Diabetes Mellitus and Cardiovascular Disease

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Preview of This Episode:

- The Burden of Diabetes Mellitus in Cardiovascular Disease
- Mechanistic Implication of DM in Cardiovascular Disease
- Medical Therapy in Diabetes Mellitus
- Summary of Cardiovascular Trials in Diabetic Patients
- Why GLP-1 Agonists and SGLT2 Inhibitors
- Hyperglycemia Management in Cardiovascular Disease
- Diabetes Mellitus in Heart Failure Patients
- ADA 2021 Recommendations
- Abidi Summary of Diabetic Medications

TABLE 31.1 American Diabetes Association Diagnostic Criteria for Diabetes Mellitus*

1. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr.

Or

2. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Or

3. Glycated hemoglobin (A_{1c}) ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

Or

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*Criteria 1 to 3 require confirmatory testing; criterion 4 does not.
Modified from American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. *Diabetes Care*. 2020;43(suppl 1):S14–S31.

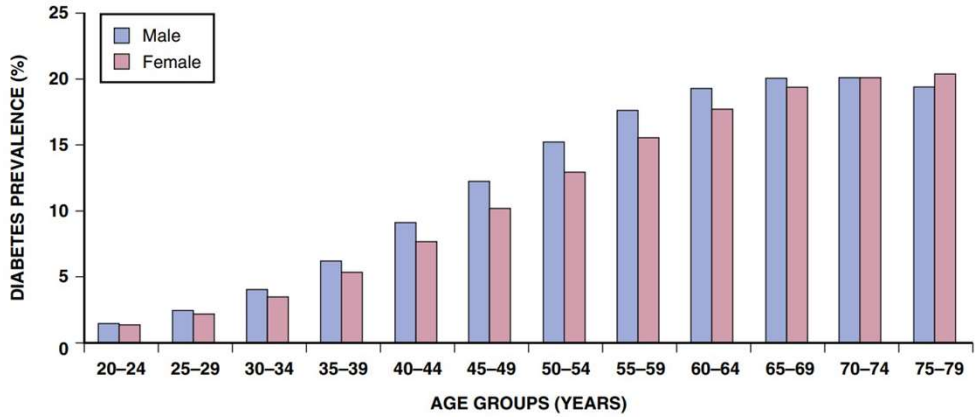


FIGURE 31.1 Diabetes mellitus prevalence by age and sex in 2019. (From Saeedi P, Petersohn I, Salpea P, et al. Global and regional DM prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International DM Federation DM Atlas, 9th edition. *DM Res Clin Pract*. 2019;157:107843.)

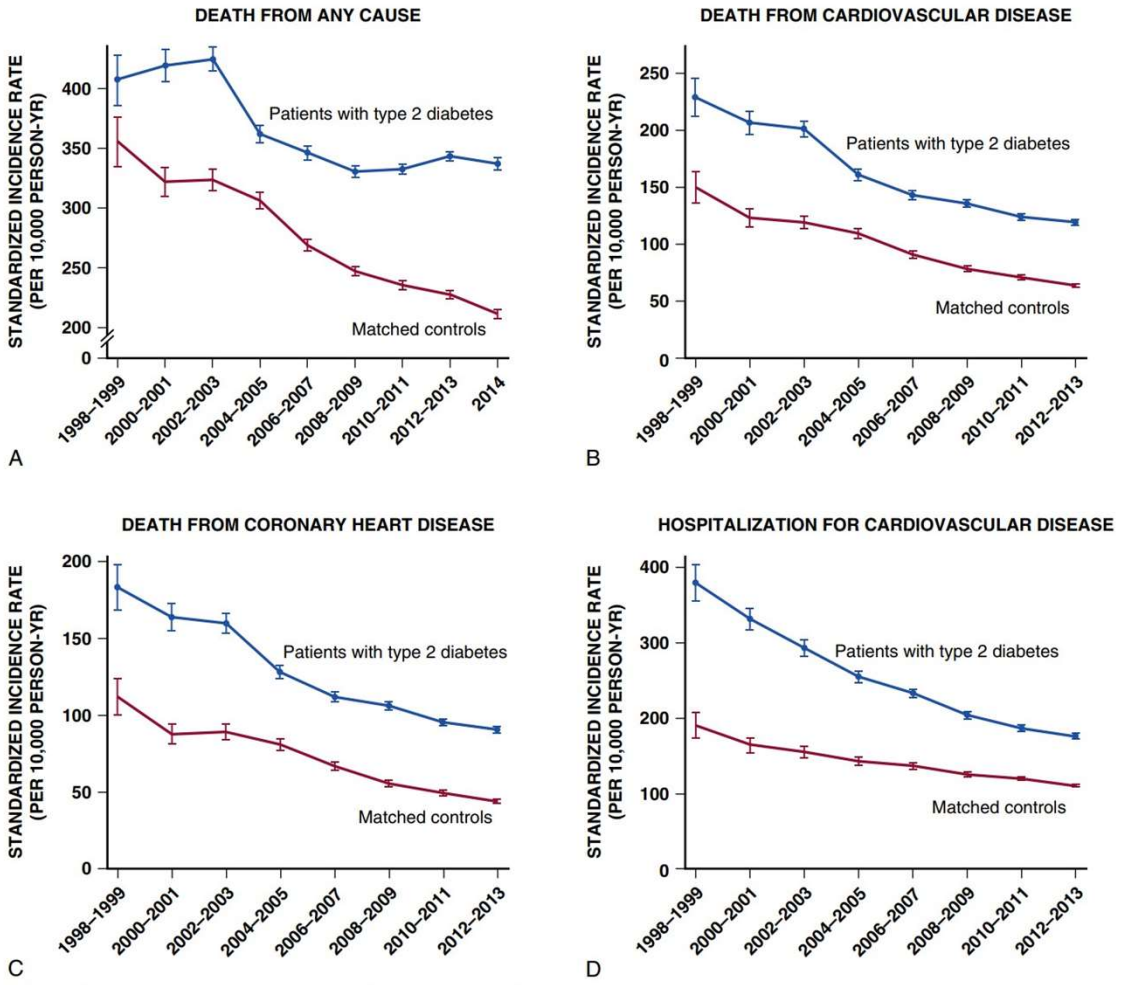


FIGURE 31.2 Major cardiovascular outcomes in patients with type 1 DM and matched controls. Controls were matched for age, sex, and country. I bars represent 95% confidence intervals. (From Rawshani A, Rawshani A, Franzen S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376:1407–1418.)

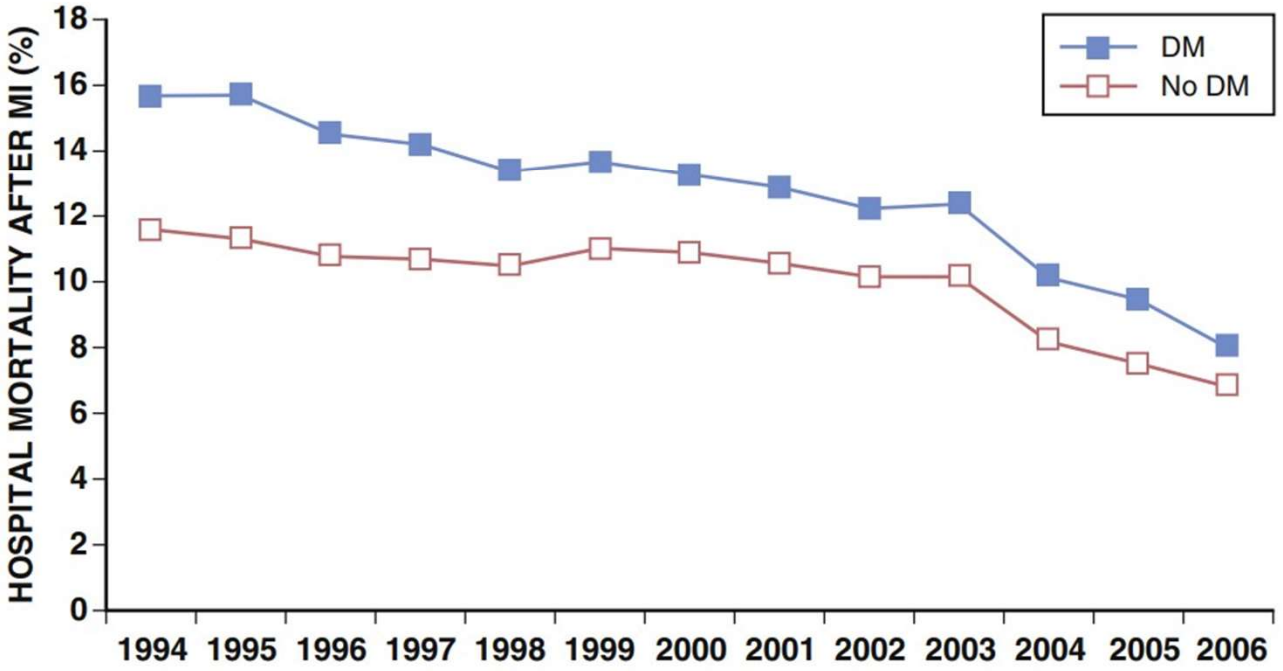


FIGURE 31.4 Unadjusted hospital mortality after myocardial infarction (MI) by year of study enrollment according to diabetes mellitus status (in-hospital deaths as percentage of total number of patients enrolled during each year of the study) among 1,734,431 patients with acute MI registered in the National Registry of Myocardial Infarction (NRMI) 1994 to 2006. (From Gore MO, Patel MJ, Kosiborod M, et al. Diabetes mellitus and trends in hospital survival after myocardial infarction, 1994 to 2006: data from the national registry of myocardial infarction. *Circulation Cardiovasc Qual Outcomes*. 2012;5:791–797.)

