Emerging Treatments of Diabetes

Gregory J. Barone, DO

Section Head, Endocrinology Division

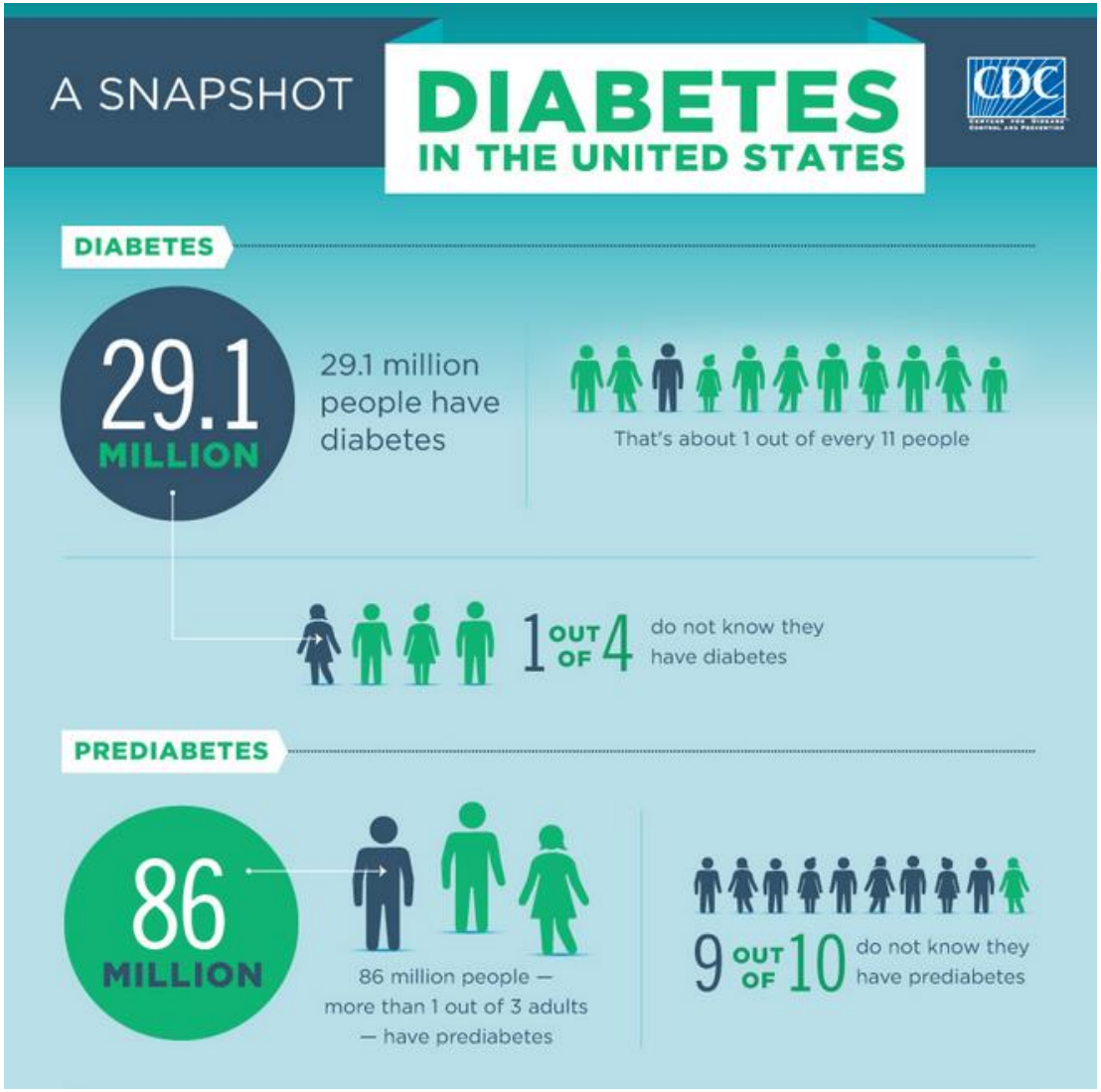
Jefferson Health-New Jersey Division

Medical Director, Diabetes Health Center

KENNEDY HEALTH

disclosures

- Lilly Diabetes, Speaker
- Novo Nordisk, Speaker
- AstraZeneca, Speaker
- Janssen, Speaker



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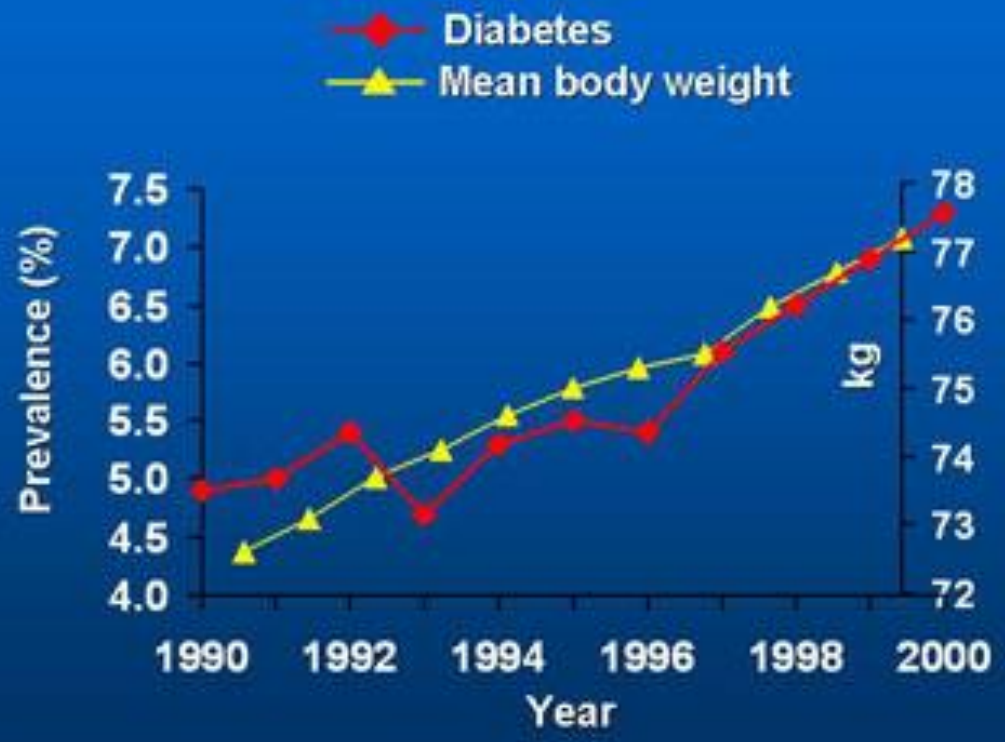
Pathogenesis

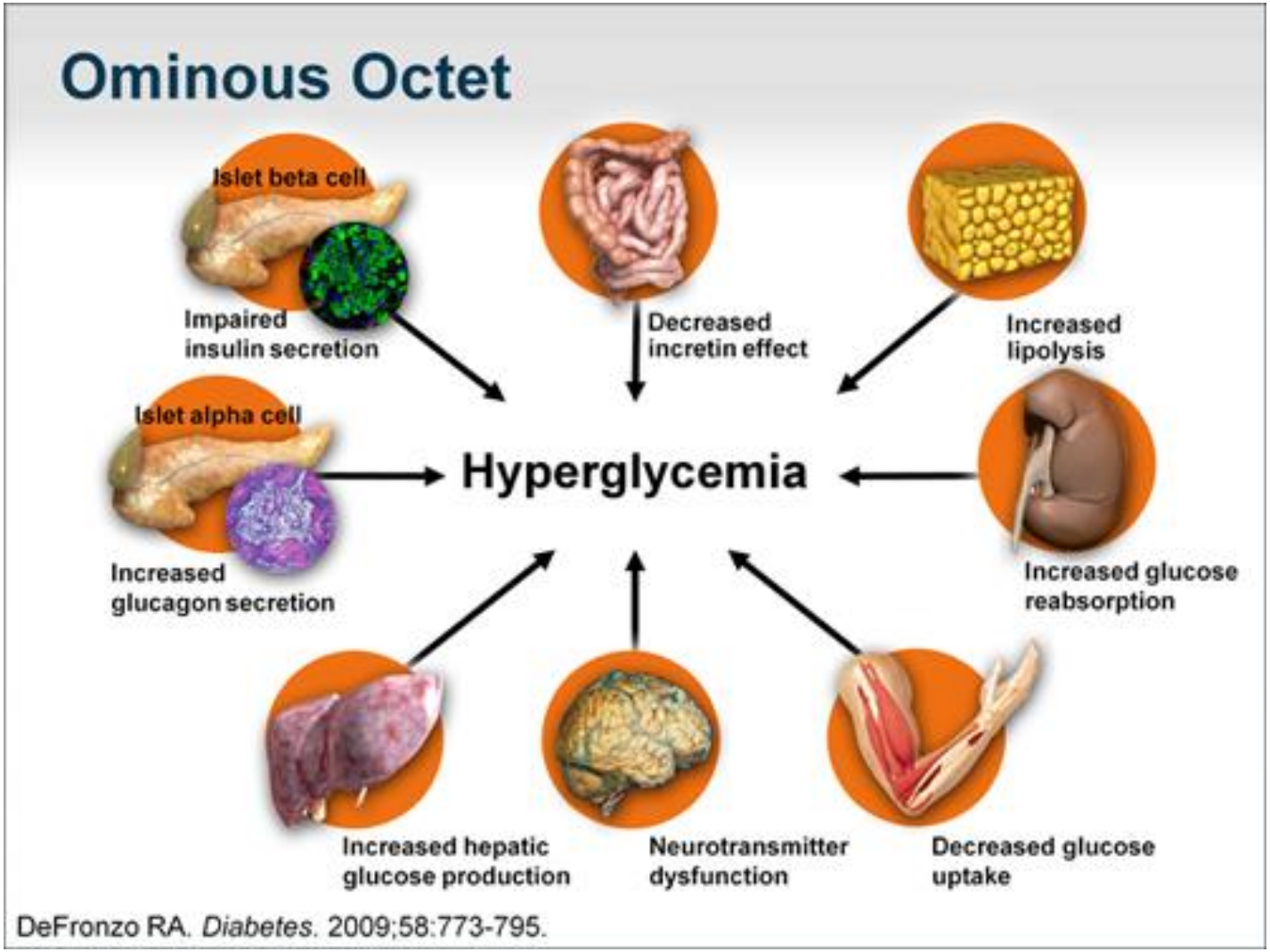
- 90-95% of all cases type 2
- 5% type 1
- Latent Autoimmune Diabetes in Adulthood (LADA)
  - THINK type 1 in Adults
- Mature Onset Diabetes in Youth (MODY)
  - THINK type 2 in younger patients
  - Without typical stigmata of DM2

Diabetes and Obesity: The Continuing Epidemic



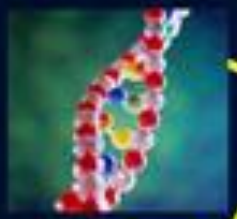
Mokdad AH et al. *Diabetes Care*. 2000;23:1278-83.
Mokdad AH et al. *JAMA*. 1999;282:1519-22.
Mokdad AH et al. *JAMA*. 2001;286:1195-200.

