"Diabetes Management Strategies in 2019: A Patient-Centered Approach"

Grazia Aleppo, MD, FACE, FACP

Professor of Medicine

Feinberg School of Medicine

Northwestern University

NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

Disclosures

- Research Support

- Astra-Zeneca
- Dexcom
- Eli Lilly
- Novo Nordisk

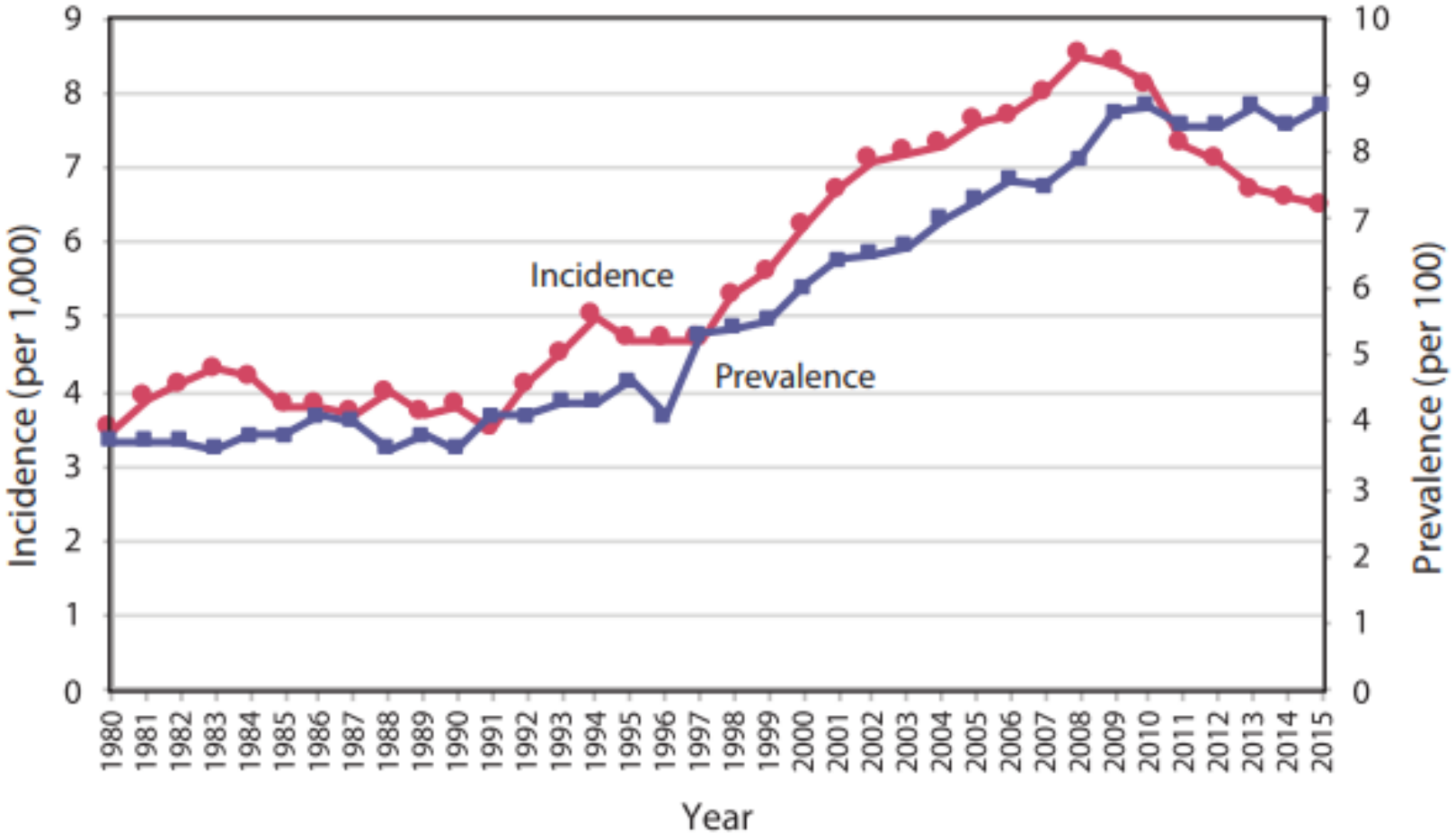
- Consultant

- Dexcom
- Insulet
- Medtronic
- Novo Nordisk

Learning Objectives

- Use available algorithms for Diabetes management based on comorbidities
- Examine challenges of medication cost and the search for suitable alternatives
- Compare strategies to personalize diabetes treatment

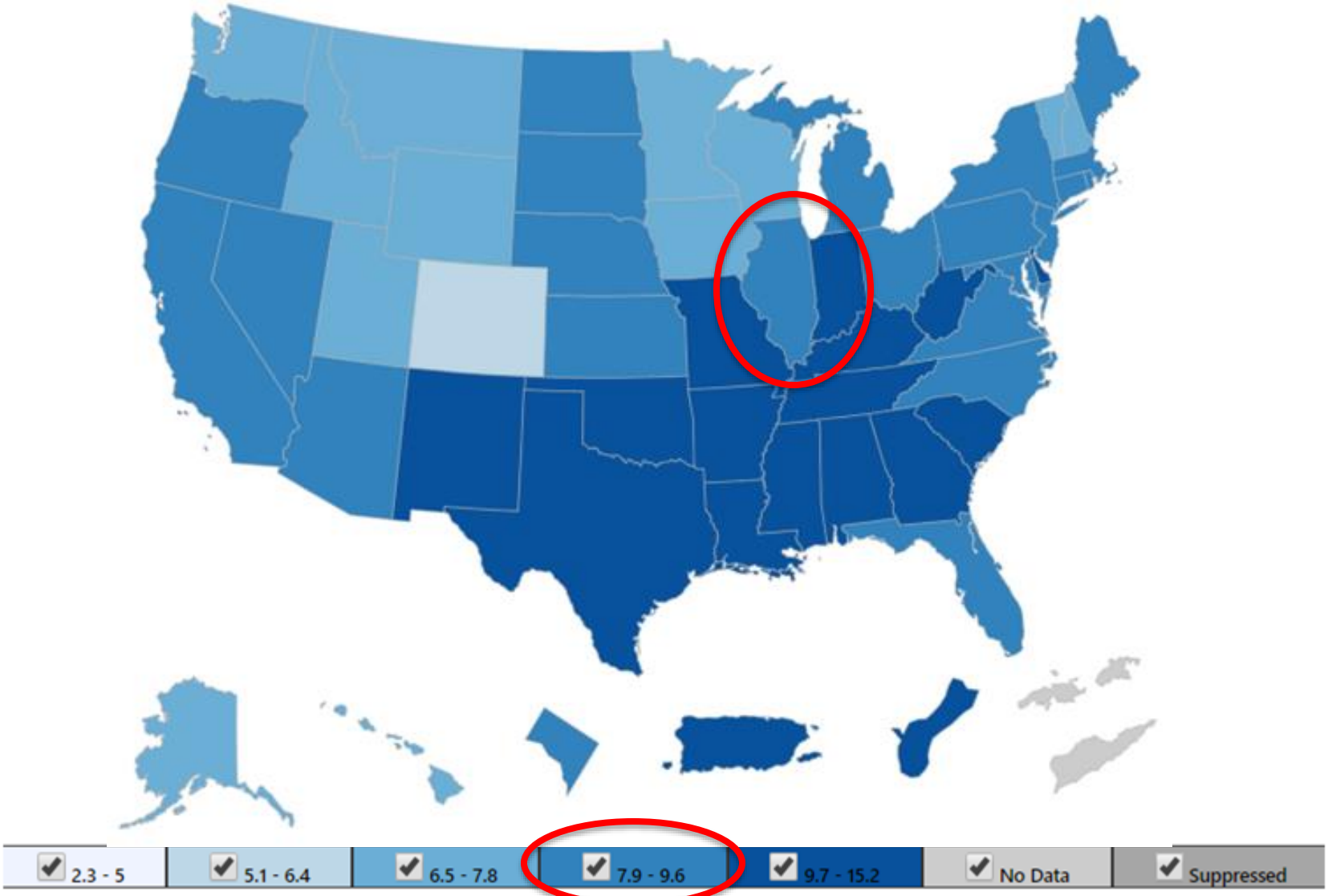
Incidence and Prevalence of Diagnosed DM 1980-2015



www.cdc.gov/diabetes/library/reports/congress.html 2017

Diagnosed Diabetes

(Age-adjusted Percentage Adults, 2015)

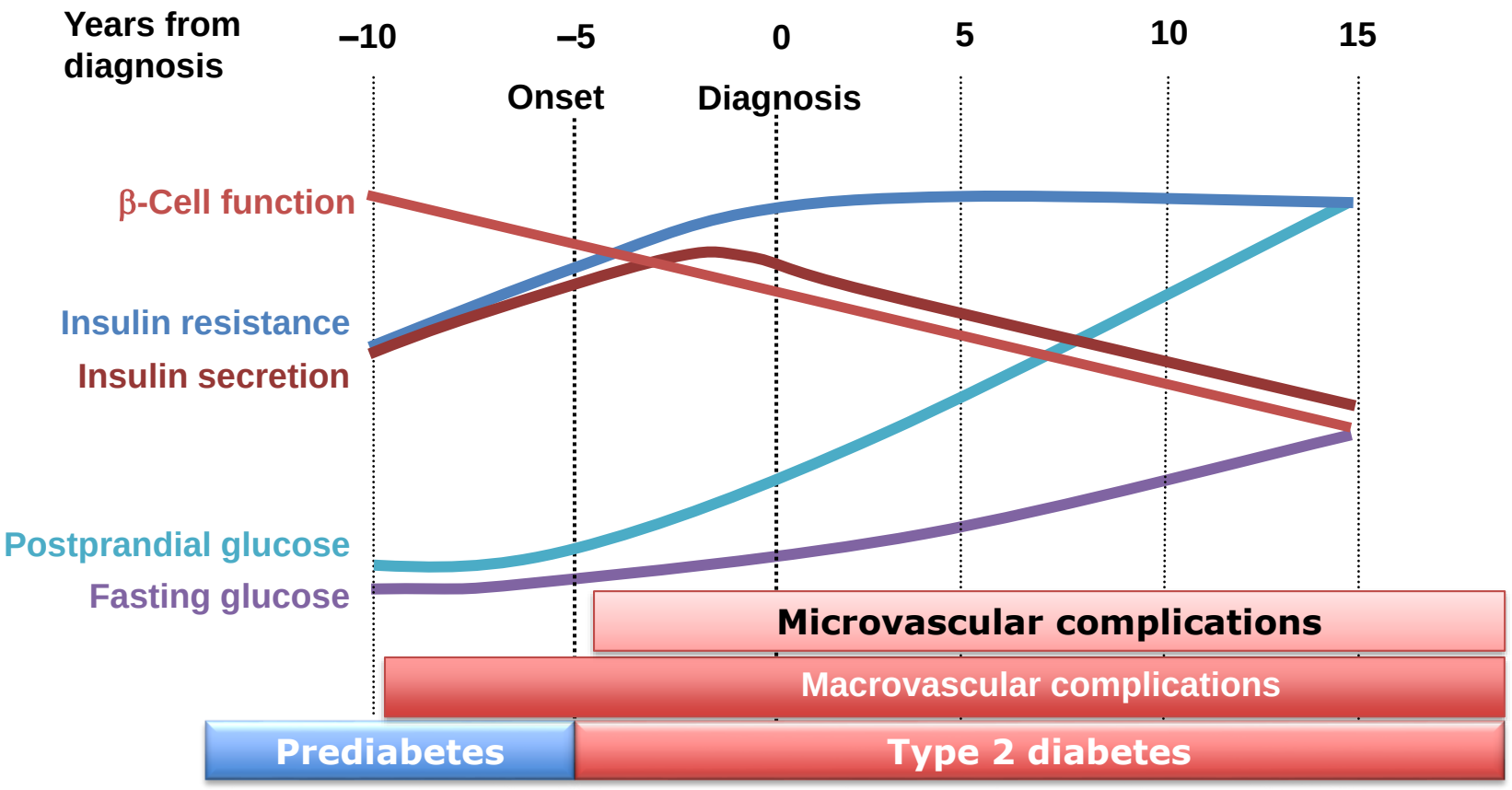


http://www.cdc.gov/surveillancepractice/reports/brfss/brfss.html

Primary Care Challenges

- Complexity of patient (more than just Diabetes)
- Time spent with patient (average 15 minutes)
- Support staff challenges
- Diabetes Education access/utilization
- Cost of medications

Natural History of Type 2 Diabetes



Adapted from Holman RR. *Diabetes Res Clin Pract*. 1998;40(suppl):S21-S25;
Ramlo-Halsted BA, Edelman SV. *Prim Care*. 1999;26:771-789;
Nathan DM. *N Engl J Med*. 2002;347:1342-1349;
UKPDS Group. *Diabetes*. 1995;44:1249-1258

Figure courtesy of CADRE, AACE

Screening for Diabetes Asymptomatic Individual

- Any Adult ≥45 years of age
- Adults of any age overweight OR obese (BMI >25 kg/m^{2}or >23 kg/m^{2}in Asian Americans) with ≥1 risk factors
- Repeat every 3 years if normal, yearly if Pre-Diabetes is present

ADA Standard of Medical Care in Diabetes. Diabetes Care;2019

Diabetes Risk Factors

- First-degree relative with Diabetes
- High-risk race/ethnicity (AA, Lat-A, N-A, As-A, Pacific I)
- History of CVD
- HTN, BP>140/90 mmHg or on therapy
- HDL <35 mg/dl AND/OR TG >250 mg/dl
- Women with PCOS
- HbA1c $\geq$ 5.7%, IGT or IFG on previous testing
- Women with GDM should be tested lifelong every 3 yrs

ADA Standard of Medical Care in Diabetes. Diabetes Care;2019

ARE YOU AT RISK FOR TYPE 2 DIABETES?

American Diabetes Association.

Diabetes Risk Test

1. **How old are you?**
   Less than 40 years (0 points)
   40—49 years (1 point)
   50—59 years (2 points)
   60 years or older (3 points)

2. **Are you a man or a woman?**
   Man (1 point) Woman (0 points)

3. **If you are a woman, have you ever been diagnosed with gestational diabetes?**
   Yes (1 point) No (0 points)

4. **Do you have a mother, father, sister, or brother with diabetes?**
   Yes (1 point) No (0 points)

5. **Have you ever been diagnosed with high blood pressure?**
   Yes (1 point) No (0 points)

6. **Are you physically active?**
   Yes (0 points) No (1 point)

7. **What is your weight status?** *(see chart at right)*

Write your score in the box.

