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Cardiometabolic Health Congress

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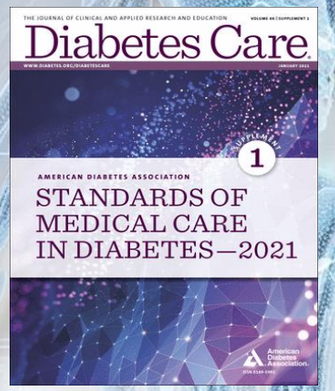
Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Pharmacologic Approaches to Type 2 Diabetes - 2021



Athena Philis-Tsimikas, MD
Lauren Vincent, MD
Division of Diabetes & Endocrinology, SCMG
Scripps Whittier Diabetes Institute

Scripps

Goals

1. Review diabetes goals of therapy and glycemic targets

2. Discuss efficacy and safety of medication classes for type 2 diabetes

3. Review guidelines for a stepwise approach to the pharmaceutical management of type 2 diabetes

4. Understand how to select therapy for patients with type 2 diabetes and comorbidities such as ASCVD, HF, or CKD

5. To provide case examples of uses in under-resourced populations in terms of access and implementation.

6. To describe technology currently offered in the ambulatory and hospital settings for management of type 2 diabetes

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Review diabetes goals of therapy and glycemic targets

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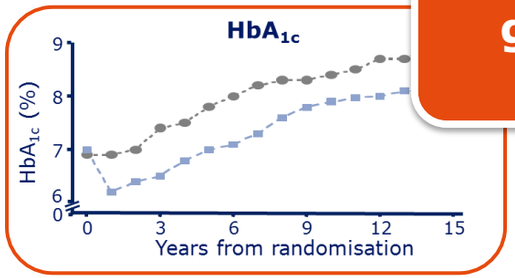
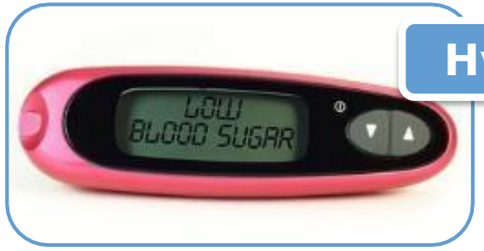
Goals of Therapy-> Overcome Practical Challenges in Diabetes

Treatment complexity



Deteriorating glycemic control



Hypoglycemia

Managing food & Weight gain

Clinical inertia

Inflexible regimens

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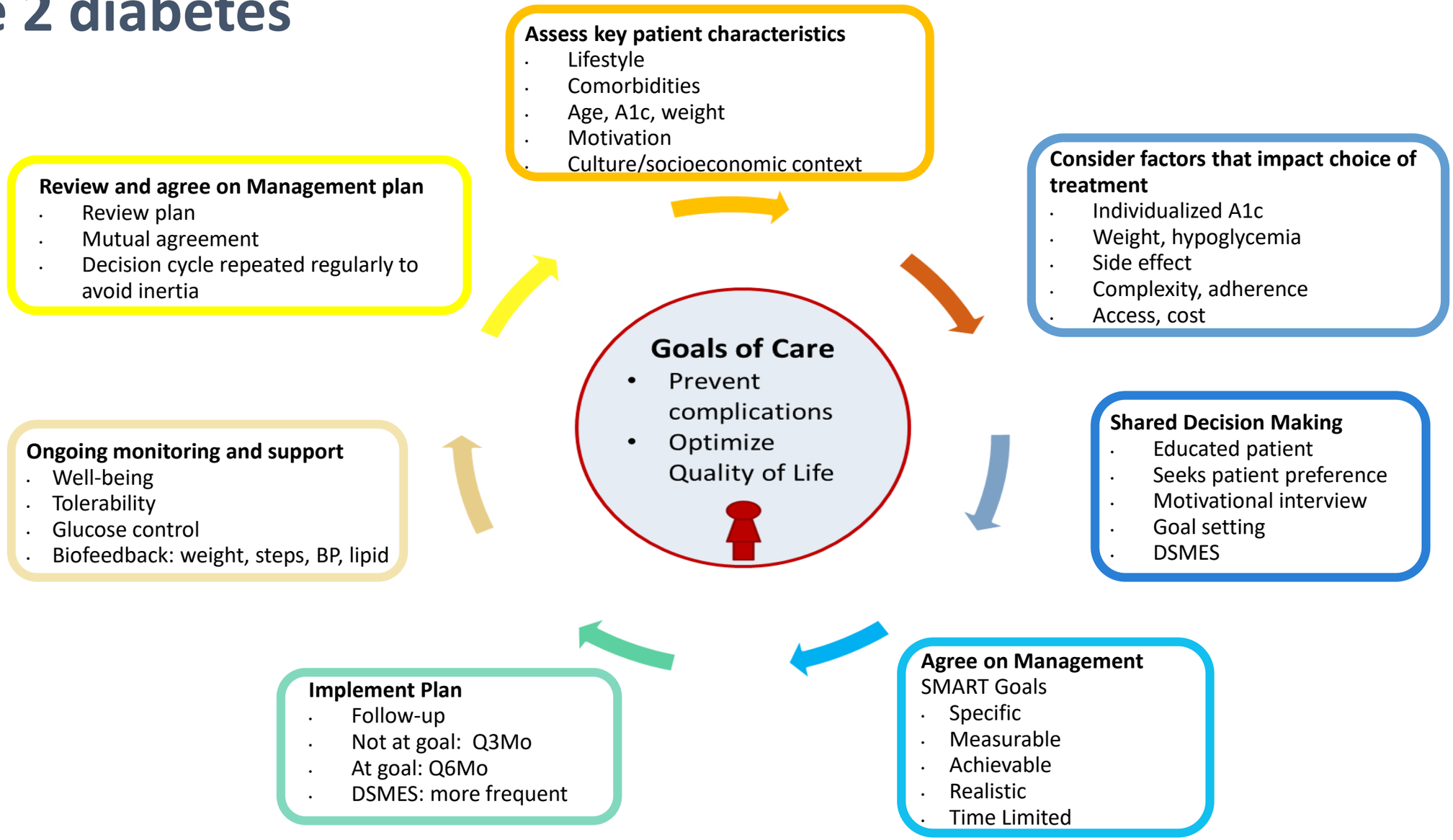
UKPDS 34. *Lancet* 1998:352:854–65

Decision cycle for patient-centered glycemic management in type 2 diabetes



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American Diabetes Association Dia Care 2021;44:S40-S52

American Diabetes Association.

ADA Basics – Obesity Management

- At least 5% (ideally 7%+) weight loss should be prescribed for overweight and obese patients with type 2 **who are ready** to achieve weight loss.
- **BMI** should be calculated and documented in the EMR at least yearly
- Diets that provide the same caloric restriction but differ in protein, carb and fat content **are equally effective** in achieving weight loss, so use patient preference to help guide plan

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Diabetes Care 2021 Jan; 44(Supplement 1): S73-S84.

ADA – Physical Activity Recommendations

150 min/week of moderate intensity aerobic physical activity spread over at least 3 days per week
50-70% of maximum heart rate

No more than 2 consecutive days without exercise

Resistance training at least 2x week unless contraindicated

Limit sedentary time spent sitting
(Get up and move every 30 min!)

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Diabetes Care 2021 Jan; 44(Supplement 1): S73-S84.

Psychosocial Care

"Address psychosocial issues in all aspects of care including self–management, mental health, communication, complications, comorbidities and life -stage considerations."

Consider using the Diabetes Distress Scale (DDS) screening tool in your practice.

Box 2 Diabetes distress screening scale

Diabetes distress screener items	Not a problem	A slight problem	A moderate problem	Somewhat serious problem	A serious problem	A very serious problem
Feeling overwhelmed with demands of living with diabetes	1	2	3	4	5	6
Feeling that I am often failing my diabetes routine	1	2	3	4	5	6

Please consider the degree the above 2 items may have distressed or bother you "during the past month" on a severity scale of 1–6.

Diabetes Care 2021 Jan; 44(Supplement 1): S73-S84.

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ADA/EASD Position Statement - Glucose Control

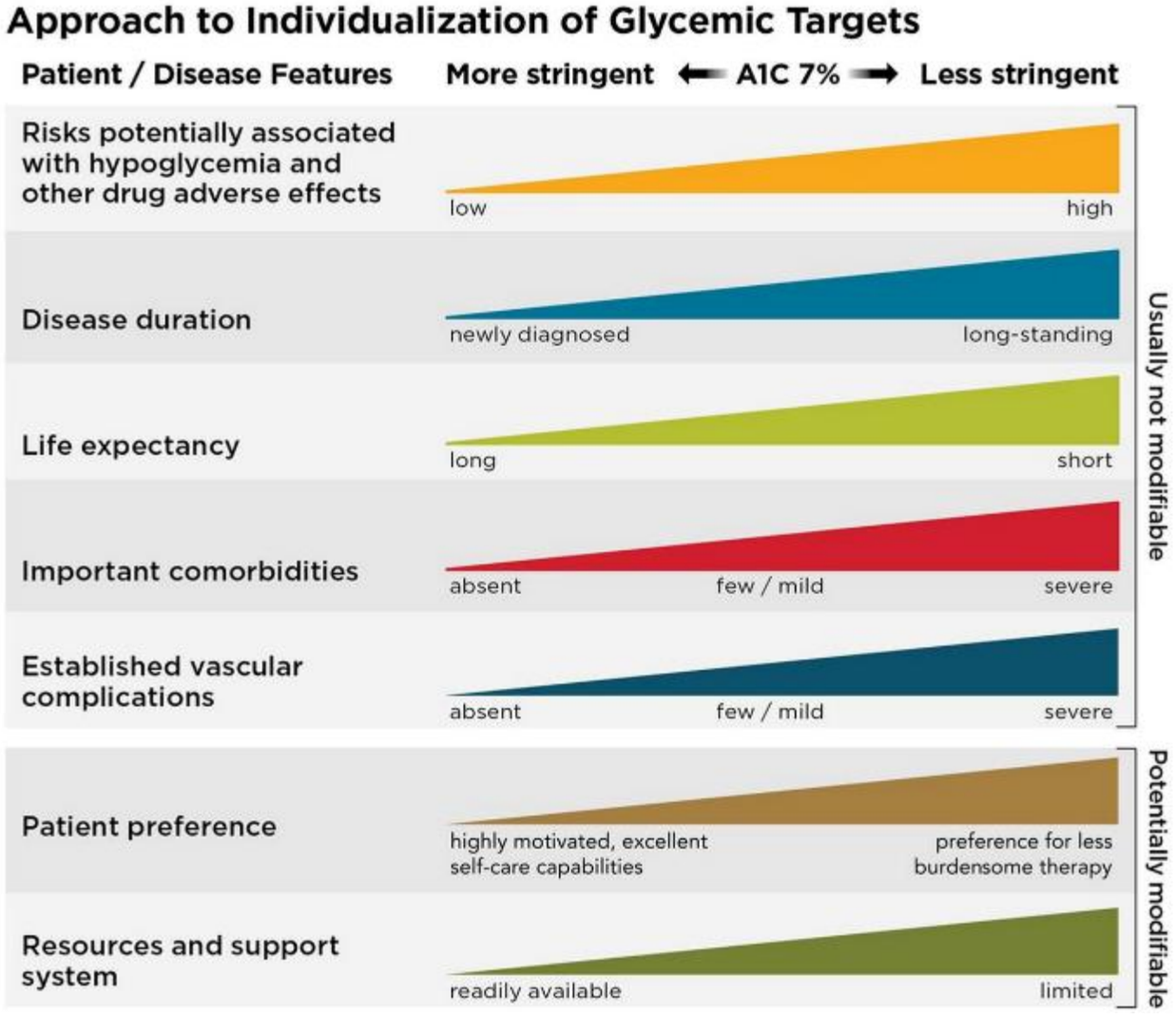
Goal a1C < 7.0% without significant hypoglycemia

Glucose goals:

- Premeal 80 to <130 mg/dL
- Postmeal <180 mg/dL
- HS 100-140 mg/dL

Individualization of goals:

- Tighter targets (6.0 - 6.5%) - younger, healthier
- Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.



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Diabetes Care 2021 Jan; 44(Supplement 1): S73-S84.

Key points included in standard ambulatory glucose profile (AGP) report

AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

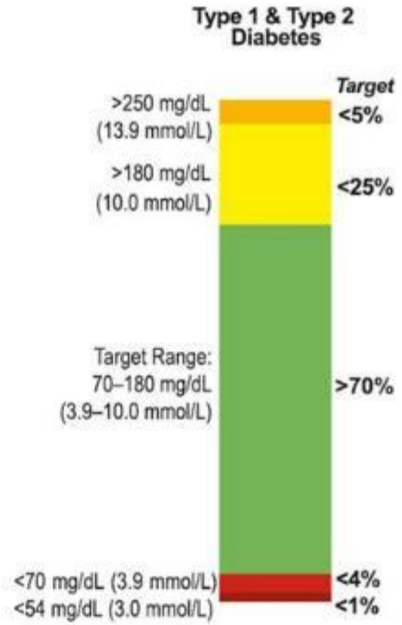
	14 days % Sensor Time
Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose
Glucose Management Indicator (GMI)
Glucose Variability

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES



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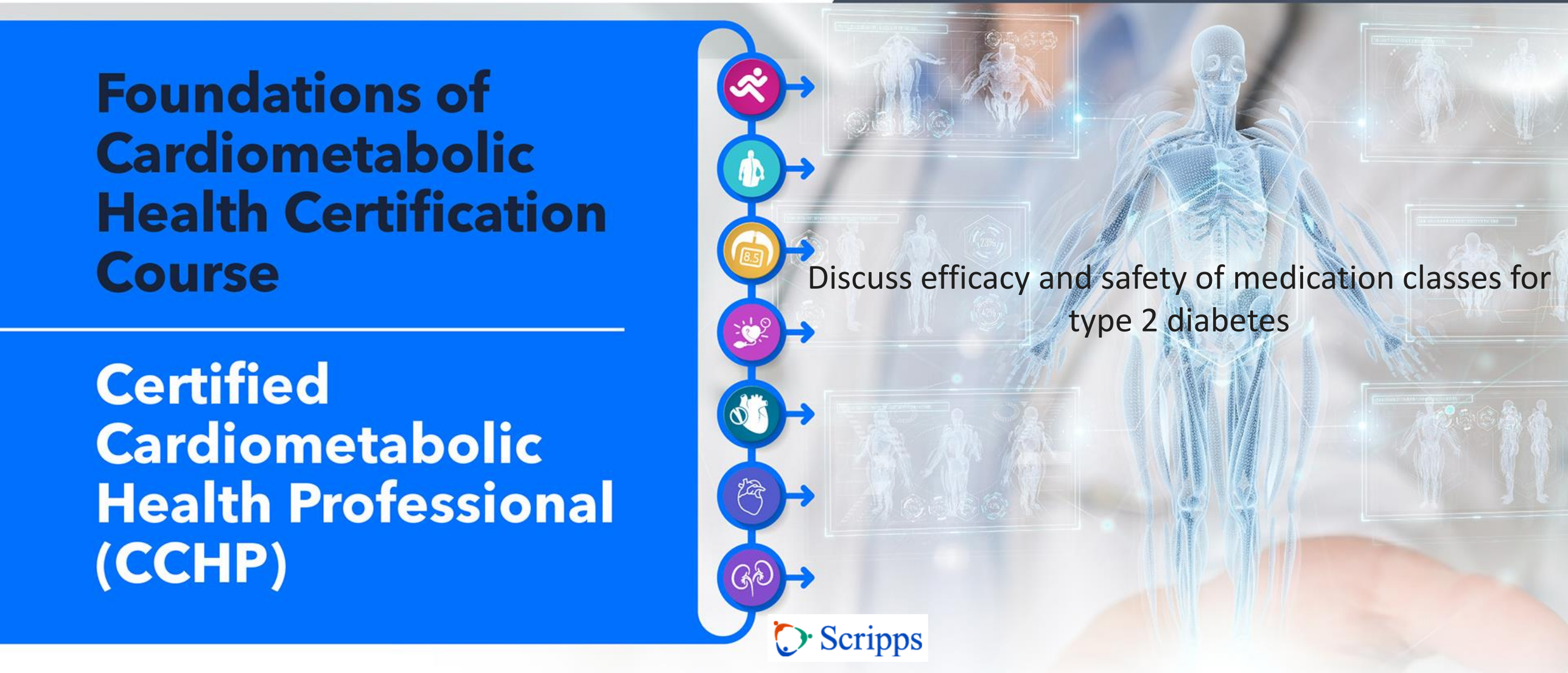

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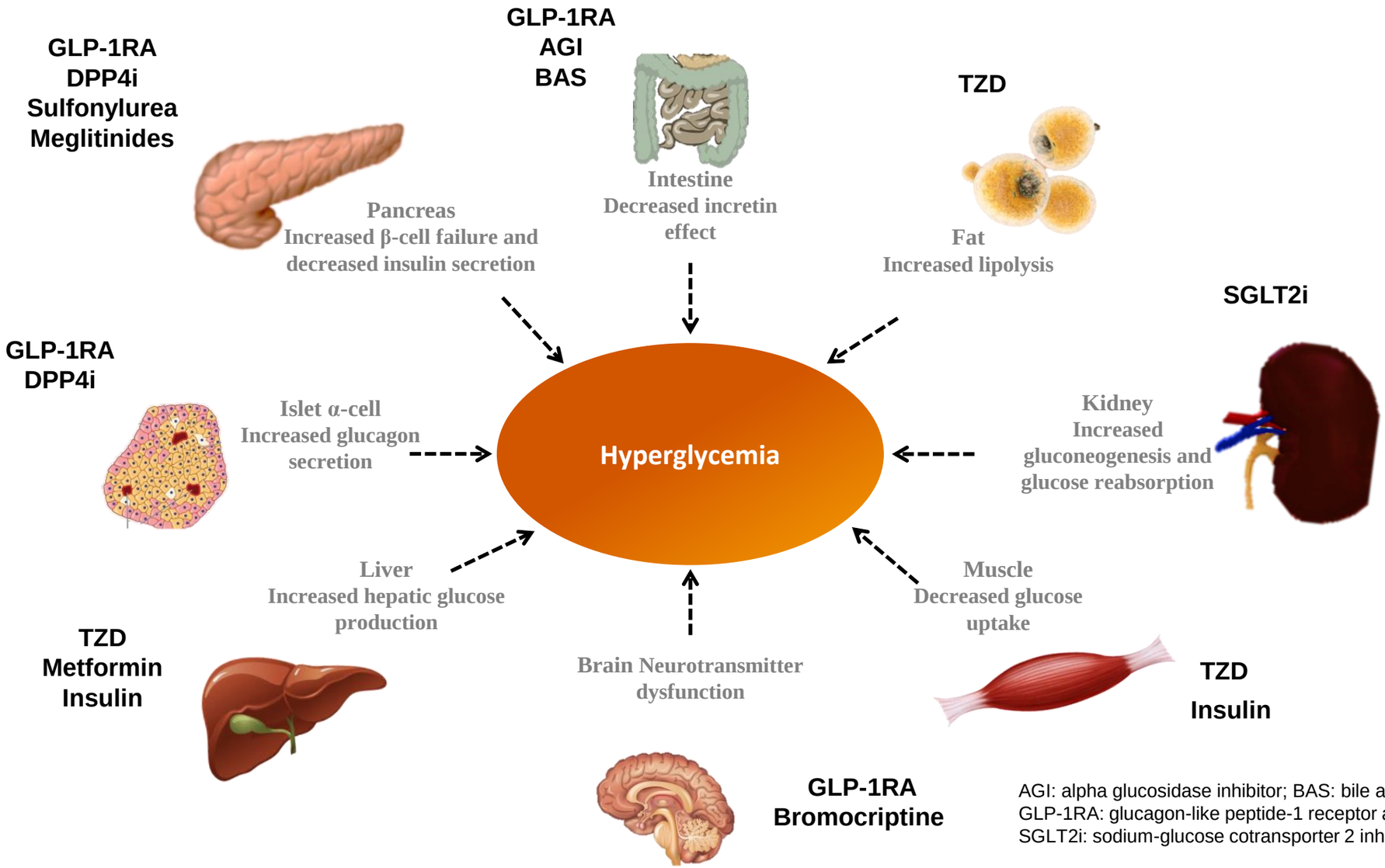
T2DM: Pathophysiologic Defects & Drug Targets



AGI: alpha glucosidase inhibitor; BAS: bile acid sequestrant;
GLP-1RA: glucagon-like peptide-1 receptor agonist;
SGLT2i: sodium-glucose cotransporter 2 inhibitor; TZD: thiazolidinediones.

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Adapted from DeFronzo RA et al. *Diabetes Care*. 2013;36(2):S127-S138.
Inzucchi SE et al. *Diabetes Care.* 2015;38(1):141-149.

Medication Classes for Management of T2DM

	Efficacy	Hypo-glycemia	Weight change	CV effects		Cost	Oral/ SQ	Renal effects		Additional Considerations
				ASCVD	HF			DKD Progression	Dosing/use considerations*	
Metformin	High	No	Neutral	Potential Benefit	Neutral	Low	Oral	Neutral	Contradiction with eGFR <30 ml/min/1.73 m^2	• GI side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Inter-mediate	No	Loss	Benefi: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	High	Oral	Benefit: empagliflozin, canagliflozin, dapagliflozin	Renal dose adjustment required (canaglifozin, dapaglifozin, empaglifozin, ertugliflozin	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk (all agents, rare in T2D) • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL-C • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide qw, lixisenatide Benefit: dulaglutide, liraglutide, semaglutide	Neutral	High	SQ; Oral (semaglutide)	Benefits on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	• Exenatide, lixisenatide: avoid for eGFR <30 ml/min/1.73 m^2 • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when starting or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe GI reactions when starting or increasing dosage.	• **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide ER, semaglutide)** • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Inter-mediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommend in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive HF **(pioglitazone, rosiglitazone)** • Fluid retention (edema, HF) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL-C (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – **Human insulin**	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – **Analogs**						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information.

American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Metformin

- Suppresses hepatic glucose production
- Improves insulin sensitivity by increasing peripheral glucose uptake and utilization

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Metformin

Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost
			ASCVD	HF	
High **A1c reduction 1-2%**	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low

Oral/SQ	Renal Effects		Additional Considerations
	Progression of DKD	Dosing/Use Considerations	
Oral	Neutral	Contraindicated with eGFR<30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency

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Adapted from American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Use of Metformin based on eGFR

eGFR level (mL/min per 1.73 m^2)	Action
≥ 60	No renal contradiction to metformin; monitor renal function annually
< 60 and ≥45	Continue use; increase monitoring of renal function (every 3-6 months)
<45 and ≥ 30	Prescribe metformin with caution; use lower dose (e.g. 50% or half-maximal dose); closely monitor renal function (every 3 months); Do not start new patients on metformin
<30	Stop metformin

Based on recommendations from National Institute for Health and Clinical Excellence Guidelines United Kingdom, Canadian Diabetes Association and Australian Diabetes Society.
http://www.kidney.org/professionals/KDOQI/guideline_diabetes/guide2.htm. http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf.
http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di19-diabetes-blood-glucosecontrol.pdf.

