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International Diabetes Center

Type 2 Diabetes: What's New?

Gregg Simonson, PhD

Director, Care Transformation and Training International Diabetes Center;
Adjunct Assistant Professor, University of Minnesota Medical School, Department of
Family Practice and Community Health

International Diabetes Center...

Ensuring that every individual with diabetes or at risk for diabetes receives the best possible care

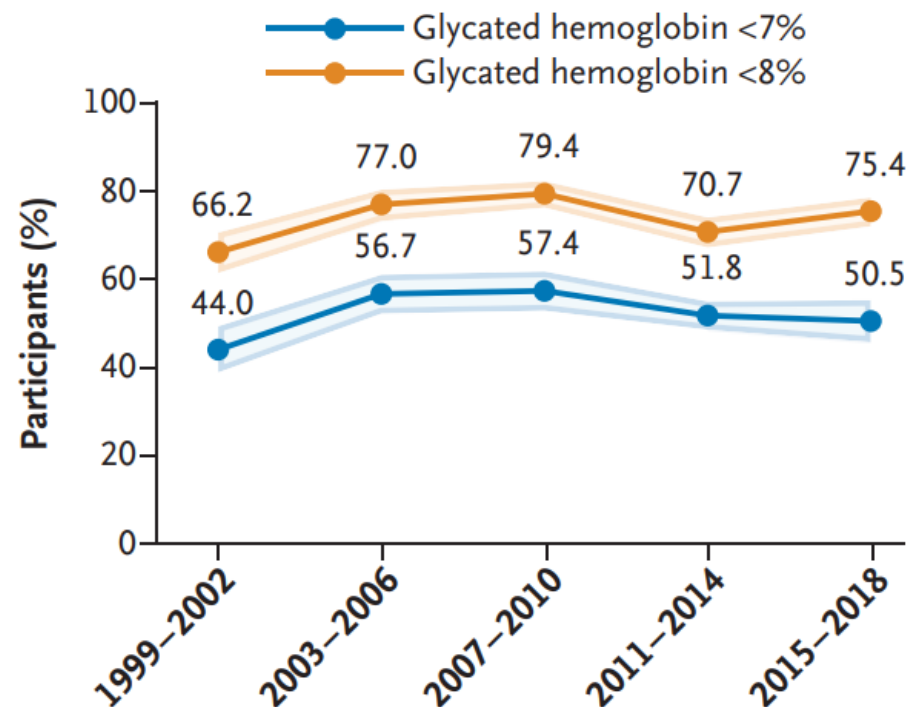


Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018

Michael Fang, Ph.D., Dan Wang, M.S., Josef Coresh, M.D., Ph.D.,
and Elizabeth Selvin, Ph.D., M.P.H.

N ENGL J MED 384;23 NEJM.ORG JUNE 10, 2021

Glycemic Control

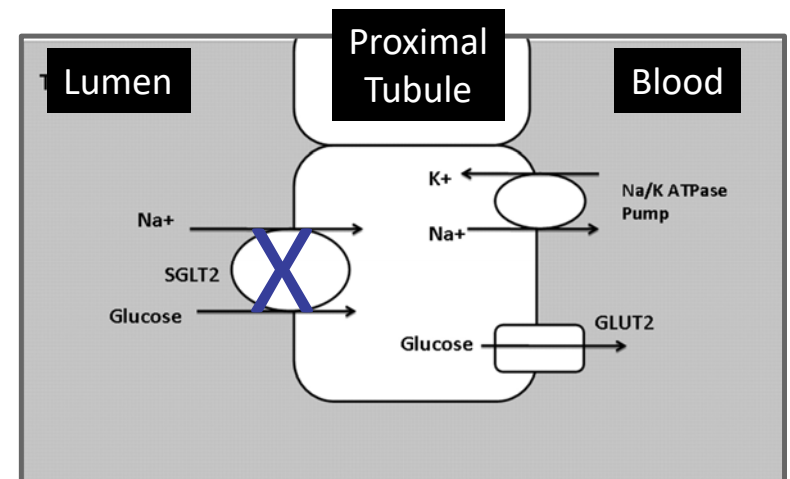


What's New in Type 2 DM Presentation Outline

- Disease modifying classes of type 2 diabetes medications
 - SGLT2 inhibitors
 - GLP-1 receptor agonists
 - American Diabetes Association (ADA) recommendations for SGLT2-i and GLP-1 receptor agonists
- New technology in type 2 diabetes
 - Continuous glucose monitoring (CGM)
 - Insulin smart pens
 - Patch pumps

Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

- Inhibits renal re-absorption through inhibition of SGLT2
 - Selective inhibitor of SGLT2 -- acts in early proximal tubule to block reabsorption of filtered glucose
 - Normally ~180 g glucose filtered/day
- Causes about 70 g (~300 kcal) glucose excretion per day; potential for weight loss



Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance) and Ertugliflozin (Steglatro)

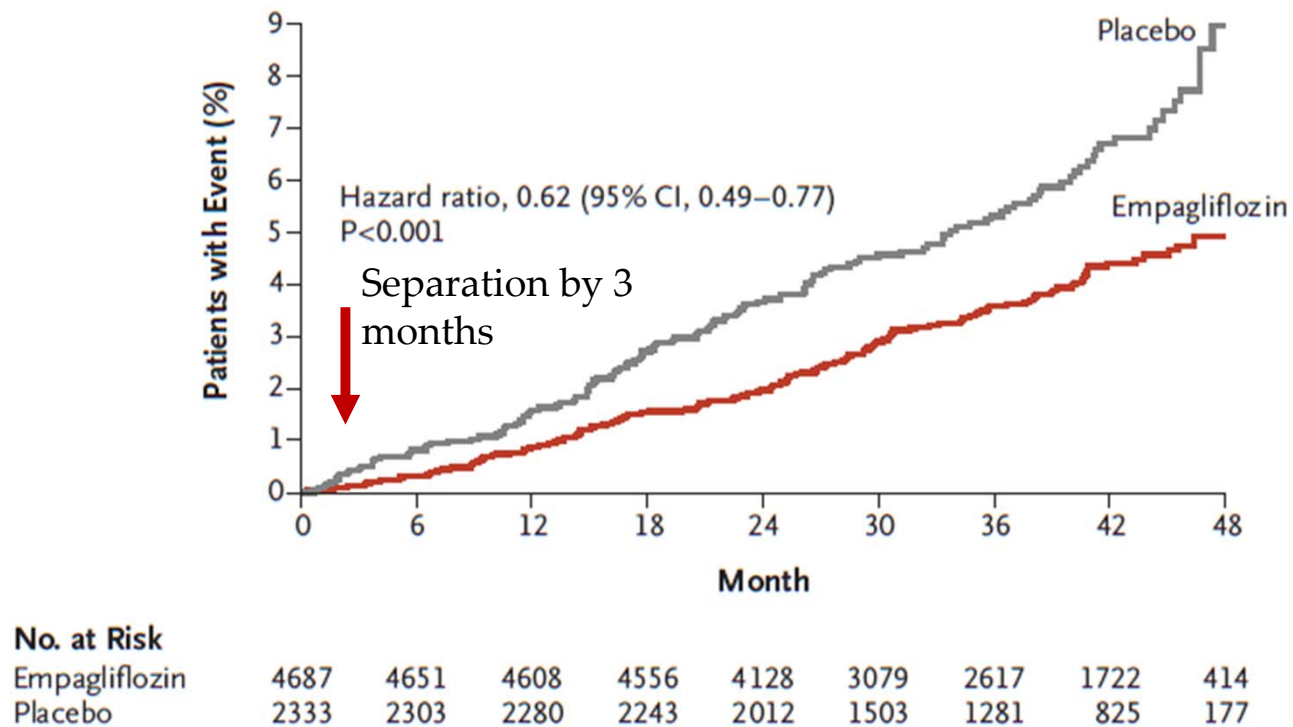
■ Clinical Indicators

- Modest reduction in both FPG and PPG
- Approved as monotherapy, and in combination with metformin, SU, pioglitazone and/or insulin
- Modest weight loss, no additional hypoglycemia

■ Precautions and contraindications

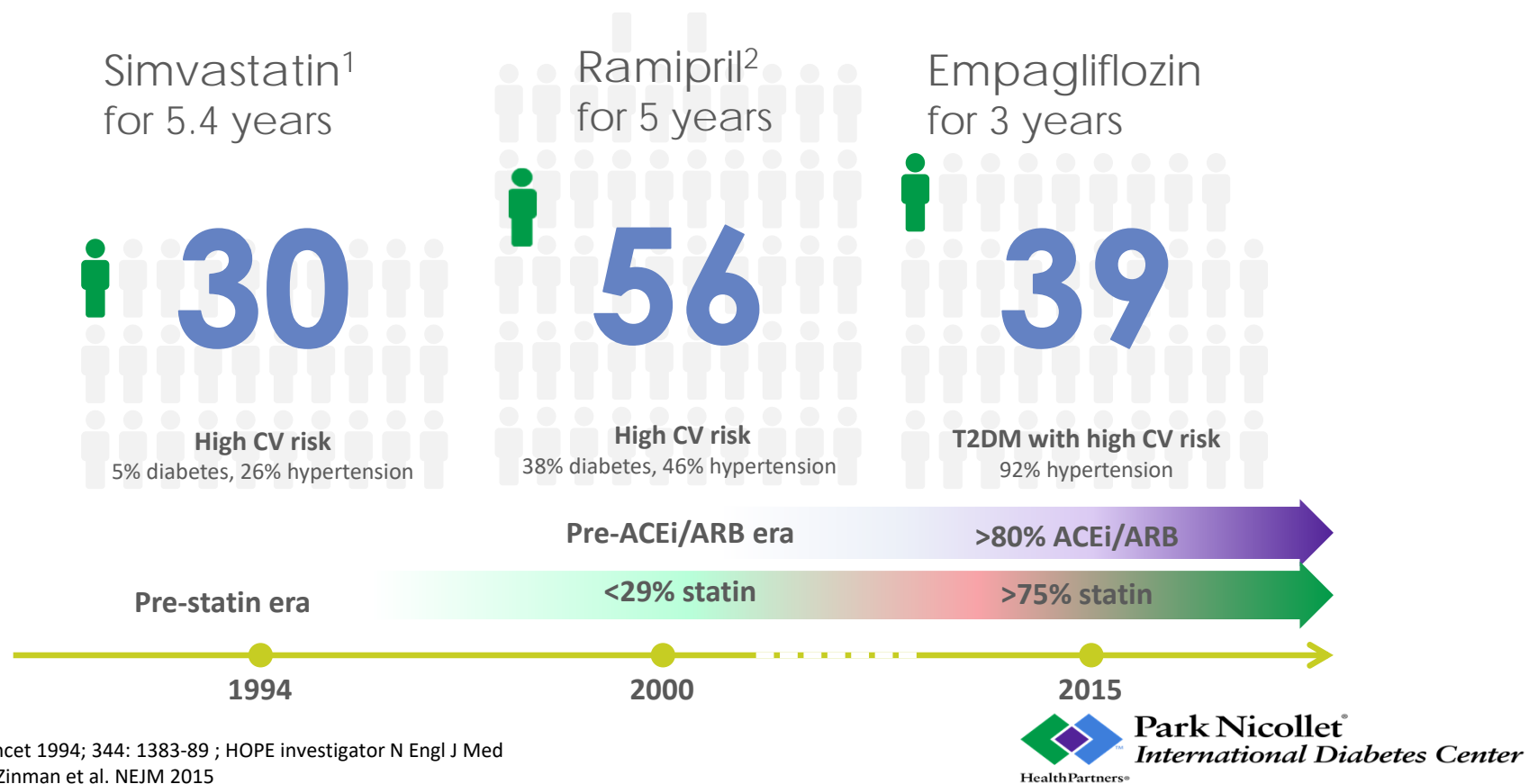
- Use caution with renal impairment (eGFR <30); contraindicated in dialysis
- Symptomatic hypotension especially in elderly, renal impairment, patients treated with loop diuretics, ACE-I, and/or ARBs
- Genital mycotic infections, especially in women or if history of mycotic infections; urinary tract infections; rare cases of necrotizing fasciitis of the perineum
- Acute kidney injury, especially with dehydration, history of CKD
- Euglycemic Diabetic Ketoacidosis (DKA)--- rare

