Oral Anti-Diabetic Drugs What Have We Learnt & NOT Learnt in The Past Decade ?



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Disclosures

Research Grants

- Abbvie
- Bayer
- Boehringer Ingelheim
- Eli Lilly
- GlaxoSmithKline
- Merck Sharp & Dohme
- Novartis
- Roche
- Sanofi
- Servier
- Takeda

Travel Grants

- Amgen
- AstraZeneca
- Boehringer Ingelheim
- Bristol-Myers Squibb
- Eli Lilly
- GlaxoSmithKline
- Merck Sharp & Dohme
- Novartis
- Novo Nordisk
- Roche
- sanofi
- Servier
- Takeda

Clarification of Misconceptions



Please do not use "oral hypoglycaemic drugs" any more !!

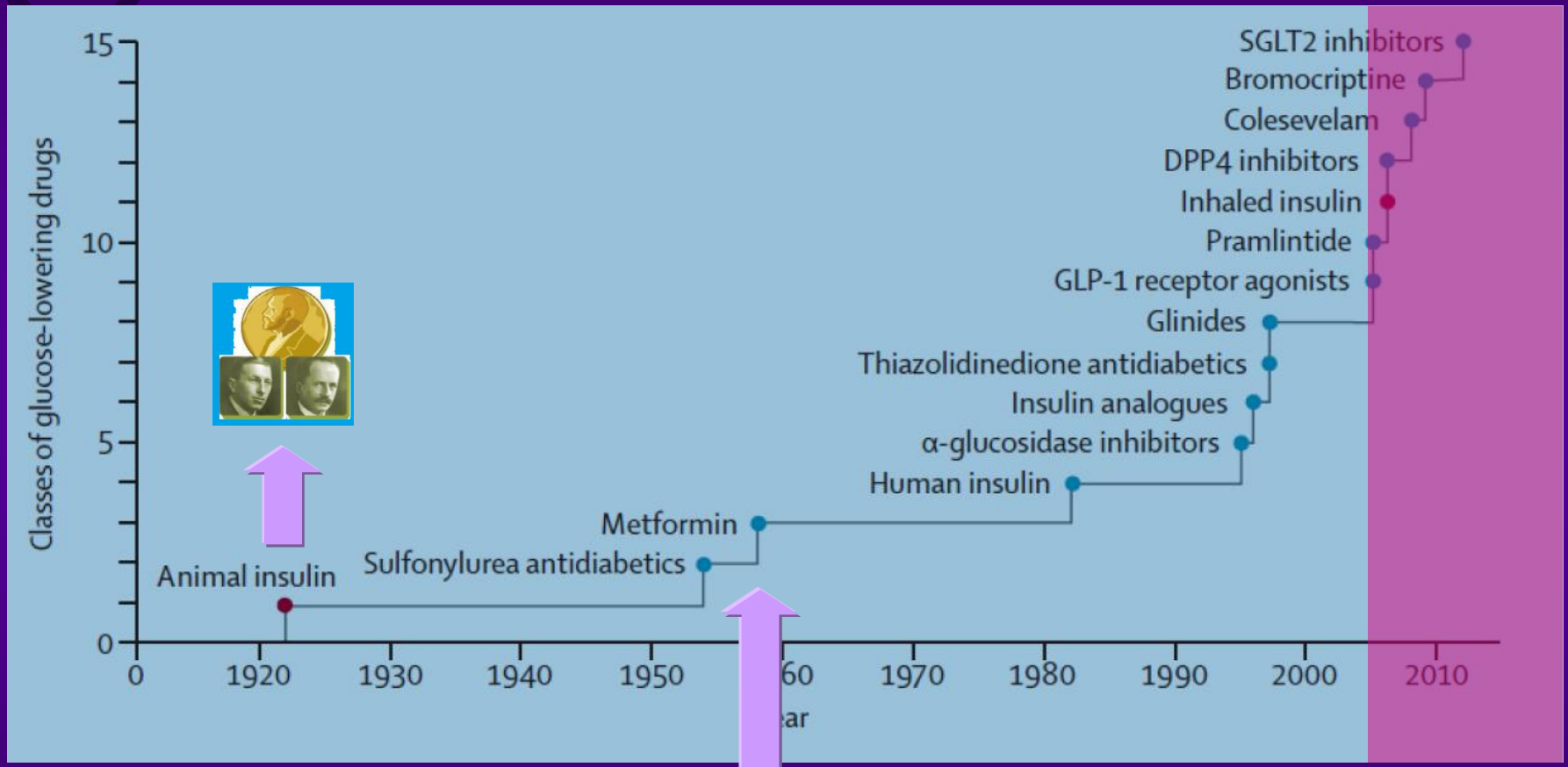
All the novel oral anti-diabetic medications very rarely cause "hypoglycaemia" when used as monotherapy

The term "Oral anti-diabetic drugs" (OADs) should be much more appropriate or just use "Oral glucose-lowering drugs" (oral GLDs)

Glucose-Lowering Drugs in HK

- Oral Anti-Diabetic Drugs (OADs)
  - Metformin
  - Sulphonylureas
  - TZD
  - DPP4i
  - SGLT2i
  - Glinide – repaglinide (Novonorm®)
  - AGI - acarbose (Glucobay®)
- Injectables
  - Human insulin
  - Insulin analogs
  - GLP-1RA

Development of Glucose-Lowering Drugs



Only approved by FDA in 1995 !

Emerging Treatments and Technologies

ORIGINAL ARTICLE

Acarbose in NIDDM Patients With Poor Control on Conventional Oral Agents

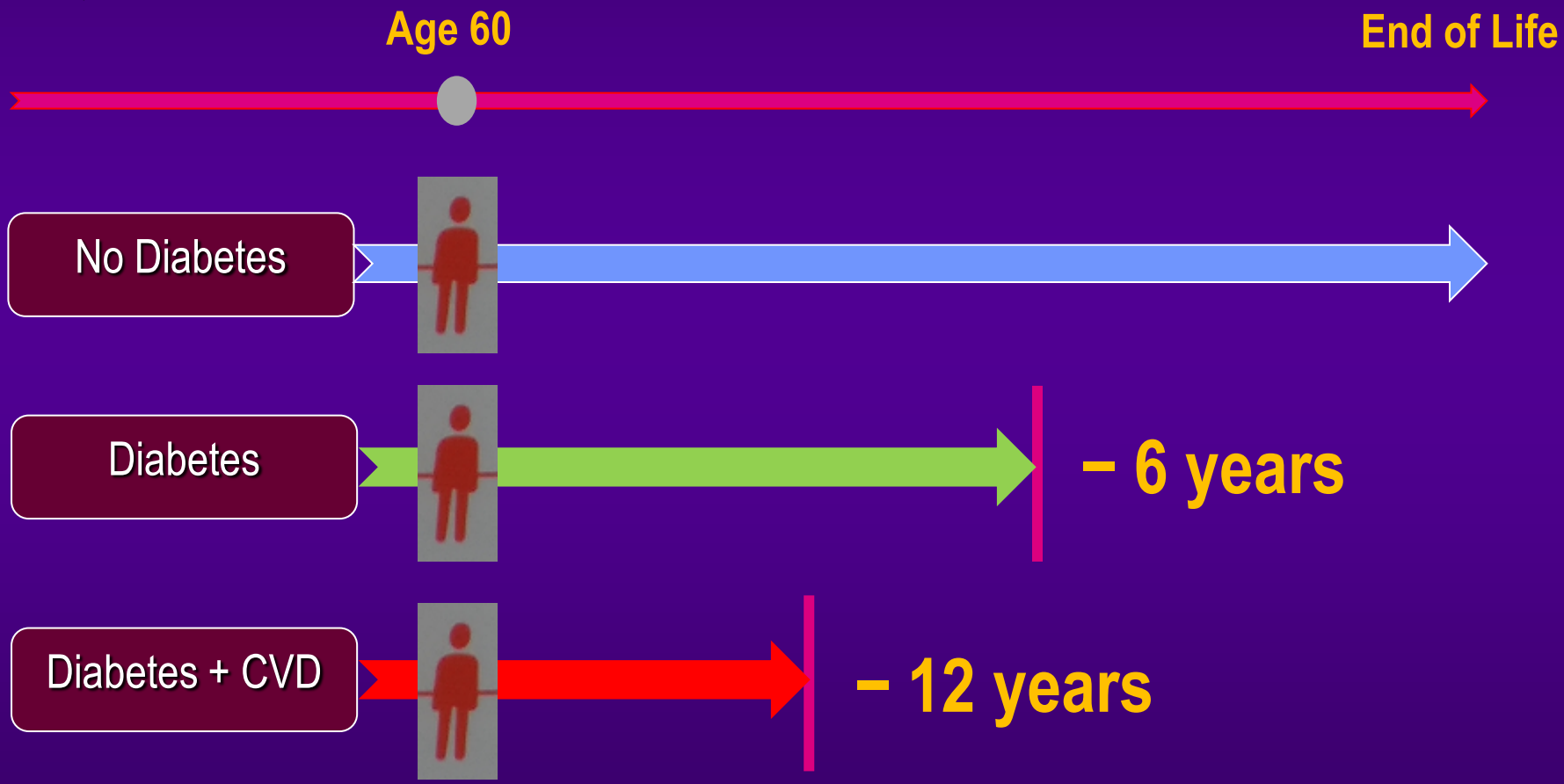
A 24-week placebo-controlled study

KAREN S.L. LAM, MD
S.C. TIU, MBBS
M.W. TSANG, MBBS
T.P. IP, MBBS
SIDNEY C.F. TAM, MBBS

Lam KSL, et al. Diabetes Care 1998;21(7);1154-8

Reduction of Life Expectancy in DM Patients

689,300 participants recruited through 1960 to 2007



The Emerging Risk Factors Collaboration JAMA 2015(1);52-60

ORIGINAL ARTICLE

Excess Mortality among Persons with Type 2 Diabetes

Mauro Tancredi, M.D., Annika Rosengren, M.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Aldina Pivodic, M.Sc., Soffia Gudbjörnsdottir, M.D., Ph.D., Hans Wedel, Ph.D., Mark Clements, M.D., Ph.D., Sofia Dahlqvist, and Marcus Lind, M.D., Ph.D.

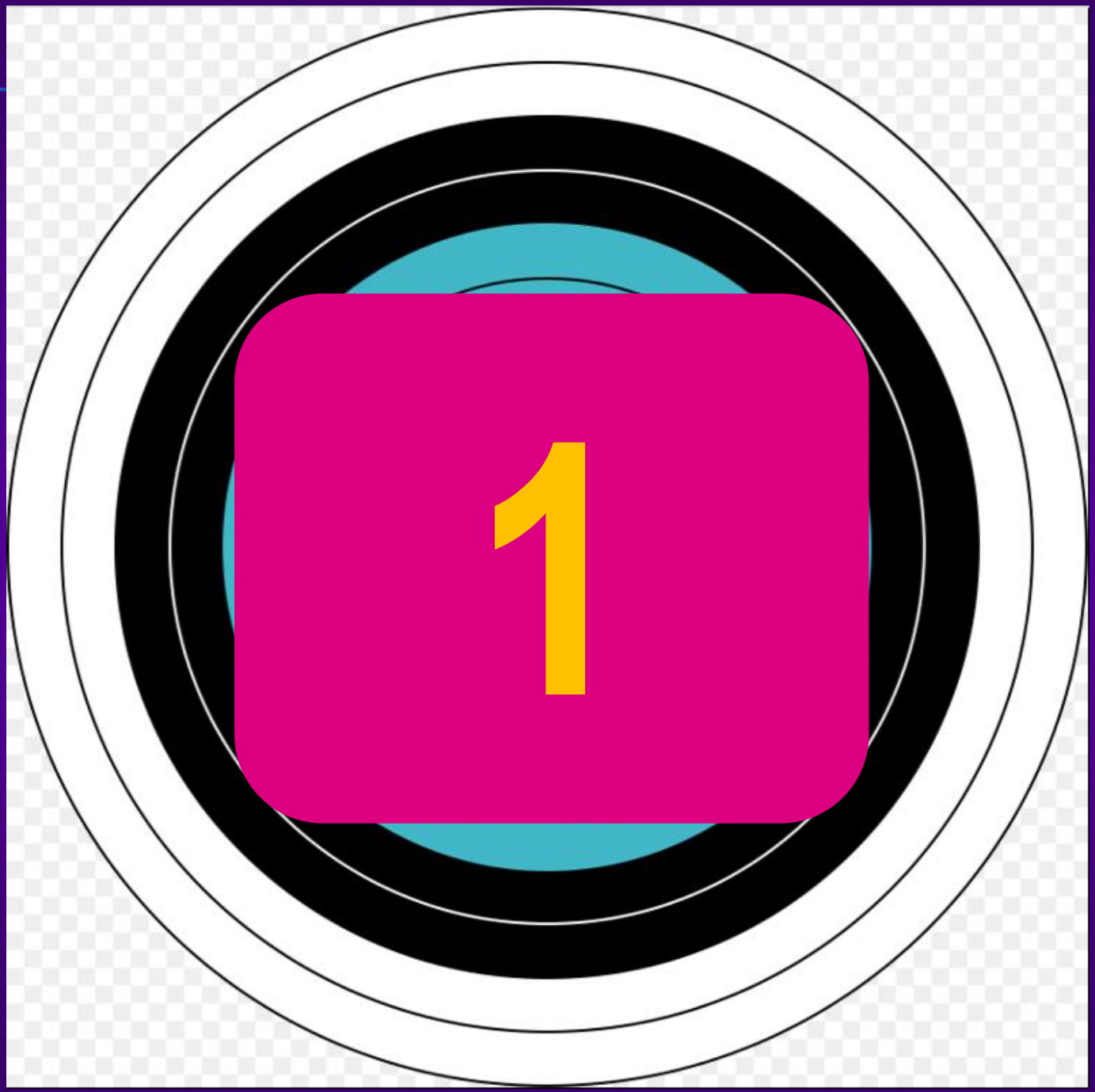
Tancredi et al. N Engl J Med 2015;373(18):1720-32

ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

Marcus Lind, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Soffia Gudbjörnsdottir, M.D., Ph.D., Aldina Pivodic, M.Sc., Hans Wedel, Ph.D., Sofia Dahlqvist, Mark Clements, M.D., Ph.D., and Annika Rosengren, M.D., Ph.D.

Lind et al. N Engl J Med 2014;371(21):1972-82


1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D. for the EMPA-REG OUTCOME Investigators

7,020 T2DM patients with established CV disease randomized to empagliflozin vs. placebo for a median FU of 3.1 years

Section A. List of investigators

Thessaloniki "G. Papanikolaou", Thessaloniki; ***Hong Kong***: R. Ozaki, Prince of Wales Hospital, Hong Kong; K. Tan, Queen Mary Hospital, Hong Kong; S. Siu, T. Ip, Tung Wah Eastern Hospital, Hong Kong; C. Tsang, Alice Ho Miu Ling Nethersole Hospital, Hong Kong; ***Hungary***: M. Dudas, Bekes County Pandy Kalman Hospital, Gyula; K. Nagy, Synexus Hungary Ltd.,

Zinman et al. N Engl Med 2015;373(22):2117-28

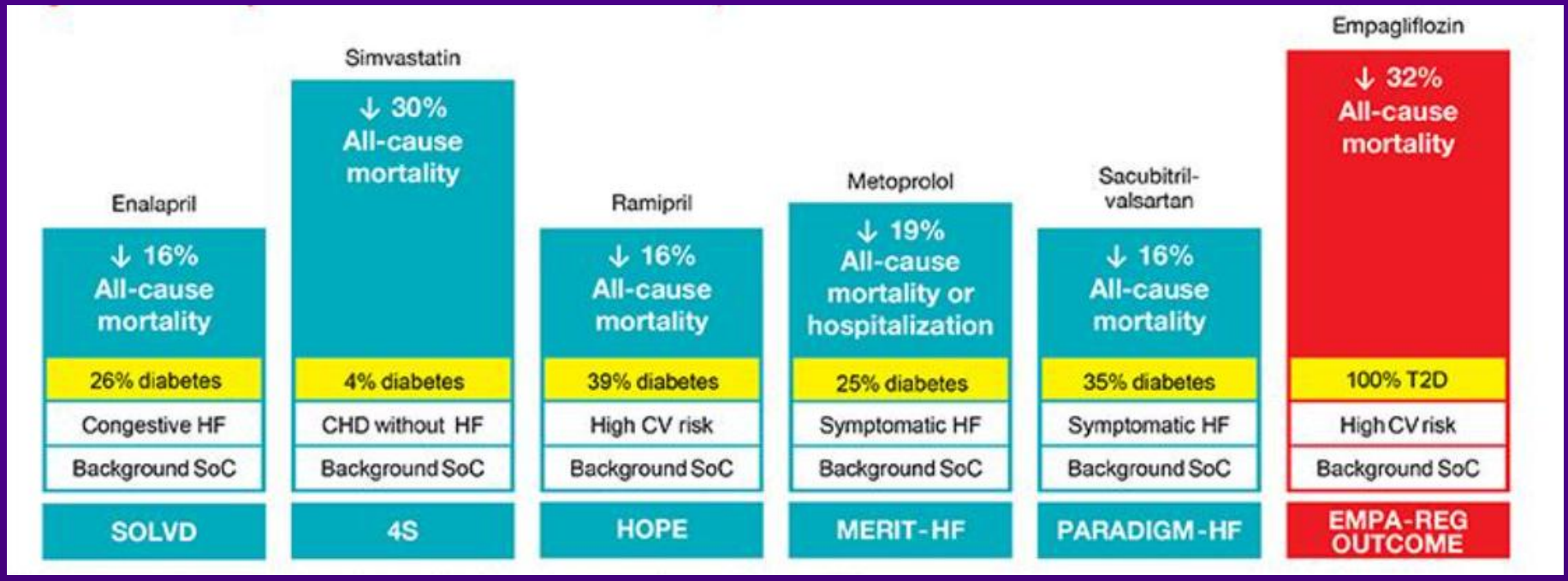
Importance of EMPA-REG Study

1. First study that conclusively demonstrate that a glucose-lowering drug (empagliflozin) can reduce
   - cardiovascular events (3-point MACE) ↓ 14%
   - cardiovascular mortality ↓ 38%
   - hospitalisation for heart failure (HHF) ↓ 35%
   - all-cause mortality ↓ 32%
2. Documented significant reduction in progression of CKD
   - doubling of creatinine levels ↓ 44%
   - renal replacement therapy ↓ 55%

   * 7.7% had eGFR 30-44 ml/min/1.73m^2 (stage 3b CKD)

Zinman et al. N Engl Med 2015;373(22):2117-28
Wanner et al. N Engl Med 2016;375(4):323-4

Mortality Outcomes in Landmark CV Outcome Trials in Patients with Established CV Diseases

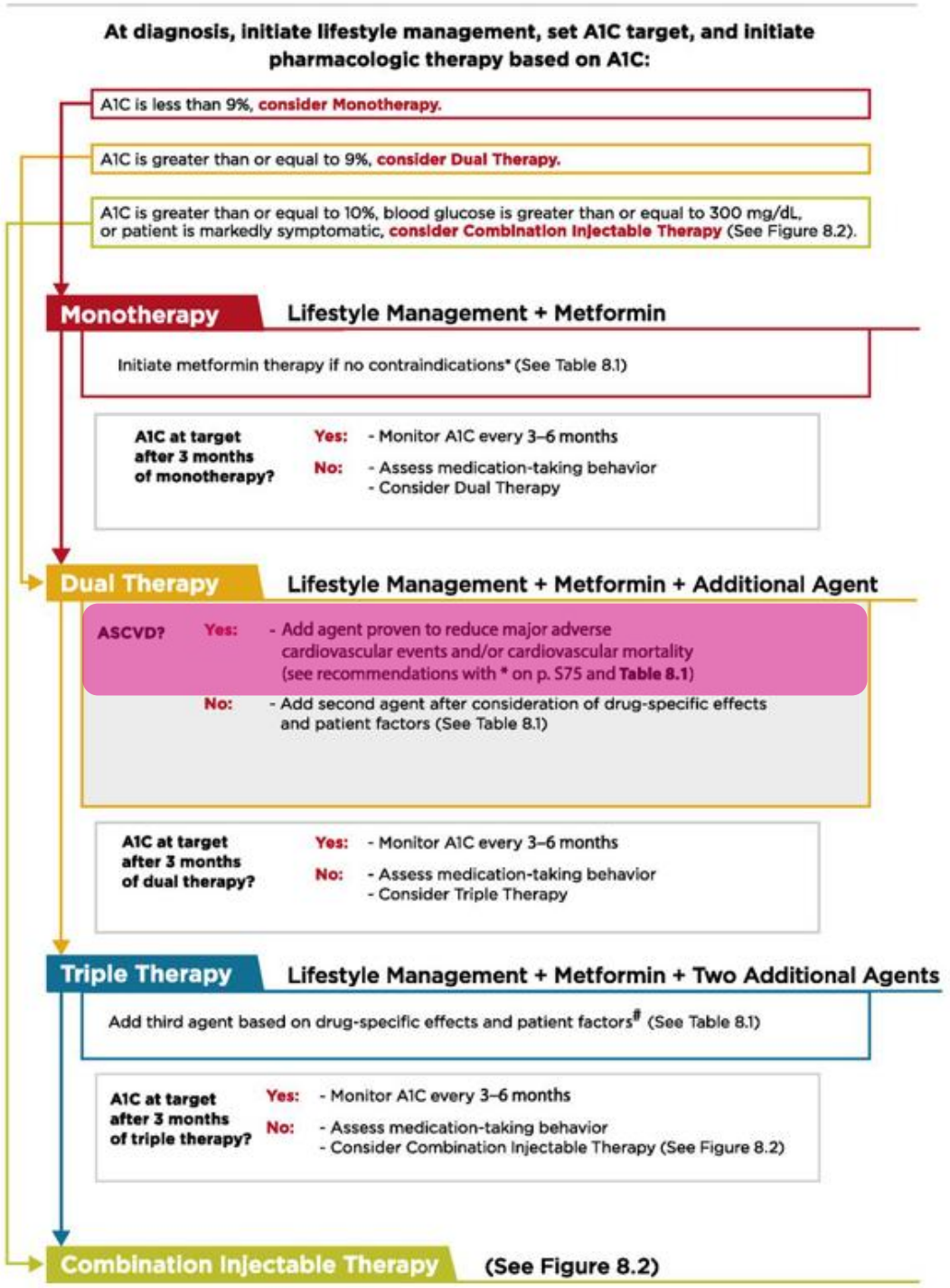


Comparing the SGLT-2 Inhibitors

	Empagliflozin (Jardiance®)	Canagliflozin (Invokana®)	Dapagliflozin (Forxiga®)
Outcome Trial	EMPA-REG	CANVAS	DECLARE-TIMI 58
3-point MACE	↓ 14%	↓ 14%	pending
CV mortality	↓ 38%	↓ 13% (NS)	pending
HHF	↓ 35%	↓ 33%	pending
All-cause mortality	↓ 32%	↓ 13% (NS)	pending
Composite renal endpoints	↓ 46%	↓ 40%	pending
Amputation (LL)	neutral	↑ 97%	pending
All fractures	neutral	↑ 26%	pending

