Prologue

For info below:

US jury orders Takeda, Eli Lilly to pay $9 billion in damages over Actos

(Ref: Interactive Investor, The Wall Street Journal, Bloomberg, Yahoo!Health, MarketWatch, BBC News, The Economic Times, PR Newswire)

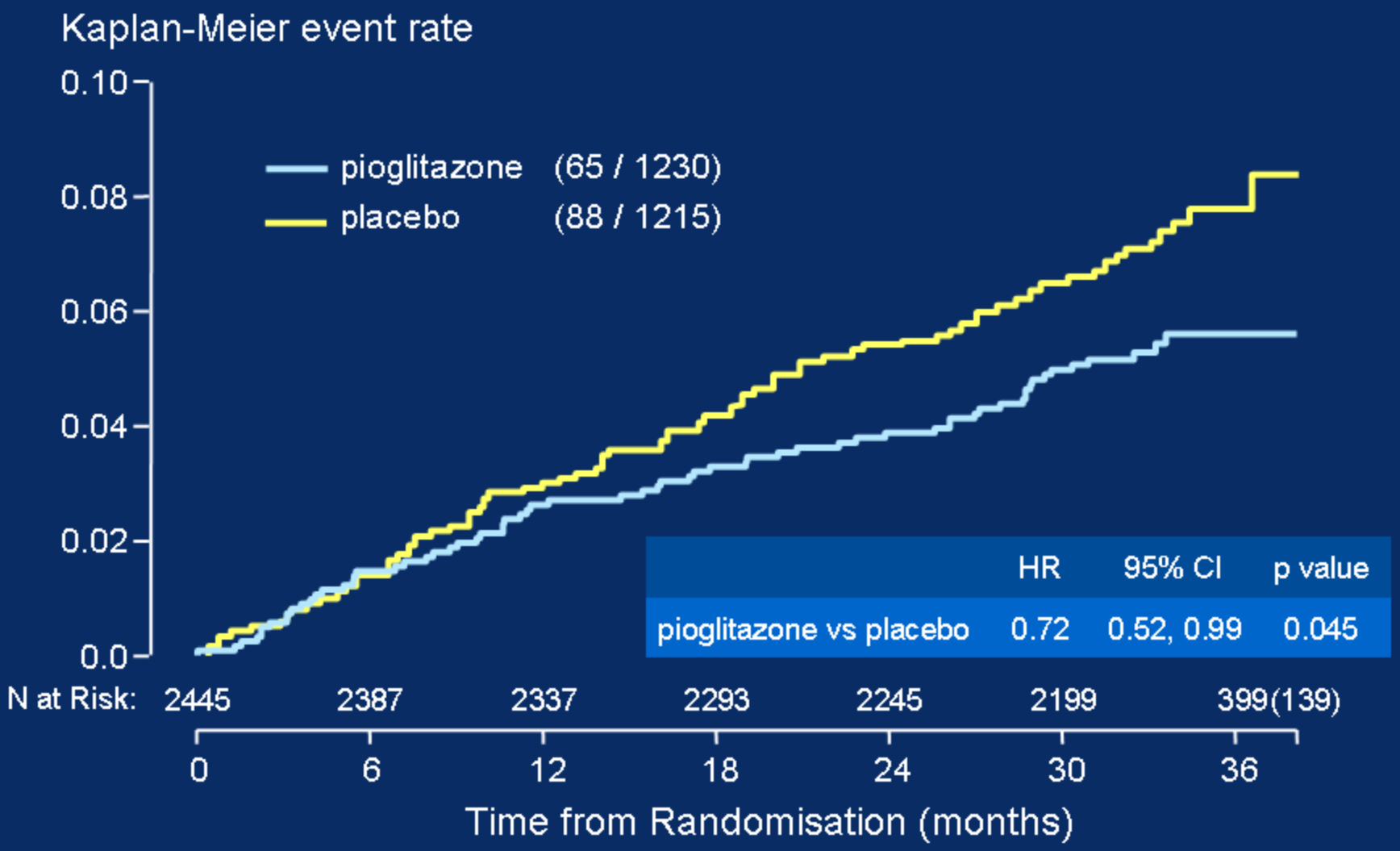
April 8th, 2014

By: Matthew Dennis

A US jury ordered Takeda and Eli Lilly to pay a combined $9 billion in punitive damages after finding that the companies concealted the cancer risks associated with the diabetes therapy Actos (pioglitazone). The jury also awarded compensatory damages to the plaintiff of nearly $1.5 million in the first federal lawsuit related to the drug to go to trial.

Specifically, the jury ordered Takeda to pay punitive damages of $6

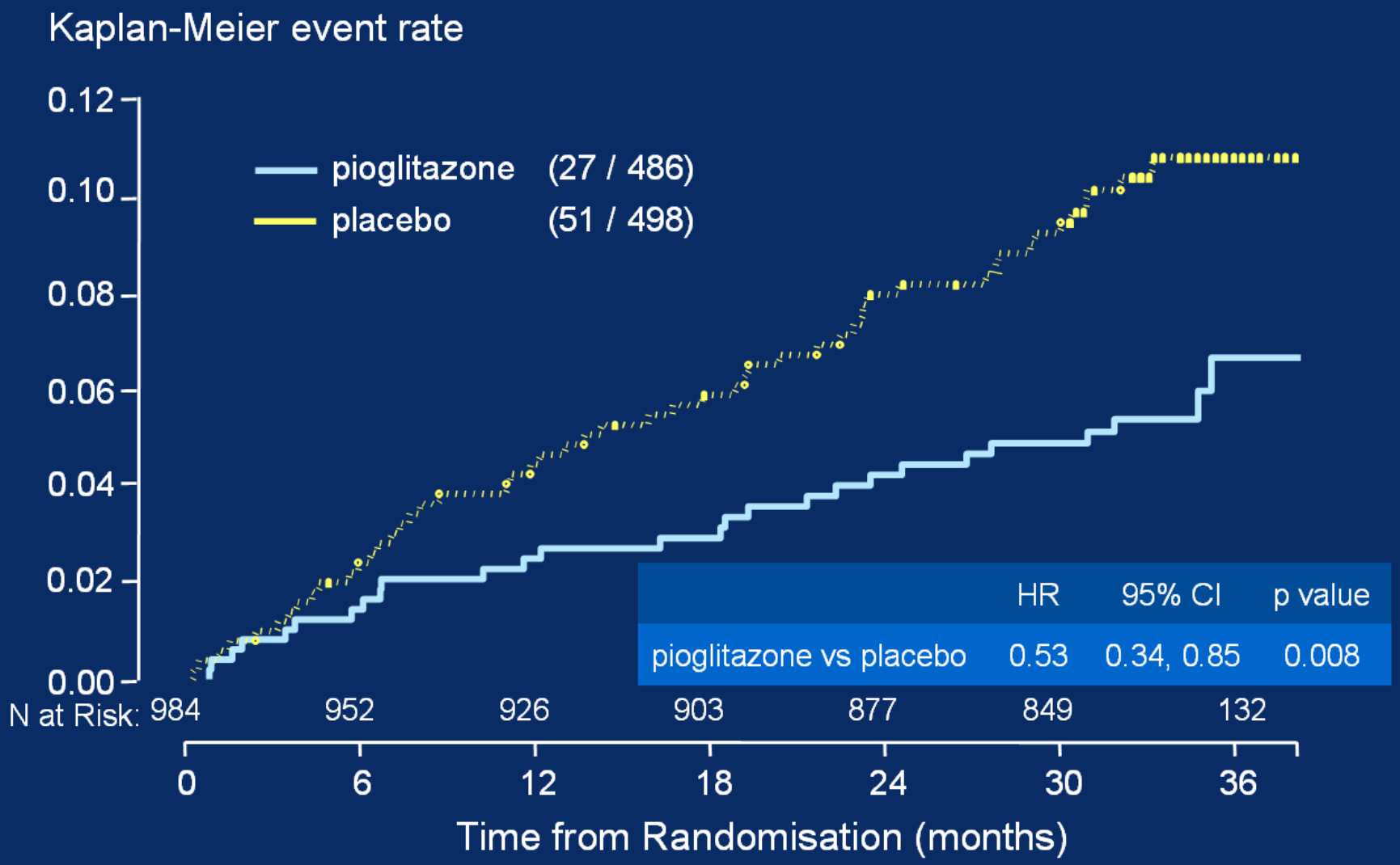
Time to Fatal/Non-fatal MI (excluding silent MI)



Erdmann E, AHA November 2005, Dallas

proactive-results.com

Time to Fatal or Non-Fatal Stroke in Patients with Previous Stroke



Wilcox RG et al, Stroke 2007; 38: 865-873

The ABCD Debate:

This house believes that incretin based therapies should continue to be used for people with type 2 diabetes

