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SGLT2 Inhibitors and GLP1RA in T1DM

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JBDS-IP Joint British Diabetes Societies for Inpatient Care
Association of British Clinical Diabetologists
Endotext

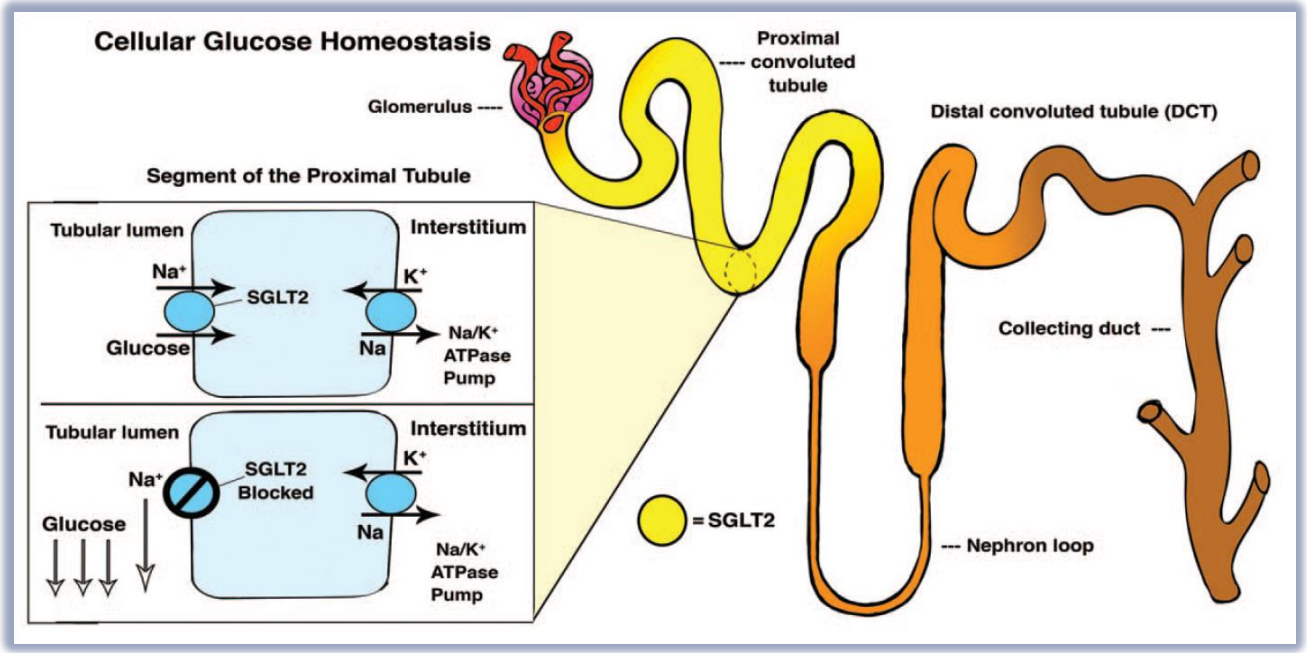
Disclosures

- In the last 12 months I have received honoraria, travel or fees for speaking or advisory boards from
  - AstraZeneca
  - Novo Nordisk
  - Boehringer-Ingelheim
  - Eli Lilly
  - Menarini

- I was an independent adjudicator for DKA and hypoglycaemia in the InTandem trials for sotagliflozin in type 1 diabetes and was a paid consultant for Sanofi to help their FDA application

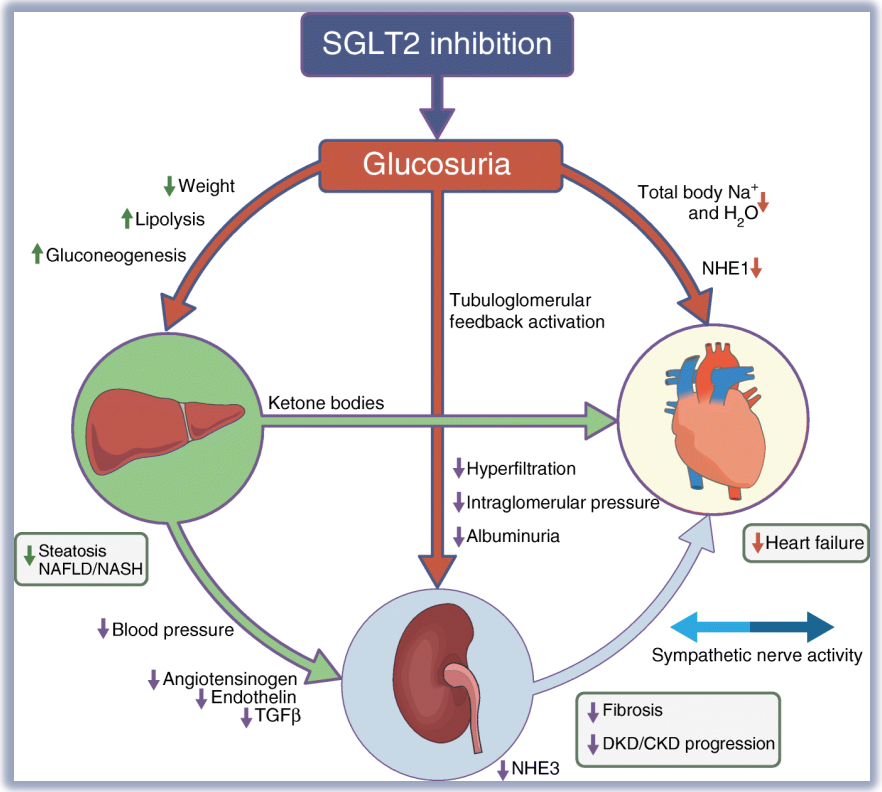
SGLT Inhibition in Type 1 – the Theory

- They work in an insulin independent manner to lower glucose



Bardia A et al Curr Op Anesthesiol 2019;32(1):80-85

SGLT2 Inhibition – Potential for Benefit



Wanner C et al Diabetologia 2018;61(10):2134-2139

SGLT Inhibitors in T1D - What Are the Data?

- EASE Trials (Empagliflozin)
- Canagliflozin
- Depict (Dapagliflozin)
- InTandem (Sotagliflozin)

Empagliflozin as Adjunctive to inSulin thErapy

	EASE 2 (52 weeks)			EASE 3 (26 weeks)			
	Placebo	10mg	25mg	Placebo	2.5mg	10mg	25mg
N = 1,707	239	243	241	238	237	244	242

Pooled Data	2.5mg	10mg	25mg	p value vs placebo
HbA_{1c} (%)	-0.28	-0.54	-0.53	<0.0001
Weight (Kg)	-1.8	-3.0	-3.4	<0.0001
TIR (%)	+1.0	+2.9*	+3.1*	*<0.0001
TDD (%)	-6.4	-13.3	-12.7	<0.0001
Systolic BP (mmHg)	-2.1	-3.9	-3.7	<0.05
Rate of DKA (%)	0.8	4.3	3.3	Placebo 1.2
Severe Hypoglycaemia (%)	1.2	4.1	2.7	Placebo 3.0

Rosenstock J et al Diabetes Care 2018;41(12):2560-2569

Canagliflozin – 18 Weeks

	Placebo	100mg	300mg
N = 351	117	117	117
HbA_{1c} (%)	+0.01	-0.29	-0.25
HbA_{1c} reduction of >0.4%	14.5%	36.9%	41.4%
Weight (Kg)	+0.3	-2.6	-4.2
TDD (%) vs Placebo	-	-8.9	-12.9
Rate of DKA (%)	0	4.3	6.0
Severe Hypoglycaemia (%)	1.7	2.6	6.8

Henry RR et al Diabetes Care 2015;38(12):2258-2265

Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes

	DEPICT 1 (52 weeks)			DEPICT 2 (52 weeks)		
	Placebo	5mg	10mg	Placebo	5mg	10mg
N = 1439	257	254	255	216	231	226
HbA_{1c} (%)	0.06	-0.27	-0.31	0.09	-0.11	-0.16
HbA_{1c} reduction of ≥0.5%	25.3%	43%	45.7%	22.3%	35.3%	35.2%
Weight (Kg)	0.25	-2.31	-3.83	0.6	-3.2	-3.0
TIR (%)		2.2	2.6		2.2	2.6
TDD (%)	-2	-8	-9.5	0	-10.5	-8.5
Rate of DKA (%)	1.9	4	3.4	0.4	4.1	3.7
Severe Hypoglycaemia (%)	1.1	0.6	0.7	0.7	1.8	0.4

Dandona P et al Diabetes Care 2018;41(12):2552-2559
Mathieu C et al DOM 2020;22(9):1516-1526

Type 1 Approval in 2019!

Forxiga approved in Europe for type-1 diabetes

PUBLISHED
25 March 2019

25 March 2019 07:00 GMT

Forxiga is the first oral medicine approved in Europe as an adjunct to insulin for adults with type-1 diabetes and the first AstraZeneca medicine ever approved for type-1 diabetes

The European Commission (EC) has approved *Forxiga* (dapagliflozin) for use in type-1 diabetes (T1D) as an adjunct to insulin in patients with a BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy. This is the first approval of *Forxiga* for the treatment of patients with T1D.

Forxiga approved in Europe for type-1 diabetes (astrazeneca.com)

Type 1 Withdrawal in 2021!

NICE National Institute for Health and Care Excellence

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Dapagliflozin with insulin for treating type 1 diabetes

Technology appraisal guidance [TA597] Published: 28 August 2019

Guidance

In **November 2021**, we withdrew this guidance because dapagliflozin (Forxiga) with insulin is no longer licensed for treating type 1 diabetes.

https://www.nice.org.uk/guidance/ta597

Sotagliflozin

	Placebo	200mg	400mg
N = 3479			
HbA_{1c} (%)*	-	-0.25	-0.41
Weight (%)*	-	-3.17	-3.76
TDD (%)*		-7.1	-10.7
Systolic BP (mmHg)*	-	-3.01	-4.26
Rate of DKA (%)	0.2	2.9	3.8
Severe Hypoglycaemia (events per patient year)*	-	0.79	0.66

* = vs Placebo

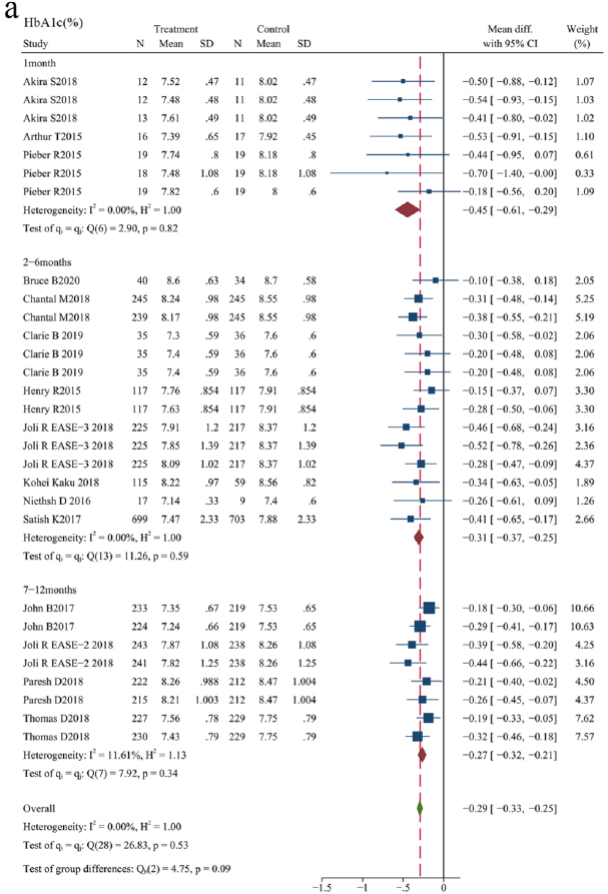
Musso G et al BMJ 2019;365:l1328
Peters A et al Diabetes Care 2020;43(11):2713-2720

