

## GLP1 receptor agonists: current status of development

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### Disclosure statement

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**I do not receive any honorarium for this lecture**  
 The complete presentation can be downloaded from <http://www.gmed.nl/lezingen>

### Presentation outline

- Current therapy is not perfect
- Important studies with GLP1 receptor agonists
- Can GLP1 agonists modify natural course of T2DM ?
- Long-term and real-world data are needed to really really judge the merit of GLP1 treatment
- Some thoughts on costs of T2DM treatment
- A small personal wish list

### Treatment of type 2 diabetes: a stairway to heaven ?

**Several drug choices:**  
 Sulphonylurea  
 Thiazolidinediones  
 DPP-4 inhibitors  
 GLP1 receptor agonists  
 SGLT2 inhibitors

**Do not forget, T2DM integrative approach includes:**  
 BP lowering  
 Cholesterol lowering  
 Weight reduction  
 Secondary prevention

### There are no Dutch guidelines for internists; instead we use the 2015 updated ADA-EASD recommendations

Inzucchi SE, et al. Diabetes Care 2015;38:140-149

### Or those of the AACE

[https://www.aace.com/files/aace\\_algorithm.pdf](https://www.aace.com/files/aace_algorithm.pdf)

### Individualize!! Current treatment algorithms are of limited help in caring for individuals with T2DM.

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### What patients don't like

1. Hypoglycaemia
2. Weight gain
3. Interference with normal life
- 4.
- 5.
6. Injections
- 7.
- ..
21. Brussels sprouts

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### Not Everything is perfect

Current therapy is not perfect

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### What if the UKPDS had stopped after 3-4 years ...

Remember: These data apply to recently diagnosed diabetes w. obesity!

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### Metformin and SU in T2DM

Metformin is a cheap BG-lowering without promoting weight gain, but also without (significant) effect on CVD

SU lower BG, but stimulate appetite, increase body weight, may provoke nasty hypoglycaemia, and higher CVD incidence (RR 1.26)

If you want to prescribe an SU, probably gliclazide is associated with lowest incidence of hypoglycaemia

Study or Subgroup	Events	Events	Events	Weight	RR, Random, 95% CI	RR, Random, 95% CI
Metformin	10	10	10	100%	1.00	1.00
Sulphonylurea	12	12	12	100%	1.26	1.26
Total (95% CI)	22	22	22	100%	1.26	1.26

Systematic Review  
Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis

O. J. Phung<sup>1,2</sup>, E. Schwartzman<sup>1,2</sup>, R. W. Allen<sup>1</sup>, S. S. Engel<sup>1</sup> and S. N. Rajpathak<sup>3</sup>

The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulphonylureas: a systematic review and meta-analysis

Boussageon et al, PLoS ONE 2012; Phung et al, Diab Med 2014; Schopman et al, DMRR2014

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### The CIMT-study: insulin+metformin vs. insulin+placebo

HbA<sub>1c</sub>: Equal HbA<sub>1c</sub> 0.18 with P=0.000, Equal HbA<sub>1c</sub> at end P=0.007

INSULIN DOSE: Equal insulin dose 0-15 with P=0.000, Equal insulin dose at end P=0.000

WEIGHT: Equal weight change 0.18 with P=0.000, Equal weight change end P=0.000

MEAN CAROTID INTIMA-MEDIA THICKNESS: Metformin 10n - baseline P=0.011, Metformin vs. Placebo change P=0.109

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### Insulin: the best there is ??

Insulin treatment in type 2 diabetes is associated with:

- Increase in body weight
- Hypoglycaemia

but also:

- Heart rhythm disturbances <sup>1</sup>
- Sodium retention and ↑ BP <sup>2,3</sup>
- Inflammation of the vascular wall <sup>4,5</sup>
- Mitogenic effects <sup>6,7</sup>
- Inflammation of adipose tissue <sup>8</sup>

