Backgrounder

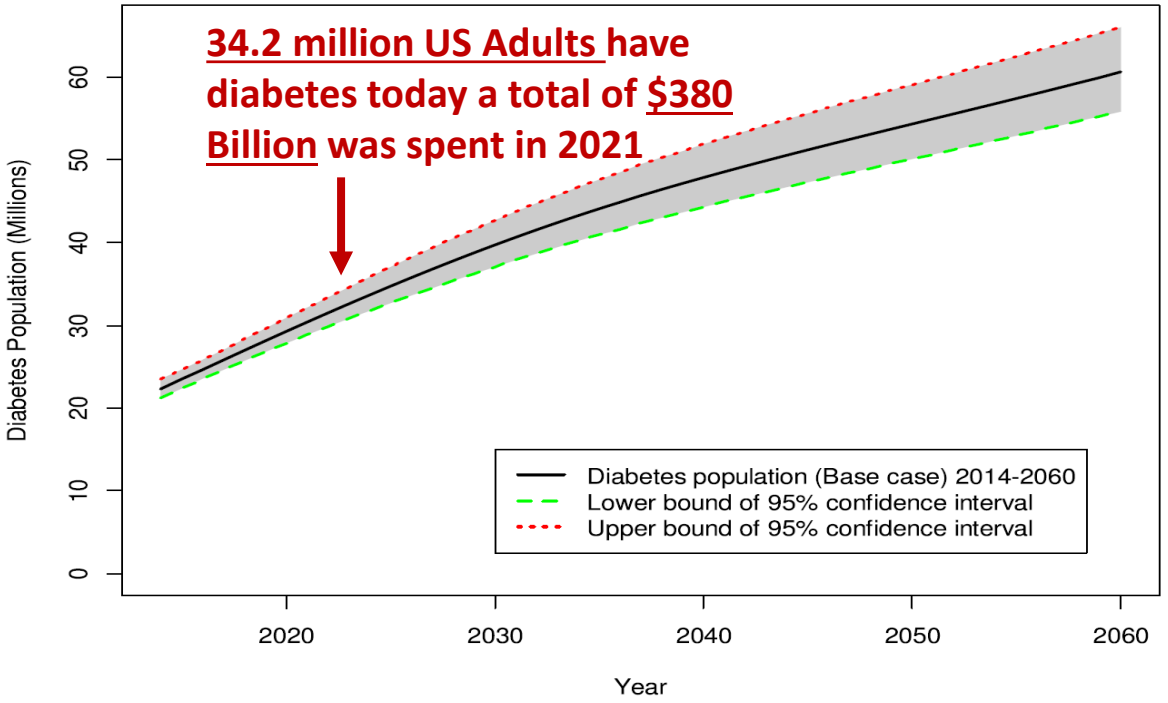
Diabetes (Type 2 & 1) Current Standard of Care Solutions and Unmet Need

biomea FUSION

Disease Background – Type 2 Diabetes

2 in 5 Americans will Develop Diabetes in their Lifetime

- One of the largest economic burdens on the US health care system and the 7th leading cause of death in the US Source: Diabetes.org
- 80% of people with diabetes will die from this disease. Premature mortality caused by diabetes results in an estimated 12-14 years of life lost. Source: National library of Medicine 1(2); 200[illegible] Jul PMC3068646
- In the United States $1 out of every $4 in US health care costs is being spent on caring for people with diabetes. In 2021 the US spent $380 Billion to treat diabetes.
- Diabetes Remains Unresolved For Almost 50% of Patients on Current Standard of Care *Source: Clin Diabetes. 2020 Jul*

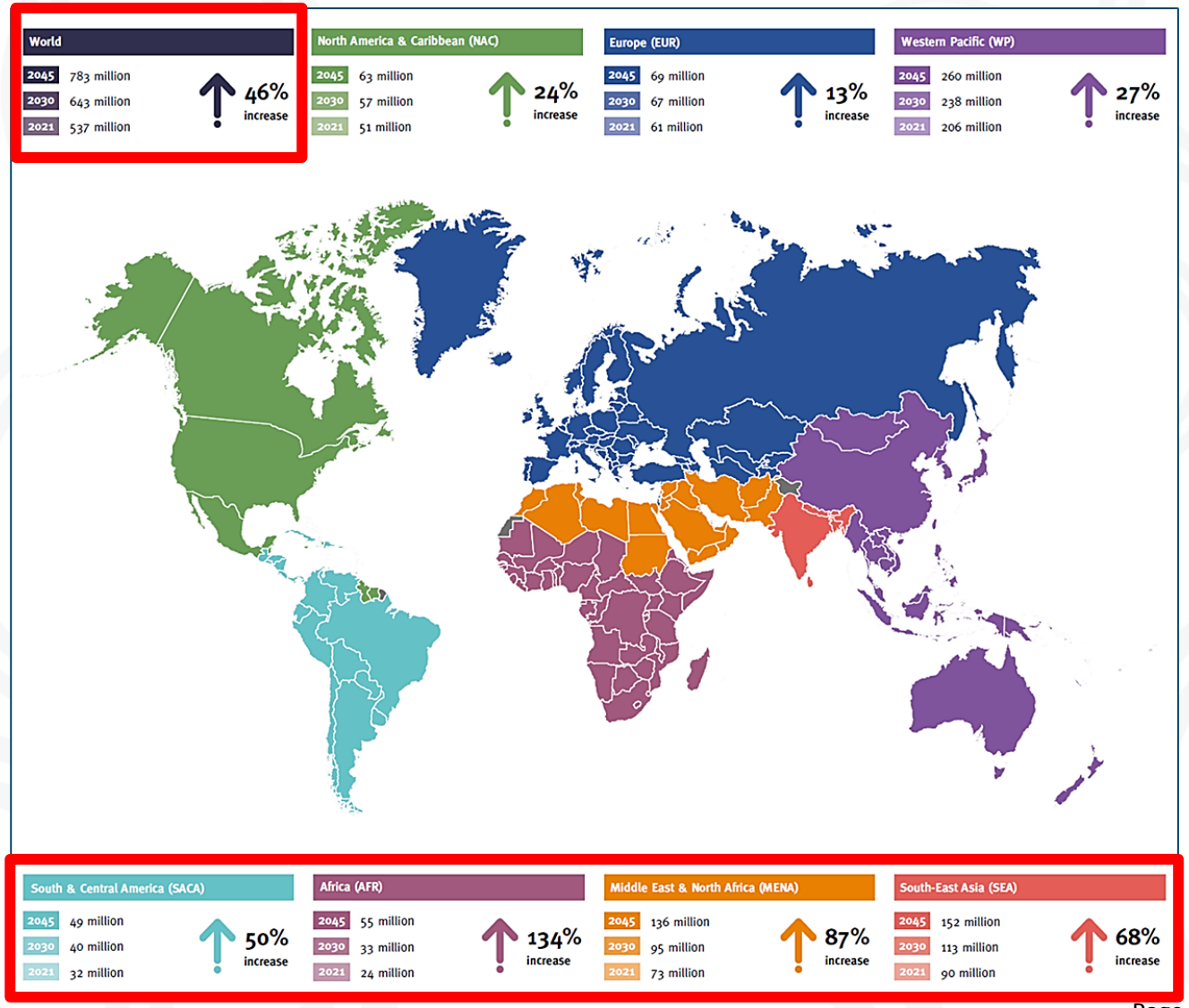


- According to the International Diabetes Foundation, worldwide 537 million adults have diabetes growing to 643 million by 2030. In the United States alone, 34.2 million adults have diabetes, 10.5% of the population. 96 million adults (more than 1 in 3) in the US have pre-diabetes.

Ever-Increasing Global Prevalence of Diabetes

- ↑ Complications
- ↓ Life expectancy
- ↓ Quality of life
- ↑ Healthcare costs

- A significant unmet need exists for developing therapeutics that address the root cause of diabetes (beta cell dysfunction) and that are potentially disease modifying
- We, at Biomea Fusion, are at the forefront of this effort!



IDF Diabetes Atlas, 10th edition

Over 60 Approved Therapies but Diabetes Remains Unresolved

"Diabetes is a common disease that affects nearly 40 million people in the U.S. and is projected to affect more in the coming years. **The need for more antidiabetic treatment options is clear**," said Lisa Yanoff, M.D., deputy director of the FDA's Center for Drug Evaluation and Research, alongside FDA's updated draft guidance for industry titled, "Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products Guidance for Industry" published on **May 25, 2023**.

"Among those individuals who initiated GLP-1a drugs for weight loss at one year follow-up, […] Adherence to these drugs was also poor, with just **27% of individuals taking GLP-1a drugs after one year**." Source: Real-world analysis of GLP-1a drugs by Prime Therapeutics and MagellanRx based on 16M insured members

We've come a long way in the management of T2D…

Efficacy of B
NPH Insulin
Sulfonylurea
of Type II Di

Riddle MC, et al. *Diabete*

POSITION STATEMENT

Standards of Medical Care for Patients With Diabetes Mellitus

Diabetes is a chronic illness that requires continuing medical care and education to prevent acute complications and to reduce the risk of long-term complications. People with diabetes should receive their treatment and care from physicians with expertise and a special interest in diabetes. The following standards define basic medical care for people with diabetes. These standards are not intended to preclude more extensive evaluation and management of the patient.

INITIAL VISIT

Medical history. The comprehensive medical history can uncover symptoms that will help establish the diagnosis in the patient with previously unrecognized diabetes. If the diagnosis of diabetes has already been made, the history should confirm the diagnosis, review the previous treatment, help evaluate the present degree of glycemic control, determine the presence or absence of the chronic complications of diabetes, assist in formulating a management plan, and provide a basis for continuing care. Elements of the medical history of *particular* concern in patients with diabetes include:

- Symptoms and laboratory test results related to the diagnosis of diabetes
- Dietary habits, nutritional status, and weight history; Growth and development in children
- Details of previous treatment programs, including diabetes education
- Current treatment of diabetes, including medications, diet, and results of glucose monitoring
- Exercise history
- Frequency, severity, and cause of acute complications such as ketoacidosis and hypoglycemia
- Prior or current infections, particularly skin, foot, dental, and genitourinary
- Symptoms and treatment of chronic complications associated with diabetes: eye, heart, kidney, nerve, sexual function, peripheral vascular, and cerebral vascular
- Other medications that may affect blood glucose concentration
- Risk factors for atherosclerosis: smoking, hypertension, obesity, hyperlipidemia, and family history
- Psychosocial and economic factors that might influence the management of diabetes
- Family history of diabetes and other endocrine disorders
- Gestational history: hyperglycemia, delivery of an infant weighing >9 lb, toxemia, stillbirth, polyhydramnios, or other complications of pregnancy

Physical examination. A complete physical examination should be performed during the initial evaluation. Individuals with diabetes are at high risk of developing eye, kidney, nerve, cardiac, and vascular complications. Patients with type I (insulin-dependent) diabetes also have an increased frequency of thyroid disease, and all individuals with diabetes are at increased risk of infections. Children may have delayed growth and maturation. Therefore, certain aspects of the physical examination require *special* attention. These include:

- Height and weight measurement (and comparison to norms in children)
- Sexual maturation staging
- Blood pressure determination (with orthostatic measurements)

DIABETES CARE, VOL. 12, NO. 5, MAY 1989 365

Diabetes Care **1989**;12:365-368.

Matthew C. Ric
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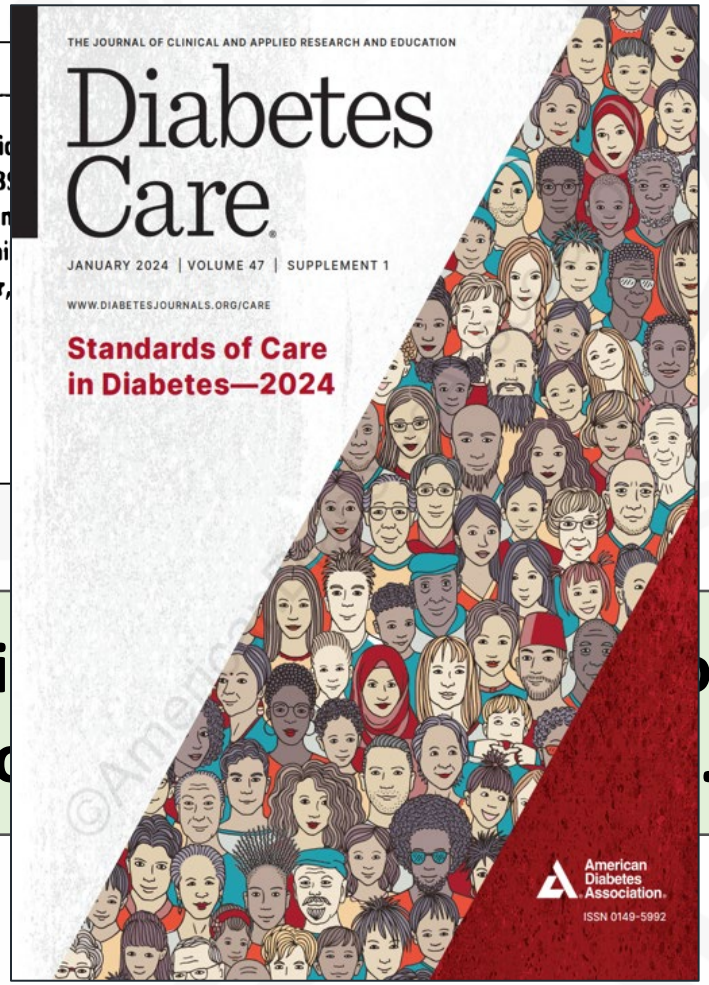
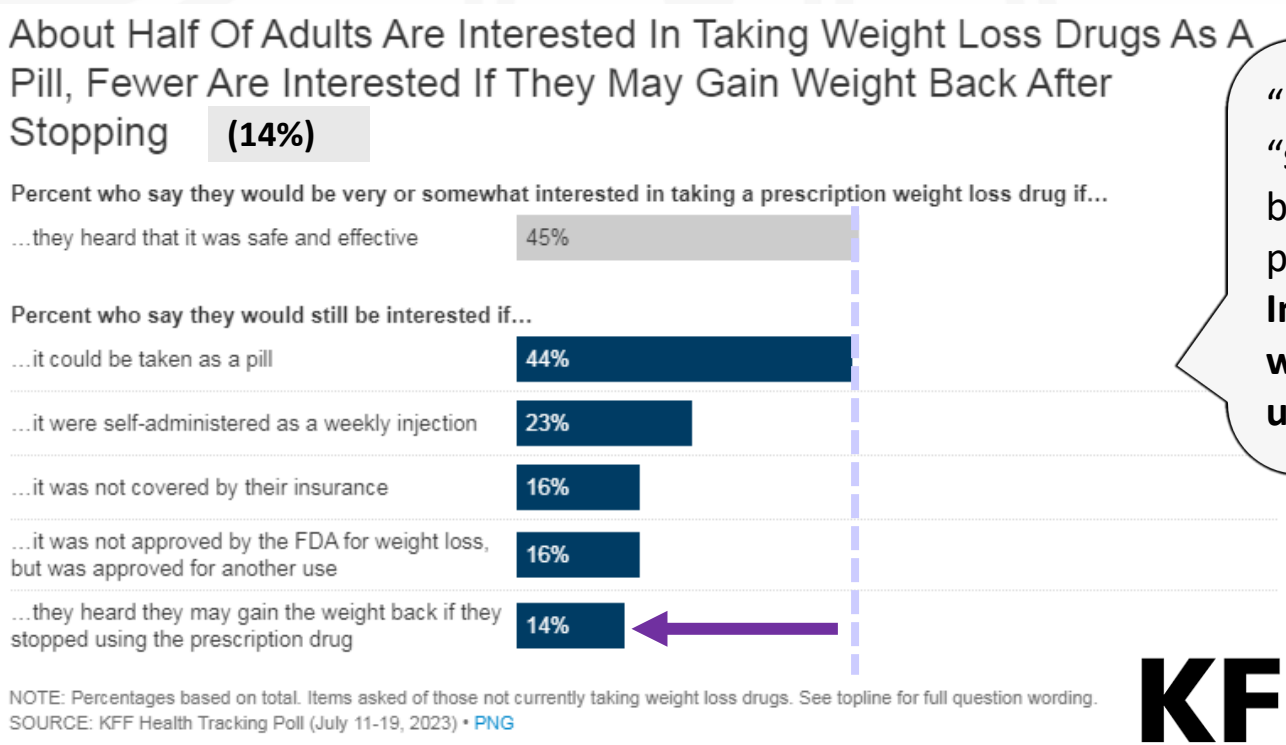


Diabetes Care **2024**;47(Suppl. 1):S1-341.

