Outcome- vs Glycemic-Based Approach: Are We Ready?

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Learning objectives

By the end of this session, you will be able to:

- *Differentiate between an outcome-based vs glycemic-based approach to antihyperglycemic management*
- *Utilize multifactorial approach to managing diabetes*

2018 Diabetes Canada CPG – The Essentials

2018

ABCDES³ of Diabetes Care

- ✓**A** • A1C – optimal glycemic control (usually ≤7%)
- ✓**B** • BP – optimal blood pressure control (<130/80)
- ✓**C** • Cholesterol – LDL <2.0 mmol/L or >50% reduction
- ✓**D** • Drugs to protect the heart
  - A – ACEi or ARB | S – Statin | A – ASA if indicated | SGLT2i/GLP-1 RA with demonstrated CV benefit if type 2 DM with CVD and A1C not at target
- ✓**E** • Exercise / Healthy Eating
- ✓**S** • Screening for complications
- ✓**S** • Smoking cessation
- ✓**S** • Self-management, stress and other barriers

DIABETES CANADA

2018 Diabetes Canada CPG – Chapter 23. Cardiovascular Protection in People with Diabetes

2018

Who Should Receive ACEi or ARB Therapy?

(regardless of baseline blood pressure)

- **Clinical CVD**
- **Age >55 years with an additional CV risk factor or end organ damage** (albuminuria, retinopathy, left ventricular hypertrophy)

At doses that have shown vascular protection
[perindopril 8 mg daily (EUROPA), ramipril 10 mg daily (HOPE), telmisartan 80 mg daily (ONTARGET)]

Among women with childbearing potential, ACEi or ARB should only be used in the presence of proper preconception counselling & reliable contraception. Stop ACEi or ARB either prior to conception or immediately upon detection of pregnancy.

EUROPA Investigators, Lancet 2003;362(9386):782-788.
HOPE study investigators. *Lancet*. 2000;355:253-59.
ONTARGET study investigators. *NEJM*. 2008:358:1547-59

DIABETES CANADA

2018 Diabetes Canada CPG – Chapter 25. Dyslipidemia

Who Should Receive Statins?

(regardless of baseline LDL-C)

- **Cardiovascular disease** *or*
- **Age ≥40 yrs** *or*
- **Microvascular complications** *or*
- **DM >15 yrs duration and age >30 yr** *or*
- **Warrants therapy** based on other guidelines

Among women with childbearing potential, statins should only be used in the presence of proper preconception counselling & reliable contraception. Stop statins prior to conception.

DIABETES CANADA

SGLT2 CVOT in Diabetes Demonstrating Superiority

		PRIMARY OUTCOME	SECONDARY OUTCOMES			
	Medication		CV Death	Nonfatal MI	Nonfatal Stroke	Hospitalization for Heart Failure
EMPA-REG OUTCOME[1] **HR (95% CI)**	Empagliflozin	CVD/MI/Stroke 0.86 (0.74, 0.99)	0.62 (0.49, 0.77)	NS	NS	0.65 (0.50, 0.85)
CANVAS[2] **HR (95% CI)**	Canagliflozin	CVD/MI/Stroke 0.86(0.75, 0.97)	NS	NS	NS	0.67 (0.52, 0.87)
DECLARE[3] **HR (95% CI)**	Dapagliflozin	CVD/HHF 0.83(0.73, 0.95)	NS	NS	NS	0.73 (0.61, 0.88)
CREDENCE[4] **HR (95% CI)**	Canagliflozin	Renal Composite/CVD 0.70 (0.59, 0.82)	0.78 (0.61, 1.00) P=0.0502	NS	NS	0.67 (0.52, 0.87)

CV, cardiovascular; CVOT, cardiovascular outcome trial, HR, hazard ratio; NS, not significant; MI, myocardial infarction; CVD, cardiovascular death

1 Zinman B, et al. *N Engl J Med* 2015;373(22):2117-28. 2 Neal B, et al, *N Engl J Med* 2017;377:644-57. 3 Wiviott et al N Engl J Med 2018; DOI 10.1056/NEJMoa1812389 4 Percovic et al N Engl J Med 2019; DOI 10.1056/NEJMoa1812389

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

This article was published on September 19, 2019, at NEJM.org.

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GLP-1A CVOT in Diabetes Demonstrating Superiority

		PRIMARY OUTCOME	SECONDARY OUTCOMES			
	Medication	CV Death, Nonfatal MI, Nonfatal Stroke	CV Death	Nonfatal MI	Nonfatal Stroke	Hospitalization for Heart Failure
LEADER[1] HR (95% CI)	Liraglutide	0.87 (0.78, 0.97)	0.78 (0.66, 0.93)	NS	NS	NS
SUSTAIN-6[2] HR (95% CI)	Semaglutide	0.74 (0.58, 0.95)	NS	NS	0.61 (0.38, 0.99)	NS
REWIND[3]	Dulaglutide	0.88 (0.79,0.99)	NS	NS	0.76 (0.71, 0.95)	NS

CV, cardiovascular; CVOT, cardiovascular outcome trial, HR, hazard ratio; NS, not significant; MI, myocardial infarction

1 Marso S, et al. *N Engl J Med* 2016;375(4):311-22. 4 Marso S, et al. *N Engl J Med* 2016;375:1834-44. 3. Gerstein HC et al. *Lancet* 2019 epub June 10

