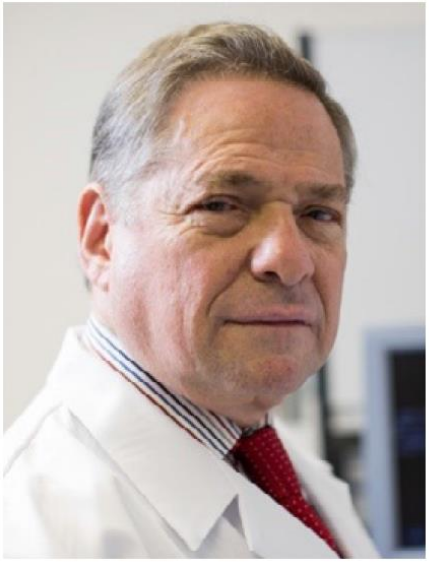
Primary Care & Population Health

GRAND ROUNDS

NYC HEALTH+ HOSPITALS | ONECITY HEALTH

Today's Presenter



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Montefiore Medical Center

The University Hospital
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College of Medicine
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Disclosures

The presenter has the following to disclose:

- Speakers' Bureau, Consultant for:
  - Novo Nordisk
  - Merck
  - Boehringer Ingelheim

The members of the Grand Rounds Planning Committee have no actual or potential conflict of interest in relation to this presentation.

Managing Type 2 Diabetes in the 21st Century

Joel Zonszein, MD, CDE, FACP, FACE

Montefiore Medical Center, the University Hospital for Albert Einstein College of Medicine

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EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Montefiore

DIABETES

Worldwide: Quadrupled to 422 million ~8.8%

USA: 29.1 million (9.3%) 10 to 27.8% undiagnosed

2014 www.cdc.gov/diabetes/data/ & Ann Intern Med. 2017;167(11):769-776

The BRONX 14.6%

Diabetes "discriminates minority populations"

More diabetes > late diagnosis and treatment > more complications > more hospitalizations > higher mortality

2013 https://www1.nyc.gov/assets/doh/

PATHOPHYSIOLOGY AND LANDMARK STUDIES

TREATMENT –NEWER MEDICATIONS

CARDIOVASCULAR OUTCOME TRIALS (CVOT)

NEW PARADIGM

Managing Type 2 Diabetes, a New Paradigm

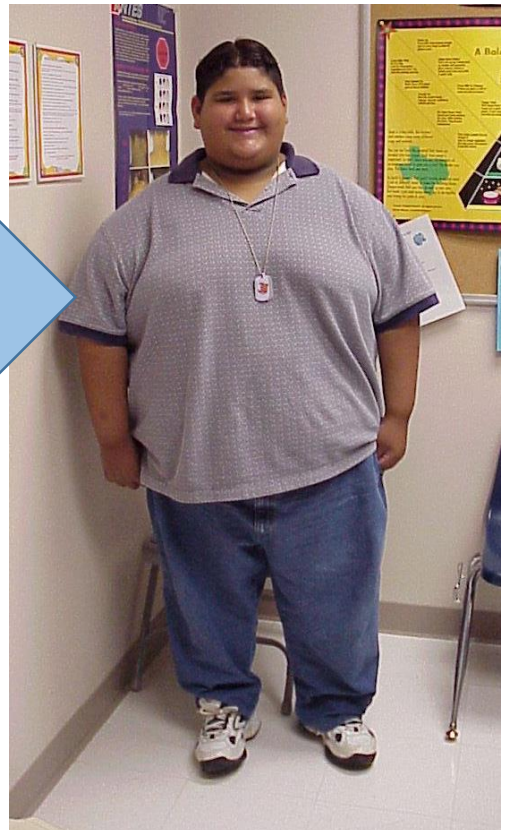
Diabetes an evolving disease...

Early 20th Century

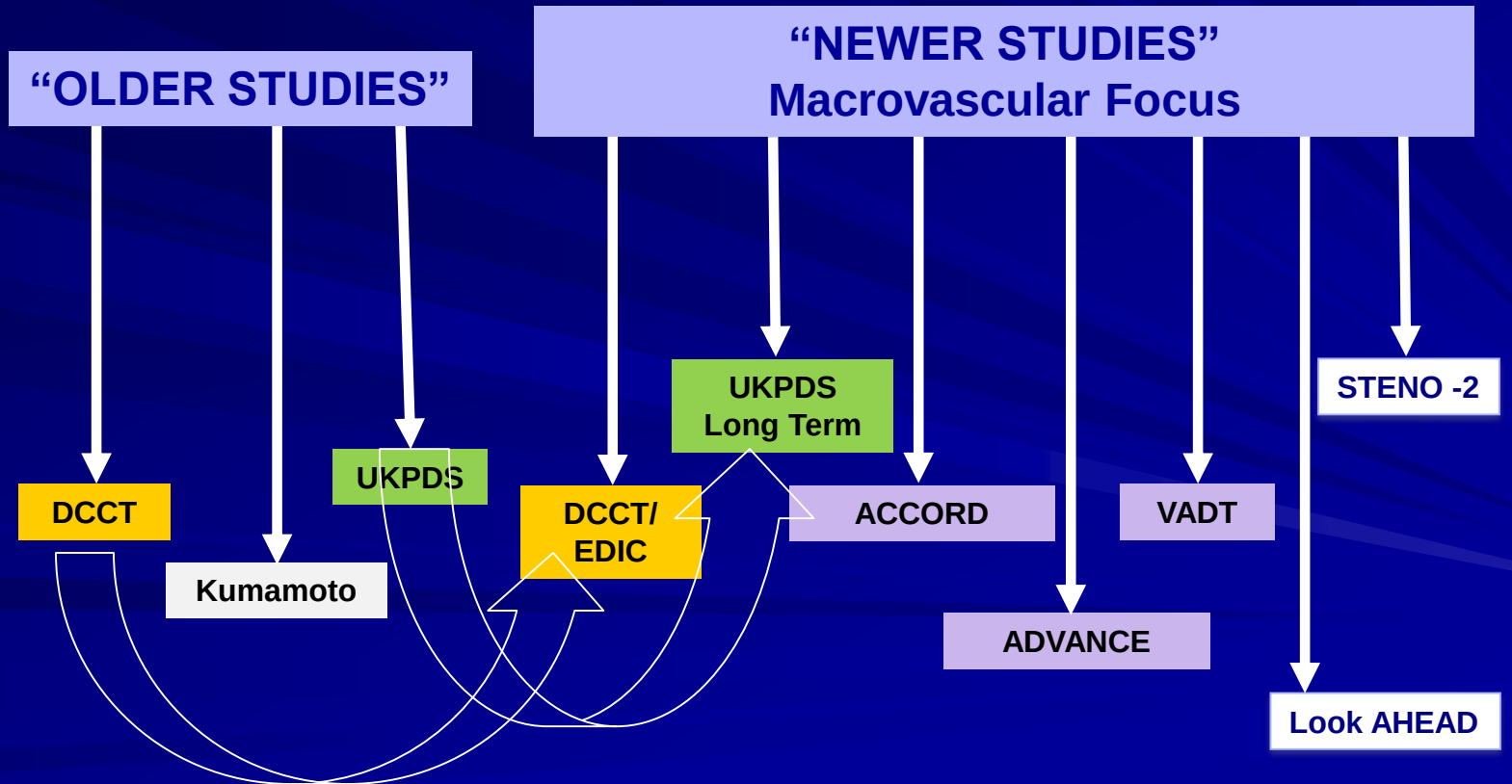
Different diseases

Different treatments

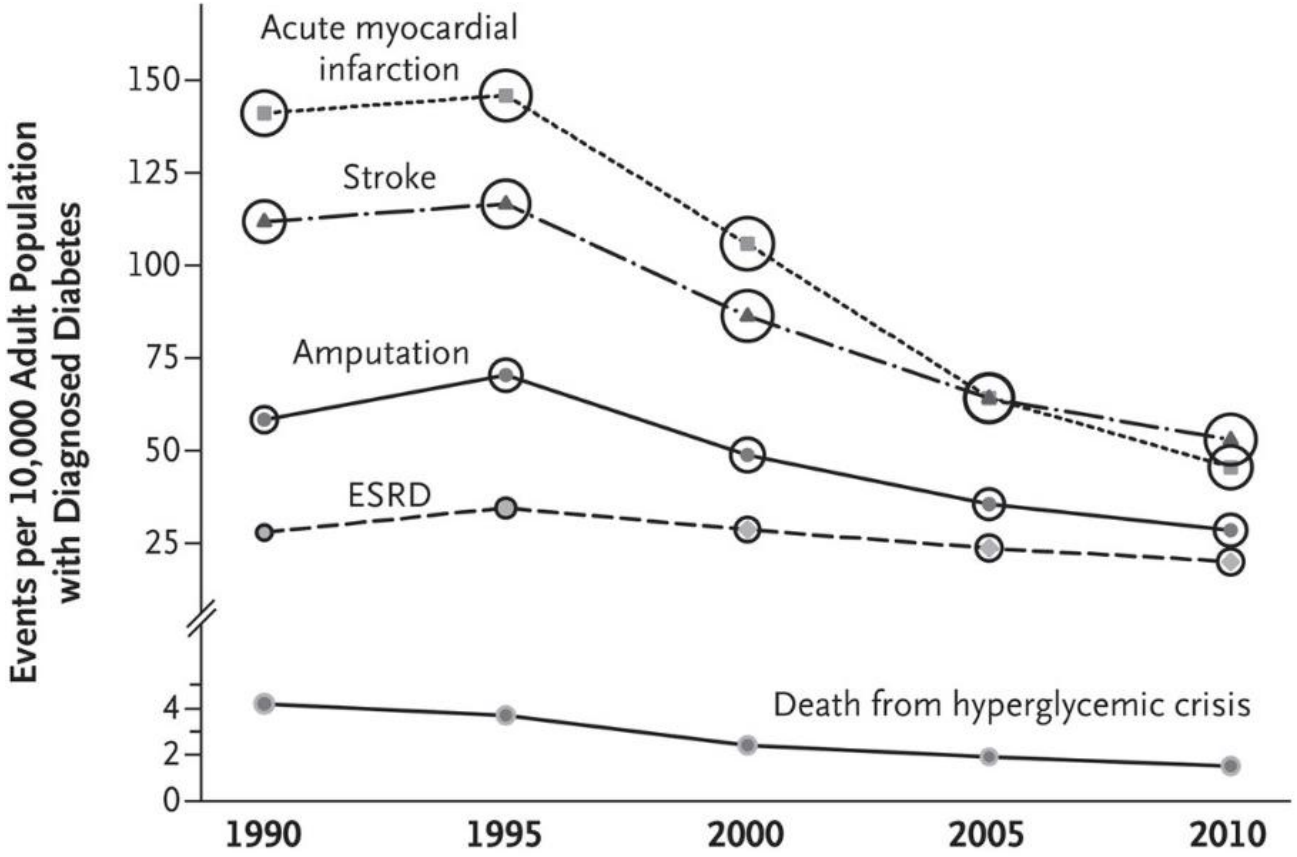
Early 21st century



Landmark Interventional Clinical Trials



GOOD NEWS! Complications 1990–2010.



Gregg EW et al. N Engl J Med 2014;370:1514-1523

Managing Type 2 Diabetes in the 21st Century

Joel Zonszein, MD

I declare no conflict of interest for this presentation

Disclosure past 5 years -Speaker's Bureau or Advisory Board:

Novo nordisk
Merck/Schering-Plough Pharmaceuticals
Boehringer Ingelheim

I thank our patients -the ones who ultimately benefit

PATHOPHYSIOLOGY AND LANDMARK STUDIES

TREATMENT –NEWER MEDICATIONS

CARDIOVASCULAR OUTCOME TRIALS (CVOT)

NEW PARADIGM

Managing Type 2 Diabetes, a New Paradigm

TREATING T2DM = CVD

Patient education
Lifestyle modification

Dyslipidemia
Blood Pressure
Glycemia

Weight
Platelet inhibition
Smoking cessation

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

2018

TASK FORCE

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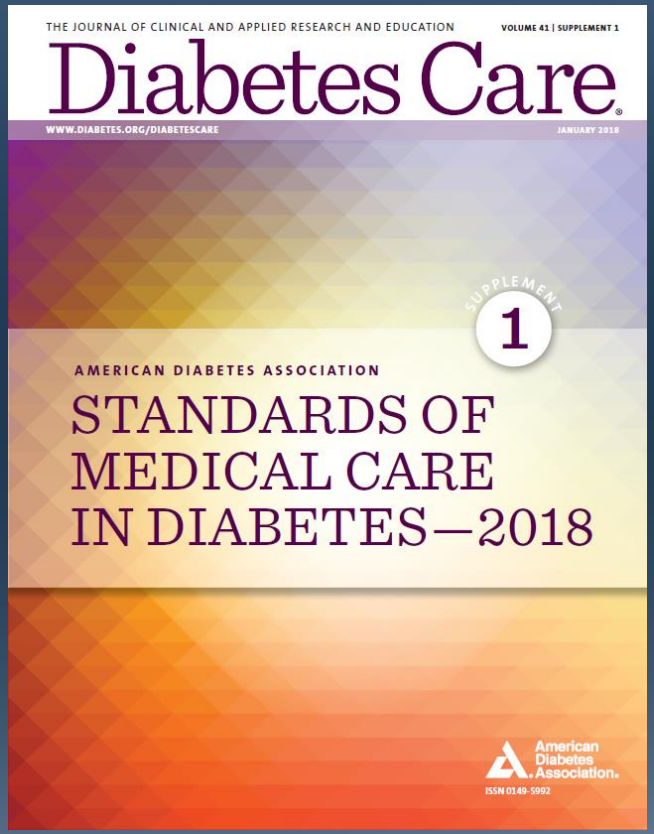
 DOI 10.4158/CS-2017-0153