For the motion: Dr Bob Ryder,
Consultant Physician and Diabetologist,
City Hospital, Birmingham

May 2, 2014

Sandwell and West Birmingham Hospitals NHS
NHS Trust

Where EVERYONE Matters

Disclosures

- Bob Ryder has received speaker fees, consultancy fees and/or educational sponsorships from Bristol-Myers Squibb/AstraZeneca Alliance, Eli Lilly, GlaxoSmithKline, Novo Nordisk, Sanofi-Aventis and Takeda

David versus Goliath

Pharma

Edwin

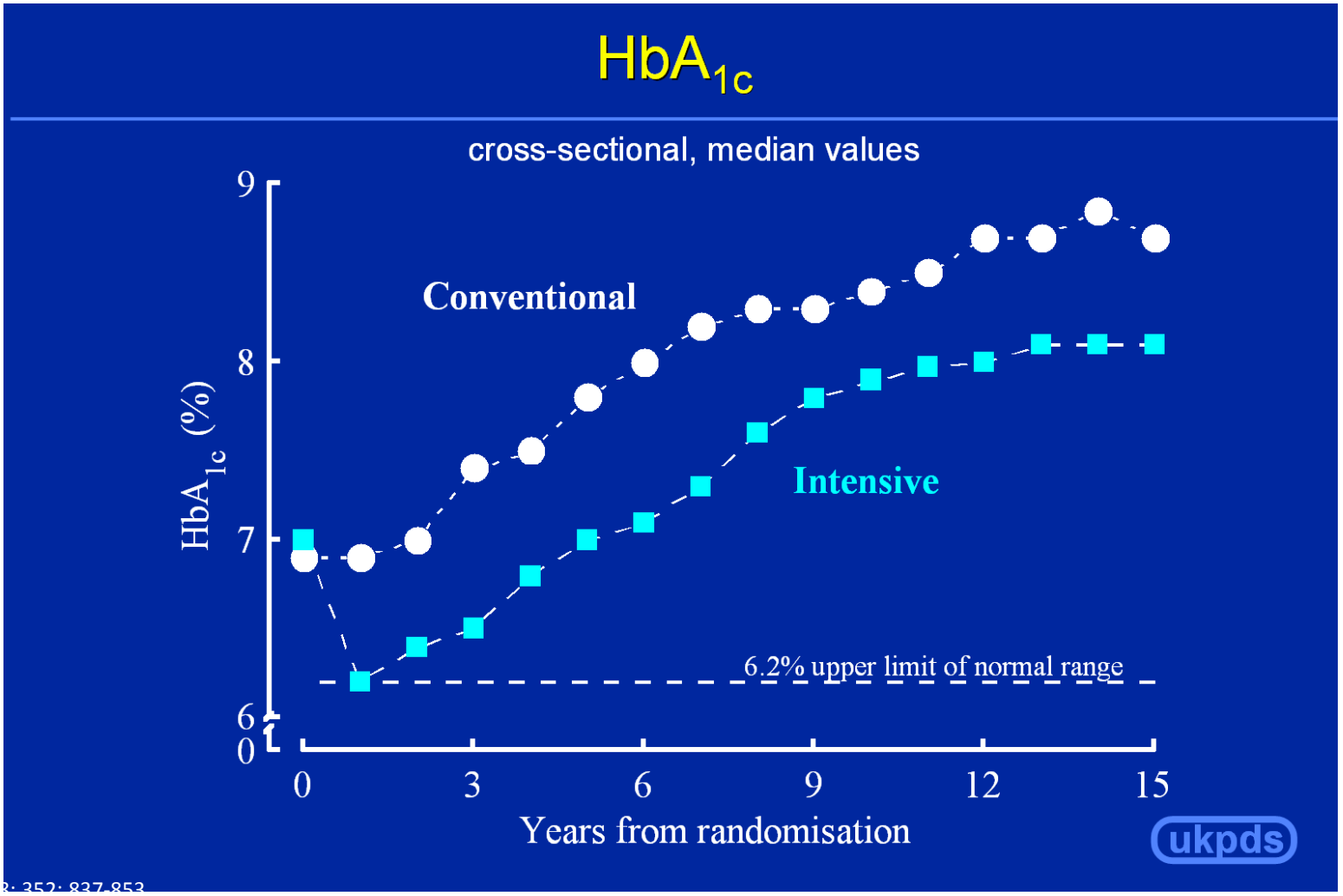
David versus Goliath

Edwin

Bob

David versus Goliath

Diabetes management in the era of only metformin, sulphonylureas and insulin

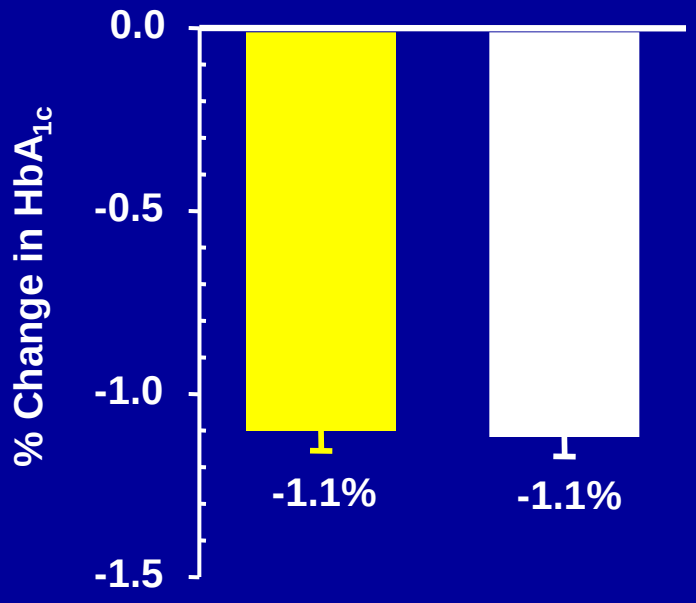


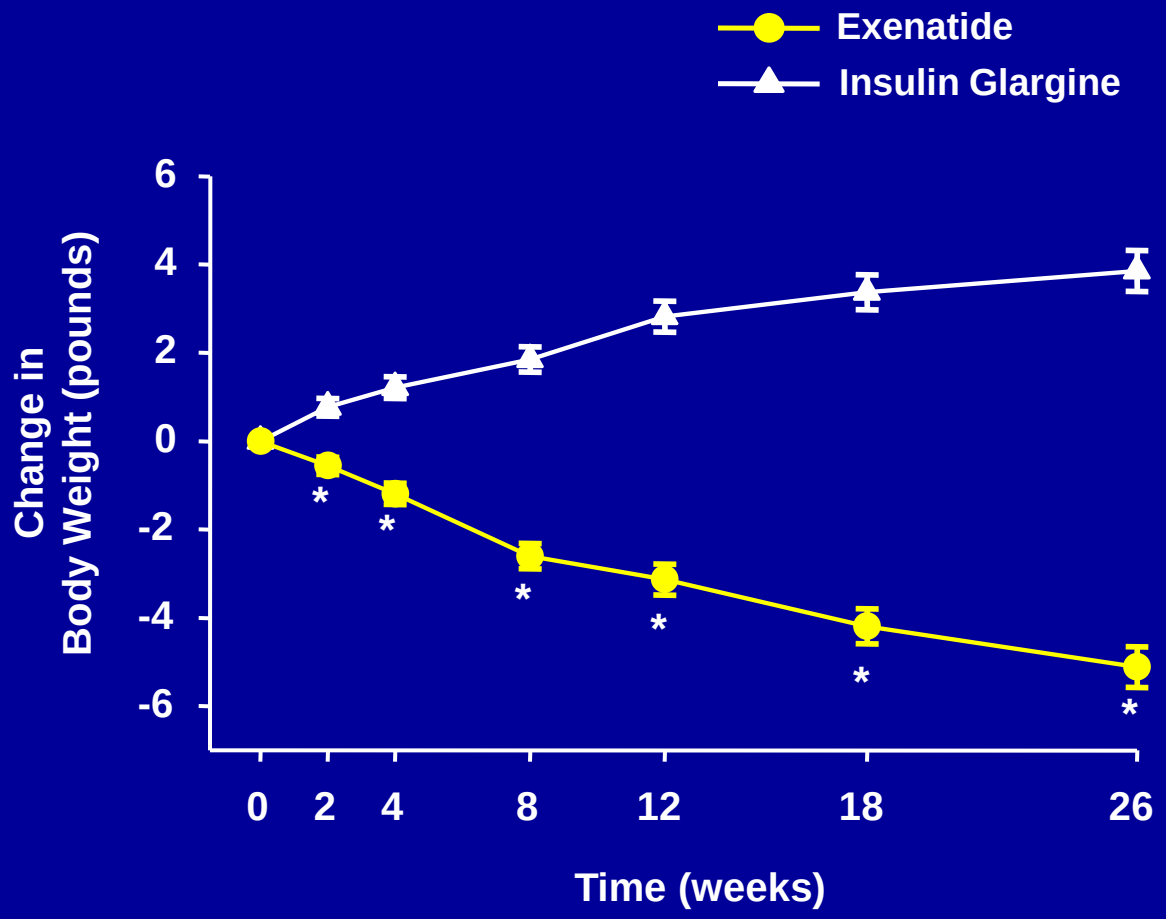
UK exenatide launch meeting, Glasgow, March 2007

UK exenatide launch meeting, Glasgow, March 2007

- “ … and then the patient hugged me!”

