SGLT2 Inhibitors: A novel and important new class of antihyperglycemic agent

Lawrence A Leiter, MD FRCPC FACP FAHA
Division of Endocrinology & Metabolism,
St. Michael's Hospital
Professor of Medicine & Nutritional Sciences,
University of Toronto

Disclosure

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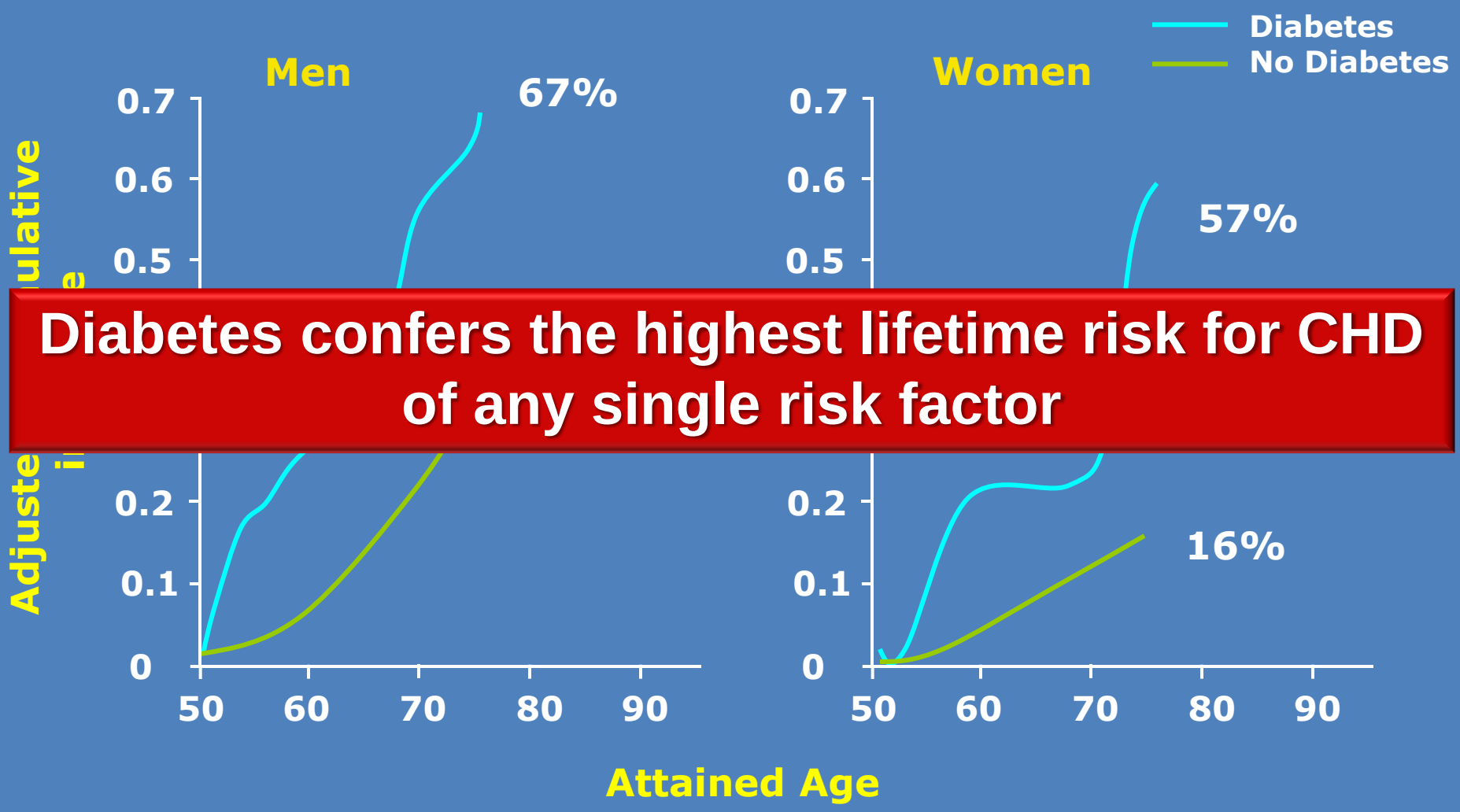
AstraZeneca, BMS, BI, Eli Lilly
GSK, Janssen, Merck, Novo Nordisk
Roche, Sanofi, Servier, Takeda

Diabetes and Lifetime Risk for CHD



Diabetes confers the highest lifetime risk for CHD of any single risk factor

Lloyd Jones et al Circ 2006;113:791

Americans More Fearful of Shark Bites than Diabetes

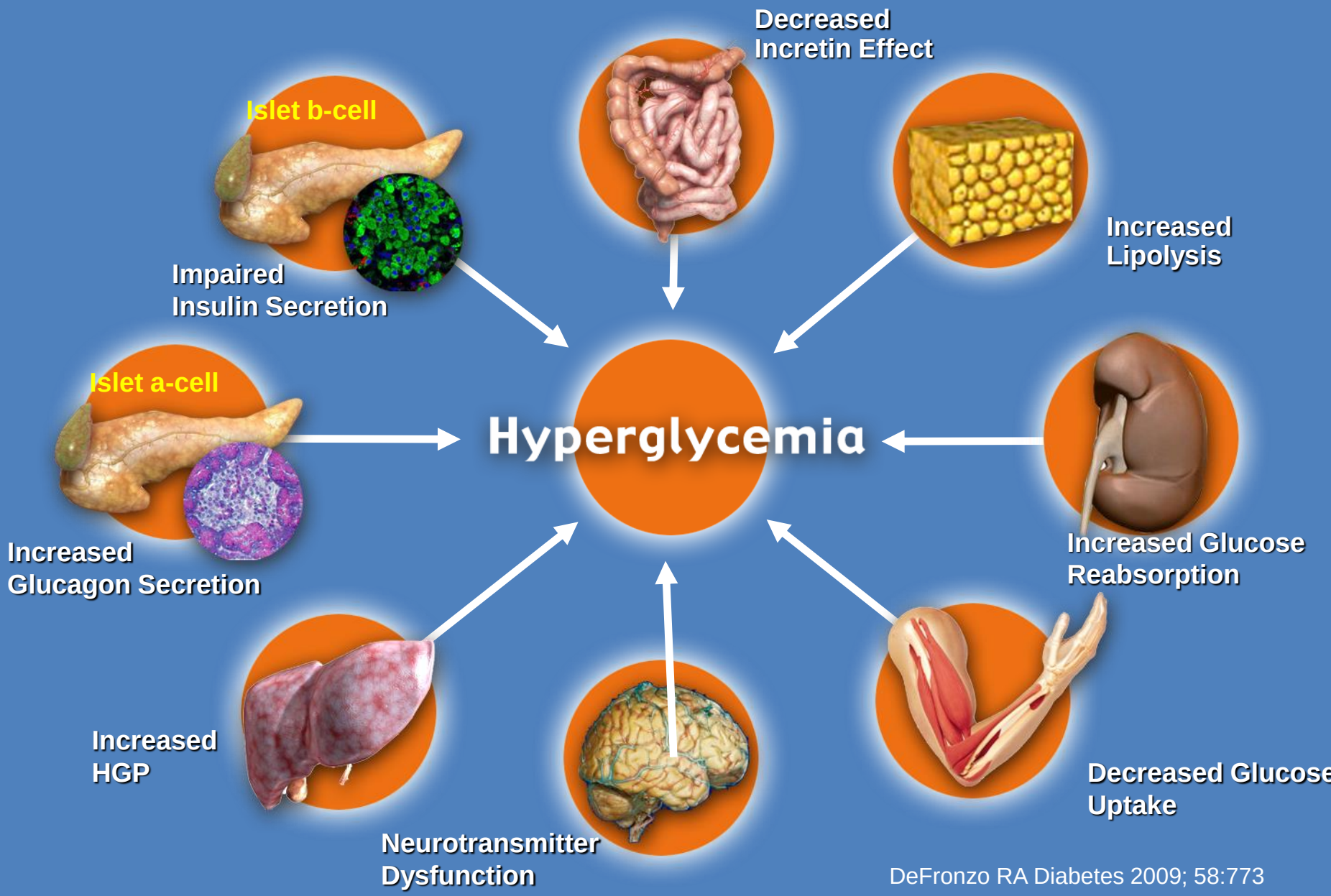
ADA Survey 2008

Fear of health problem

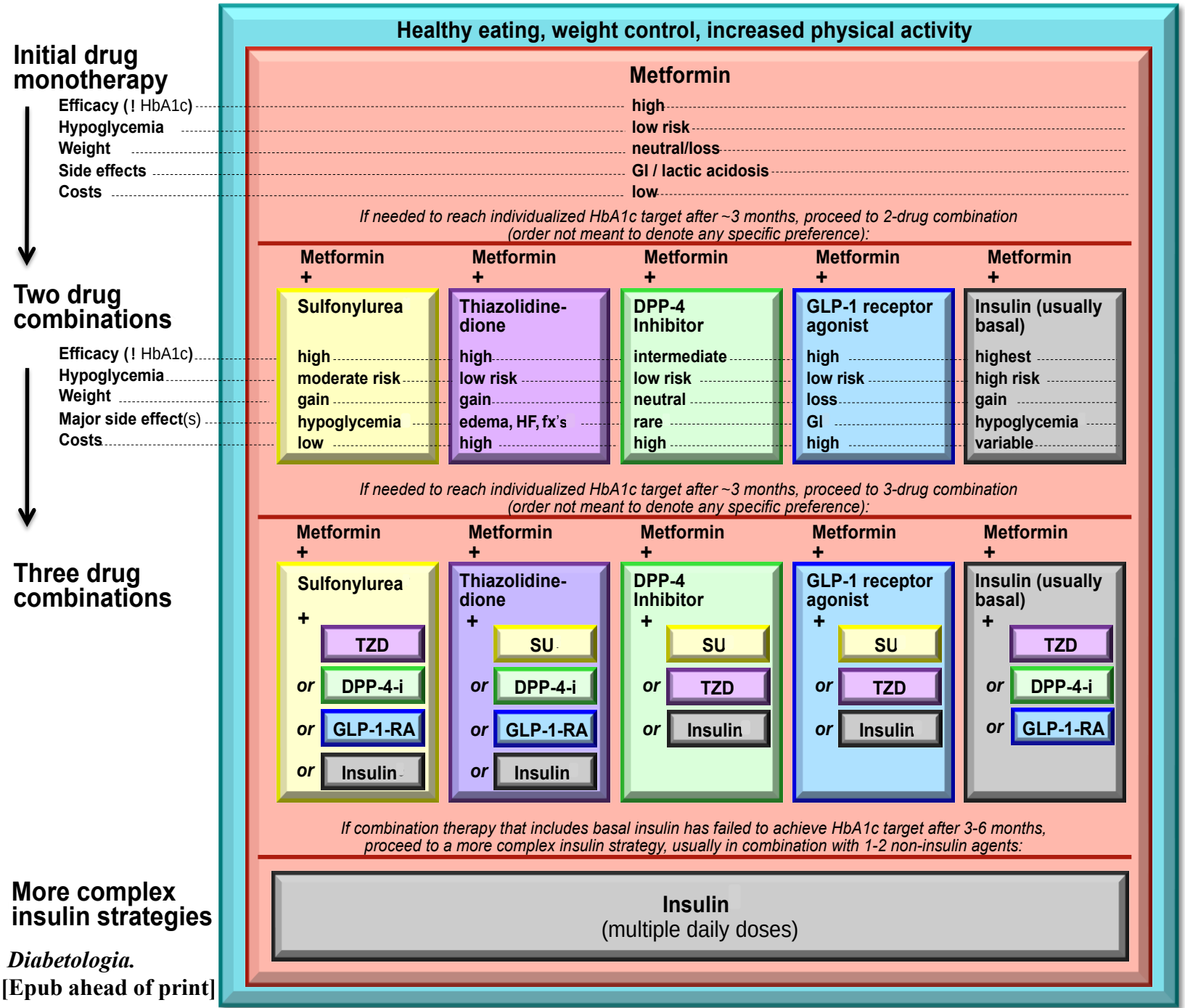
- Cancer 49%
- Heart disease 12%
- Stroke 11%
- Shark bite 4%
- Diabetes 3%

Shark attacks	70 / year
Deaths related to diabetes	233,000 /year

Pathophysiological Defects of Type 2 Diabetes
DeFronzo's "Ominous Octet"



DeFronzo RA Diabetes 2009; 58:773



Diabetes Care, Diabetologia.
19 April 2012 [Epub ahead of print]

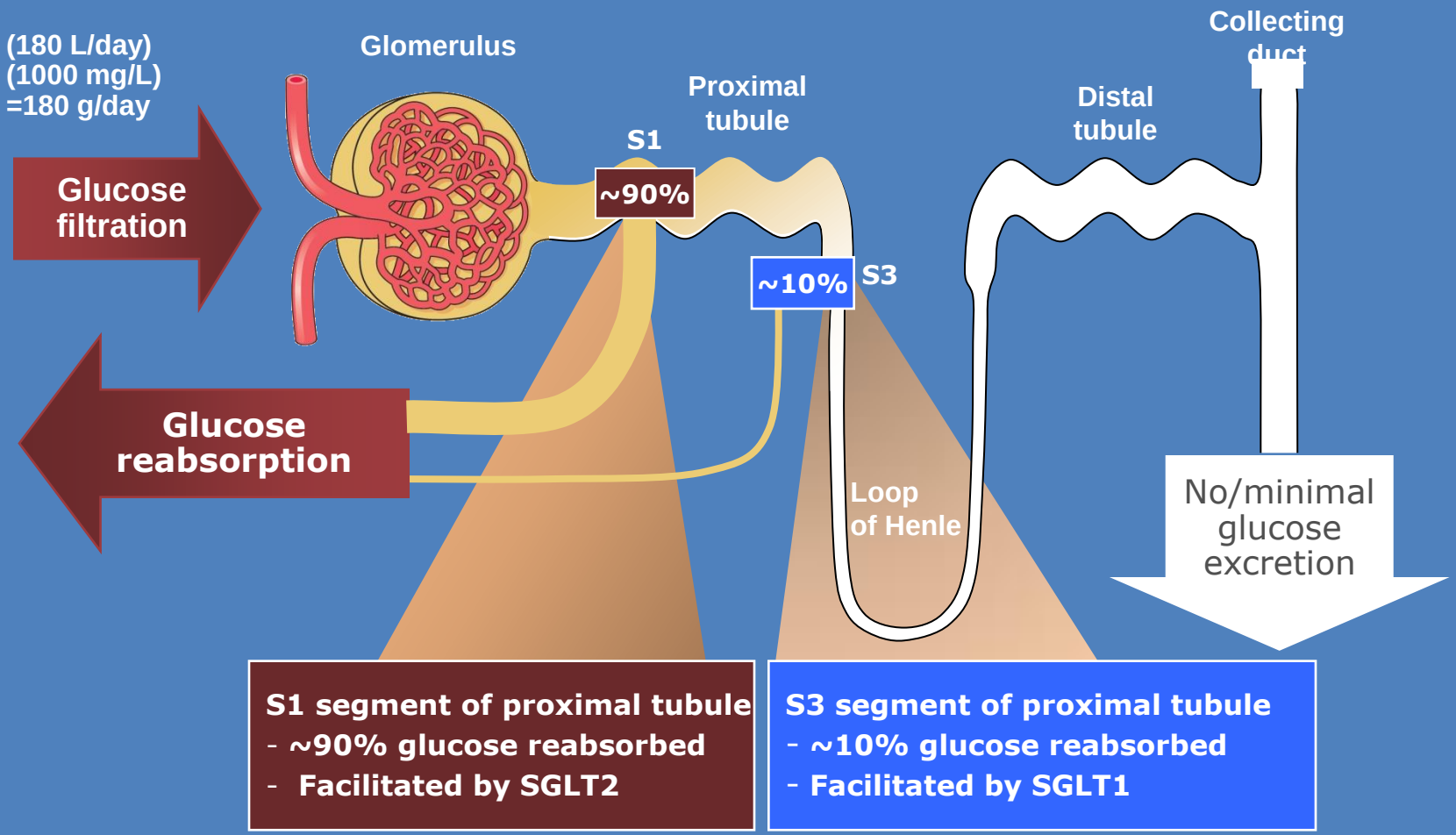
What is the ideal first add-on to metformin?

Network meta-analysis comparing non-insulin antihyperglycaemic drugs with placebo as add-on to metformin

	Change in HbA_{1C}	HbA_{1C} goal achieved	Change in body weight	Overall hypoglycemia
	Mean difference	RR	Mean difference	RR
Placebo (ref)	0	1	0	1
Sulfonylureas	–0.79	2.49	2.06	4.57
Meglitinides	–0.65	2.25	1.77	7.50
TZDs	–0.85	2.71	2.08	0.56
AGIs	–0.64	ND	–1.80	0.42
DPP-4 inhibitors	–0.78	2.51	–0.14	0.63
GLP-1 agonists	–0.97	3.20	–1.74	0.89

Phung O, *et al*. *JAMA* 2010;303:1410–18.

Renal handling of glucose in non-diabetic individuals



SGLT = Sodium-dependent glucose transporter

Adapted from:
1. Bailey CJ. Trends in Pharmacol Sci 2011;32:63-71.
2. Chao EC. Core Evidence 2012;7:21-28.

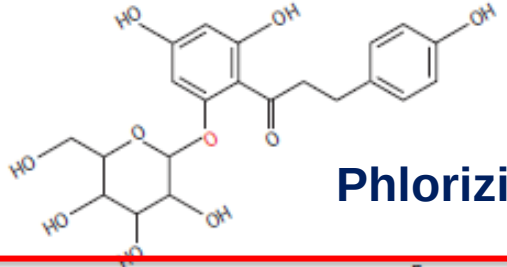
SGLT Family of Transporters

Transporter	Distribution	Function
SGLT1	Small intestine, heart, trachea, kidney	Active cotransport of sodium, glucose, and galactose across the brush border of intestine and proximal tubule of kidney
SGLT2	Kidney	Active cotransport of sodium and glucose in the S1 segment of the proximal tubule of kidney
SGLT3	Small intestine, uterus, lungs, thyroid, and testis	Active transport of sodium (not glucose)
SGLT4	Small intestine, kidney, liver, stomach, lung	Transport of glucose and mannose
SGLT5	Kidney	Unknown
SGLT6	Spinal cord, kidney, brain, and small intestine	Transport of myo-inositol and glucose

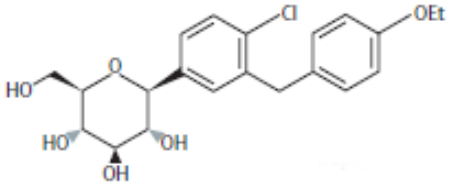
SGLT = Sodium-dependent glucose transporter

Adapted from:
1. Bays H. Curr Med Res Opin. 2009;25:671-681.