Ominous Octet



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

Etiology of Type 2 Diabetes: Insulin Resistance and Diminished Insulin Secretion



Insulin Resistance

Adequate Compensatory β-cell function

Compensatory Hyperinsulinemia "Normoglycemia"

Metabolic Syndrome

Inadequate Compensatory β-cell function

Relative insulin deficiency Hyperglycemia

Type 2 Diabetes

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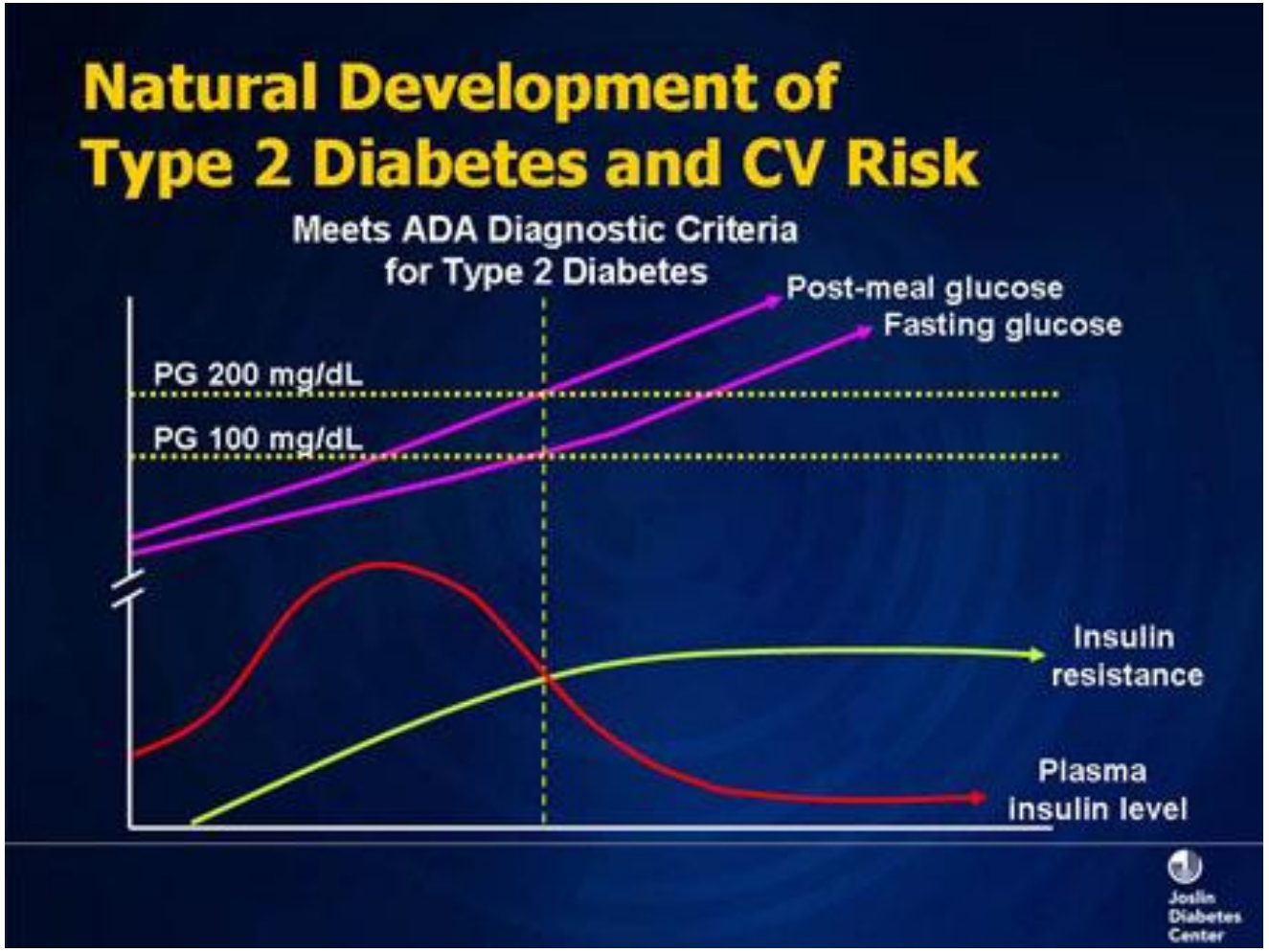
Natural Development of
Type 2 Diabetes and CV Risk
Meets ADA Diagnostic Criteria
for Type 2 Diabetes
Post-meal glucose
Fasting glucose
PG 200 mg/dL
PG 100 mg/dL
Insulin
resistance
Plasma
insulin level
Joslin
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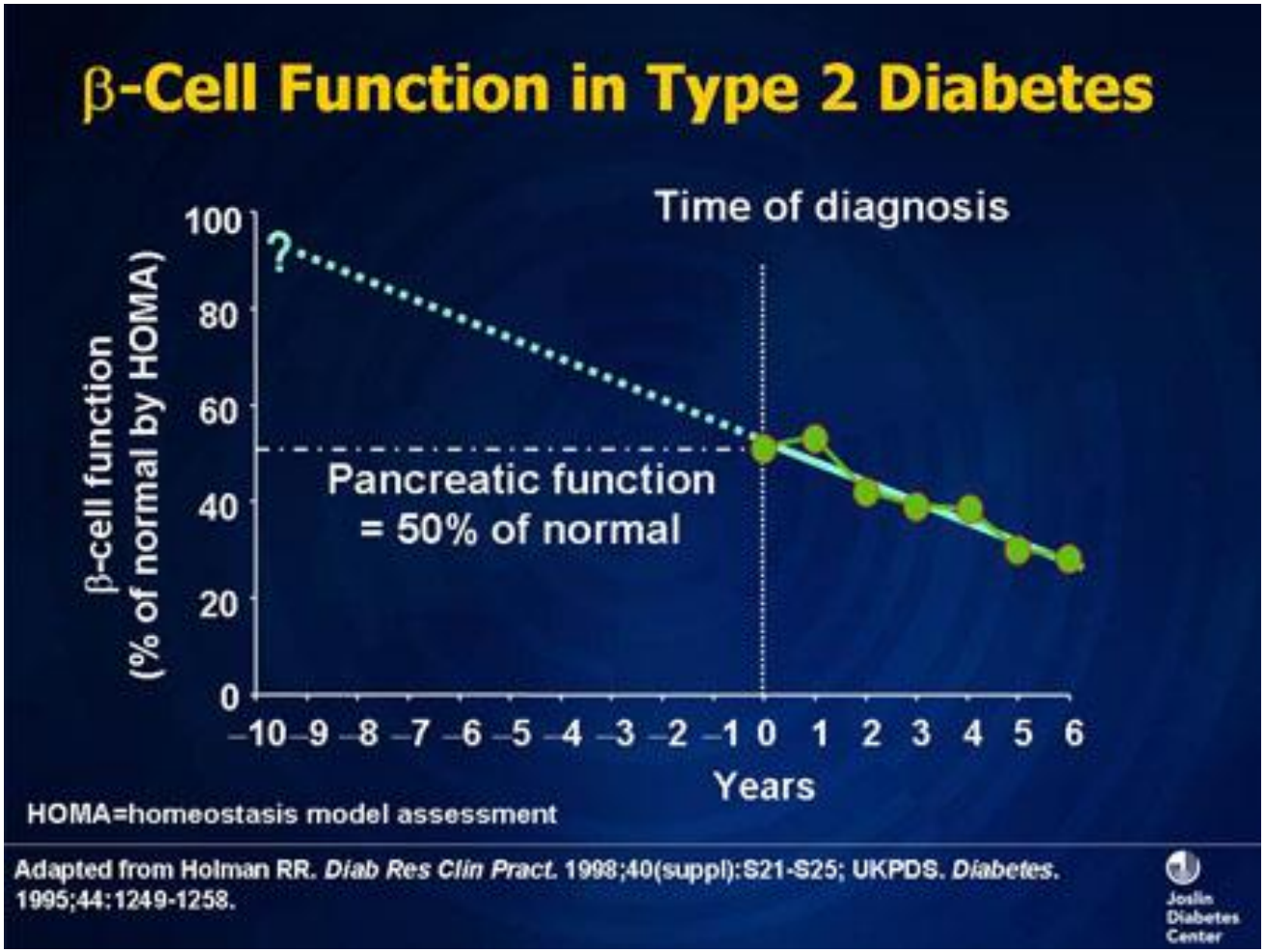
Center


