Cardiovascular Safety of Hypoglycaemic drugs: What the fuss is all about ?

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In 6 short years…..

- Series of landmark trials on hypoglycaemic agents
  - Cardiovascular outcomes
- Significant academic, public and media interests
- Almost identical design
- New classes of hypoglycaemic agents
- Unprecedented scrutiny

Dipeptidyl peptidase-4 inhibitors

ORIGINAL ARTICLE

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Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B., for the TECOS Study Group*

2013

Sodium glucose cotransport-2 inhibitors

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes,

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

N ENGL J MED 380;4 NEJM.ORG JANUARY 24, 2019

Glucagon like peptide 1 agonists

NEW ENGLAND

ORIGINAL ARTICLE

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

Rury R. Holman, F.Med.Sci., M. Angelyn Bethel, M.D., Robert J. Mentz, M.D., Vivian P. Thompson, M.P.H., Yuliya Lokhnygina, Ph.D., John B. Buse, M.D., Ph.D., Juliana C. Chan, M.D., Jasmine Choi, M.S., Stephanie M. Gustavson, Ph.D., Nayyar Iqbal, M.D., Aldo P. Maggioni, M.D., Steven P. Marso, M.D., Peter Öhman, M.D., Ph.D., Neha J. Pagidipati, M.D., M.P.H., Neil Poulter, F.Med.Sci., Ambady Ramachandran, M.D., Bernard Zinman, M.D., and Adrian F. Hernandez, M.D., M.H.S., for the EXSCEL Study Group*

What the fuss is it all about ?

- Why the fuss ?
- How did it come about ?
- Is the fuss justified ?
- What are trial design and why so similar ?
- Has anything good come out of it ?

Thiazolidinediones (TZDs)

- Rosiglitazone approved by FDA in 1999
- Favourable effects on lowering blood glucose and HbA1c
- Little data on cardiovascular (CV) outcome

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

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

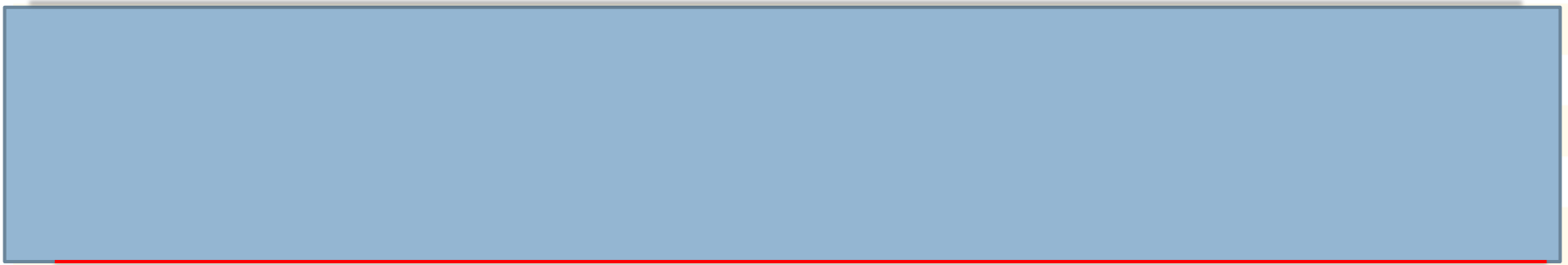
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

- 42 randomised trials
- From GlaxoSmithKline clinical trial websites, phase 2,3,4 trials submitted to FDA for approval and
- 2 published clinical trials
  - DREAM
  - ADOPT
- Rosiglitazone, n=15,560; Control, n=12,283

Nissen meta-analysis

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

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
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



Nissen meta-analysis

- Included studies that reported myocardial infarction or CV death (not as primary endpoints)
  - Not adjudicated in all except one (DREAM)
- Fixed effect model
- Cochrane Q statistics used to assess heterogeneity
  - Justified use of fixed effect models as $p > 0.1$
- No information on the weighting of the trials

