Cleveland Clinic
Florida

Pharmacologic Advances in the Management of Type 2 Diabetes 2016

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Scripps Research Institute

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Financial Disclosure Statement

"I do not have any financial relationships relative to the content of this program."

OUTLINE

- Drugs available to treat DM2
- Treatment algorithms
- In depth look at GLP1s, DPP4s, SGLT2s
- Medication risks/warnings
- Cardiovascular benefit of DM drugs
- Insulin landscape
- Patient cases

World Health Organization

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World Health Day 2016: Beat diabetes

World Health Day 2016: Action needed to halt rise in diabetes

6 April 2016 -- The number of people living with diabetes has nearly quadrupled since 1980 to 422 million adults, with most living in developing countries. WHO is marking World Health Day, 7 April, by calling for action on diabetes. In its first "Global report on diabetes", WHO highlights the need to step up prevention and treatment of the disease.

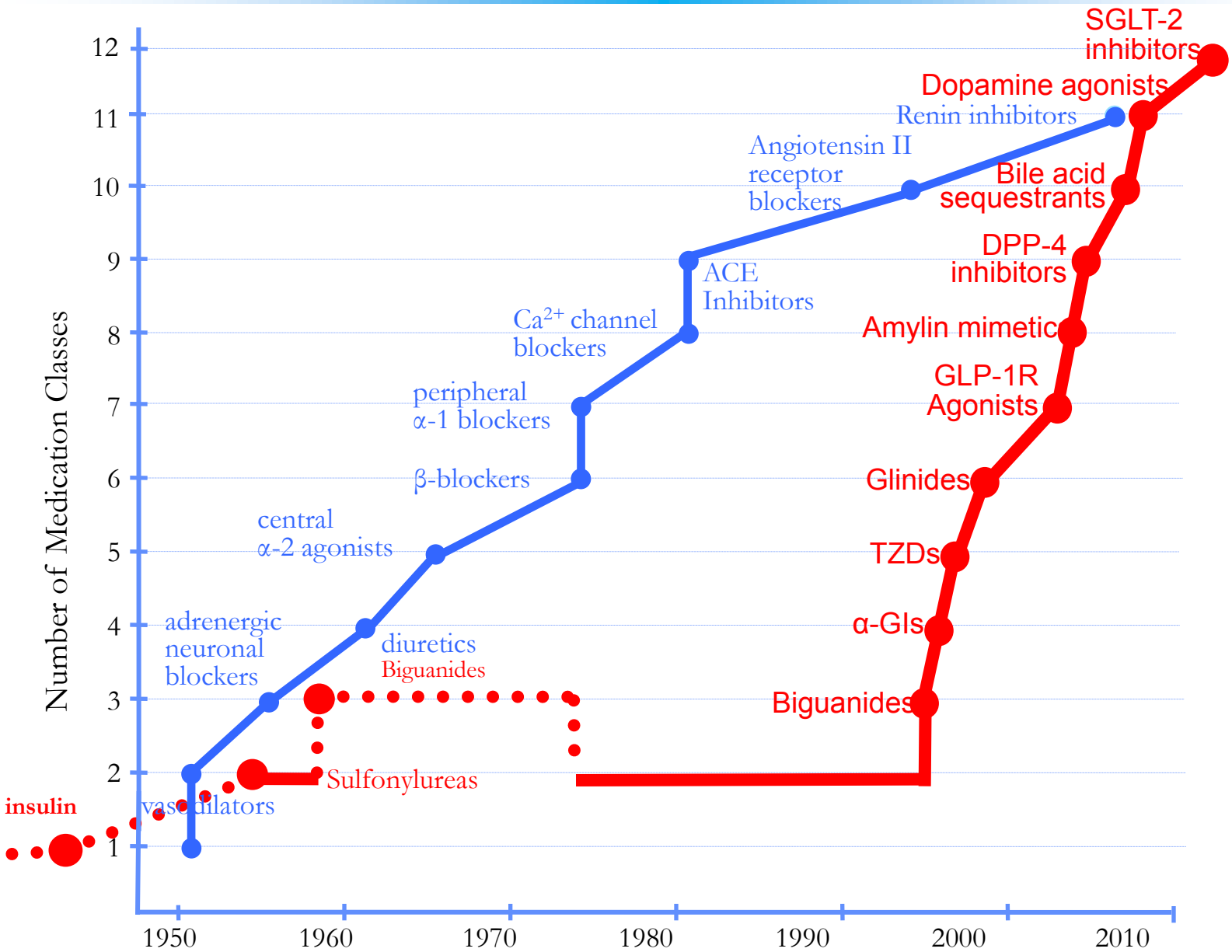
WHO Director-General launches diabetes report

Read the Global report on diabetes

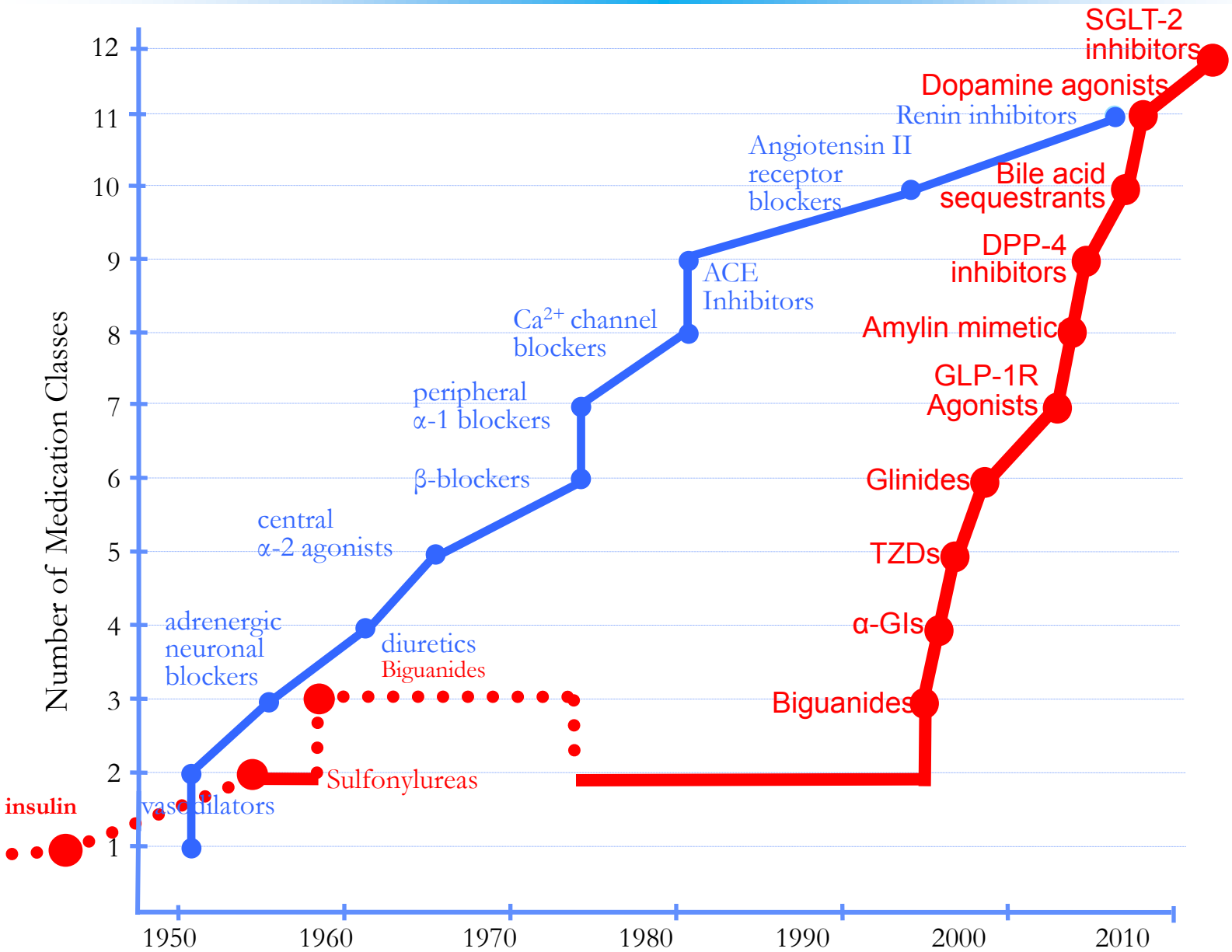
Read the news release

April 7, 2016

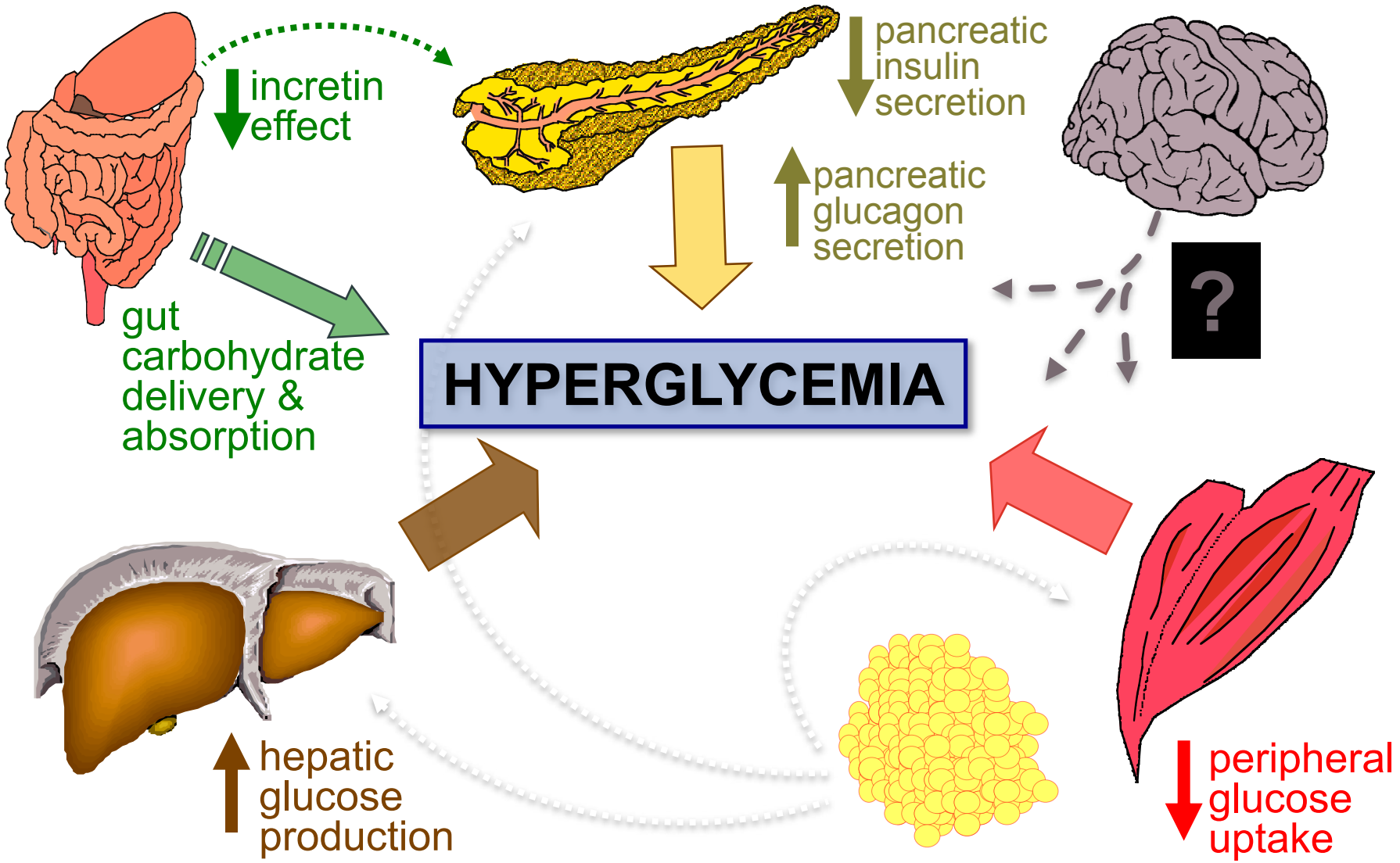
Half-Century of HTN & T2DM Medications in U.S.



Half-Century of HTN & T2DM Medications in U.S.



The Complex Pathogenesis of T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Glycemic Targets

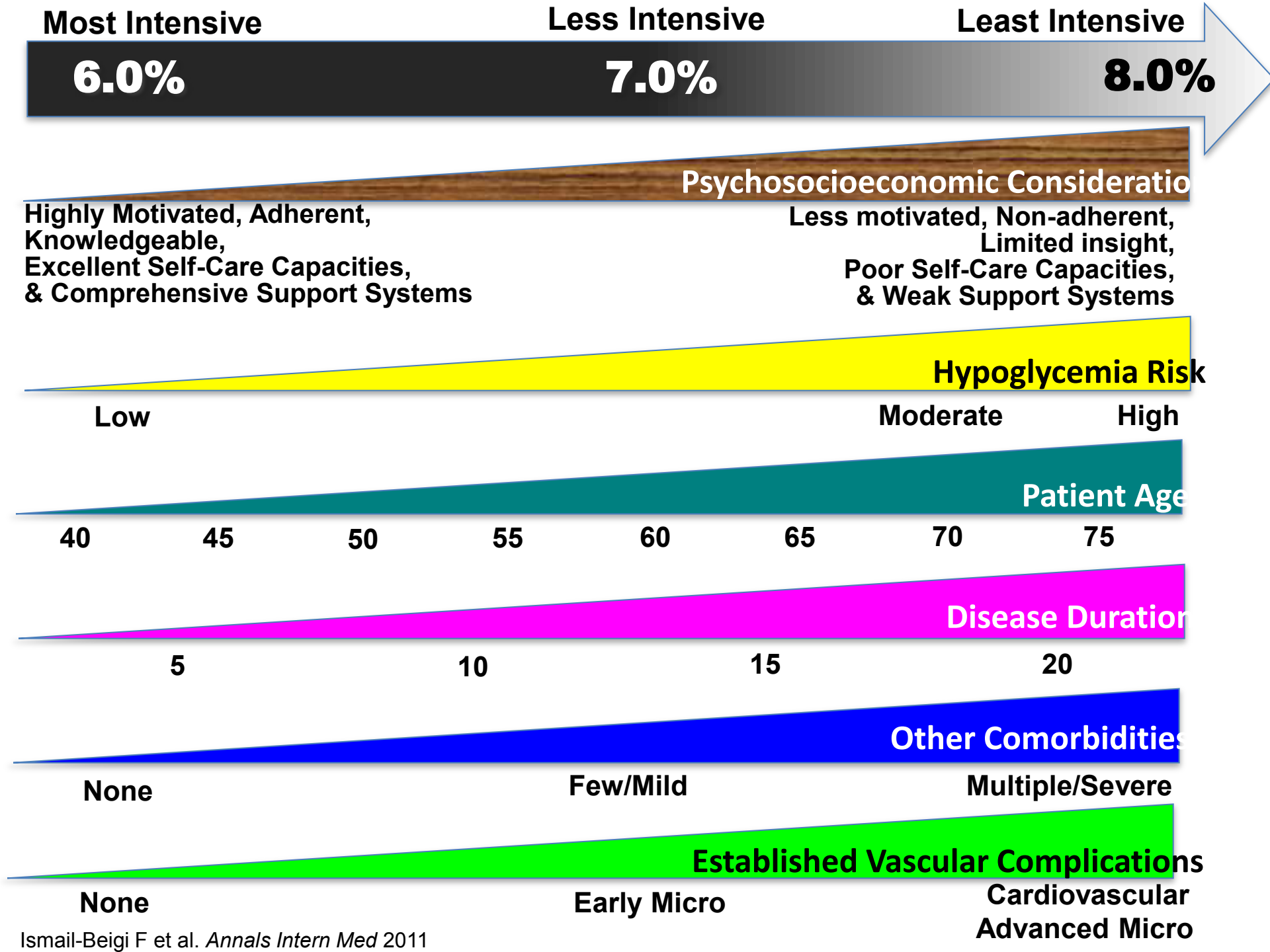
Table 6.2—Summary of glycemic recommendations for nonpregnant adults with diabetes

A1C	<7.0%*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

†Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Diabetes Care, Vol 39, Supplement 1, Jan 2016



Ismail-Beigi F et al. *Annals Intern Med* 2011

Biguanides

- **Metformin**
- **Mechanism: Activates AMP-kinase**
- **Primary action: Decrease hepatic glucose production**
- **Advantages: Extensive experience, no HYPOs, weight loss**
- **Disadvantages: GI, B12 deficiency, lactic acidosis (CKD/CHF/liver disease)**
- **Costs: LOW**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

Sulfonylureas

- **Glyburide, Glipizide, Glimepiride**
- **Mechanism: Closes K ATP channels on Bcell plasma membrane**
- **Primary action: Increase insulin secretion**
- **Advantages: Extensive experience**
- **Disadvantages: HYPOglyemia, weight gain**
- **Costs: LOW**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

Meglitinides

- **Repaglinide, Nateglinide**
- **Mechanism: Closes K ATP channels on Bcell plasma membrane**
- **Primary action: Increase insulin secretion**
- **Advantages: Decrease postprandial excursions, flexible dosing**
- **Disadvantages: HYPOglyemia, weight gain, frequent dosing**
- **Costs: MODERATE**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

TZDs

- **Pioglitazone, Rosiglitazone**
- **Mechanism: Activates PPAR-gamma**
- **Primary action: Increase insulin sensitivity**
- **Advantages: No HYPOs, durability, inc HDL/dec TGs, reduced CVD events?**
- **Disadvantages: Weight gain, edema, HF, fractures, inc LDL, inc MI ?**
- **Costs: LOW**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

