Comprehensive education course for

Asian Diabetes Educators:

Oral Hypoglycemic Agents for Diabetes Mellitus

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Conflict of interest disclosure

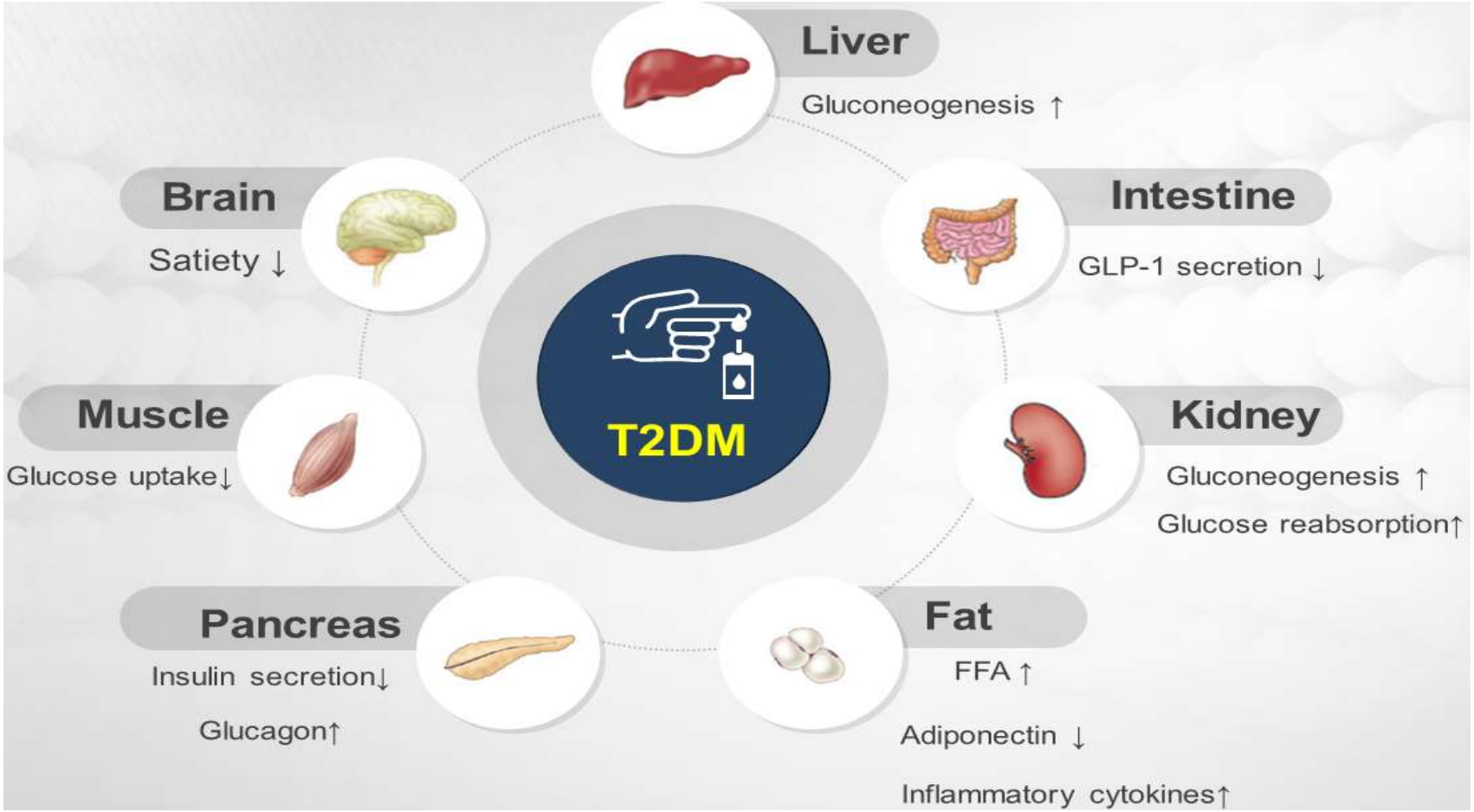
None

Committee of Scientific Affairs

Agenda

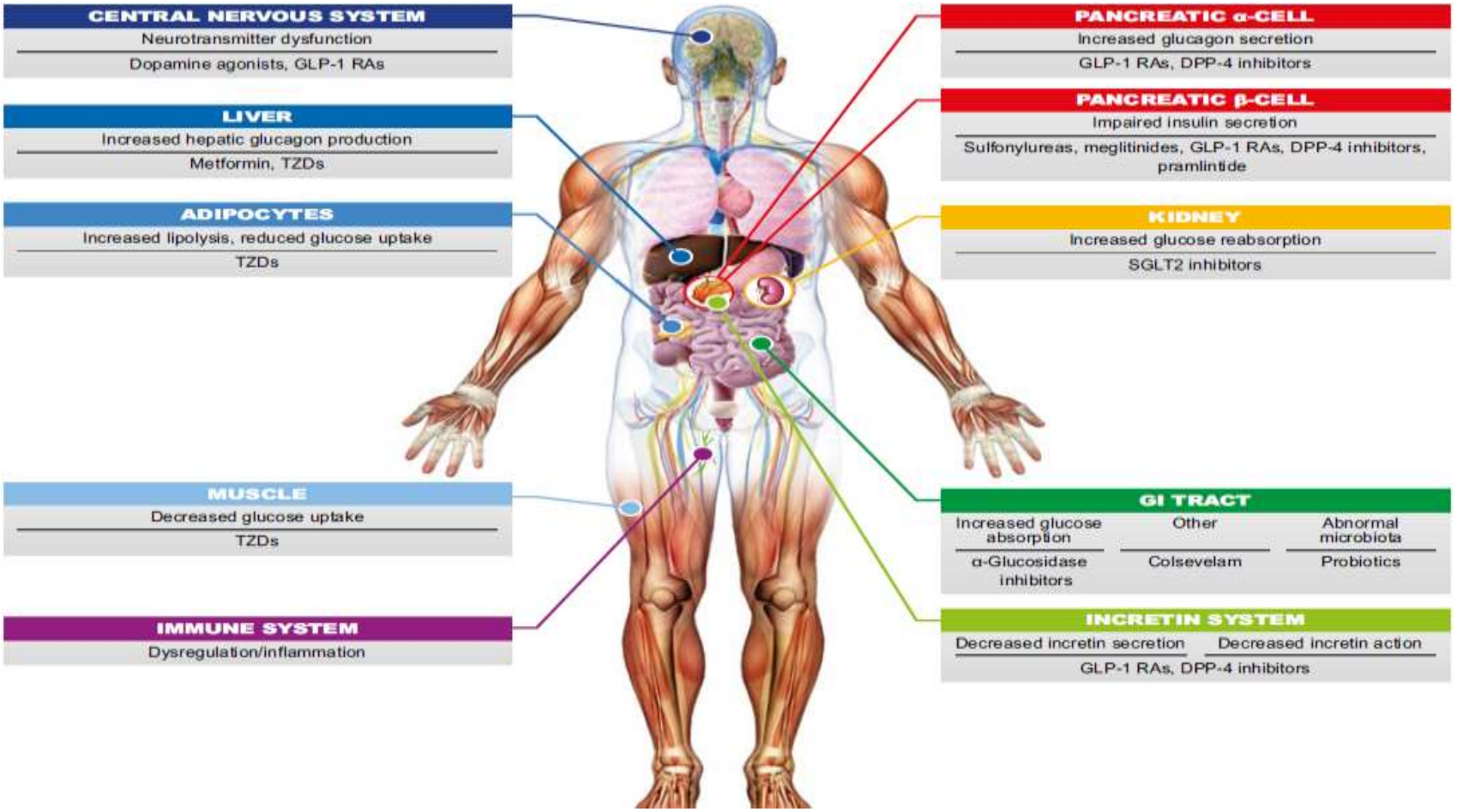
1. Pathophysiology based Treatment
2. Early Intensive Treatment
3. New kids on the block: DPP4i & SGLT2i
4. Cardiovascular safety of OHAs

Pathophysiology of T2DM



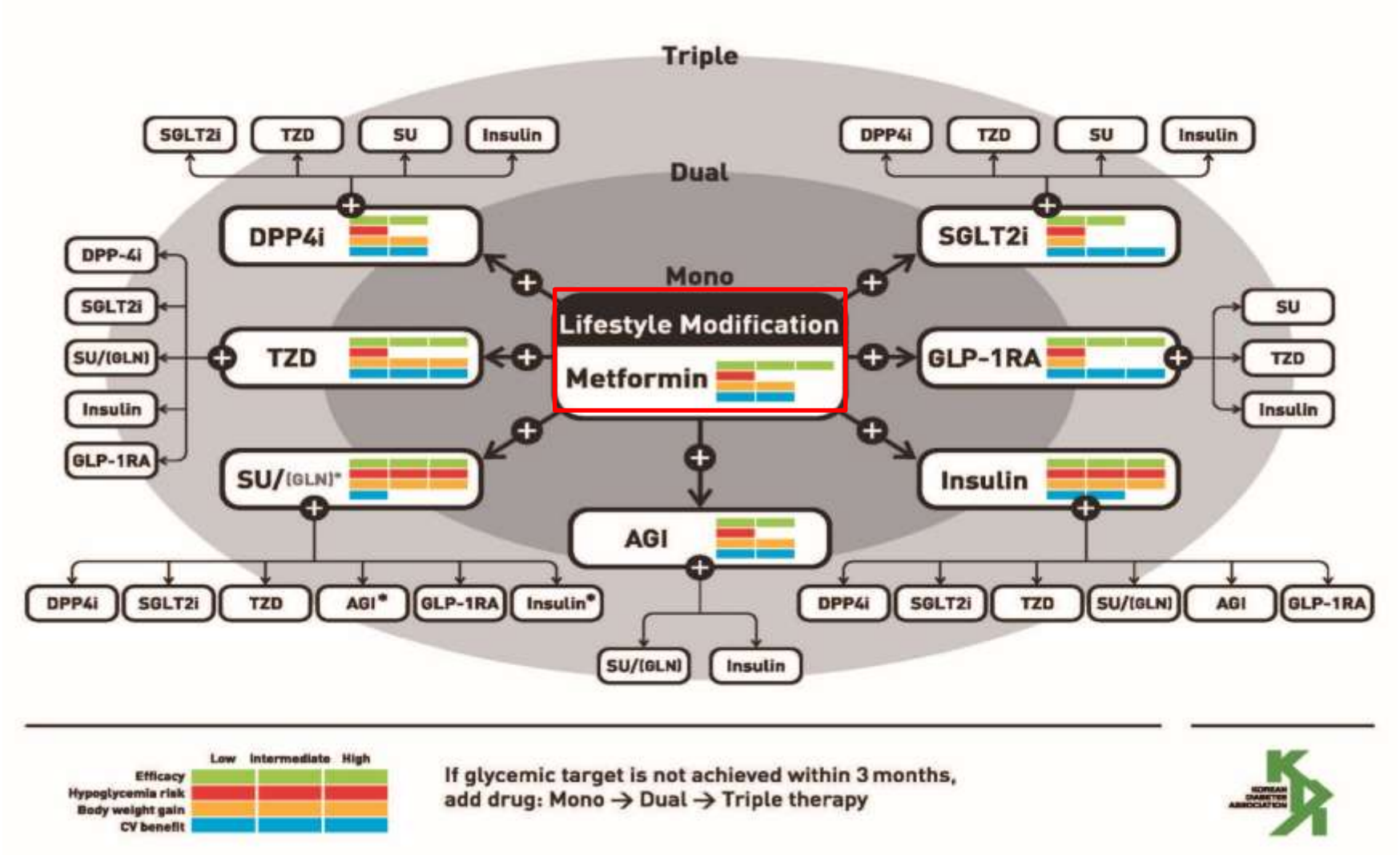
Ther Clin Risk Manag 2015;11: 621–632.

Pathophysiology based Tx

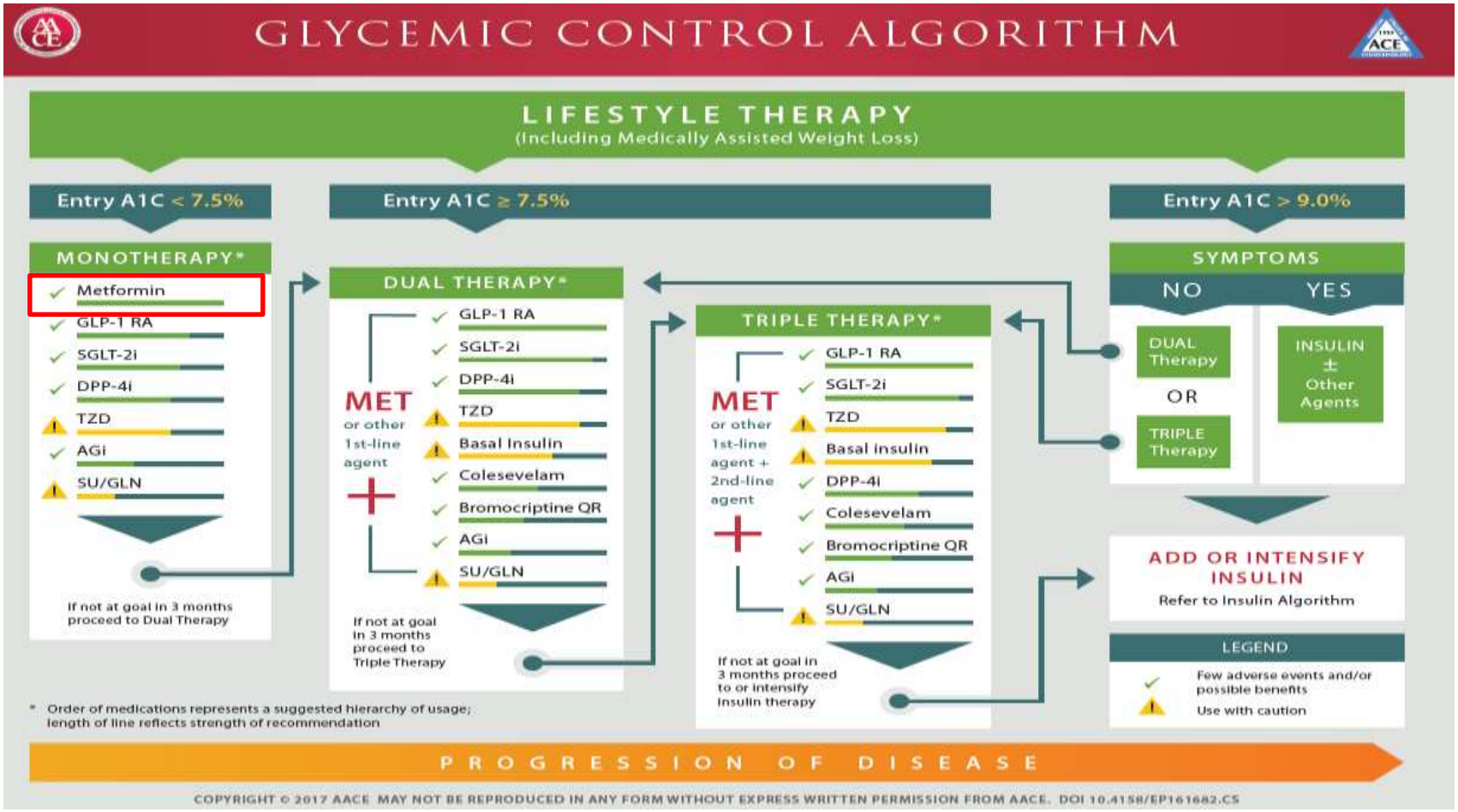


Endocrine Practice 2017. 10.4158/EP161725.RA

2017 KDA Guidelines

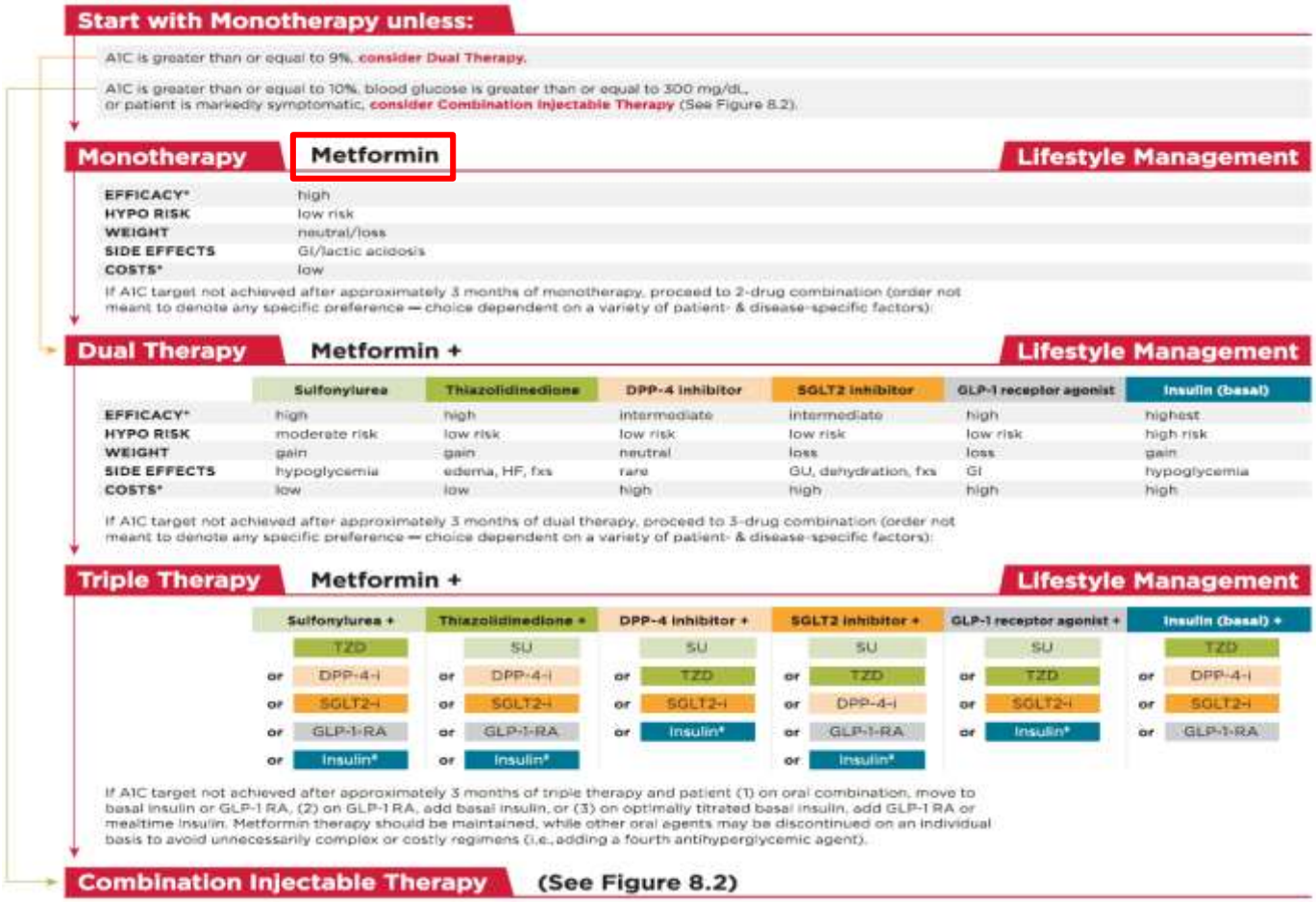


Glycemic control Algorithm



Endocrine Pract. 2017;23(No.2):207-238.

2017 ADA Guidelines



Diabetes Care 2017;40(Suppl. 1):S1–S125.

Pharmacologic Tx for T2DM

- **Metformin**, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM. **A**
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. **B**
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target **after 3 months**, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin. **A**

Diabetes Care 2017;40(Suppl. 1):S1–S125.

