



Diabete Mellito di tipo 2. Vecchi e nuovi farmaci. Una via di mezzo è possibile? SGLT2 e GLP-1 a tutti?

Angelo Avogaro
Università di Padova

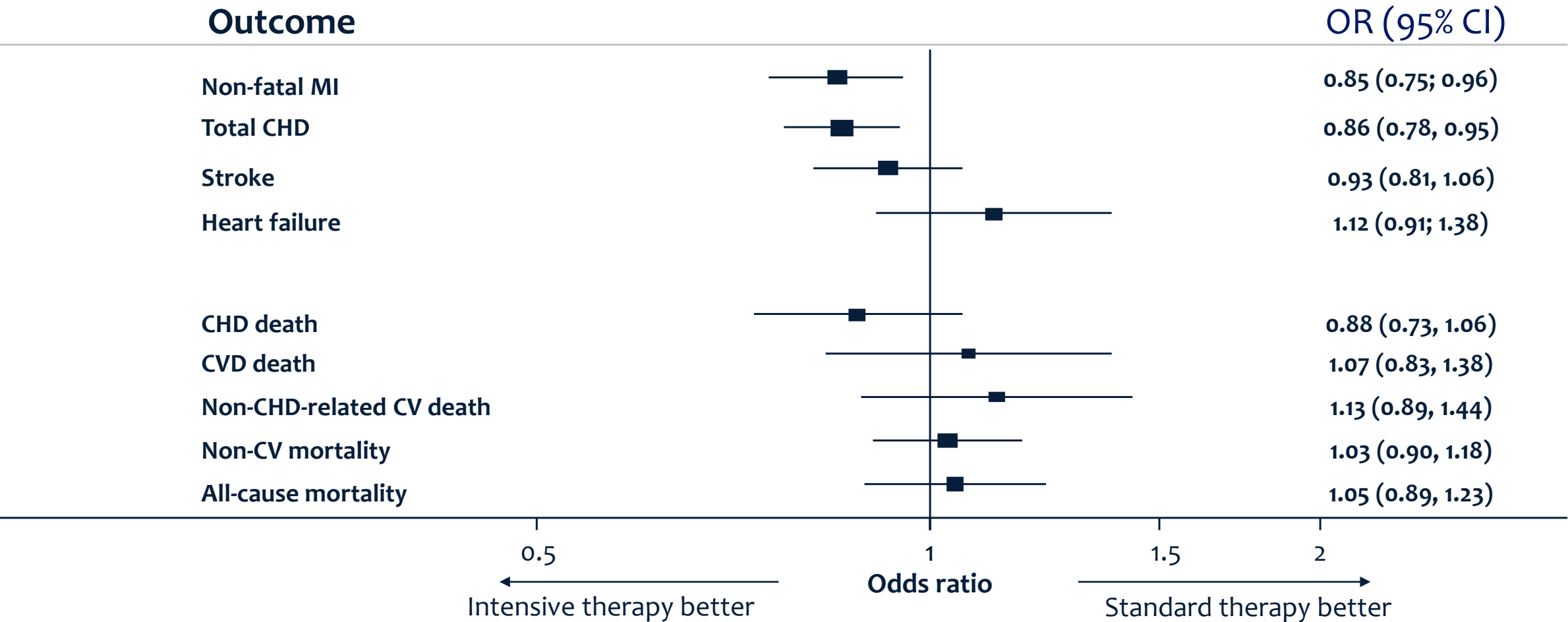
Conflitti di interesse di Angelo Avogaro

Dichiaro di aver ricevuto negli ultimi 2 anni compensi dalle seguenti aziende:

Pharma International Company, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Bruno Farmaceutici, Mundipharma, Neopharmed, Amgen, Servier, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda.

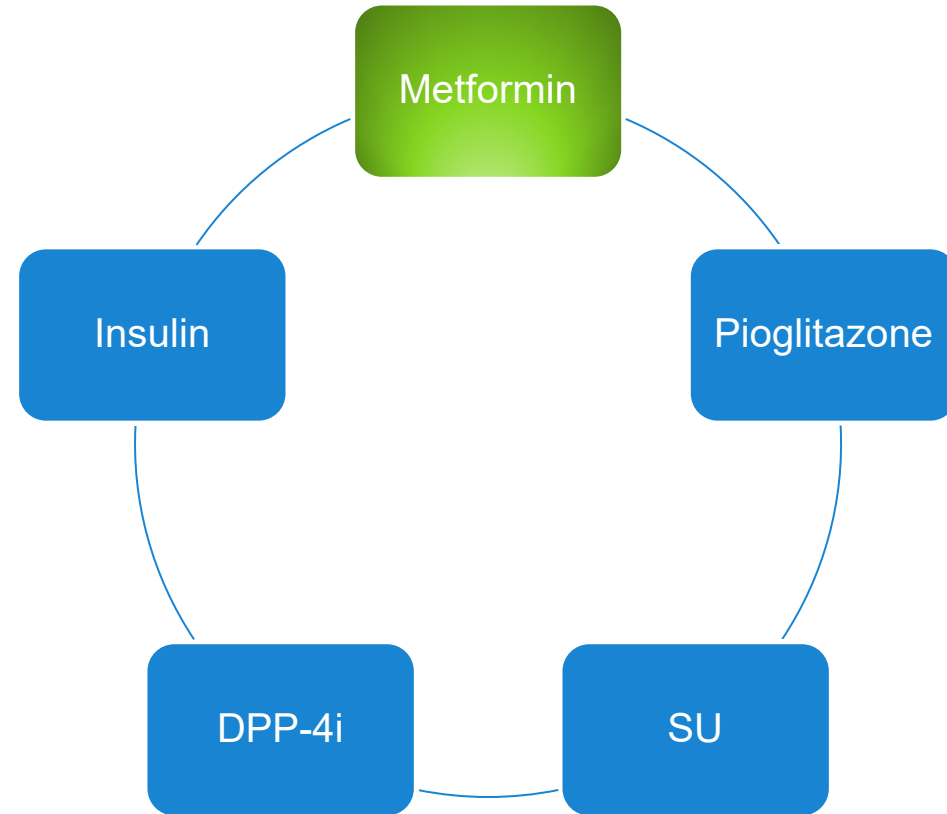
Vecchi o nuovi Farmaci

Meta-analysis: Comparison of effect of more intensive glycaemic control on clinical outcomes



*Contributing studies include: PROactive, ADVANCE, VADT & ACCORD
CI, confidence interval; CHD, chronic heart disease; CVD, cardiovascular death; MI, myocardial infarction; OR, odds ratio.
Ray KK. *Lancet* 2009;373:1765–1772, supplementary figure 4.

