The Scientific Times

Year 2020 ● Vol. 9

Cardiovascular Risk Reduction in Diabetes: New Guidance

ECDP Preface

The American College of Cardiology (ACC) has a long history of developing documents (e.g., decision pathways, health policy statements) to provide clinicians with guidance on both clinical and nonclinical topics relevant to cardiovascular (CV) care.

ACC has evolved from developing isolated documents to the development of integrated "solution sets."

ECDPs represent a key component of solution sets.

ACC Expert Consensus Decision Pathway (ECDP) 2020 Highlights

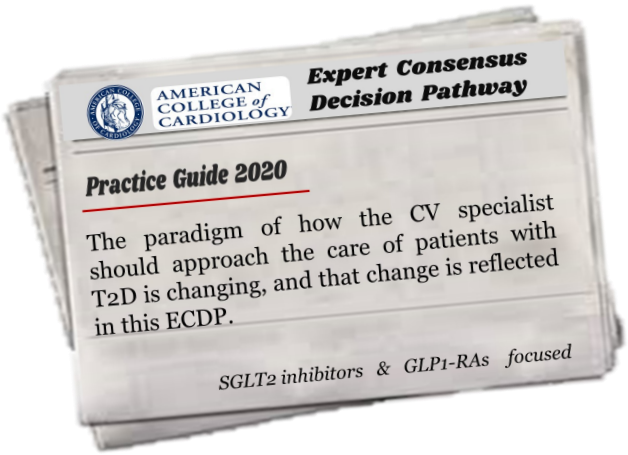
Despite major therapeutic advances leading to improved outcomes over the past 2 decades, CV disease remains the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2D).

The opportunities for improving clinical outcomes in patients with T2D and CV disease have recently expanded.

Many sodium-glucose cotransporter 2 (**SGLT2**) inhibitors and glucagon-like peptide 1 receptor agonists (**GLP-1RAs**) have been demonstrated to significantly reduce the risk of major adverse CV events (MACE). SGLT2 inhibitors also substantially diminish the risks of heart failure (HF) hospitalization and progression of diabetic kidney disease (DKD).

Evidences suggesting SGLT2 inhibitors and GLP-1RAs improving outcomes in patients with T2D and CV disease have triggered a major paradigm shift beyond glucose control to a broader strategy of comprehensive CV risk reduction.

This ECDP is primarily focused on management in the outpatient ambulatory setting. However, relevant portions of these recommendations in the acute inpatient setting may also be reasonable.



For full text click link:

https://www.onlinejacc.org/content/early/2020/07/27/j.jacc.2020.05.037

Considerations for Optimal Therapy Initiation and Treatment Individualization

In several circumstances clinicians might consider starting 1 of these agents with demonstrated CV benefit

Patients with T2D may become eligible for initiation of these therapies if they are subsequently ***hospitalized*** or ***diagnosed*** with ASCVD, HF, and/or DKD

Opportunities to Initiate an SGLT2 inhibitor or a GLP-1RA
▪ In a patient with **T2D** and **ASCVD**
▪ **At the time of diagnosis** of clinical ASCVD, DKD, and/or HF in T2D patient NOT on SGLT2i or GLP-1RA
▪ **At the time of diagnosis** of T2D in a patient with clinical ASCVD, DKD and/or HF
▪ **At hospital discharge** after admission for an ASCVD or HF event
▪ In a patient with **T2D** and **DKD**
▪ In patients **determined to be** at high risk of **ASCVD**

