

Diabetes and Cardiovascular Disease: Time for multifactorial approach

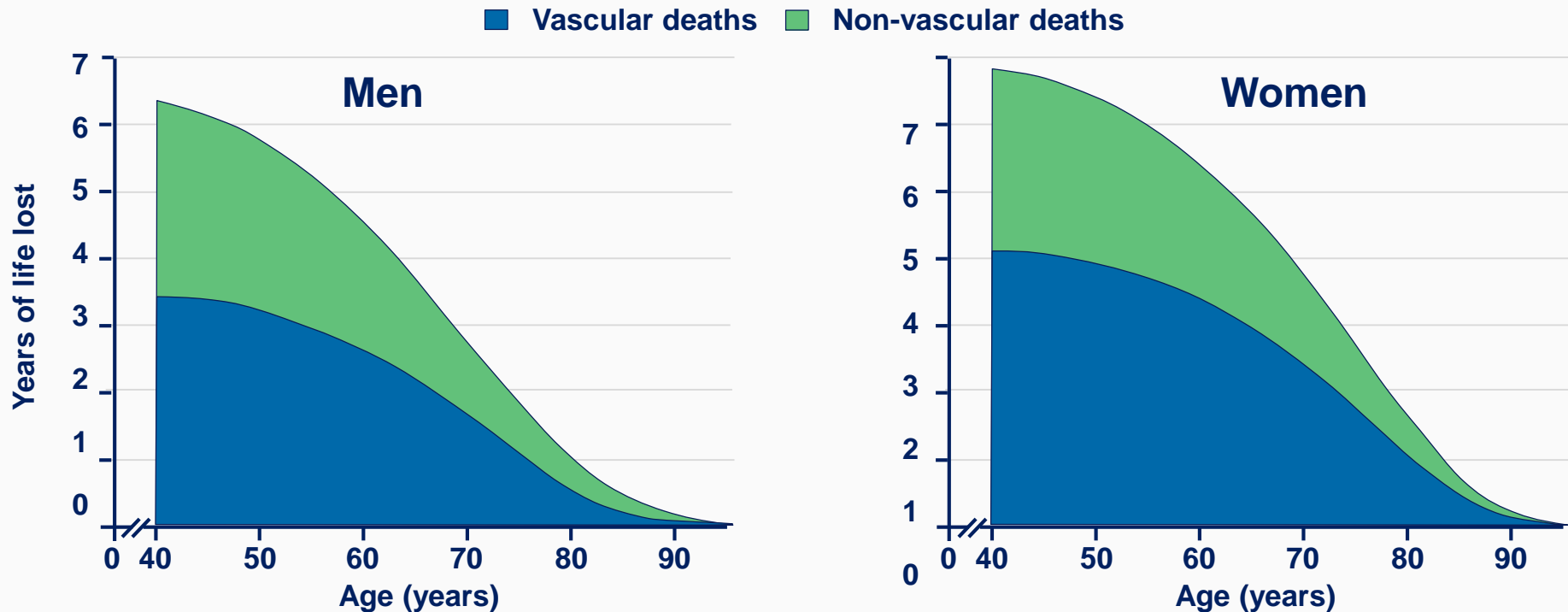


Professor John Deanfield - University College London, UK
Monday 27 August 2018

Professor John Deanfield : Disclosures

- Received CME honoraria and/or consulting fees from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, Bayer
- Member of Study Steering Committees for Novo Nordisk
- Research grants from British Heart Foundation, MRC(UK), NIHR, PHE, MSD, Pfizer, Aegerion, Colgate, Roche
- No conflicts of interest for this presentation

Diabetes Is Associated With Significant Loss of Life Years

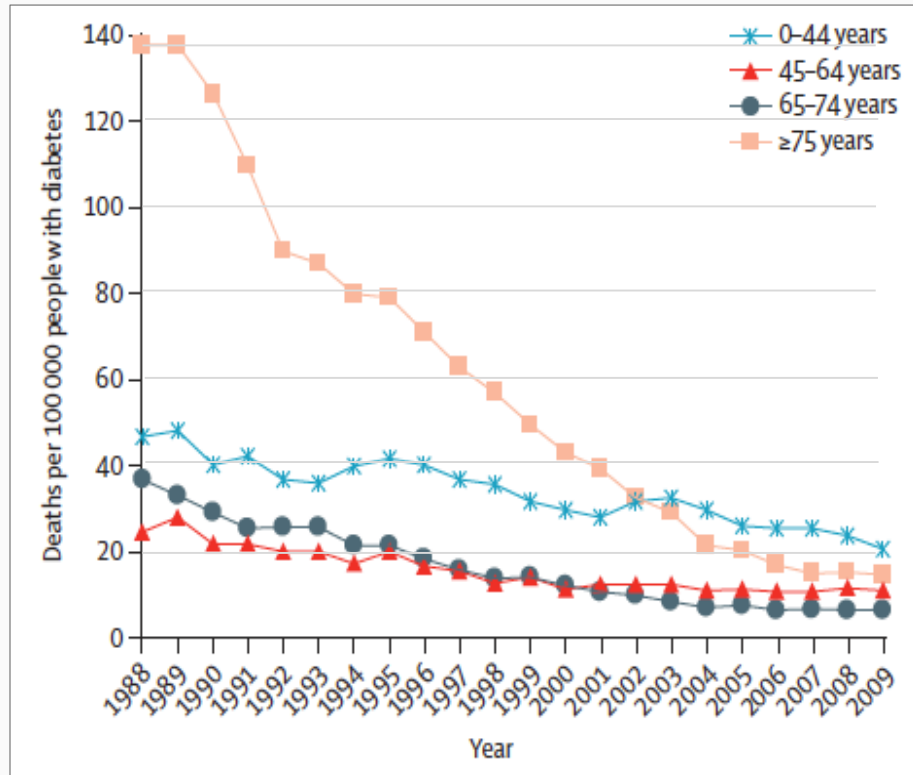


On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes

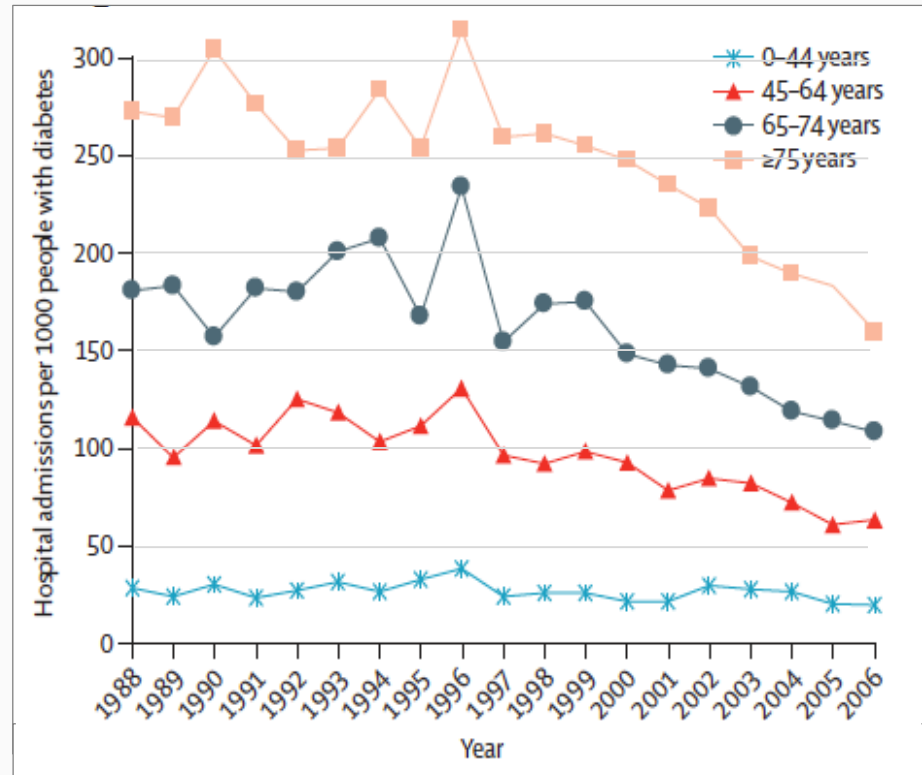
Source: Seshasai et al, *N Engl J Med* 2011; 364:829-41