Height	Weight (lbs.)		
4' 10"	119-142	143-190	191+
4' 11"	124-147	148-197	198+
5' 0"	128-152	153-203	204+
5' 1"	132-157	158-210	211+
5' 2"	136-163	164-217	218+
5' 3"	141-168	169-224	225+
5' 4"	145-173	174-231	232+
5' 5"	150-179	180-239	240+
5' 6"	155-185	186-246	247+
5' 7"	159-190	191-254	255+
5' 8"	164-196	197-261	262+
5' 9"	169-202	203-269	270+
5' 10"	174-208	209-277	278+
5' 11"	179-214	215-285	286+
6' 0"	184-220	221-293	294+
6' 1"	189-226	227-301	302+
6' 2"	194-232	233-310	311+
6' 3"	200-239	240-318	319+
6' 4"	205-245	246-327	328+
	(1 Point)	(2 Points)	(3 Points)

You weigh less than the amount in the left column (0 points)

Adapted from Bang et al., Ann Intern Med 151:775-783, 2009.
Original algorithm was validated without gestational diabetes as part of the model.

Add up your score.

If you scored 5 or higher:
You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes (a condition that precedes type 2 diabetes in which blood glucose levels are higher than normal). Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, American Indians, and Asian Americans and Pacific Islanders.

Higher body weights increase diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weights than the rest of the general public (about 15 pounds lower).

For more information, visit us at diabetes.org or call 1-800-DIABETES (1-800-342-2383)

Lower Your Risk

The good news is that you can manage your risk for type 2 diabetes. Small steps make a big difference and can help you live a longer, healthier life.

If you are at high risk, your first step is to see your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (1-800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Diabetes Mellitus: Diagnosis

- **FPG ≥126 mg/dl * OR**
- **2-h plasma glucose ≥200 mg/dl during an OGTT* OR**
- **A1C ≥6.5%* OR**

- A random plasma glucose ≥200 mg/dl with symptoms
- In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing

*Equally meaningful for diagnosis

ADA Standard of Medical Care in Diabetes. Diabetes Care; 2019

Table 4.1 – Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
1 PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	• Characteristics at onset (e.g., age, symptoms)	✓		
	• Review of previous treatment regimens and response	✓		
	• Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	• Family history of diabetes in a first-degree relative	✓		
	• Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	• Macrovascular and microvascular	✓		✓
	• Common comorbidities (e.g., obesity, OSA)	✓		
	• Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	• Presence of hemoglobinopathies or anemias	✓		
	• High blood pressure or abnormal lipids	✓		✓
	• Last dental visit	✓		✓
	• Last dilated eye exam	✓		✓
	• Visits to specialists	✓	✓	✓
	Interval history			
	• Changes in medical/family history since last visit		✓	✓
2 LIFESTYLE FACTORS	• Eating patterns and weight history	✓	✓	✓
	• Physical activity and sleep behaviors	✓	✓	✓
	• Tobacco, alcohol, and substance use	✓		✓
3 MEDICATIONS AND VACCINATIONS	• Current medication regimen	✓	✓	✓
	• Medication-taking behavior	✓	✓	✓
	• Medication intolerance or side effects	✓	✓	✓
	• Complementary and alternative medicine use	✓	✓	✓
	• Vaccination history and needs	✓		✓
4 TECHNOLOGY USE	• Assess use of health apps, online education, patient portals, etc.	✓		✓
	• Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	• Review insulin pump settings and use	✓	✓	✓
5 BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS	**Psychosocial conditions**			
	• Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓		✓
	• Identify existing social supports	✓		
	• Consider assessment for cognitive impairment*	✓		✓
	Diabetes self-management education and support			
	• History of dietician/diabetes educator visits/classes	✓	✓	✓
	• Assess diabetes self-management skills and barriers	✓		✓
	• Assess familiarity with carbohydrate counting (type 1 diabetes)	✓		
	Pregnancy planning			
	• For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

Table 4.1 (cont.)– Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
6 PHYSICAL EXAMINATION	• Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	• Blood pressure determination	✓	✓	✓
	• Orthostatic blood pressure measures (when indicated)	✓		
	• Fundoscopic examination (refer to eye specialist)	✓		✓
	• Thyroid palpation	✓		✓
	• Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	• Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses–refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
7 LABORATORY EVALUATION	• A1C, if the results are not available within the past 3 months	✓	✓	✓
	• If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate*	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		✓
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics*	✓		✓

7 Components Available on Diabetes Care 2019 Supplement 1, page S38-39

ADA Standard of Medical Care in Diabetes. Diabetes Care; 2019

Diabetes Education

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS	**Psychosocial conditions**			
	▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓		✓
	▪ Identify existing social supports	✓		
	▪ Consider assessment for cognitive impairment*	✓		✓
	Diabetes self-management education and support			
	▪ History of dietician/diabetes educator visits/classes	✓	✓	✓
	▪ Assess diabetes self-management skills and barriers	✓		✓
	▪ Assess familiarity with carbohydrate counting (type 1 diabetes)	✓		

What is covered for DSME:
MEDICARE and Commercial Insurance:
Year 1= 10 hours
1 hour initial assessment
9 hours of group education
Year 2 and more= 2 hours follow up

What is covered for MNT:
MEDICARE and Commercial Insurance:
Year 1= 3 hours

Year 2 and more= 2 hours follow-up

Only 5% of CMS eligible beneficiaries are sent to Diabetes Education

ADA Standard of Medical Care in Diabetes. Diabetes Care; 2019

Diabetes Self-Management Education and Support for Adults with Type 2 Diabetes: **ALGORITHM of CARE**

ADA *Standards of Medical Care in Diabetes* recommends all patients be assessed and referred for:

NUTRITION
Registered dietitian for medical nutrition therapy

EDUCATION
Diabetes self-management education and support

EMOTIONAL HEALTH
Mental health professional if needed

WHEN PRIMARY CARE PROVIDER OR SPECIALIST SHOULD CONSIDER REFERRAL:

FOUR CRITICAL TIMES TO ASSESS, PROVIDE, AND ADJUST DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

1 AT DIAGNOSIS

- ☐ Newly diagnosed. All newly diagnosed individuals with type 2 diabetes should receive DSME/S
- ☐ Ensure that both nutrition and emotional health are appropriately addressed in education or make separate referrals

2 ANNUAL ASSESSMENT OF EDUCATION, NUTRITION, AND EMOTIONAL NEEDS

- ☐ Needs review of knowledge, skills, and behaviors
- ☐ Long-standing diabetes with limited prior education
- ☐ Change in medication, activity, or nutritional intake
- ☐ HbA_{1c} out of target
- ☐ Maintain positive health outcomes
- ☐ Unexplained hypoglycemia or hyperglycemia
- ☐ Planning pregnancy or pregnant
- ☐ For support to attain or sustain behavior change(s)
- ☐ Weight or other nutrition concerns
- ☐ New life situations and competing demands

3 WHEN NEW **COMPLICATING FACTORS** INFLUENCE SELF-MANAGEMENT

CHANGE IN:

- ☐ Health conditions such as renal disease and stroke, need for steroid or complicated medication regimen
- ☐ Physical limitations such as visual impairment, dexterity issues, movement restrictions
- ☐ Emotional factors such as anxiety and clinical depression
- ☐ Basic living needs such as access to food, financial limitations

4 WHEN **TRANSITIONS** IN CARE OCCUR

CHANGE IN:

- ☐ Living situation such as inpatient or outpatient rehabilitation or now living alone
- ☐ Medical care team
- ☐ Insurance coverage that results in treatment change
- ☐ Age-related changes affecting cognition, self-care, etc.

American Diabetes Association. | AADE American Association of Diabetes Educators | eat right. Academy of Nutrition and Dietetics

ADA Targets 2019

HbA1c	**<7.0%**
Pre-prandial capillary plasma glucose	**80–130 mg/dl**
Peak post-prandial capillary plasma glucose	**<180 mg/dl**

- **HbA1c <6.5% or closer to normal without hypoglycemia in patients with short duration of DM, long life expectancy, and no ASCVD**

- **Less stringent A1C goals for**

- Patient with severe hypoglycemia
- Limited life expectancy
- Advanced complications
- Extensive comorbidities

ADA Standard of Medical Care in Diabetes. Diabetes Care;2019

Older Adults Treatment Goals

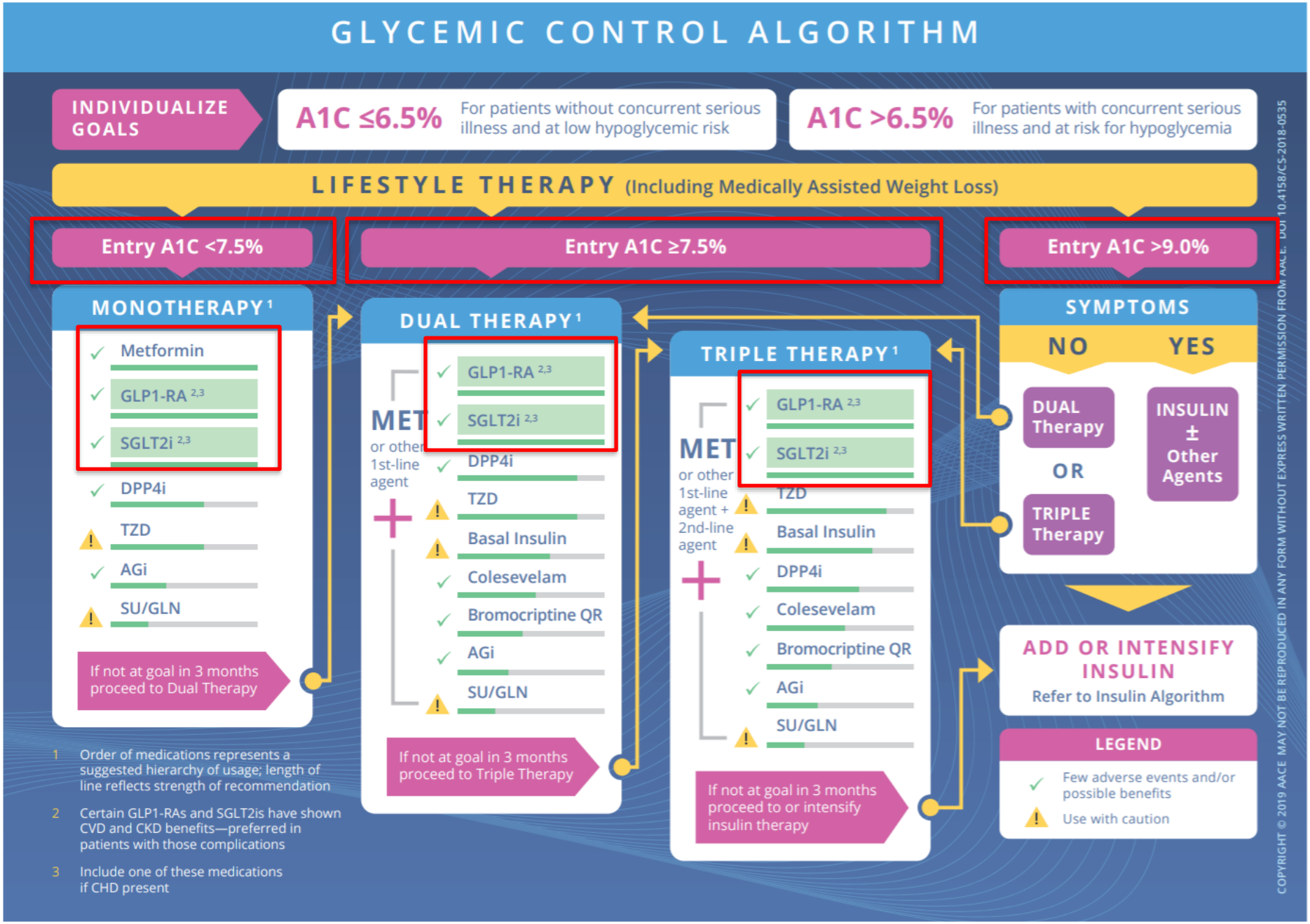
Patient Status	Rationale	HbA1c Goal	BG targets (AM-PM)	BP (mmHg)	Lipids Statin
Healthy	Longer life expectancy	**<7.5%**	**90-130 mg/d** 90-150 mg/dl	<140/90	Yes
Complex/ intermediate	Intermediate	**<8%**	**90-150 mg/dl** 100-180 mg/dl	<140/90	Yes
Very complex	Limited	**<8.5%**	**100-180 mg/dl** 110-200 mg/dl	<150/90	Maybe

