Dapagliflozin e Exenatide LAR: l'innovazione come risposta efficace ai bisogni del paziente

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AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2017

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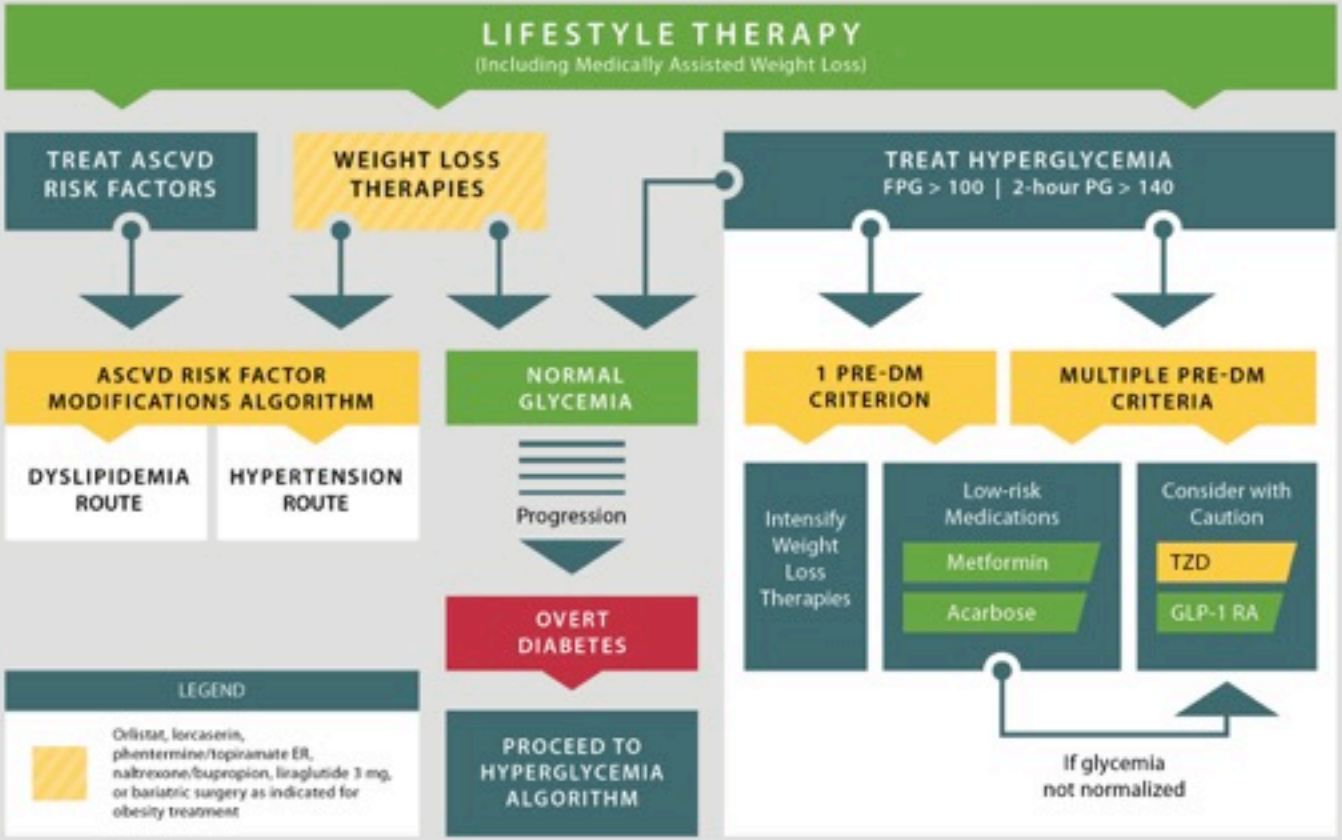
 DOI 10.4158/EP161682.CS

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



 DOI 10.4158/EP161682.CS

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/EP161682.CS

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%

TDD 0.1–0.2 U/kg

A1C > 8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i

Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- Start: 10% of basal dose or 5 units

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

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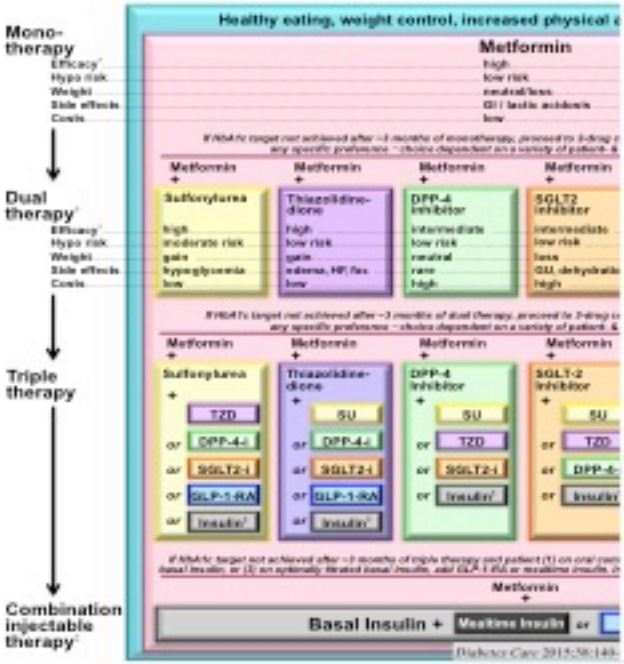
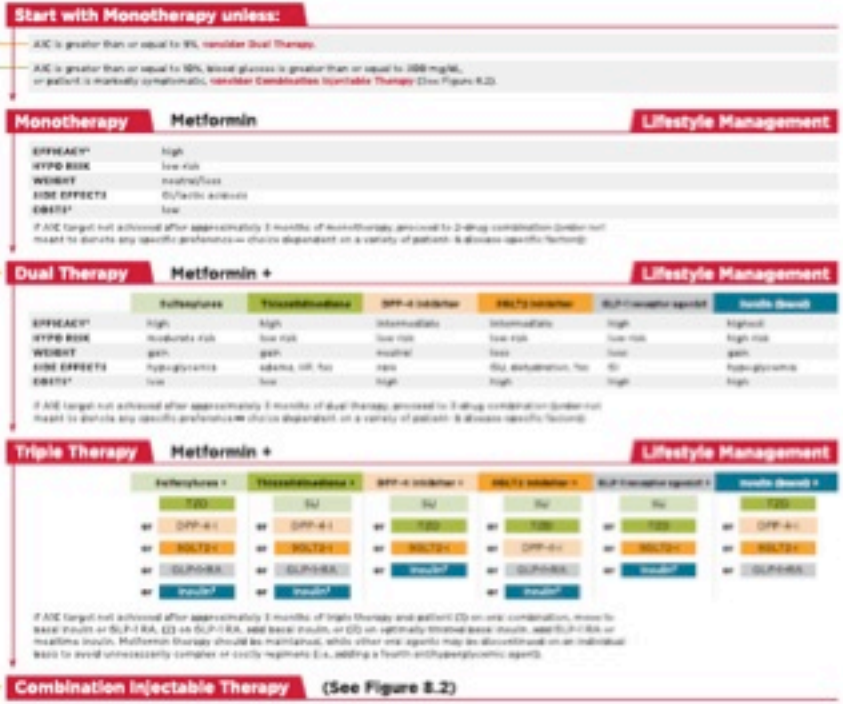
Il Position Statement ADA-EASD (2016) e gli Standard di Cura ADA (2016) suggeriscono un approccio sequenziale dopo la Metformina



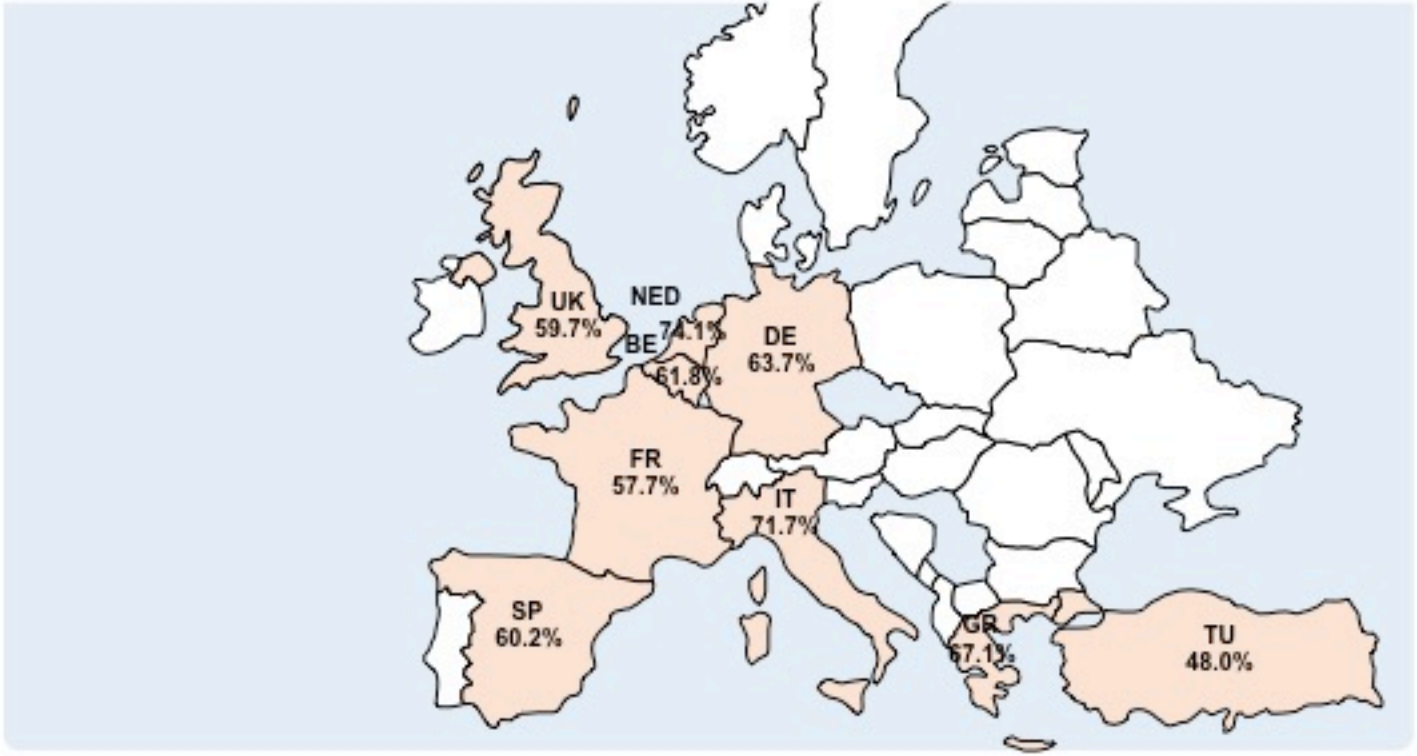


Una significativa quota di pazienti con DM 2 in Europa non raggiunge i target glicemici [1]

STUDIO PANORAMA :
su 5817 pazienti arruolati

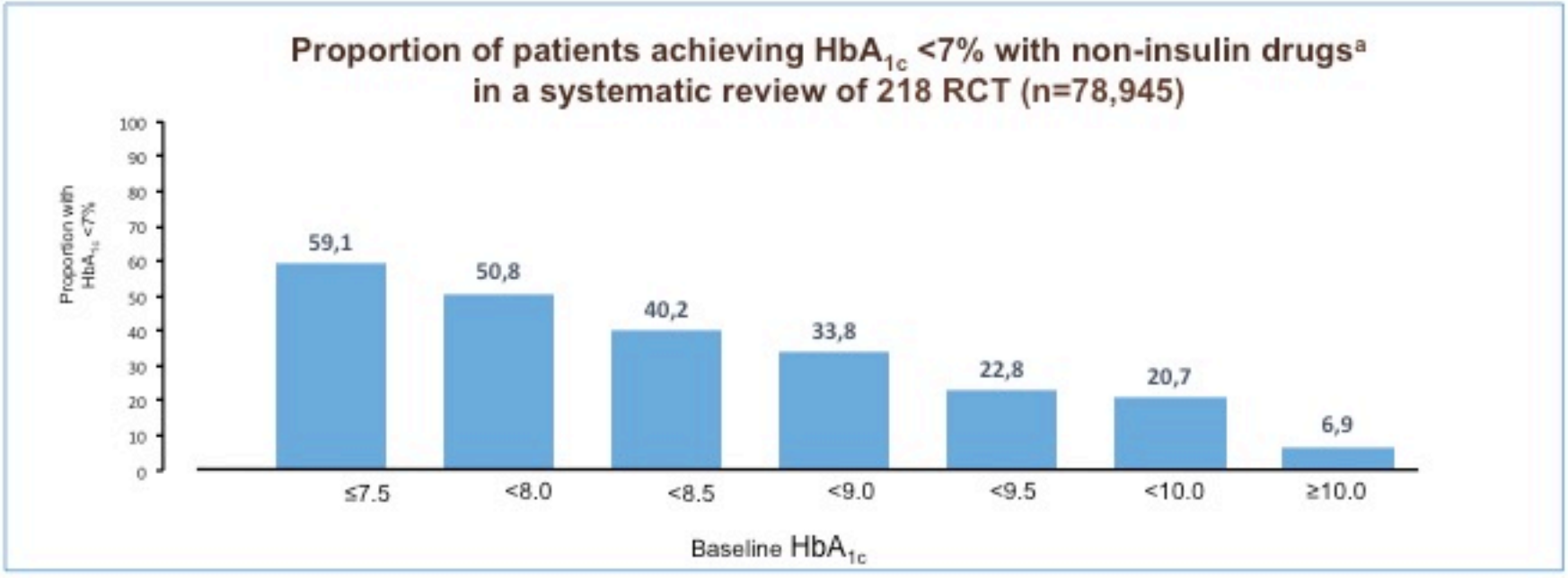
solo il 62,6% raggiungevano

HbA1c <7%



1. de Pablos-Velasco P *et al. Clin Endocrinol*. 2014; 80:47–56.

