Important changes in diabetes guidelines

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- **Self-management education and support (DSMES)**

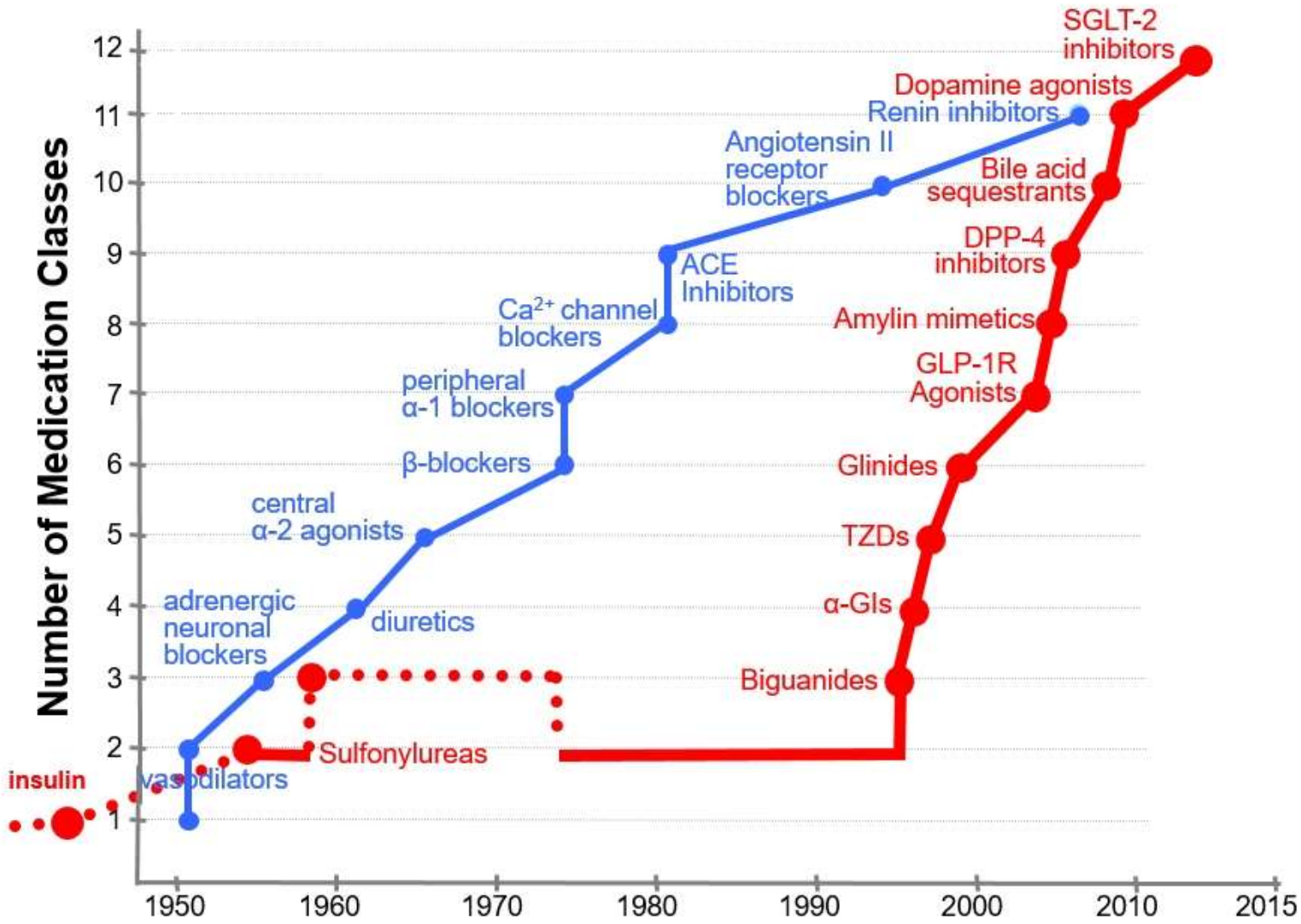
  to support informed decision making, self-care behaviors, problem solving, and active collaboration with the health care team to improve clinical outcomes, health status, and well-being in a cost-effective manner

- **PERSON-CENTERED COLLABORATIVE CARE**

  A close working relationship between the person with diabetes and clinicians involved in treatment planning.

- **Diabetes Technology**

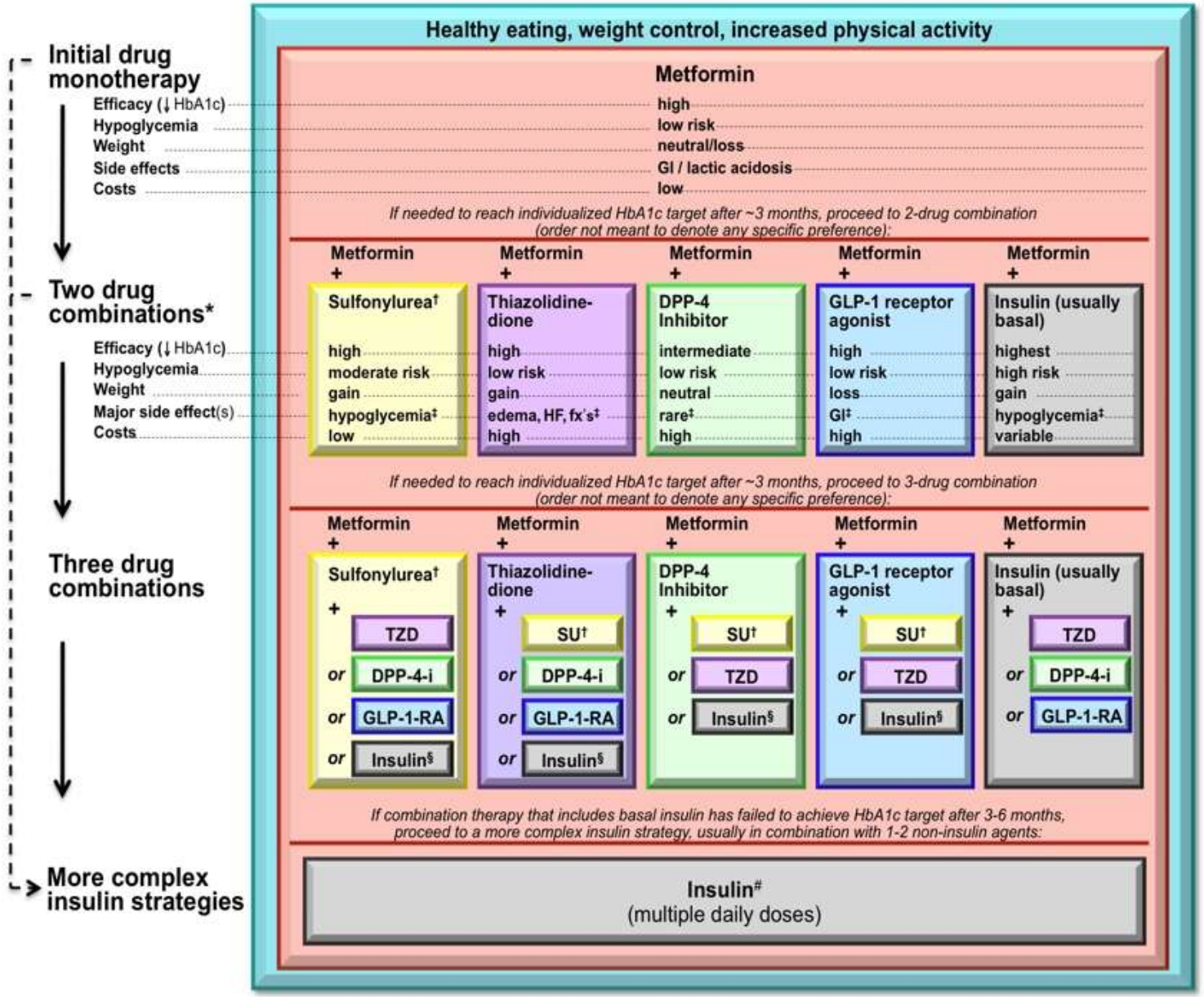
Contrasting the availability of medications to treat HTN & T2DM over one-half century in the United States



Adapted from: Inzucchi SE. "Comparing and Choosing Oral Agents", in *Clinical Diabetes*, Fonseca VA, WB Saunders, 2006.

ADA-EASD Position Statement on the Management of Hyperglycemia in Type 2 Diabetes: A *Patient-Centered* Approach

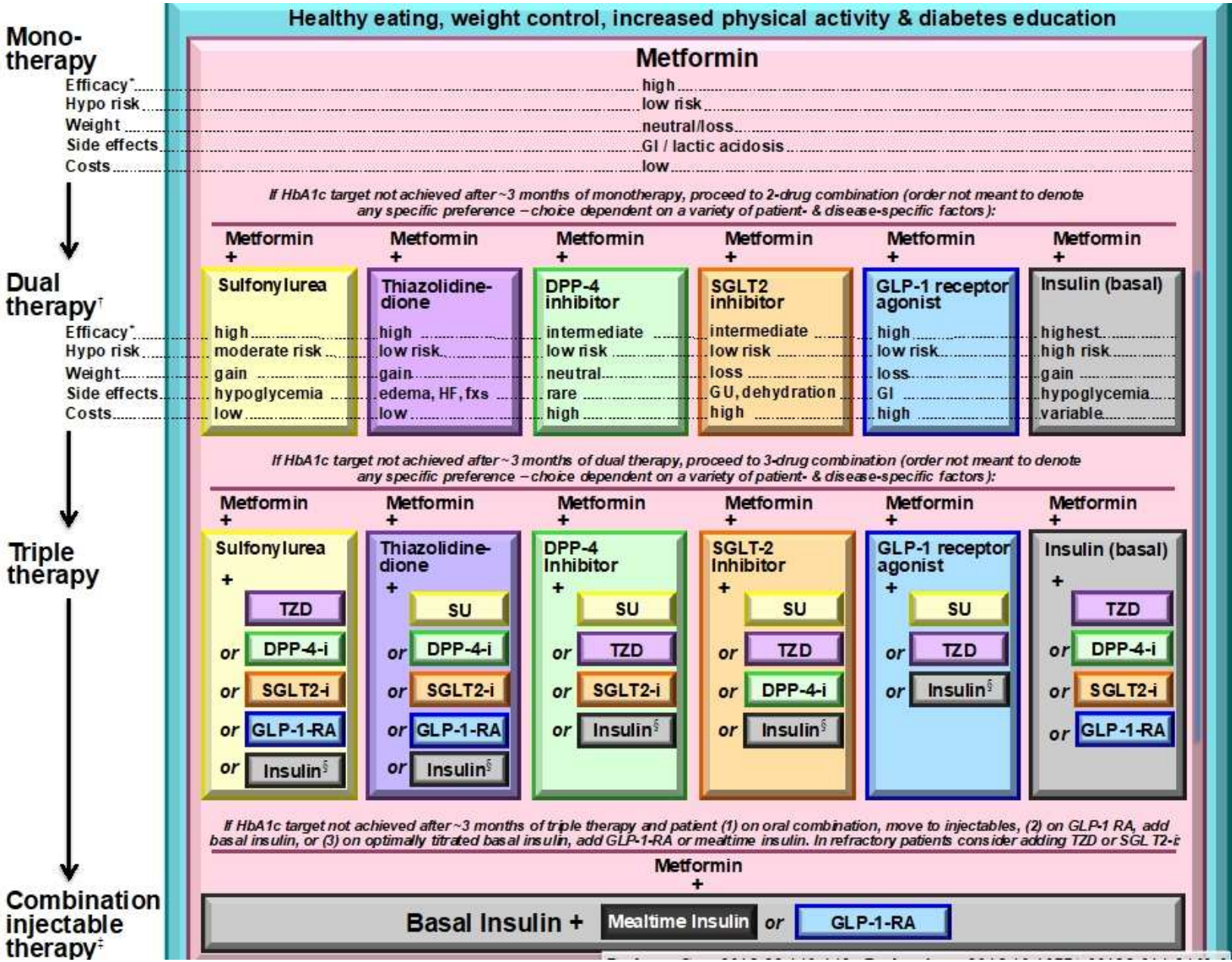
Diabetes Care 2012;35:1364-1379
Diabetologia 2012;55:1577-1596



American Diabetes Association.
EASD European Association for the Study of Diabetes

ADA-EASD Position Statement on the Management of Hyperglycemia in Type 2 Diabetes: A *Patient-Centered* Approach (Update)

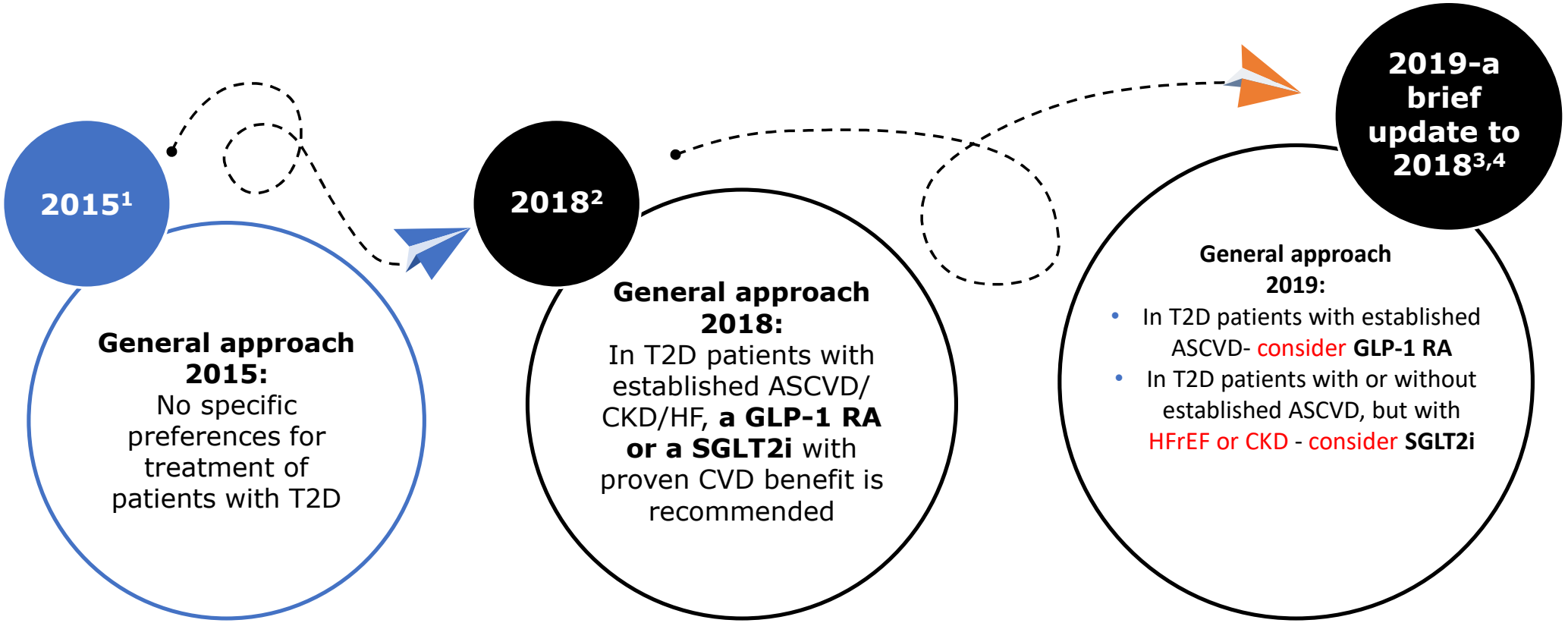
Diabetes Care 2015;38:140-149
Diabetologia 2015;58:429-442



American Diabetes Association.
EASD
European Association for the Study of Diabetes