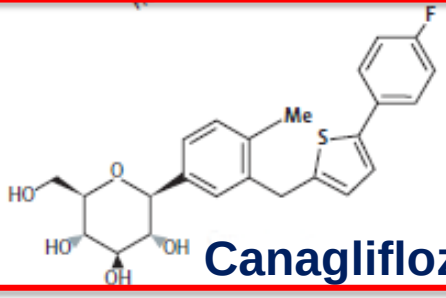
SGLT1 and SGLT2 Inhibitors



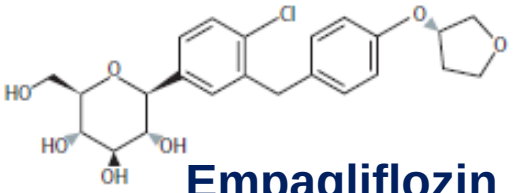
Phlorizin



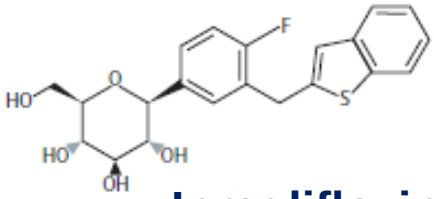
Dapagliflozin



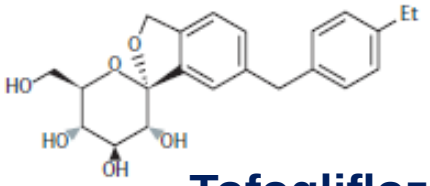
Canagliflozin



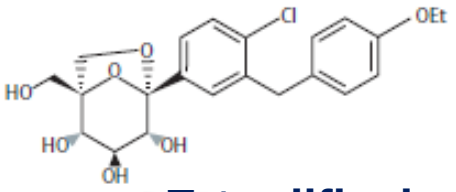
Empagliflozin



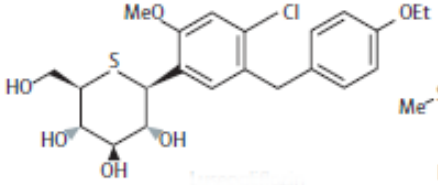
Ipragliflozin



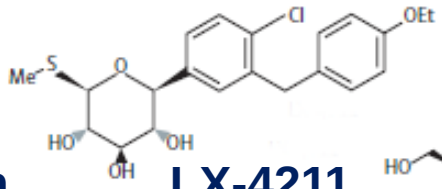
Tofogliflozin



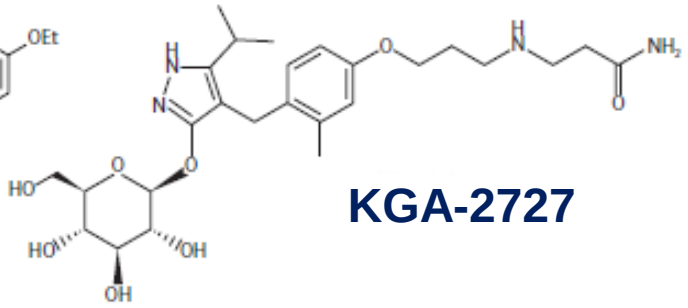
Ertugliflozin



Luseogliflozin



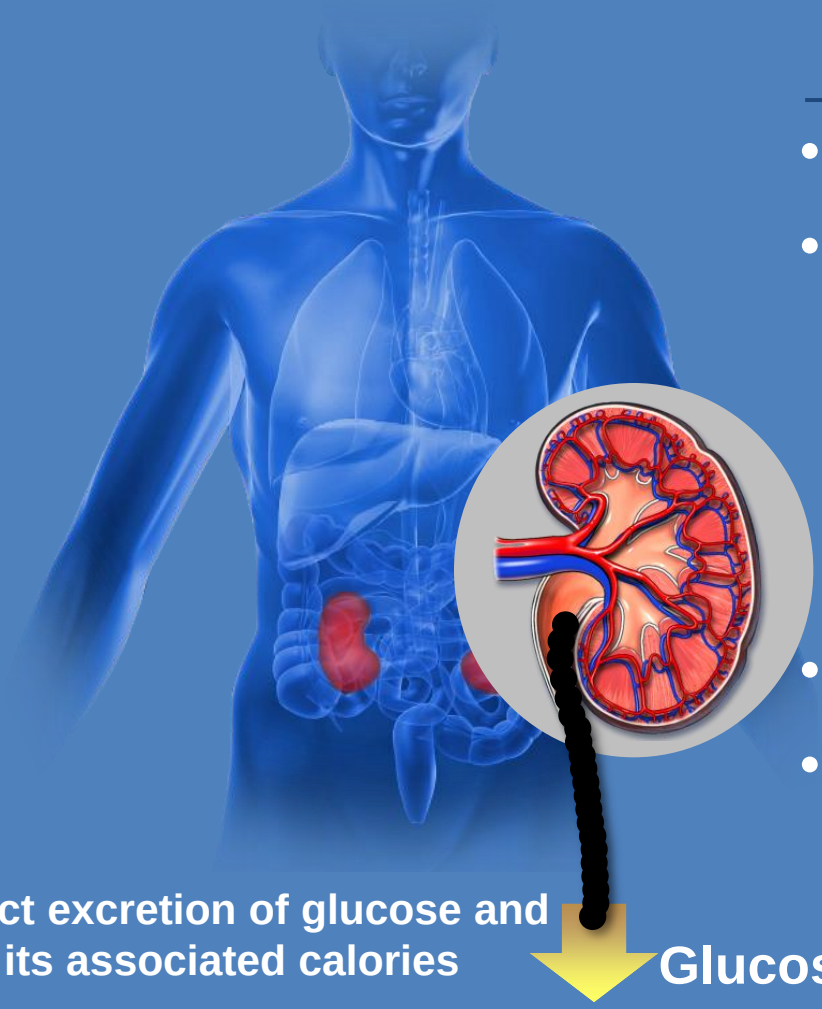
LX-4211



KGA-2727

Tahrani AA. The Lancet Diabetes & Endocrinology. 2013. http://dx.doi.org/10.1016/S2213-8587(13)70050-0.

Effect of SGLT2 Inhibition (Mode of Action)



Direct excretion of glucose and its associated calories

Glucosuria

SGLT: sodium-glucose co-transporter

Potential Benefits

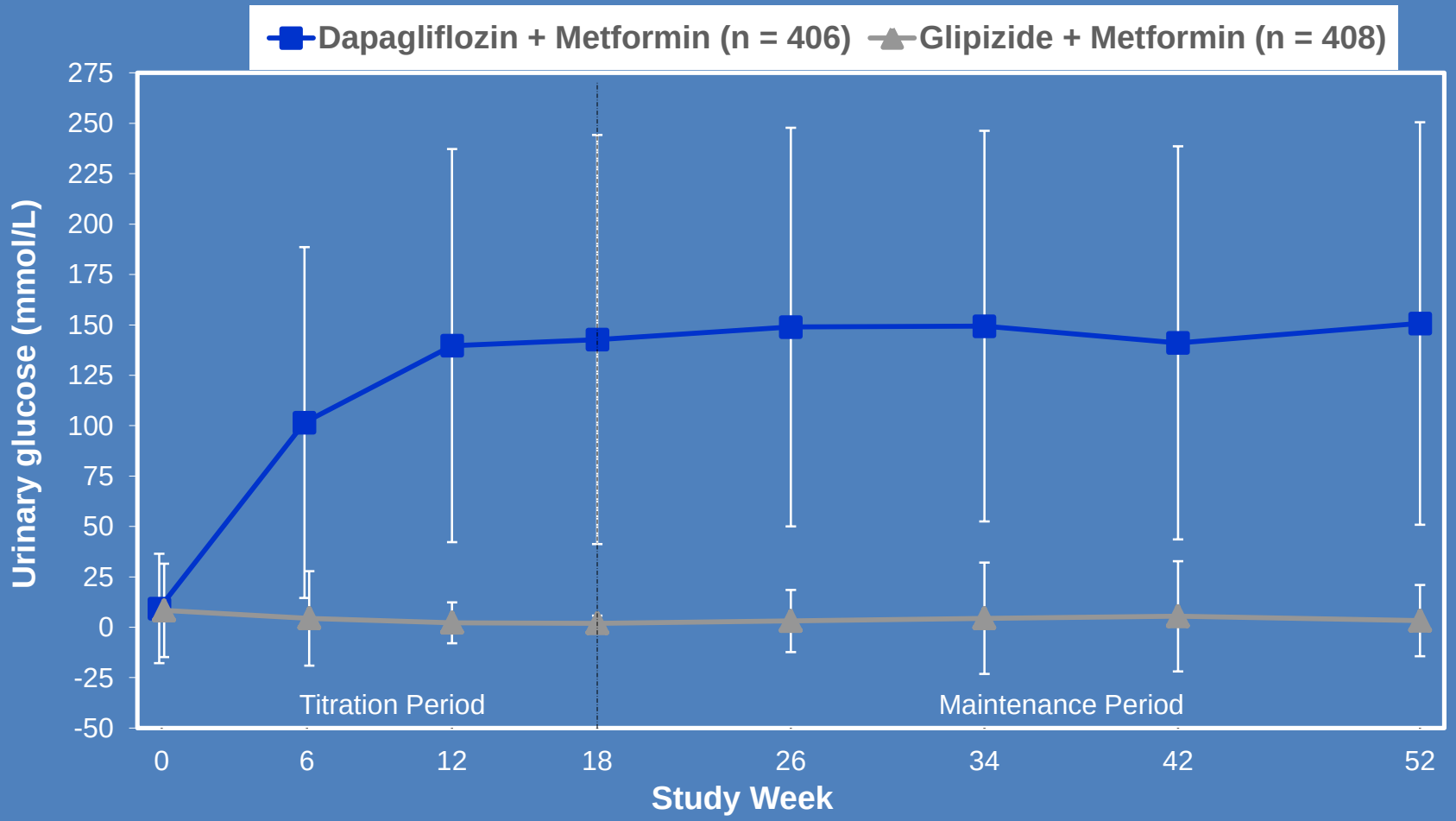
- Insulin-independent
- Glycaemic benefits
  - HbA1c
  - Fasting plasma glucose (FPG)
  - Postprandial glucose (PPG)
- Body weight benefits
- Blood pressure benefits

Potential Risks

- Hypoglycaemia
- Renal function
- Diuretic effect
  - Hypovolaemia
  - Hypotension
  - Dehydration
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis

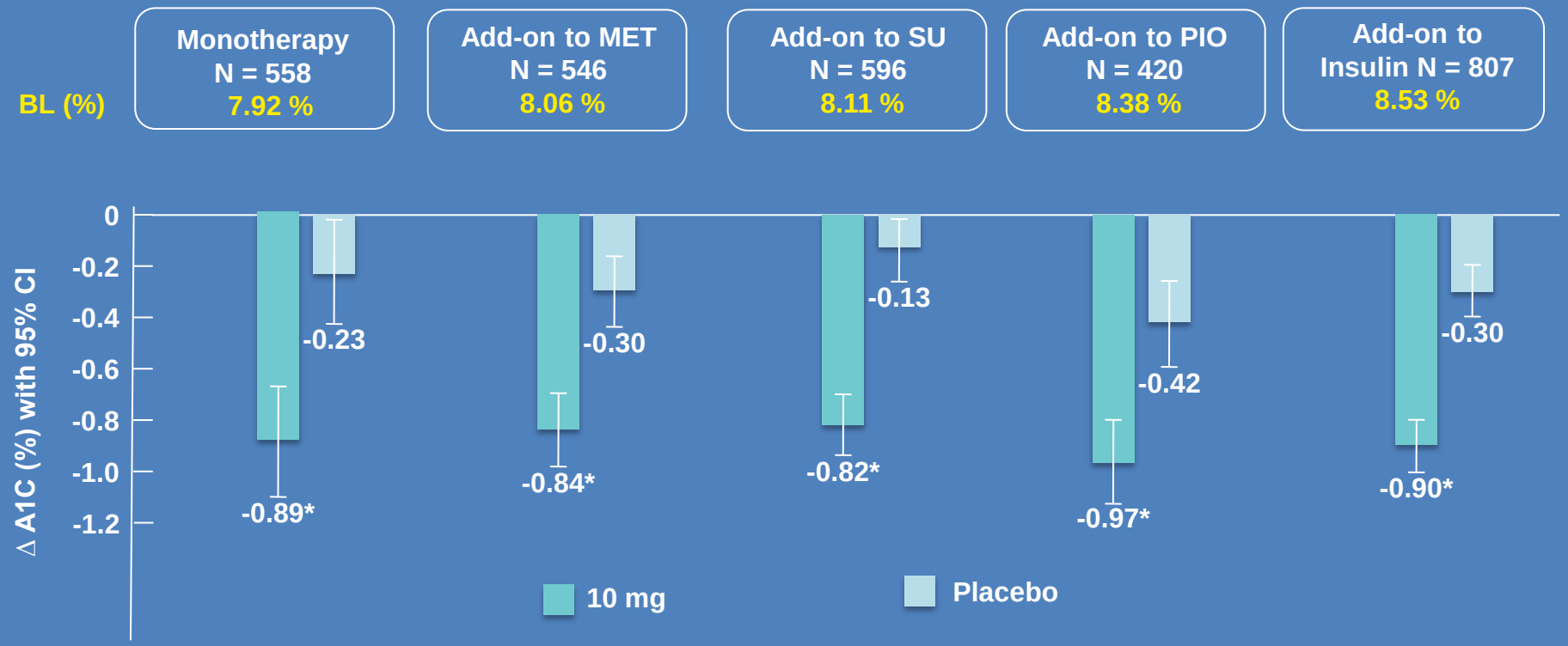
FDA Advisory Committee 19th July 2011: http://www.fda.gov

Increased Urinary Glucose Excretion in Longer Term with Dapagliflozin



Nauck MA, et al. *Diabetes* 2011;34:2015-22.

Dapagliflozin: A1C Change from Baseline in Placebo-Controlled Studies

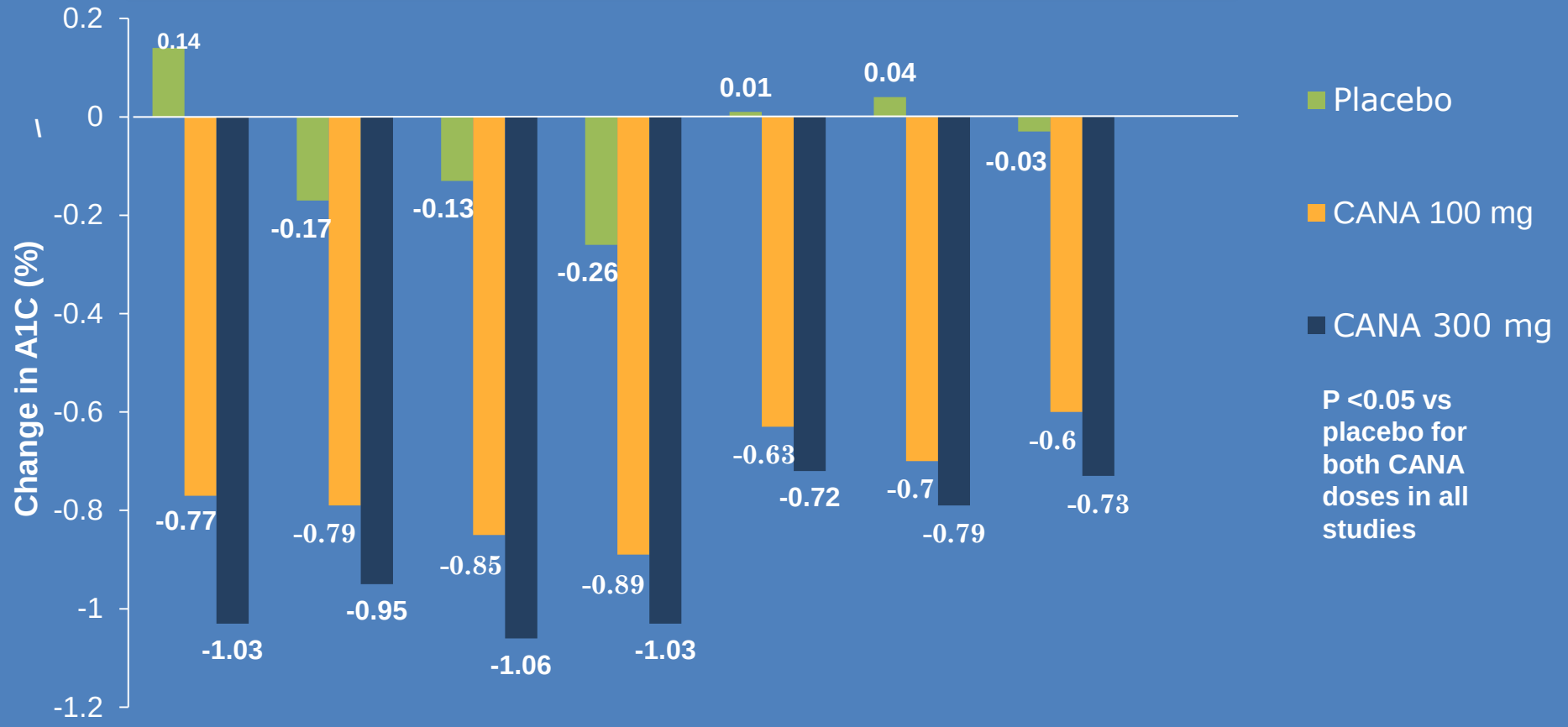


*Statistically significant vs. placebo using Dunnett's correction
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

1. Ferrannini E, et al. Diabetes Care 2010; doi:10.2337/dc10-0612.
2. Bailey CJ, et al. Lancet 2010; 375:2223-33.
3. Nauck M, et al. Diabetologia 2010; 53 (suppl 1):S107. Abstract 241.
4. Stroiek K. Diabetologia 2010; 53 (suppl 1):S347. Abstract 870.
5. Wilding J, et al. Diabetes 2010; 59 (suppl 1):A21-A22. Abstract 0078-OR.
6. Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

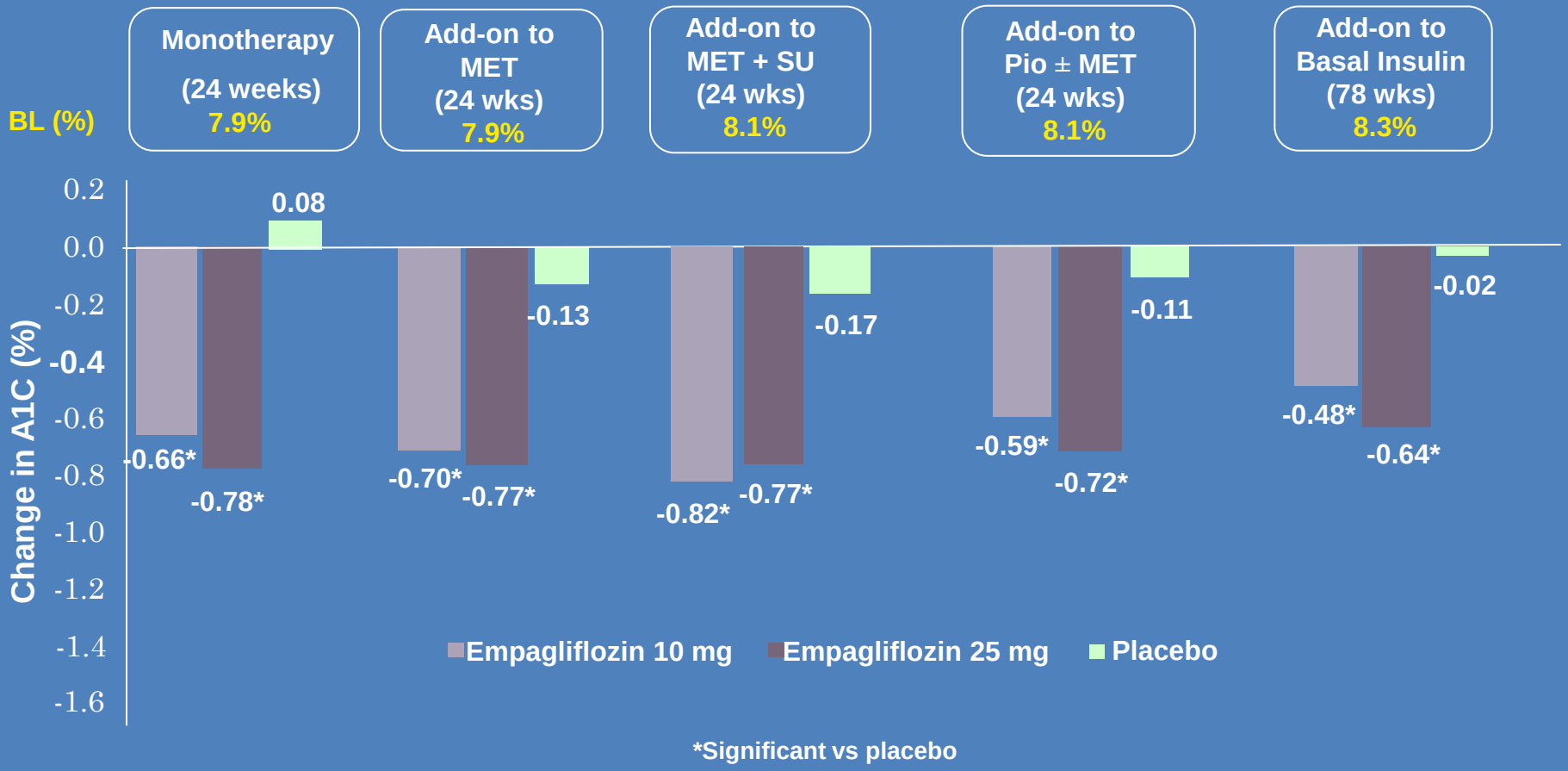
Canagliflozin: A1C Change from Baseline in Placebo-Controlled Studies