Alpha-Glucosidase Inhibitors

- **Acarbose, Miglitol**
- **Mechanism: Inhibits intestinal alpha glucosidase**
- **Primary action: Slow intestinal CHO digestion/absorpion**
- **Advantages: No HYPOs, dec postprandial excursions, non-systemic**
- **Disadvantages: Modest ha1c lowering, GI SEs, frequent dosing**
- **Costs: LOW-MODERATE**

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DPP4 Inhibitors

- **Sitagliptin, Saxagliptin, Linagliptin, Alogliptin**
- **Mechanism: Inhibits DPP4, increasing posprandial incretins (GIP/GLP1)**
- **Primary action: Increase insulin secretion, dec glucagon secretion**
- **Advantages: No HYPOs, well tolerated**
- **Disadvantages: angioedema/urticaria, pancreatitis, inc HF hospitalizations**
- **Costs: HIGH**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

Bile Acid Sequestrants

- **Colesevelam**
- **<u>Mechanism</u>: Intestinal BA binding, increase hepatic BA production**
- **<u>Primary action</u>: Decreased hepatic glucose production, inc incretins**
- **<u>Advantages</u>: No HYPOs, dec LDL**
- **<u>Disadvantages</u>: Modest ha1c lowering, constipation, inc TGs, medication binding**
- Costs: **HIGH**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

Dopamine 2 Agonists

- **Bromocriptine-quick release**
- **Mechanism: Activates DA receptors**
- **Primary action: Modulates hypothalamic regulation of metabolism, inc insulin sensitivity**
- **Advantages: No HYPOs, dec CVD events**
- **Disadvantages: Modest ha1c lowering, dizziness/syncope/nausea/fatigue, rhinitis**
- **Costs: HIGH**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

SGLT2 inhibitors

- **Canagliflozin, Dapagliflozin, Empagliflozin**
- **Mechanism: Inhibits SGLT2 in kidney**
- **Primary action: Blocks renal glucose absorption, promotes glucosuria**
- **Advantages: No HYPOs, weight loss, lower BP, effective at all DM stages, lower CVD event rate and mortality**
- **Disadvantages: GU infections, polyuria, hypotension, inc LDL, inc creatinine, DKA**
- **Costs: HIGH**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

GLP1 Receptor Agonists

- **Exenatide/ER, Liraglutide, Albiglutide, Dulaglutide**
- **Mechanism: Activates GLP1 receptors**
- **Primary action: Inc insulin secretion, dec glucagon secretion, slowed gastric emptying, inc satiety**
- **Advantages: No HYPOs, weight loss, dec PP excursion, dec CV risk**
- **Disadvantages: GI SEs, inc HR, pancreatitis, MTC, injectable/training**
- **Costs: HIGH**

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Amylin mimetics

- **Pramlintide**
- **Mechanism: Activates amylin receptors**
- **Primary action: Decreased glucagon secretion, slowed gastric emptying, inc satiety**
- **Advantages: Dec postprandial excursions, dec weight**
- **Disadvantages: Modest ha1c effect, GI SEs, HYPOs, injected/training, frequent dosing**
- **Costs: HIGH**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

Insulins

- **MANY**
- **Mechanism: Activates insulin receptors**
- **Primary action: Inc glucose disposal, dec hepatic glucose production, suppresses ketogenesis**
- **Advantages: Universal response, unlimited efficacy, dec microvascular risk**
- **Disadvantages: HYPOs, weight gain, mitogenic?, injectable/training, patient resistance**
- **Costs: MODERATE-HIGH**

Diabetes Care, Vol 39, Supplement 1, Jan 2016

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

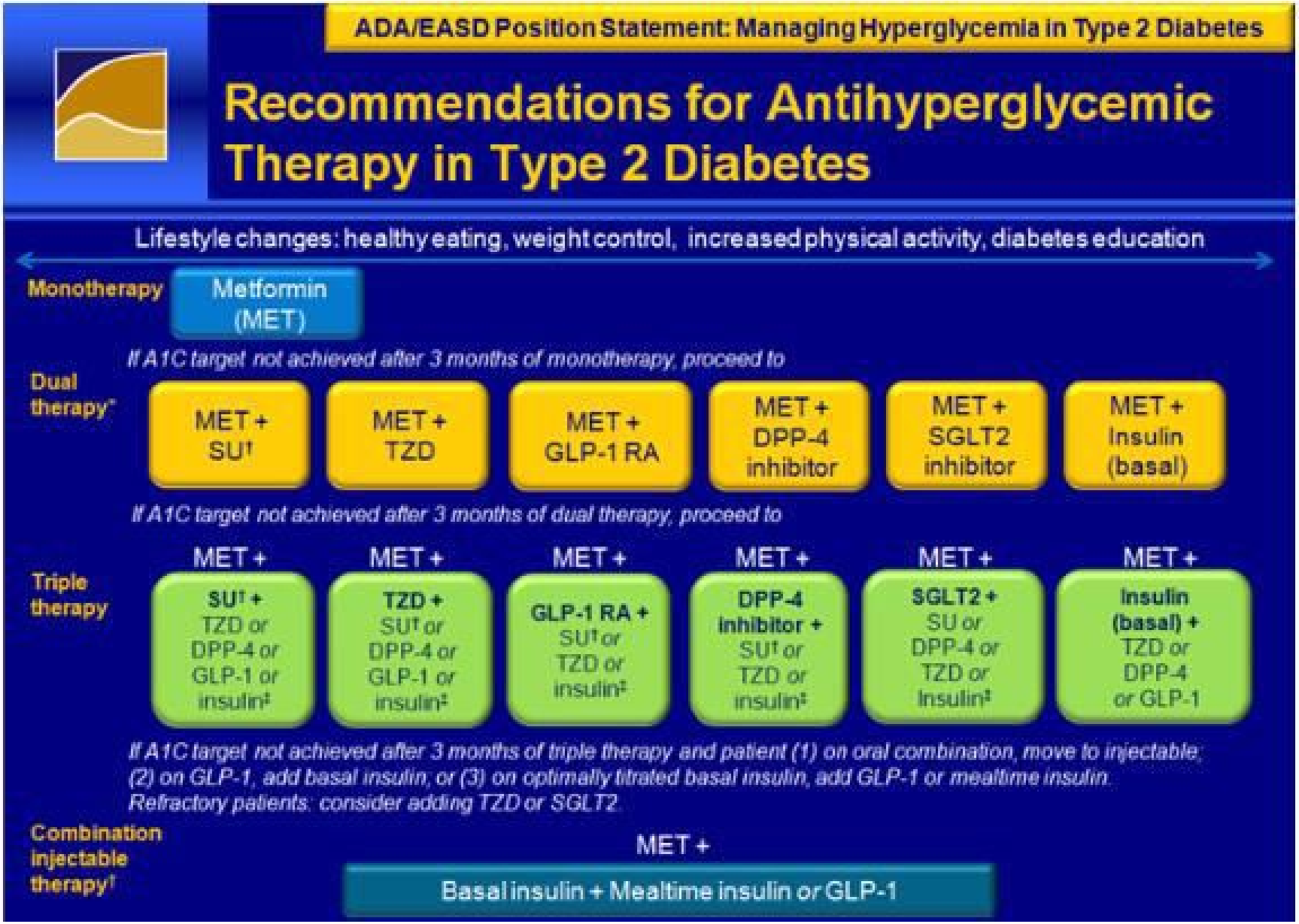
Refer to Insulin Algorithm

LEGEND

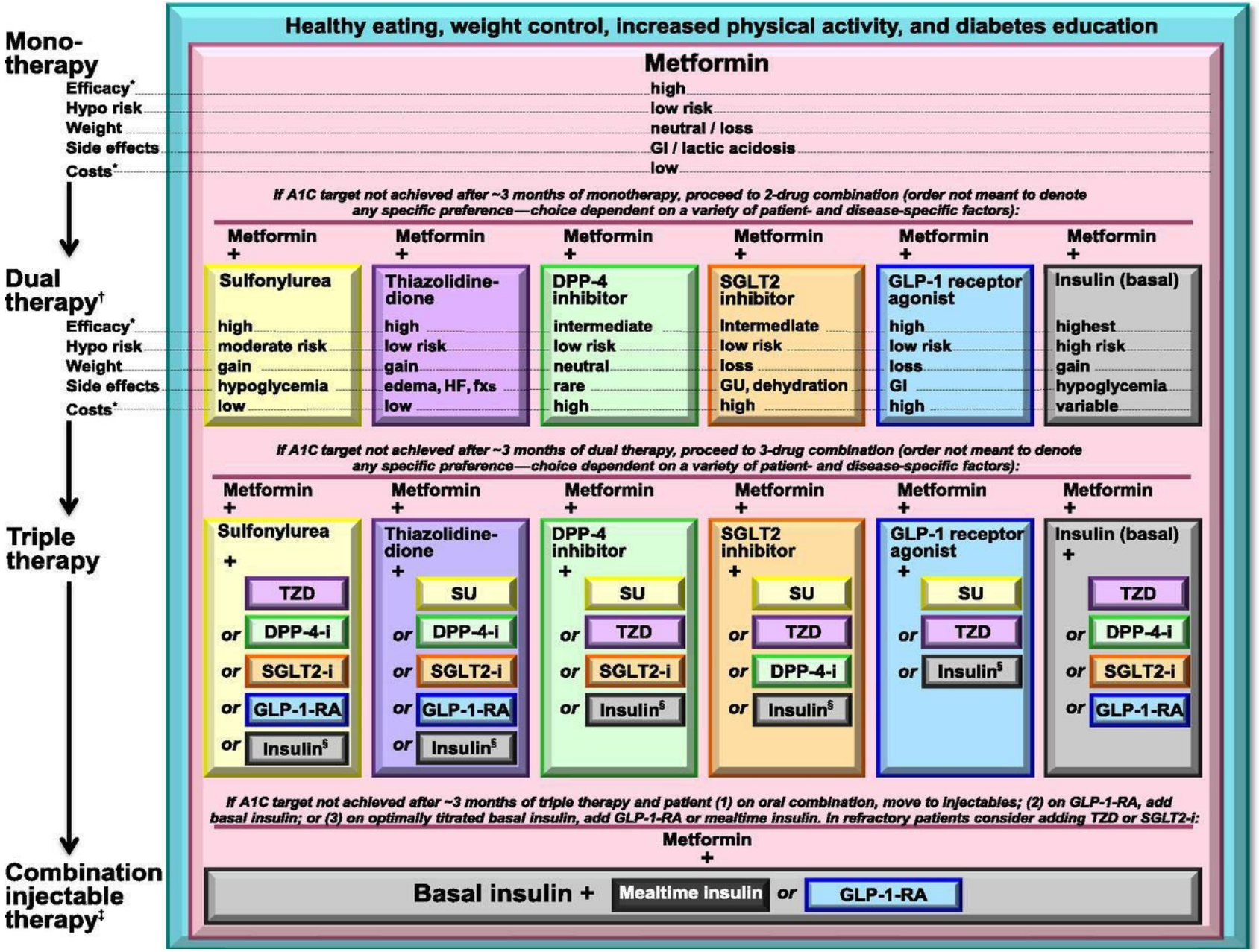
- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE



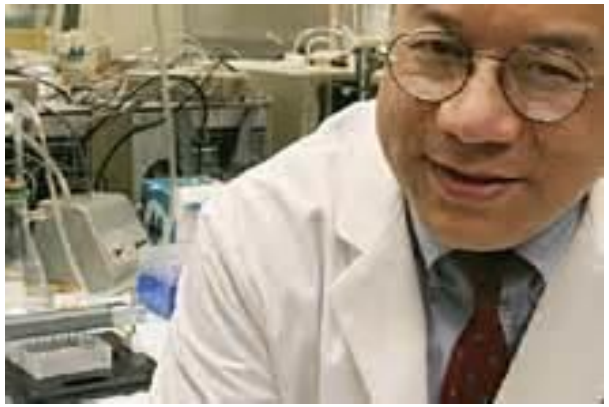
Inzucchi, SI. Diabetes Care. 2015; 38 (1): 140-149



American Diabetes Association.

“Lizard Spit”

- **Exendin-4, a protein naturally secreted in the saliva and concentrated in the tail of the Gila monster.**
  - **Shares homology and function with mammalian GLP-1**
  - **Resistance to degradation by DPP-IV (allowing for a longer pharmacological half life).**
  - **Subsequent clinical testing showed desirable glucagon and appetite-suppressant effects.**

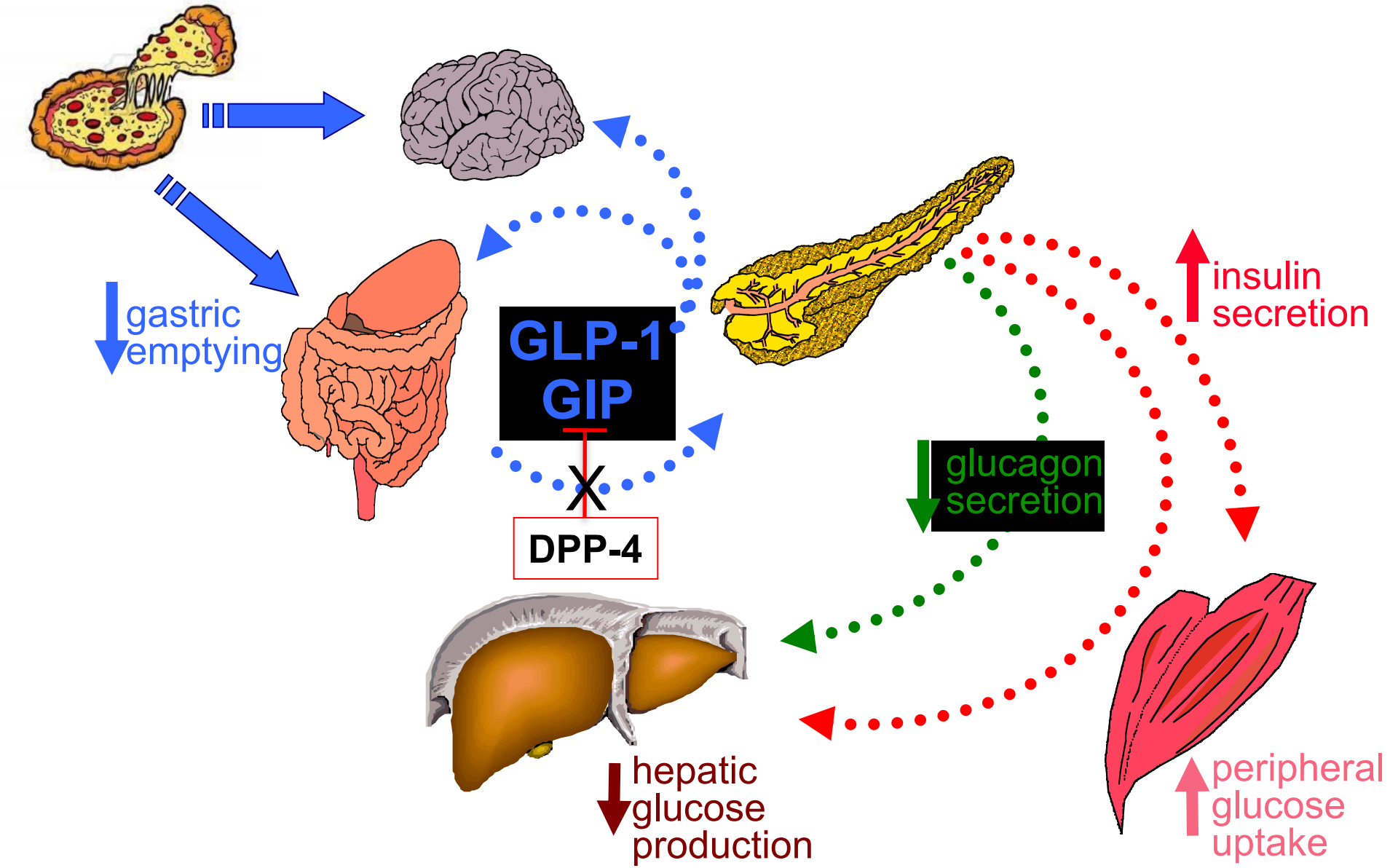


Exendin-4

-First isolated by Dr. John Eng in 1992 while working at the Veterans Administration Medical Center, in The Bronx, NY

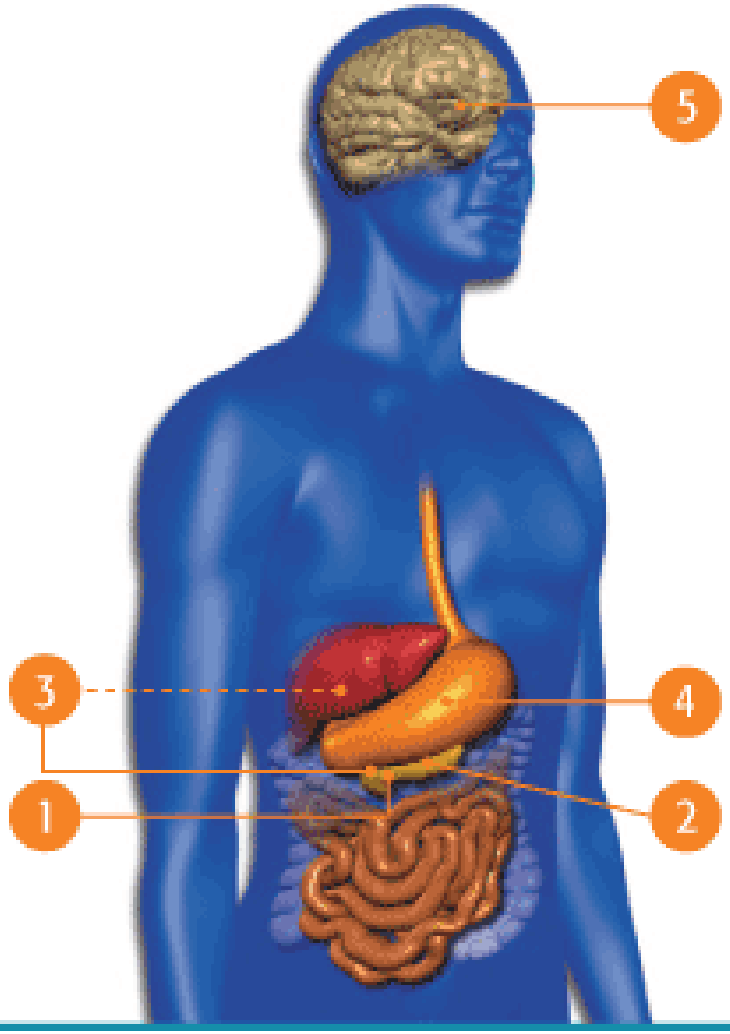
-Synthetic form=Exenatide (Byetta) approved in 2005

The Incretin System: Key Regulator of Post-Prandial Glucose Metabolism



Glucagon-Like-Peptide-1 Agonists

GLP-1 is an important component in glycemic regulation



The actions of GLP-1 are dependent on food intake, and GLP-1 is short-lived

1. Stimulates glucose-dependent insulin secretion[2]
2. Improves first-phase insulin response[3]
3. Suppresses postprandial glucagon secretion, which decreases hepatic glucose production[4]
4. Slows gastric emptying[2]
5. Reduces food intake*[5]

*This effect is postulated to be mediated through the central nervous system.

