PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION

3RD SNAPSHOT

Diabetes and reducing CVD: Are novel interventions living up to their promise?

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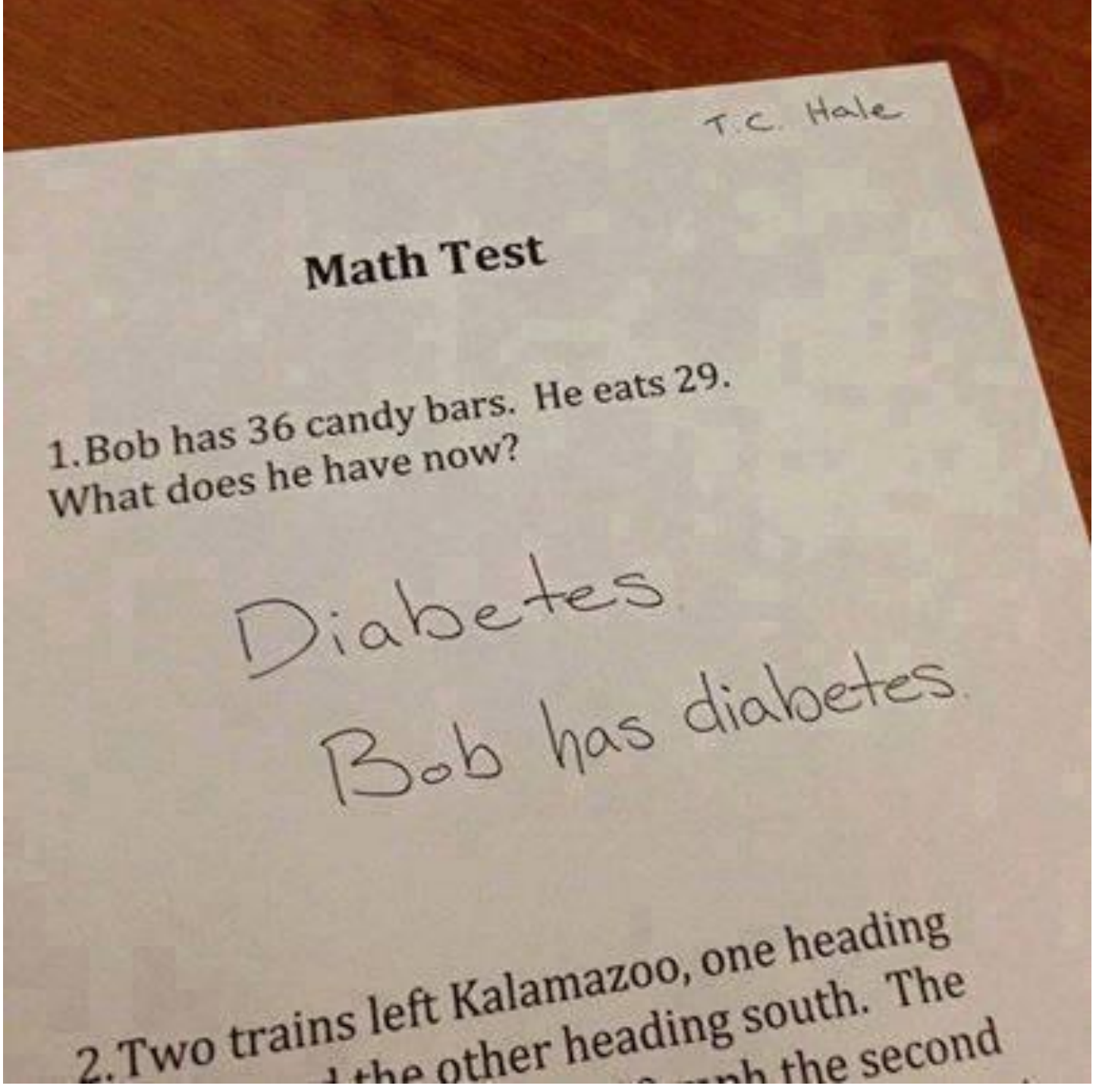