	Mono	Add on to MET	Add on to MET/SU	Add on to Met/Pio	Add on to Insulin	Add on to SU	Add on to AHA's in older subjects
Baseline A1C (%)	8.01%	7.94%	8.13%	7.9%	8.27%	8.35%	7.7%



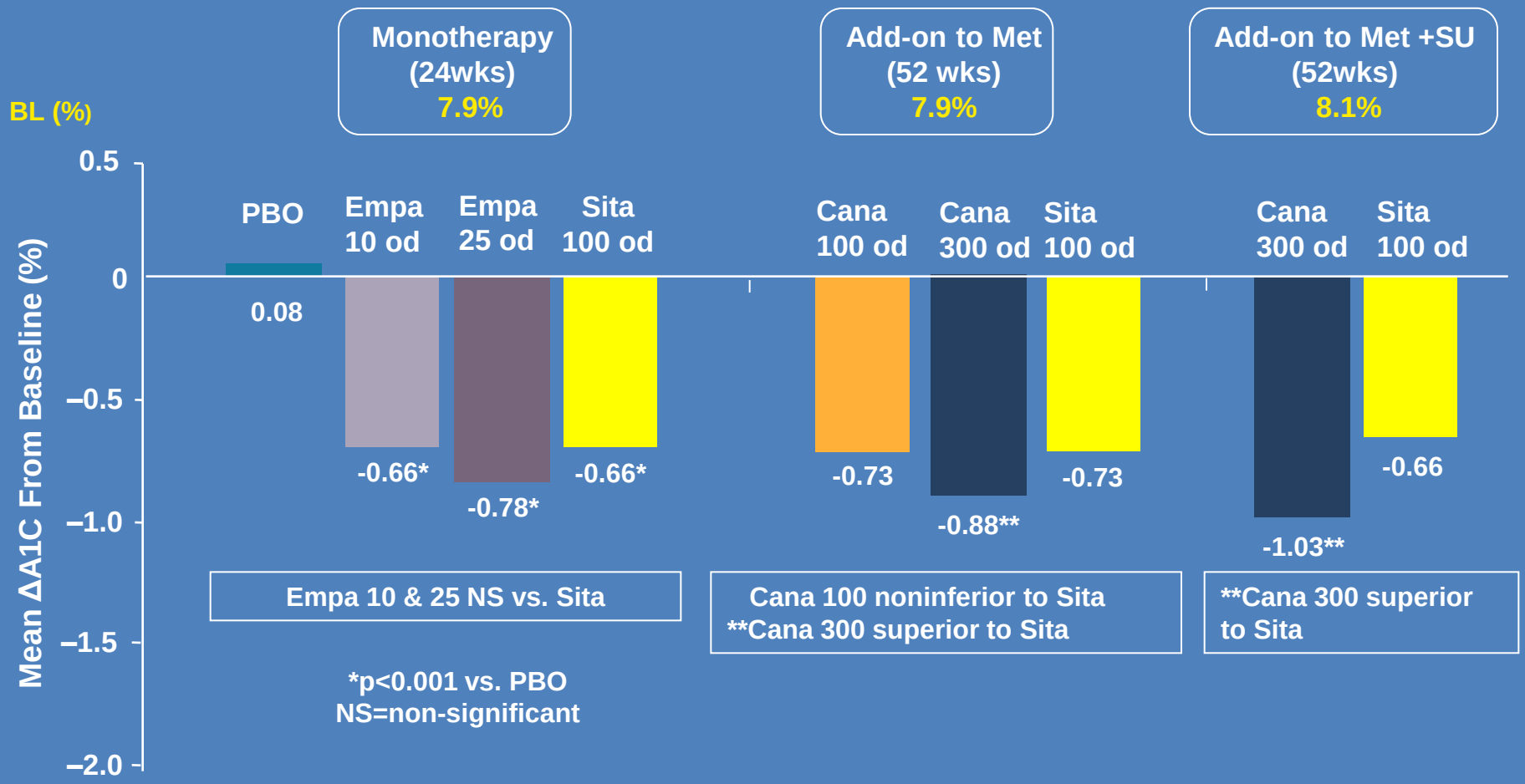
Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

Empagliflozin: A1C Change from Baseline in Placebo-Controlled Trials



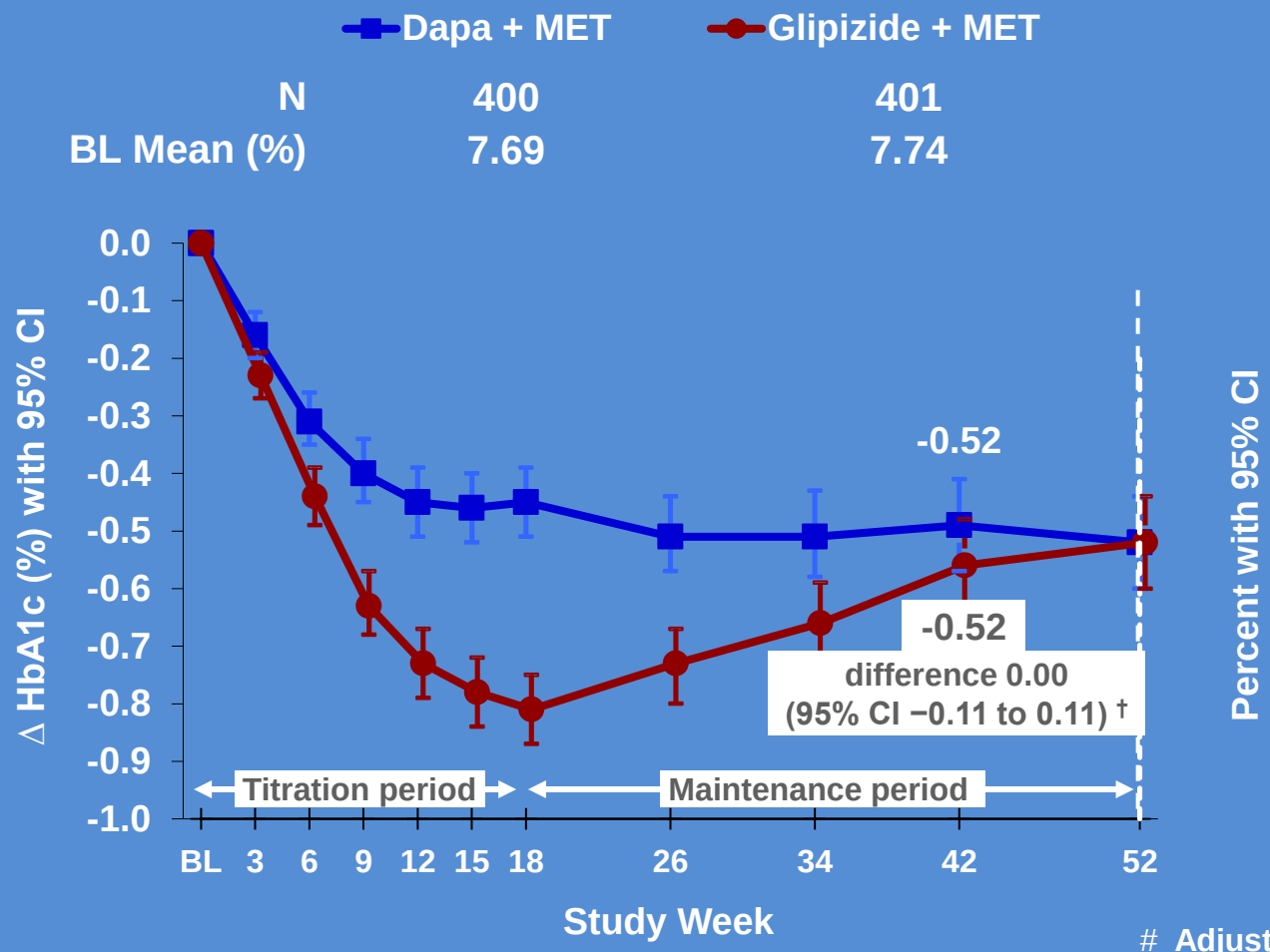
Roden M et al. ADA Annual Meeting 2013. Abstract 1085-P. Haring H et al. ADA Annual Meeting 2013. Abstract 1092-P. Haring H et al. ADA Annual Meeting 2013. Abstract 1082-P. Kovacs C et al. ADA Annual Meeting 2013. Abstract 1120-P. Rosenstock J et al. ADA Annual Meeting 2013. Abstract 1102-P.

Change in A1C with SGLT2 Inhibitors vs DPP-4 Inhibitors



Roden M et al. ADA Annual Meeting 2013; 1085-P. Lavalle Gonzalez FJ et al. ADA Annual Meeting 2013; 238-OR.
Schernthaner G et al. Diabetes Care 2013.

Change in HbA1c at 52 Weeks in Dapagliflozin vs. SU Add-on to Metformin Study

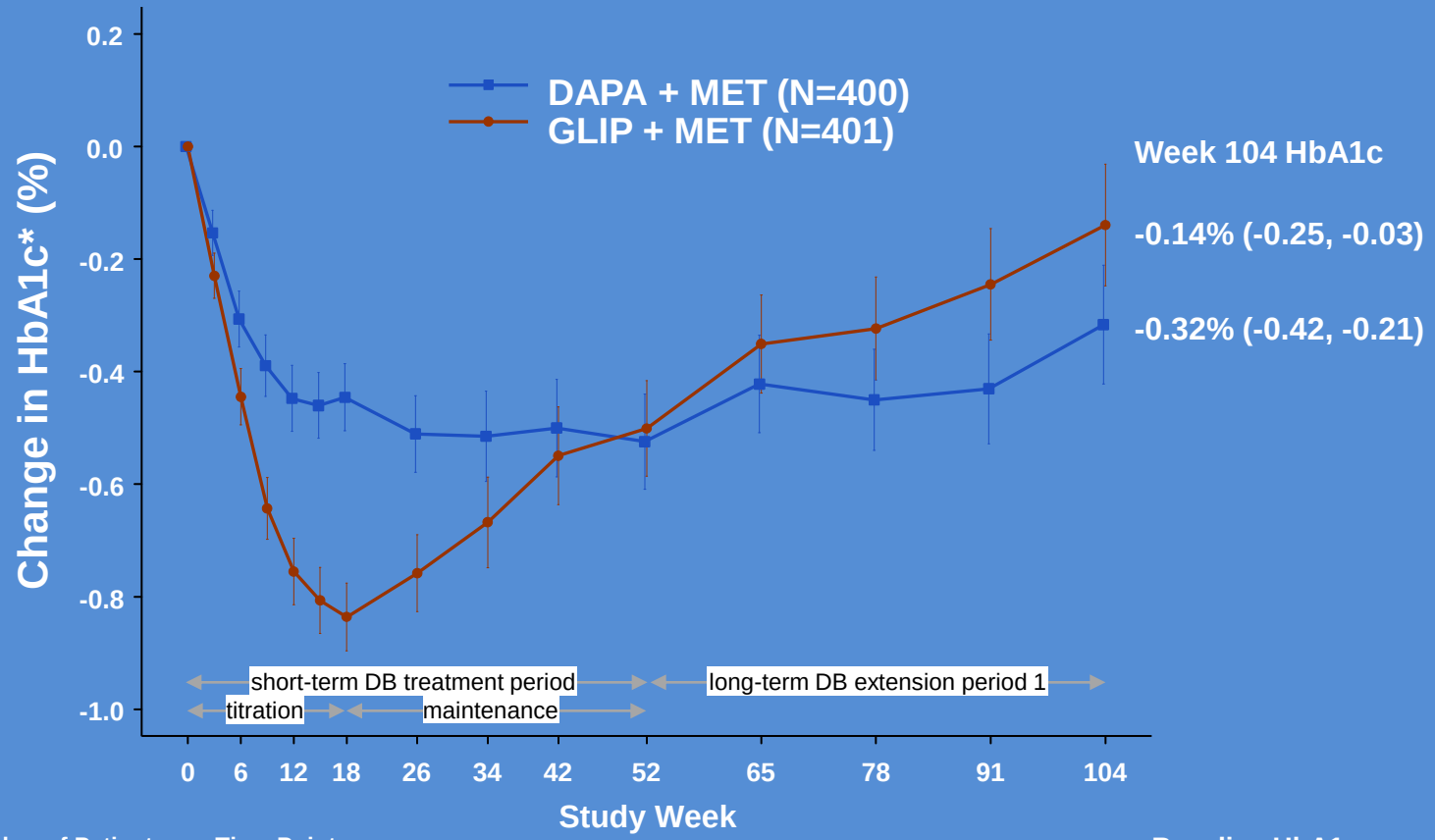


Adjusted mean change from baseline using ANCOVA (LOCF)
N's at Week 52 equal N's at baseline
†Non-inferior compared to limit of 0.35%

Adjusted percent using modified logistic regression analysis:
** Statistically significant by heirarchical testing rule.

Nauck M, et al. *Diabetes Care* 34:2015-2022, 2011

Change in HbA1c to 104 Weeks in Dapa vs. SU Add-on to Met Study



Number of Patients per Time Point

													Baseline HbA1c
DAPA + MET	400	385	367	369	354	339	334	321	311	271	242	233	7.69%
GLIP + MET	401	379	364	361	354	342	331	315	303	248	226	208	7.74%

*Data are adjusted mean change from baseline ± 95% CI derived from a repeated measures mixed model.
DAPA, dapagliflozin. DB, double-blind. MET, metformin.

Del Prato S, et al. Annual Meeting of the EASD, 12-16 September, 2011 (Presentation no #852).

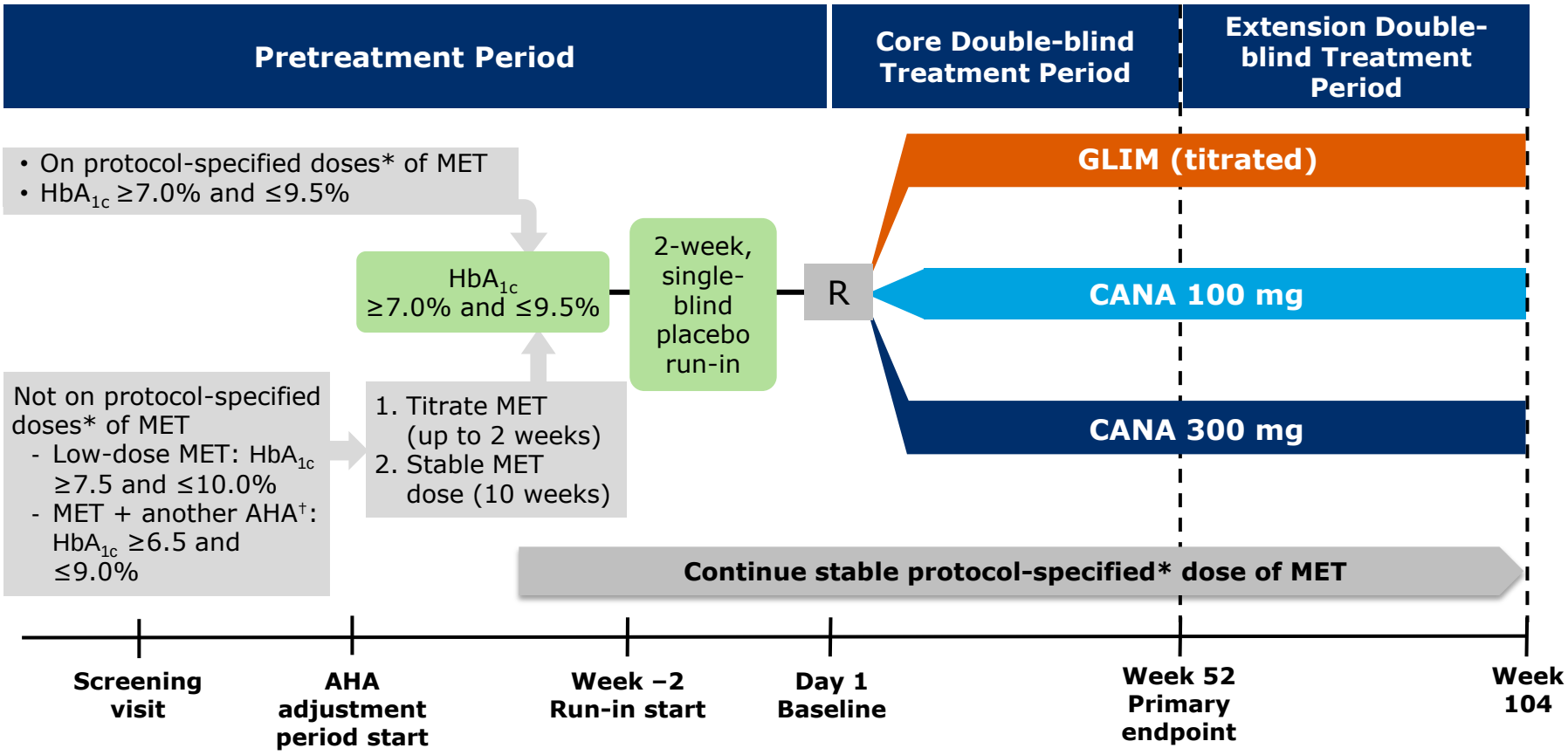
Canagliflozin Demonstrates Durable Glycaemic Improvements Over 104 Weeks Compared With Glimepiride in Subjects With Type 2 Diabetes Mellitus on Metformin

Gisle Langslet,[1] William T. Cefalu,[2] Lawrence A. Leiter,[3] Kun-Ho Yoon,[4] Pablo Arias,[5] John Xie,[6] Dainius Balis,[6] Dawn Millington,[6] Frank Vercruysse,[7] William Canovatchel,[6] Gary Meininger[6]

[1]Lipid Clinic, Oslo University Hospital, Oslo, Norway
[2]Pennington Biomedical Research Center, Baton Rouge, LA, USA and LSUHSC School of Medicine, New Orleans, LA, USA
[3]Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
[4]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea
[5]University of Rosario Medical School, Rosario, Argentina and Litoral University Medical School, Santa Fe, Argentina
[6]Janssen Research & Development, LLC, Raritan, NJ, USA
[7]Janssen Research & Development, Beerse, Belgium

