Diabetes *Management in 2020: New Medications and New Technology*

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Disclosures: None

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Objectives

- To Review Noninsulin Pharmacotherapy for diabetes
  - Brief overview of medication classes
  - Important new indications, adverse effects and protective effects of newer medications
- To Review Emerging Diabetes Technologies, including:
  - Continuous Glucose Monitors (CGM)
  - Insulin pump basics
  - Insulin Pump and CGM Integration
  - Artificial Pancreas/Hybrid Closed Loop Technology
  - Other Diabetes Technology on the horizon

Pharmacotherapy for Diabetes

- 12 classes of medications now available for treatment of diabetes
- Several new medications approved in the past two years
- New data about CV, renal and other effects of several medications

Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
α-Glucosidase inhibitors	• Delay carbohydrate absorption from intestine	Acarbose Miglitol	Precose or generic Glyset
Amylin analogue	• Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Pramlintide	Symlin
Biguanide	• Decrease HGP • Increase glucose uptake in muscle	Metformin	Glucophage or generic
Bile acid sequestrant	• Decrease HGP? • Increase incretin levels?	Colesevelam	WelChol
DPP-4 inhibitors	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
Dopamine-2 agonist	• Activates dopaminergic receptors	Bromocriptine	Cycloset
Glinides	• Increase insulin secretion	Nateglinide Repaglinide	Starlix or generic Prandin

DPP-4, dipeptidyl peptidase; HGP, hepatic glucose production.

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.
Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

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Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
GLP-1 receptor agonists	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide Lixisenatide Semiglutide	Tanzeum Trulicity Byetta Bydureon Victoza Adlyxin, Soliqua Ozempic, Rybelus
SGLT2 inhibitors	• Increase urinary excretion of glucose	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Invokana Farxiga Jardiance Steglatro
Sulfonylureas	• Increase insulin secretion	Glimepiride Glipizide Glyburide	Amaryl or generic Glucotrol or generic Diaβeta, Glynase, Micronase, or generic
Thiazolidinediones	• Increase glucose uptake in muscle and fat • Decrease HGP	Pioglitazone Rosiglitazone	Actos Avandia

GLP-1, glucagon-like peptide; HGP, hepatic glucose production; SGLT2, sodium glucose cotransporter 2.

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.
Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

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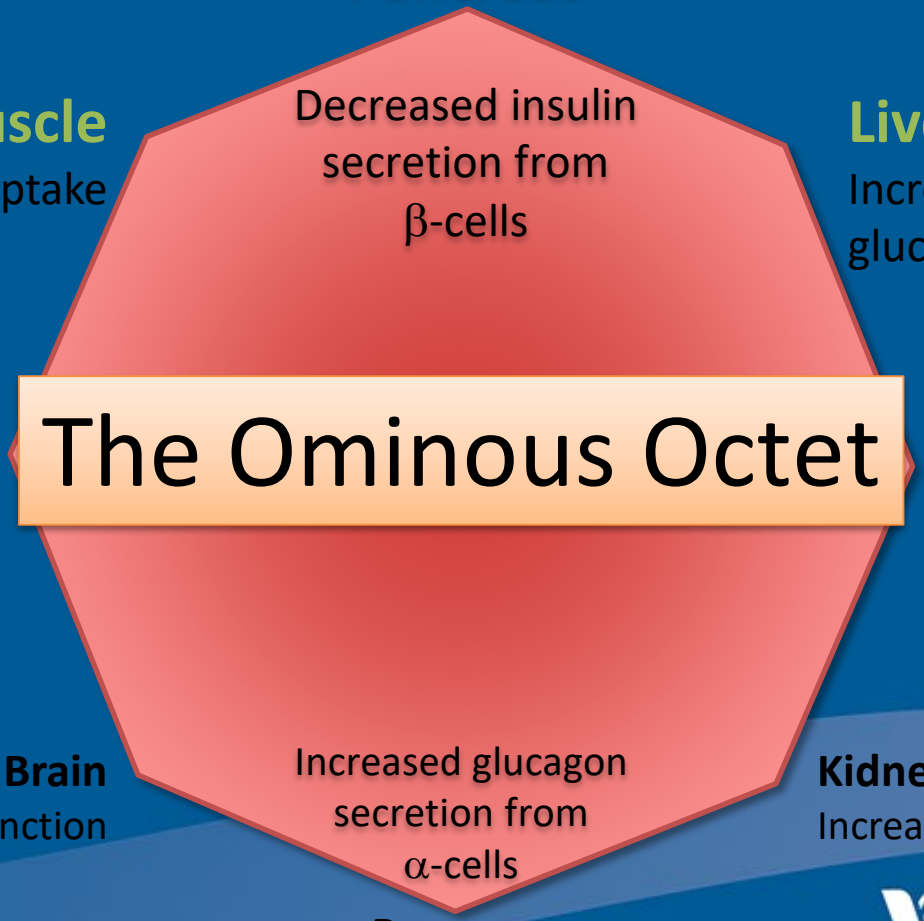
Pathophysiology of Diabetes