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Lipska et al. Diabetes Care 34: 1431, 2011

Medication Classes for Management of T2DM

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Thiazolidinediones	High	No	Gain	Potential benefit pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommend in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive HF **(pioglitazone, rosiglitazone)** • Fluid retention (edema, HF) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL-C (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide)
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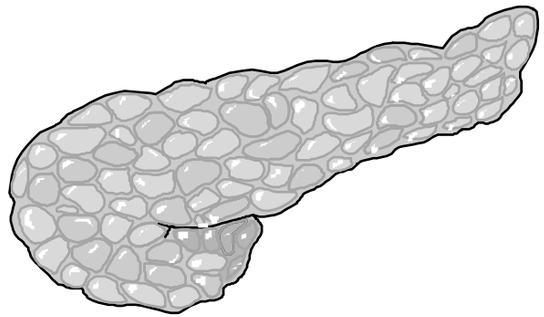
Insulin **Analogs**						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information.

American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Sulfonylureas

- Increase endogenous insulin secretion from pancreatic beta cells
- Glyburide, glipizide and glimepiride (2nd generation)



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Sulfonylureas (2nd Generation)

Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost
			ASCVD	HF	
High **A1c reduction 1-2%**	**Yes**	**Gain**	Neutral	Neutral	Low

Oral/SQ	Renal Effects		Additional Considerations
	Progression of DKD	Dosing/Use Considerations	
Oral	Neutral	• Glyburide not recommended • Glipizide and glimepiride: Initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)

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Medication Classes for Management of T2DM

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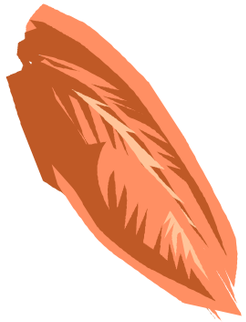
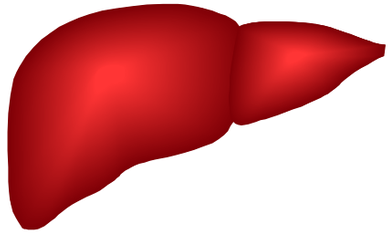
Thiazolidinediones (TZDs)

- Decrease insulin resistance in muscle, liver, and adipose cells by activating nuclear receptors (PPARγ)
- **Pioglitazone & Rosiglitazone**





Thiazolidinediones (TZDs)

Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost
			ASCVD	HF	
High A1c reduction 1.5%	No	Gain	Potential Benefit: pioglitazone	Increased risk	Low

Oral/SQ	Renal Effects		Additional Considerations
	Progression of DKD	Dosing/Use Considerations	
Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure (pioglitazone, rosiglitazone) • Fluid retention (edema, heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑ LDL cholesterol (rosiglitazone)

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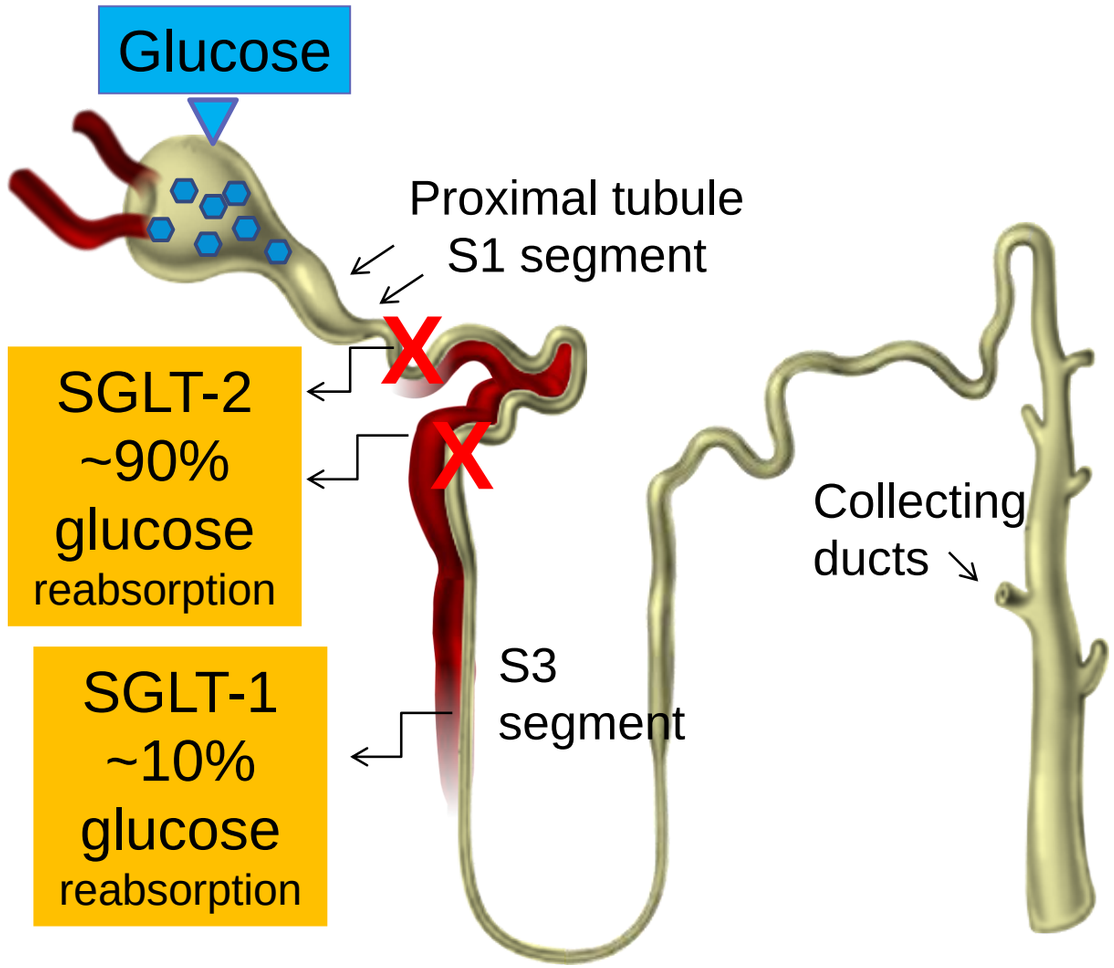
Thiazolidinediones	High	No	Gain	Potential benefit pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommend in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive HF **(pioglitazone, rosiglitazone)** • Fluid retention (edema, HF) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL-C (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – **Human insulin**	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – **Analogs**						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information.

American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors

Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin



Scripps

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors

Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost
			ASCVD	HF	
Intermediate A1c reduction 0.6-1%	No	Loss	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin, dapagliflozin	High

Oral/SQ	Renal Effects		Additional Considerations
	Progression of DKD	Dosing/Use Considerations	
Oral	Benefit: canagliflozin, empagliflozin, dapagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin)	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk (all agents, rare in T2DM) • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • ↑ LDL cholesterol • Risk of Fournier's gangrene ~~FDA Black Box~~: ~~risk of amputation (canagliflozin)~~

Scripps

Adapted from American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Medication Classes for Management of T2DM

	Efficacy	Hypo-glycemia	Weight change	CV effects		Cost	Oral/ SQ	Renal effects		Additional Considerations
				ASCVD	HF			DKD Progression	Dosing/use considerations*	
Metformin	High	No	Neutral	Potential Benefit	Neutral	Low	Oral	Neutral	Contradiction with eGFR <30 ml/min/1.73 m^2	• GI side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Inter-mediate	No	Loss	Benefi: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	High	Oral	Benefit: empagliflozin, canagliflozin, dapagliflozin	Renal dose adjustment required (canaglifozin, dapaglifozin, empaglifozin, ertugliflozin	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk (all agents, rare in T2D) • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL-C • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide qw, lixisenatide Benefit: dulaglutide, liraglutide, semaglutide	Neutral	High	SQ; Oral (semaglutide)	Benefits on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	• Exenatide, lixisenatide: avoid for eGFR <30 ml/min/1.73 m^2 • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when starting or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe GI reactions when starting or increasing dosage.	• **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide ER, semaglutide)** • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Inter-mediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommend in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive HF **(pioglitazone, rosiglitazone)** • Fluid retention (edema, HF) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL-C (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – **Human insulin**	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – **Analogs**						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information.

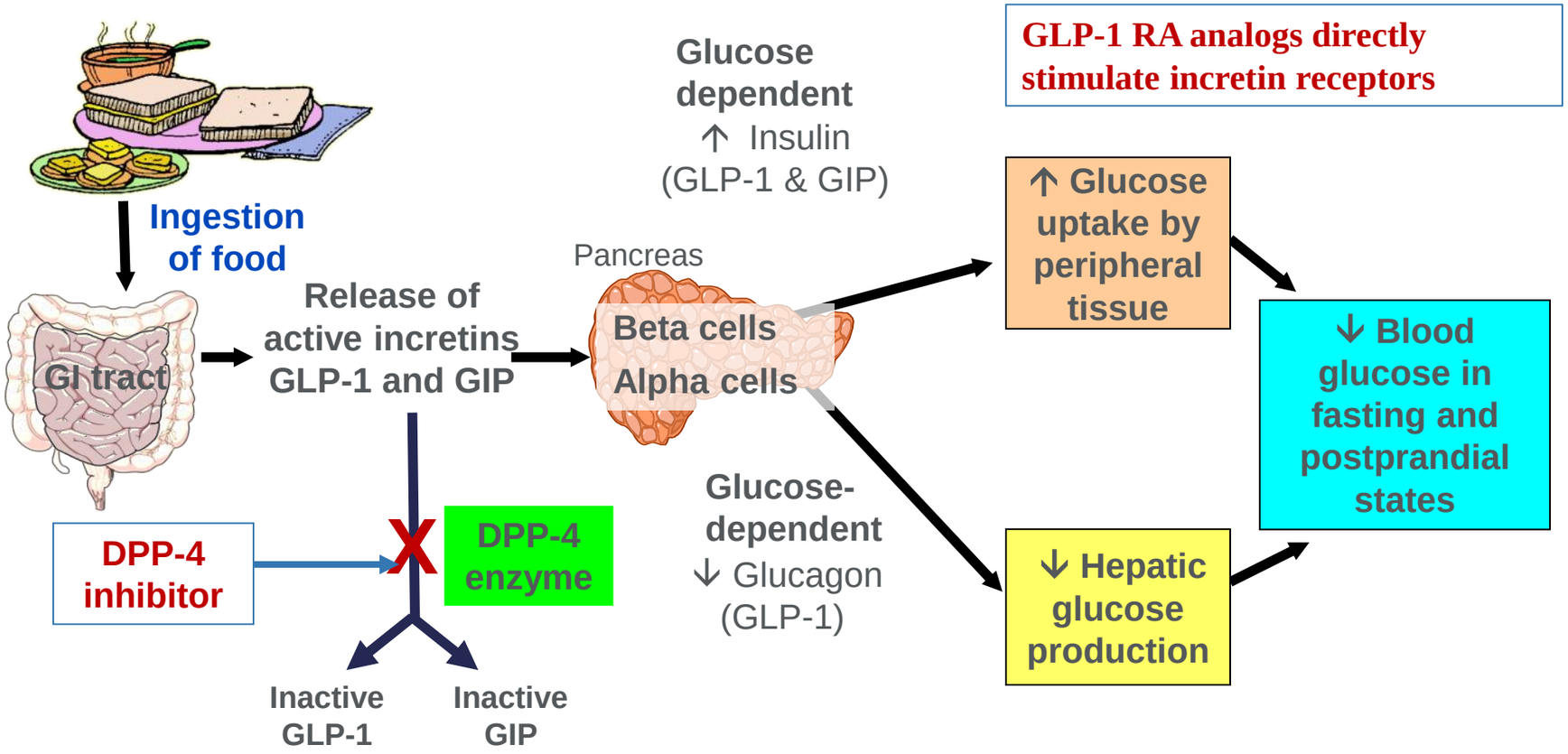
American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Incretins

- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like Peptide-1 (GLP-1) Receptor Agonist analogs

Scripps

Incretins – Mechanism of Action

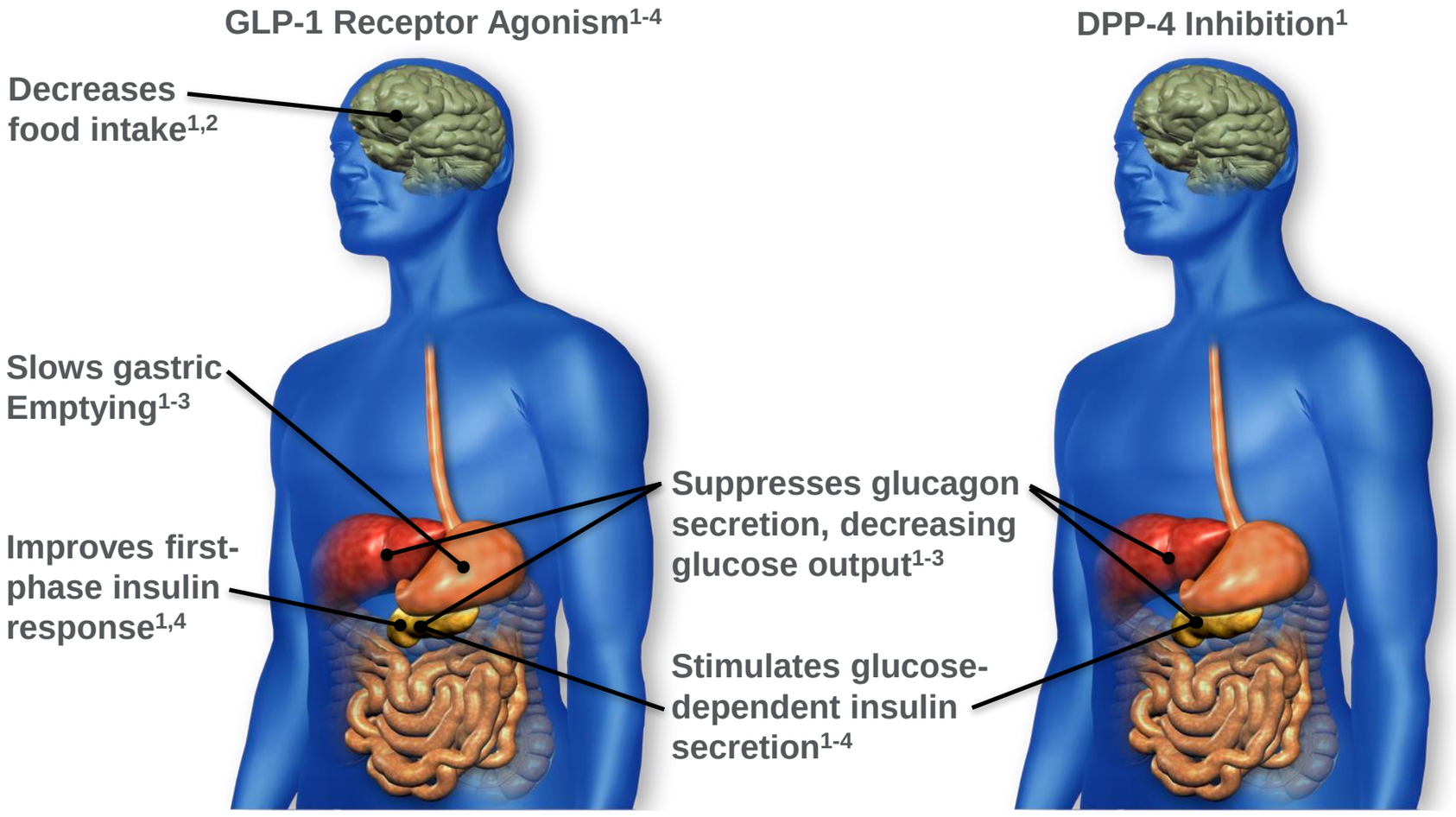


- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal
- Half-lives: GLP-1 ~2 minutes; GIP ~5 minutes.

1. Deacon CF et al. *Diabetes*. 1995;44:1126–1131.
2. Meier JJ et al. *Diabetes*. 2004;53:654–662.

Scripps

GLP-1 RA vs. DPP-4 Inhibitor



1. Stonehouse A, et al. *Curr Diabetes Rev* 2008;4:101-109; 2. Nielsen LL, et al. *Regul Pept* 2004;117:77-88
3. Kolterman OG, et al. *J Clin Endocrinol Metab* 2003;88:3082-3089; 4. Fehse F, et al. *J Clin Endocrinol Metab* 2005;90:5991-5997

DPP-4 Inhibitors

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

- Anagliptin
- Vildagliptin
- Teneligliptin
- Gemigliptin
- Dutogliptin

Scripps

DPP-4 Inhibitors

Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost
			ASCVD	HF	
Intermediate A1c reduction 0.6-0.8%	No	Neutral	Neutral	Potential risk: saxagliptin	High

Oral/SQ	Renal Effects		Additional Considerations
	Progression of DKD	Dosing/Use Considerations	
Oral	Neutral	• Can be used in renal impairment. • Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); no dose adjustment for linagliptin	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain

Scripps

Adapted from American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

GLP-1 Receptor Agonists

Exenatide bid	Introduced 2005
Liraglutide daily	2010
Exenatide weekly LAR	2012
~~Albiglutide weekly~~	~~2014~~
Dulaglutide weekly	2014
Lixisenatide daily	2017
Semaglutide weekly	2017
Semaglutide oral	2019

Scripps

GLP-1 Receptor Agonists

Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost
			ASCVD	HF	
High (A1c reduction 1-1.5%)	No	Loss	Neutral: lixisenatide, weekly exenatide Benefit: dulaglutide, liraglutide, semaglutide	Neutral	High

Oral/SQ	Renal Effects		Additional Considerations
	Progression of DKD	Dosing/Use Considerations	
SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	• Exenatide, lixisenatide: avoid if GFR<30 • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, dehydration	• **FDA Black Box:** Risk of thyroid C-cell tumors in rodents (liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide); human relevance not determined • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality not established. Discontinue if pancreatitis is suspected.

Scripps

Adapted from American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Medication Classes for Management of T2DM

	Efficacy	Hypo-glycemia	Weight change	CV effects		Cost	Oral/ SQ	Renal effects		Additional Considerations
				ASCVD	HF			DKD Progression	Dosing/use considerations*	
Metformin	High	No	Neutral	Potential Benefit	Neutral	Low	Oral	Neutral	Contradiction with eGFR <30 ml/min/1.73 m^2	• GI side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Inter-mediate	No	Loss	Benefi: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	High	Oral	Benefit: empagliflozin, canagliflozin, dapagliflozin	Renal dose adjustment required (canaglifozin, dapaglifozin, empaglifozin, ertugliflozin	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk (all agents, rare in T2D) • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL-C • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide qw, lixisenatide Benefit: dulaglutide, liraglutide, semaglutide	Neutral	High	SQ; Oral (semaglutide)	Benefits on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	• Exenatide, lixisenatide: avoid for eGFR <30 ml/min/1.73 m^2 • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when starting or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe GI reactions when starting or increasing dosage.	• **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide ER, semaglutide)** • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
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Insulin – **Human insulin**	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – **Analogs**						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information.

American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Insulin

Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost	
			ASCVD	HF		
Highest	Yes	Gain	Neutral	Neutral	Human insulin	Low (SQ)
					Analogs	High

Oral/SQ		Renal Effects		Additional Considerations
		Progression of DKD	Dosing/Use Considerations	
Human insulin	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Analogs	SQ			

Scripps

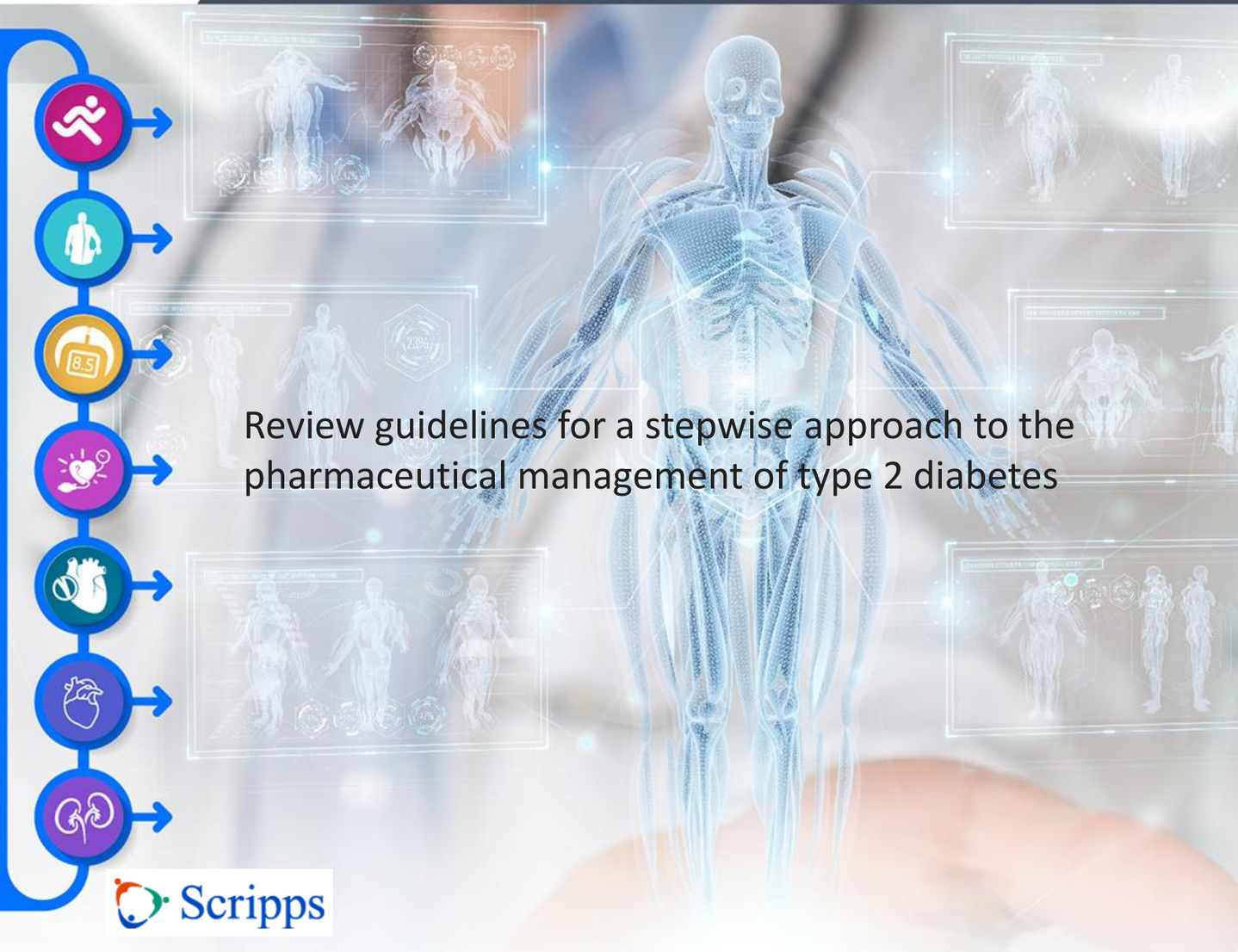
Adapted from American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)