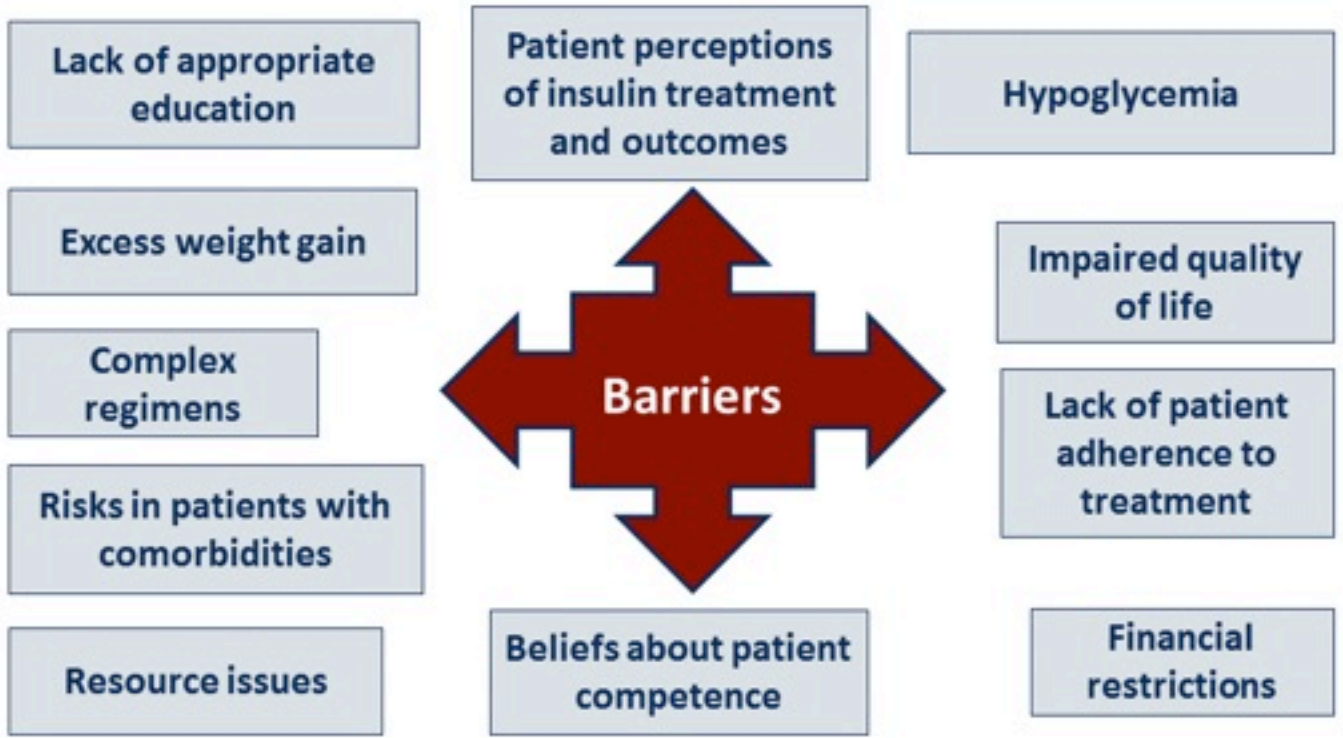
Più alta è la HbA1c di partenza e più è difficle raggiungere il target [1]



[a]Metformin, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, glinides, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 analogues
RCT, randomized controlled trial

1. Esposito K. et al. Diabetes Obes Metab. 2012; 14:228–233.

Clinical Inertia: Patient and Physician Barriers

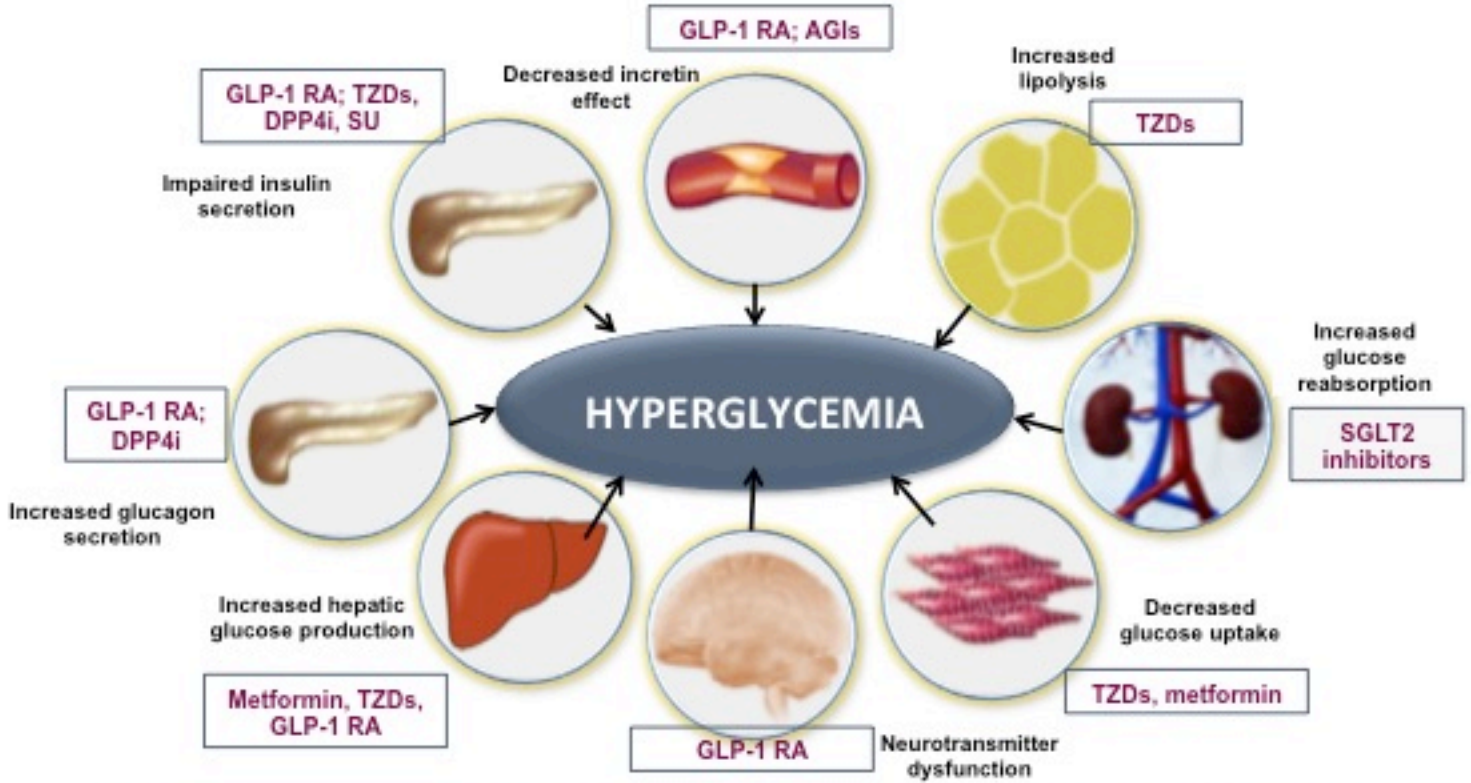


Peyrot M, et al. *Diabetes Care*. 2005;28:2673-2679; Elgrably F, et al. *Diabetes Med*. 1991;8:773-777; Wallace TM, et al. *QJM*. 2000;93:369-374; Kunt T, et al. *Int J Clin Pract Suppl*. 2009;63:6-10.

Properties of the Ideal Drug for T2DM

- Efficacious
- Good safety profile
- Slows/halts disease progression
- Well tolerated
- Low risk for hypoglycemia
- Causes weight loss
- Improves other risk factors/comorbidities
- Easy to use
- Can be used in renal and hepatic impairment
- Can be used at any stage of the disease and in any combination

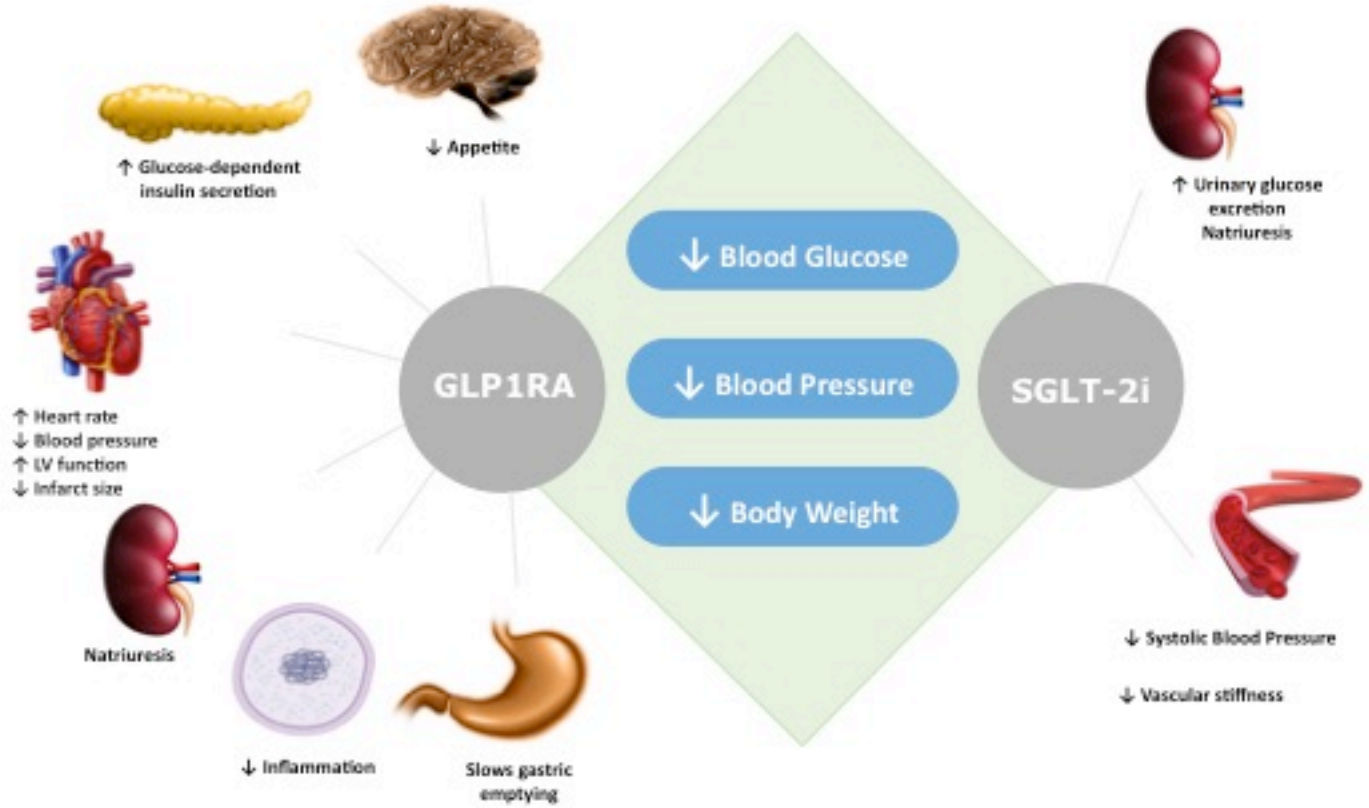
L'approccio pato-fisiologico: dal " *triumvirato" all'* "ottetto minaccioso "