β-Cell Function in Type 2 Diabetes
Time of diagnosis
?
Pancreatic function
= 50% of normal
β-cell function
(% of normal by HOMA)
100
80
60
40
20
0
–10 –9 –8 –7 –6 –5 –4 –3 –2 –1 0 1 2 3 4 5 6
Years
HOMA=homeostasis model assessment
Adapted from Holman RR. Diab Res Clin Pract. 1998;40(suppl):S21-S25; UKPDS. Diabetes. 1995;44:1249-1258.
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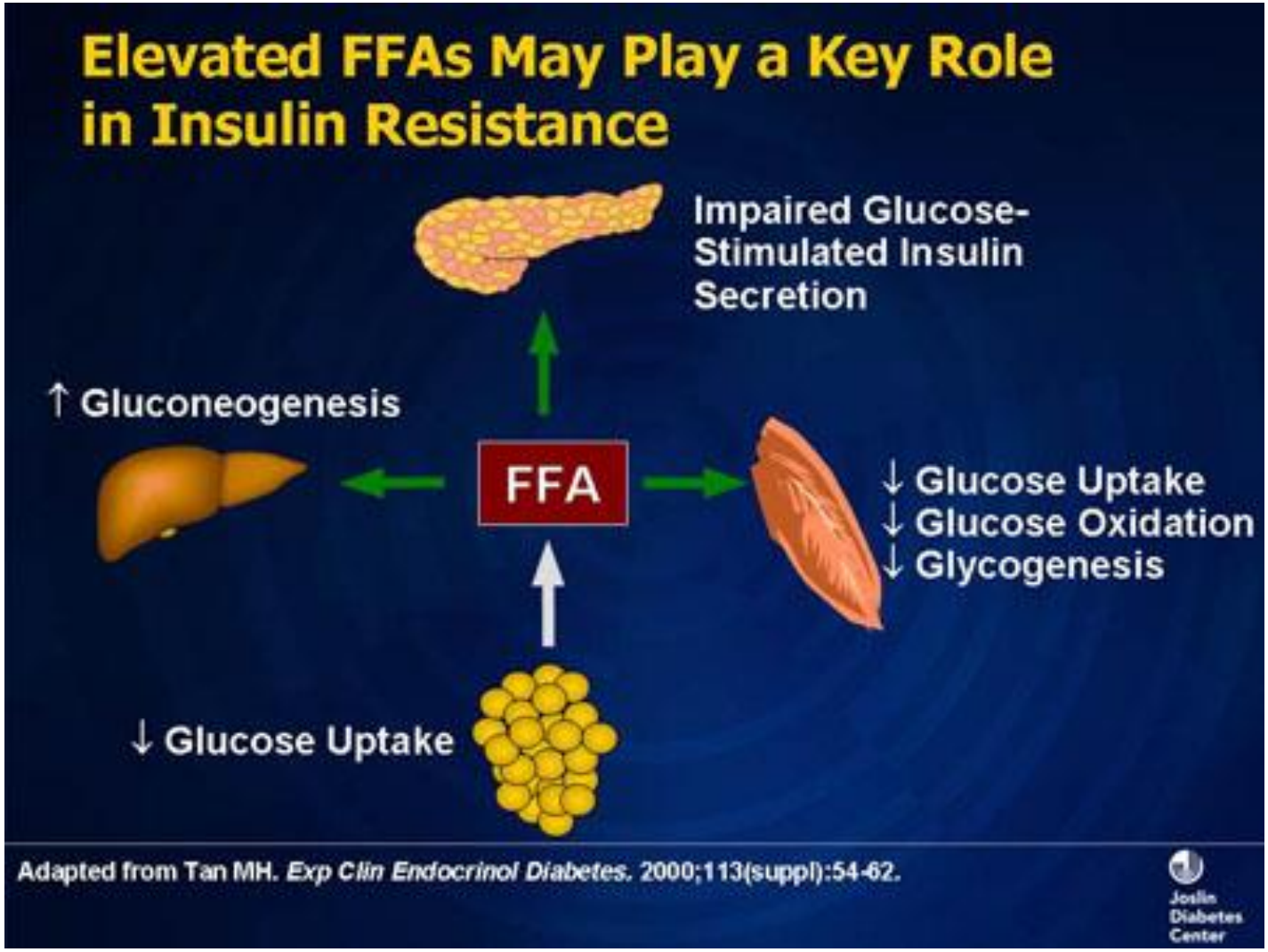
Elevated FFAs May Play a Key Role in Insulin Resistance
Impaired Glucose-Stimulated Insulin Secretion
↑ Gluconeogenesis
FFA
↓ Glucose Uptake
↓ Glucose Oxidation
↓ Glycogenesis
↓ Glucose Uptake
Adapted from Tan MH. Exp Clin Endocrinol Diabetes. 2000;113(suppl):54-62.
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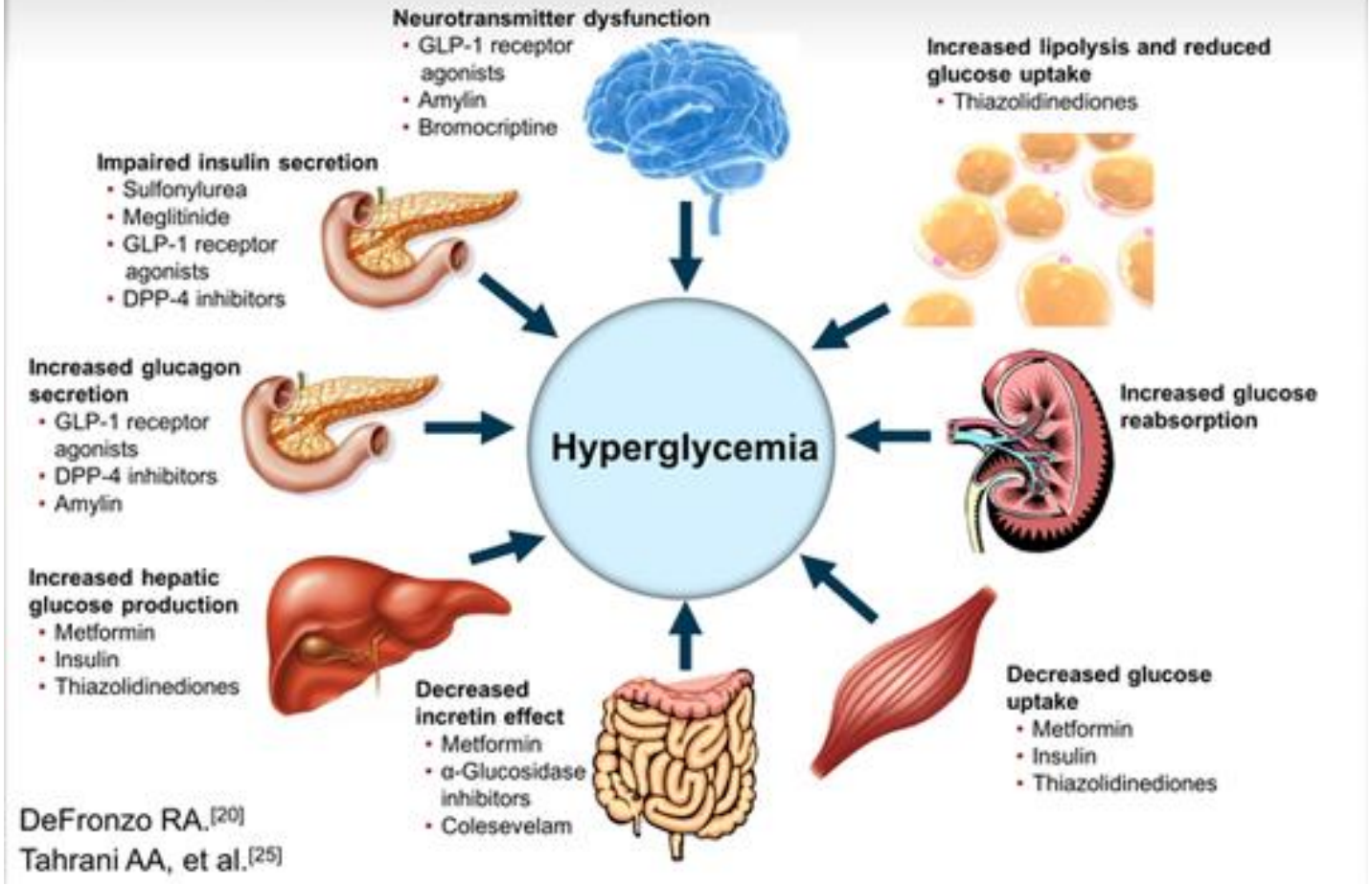
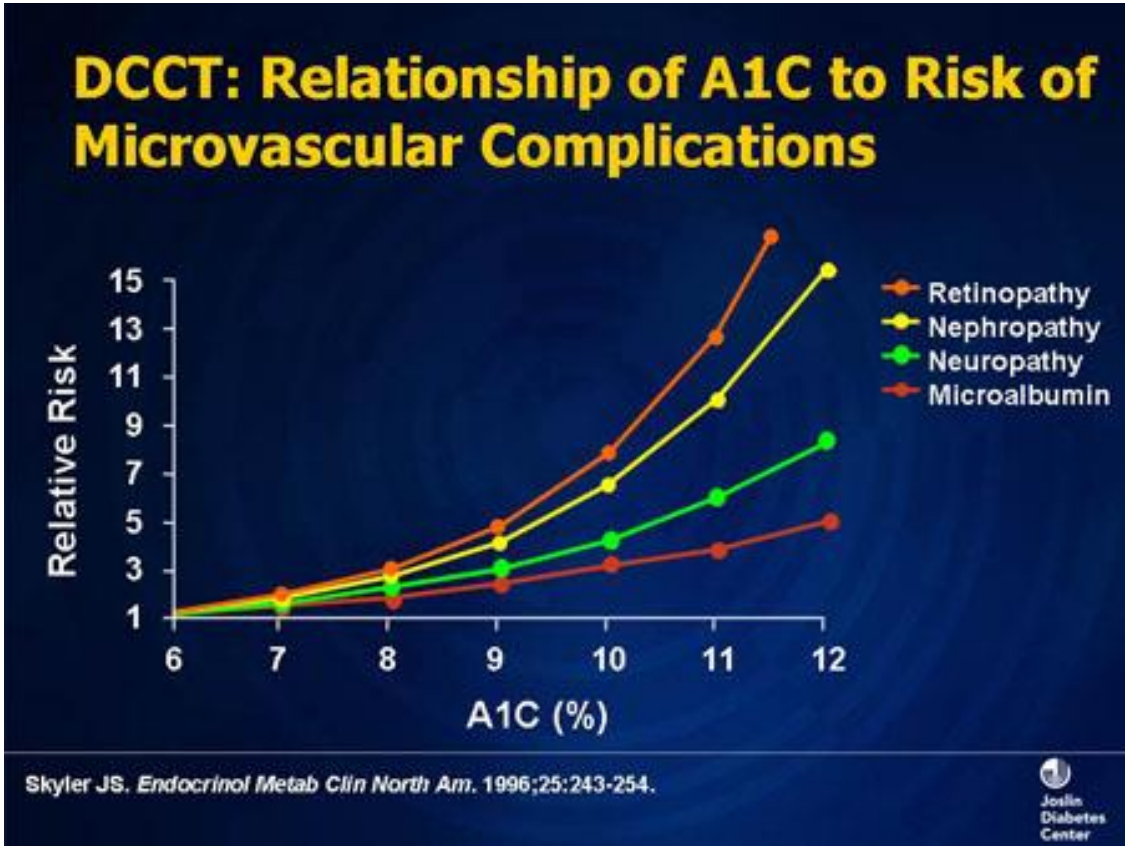
Hyperglycemia in Type 2 Diabetes



DeFronzo RA.[20]
Tahrani AA, et al.[25]

How low to go?


DCCT: Relationship of A1C to Risk of Microvascular Complications
Relative Risk
15
13
11
9
7
5
3
1
6
7
8
9
10
11
12
A1C (%)
Retinopathy
Nephropathy
Neuropathy
Microalbumin
Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243-254.
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2017 ADA algorithm

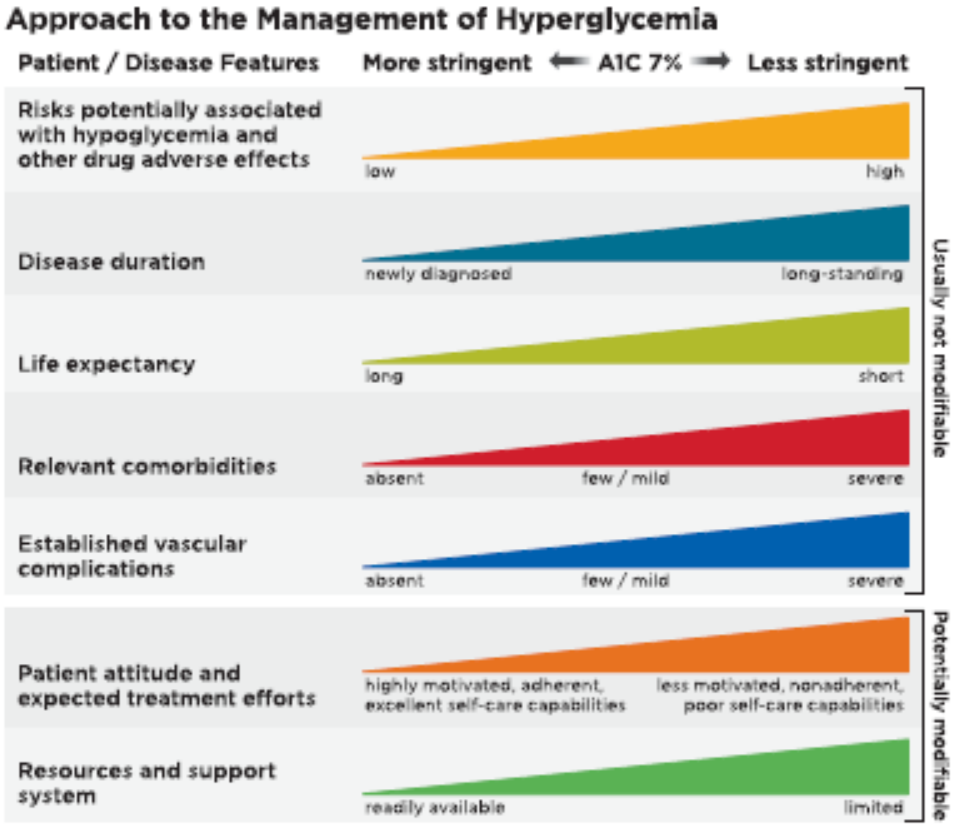

Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (58).