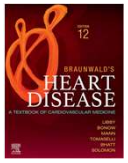
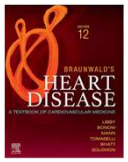


TABLE 31.2 Examples of Mechanisms Implicated in Diabetic Vascular Disease

Endothelium	↑ NF-κB activation
	↓ Nitric oxide production
	↓ Prostacyclin bioavailability
	↑ Endothelin 1 activity
	↑ Angiotensin II activity
	↑ Cyclooxygenase type 2 (COX-2) activity
	↑ Thromboxane A_2 activity
	↑ Reactive oxygen species
	↑ Lipid peroxidation products
	↓ Endothelium-dependent relaxation
	↑ RAGE expression
Vascular smooth muscle cells and vascular matrix	↑ Proliferation and migration into intima
	↑ Increased matrix degradation
	Altered matrix components
Inflammation	↑ IL-1β, IL-6, CD36, MCP-1
	↑ ICAMs, VCAMs, and selectins
	↑ Activity of protein kinase C
	↑ AGEs and AGE-RAGE interactions

AGEs, Advanced glycation end products; *ICAMs,* intracellular adhesion molecules; *IL,* interleukin; *MCP,* monocyte chemoattractant protein; *NF,* nuclear factor; *RAGE,* receptor for advanced glycation end products; *VCAMs,* vascular cell adhesion molecules.

Modified from Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. *J Am Coll Cardiol*. 2009;53:S35.



CLASS	COMPOUND(S)	CELLULAR MECHANISM	MAIN PHYSIOLOGIC ACTION(S)	ADVANTAGES	DISADVANTAGES	COST
Biguanides	Metformin	Activates AMP-kinase ? Other	↓ Hepatic glucose production ? Other	Extensive experience No weight gain No hypoglycemia Likely ↓ CVD events (UKPDS)	GI side effects (diarrhea, abdominal cramping) Lactic acidosis risk (rare) Vitamin B_{12} deficiency Multiple contraindications: advanced CKD, acidosis, hypoxia, dehydration, ethanol abuse, other	Low
Sulfonylureas	*Second generation*: Glyburide (glibenclamide) Glipizide Gliclazide* Glimepiride	Closes K_{ATP} channels on beta cell plasma membranes	↑ Insulin secretion	Extensive experience ↓ Microvascular risk (UKPDS)	Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning Low durability	Low
Meglitinides (glinides)	Repaglinide Nateglinide	Closes K_{ATP} channels on beta cell plasma membranes	↑ Insulin secretion	↓ Postprandial glucose excursions Dosing flexibility	Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning Frequent dosing schedule	High
Thiazolidinediones	Pioglitazone Rosiglitazone†	Activates the nuclear transcription factor PPAR-γ	↑ Insulin sensitivity	No hypoglycemia Durability ↑ HDL-C ↓ Triglycerides (pioglitazone) ↓ Albuminuria ? ↓ CVD events (pioglitazone)	Weight gain Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone) ? ↑ MI (meta-analyses, rosiglitazone)	Moderate
α-Glucosidase inhibitors‡	Acarbose Miglitol Voglibose*§	Inhibits intestinal α-Glucosidase	Slows intestinal carbohydrate digestion/absorption	No hypoglycemia ↓ Postprandial glucose excursions Nonsystemic	Generally modest HbA_{1c} efficacy GI side effects (flatulence, diarrhea) Frequent dosing schedule	Moderate
DPP4 inhibitors	Vildagliptin* Sitagliptin Saxagliptin Alogliptin Linagliptin	Inhibits DDP4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	↑ Insulin secretion (glucose dependent) ↓ Glucagon secretion (glucose-dependent)	No hypoglycemia Well tolerated	Generally modest HbA_{1c} efficacy Urticaria/angioedema ? Pancreatitis Possible ↑ heart failure (saxagliptin; alogliptin)	High
Bile acid sequestrants‡	Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production ? Activation of farnesoid receptor (FXR) in liver	Unknown ? ↓ Hepatic glucose production ? ↑ Incretin levels	No hypoglycemia ↓ LDL-C	Generally modest HbA_{1c} efficacy Constipation ↑ Triglycerides May alter absorption of other medications	High
Dopamine-2 agonists‡	Bromocriptine (quick release)§	Activates dopaminergic receptors	Modulates hypothalamic regulation of metabolism ↑ Insulin sensitivity	No hypoglycemia ? ↓ CVD events (Cycloset Safety Trial)	Generally modest HbA_{1c} efficacy Dizziness/syncope Nausea Fatigue Rhinitis	High

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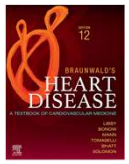
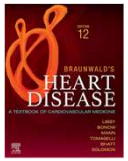
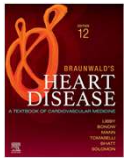


CLASS	COMPOUND(S)	CELLULAR MECHANISM	MAIN PHYSIOLOGIC ACTION(S)	ADVANTAGES	DISADVANTAGES	COST
SGLT2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin Ertugliflozin	Inhibits SGLT2 in the proximal renal tubule	Decreases glucose reabsorption, leading to glucosuria	Effective at all disease stages No hypoglycemia Weight loss ↓ Blood pressure r ↓ Albuminuria ↓ MACE (empa, cana) ↓ HF hospitalization (all) ↓ CV death (empa, cana) ↓ CKD progression (all but ertu)	Diabetic ketoacidosis Genitourinary infections Polyuria Volume depletion ↑ LDL-C Reversible ↓ eGFR ? Amputation risk (cana) ? Fracture risk (cana)	High
GLP-1 receptor agonists	Exenatide Exenatide (weekly) Liraglutide Albiglutide Dulaglutide Semaglutide Semaglutide (oral) Lixisenatide	Activates GLP-1 receptors	↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent) Slows gastric emptying ↑ Satiety	No hypoglycemia Weight reduction ↓ CV risk factors ↓ MACE (lira, sema, dula) ↓ CV death (lira) ↓ macroalbuminuria	GI side effects (nausea/vomiting) ↑ Pulse rate ↑ Gallbladder events ? Pancreatitis ? Mitogenicity/cancer risk Injectable Training requirements (injectables)	High
Amylin mimetics[‡]	Pramlintide[§]	Activates amylin receptors	↓ Glucagon secretion Slows gastric emptying ↑ Satiety	↓ Postprandial glucose excursions Weight reduction	Generally modest HbA_{1c} efficacy GI side effects (nausea/vomiting) Hypoglycemia unless insulin dose is simultaneously reduced Injectable Training requirements Frequent dosing schedule	High
Insulins	Human NPH Human regular Lispro Aspart Glulisine Glargine Detemir Degludec Premixed (several types)	Activates insulin receptors	↑ Glucose disposal ↓ Hepatic glucose production	Universally effective Theoretically unlimited efficacy ↓ Microvascular risk (UKPDS)	Hypoglycemia Weight gain ? Mitogenicity/cancer risk Injectable Training requirements "Stigma" (for patients)	Variable[¶]



TRIAL	DRUG*	PATIENTS (*n*)	STAGE	NCT
Completed Trials				
SAVOR-TIMI 53[60]	Saxagliptin	16,492	Completed	NCT01107886
EXAMINE[61]	Alogliptin	5,380	Completed	NCT00968708
TECOS[63]	Sitagliptin	14,671	Completed	NCT00790205
ELIXA[66]	Lixisenatide	6,068	Completed	NCT01147250
EMPA-REG-OUTCOME[75]	Empagliflozin	12,500	Completed	NCT01131676
LEADER[67]	Liraglutide	9,340	Completed	NCT01179048
SUSTAIN 6[70]	Semaglutide	3,299	Completed	NCT01720446
CANVAS[81]	Canagliflozin	4,330	Completed	NCT01032629
EXSCEL[68]	Exenatide LAR	14,752	Completed	NCT01144338
CV Outcomes-ITCA 650	Exenatide ITCA 650	4,156	Completed	NCT01455896
DEVOTE[59]	Insulin degludec	7,637	Completed	NCT01959529
CANVAS-R[81]	Canagliflozin	5,812	Completed	NCT01989754
CAROLINA[46]	Linagliptin versus glimepiride	6,000	Completed	NCT01243424
REWIND[72]	Dulaglutide	9,600	Completed	NCT01394952
VERTIS[85]	Ertugliflozin	8,246	Completed	NCT01986881
DECLARE-TIMI 58[82]	Dapagliflozin	17,160	Completed	NCT01730534
CARMELINA[47]	Linagliptin	6,980	Completed	NCT01897532
VERTIS CV[85]	Ertugliflozin	3,900	Completed	NCT01986881
CREDENCE[83]	Canagliflozin	3,627	Completed	NCT02065791
Ongoing Trials				
SOUL	Oral semaglutide	9,642	Started July, 2019	NCT03914326
SURPASS-CVOT	Tirzepatide vs. dulaglutide	12,500	Started May, 2020	NCT04255433

*All versus placebo except where noted.
NCT, National Clinical Trial [registration number].



