IN DOCTRINA ET IN USU

Praticamente ... diabetologia

TORINO 01.06.24

HOMO EST QUOD EST

Nutrire il futuro: strategie di prevenzione e cura

POLLENZO 23.11.24

PRIMA SESSIONE | "Il mestiere di vivere" C. Pavese

Moderatori: **Chiara Bima, Maria Elena Valera Mora**

Rischio cardiovascolare nel diabete autoimmune: criticità e opportunità

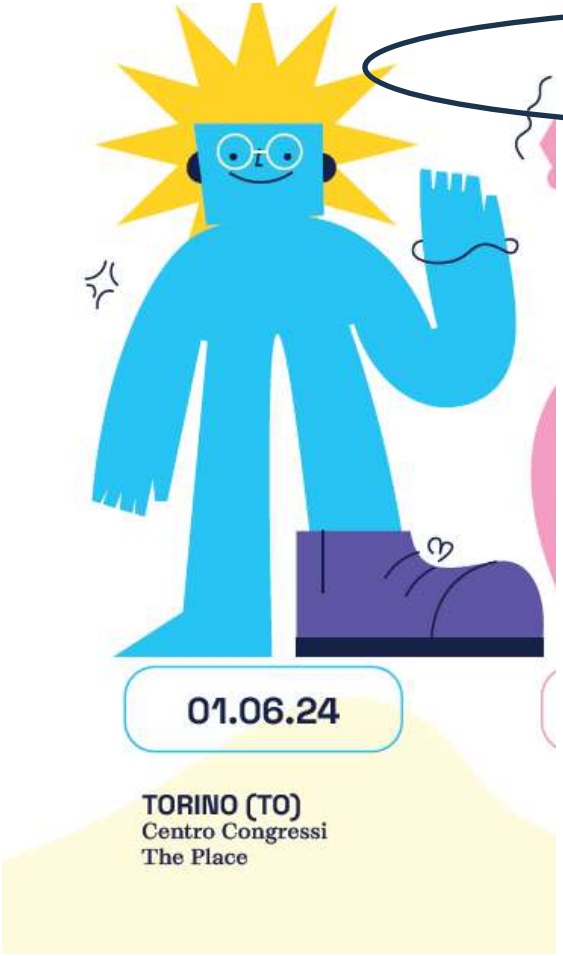
Maria Chantal Ponziani
Dirigente Responsabile
SSD di Diabetologia
ASL Novara

Dichiarazione dei conflitti d'interesse

- *La sottoscritta Maria Chantal Ponziani*
  ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato - Regione del 5 novembre 2009

  dichiara
  di non aver avuto rapporti di finanziamento diretto con soggetti portatori di interessi commerciali in campo sanitario

Ogni relatore dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.)



Criticità

Quale rischio ?

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

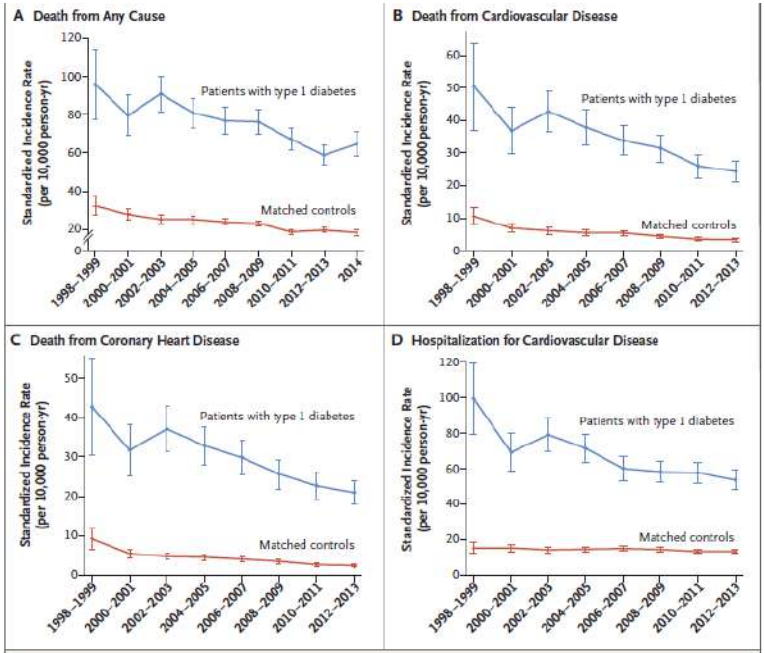


Figure 1. Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

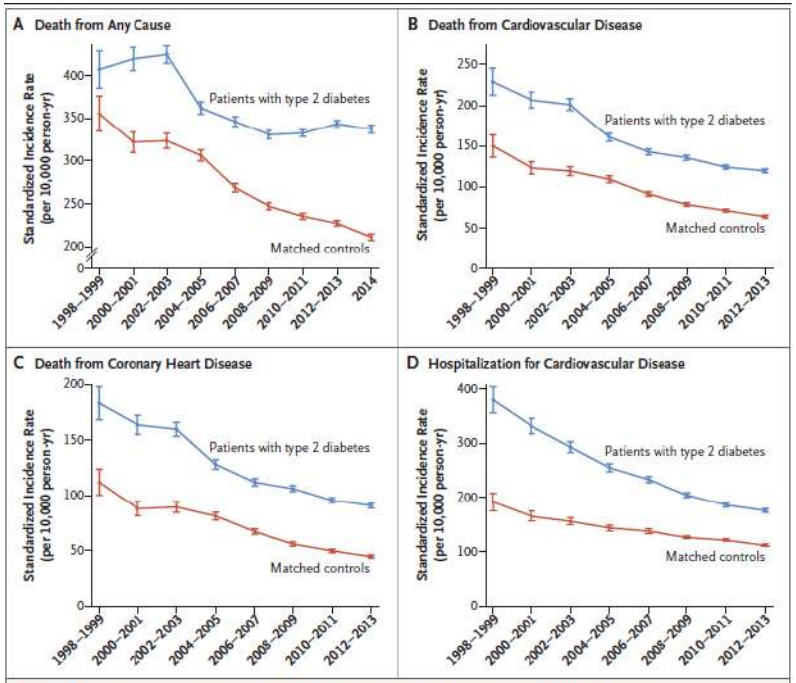


Figure 2. Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

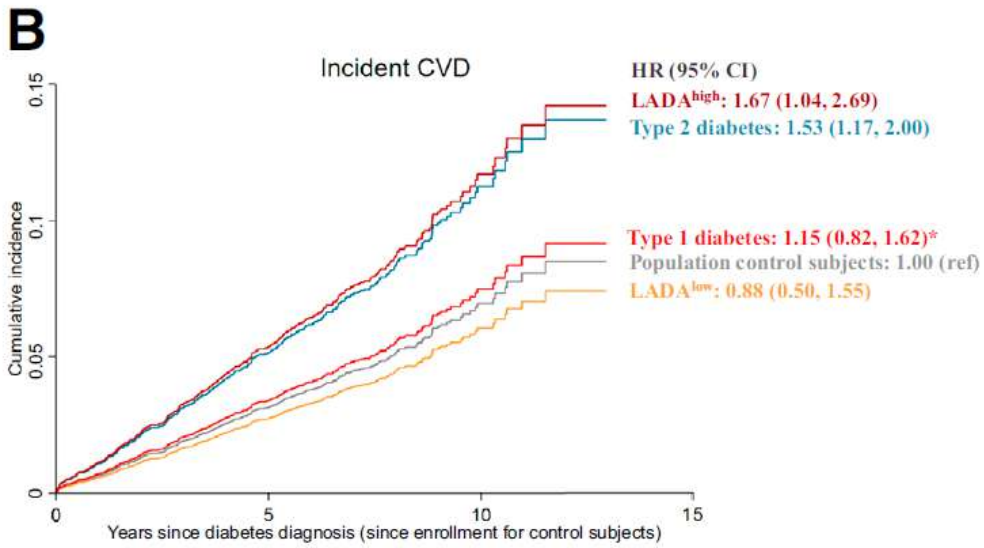
All-Cause Mortality and Cardiovascular and Microvascular Diseases in Latent Autoimmune Diabetes in Adults