GLP1 agonists

- **Byetta (*exenatide*), 4/2005**
  - **Bydureon , 2/2012, pen 3/2014**
- **Victoza (*liraglutide*), 1/2010**
- **Tanzeum (*albiglutide*), 4/2014**
- **Trulicity (*dulaglutide*), 9/2014**

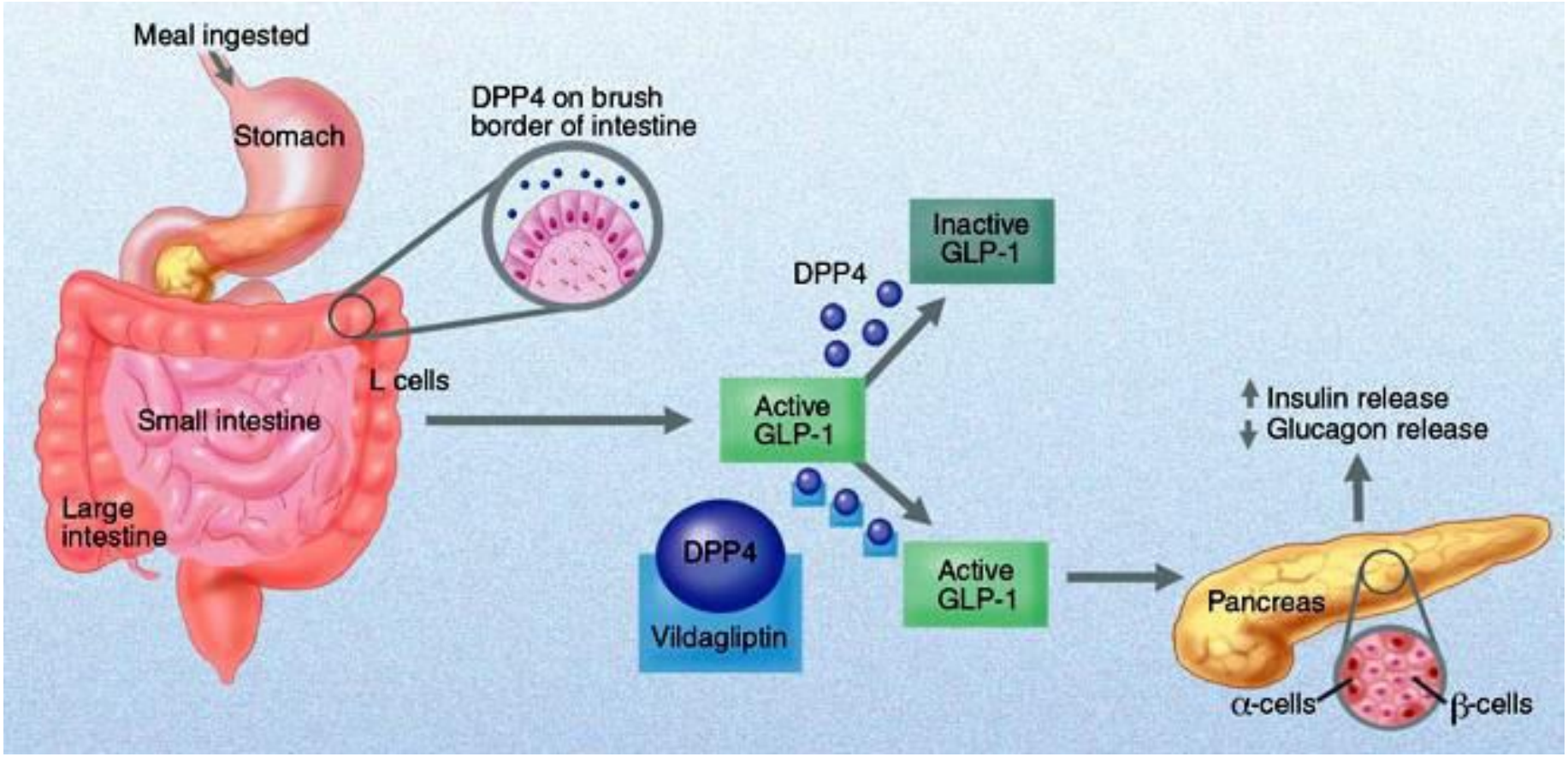
- **Saxenda (*liraglutide* 3.0mg), approved 12/23/14 for weight loss**

GLP1 Comparisons

- Daily injections: Victoza
- Once weekly: Bydureon, Tanzeum, Trulicity
- Renal safety: Tanzeum, Trulicity
- Improved GI profile: Tanzeum, Trulicity
  - Less weight loss seen compared to Victoza

- Class warnings: pancreatitis, medullary thyroid cancer
- Ha1c lowering 1-1.5% on average

Dipeptidyl Peptidase-4 inhibitors



DPP4 inhibitors

- **Januvia (sitagliptin), 10/2006**
- **Onglyza (saxagliptin), 7/2009**
- **Tradjenta (linagliptin), 5/2011**
- **Nesina (alogliptin), 1/2013**

SNAP SHOT:

-Ha1c lowering 0.5-0.8%
-Weight neutral
-Once daily oral medication
-Linagliptin does NOT need adjustment for renal insufficiency

The Kidney's Role in Normal Glucose Homeostasis[1,2]

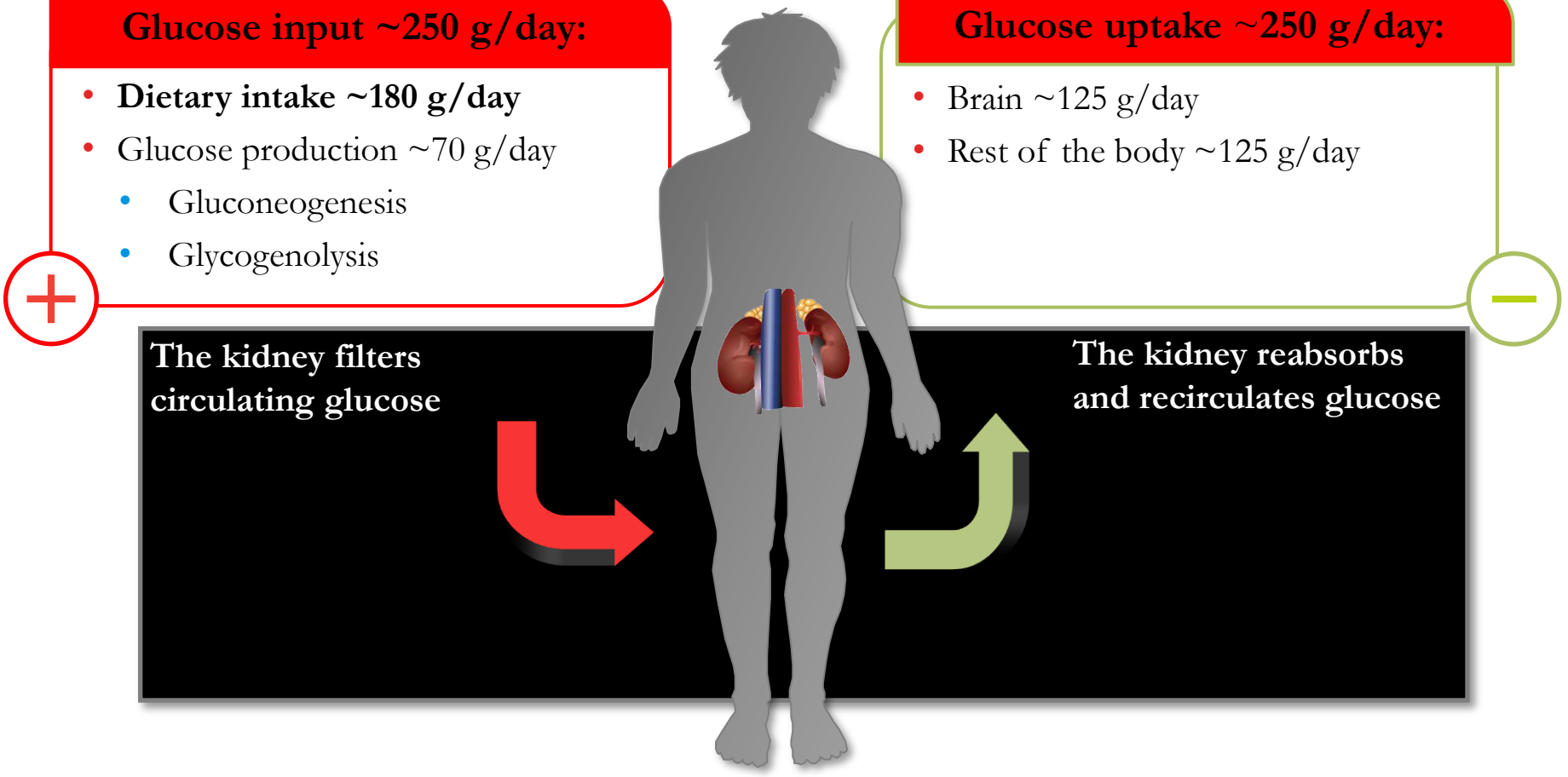
Net balance ~0 g/day

Glucose input ~250 g/day:

- **Dietary intake ~180 g/day**
- Glucose production ~70 g/day
  - Gluconeogenesis
  - Glycogenolysis

Glucose uptake ~250 g/day:

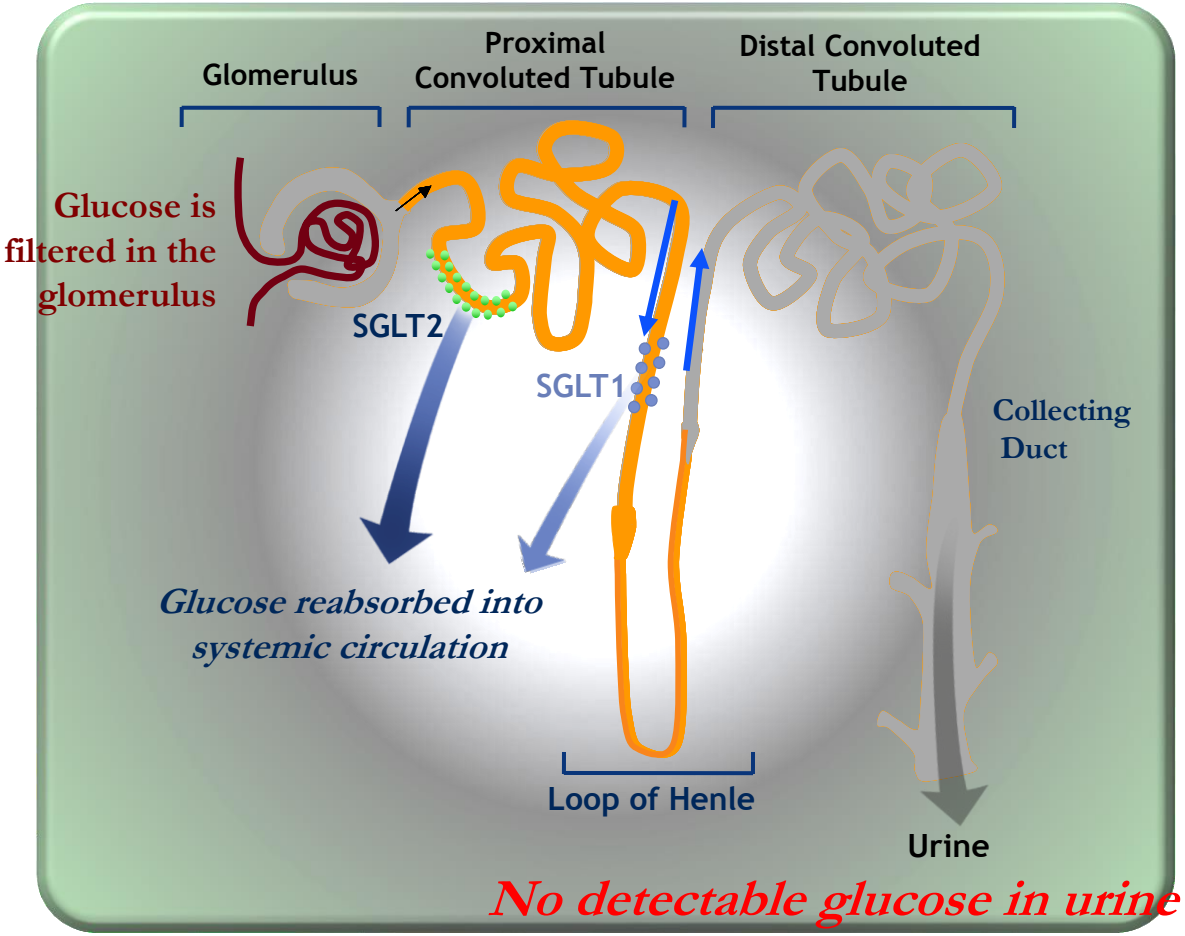
- Brain ~125 g/day
- Rest of the body ~125 g/day



Glucose filtered ~180g/day = Glucose reabsorbed ~180g/day

SGLTs and Normal Renal Handling of Glucose

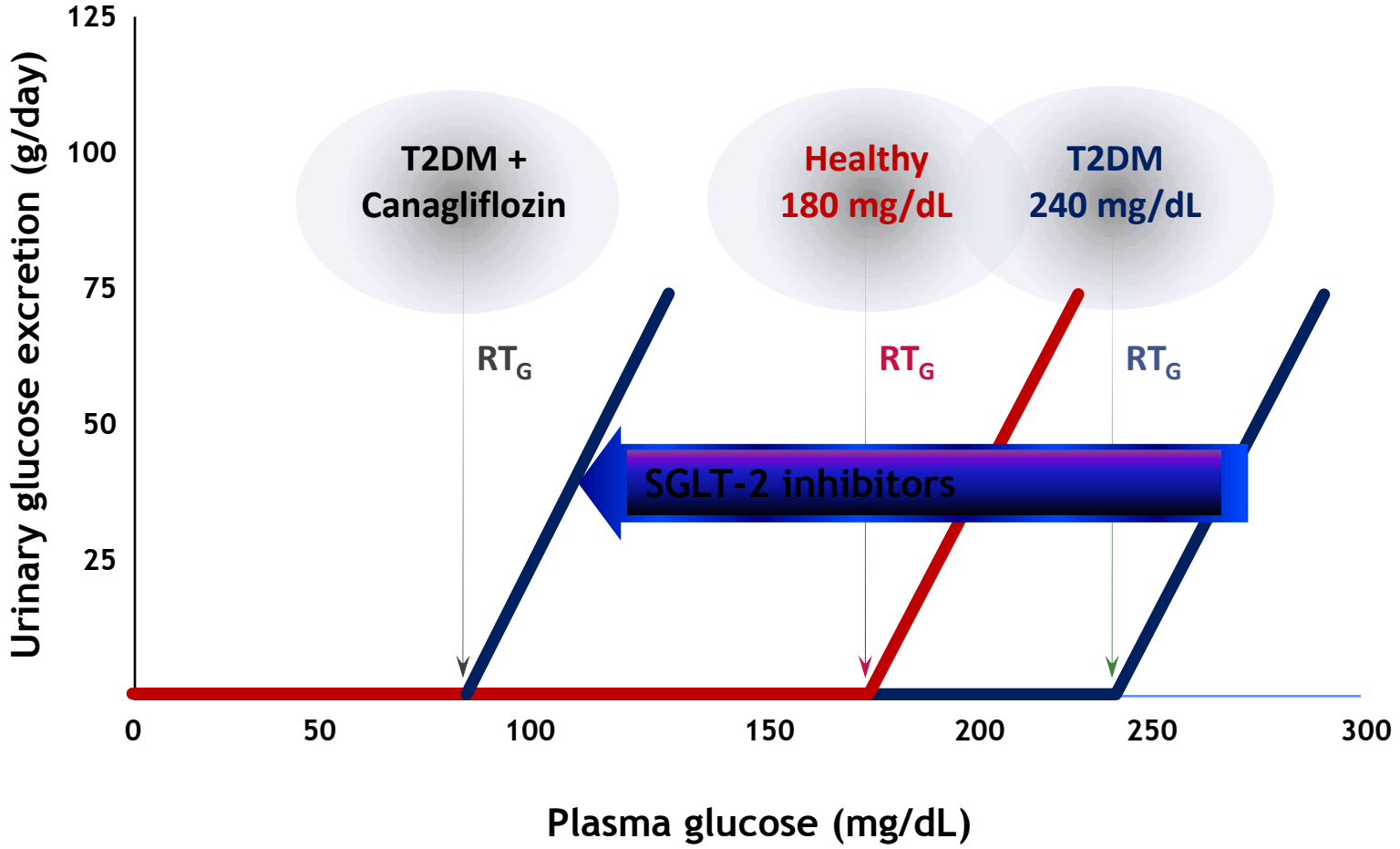
- 180 g/day/1.73 m^2 is filtered glucose load[1]
- SGLT2 transports 90% of filtered glucose out of the tubular lumen[1-4]
- SGLT1 transports the remaining 10% of filtered glucose[1-4]
  - SGLT1 is the primary SGLT in the small intestine[1,2]



SGLT, sodium-glucose co-transporter

1. Wright EM et al. *J Intern Med.* 2007;261(1):32-43.
2. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404.
3. You G et al. *J Biol Chem.* 1995;270(49):29365-29371.
4. Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18.