Foundational Anti-Hyperglycemic therapies



Antidiabetic drugs and Heart Protection

Drugs	Trial	Patients	HR for MI	HR for HF
Metformin	UKPDS	Newly diagnosed	0.61 (0.41-0.89)**	NA
Pioglitazone	PROACTIVE	Evidence of extensive macrovascular disease	0.83 (0.65-1.06)^	1.39 (1.19-1.63)
DPP-4 inhibitors	Meta-analysis of trials	Primary and secondary prevention	0.97 (0.88-1.08)*	0.99 (0.80-1.23)
Insulin Glargine	ORIGIN	59% prior MI	1.02 (0.88-1.19)§	0.90 (0.77-1.05)

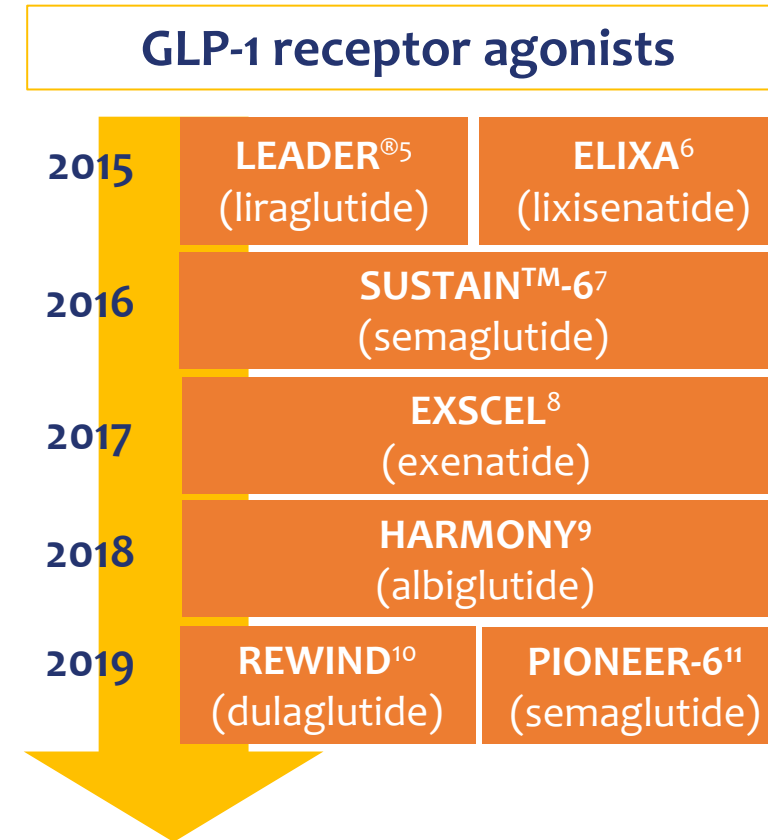
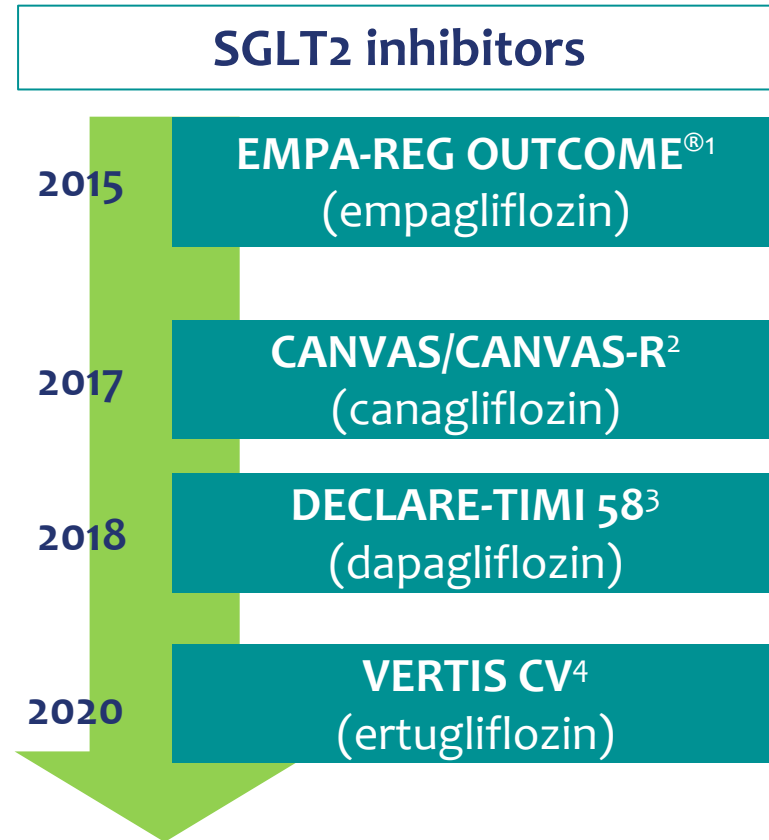
§: ORIGIN Trial Investigators N Engl J Med. 2012

** : UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998

^ Dormandy JA, et al. Lancet. 2005

* Kanie T, et al. Cochrane Database Syst Rev. 2021

During the past 6 years, multiple CVOTs have demonstrated various CV and renal benefits for diabetic patients



Effects of Intensive Glycemic control vs. specific drug effects on long-term complications risk

	Albuminuria	CKD	Death	AMI	Stroke	HF	PAD
Intensive vs conventional ¹	↓	=	↑?	↓	=	=	↓
SGLT2i vs placebo ^{2,3}	↓↓	↓↓	↓	=	=	↓↓	↑?
GLP-1RA vs placebo ⁴	↓	=	↓	↓	↓↓	↓	↓

¹ Hemmingsen et al. Cochrane Database Syst Rev. 2013 Nov 11;(11):CD008143

² Zelniker et al. Lancet. 2019 Jan 5;393(10166):31-39

³ Neuen et al. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.

⁴ Kristensen et al. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785

Una via di mezzo è possibile?

Treat
To
Benefit

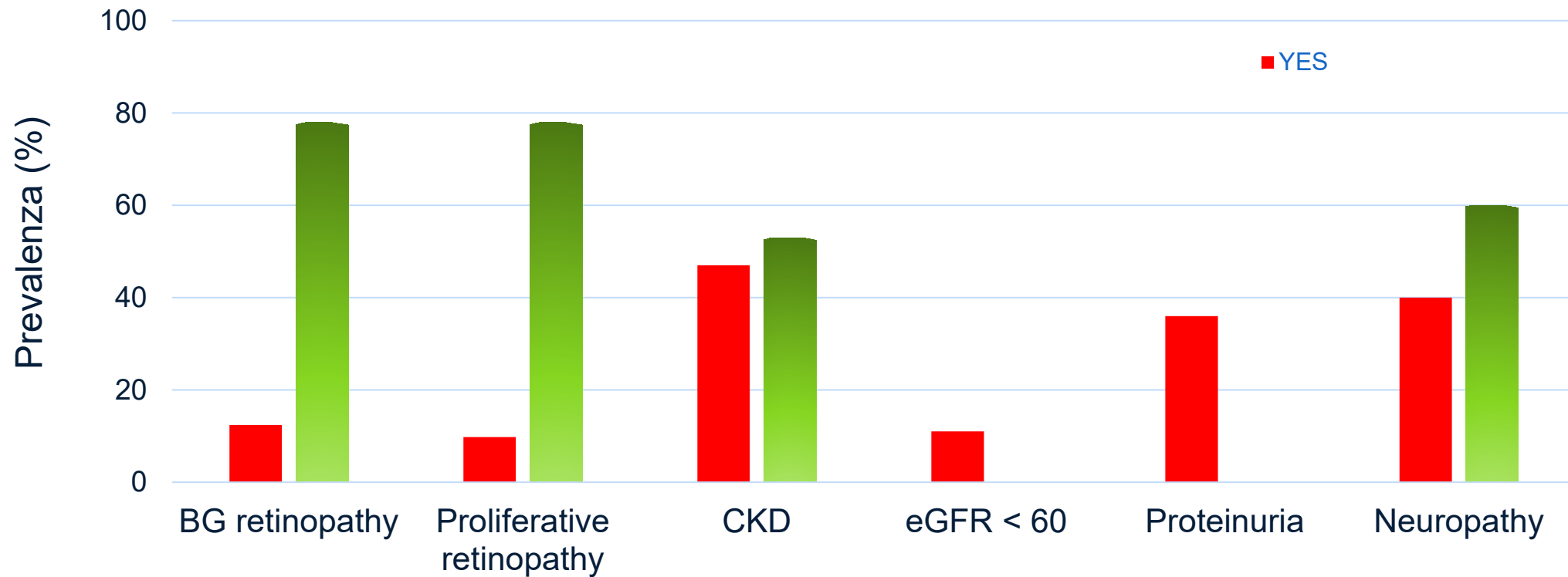


Treat to
Target



Treat
Diabetes

Prevalence of microvascular complications in patients with diabetes



Effects of Intensive Glycemic control vs. specific drug effects on long-term complications risk

