Interactive type 2 Diabetes Cases

Objectives:

As a result of attending this session, the participants will gain abilities in selecting appropriate antihyperglycemic therapies based on the patient's clinical characteristics.

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Endocrinologist
McGill University Health Centre, Montreal, Canada

December 2022

Interactive type 2 Diabetes Cases

Disclosures

Lectures, advisory boards:
Merck, AstraZeneca, Takeda, Boehringer-Ingelheim, Janssen, Novo Nordisk, Eli Lilly, Sanofi, Abbott, Medtronic, Bayer, Omnipod

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Merck, AstraZeneca, Boehringer-Ingelheim, Janssen, Novo Nordisk,
Eli Lilly, Sanofi, Medtronic, Bayer, Mylan

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Through a series of questions, you will be asked to create our case:

Age and gender
CVD ?
A1c ?
Renal status
Current antihyperglycemic therapy

Over 32,000 possible scenarios...

Select the age and gender of our patient

44 year old man with T2D de novo

52 yo woman with T2D x 2 years

61 yo man with T2D x 5 years

70 yo woman with T2D x 11 years

77 year old man with T2D x 17 years

86 year old woman with T2D x 33 years

Does our patient have cardiovascular disease ?

No

Yes, myocardial infarct and stent x 3 4 years ago

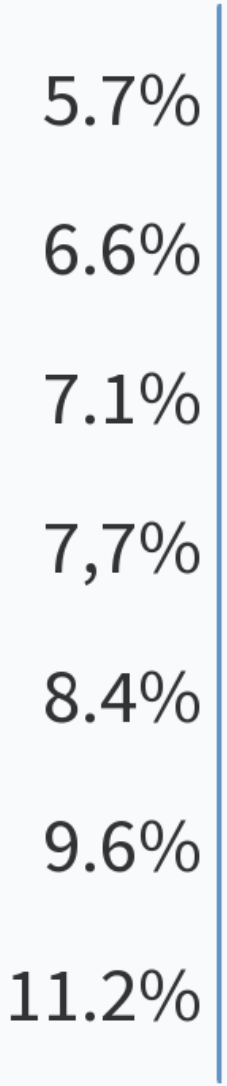
Yes, documented heart failure

Yes, peripheral artery disease

Yes, history of mild stroke

Yes, history of angina, positive stress test

What is the A1c of our patient ?



Select the renal status of our patient

eGFR > 60, no microalbuminuria

eGFR > 60, Alb/Creat ratio 4.7

eGFR 55, no microalbuminuria

eGFR 55, Alb/Creat ratio 12.7

eGFR 43, Alb/Creat ratio 22.0

eGFR 31, Alb/Creat ratio 145.6

eGFr 22, Alb/Creat ratio 44

eGFR 15,m Alb/Creat 456

Our patient is on metformin. How many other antihyperglycemic agents is the patient on ?

Select the current therapy of our patient (0)

Metformin 500 mg per day

Metformin 500 mg bid

Metformin 850 mg bid

Metformin 1000 mg bid

Select the current therapy of our patient (1)

Metformin 850 mg bid + Sitagliptin 100 mg die

Metformin 850 mg bid + Empagliflozin 10 mg die

Metformin 850 mg bid + Gliclazide MR 60 mg die

Metformin 850 mg bid + Semaglutide oral 7 mg die

Metformin 850 mg bid + Semaglutide 0.5 mg per week

Metformin 850 mg bid + Glargine 100u/ml 34 units at bedtime

Select the current therapy of our patient, in addition to metformin 850 mg bid (2)

Sitagliptin 100 mg die + Dapagliflozin 10 mg die

Gliclazide MR 60 mg die + Linagliptin 5 mg die

Canagliflozin 100 mg die + Semaglutide 0.5 mg per week

Gliclazide MR 60 mg die + Empagliflozin 10 mg die

Semaglutide 0.5 mg per week + Degludec 46 units per day

Glargine 300 u/ml 42 units per day + Lispro insulin 16 units before each meal

Select the current therapy of our patient, in addition to metformin 850 mg bid (3)

Gliclazide MR 60 mg die + Sitagliptin 100 mg die + Empagliflozin 10 mg die

Gliclazide mR 60 mg die + Dapagliflozin 10 mg die + Semaglutide 0.5 mg per week

Canagliflozin 100 mg die + Dulaglutide 0.75 mg per week + Glargine 300u/ml 22 units die

Empagliflozin 25 mg die + Degludec 67 units die + Insulin Aspart 20 units before each meal

Patient with type 2 diabetes

Age and gender	year old man	Current medication	
Occupation		Metformin	850 mg BID
Insurance coverage	Private	Sulfonylurea	
		DPP-4 inhibitor	
Type 2 diabetes	x	SGLT2 inhibitor	
A1c		GLP-1 receptor agonist	
Cardiovascular disease?		Basal insulin	
Cholesterol LDL	1.88	Prandial insulin	
Blood Pressure	118/75	Correction factor	
BMI	31.5		
Smoking ?	NO	Statin	NO
		ACEi/ARB	NO
Retinopathy ?		ASA	
Neuropathy ?		Others	
eGFR		Problems with Rx ?	
Alb/Creat Ratio		Other	

Answer my question....

Give me only one word...

Do you agree with my statement ?

Yes

No

Unsure

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Alb/Creat Ratio		Other	

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Alb/Creat Ratio		Other	

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eGFR		Problems with Rx ?	
Alb/Creat Ratio		Other	

DIABETES CANADA

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www.canadianjournalofdiabetes.com

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DIABETES CANADA

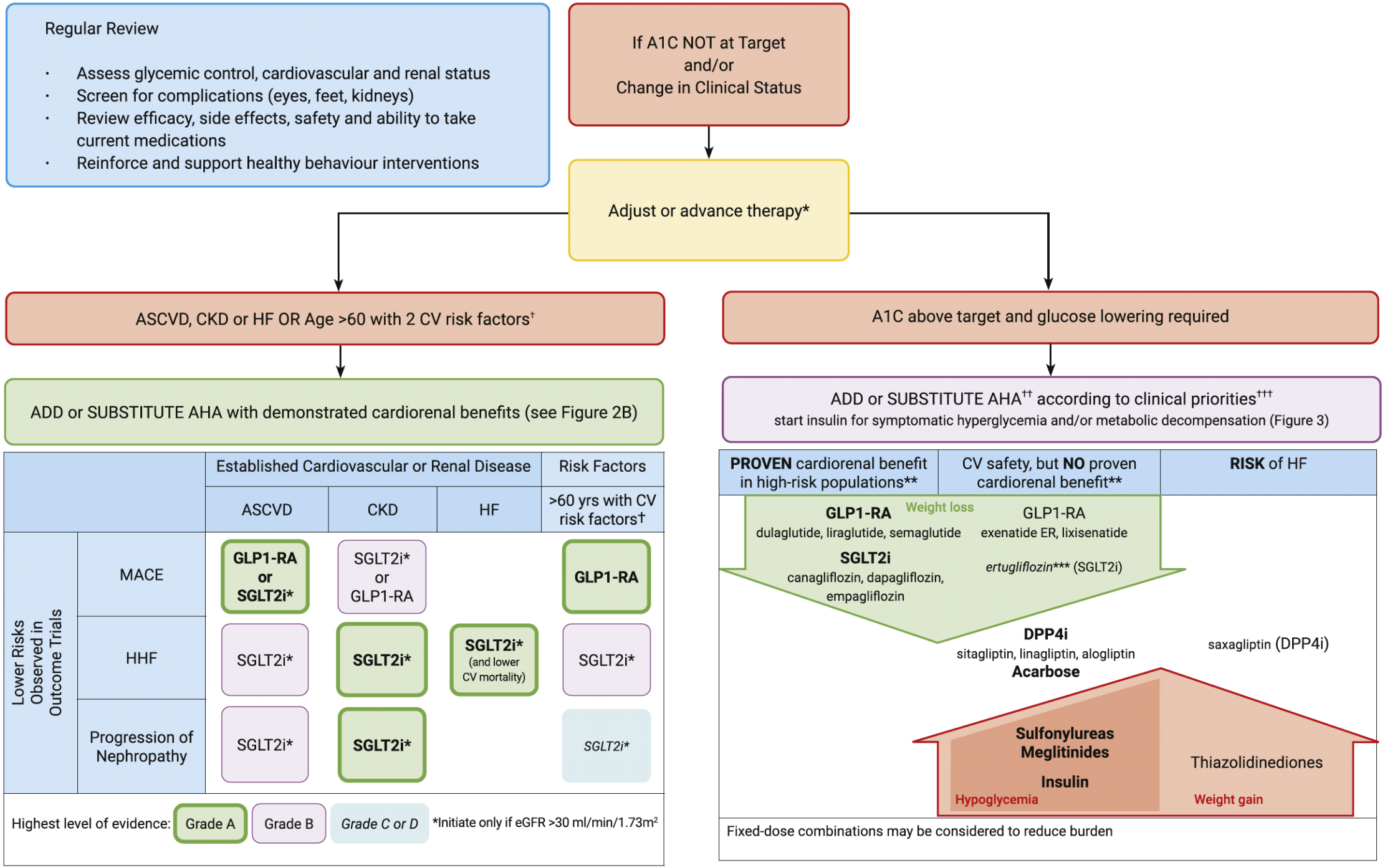
Special Article

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update

Diabetes Canada Clinical Practice Guidelines Expert Committee

CPG2018: Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 42(Suppl 1): S1-325, 2018.

CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.



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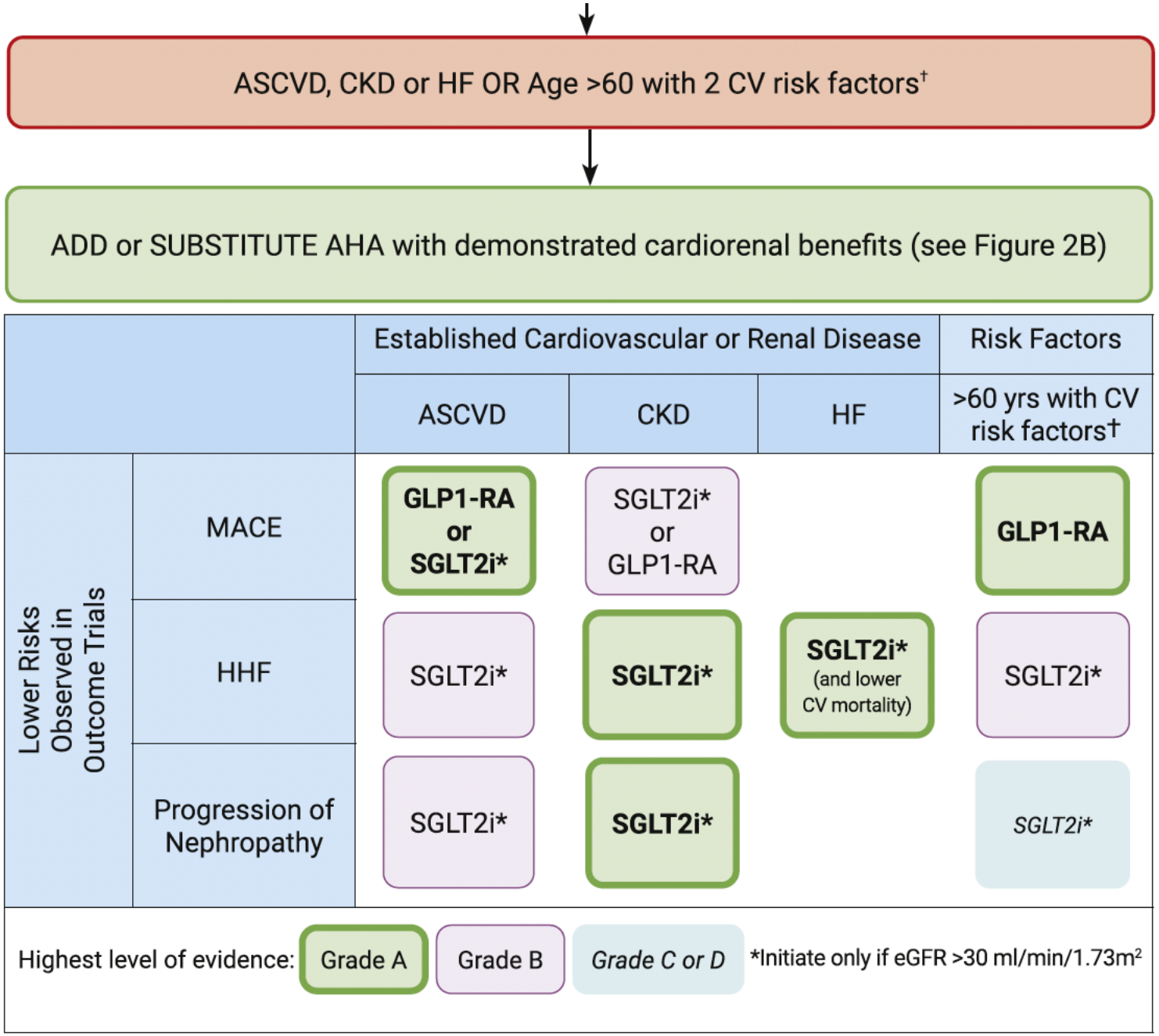


CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.

ASCVD, CKD or HF OR Age >60 with 2 CV risk factors†

ADD or SUBSTITUTE AHA with demonstrated cardiorenal benefits (see Figure 2B)

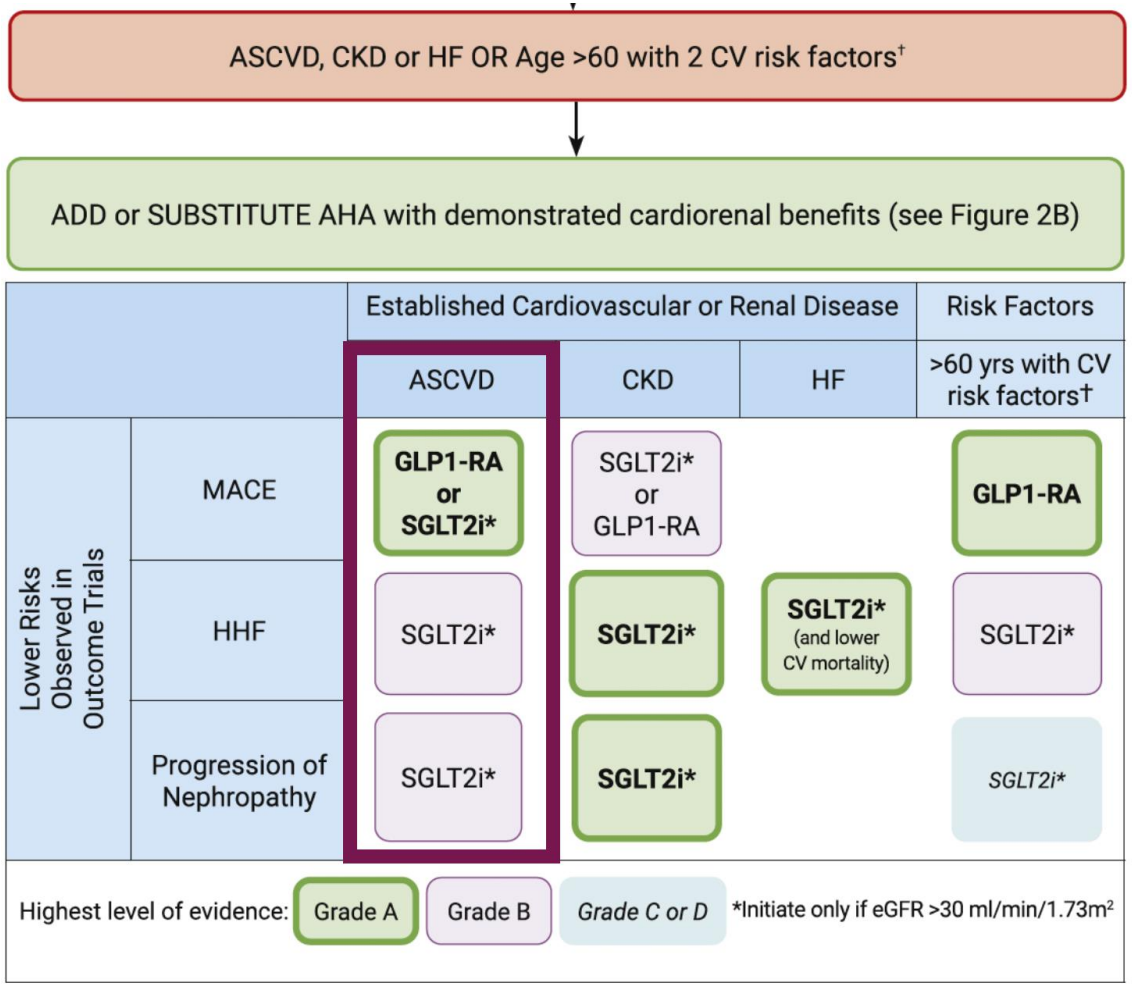
		Established Cardiovascular or Renal Disease			Risk Factors
		ASCVD	CKD	HF	>60 yrs with CV risk factors†
Lower Risks Observed in Outcome Trials	MACE	**GLP1-RA or SGLT2i***	SGLT2i* or GLP1-RA		**GLP1-RA**
	HHF	SGLT2i*	**SGLT2i***	**SGLT2i*** (and lower CV mortality)	SGLT2i*
	Progression of Nephropathy	SGLT2i*	**SGLT2i***		*SGLT2i**

Highest level of evidence: Grade A | Grade B | *Grade C or D*

*Initiate only if eGFR >30 ml/min/1.73m²

CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.