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Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

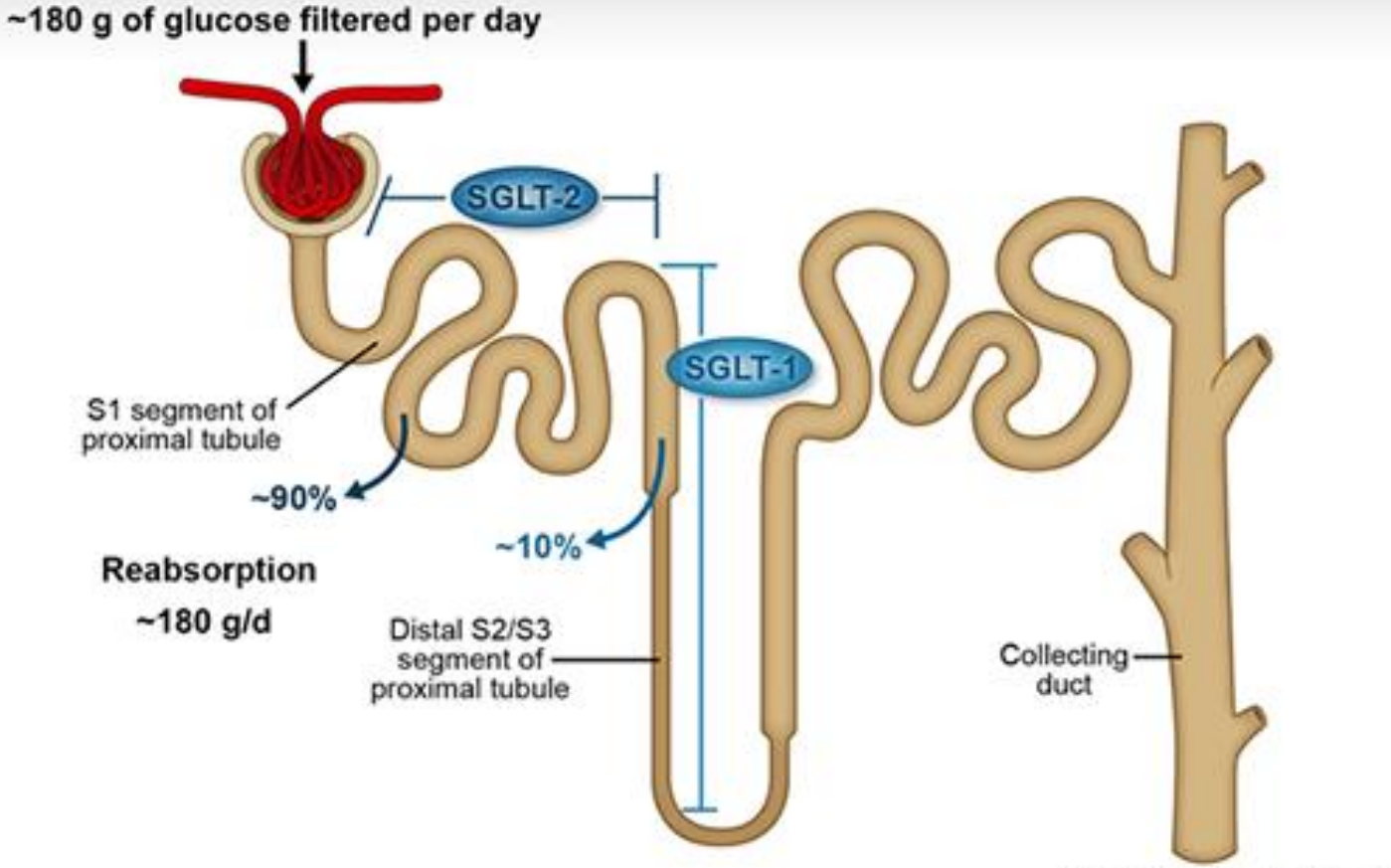
Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

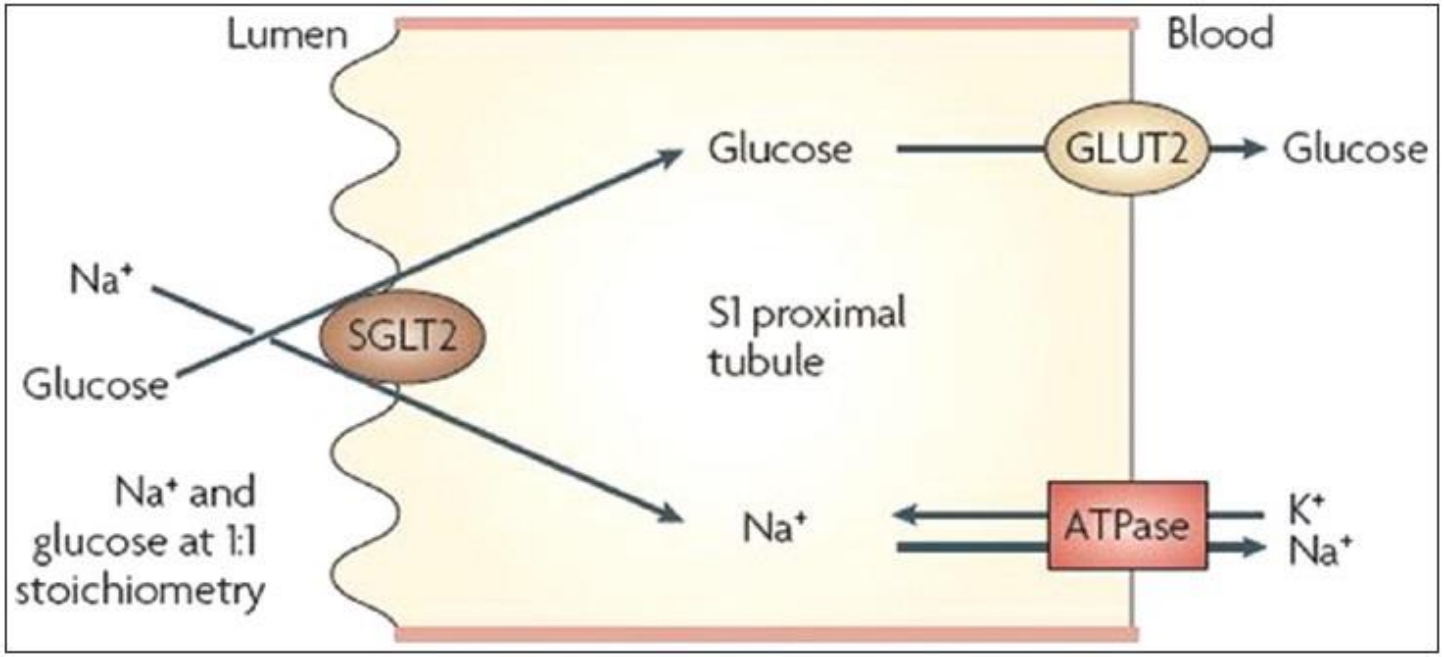
Combination Injectable Therapy (See Figure 8.2)

The Kidney and Glucose Homeostasis



Chao EC, Henry RR. *Nat Rev Drug Discov*. 2010;9:551-559.[2]

SGLT2 activity



SGLT-2 Inhibitor

- Blocks glucose reabsorption at the kidney
- Leads to incr glucosuria
- Incr risk for UTI, yeast infections, need intact GFR
- Benefits: low risk for hypo, weight loss, decr BP, no GI effects, potential cardiovascular benefit

SGLT-2 Inhibitor

- Invokana = canagliflozin
- Farxiga = dapagliflozin
- Jardiance = empagliflozin

EMPA-REG

- DM2, A1c 7-10%, BMI < 45, age > 18 with est CVD
- 3 arms: Empagliflozin 10 mg/25 mg/placebo
- Primary outcome: composite of death from cardiovascular causes, nonfatal MI, (excluding silent MI), or nonfatal stroke.
- 7020 pt, 2.8 yr follow up

EMPA-REG

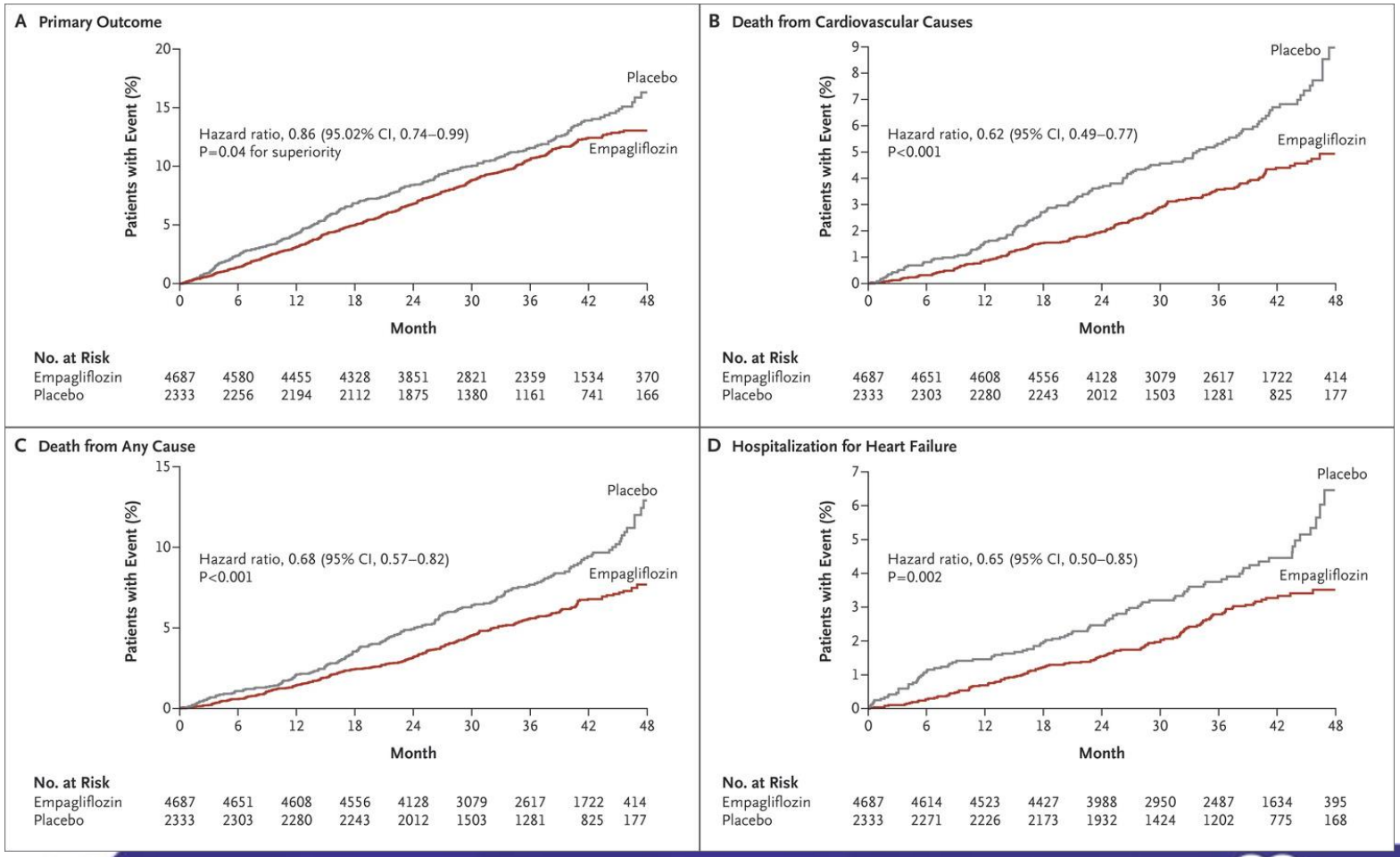


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Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

* Data were analyzed with the use of a four-step hierarchical-testing strategy for the pooled empagliflozin group versus the placebo group in the following order: noninferiority for the primary outcome, noninferiority for the key secondary outcome, superiority for the primary outcome, and superiority for the key secondary outcome. Each successive hypothesis could be tested, provided that those preceding it met the designated level of significance. Data are based on Cox regression analyses in patients who received at least one dose of a study drug.

† One-sided P values are shown for tests of noninferiority, and two-sided P values are shown for tests of superiority.

‡ Silent myocardial infarction was analyzed in 2378 patients in the empagliflozin group and 1211 patients in the placebo group.