Evolution of ADA/EASD guidelines for T2D

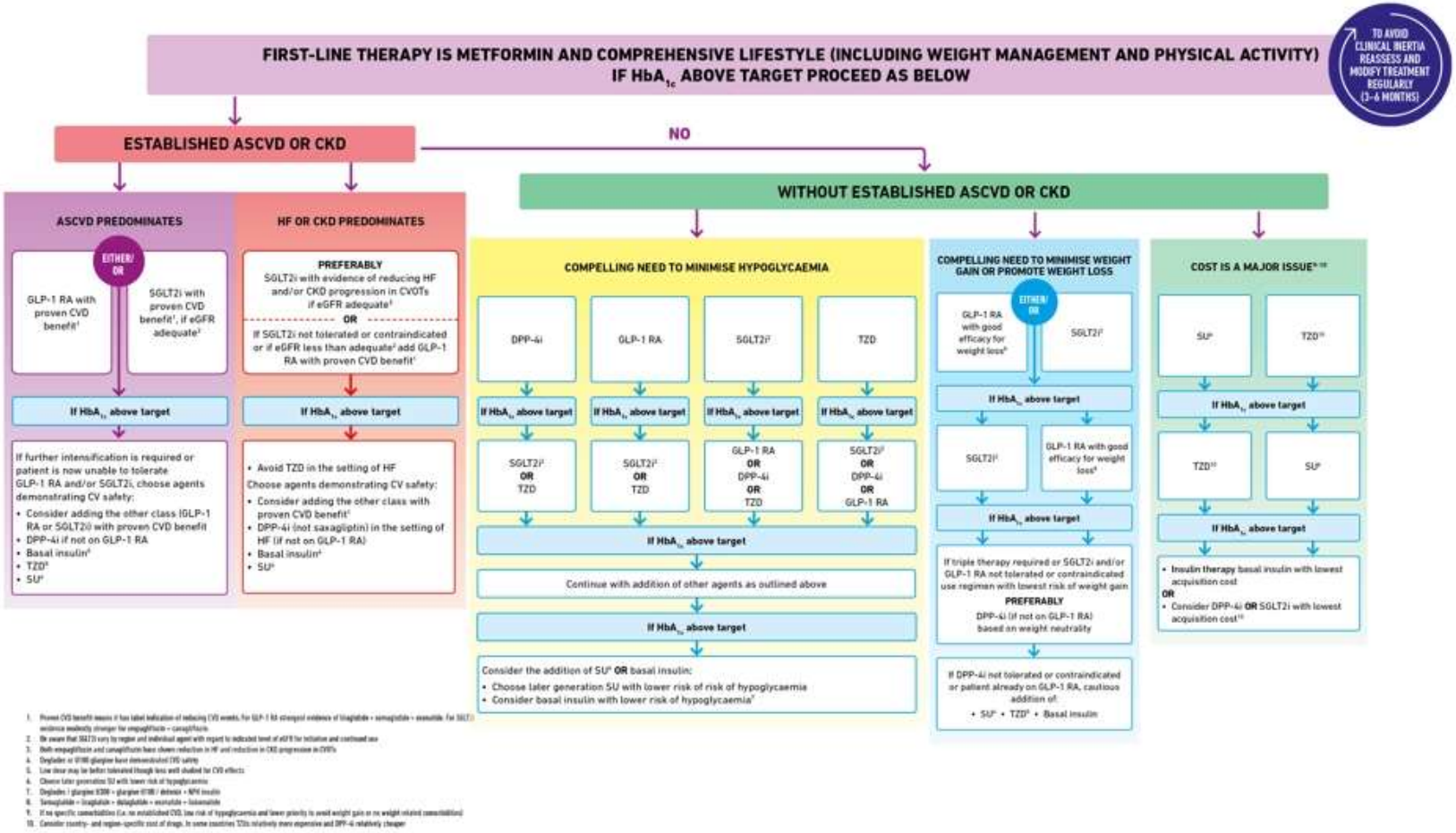
What are the changes?



ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

1. Inzucchi SE et al. Diabetologia 2015;58:429–442 ; 2. Davies MJ et al. Diabetologia 2018;61:2461-2498; 3 Buse JB et al. Diabetologia 2019;doi:10.1007/s00125-019-05039-w; 4. Diabetes Care; 2019:dci190066

ADA-EASD Consensus Report : Glucose-Lowering Medication in T2DM (2018)



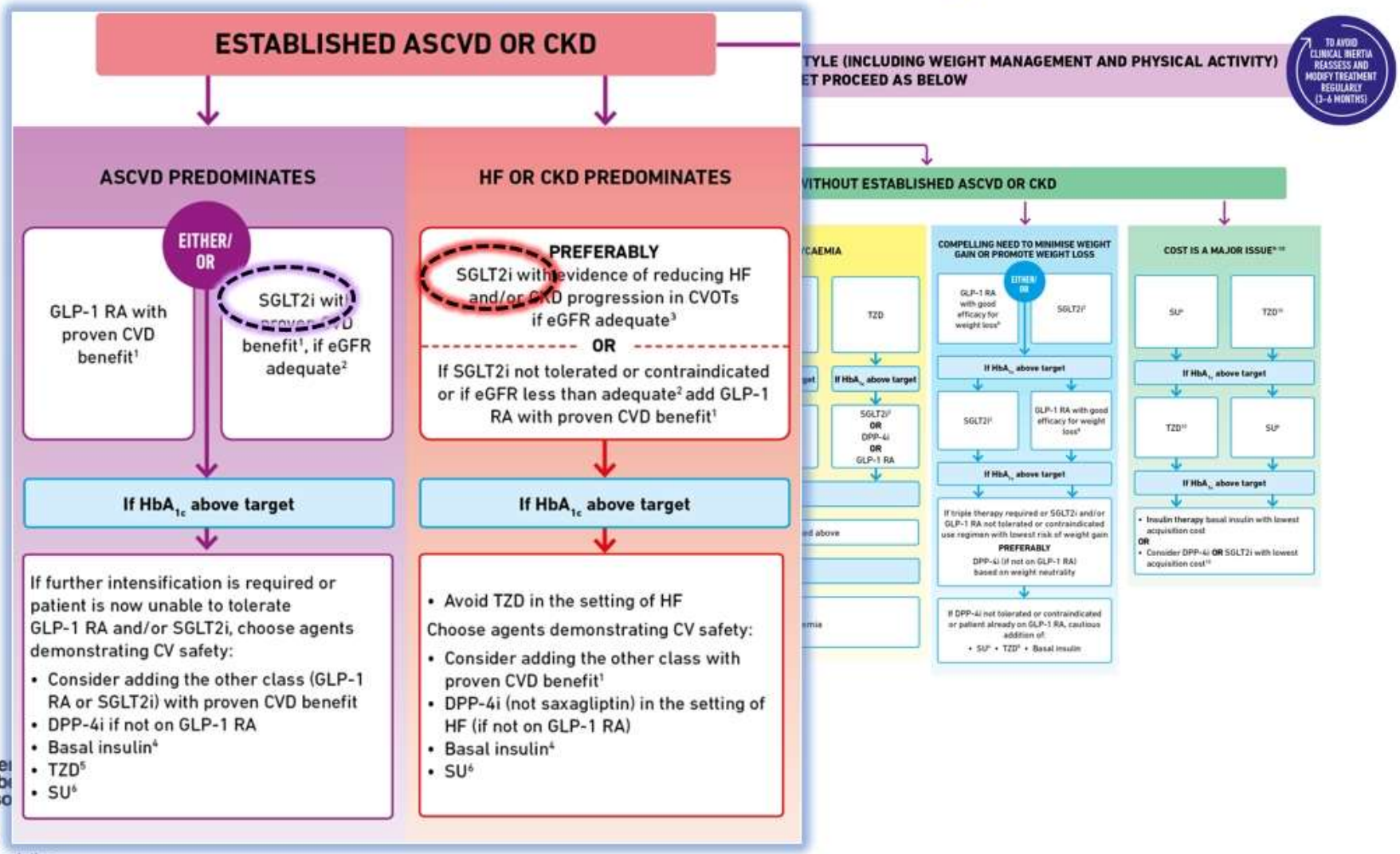
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated 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. Pioglitazone or GTNR 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 hypoglycaemia
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 hypoglycaemia 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

American Diabetes Association.

EASD
European Association for the Study of Diabetes

Diabetes Care 2018;41:2669-2701; Diabetologia 2018;61:2461-2498

ADA-EASD Consensus Report : Glucose-Lowering Medication in T2DM (2018)



American Diabetes Association

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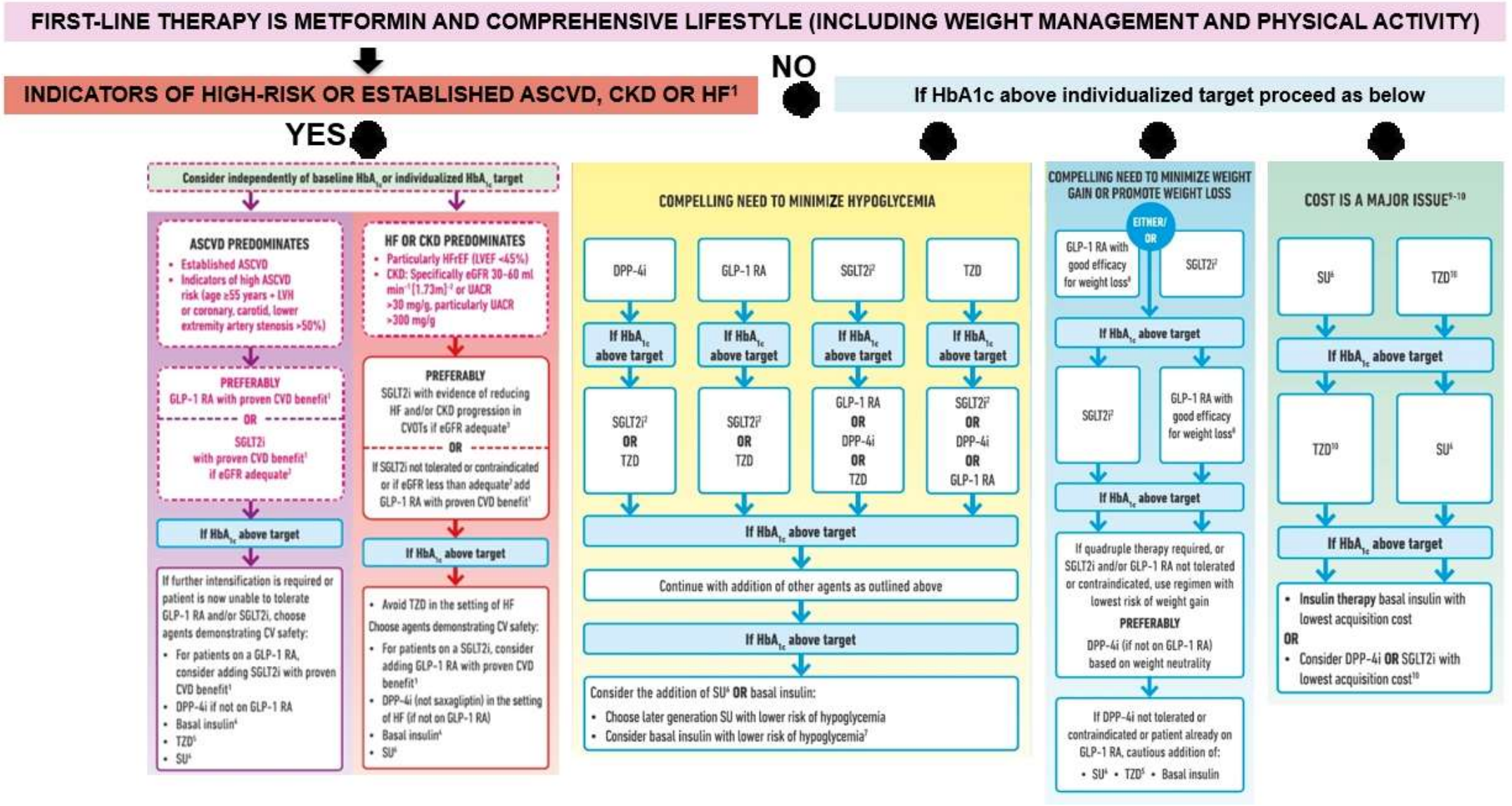
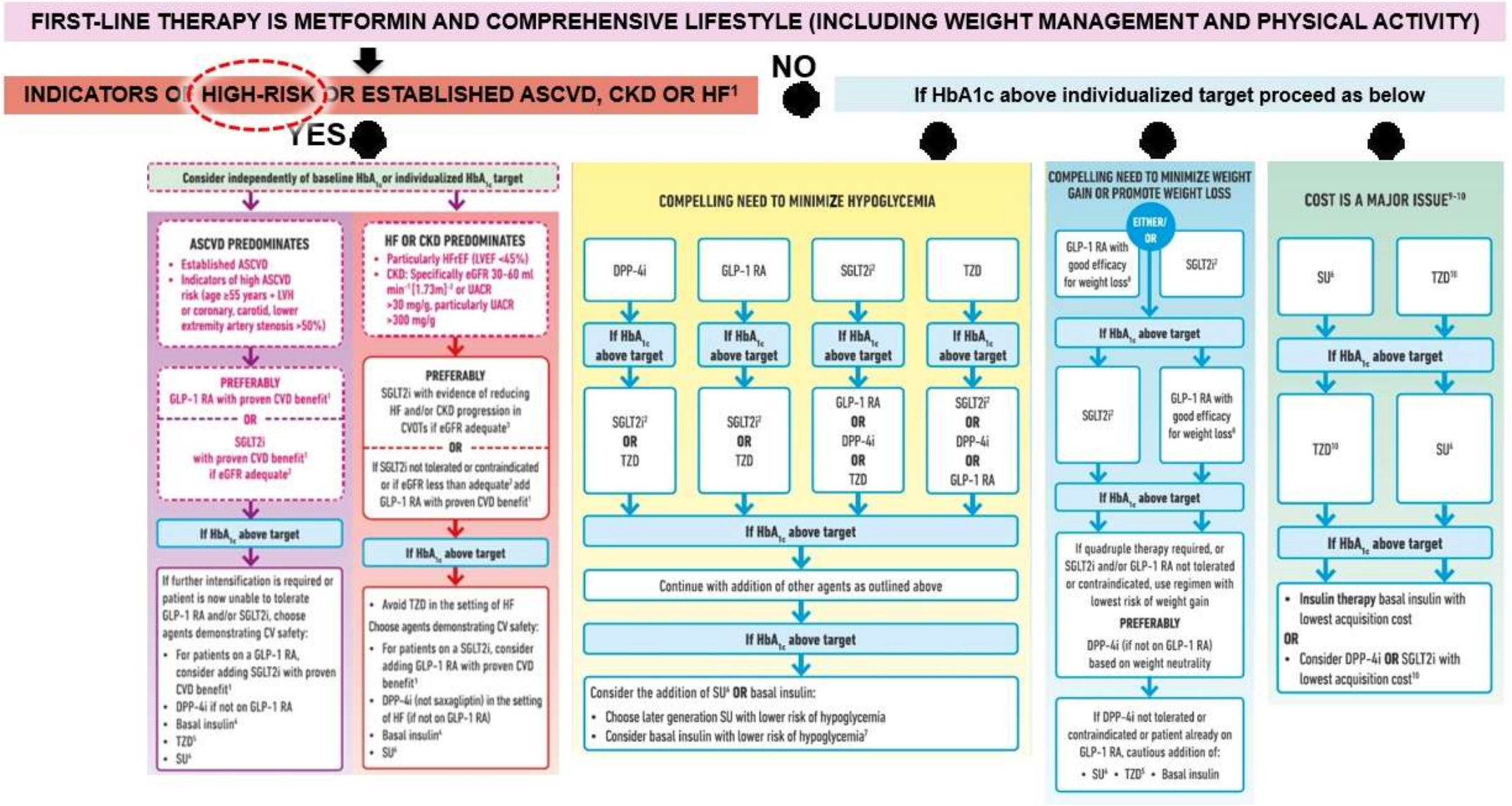
Diabetes Care 2018;41:2669-2701; Diabetologia 2018;61:2461-2498

ADA-EASD Consensus Report Update: Management of Hyperglycemia in T2DM (2019)



ADA-EASD Consensus Report Update: Management of Hyperglycemia in T2DM (2019)



Important updates from 2018

2018[1]

- T2D with established CVD was a compelling indication for treatment with a GLP-1 RA or SGLT2i

2019[2]

- **In high-risk individuals with established T2D**, the decision to treat with a **GLP-1 RA or SGLT2i** to reduce MACE, hHF, CV death, or CKD progression should be considered **independently of baseline HbA_{1c} or individualized HbA_{1c} target**