T.C. Hale

Math Test

1. Bob has 36 candy bars. He eats 29. What does he have now?

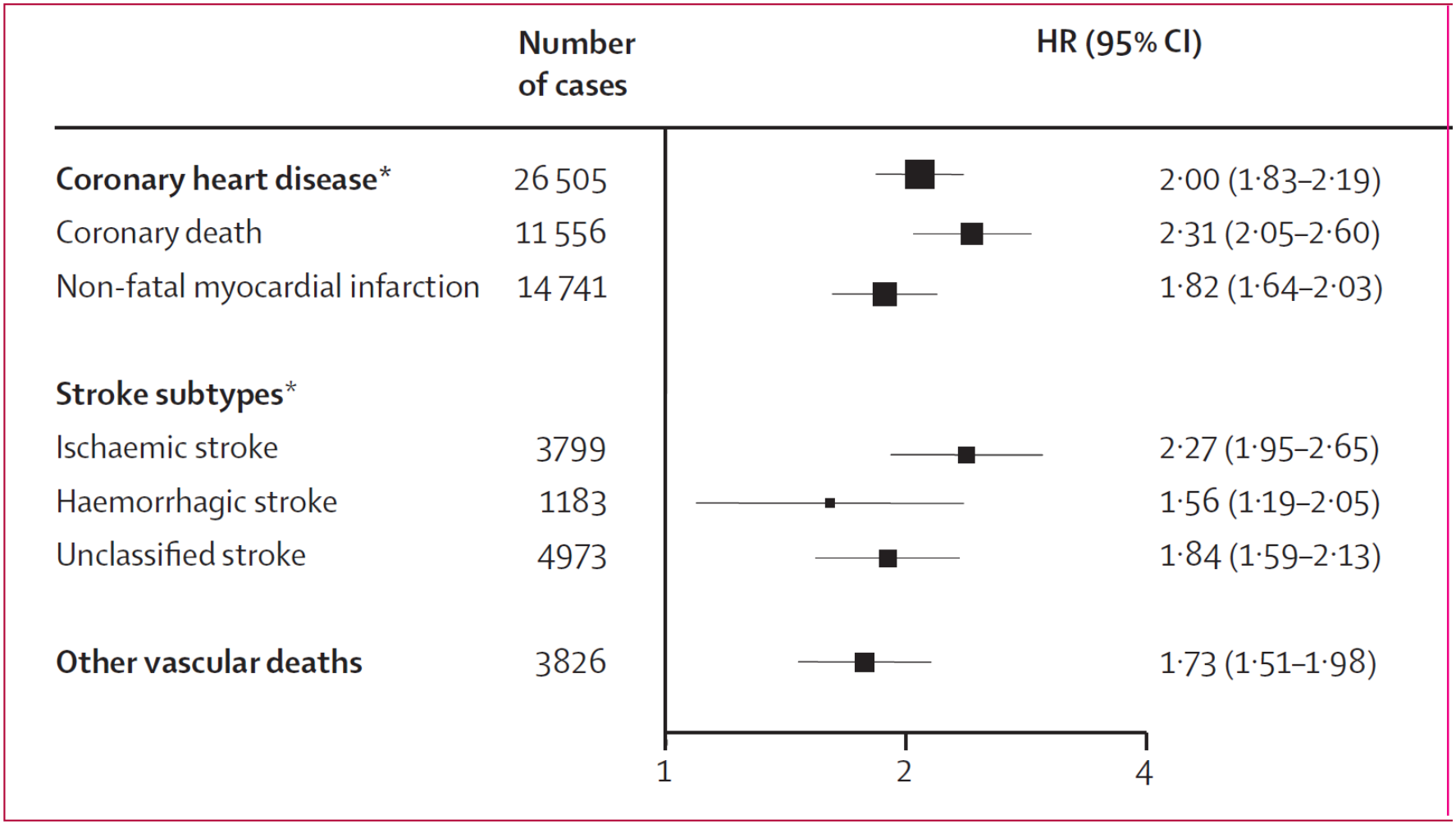
Diabetes

Bob has diabetes.