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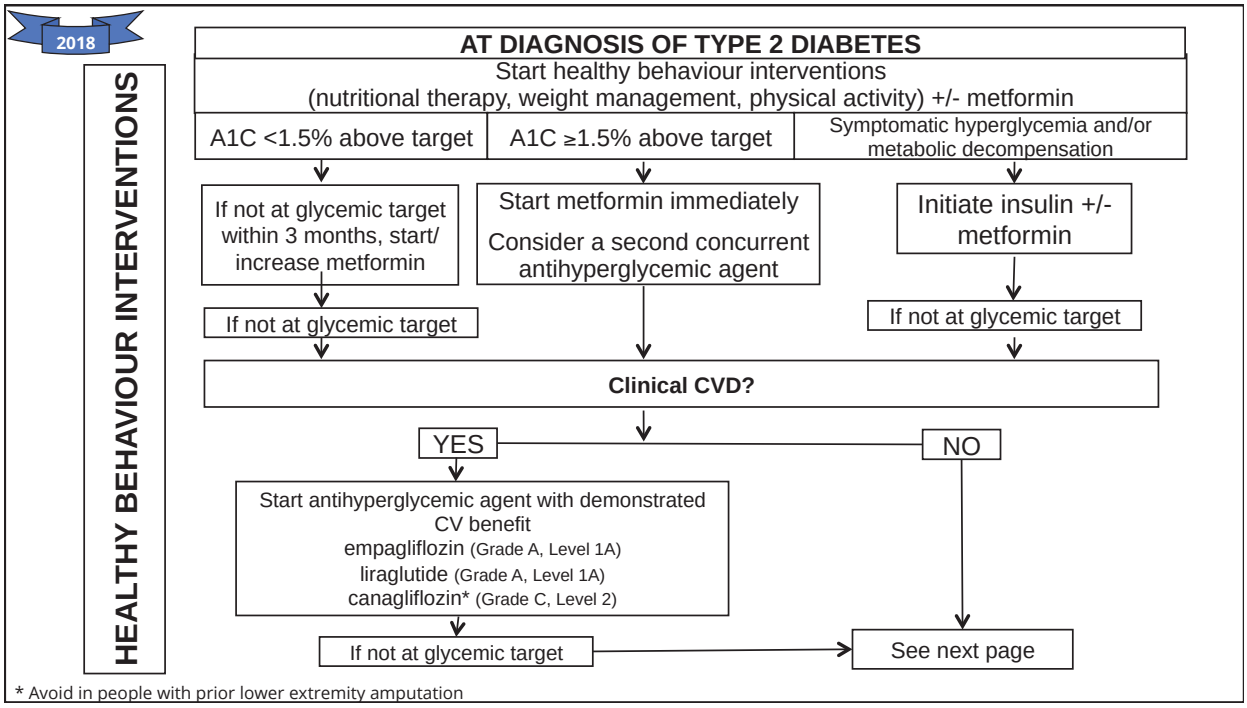
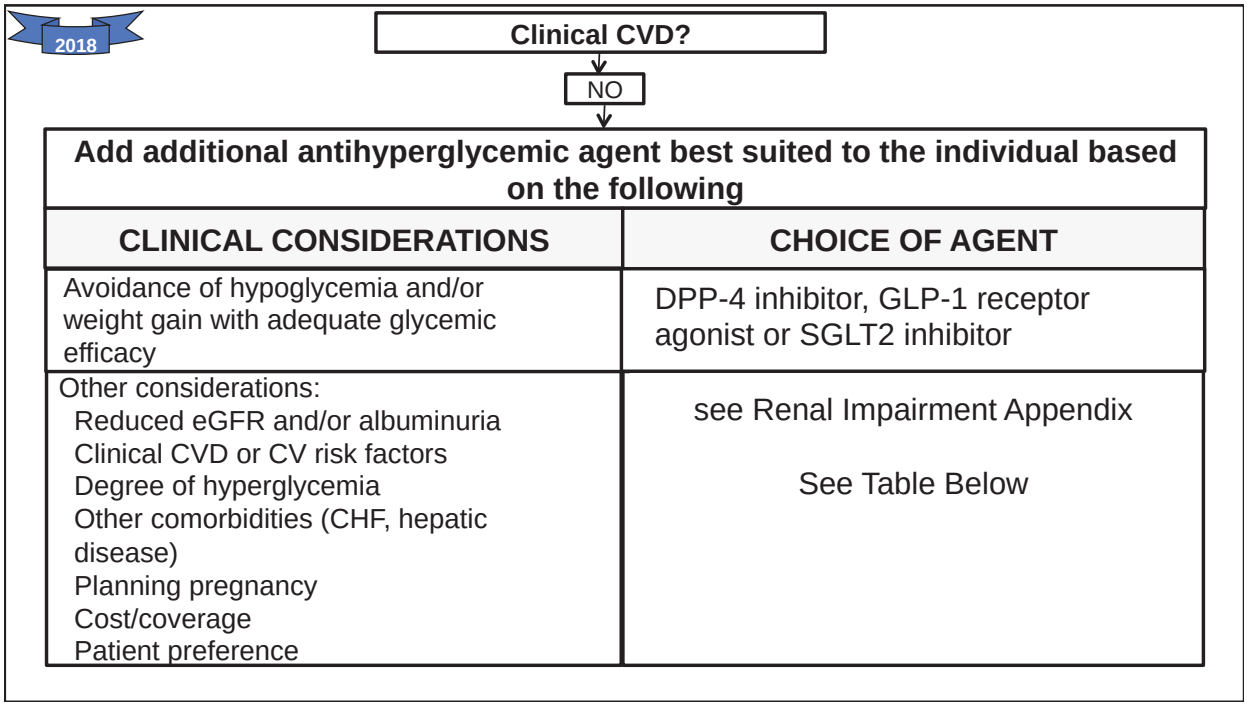
Practical Considerations

