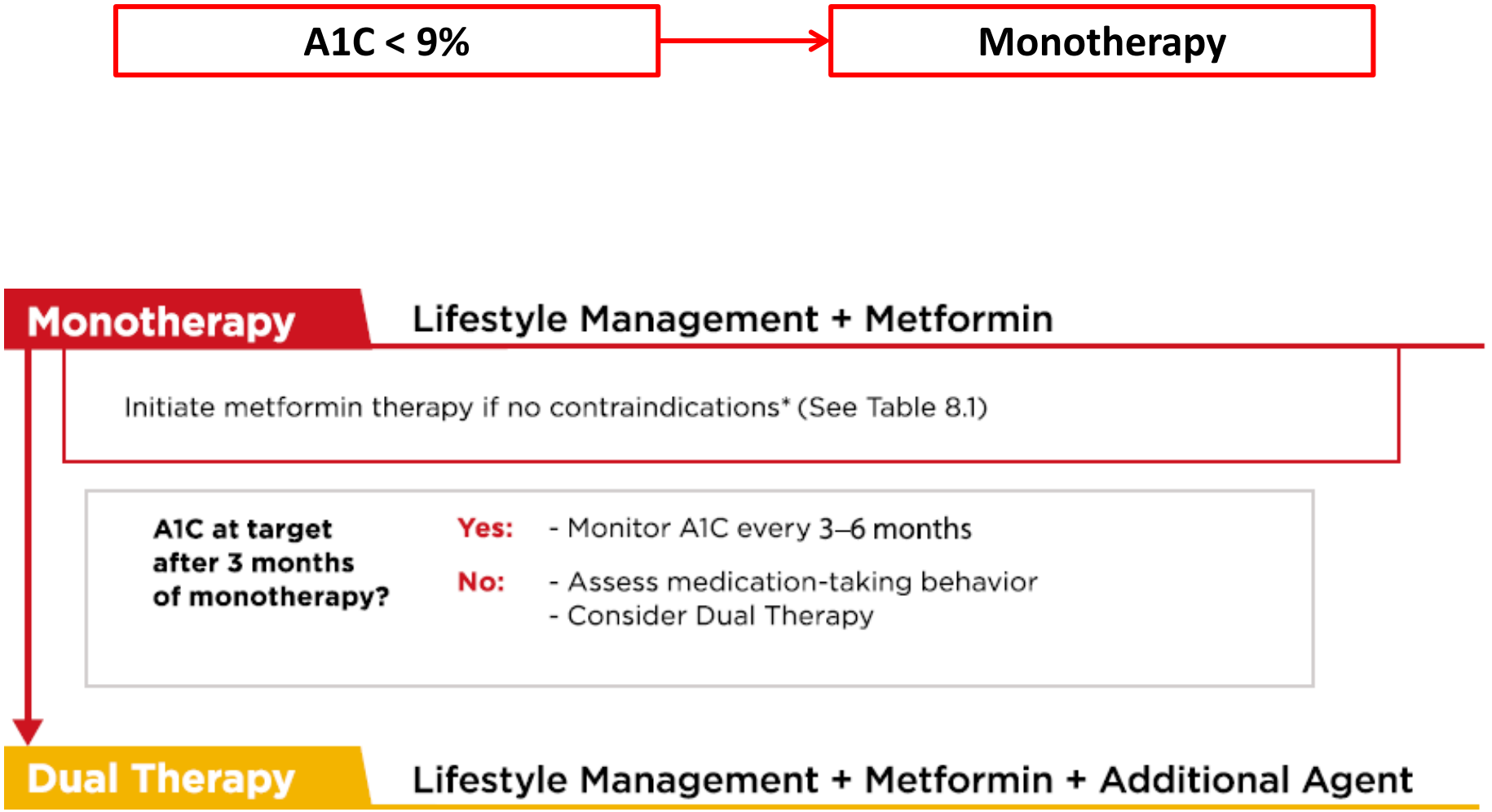
8. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*

American Diabetes Association

Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008

- **For patients with ASCVD, add a second agent with evidence of cardiovascular risk reduction after consideration of drug-specific and patient factors"**

- **In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, Antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors. A"**


