Place des gliflozines dans la prise en charge du diabète de type 2

J.Philippe

21.02.2018

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG Hôpitaux Universitaires Genève

Conflits d'intérêt

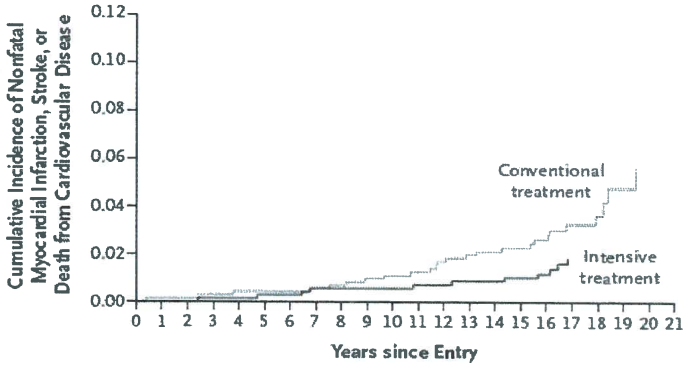
- Conférences : BM, ASTRA-ZENECA, Jansen, Mundipharma
- Subside de recherche: NovoNordisk
- Advisory Board: ASTRA-ZENECA, BM, SANOFI

Buts du traitement

- Eviter les complications du diabète

- Microangiopathie (nerfs, cerveau, reins, yeux, peau, articulations, poumons, cœur, dents, etc..)
- Macroangiopathie (système vasculaire)
- Cancer

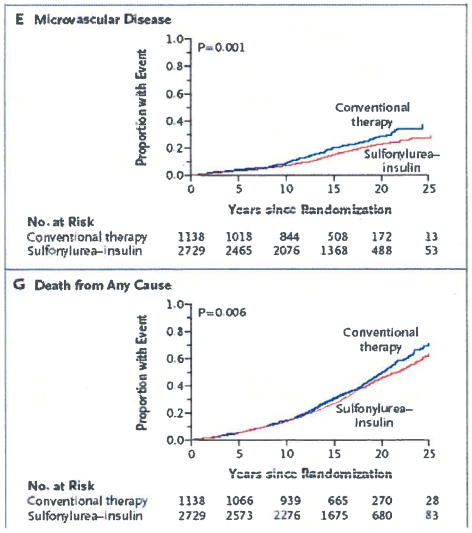
Glycemic control and cardiovascular complications: the DCCT/EDIC studies



No. at Risk				
Intensive treatment	705	686	640	118
Conventional treatment	721	694	637	96

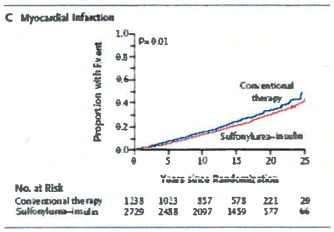
Nathan DM et al., N.Engl J.Med., 2005

UKPDS - Suivi et résultats



Holman R et al., N.Engl.J.Med., 2008

UKPDS-follow-up at 25 years



Holman R et al., NEJM,2008

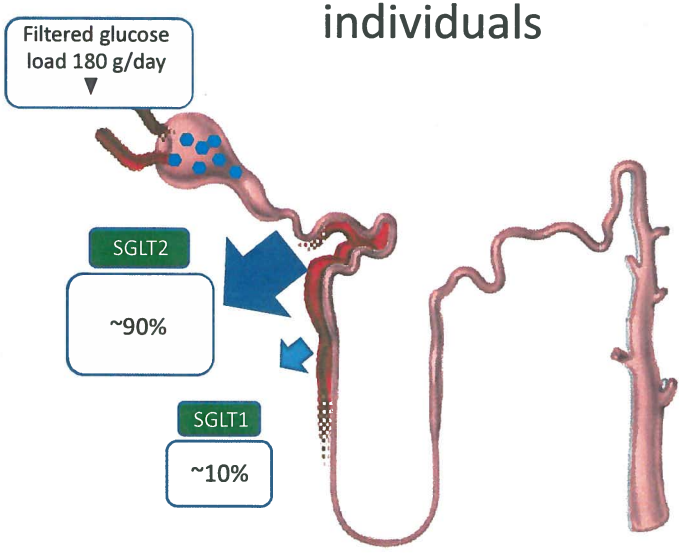
Etudes d'intervention cardio-vasculaire-diabète type 2

	Événements CV	Mortalité
Contrôle intensif vs moins intensif de la glycémie[1]		
ACCORD	↔	↑ (HR 1.22)
ADVANCE	↔	↔
UKPDS	↔	↔
VADT	↔	↔
Médicament hypoglycémiant individuel vs placebo (depuis les directives 2008 de la FDA)		
ELIXA[2]	↔	↔
EXAMINE[3]	↔	↔
SAVOR[4]	↔	↔
TECOS[5]	↔	↔
EMPA-REG OUTCOME[6]	↓ (HR 0.86)	↓ (HR 0.68)
LEADER[7]	↓ (HR 0.87)	↓ (HR 0.85)
CANVAS[8]	↓ (HR 0.86)	↔
SUSTAIN 6[9]	↓ (HR 0.74)	↔
EXSCEL[10]	↔	↔

1. Bergenstal RM et al. Am J Med 2010;123:374.e1-9; 2. Pfeffer MA et al. N Engl J Med 2015;373:2247-57; 3. White WB et al. N Engl J Med 2013;369:1327-35; 4. Leiter LA et al. N Engl J Med 2013;369:1317-26; 5. Green JB et al. N Engl J Med 2015;373:232-42; 6. Zinman B et al. N Engl J Med 2015;373:2117-28; 7. Marso SP et al. N Engl J Med 2016;375:311-22; 8. Neal B et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1611925; 9. Marso SP et al. NEJM 2016;375:1834-44; 10. Holman RR et al. NEJM 2017

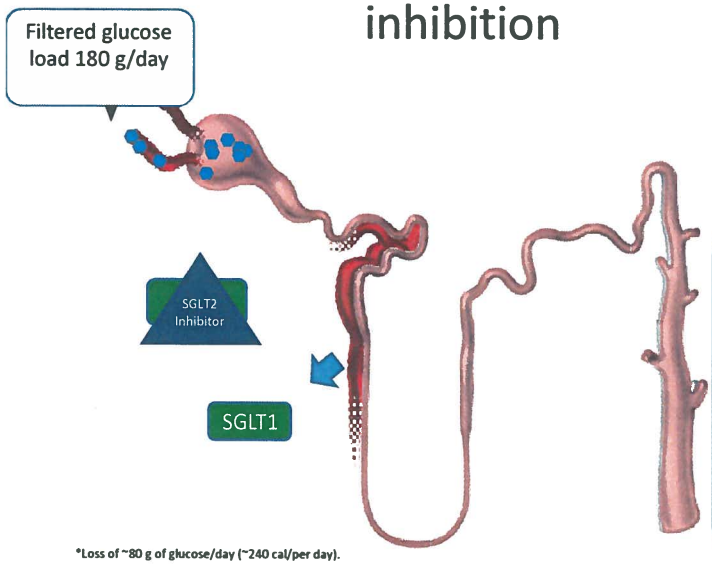
Gliflozines et diabète

Renal glucose re-absorption in healthy individuals



Gerich JE. *Diabet Med.* 2010;27:136–142.

