Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Do New Drugs for Diabetes Hold Cardiovascular Promise?

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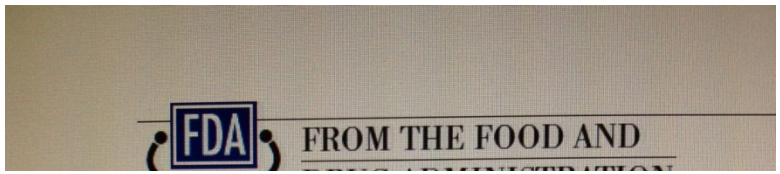
Norfolk and Norwich University Hospitals

Who is this Man?

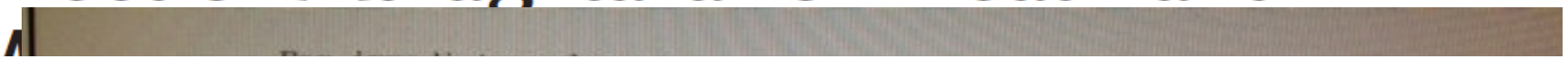
- I am a consultant in diabetes and endocrinology in Norwich
- I am an executive officer of the Association of British Clinical Diabetologists
- I am the medical secretary for the SCE in diabetes and endocrinology
- I am on the steering committee of the Joint British Diabetes Societies Inpatient Care group and am an author on several national guidelines

BMJ 11th September 2010

It's Been a Bad Few Years



Effect of Muraglitazar on Death and



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NeLM news service

Discontinuation of trial of bardoxolone for chronic kidney disease and diabetes

Source: FirstWord, Reuters Health News
Date published: 19/10/2012 17:02

Summary
by: Yuet Wan

Abbott Laboratories Inc has announced that its partner Reata Pharmaceuticals is discontinuing a late-stage trial of bardoxolone for advanced chronic kidney disease and type 2 diabetes because of safety issues.

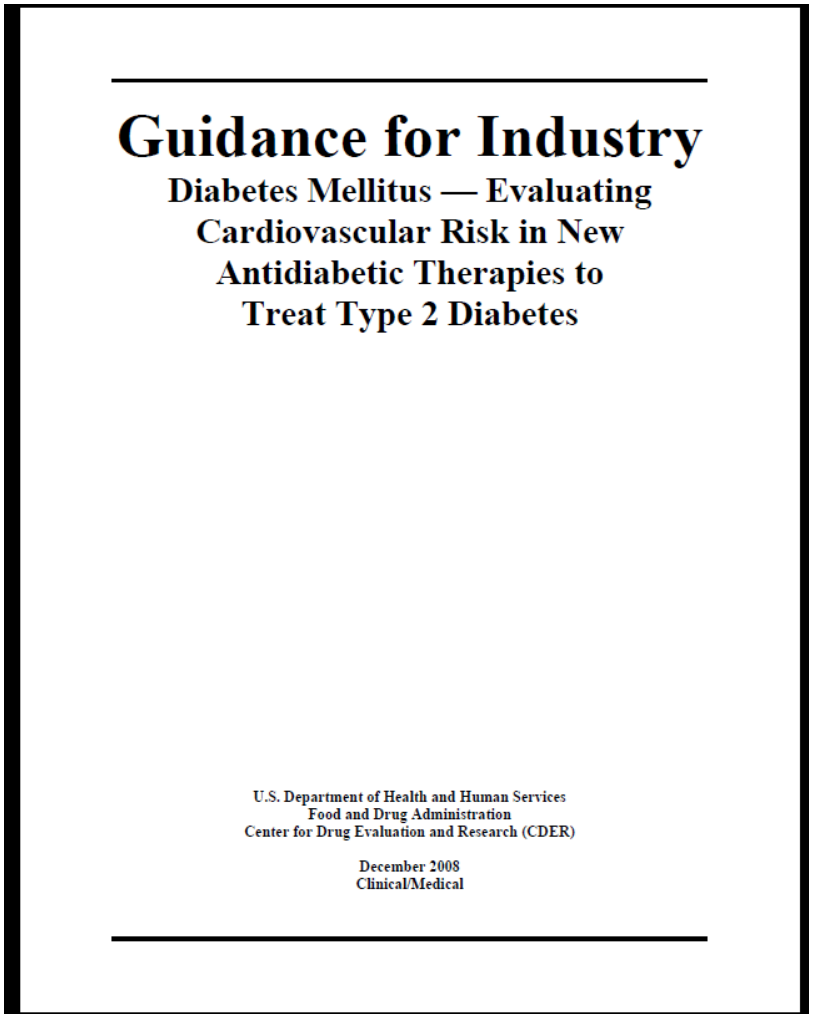
The decision to halt the BEACON trial was based on a recommendation by the study's independent data monitoring committee

and Bryan Brewer, M.D., Ph.D., for the ILLUMINATE Investigators*

The Driver?

Yudkin J et al BMJ 2011;343:d7995

The Result



Guidance for Industry

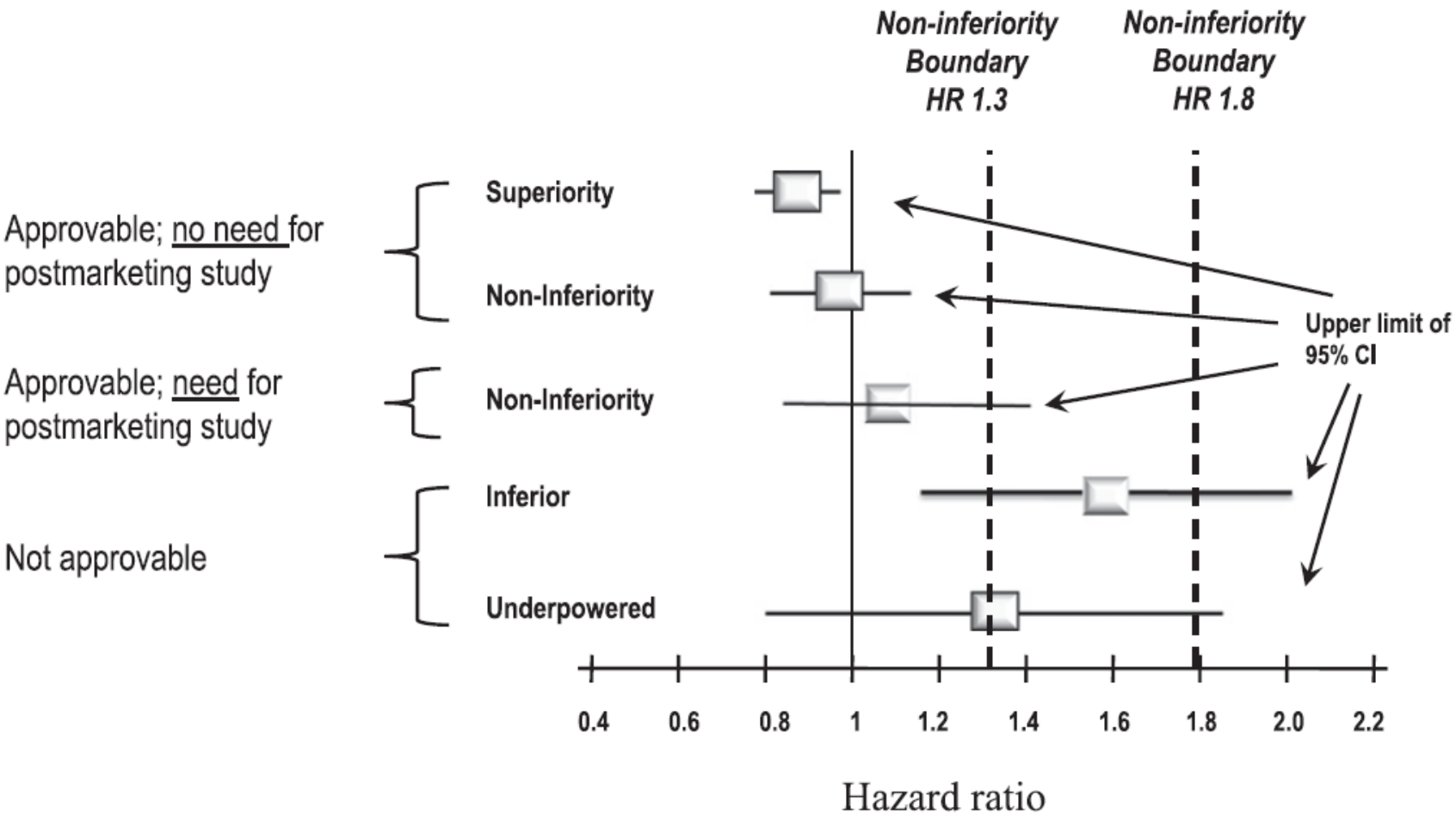
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