EMPA- REG Outcome: Death From Cardiovascular Causes



In addition a 35% risk reduction in hospitalization for heart failure

Number Needed to Treat (NNT) to Prevent one Death Across Landmark Trials in Patients with High CV Risk



Overview of SGLT2 CVOTs Results

	MACE HR (95% CI)	CV Death HR (95% CI)	HHF HR (95% CI)
EMPA-REG OUTCOME¹ Empagliflozin	0.86 (0.74, 0.99)	0.62 (0.49, 0.77)	0.65 (0.50, 0.85)
CANVAS Program² Canagliflozin	0.86 (0.75, 0.97)	0.87 (0.72, 1.06)	0.67 (0.52, 0.87)
DECLARE-TIMI 58³ Dapagliflozin	0.93 (0.84, 1.03)	0.98 (0.82, 1.17)	0.73 (0.61, 0.88)
VERTIS CV Ertugliflozin	0.97 (0.85, 1.11)	0.92 (0.77, 1.11)	0.70 (0.54, 0.90)

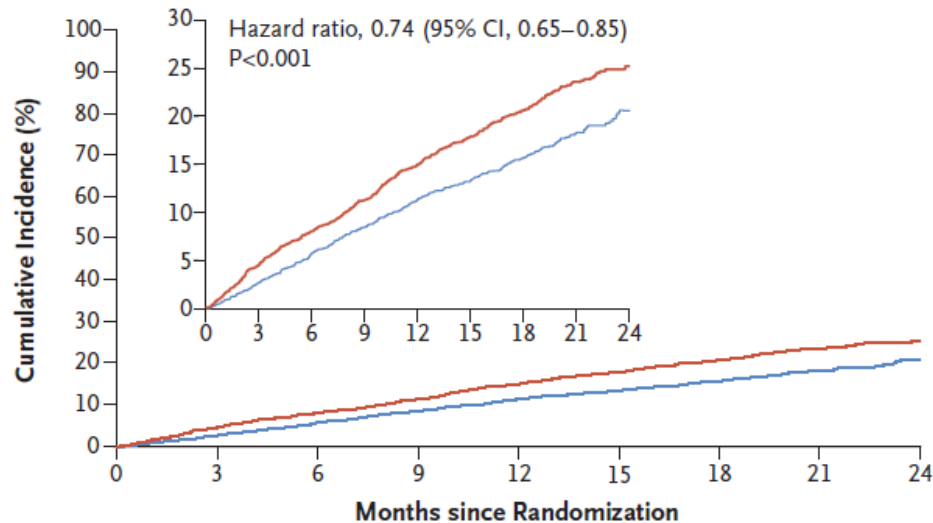
1. Zinman B et al. N Engl J Med 2015;373:2117-2128. 2. Neal B et al. N Engl J Med 2017;377:644-657. 3. Wiviott SD et al. N Engl J Med 2019;380:347-357

DAPA-HF Trial: SGLT2 Inhibitors in Patients with Established HF

- Patients with or without diabetes (60%) and EF \leq 40% (HFrEF)

— Placebo — Dapagliflozin 10 mg

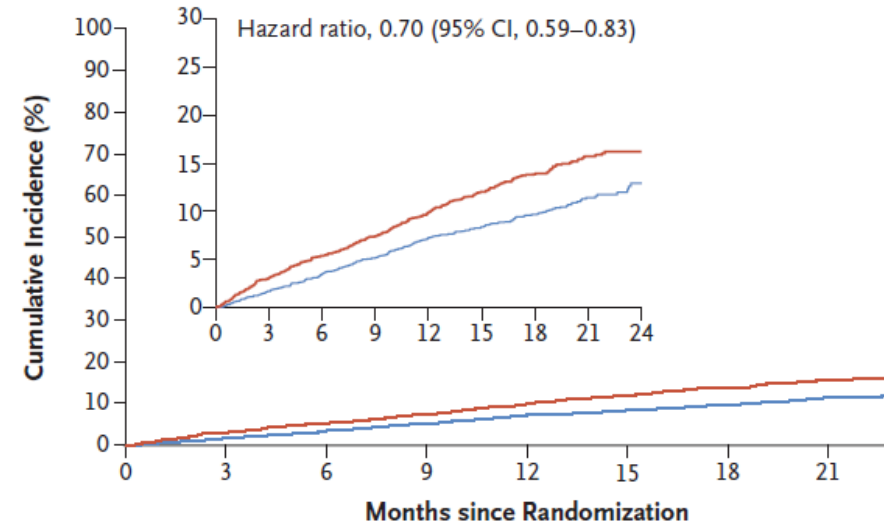
A Primary Outcome Worsening HF (hospitalization or urgent visit for IV therapy for HF) or CV Death



No. at Risk

Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

B Hospitalization for Heart Failure



No. at Risk

Placebo	2371	2264	2168	2082	1924	1483	1101	596
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Ph.D., João P. Ferreira, M.D., Edimar Bocchi, M.D., Michael Böhm, M.D., Ph.D., Hans-Peter Brunner-La Rocca, M.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure-Valenzuela, M.D., Nadia Giannetti, M.D., Juan Esteban Gomez-Mesa, M.D., *et al.*, for the EMPEROR-Preserved Trial Investigators*

