Updates in the Management of Prediabetes and Type II Diabetes

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MedNet21
Center for Continuing Medical Education

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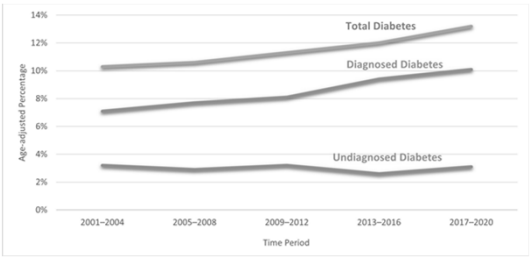
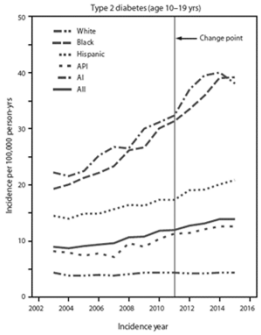
Objectives

- Understand the epidemiology and definition of Prediabetes and Type II diabetes (T2DM).
- Be familiar with the different treatment options for Prediabetes to prevent progression to T2DM.
- Understand the pharmacologic and non-pharmacologic treatments for T2DM.
- Recognize the place in therapy of Glucagon-Like Peptide Receptor Agonists (GLP-1 RA) and Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) for T2DM.
- Explore a new class of medications for diabetes treatment, the Glucose-Dependent Insulinotropic Polypeptide (GIP)/Glucagon-Like Peptide Receptor Agonist (GLP-1 RA).

Trends in Prevalence of Diagnosed Diabetes, Undiagnosed Diabetes, and Total Diabetes Among Adults Aged 18 Years or Older, United States, 2001–2004 to 2017–2020



SEARCH for Diabetes in Youth Study 2002-2015



Divers, et al, MMWR 2020

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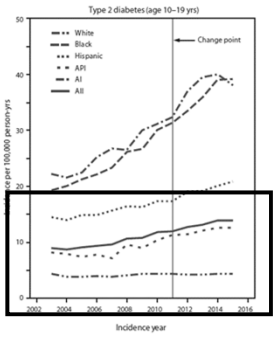

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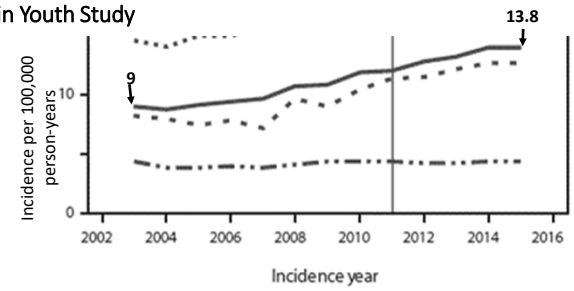


Prediabetes

Prediabetes = at increased risk for diabetes

Symptoms: none

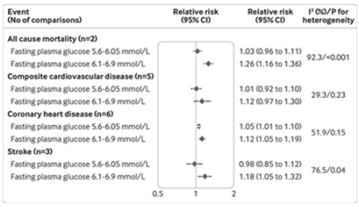
Risk factors:

- BMI>25
- >45years old
- Sedentary lifestyle
- First degree relative with diabetes
- History of Gestational Diabetes or baby >9lbs
- History of PCOS
- African Americans, Hispanic/Latino, Asians

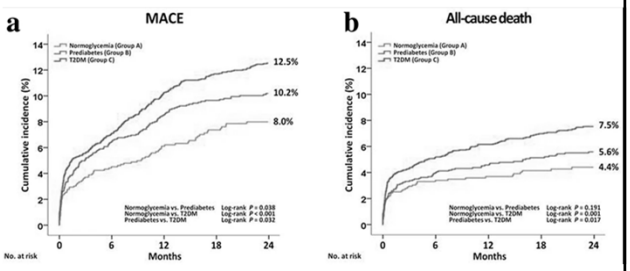
Source: CDC

Prediabetes and all cause mortality

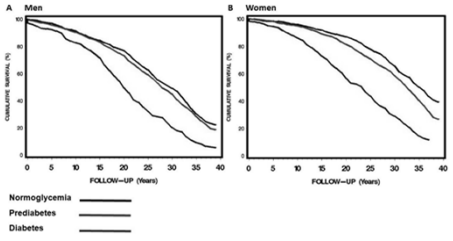
2020 Meta-analysis
- 129 studies
- >10 million individuals
- ↑ risk:
  - All cause mortality (RR 1.13)
  - Composite CV disease (RR 1.15)
  - CAD (RR 1.16)
  - Stroke (RR 1.14)



Prediabetes outcomes



Prediabetes outcomes



Prediabetes = at increased risk for diabetes

Impaired Fasting Glucose
Fasting Glucose 100-125 mg/dl

Impaired Glucose Tolerance
2-hour 75g OGTT 140-199 mg/dl

Hemoglobin A1c 5.7-6.4%

Prediabetes = at increased risk for diabetes

Impaired Fasting Glucose
Fasting Glucose 100-125 mg/dl

Impaired Glucose Tolerance (most sensitive)
2-hour 75g OGTT 140-199 mg/dl

Hemoglobin A1c 5.7-6.4%

CASE 1: "busy resident"

Goes for biometric screening needed to get insurance discount.

