Critical Appraisal and Formulary Review in Type 2 Diabetes Mellitus

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Drug Class

SGLT-2 Inhibitors

- **Empagliflozin**
- Canagliflozin
- Dapagliflozin

Mechanism of Action

- Decreases reabsorption of glucose in the renal tubules
- Increases urinary glucose excretion

Place in Therapy

- First line in patients already on anti-hyperglycemics not meeting targets

Empagliflozin; Indications/Warnings

Indication

- Approved as both monotherapy or in combination with other anti-hyperglycemics (not approved for use with mixed insulin)

Not recommended/Not studied

- Type 1 diabetes
- Diabetic ketoacidosis
- Pregnancy
- Pediatrics (< 18 years old)
- Volume depletion (correct before initiating empagliflozin)

Contraindications

- Hypersensitive to this drug/any ingredient in the formulation
- Renal impairment (eGFR<45 ml/min), end stage renal disease or dialysis
- Severe hepatic impairment

Empagliflozin; Pharmacokinetics

Absorption

- Peak concentrations 1.5hours post dose
- Dose proportional increase in C_{max} and AUC

Distribution

- Steady state V_d of 73.8L
- 86.2% protein binding

Metabolism

- Glucuronidation
- No major metabolites

Excretion

- Half life of 12.4hours
- 95.6% of the drug was eliminated unchanged in either feces or urine

EMPA-REG; Critical Appraisal

- Published in 2015, EMPA-REG is a landmark trial for empagliflozin in type 2 diabetes mellitus
- The first anti-hyperglycemic to show *favourability* towards cardiovascular benefit

Primary Outcome

- Composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent MI), or nonfatal stroke

Secondary Outcome

- Composite of the primary outcomes + hospitalization for unstable angina

Methods

Patients were randomly assigned either;

- empagliflozin 10mg
- empagliflozin 25mg
- placebo

Inclusion;>18y.o, (avg. 63), BMI ≤45, established CVD, A1c 7%-10% (7%-9% if the patient was not on glucose lowering agents in the past 12 weeks), eGFR ≥30mL/min

Exclusion; uncontrolled hyperglycemia, liver disease, eGFR<30mL/min, stroke/TIA or ACS within the last 2 months

Are the Results Valid?

- Were the patients truly randomized?
  - Yes
- Were all patients who entered the study accounted for appropriately at the end?
  - Number of patients in the results vs. number of patients that underwent randomization
  - Were patients analyzed in the groups they were allocated to at the start of the trial
- What about blinding?

Between Group Characteristics

- Was similarity between groups documented?
  - Yes
- Were difference controlled for in the analysis?
  - Yes… How?
- Aside from intervention, were groups treated the same way?
  - Unsure

Sources of Bias

Results

- Median observation time was 3.1 years

RESULTS — **follow-up: Mean 3yrs/Median 3.1yrs**

TABLE 1: EFFICACY & SAFETY NON-INFERIORITY DATA SUPERIORITY DATA {NNT/H = number needed to Treat for Benefit / Harm}

CLINICAL ENDPOINTS ITT ANALYSIS	EMPAGLIFLOZIN (10MG & 25MG) n=4687	PLACEBO n=2333	HR (95% CI)	P VALUE	ARR/ARI	NNT/NNH /3.1YRS	COMMENTS
PRIMARY ENDPOINT							
Death from CV causes, non-fatal MI, or non-fatal stroke	10.5% (n=490)	12.1% (n=282)	0.86 (0.74-0.99)	<0.001 0.04	↓1.6%	63	
SECONDARY ENDPOINTS							
1° endpoint plus hospitalization for unstable angina	12.8% (n=599)	14.3% (n=333)	0.89 (0.78-1.01)	<0.001 0.08	↓1.5%	67	
All-cause Death	5.7% (n=269)	8.3% (n=194)	0.68 (0.57-0.82)	<0.001	↓2.6%	38	
CV Death	3.7% (n=172)	5.9% (n=137)	0.62 (0.49-0.77)	<0.001	↓2.2%	45	
Hospitalization for HF	2.7% (n=126)	4.1% (n=95)	0.65 (0.50-0.85)	0.002	↓1.4%	71	
Hospitalization for HF or death from CV causes excluding fatal stroke	5.7% (n=265)	8.5% (n=198)	0.66 (0.55-0.79)	<0.001	↓2.8%	36	Consistent benefit on HF endpoints whether HF pre-existent or not.