Exenatide/Insulin Glargine Comparator Trial:
Equivalent reductions in HbA1c but weight increase with insulin, weight loss with exenatide





Heine RJ, et al. *Ann Intern Med.* 2005;143:559-569.

Mrs KU, age 55, type 2 diabetes 18 years, on insulin 8 years

- June 2008
- Wt = 87 kg
- BMI = 35.3
- A1c = 9.0%
- Insulin 82 units, Repaglinide 4mg tds, Metformin 1gm BD

Prediction if stay within guidelines – keep titrating the insulin

- June 2008
- Wt = 87 kg
- BMI = 35.3
- A1c = 9.0%
- Insulin 82 units, Repaglinide 4mg tds, Metformin 1gm BD

- April 2011
- Wt = 93 kg
- BMI = 37.7
- A1c = 8.2%
- Insulin 132 units, Repaglinide 4mg tds, Metformin 1gm BD

Exenatide – coming off insulin, improving control, and losing weight

- June 2008
- Wt = 87 kg
- BMI = 35.3
- A1c = 9.0%
- Insulin 82 units, Repaglinide 4mg tds, Metformin 1gm BD

- April 2011
- Wt = 65 kg
- BMI = 26.7
- A1c = 7.2%
- Exenatide 10ug BD, Metformin 1gm BD

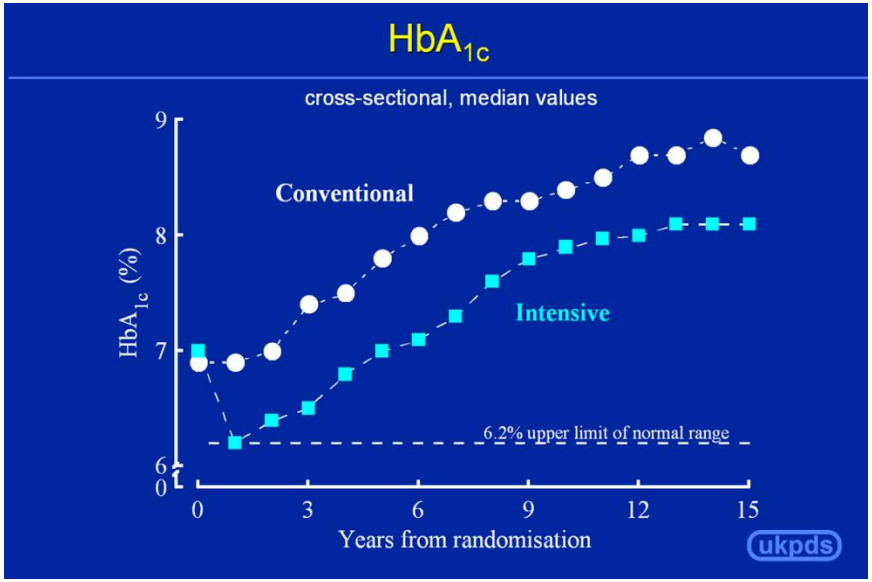
Sitagliptin – launched 2007

- Once daily tablet
- Reduces HbA1c
- Weight neutral or even slight weight loss
- No hypos
- No side effects!


FOTOSEARCH

- GLP-1 receptor agonists
  - Exenatide
  - Liraglutide
  - Exenatide QW
  - Lixisenatide
- DPP4 inhibitors
  - Sitagliptin
  - Vildagliptin
  - Saxagliptin
  - Linagliptin
  - Alogliptin

- Metformin
- Sulphonylureas
- Insulin



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BMJ

BMJ 2013;346:f1263 doi: 10.1136/bmj.f1263 (Published 27 February 2013)

EDITORIALS

GLP-1 based agents and acute pancreatitis

Drug safety falls victim to the three monkey paradigm

Edwin A M Gale *emeritus professor of diabetic medicine*

Department of Diabetes and Metabolism, Southmead Hospital, Bristol BS10 5NB, UK

Investment companies knew that the Food and Drug Administration safety database carried a signal for acute pancreatitis with the antidiabetic drug exenatide (a glucagon-like peptide 1 (GLP-1) agonist) in 2006, a year before the agency alerted doctors[1]—a curious reflection on the way we mix business with medicine. The signal had reached astronomical dimensions (more than 10 times that in control drugs) by 2011 and has accelerated since.[2] Furthermore, all GLP-1 based agents that have been on the market for more than two years have also generated a signal for acute pancreatitis, suggesting a class effect.

The regulators asked companies to provide more data, and companies have responded with studies showing that acute pancreatitis is more common in diabetes than previously thought and that clear evidence of an increased risk of pancreatitis with GLP-1 based treatments is lacking.[3] Warnings on the label notwithstanding, the industry has been able to maintain that the problem does not exist—and has a huge incentive to do so.

This is no longer tenable. A report in *JAMA Internal Medicine* describes a case-control study of more than a million people with diabetes, which yielded 1269 cases of acute pancreatitis in people aged 35-64 years using exenatide or sitagliptin, and an equal number of cases in people on non-GLP based drugs for diabetes. However, after multiple adjustments, current users and recent users (one month to two years) of GLP-1 based treatments had a twofold increased risk of acute pancreatitis (adjusted odds ratio 2.24 (95% confidence interval 1.36 to 3.68) for current use and 2.01 (1.27 to 3.18) for recent use) compared with those taking non-GLP based drugs for diabetes.[4] A company sponsored study previously found an increase in episodes of pancreatitis in recent users of exenatide, but it discounted the observation because those affected were no longer taking the drug.[5]

Should we be worried about this? Very much so. GLP-1 is a pleiotropic agent that has many actions apart from its therapeutic effects in promoting insulin secretion, inhibiting glucagon release, delaying gastric emptying, and reducing appetite. It also interacts, for example, with receptors in the heart, kidneys, thyroid, and exocrine pancreas. Furthermore, GLP-1 is a very short acting peptide, and the consequences of long term pharmacological stimulation in humans are unknown. GLP-1 promotes cell replication in some tissues, and it was hoped that it would promote pancreatic β cell regeneration until this action was found to be restricted to immature rodents. This may have distracted attention from the fact that it also stimulates pancreatic duct cells to divide, regardless of age. It has been known for more than a decade that animal pancreas tissue increases in weight on exposure to GLP-1 and that this must represent overgrowth of the exocrine pancreas.[5]

Further observations in experimental animals prompted the hypothesis that overgrowth of pancreatic duct cells produces occasional obstruction of the smallest ducts, with the potential to cause subclinical pancreatic inflammation in many users and full blown acute pancreatitis in rare instances.[6] Acute pancreatitis is unpleasant enough, but the major concern relates to subclinical inflammation of the pancreas. Postmortem analysis of humans exposed to GLP-1 based agents has yet to be reported, but it is well known that concentrations of pancreatic enzymes rise in animals and humans taking GLP-1 based drugs compared with other treatments for diabetes. Companies have modestly omitted these data from their published trials, sometimes with the comment that no "clinically significant" changes were seen. As a result, there is only one formal description of the phenomenon—from an independent group—in the literature.[7] Subclinical increases in enzyme concentrations may not prove subclinical pancreatitis, but they provide no reassurance about its absence.

One reason why the merest possibility of pancreatitis has been contested so vigorously is that all forms of pancreatitis, clinical or subclinical, predispose to carcinoma of the pancreas. The harbingers of this unpleasant cancer, known as pancreatic intraepithelial lesions, are widely present as potential seeds of cancer in the adult population. These lesions carry the GLP-1 receptor, as do pancreatic carcinomas. Increased reporting of pancreatic cancer was independently noted in both the FDA and German regulatory databases.[2 8]

Why have the companies been so slow to respond to this threat? Because of the "three monkey paradigm," which operates as follows. Companies are legally responsible for monitoring the safety of their own products, but self evidently cannot be held responsible for tackling a safety concern that does not exist. A concern that can be plausibly doubted or denied carries no legal

Gale EAM. Br Med J 2013; 346: f1263

BMJ

BMJ 2013;346:f2607 doi: 10.1136/bmj.f2607 (Published 23 April 2013)

NEWS

Reports of pancreatitis are 20-30 times more likely with GLP-1 drugs, analysis finds

Deborah Cohen

BMJ

A class of antidiabetes drugs is associated with an increase in safety alerts for pancreatitis and pancreatic cancer, a new analysis has found.