	Retino	Neuro	Albuminuria	CKD	Death	AMI	Stroke	HF	PAD
Intensive vs conventional ¹	↓	?	↓	=	↑?	↓	=	=	↓
SGLT2i vs placebo ^{2,3}	=	?	↓↓	↓↓	↓	=	=	↓↓	↑?
GLP-1RA vs placebo ⁴	↑?	?	↓	=	↓	↓	↓↓	↓	↓

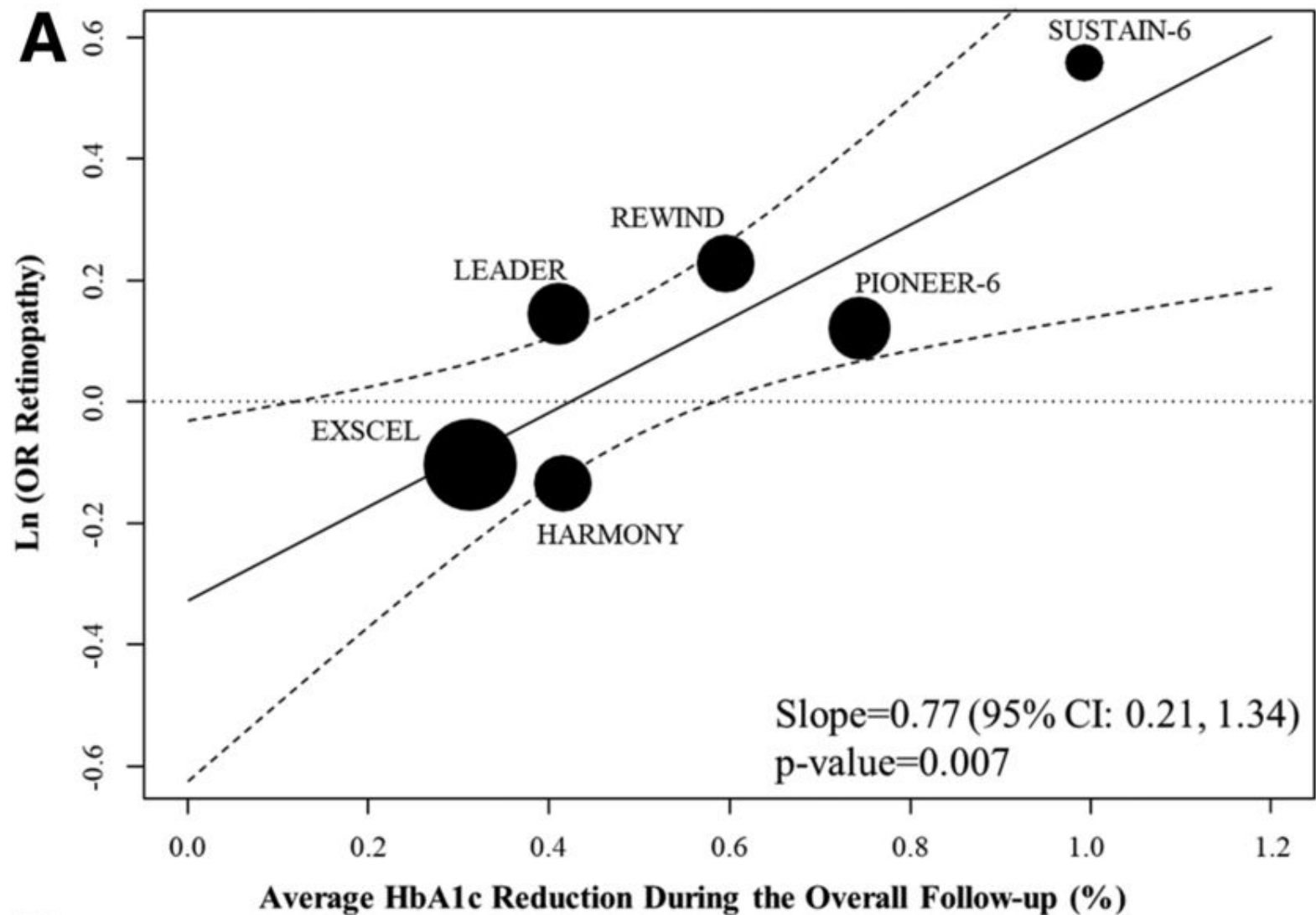
¹ Hemmingsen et al. Cochrane Database Syst Rev. 2013 Nov 11;(11):CD008143

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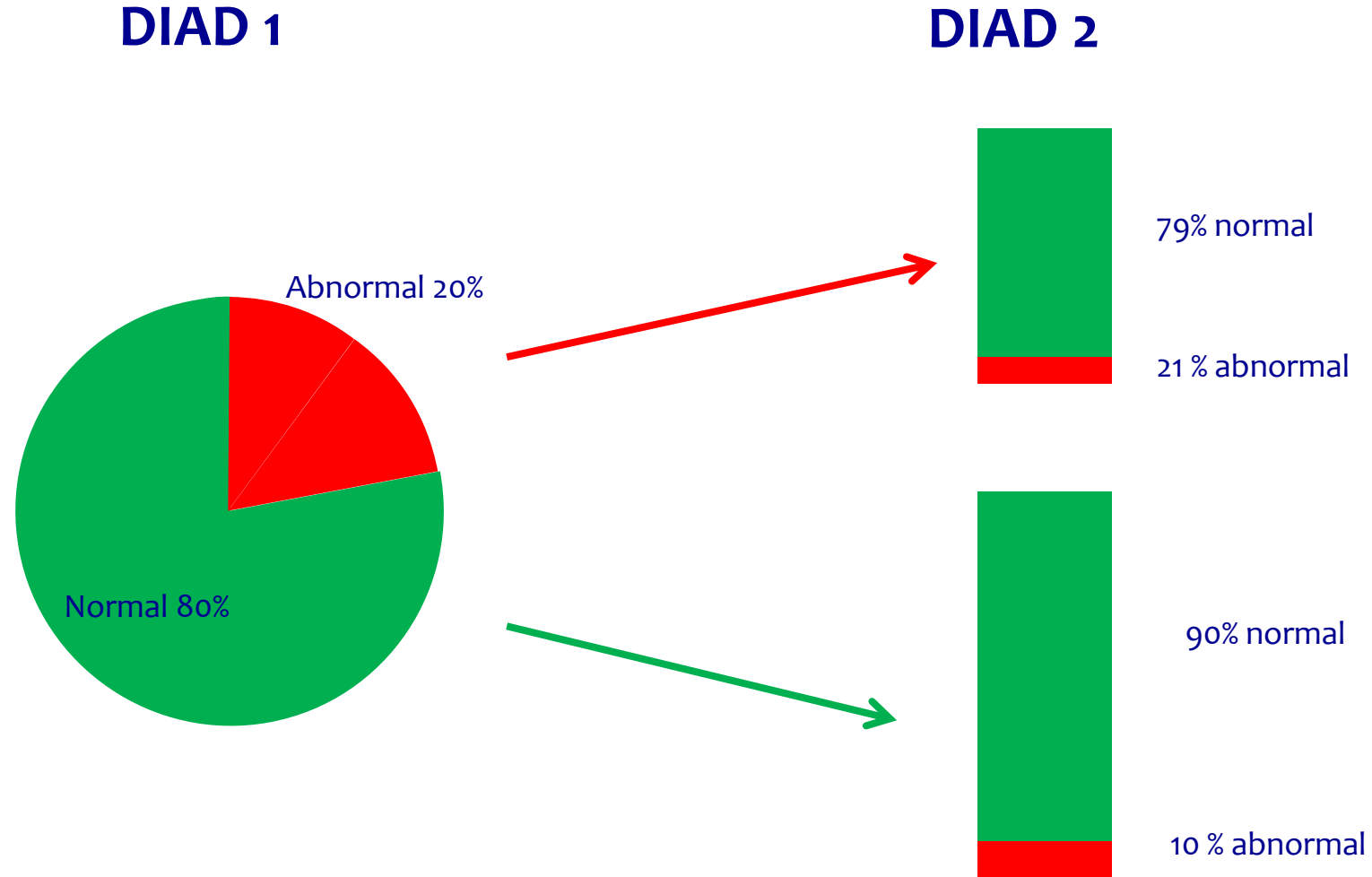
³ Neuen et al. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.