Review guidelines for a stepwise approach to the pharmaceutical management of type 2 diabetes

Scripps

Goals

1. Review diabetes goals of therapy and glycemic targets
2. Discuss efficacy and safety of medication classes for type 2 diabetes
3. Review guidelines for a stepwise approach to the pharmaceutical management of type 2 diabetes
4. Understand how to select therapy for patients with type 2 diabetes and comorbidities such as ASCVD, HF, or CKD
5. To provide case examples of uses in under-resourced populations in terms of access and implementation.
6. To describe technology currently offered in the ambulatory and hospital settings for management of type 2 diabetes

Scripps

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6. To describe technology currently offered in the ambulatory and hospital settings for management of type 2 diabetes

Scripps

Patient-Centered Approach: Individualized Care

- Individualized A1C target and glucose goals
- Comorbidities: ASCVD, HF, CKD
- Impact on hypoglycemia and weight
- Side effect profile of medication
- Financial concerns
- Complexity of treatment regimen
- Other: mental status, self-care, home support, language/cultural considerations
- Patient preferences and goals

American Diabetes Association Diabetes Care 2021;44:S40-S52

Pharmacologic Approaches in T2D - 2021

FIRST LINE THERAPY IS METFORMIN

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 yrs with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1]

If A1C is above target

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

↓

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD & Albuminuria[8]

NO

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2 with evidence of reducing CKD progression in CVOTs[5,6,8]

OR

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated

For patients w/ T2D and CKD (eGFR <60 mL/min/1.73m^2) & thus at increased risk of CV events

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i	GLP-1 RA	SGLT2i	TZD
If A1C is above the target			
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C is above the target

Continue with addition of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] **EITHER /OR** SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

Assess for indicators of high-risk or established ASCVD, CKD, or HF

NO

If A1C Above Individualized Target Proceed as Below

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 yrs with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1]

If A1C is above target

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD & Albuminuria[8]

NO

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2 with evidence of reducing CKD progression in CVOTs[5,6,8]

OR

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated

For patients w/ T2D and CKD (eGFR <60 mL/min/1.73m^2) & thus at increased risk of CV events

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

Compelling Need to Minimize Hypoglycemia

DPP-4i	GLP-1 RA	SGLT2i	TZD
If A1C is above the target			
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **OR** GLP-1 RA
If A1C is above the target			

Continue with addition of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] **EITHER /OR** SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] TZD[2] Basal insulin

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider independently of baseline A1c, individualized A1c target, or Metformin use

If A1C Above Individualized Target Proceed as Below

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 yrs with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1]

If A1C is above target

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

DKD & Albuminuria[8]

NO

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2 with evidence of reducing CKD progression in CVOTs[5,6,8]

OR

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated

For patients w/ T2D and CKD (eGFR <60 mL/min/1.73m^2) & thus at increased risk of CV events

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

pelling Need to Minimize Hypoglycemia

-4i | GLP-1 RA | SGLT2i | TZD

If A1C is above the target

SGLT2i	SGLT2i	GLP-1 RA	SGLT2i
OR	**OR**	**OR**	**OR**
TZD	TZD	DPP-4i	DPP-4i
		OR	**OR**
		TZD	GLP-1 RA

If A1C is above the target

Continue with addition of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
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GLP-1 RA with good efficacy for weight loss[10] **EITHER /OR** SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

ASCVD or Indicators of High Risk
-Age ≥ 55 with coronary, carotid, or lower-extremity artery stenosis >50%
-LVH

HF

CKD

Particularly LV EF<45%

OR
SGLT2 with evidence of reducing CKD progression in CVOTs[5,6,8]

OR
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GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i | GLP-1 RA | SGLT2i | TZD

If A1C is above the target

SGLT2i **OR** TZD | SGLT2i **OR** TZD | GLP-1 RA **OR** DPP-4i **OR** TZD | SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C is above the target

Continue with addition of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:
- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] **EITHER /OR** SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

ASCVD or Indicators of High Risk

- Established ASCVD
- Indicators of high

either/or

GLP-1 RA with proven CVD benefit

Liraglutide
Semaglutide
Dulaglutide

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

+CKD

Partic… (LVEF …

& Albuminuria[8]

NO

SGLT2i with proven CVD benefit

SGLT2 with evidence of r… prog… [5,6,8]

OR

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated

Empagliflozin
Canagliflozin

For patients w/ T2D and CKD (eGFR <60 mL/min/1.73m^2) & thus at increased risk of CV events

GLP-1 RA with proven CVD benefit[1] — EITHER /OR — SGLT2i with proven CVD benefit[1,7]

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i | GLP-1 RA | SGLT2i | TZD

If A1C is above the target

T2i … D | GLP-1 RA **OR** DPP-4i **OR** TZD | SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C is above the target

…of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] — EITHER /OR — SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 yrs with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1]

If A1C is above target

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

HF

Particularly LV EF<45%

SGLT2i with proven benefit in this population

Empagliflozin
Dapagliflozin
Canagliflozin

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

+CKD

DKD & Albuminuria[8]

NO

OR

SGLT2 with evidence

tolerated or

at increased risk of CV events

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i | GLP-1 RA | SGLT2i | TZD

If A1C is above the target

SGLT2i	SGLT2i	GLP-1 RA	SGLT2i
OR	**OR**	**OR**	**OR**
TZD	TZD	DPP-4i	DPP-4i
		OR	**OR**
		TZD	GLP-1 RA

If A1C is above the target

Continue with addition of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] **EITHER /OR** SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

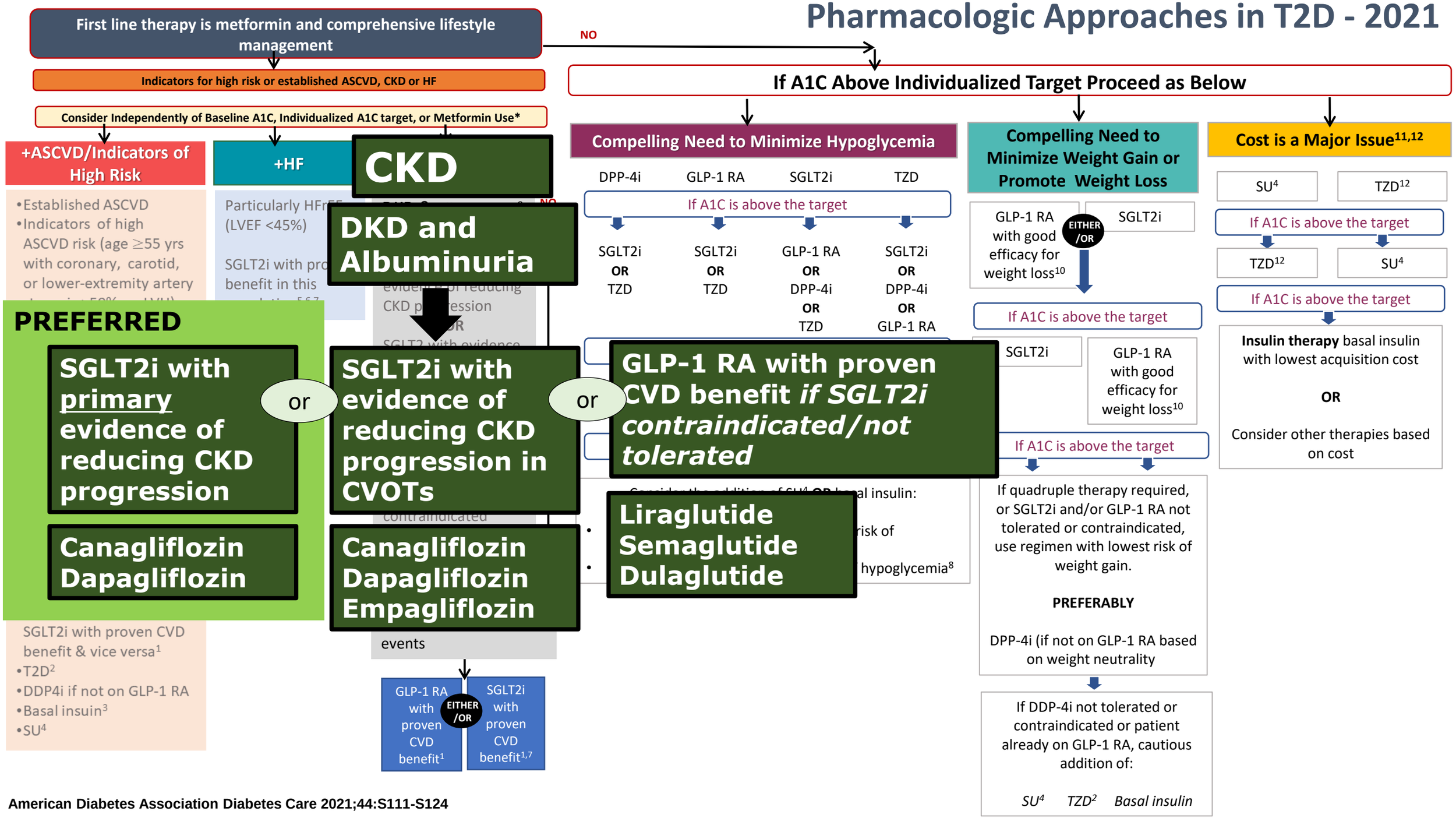
Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

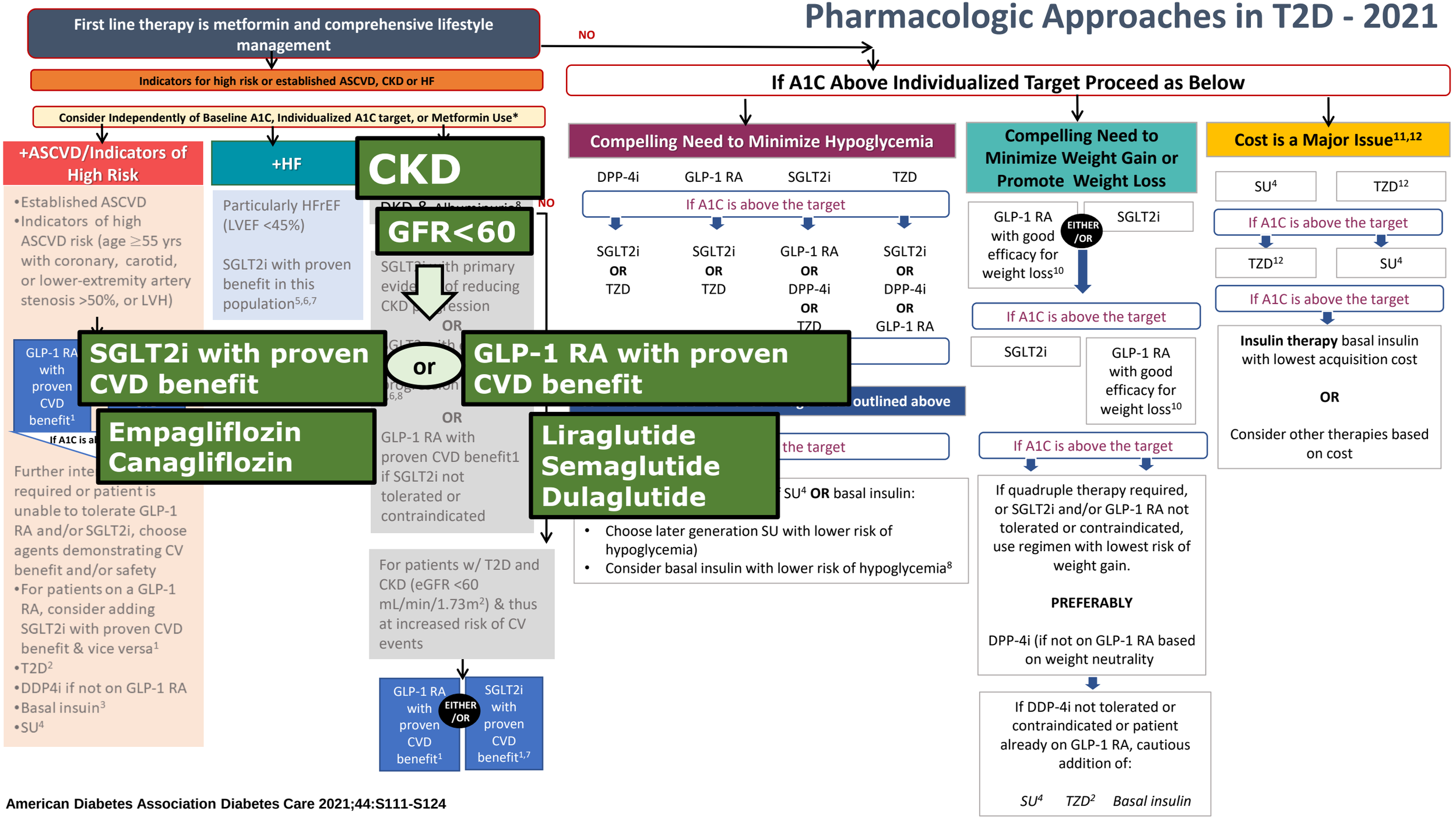
American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021



American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021



American Diabetes Association Diabetes Care 2021;44:S111-S124

Cardiovascular Outcome Trials – Historical Perspective

Pre-2008
Anti-DM Meds focused on glycemic control

→ Some DM drugs lowered glucose but increased CV adverse events (e.g. TZD)

→ **2012**
FDA: New DM Meds must not be associated with adverse CV events

DPP-4 i
SGLT- 2 i
GLP-1 RA

→ Prospective CV Outcome Trials (CVOTs)

→ Three-Point Major Adverse CV events:
1. CV Death
2. Non-fatal Stroke
3. Non-fatal Myocardial Infarction

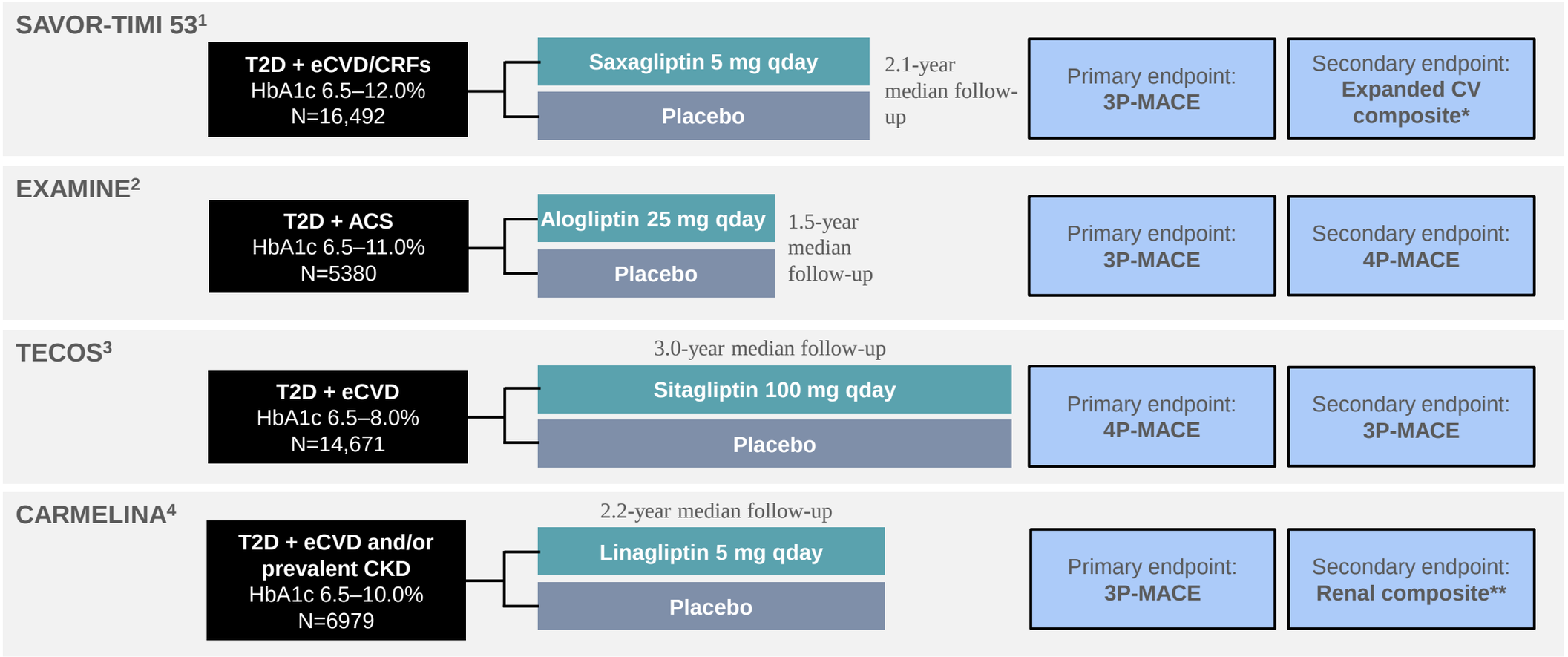
→ Trials including more persons with DM and CV disease

→ CV Non-inferiority or **BENEFIT** in secondary prevention of CV outcomes

Scripps

Rehman SU *et al. Cureus*, *12*(8), e9655.

Completed DPP-4i CVOTs (vs placebo)



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

* 3P-MACE, HHF, coronary revascularization, hospitalization for unstable angina

**sustained eGFR decrease ≥40%, progression to sustained ESKD, death due to kidney disease

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327; 3. Green JB *et al. N Engl J Med* 2015;373:232; 4. Rosenstock J *et al. JAMA* 2019;321:69

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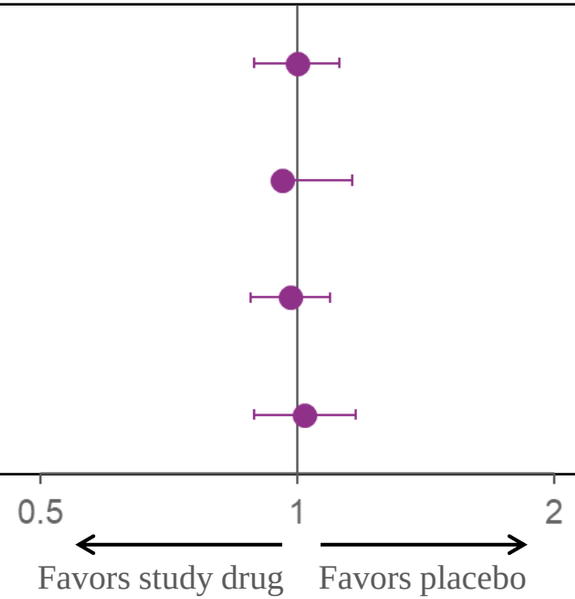
Primary endpoint in completed DPP-4i CVOTs (vs placebo)

DPP-4 inhibitor CVOTs reported to date met the FDA-mandated criteria for demonstrating CV safety

	Study drug	Placebo	HR (95% CI)	*p*-value*
	n with event/N analysed (%)			
SAVOR-TIMI 53[1] (saxagliptin)	613/8280 (7.3)	609/8212 (7.2)	1.00 (0.89, 1.12)	0.99
EXAMINE[2] (alogliptin)	305/2701 (11.3)	316/2679 (11.8)	0.96 (≤1.16)	0.32
TECOS[3] (sitagliptin)	695/7257 (9.6)	695/7266 (9.6)	0.98 (0.88, 1.09)	0.65
CARMELINA[4] (linagliptin)	434/3494 (12.4)	420/3485 (12.1)	1.02 (0.89, 1.17)	0.74



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology
*p-value for superiority; †Upper boundary of one-sided repeated CI. CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Scirica BM et al. N Engl J Med 2013;369:1317; 2. White WB et al. N Engl J Med 2013;369:1327; 3. Green JB et al. N Engl J Med 2015;373;232; 4. Rosenstock J et al. JAMA 2019;321:69

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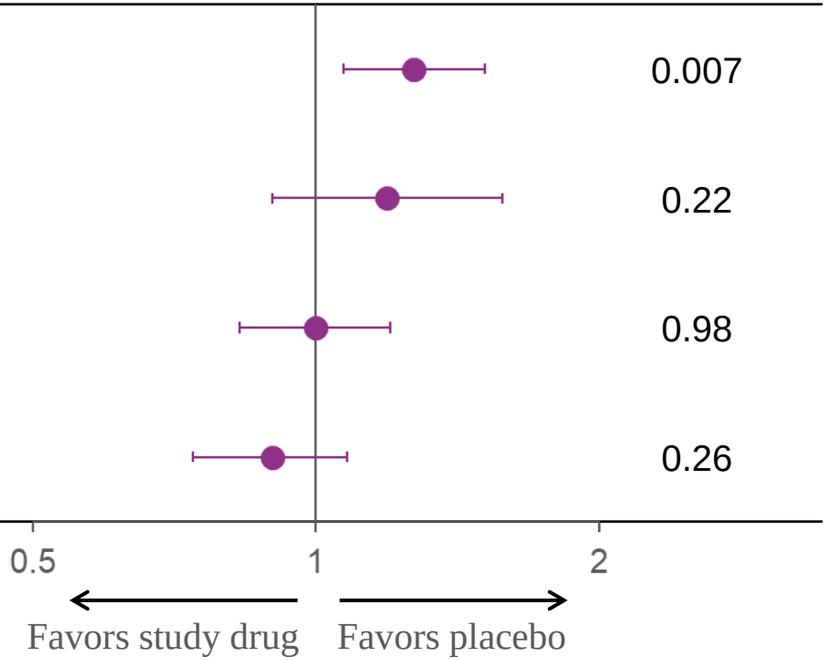
Hospitalization for HF in completed DPP-4i CVOTs (vs placebo)

Saxagliptin was associated with a significantly increased risk of hospitalization for heart failure

	Study drug	Placebo	HR (95% CI)	*p*-value
	n with event/N analysed (%)			
SAVOR-TIMI 53*[1] (saxagliptin)	289/8280 (3.5)	228/8212 (2.8)	1.27 (1.07, 1.51)	0.007
EXAMINE*[2] (alogliptin)	106/2701 (3.9)	89/2679 (3.3)	1.19 (0.90, 1.58)	0.22
TECOS†[3] (sitagliptin)	228/7332 (3.1)	229/7339 (3.1)	1.00 (0.83, 1.20)	0.98
CARMELINA[4] (linagliptin)	209/3494 (6.0)	226/3485 (6.5)	0.90 (0.74, 1.08)	0.26



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

*According to an FDA safety review, saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. A warning has been added to the labels of these drugs[5]; †Heart failure risk was not assessed at the time of the trial

CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. Zannad F *et al. Lancet* 2015;385:2067; 3. Green JB *et al. N Engl J Med* 2015;73:232; 4. Rosenstock J *et al. JAMA* 2019;321:69; 5. FDA Drug Safety Communication. Feb 2014. https://www.fda.gov/drugs/drugsafety/ucm486096.htm (accessed Mar 2019)

