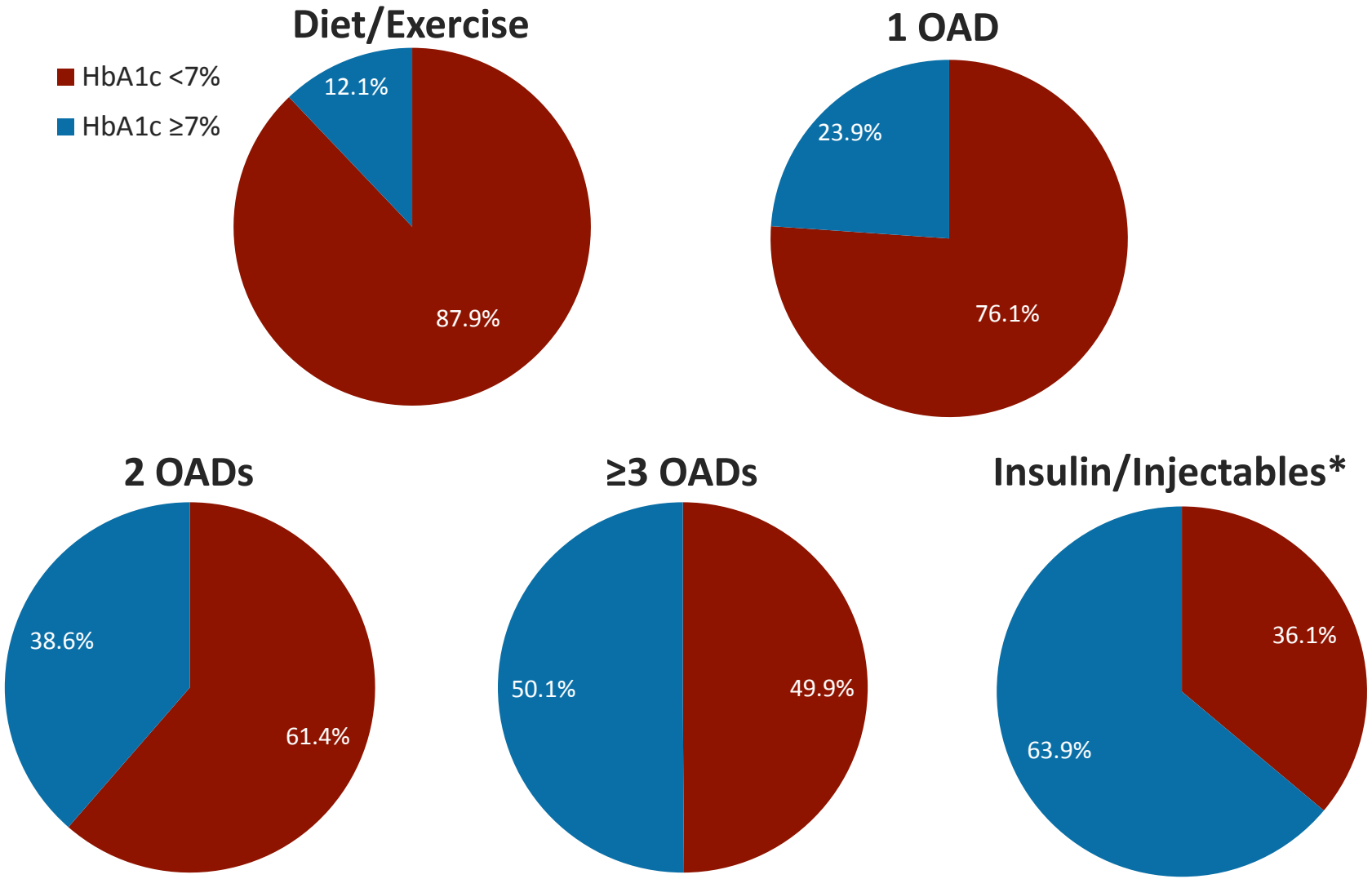
INSULIN AND INCRETINS: THE PERFECT PARTNERSHIP?