⁴ Kristensen et al. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785

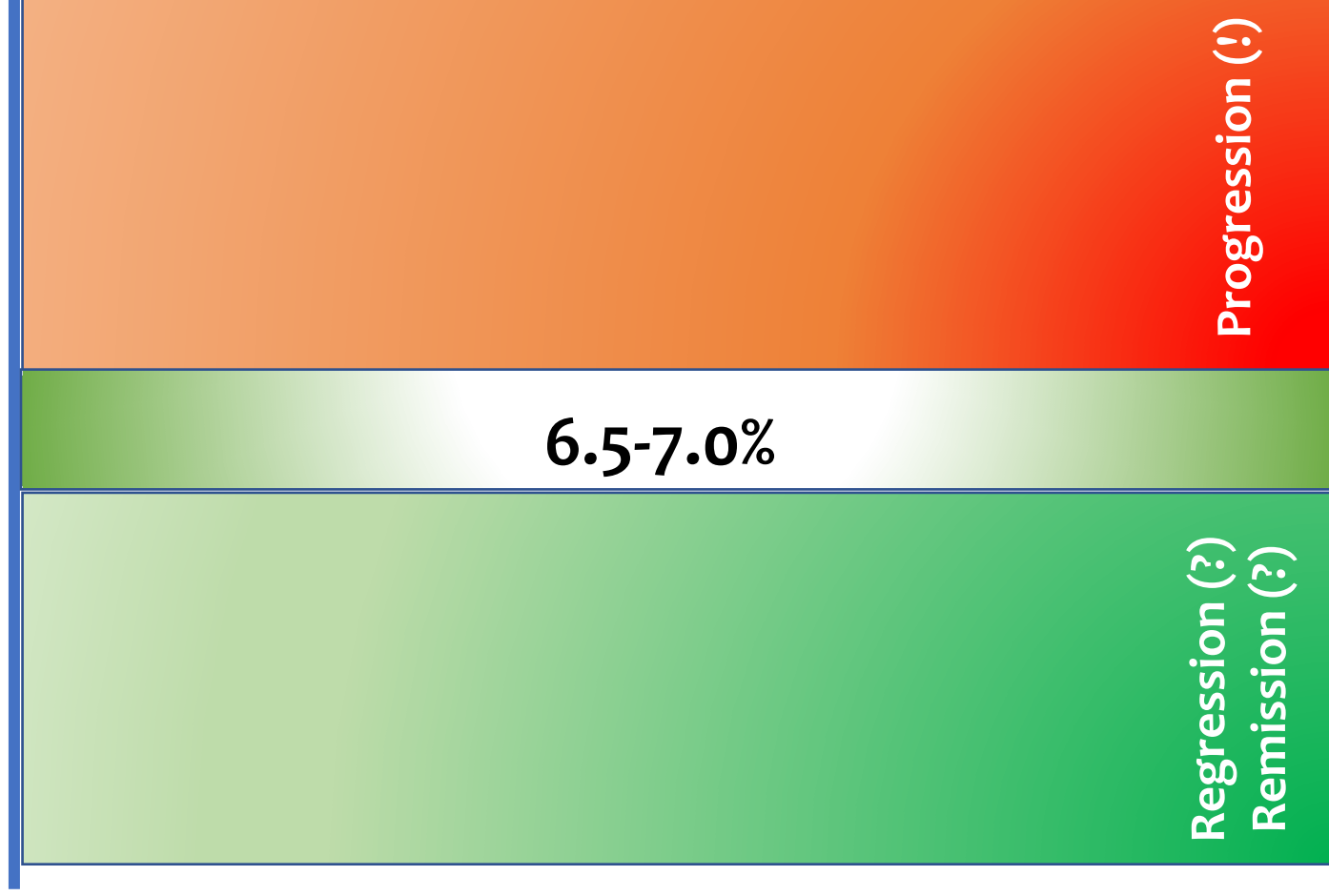
HbA_{1c} Change and Diabetic Retinopathy During GLP-1 Receptor Agonist Cardiovascular Outcome Trials: A Meta-analysis and Meta-regression



Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects: the DIAD Study.