CANVAS

- Cangliflozin Cardiovascular Assessment Study (CANVAS)
- DM2, A1c 7-10.5%, age > 18
- Age >30, symptomatic ASCVD
- Age >50, 2 or more risks
  - DM>10 yr, BP>140/90, tob, albuminuria, HDL <38,
- 3 arms: Canagliflozin 100 mg/ 300 mg/ placebo
- Primary outcome: death from CV causes, nonfatal MI, nonfatal stroke
- 9734 pt, 3.6 yr follow up

CANVAS

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

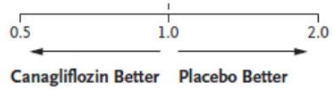

Figure 3. Effects of Canagliflozin on Cardiovascular, Renal, Hospitalization, and Death Events in the Integrated CANVAS Program.

Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, with stratification according to trial and history of cardiovascular disease for all canagliflozin groups combined versus placebo. For the primary outcome (the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), $P<0.001$ for noninferiority and $P=0.02$ for superiority. Progression of albuminuria was evaluated with data from the 9015 participants with normoalbuminuria or microalbuminuria at baseline. The composite renal outcome was a 40% reduction in the estimated glomerular filtration rate (eGFR), the need for renal-replacement therapy, or death from renal causes. The 40% reduction in eGFR was required to be sustained, which was defined as being present on at least two consecutive measurements more than 30 days apart, and adjudicated by an expert committee. The need for renal-replacement therapy owing to end-stage kidney disease was defined as a need for dialysis for at least 30 days or transplantation and was required to be adjudicated by an expert committee. Death from renal causes was defined as death for which the proximate cause was renal as defined by the end-point adjudication committee. There were three deaths from renal causes, all in the placebo group.

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CANVAS

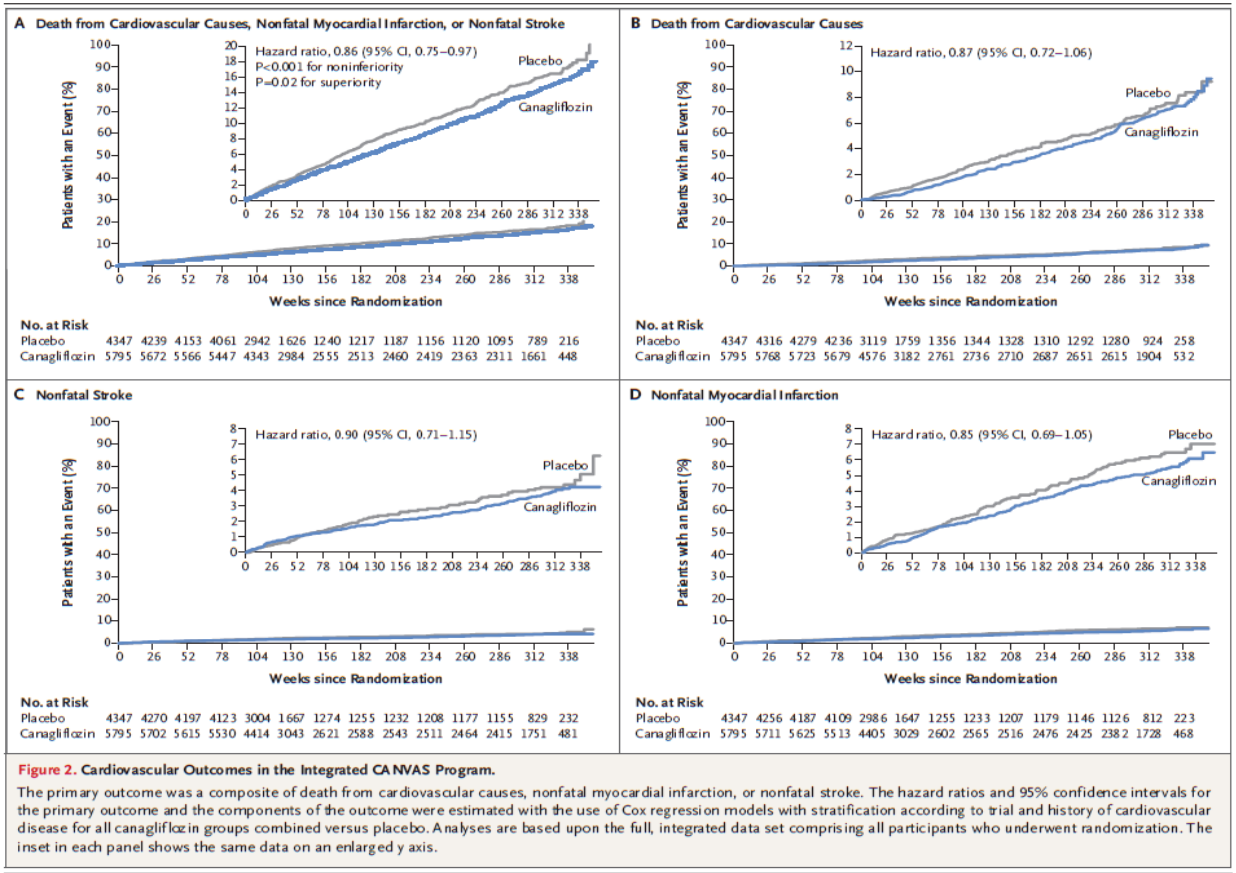

Figure 2. Cardiovascular Outcomes in the Integrated CANVAS Program.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The hazard ratios and 95% confidence intervals for the primary outcome and the components of the outcome were estimated with the use of Cox regression models with stratification according to trial and history of cardiovascular disease for all canagliflozin groups combined versus placebo. Analyses are based upon the full, integrated data set comprising all participants who underwent randomization. The inset in each panel shows the same data on an enlarged y axis.

CANVAS

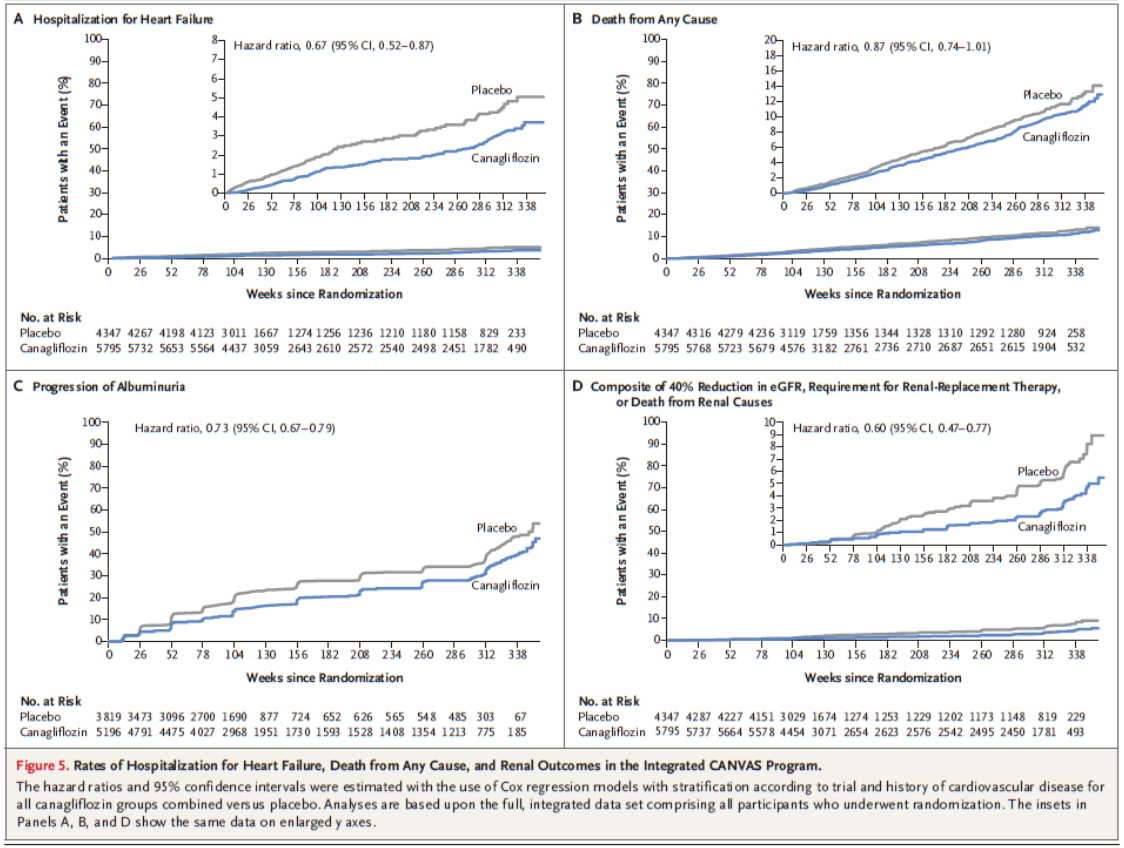

Figure 5. Rates of Hospitalization for Heart Failure, Death from Any Cause, and Renal Outcomes in the Integrated CANVAS Program.

The hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models with stratification according to trial and history of cardiovascular disease for all canagliflozin groups combined versus placebo. Analyses are based upon the full, integrated data set comprising all participants who underwent randomization. The insets in Panels A, B, and D show the same data on enlarged y axes.

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CANVAS

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

* Analyses were performed on data from the on-treatment data set (patients who had a safety outcome while they were receiving canagliflozin or placebo or within 30 days after discontinuation of the drug or placebo), except for fracture, amputation, cancer, and diabetic ketoacidosis outcomes, which included all events at any time point in all patients who underwent randomization and received at least one dose of canagliflozin or placebo.

† P values were estimated from Cox regression models.

‡ Low-trauma fracture was the prespecified primary fracture outcome, and all fracture was a secondary outcome.

§ Infection of male genitalia included balanitis, phimosis, and events leading to circumcision.

¶ For these adverse events, the annualized incidence rates are reported with data from CANVAS alone through January 7, 2014, because after this time, only serious adverse events or adverse events leading to discontinuation were collected. In CANVAS-R, only serious adverse events or adverse events leading to discontinuation were collected. Owing to the differences between the two trials in methods of collection of the data, an integrated analysis of these adverse events is not possible.

KENNEDY HEALTH

CVD-REAL

Circulation

American Heart Association

Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study

Mikhail Kosiborod, Matthew A. Cavender, Alex Z. Fu, John P. Wilding, Kamlesh Khunti, Reinhard W. Holl, Anna Norhammar, Kåre I. Birkeland, Marit Jørgensen, Marcus Thuresson, Niki Arya, Johan Bodegård, Niklas Hammar, Peter Fenici and on behalf of the CVD-REAL Investigators and Study Group