27 year old east Asian female
- Family history of DM (MGF)
- Just started residency training
- Sedentary lifestyle
- Poor diet
- High stress
- Poor sleep (shift work)

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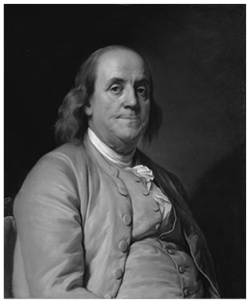
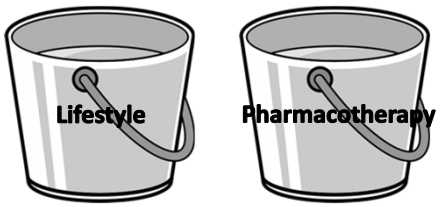
	This year	Last year
BMI	19	19
Waist circumference	28	28
Blood Pressure	110/70	108/80
Cholesterol	Total: 158 HDL: 69	Total 176 HDL 78
A1c	**5.8%**	A1c 5.6%

"an ounce of prevention is worth a pound of cure"

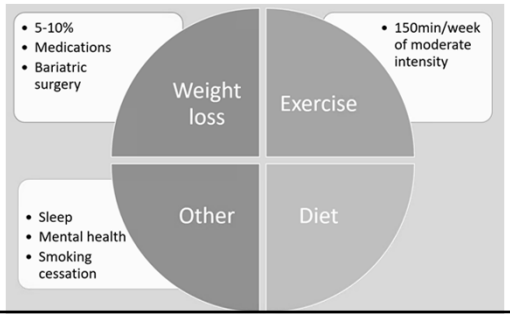
- Benjamin Franklin, 1736



Prediabetes Treatment = Preventing T2DM



Prediabetes Treatment - Lifestyle



Prediabetes Treatment - Lifestyle

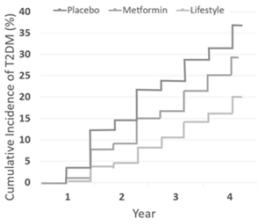
- Comprehensive Lifestyle program
  - Behavior modification
  - Dietary counseling
  - Physical activity
  - Smoking cessation
- Lifestyle Change program - CDC-recognized program can decrease risk of developing T2DM by 58%
  - Partially covered by Medicare Part B- lower risk 71%
  - Curriculum, lifestyle coach, support group
  - 1 year program

Prediabetes Pharmacotherapy

- **Biguanides**
- TZDs
- Alpha-glucosidase inhibitors
- Inhibitors of pancreatic lipase
- PPAR-gamma agonists
- Meglitinides
- SGLT2i
- GLP-1 RA

Prediabetes Pharmacotherapy

- Metformin
  - <60, history of GDM, BMI>35
  - Failed lifestyle
  - Reduces incidence of DM by 31%
  - More GI side effects
- Lifestyle
  - Reduces incidence of T2DM by 58%

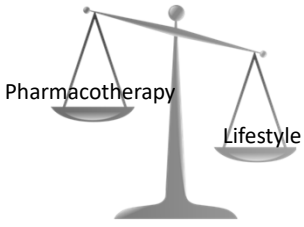


Adapted from Diabetes Prevention Program Research Group. NJEM 2002;346:393-403

Prediabetes Treatment - Assessing response

- Yearly reassessment of FBG or A1c
  - Improve or maintain indices = success
  - Worsening indices = consider increasing intervention

Prediabetes Treatment = Preventing T2DM



CASE 1: "busy resident"

Patient makes lifestyle changes:

- Starts sleeping more regularly
- Progresses in residency, stress decreases
- Cooks more, eating healthier
- Exercising at least 2 days a week + 1 day of "being active"

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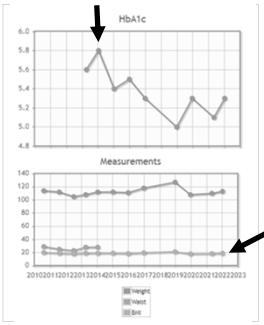


Gestational Diabetes (GDM)

#1 risk factor for development of Type II Diabetes

25% of Prediabetics go on to develop Diabetes
50% of Gestational diabetics go on to develop Diabetes

Up to 10% of pregnancies are affected by GDM
GDM is associated with risks to both mom & baby

Gestational Diabetes (GDM)

Short term consequences
- Birth defects
- Spontaneous abortions
- LGA/Macrosomia babies
- Preeclampsia and gestational hypertension
- Polyhydraminos
- Prematurity
- Increased birth interventions
- Stillbirth
- Neonatal morbidity (hypoglycemia, hyperbilirubinemia, RDS, etc)
- Double the risk of perinatal depression

Long term risks
- Maternal development of T2DM
- Childhood obesity
- Diabetes in the child
- Worse neurodevelopmental outcomes
- 2x the maternal risk of cardiovascular events 10 years post-partum

Type II Diabetes: Non-pharmacologic therapies

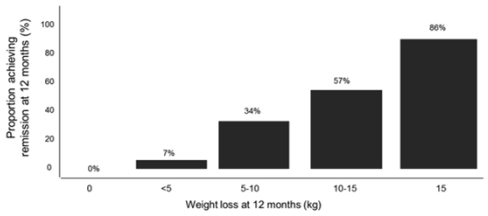
Type II Diabetes: Lifestyle

DiRECT trial - Primary Care Led Weight Management

- T2DM dx in past 6 years, 20–65 years, BMI 27–45 kg/m2, not on insulin

Intervention (n=149)	Control group (n = 149)
Stopped diabetes & HTN meds	
Total diet replacement with formula (825-853 kcal/d x3-5 months)	
Stepped food reintroduction	
Structured long-term weight loss support	
Physical activity support begins at food introduction to reach individual sustainable max	