A1C < 9%
Monotherapy
Monotherapy
Lifestyle Management + Metformin
Initiate metformin therapy if no contraindications* (See Table 8.1)
A1C at target after 3 months of monotherapy?
Yes: - Monitor A1C every 3–6 months
No: - Assess medication-taking behavior
- Consider Dual Therapy
Dual Therapy
Lifestyle Management + Metformin + Additional Agent

A1C ≥ 9% → Dual Therapy

Dual Therapy Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: – Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: – Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

- ✓ For patients with **ASCVD**, **add a second agent with evidence of cardiovascular risk reduction** after consideration of drug-specific and patient factors
- ✓ The **empagliflozin** and **liraglutide** trials demonstrated **significant reductions in cardiovascular death**

Triple Therapy Lifestyle Management + Metformin + Two Additional Agents

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

2018

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 DOI 10.4158/CS-2017-0153

Glycemic Control Algorithm

INDIVIDUALIZE GOALS

A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5% For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2017-0153

Profiles of Antidiabetic Medications

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe: Mild	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Gain	Loss
RENAL / GU	Contra-indicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Neutral	
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits

Likelihood of adverse effects

Use with caution

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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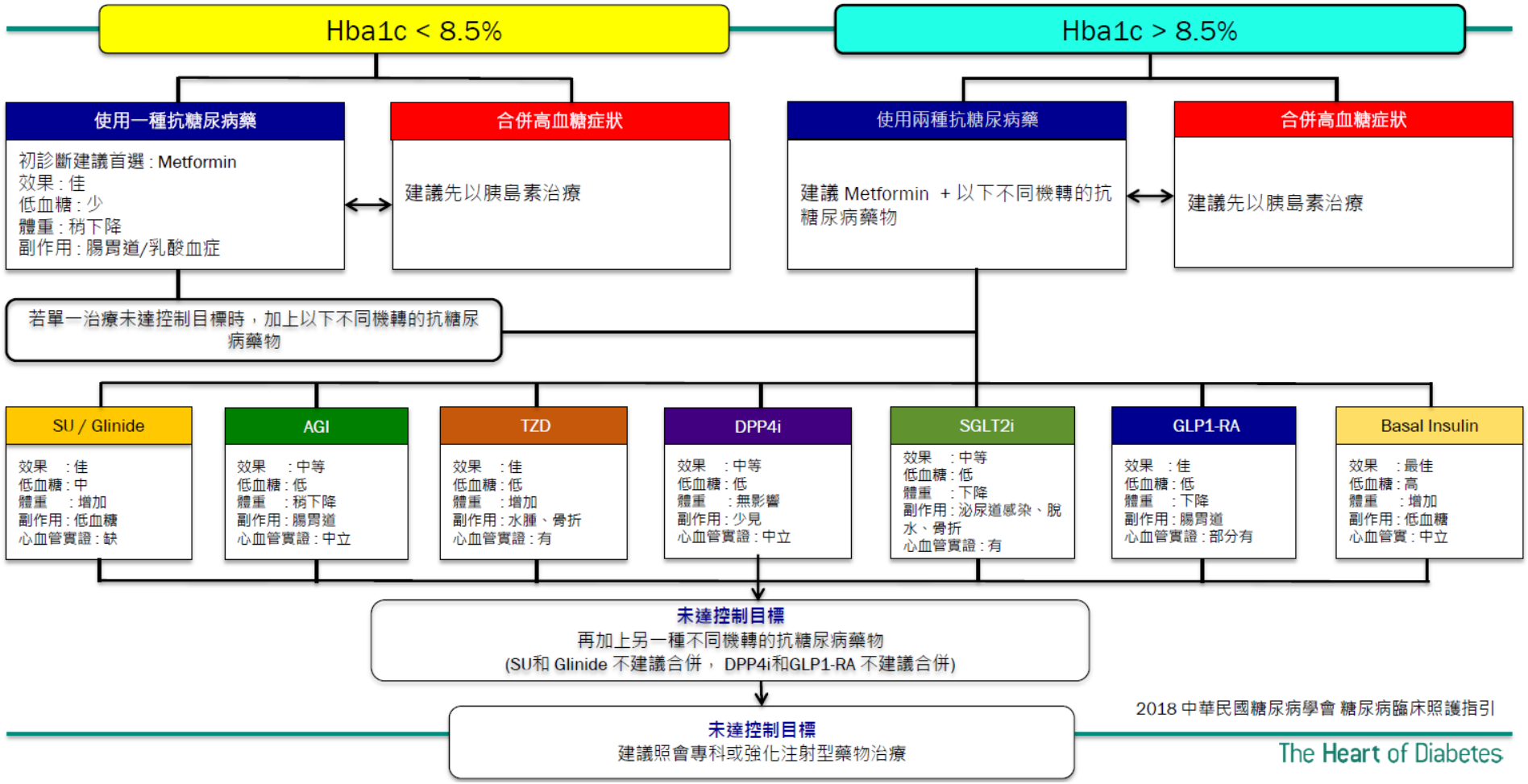
2018 中華民國糖尿病學會
糖尿病臨床照護指引