on behalf of the CVD-REAL Investigators and Study Group

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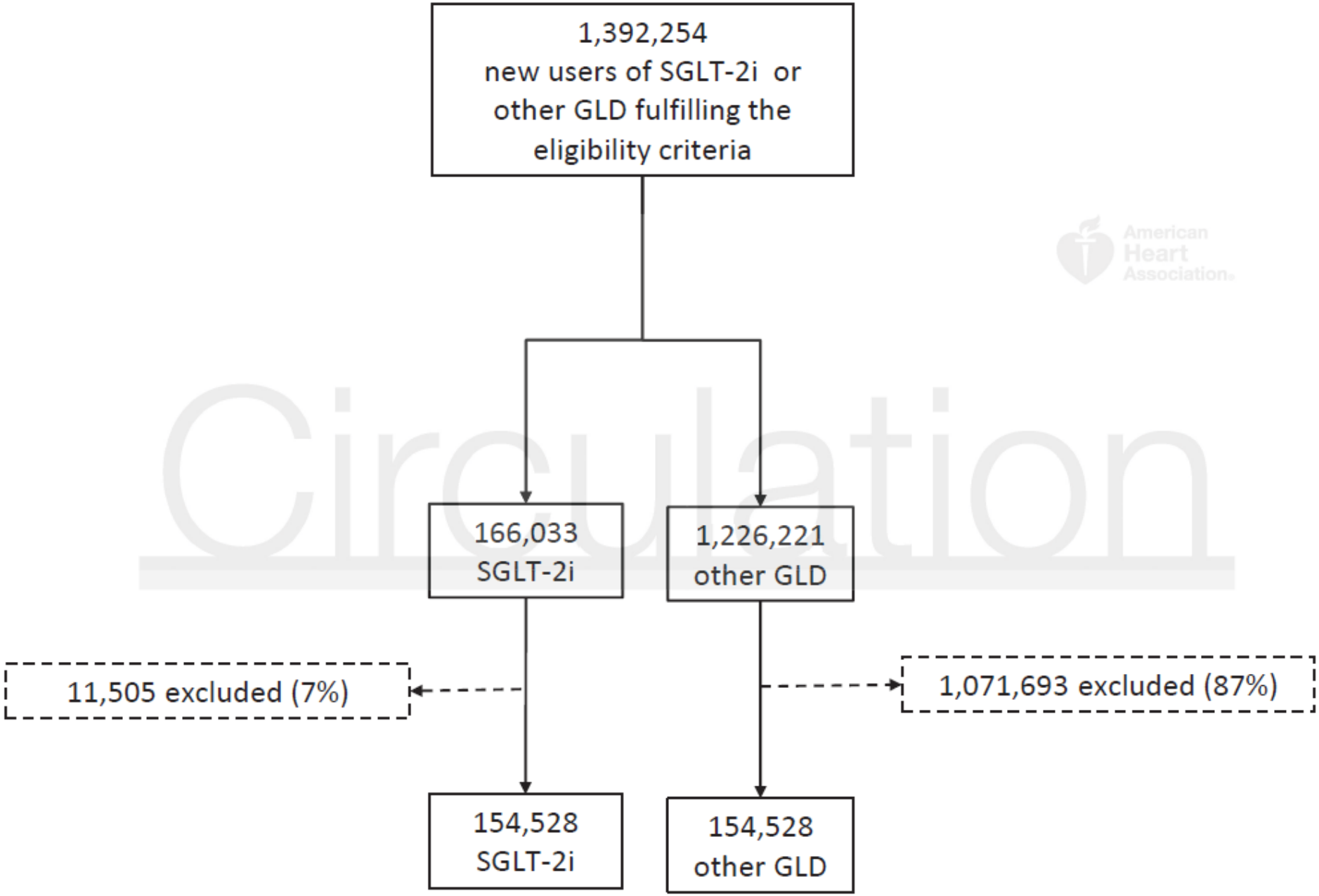
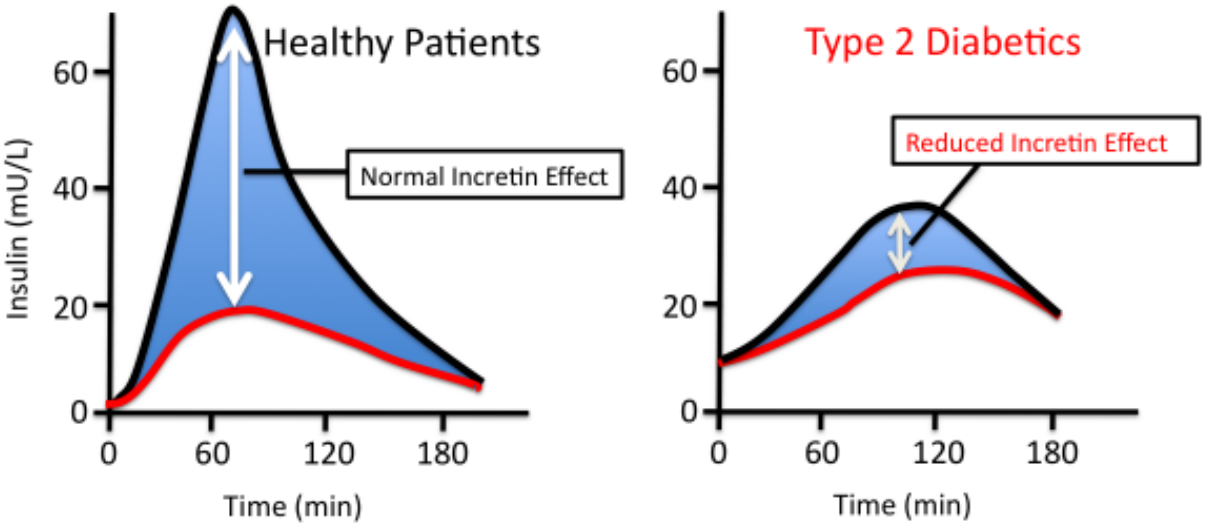

1,392,254
new users of SGLT-2i or
other GLD fulfilling the
eligibility criteria
166,033
SGLT-2i
1,226,221
other GLD
11,505 excluded (7%)
1,071,693 excluded (87%)
154,528
SGLT-2i
154,528
other GLD

CVD-REAL

Results—After propensity matching, there were 309,056 patients newly initiated on either SGLT-2i or oGLD (154,528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42% and 5% of the total exposure time in the SGLT-2i class, respectively. Baseline characteristics were balanced between the two groups. There were 961 HHF cases during 190,164 person-years follow up (incidence rate [IR] 0.51/100 person-years). Of 215,622 patients in the US, Norway, Denmark, Sweden, and UK, death occurred in 1334 (IR 0.87/100 person-years), and HHF or death in 1983 (IR 1.38/100 person-years). Use of SGLT-2i, versus oGLDs, was associated with lower rates of HHF (HR 0.61; 95% CI 0.51–0.73; $p<0.001$); death (HR 0.49; 95% CI 0.41–0.57; $p<0.001$); and HHF or death (HR 0.54; 95% CI 0.48–0.60, $p<0.001$) with no significant heterogeneity by country.

Conclusions—In this large multinational study, treatment with SGLT-2i versus oGLDs was associated with a lower risk of HHF and death, suggesting that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of T2D patients in real-world practice (NCT02993614).

Diabetes & The "Incretin Effect"



Nauck M et al.
Diabetologia (1986) 29:46-52

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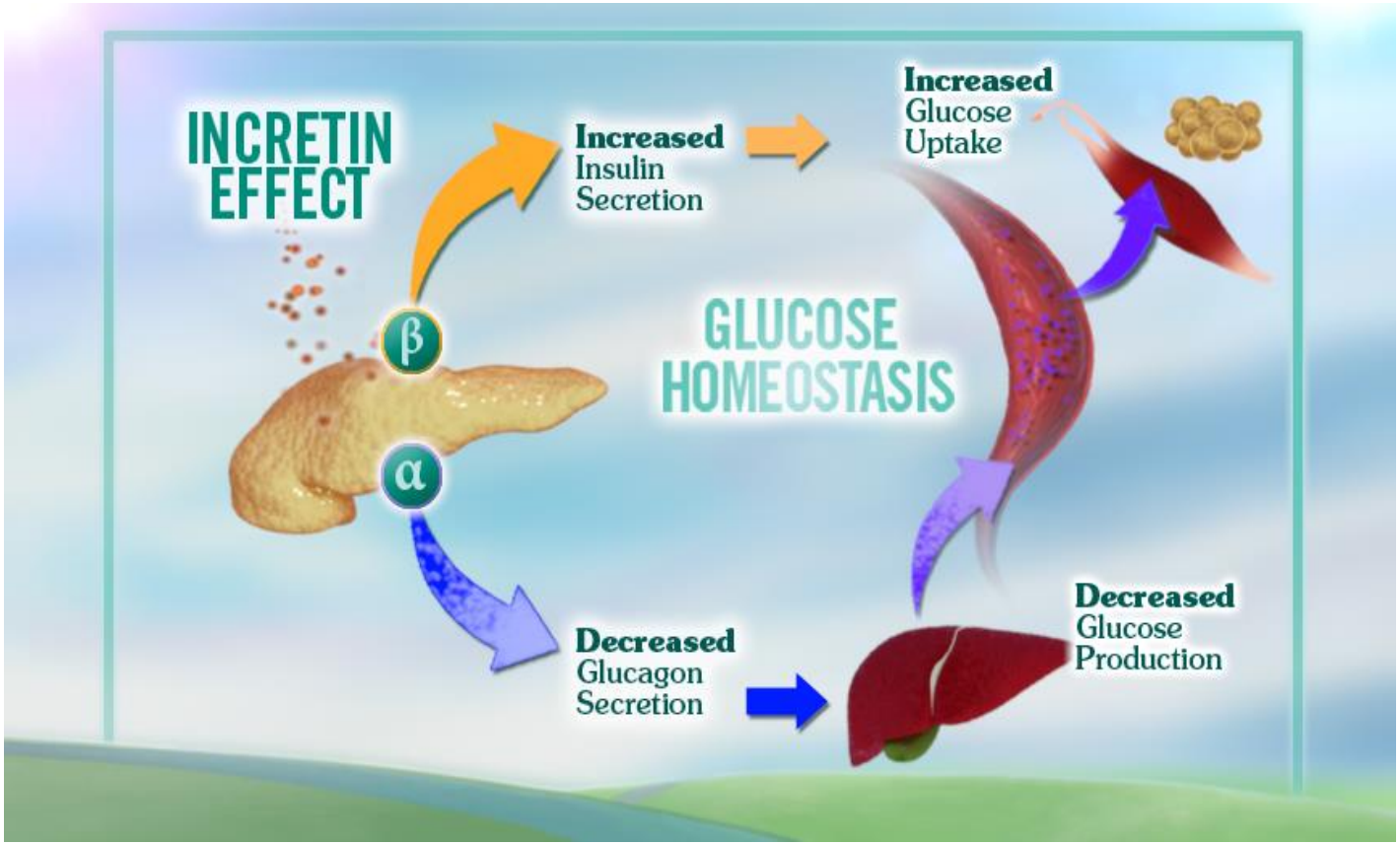
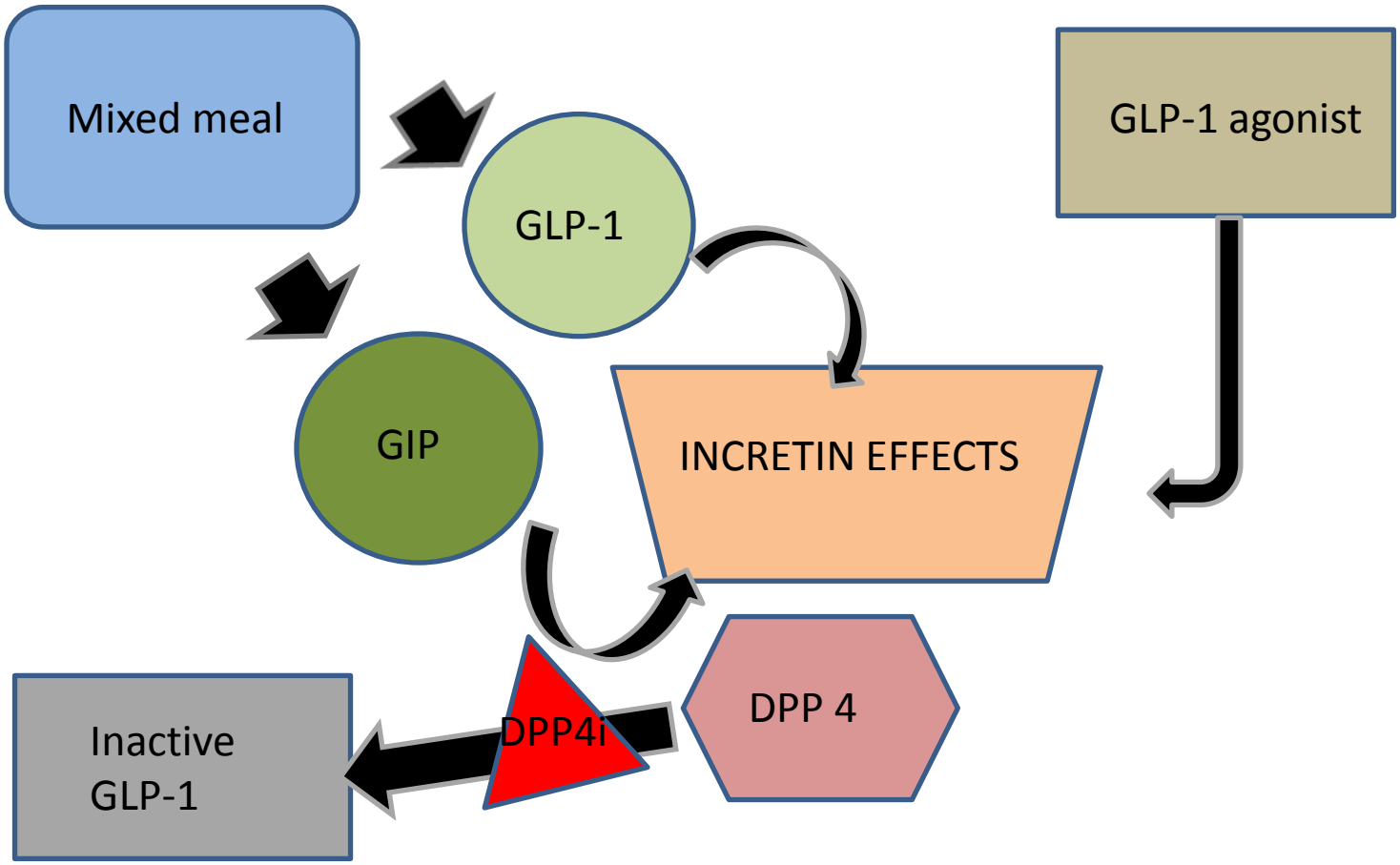