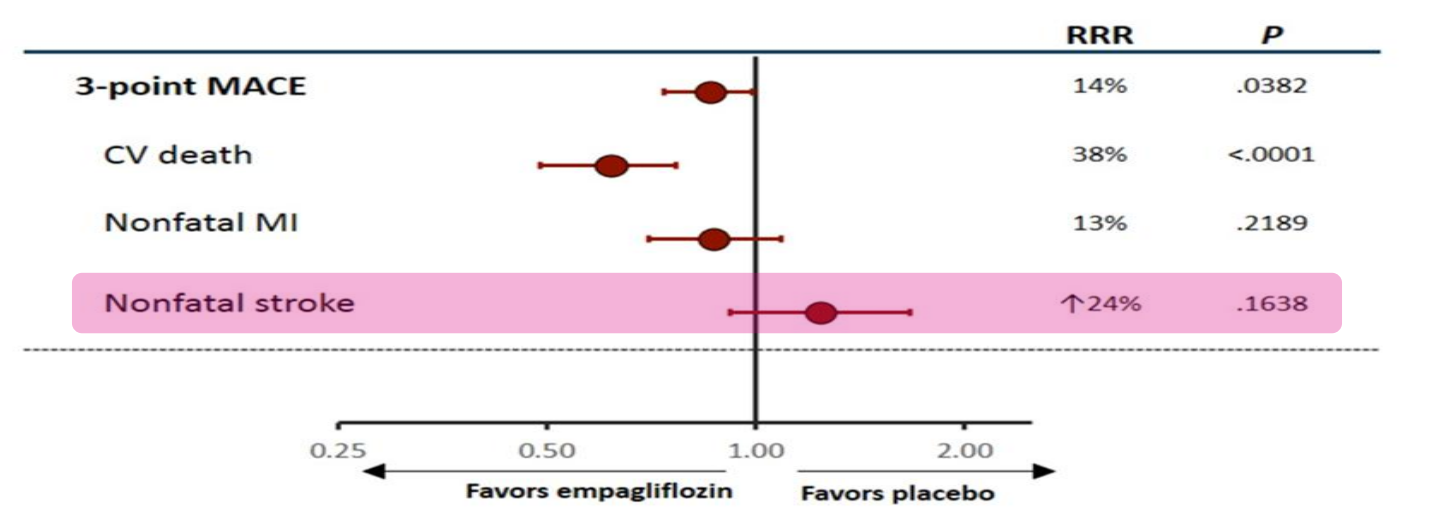
4th SGLT-2i – Ertugliflozin approved by FDA in Dec 2017

2018 ADA Anti-Hyperglycaemic Management Algorithm



ADA. Standards of Medical Care in Diabetes – 2018. Diabetes Care 2018; 41(Suppl 1):S73-85

Effects of SGLT2i on CV Outcomes



Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)

Zinman et al. N Engl Med 2015;373(22):2117-28
Wanner et al. N Engl Med 2016;375(4):323-4

SGLT-2 Inhibitors: the Learnt

- Insulin-independent mechanism : reduce renal glucose reabsorption
- Lower HbA1c by 0.5-1.0%

Merits	Adverse Effects / Cautions
no hypoglycaemia with monotherapy	genito-urinary infection
weight loss (0.1-4.0 kg)	polyuria, dehydration
BP improvement (3-6 mmHg)	hypotension
can be combined with all types of regimen	slight ↑ LDL
can be used at any stage of T2DM	euglycaemic ketoacidosis
reduction of CV & all-cause mortality (EMPA) CVOT pending (DAPA)	fracture, ↓BMD (CANA-FDA Alert)
retardation of CKD progression (EMPA, CANA)	amputation (CANA- FDA Alert)
	AKI (CANA/DAPA- FDA Alert)

SGLT-2 Inhibitors – the Not Learnt

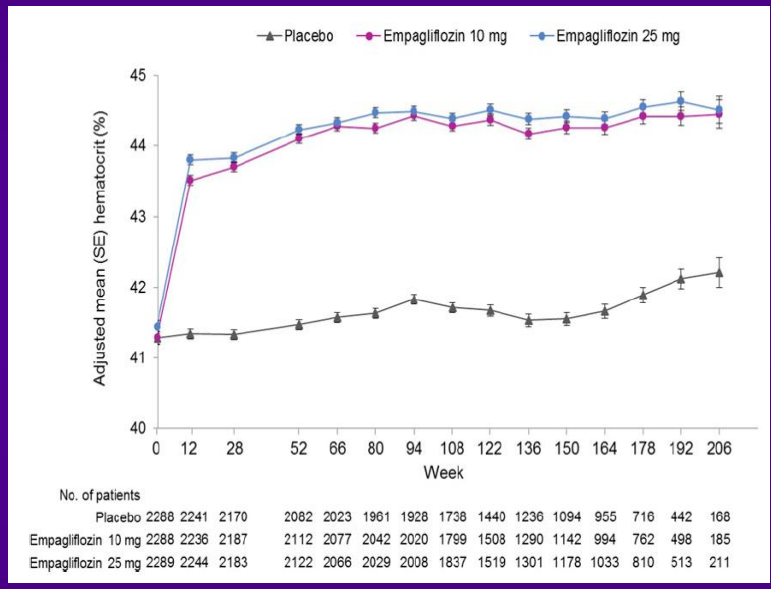
1. What is the underlying mechanisms for the CV / renal benefits ?
2. Whether the reductions in CV / renal events are a class effect? pending results from the DECLARE-TIMI 58 Trial
3. Whether the signal of a potential increase in CVA is true; caution needed when considering SGLT2i in patients with previous history of stoke
4. Whether SGLT2i can be safely used in patients with T1DM – the EASE Trial
5. Whether SGLT2i have the same CV benefits for DM patients NOT at high CV risk or at high CV risk but without T2DM

Factors Contributing to the Mortality Reduction in the EMPA-REG Study

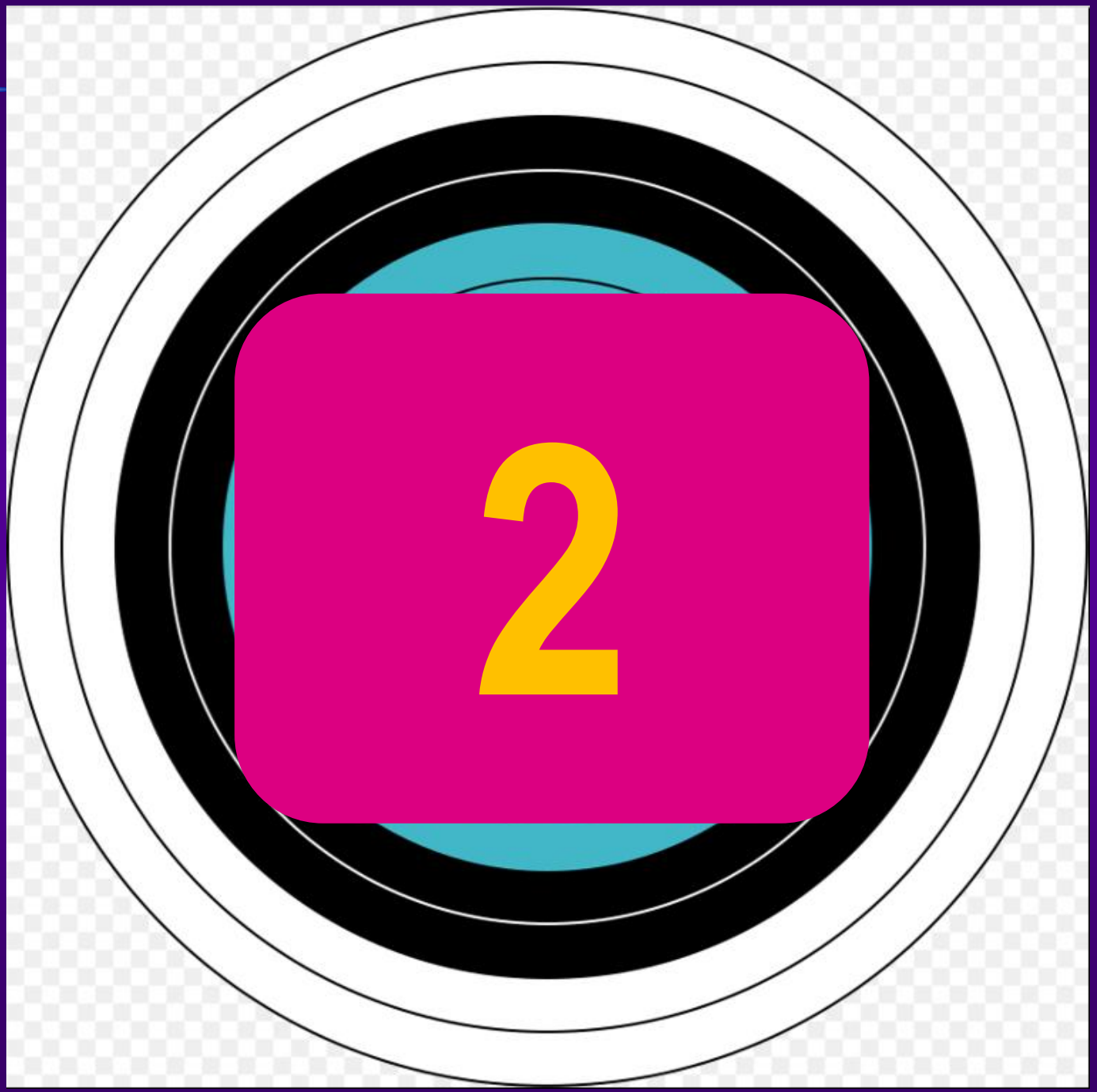
Table 3—Univariable mediation analysis of risk of CV death with empagliflozin versus placebo: time-dependent covariate analysis adjusting for the updated mean of each variable

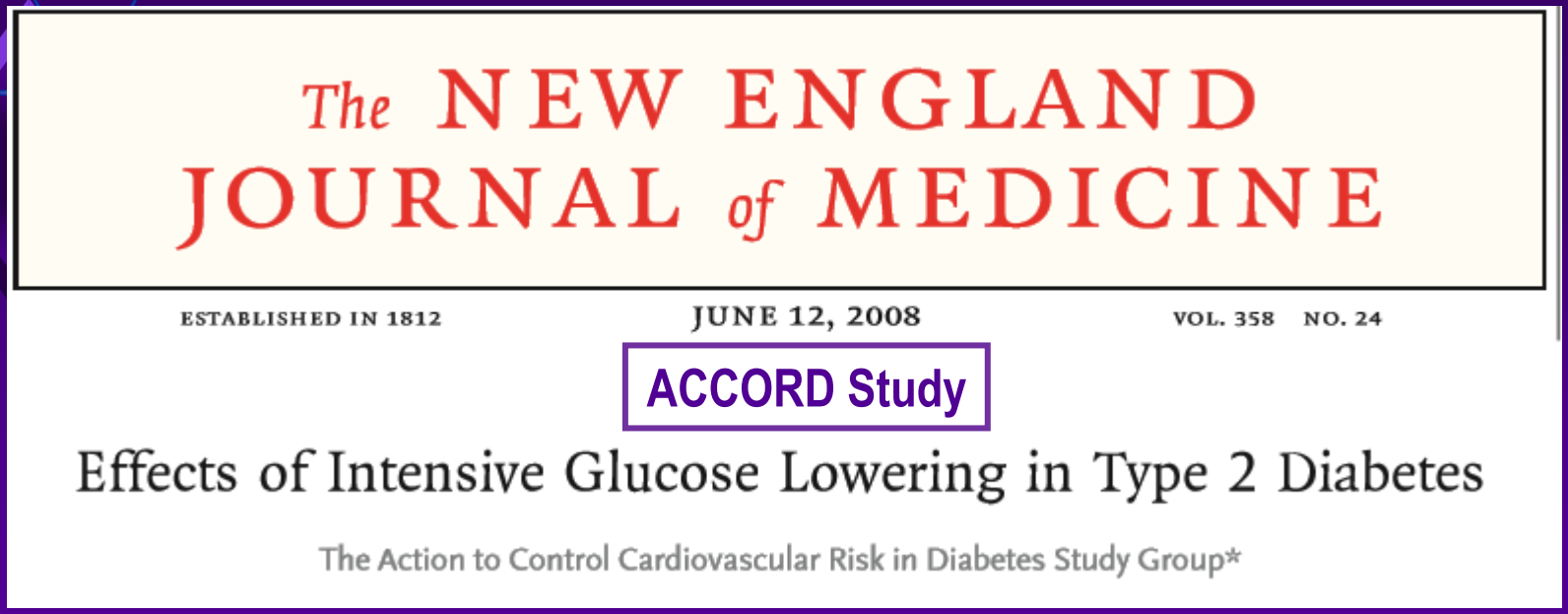
	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA_{1c}	0.687 (0.543, 0.868)	22.8
FPG	0.709 (0.559, 0.898)	29.3
SBP	0.610 (0.485, 0.766)	−1.7
DBP	0.618 (0.493, 0.774)	1.0
Heart rate	0.623 (0.497, 0.782)	2.7
LDL-C	0.591 (0.471, 0.741)	−8.2
HDL-C	0.629 (0.500, 0.789)	4.6
logTG	0.603 (0.481, 0.757)	−4.1
FFAs	0.587 (0.463, 0.743)	−9.6
logUACR	0.672 (0.536, 0.844)	18.2
eGFR (MDRD)	0.601 (0.480, 0.752)	−4.7
eGFR (CKD-EPI)	0.597 (0.477, 0.748)	−6.1
Weight	0.588 (0.466, 0.741)	−9.2
BMI	0.588 (0.466, 0.742)	−9.2
WC	0.602 (0.480, 0.755)	−4.4
Hematocrit	0.791 (0.620, 1.009)	51.8
Hemoglobin	0.768 (0.604, 0.978)	45.7
Albumin	0.717 (0.571, 0.900)	31.6
Uric acid	0.673 (0.536, 0.845)	18.5

Cox proportional hazards regression analysis in patients treated with one or more doses of study drug. FFA, free fatty acid; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; WC, waist circumference.



Inzucchi et al. Diabetes Care 2018;41(41):356-63


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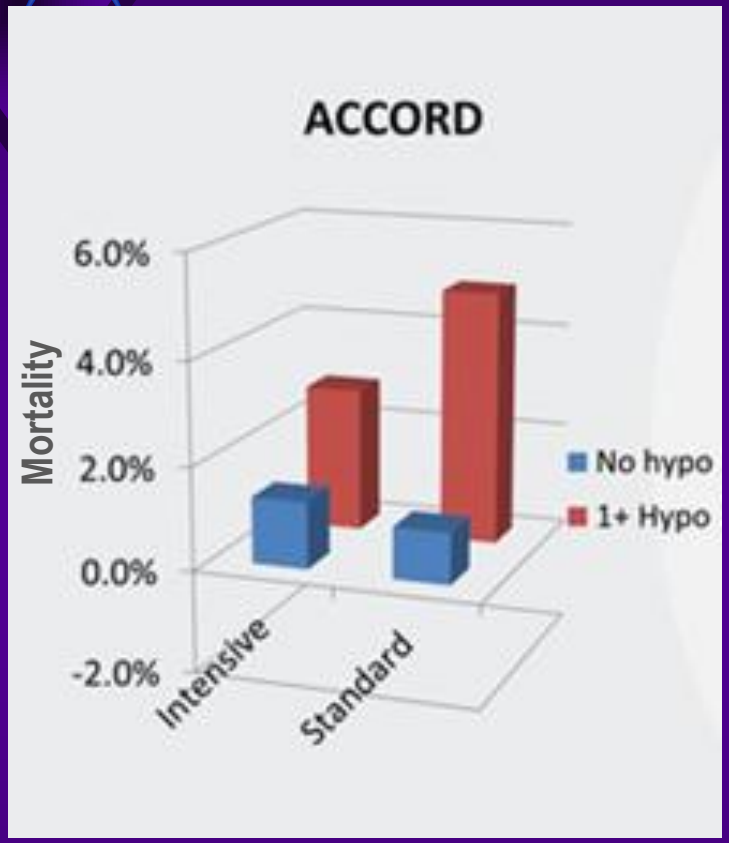


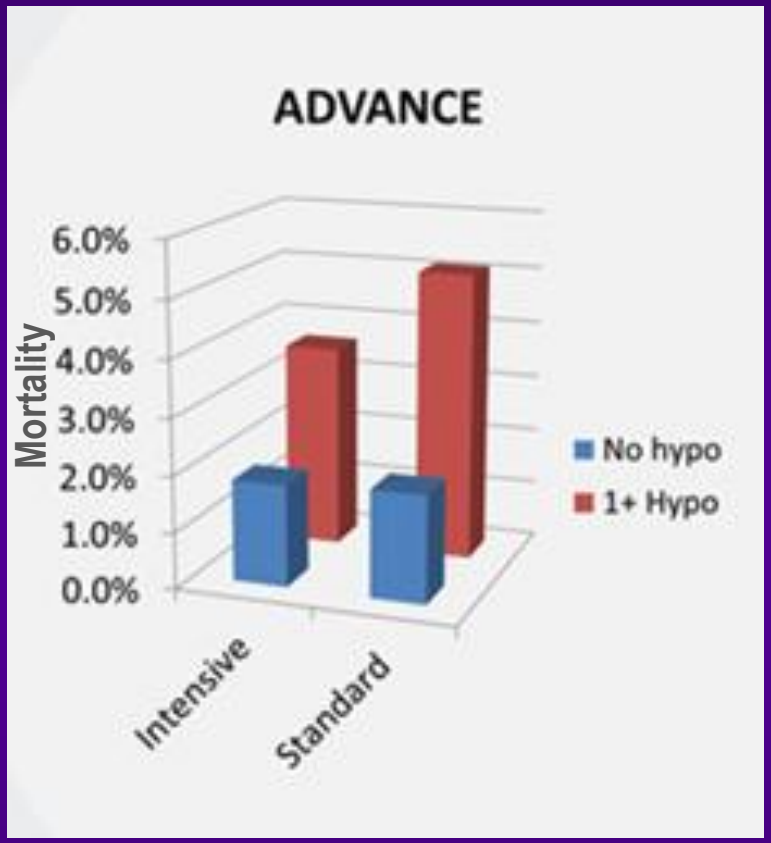
10,251 patients (mean age 62.2 y) with a median HbA1c of 8.1% were randomised to receive intensive therapy (target HbA1c <6.0%) or standard therapy (target HbA1c 7.0-7.99%)

- This study identified a previously unrecognized harm of intensive glucose lowering leading to increase in mortality in high-risk patients with T2DM
- The culprit in subsequent analyses was believed to be related to hypoglycaemia