Meta-analysis – HbA_{1c}

At 1 month

At 2-6 months

At 7-12 months



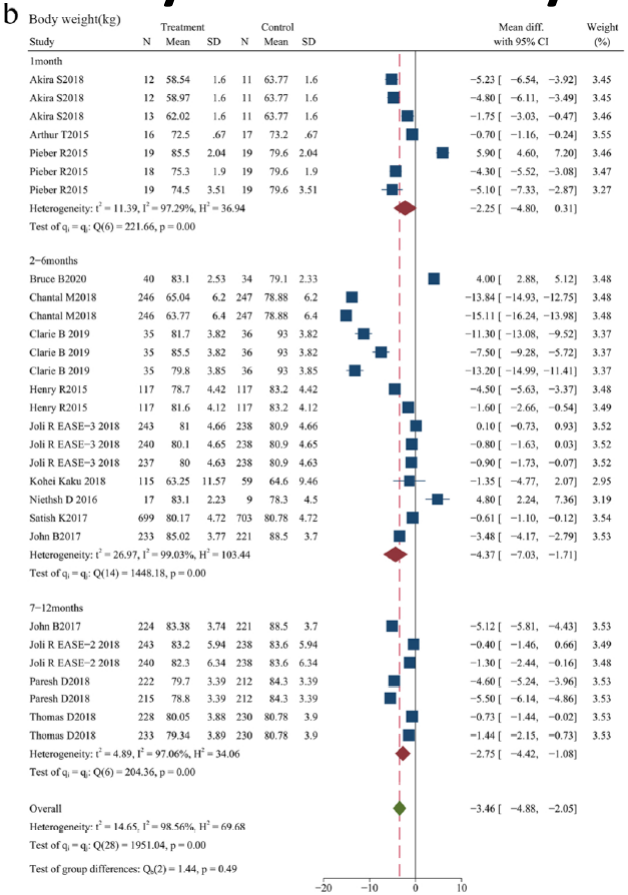
Nan J et al Prim Care Diabet 2024;18(1):17-24