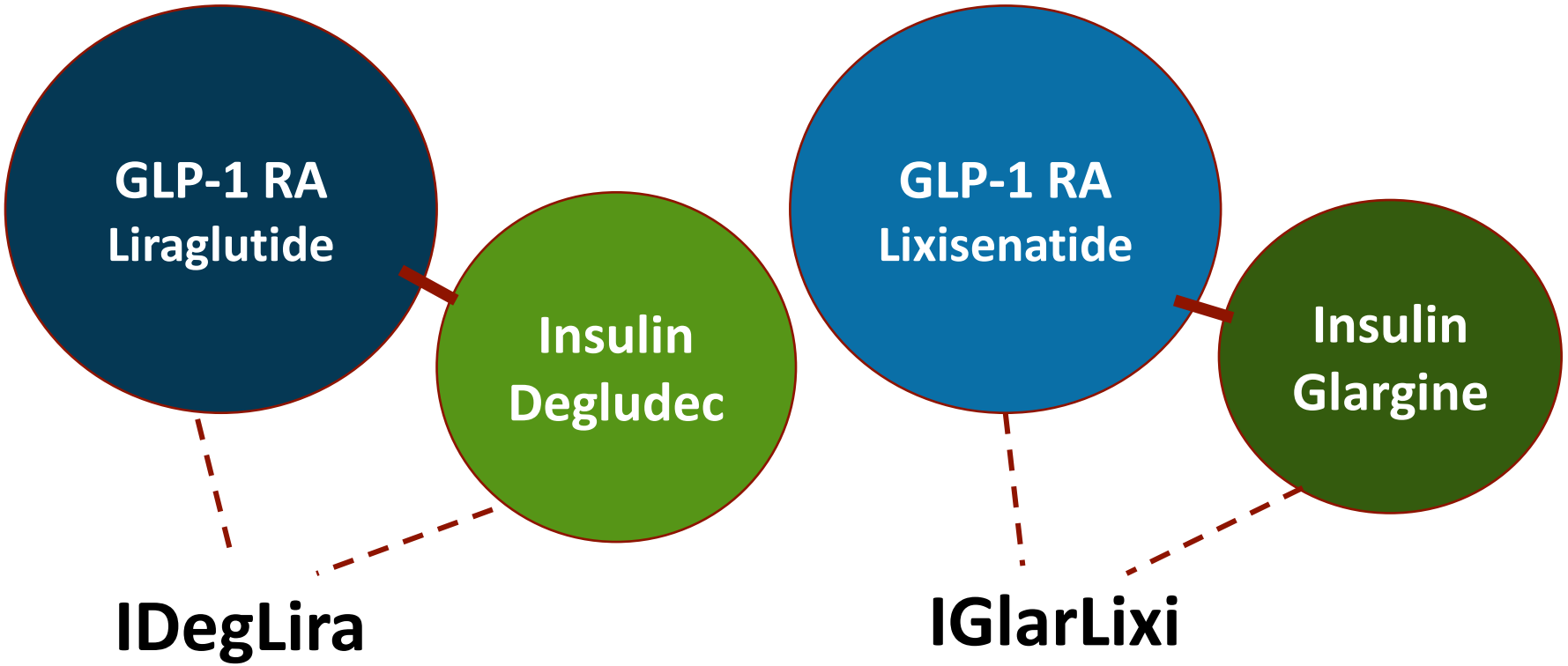
Fewer T2DM Patients at Target When Treated With Insulin/Injectables: PANORAMA Study



de Pablos-Velasco P, et al. *Clin Endocrinol.* 2014;80:47-56.

*Insulin or GLP-1 RA

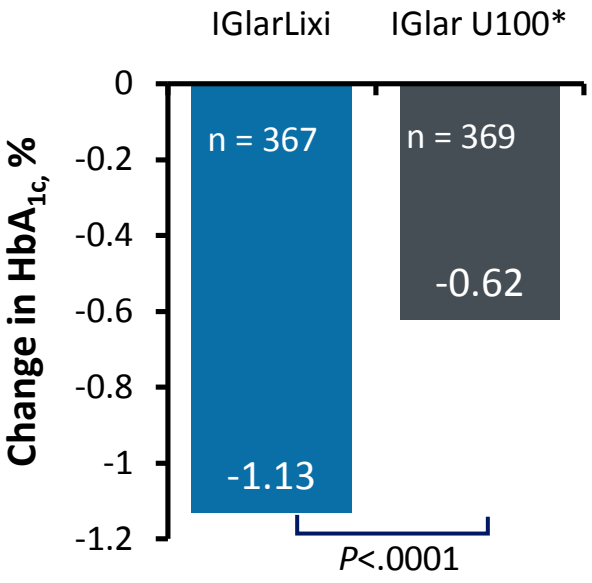
Fixed-Ratio Combinations of Basal Insulin and GLP-1 RAs