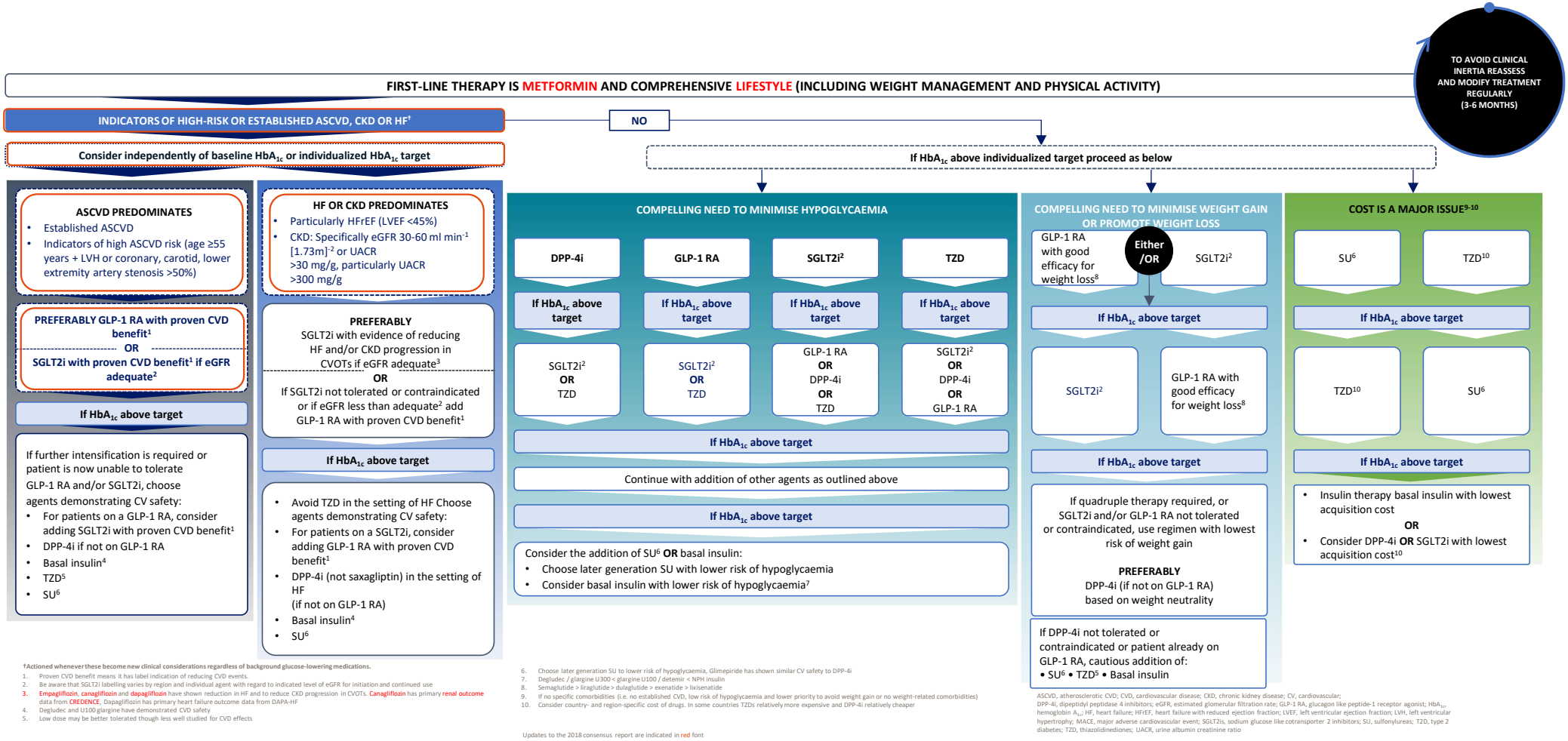
- Shared decision making for initial combination therapy in **new-onset cases of T2D**

- GLP-1 RA can be considered in patients **with T2D without established CVD** but with the presence of specific indicators of high risk

- **SGLT2is** are recommended in T2D patients with HF, particularly HFrEF, as well as in T2D patients with CKD* to reduce the progression of CKD, hHF, MACE and CV death
- For patients at risk of foot ulcers and amputation should be given proper care while using SGLT2i

*eGFR 30 to 60 ml/min/1.73 m^2 or urinary albumin-to-creatinine ratio >30 mg/g, particularly >300 mg/g
ASCVD, atherosclerotic CVD; CVD, cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon like peptide-1 receptor agonist; hHF, hospitalization for heart failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular event; SGLT2is, sodium glucose like cotransporter 2 inhibitors
1. Davies MJ et al. Diabetologia. 2018;61:2461-2498; 2. Buse JB et al. Diabetologia 2019;doi:10.1007/s00125-019-05039-w

Glucose-lowering medication in T2D: overall approach



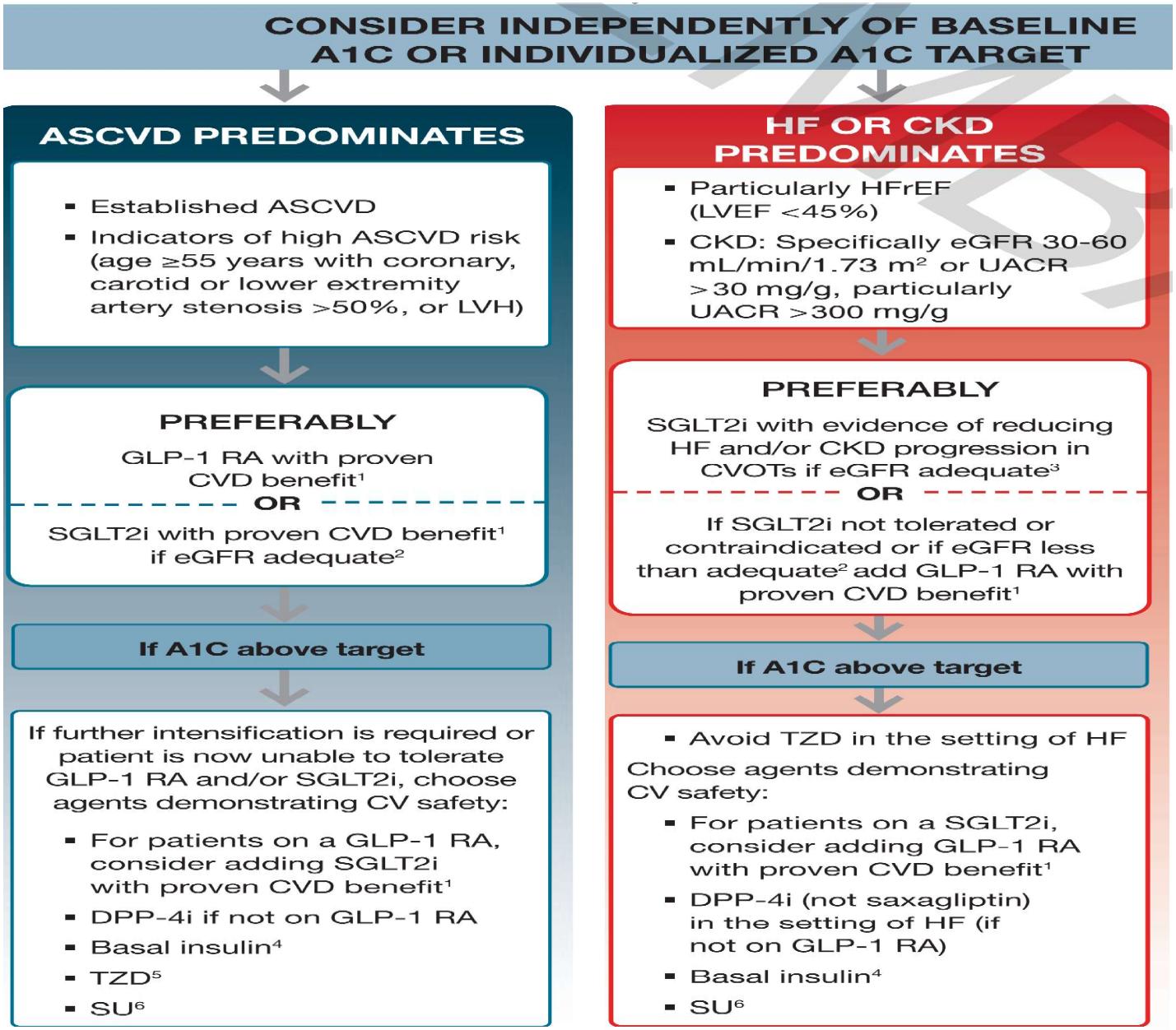
†Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

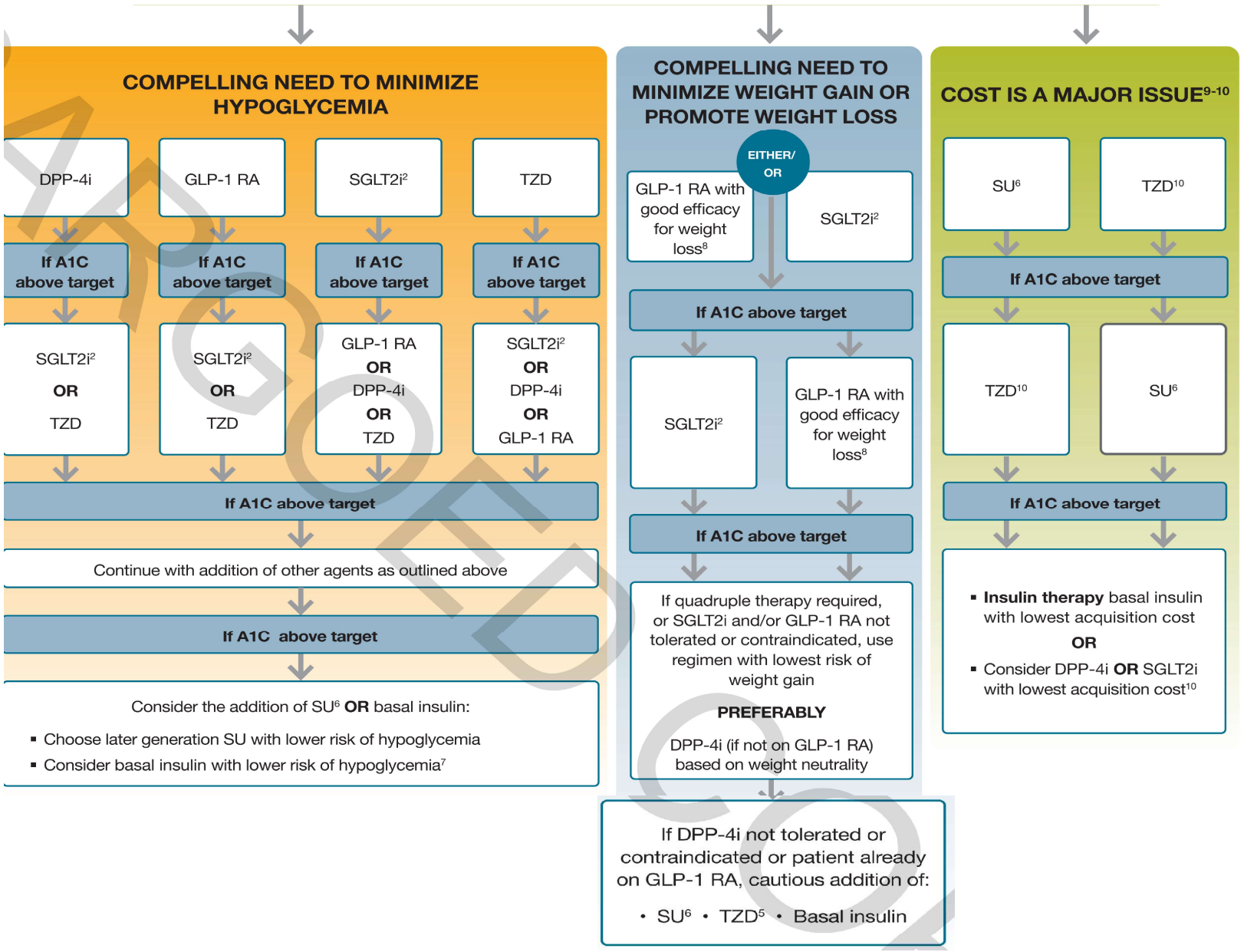
1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE, Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec and 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 to lower risk of hypoglycaemia, Glimepiride has shown similar CV safety to DPP-4i
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 hypoglycaemia 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

Updates to the 2018 consensus report are indicated in red font

ASCVD, atherosclerotic CVD; CVD, cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MACE, major adverse cardiovascular event; SGLT2is, sodium glucose like cotransporter 2 inhibitors; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinediones; UACR, urine albumin creatinine ratio

Diabetes Care; 2019:dci190066; Buse JB et al. Diabetologia 2019;doi:10.1007/s00125-019-05039-w


CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET
ASCVD PREDOMINATES
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)
PREFERABLY
GLP-1 RA with proven CVD benefit[1]
OR
SGLT2i with proven CVD benefit[1] if eGFR adequate[2]
If A1C above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
DPP-4i if not on GLP-1 RA
Basal insulin[4]
TZD[5]
SU[6]
HF OR CKD PREDOMINATES
Particularly HFrEF (LVEF <45%)
CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If A1C above target
Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin[4]
SU[6]


COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i[2]
TZD
If A1C above target
SGLT2i[2] OR TZD
SGLT2i[2] OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i[2] OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU[6] OR basal insulin:
▪ Choose later generation SU with lower risk of hypoglycemia
▪ Consider basal insulin with lower risk of hypoglycemia[7]
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[8]
SGLT2i[2]
If A1C above target
SGLT2i[2]
GLP-1 RA with good efficacy for weight loss[8]
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU[6] • TZD[5] • Basal insulin
COST IS A MAJOR ISSUE[9-10]
SU[6]
TZD[10]
If A1C above target
TZD[10]
SU[6]
If A1C above target
▪ Insulin therapy basal insulin with lowest acquisition cost
OR
▪ Consider DPP-4i OR SGLT2i with lowest acquisition cost[10]

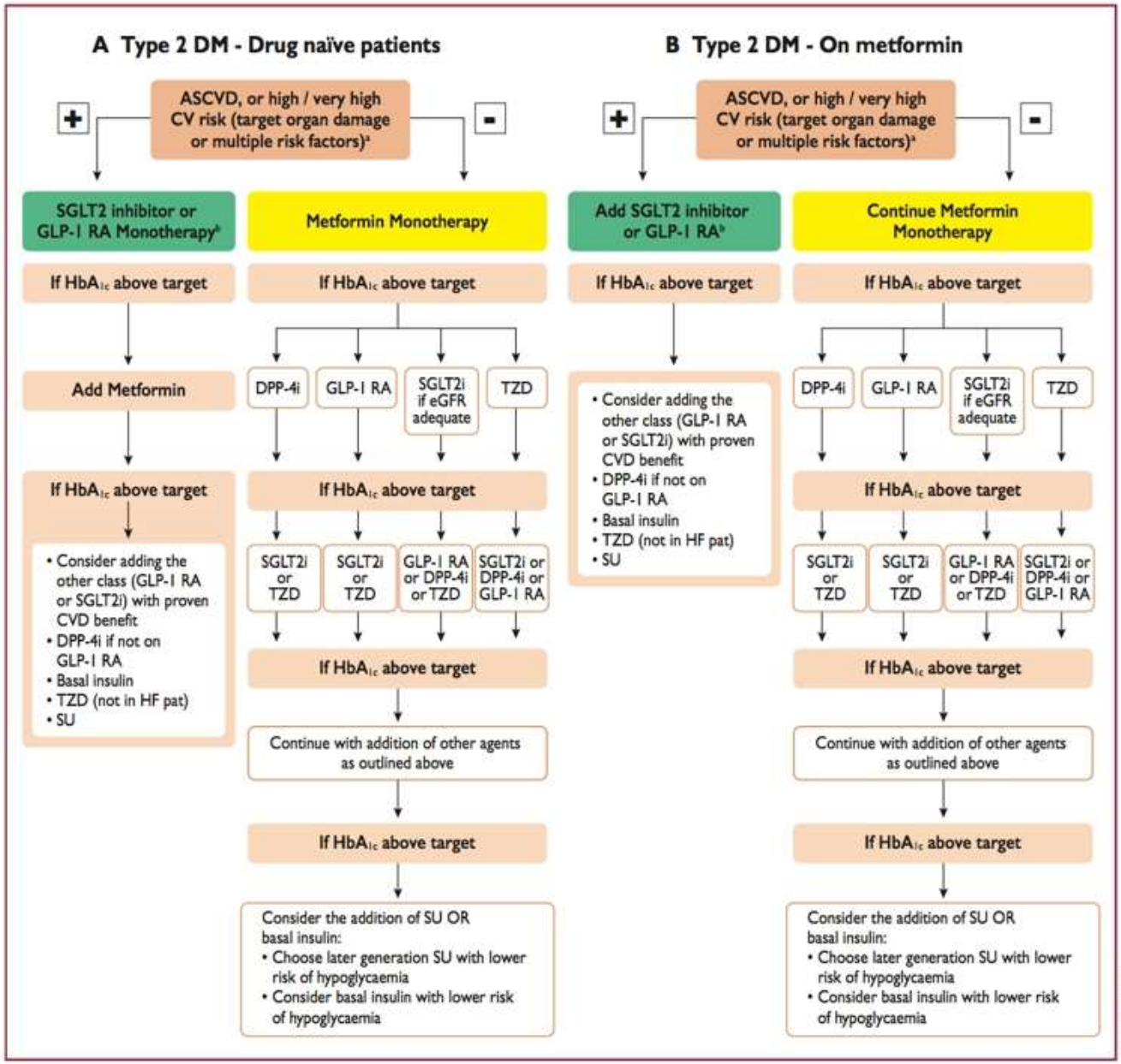
ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486