The Institute for Safe Medication Practices, a US non-profit organisation that promotes the safe use of drugs, monitored reports of serious adverse events to the US Food and Drug Administration from 1 July 2011 to 30 June 2012 concerning five glucagon-like peptide-1 (GLP-1) based agents (exenatide, liraglutide, sitagliptin, saxagliptin, and linagliptin) used to lower blood glucose concentrations.

It compared these against the rates of adverse event reporting for a control group of drugs comprising other drugs used to treat type 2 diabetes (three sulfonylureas and metformin) and drugs for treating other diseases.

GLP-1 is one of the many hormones involved in the complex process of regulating blood glucose concentrations, and the drugs that modify the circulating GLP-1 concentration do so in one of two ways. Exenatide and liraglutide are analogues of GLP-1 itself and are taken by injection. Sitagliptin, saxagliptin, and linagliptin are oral agents that prevent the rapid breakdown of GLP-1 by inhibiting the enzyme dipeptidylpeptidase-4.

The institute's analysis, published in its *Quarterwatch* report, found that after adjusting for differences in report characteristics the injectable drugs were 28.5 times (95% confidence interval 17.4 to 46.4 times) as likely to result in reports of pancreatitis than the controls.[1] The three oral agents were 20.8 (12.6 to 34.5) times as likely as controls to result in reports of pancreatitis.

The two injectable drugs and three oral agents all had greatly increased adjusted odds of being associated with reported cases of pancreatic cancer—23.3 (5.7 to 95.1) and 13.5 (3.1 to 58.5), respectively—when compared with the control drugs. However, the two newest drugs, linagliptin and saxagliptin, had just a single reported case each.

Furthermore, the injectable GLP-1 analogues, exenatide and liraglutide, were associated with reports of thyroid cancer, but the three oral agents were not, the report said.

However, the data should be interpreted with caution, the authors warned. The submission of an individual report does not establish that the drug caused the event—only that someone suspected a relation. They also point out that an association in adverse event data does not indicate how often this adverse event might occur.

Quarterwatch is not the first publication to report the relation between this class of drugs and pancreatitis, pancreatic cancer, and thyroid cancer. A study published in *Gastroenterology* in 2011 found that safety signals were associated with some GLP-1 based drugs.[2]

The *Quarterwatch* authors said that prior studies involving animal and human tissue indicated that the drugs might be cancer promoters and pointed to the fact that premalignant pancreatic lesions have GLP-1 receptors.

The *BMJ* asked the companies that make the drugs whether, if there was a risk that the GLP-1 receptor was expressed in many different places, patients would be at risk of unwanted proliferation. None answered the question directly.

The *Quarterwatch* authors concluded, "These data and other recent studies establish the need to reassess the safety of this class of drugs. It underlines the truth of the observation that drugs have many effects and the measured benefit—in this case lowered blood sugar levels—is only one. Not enough is known about the long-term pathophysiological effects of these drugs on the pancreas and thyroid."

Drug regulators in the United States and European Union told the *BMJ* that they were conducting their own assessment of non-clinical and adverse reaction data on the drugs.

1 Institute for Safe Medication Practices. Perspectives on GLP-1 agents for diabetes. 18 Apr 2013. www.ismp.org/QuarterWatch/pdfs/2012Q3.pdf.
2 Cohen D. Journal withdraws article after complaints from drug manufacturers. *BMJ* 2011;342:d2335.

Cite this as: *BMJ* 2013;346:f2607

Cohen D. Br Med J 2013; 346: f2607

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Next on 4 8pm, Mon 25 Nov

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Dispatches is Channel 4's award-winning investigative current affairs programme

Diets, Drugs and Diabetes

Dr Deborah Cohen, investigations editor at the British Medical Journal, examines a new generation of diabetes drugs that some drug companies hope could also be a magic treatment for obesity.

See more

BMJ

BMJ 2013;346:f3680 doi: 10.1136/bmj.f3680 (Published 10 June 2013)

FEATURE

DIABETES DRUGS

Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed?

Incretin mimetics have been called "the darlings of diabetes treatment" and they may soon also be licensed for treating obesity. But a *BMJ* investigation has found growing safety concerns linked to the drugs' mechanism of action. **Deborah Cohen** asks why patients and doctors have not been told.

Deborah Cohen *investigations editor*

BMJ, London WC1H 9JR, UK

They've been touted as the "new darlings of diabetes treatment"—the biggest breakthrough since the discovery of insulin nearly a hundred years before. The so called incretin therapies—glucagon-like peptide-1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors—looked as if they might change the face of type 2 diabetes. Their dual action of switching on insulin and suppressing glucagon to help control blood glucose was the ultimate in diabetes care.

The promise of a Nobel prize for the investigators loomed large. Scientists had discovered a treatment that could potentially modify disease progression. Studies in experimental animals showed that GLP-1 caused a proliferation in new insulin producing β cells. The hope was that these new cells might be able to replace those that died off in the course of human diabetes.

Nor did the promise end there. GLP-1 acts on the brain to makes people feel less hungry and the more powerful drugs aid weight loss—rather than weight gain like many antidiabetic drugs before them.

It's an effect companies are seeking to market in its own right. Spurred on by the US Food and Drug Administration's willingness to license new obesity treatment, Novo Nordisk's chief science officer Mads Krogsgaard Thomsen said last year that the "political establishment in the US now knows that behaviour change alone is not enough."[1]

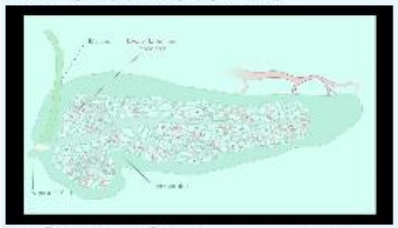
His company's drug, liraglutide, is in the process of late stage clinical tests, which Thomsen says show promising results.

But an investigation by the *BMJ* suggests Thomsen's confidence might be optimistic. Concerns held by some specialists about the potential side effects of GLP-1 drugs have emerged into the mainstream after both the FDA and the European Medicines Agency announced in March that they would launch a review into whether the drugs may cause or contribute to the development of pancreatic cancer.

As yet neither agency has reached any conclusions, but they are meeting to discuss the matter later this month. And, as this investigation has found, for the regulators it is not a new

dcohen@bmj.com

Video on bmj.com (see also http://bmj.com/video)



Cohen D. Br Med J 2013; 346: f3680

BMJ conclusion, echoed in the editor's summary of the issue on June 12, 2013

- '.. after careful reflection, most patients and clinicians may opt to avoid GLP-1-based drugs at all, or to avoid using them early in the disease course, alone, or for long periods'

Godlee F. Br Med J 2013; 346: f3819

Victor Montori, Professor of Medicine, Mayo Clinic

Fiona Godley, Editor, BMJ

- So what is this evidence which has led to BMJ coming to such a conclusion against GLP-1-based therapies, regardless of the obvious benefits of these therapies …..

The BMJ case was based on:

- Animal studies
- A observational study by Singh and colleagues
- A study by Butler and colleagues of the pancreases from organ donors with and without diabetes
- Two papers looking at reports in the US Food and Drug Administration adverse event reporting system

Animal studies – case for a risk

- In some studies of GLP1-based therapies given to rodents, histological changes are found suggestive of pancreatic damage, with cases of pancreatitis occurring
- From this an hypothesis has emerged, supported by some of the animal studies. Hypothesis:
  - GLP1-based therapies lead to proliferation of pancreatic acinar and duct cells and an increase in pancreatic weight
  - The duct cell proliferation leads to duct occlusion, which causes back pressure on the pancreas, thus stressing the acinar cells
  - Under such stress, digestive enzymes are released triggering pancreatitis
  - In some animal studies there has been evidence of chronic pancreatitis and preneoplastic lesions and it has been hypothesised that these changes could lead to pancreatic cancer

Butler PC et al. Diabetes Care 2013; 36: 2118–2125

Animal studies – weaknesses in the case for a risk

- The changes are not reproducible across all animal studies and do not necessarily occur with all GLP1-based therapies
- With sitagliptin tissue samples from preclinical studies in multiple animal species did not reveal any evidence of treatment-related pancreatitis

Ryder REJ. Diabet Med 2013; 30: 1148-1155

Doses used in animal experiments

- Regulatory authorities deliberately choose high doses for animal studies
- In the rat study in which one of the eight rats “developed hemorrhagic pancreatitis following exposure to sitagliptin, and some of the remaining animals showed marked acinar to ductal metaplasia, a potentially premalignant change characteristic of chronic pancreatitis”, the dose of sitagliptin used was 200 mg/kg over 12 weeks.
- Giving such a dose to a 70 kg man would amount to 14 grams of sitagliptin/day – i.e. 140 x 100mg tablets each day
- Perhaps such a dose given to humans over 12 weeks would cause similar changes to the human pancreas
- That does not necessarily mean that the same could happen in man at the standard 100 mg/day dose used in routine clinical practice

Ryder REJ. Diabet Med 2013; 30: 1148-1155

Conclusion from animal experiments

- The changes reported from some animal experiments are sufficient to promote vigilance …

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ORIGINAL INVESTIGATION

ONLINE FIRST

Glucagonlike Peptide 1–Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus

A Population-Based Matched Case-Control Study

Sonal Singh, MD, MPH; Hsien-Yen Chang, PhD; Thomas M. Richards, MS; Jonathan P. Weiner, DrPH; Jeanne M. Clark, MD, MPH; Jodi B. Segal, MD, MPH

Importance: Acute pancreatitis has significant morbidity and mortality. Previous studies have raised the possibility that glucagonlike peptide 1 (GLP-1)–based therapies, including a GLP-1 mimetic (exenatide) and a dipeptidyl peptidase 4 inhibitor (sitagliptin phosphate), may increase the risk of acute pancreatitis.