ACCORD Study Group. N Engl J Med 2008;358(24):2545-59

Hypoglycaemia & Mortality

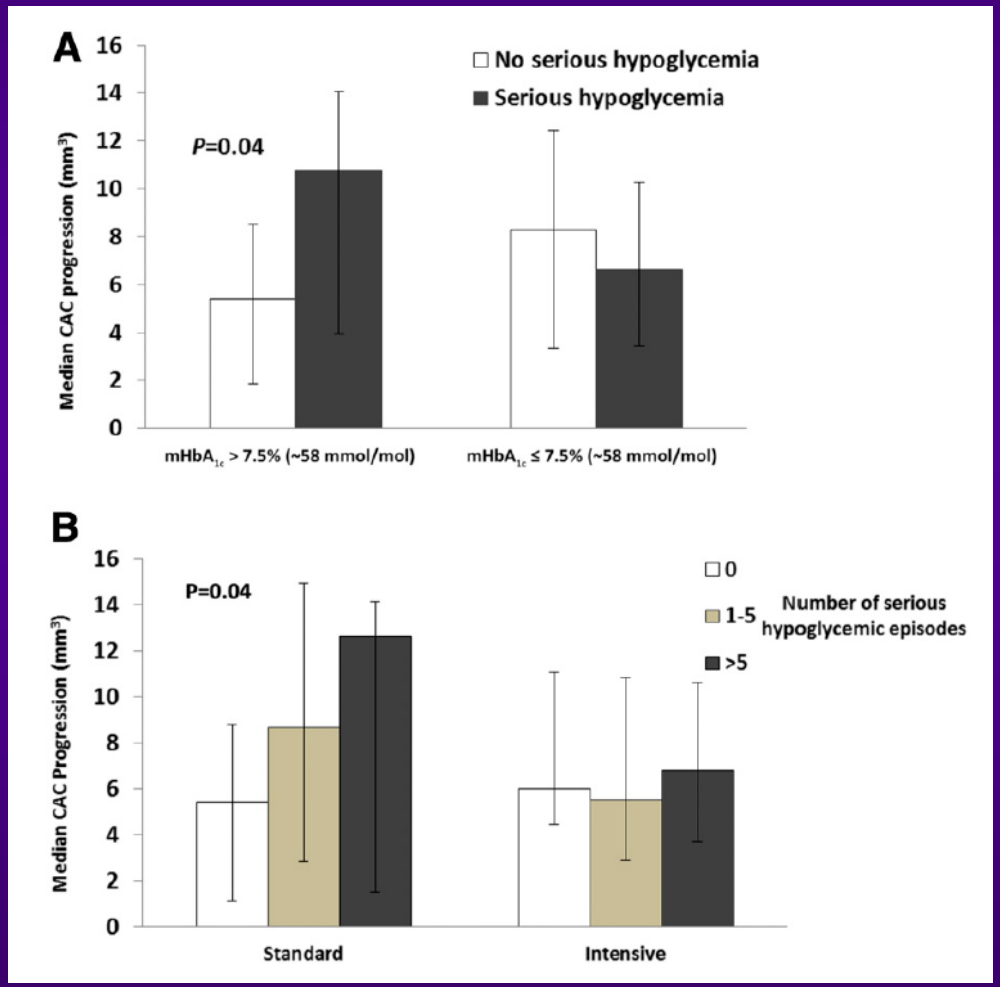




Hypoglycaemia caused more death in the group with poorer diabetic control

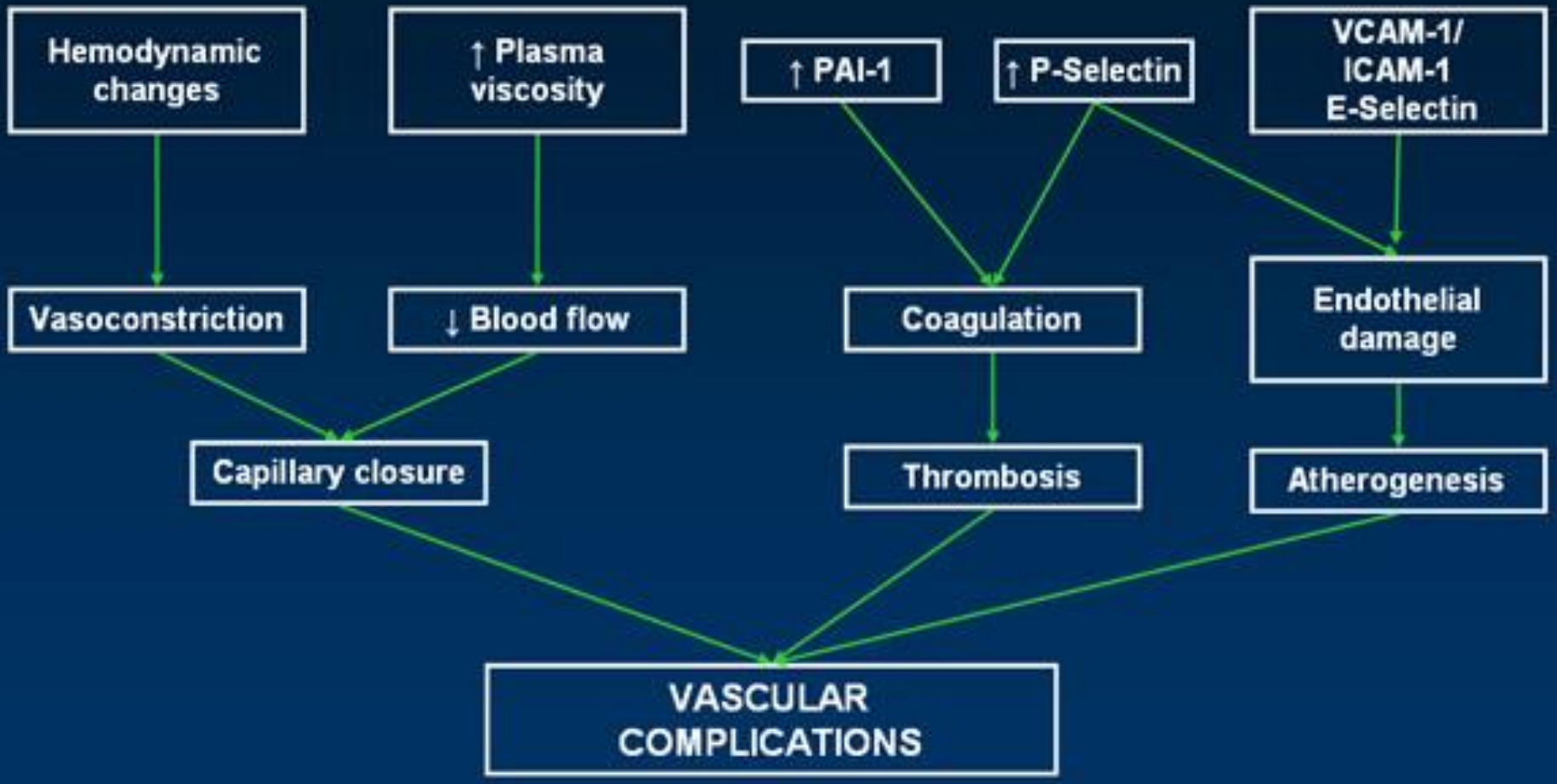
Bonds et al. BMJ 2010:340:b4909
Zoungas et al. N Engl J Med 2010;363(15):1410-8

Hypoglycaemia Caused Progression of Atherosclerosis in Patients with Poor Diabetic Control



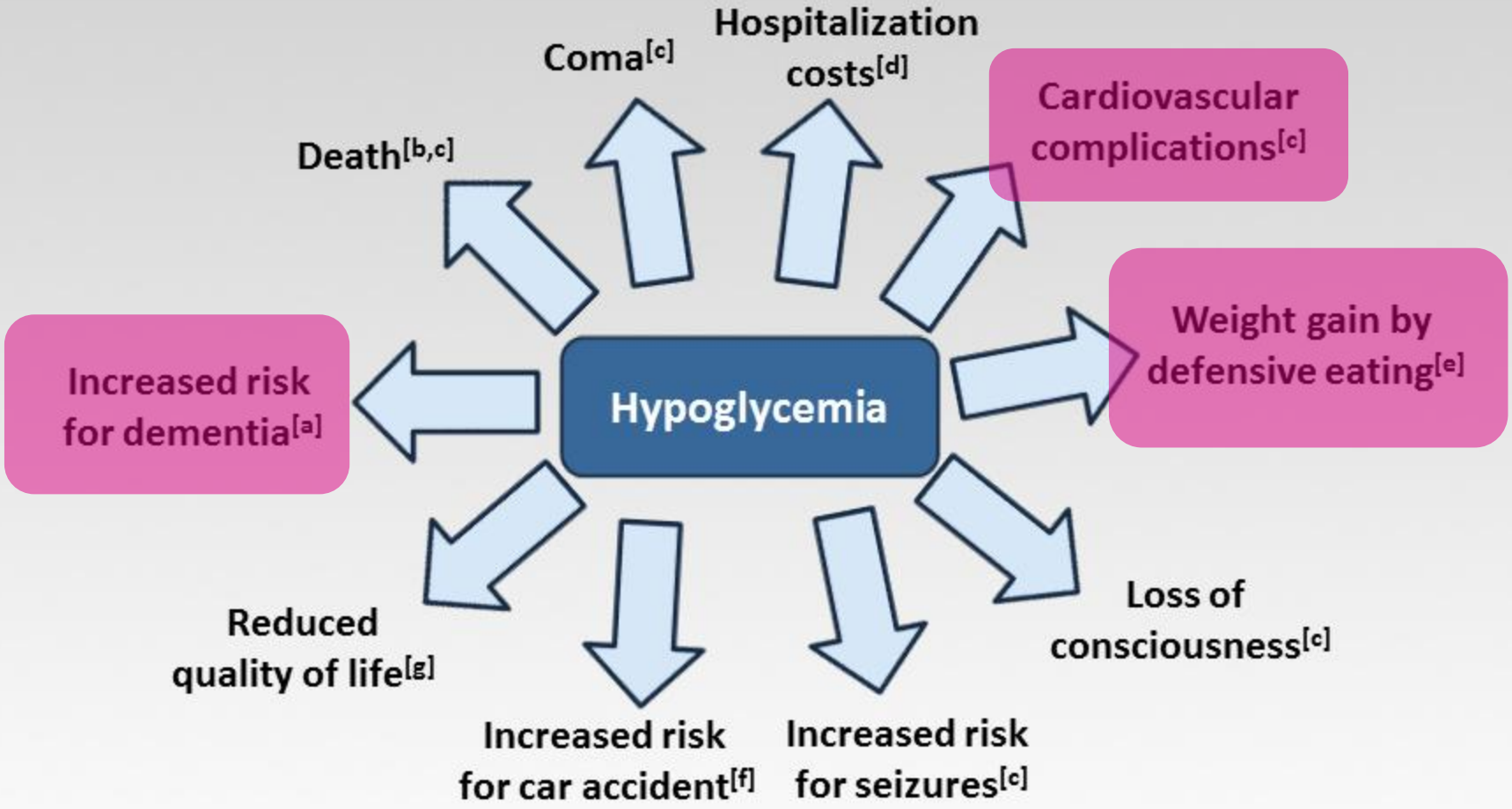
VADT Study Group. Diabetes Care 2016;39;448-54

Hematologic & Inflammatory Alterations Following Acute and Repeated Hypoglycemia & Postulated Mechanisms of Hypoglycemia-Induced Vascular Damage



Wright and Frier. *Diabetes Metab Res Rev*. 2008.

The Consequences of Hypoglycemia



a. Whitmer RA, et al. *JAMA.* 2009;301(15):1565-1572; b. Bonds DE, et al. *BMJ.* 2010;340:b4909;
c. Barnett AH. *Curr Med Res Opin.* 2010;26(6):1333-1342; d. Jönsson L, et al. *Value Health.* 2006;9(3):193-198;
e.Foley JE, et al. *Vasc Health Risk Manag.* 2010;6:541-548; f. Begg IS, et al. *Can J Diabetes.* 2003;27:128-140;
g. McEwan P, et al. *Diabetes Obes Metab.* 2010;12(5):431-436.

Original Investigation

Association Between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults With Diabetes Mellitus

Kristine Yaffe, MD; Cherie M. Falvey, MPH; Nathan Hamilton, MA; Tamara B. Harris, MD; Eleanor M. Simonsick, PhD; Elsa S. Strotmeyer, PhD, MPH; Ronald I. Shorr, MD, MS; Andrea Metti, MPH; Ann V. Schwartz, PhD, MPH; for the Health ABC Study

Yaffe K, et al. JAMA Int Med 2013;173(14):1300-6

Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

Rachel A. Whitmer, PhD
Andrew J. Karter, PhD
Kristine Yaffe, MD
Charles P. Quesenberry Jr, PhD
Joseph V. Selby, MD

Context Although acute hypoglycemia may be associated with cognitive impairment in children with type 1 diabetes, no studies to date have evaluated whether hypoglycemia is a risk factor for dementia in older patients with type 2 diabetes.

Objective To determine if hypoglycemic episodes severe enough to require hospitalization are associated with an increased risk of dementia in a population of older patients with type 2 diabetes followed up for 27 years.

Whitmer RA, et al. JAMA 2009;301:1565-72

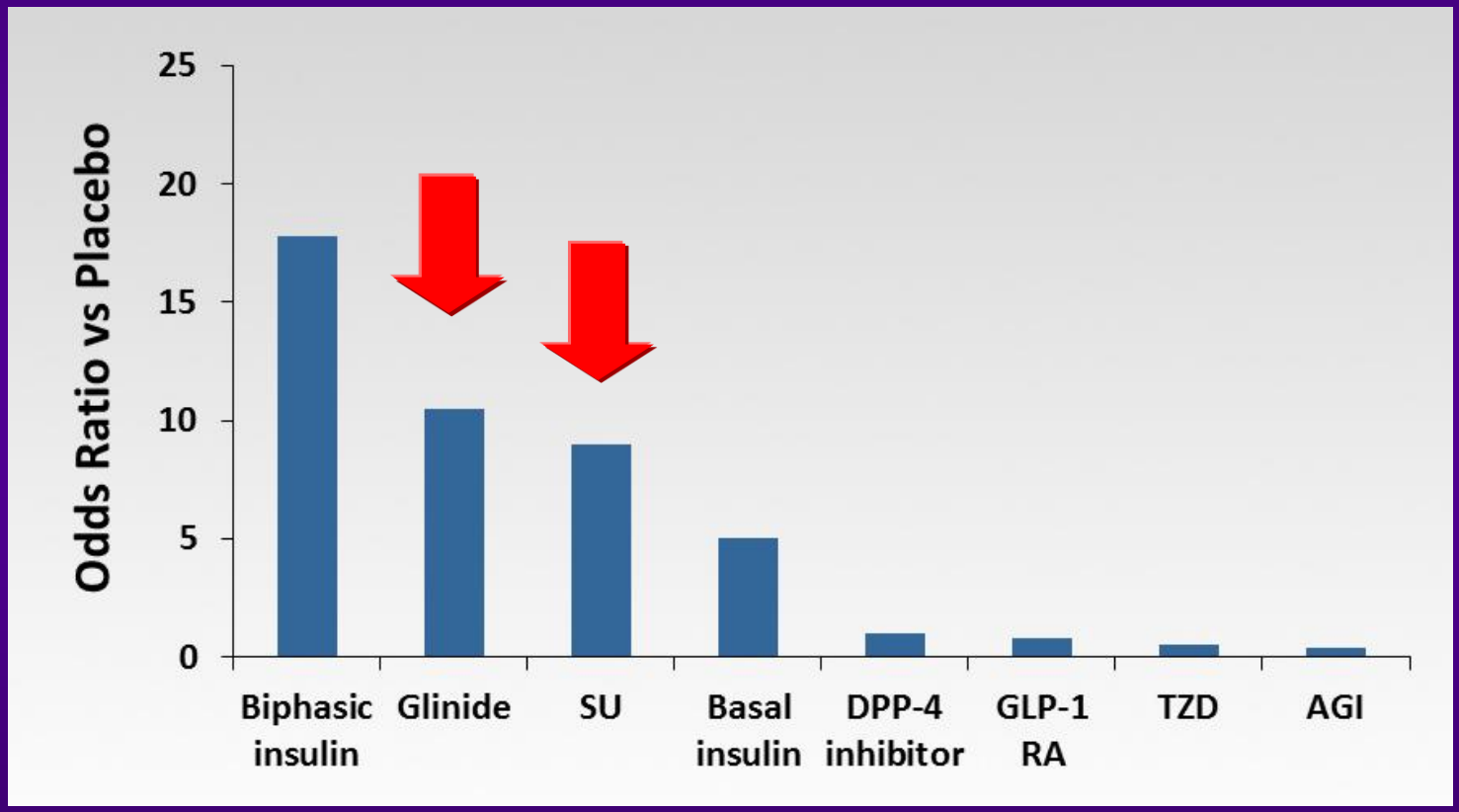
Major Hypoglycemia Significantly Increases the Risk for Adverse Outcomes in Patients with T2DM

Hazard ratios for incident vascular outcomes and death among patients who had major hypoglycemia as compared with those who did not

Clinical outcome and interval after hypoglycemia	No. of events	Hazard ratio adjusted for treatment assignment (95% CI)	*p*-value
Macrovascular events	1147	4.05 (2.86 – 5.74)	< .001
Microvascular events	1131	2.39 (1.60 – 3.59)	< .001
Death from any cause	1031	4.86 (3.60 – 6.57)	< .001
Death from cardiovascular cause	542	4.87 (3.17 – 7.49)	< .001
Death from non-cardiovascular cause	489	4.82 (3.16 – 7.35)	< .001

Zoungas et al. N Engl J Med 2010;363(15):1410-8

Meta-Analyses: Risk of Hypoglycaemia With 2nd Line Drugs Add-On To Metformin



Liu SC, et al Diabetes Obes Metab 2012;14:810-20

SU Treatment is associated with a Higher All-Cause & CV-Related Mortality as Compared to Other Treatments

	84 RCTs 36,573 patients	26 studies 1,553,856 patients	
	RCT	**Observational**	
SU vs	HR (95% CI)	HR (95% CI)	I^2% (95% CI)
No active treatment/placebo	1.07 (0.90-1.28)	**1.13 (1.07-1.19)**	63.5 (14.2-79.3)*
Biguanide	**1.37 (1.03-1.84)**	**1.57 (1.48-1.66)**	0.0 (0.0-64.1)
DPP-4 inhibitor	**2.03 (1.22-3.58)**	**1.58 (1.36-1.83)**	0.0 (0.0-72.9)
GLP-1 RA	1.85 (0.80-5.19)	NA	NA
SGLT2 inhibitor	NA	NA	NA
TZD	**1.54 (1.12-2.10)**	**1.50 (1.32-1.71)**	96.6 (93.9-97.8)†
Insulin	**1.12 (1.01-1.45)**	**0.82 (0.77-0.89)**	92.4 (86.7-95.0)†
Combined	**1.26 (1.10-1.44)**	**1.22 (1.18-1.26)**	92.4 (90.6-93.7)†

Bold text indicates statistical significance.
*P<.01; †P<.001

Baxter et al. EASD Annual Meeting 2015. Abstract 128

ADA/EASD Position Statement

American Diabetes Association.

EASD

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

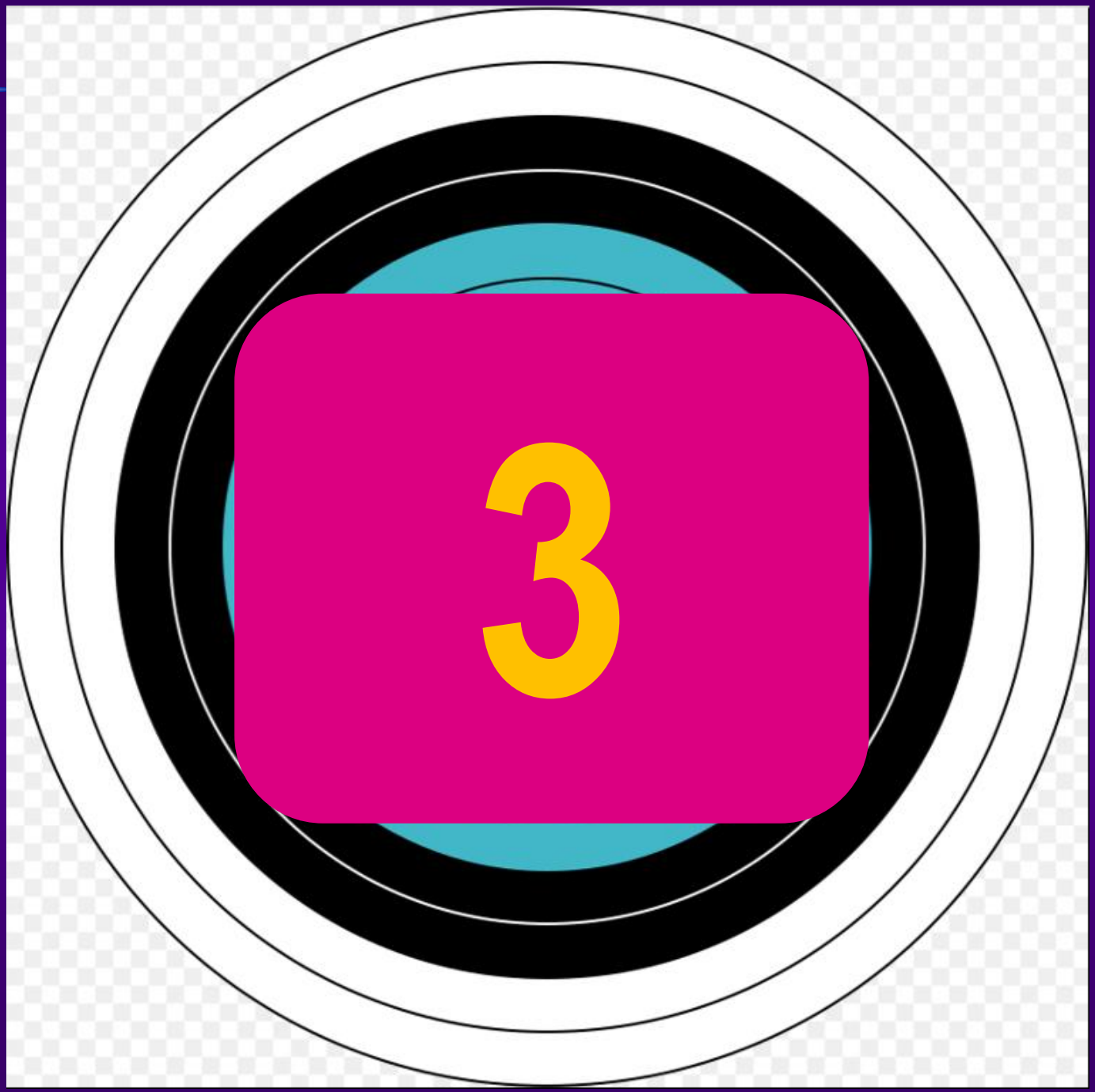
Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