← related to hypoglycaemia

← obesity & insulin resistance

← insulin growth-factor

← influx macrophages

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1. Chow E, et al. Diabetes 2014; 63: 1738-47; 2. Kanoun F, et al. Diabetes Metab. 2001; 27:695-700  
 3. Sarafidis PA, Am J Nephrol 2007; 27: 44-54; 4. Andersson CK, et al. Diabetes Metab Res Rev 2008; 24: 595-603  
 5. Barrett EJ, Liu Z. Rev Endocr Metab Disord 2013; 14: 21-7; 6. Lundby A, et al. J Appl Toxicol. 2014. doi: 10.1002/jat.3082  
 7. Rostoker R, et al. Endocr Relat Cancer 2015; 22: 145-57; 8. Jansen HJ, et al. Diabetologia 2013; 56: 2573-81

### Insulin use and dose is associated with increased risk of CVD and mortality

"In T2DM, exogenous insulin may be associated with increased risk of diabetes-related complications"

Group	Low dose	Mid dose	High dose
All-cause mortality	18.0	23.3	20.1
Insulin + metformin	34.8	43.7	54.0
Insulin only	56.4	63.4	78.4
Insulin + metformin	39.6	43.0	44.3
Insulin only	54.9	68.0	71.6
Insulin only	81.4	80.6	95.8

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Currie CJ, et al. J Clin Endocrinol Metab 2013;98:668-677

### Insulin use and dose is associated with increased risk of CVD and mortality

"In T2DM, exogenous insulin may be associated with increased risk of diabetes-related complications"

more insulin needed

more insulin resistance

more (severe) co-morbidity (poor renal function, inflammation, COPD, other medications)

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Currie CJ, et al. J Clin Endocrinol Metab 2013;98:668-677

THE NEW GUY

NL 10-GLP-1

KENMERKELIJKE TV - DE KENMERKENISTE VAN NEDERLAND

Come in these new guys

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### Classification of GLP-1 receptor agonists according to chemical structure

Exendin-4 based (GLP-1-mimetics "-natide")

Human GLP-1 based (GLP-1 analogs "-glutide")