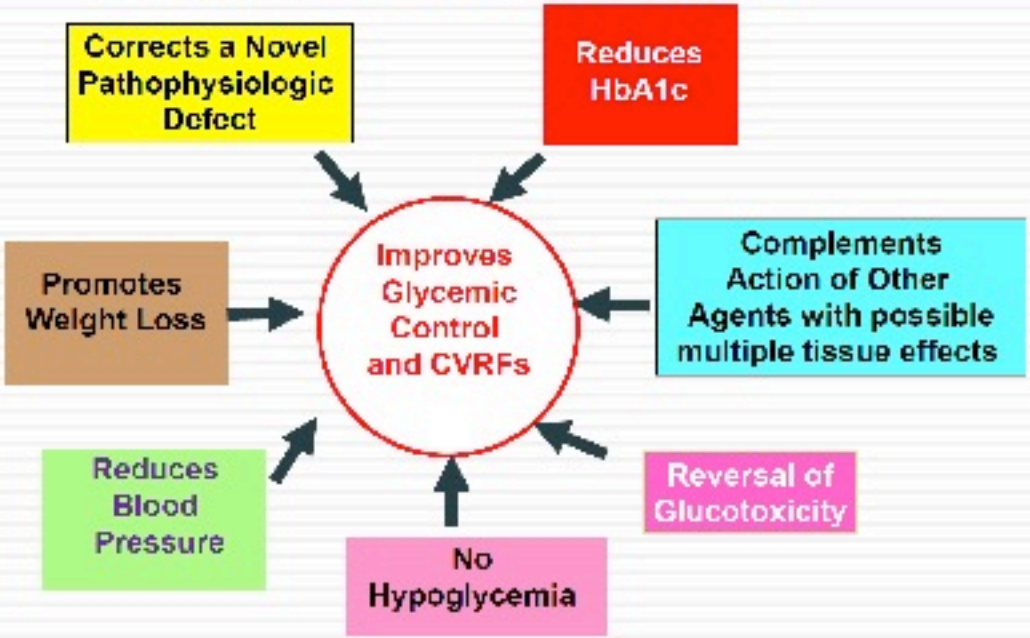
AGI, alpha-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; TZD, thiazolidinedione.

DeFronzo RA. *Diabetes*. 2009;58(4):773–795; Tahrani AA, et al. *Lancet*. 2011;378:182–197.

GLP1 RA e SGLT-2i impattano su un ampio range di meccanismi patofisiologici nel DMt 2

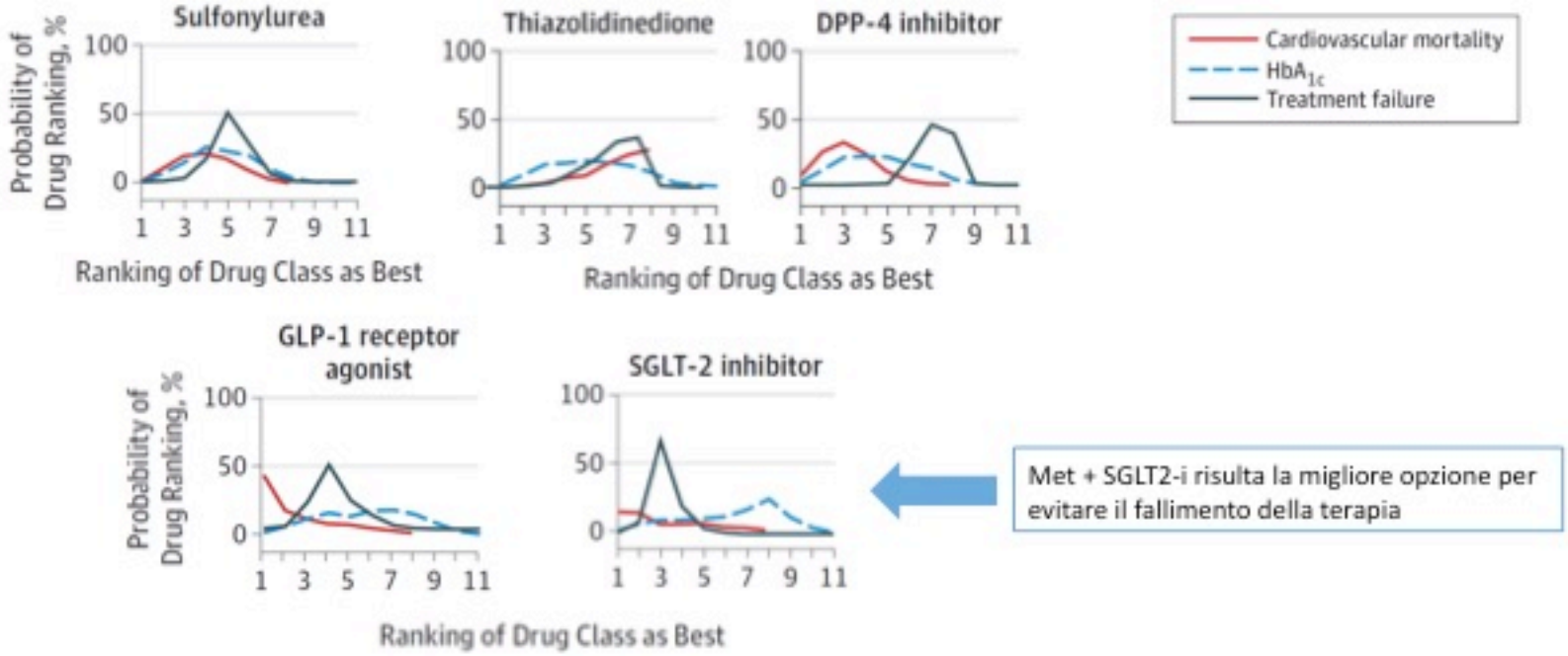


THE KIDNEY EMERGES AS A PREFERRED TARGET FOR GLUCOSE CONTROL THROUGH SGLT2 INHIBITION: A NEW PARADIGM MEETING UNMET NEEDS IN THE FUTURE OF DIABETES CARE



Sglt2 inibitori : “ grading” *per efficacia*

- 26 studi (20 690 pazienti) :
  - Gli SGLT2 inib. GLP1 ag. hanno mostrato un’associazione significativa con il rischio di mortalità CV
  - Tutte le classi in duplice terapia hanno mostrato di ridurre i livelli di HbA1C in misura simile

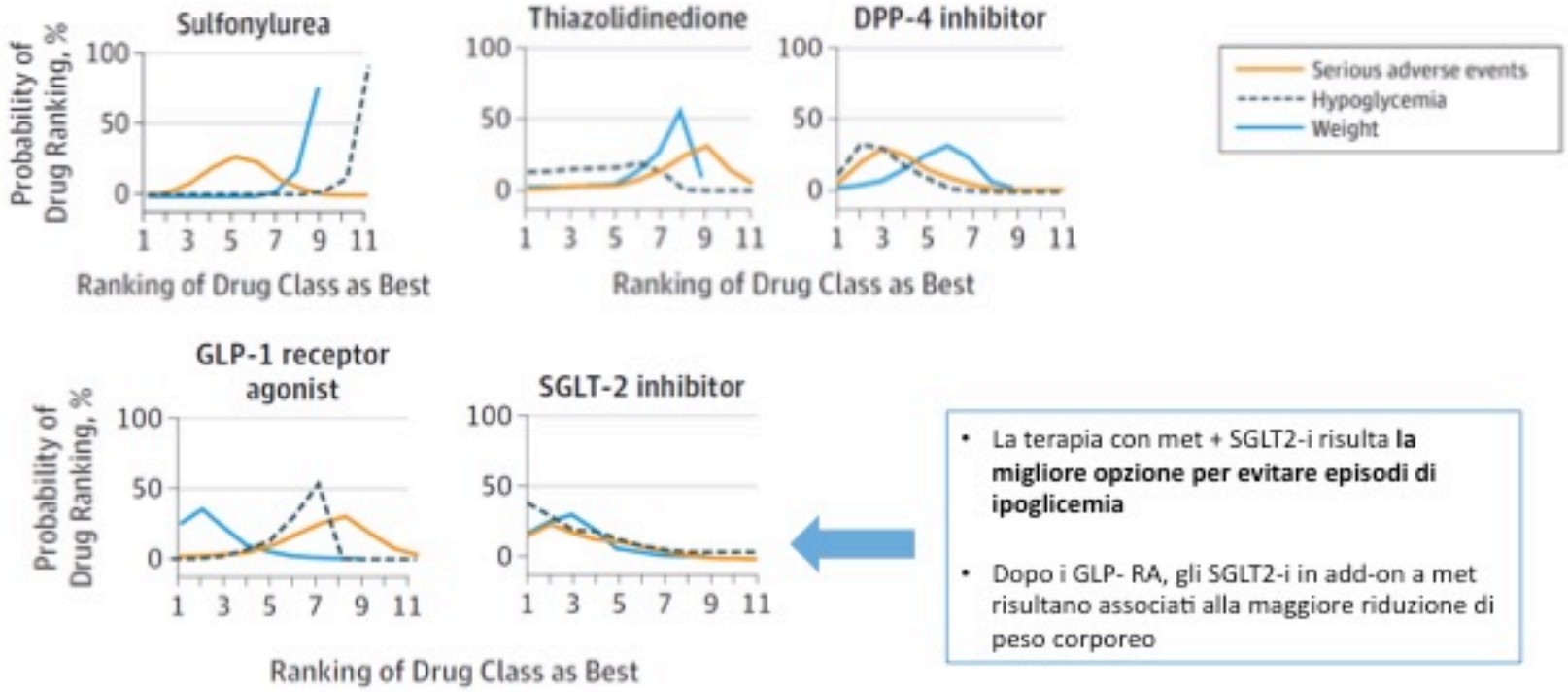


Met + SGLT2-i risulta la migliore opzione per evitare il fallimento della terapia

Palmer SC et al, 2016;JAMA 316(3):313-24.

Sglt2 inibitori: " grading" *per sicurezza*

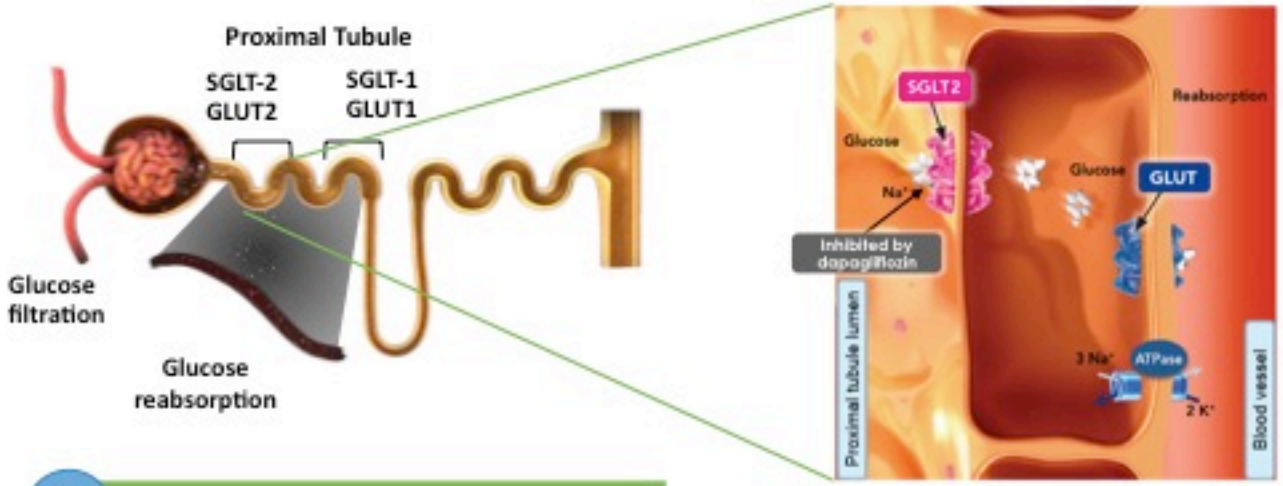
- Non sono state riscontrate differenze significative tra le classi relativamente al rischio di SAE



- La terapia con met + SGLT2-i risulta **la migliore opzione per evitare episodi di ipoglicemia**
- Dopo i GLP- RA, gli SGLT2-i in add-on a met risultano associati alla maggiore riduzione di peso corporeo

Palmer SC et al, 2016; JAMA 316(3):313-24.

