Latest Pharmacologic Therapy for the Treatment of Type 2 Diabetes

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Objectives

- Evaluate the importance of glycemic control in preventing complications in type 2 diabetes
- Describe the new drug classes and treatment options for treating type 2 diabetes
- Discuss the uses of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors and Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists in high cardiovascular risk
- Individualize type 2 diabetes regimens in different clinical settings

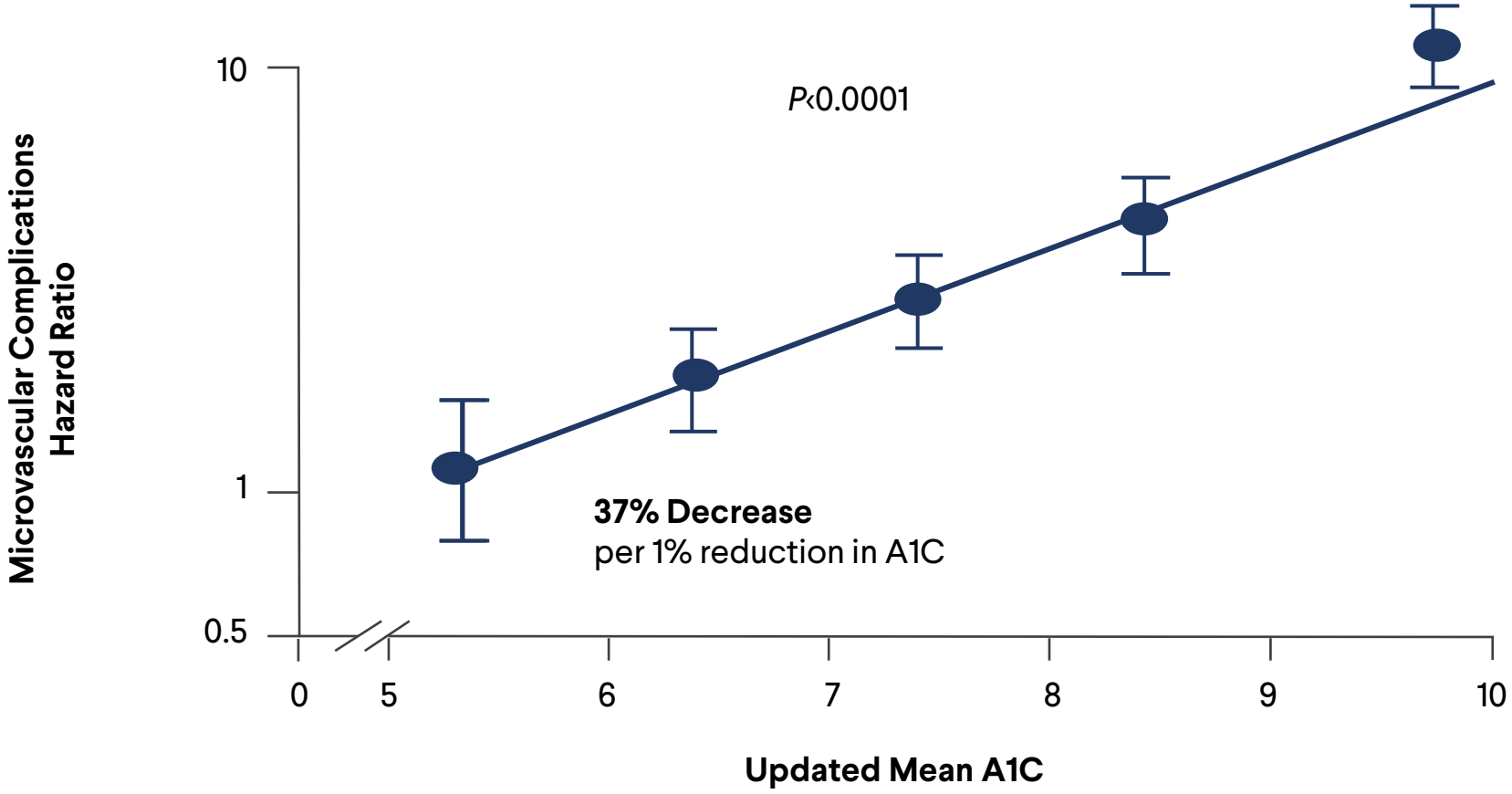
Wexler DJ. Presented at ADA 29: June 12-16, 2020

Diabetes: Beyond a Metabolic Disease

Diabetes Mellitus is associated with an increased risk of both micro- and macrovascular disease	
Microvascular Disease	**Macrovascular Disease**
Retinopathy	Atherosclerotic Cardiovascular Disease (ASCVD)
Nephropathy	Stroke
Neuropathy	Heart Failure (HF)
	Peripheral arterial disease

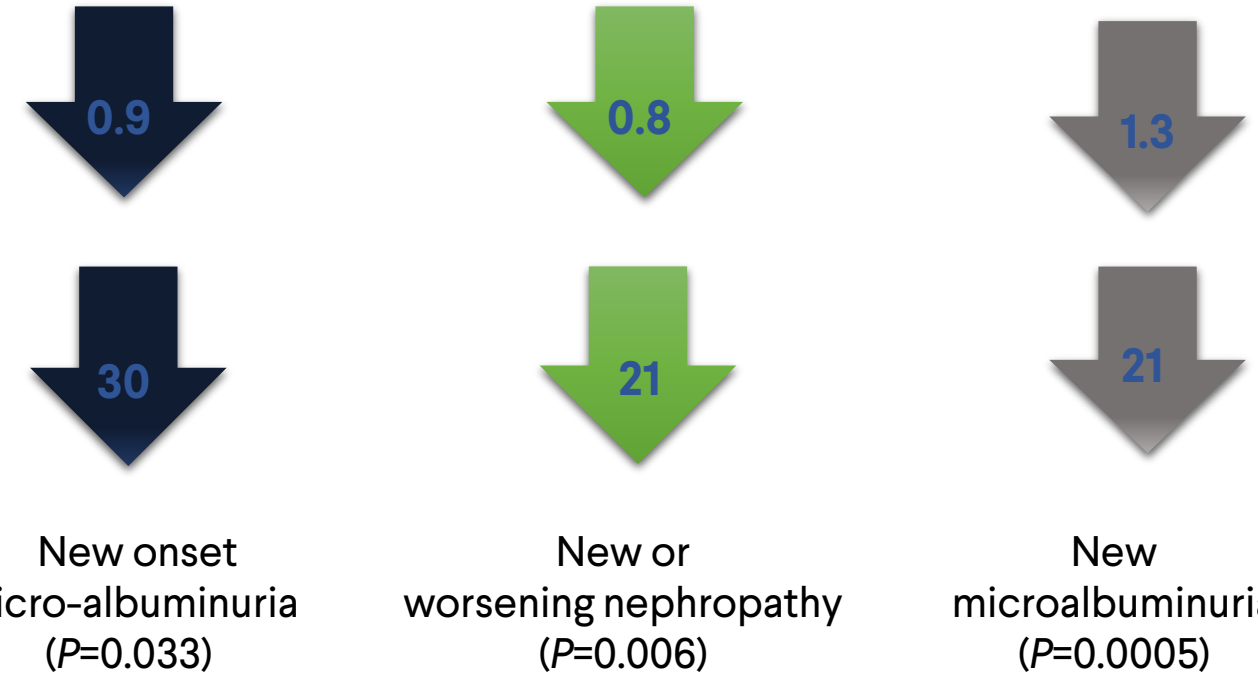
Reducing A1C Reduces Microvascular Risk

United Kingdom Prospective Diabetes Study



Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405-12.