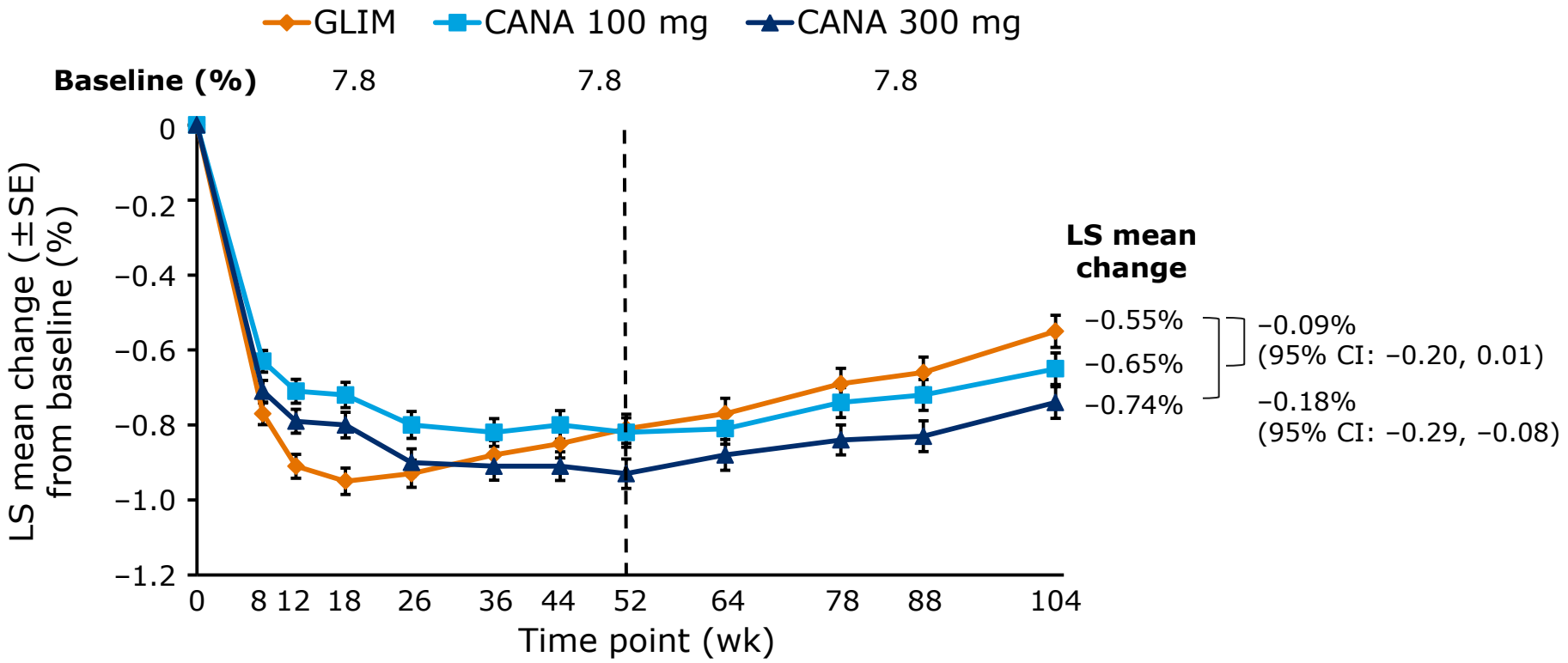
EASD 26 September 2013

Study Design



*Protocol-specified = ≥2,000 mg (or ≥1,500 mg, if unable to tolerate higher dose).
†To be discontinued before titrating MET.

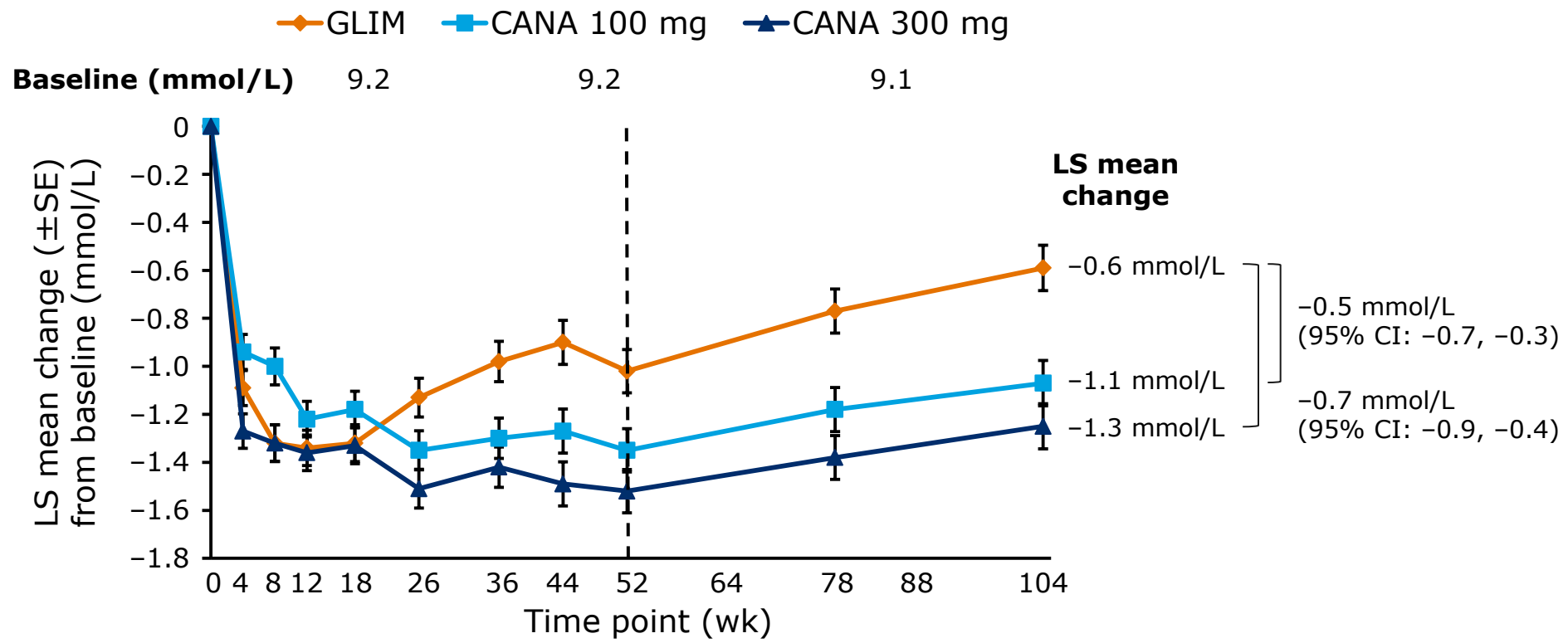
Change in HbA_{1c}



- Coefficient of durability was lower with CANA 100 and 300 mg than GLIM (0.16%, 0.16%, and 0.37%, respectively)

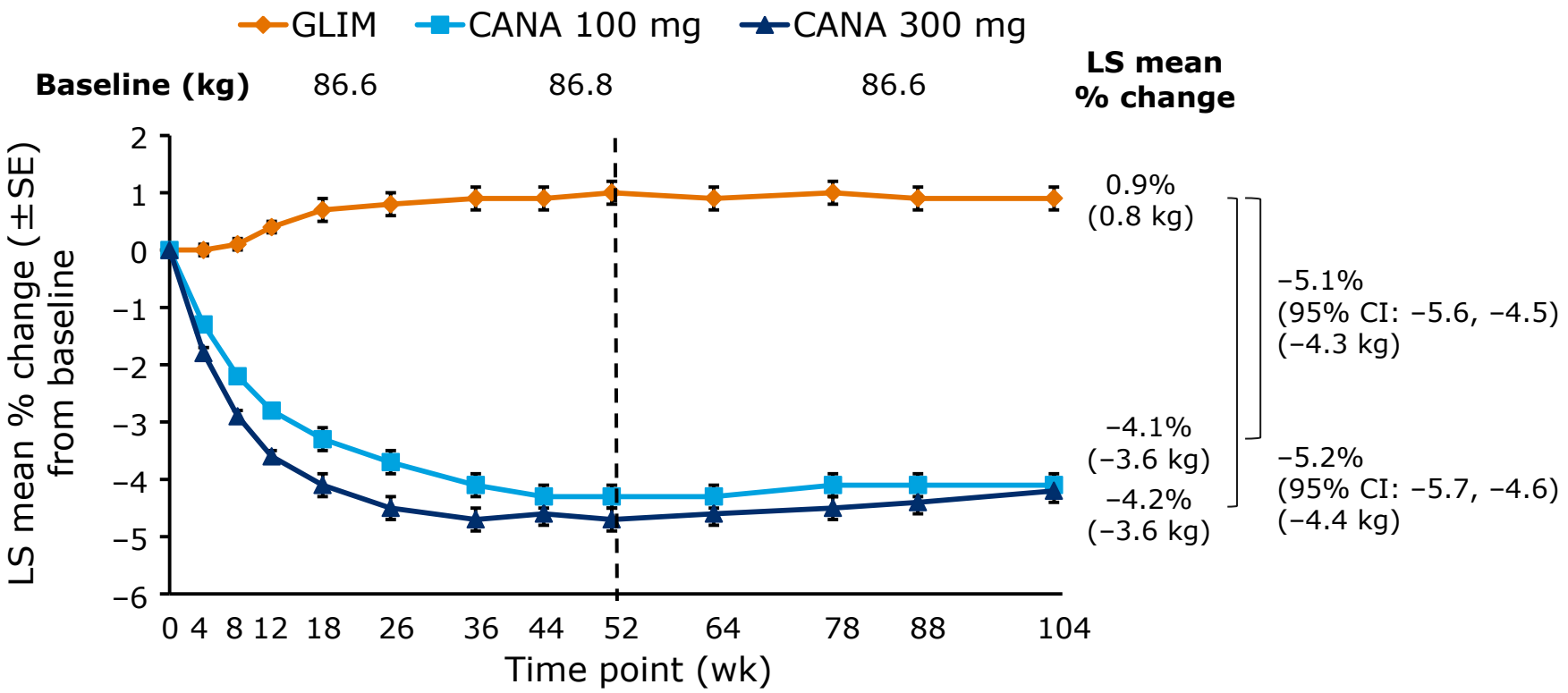
mITT, LOCF

Change in FPG



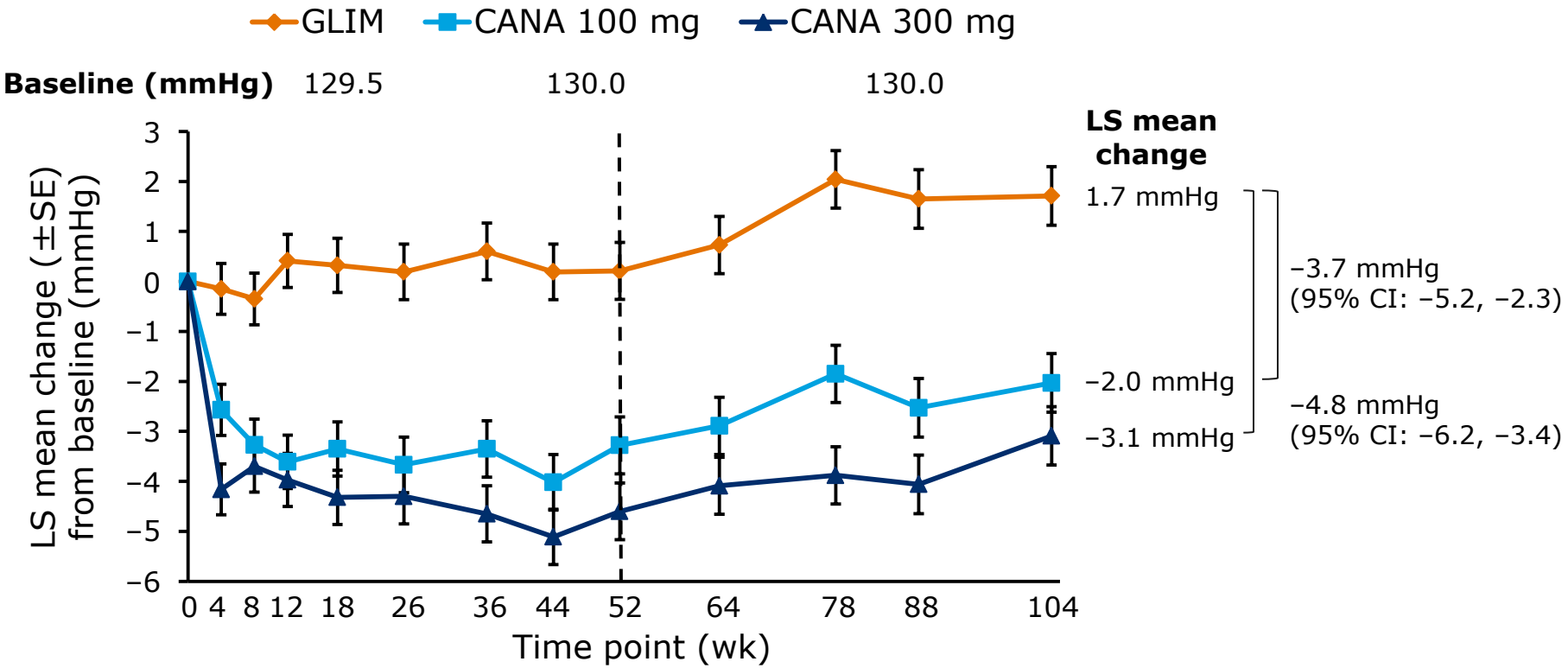
mITT, LOCF

Percent Change in Body Weight



mITT, LOCF

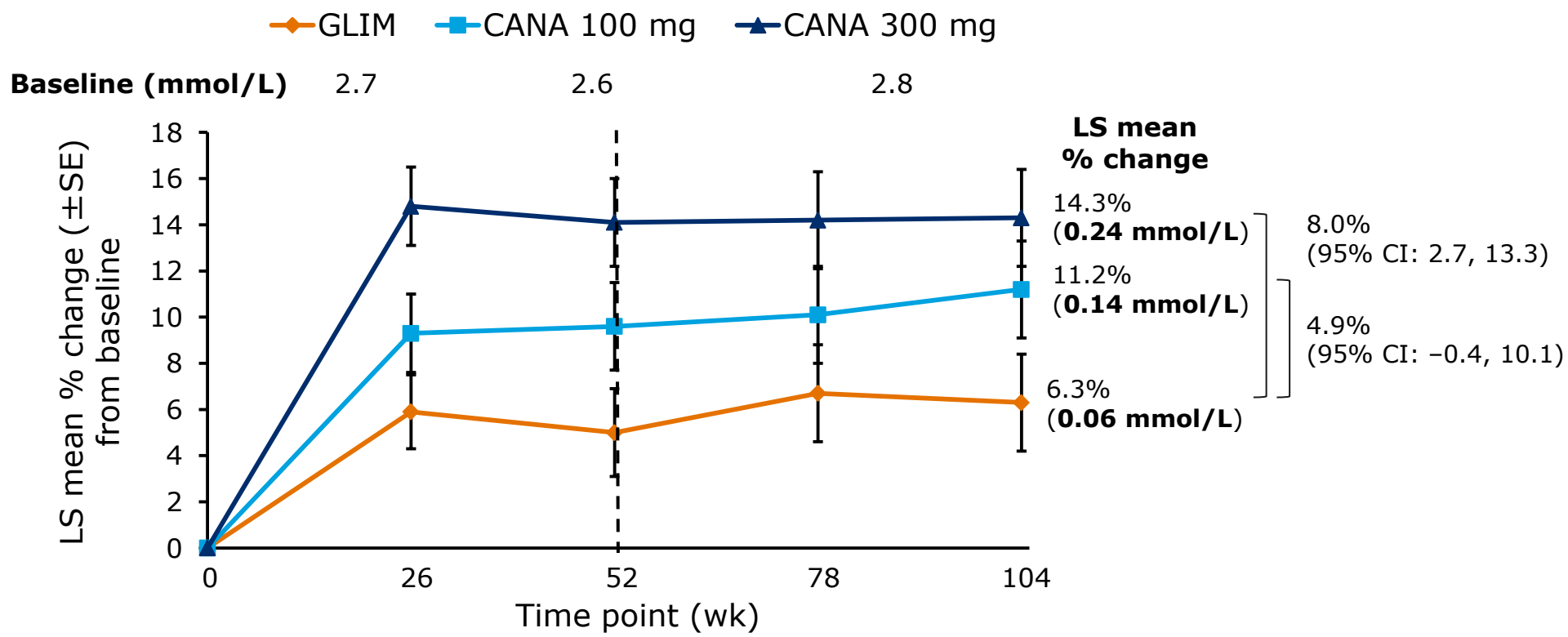
Change in Systolic BP



- With CANA 100 and 300 mg and GLIM, LS mean changes from baseline in diastolic BP were −1.3, −2.2, and −0.02 mmHg, respectively; no notable changes in pulse rate were observed across groups