What The FDA Want



Hirshberg B et al Diabetes Care 2011;34(Suppl 2):S101-106

CV Outcome Trials in T2DM: DPP4 Inhibitors

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 – recruited	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

Thanks to John Petrie for these slides

CV Outcome Trials in T2DM: GLP-1 Agonists

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
ELIXA NCT01147250	Placebo Lixisenatide -Sanofi	T2DM HbA1c 6.0% - 10.0% ACS	CV death, MI, UA or stroke ≡4 years	6000 Jan 2016
EXSCEL NCT01144338	Placebo Exenatide *wkly* -Eli Lilly	T2DM HbA1c 7.0% - 10.0% CVD in 60%	CV death, MI or stroke ≡ 6.5 years	9500 Mar 2017
LEADER NCT01179048	Placebo Liraglutide -Novo Nordisk	T2DM HbA1c ≥ 7.0% ≥50 years + CVD ≥60 years + CV risk factors	CV death, MI or stroke ≡ 5 years – recruited	8754 Jan 2016
REWIND NCT01394952	Placebo Dulaglutide *wkly* -Eli-Lilly	T2DM ≥50 years+CVD ≥55 years+subclinical CVD ≥60 years+CV risk factors	CV death, MI or stroke ≡ 8 years	9600 April 2019

Thanks to John Petrie for these slides

CV Outcome Trials in T2DM: SGLT-2 Inhibitors

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
BI 10773 NCT01131676	Placebo Empagliflozin (low) Empagliflozin (high) -Boehringer Ingelheim	T2DM ≥ 18 years HbA1c 7.0 – 10.0% (7.0 – 8.0% drug naïve) CVD (CHD, stroke, PAD)	CV death, MI or stroke ≡ 4 years	7000 March 2018
CANVAS NCT01032629	Placebo Canagliflozin 100mg Canagliflozin 300mg -Janssen	T2DM ≥ 30 years HbA1c 7.0 – 10.5% History of/high risk of CVD	CV death, MI, UA or stroke ≡ 4 years - recruited	4363 Apr 2013

Thanks to John Petrie for these slides

CV Outcome Trials in 'Pre-Diabetes' - IFG/IGT

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
ORIGIN NCT00069784	2 x 2 factorial Insulin glargine n-3 fatty acids -Sanofi	IGT/IFG Early T2DM ≥50 years CVD/CVD risk factors	i) CV death, MI or stroke ii) CV death, MI, stroke, revasc. or HF Completed	12500 2003-2011
ACE NCT00829660	Placebo Acarbose (α-glucosidase inhibitor) -Bayer	IGT ≥50 years CHD	CV death, MI or stroke 4 years	7500 Oct 2014

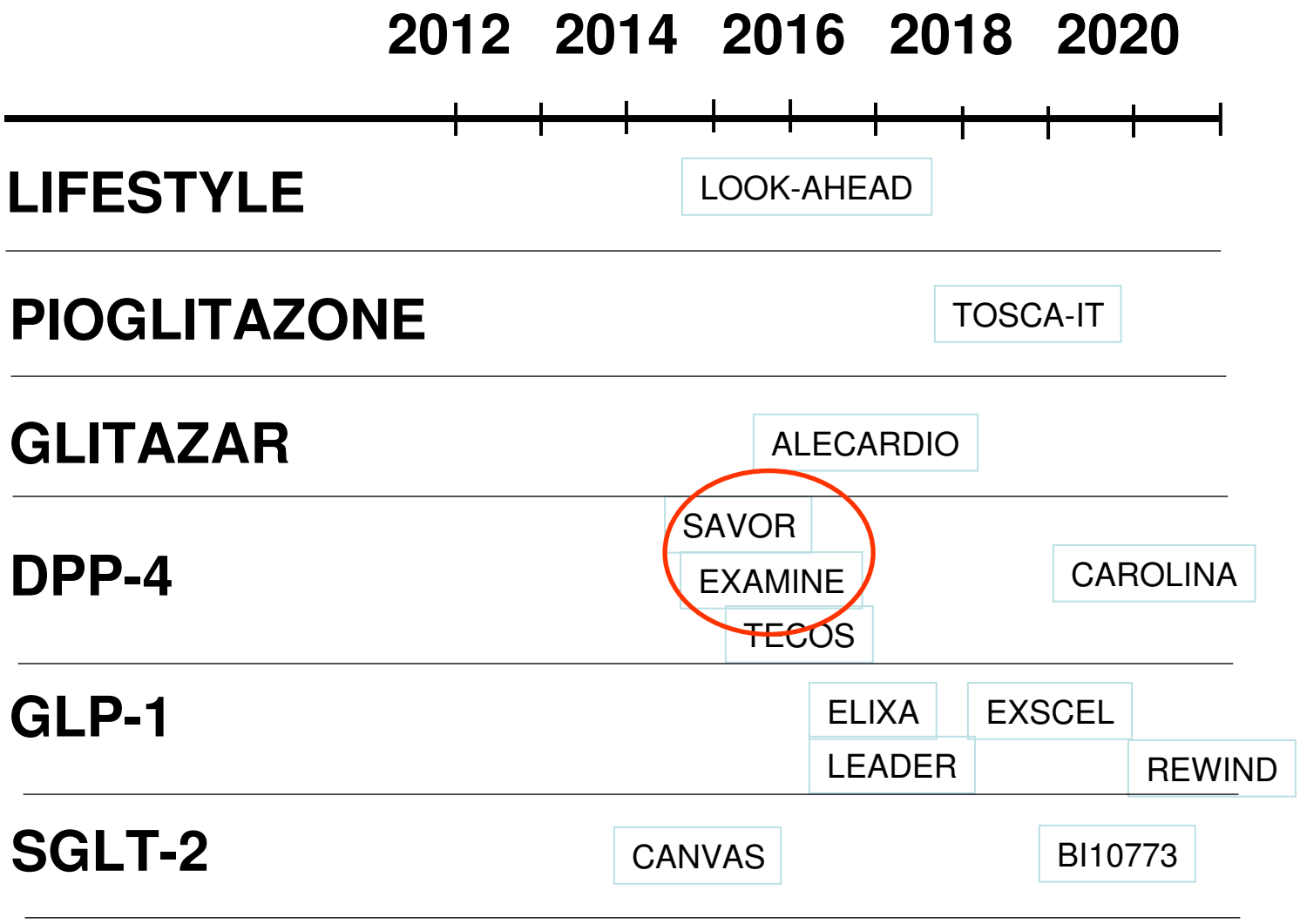
Thanks to John Petrie for these slides

CV Outcome Trials in 'Pre-Diabetes' - IR

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
IRIS NCT00091949	Placebo Pioglitazone 45mg Yale	Insulin resistance (HOMA-IR >3.0) ≥40 years 2wks-6mo after stroke/TIA	Fatal/non-fatal stroke Fatal/non-fatal MI 3 years	3136 May 2015

Thanks to John Petrie for these slides

Timeline



Thanks to John Petrie for these slides

What About Old Drugs?