Yuxia Wei, Katharina Herzog, Emma Ahlqvist, Tomas Andersson, Thomas Nyström, Yiqiang Zhan, Tiinamaija Tuomi, and Sofia Carlsson

ESTRID study
LADA (n=550)
T2DM (n=2,001)
Controls (n=2,355)

Swedish National Diabetes Register
Adult-onset T1DM (n=1,573)

Register follow-up 2007-2020
- ✓ Causes of Death
- ✓ Patient
- ✓ Prescribed Drug
- ✓ Diabetes



All-Cause Mortality and Cardiovascular and Microvascular Diseases in Latent Autoimmune Diabetes in Adults

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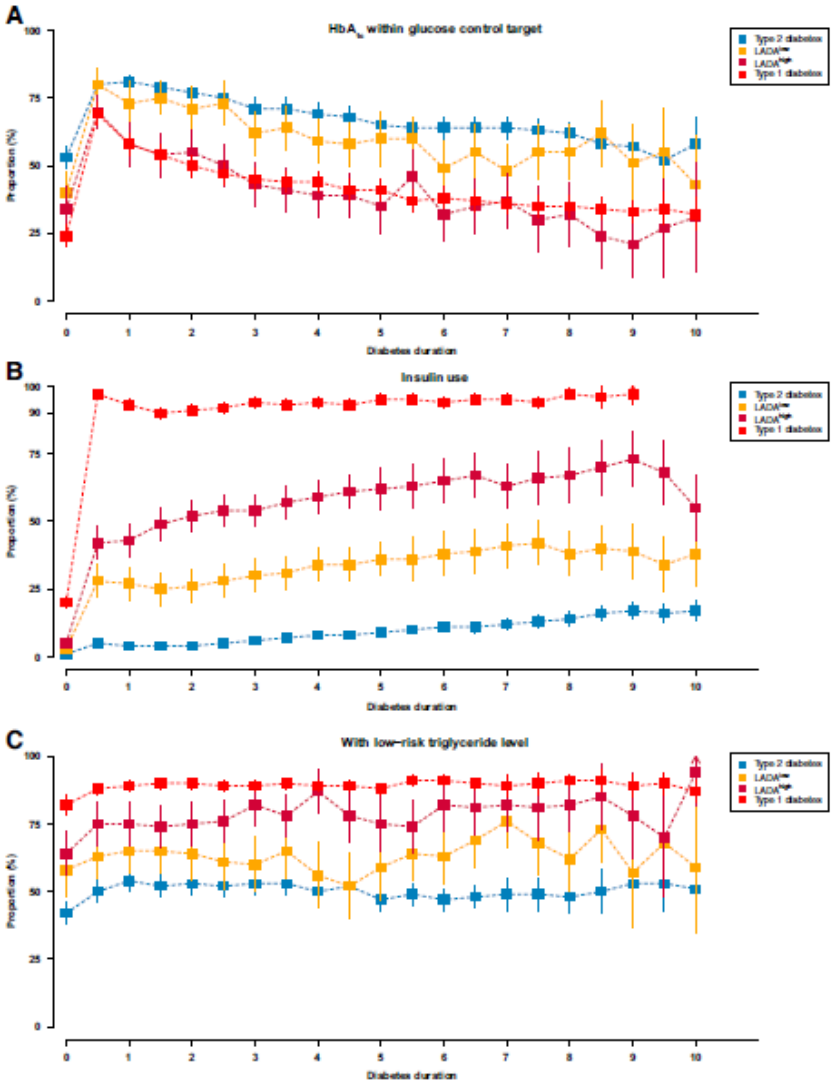


Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK

Nathalie Conrad, Geert Verbeke, Geert Molenberghs, Laura Goetschalckx, Thomas Callender, Geraldine Cambridge, Justin C Mason, Kazem Rahimi,

	Cohort		Events		Hazard ratio (95% CI)
	Autoimmune disease	Matched controls	Autoimmune disease	Matched controls	
Any autoimmune disease	446 449	2 102 830	68 413	231 410	1·56 (1·52–1·59)
Number of autoimmune diseases					
1	404 547	1 902 682	55 301	198 769	1·41 (1·37–1·45)
2	37 226	177 676	11 005	28 570	2·63 (2·49–2·78)
≥3	4676	22 472	2107	4071	3·79 (3·36–4·27)
Connective tissue diseases	160 217	761 918	36 846	118 391	1·68 (1·63–1·74)
Ankylosing spondylitis	9864	46 121	1423	3822	1·97 (1·65–2·35)
Polymyalgia rheumatica	48 102	231 802	15 390	55 870	1·47 (1·40–1·54)
Rheumatoid arthritis	66 796	318 456	15 520	46 594	1·83 (1·74–1·92)
Sjögren's syndrome	9933	47 330	2327	6139	2·08 (1·81–2·39)
Systemic lupus erythematosus	10 483	49 402	2204	4227	2·82 (2·38–3·33)
Systemic sclerosis	2159	10 310	752	1320	3·59 (2·81–4·59)
Vasculitis	37 940	178 494	7839	22 658	1·87 (1·73–2·01)
Organ-specific diseases	407 078	1 909 992	53 706	175 205	1·60 (1·56–1·64)
Addison's disease	2548	12 055	604	1218	2·83 (1·96–4·09)
Coeliac disease	24 895	115 692	2507	8618	1·50 (1·33–1·69)
Type 1 diabetes	50 264	235 540	9697	23 568	2·36 (2·21–2·52)
Inflammatory bowel disease	49 214	230 236	6470	19 532	1·71 (1·59–1·85)
Graves' disease	44 001	207 508	6409	20 535	1·61 (1·49–1·74)
Hashimoto's thyroiditis	7630	35 650	822	2364	1·76 (1·41–2·19)
Multiple sclerosis	12 006	56 523	1356	3876	1·85 (1·56–2·20)
Myasthenia gravis	2171	10 319	544	1812	1·61 (1·21–2·15)
Pernicious anaemia	32 910	156 887	8228	27 099	1·61 (1·50–1·73)
Psoriasis	185 178	869 184	21 197	73 465	1·47 (1·41–1·53)
Primary biliary cirrhosis	4612	21 973	1086	3060	2·00 (1·66–2·41)
Vitiligo	23 709	109 914	1791	6526	1·38 (1·19–1·60)