SGLT-2 inhibitors Lower Renal Threshold for Glucose Excretion (RT_G)



T2DM , type 2 diabetes mellitus.

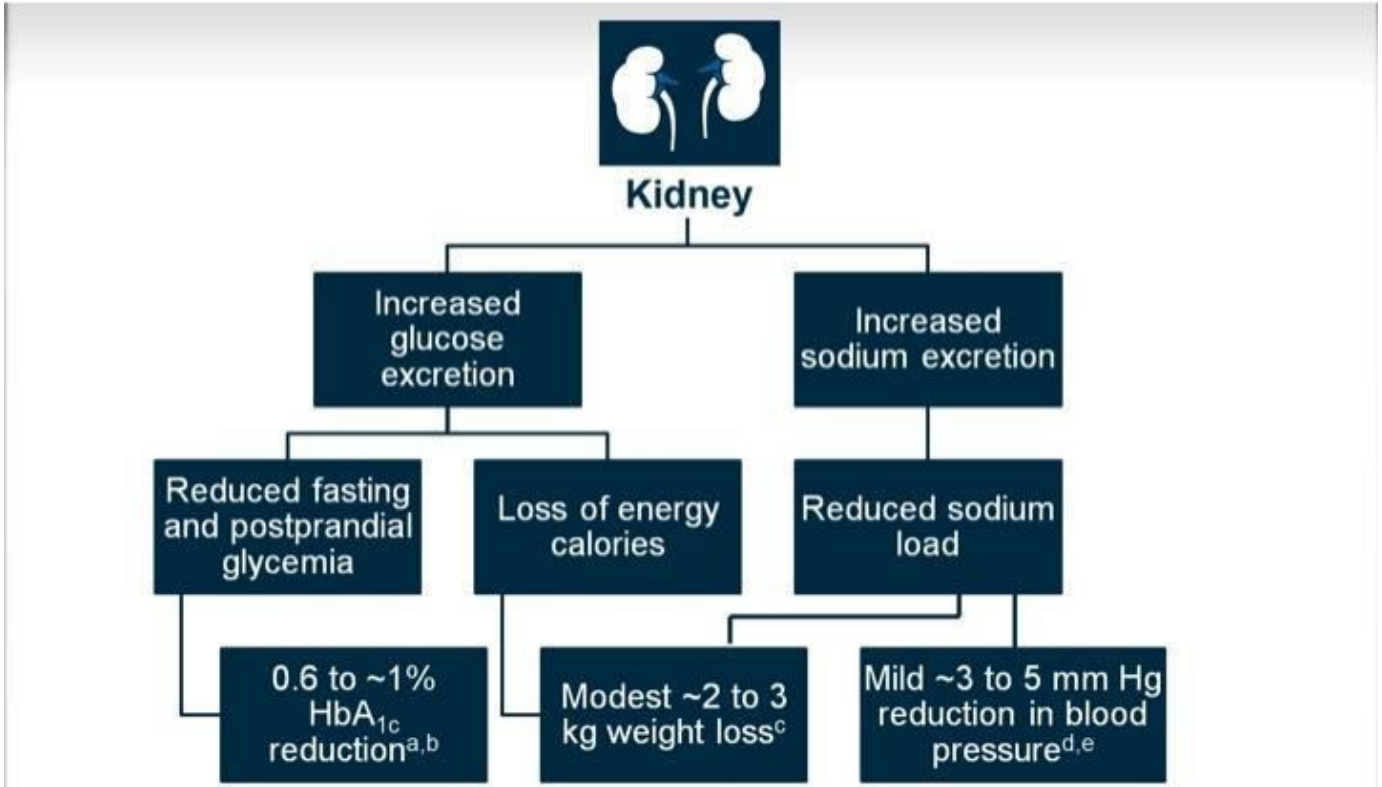
Adapted with permission from Abdul-Ghani MA, DeFronzo RA.

1.Abdul-Ghani MA, DeFronzo RA. *Endocr Pract.* 2008;14(6):782-790.

2.Nair S, Wilding JP. *J Clin Endocrinol Metab.* 2010;95(1):34-42.

3.Invokana™ (canagliflozin) prescribing information.

SGLT-2 Inhibitors



a. Wilding JP, et al. *Diabetes Obes Metab*. 2014;16:124-136[5]; b. Forst T, et al. *Diabetes Obes Metab*. 2014. 16:467-477[6]; c. Valentine V. *Clin Diabetes*. 2012;30:151-155[9]; d. Rosenstock J, et al. *Diabetes Obes Metab*. 2014;15:1154-1160[7]; e. Goring S, et al. *Diabetes Obes Metab*. 2014;16:433-442.[8]

PRO: Low risk of HYPOglycemia

CON: 10-15% risk of mycotic genital infections

4. Dosage Adjustments for Renal Insufficiency

eGFR mL/min/1.73m²	Canagliflozin	Dapagliflozin	Empagliflozin
≥ 60	No dosage adjustment 100 to 300 mg/d	No dosage adjustment 5 to 10 mg/d	No dosage adjustment 10 to 25 mg/d
45 to 60	100 mg/d	Not recommended eGFR <60	10 mg/d
30 to 45	Not recommended eGFR <45	N/A	Not recommended eGFR <45
<30	Contraindicated	Contraindicated	Contraindicated

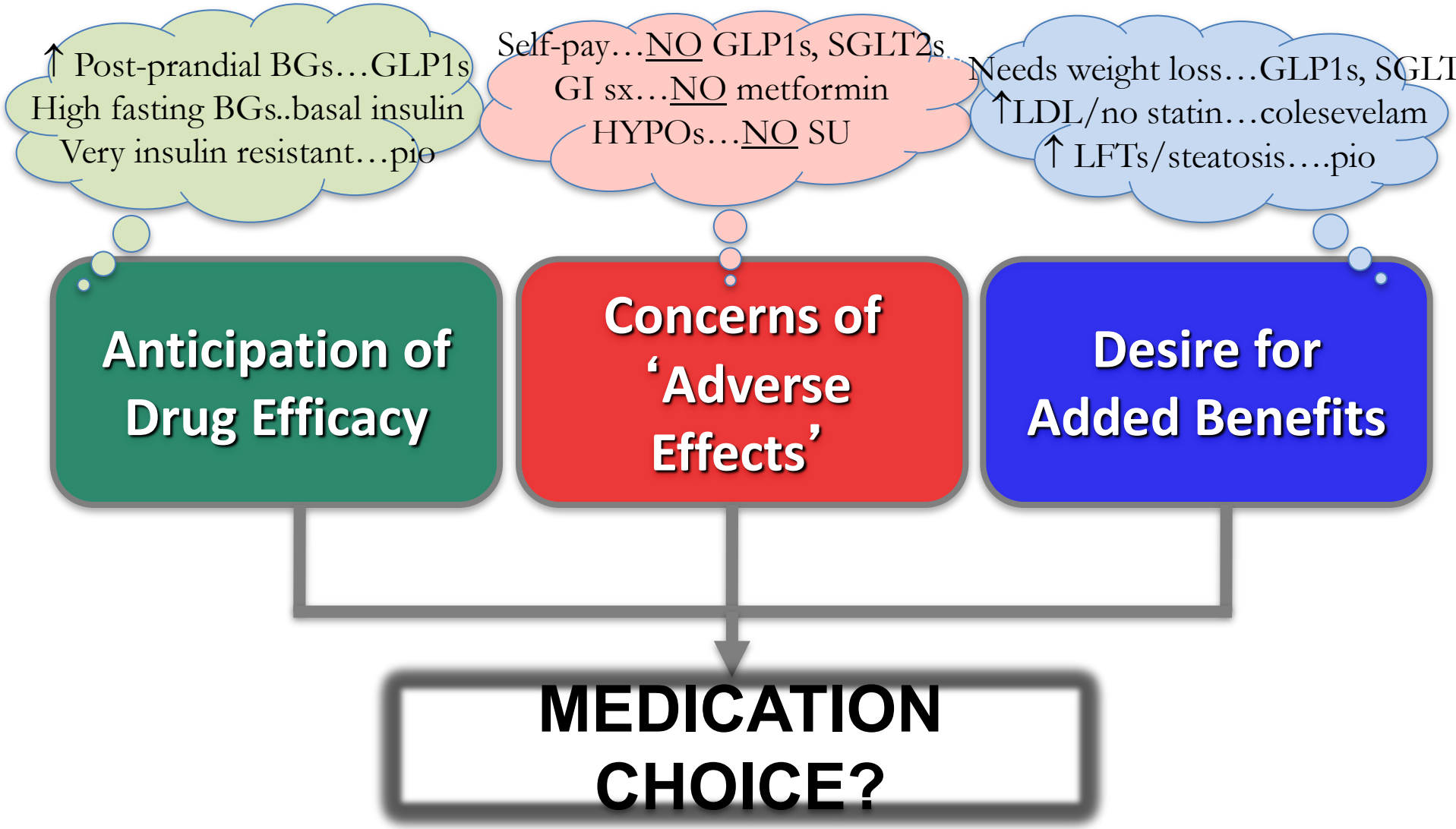
SLGT2 inhibitors

- **Invokana (canagliflozin), 3/2013**
- **Farxiga (dapagliflozin), 1/2014**
- **Jardiance (empagliflozin), 8/2014**

SNAP SHOT:

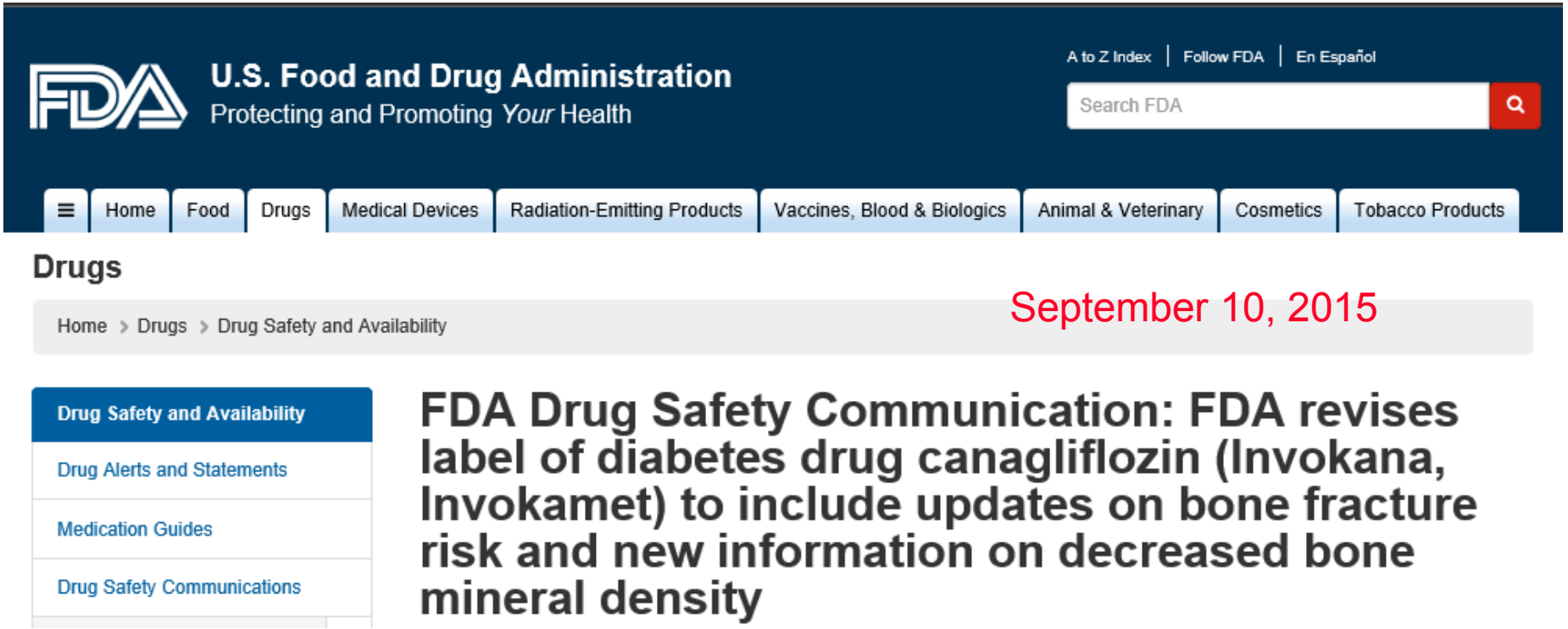
-Ha1c lowering 0.6-1.0%
-Weight lowering
-Once daily oral medication
-Do not use in GFR <45
-Risk of UTI/yeast infections

"Personalizing" Type 2 Diabetes Therapy



"Each capsule contains your medication, plus a treatment for each of its side effects."

- **Symptom onset 1 day to years after start of DPP-4 inhibitor.**
- **Symptom resolution in <1month after medication discontinuation.**
- **Some with symptom return on same or alternate DPP-4 restart.**



- **Fractures occur more frequently, can occur as early as 12 weeks after star, with minor trauma.**
- **Decreased BMD at spine and hip.**

- **73 cases of ketoacidosis in patients with type 1 or type 2 diabetes.**
- **19 cases of urosepsis and pyelonephritis that started as urinary tract infections.**

- **More patients were hospitalized for heart failure compared to placebo.**
- **Saxagliptin trial, 3.5% vs. 2.8% placebo.**
- **Alogliptin trial, 3.9% vs. 3.3% placebo.**

"There is your prescription, Mrs. Hickford, and here is the pamphlet of side effects."

- **Prior: Unsafe in creatinine>1.5mg/dL (M) or >1.4mg/dL (F).**
- **Current: Unsafe in eGFR <30mL/min and do not start if eGFR 30-45mL/min.**

Could diabetes drugs have a cardiovascular benefit?

- **EMPA-REG: empagliflozin, Sept 2015**
- **LEADER: liraglutide, March 2016**
- **IRIS: pioglitazone, April 2016**

Zinman et al, NEJM Nov 2015; 373: 2117-2128
Kernan et al, NEJM April 2016; 374: 1321-1331

Original Article

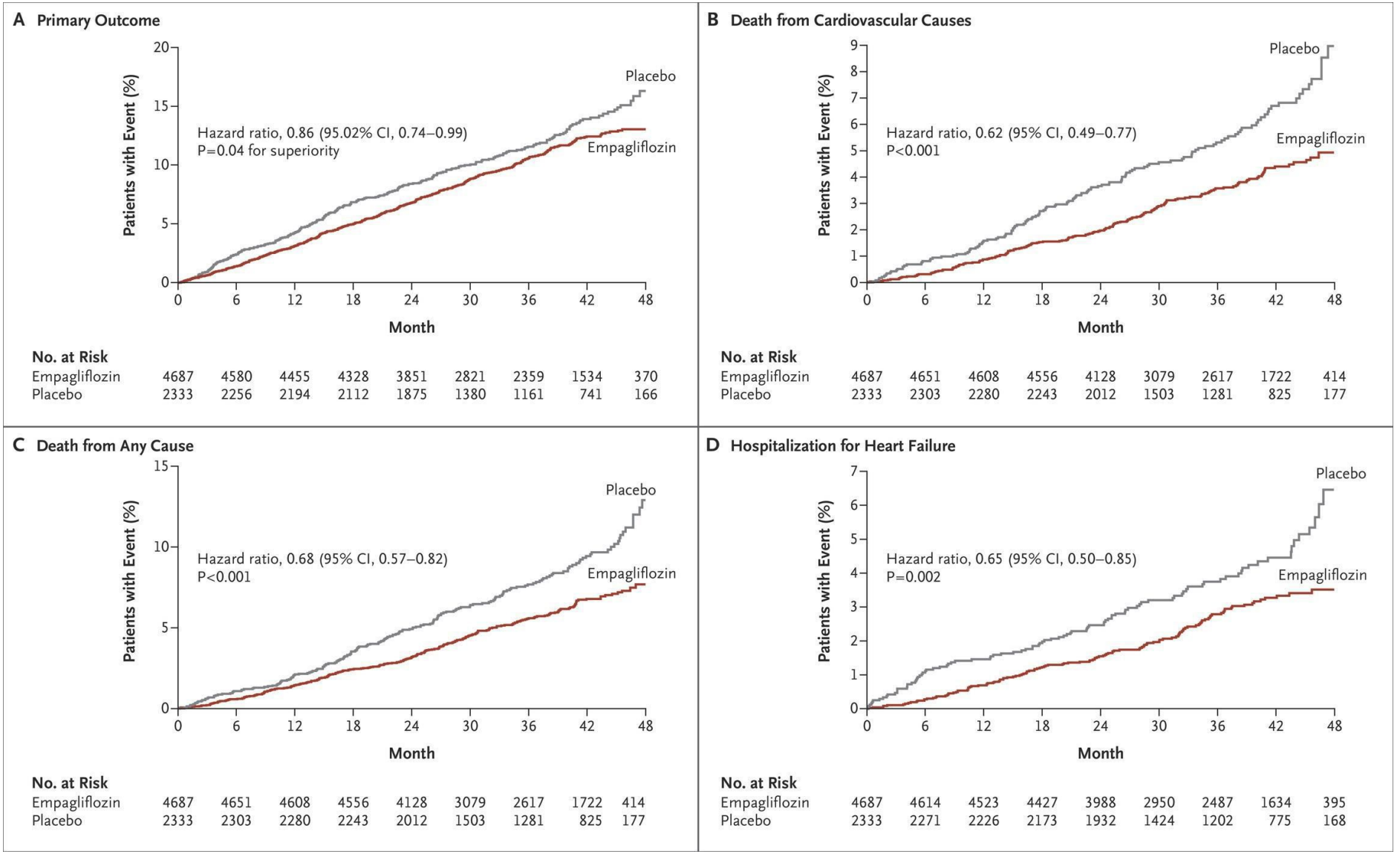
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N Engl J Med
Volume 373(22):2117-2128
November 26, 2015

The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular Outcomes and Death from Any Cause



Zinman B et al. N Engl J Med 2015;373:2117-2128

The NEW ENGLAND JOURNAL of MEDICINE

Primary and Secondary Cardiovascular Outcomes

Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

* Data were analyzed with the use of a four-step hierarchical-testing strategy for the pooled empagliflozin group versus the placebo group in the following order: noninferiority for the primary outcome, noninferiority for the key secondary outcome, superiority for the primary outcome, and superiority for the key secondary outcome. Each successive hypothesis could be tested, provided that those preceding it met the designated level of significance. Data are based on Cox regression analyses in patients who received at least one dose of a study drug.
† One-sided P values are shown for tests of noninferiority, and two-sided P values are shown for tests of superiority.
‡ Silent myocardial infarction was analyzed in 2378 patients in the empagliflozin group and 1211 patients in the placebo group.