INCRETIN EFFECT
Increased Insulin Secretion
Increased Glucose Uptake
GLUCOSE HOMEOSTASIS
β
α
Decreased Glucagon Secretion
Decreased Glucose Production

Role of DPP4i



GLP-1

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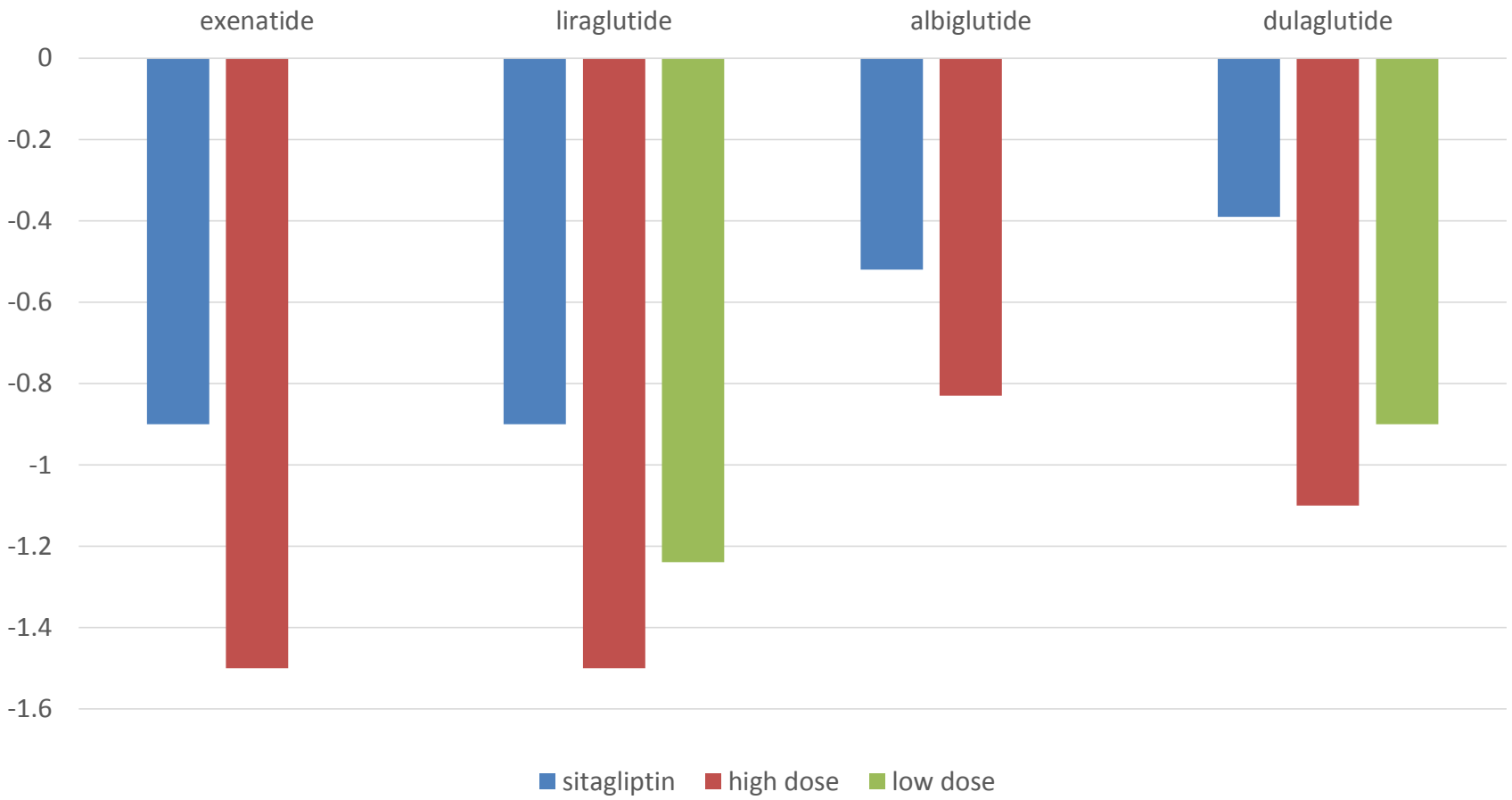
GLP-1 analogs

- Exenatide
  - Byetta
  - Bydureon
- Liraglutide
  - Victoza
  - Saxenda (weight loss)
- Albiglutide
  - Tanzeum
- Dulaglutide
  - Trulicity
- Lixisenatide
  - Lyxumia

GLP1 vs DPP4i



Comparison

	Dose	Daily	Weekly	FBS	PPG	GI	CV
Byetta exenatide	5 mcg 10 mcg	✓	---	---	↓	++++	?
Bydureon exenatide ER	2 mg	---	✓	↓	↓	+++	X
Victoza liraglutide	1.2 mg 1.8 mg	✓	---	↓	↓	+++	✓
Tanzeum albiglutide	30 mg 50 mg	---	✓	↓	↓	+	?
Trulicity dulaglutide	0.75mg 1.5 mg	---	✓	↓	↓	+++	?
Lyxumia lixisenatide	10 mcg 20 mcg	✓	---	---	↓	+++	X

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- Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial
- DM2, A1c > 7%
- Age >50 with est CVD/CKD3/NYHA CHF3 or 4
- Age >60 with CV risk (albuminuria, incr ABI, HTN w LVH, diastolic/systolic dysfunction)
- Primary composite outcome: death from cardiovascular causes, nonfatal MI, or nonfatal stroke.
- 9340 pt, 3.8 yr follow up

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Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (181 patients in the liraglutide group vs. 227 in the placebo group), nonfatal (including silent) myocardial infarction (275 vs. 304), or nonfatal stroke (152 vs. 163). The P value is for superiority.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure.
§ This analysis was not prespecified.

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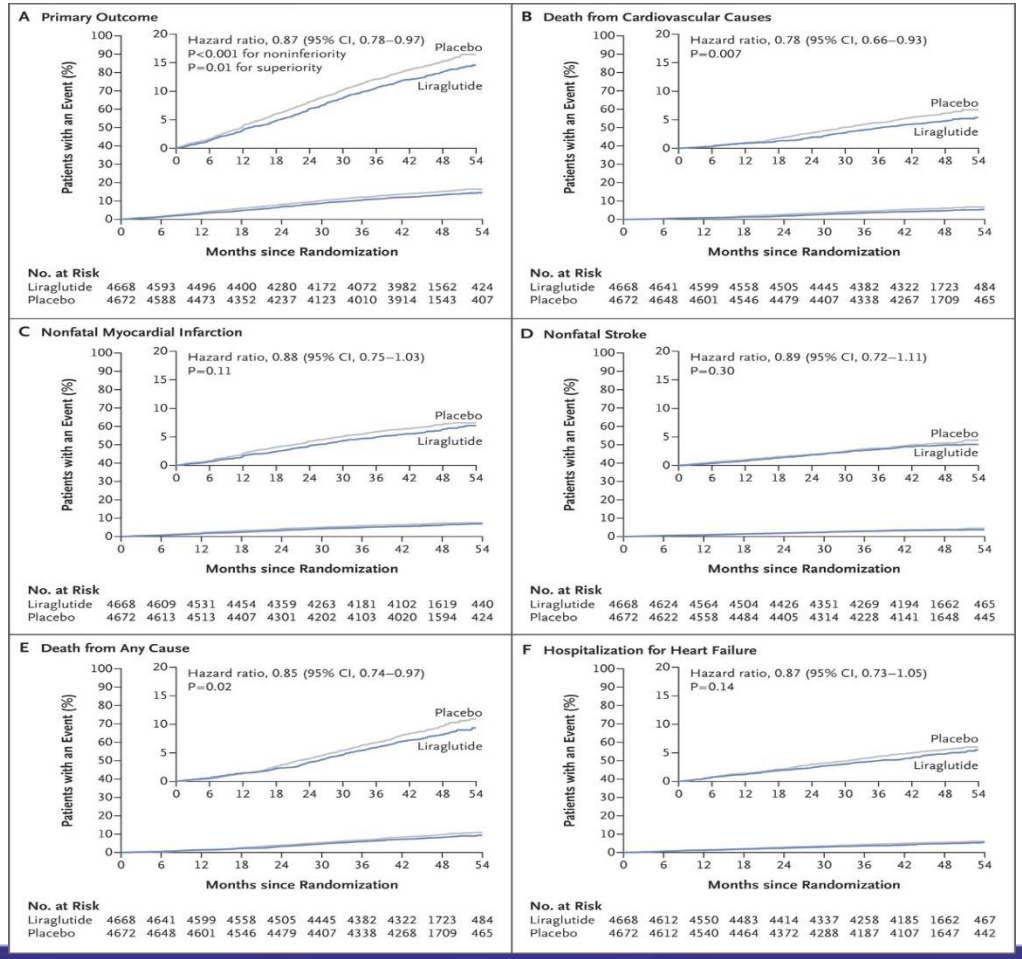