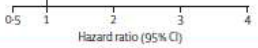
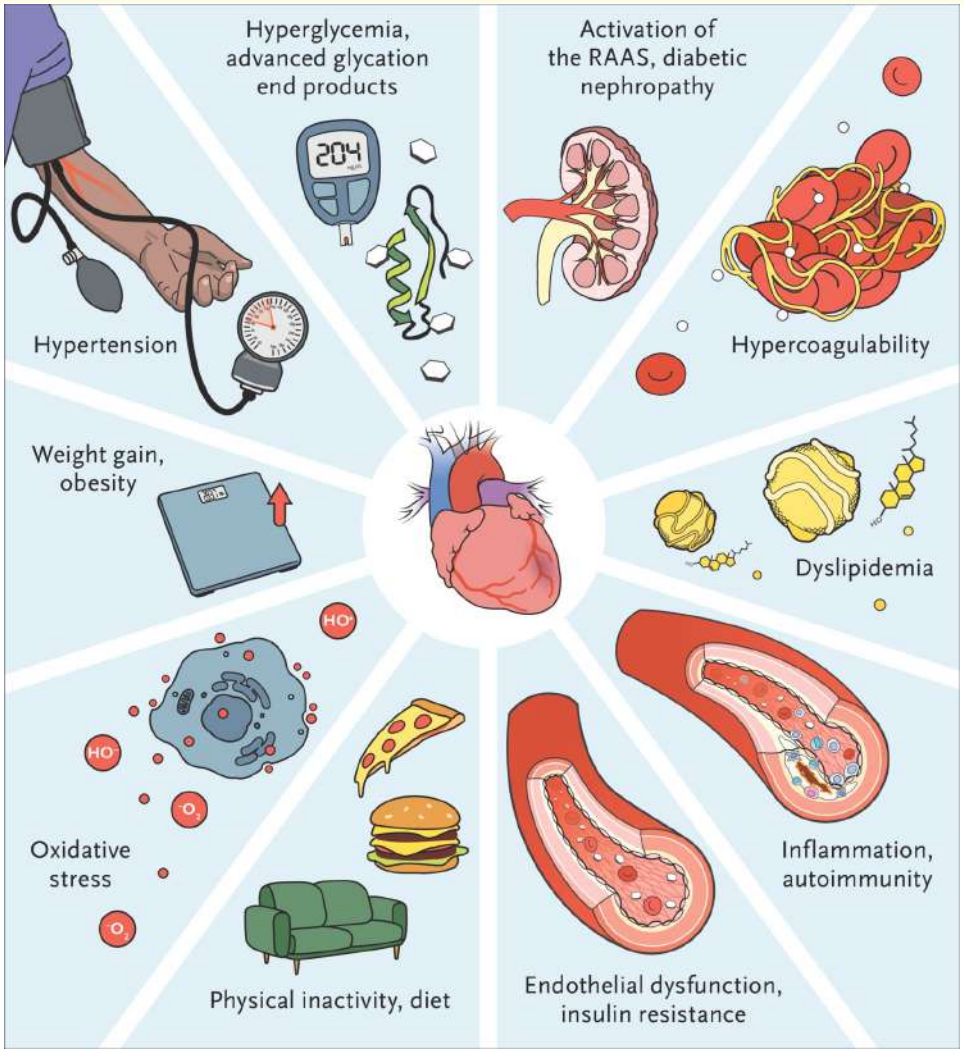


Figure 2: Hazard ratios for incident cardiovascular disease among patients with autoimmune diseases compared with matched controls, stratified by autoimmune disease

Patients with autoimmune diseases were compared with up to five individuals matched on age, calendar year, sex, socioeconomic status, and region, free of autoimmune disease at any time. Hazard ratios and 95% CIs were calculated using Cox proportional hazards models, clustered by matching set.

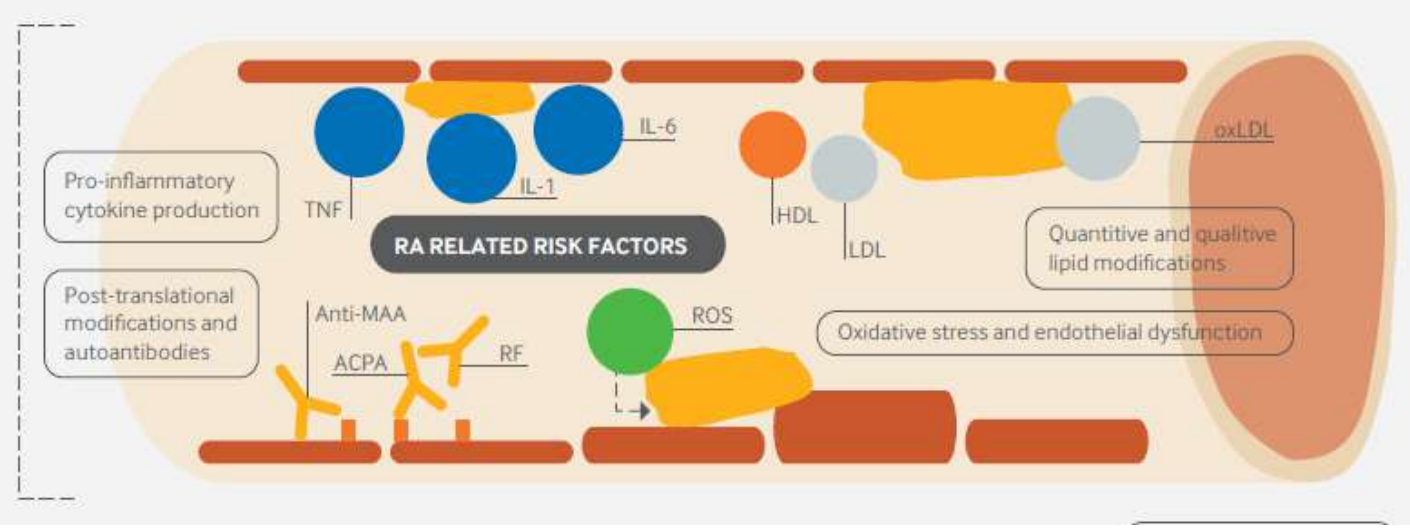


Manrique-Acevedo C et al. N Engl J Med2024;390:1207-1217

The NEW ENGLAND JOURNAL of MEDICINE

Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications

Bryant R England,[1 2] Geoffrey M Thiele,[1 2] Daniel R Anderson,[3] Ted R Mikuls[1 2]



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Criticità

Come stimo Il rischio ?

Prediction of First Cardiovascular Disease Event in Type 1 Diabetes Mellitus

The Steno Type 1 Risk Engine

Dorte Vistisen, PhD; Gregers Stig Andersen, PhD; Christian Stevns Hansen, MD; Adam Hulman, PhD; Jan Erik Henriksen, PhD; Henning Bech-Nielsen, Marit Eika Jørgensen

Table 2. Rate Ratios (RR) With 95% Confidence Intervals for Risk Factors in the Prediction Model for the Composite CVD Outcome

	Original Results		Postestimation Shrinkage	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Age (10 y)	1.51 (1.38–1.65)	<0.001	1.50 (1.38–1.64)	<0.001
Male sex (vs female sex)	1.30 (1.13–1.51)	<0.001	1.26 (1.09–1.46)	0.002
Diabetes duration (10 y)	1.14 (1.08–1.20)	<0.001	1.14 (1.08–1.20)	<0.001
Systolic blood pressure (10 mm Hg)	1.06 (1.02–1.10)	0.001	1.06 (1.02–1.10)	0.002
LDL cholesterol (mmol/L)	1.09 (1.00–1.19)	0.045	1.09 (1.00–1.18)	0.046
HbA_{1c} (10 mmol/mol)	1.14 (1.08–1.20)	<0.001	1.13 (1.07–1.19)	<0.001
Microalbuminuria (vs normoalbuminuria)	1.55 (1.29–1.86)	<0.001	1.55 (1.29–1.86)	<0.001
Macroalbuminuria (vs normoalbuminuria)	2.19 (1.69–2.84)	<0.001	2.09 (1.62–2.71)	<0.001
eGFR age <40 y (halving)	1.53 (1.30–1.80)	<0.001	1.50 (1.27–1.76)	<0.001
eGFR age ≥40 y (halving)	1.45 (1.24–1.70)	<0.001	1.41 (1.21–1.65)	<0.001
Smoking (vs no smoking)	1.22 (1.01–1.47)	0.041	1.23 (1.02–1.48)	0.034
No regular exercise (yes vs no)	1.29 (1.11–1.49)	<0.001	1.26 (1.08–1.46)	0.002

P value is for the test of significance of the risk factor. CVD indicates cardiovascular disease (ischemic heart disease, ischemic stroke, heart failure and peripheral artery disease); eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; and LDL, low-density lipoprotein.