Recommendations of ACP

Recommendation 1: *ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.*

Ann Intern Med. 2017;166:279-290.

Guideline update from ACP

Disease/Condition	Type 2 diabetes
Target Audience	Internists, family physicians, other clinicians
Target Patient Population	Adults with type 2 diabetes
Interventions Evaluated	Oral pharmacologic treatments: metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors
Outcomes Evaluated	Clinical outcomes: all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, neuropathy Intermediate outcomes: HbA_{1c}; weight; systolic blood pressure; harms: hypoglycemia, gastrointestinal side effects, genital mycotic infections
Benefits	Clinical Outcomes Metformin monotherapy was associated with a lower risk for cardiovascular mortality than sulfonylurea monotherapy. HbA_{1c} Most drugs reduced HbA_{1c} to similar levels. DPP-4 inhibitors reduced HbA_{1c} levels less than metformin or sulfonylureas. All combination therapies with metformin were superior to metformin monotherapy. Weight Metformin was better than thiazolidinediones, sulfonylureas, or DPP-4 inhibitors for weight. Combinations of metformin and SGLT-2 inhibitor agonists reduced weight more than metformin monotherapy. Thiazolidinediones and sulfonylureas, either alone or in combination therapy, were associated with worse weight outcomes. Systolic Blood Pressure SGLT-2 inhibitors, as monotherapy or combined with metformin, reduced systolic blood pressure compared with metformin monotherapy.
Harms	Metformin: increased risk for gastrointestinal side effects Sulfonylureas: increased risk for hypoglycemia compared with other drugs Thiazolidinediones: increased risk for heart failure SGLT-2 inhibitors: increased genital mycotic infections

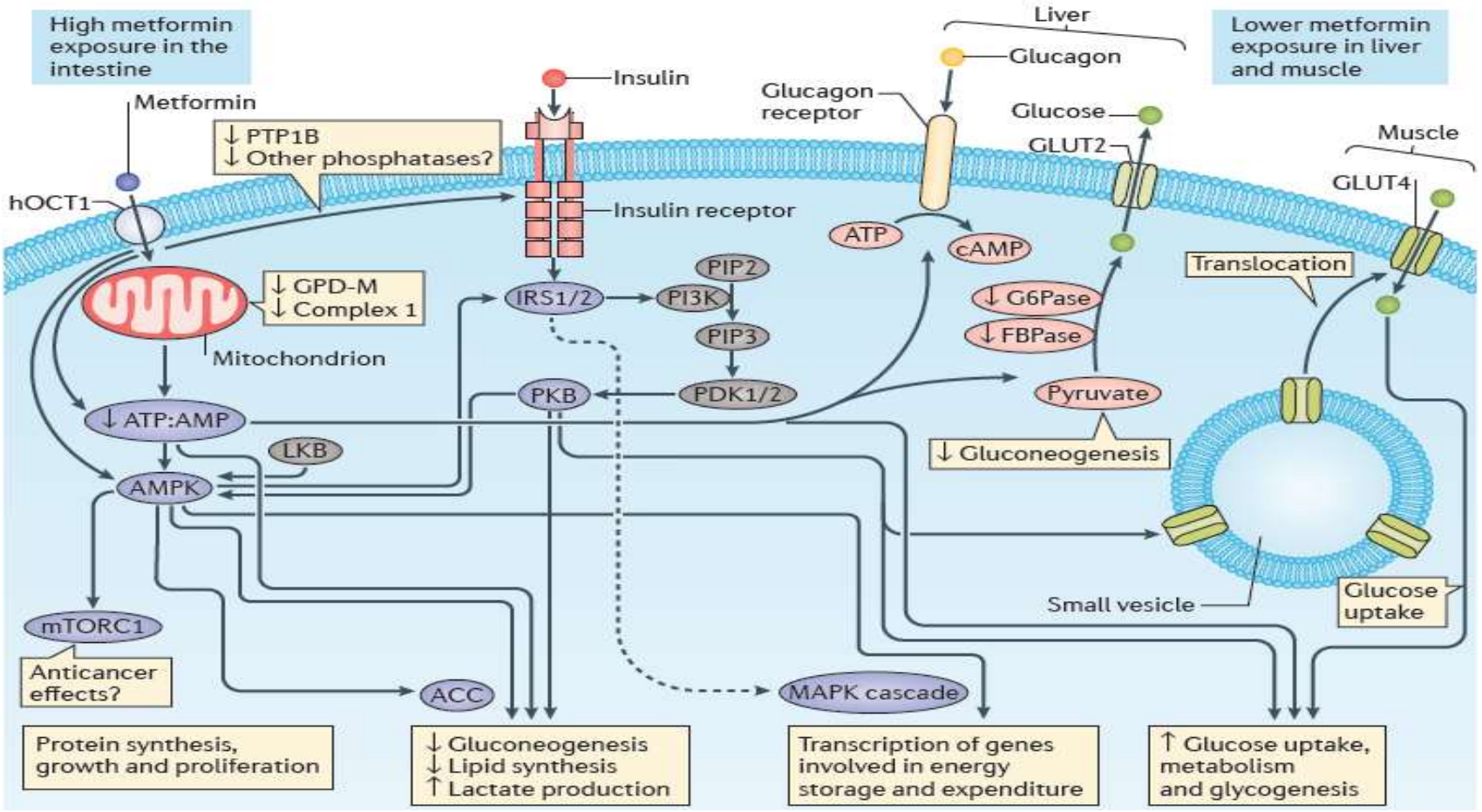
Ann Intern Med. 2017;166:279-290.

Clinical Considerations of ACP

Clinical Considerations	Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. Management of type 2 diabetes often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors. Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss or lifestyle modification fails. Metformin monotherapy effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight. Although combination therapy reduces HbA_{1c} levels more effectively than monotherapy, it is associated with more adverse events. The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease. Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m^2).

Ann Intern Med. 2017;166:279-290.

Cellular actions of Metformin



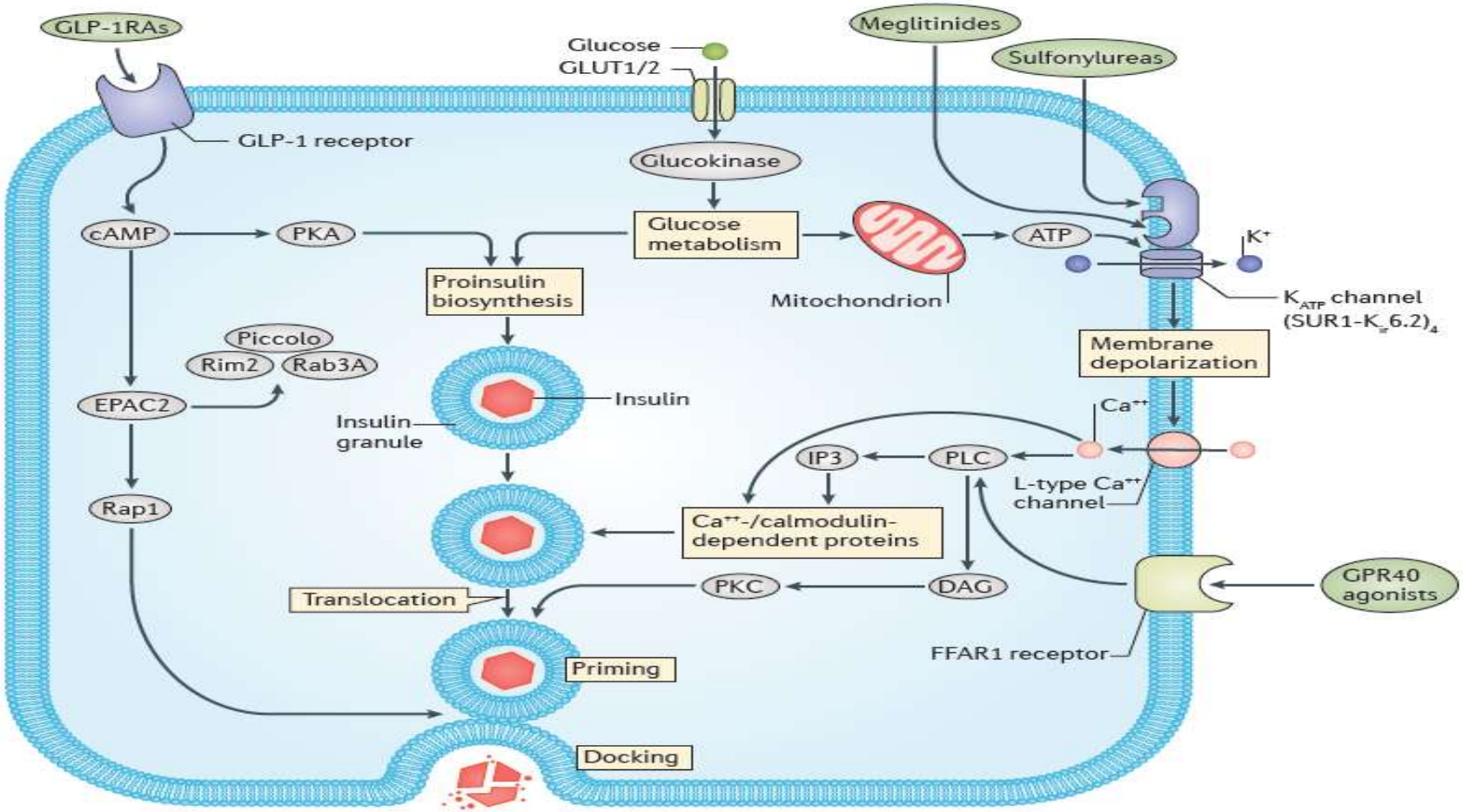
Nat Rev Endocrinol. 2016 Oct;12(10):566-92.

OHA in patients with T2DM (1)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS) • Relatively higher A1C efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Contraindications: eGFR <30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd generation • Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Relatively higher A1C efficacy	• Hypoglycemia • ↑ Weight	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• Rare hypoglycemia • Relatively higher A1C efficacy • Durability • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone) • ↓ Risk of stroke and MI in patients without diabetes and with *insulin resistance* and history of recent stroke or TIA (IRIS study [42], pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• Rare hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events in prediabetes (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• Rare hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ↑ Heart failure hospitalizations (saxagliptin; ? alogliptin)	High

Diabetes Care 2017;40(Suppl. 1):S1–S125.

SU, Glinides act on Pancreas



Nat Rev Endocrinol. 2016 Oct;12(10):566-92.

OHA in patients with T2DM (2)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ? ↓ CVD events (Cycloset Safety Trial) • ↑ Insulin sensitivity	• Rare hypoglycemia	• Modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• Rare hypoglycemia • ↓ LDL-C	• Modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High

Diabetes Care 2017;40(Suppl. 1):S1–S125.

Maximum Approved Daily dose

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR) 850 mg (IR) 1,000 mg (IR) 500 mg (ER) 750 mg (ER) 1,000 mg (ER)	$84 ($5, $94) $108 ($5, $108) $86 ($4, $87) $90 ($82, $6,672) $72 ($65, $92) $1,028 ($1,010, $7,213)	2,000 mg 2,550 mg 2,000 mg 2,000 mg 1,500 mg 2,000 mg
Sulfonylureas (2nd Gen)	• Glyburide	5 mg 6 mg (micronized)	$94 ($64, $103) $50 ($48, $71)	20 mg 12 mg (micronized)
	• Glipizide	10 mg (IR) 10 mg (XL)	$74 ($67, $97) $97	40 mg (IR) 20 mg (XL)
	• Glimepiride	4 mg	$74 ($71, $198)	8 mg
Meglitinides (glinides)	• Repaglinide • Nateglinide	2 mg 120 mg	$799 ($163, $878) $156	16 mg 360 mg
TZDs	• Pioglitazone • Rosiglitazone	45 mg 4 mg	$349 ($348, $349) $355	45 mg 8 mg
α-Glucosidase inhibitors	• Acarbose • Miglitol	100 mg 100 mg	$104 ($104, 105) $241	300 mg 300 mg
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin	100 mg 5 mg 5 mg 25 mg	$436 $436 $428 $436	100 mg 5 mg 5 mg 25 mg
Bile acid sequestrant	• Colesevelam	625 mg tabs 1.875 g suspension	$679 $1,357	3.75 g 3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	$719	4.8 mg
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin • Empagliflozin	300 mg 10 mg 25 mg	$470 $470 $470	300 mg 10 mg 25 mg

Diabetes Care 2017;40(Suppl. 1):S1–S125.

Comparison of OHAs (KDA)

	Reduction of HbA1c (Mono therapy, %)	Weight change	Hypo	Side effect	Caution
Metformin	1.0-2.0	Neutral	X	Digestive disorder (Anorexia, nausea, vomiting, diarrhea, Lactic acidosis)	Severe liver, renal impairment, infection, Dehydration, cardiopulmonary insufficiency, radiation contrast test 48 hours before stopping
Sulfonylurea	1.0-2.0	Increase	O	Joint pain, arthritis, Back pain, bronchitis	Severe liver, renal impairment
AGI	0.5-0.8	Neutral	X	Digestive disorder	Severe liver, renal impairment ,Involving the digestive malabsorption, Chronic bowel disease, severe infection
TZD	0.5-1.4	Increase	X	Weight gain, edema, Decreased hemoglobin, fractures, Heart Failure	Severe heart failure, liver dysfunction, Severe renal impairment, bladder cancer (Contraindication)
Glinide	0.5-1.5	Increase	O	Constipation, upper respiratory infection, Sinusitis	Severe liver, renal impairment
DPP-4 inhibitor	0.5-0.8	Neutral	X	Nasopharyngitis, upper respiratory tract infection, Gastrointestinal disorders	There is no long-term study for renal impairment patients, Increase pancreatitis risk
SGLT-2 inhibitor	0.5-0.8	Decrease	X	Urogenital infections, dehydration	There is no evidence for long tern safety

2015 Korea Diabetes Treatment guideline

Treatments for β-cell

Agents	Mode of action in β-cell	Animal data	Human data
PPARγ agonists	Upregulate Pdx-1 expression [25] Increase insulin gene transcription, GLUT2, and glucokinase [26] Reverse lipotoxicity [27]	Reduced oxidative stress [28] Inhibited β-cell apoptosis [29] Increased β-cell mass and function [28,29]	Slow the rate of loss of β-cell function and improve insulin sensitivity in ADOPT trial [23], ACT NOW study [30], PIPOD, and TRIPOD study [31]
GLP-1 analogues	Enhance glucose-stimulated insulin secretion [33] Act as a growth factor by promoting β-cell proliferation and inhibiting β-cell apoptosis [33] Stimulate insulin gene expression and biosynthesis [34] Attenuate ER stress [35]	Increased β-cell mass [36] Modulated the expression of β-cell specific genes [37] Inhibited β-cell apoptosis [38]	Improved insulin secretory capacity and insulin sensitivity [39] Reduced proinsulin to insulin ratio [40] Restore 1st and 2nd phase insulin secretion [41]
DPP-4 inhibitors	Inhibit the incretin degrading enzyme DPP-4 [32] Increase the bioavailability of active GLP-1 [42]	Increased β-cell mass and pancreatic insulin content [42,43] Enhanced insulin secretion [42]	Improved β-cell function [44,45]
GSK3β inhibitors	Regulate glycogen metabolism by inhibiting glycogen synthase [48] Inhibit ER stress induced β-cell apoptosis [51] Improve β-cell function by preserving β-cell transcriptional factor Pdx1 [52]	Enhanced insulin signaling [53] Improved insulin resistance [53] Increased β-cell mass [54]	–
GPR40 agonists	Induce insulin secretion by modulating G protein-coupled receptor involved in free fatty acid [55]	Enhanced glucose-dependent insulin secretion with elevation of Ca^{2+} [57] Decreased glucose and insulin level [58]	Increased insulin secretion [59]

Diabetes Metab J 2014;38:426-436.

Agenda

1. Pathophysiology based Treatment
2. Early Intensive Treatment
3. New kids on the block: DPP4i & SGLT2i
4. Cardiovascular safety of OHAs

Early Intensive Treatment

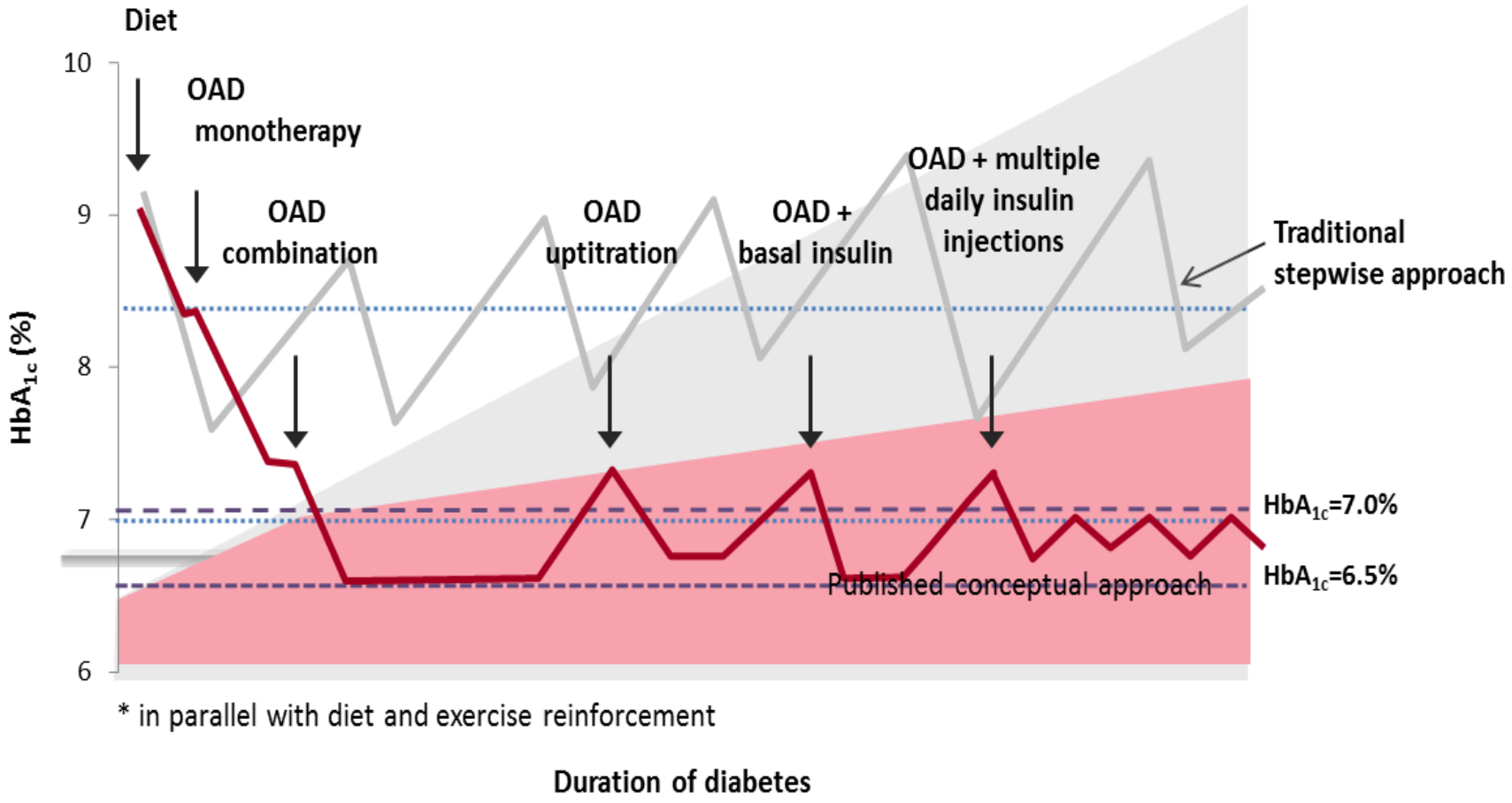
Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
*DCCT / EDIC** * in T1DM	↓	↓	↔	↓	↔	↔

Initial Trial

Long Term Follow-up

1. Lancet 1998;352. 2. NEJM 2008;359:1577. 3. NEJM 2009;361:1024.

from REACTIVE to PROACTIVE

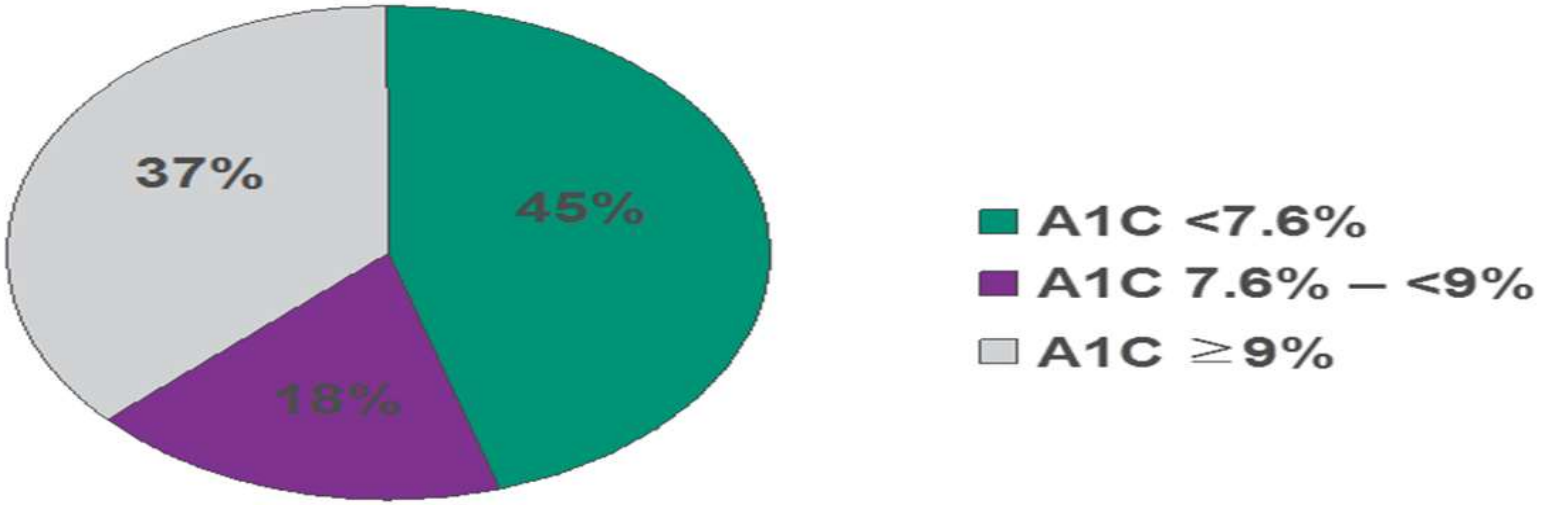


Int J Clin Pract 2005;59:1345–55.