August 27, 2021

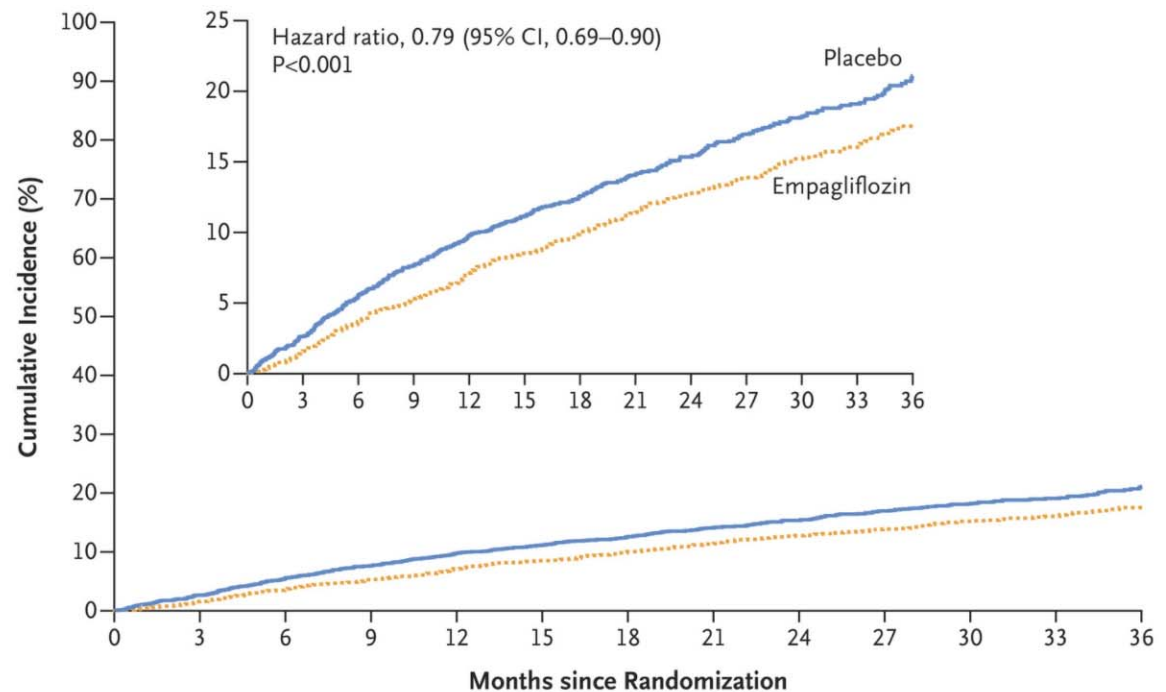
DOI: 10.1056/NEJMoa2107038



The NEW ENGLAND
JOURNAL of MEDICINE

Composite of CV Death and HHF

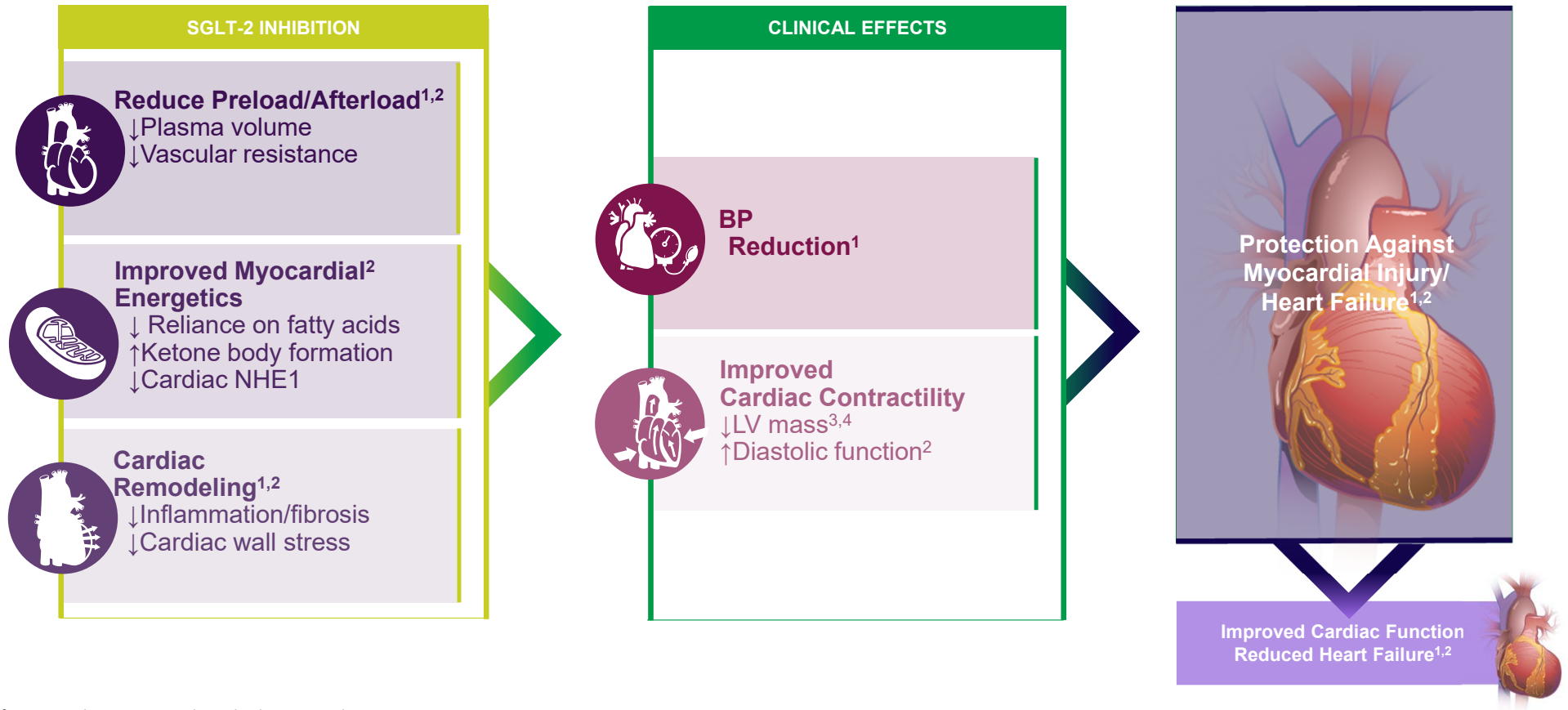
- n = 5988 patients with class II–IV heart failure and an ejection fraction of more than 40%
- Empagliflozin (10 mg once daily) or placebo, in addition to usual therapy
- Primary outcome was a composite of cardiovascular death or hospitalization for heart failure
- Equally effective in patients with or without diabetes



No. at Risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Potential Effects by Which SGLT2 Inhibition Improves Heart Failure



2
LV=left ventricular; NHE1=sodium-hydrogen exchanger 1.

1. Heerspink HJL, et al. *Kidney Int.* 2018;94(1):26-39. 2. Tamargo J. *Eur Cardiol.* 2019;14(1):23-32. 3. Verma S, et al. *Diabetes Care.* 2016;39(12):e212-e213. 4. Verma S. Presented at: American Heart Association Scientific Sessions; Nov. 10-12, 2018; Chicago.

Overview of SGLT2 Renal Outcomes

Renal-related Composite Outcomes

EMPA-REG OUTCOME¹

Empagliflozin

Doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease

HR (95% CI)

0.54
(0.40, 0.75)

CANVAS Program²

Canagliflozin

Sustained 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes

0.60
(0.47, 0.77)

DECLARE-TIMI 58³

Dapagliflozin

Sustained $\geq 40\%$ decrease in eGFR to < 60 mL/min/1.73 m² and/or end-stage renal disease and/or renal or CV death

0.53
(0.43, 0.66)

VERTIS CV

Ertugliflozin

Renal death, dialysis/transplant, or doubling of serum creatinine from baseline

0.81
(0.64, 1.03)

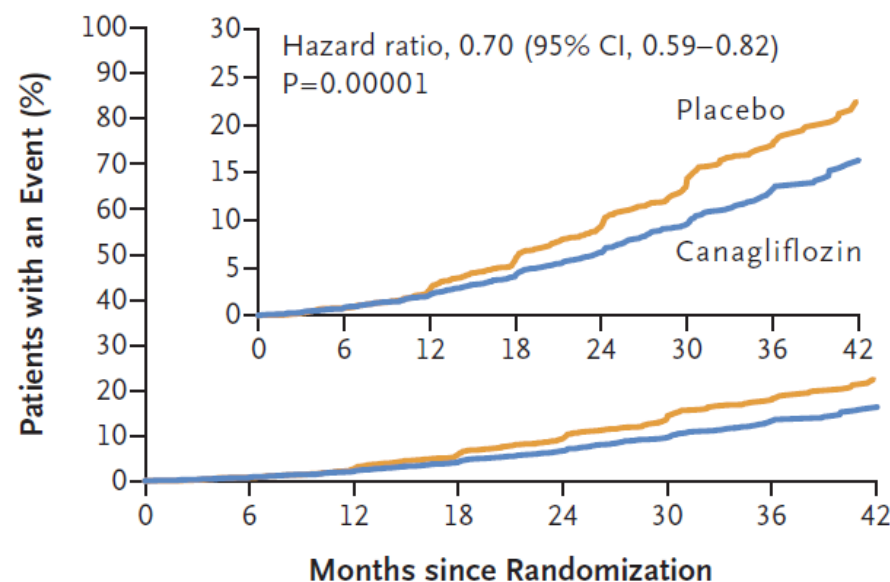
1. Wanner C et al. N Engl J Med 2016;374:323-334. 2. Neal B et al. N Engl J Med 2017;377:644-657. 3. Wiviott SD et al. N Engl J Med 2019;380:347-357.

CREDENCE: Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation

- Comparing efficacy and safety of canagliflozin (Invokana) vs. placebo for adults with T2 DM and CKD
- Patient population
 - A1C 6.5%-12%
 - eGFR 30 to <90 ml/min
 - Albumin creatinine ratio >300 to ≤5000 mg/g
 - Patients to be treated with ACE inhibitor or ARB
- Study halted early based on meeting prespecified criteria showing benefit

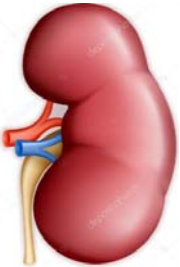
ESKD, doubling SrCr, or death from renal or CV causes