2018 Standards of Care - Resources



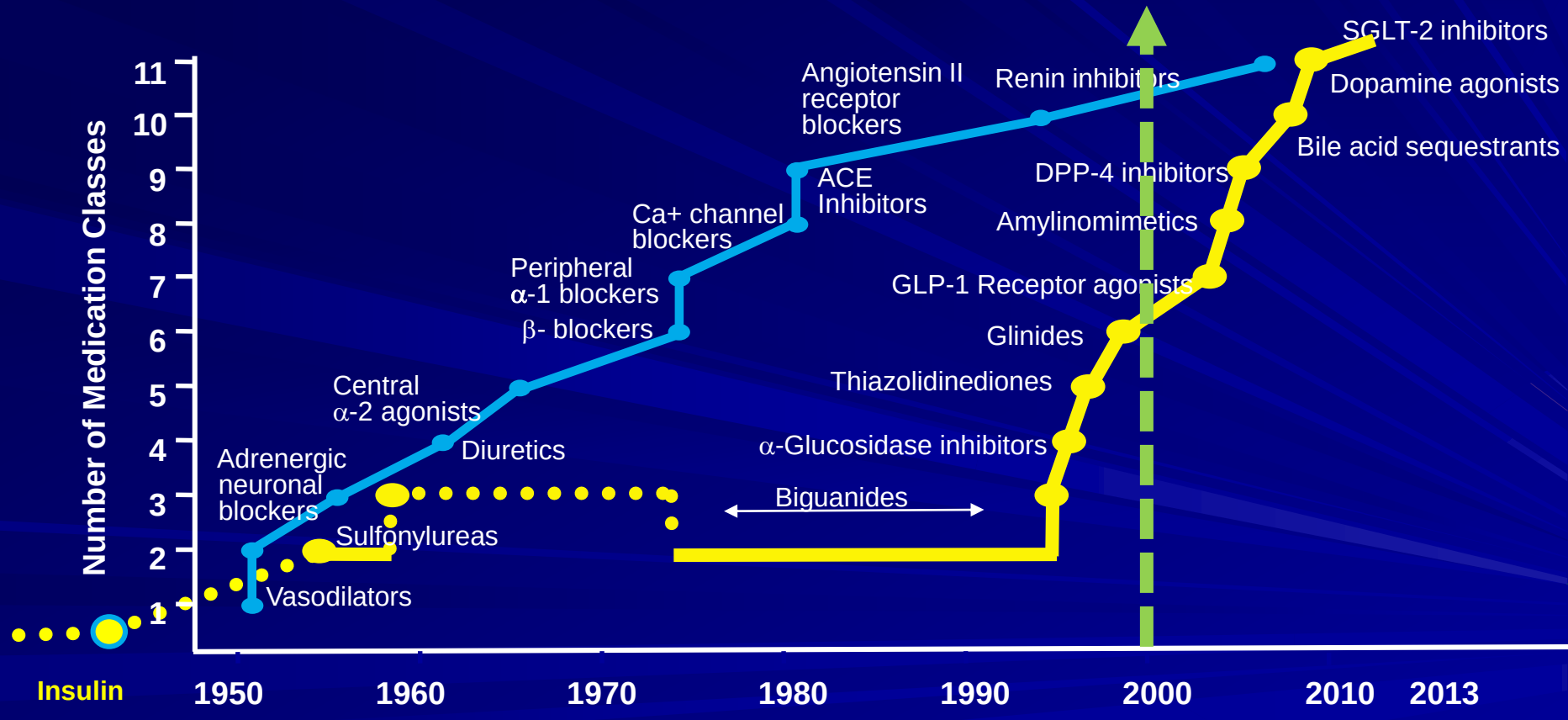
- Full version available
- Abridged version for PCPs
- Free app (February 2018)
- Pocket cards with key figures
- Free webcast for continuing education credit

Professional.Diabetes.org/SOC

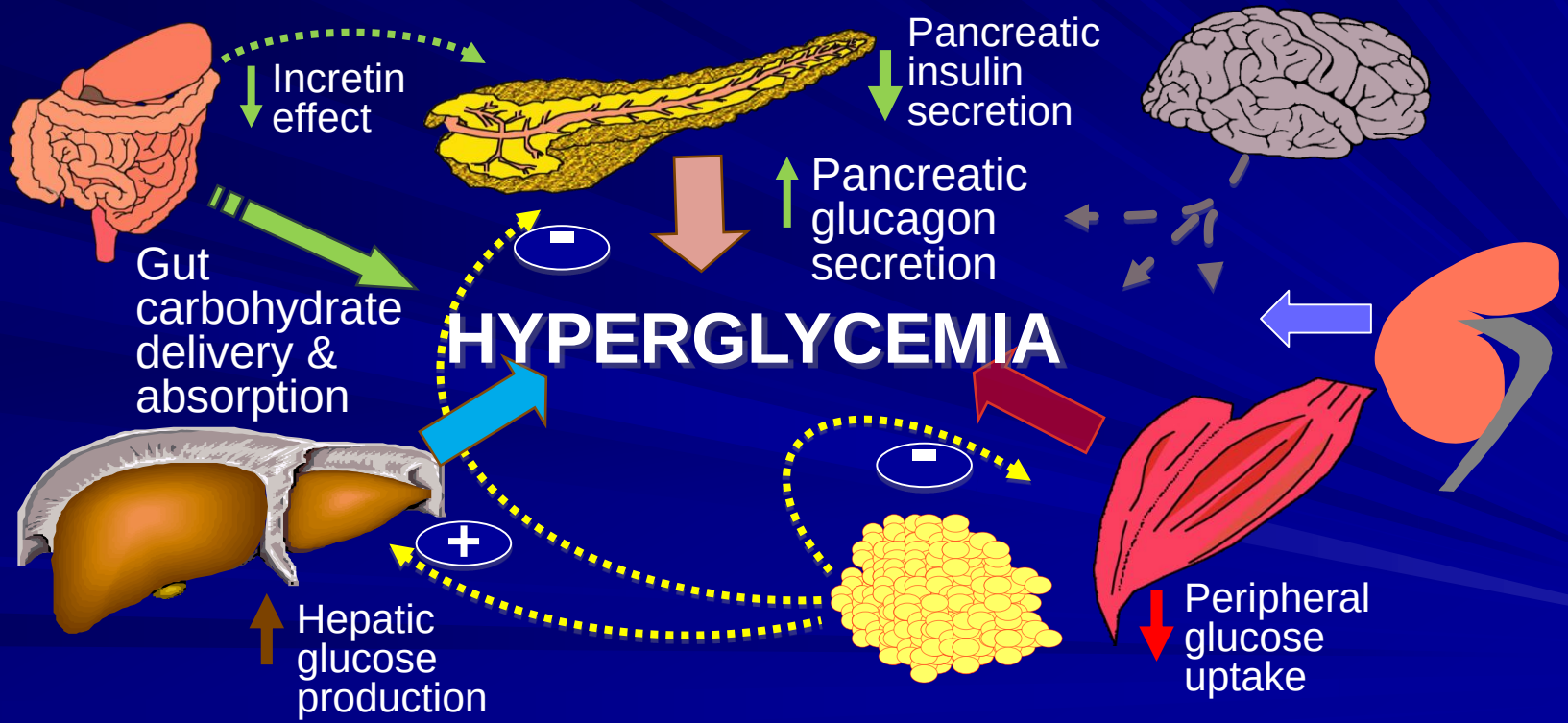
Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018; 41 (Suppl. 1)

American Diabetes Association.

US Drug classes during the last decades

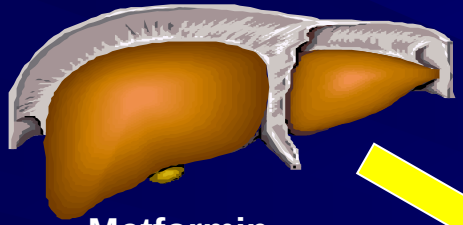


Pathophysiological Defects in T2DM

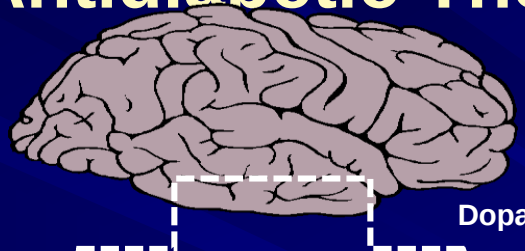


Inzucchi SE, Sherwin RS. Type 2 Diabetes Mellitus. In: Goldman L, Shafer AI. *Cecil Medicine.* 24th Edition. Philadelphia, PA: Saunders Elsevier: 2011; Chapter 248.

Targets for Antidiabetic Therapies in T2DM



Metformin

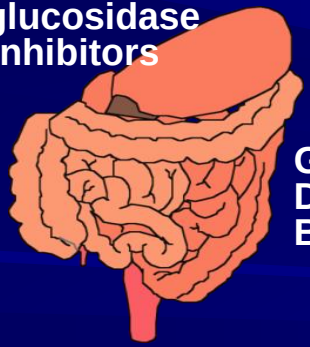


Dopamin agonists

Thiazolidinediones

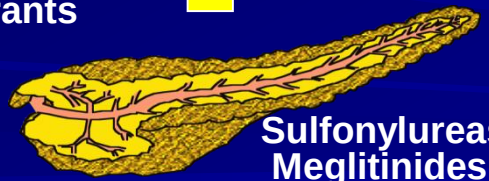
Reduce Hyperglycemia

α-glucosidase inhibitors



GLP-1 analogues
DPP-4 inhibitors
Bile acid sequestrants

Insulin



Sulfonylureas
Meglitinides
Amylin analogues

SGLT-2 inhibitors

GLP, glucagon-like peptide;
DPP, didpeptidyl peptidase

Approved antidiabetic medications in the US

Medication	Route	Hypoglycemia	Weight
Insulin → Basal, Prandials, Mixed, Afrezza	Parenteral	YES	↑
Sulfonylureas → 1st and 2nd generation	Oral	YES	↑
Meglitinides (glinides) -nateglinide, rapeglinide	Oral	YES	↑
Biguanides -metformin	Oral	NO	↔
Alpha-glycosidase inhibitors acarbose, miglitol	Oral	NO	↔
Thiazolidinedione (s) –pioglitazone, rosiglitazone	Oral	NO	↑↑
Incretinomimetics: DPP-IV inhibitors sitagliptin, saxagliptin, linagliptin, alogliptin,	Oral	NO	↔
Incretinomimetics: GLP-1 analogues: exenatide, exanatide ER, lixisenatide, liraglutide, albiglutide, dulaglutide, semeglutide	Parenteral	NO	↓↓
Amylin analogue pramlintide	Parenteral	NO/YES	↓↓
Bile Acid Sequestrant -colesevelam	Oral	NO	↔
Dopamine agonists bromocriptine	Oral	NO	↓
SGLT-2 inhibitors canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Oral	NO	↓↓

Insulin + 11 more classes of medications; > 30 different medications + > 21 combination pills

Approved antidiabetic medications in the US

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Amylin analogue pramlintide	Parenteral	NO/YES	↓↓
Bile Acid Sequestrant -colesevelam	Oral	NO	↔
Dopamine agonists bromocriptine	Oral	NO	↓
SGLT-2 inhibitors canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Oral	NO	↓↓

Commonly used antidiabetic -non-hypoglycemic classes of medications generic –brand name

Medication	Route	Hypoglycemia	Weight
metfromin –Glucophage	Oral	NO	↔
thiazolidinediones: Pioglitazone Actos, rosiglitazone Avandia	Oral	NO	↑↑
DPP-IV inhibitors: sitagliptin Januvia, saxagliptin Onglyza, linagliptin Tradjenta, alogliptin Nesina	Oral	NO	↔
GLP-1 analogues: Exenatide Byeta, liraglutide -Victoza, exanatide ER -Bydureon, albiglutide –Tanzeum, dulaglutide –Trulicity, semeglutide -Ozempic	Parenteral	NO	↓↓
SGLT-2 inhibitors: canagliflozin –Invokana, dapagliflozin –Farxiga, empagliflozin -Jardiance,, ertugliflozin –Steglatro	Oral	NO	↓↓

SINGLE-PILL COMBINATIONS

Class	Combination	Brand	Dosing frequency
With metformin			
DPP-4i + metformin	Alogliptin + metformin	Kazano® generic	Twice daily
	Linagliptin + metformin	Jentadueto®	Twice daily
	Linagliptin + metformin XR	Jentadueto XR®	Once daily
	Saxagliptin + metformin XR	Kombiglyze XR®	Once daily
	Sitagliptin + metformin	Janumet®	Twice daily
	Sitagliptin + metformin XR	Janumet XR®	Once daily
SGLT-2i + metformin	Canagliflozin + metformin	Invokamet®	Twice daily
	Canagliflozin + metformin XR	Invokamet XR®	Once daily
	Dapagliflozin + metformin XR	Xigduo XR®	Once daily
	Empagliflozin + metformin	Synjardy®	Twice daily
	Ertugliflozin + metfromin	Segluromet	Twice daily
TZD + metformin	Pioglitazone + metformin	Actoplus Met® generic	Twice daily
	Pioglitazone + metformin XR	Actoplus Met XR® generic	Once daily
	Rosiglitazone + metformin	Avandamet® generic	Twice daily
SU + metformin	Glyburide + metformin	Glucovance generic	Twice daily
Without metformin			
DPP-4i + TZD	Alogliptin + pioglitazone	Oseni® -generic	Once daily
SGLT-2i + DPP-4i	Empagliflozin + linagliptin	Glyxambi®	Once daily
	Dapagliflozin +saxagliptin	Qtern®	Once daily
	Ertugliflozin + sitagliptin	Steglujan®	On ce daily
TZD + SU	Pioglitazone + glimepiride	Duetact® generic	Once daily
	Rosiglitazone + glimepiride	Avandaryl generic	Once daily