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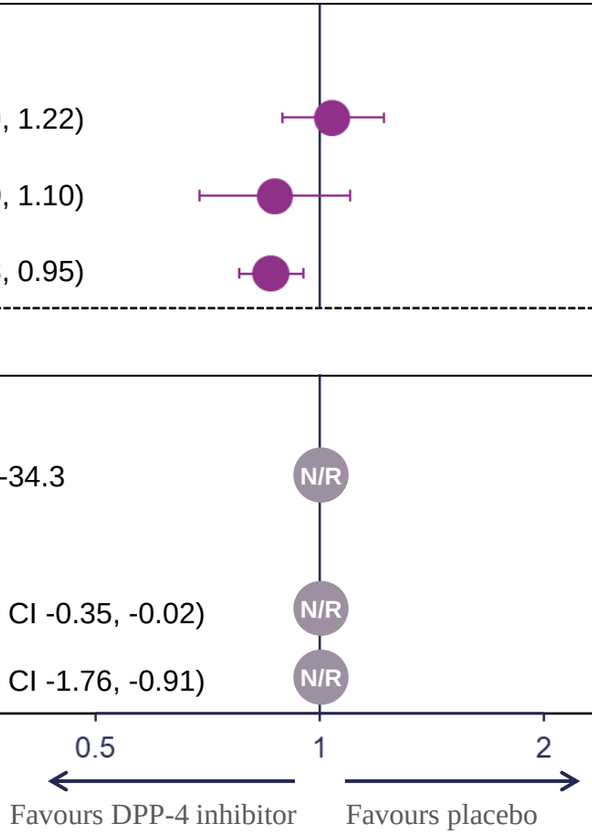
Prespecified kidney endpoints from DPP-4i CVOTs (vs placebo)

Prespecified adjudicated kidney endpoints	DPP-4 inhibitor: Linagliptin	Placebo	HR (95% CI)	*p*-value
CARMELINA[1] (linagliptin)				
Sustained ESKD, sustained ≥40% eGFR decrease from baseline or death due to kidney disease	327/3494	306/3485	1.04 (0.89, 1.22)	0.62
Sustained ESKD or death due to kidney disease	136/3494	154/3485	0.87 (0.69, 1.10)	0.24
Albuminuria progression	763/2162	819/2129	0.86 (0.78, 0.95)	0.003
Other prespecified exploratory kidney endpoints				
SAVOR-TIMI 53[2] (saxagliptin)				
UACR (mg/g)	Mean treatment difference at 2 years: -34.3		N/R	0.001
TECOS[3] (sitagliptin)				
UACR (mg/g)	Mean treatment difference at 4 years: -0.18 (95% CI -0.35, -0.02)		N/R	0.031
eGFR (ml/min/1.73 m^2)	Mean treatment difference at 4 years: -1.34 (95% CI -1.76, -0.91)		N/R	<0.0001



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology
See slide notes for abbreviations
1. Rosenstock J et al. JAMA 2019;321:69; 2. Mosenzon O et al. Diabetes Care 2017;40:69; 3. Cornel JH et al. Diabetes Care 2016;39:2304

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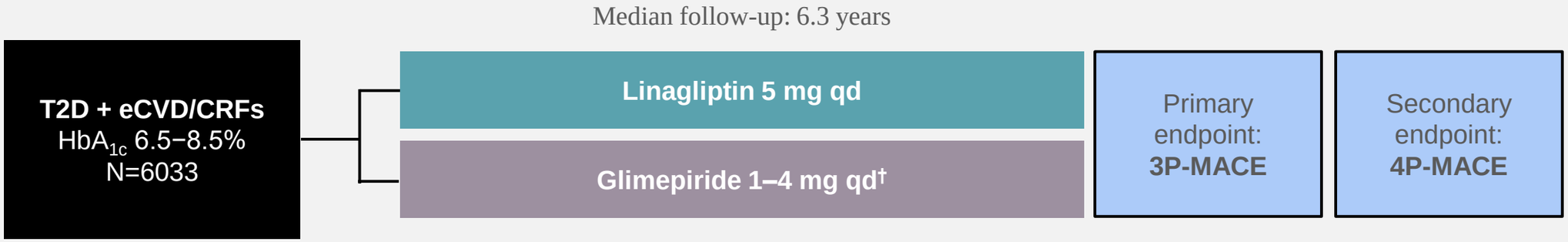
Completed DPP-4 inhibitor CVOT (vs SU)

CAROLINA (active comparator)[1,2]



†Starting dose of 1 mg qday up-titrated to a potential maximum of 4 mg qd every 4 weeks for the first 16 weeks. Visit schedule after this period: 16 weeks. Doses could be up- or down-titrated at any point of the study as required. Patients on previous glimepiride treatment were continued on their current dose if randomised to the glimepiride arm

1. Marx N et al. Diab Vasc Dis Res 2015;12:164; 2. Marx N (June 2019). The CAROLINA Trial – First Results of the Cardiovascular Outcomes Trial Comparing Linagliptin vs Glimepiride. Presented at the 2019 ADA Scientific Sessions. San Francisco, USA.

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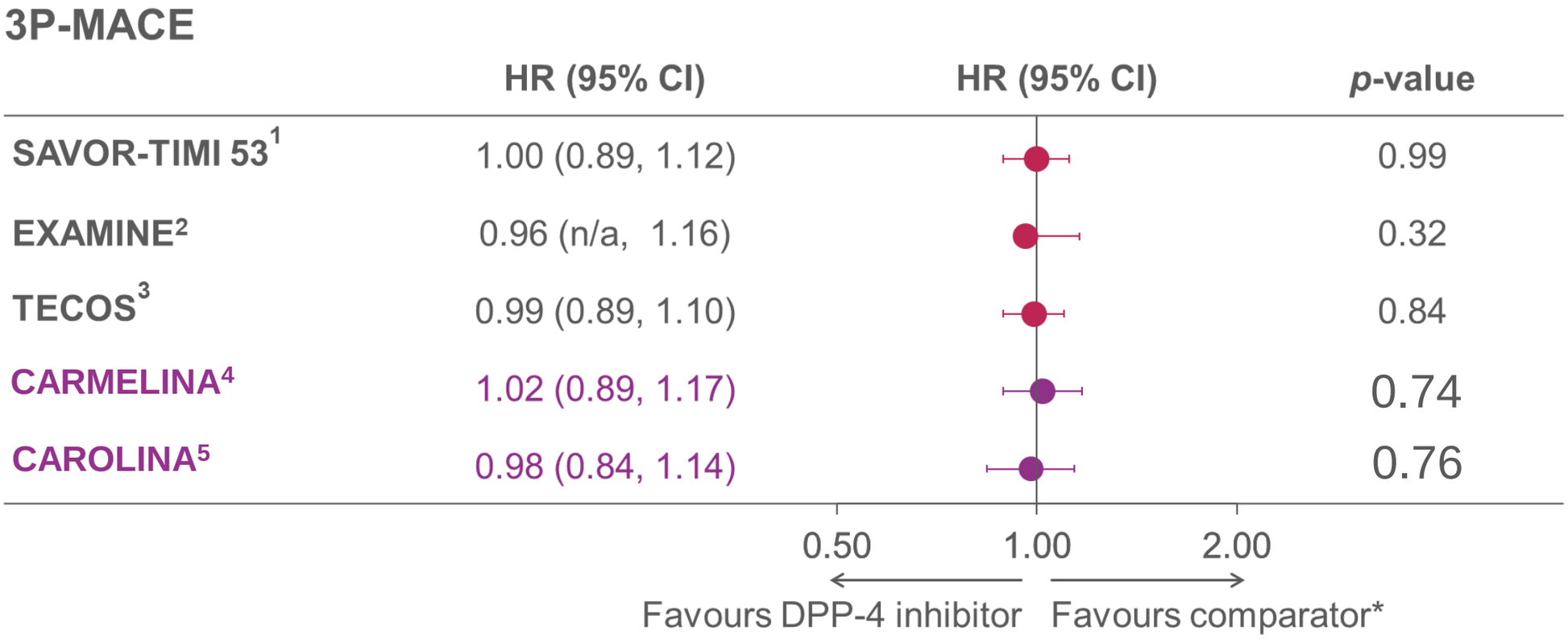
CV safety demonstrated by completed DPP-4i CVOTs



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology
*Comparator was placebo in all CVOTs except CAROLINA (glimepiride)

1. Scirica BM et al. N Engl J Med 2013;369:1317; 2. White WB et al. N Engl J Med 2013;369:1327; 3. Green JB et al. N Engl J Med 2015;373:232;
4. Rosenstock J et al. JAMA 2019;321:69; 5. Rosenstock J et al. ADA 2019

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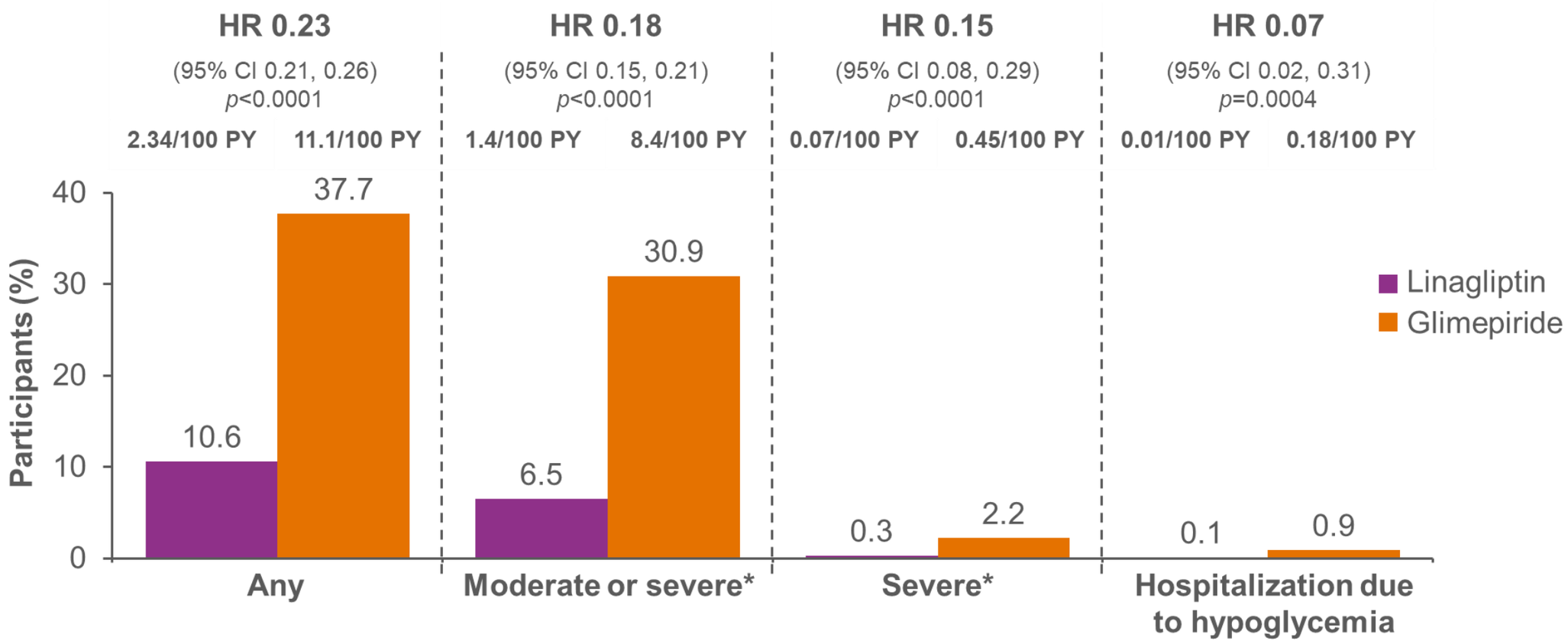
Lower risk of hypoglycemia with linagliptin vs glimepiride



Marx N (June 2019). The CAROLINA Trial – First Results of the Cardiovascular Outcomes Trial Comparing Linagliptin vs Glimepiride. Presented at the 2019 ADA Scientific Sessions. San Francisco, USA.

DPP-4 inhibitor CVOTs: summary

Primary outcome

All DPP-4 inhibitor CVOTs reported to date were non-inferior to comparator (placebo or SU) for the primary endpoint (3P-MACE or 4P-MACE)[1–4]

Other CV endpoints

Saxagliptin was associated with an increased risk of HHF[1]

Microvascular outcomes

CARMELINA is the only DPP-4 inhibitor CVOT with prespecified hard kidney outcomes; no increased risk in the composite kidney endpoints was demonstrated[1–7]

Safety

CVOTs demonstrated no significant difference in the incidence of severe hypoglycaemia between DPP-4 inhibitors and placebo[1–4]

The risk of hypoglycemia was significantly lower with linagliptin compared with glimepiride[8]

Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

1. Scirica BM et al. N Engl J Med 2013;369:1317; 2. White WB et al. N Engl J Med 2013;369:1327; 3. Green JB et al. N Engl J Med 2015;373:232;
4. Rosenstock J et al. JAMA 2019;321:69; 5. Zannad F et al. Lancet 2015;385:2067; 6. Mosenzon O et al. Diabetes Care 2017;40:69;
7. Cornel JH et al. Diabetes Care 2016;39:2304; 8. Rosenstock J et al. ADA 2019

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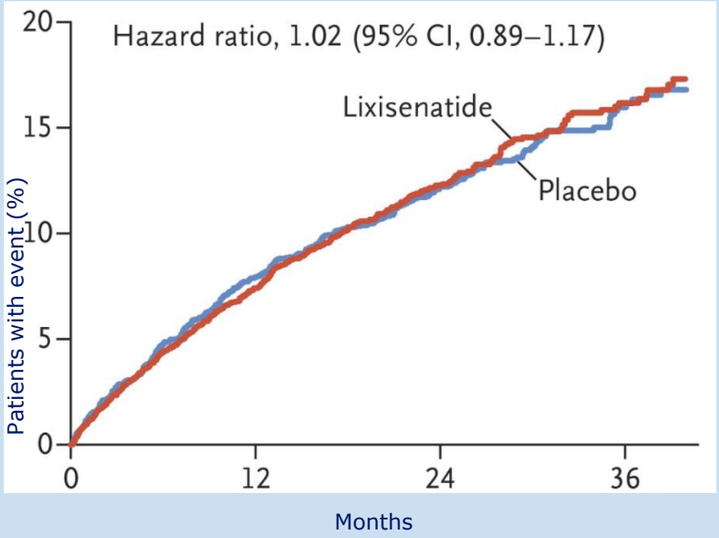
GLP-1 RA - CVOTs showing CV non-inferiority

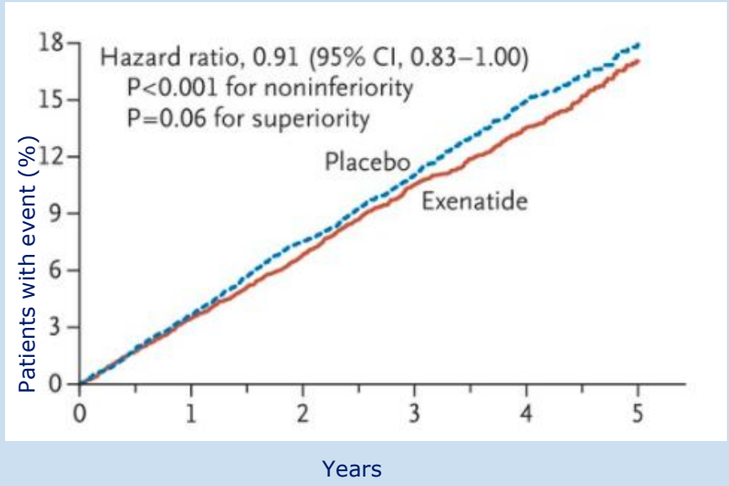
ELIXA[1]

- Lixisenatide was non-inferior to placebo for time to 4-point MACE in T2DM with history of ACS (<180 days)



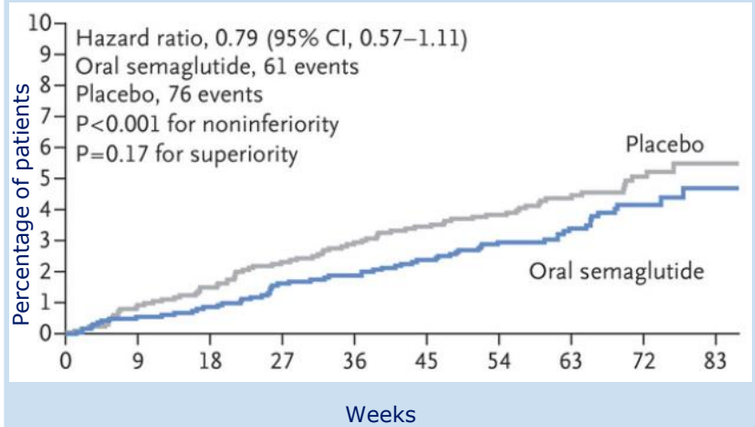
EXSCEL[2]

- Exenatide weekly was non-inferior to placebo for time to 3-point MACE in T2DM with or without preexisting CVD



PIONEER 6[3]

- Semaglutide (oral) was non-inferior to placebo for time to 3-point MACE in T2DM with high CV risk (aged ≥50 years with established CVD or CKD or aged ≥60 years with CV risk)



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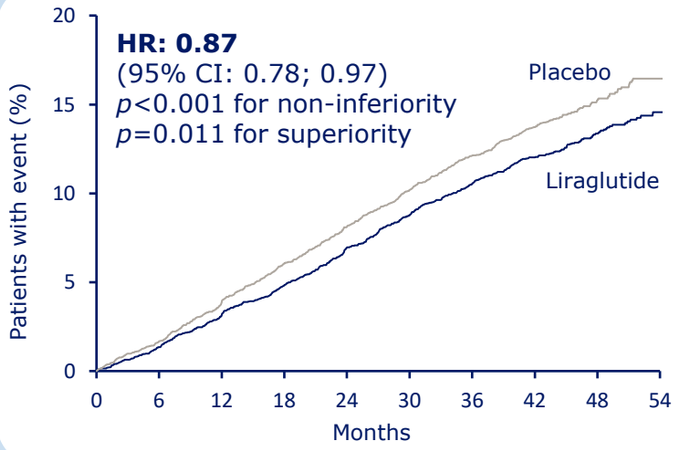
1. Pfeffer M *et al.*, *N Engl J Med* 2015; 373:2247-2257; 2. Holman RR *et al. N Engl J Med* 2017; 377:1228-1239; 3. Husain M *et al.*, *N Engl J Med* 2019; 381:841-851

GLP-1 RA - CVOTs showing CV benefit

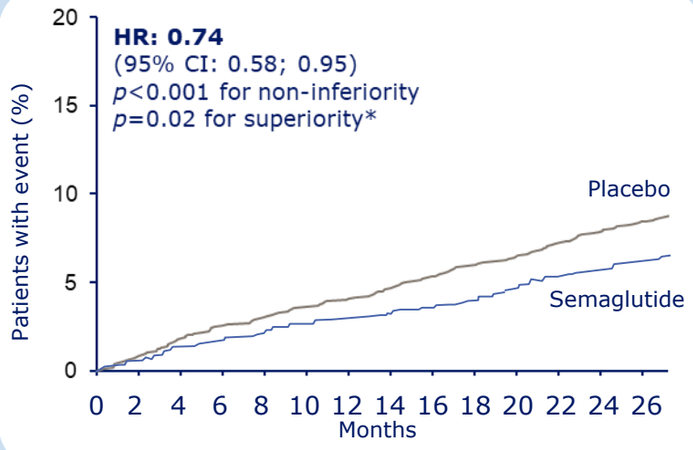
LEADER[1]

- Liraglutide was superior to placebo for time to 3-point MACE in T2D aged ≥50 years with established CVD, CKD, or HF or aged ≥60 years with CV risk



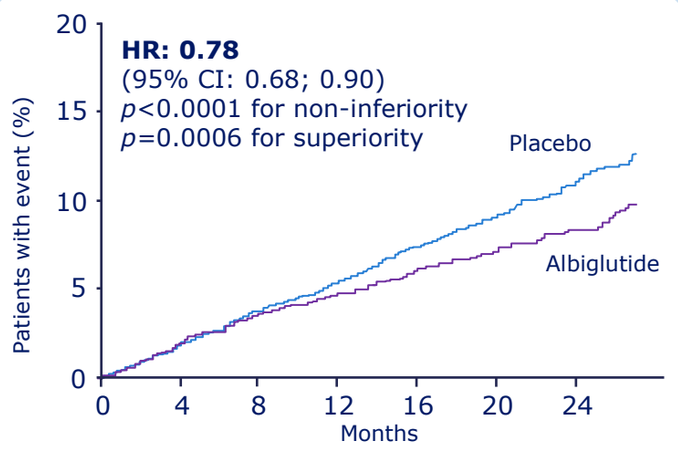
SUSTAIN-6[2]

- Semaglutide (s.c.) superior* to placebo for time to 3-point MACE in T2D aged ≥50 years with established CVD, HF, or CKD or aged ≥60 years with CV risk



HARMONY[3]

- Albiglutide superior to placebo for time to 3-point MACE in T2D aged ≥40 years with established CVD



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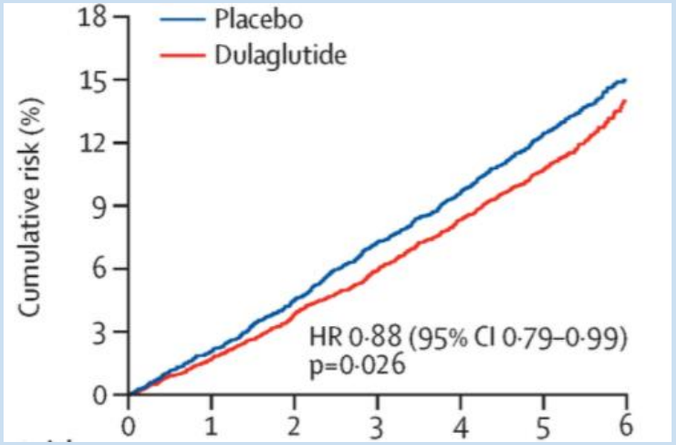
*Not pre-specified. CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular events; T2D, type 2 diabetes

1. Marso SP et al. *N Engl J Med* 2016;375:311–322; 2. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 3. Hernandez AF et al. *Lancet* 2018;392:1519–1529

GLP-1 RA - CVOTs showing CV benefit

REWIND[1]

- Dulaglutide was superior to placebo for time to 3-point MACE in T2DM with prior ASCVD event or ASCVD risk



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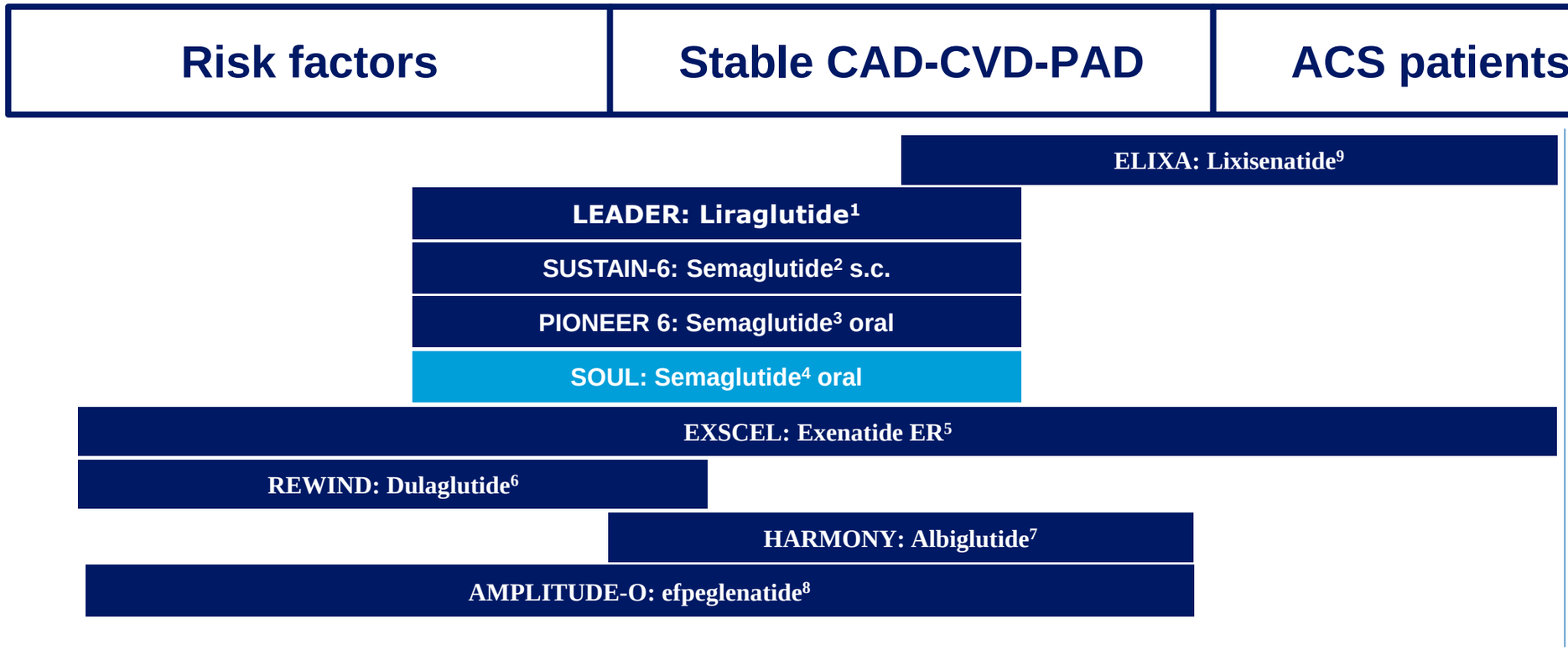
1. Gerstein HC *et al*., *Lancet*. 2019 Jul 13;394(10193): 121-130.