A Primary Composite Outcome

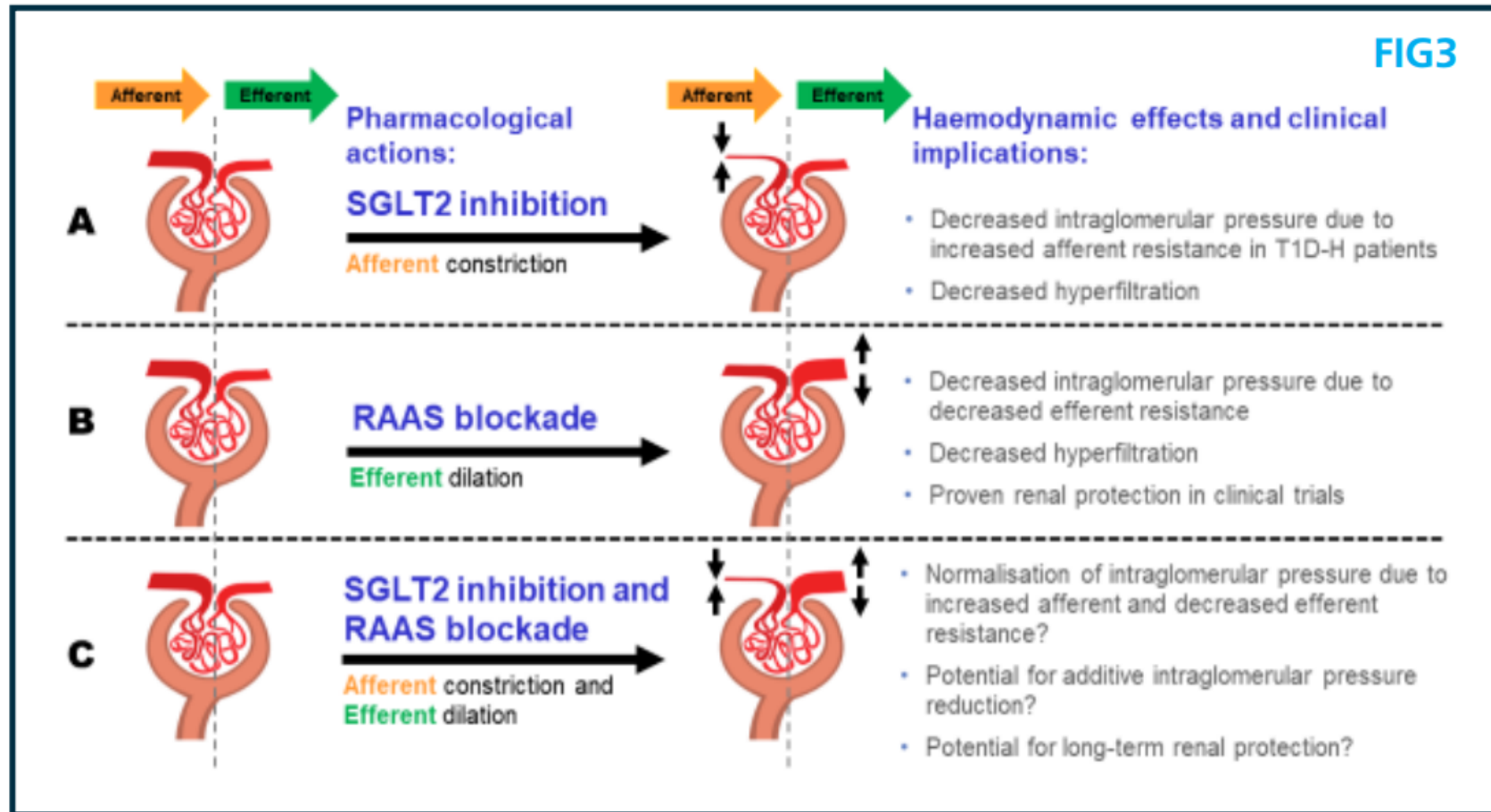


No. at Risk

Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196



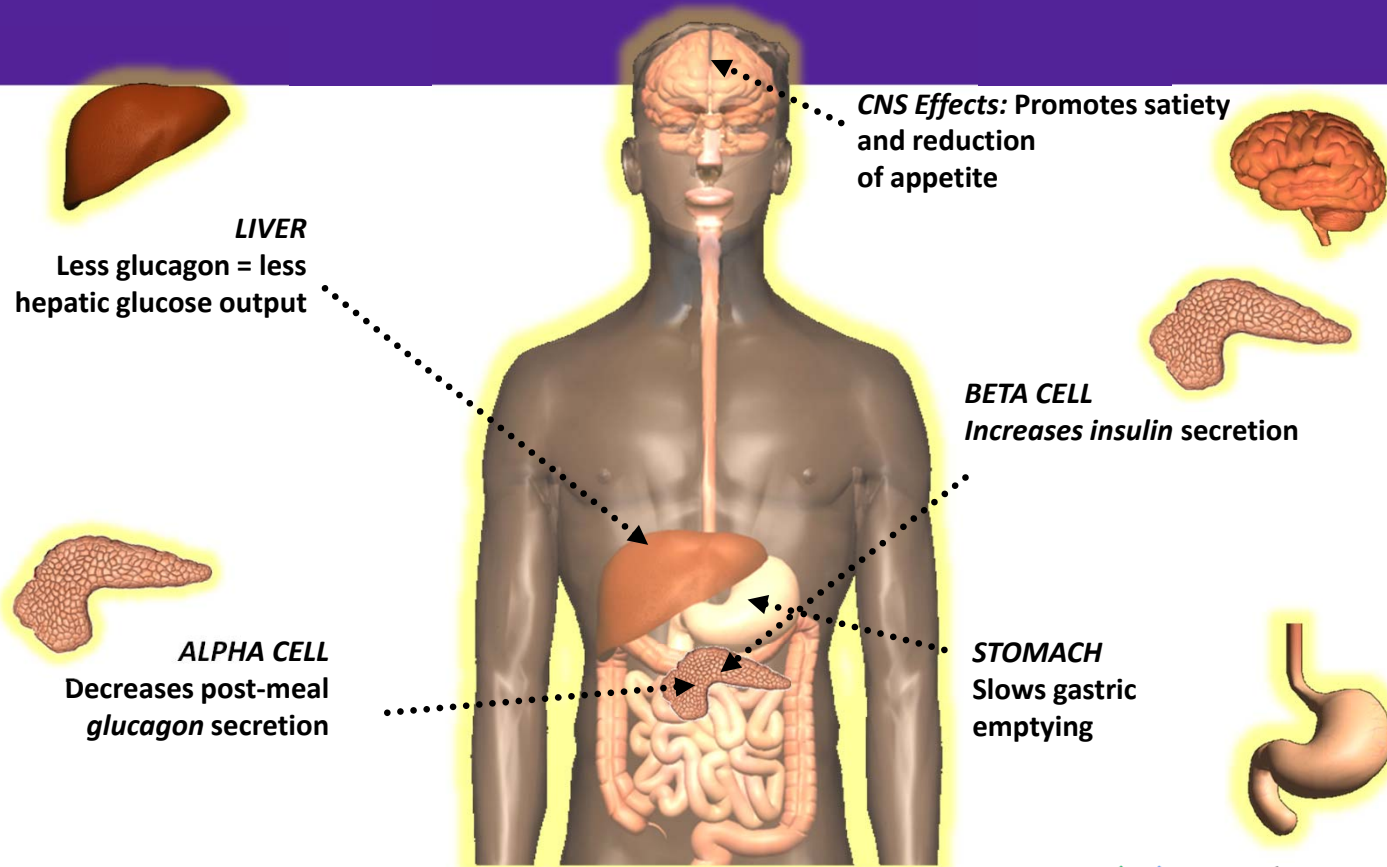
How do SGLT2 Inhibitors Protect the Kidneys



SGLT2 Inhibitor Scorecard

Potential Advantages	Potential Disadvantages
Good BG lowering efficacy	Mycotic infections, necrotizing fasciitis of perineum
No G.I. side effects	Dehydration, hypotension
Modest weight loss (2-3%) in a pill	Limited use with low GFR (<30 ml/min)
Low risk of hypoglycemia	Risk of acute kidney injury???
Lowers BP (~4 mmHg systolic)	DKA (rare but real)
Cardioprotective, especially reduces risk of HHF	Possible increased amputation risk with canagliflozin and ertugliflozin???
Renal protection	Higher cost (~\$590/month)

Glucagon-Like Peptide-1 (GLP-1) Action



Ahren B Curr Diab Rep 2003; 3:365-372.
Baggio LL and Drucker DJ. Gastroenterology 2007; 132:2131-2157.

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

Dulaglutide (Trulicity), Exenatide (Byetta), ExenatideQW (Bydureon), Liraglutide (Victoza), and Semaglutide (Ozempic)

- **Action**
 - Enhances glucose-dependent insulin secretion and glucagon suppression
 - Slows gastric emptying
 - Induce satiety and reduce food intake
- **Clinical Indicators**
 - Elevated postmeal BG (exenatide), elevated postmeal and fasting BG (all others)
 - In combination with metformin, sulfonylurea, thiazolidinedione or insulin
- **Side effects**
 - Transient nausea (up to 40% patients) vomiting (~10%) and diarrhea (~10%)
 - Low risk of hypoglycemia unless used in combination with SU or insulin
 - Modest weight loss in >85% of patients
- **Precautions and Contraindications**
 - Kidney Disease (no exenatide if eGFR <30 ml/min) others use with caution
 - Gastrointestinal disease, pancreatitis (rare)
 - Pregnancy (Category C)

Examples of Injectable GLP-1 Agonists

Exenatide (Byetta) 2 injections/day (32G)



Liraglutide (Victoza) 1 injection/day (32G)



Exenatide QW (Bydureon) 1 injection/week (23G)



Dulaglutide (Trulicity) 1 injection/week (29G)

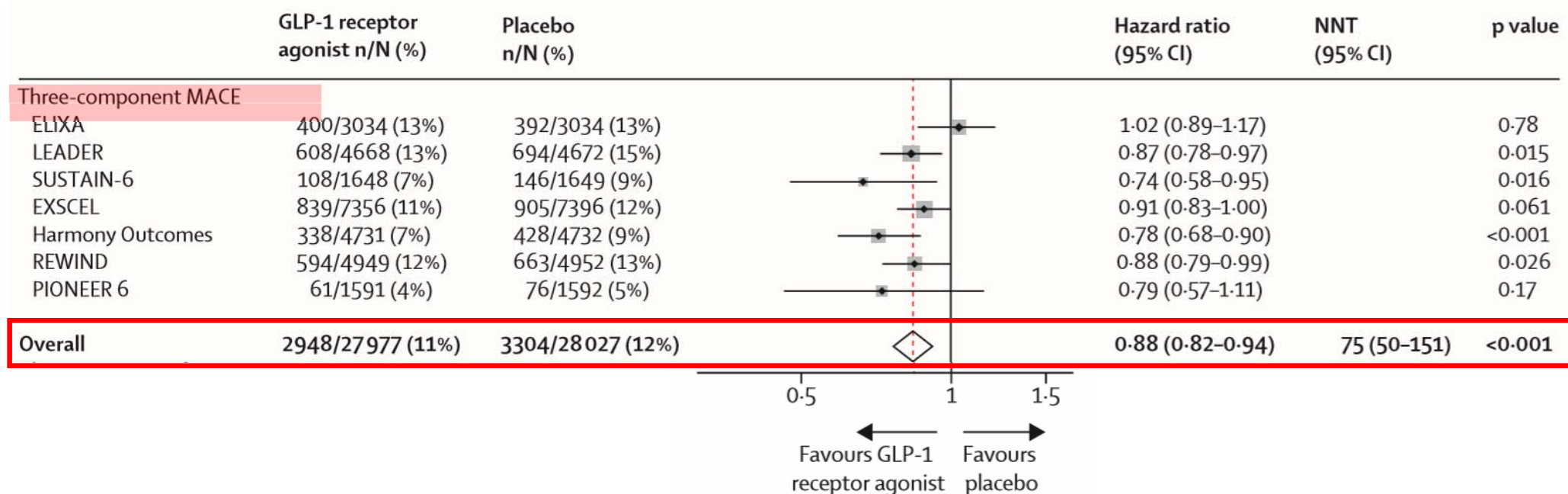


Semaglutide (Ozempic) 1 injection/week (29G)



Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John JV McMurray

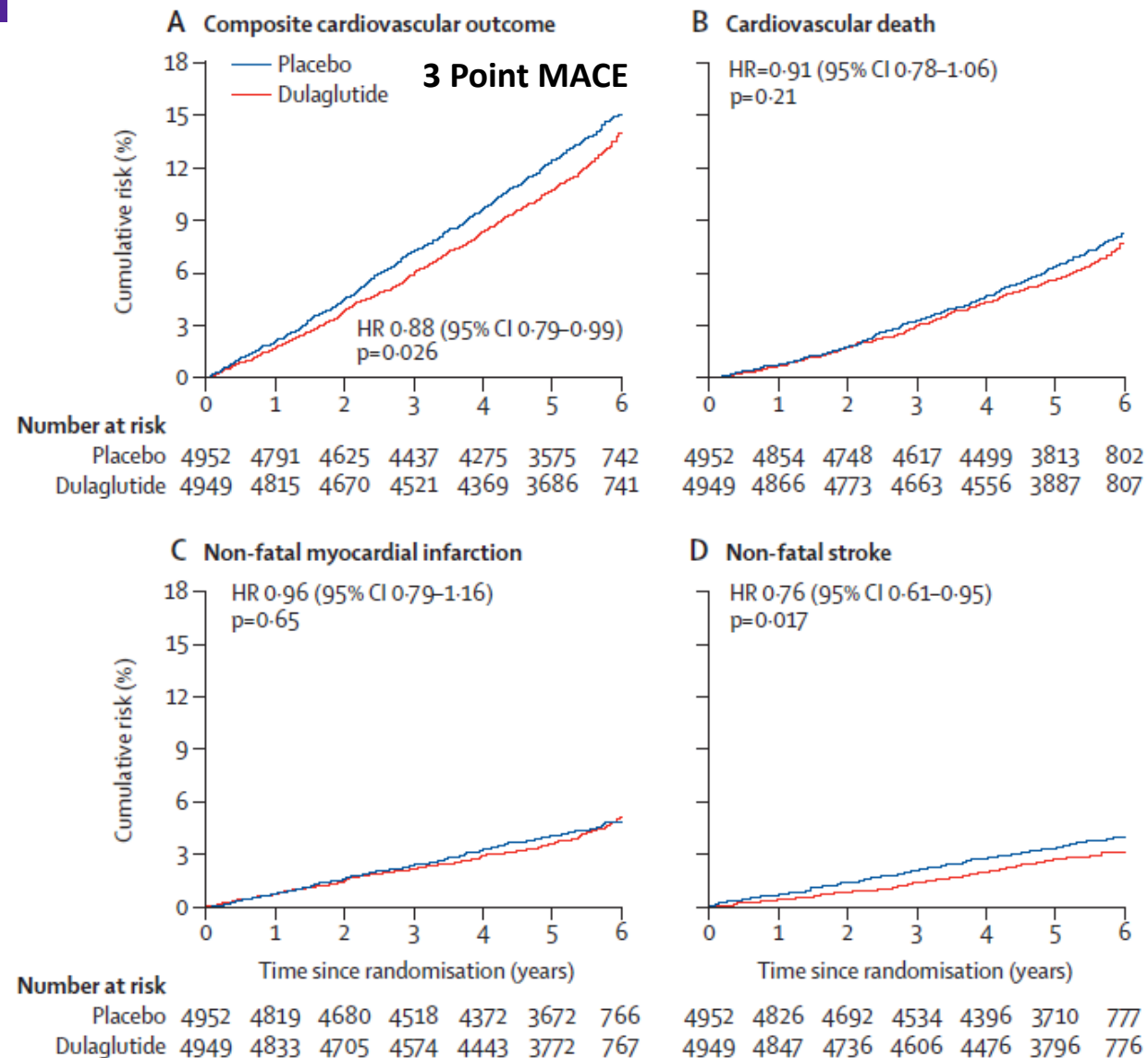


Kristensen et al. *Lancet Diab & Endo* 2019; 7:776-785.