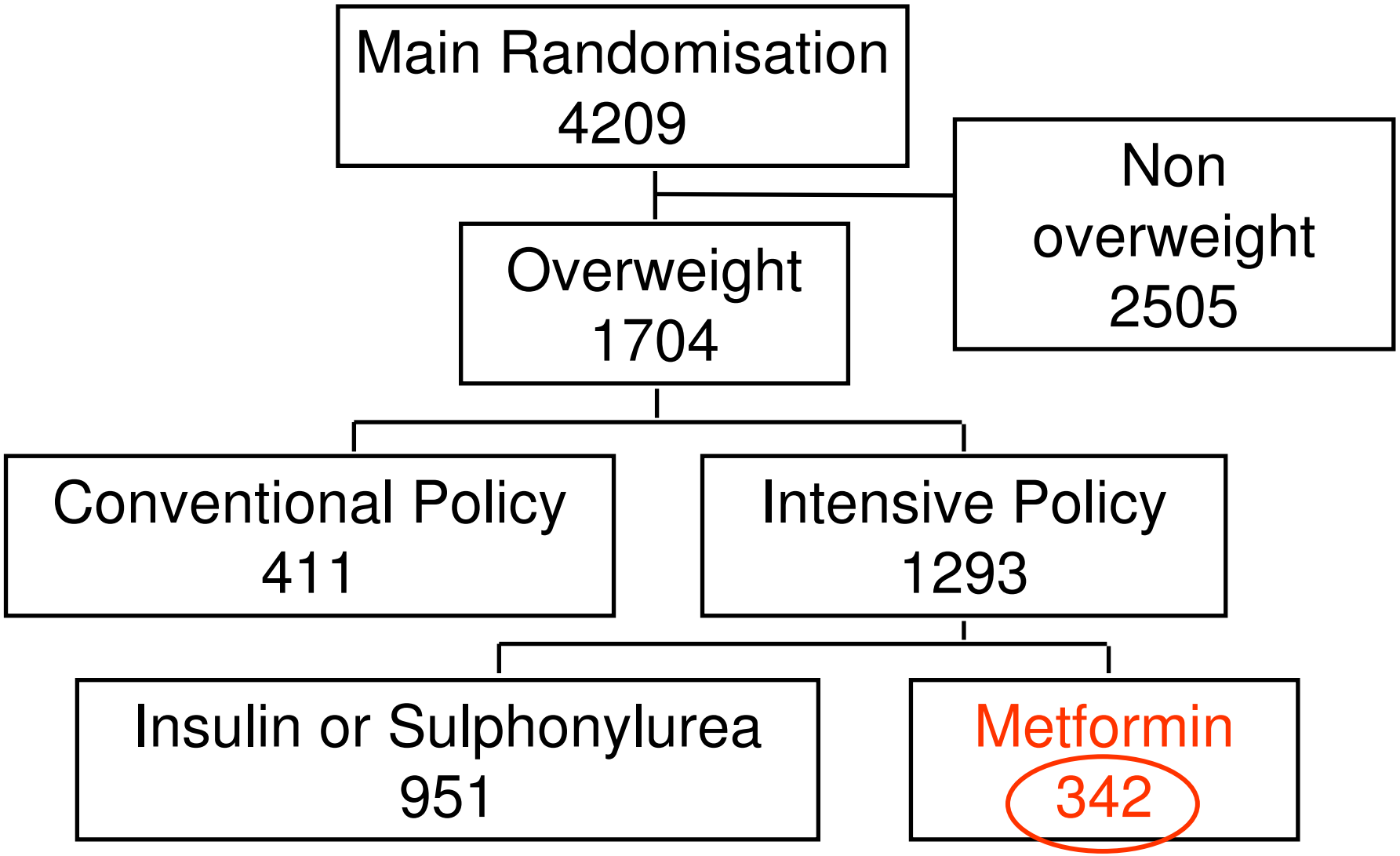
- A recent meta-analysis of 1.3 million sulphonylurea users followed for up to 10.4 years found
  - Significantly raised risk of CV death (RR 1.27)
  - Significantly raised risk of CV event (RR 1.10)
- When compared to metformin
  - Significantly raised risk of CV death (RR 1.26)
  - Significantly raised risk of CV event (RR 1.1)

Phung OJ et al Diabet Med 2013;30(10):1160-1171

Is There Any Good News?

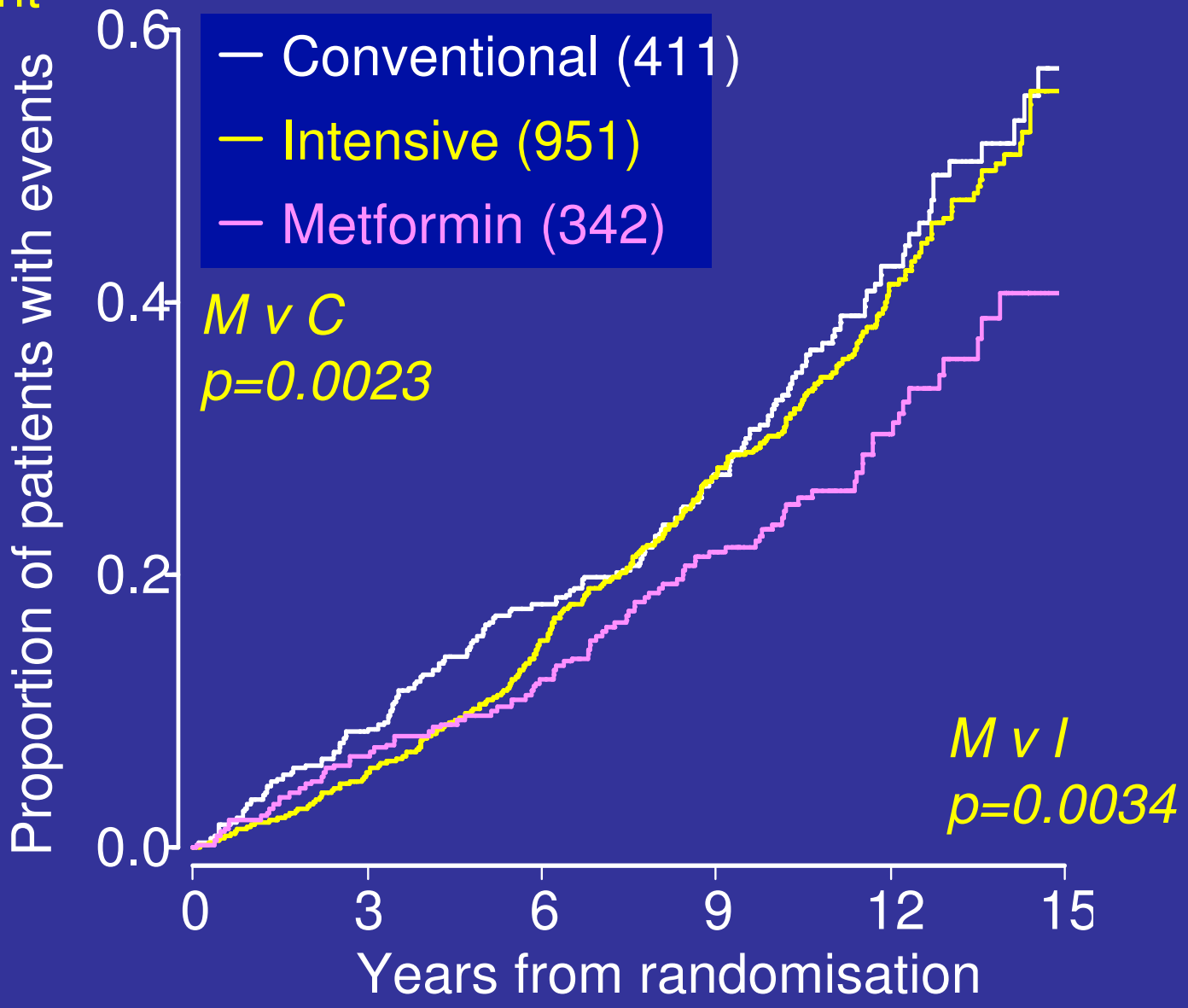
- Yes!
- Metformin reduces the risk of CVD