- **A1C** ↓ by 0.6% or less.
- **Systolic BP** ↓ by 3-4mmHg
- **Weight** ↓ by 1-2 kg

Non-significant 2° outcomes; Trend for better outcome on empagliflozin: fatal or non-fatal MI excluding silent MI, non-fatal MI, silent MI, hospitalization for unstable angina, coronary revascularization procedure, and TIA. Trend for worse on empagliflozin: fatal or nonfatal stroke, silent MI.

Clinical Trials; EMPA-REG

Trial Qualities

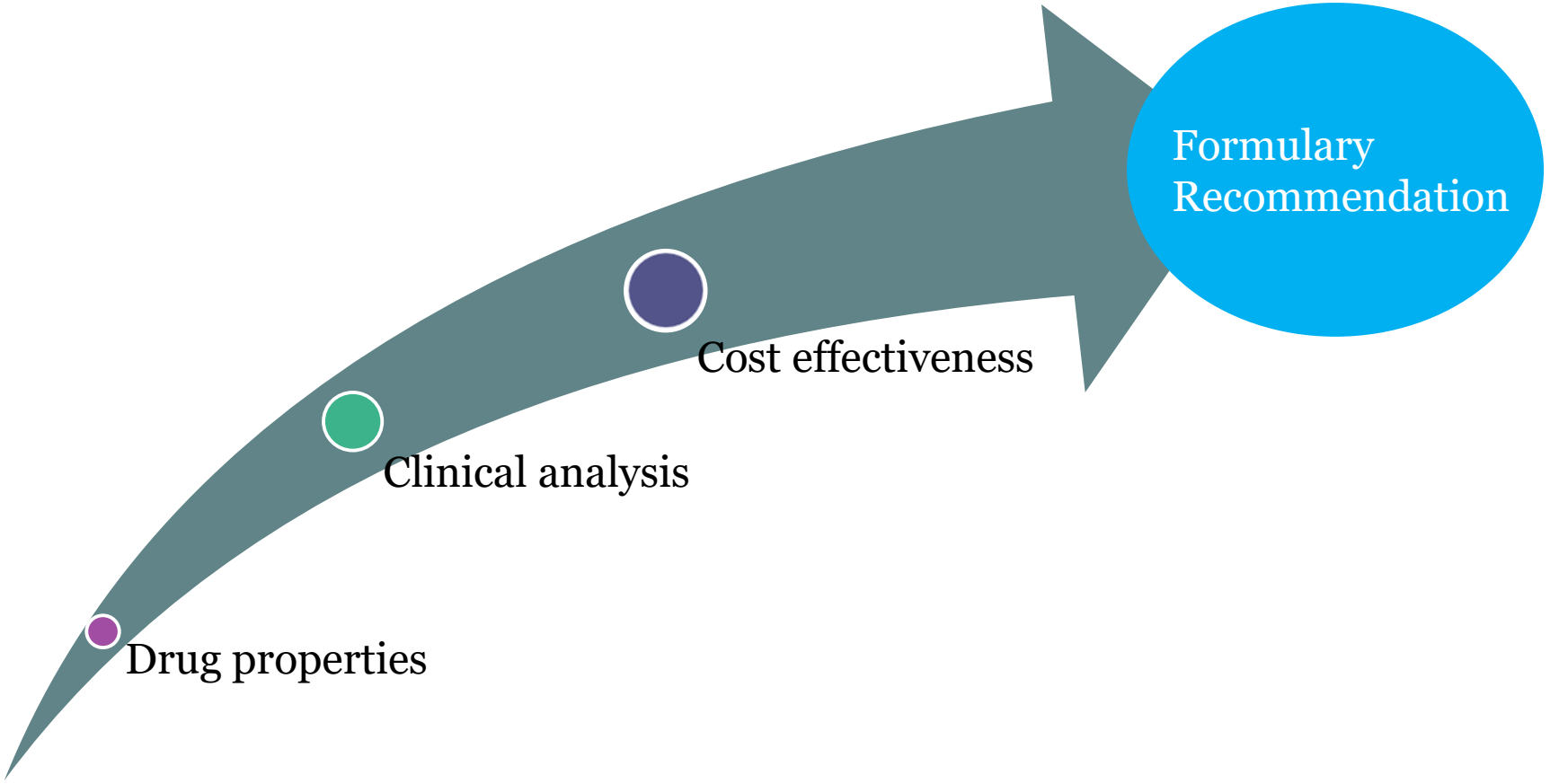
- **Internal validity**; High.