Prediction of First Cardiovascular Disease Event in Type 1 Diabetes Mellitus

The Steno Type 1 Risk Engine

Dorte Vistisen, PhD; Gregers Stig Andersen, PhD; Christian Stevns Hansen, MD; Adam Hulman, PhD; Jan Erik Henriksen, PhD; Henning Bech-Nielsen, Marit Eika Jørgensen

Table 3. Performance of Existing CVD Risk Models in Derivation and Validation Data for Predicting 5-Year Risk of Fatal or Nonfatal CVD

	Steno T1D Risk Engine	Swedish T1D Risk Score[11]	UKPDS Risk Engine[8]	ASCVD Risk Equation[38]
Predicting composite CVD outcome (IHD, stroke, HF, or PAD)				
Original CVD outcome*	IHD, stroke, HF, or PAD	IHD or stroke	IHD	IHD or stroke
Derivation data				
C-statistic (95% CI)	0.826 (0.807–0.845)	0.794 (0.772–0.816)	0.766 (0.743–0.789)	0.748 (0.724–0.771)
C-statistic test†	–	P=0.031	P<0.001	P<0.001
Calibration‡	χ^2=12.4, P=0.136	χ^2=430.4, P<0.001	χ^2=711.8, P<0.001	χ^2=402.5, P<0.001
Validation data				
C-statistic (95% CI)	0.803 (0.767–0.839)	0.780 (0.745–0.815)	0.737 (0.699–0.775)	0.748 (0.713–0.789)
C-statistic test†	–	P=0.377	P=0.014	P=0.036
Calibration‡	χ^2=10.9, P=0.207	χ^2=206.9, P<0.001	χ^2=210.9, P<0.001	χ^2=130.3, P<0.001
Predicting IHD or stroke				
Original CVD outcome*	IHD or stroke	IHD or stroke	IHD	IHD or stroke
Derivation data				
C-statistic (95% CI)	0.814 (0.793–0.834)	0.796 (0.775–0.817)	0.770 (0.747–0.793)	0.749 (0.725–0.773)
C-statistic test†	–	P=0.002	P<0.001	P<0.001
Calibration‡	χ^2=11.4, P=0.179	χ^2=223.7, P<0.001	χ^2=371.8, P<0.001	χ^2=251.9, P<0.001
Validation data				
C-statistic (95% CI)	0.795 (0.755–0.834)	0.781 (0.742–0.819)	0.728 (0.686–0.770)	0.736 (0.697–0.774)
C-statistic test†	–	P=0.614	P=0.024	P=0.036
Calibration‡	χ^2=10.3, P=0.244	χ^2=78.8, P<0.001	χ^2=114.3, P<0.001	χ^2=117.8, P<0.001

ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease (ischemic heart disease, ischemic stroke, heart failure and peripheral artery disease); HF: heart failure; IHD: ischemic heart disease; PAD: peripheral artery disease; T1D, type 1 diabetes mellitus; and UKPDS, United Kingdom Prospective Diabetes Study.

*Original CVD outcome: the outcome for which the model was originally developed.

†C-statistic test: test of difference in C-statistic in comparison with the Steno T1 risk engine using the DeLong method.

‡Calibration is Hosmer-Lemeshow test of goodness of fit. P value <0.05 indicates lack of model fit.

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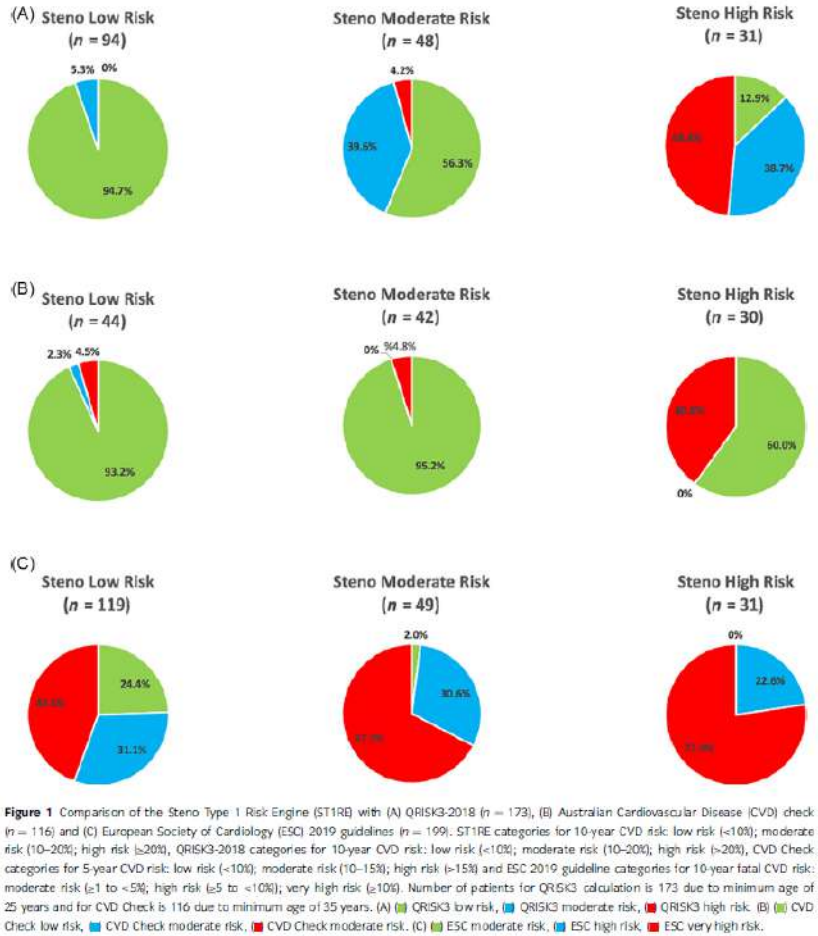

Figure 1 Comparison of the Steno Type 1 Risk Engine (ST1RE) with (A) QRISK3-2018 ($n = 173$), (B) Australian Cardiovascular Disease (CVD) check ($n = 116$) and (C) European Society of Cardiology (ESC) 2019 guidelines ($n = 199$). ST1RE categories for 10-year CVD risk: low risk (<10%); moderate risk (10–20%); high risk (≥20%), QRISK3-2018 categories for 10-year CVD risk: low risk (<10%); moderate risk (10–20%); high risk (>20%), CVD Check categories for 5-year CVD risk: low risk (<10%); moderate risk (10–15%); high risk (>15%) and ESC 2019 guideline categories for 10-year fatal CVD risk: moderate risk (≥1 to <5%; high risk (≥5 to <10%); very high risk (≥10%). Number of patients for QRISK3 calculation is 173 due to minimum age of 25 years and for CVD Check is 116 due to minimum age of 35 years. (A) QRISK3 low risk, QRISK3 moderate risk, QRISK3 high risk. (B) CVD Check low risk, CVD Check moderate risk, CVD Check moderate risk. (C) ESC moderate risk, ESC high risk, ESC very high risk.