exenatide BID, exenatide QW, lixisenatide

liraglutide, semaglutide, C-16 or C-18, albiglutide, dulaglutide

GLP-1 linker, Fc IgG4, albumin

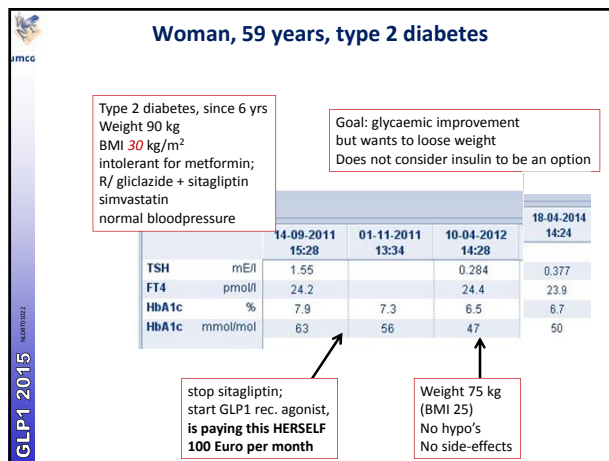
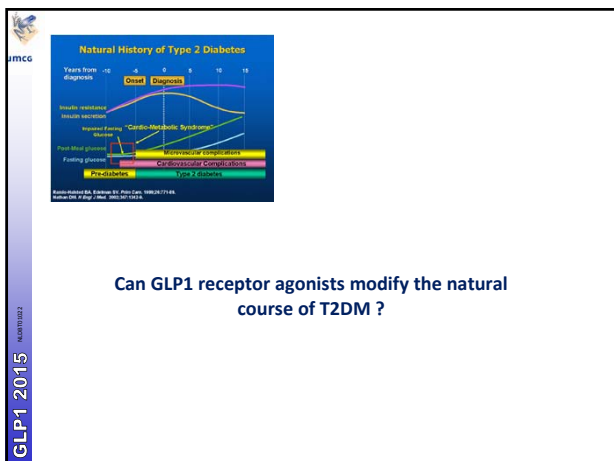
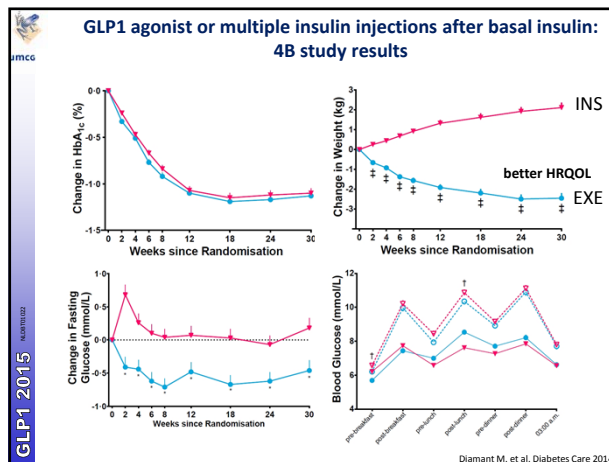
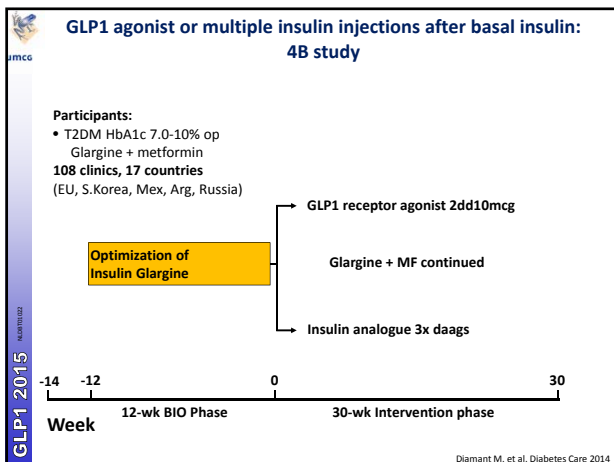
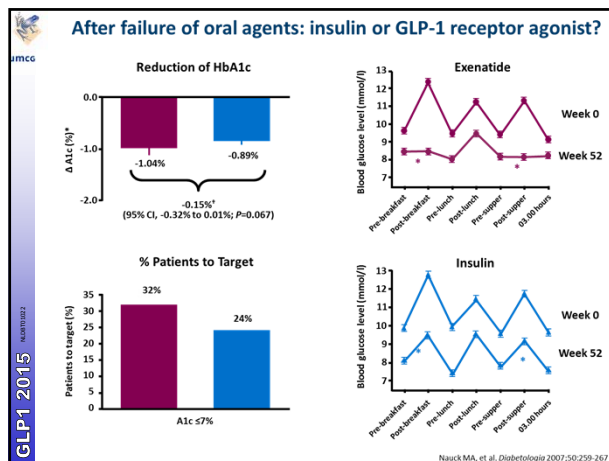
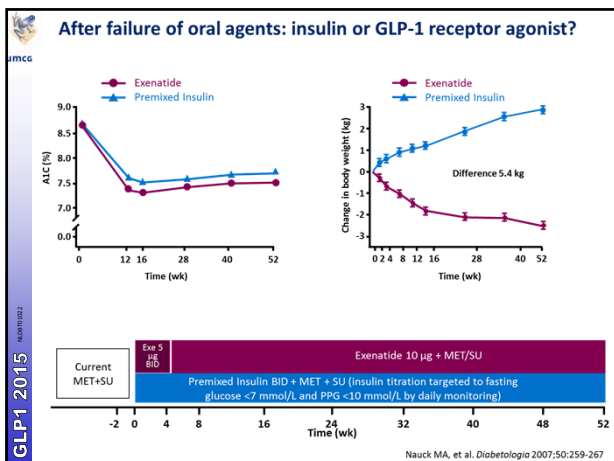
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Gorgojo-Martinez JJ. Hipertens Riesgo Vasc 2014;31:45-57

### When can GLP-1 receptor agonists be used?

- Early: *instead* of metformin ?
- 2nd stage: *combi* treatment in metformin failure ?
- 3rd stage: *instead* of insulin after failure of oral agents ?
- 4th stage: *in combination* with existing insulin therapy ?
- How about *early* combination therapy ?