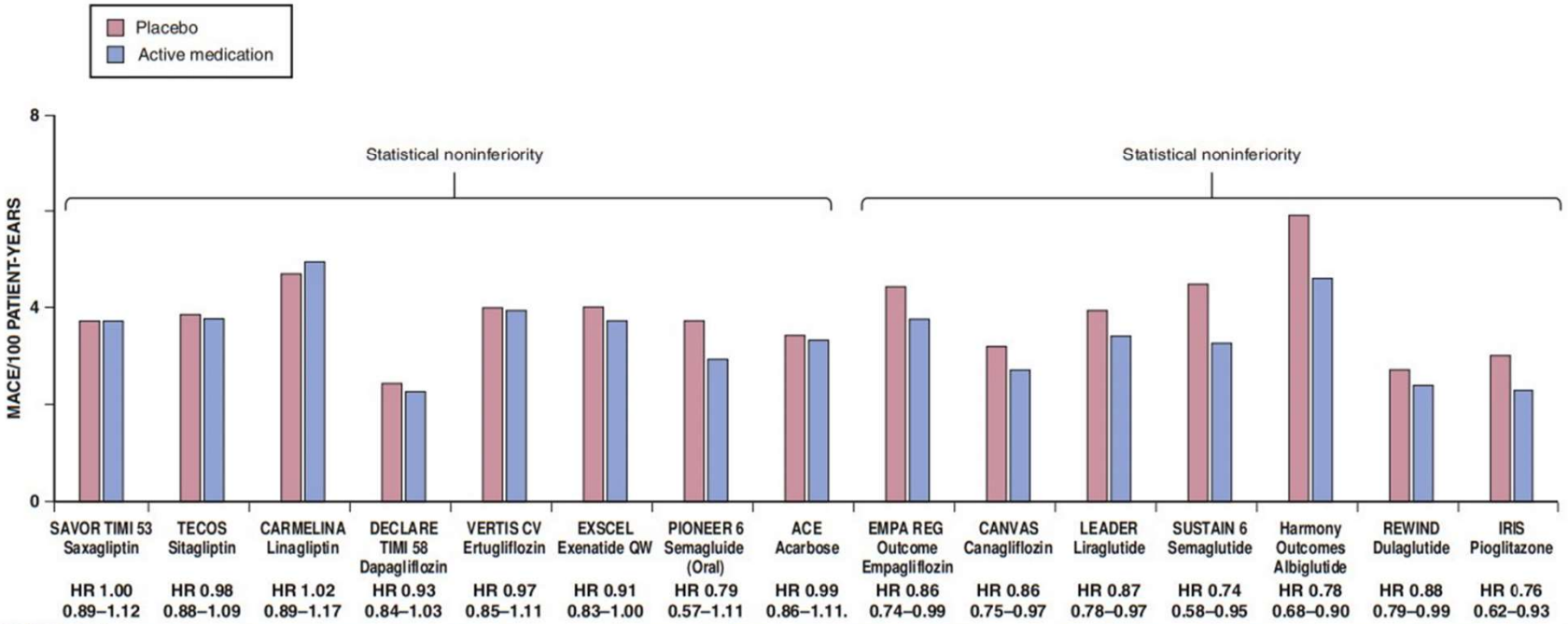
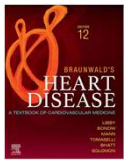
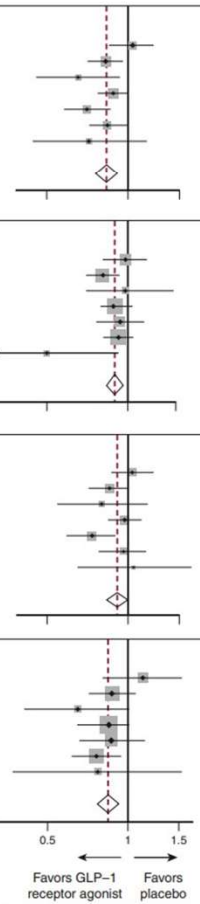


FIGURE 31.7 Summary results of the comparative incident rates (active medication vs. placebo) from large, randomized, placebo-controlled clinical trials of antihyperglycemic medications in patients with stable CV disease / CV risk factors using major adverse CV events (MACE) as primary outcomes. SAVOR TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction); TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin); CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus); DECLARE TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis in Myocardial Infarction); VERTIS CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease); EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial); PIONEER 6 (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes); ACE (Acarbose Cardiovascular Evaluation Trial); EMPA REG Outcome (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients); CANVAS (Canagliflozin Cardiovascular Assessment Study); LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results); SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes); Harmony Outcomes (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease); REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes); IRIS (Insulin Resistance Intervention after Stroke). (Data from References 47, 52, 60, 63, 68, 70-73, 75, 81, 82, 85, 88.)



	GLP–1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-component MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1.02 (0.89–1.17)		0.78
LEADER	608/4668 (13%)	694/4672 (15%)	0.87 (0.78–0.97)		0.015
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0.74 (0.58–0.95)		0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91 (0.83–1.00)		0.061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0.78 (0.68–0.90)		<0.001
REWIND	594/4949 (12%)	663/4952 (13%)	0.88 (0.79–0.99)		0.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0.79 (0.57–1.11)		0.17
Overall (I^2=40.9%, p=0.118)	**2948/27977 (11%)**	**3304/28027 (12%)**	**0.88 (0.82–0.94)**	**75 (50–151)**	**<0.001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0.98 (0.78–1.22)		0.85
LEADER	219/4668 (5%)	278/4672 (6%)	0.78 (0.66–0.93)		0.007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0.98 (0.65–1.48)		0.92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0.88 (0.76–1.02)		0.096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0.93 (0.73–1.19)		0.58
REWIND	317/4949 (6%)	346/4952 (7%)	0.91 (0.78–1.06)		0.18
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0.49 (0.27–0.92)		0.021
Overall (I^2=13.5%, p=0.327)	**1213/27977 (4%)**	**1371/28027 (5%)**	**0.88 (0.81–0.96)**	**175 (110–524)**	**0.003**
Fatal or non-fatal myocardial infarction					
ELIXA	270/3034 (9%)	261/3034 (9%)	1.03 (0.87–1.22)		0.71
LEADER	292/4668 (6%)	339/4672 (7%)	0.86 (0.73–1.00)		0.046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0.81 (0.57–1.16)		0.26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0.97 (0.85–1.10)		0.62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0.75 (0.61–0.90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0.96 (0.79–1.15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1.04 (0.66–1.66)		0·49
Overall (I^2=27.4%, p=0.219)	**1540/27977 (6%)**	**1666/28027 (6%)**	**0.91 (0.84–1.00)**	**193 (108–NA)**	**0·043**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1.12 (0.79–1·58)		0.54
LEADER	173/4668 (4%)	199/4672 (4%)	0.86 (0.71–1·06)		0.16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0.65 (0.41–1.03)		0.066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0.85 (0.70–1.03)		0.095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0.86 (0.66–1.14)		0.30
REWIND	158/4949 (3%)	205/4952 (4%)	0.76 (0.62–0.94)		0.01
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0.76 (0.37–1.56)		0.43
Overall (I^2=0.0%, p=0.557)	**722/27977 (3%)**	**853/28027 (3%)**	**0.84 (0.76–0.93)**	**209 (139–477)**	**<0.001**