Reducing A1C Reduces Nephropathy Risk in Type 2 Diabetes



UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53. Erratum in: Lancet 1999 Aug 14;354(9178):602.

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ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010 Aug 7;376(9739):419-30.

Use of Antihyperglycemic Agents in Kidney Disease

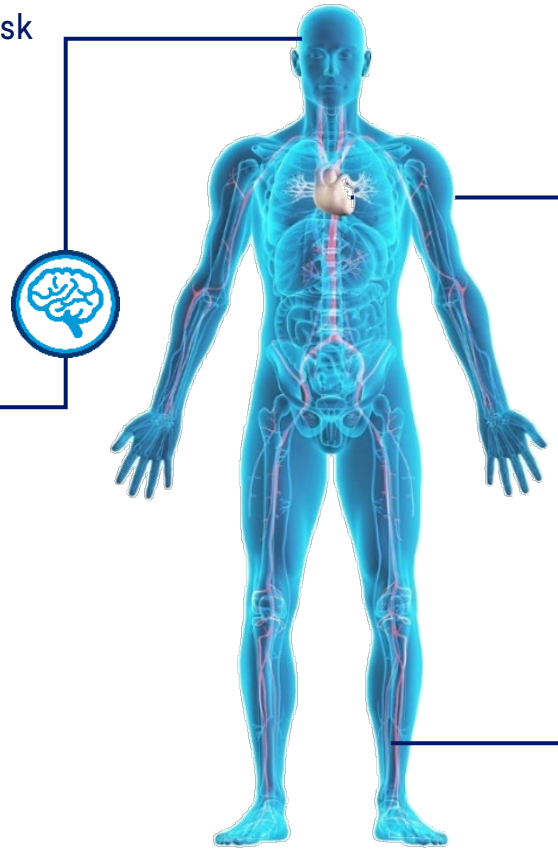
Class: Medication(s) 5	Kidney Disease Recommendation
Amylin analog: pramlintide	Not recommended for CKD stage ≥4
Biguanide: metformin	GFR ‹45 avoid initiation of drug, for existing users does reduce to maximum 500mg twice daily; GFR ‹30 use contraindicated
Bile acid sequestrant: colesevelam	No dosage adjustment
Dopamine-2 agonist: bromocriptine	Use with caution
DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin	Reduce dosage for alogliptin, saxagliptin and sitagliptin if CrCl ‹50 mg/dL
Glinides: nateglinide, repaglinide	Start at lowest effective dose if GFR ‹30 mL/min/1.73 m^2
GLP-1 receptor agonists: albiglutide, dugalutide, exenatide, exenatide XR, liraglutide	Albiglutide has been removed from the market Dugalutide not recommended for kidney adjustment Exenatide not recommended with GFR ‹30 mL/min/ ; Exenatide XR not recommended for GFR ‹45
α-Glucosidase inhibitors: acarbose, miglitol	Avoid if GFR ‹25 (miglitol) or ‹30 (acarbose) mL/min/1.73 m^2
Insulin: aspart, degludec, detemir, glargine, glulisine, lispro, NPH, regular	Adjust dose based on patient response
SGLT inhibitors: canagliflozin, dapagliflozin, empagliflozin	Ineffective if GFR ‹30 mL/min/1.73 m^2
Sulfonylureas: glimepiride, glipizide, glyburide	No dose adjustment for glipizide; start glimepiride conservatively; avoid glyburide and all other SUs
Thiazolidinediones: pioglitazone, rosiglitazone	No dosage adjustment

Cardiovascular complications are the main cause of mortality in diabetes

Patients with microvascular complications due to T2D are more likely to have a major CV event[1]

Hyperglycaemia has a causal effect on the risk of major CV events[2]

Chronic hyperglycaemia is associated with low-grade inflammation and accelerated atherosclerosis[3]



Brain

4x

higher risk of coronary artery disease and stroke[4]

For every 1% increase in HbA_{1c}, the risk of stroke is increased by up to

30%[5]

Heart

2/3

of deaths in T2D are attributable to CV disease[7]

2–6x higher risk of mortality from CV events[8]

2.5x

higher risk of developing congestive heart failure[9]

PAD

1/3

of patients with T2D over 50 years of age have PAD. This increases the risk of heart attack and stroke[6]

Macrovascular Risk Reduction in Type 2 Diabetes

- Hypertension control
- Dyslipidemia control
- Smoking cessation
- Glycemic control
- Aspirin therapy
- Lifestyle modification
- Weight loss

Medications for T2D with CV Benefit

SGLT2 Inhibitors	GLP-1 RAs
Oxidative stress-induced endothelial cell dysfunction	Oxidative stress-induced endothelial cell dysfunction
Inflammation and atherogenesis	Inflammation and atherogenesis
Glucose lowering effect	Glucose lowering effect
Natriuretic / diuretic effect	Natriuretic / diuretic effect
RAAS effect	RAAS effect
Uriscosuric effect	
Beta hydroxybutyrate increase	

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

Currently available drugs:

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)

SGLT2 inhibitors

Physiological actions

- Selectively blocks the SGLT2 transporter responsible for › 90% of glucose reabsorption in the nephron.
- Reduced absorption of glucose and sodium, leads to glycosuria and natriuresis.
- Greatest rate of glycosuria occurs during periods of hyperglycemia.
- Minimal risk of hypoglycemia as the action is independent of insulin