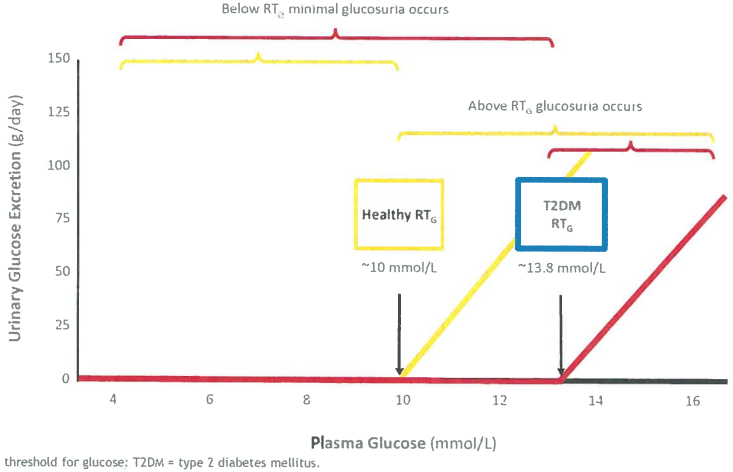
Urinary glucose excretion via SGLT2 inhibition



SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

*Loss of ~80 g of glucose/day (~240 cal/per day).
Gerich JE. *Diabet Med.* 2010;27:136–142.

Renal Threshold for Glucose (RT_G) Increased in T2DM

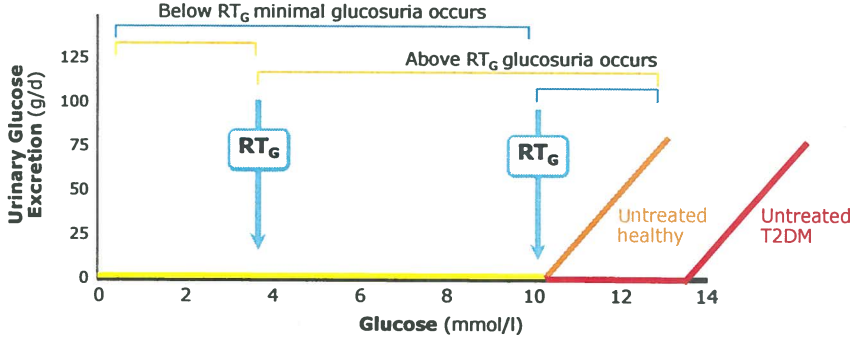


RT_G = Renal threshold for glucose; T2DM = type 2 diabetes mellitus.

1. Polidori D., et al. (2010). The Renal Glucose Threshold is Increased in Patients with Type 2 Diabetes: Results from a Novel Method for Measuring the Renal Threshold. Abstract 2186-PO. American Diabetes Association. Orlando, Florida. 2. Polidori D., et al. (2010) Canagliflozin lowers the renal threshold for glucose excretion in lean, obese and type 2 diabetic subjects. Poster presented at the 46th EASD 2010; September 20-24; Stockholm, Sweden. Abstract #675.

SGLT2 Inhibition Lowers RT_G

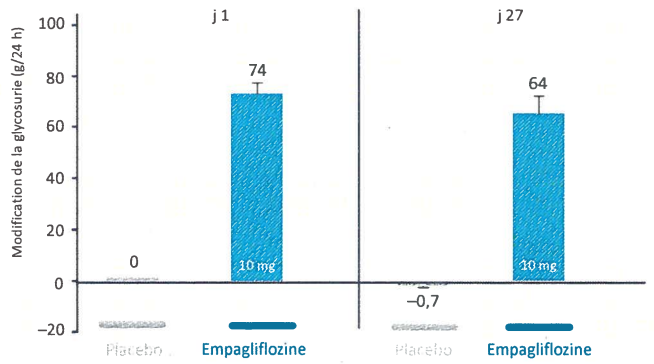
- Healthy subjects



L'empagliflozine entraîne une élimination du glucose dans les urines chez les patients atteints de diabète de type 2

Etude de phase I

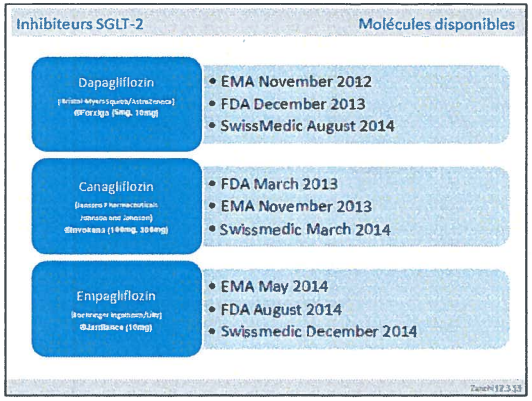
Glycosurie * après prise orale unique ou répétée d'empagliflozine chez des patients adultes présentant un diabète de type 2



L'empagliflozine entraîne une élimination de ~ 65 g de glucose par jour dans les urines# ≙ ~ 250 kcal/jour. Ceci correspond à une inhibition de la réabsorption du glucose d'environ 36 %.

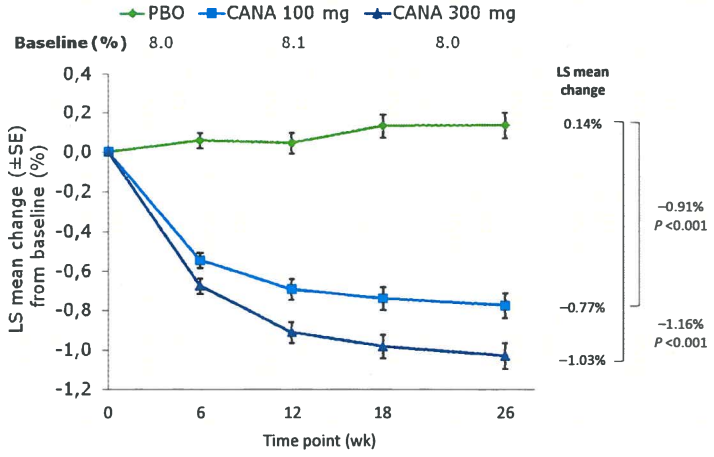
Glycosurie = élimination du glucose dans les urines, Placebo, n=16; 10 mg empagliflozine, n=16. *les glycosuries initiales étaient de 4 6 g/24h (Placebo) et de 7 à g/24h (10 mg d'empagliflozine). Modification moyenne de la glycosurie par rapport à la valeur initiale (g/24 h ± écart-type). #glycosurie au vingt-septième jour par rapport à la valeur initiale
Référence: Heise T, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. *Diabetes Obes Metab* 2013;15(7):613-621.

Les gliflozines



CANTATA-M (DIA3005)
Monotherapy vs Placebo

Change in HbA_{1c} (LOCF)

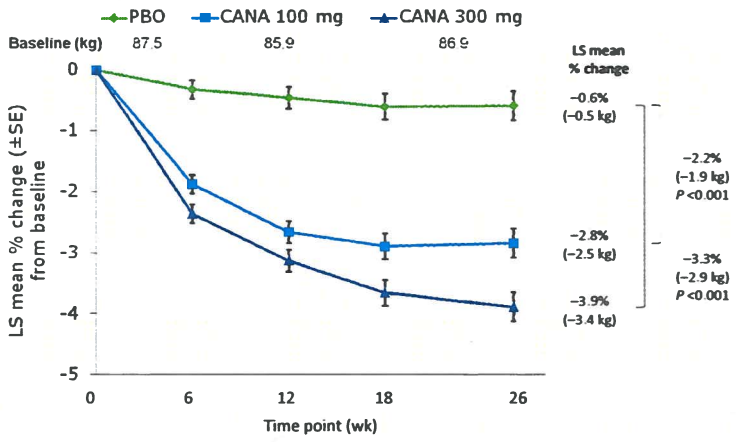


LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; LS, least squares; SE, standard error.