Patients with atherosclerotic cardiovascular disease



	SGLT2 Inhibitors			GLP-1 Receptor Agonists			
	Empa-gliflozin	Cana-gliflozin	Dapa-gliflozin	Lira-glutide	Semaglutide S/C	Semaglutide oral	Dulaglutide
	Jardiance	Invokana	Forxiga	Victoza	Ozempic	Rybelsus	Trulicity
Trial	EMPAREG	CANVAS	DECLARE	LEADER	SUSTAIN-6	PIONEER-6	REWIND
Population	N=7020 CVD 100%	N=10142 CVD 65%	N=17160 CVD 41%	N=9540 CVD 80%	N=3297 CVD 80%	N=3183 CVD 85%	N=9901 CVD 31%
Duration	3.2 yrs	2.4 yrs	4.2 yrs	3.8 yrs	2.0 yrs	1.3 yrs	5.4 yrs
RENAL	↓ 39 %	↓ 40 %	↓ 47 %	↓ 22 %	↓ 36%		↓ 15%

Practical point: If your patient has a history of ischemic heart disease, a GLP-1RA and/or an SGLT2i should be initiated, independently of the current A1c level. You may need to stop or reduce the dose of another agent.

CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.
EMPAREG Outcome: Zinman B et al. NEJM 373:2117-2128, 2015. CANVAS: Neal B. Et al. NEJM 377:644, 2017. DECLARE: Wiviott SD et al. NEJM 380: 347-357, 2019.
LEADER: Marso SP et al. NEJM 375: 211-322, 2016. SUSTAIN-6: Marso SP et al. NEJM 375: 1834-44, 2016. PIONEER-6: Husain M et al. NEJM 381: 841-51, 2019.
REWIND: Gerstein HC et al. The Lancet June 2019 DOI: 10.1016/SO

ASCVD, CKD or HF OR Age >60 with 2 CV risk factors†

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Lower Risks Observed in Outcome Trials	MACE	**GLP1-RA or SGLT2i***	SGLT2i* or GLP1-RA		**GLP1-RA**
	HHF	SGLT2i*	**SGLT2i***	**SGLT2i*** (and lower CV mortality)	SGLT2i*
	Progression of Nephropathy	SGLT2i*	**SGLT2i***		*SGLT2i**

Highest level of evidence: Grade A | Grade B | *Grade C or D*

*Initiate only if eGFR >30 ml/min/1.73m²

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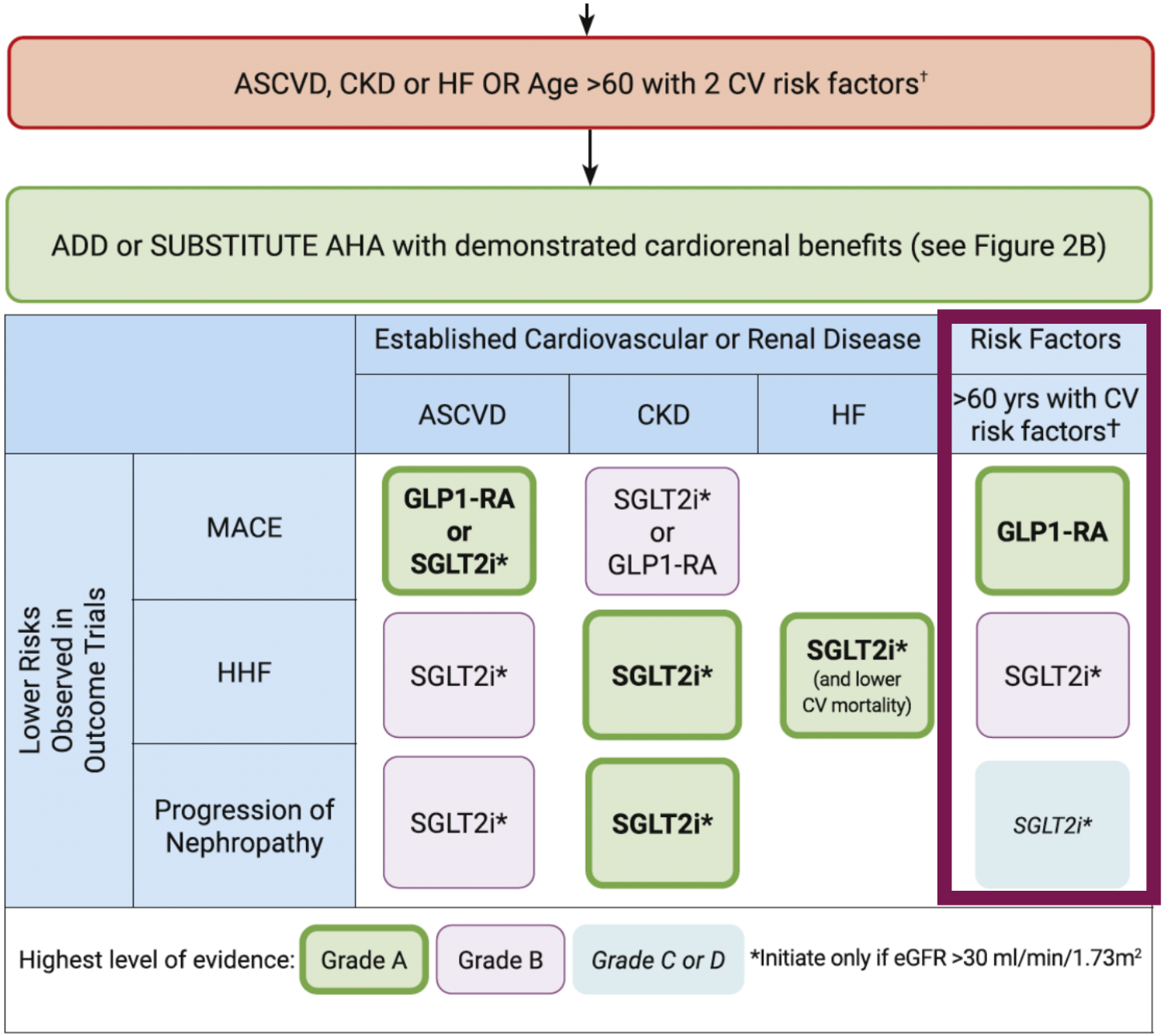
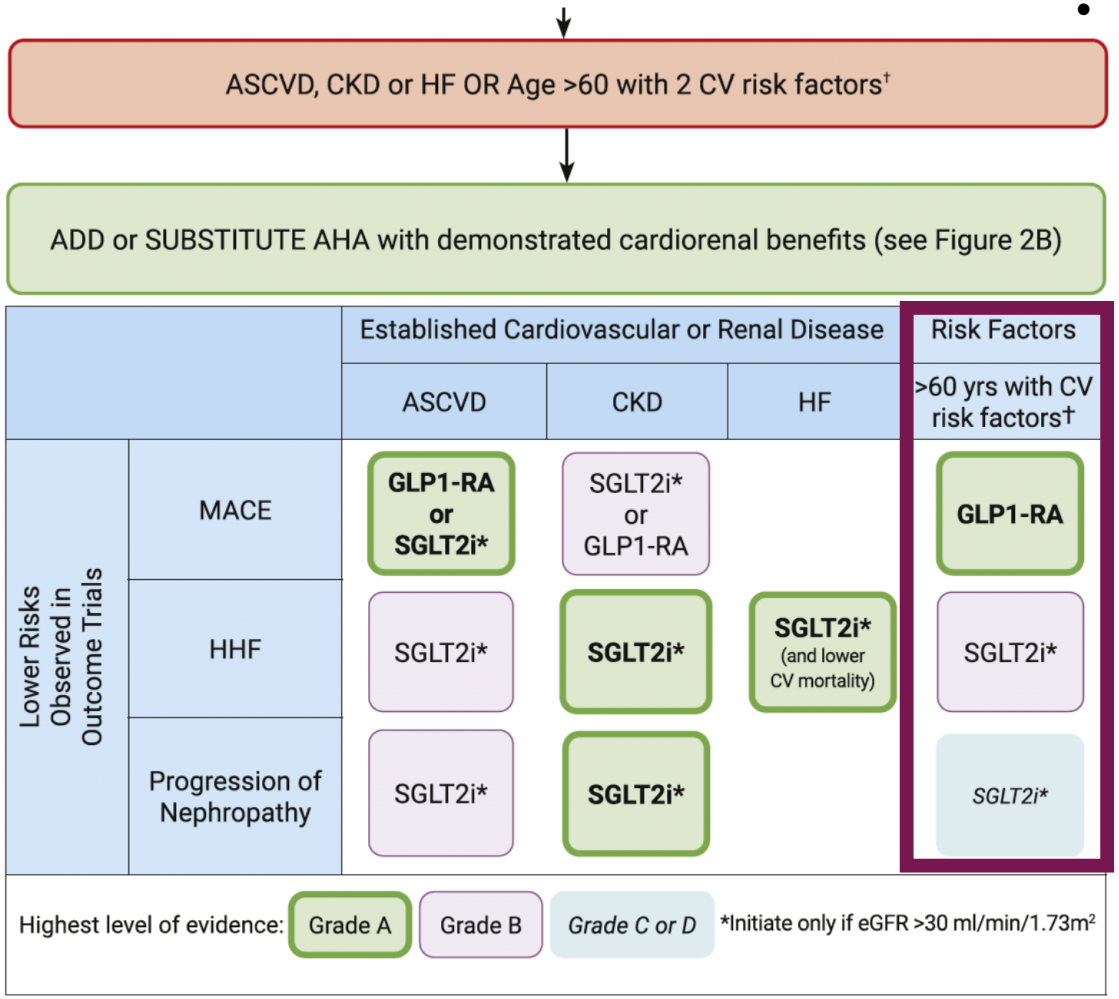


CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.

Patients above 60 years of age with 2 cardiovascular risk factors



Definition of CV risk factors:

- Tobacco use
- Dyslipidemia (use of lipid-modifying therapy or documented untreated LDL ≥ 3.4mM or HDL < 1.0 for men and 1.3 for women, or triglycerides ≥ 2.3)
- Hypertension (use of BP drug or untreated SBP ≥ 140 mm Hg or DBP ≥ 95 mm Hg)

	SGLT2 Inhibitors			GLP-1 Receptor Agonists			
	Empa-gliflozin	Cana-gliflozin	Dapa-gliflozin	Lira-glutide	Semaglutide S/C	Semaglutide oral	Dulaglutide
	Jardiance	Invokana	Forxiga	Victoza	Ozempic	Rybelsus	Trulicity
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Duration	3.2 yrs	2.4 yrs	4.2 yrs	3.8 yrs	2.0 yrs	1.3 yrs	5.4 yrs
MACE	x						↓ 13%

Practical point: If your patient is older than 60 years old, a GLP-1RA and/or an SGLT2i should be initiated, independently of the current A1c level. You may need to stop or reduce the dose of another agent.

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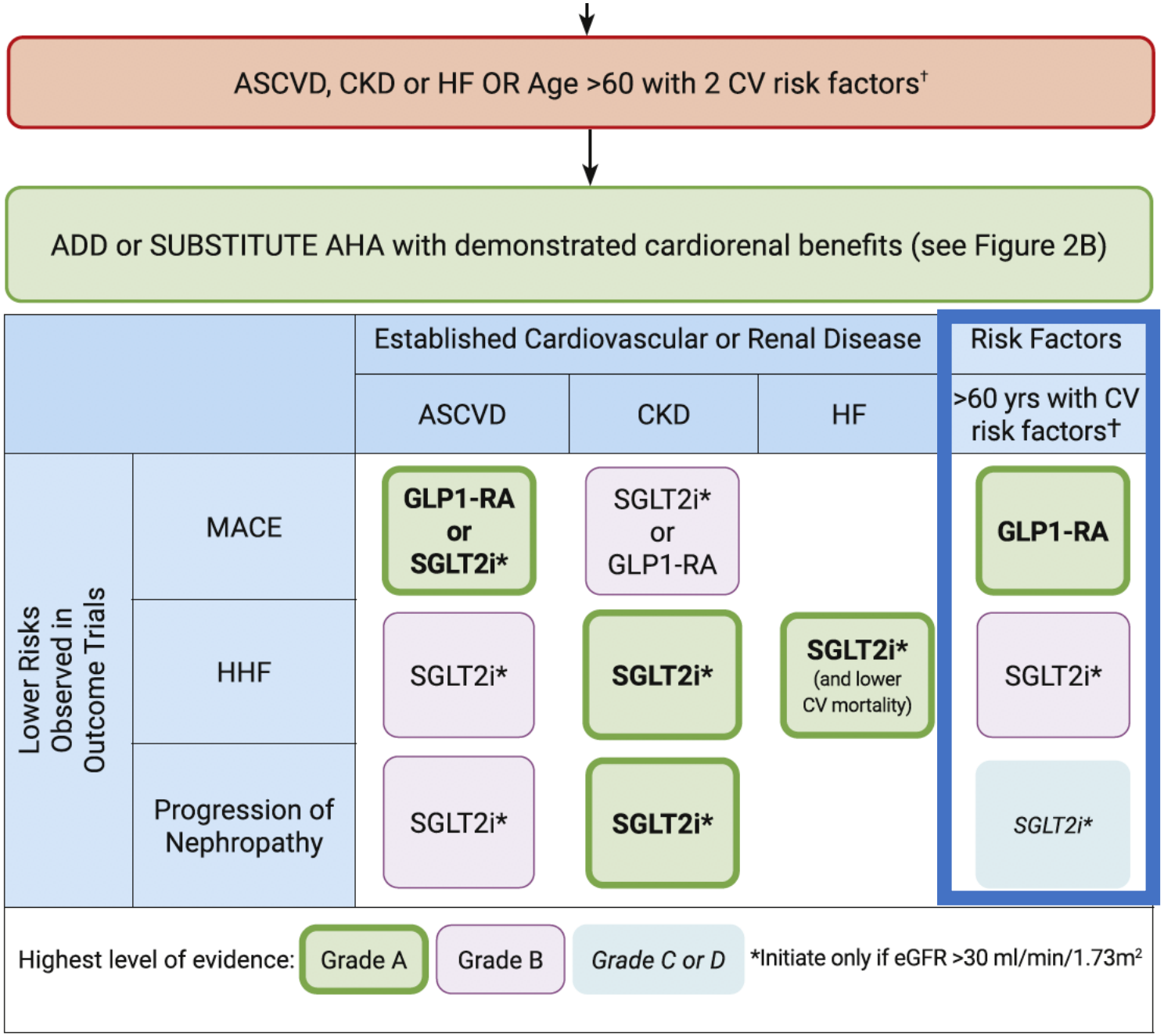
REWIND: Gerstein HC et al. The Lancet June 2019 DOI: 10.1016/SO

Glycemic Control	Vascular Protection	Blood Pressure Control
Metformin	ASA	Diuretics
Secretagogues	Statins	Calcium Channel Blockers
Insulin		ACE Inhibitors
DPP-4 Inhibitors		Angiotensin-receptor Antagonists
SGLT2 Inhibitors		Beta-Blockers
GLP-1R Agonists		



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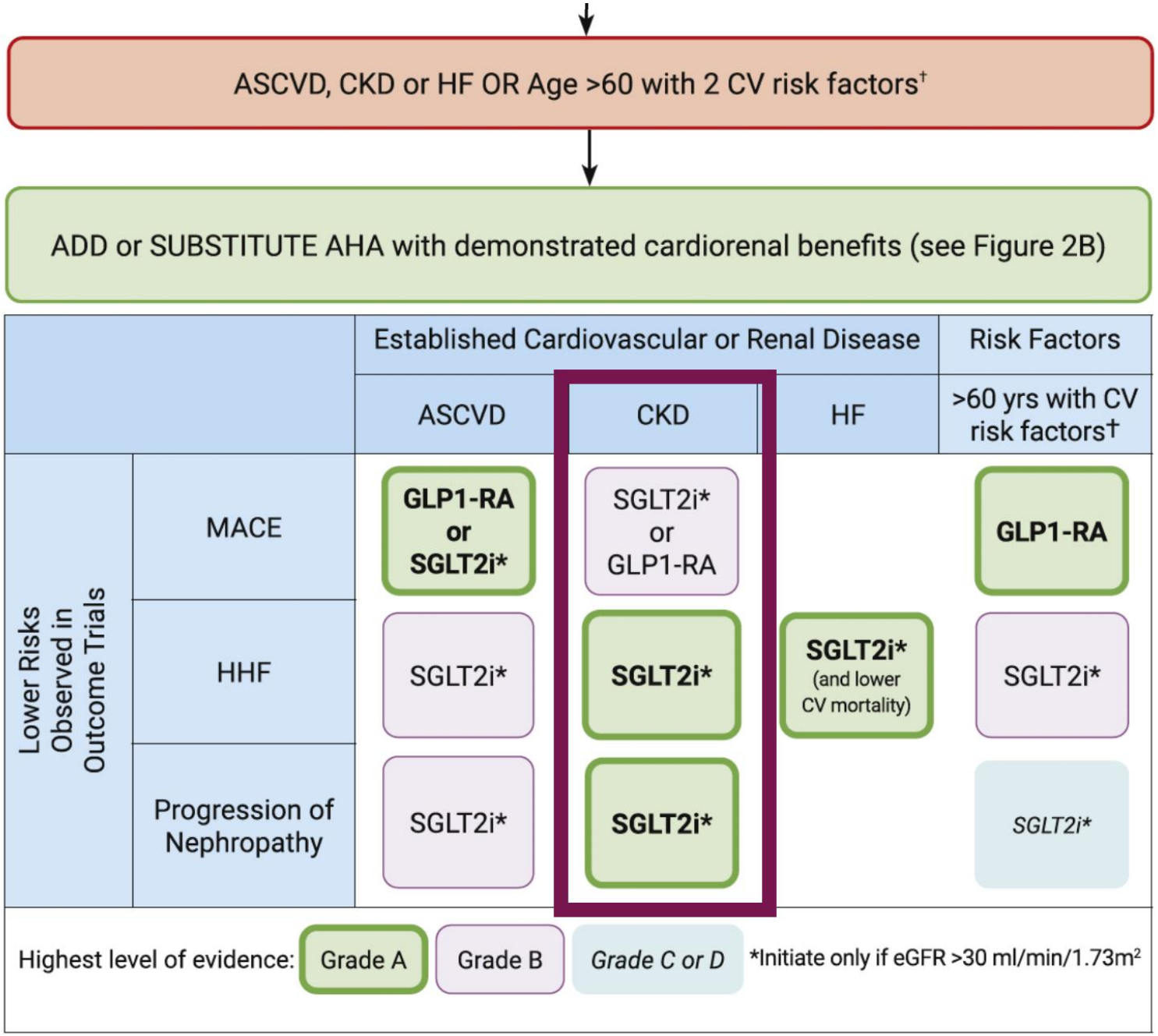