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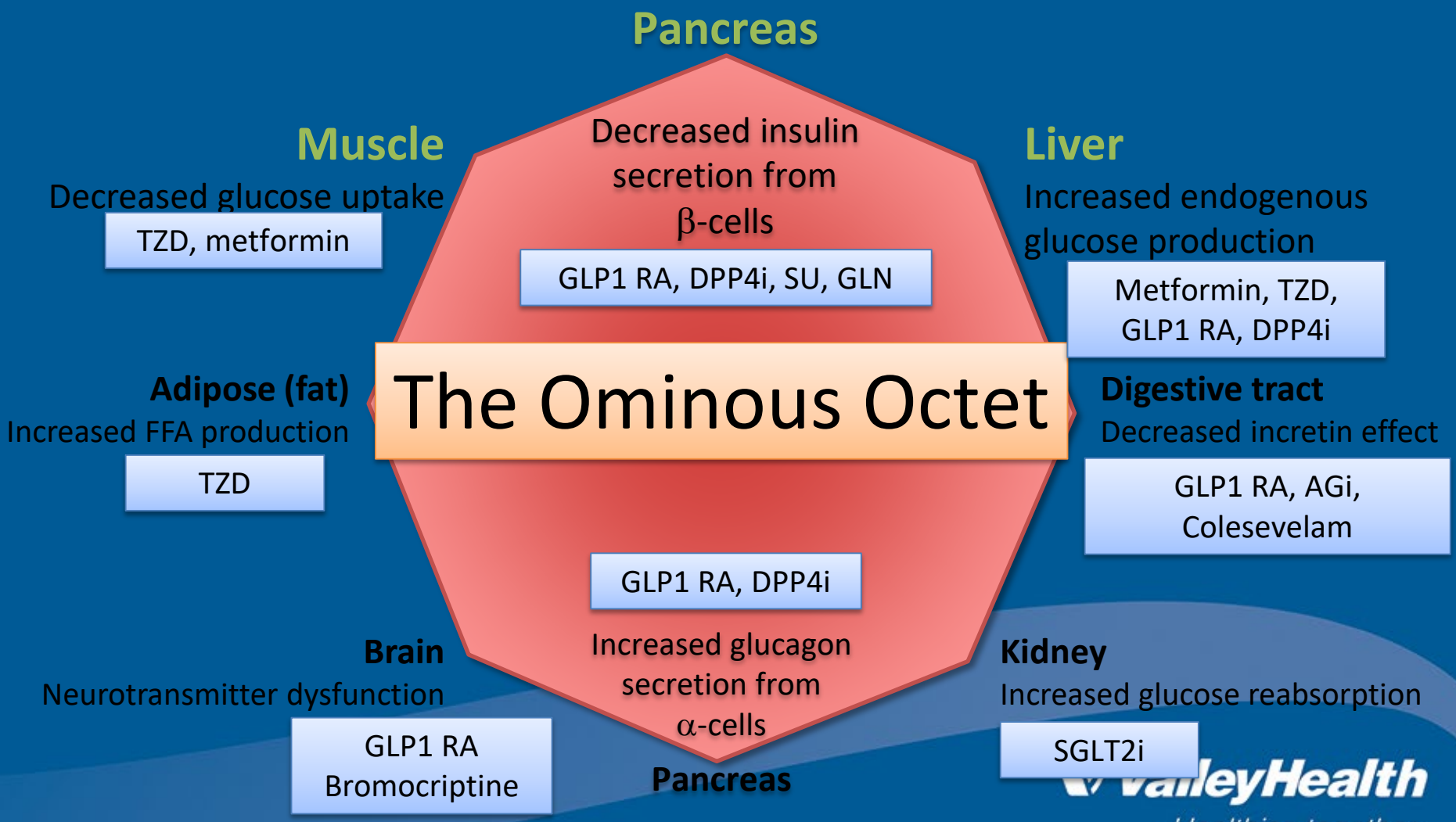
DeFronzo RA. *Diabetes*. 2009;58:773-795

Sites of Action of Diabetes Pharmacotherapy



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Diabetes Pharmacotherapy and CV Risk

- Substantial historical evidence indicates that intensive, ongoing glucose control in newly diagnosed T2D patients may decrease long-term CVD rates[1]
- In 2008, FDA guidance mandated CV safety assessment of all new antihyperglycemic agents[2]
  - RCT studies required to demonstrate that study drug was not associated with more major adverse CV events than placebo (noninferiority)
    - Some studies tested for superiority if noninferiority criteria were met
  - **Primary outcome:** Composite of CV death, nonfatal MI, and nonfatal stroke
    - Some studies included additional endpoints
- Several studies of SGLT-2 inhibitors and GLP-1 RA have shown superiority compared with placebo.

CV, cardiovascular; CVD, cardiovascular disease; FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MI, myocardial infarction; RCT, randomized controlled trial; SGLT-2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

1. American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.

2. FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. https://www.fda.gov/media/71297/download.

Metformin

Recommended for All Patients, Unless Contraindicated or Not Tolerated

Hypoglycemia	Neutral
Weight	Slight loss
Renal / Genitourinary	Contraindicated if eGFR <30 mL/min/1.73 m^2
Gastrointestinal adverse effects	Moderate
Cardiac	Neutral
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

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eGFR = estimated glomerular filtration rate.