Stenlöf K. et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov 8-11; Barcelona, Spain, (P71)

CANTATA-M (DIA3005)
Monotherapy vs Placebo

Percent Change in Body Weight (LOCF)



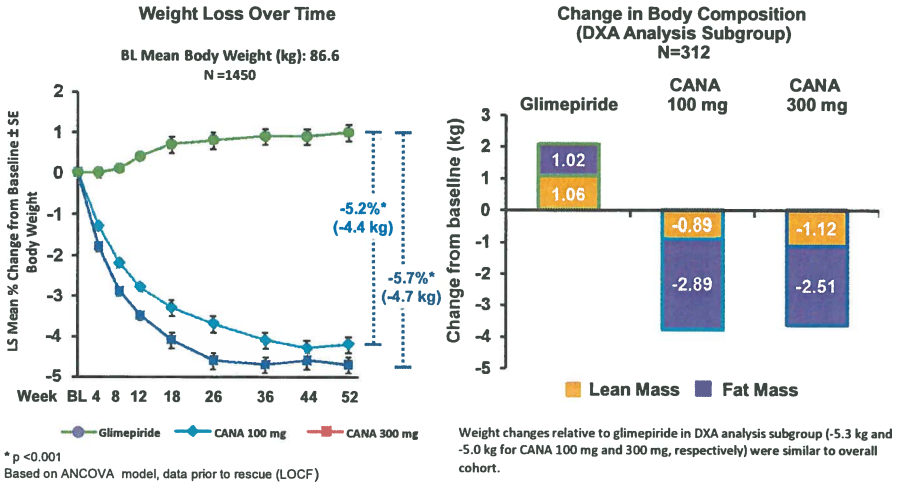
LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; LS, least squares; SE, standard error.

Stenlöf K. et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov 8-11; Barcelona, Spain, (P71)

For internal use only.

Summary- Changes in Body Composition and Weight

Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)



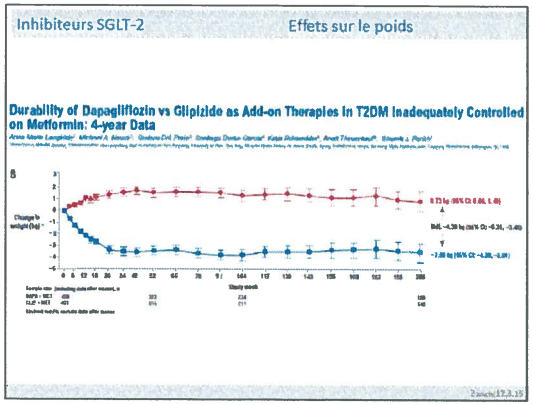
* p <0.001

Based on ANCOVA model, data prior to rescue (LOCF)

Weight changes relative to glimepiride in DXA analysis subgroup (-5.3 kg and -5.0 kg for CANA 100 mg and 300 mg, respectively) were similar to overall cohort.

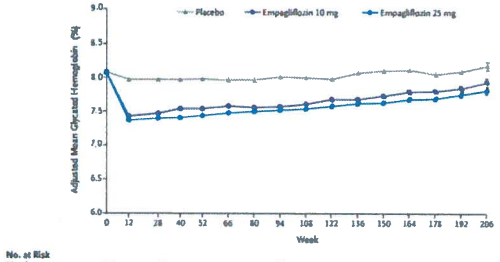
Toubro S. et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov 8-11; Barcelona, Spain, (P72).
Cefalu WT et al. Lancet. 2013; 382(9896):941-50.

Durabilité de l'effet



Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators



N.Engl.J.Med., 2015

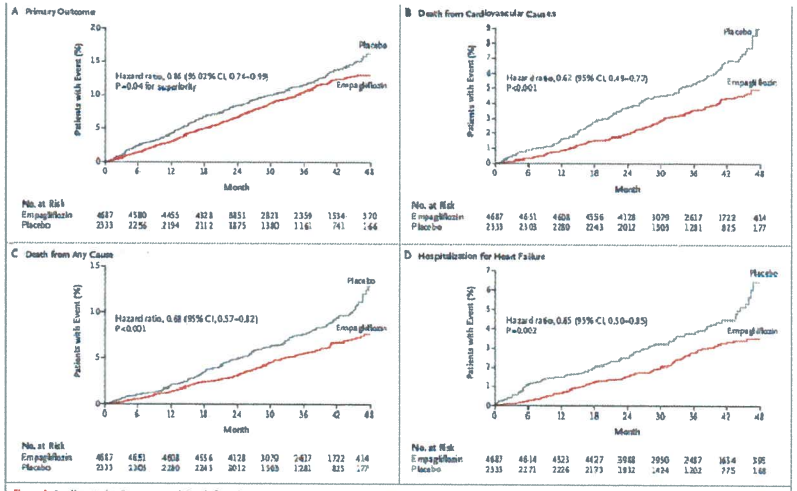
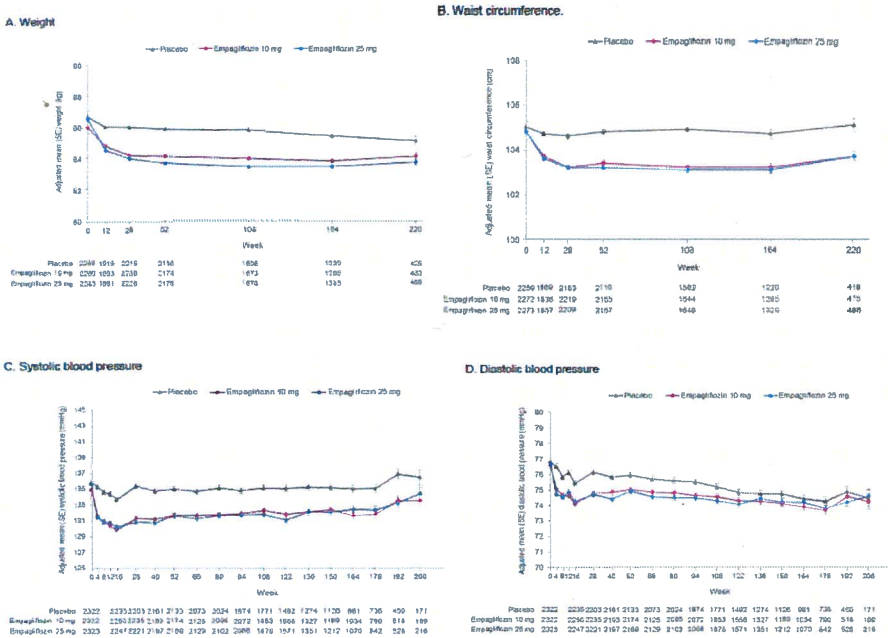


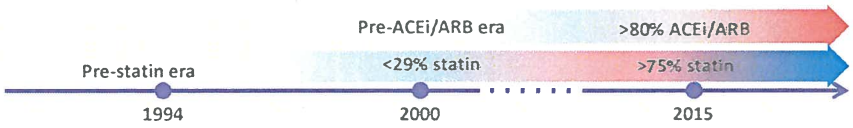
Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.



Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin[1] for 5.4 years	Ramipril[2] for 5 years	Empagliflozin for 3 years
30	**56**	**39**
High CV risk 5% diabetes, 26% hypertension	High CV risk 38% diabetes, 46% hypertension	T2DM with high CV risk 93% hypertension



1. 4S Investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm
2. Yusuf et al. N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

Adverse events consistent with urinary tract infection

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Events consistent with UTI	423 (18.1%)	8.21	426 (18.2%)	8.02	416 (17.8%)	7.75
Events leading to discontinuation	10 (0.4%)	0.17	22 (0.9%)	0.37	19 (0.8%)	0.31
By sex						
Male	158 (9.4%)	3.96	180 (10.9%)	4.49	170 (10.1%)	4.09
Female	265 (40.6%)	22.81	246 (35.5%)	18.83	246 (37.3%)	20.38

Rate = per100 patient-years

Patients treated with ≥1 dose of study drug
Based on 79 MedDRA preferred terms

Adverse events consistent with genital infection

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Events consistent with genital infection	42 (1.8%)	0.73	153 (6.5%)	2.66	148 (6.3%)	2.55
Serious events	3 (0.1%)	0.05	5 (0.2%)	0.08	4 (0.2%)	0.07
Events leading to discontinuation	2 (0.1%)	0.03	19 (0.8%)	0.32	14 (0.6%)	0.23
By sex						
Male	25 (1.5%)	0.60	89 (5.4%)	2.16	77 (4.6%)	1.78
Female	17 (2.6%)	1.09	64 (9.2%)	3.93	71 (10.9%)	4.31

Rate = per100 patient-years

Patients treated with ≥1 dose of study drug
Based on 88 MedDRA preferred terms

Other adverse events (1)

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Diabetic ketoacidosis*	1 (<0.1%)	0.02	3 (0.1%)	0.05	1 (<0.1%)	0.02
Acute kidney injury†	155 (6.6%)	2.77	121 (5.2%)	2.07	125 (5.3%)	2.12
Events consistent with volume depletion§	115 (4.9%)	2.04	115 (4.9%)	1.97	124 (5.3%)	2.11
Serious events	24 (1.0%)	0.42	19 (0.8%)	0.32	26 (1.1%)	0.43
Events leading to discontinuation	7 (0.3%)	0.12	1 (<0.1%)	0.02	4 (0.2%)	0.07
Venous thrombotic events**	20 (0.9%)	0.35	9 (0.4%)	0.15	21 (0.9%)	0.35

Rate = per100 patient-years

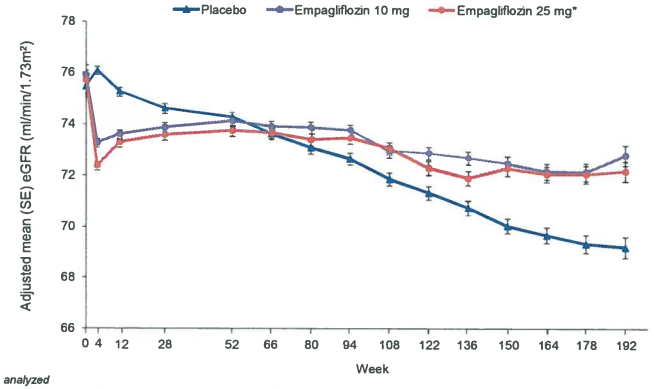
Patients treated with ≥1 dose of study drug

*Based on 4 MedDRA preferred terms. †Based on 1 standardised MedDRA query

§Based on 8 MedDRA preferred terms. **Based on 1 standardised MedDRA query

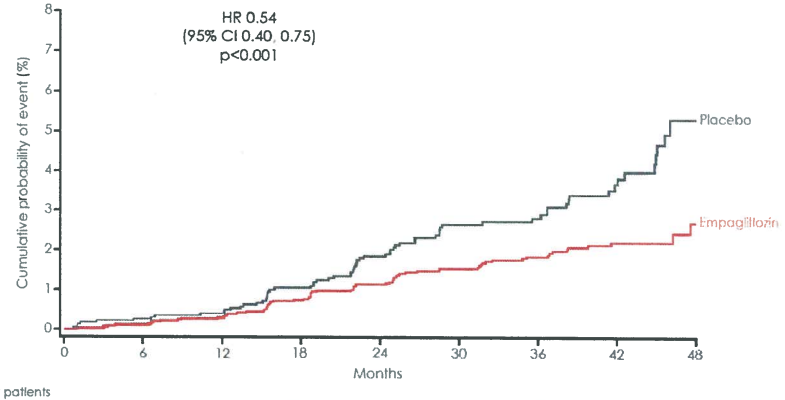
Renal function

eGFR (CKD-EPI formula) over 192 weeks



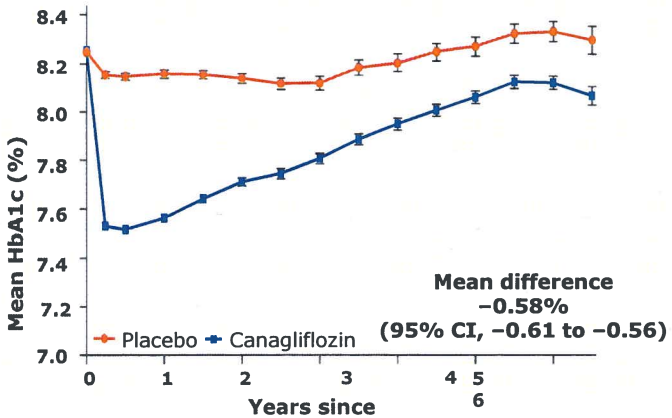
No. analyzed														
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg*	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in follow-up for adverse/outcome events															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6088	5114	4443	3961	3488	2707	1703

Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease



No. of patients									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

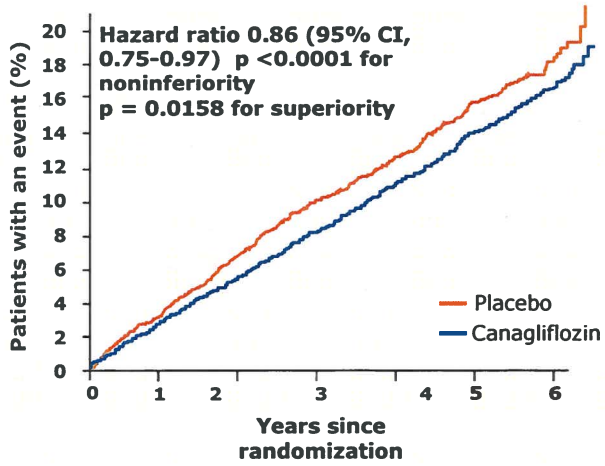
Effects on HbA1c



No. of patients							
Placebo	4231	3854	2891	1014	899	805	695
Canagliflozin	5644	5211	4228	2206	2042	1889	1661