Zinman B et al. N Engl J Med 2015;373:2117-2128

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Adverse Events.*

Event	Placebo (N = 2333)	Empagliflozin, 10 mg (N = 2345)	Empagliflozin, 25 mg (N = 2342)	Pooled Empagliflozin (N = 4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Zinman B et al. N Engl J Med 2015;373:2117-2128

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

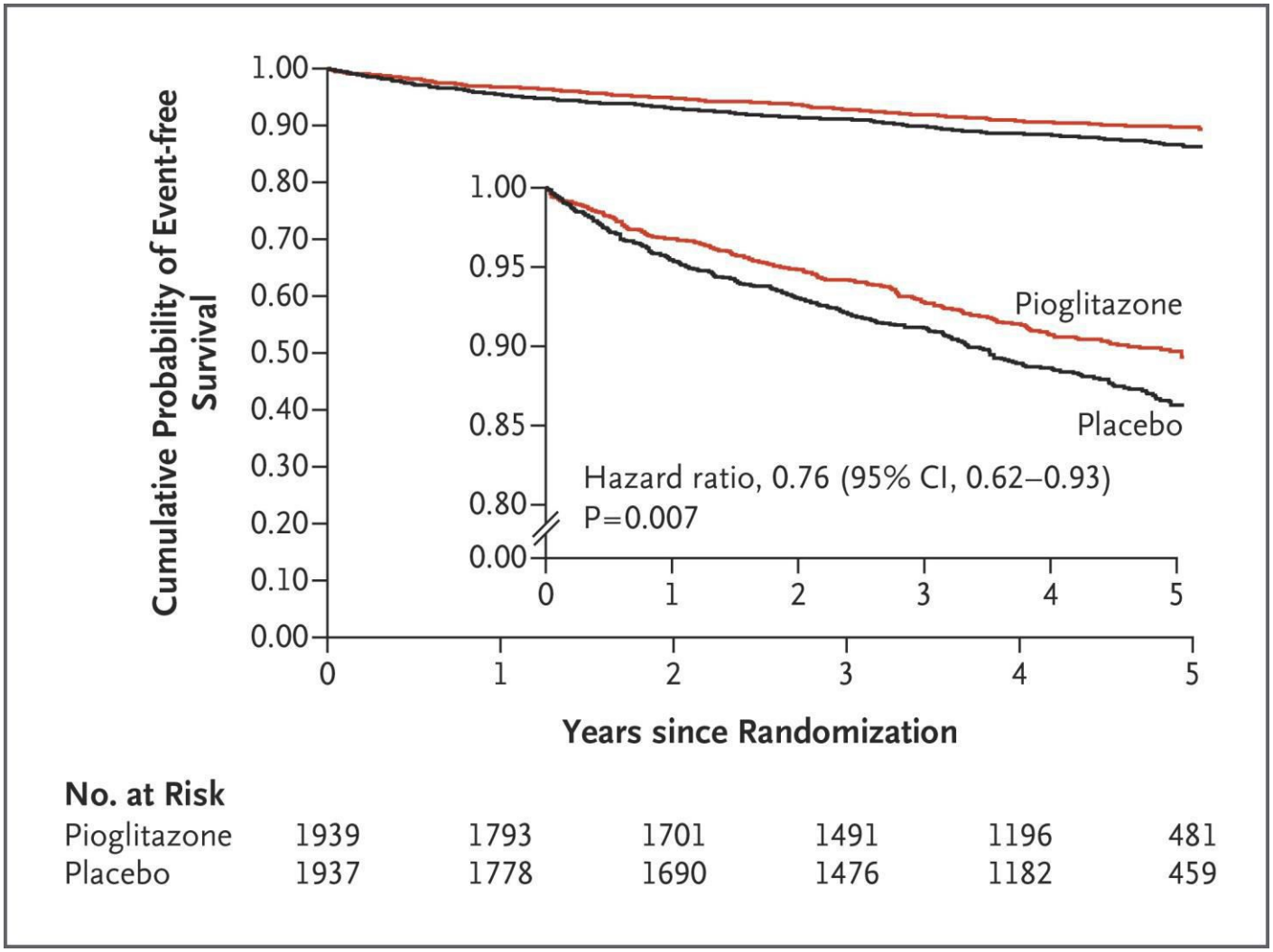
Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

Walter N. Kernan, M.D., Catherine M. Viscoli, Ph.D., Karen L. Furie, M.D., M.P.H., Lawrence H. Young, M.D., Silvio E. Inzucchi, M.D., Mark Gorman, M.D., Peter D. Guarino, Ph.D., Anne M. Lovejoy, P.A.-C., Peter N. Peduzzi, Ph.D., Robin Conwit, M.D., Lawrence M. Brass, M.D., Gregory G. Schwartz, M.D., Ph.D., Harold P. Adams, Jr., M.D., Leo Berger, M.D., Antonio Carolei, M.D., Wayne Clark, M.D., Bruce Coull, M.D., Gary A. Ford, M.B., B.Chir., Dawn Kleindorfer, M.D., John R. O'Leary, M.A., Mark W. Parsons, M.D., Peter Ringleb, M.D., Souvik Sen, M.D., J. David Spence, M.D., David Tanne, M.D., David Wang, M.D., Toni R. Winder, M.D., for the IRIS Trial Investigators

N Engl J Med
Volume 374(14):1321-1331
April 7, 2016

The NEW ENGLAND JOURNAL of MEDICINE

Primary Outcome.



No. at Risk

Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

Kernan WN et al. N Engl J Med 2016;374:1321-1331

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Primary and Secondary Outcomes.

Table 2. Primary and Secondary Outcomes.

Outcome	Pioglitazone (N=1939)	Placebo (N=1937)	Hazard Ratio (95% CI)*	Adjusted P Value†
	no. of patients (%)			
Primary outcome				
Stroke or myocardial infarction‡	175 (9.0)	228 (11.8)	0.76 (0.62– 0.93)	0.007
Stroke	123 (6.3)	150 (7.7)		
Fatal	9 (0.5)	13 (0.7)		
Nonfatal	114 (5.9)	137 (7.1)		
Myocardial infarction	52 (2.7)	78 (4.0)		
Fatal	7 (0.4)	14 (0.7)		
Nonfatal	45 (2.3)	64 (3.3)		
Secondary outcome§				
Stroke	127 (6.5)	154 (8.0)	0.82 (0.61–1.10)	0.19
Acute coronary syndrome: myocardial infarction or unstable angina	96 (5.0)	128 (6.6)	0.75 (0.52–1.07)	0.11
Stroke, myocardial infarction, or serious heart failure¶	206 (10.6)	249 (12.9)	0.82 (0.65–1.05)	0.11
Diabetes mellitus	73 (3.8)	149 (7.7)	0.48 (0.33–0.69)	<0.001
Death from any cause	136 (7.0)	146 (7.5)	0.93 (0.73–1.17)	0.52

* Hazard ratios were calculated by means of a Cox regression model with corresponding 95% confidence intervals. The confidence interval for the primary outcome was adjusted for interim monitoring; confidence intervals for the secondary outcomes were adjusted for multiple comparisons.

† The P value for the primary outcome was adjusted for interim monitoring. P values for the five secondary outcomes were adjusted for multiple comparisons by the Hochberg procedure using an overall familywise type I error of 5%.

‡ Only the first event, stroke or myocardial infarction, was counted for each patient.

§ In the composite categories, only the first event was counted for each patient (e.g., a patient with myocardial infarction followed by unstable angina would be counted only as having a myocardial infarction in the category for acute coronary syndrome). More strokes are listed as occurring as a secondary outcome than a primary outcome because the secondary outcome included strokes occurring after myocardial infarction.

¶ Serious heart failure was defined as an episode resulting in hospitalization or death.

Kernan WN et al. N Engl J Med 2016;374:1321-1331

The NEW ENGLAND JOURNAL of MEDICINE

Adverse Events According to Severity

Table 3. Adverse Events, According to Severity.*

Event	Pioglitazone (N = 1939)	Placebo (N = 1937)	P Value
	no. of patients (%)		
Serious adverse event			
Hospitalization	908 (46.8)	946 (48.8)	0.21
Death	136 (7.0)	146 (7.5)	0.53
Incident cancer			
Any	133 (6.9)	150 (7.7)	0.29
Prostate	28 (1.4)	25 (1.3)	0.68
Breast	10 (0.5)	16 (0.8)	0.24
Lung	13 (0.7)	11 (0.6)	0.68
Bladder	12 (0.6)	8 (0.4)	0.37
Other	75 (3.9)	93 (4.8)	0.15
Bone fracture†	99 (5.1)	62 (3.2)	0.003
Heart failure‡	51 (2.6)	42 (2.2)	0.35
Other§	2 (0.1)	1 (0.1)	0.50
Other adverse event			
Bone fracture¶	133 (6.9)	94 (4.9)	0.008
Heart failure¶	29 (1.5)	32 (1.7)	0.70
Weight gain			
>4.5 kg	1013 (52.2)	653 (33.7)	<0.001
>13.6 kg	221 (11.4)	88 (4.5)	<0.001
Edema‖	691 (35.6)	483 (24.9)	<0.001
Shortness of breath	342 (17.6)	292 (15.1)	0.03
Alanine aminotransferase >ULN	26 (1.3)	59 (3.0)	<0.001
Macular edema	3 (0.2)	2 (0.1)	0.66

Kernan WN et al. N Engl J Med 2016;374:1321-1331

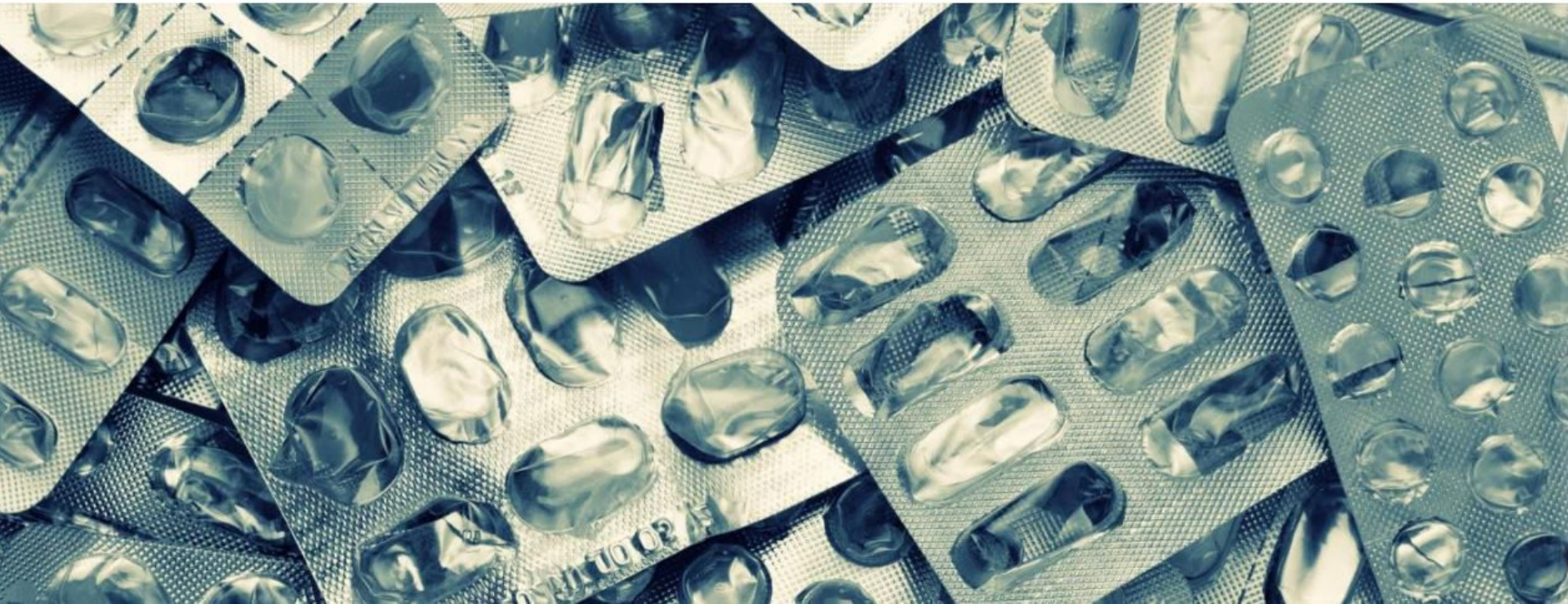
The NEW ENGLAND JOURNAL of MEDICINE

Newsweek

TECH & SCIENCE

THE DIABETES DRUG THAT COULD BE AN ANTI-AGING MIRACLE

BY ALISSA FLECK ON 12/12/15 AT 1:12 PM

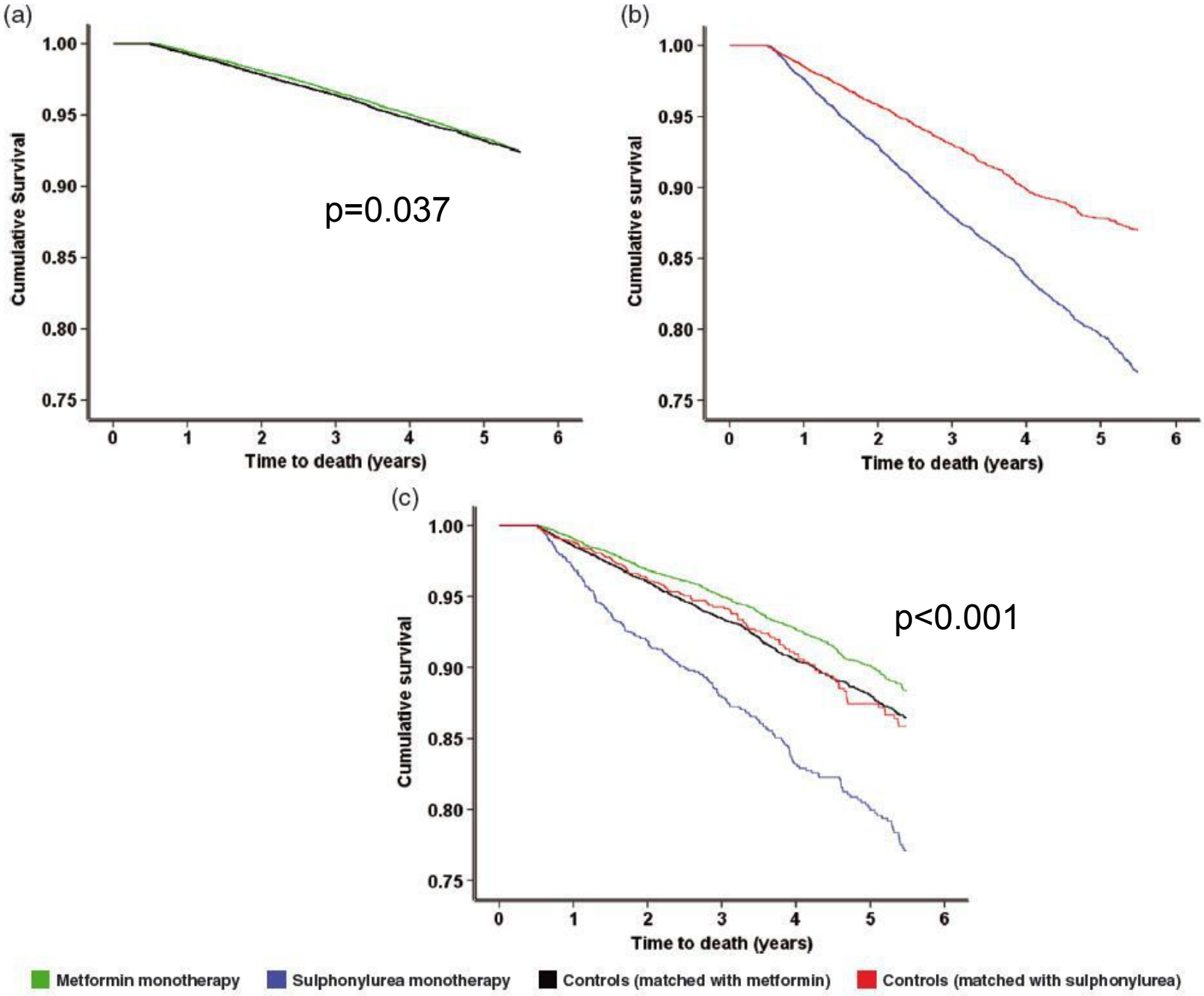


Can diabetes drug Metformin extend your life?