Meta-analysis – Body Weight

At 1 month

At 2-6 months

At 7-12 months

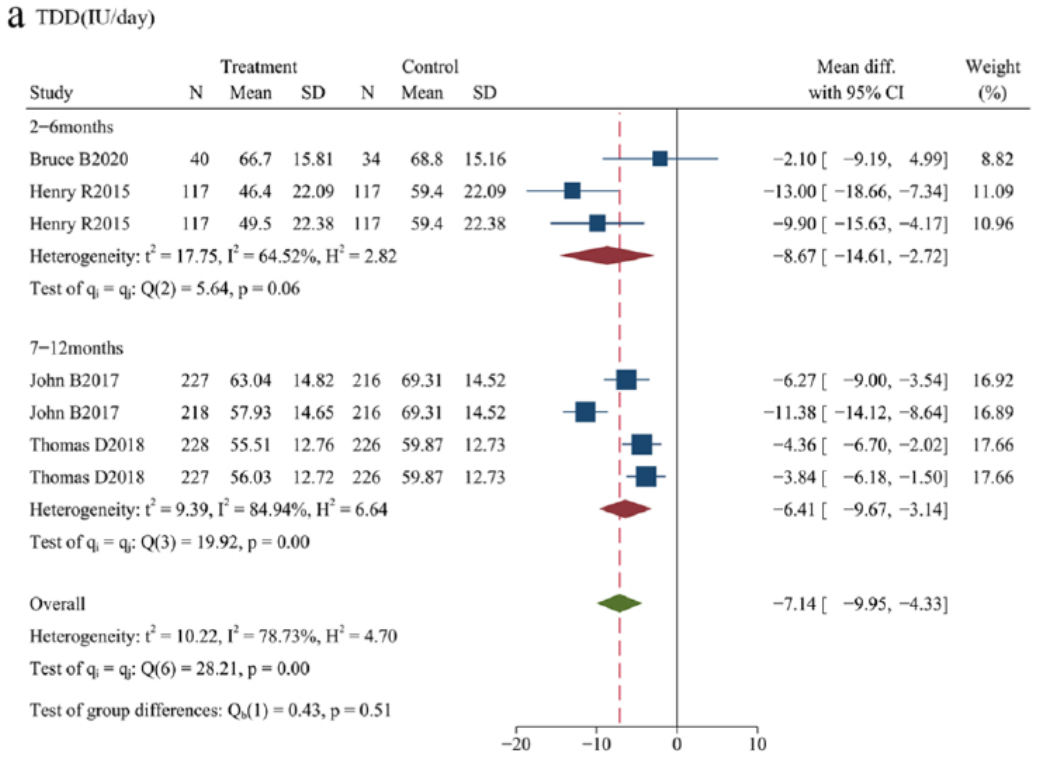


Nan J et al Prim Care Diabet 2024;18(1):17-24

Meta-analysis – Total Daily Dose

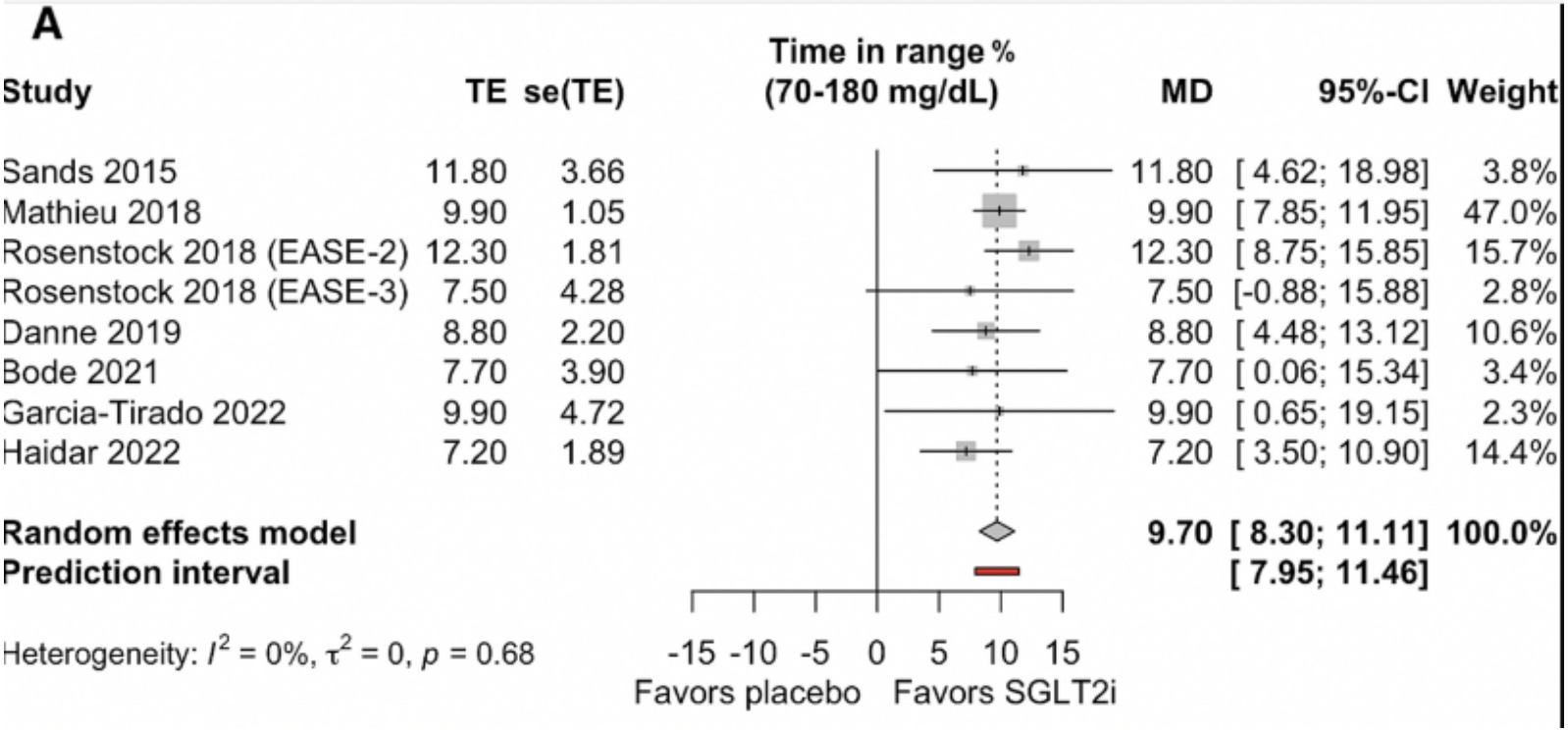
At 2-6 months

At 7-12 months



Nan J et al Prim Care Diabet 2024;18(1):17-24

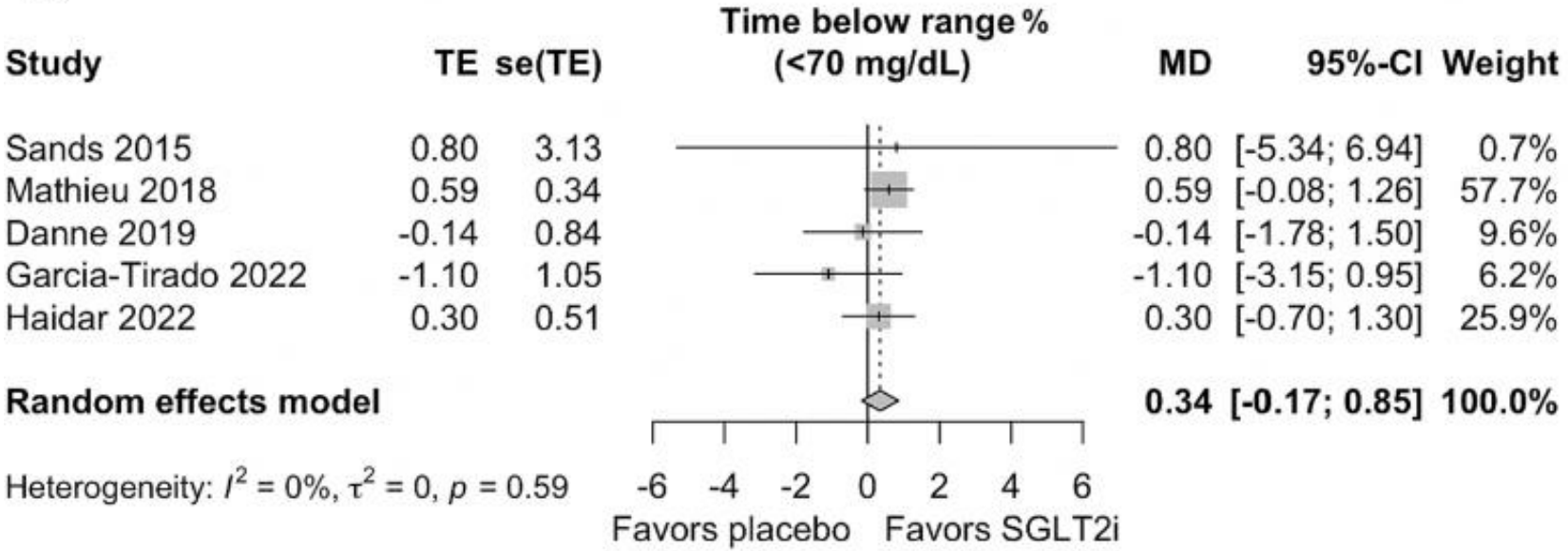
Meta-analysis – TIR



Popovic DS et al Metabolism 2024;1513:155791

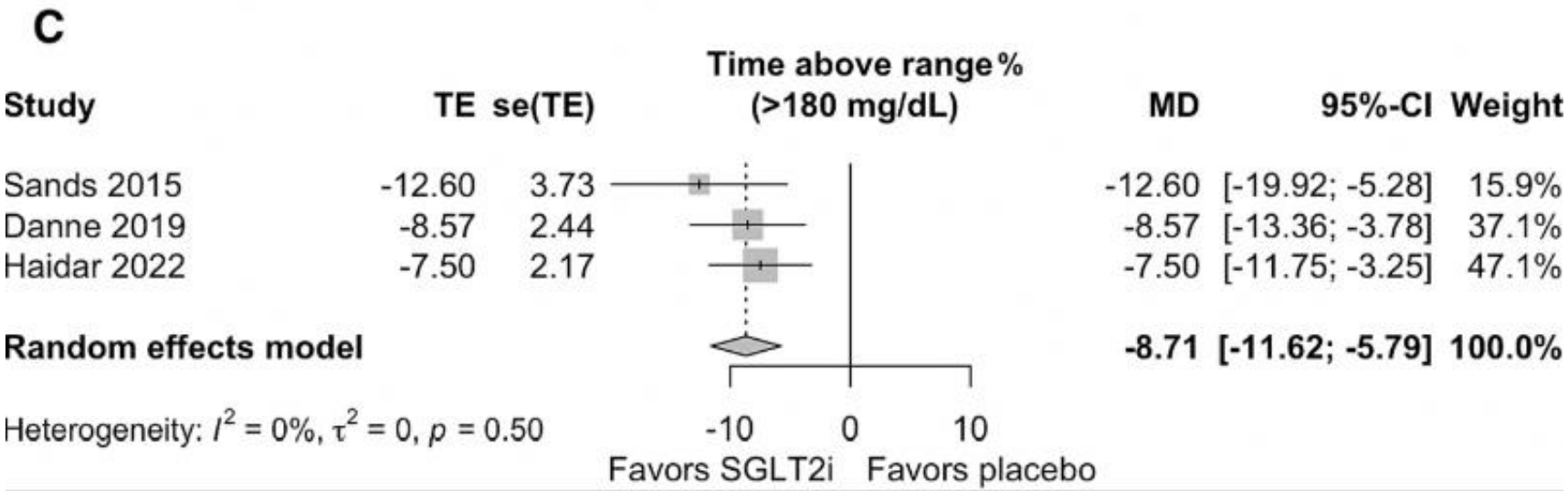
Meta-analysis – TBR

B



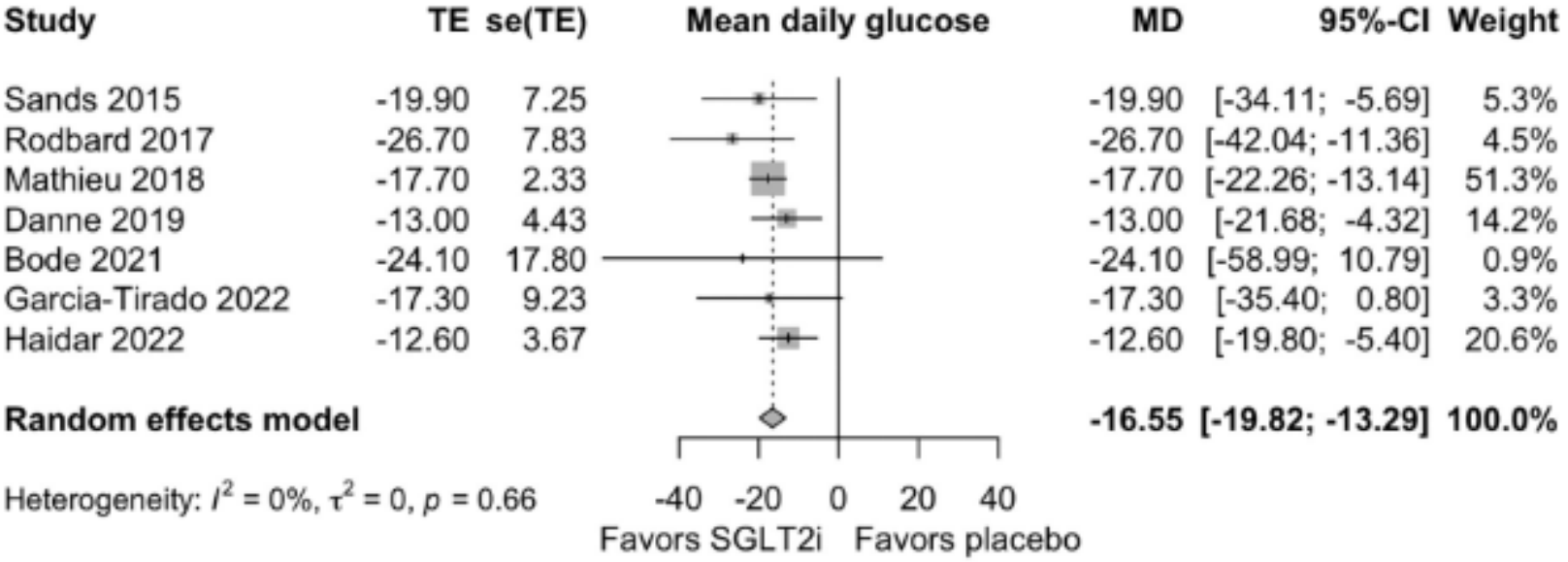
Popovic DS et al Metabolism 2024;1513:155791

Meta-analysis – TAR



Popovic DS et al Metabolism 2024;1513:155791

Meta-analysis – Mean Daily Glucose



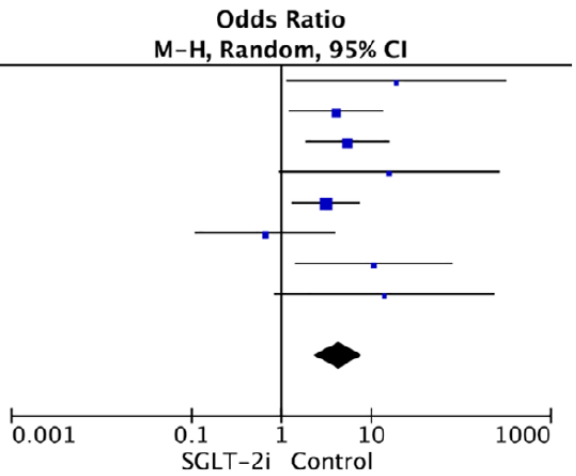
Popovic DS et al Metabolism 2024;1513:155791

Meta-analysis – DKA (1)

(a)

Study or Subgroup	SGLT-2i Events	SGLT-2i Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Henry RR-2015-Cana	17	234	0	117	4.3%	18.91 [1.13, 317.24]	2015
Dandona P-2018-Depict-1	26	573	3	260	18.6%	4.07 [1.22, 13.58]	2017
Garg SK-2017-Sota	21	699	4	703	21.9%	5.41 [1.85, 15.85]	2017
Danne T-2018-Sota	15	524	0	258	4.3%	15.73 [0.94, 263.90]	2018
Rosenstock J-2018-EASE2	37	980	6	484	28.7%	3.13 [1.31, 7.46]	2018
Rosenstock J-2018-EASE3	2	241	3	241	9.8%	0.66 [0.11, 4.01]	2018
Buse BJ-2018-Sota	20	525	1	268	8.0%	10.57 [1.41, 79.22]	2018
Mathieu C-2018-Dapa	13	541	0	272	4.3%	13.92 [0.82, 235.07]	2018
Total (95% CI)		**4317**		**2603**	**100.0%**	**4.34 [2.37, 7.96]**	
Total events	151		17				

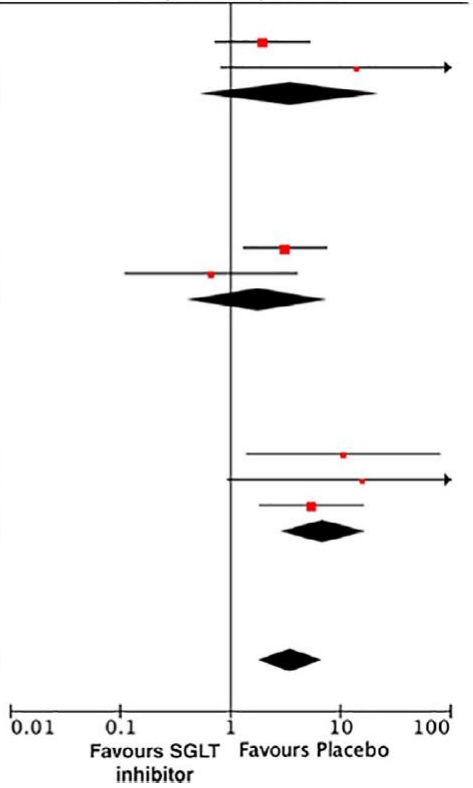
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 8.57$, df = 7 ($P = .28$); $I^2 = 18\%$
Test for overall effect: Z = 4.74 ($P < .00001$)



Wang W et al DOM 2020;22(10):1767-1776

Meta-analysis – DKA (2)