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### Obesity – a risk factor for many chronic disorders

- Sleep apnoea
- Heart attack
- Stroke
- Psychological disorders
- High blood pressure
- High blood fat
- High cholesterol
- Diabetes
- Metabolic syndrome
- Osteoarthritis
- Back pain
- Carpal tunnel syndrome
- Gout
- Prostate cancer
- Breast cancer (Female)
- Gallstones
- Fatty liver disease
- Cancer (colorectal, endometrial, Pancreas, Ovaries, prostate, kidney)
- Skin tags
- Cholesterol
- Dark skin patches
- Deep vein thromboses
- Hypertension
- Poor wound healing
- Flat feet
- Gonorrhoea
- Progesterone
- Progesterone (Female)

**'Metabolic consequences'**  
Diabetes  
Cardiovascular disease

**'Dynamic consequences'**  
Arthrosis/arthritis/gout  
Pulmonary complaints  
Sleep apnoea  
Esophageal reflux

**'Cancer'**  
Various types of cancer

**'Other'**  
Gall stones  
Alzheimer's disease  
Cognitive disturbances  
Outcome of car accidents  
Postoperative complications

**-5 - -15 kg during GLP1 RA therapy = fewer long-term sequelae ??**

### Possible scenarios regarding body weight benefit of GLP1 agonists

Body weight (kg)

Time (years)

Long-term reduction of consequences of excess body weight ??  
'Metabolic' / 'Dynamic' / 'Cancer' / 'Other'

### Assessing Time to Insulin Use Among Type 2 Diabetes Patients Treated With Sitagliptin or Sulfonylurea Plus Metformin Dual Therapy

Liasson Branch, Ying Qiu, Resanjit Rajpathak, Chinyere O. Sotolu, Robert S. Engeli, Parag Mehta, Larry Raskin

Diabetes Care 2014;37:1411-1418

OBJECTIVE: To assess the time to insulin initiation among type 2 diabetes patients treated with sitagliptin or sulfonylurea plus metformin dual therapy.

DESIGN: Retrospective cohort study.

SETTING: Large integrated health care system.

PARTICIPANTS: 10,000 patients with type 2 diabetes treated with sitagliptin or sulfonylurea plus metformin dual therapy.

MEASUREMENTS AND MAIN RESULTS: The time to insulin initiation was significantly longer for patients treated with sitagliptin compared with sulfonylurea plus metformin dual therapy (P < 0.001).

CONCLUSIONS: The time to insulin initiation was significantly longer for patients treated with sitagliptin compared with sulfonylurea plus metformin dual therapy.

### Metformin + SU vs. Metformin + sitagliptin; can DPP4 inhibitor therapy postpone insulin therapy ?

Index period

Initiate sitagliptin or SU as add-on to metformin (INDEX DATE)

Insulin initiation

12-month baseline period

Follow-up until insulin initiation or subject censored

Oct 17, 2005 Oct 17, 2006 May 31, 2013 August 31, 2013

Blonde L, et al. Diabetes 2014

### Treatment with DPP4-inhibitor sitagliptin will postpone the transition to insulin therapy

Cumulative Probability of Insulin Use

Years From the Index Date

P-value using likelihood-ratio tests = 0.0034

4.1% 3.6% 9.4% 8.4% 14.6% 12.9% 17.7% 21.0% 22.4% 27.1% 26.6% 34.1%

— SU

— Sitagliptin

Blonde L, et al. Diabetes 2014

Long-term and real-world data are needed to really really judge the merit of GLP1 treatment

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### 'Real World' experiences

GLP-1 receptor agonists in type 2 diabetes - NICE guidelines versus clinical practice