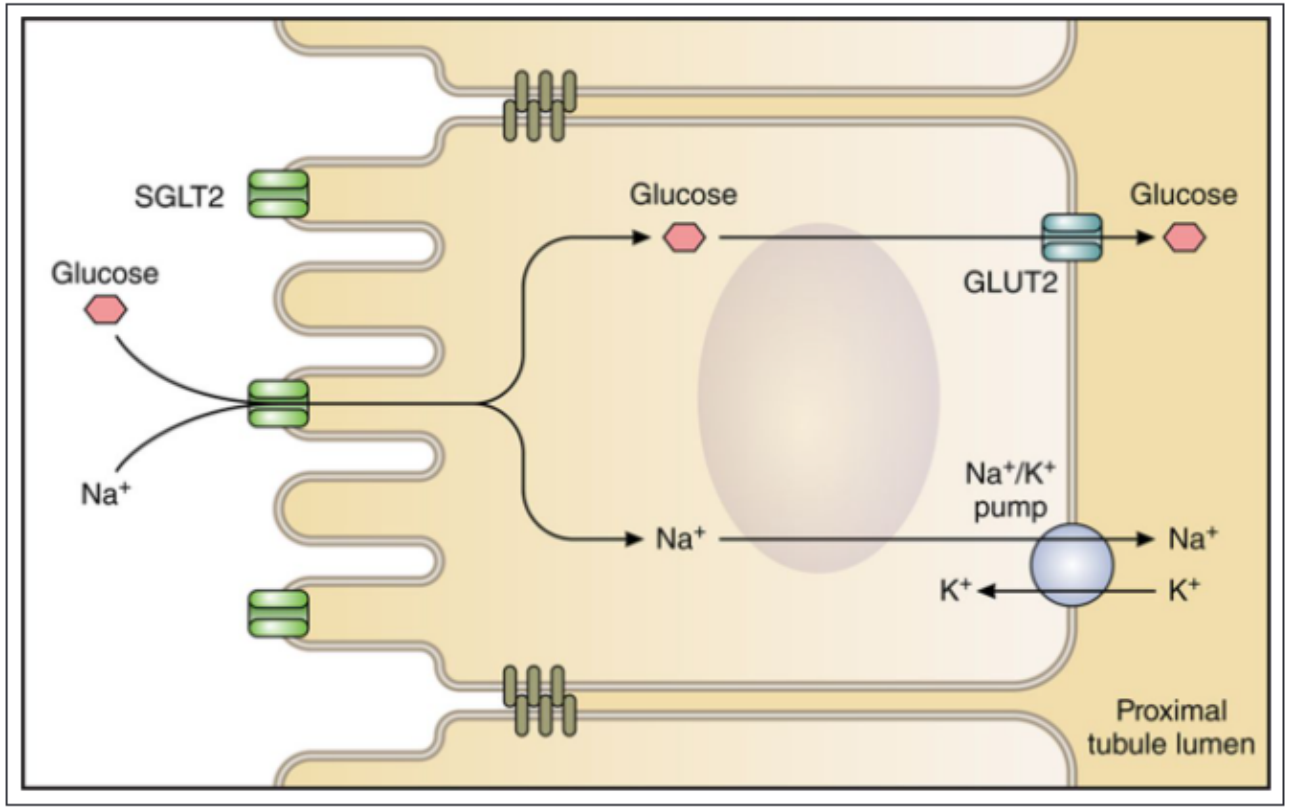


Figure 1. The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule. Modified from Bakris et al[4] with permission of the publisher. Copyright © 2009, Elsevier.

SGLT2 Inhibitors

Mechanisms for Cardioprotection

- Reduce preload and afterload segment
- Improved profile of anti-inflammatory vs. pro-inflammatory cytokine
- Reduced cardiac fibrosis
- Increased hematocrit and erythropoietin production
- Increased cardiac metabolic efficiency

Mechanisms for Renoprotection

- Glycosuria
- Natriuresis
- Decreased glomerular pressure
- Reduced albuminuria

SGLT2 Inhibitors

Summary of CV outcome trials

	MACE HR (95%CI)	CV Death HR (95%CI)	HHF HR (95%CI)
EMPA-REG (empagliflozin)	0.86 (0.74-0.99)	0.62 (0.49-0.77)	0.65 (0.50-0.85)
CANVAS (canagliflozin)	0.86 (0.75-0.97)	0.87 (0.72-1.06)	0.67 (0.52-0.87)
DECLARE-TIMI (dapagliflozin)	0.93 (0.84-1.03)	0.98 (0.82-1.17)	0.73 (0.61-0.88)
VERTIS-CV (ertugliflozin)	0.97 (0.85-1.11)	0.92 (0.77-1.11)	0.70 (0.54-0.90)

MACE = composite of death from CV cause, nonfatal MI and nonfatal stroke
CV death = cardiovascular death
HHF = hospitalization for heart failure

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

Currently available drugs:

- Exenatide (Byetta, Bydureon)
- Liraglutide (Victoza)
- Lixisenatide (Adlyxin, component of Soliqua)

  (Available in US as a fixed ratio combination drug)
- Semaglutide (Ozempic, Rybelsus)
- Dulaglutide (Trulicity)

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

Mechanisms for Cardioprotection

- GLP-1 receptor is also expressed in cardiomyocytes and coronary endothelial cells

Mechanisms for Renoprotection

- Increased natriuresis
- Increased diuresis
- Blood glucose lowering
- Blood pressure lowering effects
- Decreased insulin levels
- Weight loss

GLP-1 RA: Summary of CV Outcome Trials

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

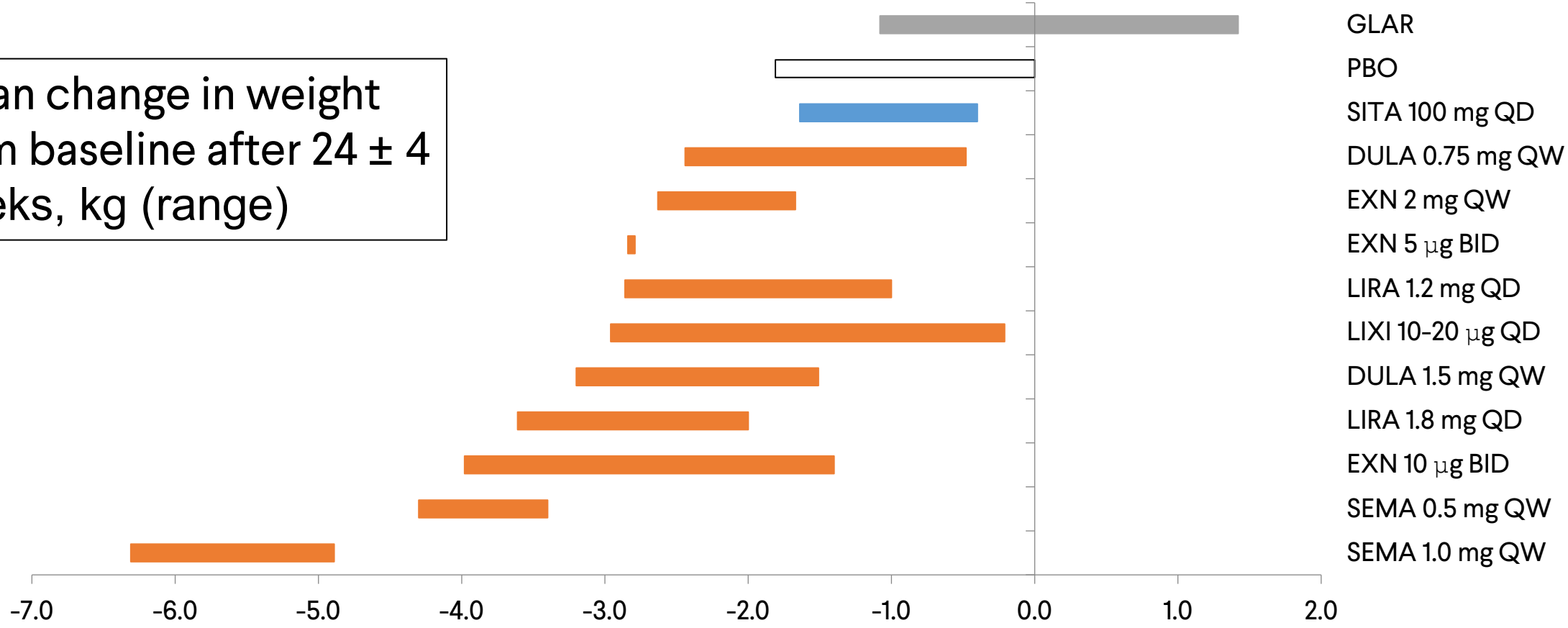
Improved Renal Outcomes in GLP-1 RA and SGLT2 Inhibitor Trials

Study	Intervention	HR (95% CI)	P-value
LEADER[1,a]	Liraglutide	0.78 (0.67, 0.92)	0.003
SUSTAIN 6[2,b]	Semaglutide	0.64 (0.46, 0.88)	0.005
EMPA-REG OUTCOME[3,c]	Empagliflozin	0.61 (0.53, 0.70)	‹ 0.001
CANVAS[4,d]	Canagliflozin	0.60 (0.47, 0.77)	
DAPA-CKD[5,e]	Dapagliflozin	0.56 (0.45, 0.68)	‹ 0.001
CREDENCE[6,f]	Canagliflozin	0.70 (0.59, 0.82)	‹ 0.001