UKPDS - Randomisation



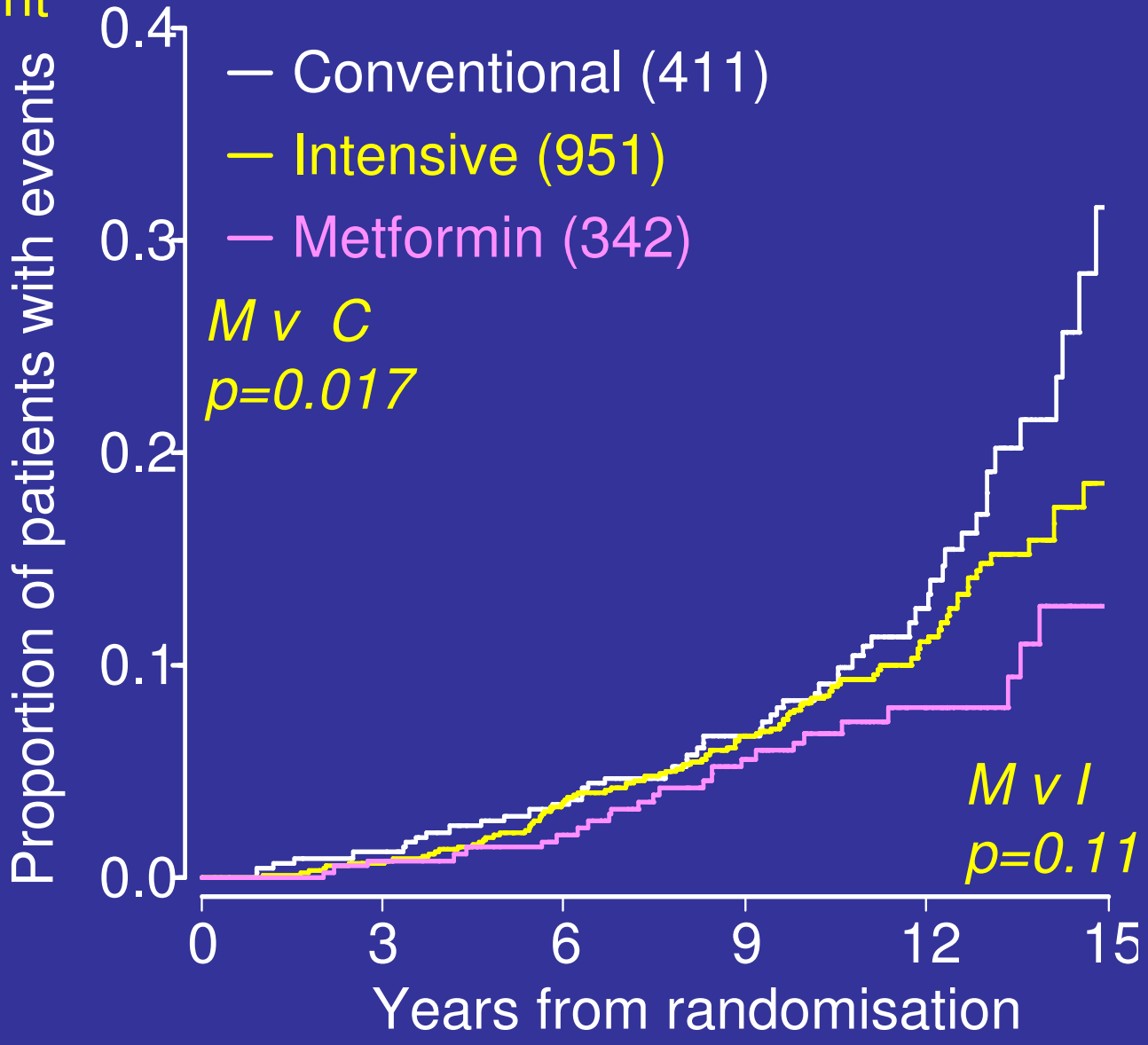
Any Diabetes Related Endpoint

Overweight patients



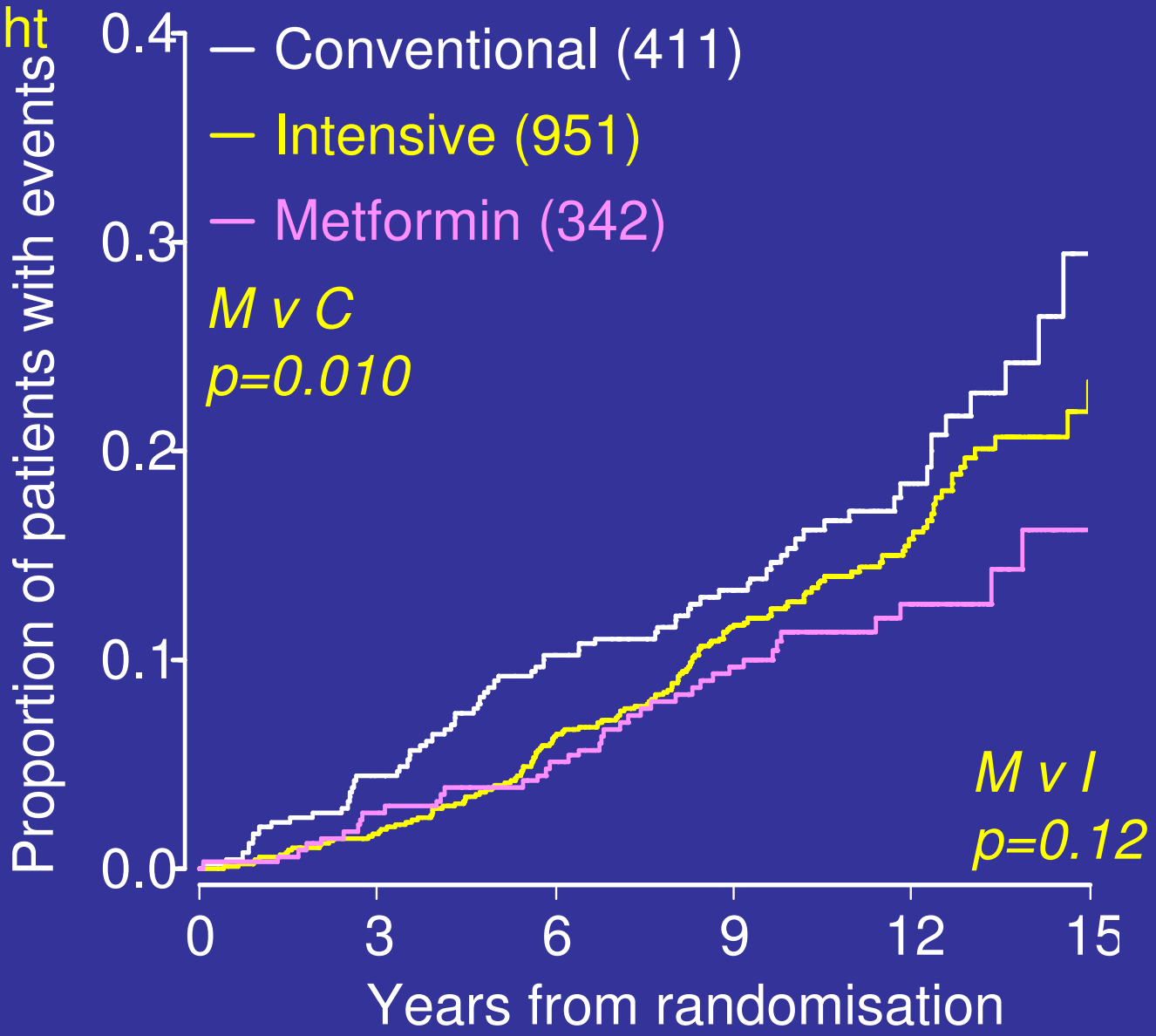
Diabetes Related Deaths

Overweight patients



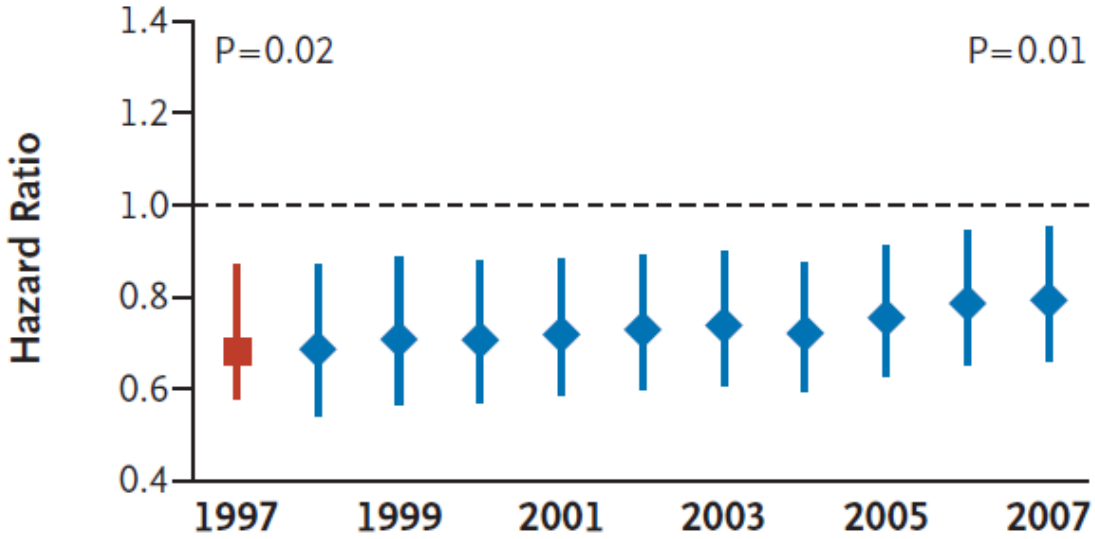
Myocardial Infarction

Overweight patients



10 Year Follow up Data

B Any Diabetes-Related End Point

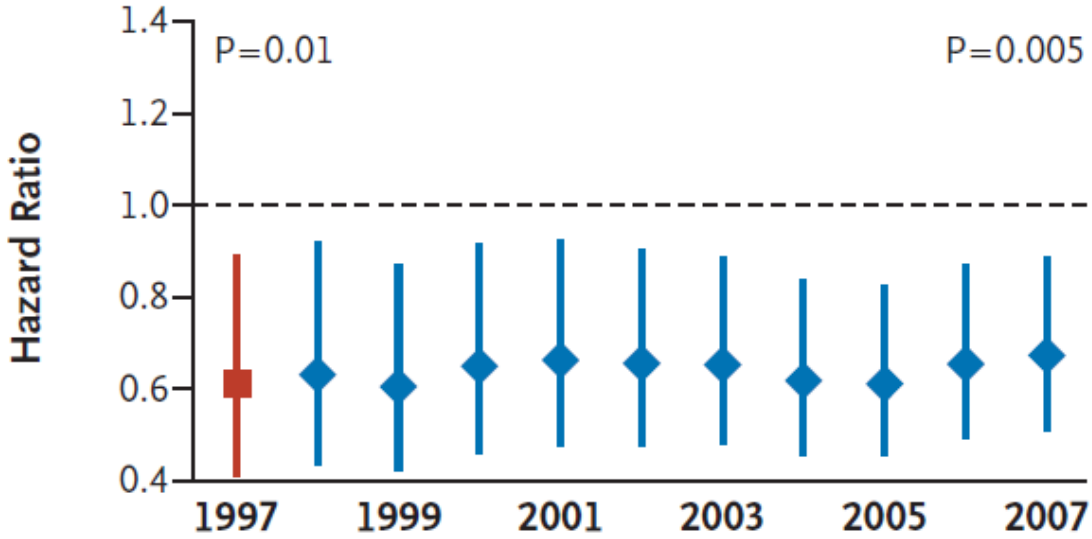


No. of Events						
Conventional therapy	160	190	220	240	252	262
Metformin	98	126	152	175	189	209