Type II Diabetes: Lifestyle – DiRECT trial



Adapted from Lean et al. *Lancet*, 2018

Type II Diabetes: Lifestyle – Look AHEAD trial

- >5000 overweight/obese patients with T2DM randomized
  - Intensive lifestyle intervention
  - DM support/education (control)
- Primary outcome: death from CV causes
  - Nonfatal MI, stroke, hospitalization for angina

Stopped early at 9.6 years for futility

- Intervention group showed improvements in:
  - Weight loss
  - A1c
  - Fitness
  - CV risk factors
  - Sleep apnea
  - Decreased meds
  - Lower costs
  - Quality of life

Type II Diabetes

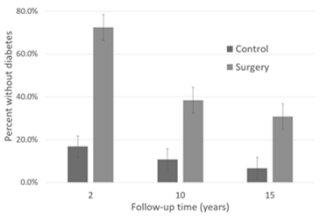
- Diabetes self-management education and support (DSMES)
  - "the **ongoing** process of facilitating the knowledge, skills, and ability necessary for diabetes self-care, as well as activities that assist a person in implementing and **sustaining** the behaviors needed to manage his or her condition on an ongoing basis, beyond or outside of formal self-management training."
  - Improves clinical outcomes, quality of life, decreases hospitalizations, healthcare costs, all cause mortality
  - Improves A1c 0.6%, especially if engages >10 hours
  - At diagnosis, annually, when complications occur, transitions of care

Type II Diabetes: Bariatric surgery

Swedish Obese Subjects study

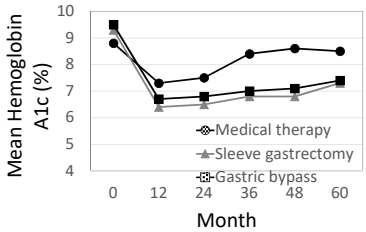
Surgery group showed lower rates of:

- T2DM
- Microvascular complications
- Macrovascular complications



Adapted from Sjostrom et al JAMA 2014

Type II Diabetes: Bariatric surgery

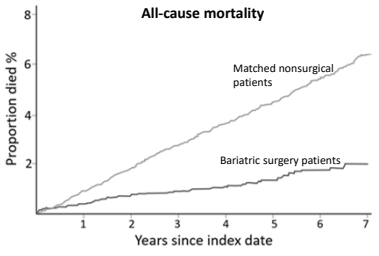


Adapted from Schauer PR et al. N Engl J Med 2017;376:641-651.

Type II Diabetes: Bariatric surgery

Lower rates compared to nonsurgical controls:

- All cause mortality
- All macrovascular disease events
- Coronary artery disease events
- Cerebrovascular events
- Microvascular complications



Adapted from Fisher et al, JAMA 2018

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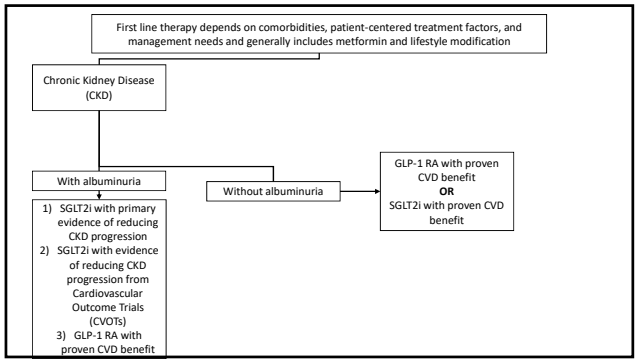
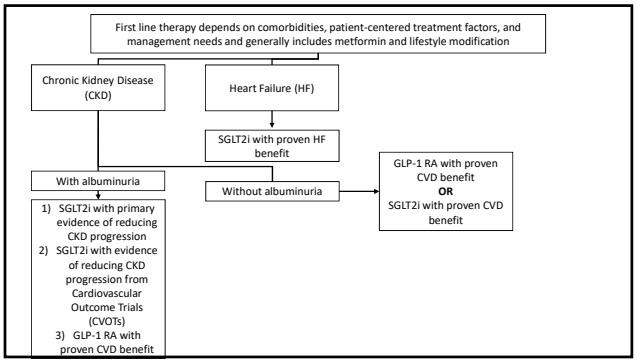
Type II Diabetes: Pharmacotherapy

A Shift in Diabetes Management

- Diabetes comorbidities
  - 39% have chronic kidney disease (CKD, Stages 1-4)
  - 20% have coronary artery disease (CAD)
  - 15% have heart failure (HF)
- People with diabetes are 2x more likely to have heart disease or a stroke as people without diabetes
- Cardiovascular disease is responsible for half of the deaths in this patient population
- Diabetes is the leading cause of kidney failure in the United States

First line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and lifestyle modification