Interest in Taking Weight Loss Drugs Drops to 14% with the Understanding the Weight is Coming back once they Stop Taking the Medication

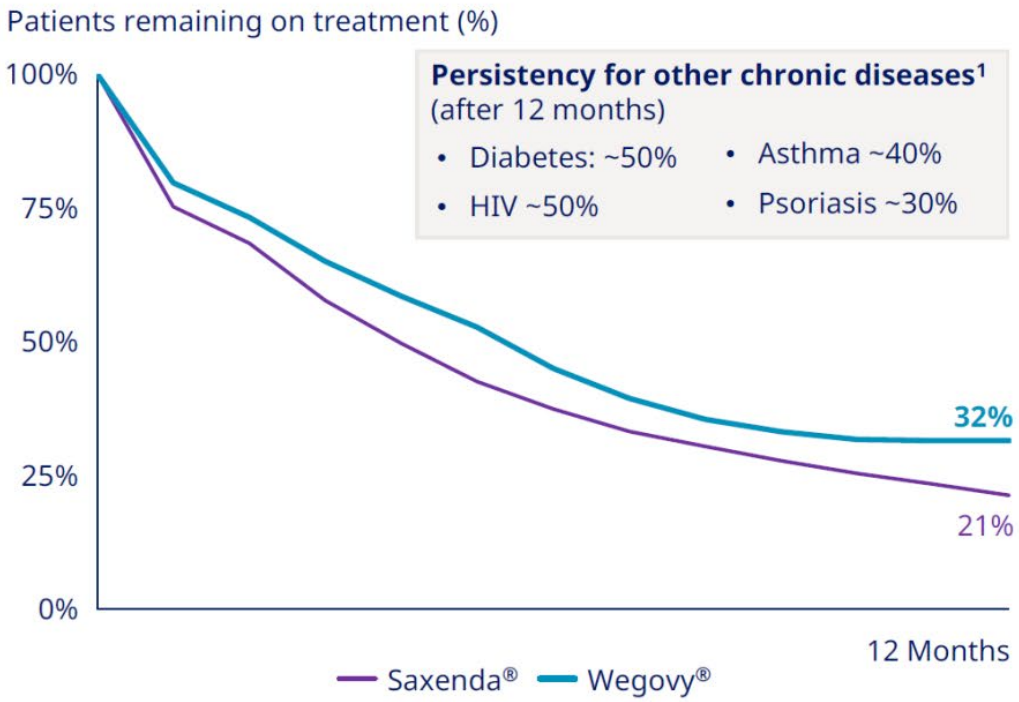


"Nearly half of all adults (45%) continue to be either "very" or "somewhat" interested in taking medication like this if it could be taken as a pill.[1] Interest decreases substantially to 23% once people understand they would need routine injections. **Interest in taking a medication for weight loss drops to 14% when people hear they may gain weight back after stopping use.**" Source: KFF Health Tracking Poll (July 11-19, 2023) "

KFF

Only 32% of Wegovy Users Remain on Treatment after 12 Months

Patient persistency on anti-obesity medications after 12 months



Characteristics for patients on Wegovy® in the US

≈ 75% naïve to AOM treatment

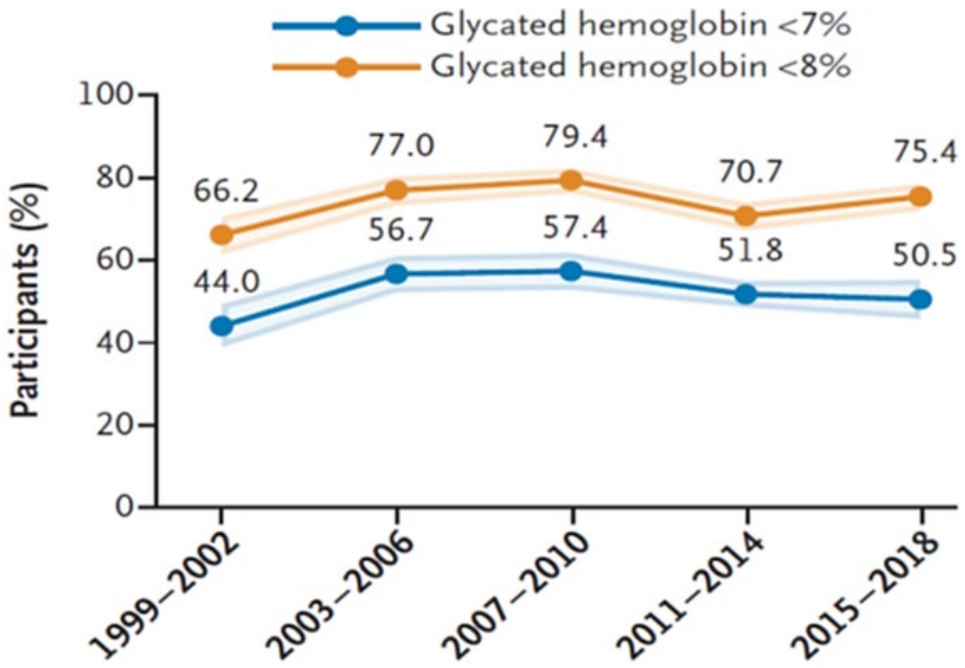
- 81% female
- Age: Average of 47 years
- Average BMI of 38
- Patients on Wegovy® with type 2 diabetes diagnosis: 8%
- With comorbidities: ≥1: 78% ≥2: 53% ≥3: 32%
- Average Wegovy® stay time >6 months despite supply constraints[2]

[1]Hichborn, et al. (2018). Improving patient adherence through data-driven insights. McKinsey & Company; [2] Based on real world data, patient cohort included those initiating therapy between Oct '21 and Mar '22, followed for 1 year;
AOM: Anti-obesity medications; BMI: Body mass index; HbA1c: Haemoglobin A1c; HIV: Human Immunodeficiency Virus; US: United States
Source: IQVIA LAAD AOM Rx August 2023; Real world evidence based on prescription data

CMD24 CAPITAL MARKETS DAY

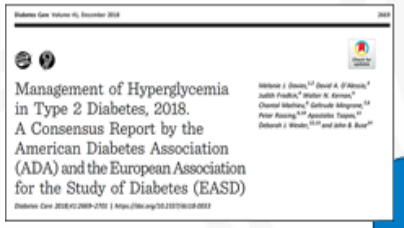
Inadequate Glycemic Control and Poor Adherence and Persistence is Common and have not Changed over the Years

Poor glycemic control



Fang et al. *N Engl J Med* 2021

Poor adherence and persistence


Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

EASD American Diabetes Association

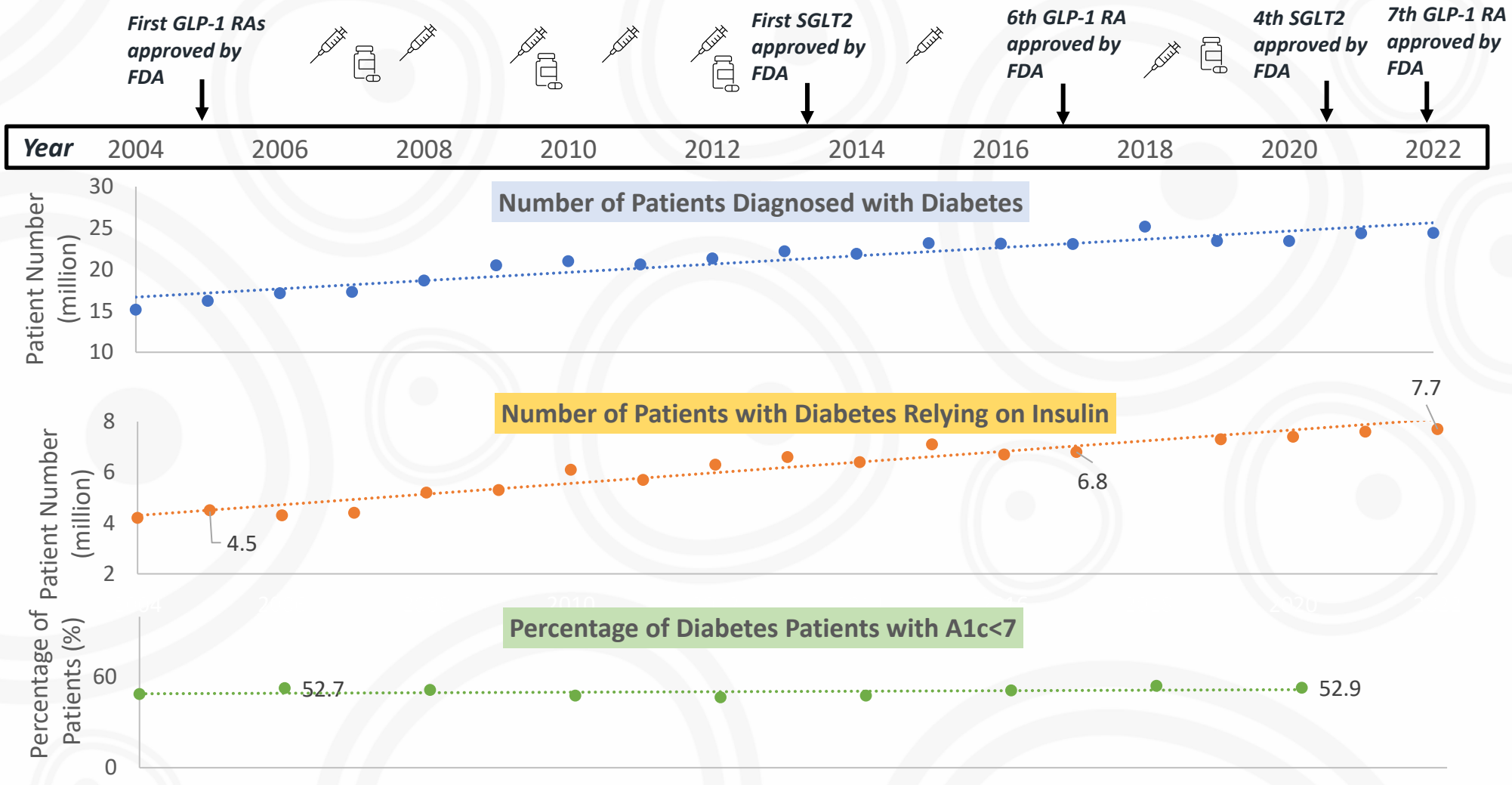
"Suboptimal adherence, including poor persistence, to therapy affects almost half of people with diabetes…"

Davies MJ, et al. *Diabetes Care*. 2018;41:2669-2701

About 50% patients still fail to achieve the A1c goal of <7% (based on a cross-sectional analysis of data from over 6600 adults with diabetes in the United States participating in the National Health and Nutrition Examination Survey (NHANES) to assess national trends in diabetes treatment and risk-factor control from 1999 through 2018)

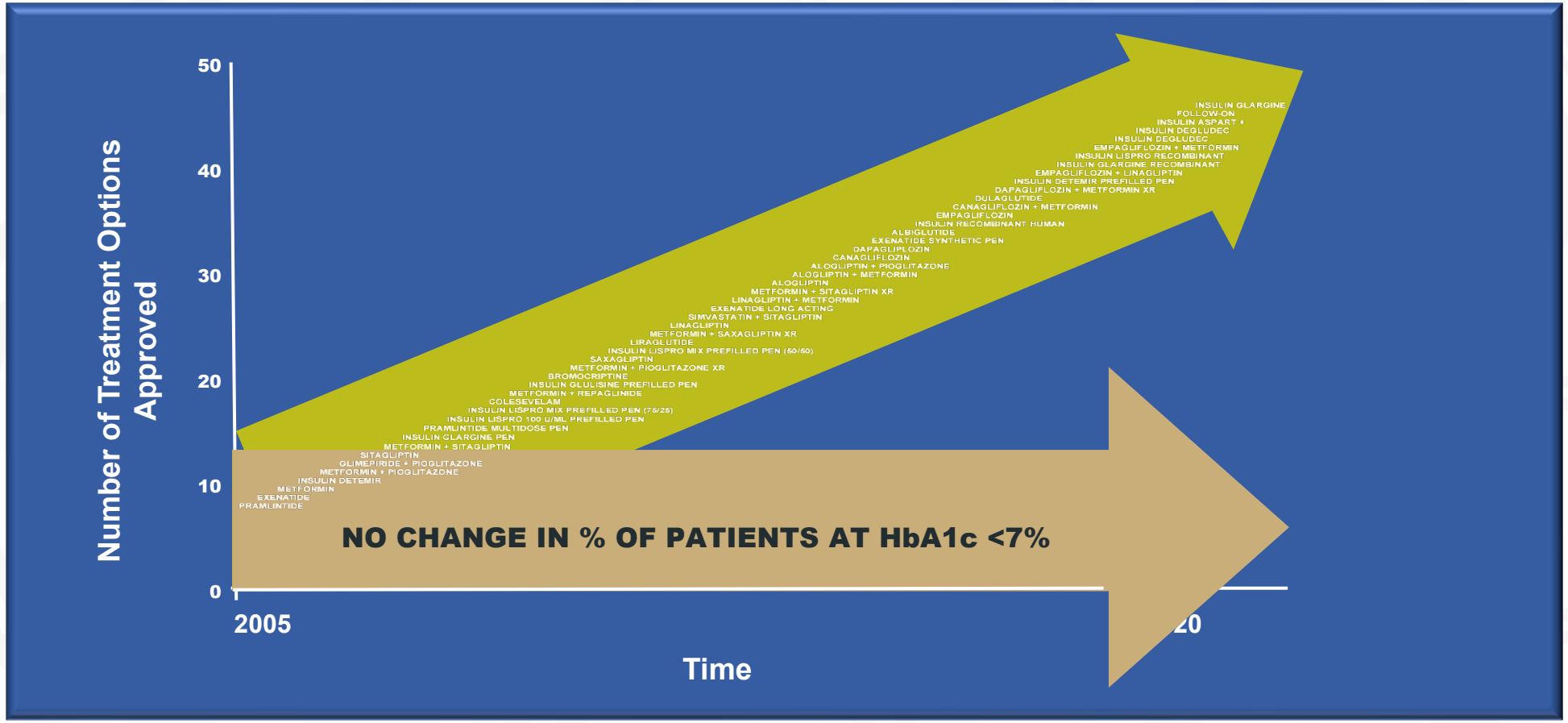
N Engl J Med 2021;384:2219-28.
DOI: 10.1056/NEJMsa2032271

Number of Patients with Diabetes and Relying on Insulin Continues to Rise



United States Diabetes Surveillance System. Diabetic medication use. Centers for Disease Control and Prevention. Available from https://gis.cdc.gov/grasp/diabetes/diabetesatlas-surveillance.html#. Accessed 6 Jan 2024

Glycemic Control among Patients with Diabetes Has not Improved Over the Years

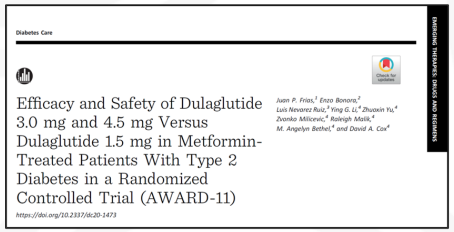


Type 2 diabetes U.S. drug approvals: 2005-2015. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

Even in Controlled Clinical Trials many Patients do not Achieve Target HbA1c

Despite better glycemic control with higher-dose dulaglutide (3.0 and 4.5 mg) and semaglutide (2.0 mg)

AWARD-11:
High-dose dulaglutide (3.0 and 4.5 mg) in T2D

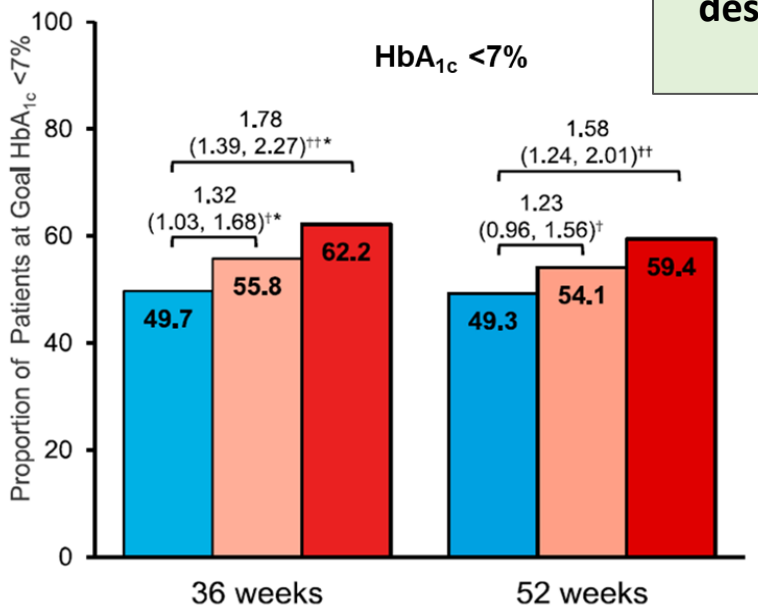

Diabetes Care

Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg Versus Dulaglutide 1.5 mg in Metformin-Treated Patients With Type 2 Diabetes in a Randomized Controlled Trial (AWARD-11)

Juan P. Frías, Enzo Bonora, Luis Nevarez Ruiz, Ying G. Li, Zhuoxin Yu, Ivanka Milicevic, Raleigh Malik, M. Angelyn Bethel, and David A. Cox

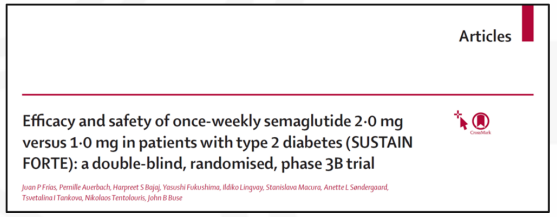
https://doi.org/10.2337/dc20-1473

Frías JP, et al. *Diabetes Care* 2021;44:765-73



41% did not achieve target HbA1c despite high-dose TRULICITY

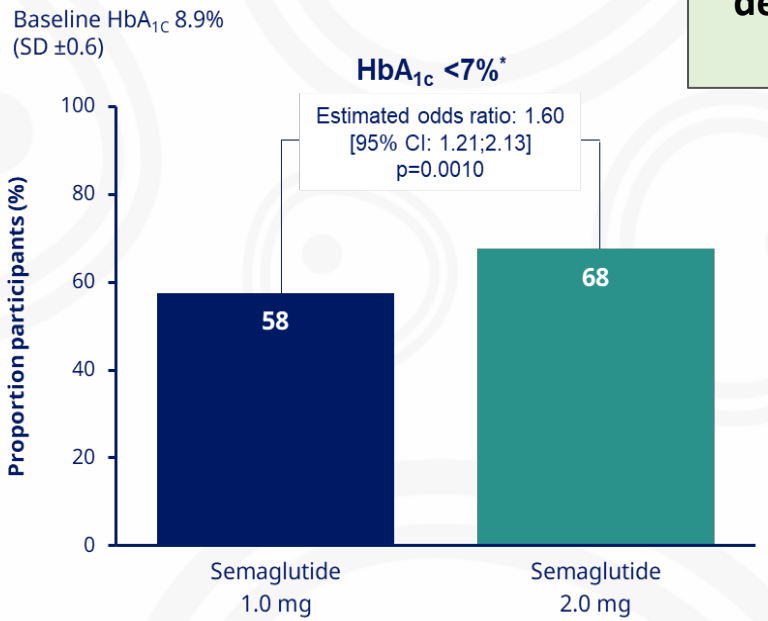
SUSTAIN FORTE:
High-dose once-weekly semaglutide (2.0 mg) in T2D


Articles

Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial

Juan P Frías, Pernille Auerbach, Harpreet S Bajaj, Yasushi Fukushima, Ildiko Lingvay, Stanislava Macura, Anette L Sørdergaard, Tsvetalina I Tankova, Nikolaos Tentolouris, John B Buse

Frías JP, et al. *Lancet Diabetes Endocrinol.* 2021;9:563-574

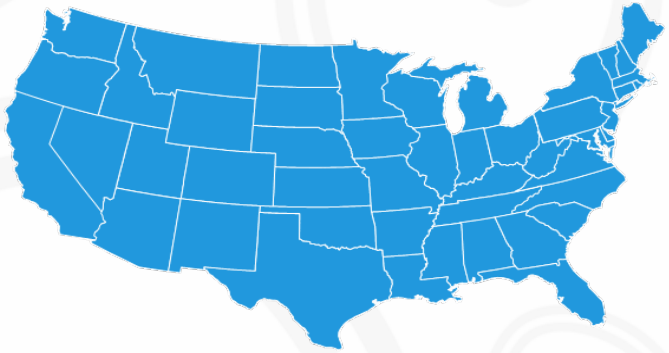


32% did not achieve target HbA1c despite high-dose OZEMPIC

Frias JP, et al. Diabetes Care 2021;44:765-73
Frias JP, et al. Lancet Diabetes Endocrinol 2021;9:563-74