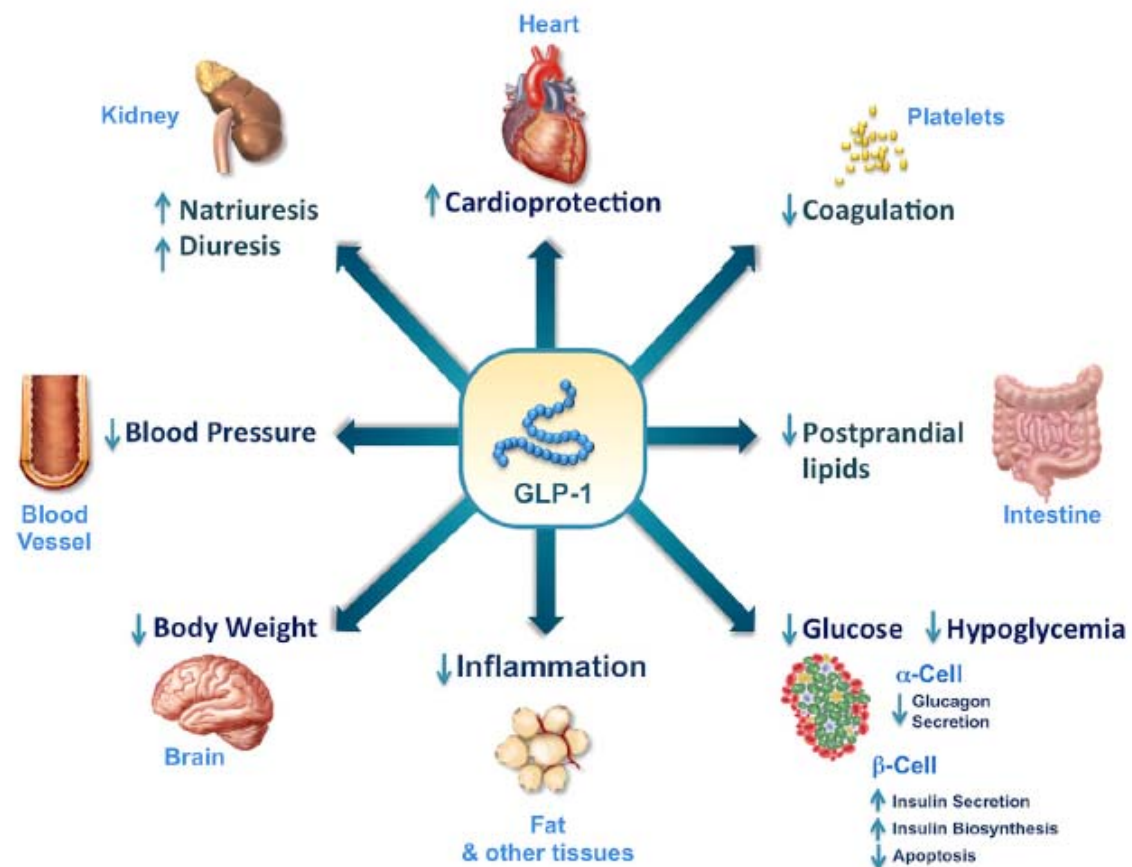
REWIND Trial

- 371 sites, 24 counties
- 1.5 mg dulaglutide vs. placebo
- 31.5% with CVD and 68.5% with risk factors for CVD
- Mean follow-up 5.4 years
- Mean A1C 7.3%; 0.6% difference between groups
- Similar CV benefit in both primary and secondary prevention groups

Gerstein et al. Lancet Online June 10, 2019

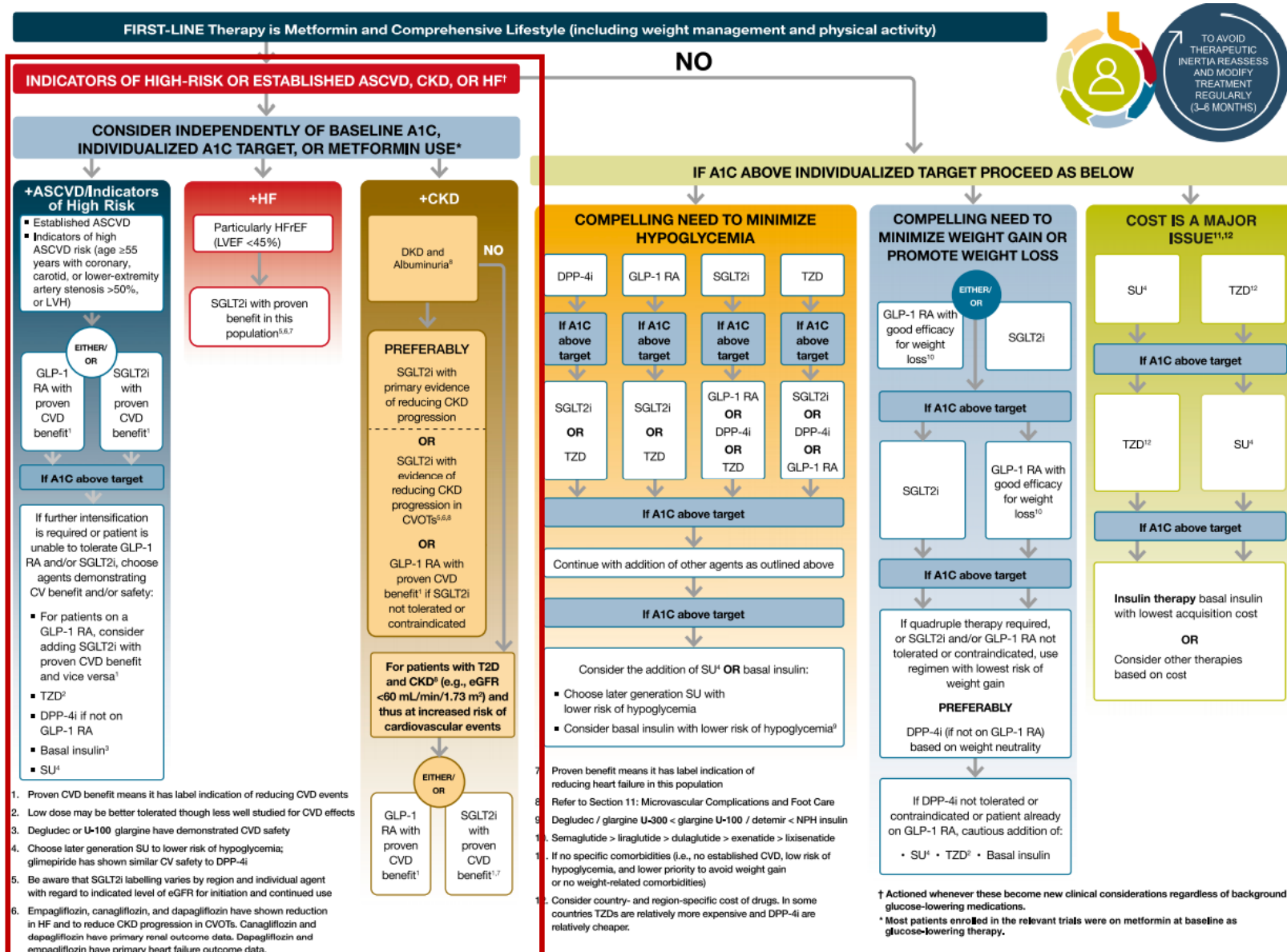


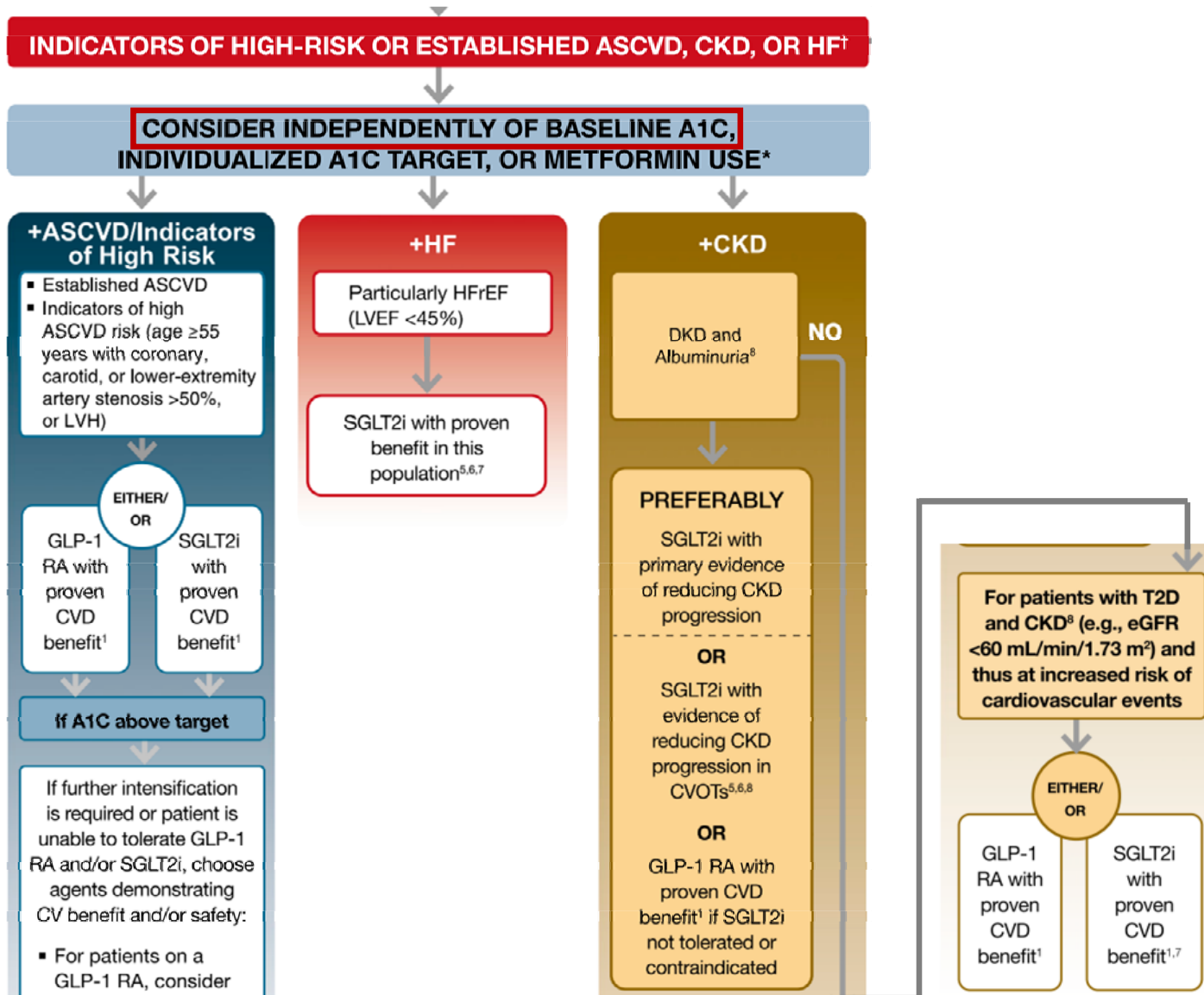
Potential CV Benefits of GLP-1 Agonists



GLP-1 Agonist Scorecard

Potential Advantages	Potential Disadvantages
Good BG lowering efficacy	G.I. side effects
Significant weight loss (5-8%)	Injection for most
Low risk of hypoglycemia	Pancreatitis? (rare)
Modest improvement in BP, lipids	Thyroid C-cell tumors?
Works well in combination therapy; BID, daily and weekly formulations	Highest cost (\$900-\$1,100/month)
CV protection with liraglutide, semaglutide (injection), dulaglutide	