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

Secretagogues

	SU	GLN
Hypoglycemia	Moderate / severe	Mild
Weight	Gain	
Renal / Genitourinary	More hypoglycemia risk	
Gastrointestinal adverse effects	Neutral	
Cardiac—CHF	More CHF risk	
Cardiac--ASCVD	?	
Bone	Neutral	
Ketoacidosis	Neutral	

Few adverse events or possible benefits Use with caution Likelihood of adverse effects ? Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; GLN = glinide; SU = sulfonylurea.

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

Dipeptidyl Peptidase 4 Inhibitors (DPP4is)

Hypoglycemia	Neutral
Weight	Neutral
Renal / Genitourinary	Dose adjustment necessary (except linagliptin) Effective in reducing albuminuria
Gastrointestinal adverse effects	Neutral
Cardiac—CHF	Possible risk for saxagliptin and alogliptin
Cardiac--ASCVD	Neutral
Bone	Neutral
Ketoacidosis	Neutral

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ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure.

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

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Summary of Published DPP4i Cardiovascular Outcomes Trials

	EXAMINE**	SAVOR-TIMI 53 (Saxagliptin (Onglyza))	TECOS	CARMELINA
Primary outcome, HR (95% CI)	0.96 (≤1.16)‡	1.00 (0.89-1.12)	0.98 (0.88-1.09)	1.02 (0.89-1.17)
CV death, HR (95% CI)	0.79 (0.60-1.04)	1.03 (0.87-1.22)	1.03 (0.89-1.19)	0.96 (0.81-1.14)
Fatal or nonfatal MI, HR (95% CI)	1.08 (0.88-1.33)	0.95 (0.80-1.12)	0.95 (0.81-1.11)	1.12 (0.90-1.40)
Fatal or nonfatal stroke, HR (95% CI)	0.91 (0.55-1.50)	1.11 (0.88-1.39)	0.97 (0.79-1.19)	0.91 (0.67-1.23)
All-cause mortality, HR (95% CI)	0.88 (0.71-1.09)	1.11 (0.96-1.27)	1.01 (0.90-1.14)	0.98 (0.84-1.13)
HF hospitalization, HR (95% CI)		1.27 (1.07-1.51)	1.00 (0.83-1.20)	0.90 (0.74-1.08)

‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01. * Numerical imbalance (not statistically significant) with increased hospitalizations for heart failure with alogliptin.

CI, confidence interval; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CV, cardiovascular; DPP4i, dipeptidyl peptidase-4 inhibitors; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin

1. White WB, et al. *N Engl J Med*. 2013 Oct 3;369(14):1327-35.

2. Scirica BM, et al. *N Engl J Med*. 2013 Oct 3;369(14):1317-26.

3. Green JB, et al. *N Engl J Med*. 2015 Jul 16;373(3):232-42.

4. Rosenstock J, et al. *JAMA*. 2019 Jan 1;321(1):69-79.

Glucagon-like Peptide 1 Receptor Agonists (GLP1 RAs)

Hypoglycemia	Neutral
Weight	Loss
Renal / Genitourinary	Exenatide not indicated if CrCl <30 mL/min
	Possible benefit of liraglutide
Gastrointestinal adverse effects	Moderate
Cardiac—CHF	Possible benefit of liraglutide
Cardiac--ASCVD	Possible cardiovascular benefit
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits Use with caution Likelihood of adverse effects ? Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance.

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

Summary of Published GLP-1 RA Cardiovascular Outcomes Trials

	Liraglutide (Victoza)	Semaglutide (Ozempic)	Exenatide Bydureon	Lixisenatide (Adlyxin)	Albiglutide (Tanzeum)	Dulaglutide (Trulicity)
	LEADER	**SUSTAIN-6**	**EXSCEL**	**ELIXA**	**HARMONY**	**REWIND**
Primary outcome, HR (95% CI)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.91 (0.83-1.00)	1.02 (0.89-1.17)	0.78 (0.68-0.90)	**0·88 (0.79-0.99)**
CV death, HR (95% CI)	0.78 (0.66-0.93)	**0.98 (0.65-1.48)**	**0.88 (0.76-1.02)**	0.98 (0.78-1.22)	0.93 (0.73-1.19)	**0·91 (0.78-1.06)**
Fatal or nonfatal MI, HR (95% CI)	0.86 (0.73-1.00)	**0.74 (0.51-1.08)**	**0.97 (0.85-1.10)**	1.03 (0.87-1.22)	0.75 (0.61-0.90)	**0·96 (0.79-1.15)**
Fatal or nonfatal stroke, HR (95% CI)	**0.86 (0.71-1.06)**	**0.61 (0.38-0.99)**	0.85 (0.70-1.03)	1.12 (0.79-1.58)	0.86 (0.66-1.14)	**0·76 (0.62-0.94)**
All-cause mortality, HR (95% CI)	0.85 (0.74-0.97)	**1.05 (0.74-1.50)**	0.86 (0.77-0.97)	0.94 (0.78-1.13)	0.95 (0.79-1.16)	**0.90 (0.80-1.01)**
HF hospitalization, HR (95% CI)	**0.87 (0.73-1.05)**	1.11 (0.77-1.61)	0.94 (0.78-1.13)	0.96 (0.75-1.23)		**0·93 (0.77-1.12)**

CV, cardiovascular; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HARMONY, Harmony Outcomes (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus); HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