Need for Early Combination Tx

Approximately **55% of Newly diagnosed patients with T2DM** have a baseline A1C value that may be eligible for combination therapy.

Percent of Patients with T2DM Eligible for Combination Therapy [1]



Mean A1C=8.57% (N=10,361)[1]

Data on File OR META 002. BMS, Princeton, NJ

Benefits of Combination Tx

- Considering the complexity and progressive nature of T2DM, monotherapy might not yield long-term benefits. Therefore, even at the time diabetes is diagnosed, it might be appropriate to consider combination therapies to achieve adequate glycemic control in patients with T2DM.

- Combination therapy in T2DM should address the various pathophysiological mechanisms that cause hyperglycemia.

- Combination treatment showed good safety profiles.

Journal of Diabetes Research 2017:Article ID 5282343.

Combination Therapy (1)

Comparative Efficacy vs. Other Combinations With Metformin (Quality of Evidence)	Comparative Harms vs. Other Combinations With Metformin/Class Adverse Effects and FDA Warnings	Agents	Fair Price for a 60-d Supply, $*	Adverse Effects
SUs				
SU + metformin favored for weight vs. TZD + metformin (moderate)	Higher risk for hypoglycemia than with metformin combinations with TZD, DPP-4 inhibitor, or SGLT-2 inhibitor	Glipizide, 5 mg	9	Diarrhea, gas, jitteriness, dizziness, uncontrollable shaking, red or itchy skin, rash, hives, and blisters
		Glimepiride, 4 mg	14	Dizziness and nausea
		Glyburide (DiaBeta, Sanofi-Aventis), 5 mg	111	Nausea and upper abdominal fullness
		Glyburide (Glynase, Pfizer), 6 mg	226	Nausea and upper abdominal fullness
TZDs				
TZD + metformin favored for short-term CVD mortality (rosiglitazone only) (low) and HbA_{1c} vs. DPP-4 inhibitor + metformin (moderate)	TZDs increase risk for congestive heart failure May also be associated with increased risk for fracture or bladder cancer	Pioglitazone, 30 mg	24	Headache; muscle, arm, or leg pain; sore throat; and gas
		Rosiglitazone (Avandia, GlaxoSmithKline), 2 mg	178	Headache, runny nose and other cold symptoms, sore throat, and back pain

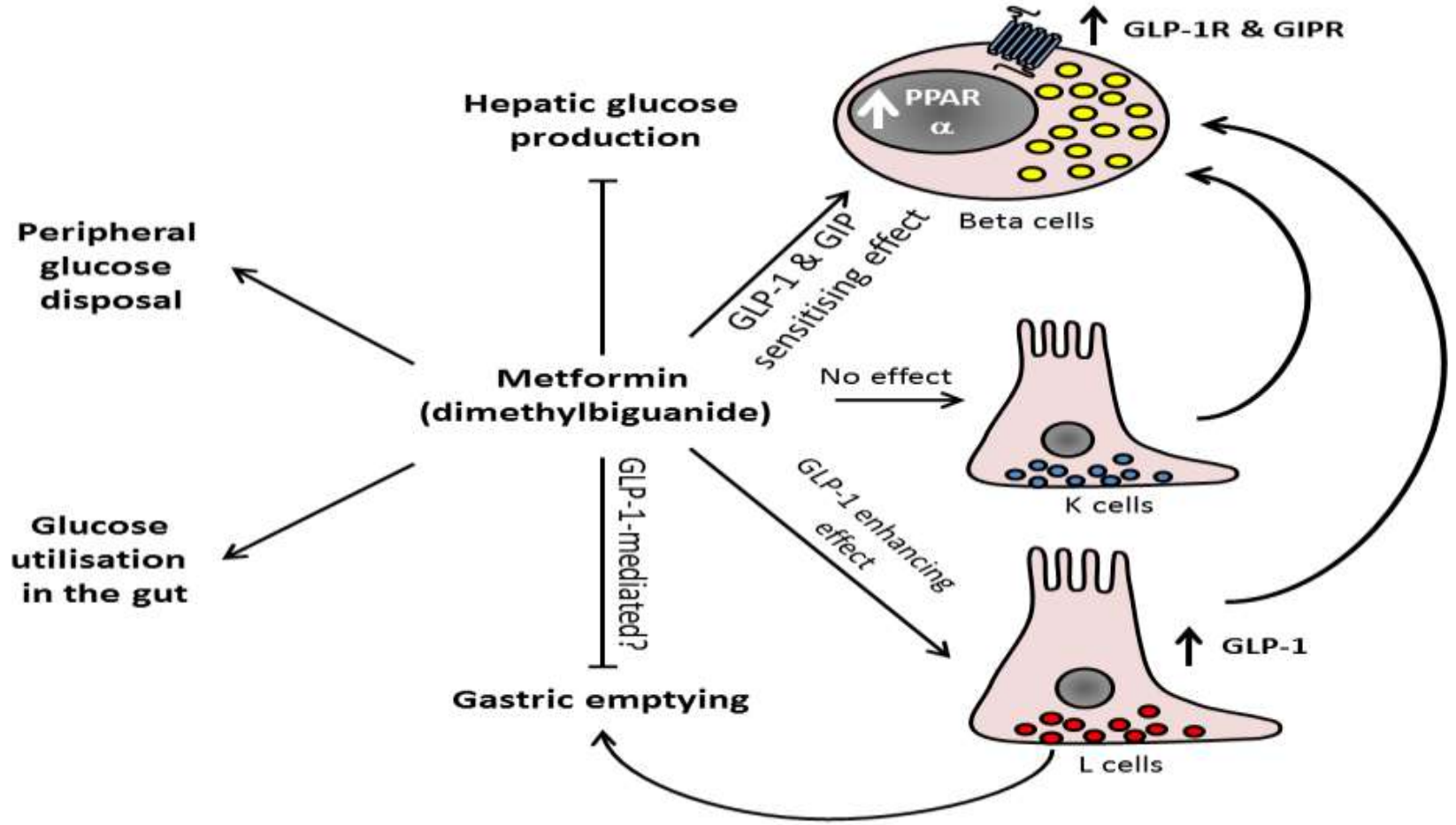
Ann Intern Med. 2017;166:279-290.

Combination Therapy (2)

Comparative Efficacy vs. Other Combinations With Metformin (Quality of Evidence)	Comparative Harms vs. Other Combinations With Metformin/Class Adverse Effects and FDA Warnings	Agents	Fair Price for a 60-d Supply, $*	Adverse Effects
DPP-4 inhibitors				
DPP-4 inhibitor + metformin favored for long-term all-cause mortality, long-term CVD mortality, and CVD morbidity vs. SU + metformin (low) DPP-4 inhibitor + metformin favored for short-term CVD morbidity vs. pioglitazone + metformin (low) DPP-4 inhibitor + metformin favored for weight vs. SU + metformin (high) or TZD + metformin (moderate)	FDA warns that sitagliptin, saxagliptin, linagliptin, and alogliptin may be associated with potentially severe and disabling joint pain	Alogliptin, 25 mg	335	Headache, stuffy or runny nose, sore throat, and joint pain
		Linagliptin (Tradjenta, Boehringer Ingelheim), 5 mg	734	Headache and joint pain
		Saxagliptin (Onglyza, AstraZeneca), 5 mg	752	Sore throat, headache, and joint pain
		Sitagliptin (Januvia, Merck), 100 mg	746	Stuffed or runny nose, sore throat, headache, diarrhea, nausea, and joint pain
SGLT-2 inhibitors				
SGLT-2 inhibitor + metformin favored for CVD mortality (low), HbA_{1c} (moderate), weight (high), systolic blood pressure (high), and heart rate (moderate) vs. SU + metformin SGLT-2 inhibitor + metformin favored for weight and systolic blood pressure (moderate) vs. DPP-4 inhibitor + metformin	Higher risk for genital mycotic infection than metformin alone or metformin combinations with SU or DPP-4 inhibitor FDA warns that canagliflozin may be associated with increased risk for bone fracture and risk for decreased bone mineral density	Canagliflozin (Invokana, Janssen), 300 mg	808	Excessive urination, including at night; increased thirst; constipation; and dry mouth
		Dapagliflozin (Farxiga, AstraZeneca), 10 mg	812	Excessive urination, including at night, and increased thirst
		Empagliflozin (Jardiance, Boehringer Ingelheim), 25 mg	812	Excessive urination, including at night, and increased thirst

Ann Intern Med. 2017;166:279-290.

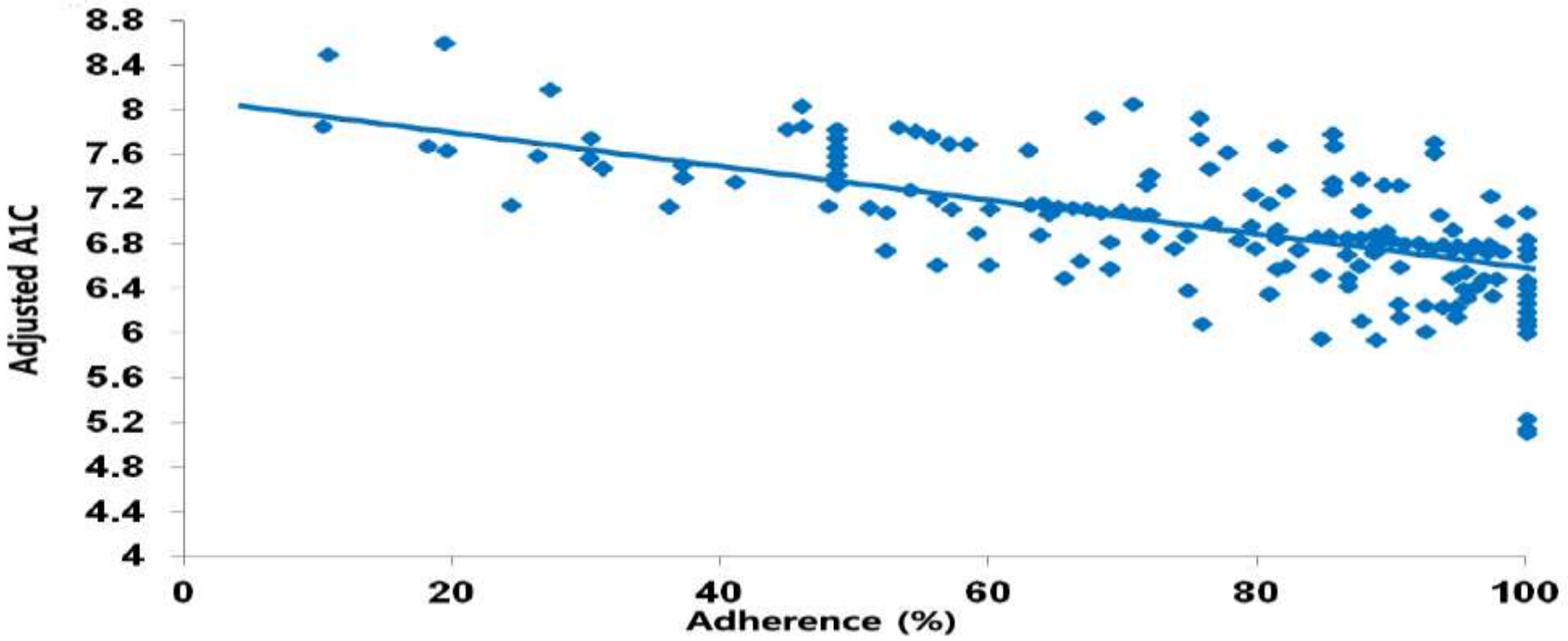
Metformin: GLP-1 enhancer



Diabetologia 2011;54(2):219-222.

Better Adherence and HbA1c

A 10% increase in concordance with oral glucose-lowering agents was associated with a 0.1% decrease in HbA1c (P=0.0004)



Am J Manag Care 2008;14:71-75.

How to improve Adherence

- Counselling
- Number of daily single doses
- Dose-dispensed medicine
- **Fixed combinations (polypills)**
  to reduce the number of tablets.

European Heart Journal 2011;32:264–268.

Better HbA1c Reduction in FDC

The meta-analysis revealed a significantly greater HbA1c reduction with FDC than CDT.

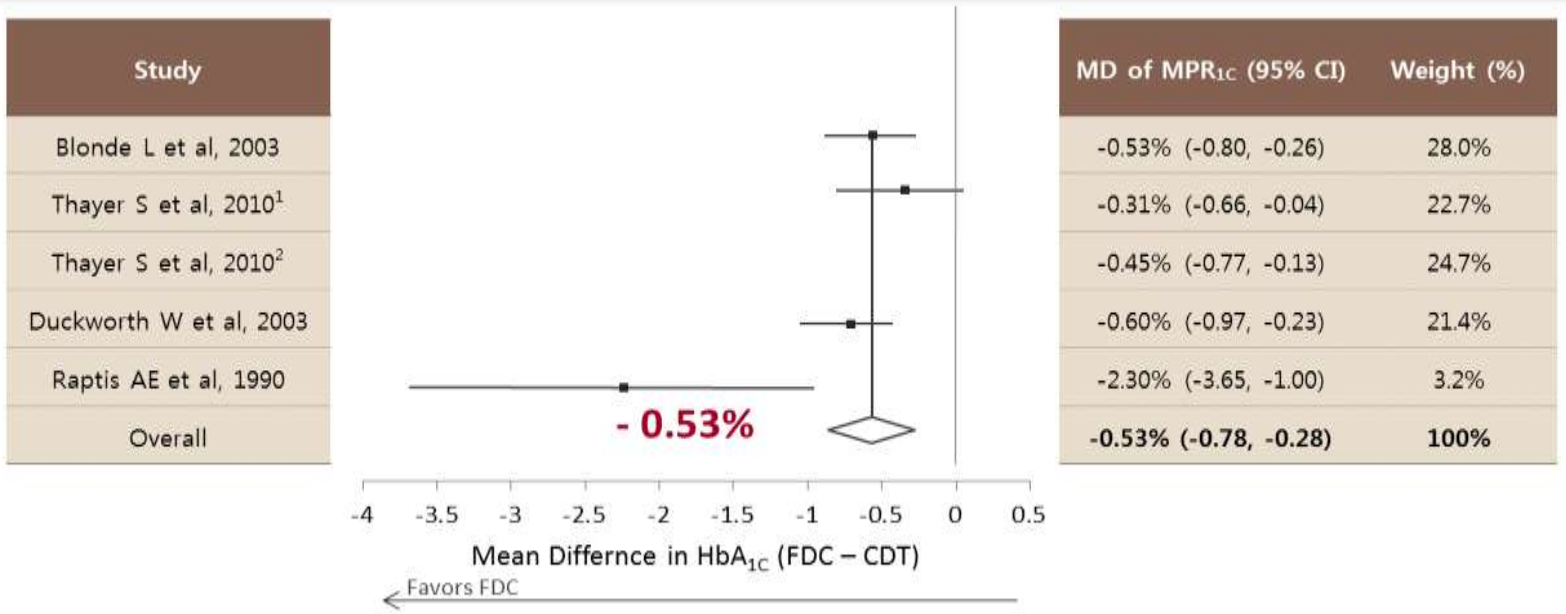
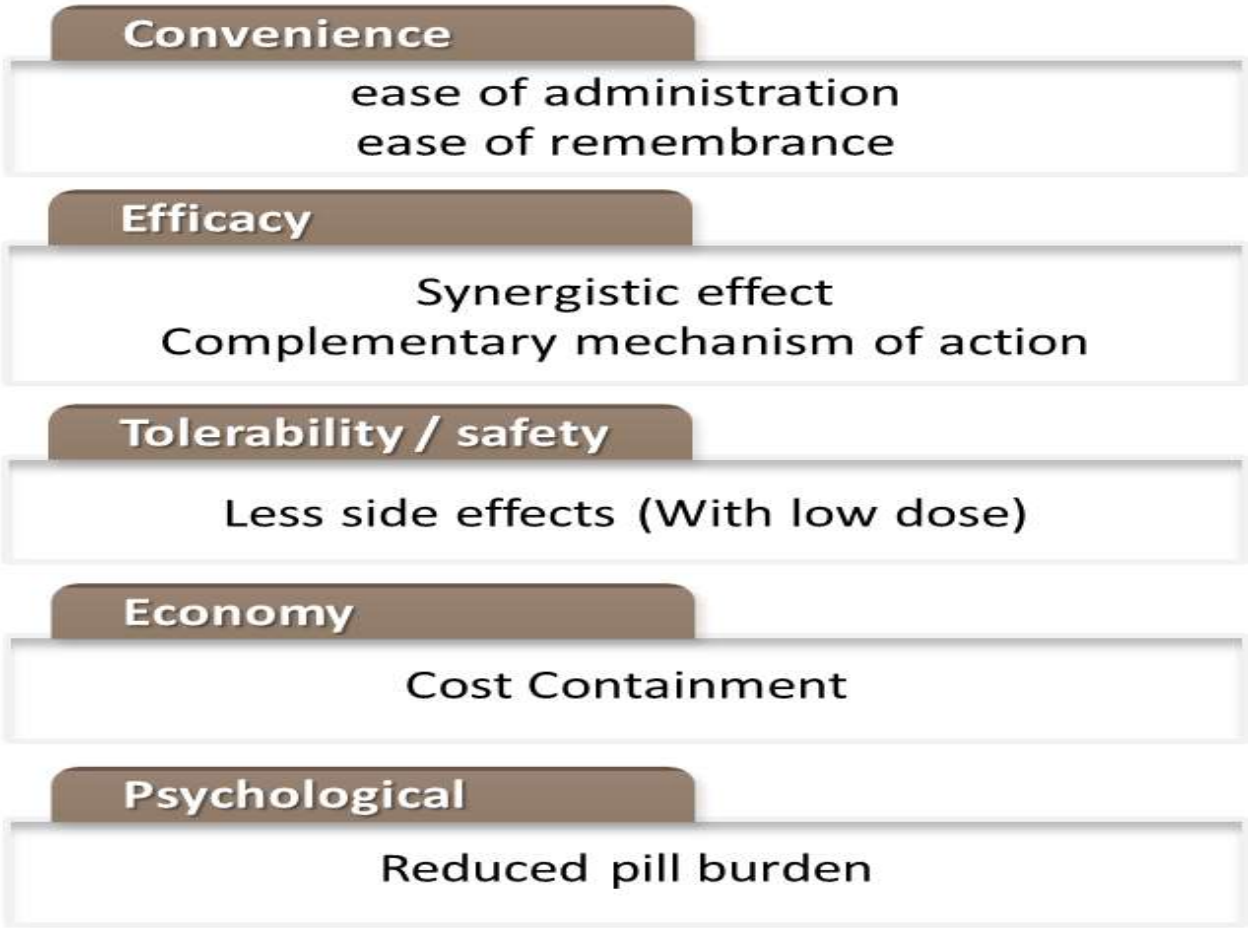


Figure 2. Weighted mean differnce (MD) for change in HbA_{1C} between fixed-dosed combination (FDC) and coadministered dual therapy (CDT). Baseline HbA_{1C} values were 9.1 – 9.2% in Blond *et al.*; 8.0 – 8.1% in the 7.3 – 7.8% in the dual therapy cohort form Thayer *et al.*; 8.3% in Duckworth et al.; and 10.6% in Raptis *et al.*

FDC: Fixed dose combination, CDT: Coadministration dual therapy

Curr Med Res Opin. 2012;28:969-77.