Study or Subgroup	SGLT inhibitor Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dapagliflozin						
DEPICT-1 (Dapa 5 mg & 10 mg)	21	573	5	260	23.2%	1.94 [0.72, 5.20]
DEPICT-2 (Dapa 5 mg & 10 mg)	13	541	0	272	5.0%	13.92 [0.82, 235.07]
Subtotal (95% CI)		**1114**		**532**	**28.2%**	**3.45 [0.53, 22.44]**
Total events	34		5			
Heterogeneity: $Tau^2 = 1.04$; $Chi^2 = 1.89$, df = 1 ($P = 0.17$); $I^2 = 47\%$						
Test for overall effect: Z = 1.30 ($P = 0.19$)						
Empagliflozin						
EASE-2/3 (Empa 10 mg & 25 mg)	37	980	6	484	26.2%	3.13 [1.31, 7.46]
EASE-3 (Empa 2.5 mg)	2	241	3	241	10.6%	0.66 [0.11, 4.01]
Subtotal (95% CI)		**1221**		**725**	**36.8%**	**1.77 [0.41, 7.69]**
Total events	39		9			
Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 2.32$, df = 1 ($P = 0.13$); $I^2 = 57\%$						
Test for overall effect: Z = 0.76 ($P = 0.44$)						
Sotagliflozin						
InTandem1 (Sota 200 mg & 400 mg)	20	525	1	268	8.9%	10.57 [1.41, 79.22]
InTandem2 (Sota 200 mg & 400 mg)	15	524	0	258	5.0%	15.73 [0.94, 263.90]
InTandem3 (Sota 200 mg & 400 mg)	21	699	4	703	21.2%	5.41 [1.85, 15.85]
Subtotal (95% CI)		**1748**		**1229**	**35.1%**	**6.89 [2.81, 16.93]**
Total events	56		5			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.76$, df = 2 ($P = 0.69$); $I^2 = 0\%$						
Test for overall effect: Z = 4.21 ($P < 0.0001$)						
Total (95% CI)		**4083**		**2486**	**100.0%**	**3.47 [1.78, 6.75]**
Total events	129		19			
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 8.91$, df = 6 ($P = 0.18$); $I^2 = 33\%$						
Test for overall effect: Z = 3.66 ($P = 0.0003$)						
Test for subgroup differences: $Chi^2 = 2.49$, df = 2 ($P = 0.29$), $I^2 = 19.7\%$						



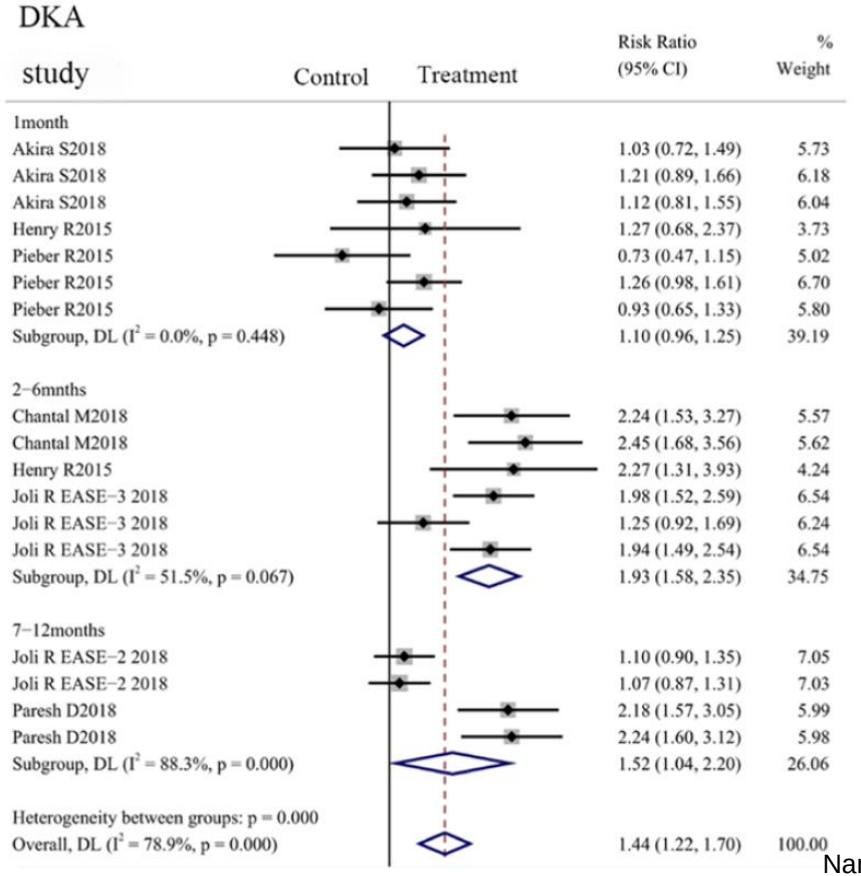
Goldenberg RM et al DOM 2019;21(10):2192-2202

Meta-analysis – DKA (3)

At 1 month

At 2-6 months

At 7-12 months



Nan J et al Prim Care Diabet 2024;18(1):17-24

Caution! A Call for Standardisation

DIABETES RESEARCH AND CLINICAL PRACTICE 155 (2019) 107797

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Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Review

Defining and characterising diabetic ketoacidosis in adults

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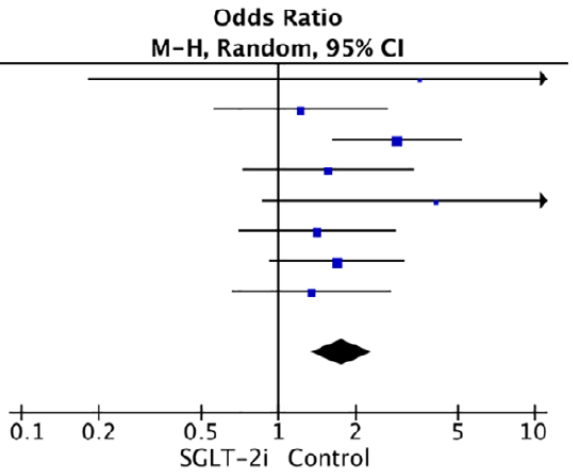
Norwich Medical School, University of East Anglia, Norwich, Norfolk NR4 7TJ, UK

Meta-analysis – Discontinuation

(b)

Study or Subgroup	SGLT-2i Events	SGLT-2i Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Henry RR-2015-Cana	3	234	0	117	0.8%	3.55 [0.18, 69.36]	2015
Dandona P-2018-Depict-1	24	573	9	260	12.1%	1.22 [0.56, 2.66]	2017
Garg SK-2017-Sota	44	699	16	703	21.8%	2.88 [1.61, 5.16]	2017
Danne T-2018-Sota	28	524	9	258	12.6%	1.56 [0.73, 3.36]	2018
Rosenstock J-2018-EASE3	8	241	2	241	3.0%	4.10 [0.86, 19.52]	2018
Buse BJ-2018-Sota	30	525	11	268	14.8%	1.42 [0.70, 2.87]	2018
Rosenstock J-2018-EASE2	47	980	14	484	20.1%	1.69 [0.92, 3.10]	2018
Mathieu C-2018-Dapa	29	541	11	272	14.7%	1.34 [0.66, 2.73]	2018
Total (95% CI)		**4317**		**2603**	**100.0%**	**1.76 [1.34, 2.31]**	
Total events	213		72				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.00$, df = 7 ($P = .54$); $I^2 = 0\%$
Test for overall effect: Z = 4.07 ($P < .0001$)



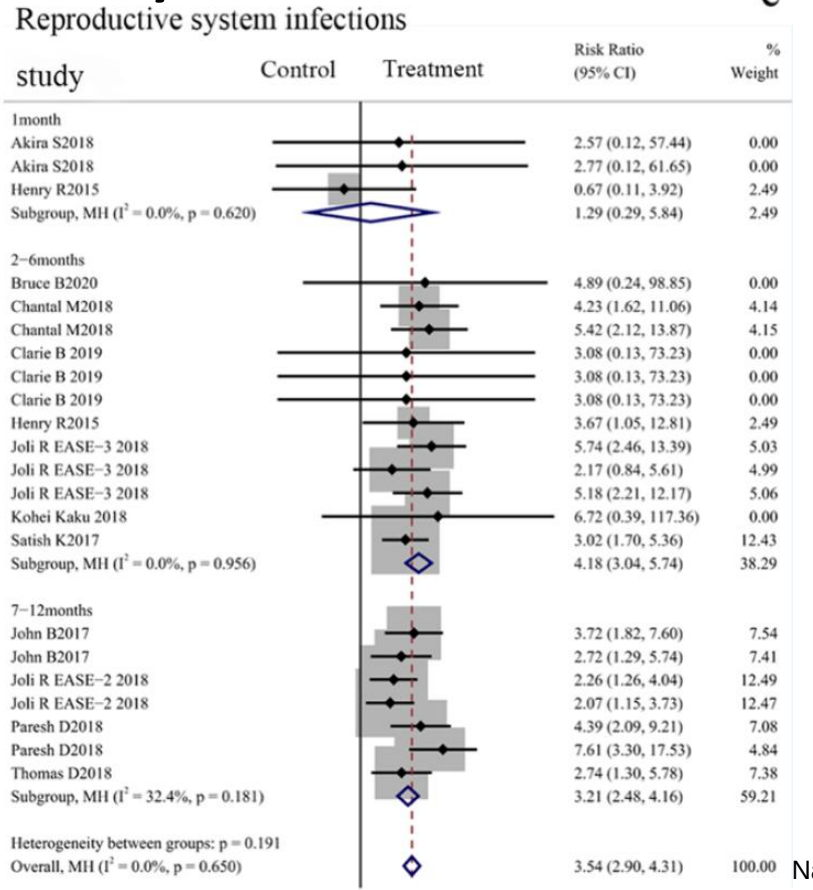
Wang W et al DOM 2020;22(10):1767-1776

Meta-analysis – Genital Infections

At 1 month

At 2-6 months

At 7-12 months



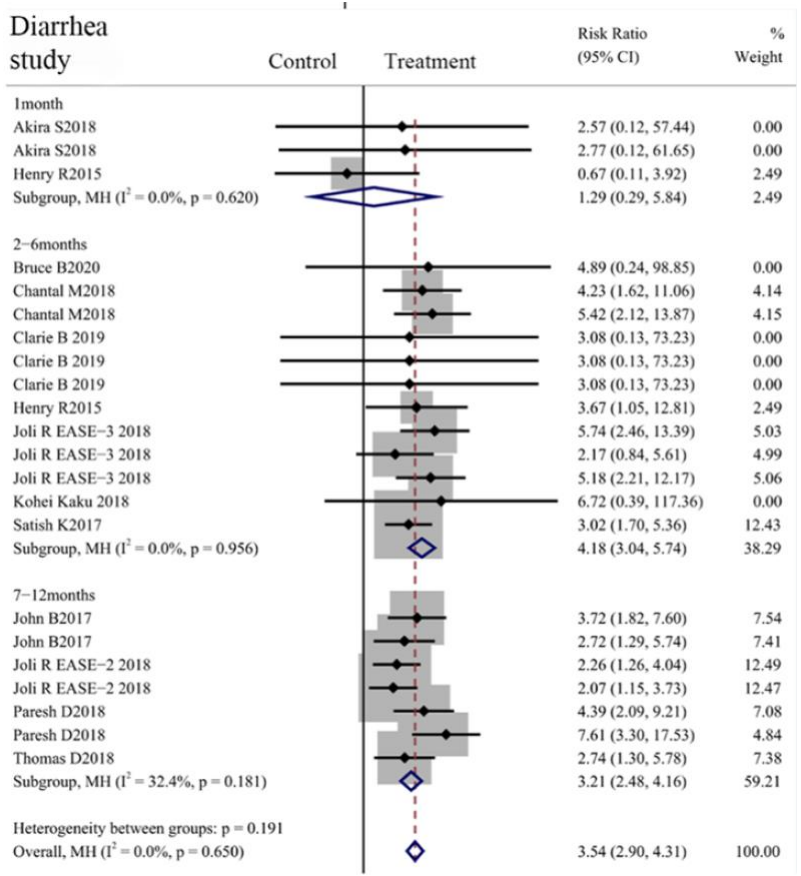
Nan J et al Prim Care Diabet 2024;18(1):17-24