DPP-4, dipeptidyl dipeptidase-4 ; i, inhibitor; SGLT2, sodium glucose cotransporter 2; SU, sulfonylurea; TZD, thiazolidinedione

>21 different combination pills, some generic

Zonszein, J. & Groop, PH. Diabetes Ther (2016)

1950
NPH

1980's
Human
insulins

U 40 ➔ U 80 ➔ U 100
Globin, PZI, Regular,
NPH > Semi-Lente, Lente,
Ultralente

Insulin
Discovery

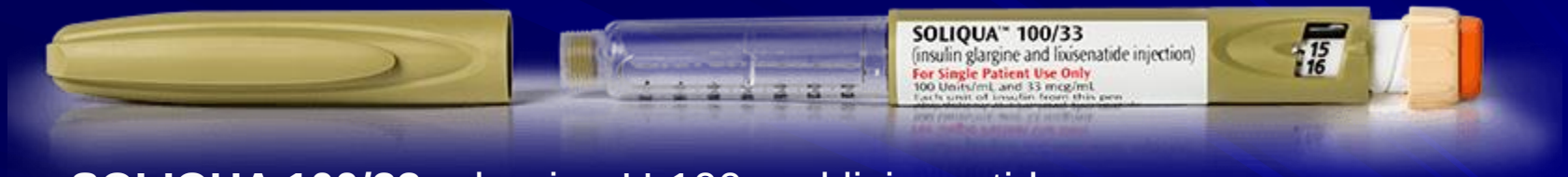
Beef, Pork, Mixed Beef/Pork
monocomponent "purified"
Analogues –prandial, basal, Fixed Mixtures

1921 1936 1946 1954 1977 1990 2000 2018 2021

1940's PZI –Protamin Zinc Insulin

Rapid
Acting
Analogu

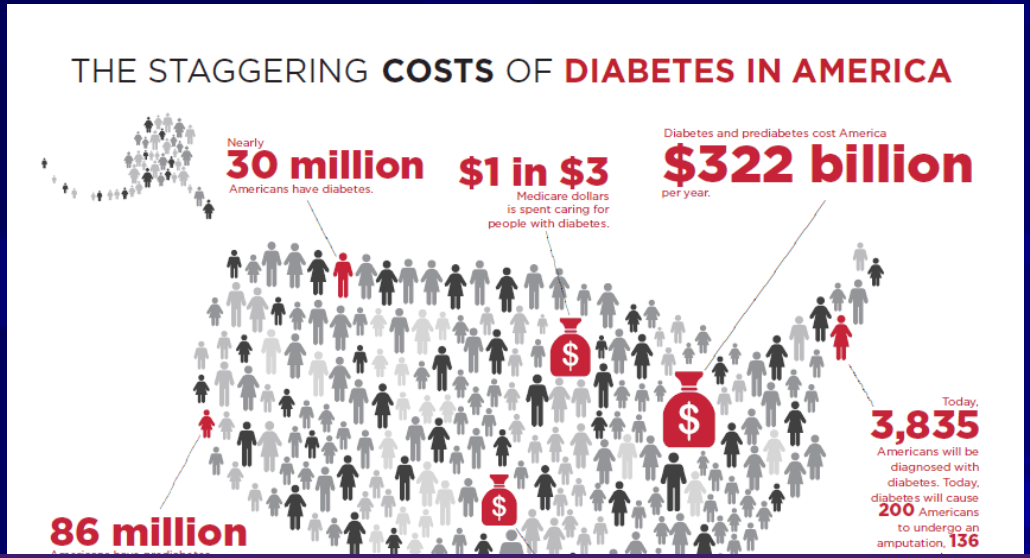
SINGLE-SYRINGE FIXED COMBINATION: Basal Insulin + GLP-1 RA



SOLIQUA 100/33 -glargine U-100 and lixisenatide

XULTOPHY 100/3.6 –degludec U-100 and liraglutide

Expenses of diabetes care



Hospital care	43%
Medications for complications	18%
Nursing/residential facility stays	8%
Physician office visits	9%
Anti-diabetic agents and supplies	12%

Despite new branded medications Anti-diabetic agents + supplies remain unchanged @ 12%

Medical cost is dedicated to treat complications, not disease prevention

http://www.diabetes.org/diabetes

Scientific Statement. *Diabetes Care April 2013*

Managing hyperglycemia in 2013…

What to do when metformin is not enough?

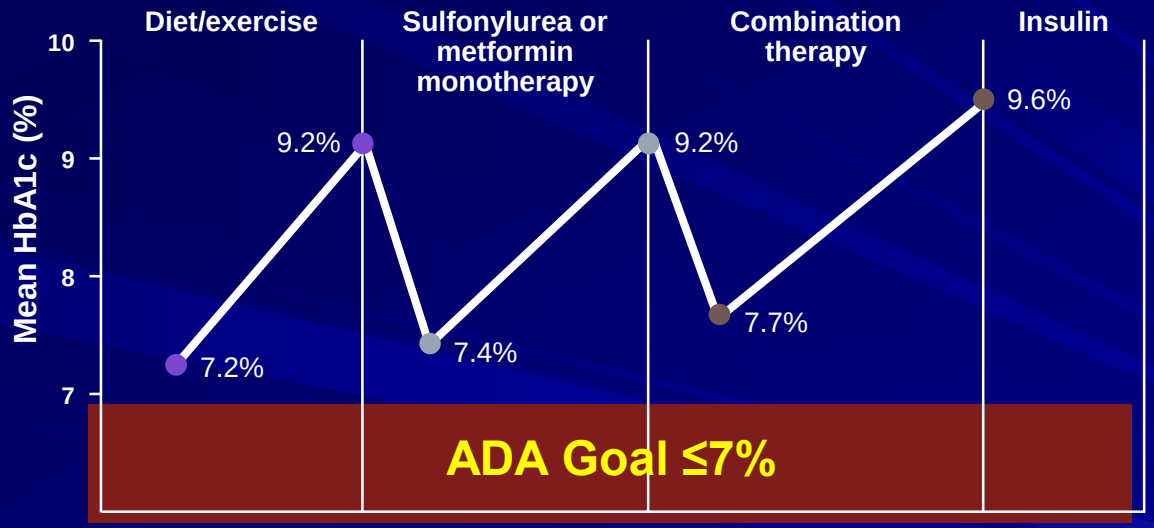
Agnes, a 51 y/o widow

- **HTN + T2DM for 10 years**
- **A1c 7.0% X 1 year, ↑ to 9.0% past 2 years**
- **Metformin 2 g/D + statin + ACE-I**
- **Weight 165 lbs., motivated, exercises, good diet "hates needles" and won't use insulin or SUO because of weight gain and or hypoglycemia**
- **Her sister recommends saxagliptin or one of the "new drugs"**
- **You explain differences between DPP-4 inhibitors ("gliptins") and SGLT2 inhibitors ("gliflozins"), their MOA, side-effect profiles and efficacy**

Do you add a *gliptin* or a *gliflozin*?

Case Vignette N Engl J Med 2013; 369:1370-1372 October 3, 2013

Clinical Inertia and Hyperglycemia



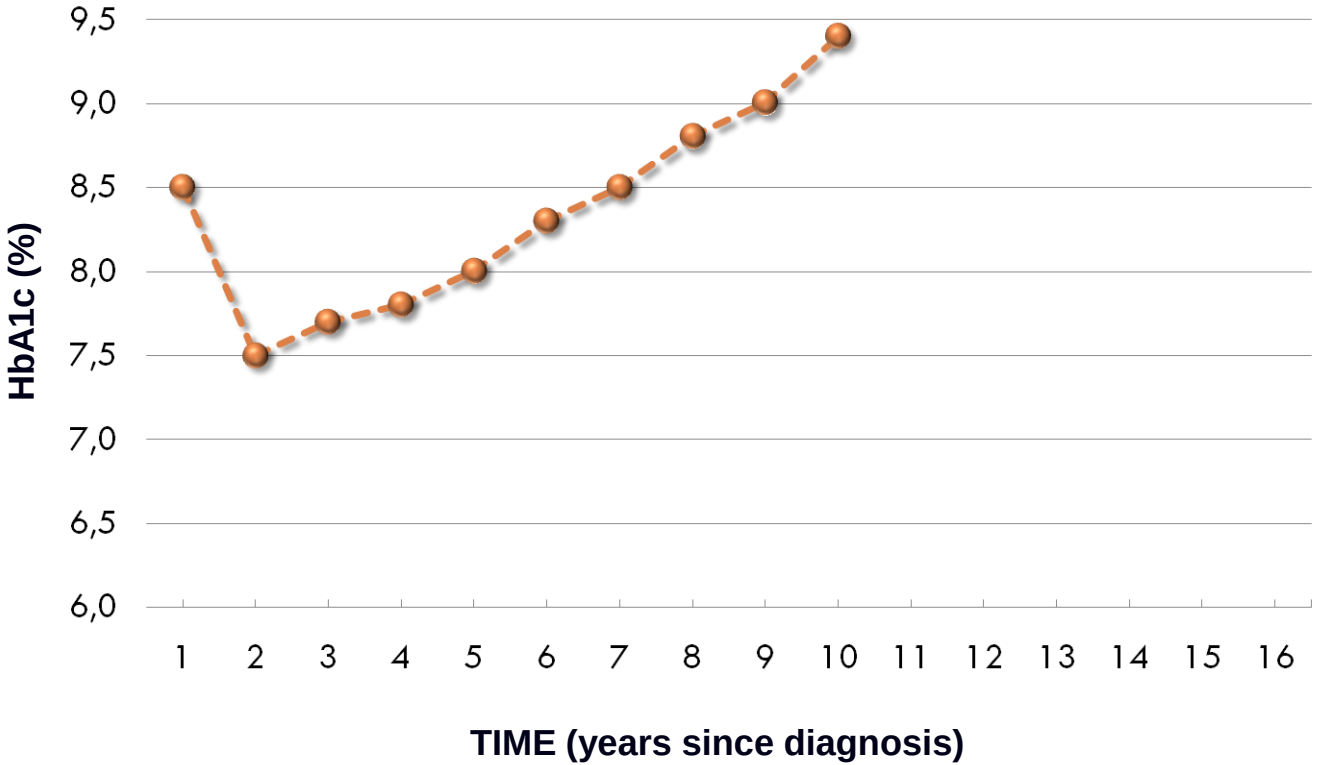
At insulin initiation, the average patient had

- 5 Years with A1C >8%
- 10 Years with A1C >7%

ADA = American Diabetes Association.

Brown JB, et al. *Diabetes Care*. 2004;27(7):1535-1540.

VADT in the context of the “natural history” of Type 2 Diabetes



Del Prato S ***Diabetologia*** 2009;52:1259

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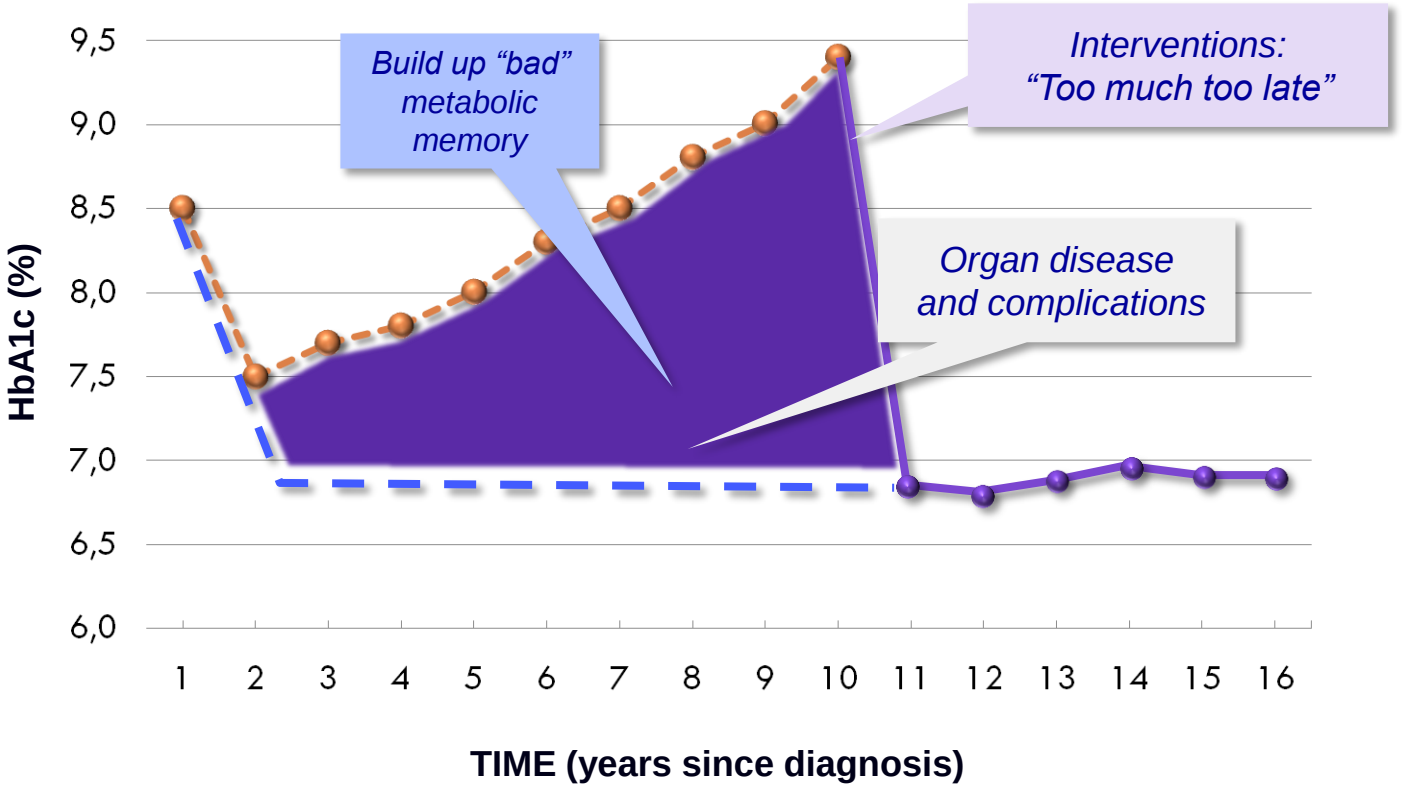


Del Prato S ***Diabetologia*** 2009;52:1259

Managing hyperglycemia in 2013…

What to do when metformin is not enough?