Multiple Benefits of FDC



Medicine Update 2012;22:249-253.

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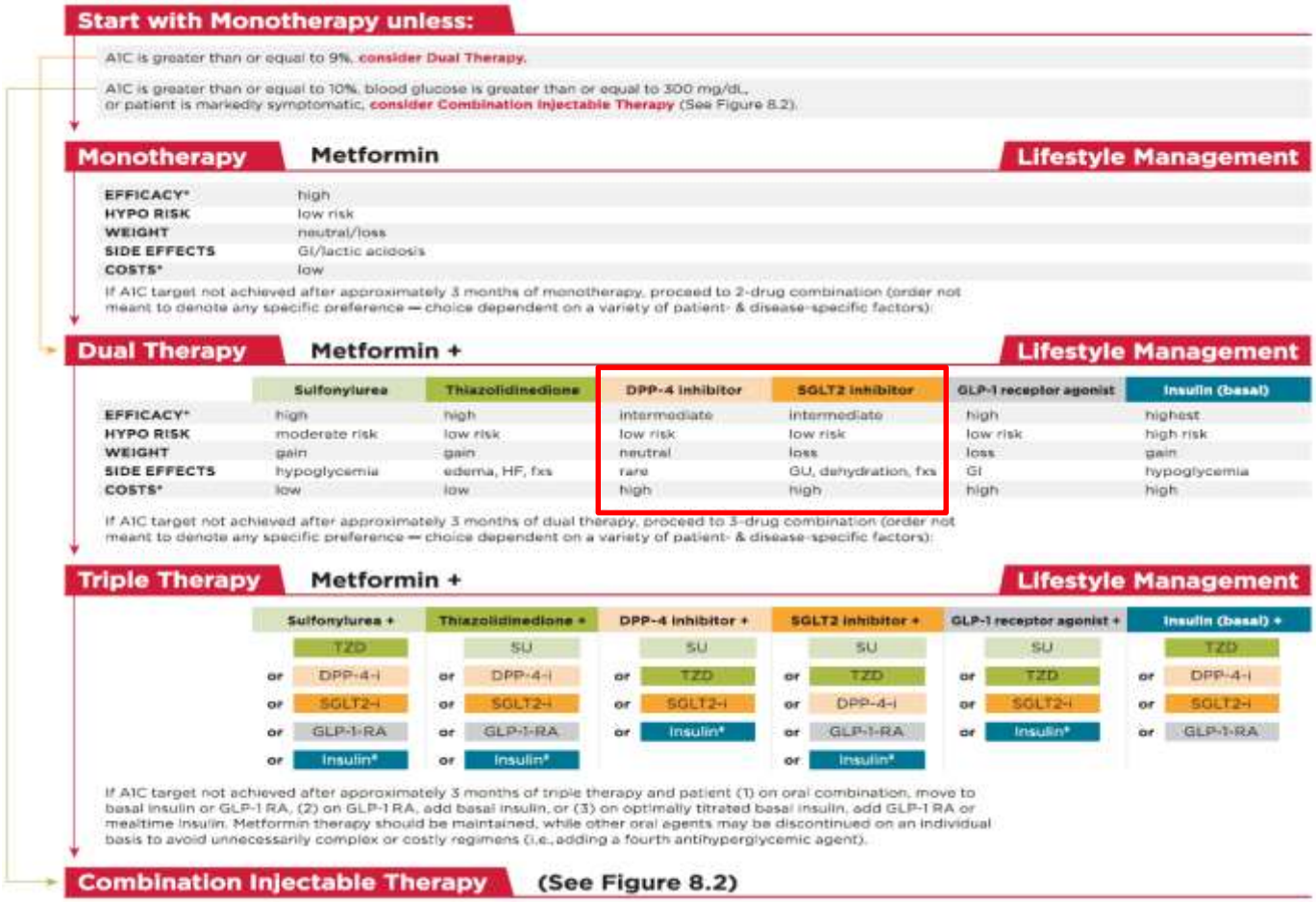
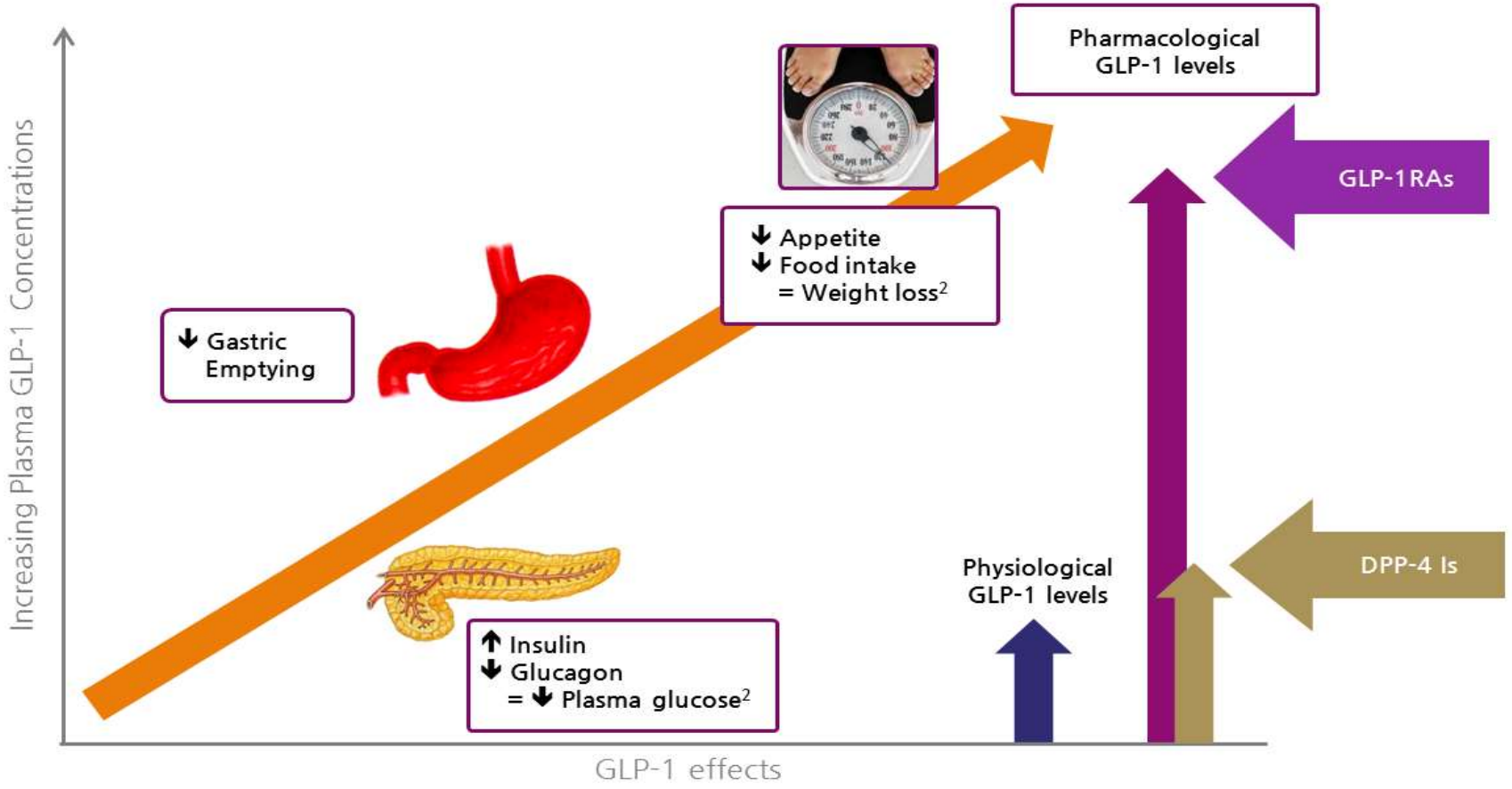
2017 ADA Guidelines



Diabetes Care 2017;40(Suppl. 1):S1–S125.

Dose-dependent effect

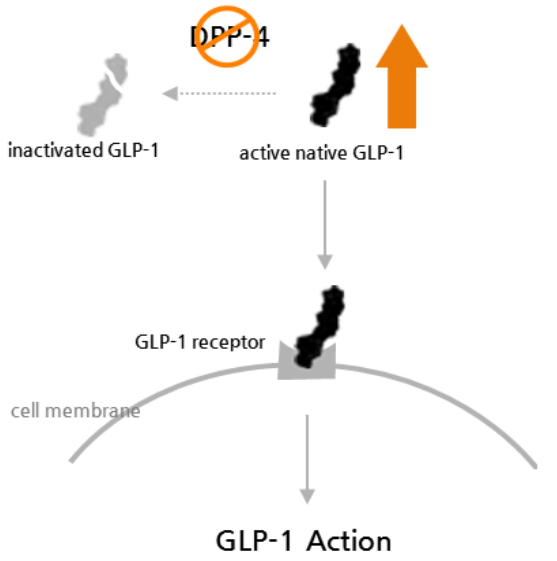


Trends Mol Med 2008;14:161–168.

Two ways to Increase GLP-1

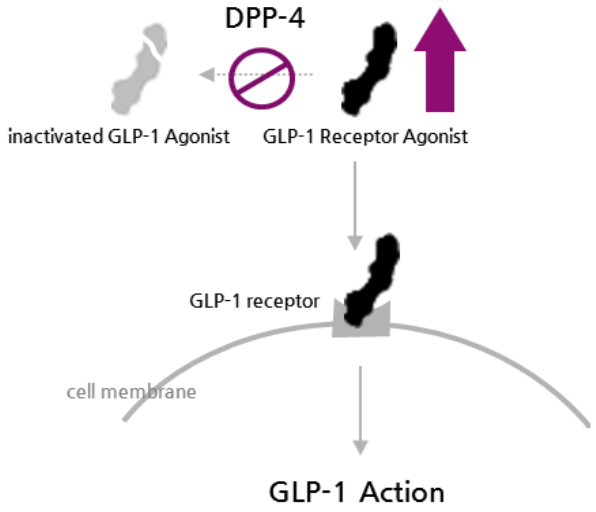
DPP-4 Inhibitors

Increase circulating native GLP-1 levels by inhibiting the DPP-4 enzyme



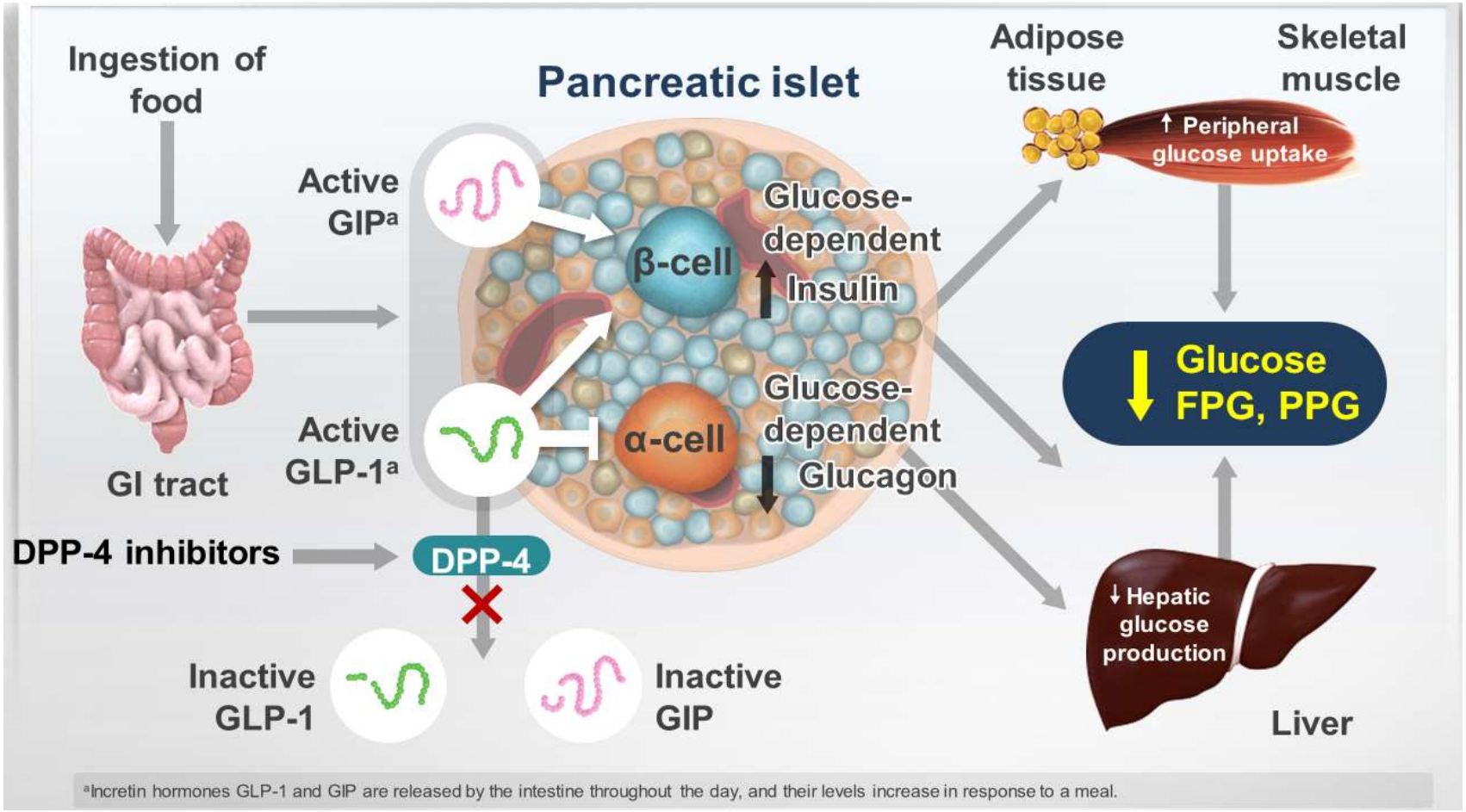
GLP-1 Receptor Agonists

Bind & activate the GLP-1 receptor and are resistant to degradation by the DPP-4 enzyme



Curr Med Res Opin. 2008;24:2943-2952.

Mechanism of DPP-4 inhibitors



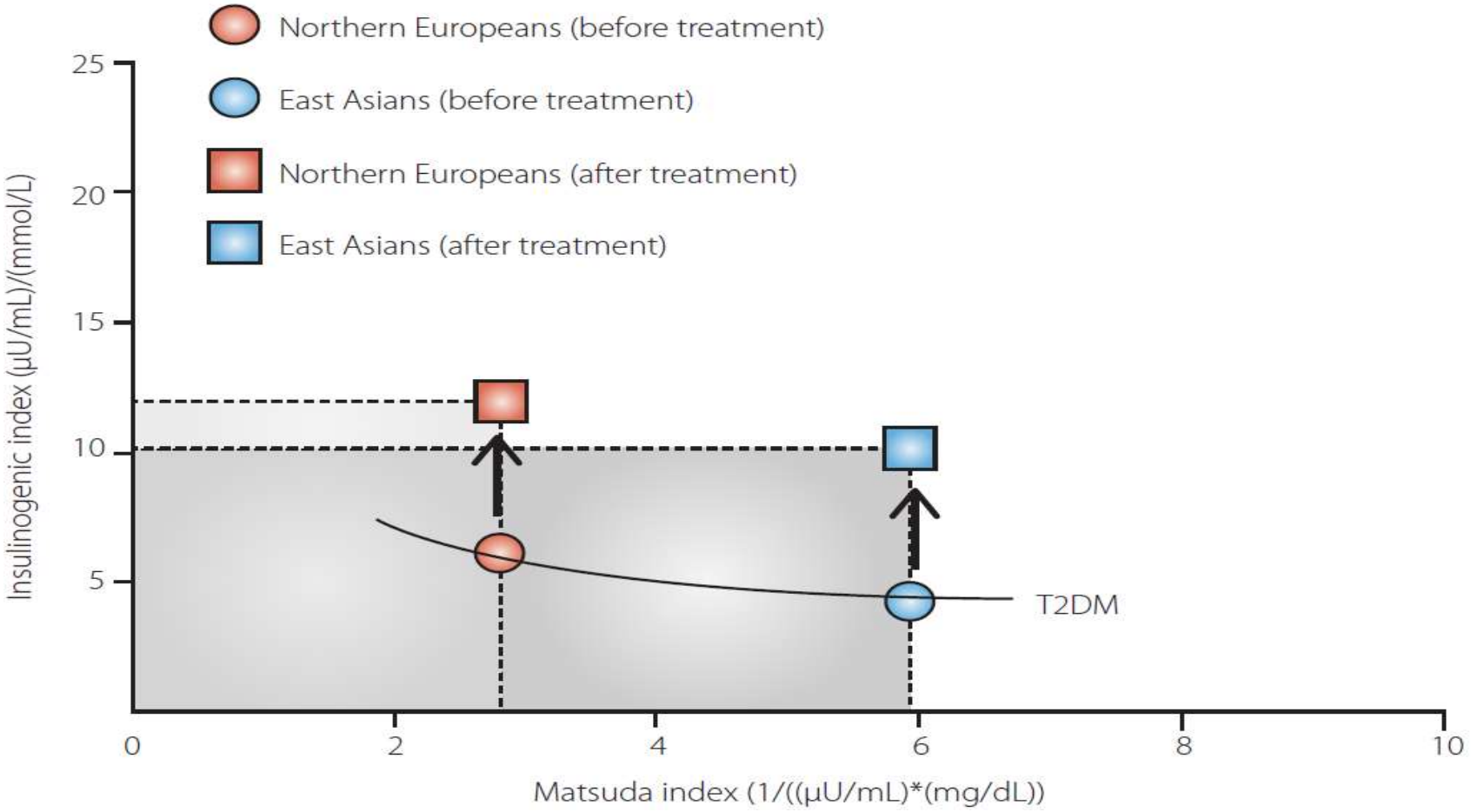
1. Curr Diabetes Rep 2003;3:365–372. 2. Diabetes Care 2003;26:2929–2940.
3. Diabetes Metab Res Rev 2002;18:430–441. 4. J Clin Invest 2007;117:24–32.