LixiLan-L Trial: Patients Uncontrolled on Insulin

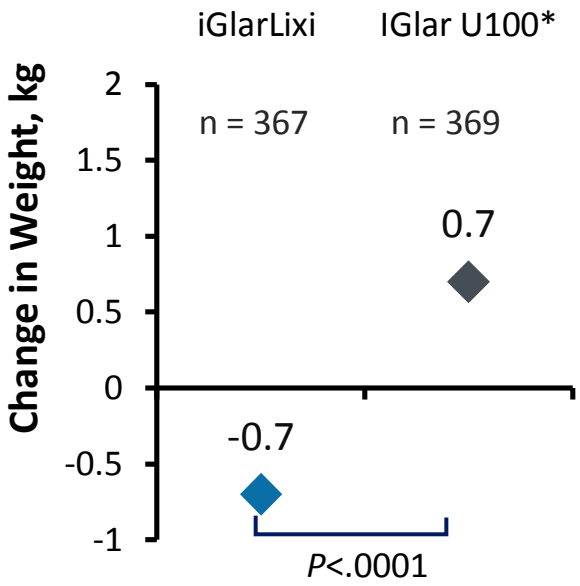
Key Clinical Findings

HbA_{1c}

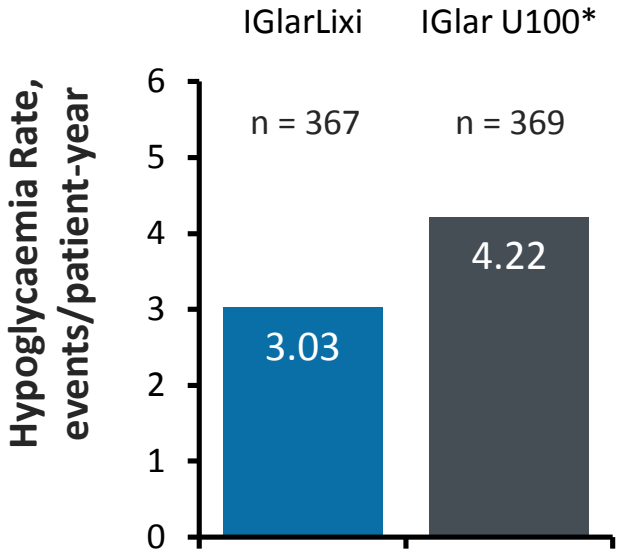


EOT HbA_{1c}	6.94%	7.48%

Weight



Documented symptomatic Hypoglycaemia



Severe hypoglycaemia in 4 IGlarLixi subjects and 1 Gla-100 subject

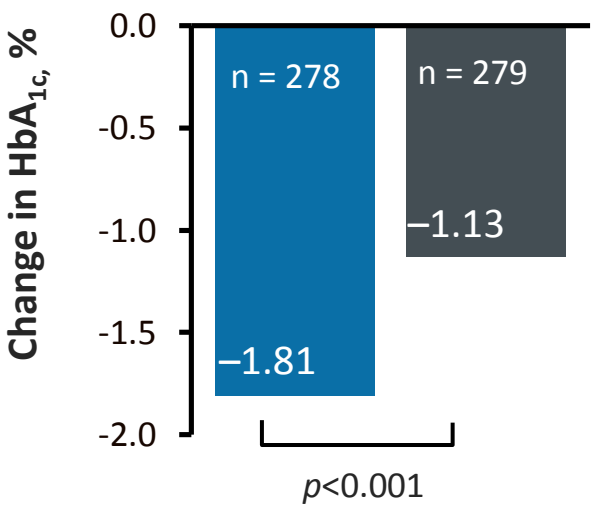
*Max. dose 60 U. Documented symptomatic hypoglycemia (PG ≤70 mg/dL).

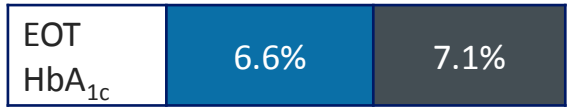
Aroda VR, et al. *Diabetes Care.* 2016 Sep 20. [Epub ahead of print].

DUAL V Trial: Patients Uncontrolled on Insulin

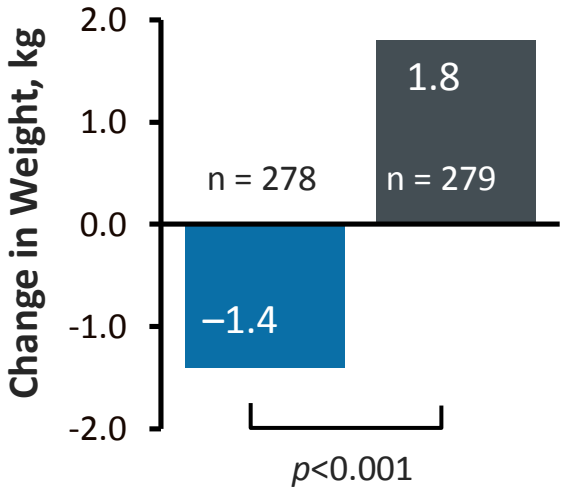
Key Clinical Findings

HbA_{1c}

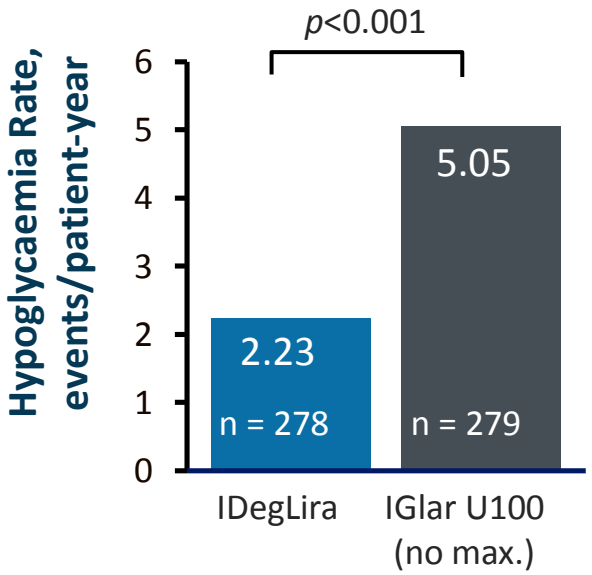




Weight



Confirmed Hypoglycaemia*



Severe hypoglycaemia in one IGlar U100 subject‡

*Hypoglycemia was defined as severe or <3.1 mmol/L.

†Severe: An episode requiring assistance from another person to actively administer carbohydrate, glucagon, or other resuscitative actions

Lingvay I, et al. *JAMA.* 2016;315:898-907.

New Drug Approval

- **FDA approves first-in-class Glyxambi (empagliflozin/linagliptin) tablets for adults with type 2 diabetes**
  - Only SGLT2/DPP-4 inhibitor combination to improve glycemic control as an adjunct to diet and exercise
  - As an add-on to metform, Glyxambi was superior in reducing A1C when compared with either empagliflozin or linagliptin alone

03/24/2015 FDA News and Events

DPP-4 Saxagliptin and SGLT 2 Dapagliflozin combination Qtern drug to control blood sugar levels

America's First Biosimilar Insulin: Coming to Your Drugstore

FDA Approves New Insulin Glargine (Basaglar)
The First "Biosimilar" Insulin in the US

1st ever "biosimilar" insulin approved in US – potential to come cheaper than other insulins, with launch in December 2016

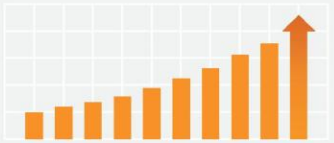
THE NEED FOR U.S. BIOSIMILARS

EXPRESS SCRIPTS

Generic drugs were introduced 30 years ago, saving billions of dollars, improving patient access and changing healthcare forever. Biosimilars now hold the same potential.