What's New in Type 2 DM Presentation Outline

- Disease modifying classes of type 2 diabetes medications
 - SGLT2 inhibitors
 - GLP-1 receptor agonists
 - American Diabetes Association (ADA) recommendations for SGLT2-i and GLP-1 receptor agonists
- **New technology in type 2 diabetes**
 - **Continuous glucose monitoring (CGM)**
 - **Insulin smart pens**
 - **Patch pumps**

CGM Devices/Systems

Dexcom G6 and G6 Pro



Abbott FreeStyle Libre, Libre 2 and Libre Pro



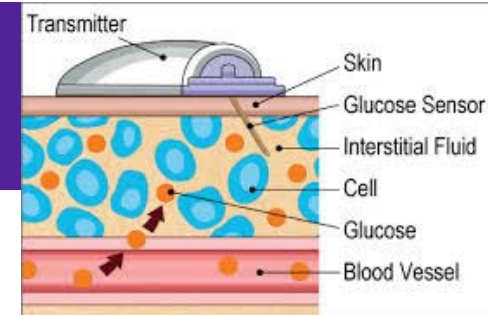
**Eversense CGM
(Eversense XL- Europe)
Senseonics**



**Medtronic
Guardian
Connect CGM
(iPro2)**



Continuous Glucose Monitoring (CGM)



- Tiny filament sensor inserted under skin measuring interstitial glucose every 1-5 minutes and sent to receiver/phone to store data
- Lag time of 5-6 minutes between intravascular and interstitial compartments
- Three categories
 - **Real-time CGM:** used continuously with alarms and alerts
 - **Intermittently-scanned CGM:** glucose measured continuously but displayed when patient swipes over the sensor with a reader or smart phone using CGM app
 - **Professional CGM:** clinic owned and used for one blinded or un-blinded session

What Patients with Type 2 Diabetes Should be Considered For CGM?

Real-time CGM

- Lowers A1C and reduces hypoglycemia risk for all ages
- Multiple daily insulin (MDI) and insulin pump (Grade A)
- Other insulin therapies (Grade C)

Intermittently-scanned CGM

- Useful to lower A1C and reduce hypoglycemia risk for all ages
- Multiple daily insulin (MDI) and insulin pump (Grade B)
- Other insulin therapies (Grade C)

Professional CGM

- Useful to identify and correct hyper- and hypoglycemia
- Consider for noninsulin and basal insulin regimens (Grade C)



QUESTION For adults with poorly controlled type 2 diabetes treated with basal insulin without prandial insulin in primary care practices, does continuous glucose monitoring (CGM) improve hemoglobin A_{1c} (HbA_{1c}) levels compared with blood glucose meter (BGM) monitoring?

CONCLUSION This randomized clinical trial found there was a significantly greater decrease in HbA_{1c} level over 8 months with CGM than with BGM monitoring.

POPULATION

88 Women
87 Men



Adults with type 2 diabetes treated with basal insulin without prandial insulin

Mean age: 57 years

LOCATIONS

15
Primary care practices in the US



INTERVENTION



116
Continuous glucose monitoring
CGM with BGM testing performed as needed

175 Patients randomized



59
Blood glucose meter monitoring
BGM testing performed when fasting and postprandial 1 to 3 times daily

PRIMARY OUTCOME

HbA_{1c} level at 8 months adjusted for the baseline value

FINDINGS

Mean HbA_{1c} level at 8 months

Continuous glucose monitoring

HbA _{1c}	Baseline	8 Months
	9.1%	8.0%

Blood glucose meter monitoring

HbA _{1c}	Baseline	8 Months
	9.0%	8.4%

Risk-adjusted difference was significant,

-0.4% (95% CI, -0.8% to -0.1%)

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Martens T, Beck RW, Bailey R, et al; MOBILE Study Group. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: a randomized clinical trial. *JAMA*. Published online June 2, 2021. doi:10.1001/jama.2021.7444

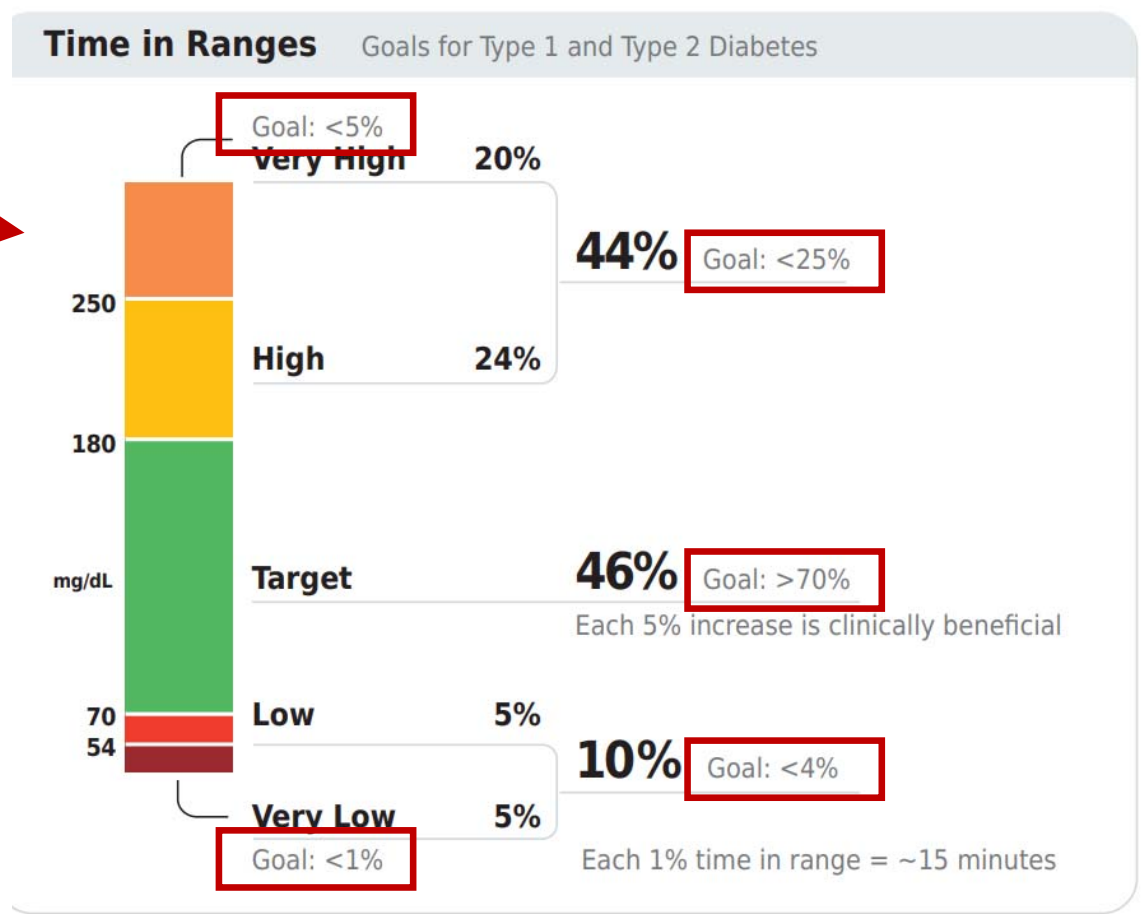
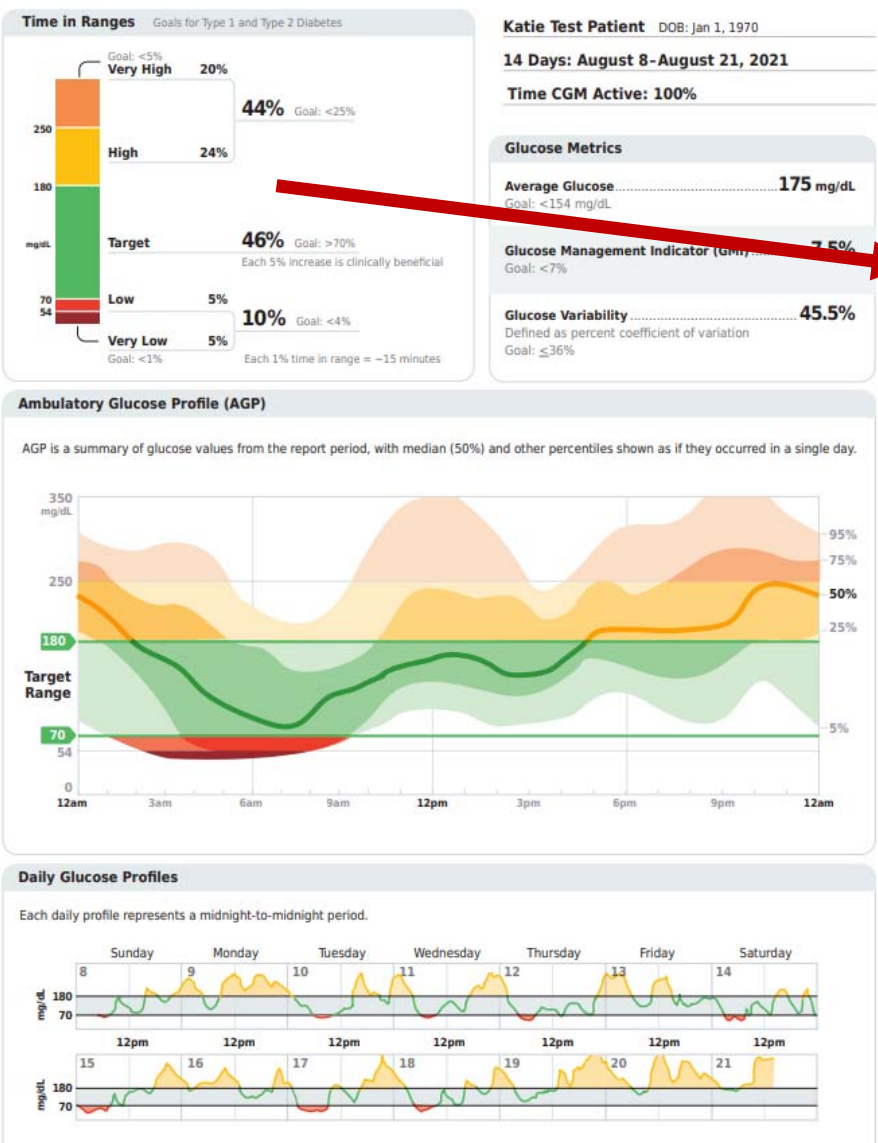
Thomas Martens, MD; Roy W. Beck, MD, PhD; Ryan Bailey, MS; et al for the MOBILE Study Group