Major Diabetes Complications in USA

Hyperglycaemic Deaths



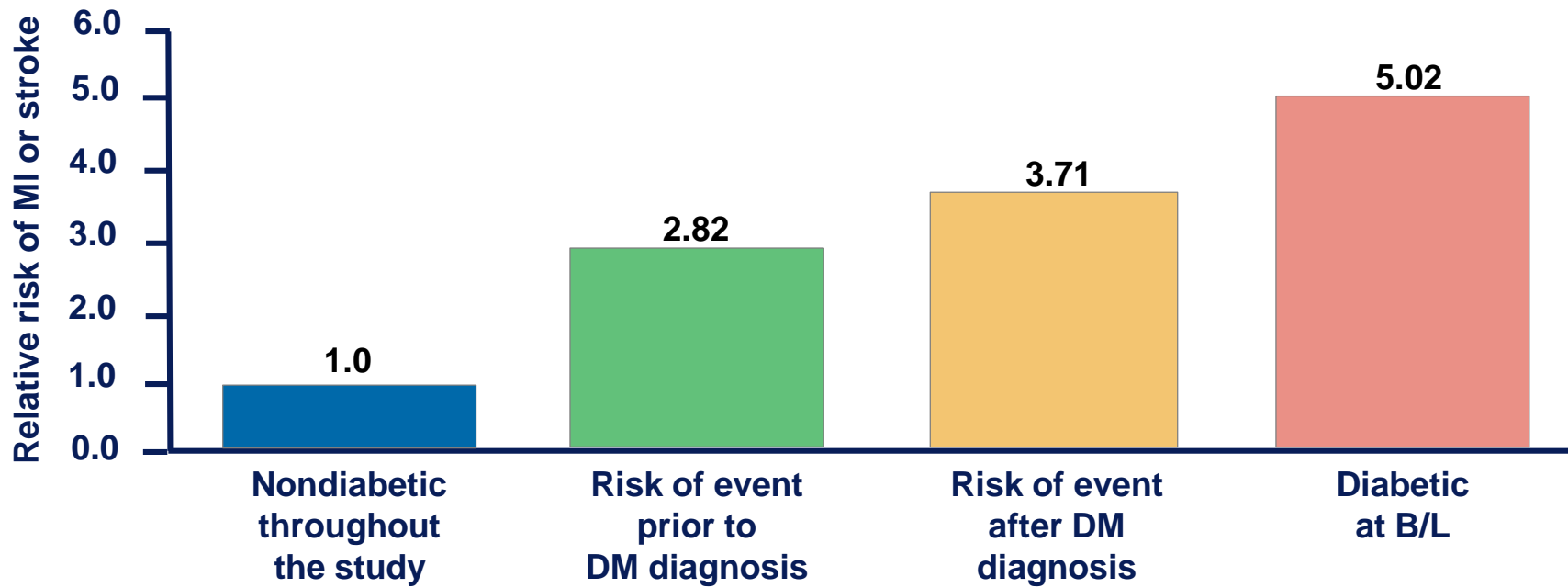
CVD Admissions



Source: Gregg et al, *The Lancet Diabetes & Endocrinology* 2016 4, 537-547

The Ticking Clock: ↑ CV Risk Before ↑ Glucose (Nurses' Health Study)

20 yr F/U of 117,629 women: n=1,508 diabetes at B/L;
n=5,894 developed diabetes; n=110,227 free from diabetes

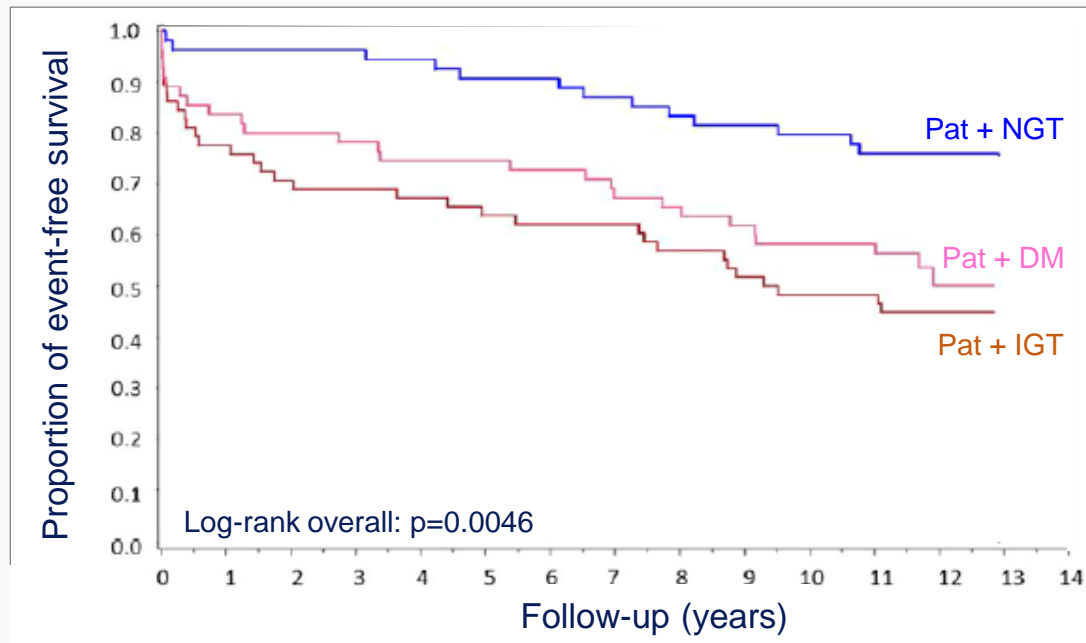
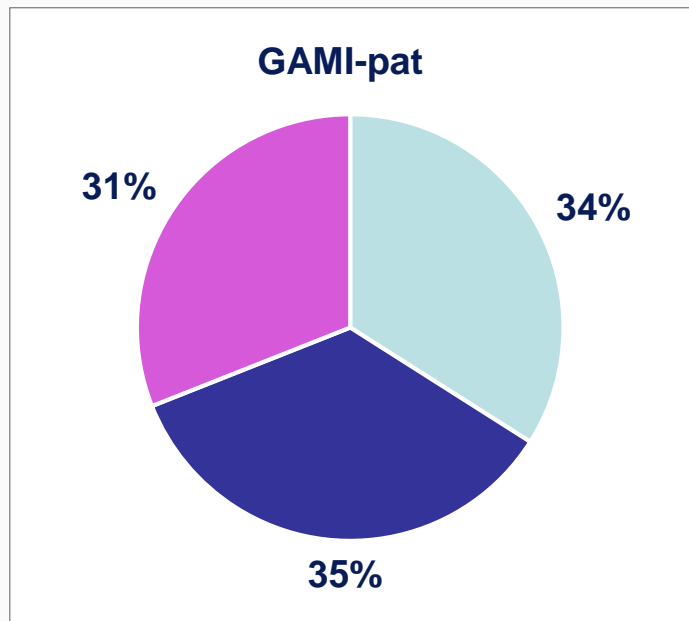


Source: Hu et al, Diabetes Care 2002; 25: 1129-1134

Dysglycaemia and CV risk: Impact of glucose perturbations in patients who have experienced MIs

GAMI – long-term follow-up

First major event (death, MI, stroke, or severe HF)