	GLP–1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0.94 (0.78–1.13)		0.50
LEADER	381/4668 (8%)	447/4672 (10%)	0.85 (0.74–0.97)		0.02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1.05 (0.74–1.50)		0.79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0.86 (0.77–0.97)		0.016*
Harmony Outcomes	196/4731 (4%)	205/4732 (4%)	0·95 (0.79–1.16)		0.64
REWIND	536/4949 (11%)	592/4952 (12%)	0.90 (0.80–1.01)		0.067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0.51 (0.31–0.84)		0.008
Overall (I^2=16.5%, p=0.304)	**1916/27977 (7%)**	**2156/28027 (8%)**	**0.88 (0.83–0.95)**	**113 (80 to 271)**	**0.001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0.96 (0.75–1.23)		0.75
LEADER	218/4668 (5%)	248/4672 (5%)	0.87 (0.73–1.05)		0.14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1.11 (0.77–1.61)		0.57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0.94 (0.78–1.13)		0.51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0.71 (0.53–0.94)		0.019
REWIND	213/4949 (4%)	226/4952 (5%)	0.93 (0.77–1.12)		0.46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0.86 (0.48–1.55)		0.59
Overall (I^2=0.0%, p=0.595)	**931/27977 (3%)**	**1021/28027 (4%)**	**0.91 (0.83–0.99)**	**311 (164 to 2797)**	**0.028**
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0.84 (0.68–1.02)		0.083
LEADER	268/4668 (6%)	337/4672 (7%)	0.78 (0.67–0.92)		0.003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0.64 (0.46–0.88)		0.006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0.88 (0.76–1.01)		0.065
REWIND	848/4949 (17%)	970/4952 (20%)	0.85 (0.77–0.93)		<0.001
Overall (I^2=0.0%, p=0.413)	**1716/20168 (9%)**	**2017/20134 (10%)**	**0.83 (0.78–0.89)**	**62 (48 to 96)**	**<0.001**
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1.16 (0.74–1·83)		0.513
LEADER	87/4668 (2%)	97/4672 (2%)	0.89 (0.67–1·19)		0.43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1.28 (0.64–2.58)		0.48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0.88 (0.74–1.05)		0.164
REWIND	169/4949 (3%)	237/4952 (5%)	0.70 (0.57–0.85)		<0.001
Overall (I^2=42.7%, p=0.137)	**561/20752 (3%)**	**656/20763 (3%)**	**0.87 (0.73–1.03)**	**247 (119 to –10721)**	**0.098**

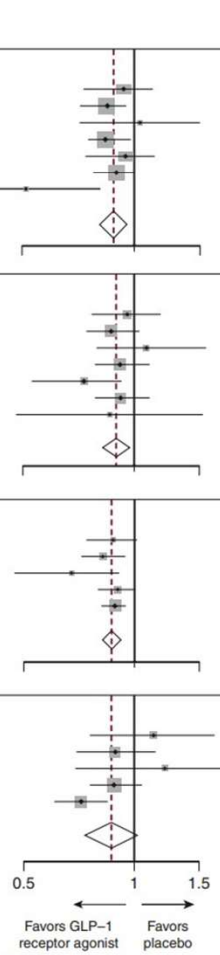
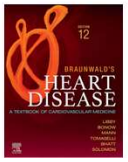


FIGURE 31.8 Meta-analysis of GLP-1 receptor agonist cardiovascular (CV) outcome trials (ELIXA, LEADER, SUSTAIN-6, ESXCEL, Harmony Outcomes, REWIND, PIONEER 6) w outcomes of 3-component major adverse CV events (MACE), CV death, fatal or non-fatal myocardial infarction, stroke, all-cause mortality, hospital admission for heart fail (HHF), composite kidney outcome (including macroalbuminuria), worsening of kidney function, and the composite for the progression of chronic kidney disease (CKD.) Haza ratios (individual and overall) represent the comparison of the incidence rates in the active therapy versus the placebo groups. (From Kristensen SL, Rorth R, Jhund PS, et al. 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. *Lancet Diabetes Endocrinol.* 2019;7:776–785.)



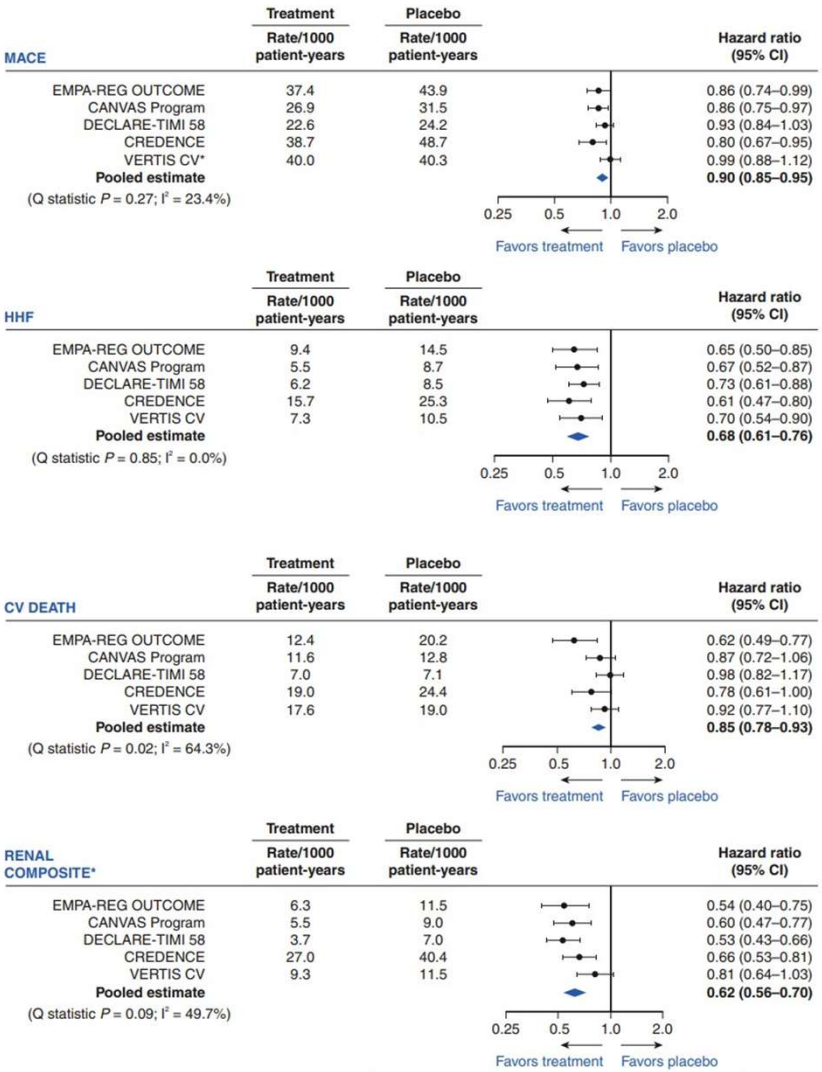
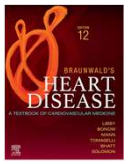


FIGURE 31.9 Meta-analysis of SGLT2 inhibitor cardiovascular (CV) outcome trials (EMPA-REG OUTCOME, CANVAS, DECLARE, CREDENCE, and VERTIS CV) with outcomes of major adverse CV events (MACE), hospitalization for heart failure (HHF), CV death, and the composite for the progression of chronic kidney disease (CKD). Hazard ratios (individual and pooled) represent the comparisons of the incidence rates in the active therapy versus the placebo groups. (From McGuire DK. Metaanalysis Placeholder. 2020.)



APPROACH TO THE MANAGEMENT OF HYPERGLYCEMIA:

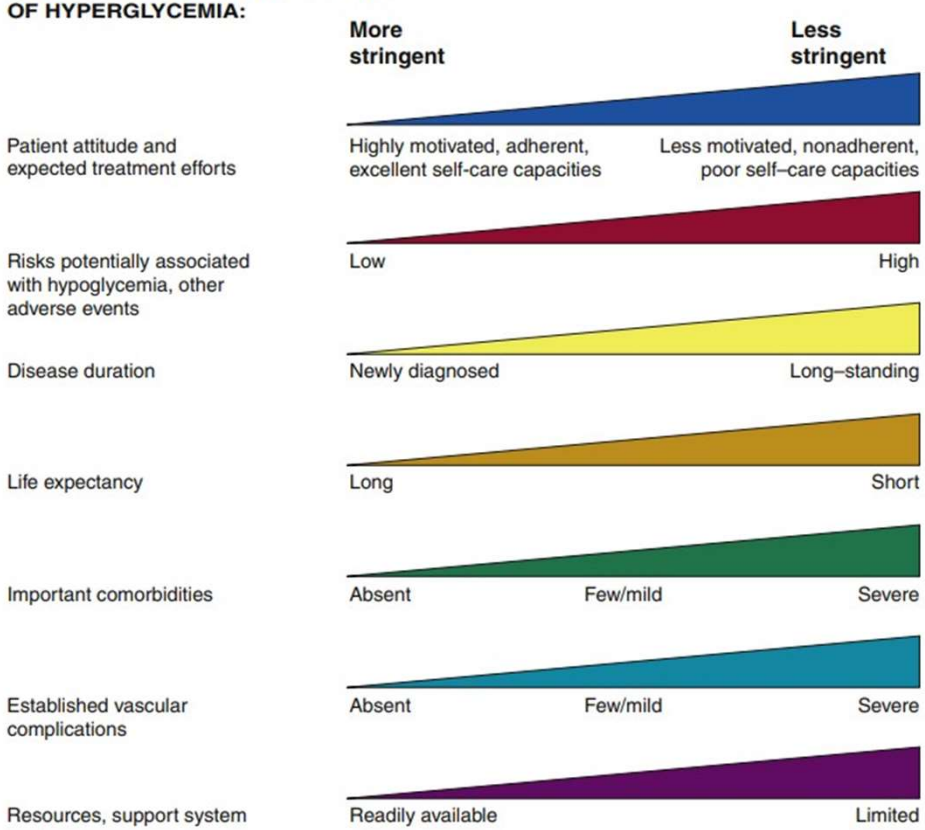
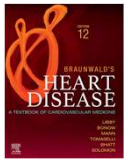


FIGURE 31.10 Modulation of the intensiveness of glucose lowering in type 2 diabetes mellitus (DM). Depiction of patient and disease factors that may be used by the practitioner to determine optimal hemoglobin A_{1c} (HbA_{1c}) targets in patients with type 2 DM. Greater concerns regarding a particular domain are represented by increasing height of the corresponding ramp. Thus, characteristics/predicaments toward the left justify more stringent efforts to lower HbA_{1c}, whereas those toward the right suggest (indeed, sometimes mandate) less stringent efforts. Where possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values. This "scale" is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision making. (From Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149.)