ASCVD: Atherosclerotic cardiovascular disease

SGLT 2 inhibitors

	Canagliflozin	Dapagliflozin	Empagliflozin
Recommended doses for CV benefit	■ 100 mg PO daily	■ 10 mg PO daily	■ 10 mg PO daily
Indications	■ Improve glycemic control in adults with T2D as an adjunct to diet and exercise ■ Reduce risk of MI, stroke, or CV death in adults with T2D and CV disease ■ Reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF in patients with T2D and diabetic nephropathy with albuminuria	■ Improve glycemic control in adults with T2D as an adjunct to diet and exercise ■ Reduce the risk of hospitalization for HF in adults with T2D and established CV disease or multiple CV risk factors ■ Reduce the risk of CV death and hospitalization for HF in adults with HFrEF	■ Improve glycemic control in adults with T2D as an adjunct to diet and exercise ■ Reduce risk of CV death in adults with T2D and established CV disease
Dose modifications	■ eGFR 30 to 59 ml/min/1.73 m^2: max dose 100 mg daily ■ eGFR <30 ml/min/1.73 m^2: use is not recommended for glycemic control	■ eGFR <45 ml/min/1.73 m^2: use is not recommended for glycemic control ■ eGFR <30 mL/min/1.73 m^2: use is contraindicated.	■ eGFR <45 mL/min/1.73 m^2: use is not recommended.

HFrEF: Heart failure with reduced ejection fraction

SGLT 2 inhibitors: Contraindications, Cautions & AEs

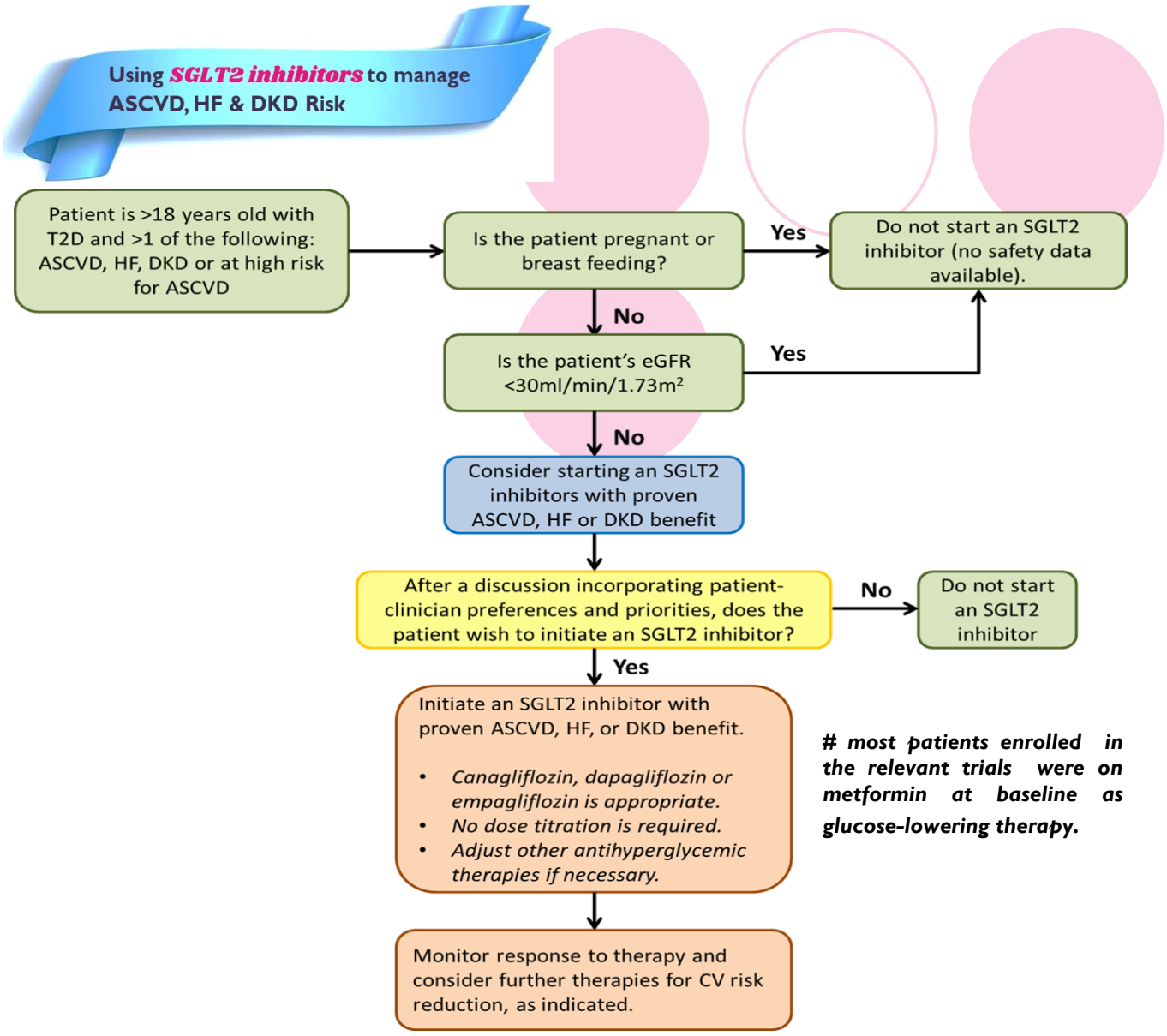
Contraindications	■ History of serious hypersensitivity reaction to drug ■ Pregnancy or breastfeeding ■ On dialysis ■ eGFR <30 mL/min/1.73 m^2 (dapagliflozin) ■ ESRD (dapagliflozin and empagliflozin) ■ Severe renal impairment (empagliflozin)
Cautions	■ Discontinue at least 3 days before a planned surgery to prevent postoperative ketoacidosis. ■ If HbA1c well-controlled at baseline, or known history of frequent hypoglycemic events, wean or stop sulfonylurea or glinide and consider reducing total daily insulin dose by ~20% when starting therapy. ■ May contribute to intravascular volume contraction; consider stopping or reducing diuretic dose if applicable. ■ Use with caution in patients with prior amputation, severe peripheral neuropathy, severe peripheral vascular disease, or active diabetic foot ulcers or soft tissue infections. ■ Possible increased risk of bone fractures (canagliflozin).
Adverse effects to monitor	■ Genital fungal infections ■ Urinary tract infections ■ Euglycemic diabetic ketoacidosis ■ Lower limb ulcerations and soft tissue infections