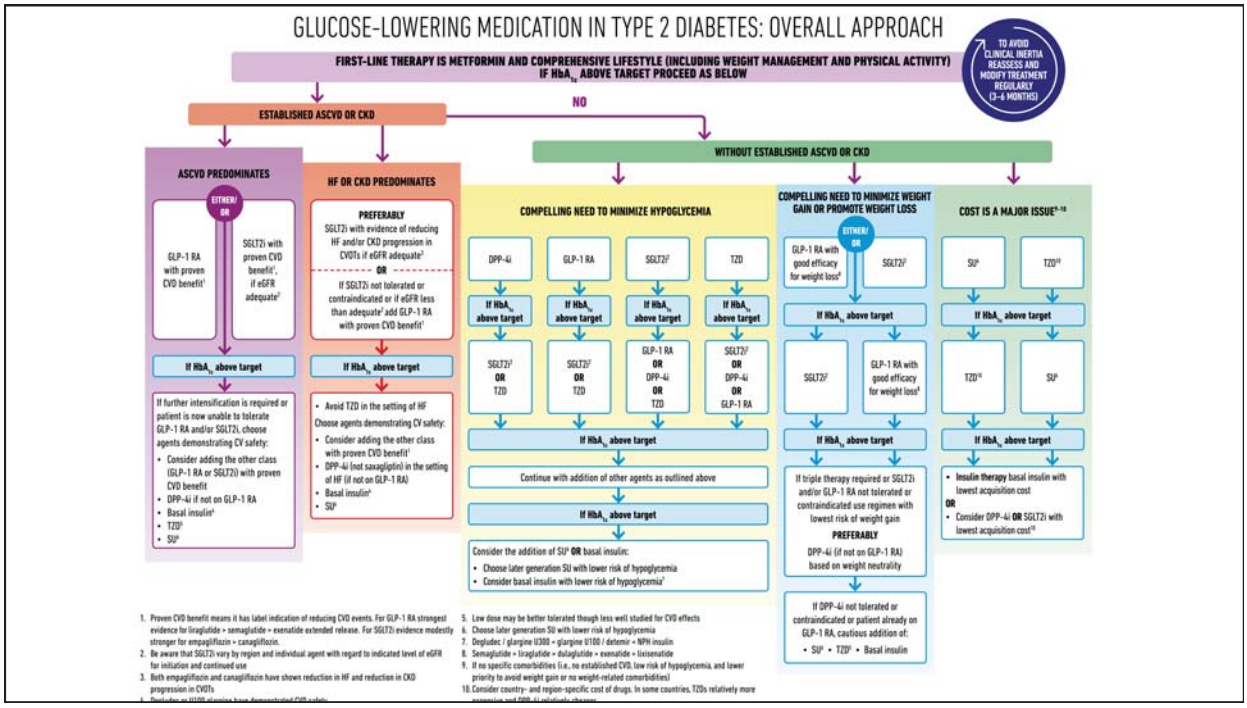
Characteristic	Empagliflozin	Canagliflozin	Dapagliflozin	Liraglutide	Semaglutide	Dulaglutide
Class	SGLT2 inhibitor			GLP-1 receptor agonist		
Route of administration	Oral once daily			SC injection daily	SC injection once weekly	
Dosage	10 mg or 25 mg	100 mg or 300 mg	5mg or 10 mg	0.6 mg x 1 wk then 1.2 mg x 1 wk then 1.8mg SC	0.25 mg x 4 wk then 0.5 mg May increase to 1 mg SC per week	0.75 mg or 1.5 mg
Cost	~$90/month			~$225/month		
eGFR	eGFR > 30	eGFR > 30 eGFR 30-59, use 100 mg	eGFR >45	eGFR >15	eGFR >15 (caution 15-29)	Caution if eGFR<30

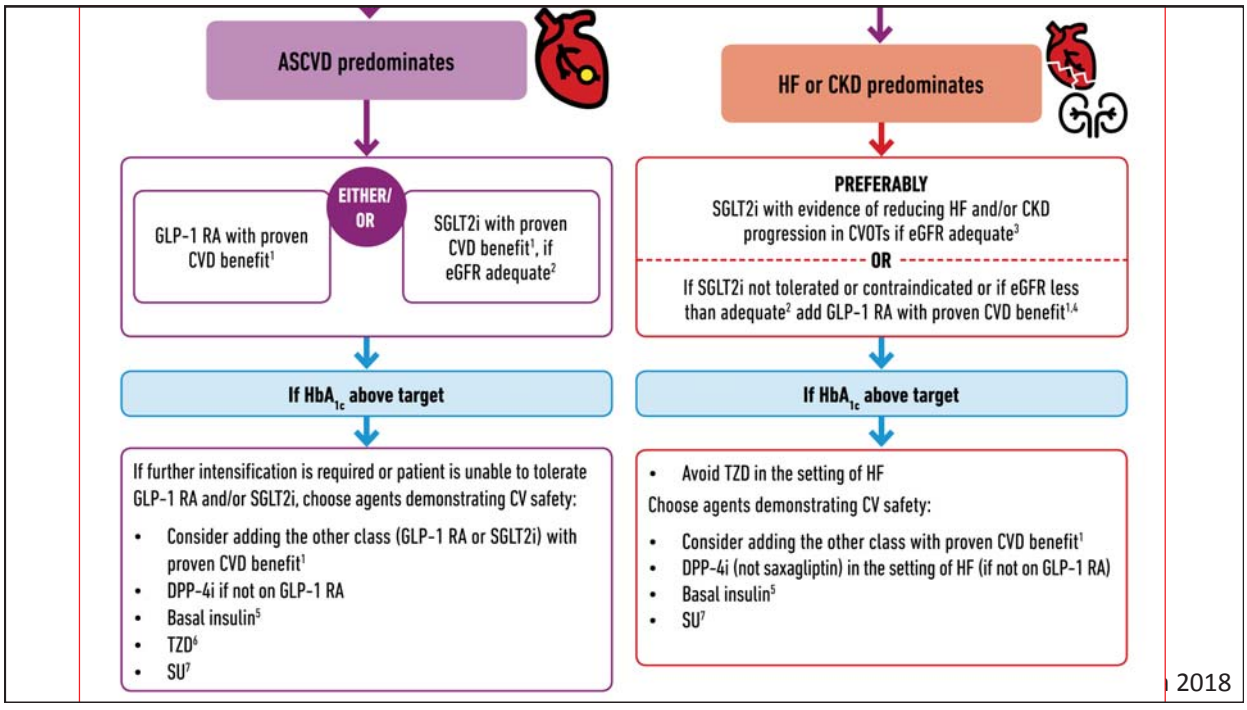
eGFR, estimated glomular filtration rate; GLP-1, glucagon-like peptide 1; SC, subcutaneous; SGLT2, sodium glucose cotransporter 2

What do the guidelines say?