Disease Background – Type 1 Diabetes

Type 1 diabetes is A Growing Disease Burden in the US and Globally and is Associated with Significant Morbidity



Approximately

1.6 million Americans are living with T1D[1]

187,000 youths / 1.4 million adults

INCIDENCE

Approximately

64,000 people

are diagnosed with T1D each year[2]

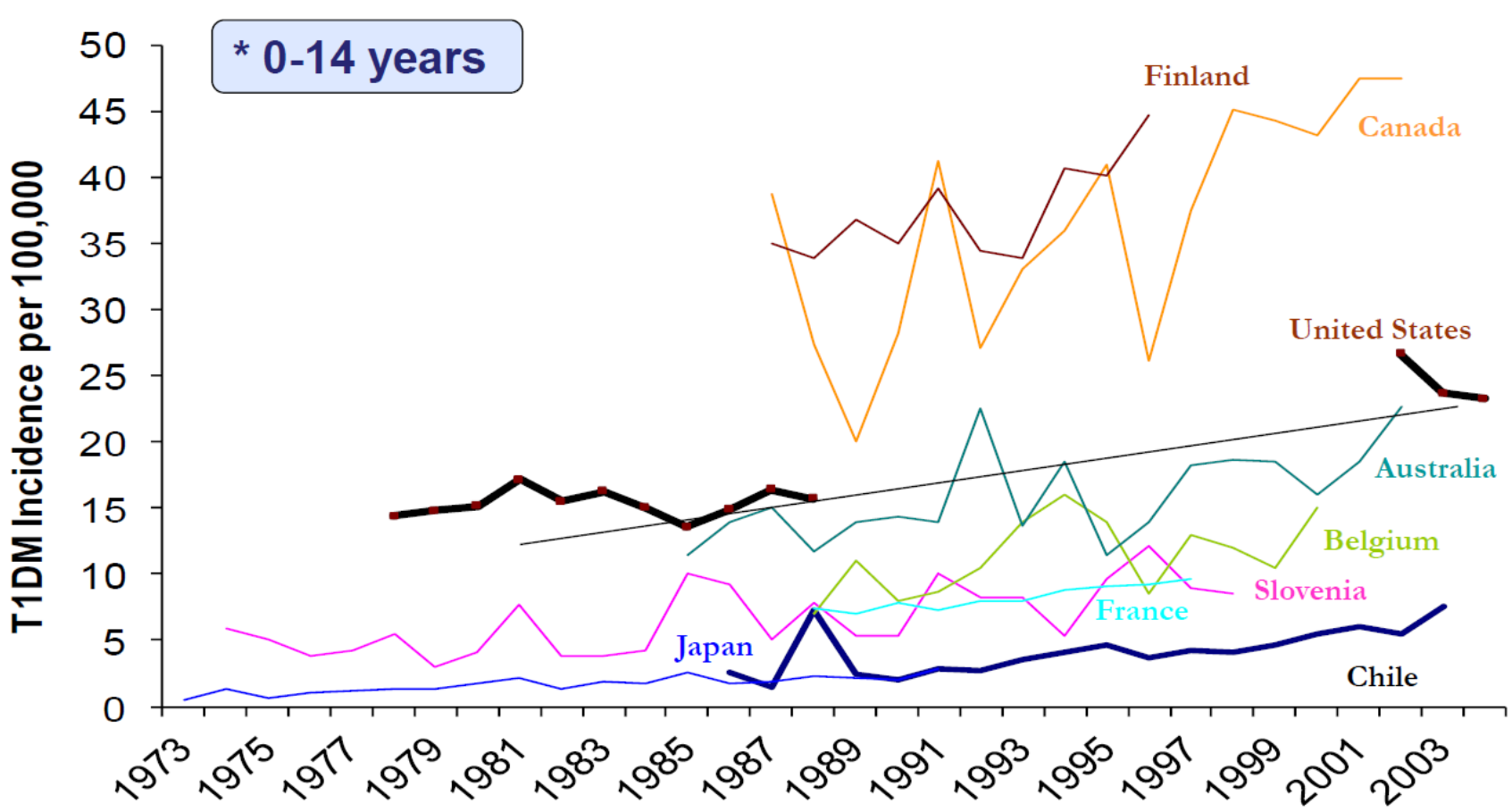
T1D incidence **is increasing[3]**

Overall increase

2% PER YEAR

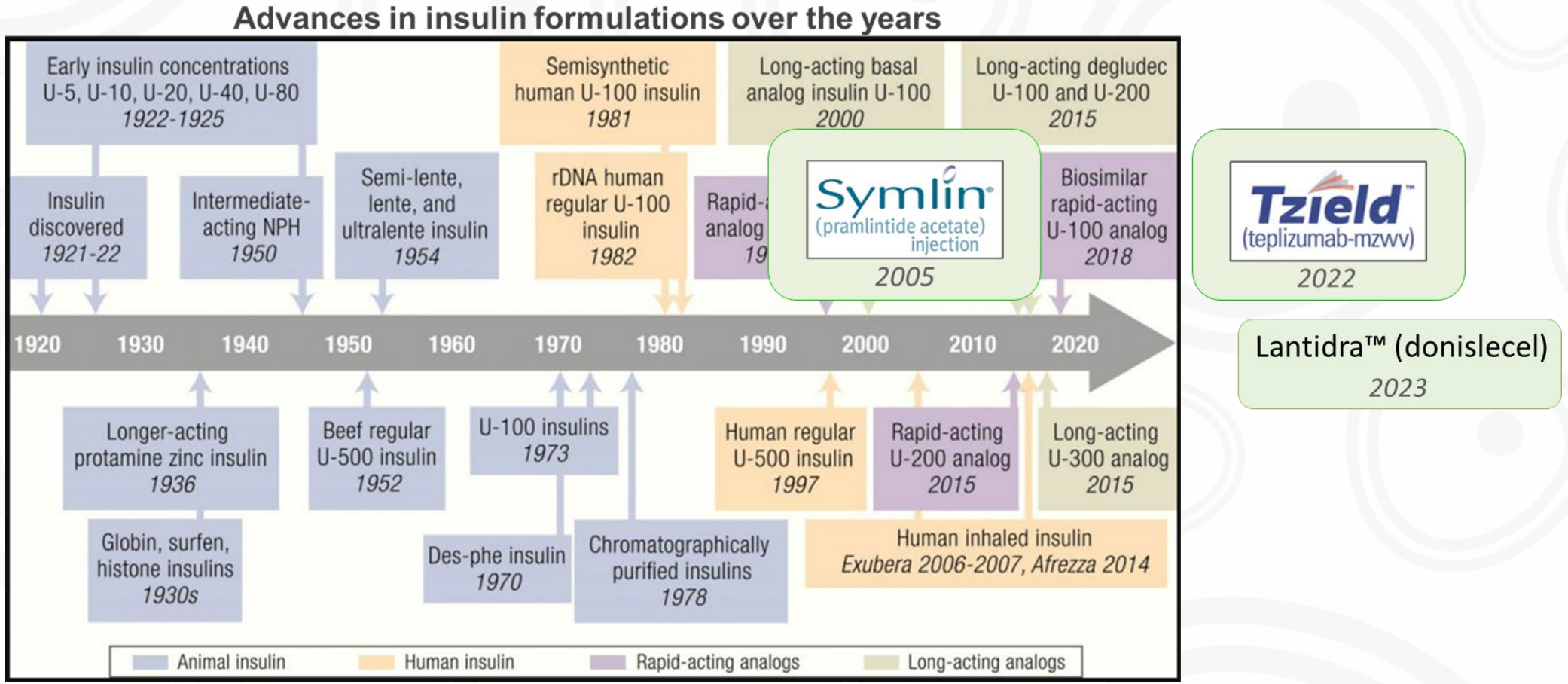
1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020. 2. Rogers MAM, et al. *BMC Med*. 2017;15(1):199. 3. Divers J, et al. *MMWR Morb Mortal Wkly Rep*. 2020;69(6):161-165.

Worldwide Trends in T1D Incidence: Number of New Cases Doubling Every 20 Years

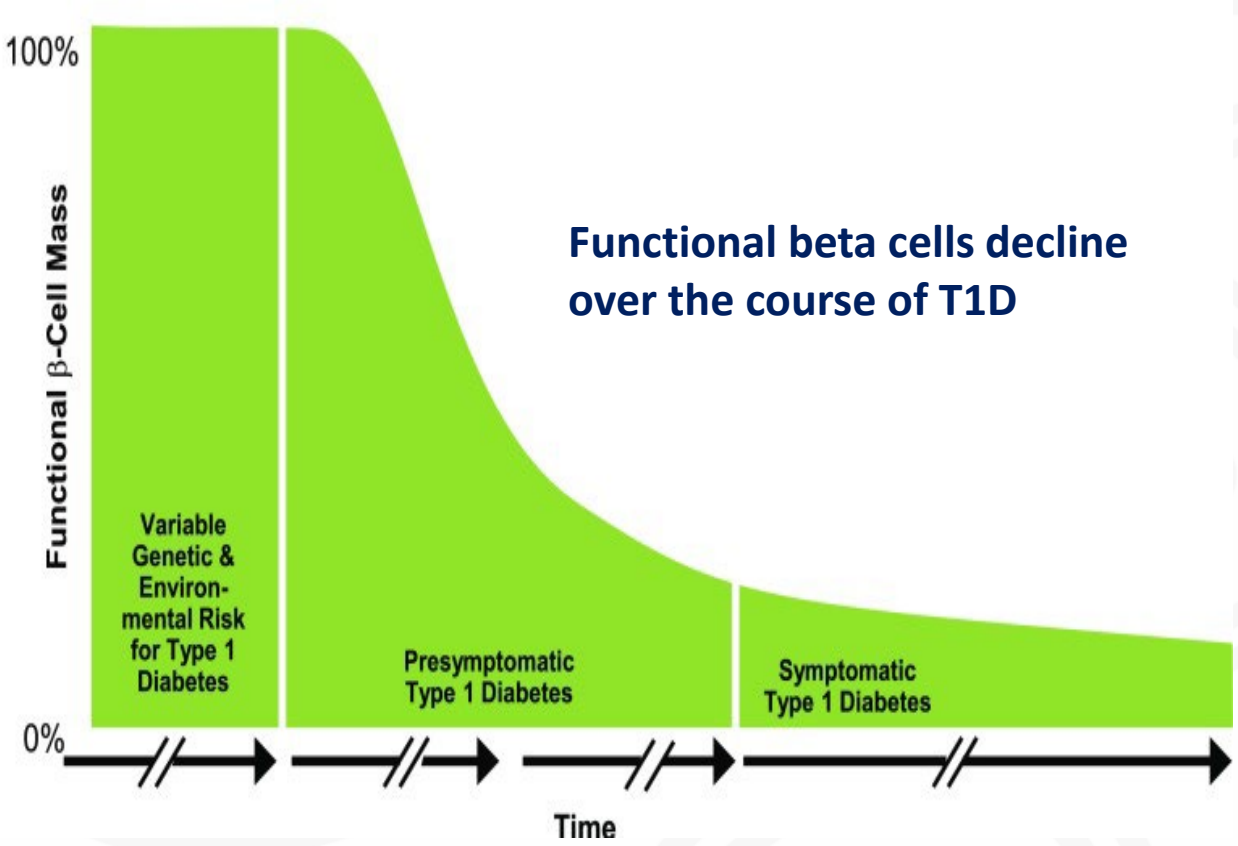


Vehik & Dabelea . DMRR 27: 3-13, 2011

Since the Discovery of Insulin in 1920's, there Have Been Advances in Insulin Formulations, but No Therapies that Directly Affect Beta Cells and Function



Insulin is the Only Approved Therapy for Type 1 Diabetes Patients

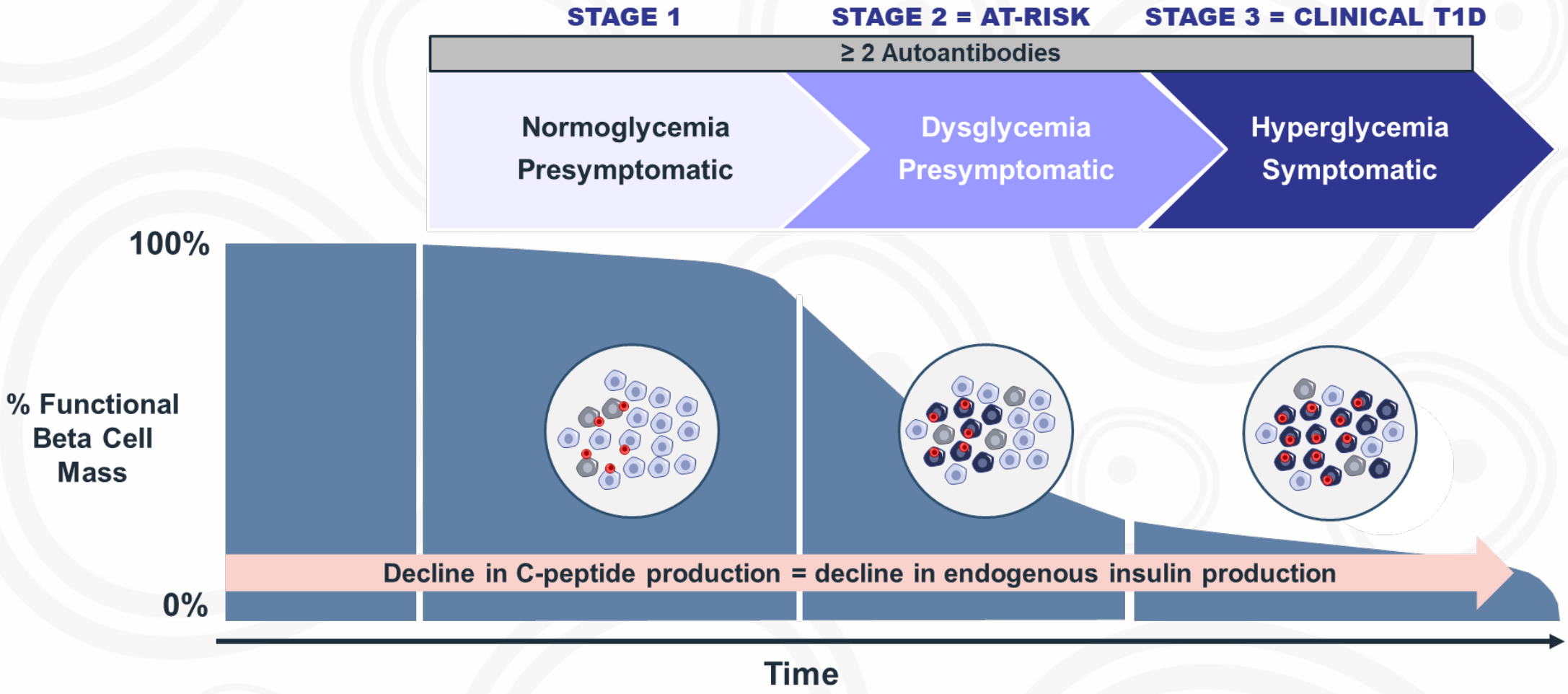


Functional beta cells decline over the course of T1D

- Type 1 diabetes is a chronic autoimmune disease characterized by T-cell mediated destruction of insulin-producing **pancreatic beta cells**.
- The loss of beta-cell function requires exogenous insulin for metabolic control and survival. Insulin is the only approved therapy for T1D patients, with the risk of hypoglycemia, increased morbidity and mortality.
- Teplizumab is the only drug approved to delay the onset of stage 3 T1D.

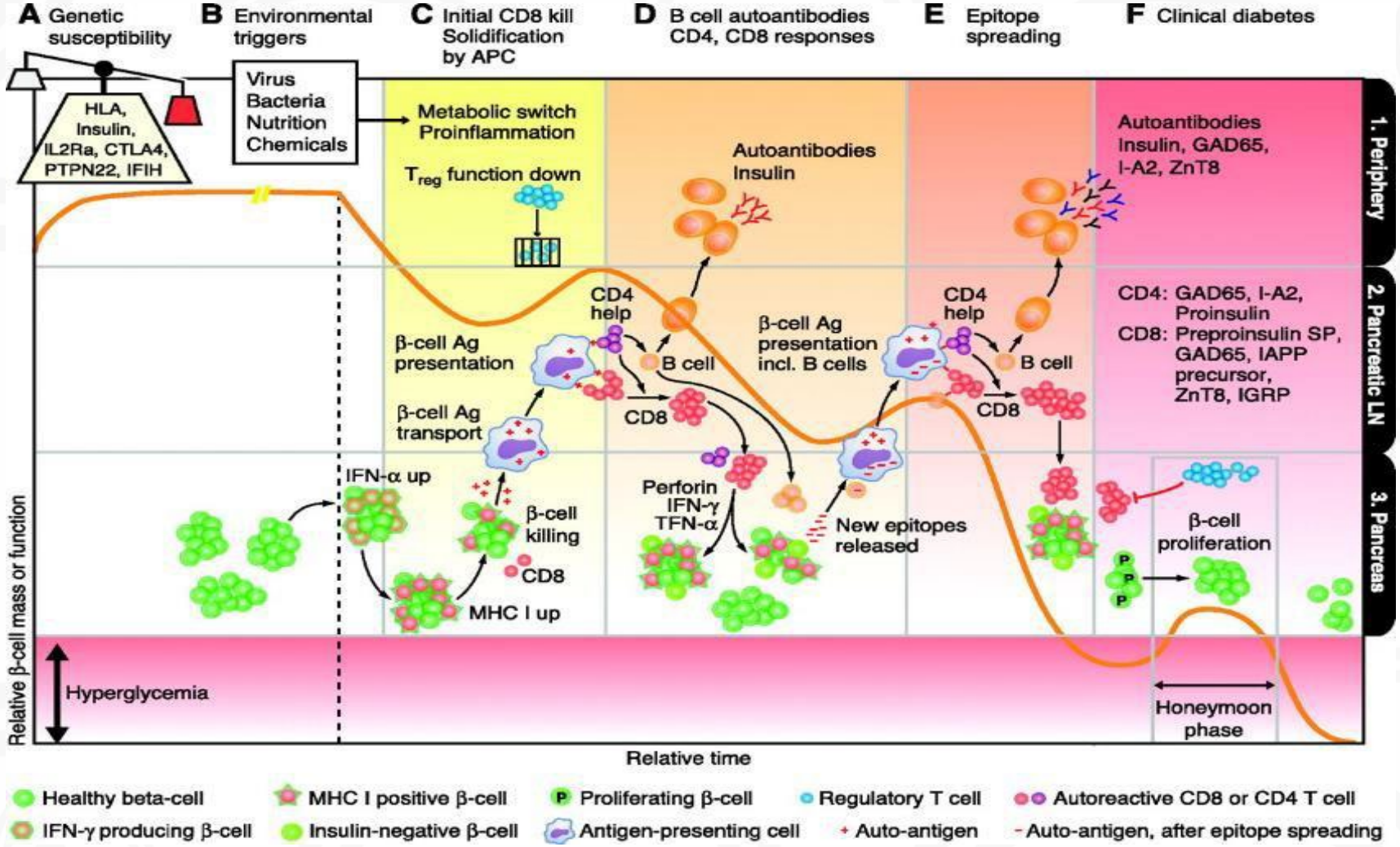
Insel, et al. (JDRF) Diabetes Care. 2015 Oct; 38(10): 1964–1974
Roep, et al. Nature Reviews Endo. 2020 Dec; 17, pages150–161