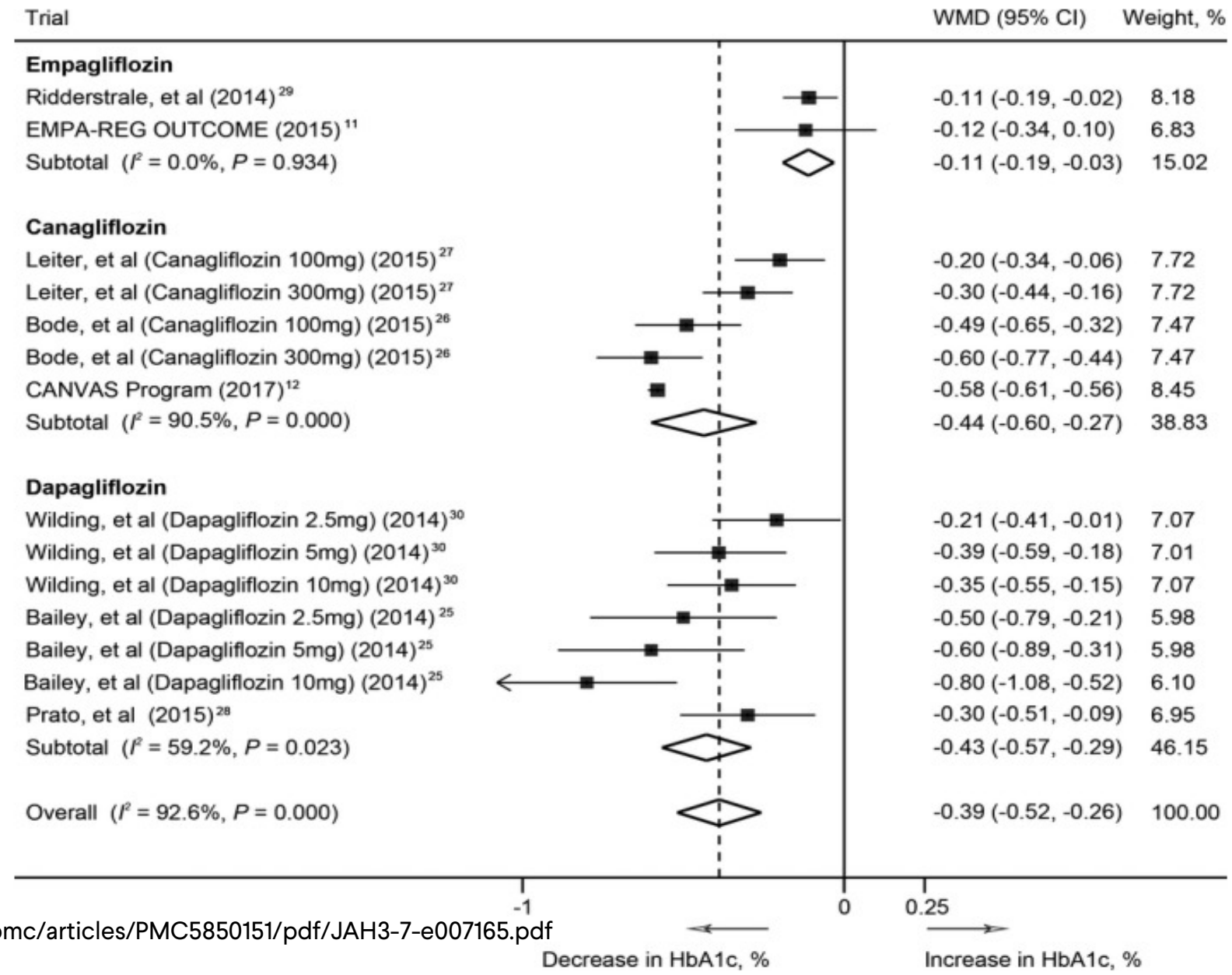
Composite Renal Outcomes: [a]Macroalbuminuria, doubling of serum creatinine, and eGFR ≤45 mL/min/1.73 m^2, ESRD, or renal death; [b]Macroalbuminuria, doubling of serum creatinine, and eGFR ≤45 mL/min/1.73 m^2 or need for continuous renal replacement therapy; [c]Macroalbuminuria, doubling of serum creatinine level, eGFR ≤45 mL/min/1.73 m^2, initiation of renal-replacement therapy or renal death; [d]40% reduction in eGFR, ESRD, or renal death; [e] sustained decline in eGFR ≥ 50%, ESRD, or death from renal causes; [f] doubling of serum creatinine, ESRD (GFR ‹15 mL/min/1.73 m^2, dialysis or transplant), renal death or CV death.

GLP-1 RAs Added to 1-2 Oral Agents: Weight Effects

Mean change in weight from baseline after 24 ± 4 weeks, kg (range)



[a] Systematic review of 41 randomized controlled clinical trials



Meta-analyses of effects of SLGT2 inhibitors vs Control on HbA1C levels.

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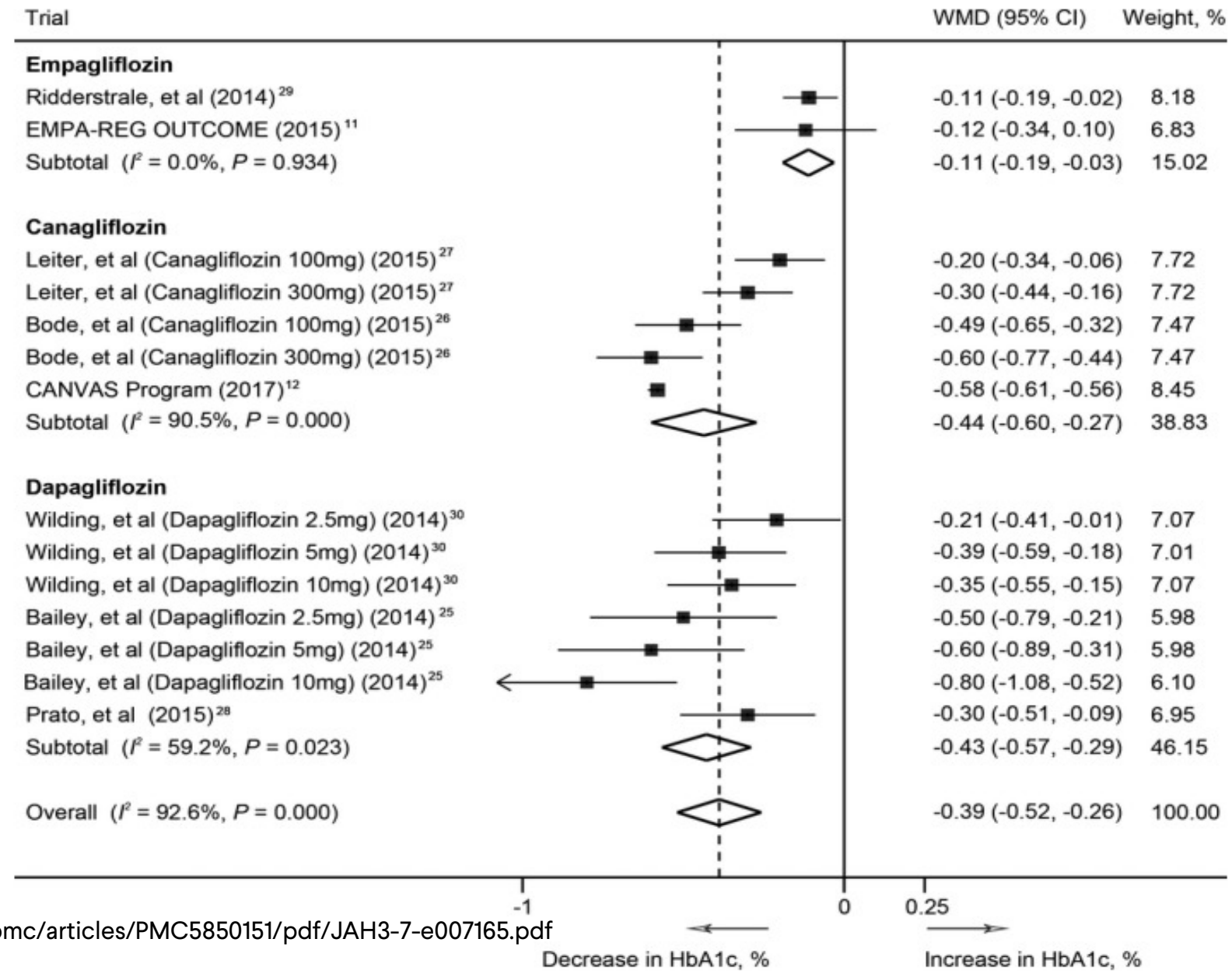