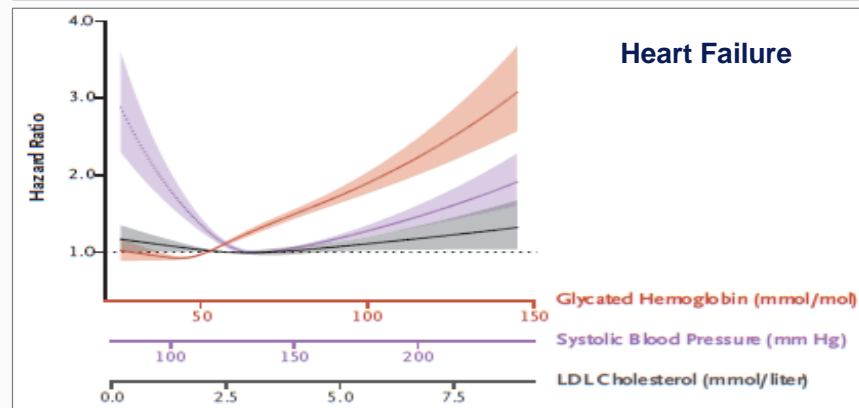
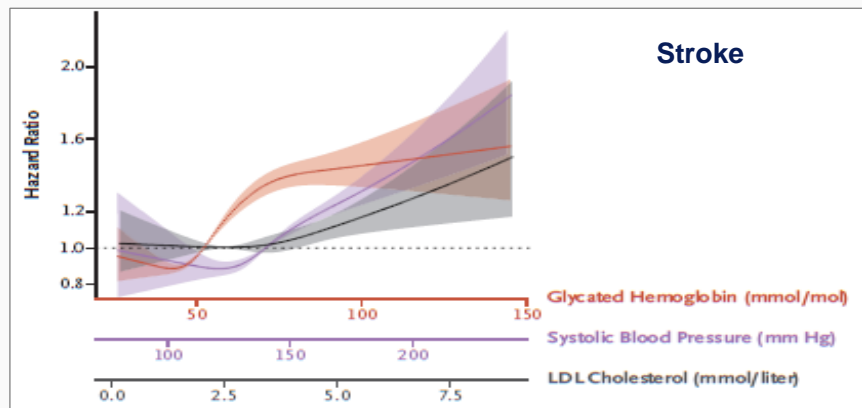
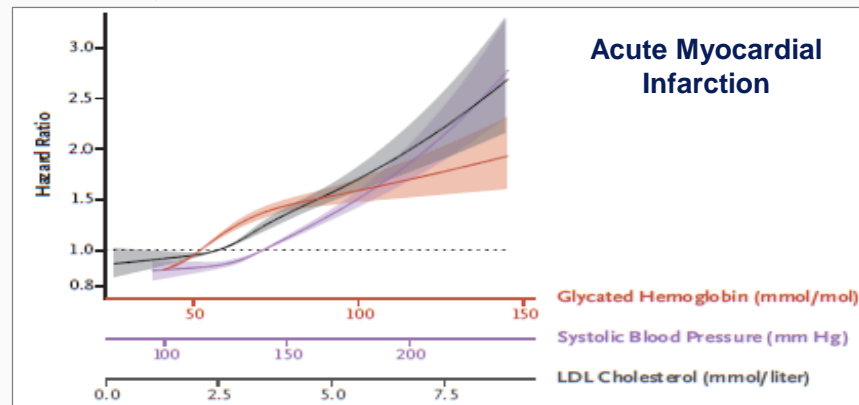
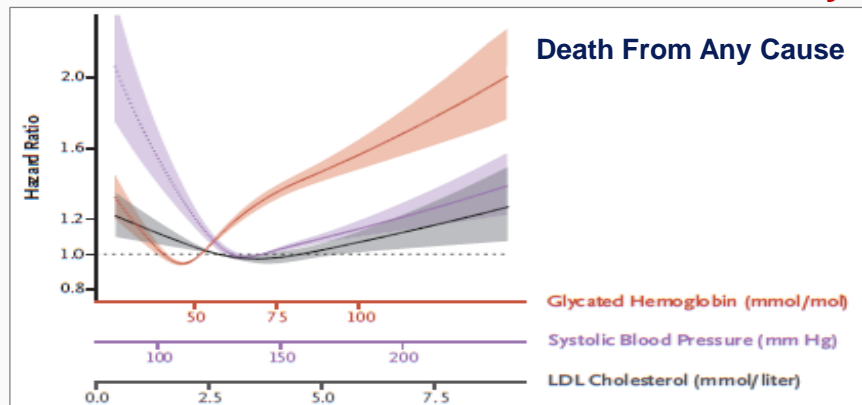
DM, diabetes mellitus; GAMI, Glucose Tolerance in Patients with Acute Myocardial Infarction; HF, heart failure; IGT, impaired glucose tolerance; MI, myocardial infarction; NGT, normal glucose tolerance; Pat, patients

Source: Ritsinger et al, *Diab Vasc Dis Res* 2015;12:23–32

Risk Factors for CVD in patients with T2DM

271,174 pts with T2DM matched to 1,355,870 controls

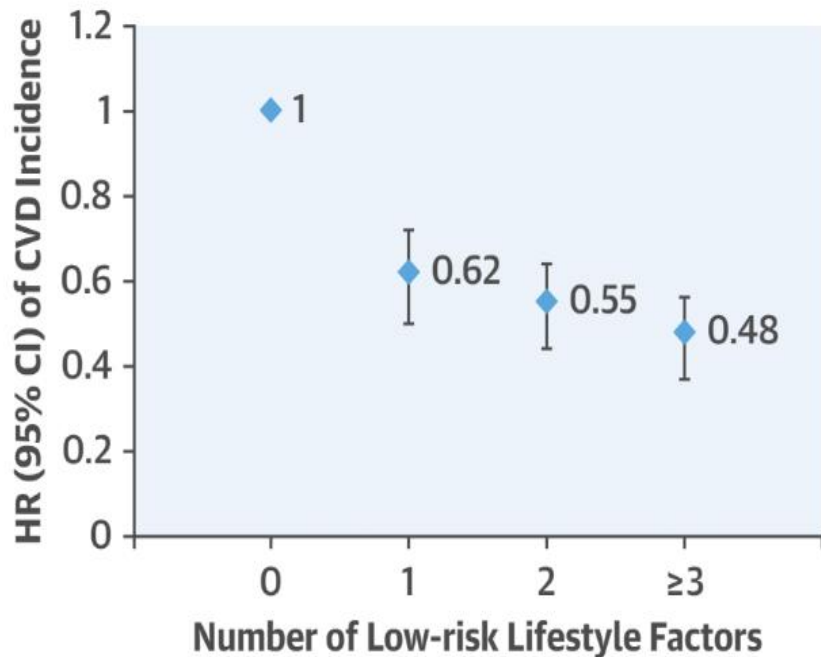
Median F/U = 5.7 years with 175,345 deaths