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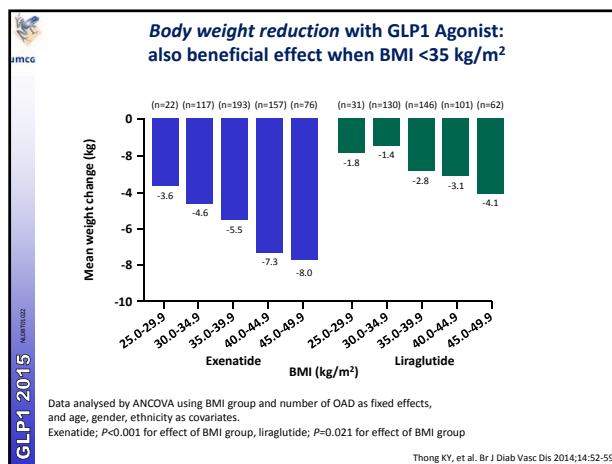
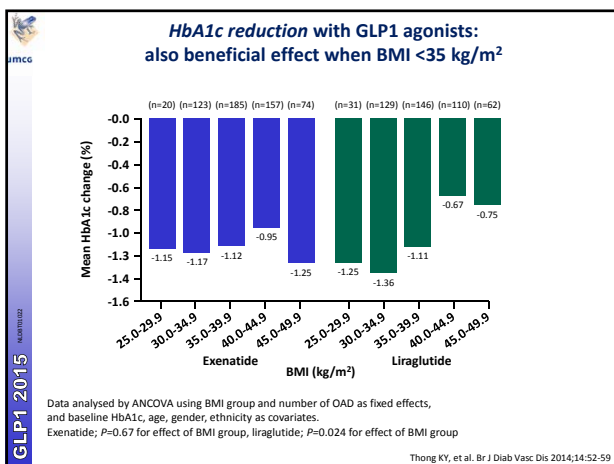
GLP1 2015 N4011022

Thong KY, et al. Br J Diab Vasc Dis 2014;14:52-59

### Patients in the ABCD Nationwide Exenatide and Liraglutide Audit

Total exenatide and liraglutide patients: n=12,955

- Exenatide: n=6,717
  - Excluding switching to liraglutide: n=2,487
    - Patients with 20-32 week HbA1c and 20-32 week weight: n=1,882
      - Non-insulin: n=1,027 (BMI 25-50 kg/m<sup>2</sup>: n=559)
      - Insulin: n=400
    - Patients using exenatide or liraglutide as add-on therapy: n=1,427
      - Non-insulin: n=495 (BMI 25-50 kg/m<sup>2</sup>: n=478)
      - Insulin: n=353
- Liraglutide: n=6,238
  - Excluding switching to liraglutide and liraglutide 1.8 mg: n=1,221
    - Patients with 20-32 week HbA1c and 20-32 week weight: n=1,023
      - Non-insulin: n=495 (BMI 25-50 kg/m<sup>2</sup>: n=478)
      - Insulin: n=353
    - Patients using exenatide or liraglutide as add-on therapy: n=848
      - Non-insulin: n=495 (BMI 25-50 kg/m<sup>2</sup>: n=478)
      - Insulin: n=353



### Original Article

## ADDING RAPID-ACTING INSULIN OR GLP-1 RECEPTOR AGONIST TO BASAL INSULIN: OUTCOMES IN A COMMUNITY SETTING

Mehul R. Dalal, PhD<sup>1</sup>; Liu Xie, MA, MS<sup>2</sup>;  
 Onur Baser, MS, PhD<sup>2,3,4</sup>; Andres DiGenio, MD, PhD<sup>5</sup>

ENDOCRINE PRACTICE Vol 21 No. 1 January 2015

Retrospective analysis of U.S. health insurance claims data from the IHCS IMPACT database, which contains medical and pharmacy claims, eligibility data, and laboratory results from 86.4 million covered patients.

Of these, 63.7 million (74%) have pharmacy benefits and 12.6 million (15%) have laboratory results; the database includes all data for individuals in all U.S. census regions and represents 46 health plans.

Dalal MR, et al. Endocr Pract 2015

GLP1 2015 N4011022

### Table 1

#### Baseline Demographic and Clinical Characteristics (Unmatched Analysis)

Characteristic	Basal + RA1 (n = 9,633)	Basal + GLP-1 (n = 1,705)	P
Age, mean (SD), years	54.37 (12.16)	54.36 (9.17)	.9718
Females, n (%)	4,319 (44.84)	805 (47.21)	.0689
A1C			
Evaluable at baseline, n (%)	1,819 (18.88)	401 (23.52)	<.0001
<7.0%	193 (10.61)	56 (13.97)	.0540
≥7.0% to <8.0%	349 (19.19)	93 (23.19)	.0690
≥8.0% to <9.0%	377 (20.73)	99 (24.69)	.0801
≥9.0%	900 (49.48)	153 (38.15)	<.0001
Mean (SD), %	9.23 (2.01)	8.71 (1.68)	<.0001