2. Two trains left Kalamazoo, one heading
the other heading south. The
the second

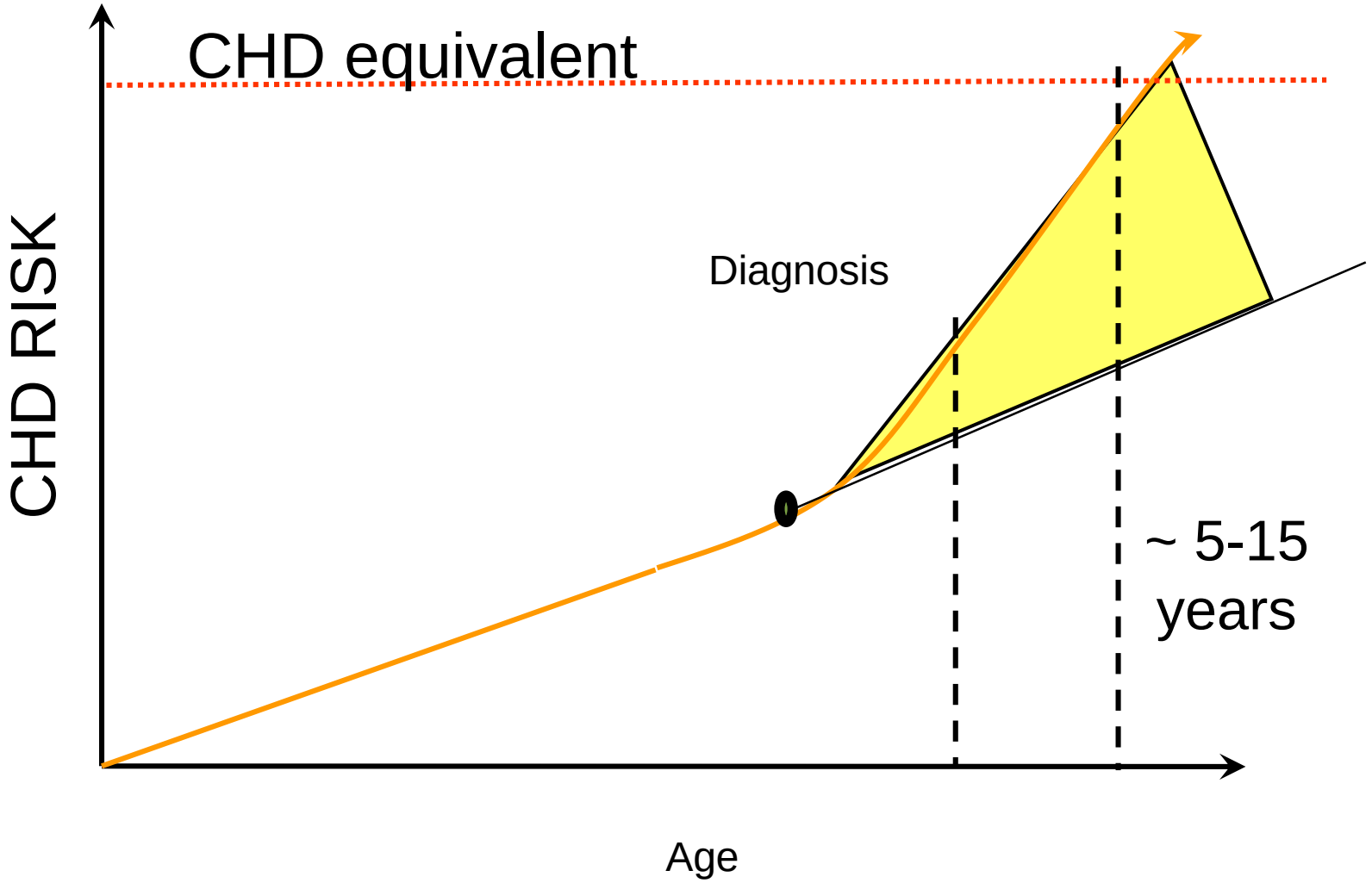
Relative risk in DM vs Non-DM

ERFC (2010) Lancet



Hazard ratios for vascular outcomes DM vs. no DM

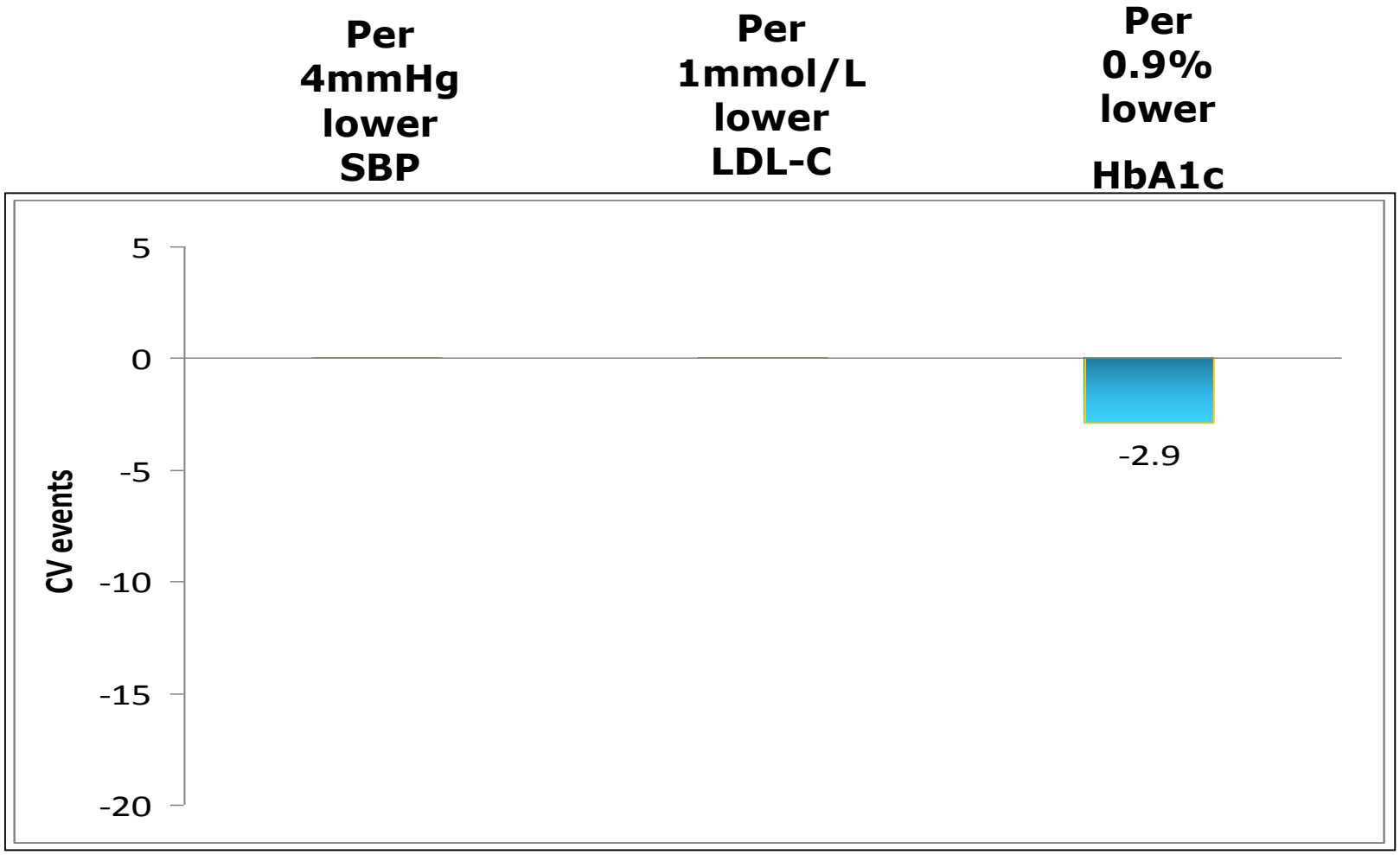
Several years of diabetes before CVD equivalence



Sattar (2013) Diabetologia

Benefit per 200 diabetes pts treated for 5 years

BP and LDL-c lowering trump HbA1c reduction



Ray et al Lancet 2009 Meta-analysis of intensive glucose-lowering trials

Why does glucose lowering appear to work less well for CVD?