ESRD: End stage renal disease

SGLT 2 inhibitors: Summary of CV Renal Outcomes Trials

	EMPA-REG OUTCOME	CANVAS/CANVAS-R	DECLARE-TIMI 58	CREDENCE	DAPA-HF*
Patients enrolled, n	7,020	10,142	17,160	4,401	4,744
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin
Dose	10 or 25 mg PO daily	100 or 300 mg PO daily	10 mg PO daily	100 mg PO daily	10 mg PO daily
Median duration of follow-up (years)	3.1	2.4	4.2	2.6	1.5
Mean baseline HbA1c (%)	8.1	8.2	8.3	8.3	*
Mean duration of diabetes (years)	N/A	13.5	11.0	15.8	*
Baseline statin use (%)	77	75	75	69	n/a
Baseline prevalence of CV disease/HF (%)	99	72	41	50	Not reported
Baseline prevalence of HF (%)	10	14	10	15	100*
MACE outcome, HR (95% CI)	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)	0.80 (0.67-0.95)	Not reported
Hospitalization for HF or CV death, HR (95% CI)	0.66 (0.55-0.79)	0.78 (0.67-0.91)	0.83 (0.73-0.95)	0.69 (0.57-0.83)	0.75 (0.65-0.85)
CV death, HR (95% CI)	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.61-1.00)	0.82 (0.69-0.98)
Fatal or nonfatal MI, HR (95% CI)	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)	Not reported	Not reported
Fatal or nonfatal stroke, HR (95% CI)	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	Not reported	Not reported
All-cause mortality, HR (95% CI)	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.83 (0.68-1.02)	0.83 (0.71-0.97)
HF hospitalization, HR (95% CI)	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47-0.80)	0.70 (0.59-0.83)
Renal composite endpoint, HR (95% CI)	0.54 (0.40-0.75)	0.60 (0.47-0.77)	0.53 (0.43-0.66)	0.70 (0.59-0.82)	0.71 (0.44-1.16)

* *58.2% of patients enrolled in DAPA-HF did not have diabetes. All patients enrolled in DAPA-HF had HFrEF*