T1D Clinical Progression Well-Understood Continuum of 3 Predictable Stages



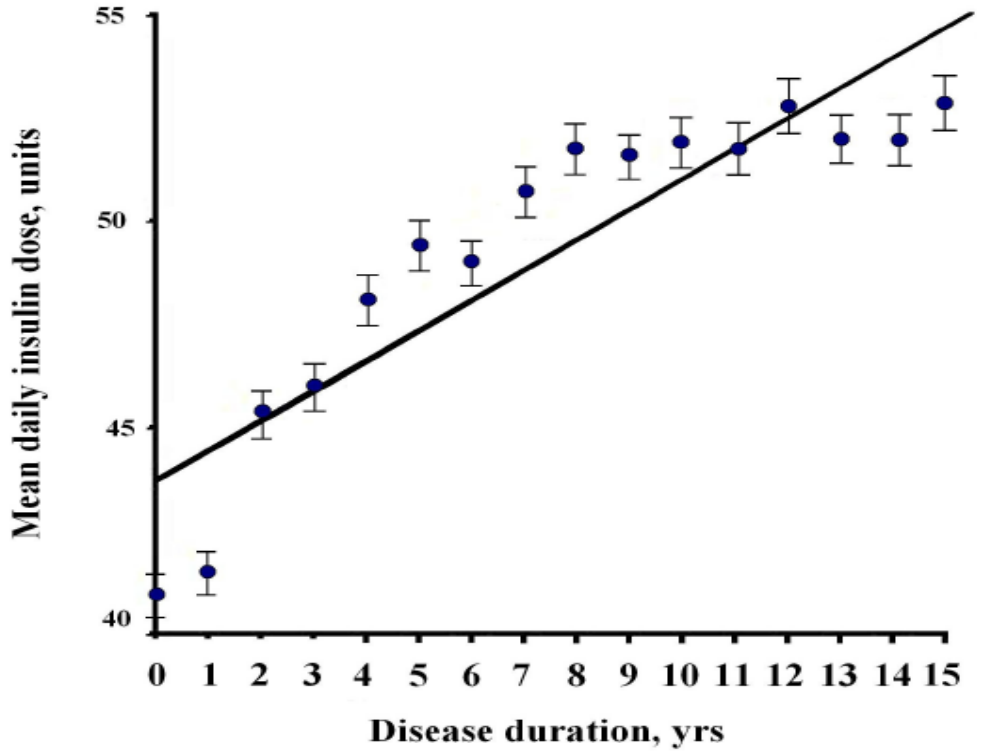
Adapted from Insel RA, et al. Diabetes Care. 2015;38:1964-74.
Teplizumab Endocrinology and Metabolic Drugs FDA Advisory Committee, May 27, 2021. www.fda.gov/media. Accessed February 12, 2023

Progression of Type 1 Diabetes



Dirice E. and Kulkarni R.N., *LandesBioscience*, 2011

Insulin Doses of Type 1 Diabetes Patients Rise with Disease Duration



Based on a meta data analysis of 23,633 T1D patients, the regression analysis indicated that the daily insulin doses of type 1 diabetes patients rises with the progression of the disease, in the range of disease duration of 0-15 years.

Insulin (units/day) = 0.7326 × duration (years) + 43.74 (coefficient of linear correlation, $R = 0.899$, $p < 0.001$).

Khalangot et al., 2009

Some Type 1 Diabetes Patients Show Insulin Production even after 50 Years

ORIGINAL ARTICLE

Residual Insulin Production and Pancreatic β-Cell Turnover After 50 Years of Diabetes: Joslin Medalist Study

Hillary A. Keenan,[1,2] Jennifer K. Sun,[1,3,4] Jared Levine,[1,2] Alessandro Doria,[1,2] Lloyd P. Aiello,[1,3,4] George Eisenbarth,[5] Susan Bonner-Weir,[1,2] and George L. King[1,2]

Keenan HA, et al. Diabetes 2010;59:2846–2853

"Demonstration of persistence and function of insulin-producing pancreatic cells suggests the possibility of a steady state of turnover in which stimuli to enhance endogenous beta-cells could be a viable therapeutic approach in a significant number of patients with type 1 diabetes, even for those with chronic duration."

Increased Beta Cell Proliferation Prevents Progression of Type 1 Diabetes

nature metabolism

LETTERS

https://doi.org/10.1038/s42255-019-0061-8

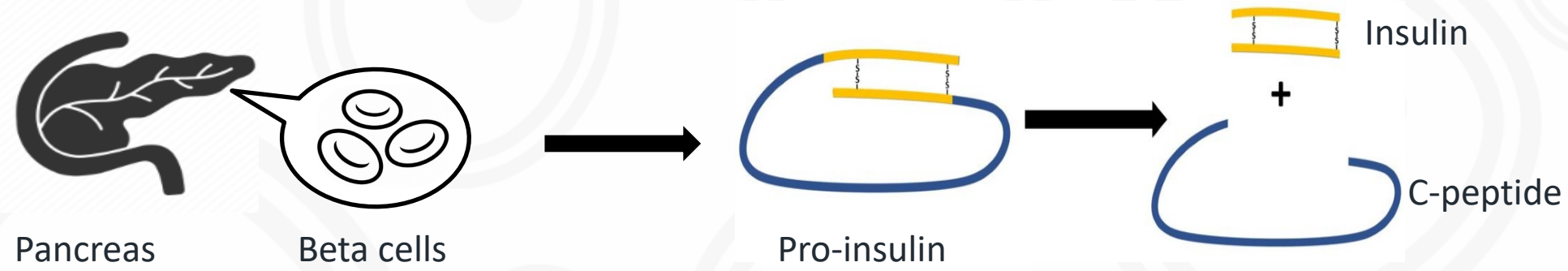
Increased β-cell proliferation before immune cell invasion prevents progression of type 1 diabetes

Ercument Dirice[1,2], Sevim Kahraman[1,2,10], Dario F. De Jesus[1,2,3,10], Abdelfattah El Ouaamari[1,2], Giorgio Basile[1,2], Rocky L. Baker[4], Burcu Yigit[5], Paul D. Piehowski[6], Mi-Jeong Kim[7], Alexander J. Dwyer[8], Raymond W. S. Ng[1,2], Cornelia Schuster[7], Heidrun Vethe[1], Tijana Martinov[8], Yuki Ishikawa[7], Adrian Kee Keong Teo[1,2], Richard D. Smith[6], Jiang Hu[1,2], Kathryn Haskins[4], Thomas Serwold[7], Wei-Jun Qian[6], Brian T. Fife[8], Stephan Kissler[7] and Rohit N. Kulkarni[1,2,9*]

Volume 1 Issue 5, May 2019

Link to Nat Metab: https://www.nature.com/articles/s42255-019-0061-8

C-Peptide is Established as a Quantitative Biomarker of Beta-Cell Function



- C-peptide and insulin are secreted in a 1:1 molar ratio
- C-peptide is a quantitative biomarker of beta-cell function
- C-peptide can be measured in the peripheral blood (most of insulin is cleared by liver)
- C-peptide levels are not affected by insulin that one may take.

Latres et al. JDRF. Diabetes. 2024 Feb;

Improvements in HbA1c are Directly Proportional to the Degree of C-Peptide Preservation

C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis

Peter N Taylor*, Kimberly S Collins*, Anna Lam*, Stephen R Karpen, Brianna Greeno, Frank Walker, Alejandro Lozano, Elnaz Atabakhsh, Simi T Ahmed, Marjana Marinac, Esther Latres, Peter A Senior, Mark Rigby, Peter A Gottlieb, Colin M Dayan on behalf of the Trial Outcome Markers Initiative collaboration†

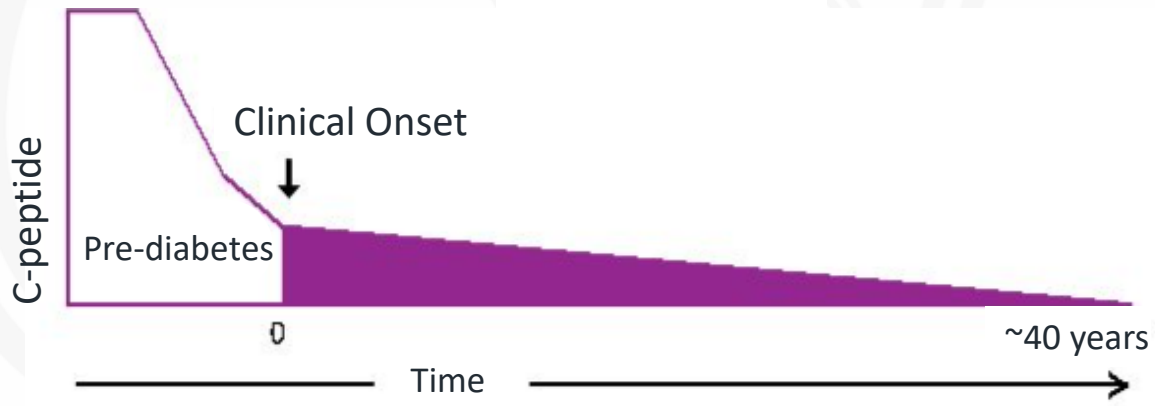
"Interventions that preserve beta-cell function are effective at improving metabolic outcomes in new-onset type 1 diabetes, confirming their potential as adjuncts to insulin."

"We have shown that improvements in HbA_{1c} are directly proportional to the degree of C-peptide preservation, quantifying this relationship, and supporting the use of C-peptide as a surrogate endpoint in clinical trials."

Taylor PN, et al. Lancet Diabetes Endocrinol. 2023;11:915–25

C-Peptide Levels in T1D Patients Gradually Decline over Decades
Slowing the Decline is Directly Associated with Improvements in Clinical Outcomes

C-peptide levels decreased constantly over the course of type 1 diabetes, following initial diagnosis.



Faustman and Davis. Major Topics in Type 1 Diabetes;
Taylor et al. The Lancet. Dec 2023. P915-925;
Oram, et al. Diabetologia. 2014 Oct; 57(1): 187–191


THE LANCET
Diabetes & Endocrinology

ARTICLES | VOLUME 11, ISSUE 12, P915-925, DECEMBER 2023 Download Full Issue

C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis

Peter N Taylor, PhD * • Kimberly S Collins, PhD * • Anna Lam, MD * • Stephen R Karpen, PharmD • Brianna Greeno, PMP • Frank Walker, BSc • et al. Show all authors • Show footnotes

- Persistence of even modest concentrations of C-peptide in T1D are associated with better clinical outcomes including reductions in hypoglycemia, neuropathy, retinopathy and other co-morbidities.
- HbA1c are directly proportional to the degree of C-peptide preservation, supporting the use of C-peptide as a surrogate endpoint in T1D clinical trials.

C-peptide is Considered as an Appropriate Endpoint for T1D Clinical Trials

ADA Workshop Report

C-Peptide Is the Appropriate Outcome Measure for Type 1 Diabetes Clinical Trials to Preserve β-Cell Function

Report of an ADA Workshop, 21–22 October 2001

Jerry P. Palmer,[1,2] G. Alexander Fleming,[3] Carla J. Greenbaum,[4] Kevan C. Herold,[5] Lisa D. Jansa,[3] Hubert Kolb,[6] John M. Lachin,[7] Kenneth S. Polonsky,[8] Paolo Pozzilli,[9] Jay S. Skyler,[10] and Michael W. Steffes[11]

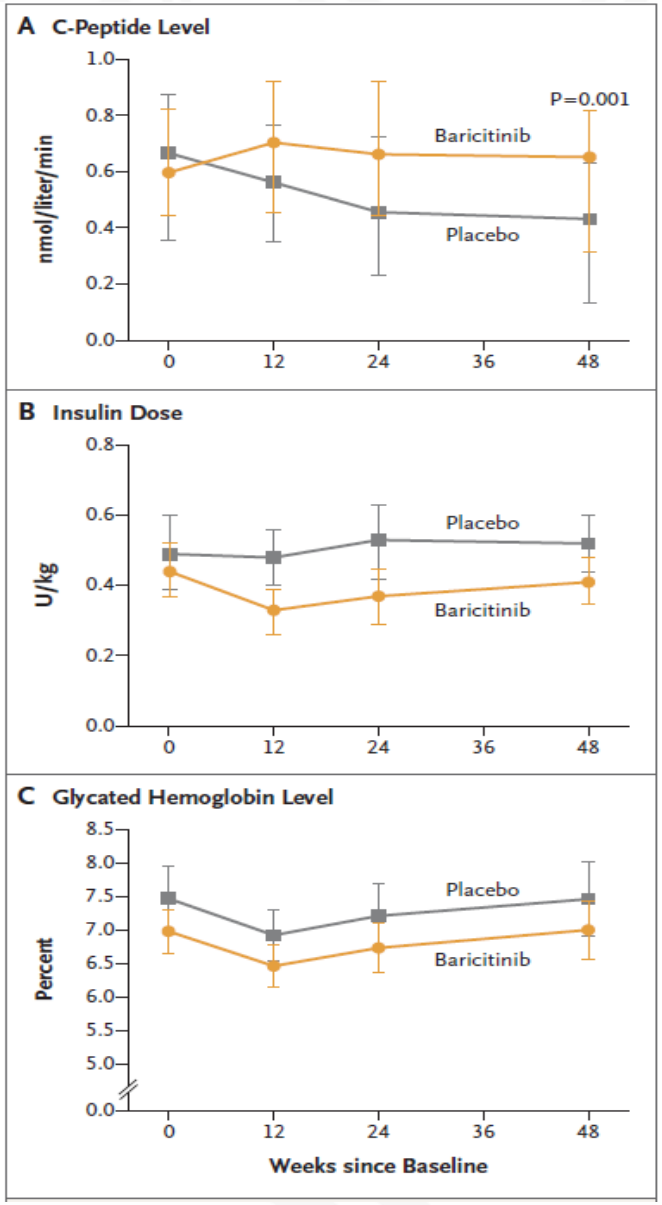
"Measurement of C-peptide under standardized conditions provides a sensitive, well accepted, and clinically validated assessment of β-cell function."

"C-peptide measurement is the most suitable primary outcome for clinical trials of therapies aimed at preserving or improving endogenous insulin secretion in type 1 diabetes patients."

Palmer et al. ADA Workshop Report. Jan 2004

C-Peptide Level was Used as the Primary Outcome for A Phase 2 Type 1 Diabetes Trial Funded by JDRF

BANDIT Trial (A Phase 2 Trial Funded by JDRF)	
Aim of the study	To assess whether the JAK inhibitor baricitinib can slow the progressive, immune-mediated loss of beta cell mass and function that occurs after clinical presentation.
Baseline Characteristics / N	Patients with type 1 diabetes diagnosed during the previous 100 days; N=91
Treatment Period	48 weeks
Primary Outcome (C-peptide level)	At Week 48, median of 2-hr MMTT C-peptide AUC was: • 0.65 nmol/L (~8% improvement compared to baseline 0.65 nmol/L) in barticitinib group • 0.43 nmol/L (~36% decrease) in placebo group
Secondary Outcome (Insulin dose)	At week 48, barticitinib demonstrated a ~5% reduction in mean daily insulin dose
Safety	The frequency and severity of adverse events were similar in the two trial groups, and no serious adverse events were attributed to baricitinib or placebo.