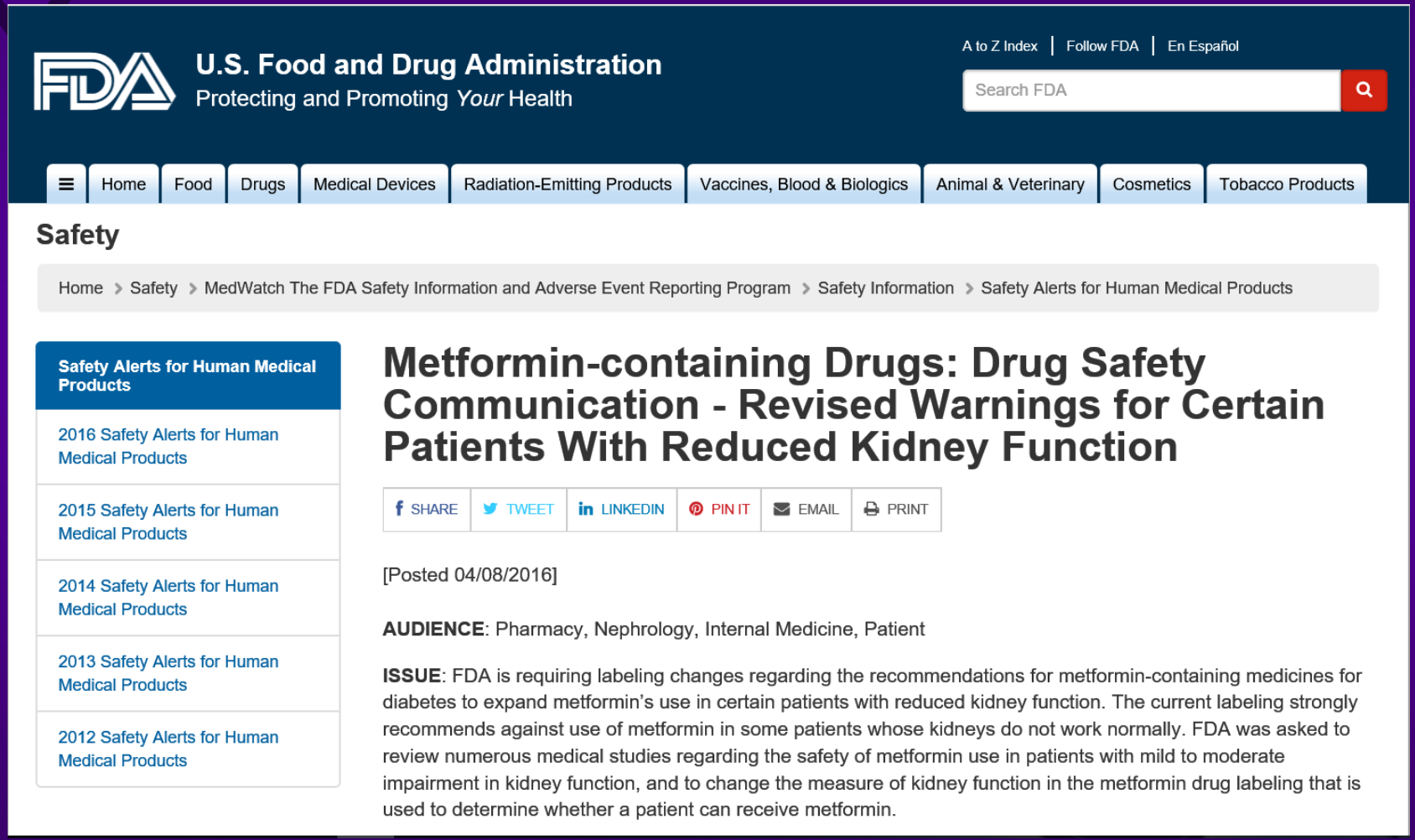
1. Treatment targets & treatment strategies should be personalized
2. Balance the benefits of glycaemic control with its potential risks particularly hypoglycemia

Advice on Selection of GLDs

- Treat according to the potential pathophysiology of the individual DM patients; early drug combination may be required
- Avoid GLDs which may induce hypoG if possible
- Priorities should be given to GLDs with proven CV benefits


3

FDA Relaxed the Use of Metformin in Patients with Impaired Renal Function



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Safety Alerts for Human Medical Products

- 2016 Safety Alerts for Human Medical Products
- 2015 Safety Alerts for Human Medical Products
- 2014 Safety Alerts for Human Medical Products
- 2013 Safety Alerts for Human Medical Products
- 2012 Safety Alerts for Human Medical Products

Metformin-containing Drugs: Drug Safety Communication - Revised Warnings for Certain Patients With Reduced Kidney Function

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[Posted 04/08/2016]

AUDIENCE: Pharmacy, Nephrology, Internal Medicine, Patient

ISSUE: FDA is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. FDA was asked to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function, and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin.

FDA Guidelines in the Use of Metformin

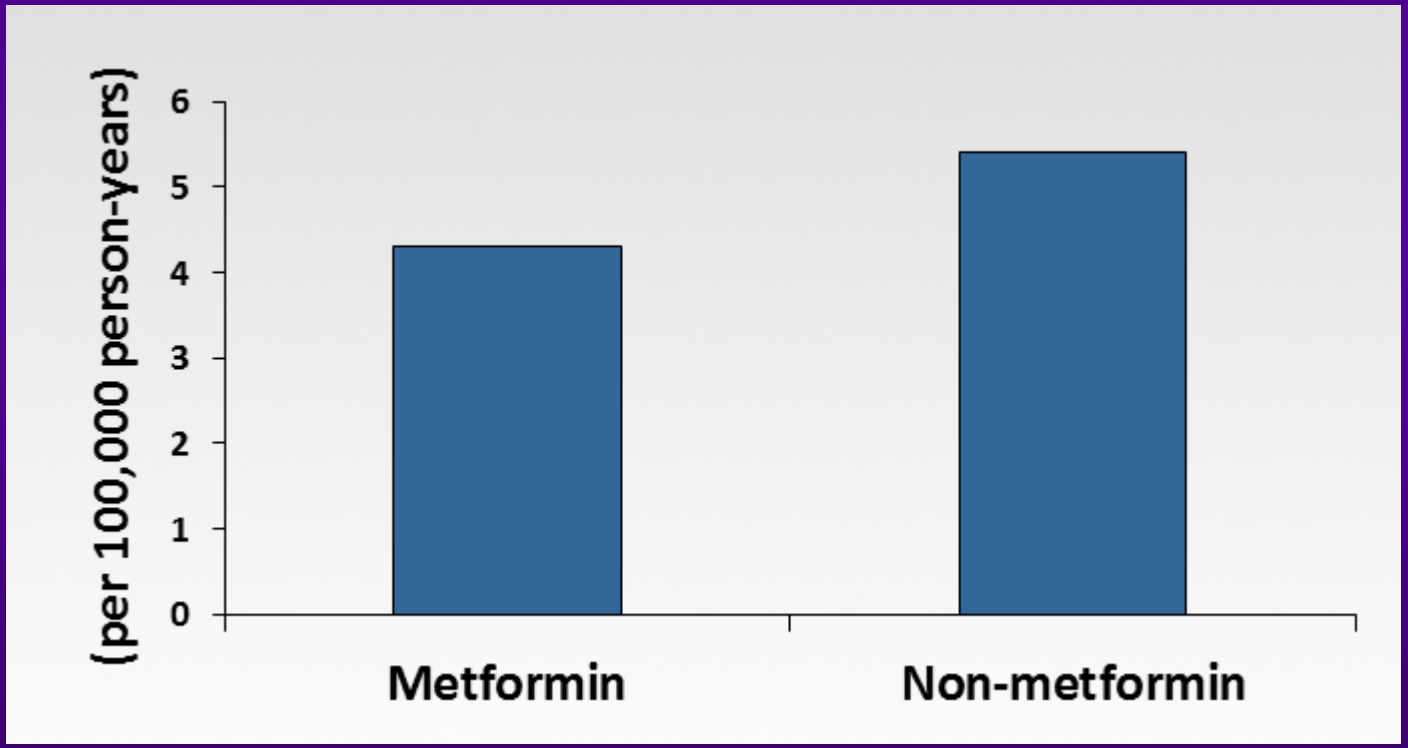
- FDA has relaxed the use of metformin in patients with moderate renal impairment since April 2016 because the benefits of metformin markedly outweigh the potential risks

CKD Stage	eGFR, mL/min per 1.73 m^2	Maximal Total Daily Dose, mg	Other Recommendations
1	≥90	2550	
2	60 -<90	2550	
3A	45 -<60	2000	Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
3B	30 -<45	1000	Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
4	15 -<30	Do not use	
5	<15	Do not use	

Inzucchi et al. JAMA 2014;312(24):2668-75

Incidence of Lactic Acidosis NOT Increased in Metformin-Treated Patients

Pooled data from 347 comparative trials & cohort studies in 70,490 patient-years of metformin use & 55,451 patient-years of non-metformin use in T2DM

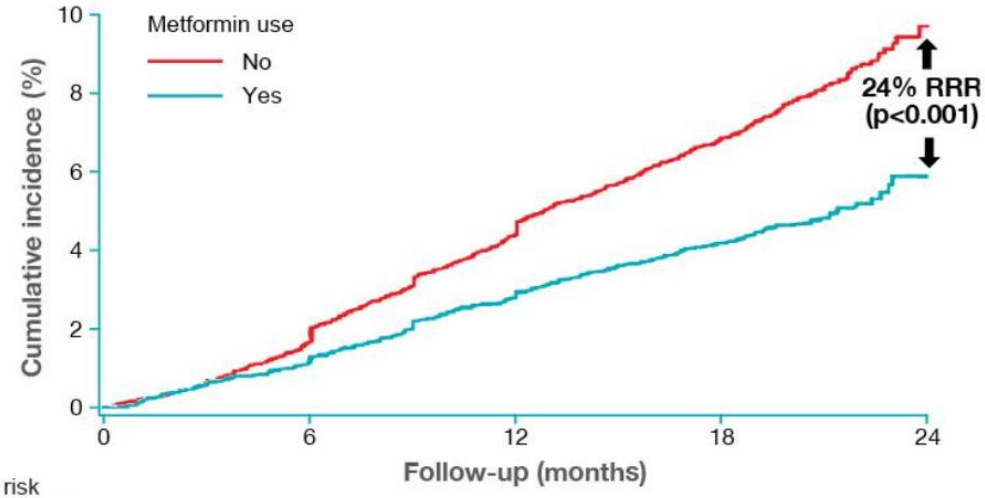


Salpeter et al. Cochrane Database Syst Rev 2014;(4):CD002967

Metformin in Patients with Established CVD

19,691 diabetic patients with established atherosclerosis in the Reduction of Atherothrombosis for Continued Health (REACH) Registry between 2003-2004 treated with or without metformin

Figure 2. Risk of all-cause mortality in T2DM patients with atherosclerosis



No. at risk
Metformin use

Yes	7,397	7,234	6,848	6,119	3,340
No	12,156	11,805	10,979	9,769	5,808

RRR = relative risk reduction; T2DM = type 2 diabetes mellitus

Subgroups	HR	P value
Age ≥ 65	0.77 (0.62-0.95)	0.02
CHF	0.69 (0.54-0.90)	0.006
eGFR 30-60	0.64 (0.48-0.86)	0.003

Roussel et al. Arch Intern Med 2010;170(21):1892-9

Annals of Internal Medicine®

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REVIEWS | 3 JANUARY 2017

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

Matthew J. Crowley, MD, MHS; Clarissa J. Diamantidis, MD, MHS; Jennifer R. McDuffie, PhD; C. Blake Cameron, MD, MBI; John W. Stanifer, MD, MSc; Clare K. Mock, MD; Xianwei Wang, MD; Shuang Tang, PhD; Avishek Nagi, MS; Andrzej S. Kosinski, PhD; John W. Williams, Jr., MD, MHS

Metformin was associated with reduced all-cause mortality in patients with

- moderate to severe CKD (HR 0.78)
- congestive heart failure (HR 0.78)
- chronic liver disease (HR 0.43)

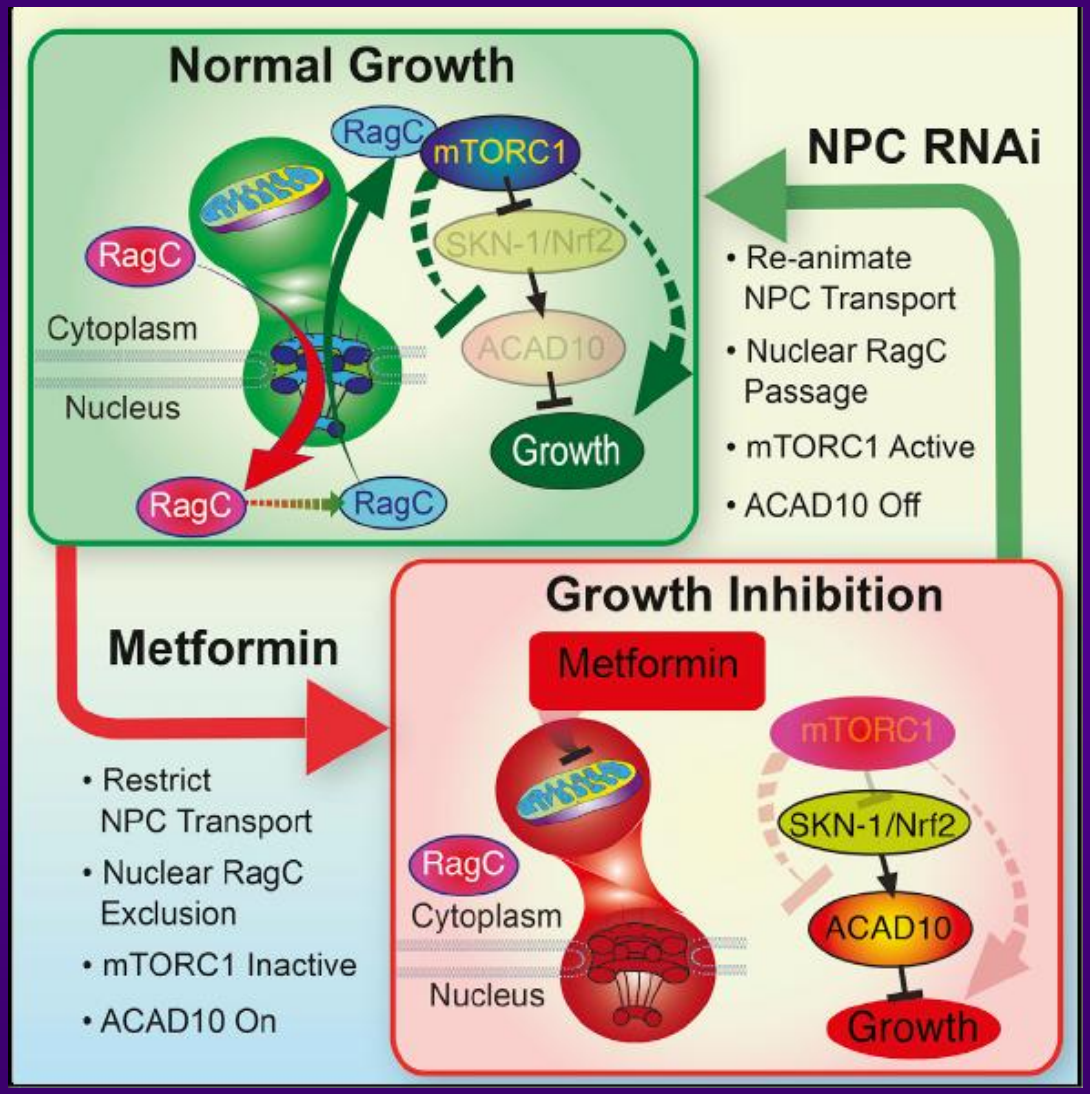
Metformin was also associated with fewer heart failure readmissions in patients with CKD or CHF

Crowley et al. Ann Intern Med 2017;166(3):191-200

Practical Tips in the Use of Metformin

1. Optimal dose should be ≥1,600 mg daily to confer CV benefits
2. If patient cannot tolerate conventional metformin, please change to metformin XR preparation with much lower incidence of GI adverse effects
3. Do not prematurely stop metformin just because of mild impairment of RFT (use eGFR as guide)
4. Risk of metformin-associated lactic acidosis is very much lower than its glucose-lowering and CV benefits

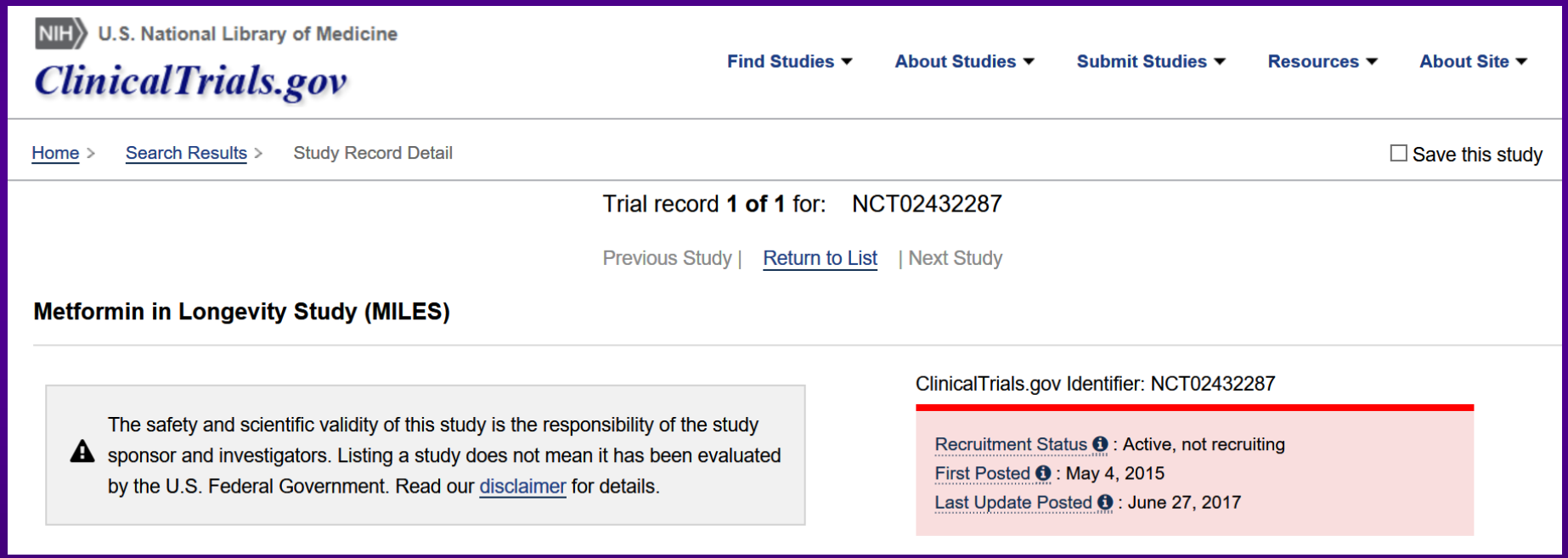
Metformin Inhibit Cancer Cell Growth



Wu et al. Cell 2016;167(7):1705-18

Metformin – the NOT Learnt

Potential anti-inflammatory, anti-atherogenic, anti-thrombotic, anti-oxidant, anti-cancer & anti-aging effects of metformin



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Trial record **1 of 1** for: NCT02432287

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Metformin in Longevity Study (MILES)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

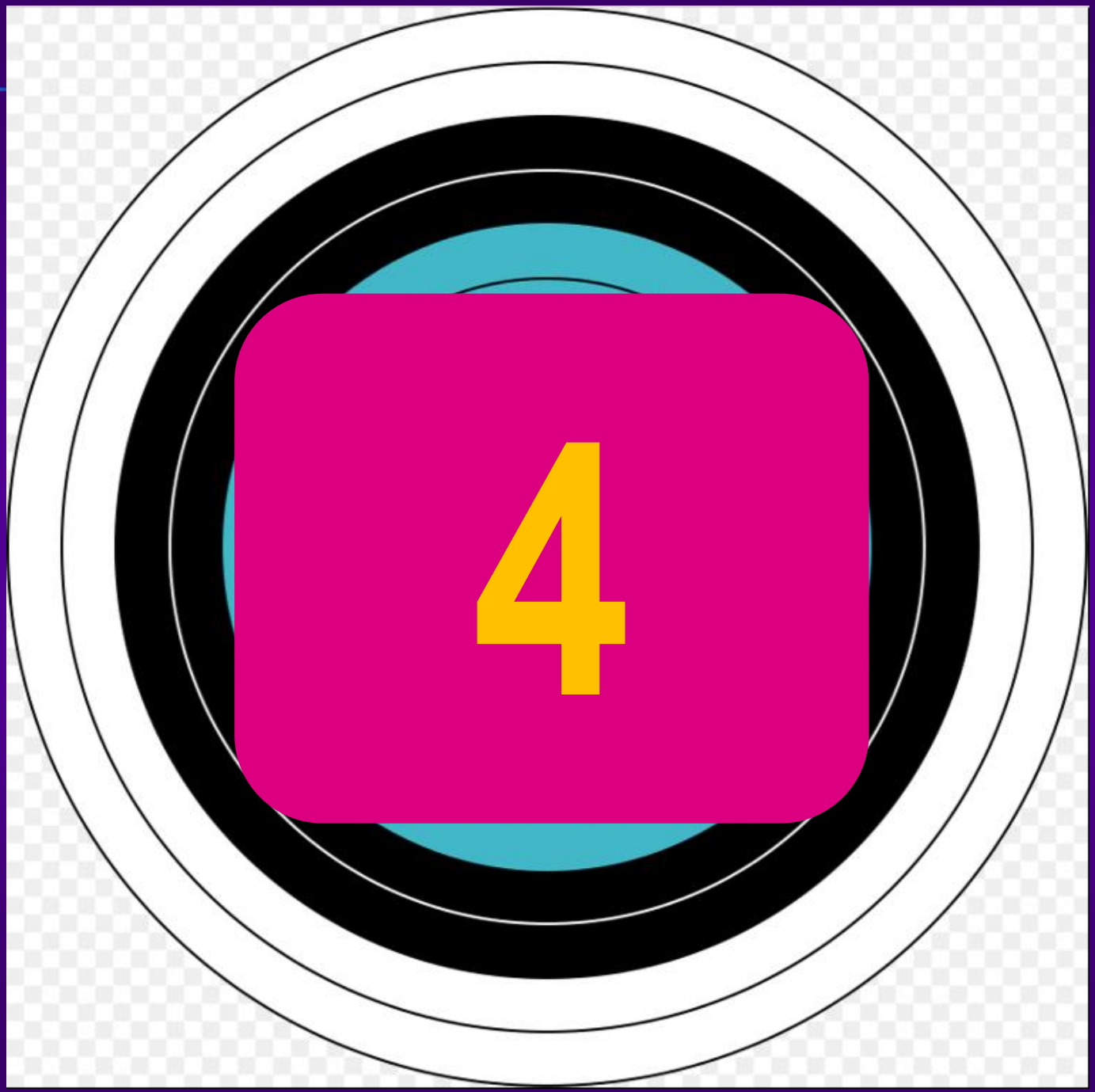
ClinicalTrials.gov Identifier: NCT02432287