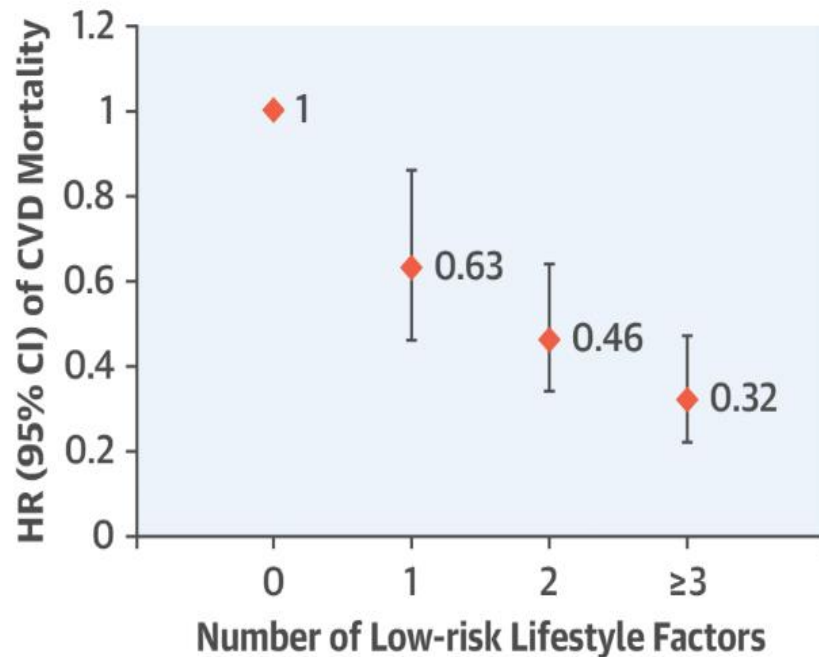
Source: Rawshani et al, *N Engl J Med* 2018;379:633-44

Healthy Lifestyle and CVD in T2DM

CVD Incidence



CVD Mortality



Source: Lui, G et al, JACC 2018;71(25):2867-76

T2DM: Change in Approach

**Diabetes is a condition which
causes CVD
to
Diabetes is a state of
enhanced CV risk**

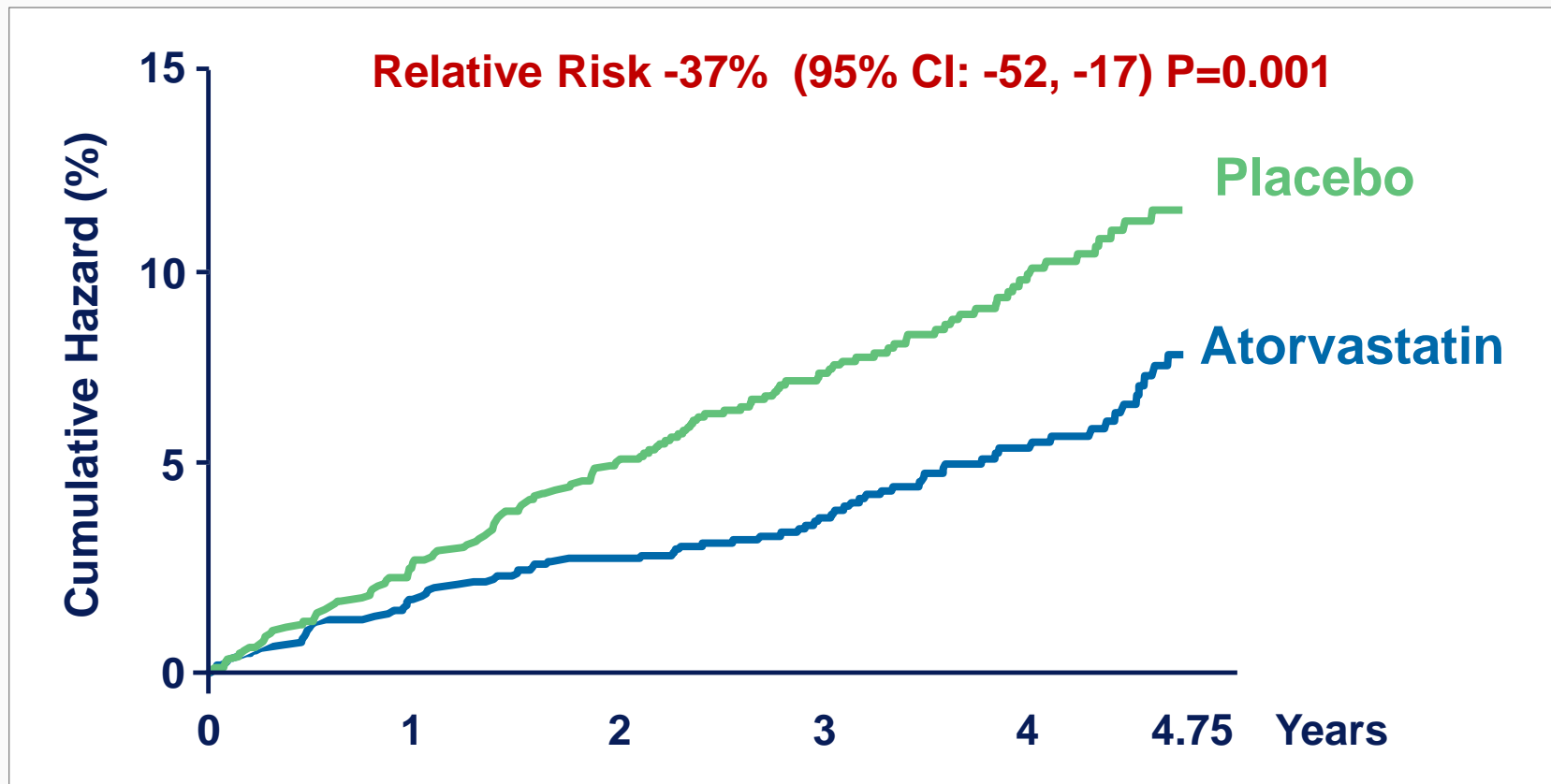
Source: Goldner MG, JAMA 1971;218, 1400-10

Treatment Goals in T2DM in 2018 and beyond...

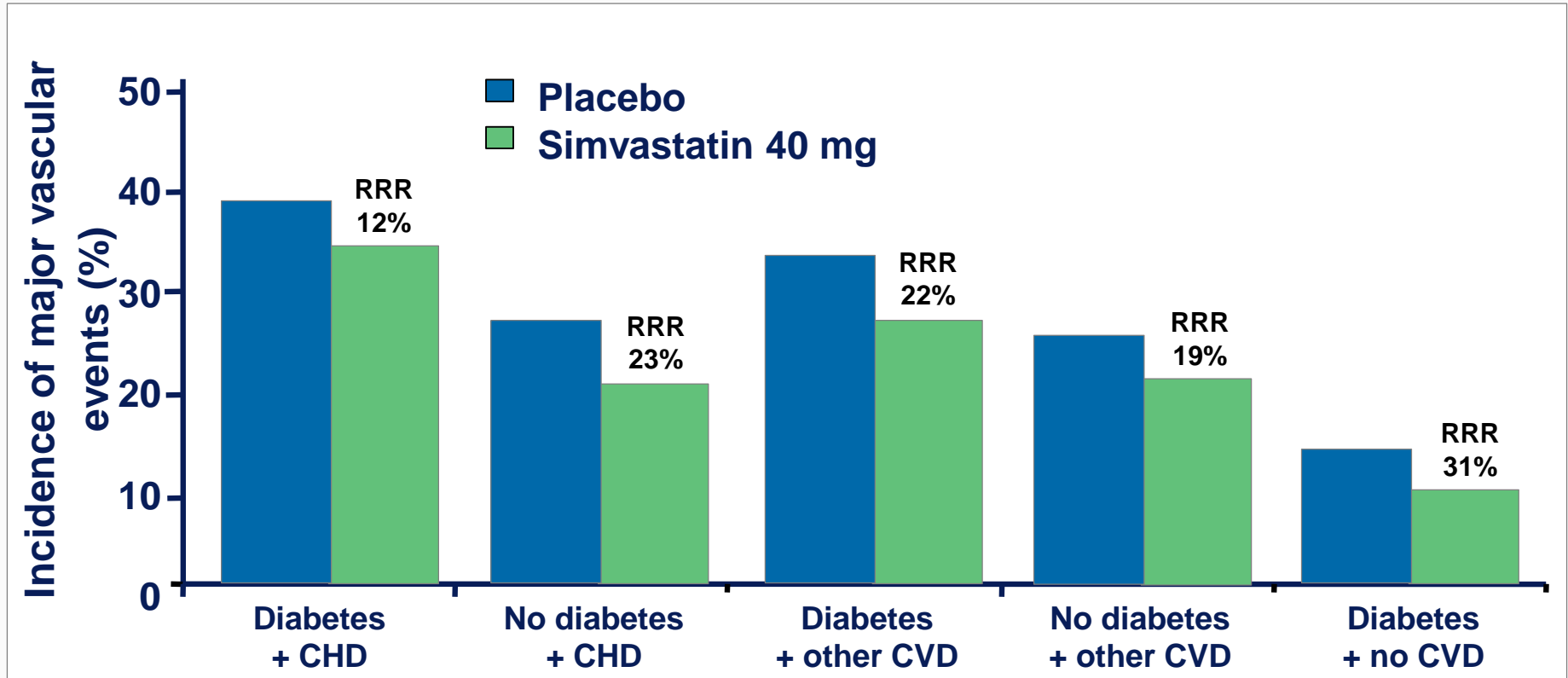
- **Management should be targeted at reducing/delaying CV complications in patients with T2DM with and without clinical CVD and in those with pre-diabetes**
- **Most cardiologists have focused efforts on 'traditional' CVRFs and not on glucose lowering**