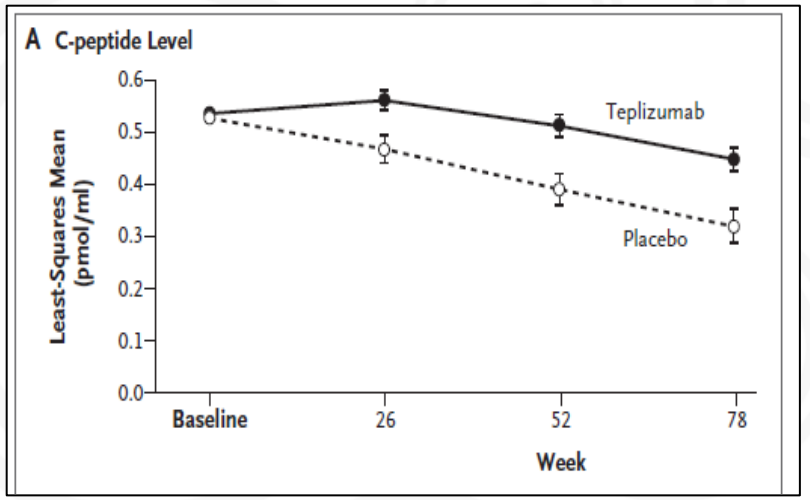


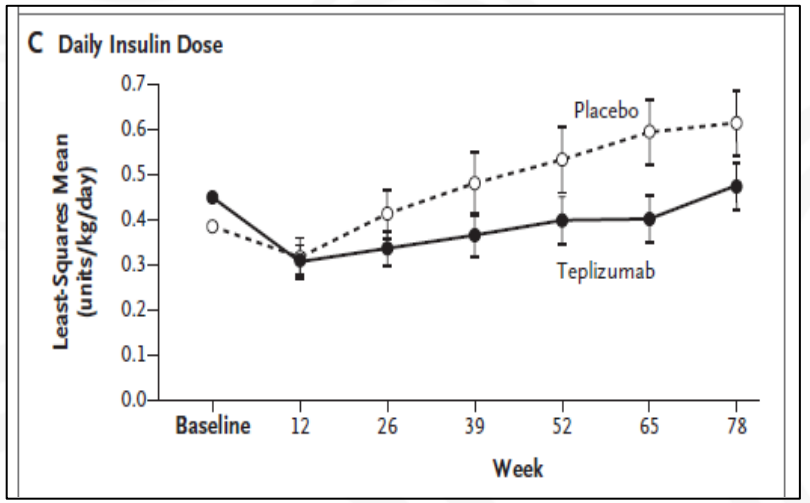
BANDIT Trial: *Waibel et al. NEJM. 2023 Dec; 383;23*

C-Peptide Level is the Primary Outcome for the Ph3 Trial Assessing Teplizumab in T1D

Teplizumab was approved by FDA to delay the onset of clinical type 1 diabetes in patients 8 years of age or older with stage 2 type 1 diabetes

PROTECT Trial (A Ph3 Trial Funded by Provention Bio and Sanofi)	
Aim of the Study	To determine whether teplizumab slows the loss of beta cells and preserves beta cell function in children and adolescent 8-17 years old who have been diagnosed with T1D in the previous 6 weeks
N	N=328 (N = 76 in Phase 2, followed by FDA approval)
Treatment Period	78 weeks
Primary Outcome (C-peptide level)	At Week 78, median of 4-hr MMTT C-peptide AUC was: • 0.46 nmol/L (~15% decrease compared to baseline 0.54 nmol/L) in teplizumab group • 0.34 nmol/L (~36% decrease) in placebo group
Secondary Outcome (Insulin dose)	• No significant differences were not shown between teplizumab vs. placebo arms
Safety	Adverse events occurred primarily in association with administration of teplizumab or placebo and included headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome





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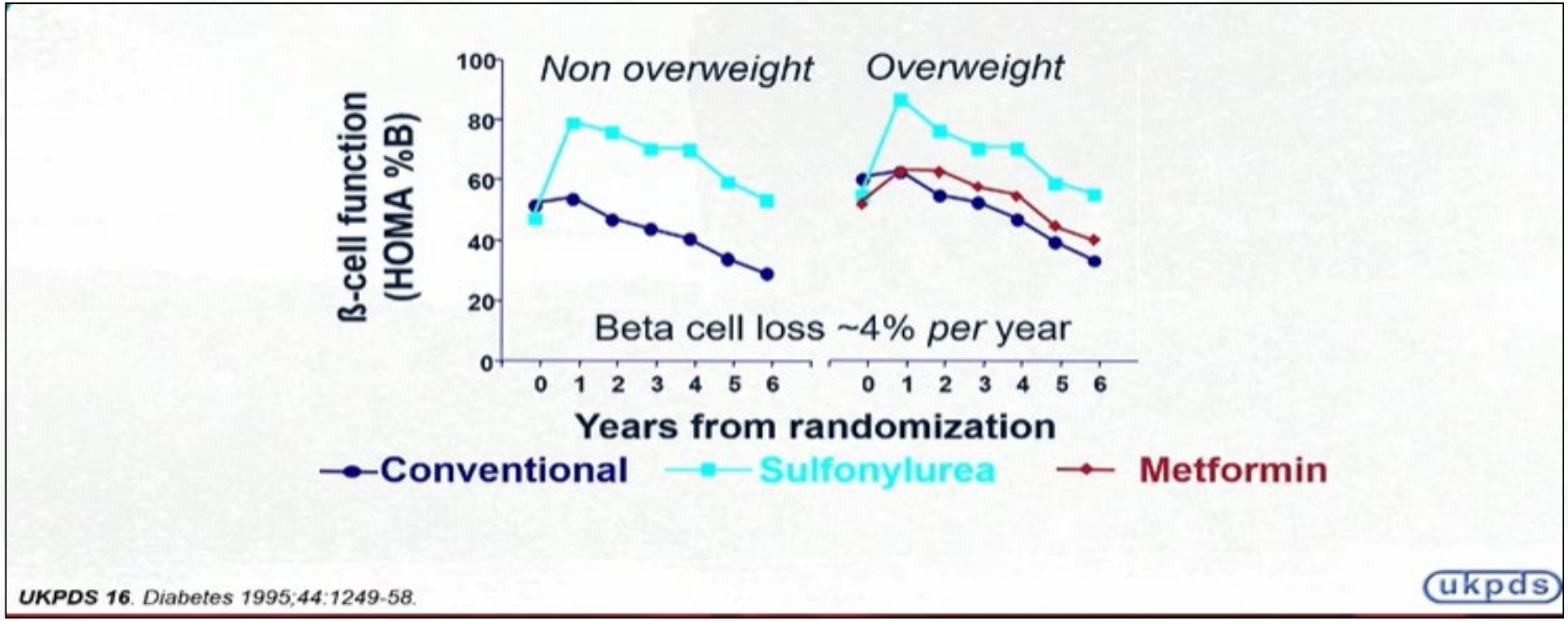
PROTECT Trial: *Ramos et al. NEJM. 2023 Dec; 389;23*

Diabetes
– Root Cause Analysis

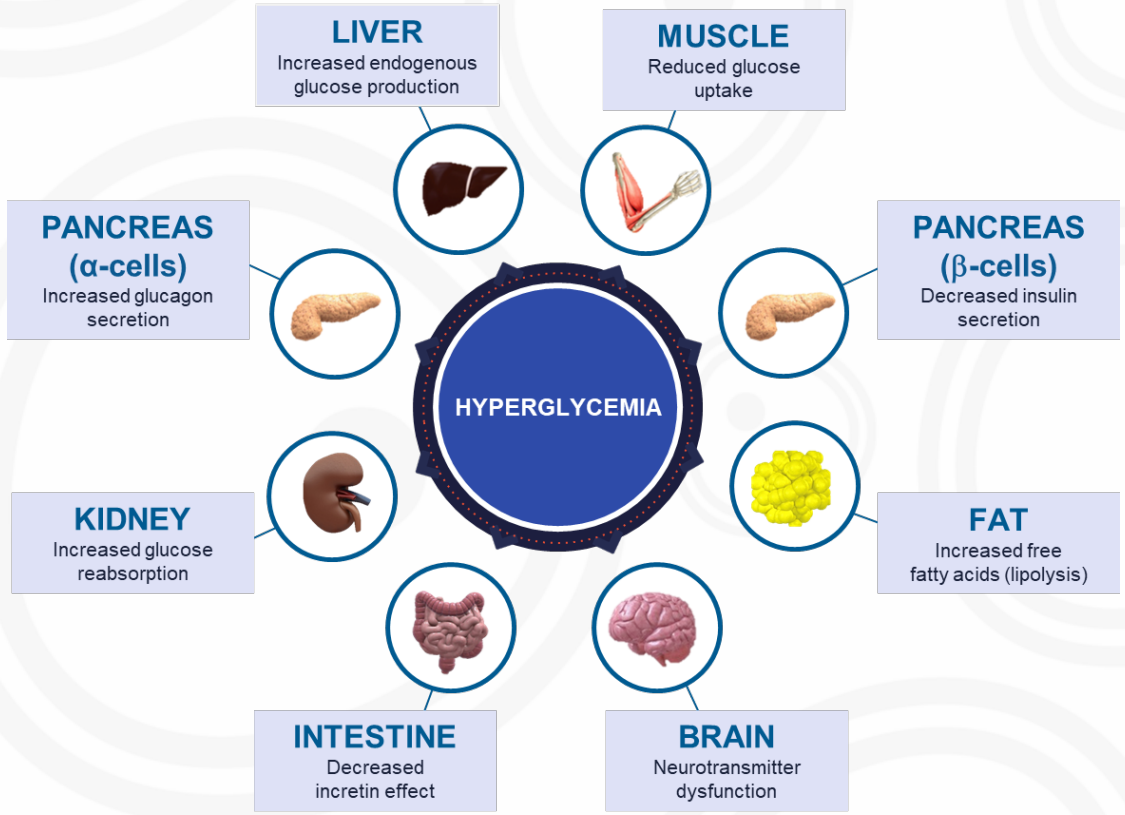
Progressive Hyperglycemia Driven by Declining Beta-Cell Function

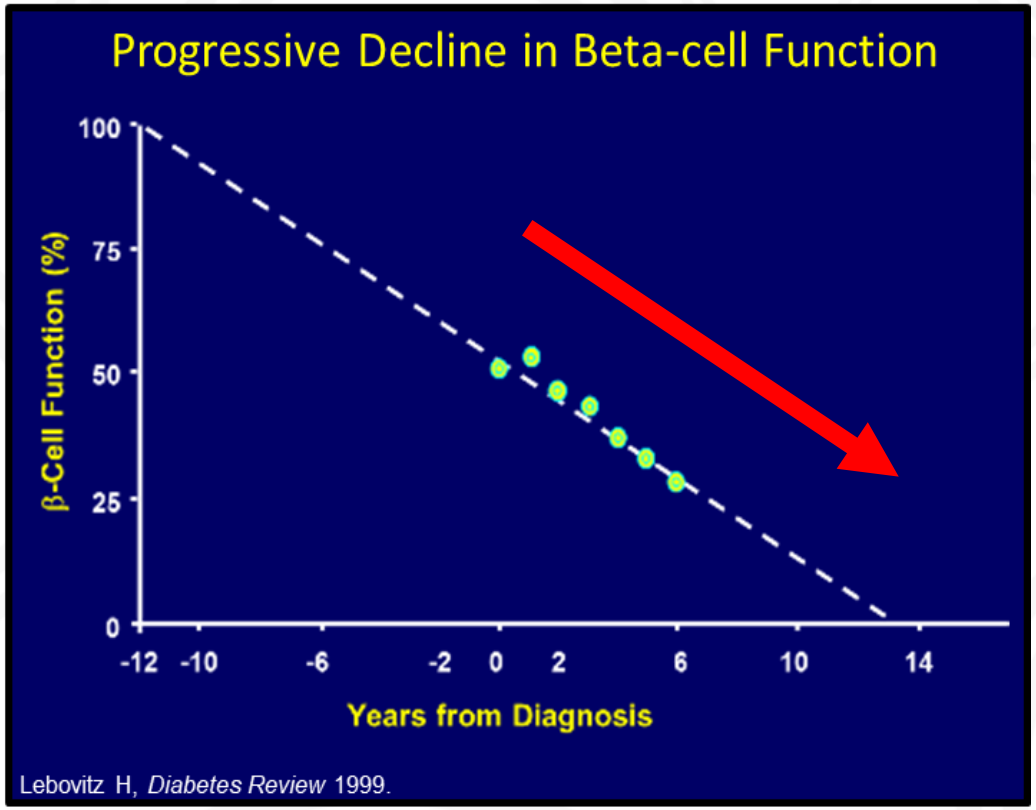


The study has shown that progressively increasing hyperglycemia was associated with **decreasing beta-cell function**, a marked feature irrespective of the therapy used. No deterioration in insulin sensitivity was observed.

None of Today's Type 2 Diabetes Agents Address the Root Cause of Diabetes

– The progressive decline in beta-cell mass and function





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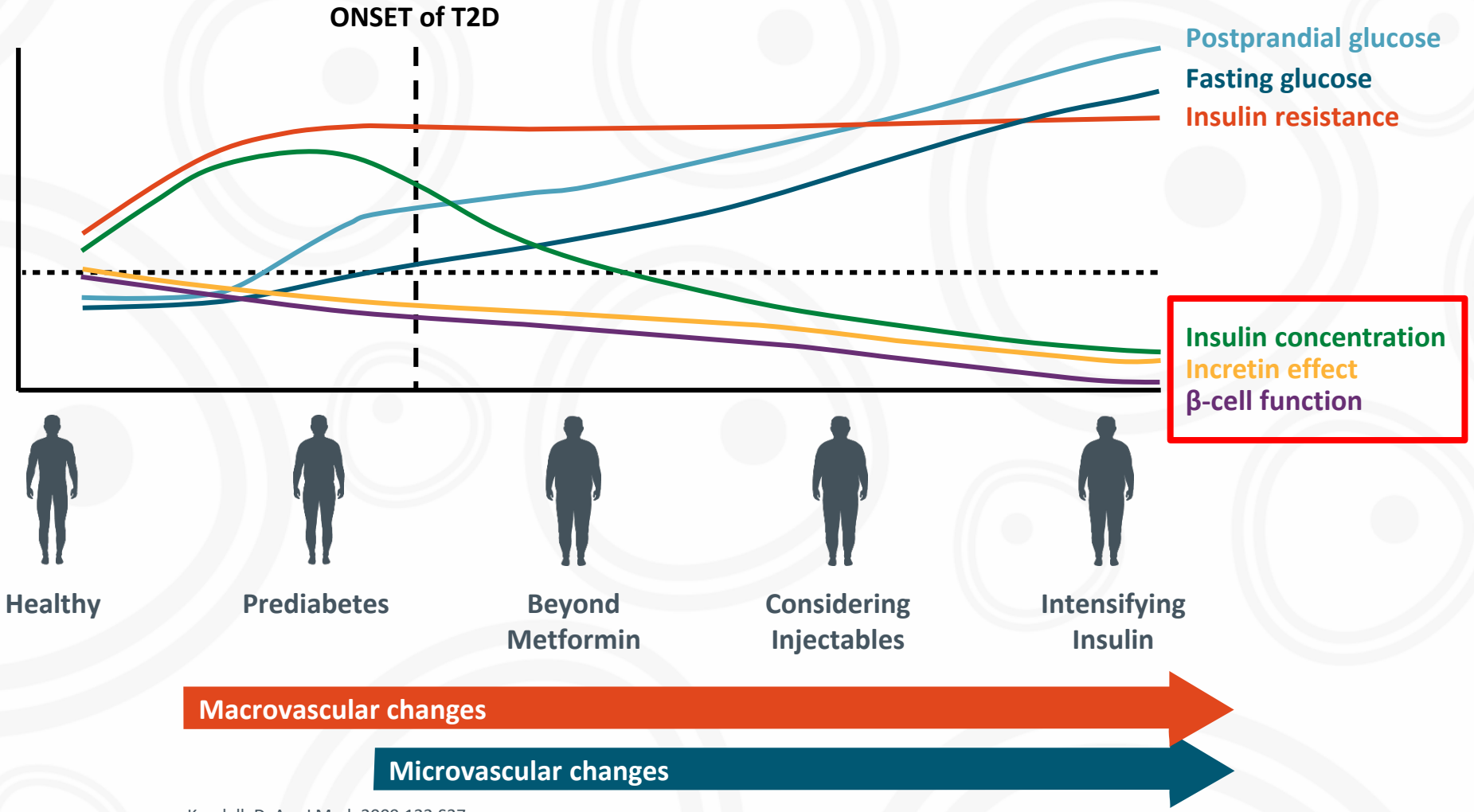
Adapted from DeFronzo RA. *Diabetes.* 2009;58(4):773-795.

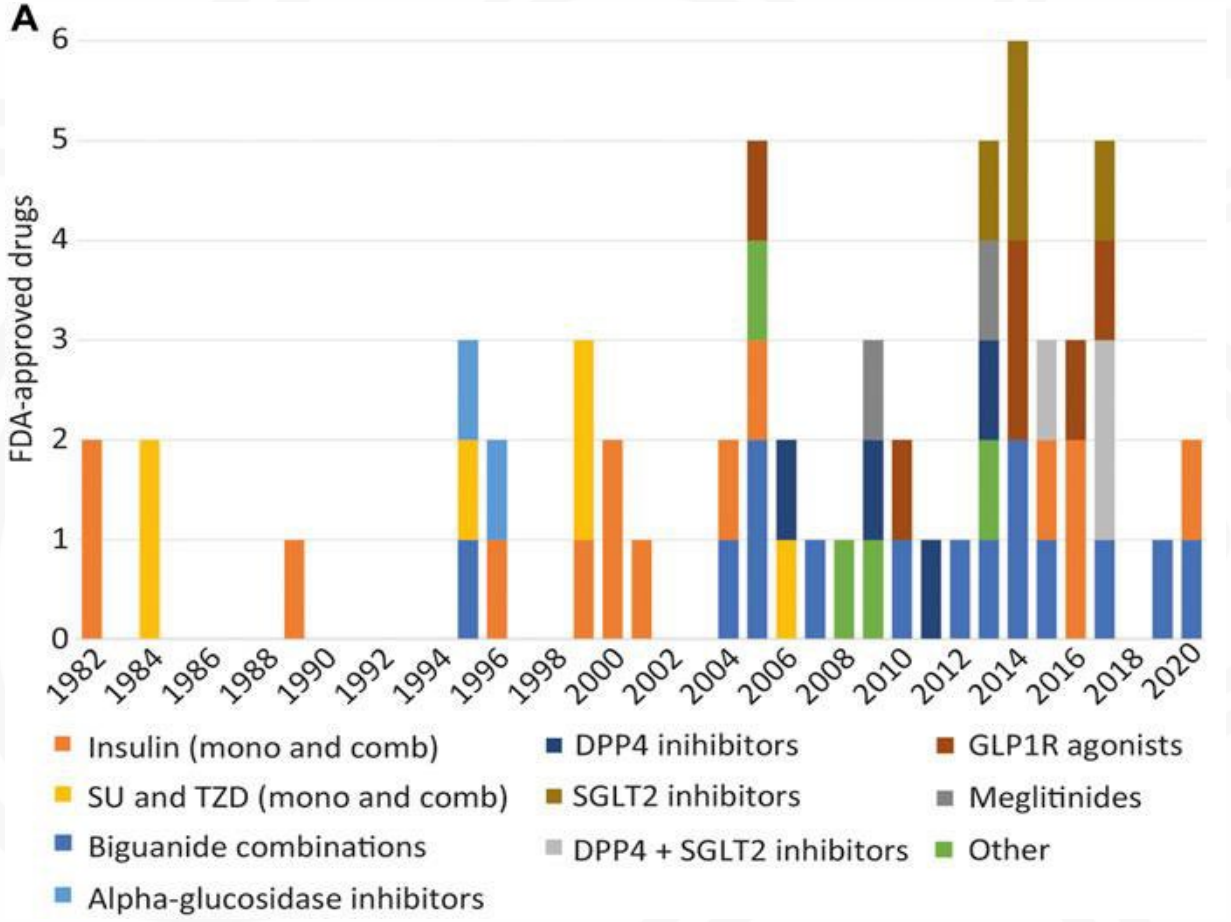
Natural History of Types 2 Diabetes – A Progressive Decline in Beta Cell Function

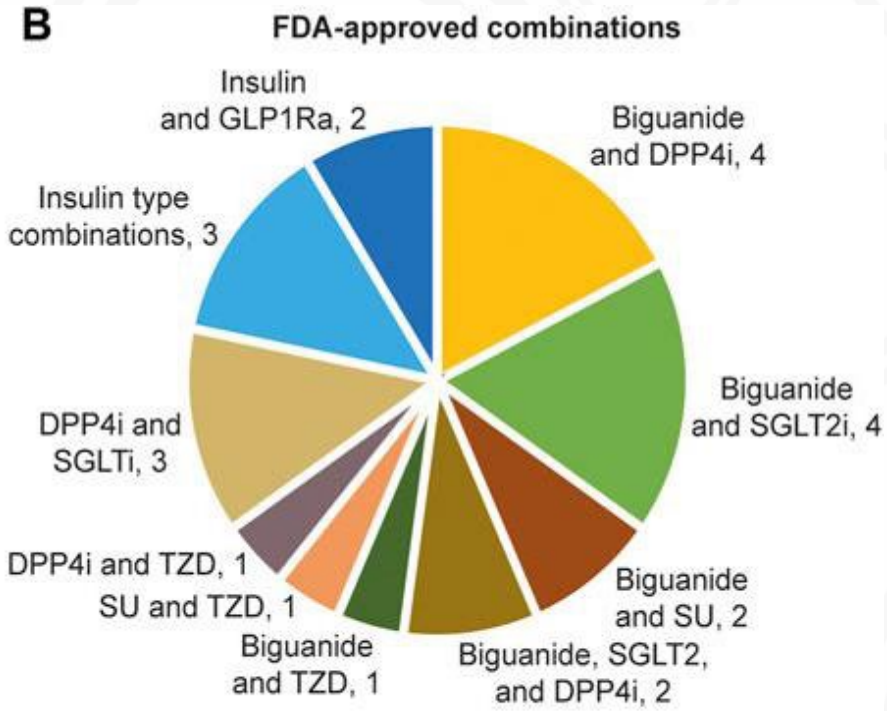


Kendall, D. Am J Med. 2009;122:S37.