SGLT-2i: Dapagliflozin



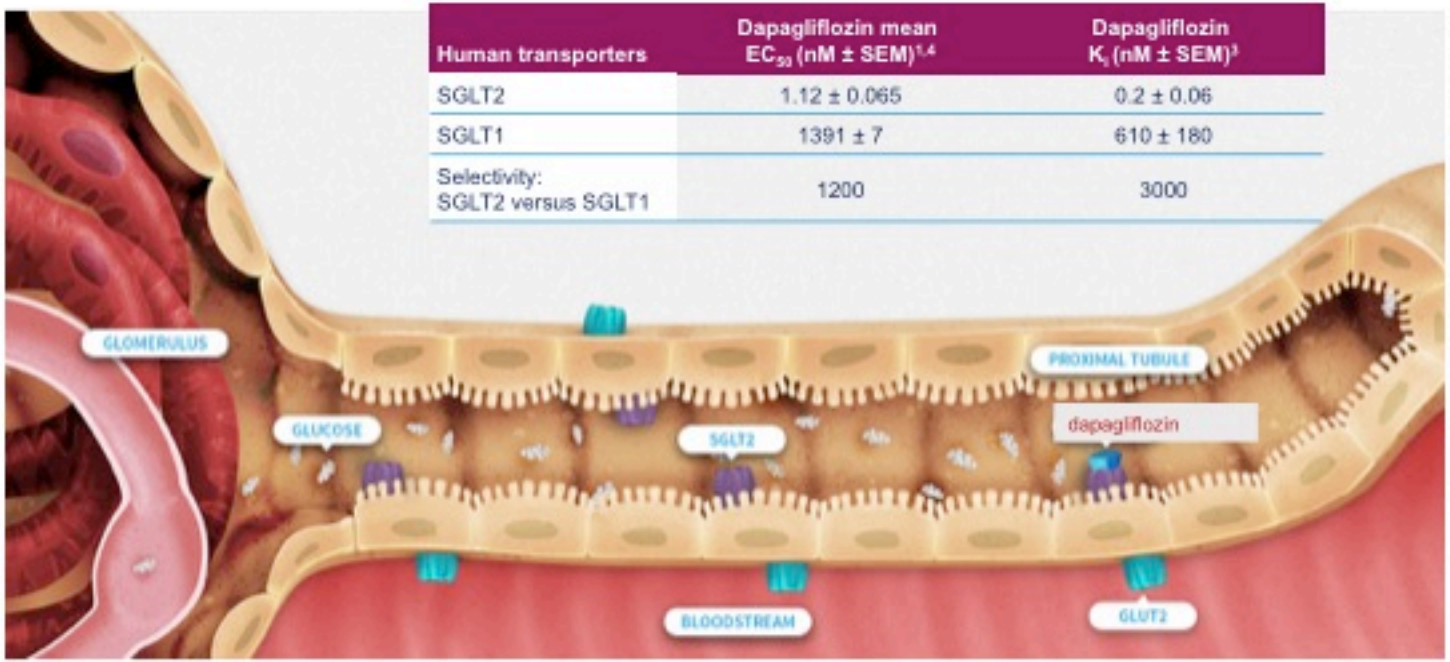
Effect of SGLT-2i

- ↑ Urinary glucose excretion
- ↓ FPG and PPG
- ↓ Body weight
- ↓ Systolic blood pressure
- ↓ Vascular stiffness
- ↓ A1C levels

- 1. Bays H. *Curr Med Res Opin*. 2009;25;671-681. 2. Abdul-Ghani MA et al. *Endocr Pract*. 2008;14:782-790. 3. Marsenic O. *Am J Kidney Dis*. 2009;53:875-883. 4. Mather A et al. *Kidney Int*. 2011;79(suppl 120):S1-S6. 5. FARXIGA PI. 6. Inzucchi SE. *Diab Vasc Dis Res*. 2015;12(2):90-100. 7. Asano T et al. *Curr Med Chem*. 2004;11:2717-2724.

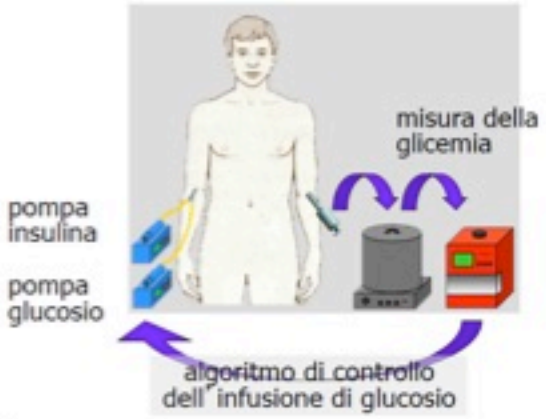
Il Dapagliflozin è un inibitore dell'SGLT2 altamente selettivo e reversibile[1]

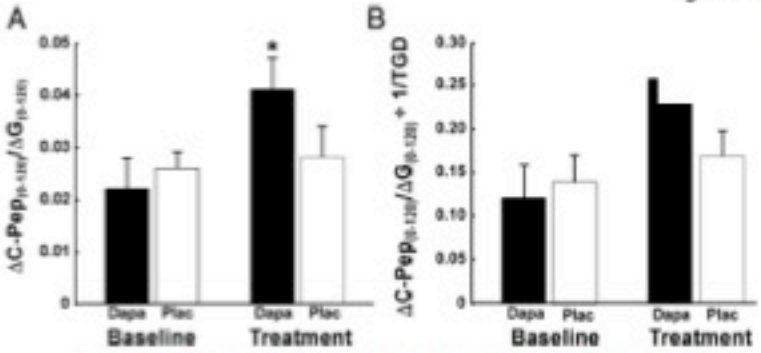
Human transporters	Dapagliflozin mean EC_{50} (nM ± SEM)[1,4]	Dapagliflozin K_i (nM ± SEM)[3]
SGLT2	1.12 ± 0.065	0.2 ± 0.06
SGLT1	1391 ± 7	610 ± 180
Selectivity: SGLT2 versus SGLT1	1200	3000



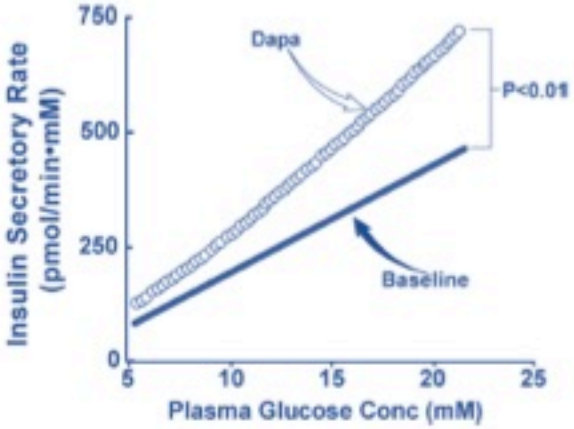
1. Meng W, et al. J Med Chem 2009;51:1145; 2. Washburn W. J Med Chem 2008;52:1785; 3. Bellamine A, et al. Presented at Biomedical Transporters 2009, Thun Switzerland (9 Aug 2008); 4. Han S, et al. Diabetes 2008;57:1723–9.

Dapagliflozin riducendo la glicemia migliora la funzione beta cellulare (effetto sulla gluco - tossicità) [1]





Beta cell function measured as C-Pep0–120/G0–120 IR, in DMT2 patients treated with Dapagliflozin or PBO at baseline and after 2 weeks * *P* .05 vs baseline and vs placebo.

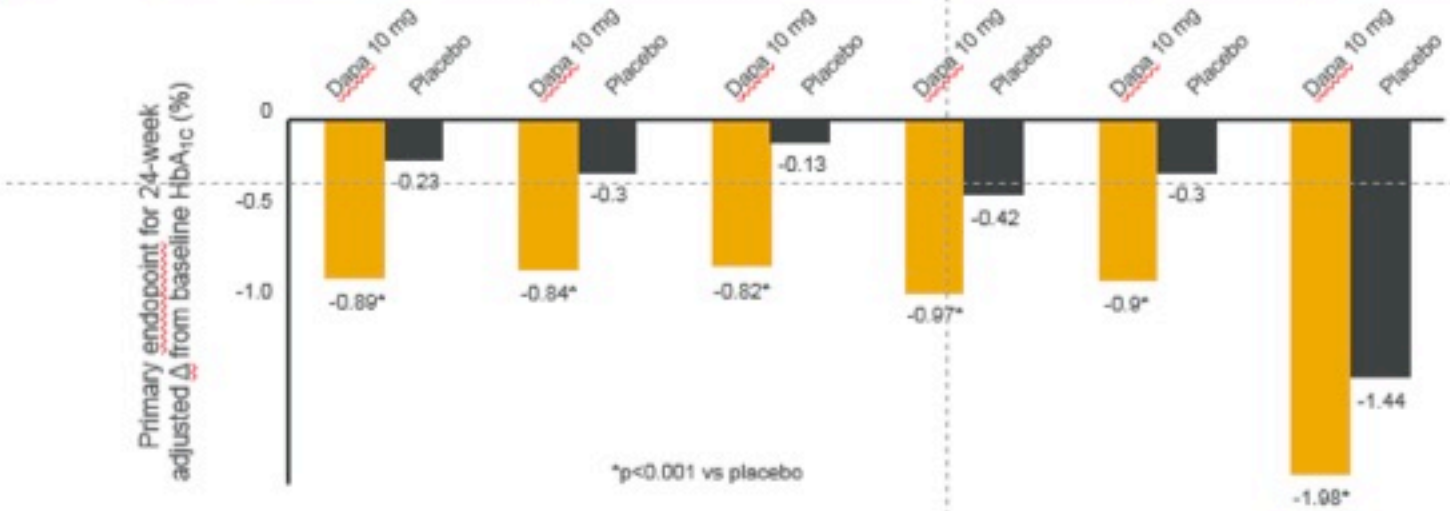


Beta cell glucose-sensibility measured before and after Dapagliflozin

[1] Merovci et al. J Clin Endocrinol Metab. 2015 May;100(5):1927-32.

Dapagliflozin : efficacia su HbA1c sia in monoterapia che in terapia di associazione

	Monotherapy[1]	Add-on to Met[2]	Add-on to Glim[3]	Add-on to Pio[4]	Add-on to Ins[5]	Add-on to Met XR[6]
Baseline HbA_{1C}	7.92	8.06	8.11	8.37	8.53	9.05



- Dapagliflozin reduces HbA_{1C} vs. placebo over 24 weeks (as monotherapy or add-on therapy)[1-6]

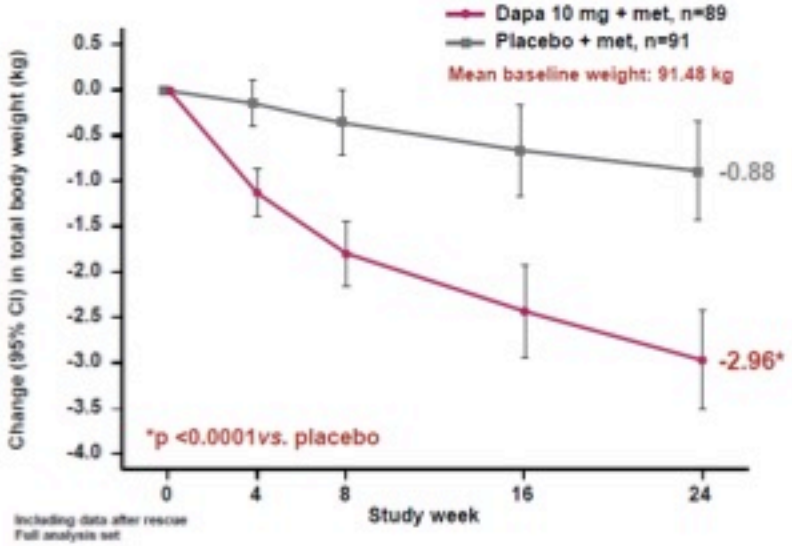
Dapa=dapagliflozin; MET=metformin; Glim=glimepiriade; Pio=pioglitazone; Ins=insulin; HbA1C=glycated haemaglobin

1. Ferrannini E, et al. Diabetes Care 2010;33:2217–24. 2. Bakley CJ, et al. Lancet 2010;375:2223–33. 3. Strojek K, et al. Diabetes Obes Metab 2011;13:928-38. 4. Rosenstock J, et al., Diabetes Care, 2012 Jul;35(7):1473-8. 5. Wilding J, et al. Diabetes. 2010; 59 (Suppl 1): A21–A22. Abstract 0078-OR. 6. Henry R, al. Int J Clin Pract. 2012 May;66(5):446-56

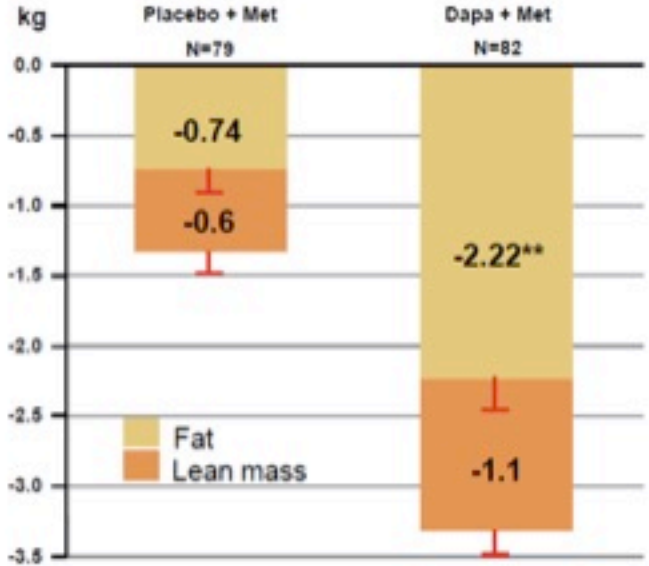
Dapagliflozin in add on a Metformina:efficacia su peso corporeo e massa grassa