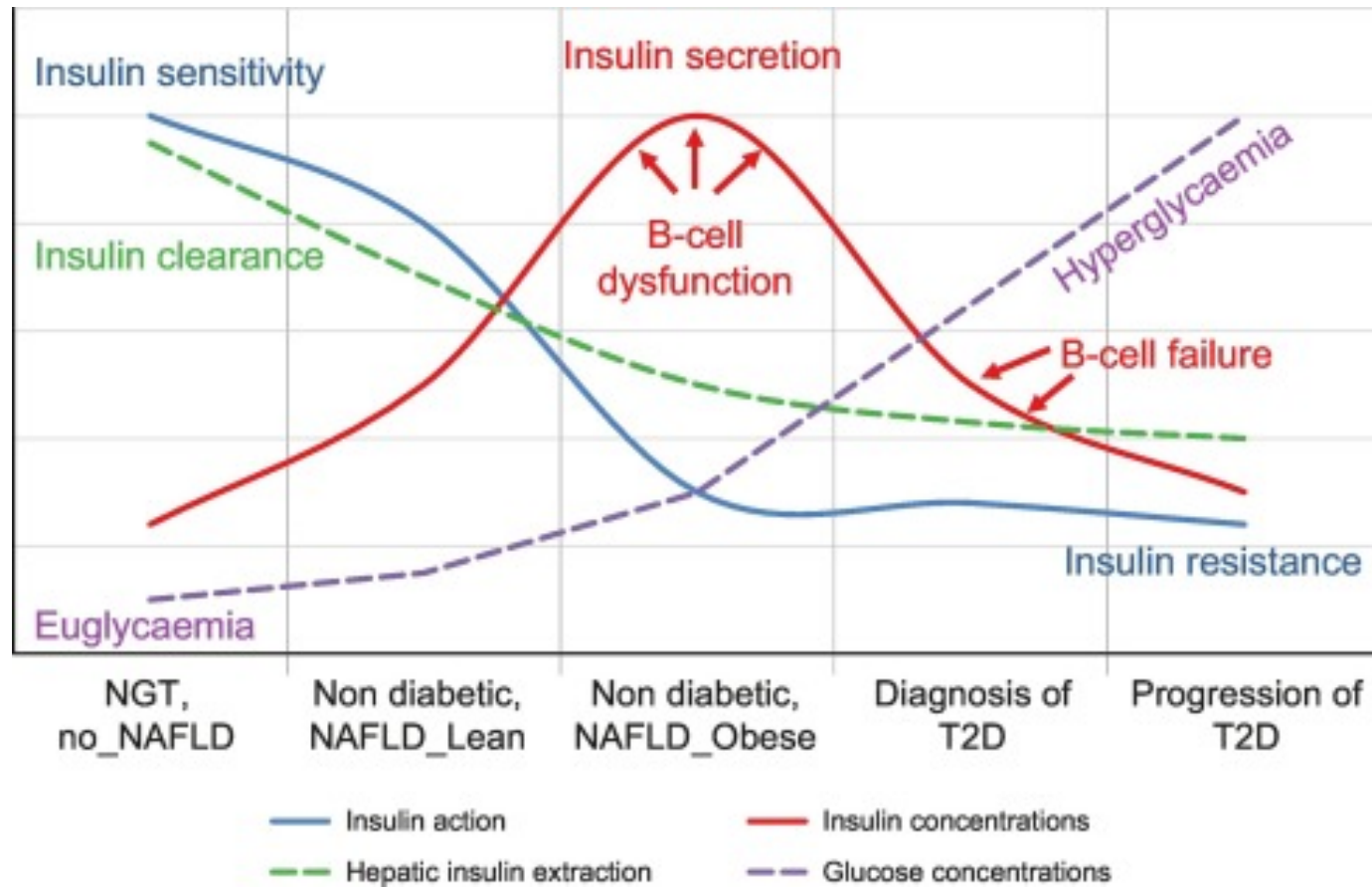


Complication burden

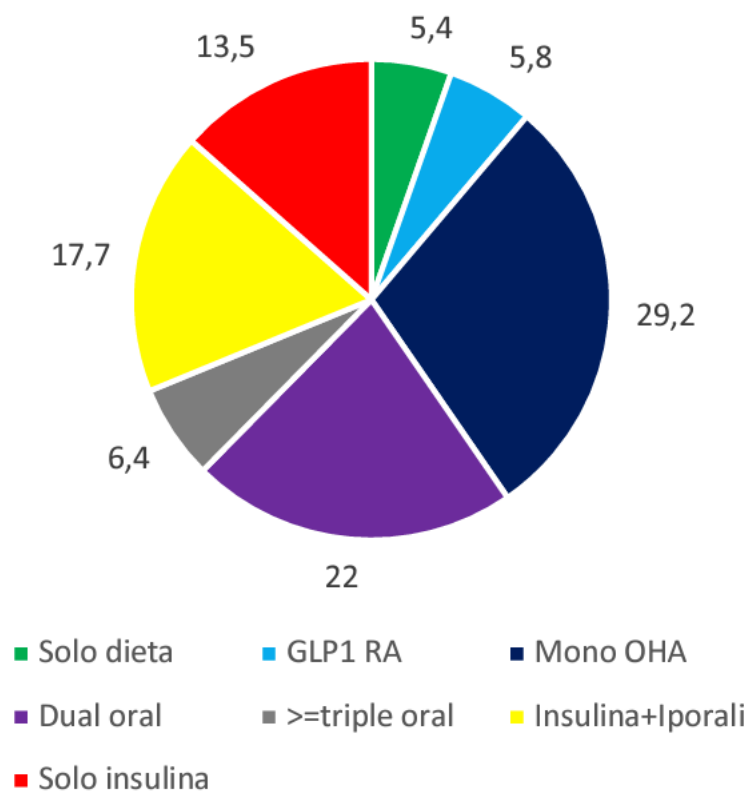


SGLT2i e GLP-1RA a tutti?

The Natural History of Insulin secretion



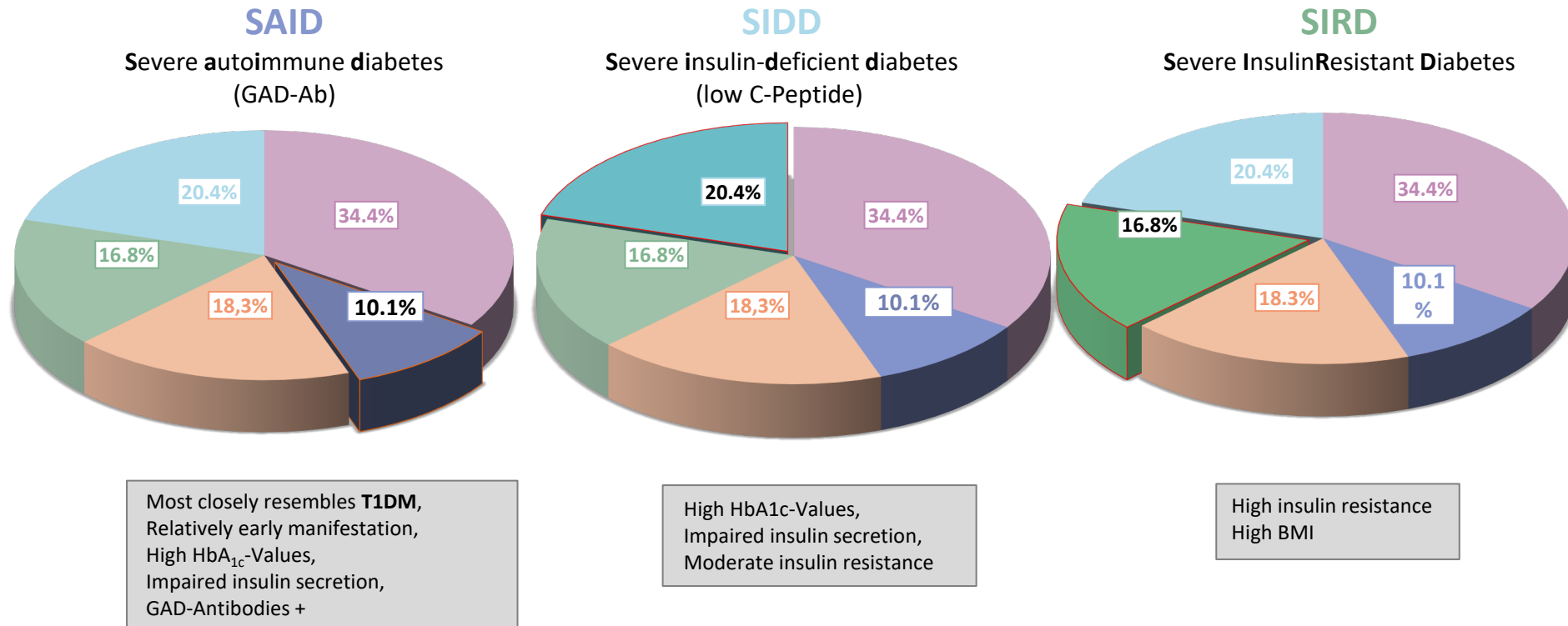
Distribuzione dei pazienti per intensità di trattamento ipoglicemizzante nel DM2 (%)