1. Adapted from Das SR, et al. J Am Coll Cardiol. 2018;72:3200-3223.

2. Gerstein HC, et al. Lancet. 2019; http://dx.doi.org/10.1016/S0140-6736(19)31149-3; e-pub ahead of print.

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2is)

Hypoglycemia	Neutral
Weight	Loss
Renal / Genitourinary	Not indicated for eGFR <30 or <45 mL/min/1.73 m^2 Genital mycotic infections, UTIs
	Possible benefit (delayed progression of CKD) of empagliflozin, dapagliflozin, canagliflozin
Gastrointestinal adverse effects	Neutral
Cardiac—CHF	Possible benefit (Dapagliflozin now approved for CHF w/ or w/out DM)
Cardiac--ASCVD	Possible cardiovascular benefit
Bone	Canagliflozin warning
Ketoacidosis	DKA occurring in T2D in various stress settings

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

Summary of Published SGLT-2i Cardiovascular Outcomes Trials

	Empaglifozin (Jardiance)	Canaglifozin (Invokana)	Dapaglifozin (Farxiga)	Canaglifozin (Invokana)
	EMPA-REG OUTCOME	**CANVAS/CANVAS-R**	**DECLARE - TIMI 58**	**CREDENCE‡**
MACE outcome (HR [95% CI])*	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)**	0.80 (0.67-0.95)
CV death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.61-1.00)
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)	
Fatal or nonfatal stroke	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	
All-cause mortality	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.83 (0.68–1.02)
Heart failure hospitalization	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47–0.80)

*MACE outcome: cardiovascular death, non-fatal MI, non-fatal stroke (primary outcome in EMPA-REG, CANVAS/CANVAS-R, and DECLARE-TIMI 58, secondary outcome in CREDENCE). **Additional primary outcome in DECLARE-TIMI 58: CV death and hospitalization for heart failure, HR= 0.83 (0.73−0.95). ‡ CREDENCE enrolled patients with diabetic kidney disease. Primary outcome included composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 sustained for at least 30 days), doubling of the serum creatinine level, or death from renal or cardiovascular disease. The primary outcome was lower in those receiving canagliflozin HR= 0.7 (0.59-0.82).

CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus; CV, cardiovascular; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MI, myocardial infarction; SLGT2, sodium-glucose cotransporter 2. CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation.

Adapted from Das SR, et al. *J Am Coll Cardiol.* 2018;72:3200-3223.

Newer Studies re: SGLT2i Benefits

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

Christopher P. Cannon, M.D., Richard Pratley, M.D., Samuel Dagogo-Jack, M.D., D.Sc., James Mancuso, Ph.D., Susan Huyck, Dr.P.H., Urszula Masiukiewicz, M.D., Bernard Charbonnel, M.D., Robert Frederich, M.D., Ph.D., Silvina Gallo, M.D., Francesco Cosentino, M.D., Ph.D., Weichung J. Shih, Ph.D., Ira Gantz, M.D., et al., for the VERTIS CV Investigators*

METHODS

In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to

CONCLUSIONS

Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.)

event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P=0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.

CONCLUSIONS

Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.)

October 8, 2020

N Engl J Med 2020; 383:1425-1435

Newer Studies re: SGLT2i Benefits

The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer, M.D., Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., Subodh Verma, M.D., Ph.D., Hiroyuki Tsutsui, M.D., Martina Brueckmann, M.D., Waheed Jamal, M.D., Karen Kimura, Ph.D., et al., for the EMPEROR-Reduced Trial Investigators*

Abstract

BACKGROUND Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

METHODS In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in

CONCLUSIONS Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.)

0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (–0.55 vs. –2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

CONCLUSIONS Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.)

October 8, 2020
N Engl J Med 2020; 383:1413-1424

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Newer Studies re: SGLT2i Benefits

The NEW ENGLAND JOURNAL of MEDICINE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., et al., for the DAPA-CKD Trial Committees and Investigators*

October 8, 2020
N Engl J Med 2020; 383:1436-1446
DOI: 10.1056/NEJMoa2024816

Abstract

BACKGROUND Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body surface area and a urinary albumin-to-creatinine ratio

primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

CONCLUSIONS Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

October 8, 2020
N Engl J Med 2020; 383:1436-1446

Normoglycemic DKA with SGLT2i Drugs

- DKA occurs infrequently
- Risk factors include:
  - anorexia, gastroparesis, fasting, ketogenic diet, and alcoholism
- Other triggers include:
  - pregnancy, pancreatitis, glycogen storage disorders, surgery, infection, cocaine toxicity, cirrhosis, and insulin pump use
- DKA diagnosis may be missed or delayed due to atypical presentation involving lower-than-anticipated glucose levels or other misleading laboratory values
- SGLT2i should be held prior to surgeries and in inpatient settings

DKA = diabetic ketoacidosis; SGLT2 = sodium glucose cotransporter 2.

Handelsman Y, et al. *Endocr Pract*. 2016;22:753-762.