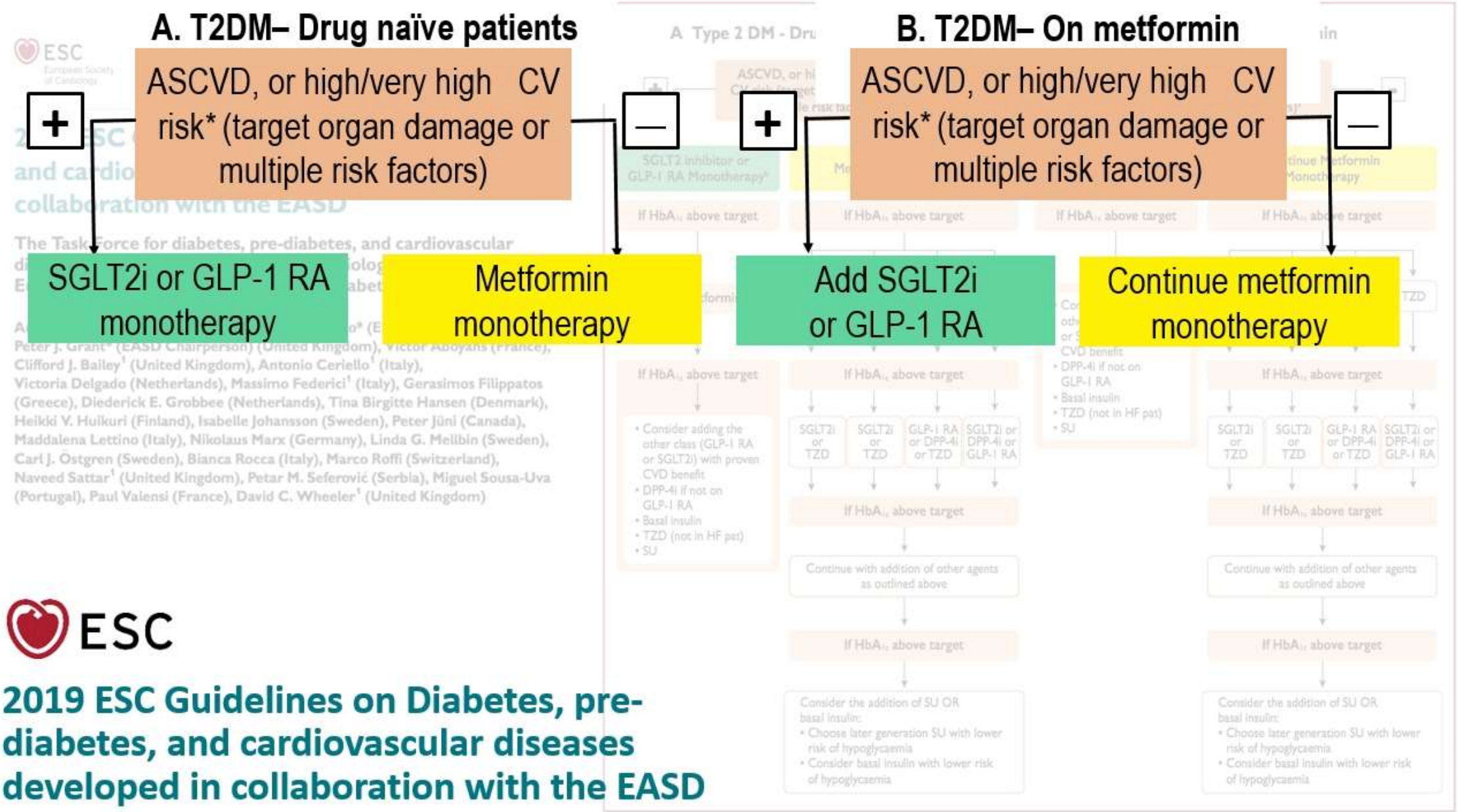
ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

Authors/Task Force Members: Francesco Cosentino* (ESC Chairperson) (Sweden), Peter J. Grant* (EASD Chairperson) (United Kingdom), Victor Aboyans (France), Clifford J. Bailey[1] (United Kingdom), Antonio Ceriello[1] (Italy), Victoria Delgado (Netherlands), Massimo Federici[1] (Italy), Gerasimos Filippatos (Greece), Diederick E. Grobbee (Netherlands), Tina Birgitte Hansen (Denmark), Heikki V. Huikuri (Finland), Isabelle Johansson (Sweden), Peter Jüni (Canada), Maddalena Lettino (Italy), Nikolaus Marx (Germany), Linda G. Mellbin (Sweden), Carl J. Östgren (Sweden), Bianca Rocca (Italy), Marco Roffi (Switzerland), Naveed Sattar[1] (United Kingdom), Petar M. Seferović (Serbia), Miguel Sousa-Uva (Portugal), Paul Valensi (France), David C. Wheeler[1] (United Kingdom)





ESC

2019 ESC Guidelines on Diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

A. T2DM– Drug naïve patients

ASCVD, or high/very high CV risk* (target organ damage or multiple risk factors)

\+ → SGLT2i or GLP-1 RA monotherapy

– → Metformin monotherapy

B. T2DM– On metformin

ASCVD, or high/very high CV risk* (target organ damage or multiple risk factors)

\+ → Add SGLT2i or GLP-1 RA

– → Continue metformin monotherapy

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.
[c]Age, hypertension, dyslipidemia, smoking, obesity.

ESC

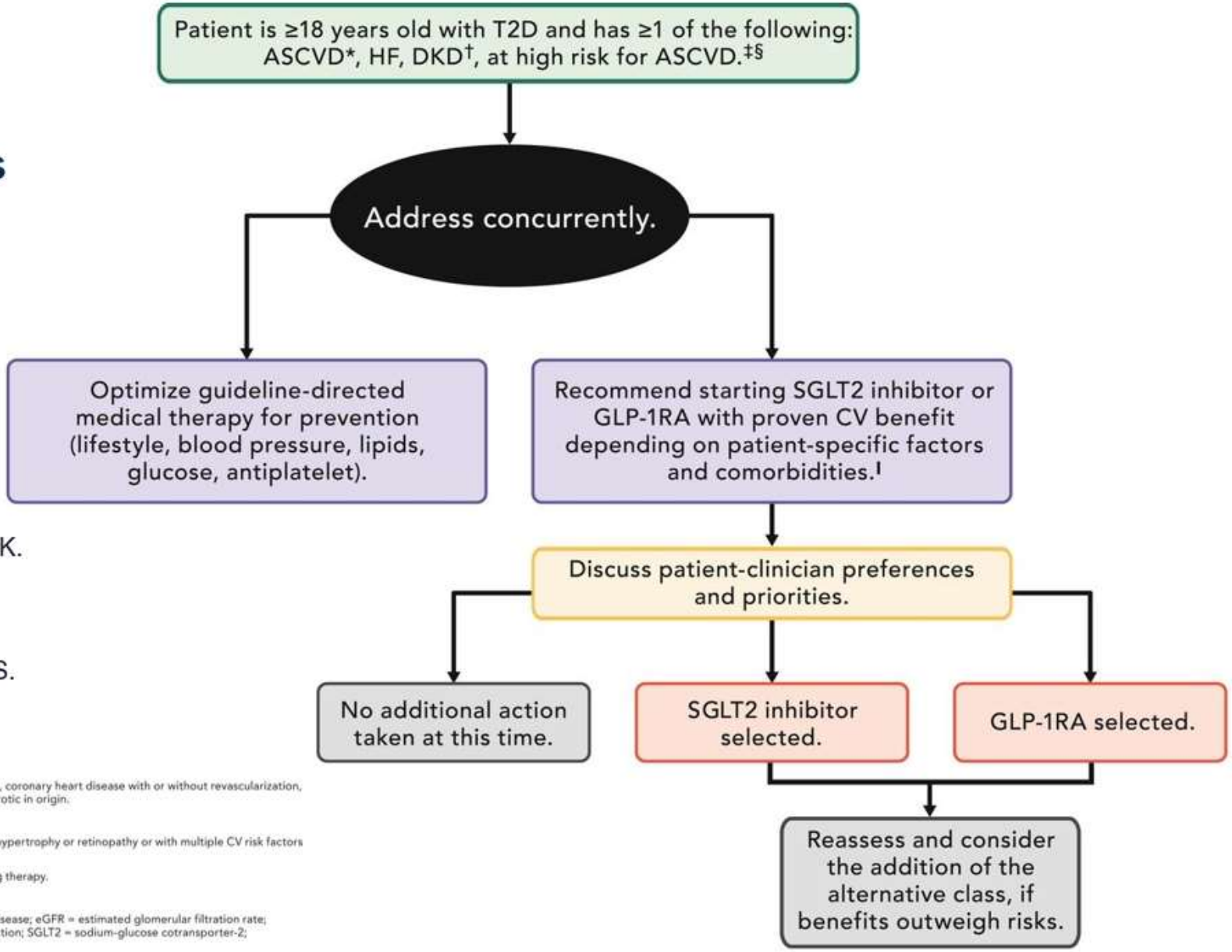
2019 ESC Guidelines on Diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

AMERICAN COLLEGE of CARDIOLOGY

2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes

A Report of the ACC Solution Set Oversight Committee

Sandeep R. Das, Brendan M. Everett, Kim K. Birtcher, Jenifer M. Brown, James L. Januzzi Jr., Rita R. Kalyani, Mikhail Kosiborod, Melissa Magwire, Pamela B. Morris, Joshua J. Neumiller and Laurence S. Sperling (*JACC* 2020;76:1117-1145)



* ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

† DKD is a clinical diagnosis marked by reduced eGFR , the presence of albuminuria, or both.

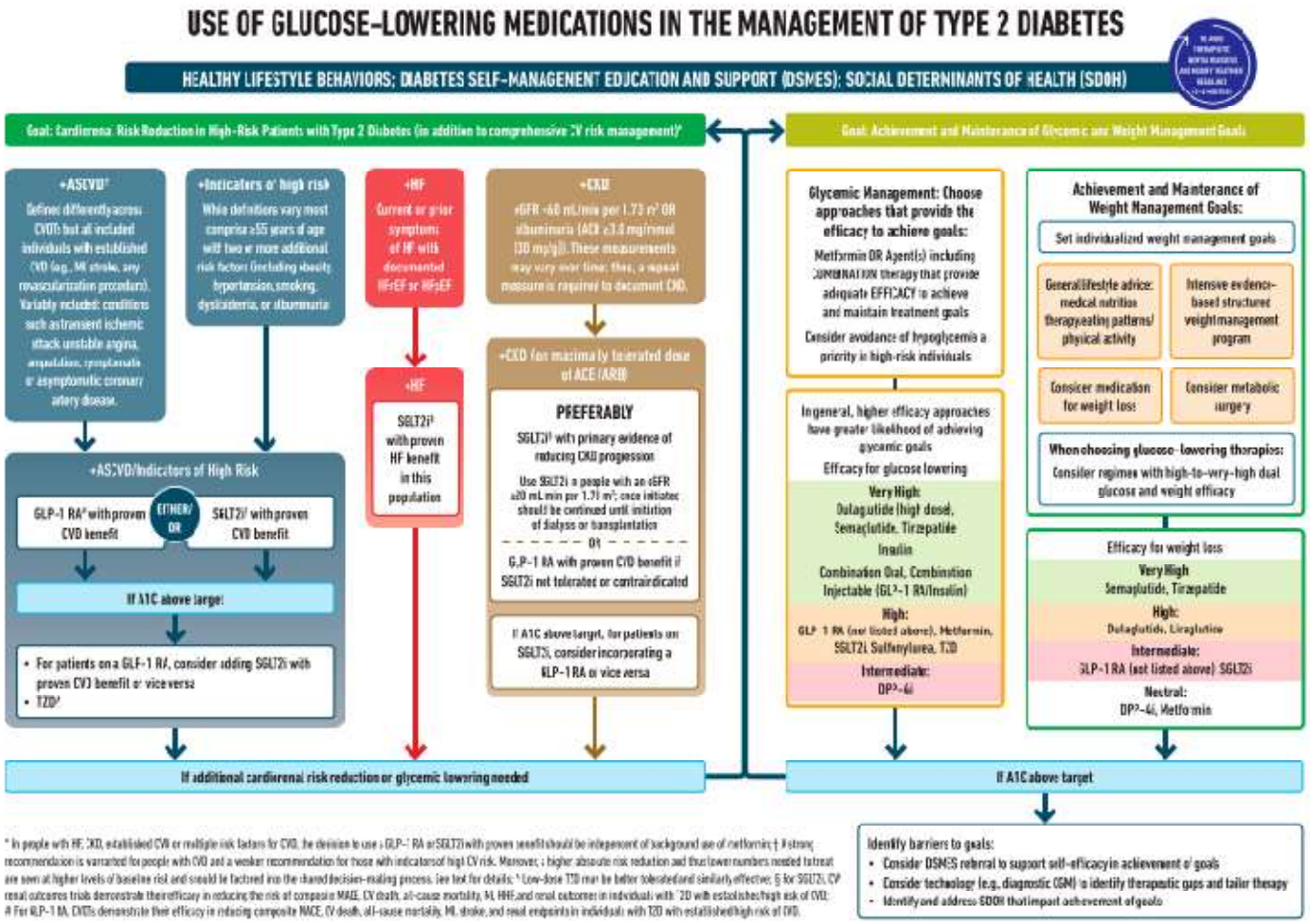
‡ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

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

‖ This may include the addition of a GLP-1RA in the appropriate patient (see Section 5.3.3).

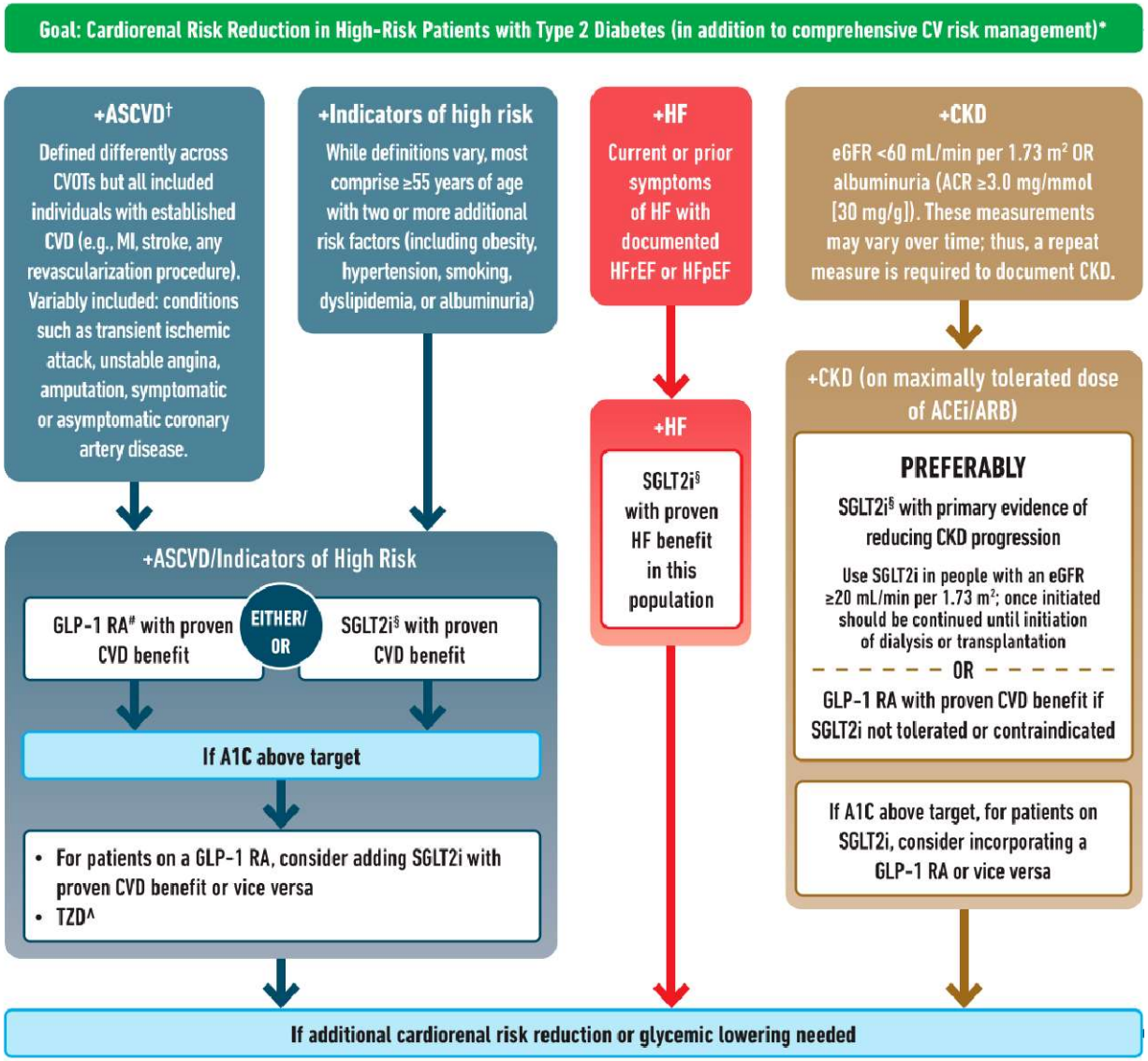
ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