SGLT2 Inhibitor : Considerations for Drug Initiation and Monitoring
• If HbA1c is well-controlled at baseline, or known history of frequent hypoglycemic events, wean or stop SU and consider reducing total daily insulin dose by ~20% when starting therapy.
• Educate patients regarding potential for ***genital mycotic infections*** and importance of ***genital hygiene.***
• ***Avoid hypovolemia***. May need to reduce diuretic dose if the patient has symptoms of dehydration. • ***Educate patients regarding*** symptoms of ***dehydration*** and to hold medication if low oral intake.
• Instruct patients to more ***closely monitor glucose at home*** for the first 4 weeks of therapy. • Consider discontinuing any SU or glinide. For patients taking insulin, consider modestly reducing total daily insulin dose (by up to 20%).
• ***Educate patients regarding*** symptoms of ***diabetic ketoacidosis*** (DKA) and that it can occur even if blood glucose readings are in the 150–250 mg/dL range. • If patient experiences DKA-like symptoms, he/she should be instructed to seek urgent medical attention.
• ***Educate patients regarding foot care***, especially in patients with diabetic neuropathy. • Ask patients to ***report any foot wounds immediately***.

GLP-1 RAs

	Dulaglutide	Exenatide QW	Liraglutide	Lixisenatide	Semaglutide SC	Semaglutide PO
Recommended doses for CV benefit	■ Initiate 0.75 mg SC per week ■ Titrate slowly to 1.5 mg or maximally tolerated dose based on prescribing information.	■ 2 mg SC per week	■ Initiate 0.6 mg SC daily. ■ Titrate slowly to 1.8 mg or maximally tolerated dose based on prescribing information.	■ 10 mcg SC daily ■ Titrate as tolerated to 20 mcg daily based on prescribing information.	■ Initiate 0.25 mg SC per week. ■ Titrate slowly to 1 mg once weekly or maximally tolerated dose based on prescribing information.	■ Initiate 3 mg PO per day for the first 30 days. ■ Titrate slowly to 14 mg daily or maximally tolerated dose based on prescribing information.
Indications	■ Improve glycemic control in adults with T2D. ■ Reduce MACE for people with T2D with and without established CV disease.	■ Improve glycemic control in adults with T2D.	■ Improve glycemic control in adults with T2D. ■ Reduce risk of MI, CVA, or CV death in adults with T2D and CV disease.	■ Improve glycemic control in adults with T2D.	■ Improve glycemic control in adults with T2D. ■ Reduce risk of MI, CVA, or CV death in adults with T2D and CV disease.	■ Improve glycemic control in adults with T2D.
Dose modifications	■ Up-titrate slowly to reduce nausea and vomiting. ■ Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed. ■ No dose adjustment necessary with renal or hepatic impairment; data in end-stage renal disease are limited.	■ Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed. ■ eGFR <45 mL/min/1.73 m^2: Use is not recommended.	■ Up-titrate slowly to reduce nausea and vomiting. ■ Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed. ■ No dose adjustment is necessary with renal or hepatic impairment.	■ Up-titrate slowly to reduce nausea and vomiting. ■ Discontinue if pancreatitis is suspected, and do not restart if pancreatitis is confirmed . ■ eGFR ≥30 mL/min/1.73 m^2: No dosage adjustment is required. ■ eGFR 15 to 29 mL/min/1.73 m^2: Use caution and monitor renal function. ■ eGFR <15 mL/min/1.73 m^2: Use is not recommended.	■ Up-titrate slowly to reduce nausea and vomiting. ■ Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed. ■ No dose adjustment is necessary with renal or hepatic impairment.	■ Up-titrate slowly to reduce nausea and vomiting. ■ Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed. ■ No dose adjustment is necessary with renal or hepatic impairment.

GLP-1RAs: Contraindications, Cautions & AEs

Contraindications	■ History of serious hypersensitivity reaction to drug ■ Pregnancy or breast feeding ■ Severe renal impairment or end-stage renal failure (exenatide, lixisenatide) ■ Personal or family history of medullary thyroid cancer ■ Personal or family history of MEN2
Cautions	■ Hypoglycemia risk increased with insulin, sulfonylureas, or glinides. ■ May delay gastric emptying; not recommended in patients with clinically meaningful gastroparesis. This effect is usually transient with longer-acting GLP-1Ras. ■ Care should be taken in patients with prior gastric surgery, including bariatric surgery. ■ Diabetic retinopathy complications were reported with semaglutide (injectable), although it is unclear if this is a direct effect of the drug or due to other factors such as rapid improvement in blood glucose control.
Adverse effects to monitor	■ Nausea, vomiting, diarrhea, headache, weakness, or dizziness ■ Hypoglycemia when given with insulin, sulfonylureas, or glinides. ■ Weight loss ■ Injection site reactions

