Role of SGLT2 Inhibitors in Current Treatment Paradigms

How does inhibition of excessive renal glucose absorption improve glycemic control (HbA_{1c})?

SGLT2 Inhibitors

- 1°: Reduce increased renal glucose absorption ~150 gm/24 hr
- 2°: Reduce glucose toxicity
  - Improvement in β cell function
  - Improvement in insulin sensitivity

A Patient-centered Approach

Patient/Disease Features

Risks potentially associated with hypoglycemia and other drug adverse effects

Disease duration

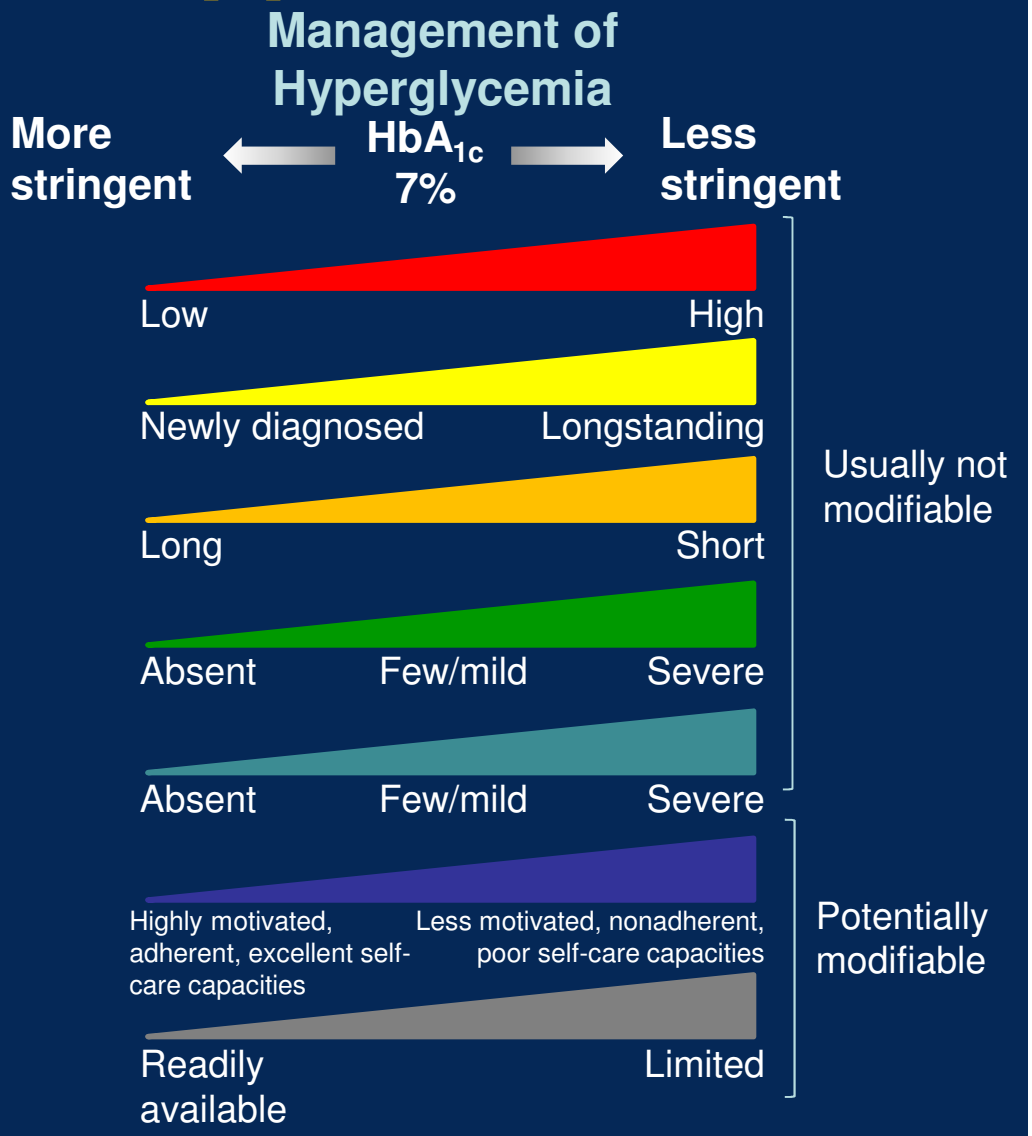
Life expectancy

Important comorbidities

Established vascular complications

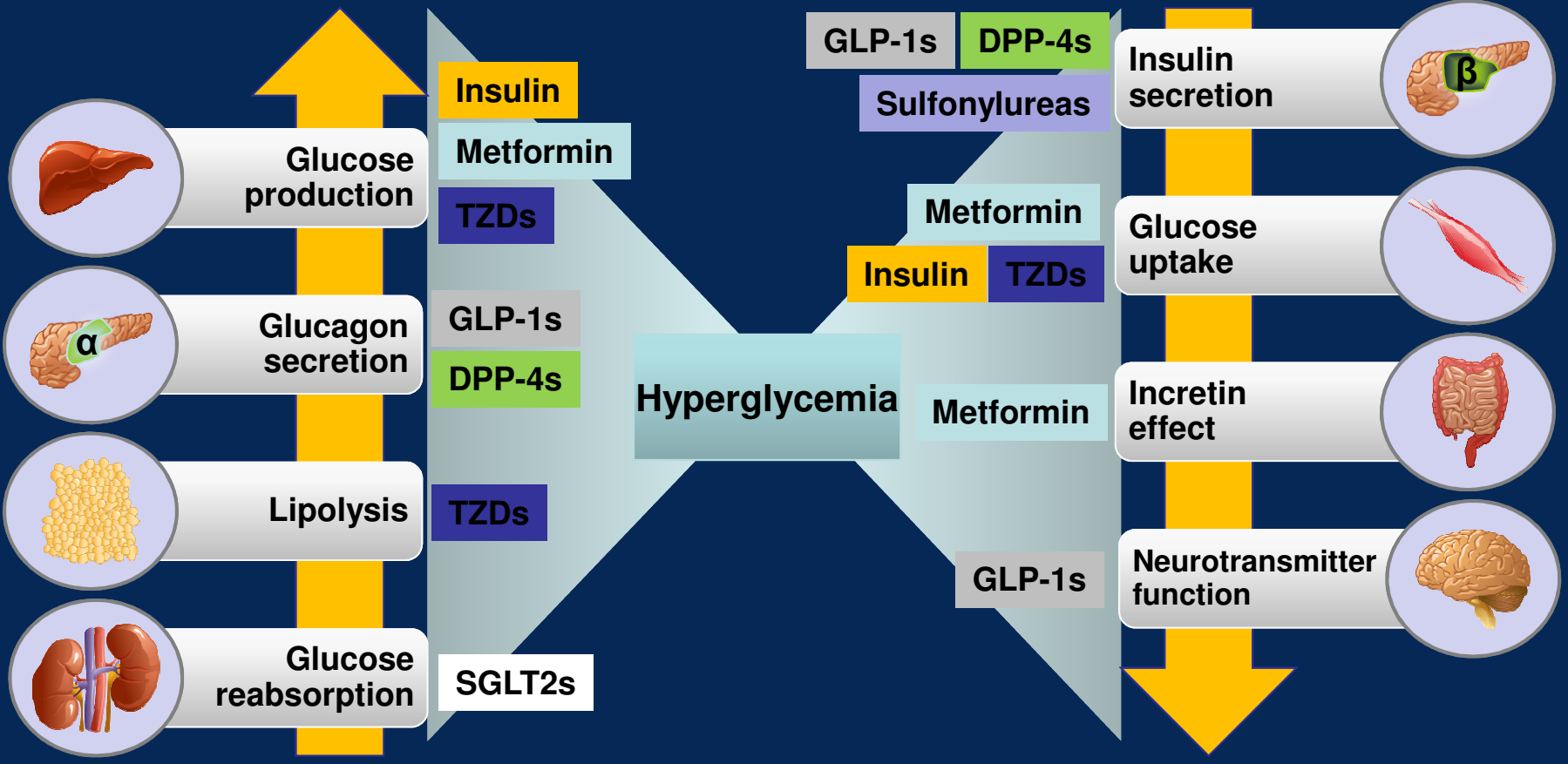
Patient attitude and expected treatment efforts