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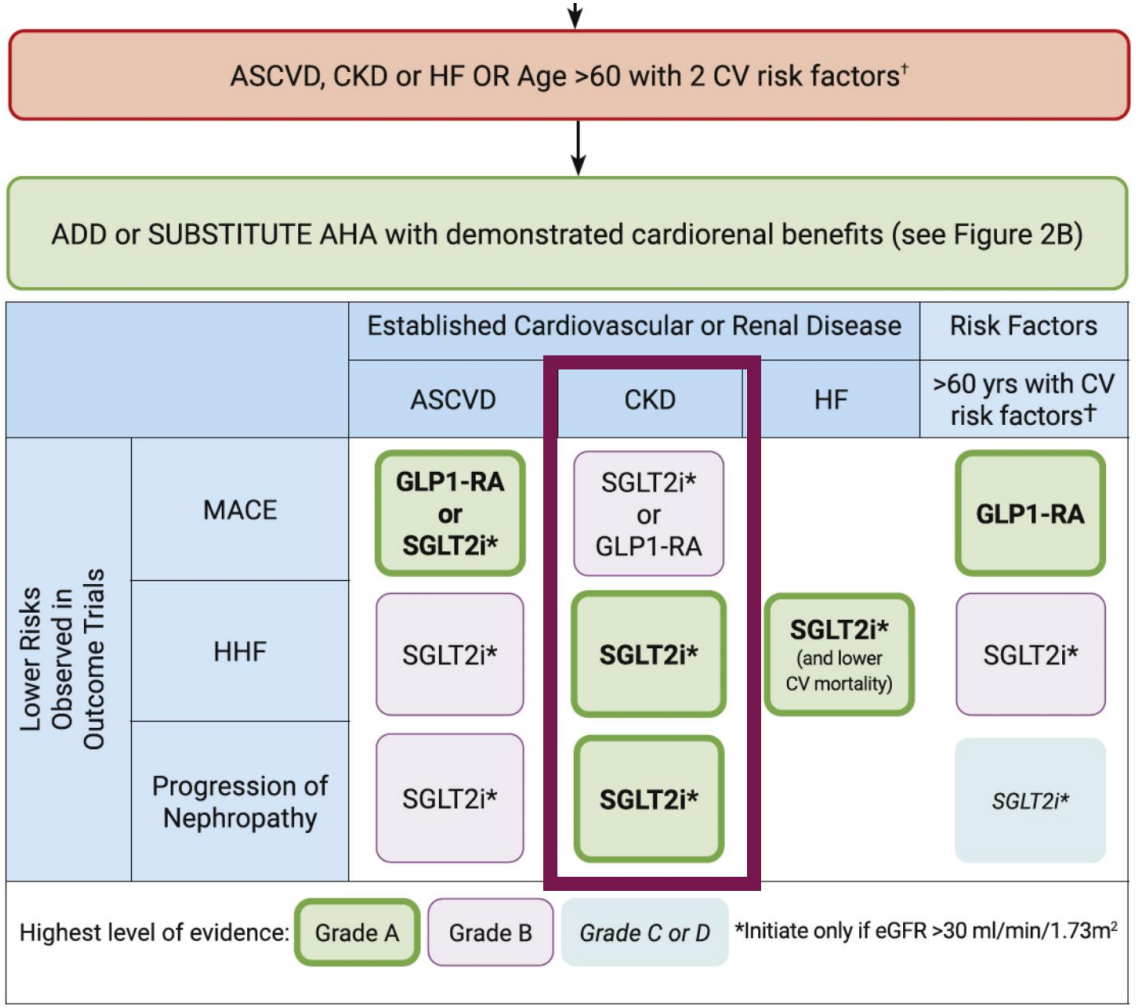
Chronic Kidney Disease Population



	SGLT2 Inhibitors			GLP-1 Receptor Agonists			
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Trial	EMPAREG	CREDENCE	DAPA-CKD	LEADER	SUSTAIN-6	PIONEER-6	REWIND
Population	N=7020 CVD 50%	N=4401 CVD 65%	N=17160 CVD 41%	N=9540 CVD 80%	N=3297 CVD 80%	N=3183 CVD 85%	N=9901 CVD 31%
Duration	3.2 yrs	2.6 yrs	4.2 yrs	3.8 yrs	2.0 yrs	1.3 yrs	5.4 yrs
MACE	X	↓ 20 %	↓ 31 % All cause mortality	↓ 11 % < 30 ml/min	↓ 27% < 30 ml/min		↓ 27% Micro/macro-albuminuria

Practical point: If your patient has an eGFR between 30 and 60 ml/min or microalbuminuria, a GLP-1RA and/or an SGLT2i should be initiated, independently of the current A1c level.

You may need to stop or reduce the dose of another agent.
You can use a GLP-1RA at any eGFR. You should only initiate an SGLT2i if the eGFR is above 30.
Start at a low dosage and titrate slowly, to avoid nausea and vomiting with GLP-1RA, and hypotension with SGLT2i.

CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.
EMPAREG Outcome: Zinman B et al. NEJM 373:2117-2128, 2015. CREDENCE: Perkovic V et al. NEJM 380: 229
LEADER: Marso SP et al. NEJM 375: 211-322, 2016. SUSTAIN-6: Marso SP et al. NEJM 375: 1834-44, 2016. P
REWIND: Gerstein HC et al. The Lancet June 2019 DOI: 10.1016/SO REWIND: Colhoun H et al. Poster EASD20

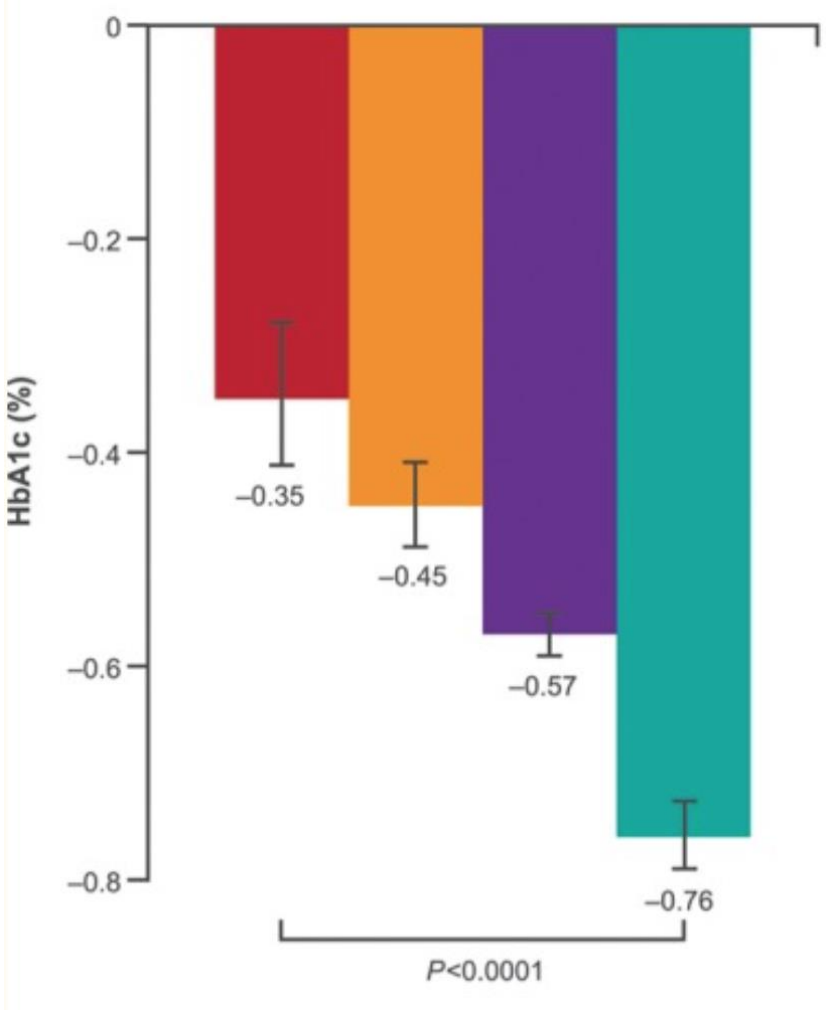
Practical point: If your patient has an eGFR between 30 and 60 ml/min or microalbuminuria, a GLP-1RA and/or an SGLT2i should be initiated, independently of the current A1c level.

What a change !

Not so long ago, we were telling you to
AVOID USING an SGLT2i if the eGFR was under 60

A1c reduction as a function of eGFR

Lower eGFR = Less glucosuria = Lower efficacy



Baseline eGFR (ml/min/1.73m^2)

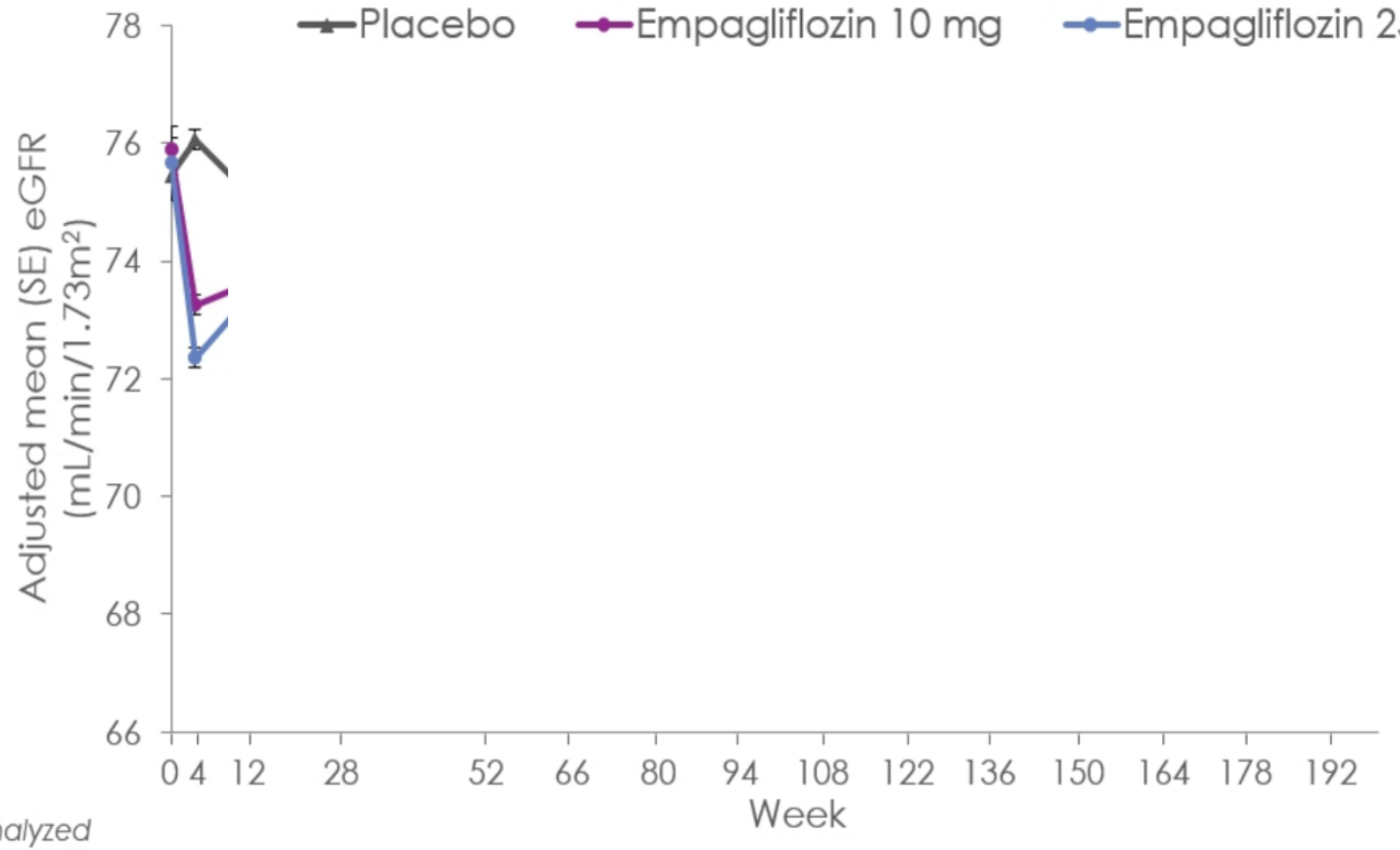
≥ 90

60-<90

45-<60

< 45

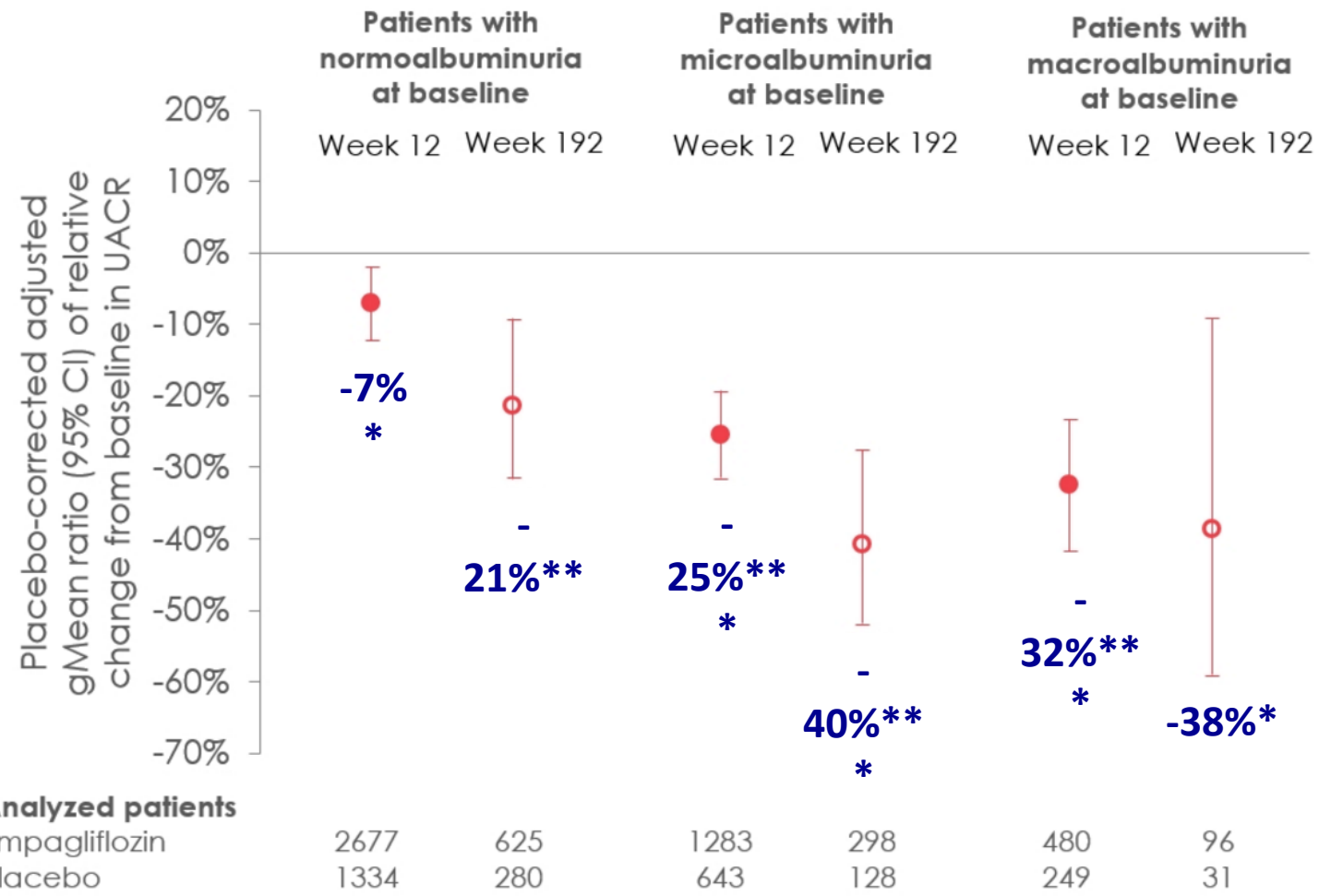
eGFR (CKD-EPI formula) over 192 weeks



No. analyzed															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524

EMPAREG Outcome: Zinman B. Et al. NEJM 373:2117-2128, 2015

Placebo-corrected change in UACR from baseline at week 12 and week 192



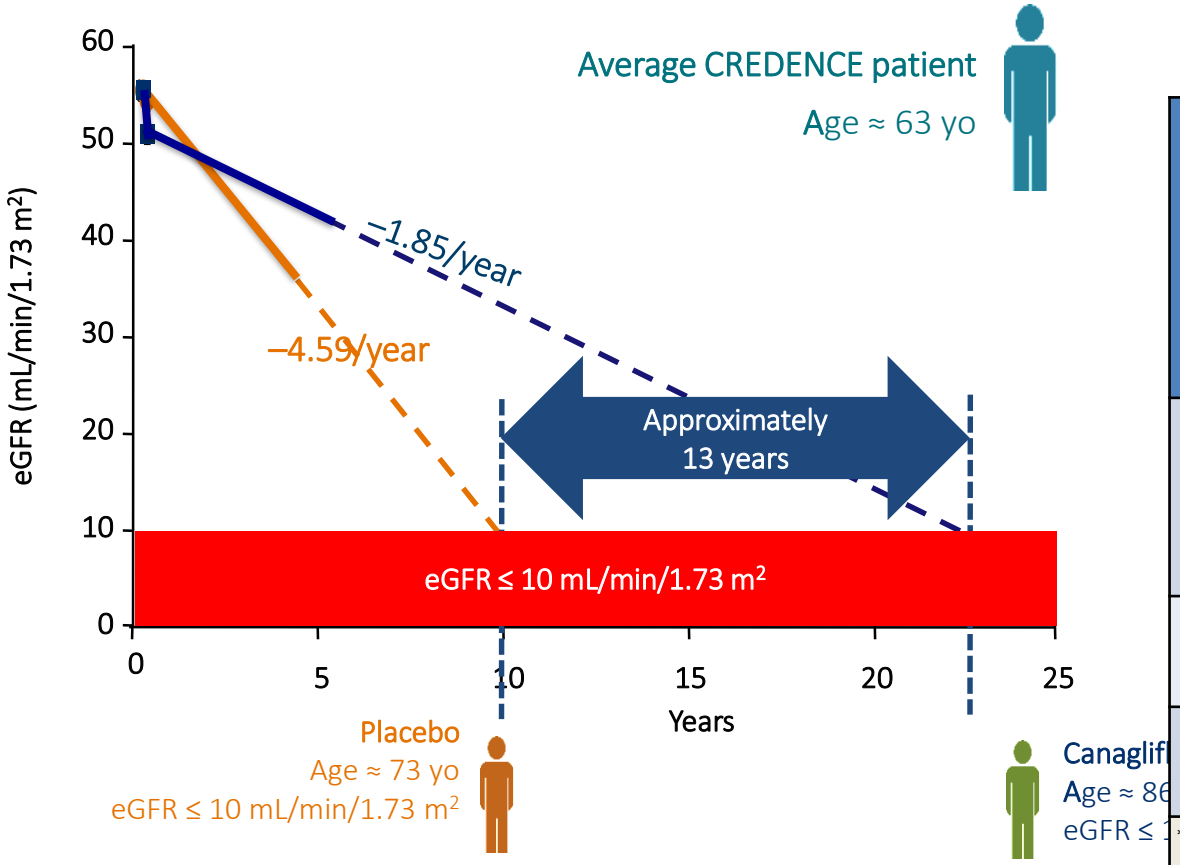
Analyzed patients						
Empagliflozin	2677	625	1283	298	480	96
Placebo	1334	280	643	128	249	31

MMRM in the treated set (OC-AD). Normoalbuminuria: UACR <30 mg/g; microalbuminuria: UACR ≥30 to ≤300 mg/g; macroalbuminuria: UACR >300 mg/g.
*p<0.05; **p<0.01; ***p<0.001 for difference vs placebo.

