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Sandra Trkulja, PharmD Student
Reviewed by Trudy Huyghebaert

Is there a benefit to using higher doses of SGLT-2 inhibitors?

Clinical Question: Would increasing the dose of SGLT2i improve outcomes without compromising patient safety?

Bottom line: SGLT-2 inhibitors show a relatively flat dose-response curve in glycemic effects small but not clinically significant differences in Hg1Ac decrease with the SGLT-2 dose increase with HbA1c of 0.2 % at best. A higher dose could be considered for younger patients with stable preserved renal function tolerating lower doses without significant risk of volume depletion but not achieving adequate glycemic control. At this time, there is no evidence that the higher dose would achieve additional CV and renal benefits. A higher, 10mg dapagliflozin dose should be used for HF indication.

Empagliflozin (EMPA)	**10mg vs 25mg**
Efficacy	**% Achieving Hb1Ac<7%:** Baseline HbA1c ~8% **10 mg: NNT 4 ARR 23%** **25 mg: NNT 3 ARR** 32%, **CV effect**-EMPA-Reg[2] study, both empagliflozin doses (10 mg and 25 mg) demonstrated equivalent CV benefits.
Safety	**Volume depletion AE: patients >75yo** **10 mg: NNH 500 AR 0.2%** **25 mg: NNH 43** AR 2.3%
Canagliflozin (CANA)	**100mg vs 300mg**
Efficacy	**% Achieving Hg1Ac<7% with monotherapy:** Baseline HbA1c ~8% **100 mg**: **NNT 4 ARR 23.9%** **300 mg**: **NNT 2 ARR** 41.8% **≥5%reduction in body weight at 26 weeks:** 100 mg: **NNT 8, ARR 12.1%** **300 mg NNT 7 ARR 14.1%** **CV effects-↓MACE:** CANVAS trial didn't differentiate between **100 and 300mg dose** **Reno-protective effects** (reduced risk of ESKD, doubling of SCr & renal or CV death)**-**CREDENCE trial used **only canagliflozin 100mg dose**
Safety **300mg CI eGFR<60** **100 mg CI eGFR <30**	**Hypoglycemia** **patients>75yo** **100 mg: NNH 13 AR 7.5%** **300 mg: NNH 10 AR** 9.9% **patients<75 yo** **100 mg: NNH 31, AR 3.2%** **300 mg**: N**NH 7 AR 13.5%** **Volume depletion AE:** **patients >75y.o.** **100 mg: NNH 43 AR** 2.3% **300 mg: NNH 16 AR 6.1** **Bone # (CANVAS)**: **100 mg NNH 333 AR** 0.3% **300 mg: NNH 250 AR** 0.4%
Dapagliflozin (DAPA)	**5mg vs 10mg**
Efficacy	**% Achieving Hg1Ac<7%** Baseline HbA1c ~8%: **5 mg: NNT 8 ARR** 12.6% 10 mg: **NNT 5 ARR** 19.2% **HF-**DAPA-HF trial used only dapagliflozin **10mg dose**
Safety	**No significant differences**

SGLT2 Inhibitors Quick Overview:

How do SGLT2 inhibitors work?

Inhibition of SGLT2 cotransporters in proximal renal tubules reduces hyperglycemia by decreasing renal glucose threshold and increasing urinary glucose excretion. The amount of glucose excreted in the urine depends on both the level of hyperglycemia and the glomerular filtration rate. Thanks to this mechanism, they do not usually cause hypoglycemia in the absence of therapies that otherwise cause hypoglycemia, and their effects decrease with decreased renal function. They have moderate effects on reducing HgA1c for 0.6-0.9%

SGLT2i-THERAPEUTIC OVERVIEW	**Canagliflozin (INVOKANA®)**	**Dapagliflozin (FORXIGA®)**	**Empagliflozin (JARDIANCE®)**
Labelled indications *Indicated in adults>18 y.o.; non-pregnant or lactating ***Not indicated in DM1**	**DM2-monotherapy** (2nd line if metformin inappropriate) **DM2 -add-on therapy** (metformin, sulfonylurea (with or without metformin), pioglitazone with metformin, metformin and sitagliptin, insulin (with or without metformin) **DM2+CVD**-↓MACE	**DM2-monotherapy** (2nd line if metformin inappropriate) **DM2 -add-on therapy** (metformin, sulfonylurea (with or without metformin), pioglitazone(with or without metformin), metformin and linagliptin, insulin(not mix) (with or without metformin) **DM2+CVD/risk factors for CVD** ↓hospitalization for HF **HFrEF-10mg dose only** ↓CVdeath; urgent HF visit;↓hospitalization for HF	**DM2-monotherapy** (2nd line if metformin inappropriate) **DM2 -add-on therapy** (metformin, sulfonylurea (with or without metformin) sitagliptin with or without metformin)insulin(with or without metformin **DM2+CVD**-↓CV death **DM2+diabetic nephropathy +albuminuria(>33.9mg/mmol)** ↓CV death; end-stage renal disease and doubling SCr
Dosing **No adjustment in mild or moderate hepatic impairment** **CI: ESR, dialysis; severe hepatic dysfunction, hypersensitivity to a product** *eGFR<45 limited glycemic efficacy*	**100 -300mg OD**, before the first meal of the day **300 mg OD** if eGFR ≥60 **eGFR 30 to <60**:100 mg once daily. **eGFR <30:** with urinary albumin excretion >300 mg/day: Do not initiate; but established may continue 100 mg once daily.	**5 -10mg OD**, in the morning with or without food **10mg OD for HF** **eGFR ≥45:** No dosage adjustment necessary **eGFR 30 to <45:** Use alternative agent due to lack of glycemic efficacy **HF**-no dose adjustment **DKD**- no dose adjustment	**10-25 mg OD**, in the morning with or without food **eGFR >30**: No dosage adjustment necessary
Precautions	**DKA-** Hx of DKA, nephropathy, low carb diet, latent immunodiabetes, alcohol use **Reduced intravascular V**-≥65 y.o**.** (↑ ≥75y.o. and **300mg dose**), low SBP,loop-diuretics ,ACEI/ARB,NSAIDs **UTI-** Hx of frequent UTIs **Fournier's Gangrene**-Hx of it **(CANA) Lower limb amputation-**PVD, prior amputation, neuropathy, diabetic ulcer **(CANA) Bone fractures-**low BMD**, ↑**risk of falls and fractures		
Cost/Coverage	~113 $/month(both doses) ABC special auth	~109 $/month(both doses) ABC special auth	~108$/month(both doses) ABC special auth

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