DXA: dual X-ray absorptiometry

Mean change in total body weight at week 24
(primary efficacy endpoint)



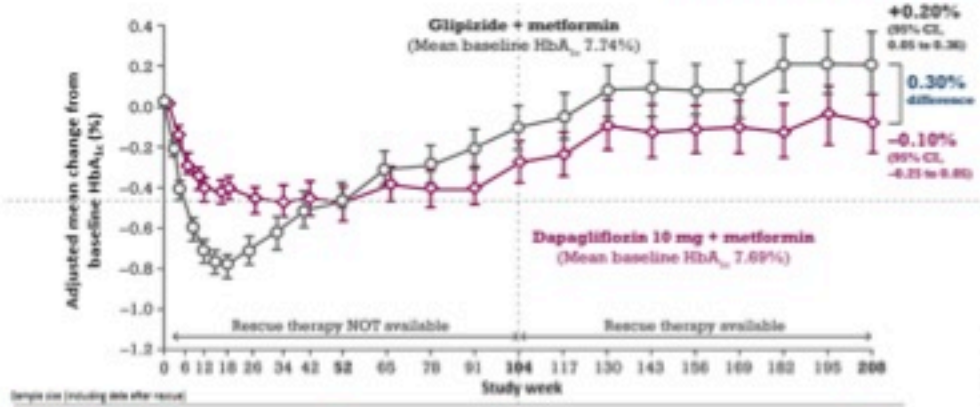
Mean (SE) change in fat and lean mass at week 24 by DXA



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

BOLINDER J. - J Clin Endocrinol Metab. 2012 Mar;97(3):1020-31

Dapagliflozin in associazione a Metformina verso SU, risultati a 4 anni: “ efficacia e durability ” su HbA1c con basso rischio ipoglicemico



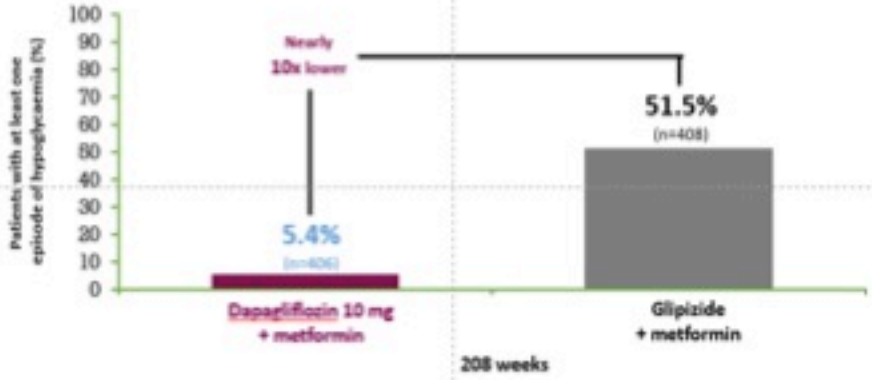
Sample size (including data after rescue)				
Dapagliflozin + metformin	400	326	220	79
Placebo + metformin	401	318	206	75

Data are adjusted mean change from baseline derived from a longitudinal repeated measures mixed model.

A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety profile of dapagliflozin 10 mg + metformin (≥500–≤2000 mg/day) versus glipizide + metformin (≥500–≤2000 mg/day) in patients with inadequate glycaemic control (HbA1c >6.5% and ≤10%) on metformin alone.

CI, confidence interval.

1. De Pablo S, *et al. Diabetes Obes Metab* 2015;17:761–67; 2. Yki-Järvinen H, *et al. Diabetes Care* 2011;34:2013–22.

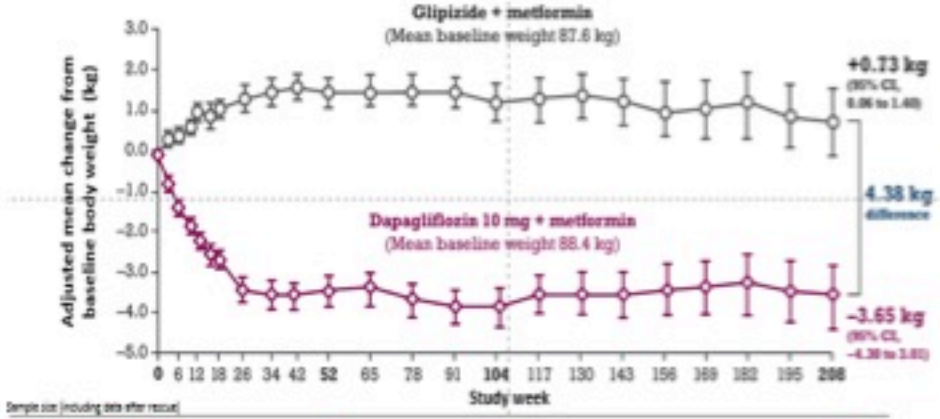


“The risk of hypoglycaemia with dapagliflozin is dependent on the type of background therapy used.”

A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety profile of dapagliflozin 10 mg + metformin (≥500–≤2000 mg/day) versus glipizide + metformin (≥500–≤2000 mg/day) in patients with inadequate glycaemic control (HbA1c >6.5% and ≤10%) on metformin alone.

SU, sulphonylurea.

1. De Pablo S, *et al. Diabetes Obes Metab* 2015;17:761–67; 2. FORXIGA. Summary of product characteristics, 2014.



Sample size (including data after rescue)				
Dapagliflozin + metformin	400	323	234	139
Placebo + metformin	401	315	221	140

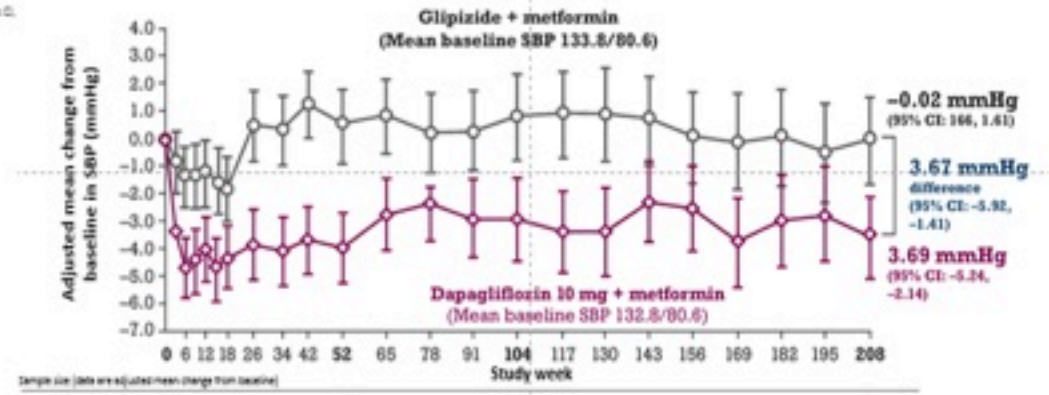
Dapagliflozin is not indicated for the management of weight loss. Weight change was a secondary endpoint in clinical trials.

Data are adjusted mean change from baseline derived from a longitudinal repeated measures mixed model.

A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety profile of dapagliflozin 10 mg + metformin (1500–2000 mg/day) versus glipizide + metformin (1500–2000 mg/day) in patients with inadequate glycaemic control (HbA$_{1c}$ >6.5% and ≤10%) on metformin alone. CI, confidence interval.

1. De Fronzo S, *et al. Diabetes Obes Metab* 2015;17:763–60. 2. Vasudi MA, *et al. Diabetes Care* 2011;34:2015–22.

Dapagliflozin in associazione a Metformina verso SU risultati a 4 anni : efficacia su peso corporeo e pressione arteriosa



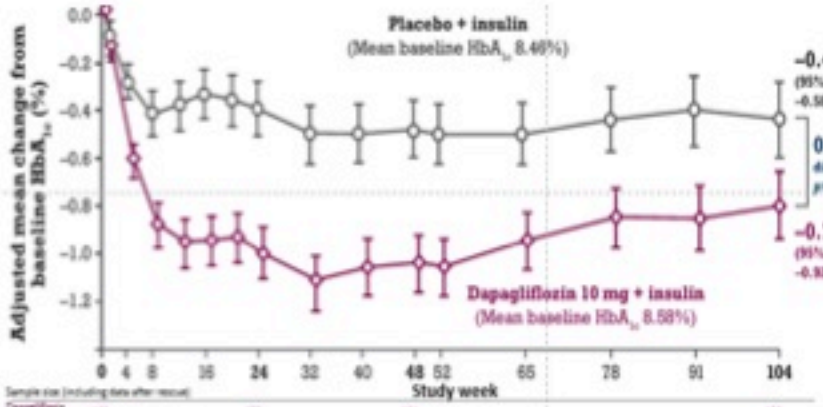
Sample size (data are adjusted mean change from baseline)				
Dapagliflozin + metformin	399	323	234	139
Placebo + metformin	396	314	231	140

Dapagliflozin is not indicated for the management of high blood pressure.

A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety profile of dapagliflozin 10 mg + metformin (1500–2000 mg/day) versus glipizide + metformin (1500–2000 mg/day) in patients with inadequate glycaemic control (HbA$_{1c}$ >6.5% and ≤10%) on metformin alone.

CI, confidence interval; SBP, systolic blood pressure; SU, sulphonylurea.

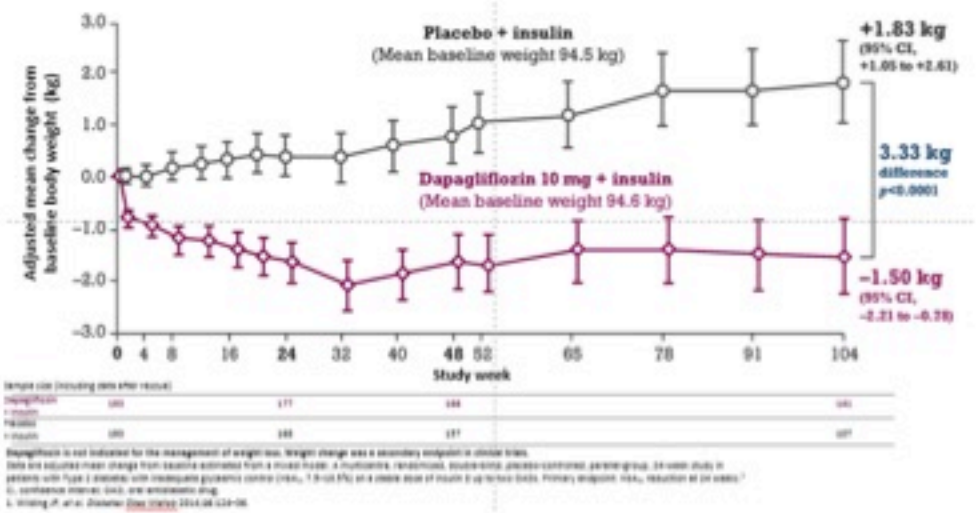
Dapagliflozin in associazione a Insulina ,risultati a 2 anni : efficacia su HbA1c e peso corporeo (con risparmio di dosi insuliniche)



Dapagliflozin stabilises glycaemic control in difficult-to-treat patients on high doses of insulin (mean baseline insulin dose 77.1 IU)[1,2]