Randomization was obtained by a computer generated sequence and stratified in various categories (ex A1c %). Not statements were made on how allocation/blinding was performed. Analysis performed by Boehringer Ingelheim was confirmed by an independent company.

- **External validity**; High.

Trial included all age groups and was conducted in 42 countries as well as made no specification of particular meds they had to be on just "local standard of care". Protocol followed was intention to treat. However, not representative of all patients with T2DM as not all are at a high risk for cardiovascular events and patients with uncontrolled hyperglycemia were not included.

Formulary Decision Making



Drug Class

SGLT-2 Inhibitors

- Empagliflozin
- Canagliflozin
- Dapagliflozin

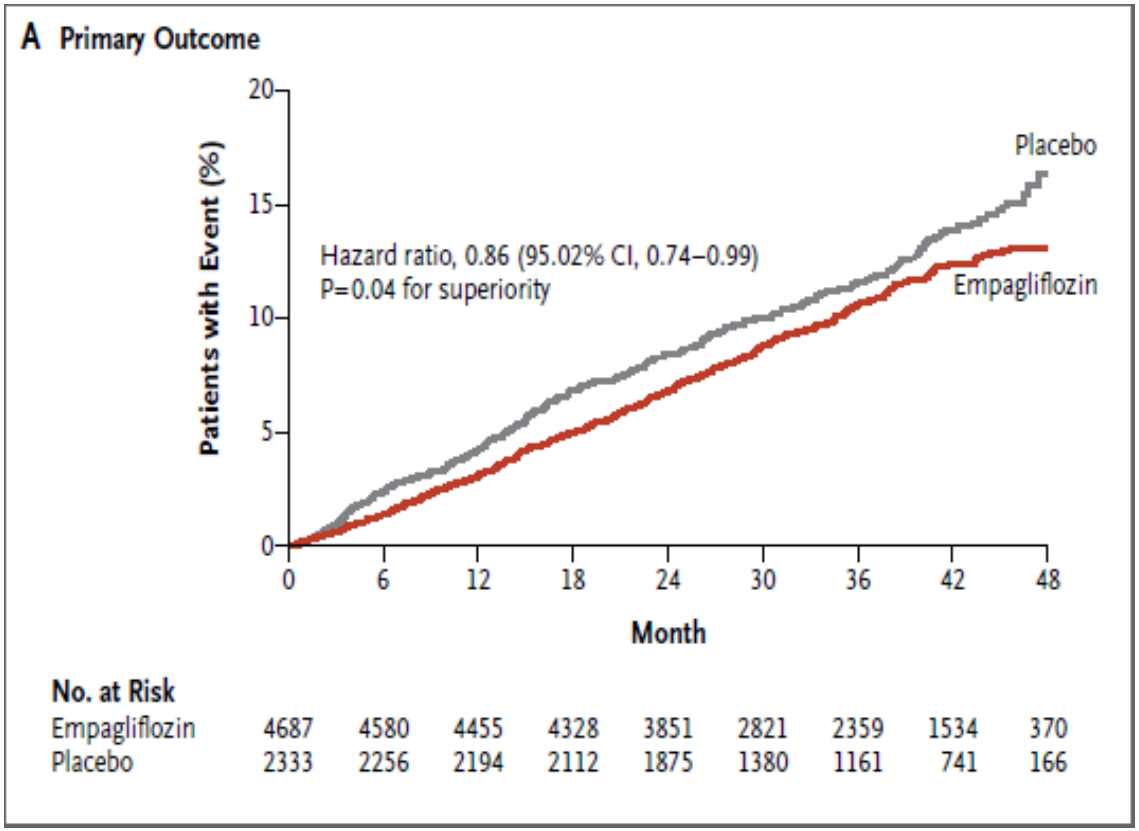
In this review, empagliflozin will be compared with canagliflozin in terms of efficacy, drug interactions, adverse effects, and cost.