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850151/pdf/JAH3-7-e007165.pdf

GLP-1 RAs and Cognitive Impairment

	Dulaglutide (REWIND Trial) [a]	Liraglutide [b]
Primary Cognitive Outcome	≥ 1.5 SDs on MoCA or DSST below the baseline mean score	Change in neuropsychological assessment (attention, memory, and executive control) after achievement of target weight loss
Trial Findings	Baseline MoCA score: 25 Baseline DSST score: 37 HI 0.86 (95% CI 0.79, 0.95; P = .0018)*	Mean Di8git Span Z score: -0.06 to 0.80, P = .024 Mean memory composite z-score: -0.67 to 0.032, P = .0065
Conclusions	Patients on dulaglutide had a 14% reduction in substantive cognitive impairment	Liraglutide might slow down memory function decline in diabetes patients early, and possibly preclinical stages of the disease

*After post hocadjustment for individual standardized baseline scores.

[a]. Cukierman-Yaffe T, et al. Lancet Neurol. 2020; 19:582-590

[b]. Vandini E, et al. Int J Obes (Lond). 2020;44:1254-1263.

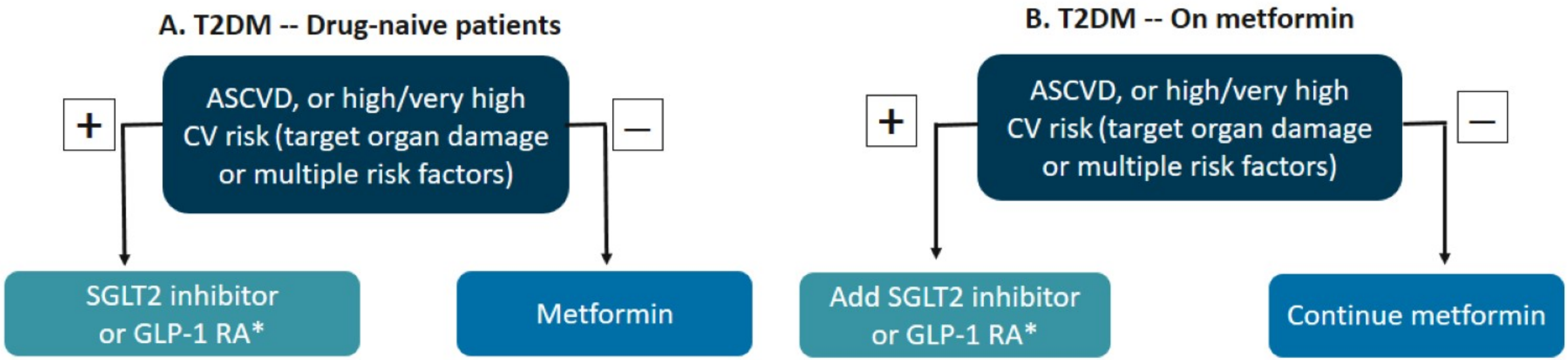
Drug selection: SGLT2 inhibitor vs. GLP1-RA

AACE/ADA/EASD/ACC

- Can begin with metformin monotherapy for DM2, but consider adding GLP-1 RA or SGLT2 inhibitor independent of HbA1c target.
- Can consider beginning therapy with GLP-1 RA or SGLT2 inhibitor prior to metformin in patients with higher cardiovascular risk.

- **If atherosclerotic CVD or stroke predominates:**
  Choose GLP-1 RA with proven benefit
- **If heart failure or CKD predominates:**
  Choose SGLT2 inhibitor with proven benefit

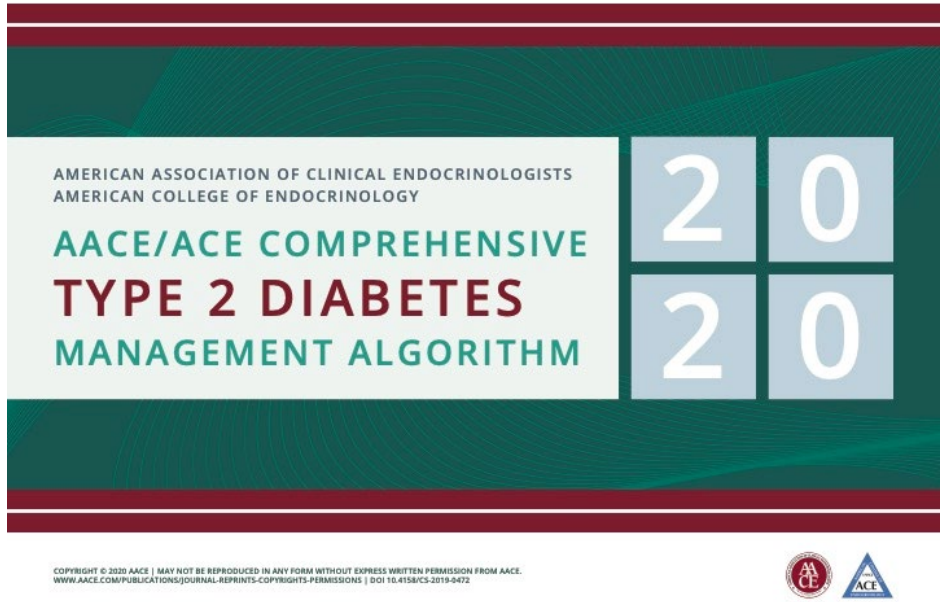
ESC/EASD Guidelines: Novel Glucose-Lowering Drugs