Resources and support system



Adapted from Inzucchi SE, et al. *Diabetologia*. 2015;58(3):429-42.

Pathophysiology of Type 2 Diabetes: Therapies



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Diabetes Drugs Impact Multiple Endpoints

Drug	BW	Hyper-tension	Dys-lipidemia (↑ LDL, ↑ HDL, ↓ TG)	Hypoglycemia Risk
α-glucosidase inhibitors	Neutral	Improved	Neutral/ Improved	Low
DPP-4 inhibitors	Loss/Neutral	Neutral	Improved	Low
GLP-1 agonists	Loss	Improved	Improved	Low
Insulin	Gain	Neutral*	Improved	High
Meglitinides	Gain	Neutral	Neutral	Moderate
Metformin	Loss/Neutral	Neutral	Improved	Low
SGLT2 inhibitors	Loss	Improved	?	Low
Sulfonylureas	Gain	Neutral	Variable	Moderate
TZD	Gain	Improved	Improved	Low

*Hyperinsulinemia is associated with hypertension

Basile JN. *J Diabetes Complications*. 2013;27(3):280-286.

SGLT2 Inhibitors Reduce Systolic Blood Pressure: Monotherapy

	Trial Duration (wks)	Baseline (mm Hg)	Change from Baseline	
Canagliflozin[1]	26	126.7-128.5	100 mg/d -3.3%	300 mg/d -5.0%
Dapagliflozin[2]	24	NR	5 mg/d -2.3%	10 mg/d -3.6%
Empagliflozin[3]	90	131.6-131.9	10 mg/d 0.1%	25 mg/d -1.7%

1. Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15:372-382.
2. Ferrannini E, et al. *Diabetes Care*. 2010;33(10):2217-24.
3. Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.

SGLT2 Inhibitors Increase LDL: Monotherapy

	Trial Duration (wks)	Baseline (mg/dL)	Change from Baseline	
Canagliflozin[1]	26	112-120	100 mg/d +2.9%	300 mg/d +7.1%
Dapagliflozin[2]	12	101.2	5 mg/d NR	10 mg/d +2.9%
Empagliflozin[3]	12	66	10 mg/d -0.3%	25 mg/d +2.6%