Cardiovascular risk stratification in type 1 diabetes: do risk calculators and guidelines align?

Internal Medicine Journal **53** (2023) 879–881

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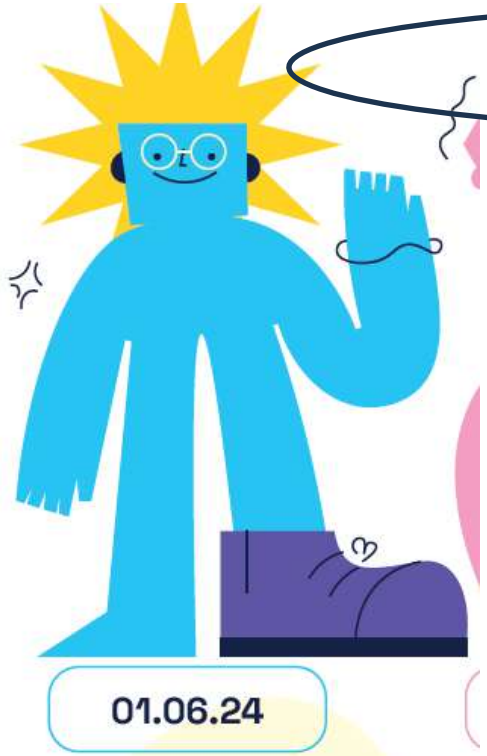

Opportunità

Agire presto

Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up

*The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group**

Diabetes Care 2016;39:686–693 | DOI: 10.2337/dc15-1990

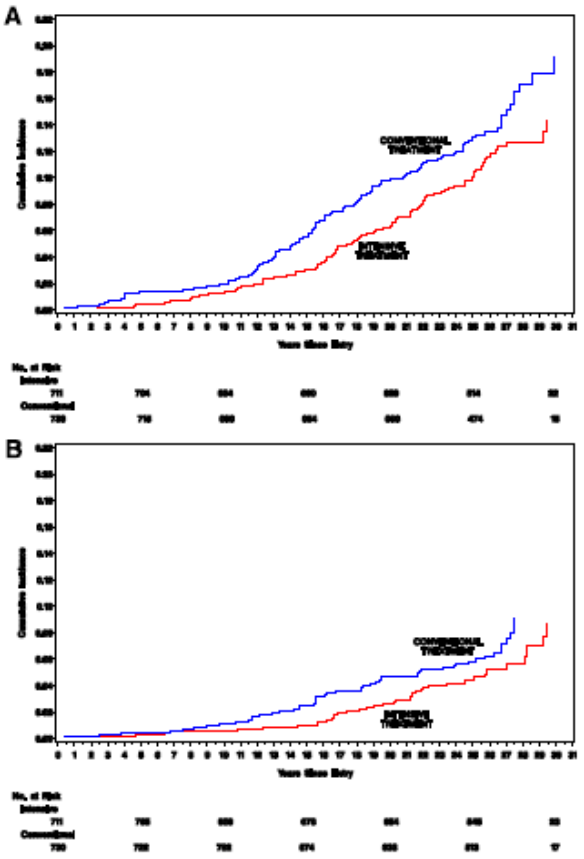

Figure 1—Cumulative incidence of cardiovascular outcomes in the conventional treatment and intensive treatment groups during up to 30 years of DCCT/EDIC treatment and follow-up. *A*: The first of any of the predefined CVD outcomes. The risk reduction with intensive therapy was 30% (95% CI 7, 48; $P = 0.016$). *B*: The first occurrence of MACE. The risk reduction with intensive therapy was 32% (95% CI −3, 56; $P = 0.07$).

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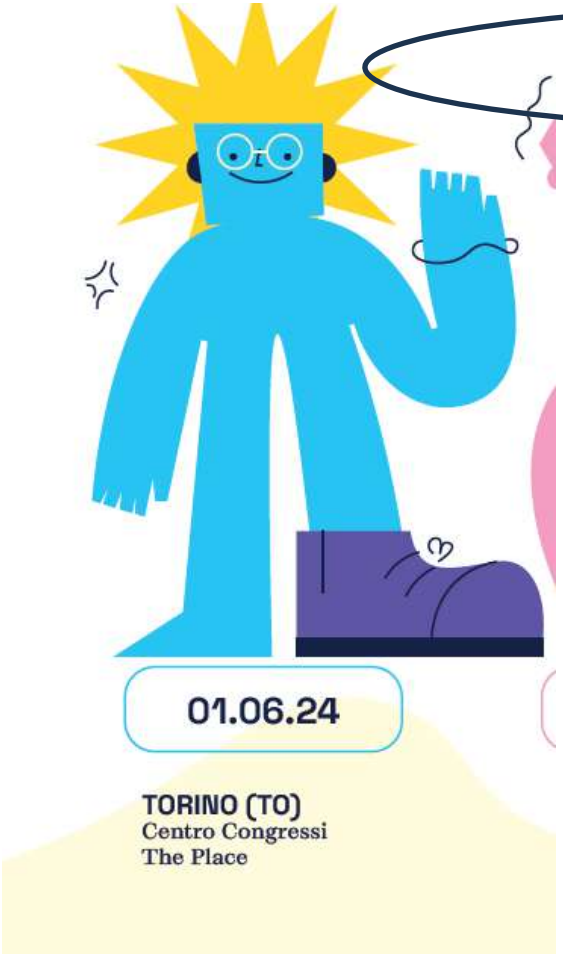
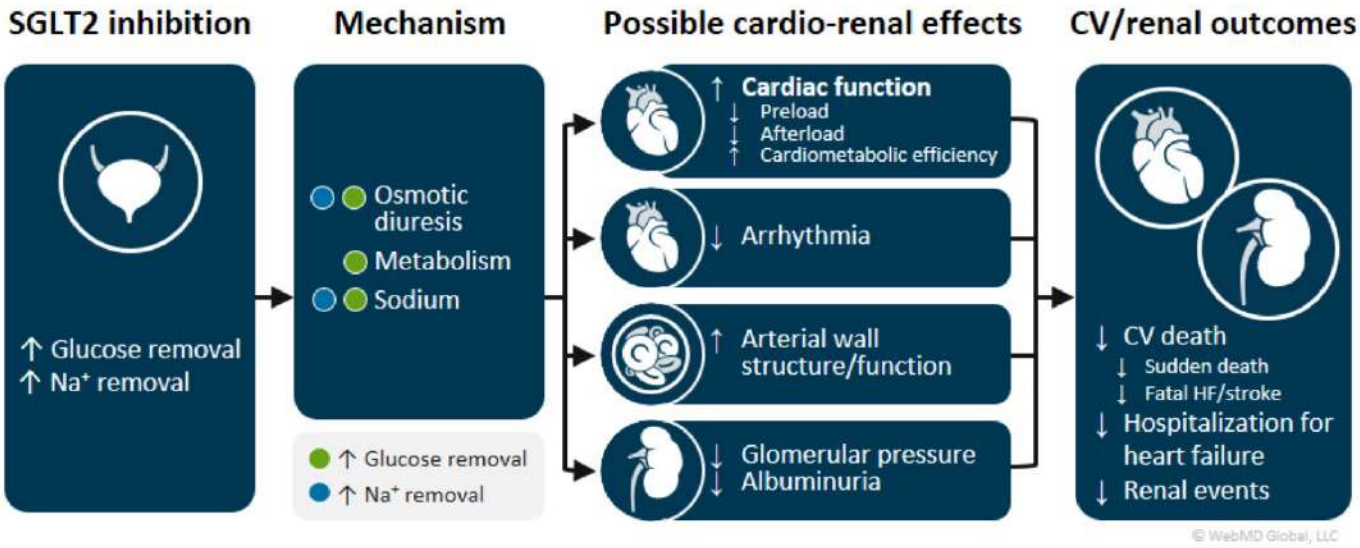