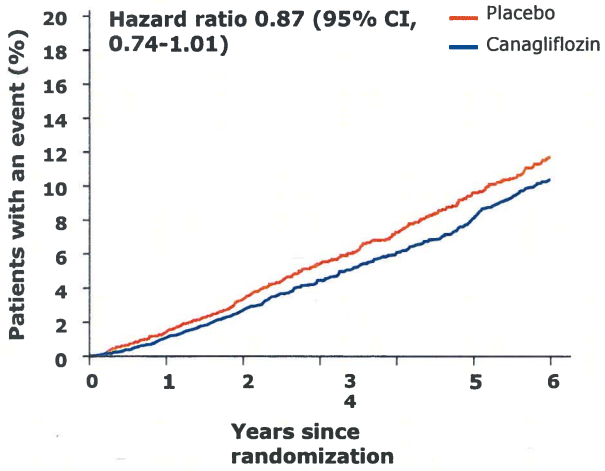
Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



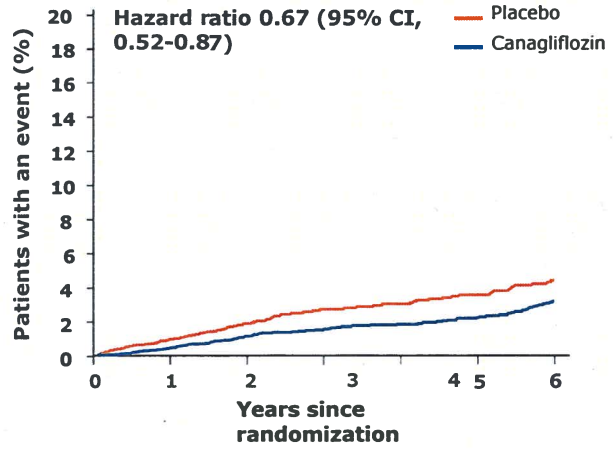
No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

All-Cause Mortality



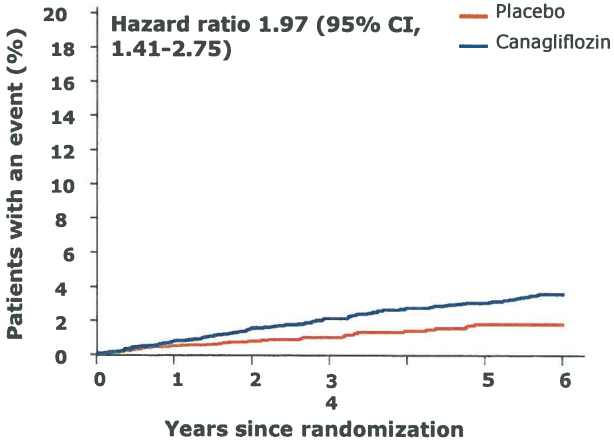
No. of patients							
Placebo	4347	4279	3119	1356	1328	1292	924
Canagliflozin	5795	5723	4576	2761	2710	2651	1904

Hospitalization for Heart Failure



No. of patients							
Placebo	4347	4198	3011	1274	1236	1180	829
Canagliflozin	5795	5653	4437	2643	2572	2498	1782

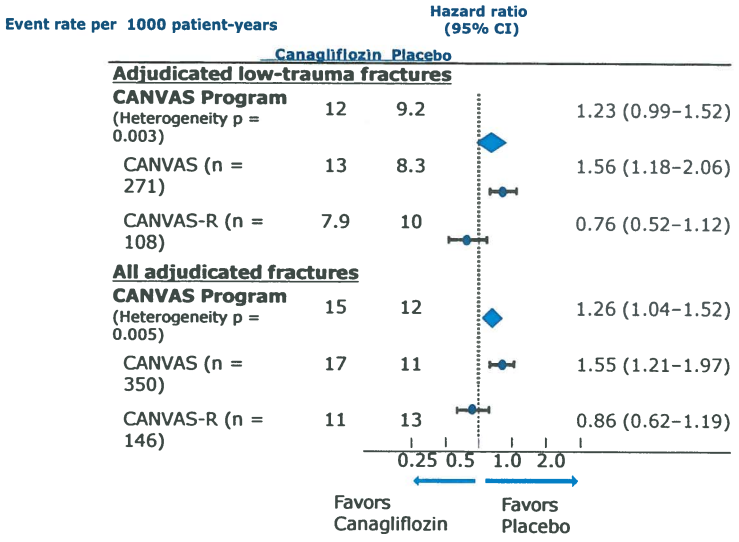
Lower-extremity Amputations



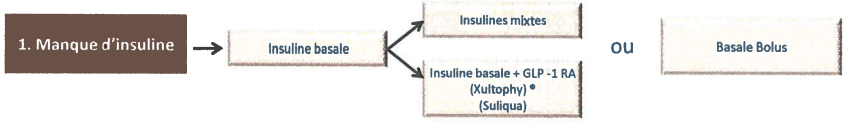
No. at risk

Placebo	4344	4217	3037	1289	1247	1194	844
Canagliflozin	5790	5634	4420	2618	2536	2460	1765

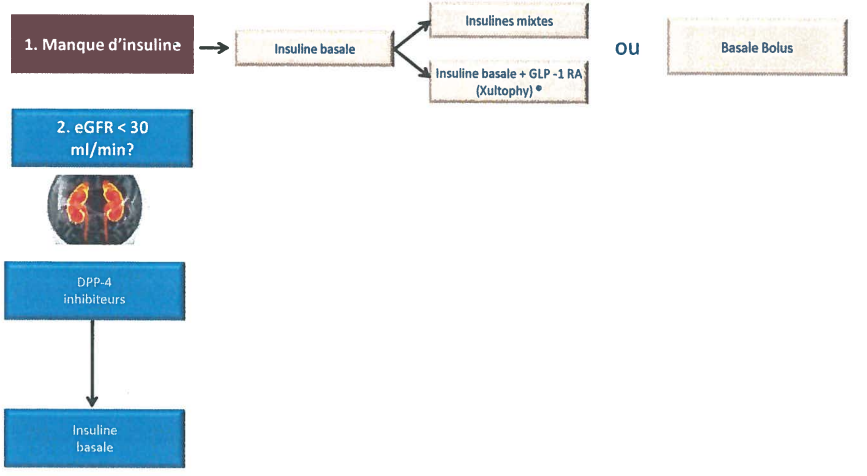
Fractures



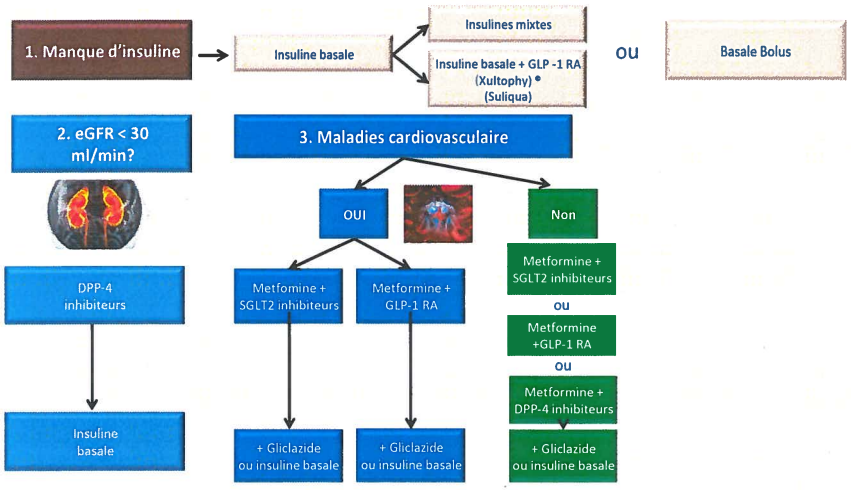
Les quatre questions cléfs des recommandations de la SSED/SGED: 1. Manque d'insuline