First line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and lifestyle modification
Chronic Kidney Disease (CKD)
With albuminuria
1) SGLT2i with primary evidence of reducing CKD progression
2) SGLT2i with evidence of reducing CKD progression from Cardiovascular Outcome Trials (CVOTs)
3) GLP-1 RA with proven CVD benefit
Without albuminuria
GLP-1 RA with proven CVD benefit
OR
SGLT2i with proven CVD benefit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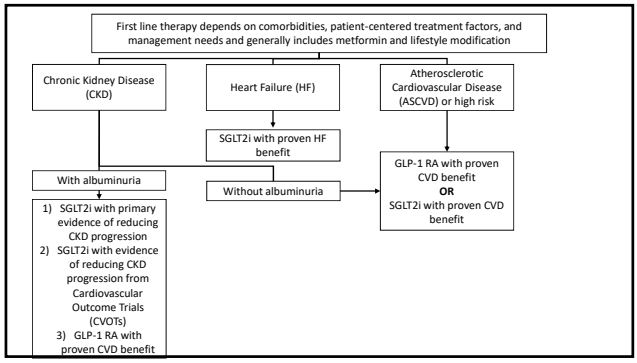
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Chronic Kidney Disease (CKD)
Heart Failure (HF)
Atherosclerotic Cardiovascular Disease (ASCVD) or high risk
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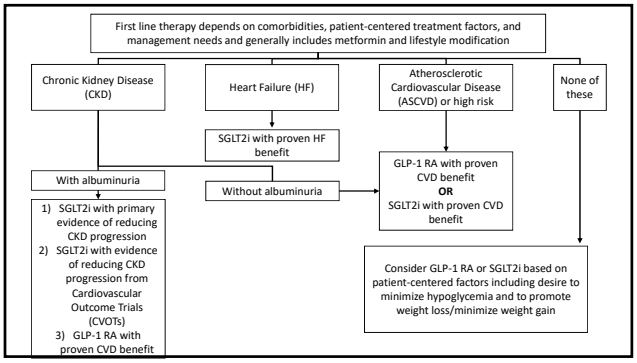
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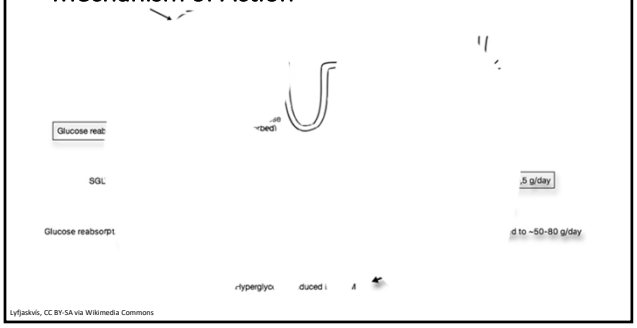
Heart Failure (HF)
Atherosclerotic Cardiovascular Disease (ASCVD) or high risk
None of these
SGLT2i with proven HF benefit
With albuminuria
1) SGLT2i with primary evidence of reducing CKD progression
2) SGLT2i with evidence of reducing CKD progression from Cardiovascular Outcome Trials (CVOTs)
3) GLP-1 RA with proven CVD benefit
Without albuminuria
GLP-1 RA with proven CVD benefit
OR
SGLT2i with proven CVD benefit
Consider GLP-1 RA or SGLT2i based on patient-centered factors including desire to minimize hypoglycemia and to promote weight loss/minimize weight gain

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

Mechanism of Action



Available SGLT2 Inhibitors

Drug	Approval	Dose	% A1c lowering*	Weight lowering (kg)*	Cost/28 days
Canagliflozin (Invokana®)	2013	100mg	-0.9	-1.9	$638
		300mg	-1.2	-2.9	
Dapagliflozin (Farxiga®)	2014	5mg	-0.5	-2.8	$615
		10mg	-0.6	-3.2	
Empagliflozin (Jardiance®)	2014	10mg	-0.7	-2.3	$639
		25mg	-0.9	-2.5	
Ertugliflozin (Steglatro®)	2017	5mg	-0.5	-3.6	$363
		15mg	-0.5	-3.7	

*When used as monotherapy

Cardiovascular Outcome Trials

Drug	CVOT	MACE*	CV death	HF hospitalization
Canagliflozin (Invokana®)	CANVAS[¤]	↓14%	Not significant	↓33%
Dapagliflozin (Farxiga®)	DECLARE-TIMI 58[¤]	Not significant	↓17%	↓27%
Empagliflozin (Jardiance®)	EMPA-REG OUTCOME[§]	↓14%	↓38%	↓35%
Ertugliflozin (Steglatro®)	VERTIS-CV[§]	Not significant	Not significant	↓30%

*MACE = Major Atherosclerotic Cardiovascular Events (composite CV death, hospitalization for HF, and ischemic stroke)

¤ Included patients with DM who had CV disease or multiple risk factors for CV disease

§ Included patients with DM who had CV disease

Cardiovascular Outcome Trials

Drug	CVOT	MACE*	CV death	HF hospitalization
Canagliflozin (Invokana®)	CANVAS¤	With ASCVD: ↓14% Without ASCVD: Not significant	Not significant	↓33%
Dapagliflozin (Farxiga®)	DECLARE-TIMI 58¤		↓17%	↓27%
Empagliflozin (Jardiance®)	EMPA-REG OUTCOME§		↓38%	↓35%
Ertugliflozin (Steglatro®)	VERTIS-CV§	Not significant	Not significant	↓30%

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Cardiovascular Outcome Trials

Drug	CVOT	MACE*	CV death	HF hospitalization
Canagliflozin (Invokana®)	CANVAS¤	↓14%	With or without ASCVD or HF: 23% relative risk reduction	
Dapagliflozin (Farxiga®)	DECLARE-TIMI 58¤	Not significant		
Empagliflozin (Jardiance®)	EMPA-REG OUTCOME§	↓14%		
Ertugliflozin (Steglatro®)	VERTIS-CV§	Not significant	Not significant	↓30%