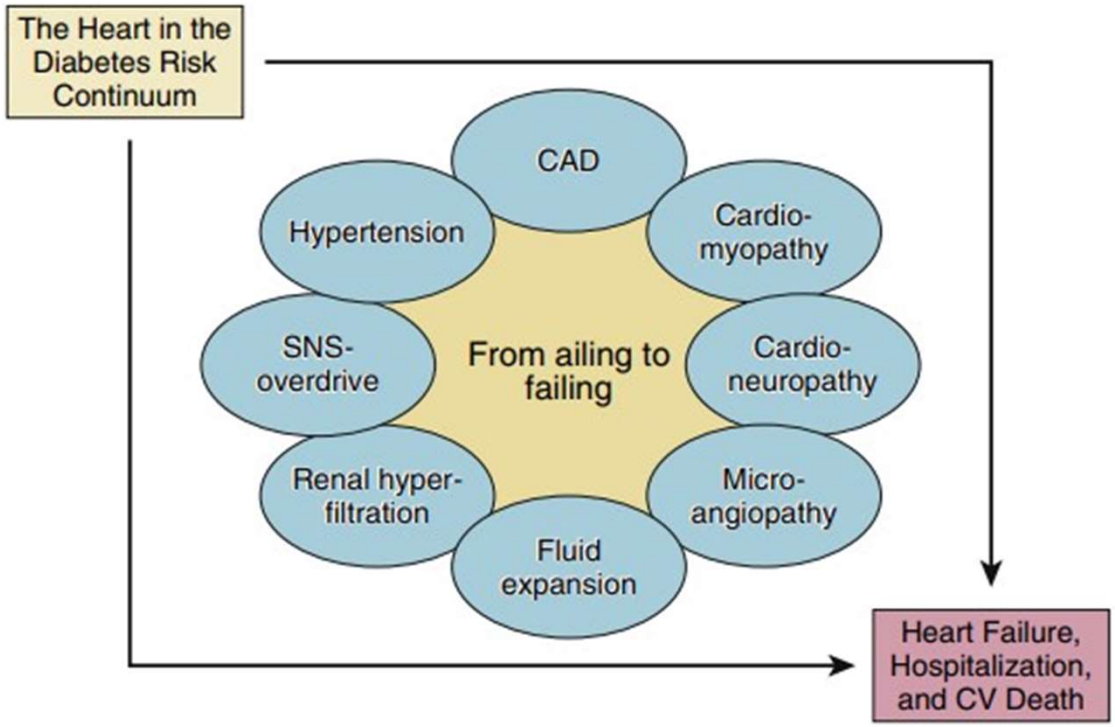
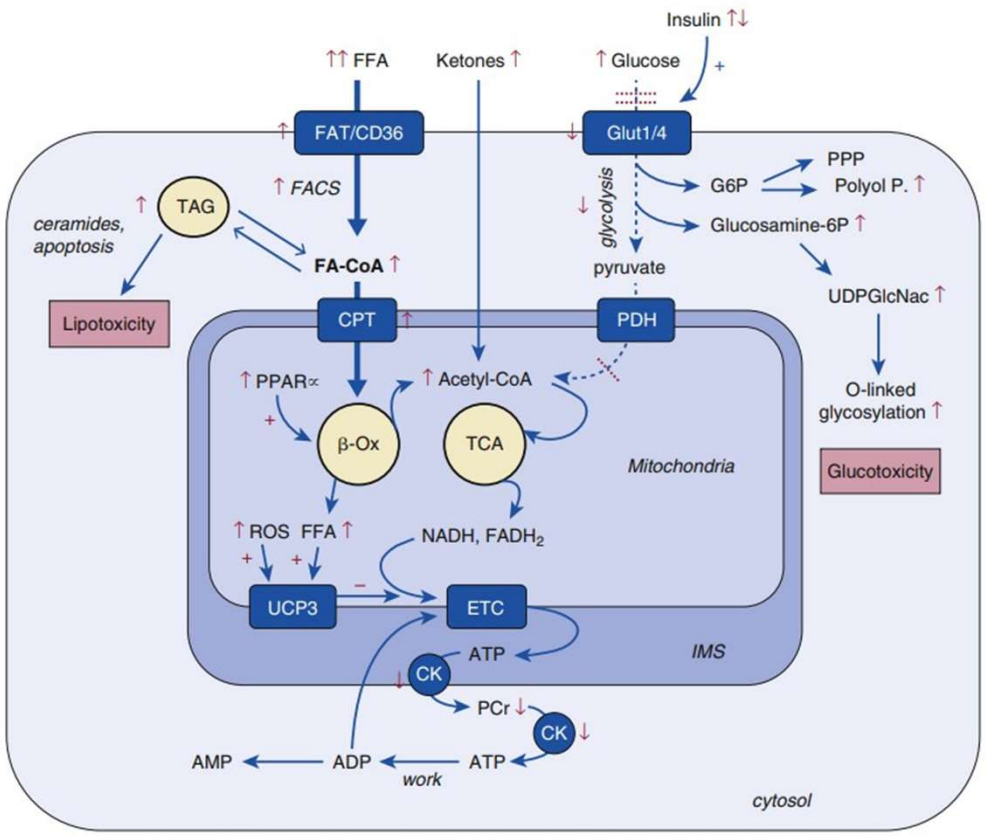


FIGURE 31.11 Heart failure in type 2 diabetes mellitus (DM): the ominous octet-multiple comorbidities commonly associated with type 2 DM that individually and in aggregate contribute to the increased risk for heart failure in such patients. *CAD*, Coronary artery disease; *CV*, cardiovascular; *SNS*, sympathetic nervous system. (From Standl E, Schnell O, McGuire DK. Heart failure considerations of antihyperglycemic medications for type 2 diabetes. *Circ Res*. 2016;118:1830–1843.)



EFIGURE 31.1 Cardiac metabolic alterations in diabetes mellitus (DM). In DM, strongly increased free fatty acid activate peroxisome proliferator-activated receptor α (PPARα), which up-regulates expression of genes involved in fatty acid (FA) oxidation. Increased FA oxidation shuts down glucose uptake and oxidation (insulin resistance), thereby blunting metabolic flexibility. Excessive FA are stored as triacylglycerol (TAG), which can mediate lipotoxicity. FA and reactive oxygen species (ROS) activate uncoupling protein 3 (UCP3), which makes adenosine triphosphate (ATP) production less efficient. *β-Ox.*, *β*-oxidation; *CPT-1/2*, carnitine palmitoyltransferase type 1/2; *FA-CoA*, fatty acyl-coenzyme A; *FACS*, fatty acyl-coenzyme A synthetase; *FAT/CD36*, fatty acid translocase; *GLUT 1/4*, glucose transporters 1/4; *G6P*, glucose-6-phosphate; *PDH*, pyruvate dehydrogenase complex; *PPP*, pentose phosphate pathway; *Polyol P.*, Polyol pathway; *TAG*, triacylglycerol; *UDPGlcNac*, UDP-N-acetyl glucosamine. (From Maack C, Lehrke M, Backs J, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *Eur Heart J.* 2018;39:4243–4254.)