U.S. SPECIALTY Rx SPEND

4X SINCE 2006

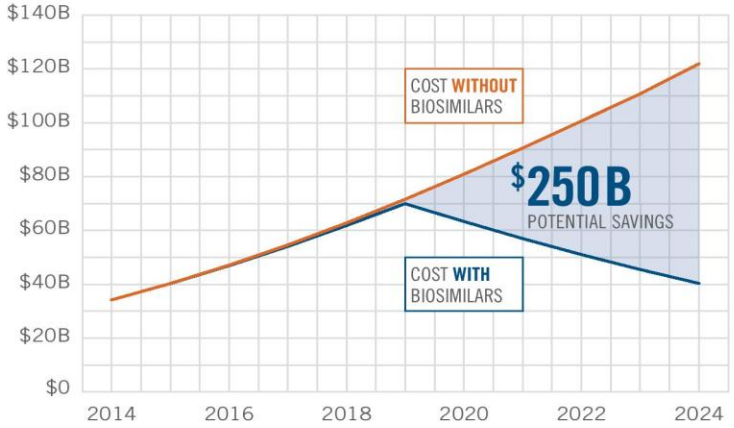


BY 2018, SPECIALTY DRUGS WILL ACCOUNT FOR:

1% OF ALL U.S. PRESCRIPTIONS

50% OF ALL Rx COST

$250 BILLION COULD BE SAVED IN THE NEXT DECADE IF THESE 11 BIOSIMILARS ARE APPROVED



- Avastin® *(bevacizumab)*
- Epogen® *(epoetin alfa)*
- Herceptin® *(trastuzumab)*
- Humira® *(adalimumab)*
- Intron A® *(interferon alfa-2a)*
- Neulasta® *(pegfilgrastim)*
- Neupogen® *(filgrastim)**
- Pegintron® *(peginterferon alfa-2b)*
- Procrit® *(epoetin alfa)*
- Remicade® *(infliximab)**
- Rituxan® *(rituximab)*

*Awaiting FDA approval.

WE KNOW
BIOSIMILARS CAN DRIVE COST DOWN SAFELY

Biosimilars have been lowering healthcare costs around the globe **since 2006 with no related safety issues.**

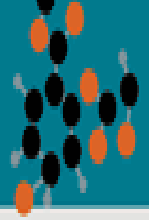
WE NEED
A CLEAR PATH FORWARD IN THE U.S.

FDA APPROVAL

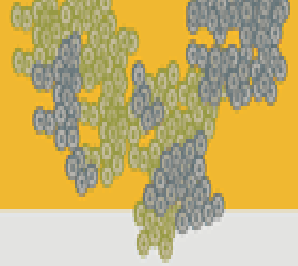
NO UNNECESSARY HURDLES IN STATE SUBSTITUTION LAWS

EASY-TO-USE NAMING STRUCTURE

For the latest Express Scripts research, visit: http://Lab.Express-Scripts.com.



Chemical generic



Biosimilar

2.) Biosimilars require more time and investment

Chemicals can be copied quickly and inexpensively

Development time	Development costs
2-3 years	$2-5 million

Complex biologics take longer & cost more to duplicate

Development time	Development costs
> 5 years	$100 million

Lower up-front investment means greater savings

Chemical generic

Avg. savings for generics: -75%

Lower up-front investment means greater savings

Biosimilar

Avg. savings for biosimilars (est.): ~20%

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

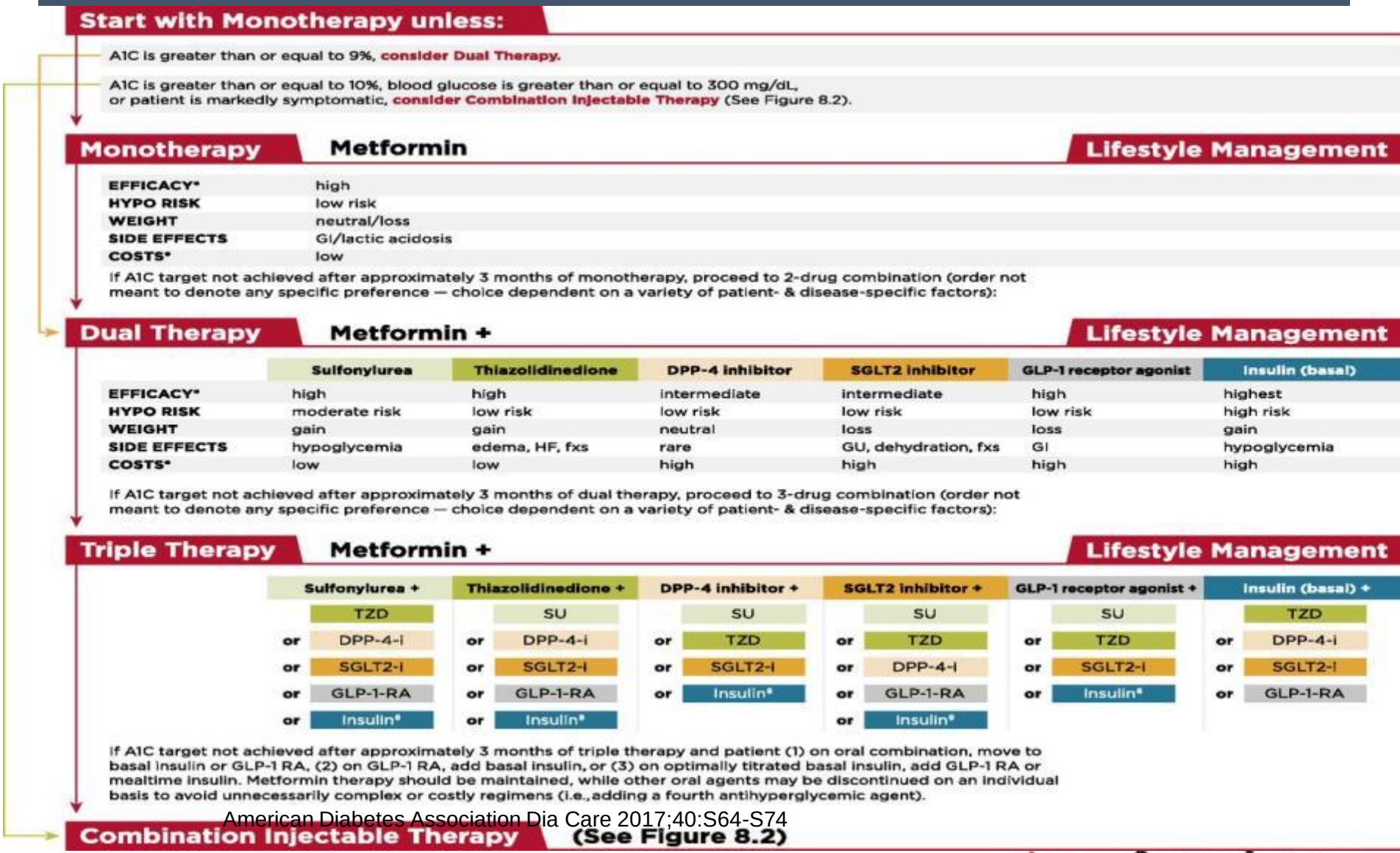
- ✓ Few adverse events and/or possible benefits
- ! Use with caution