Source: Goldner MG, JAMA 1971;218, 1400-10

CARDS: Cumulative Hazard for MI and CV Death



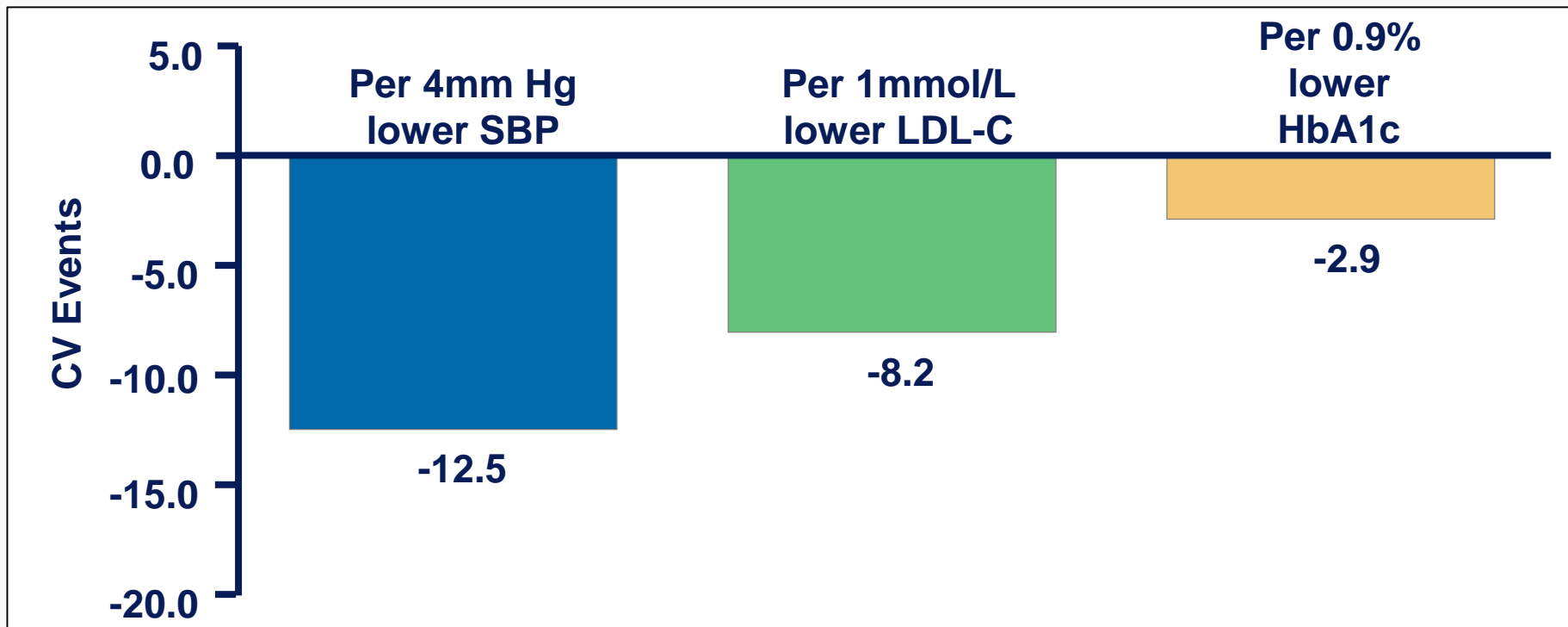
Heart Protection Study: Impact of Diabetes on CV outcome



Source: HPS Collaborative Group. Lancet. 2003;361:2005

Benefit of Different Interventions per 200 Diabetes Patients Treated for 5 years

Using traditional Glucose lowering treatments



Source: Ray, Lancet 2009 Meta-analysis of intensive glucose-lowering trials

Diabetes and Cardiovascular Disease: The Perfect Storm

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group <i>no. of events/total no. (%)</i>	Control Group <i>no. of events/total no. (%)</i>	Odds Ratio (95% CI)	P Value
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06



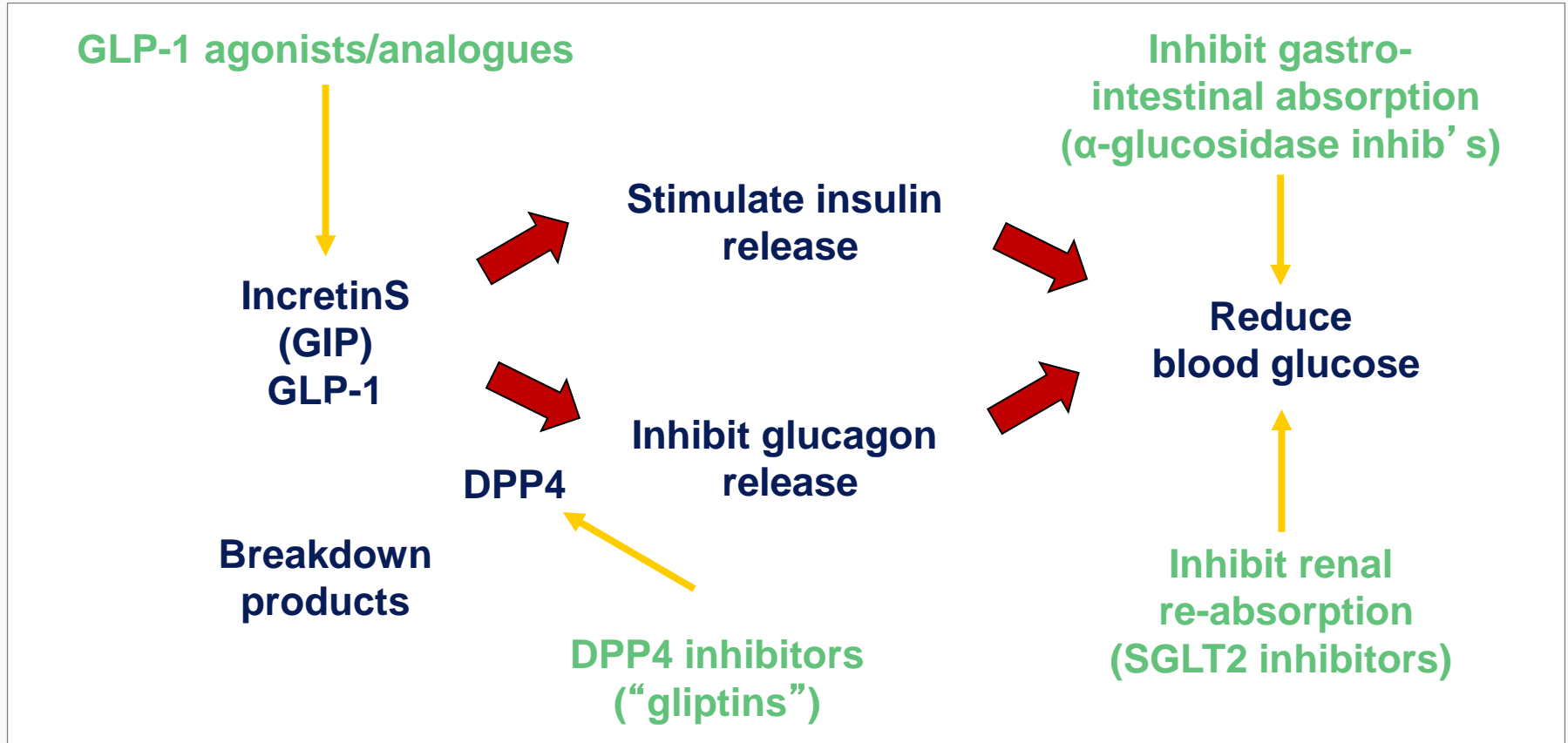
Source: Nissen SE, Wolski K. N Engl J Med 2007; 356: 2457-2471