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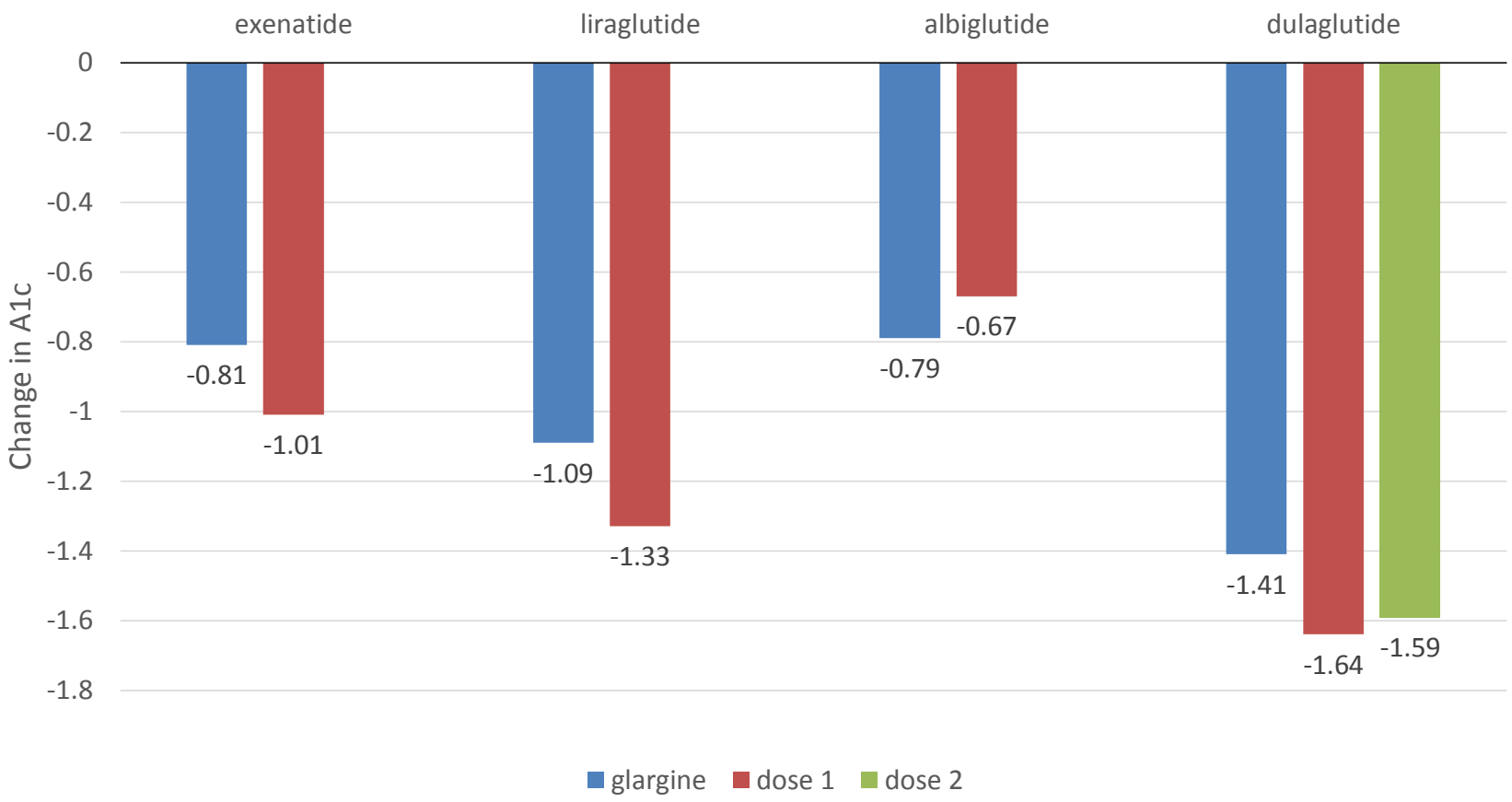
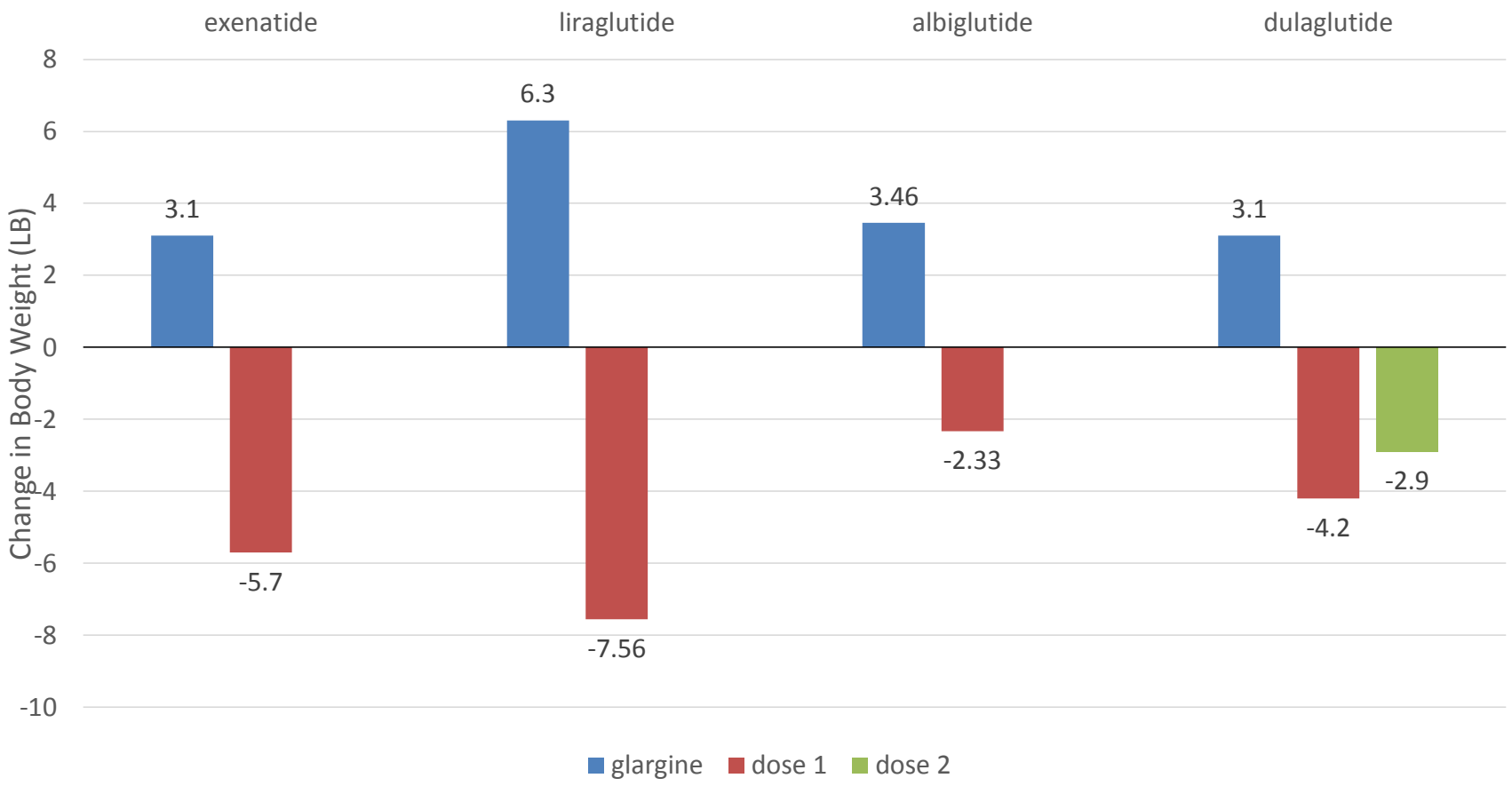
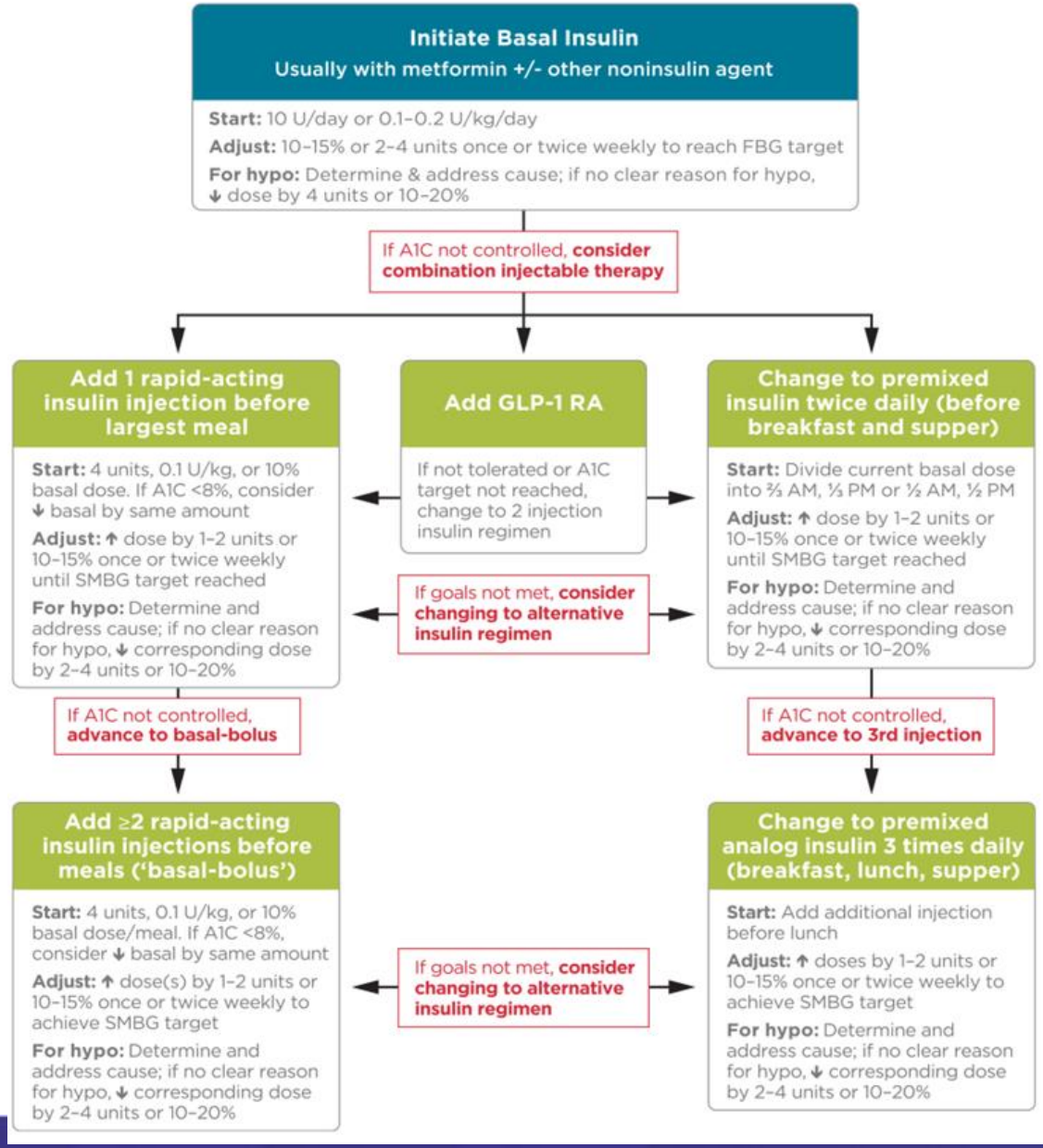
GLP1 vs basal insulin



GLP1 vs basal insulin





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Insulin options

Not actual size

Basal Insulin

Insulin	concentration	Duration	½ Life	Pen	Vial
Levemir (detemir)	U100	24 hr	5-7 hr	✓	✓
Lantus (glargine)	U100	24 hr	15 hr	✓	✓
Toujeo (glargine)	U300	36 hr	19 hr	✓	✗
Basaglar (glargine)	U100	24 hr	12 hr	✓	✗
Tresiba (degludec)	U100 U200	42 hr	25 hr	✓	✗
NPH Novolin/Humulin	U100	10-16 hr	4-5 hr	✓	✓

Short Acting Insulin

Insulin	Onset	Peak	Duration	Pen
Regular Humulin/Novolin	30-60 min	2-5 hr	6-8 hr	✗
Humalog (lispro)	10-30 min	90 min	3-4 hr	✓
NovoLog (aspart)	10-30 min	90 min	3-4 hr	✓
Apidra (glulisine)	5-15 min	60-90 min	3-4 hr	✓
Afrezza (human R)	<10 min	45-50 min	2.5-3 hr	**Inhaled**

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