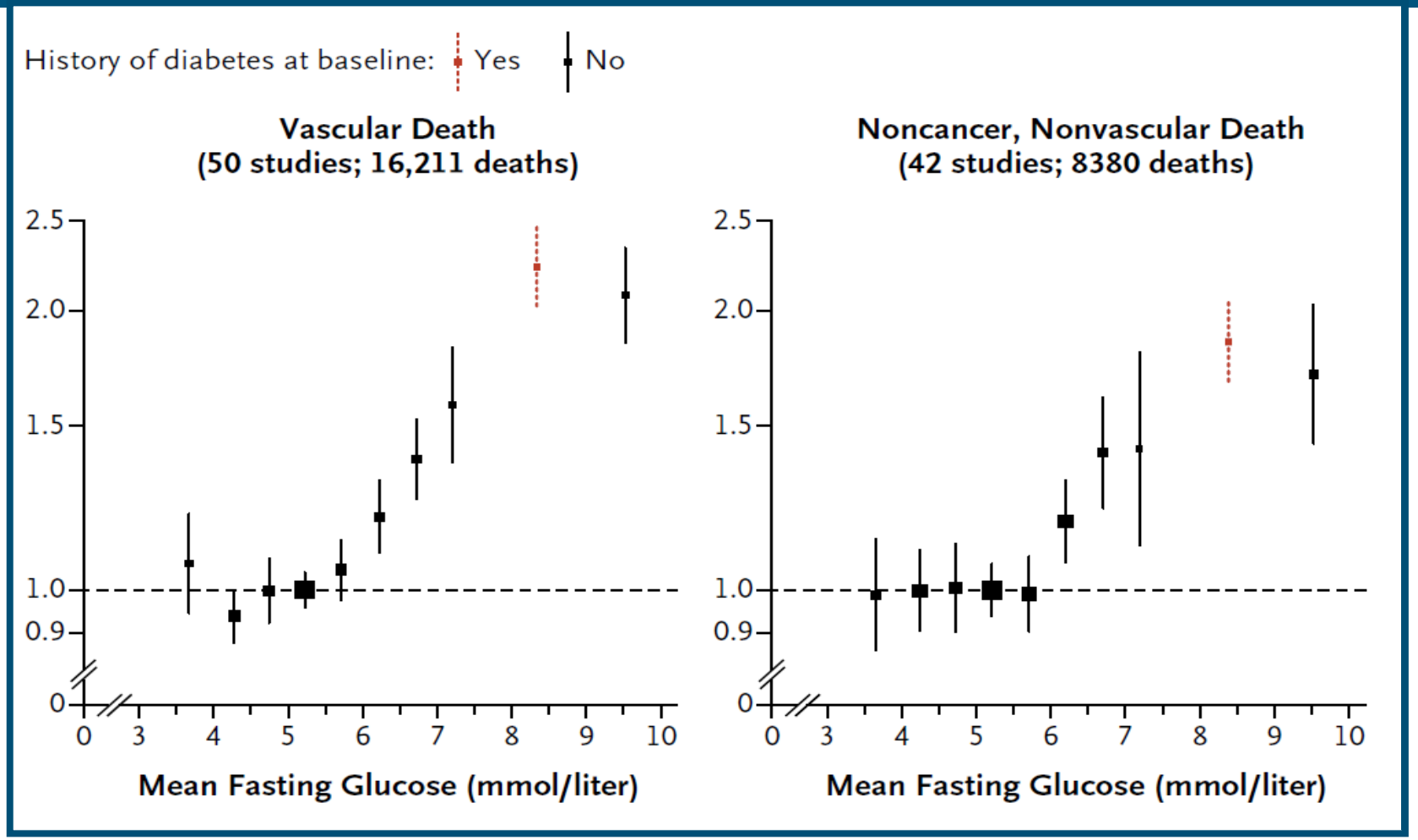
T2DM-CVD risk not just ⇑ glucose

HbA1c targets hardest

DM agents have other effects

Glycaemia vs. CVD risk relationship still not fully understood

Glucose is not continuous risk factor for vascular risk or non-CVD



ERFC (2011) NEJM

Glucose, HbA1c vs. CVD: thresholds of risk apply

- **IFG alone ≠ high CVD risk (HR only 1.1)**
- **ADVANCE:**
  - micro risk ≥ 6.5% HbA1c (=DETECT2),
  - **macro risk ≥ 7.0%**
  - Zoungas et al (2012) Diabetologia
- **Best to recruit above these levels (ORIGIN below this / but hoping for some insulin effect)**

Diabetes field in a ‘brave’ new world

- **FDA 2008: new approach to diabetes drugs as:**
  - Drugs ⇓ sugar (“surrogate”) levels ≠ ⇓ CVD or ⇓ mortality and may increase?
  - Sattar (2013) Diabetologia
- **Proof of CVD safety for all new anti-diabetic agents**
  - Non-inferiority with upper confidence interval 1.3
  - Study designs “forced” / expediency