Diabetes Medications and Possible Increased CV Risk

FDA / EMA requirements:

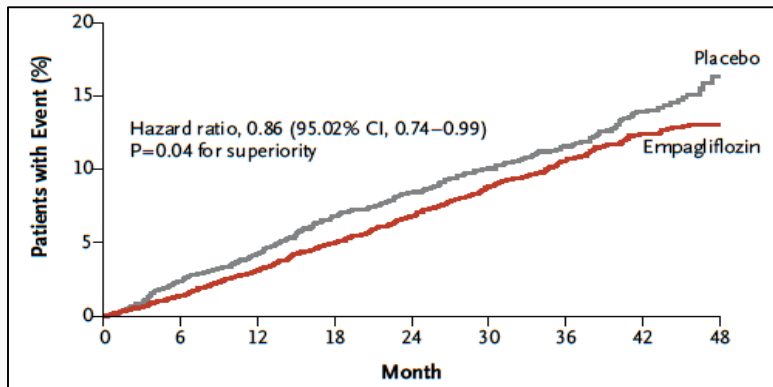
- **New diabetes drugs should demonstrate CV safety with meta-analysis and CV outcome trial**

New Approaches To Reducing Blood Glucose

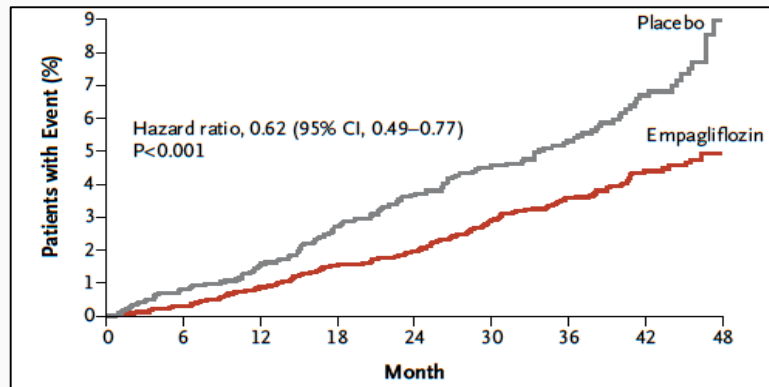


Empagliflozin, CV Outcomes and Mortality in T2DM

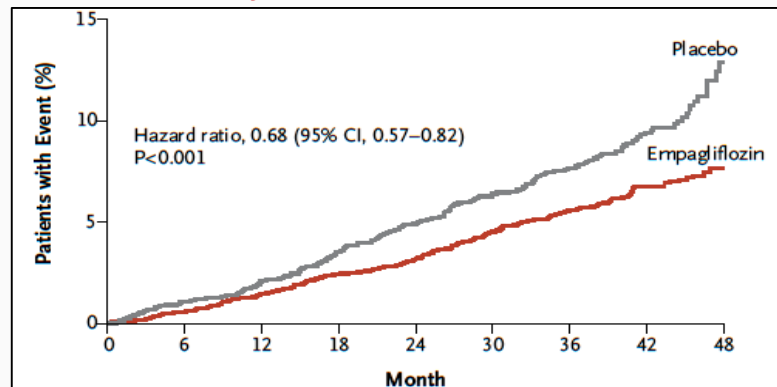
Primary Outcome



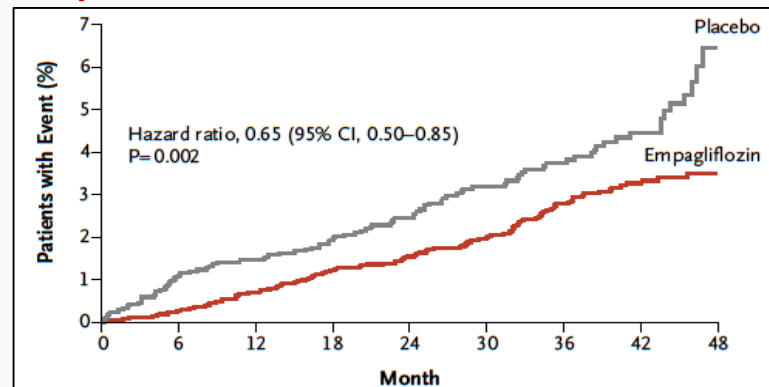
Death from Cardiovascular Causes