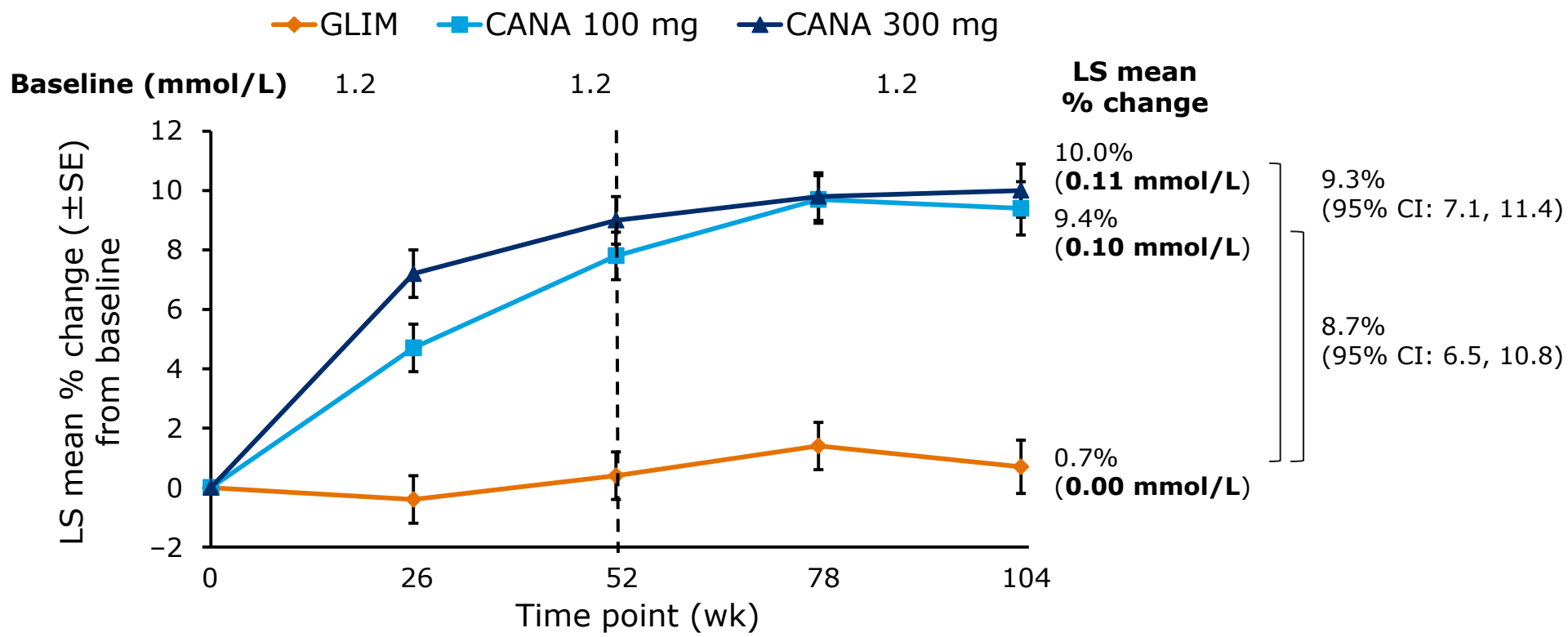
mITT, LOCF

Percent Change in LDL-C



mITT, LOCF

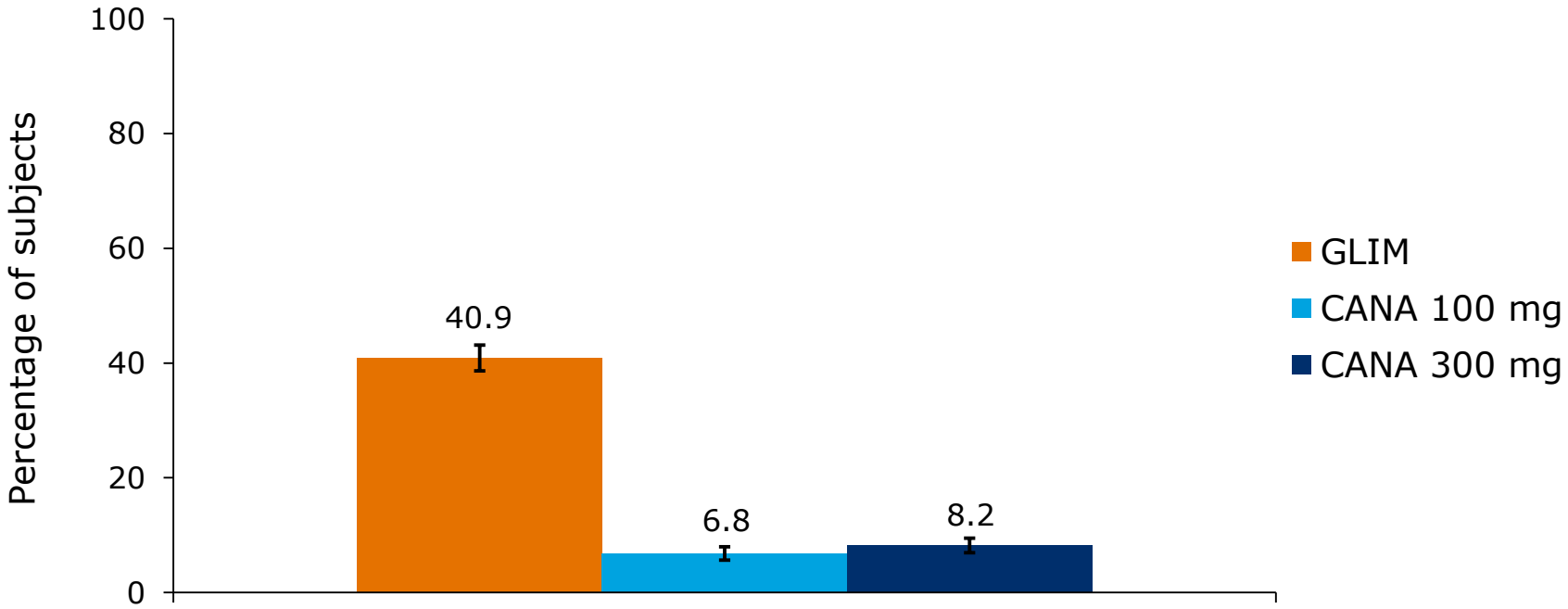
Percent Change in HDL-C



- Relative to GLIM, CANA 100 and 300 mg were associated with decreases in triglycerides and LDL-C/HDL-C ratio, and increases in non–HDL-C that were smaller than those seen in LDL-C; changes in lipids were generally similar at Week 52 and Week 104

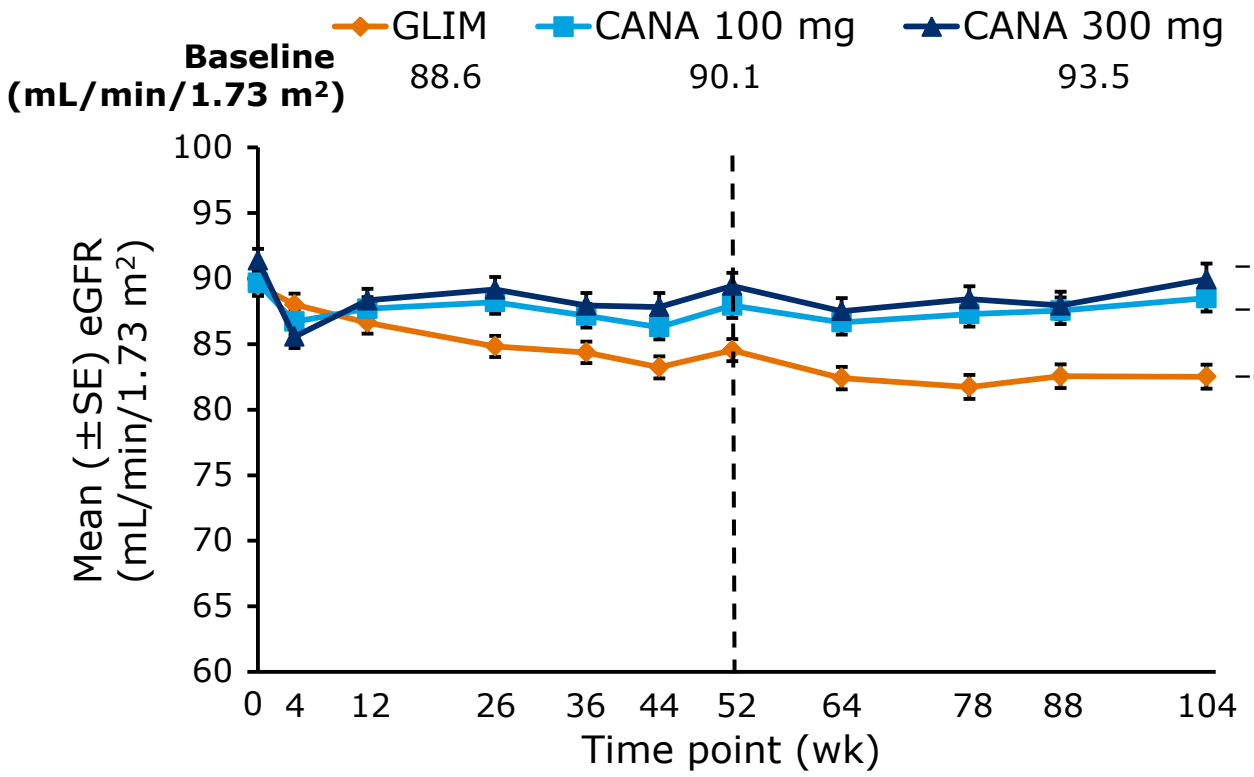
mITT, LOCF

Documented Hypoglycaemia Episodes



- Rates of severe hypoglycaemia were lower with CANA 100 and 300 mg relative to GLIM (0.6%, 0.2%, and 3.3%, respectively)

Mean eGFR Over Time



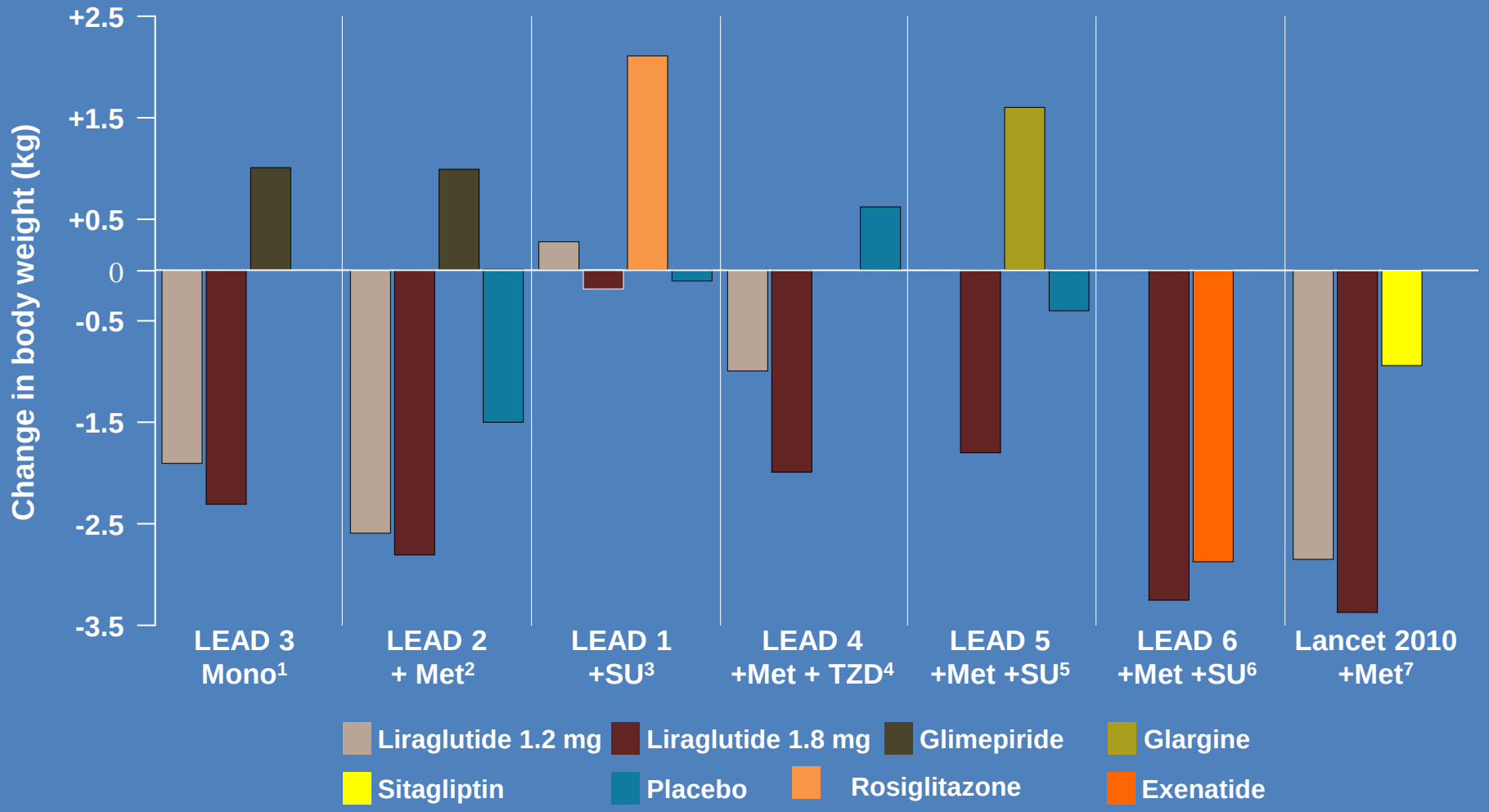
	Mean change from baseline (Observed)	Mean change from baseline (LOCF)
GLIM	−3.5 mL/min/1.73 m²	−3.8 mL/min/1.73 m²
CANA 100 mg	−1.6 mL/min/1.73 m²	−2.0 mL/min/1.73 m²
CANA 300 mg	−6.1 mL/min/1.73 m²	−6.2 mL/min/1.73 m²

Summary

- In subjects with T2DM on background MET, CANA 100 and 300 mg provided HbA_{1c} reductions that were durable over 104 weeks; reductions in FPG, body weight, and systolic BP at Week 104 were similar to those seen at Week 52[1]
- Both CANA doses were associated with increases in HDL-C and LDL-C that were stable from Week 26 to Week 104
- The overall safety profile of CANA over 104 weeks was generally consistent with that seen at 52 weeks[1]
  - CANA was associated with increased incidences of genital mycotic infections, UTIs, and osmotic diuresis-related AEs compared with GLIM; these led to few discontinuations
- The incidence of hypoglycaemia was lower with both CANA doses than with GLIM

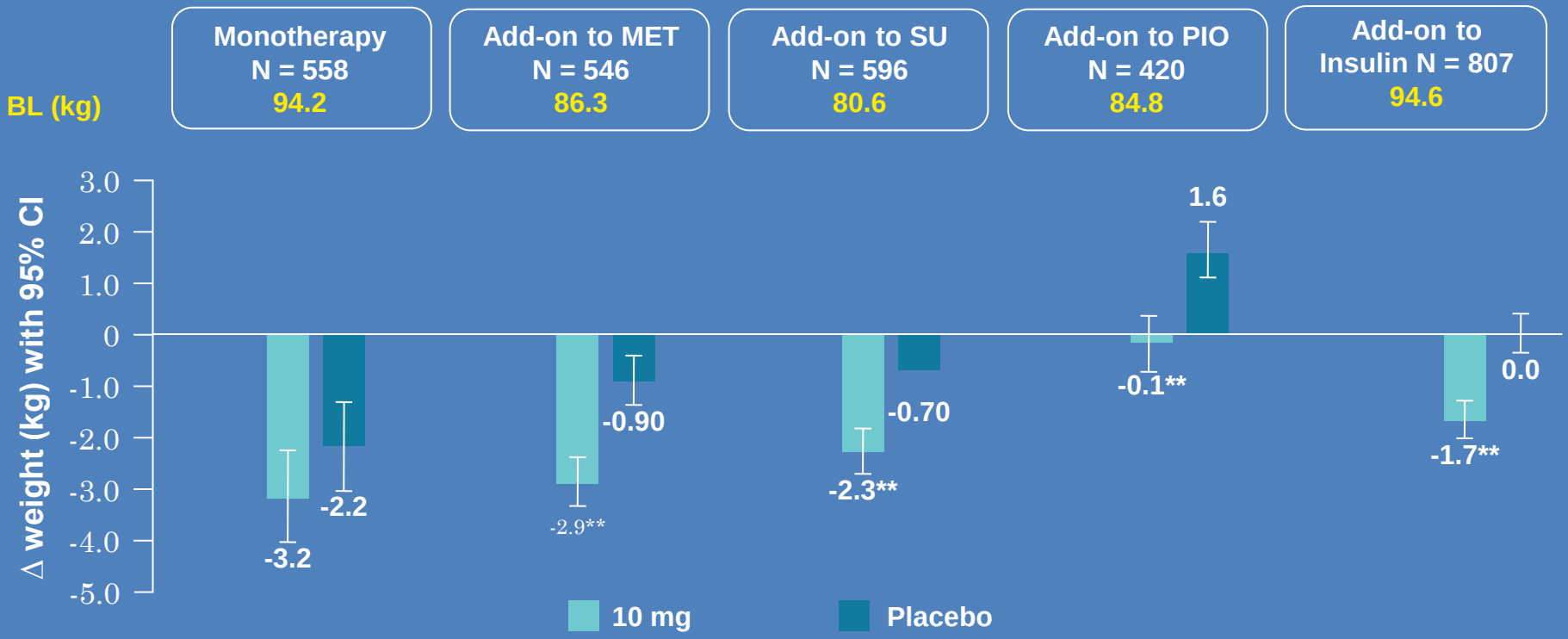
1. Cefalu WT, et al. *Lancet.* doi: 10.1016/S0140-6736(13)60683-2.

Liraglutide: Effect on Body Weight (Kg)



1. Marre M, et al. Diabet Med 2009;26:268-78.
2. Nauck M, et al. Diabetes Care 2009;32:84-90.
3. Garber A, et al. Lancet 2009;373:473-81.
4. Zinman B, et al. Diabetes Care 2009;32:1224-30.
5. Russell-Jones D, et al. Diabetologia 2009;52:2046-55.
6. Buse JB, et al. Lancet 2009;374:39-47.
7. Pratley RE, et al. Lancet 2010;375:1447-56.

Dapagliflozin: Effect on Body Weight in Placebo-Controlled Studies (Kg)



*Statistically significant vs. placebo by hierarchical testing rule: *p<0.05; **p<0.001
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

2/3 of the weight loss is fat mass

1. Ferrannini E, et al. Diabetes Care 2010; doi:10.2337/dc10-0612.
2. Bailey CJ, et al. Lancet 2010; 375:2223-33.
3. Nauck M, et al. Diabetologia 2010; 53 (suppl 1):S107. Abstract 241.
4. Stroiek K. Diabetologia 2010; 53 (suppl 1):S347. Abstract 870.
5. Wilding J, et al. Diabetes 2010; 59 (suppl 1):A21-A22. Abstract 0078-OR.
6. Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm
7. Bolinder J et al. J Clin Endocrinol Metab. 97; 2012.

Canagliflozin: Effect on Body Weight in Placebo-Controlled Studies (%)

% LS Mean Change from Baseline

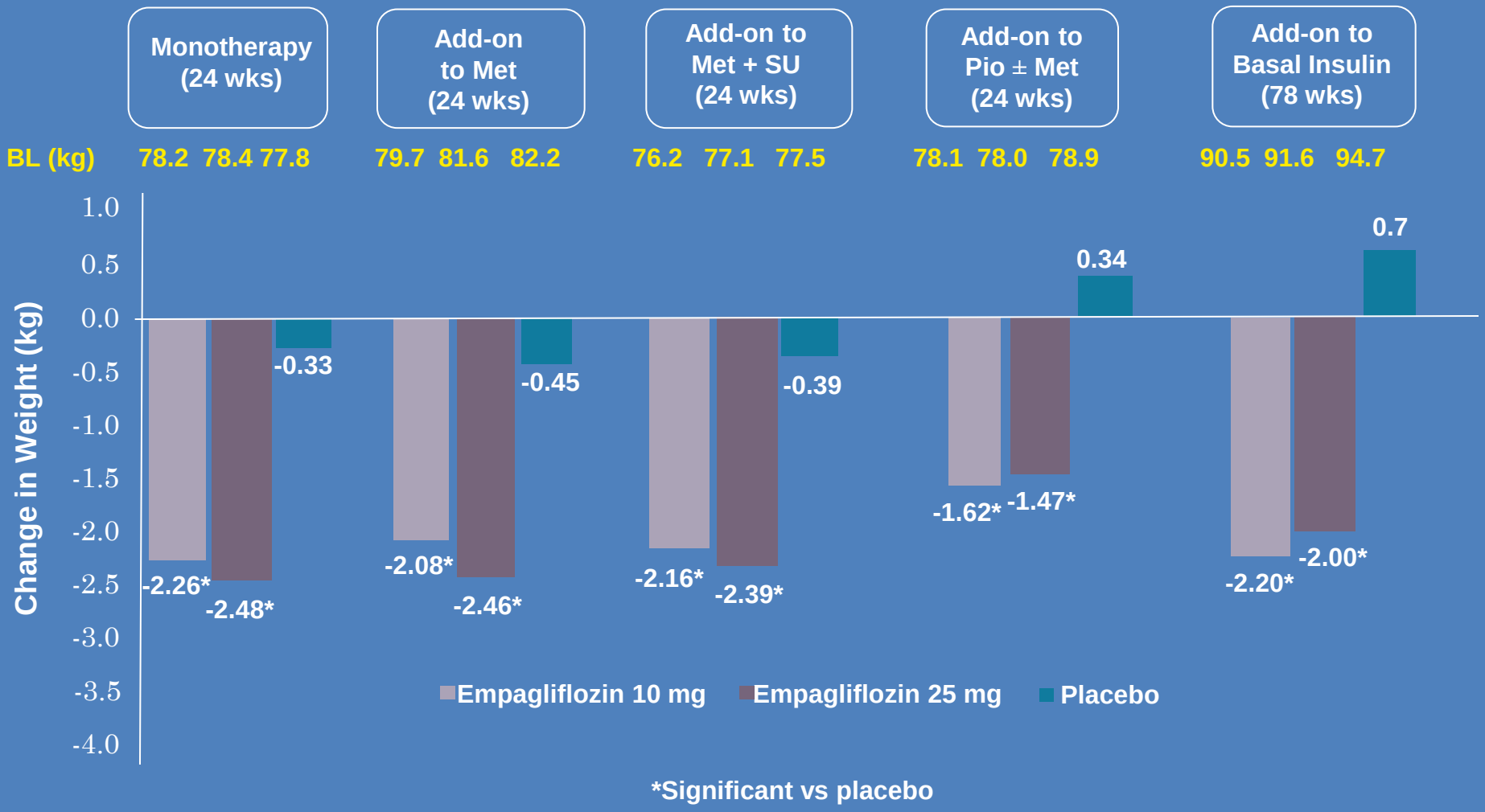
	Mono	Add on to MET	Add on to MET/SU	Add on to Met/Pio	Add on to Insulin	Add on to SU	Add on to AHA's in older subjects
Baseline (kg)	86.8 kg	87.2 kg	92.8 kg	94.1 Kg	97 kg	97 Kg	89.5 kg