New Subtypes of Diabetes in Adults

(Scania Diabetes Registry, N=8980)

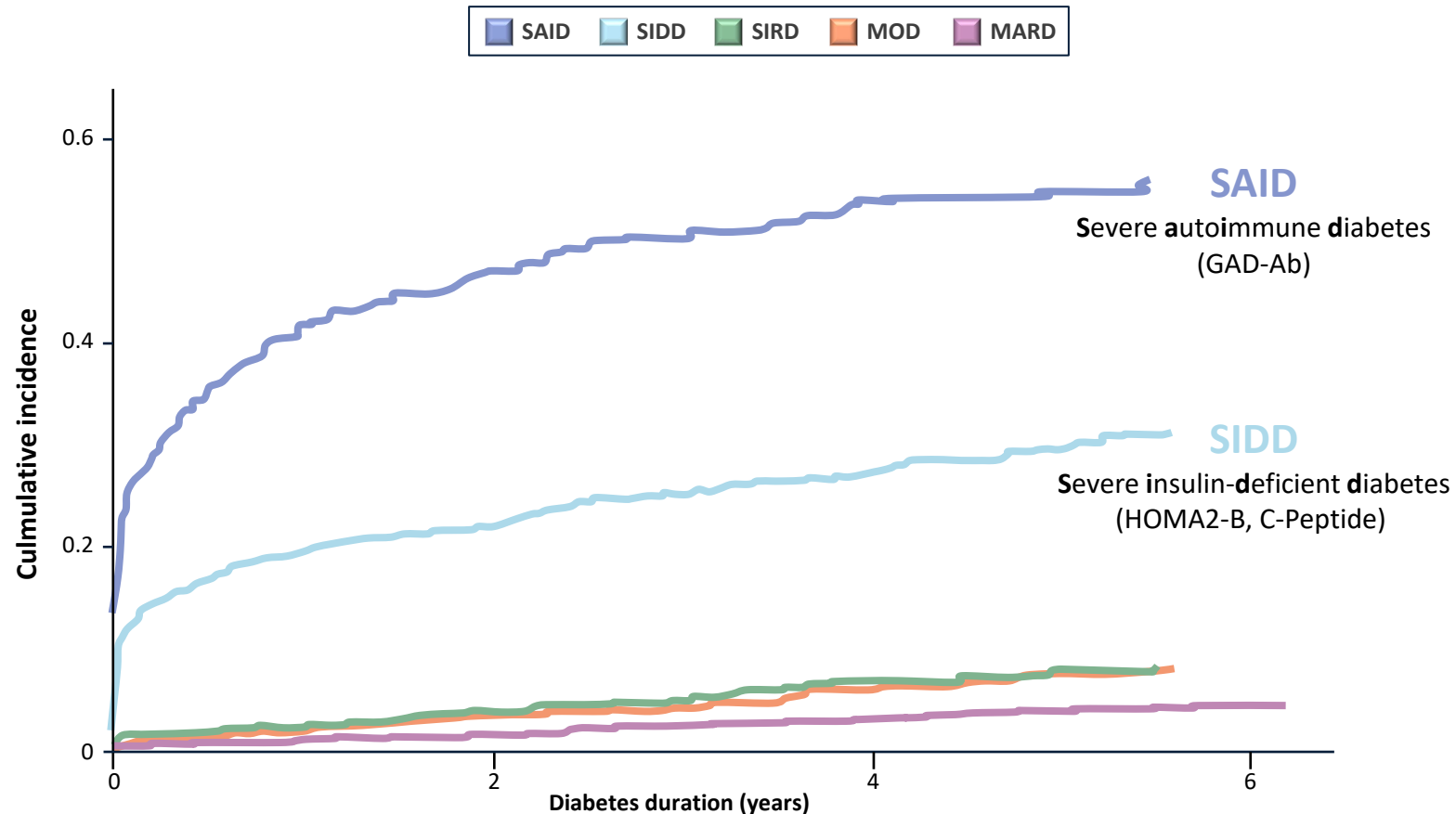
Cluster: Age at diagnosis, BMI, GAD Auto-Antibodies, HbA1c, HOMA2-B (C-Peptide), HOMA2-IR (C-Peptide)



New Subtypes of Diabetes in Adults

Diabetes types in ANDIS and duration until insulin treatment

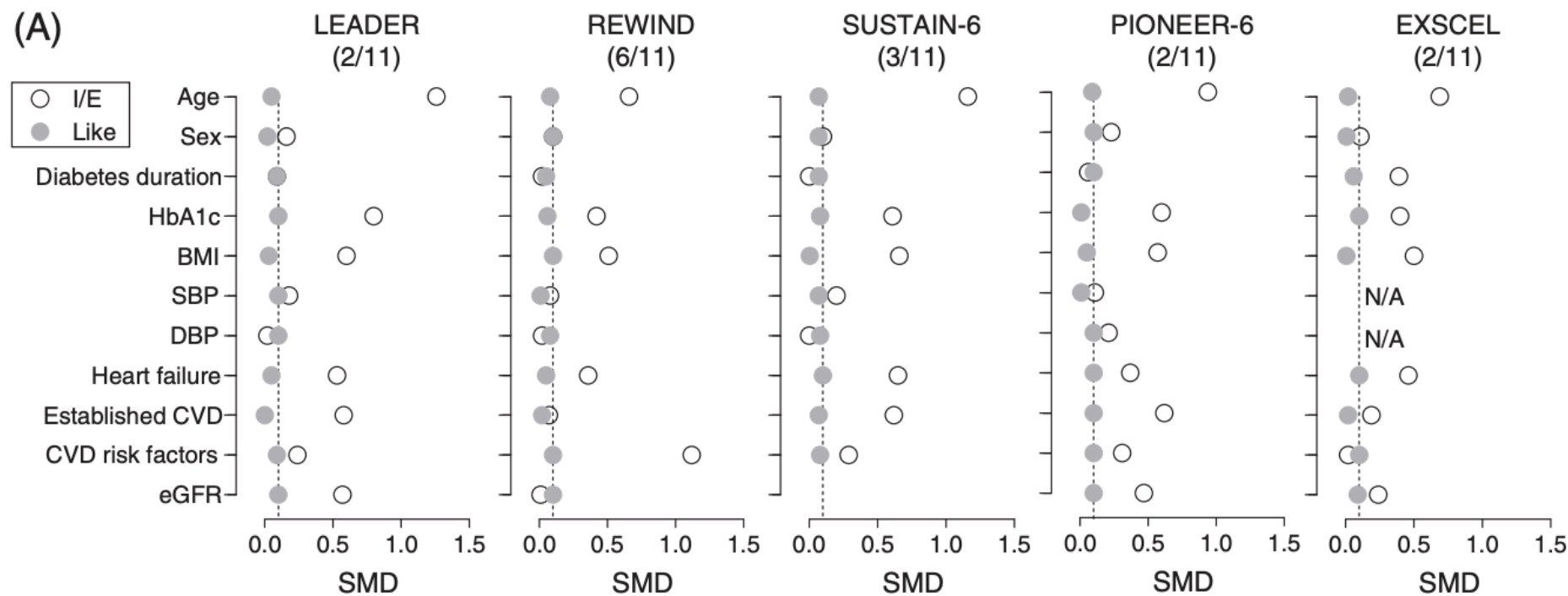
Cluster: Age at diagnosis, BMI, GAD Auto-Antibodies, HbA1c, HOMA2-B (C-Peptide), HOMA2-IR (C-Peptide)