2018 中華民國糖尿病學會糖尿病臨床照護指引

第二型糖尿病人高血糖處理流程圖



中華民國心臟學會
TAIWAN SOCETY OF CARDIOLOGY

中華民國糖尿病學會
The Diabetes Association of the Republic of China (Taiwan)

2018 Consensus of Taiwan Society of Cardiology and the Diabetes Association of Republic of China on the pharmacological management of patients with T2DM and CVD

2018 consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on the pharmacological management of patients with type 2 diabetes and cardiovascular diseases

Table 2
Treatment algorithm in diabetic patients with hypertension.

Target HbA1c	<7%			
Monotherapy	Metformin			
Dual therapy	Metformin + SGLT-2 i			
Triple therapy	Metformin + SGLT-2 i + GLP-1 RA[a]	Metformin + SGLT-2 i + TZD[b]	Metformin + SGLT-2 i + DPP-4 i	Metformin + SGLT-2 i + SU or Glinide or AGI
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents			

AGI = alpha-glucosidase inhibitor; DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

[a] Liraglutide and semaglutide.

[b] Pioglitazone.

Table 3
Treatment algorithm in diabetic patients with CHD.

Target HbA1c	<7%		
Monotherapy	Metformin		
Dual therapy	Metformin + TZD[a]	Metformin + SGLT-2 i	Metformin + GLP-1 RA[b]
Triple therapy	Metformin + TZD[a] + SGLT-2 i	Metformin + TZD[a] + GLP-1 RAs[b]	Metformin + SGLT-2 i + GLP-1 RAs[b]
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents		

CHD = coronary heart disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; TZD = thiazolidinedione.

[a] Pioglitazone.

[b] Liraglutide and semaglutide.

2018 consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on the pharmacological management of patients with type 2 diabetes and cardiovascular diseases

Table 6
Treatment algorithm in diabetic patients with heart failure.

Target HbA1c	<8%			
Monotherapy	SGLT-2 i or metformin			
Dual therapy	SGLT-2 i + metformin			
Triple therapy	SGLT-2 i + metformin + GLP-1 RA	SGLT-2 i + metformin + DPP-4 i (except saxa., alo., and vilda.)	SGLT-2 i + metformin + SU or AGI	SGLT-2 i + metformin + Glinide
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents			

AGI = alpha-glucosidase inhibitor; alo = alogliptin; DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; saxa = saxagliptin; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione; vilda = vildagliptin.

Table 5
Treatment algorithm in diabetic patients with a history of stroke.

Target HbA1c	<7%		
Monotherapy	Metformin		
Dual therapy	Metformin + TZD[a]	Metformin + GLP-1 RA[b]	Metformin + SGLT-2 i
Triple therapy	Metformin + TZD[a] + GLP-1 RA[b]	Metformin + TZD[a] + SGLT-2 i	Metformin + GLP-1 RA[b] + SGLT-2 i
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents		

DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; TZD = thiazolidinedione.

[a] Pioglitazone.

[b] Liraglutide and semaglutide.

CV disease in T2D remains a clinical challenge, but we can see a sliver lining now…

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

1. Mannucci E *et al. Diabetes Care*. 2013; 36(Suppl 2): S259-S263.