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

PROGRESSION OF DISEASE

 DOI 10.4158/EP161682.CS

Antihyperglycemic therapy in type 2 diabetes: general recommendations.



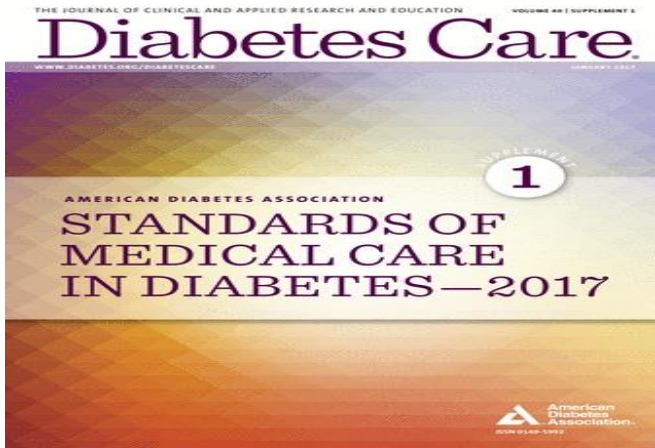
American Diabetes Association Dia Care 2017;40:S64-S74

American Diabetes Association.

American Diabetes Association® Releases 2017 Standards of Medical Care in Diabetes

The Standards have expanded the indications for metabolic surgery to include patients with inadequately controlled type 2 diabetes who have a BMI as low as 30 kg/m² (27.5 kg/m² in Asian Americans).

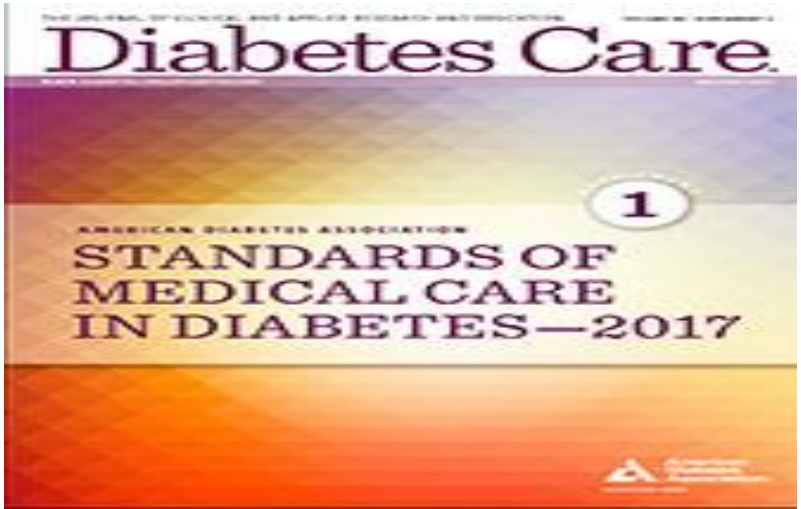
standards of Medical Care in Diabetes'' ADA 2017



Metformin therapy for prevention of type 2 diabetes in prediabetes, especially in:

- BMI ＞35 kg/m2
- Aged 60 years
- Women with prior GDM

American Diabetes Association. Prevention or delay of type 2 diabetes. Sec. 5. In *Standards of Medical Care in Diabetes—2017*. Diabetes Care 2017;40(Suppl. 1):S44–S47 © 2017 by the American Diabetes Association



PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

WEIGHT LOSS THERAPIES

TREAT HYPERGLYCEMIA
FPG > 100 | 2-hour PG > 140

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO HYPERGLYCEMIA ALGORITHM

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

Intensify Weight Loss Therapies

Low-risk Medications
- Metformin
- Acarbose

Consider with Caution
- TZD
- GLP-1 RA

If glycemia not normalized

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

 DOI 10.4158/EP161682.CS

How do you diagnose pre-diabetes?