	Treatment		Placebo			
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weight (%)	Hazard ratio (95%CI)
Patients with history of heart failure						
EMPA-REG	75/462	63.6	49/244	85.5	13.27	0.72 (0.50, 1.04)
CANVAS Program	NA/803	35.4	NA/658	56.8	23.25	0.61 (0.46, 0.80)
DECLARE-TIMI 58	142/852	45.1	172/872	55.5	34.85	0.79 (0.63, 0.99)
VERTIS CV	164/1286	40.1	99/672	47.1	28.63	0.85 (0.66, 1.09)
Fixed effects model	(Q = 3.36, df = 3, p = 0.339; I^2 = 10.7%)					**0.75 (0.66, 0.86)**
Patients with no history of heart failure						
EMPA-REG	190/4225	15.5	149/2089	24.9	19.45	0.63 (0.51, 0.78)
CANVAS Program	NA/4992	13.6	NA/3689	15.2	23.48	0.87 (0.72, 1.06)
DECLARE-TIMI 58	275/7730	8.9	324/7706	10.5	34.63	0.84 (0.72, 0.99)
VERTIS CV	280/4213	18.8	151/2075	20.6	22.44	0.91 (0.75, 1.11)
Fixed effects model	(Q = 7.41, df = 3, p = 0.060; I^2 = 59.5%)					**0.82 (0.74, 0.90)**

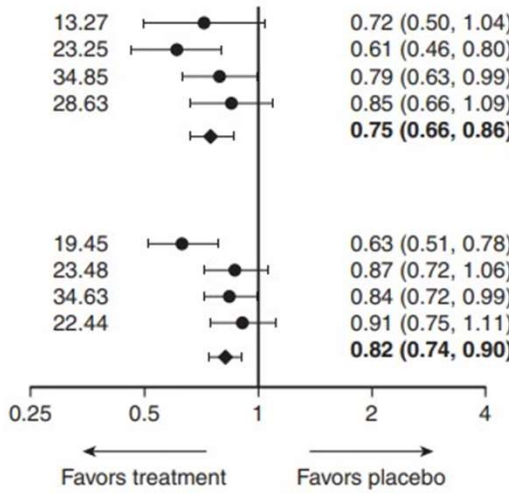
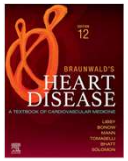


FIGURE 31.12 Meta-analysis of SGLT2 inhibitor cardiovascular (CV) outcome trials (EMPA-REG OUTCOME, CANVAS, DECLARE, and VERTIS CV) with outcome hospitalization for heart failure (HHF), stratified by the presence or absence of heart failure at baseline. Hazard ratios (individual and fixed effects model) represent the comparisons of the incidence rates in the active therapy versus the placebo groups. (From McGuire DK. Metaanalysis Placeholder. 2020.)



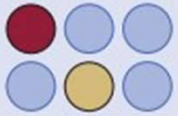
Drug	Effect on heart failure	
Thiazolidinediones/Glitazones	Unfavorable	
DPP4 inhibitors	Saxagliptin: unfavorable Sitagliptin, Alogliptin, Linagliptin: neutral	
GLP-1 receptor agonists	Lixisenatide, Liraglutide, Semaglutide, Exenatide:neutral	
Insulin	Neutral	
Sulfonylureas	Neutral	
Alpha-Glucosidase inhibitors	Acarbose:neutral	
Metformin	Neutral; potentially beneficial	
SGLT2 inhibitors	Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin: beneficial	

FIGURE 31.13 Effect of antidiabetic drugs on heart failure. (From Schütt K, Marx N. Heart failure and diabetes: management and open issues. *Herz*. 2019;44:203–209.)

DPP-4 Inhibitors

-Sitagliptin
-Linagliptin

Sitagliptin (Ziptin)

Indications and Usage:

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dosage and Administration:

The recommended dose of Sitagliptin is 100 mg once daily. Sitagliptin can be taken with or without food.

Dosage adjustment is recommended for patients with eGFR less than 45 mL/min/1.73 m^2.

Dosage Adjustment in Patients with Renal Impairment	
eGFR greater than or equal to 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2	**eGFR less than 30 mL/min/1.73 m^2 (including patients with end stage renal disease [ESRD] on dialysis)**
50 mg once daily	**25 mg once daily**

FDA Label Sitagliptin, Reference ID: 4712165.

Sitagliptin (Ziptin)

Dosage Forms and Strengths:

Tablets: 100 mg, 50 mg, and 25 mg

FDA Label Sitagliptin, Reference ID: 4712165.

abidi
DIABETES

Linagliptin (Lirenta)

Indications and Usage:

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dosage and Administration:

The recommended dose of Linagliptin is 5 mg once daily.

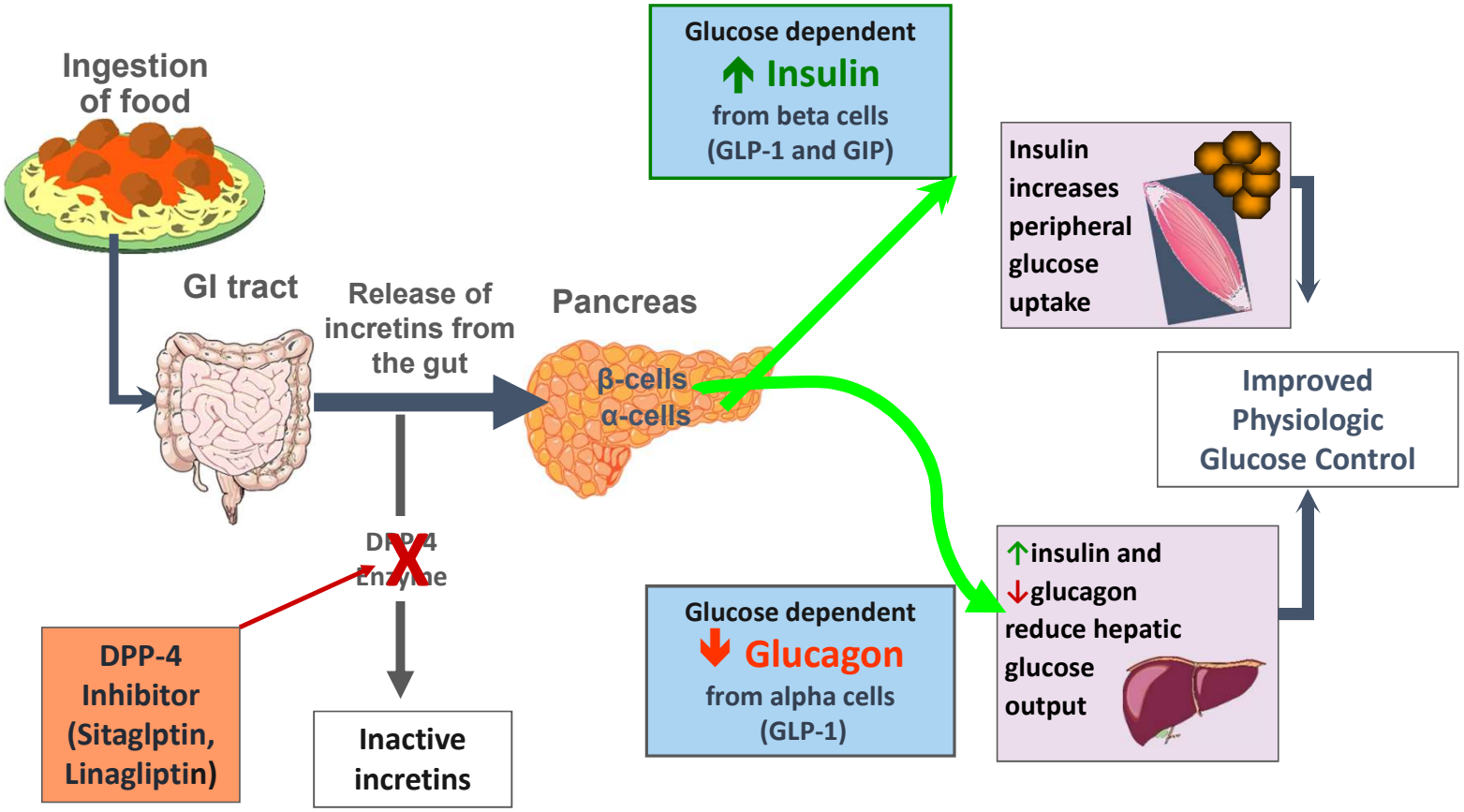
Linagliptin can be taken with or without food.

Dosage Forms and Strengths:

Tablets: 5 mg

FDA Label Linagliptin, Reference ID: 4583067.

DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes[1-4]



DPP-4 = dipeptidyl peptidase 4

1-Endocrinology. 2004 ;145(6):2653-9. 2- Lancet. 2002 ;359(9309):824-30; 3-Curr Diab Rep. 2003;3(5):365-72; 4-Buse JB et al. In *Williams Textbook of Endocrinology*. 10th ed., 2003:1427–1483.

Sitagliptin and Metformin Hydrochloride (Zipmet)

Indications and Usage:

Zipmet is a combination of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dosage and Administration:

- Individualize the starting dose of Zipmet based on the patient's current regimen.
- Adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.
- Give twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal effects due to metformin.
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR).
  - Do not use in patients with eGFR below 30 mL/min/1.73 m^2.
  - Zipmet is not recommended in patients with eGFR between 30 and less than 45 mL/min/1.73 m^2.
  - Zipmet may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.