- All the attributes of a bad meta-analysis
- Significant ripple effects

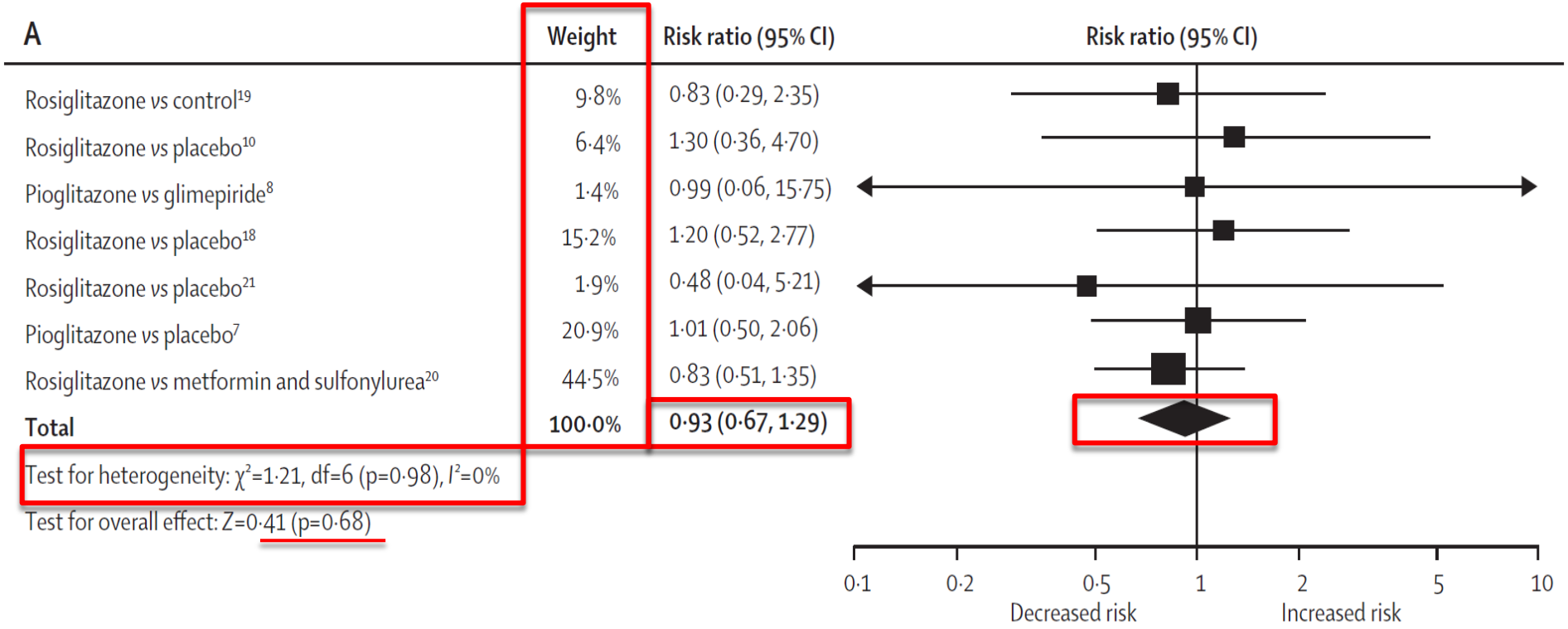
Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

Rodrigo M Lago, Premranjan P Singh, Richard W Nesto

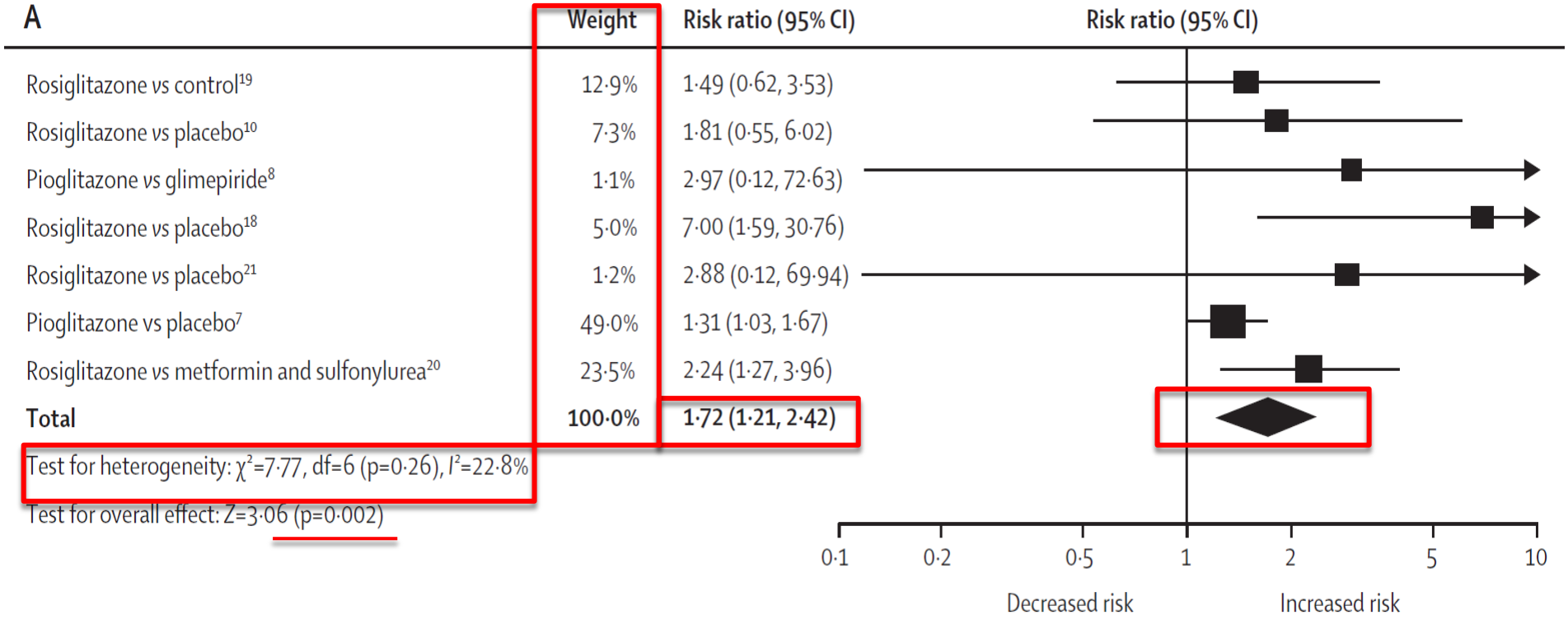
- 7 Randomised, double blind, controlled clinical trials
- N=20,191
- Random effects model
- Assessment of heterogeneity
- Information on weighting of each trial