Agnes …

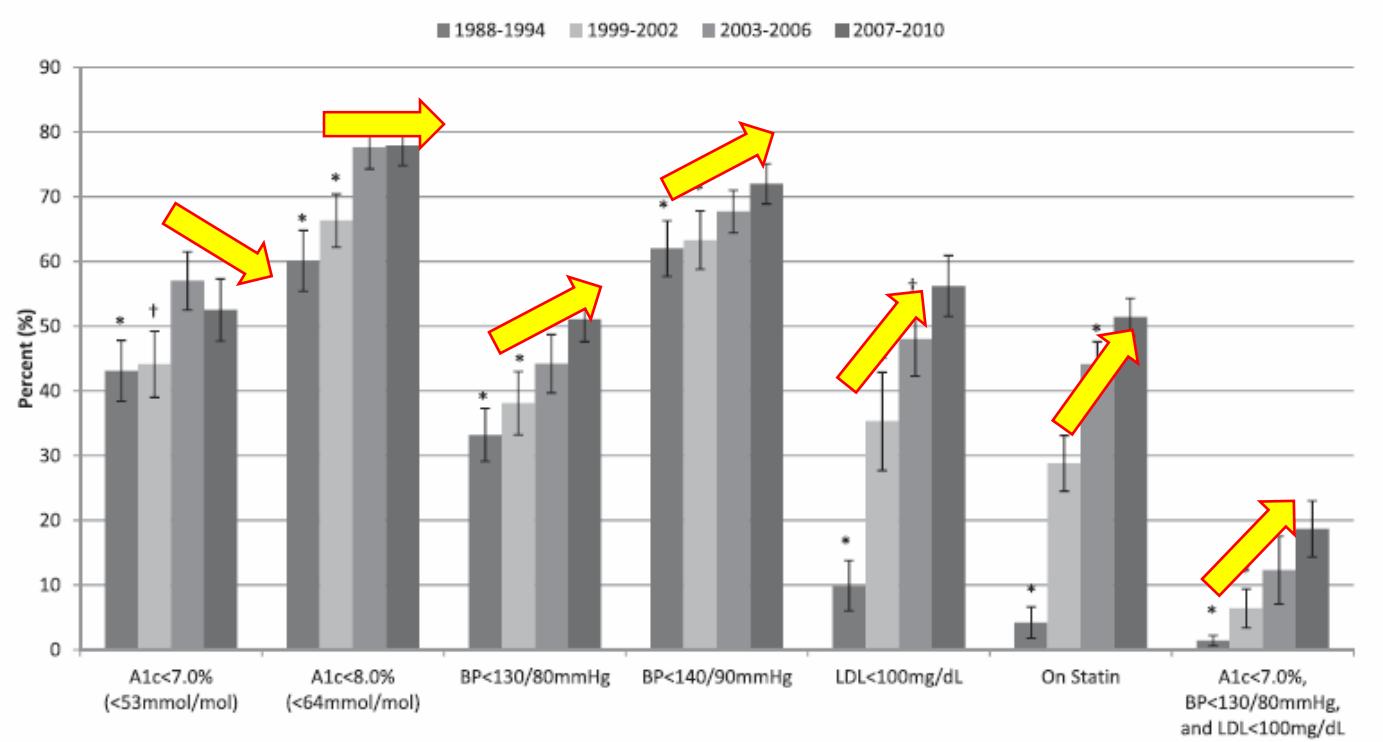
- Readers from 76 Countries
  - **Add a gliptin 72.3% vs. 27.7% gliflozin**
- U.S. readers from 43 states & DC
  - **Add a gliptin 62.3% vs. 37.7% gliflozin**

- <20% opposed to adding a second drug and preferred renewed effort to lose weight.

Why <u>after metformin</u> and no <u>initial combination therapy</u>?

N Engl J Med 2014; 370

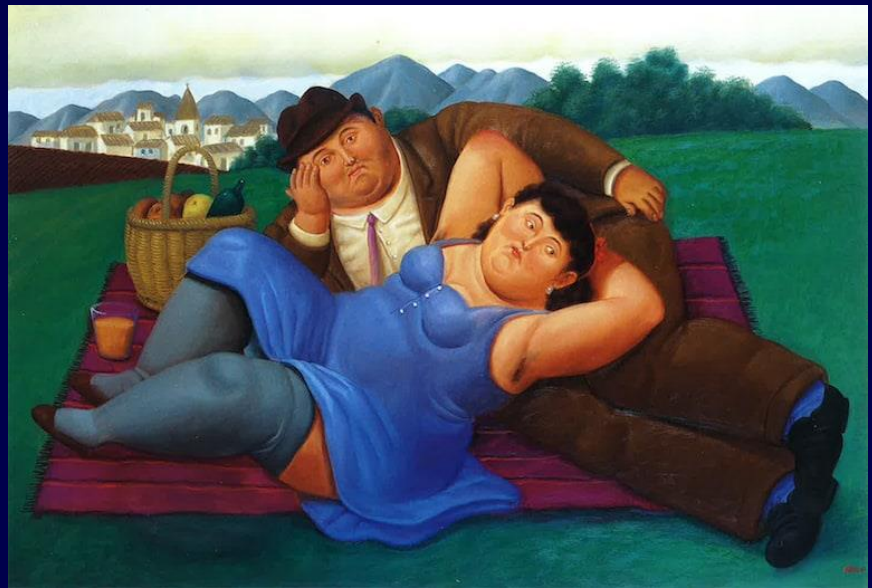
Meeting ABC goals in people with diabetes 1988–2010



care.diabetesjournals.org January 2013.

What have we learned?

- Diabetes is a common and *treatable disease*
- Treatment should not be *glycemic centered*
- Diagnosed late, many not treated, *those treated are not at goal*
- Medical *cost allocated to complications* and not prevention
- Outcomes have improved



PATHOPHYSIOLOGY AND LANDMARK STUDIES

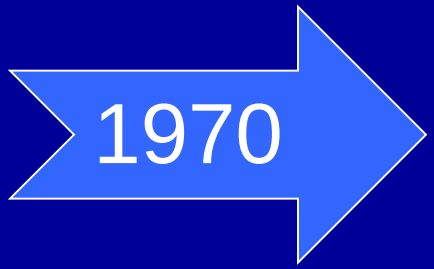
TREATMENT –NEWER MEDICATIONS

CARDIOVASCULAR OUTCOME TRIALS (CVOT)

NEW PARADIGM

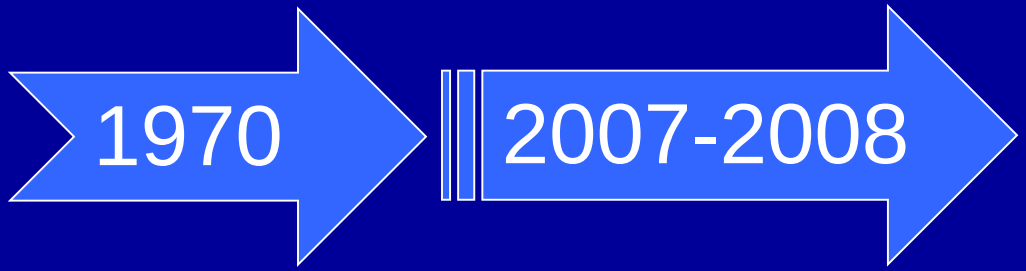
Managing Type 2 Diabetes, a New Paradigm

Why cardiovascular outcome trials (CVOT)?



UGDP Trial: Phenformin and Tolbutamide discontinued

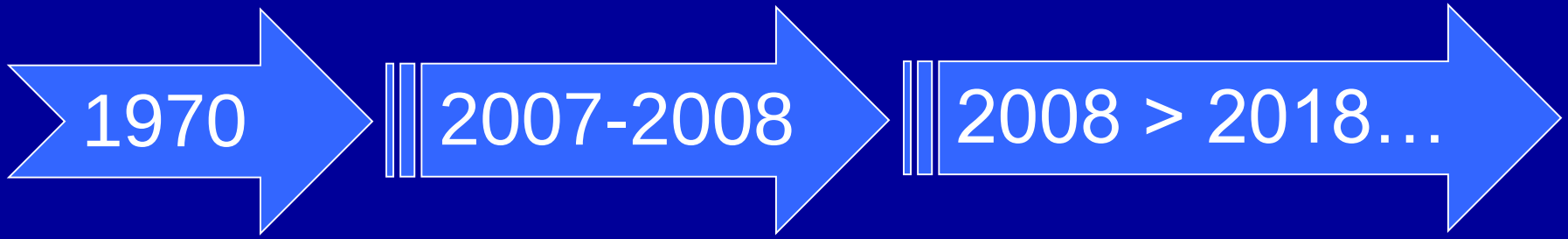
Why cardiovascular outcome trials (CVOT)?



UGDP Trial:
Phenformin and Tolbutamide discontinued

Rosiglitazone asociated with CV disease and CVD related death
Restricted in the US

Why cardiovascular outcome trials (CVOT)?



UGDP Trial: Phenformin and Tolbutamide discontinued

Rosiglitazone asociated with CV disease and CVD related death Restricted in the US

FDA: All new diabetes agents need to demostrate CV safety with metanalysis and or cardiovascular outcome trials (CVOT)

***FDA 2013 reduced the restrictions**

Am Heart J 2013;166:240–249

CVOT -noninferiority of drugs in major adverse cardiac event (MACE) composite endpoint –The FDA Gold Standard

Non-fatal stroke

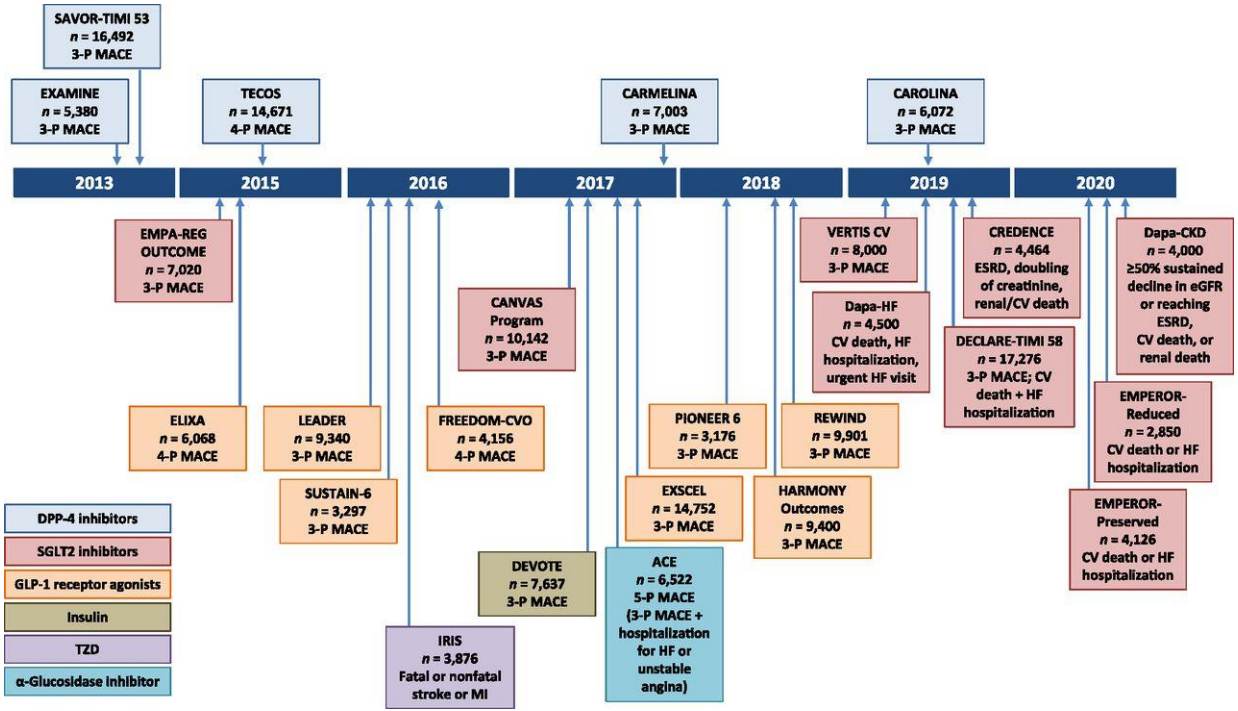
Non-fatal myocardial infarction

Cardiovascular death

Additional components

HF, hospitalization for ACS, Urgent revascularization,etc.)