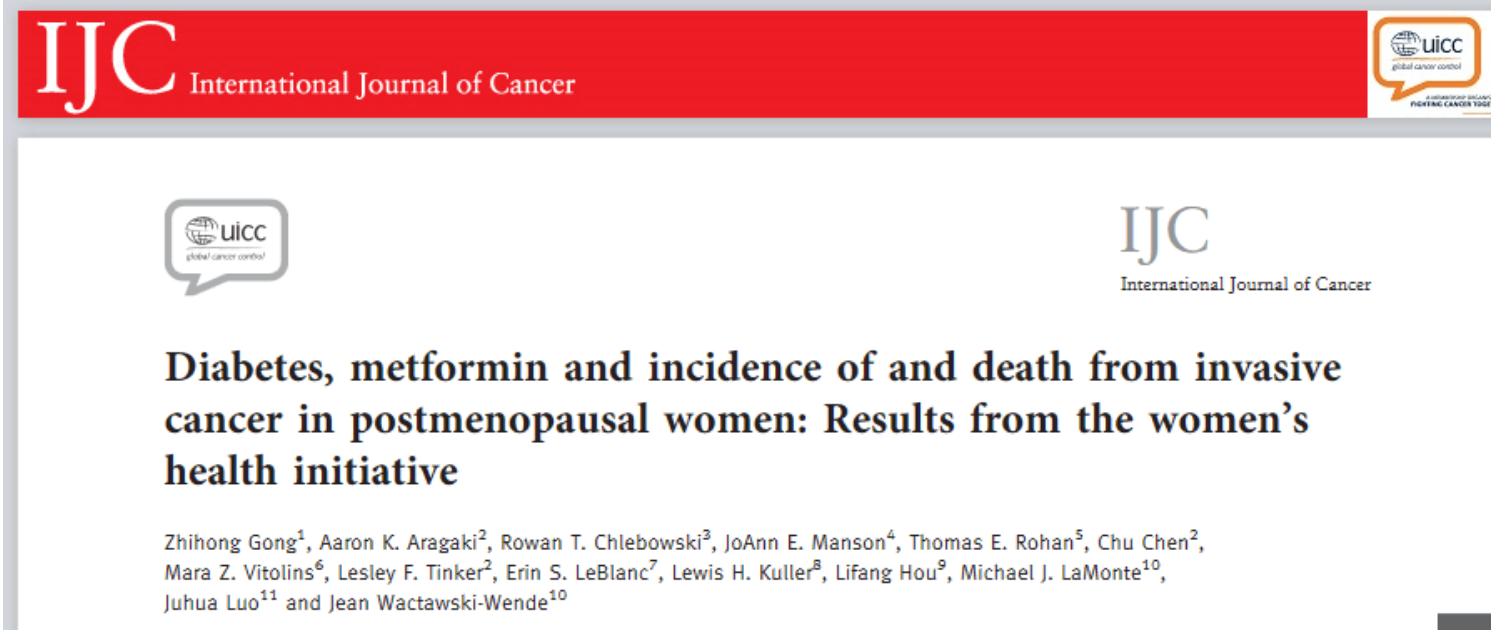
LIFESTYLES By Steve Dorfman - Palm Beach Post Staff Writer

Posted: 7:00 a.m. Tuesday, Dec. 15, 2015

- Improved survival
- Anti-cancer benefits
- Cardiovascular benefit
- Cognitive benefits
- Reduce pre-diabetes progression



Diabetes, Obesity and Metabolism 16: 1165-1173, 2014



IJC International Journal of Cancer

uicc global cancer control

IJC
International Journal of Cancer

Diabetes, metformin and incidence of and death from invasive cancer in postmenopausal women: Results from the women's health initiative

Zhihong Gong[1], Aaron K. Aragaki[2], Rowan T. Chlebowski[3], JoAnn E. Manson[4], Thomas E. Rohan[5], Chu Chen[2], Mara Z. Vitolins[6], Lesley F. Tinker[2], Erin S. LeBlanc[7], Lewis H. Kuller[8], Lifang Hou[9], Michael J. LaMonte[10], Juhua Luo[11] and Jean Wactawski-Wende[10]

- **45% higher odds of dying from cancer if diabetic compared to non-diabetic**
- **Women with cancer and DM2 on metformin had the same risk of dying as non-diabetic women**

Int. J. of Cancer: 138, 1915-1927 (2016)

Break Up the Insulin Racket

By KASIA LIPSKA FEB. 20, 2016

Table. Weighted Characteristics of Treated Patients With Diabetes in the Medical Expenditure Panel Survey (MEPS), 2002-2013

Characteristics	MEPS Survey Years			
	2002-2004 (n = 5799)[a]	2005-2007 (n = 6486)	2008-2010 (n = 7237)	2011-2013 (n = 8356)
Treated diabetes, % (95% CI)[b]	5.2 (4.9-5.4)	6.2 (5.9-6.5)	7.1 (6.8-7.4)	7.7 (7.4-8.0)
Age, mean (SD), y	60.2 (15.0)	60.3 (14.6)	60.3 (14.8)	60.7 (14.6)
Men, No. (%)	2496 (47.7)	2850 (48.3)	3182 (47.9)	3845 (50.0)
Race, No. (%)[c]				
White	2951 (65.3)	3209 (65.0)	3089 (64.9)	3210 (62.0)
Black	1202 (16.2)	1350 (15.1)	1805 (15.0)	2197 (15.5)
Hispanic	1334 (12.5)	1533 (13.5)	1699 (12.9)	2202 (15.1)
Others	312 (6.1)	394 (6.5)	644 (7.2)	747 (7.4)
Use of medications, % (95% CI)				
Insulin	28.1 (26.2-29.8)	24.1 (22.4-25.8)	25.3 (23.7-27.0)	29.2 (27.6-30.8)
Metformin	36.1 (34.2-38.0)	43.6 (41.6-45.5)	47.3 (45.4-49.2)	51.5 (49.8-53.1)
Sulfonylureas	38.2 (36.2-40.1)	35.1 (33.2-36.9)	30.7 (28.9-32.4)	27.5 (25.8-29.3)
Thiazolidinediones	21.1 (19.5-22.7)	23.2 (21.5-24.9)	13.0 (11.6-14.3)	5.8 (5.0-6.6)
α-Glucosidase inhibitors and nonsulfonylurea secretagogues	2.6 (2.0-3.2)	2.8 (2.2-3.4)	1.4 (1.0-1.8)	0.7(0.5-1.0)
DPP-4 inhibitors		1.2 (0.8-1.5)	5.6 (4.7-6.5)	7.7 (6.8-8.7)
Combinations	6.8 (5.8-7.7)	8.9 (7.8-9.9)	8.0 (7.0-9.0)	6.0 (5.1-6.9)
All orals[d]	68.9 (66.9-70.8)	72.6 (70.9-74.4)	70.8 (69.2-72.5)	69.5 (67.9-71.1)
Amylin analogs		0.1 (0-0.1)	0.2 (0.1-0.4)	0.1 (0-0.2)
GLP-1 receptor agonists			2.2 (1.6-2.8)	2.7 (2.1-3.4)
All noninsulin injectables[e]			2.4 (1.8-3.1)	2.8 (2.1-3.4)
Quantity of medications (95% CI)[f]				
Insulin, mL	171 (160-181)	150 (137-164)	205 (191-218)	206 (193-220)
All orals, tablets	611 (580-641)	632 (607-657)	775 (746-804)	800 (772-828)
All noninsulin injections, mL			21 (16-25)	36 (30-42)

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

[a] The reported statistics were based on a pooled sample across 3 waves of MEPS.

[b] Percentage of all survey respondents. People treated for diabetes were identified using 3-digit *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes.

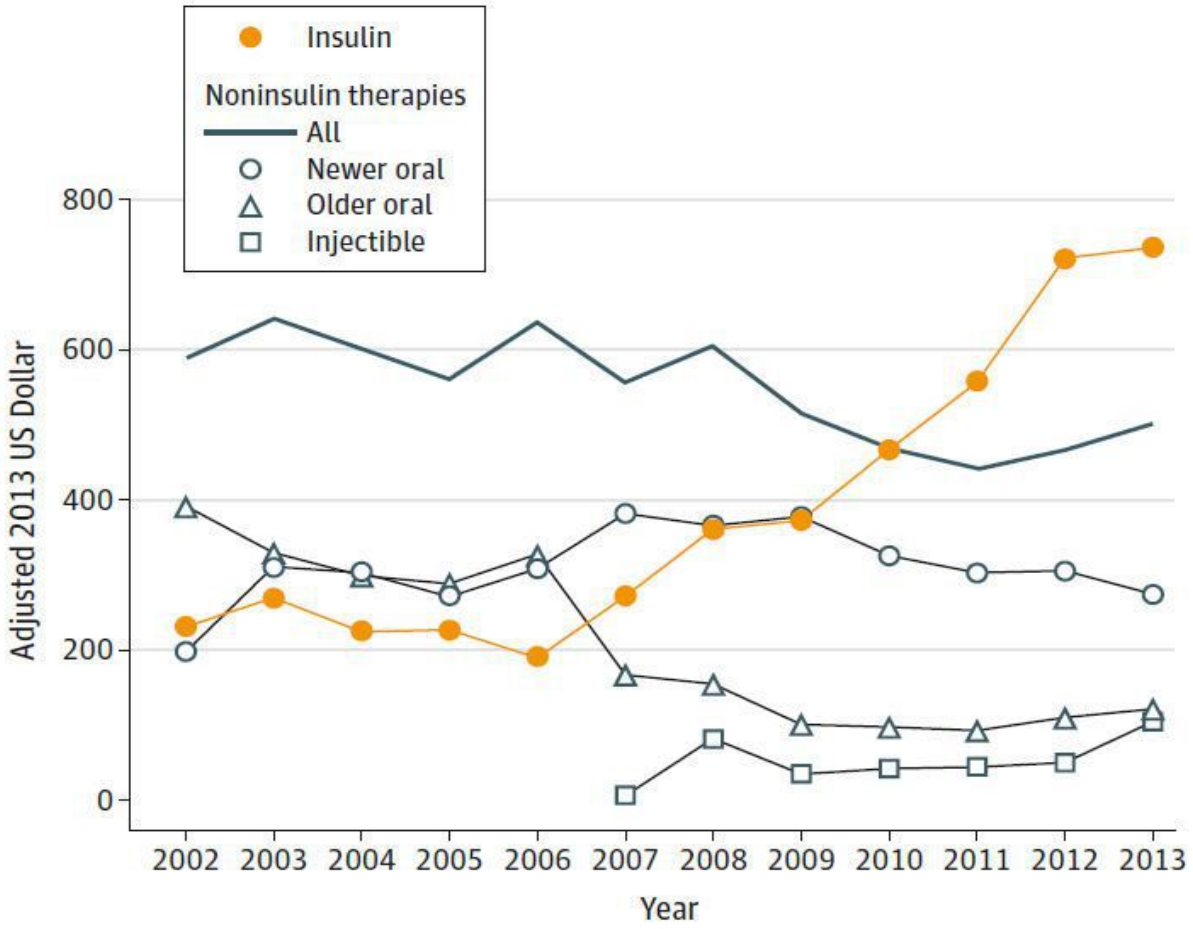
[c] Race was included as part of the descriptive analysis. As defined by MEPS, classification by race and ethnicity was mutually exclusive and based on information reported for each family member. All persons whose main national origin or ancestry was reported as Hispanic, regardless of racial background, were classified as Hispanic.

[d] Included metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, and nonsulfonylurea secretagogues, combinations, and DPP-4 inhibitors.

[e] Included amylin analogs and GLP-1 receptor agonists from 2008.

[f] Quantities of medication used were means per patient per year, conditional on some recorded use of the drug over the given period.

Figure. Mean Expenditure per Patient for Antihyperglycemic Medications, 2002-2013



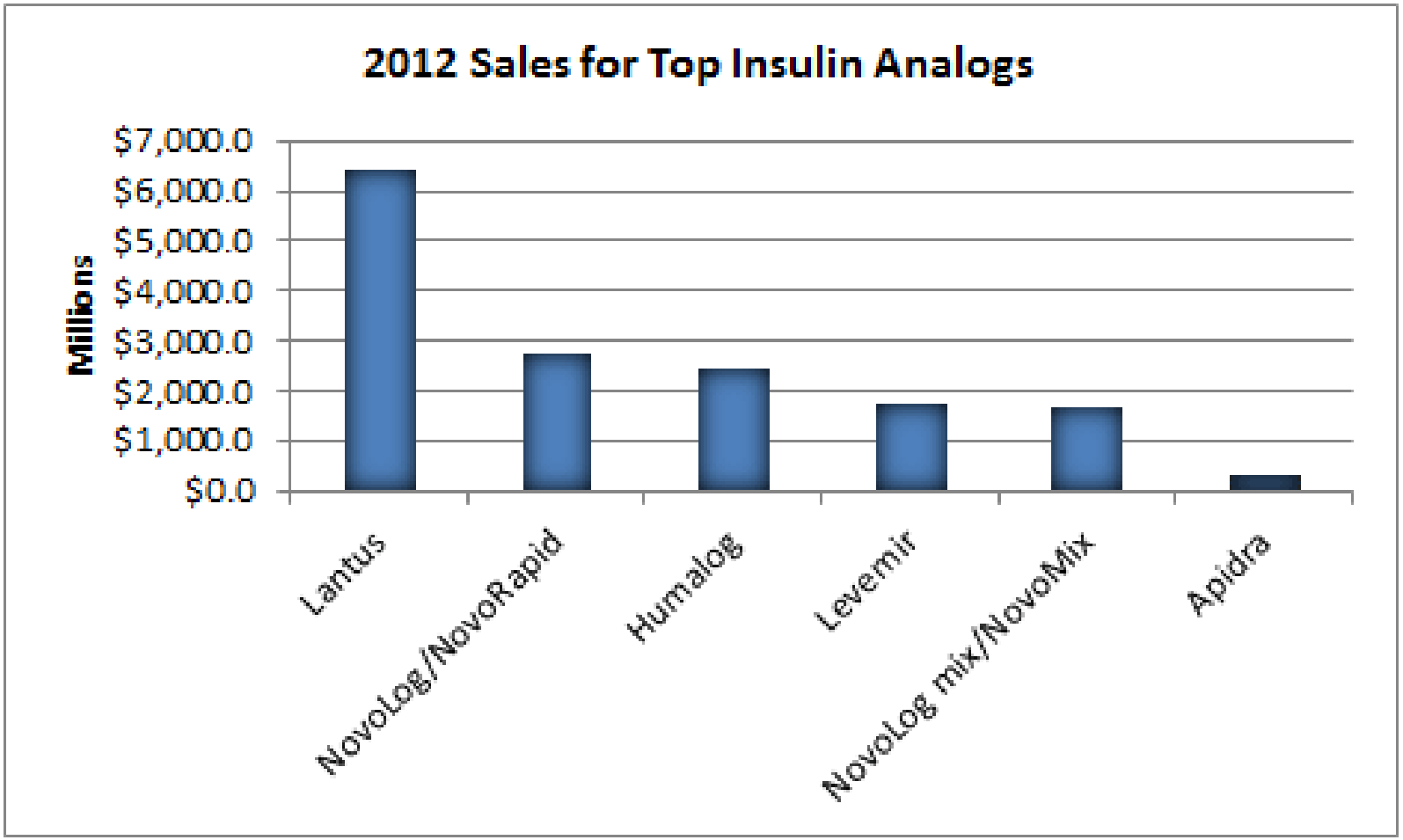
Medications were classified as follows: insulin (human and analog); newer oral therapies (thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and combinations); older oral therapies (metformin, sulfonylureas, α-galactosidase inhibitors, and nonsulfonylurea secretagogues); noninsulin-based injectable therapies (glucagon-like peptide-1 receptor agonists and amylin analogs).

-Cost of insulin up $231.48>$736.09

-Price of insulin per mL up 197%

-Cost greater than all other DM meds combined

JAMA April 5, 2016 Volume 315, Number 13



- **Eli Lily, Sanofi and NovoNordisk hold patents to manufacture insulin**
- **No generics or "biosimilars" yet**

http://www.fool.com/investing/general/2013/05/23/the-coming-diabetes-wars.aspx

New insulins

- Novo-Nordisk
  - Tresiba U-100 and U-200
  - Ryzodeg 70/30 (degludec/aspart)
  - Ultra rapid/NovoRapid (phase 3)
- Lilly
  - U-500 Humulin R pen
  - Basaglar (glargine biosimilar)
  - Ultra rapid (phase 1)
- Sanofi
  - Toujeo U-300
  - Lispro biosimilar (phase 3)

Are newer insulins worth the cost?