ADA Standard of Medical Care in Diabetes. Diabetes Care;2018 40:(S1)1-112

AACE 2019 Principles of type 2 DM Management

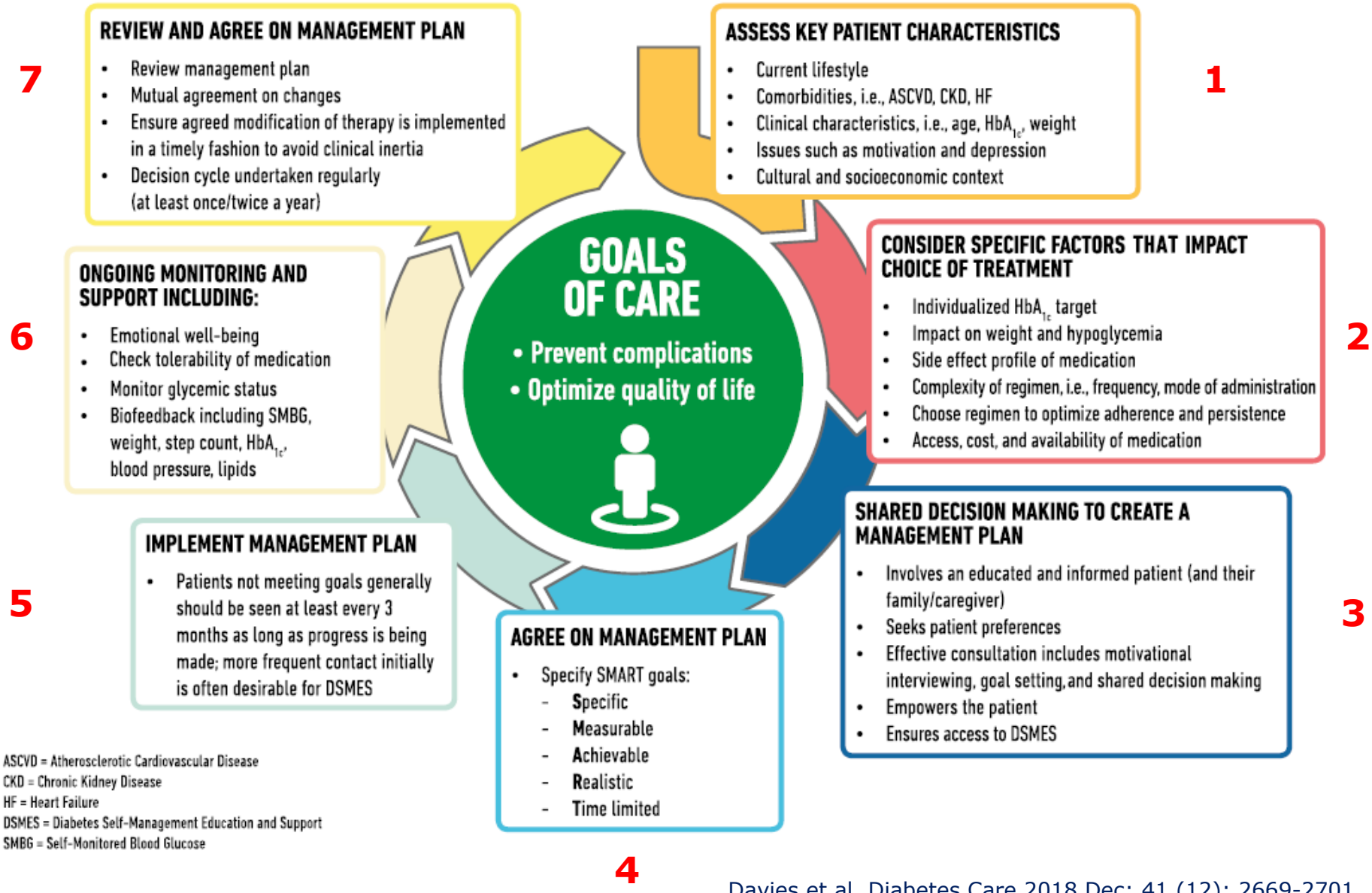
1.	Lifestyle modification underlies all therapy (e.g., weight control, physical activity, sleep, etc.)
2.	Avoid hypoglycemia
3.	Avoid weight gain
4.	Individualize all glycemic targets (A1C, FPG, PPG)
5.	Optimal A1C is ≤6.5%, or as close to normal as is safe and achievable
6.	Therapy choices are affected by initial A1C, duration of diabetes, and obesity status
7.	Choice of therapy reflects cardiac, cerebrovascular, and renal status
8.	Comorbidities must be managed for comprehensive care
9.	Get to goal as soon as possible—adjust at ≤3 months until at goal
10.	Choice of therapy includes ease of use and affordability
11.	A1C ≤6.5% for those on any insulin regimen as long as CGM is being used

AACE, Endocrine Practice. 2019



AACE, Endocrine Practice. 2019

DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

PT-Centered Decision Cycle

1

ASSESS KEY PATIENT CHARACTERISTICS

- Current lifestyle
- Comorbidities, i.e., ASCVD, CKD, HF
- Clinical characteristics, i.e., age, HbA_{1c}, weight
- Issues such as motivation and depression
- Cultural and socioeconomic context

2

3

4

5

6

7

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Pharmacological Agents

First Line Drug

Metformin! Use XR, 500 mg

Start low and go slow

OK to use with GFR 30-45 mg/min/1.73m2

Replace Vitamin B12 (if <400 ng/ml)*

*Bloomgarden Z, Diabets Care, 2010 Jun; 33(6): e73–e78.

Sulfonylureas

- Glyburide – long half life, parent drug and active metabolites (renally excreted)
- Glimepiride – parent drug and metabolites renally excreted
- Glipizide – hepatically metabolized and metabolites are inactive: least likely to cause hypoglycemia
- Should be third line (or fourth) drug today

DPP-4 Inhibitors

Name	Doses	Renal dosing Adjustment
Sitagliptin	100mg	CrCl<50=50 mg daily CrCl<30=25 mg daily
Saxagliptin	5 mg	CrCl<50=2.5 mg daily
Linagliptin	5mg	None
Alogliptin	25 mg	CrCl<60=12.5 mg daily CrCl<30=6.25 mg daily

GLP-1 Agonists

Name	Doses	Frequency
Exenatide	5 mcg 10 mcg	Twice Daily
Lixisenatide	10 mcg 20 mcg	Daily
Liraglutide	0.6 mg 1.2 mg 1.8 mg	Daily
Dulaglutide	0.75 mg 1.5 mg	Weekly
Exenatide- XR	2 mg	Weekly
Semaglutide	0.25 mg 0.5 mg 1 mg	Weekly
Oral Semaglutide	7 mg 14 mg	Daily

SGLT2 Inhibitors

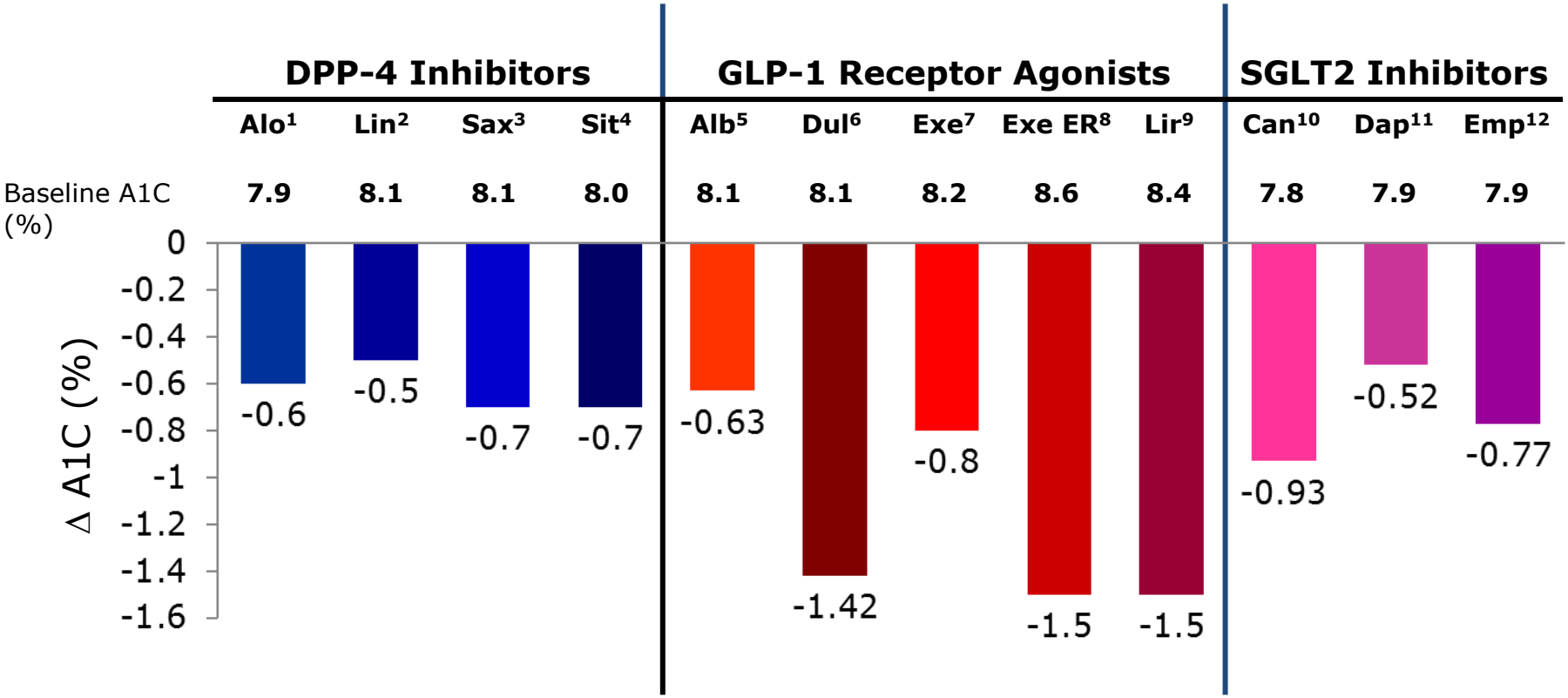
Name	Dosing (QD)	Renal dosing adjustment
CANAGLIFLOZIN	100 mg 300 mg	eGFR <30 mL/min/1.73 m²** eGFR <45 mL/min/1.73 m²: do not increase to 300 mg
DAPAGLIFLOZIN	5 mg 10 mg	eGFR <60 mL/min/1.73 m²: Do not initiate
EMPAGLIFLOZIN	10 mg 25 mg	eGFR <45 mL/min/1.73 m²: Do not initiate
ERTUGLIFLOZIN	5 mg 15 mg	eGFR <60 mL/min/1.73 m²: Do not initiate

** Perkovic V et al. N Engl J Med 2019;380:2295-2306

Courtesy of AACE

Glucose Reduction- New Meds

DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin
(Absolute Changes from Baseline; Not Head-to-Head Trials)

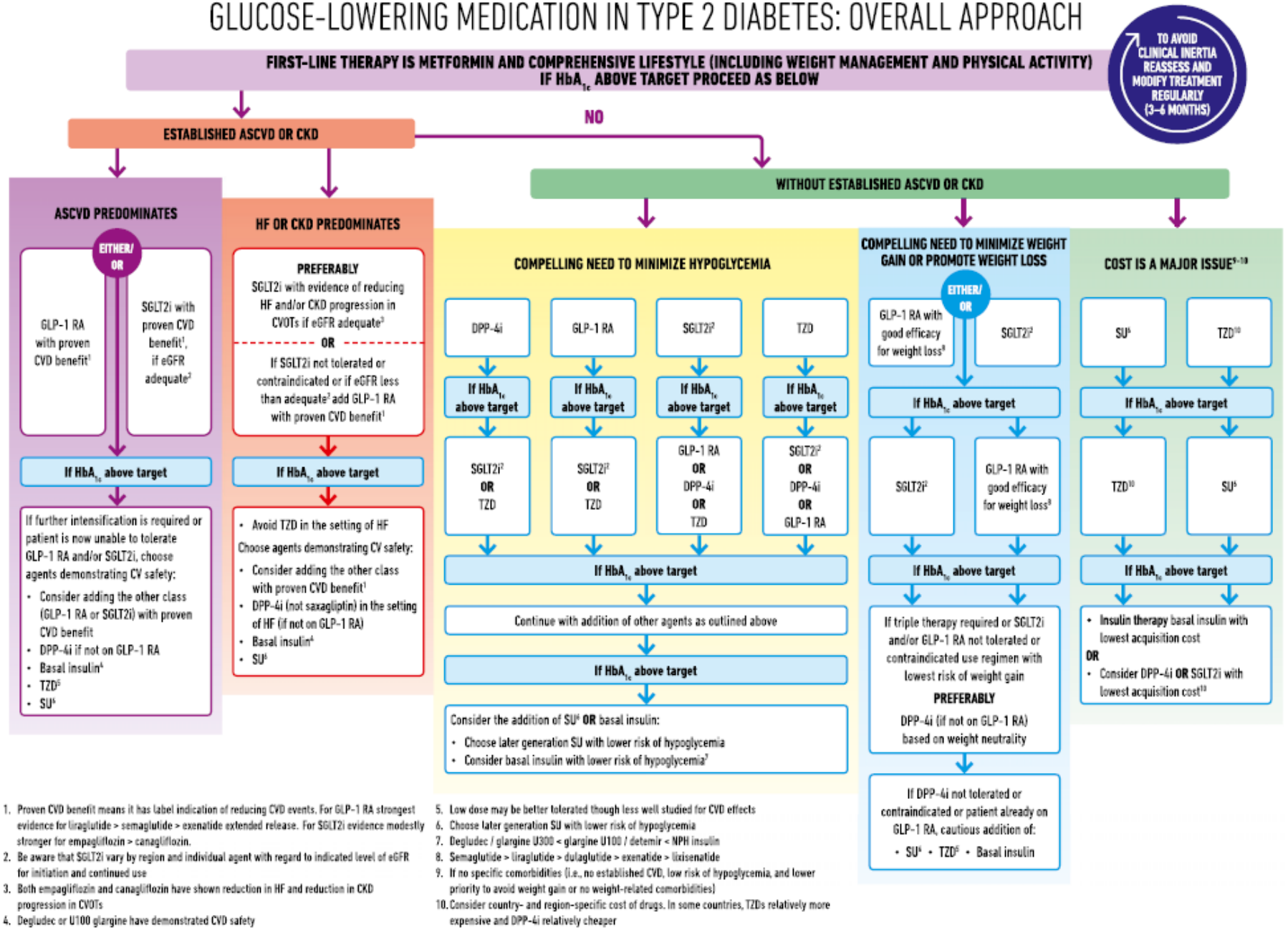


1. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 2. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 3. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 4. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 5. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 6. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 7. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 8. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 9. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 10. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 11. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 12. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659.