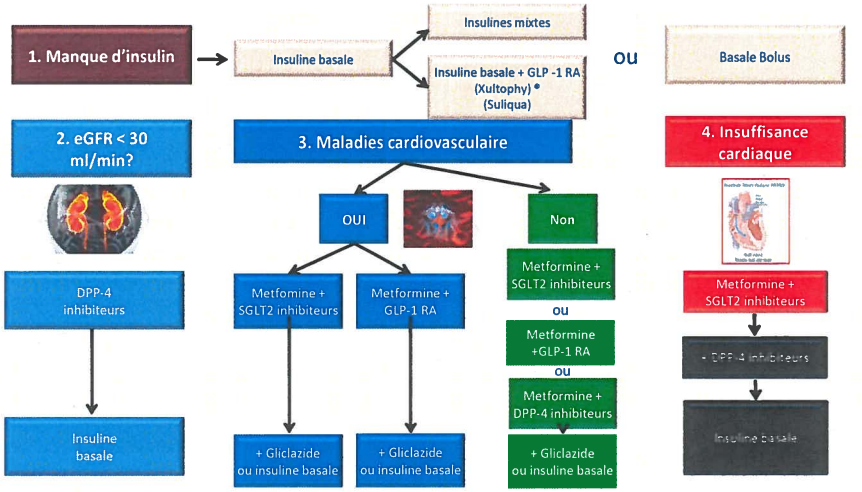
Les quatre questions cléfs des recommandations de la SSED/SGED: 2. Fonction Rénale?



Les quatre questions cléfs des recommandations de la SSED/SGED: 3. Maladies Cardiovasculaires?



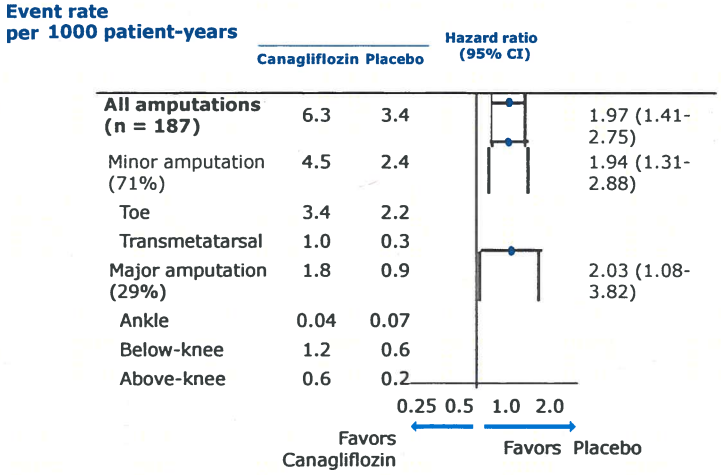
Les quatre questions cléfs des recommandations de la SSED/SGED: 4. Insuffisance Cardiaque?



Conclusions

- Les gliflozines sont devenues des traitements utiles, efficaces sur le contrôle glycémique et qui diminue la mortalité cardio-vasculaire
- Elles s'accompagnent d'une perte de poids sans hypoglycémie
- Les effets secondaires(infections urinaires et génitales, autres…) sont à prendre en considération chez des patients à risque

Highest Level of Amputation



Amputation Risk Factors - Multivariate Analysis

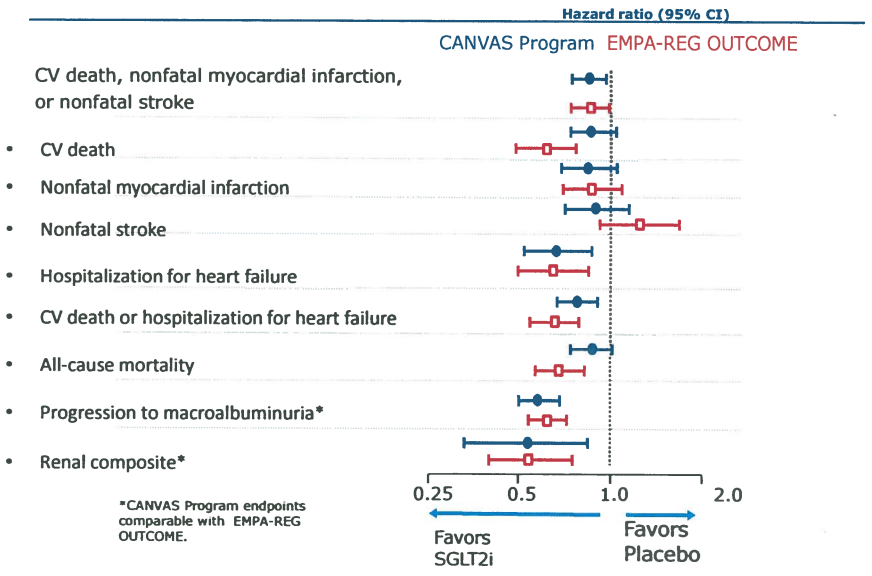
Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.4	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

* Excludes amputations

Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

Risk reduction across CVOT studies

	EMPA-REG[1]	CANVAS[2]	LEADER
MACE	14% (HR: 0.86; CI 0.74-0.99) (p=0.04)	14% (HR: 0.86; CI 0.75-0.97) (p=0.02)	13% (HR: 0.87; CI 0.78-0.97) (p<0.001)
- non-fatal stroke	NS (HR: 1.24; CI 0.92-1.67) (p=0.16)	NS (HR: 0.90; CI 0.71-1.15)	NS (HR: 0.89; CI 0.72-1.11) (p=0.30)
- non-fatal MI	NS (HR: 0.87; CI 0.70-1.09) (p=0.22)	NS (HR: 0.85; CI 0.69-1.05)	NS (HR: 0.88; CI 0.75-1.03) (p=0.11)
- CV death	38% (HR: 0.62, CI: 0.49–0.77) (p<0.001)	NS (HR: 0.87; CI 0.72-1.06)	22% (HR: 0.78; CI 0.66-0.93) (p=0.007)
All-cause mortality	32% (HR: 0.68, CI: 0.57–0.82) (p<0.001)	-	15% (HR: 0.85; CI 0.74-0.97) (p=0.02)
Hospitalization for HF	35% (HR: 0.65, CI: 0.50–0.85) (p<0.001)	33% (HR: 0.67; CI 0.52-0.87)	NS (HR: 0.87; CI 0.73-1.05) (p=0.14)
Hospitalization for CKD	-	-	

CV, cardiovascular; DAPA, dapagliflozin; HF, heart failure; MACE, major adverse cardiac event; MI, myocardial infarction.
1. Zinman B, *et al. N Engl J Med* 2015;373:2117–212; 2. CANVAS results; 3. Kosiborod M on behalf of the CVD-REAL Investigators and Study Team. Presented at: 66th Annual Scientific Session & Expo of the American College of Cardiology; March 17–19, 2017; Washington, DC; 4. Norhammar A on behalf of the CVD-REAL Investigators and Study Team. Poster presented at: European Society of Cardiology Heart Failure and 4th World Congress on Acute Heart Failure; April 29–May 2, 2017; Paris.