- Impaired Fasting Glucose (IFG): fasting plasma glucose ≥ 100 mg/dl and ≤ 125 mg/dl, or

- Impaired Glucose
- Tolerance (IGT): 2 hour plasma glucose ≥ 140 mg/dl and ≤ 200 mg/dl during an oral glucose tolerance test, or
- HBA1C 5.7 - 6.4%.

- All should be repeated before making the diagnosis.

ADA.*Diabetes Care*.2014;37(Suppl 1):S5-S80.

Summary of CV outcome trials with SGLT2 inhibitors

	EMPA-REG OUTCOME™[1]	CANVAS[2]	CANVAS-R[3]	CREDENCE[4]	DECLARE-TIMI 58[5]	Ertugliflozin CVOT[6]
Interventions	Empagliflozin/ placebo	Canagliflozin/ placebo	Canagliflozin/ placebo	Canagliflozin/ placebo	Dapagliflozin/ placebo	Ertugliflozin/ placebo
Main inclusion criteria	Est. vascular complications	Est. vascular complications or ≥ 2 CV risk factors	Est. vascular complications or ≥ 2 CV risk factors	Stage 2 or 3 CKD + macroalbuminuria	High risk for CV events	Est. vascular complications
No. of patients	7034	4339	5700	3627	17,150	3900
Primary outcome	3P-MACE	3P-MACE	Progression of albuminuria	ESKD, S-creatinine doubling, renal/CV death	3P-MACE	3P-MACE
Key secondary outcome	4P-MACE	Fasting insulin secretion, progression of albuminuria	Regression of albuminuria, change in eGFR	4P-MACE + HHF	4P-MACE + HHF + revascularisation	4P-MACE
Target no. of events	691	≥ 420	TBD	TBD	1390	TBD
Estimated median FU	~3 years	6–7 years	3 years	~4 years	4–5 years	5–7 years
Estimated completion	2015	Apr 2017	2017	2019	2019	2021

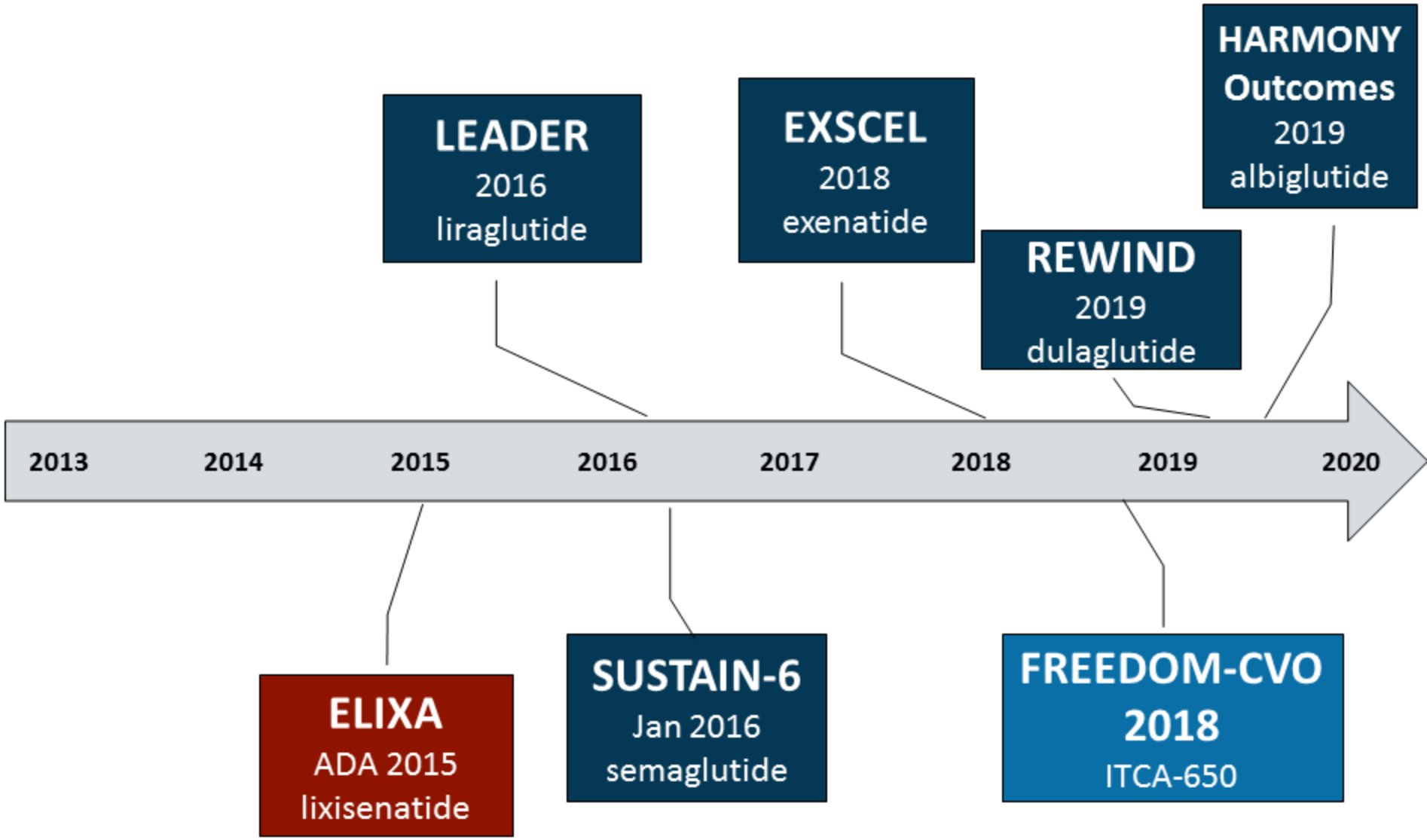
Adapted from Inzucchi et al. Diabetes Vasc Dis Res 2015;12:90–100.