Medication Cost

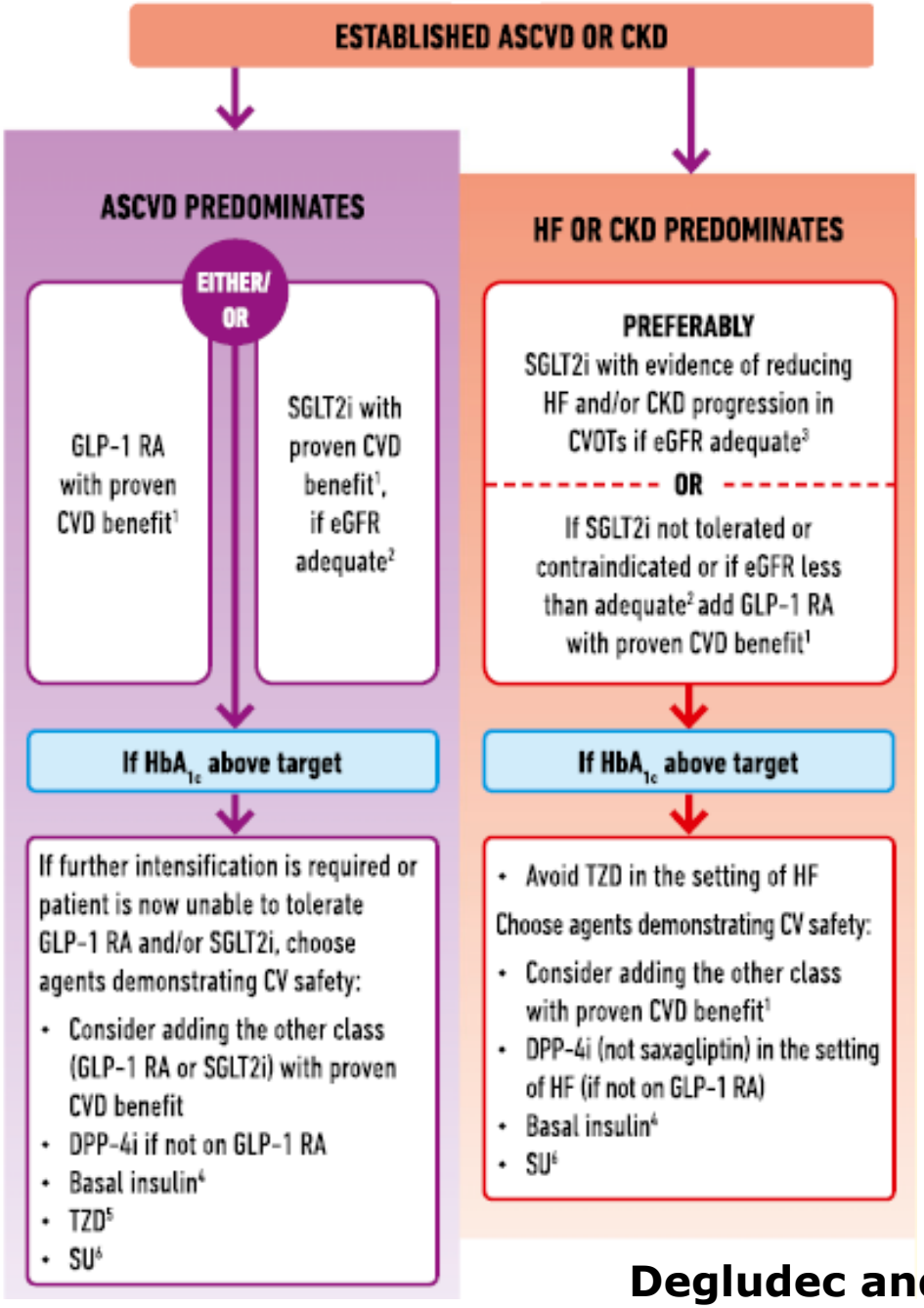
- Average cost of Metformin:$0-5/month
- Average cost of Glipizide: $5-10/month
- Average cost of DPP-IV:$104-500/month
- Average cost of SGLT2-I:$500-600/month
- Average cost of GLP-1:$600-900/month
- Average cost of Insulin: $600-1500/month

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. 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)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701



ASCVD predominates

GLP1-RA
(Liraglutide>Semaglutide>Dulaglutide>Exenatide XR)

SGLT2i (if GFR 45-60)
(Empagliflozin>canagliflozin)

HF or CKD predominates

SGLT2i (if GFR 45-60)
(empagliflozin=canagliflozin)
SGLT2i (GFR<45)= <u>Canagliflozin</u>

HF: Dapagliflozin

GLP-1RA if SGLT2i not tolerated

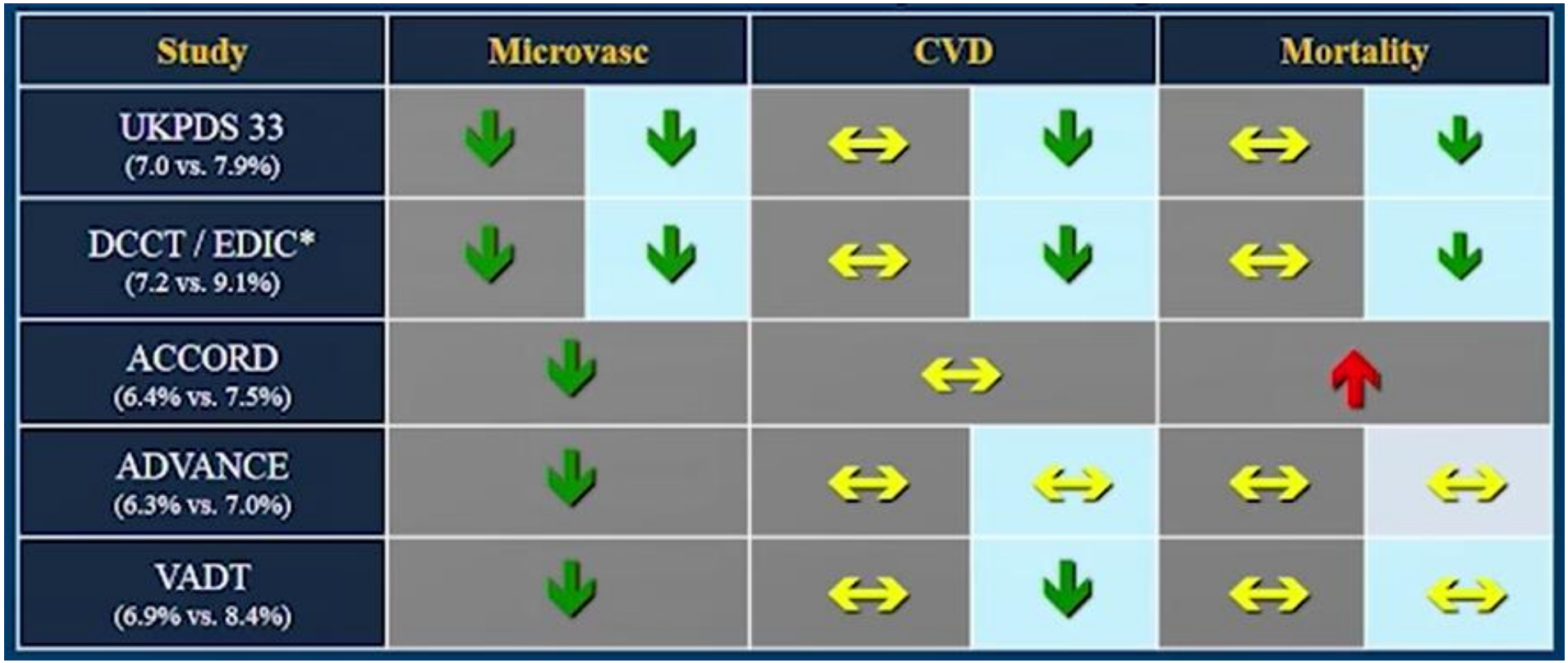
Degludec and Glargine U-100 have CVD safety

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701
Perkovic et al. NEJM 2019

Evidence Supporting 2019 Algorithm

NORTHWESTERN UNIVERSITY
FEINBERG SCHOOL OF MEDICINE

Older Large Clinical Trials



Courtesy Dr. Silvio Inzucchi, Yale

GLP1-RA CVOT Trials

- A total of 50,544 subjects studied!
- 7 major RCT

NAME	DRUG	N
ELIXA	Lixisenatide	6,068
LEADER	Liraglutide	9,340
SUSTAIN-6	Semaglutide	3,297
EXCSEL	Exenatide	14,752
HARMONY OUTCOME	Albiglutide	9,463
REWIND	Dulaglutide	9,901
PIONEER 6	Oral Semaglutide	3,183

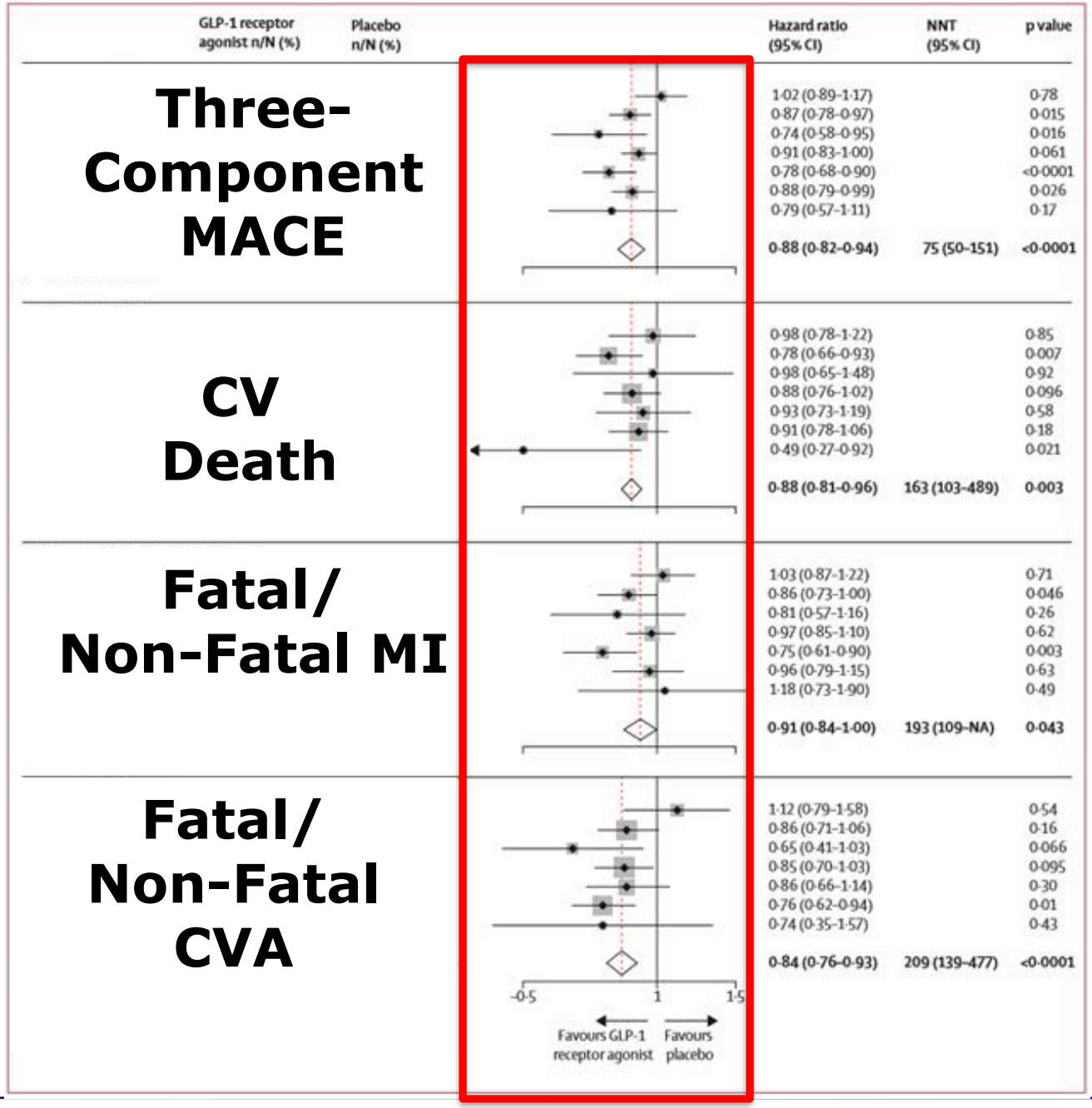
Major CVOT with GLP-1RA

	ELIXA (n=6068)[7]	LEADER (n=9340)[8,14]	SUSTAIN-6 (n=3297)[9]	EXSCEL (n=14 752)[11]	Harmony Outcomes (n=9463)[10]	REWIND (n=9901)[12,13]	PIONEER 6 (n=3183)[14]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide (oral)
Dose	20 µg per day	1·8 mg per day	0·5 or 1 mg per week	2 mg per week	30 or 50 mg per week	1·5 mg per week	14 mg per day
Age (years)	60 (10)	64 (7)	65 (7)	62 (9)	64 (7)	66 (7)	66 (7)
BMI (kg/m²)	30·1 (5·6)	32·5 (6·3)	32·8 (6·2)	32·7 (6·4)	32·3 (5·9)	32·3 (5·7)	32·3 (6·5)
Diabetes duration (years)	9·2 (8·2)	12·8 (8·0)	13·9 (8·1)	13·1 (8·3)	14·2 (8·8)	10·6 (7·2)	14·9 (8·5)
HbA_{1c} (%)	7·7 (1·3)	8·7 (1·6)	8·7 (1·5)	8·1 (1·0)	8·7 (1·5)	7·3 (1·1)	8·2 (1·6)
Established cardiovascular disease	6068 (100%)	7598 (81%)	2735 (83%)	10 782 (73%)	9463 (100%)	3114 (31%)	2695 (85%)
History of heart failure	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	853 (9%)	388 (12%)
Systolic blood pressure (mm Hg)	129 (17)	136 (18)	136 (17)	135 (17)	135 (17)	137 (17)	136 (18)
eGFR (mL/min per 1·73 m²)*	78 (21)	80 (NR)	80 (61–92)	77 (61–92)	79 (25)	75 (24)	74 (21)
Glucose-lowering drugs used							
Insulin	2374 (39%)	4169 (45%)	1913 (58%)	6838 (46%)	5597 (59%)	2363 (24%)	1930 (61%)
Biguanides	4021 (66%)	7144 (76%)	2414 (73%)	11 295 (77%)	6969 (74%)	8037 (81%)	2463 (77%)
Sulfonylurea	2004 (33%)	4733 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	4552 (46%)	1027 (32%)
Thiazolidinedione	95 (2%)	575 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	118 (4%)
DPP-4 inhibitor	NA	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	88 (1%)	2 (<1%)
SGLT2 inhibitor	NA	NA	5 (<1%)	77 (1%)	575 (6%)	12 (<1%)	305 (10%)

Numerical data are mean (SD) or n (%), unless otherwise specified. GLP-1=glucagon-like peptide-1. eGFR=estimated glomerular filtration rate. NR=not reported. DPP-4=dipeptidyl peptidase-4. SGLT2=sodium-glucose co-transporter-2. *eGFR data are median (IQR) for SUSTAIN-6 and EXSCEL.