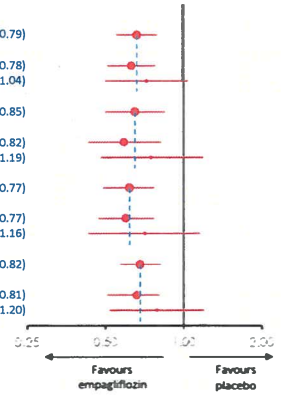
Contents(Cont.)

Contents(Cont.)

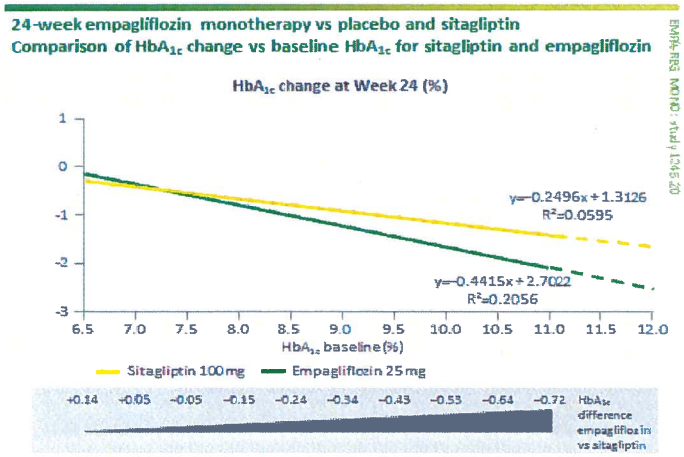
- Pharmacological properties
  - Pharmacokinetic properties – **Elimination**
    - 50% excreted in faeces.
    - 30% excreted in urine.
    - Renal clearance of 100 mg and 300 mg doses ranged from 1.30 mL/min to 1.55 mL/min.
    - Enterohepatic circulation of canagliflozin was negligible.

Outcomes in patients with and without heart failure at baseline

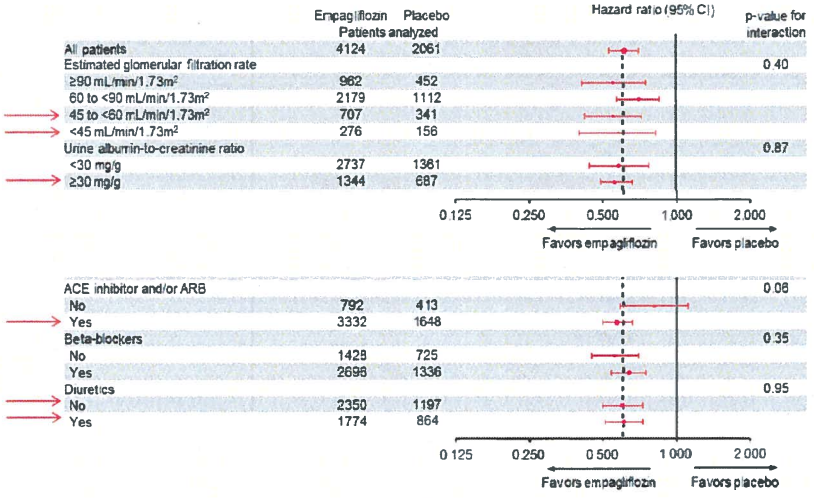
	Empagliflozin		Placebo		
	n with event/*n*	%	*n* with event/*n*	%	HR (95% CI)
Heart failure hospitalisation or cardiovascular death					
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline					
No	190/4225	4.5	149/2089	7.1	0.63 (0.51–0.78)
Yes	75/462	16.2	49/244	20.1	0.72 (0.50–1.04)
Hospitalisation for heart failure					
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline					
No	78/4225	1.8	65/2089	3.1	0.59 (0.43–0.82)
Yes	48/462	10.4	30/244	12.3	0.75 (0.48–1.19)
Cardiovascular death					
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49–0.77)
Heart failure at baseline					
No	134/4225	3.2	110/2089	5.3	0.60 (0.47–0.77)
Yes	38/462	8.2	27/244	11.1	0.71 (0.43–1.16)
All-cause mortality					
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline					
No	213/4225	5.0	159/2089	7.6	0.66 (0.51–0.81)
Yes	56/462	12.1	35/244	14.3	0.79 (0.52–1.20)



Effet comparé de la sitagliptine et de l'empagliflozine selon l'HbA1c



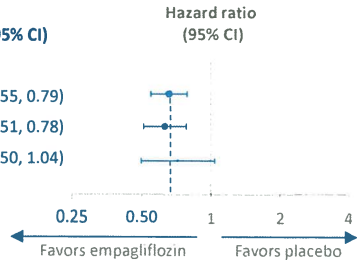
EMPA-REG Subgroup analyses for incident or worsening nephropathy



No increased events of volume depletion or acute renal failure

Heart failure hospitalization or CV death by heart failure at baseline

	Patients with event/analyzed		
	Empagliflozin	Placebo	HR (95% CI)
Heart failure hospitalization or CV death			
All patients	265/4687	198/2333	0.66 (0.55, 0.79)
Baseline HF: No	190/4225	149/2089	0.63 (0.51, 0.78)
Baseline HF: Yes	75/462	49/244	0.72 (0.50, 1.04)



Inhibiteurs SGLT-2 — Propriétés pharmacocinétiques

- Excellent oral bioavailability
- Long elimination half life allowing once-daily administration
- Low accumulation index
- No active metabolites
- Limited renal excretion
- No clinically relevant drug-drug interactions

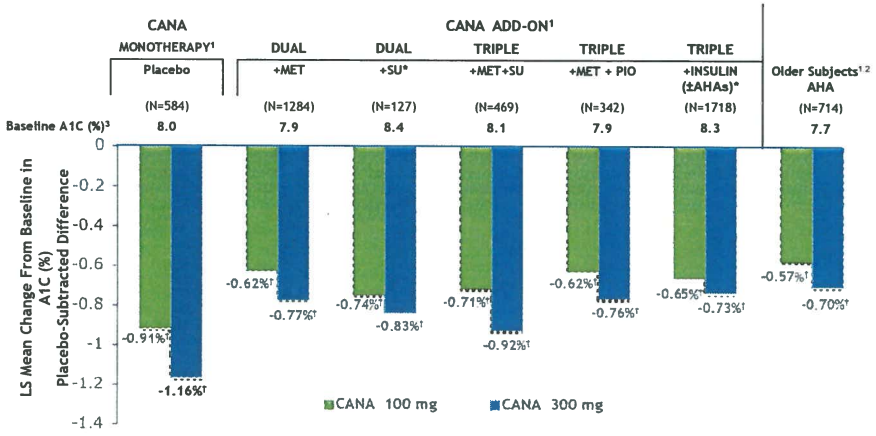
Table 2. Pharmacokinetics and Pharmacodynamics of SGLT-2 Inhibitors[33–40]

	Dapagliflozin	Canagliflozin	Empagliflozin
Half-life ($t_{1/2}$)	8.1–18.25 hrs	12 hrs	NA
T_{max}	1–4 hrs	1 hr	0.7–3 hrs[a]
24-hr urinary glucose excretion	52–85 g 11–13 g with $Cl_{cr} \leq 30$ ml/min	~70 g	NA
SGLT-2 selectivity	> 1200-fold over SGLT-1	> 250-fold over SGLT-1	> 2500-fold over SGLT-1

[a]In rats and dogs.