Objective: To test whether GLP-1–based therapies such as exenatide and sitagliptin are associated with an increased risk of acute pancreatitis. We used conditional logistic regression to analyze the data.

Design: Population-based case-control study.

Setting: A large administrative database in the United States from February 1, 2005, through December 31, 2008.

Participants: Adults with type 2 diabetes mellitus aged 18 to 64 years. We identified 1269 hospitalized cases with acute pancreatitis using a validated algorithm and 1269 control subjects matched for age category, sex, enrollment pattern, and diabetes complications.

Main Outcome Measure: Hospitalization for acute pancreatitis.

Results: The mean age of included individuals was 52 years, and 57.45% were male. Cases were significantly more likely than controls to have hypertriglyceridemia (12.92% vs 8.35%), alcohol use (3.23% vs 0.24%), gallstones (9.06% vs 1.34), tobacco abuse (16.39% vs 5.52%), obesity (19.62% vs 9.77%), biliary and pancreatic cancer (2.84% vs 0%), cystic fibrosis (0.79% vs 0%), and any neoplasm (29.94% vs 18.05%). After adjusting for available confounders and metformin hydrochloride use, current use of GLP-1–based therapies within 30 days (adjusted odds ratio, 2.24 [95% CI, 1.36-3.68]) and recent use past 30 days and less than 2 years (2.01 [1.37-3.18]) were associated with significantly increased odds of acute pancreatitis relative to the odds in nonusers.

Conclusions and Relevance: In this administrative database study of US adults with type 2 diabetes mellitus, treatment with the GLP-1–based therapies sitagliptin and exenatide was associated with increased odds of hospitalization for acute pancreatitis.

JAMA Intern Med.
Published online February 25, 2013.
doi:10.1001/jamainternmed.2013.2720

Author Affiliations:
Department of Medicine, The Johns Hopkins University School of Medicine (Drs Singh, Clark, and Segal), and Center for Public Health and Human Rights (Dr Singh) and Department of Health Policy and Management (Drs Chang and Weiner and Mr Richards), The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

THE GLUCAGONLIKE PEPTIDE 1 (GLP-1)–based therapies include a GLP-1 mimetic, exenatide, and a dipeptidyl peptidase 4 inhibitor, sitagliptin phosphate. These therapies are used in patients with type 2 diabetes mellitus to lower blood glucose levels. Exenatide is a subcutaneous injectable GLP-1 agonist that enhances glucose-mediated insulin secretion. Sitagliptin is an oral dipeptidyl peptidase 4 inhibitor that prevents the proteolysis of endogenous GLP-1.[1]

Sitagliptin and exenatide have been shown to cause acute pancreatitis in rodent models via amplification of ductal replication and induction of acinar to ductal metaplasia.[2,3] Mouse models have also shown that GLP-1–based therapy may induce focal proliferation in the exocrine pancreas and accelerate formation of dysplastic lesions and pancreatitis.[4] Reports

See related article

of spontaneous acute pancreatitis in humans have been published[5,6]; however, the strength of this association and causality cannot be inferred from these reports.

Previous observational studies of this association have yielded inconsistent re-

Singh S, et al. JAMA Intern Med 2013; 173: 534–539

- “an independent analysis of health insurance data published in February found that people taking exenatide and sitagliptin were at twice the risk of hospital admission for acute pancreatitis compared with people taking other antidiabetic drugs”

Cohen D. Br Med J 2013; 346: f3680

What are the common causes of pancreatitis?

- Most common
  - gall bladder disease (gall stones)
  - alcoholism
- Other common
  - drugs
  - infectious agents
  - hypertriglyceridemia
  - trauma
  - pancreatic ductal obstruction
  - Procedures – ERCP etc
  - Idiopathic

Banks PA. Gastrointest Endosc 2002; 56: S226-230
Venneman NG et al. Ann Hepatol 2003; 2: 30-35
Sekimoto M et al. J Hepatobil Pancreat Surg 2006; 13: 10-24

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Who are these people who get gall bladder disease and as a result are at high risk of pancreatitis?

Gall bladder disease at the birth of clinical medicine

Gall bladder disease at the birth of clinical medicine

- Fair
- Fat
- Fertile
- Female
- Forty

Who are these people who get gall bladder disease and as a result are at high risk of pancreatitis?

- Fair
- Fat
- Fertile
- Female
- Forty

Who are these people who get gall bladder disease and as a result are at high risk of pancreatitis?

- Fair
- Fat people also get type 2 diabetes !
- Fertile
- Female
- Forty

Who are these people who get gall bladder disease and as a result are at higher risk of pancreatitis?

- Fair
- Fat people with diabetes are more likely to get GLP-1 based therapies!
- Fertile
- Female
- Forty

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Author Affiliations: Department of Medicine, The Johns Hopkins University School of Medicine (Drs Singh, Clark, and Segal), and Center for Public Health and Human Rights (Dr Singh) and Department of Health Policy and Management (Drs Chang and Weiner and Mr Richards), The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

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Sitagliptin and exenatide have been shown to cause acute pancreatitis in rodent models via amplification of ductal replication and induction of acinar to ductal metaplasia.[2,3] Mouse models have also shown that GLP-1–based therapy may induce focal proliferation in the exocrine pancreas and accelerate formation of dysplastic lesions and pancreatitis.[4] Reports

See related article

of spontaneous acute pancreatitis in humans have been published[5,6]; however, the strength of this association and causality cannot be inferred from these reports.

Previous observational studies of this association have yielded inconsistent re-

Cases were significantly more likely than controls to have hypertriglyceridemia (12.92% vs 8.35%), alcohol use (3.23% vs 0.24%), gallstones (9.06% vs 1.34), obesity (19.62% vs 9.77%),

. After adjusting for available confounders

GLP-1–based therapies

were associated with significantly increased odds of acute pancreatitis relative to the odds in nonusers.

Singh S, et al. JAMA Intern Med 2013; 173: 534–539

JAMA Intern Med. 2013;173(7):534-539. doi:10.1001/jamainternmed.2013.2720.

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Article | Figures | Tables | References | Comments (2)

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Acute pancreatitis and glucagon like peptide 1-based therapies – caution over what to conclude from observational studies

Posted on June 10, 2013

Dr REJ Ryder MD FRCP, Dr A Blann PhD FRCPath, Dr KY Thong MBBS FRACP

Sandwell and West Birmingham Hospitals, UK. Diabetes(Dr. Ryder); Trust statistician(Dr. Blann); Rockingham General Hospital, Perth, Australia. Diabetes(Dr. Thong)

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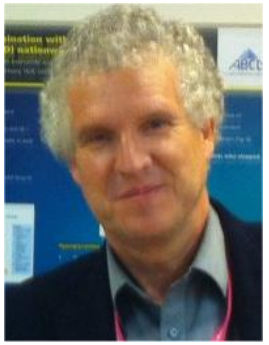

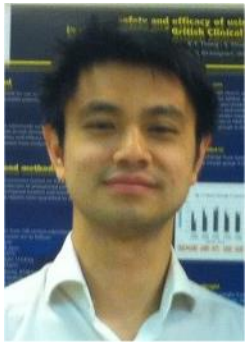

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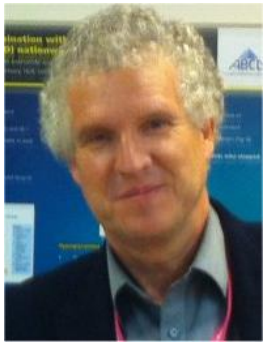