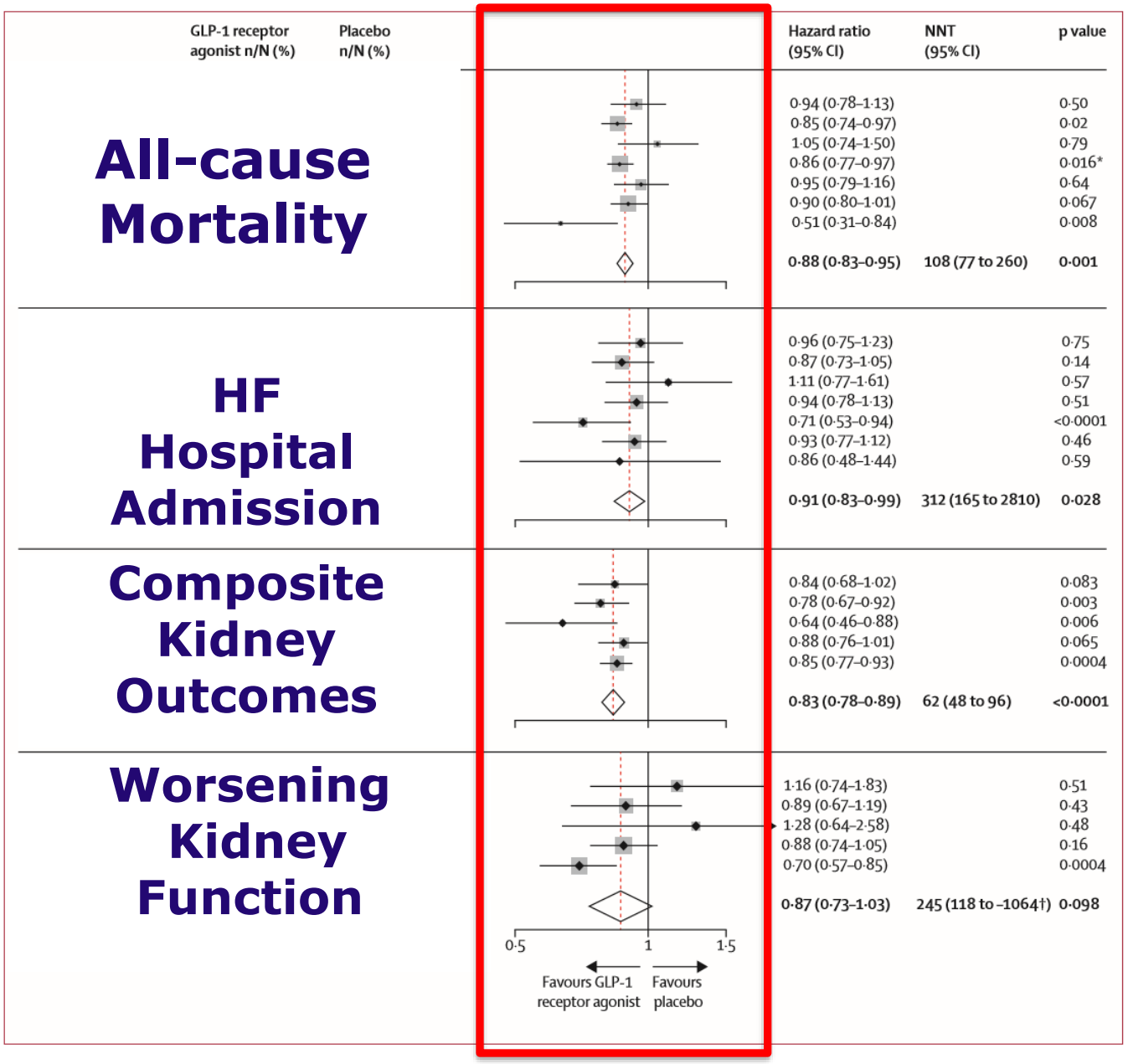
Kristensen SL et al. Lancet Diabetes Endocrinol 2019 Epub ahead of print August 14, 2019 http://dx.doi.org/10.1016/ S2213-8587(19)30249-9

MACE Risks: Combined And Individual



Kristensen SL et al. Lancet Diabetes Endocrinol 2019 Epub ahead of print August 14, 2019 http://dx.doi.org/10.1016/S2213-8587(19)30249-9

Additional Outcomes



Kristensen SL et al. Lancet Diabetes Endocrinol 2019 Epub ahead of print August 14, 2019 http://dx.doi.org/10.1016/S2213-8587(19)30249-9

STLG2i Outcome Trials

Total of 4 studies
(+Credence) 38,723 subjects

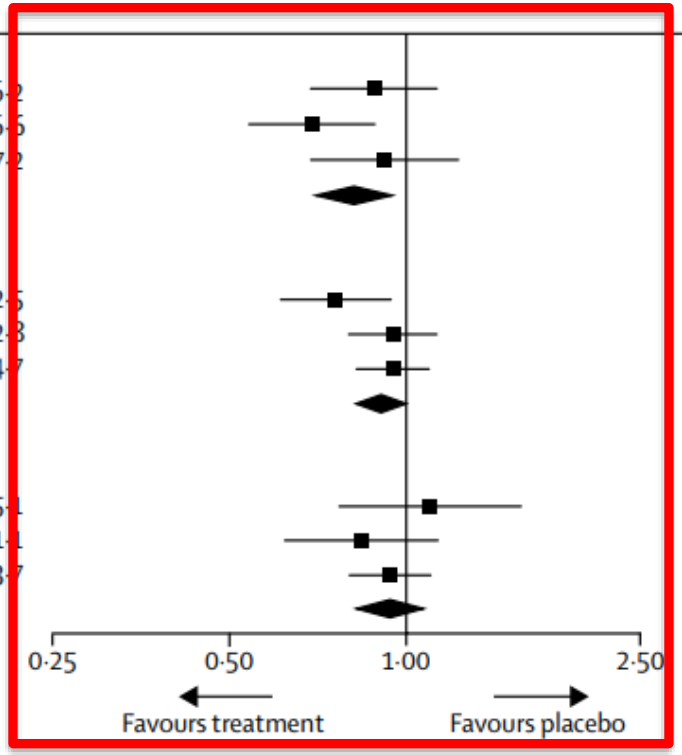
	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Zelniker TA et al. The Lancet 2019; 393: 10166:31-39

Effects on MACE (By GFR)

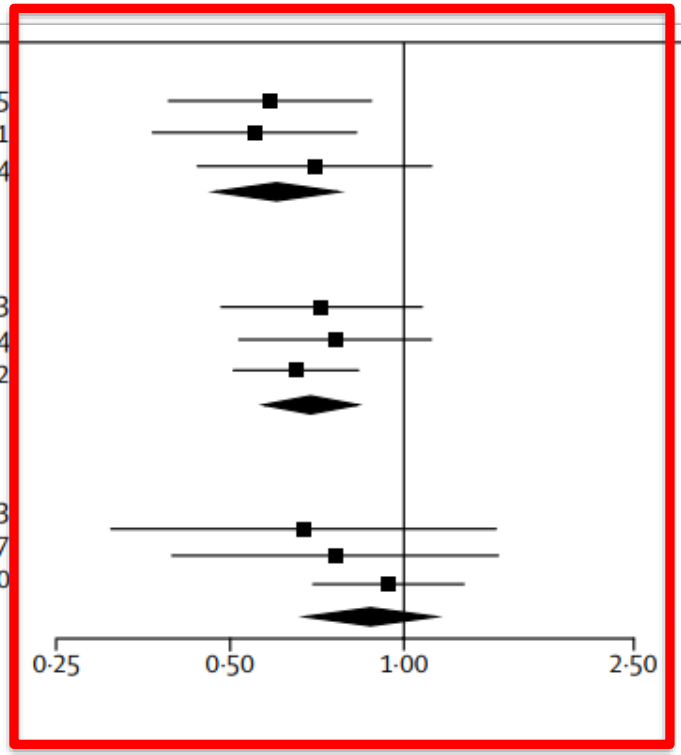
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1212	607	275	52·7	60·5	36·2	0·88 (0·69–1·13)
CANVAS Program	NA	NA	261	36·3	49·5	36·5	0·69 (0·54–0·89)
DECLARE-TIMI 58	606	659	189	37·3	43·1	27·2	0·92 (0·69–1·23)
Fixed effects model for eGFR <60 (p=0·0077)							**0·82 (0·70–0·95)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2423	1238	351	30·8	40·6	22·5	0·76 (0·61–0·94)
CANVAS Program	NA	NA	563	26·8	29·0	32·8	0·95 (0·80–1·13)
DECLARE-TIMI 58	3838	3894	757	24·5	25·8	44·7	0·95 (0·82–1·09)
Fixed effects model for eGFR 60 to <90 (p=0·0520)							**0·91 (0·82–1·00)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1050	488	146	35·4	32·2	15·1	1·10 (0·77–1·57)
CANVAS Program	NA	NA	187	20·8	23·6	21·1	0·84 (0·62–1·13)
DECLARE-TIMI 58	4137	4025	613	18·8	19·7	63·7	0·94 (0·80–1·10)
Fixed effects model for eGFR ≥90 (p=0·35)							**0·94 (0·82–1·07)**



Zelniker TA et al. The Lancet 2019; 393: 10166:31-39

Effects On HF Hospitalization (By GFR)

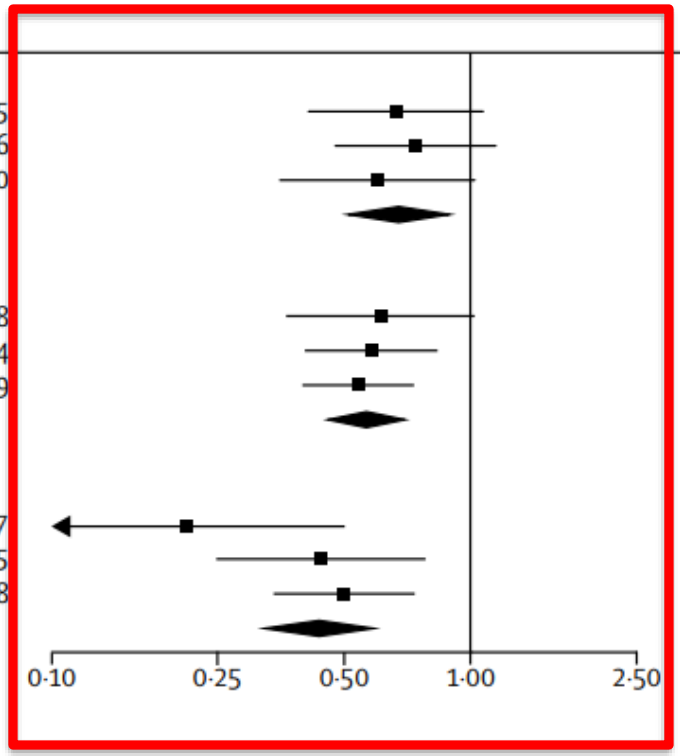
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1212	607	94	14·9	25·8	36·5		0·59 (0·39–0·88)
CANVAS Program	NA	NA	98	11·6	21·3	36·1		0·55 (0·37–0·83)
DECLARE-TIMI 58	606	659	77	12·3	19·3	27·4		0·70 (0·44–1·12)
Fixed effects model for eGFR <60 (p<0·0001)								**0·60 (0·47–0·77)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2423	1238	100	8·4	11·7	21·3		0·72 (0·48–1·07)
CANVAS Program	NA	NA	108	4·6	6·1	23·4		0·76 (0·52–1·12)
DECLARE-TIMI 58	3838	3894	251	6·5	9·9	55·2		0·65 (0·51–0·84)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·69 (0·57–0·83)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1050	488	27	5·4	7·9	11·3		0·67 (0·31–1·44)
CANVAS Program	NA	NA	37	3·7	5·1	15·7		0·76 (0·40–1·47)
DECLARE-TIMI 58	4137	4025	170	5·1	5·4	73·0		0·94 (0·69–1·26)
Fixed effects model for eGFR ≥90 (p=0·31)								**0·88 (0·68–1·13)**



Zelniker TA et al. The Lancet 2019; 393: 10166:31-39

Effects On Composite Renal Function/ESRD/Death (By GFR)

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo		
eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1196	605	NA	NA	NA	33·5	0·66 (0·41–1·07)
CANVAS Program	NA	NA	83	11·4	15·1	39·6	0·74 (0·48–1·15)
DECLARE-TIMI 58	606	659	59	8·9	15·2	27·0	0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)							**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2406	1232	NA	NA	NA	16·8	0·61 (0·37–1·03)
CANVAS Program	NA	NA	118	4·6	7·4	34·4	0·58 (0·41–0·84)
DECLARE-TIMI 58	3838	3894	186	4·2	7·8	48·9	0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)							**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1043	486	NA	NA	NA	11·7	0·21 (0·09–0·53)
CANVAS Program	NA	NA	48	3·8	8·1	27·5	0·44 (0·25–0·78)
DECLARE-TIMI 58	4137	4025	120	2·5	4·9	60·8	0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)							**0·44 (0·32–0·59)**



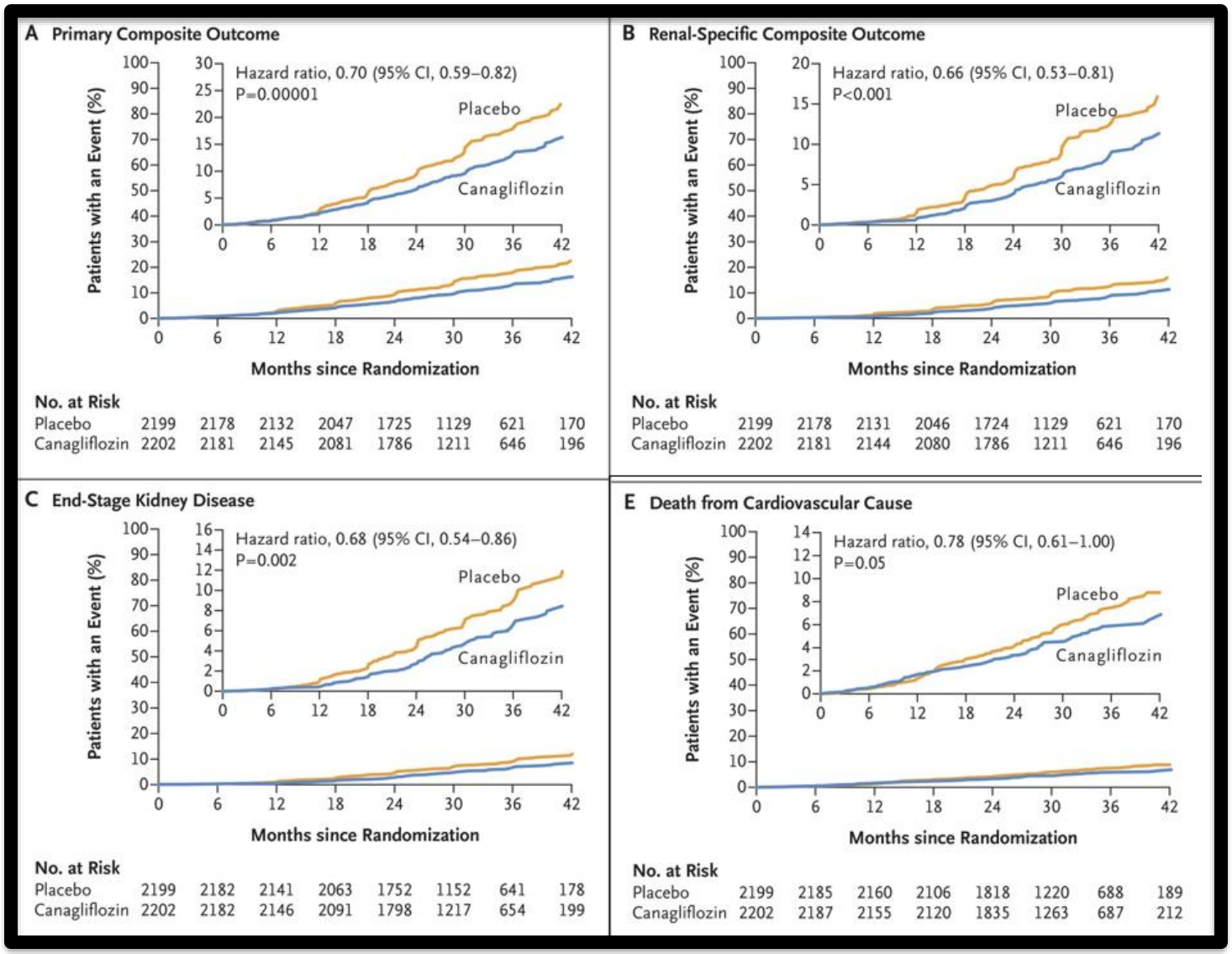
Zelniker TA et al. The Lancet 2019; 393: 10166:31-39