Opportunità

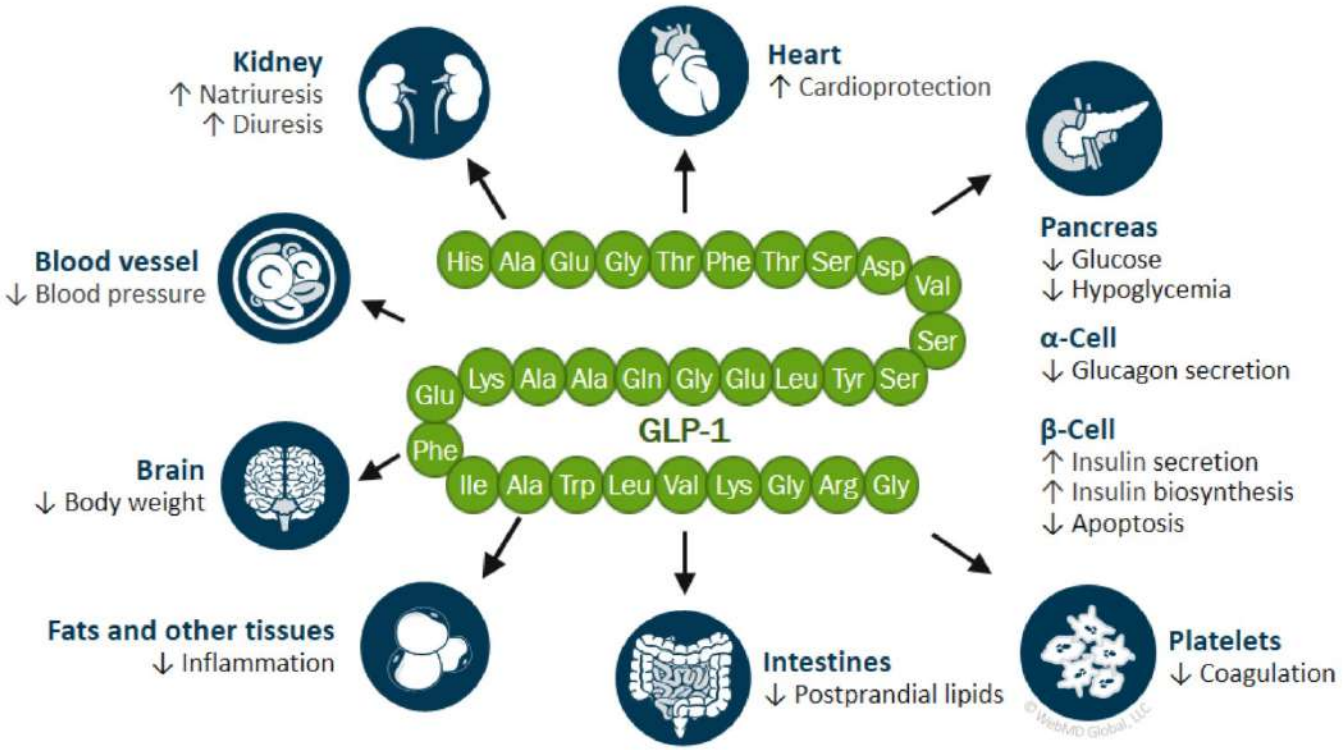
Non ancora

SGLT2 Inhibitors: Mechanism of Action



Butler J, et al; the EMPEROR Trials Program. *Eur J Heart Fail.* 2017;19:1390–1400.

GLP-1 RAs: Mechanism of Action



Drucker DJ. *Cell Metab.* 2016;24:15-30.

Clinical and Safety Outcomes With GLP-1 Receptor Agonists and SGLT2 Inhibitors in Type 1 Diabetes: A Real-World Study

Khary Edwards,[1,*] Xilong Li,[2,*] and Ildiko Lingvay[1,2]

[1]Department of Internal Medicine/Endocrinology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-8857, USA
[2]Department of Population and Data Sciences, University of Texas Southwestern Medical Center, Dallas, Texas 75390-8857, USA

Correspondence: Khary Edwards, MD, Department of Internal Medicine/Endocrinology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8857, USA. Email: edwardskhary@gmail.com.
*K.E. and X.L. are co-primary authors of this work.

Table 3. Change in outcomes over 12 months of GLP-1RA/SGTL2i use

	GLP-1RA	SGLT2i	Between-group *P*[a]
HbA_{1c}, %			
Baseline	7.7 (7.4-8.0)	7.9 (7.5- 8.4)	
12 mo	7.3 (7.0-7.7)	7.3 (6.9-7.7)	
P (within-group change over 12 mo)	.007	< .001	.248
Weight, kg			
Baseline	90.4 (85.3-95.8)	89.2 (82.1-96.9)	
12 mo	85.4 (80.3-90.8)	87.5 (80.1-95.5)	
P (within-group change over 12 mo)	< .001	.168	.027
TDD insulin, units			
Baseline	61.8 (53.3-71.7)	58.0 (47.5-71.5)	
12 mo	49.9 (42.4-58.8)	57.0 (44.3-72.3)	
P (within-group change over 12 mo)	< .001	0.798	.073
Basal insulin, units			
Baseline	30.7 (27.1-34.7)	31.3 (26.2-37.5)	
12 mo	26.0 (22.6-29.8)	25.6 (21.0-31.3)	
P (within-group change over 12 mo)	< .001	.003	.689
Bolus insulin, units			
Baseline	37.9 (30.6-45.1)	32.9 (22.5-43.4)	
12 mo	27.9 (19.5-36.1)	35.0 (22.1-47.8)	
P (within-group change over 12 mo)	.004	.719	.068
eGFR, mL/min/1.73 m^2			
Baseline	85.2 (78.5-91.2)	82.3 (73.6-91.0)	
12 mo	83.5 (74.4-92.3)	81.1 (71.0-91.2)	
P (within-group change over 12 mo)	.653	.762	.915
Microalbumin:creatinine ratio, mg/g			
Baseline	10.4 (6.4-17.1)	25.1 (13.3-47.2)	
12 mo	10.4 (3.6-30.4)	22.9 (6.4-82.0)	
P (within-group change over 12 mo)	.999	.878	.907
Total cholesterol, mg/dL			
Baseline	183.0 (173.5-192.5)	170.1 (157.2-183.0)	
12 mo	156.6 (135.1-178.0)	168.8 (148.0-189.5)	
P (within-group change over 12 mo)	.015	.893	.086
LDL, mg/dL			
Baseline	103.9 (95.7-112.0)	92.4 (81.4-103.3)	
12 mo	77.0 (58.2-95.8)	88.6 (70.5-106.7)	
P (within-group change over 12 mo)	.005	.661	.074
Triglycerides, mg/dL			
Baseline	93.4 (81.8-106.7)	91.4 (76.5-109.2)	
12 mo	89 (52.1-95.8)	92.1 (68.7-123.5)	
P (within-group change over 12 mo)	.678	.958	.915

Data presented are estimated (least square) means (95% CI). A *P* value of less than .05 (2-tailed) was selected to indicate statistical significance. HbA_{1c}, weight, TDD insulin, basal insulin, triglycerides, and microalbuminscreatinine ratio were exponentiated back from the least square means of log data.
Abbreviations: eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin A_{1c}; LDL, low-density lipoprotein; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TDD insulin, total daily dose of insulin.
[a]Between-group *P* value represents *P* for the difference in change in variable from baseline to 12 months between GLP-1RA and SGLT2i users.