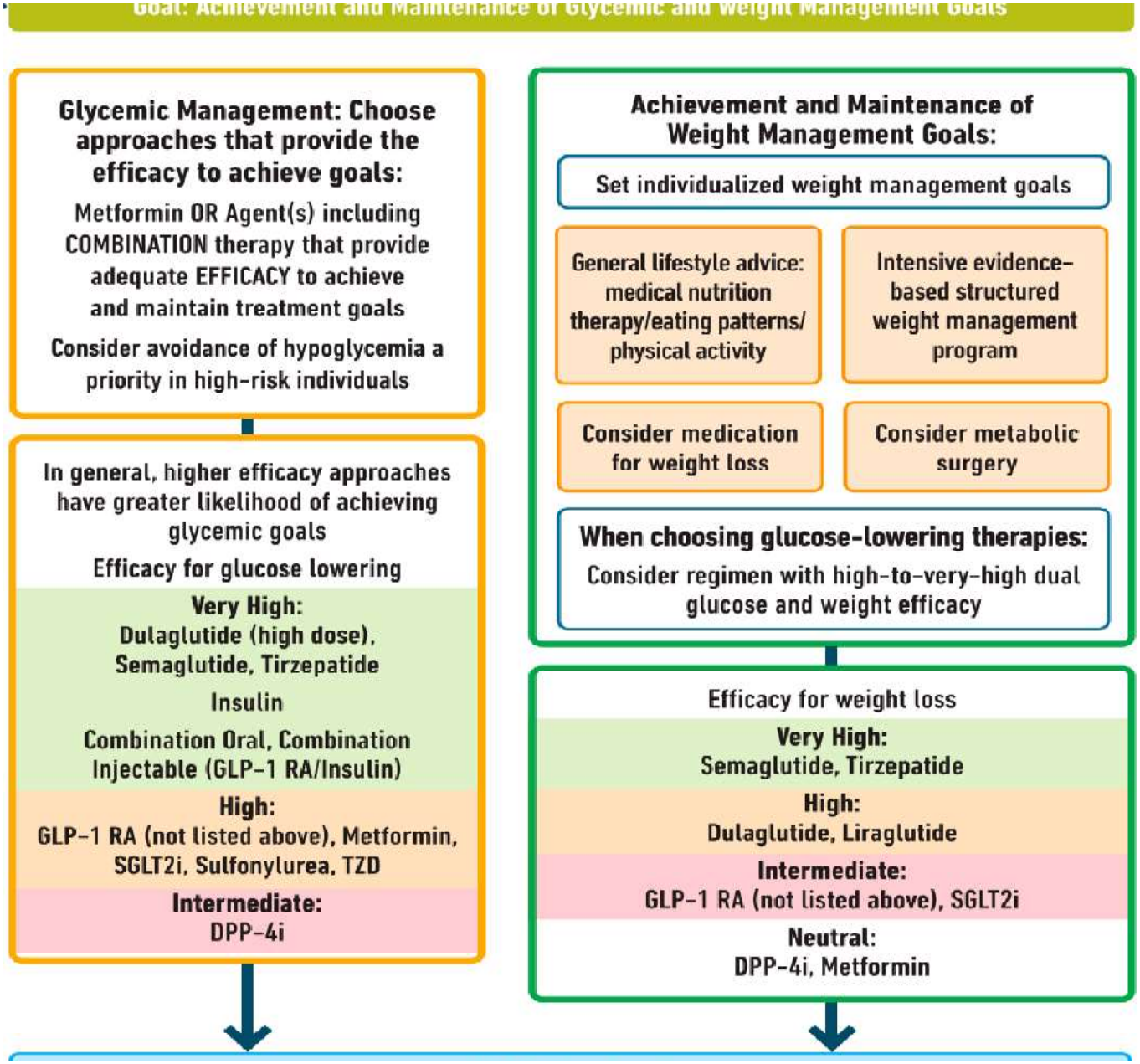
ADA 2023

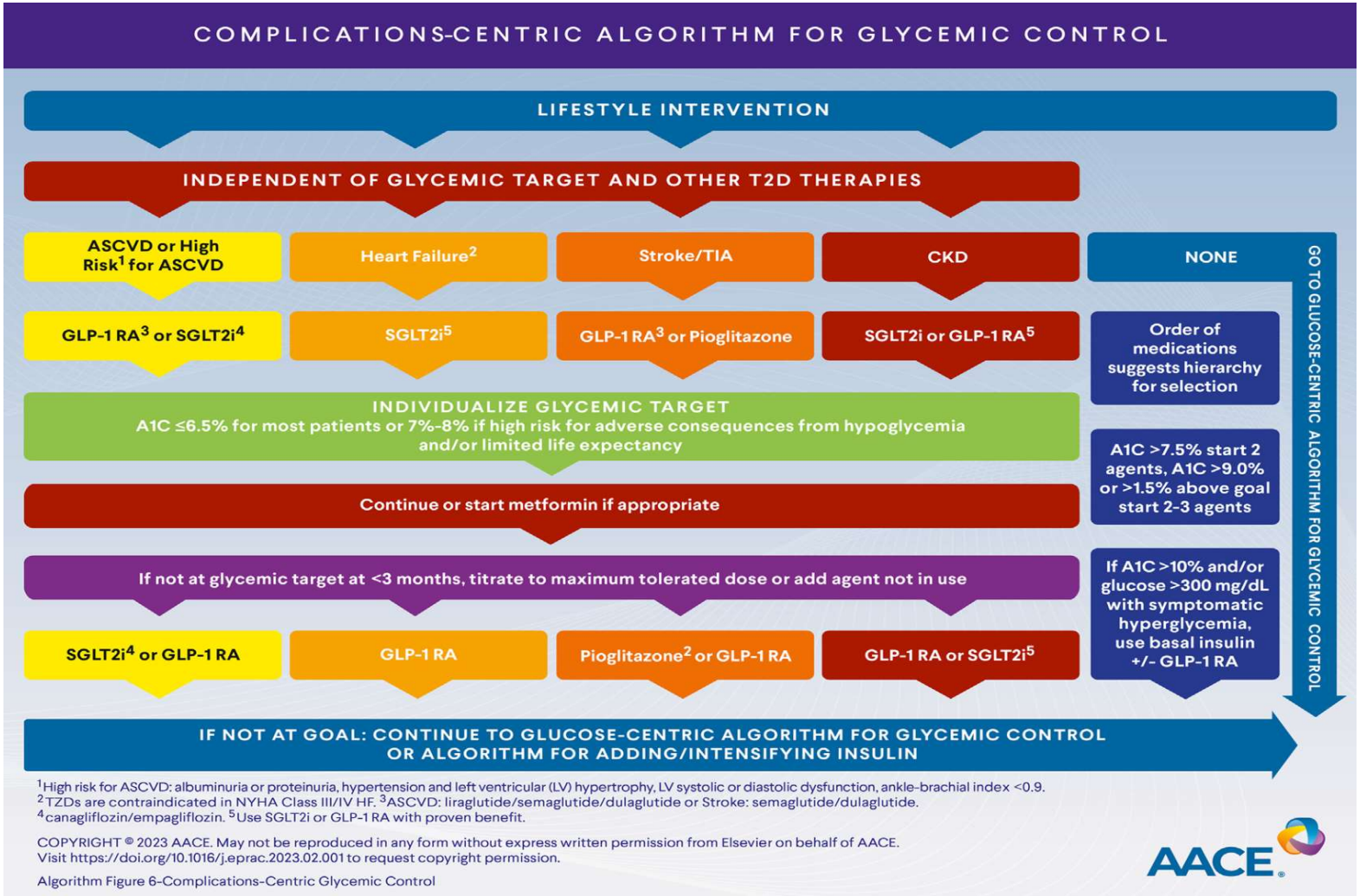


* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ‡ Low-dose TZD may be better tolerated and similarly effective; § for SGLT2i, CV renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established high risk of CVD; ¶ For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established high risk of CVD.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

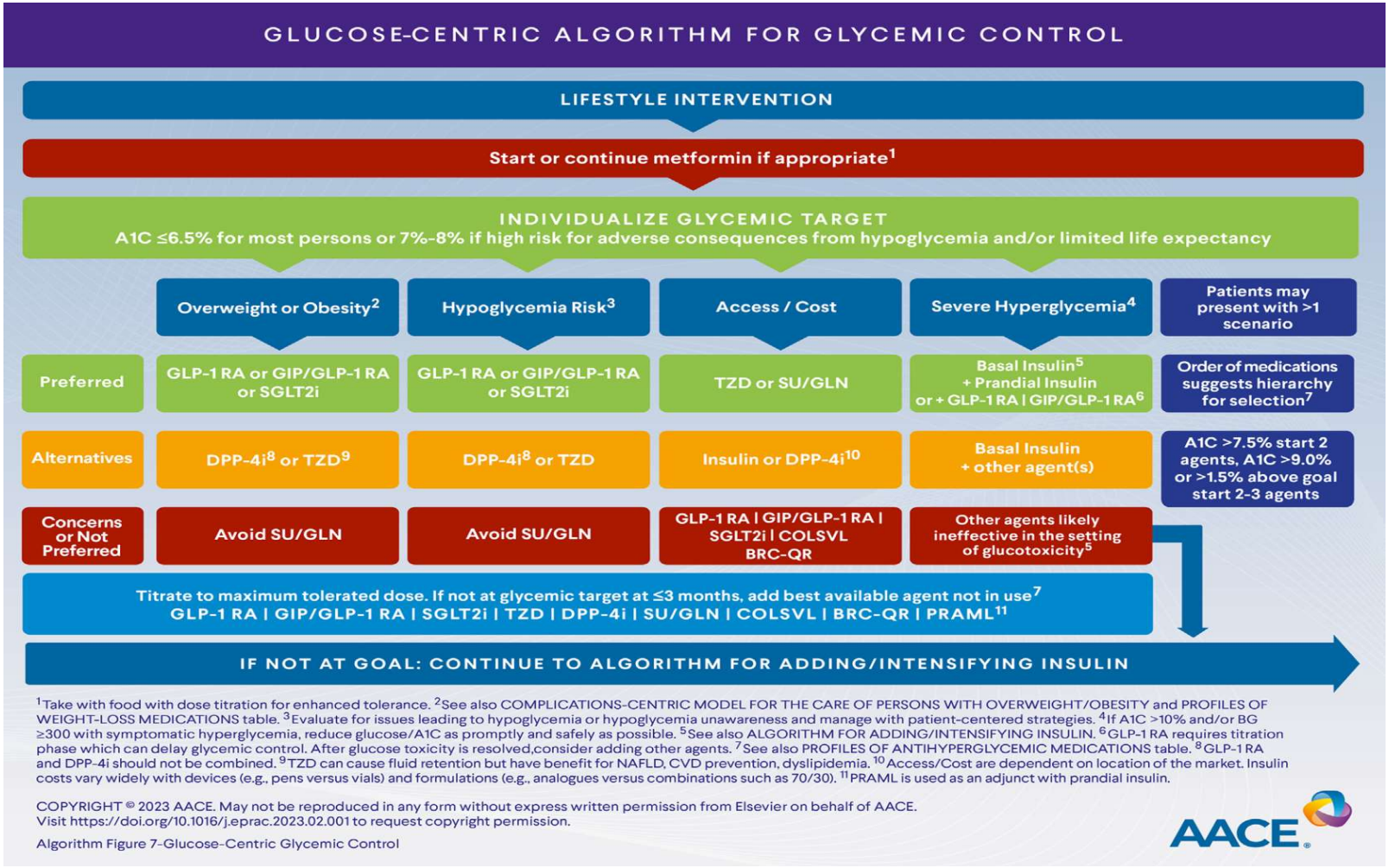

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*
+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.
+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.
+ASCVD/Indicators of High Risk
GLP-1 RA# with proven CVD benefit
EITHER/ OR
SGLT2i§ with proven CVD benefit
If A1C above target
• For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
• TZD^
+HF
SGLT2i§ with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiorenal risk reduction or glycemic lowering needed


Goal: Achievement and Maintenance of Glycemic and Weight Management Goals
Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycemia a priority in high-risk individuals
In general, higher efficacy approaches have greater likelihood of achieving glycemic goals
Efficacy for glucose lowering
Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate:
DPP-4i
Achievement and Maintenance of Weight Management Goals:
Set individualized weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management program
Consider medication for weight loss
Consider metabolic surgery
When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy
Efficacy for weight loss
Very High:
Semaglutide, Tirzepatide
High:
Dulaglutide, Liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
DPP-4i, Metformin



[1]High risk for ASCVD: albuminuria or proteinuria, hypertension and left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, ankle-brachial index <0.9.
[2]TZDs are contraindicated in NYHA Class III/IV HF. [3]ASCVD: liraglutide/semaglutide/dulaglutide or Stroke: semaglutide/dulaglutide.
[4]canagliflozin/empagliflozin. [5]Use SGLT2i or GLP-1 RA with proven benefit.

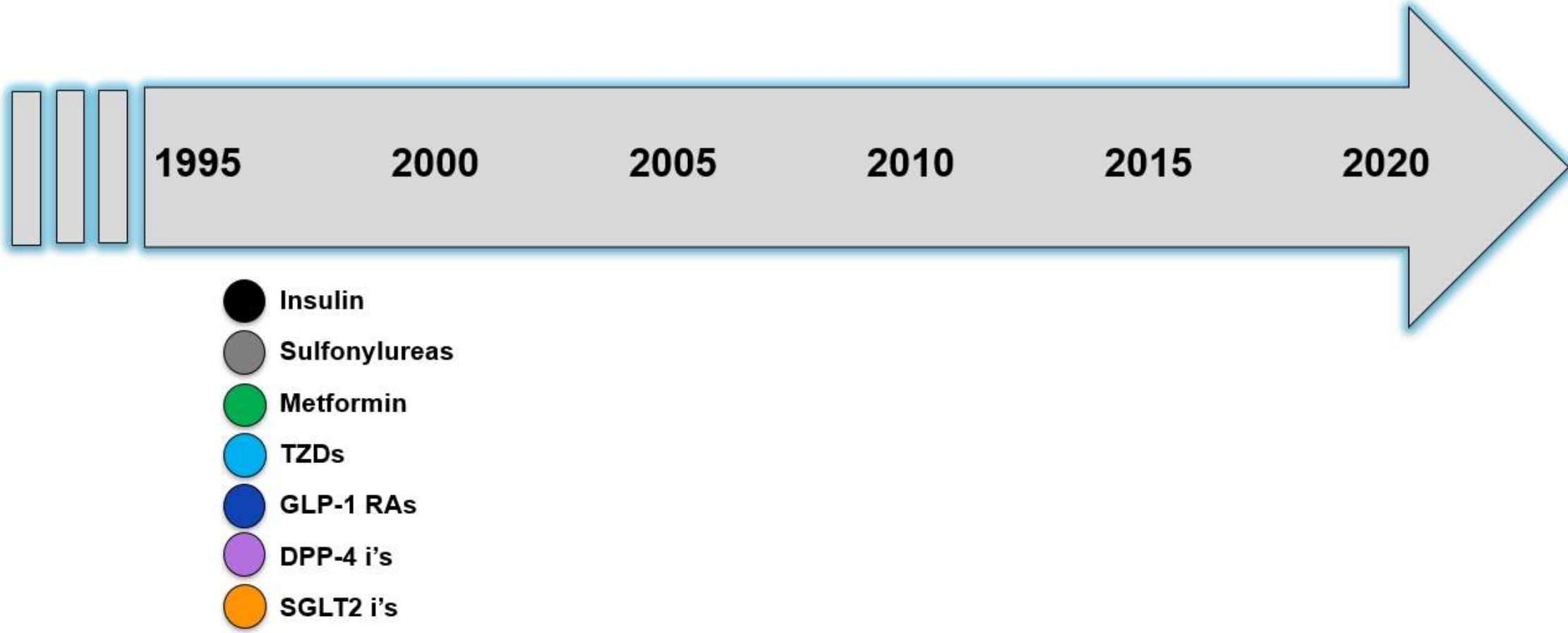
Algorithm Figure 6-Complications-Centric Glycemic Control