DPP4i is more effective in Asia

Types of therapies and reference/clinical end-points	Asian-dominant studies		Non-Asian-dominant studies	Difference and/or statistical significance
DPP-4 inhibitors[60]				
HbA1c-lowering from baseline (%)	−0.92 (−1.03 to −0.82)	>	−0.65 (−0.69 to −0.60)	−0.26 (−0.36 to −0.17), $P < 0.001$
RR of achieving HbA1c <7.0%	3.4 (2.6 to 4.7)		1.9 (1.8 to 2.0)	$P < 0.05$
GLP-1 receptor agonists[62]				
HbA1c-lowering from baseline (%)	−1.16 (−1.48 to −0.85)		−0.83 (−0.97 to −0.70)	−0.32 (−0.64 to −0.01), $P < 0.05$
RR of achieving HbA1c <7.0%	5.7 (3.8 to 8.7)		2.8 (2.4 to 3.3)	$P = 0.082$

J Diabetes Invest 2014

DPP4i is more effective in Asia



J Diabetes Invest 2014

Other concerns

Table 3. Safety End Points.

End Point	Saxagliptin (N = 8280)	Placebo (N = 8212)	P Value*
	no. (%)		
Thrombocytopenia	55 (0.7)	65 (0.8)	0.36
Lymphocytopenia	49 (0.6)	40 (0.5)	0.40
Severe infection	590 (7.1)	576 (7.0)	0.78
Opportunistic infection	21 (0.3)	35 (0.4)	0.06
Hypersensitivity reaction	93 (1.1)	89 (1.1)	0.82
Bone fracture	241 (2.9)	240 (2.9)	1.00
Skin reaction	228 (2.8)	232 (2.8)	0.81
Renal abnormality	483 (5.8)	418 (5.1)	0.04
Any hypoglycemia†	1264 (15.3)	1104 (13.4)	<0.001
Major	177 (2.1)	140 (1.7)	0.047
Minor	1172 (14.2)	1028 (12.5)	0.002
Cancer	327 (3.9)	362 (4.4)	0.15
Any liver abnormality†	55 (0.7)	67 (0.8)	0.28
AST >3× ULN	60 (0.7)	61 (0.7)	0.93
AST >10× ULN	12 (0.1)	15 (0.2)	0.57
ALT or AST >3× ULN and total bilirubin >2× ULN	13 (0.2)	23 (0.3)	0.097
Any pancreatitis†	24 (0.3)	21 (0.3)	0.77
Acute: definite or possible	22 (0.3)	16 (0.2)	0.42
Acute: definite	17 (0.2)	9 (0.1)	0.17
Acute: possible	6 (0.1)	7 (0.1)	0.79
Chronic	2 (<0.1)	6 (0.1)	0.18

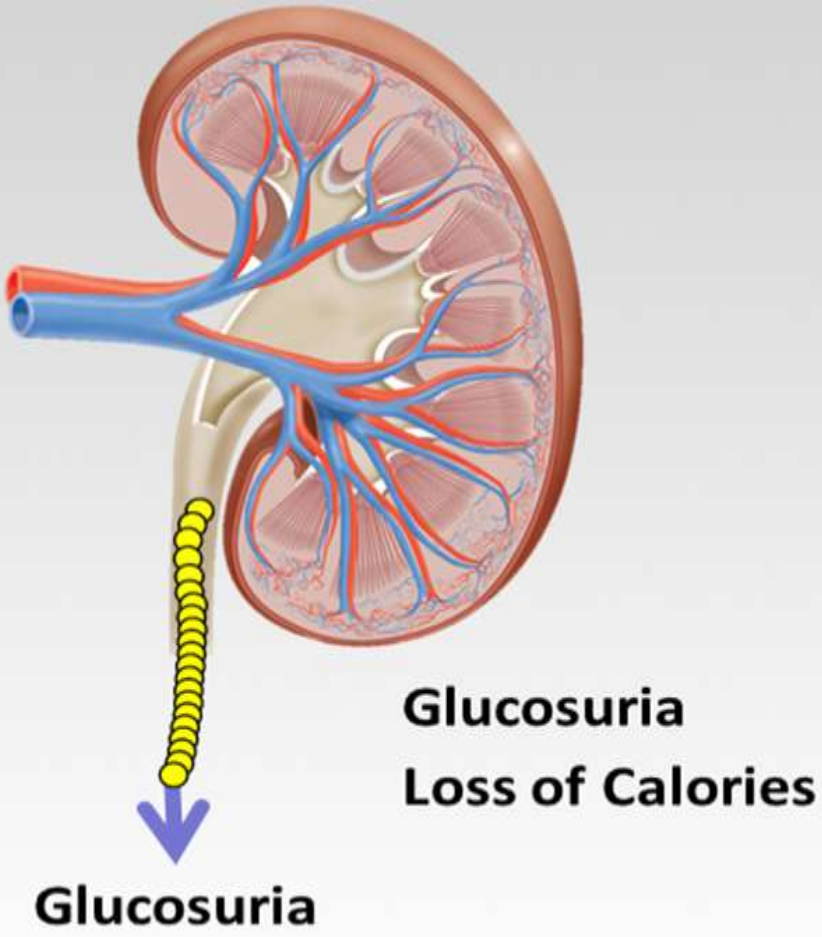
Table 2. Serious Adverse Events.*

Event	Sitagliptin (N = 7332)		Placebo (N = 7339)	
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*
Benign, malignant, or unspecified neoplasm	341 (4.7)	405	371 (5.1)	470
Injury, poisoning, or procedural complication	146 (2.0)	165	133 (1.8)	153
Gastrointestinal disorder	130 (1.8)	143	102 (1.4)	121
Musculoskeletal or connective-tissue disorder	118 (1.6)	136	93 (1.3)	102
Respiratory, thoracic, or mediastinal disorder	66 (0.9)	81	77 (1.0)	95

N Engl J Med 2013;369:1317-1326.
N Engl J Med 2015;373:232-242.

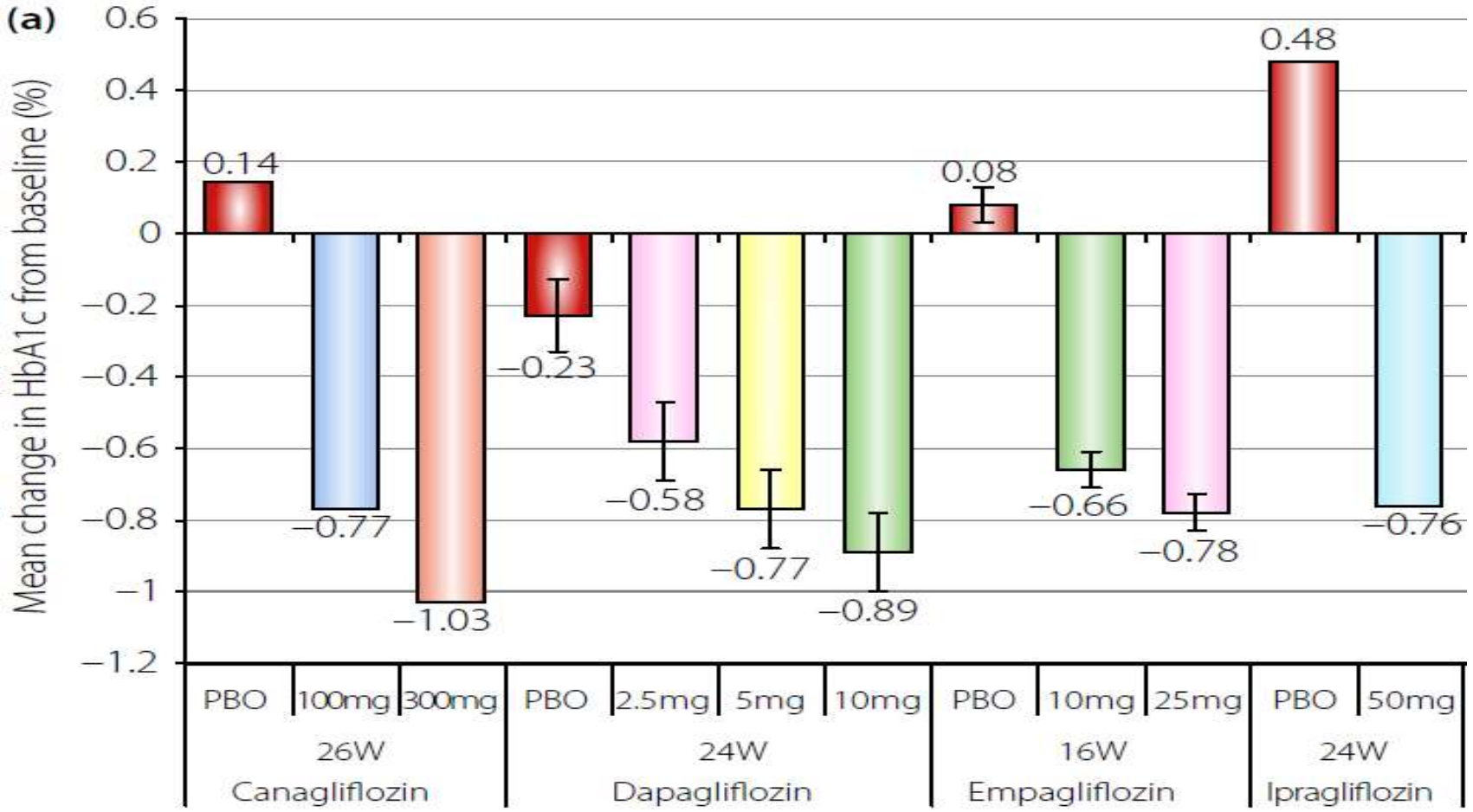
Mechanism of SGLT2i

- Insulin-independent
- HbA1c Reduction
- Reduction of
  - FPG
  - PPG
  - Weight
- Reduction of blood pressure



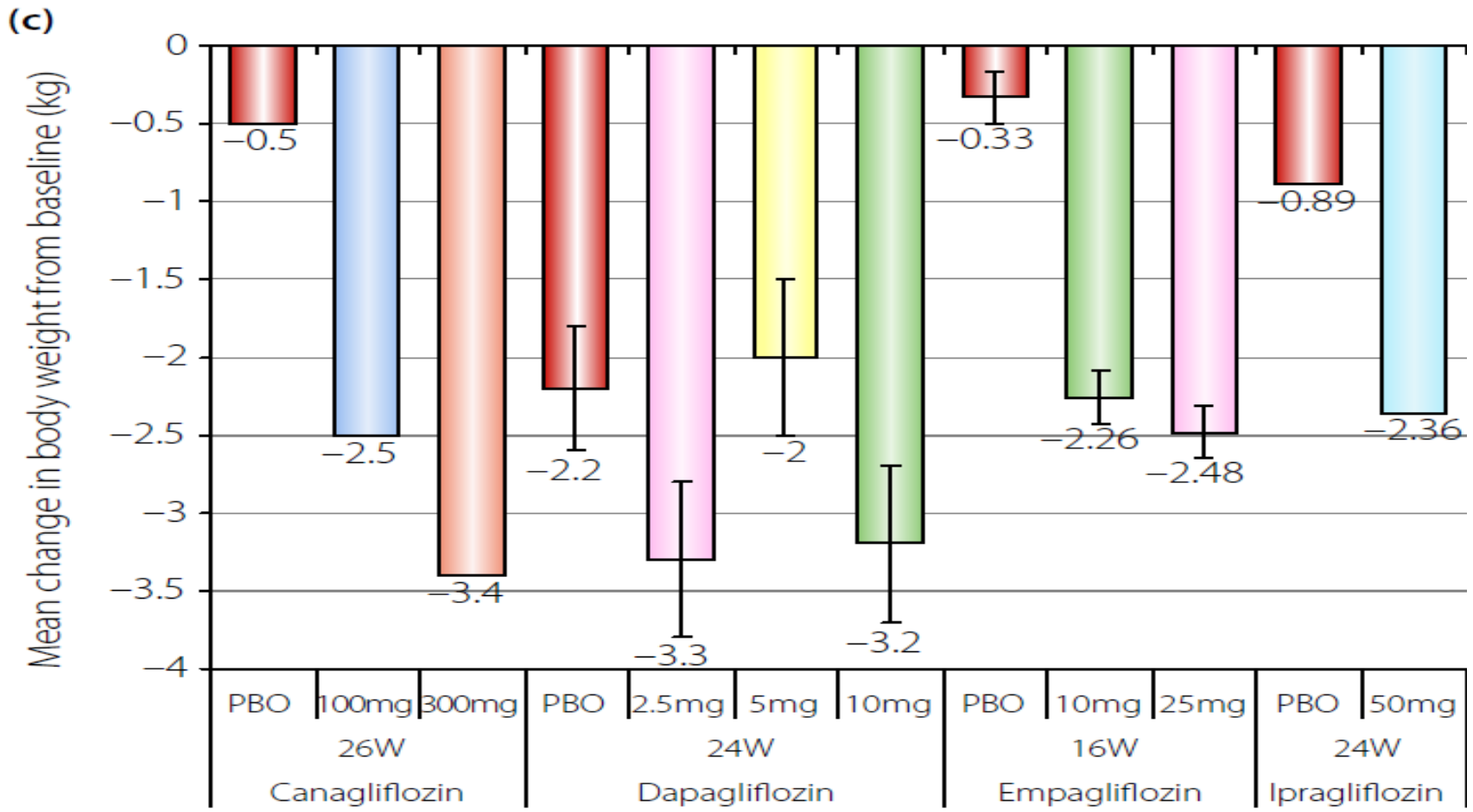
Drugs 2010;70:377-385.