Table 4. Adverse events experienced during GLP-1RA or SGLT2i use

Event	GLP-1RA (N = 76)		SGLT2i (N = 39)	
	% (n)[a]	Rate[b]	% (n)	Rate[b]
DKA	3.9 (3)	1.6	12.8 (5)	6.6
Severe hypoglycemia	1.3 (1)	0.5	2.6 (1)	0
Pancreatitis	0 (0)	0	0 (0)	1.1
Hospitalizations[c]	21.1 (16)	13.6	28.2 (11)	15.4
Emergency room visits[c]	19.7 (15)	13.6	7.7 (3)	3.3

Abbreviations: DKA, diabetic ketoacidosis; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
[a]Number of patients with at least one event.
[b]Rate reported as events/100 patient-years.
[c]For any reason, not just diabetes related.

Combination SGLT2 Inhibitor and Glucagon Receptor Antagonist Therapy in Type 1 Diabetes: A Randomized Clinical Trial

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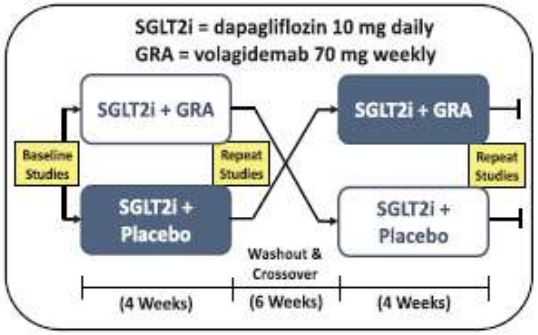
Combination Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor + Glucagon Receptor Antagonist (GRA) in Adults With Type 1 Diabetes Using CGM and Continuous Subcutaneous Insulin Infusion

Hypothesis

Combining an SGLT2 inhibitor with a GRA will:

1. Improve glycemia
2. Reduce insulin use
3. Reduce ketogenesis during insulinopenia

Study Design (*n*=12)



Results

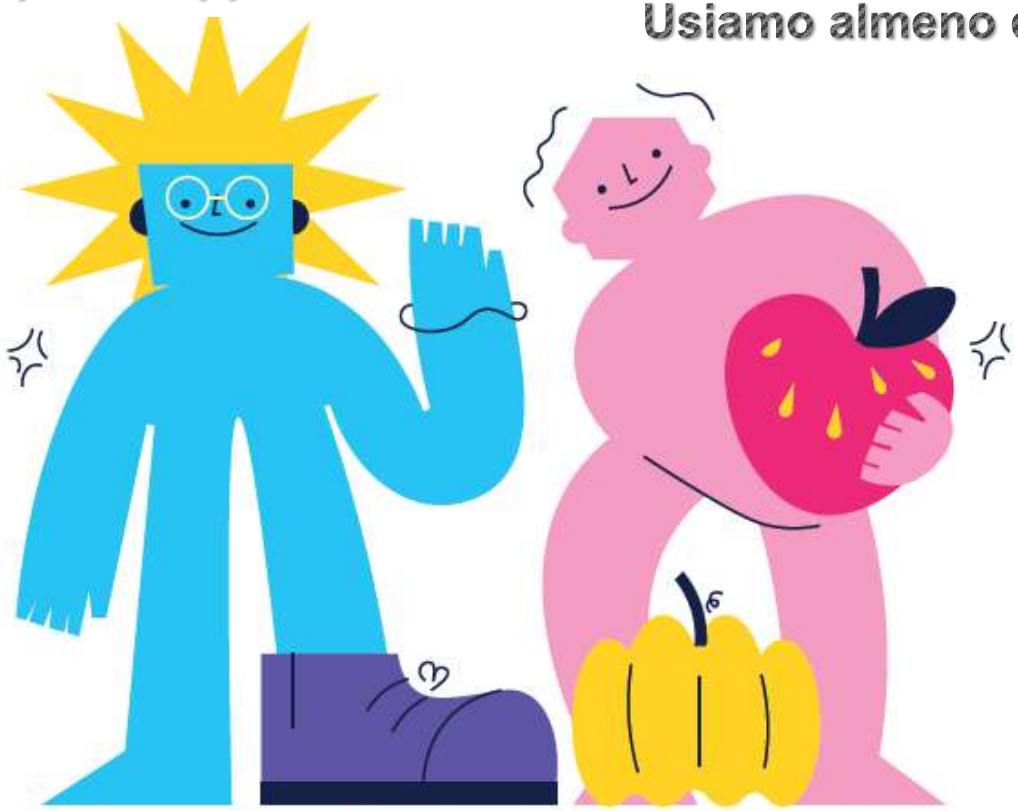
With combination therapy:

- Average glucose ⬇ 19 mg/dL
- Time in range ⬆ 16%
- No increased hypoglycemia
- Total insulin use ⬇ 27%
- Ketones in insulinopenia ⬇ 17%

Conclusion: Combination SGLT2 inhibitor + GRA is a promising adjunctive therapy strategy for type 1 diabetes

Che peccato non poter sfruttare queste opportunità

Usiamo almeno quelle esistenti



Cardiovascular risk management in people with type 1 diabetes: performance using three guidelines

Rita Delphine Maiko Varkevisser ,[1] Erwin Birnie,[2,3] Charlotte E Vollenbrock ,[1] Dick Mul,[2] Peter R van Dijk ,[1] Melanie M van der Klauw,[1] Henk Veeze,[2] Bruce H R Wolffenbuttel ,[1] Henk-Jan Aanstoot[2]

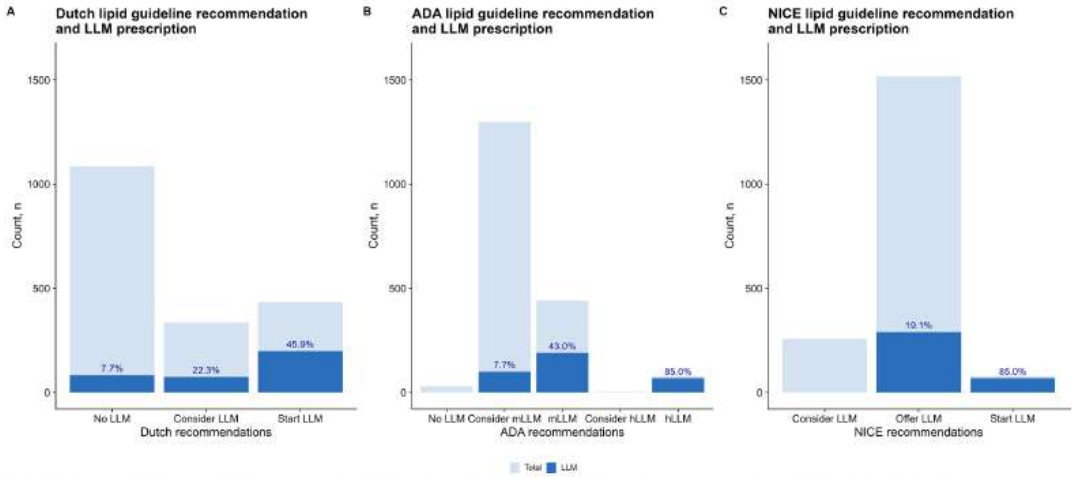


Figure 1 Frequency of lipid guideline recommendations in the study population based on the (A) Dutch, (B) American Diabetes Association (ADA) and (C) National Institute for Health and Care Excellence (NICE) guidelines and the prescription of lipid-lowering medication (LLM) for each recommendation group. Percentages presented are the percentage of LLM use per recommendation.