MEN2: multiple endocrine neoplasia, type 2

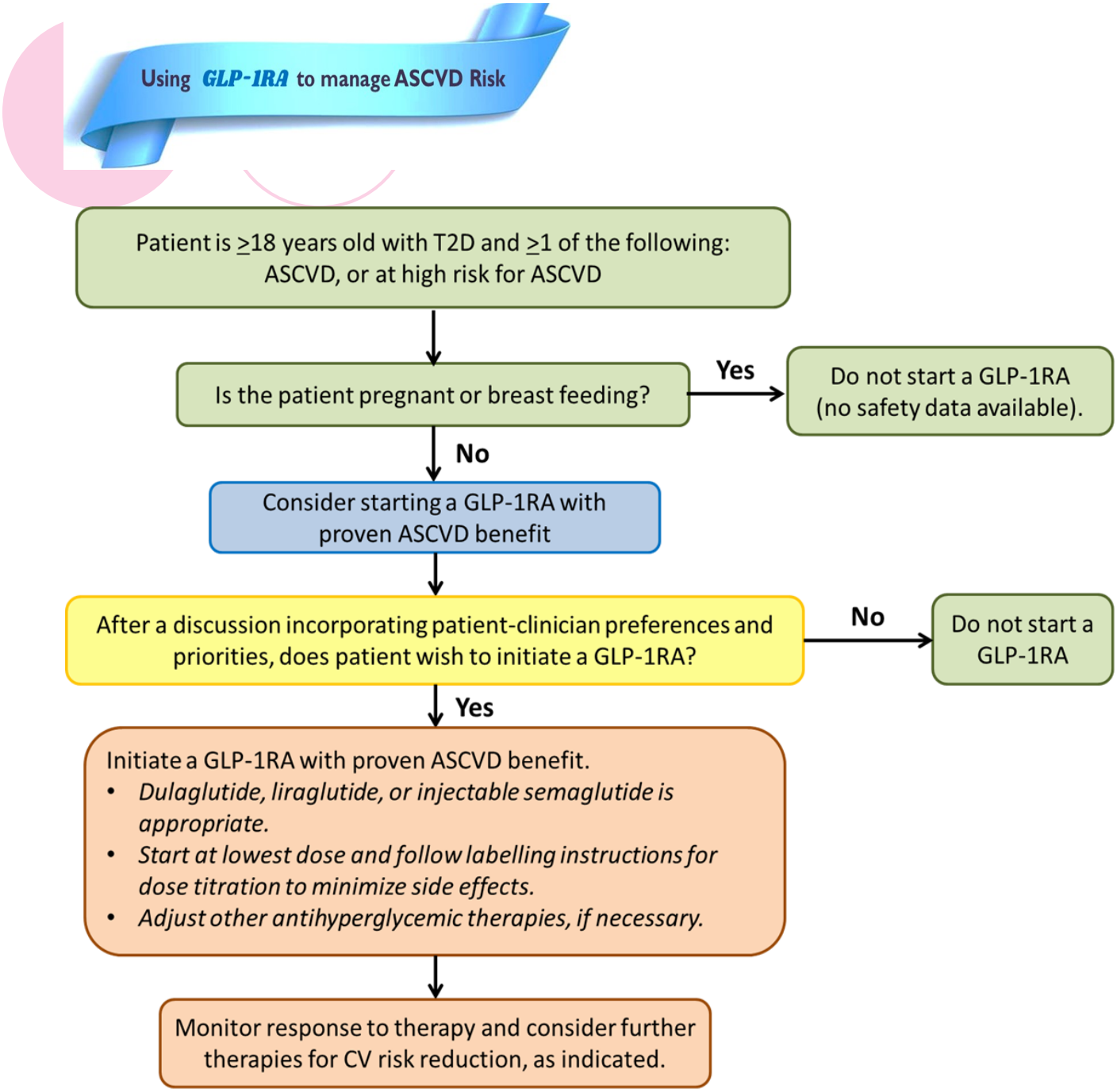
GLP-1RAs: Summary of CV Renal Outcomes Trials