SGLT2i: HbA1c reduction



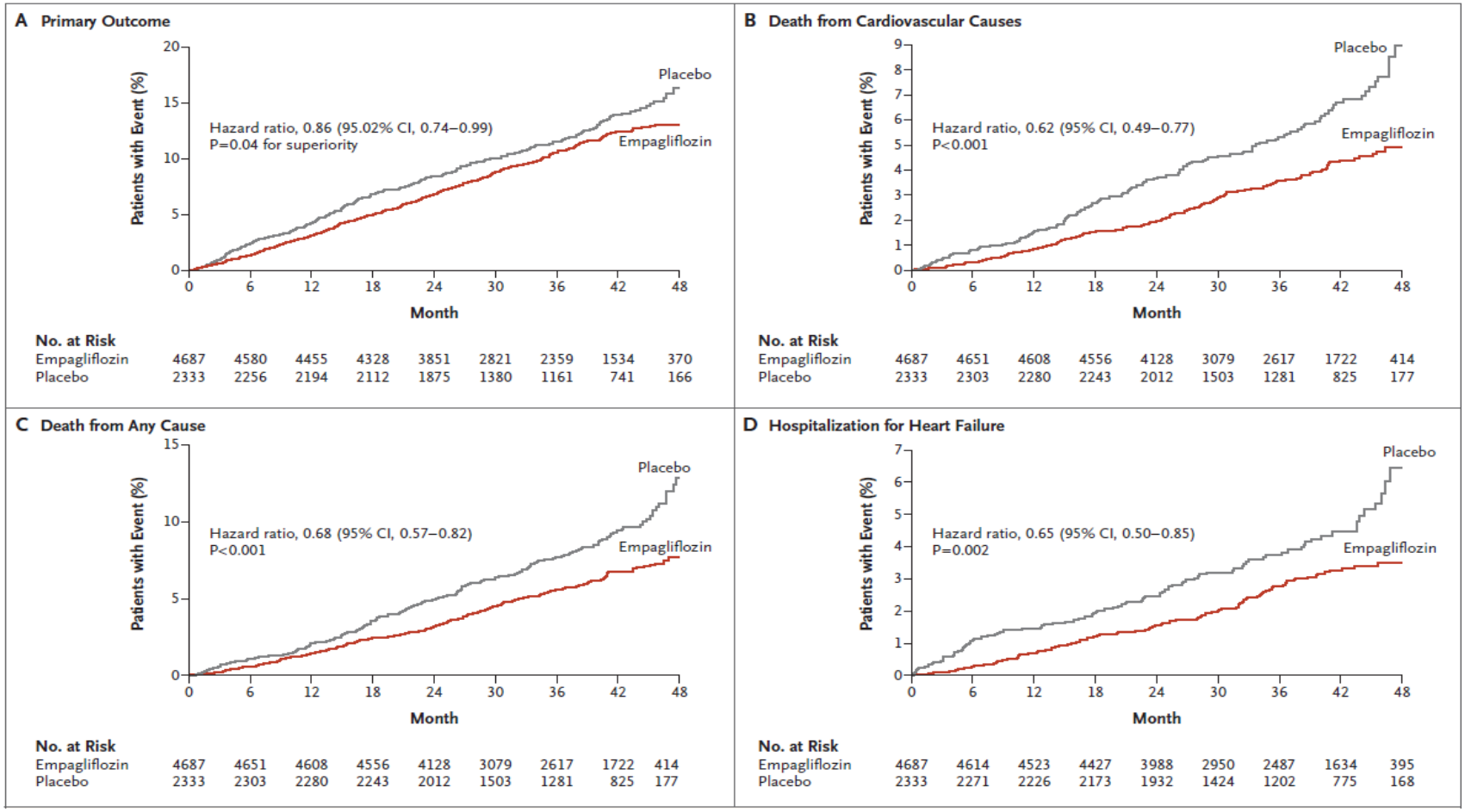
J Diabetes Invest 2014

SGLT2i: Weight reduction



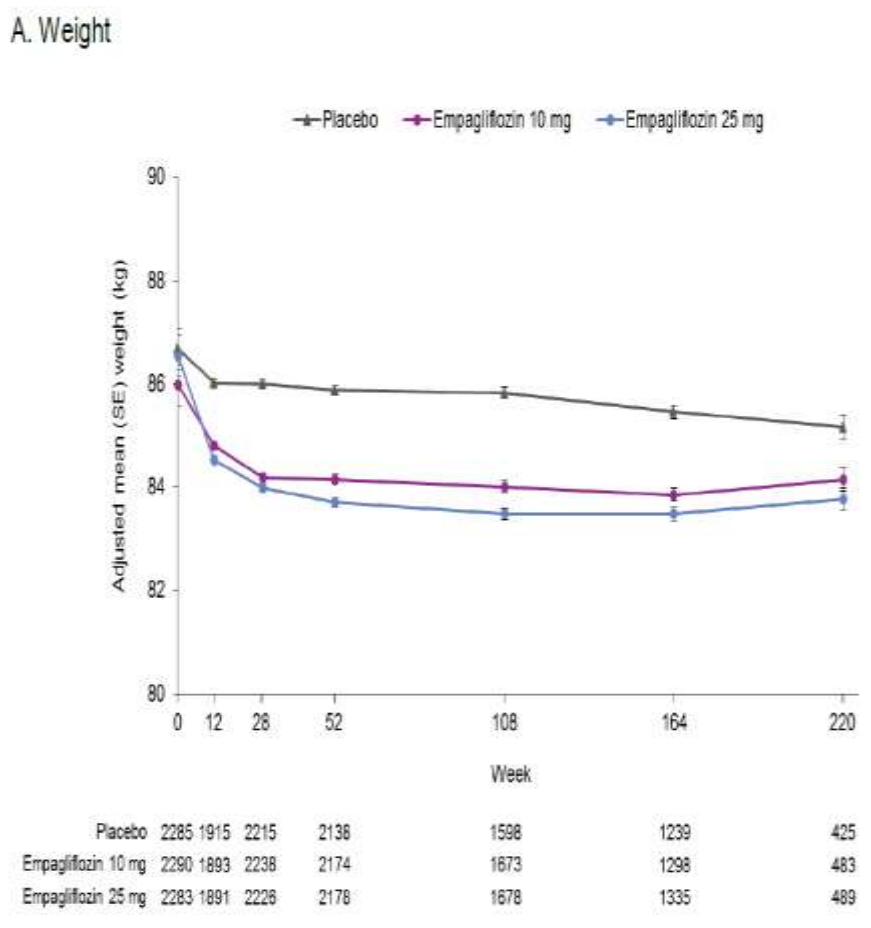
J Diabetes Invest 2014

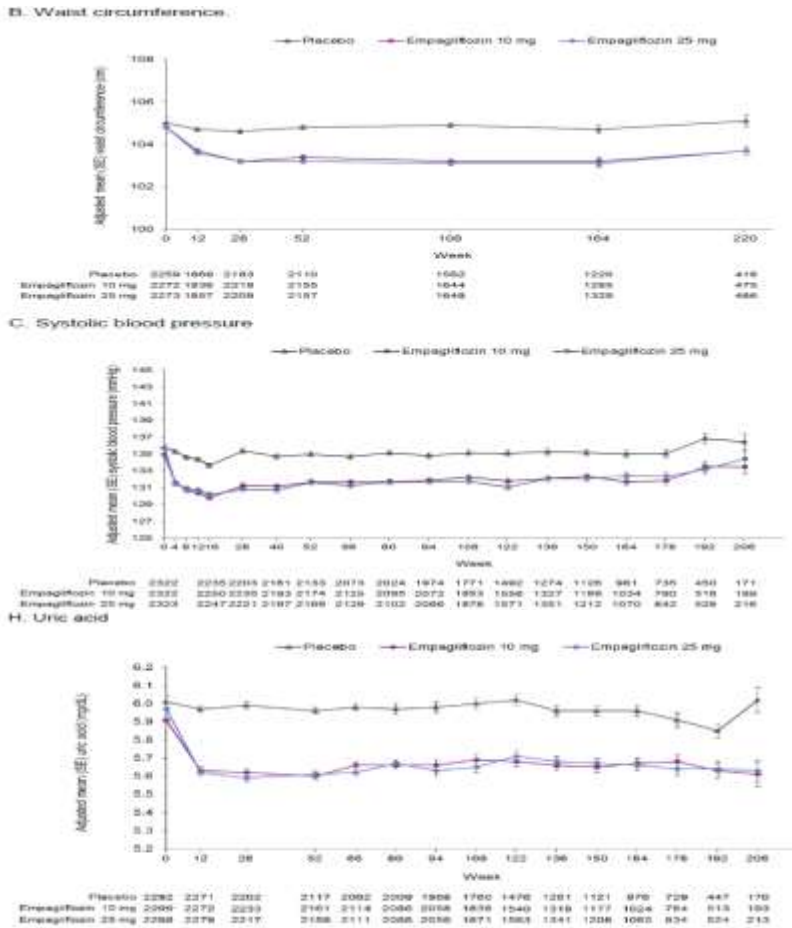
EMPA-REG Results



N Engl J Med. 2015 Nov 26;373(22):2117-28.

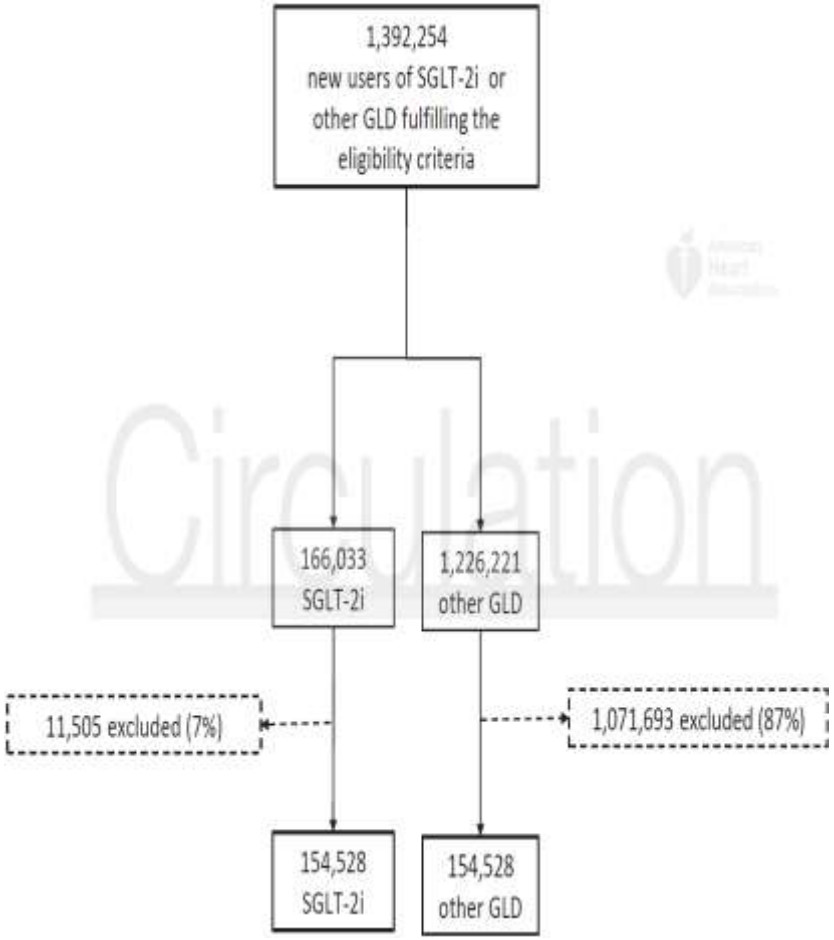
Empagliflozin effects

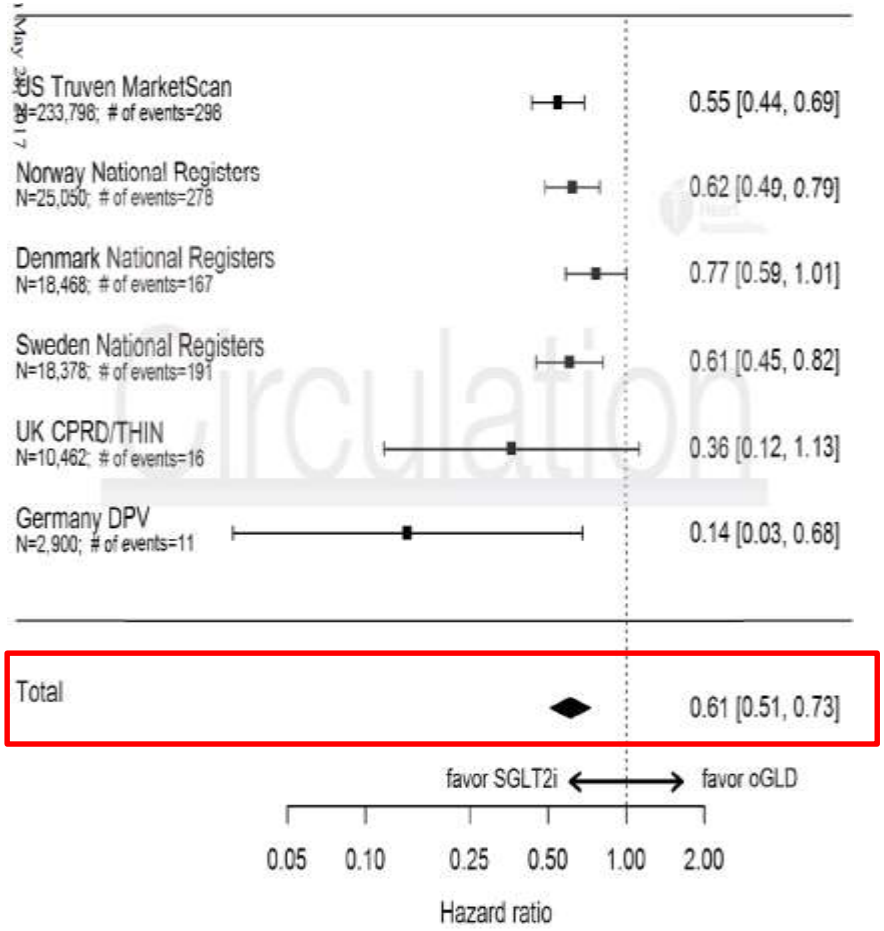




N Engl J Med. 2015 Nov 26;373(22):2117-28.

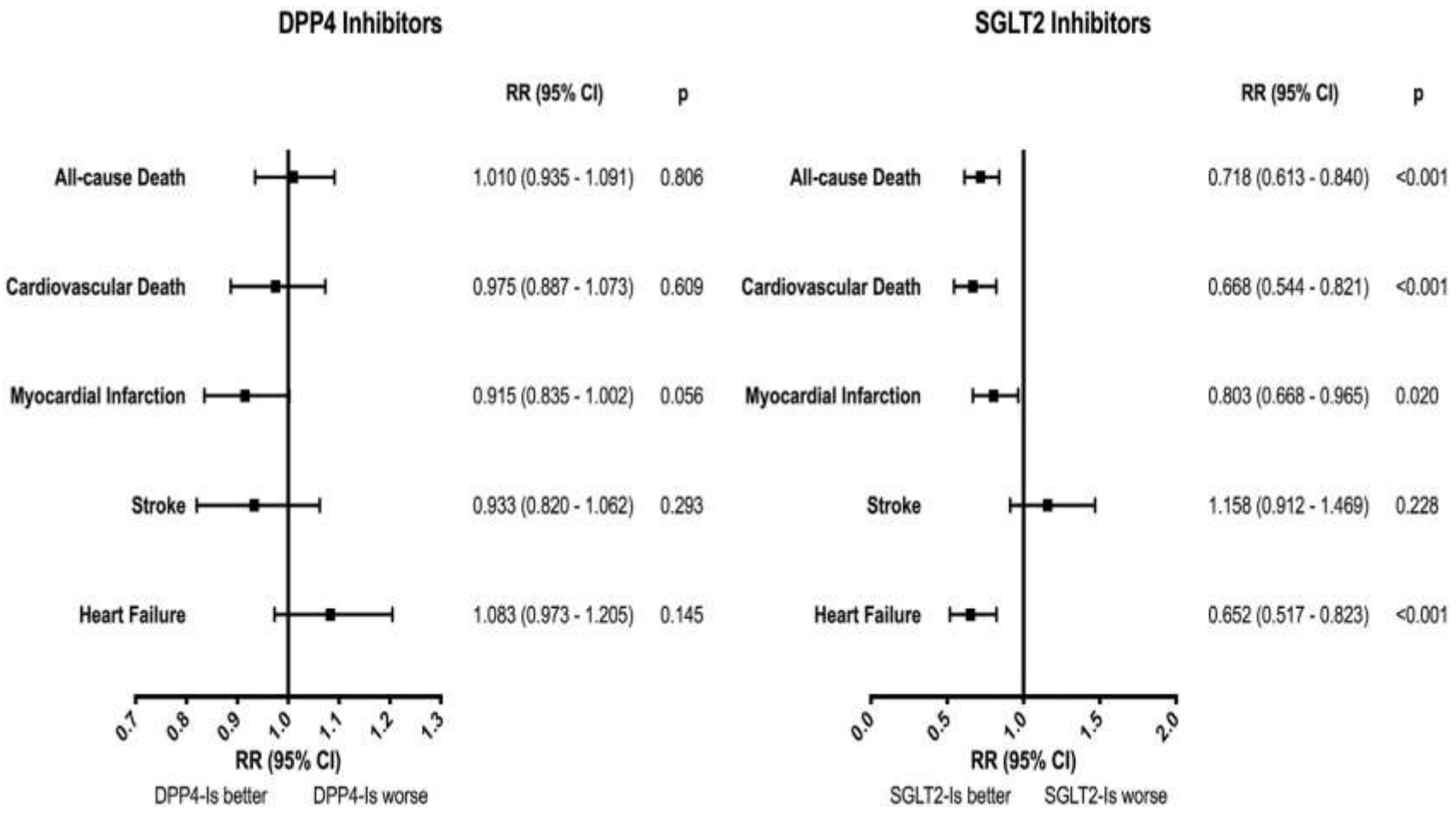
The CVD-REAL Study





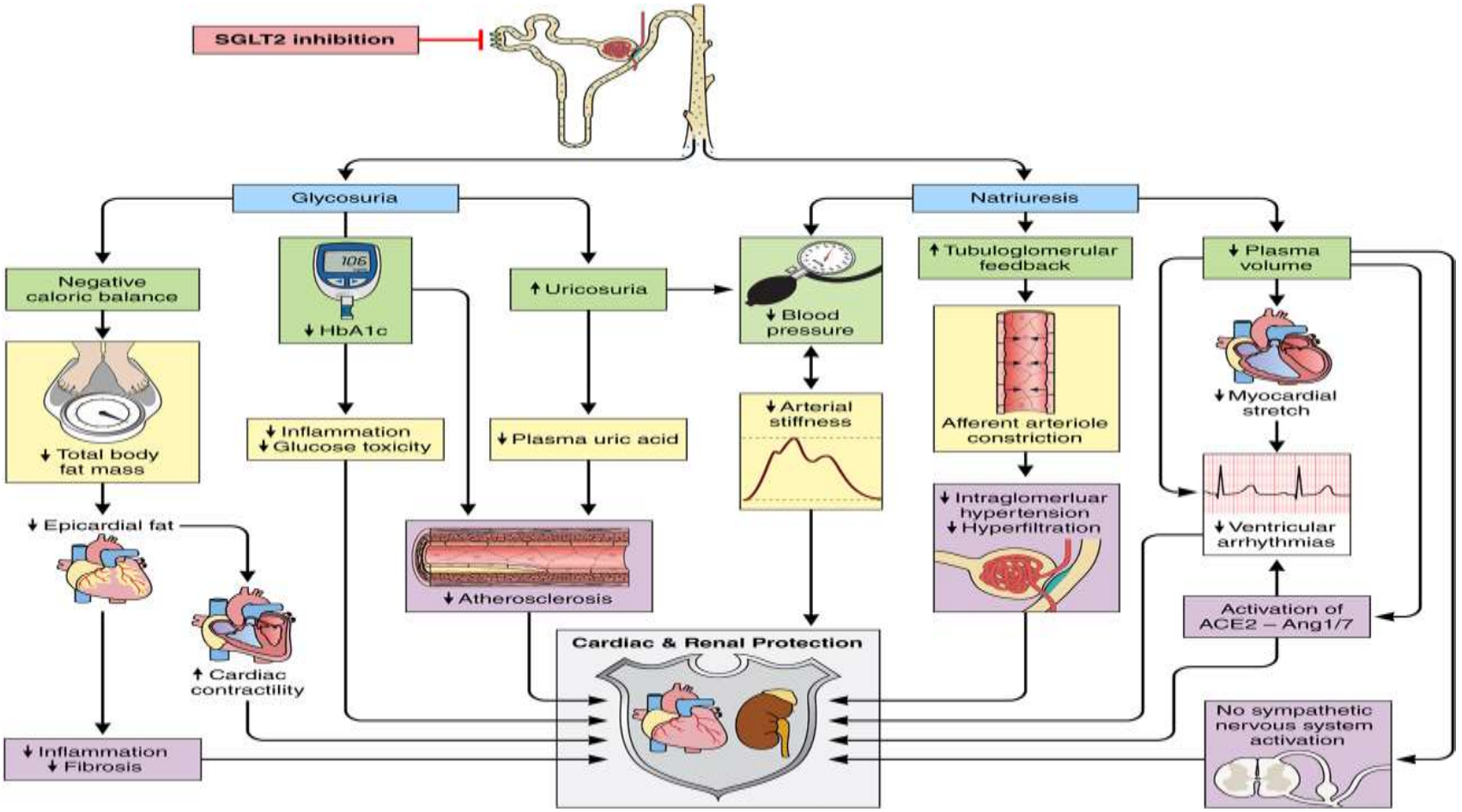
Circulation May 18, 2017. 10.1161/CIRCULATIONAHA.117.029190.

DPP4i vs. SGLT2i



International Journal of Cardiology 220 (2016) 595–601.

CV and Renal protection



Circulation. 2016 Sep 6;134(10):752-72.

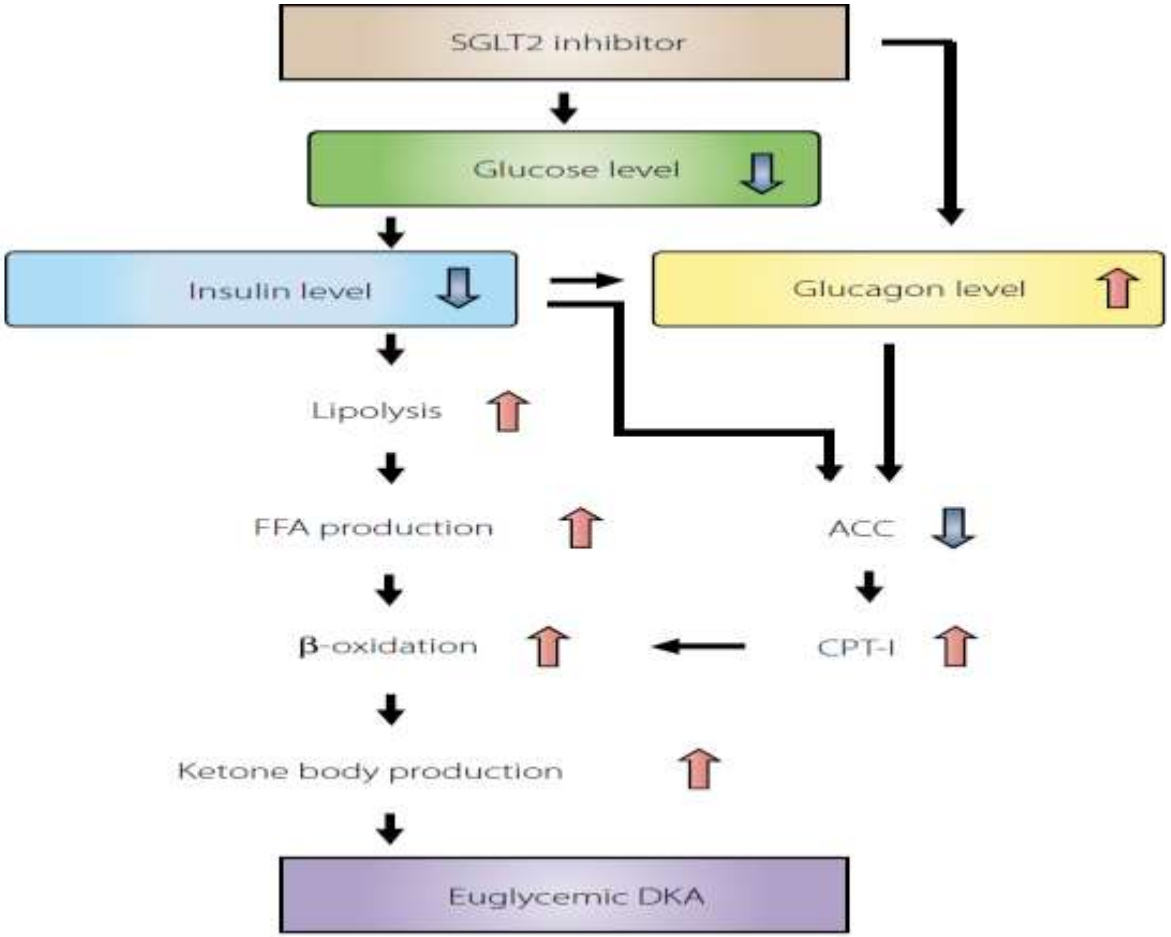
Adverse Events

Table 2. Adverse Events.*

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

N Engl J Med. 2015 Nov 26;373(22):2117-28.