Sotagliflozin as adjunctive therapy for type 1 diabetes

Sotagliflozin, an investigational dual sodium-glucose co-transporter (SGLT) 1 and 2 inhibitor

rate of diabetic ketoacidosis was higher in the sotagliflozin group (3 versus 0.6 percent) as was the frequency of dehydration and genital infections

Timeline of Future GLP-1 RA CV Outcome Trials



ClinicalTrials.gov

The change will ensure CAROLINA® generates robust, clinically relevant evidence

Clinically meaningful composite endpoint

- Hospitalisation for angina can dilute the effect of other endpoint components – CV death, MI and stroke – which are considered more specific CV endpoints[1,2]
- The change takes into account the most recent clinical evidence

Supported by regulatory guidance

- Both the FDA and EMA recommend 3P-MACE as the primary endpoint in CVOTs of glucose-lowering agents[3,4]

Most recently completed and ongoing CVOTs[5–9] use 3P-MACE as the primary endpoint, which will improve comparability across trials given the fast-evolving scientific environment

3P-MACE, 3-point major adverse CV event; CV, cardiovascular; CVOT, CV outcomes trial; EMA, European Medicines Agency; FDA, Federal Drug Administration; MI, myocardial infarction. 1. Hicks KA *et al. J Am Coll Cardiol* 2015;66:403; 2. Pocock SJ *et al. J Am Coll Cardiol* 2015;66:2757; 3. FDA Guidance for Industry. 2008. www.fda.gov; 4. EMA Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. 2012. www.ema.europa.eu; 5. NCT01179048; 6. NCT01144338; 7. NCT01394952; 8. NCT01032629; 9. NCT01730534

Acarbose CV Evaluation

UNIVERSITY OF OXFORD

DIABETES TRIALS UNIT
The Oxford Centre for Diabetes, Endocrinology and Metabolism

Radcliffe Department of Medicine

Home | About Us | OUBST | Diabetes | Multicentre Trials | Translational Trials | Software | Publications

Overview | 4-T | ACE | ADOPT | AFORRD | DREAM | EDIT | EXSCEL | FHS | GLINT | ISAT | LDS | NAVIGATOR | TECOS | UKPDS

Acarbose Cardiovascular Evaluation (Ongoing)

ACE
Acarbose Cardiovascular Evaluation

Overview | News | Organisation | Protocol | Ancillary studies | Academic Presentations | Publications | Slides

The Acarbose Cardiovascular Evaluation (ACE) clinical trial will find out if a drug called acarbose can prevent people with coronary heart disease and impaired glucose tolerance (IGT) from experiencing, or dying from, further heart attacks and strokes.

The ACE trial will also look to see if acarbose, which reduces blood glucose following a meal, can prevent or delay people progressing from IGT to type 2 diabetes.

Coordinated by DTU and sponsored by Bayer Healthcare, this phase IV multinational trial began in 2008. It is being conducted in around 150 hospitals in mainland China and Hong Kong. The participating hospitals will be managed on a day-to-day basis through DTU's ACE Project Office in Beijing.

7,500 people with heart and circulatory disease aged 50 years or older who have impaired glucose tolerance will be recruited to the trial. Each participant will receive a 50mg acarbose tablet or a placebo (dummy drug) three times a day, and will be followed for a minimum of four years.

We expect that results of this trial will be available in 2018.

VERIFY trial: a randomized double-blind trial.

Study to determine the durability of glycaemic control with early treatment with a vildagliptin-metformin combination regimen vs. standard-of-care metformin monotherapy-

To test the hypothesis that early combined treatment of metformin and vildagliptin slows β-cell deterioration as measured by HbA1c .

Del Prato S[1], Foley JE, Kothny W, Kozlovski P, Stumvoll M, Paldánius PM, Matthews DR. Diabet Med. 2014 Oct;31(10):1178-84. doi: 10.1111/dme.12508. Epub 2014 Jul 17.

Inclusion Criteria:

- Type 2 Diabetes Mellitus (T2DM) diagnosed ≤ 24 months ago
- glycosylated hemoglobin (HbA1c) ≥6.5% and ≤7.5% at Visit 1
- Treatment-naïve.
- Body mass index (BMI) ≥22 and ≤40 kg/m2 at Visit

Exclusion Criteria:

- Pregnant or nursing (lactating) women
- Fasting plasma glucose (FPG) ≥ 270 mg/dL (≥ 15.0 mmol/L)
- Concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study.
- Donation of blood or significant blood loss equaling to at least one unit of blood within the past 2 weeks of start of study or a blood transfusion within the past 12 weeks or planned regular transfusions during the study period

Del Prato S[1], Foley JE, Kothny W, Kozlovski P, Stumvoll M, Paldánius PM, Matthews DR. Diabet Med. 2014 Oct;31(10):1178-84. doi: 10.1111/dme.12508. Epub 2014 Jul 17.

Evolution of Glucose Monitoring

SMBG[a]

- Advances have been made to increase accuracy of glucose meters, but patient education still key

CGM[a]

- Allows for blood glucose monitoring over a 24-hour period

- Dexcom G5 – personal
- Dexcom G4 Platinum – professional
- iPro2 Professional
- Freestyle Libre Pro

FGM[b]

- CGM with no finger sticks
- No need for calibration

- Freestyle Libre - personal

a. Mazze RS. *Diabetes Technol Ther*. 2005;7:784-787; b. Hirsh IB. *Postgrad Med*. 2017. [Epub ahead of print]

Smart insulin

Smart insulin is a form of insulin that turns on when it’s needed to lower blood sugar and off when blood sugar is at a safe level.