Recruitment Status : Active, not recruiting

First Posted : May 4, 2015

Last Update Posted : June 27, 2017

https://www.clinicaltrials.gov/ct2/show/NCT03309007?term=metformin+and+antiaging&rank=1


4

ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

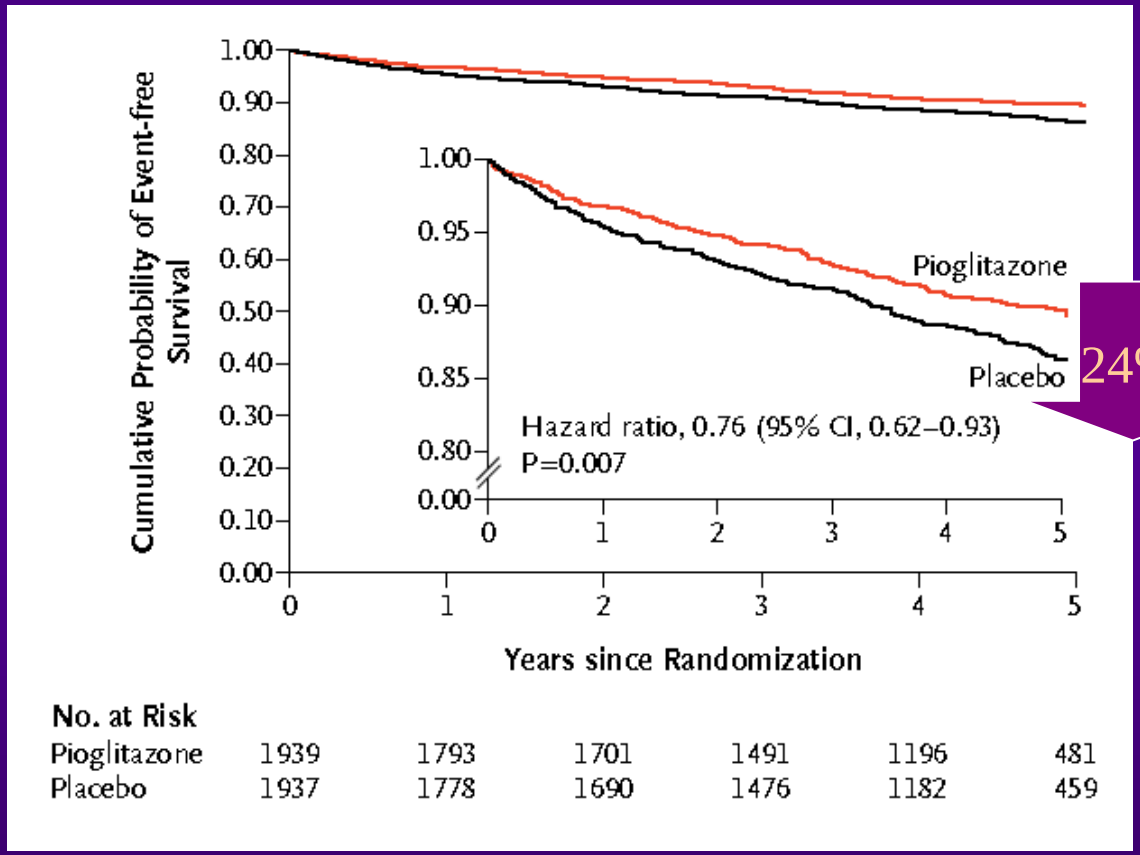
W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, L.M. Brass,* G.G. Schwartz, H.P. Adams, Jr., L. Berger, A. Carolei, W. Clark, B. Coull, G.A. Ford, D. Kleindorfer, J.R. O'Leary, M.W. Parsons, P. Ringleb, S. Sen, J.D. Spence, D. Tanne, D. Wang, and T.R. Winder, for the IRIS Trial Investigators†

3,876 patients age ≥40 with a recent history of ischaemic stroke or TIA and who had insulin resistance (HOMA-IR index >3.0) randomised to receive PIO or placebo

Kernan et al. N Engl J Med 2016;374(14):1321-31

IRIS TRIAL - CVOT

Primary endpoint: (3-point MACE)

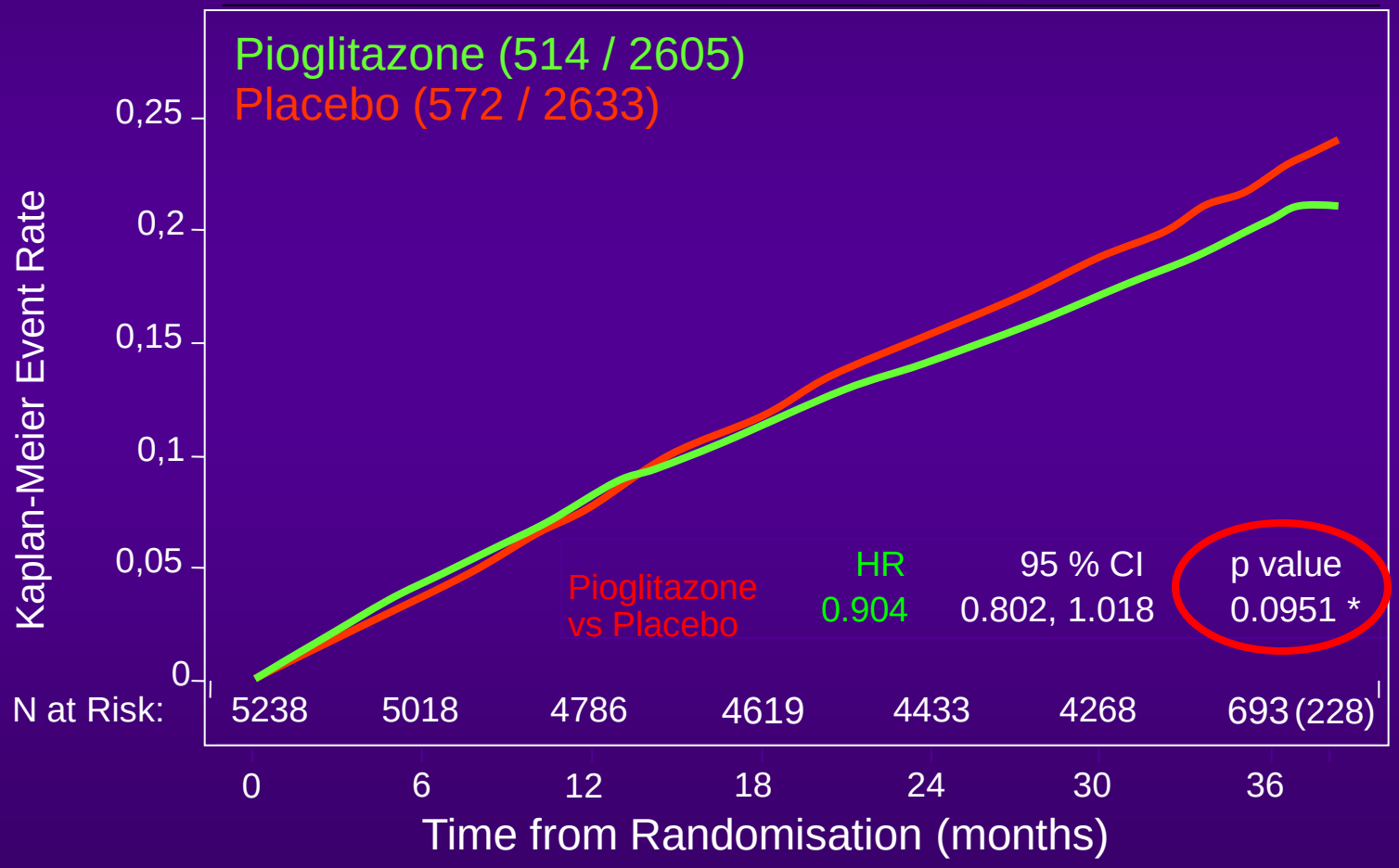


Kernan et al. N Engl J Med 2016;374(14):1321-31

PROactive Study

5,238 T2DM patients with pre-existing macrovascular diseases

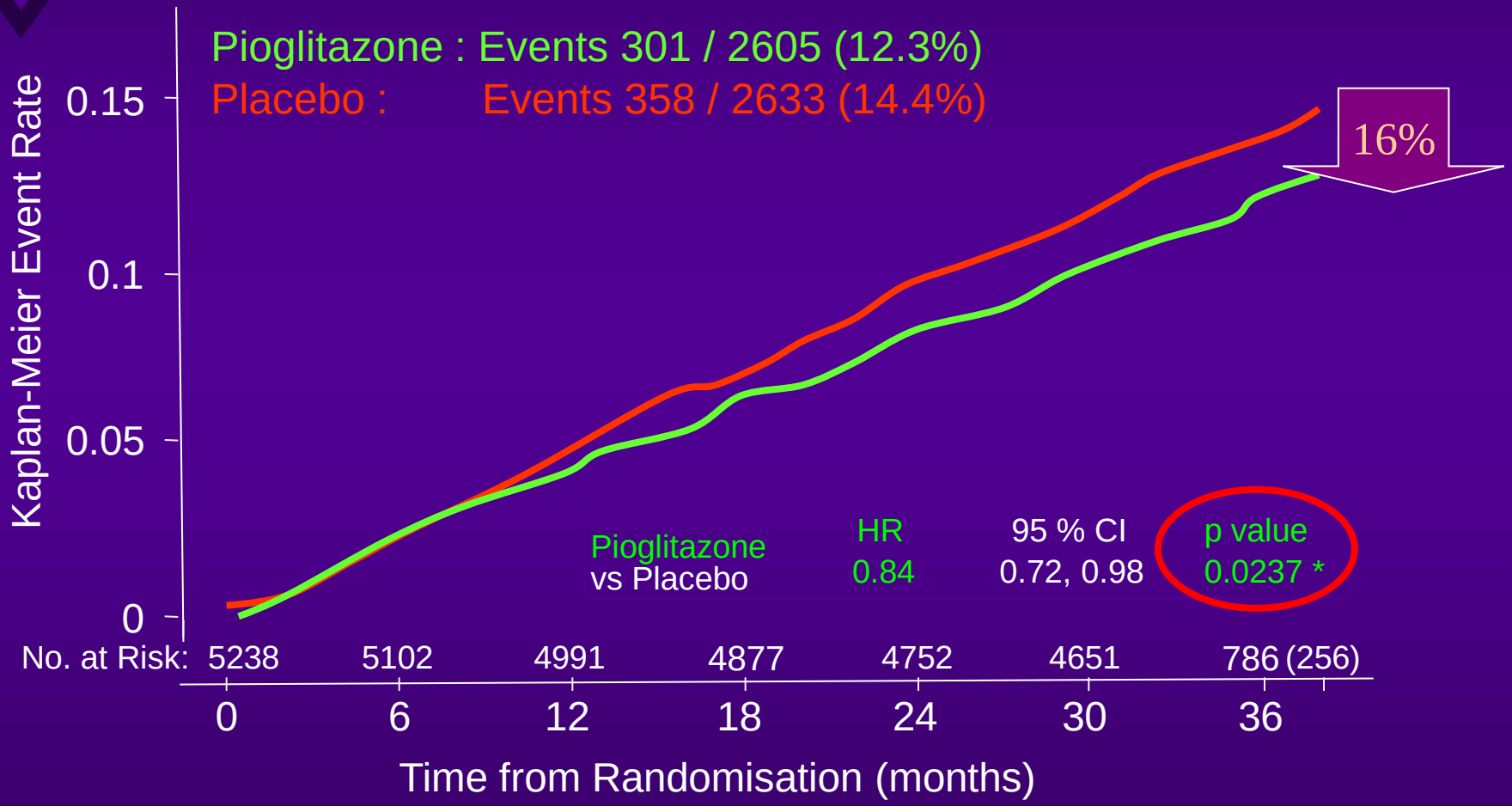
Primary Composite Endpoint * Death from any cause, non-fatal MI, stroke, ACS, leg ampuation, coronary revascularisation, bypass surgery/revascularisation of the leg



Dormandy G et al. Lancet 2005;366:1279-89

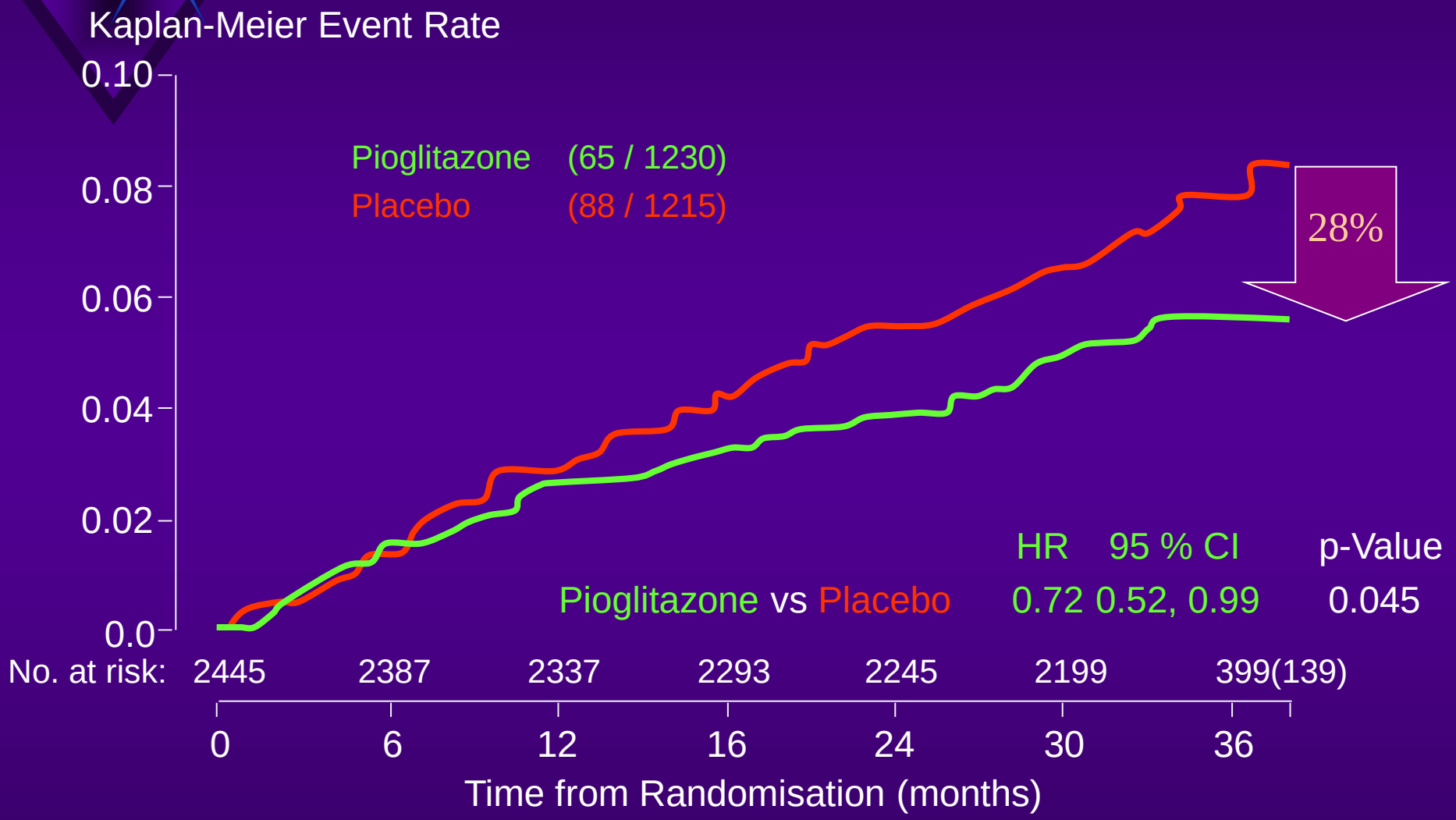
PROactive Study: Significant Reduction of the Combined 3-Point MACE

(Death, Non-fatal MI & Non-fatal-Stroke)



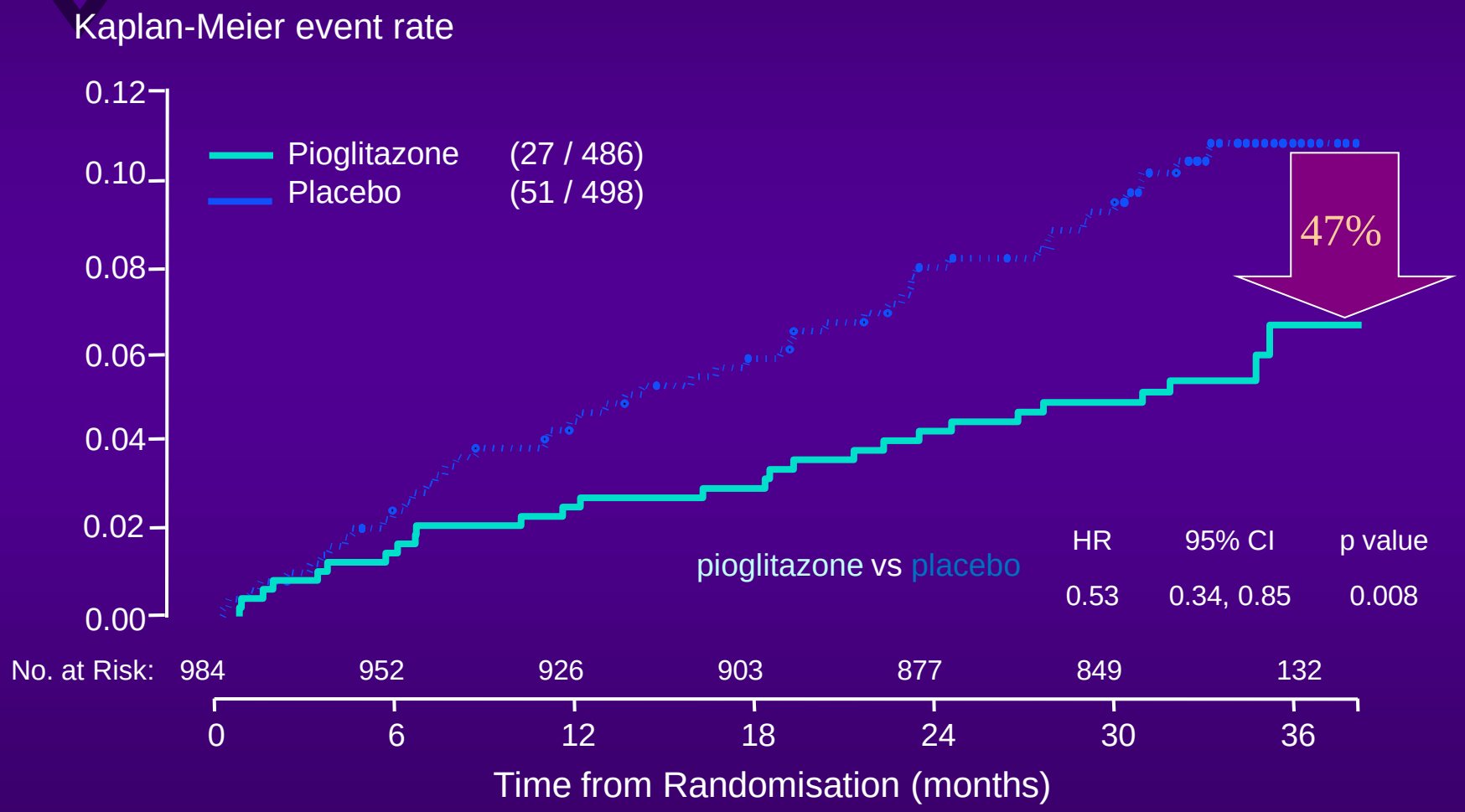
Dormandy G et al. Lancet 2005;366:1279-89

PROactive Study: Pioglitazone's Effect on Recurrent MI in Patients with Previous MI



Erdmann et al. J Am Coll Cardiol 2007;49:1772-80

PROactive Study: Pioglitazone Effect on Recurrent Stroke in Patients with Previous Stroke