Effect of Continuous Glucose Monitoring on Glycemic Control in Patients With Type 2 Diabetes Treated With Basal Insulin A Randomized Clinical Trial

Published June 2, 2021

JAMA.
doi:10.1001/jama.2021.7444

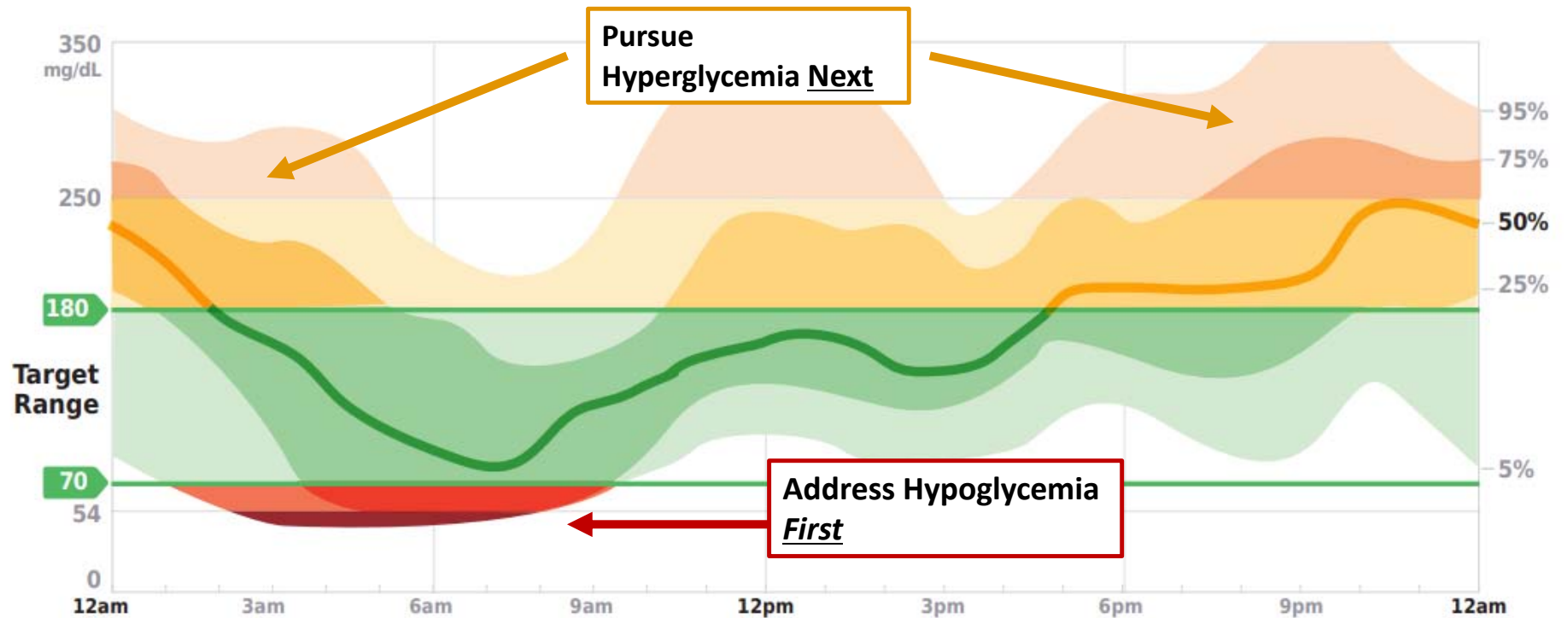
AGP Report: Continuous Glucose Monitoring



More Green, Less Red

Ambulatory Glucose Profile (AGP)

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



Very High

High

Target Range

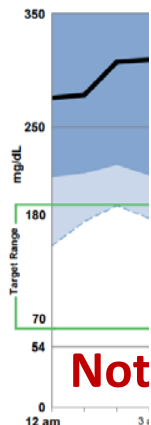
Low

Very Low

What are we striving for in the AGP?

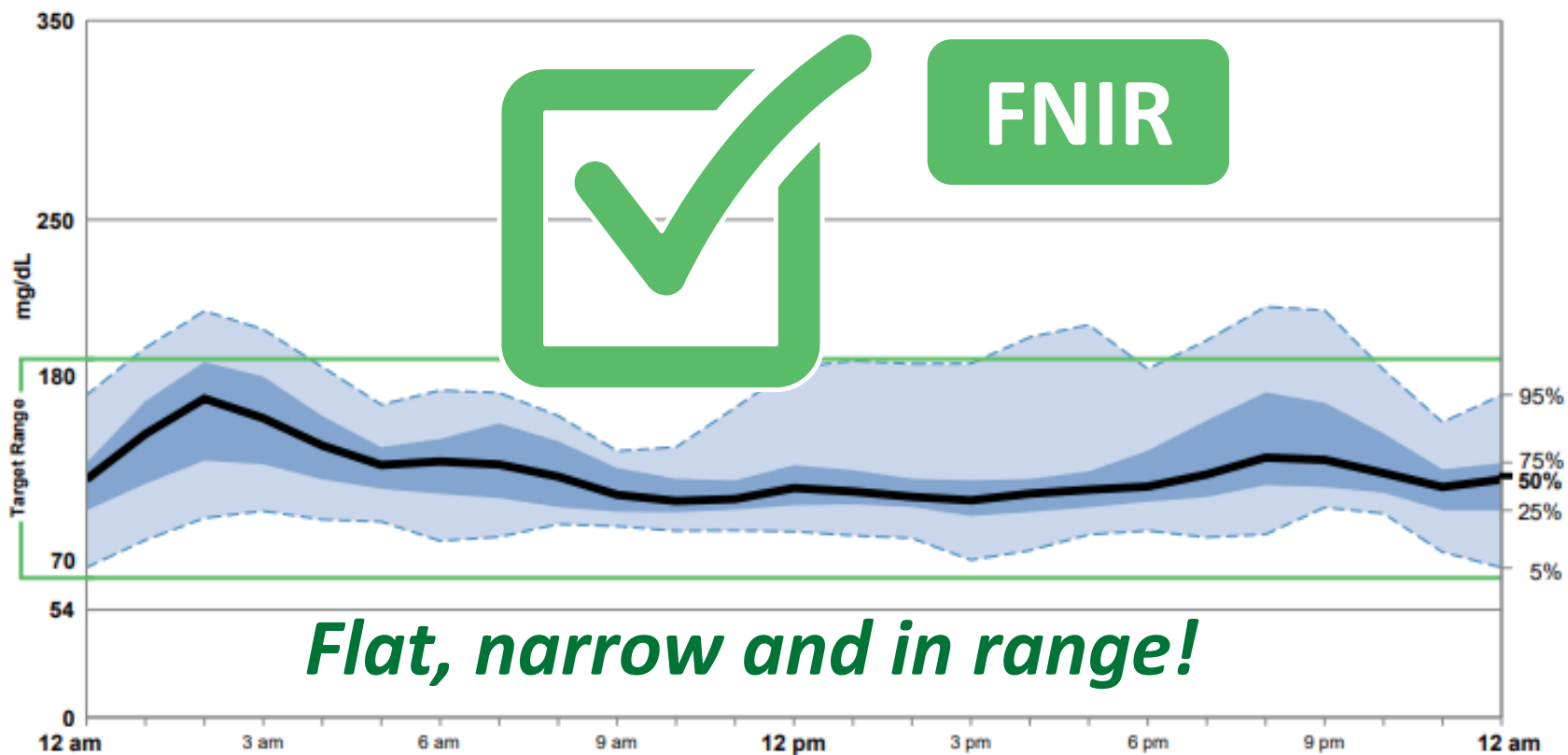
AMBULATORY GLUCOSE PROFILE (AGP)

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



AMBULATORY GLUCOSE PROFILE (AGP)

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



Smart Pens Will Improve Insulin Therapy

**David C. Klonoff, MD, FACP, FRCPE, Fellow AIMBE¹,
and David Kerr, MBChB, DM, FRCPE²**

Journal of Diabetes Science and Technology
2018, Vol. 12(3) 551–553

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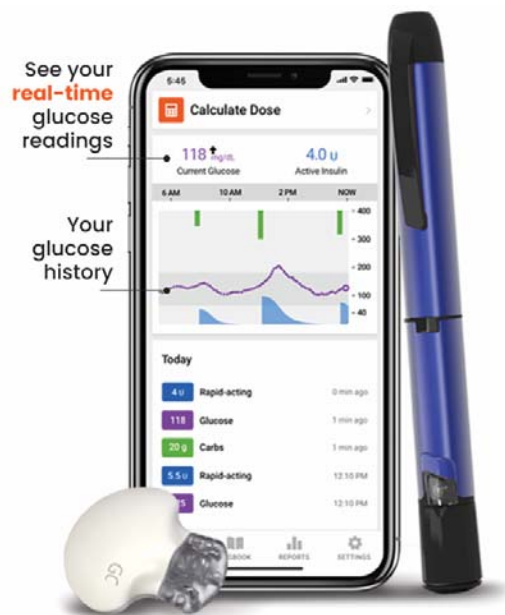
DOI: 10.1177/1932296818759845

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- A reusable pen or smart pen cap paired with CGM or BGM to track/record insulin and glucose metrics
- Linked to app on smartphone
- Data can be shared with the clinic
- Tracks “insulin-on-board” (IOB) to prevent insulin stacking
- Built in dose calculators
- Useful tools such as reminders, low glucose alerts, insulin expiration dates, and temperature

Currently Approved Insulin Smart Pen Technology



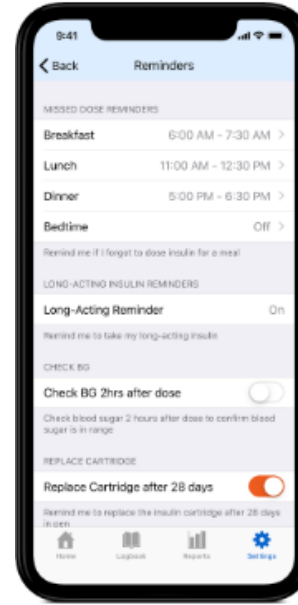
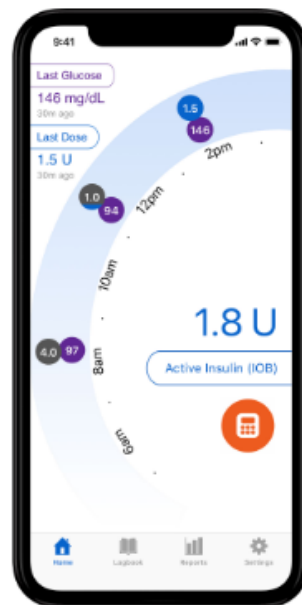
Medtronic InPen with Guardian Connect or Dexcom G6