FDA Label Janumet, Reference ID: 4712165.

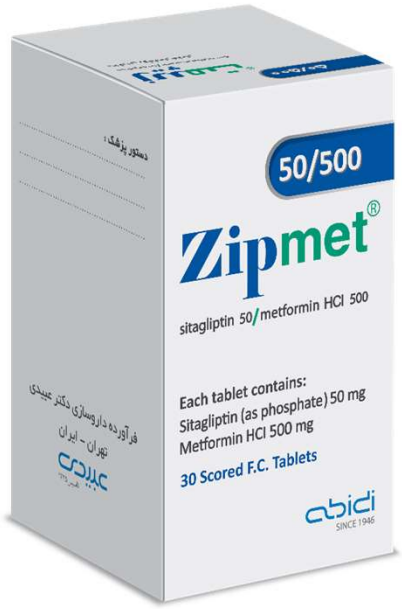
Sitagliptin and Metformin Hydrochloride (Zipmet)

Dosage Forms and Strengths:

Tablets:

50 mg sitagliptin/500 mg metformin HCl

50 mg sitagliptin/1000 mg metformin HCl



FDA Label Janumet, Reference ID: 4712165.

abidi DIABETES

Empagliflozin (Gloripa)

Indications and Usage:

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Dosage and Administration:

- The recommended dose of Empagliflozin is 10 mg once daily, taken in the morning, with or without food.
- Dose may be increased to 25 mg once daily.
- Assess renal function before initiating Empagliflozin. Do not initiate Empagliflozin if eGFR is below 45 mL/min/1.73 m^2.
- Discontinue Empagliflozin if eGFR falls persistently below 45 mL/min/1.73 m^2.

FDA Label Jardiance, Reference ID: 4843332.

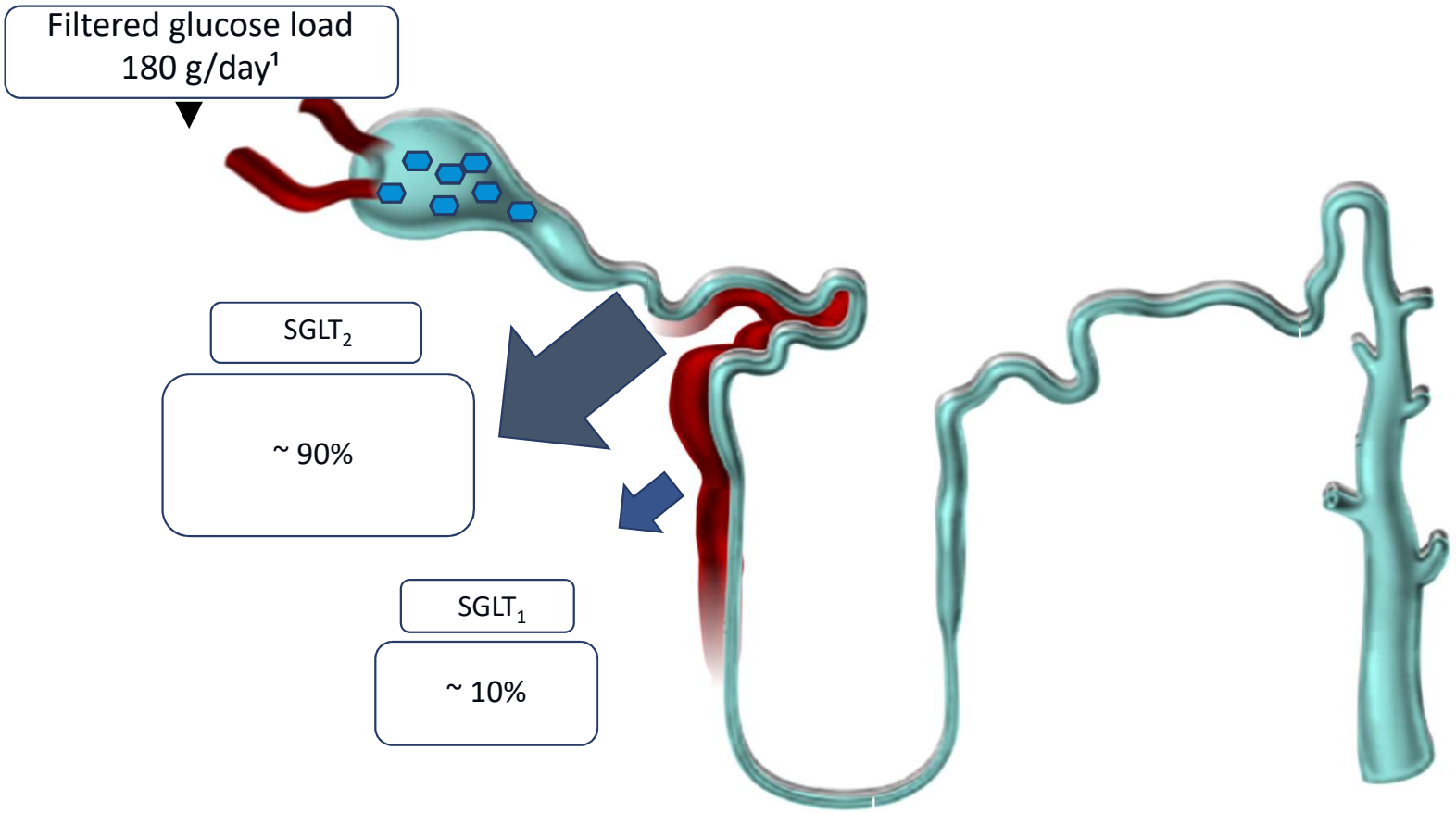
Empagliflozin (Gloripa)

Dosage Forms and Strengths:

Tablets: 10 mg, 25 mg

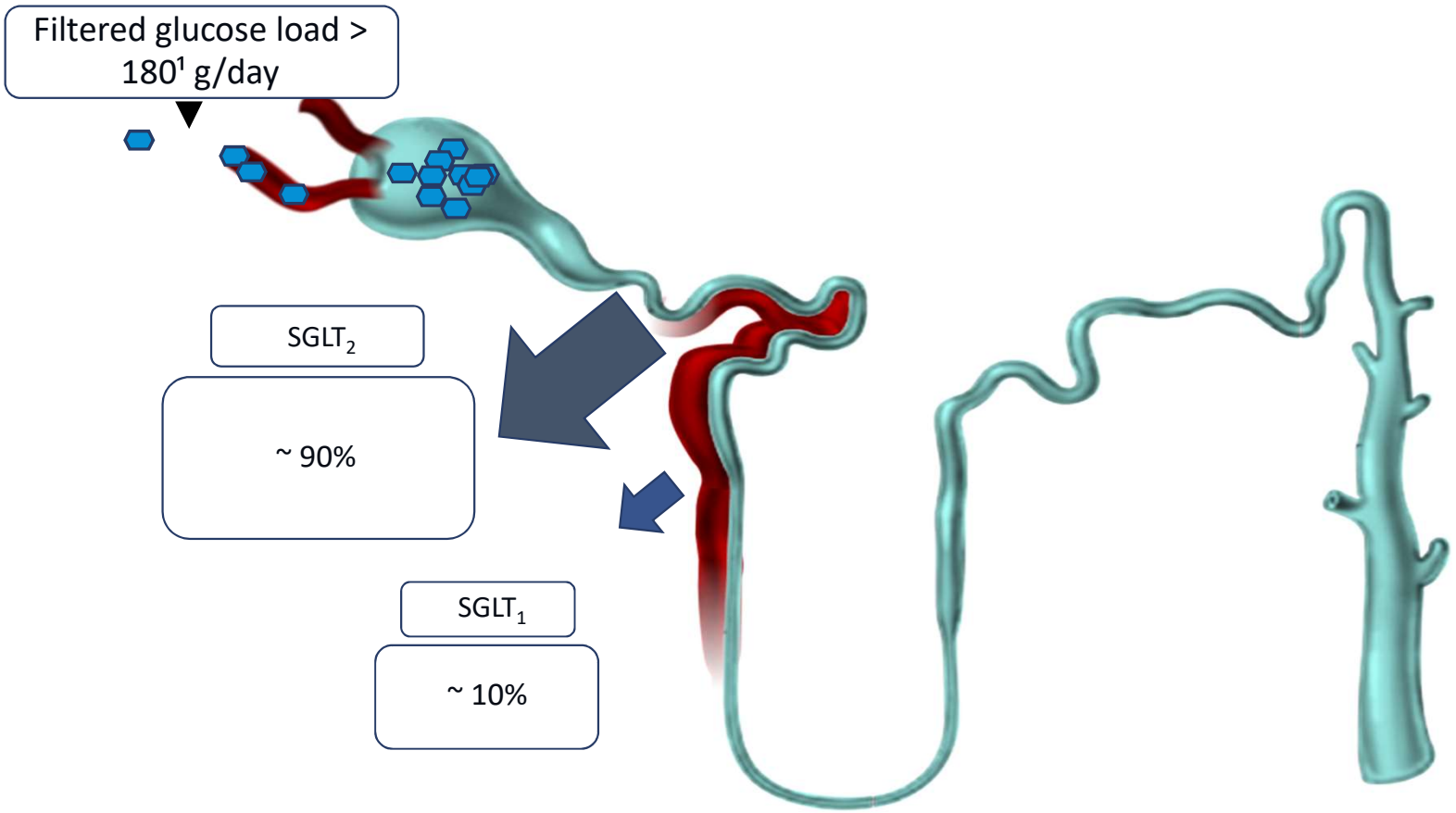
FDA Label Jardiance, Reference ID: 4843332.