Dapagliflozin was not compared due to its increased cost relative to empagliflozin and canagliflozin (discussed in a later slide)

Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes

(EMPA-REG)

Clinical Trials; EMPA-REG



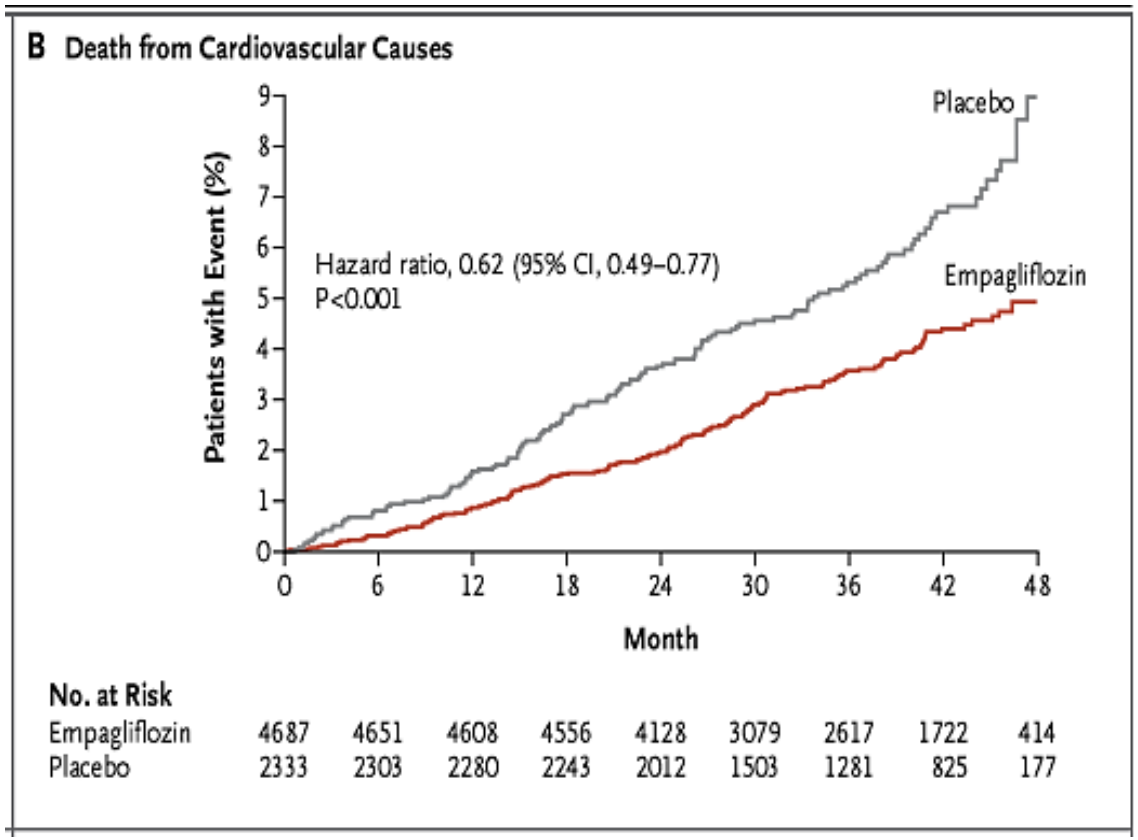
Significantly less primary outcome events in pooled empagliflozin group