EMPA-REG OUTCOME®

EMPAREG Outcome: Zinman B. Et al. NEJM 373:2117-2128, 2015

Potential Importance of SGLT2 Inhibition



Dialysis, kidney transplantation or drenal death (number of events)*	
Canagliflozin (n=2202)	Placebo (n=2199)
78	105
RR 0.72 (95% CI 0.54–0.97)	

*Post-hoc analysis

- Adapted from: Perkovic et al., *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1811744.
- Rivara & Mehrotra, *Semin Nephrol*. 2017; 37(2): 181–193.

Antihyperglycemic Agents and Renal Failure

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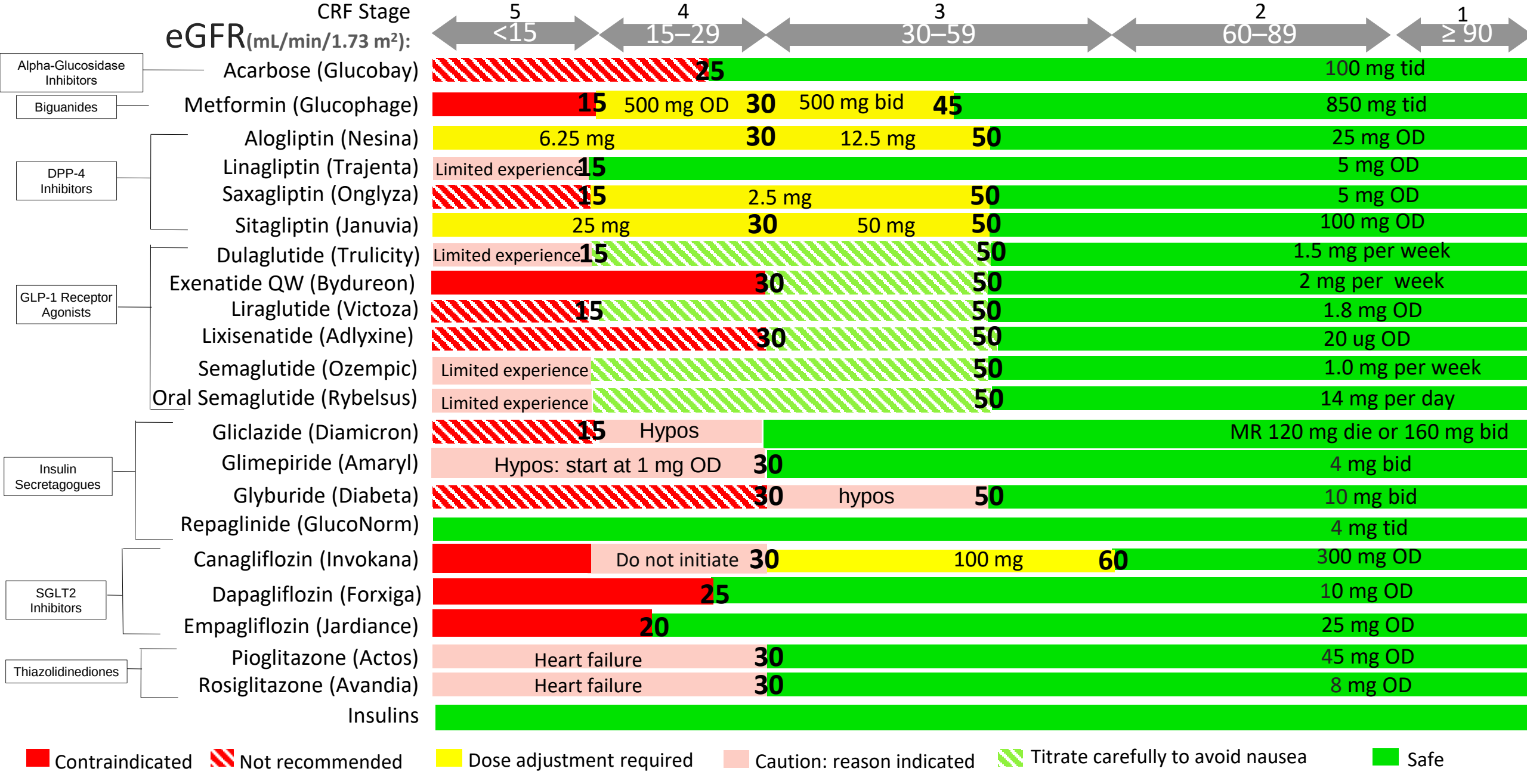
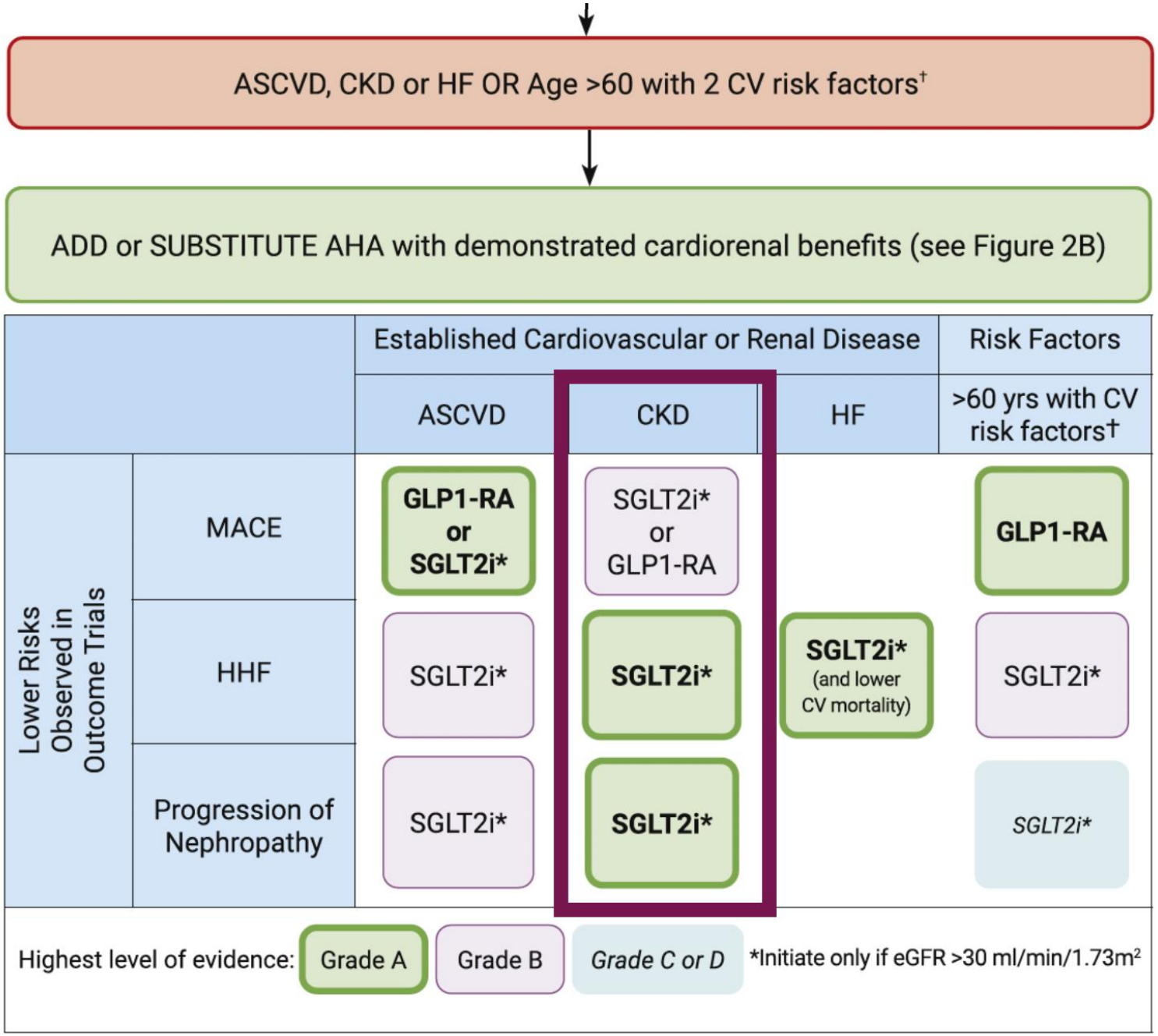


The dose indicated is the highest dose that can be used at that eGFR



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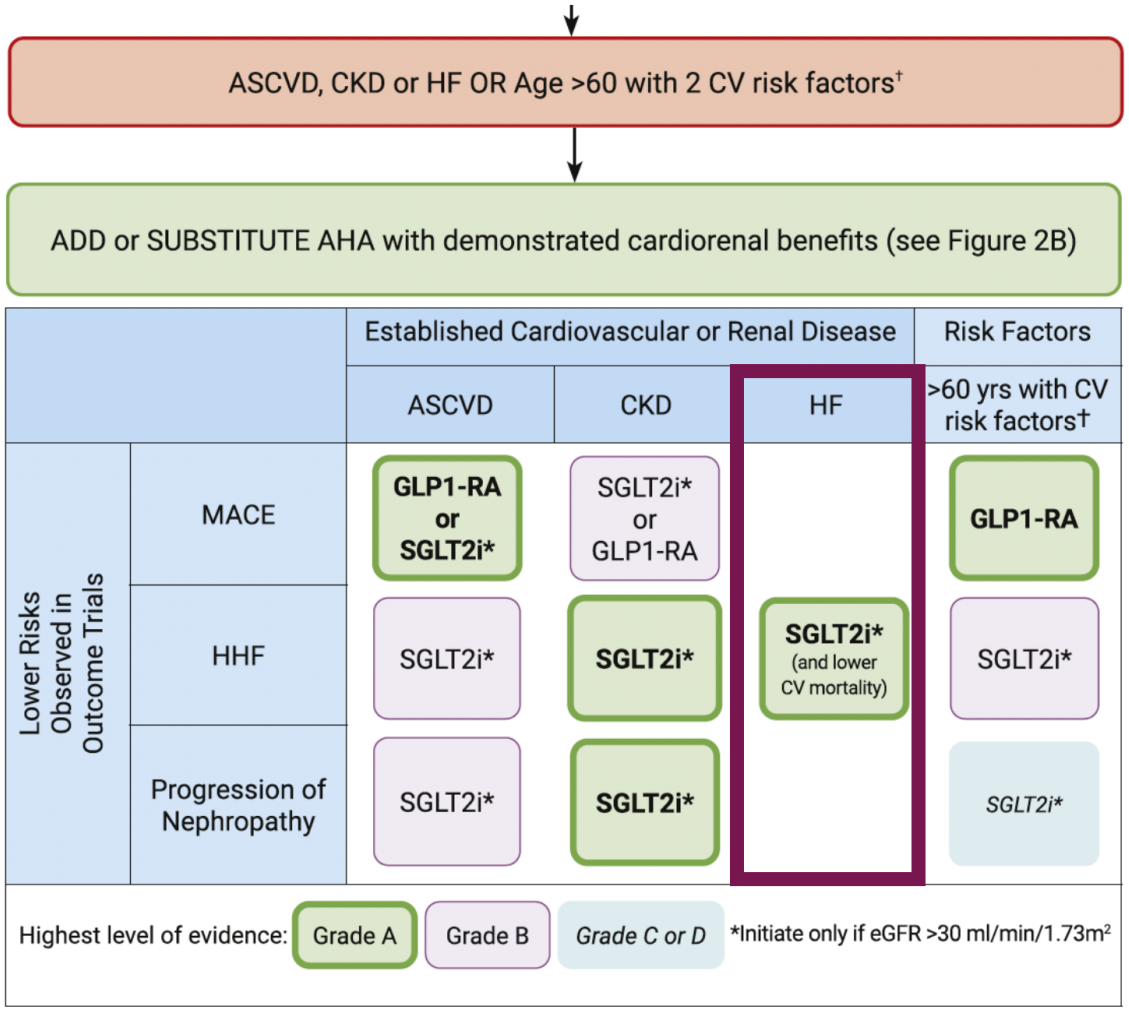
	HHF	SGLT2i*	**SGLT2i***	**SGLT2i*** (and lower CV mortality)	SGLT2i*
	Progression of Nephropathy	SGLT2i*	**SGLT2i***		*SGLT2i**

Highest level of evidence: Grade A | Grade B | *Grade C or D*

*Initiate only if eGFR >30 ml/min/1.73m²

CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.