Holman RR et al NEJM 2008;359(15):1577-1589

10 Year Follow up Data

D Myocardial Infarction

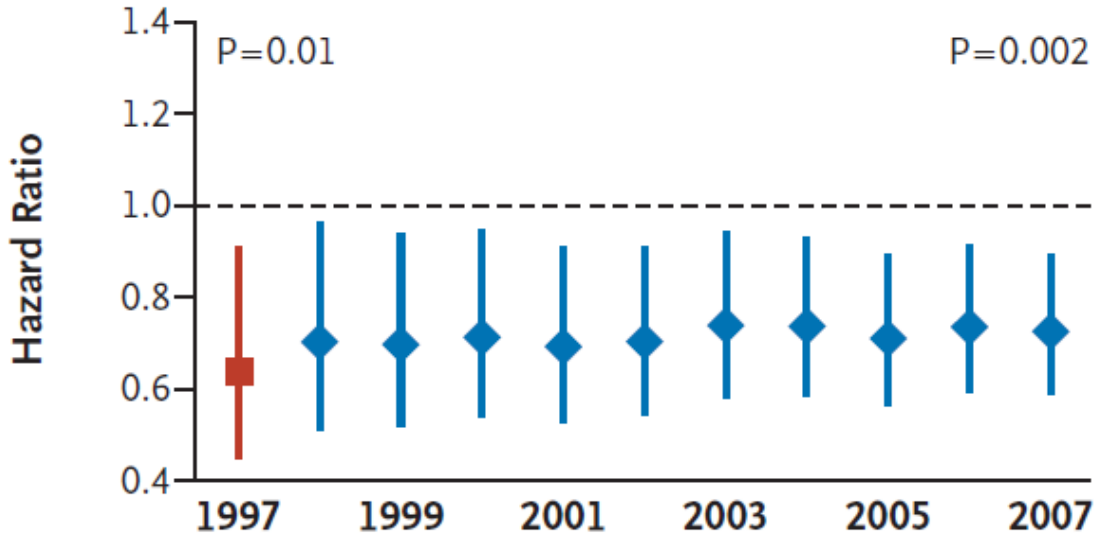


No. of Events						
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

Holman RR et al NEJM 2008;359(15):1577-1589

10 Year Follow up Data

H Death from Any Cause



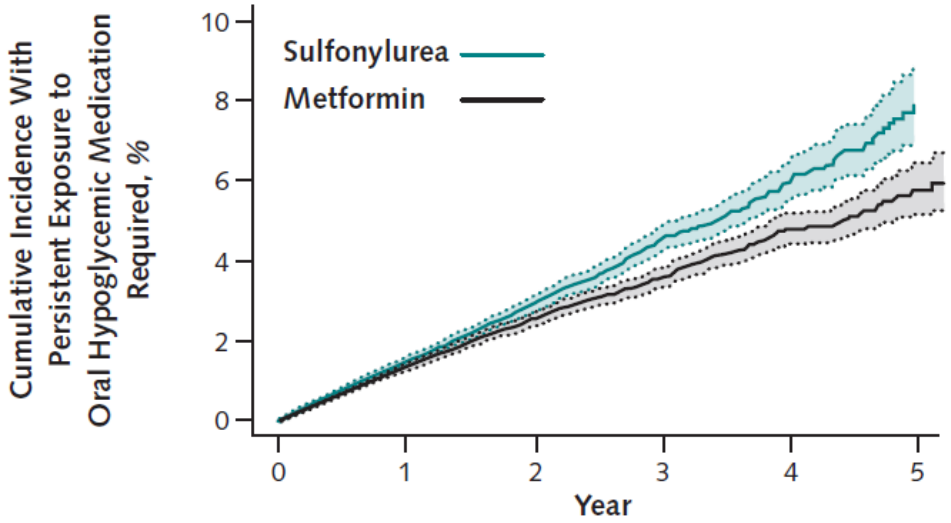
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	89	113	136	160	183	217
Metformin	50	70	86	110	123	152

Holman RR et al NEJM 2008;359(15):1577-1589

But That Was Only 342 Patients!

- There is more robust data now – data on 250,000 people on a VA registry
- HR SU 2.2 vs Metformin

Figure 2. **Cumulative incidence (95% CIs) of cardiovascular disease or death.**

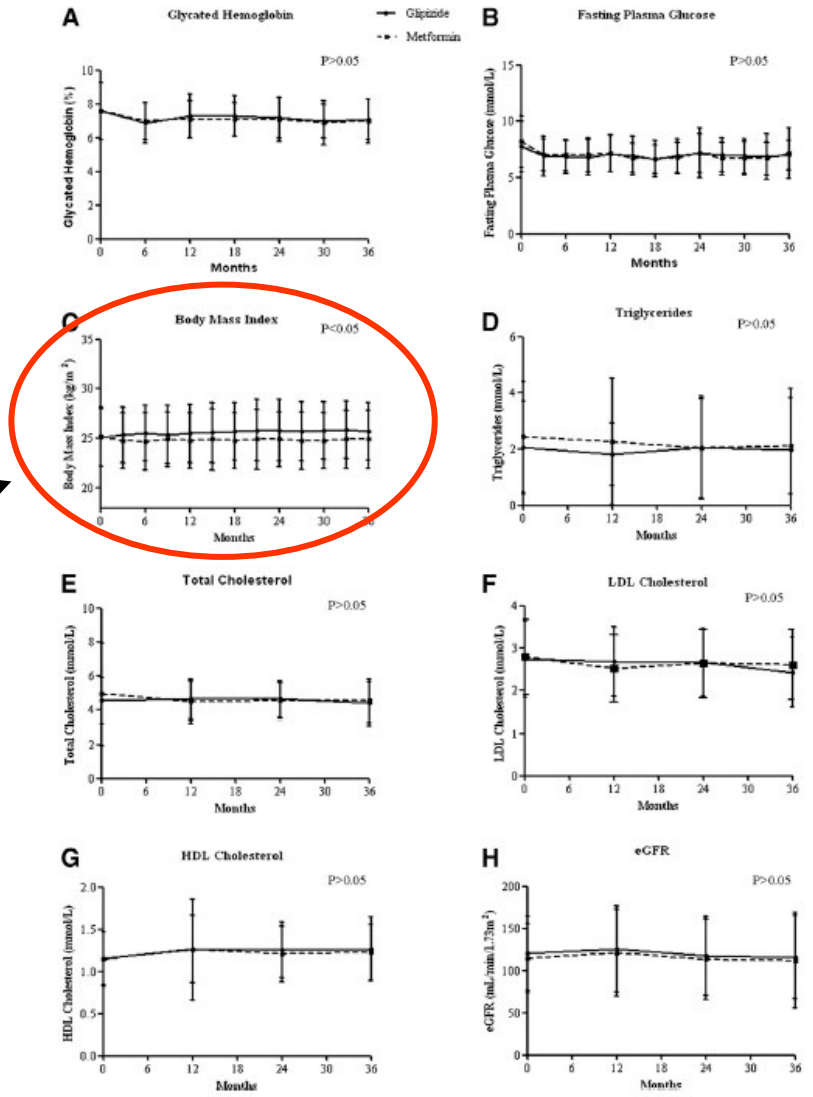


Patients receiving metformin, *n*	80 648	33 418	16 887	7976	3297	718
Patients receiving sulfonylurea, *n*	80 648	29 502	14 118	6185	2301	462

Roumie CL et al Ann Intern Med 2012;157(9):601-610

More Support for Metformin

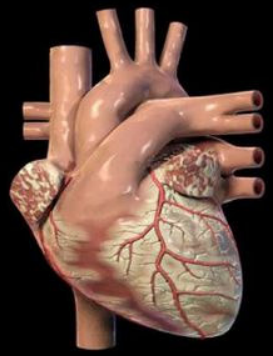
- This study compared CV outcomes between glipizide and metformin in people with T2DM with CHD
- No change in any CV risk factor except for weight over 3 years of follow up
- All CV outcomes Hazard Ratio of 0.54 when compared with SU



Hong J et al Diabetes Care 2013;36(5):1304-1311

What about Pioglitazone?