Possible mechanism of DKA



J Diabetes Investig. 2016 Mar;7(2):135-8.

SGLT2i and DKA (FDA)

DKA report	Drug listed as suspect or concomitant				
	Dapagliflozin	Canagliflozin	Empagliflozin	Any SGLT2i	No SGLT2i (any other non-SGLT2i drug)
All FAERS					
Unique patients	5696	13,253	2783	21,636	8,532,895
No. of DKA reports	752	1466	378	2589	10,247
Rate/1000	131.8	110.6	135.8	119.4	1.2
Safety signal (IC)	4.6	4.4	4.7	4.4	Reference
PRR (95% CI)	109.9 (102.6, 117.8)	92.3 (87.6, 97.2)	113.7 (103.3, 125.1)	99.6 (95.6, 103.8)	Reference
Diabetes indication					
Unique patients	3876	8987	1845	14,639	427,085
No. of DKA reports	548	1187	302	2028	2299
Rate/1000	141.4	132.1	163.7	138.5	5.4
Safety signal (IC)	3.1	2.8	3.3	2.6	Reference
PRR (95% CI)	26.3 (24.1, 28.7)	24.5 (22.9, 26.2)	30.4 (27.2, 34.0)	25.7 (24.3, 27.3)	Reference
Type 1 diabetes					
Unique patients	128	297	48	472	16,938
No. of DKA reports	85	206	26	317	201
Rate/1000	664.1	693.6	541.7	671.6	11.9
Safety signal (IC)	3.7	3.4	3.7	3.1	Reference
PRR (95% CI)	56.6 (47.1, 68.1)	59.1 (50.6, 60.2)	46.2 (34.4, 62.0)	57.3 (49.2, 66.6)	Reference
Custom search					
Unique patients	5694	14,117	2719	22,530	141,823
No. of DKA reports	680	1362	355	2397	1930
Rate/1000	119.4	96.4	130.5	106.4	13.6
Safety signal (IC)	1.9	1.5	2.1	1.4	Reference
PRR (95% CI)	8.9 (8.2, 9.7)	7.2 (6.7, 7.7)	9.7 (8.7, 10.8)	7.9 (7.5, 8.4)	Reference

Diabetologia 2017;60:1385–1389.

DPP4i vs. SGLT2i (DKA)

Table 2. Primary and Other Outcomes.*

Days of Follow-up	DPP4 Inhibitor (N=38,045)		SGLT2 Inhibitor (N=38,045)	
	Diabetic Ketoacidosis *no. of patients (rate per 1000 person-yr)*	Hazard Ratio	Diabetic Ketoacidosis *no. of patients (rate per 1000 person-yr)*	Hazard Ratio (95% CI)
180 Days of follow-up†	26 (2.2)	1.0	55 (4.9)	2.2 (1.4–3.6)
60 Days of follow-up	13 (2.3)	1.0	31 (5.6)	2.5 (1.3–4.7)
30 Days of follow-up	10 (3.3)	1.0	22 (7.5)	2.3 (1.1–4.8)
180 Days of follow-up among patients not receiving insulin‡	9 (1.0)	1.0	21 (2.5)	2.5 (1.1–5.5)

* CI denotes confidence interval.
† The data in this category were evaluated in the primary analysis.
‡ The data in this category were evaluated in a post hoc analysis.

N Engl J Med 2017:376;23:2300-2302.

Risk Factors of DKA

- Long standing T2DM patients
  with marked β cell insufficiency
- Latent autoimmune diabetes in adults
- Prolonged starvation
- After surgery
- During intercurrent illness

Diabetes Care 2015 Sep; 38(9): 1638-1642.

Preventions of DKA

- Because of prolonged action on SGLT-2 transporters, these agents **should be stopped at least 24 hours before scheduled surgery** or other planned activities that might precipitate DKA, such as invasive procedures or extreme physical activity (e.g., running a marathon).
- For patients with diabetes undergoing **emergency surgery** or a sudden external severe stress event, **the drug should be stopped immediately** and, if DKA develops, management with intravenous insulin and glucose considered along with monitoring of anion gap, serum b-hydroxybutyrate, and arterial pH.
- **Routine measurement of urine ketones is not recommended** during use of SGLT-2 inhibitors in T2D because it can be misleading. Measurement of blood ketones is preferred for diagnosis and monitoring of DKA.
- Patients taking SGLT-2 inhibitors should **avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets.**

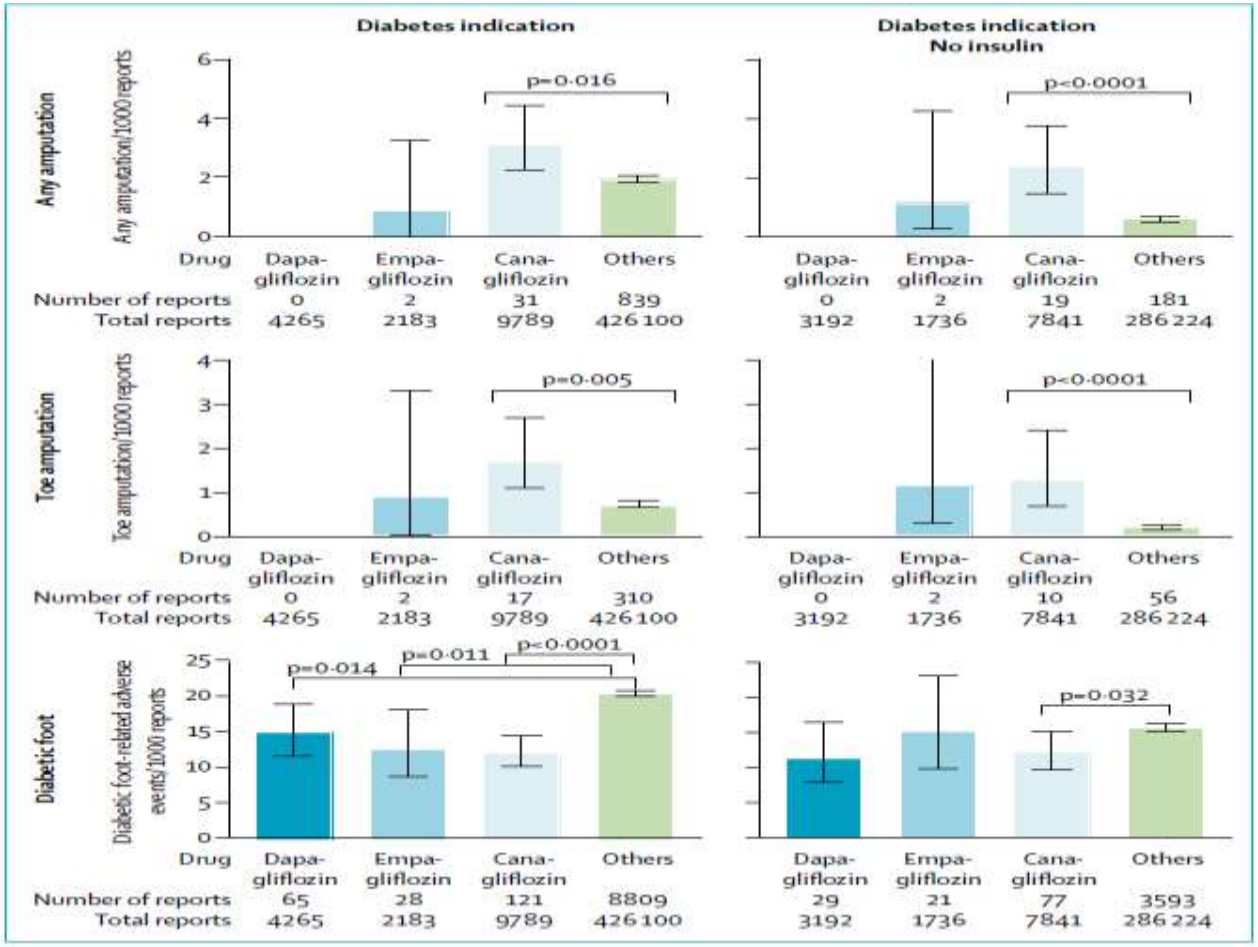
Endocr Pract. 2016;22(No. 6).

Amputation and Fracture

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

N Engl J Med. 2017 Jun 12. [Epub]

SGLT2i and Amputations

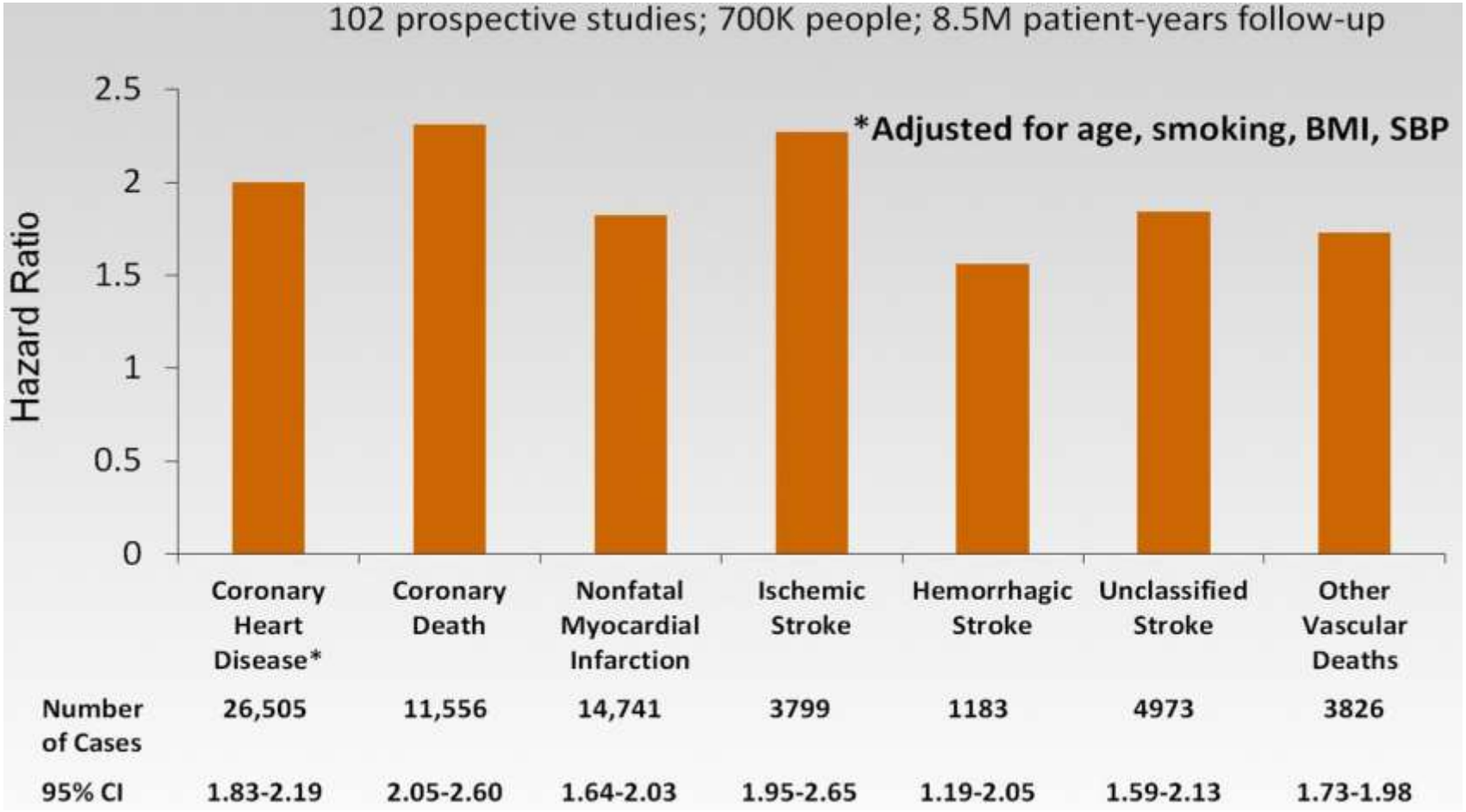


Lancet Diabetes Endocrinol 2017 July 18. [Epub]

Agenda

1. Pathophysiology based Treatment
2. Early Intensive Treatment
3. New kids on the block: DPP4i & SGLT2i
4. Cardiovascular safety of OHAs

DM and Risk of CVD

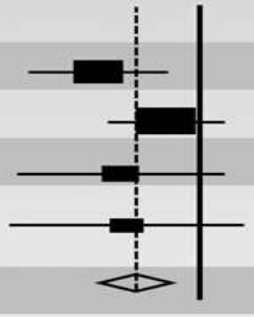


	Coronary Heart Disease*	Coronary Death	Nonfatal Myocardial Infarction	Ischemic Stroke	Hemorrhagic Stroke	Unclassified Stroke	Other Vascular Deaths
Number of Cases	26,505	11,556	14,741	3799	1183	4973	3826
95% CI	1.83-2.19	2.05-2.60	1.64-2.03	1.95-2.65	1.19-2.05	1.59-2.13	1.73-1.98

Lancet 2010;375:2215-2222.

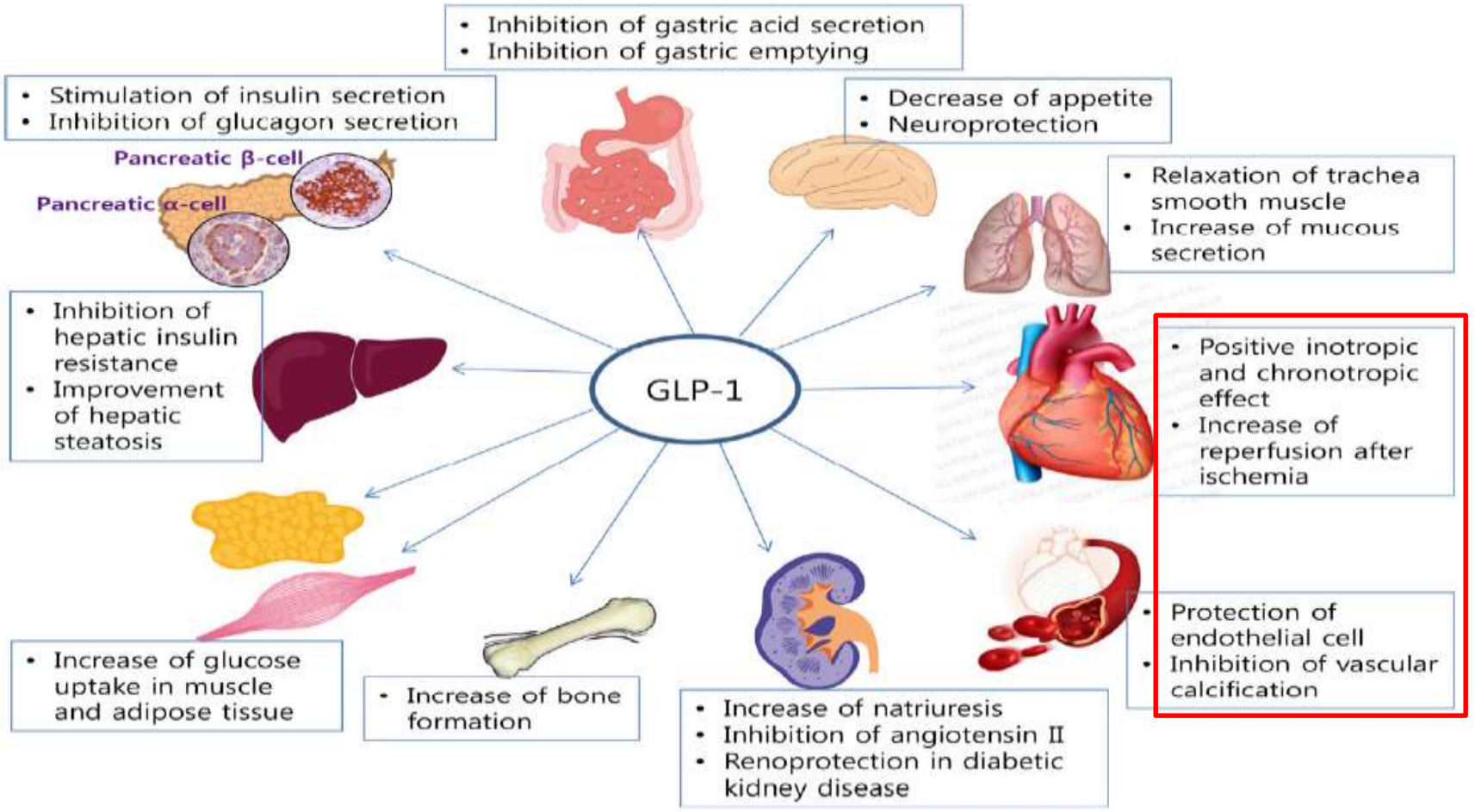
CV outcomes Trials in T2DM

Trials	Number of Events, Annual Event Rate, % More Intensive	Less Intensive	ΔHBA$_{1c}$, %	Favors more Intensive	Favors less Intensive	HR, 95% CI
Myocardial Infarction						
ACCORD	198 (1.18)	245 (1.51)	-1.01			0.77 (0.64-0.93)
ADVANCE	310 (1.18)	337 (1.28)	-0.72			0.92 (0.79-1.07)
UKPDS	150 (1.20)	76 (1.40)	-0.66			0.81 (0.62-1.07)
VADT	72 (1.65)	87 (1.99)	-1.16			0.83 (0.61-1.13)
Overall	730	745	-0.88			0.85 (0.76-0.94) (Q = 2.25; *P* = .52; I^2 = 0.0%)
Major Cardiovascular Events						
Overall	1194	1176	-0.88			0.91 (0.84-0.99) (Q = 1.32; *P* = .72; I^2 = 0.0%)
Stroke						
Overall	378	370	-0.88			0.96 (0.83-1.10) (Q = 0.40; *P* = .94; I^2 = 0.0%)
Hospitalized/Fatal Heart Failure						
Overall	459	446	-0.88			1.00 (0.86-1.16) (Q = 3.59; *P* = .31; I^2 = 16.4%)



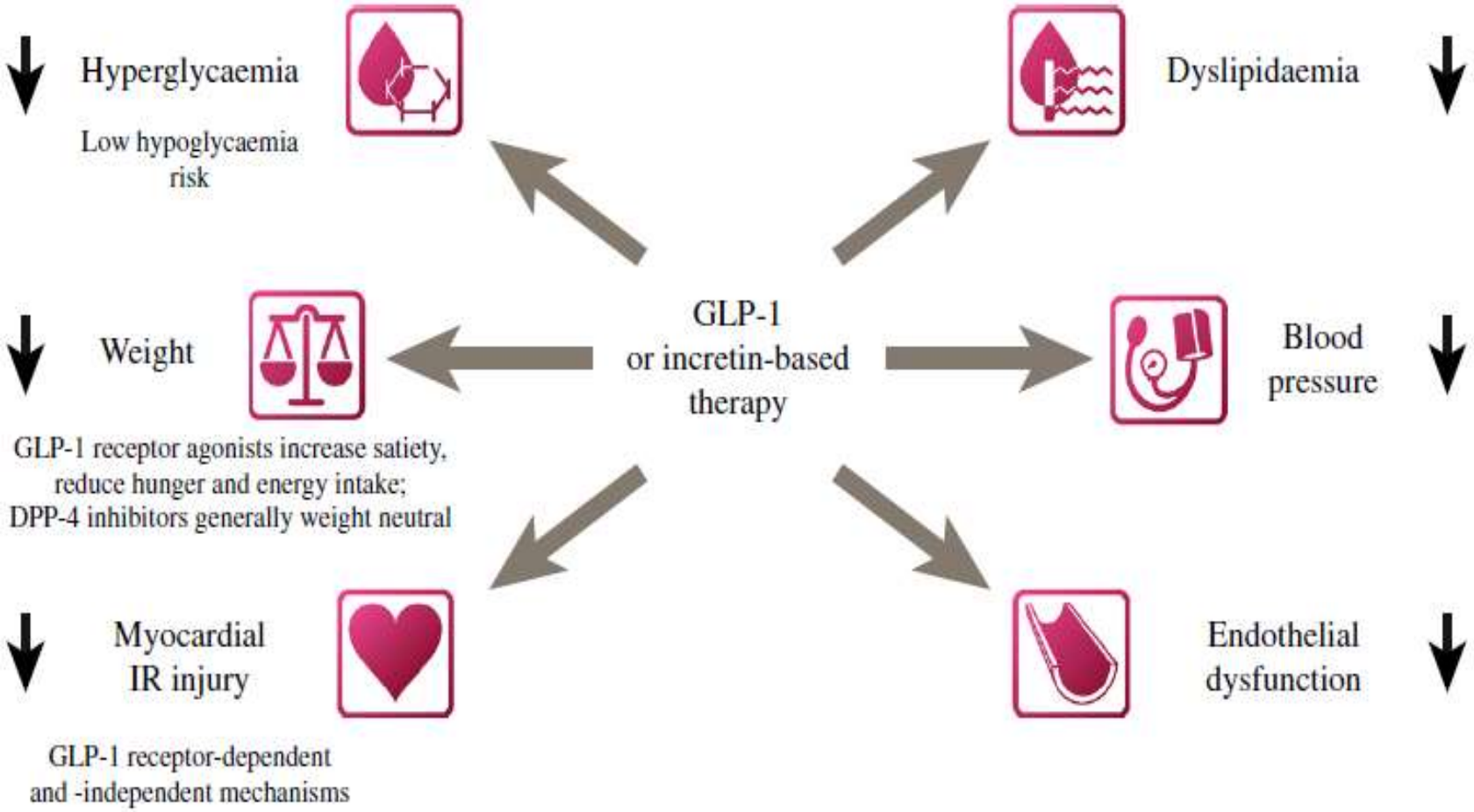
Diabetologia 2009;52:2288-2298.