CREDENCE

- Double-blind, RCT
- 4,401 patients, > 30 y.o., T2DM, albuminuria, CKD on max tolerated ACEi/ARB
- Designed for renal outcomes
- Primary outcome: CV death, progression to ESRD, doubling creatinine, renal death

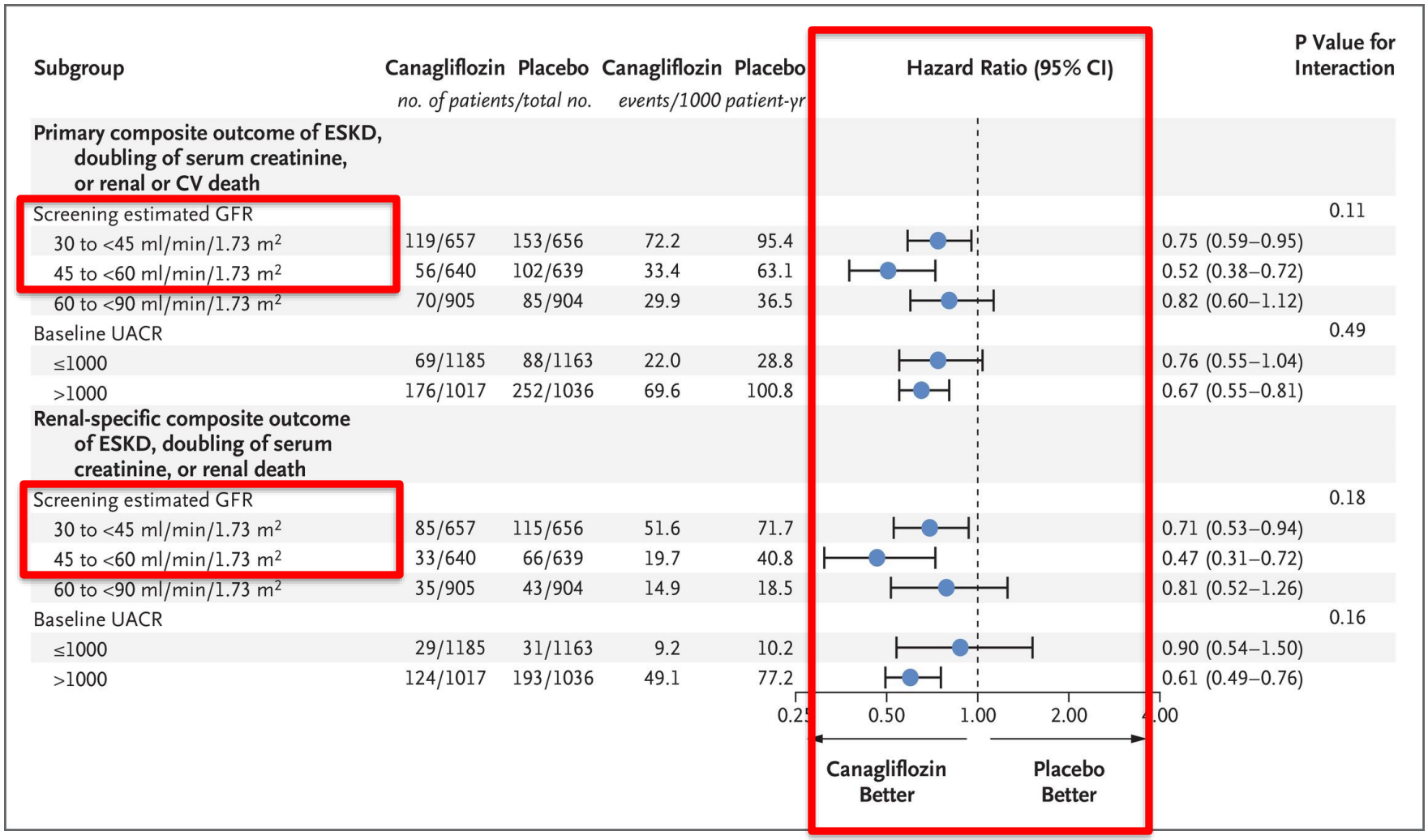
Perkovic V et al. N Engl J Med 2019;380:2295-2306

Credence



Perkovic V et al. N Engl J Med 2019;380:2295-2306

Credence

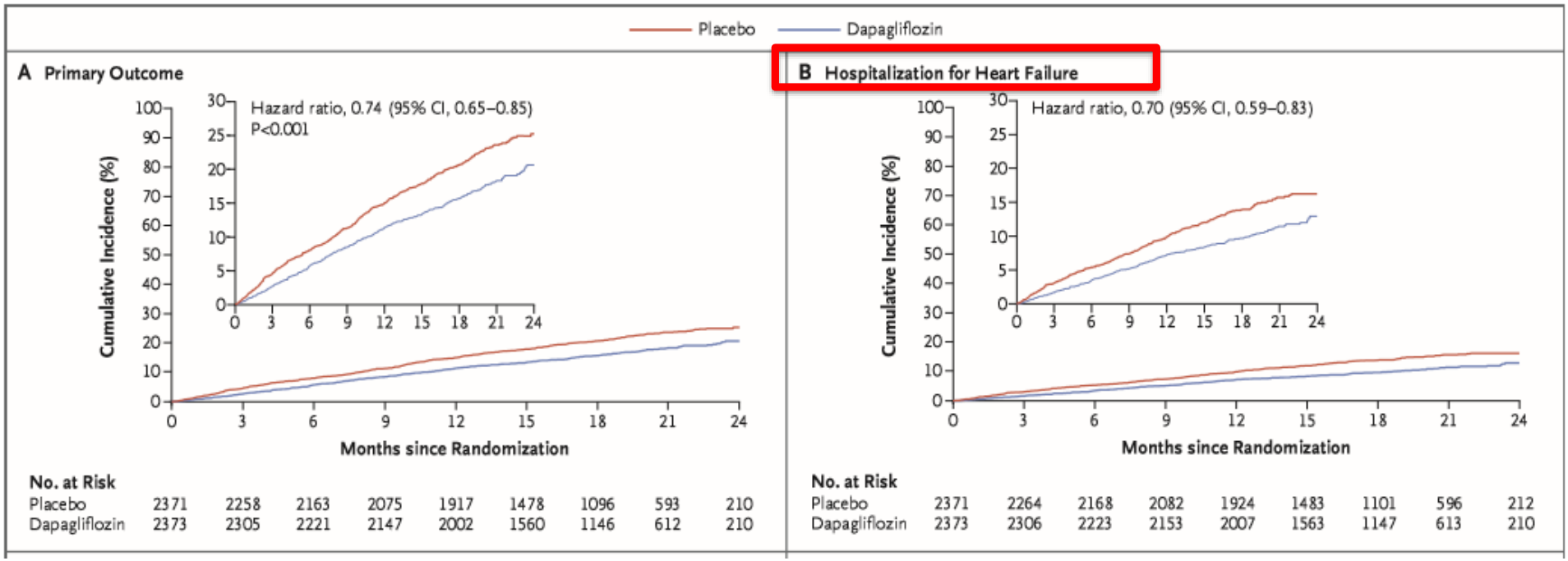


Subgroup	Canagliflozin (no. of patients/total no.)	Placebo (no. of patients/total no.)	Canagliflozin (events/1000 patient-yr)	Placebo (events/1000 patient-yr)	Hazard Ratio (95% CI)	P Value for Interaction
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m²	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m²	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m²	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	

Perkovic V et al. N Engl J Med 2019;380:2295-2306

DAPA-HF

Dapagliflozin (N=2373)	Placebo (N=2371)



McMurray et al. NEJM 2019 sept 19, DOI: 10.1056/NEJM 1911303

What About DKA Risk With SGLT2i?

Risk Factors for DKA with SGLT2i

Risk level for DKA	Factor
Moderate/high	• Reduced basal insulin by more than 10–20% • Insulin pump or infusion site failure • Reduced or inconsistent carbohydrate intake • Excessive alcohol use • Use of illicit drugs • Volume depletion/dehydration • Acute illness of any sort (viral or bacterial) • Vomiting
Low/moderate	• Vigorous or prolonged exercise • Reduced prandial insulin dose by more than 10–20% • Travel with disruption in usual schedule/insulin regimen • Insulin pump use
Minimal/low	• Low BMI (<25 kg/m^2) • Inconsistent caloric intake • Moderate alcohol use* • Female sex

*If ketone levels increase from baseline.

Danne T et al, Diabetes Care 2019;42:1147–1154

SGLT2i and DKA Risk
Checking the BLOOD KETONES!

Blood ketone (BHB) level	Urine ketone*	Remedial actions
<0.6 mmol/L (normal)	Negative	No action needed
0.6–1.5 mmol/L (ketonemia)	Trace or small	Treat as follows or per clinician instructions: • Ingest 15–30 g rapidly absorbed carbohydrate and maintain fluid consumption (300–500 mL) hourly • Administer rapid-acting insulin based on carbohydrate intake (hourly) • Check blood/urine ketones (every 3–4 h) until resolution • Check blood glucose frequently to avoid hyperglycemia and hypoglycemia Seek medical attention if levels persist and symptoms present
1.6–3.0 mmol/L (impending DKA)	Moderate	Follow treatment recommendations listed above Consider seeking immediate medical attention
>3.0 mmol/L (probable DKA)	Large to very large	Seek immediate medical attention

BHB, β-hydroxybutyrate. *Urine ketone concentrations are dependent on hydration and other factors; these values do not closely correlate with blood BHB levels.

Need to purchase (Not covered by insurance) either PRECISION XTRA OR NOVAMAX glucose/ketone meters and ketone strips

Danne T et al, Diabetes Care 2019;42:1147–1154

Education for SGLT2i in T1DM or insulin treated T2DM

Patient education	• All patients initiating SGLT inhibitor therapy should receive through training/education in the following areas: ◦ DKA causes and symptoms ◦ Euglycemic ketoacidosis ◦ Importance of ketone monitoring ◦ Use of ketone monitoring—training in testing procedure, proactive monitoring, situations when monitoring is indicated ◦ Treatment protocol for addressing ketosis ◦ Guidance in when to seek medical attention
Clinician education	• All prescribing clinicians should acquire full understanding of the safe use and risks associated with SGLT inhibitor therapy: ◦ Criteria for patient selection—baseline ketone level, demographic/behavioral considerations ◦ Training/educational needs of patients—detection (ketone levels, symptoms), prevention strategies, treatment ◦ Potential for missed DKA, euDKA ◦ Treatment strategies—STICH protocol recommended: ■ **ST**op SGLT inhibitor treatment for a few days ■ **I**nsulin administration ■ **C**arbohydrate consumption ■ **H**ydration with a suitable drink (e.g., water or noncaloric athletic drink with balanced electrolytes)
Risk Communication	• Product labeling, website • Health care professional education • Medication guide, patient alert card*

ST
I
C
H

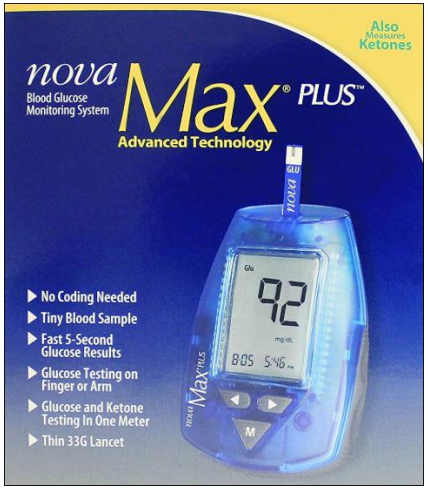
Danne T et al, Diabetes Care 2019;42:1147–1154

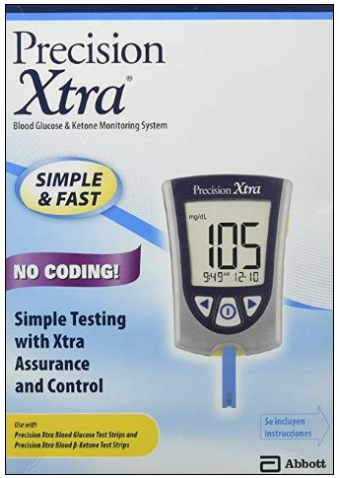
Check Ketones Before Starting SGLT2i (If On Insulin)