PRO

- Only 30% of DM2 on insulin at goal ha1c
- Lower risk of Nocturnal HYPOglycemia
- Less weight gain
- Longer, smoother, more predictable response
- Convenient, more flexible dosing

CON

- Nocturnal HYPO 20x lower in DM2 vs. DM1
- Prandial insulin less important in DM2
- Small difference in Ha1c (<0.1%)

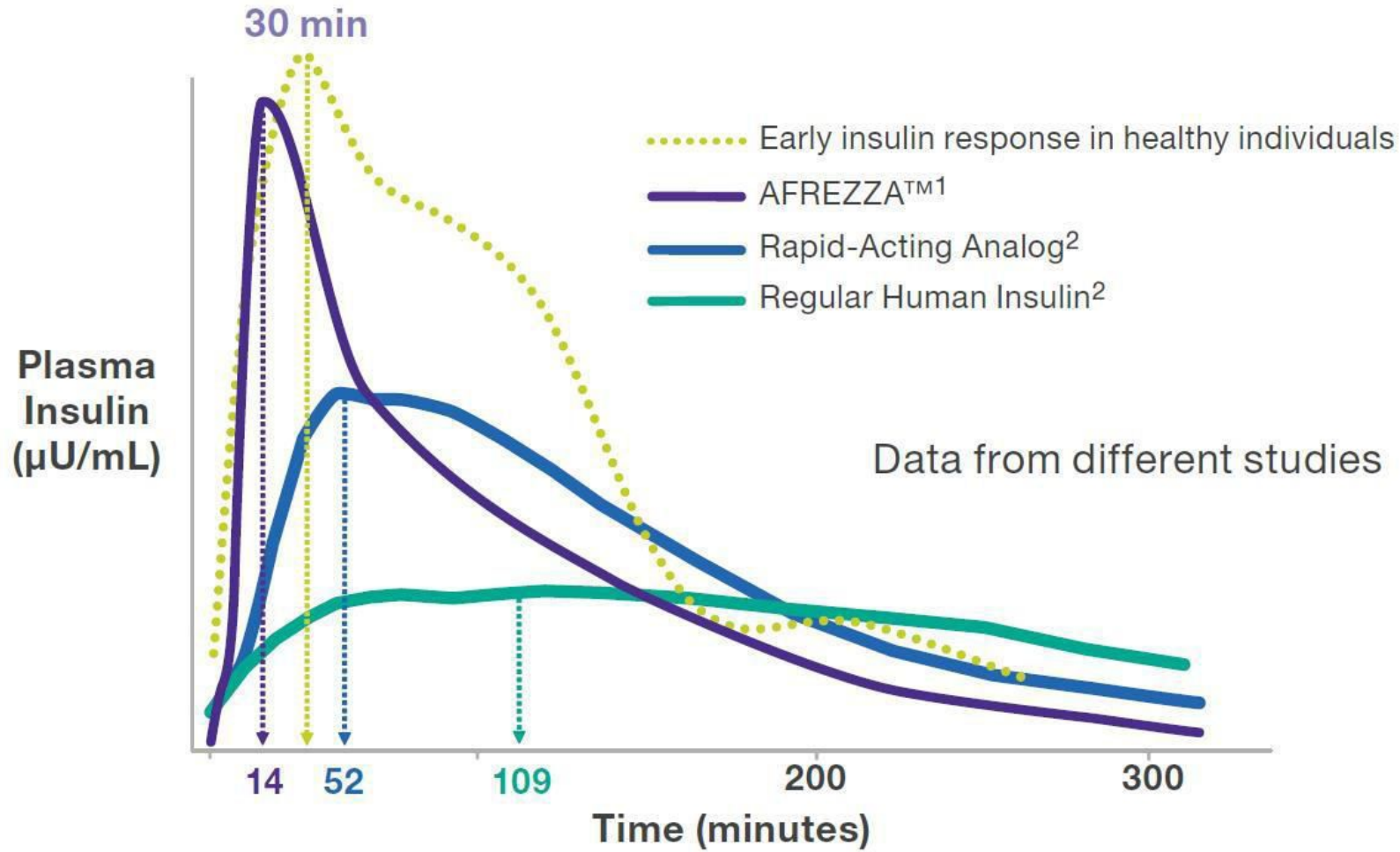
Afreeza

Approved 6/2014

- **PROS:**
- **-More rapid onset/duration mimics native insulin secretion**
- **-Less weight gain, less HYPOs**
- **-Avoid injections**
- **-Approved for DM1 and DM2**

- **CONS:**
- **-Throat pain, irritation**
- **-Do not use with asthma/COPD**
- **-Do not use in smokers or recent smokers**
- **-Long term pulmonary safety data?**

Time to Peak Insulin Level



1. Non-diabetic obese subjects after 100 g oral glucose. Adapted from Kipnis D. *Ann Intern Med*. 1968;69:891-900.
2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. *Diabetes Care*. 1999;22:1501-1506.

MNKD: Afrezza Launch Will Propel MannKind Stock

MNKD stock is still a screaming buy as Afrezza launch nears

By John Divine, InvestorPlace Assistant Editor | Jan 23, 2015, 2:00 pm EST

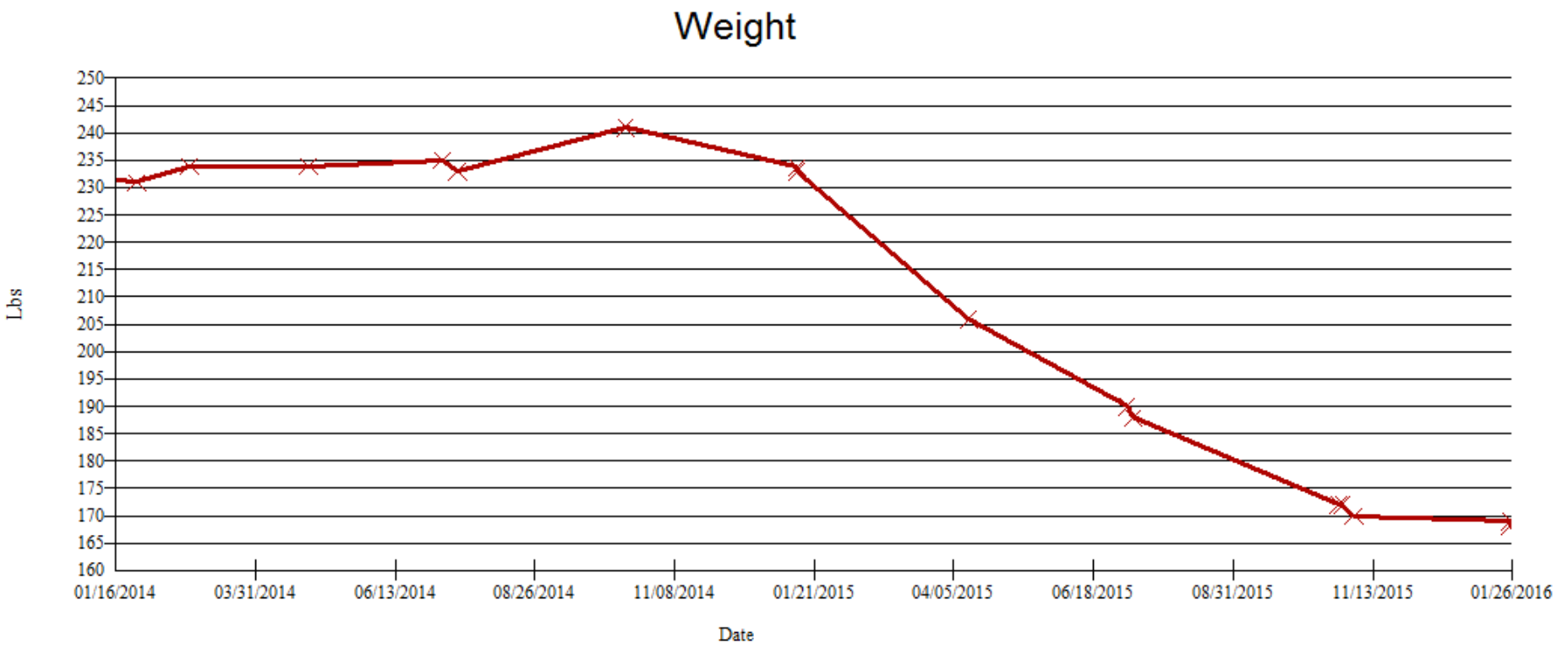
MannKind Corporation (NASDAQ:MNKD) stock is primed to take off higher as the much-awaited launch of its inhalable insulin drug, Afrezza, approaches.

MNKD stock and its $2.3 billion market capitalization hang in the balance, as its fate could

Cleveland Clinic
Florida

Patient Cases

GR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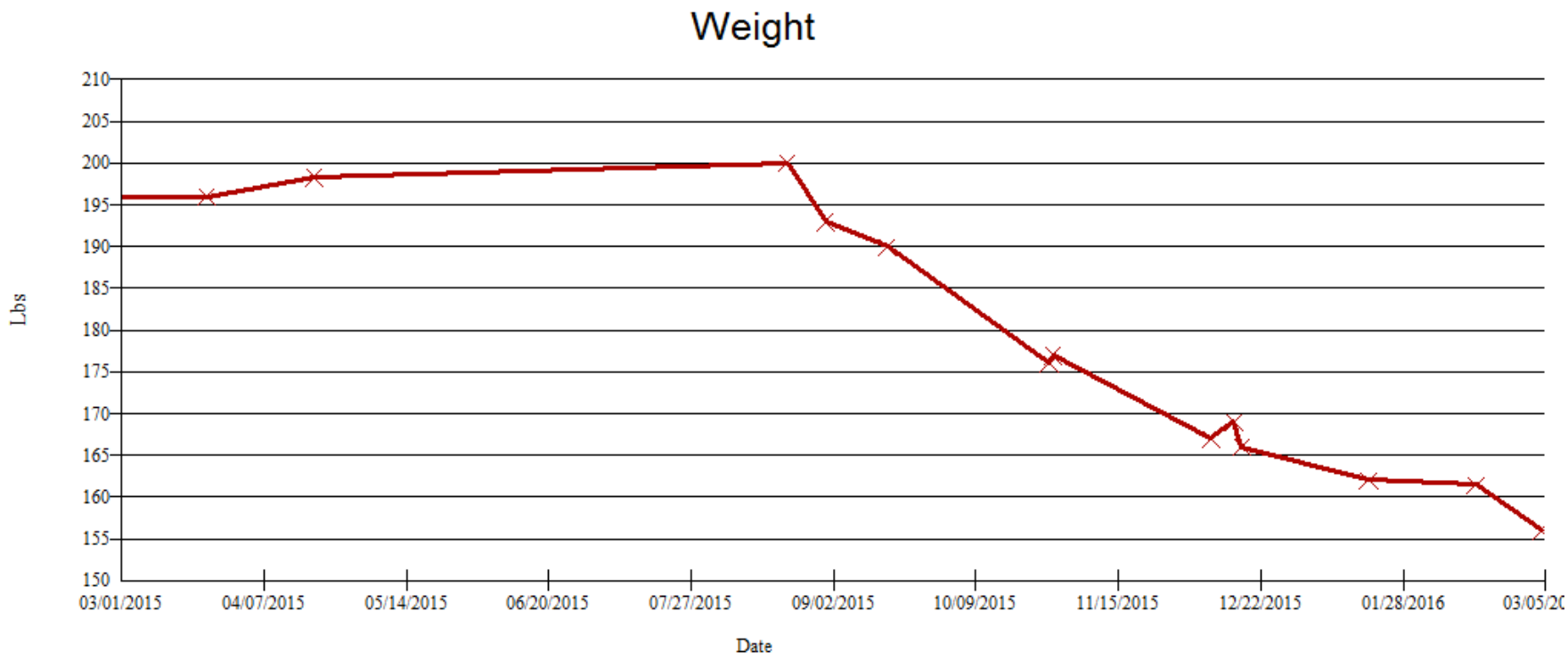
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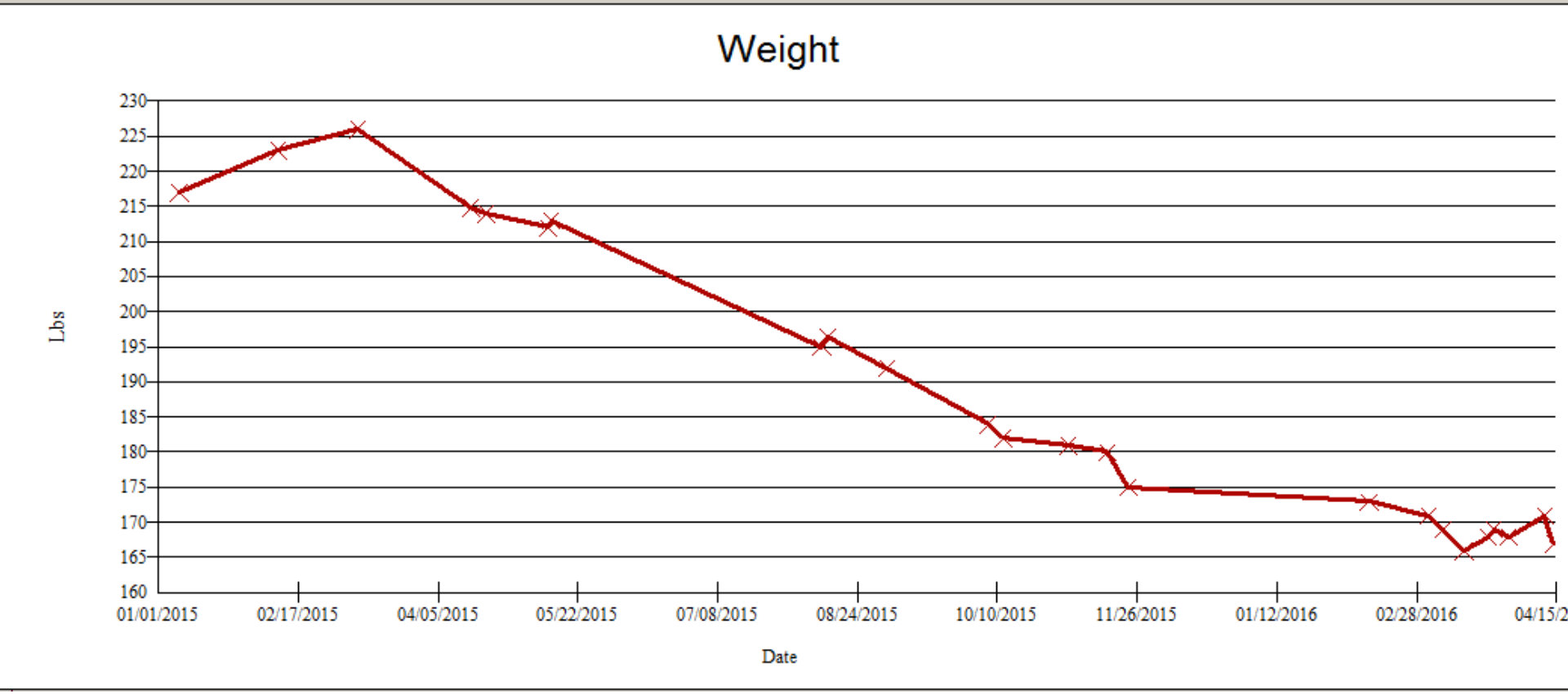
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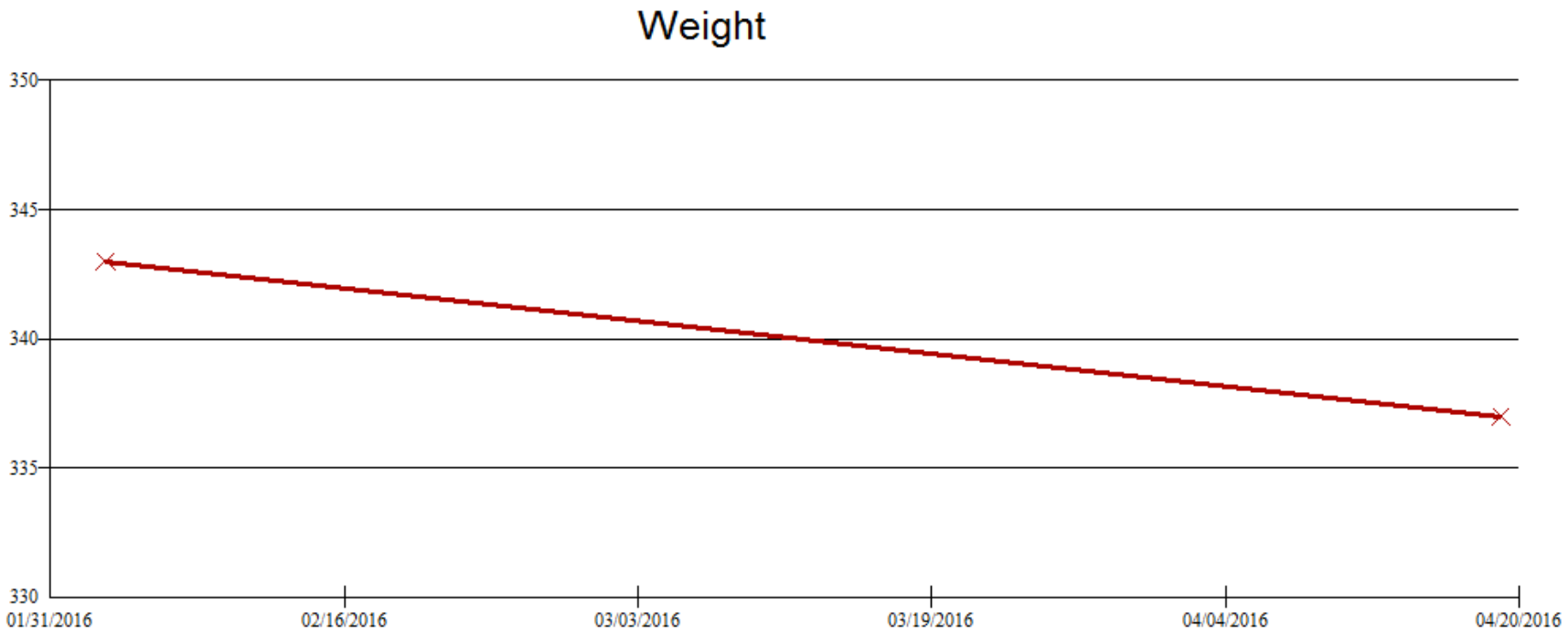
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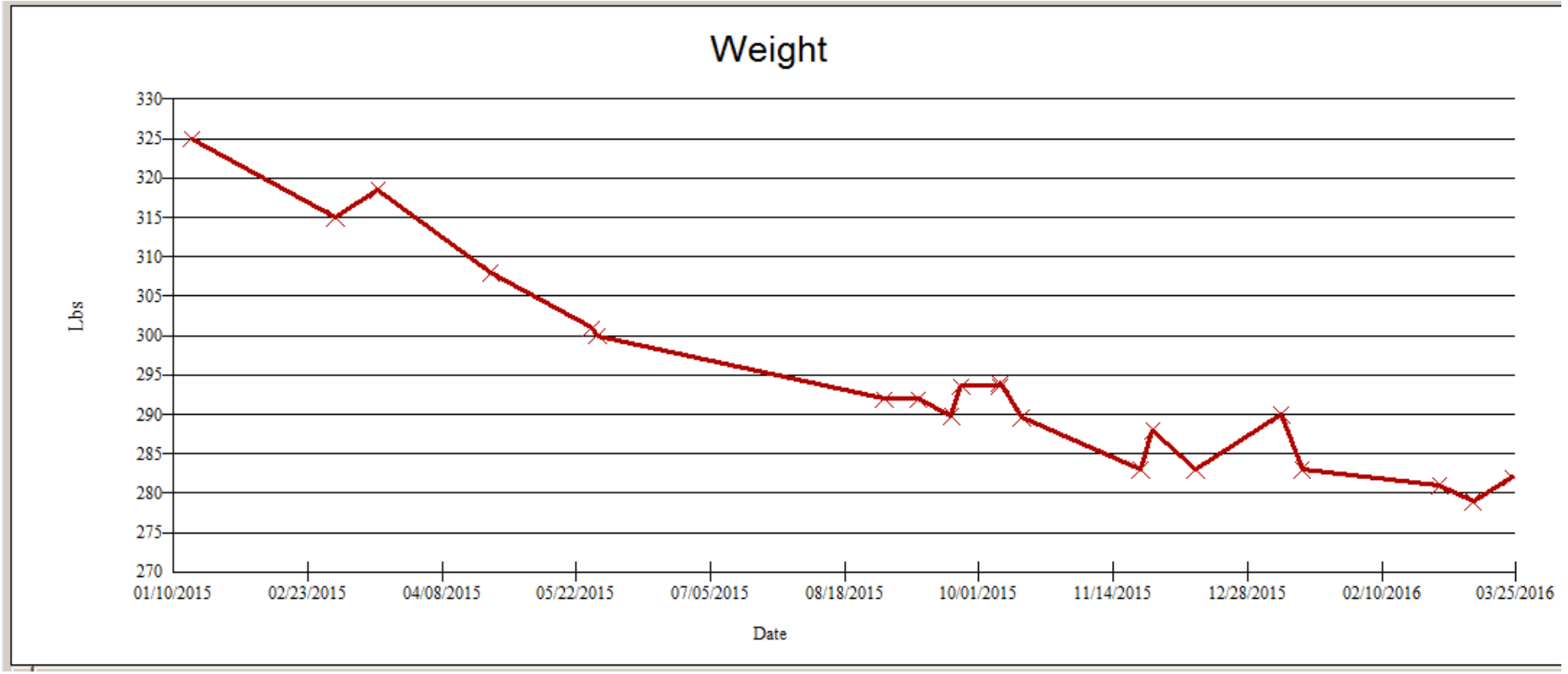
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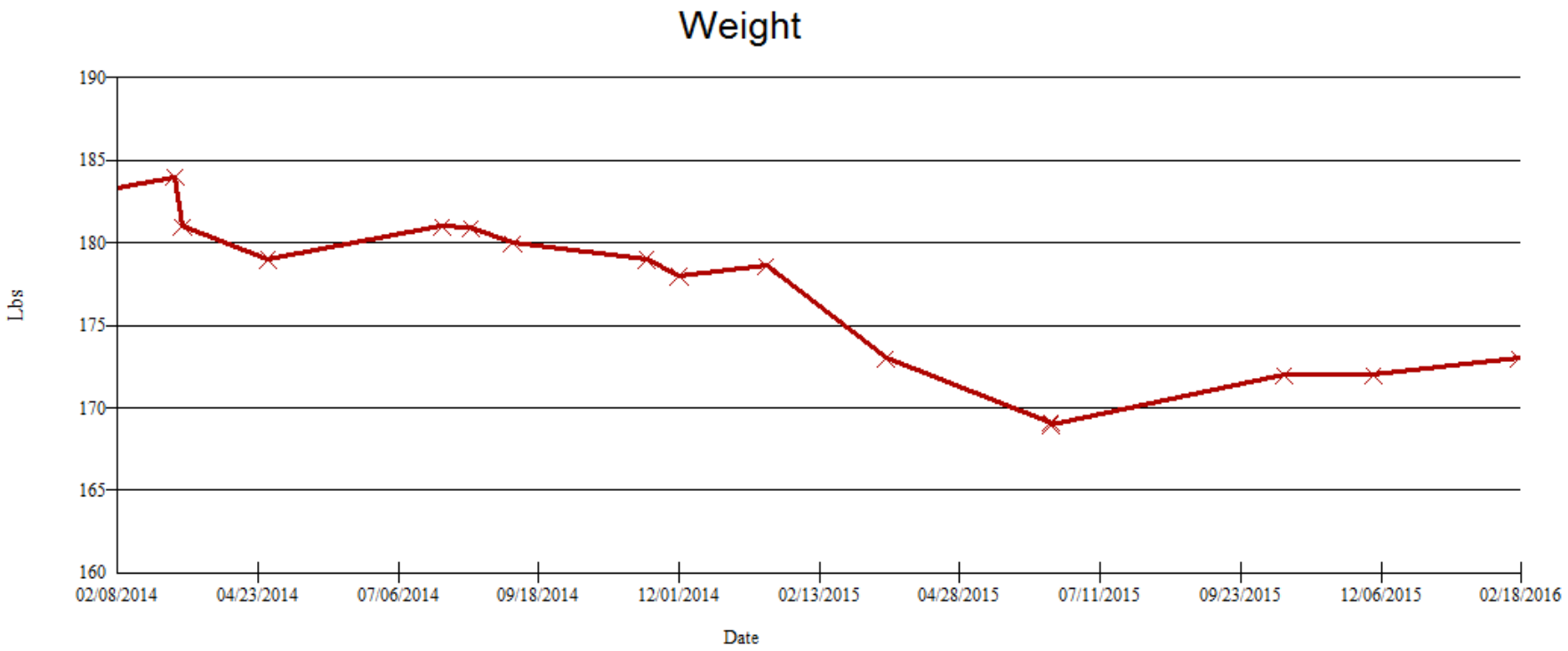
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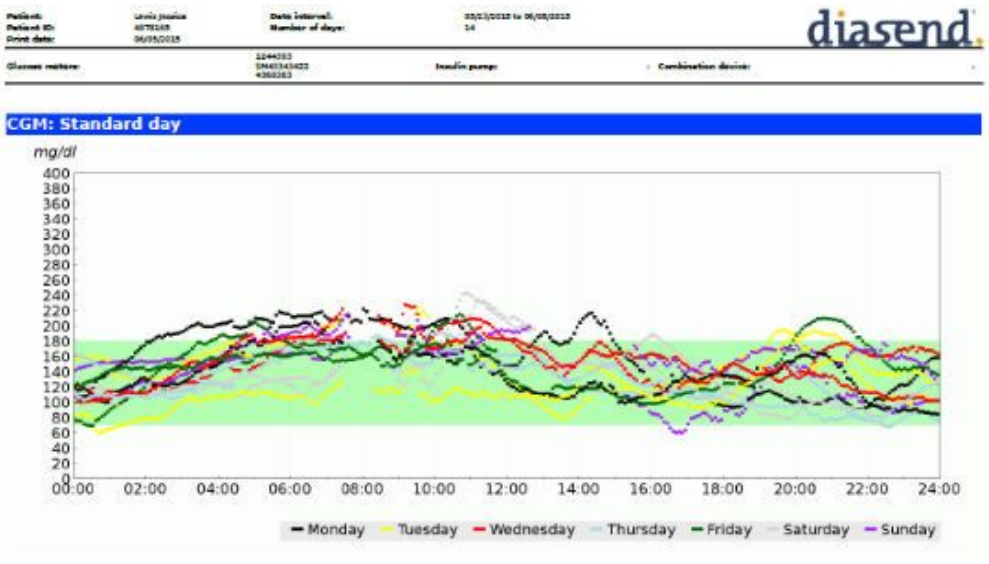
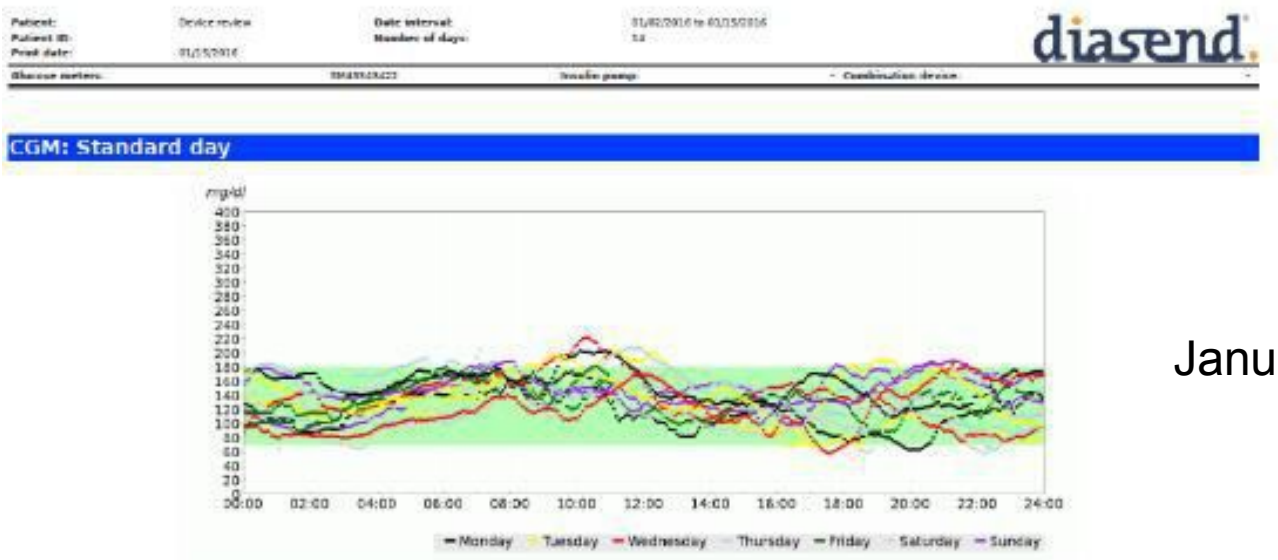