  - Cost management as big numbers

!8 ongoing trials 170K patients

- **6 DPP-4**
- **5 GLP-1**
- **5 SGLT2**
  - most vs. placebo, one versus SU

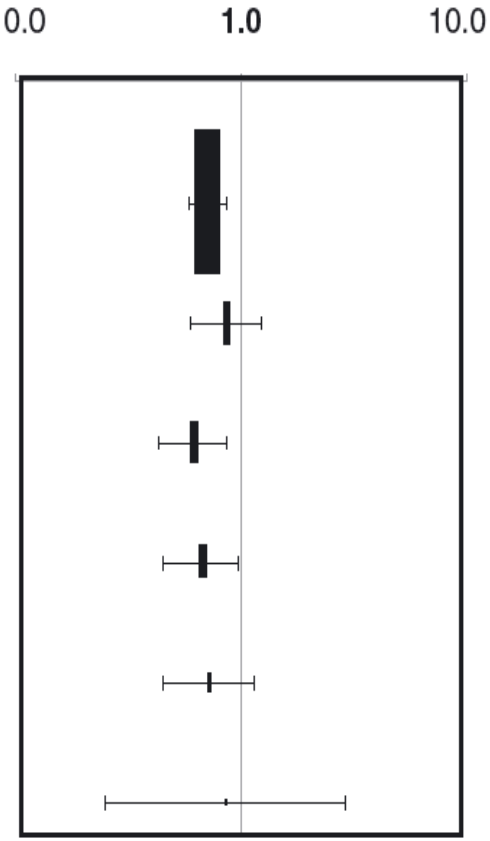
CV outcome trials in T2DM: DPP4 inhibitors ("gliptins")

Trial	Treatment Company	Inclusion criteria	Primary endpoint	Number End date
EXAMINE NCT00968708	Placebo Alogliptin -Takeda	T2DM HbA1c 6.5 – 11.0% ≥ 18 years ACS	CV death, MI or stroke ≡ 4.75 years	5400 May 2014
TECOS NCT00790205	Placebo Sitagliptin -Merck	T2DM HbA1c 6.5 – 8.0% ≥ 50 years CVD	CV death, MI, UA or stroke ≡ 5 years	14000 Dec 2014
SAVOR (TIMI-53) NCT01107886	Placebo Saxagliptin -BMS	T2DM HbA1c ≥ 6.5% ≥ 40 years CVD/CV risk factors	CV death, MI or stroke ≡ 5 years	12000 Apr 2014
CAROLINA NCT01243424	Glimepiride Linagliptin -Eli Lilly	T2DM HbA1c 6.5-8.5% 40-85 years CVD/CV risk factors/ diabetes end organ damage	CV death, MI, UA or stroke ≡ 7-8 years	6000 Sep 2018

DPP-4 and CVD: meta-analysis ‘hints’