Meta-analysis – Diarrhoea

At 1 month

At 2-6 months

At 7-12 months



Nan J et al Prim Care Diabet 2024;18(1):17-24

Real World Data

- 992 people with type 1 having taken only an SGLT2i in addition to insulin – 933 after propensity matching
  - 47% empagliflozin
  - 27% dapagliflozin
  - 25% canagliflozin
- 65% for at least 3 years
- 87% from the USA, 13% EU/UK

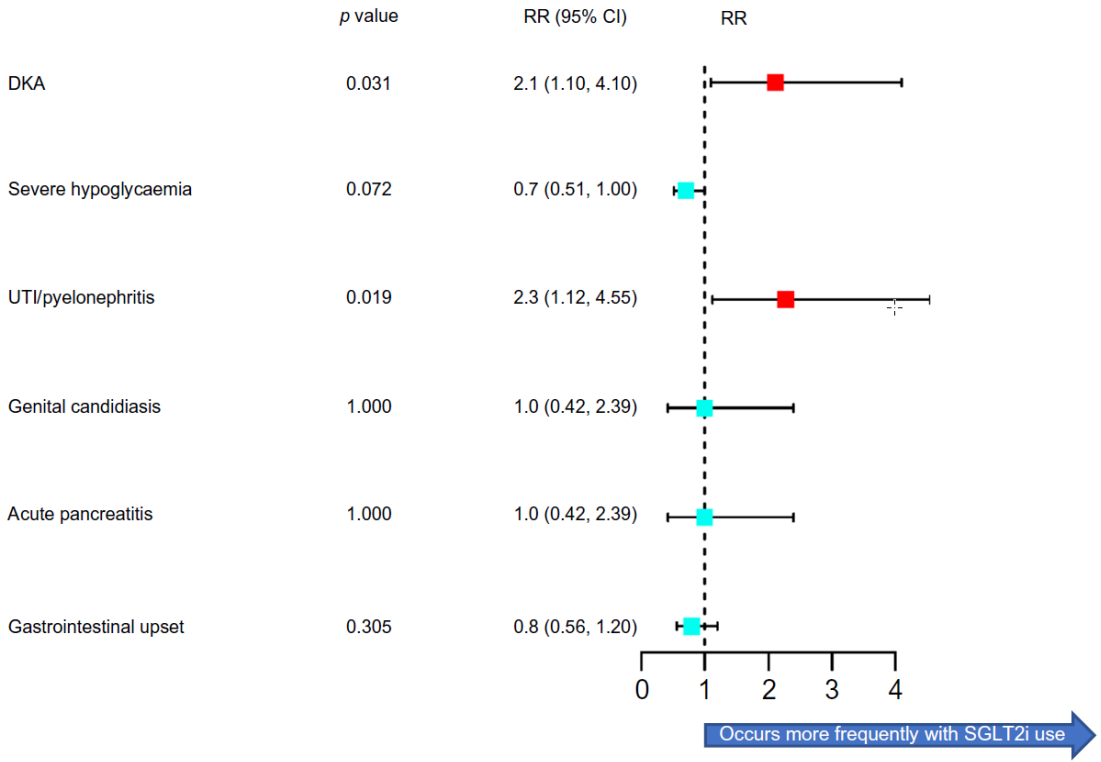
Anson M et al Diabetologia 2023;66(9):1869-1881

Real World Data Over 5 years

Characteristic	SGLT2i (n=933)		
	Baseline	Post initiation	Change
HbA_{1c} (mmol/mol)	65.0±20.9	62.8±17.6	−2.6
HbA_{1c} (%)[a]	8.1±1.9	7.9±1.6	−0.2
Weight (kg)	91.2±21.9	88.8±21.4	−2.4
BMI (kg/m^2)	30.2±6.6	30.0±5.9	−0.2
eGFR (ml/min per $1.73m^2$)	79.9±28.6	83.4±28.3	+3.5
Cholesterol (mmol/l)	4.4±1.1	4.3±1.1	−0.1

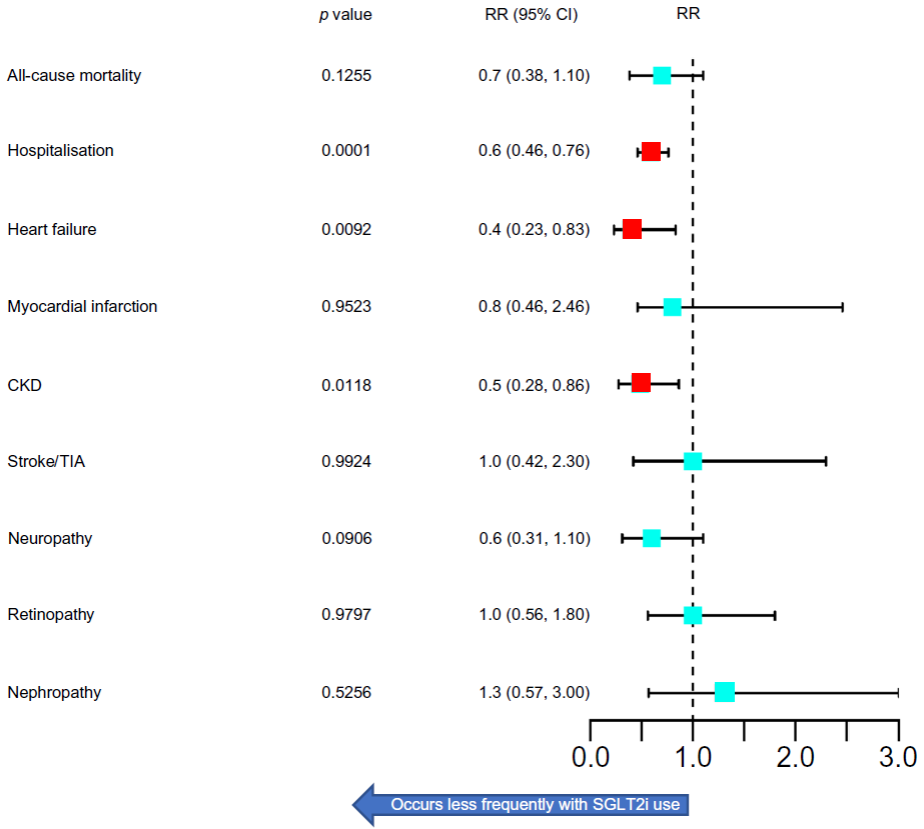
Anson M et al Diabetologia 2023;66(9):1869-1881

Real World Data



Anson M et al Diabetologia 2023;66(9):1869-1881

Real World Data



Anson M et al Diabetologia 2023;66(9):1869-1881

Current State

- As far as I am aware, SGLT inhibitors are not licensed anywhere in the world for type 1 diabetes
- If used cautiously, can they be of benefit to those with type 1 – or pancreatectomised (no glucagon)?

Giaccari A Diabetes Care 2024;47(1):50-51

But….Do Not Use In Inpatients

Check for updates

Initiation and Continuation of Sodium–Glucose Cotransporter 2 Inhibitors in Hospital Inpatients: Ready for Prime Time?

Ketan Dhatariya

Diabetes Care 2022;45:2806–2807 | https://doi.org/10.2337/dci22-0039

Dhatariya K Diabetes Care 2022;45(12):2806-2807

SGLT Induced DKA Mitigation Strategies

General principles for reducing ketosis and mitigating risk of diabetic ketoacidosis in symptomatic SGLT inhibitor-treated individuals with type 1 diabetes

- Recognize the symptoms of DKA
  - Nausea | vomiting | abdominal pain | malaise | worsening polyuria | polydypsia | shortness of breath
- Avoid very low carbohydrate and ketogenic diets
- Avoid excess alcohol
- Exert caution with extreme exercise
- Stop SGLT inhibitor at least 3 days prior to a major surgery
- Never stop taking insulin

- Sick-day management
  - Stop SGLT inhibitor
  - If symptomatic, check blood ketones and glucose
  - Consult the **STOP DKA** table for supplemental bolus insulin and carbohydrate recommendations even if blood glucose is normal
- Keep hydrated during acute illness
  - Ingest at least 250–500 mL of sugar-free and/or carbohydrate-containing fluids every 2–4 hours
- Check insulin pump for potential delivery issue
  - Inject insulin subcutaneously if necessary
- Seek medical attention if
  - high levels of ketones persist despite extra insulin and/or increased carbohydrate intake over a 6–10 hours period
  - vomiting
  - unable to keep down fluids
  - there are persistent symptoms of DKA

S

T **STop** SGLT inhibitor

I inject bolus **Insulin**

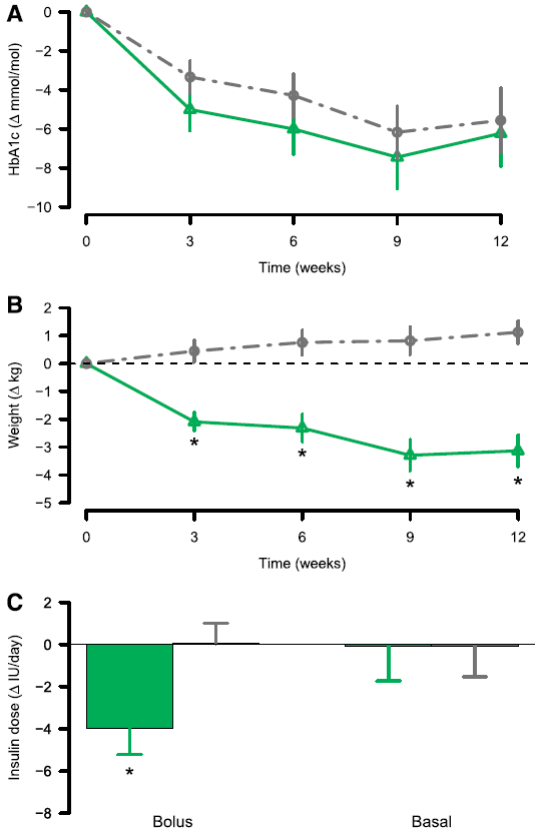
C consume 30 g **Carbohydrates**

H **Hydrate** (drink water)

Goldenberg RM et al DOM 2019;21(10):2192-2202
Garg S et al Diabetes Technology & Therapeutics 2018:20(9):571-575