Type 2 Diabetes
- Standard of Care Agents

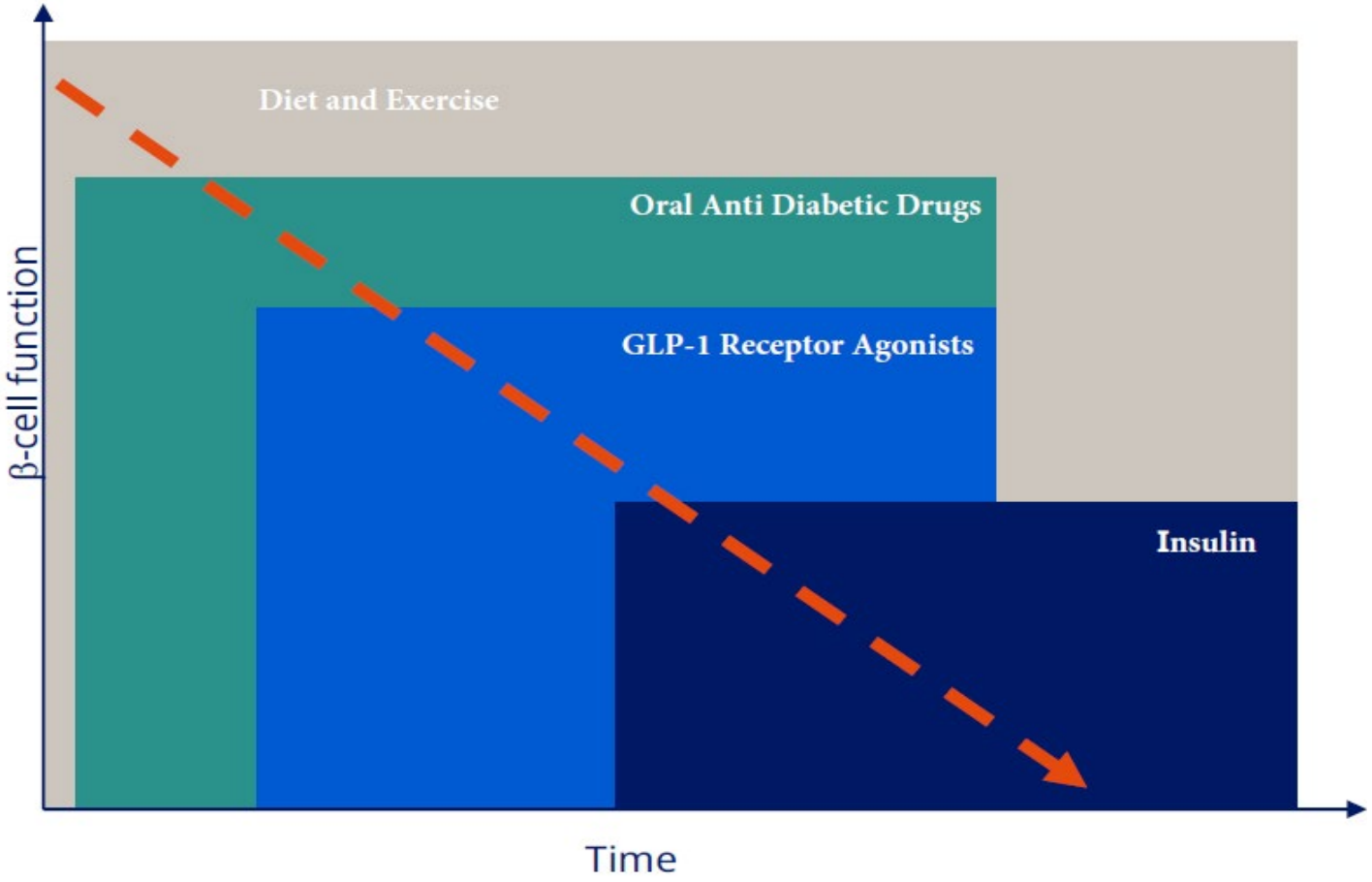
There Are over 60* Approved Single and Combination Agents for Diabetes





Dahlen et al., 2022 * Including the 2022 approval of tirzepatide, a dual GLP1/GIP agonist

Typical Treatment Sequence in Type 2 Diabetes

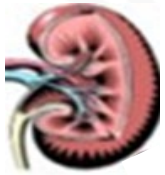


- Initiation typically is with an oral anti-diabetic drugs, like Metformin
- Added/followed by DPP-4 Inhibitors, SGLT2 Inhibitors and Oral GLP-1 receptor agonists
- Added/followed by injectable GLP-1 receptor agonists
- Once all drugs and drug combinations are no longer supporting the patient then injection of pure insulin is the only available treatment
  ~30% of T2D patients take insulin
  - 14.7% take both insulin and oral medication
  - 14% take insulin only

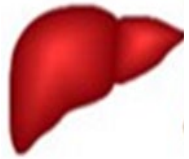
IQVIA disease analyser Nov 2022; *UCSF FAQ*; *Diabetes.org Fast Facts*

Major Treatment Classes for Type 2 Diabetes *as of 2022*

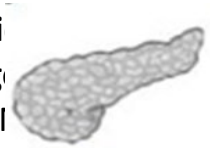
Traditional Oral Agents e.g. Metformin
GLUCOSE UPTAKE / OUTPUT LOWERING
40% of Patients / 3% Market Share
Traditional Agents stimulate the pancreas to produce more insulin and lower the amount of glucose being produced by the liver. They also make the body more sensitive to insulin.



Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors
GLUCOSE REABSORBTION
(oral) 20% Market Share
SGLT-2 Inhibitors lower blood sugar by causing the kidneys to remove glucose from the body through urine.



Dipeptidyl peptidase-4 (DPP-4) Inhibitors
INSULIN SECRETION IMPROVEMENT
(oral) 13% Market Shares
DPP-4 inhibitors work by blocking the enzyme DPP-4, which destroys hormones, called incretins that help the body produce more insulin when needed.



Glucagon-like pepti
(GLP-1) receptor ag
INSULIN STIUMULAI
(injectable) 31% Market Share
GLP-1 is an incretin hormone that stimulates the body to produce more insulin. People with type 2 diabetes have lower levels of incretin hormones, which leads to high blood sugar.

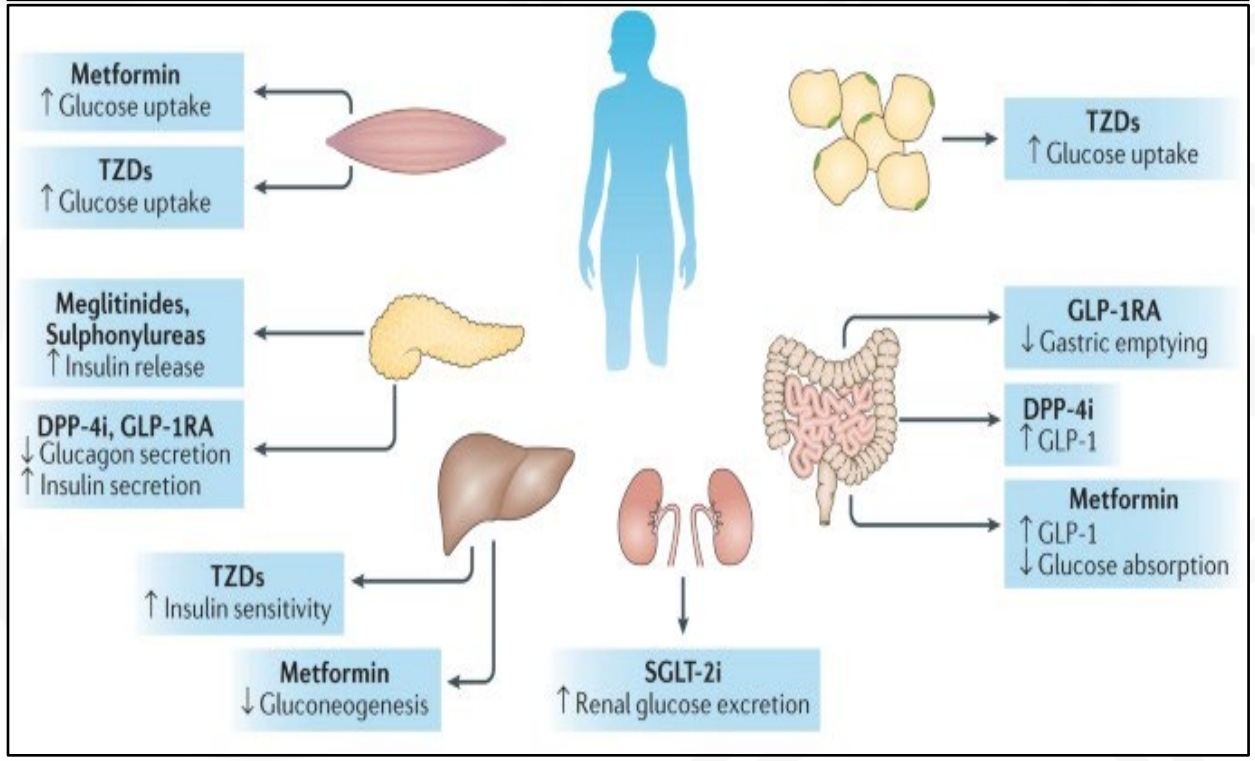
INSULIN SUPPLEMENTATION
(injectable) 30% Market share
Direct injection of Insulin once all agents have failed controlling blood glucose levels.

Feb 2023	Scripts Share	Sales Share
Metformin	33%	0.8%
Other Oral Antidiabetics	14%	0.5%
DPP4	5%	**9.0%**
SGLT2	11%	**19.8%**
GLP-1	18%	**45.3%**
Short / Long Acting Insulin	19%	**24.8%**
Total	100%	100%

IQVIA disease analyser Nov 2022

BMF-219 is a Potential First-in-Class Diabetic Agent to Address Insulin/Beta-Cell Function Deficiency by Regenerating the Pool of Beta Cells

Currently approved therapies are primarily targeting the **Symptoms of Type 2 Diabetes: Hyperglycemia**



Nat Rev Endocrinol 12, 337–346 (2016). https://doi.org/10.1038/nrendo.2016.51

Currently Approved Agents - Chronic Treatments		
Drug MoA	Avg Duration of Glycemic Control	Global Share by Volume in 2022
DPP4	23 months	5%
SGLT2	18 months	15%
GLP1	29 months	14%
MET	45 months	21%
Insulin	-	43%

NIH.gov; *Nathan et al., NEJM 2022*; *Khan et al., NEJM 2006*;
Thewjitcharoen et al. Diabetol Metab Syndr. 2017; 9: 96.
Top 15 Diabetes Drugs in 2023 by 2022 Sales Statistics

Most Prescribed Type 2 Diabetes Agents Achieve

HbA1c Reductions of 0.7% - 1.7% and HbA1c Levels < 7 % in 0.35% - 82%

Currently Approved Type 2 Diabetes Agents w/Chronic Dosing				
Drug (Mechanism of Action)	**Medication Route**	**Week**	**Mean HbA1c Reduction (placebo adj., %)**	**Patients (%) achieving HbA1c <7%**
Ozempic (GLP 1 Agonist), Chronic Dosing	Injectable	Week 30	-1.2 (0.5mg), -1.4 (1mg)	73% (0.5mg), 70% (1mg),
Mounjaro (GLP-1/GIP Agonist), Chronic Dosing	Injectable	Week 40	-1.7 (5mg), -1.6 (15mg)	82% (5mg), 78% (15mg)
Jardiance (SGLT2 Inhibitor), Chronic Dosing	Oral	Week 24	-0.7 (10mg), -0.9 (25mg)	35% (10mg), 44% (25mg)
Januvia (DPP4 Inhibitor), Chronic Dosing	Oral	Week 24	-0.8 (100mg)	41% (100mg)
Summary	-	-	**0.7% ~ 1.7%**	**35% - 82%**

Mounjaro FDA Label; Ozempic FDA Label; Jardiance FDA Label;

Oral Agents – Efficacy Benchmarks for Chronic Treatments

HbA1c Reduction by 0.5% - 1.67% at Week 26

Drug	Development Status	MOA	Mean Reduction HbA1c (Wk 26, pbo adj.)
Rybelsus (Oral Semaglutide)	Approved	GLP-1	0.9% (7mg); 1.1% (14mg)
Structure Therapeutics	Clinical Development	GLP-1	1.02% (Wk 12)
Orforglipron	Clinical Development	GLP-1	1.67%
Jardiance (Empagliflozin)	Approved	SGLT-2	0.7% (10mg); 0.9% (25mg)
Farxiga (Dapaglifozin)	Approved	SGLT-2	0.5% (5mg); 0.7% (10mg)
Invokana (Canagliflozin)	Approved	SGLT-2	0.91% (100mg); 1.16% (300mg)
MET	Approved	MET	1.0%

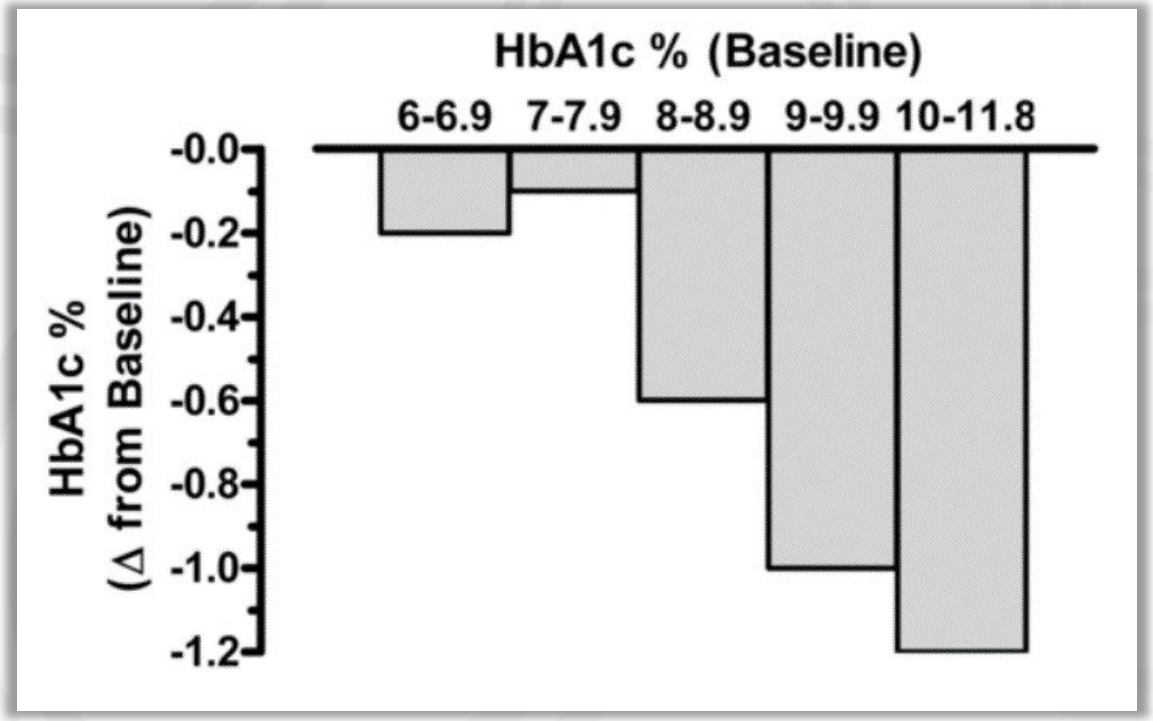
Rybelsus FDA label; Structure Therapeutics Provides Comprehensive GSBR-1290 Program Update Including Clinically Meaningful Proof-of-Concept Data From Phase 2a Clinical Study; Frias et al. 2023 Aug 5;402(10400):472-483 ; Jardiance FDA label; Farxiga FDA label; Invokana FDA label; MET FDA label;

Type 2 Diabetes
– Diabetes Agents Efficacy Analysis

Comparing Type 2 Diabetes Agents and Treatments

- Is the treatment a single agent or a combination of multiple therapies?
- Is it an oral or injected treatment? Is it a chronic therapy or a short term, one-time, curing solution?
- What types of patients are enrolled in the study e.g. 10 years type 2 diabetic, failing or newly diagnosed?
- What is the average A1c level of the patients at the beginning of the trial, e.g. 7.5 or 10?
  The higher the number when the trial started, the greater the expected effect
- When was A1c measured for the first time after therapy, e.g. at 28 days, 90 days, or at max time of effect?
  A1c requires a minimum of 90 days look back to provide a complete view of the effect size
- How many patients achieved a benefit from therapy, i.e. normalization of A1c below 7%?
  A1c below 7% is considered no longer diabetic, a key benchmark for all diabetes therapies
- How many patients discontinued the treatment?
- How many patients had treatment related adverse events?
- Is the diabetes treatment chronic or just for a fixed, short period of time?
  All approved treatments today are chronic treatments