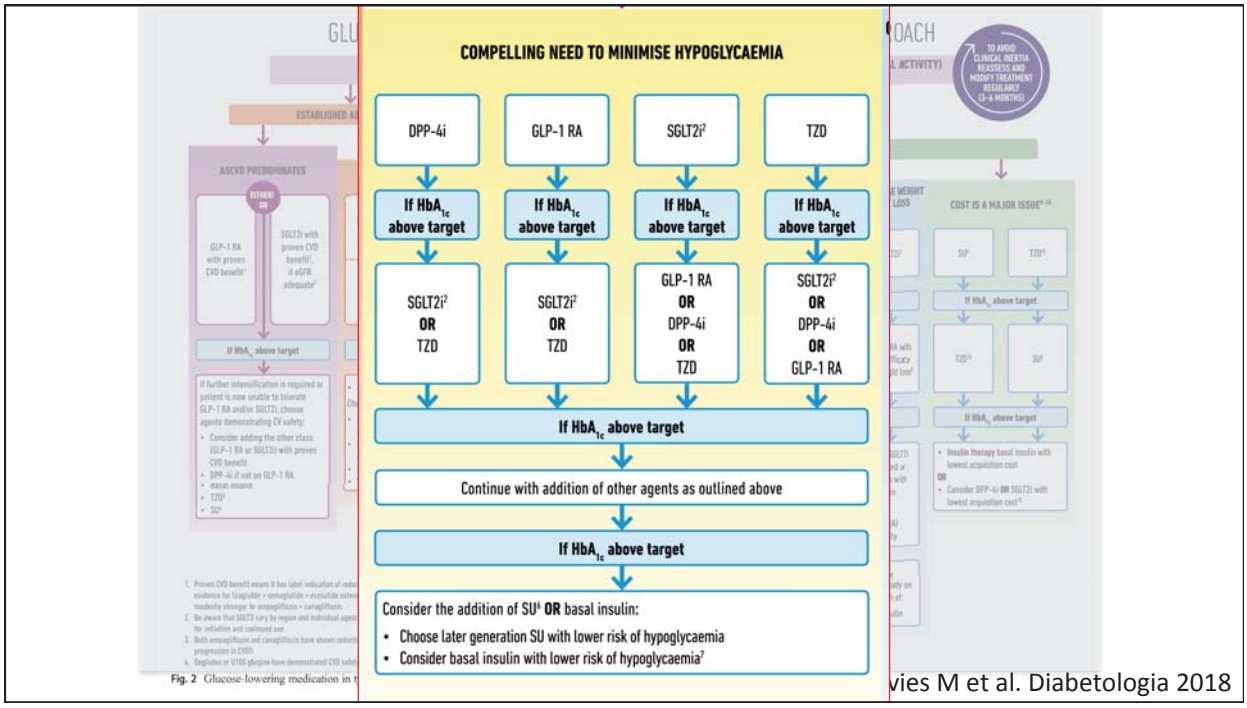

2018
HEALTHY BEHAVIOUR INTERVENTIONS
AT DIAGNOSIS OF TYPE 2 DIABETES
Start healthy behaviour interventions
(nutritional therapy, weight management, physical activity) +/- metformin
A1C <1.5% above target
A1C ≥1.5% above target
Symptomatic hyperglycemia and/or metabolic decompensation
If not at glycemic target within 3 months, start/ increase metformin
Start metformin immediately
Consider a second concurrent antihyperglycemic agent
Initiate insulin +/- metformin
If not at glycemic target
If not at glycemic target
Clinical CVD?
YES
NO
Start antihyperglycemic agent with demonstrated CV benefit
empagliflozin (Grade A, Level 1A)
liraglutide (Grade A, Level 1A)
canagliflozin* (Grade C, Level 2)
If not at glycemic target
See next page
* Avoid in people with prior lower extremity amputation


2018
Clinical CVD?
NO
Add additional antihyperglycemic agent best suited to the individual based on the following
CLINICAL CONSIDERATIONS
CHOICE OF AGENT
Avoidance of hypoglycemia and/or weight gain with adequate glycemic efficacy
DPP-4 inhibitor, GLP-1 receptor agonist or SGLT2 inhibitor
Other considerations:
Reduced eGFR and/or albuminuria
Clinical CVD or CV risk factors
Degree of hyperglycemia
Other comorbidities (CHF, hepatic disease)
Planning pregnancy
Cost/coverage
Patient preference
see Renal Impairment Appendix
See Table Below