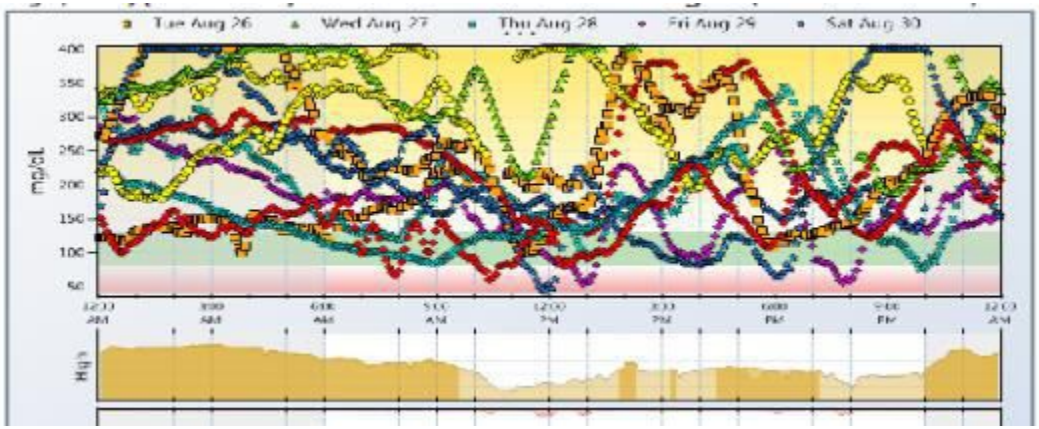
June 5, 2015



January 15, 2016

NB

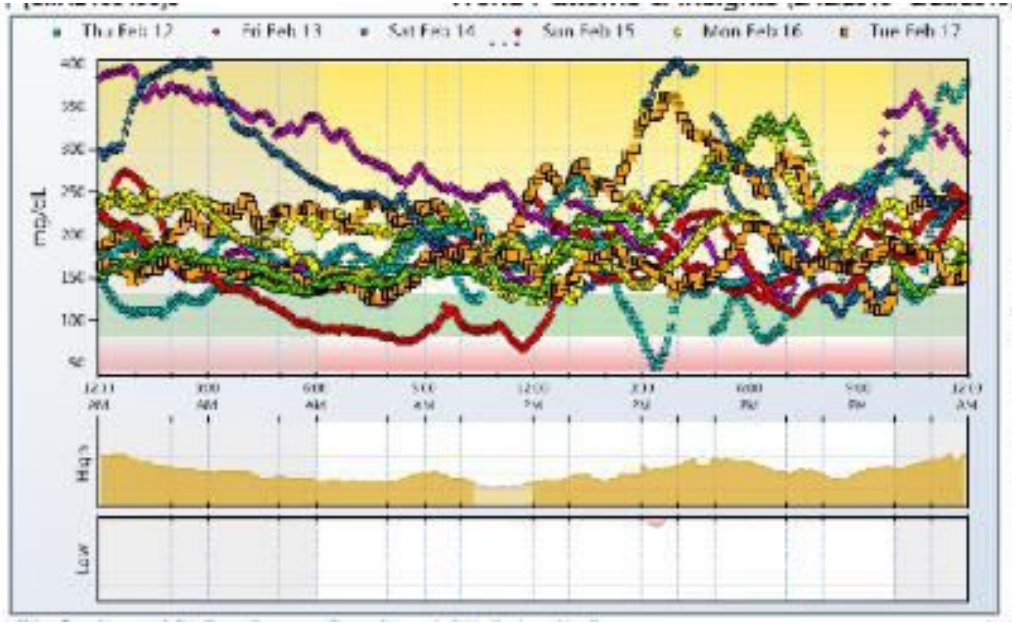
9/18/14



Statistics	
Average Glucose	230 mg/dL
Sensor Usage	14 of 14 Days
Calibrations / day	0.9
Standard Deviation	± 90 mg/dL
	86 % High
	12 % Target
	1 % Low
Target Range	80 - 130 mg/dL
Nighttime	10:00 PM - 6:00 AM

Interpretation

2/25/15



Statistics	
Average Glucose	198 mg/dL
Sensor Usage	14 of 14 Days
Calibrations / day	0.7
Standard Deviation	± 62 mg/dL
	92 % High
	7 % Target
	1 % Low
Target Range	80 - 130 mg/dL
Nighttime	10:00 PM - 6:00 AM

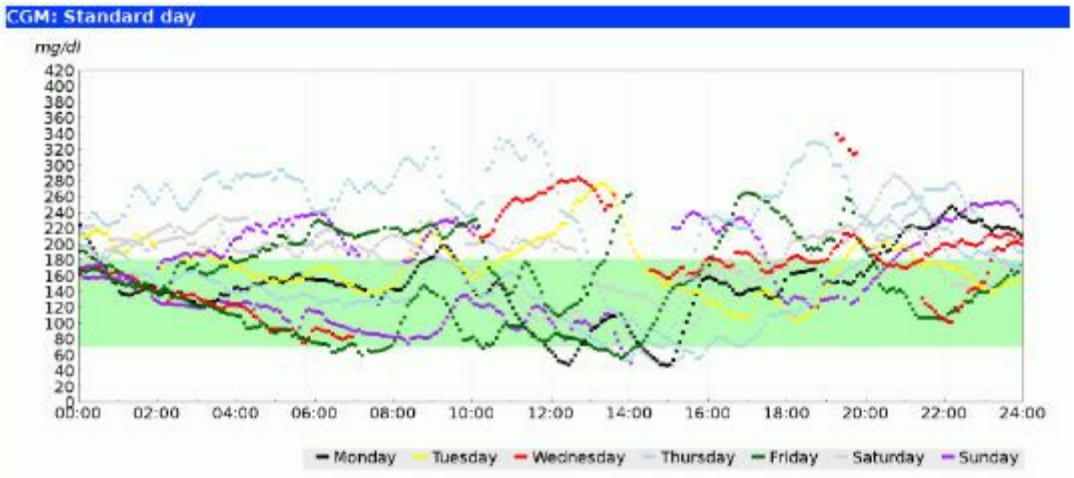
Interpretation

NB

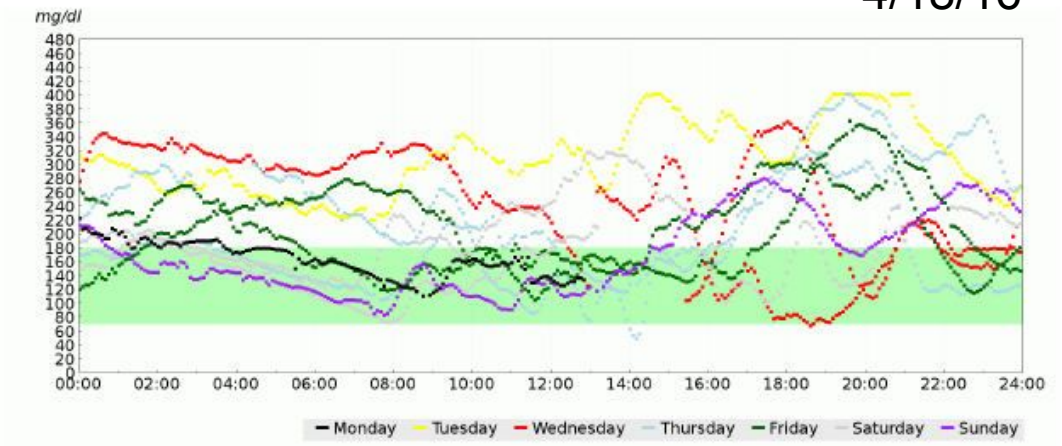
9/5/15

diasend.

Glucose meters: SN42160453 Insulin pump: Combination device:



4/18/16



Cleveland Clinic

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