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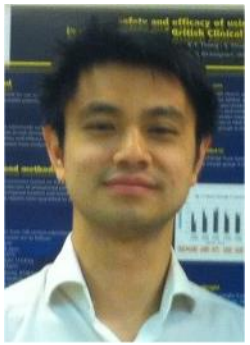

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Problems with Singh's observational study

- Thus the association found by Singh and colleagues could be because patients with diabetes and obesity are at the same time:
  - more likely to have gall stones and hypertriglyceridaemia increasing their risk of pancreatitis
  - more likely to be treated with GLP1-based therapies

Ryder REJ. Diabet Med 2013; 30: 1148-1155

Problems with Singh's observational study

- The other observational studies have confirmed that obese type 2 diabetes subjects are more prone to developing acute pancreatitis than people without diabetes, but have not found any link between GLP1-based therapies and pancreatitis

Ryder REJ. Diabet Med 2013; 30: 1148-1155

ABCD nationwide audits of GLP-1RAs

- The audits combined contain data on 12,727 ‘real-world’ UK patients with Type 2 diabetes treated with either exenatide or liraglutide .

http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsExenatide.htm
http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsLiraglutide.htm

Rates of acute pancreatitis in people with type 2 diabetes

- Not on GLP-1 based therapy:
  - between 5 and 56 per 10,000 person years
- ABCD nationwide exenatide audit
  - 12 per 10,000 person year
- ABCD nationwide liraglutide audit
  - 10.8 per 10,000 person years

Ryder REJ et al. Diabet Med 2013; 30(12): 1510-1511

Rates of acute pancreatitis in people with type 2 diabetes

- Thus the rates of acute pancreatitis in the ABCD exenatide and liraglutide audits are at the low end of the rates expected for people with type 2 diabetes in general.

AND

- 75% of the cases of acute pancreatitis in the ABCD exenatide and liraglutide audits had other causes for acute pancreatitis, in particular gall bladder disease

Ryder REJ et al. Diabet Med 2013; 30(12): 1510-1511

The BMJ case was based on:

- Animal studies
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BMJ

BMJ 2013;346:f2607 doi: 10.1136/bmj.f2607 (Published 23 April 2013)

NEWS

Reports of pancreatitis are 20-30 times more likely with GLP-1 drugs, analysis finds

Deborah Cohen

BMJ

A class of antidiabetes drugs is associated with an increase in safety alerts for pancreatitis and pancreatic cancer, a new analysis has found.

The Institute for Safe Medication Practices, a US non-profit organisation that promotes the safe use of drugs, monitored reports of serious adverse events to the US Food and Drug Administration from 1 July 2011 to 30 June 2012 concerning five glucagon-like peptide-1 (GLP-1) based agents (exenatide, liraglutide, sitagliptin, saxagliptin, and linagliptin) used to lower blood glucose concentrations.

It compared these against the rates of adverse event reporting for a control group of drugs comprising other drugs used to treat type 2 diabetes (three sulfonylureas and metformin) and drugs for treating other diseases.

GLP-1 is one of the many hormones involved in the complex process of regulating blood glucose concentrations, and the drugs that modify the circulating GLP-1 concentration do so in one of two ways. Exenatide and liraglutide are analogues of GLP-1 itself and are taken by injection. Sitagliptin, saxagliptin, and linagliptin are oral agents that prevent the rapid breakdown of GLP-1 by inhibiting the enzyme dipeptidylpeptidase-4.

The institute's analysis, published in its *Quarterwatch* report, found that after adjusting for differences in report characteristics the injectable drugs were 28.5 times (95% confidence interval 17.4 to 46.4 times) as likely to result in reports of pancreatitis than the controls.[1] The three oral agents were 20.8 (12.6 to 34.5) times as likely as controls to result in reports of pancreatitis.

The two injectable drugs and three oral agents all had greatly increased adjusted odds of being associated with reported cases of pancreatic cancer—23.3 (5.7 to 95.1) and 13.5 (3.1 to 58.5), respectively—when compared with the control drugs. However, the two newest drugs, linagliptin and saxagliptin, had just a single reported case each.

Furthermore, the injectable GLP-1 analogues, exenatide and liraglutide, were associated with reports of thyroid cancer, but the three oral agents were not, the report said.

However, the data should be interpreted with caution, the authors warned. The submission of an individual report does not establish that the drug caused the event—only that someone suspected a relation. They also point out that an association in adverse event data does not indicate how often this adverse event might occur.

Quarterwatch is not the first publication to report the relation between this class of drugs and pancreatitis, pancreatic cancer, and thyroid cancer. A study published in *Gastroenterology* in 2011 found that safety signals were associated with some GLP-1 based drugs.[2]

The *Quarterwatch* authors said that prior studies involving animal and human tissue indicated that the drugs might be cancer promoters and pointed to the fact that premalignant pancreatic lesions have GLP-1 receptors.

The *BMJ* asked the companies that make the drugs whether, if there was a risk that the GLP-1 receptor was expressed in many different places, patients would be at risk of unwanted proliferation. None answered the question directly.

The *Quarterwatch* authors concluded, "These data and other recent studies establish the need to reassess the safety of this class of drugs. It underlines the truth of the observation that drugs have many effects and the measured benefit—in this case lowered blood sugar levels—is only one. Not enough is known about the long-term pathophysiological effects of these drugs on the pancreas and thyroid."

Drug regulators in the United States and European Union told the *BMJ* that they were conducting their own assessment of non-clinical and adverse reaction data on the drugs.

1 Institute for Safe Medication Practices. Perspectives on GLP-1 agents for diabetes. 18 Apr 2013. www.ismp.org/QuarterWatch/pdfs/2012Q3.pdf.
2 Cohen D. Journal withdraws article after complaints from drug manufacturers. BMJ 2011;342:d2335.

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Cite this as: *BMJ* 2013;346:f2607

Cohen D. Br Med J 2013; 346: f2607

Problems with interpreting from adverse event reporting systems

- It is widely known that there might be an association between pancreatic disease and GLP1-based therapies
- Not surprisingly therefore, when clinicians meet cases of these diseases in patients on the GLP1-based therapies, they will naturally report the cases
- Sulphonylureas and metformin have been used for decades and nobody is suspecting that there is an association between them and pancreatic disease; it is unlikely that clinicians will therefore report the cases where these conditions occur on those therapies
- A temporal analysis found “a striking influence of relevant FDA warnings on reporting of pancreatitis” (the so-called notoriety bias)
- Hence it is impossible to come to any conclusion based on the fact that there are more reports of pancreatic disease amongst patients on the new GLP1-based therapies compared to other much older drugs

Ryder REJ. Diabet Med 2013; 30: 1148-1155

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Pancreases from organ donors

- The study examined pancreases from organ donors –
  - 8 from patients with type 2 diabetes treated with incretin therapy (seven sitagliptin, one exenatide),
  - 12 from patients with diabetes not treated with incretin therapy
  - 14 controls without diabetes
- The study concluded that:
  - "in humans, incretin therapy resulted in a marked expansion of the exocrine and endocrine pancreatic compartments, the former being accompanied by increased proliferation and dysplasia, the latter by α cell hyperplasia with the potential for evolution into neuroendocrine tumors"

Alexandra Butler, Assistant Adjunct Professor of Medicine, Hillblom Islet Research Center, University of California at Los Angeles

Butler AE et al. Diabetes 2013; 62: 2595–2604

Khan's comments on the organ donors study

- There may have been patients with type 1 diabetes in the diabetes control group in view of their much younger age and greater use of insulin and the fact that two died with diabetic ketoacidosis
  - Magnetic resonance imaging has shown that pancreatic volume in type 1 diabetes is reduced
- There is a possibility that the increased β cell mass in patients treated with GLP1-based therapies could be due to the GLP1-based therapies reducing the increased β cell apoptosis observed in type 2 diabetes
- Preterminal clinical status of donors on prolonged life support has been shown to increase replication of both endocrine and non-endocrine cells and this could be another possible factor
- With regard to neuroendocrine tumours, we surely would have seen evidence of these by now in view of the millions of years of exposure that there has been to GLP1-based therapies. They are so rare that even a slight increase would have been noted if these tumours were occurring in incretin treated patients
- Patients who have undergone gastric bypass surgery experience increased GLP-1 levels similar to or higher than those observed with DPP-4 inhibitors without similar findings in both endocrine and exocrine tissue being reported despite the long-term exposure of many of these patients

Steven E. Kahn, Professor of Medicine, University of Washington

Diabetes 2013; 62: 2178–2180

The BMJ case was based on:

- Animal studies inconsistent, promote vigilance but NB dose factor
- A observational study by Singh and colleagues

Obese people get gall stones (pancreatitis risk) and diabetes (treated with incretin therapy)