Death from Any Cause



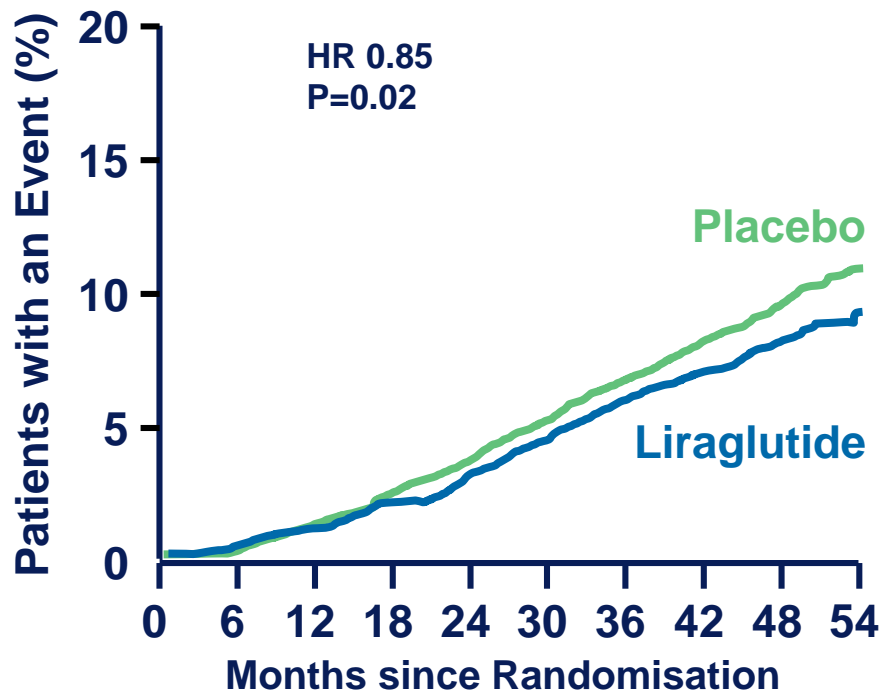
Hospitalization for Heart Failure



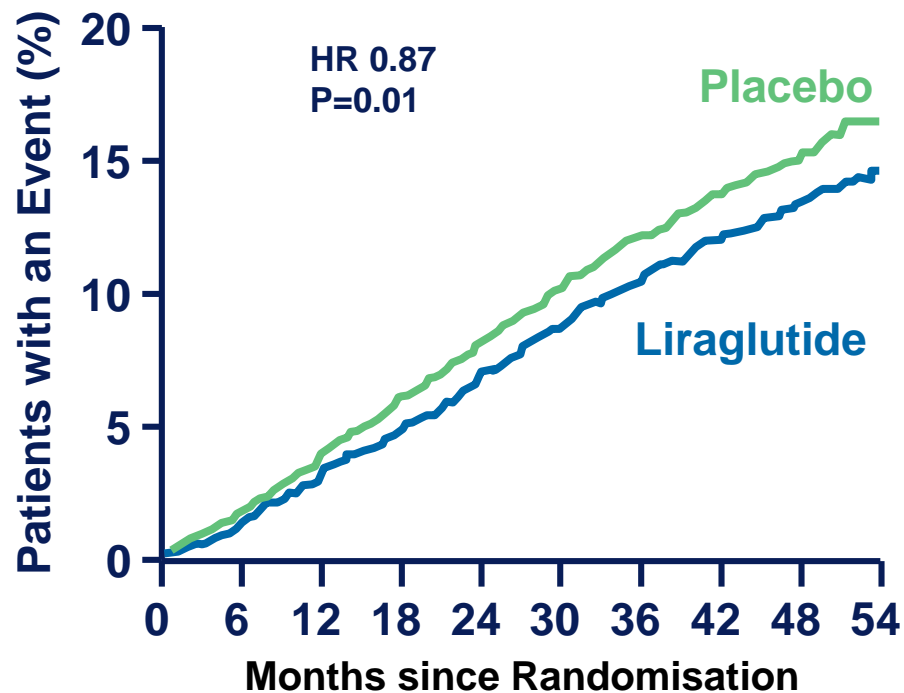
Source: Zinman *N Engl J Med* 2015;373:2117-28

GLP1-RA: Liraglutide and CV Outcomes in T2DM - LEADER Trial

Primary Outcome

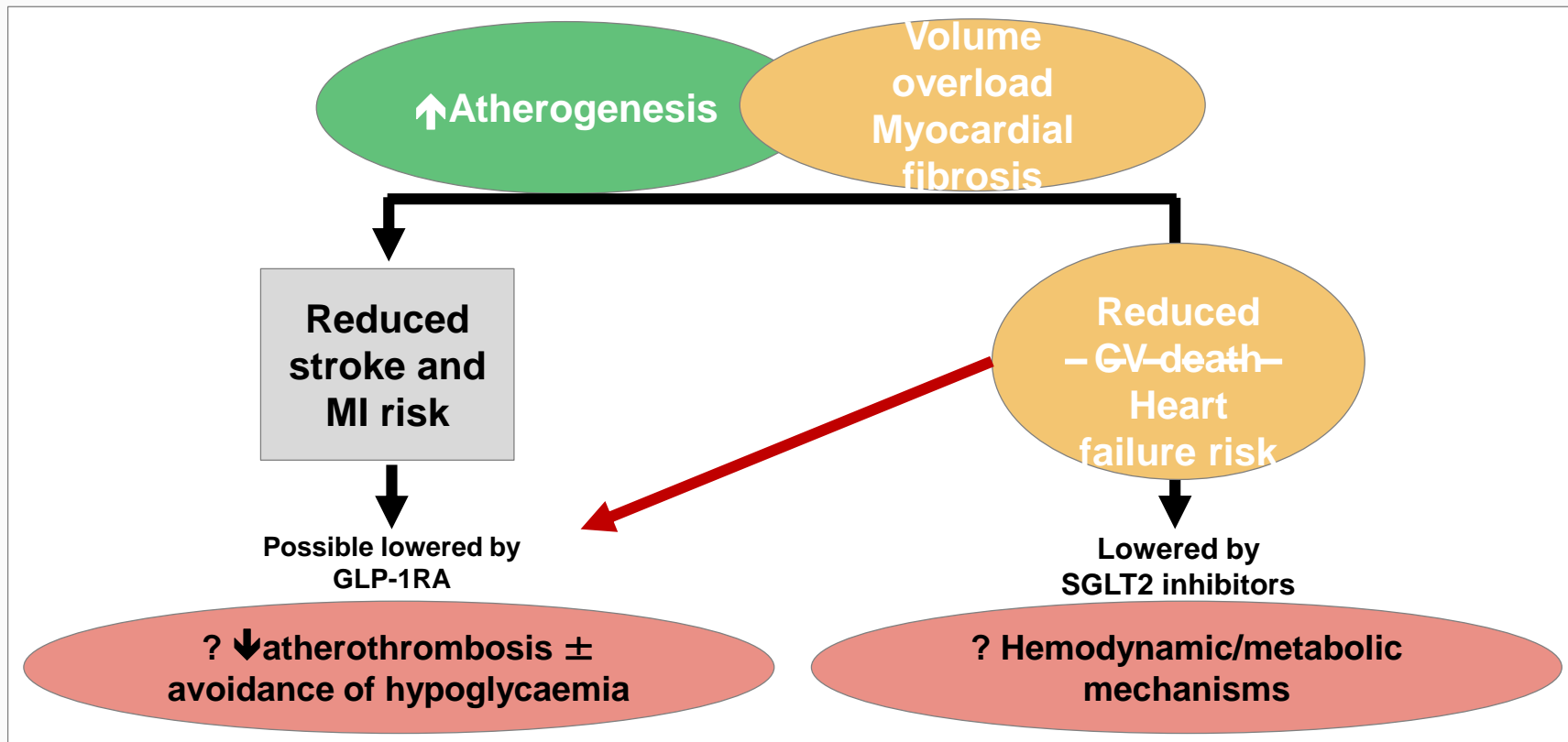


Death from Any Cause



Source: Marso N Engl J Med 2016; 375: 311-22

New Diabetes Drugs and Patterns of CV Benefits in Patients With T2DM and CV Disease