Presentation and Diagnosis of DKA

- Atypical presentation of DKA: high anion gap metabolic acidosis with elevated blood or urine ketones and normal, or slightly high blood glucose[a]
- Signs and symptoms: difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue and sleepiness[a]
- If acidosis confirmed, the SGLT2 inhibitor should be discontinued; appropriate steps then taken to correct the acidosis; and blood glucose levels monitored[b]

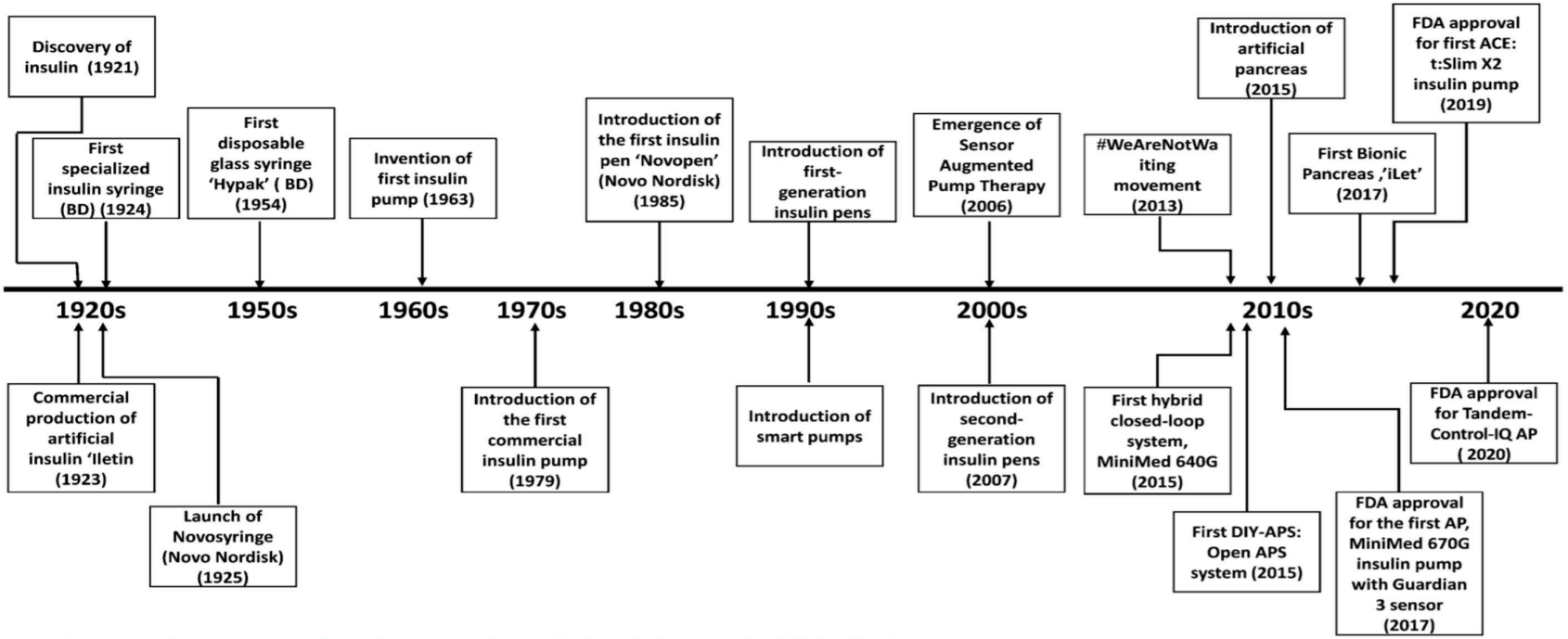
Encourage patients to read the Medication Guide or Patient Package Insert that accompanies their SGLT2 inhibitor prescription.

a. FDA website.[4]

b. Westerberg DP. *Am Fam Physician*. 2013;87:337-346.[6]