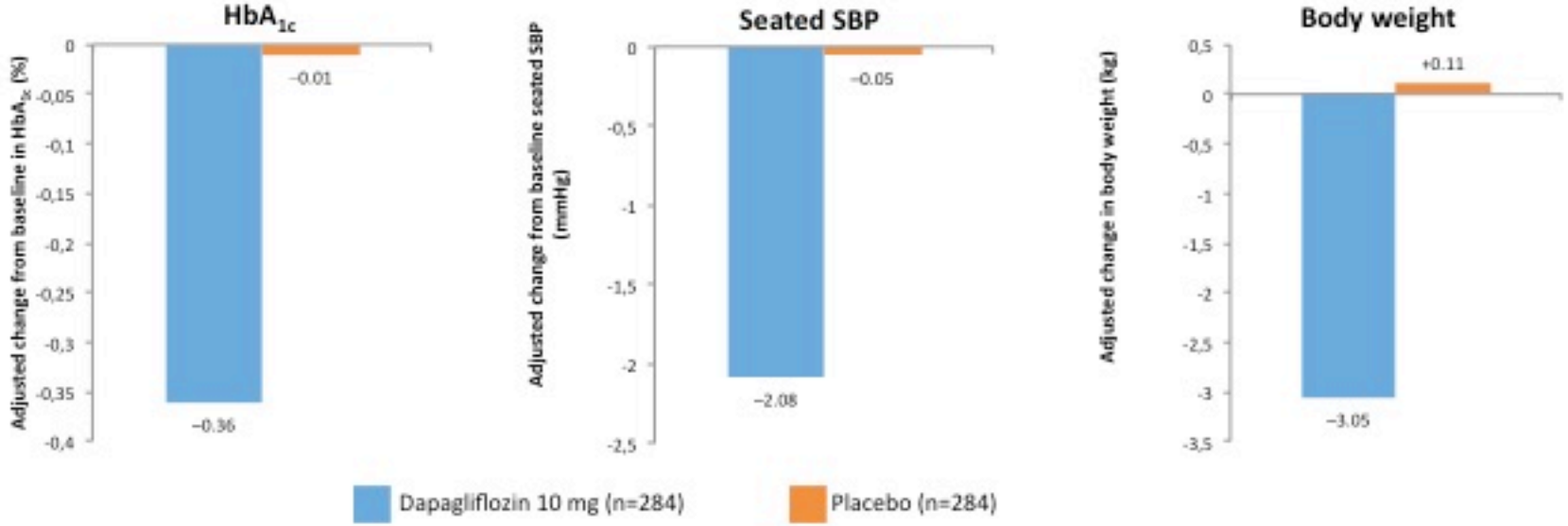
Insulin requirement increased progressively in the placebo group but remained stable over 104 weeks in with dapagliflozin (19.2 IU difference, p<0.0001)[1]

↓ 19 U Ins/die



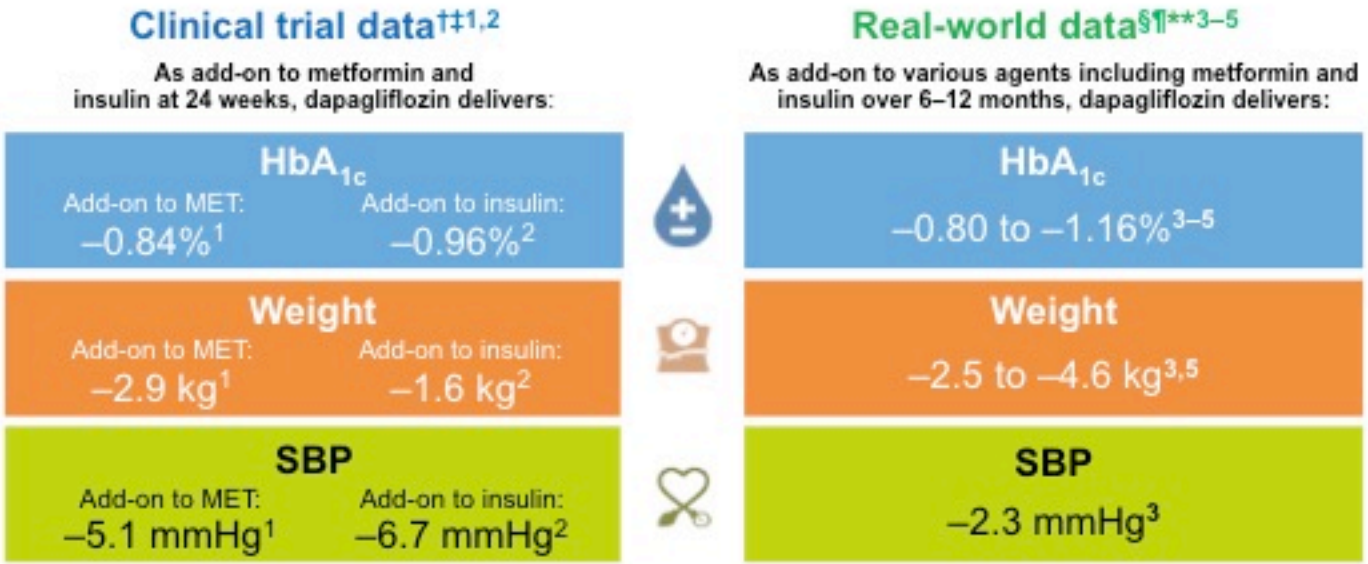
Dapagliflozin: efficacia su HbA1c, Peso corporeo e pressione arteriosa in pazienti con malattia cardiovascolare e ipertensione arteriosa

1. In questa popolazione di pazienti diabetici ad alto rischio CV l'efficacia di Dapagliflozin si associa a unbuon profilo di sicurezza CV a 2 anni[1]



Cardiac failure: Experience in NYHA Class I–II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA Class III–IV.
Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).
Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known CVD, patients on antihypertensive therapy with a history of hypotension or elderly patients.
CV, cardiovascular; CVD, cardiovascular disease; NYHA, New York Heart Association; SBP, systolic blood pressure.
1. Cefalu WT, *et al.* Presented at the 75th American Diabetes Association Scientific Sessions, Boston, USA, 5–9 June 2015. Abstract 2611.

Dapagliflozin: dal "Trial Clinico" *alla* "Real Life"



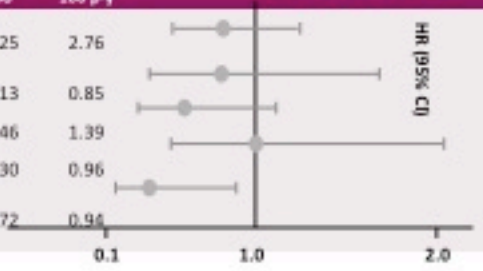
*Dapagliflozin is not indicated for the management of weight loss or blood pressure, and any changes were secondary endpoints in clinical trials.

Study details are available in slide notes. MET, metformin; SBP, systolic blood pressure.

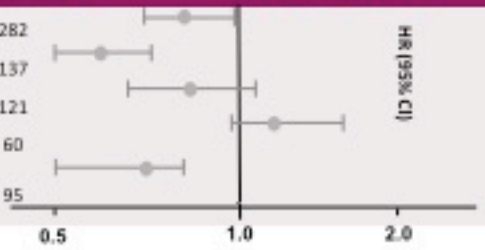
1. Bailey CJ, *et al. Lancet* 2010;375:2223–33; 2. Wilding JPH, *et al. Ann Intern* Med 2012;156:405–15; 3. Scheerer M, *et al. Diabetologie und Stoffwechsel* 2015;10:98; 4. Scheerer M, *et al. Diabetologie und Stoffwechsel* 2015;10:99; 5. Wilding JPH, *et al.* Poster presented at the 51st European Association for the Study of Diabetes, Stockholm, Sweden. 14–18 September 2015; Abstract A-15-209.

Dapagliflozin: " Potenziale di protezione cardiovascolare"

DAPA[1] n/N	Patients with Events: DAPA n=1856	Event rate/ 100 p-y	CTRL n=1358	Event rate/ 100 p-y	Favors DAPA ← • → Control	Hazard Ratio vs Control (95% CI)
MACE in patients with CVD history	50/1799	2.21	45/1325	2.76		0.80 (0.53, 1.22)
CV death	16/1632	0.74	13/1213	0.85		0.79 (0.37, 1.69)
MI	18/1677	0.82	22/1246	1.39		0.58 (0.30, 1.11)
Stroke	18/1388	0.95	14/1130	0.96		1.01 (0.49, 2.07)
Hospitalization for heart failure	10/1486	0.51	14/1172	0.94		0.37 (0.16, 0.89)



EMPA[2] Event	Patients with Events: EMPA=4687	Placebo=2333	Favors EMPA ← • → Control	Hazard Ratio vs Control (95% CI)
MACE	490	282		0.86 (0.74, 0.99)
CV death	172	137		0.62 (0.49, 0.77)
MI	213	121		0.87 (0.70, 1.09)
Stroke	150	60		1.24 (0.92, 1.67)
Hospitalization for heart failure	126	95		0.65 (0.50, 0.85)

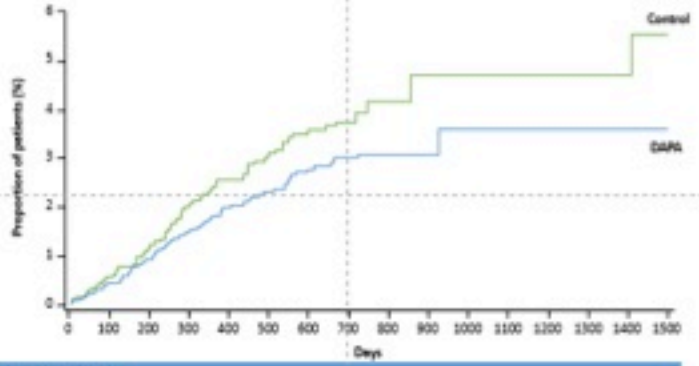


1. Sonesson C et al. *Cardiovasc Diabetol*. 2016;15:37

2. Zinman, B et al. *NEJM* 2015;373:2117-28

Dapagliflozin: sicurezza CV

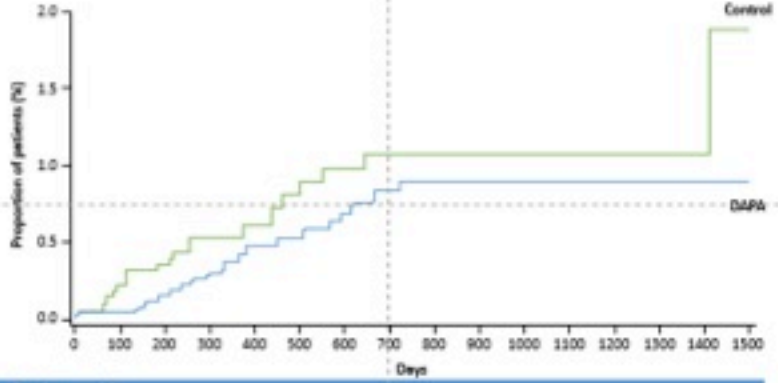
Primary Composite (MACE + UA)



No. of patients at risk																
DAPA	5699	5333	4036	3417	1895	1748	1635	1543	261	249	239	234	221	211	189	8
Control	5240	2997	2227	1878	1005	905	835	782	156	129	124	119	111	107	90	4

Primary composite end point: CV death, myocardial infarction, stroke, and hospitalization for unstable angina.
Cumulative incidence of primary CV composite end point over time (Kaplan-Meier estimate) for the overall population
MACE=Major Adverse Cardiovascular Event; UA=unstable angina; DAPA=dapagliflozin; CV=cardiovascular.

CV Death

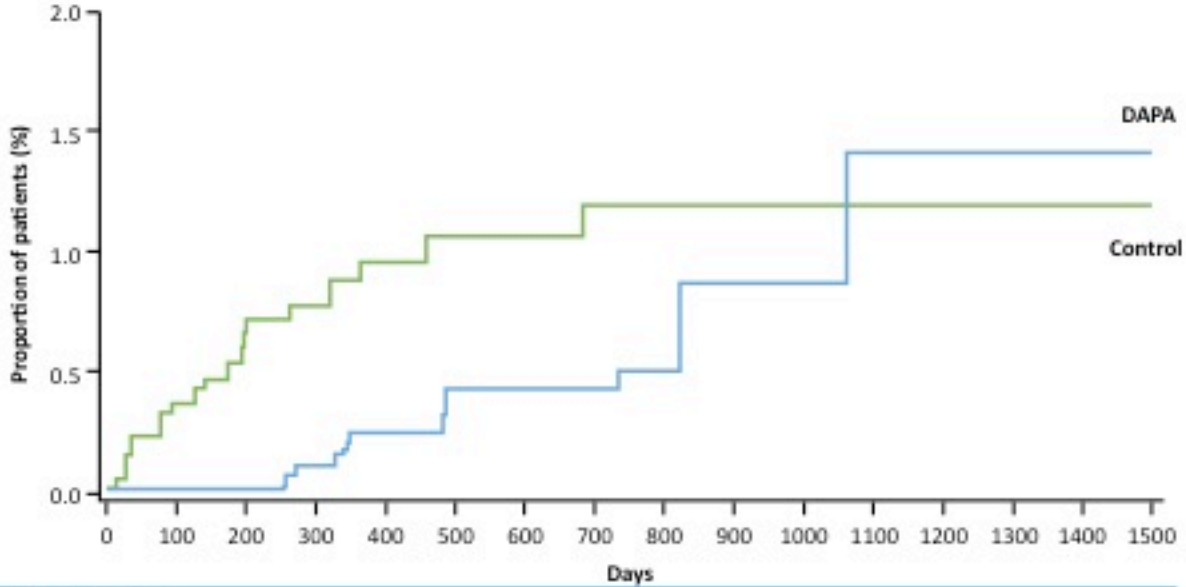


No. of patients at risk																
DAPA	3825	3586	3096	2859	1809	1666	1567	1476	261	249	239	234	221	211	190	8
Control	2200	2029	1737	1594	962	867	803	755	138	133	127	122	114	109	92	4

Cumulative incidence of CV death over time (Kaplan-Meier estimate) for the overall population
CV=cardiovascular; DAPA=dapagliflozin.