Baseline HbA1c Influences Magnitude of Efficacy

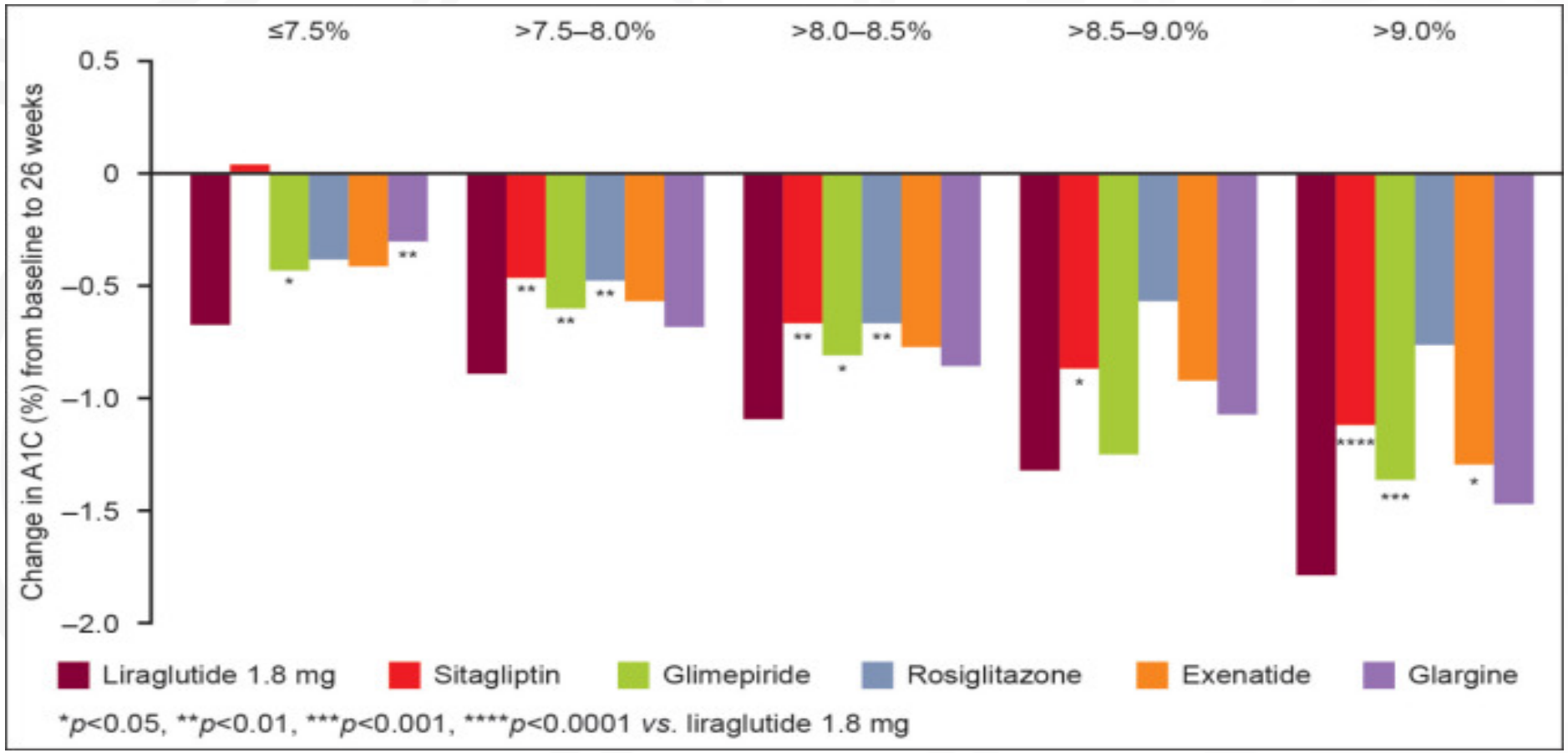


Baseline A1C (%)	n enrolled in clinical trials	Change in A1C (%)	Change in FPG (mmol/l)
6.0–6.9	410	-0.2%	-0.5
7.0–7.9	1,620	-0.1%	-0.8
8.0–8.9	5,269	-0.6%	-1.6
9.0–0.9.9	1,228	-1.0%	-2.3
10.0–11.8	266	-1.2%	-3.4

meglitinides, metformin, thiazolidinediones, α-glucosidase inhibitors). The baseline glycemic control markedly influenced the overall magnitude of efficacy irrespective of drug class. After >90 days.

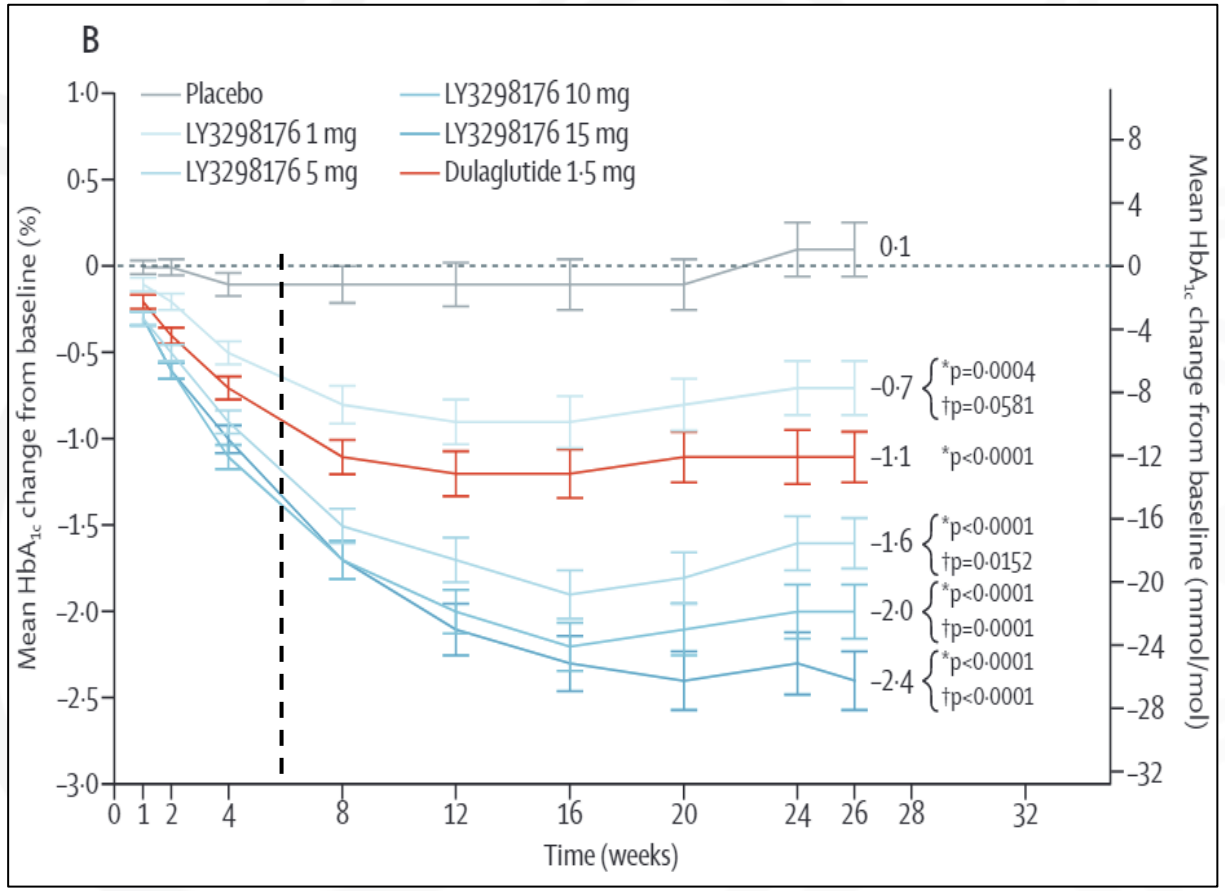
Feingold 2022; Bloomgarden et al., 2006

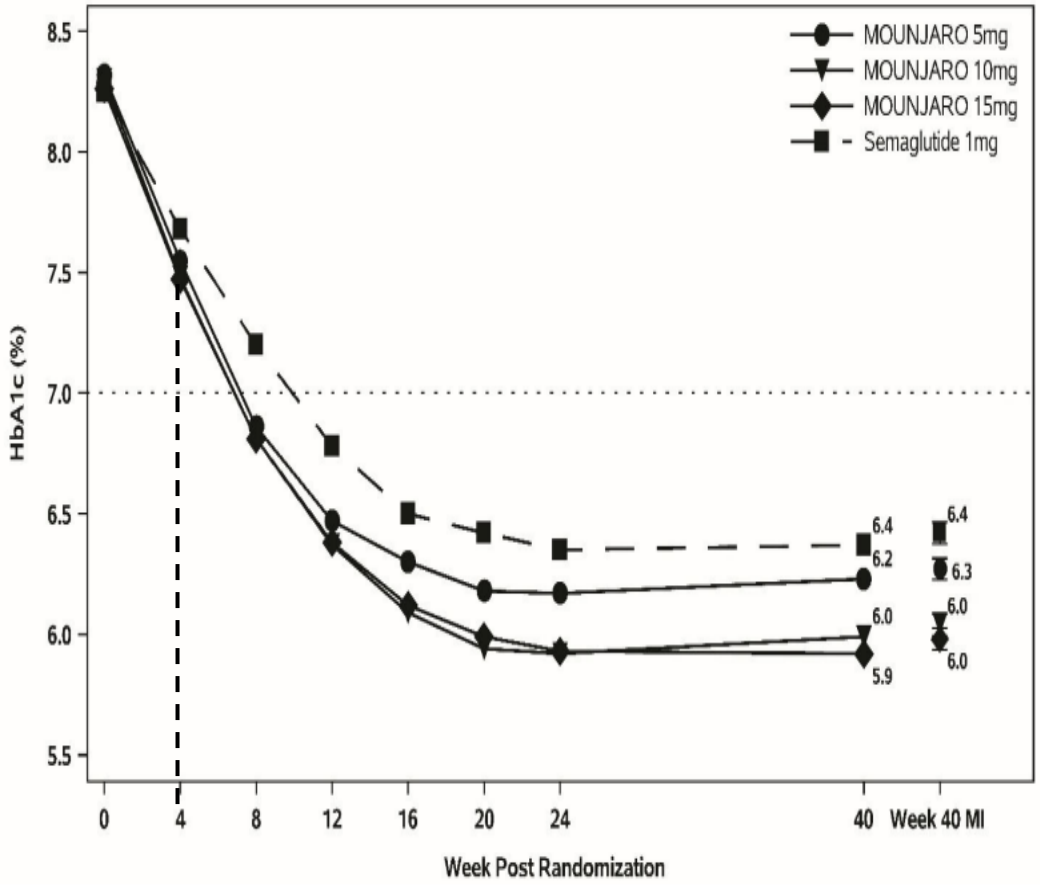
Baseline HbA1c Influences Magnitude of Efficacy for Injectable GLP-1s



Henry er al. 2011

T2D Medications Show Dose and Time Dependent Responses e.g. Tirzepatide

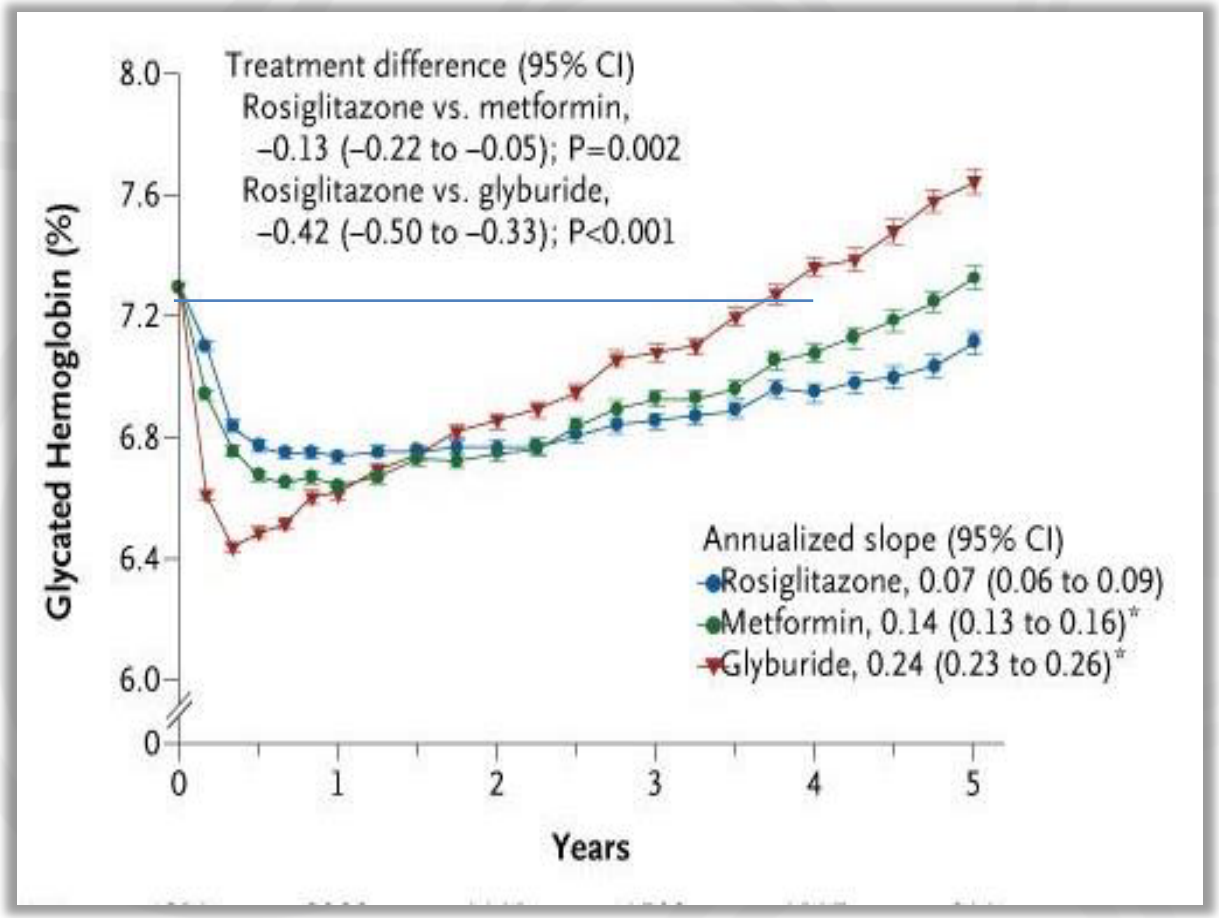




Frias et al 2018 NCT03131687

Majority of Patients Lose Glucose Control Within 4 Years of First Line Single Agent Therapy

published in NEJM 2006



Khan et al., NEJM 2006

	Time to Max HbA1c Effect	Duration of Glucose Control (A1c <7%)	Glucose control (A1c <7%) at 4 years
TZD (Rosiglitazone)	12 months	57 months	40%
Metformin	12 months	45 months	36%
2nd Generation SU (Glyburide)	4 months	33 months	26%

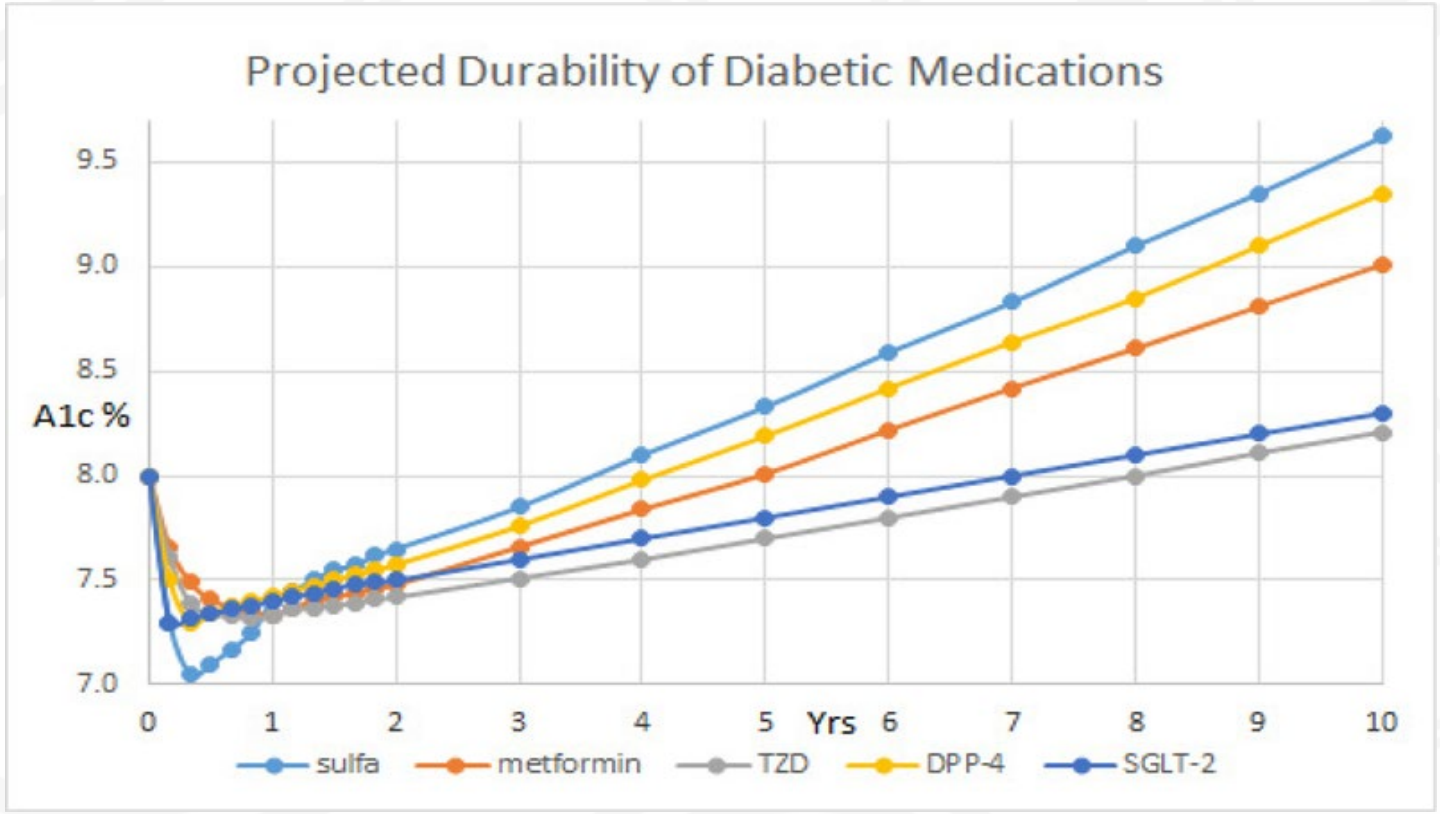
"Loss of control of blood glucose **— The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time**. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy

RIOMET IR 2003 FDA Approval;
GLUMETZA 2005 FDA Approval

;