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Primary HFrEF± Outcomes

Drug	Trial	Composite HF hospitalization* or CV death	CV death	HF hospitalization*
Canagliflozin (Invokana®)	-	-	-	-
Dapagliflozin (Farxiga®)	DAPA-HF	↓26%, NNT 20	↓18%	↓30%
Empagliflozin (Jardiance®)	EMPEROR-Reduced	↓25%, NNT 19	↓8%	↓30%
Ertugliflozin (Steglatro®)	-	-	-	-

±NYHA II, III, IV with EF ≤40 with or without T2DM with elevated NT-proBNP

*DAPA-HF included unplanned hospitalization for heart failure or an urgent visit resulting in intravenous therapy or mechanical or surgical intervention for heart failure

Primary HFpEF± Outcomes

Drug	Trial	Composite HF hospitalization* or CV death	CV death	HF hospitalization*
Canagliflozin (Invokana®)	-	-	-	-
Dapagliflozin (Farxiga®)	DELIVER	↓18%, NNT 32	↓12%	↓21%
Empagliflozin (Jardiance®)	EMPEROR-Preserved	↓21%, NNT 31	↓9%	↓29%
Ertugliflozin (Steglatro®)	-	-	-	-

±NYHA II, III, IV with EF >40 with or without T2DM with elevated NT-proBNP

*DELIVER included unplanned hospitalization for heart failure or an urgent visit resulting in intravenous therapy or mechanical or surgical intervention for heart failure

CVOT Renal Outcomes

Drug	CVOT	Composite renal endpoint*
Canagliflozin (Invokana®)	CANVAS	↓40%
Dapagliflozin (Farxiga®)	DECLARE-TIMI 58	↓47%
Empagliflozin (Jardiance®)	EMPA-REG OUTCOME	↓39%
Ertugliflozin (Steglatro®)	VERTIS-CV	Not significant

*Composite renal endpoint varied by trial:

- CANVAS = sustained decrease in eGFR at least 40%, need for renal replacement therapy, or renal death
- DECLARE-TIMI 58 = ESRD, sustained decrease in eGFR at least 40% to <60mL/min/1.73m^2, or renal death
- EMPA-REG OUTCOME = progression to macro-albuminuria, doubling of sCr with GFR ≤ 45mL/min/1.73m^2, need for renal replacement therapy, or renal death
- VERTIS-CV = renal replacement therapy, doubling of sCr, or renal death

Primary Renal Outcomes

Drug	Trial	Composite renal endpoint ESRD, worsening CKD*, or renal/CV death
Canagliflozin (Invokana®)	CREDENCE±	↓30%, NNT 22
Dapagliflozin (Farxiga®)	DAPA-CKD¤	↓39%, NNT 19
Empagliflozin (Jardiance®)	-	-
Ertugliflozin (Steglatro®)	-	-

±CREDENCE studied patients with DMII and CKD with macroalbuminuria on an ACEI/ARB

¤DAPA-CKD studied patients with CKD with macroalbuminuria with or without DMII or ACEI/ARB

*Worsening CKD defined as doubling of sCr for CREDENCE, sustained decline in eGFR at least 50% in DAPA-CKD

Prediabetes Pharmacotherapy

- Biguanides
- TZDs
- Alpha-glucosidase inhibitors
- Inhibitors of pancreatic lipase
- PPAR-gamma agonists
- Meglitinides
- **SGLT2i**
- GLP-1 RA

News & Views | Published: 07 February 2022

DIABETES

SGLT2 inhibitors may prevent diabetes

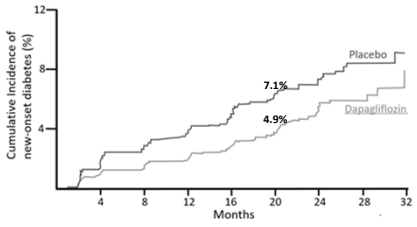
Daniel V. O'Hara & Meg J. Jardine

Nature Reviews Nephrology **18**, 203–204 (2022) | Cite this article

858 Accesses | 22 Altmetric | Metrics

Dapagliflozin reduces the risk of new-onset diabetes mellitus, according to results from a pre-specified pooled analysis of the DAPA-CKD and DAPA-HF trials. The study adds to the growing list of sodium–glucose co-transporter 2 inhibitor benefits and raises the possibility of an expanded target patient population.

Prediabetes Pharmacotherapy: SGLT2 Inhibitors



Adapted from Diabetes Care. 2021;44(2):586-594. doi:10.2337/dc20-1675

Dosing (mg) by Labeled Indication

Drug	T2DM	CV risk reduction in T2DM with CVD*	Renal risk reduction in T2DM with DKD± and albuminuria >300 mg/day	CKD	HFrEF	HFpEF
Canagliflozin (Invokana®)	100-300	100-300	100-300	-	-	-
Dapagliflozin (Farxiga®)	5-10	10	-	10	10	-
Empagliflozin (Jardiance®)	10-25	10-25	-	-	10	10
Ertugliflozin (Steglatro®)	5-15	-	-	-	-	-

*Dapagliflozin indicated for DM with CVD OR multiple risk factors for CVD

±DKD = Diabetic Kidney Disease

Renal Dosing by Labeled Indication

Drug	T2DM	CV risk reduction in T2DM with CVD*	Renal risk reduction in T2DM with DKD± and albuminuria >300 mg/day	CKD	HFrEF	HFpEF
Canagliflozin (Invokana®)	eGFR 30-59 Max 100mg; eGFR <30 Not recommended		eGFR 30-59 Max 100mg; eGFR <30 Max 100mg	-	-	-
Dapagliflozin (Farxiga®)	eGFR <45 Not recommended	eGFR <25	-	eGFR <25 Initiation not recommended		-
Empagliflozin (Jardiance®)	eGFR <30 Not recommended		-	-	eGFR <20 Not recommended	
Ertugliflozin (Steglatro®)	eGFR <45 Not recommended	-	-	-	-	-