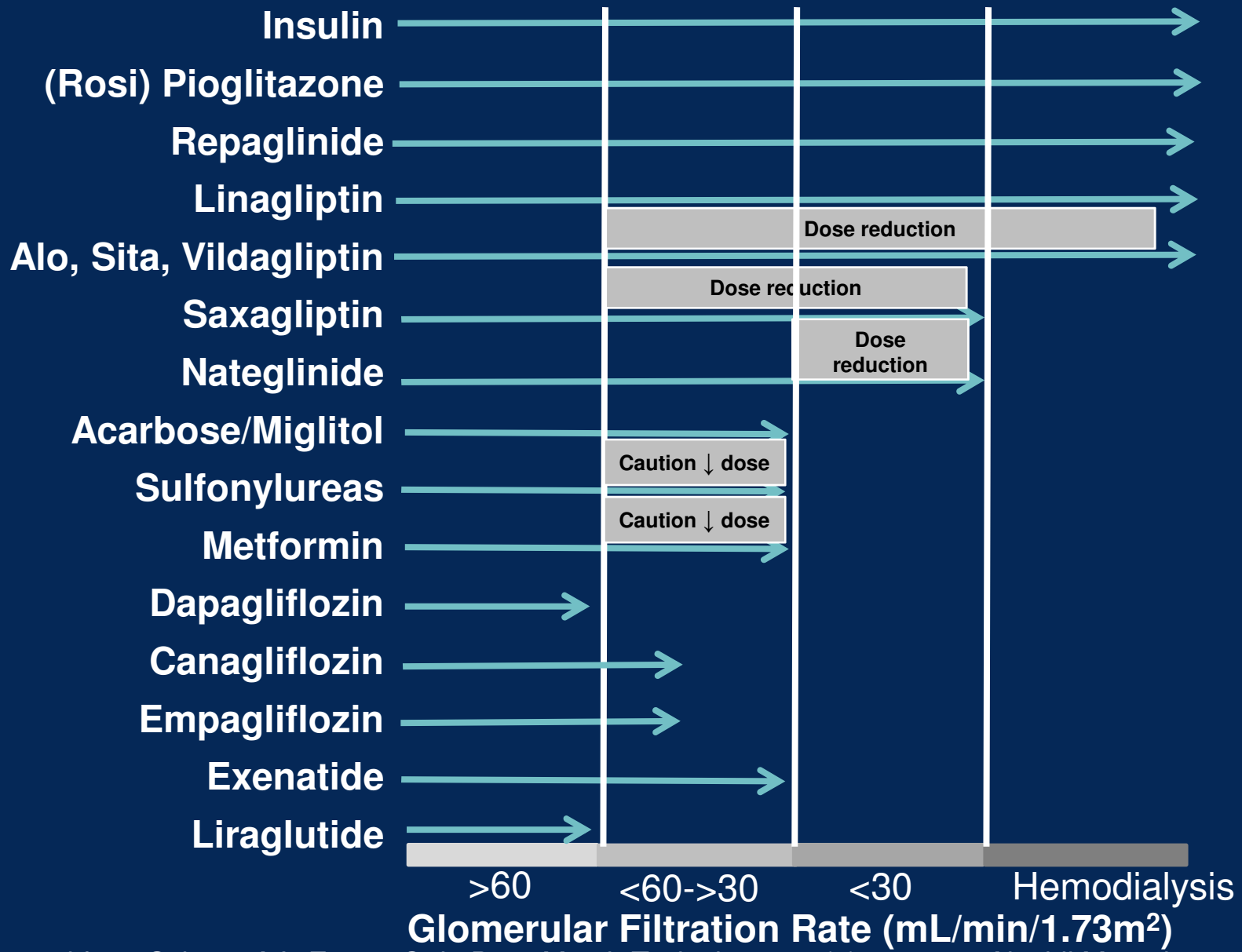
1. Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15:372-382.
2. FDA Background Document Dapagliflozin. www.fda.gov. Accessed March 2015.
3. Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.

Cardiovascular Outcomes:
CV Death, MI, Stroke

- Canagliflozin HR=0.91 (95% CI: 0.68, 1.22)
- Dapagliflozin HR=0.81 (95% CI: 0.59, 1.09)

Inzucchi SE et al. *Diab Vasc Dis Res*. 2015;12(2):90-100.

Renal Impairment Restricts Options



Adapted from Scheen AJ. *Expert Opin Drug Metab Toxicol*. 2013;9(5):529-550; Alsahli M et al. *Mayo Clin Proc*. 2014;89(11):1564-71.

SGLT2 Inhibitors in Renal Insufficiency

eGFR	Dapagliflozin	Canagliflozin	Empagliflozin
>60 mL/min/1.73 m^2	Up to 10 mg/d	Up to 300 mg/d	-
45-60 mL/min/1.73 m^2	Discontinue	Up to 100 mg/d	-
<45 mL/min/1.73 m^2	Discontinue	Discontinue	Discontinue

Candidates for SGLT2 Inhibitors

- Those who do not tolerate metformin
- Lack of glycemic control on metformin
  - Addition of SGLT2 inhibitor
  - Triple combination therapy
- Patients desiring weight loss
- Good renal function