Cardiovascular risk management in people with type 1 diabetes: performance using three guidelines

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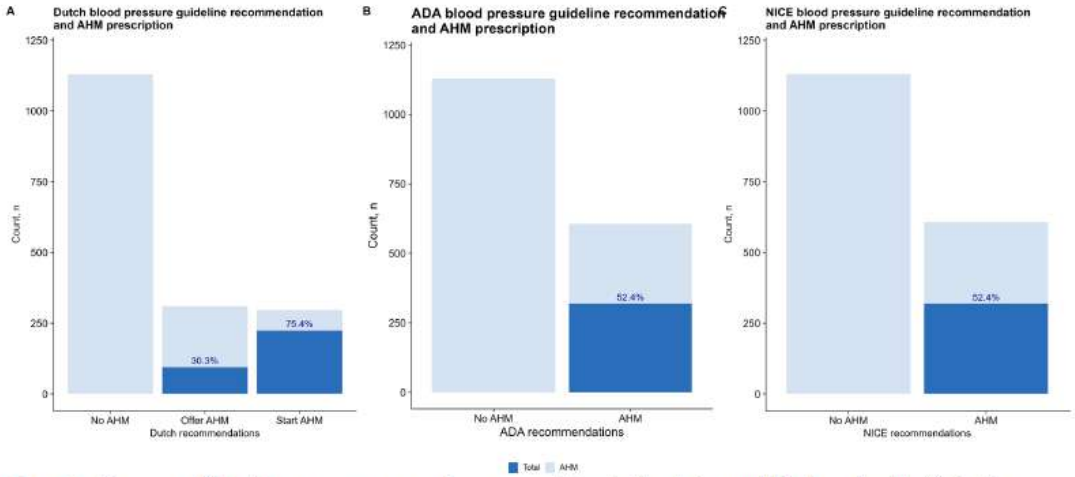

Figure 3 Frequency of blood pressure management recommendations in the study population based on the (A) Dutch, (B) American Diabetes Association (ADA) and (C) National Institute for Health and Care Excellence (NICE) guidelines and the prescription of antihypertensive medication (AHM) for each recommendation group. Percentages presented are the percentage of AHM use per recommendation.

Excess mortality in Type 1 diabetes diagnosed in childhood and adolescence: a systematic review of population-based cohorts

Eileen Morgan · Christopher R. Cardwell · Catherine J. Black · David R. McCance · Christopher C. Patterson

Location (Reference)	Age at dx	Period of dx (end of follow-up)	Cohort size	Observed* (Expected)	Mortality rate per 1000 person years	SMR (95%CI)
UK (Leicestershire) [15]	<17y	1970-1989 (1991)	582	10 (3.4)	1.35	293 (140-539)†
Cuba (Havana) [17]	<15y	1965-1980 (1991)	504	70 (8.3)	7.94	854 (666-1079)
Austria [8]	<15y	1979-1990 (1990)	1185	4 (2.6)	0.80	153 (68-346)
Estonia [6]	<15y	1980-1994 (1995)	518	11 (2.8)	3.79	399 (199-714)
Lithuania [6]	<15y	1983-1994 (1995)	698	23 (3.3)	5.64	695 (441-1043)
Israel [18]	<18y	1965-1993 (1996)	1,861	37 (12.4)	1.55	298 (209-410)
Sweden [9]	<15y	1977-2000 (2000)	10,200	72 (36.3)	0.96	198 (155-250)
Norway [13]	<15y	1973-1982 (2002)	1,906	101 (26.1)	2.19	387 (315-470)
Lithuania [4]	<15y	1989-2003 (2005)	1,006	2 (1.6) ‡	0.64	125 (15-452)
Bulgaria (Eastern) [4]	<15y	1989-1999 (2004)	443	10 (2.1)	2.46	476 (228-876)
Hungary (ex. Budapest) [4]	<15y	1989-2002 (2002)	1,968	5 (4.5)	0.37	111 (36-259)
Austria [4]	<15y	1989-2002 (2003)	1,989	3 (3.7) ‡	1.07	81 (17-237)
Spain (Catalonia) [4]	<15y	1989-2002 (2005)	1,809	3 (7.1)	0.16	42 (9-124)
Germany (Dusseldorf) [4]	<15y	1989-2001 (2005)	757	4 (1.4)	0.80	286 (78-732)
Iceland [4]	<15y	1989-2004 (2005)	151	0 (0.5)	0.00	0 (0-738)
Denmark [4]	<15y	1989-2002 (2002)	2,285	10 (3.3)	0.76	303 (145-557)
Norway [4]	<15y	1989-2003 (2005)	3,130	19 (9.5)	0.69	200 (120-312)
UK (Northern Ireland) [4]	<15y	1989-2002 (2003)	1,310	9 (3.2)	0.95	281 (129-534)
UK (Yorkshire) [2]	<15y	1978-2004 (2005)	3,349	74 (17.7)	1.72	418 (328-525)
Italy [16]	<19y	1974-2000 (2003)	677	12 (6.1)	1.84	198 (102-346)
U.S. (Pittsburgh) [19]	<18y	1965-1979 (2008)	1,075	279 (40.4)	8.12	691 (612-777)
Finland [14]	<15y	1970-1999 (2007)	10,492	541 (148.8)	1.46	364 (334-396)
Australia [20]	<18y	1987-2007 (2011)	1,873§	11 (4.2)	0.63	262 (131-469)

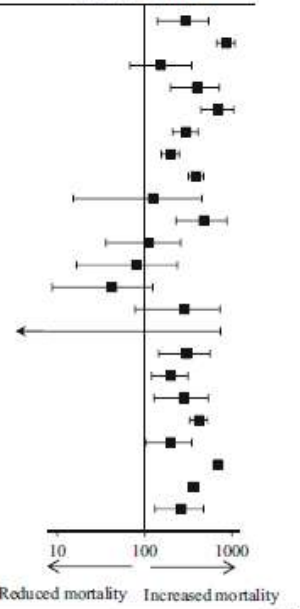

Fig. 2 Characteristics and forest plot of included studies, ordered by publication date. *Dx* diagnosis, *SMR* standardised mortality ratio. *The observed deaths noted here do not include deaths which occurred at onset and therefore may not correspond to those published. †SMR was calculated only for diagnosis period of 1970–1989. ‡Data were reanalysed to exclude overlapping periods with other studies. §This value was taken from another publication on the register [31] covering cases diagnosed during 1985–2010 and is therefore an approximation of the cohort used in this review

Grazie per l'ascolto