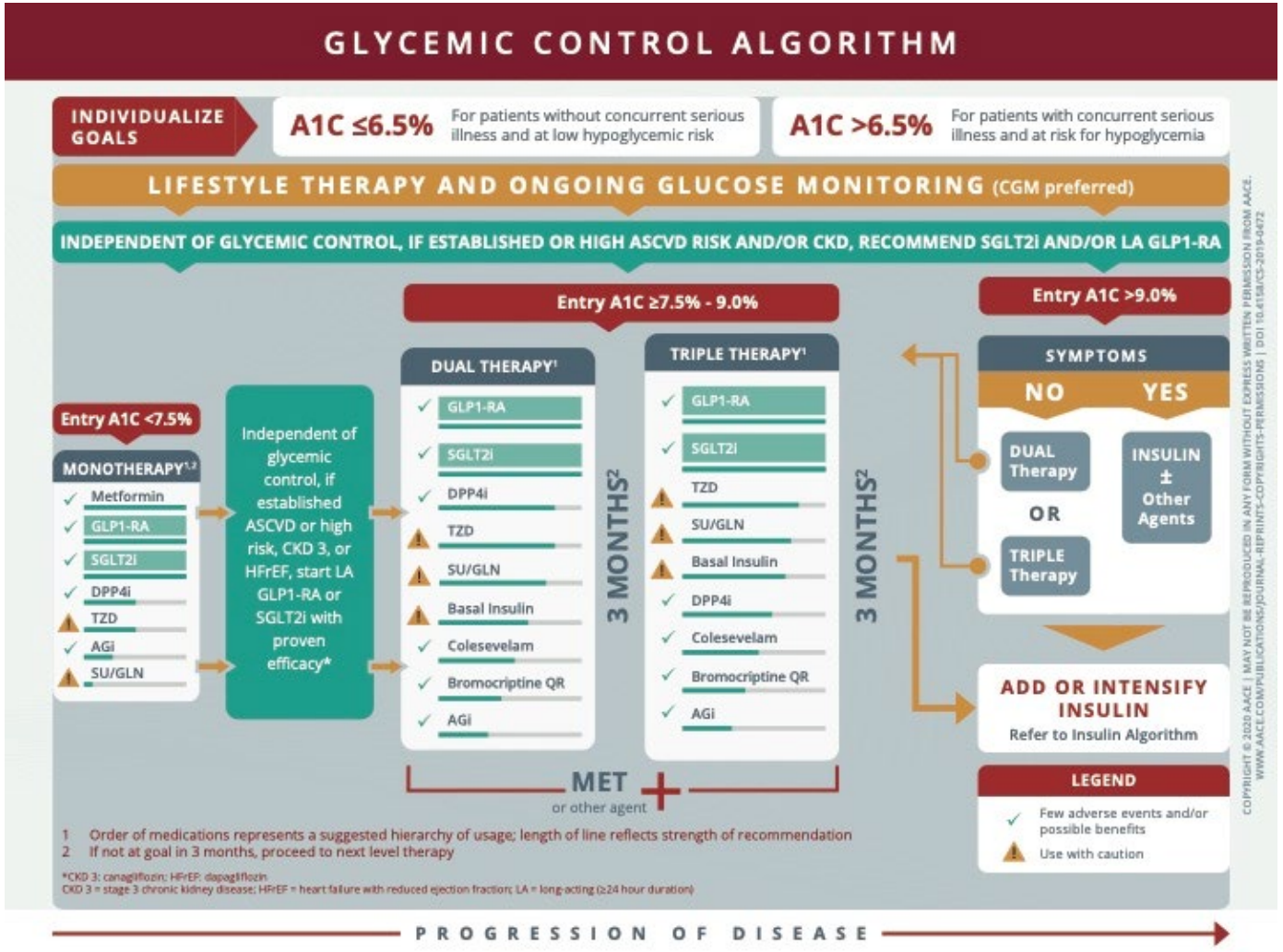


Very high CV risk	High CV risk
Patients with DM and established CVD • or other target organ damage† • or three or more major risk factors‡ • or early onset T1DM of long duration (> 20 years)	Patients with DM duration ≥ 10 years without target organ damage plus any other additional risk factor

*Use drugs with proven CVD benefit.
†Proteinuria, renal impairment defined as eGFR < 30 mL/min/1.73 m^2, LVH, or retinopathy.
‡Age, hypertension, dyslipidemia, smoking, obesity.
Cosentino F, et al. *Eur Heart J.* 2020;41:255-323.

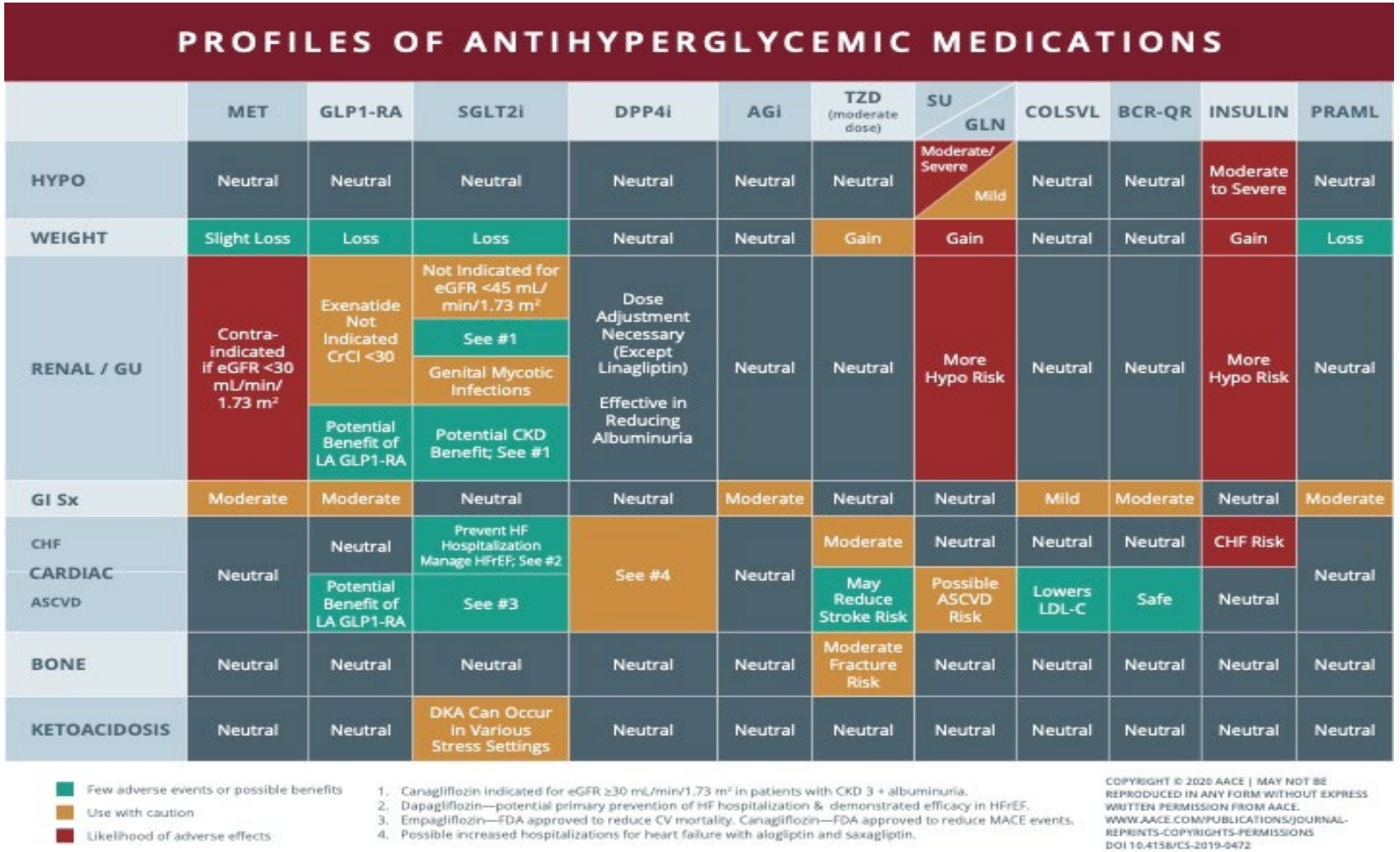
AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm





AACE/ACE Comprehensive Type 2 Diabetes Algorithm App. American Association of Clinical Endocrinologists (AACE) 25th Annual Scientific & Clinical Congress, May 25-29, 2016. Orlando, FL.