www.thelancet.com **Vol 370 September 29, 2007**

Thiazolidinediones and CV death



Thiazolidinediones and heart failure



As a result …

- FDA issued a black box warning for TZDs in 2008
- Required ***post-marketing*** assessment of CV safety of new hypoglycaemic agents
  - Phase 4 trials

Is the fuss justified ?

- You form your own opinion

Thiazolidinediones and heart failure

- Increased incidence of heart failure
  - 0.9%/year
  - Comparator: 0.5%/year
- Fluid retention as a side effect
  - Effects on the distal renal tubules
- Fluid retention vs heart failure
- No documented detrimental effects on left ventricular function*
- ? Implications of heart failure

*Dargie et al. JACC 2007;49:1705
*St John Sutton et al. Diabetes Care 2002;25:2058

Heart failure and diabetes

- Increased incidence of heart failure in diabetes
  - Multiple etiologies
- Dyspnoea and ankle swelling common in diabetes
  - Even without heart failure
- Poor physical fitness, obesity, Immobility, chronic kidney disease, proteinuria and hypoalbuminaemia, varicose veins (deep vein thrombosis), treatment related

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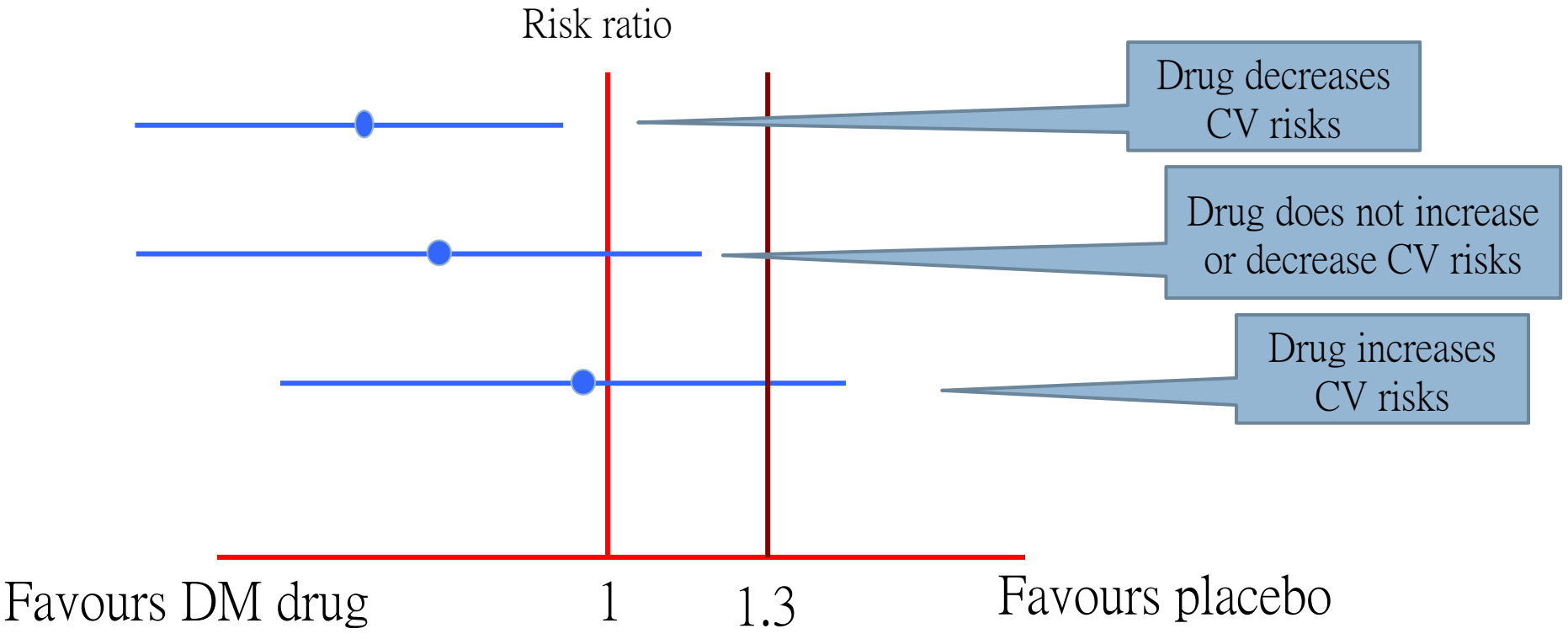
Cardiovascular outcome trial design