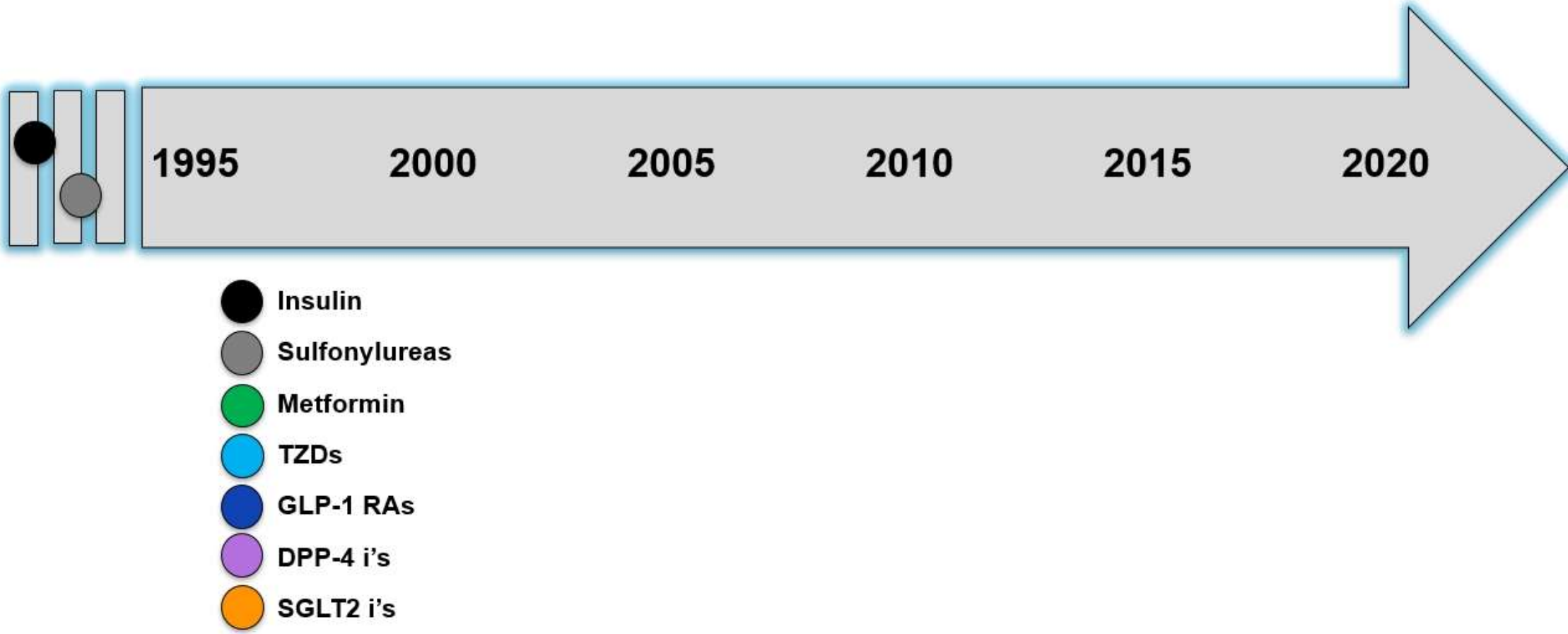
[1]Take with food with dose titration for enhanced tolerance. [2]See also COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY and PROFILES OF WEIGHT-LOSS MEDICATIONS table. [3]Evaluate for issues leading to hypoglycemia or hypoglycemia unawareness and manage with patient-centered strategies. [4]If A1C >10% and/or BG ≥300 with symptomatic hyperglycemia, reduce glucose/A1C as promptly and safely as possible. [5]See also ALGORITHM FOR ADDING/INTENSIFYING INSULIN. [6]GLP-1 RA requires titration phase which can delay glycemic control. After glucose toxicity is resolved,consider adding other agents. [7]See also PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS table. [8]GLP-1 RA and DPP-4i should not be combined. [9]TZD can cause fluid retention but have benefit for NAFLD, CVD prevention, dyslipidemia. [10]Access/Cost are dependent on location of the market. Insulin costs vary widely with devices (e.g., pens versus vials) and formulations (e.g., analogues versus combinations such as 70/30). [11]PRAML is used as an adjunct with prandial insulin.

Algorithm Figure 7-Glucose-Centric Glycemic Control

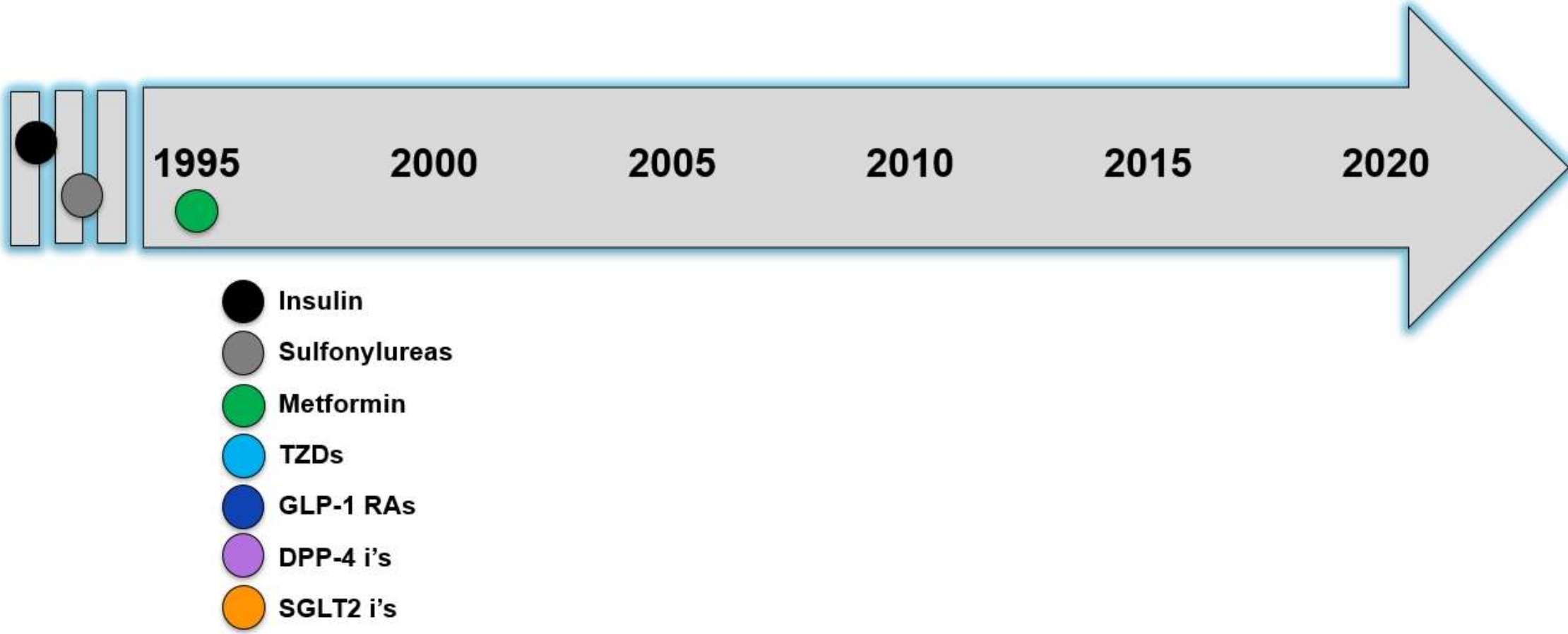
Treatment of T2DM over the Past 25+ Years



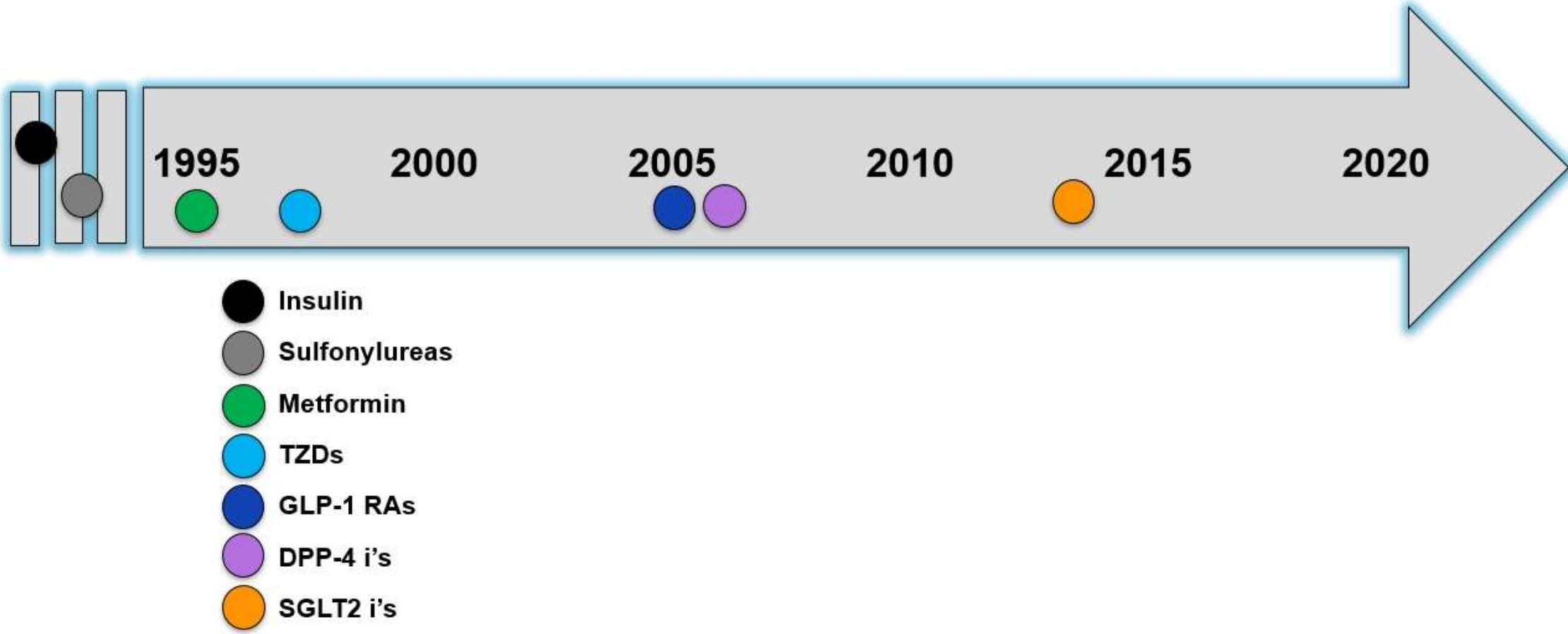
Treatment of T2DM over the Past 25+ Years



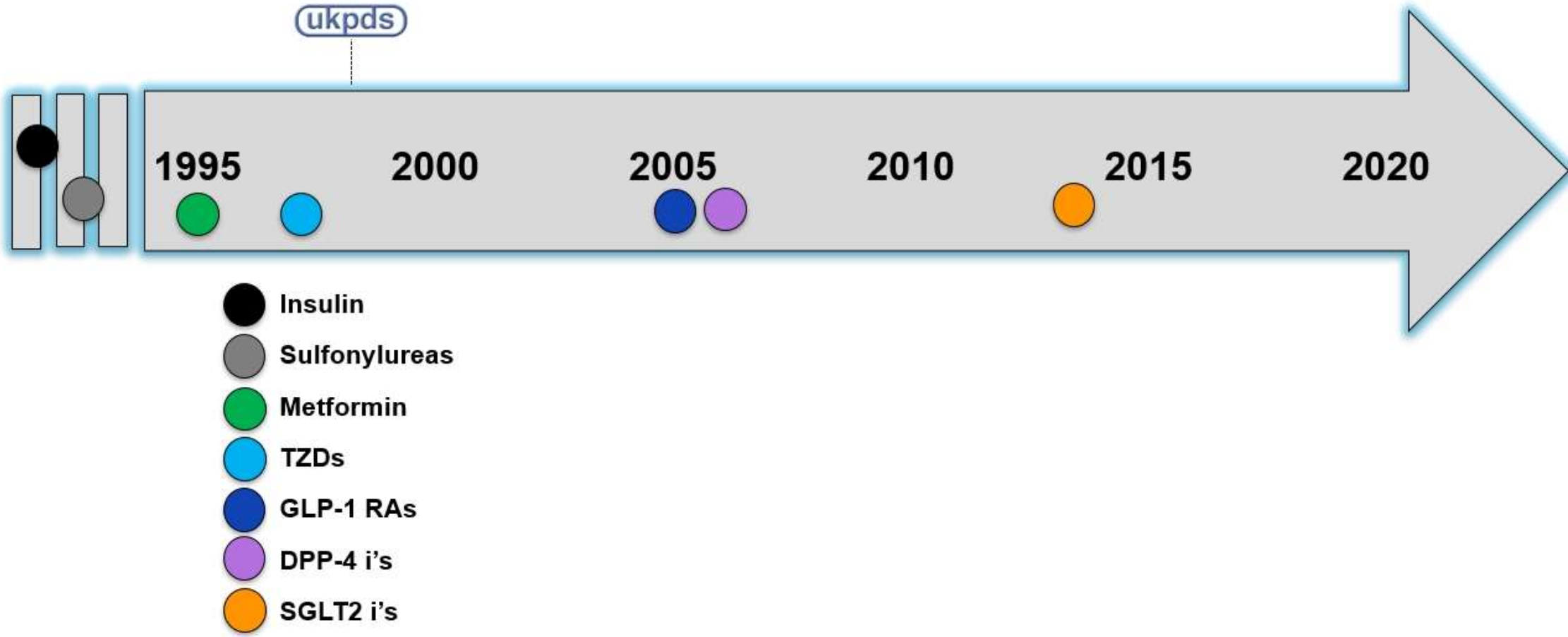
Treatment of T2DM over the Past 25+ Years



Treatment of T2DM over the Past 25+ Years



Treatment of T2DM over the Past 25+ Years



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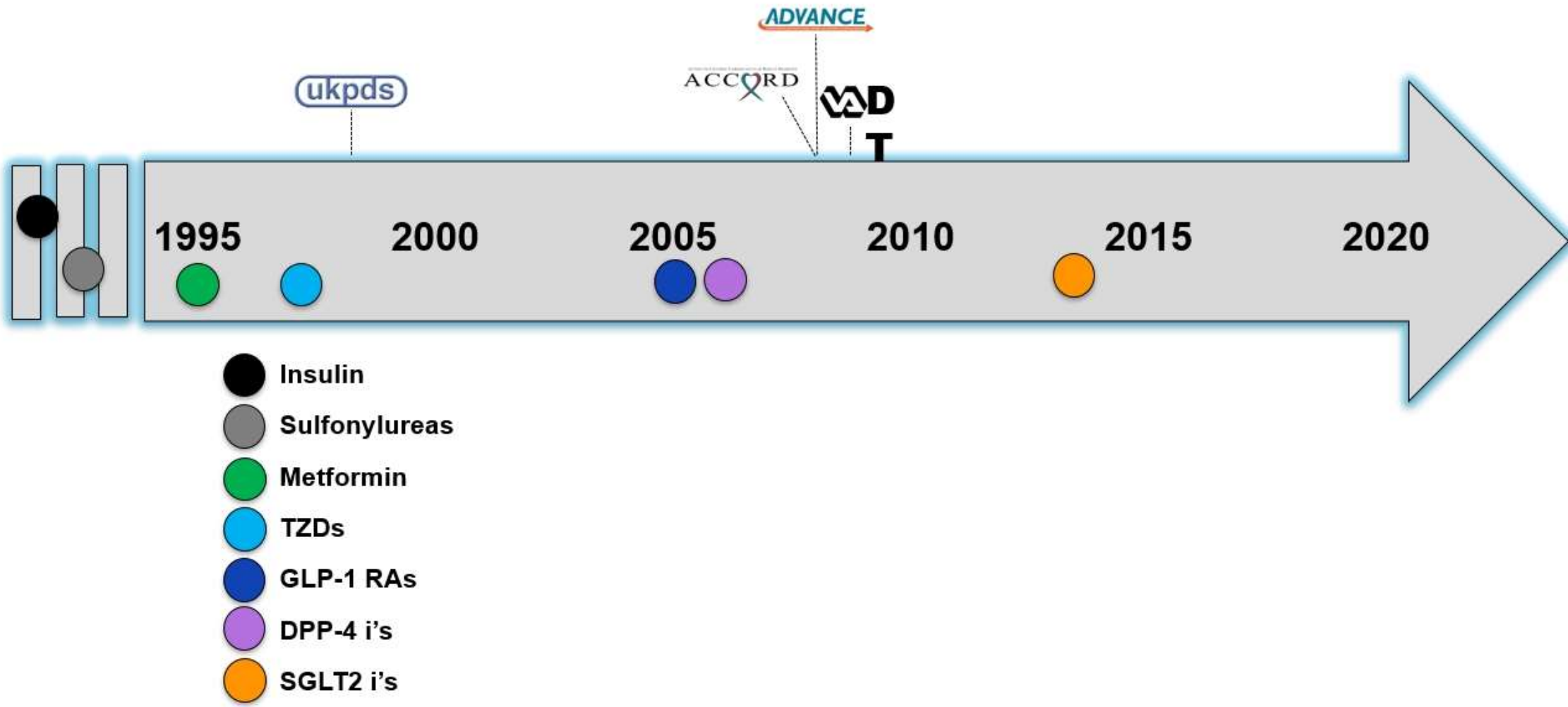