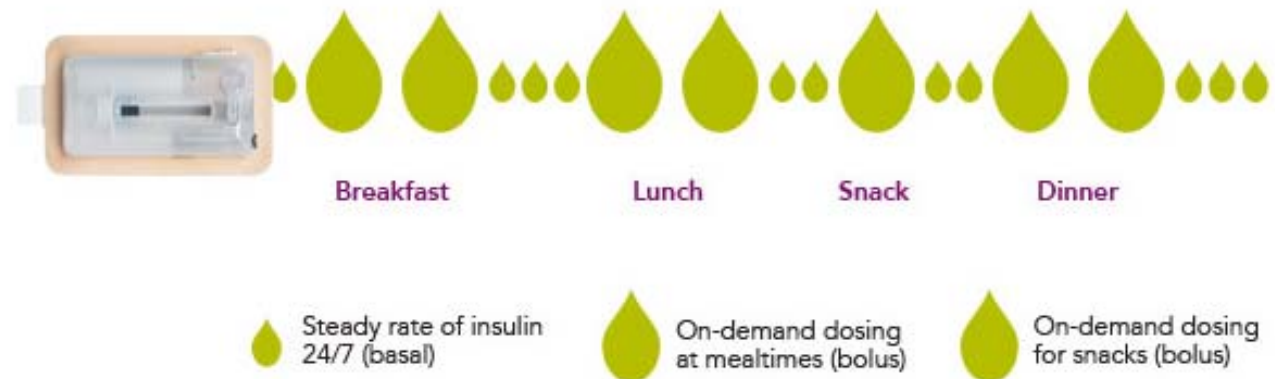
Bigfoot Unity with Abbott Freestyle Libre 2

InPen app

Dose calculator, insulin on board, dose settings, alerts, reports



V-Go: Disposable Patch Pump Insulin Delivery



- One V-Go patch pump each day
- Patient fills V-Go with rapid-acting insulin (requires separate prescription)
- One push = 2 units (36 units total available for mealtime bolus)
- Three V-Go Basal Rate Options; 20, 30, and 40 units/24-hour period

V-Go website: www.go-vgo.com

CeQur Simplicity

- Insulin patch pump worn for 3 days
- Gives bolus insulin only
- Holds up to 200 units of rapid-acting insulin
- Boluses in 2-unit increments
- Can bolus through clothing
- Water-resistant



Comparing Patch vs Pen Bolus Insulin Delivery in Type 2 Diabetes Using Continuous Glucose Monitoring Metrics and Profiles

Richard M. Bergenstal, MD¹ , Mary L. Johnson, RN, CDCES¹, et al.

Journal of Diabetes Science and Technology
1-7

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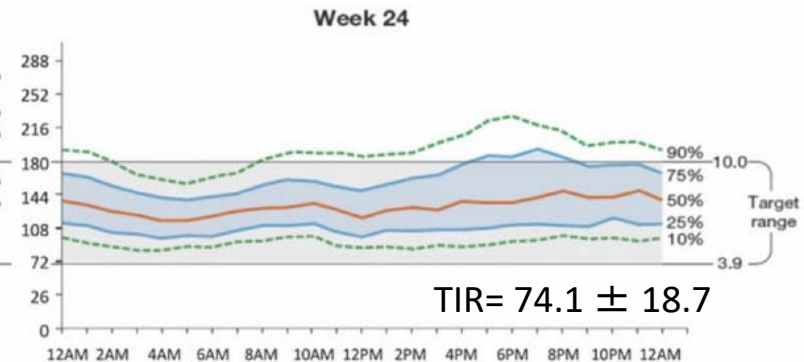
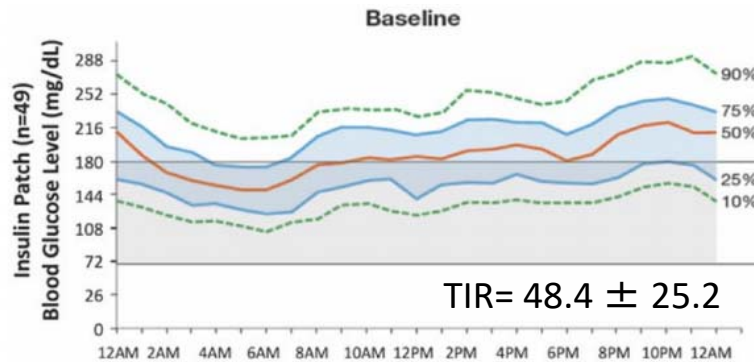
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DOI: 10.1177/19322968211016513

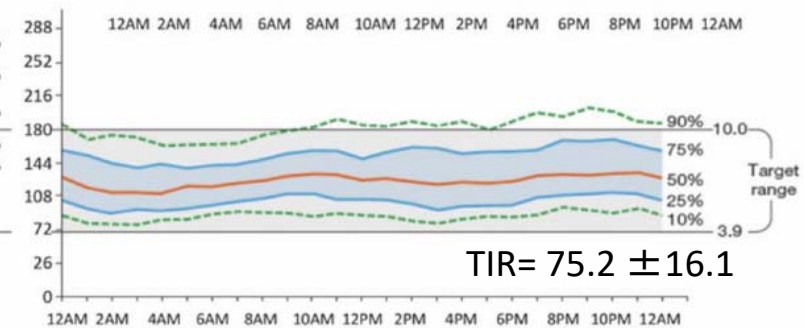
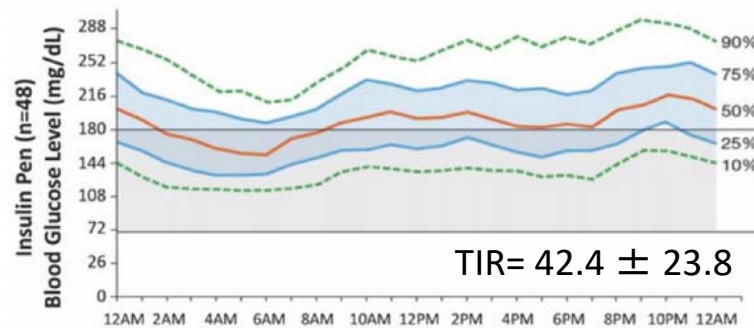
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Insulin
Patch
Pump
(n=49)




Standard
Insulin
Pen
(n=48)



Comparing Patch vs Pen Bolus Insulin Delivery in Type 2 Diabetes Using Continuous Glucose Monitoring Metrics and Profiles

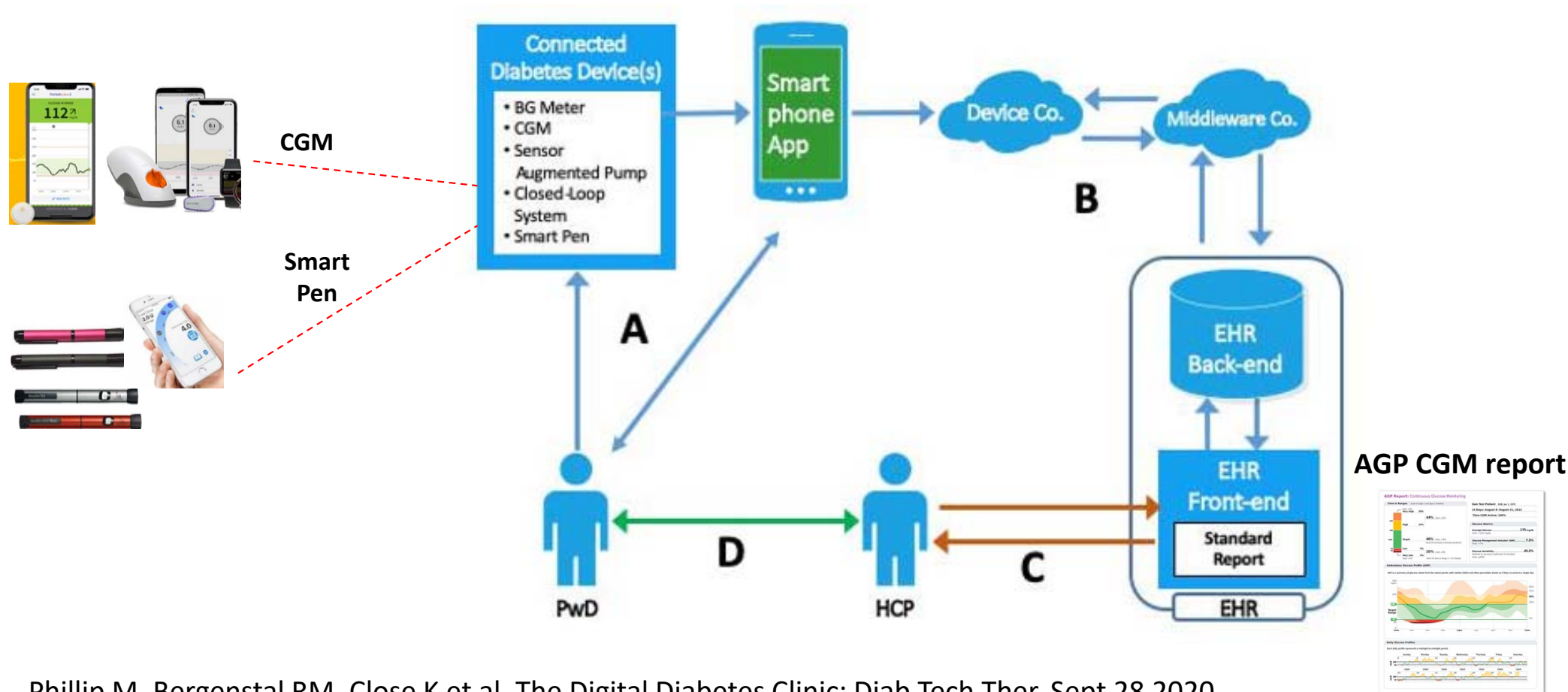
Richard M. Bergenstal, MD¹, Mary L. Johnson, RN, CDCES¹, et al.

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1–7
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DOI: 10.1177/19322968211016513
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Participant preference (patch vs pen)	Percentage who used patch for 44 weeks, (n = 45)	95% CI	P-value
More satisfied using the patch vs the pen for mealtime insulin therapy	77.8%	62.9, 88.8	<.0001
Prefer using the patch vs the pen for mealtime insulin therapy	77.8%	62.9, 88.8	<.0001
Had to carry fewer diabetes supplies with me	88.6%	75.4, 96.2	<.0001
Feel less constrained with my diabetes management	84.4%	70.5, 93.5	<.0001
Feel more freedom with my diabetes management	82.2%	67.9, 92.0	<.0001
Would recommend the patch vs the pen to other patients who are on mealtime insulin therapy	80.0%	65.4, 90.4	<.0001
Want to switch from the pen to the patch	77.8%	62.9, 88.8	<.0001

The Digital/Virtual Diabetes Clinic - the Future State

Recommendations from International Panel on Diabetes Digital Technology



Phillip M, Bergenstal RM, Close K et al. The Digital Diabetes Clinic: Diab Tech Ther. Sept 28 2020

Questions?