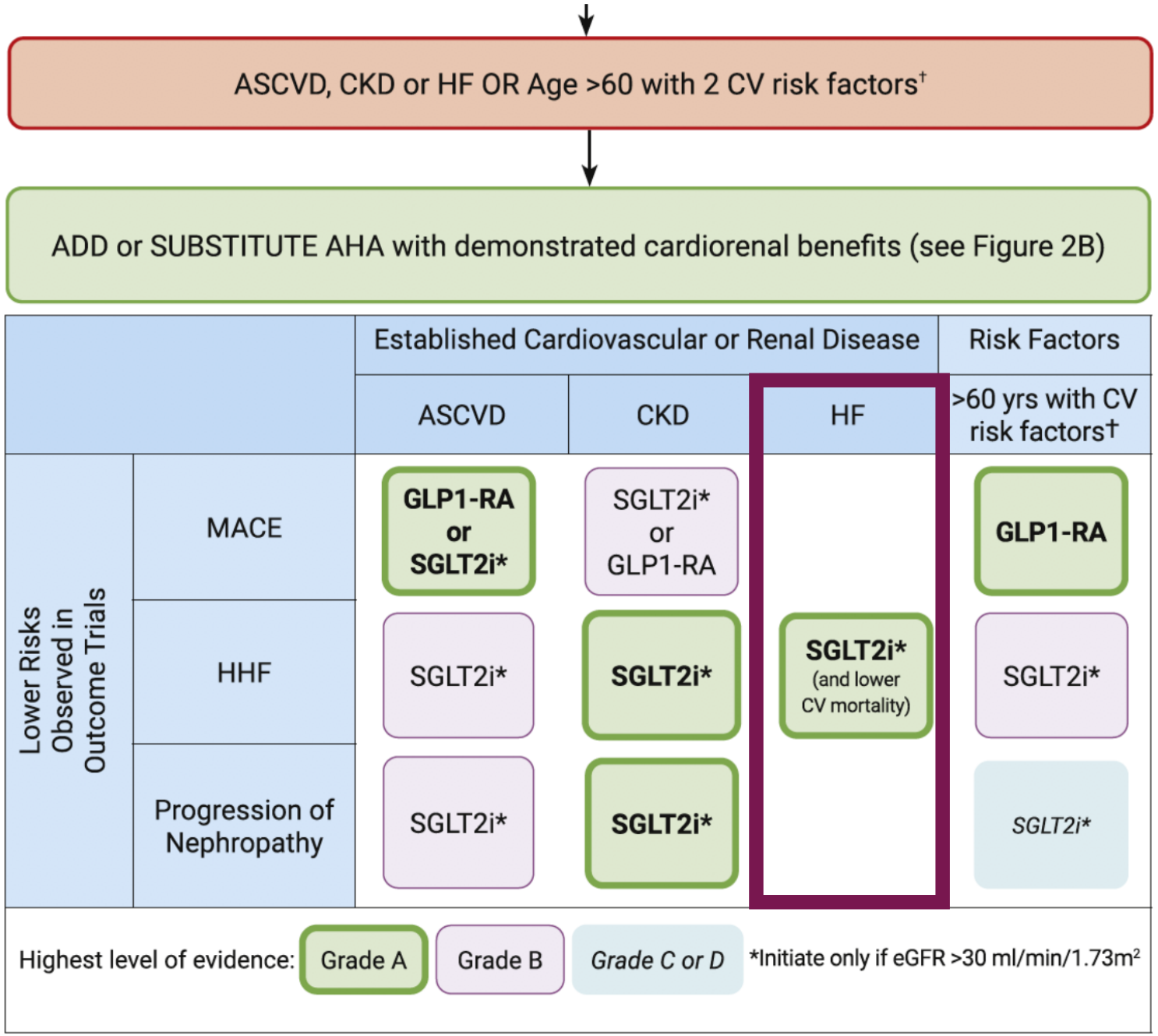
Heart Failure Population



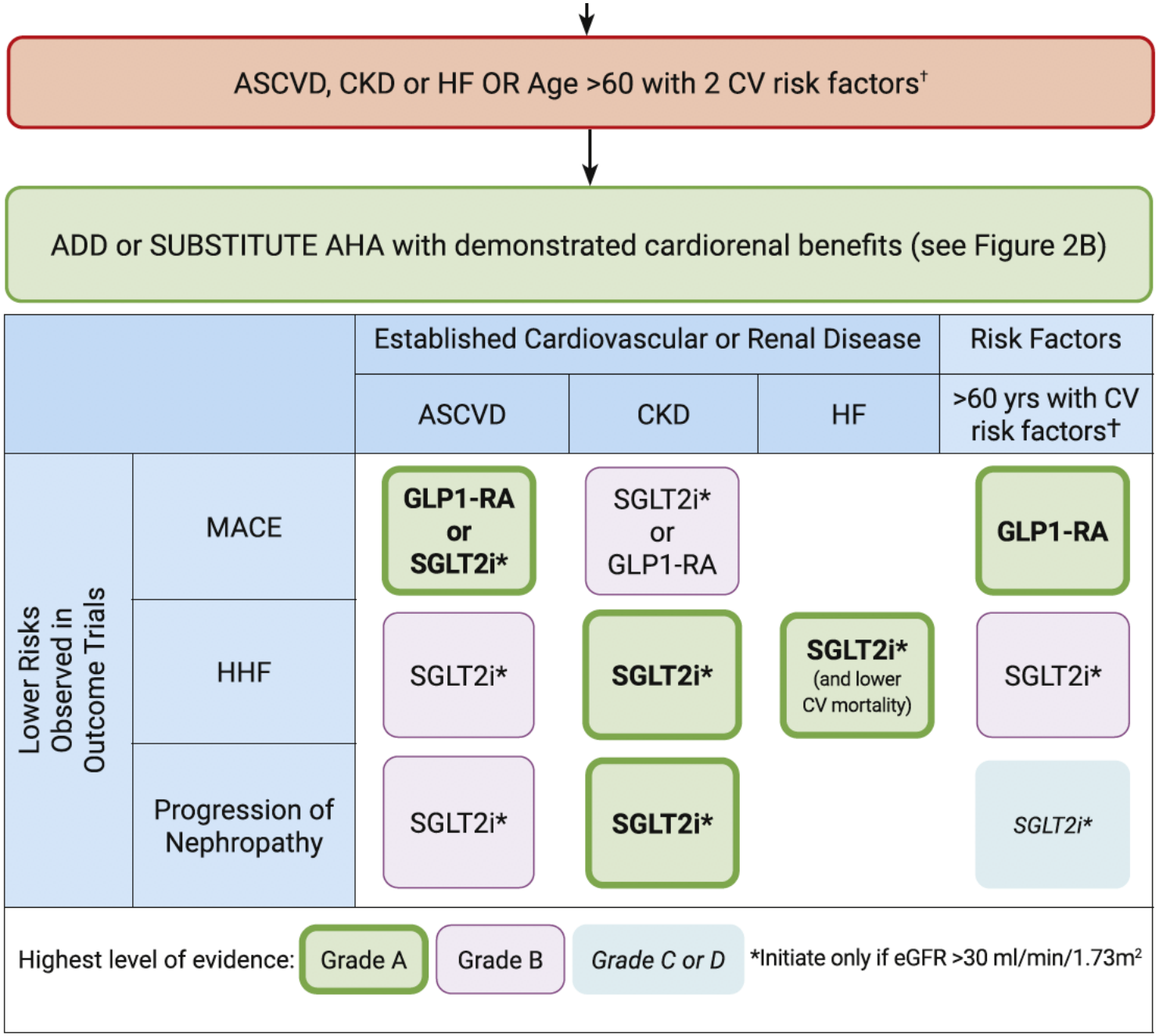
	SGLT2 Inhibitors		
	Empa-gliflozin	Cana-gliflozin	Dapa-gliflozin
	Jardiance	Invokana	Forxiga
Trial	Emperor reduced		DAPA-HF
Population	N=3730		N=4744
Duration	1.3 yrs		1.5 yrs
MACE			
HHF	↓ 25		↓ 26

Practical point: Your patient with heart failure may not have been diagnosed. Shortness of breath and ankle edema are frequent in our patients with type 2 diabetes.
Ankle edema will frequently respond dramatically to the addition of an SGLT2 inhibitor

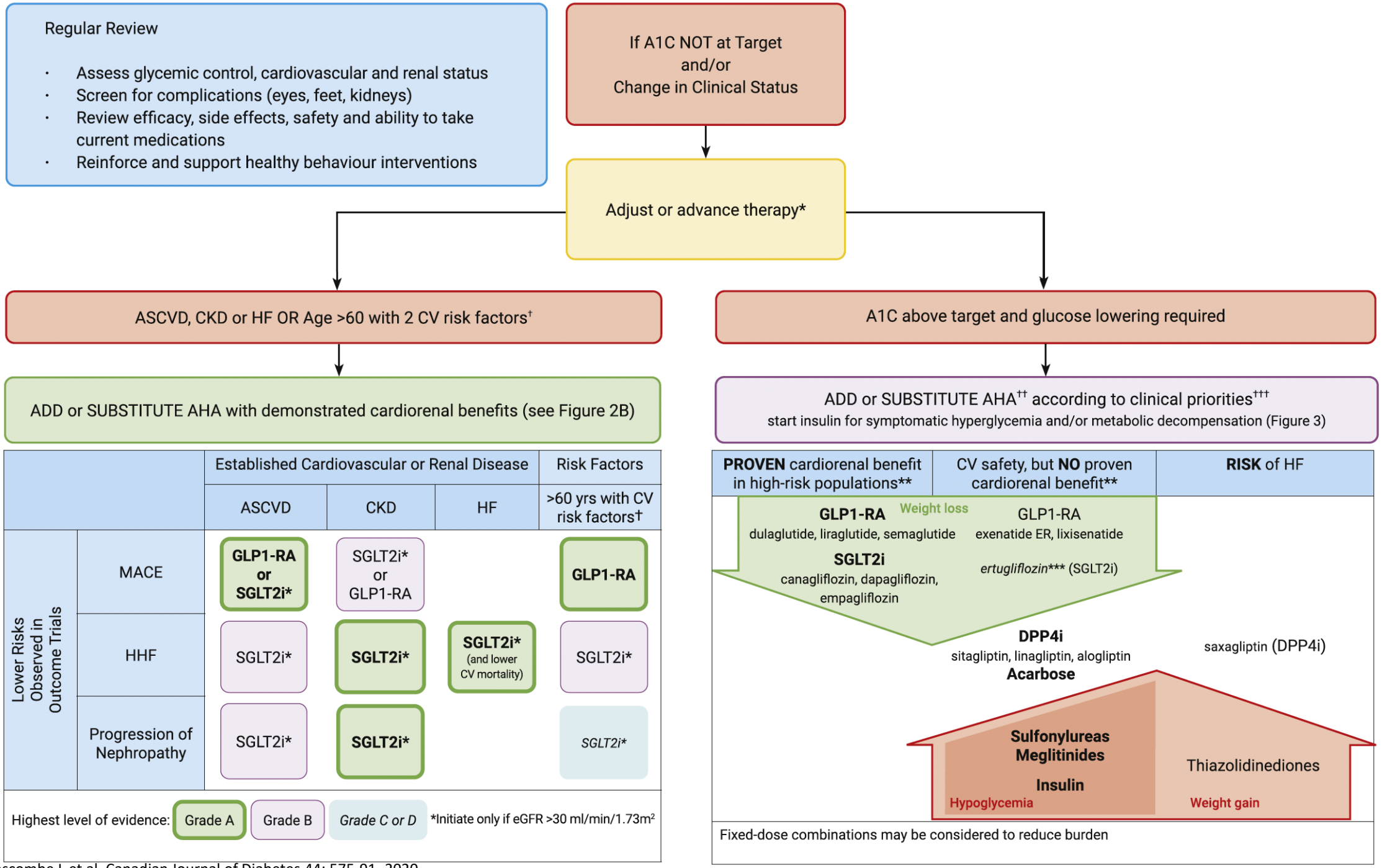
CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.
DAPA-HF: McMurray JJV et al. NEJM 381: 1995-2008, 2019.
EMPEROR-Reduced: Packer M et al. NEJM DOI: 10.1056/NEJMoa 2022190



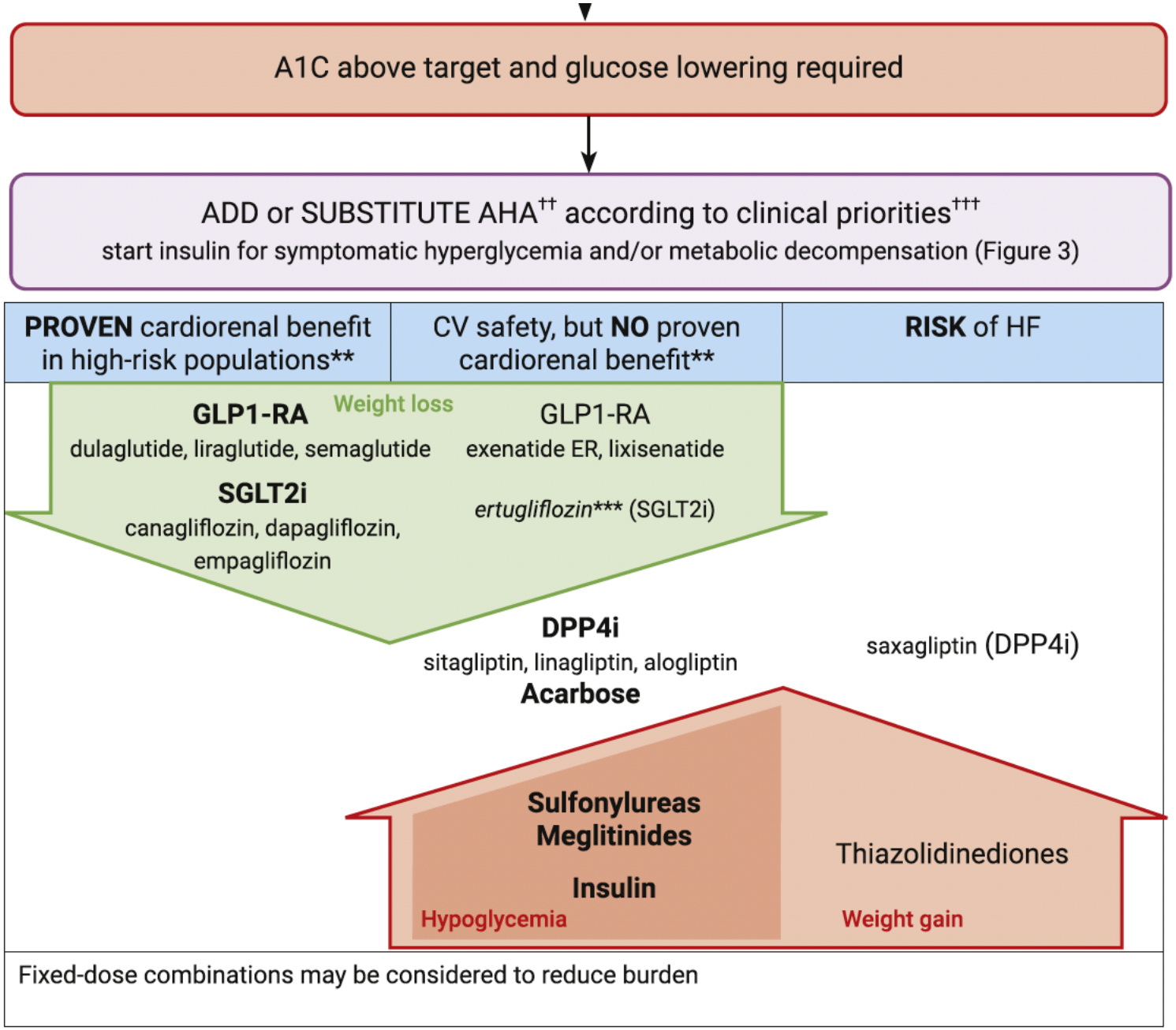
CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.



CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.



CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.



CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.

Discussion With Patient:
Choice of Treatment to Add to Metformin

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	Public Coverage	Tablet vs Injection
Sulfonylureas	□□		YES				YES	Tablet
SGLT-2i	□□□	□□	NO	GOOD	GOOD	Mycosis	Varies	Tablet
DPP-4i	□□	0	NO				Varies	Tablet
GLP-1RA	□□□□	□□	NO	GOOD	good	Nausea	Varies	Tablet Injection
INSULIN	□□□□		YES				YES	Injection

The choice has to be individualized according to the patient's characteristics:
which of these factors are to be prioritized for THIS patient ?

Discussion With Patient:
Choice of Treatment to Add to Metformin

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	Public Coverage	Tablet vs Injection
Sulfonylureas	□□		YES				YES	Tablet
SGLT-2i	□□□	□□	NO	**GOOD**	GOOD	Mycosis	Varies	Tablet
DPP-4i	□□	0	NO				Varies	Tablet
GLP-1RA	□□□□	□□	NO	**GOOD**	good	Nausea	Varies	Tablet Injection
INSULIN	□□□□		YES				YES	Injection

Patient with cardiovascular disease or > 60 yo with risk factors

Discussion With Patient:
Choice of Treatment to Add to Metformin

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	Public Coverage	Tablet vs Injection
Sulfonylureas	□□		YES				YES	Tablet
SGLT-2i	□□□	□□	NO	**GOOD**	GOOD	Mycosis	Varies	Tablet
DPP-4i	□□	0	NO				Varies	Tablet
GLP-1RA	□□□□	□□	NO	**GOOD**	good	Nausea	Varies	Tablet Injection
INSULIN	□□□□		YES				YES	Injection

Patient with heart failure

Discussion With Patient:
Choice of Treatment to Add to Metformin

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	Public Coverage	Tablet vs Injection
Sulfonylureas	□□		YES				YES	Tablet
SGLT-2i	□□□	□□	NO	GOOD	**GOOD**	Mycosis	Varies	Tablet
DPP-4i	□□	0	NO				Varies	Tablet
GLP-1RA	□□□□	□□	NO	GOOD	good	Nausea	Varies	Tablet Injection
INSULIN	□□□□		YES				YES	Injection

Patient with pre-existing renal disease (microalbuminuria)

Discussion With Patient:
Choice of Treatment to Add to Metformin

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	Public Coverage	Tablet vs Injection
Sulfonylureas	□□		YES				YES	Tablet
SGLT-2i	□□□	□□	NO	GOOD	GOOD	Mycosis	Varies	Tablet
DPP-4i	□□	0	NO				Varies	Tablet
GLP-1RA	□□□□	□□	NO	GOOD	good	Nausea	Varies	Tablet Injection
INSULIN	□□□□		YES				YES	Injection

Patient that needs to lose weight

Discussion With Patient:
Choice of Treatment to Add to Metformin

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	Public Coverage	Tablet vs Injection
Sulfonylureas	□□		YES				YES	Tablet
SGLT-2i	□□□	□□	**NO**	GOOD	GOOD	Mycosis	Varies	Tablet
DPP-4i	□□	0	**NO**				Varies	Tablet
GLP-1RA	□□□□	□□	**NO**	GOOD	good	Nausea	Varies	Tablet Injection
INSULIN	□□□□		YES				YES	Injection

Patient that needs to avoid hypoglycemia

Discussion With Patient:
Choice of Treatment to Add to Metformin

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	Public Coverage	Tablet vs Injection
Sulfonylureas	□□		YES				YES	Tablet
SGLT-2i	□□□	□□	NO	GOOD	GOOD	Mycosis	Varies	Tablet
DPP-4i	□□	0	NO				Varies	Tablet
GLP-1RA	□□□□	□□	NO	GOOD	good	Nausea	Varies	Tablet Injection
INSULIN	□□□□		YES				YES	Injection

But of course the majority of our patients have a list of priorities

Antihyperglycemic Coverage by RAMQ

Class	Medication	$/day at max dose	MONO if SU and MET NT or CI	+ MET if SU CI,NT or INEFF	+ SU if Met CI, NT or INEFF	IF CVD + A1c>7	+ MET if DPP4i INEFF, NT or CI and BMI > 30 and high A1c	If other SU NT or INEFF
Biguanides	Metformin (Glucophage)	0.18						
α-Glucosidase Inhibitors	Acarbose (Glucobay)	1.03						
DPP-4 Inhibitors	Alogliptin (Nesina)	2.10	EN167	EN148 (EN150 Kazano)	EN149			
	Linagliptin (Trajenta)	2.25	EN167	EN148 (EN150Jentaduetto)				
	Saxagliptin (Onglyza)	2.30		EN148 (EN150 Komboglyze)	EN149			
	Sitagliptin (Januvia)	2.62	EN167	EN148 (EN150 Janumet et XR)				
SGLT2 Inhibitors	Canagliflozin (Invokana)	2.62	EN167	EN148	EN149			
	Dapagliflozin (Forxiga)	2.45		EN148 (EN150 Xigduo)	EN149			
	Empagliflozin (Jardiance)	2.62	EN167	EN148 (EN219 Synjardy)		EN179		
GLP-1R Agonists	Liraglutide (Victoza)	6.85					Form	
	Exenatide (Byetta)	2.49						
	Exenatide QW (Bydureon)	6.85						
	Dulaglutide (Trulicity)	6.85					Form	
	Semaglutide (Ozempic)	6.85					Form	
Thiazolidine-diones	Pioglitazone (Actos)	1.05	EN121	EN118	EN119			
	Rosiglitazone (Avandia)	2.87	EN121	EN118 (EN81 Avandamet)	EN119			
Insulin Secretagogues	Gliclazide (Diamicron)	0.50						
	Glimepiride (Amaryl)	0.77						EN23
	Glyburide (Diabeta)	0.23						
	Repaglinide (GlucoNorm)	0.84						