Completed and ongoing CVOTs. 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.



Ongoing CVOTs (26 trials) collectively >190,000 participants

William T. Cefalu et al. Dia Care 2018;41:14-31

CVOTs in type 2 diabetes

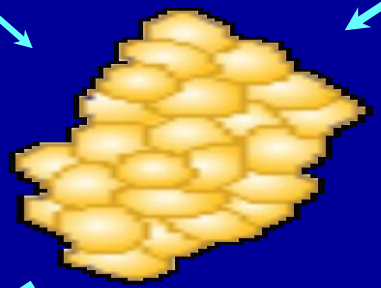
Antidiabetic non-hypoglycemic

- **Metformin**
- **Pioglitazone**
- **DPP-IV inhibitors**
- **GLP-1 Receptor analogues**
- **SGLT-2 inhibitors**

TZD's and adipocytes

FREE FATTY ACIDS

GLUCOSE



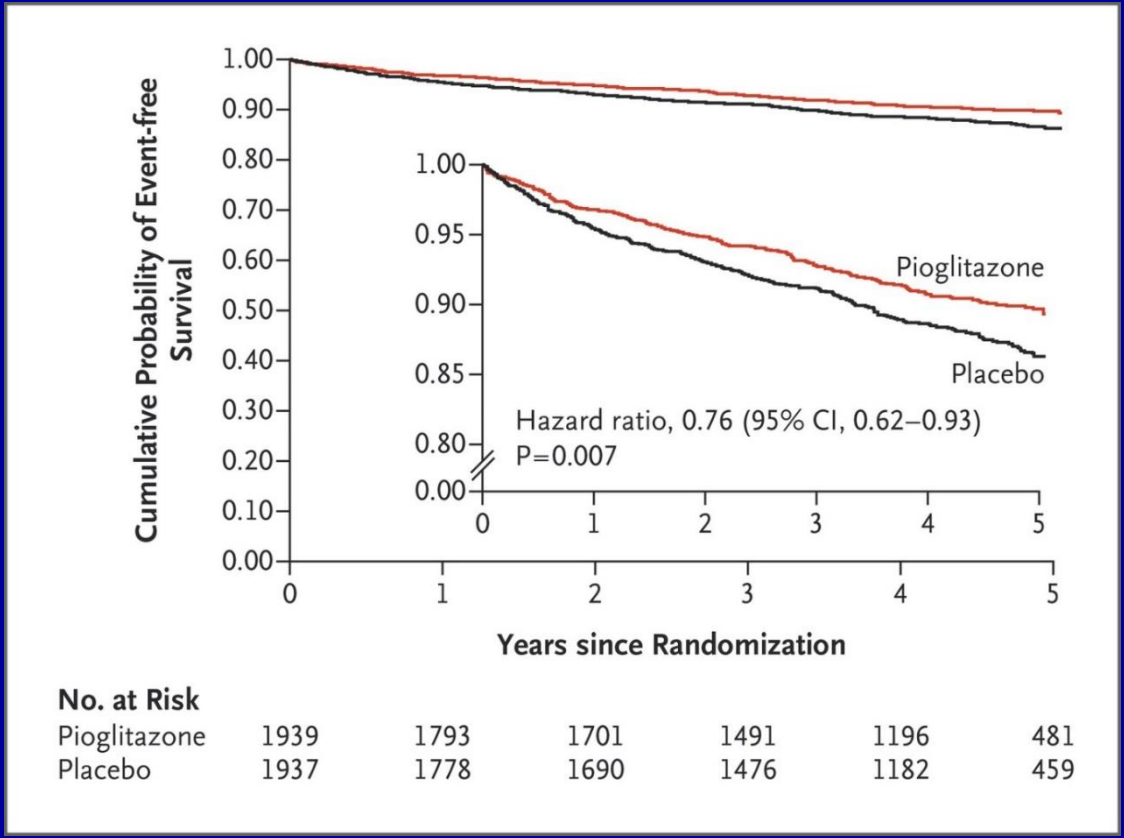
FREE FATTY ACIDS

ADIPONECTIN

HS-CRP
TNF–α
PAI -1
IL-1,6
Serum Amyloid-A
Dyslipidemia

IRIS: Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

non-FDA mandated



3P MACE
5 years
24% RR MI or CVA

Secondary prevention, targeting pioglitazone *NNT = 21*.
JAMA Neurology - online September 18, 2017

Prospective Pioglitazone Clinical Trial in Macrovascular Events (**PROactive**) Secondary prevention:
MI RR 28% p-0.045
CVA RR 47% p-0.008
Dormandy JA et al. Lancet 2005;366:1279-1289

Kernan WN et al. N Engl J Med February 2016.

PIOGLITAZONE generic

EFFICACY

- Addresses “metabolic syndrome” and “CV
- Improves NASH and dyslipide
- Insulin sensitizer

SIDE EFFECTS

Pioglitazone CVOT not mandated as part of the 2008 FDA CVOT guidance

24 % RR for MI and Ischemic Stroke

-277

Mandated CVOTs in type 2 diabetes

Antidiabetic non-hypoglycemic

- Metformin
- Pioglitazone
- **DPP-IV inhibitors**
- **GLP-1 Receptor analogues**
- **SGLT-2 inhibitors**

Cardiovascular outcome trials (CVOT) in type 2 diabetes

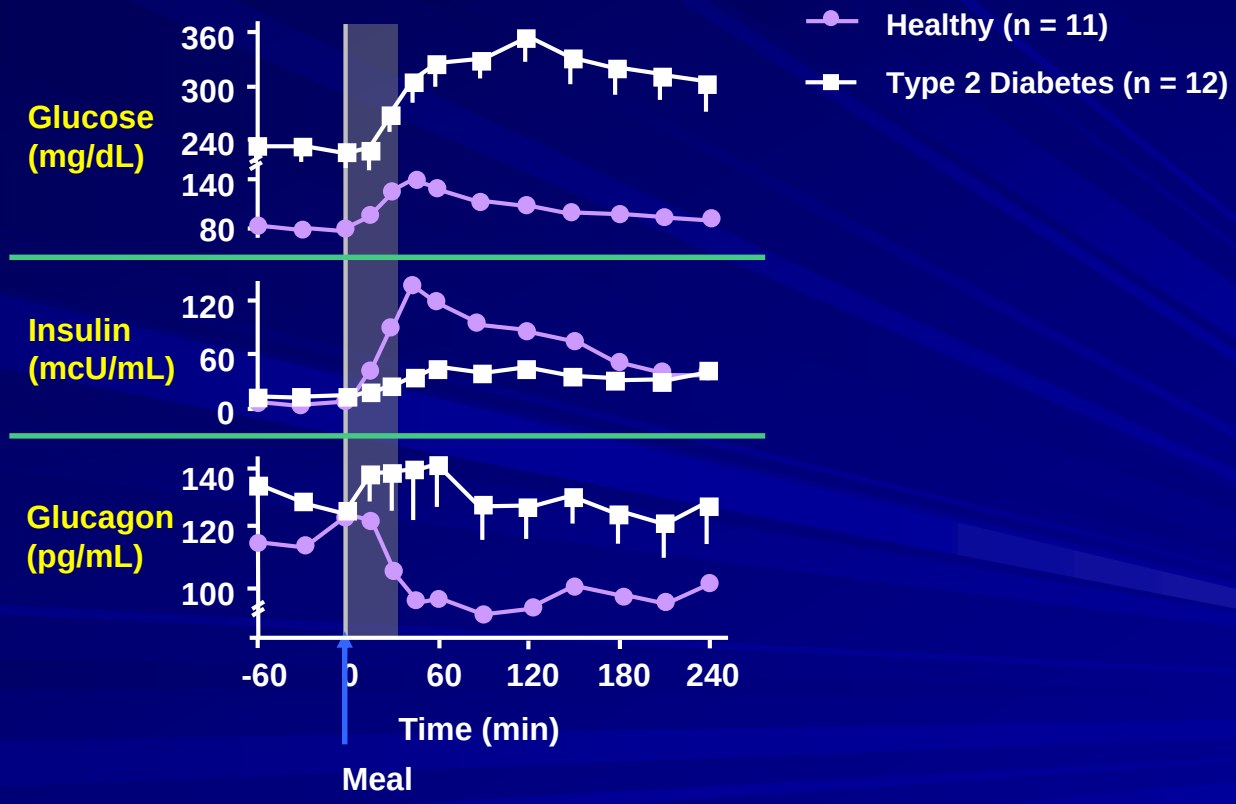
DPP-4i	SAVOR TIMI-53	EXAMINE	TECOS	CAROLINA	CARMELINA
drug	SAXAGLIPTIN	ALOGLIPTIN	SITAGLIPTIN	LINAGLIPTIN	LINAGLIPTIN
Number (year)	16,500 (2013)	5,400 (2013)	14,000 (2015)	6.000 (2018)	8,300 (2018)
GLP-1 RA	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
drug	LIRAGLUTIDE	LIXISENITIDE	SEMAGLUTIDE	EXENATIDE LR	DULAGLUTIDE
Number (year)	8,754 (2017)	6,000 (2015)	6,000 (2016)	9,500 (2017)	9,600 (2018)
SGLT-2i	EMPA –REG	CANVAS	DECLARE	VERTIS	
drug	EMPAGLIFLOZIN	CANAGLIFLOZIN	DAPAGLIFLOZIN	ERTUGLIFLOZIN	
Number (year)	7300 (2015)	7,000 (2017)	22,200 (2019)	3,900 (2019)	

INCRETINOMIMETIC AGENTS

DPP-4 inhibitors –oral agents

- ❑ **saxagliptin**
- ❑ **alogliptin** *generic-April 2016*
- ❑ **sitagliptin**
- ❑ **linagliptin**

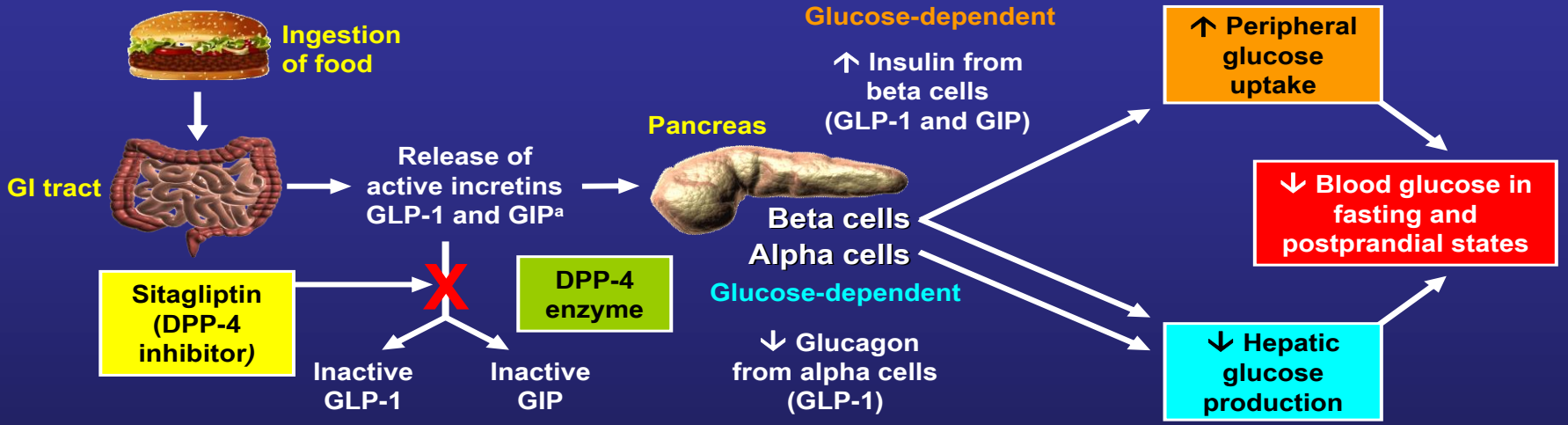
Abnormal Insulin and Glucagon Responses Contribute to Hyperglycemia in Type 2 Diabetes



Mean ± SE

Data from Müller WA, et al. *N Engl J Med*. 1970;283:109-115

Sitagliptin Enhances Incretin Levels Through Inhibition of DPP-4[1–4]