- 10.5% vs. 12.1%;

Non-inferiority; p<0.001
Superiority; p=0.04

- NNT= ~61

Clinical Trials; EMPA-REG



Significant reduction in cardiovascular deaths (RRR of 38%)

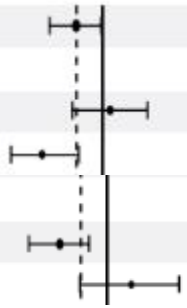
- 35% RRR in hospitalization for heart failure
- 32% RRR in total mortality
- No change in non-fatal MI or non-fatal stroke

*RRR= relative risk reduction

Clinical Trials; EMPA-REG

- Baseline characteristics that alter results
  - Age
  - Glycated hemoglobin

Subgroup	Empagliflozin	Placebo	Primary Outcome: Hazard Ratio (95% CI)	Primary Outcome: P Value for Interaction
	no. in subgroup			
All patients	4687	2333		
Age				0.01
<65 yr	2596	1297		
≥65 yr	2091	1036		
Glycated hemoglobin				0.01
<8.5%	3212	1607		
≥8.5%	1475	726		



Clinical Trials; EMPA-REG

Adverse Events

- Proportion of patients with adverse events or serious adverse events were similar between study groups and placebo groups ($p<0.001$ respectively and $p<0.05$)
- All events while taking a study drug or within 7 days after discontinuation