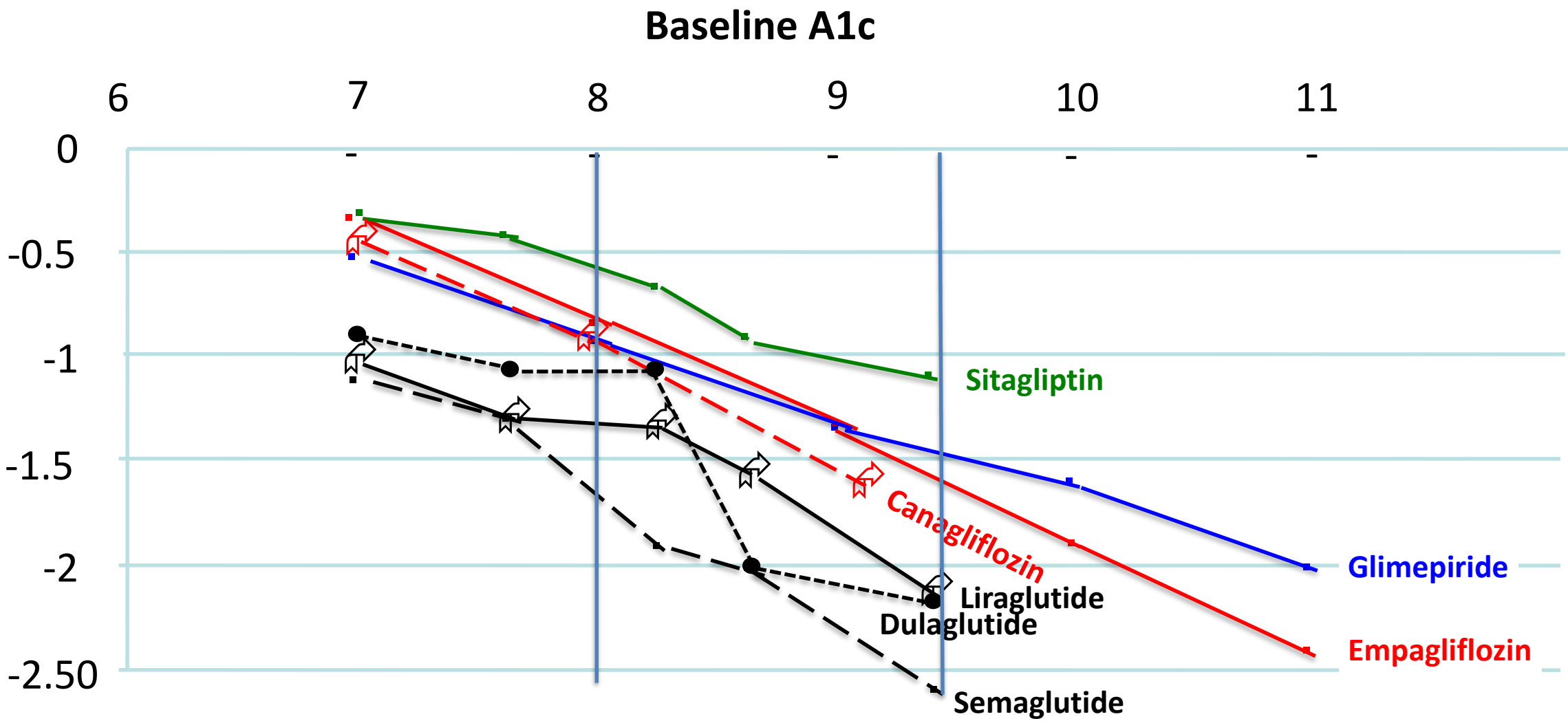
Code EN179 Empagliflozin: if CVD and A1c > 7%

Form: Liraglutide Dulaglutide: + metformin BMI > 30 A1c > 6.5% despite DPP-4i Annual renewal.

Form: Semaglutide: + metformin + SU CI, NT or INEFF No annual renewal

Green = on general list: no code or form required Orange = Médicament d'exception: code or form required
NT=Not tolerated INEFF=Inefficacious CI=Contraindicated SU=Sulfonylurea MET=Metformin Mono=Monotherapy Form=Médicament d'exception form required

Impact of Baseline A1c on Efficacy



1. Pratley et al. Int J Clin Pract. 65:397, 2011 2. Rosenstock J et al. Diabetes Care 38:376,2015 3. Matthews et al. ADA Poster 1096-P, 2014
4. De Fronzo et al. ADA Poster 1276-P, 2015 5. Ahrens B et al. Lancet Diabetes Endocrinology 5:341, 2017 6. Pratley RE et al. ADA 2018 abstact 122-OR

GLP-1 Receptor Agonists
Available in Canada

DAILY INJECTABLES

Exenatide BID (Byetta)

Lixisenatide (Adlyxine)

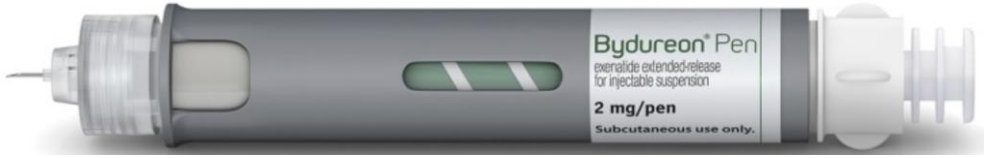
Liraglutide (Victoza)

DAILY ORAL

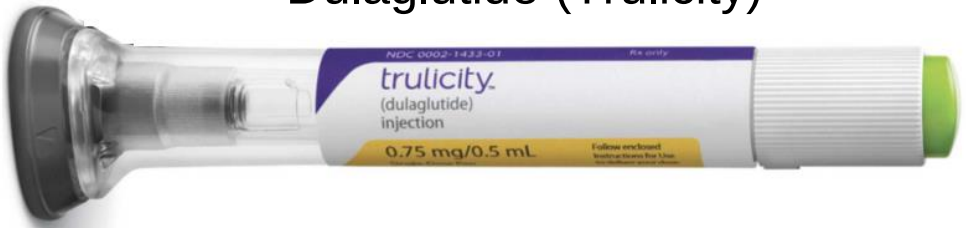
Oral semaglutide (Rybelsus)

WEEKLY INJECTABLES

Exenatide QW (Bydureon)

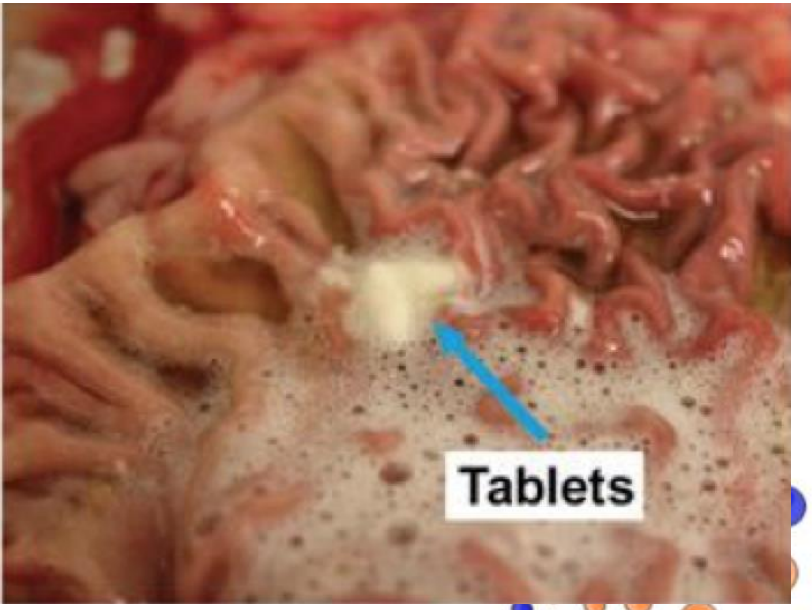


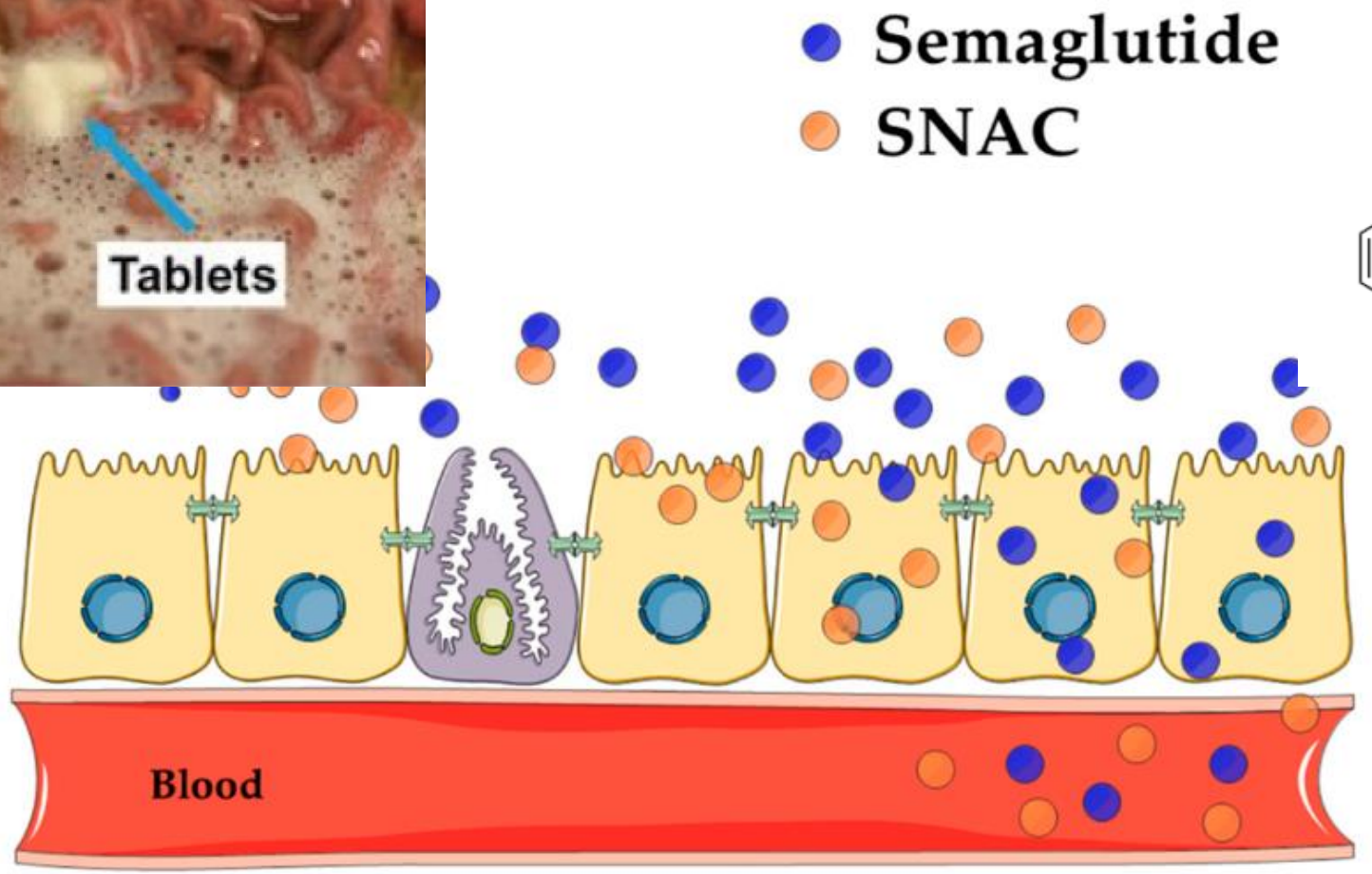
Dulaglutide (Trulicity)



Semaglutide (Ozempic)

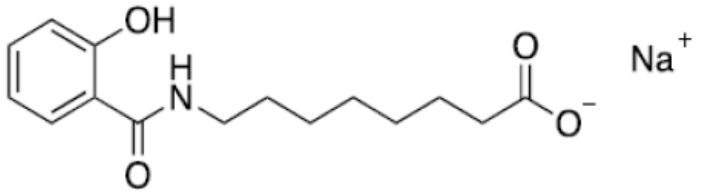
Oral Semaglutide





salcaprozate sodium (SNAC)

MW 301 Da, pKa = 5.0



SNAC:

- Increases pH to 7.0 in a 3cm area around the pill
- Inactivates pepsin
- Monomerises semaglutide
- Increases fluidity of membranes

Twarog C et al. Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C10). Pharmaceutics 2019; 11: 78

Oral semaglutide dosing and administration*

Dosing

STARTING DOSE

3 mg Start with 3 mg OD for 1 month

MAINTENANCE DOSES

7 mg Increase dose to 7 mg OD for at least 1 month

14 mg Based on individual needs, you may increase dose to 14 mg OD

Administration

Take on an empty stomach upon waking

Take with a sip of water (no more than 120 mL)

Wait at least 30 minutes before eating, drinking, or taking any other oral medication

Drug-Drug Interactions

- **No dose adjustment is required** for drugs taken with oral semaglutide
- **Monitoring of thyroid parameters should be considered** when treating patients with **oral semaglutide** at the same time as **levothyroxine**

*Proposed dosing instructions for oral semaglutide (Rybelsus©) Product Monograph in Canada. OD, once daily.

Hauge, C., et al. Endocrine Society (ENDO) – 101st Annual Meeting and Expo. 2019: New Orleans, USA.

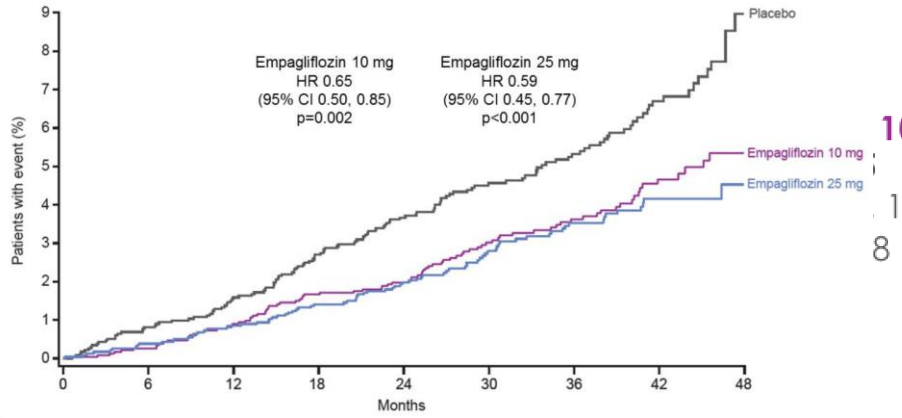
The use of these newer therapies can be less expensive than conventional therapies

One Barrier:

Cost

Impact of Empagliflozin Dose

Cardiovascular Deaths



No. of patients

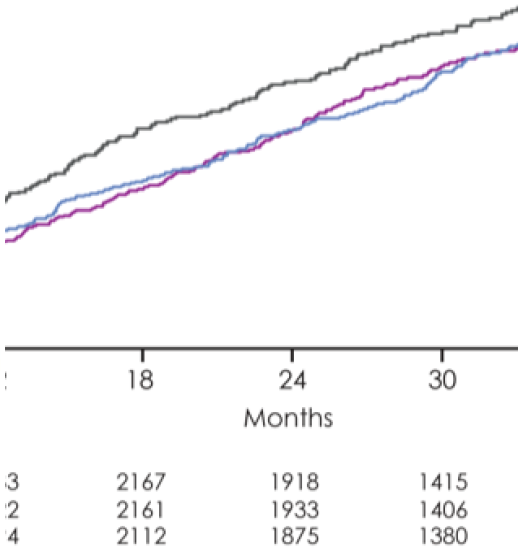
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

10 mg

1.01)

8

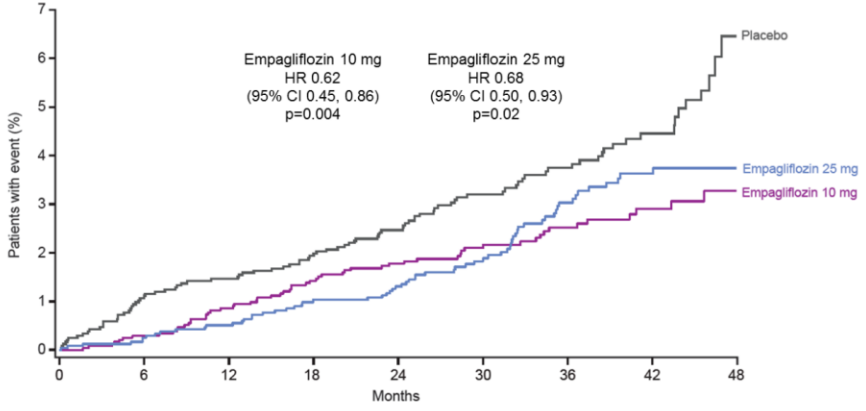
Empagliflozin 25 mg
HR 0.86
(95% CI 0.73, 1.02)
p=0.0865