Diabetes Technology

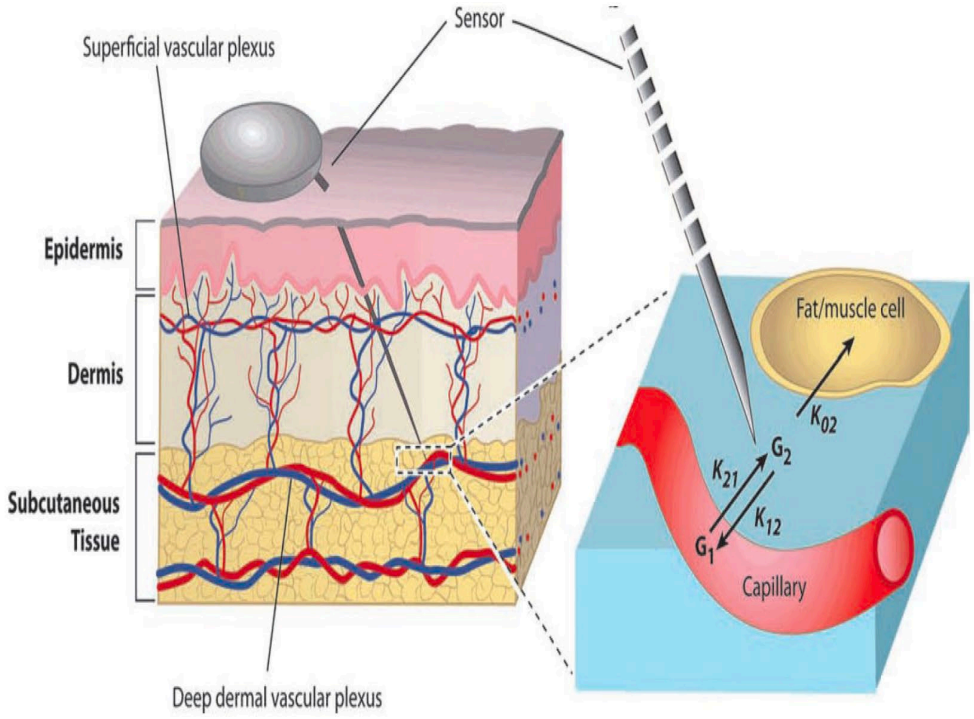
Diabetes Technology Timeline



Kesavadev et al. Diabetes Ther. 2020 Jun;11(6):1251-1269. doi: 10.1007/s13300-020-00831-z.

Continuous Glucose Monitoring (CGM)

Monitoring Glycemic Control: Continuous Glucose Monitoring (CGM)



- With CGM, a small sensor is placed under the skin, to measure the interstitial glucose levels in intervals of 5 to 15 minutes[1]
- CGM provides a more comprehensive assessment of glycemic control
- CGM can inform patients of impending glucose excursions using glucose trend arrows and influence treatment decisions[2]
- CGM devices continue to become easier to use, more accurate, and more accessible to patients[2]

Figure: Cengiz and Tamborlane. Diabetes Technol Ther. 2009. Jun;11 (Suppl 1)

1. Bergenstal et al. *Diabetes Care*. 2018 Nov;41(11):2275-2280.
2. Ajjan et al. *Adv Ther*. 2019 Mar;36(3):579-596.

Continuous Glucose Monitoring

- 3 types of CGM systems:
  - Real-time CGM
    - Provides continuous data on sensor glucose values, trends and alarms to the CGM receiver or smartphone
  - Intermittent scanned CGM
    - Glucose data and trend information are available after scanning the CGM sensor with the receiver or smartphone
    - Newer versions have real-time optional alarms
  - Professional CGM
    - A blinded CGM sensor is placed on the patient and worn for two weeks to obtain data on glucose values and trends
    - No real-time glucose data or alarms, only retrospective review of sensor glucose data

Current Commercially-Available CGM Systems

FreeStyle Libre
FLASH GLUCOSE MONITORING SYSTEM

Abbott

No user calibration required

Medtronic

eversense
Continuous Glucose Monitoring System

Only implantable CGM

dexcom
CONTINUOUS GLUCOSE MONITORING

No user calibration required

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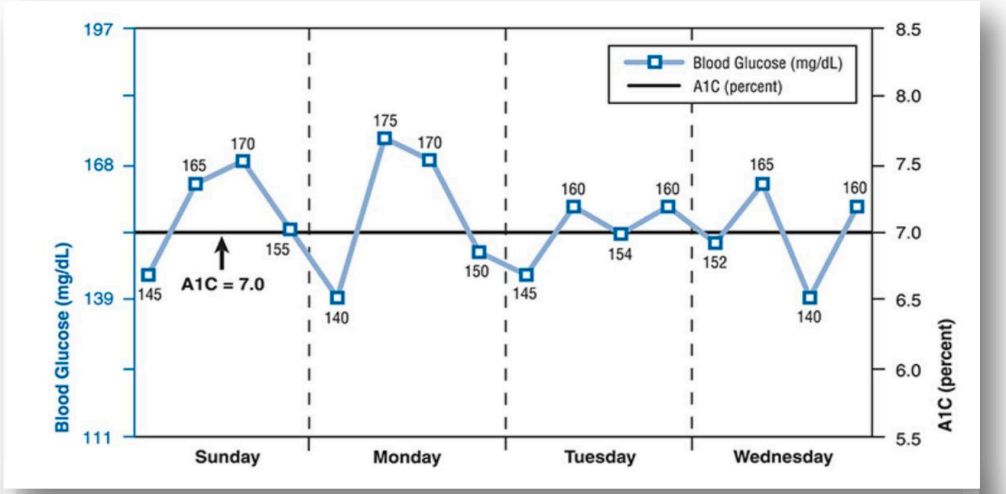
Assessing Glycemic Control: Hemoglobin A1c

- Hemoglobin A1C (A1C) indirectly measures average blood glucose levels over a 3-month period
- Has advantages over fasting plasma glucose or oral glucose tolerance tests, providing a longer-term average of glucose levels
- Widely used and accepted metric of glycemic control with strong predictive value for diabetic complications



Blood glucose (mg/dL) measurements were taken four times per day (fasting or pre-breakfast, pre-lunch, pre-dinner, and bedtime).

The straight black line shows an A1C measurement of 7.0 percent. The blue line shows an example of how blood glucose test results might look from self-monitoring four times a day over a 4-day period.

ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S61-S70.
Image: https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test#diagnose
Accessed January 9, 2020.