P <0.05 vs placebo for both CANA doses in all studies except CANA 100 mg in Add-on to SU Study

More than 2/3 of the weight loss is fat mass

Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013. Toubro S et al. EASD Annual Meeting 2012. Abstract 762

Empagliflozin: Effect on Body Weight in Placebo-Controlled Trials (Kg)

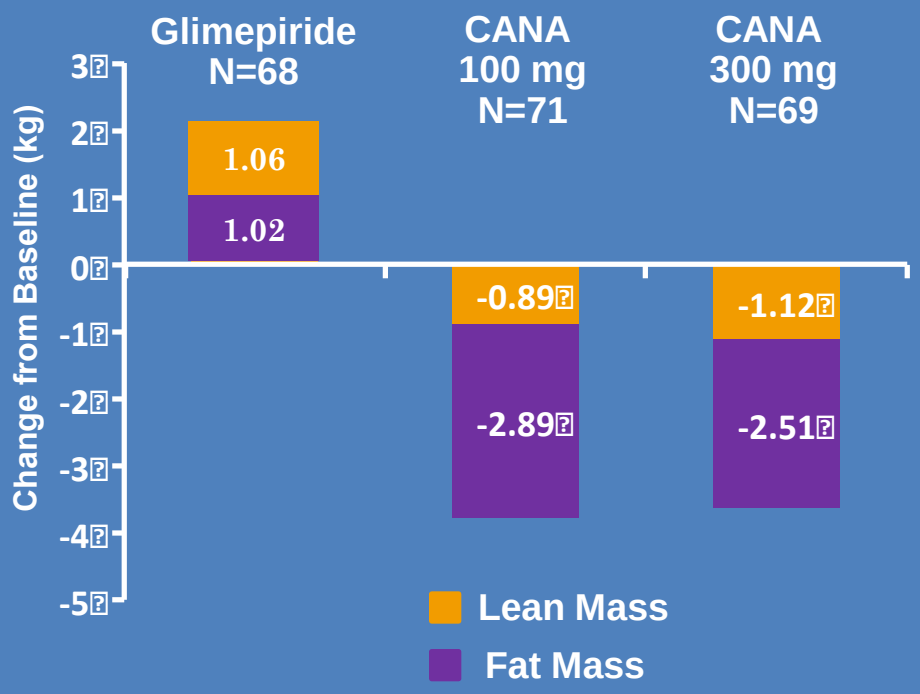


Roden M et al. ADA Annual Meeting 2013. Abstract 1085-P. Haring H et al. ADA Annual Meeting 2013. Abstract 1092-P. Haring H et al. ADA Annual Meeting 2013. Abstract 1082-P. Kovacs C et al. ADA Annual Meeting 2013. Abstract 1120-P. Rosenstock J et al. ADA Annual Meeting 2013. Abstract 1102-P.

SGLT2 Inhibitors: Weight loss is Mostly Fat

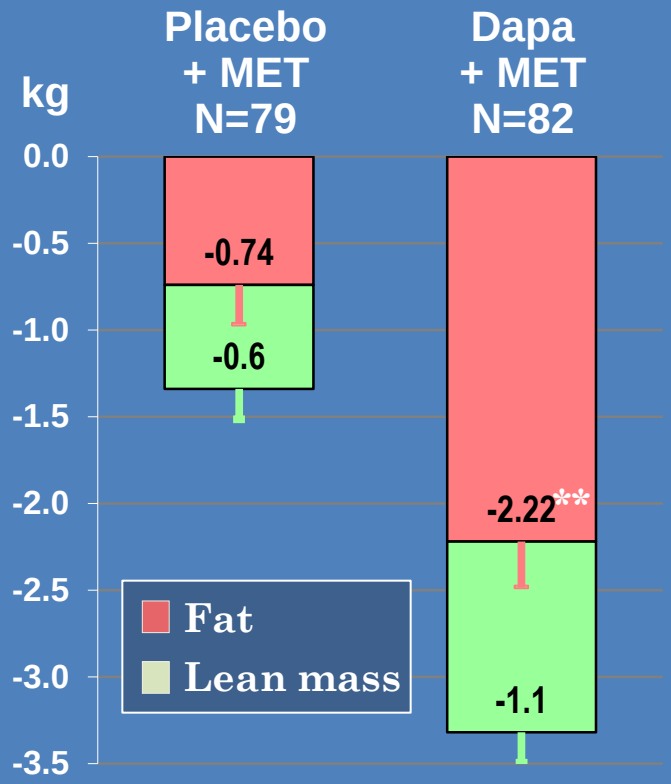
Canagliflozin

Δ Body Fat and Lean Mass (kg) at Week 52 by DXA



Dapagliflozin

Δ Body Fat and Lean Mass (kg) at Week 24 by DXA (SE)



** Statistically significant vs. placebo by Hochberg's method (p<0.001)

Toubro S et al. EASD Annual Meeting 2012. Abstract 762.
Bolinder J et al. J Clin Endocrinol Metab. 97; 2012.

Dapagliflozin: Rates of Hypoglycemia

Rates of Hypoglycemia Across all Dapagliflozin Treatment Regimens

	Percent of patients			
	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Placebo
Placebo-controlled pool	n=814 15.5	n=1,145 10.9	n=1,193 10.2	n=1,393 7.0
Monotherapy pool	n=321 2.5	n=316 2.2	n=245 2.9	n=251 2.0
Add-on combination + MET (pool)			n=226 3.1	n=228 3.1
+ PIO		n=141 2.1	n=140 0	n=139 0.7
+ SU	n=154 7.1	n=145 6.9	n=151 7.3	n=146 4.8
+ insulin	n=202 51.5	n=212 45.3	n=196 42.3	n=197 35.0

List J. Presented at the FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting, July 19, 2011.
Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

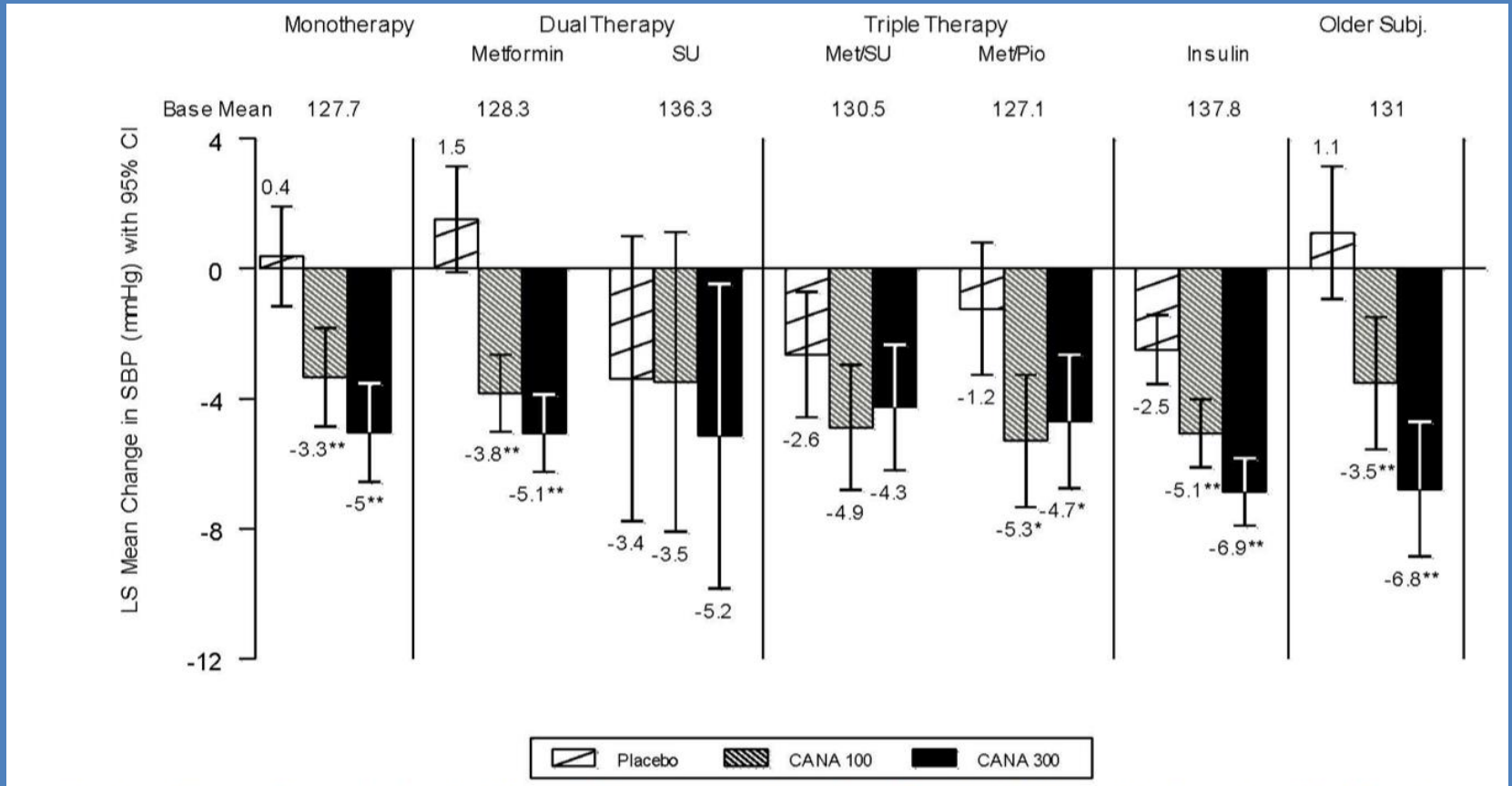
Canagliflozin: Rates of Hypoglycemia

- **Increased with insulin and SU background therapy**
- **Low rate of hypoglycemia in studies of subjects not on agents associated with hypoglycemia**

	Placebo	CANA 100 mg	CANA 300 mg
Not on SU or insulin therapies	%	%	%
PBO-controlled population	2.2	3.8	4.3
On SU or insulin therapies			
MET + SU	15.4	27.4	30.1
SU	5.8	4.1	12.5
Insulin (initial 18 weeks)	36.8	49.3	48.6

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

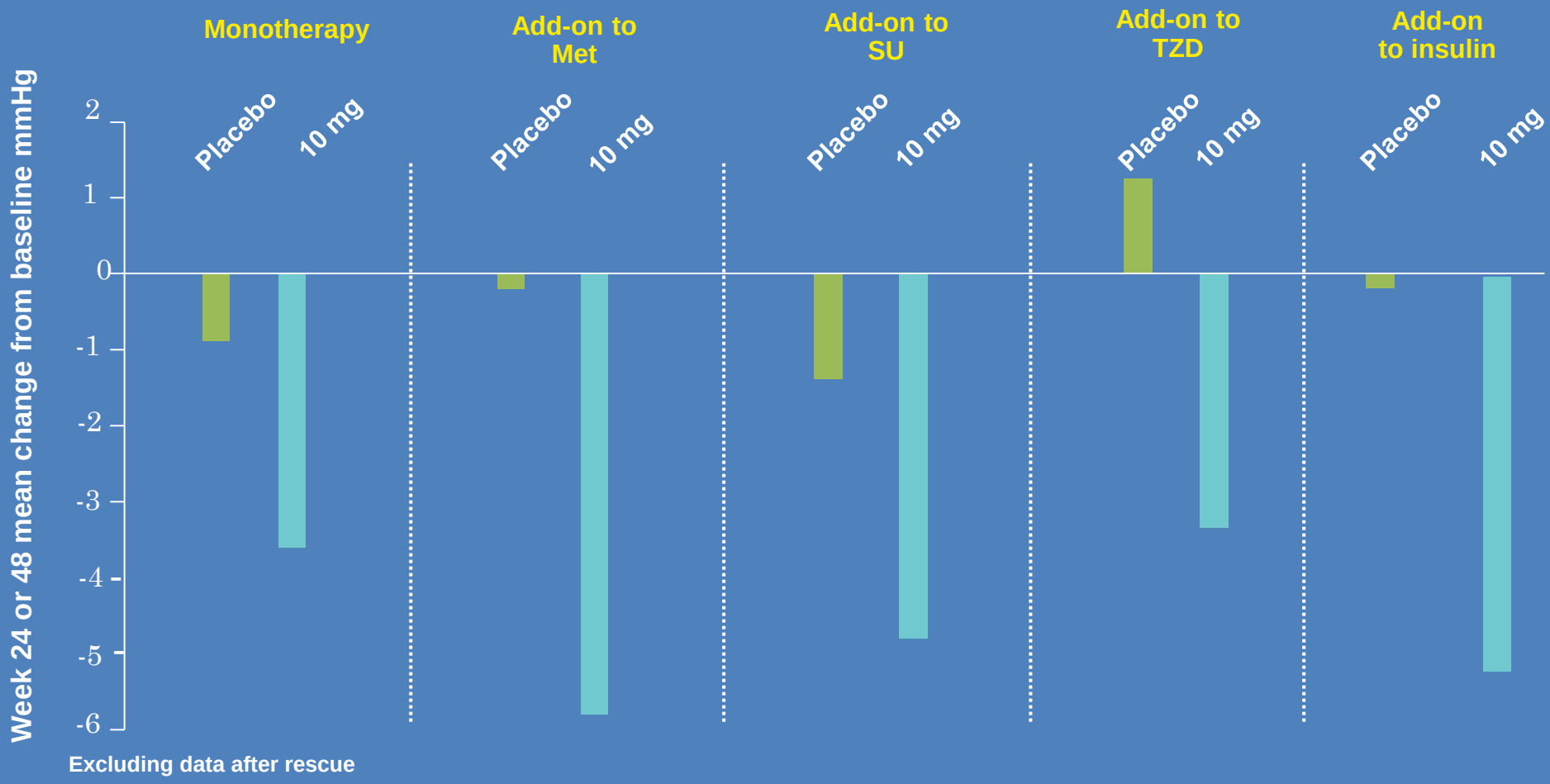
Canagliflozin: Systolic Blood Pressure Change from Baseline in Placebo-Controlled Phase 3 Studies



** Statistically significant ($p<0.001$) [(*$p<0.05$)] vs placebo based on the ANCOVA models from individual studies.
Note: LOCF; mITT analysis set

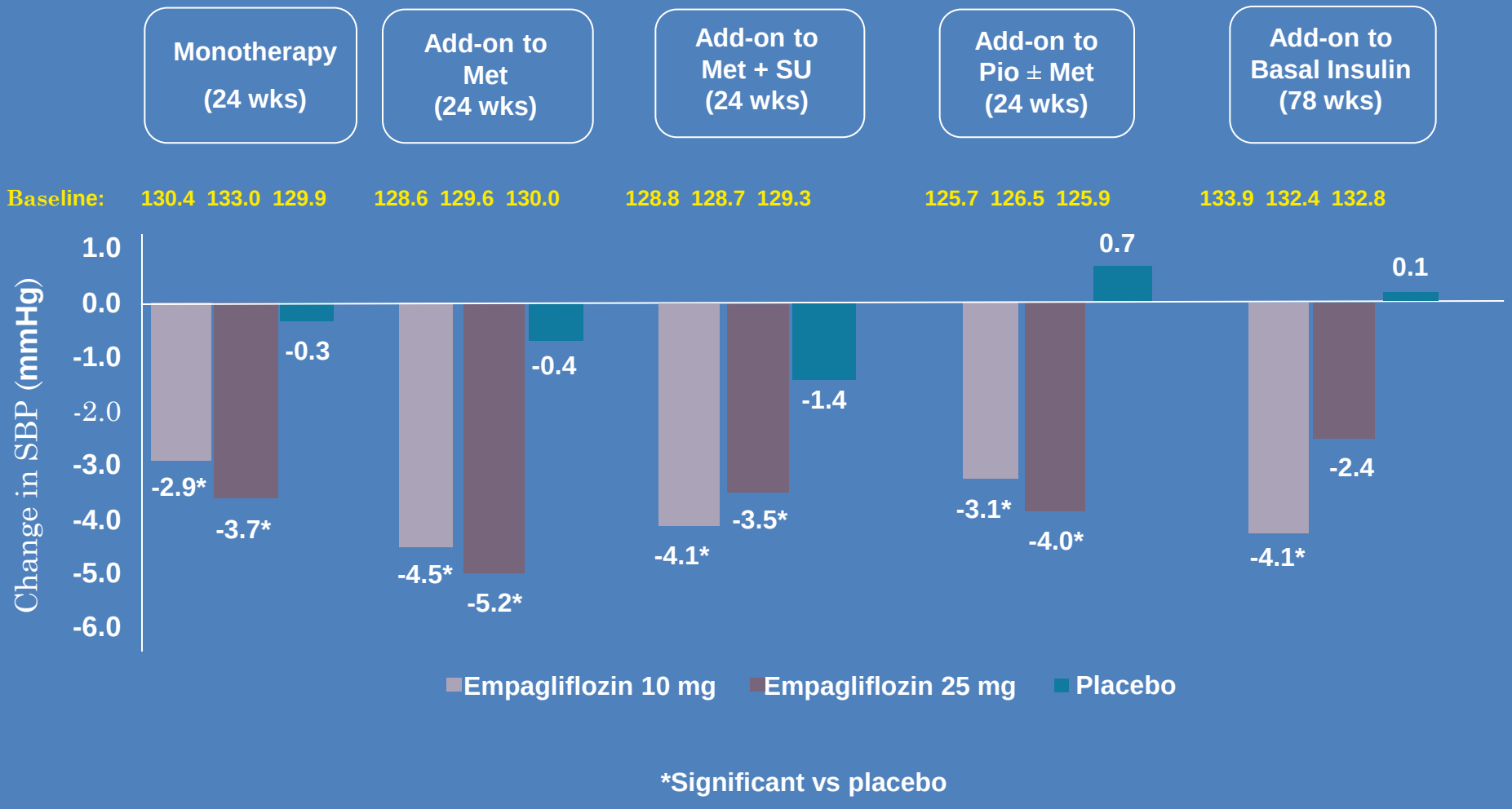
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

Dapagliflozin: Systolic Blood Pressure Change from Baseline in Placebo-Controlled Phase 3 Studies



Presented at the FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting, July 19, 2011.
Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