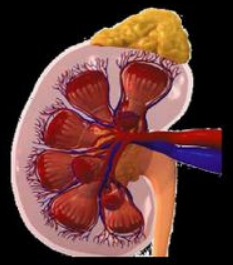
↓ 47% of Secondary Stroke in Patients with previous Stroke (PROactive)



↓ - 28% of Re-Infarction in Patients with previous MI (PROactive)

↓ - 37% of Acute Coronary Syndrome after previous MI (PROactive)

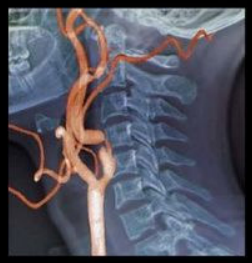
Stop Progression of Coronary Atherosclerosis (PERISCOPE)



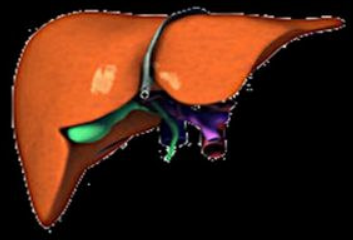
↓ MI, Stroke & Death in Patients with CKD (PROactive)

↓ Microalbuminuria (QUARTET)

↓ - 51% Mortality In Incident Patients on Hemodialysis (USA)



↓ Reduction of CIMT (Carotid artery Intima-Media Thickness) CHICAGO

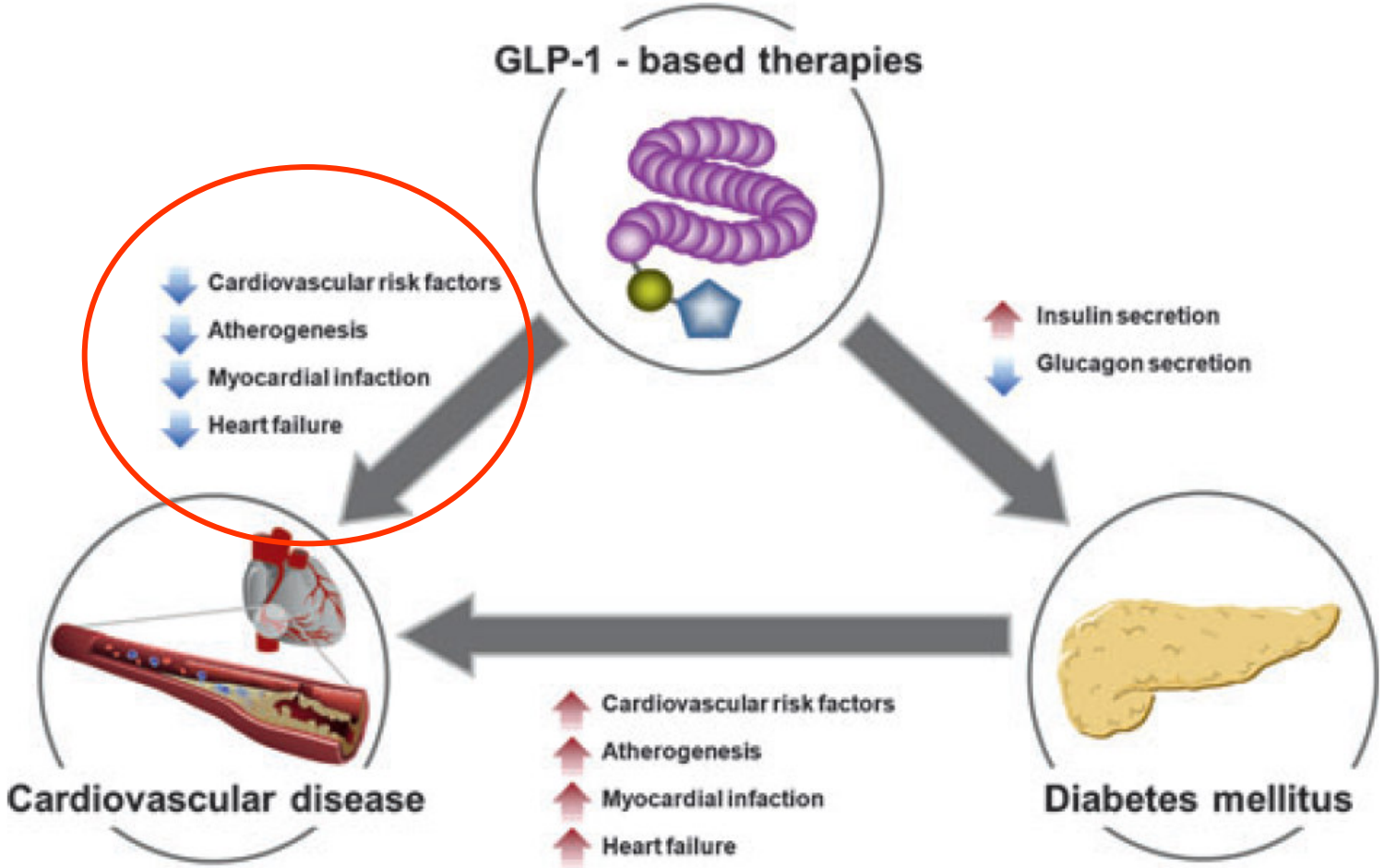


Reduction of Inflammation & Necrosis in NASH (Nonalcoholic Steatohepatitis)

↓ 50% Risk for Hepatocellular Ca

Schernthaner G Diabetes Care 2013;36:S155-S161

We Knew That – What About New Drugs?



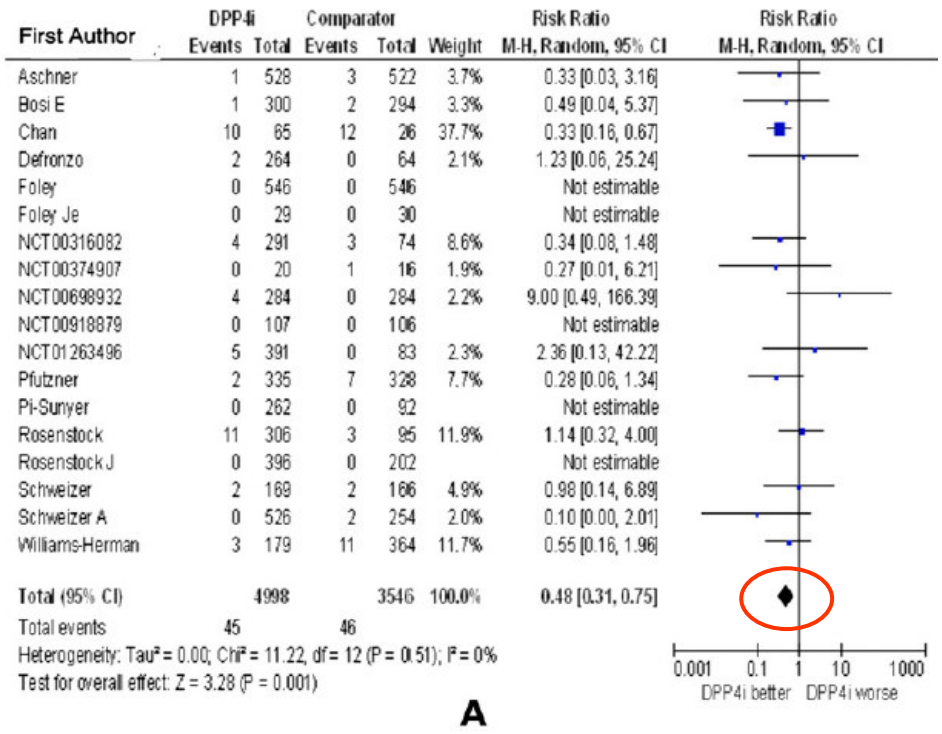
Burgmaier M et al Diabetic Med 2013;30(2):289-299

Effects of GLP-1 Based Treatments on the Cardiovascular 'Continuum'