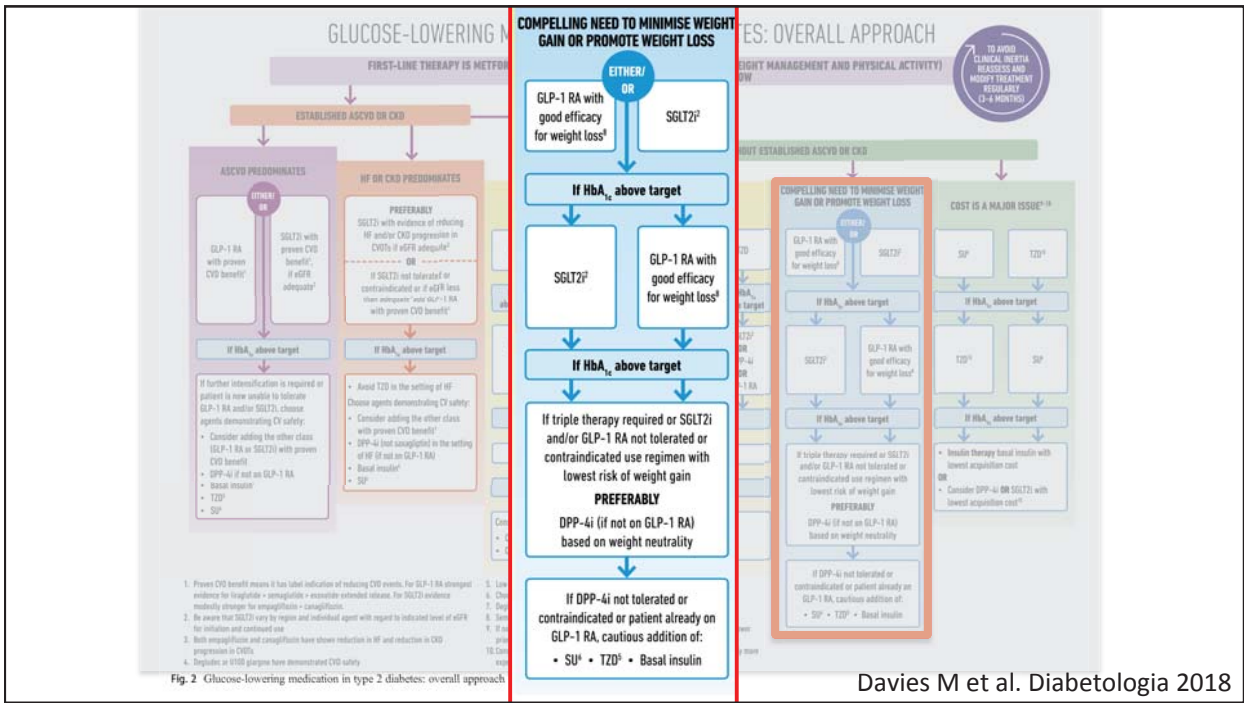

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH
FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA1c ABOVE TARGET PROCEED AS BELOW
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ESTABLISHED ASCVD OR CKD
NO
WITHOUT ESTABLISHED ASCVD OR CKD
ASCVD PREDOMINATES
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1], if eGFR adequate[2]
If HbA1c 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:
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
• DPP-4i if not on GLP-1 RA
• Basal insulin[5]
• TZD[6]
• SU[7]
HF OR CKD PREDOMINATES
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 HbA1c above target
• Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
• Consider adding the other class with proven CVD benefit[1]
• DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
• Basal insulin[5]
• SU[7]
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i[3]
TZD
If HbA1c above target
SGLT2i[3] OR TZD
SGLT2i[3] OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i[3] OR DPP-4i OR GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU[7] 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[3]
If HbA1c above target
SGLT2i[3]
GLP-1 RA with good efficacy for weight loss[8]
If HbA1c above target
If triple 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[7] • TZD[6] • Basal insulin
COST IS A MAJOR ISSUE[9–10]
SU[7]
TZD[10]
If HbA1c above target
TZD[10]
SU[7]
If HbA1c above target
• Insulin therapy basal insulin with lowest acquisition cost
OR
• Consider DPP-4i OR SGLT2i with lowest acquisition cost[10]
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
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


ASCVD predominates
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1], if eGFR adequate[2]
If HbA1c above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit[1]
• DPP-4i if not on GLP-1 RA
• Basal insulin[5]
• TZD[6]
• SU[7]
HF or CKD predominates
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[1,4]
If HbA1c above target
• Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
• Consider adding the other class with proven CVD benefit[1]
• DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
• Basal insulin[5]
• SU[7]

2018



Davies M et al. Diabetologia 2018



Davies M et al. Diabetologia 2018

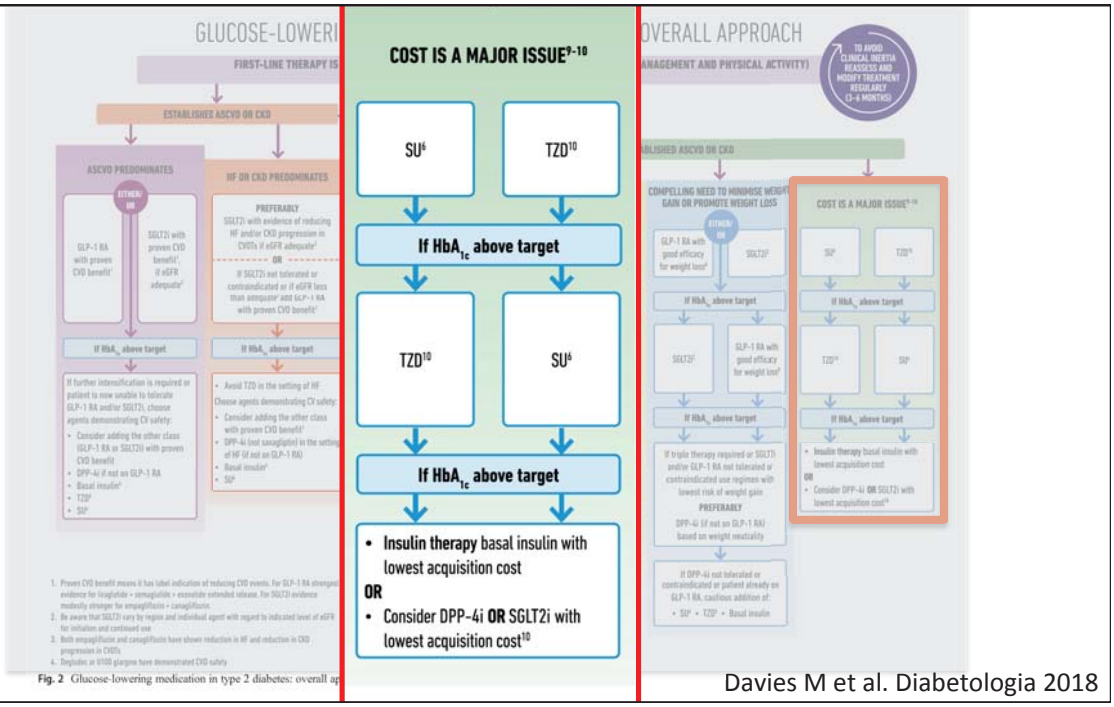


Fig. 2 Glucose-lowering medication in type 2 diabetes: overall ap

Davies M et al. Diabetologia 2018

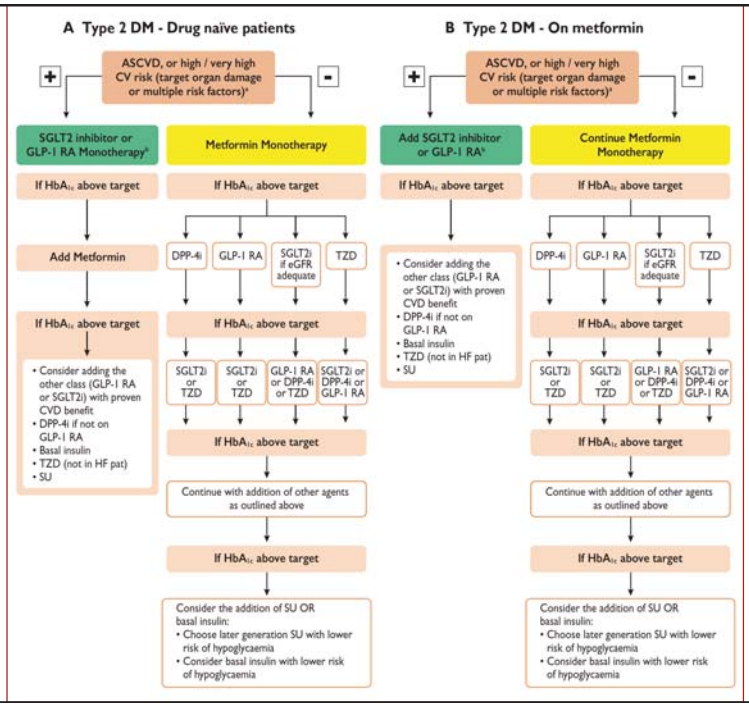
ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