3	2167	1918	1415
2	2161	1933	1406
4	2112	1875	1380

Adverse Cardiovascular Event; HR, hazard ra

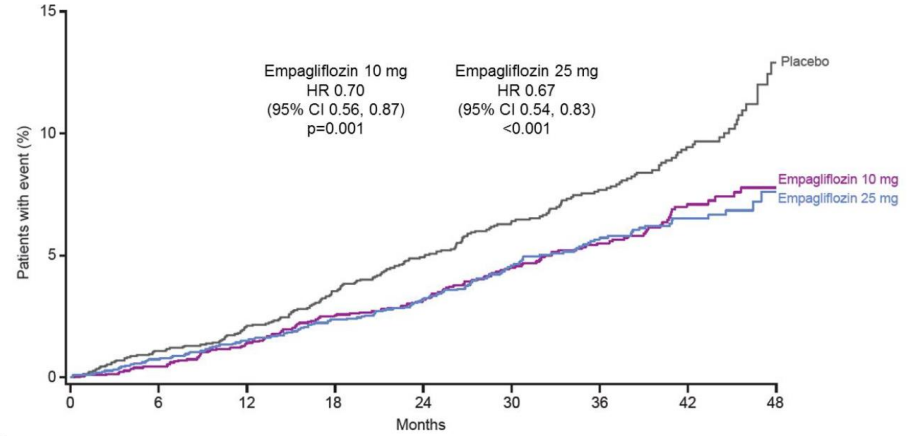
Hospitalizations for HF



No. of patients

Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Total Mortality



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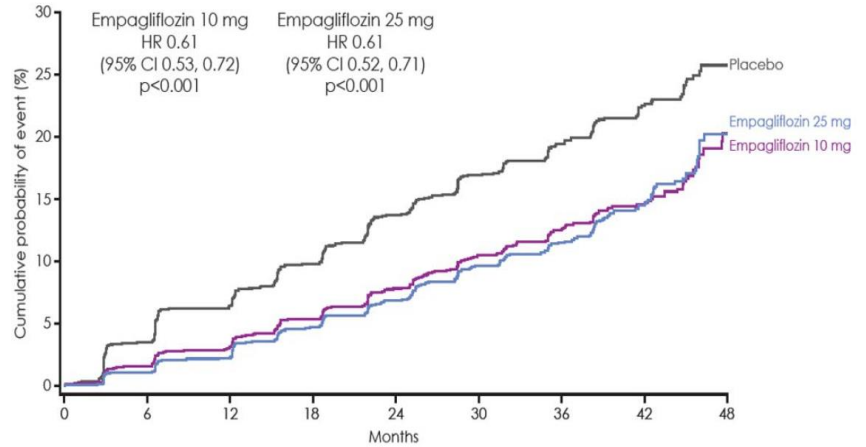
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Worsening of nephropathy

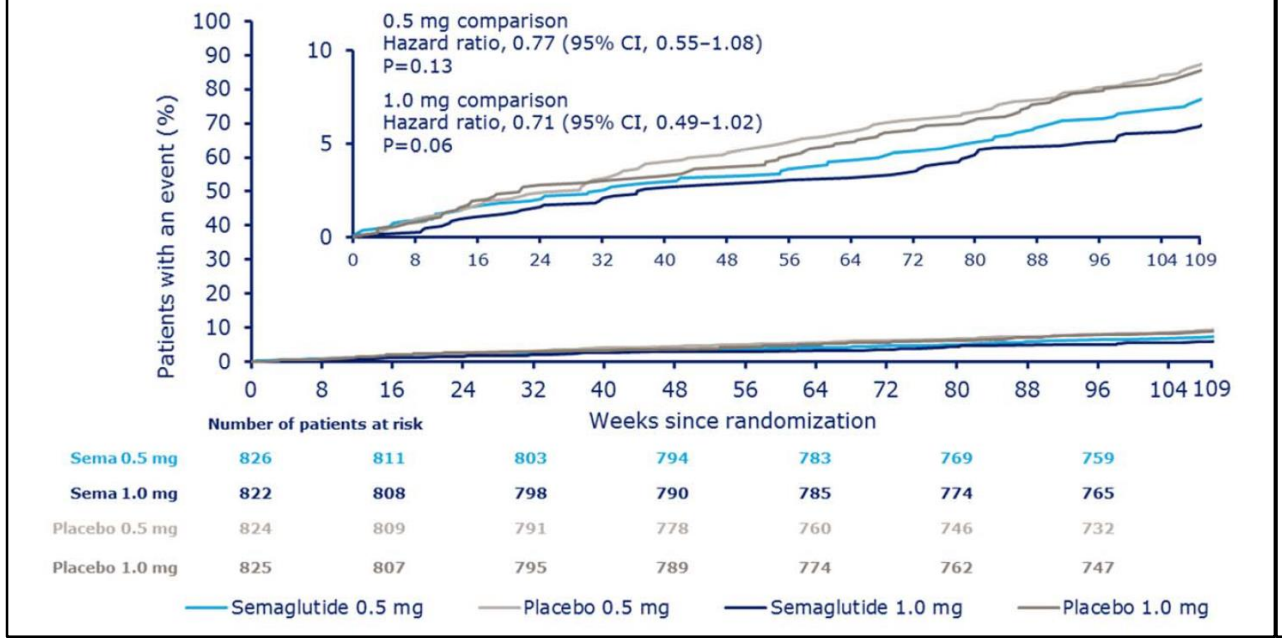


No. of patients

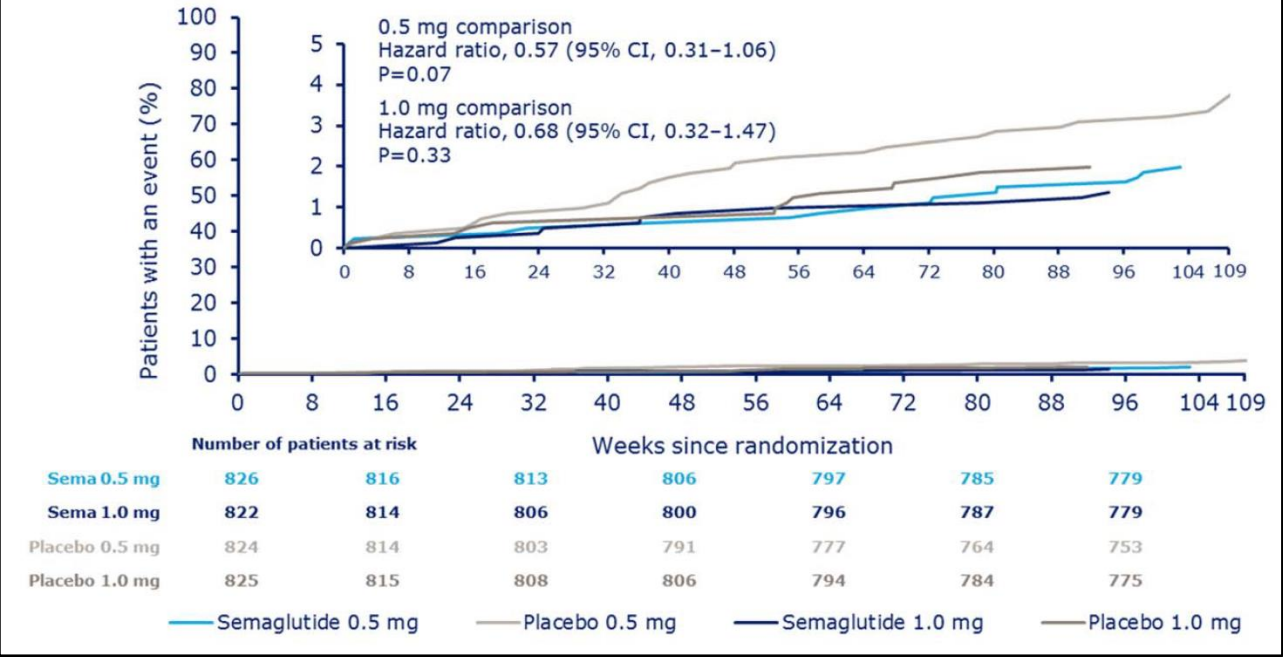
Empagliflozin 10 mg	2055	1991	1912	1825	1571	1122	922	593	136
Empagliflozin 25 mg	2069	2003	1936	1844	1600	1157	965	626	154

Impact of semaglutide dose on cardio-renal benefits

Primary Outcome



Non fatal Stroke



Decreasing SGLT2i Cost

Canagliflozin 100 mg	2.62/day	
Canagliflozin 300 mg	2.62/day	
Empaglifloxin 10 mg	2.62/day	
Empagliflozin 25 mg	2.62/day	
Dapagliflozin 5 mg	2.45/day	
Dapagliflozin 10 mg	2.45/day	

Reducing the Cost of a GLP-1R Agonist

Pen 0.25/0.5 mg

0.5 mg per week = $ 6.25 per day
One 2 mg pen = $ 175,00

Pen 1.0 mg

1.0 mg per week = $ 6.25 per day
One 4 mg pen = 175,00$

Using this pen to give 0.5 mg per week reduces the cost to $ 3.12 per day.
But they must count the clicks… 36 clicks

How to decrease the cost of new medications

Classical Approach

Agent	Cost $/d	A1c drop
Metformin 850 BID	0.06	-1.1
Gliclazide MR 120 die	0.12	-0.8
Sitagliptin 100 die	2.62	-0.7
1 strip / day	0.70	
Total Cost	3.50	

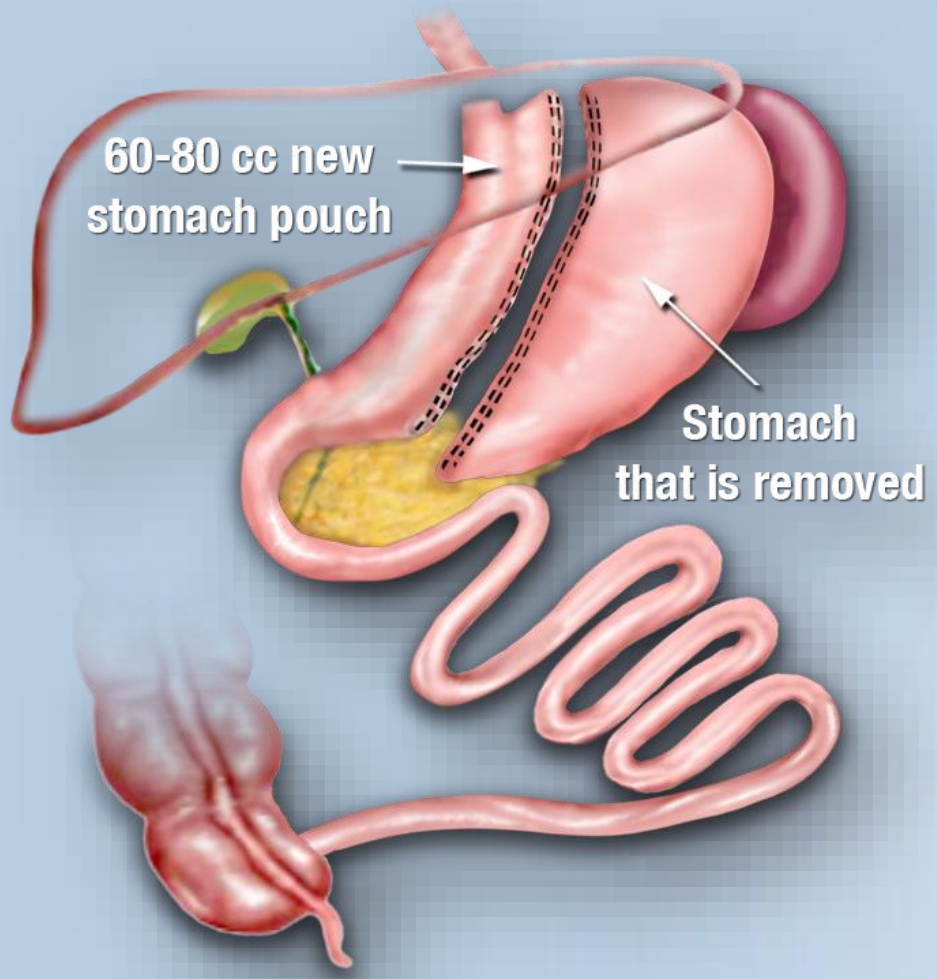
$4.43 x 365 = Savings of $1600 / year

New Approach

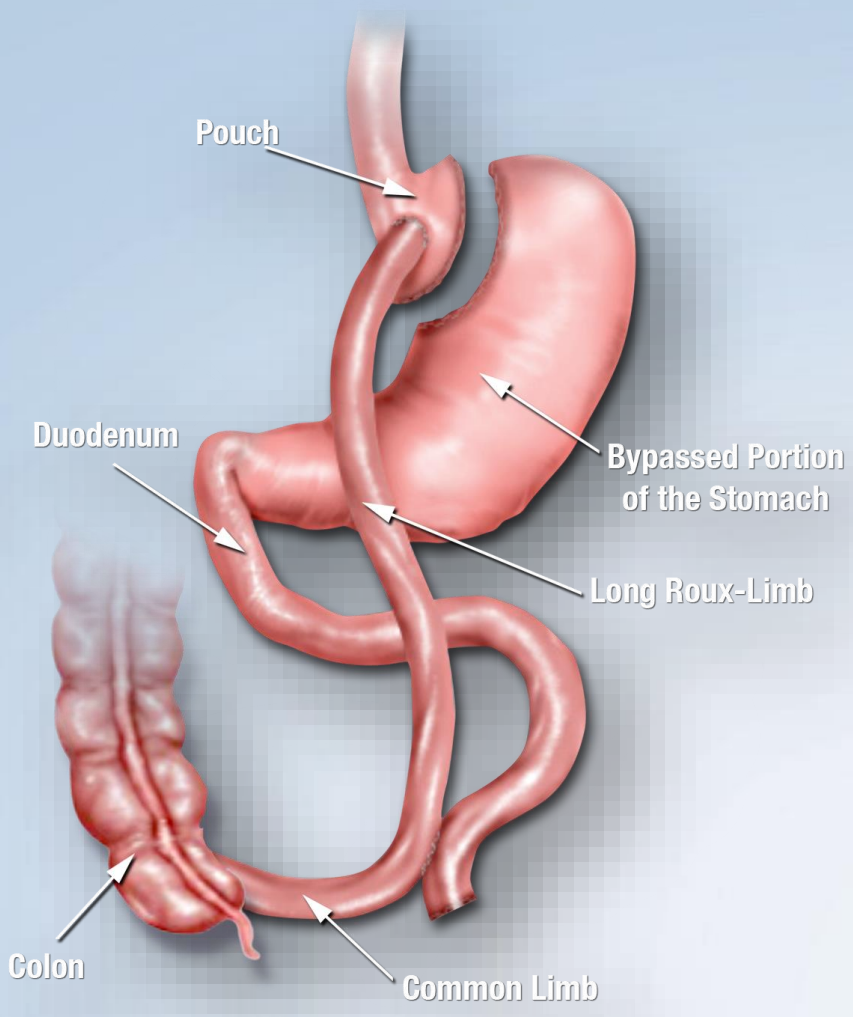
Agent	Cost $/d	A1c drop
Metformin 850 BID	0.06	-1.1
Empagliflozin 10 die	2.62	-0.7
Semaglutide 0.5/week	6.25	-1.3
0 strip / day	0	
Total Cost	8.93	

Bariatric Surgery (if BMI>35)

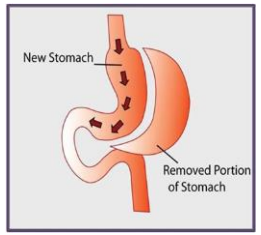
Sleeve Gastrectomy

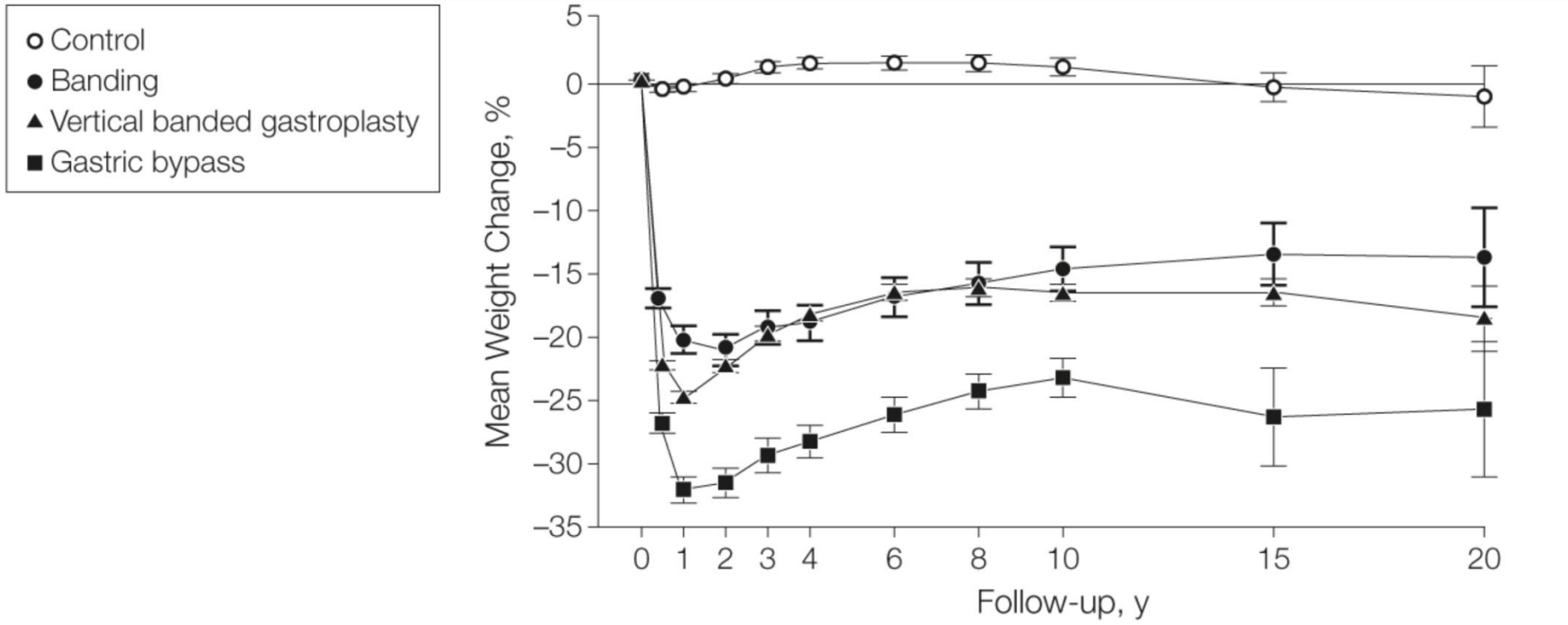


Roux-en-Y Gastric Bypass



Swedish Obese Subjects (SOS) Data

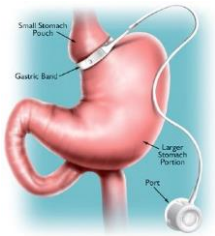


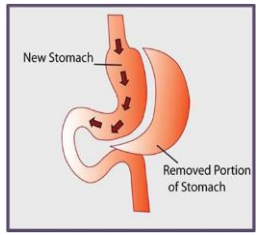


No. of patients						
Control	2037	1490	1242	1267	556	176
Banding	376	333	284	284	150	50
Vertical banded gastroplasty	1369	1086	987	1007	489	82
Gastric bypass	265	209	184	180	37	13

JAMA. 2012;307(1):56-65. doi:10.1001/jama.2011.1914

Weight Loss and Diabetes Remission





	Banding	Sleeve	Bypass
Mortality	0.0%	0.0%	0.22%
Diabetes Remission (old)	57 %	80 %	80 %
Diabetes Remission (new)	6 %	26 %	41 %
A1c pre	7.7	7.5	8.1
A1c post	6.3	6.8	6.2

New Definition of Remission: A1c < 6% + FPG < 5.6mM for 1 year post surgery, with no active hypoglycemic pharmacologic therapy or ongoing procedures.