Monami et al (2013) DOM

	# trials	# trials with events	# events (*DPP4i*)	# events (*Comparator*)	MH-OR [95%, CI]	p	Kendall's tau	p
MACE	**70**	**63**	**263**	**232**	**0.71[0.59;0.86]**	**<0.001**	**0.04**	**0.64**
Sitagliptin	27	24	77	67	0.86[0.60;1.24]	0.430	0.04	0.80
Vildagliptin	16	15	75	74	0.61[0.43;0.86]	0.005	0.03	0.89
Saxagliptin	13	12	62	46	0.67[0.45;0.99]	0.047	0.36	0.10
Linagliptin	9	8	37	41	0.72[0.45;1.16]	0.18	0.00	1.00
Alogliptin	5	4	12	4	0.86[0.25;2.93]	0.81	0.30	0.15



MACE HR 0.71 [0.59 to 0.86]

Perception of “protective” effects

But ‘only’ Non-inferiority achieved

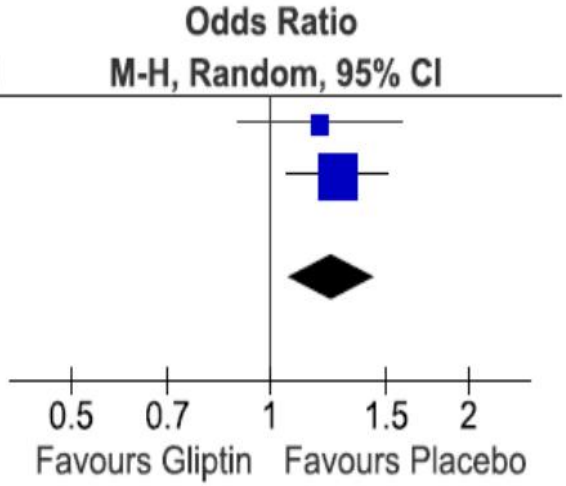
- **SAVOUR HR 1.00 [0.89-1.12]**
- **EXAMINE HR 0.96 (x - 1.16) NS**

- **Should we surprised? No**
  - HbA1c ↓ ~0.30% / 0.35% (not glucose efficacy trials)
  - Median durations of follow-up short: 1.5 to ~2 years
  - DPP-4 inhibitors minimal effects on BP/lipids

- **DPP4i need strong ‘pleiotropic’ actions for CVD benefit**
  - Clearly not there

↑ Heart Failure Hospitalisations unexpected: real? Take seriously

Study or Subgroup	Gliptin Events	Gliptin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
EXAMINE	106	2701	89	2679	27.4%	1.19 [0.89, 1.58]
SAVOR-TIMI	289	8280	228	8212	72.6%	1.27 [1.06, 1.51]
Total (95% CI)		**10981**		**10891**	**100.0%**	**1.24 [1.07, 1.45]**
Total events	395		317			



Sig. in <u>top quarter</u> NT pro-BNP (333 to 44K pg/ml)
But 13% only HF at baseline

EXAMINE data post hoc (recurrent events important)

WHAT WILL TECOS SHOW?

More reasons to be optimistic re: GLP-1 and SGLT2?

	DPP-4	GLP-1	SGLT2
Hypo risk	Low	Low	Low
Weight	neutral	Lower	Lower
BP	neutral	Lower	Lower
Lipids	Neutral	Improved	LDL↑
Other effects	HF signal?	HR ↑	Infections

Putting together Ferguson & Sattar (2013) DOM

	Glucose-lowering	BP lowering	Statins
CHD*	↓*	↓↓↓	↓↓↓
Affordability	+	+/++	+++
Simplicity	+	++	+++

Summary: target usual risk factors to ↓CVD risk: watch future trials

- **Evidence ⇓ CVD in DM over several decades**
  - Better management CVD risk factors big part
    - BP and LDL-c reduction >> glucose reduction
    - But many still sub-optimally treated
    - Trials require ever bigger numbers
- **Whether new DM agents ↓CVD not known**
    - Must alter usual risk factors?
    - GLP-1 & SGLT2 more promise than DPP-4
    - Only trials can prove / but neutrality ok?