Modified after Ahlqvist E et al. Lancet D&E 2018

Enrolment criteria for diabetes cardiovascular outcome trials
do not inform on generalizability to clinical practice: The case
of glucagon-like peptide-1 receptor agonists

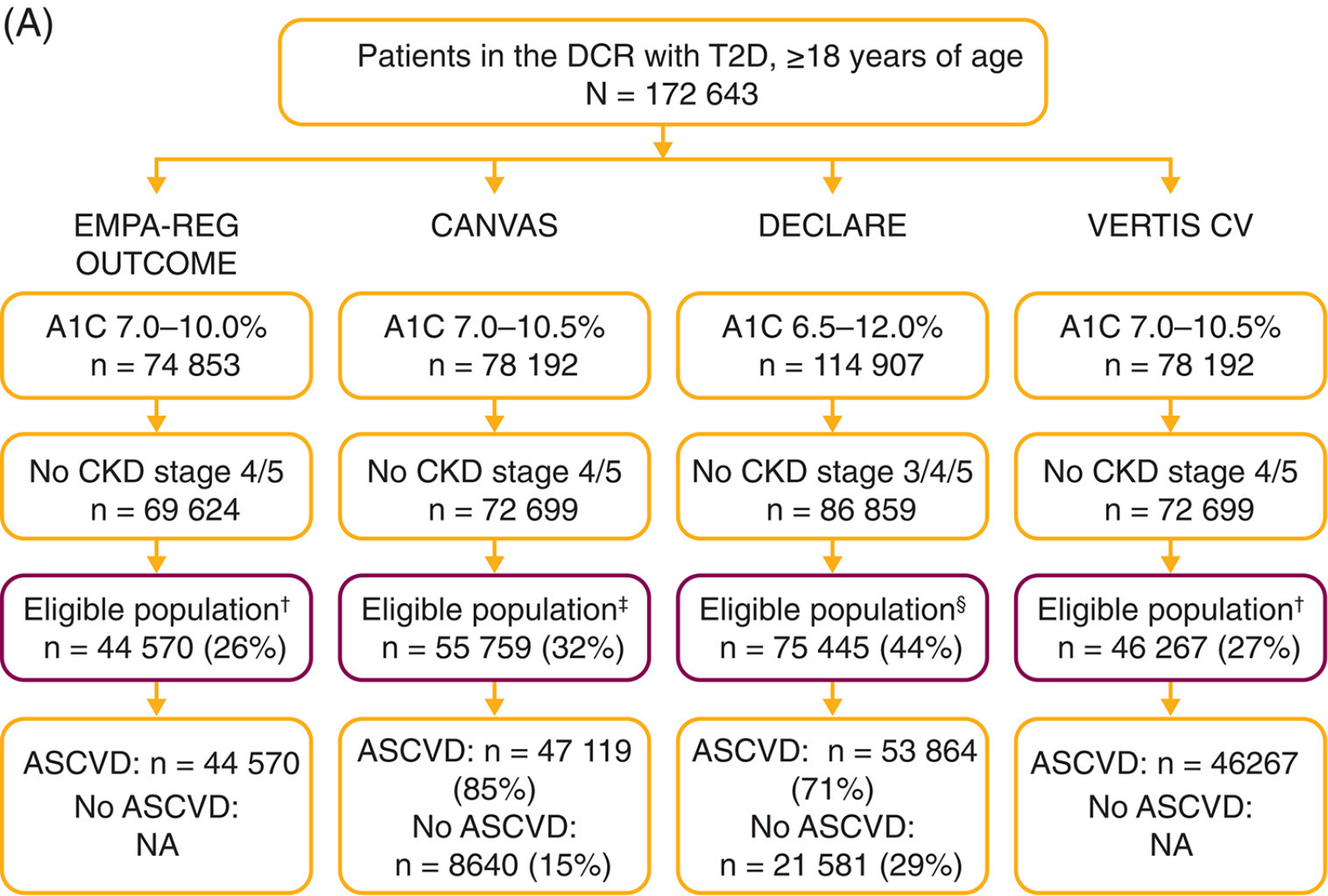
Veronica Sciannameo¹ | Paola Berchialla² | Emanuela Orsi³ | Olga Lamacchia⁴ |
Susanna Morano⁵ | Fabrizio Querci⁶ | Agostino Consoli⁷ | Angelo Avogaro⁸ |
Gian Paolo Fadini on behalf of the DARWIN-T2D study