- Patient population
  - Established CV disease or at high risks
- Non inferiority design
- Sequential testing
- Hypoglycaemic drug versus placebo
  - In contrast to other non inferior trials
  - Active controls

Cardiovascular outcome trial design

- Endpoint:
  - 3 point MACE (major adverse CV events)
  - CV death, non fatal myocardial infarction, non fatal stroke
- Non-inferior margin
  - 1.3
  - Mandated by FDA

Non-inferiority trial vs placebo



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EXAMINE

Table 3. Major Safety End Points.

End Point	Placebo (N = 2679)	Alogliptin (N = 2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

SAVOR TIMI 53

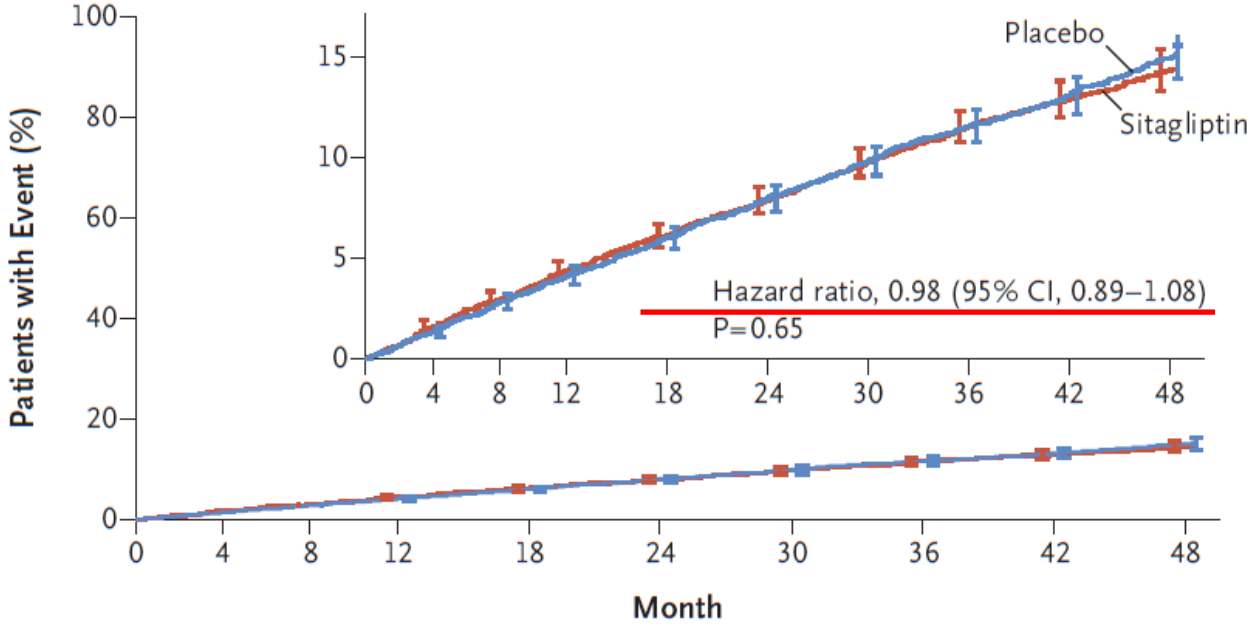
End Point	Saxagliptin (N = 8280)	Placebo (N = 8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