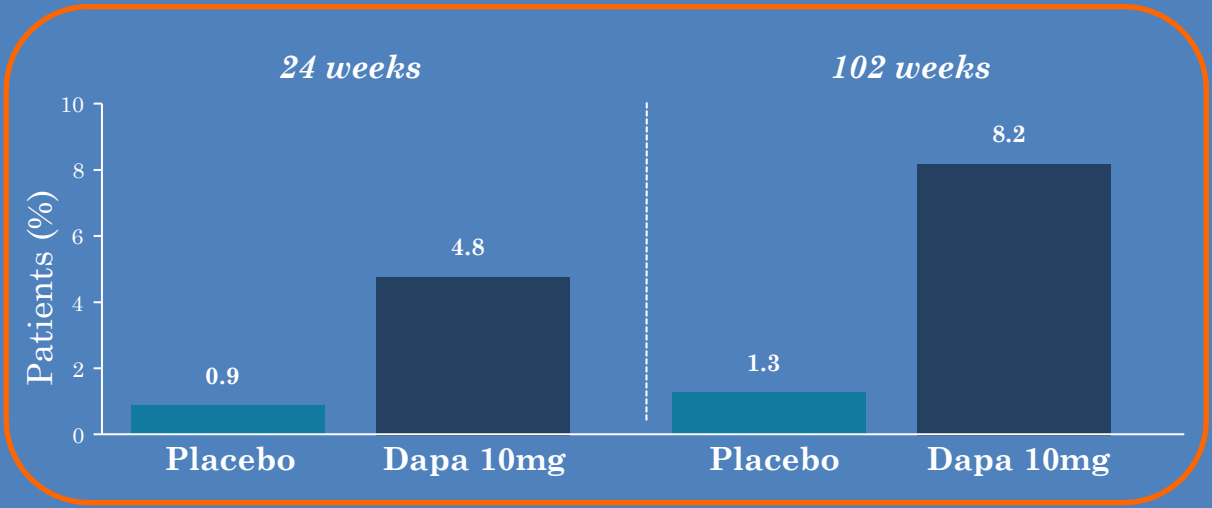
Empagliflozin: Systolic Blood Pressure Change from Baseline in Placebo-Controlled Phase 3 Studies

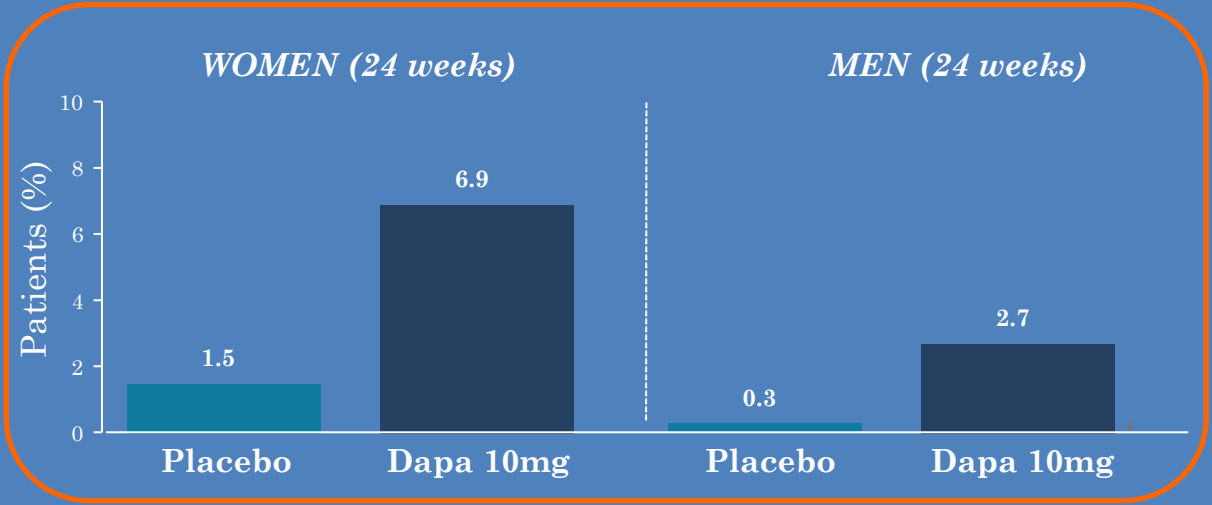


*Significant vs placebo

Roden M et al. ADA Annual Meeting 2013. Abstract 1085-P. Haring H et al. ADA Annual Meeting 2013. Abstract 1092-P. Haring H et al. ADA Annual Meeting 2013. Abstract 1082-P. Kovacs C et al. ADA Annual Meeting 2013. Abstract 1120-P. Rosenstock J et al. ADA Annual Meeting 2013. Abstract 1102-P.

Dapagliflozin: Genital Infections – Summary

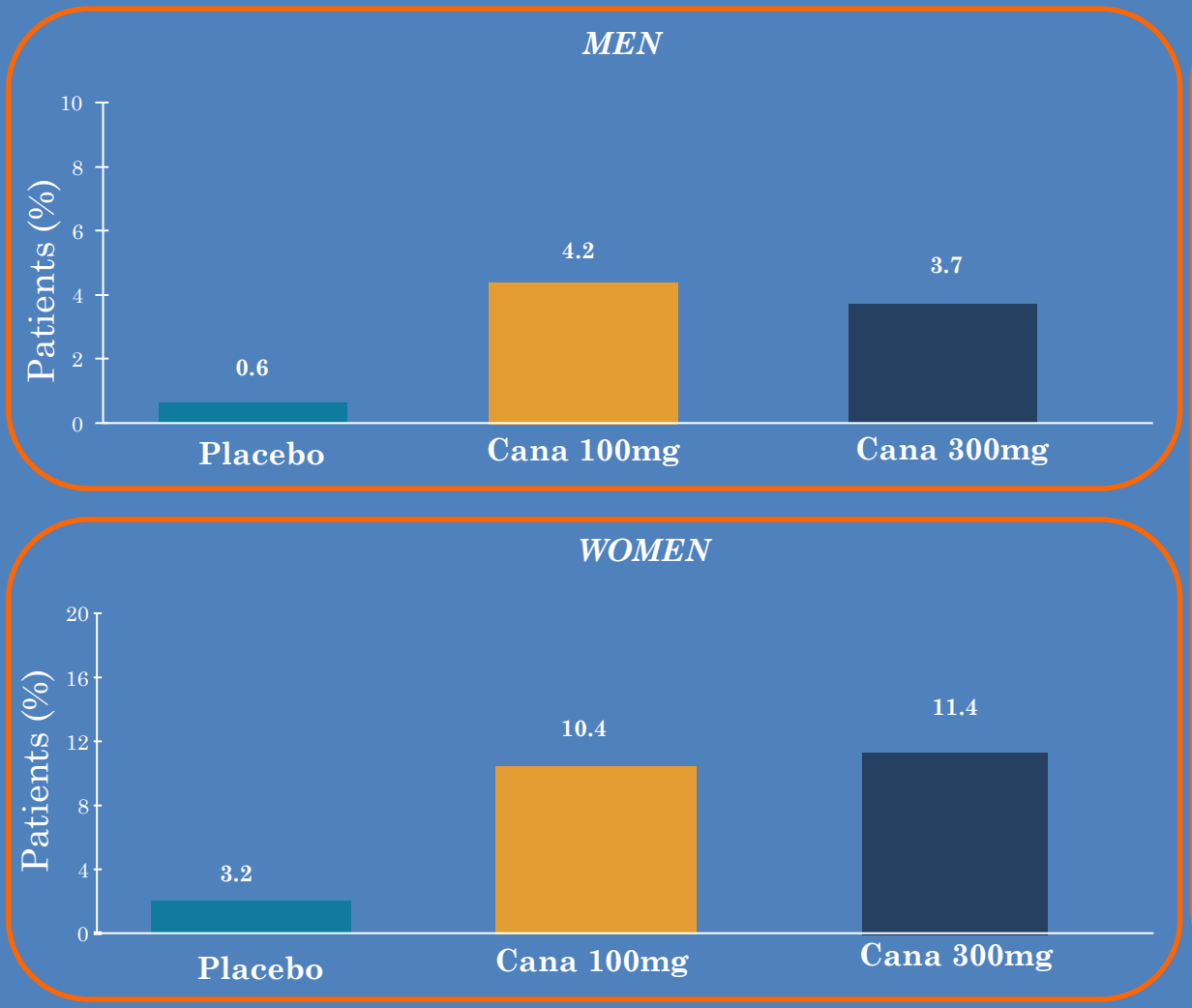




- Most mild-to-moderate in intensity with dapa
- Most responded to initial course of standard treatment
- Rarely led to discontinuation (0.2%)
- Most patients who had an event had only one over 102 weeks (74.6% dapa vs 77.8% placebo)

Presented at the FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting, July 19, 2011.
Available at:
www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

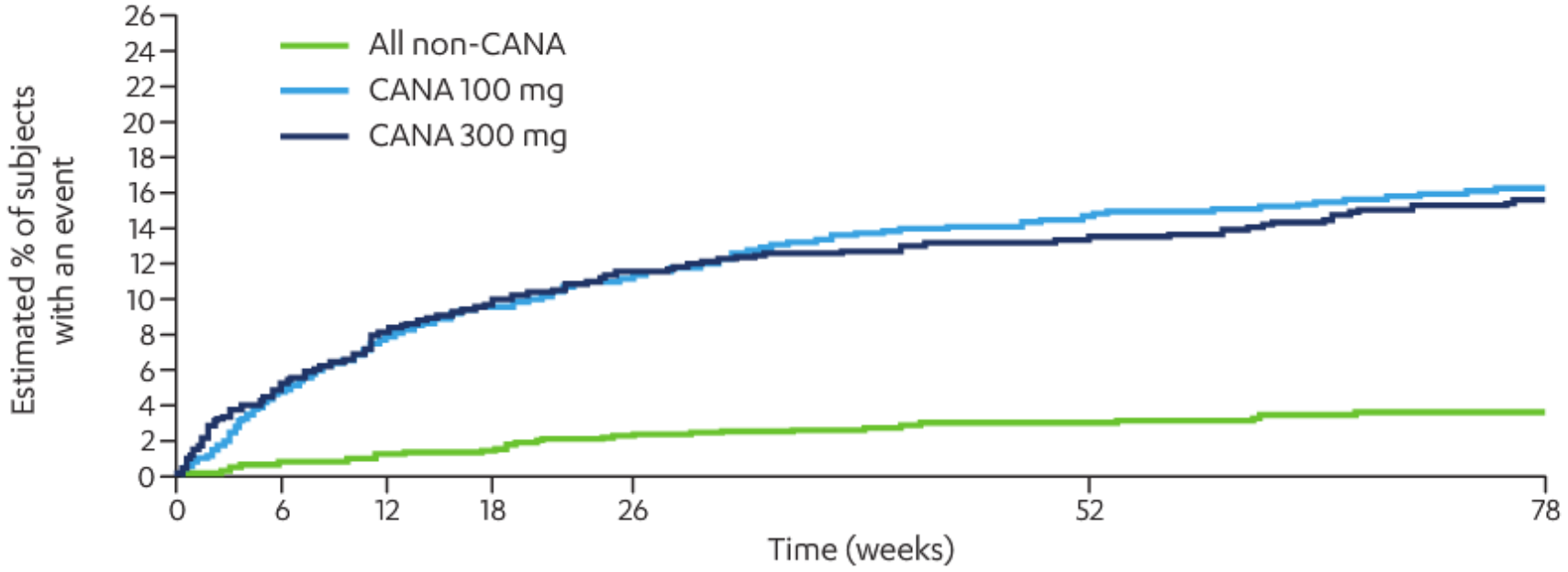
Canagliflozin: Frequency of Genital Infections Over 26 Weeks in Four Placebo-Controlled Studies



- Most mild or moderate in intensity with cana
- More common in women than men and in those with history of genital infection
- Rarely led to discontinuation (0.5-0.9%)
- Most patients had only one event over 26 weeks
  - women: 79% with GTI on cana had one one event
  - men: 78% with GTI on cana had one event

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013.
Nyirjesky P et al. ADA Annual Meeting 2013. Abstract 1069-P.

Canagliflozin: Time to First Female Genital Mycotic Infection Over 78 Weeks in 8 Pooled Studies

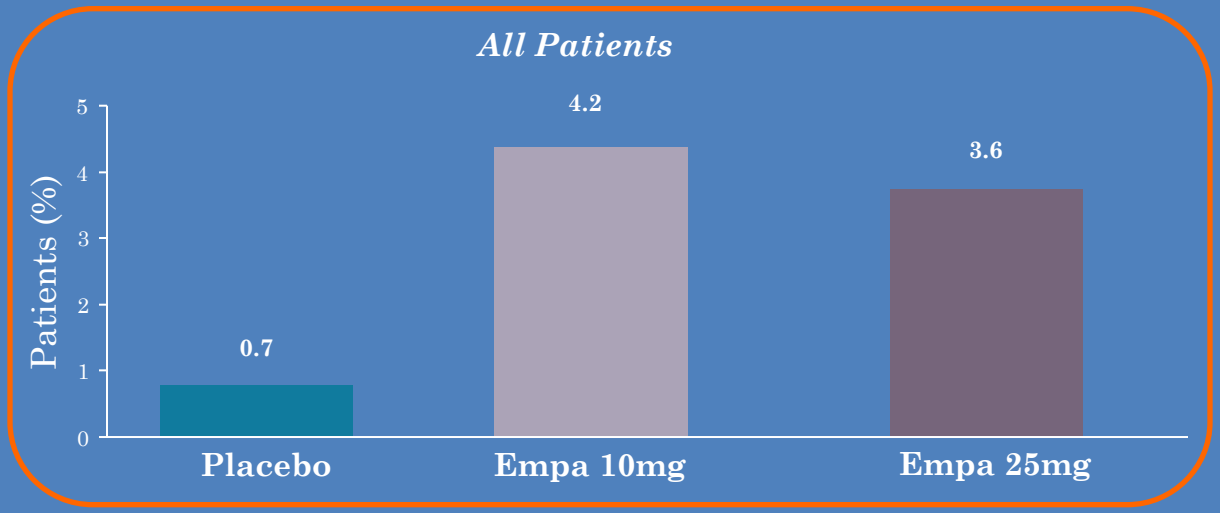


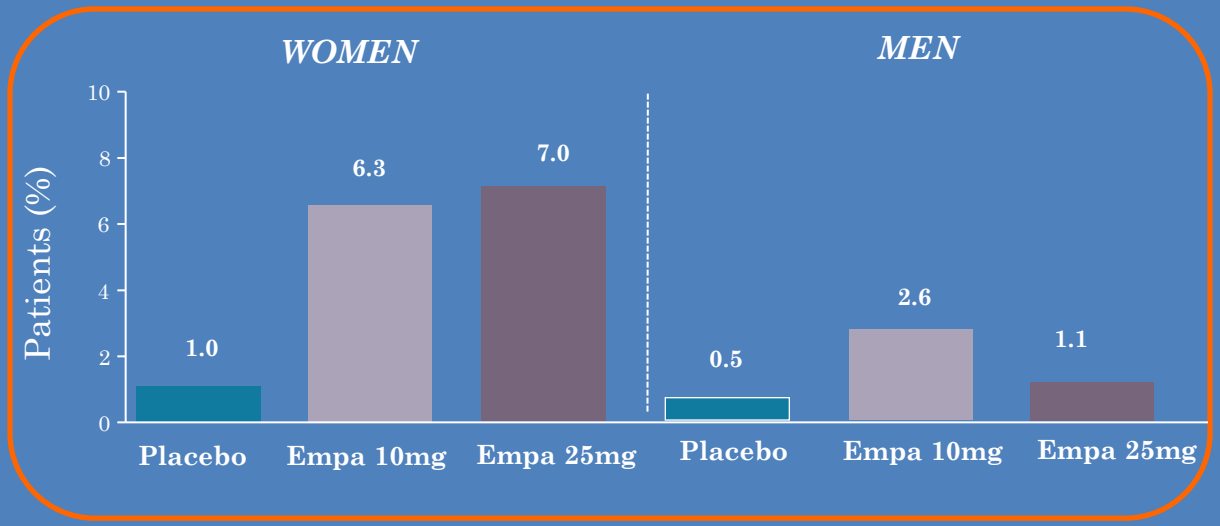
All non-CANA	1,338	1,312	1,250	1,209	1,135	993	443
CANA 100 mg	1,289	1,217	1,143	1,087	1,034	908	421
CANA 300 mg	1,319	1,243	1,153	1,101	1,036	945	440

The highest rate of occurrence was observed during the first 4 months of treatment, followed by an attenuation in the rate of increase

Nyirjesky P et al. ADA Annual Meeting 2013. Abstract 1069-P.

Empagliflozin: Frequency of Genital Infections Over 24 Weeks in Four Placebo-Controlled Studies

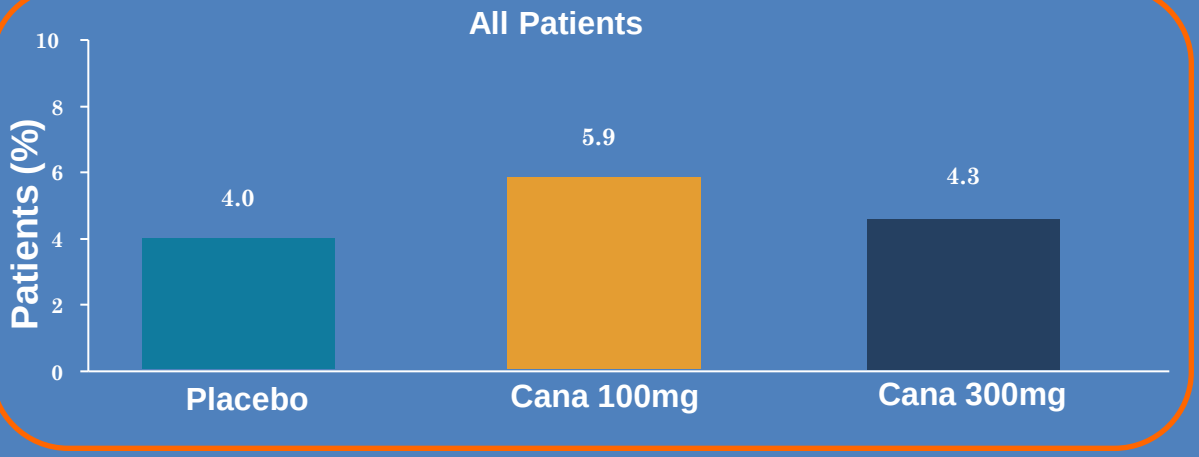


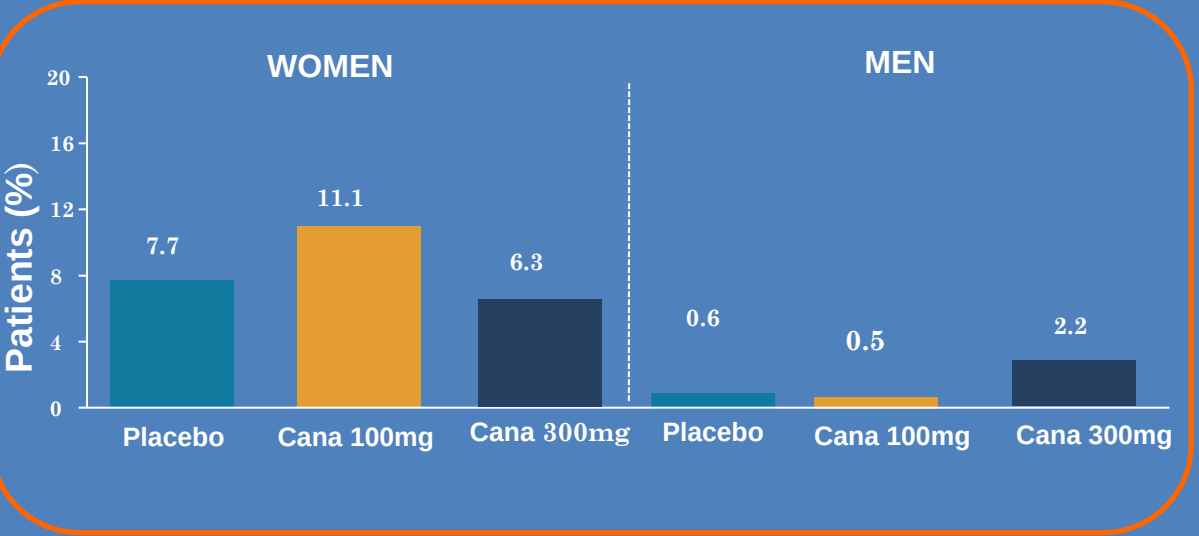


- Most mild in intensity with empa
- More common in women than men and in those with history of genital infection
- Rarely led to discontinuation (0.1-0.2%)
- Most patients had only one event over 24 weeks (84.6% of empa vs 83.3% placebo)