*Dapagliflozin indicated for DM with CVD OR multiple risk factors for CVD

±DKD = Diabetic Kidney Disease

Adverse Effects

- Genital mycotic and urinary tract infections
- Increased thirst, increased urination
- Associated with BP lowering of 1.4-3.4/0.6-2mmHg
- Hypoglycemia is rare

Warnings and Precautions

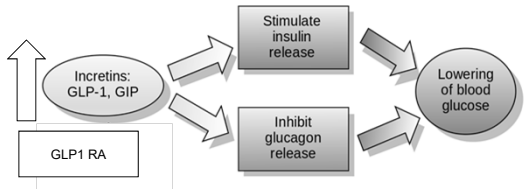
- Ketoacidosis
- Hypotension, volume depletion, dehydration
- Lower limb amputation

SGLT2i Summary

- Reduce HgbA1c 0.5-1.2% and weight 1.9-3.7kg
- Canagliflozin, dapagliflozin, and empagliflozin have direct evidence for CV benefit
- Empagliflozin and dapagliflozin have primary evidence in both HFrEF and HFpEF
- Canagliflozin and dapagliflozin have direct evidence and empagliflozin has secondary evidence for renal benefit
- Educate on potential for genital infections and dehydration
- Use limited by cost

Glucagon-Like Peptide Receptor Agonists (GLP-1 RA)

Mechanism of Action



GLP-1 = Glucagon-Like Peptide 1

GIP = Glucose-dependent Insulinotropic Polypeptide

Available GLP-1 RAs

Type	Drug	Approval	Frequency	Doses	Form	Cost/28 days
Short acting	Exenatide (Byetta®)	2005	Twice daily	5mcg, 10mcg	Prefilled pen	$897
	Lixisenatide (Adlyxin®)	2016	Daily	*10mcg**, 20mcg	Prefilled pen	$760
Long acting	Liraglutide (Victoza®)	2010	Daily	*0.6mg**, 1.2mg, 1.8mg	Prefilled pen	$604
	Exenatide ER (Bydureon®)	2012	Weekly	2mg	Autoinjector	$936
	Dulaglutide (Trulicity®)	2014	Weekly	0.75mg, 1.5mg, 3mg, 4.5mg	Autoinjector	$1064
	Semaglutide (Ozempic®)	2017	Weekly	*0.25mg**, 0.5mg, 1mg, 2mg	Prefilled pen	$1214
	Semaglutide (Rybelsus®)	2019	Daily	*3mg**, 7mg, 14mg	Oral tablet	$999

**Starting dose used for tolerability not considered effective for glycemic control*

Sample GLP-1 RA injection devices

- Prefilled pen (ex: Liraglutide)

- Autoinjector (ex: Dulaglutide)

Phase III Efficacy Studies

Type	Drug	Trials	Dose	% A1c Lowering*	Weight Loss (kg)*
Short acting	Exenatide (Byetta®)	AMIGO	5mcg	-0.4	-1.3
			10mcg	**-0.8**	**-2.6**
	Lixisenatide (Adlyxin®)	GetGoal	20mcg	**-0.7**	**-2.7**
Long acting	Liraglutide (Victoza®)	LEAD	1.2mg	-1.0	-2.6
			1.8mg	**-1.0**	**-2.8**
	Exenatide ER (Bydureon®)	DURATION	2mg	**-1.5**	**-2.3**
	Dulaglutide (Trulicity®)	AWARD	0.75mg	-0.7	-2.4
			1.5mg	-1.5	-3.1
			3mg	-1.6	-3.8
			4.5mg	**-1.8**	**-4.6**
	Semaglutide (Ozempic®)	SUSTAIN	0.5mg	-1.5	-4.6
			1mg	-1.8	-6.5
			2mg	**-2.2**	**-6.9**
	Semaglutide (Rybelsus®)	PIONEER	7mg	-1.0	-2.2
			14mg	**-1.3**	**-3.1**

*When added to metformin

Head-to-Head Comparisons

Type	Drug	A1c Lowering	Weight Loss	Adverse effects
Short acting	Exenatide (Byetta®)	Low	Low	Highest
	Lixisenatide (Adlyxin®)	Low	Low	Intermediate
Long acting	Liraglutide (Victoza®)	High	High	Intermediate
	Exenatide ER (Bydureon®)	Intermediate	Low	Low
	Dulaglutide (Trulicity®)	High	Intermediate	Intermediate/High
	Semaglutide (Ozempic®)	Highest	Highest	High
	Semaglutide (Rybelsus®)	High/Highest	Highest	Intermediate/High

Adapted from Ther Adv Endocrinol Metab. 2021 Mar 9;12:2042018821997320.