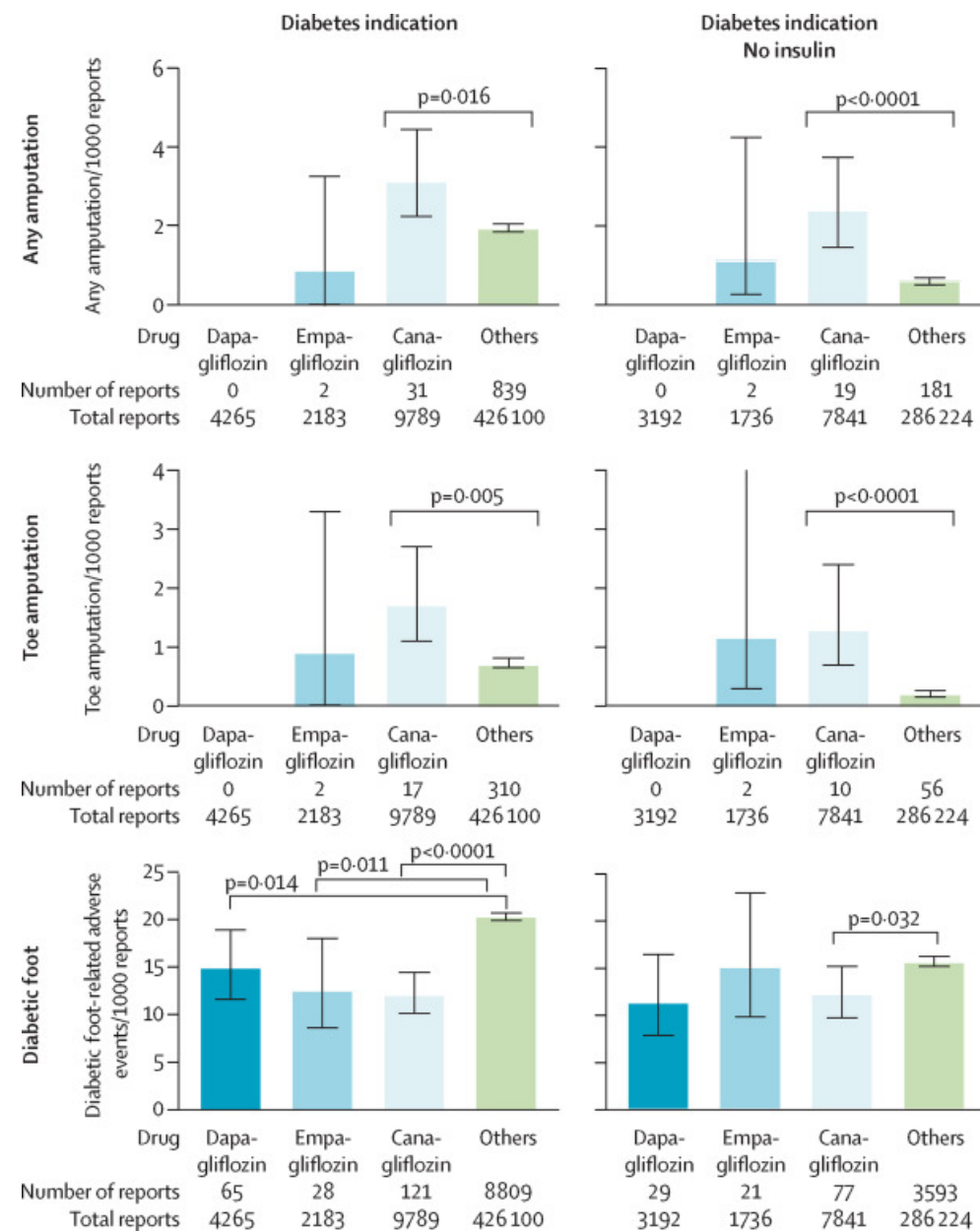
SMD: Standardized mean Difference

Eligibility of patients with type 2 diabetes for sodium-glucose co-transporter-2 inhibitor cardiovascular outcomes trials:
An assessment using the Diabetes Collaborative Registry

Eric Wittbrodt PharmD¹ | David Chamberlain PharmD¹ |
Suzanne V. Arnold MD^{2,3} | Fengming Tang MS² | Mikhail Kosiborod MD^{2,3}



Frequencies of any amputation, toe amputation, and diabetic foot-related adverse events associated with SGLT2 inhibitor and non-SGLT2 inhibitor drugs



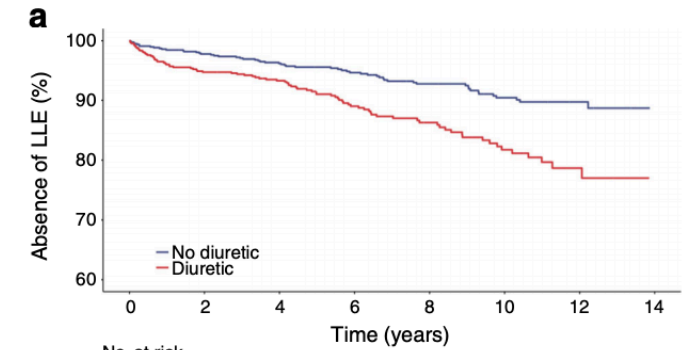
Effect of Diuretics + SGLT2i combination therapy in patients with lower limb ischemia.

Diabetologia (2019) 62:939–947
<https://doi.org/10.1007/s00125-019-4835-z>

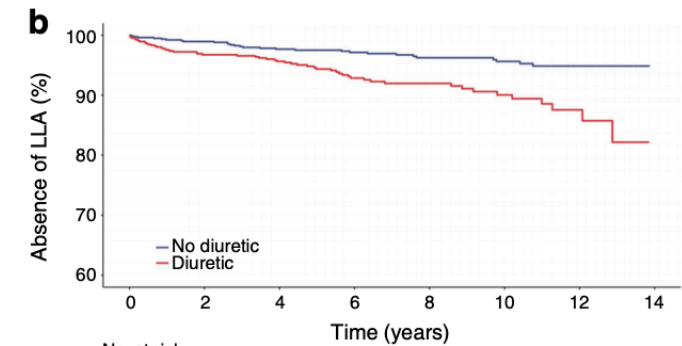
ARTICLE

Lower limb events in individuals with type 2 diabetes: evidence for an increased risk associated with diuretic use

Louis Potier^{1,2,3} · Ronan Roussel^{1,2,3} · Gilberto Velho³ · Pierre-Jean Saulnier^{4,5,6} · Anisoara Bumbu¹ · Odette Matar¹ · Fabrice Schneider^{4,5,6,7} · Stéphanie Ragot^{4,5,6} · Michel Marre^{1,2,3,8} · Kamel Mohammadi^{9,10,11} · Samy Hadjadj¹²



No. at risk								
No diuretic	789	715	635	494	375	281	105	0
Diuretic	670	576	492	333	224	147	50	0
Cumulative no. of events								
No diuretic	0	17	28	37	46	54	56	57
Diuretic	0	34	42	61	70	80	84	85



No. at risk								
No diuretic	789	724	644	506	387	296	112	0
Diuretic	670	588	502	341	231	153	53	0
Cumulative no. of events								
No diuretic	0	8	17	20	24	26	28	28
Diuretic	0	21	27	39	42	46	49	51

Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium–Glucose Cotransporter 2 Inhibition

Anne L. Peters,¹ Elizabeth O. Buschur,²
John B. Buse,³ Pejman Cohan,⁴
Jamie C. Diner,³ and Irl B. Hirsch⁵

Table 1—Clinical characteristics of euDKA cases

Case patient	1	2	3	4	5	6	7	8	9				
Age (years)	40	58	27	28	31	55	26	39	64				
Sex	Female	Male	Female	Female	Female	Female	Female	Female	Female				
T1/T2	T1	T2	T1	T1	T1	T1	T1	T1	T2				
MDI/CSII	MDI	N/A	MDI	CSII	CSII	CSII	CSII	CSII	N/A				
Duration (years)	17	2	25	6	15	18	13	26	6				
BMI (kg/m ²)	26.5	26.5	24.3	25.9	33.2	22.0	22.0	26.1	32.8				
Prior A1C [% (mmol/mol)]	11.4 (101.1)	9.8 (83.6)	7.8 (61.7)	8.0 (63.9)	7.0 (53.0)	7.2 (55.2)	6.6 (48.6)	7.0 (53.0)	7.8 (62.0)				
Canagliflozin dose (mg)	300	300	300	100	300	100	300	300	300				
Potential contributors	URI	Surgery 1 week prior	URI, alcohol	Alcohol	Alcohol	Exercise, alcohol	Exercise	GI	None	URI	Surgery 12 h prior		
Insulin dose reduction just prior to euDKA	Yes	N/A	Yes	No	Yes	Yes	Yes	Unknown	No	No	No	Yes	N/A
Presenting plasma glucose [mg/dL (mmol/L)]	220 (12.2)	150 (8.3)	150 (8.3)	96 (5.3)	224 (12.4)	158 (8.8)	~125 (~6.9)	203 (11.3)	190 (10.6)	150 (8.3)		233 (12.9)	169 (9.4)
pH	6.9	7.12	6.89						7.15				
Pco ₂ (mmHg)	10								26				
Bicarbonate (mEq/L)	6	10	6		11	18		15	9			9	13 and then 5
Anion gap (mEq/L)	25	17	35		22	18		26	21			24	16 and then 19
Ketones*	Yes (serum and urine)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (serum and urine)
Where treated	ICU	ICU	ICU	Outpt.	ICU	Inpt.	Outpt.	ICU	ICU	Outpt.	Outpt.	ICU	ICU

CSII, continuous subcutaneous insulin infusion; GI, gastrointestinal; Inpt., inpatient; N/A, not available; Outpt., outpatient. *Urine ketones were strongly positive in all cases.

Conclusioni

Diabete Mellito di tipo 2: una malattia complessa da trattare

Vecchi e nuovi farmaci: meglio i nuovi perché più efficaci nella riduzione della glicemia e nella protezione CV

Una via di mezzo è possibile? Sì, perché è necessario il treat-to-target oltre al treat-to-benefit

SGLT2 e GLP-1 a tutti? Sì. Con rare eccezioni