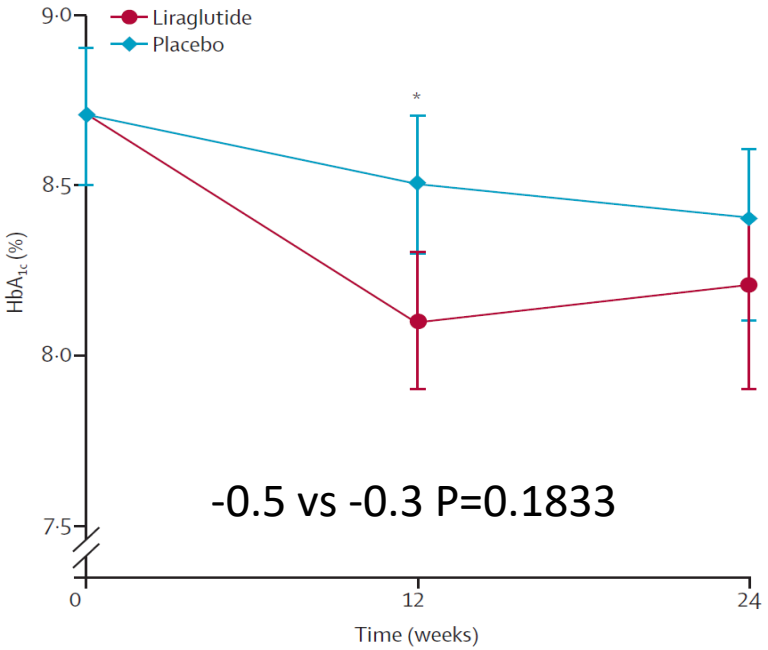
GLP1 RA in Type 1 Diabetes

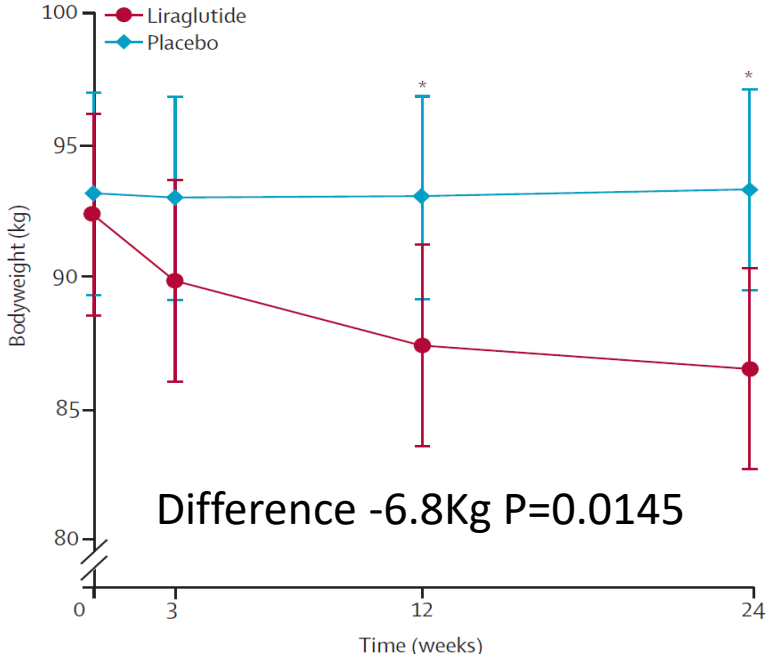
- Liraglutide 1.2mg daily effect on
  - HbA_{1c}
  - Body weight
  - Total daily insulin dose



Frandsen CS et al Diabetes Care 2015;38(12):2250-2257

1.8mg Dose

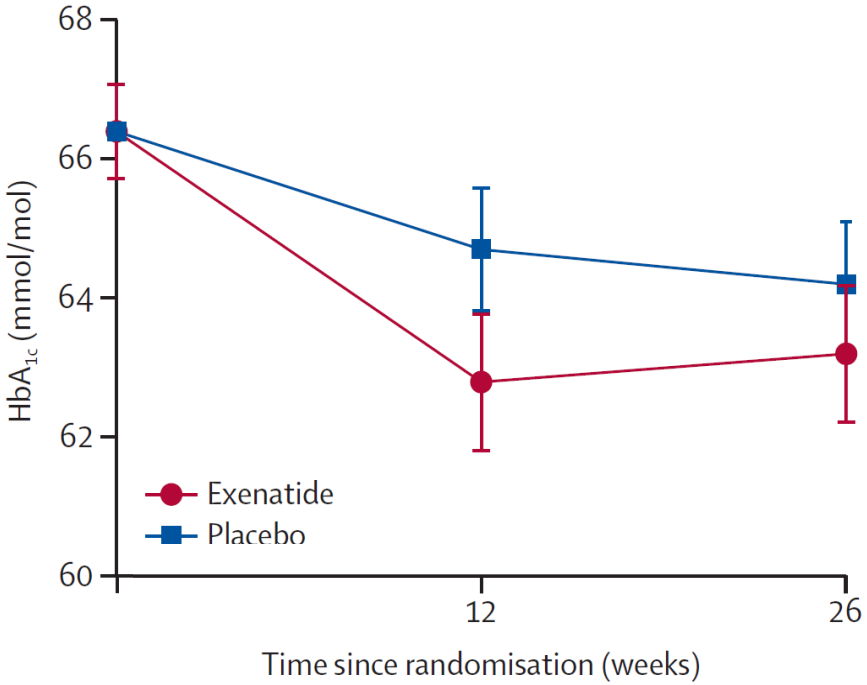


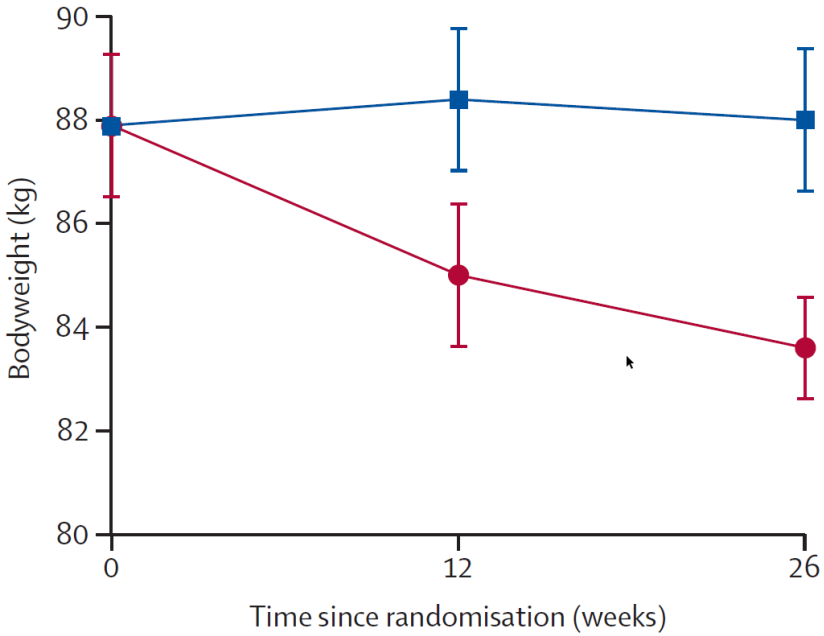


Other difference: TDD -5.8 units/day (p=0.023)
No significant differences in BP, TIR, or TBR