Wilcox et al. Stroke 2007;38:865-73

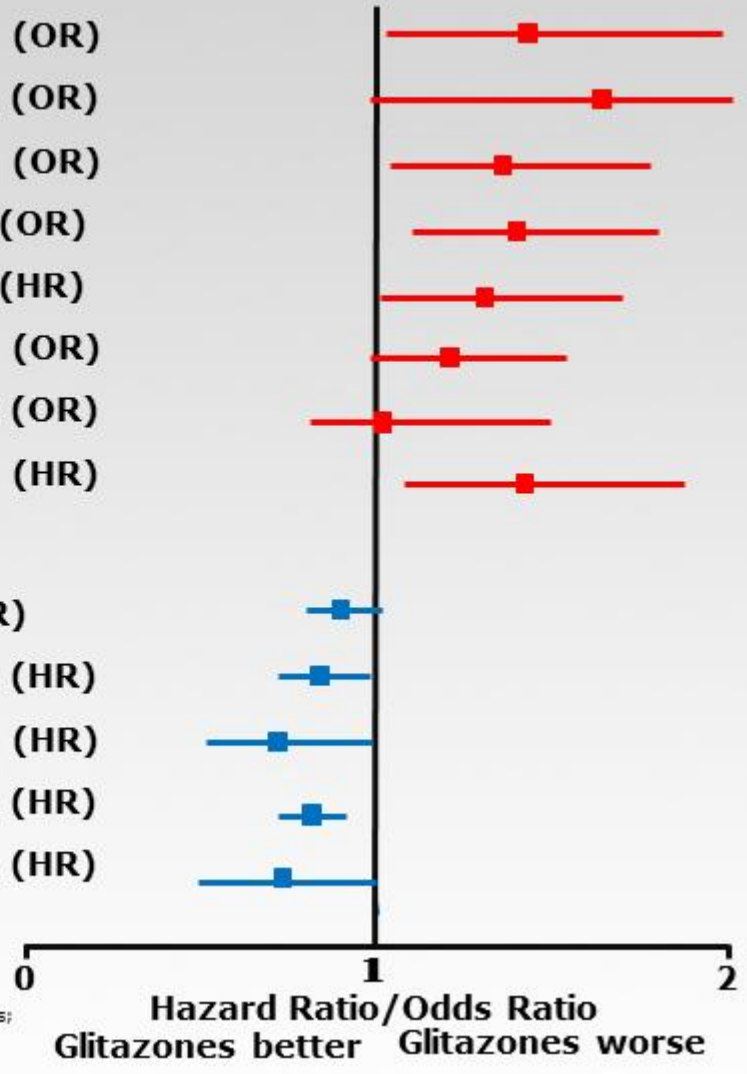
CV Events with the TZDs

Rosiglitazone

Meta-analysis, Nissen et al[a]	Myocardial Infarction (OR)
Meta-analysis, Nissen et al[a]	Cardiovascular Death (OR)
Meta-analysis, Krall[b]	Myocardial Infarction (OR)
Meta-analysis, FDA[c]	Myocardial Ischemia (OR)
Meta-analysis, GSK[d]	Myocardial Ischemia (HR)
Data from Nissen and RECORD[e]	Myocardial Infarction (OR)
Data from Nissen and RECORD[e]	Cardiovascular Death (OR)
Meta-analysis, Singh[f]	Myocardial Infarction (HR)

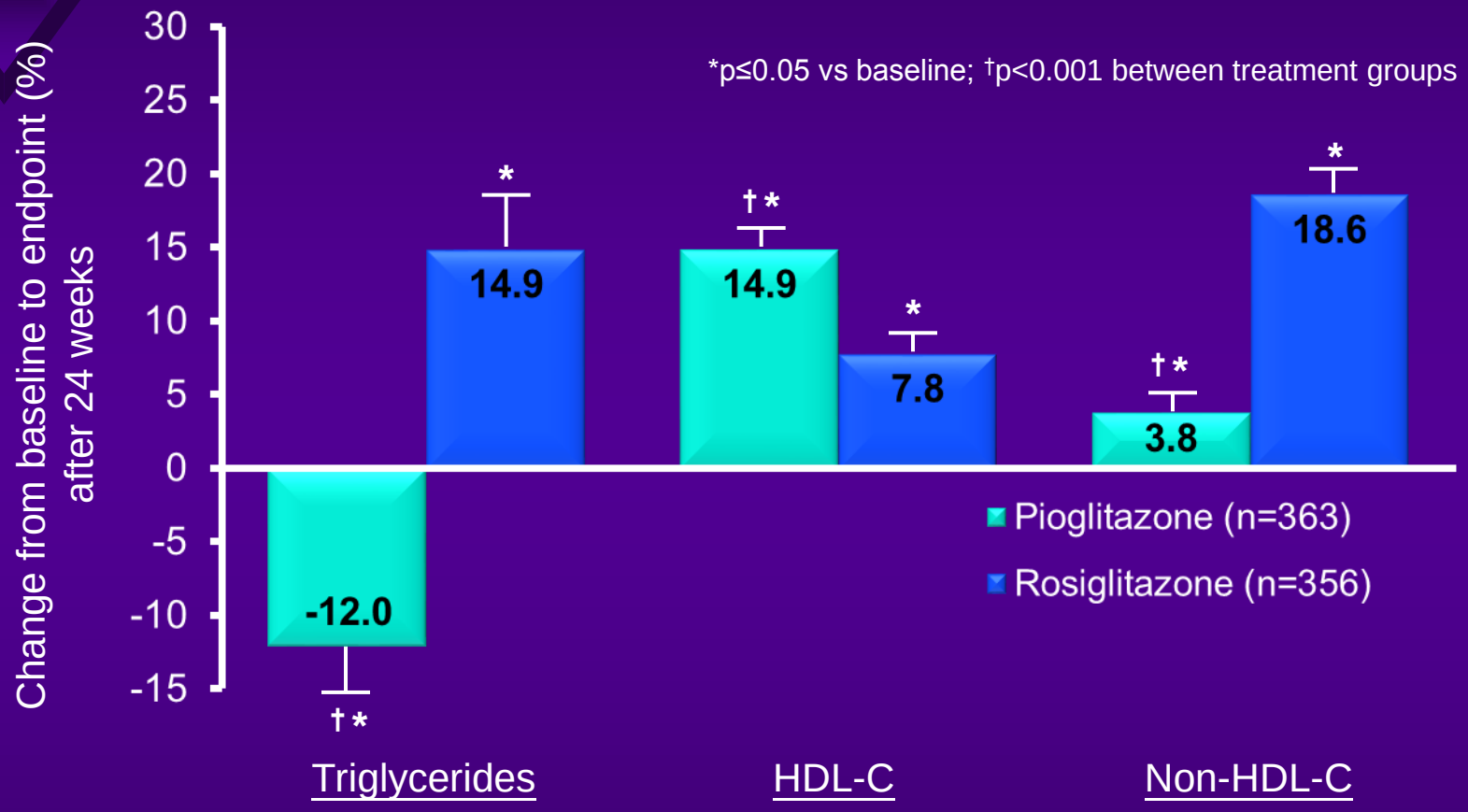
Pioglitazone

PROactive[g]	Primary Endpoint (HR)
PROactive[h]	MI, Stroke and Death (HR)
PROactive MI-Subgroup[i]	Myocardial Infarction (HR)
Meta-analysis, Lincoff et al[j]	MI, Stroke and Death (HR)
Meta-analysis, FDA 2007[c]	MI, Stroke and Death (HR)



[a]Nissen SE, et al. *N Engl J Med*. 2007;356:2457-2471; [b]Krall RL. *Lancet*. 2007;369:1995-1996; [c]FDA-Homepage www.fda.gov; FDA-Hearing 30.07.2007; [d]SPCAvandia®; [e]Bracken MB. *N Engl J Med*. 2007;357:937; [f]Singh S et al. *JAMA*. 2007;298:1189-1195; [g]Diamond G, et al. *Ann Int Med*. 2007;in press; [h]Dormandy JA, et al. *Lancet*. 2005;366:1279-1289; [i]Erdmann E, et al. *J Am Coll Cardiol*. 2007;49:1772-1780; [j]Lincoff AM, et al. *JAMA*. 2007;298;1180-1188.

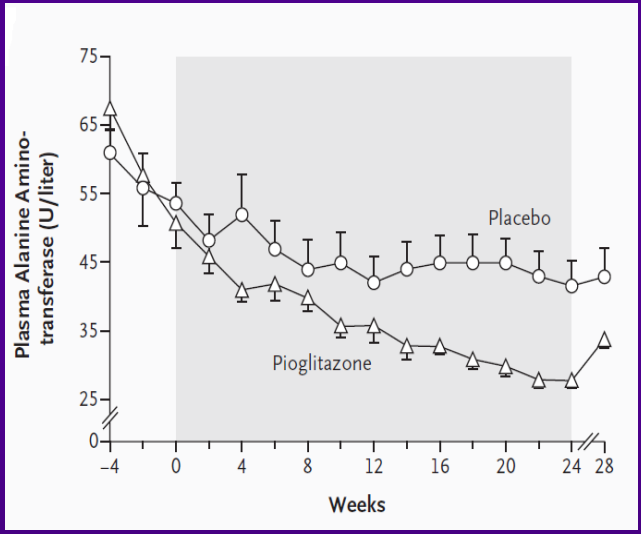
Pioglitazone vs Rosiglitazone: Effects on Lipid

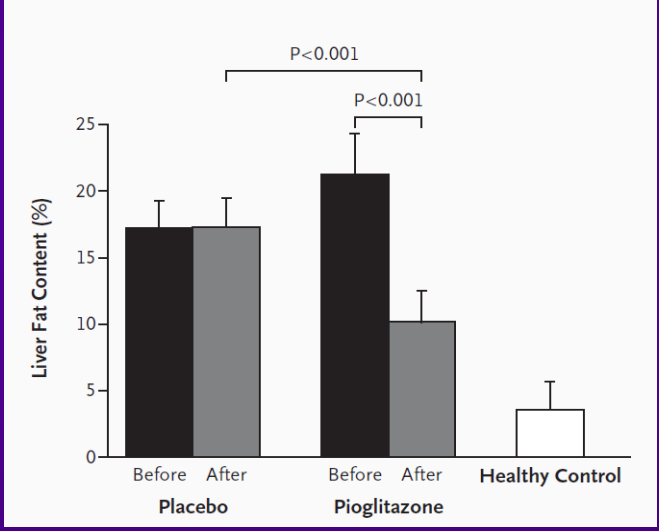


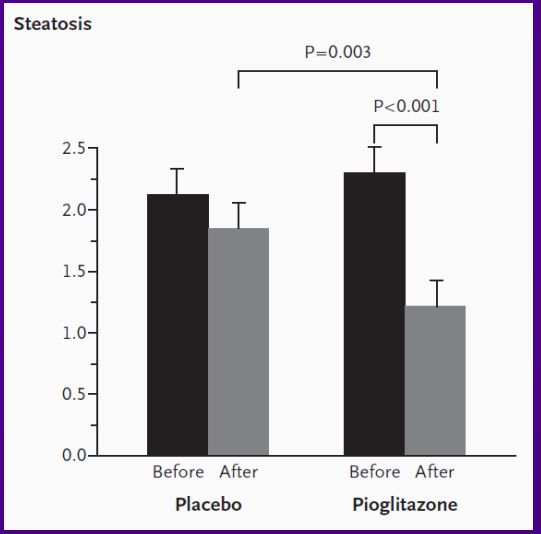
Goldberg et al. Diabetes Care 2005;28:1547-54
Goldberg et al. Circulation 2005;111:1727-8

Pioglitazone Effects on NASH

55 patients with T2DM/IGT and liver biopsy-confirmed nonalcoholic steatohepatitis to 6 months of treatment with a hypocaloric diet (↓500 kcal per day) plus pioglitazone (45 mg daily) or a hypocaloric diet plus placebo

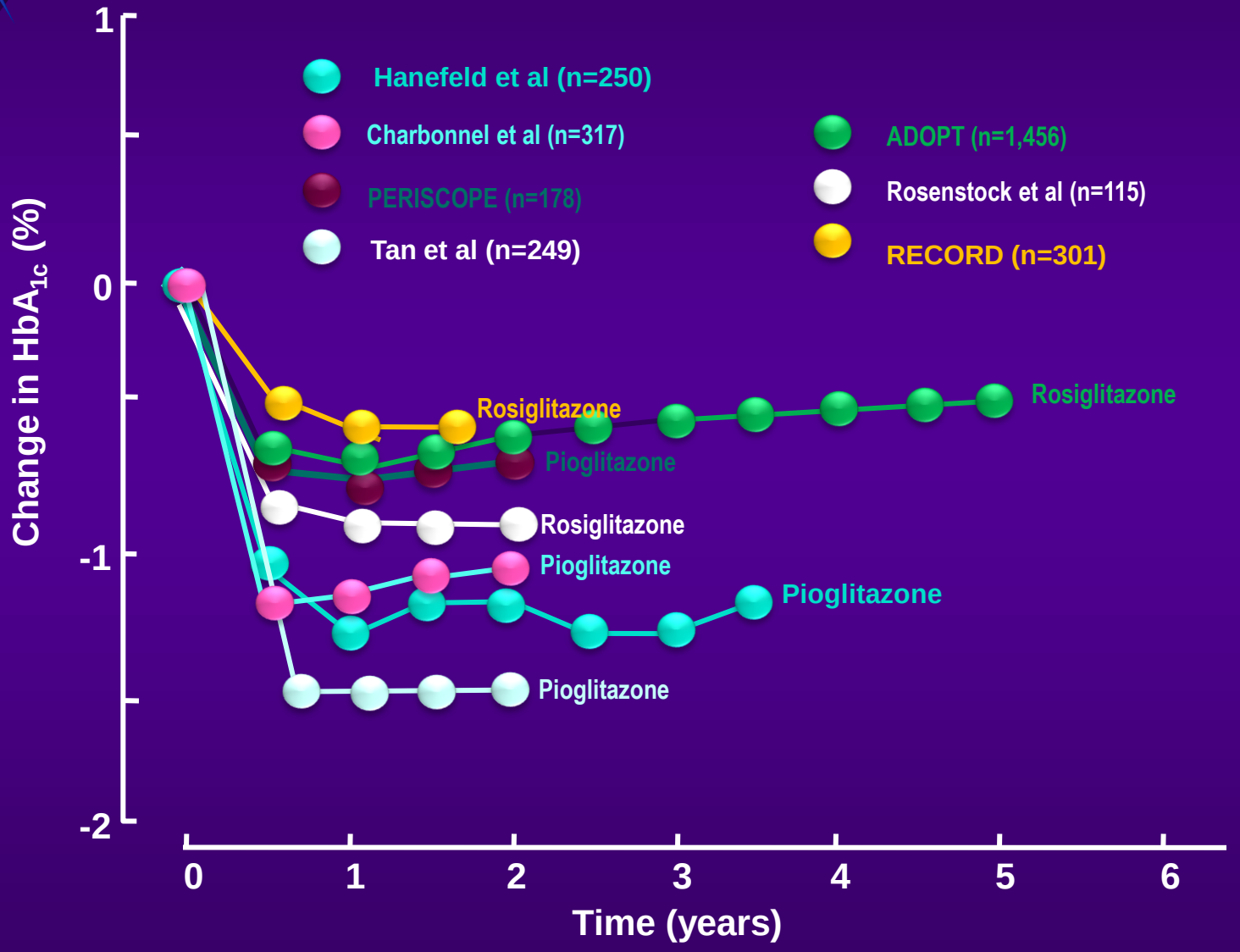




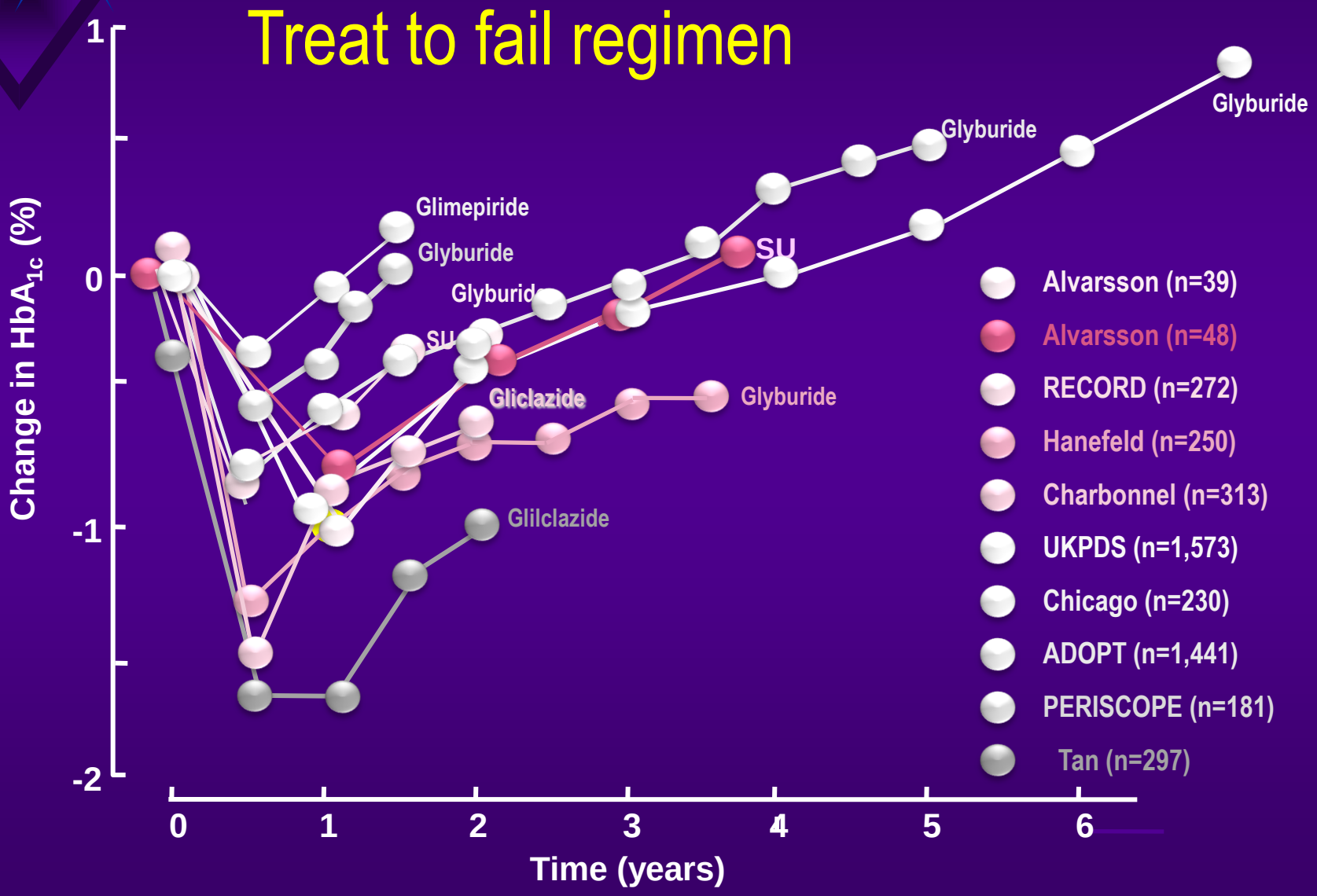


Belfort et al. N Engl J Med 2006;355(14):2297-307

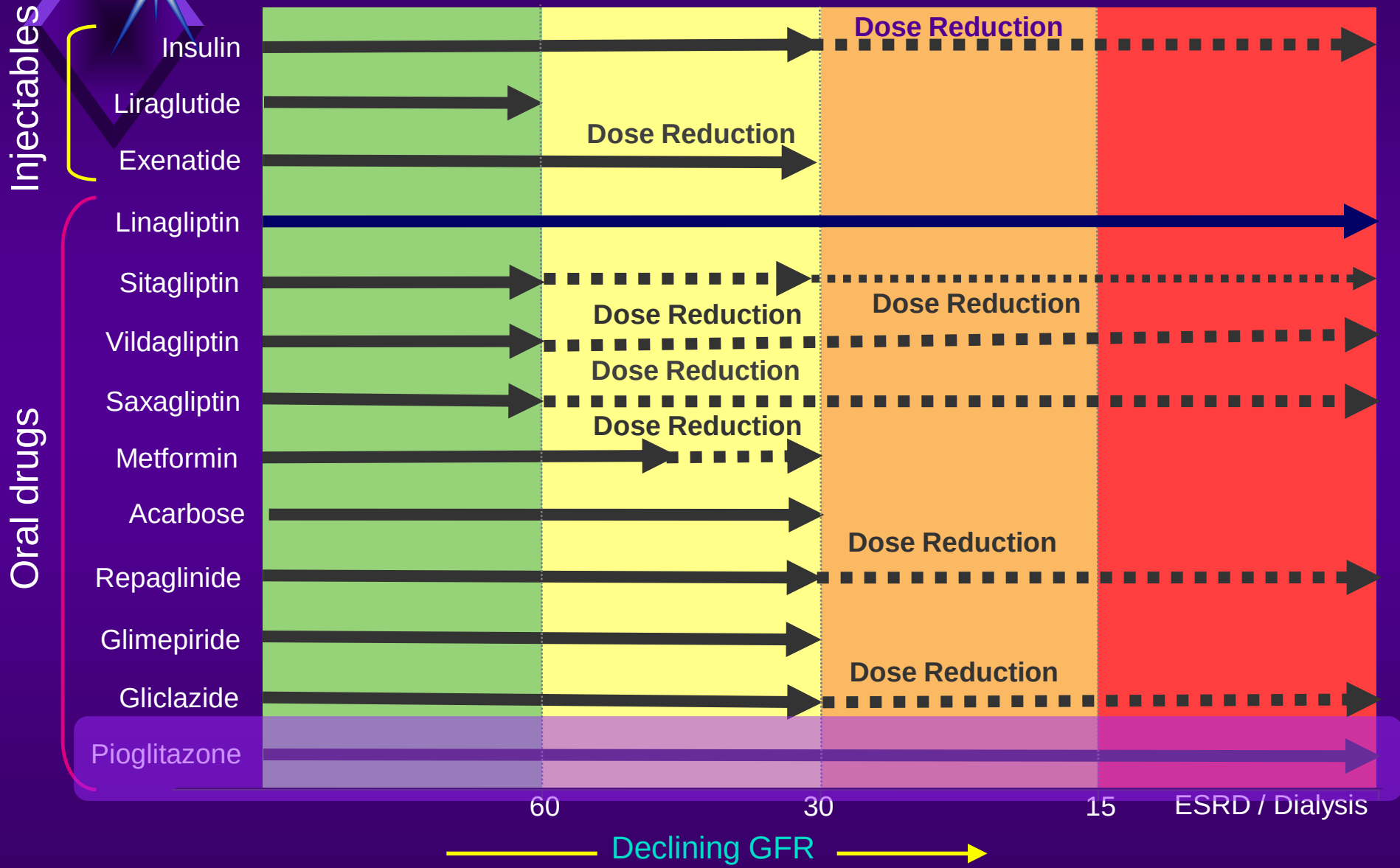
Good Durability of Glycemic Control with TZDs