Subgroup analysis

- Multiple comparisons (problem of multiplicity)
- $P < 0.05$
  - Type 1 error (α)
  - 1 in 20 of "false positive"
- Risks of "false positives" with multiple testing
  - 40% with 10 tests
  - 64% with 20 tests
  - $1 - (0.95)^n$
- Only hypotheses generating

TECOS

A Primary Cardiovascular Outcome



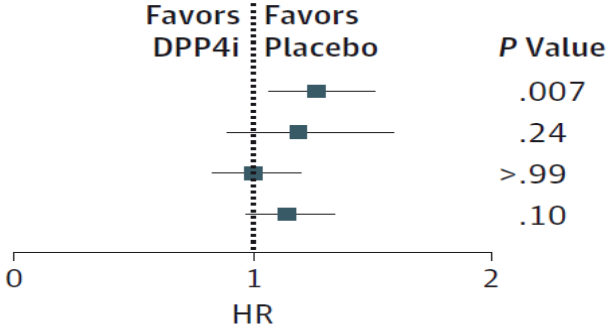
No. at Risk

Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234

Figure 3. Meta-Analysis of SAVOR-TIMI 53, EXAMINE, and TECOS

A First hospitalization for heart failure

	HR (95% CI)	*P* Value
SAVOR-TIMI 53	1.27 (1.07-1.51)	.007
EXAMINE	1.19 (0.89-1.59)	.24
TECOS	1.00 (0.84-1.20)	>.99
SAVOR-TIMI 53 plus EXAMINE plus TECOS ($P = .16$, $I^2 = 44.9$)	1.14 (0.97-1.34)	.10