Dejgaard TF et al Lancet Diab Endocrinol 2016;4(3):221-232

Exenatide 10µg Three Times Daily



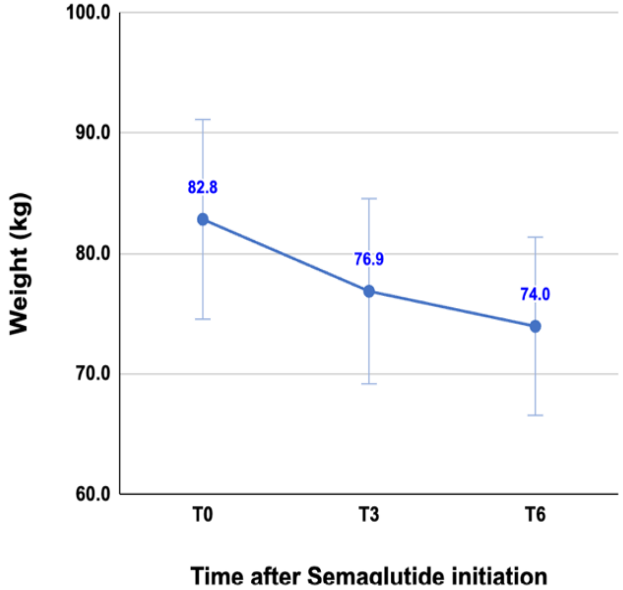


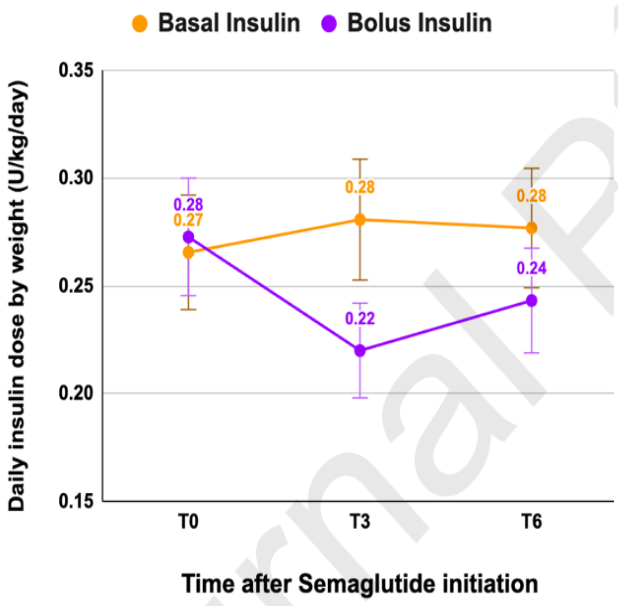
-3.2 vs -2.2 p=0.36

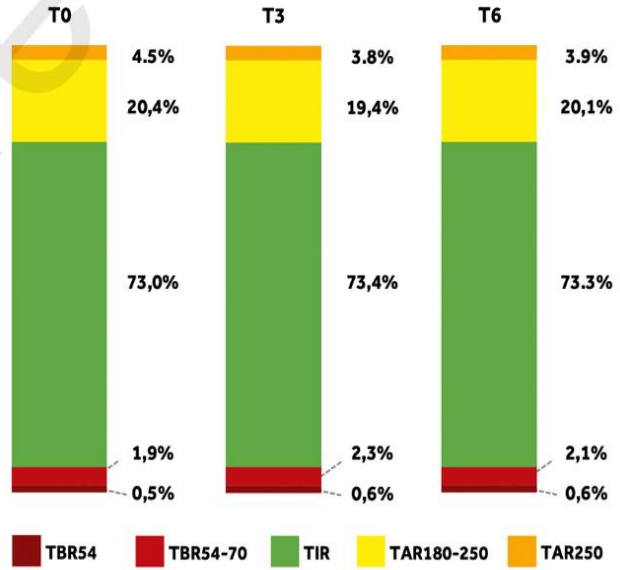
Difference -4.4Kg p<0.001

Johansen NJ et al Lancet Diab Endocrinol 2020;8(4):313-324

Semaglutide 0.5mg weekly

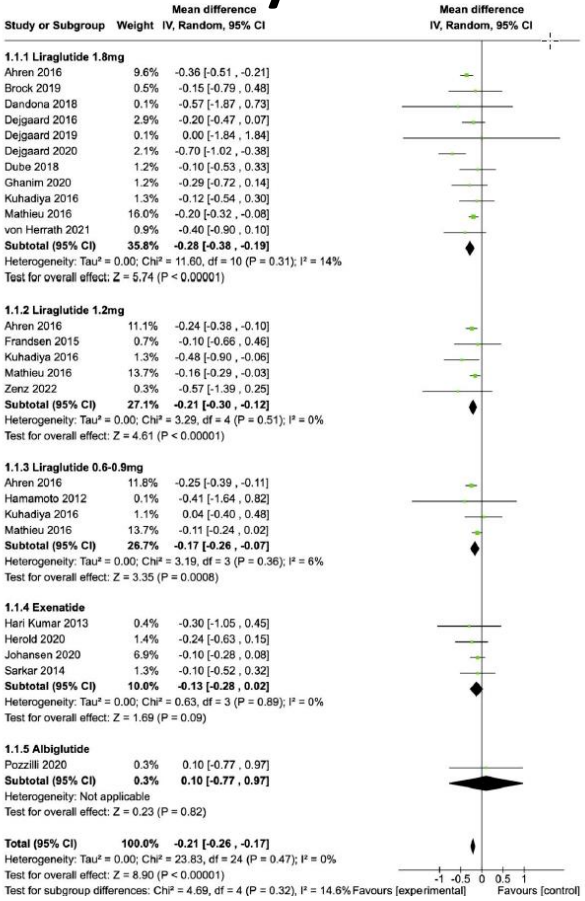






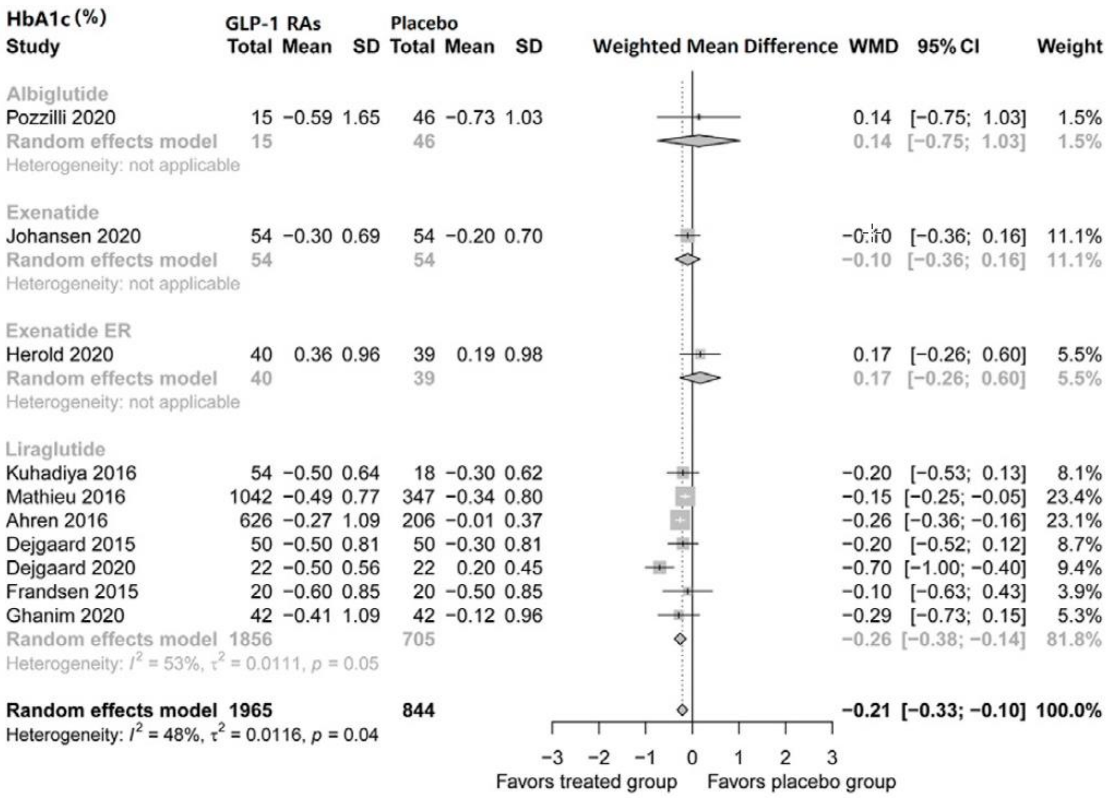
Grassi BA DRCP 2024; https://doi.org/10.1016/j.diabres.2024.111593

Meta-analysis – HbA_{1c}



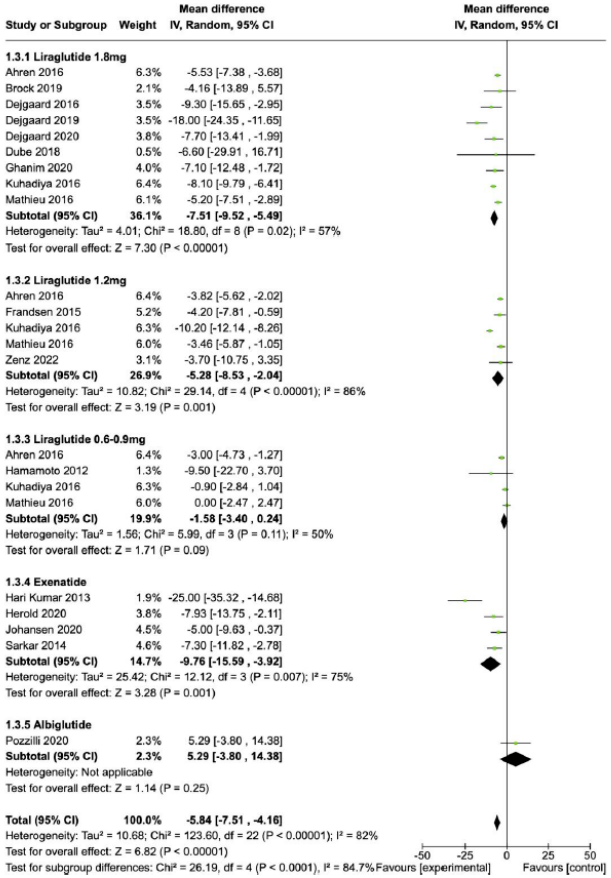
Park J et al JCEM 2024;109(1):279-292

Meta-analysis – HbA_{1c}



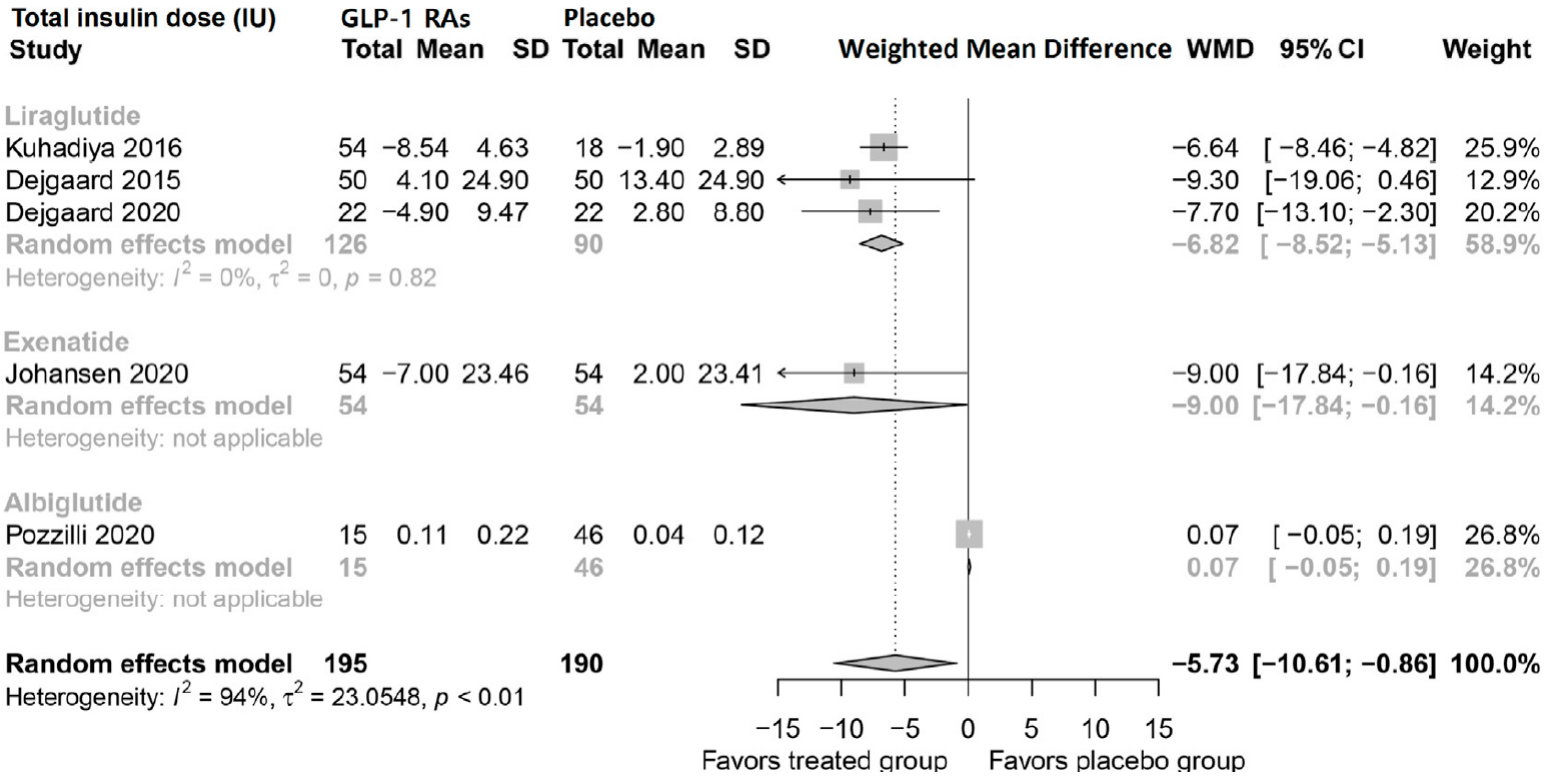
Tan X et al Frontiers in Pharmacology 2023;14:975880