- A study by Butler and colleagues of the pancreases from organ donors with and without diabetes significant study limitations - alternative explanations
- Two papers looking at reports in the US Food and Drug Administration adverse event reporting system notoriety bias

Meta-analysis of RCT'S: GLP-1 receptor agonists

- A meta-analysis of randomised controlled trials (RCTs) reviewed 28 RCTS from 170 articles which involved 10,910 patients treated with GLP1RAs and found only two reported cases of pancreatitis

Shyangdan DS et al. BMC Endocr Disord 2010; 10: 20
Barnett AH, O'Hare JP. Br Med J 2013; 347: f4382

Meta-analysis of RCT'S: DPP-4 inhibitors

- A meta-analysis combined the results from 53 RCTs that included 20,312 patients treated with different DPP-4 inhibitors did not find an increased risk of pancreatitis in DPP-4 treated patients
- A pooled analysis of 19 RCTs, comprising 10,246 patients treated for up to 2 years with sitagliptin revealed similar incidence rates of pancreatitis in patients treated with sitagliptin compared with those not treated with sitagliptin

Monami M et al. Exp Diabetes Res 2011; 27:57–64
Engel SS et al. Int J Clin Pract 2010; 64: 984–990

Long-term cardiovascular safety studies

Table 1 Long-term studies examining the safety of incretin-based therapies*†

Medication	Study name	ClinicalTrials.gov identifier	Comparator estimated	Number of subjects	Study start date	Estimated/confirmed study end date	Status (at 29 June 2013)
Saxagliptin (DPP-4 inhibitor)	SAVOR-TIMI53	NCT 01107886	Placebo	16492	May 2010	May 2013	Completed
Alogliptin (DPP-4 inhibitor)	EXAMINE	NCT 00968708	Placebo	5384	October 2009	June 2013	Completed
Lixisenatide (GLP-1 receptor agonist)	ELIXA	NCT 01147250	Placebo	6000	June 2010	May 2014	Recruiting
Sitagliptin (DPP-4 inhibitor)	TECOS	NCT 00790205	Placebo	14000	December 2008	December 2014	Active, not recruiting
Liraglutide (GLP-1 receptor agonist)	LEADER	NCT 01179048	Placebo	9340	August 2010	January 2016	Active, not recruiting
Exenatide (GLP-1 receptor agonist)	EXSCEL	NCT 01144338	Placebo	9500	June 2010	March 2017	Recruiting
Linagliptin (DPP-4 inhibitor)	CAROLINA	NCT 01243424	Glimepiride	6000	October 2010	September 2018	Active, not recruiting
Duraglutide (GLP-1 receptor agonist)	REWIND	NCT 01394952	Placebo	9622	July 2011	April 2019	Recruiting

*Studies presented in the order of estimated study end date.
†Source: ClinicalTrials.gov accessed on 29 June 2013 and for SAVOR-TIMI53 and EXAMINE, on 6 September 2013.
SAVOR-TIMI53, Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications; EXAMINE, Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); TECOS, Sitagliptin Cardiovascular Outcome Study (0431-082 AM1); LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long-Term Evaluation; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial: A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus; CAROLINA, Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes.

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Saxagliptin - SAVOR-TIMI RCT

- 16,492 patients randomised to saxagliptin or placebo and followed for a median on 2.1 years

Scirica B et al. N Engl J Med 2013;369:1317-26

Table 3. Safety End Points.

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	P Value*
	no. (%)		
Thrombocytopenia	55 (0.7)	65 (0.8)	0.36
Lymphocytopenia	49 (0.6)	40 (0.5)	0.40
Severe infection	590 (7.1)	576 (7.0)	0.78
Opportunistic infection	21 (0.3)	35 (0.4)	0.06
Hypersensitivity reaction	93 (1.1)	89 (1.1)	0.82
Bone fracture	241 (2.9)	240 (2.9)	1.00
Skin reaction	228 (2.8)	232 (2.8)	0.81
Renal abnormality	483 (5.8)	418 (5.1)	0.04
Any hypoglycemia†	1264 (15.3)	1104 (13.4)	<0.001
Major	177 (2.1)	140 (1.7)	0.047
Minor	1172 (14.2)	1028 (12.5)	0.002
Cancer	327 (3.9)	362 (4.4)	0.15
Any liver abnormality†	55 (0.7)	67 (0.8)	0.28
AST >3× ULN	60 (0.7)	61 (0.7)	0.93
AST >10× ULN	12 (0.1)	15 (0.2)	0.57
ALT or AST >3× ULN and total bilirubin >2× ULN	13 (0.2)	23 (0.3)	0.097
Any pancreatitis†	24 (0.3)	21 (0.3)	0.77
Acute: definite or possible	22 (0.3)	16 (0.2)	0.42
Acute: definite	17 (0.2)	9 (0.1)	0.17
Acute: possible	6 (0.1)	7 (0.1)	0.79
Chronic	2 (<0.1)	6 (0.1)	0.18

* P values were calculated with the use of a chi-square test or Fisher's exact test. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† Patients may have had more than one type of event.

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Table 2. Prespecified Clinical End Points.*

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

* Event rates and percentages are 2-year Kaplan–Meier estimates.

Scirica B et al. N Engl J Med 2013;369:1317-26

Alogliptin - Examine RCT

- 5380 patients randomised to alogliptin or placebo and followed for a median on 18 months

White WB et al. N Engl J Med. 2013 Oct 3;369(14):1327-35

Supplementary Table 2. Other Safety End Points

	Placebo (n=2679)	Alogliptin (n=2701)	P value*
Any Serious Adverse Event,	952 (35.5)	907 (33.6)	0.14
Serious hypoglycemia**	16 (0.6)	18 (0.7)	0.86
Any Adverse Event	2111 (78.8)	2160 (80.0)	0.30
Any hypoglycemia **	173 (6.5)	181 (6.7)	0.74
Pancreatitis†			
Acute	8 (0.3)	12 (0.4)	0.50
Chronic	4 (0.1)	5 (0.2)	1.00
Angioedema	13 (0.5)	17 (0.6)	0.58
Malignancy	51 (1.9)	55 (2.0)	0.77
Renal dialysis	22 (0.8)	24 (0.9)	0.88
Laboratory Results			
Serum aminotransferases >3 times upper limit of normal at any time during trial			
Alanine aminotransferase‡	46 (1.7)	64 (2.4)	0.10
Aspartate aminotransferase§	43 (1.6)	48 (1.8)	0.67

*P values were calculated by Fisher's exact test with no adjustment for multiple comparisons; **hypoglycemia was reported by site investigators; †terms included pancreatitis acute, relapsing pancreatitis, and pancreatitis; ‡The upper limit of normal for the alanine aminotransferase was 25 U/L. §The upper limit of normal for aspartate aminotransferase was 22 U/L

White WB et al. N Engl J Med. 2013 Oct 3;369(14):1327-35

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White WB et al. N Engl J Med. 2013 Oct 3;369(14):1327-35

ADA, EASD and IDF: joint recommendations concerning the use of incretin therapy and pancreatc disease

- “at this time, there is insufficient information to modify current treatment recommendations”.

http://easd.org/index.php?option=com_content&view=article&id=172

ABCD position statement

- “The strength of the data in support of GLP-1 based therapies causing pancreatic damage does not justify the alarm that has been caused to patients taking these therapies. By stopping these agents in response to the scare that has been created, harm to patients may occur because of the discontinuation of the agents in whom they were working well”

Practical Diabetes 2013; 30(9): 388-391

What is the real risk to overweight patients with type 2 diabetes

- Microvascular disease, including retinopathy and blindness, nephropathy and renal failure, and neuropathy, foot ulceration and amputation

What is the real risk to overweight patients with type 2 diabetes

- Microvascular disease, including retinopathy and blindness, nephropathy and renal failure, and neuropathy, foot ulceration and amputation
  - GLP-1 based therapies improve glycaemic control and by implication (based on UKPDS*) the likelihood of microvascular complications