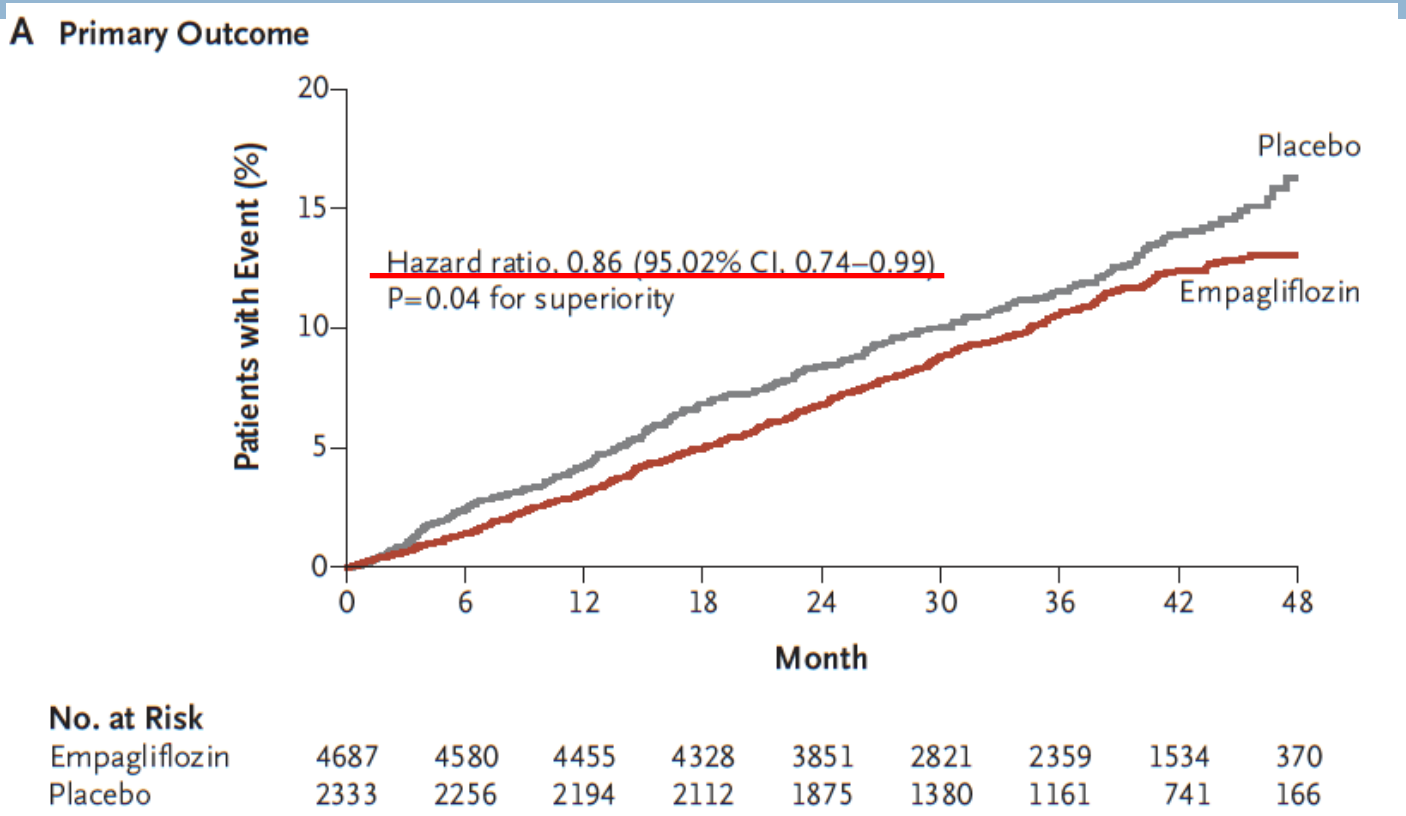
Random effects model

JAMA Cardiol. 2016;1(2):126-135. doi:10.1001/jamacardio.2016.0103
Published online April 13, 2016.

Dipeptidyl peptidase-4 inhibitors

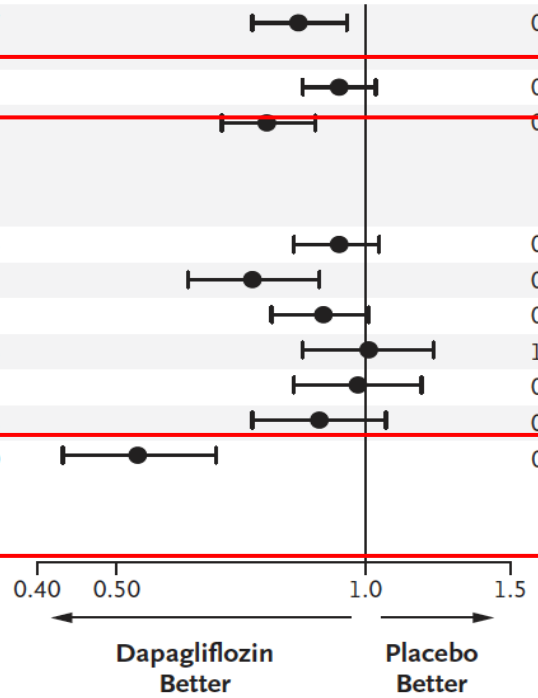
- No increase in cardiovascular adverse outcome
  - Including heart failure
- Not superior to placebo
  - Cardiovascular outcomes