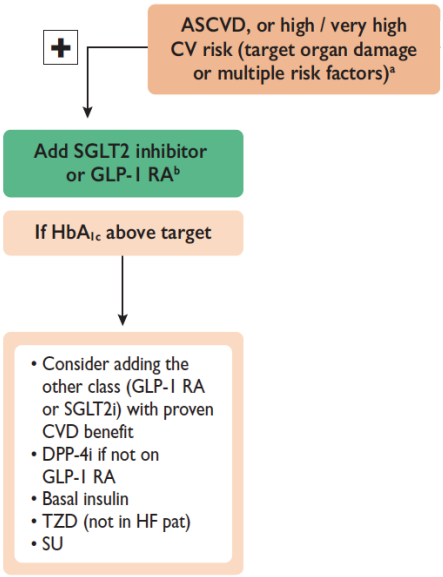
ESC GUIDELINES

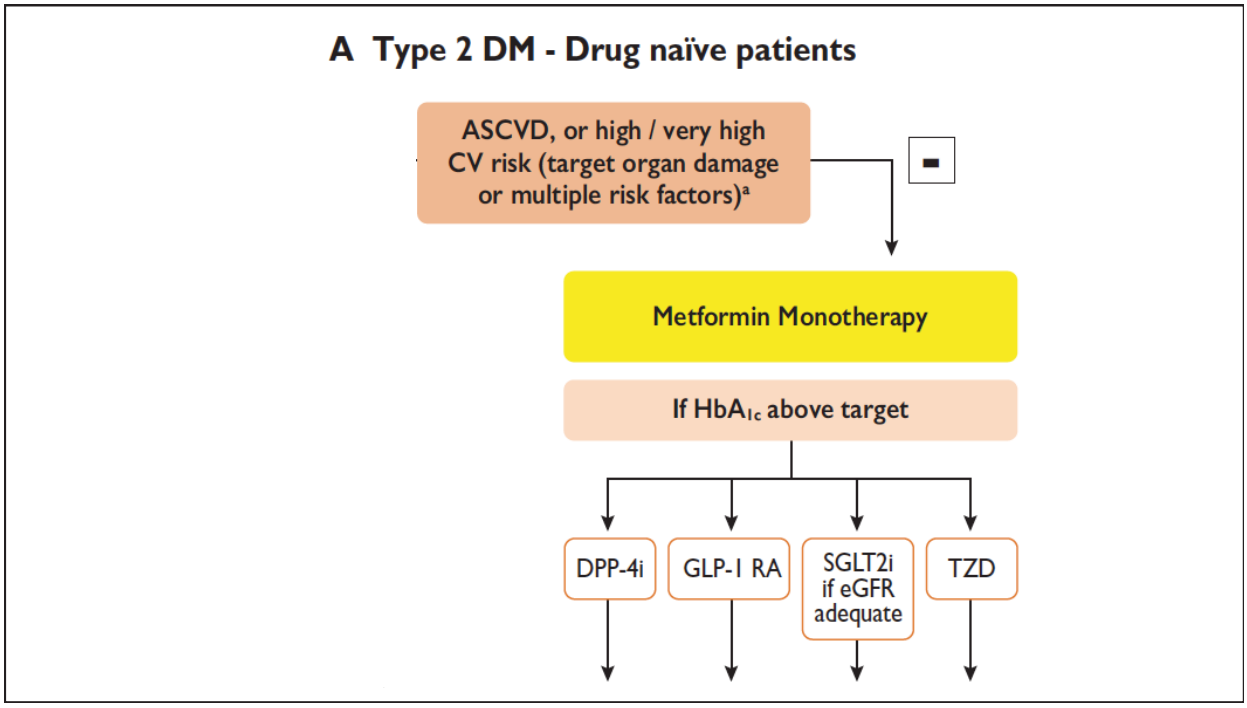
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

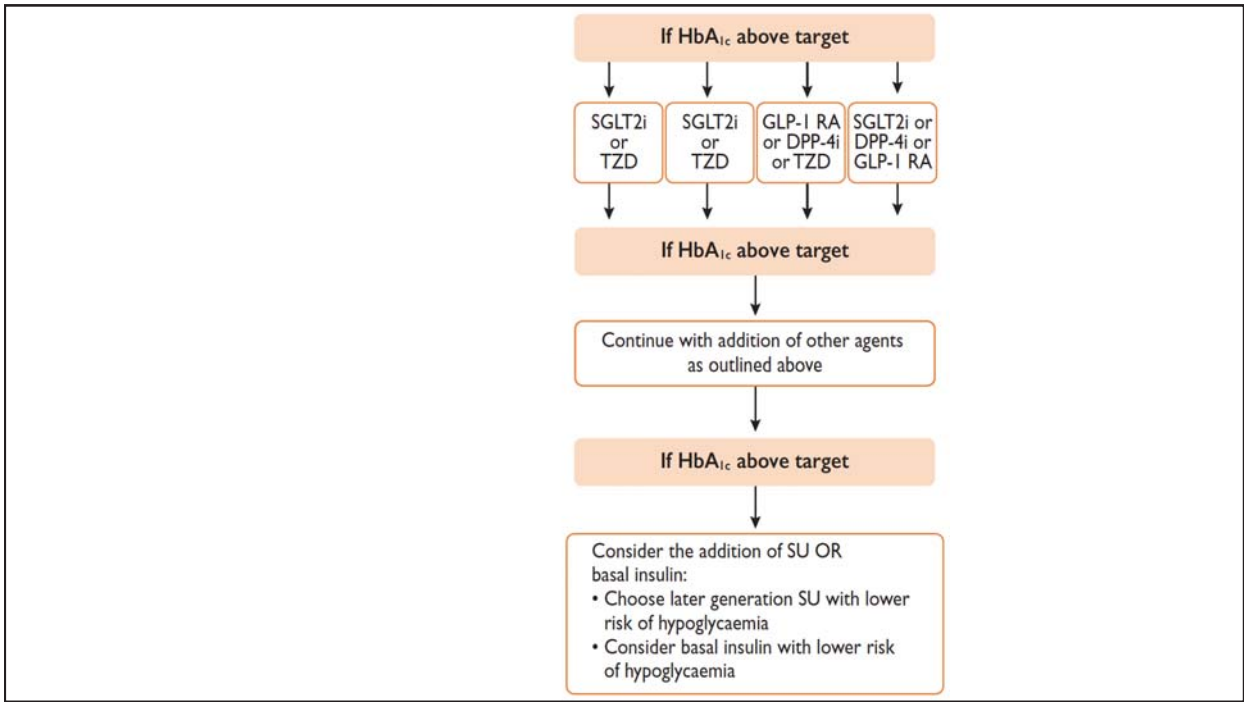
The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