*Stratton IM et al, Br Med J 2000; 321: 405–412

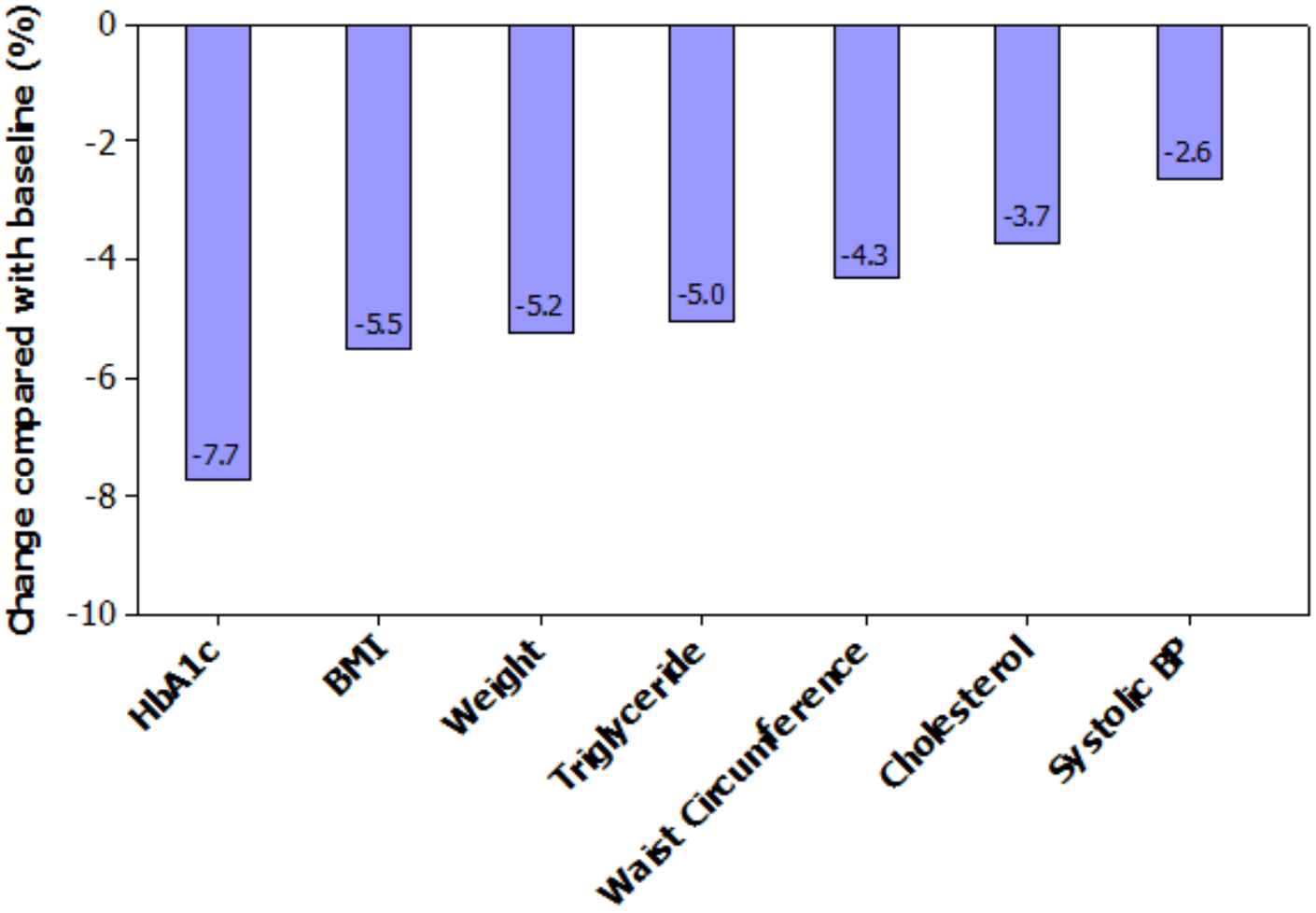
What is the real risk to overweight patients with type 2 diabetes

- Microvascular disease, including retinopathy and blindness, nephropathy and renal failure, and neuropathy, foot ulceration and amputation
- Macrovascular disease, of particular importance to the overweight patients with type 2 diabetes, leading to premature death, myocardial infarction and stroke

- GLP-1 receptor agonists reduce the major risk factors for cardiovascular disease

Ryder REJ. Diabet Med 2013; 30: 1148-1155

ABCD nationwide exenatide audit



From slides presented at ABCD Spring meeting, Newcastle, May 7, 2010 by Bob Ryder. See: https://www.diabetologists.org.uk/GLP1_Audits/PresentationsPostersAbstractsExenatide.htm

- In a meta-analysis of 53 RCTs that included 20,312 patients treated with DPP4 inhibitors, and 13,569 controls treated with placebo or active comparators, DPP4 inhibitors were associated with a significantly reduced risk of major adverse cardiac events (odds ratio 0.689 [0.528-0.899], p = 0.006)

Monami M et al. Exp Diabetes Res 2011; 27:57–64

Table 1 Long-term studies examining the safety of incretin-based therapies*†

Medication	Study name	ClinicalTrials.gov identifier	Comparator estimated	Number of subjects	Study start date	Estimated/confirmed study end date	Status (at 29 June 2013)
Saxagliptin (DPP-4 inhibitor)	SAVOR-TIMI53	NCT 01107886	Placebo	16492	May 2010	May 2013	Completed
Alogliptin (DPP-4 inhibitor)	EXAMINE	NCT 00968708	Placebo	5384	October 2009	June 2013	Completed
Lixisenatide (GLP-1 receptor agonist)	ELIXA	NCT 01147250	Placebo	6000	June 2010	May 2014	Recruiting
Sitagliptin (DPP-4 inhibitor)	TECOS	NCT 00790205	Placebo	14000	December 2008	December 2014	Active, not recruiting
Liraglutide (GLP-1 receptor agonist)	LEADER	NCT 01179048	Placebo	9340	August 2010	January 2016	Active, not recruiting
Exenatide (GLP-1 receptor agonist)	EXSCEL	NCT 01144338	Placebo	9500	June 2010	March 2017	Recruiting
Linagliptin (DPP-4 inhibitor)	CAROLINA	NCT 01243424	Glimepiride	6000	October 2010	September 2018	Active, not recruiting
Duraglutide (GLP-1 receptor agonist)	REWIND	NCT 01394952	Placebo	9622	July 2011	April 2019	Recruiting

*Studies presented in the order of estimated study end date.
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Exenatide – coming off insulin, improving control, and losing weight

- June 2008
- Wt = 87 kg
- BMI = 35.3
- A1c = 9.0%
- Insulin 82 units, Repaglinide 4mg tds, Metformin 1gm BD

- April 2011
- Wt = 65 kg
- BMI = 26.7
- A1c = 7.2%
- Exenatide 10ug BD, Metformin 1gm BD

Mrs SH, age 53, type 2 diabetes 13 years, on insulin 8 years

- September 2009
- Wt = 93.9 kg
- BMI = 36.7
- A1c = 9.3%
- Insulin 60 units, Metformin 1gm BD

Liraglutide – coming off insulin, improving control, losing weight and “never felt so good”

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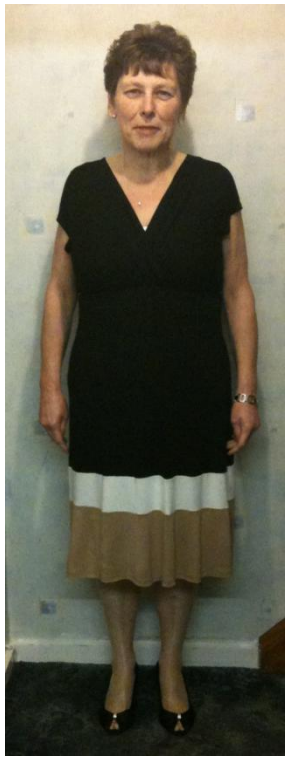
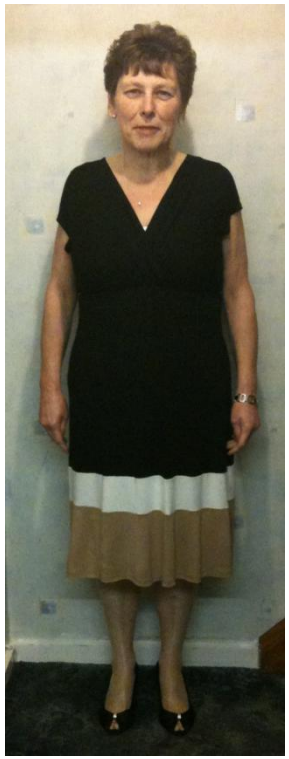
- Wt = 93.9 kg
- BMI = 36.7
- A1c = 9.3%
- Insulin 60 units, Metformin 1gm BD



- February 2012
- Wt = 70 kg
- BMI = 26.3
- A1c = 7.2%
- Liraglutide 1.2mg daily, Metformin 1gm BD

Liraglutide – coming off insulin, improving control, losing weight and “never felt so good”

“I would like to add that since I was prescribed liraglutide and started a healthy eating diet I have never felt so good. Yes I had a couple of weeks at the start of Liraglutide when I had stomach upsets and nausea but I am so glad I persevered as I haven't looked back since September 2009. The icing on the cake is that I no longer have to take insulin. Although you have to accept that taking insulin is part of your life and you obviously have no choice there is definitely no feeling like it when you realize you are 'insulin free‘ ”



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Conclusion

- Incretin based therapies should (most definitely) continue to be used for people with type 2 diabetes!