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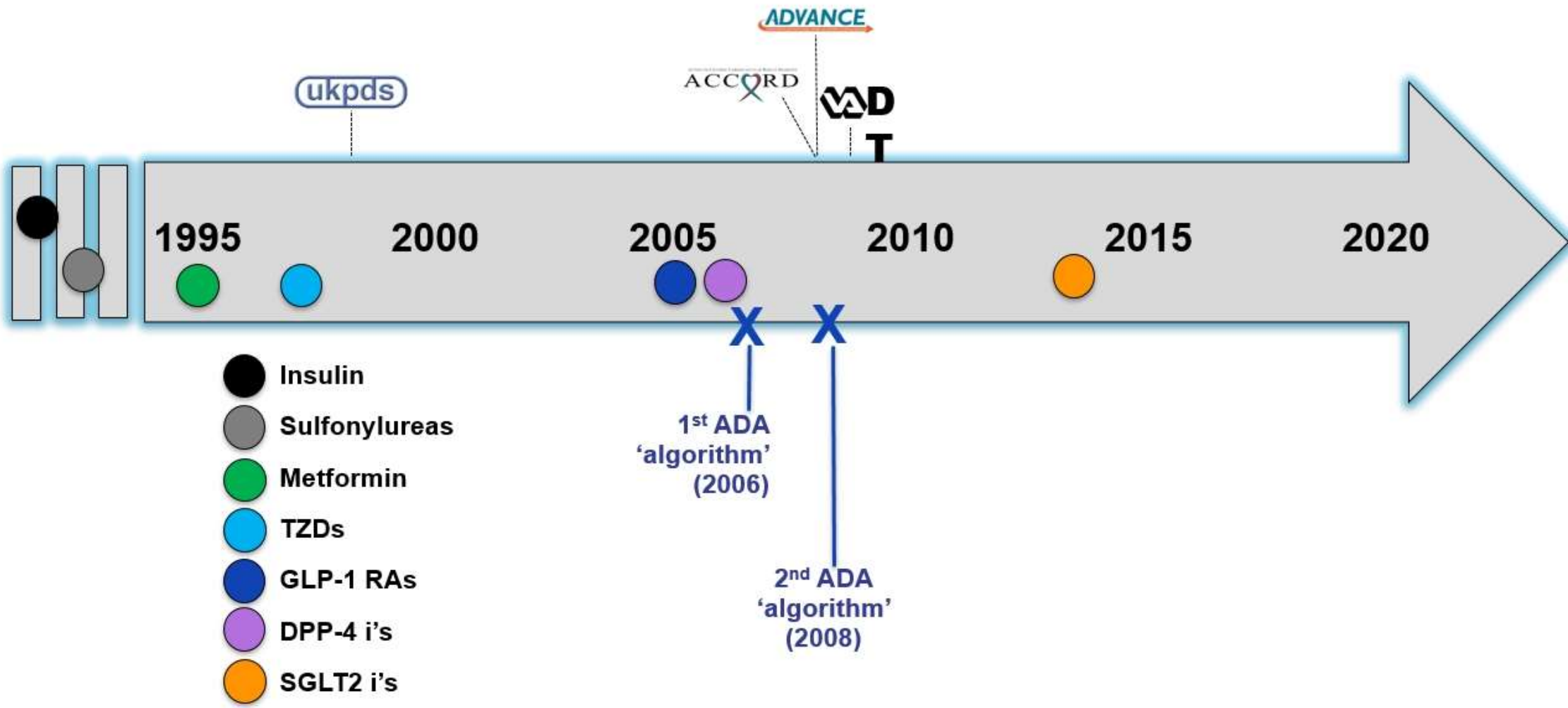
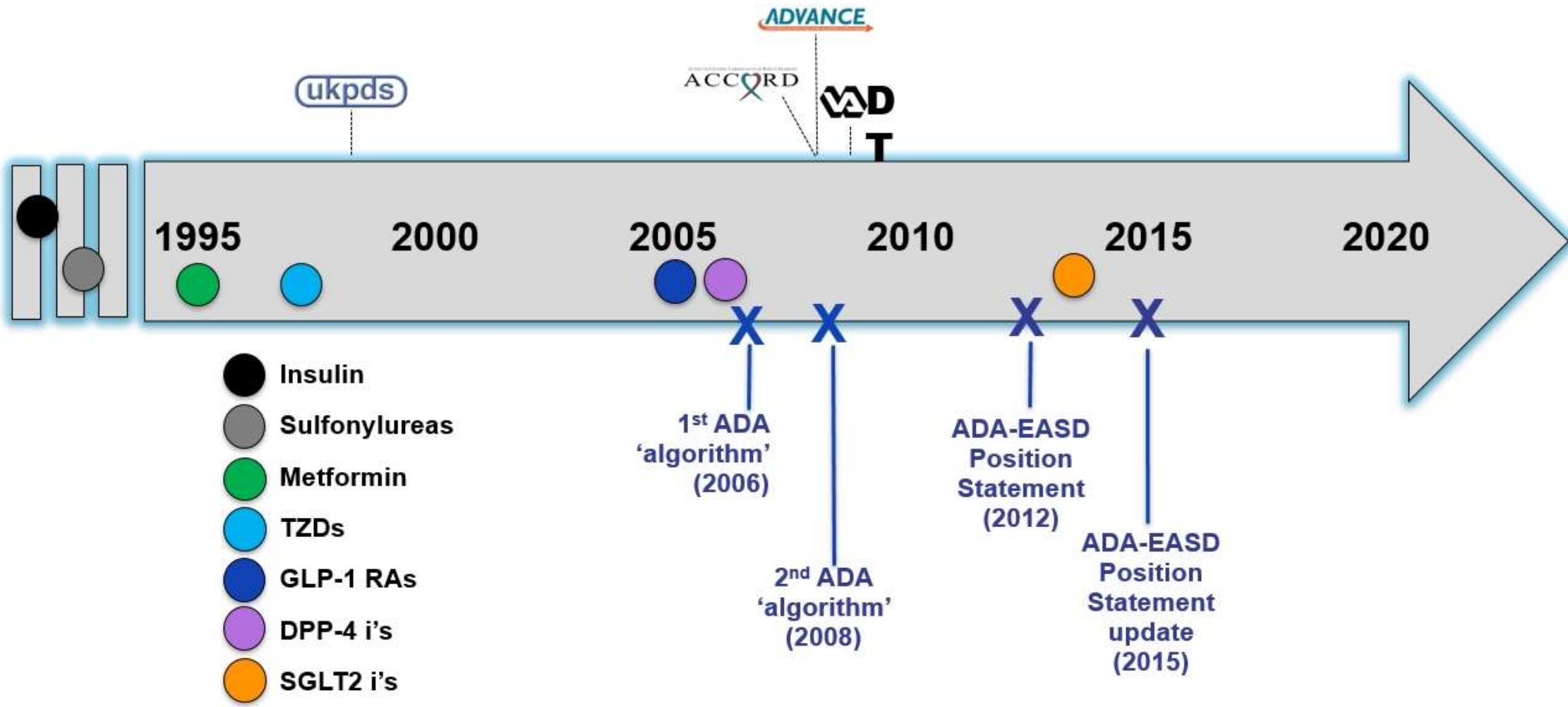


Treatment of T2DM over the Past 25+ Years



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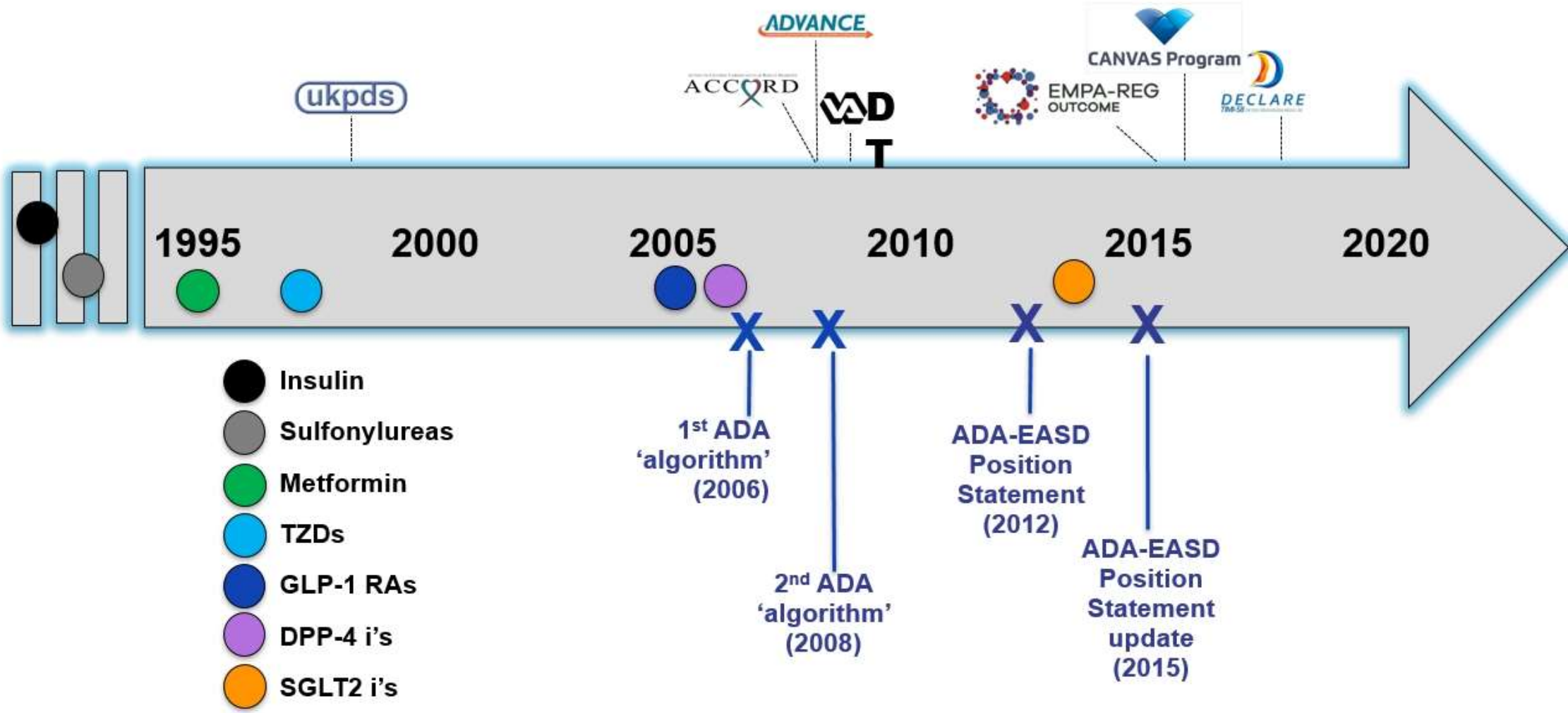

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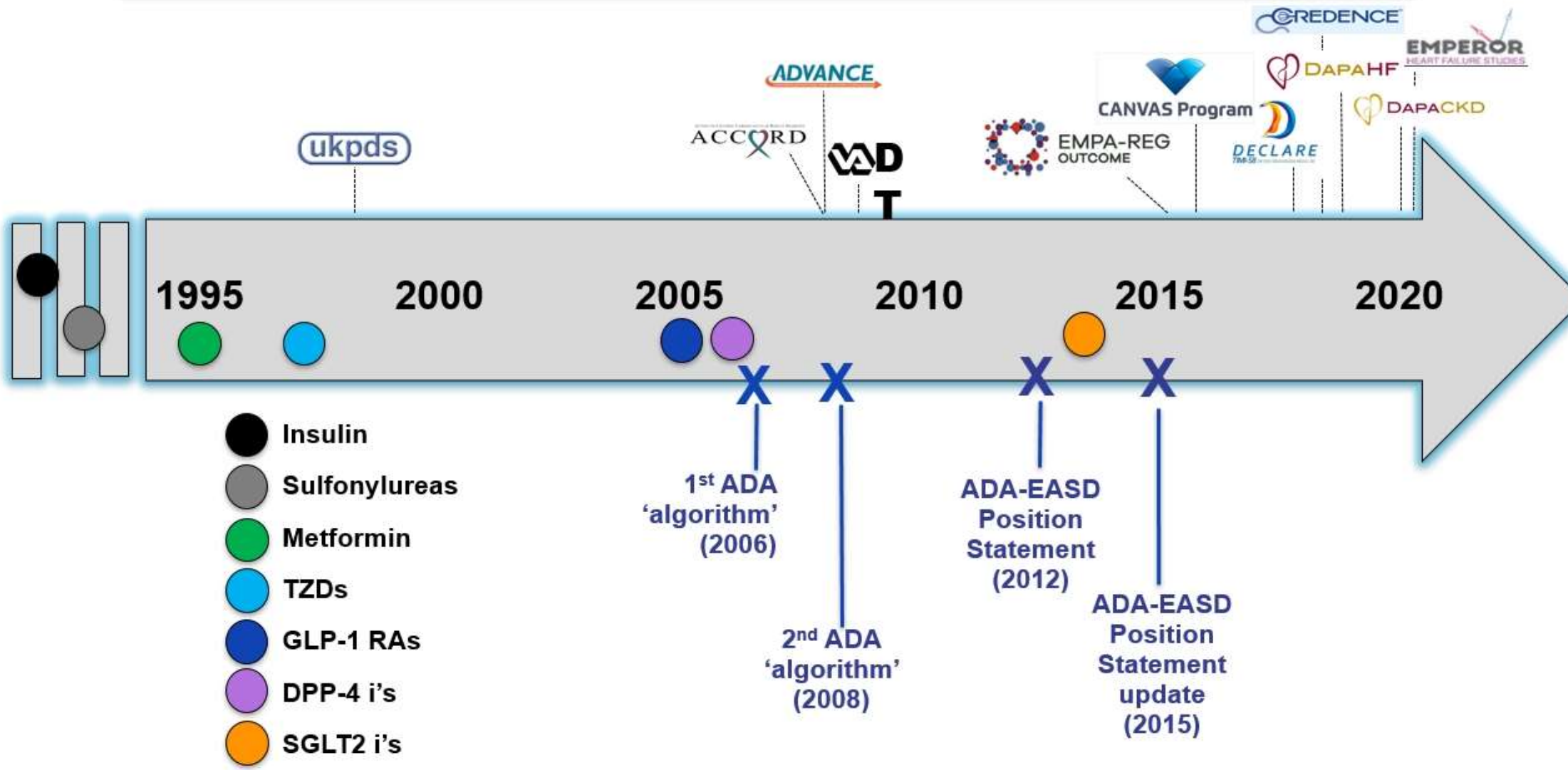