Cardiovascular Outcome Trials

Type	Drug	CVOT	CV benefit	Renal benefit±
Short acting	Exenatide (Byetta®)	-	-	-
	Lixisenatide (Adlyxin®)	ELIXA	✗	-
Long acting	Liraglutide (Victoza®)	LEADER	✓	✓
	Exenatide ER (Bydureon®)	EXSCEL	✗	-
	Dulaglutide (Trulicity®)	REWIND	✓	✓
	Semaglutide (Ozempic®)	SUSTAIN-6	✓	✓
	Semaglutide (Rybelsus®)	PIONEER-6, SOUL*	✗	-

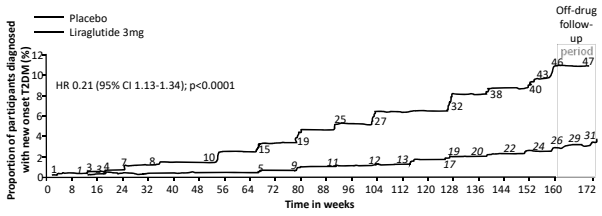
± Secondary endpoints from the Cardiovascular Outcomes Trials, not from dedicated renal outcomes trials
*SOUL is ongoing (NCT03914326)
MACE = Major Atherosclerotic Cardiovascular Events (composite CV death, hospitalization for HF, and ischemic stroke)

Prediabetes Pharmacotherapy: GLP-1 RAs

- Biguanides
- TZDs
- Alpha-glucosidase inhibitors
- Inhibitors of pancreatic lipase
- PPAR-gamma agonists
- Meglitinides
- SGLT2i
- **GLP-1 RA**

- Exenatide vs placebo along with lifestyle intervention
  - Patients with obesity and without diabetes with normal or impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
  - Weight loss 5.1kg with Exenatide vs 1.6kg with placebo
  - 77% in Exenatide group with IGT or IFG at baseline achieved normalized glucose tolerance at 24 weeks vs 56% in placebo group
  - Nausea was experienced by 25 and 4% and diarrhea by 14 and 3% of exenatide- and placebo-treated subjects, respectively

Prediabetes Pharmacotherapy: GLP-1 RAs



Adapted from Lancet. 2017 Apr 8;389(10077):1399-1409.

Prediabetes Pharmacotherapy: GLP-1 RAs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Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

- Prediabetes→normoglycemia in 84.1% semaglutide vs 47.8% placebo

Adverse Effects

- Most common: nausea, vomiting, diarrhea, bloating, abdominal pain
- Injection site reactions
- Low risk of hypoglycemia

Switching Between GLP-1 RAs

Type	Drug	Frequency	Equivalent Dose*			
Short acting	Exenatide (Byetta®)	Twice daily	5mcg	10mcg		
	Lixisenatide (Adlyxin®)	Daily	10mcg	20mcg		
Long acting	Liraglutide (Victoza®)	Daily	0.6mg	1.2mg	1.8mg	
	Exenatide ER (Bydureon®)	Weekly			2mg	
	Dulaglutide (Trulicity®)	Weekly		0.75mg	1.5mg	
	Semaglutide (Ozempic®)	Weekly		0.25mg	0.5mg	1mg
	Semaglutide (Rybelsus®)	Daily	3mg	7mg	14mg	

*Assessment of equivalent dose is entirely based on authors' opinion, based on head-to-head clinical trials when available and/or clinical experience. Does not include higher doses of dulaglutide 3mg, 4.5mg and semaglutide 2mg, which were approved after publication.

Adapted from Clin Diabetes. 2020 Oct;38(4):390-402.

Warnings and Precautions

- Severe GI disorders
- Pancreatitis
- Thyroid cancer
- Retinopathy
- Altered kidney function
  - Semaglutide, liraglutide, dulaglutide no cutoff
  - Exenatide not recommended eGFR <30mL/min
  - Lixisenatide not recommended eGFR <15mL/min

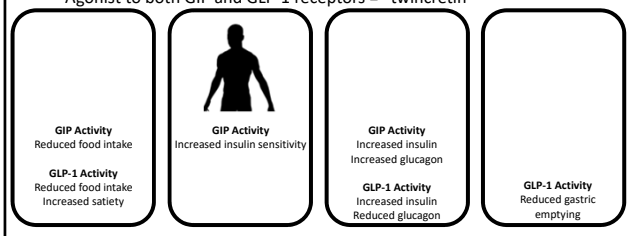
GLP-1 RA Summary

- Effectively reduce HgbA1c and weight
- Liraglutide, dulaglutide, and semaglutide have direct evidence for CV benefit and secondary evidence for renal benefit
- Educate on potential for adverse GI effects and mitigation strategies
- Use limited by cost

Glucose-Dependent Insulinotropic Polypeptide (GIP)/Glucagon-Like Peptide (GLP-1) Receptor Agonist

Tirzepatide (Mounjaro®)

- Agonist to both GIP and GLP-1 receptors = "twincretin"



Tirzepatide (Mounjaro®)

- Superior A1c results when compared head-to-head with Ozempic®
- Dose increased from 2.5mg to 15mg weekly in increments of 2.5mg per month and not much extra A1c lowering beyond 5mg/week
- May lead to weight loss up to 25lb over 10 months in patients with diabetes
- CVOT data not expected until 2025
- Similar GI adverse effects to GLP-1 RAs
- Caution on reduced efficacy of oral contraceptives
- $1169/28 day supply

Updates in the Management of Prediabetes and Type II Diabetes

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The Ohio State University Wexner Medical Center

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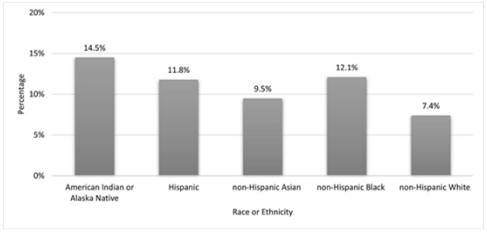
Center for Continuing Medical Education