Dalal MR, et al. Endocr Pract 2015

GLP1 2015 N4011022

Table 2  
Selected Clinical Endpoints at 1-Year Follow-Up (Matched Analysis)


Endpoint	Basal + RAI (n = 5,013)	Basal + GLP-1 (n = 1,705)	P
<b>Hypoglycemic events, n (%)</b>			
Any	359 (7.16)	112 (6.57)	.4079
Any inpatient	23 (0.46)	2 (0.12)	.0454
Any ED	117 (2.33)	29 (1.70)	.1215
Any outpatient	254 (5.07)	88 (5.16)	.8782
Leading to hospitalization <sup>a</sup>	135 (2.69)	31 (1.82)	.0444
<b>Pancreatic events, n (%)</b>			
Any	93 (1.86)	20 (1.17)	.0585
Any inpatient	21 (0.42)	3 (0.18)	.1464
Any ED	35 (0.70)	10 (0.59)	.6253
Any outpatient	69 (1.38)	14 (0.82)	.0730

Dalal MR, et al. Endocr Pract 2015

Table 1  
Baseline Demographic and Clinical Characteristics (Unmatched Analysis)

Characteristic	Basal + RAI (n = 9,633)	Basal + GLP-1 (n = 1,705)	P
<b>All-cause health care costs, mean (SD), \$</b>			
Total costs	13,546 (28,216)	7,527 (10,260)	<.0001
Inpatient costs	6,214 (23,458)	1,427 (7,945)	<.0001
Outpatient costs	4,119 (9,898)	2,680 (4,493)	<.0001
ED costs	401 (1,488)	248 (1,044)	<.0001
Treatment costs	2,813 (2,978)	3,173 (2,486)	<.0001
<b>Diabetes-related health care costs, mean (SD), \$</b>			
Total costs	4,898 (10,429)	3,410 (5,288)	<.0001
Inpatient costs	2,372 (9,638)	714 (4,728)	<.0001
Outpatient costs	1,103 (2,681)	928 (1,701)	.0004
ED costs	181 (808)	112 (579)	<.0001
Treatment costs	1,048 (892)	1,475 (1,008)	<.0001
Diabetes supply costs	194 (229)	182 (202)	.0196
Cost of testing strips	155 (210)	138 (188)	.0008

Dalal MR, et al. Endocr Pract 2015



Objection, your honor

### Consumer Group to FDA: Take Victoza off the Market

Consumer Watchdog Group 'Public Citizen' Challenges Safety of Popular Type 2 Diabetes Drug

"More and more people are taking this drug, and more people are experiencing serious health problems as a result," Public Citizen director Sidney Wolfe, MD, said in a statement. "Clearly, the FDA's warning system is not sufficient. The drug should be taken off the market."

### Victoza: EMA Moving Forward While FDA Idles Over Victoza and Cancer


May 20, 2014, 08:00:00AM. By Gordon Gibb

Washington, DC: While cautious concern still exists with regard to Victoza side effects, the European Medicines Agency (EMA) has begun the process of actually allowing for expanded use of Victoza in the areas of the world governed by the EMA.



Specifically, the EMA is considering a label expansion for Victoza (liraglutide) that will allow physicians to prescribe GLP-1 receptor agonists such as Victoza in combination with a basal insulin such as Tresiba (insulin degludec). Driving the expanded use, according to *Business Monitor Online* (3/24/14), is the Committee for Medicinal Products for Human Use (CHMP), an entity that exists within the EMA framework.

The EMA's North American counterpart, the US Food and Drug Administration (FDA), thus far has shown no desire to expand the usages of Victoza beyond that for which the type 2 diabetes drug is already indicated. However, the posturing of regulators in Europe is hardly surprising given a joint statement published by both regulators in which they could find no causal link between Victoza and cancer.