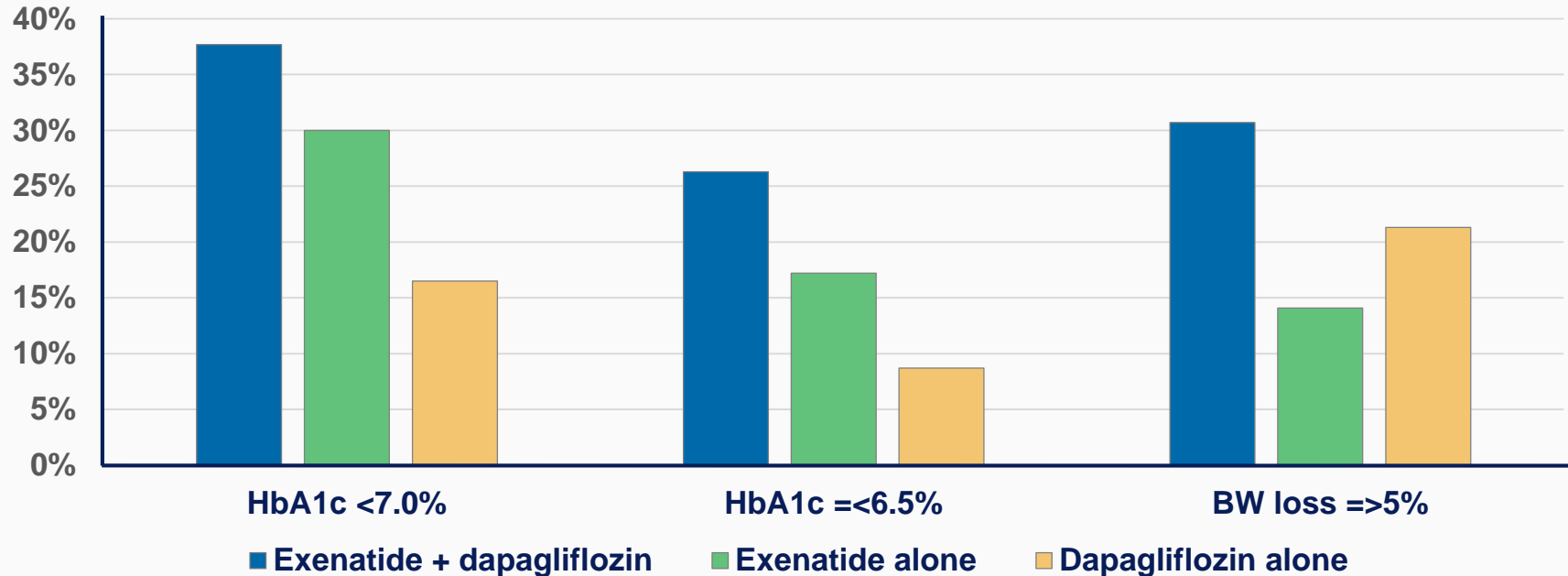


Source: Sattar *J Am Coll Cardiol* 2017; 69: 2646–56

GLP-1 RA in combination with SGLT2-i better than monotherapy in diabetic patients (on HbA1c)

52 weeks results of the DURATION-8 study

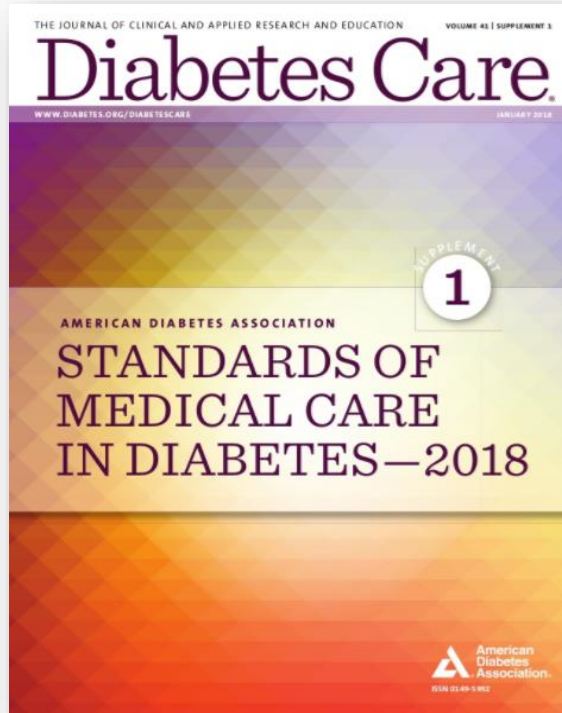
Percentage of patients achieving their glycemic and weight targets



Source: Jabbour et al, Diab Care July 2018, pub ahead of print, doi:10.2337/dc18-0680/-/DC1

CVOT Impact on Clinical Guidelines

ADA 2018 recommendation



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 (Table 8.1).

Source: American Diabetes Association. *Diabetes Care* 2018;41 (Suppl 1):S73–S85

Novel 'Diabetes' Drugs: Unanswered Questions

?

Are these drugs equally effective in patients without CVD or without DM (primary prevention)?

?

Which patients benefit most from each drug?
e.g. patients with HF or kidney disease

?

Mechanisms by which drugs mediate CV benefit?

?

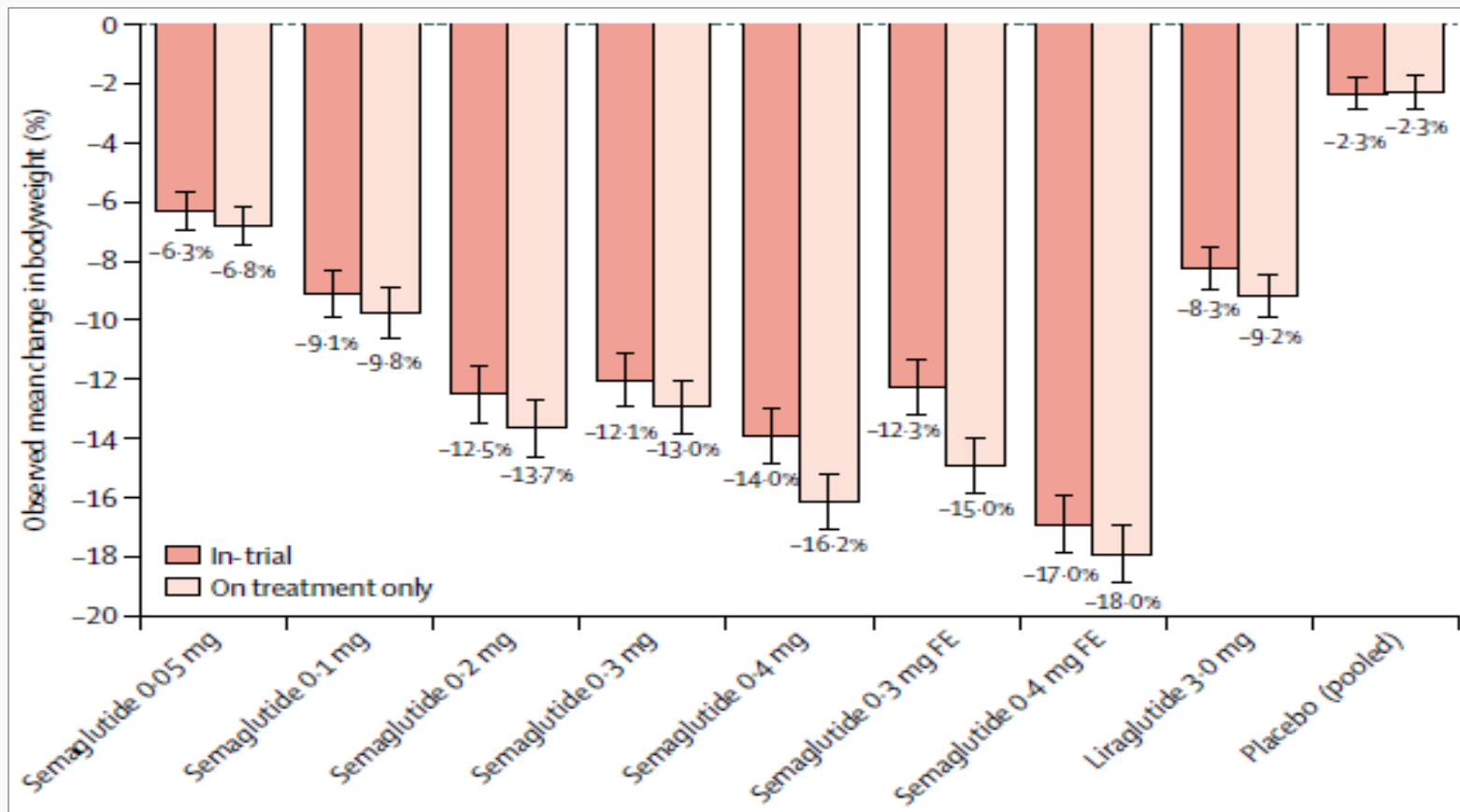
Heart failure

Diabetic nephropathy

Obesity

Future CVOTs

Impact of GLP1-RA on Obesity



Source: O'Neil et al, Lancet 2018; 392: 637-49

New Era for CVD Management in DM: Some Thoughts

Diabetologists

Cardiologists

- In addition to BP and Cholesterol lowering, CVD and renal benefit with two new glucose lowering drug classes, SGLT2i and GLP1-RA
- Has already changed guidelines for DM care
- Novel multiple mechanisms, especially with lack of hypoglycaemia may broaden indications towards early treatment, prevention, even without DM