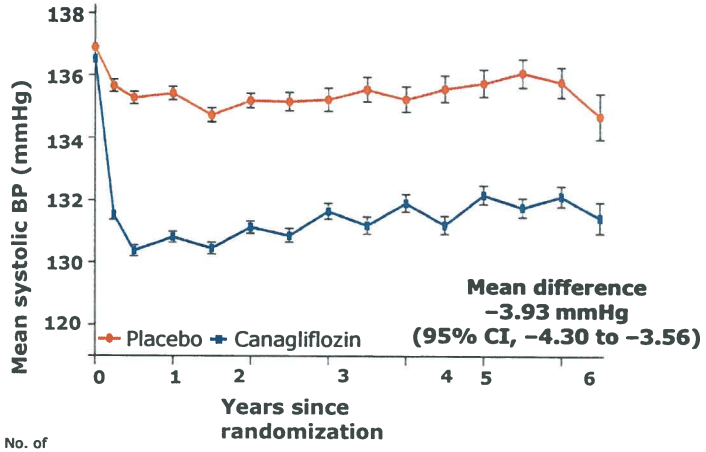
Riser Taylor, Harris KB, *Pharmacotherapy. 2013*
Scheen *Drugs 1.2015*

Efficacy Summary:
CANA Placebo-Controlled Studies at week 26



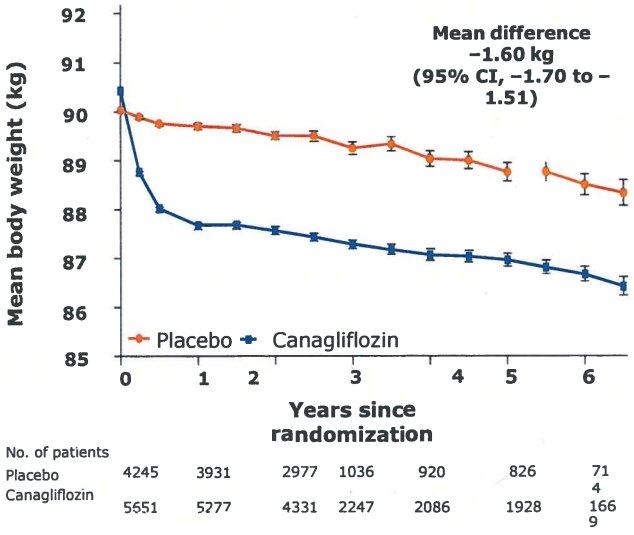
*Studies for combinations including SU or insulin were 18 weeks in duration; all others were 26 weeks in duration.
†$P<.001$ for reduction vs control.

Effects on Systolic BP



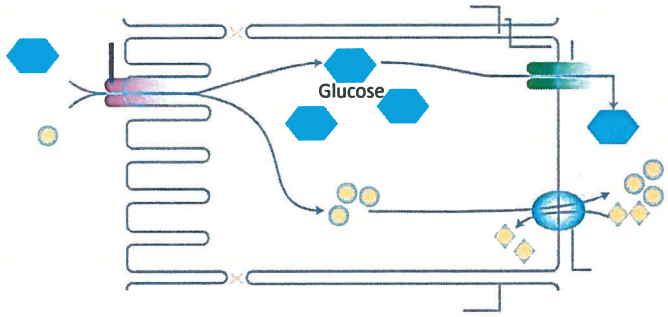
No. of patients							
Placebo	4247	3945	2979	1038	922	828	713
Canaoliflozin	5652	5293	4338	2255	2092	1936	1675

Effects on Body Weight



No. of patients							
Placebo	4245	3931	2977	1036	920	826	714
Canagliflozin	5651	5277	4331	2247	2086	1928	1669

SGLT2 is a sodium glucose cotransporter[1,2]



- SGLTs transfer glucose and sodium (Na^+:glucose coupling ratio for SGLT1=2:1 and for SGLT2=1:1) from the lumen into the cytoplasm of tubular cells through a secondary active transport mechanism

1. Wright EM, et al. *Physiology*. 2004;19:370–376; 2. Bakris GI, et al. *Kidney Int*. 2009;75:1272–1277.

Other adverse events (2)

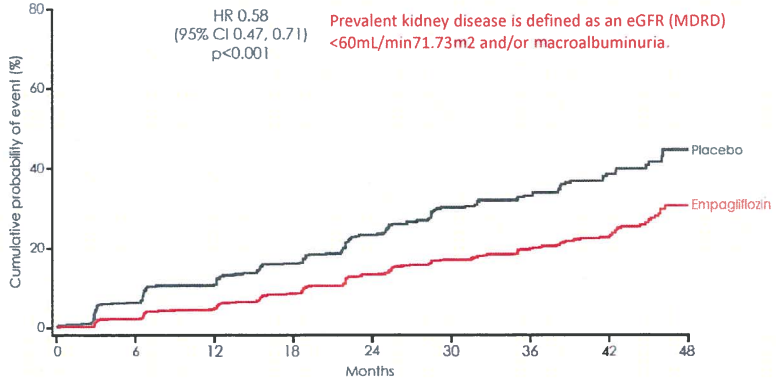
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Hepatic injury*	108 (4.6%)	1.91	80 (3.4%)	1.35	88 (3.8%)	1.48
Hypersensitivity*	197 (8.4%)	3.59	158 (6.7%)	2.75	181 (7.7%)	3.14
Bone fractures†	91 (3.9%)	1.61	92 (3.9%)	1.57	87 (3.7%)	1.46

Rate = per100 patient-years

Patients treated with ≥1 dose of study drug
*Based on standardised MedDRA queries
†Based on 62 MedDRA preferred terms

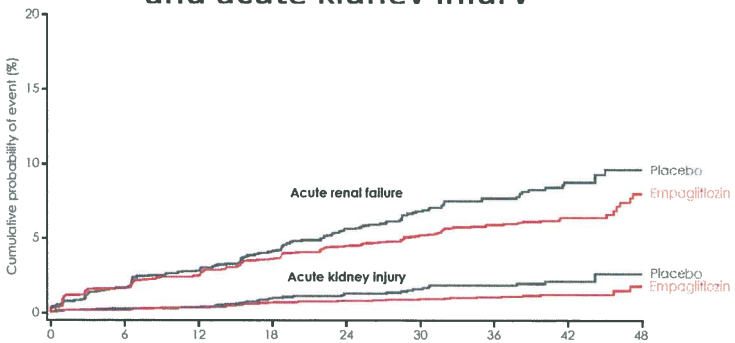
55

Incident or worsening nephropathy in patients with prevalent kidney disease*



No. of patients									
Empagliflozin	998	952	895	836	694	516	420	273	69
Placebo	507	462	425	377	302	206	172	102	23

Acute renal failure and acute kidnev iniurv



No. of patients									
Acute renal failure									
Empagliflozin	4687	4359	4159	3937	3398	2463	1897	975	268
Placebo	2333	2167	2031	1889	1588	1133	866	403	108
Acute kidney injury									
Empagliflozin	4687	4415	4238	4037	3505	2545	1965	1014	279
Placebo	2333	2194	2078	1944	1653	1178	902	427	111