CVOTs assessing CV safety of GLP-1RA



Results:

- **Available:** Neutral
- **Available:** Positive for MACE
- **Available:** Positive for MACE
- **Completed:** Neutral + ⬇ CV death

Ongoing

- **Available:** Neutral + ⬇ death
- **Available:** Positive for MACE
- **Available:** Positive for MACE
- **Available:** Positive for MACE

ACS, acute coronary syndrome; CAD, coronary artery disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcome trials; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; S.C., subcutaneous, Q2, quarter 2

1. Marso SP et al. *N Engl J Med* 2016; 375:311-322; 2. Marso SP et al. *N Engl J Med* 2016; 375:1834-1844; 3. Husain M *et al*., *N Engl J Med* 2019; 381:841-851; 4. https://clinicaltrials.gov/ct2/show/NCT03914326; 5. Holman RR et al. *N Engl J Med* 2017; 377:1228-1239; 6. Gerstein HC et al., Lancet. 2019 Jul 13;394(10193):121-130; 7. Hernandez AF et al. *Lancet*. 2018;392:1519-1529; 8. Gerstein et al. *N Engl J Med*. 2021 Sep 2;385(10):896-907; 9. Pfeffer M *et al*., *N Engl J Med* 2015; 373:2247-2257

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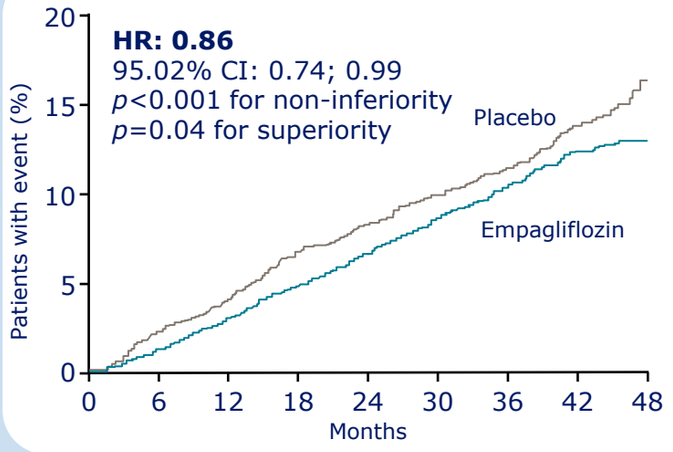
SGLT-2 Inhibitor CVOTs – Primary CV Outcomes

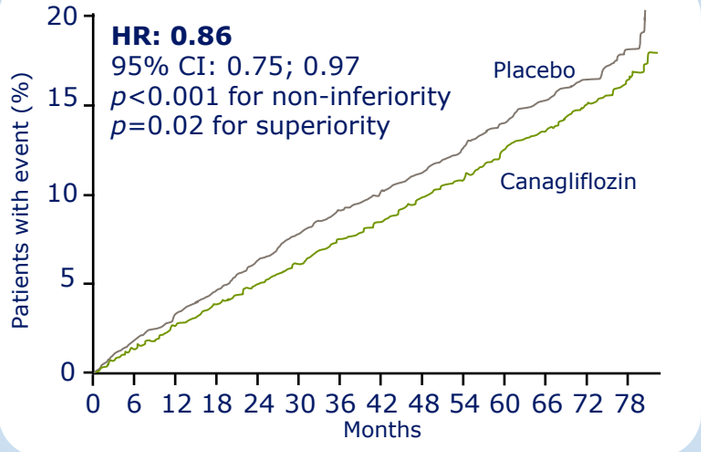
EMPA-REG OUTCOME[1]

- Empagliflozin was superior to placebo for time to 3-point MACE in T2D with established CVD



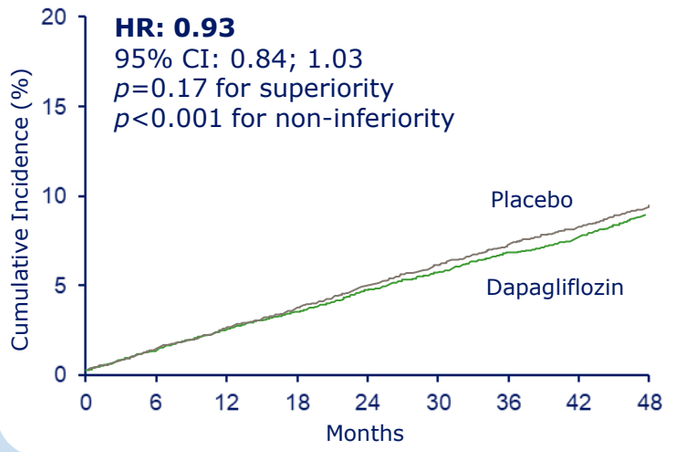
CANVAS[2]

- Canagliflozin was superior to placebo for time to 3-point MACE in T2D with established CVD or ≥50 years with high-risk CVD



DECLARE-TIMI 58[3]

- Dapagliflozin was non-inferior to placebo for time to 3-point MACE in T2D with established or high-risk CVD



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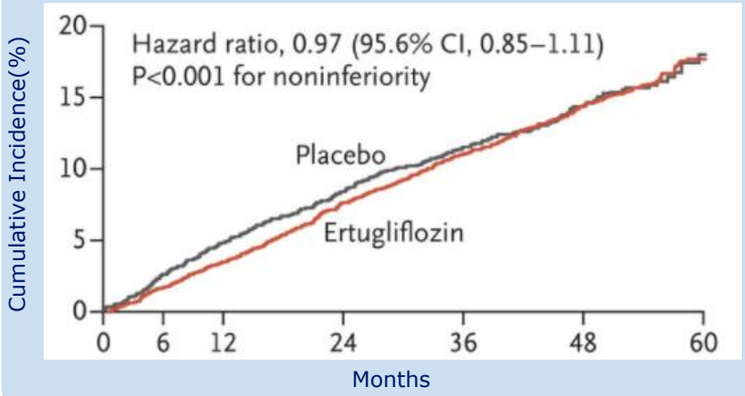
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; SGLT-2i, sodium–glucose co-transporter-2 inhibitor; T2D, type 2 diabetes

1. Zinman B et al. *N Engl J Med* 2015;373:2117–2128; 2. Neal B et al. *N Engl J Med* 2017;377:644–657; 3. Wiviott SD et al. *N Engl J Med* 2018; doi:10.1056/NEJMoa1812389 [Epub ahead of print]

SGLT-2 Inhibitor CVOTs – Primary CV Outcomes

VERTIS CV[1]

- Ertugliflozin was non-inferior to placebo for time to 3-point MACE in T2D with established CVD

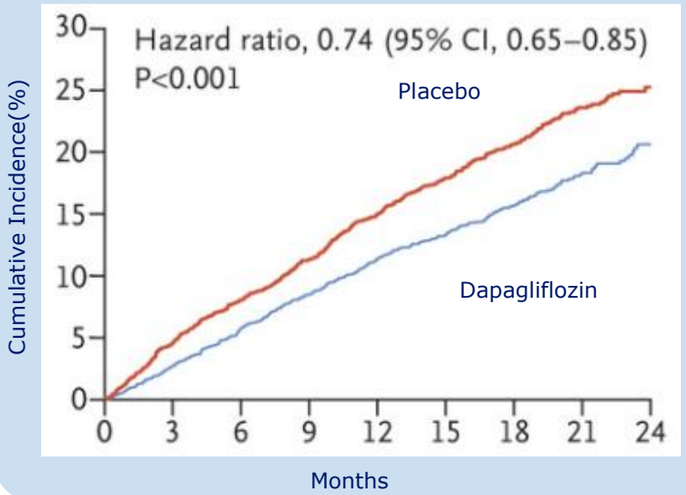


1. Cannon C *et al.*, *N Engl J Med* 2020; 383:1425-1435

SGLT-2 Inhibitors – Heart Failure Outcomes

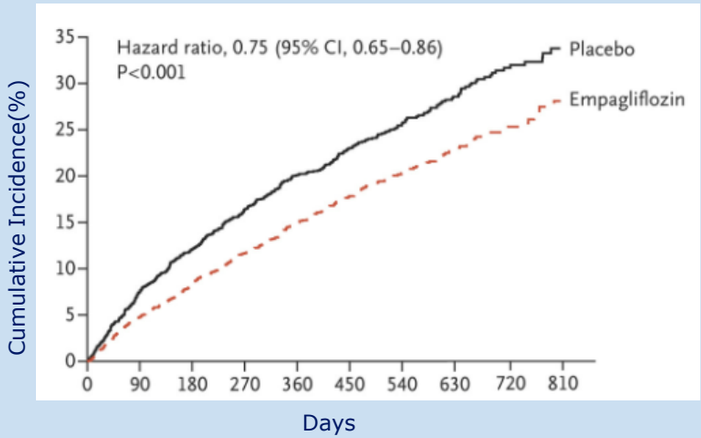
DAPA-HF[1]

- Dapagliflozin was superior to placebo for death from CV causes, hospitalization for HF, or an urgent visit resulting in IV therapy for HF in patients with CHF



EMPEROR-Reduced[2]

- Empagliflozin was superior to placebo for CV death or hospitalization for worsening HF in patients with CHF



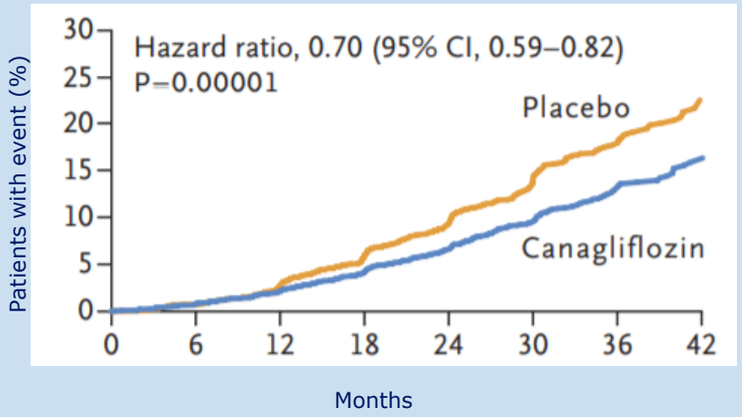
Scripps

1. McMurray J *et al.*, *N Engl J Med* 2019; 381:1995-2008. 2. Packer M et al., N Engl J Med 2020; 383:1413-1424

SGLT-2 Inhibitors - Cardiorenal Outcomes

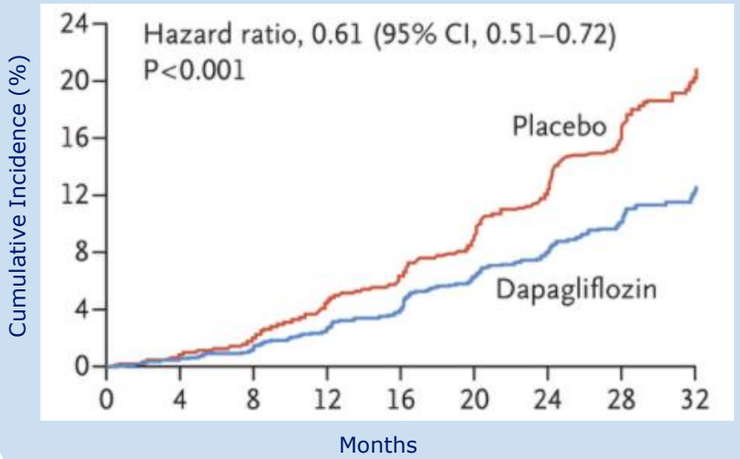
CREDENCE[1]

- Canagliflozin was superior to placebo for composite outcome of ESRD, doubling of creatinine, or death from renal or CV cause in T2DM with albuminuric kidney disease



DAPA-CKD[2]

- Dapagliflozin was superior to placebo for 1st occurrence of a 50% decline in eGFR, or ESRD, or CV or renal death in patients with T2DM with albuminuric kidney disease



Scripps

1. Perkovic V *et al.*, *N Engl J Med*. 2019 Jun 13;380(24):2295-2306. 2. Heerspink H *et al.*, *N Engl J Med* 2020; 383:1436-1446

Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

ASCVD or Indicators of High Risk

- Established ASCVD
- Indicators of high

either/or

GLP-1 RA with proven CVD benefit

Liraglutide
Semaglutide
Dulaglutide

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

+CKD

Partic… (LVEF …

& Albuminuria[8]

NO

SGLT2i with proven CVD benefit

SGLT2 with evidence of r… prog… [5,6,8]

OR

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated

Empagliflozin
Canagliflozin

For patients w/ T2D and CKD (eGFR <60 mL/min/1.73m^2) & thus at increased risk of CV events

GLP-1 RA with proven CVD benefit[1] — EITHER /OR — SGLT2i with proven CVD benefit[1,7]

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i | GLP-1 RA | SGLT2i | TZD

If A1C is above the target

T2i … D | GLP-1 RA **OR** DPP-4i **OR** TZD | SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C is above the target

…of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] — EITHER /OR — SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 yrs with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1]

If A1C is above target

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

HF

Particularly LV EF<45%

SGLT2i with proven benefit in this population

Empagliflozin
Dapagliflozin
Canagliflozin

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

+CKD

DKD & Albuminuria[8]

NO

OR

SGLT2 with evidence

tolerated or

at increased risk of CV events

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i | GLP-1 RA | SGLT2i | TZD

If A1C is above the target

SGLT2i	SGLT2i	GLP-1 RA	SGLT2i
OR	**OR**	**OR**	**OR**
TZD	TZD	DPP-4i	DPP-4i
		OR	**OR**
		TZD	GLP-1 RA

If A1C is above the target

Continue with addition of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] **EITHER /OR** SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

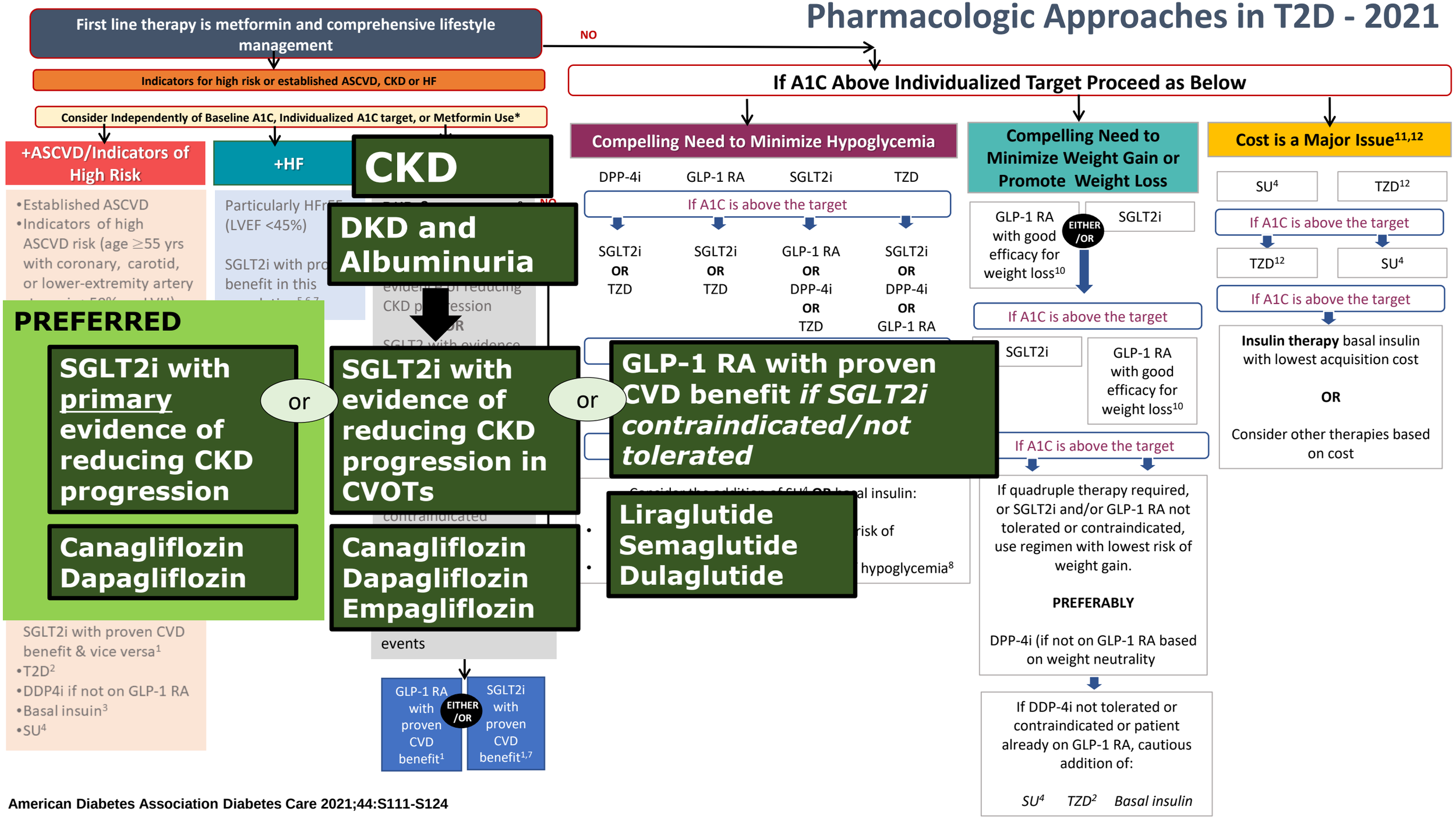
Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

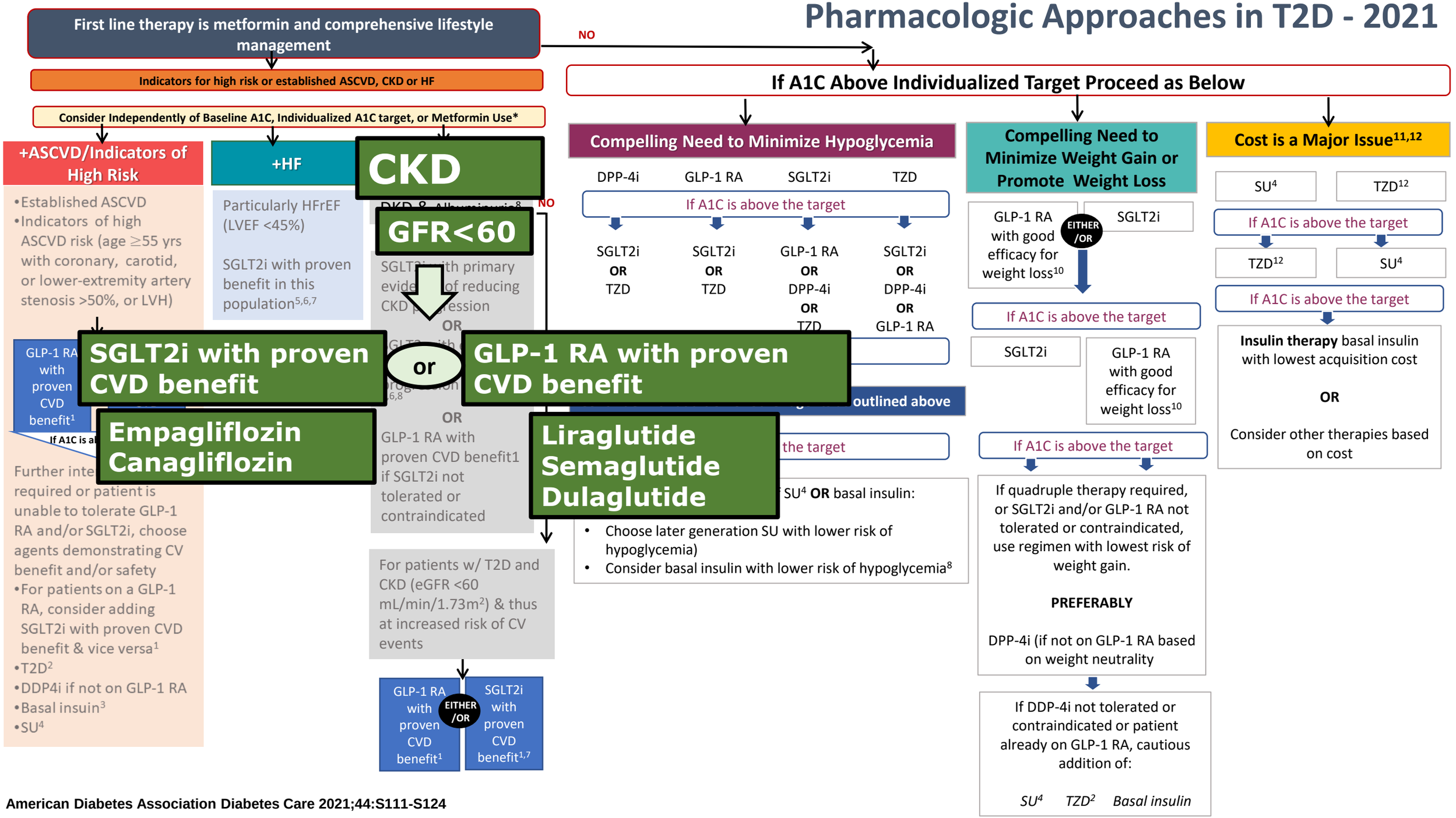
American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021