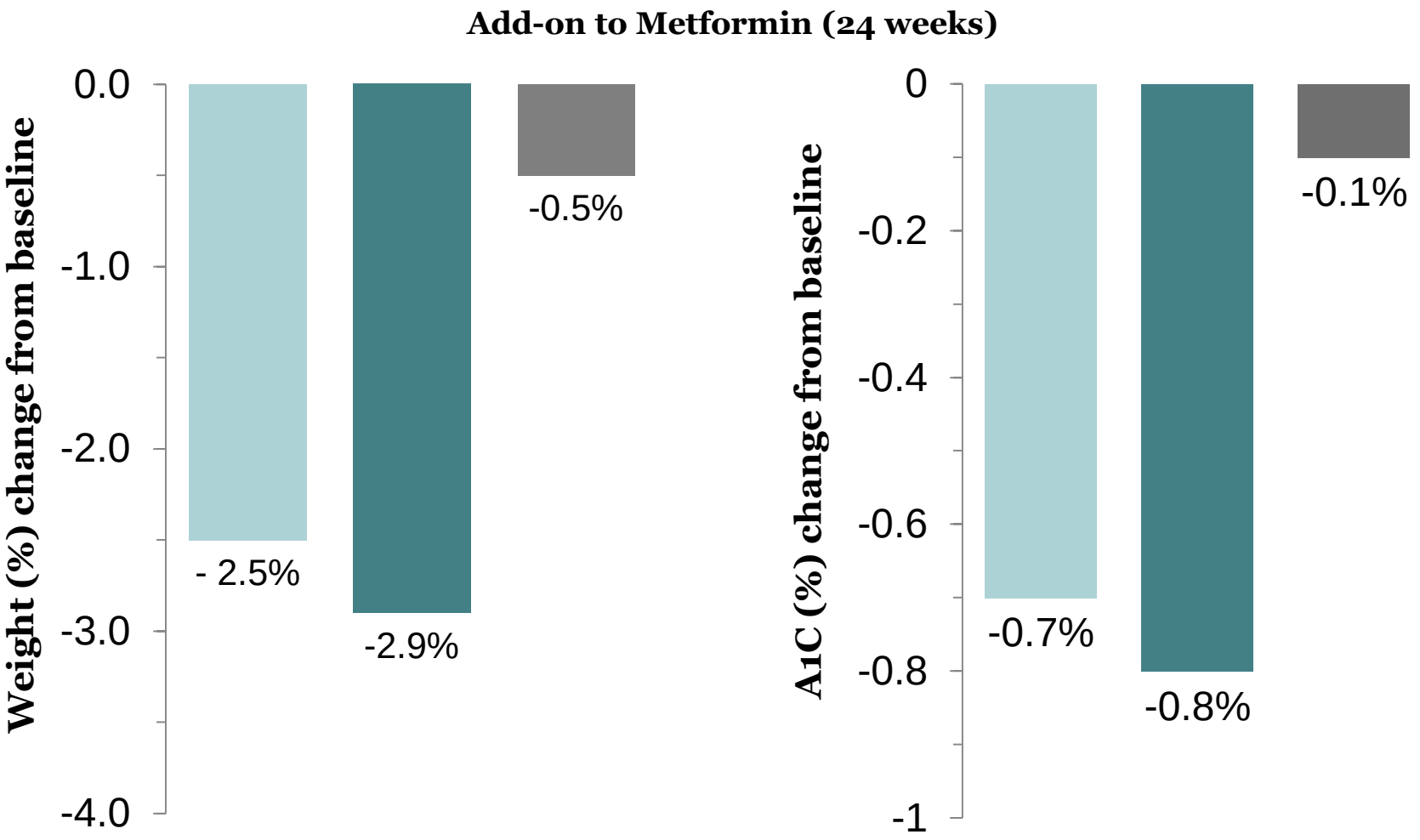
Adverse Event	Pooled empagliflozin	Placebo	Significant?
Genital Infections	6.4%	1.8%	YES ($p<0.001$)
Urinary Tract Infection	18%	18.1%	NO
Volume Depletion	5.1%	4.9%	NO
Acute renal failure	5.2%	6.6%	YES ($p<0.01$)
Acute kidney injury	1.0%	1.6%	YES ($p<0.05$)

Clinical Trials; Boehringer Ingelheim

Multiple trials done by Boehringer Ingelheim
Keep in mind all but the primary +/- secondary author are employees of the company.

- Metformin (≥1500mg/day)
- A1c 7%-10%
- Randomized to add;
  - Emplagliflozin 10mg
  - Empagliflozin 25mg
  - Placebo
- Inclusion/exclusion matches EMPA-REG

Clinical Trials; Boehringer Ingelheim



Reviews

- In a review of multiple smaller studies with empagliflozin the following results were obtained
- Similar results to the EMPA-REG trial

Table 2 Clinical properties of empagliflozin when given orally at clinically available doses of either 10 mg/d or 25 mg/d

Clinical properties of empagliflozin (10–25 mg/d)	
Decrease in HbA1c	−−0.6%–0.9%
Decrease in fasting plasma glucose	−−20 mg/dL to −35 mg/dL
Decrease in HbA1c with baseline A1c ≥8.5%	−1.2%–1.4%
Decrease in HbA1c with baseline A1c ≥10%	−3%
Decrease in HbA1c with stage 2 or 3 CKD	−−0.4% to −0.6%
Decrease in body weight	−2–3 kg
Decrease in fasting plasma glucose	−20–30 mg/dL
Decrease in systolic blood pressure	−3–7 mmHg
Decrease in diastolic blood pressure	−1–3 mmHg
Decrease in waist circumference	−1–1.5 cm
Decrease in uric acid	−0.5–1 mg/dL
Decreased risk of death from cardiovascular cause	−38%
Decreased all-cause mortality	−32%
Decreased hospitalization for congestive heart failure	−35%
Decreased new onset or worsening of neuropathy	−39%
Hypoglycemia	−3%–5%
Genital infections	−3%–5%