Author	Type of study	Effect
1. Cardiovascular risk factors:		
Drucker *et al.*	Clinical	Exenatide reduces LDL cholesterol, triglycerides and total cholesterol
Zinman *et al.*	Clinical	Liraglutide reduces free fatty acids, triglycerides and LDL cholesterol
Scott *et al.*	Clinical	Sitagliptin reduces triglycerides and free fatty acids and increases HDL cholesterol
Matikainen *et al.*	Clinical	Vildagliptin reduces postprandial triglyercide-rich lipoprotein particles
Schwartz *et al.*	Clinical	Exenatide reduces postprandial triglycerides, apolipoprotein B-48, apolipoprotein CIII, remnant cholesterol and remnant triglycerides
Garber *et al.*	Clinical	Liraglutide reduces systolic blood pressure
Mistry *et al.*	Clinical	Sitagliptin reduces systolic blood pressure
Pi-Sunyer *et al.*	Clincial	Vildagliptin has no effect on blood pressure
Okerson *et al.*	Meta analysis	Exenatide reduces systolic blood pressure
Drucker et al.	Clinical	Exenatide reduces weight
Zinman *et al.*	Clinical	Liraglutide reduces weight
Moretto *et al.*	Clinical	Exenatide reduces weight
Amori *et al.*	Meta analysis	DPP-4 inhibition is weight neutral
2. Mechanisms of atherogensis:		
Masur *et al.*	*In vitro*	GLP-1 inhibits lymphocyte chemotaxis
Kim *et al.*	*In vitro*	Sitagliptin inhibits splenic CD4-positive lymphocyte migration
Marx *et al.*	*In vitro*	GLP-1(1-37) inhibits human CD4-positive lymphocyte migration
Liu *et al.*	*In vitro*	GLP-1 reduces PAI-1, VCAM-1 and ICAM-1 expression
Yu *et al.*	*Ex vivo*	GLP-1 improves endothelial dysfunction
Nagashima *et al.*	Mouse	GLP-1 reduces plaque inflammation and atherosclerosis
Matsubara *et al.*	Mouse	Des-fluoro-sitagliptin reduces atherosclerosis and plaque inflammation
Arakawa *et al.*	Mouse	Exendin-4 reduces monocyte adhesion and atherosclerosis
Courreges *et al.*	Clinical	Liraglutide reduces plasma concentrations of PAI-1 and C-reactive protein
Nystrom *et al.*	Clinical	GLP-1 infusion improves endothelial function
Basu *et al.*	Clinical	GLP-1 enhances endothelial function
Koska *et al.*	Clinical	Exenatide improves endothelial dysfunction
3. Myocardial infarction		
Nikolaidis *et al.*	Canines	GLP-1 limits myocardial stunning
Timmers *et al.*	Pigs	Exenatide reduces infarct size and improves heart function
Noyan-Ashraf *et al.*	Mouse	Liraglutide reduces infarct size and improves cardiac output
Nikolaidis *et al.*	Clinical	GLP-1 improves left ventricular-function after myocardial infaction
Read *et al.*	Clinical	GLP-1 reduces ischaemic left ventricular-dysfunction after balloon occlusion
Lonborg *et al.*	Clinical	Exenatide improves myocardial salvage in patients with ST-segment elevation myocardial infarction
4. Heart failure:		
Poornima *et al.*	Rats	GLP-1 improves heart failure and survival
Nikolaidis *et al.*	Canines	GLP-1 improves pacing-induced heart failure
Courreges *et al.*	Clinical	Liraglutide decreases plasma brain natriuretic peptide levels
Sokos *et al.*	Clinical	GLP-1 improves left ventricular function and functional status
Sokos *et al.*	Clinical	GLP-1 reduces inotropic support after coronary artery bypass grafting

Burgmaier M et al Diabetic Med 2013;30(2):289-299

DPP-4 Inhibitors?



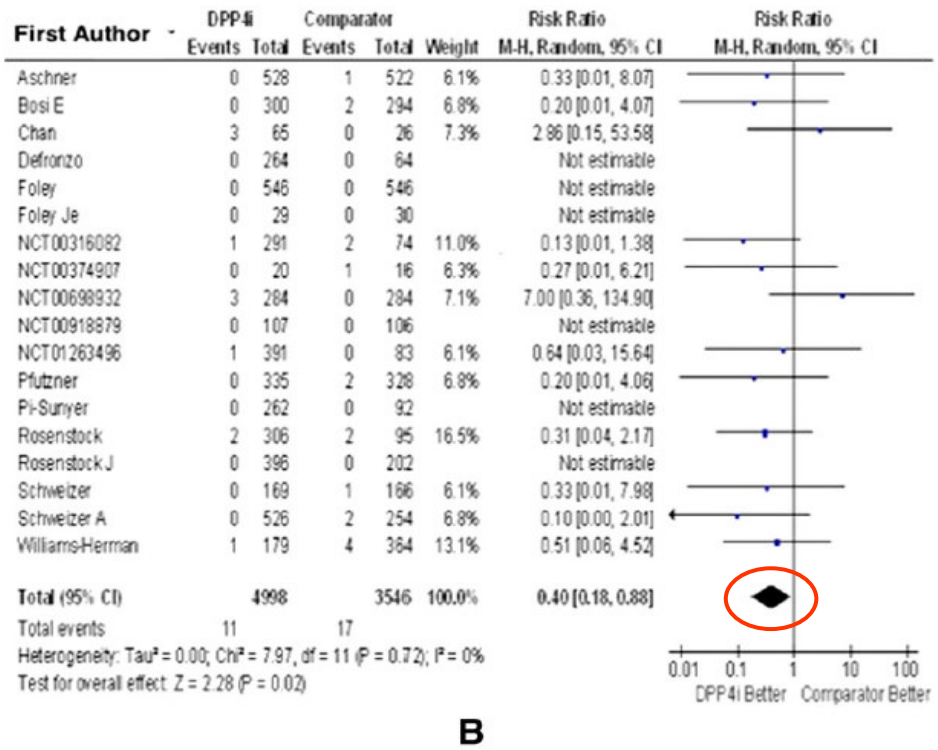
First Author	DPP4i Events	DPP4i Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
Aschner	1	528	3	522	3.7%	0.33 [0.03, 3.16]
Bosi E	1	300	2	294	3.3%	0.49 [0.04, 5.37]
Chan	10	65	12	26	37.7%	0.33 [0.16, 0.67]
Defronzo	2	264	0	64	2.1%	1.23 [0.06, 25.24]
Foley	0	546	0	546		Not estimable
Foley Je	0	29	0	30		Not estimable
NCT00316082	4	291	3	74	8.6%	0.34 [0.08, 1.48]
NCT00374907	0	20	1	16	1.9%	0.27 [0.01, 6.21]
NCT00698932	4	284	0	284	2.2%	9.00 [0.49, 166.39]
NCT00918879	0	107	0	106		Not estimable
NCT01263496	5	391	0	83	2.3%	2.36 [0.13, 42.22]
Pfutzner	2	335	7	328	7.7%	0.28 [0.06, 1.34]
Pi-Sunyer	0	262	0	92		Not estimable
Rosenstock	11	306	3	95	11.9%	1.14 [0.32, 4.00]
Rosenstock J	0	396	0	202		Not estimable
Schweizer	2	169	2	166	4.9%	0.98 [0.14, 6.89]
Schweizer A	0	526	2	254	2.0%	0.10 [0.00, 2.01]
Williams-Herman	3	179	11	364	11.7%	0.55 [0.16, 1.96]
Total (95% CI)		**4998**		**3546**	**100.0%**	**0.48 [0.31, 0.75]**
Total events	45		46			

Heterogeneity: Tau² = 0.00; Chi² = 11.22, df = 12 (P = 0.51); I² = 0%
Test for overall effect: Z = 3.28 (P = 0.001)

Risk Ratio M-H, Random, 95% CI
0.001 0.1 1 10 1000
DPP4i better DPP4i worse

A

Adverse CV events



First Author	DPP4i Events	DPP4i Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
Aschner	0	528	1	522	6.1%	0.33 [0.01, 8.07]
Bosi E	0	300	2	294	6.8%	0.20 [0.01, 4.07]
Chan	3	65	0	26	7.3%	2.86 [0.15, 53.58]
Defronzo	0	264	0	64		Not estimable
Foley	0	546	0	546		Not estimable
Foley Je	0	29	0	30		Not estimable
NCT00316082	1	291	2	74	11.0%	0.13 [0.01, 1.38]
NCT00374907	0	20	1	16	6.3%	0.27 [0.01, 6.21]
NCT00698932	3	284	0	284	7.1%	7.00 [0.36, 134.90]
NCT00918879	0	107	0	106		Not estimable
NCT01263496	1	391	0	83	6.1%	0.64 [0.03, 15.64]
Pfutzner	0	335	2	328	6.8%	0.20 [0.01, 4.06]
Pi-Sunyer	0	262	0	92		Not estimable
Rosenstock	2	306	2	95	16.5%	0.31 [0.04, 2.17]
Rosenstock J	0	396	0	202		Not estimable
Schweizer	0	169	1	166	6.1%	0.33 [0.01, 7.98]
Schweizer A	0	526	2	254	6.8%	0.10 [0.00, 2.01]
Williams-Herman	1	179	4	364	13.1%	0.51 [0.06, 4.52]
Total (95% CI)		**4998**		**3546**	**100.0%**	**0.40 [0.18, 0.88]**
Total events	11		17			

Heterogeneity: Tau² = 0.00; Chi² = 7.97, df = 11 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
DPP4i Better Comparator Better

B

Episodes of ACS

Patil HR et al Am J Cardiol 2012;110:826-833

SAVOR and EXAMINE

- Saxagliptin and Alogliptin
  - 16,492 and 5,380 patients respectively
  - At high risk of or with a history of CV disease
  - Followed up for between 18 and 24 months

- Neither drug had any impact of CV outcomes

- But Saxagliptin use was associated with a 25% increase in admissions for heart failure

Scirica BM et al NEJM 2013 Published on line 2nd September 2013 DOI: 10.1056/NEJMoa1307684

White WB et al NEJM 2013 Published on line 2nd September 2013 DOI: 10.1056/NEJMoa1305889

But Are They Safe?

Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors

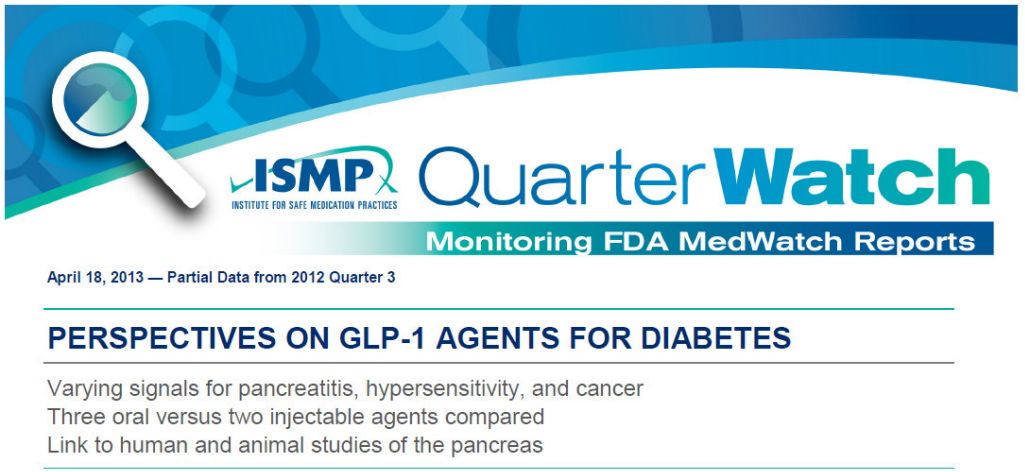
Alexandra E. Butler,[1] Martha Campbell-Thompson,[2] Tatyana Gurlo,[1] David W. Dawson,[3] Mark Atkinson,[2] and Peter C. Butler[1]

Pancreata of 8 patients with T2DM who had died having take these drugs were found to have α-cell hyperplasia, glucagon expressing microadenomas and 1 neuro-endocrine tumour

Butler AE et al Diabetes 2013;62(7):2595-2604

But Are They Safe?

- After adjustment ,the OR for pancreatitis for GLP-1 agonists was 28.5 (95% CI 17.4-46.4) times higher than the diabetes drug controls
- For the DPP-IV antagonists the OR for pancreatitis was 20.8 (95% CI 12.6-34.5) times higher.



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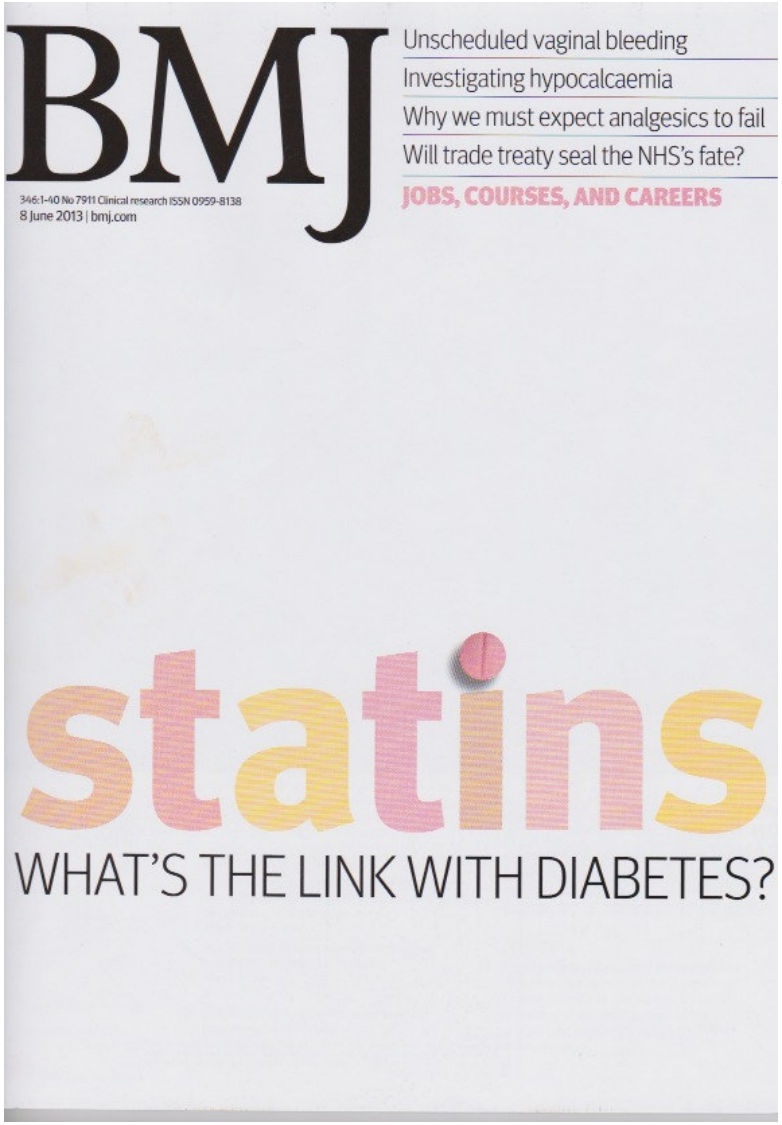

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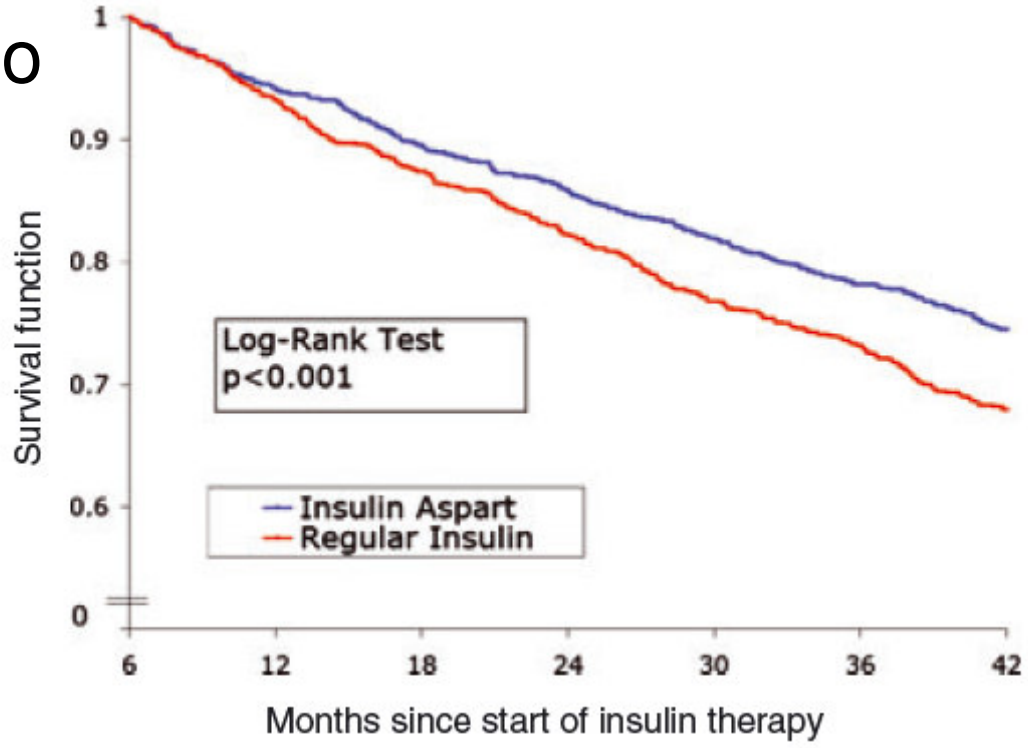
What About Newer Insulins?

- 6308 patients equally divided into aspart or regular insulin use
- Looking at macrovascular even rates
- HR for incident CVA & MI 0.58 and 0.69



Rathmann W et al Diab Obes Metabol 2013;15(4):358-363

In Summary

- Diabetes doctors have been bitten very hard in the past few years and are now very cautious
- The newer agents are currently under evaluation and meta-analyses show promise but there are side effects – watch this space!
- Metformin still has most robust data behind it
- Retain a modicum of scepticism about what you are told

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Do New Drugs for Diabetes Hold Cardiovascular Promise?

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