Renal Glucose Re-absorption in Healthy Individuals



1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2): 136-42.

Renal Glucose Re-absorption in Patients With Diabetes

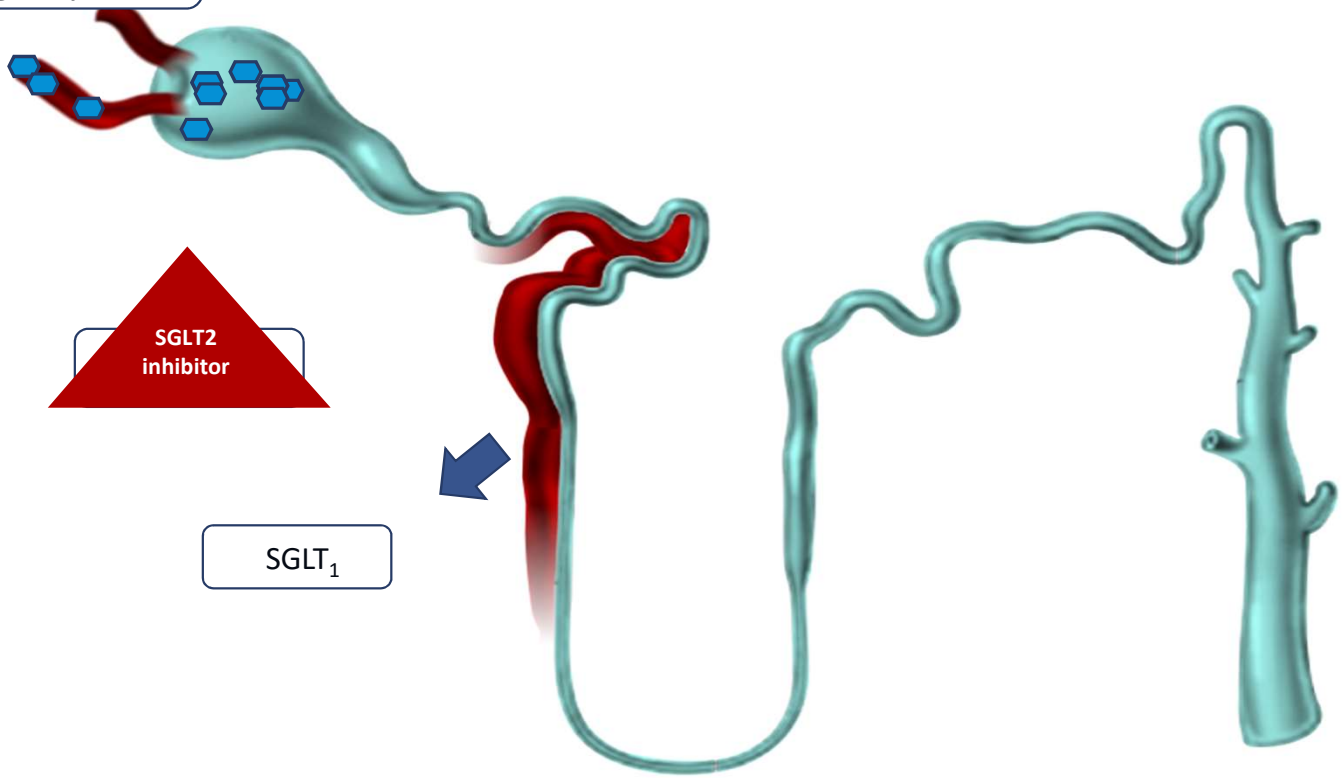


When blood glucose increases above the renal threshold *(~ 180 mg/dL),* the capacity of the transporters is exceeded, resulting in urinary glucose excretion[1]

1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2): 136-42.

Urinary Glucose Excretion via SGLT2 Inhibition

Filtered glucose load
> 180 g/day



$SGLT_2$ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis[1]

***Loss of ~ 80 g of glucose/day**

1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2):136-42.

Empagliflozin and Metformin hydrochloride (Synoripa)

Indications and Usage:

Synoripa is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin hydrochloride, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin hydrochloride is appropriate.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of Synoripa on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

FDA Label Synjardy, Reference ID: 4810096.

Empagliflozin and Metformin hydrochloride (Synoripa)

Dosage and Administration:

- Individualize the starting dose of Synoripa based on the patient's current regimen.
- The maximum recommended dose is 12.5 mg empagliflozin/1000 mg metformin hydrochloride twice daily.
- Take twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.
- Assess renal function before initiating. Synoripa is contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2.
- Synoripa may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.

FDA Label Synjardy, Reference ID: 4810096.

Empagliflozin and Metformin hydrochloride (Synoripa)

Dosage Forms and Strengths:

Tablets:

5 mg empagliflozin/500 mg metformin hydrochloride

5 mg empagliflozin/1000 mg metformin hydrochloride

12.5 mg empagliflozin/500 mg metformin hydrochloride

12.5 mg empagliflozin/1000 mg metformin hydrochloride

FDA Label Synjardy, Reference ID: 4810096.

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DIABETES

Empagliflozin and Linagliptin (Glorenta)

Indications and Usage:

- Glorenta is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

FDA Label Glyxambi, Reference ID: 4810096.

Empagliflozin and Linagliptin (Glorenta)

Dosage and Administration:

- Assess renal function before initiating and as clinically indicated.
- The recommended dose of Glorenta is 10 mg empagliflozin and 5 mg linagliptin once daily, taken in the morning, with or without food.
- Dose may be increased to 25 mg empagliflozin and 5 mg linagliptin once daily.

Empagliflozin and Linagliptin (Glorenta)

Dosage Forms and Strengths:

Tablets:

10 mg empagliflozin/5 mg linagliptin

25 mg empagliflozin/5 mg linagliptin

abidi DIABETES

Empagliflozin, Linagliptin, and Metformin hydrochloride extended-release tablets (Glotrio)

Indications and Usage:

- Glotrio ER is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

FDA Label Glyxambi, Reference ID: 4810096.

Empagliflozin, Linagliptin, and Metformin hydrochloride extended-release tablets (Glotrio)

Dosage and Administration:

- Assess renal function before initiating and as clinically indicated.
- Individualize the starting dose of Glotrio ER based on the patient's current regimen and renal function.
- Initiation of Glotrio ER is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component.
- The maximum recommended dose of Glotrio ER is 25 mg empagliflozin, 5 mg linagliptin and 2000 mg metformin HCl.
- Take once daily with a meal in the morning.
- Swallow whole; do not split, crush, dissolve, or chew.
- Glotrio ER may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.

FDA Label Glyxambi, Reference ID: 4810096.

Empagliflozin, Linagliptin, and Metformin hydrochloride extended-release tablets (Glotrio)

Dosage Forms and Strengths:

Tablets:

- ❑ 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin HCl extended-release
- ❑ 10 mg empagliflozin/5 mg linagliptin/1000 mg metformin HCl extended-release
- ❑ 12.5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin HCl extended-release
- ❑ 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin HCl extended-release

FDA Label Glyxambi, Reference ID: 4810096.

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DIABETES

Linagliptin and Metformin hydrochloride (Liroprim)

Indications and Usage:

Liroprim contains linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin hydrochloride (HCl), a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

FDA Label Jentadueto, Reference ID: 4583067.

Linagliptin and Metformin hydrochloride (Liroprim)

Dosage and Administration:

- Individualize the starting dose of Liroprim based on the patient's current regimen.
- The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin HCl twice daily.
- Give twice daily with meals, with gradual dose escalation to reduce the gastrointestinal effects due to metformin.
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR).
  - o Do not use in patients with eGFR below 30 mL/min/1.73 m^2
  - o Initiation is not recommended in patients with eGFR between 30 -45 mL/min/1.73 m^2
  - o Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2
  - o Discontinue if eGFR falls below 30 mL/min/1.73 m^2
- Liroprim may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.

FDA Label Jentadueto, Reference ID: 4583067.

Linagliptin and Metformin hydrochloride (Liroprim)

Dosage Forms and Strengths:

Tablets:

- ❑ 2.5 mg linagliptin/500 mg metformin HCl
- ❑2.5 mg linagliptin/1000 mg metformin HCl

FDA Label Jentadueto, Reference ID: 4583067.


Thank you