As a glucose- responsive insulin

Table-2: Components of nanonetwork.

BASED SMART INSULIN

- Acid -degradable polymeric matrix of dextran (83% weight)
- Surface coatings
  - Chitosan (positively charged)
  - Alginate (negatively charged)

Encapsulated enzymes (1.3% weight)

  - Glucose oxidase (GOx)
  - Catalase (CAT)

- Recombinant insulin (17%, weight)

Injectable Nano-Network Controls Blood Sugar in Diabetics for Days at a Time

The new, injectable nano-network is composed of a mixture containing nanoparticles with a solid core of insulin, modified dextran and glucose oxidase enzymes.

When the enzymes are exposed to high glucose levels they effectively convert glucose into gluconic acid, which breaks down the modified dextran and releases the insulin.
The insulin then brings the glucose levels under control.

The gluconic acid and dextran are fully biocompatible and dissolve in the body.

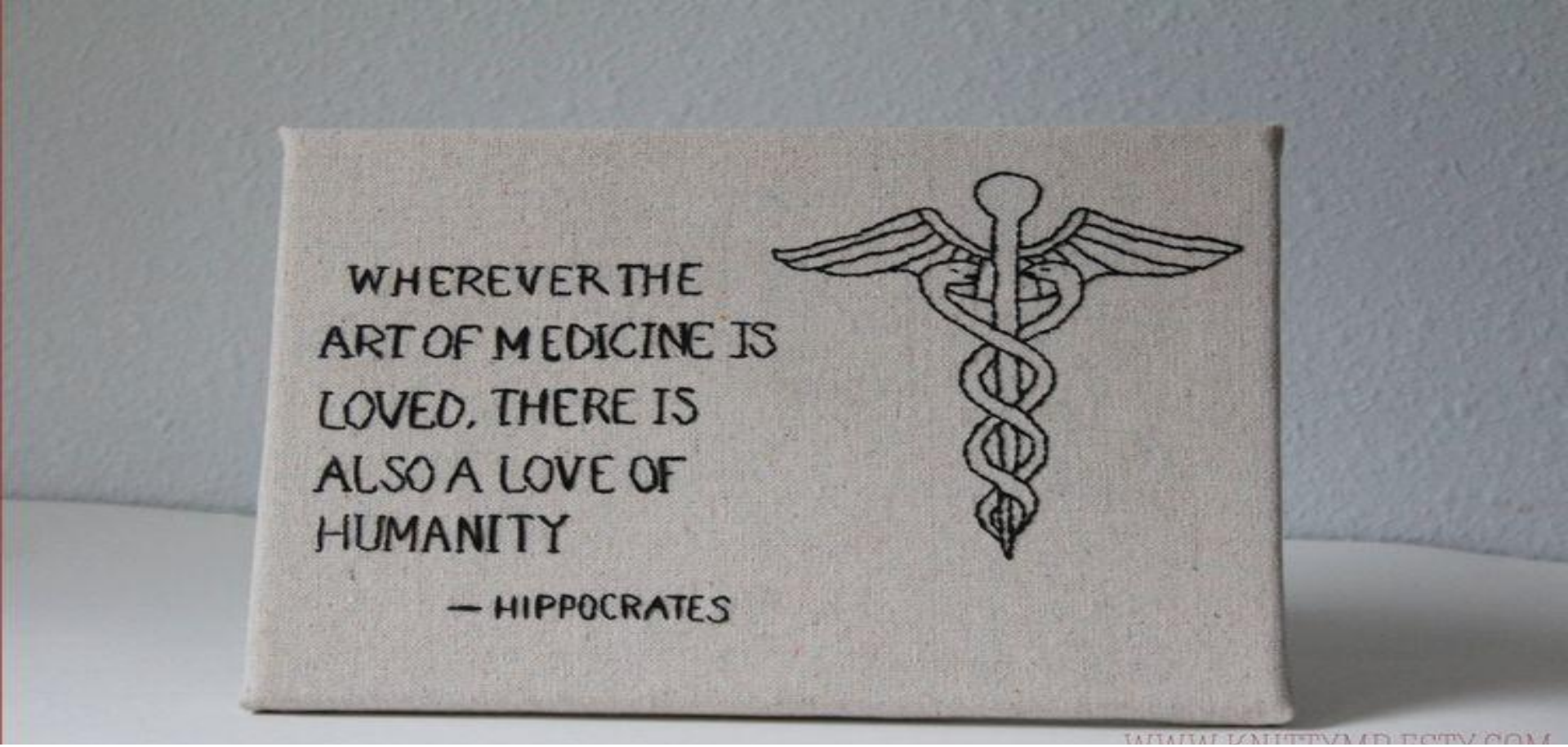
The Ideal Antidiabetes Medication

- Produces a robust decrease in HbA1c
- No risk for hypoglycemia
- Weight loss-inducing or weight-neutral
- Durable
- No significant side effects
- Good long-term safety profile
- Simple route of administration
- Decreases LDL-C
- Increases HDL-C
- Reduces blood pressure
- Improves cardiovascular outcomes

HbA1c = glycated hemoglobin; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol

Our understanding and management of DM Continues to improve and change is Rapid

Hopefully this will result in improved outcomes for our patients



Thank you for your attention