American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021



American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

+ASCVD/Indicators of High Risk

- Established ASCVD
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GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1]

If A1C is above target

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD & Albuminuria[8]

NO

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2 with evidence of reducing CKD progression in CVOTs[5,6,8]

OR

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated

For patients w/ T2D and CKD (eGFR <60 mL/min/1.73m^2) & thus at increased risk of CV events

GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

NO

If A1c is above individualized target

Compelling need to MINIMIZE HYPOGLYCEMIA

DPP-4i
GLP-1 RA
SGLT2i
TZD

OR OR OR

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling need to MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1RA
SGLT2i

efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a major issue

SU
TZD

TZD[12]

If A1C is above the target

SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Diabetes Care 2021;44:S111-S124

Pharmacologic Approaches in T2D - 2021

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NO

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- Indicators of high ASCVD risk (age ≥55 yrs with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

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GLP-1 RA with proven CVD benefit[1] **EITHER /OR** SGLT2i with proven CVD benefit[1,7]

NO

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i	GLP-1 RA	SGLT2i	TZD
If A1C is above the target			
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C is above the target

Continue with addition of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] **EITHER /OR** SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] TZD[2] Basal insulin

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

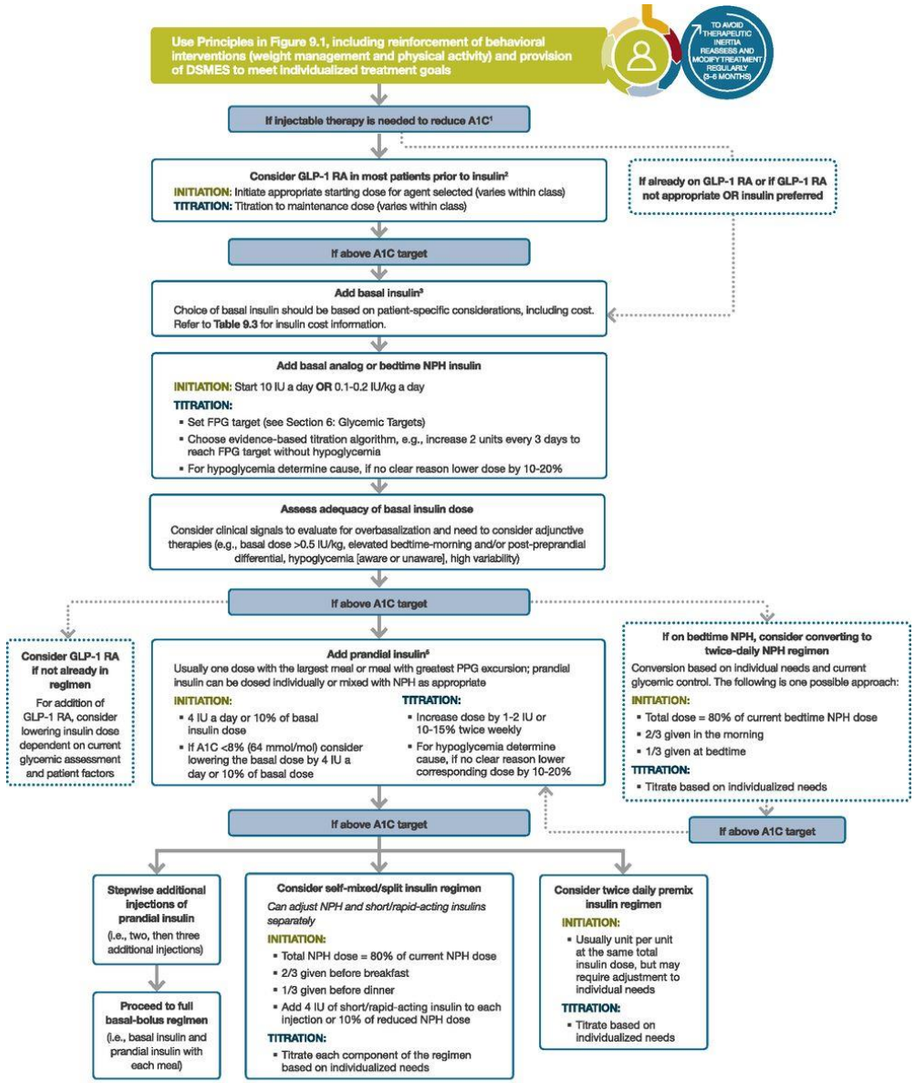
Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

American Diabetes Association Dia Care 2021;44:S111-S124

Pharmacologic Approaches in Type 2 Diabetes - 2021



American Diabetes Association

American Diabetes Association
Diabetes Care 2021;44:S111-S124

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Pharmacologic Approaches in Type 2 Diabetes - 2021

Use pharmacologic principles already reviewed as well as reinforcement of behavioral intervention (weight management and physical activity) and provision of DMES to meet treatment goals

If injectable therapy is needed to reduce A1c

Consider GLP-1 RA in most patients PRIOR TO INSULIN

If above A1c target

Add basal insulin

If already on GLP-RA or GLP-1 RA is not appropriate or insulin is preferred

American Diabetes Association

American Diabetes Association
Diabetes Care 2021;44:S111-S124

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CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Provide case examples of uses in under-resourced populations in terms of access and implementation.

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Goals

1. Review diabetes goals of therapy and glycemic targets
2. Discuss efficacy and safety of medication classes for type 2 diabetes
3. Review guidelines for a stepwise approach to the pharmaceutical management of type 2 diabetes
4. Understand how to select therapy for patients with type 2 diabetes and comorbidities such as ASCVD, HF, or CKD
5. To provide case examples of uses in under-resourced populations in terms of access and implementation.
6. To describe technology currently offered in the ambulatory and hospital settings for management of type 2 diabetes

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Case Examples

CASE 1

74 yo Female with history of type 2 DM presenting for initial evaluation

PMH: T2DM, CAD, HTN, HLD, CKD3

DM Medications: glargine 30 units qhs, regular insulin 5 units pre-meal, linagliptin 5mg daily

Prior DM Medications: metformin

BMI 34.6

Labs: A1c 8.8%, GFR 51

Insurance: Medicaid

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Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

ASCVD or Indicators of High Risk

- Established ASCVD
- Indicators of high

either/or

GLP-1 RA with proven CVD benefit

Liraglutide
Semaglutide
Dulaglutide

Further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

+CKD

Partic… (LVEF …) & Albuminuria[8]

NO

SGLT2i with proven CVD benefit

OR

SGLT2 with evidence of r… prog… [5,6,8]

OR

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated

Empagliflozin
Canagliflozin

For patients w/ T2D and CKD (eGFR <60 mL/min/1.73m^2) & thus at increased risk of CV events

GLP-1 RA with proven CVD benefit[1] — EITHER /OR — SGLT2i with proven CVD benefit[1,7]

If A1C Above Individualized Target Proceed as Below

Compelling Need to Minimize Hypoglycemia

DPP-4i | GLP-1 RA | SGLT2i | TZD

If A1C is above the target

T2i … D | GLP-1 RA **OR** DPP-4i **OR** TZD | SGLT2i **OR** DPP-4i **OR** TZD **OR** GLP-1 RA

If A1C is above the target

…of other agents as outlined above

If A1C is above the target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia)
- Consider basal insulin with lower risk of hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] — EITHER /OR — SGLT2i

If A1C is above the target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] | TZD[12]

If A1C is above the target

TZD[12] | SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

Case Examples

CASE 1

74 yo Female with history of type 2 DM presenting for initial evaluation

PMH: T2DM, CAD, HTN, HLD, CKD3

DM Medications: glargine 30 units qhs, regular insulin 5 units pre-meal, linagliptin 5mg daily

Prior DM Medications: metformin

BMI 34.6

Labs: A1c 8.8%, GFR 51

Insurance: Medicaid

PLAN: START LIRAGLUTIDE

Scripps

Medication Classes for Management of T2DM

	Efficacy	Hypo-glycemia	Weight change	CV effects		Cost	Oral/ SQ	Renal effects		Additional Considerations
				ASCVD	HF			DKD Progression	Dosing/use considerations*	
Metformin	High	No	Neutral	Potential Benefit	Neutral	Low	Oral	Neutral	Contradiction with eGFR <30 ml/min/1.73 m^2	• GI side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Inter-mediate	No	Loss	Benefi: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	High	Oral	Benefit: empagliflozin, canagliflozin, dapagliflozin	Renal dose adjustment required (canaglifozin, dapaglifozin, empaglifozin, ertugliflozin	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk (all agents, rare in T2D) • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL-C • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide qw, lixisenatide Benefit: dulaglutide, liraglutide, semaglutide	Neutral	High	SQ; Oral (semaglutide)	Benefits on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	• Exenatide, lixisenatide: avoid for eGFR <30 ml/min/1.73 m^2 • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when starting or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe GI reactions when starting or increasing dosage.	• **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide ER, semaglutide)** • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Inter-mediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommend in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive HF **(pioglitazone, rosiglitazone)** • Fluid retention (edema, HF) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL-C (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – **Human insulin**	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – **Analogs**						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information.

American Diabetes Association. *Diabetes Care*. Jan 2021;44 (1):S111-S124.

Case Examples

CASE 1

74 yo Female with history of type 2 DM presenting for initial evaluation

PMH: T2DM, CAD, HTN, HLD, CKD3

DM Medications: glargine 30 units qhs, regular insulin 5 units pre-meal, linagliptin 5mg daily

Prior DM Medications: metformin

BMI 34.6

Labs: A1c 8.8%, GFR 51

Insurance: Medicaid

PLAN: START LIRAGLUTIDE

-Assess for contraindications
-Review side effects
-Review up-titration instructions
-Decrease insulin
-Stop DPP4-i
-Schedule training session
-Prescribe pen needles
-Utilize 340B Drug Pricing Program

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Case Examples

CASE 1 – 4 months later

74 yo Female with history of type 2 DM presenting for follow up

Interval: maximum tolerated dose of liraglutide 0.6mg daily

PMH: T2DM, CAD, HTN, HLD, CKD3

DM Medications: glargine **23** units qhs, regular insulin **3** units pre-meal, **liraglutide** 0.6mg daily

Prior DM Medications: metformin, linagliptin

BMI 34.6 → **32.5**

Labs: A1c 8.8% → **7.7%**

PLAN: continue current regimen, consider stopping regular insulin in follow up

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Case Examples

CASE 2

59 yo Female with history of type 2 DM

PMH: T2DM, HTN, HLD, DKD

DM Medications: detemir 22 units qhs, metformin 1000mg BID, glipizide 10mg BID

BMI 37.79

Labs: A1c 8.9%, GFR 47, urine microalbumin:cre >300 mg/g

Insurance: Medicaid

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Pharmacologic Approaches in T2D - 2021

First line therapy is metformin and comprehensive lifestyle management

NO

Indicators for high risk or established ASCVD, CKD or HF

Consider Independently of Baseline A1C, Individualized A1C target, or Metformin Use*

If A1C Above Individualized Target Proceed as Below

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 yrs with coronary, carotid, or lower-extremity artery
- SGLT2i with proven CVD benefit & vice versa[1]
- T2D[2]
- DDP4i if not on GLP-1 RA
- Basal insuin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with pro benefit in this

CKD

DKD and Albuminuria

CKD p ression

SGLT2 with evidence

contraindicated

events

PREFERRED

SGLT2i with primary evidence of reducing CKD progression

Canagliflozin
Dapagliflozin

or

SGLT2i with evidence of reducing CKD progression in CVOTs

Canagliflozin
Dapagliflozin
Empagliflozin

or

GLP-1 RA with proven CVD benefit *if SGLT2i contraindicated/not tolerated*

Liraglutide
Semaglutide
Dulaglutide

GLP-1 RA with proven CVD benefit[1] EITHER /OR SGLT2i with proven CVD benefit[1,7]

Compelling Need to Minimize Hypoglycemia

DPP-4i	GLP-1 RA	SGLT2i	TZD
If A1C is above the target			
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **OR** GLP-1 RA

Consider the addition of SU[4] OR basal insulin:

- risk of
- hypoglycemia[8]

Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss[10] EITHER /OR SGLT2i

If A1C is above the target

SGLT2i

GLP-1 RA with good efficacy for weight loss[10]

If A1C is above the target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain.

PREFERABLY

DPP-4i (if not on GLP-1 RA based on weight neutrality

If DDP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

SU[4] *TZD[2]* *Basal insulin*

Cost is a Major Issue[11,12]

SU[4] TZD[12]

If A1C is above the target

TZD[12] SU[4]

If A1C is above the target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

Case Examples

CASE 2

59 yo Female with history of type 2 DM

PMH: T2DM, HTN, HLD, DKD

DM Medications: detemir 22 units qhs, metformin 1000mg BID, glipizide 10mg BID

BMI 37.79

Labs: A1c 8.9%, GFR 47, urine microalbumin:cre: >300 mg/g

Insurance: Medicaid

PLAN: START dapagliflozin

-**Assess for contraindications**
-**Review side effects**
-**Consider reducing insulin**
-**Check formulary**

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Case Examples

CASE 2 – follow up

59 yo Female with history of type 2 DM presenting for follow up

PMH: T2DM, HTN, HLD, DKD

DM Medications: detemir 20 units qhs, metformin 1000mg BID, glipizide 10mg BID, **dapagliflozin 5mg daily**

BMI 37.79 → **37.1**

Labs: A1c 8.9% → **8.0%**

PLAN: Increase dapagliflozin to 10mg daily

Check if new prior authorization needed for dose increase

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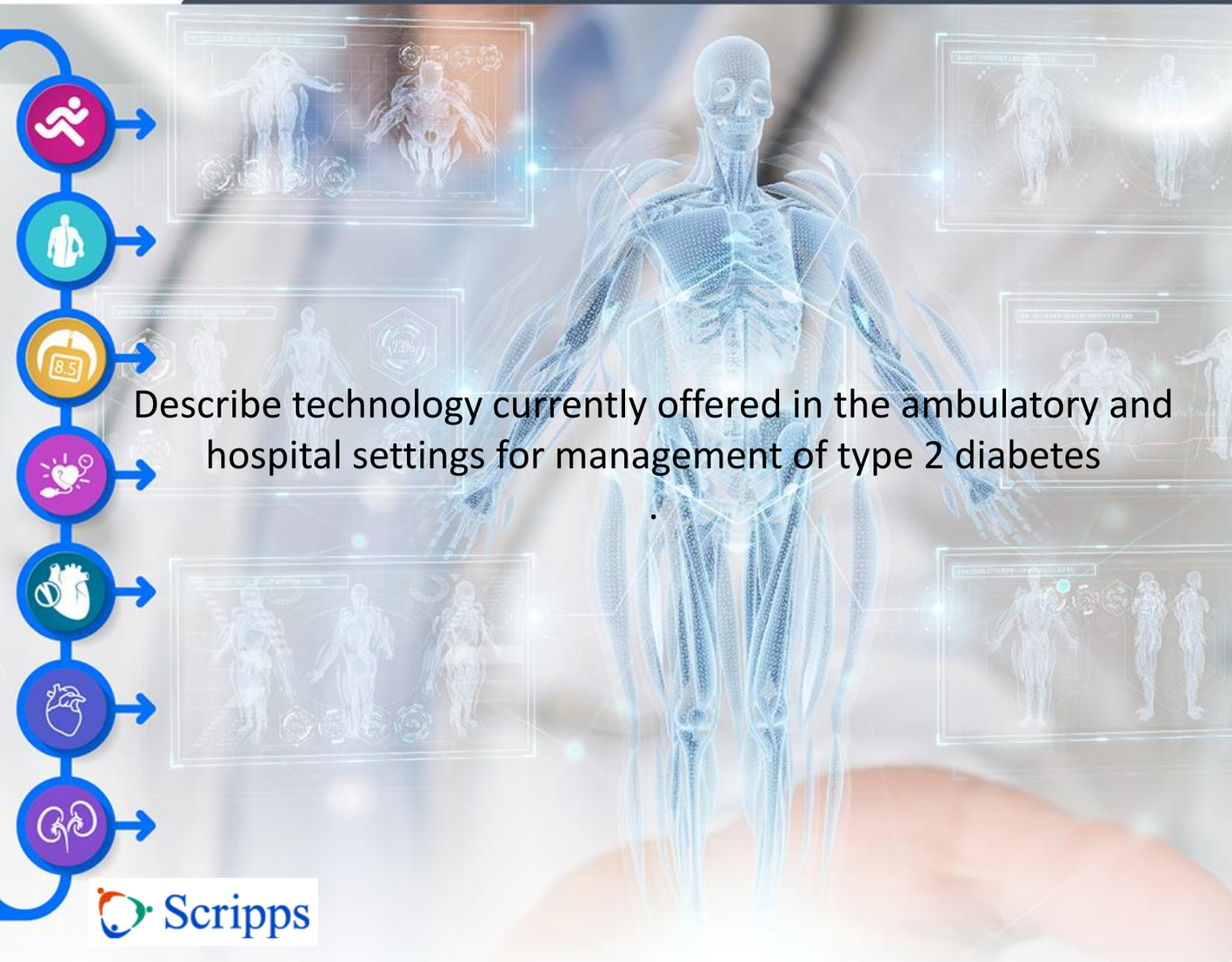
CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)



Describe technology currently offered in the ambulatory and hospital settings for management of type 2 diabetes

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Goals

1. Review diabetes goals of therapy and glycemic targets
2. Discuss efficacy and safety of medication classes for type 2 diabetes
3. Review guidelines for a stepwise approach to the pharmaceutical management of type 2 diabetes
4. Understand how to select therapy for patients with type 2 diabetes and comorbidities such as ASCVD, HF, or CKD
5. To provide case examples of uses in under-resourced populations in terms of access and implementation.
6. To describe technology currently offered in the ambulatory and hospital settings for management of type 2 diabetes

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Digital tools for diabetes in under-resourced populations

Digital Diabetes Tools

- Dulce Digital & Dulce Digital COVID Aware
- Continuous Glucose Monitoring in the Hospital

Use in High-Risk Diabetes Clinics

- Continuous Glucose Monitoring in Telehealth Visits
- Connected pens
- Hybrid closed loop pumps

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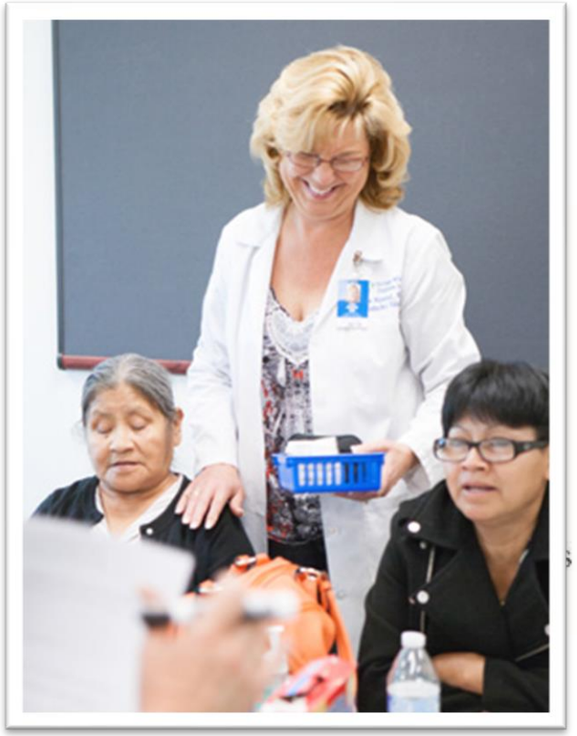
Project Dulce

Initiated in collaboration with community clinics, public health department, San Diego State University and others in 1997



Team approach to diabetes care:

- Nurse-led clinical team
- Peers/non-professionals trained to deliver classes
- Delivered in under-resourced diverse racial/ethnic communities

PBS NewsHour
Self-empowerment is sweet for diabetes patients in this innovative program
May 5, 2017 9:39 pm EDT

1. Philis-Tsimikas A, Walker C, Rivard L, Talavera G, Reimann J O F, Salmon M, Araujo R, Improvement in Diabetes Care of Underinsured Patients Enrolled in Project Dulce™: A Community-Based, Culturally Appropriate, Nurse Case Management and Peer Education Diabetes Care Model. Diabetes Care, 2004,27;1,110-115
2. Philis-Tsimikas, A., Gallo, L.C. (2014). Implementing community based diabetes programs: The Scripps Whittier Diabetes Institute experience. Current Diabetes Reports. DOI10.1007/s11892-013-0462-0.
3. Gilmer T, Philis-Tsimikas A, Walker C. Ann Pharmacother 2005;39;817-22

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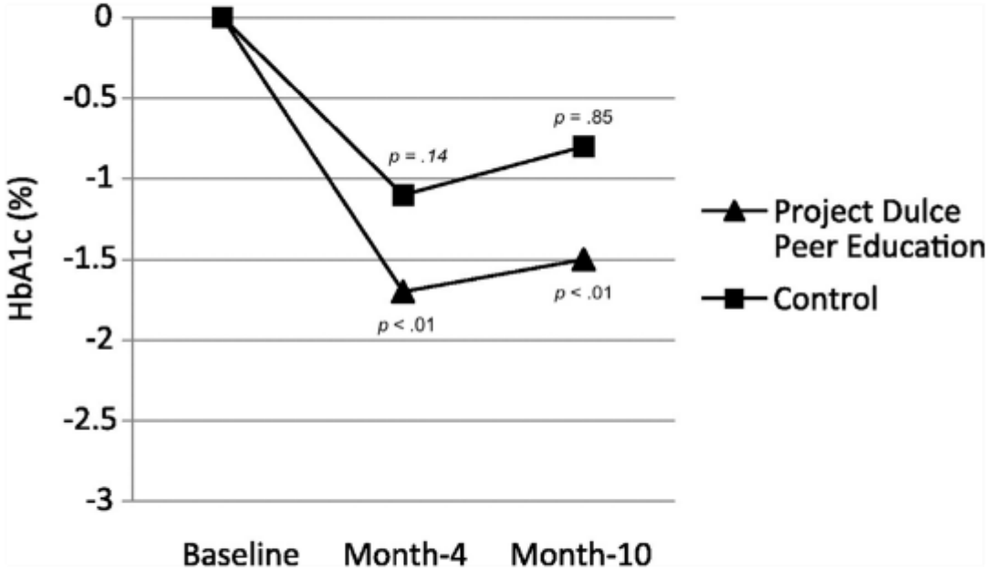
Dulce Peer Education Program

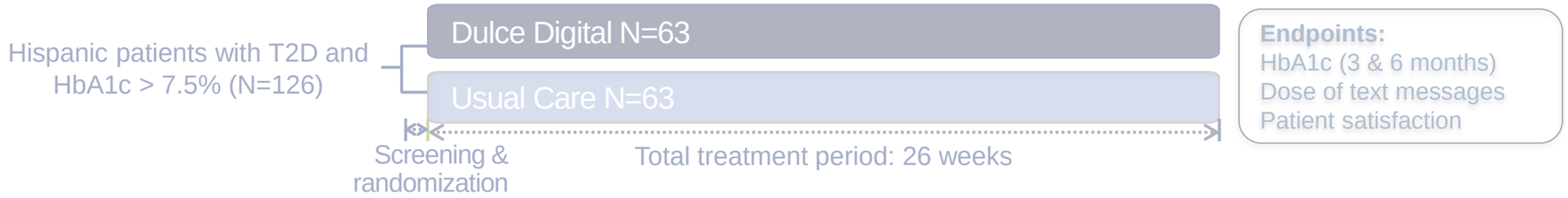
- Five 2-hour sessions
- Curriculum suitable for broad literacy levels
- Adapted for different ethnic groups and cultures
- American Diabetes Association certified program

Changes in absolute levels of HbA1c from baseline to months 4 and 10 in the Project Dulce and control groups.