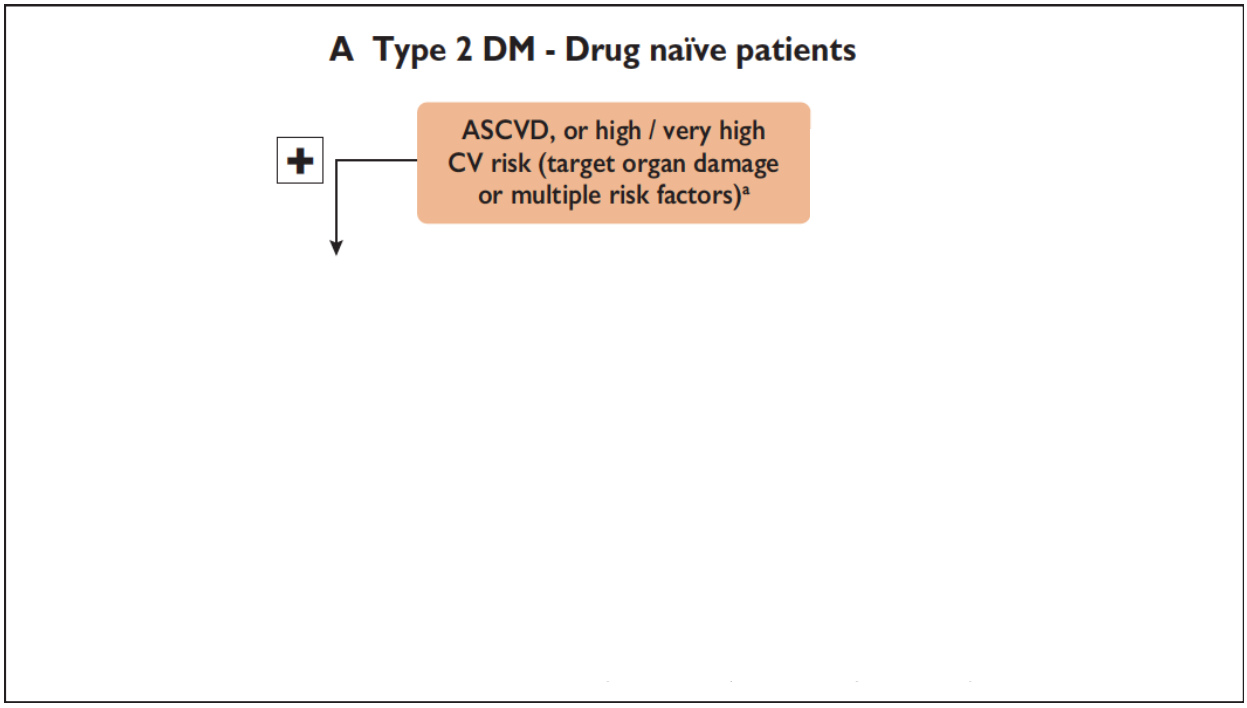


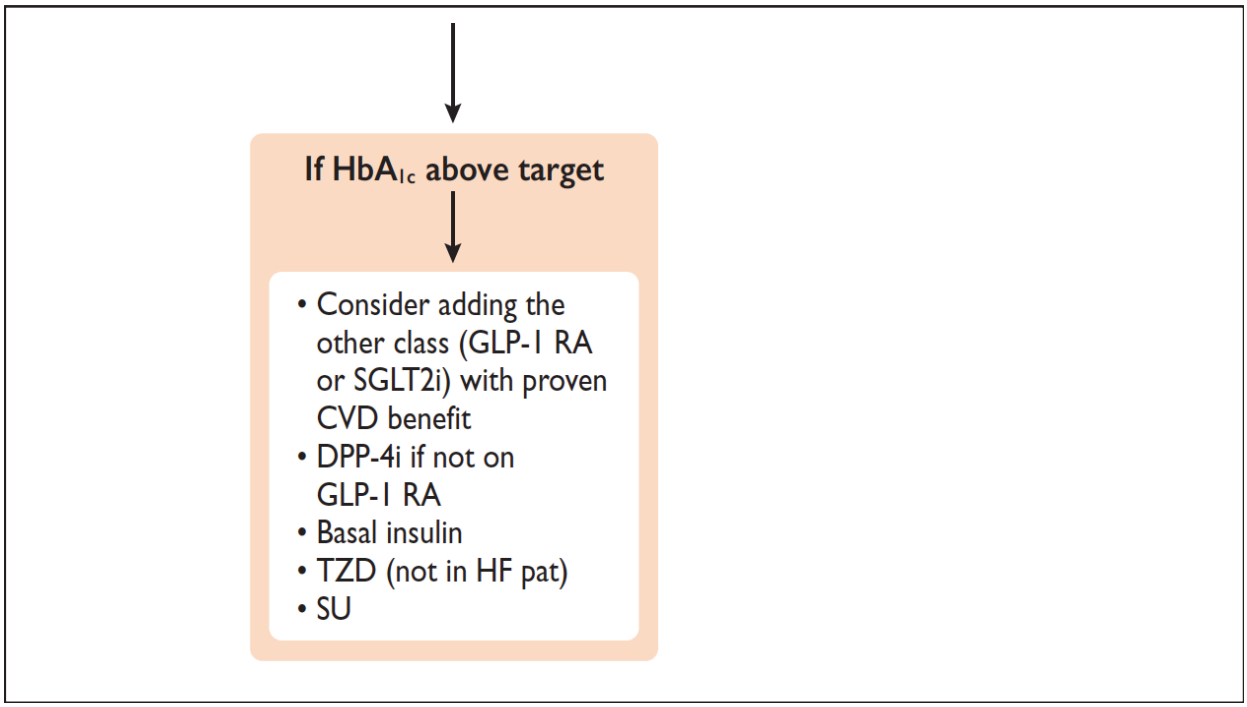
B Type 2 DM - On metformin




A Type 2 DM - Drug naïve patients
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
-
Metformin Monotherapy
If HbA1c above target
DPP-4i
GLP-1 RA
SGLT2i if eGFR adequate
TZD


If HbA1c above target
SGLT2i or TZD
SGLT2i or TZD
GLP-1 RA or DPP-4i or TZD
SGLT2i or DPP-4i or GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU OR basal insulin:
• Choose later generation SU with lower risk of hypoglycaemia
• Consider basal insulin with lower risk of hypoglycaemia


A Type 2 DM - Drug naïve patients
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]


If HbA1c above target
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
• DPP-4i if not on GLP-1 RA
• Basal insulin
• TZD (not in HF pat)
• SU

Considerations…

- Should metformin remain first-line therapy?
- Are the benefits observed dependent on A1c?
- Should we prioritize therapies that reduce outcomes independent of their primary indication?