The Ohio State University Wexner Medical Center

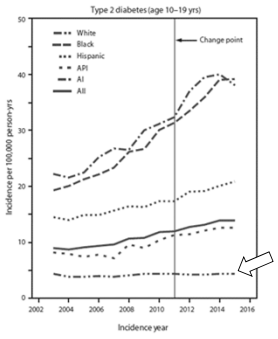
Disparities in Diabetes

Percentage of Adults Aged 18 Years or Older With Diagnosed Diabetes, by Racial or Ethnic Group, United States, 2018–2019



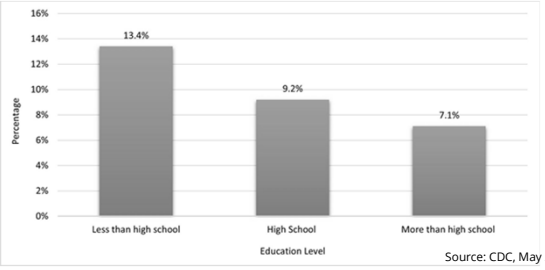
Source: CDC, May 2022

SEARCH for Diabetes in Youth Study 2002-2015



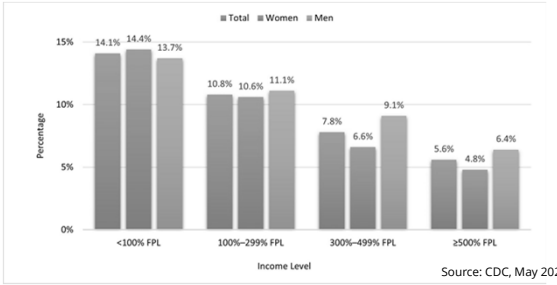
Divers, et al, MMWR 2020

Percentage of Adults Aged 18 Years or Older With Diagnosed Diabetes, by Education Level, United States, 2018–2019



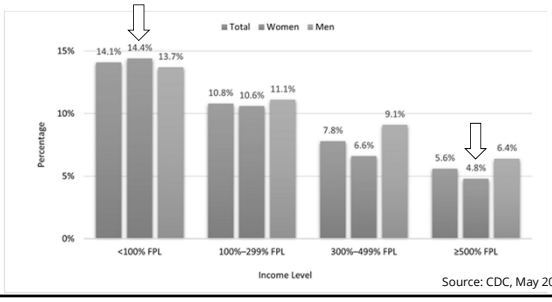
Source: CDC, May 2022

Prevalence of Diagnosed Diabetes Among US Adults 18 or Older, by Family Income and Sex, 2018–2019



Source: CDC, May 2022

Prevalence of Diagnosed Diabetes Among US Adults 18 or Older, by Family Income and Sex, 2018–2019



Source: CDC, May 2022

Disparities - Moving to Opportunity study

Randomized control trial 4498 low-income families in poverty-stricken public housing in Baltimore, Boston, Chicago, LA and NYC from 1994-1998

Housing voucher + counseling to low-poverty (<10%) neighborhoods	**Housing voucher to Section 8 housing**	**Control group**
Prevalence of Hgb A1c >= 6.5% at follow-up		
16.3% (p=0.02)	20.6%	20%

Case 2

51yo white male with HTN, autoimmune hepatitis presenting for preventative health screening. BMI is 41.46 kg/m2.

Screening A1c is 9.9% and Glucose is 229 – denies symptoms

Diagnosed with "Steroid-induced Diabetes"

What's the next step in treatment?

A) Lifestyle changes
B) Metformin
C) Insulin
D) GLP-1 RA
E) SGLT2i

Case 2

He is on a steroid taper for autoimmune hepatitis and believes his diabetes will resolve once he's off steroids so he is started on insulin.

2 months later, he is now off steroids but remains on insulin.

6 months later, BMI has increased to 43.27 kg/m2. **A1c is 6.5%**

He is exercising regularly and has improved diet.

1 year later, he is eating much healthier and swimming daily for exercise but has continued weight gain, BMI 44.5. **A1c is 8.3%. Metformin** is added.

Case 2

1 year later, he is eating much healthier and swimming daily for exercise but has continued weight gain, BMI 44.5. **A1c is 8.3%.** His current antidiabetic meds include Metformin & insulin.

What's the next step?

A) Start GLP-1 RA
B) Start SGLT2i
C) Start DPP-4
D) Start Sulfonylurea
E) Increase insulin

Case 2

You started a GLP-1 RA, and referred to clinical pharmacist for co-management. GLP-1 RA was titrated it up and at 6 month follow-up:

- Lost 30 lbs (BMI down to 41)
- off insulin
- A1c is 6.3%

Key Points

- **Prediabetes is extremely common and underdiagnosed. It carries increased risk for all cause mortality, CV disease and stroke.**
- **T2DM is a largely preventable illness and comprehensive lifestyle changes remains the most effective method of prevention.**
- T2DM is a deadly and costly disease, though modern therapies can be effective at not only controlling it but decreasing comorbidities.

Key Points

- Prediabetes is extremely common and underdiagnosed. It carries increased risk for all cause mortality, CV disease and stroke.
- T2DM is a largely preventable illness and comprehensive lifestyle changes remains the most effective method of prevention.
- **T2DM is a deadly and costly disease, though modern therapies can be effective at not only controlling it but decreasing comorbidities.**

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