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm



PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m²	Exenatide Not Indicated CrCl <30; Potential Benefit of LA GLP1-RA	Not Indicated for eGFR <45 mL/min/1.73 m²; See #1; Genital Mycotic Infections; Potential CKD Benefit; See #1	Dose Adjustment Necessary (Except Linagliptin); Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Prevent HF Hospitalization Manage HFrEF; See #2	See #4	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD		Potential Benefit of LA GLP1-RA	See #3			May Reduce Stroke Risk	Possible ASCVD Risk	Lowers LDL-C	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

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

1. Canagliflozin indicated for eGFR ≥30 mL/min/1.73 m² in patients with CKD 3 + albuminuria.
2. Dapagliflozin—potential primary prevention of HF hospitalization & demonstrated efficacy in HFrEF.
3. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
4. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

DOI 10.4158/CS-2019-0472

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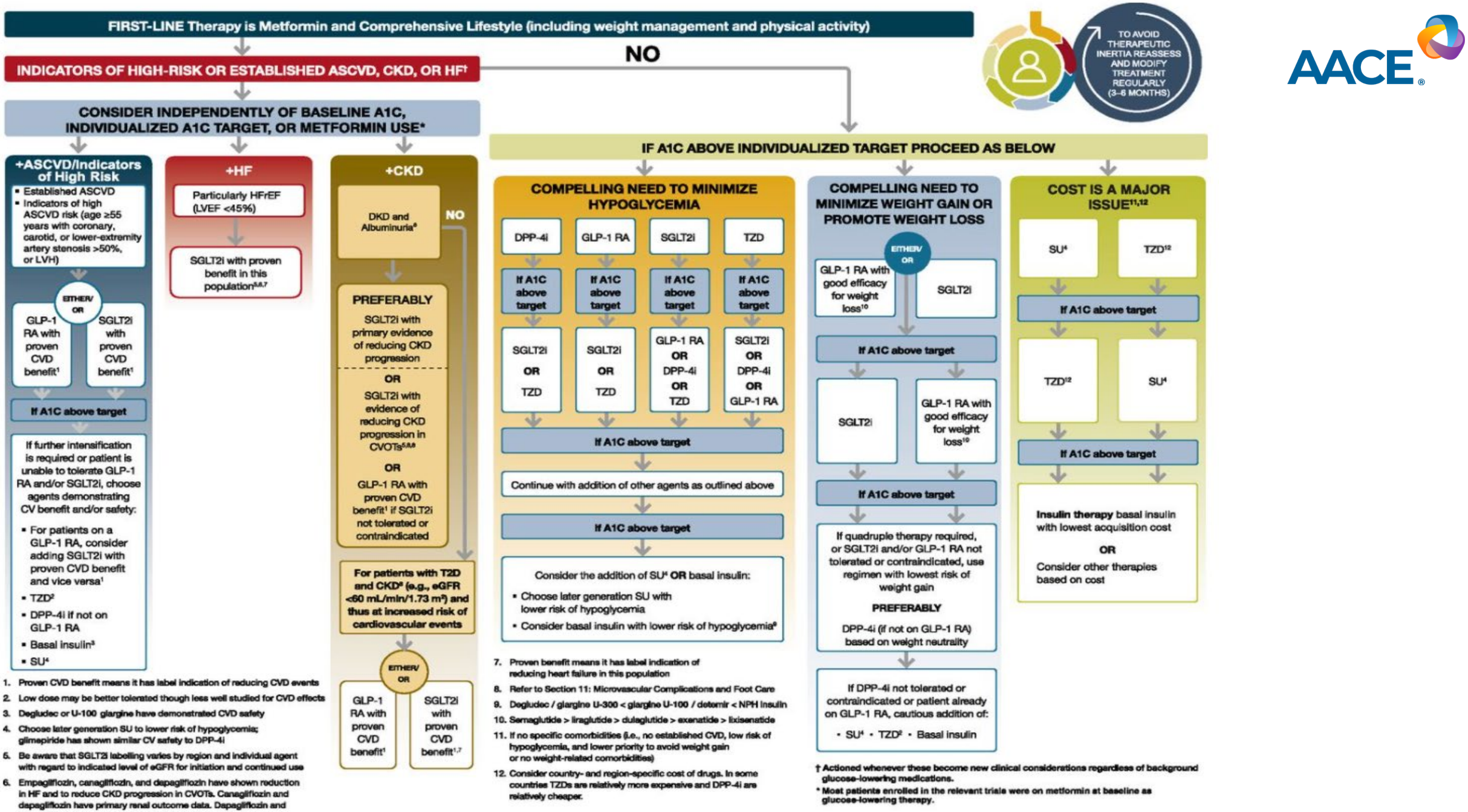

1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Medication Access/Medication Cost

- Despite promising data described above, many patients are unable to utilize these classes of medications due to high cost involved and economic hardship.
- Uninsured patients, and even some insured patients, with high copays or deductibles may be limited in their ability to obtain diabetes medications with the best profiles for organ protection.
- Often a particular insurance company will only cover one agent within a particular class so ability to select a specific drug may be limited.
- Be aware of limitations when prescribing and consider options for cost-reduction or alternative medications if cost remains prohibitive.

Conclusions

Diabetes is a multifactorial disease

Many people with T2DM have ASCVD, kidney disease, and/or HF

Role for PCPs, cardiologists, nephrologists, and diabetologists in risk management for T2DM and CVD, or CKD, or risk factors

We can prevent progression of diabetes complications

Latest guidelines recommend SGLT2 inhibitors and GLP-1 RAs for organ protection in individualized diabetes care

Novel glucose-lowering drugs have a role beyond T2DM: in HF, ASCVD, and kidney disease

References

Slide 5: Skyler JS. Diabetic complications. The importance of glucose control. Endocrinol Metab Clin North Am. 1996 Jun;25(2):243-54.

Slide 6: CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

Slide 6: Plantinga LC, Crews DC, Coresh J, Miller ER 3rd, Saran R, Yee J, Hedgeman E, Pavkov M, Eberhardt MS, Williams DE, Powe NR; CDC CKD Surveillance Team. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol. 2010 Apr;5(4):673-82.

Slide 7: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53. Erratum in: Lancet 1999 Aug 14;354(9178):602.

Slide 7: ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.

Slide 7: Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010 Aug 7;376(9739):419-30.

Slide 8: Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405-12.

References

Slide 9: American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care. 2017 Jan;40(Suppl 1):S64-S74. doi: 10.2337/dc17-S011. Erratum in: Diabetes Care. 2017 Jul;40(7):985.

Slide 9 Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, Blonde L, Bray GA, Cohen AJ, Dagogo-Jack S, Davidson JA, Einhorn D, Ganda OP, Garber AJ, Garvey WT, Henry RR, Hirsch IB, Horton ES, Hurley DL, Jellinger PS, Jovanovič L, Lebovitz HE, LeRoith D, Levy P, McGill JB, Mechanick JI, Mestman JH, Moghissi ES, Orzeck EA, Pessah-Pollack R, Rosenblit PD, Vinik AI, Wyne K, Zangeneh F. American Association of Clinical Endocrinologists and American College of Endocrinology - Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1(Suppl 1):1-87.

Slide 9: National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012 Nov;60(5):850-86. doi: 10.1053/j.ajkd.2012.07.005. Erratum in: Am J Kdney Dis. 2013 Jun;61(6):1049.