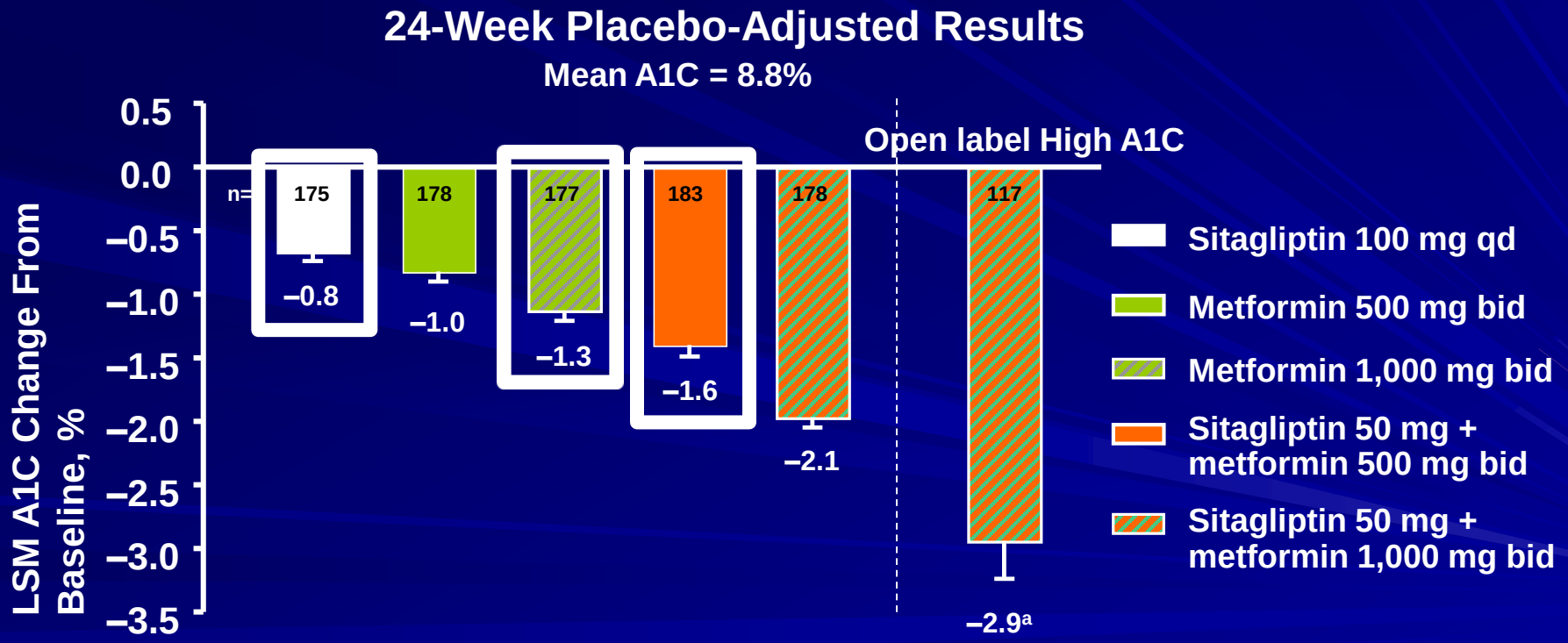


By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

DPP-4=dipeptidyl peptidase-4; GI=gastrointestinal; GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1.
[a]Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal.

1. Kieffer TJ et al. *Endocr Rev*. 1999;20(6):876–913.
2. Ahrén B. *Curr Diab Rep*. 2003;3(5):365–372.
3. Drucker DJ. *Diabetes Care*. 2003;26(10):2929–2940,
4. Holst JJ. *Diabetes Metab Res Rev*. 2002;18(6):430–441.

Sitagliptin + metformin + combination



[a]LSM change from baseline without adjustment for placebo.
qd=once a day; bid=twice a day.

INCRETINOMIMETIC AGENTS
DPP-4 inhibitors

CV safety in 5 trials, 3 outcome results published (SAVOR-TIMI 53, EXAMINE and TECOS)

49,618 patients enrolled

SUMMARY OF COMPLETED CVOT – 2008 – January, 2018

CLASS AGENT vs. PLACEBO	STUDY	POPULATION RISK NUMBER	PRIMARY ENDPT MEDIAN F/U (years)	SAFETY HR SUPERIORITY (*p value*)
DPP-4i SAXAGLIPTIN	SAVOR TIMI 53	CVD or CVRF *N=16,492*	3P-MACE 2.1	1.0 (95% CI,0.89-1.12) P=0.99
DPP-4i ALOGLIPTIN	EXAMINE	ACS N=5,380	3P-MACE 1.5	0.96 (Upper CI, 1.16) P=0.32
DPP-4i SITAGLIPTIN	TECOS	CVD N=14,671	4P-MACE 3.0	0.98 (95% CI,0.89-1.09) P=0.65

INCRETINOMIMETIC AGENTS

DPP-4 inhibitors

EFFICACY:

- Addresses pathophysiology -multip
- Well tolerated, weight neutr
- Weak without metf

SI

-
-

CV safety but no CV superiority

INCRETINOMIMETIC AGENTS

Injectable glucagon-like peptide-1 analogs: GLP-1 RA

exendin-based therapies

- ❑ exenatide (twice daily)
- ❑ lixisenatide (daily) *approved in combination with glargine*
- ❑ exenatide ER (weekly)

human glucagon-like peptide-1 analogs

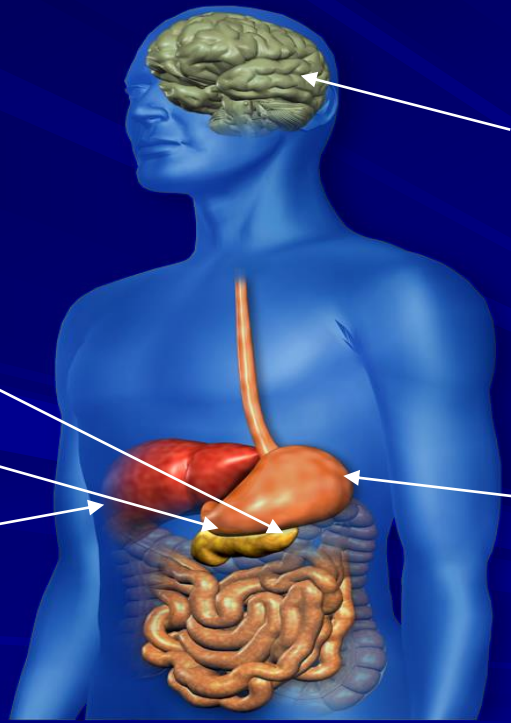
- ❑ liraglutide (daily)
- ❑ albiglutide (weekly)
- ❑ dulaglutide (weekly)
- ❑ semaglutide (weekly)

GLP-1 Receptor Analogues

Restores First-Phase Insulin Response

↑ Glucose-Dependent Insulin Production

↓ Glucagon Production



↓ Food Intake*

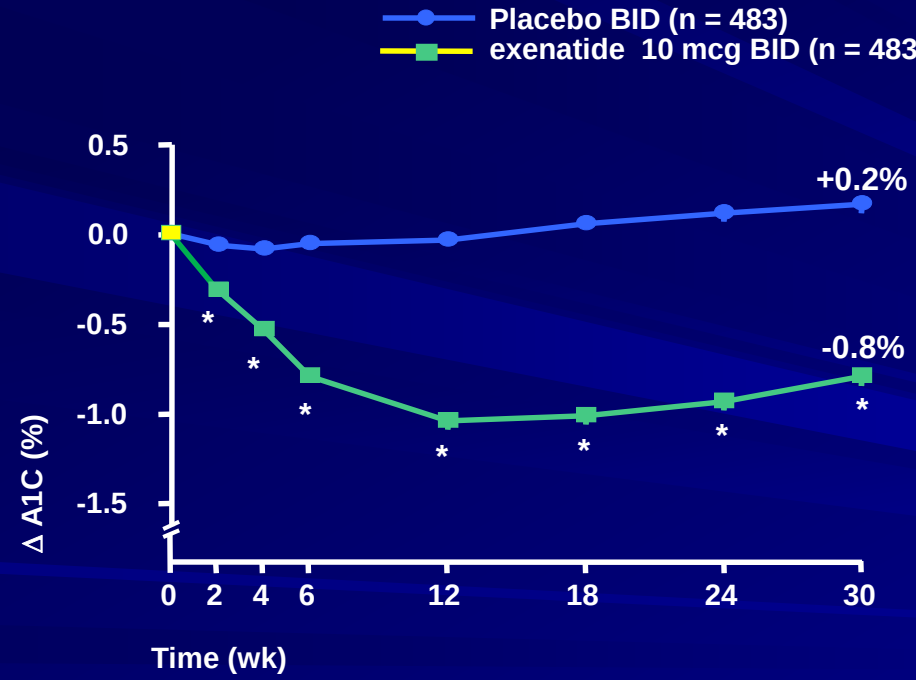
Slows Gastric Emptying

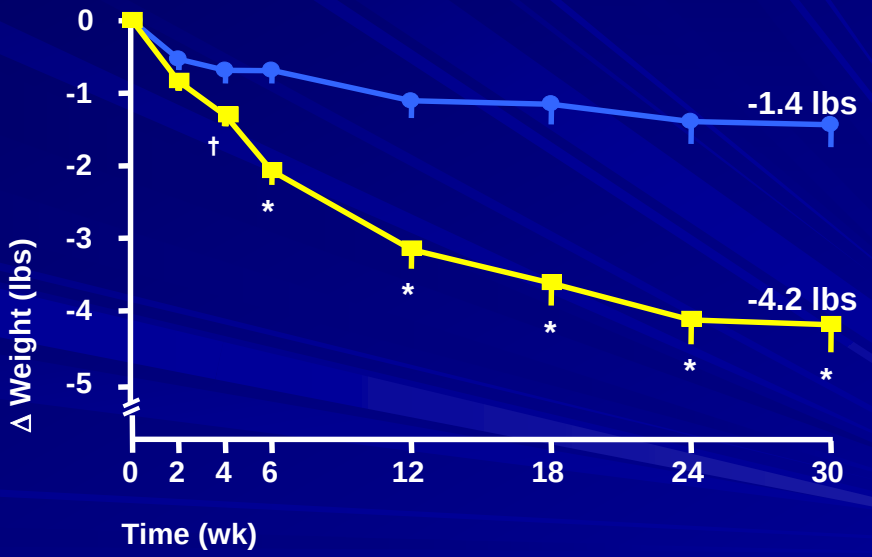
*This effect is postulated to be mediated through the central nervous system

Adapted from Kolterman OG, et al. *J Clin Endocrinol Metab*. 2003;88:3082-3089; Adapted from Fehse F, et al. *J Clin Endocrinol Metab*. 2005;90:5991-5997; Adapted from Nielsen LL, et al. *Regul Pept*. 2004;117:77-88

See accompanying Prescribing Information and safety information included in this presentation

Exenatide: A1C and Weight at 30 Weeks





30-wk data; Mean ± SE; Compared to placebo: *$P<0.0001$, †$P = 0.006$; Weight was a secondary endpoint
Data on file, Amylin Pharmaceuticals, Inc.
See accompanying Prescribing Information and safety information included in this presentation

INCRETINOMIMETIC AGENTS
GLP-1 RA's

CV safety of GLP-1 receptor agonists in 8 trials
4 outcome results reported
(ELIXA, LEADER, SUSTAIN-6 EXSCEL)

60,090 patients enrolled

SUMMARY OF COMPLETED CVOT – 2008 – January, 2018

CLASS AGENT vs. PLACEBO	STUDY	POPULATION RISK NUMBER	PRIMARY ENDPT MEDIAN F/U (years)	SAFETY HR SUPERIORITY (*p value*)
DPP-4i SAXAGLIPTIN	SAVOR TIMI 53	CVD or CVRF *N=16,492*	3P-MACE 2.1	1.0 (95% CI,0.89-1.12) P=0.99
DPP-4i ALOGLIPTIN	EXAMINE	ACS N=5,380	3P-MACE 1.5	0.96 (Upper CI, 1.16) P=0.32
DPP-4i SITAGLIPTIN	TECOS	CVD N=14,671	4P-MACE 3.0	0.98 (95% CI,0.89-1.09) P=0.65
GLP-1 RA LIXISENATIDE	ELIXA	ACS N= 6,068	4P-MACE 2.1	1.02 (95% CI,0.89-1.17) P=0.81
GLP-1 RA LIRAGLUTIDE	LEADER	CVD or CVRF N=9,340	3P-MACE 3.8	0.87 (95% CI,0.78-0.97) P=0.01
GLP-1 RA SEMAGLUTIDE	SUSTAIN-6	CVD or CRF N=3,297	3P-MACE 2.1	0.74 (95% CI,0.58-0.95) P=0.02
GLP-1 RA EXENTIDE -ER	EXCEL	CVD N=14,752	3P-MACE 3.2	0.91 (95% CI,0.83-1.00) P=0.06

INCRETINOMIMETIC AGENTS

GLP-1 RA's

EFFICACY:

- Addresses pathophysiology -multi
- Lowers fasting and *pra*
- Weight neutr
- N

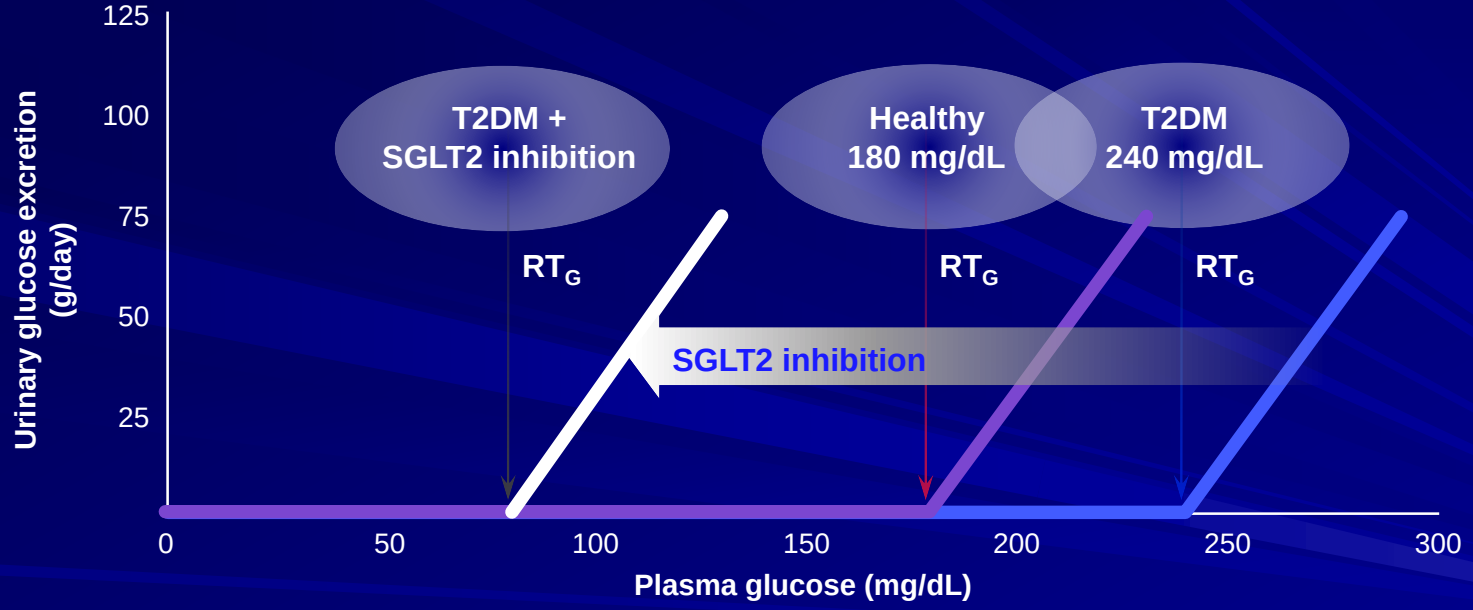
CV RR liraglutide (14%) and semaglutide (26%)
FDA liraglutide indication:
- improves glycemic control
-Reduces risk for CV (3P MACEs) disease

DR (semaglutide)

SGLT2 Inhibitors

- canagliflozin
- dapagliflozin
- empagliflozin
- ertugliflozin

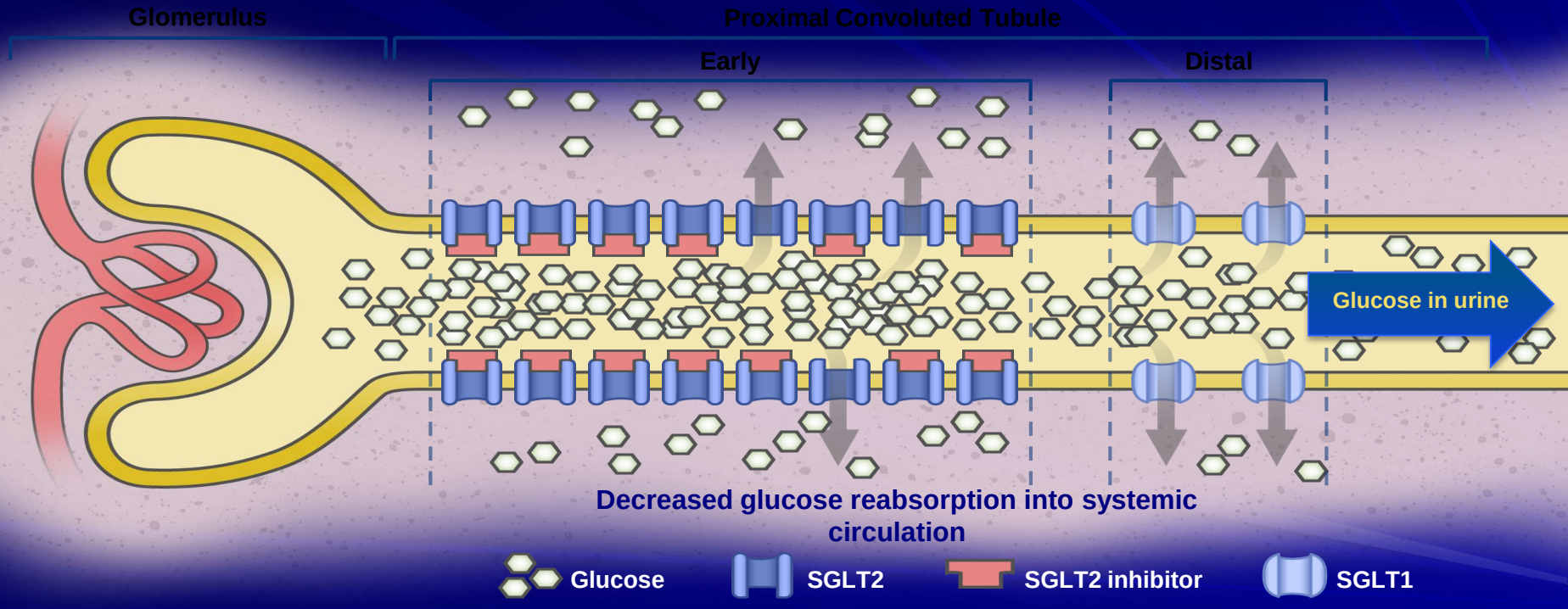
SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion (RT_G)



Adapted with permission from Abdul-Ghani MA, DeFronzo RA.
T2DM = type 2 diabetes mellitus.

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.

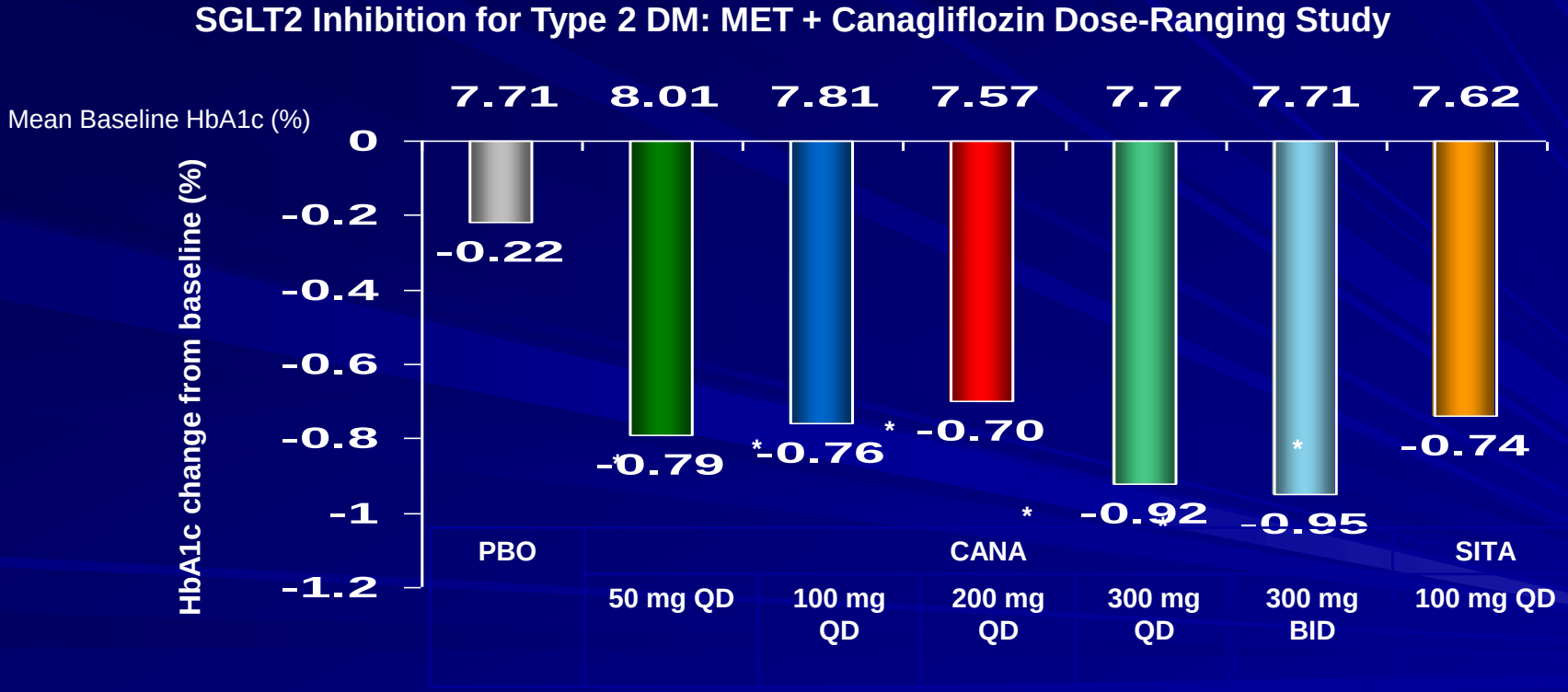
SGLT2 Inhibition Reduces Renal Glucose Reabsorption and Increases Excretion



Adapted with permission from Rothenberg PL et al.
SGLT = sodium-glucose co-transporter.

Rothenberg PL et al. Poster presented at: 46th European Association for the Study of Diabetes Annual Meeting; September 20-24, 2010; Stockholm, Sweden. 3. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 4. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract.* 2008;14(6):782-790. 5. Oku A et al. *Diabetes.* 1999;48(9):1794-1800.

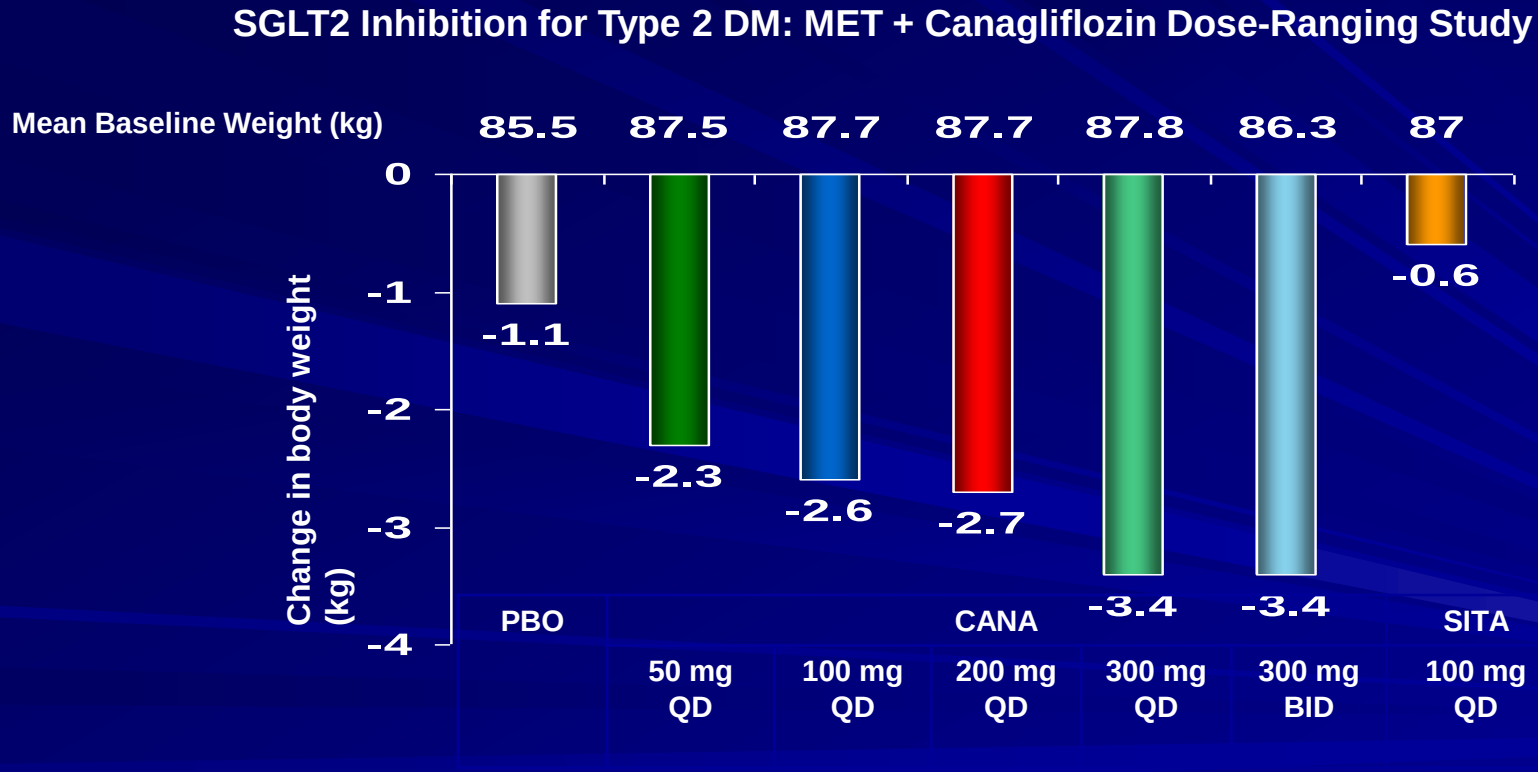
Canagliflozin: HbA1c at week 12



*$P \leq 0.001$ vs placebo calculated using LS means; SITA, sitagliptin

Rosenstock J, et al. Diabetes Care, 2012

Canagliflozin: Weight at week 12



*$P \leq 0.001$ vs placebo calculated using LS means.