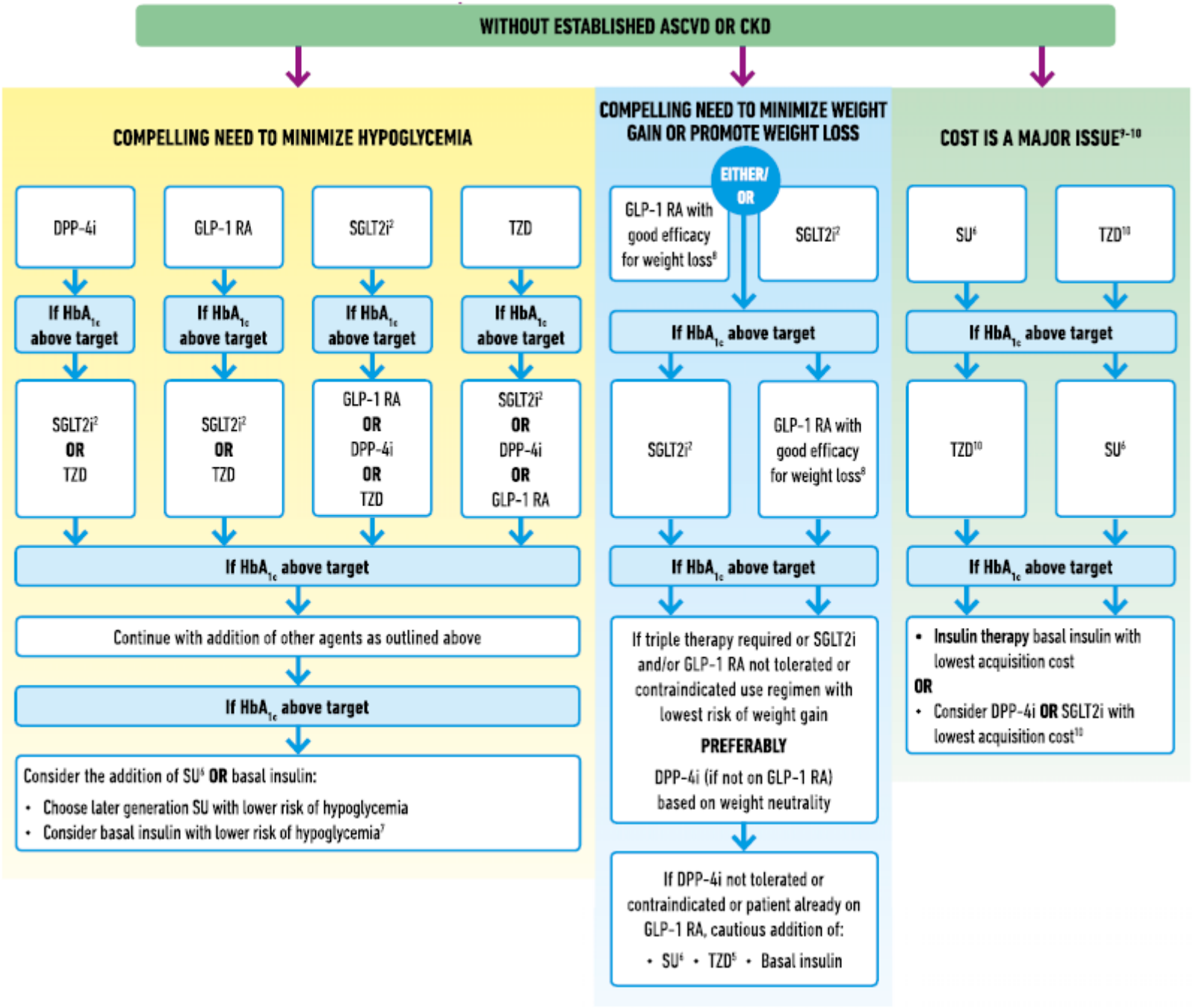
Below 0.6 mmol/L NORMAL

0.6-1.5 mmol/L monitor, start STICH protocol

>1.5 mmol/L impending DKA

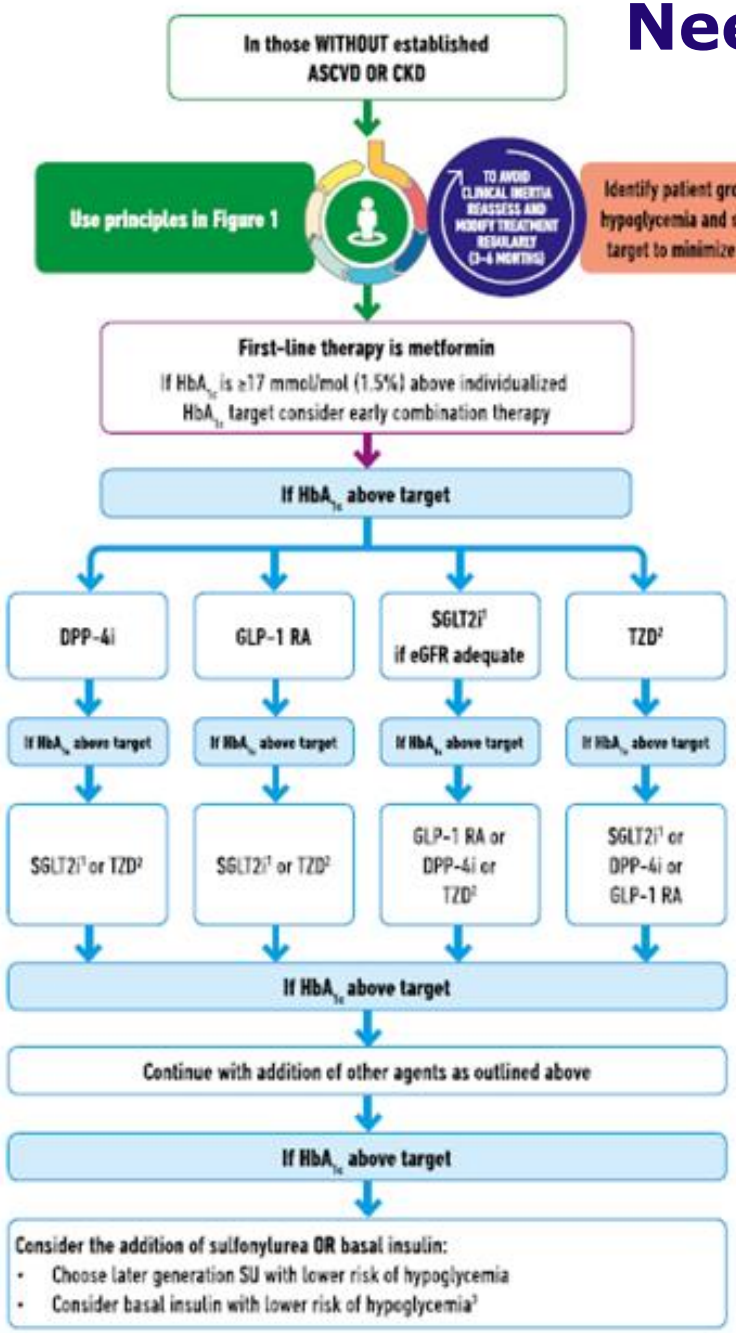






Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Need To Minimize Hypoglycemia



1) Metformin; If HbA1c 1.5% > target

2) **DPP-4i** → SGLT2i or TZD—>Insulin/SU

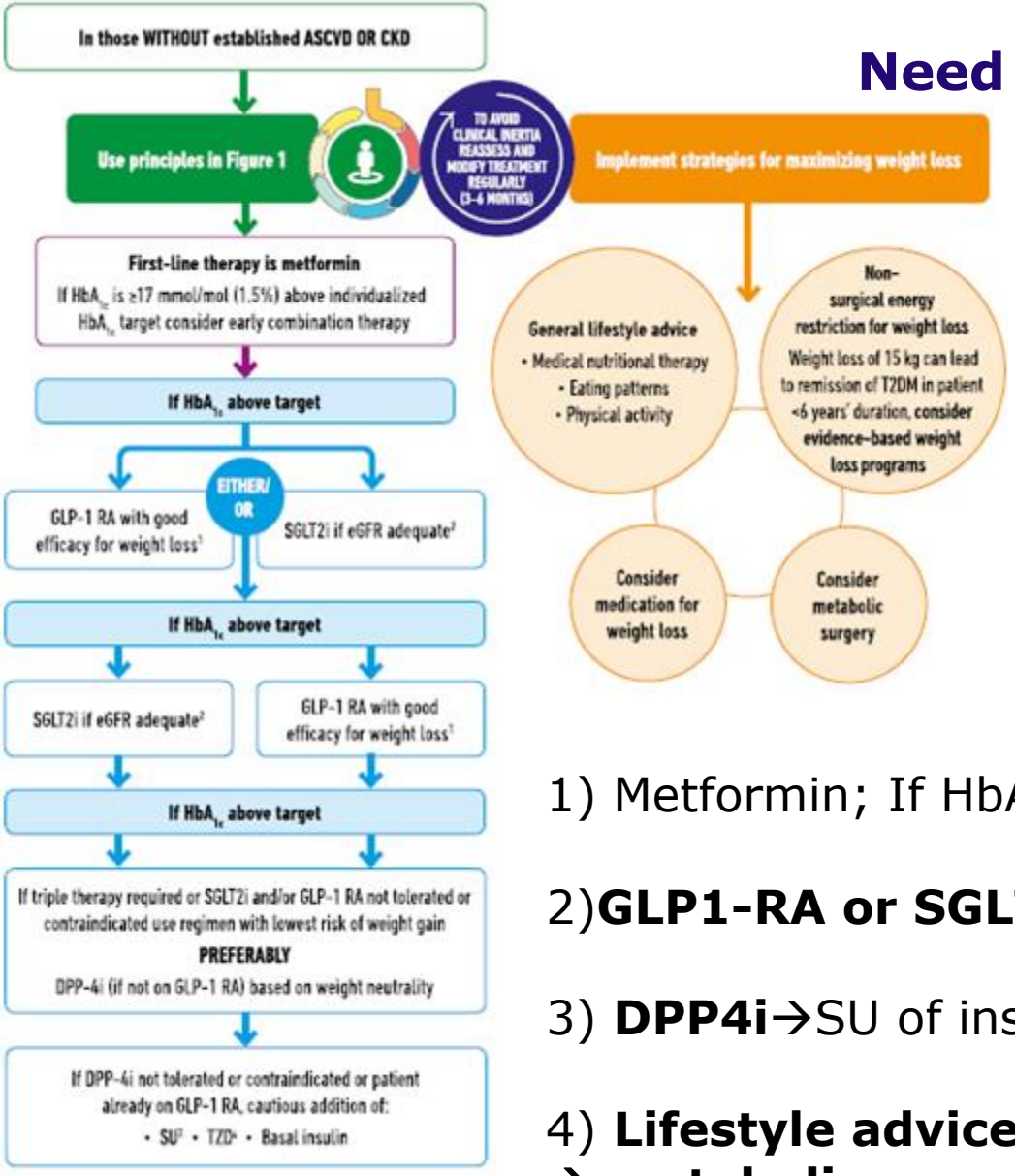
3) **GLP1-RA**→SGLT2i or TZD—>Insulin or SU

4) **SGLT2i** → DPP4i or GLP1-RA or TZD→ Insulin or SU

5) **TZD**→SGLT2i—>DPP4i or GLP1-RA →Insulin or SU

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Need To Minimize Weight Gain - Promote Weight Loss



1) Metformin; If HbA1c 1.5% > target

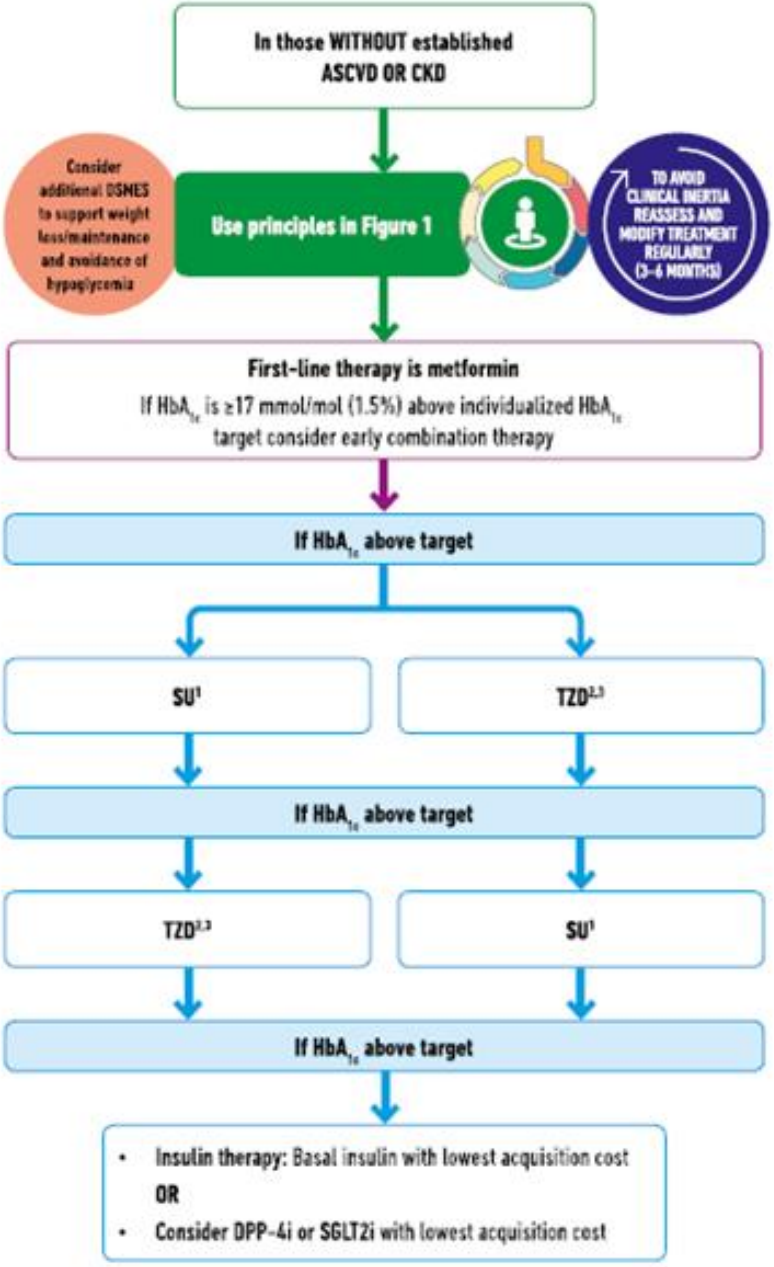
2)**GLP1-RA or SGLT2i**

3) **DPP4i**→SU of insulin or TZD (with caution)

4) **Lifestyle advice →weight loss medications → metabolic surgery**

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Cost is a Major Issue



1) **Metformin**; If HbA1c 1.5% > target

2) **SU**→ TZD→ **Lower cost DPP4i/SGLT2i** or Basal insulin

3)**TZD**→SU →Lower cost DPP4i/SGLT2i or Basal insulin

Ertugliflozin= only SGLT2 for Medicaid
Alogliptin= least expensive DPP-IV

Insulin isophane (NPH) or Regular= least expensive non analog insulin only at Walmart

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Oral Therapy With Injectables

METFORMIN

Ok with injectables
(GLP1-RA or insulin)

TZD[1]

Stop or reduce dose
with insulin

SULFONYLUREA

Reduce by 50% if starting insulin

Stop if using mealtime insulin

SGLT2i

Ok with injectables

BUT

Do not decrease too
aggressively insulin
Sick day rules

DO NOT USE
before/during/after surgeries,
hospitalization (DKA)

DPP-4i

STOP if starting
GLP1-RA

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

General Strategies

- DM:

- DM education; maximize Metformin; second drug if HbA1c >7%
- HbA1c <9% consider SGLT2i especially if on DPP IV
- HbA1c >9% start GLP-1 RA before insulin
- Consider fasting glucose, hx of pancreatitis, high TG, neuropathy, look at feet!
- GLP-1 RA or Canagliflozin with GFR <45
- Look at Ophtho report before Semaglutide