Some final thoughts on costs of type 2 diabetes treatment

### Long-term costs of diabetes treatment

Diabetes Care

## Second-line Agents for Glycemic Control for Type 2 Diabetes: Are Newer Agents Better?

DOI: 10.2337/6c13-1901

Yuanhui Zhang,<sup>1</sup> Rosalina G. McCoy,<sup>2</sup> Jennifer E. Mason,<sup>3</sup> Steven A. Smith,<sup>2,4</sup> Nilay D. Shah,<sup>4,5</sup> and Brian T. Denton<sup>6</sup>

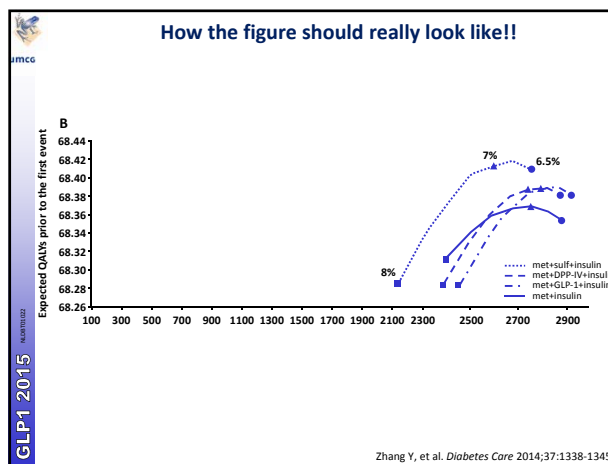
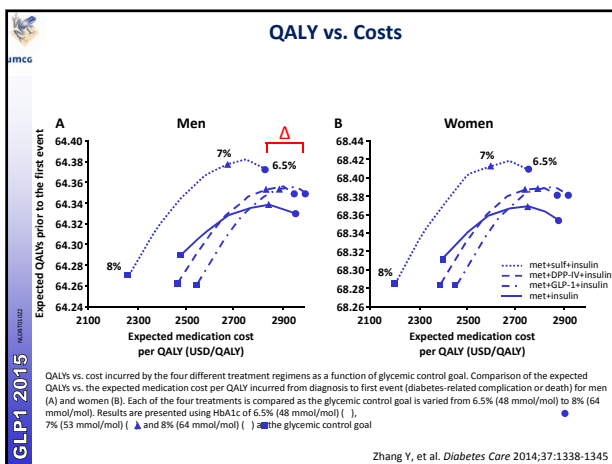
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Quality-adjusted life-year (QALY):  
 1. measure of disease burden, including both the quality and the quantity of life lived  
 2. the number of years of life that would be added by an intervention

### Methodology

- Retrospective administrative claims including medical claims, pharmacy claims, laboratory data, from large, US health plan
- Probability of diabetes complications using the UKPDS outcomes model
  - age, sex, ethnicity, smoking, BMI, HbA1c, SBP, lipids, PVD, atrial fibrillation, ischemic heart disease, and congestive heart failure; and blindness at diagnosis
- Probability of death from other cause estimated based on the US 2007 mortality tables

Zhang Y, et al. *Diabetes Care* 2014;37:1338-1345



### Drawbacks of the UKPDS Model

- Only predicts 1st event of any diabetes-related complications
- Does not allow series of events
- Does not incorporate morbidities, like neuropathy or foot ulceration
- Hypoglycaemia and hyperglycaemia also excluded
- No single allowance for other co-morbid conditions, like COPD, osteo-arthritis, depression ..... & those associated with obesity, which are predicted to be less with GLP1 RA therapy

### Things to consider when assessing LONG-TERM effectivity and costs of GLP1-based therapies

- Glycaemic effects: BMI>35 kg/m2 restriction not backed by evidence
- Health-related quality of life: incl. daily activities & work. Patients prefer GLP1RA vs insulin
- Effects on diabetic complications: Longer term studies needed, but existing therapies not perfect
- Time to insulin dependence: Will postpone insulin
- Side-effects: weight increase & hypoglycaemia; pancreatic and other organ safety. Risk of pancreatitis in real world experience not substantiated
- Long-term costs of: other medications, other co-morbidities & their complications; absenteeism from work, unemployment, social support. Inclusive models needed to assess obesity-associated disorders

My Bucket list