Extra-pancreatic effects of Incretin



Korean J Med 2015; 89(4): 404-412.

CV effects of Incretin Therapy



Cardiovascular Diabetology 2013;12:130.

CV outcome Trials of DPP4i

Variable	SAVOR-TIMI 53[53]	EXAMINE[54]	TECOS[55]
No. of patients	16,492	5380	14,671
Population	T2DM patients with CVD or high CV risk	T2DM with an acute MI or UA requiring hospitalization within the previous 15-90 d	T2DM patients with CVD or high CV risk
Intervention	Saxagliptin vs placebo	Alogliptin vs placebo	Sitagliptin vs placebo
Mean age (y)	65	61	65
Diabetes duration (y)	10	7	11.6
Established CVD (%)	78	100	74
Mean HbA_{1c} (%)	8 ± 1.4	8 ± 1.1	7.2 ± 0.5
Mean BMI (kg/m^2)	31	28.7	30.2
Prior HF (%)	12.8	28	18
Median follow-up (y)	2.1	1.5	3.0
Hypoglycemia			
Intervention	15.3	6.7	2.0*
Placebo	13.4	6.5	1.7*
Definition of primary outcome	CV death, nonfatal MI, nonfatal ischemic stroke	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke, or UA hospitalization
HR for primary outcome (95% CI)	1.00 (0.89-1.12)	0.96 (≤1.16)	0.98 (0.88-1.09)
Definition of secondary outcome	CV death, MI, stroke, hospitalization for UA, HF, or coronary revascularization	Primary outcome + urgent revascularization due to UA within 24 hours after hospital admission	CV death, nonfatal MI, or nonfatal stroke
HR for secondary outcome (95% CI)	1.02 (0.94-1.11)	0.95 (≤1.14)	0.99 (0.84-1.11)
Hospitalization for HF, HR (95% CI)	1.27 (1.07-1.51)	1.19 (0.89-1.59)	1.00 (0.83-1.20)
CV mortality, HR (95% CI)	1.03 (0.87-1.22)	0.85 (0.66-1.10)	1.02 (0.90-1.15)
All-cause mortality, HR (95% CI)	1.11 (0.96-1.27)	0.88 (0.71-1.09)	1.01 (0.90-1.14)
Comments	Subjects at greatest risk of HF hospitalization had previous HF, an eGFR ≤60 mL/min/1.73 m^2, or elevated baseline levels of NT-proBNP	Post hoc analyses showed that alogliptin increased HF incidence in patients who had signs of HF at the time of randomization (HR 1.76; 95% CI, 1.07-2.90)	A recent post hoc analysis confirmed that sitagliptin does not increase HF hospitalization even after adjustment for pre-existing HF
Adverse events	The rate of any hypoglycemic event (minor and major) was significantly increased with saxagliptin as compared with placebo (15.3% vs 13.4%, $P < .001$)	Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo	There was no significant difference between sitagliptin and placebo with respect to the overall incidence of infections, cancer, site-reported renal failure, or severe hypoglycemia

Am J Med. 2017;130(6S):S18-S29.

Clinical Considerations of ACP

Clinical Considerations	Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. Management of type 2 diabetes often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors. Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss or lifestyle modification fails. Metformin monotherapy effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight. Although combination therapy reduces HbA_{1c} levels more effectively than monotherapy, it is associated with more adverse events. The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease. Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m^2).

Ann Intern Med. 2017;166:279-290.

Recent CV outcome Trials

Variable	IRIS[46]	EMPA-REG OUTCOME[49]
No. of patients	3876	7020
Population	Patients with recent history of ischemic stroke or TIA, with insulin resistance but without T2DM	T2DM patients with CVD
Intervention	Pioglitazone vs placebo	Empagliflozin vs placebo
Median follow-up (y)	4.8	3.1
Mean age (y)	63	63
Mean HbA_{1c} (%)	5.8	8.1
Mean BMI (kg/m^2)	29.9	30.5
CKD (%)	NR	26
Prior HF (%)	0	10
Definition of primary outcome	Fatal or nonfatal stroke or MI	CV death, nonfatal MI, or nonfatal stroke
HR for primary outcome (95% CI)	0.76 (0.62-0.93), $P = .007$	0.86 (0.74-0.99), $P = .04$ for superiority
Hospitalization for HF, HR (95% CI) unless otherwise noted	3.8% vs 3.7%, $P = .80$	0.65 (0.50-0.85), $P = .002$
CV mortality, HR (95% CI)	NA	0.62 (0.49-0.77), $P < .001$
All-cause mortality, HR (95% CI)	0.93 (0.73-1.17), $P = .52$	0.68 (0.57-0.82), $P < .001$
Comments	Although pioglitazone significantly reduced the rate of stroke and MI, no between-group differences in all-cause mortality were observed. Pioglitazone was also associated with a greater frequency of weight gain, edema, and bone fractures requiring surgery or hospitalization.	Benefits of empagliflozin were seen already after 3 mo. This suggests that hemodynamic factors (ie, BP reduction, osmotic diuresis) may be significantly involved. However, utilization of β-hydroxybutyrate instead of fatty acids might also contribute to improve myocardial efficiency thus preventing HF. The exact mechanisms underlying empagliflozin-related benefits remain to be elucidated.

Am J Med. 2017;130(6S):S18-S29.

CV effects of OHAs for T2DM

Drug Class	CV Effects	Clinical Use in Patients with CVD
Biguanides	• Few randomized, but many observational studies available • Reduces risk of MI by 39%, diabetes-related endpoint by 32%, diabetes-related death by 42%, mortality by 36% (UKPDS) • Safety concerns on the association with sulfonylureas	• First choice in T2DM patients with and without atherosclerotic vascular disease • Precautions should be taken in patients with ACS, HF, CKD (stages IV and V) • Not indicated in the presence of acidosis or dehydration
Sulfonylureas	• Several observational studies available • Reduction of microvascular complications (UKPDS) • Increased CV mortality (UGDP trial) • Impairment of ischemic preconditioning (?)	• Combination therapy in T2DM patients with and without CVD (if HbA_{1c} target not achieved after ~3 mo of monotherapy with metformin) • Precautions should be taken in patients with multiple comorbidities, ACS, HF, and advanced CKD (stages IV and V)
Thiazolidinediones	• Reduce risk of MI and stroke (PROActive and IRIS trials with pioglitazone) • Improve diabetic dyslipidemia • Increase HF hospitalization	• Combination therapy in T2DM patients with and without CVD and/or CKD (up to stage V, eGFR <15 mL/min/1.73 m^2) • Precautions should be taken in patients with ACS • Contraindicated in patients with or at risk of HF
Glucagon-like peptide-1 receptor agonists	• Significant reduction of composite CV endpoints in LEADER and SUSTAIN-6 trials • No significant effects on CV mortality, nonfatal MI, and hospitalization for HF with liraglutide and semaglutide • Reduced risk of nonfatal stroke with semaglutide	• Combination therapy in T2DM patients with and without CVD (including HF and ACS) • Limited data in patients with advanced CKD (stages IV and V) • Exenatide is eliminated by renal mechanisms and should not be given in patients with severe ESRD • Liraglutide is not eliminated by renal or hepatic mechanisms, but it should be used with caution since there are only limited data in patients with renal or hepatic impairment
Dipeptidyl peptidase-4 inhibitors	• Well tolerated • No reduction of CV endpoints (SAVOR-TIMI 53, EXAMINE, TECOS) • Increased risk of HF with saxagliptin and alogliptin (?)	• Combination therapy in T2DM patients with and without CVD • Although sitagliptin seems to be safe, the use of alogliptin and saxagliptin in patients with pre-existing HF is still debated • Indicated in patients with CKD (any stage)
Sodium glucose cotransporter 2 inhibitors	• In the EMPA-REG OUTCOME trial, empagliflozin reduced CV death, HF hospitalization, and total mortality by 38%, 35%, and 32%, respectively • No direct effect on the rates of MI or stroke with empagliflozin • Reduction of systolic and diastolic BP	• Combination therapy in T2DM patients with and without CVD (paucity of data on SGLT2 in primary prevention) • Evidence of benefit in patients with HF • No evidence of benefit in ACS

Am J Med. 2017;130(6S):S18-S29.

OHA Selection in T2DM

AHA/ADA Scientific Statement

Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence

A Scientific Statement From the American Heart Association and the American Diabetes Association

- Metformin (UKPDS)
- Pioglitazone (PROactive)
- Acarbose (STOP-NIDDM)

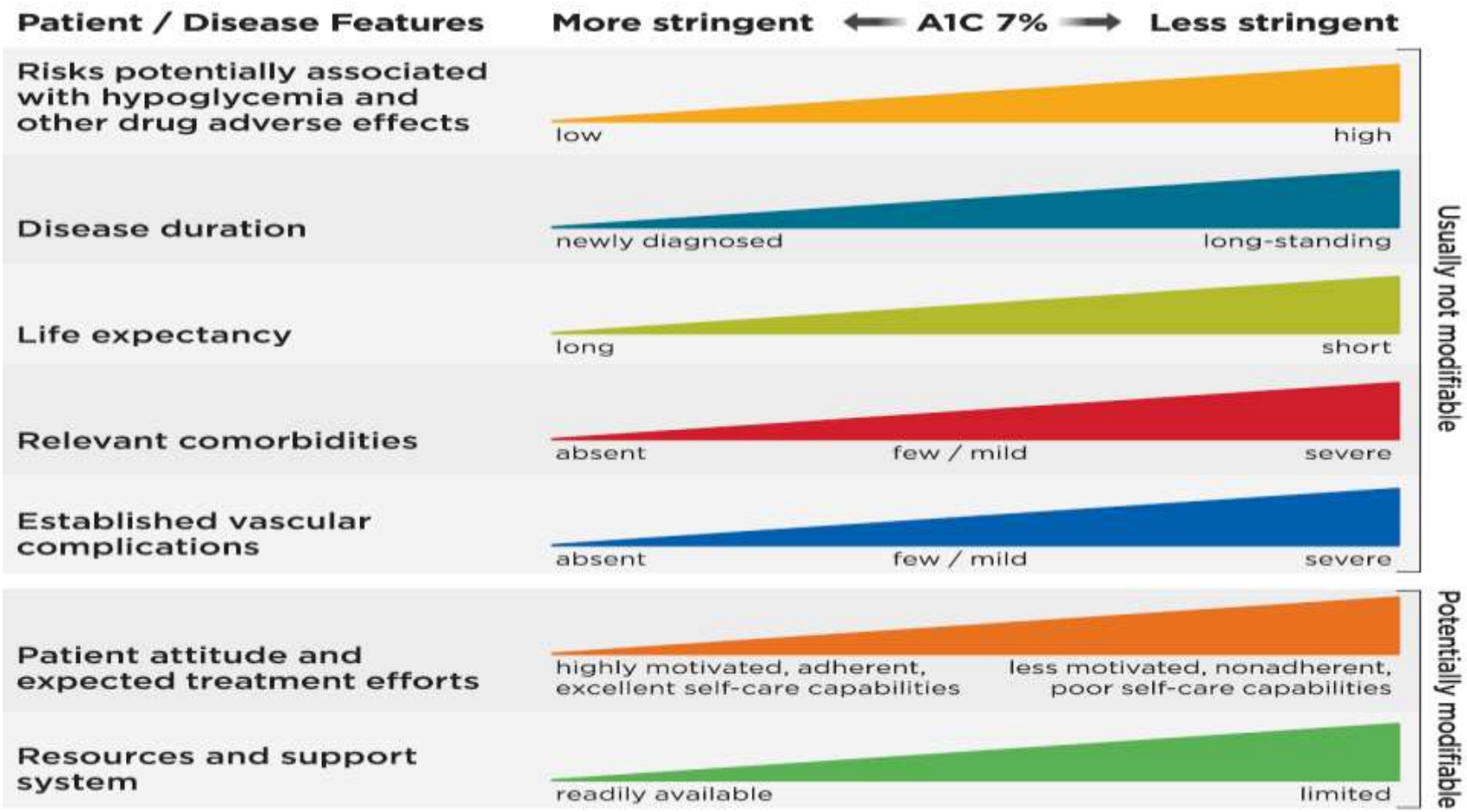
Circulation. 2015;132(8):691-718.
Diabetes Care. 2015;38(9):1777-803.

FDA Indication for CVD

- The US Food and Drug Administration (FDA) has approved a new indication for **Liraglutide** (Victoza, Novo Nordisk), for reducing the risk for myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes who have established cardiovascular disease. Today's approval marks the second time a drug initially approved for glucose lowering in type 2 diabetes has gained an additional indication for cardiovascular benefit based on results from FDA-mandated cardiovascular outcomes trials.
- The first, **Empagliflozin** (Jardiance, Boehringer Ingelheim Pharmaceuticals Inc), received an indication for improving survival in adults with type 2 diabetes and cardiovascular disease in December 2016.

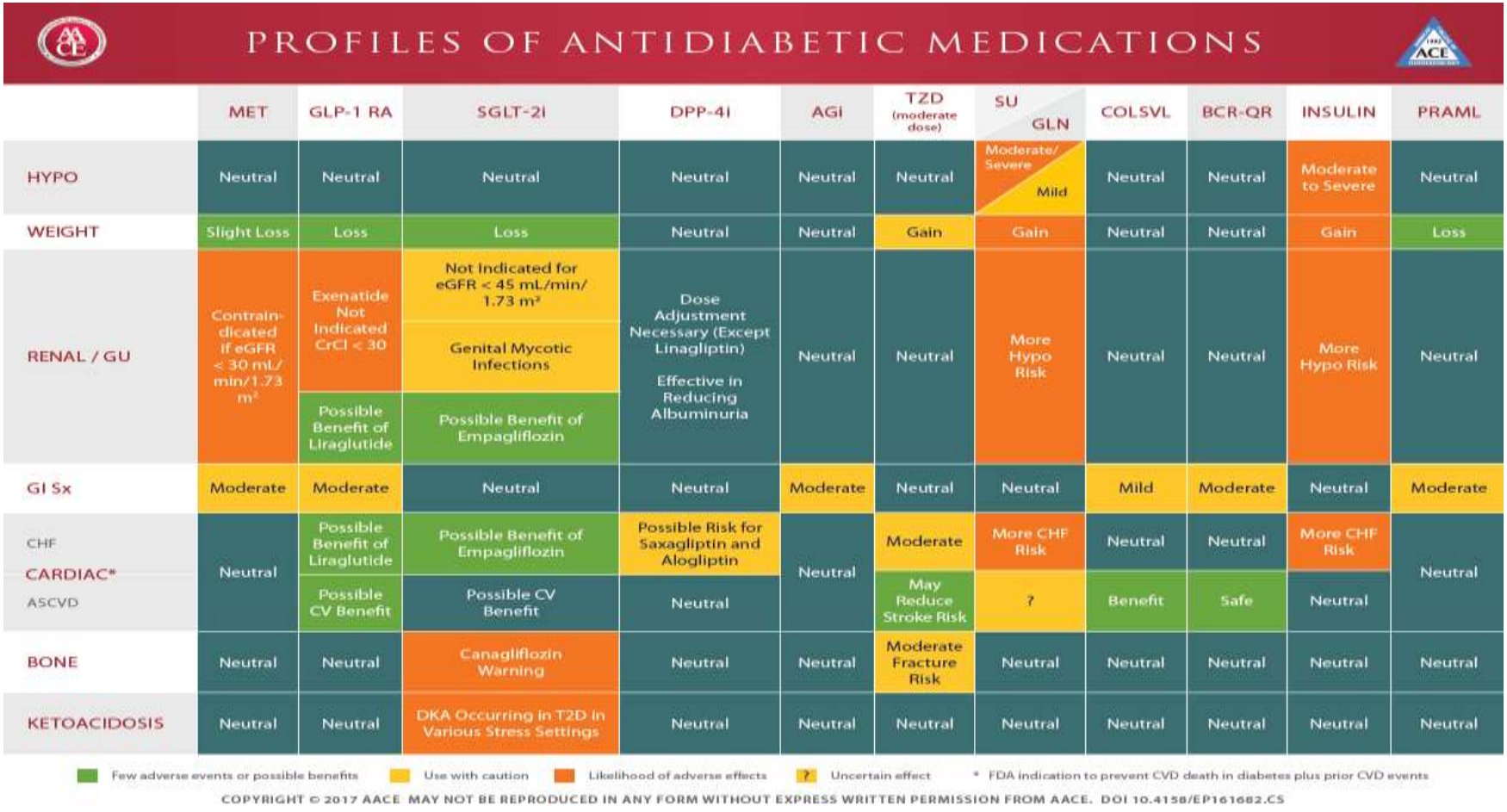
http://www.medscape.com/viewarticle/884726

Patient-Centered Approach



Diabetes Care 2017;40(Suppl. 1):S1–S125.

Profiles of Diabetic Medications



Endocrine Pract. 2017;23(No.2):207-238.

Summary

- Metformin is widely accepted as the first choice agent for glycemic lowering because it does not cause weight gain or hypoglycemia and may improve CVD outcomes.
- If the A1C target is not achieved after approximately 3 months, consider a combination of metformin or proceed to three-drug combination.
- In patients with long-standing suboptimally controlled T2DM and established ASCVD, Empagliflozin should be considered.
- Numerous aspects must be considered when setting glycemic targets. The KDA proposes optimal targets (HbA1c <6.5%), but each target must be individualized to the needs of each patient and their disease factors.

Conclusion

- Choice of OHA therapy for T2DM should be individualized based on consideration of the efficacy, safety, cost, convenience, and other non-T2DM-related benefits associated with each agent.

- It will be important to incorporate Newer agents into this individualized treatment paradigm to optimize clinical outcomes in patients with T2DM.

BUSINESS LESSONS

THERE IS NO MAGIC BULLET

and anyone who says otherwise is lying

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