Slide 10: Brownrigg JR, Hughes CO, Burleigh D, Karthikesalingam A, Patterson BO, Holt PJ, Thompson MM, de Lusignan S, Ray KK, Hinchliffe RJ. Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study. Lancet Diabetes Endocrinol. 2016 Jul;4(7):588-97.

Slide 10: Ross S, Gerstein HC, Eikelboom J, Anand SS, Yusuf S, Paré G. Mendelian randomization analysis supports the causal role of dysglycaemia and diabetes in the risk of coronary artery disease. Eur Heart J. 2015 Jun 14;36(23):1454-62.

Slide 10: Mannucci E, Dicembrini I, Lauria A, Pozzilli P. Is glucose control important for prevention of cardiovascular disease in diabetes? Diabetes Care. 2013 Aug;36 Suppl 2(Suppl 2):S259-63.

Slide 10: Lüscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part II. Circulation. 2003 Sep 30;108(13):1655-61.

Slide 10: Chen YY, Lin YJ, Chong E, Chen PC, Chao TF, Chen SA, Chien KL. The impact of diabetes mellitus and corresponding HbA1c levels on the future risks of cardiovascular disease and mortality: a representative cohort study in Taiwan. PLoS One. 2015 Apr 13;10(4):e0123116.

References

Slide 10: Diabetes UK website. Available at: https://www.diabetes.co.uk/diabetes-complications/peripheral-arterial-disease.html Accessed May 2019.
Slide 10: Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. Circulation. 2016 Jun 14;133(24):2459-502.
Slide 10: Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012 Dec 18;60(24):e44-e164.
Slide 10: Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care. 2004 Aug;27(8):1879-84.

References

Slide11: Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, Blonde L, Bray GA, Cohen AJ, Dagogo-Jack S, Davidson JA, Einhorn D, Ganda OP, Garber AJ, Garvey WT, Henry RR, Hirsch IB, Horton ES, Hurley DL, Jellinger PS, Jovanovič L, Lebovitz HE, LeRoith D, Levy P, McGill JB, Mechanick JI, Mestman JH, Moghissi ES, Orzeck EA, Pessah-Pollack R, Rosenblit PD, Vinik AI, Wyne K, Zangeneh F. American Association of Clinical Endocrinologists and American College of Endocrinology - Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1(Suppl 1):1-87.

Slide 14: Garcia-Ropero A, Badimon JJ, Santos-Gallego CG. The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments. Expert Opin Drug Metab Toxicol. 2018 Dec;14(12):1287-1302.

Slide 14: Hiddo J.L. Heerspink, PharmD, PhD, Bruce A. Perkins, MD, MPH, David H. Fitchett, MD, Mansoor Husain, MD, and David Z. I. Cherney, MD, PhD. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus. Circulation Volume 134, Issue 10, 6 September 2016, Pages 752-772 .

Slide 15: North, Emily J.; Newman, Jonathan D. Review of cardiovascular outcomes trials of sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, Current Opinion in Cardiology: November 2019 - Volume 34 - Issue 6 - p 687-692.

Slide 16: Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.

Slide 16: Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657.

References

Slide 16: Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357.

Slide 16: Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK; VERTIS CV Investigators. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. 2020 Oct 8;383(15):1425-1435.

Slide 17: Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22.

Slide 17: Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844.

Slide17: Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.

Slide 17: Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657.

Slide17: S. Bangalore, D.J. Maron, S.M. O'Brien, J.L. Fleg, E.I. Kretov, C. Briguori, U. Kaul, H.R. Reynolds, T. Mazurek, M.S. Sidhu, J.S. Berger, R.O. Mathew, O. Bockeria, S. Broderick, R. Pracon, C.A. Herzog, Z. Huang, G.W. Stone, W.E. Boden, J.D. Newman, Z.A. Ali, D.B. Mark, J.A. Spertus, K.P. Alexander, B.R. Chaitman, G.M. Chertow, and J.S. Hochman, for the ISCHEMIA-CKD Research Group.* Management of Coronary Disease in Patients with Advanced Kidney Disease. N Engl J Med 2020;382:1608-18.

References

Slide 18: Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.

Slide 19: North, Emily J.; Newman, Jonathan D. Review of cardiovascular outcomes trials of sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, Current Opinion in Cardiology: November 2019 - Volume 34 - Issue 6 - p 687-692.

Slide 19: Drucker DJ. The Cardiovascular Biology of Glucagon-like Peptide-1. Cell Metab. 2016 Jul 12;24(1):15-30.

Slide 19: Heuvelman VD, Van Raalte DH, Smits MM. Cardiovascular effects of glucagon-like peptide 1 receptor agonists: from mechanistic studies in humans to clinical outcomes. Cardiovasc Res. 2020 Apr 1;116(5):916-930.

Slide 19: Rowlands J, Heng J, Newsholme P, Carlessi R. Pleiotropic Effects of GLP-1 and Analogs on Cell Signaling, Metabolism, and Function. Front Endocrinol (Lausanne). 2018 Nov 23;9:672.

Slide 20: Cardiovasc Res, Volume 116, Issue 5, 1 April 2020, Pages 916–930, https://doi.org/10.1093/cvr/cvz323

Slide 20: Drucker DJ. The Cardiovascular Biology of Glucagon-like Peptide-1. Cell Metab. 2016 Jul 12;24(1):15-30.

Slide 20: Heuvelman VD, Van Raalte DH, Smits MM. Cardiovascular effects of glucagon-like peptide 1 receptor agonists: from mechanistic studies in humans to clinical outcomes. Cardiovasc Res. 2020 Apr 1;116(5):916-930.

Slide 22: Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC, McMurray JJ. 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. The lancet Diabetes & endocrinology. 2019 Oct 1;7(10):776-85.

References

Slide 23: Witkowski M, Wilkinson L, Webb N, Weids A, Glah D, Vrazic H. A Systematic Literature Review and Network Meta-Analysis Comparing Once-Weekly Semaglutide with Other GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Previously Receiving 1-2 Oral Anti-Diabetic Drugs. Diabetes Ther. 2018 Jun;9(3):1149-1167.
Slide 24: Witkowski M, Wilkinson L, Webb N, Weids A, Glah D, Vrazic H. A Systematic Literature Review and Network Meta-Analysis Comparing Once-Weekly Semaglutide with Other GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Previously Receiving 1-2 Oral Anti-Diabetic Drugs. Diabetes Ther. 2018 Jun;9(3):1149-1167.
Slide26: Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020 Feb;43(2):487-493.
Slide 31: American Diabetes Association. 1. Improving Care and Promoting Health in Populations: *Standards of Medical Care in Diabetes-2020*. Diabetes Care. 2020 Jan;43(Suppl 1):S7-S13.
Slide 26: Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.
Slide 26: AACE/ACE Comprehensive Type 2 Diabetes Algorithm App. American Association of Clinical Endocrinologists (AACE) 25th Annual Scientific & Clinical Congress, May 25-29, 2016. Orlando, FL.

References

Slide 28: Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, Blonde L, Bush MA, DeFronzo RA, Garber JR, Garvey WT, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Perreault L, Rosenblit PD, Samson S, Umpierrez GE. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - *2020 EXECUTIVE SUMMARY*. Endocr Pract. 2020 Jan;26(1):107-139.

Slide 29: Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, Blonde L, Bush MA, DeFronzo RA, Garber JR, Garvey WT, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Perreault L, Rosenblit PD, Samson S, Umpierrez GE. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - *2020 EXECUTIVE SUMMARY*. Endocr Pract. 2020 Jan;26(1):107-139.