Durability and Effect Size of Oral Diabetic Medications is very Limited

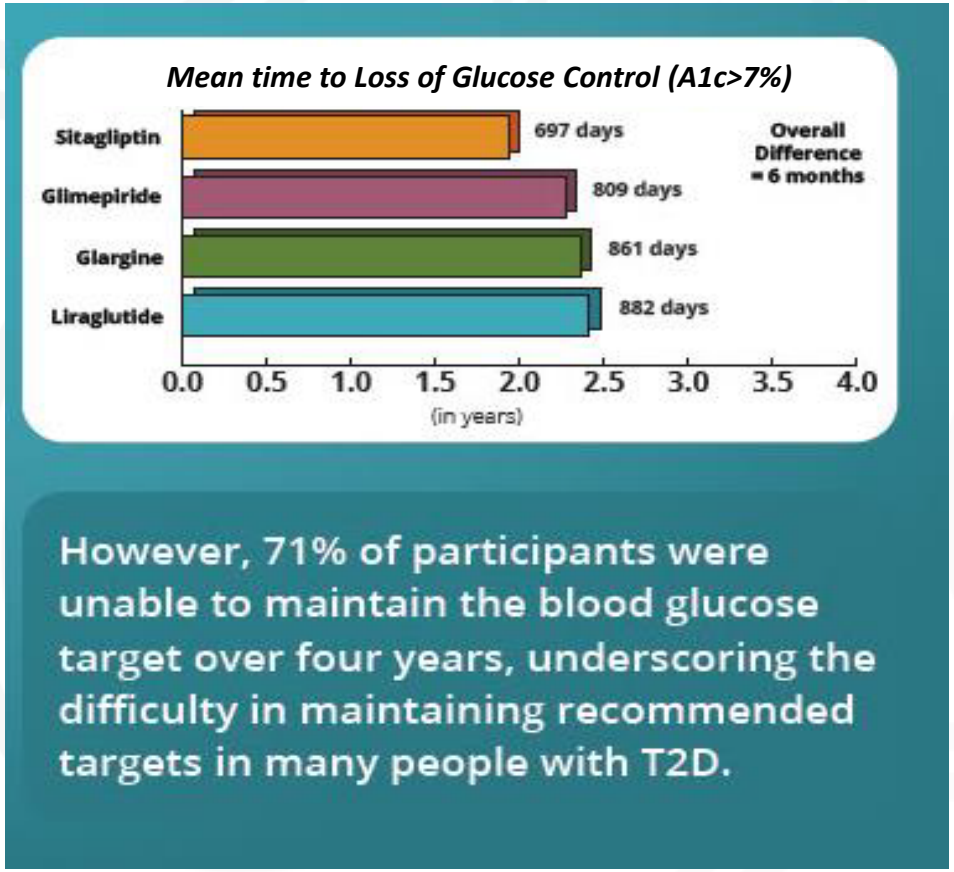
published in 2018

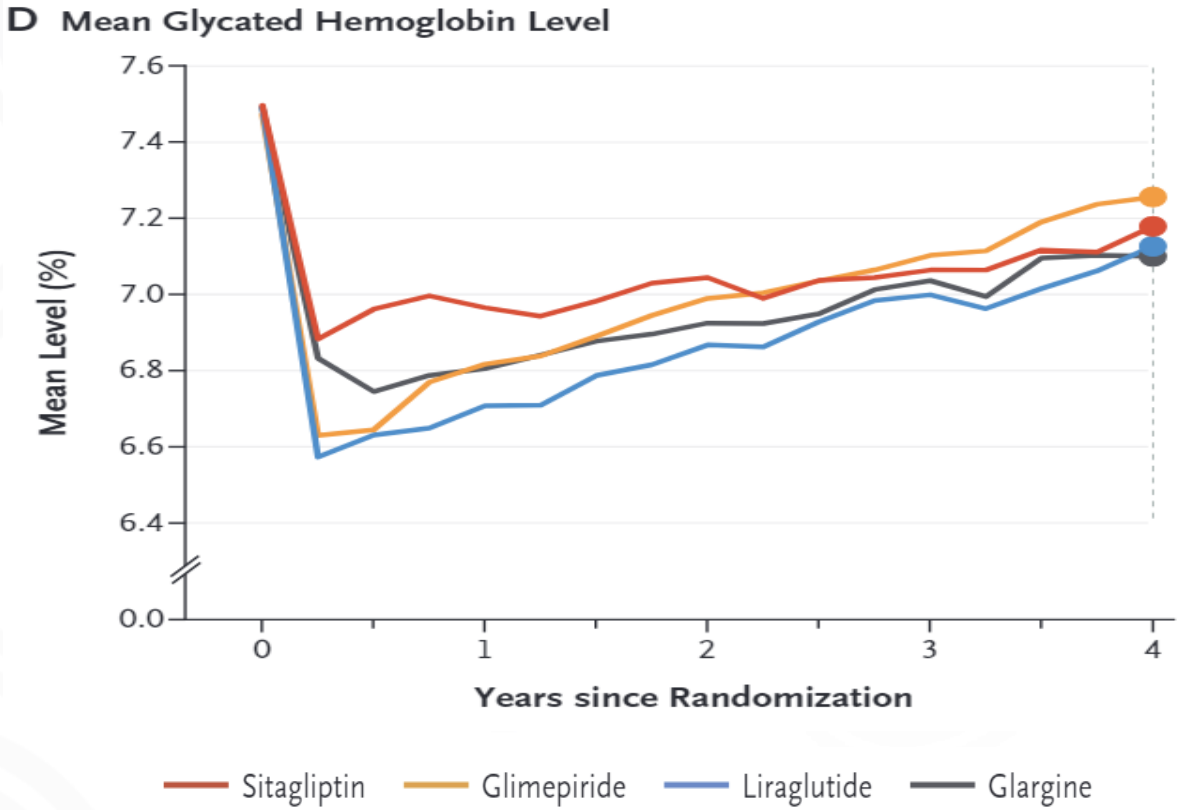


Endocrinology Diabetes Metabolism Journal , 2018 Jul 8

Even Shorter Duration of Glucose Control in Second Line Treatment with Combinations

published in NEJM 2022





;

NIH.gov; Nathan et al., NEJM 2022

Monotherapy and Combination Therapy Clinical Results *published in NEJM 2022 and 2006*

1st Line Response to Monotherapy

	Time to Max HbA1c Effect	Duration of Glucose Control (A1c <7%)	Glucose control (A1c <7%) at 4 years
Metformin	12 months	45 months	36%
Glyburide (SU)	4 months	33 months	26%
Rosiglitazone (TZD)	12 months	57 months	40%

2nd Line Response to Combination with Metformin

	Time to Max HbA1c Effect	Duration of Glucose Control (A1c <7%)	Glucose control (A1c <7%) at 4 years	Discontinuation	Use of additional glucose-lowering medication
Sitagliptin (DPP4)	3 months	22.8 months	22.6%	19%	15%
Liraglutide (GLP1)	3 months	28.9 months	31.8%	23%	11%
Glimepiride (SU)	3 months	26.5 months	27.6%	23%	17%
Glargine (Insulin)	6 months	28.2 months	32.6%	14%	14%

NIH.gov; Nathan et al., NEJM 2022
Khan et al., NEJM 2006

Published Efficacy of Widely Used Single Agents *as published in 2022*

Glucose-Lowering Drug	HbA1c, %	BMI, kg/m2	AE-Induced Discontinuations vs. Placebo
Metformin	**−0.96 (−1.16, −0.76) ***	**−1.28 (−2.26, −0.31) ***	**1.03 (0.74, 1.43)**
SUs	**−1.39 (−1.63, −1.16) ***	**1.22 (0.13, 2.31) ***	**2.25 (0.74, 6.81)**
Glyburide	−1.50 (−2.69, −0.30) *	0.27 (−1.48, 2.03)	2.24 (0.31, 16.50)
Glimepiride	−1.36 (−1.57, −1.16) *	1.79 (0.46, 3.12) *	0.99 (0.10, 9.40)
Gliclazide	−1.40 (−2.70, −0.10) *	—	1.00 (0.02, 48.82)
Glipizide	−1.47 (−1.87, −1.06) *	—	4.64 (0.74, 28.95)
TZDs (thiazolidinediones)	**−0.89 (−1.04, −0.73) ***	**0.63 (0.26, 0.99) ***	**1.25 (0.81, 1.95)**
Rosiglitazone	−0.68 (−0.98, −0.38) *	0.91 (0.48, 1.35) *	0.97 (0.43, 2.23)
Pioglitazone	−1.00 (−1.17, −0.82) *	0.38 (−0.07, 0.82)	1.38 (0.82, 2.33)
NIDEs (meglitinides)	**−0.44 (−0.69, −0.20) ***	**0.08 (−1.29, 1.44)**	**0.97 (0.24, 3.81)**
Repaglinide	−0.45 (−0.81, −0.09) *	—	0.97 (0.14, 6.77)
Nateglinide	−0.45 (−0.79, −0.10) *	0.08 (−1.29, 1.44)	0.96 (0.14, 6.67)
AGIs (alpha glucosidase inhibitors)	**−0.62 (−0.79, −0.45) ***	**−0.49 (−1.26, 0.28)**	**2.57 (1.64, 4.03) ***
Acarbose	−0.74 (−0.96, −0.52) *	−0.60 (−1.66, 0.46)	2.15 (1.23, 3.75) *
Voglibose	−0.20 (−0.33, −0.07) *	0.10 (−0.13, 0.33)	0.92 (0.19, 4.46)
Miglitol	−0.53 (−0.85, −0.21) *	—	5.37 (2.11, 13.69) *
DPP–4is (dipeptidyl peptidase IV (DPP-4) inhibitors)	**−0.63 (−0.68, −0.58) ***	**0.47 (−0.01, 0.95)**	**0.92 (0.74, 1.14)**
Sitagliptin	−0.73 (−0.82, −0.65) *	0.10 (−1.24, 1.44)	0.89 (0.62, 1.28)
Saxagliptin	−0.52 (−0.61, −0.44) *	−0.46 (−2.04, 1.12)	1.28 (0.68, 2.42)
Vildagliptin	−0.48 (−0.57, −0.38) *	−0.58 (−2.09, 0.93)	1.08 (0.73, 1.60)
Linagliptin	−0.68 (−0.79, −0.58) *	—	0.55 (0.30, 0.99) *
Alogliptin	−0.68 (−0.76, −0.61) *	0.81 (0.27, 1.35) *	0.82 (0.42, 1.60)
SGLT2is (sodium-glucose transport protein 2 (SGLT2) inhibitors)	**−0.80 (−0.87, −0.72) ***	**−0.60 (−1.89, 0.69)**	**0.89 (0.63, 1.24)**
Dapagliflozin	−0.68 (−0.77, −0.59) *	−0.60 (−1.89, 0.69)	1.66 (0.84, 3.27)
Empagliflozin	−0.79 (−0.86, −0.72) *	—	0.56 (0.36, 0.87) *
Canagliflozin	−0.99 (−1.06, −0.92) *	—	1.78 (0.78, 4.07)
GLP–1RAs	**−0.99 (−1.20, −0.78) ***	**−1.05 (−1.81, −0.29) ***	**1.23 (0.60, 2.54)**
Exenatide twice-daily	−0.64 (−0.82, −0.47) *	−1.65 (−2.26, −1.04) *	2.63 (0.49, 14.04)
Liraglutide	−1.17 (−1.47, −0.87) *	−0.80 (−1.66, 0.07)	0.63 (0.25, 1.61)
Lixisenatide	−0.60 (−0.83, −0.37) *	—	4.01 (0.85, 18.83)

Gu et al., 2022

Background Diabetes - Current Standard of Care Solutions and Unmet Need

	References
Januvia (Sitagliptin)	*A 24-week, randomized, double-blind, active-controlled clinical trial comparing bexagliflozin with sitagliptin as an adjunct to metformin for the treatment of type 2 diabetes in adults*
	Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial
Tradjenta (Linagliptin)	*Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study*
	Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study
Jardiance (Empagliflozin)	*Common Drug ReviewClinical Review Report - Empagliflozin, Study 23*
	Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial
	Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial
Farxiga (Dapagliflozin)	*Dapagliflozin Improves Glycemic Control and Reduces Body Weight as Add-on Therapy to Metformin Plus Sulfonylurea: A 24-Week Randomized, Double-Blind Clinical Trial*
	Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise: A randomized, double-blind, placebo-controlled, phase 3 trial
Trulicity (Dulaglutide)	*Efficacy and safety profile of once-weekly dulaglutide in type 2 diabetes: a report on the emerging new data - AWARD 9 Trial*
Mounjaro (Tirzepatide)	*Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes*
Ozempic (Semaglutide)	*Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial*
	Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes
	Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial
Rybelsus (Oral Semaglutide)	*PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes*
Metformin	*Should metformin remain the first-line therapy for treatment of type 2 diabetes?*

A1c Normalization Rates (A1c<7%) for Type 2 Diabetes Agents

		Patient Disposition	A1c at Baseline	A1c Normalization Rate
DPP4 Leaders	Summary: Januvia, Tradjenta	0-multiple lines of therapy	**7.85% - 8.7%**	**37.5% MONO 45.3% - 54% COMBO**
SGLT2 Leaders	Summary: Jardiance, Farxiga	0 - multiple lines of therapy	**7.8% - 8.2%**	**43.6%- 51% MONO 30% - 34% COMBO**
GLP1 Leaders	Summary: Trulicity, Mounjaro, Ozempic, Rybelsus	0 - multiple lines of therapy	**8% - 8.8%**	**72-76.9% MONO 56% - 86% COMBO**
Oral Standard of Care Agents	Metformin	0 lines of therapy	**8.4%**	**36% MONO**

A1c Reduction at 28 days and Max A1c Reduction of Type 2 Diabetes Agents?

		Patient Disposition	A1c at Baseline	Approximate average A1c Reduction at 28 days	A1c Reduction Max
DPP4 Leaders	Summary: Januvia, Tradjenta	0-multiple lines of therapy	**7.85% - 8.7%**	**0.4%-0.46% MONO 0.4-0.8% COMBO**	**0.7%-0.78% MONO 0.82%-2% COMBO**
SGLT2 Leaders	Summary: Jardiance, Farxiga	0 - multiple lines of therapy	**7.8% - 8.2%**	**0.3-0.8% MONO 0.37-0.52% COMBO**	**0.66%-0.85% MONO 0.59%-0.86% COMBO**
GLP1 Leaders	Summary: Trulicity, Mounjaro, Ozempic, Rybelsus	0 - multiple lines of therapy	**8% - 8.8%**	**0.5% MONO 0.5%-0.76% COMBO**	**1.4%-1.55% MONO 1.4 %-2.44% COMBO**
Oral Standard of Care Agents	Metformin	0 lines of therapy	**8.4%**	**0.5% MONO**	**1.4% MONO**

AE Profile and Discontinuation Rate of Standard-of-Care Type 2 Diabetes Agents

		Patient Disposition	Any Adverse Event	Serious AE	Discontinuation Rate due to AE	Total Discontinuation Rate
DPP4 Leaders	Summary: Januvia, Tradjenta	0-multiple lines of therapy	**6.7% to 56.6%**	**1.4% to 3%**	**2% - 4.2% MONO 0.5% - 1.4% COMBO**	**7.6% - 14.8% MONO 3% - 7.7% COMBO**
SGLT2 Leaders	Summary: Jardiance, Farxiga	0 - multiple lines of therapy	**48% to 71.4%**	**0.9% to 3.6%**	**2% - 7% MONO 1.8% - 3% COMBO**	**8.9% -18.6% MONO 7% - 11% COMBO**
GLP1 Leaders	Summary: Trulicity, Mounjaro, Ozempic, Rybelsus	0 - multiple lines of therapy	**56% to 68.9%**	**2.8% to 6%**	**5.4 % - 7.4% MONO 4% - 8.5% COMBO**	**9.1% - 12.3% MONO 7.1% - 13.2% COMBO**
Oral Standard of Care Agents	Metformin	0 lines of therapy	**NA**	**NA**	**10%**	**22%**

What is the Average Pricing of Standard-of-Care Type 2 Diabetes Agents?

DPP4 Leaders	Average Wholesale Price per Year
Summary Januvia, Tradjenta	$7.5K - $9K / year

SGLT2 Leaders	Average Wholesale Price per Year
Summary Jardiance, Farxiga	$7.9 - $8.7K / year

GLP1 Leaders	Average Wholesale Price per Year
Summary Trulicity, Mounjaro, Ozempic, Rybelsus	$10.6 – $14.4K / year

Oral Standard of Care Agents	Average Wholesale Price per Year
Metformin (generic)	$ less than $100 / year

Oral Agents – Efficacy Benchmarks for Chronic Treatments

HbA1c Reduction by 0.5% - 1.67% at Week 26

Drug	MOA	Mean Reduction HbA1c (Wk 26, pbo adj.)
Rybelsus (Oral Semaglutide)	GLP-1	0.9% (7mg); 1.1% (14mg)
Structure Therapeutics	GLP-1	1.02% (Wk 12)
Orforglipron	GLP-1	1.67%
Jardiance (Empagliflozin)	SGLT-2	0.7% (10mg); 0.9% (25mg)
Farxiga (Dapaglifozin)	SGLT-2	0.5% (5mg); 0.7% (10mg)
Invokana (Canagliflozin)	SGLT-2	0.91% (100mg); 1.16% (300mg)
MET	MET	1.0%

Based on surveys done with type 2 diabetes patients (Source: The REVISE study), 76.5% (n = 459) of patients preferred once-daily oral over once-weekly injectable.

Rybelsus FDA label; Structure Therapeutics Provides Comprehensive GSBR-1290 Program Update Including Clinically Meaningful Proof-of-Concept Data From Phase 2a Clinical Study; Frias et al. 2023 Aug 5;402(10400):472-483 ; Jardiance FDA label; Farxiga FDA label; Invokana FDA label; MET FDA label;

Standard-of-Care Type 2 Diabetes Drugs Have Varying Effect Sizes with Limited Duration

- Over 60 therapies are approved for diabetes in the US, many are oral, most effective treatments are injected
- There are five main classes of agents: traditional oral anti diabetic drugs (e.g. Metformin); DPP-4 and SGLT2 Inhibitors as well as GLP-1 Receptor Agonists and insulin injections. Many agents are being used in combination to improve the therapeutic effect.
- Depending on the approved treatment, 30%-86% of patients achieve normalized blood glucose (A1c lower than 7%) levels
- Average A1c reduction at week 4 ranges between 0.3% in monotherapy up to 0.8% (treatment naïve) in the best combination treatments
- Max A1c reduction ranges from 0.66% monotherapy to 2.44% in combination treatments
- The typical discontinuation rate of existing therapies ranges between 3% to 18.6%
- Many agents induce low-grade AE profiles, some with 56% to 69% Grade 1s
- Based on a NEJM study from 2022, the existing type 2 diabetes drug classes show a median normalization duration between 1.5 to 2.5 years depending on treatment

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THANK YOU

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