Sonesson C et al. *Cardiovasc Diabetol*. 2016;15:37

Dapagliflozin: Ospedalizzazione per Scompenso Cardiaco

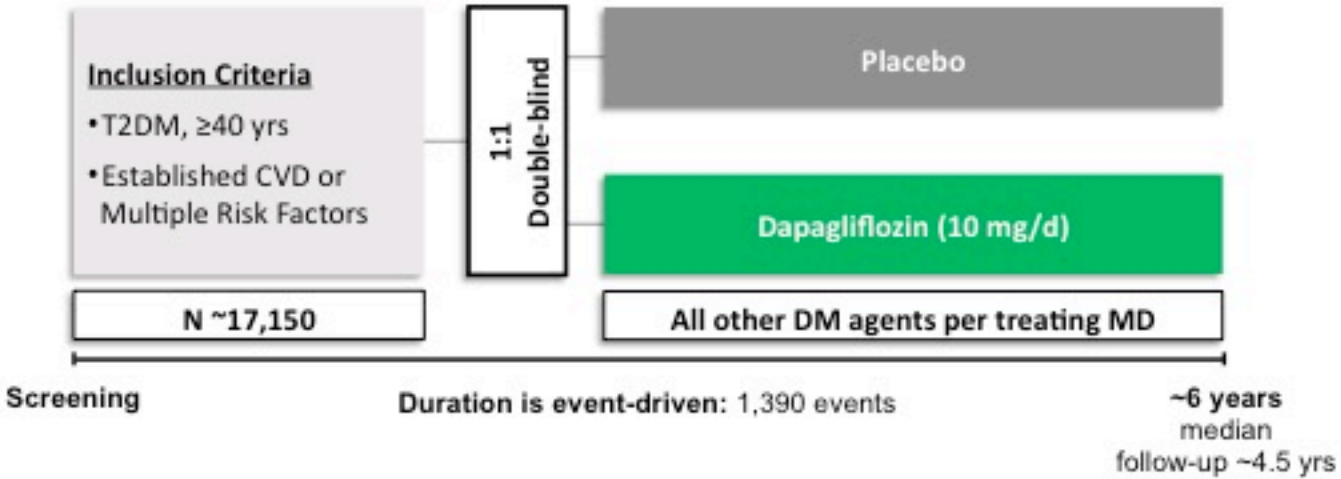


No. of patients at risk																
DAPA	2576	2429	2287	2153	1202	1089	1024	983	244	232	223	217	206	197	177	7
Control	1780	1638	1537	1451	775	691	635	606	155	148	143	137	127	122	103	4

Cumulative incidence of hospitalization for heart failure over time (Kaplan-Meier estimate) for the overall population
DAPA=dapagliflozin.

Sonesson C et al. *Cardiovasc Diabetol*. 2016;15:37.

DECLARE – Dapagliflozin Effects on CardiovascuLAR Events



Primary Endpoint

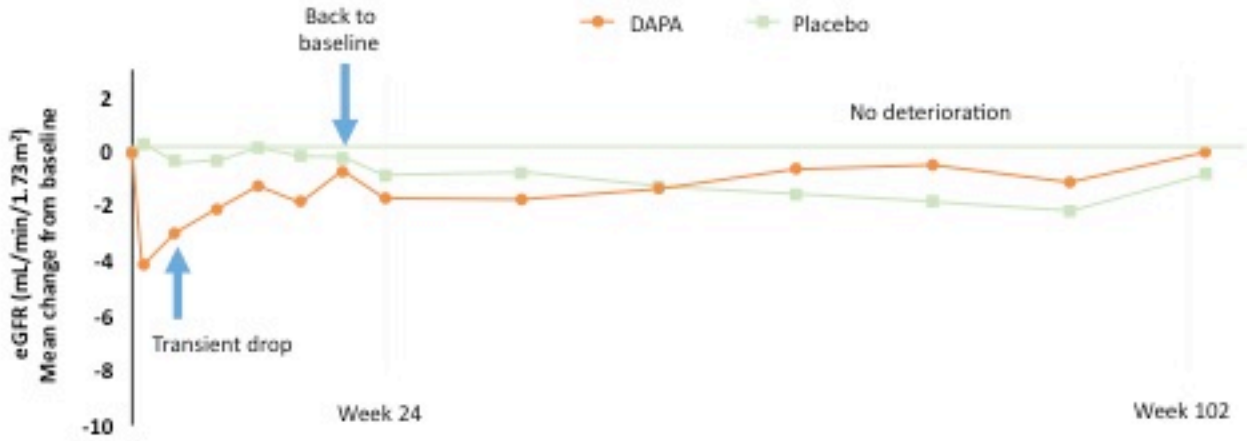
- MACE: CV Death, MI, Ischemic Stroke

CVD, cardiovascular disease

Available at: ttps://clinicaltrials.gov/ct2/show/NCT01730534

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM379659.pdf

La funzionalità renale (eGFR) rimane stabile a 2 anni



Time (weeks):	0	12	24	50	63	76	89	102
Placebo, n:	1955	873	1671	1558	605	585	551	521
DAPA 10 mg, n:	2026	961	1777	1663	712	692	656	627

eGFR, estimated glomerular filtration rate; DAPA=dapagliflozin.
Dapagliflozin should not be used in patients with moderate to severe renal impairment (eGFR persistenyl <60 mL/min/173 m² by MDRD or CrCl persistently <60 mL/min by Cockcroft-Gault.
Sonesson C, *et al. Cardiovasc Diabetol.* 2016;15:37.

Diabetes, Obesity and Metabolism 18: 590–597, 2016.

ORIGINAL ARTICLE

Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin–angiotensin blockers

H. J. L. Heerspink[1], E. Johnsson[2], I. Gause-Nilsson[2], V. A. Cain[3] & C. D. Sjöström[2]

[1] University of Groningen, University Medical Center Groningen, The Netherlands
[2] AstraZeneca, Gothenburg, Mölndal, Sweden
[3] AstraZeneca, Wilmington, DE, USA

Aims: To characterize the effect of dapagliflozin on albuminuria and estimated glomerular filtration rate (eGFR) and to determine whether effects on albuminuria were mediated through changes in glycated haemoglobin (HbA1c), systolic blood pressure (SBP), body weight or eGFR.

Methods: We conducted a *post hoc* analysis of data pooled from two phase III clinical trials in hypertensive patients with type 2 diabetes (T2DM) on stable angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, randomly assigned to dapagliflozin 10 mg/day or matched placebo. This analysis included only patients with microalbuminuria or macroalbuminuria at baseline.

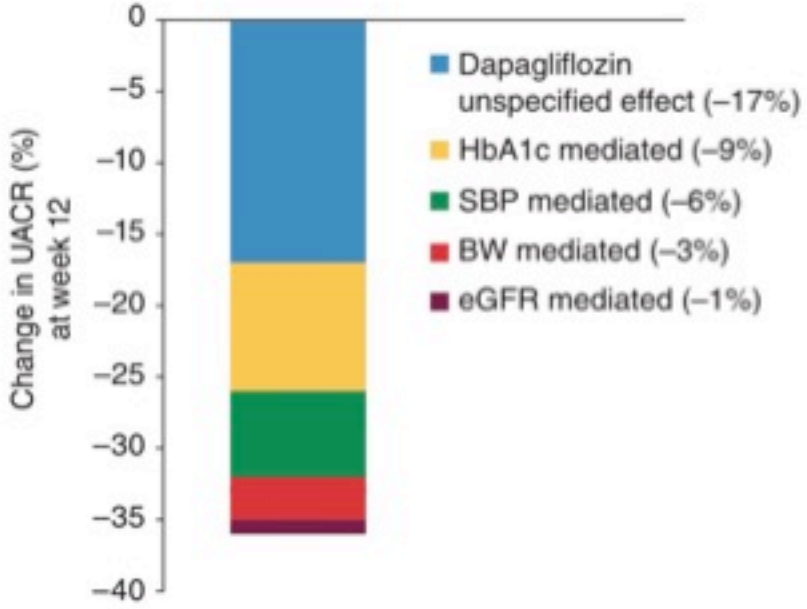
Results: Patients were randomized to receive dapagliflozin 10 mg (*n* = 167) or placebo (*n* = 180). Dapagliflozin resulted in greater 12-week reductions in albuminuria compared with placebo: −33.2% [95% confidence interval (CI) −45.4, −18.2]. The reduction in albuminuria was also present after adjusting for age, sex and changes in HbA1c, SBP, body weight and eGFR: −23.5% (95% CI −37.6, −6.3). There was a decrease in eGFR with dapagliflozin versus placebo that was readily reversed 1 week after last dose. No serious renal-related adverse events were observed in any group.

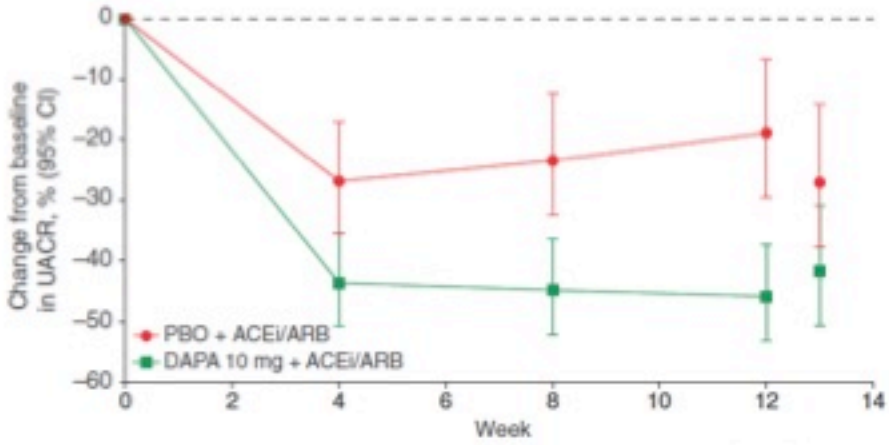
Conclusions: Dapagliflozin was effective in lowering albuminuria in patients with T2DM and hypertension using renin–angiotensin system blockade therapy. Reductions in albuminuria were still present after adjusting for changes in HbA1c, SBP, body weight and eGFR. Dapagliflozin-induced improvements in glycaemic control and reductions in SBP, coupled with other potentially beneficial renal effects, may lead to a reduced long-term renal and cardiovascular risk.

Keywords: albuminuria, dapagliflozin, diabetes, hypertension, sodium glucose cotransporter-2

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

Dapagliflozin: efficacia su UACR in diabetici ipertesi in trattamento con ACEi/ARB

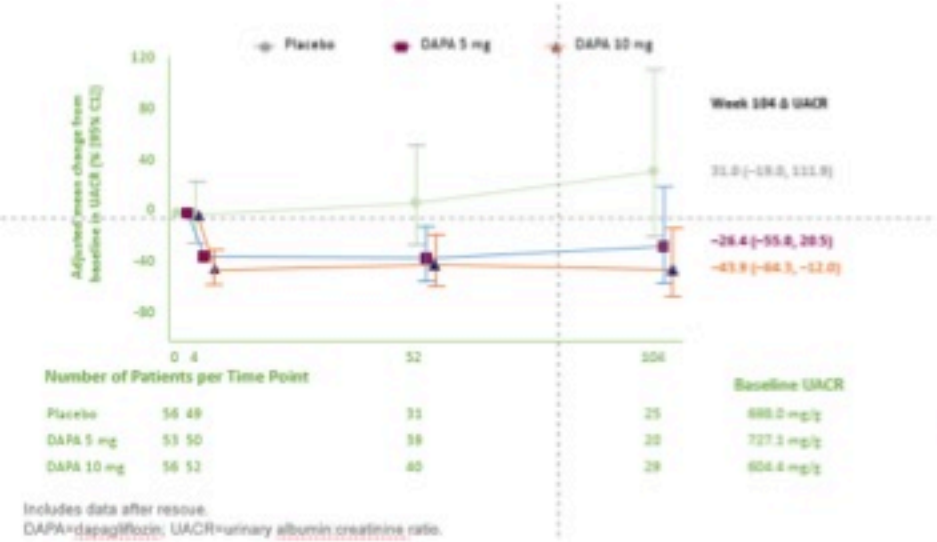




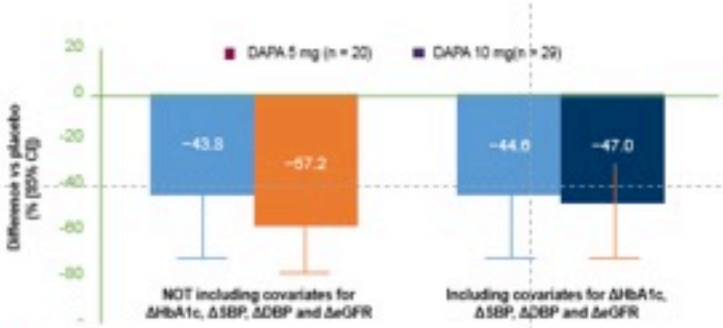
Sample size per time point, n	Baseline	Week 4	Week 8	Week 12	Follow-up (Week 13)
PBO + ACEi/ARB	185	182	172	163	158
DAPA 10 mg + ACEi/ARB	165	160	154	153	144

H E J Heerspink et al . Diabetes, Obesity and Metabolism 18: 590–597, 2016.