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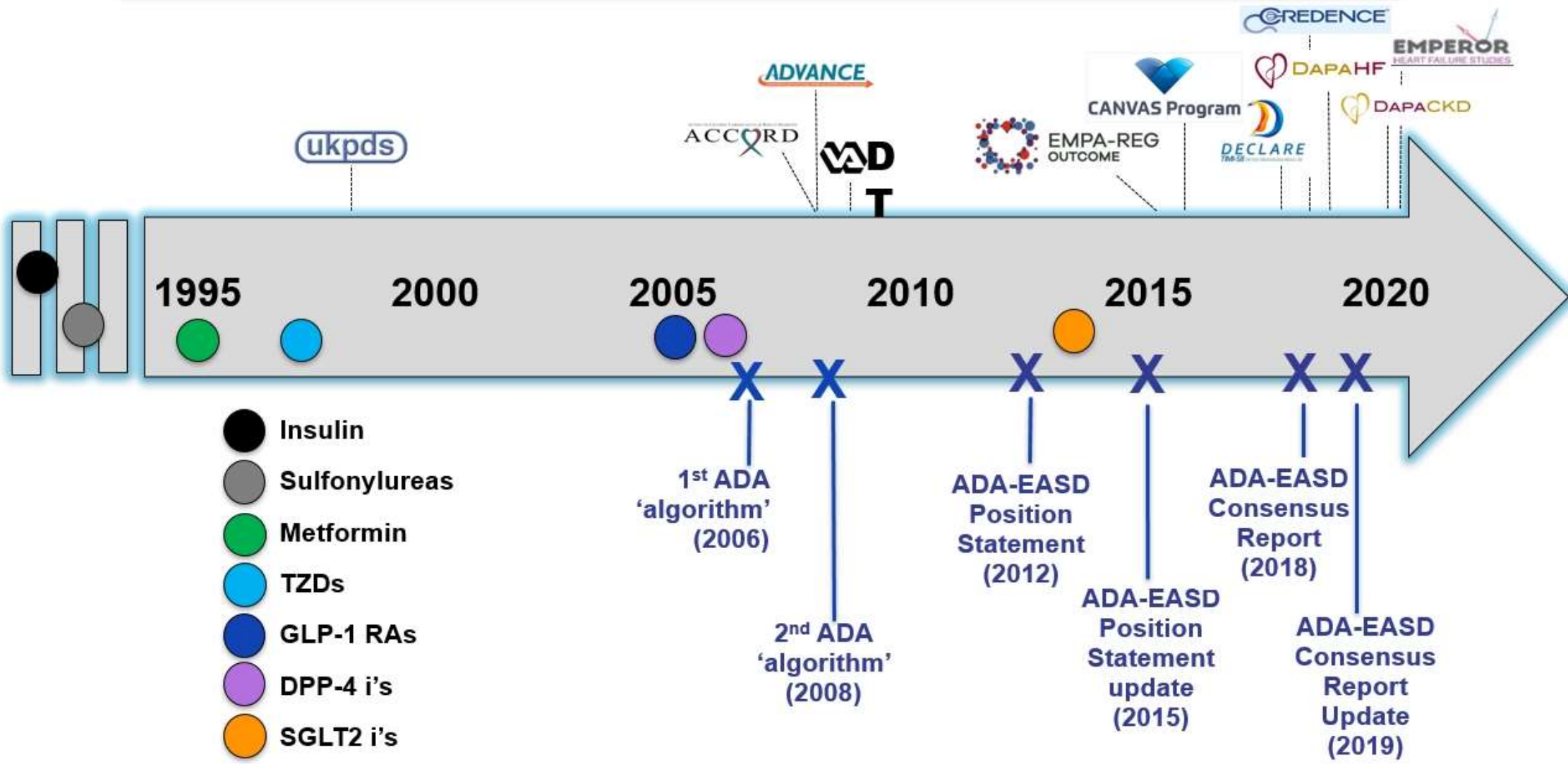

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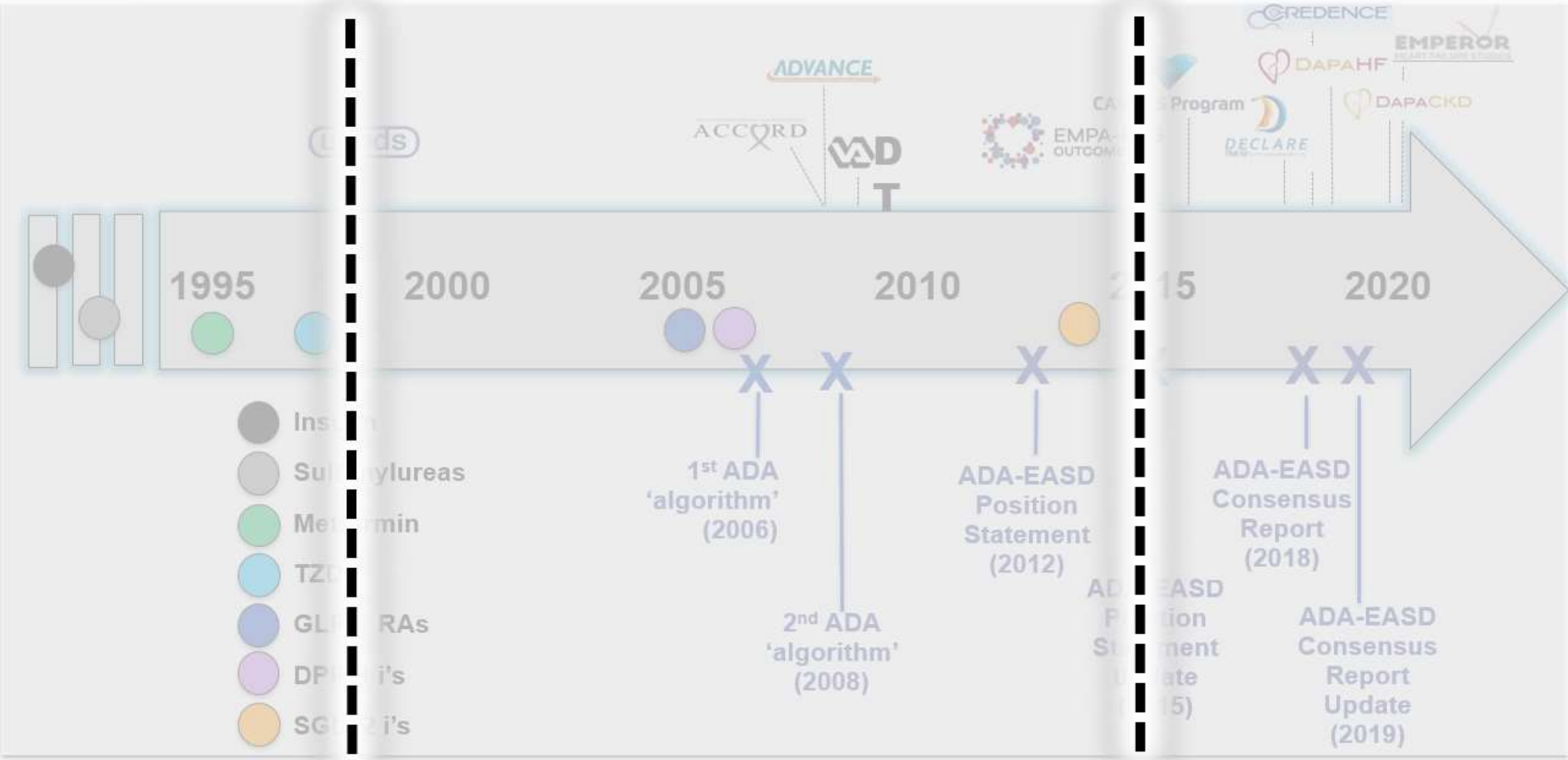
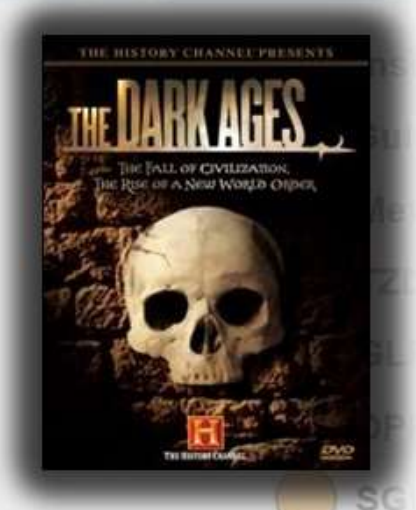


Treatment of T2DM over the Past 25+ Years

1st Era



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1st ADA 'algorithm' (2006)

2nd ADA 'algorithm' (2008)

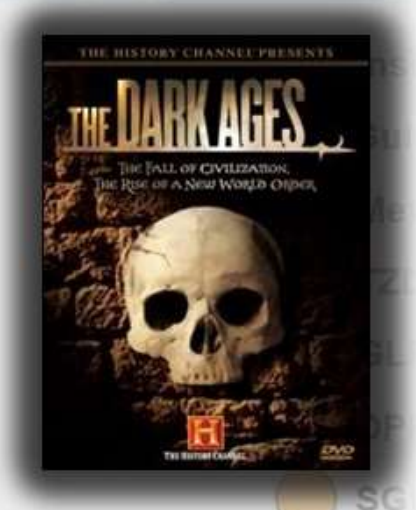
ADA-EASD Position Statement (2012)

ADA-EASD Consensus Report (2018)

ADA-EASD Consensus Report Update (2019)

Treatment of T2DM over the Past 25+ Years

1st Era



2nd Era

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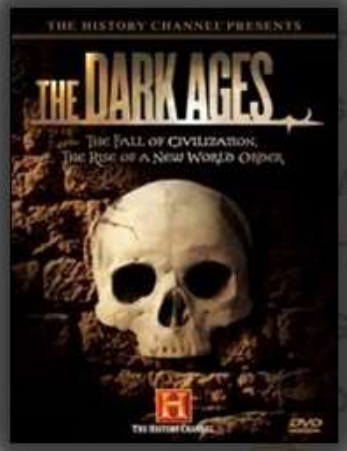
ADA-EASD Consensus Report (2018)

ADA-EASD Consensus Report Update (2019)

Treatment of T2DM over the Past 25+ Years

1st Era

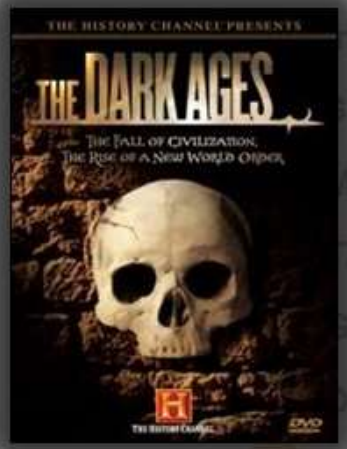


2nd Era

3rd Era

Treatment of T2DM over the Past 25+ Years

1st Era



2nd Era

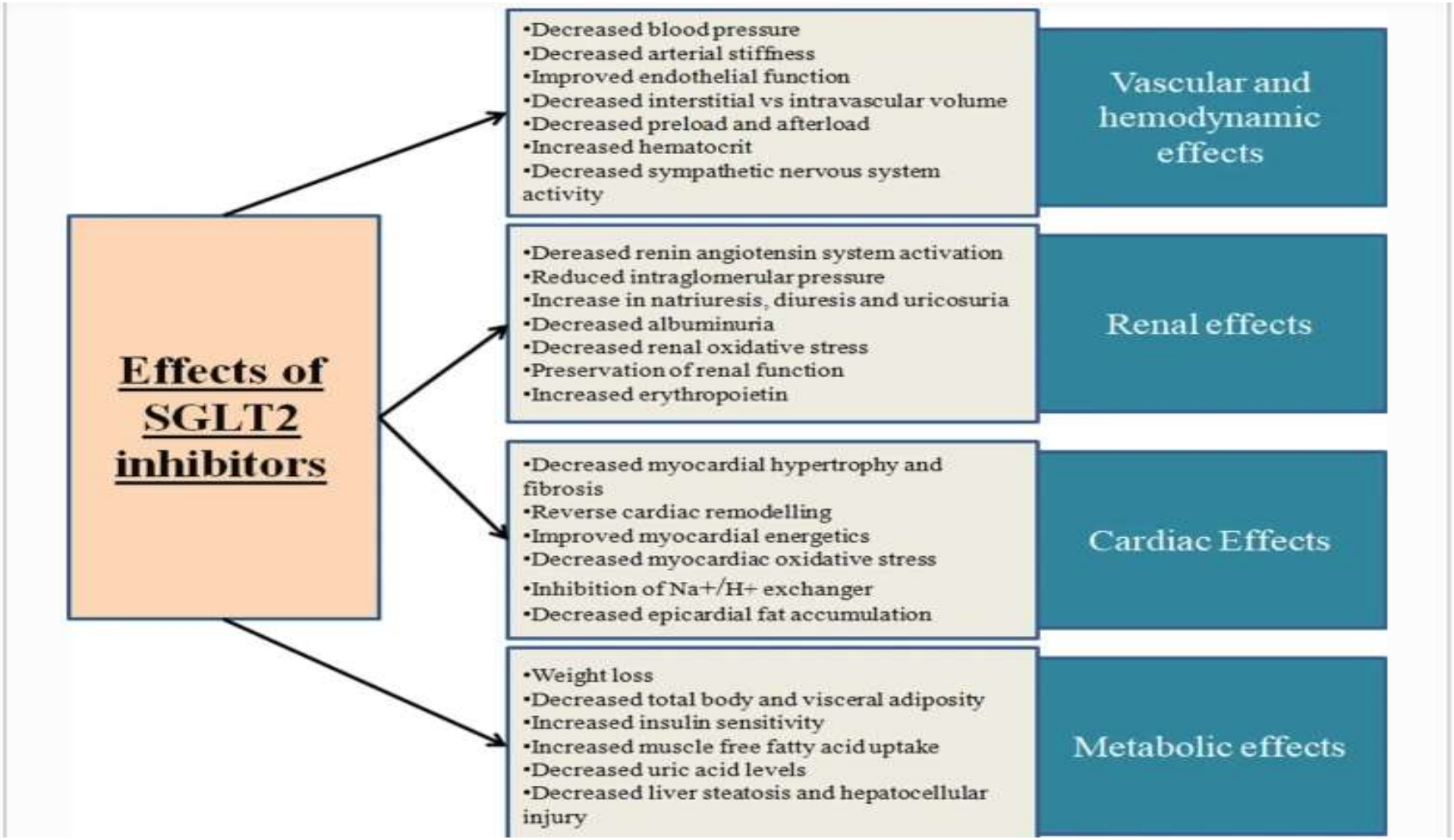
EMPA-REG OUTCOME

3rd Era

What Does the Future Hold?

Many Questions Remain!

- **What are the actual mechanisms underlying the CV and CKD benefits of the SGLT2 inhibitors?**


Effects of SGLT2 inhibitors
•Decreased blood pressure
•Decreased arterial stiffness
•Improved endothelial function
•Decreased interstitial vs intravascular volume
•Decreased preload and afterload
•Increased hematocrit
•Decreased sympathetic nervous system activity
Vascular and hemodynamic effects
•Dereased renin angiotensin system activation
•Reduced intraglomerular pressure
•Increase in natriuresis, diuresis and uricosuria
•Decreased albuminuria
•Decreased renal oxidative stress
•Preservation of renal function
•Increased erythropoietin
Renal effects
•Decreased myocardial hypertrophy and fibrosis
•Reverse cardiac remodelling
•Improved myocardial energetics
•Decreased myocardiac oxidative stress
•Inhibition of Na+/H+ exchanger
•Decreased epicardial fat accumulation
Cardiac Effects
•Weight loss
•Decreased total body and visceral adiposity
•Increased insulin sensitivity
•Increased muscle free fatty acid uptake
•Decreased uric acid levels
•Decreased liver steatosis and hepatocellular injury
Metabolic effects

Future directions

GLP-1 RA and SGLT2is

- It is not known if combined use of GLP-1 RA and SGLT2i provide additional benefit for the prevention of MACE, CV death, hHF and CKD progression
  - Trials have demonstrated the HbA_{1c}-lowering and weight loss efficacy of the combination[1,2,3] but none addresses its effect on cardiorenal endpoints

- The mechanism(s) of action by which GLP-1 RA and SGLT2i confer cardiorenal effect in diabetes are not understood
  - Research in this area will help in optimizing the clear potential of drugs to mitigate the CV and renal complications

CVD, cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; GLP-1 RA, glucagon like peptide-1 receptor agonist; hHF, hospitalization for heart failure; HF, heart failure; MACE, major adverse cardiovascular event; SGLT2is, sodium glucose like cotransporter 2 inhibitors

1. Zinmann B et al. Diabetes Endocrinol 2019; 7:356–367; Ludvik B et al. Lancet Diabetes Endocrinol 2019; 6:370–381; 3. Frias JP et al. Lancet Diabetes Endocrinol 2019; 4:1004–1016

Many Questions Remain!

- **What are the actual mechanisms underlying the CV and CKD benefits of the SGLT2 inhibitors?**
- **Might these benefits apply in primary prevention? In patients without DM?**

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- **How do we choose between an SGTL2 inhibitor vs. a GLP-1 receptor agonist in ASCVD patients (in the absence of HF, CKD)?**

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Many Questions Remain!

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- **Would the CV benefits of SGLT2 inhibitors be <u>additive to (or even synergistic with)</u> those of GLP-1 receptor agonists?**
- **Should metformin still be considered 'foundation therapy' in T2DM?**


THANK YOU