Meta-analysis – Total Daily Dose



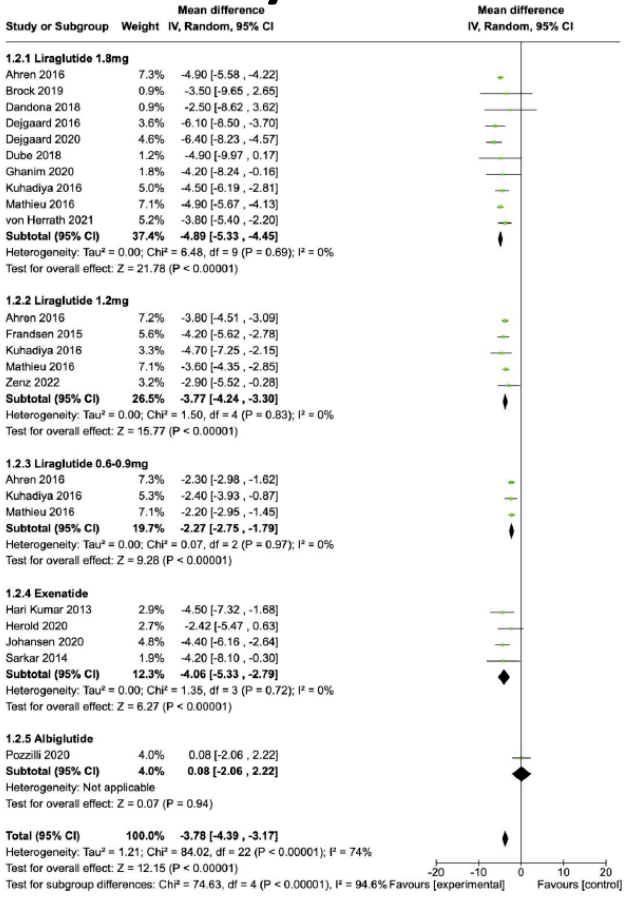
Park J et al JCEM 2024;109(1):279-292

Meta-analysis – Total Daily Dose



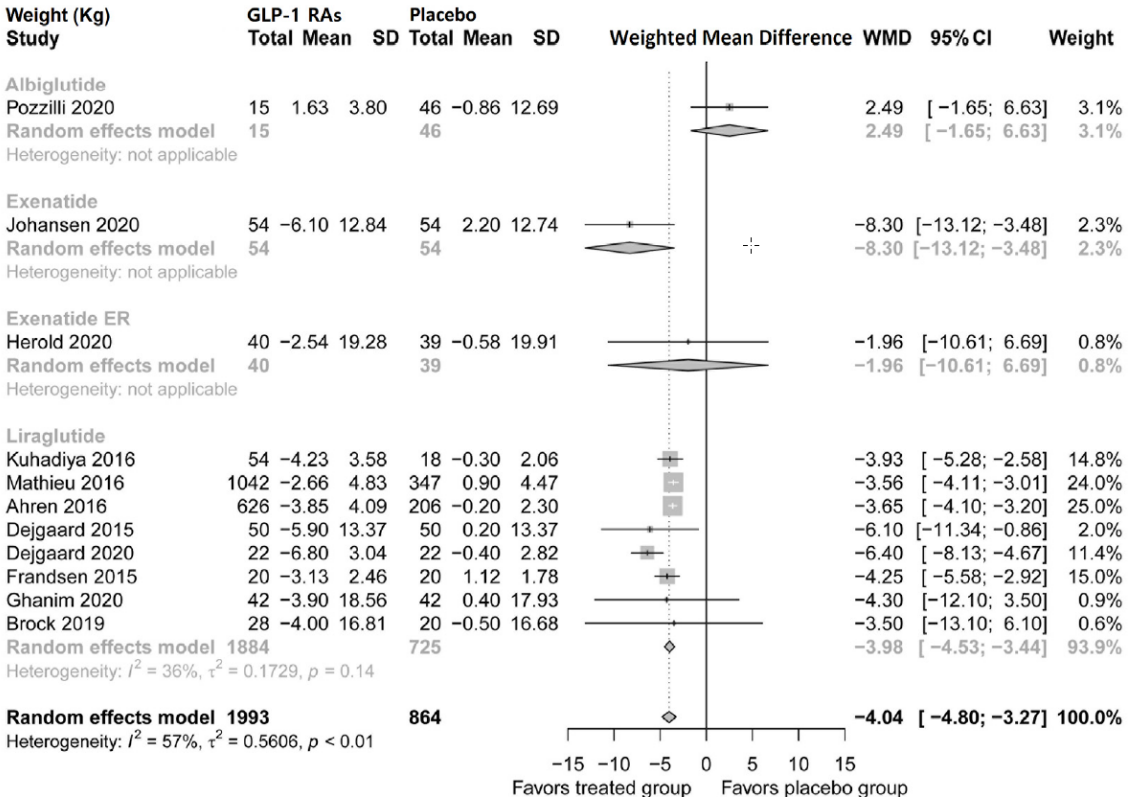
Tan X et al Frontiers in Pharmacology 2023;14:975880

Meta-analysis – Weight



Park J et al JCEM 2024;109(1):279-292

Meta-analysis – Weight



Tan X et al Frontiers in Pharmacology 2023;14:975880

Real World Data

- 1822 people with type 1 having taken only an SGLT2i in addition to insulin – 933 after propensity matching
  - 37% liraglutide
  - 25% semaglutide
  - 24% dulaglutide
  - 13% exenatide
- 72% for at least 3 years
- 97% from the USA, 3% EU/UK

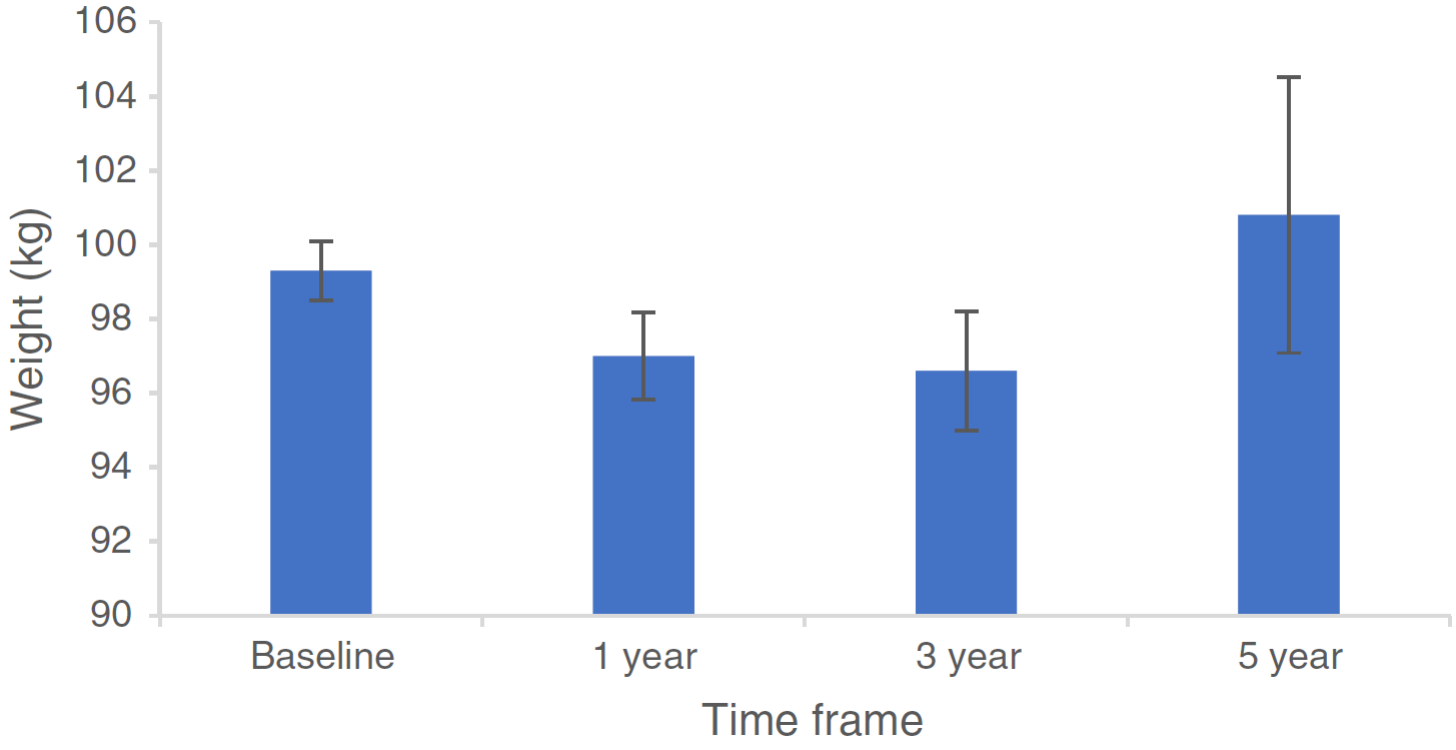
Anson M et al Diabetologia 2023;66(9):1869-1881

Real World Data Over 5 years

Characteristic	SGLT2i (*n*=933)			GLP−1 RA (*n*=933)		
	Baseline	Post initiation	Change	Baseline	Post initiation	Change
HbA_{1c} (mmol/mol)	65.0±20.9	62.8±17.6	−2.6	62.8±19.8	57.4±14.3	−5.4
HbA_{1c} (%)[a]	8.1±1.9	7.9±1.6	−0.2	7.9±1.8	7.4±1.3	−0.5
Weight (kg)	91.2±21.9	88.8±21.4	−2.4	99.3±24.4	100.8±27.0	+1.5
BMI (kg/m^2)	30.2±6.6	30.0±5.9	−0.2	33.1±6.9	33.5±7.1	+0.4
eGFR (ml/min per $1.73m^2$)	79.9±28.6	83.4±28.3	+3.5	87.7±29.6	80.5±30.0	−7.2
Cholesterol (mmol/l)	4.4±1.1	4.3±1.1	−0.1	4.6±1.0	4.2±1.6	−0.4

Anson M et al Diabetologia 2023;66(9):1869-1881

Real World Data - Weight



Anson M et al Diabetologia 2023;66(9):1869-1881

Differences in Type 1 SGLT2i vs GLP1

- Risk of incident heart failure 0.44 (95%CI 0.23, 0.83), p=0.009
- Risk of acute hospital admission 0.59 (95%CI 0.46, 0.76), p=<0.0001
- Risk of new onset CKD 0.49 (95%CI, 0.28, 0.86), p=0.012

Anson M et al Diabetologia 2023;66(9):1869-1881

Summary of GLP1 in Type 1

GLP-1 receptor agonists	Type 1 diabetes	Type 2 diabetes
HbA_{1c}	(↓) (up to 0·5 %), often not significant	↓↓ (up to 1·5 %)
Fasting plasma glucose	≈ (depending on basal insulin)	↓↓ (more pronounced with long-acting GLP-1 RAs)
Post-meal plasma glucose	(↓) (even with short-acting GLP-1 RAs)	↓↓ (more pronounced with short-acting GLP-1 RAs)
Insulin dose	↓↓ (predominantly concerning meal-related rapid-acting insulin)	↓ (variable, protocol-dependent)
Bodyweight	↓↓↓ (more pronounced than in type 2 diabetes?)	↓↓
Hypoglycaemia	≈ or ↑ (depending on appropriate adaptation of insulin dose/ timing)	≈ or ↓ or ↑ (depending on insulin dose adaptations)
Ketosis/ ketoacidosis	Potentially ↑ (related to insulin dose reduction)	≈ (generally a minor problem in type 2 diabetes)
Gastrointestinal adverse events	Nausea, vomiting, diarrhoea	Nausea, vomiting,diarrhoea
Cardio-renal endpoints	Not yet studied	MACE ↓ albumin excretion ↓

Nauck M et al Lancet Diab Endocrinol 2020;8(4):262-264

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SGLT2 Inhibitors and GLP1RA in T1DM

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Endotext