Poor Durability of Glycemic Control with SUs



Anti-Diabetic Drugs in CKD



Modified from Schernthaner et al. Nephrol Dial Transplant 2010;25(7):2044-7

Pioglitazone – the Not Leearnt

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

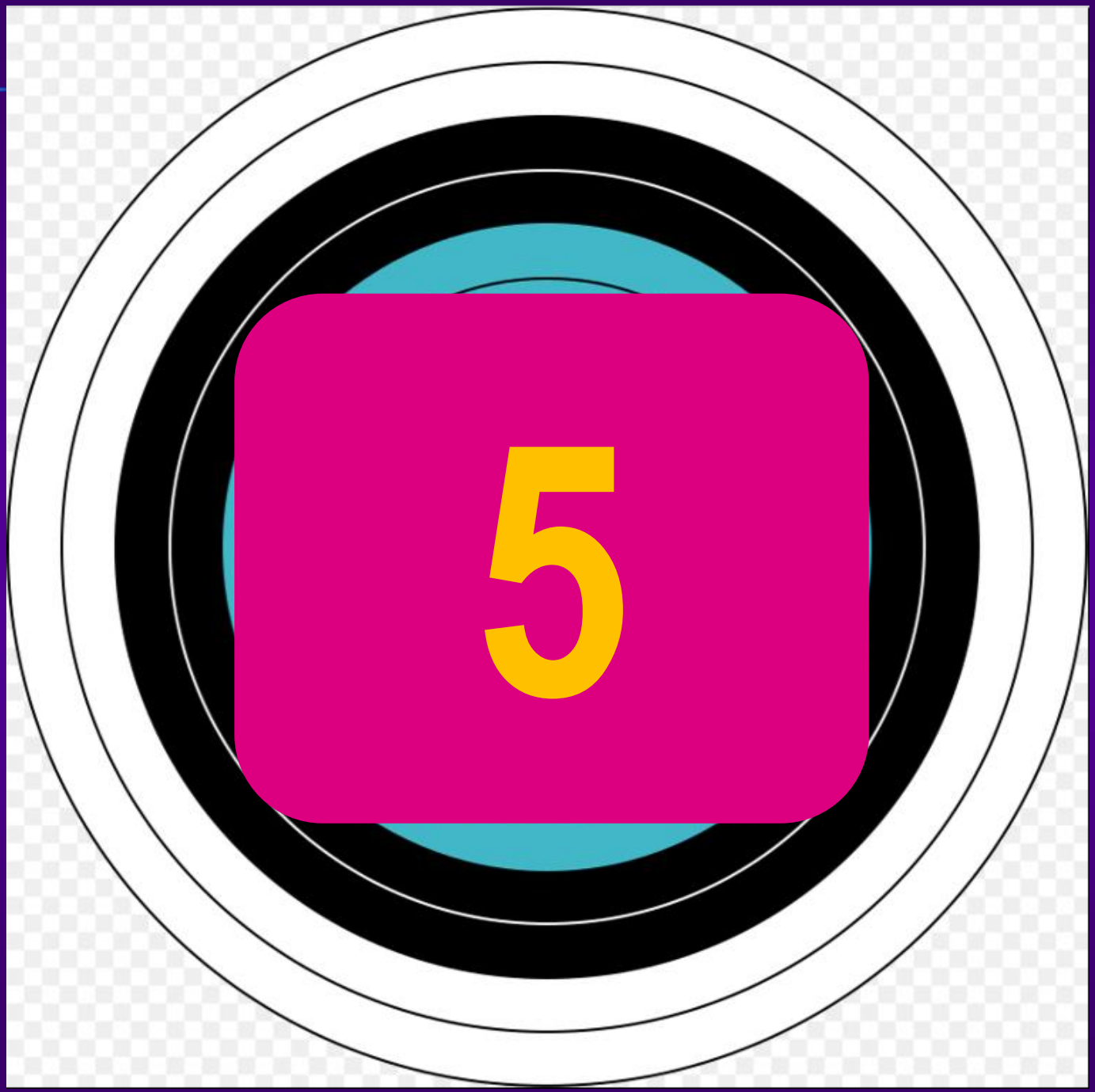
PERSPECTIVE

Revitalization of pioglitazone: the optimum agent to be combined with a sodium-glucose co-transporter-2 inhibitor

R. A. DeFronzo ✉, R. Chilton, L. Norton, G. Clarke, R. E. J. Ryder, M. Abdul-Ghani

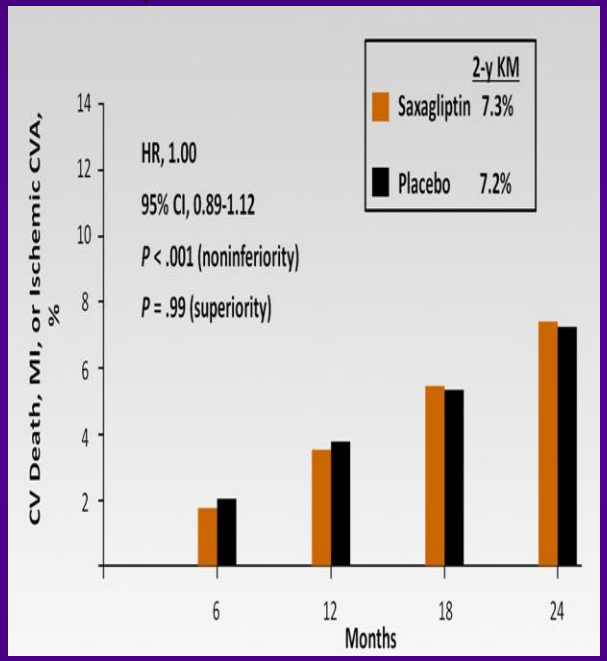
1. PIO might be an ideal agent to combine with empagliflozin to further reduce CV events in patients with high-risk T2DM
2. Empagliflozin also promotes salt/water loss and is expected to offset any fluid retention associated with PIO therapy

DeFronzo et al. Diabetes Obe Metab 2006;18(5):454-62


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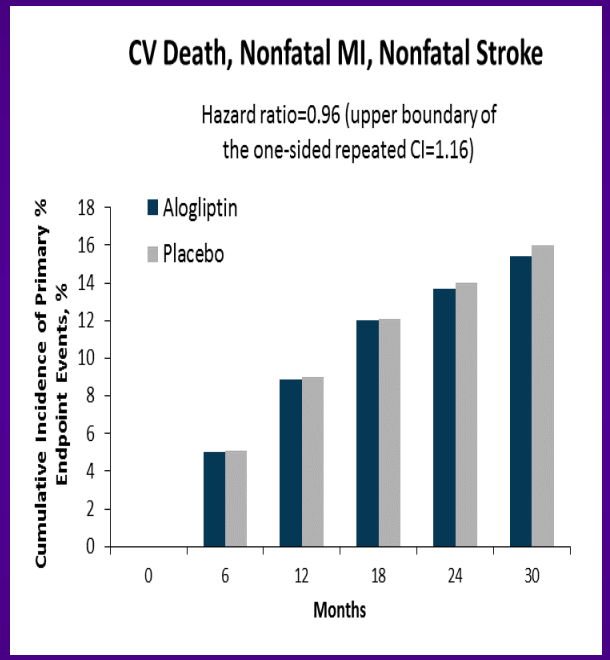
DPP4-Inhibitors: Very Disappointed CVOT Results

SAVOR-TIMI 53



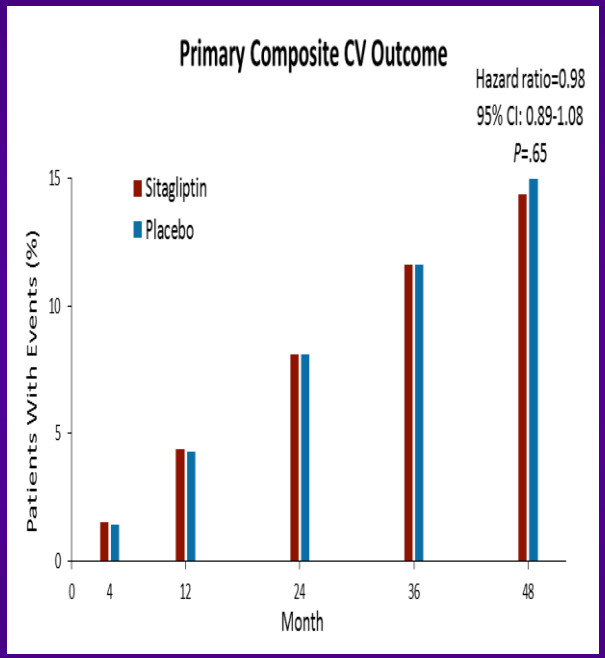
Saxagliptin

EXAMINE



Alogliptin

TECOS

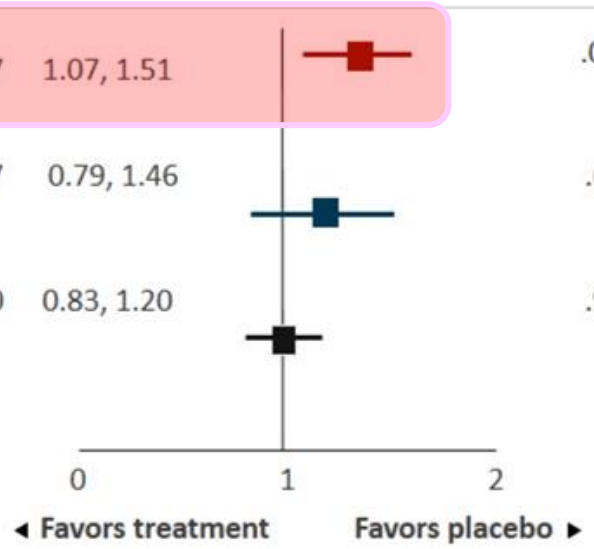


Sitagliptin

White et al. N Engl J Med 2013;369(14):1327-35
Scirica et al. N Engl J Med 2013;369(14):1317-26
Green et al. N Engl J Med 2015;373(3):232-42

Increase Risk of HFF for Saxagliptin

	Study Drug n/N (%)	Placebo n/N (%)	HR	95% CI	*P* Value
SAVOR-TIMI 53[a] (saxagliptin vs placebo)	289/8280 (3.5)	228/8212 (2.8)	1.27	1.07, 1.51	.007*
EXAMINE[b] (alogliptin vs placebo)	85/2701 (3.1)	79/2679 (2.9)	1.07	0.79, 1.46	.657
TECOS[c] (sitagliptin vs placebo)	228/7332 (3.1)	229/7339 (3.1)	1.00	0.83, 1.20	.983

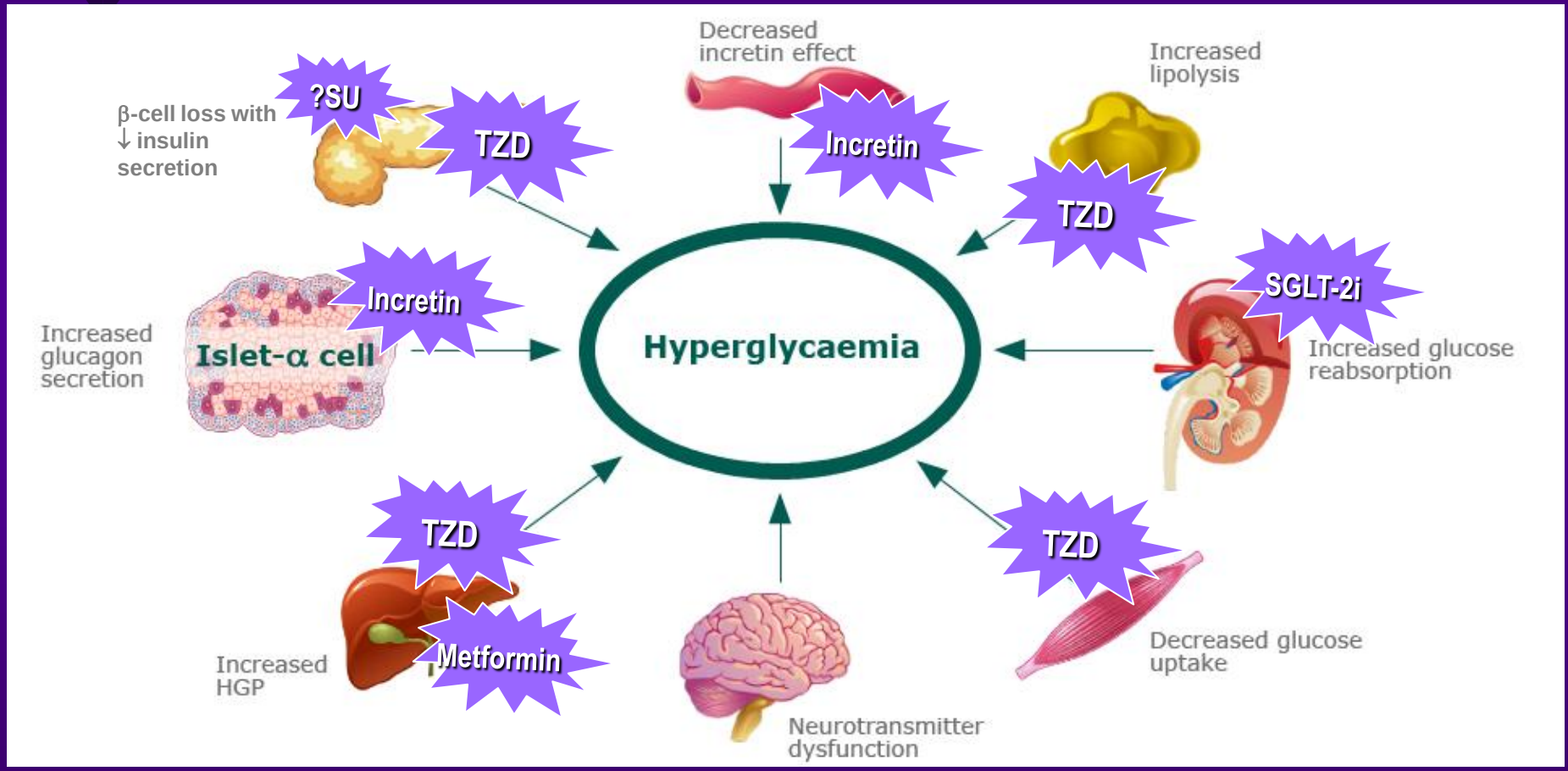


White et al. N Engl J Med 2013;369(14):1327-35
Scirica et al. N Engl J Med 2013;369(14):1317-26
Green et al. N Engl J Med 2015;373(3):232-42

DPP4-Inhibitors – the Learnt & Not Learnt

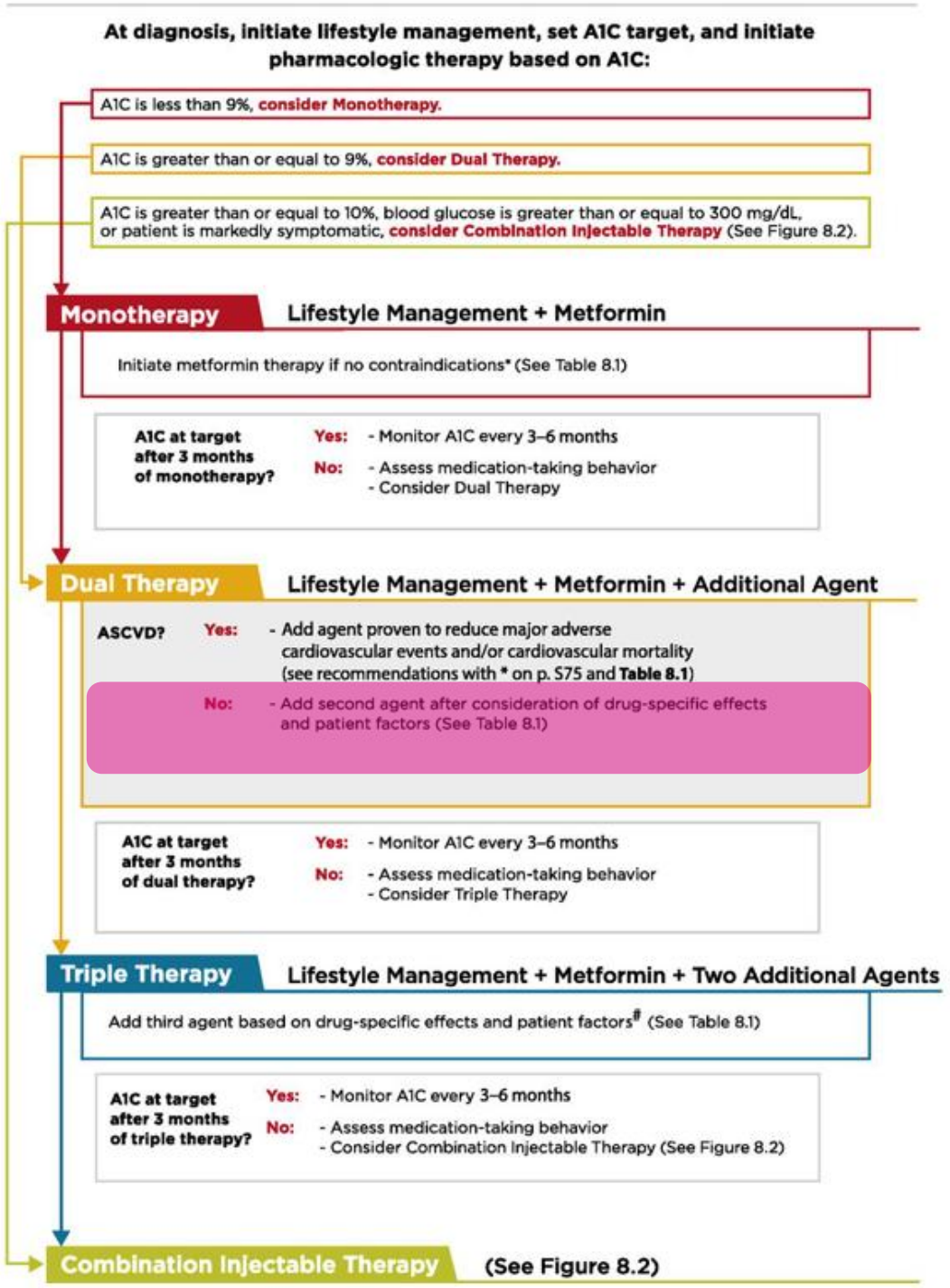
- A class of GLD with virtual absence of adverse effects BUT also with only very modest A1c reduction (0.5-0.8%)
- Neutral effects on CV risk reduction with potential increase in risk of HHF (saxagliptin)
- May have priority as a second-line GLD in elderly with multiple co-morbidities
- Very much overuse in clinical practice
- The unknown – whether CVOTs of linagliptin (CAROLINA, CARMELINA) will be favourable – very unlikely

Oral Anti-Diabetic Drugs Targeting the Different Pathophysiologies of T2DM



Modified from Defronzo RA. Diabetes 2009;58;773-95

2018 ADA Anti-Hyperglycaemic Management Algorithm

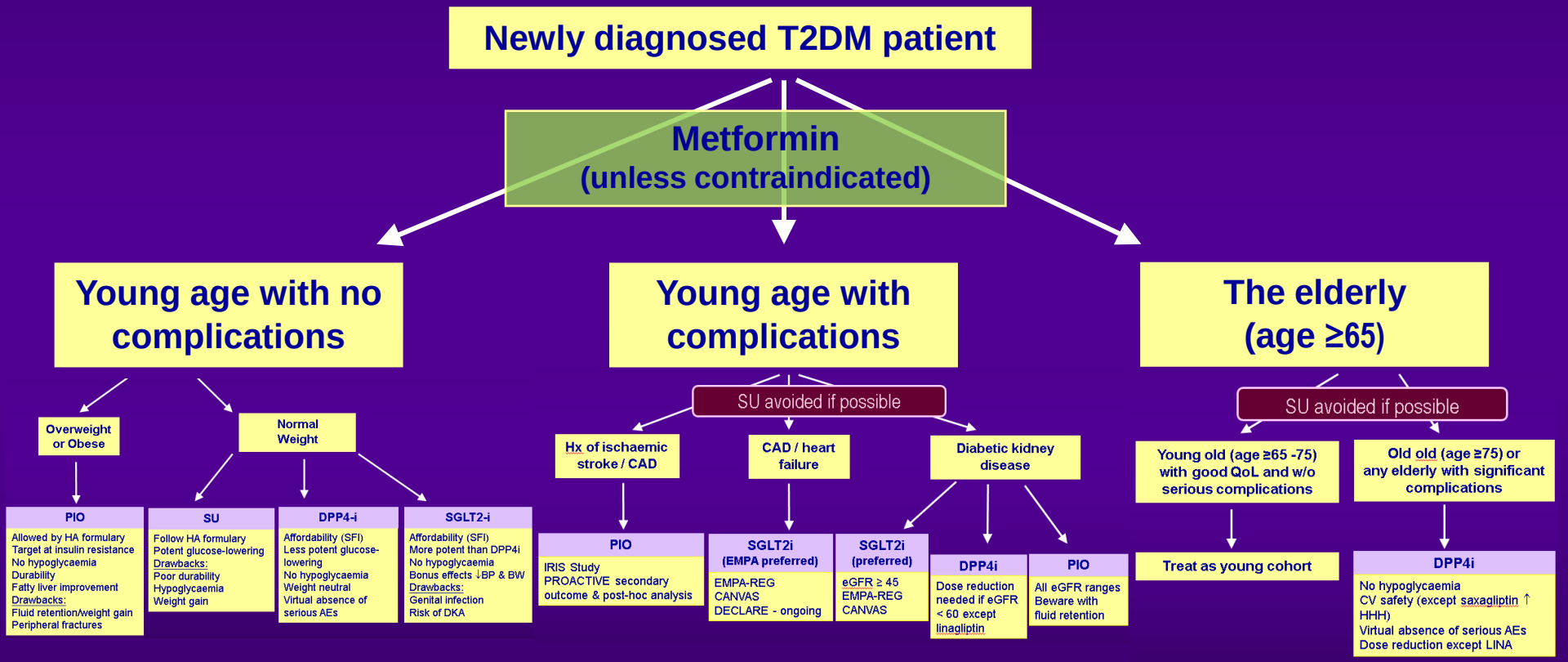


ADA. Standards of Medical Care in Diabetes – 2018. Diabetes Care 2018; 41(Suppl 1):S73-85

What's Next After Metformin in T2DM ?