Rosenstock J, et al. Diabetes Care, 2012

SGLT 2 inhibitors

CV and renal safety of SGLT2 inhibitors evaluated in 9 trials
2 outcome results published
(EMPA-REG and CANVAS)

62,378 patients enrolled

SGLT 2 inhibitors

EFFICACY

- MOA independent of insulin secreti
- Lowers fasting and prandi
- In general well t
- Impr

CV RR CANAGLIFLOZIN (14%) and EMPAGLIFLOZIN (14%)
FDA indication for empaglifozin
-glycemic improvement
-decrease CV mortality

- bone fractures *(canagliflozin)*
- ced rate of amputations *(canagliflozin)*

SUMMARY OF COMPLETED CVOT – 2008 – May, 2018

CLASS AGENT vs. PLACEBO	STUDY	SAFETY HR SUPERIORITY (*p value*)	CV SUPERIORITY	FDA APPROVED
DPP-4i SAXAGLIPTIN	SAVOR TIMI 53	1.0 (95% CI,0.89-1.12) P=0.99		
DPP-4i ALOGLIPTIN	EXAMINE	0.96 (Upper CI, 1.16) P=0.32		
DPP-4i SITAGLIPTIN	TECOS	0.98 (95% CI,0.89-1.09) P=0.65		
GLP-1 RA LIXISENATIDE	ELIXA	1.02 (95% CI,0.89-1.17) P=0.81		
GLP-1 RA LIRAGLUTIDE	LEADER	0.87 (95% CI,0.78-0.97) P=0.01	✓ YES	✓ Decrease 3P MACE ☺ NNT 53 over 3.8 years
GLP-1 RA SEMAGLUTIDE	SUSTAIN-6	0.74 (95% CI,0.58-0.95) P=0.02	✓ YES	
GLP-1 RA EXENTIDE -ER	EXCEL	0.91 (95% CI,0.83-1.00) P=0.06		
SGLT-2i CANAGLIFLOZIN	CANVAS + CANVAS-R	0.86 (95% CI0.75-0.97) P=0.02	✓ YES	
SGLT-2i EMPAGLIFLOZIN	EMPA-REG	0.86 (95% CI,0.74-0.99) P=0.04	✓ YES	✓ Decrease CV mortality ☺ NNT 63 over 3.1 years

What have we learned?

- ❑ Aggressive and early glycemic treatment improves CVD outcomes
- ❑ Treat to target –*type of antidiabetic agent*
- ❑ Medications that can ameliorate CKD and CVD

- ❑ CVOTs crafted for advanced disease
  - ❑ Translation to clinical practice

- ❑ Cost and cost effectiveness

Decisions often made by PBMs or insurance, not what is best for the patient

PATHOPHYSIOLOGY AND LANDMARK STUDIES

TREATMENT –NEWER MEDICATIONS

CARDIOVASCULAR OUTCOME TRIALS (CVOT)

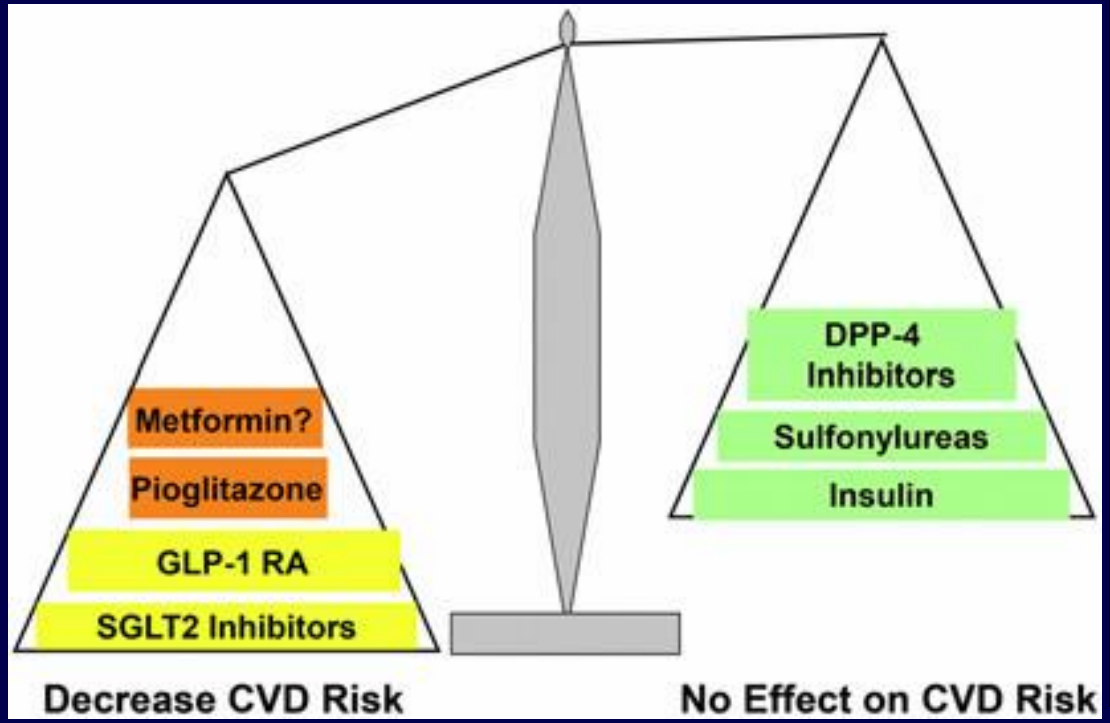
NEW PARADIGM

Managing Type 2 Diabetes, a New Paradigm

NEW PARADIGM
–personalized medicine “patient centered approach”

- **Diabetes Self-Management Education (DSME)**
- **As in oncology: phenotyping, genotyping, and metabolomic data, will help to better identify predictors of benefit or harm**
- **Rich armamentarium –*poorly utilized***
- **Avoid hypoglycemia and or weight gain**
- **Use medications that decrease CKD, CVD, and mortality**
- **Cost / affordability**

The "dawn of a new era"



The Superiority Club

1. Pioglitazone
2. Empagliflozine
3. Canagliflozine
4. Liraglutide
5. Semaglutide

Diabetes Care Volume 40, July 2017

Treat early and aggressively, avoid hypoglycemia and weight gain -How can we best utilize these agents?

Medication	Route	Hypoglycemia	Weight
Metfromin –Glucophage	Oral	NO	↔
Pioglitazone Actos	Oral	NO	↑↑
DPP-IV inhibitors: sitagliptin Januvia, saxagliptin Onglyza, linagliptin Tradjenta, alogliptin Nesina	Oral	NO	↔
GLP-1 analogues: Exenatide Byeta, liraglutide -Victoza, exanatide ER -Bydureon, albiglutide –Tanzeum, dulaglutide –Trulicity, semeglutide -Ozempic	Parenetral	NO	↓↓
SGLT-2 inhibitors: canagliflozin –Invokana, dapagliflozin –Farxiga, empagliflozin -Jardiance,, ertugliflozin –Steglatro	Oral	NO	↓↓

Treat early and aggressively, avoid hypoglycemia and weight gain – Best combination?

New onset diabetes non obese	Metformin + DPPi

Treat early and aggressively, avoid hypoglycemia and weight gain -How can we best utilize these agents?

New onset diabetes non obese	Metformin + DPPi
New onset obese	Metformin + SGLT-2i Metformin + GLP-1RA

Treat early and aggressively, avoid hypoglycemia and weight gain -How can we best utilize these agents?

New onset diabetes non obese	Metformin + DPPi
New onset obese	Metformin + SGLT-2i Metformin + GLP-1RA
Obese uncontrolled	Metformin + SGLT2i + GLP-1RA
Obese uncontrolled + ectopic fat	Metformin + GLP-1 RA + pioglitazone
Uncontrolled without dyslipidemia	Metformin + GLP1 RA + Basal insulin

Treat early and aggressively, avoid hypoglycemia and weight gain -How can we best utilize these agents?

New onset diabetes non obese	Metformin + DPPi
New onset obese	Metformin + SGLT-2i Metformin + GLP-1RA
Obese uncontrolled	Metformin + SGLT2i + GLP-1RA
Obese uncontrolled + ectopic fat	Metformin + GLP-1 RA + pioglitazone
Uncontrolled without dyslipidemia	Metformin + GLP1 RA + Basal insulin

Quadruple therapy	Metformin + GLP1 RA + pioglitazone + SGLT2i

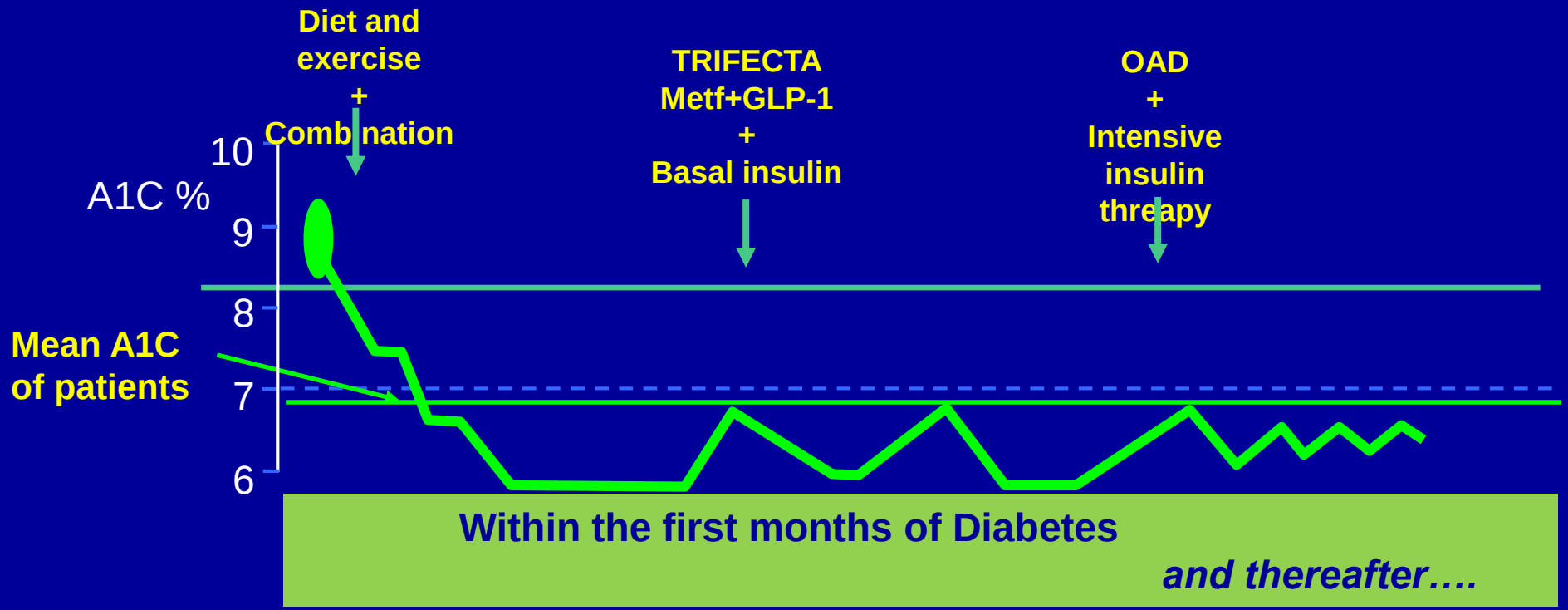
Best for complications (organ failure)…

CAD or HF	**Metformin + empagliflozin** **Metformin + liraglutide** **Metformin + empagliflozin + liraglutide**
CVA	**Metformin + pioglitazone +/- GLP-1 RA** **Metformin+ DPP4i + pioglitazone**

Best with organ failure…

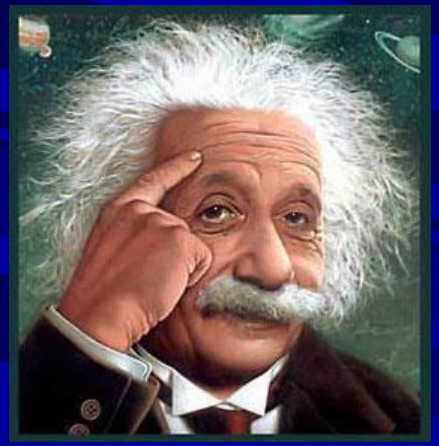
CAD or HF	Metformin + empagliflozin Metformin + liraglutide Metformin + empagliflozin + liraglutide
CVA	Metformin + pioglitazone +/- GLP-1 RA Metformin+ DPP4i + pioglitazone
CKD -early	Metformin + SGLT2i +/- GLP-1RA
Advanced CKD –dialysis	GLP-1 RA GLP-1 RA + Basal insulin GLP-1 RA + pioglitazone

Earlier and Aggressive Intervention



Adapted from Del Prato S et al. *Int J Clin Pract*. 2005;59:1345–1355.

THANK YOU!



Learn from yesterday, live for today, hope for tomorrow.
The important thing is not stop questioning.

Albert Einstein

Thank you for your participation!

To ensure you receive CME/CNE credits for your participation:

- Complete the online evaluation form, a link to the form will be sent to you via email from the OneCity Health Learning Management System
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Questions or Suggestions?:

- **Email: OCHWorkforceTeam@nychhc.org**

June 2018 Grand Rounds Presenter:

DR. OLUGBENGA OGEDEGBE

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Medicine and Population Health, Department of Medicine
Chief Med Officer NYU Global Institute of Public Health
Vice Dean, NYU Global Institute of Public Health
Director Division of Health & Behavior
Director, Center for Healthful Behavior Change

"Hypertension Guidelines"


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