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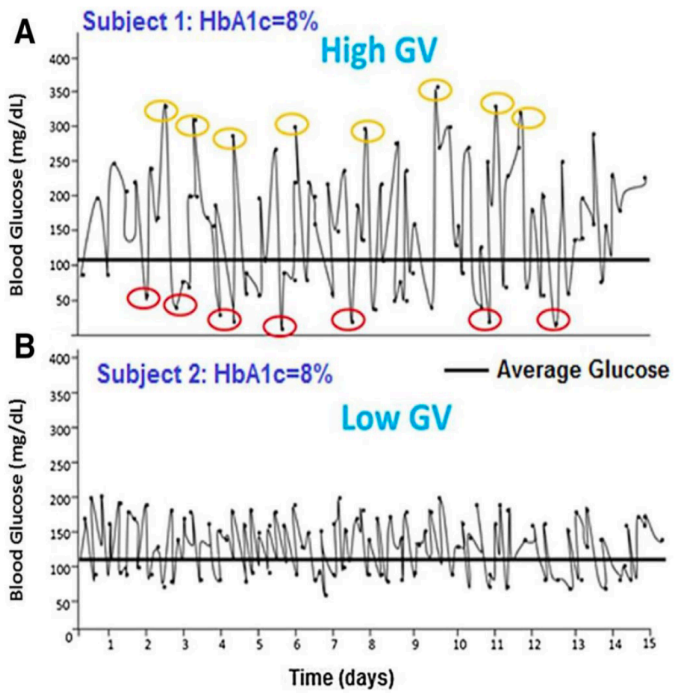
Limitations of A1c for Assessment of Glycemic Control

- Variability in the measurement of A1C
- Conditions that affect red blood cell turnover cause A1C discrepancies:
  - Hemolytic and other anemias
  - Glucose-6 phosphate dehydrogenase deficiency
  - Erythropoietic drugs
  - Recent blood transfusion
  - End-stage renal disease
  - Pregnancy
- Unreliable results in the presence of hemoglobinopathies
- Racial differences in A1C

ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S61-S70.

Glycemic Variability

- A1C is easy to measure but provides limited insight into glucose control patterns
- Wide range of mean glucose variability can correspond to the same 3 month A1C measurement
- Short-term glycemic variability or hypoglycemic events can be missed
- CGM metrics can give a better picture of glycemic variability



Foster NC, Beck RW, Miller KM, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018 [published correction appears in Diabetes Technol Ther. 2019 Apr;21(4):230]. *Diabetes Technol Ther*. 2019;21(2):66-72. doi:10.1089/dia.2018.0384

A1C, hemoglobin A1C; CGM, continuous glucose monitoring.

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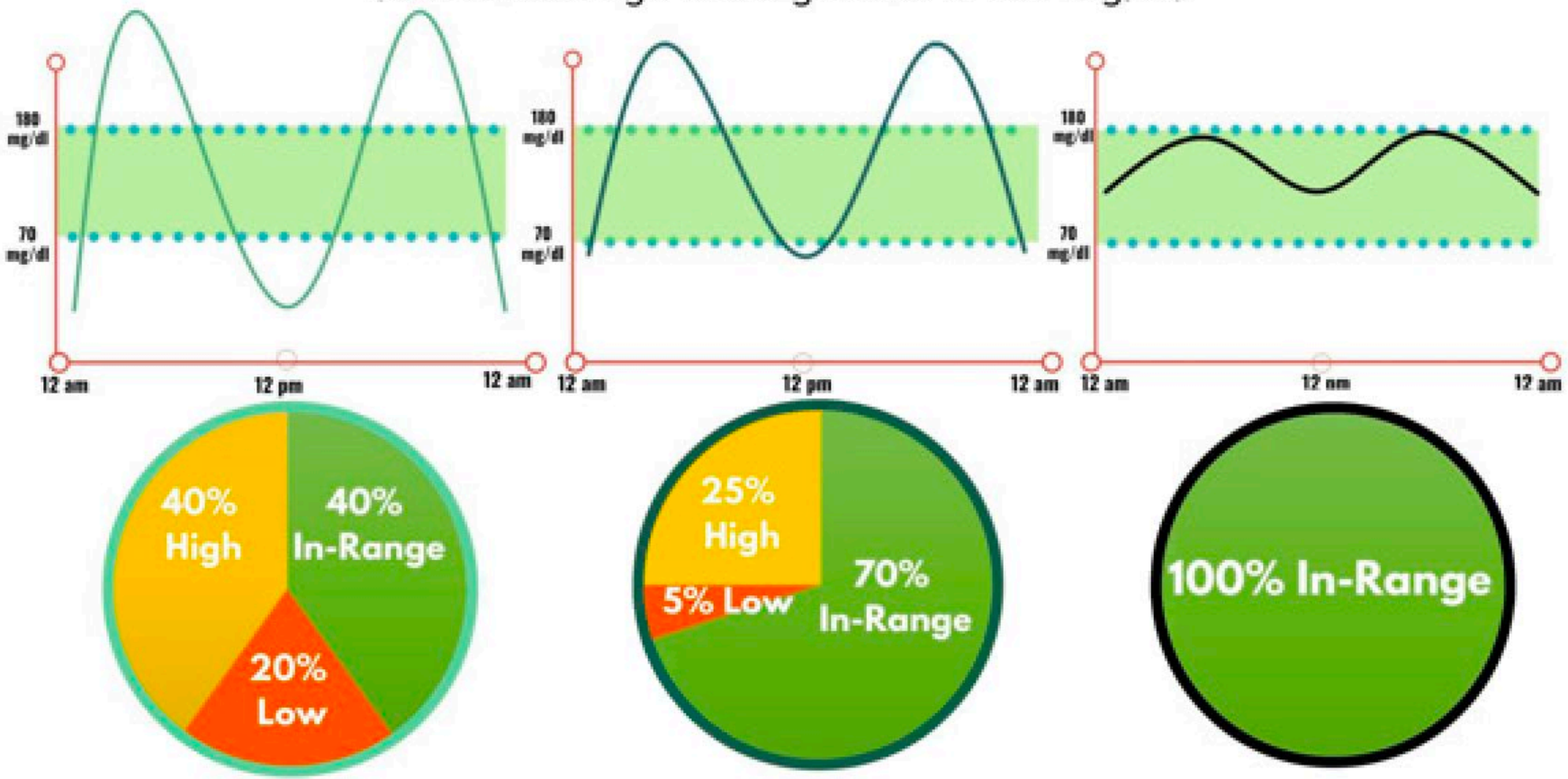
THE MANY FACES OF A 7% A1C