Athena Philis-Tsimikas et al. Dia Care 2011;34:1926-1931

Dulce Digital: Text messaging in English and Spanish



Endpoints:
HbA1c (3 & 6 months)
Dose of text messages
Patient satisfaction

Dulce Digital (n=63):

- 2-3 messages/day, with frequency tapering over 6 months
- Educational/motivational
  - *"Use small plates! Portions will look larger and you may feel more satisfied after eating."*
- Medication reminders
  - *"Tick, tock. Take your medication at the same time every day!"*
- BGM prompts
  - *"Time to check your blood sugar! Text back your results."*

Blood glucose monitoring protocol:

- Coordinator monitored BG responses on a dashboard
- Telephone outreach criteria:
  - Out of range BG values
    - *1 value of > 250 or <70 mg/dL*
    - *3 values 181-250 mg/dL in 1 month*
  - No BG values for 1 week
- During the call, assessed reasons for hyper/hypo, encouraged PCP follow-up

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McKesson Foundation Grant # 115M803379 and support from the LifeScan, Inc. Investigator-Initiated Study Program

Dulce Digital: Results

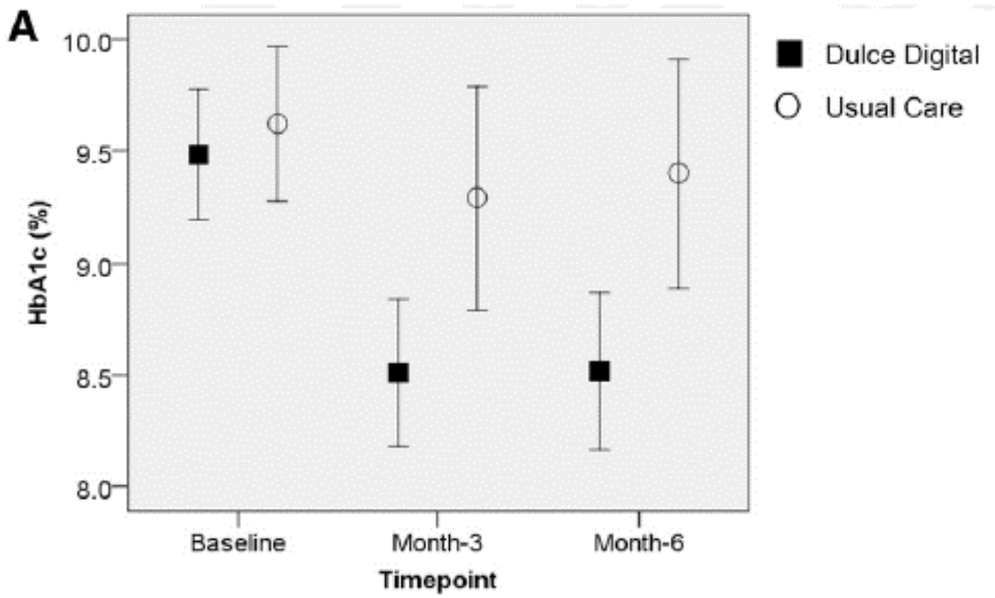
Diabetes Care Volume 40, October 2017 1349

Dulce Digital: An mHealth SMS-Based Intervention Improves Glycemic Control in Hispanics With Type 2 Diabetes

Addie L. Fortmann,[1] Linda C. Gallo,[2] Maria Isabel Garcia,[1] Mariam Taleb,[1] Johanna A. Euyoque,[1] Taylor Clark,[1] Jessica Skidmore,[1] Monica Ruiz,[1] Sapna Dharkar-Surber,[3] James Schultz,[3] and Athena Philis-Tsimikas[1]

Diabetes Care 2017;40:1349–1355 | https://doi.org/10.2337/dc17-0230

Baseline characteristics	Dulce Digital (N=63)	Usual Care (N=63)
Age years, mean (SD)	47.8 (9.0)	49.1 (10.6)
Sex, F (%)	46 (73)	48 (76)
Country of origin, Mexico (%)	59 (93)	55.0 (89)
Preferred Language, Spanish (%)	59 (94)	57 (91)
Education: Less than ninth-grade education (%)	46 (76)	44 (70)
Insurance Coverage: Uninsured	48 (76)	47 (75)
Household monthly income: <$1,000/month $1,000 to $1,999/month ≥$2,000/month	 18 (29) 35 (55) 10 (16)	 23 (37) 33 (52) 7 (11)
HbA1c % (SD)	9.5 (1.2)	9.6 (1.4)



Change in HbA1c over time

Conclusions: Use of a simple, low-cost text messaging program resulted in greater improvement in glycemic control compared to usual care. It was also found to be highly acceptable.

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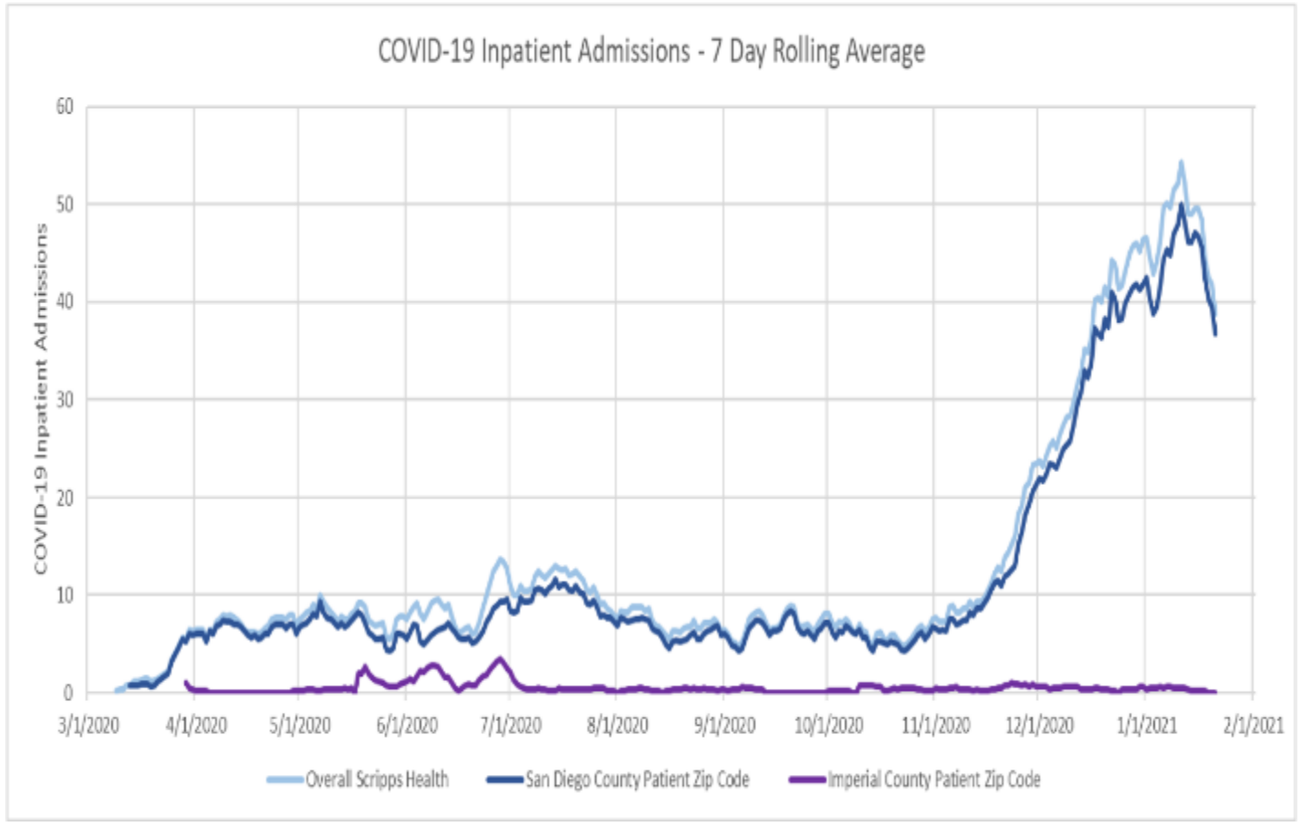
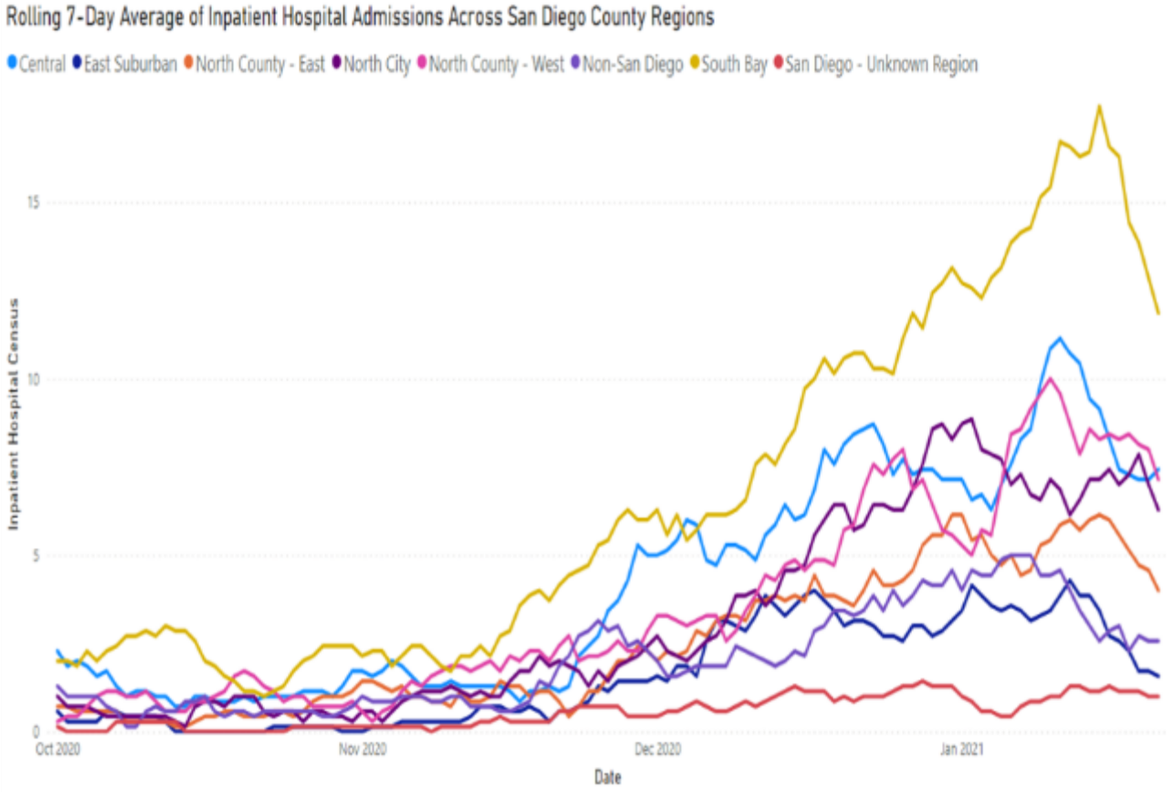
Fortmann AL, Gallo LG, Garcia MI, Taleb M, Euyoque JA, Clark T, Skidmore J, Ruiz M, Dharkar-Surber S, Schultz J, Philis-Tsimikas A. Dulce Digital: An mHealth SMS-Based Intervention Improves Glycemic Control in Hispanics With Type 2 Diabetes. Diabetes Care Jun 2017, dc170230; DOI: 10.2337/dc17-0230

Scripps Health Hospital Rates

Team nursing and expanding beyond licensed beds to accommodate surge



Five hospitals, one closest to US/Mexico border



- Low: October 14th = 5.0 Average Inpatient Admissions per day
- High: January 11th = 54.3 Average Inpatient Admissions per day
- 986% increase in average daily inpatient admissions

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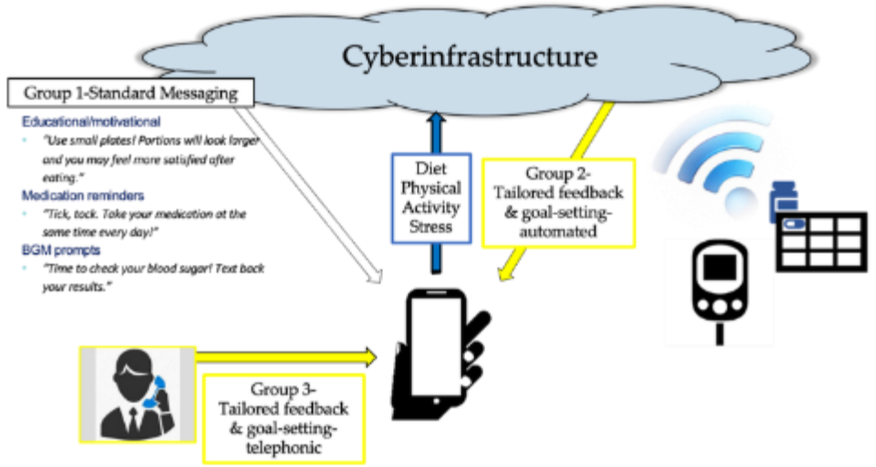
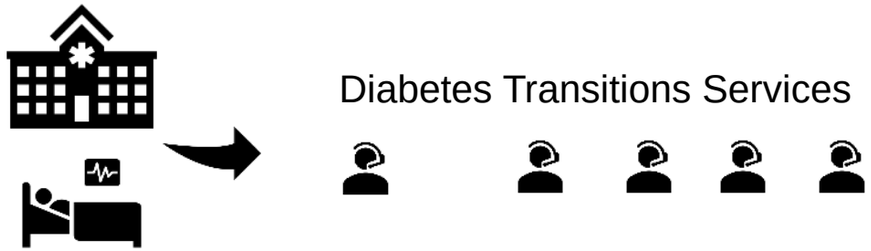
Bring together programs to create a digital resource

Dulce Digital adapted text messaging (DD-Me)



Scripps Diabetes Transitions Services



Community **E**ngagement **Al**liance (CEAL) Against COVID-19 Disparities messaging to combat misinformation and myths about COVID-19, treatments and vaccines

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Dulce Digital-Me, NIDDK 1R01DK112322-01A1(Philis-Tsimikas/Gallo Co-PI)
CEAL, NIH/NHLBI/NIMHD 1OT2HL156812-01 PI Brown (UCLA)/ subaward PI AuYoung (Scripps)
Dulce Transitions: Peer health coaches reduce hospital readmission rates in high-risk Latinos, ADA Scientific Sessions 2014, San Francisco (Philis-Tsimikas, Hoagland-Fuchs, Walker, Fortmann)

Dulce Digital-COVID Aware (DD-CA)

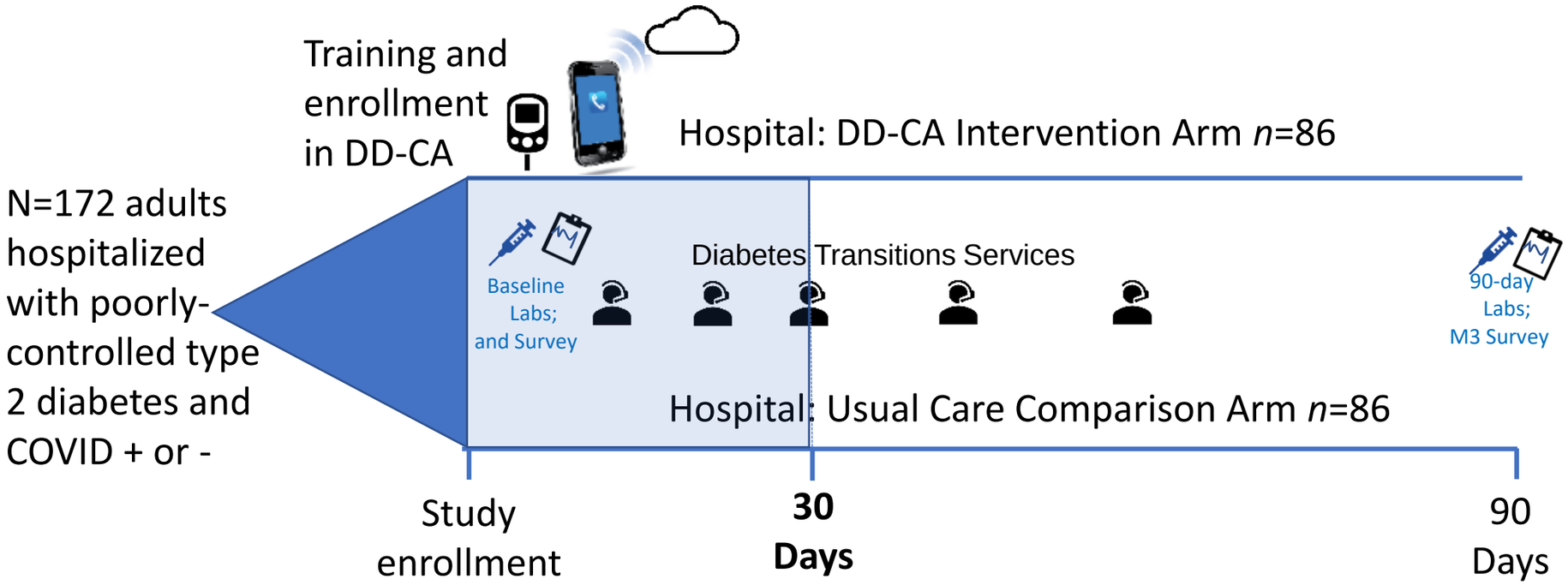

Figure 2. Study recruitment, randomization and flow

Inclusion/Exclusion Criteria

Inclusion: 1) ≥18 y/o; 2) T2D; 3) own a mobile phone; 4) HbA1c > 7 in the last 30 days

Exclusion: 1) Does not speak Eng or Span; 2) Current participation in medication or device study; 3) Other condition deemed contraindicated.

Outcomes

Primary-30-day Readmission Rate

Secondary-Change in glucose control HbA1c

Exploratory-Behavioral & Diabetes distress and readmission at 90 days

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NIDDK 1R01DK112322-05S1(Philis-Tsimikas/Fortmann Co-PI)

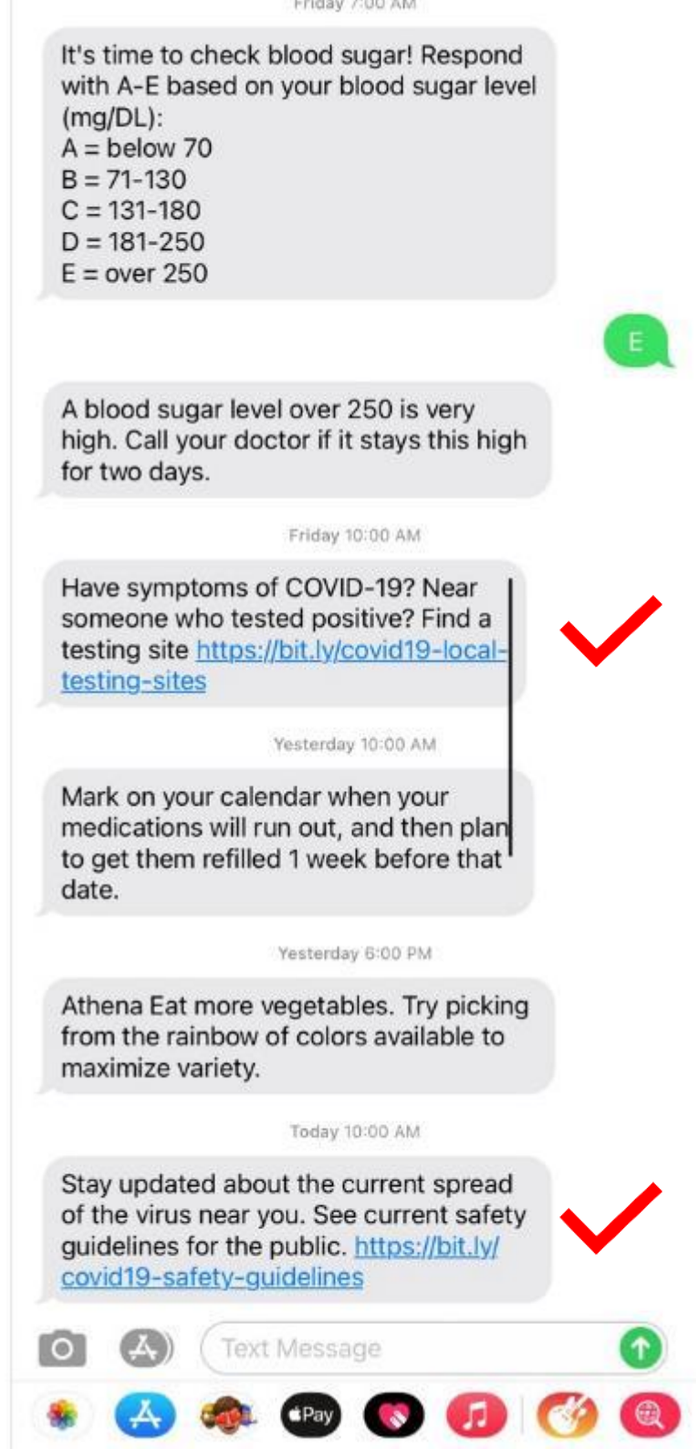
Dulce Digital-COVID Aware (DD-CA)

AIM: Reduce barriers in diverse underserved Hispanic and Latino communities to improve glucose control and lower transmission of COVID post hospitalization discharge.

PRIMARY OUTCOME: Reduce hospital readmission rates.