Clinical Trials; Comparison

EMPA-REG

- HbA1C; ↓ 0.6%
- Weight reduction; 1-2kg
- Blood Pressure ↓
  Systolic; 3-4mmHg
  Diastolic; 1-2mmHg
- Cardiovascular benefit; YES

CANTATA-MP

- HbA1C; ↓0.7%
- Weight reduction; ≤4kg
- Blood Pressure ↓
  Systolic; ~ 5mmHg
  Diastolic; not measured
- Cardiovascular benefit; NO

Drug Properties; Drug Interaction

Empagliflozin

- Antihyperglycemics; enhanced hypoglycemic effect
- SSRIs and Quinolones; enhanced hypoglycemic effect or reduction in efficacy
- Loop Diuretics; risk of dehydration and hypotension
- Agents causing hyperglycemia (ex. Antipsychotics); decreased efficacy

Canagliflozin

- Metabolized to inactive metabolites by UGT enzyme; all UGT inducers will reduce efficacy (ex. rifampin, phenytoin, carbamazepine etc.)
- Canagliflozin is a weak CYP3A4 inducer and will have a small effect on all 3A4 metabolized drugs (may not be clinically significant)
- Loop Diuretics; risk of dehydration and hypotension
- -Agents causing hyperglycemia (ex. Antipsychotics); decreased efficacy
  -Antihyperglycemics; enhanced hypoglycemic effect

Adverse Effects

Empagliflozin ≥10%

-Polyuria

-Potential hypoglycemia in combination with insulin/sulfonylureas

Canagliflozin ≥10%

-Dose dependent increase in serum potassium

-Genitourinary infections

-Renal insufficiency in patients with baseline eGFR ~ 30-50mL/min

Dosing

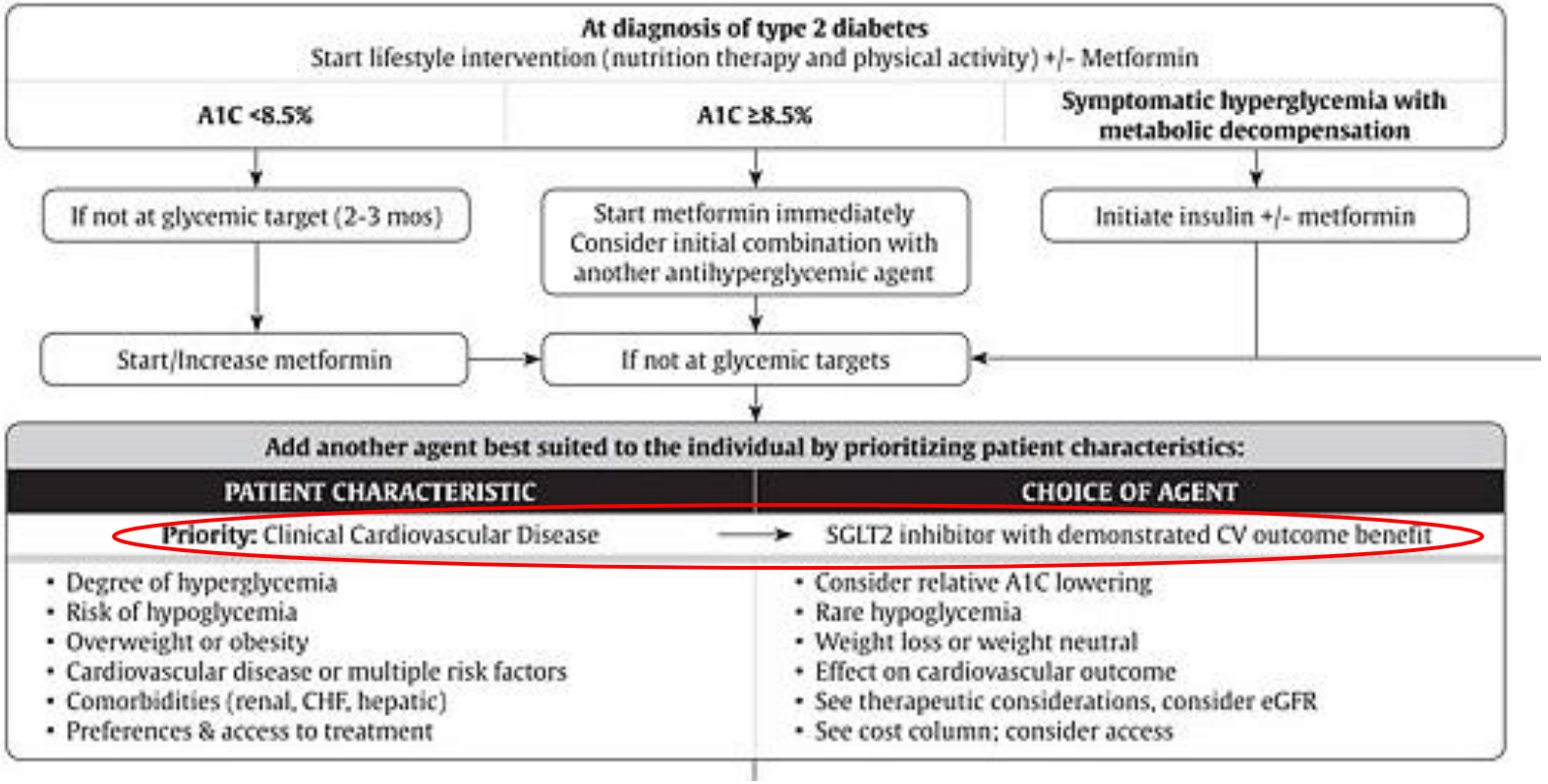
- Starting dose is 10mg which can be increased to 25mg if tolerated by the patient
- Consider dose reduction in patients:
  - On insulin/secretagogue
  - On a diuretic (especially loop diuretics)
  - If eGFR falls below 60mL/min