Buse JB et al. Diabetes Care 32: 2133-5, 2009

Pournaras DJ et al. BJS 99: 100-103, 2012

Counsel all patients about sick days medications list

Sick Days medication list

S sulfonylureas (2)
A ACE-inhibitors (1)
D diuretics, direct renin inhibitors (1,5)

M metformin (3)
A angiotensin receptor blockers (1)
N non-steroidal anti-inflammatory (1)
S SGLT2 inhibitors (4,5)

1: Stopped because if dehydration occurs, these meds can harm the kidney.
2: Stopped because if pre-renal failure occurs, these meds can cause hypoglycemia.
3: Stopped because if pre-renal failure occurs, these meds can cause lactic acidosis.
4: Stopped because if pre-renal failure occurs, these meds can cause ketosis
4: Stopped because these drugs can worsen dehydration

Comparison of Basal Insulins

	NPH	Detemir	Glargine U100	Glargine U100	NEW Glargine U300	Degludec 100 or 200
Commercial names	Humulin N Novolin NPH	Levemir	Lantus	Basaglar	Toujeo	Tresiba
Duration of action	16 h	20 h	24 h	24 h	> 24 h	42h
Potency to reduce A1C (%)	> 0.9 %	> 0.9 %	> 0.9%	> 0.9%	> 0.9 %	> 0.9%
Nocturnal hypoglycemia risk (RR)	1	0.6	0.6	0.6	0.4	0.4
Effects on body weight	↑	↔ or ↑	↑	↑	↑	↑
Long-term CV safety	UKPDS		ORIGIN			DEVOTE
Monthly cost (50 units/day)*	~$49.50	~$112.50	~$100.50	~$85.50	~$96.00	~$112.50

A1C: glycated hemoglobin; RR: relative risk; UKPDS: UK Prospective Diabetes Study; ORIGIN: Outcome Reduction With Initial Glargine Intervention

***Based on the Diabetes Canada's approximate cost reference list for insulins available at: http://guidelines.diabetes.ca/browse/appendices/appendix5_2016 Monthly cost calculated based on per unit cost provided X 50 units/day X 30 days. Insulin prices are based on the pen cartridge price and the corresponding vial price would be marginally less.**

Vora J et al. *Diabetes Ther*. 2014;5:435-46; Freemantle N et al. BMJ Open 2016; 6:e009421; Tsapas A et al. EASD 2016. Abstract 841. Marso SP, et al. *N Engl J Med* 2017;377:723-32.

What Do You Do with Background Antihyperglycemic Agents When a Patient is Started on Insulin?

Class	Kept?	Why?
Metformin	YES	Studies have shown efficacy of these agents in presence of insulin, with less hypoglycemia and weight gain vs. insulin alone.
DPP-4 inhibitors	YES	
GLP-1RAs	YES	
SGLT2 inhibitors	YES	
Acarbose	YES	
Insulin secretagogues	+/-	May be associated with more hypoglycemia and weight gain, but also reduced insulin dosing and less need for > 1 injection of insulin per day. Consider reducing the dose of insulin secretagogues when initiating insulin.
Thiazolidinediones	NO	Cause water retention and edema. These side effects have been shown to be more frequent in presence of insulin, with an increase in the risk of heart failure.

Note: When continuing non-insulin agents with insulin, the costs should be considered in addition to the benefits.

SGLT2: sodium-glucose cotransporter 2; DPP-4: dipeptidyl peptidase-4; GLP-1RAs: glucagon-like peptide-1 receptor agonists

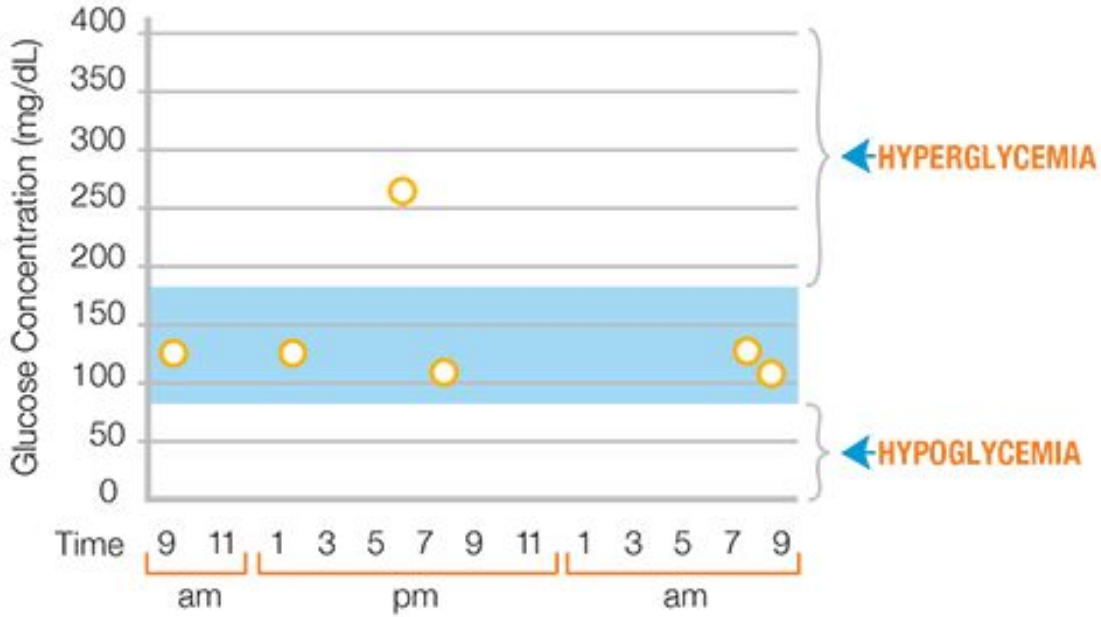
Adapted from: CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2013;37:S61-68; Swinnen SG, et al. ADA 2010. Abstract 0037-OR.

Titration Protocols with Basal Insulins

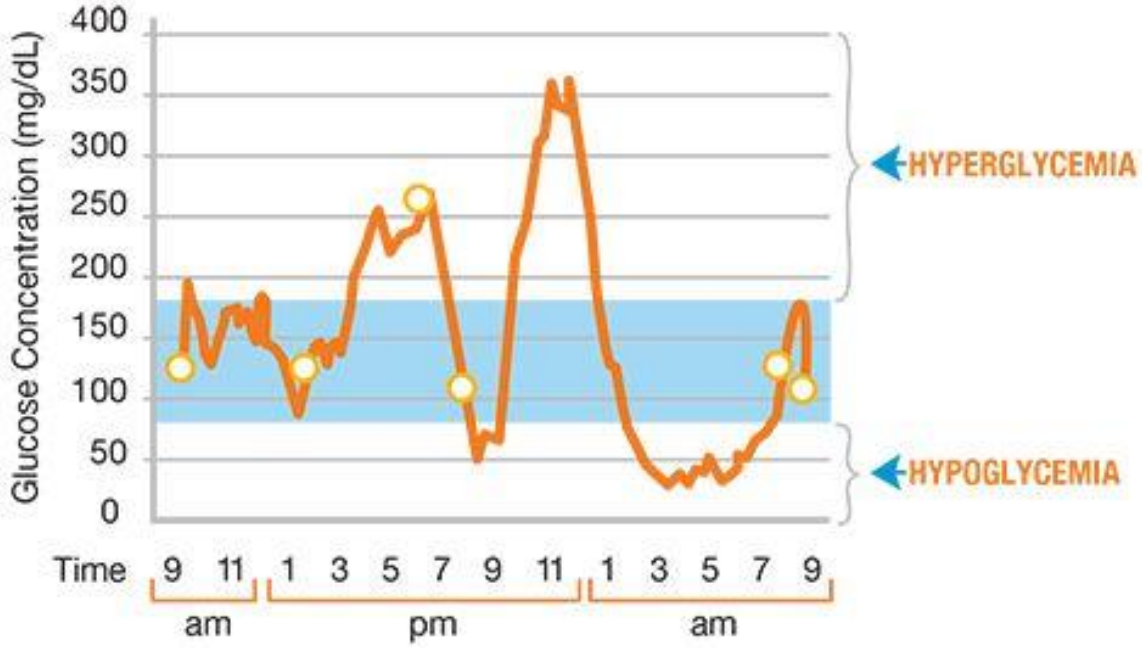
	Basal Analogue Insulins (NPH, detemir, glargine 100 or 300)	Longer-acting Basal Insulins (glargine 300, degludec)
Start with	10 units, once a day at bedtime	
Titrate	Every day	**Once a week**
Based on	Fasting blood glucose level	
Increase or reduce by	1 unit	**4 units**
Until	Reaching the target (5.5 or 7)	

Glucose Monitoring

Capillary blood glucose monitoring



Continuous glucose monitoring



Bode BW, Schwartz S, Stubbs HA, Block JE. Glycemic characteristic in continuously monitored patients with type 1 and type 2 diabetes. *Diabetes Care*. 2005 October; 28(10) : 2361-6

DexCom G6

Sensor functional for 10 days.

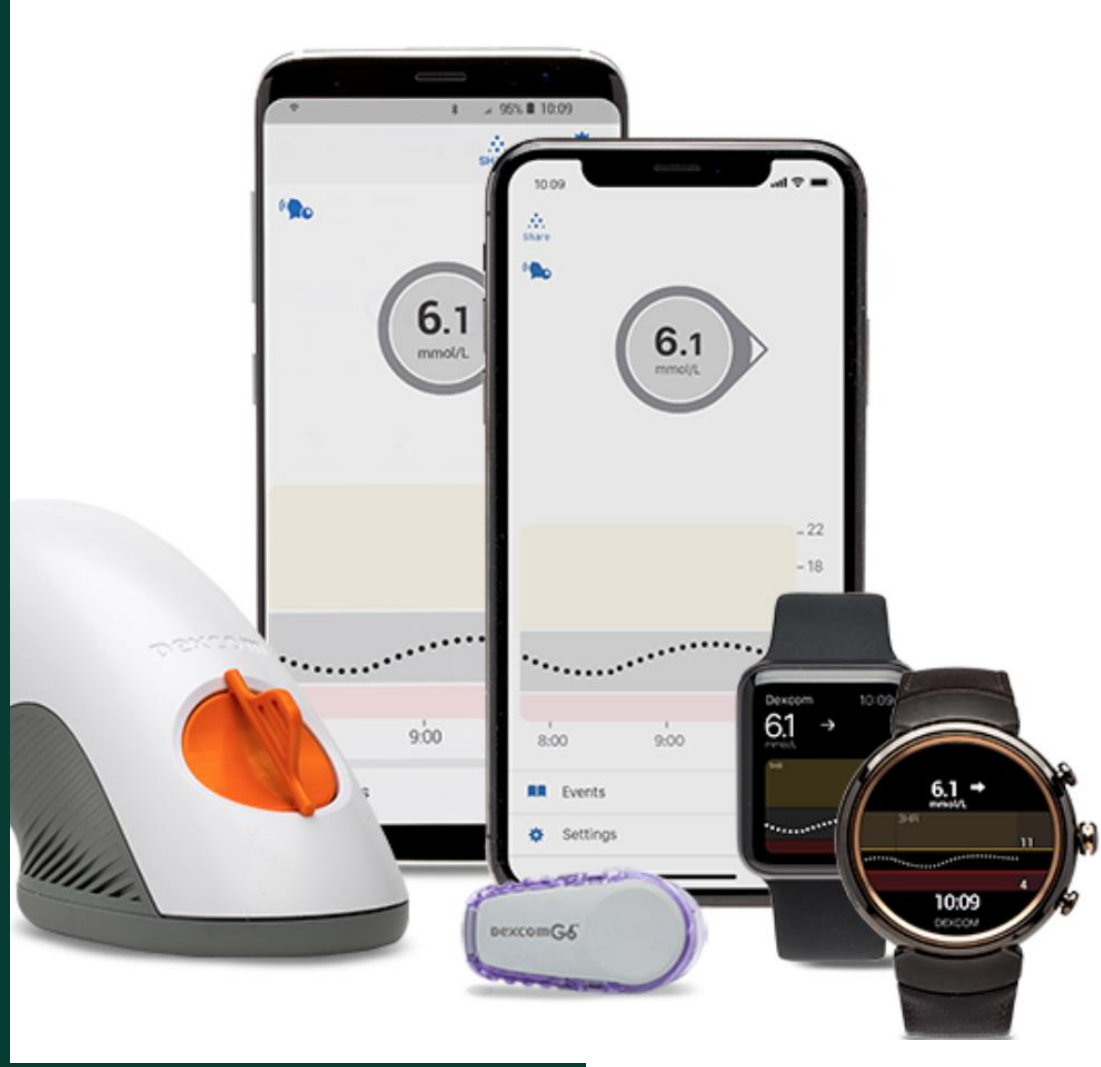
No calibration required

Values can be used to modify insulin dosages without a capillary glucose confirmation

Data sent to a cloud: can be viewed at a distance

Programmable alerts

Can be connected with Tandem pumps



Libre

Sensor functional for 14 days.

No calibration required.
Integrated capillary glucose and capillary ketones meter.

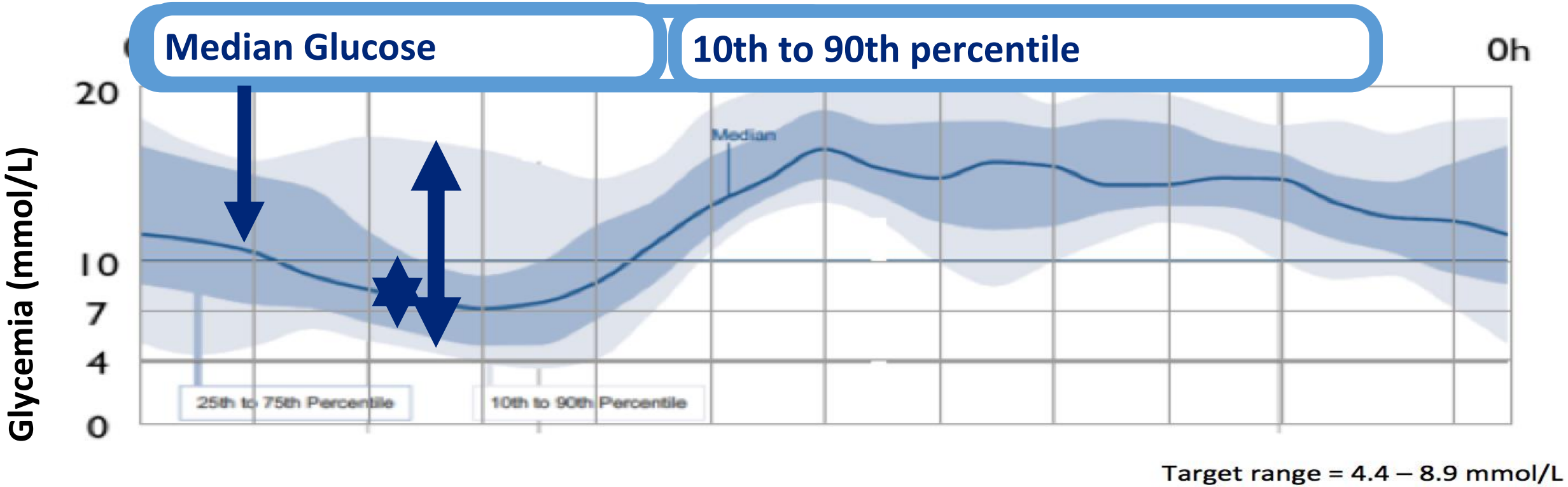
When scanning, data from last 8 hours are transferred

No continuous communication: no alerts

Cha e in glucose
i ext 15-20
inutes

> 2mM
1-2 mM
< 1 mM
1-2 mM
> 2 mM

Ambulatory Glucose



Target range = 4.4 – 8.9 mmol/L

10% risk of hypoglycemia in the morning

Median glucose Ok in AM, elevated from lunch to bedtime

Large variability, particularly at night

Nasal Glucagon

Yanai O, Phillip M, Harman I, Elitzur-Lieberman E, Pilpel D. IDDM patients' opinions on the use of glucagon emergency kit in severe episodes


The End
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