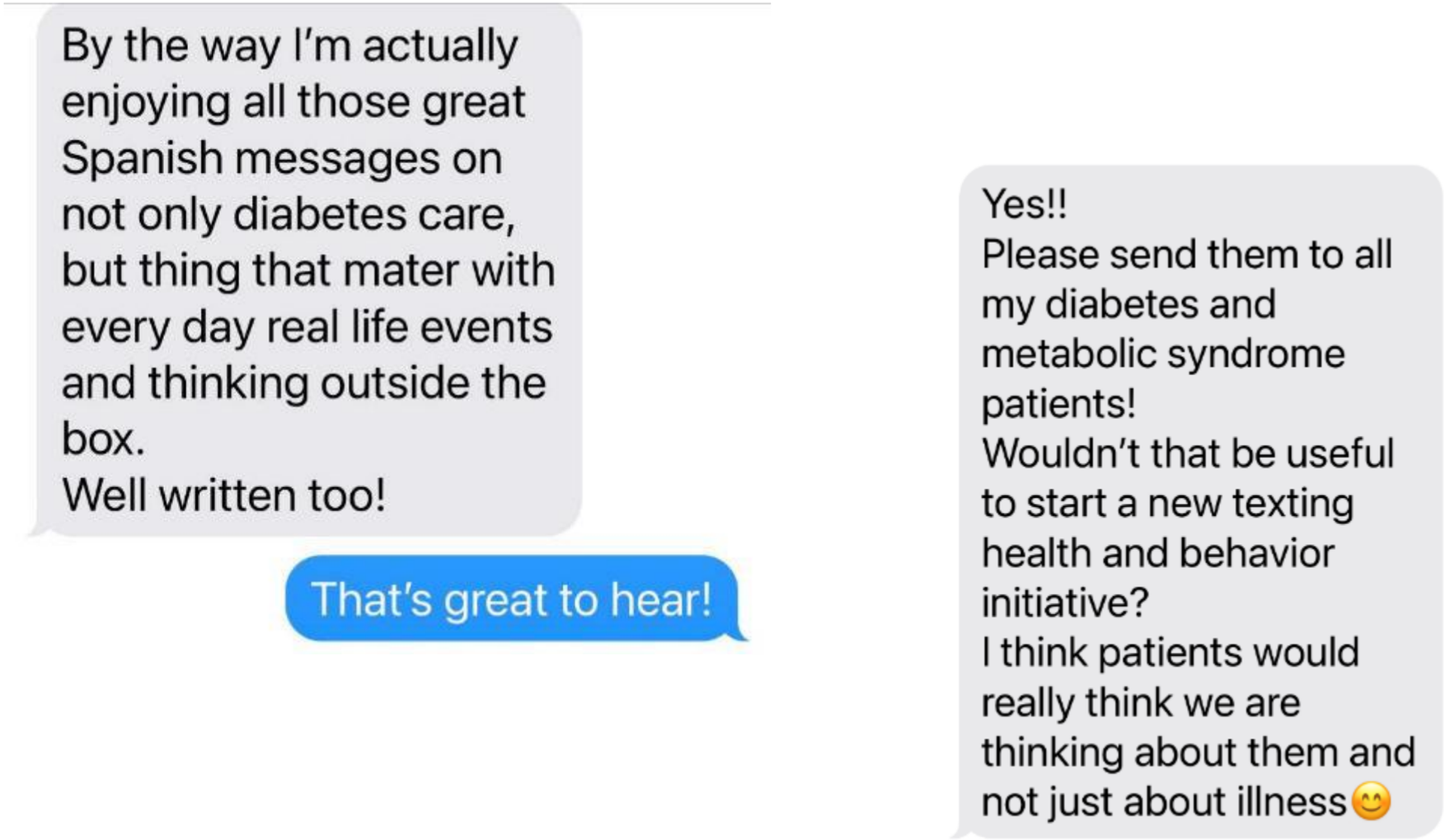
RCT to reach N=172

D & I to reach 3000-5000 California wide



1. NIDDK 1R01DK112322-05S1(Philis-Tsimikas/Fortmann Co-PI)
2. American Diabetes Association
3. Hearst Health Award

Provider feedback



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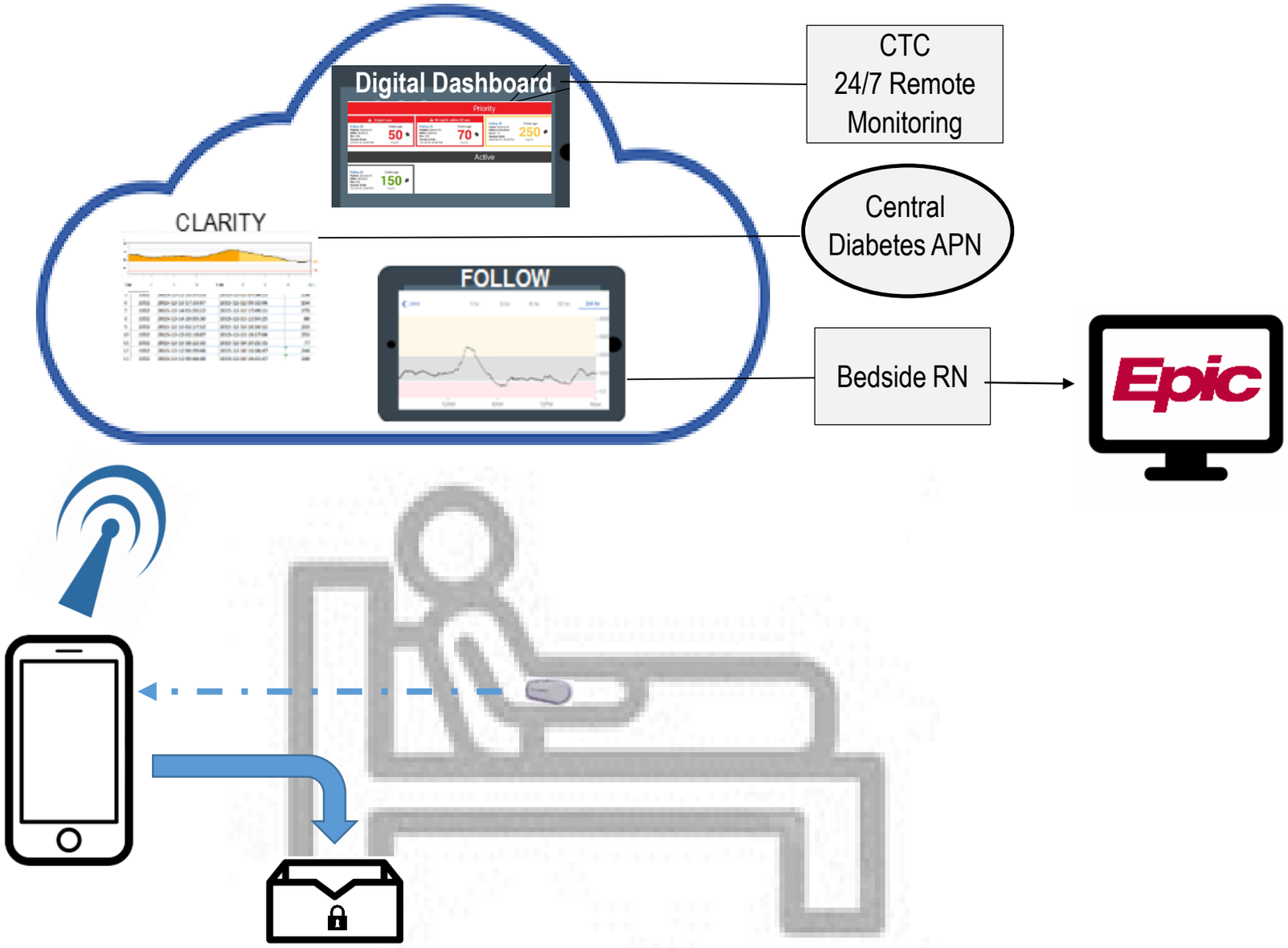
Continuous Glucose Monitoring (CGM) as Standard of Care:

OVERVIEW



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Continuous Glucose Monitoring (CGM) as Standard of Care: REACH TO-DATE

CGM as Standard of Care: Scripps Mercy San Diego			
	11/DOU (Go live 5/11/20)	**ICU** (Go live 6/1/20)	**6/COVID** (Go live 6/29/20)
T1D	10	1	1
T2D	164	42	92
Totals	222	44	**388 (132 COVID+, 34%)**

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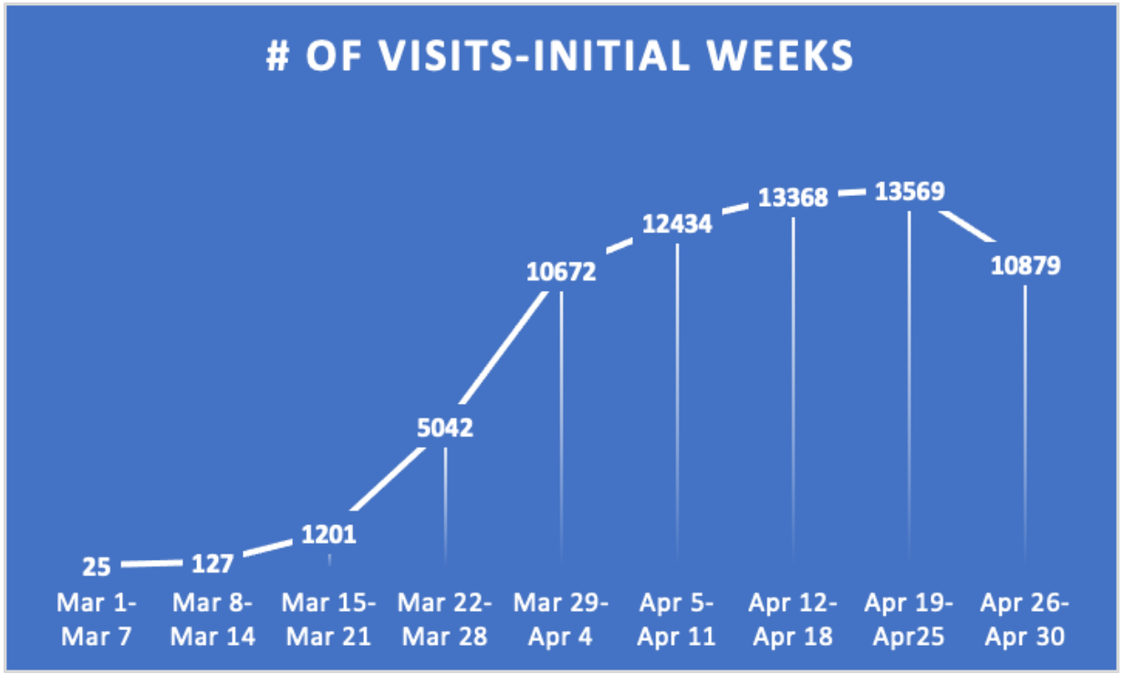
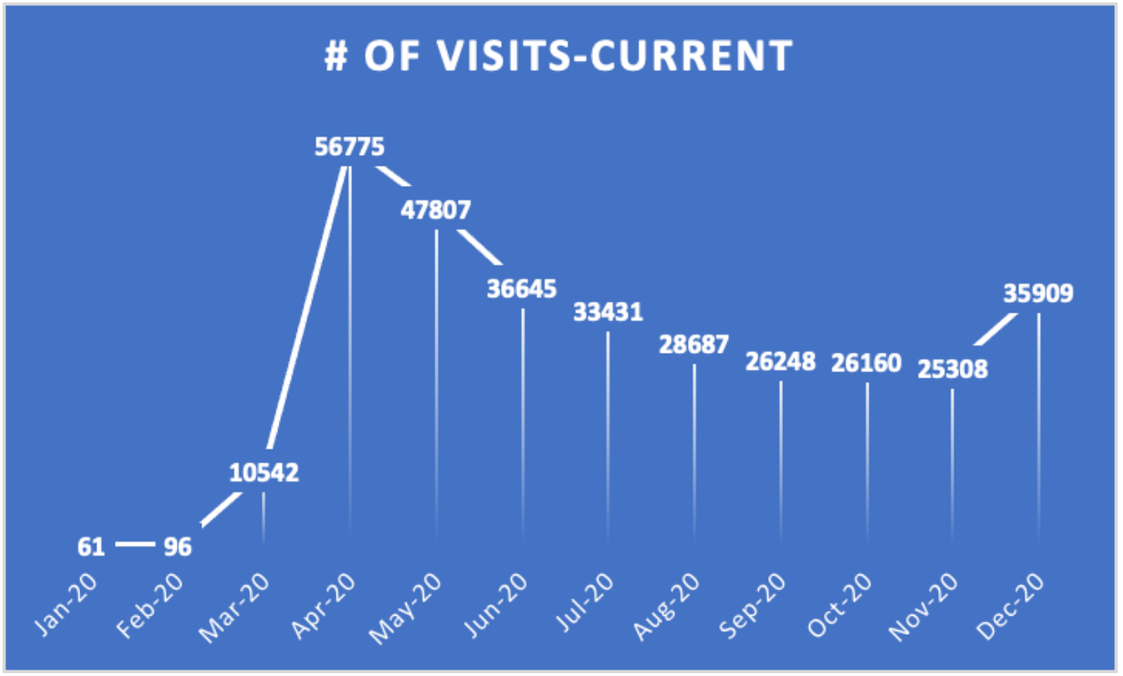
Scripps Health transition to virtual with COVID19

Ramp up from 60 video visits a month to 3,000 a day in 3 weeks



Second peak in December during COVID surge



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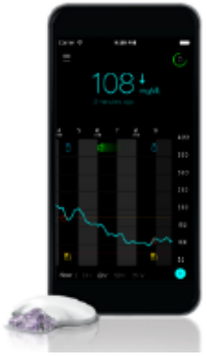
Digital options for diabetes management

Continuous Glucose Monitoring



Connected pens

Sensor augmented pumps and
Hybrid Closed Loop Pumps

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Ambulatory Glucose Report (AGP)

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019–10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

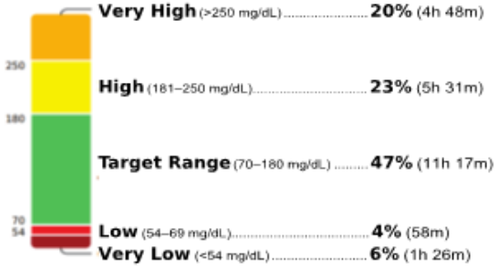
Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16hr 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6hr)
Above 250 mg/dL	Less than 5% (1hr 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

Defined as percent coefficient of variation (%CV); target ≤36%

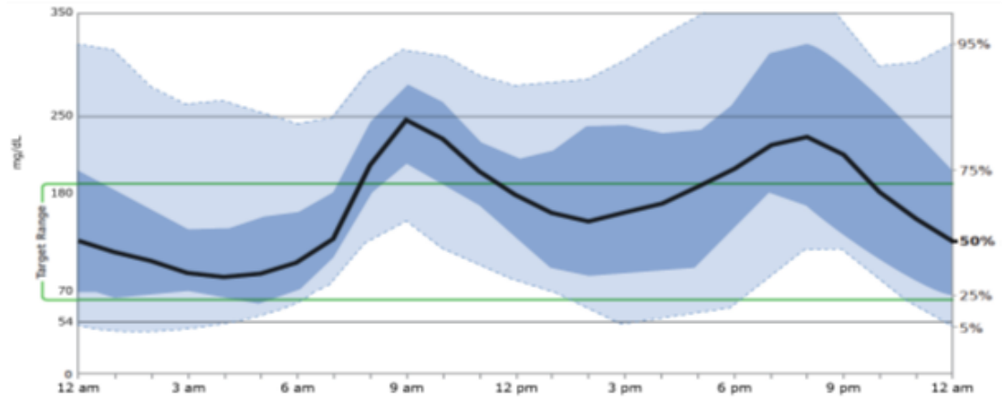
TIME IN RANGES



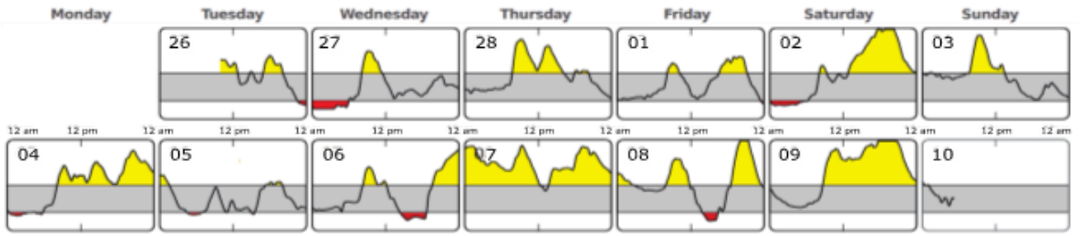
- **Very High** (>250 mg/dL) **20%** (4h 48m)
- **High** (181–250 mg/dL) **23%** (5h 31m)
- **Target Range** (70–180 mg/dL) **47%** (11h 17m)
- **Low** (54–69 mg/dL) **4%** (58m)
- **Very Low** (<54 mg/dL) **6%** (1h 26m)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES



Each daily profile represents a midnight-to-midnight period.

captürAGP®

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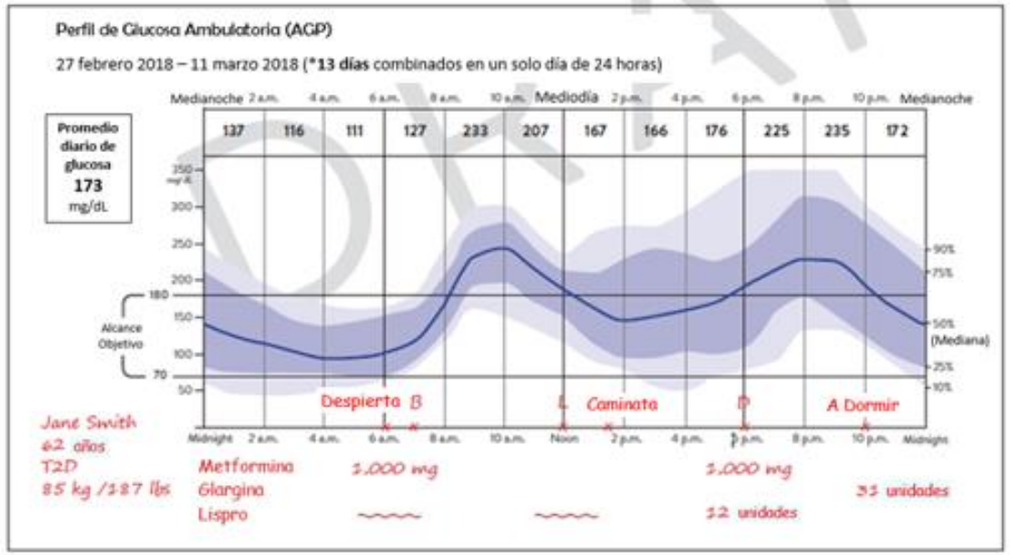
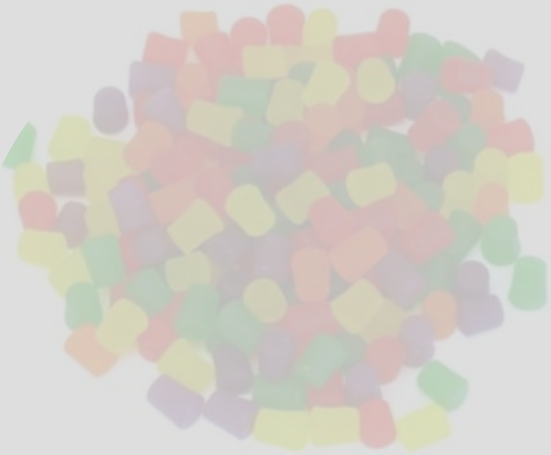
Libros de registro de práctica y reportes de CGM

	DESAYUNO		ALMUERZO		CENA		OTROS COMENTARIOS
	ANTES	DESPUES	ANTES	DESPUES	ANTES	DESPUES	
DIA-Martes 01/01/2019 NUMERO DE AZUCAR EN LA SANGRE	138	122				204	
¿QUÉ COMIÓ? ¿CUANTO? *-***	Pan tostado con mermelada-2 piezas naranja-1 Café-1 taza						
¿QUÉ TIPO DE ACTIVIDAD FÍSICA? ¿CUÁNTA?*-***			Limpieza en casa -2 horas-**				
¿ALGUN ESTRÉS EN SU DÍA? ¿CUÁNTO?*-***					**		
MEDICAMENTOS TOMADOS	Metformina 1000 mg				Lantus 24 unidades		
DÍA _____/___/_____ NUMERO DE AZUCAR EN LA SANGRE							
¿QUÉ COMIÓ? ¿CUANTO? *-***							
¿QUÉ TIPO DE ACTIVIDAD FÍSICA? ¿CUÁNTA?*-***							
¿ALGUN ESTRÉS EN SU DÍA? ¿CUÁNTO?*-***							
MEDICAMENTOS TOMADOS							
DÍA _____/___/_____ NUMERO DE AZUCAR EN LA SANGRE							
¿QUÉ COMIÓ? ¿CUANTO? *-***							
¿QUÉ TIPO DE ACTIVIDAD FÍSICA? ¿CUÁNTA?*-***							
¿ALGUN ESTRÉS EN SU DÍA? ¿CUÁNTO?*-***							
MEDICAMENTOS TOMADOS							



DW-JuJuBes Challenge



On Feb 24, 2021 1:56 PM, Patient x wrote:
Hello,

Thank you so much for arranging for me to get the CGM! It is really helping me learn how to manage my diabetes. I had been feeling sick for months and the device and app prompted to ask questions with my Providers. I discovered that I was taking my medications incorrectly and I was causing myself to go into Hypoglycemic episodes several times a day. This device literally changed my life and improved all of my symptoms, after just a few days of wearing it!

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Digital options for diabetes management

Continuous Glucose Monitoring

Connected pens

Sensor augmented pumps and
Hybrid Closed Loop Pumps

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- Offers a remote, digital solution to care management
- Provides individualized feedback with behavioral modification incentives
- Allows intelligent modification in pharmacotherapy

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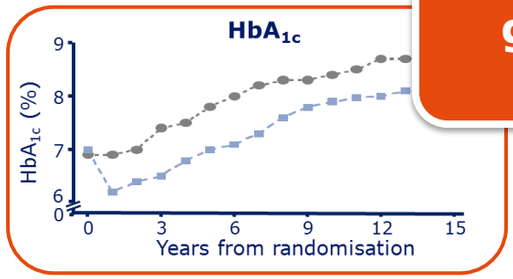
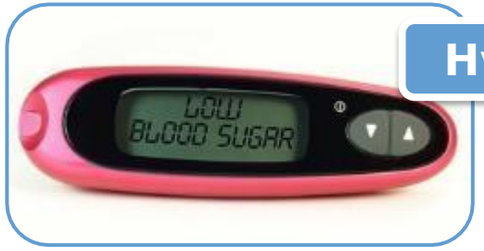
Summary of Key Take Aways

Goals of Therapy-> Overcome Practical Challenges in Diabetes

Treatment complexity



Deteriorating glycemic control



Hypoglycemia

Managing food & Weight gain

Clinical inertia

Inflexible regimens

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UKPDS 34. *Lancet* 1998:352:854–65

Thank you!

Tsimikas.athena@scrippshealth.org
Vincent.lauren@scrippshealth.org

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