Cost Comparison

SGLT-2 inhibitor	Cost per day
Empagliflozin	$2.62
Canagliflozin	$2.62
Dapagliflozin	$3.08

- More expensive than older antihyperglycemics which hover around $1-$2 per day
- Empagliflozin has a similar daily cost as a DPP-4 inhibitor and is less expensive than a GLP-1 agonist

CDA Guideline Update 2016



Recommendation

It is recommended that empagliflozin (Jardiance) be added to the hospital formulary as a tier 1 medication

Reasons for recommendation

- Cardiovascular benefit not seen with any other anti-hyperglycemic
- Lower blood pressure
- Lower HbA1C

Take-Home Points

References

- FDA Safety Communication. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Food and Drug Administration website. Available at mhttp://www.fda.gov/Drugs/DrugSafety/ucm446845.htm. Accessed May 15, 2015.
- Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; July 2016.
- Jardiance (empagliflozin) [product monograph]. Burlington, Ontario, Canada: Boehringer Ingelheim (Canada) Ltd; July 2016.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
- Smith N, Barzilay J, Kronmal R, et al. New-onset diabetes and risk of all-cause and cardiovascular mortality. Diabetes Care 2006;29:2012–17.
- Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39.
- Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S, Pinnetti S, Woerle HJ. A phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes Obes Metab. 2013;15(8):721–728.
- 24. Kadowaki T, Haneda M, Inagaki N, et al. Empagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, 12-week, double-blind, placebo-controlled, phase II trial. Adv Ther. 2014;31(6):621–638.
- Araki E, Tanizawa Y, Tanaka Y, et al. Long-term treatment with empagliflozin as add-on to oral antidiabetes therapy in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2015;17(7): 665–674.
- 66. Brunk D. Empagliflozin benefited type 2 diabetes patients with CKD. Clinical Endocrinology News Digital Network. 2015.