	SU	PIO	DPP4-i	SGLT2-i
HT	neutral	neutral	neutral	slight advantage
Obesity	avoid	preferred	neutral	preferred
NAFLD	neutral	highly preferred	neutral	neutral
CAD	avoid	preferred	neutral	preferred
CVA	avoid	highly preferred	neutral	neutral
Heart failure	neutral	avoid	neutral (avoid SAX)	highly preferred (EMPA)
Mild to mod renal impairment	avoid	neutral	neutral (dose reduction except LINA)	preferred (EMPA)

Ip's Diabetes Algorithm



Drug Name	Usual Dose	Daily Cost (HKD)
Metformin	1000 mg bd	$0.34
Metformin XR (Glucophage XR®)	1000 mg bd	$3.64
Gliclazide (Diamicron®)	80 mg bd	$0.25
Gliclazide MR (Diamicron MR®)	60 mg daily	$0.61
Glimepiride (Amaryl®)	2 mg daily	$0.16
Pioglitazone (Actos®)	30 mg daily	$0.36
Alogliptin (Nesina®)	25 mg daily	$2.45
Alo 25/ Pio 30 (Oseni 25/30®)	1 tab daily	$2.45
Linagliptin (Trajenta®)	5 mg daily	$5.03
Saxaglitin (Onglyza®)	5 mg daily	-
Sitagliptin (Januvia®)	100 mg daily	$5.00
	50 mg daily	$4.96
Vildagliptin (Galvus®)	50 mg bd	$4.07
Dapagliflozin (Forxiga®)	10 mg daily	$5.25
Empagliflozin (Jardiance®)	25 mg daily	$5.35
	10 mg daily	$5.35
Acarbose (Glucobay®)	100 mg tds	$2.67

Latest price quoted for HA at 6/2018

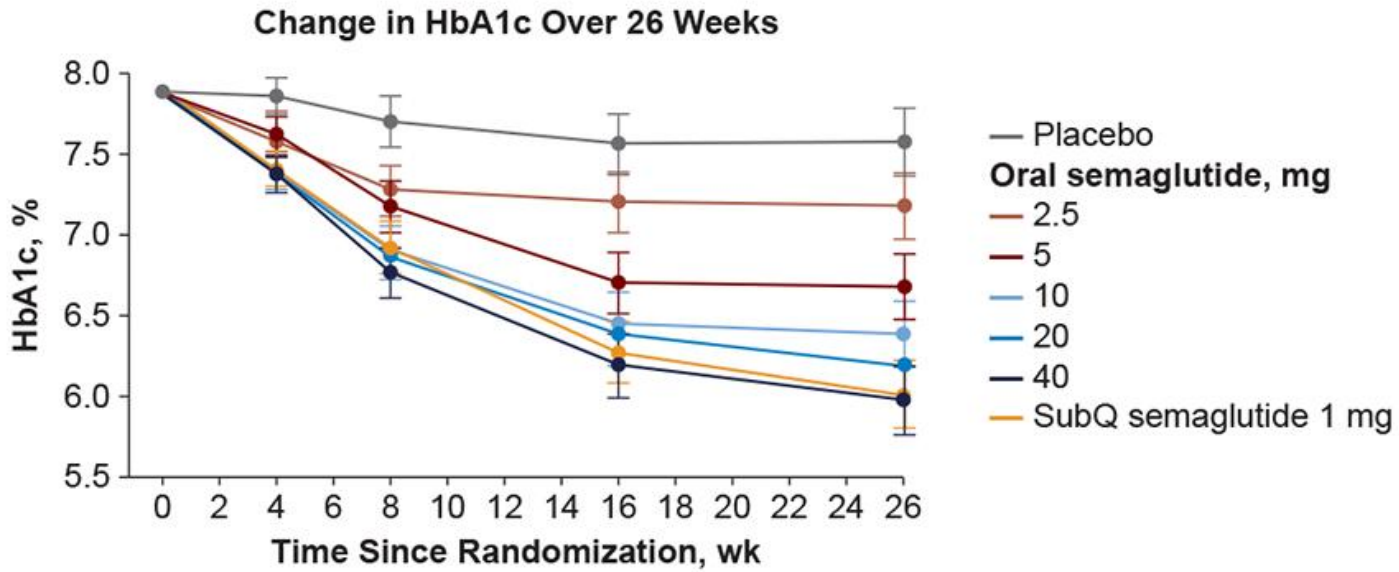
Next Classes of Oral GLD ?

Late breaking news: new classes of oral GLDs

Oral GLP1-receptor agonist	Dual SGLT-1 & 2 inhibitor
semaglutide	sotagliflozin

Oral Semaglutide (Phase 2 Study) PIONEER 1 Trial

- N = 632
- **Primary endpoint:** Change in HbA1c from baseline to week 26
- **Secondary endpoints:** Change from baseline in body weight and adverse events



Davis et el. JAMA 2017;318;1460-70

Oral Semaglutide (Phase 3 Study) PIONNER 2 Trial

52-week, open-label RCT comparing the efficacy and safety of oral semaglutide 14 mg compared with empagliflozin 25 mg daily in 816 T2DM patients inadequately controlled on metformin

	Semaglutide 14mg		Empagliflozin 25mg	
	26 week	52 week	26 week	52 week
↓ HbA1c (%)	1.4*	1.3*	0.9	0.8
↓ BW (kg)	4.2	4.7*	3.8	3.8
% A1c ≤7%	-	72*	-	47

*p<0.05 vs. empagliflozin

Novo Nordisk Announcement. 29 May 2018
https://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.2195846.html

Oral Semaglutide (Phase 3 Study) PIONNER 4 Trial

52-week double-blinded, double-dummy, RCT trial with three arms comparing the efficacy and safety of 14 mg oral semaglutide compared to liraglutide and placebo in 711 T2DM patients, inadequately controlled on metformin with or without a SGLT-2 inhibitor

	Semaglutide 14mg		Liraglutide 1.8 mg		placebo	
	26 week	52 week	26 week	52 week	26 week	52 week
↓ HbA1c (%)	1.3*#	1.2*#	1.1*	0.9*	0.1	↑0.2
↓ BW (kg)	4.7*#	5.0*#	3.2*	3.1*	0.7	1.2
% A1c ≤7%	-	69*	-	63*		18

*P<0.05 vs. placebo
#p<0.05 vs. liraglutide

Novo Nordisk Announcement. 20 Jun 2018
https://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.2200408.html

Oral Semaglutide (Phase 3 Study) PIONNER 7 Trial

52-week open-label RCT comparing the efficacy and safety of oral semaglutide using a flexible dose adjustment (3, 7 or 14 mg) based on clinical evaluation (glycaemic target and tolerability) of their response to treatment compared with sitagliptin in 504 T2DM patients inadequately controlled on 1-2 OADs

	Semaglutide 3, 7 or 14mg 52 week	Sitagliptin 100mg 52 week
↓ HbA1c (%)	1.4*	0.7
↓ BW (kg)	2.9*	0.8
% A1c ≤7%	66*	28

*p<0.05 vs. sitagliptin

Novo Nordisk Announcement. 20 Jun 2018
https://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.2200408.html

Dual SGLT-1 & 2 Inhibitor

- SGLT1 inhibition reduces glucose absorption in the proximal intestine, which significantly blunts and delays postprandial hyperglycemia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes

Satish K. Garg, M.D., Robert R. Henry, M.D., Phillip Banks, M.S., John B. Buse, M.D., Ph.D., Melanie J. Davies, M.D., Gregory R. Fulcher, M.D., Paolo Pozzilli, M.D., Diane Gesty-Palmer, M.D., Ph.D., Pablo Lapuerta, M.D., Rafael Simó, M.D., Ph.D., Thomas Danne, M.D., Darren K. McGuire, M.D., M.H.Sc., Jake A. Kushner, M.D., Anne Peters, M.D., and Paul Strumph, M.D.

Garg et al. N Engl J Med 2017;377(24):2337-48

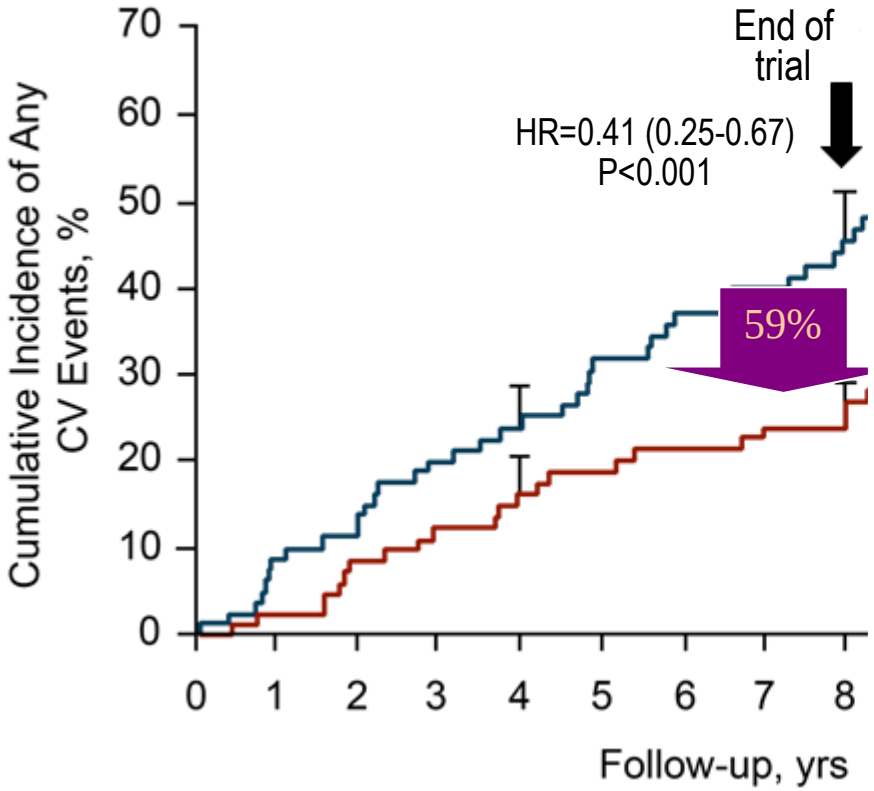
STENO-2 Study

Open, parallel trial in which T2DM patients with microalbuminuria were randomised to

1. standard treatment (n=80) or
2. comprehensive intensive program (n=80)
   - behavioural modification
   - pharmacological therapy targeting
     - HbA1c <6.5%
     - BP <130/80
     - TC<4.5, TG<1.7

Gaede et al. Lancet 1999;353(9153):617-22

Long-Term Benefits of Comprehensive Management



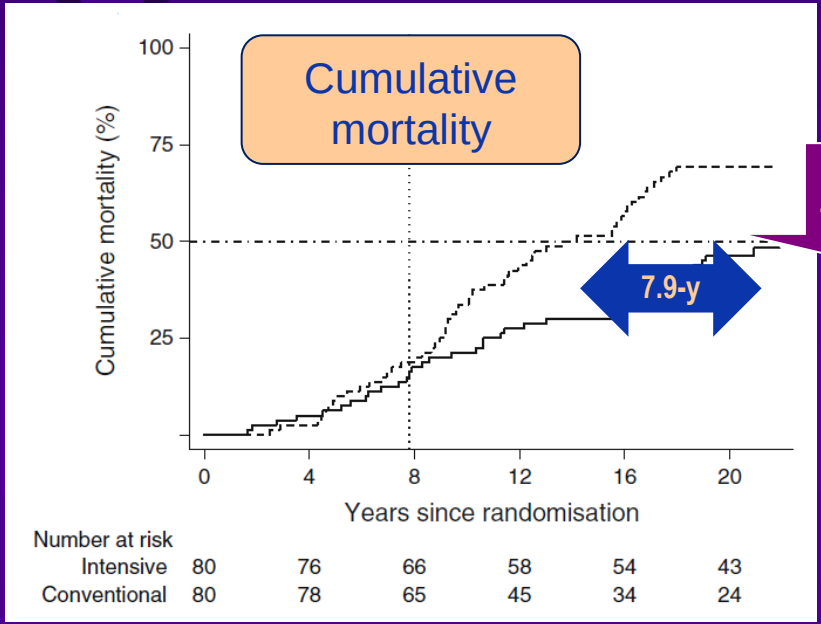
Legacy effect

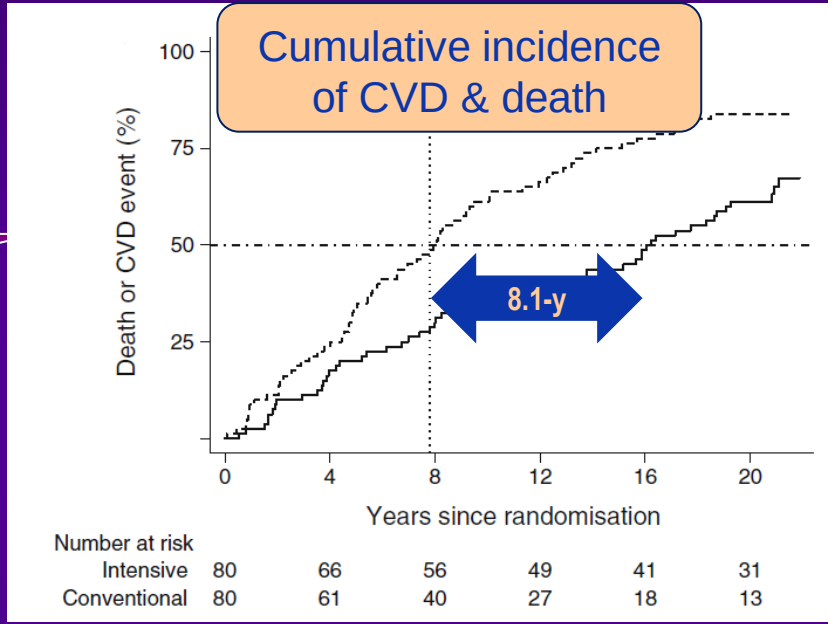
Conventional therapy

Intensive therapy

Gaede et al. Lancet 1999;353(9153):617-22
Gaede et al. N Engl J Med 2008;358:580-91

STENO-2 Long-Term FU (21 Years)





- Patients in the intensive therapy group survived for a median of 7.9 years longer than the conventional-therapy group
- Median time before first CV event after randomisation was 8.1 years longer in the intensive-therapy group

Gaede et al. Diabetologia 2016;59(11):2298-307

Excess Mortality Among T2DM Patients

Swedish Registry of 435,369 T2DM
Mean FU 4.6 years

Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 2 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level or Renal Disease Status and Time-Updated Age Category in Model 3.*

Variable	Death from Any Cause				Death from Cardiovascular Causes			
	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr
Time-updated mean glycated hemoglobin level†								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≤6.9%	1.92 (1.75–2.11)	1.40 (1.34–1.46)	1.11 (1.08–1.14)	0.95 (0.94–0.96)	2.18 (1.81–2.64)	1.57 (1.46–1.70)	1.13 (1.08–1.18)	0.92 (0.90–0.94)
7.0–7.8%	2.00 (1.77–2.27)	1.55 (1.47–1.63)	1.25 (1.21–1.29)	1.03 (1.02–1.05)	2.59 (2.04–3.28)	1.92 (1.75–2.10)	1.34 (1.27–1.41)	1.02 (0.99 –1.04)
7.9–8.7%	2.50 (2.17–2.87)	1.71 (1.60–1.83)	1.56 (1.49–1.62)	1.20 (1.18–1.23)	3.76 (2.93–4.82)	2.16 (1.93–2.41)	1.86 (1.75–1.98)	1.15 (1.11–1.19)
8.8–9.6%	2.92 (2.44–3.49)	2.31 (2.13–2.52)	1.84 (1.74–1.95)	1.34 (1.29–1.39)	4.06 (2.94–5.61)	2.96 (2.58–3.40)	2.22 (2.03–2.43)	1.29 (1.23–1.36)
≥9.7%	4.23 (3.56–5.02)	2.77 (2.51–3.05)	2.48 (2.31–2.67)	1.55 (1.47–1.63)	5.38 (3.89–7.43)	3.51 (2.99–4.11)	3.10 (2.78–3.45)	1.42 (1.32–1.53)
Time-updated renal disease								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Normoalbuminuria	1.87 (1.70–2.04)	1.27 (1.22–1.32)	0.96 (0.94–0.99)	0.83 (0.82–0.84)	2.19 (1.82–2.62)	1.43 (1.33–1.55)	0.95 (0.91–1.00)	0.79 (0.78–0.81)
Microalbuminuria	2.61 (2.19–3.10)	1.88 (1.75–2.02)	1.44 (1.38–1.50)	1.04 (1.02–1.07)	4.26 (3.19–5.70)	2.38 (2.11–2.69)	1.55 (1.44–1.66)	1.01 (0.97–1.04)
Macroalbuminuria	3.78 (3.03–4.71)	2.88 (2.65–3.13)	2.14 (2.04–2.24)	1.40 (1.37–1.44)	5.58 (3.79–8.20)	3.81 (3.33–4.35)	2.62 (2.44–2.81)	1.37 (1.32–1.42)
Stage 5 chronic kidney disease	14.63 (9.53–22.48)	7.19 (5.75–8.98)	5.97 (5.29–6.73)	3.31 (3.02–3.62)	30.03 (16.08–56.10)	9.22 (6.40–13.29)	5.45 (4.43–6.70)	2.45 (2.11–2.86)
Time-updated eGFR and stage 5 chronic kidney disease								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
>90 ml/min	2.07 (1.90–2.26)	1.47 (1.41–1.54)	1.17 (1.13–1.21)	0.88 (0.86–0.91)	2.47 (2.08–2.94)	1.56 (1.43–1.69)	1.02 (0.96–1.09)	0.72 (0.69–0.76)
>60–90 ml/min	1.92 (1.69–2.17)	1.30 (1.24–1.36)	0.96 (0.93–0.99)	0.81 (0.80–0.82)	2.59 (2.05–3.27)	1.60 (1.47–1.74)	1.04 (1.00–1.10)	0.77 (0.75–0.78)
>45–60 ml/min	3.84 (2.68–5.50)	2.60 (2.35–2.88)	1.48 (1.41–1.55)	1.02 (1.00–1.04)	5.56 (2.98–10.38)	3.83 (3.29–4.45)	1.75 (1.63–1.89)	1.02 (1.00–1.05)
>30–45 ml/min	5.52 (3.05–9.97)	4.00 (3.44–4.64)	2.42 (2.26–2.58)	1.37 (1.34–1.41)	8.59 (3.21–22.97)	4.72 (3.69–6.04)	2.94 (2.68–3.24)	1.39 (1.35–1.44)
15–30 ml/min	18.79 (11.50–30.72)	6.98 (5.75–8.48)	4.21 (3.84–4.62)	2.21 (2.12–2.30)	35.03 (16.63–73.79)	8.96 (6.59–12.19)	4.58 (3.97–5.28)	2.13 (2.01–2.25)
Stage 5 chronic kidney disease	14.70 (9.57–22.59)	7.23 (5.79–9.04)	6.09 (5.40–6.87)	3.33 (3.04–3.64)	30.26 (16.20–56.52)	9.30 (6.45–13.40)	5.57 (4.53–6.86)	2.48 (2.13–2.89)

↑ excess mortality risk

- younger age
- poorer glycaemic control
- severity of diabetic kidney disease

Tancredi et al. N Engl J Med 2015;373(18):1720-32

5 Priorities in Diabetes Care

1. Young patients i.e. age <60
2. Optimise DM control as far as possible
3. Avoid hypoglycaemia
4. Prevent DKD or retard DKD progression
5. Comprehensive control of all CV risk factors

5 Mottos of T2DM Management

Early

Aggressive

Comprehensive

Treat-To-Targets

5 Mottos of T2DM Management

Avoidance of Clinical Inertia

香港糖尿科護士協會
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