Kim G et al. ADA Annual Meeting 2013. Abstract 74-LB

Canagliflozin: Frequency of UTI Over 26 Weeks in Four Placebo-Controlled Studies

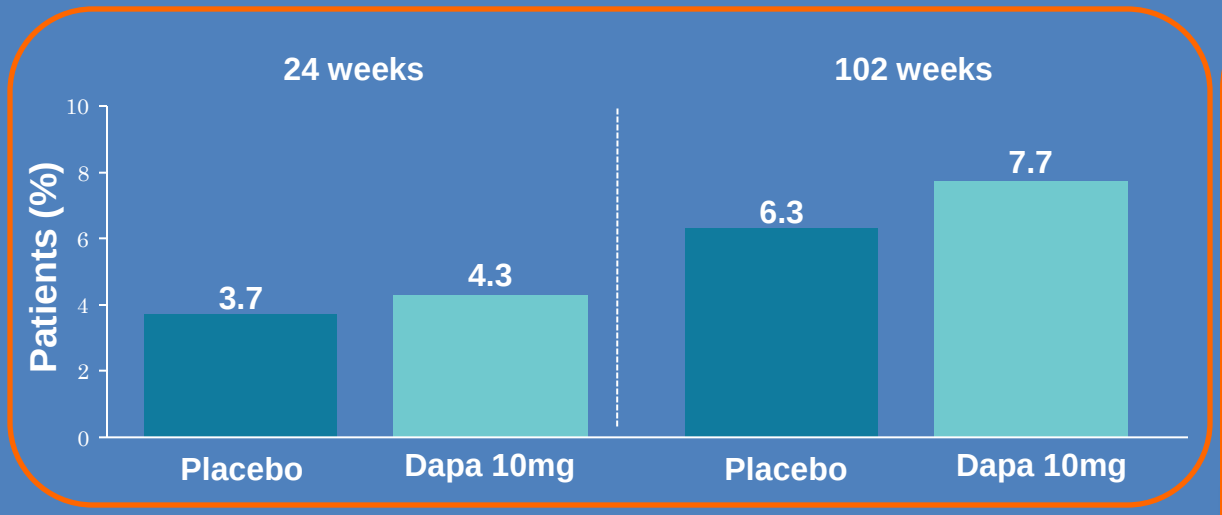


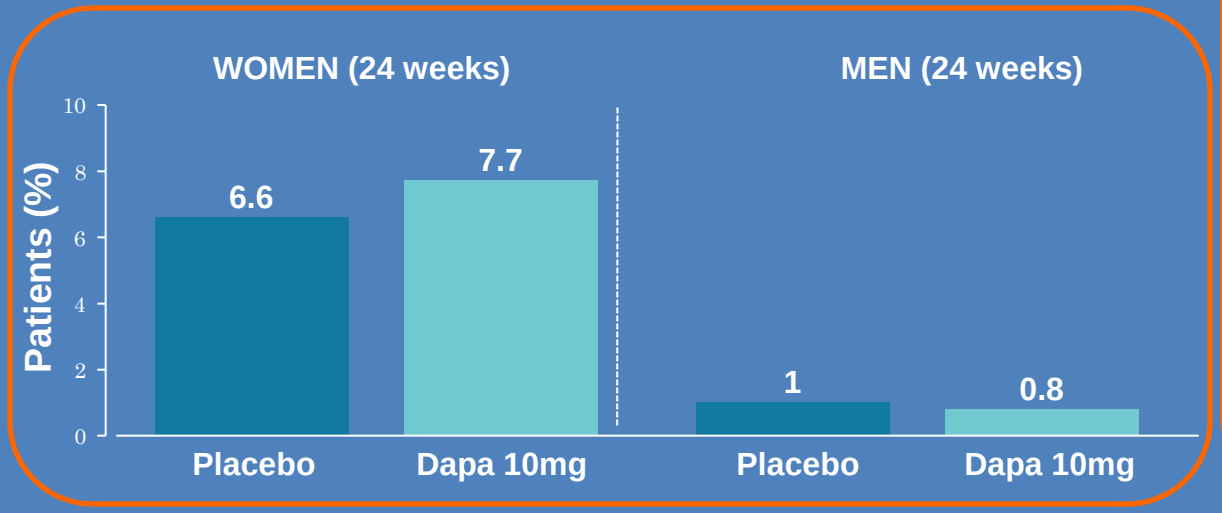


- Most mild to moderate in intensity with cana
- More common in women than men
- Rarely led to discontinuation (0.1%)
- Most patients had only one event over 24 weeks (83% of cana vs 82% placebo)
- Upper UTI were rare and balanced between groups (0-0.1%)

Nicolle L et al. ADA Annual Meeting 2013. Abstract 1139-P.

Dapagliflozin: Frequency of UTI – Summary

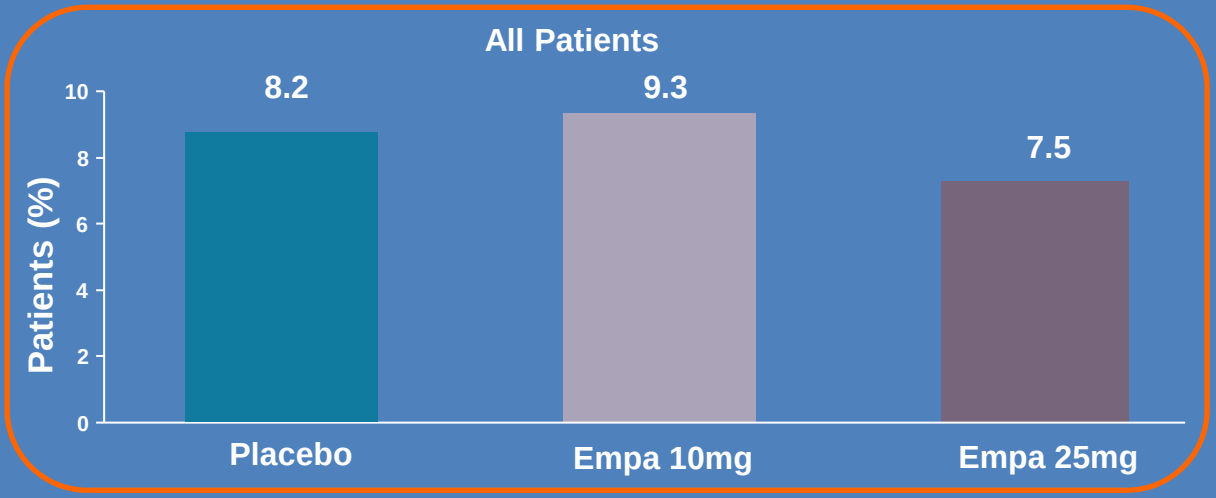


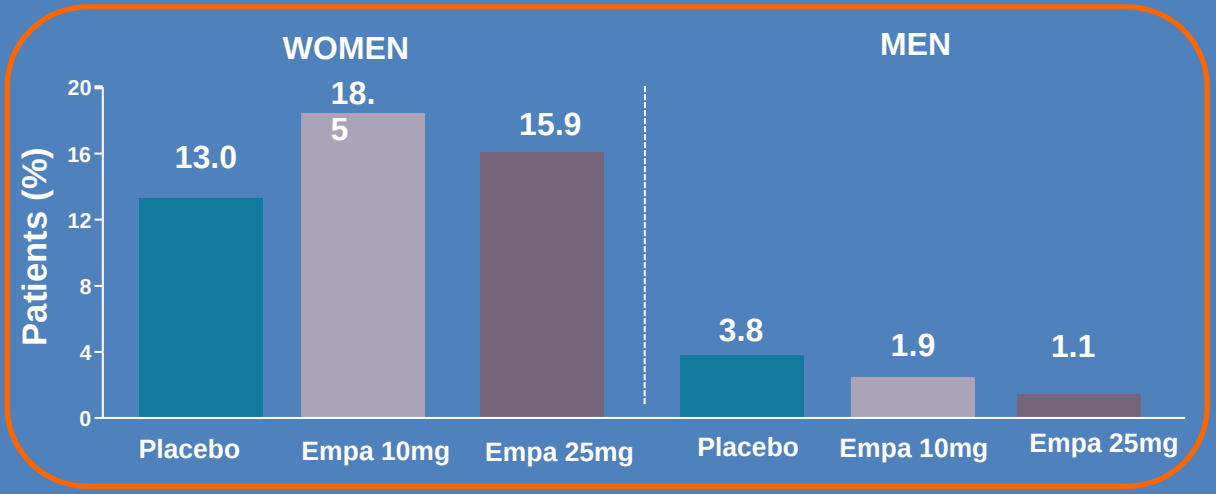


- Most mild-to-moderate in intensity with dapa
- Most responded to initial course of standard treatment
- Rarely led to discontinuation (0.3%)
- Most patients had only one event over 102 weeks (74.6% of dapa vs 86.4% placebo)
- Upper UTI were rare and balanced between groups

Presented at the FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting, July 19, 2011.
Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

Empagliflozin: Frequency of UTI Over 24 Weeks in Four Placebo-Controlled Studies





- Most mild in intensity with empa
- More common in women than men and in those with history of UTI
- Rarely led to discontinuation (0.1-0.2%)
- Most patients had only one event over 24 weeks (87.1% of empa vs 91.1% placebo)
- Severe UTI were rare and balanced between groups (0-0.2%)

Kim G et al. ADA Annual Meeting 2013. Abstract 74-LB

SGLT2 Inhibitors and Cardiovascular Effects

- Pooled phase 3 trials do not show cardiovascular harm
- Reduction in SBP and body weight
- Lipid effects (Pooled data;PBO-corrected)
  - LDL-C: ↑0.1-0.2 mmol/L
  - HDL-C: ↑0.02-0.07 mmol/L
  - TG: ↓0.05-0.22 mmol/L
- Ongoing CV outcome trials will help to determine the CV effects of this class

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013. Langkilde A el al. American Heart Assoication Annual Meeting 2011; Abstract 8947.
Hardy P et al. ADA Annual Meeting 2013. Abstract 1188-P. Hach T et al. ADA Annual Meeting 2013. Abstract 69-LB. **www.Clinicaltrials.gov**

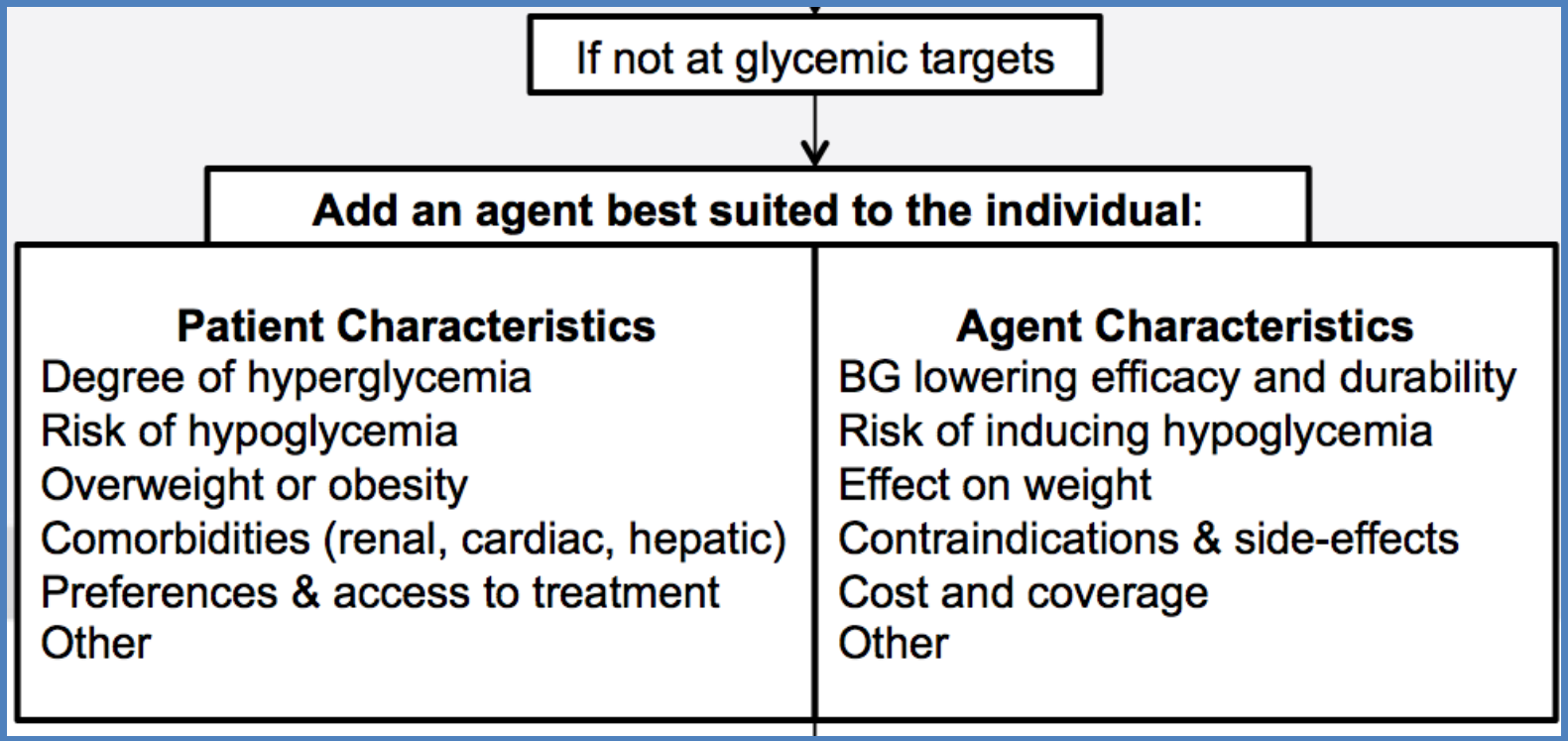
Ongoing Cardiovascular Outcome Trials: SGLT2 Inhibitors

	Therapies	#	Population	Endpoints	Results
CANVAS	Canagliflozin/ Placebo	4,363	CVD or high-risk for CVD	CV death, NF MI or NF stroke	June 2018
EMPA-REG OUTCOME	Empagliflozin/ Placebo	7,000	CVD	CV death, NF MI or NF stroke	March 2018
DECLARE	Dapagliflozin/Placebo	17,150	CVD or high-risk for CVD	CV death, NF MI or NF stroke	April 2019

Adapted from: www.Clinicaltrials.gov

Summary: Which agent to choose after metformin ?

The decision must be individualized



CDA 2013 Guidelines. Can J Diabetes. 2013;37:S61-68.

Which patients will benefit from SGLT2 inhibitors?

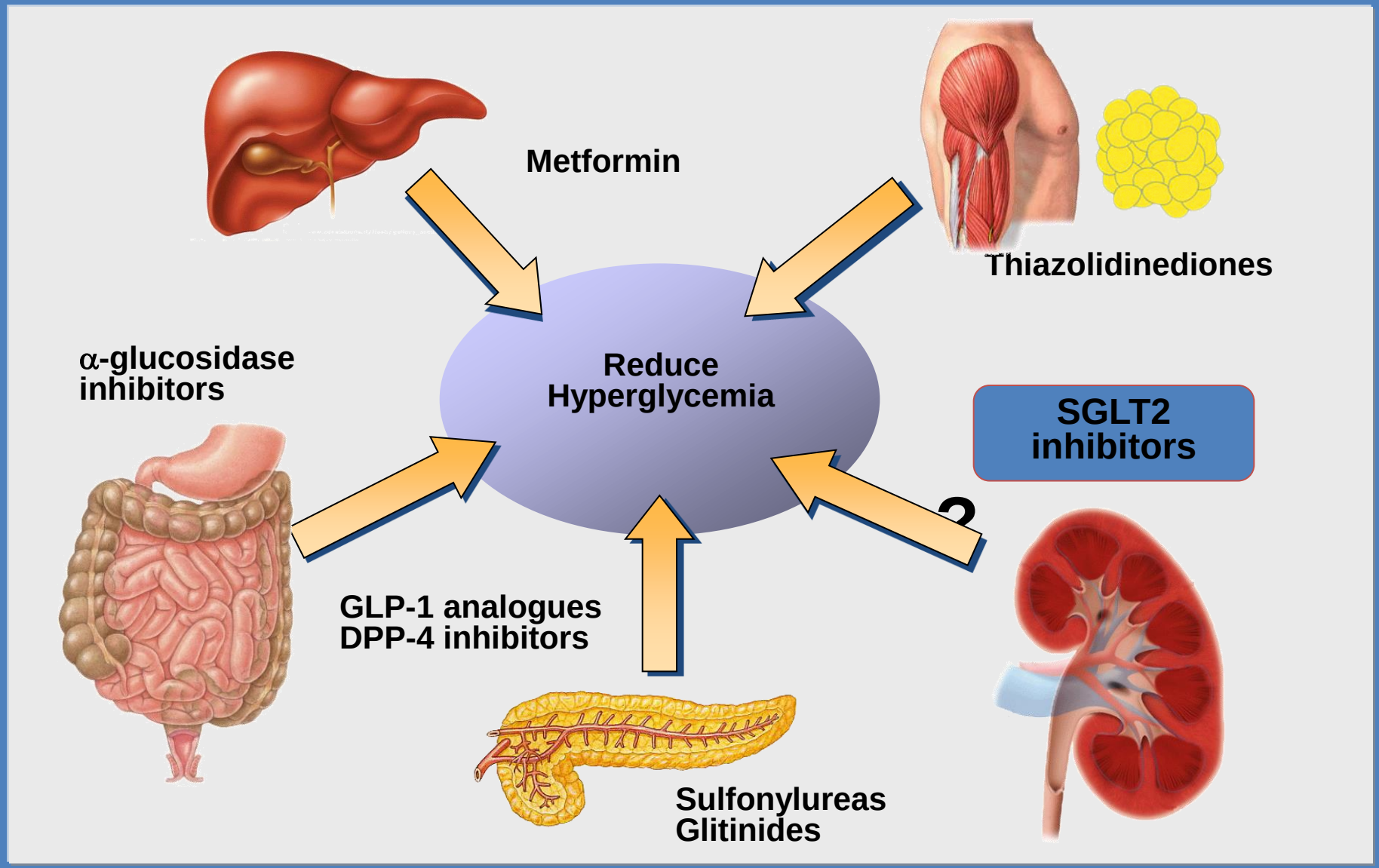
- Patients who have not achieved glycemic contorol with metformin, or those not able to take metformin
- Patients who would benefit from weight loss
- Patients with greater risk for hypoglycemia
- SGLT2 inhibitors offers improved glycemic control, weight loss and SBP reduction without increasing risk of hypoglycemia

Summary of SGLT2 Inhibitors

- **Sustained glucosuria with resultant decrease in HbA1c, FPG and PPG[1]**
- **Effective as monotherapy and in combination with other oral agents and insulin**
- **Weight loss**
- **Blood pressure lowering**
- **Sustained efficacy over duration of the long-term studies (up to 2 yrs)**
- **Increase in frequency of genital infections and possibly in UTIs**
  (Infections are manageable and did not result in discontinuation of in most cases)

1. Wilding et al. Diabetes Care. 2009;32:1656-62

Targets for Oral Antidiabetic Therapies



GLP, glucagon-like peptide;

DPP, didpeptidyl peptidase