EMPA-REG outcome trial



DECLARE

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

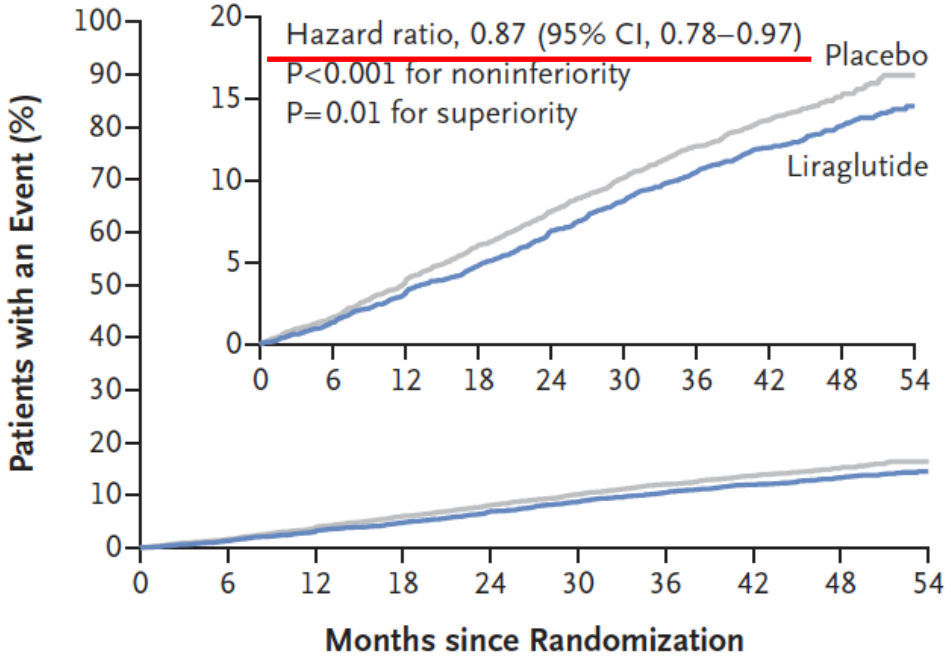


Sodium glucose cotransport-2 inhibitors

- Reduction in major adverse cardiovascular events
- Reduction in progression of renal disease and renal events
- Set out to demonstrate CV safety
- Bonus of showing cardio-renal protective effects