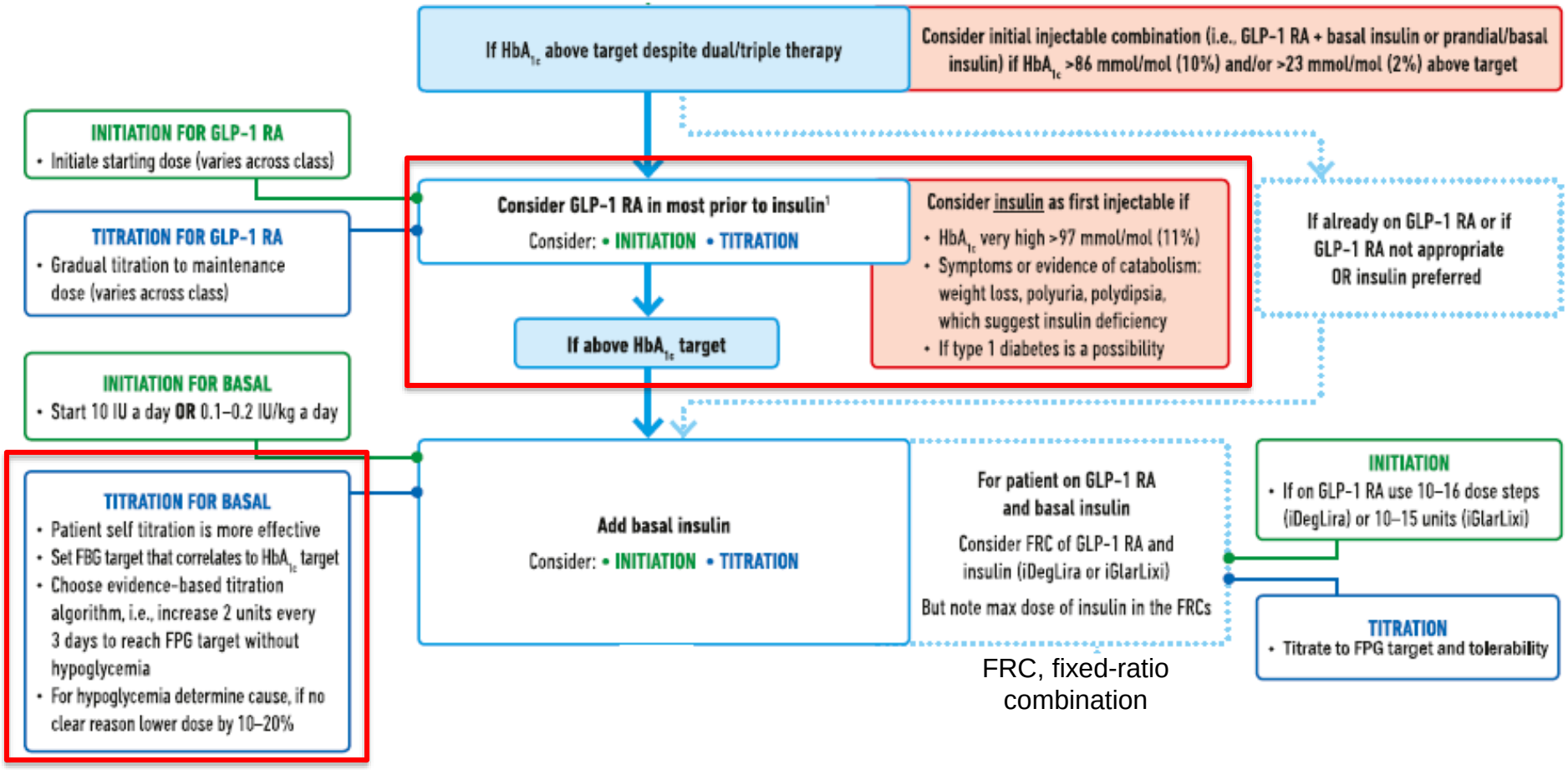
- CV:

- Hx of A Fib = monitor heart rate with Liraglutide

- HTN:

- If uncontrolled, add SGLT2i without changes to BP meds
- If BP controlled and on diuretic, hold HCTZ for 1-2 weeks, then resume if BP increases
- Contact Cardiology or Nephrology for complex pts

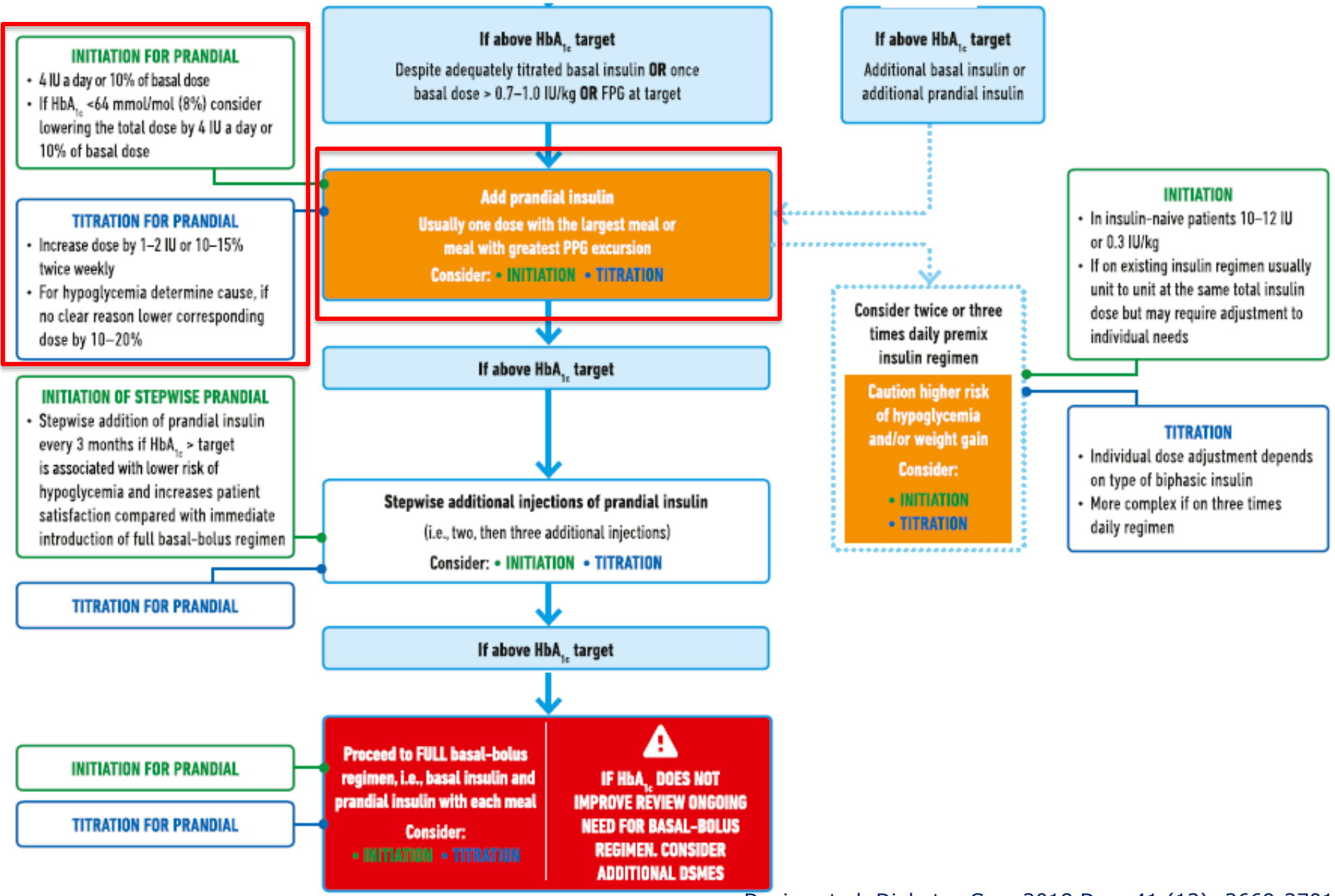
Intensifying Treatment



FRC, fixed-ratio combination

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Adding Mealtime (Prandial) Insulin



Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Available Insulins

Type	Onset	Peak	Duration	Role
Ultra-Rapid Acting Technosphere insulin	1-2 min	15-20 min	2 – 2 ½ hrs	Mealtime Inhaled
Rapid-Acting Lispro Aspart Glulisine FiAsp Lispro U-200 Sanofi Admelog	 15-30 min 10-20 min 20-30 min 0-5 min 15-30 min	 30-90 min 40-50 min 30-90 min 30-90 min 30-90 min	 3-6 hrs 3-5 hrs 3-4 hrs 2-4 hrs 3-6 hrs	Mealtime Vial, Pen, Pump Vial, Pen, Pump Vial, Pen, Pump Pen only Pen only
Short-Acting Regular insulin Regular insulin(concentrated) U-500	 30 min – 1 hr 30 min- 2 hrs	 2-5 hrs 2-5 hrs	 5-8 hrs Up to 24 hrs	Mealtime Vial Vial and pen
Intermediate-Acting NPH insulin	2-4 hrs	4-12 hrs	12-18 hrs	Basal Vial, Pen
Long-Acting Glargine Detemir Glargine U-300 (concentrated) Degludec (U-100 and U-200) Lilly Glargine	 1-1 ½ hrs 1-2 hrs 1-1 ½ hrs 1-2 hrs 1-1 ½ hrs	 “No peak” “No peak” No peak No peak No peak	 20-24 hrs Up to 24 hrs 24 hrs 24 hrs 24 hrs	Basal Vial, Pen Vial, Pen Pen only Pen only Pen only
Pre-Mixed Isophane + regular human 70/30 Lispro protamine + lispro 75/25 OR 50/50 Aspart protamine + aspart 70/30	 30 min 15-30 min 10-20 min	 2.5 /14-24 hrs 1-4 /14-24 hrs 2-4 /12-24 hrs	 Up to 24 hrs 18-24 hrs 16-20 hrs	Vial, Pen

How To Use The New Approach

- Metformin is First-line therapy
- Comprehensive lifestyle (weight management and physical activity)

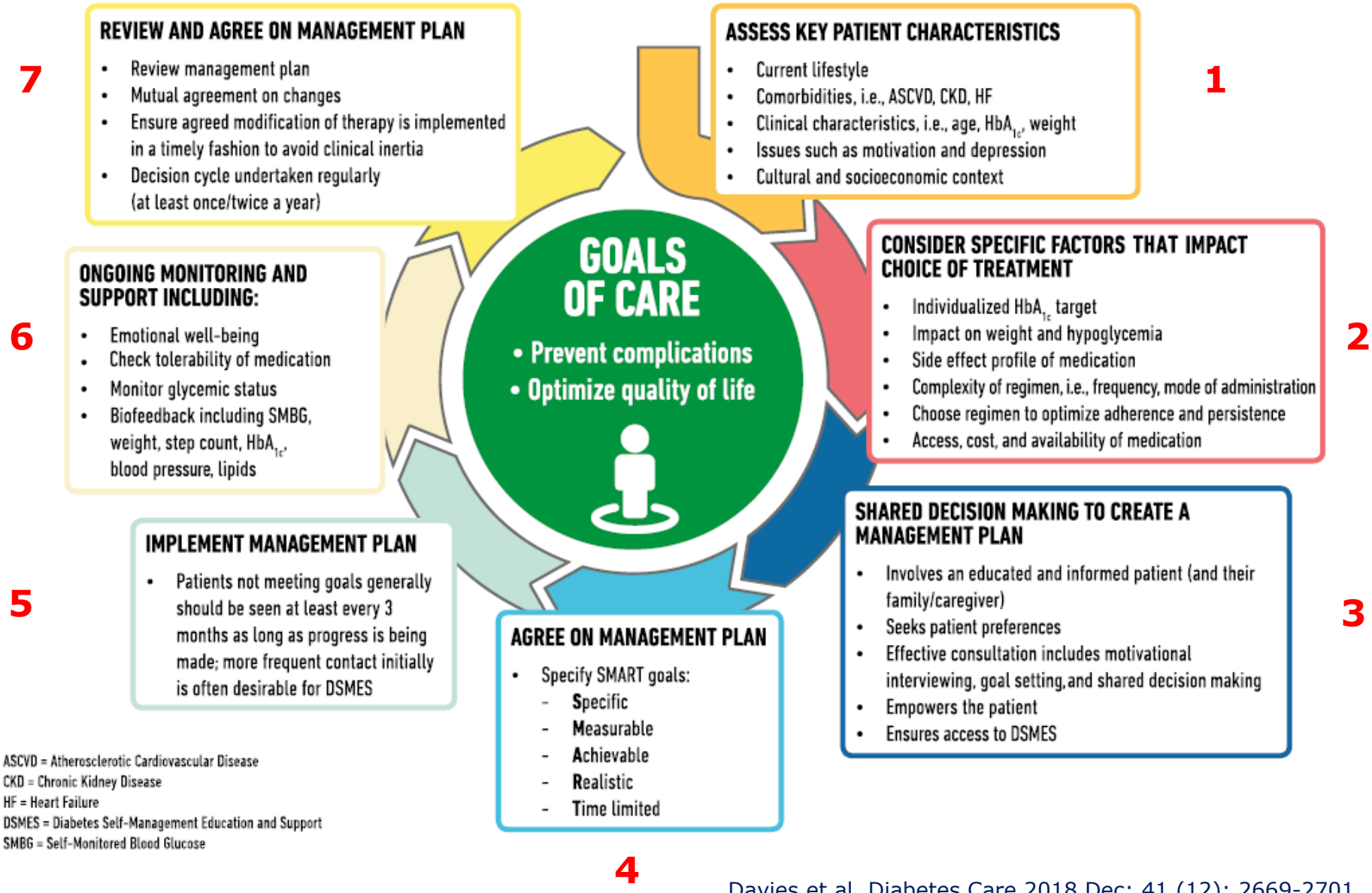
- If HbA1c above target proceed to analyze the following:

1) Patient **with** established ASCVD or CKD
   - ASCVD predominates
   - CKD predominate

2) Patient **without** established ASCVD or CKD
   - Need to minimize hypoglycemia
   - Need to minimized weight gain/promote weight loss
   - Cost is major issue

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Davies et al. Diabetes Care 2018 Dec; 41 (12): 2669-2701

Conclusions

- Start therapy early and titrate/advance early
- Send patients for DM education
- Personalize therapy based on co-morbidities, cost, hypoglycemia risk

Thank You

NORTHWESTERN UNIVERSITY
FEINBERG
SCHOOL OF MEDICINE