(and an average blood glucose of 154 mg/dl)



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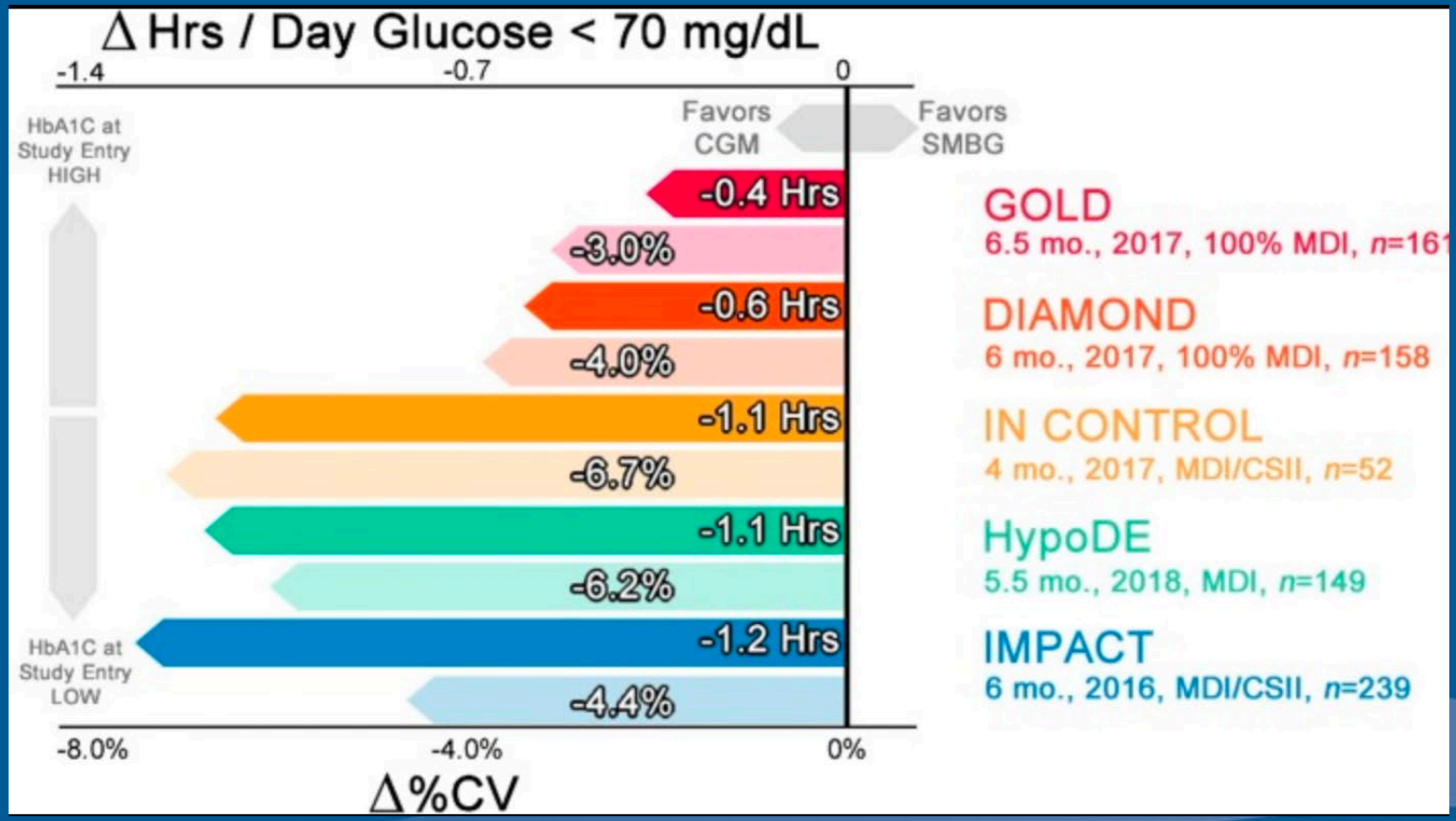
Magnitude of reduction in time in hypoglycemia and CV according to baseline A1c with CGM



Martin et al. Curr Diab Rep. 2019; 19(8): 50.Published online 2019 Jun 27. doi: 10.1007/s11892-019-1177-7

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CGM Use in Inpatient Setting