Liraglutide – LEADER trial

A Primary Outcome

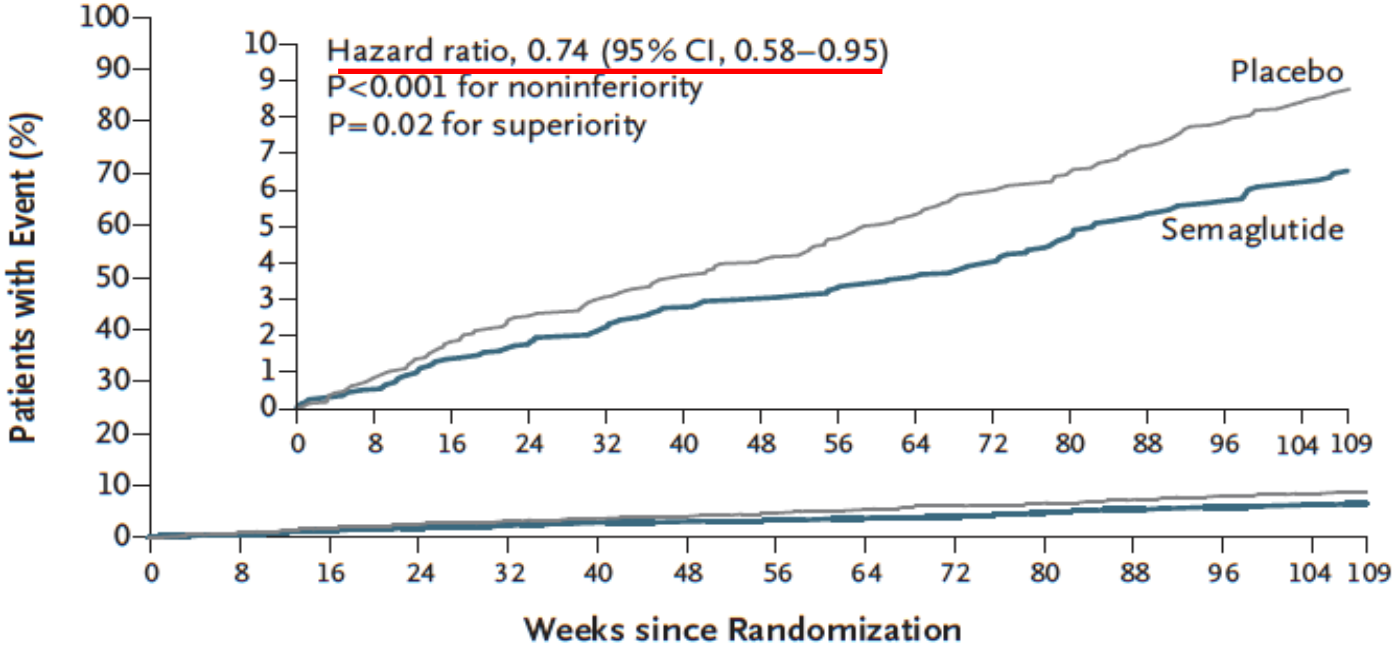


No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

Semaglutide – SUSTAIN 6

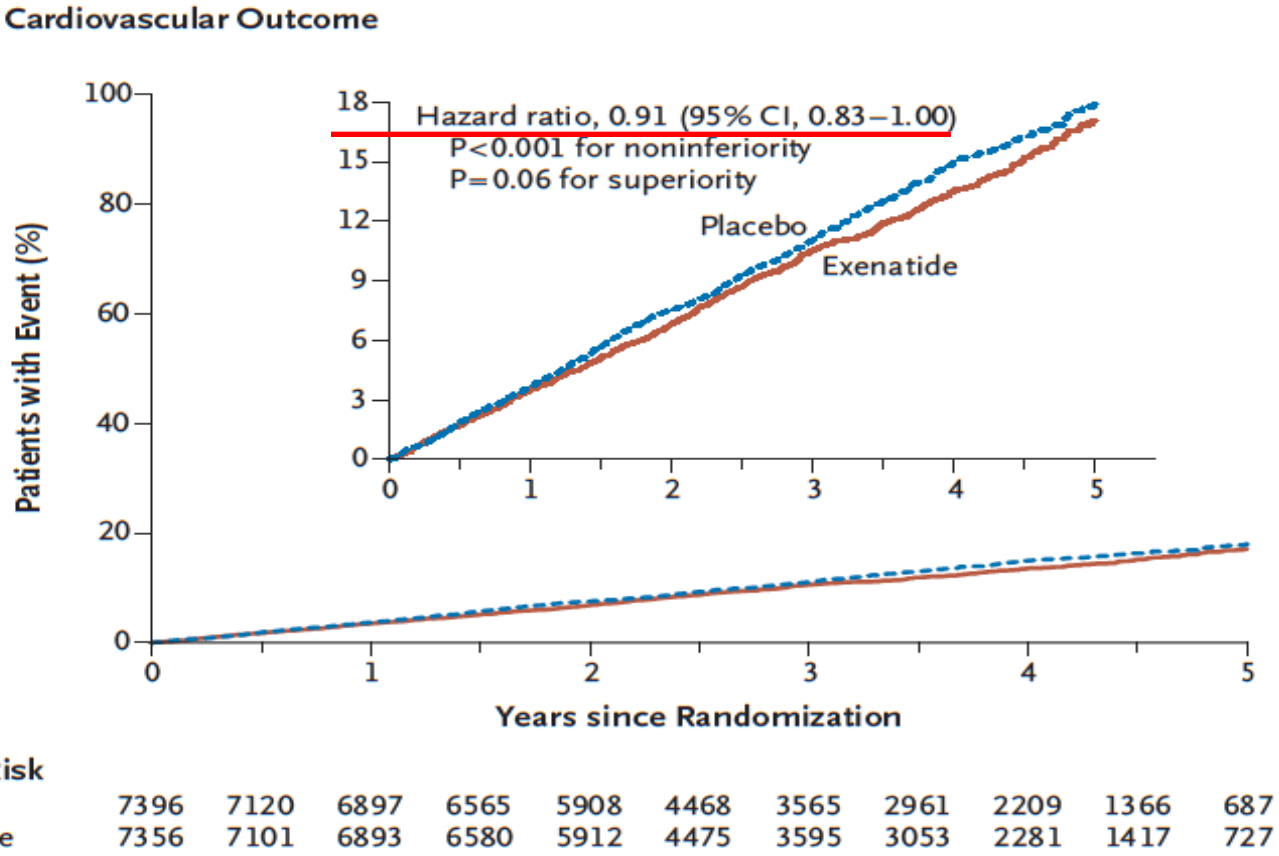
A Primary Outcome



No. at Risk

Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

Exenatide - EXSCEL



Glucagon like peptide 1 agonists

- Reduction in major adverse cardiovascular events
- Set out to demonstrate CV safety
- Bonus of showing cardio protective effects

Why lower CV risks with these agents?

- Weight loss
  - 2.3 kg lower in treatment arm in LEADER
  - 2 kg lower in EMPA REG
- Lower blood pressure
  - 1.3 mmHg lower in systolic blood pressure in treatment arm in LEADER
  - Reduced systolic and diastolic BP by 1-5 mmHg*

* Wang B et al. Diabetes, Obesity and Metabolism 15: 737 – 749, 2013.

Why lower CV risks with these agents?

- Glycaemic control (HbA1c)
  - 0.4% lower in LEADER
  - 0.53%-0.6% lower in EMPA_REG
- Lipid levels
  - Increase in LDL and HDL in EMPA-REG
  - Modest reduction in LDL and total cholesterol with GLP1 agonists*

Sun F et al, Clin Ther 2015; 37:225

Why lower CV risks with these agents?

- Heart rate
  - 3 beats/minute higher in treatment arm in LEADER
  - No increase in EMPA_REG

Cardiovascular outcome trials

- Nissen meta-analysis on the safety of rosiglitazone in 2007
- A low quality meta-analysis
- Flaws in design, studies included, analysis and interpretation
- Is it friend or foe ?

Something good has come out of it !

Story to be continued ….

- A tale of two meta-analyses

Thank you for your attention