Summary of Positive CVOTs Among Patient Types

Co-morbidities	↓ MACE	↓ CV death	↓ hHF	↓ Renal outcomes *
Cardiovascular disease		(empa) (lira)		
↓eGFR with ↑ ACR	(cana)		(cana)	(cana)
Risk factors (HTN, lipids and/or smoking)	(dula)			

= GLP1 receptor agonists[†1-5] = SGLT2 inhibitors[‡6-11]

*Composite renal endpoint: Doubling of serum creatinine, end-stage renal disease or renal death; †dulaglutide, liraglutide and semaglutide; ‡canagliflozin, dapagliflozin, empagliflozin

CV: cardiovascular; CVOT: cardiovascular outcome trial; MACE: Major adverse cardiovascular events (MI, stroke, CV death); MI: myocardial infarction; SGLT2: sodium-glucose linked transporter-2

1. Marso S, *et al. N Engl J Med* 2016; 375(4):311-22; **2.** Mann JF, *et al. N Engl J Med* 2017; 377(9):839-48; **3.** Marso S, *et al. N Engl J Med* 2016; 375:1834-44; **4.** Gerstein HC, et al. Lancet 2019; Jun 7 [epub before print]; **5.** Gerstein HC, et al. Lancet 2019; Jun 7 [epub before print]; **6.** Zinman B, *et al. N Engl J Med* 2015; 373(22):2117-28; **7.** Wanner C, *et al. N Engl J Med* 2016; 375(4):323-34; **8.** Neal B, *et al. N Engl J Med* 2017; 377(7):644-57; **9**. Wiviott SD, *et al. N Engl J Med* 2019; 380(4):347-57; **10.** Perkovic V, *et al. N Engl J Med* 2019; Apr 14 [Epub ahead of print]. **11.** Zelniker TA *et al. Lancet* 2019; 393(10166):31-9.

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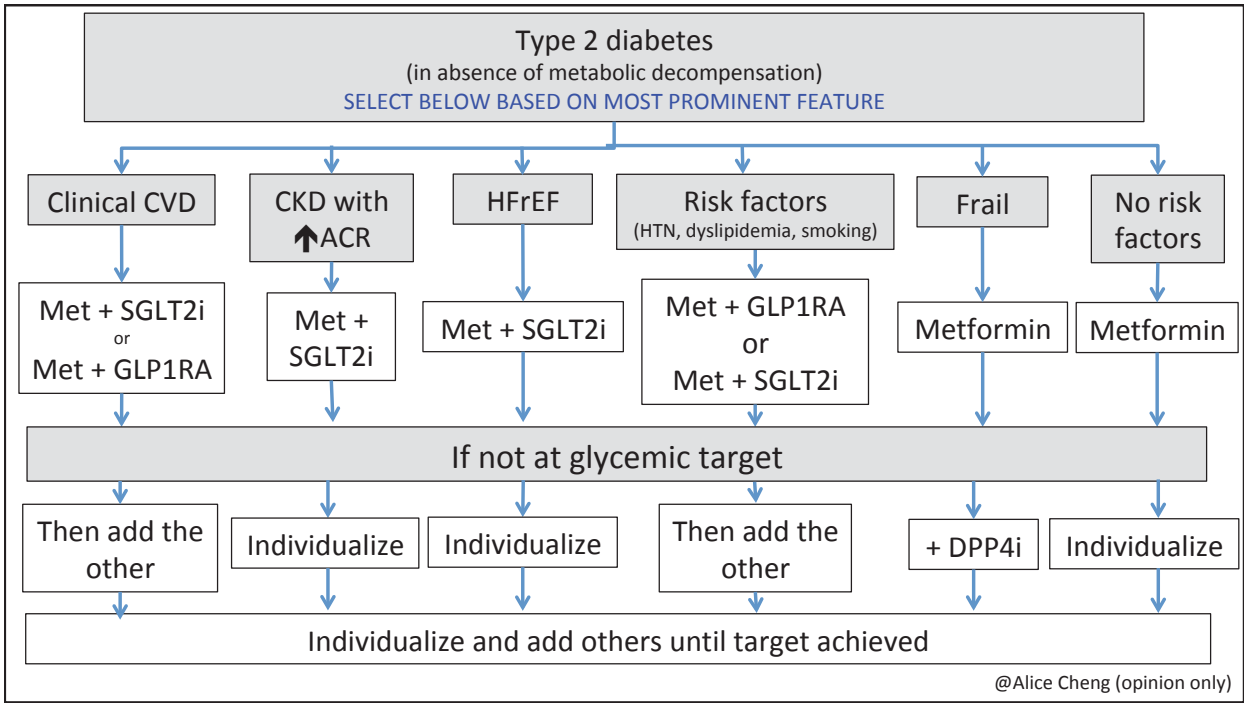

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2018

ABCDES³ of Diabetes Care

- ✓**A** • A1C – optimal glycemic control (usually ≤7%)
- ✓**B** • BP – optimal blood pressure control (<130/80)
- ✓**C** • Cholesterol – LDL <2.0 mmol/L or >50% reduction
- ✓**D** • Drugs to protect the heart

  A – ACEi or ARB | S – Statin | A – ASA if indicated | SGLT2i/GLP-1 RA with demonstrated CV benefit if type 2 DM with CVD and A1C not at target
- ✓**E** • Exercise / Healthy Eating
- ✓**S** • Screening for complications
- ✓**S** • Smoking cessation
- ✓**S** • Self-management, stress and other barriers

DIABETES CANADA

Summary

- Think of patient type when selecting therapy (CV, CKD, HFrEF, multiple RF, frail, none)
- Outcome-based therapy as a priority
- As part of ABCDESSS