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	REWIND	PIONEER-6
Patients enrolled	6,068	9,340	3,297	14,752	9,901	3183
Drug	Lixisenatide	Liraglutide	Semaglutide SQ	Exenatide QW	Dulaglutide	Semaglutide oral
Dose	10 mcg or 20 mcg per day	1.8 mg or max tolerated dose per day	0.5 mg or 1 mg per week	2 mg per week	1.5 mg per week	14 mg or max tolerated dose per day
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Baseline HbA1c	7.7	8.7	8.7	8.0	7.2	8.2
Mean duration of diabetes (years)	9.3	12.8	13.9	12.0	9.5	14.9
Baseline statin use (%)	93	72	73	74	66	85
Baseline prevalence of ASCVD†/HF (%)	100	81	72	73	31	85
Baseline prevalence of HF (%)	22	18	24	16	9	NR
Primary outcome, HR (95% CI)	4-point MACE 1.02 (0.89-1.17)	3-point MACE 0.87 (0.78-0.97)	3-point MACE 0.74 (0.58-0.95)	3-point MACE 0.91 (0.83-1.00)	3-point MACE 0.88 (0.79-0.99)	3-point MACE 0.79 (0.57-1.11)
CV death, HR (95% CI)	0.98 (0.78-1.22)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.91 (0.78-1.06)	0.49 (0.27-0.92)
Fatal or nonfatal MI, HR (95% CI)	1.03 (0.87-1.22)	0.86 (0.73-1.00)	0.74 (0.51-1.08)	0.97 (0.85-1.10)	0.96 (0.79-1.15)	1.18 (0.73-1.90)
Fatal or nonfatal stroke, HR (95% CI)	1.12 (0.79-1.58)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.85 (0.70-1.03)	0.76 (0.62-0.94)	0.74 (0.35-1.57)
All-cause mortality, HR (95% CI)	0.94 (0.78-1.13)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.90 (0.80-1.01)	0.51 (0.31-0.84)
HF hospitalization, HR (95% CI)	0.96 (0.75-1.23)	0.87 (0.73-1.05)	0.86 (0.48-1.55)	0.94 (0.78-1.13)	0.93 (0.77-1.12)‖	1.11 (0.77-1.61)
Renal composite outcome‡	0.84 (0.68-1.02)	0.78 (0.67-0.92)	0.64 (0.46-0.88)	0.88 (0.76-1.01)	0.85 (0.77-0.93)	0.64 (0.46-0.88)

SQ: subcutaneous; QW: once weekly; NR: not reported

GLP-1RA: Considerations for Drug Initiation and Monitoring

- If HbA1c is well-controlled at baseline, or known history of frequent hypoglycemic events, wean or stop SU and consider reducing total daily insulin dose by ~20% when starting therapy.
- Instruct patients to more ***closely monitor glucose at home*** for the first 4 weeks of therapy.
- ***Consider discontinuing any SU or glinide***. For patients taking insulin, consider modestly reducing total daily insulin dose (by up to 20%).
- ***Discontinue DPP-4 inhibitor*** before starting.
- To mitigate nausea, recommend ***small portion sizes for meals***, start at the ***lowest dose***, and ***up-titrate as tolerated*** toward the goal doses used in CV outcome trials.
- ***Advise*** patients to undergo appropriate, guideline-recommended ***eye examinations*** before starting therapy if not done within the last 12 months.
- ***Discuss*** potential ***risk of diabetic retinopathy*** complications (for dulaglutide or injectable semaglutide).
- ***Avoid*** in patients with ***diabetic gastroparesis*** or ***active gallbladder disease***.



For any scientific queries on above topic

Write to the Scientific Department at:

+91 8879607724 scientific@aristopharma.org

For reporting any adverse drug reaction (ADR) observed with the product(s) of Aristo Pharmaceuticals Private Limited, contact: Email- aepvc.scientific@aristopharma.org or Toll-free No. 1800225960 (Monday to Friday except on public holidays between 9.30 am to 5.30 pm) or WhatsApp: +918879607724.

(For Internal Circulation Only)