Dapagliflozin rispetto al PBO reduce l'Albuminuria a 2 anni in pazienti diabetici con CKD3 e questa riduzione della Albuminuria appare indipendente da modifiche di HbA1c, Pressione arteriosa e eGFR



Includes data after rescue.
DAPA=dapagliflozin; UACR=urinary albumin creatinine ratio.

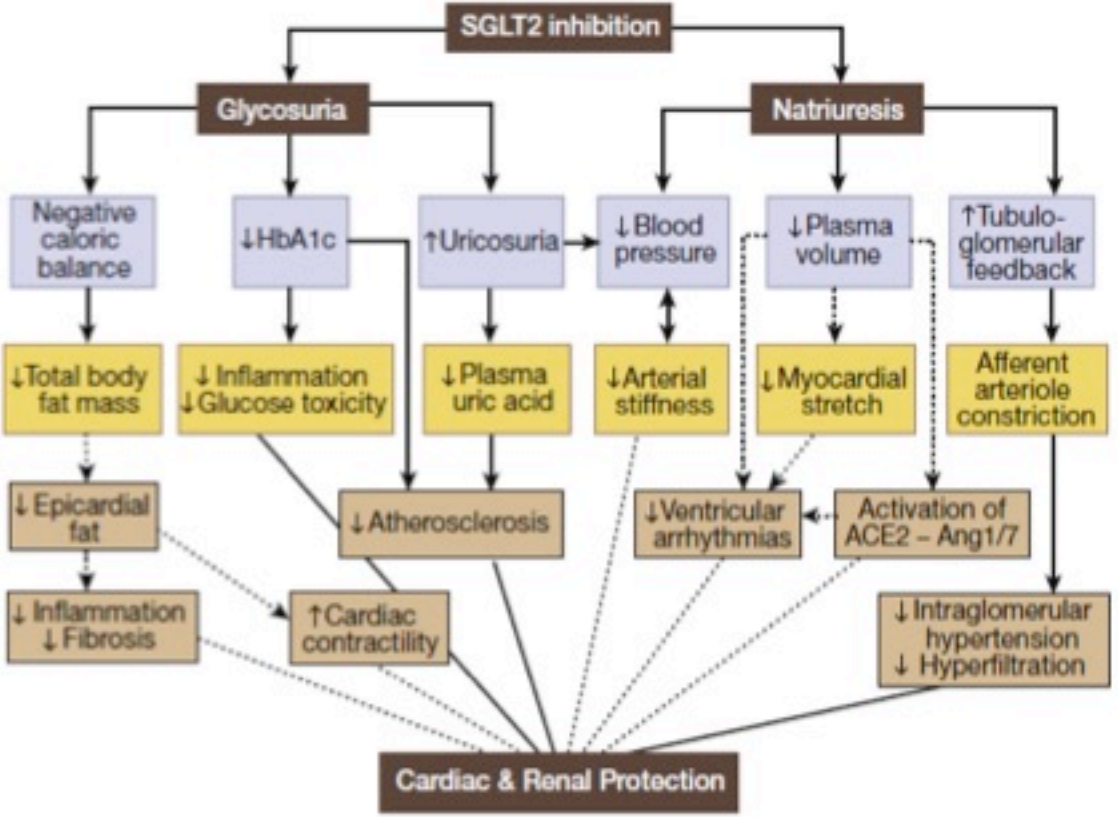


- The UACR reduction remains after adjustments for changes in blood pressure, HbA1c and eGFR
- Indicaties direct renal effects independent of changes in these variables[1]

n = number of patients at Week 104. Includes data after rescue.
UACR=urinary albumin creatinine ratio; DAPA=dapagliflozin; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; SBP=systolic blood pressure; HbA1c=glycated hemoglobin.

1. Fioretto P *et al.* . *Diabetologia 2016*.

Meccanismi di cardio e nefroprotezione con gli SGLT2i



Rajasekeran, Harindra et al. Kidney International , Volume 89 , Issue 3 , 524 – 526 2016

Dapagliflozin: Trials dedicati in pazienti diabetici nefropatici

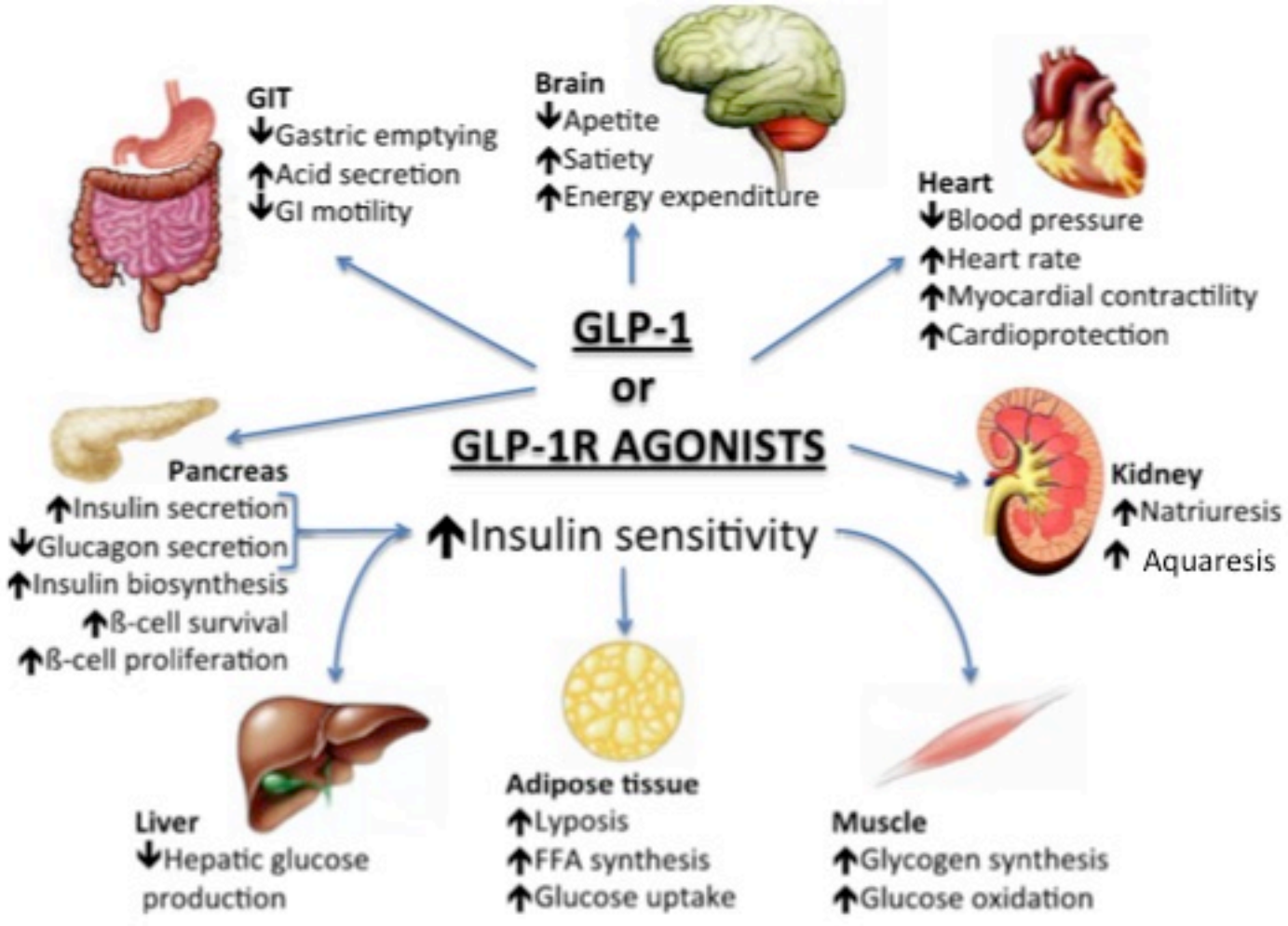
1) **DERIVE**: glycaemic impact of dapagliflozin in moderate renal impairment.[1]

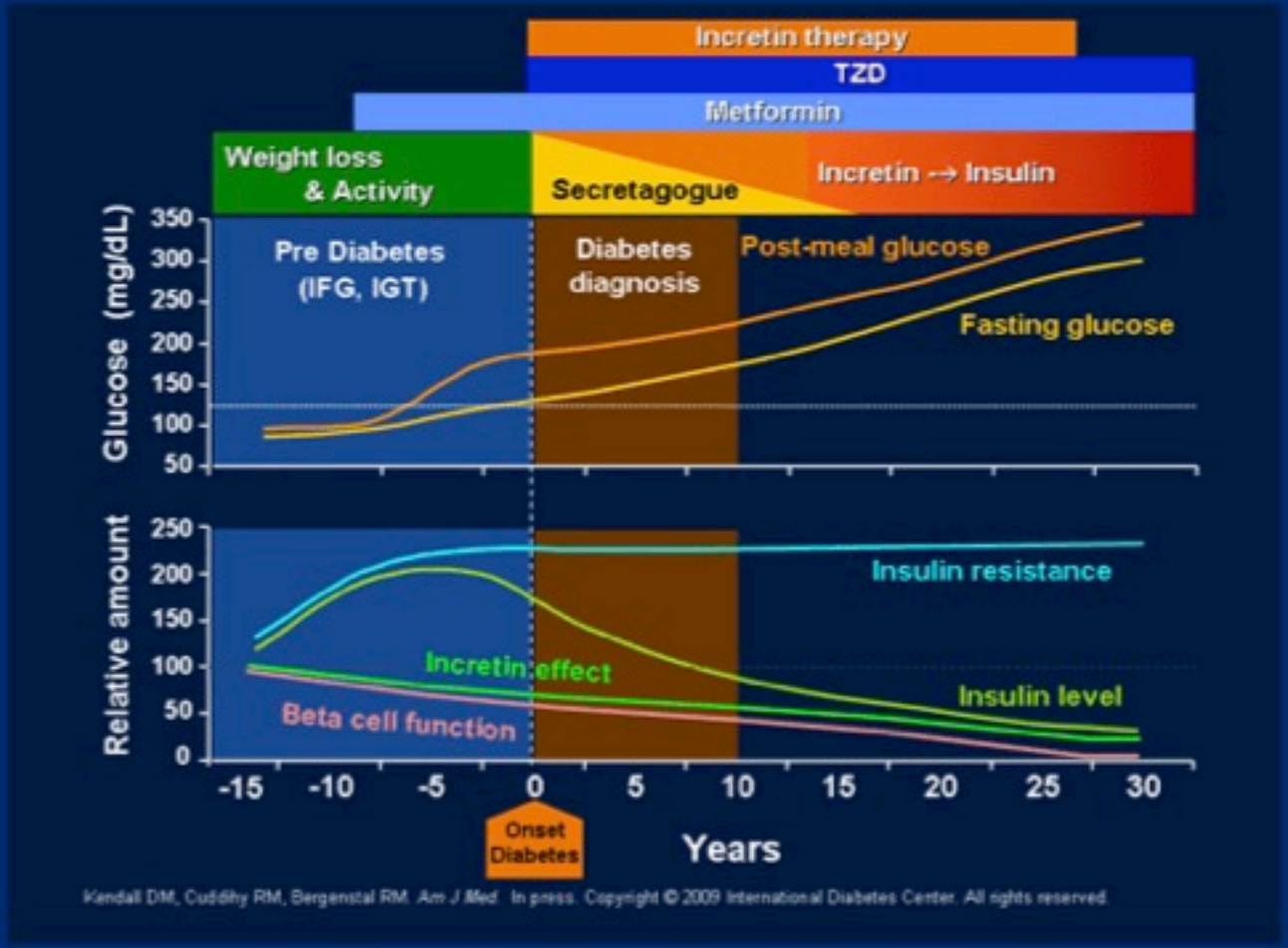
2) **DELIGHT**: 3-armed trial evaluating glycaemic efficacy and impact on renal outcomes of dapagliflozin +/- saxagliptin in moderate renal impairment vs. placebo[2].

3) Plans for 2 further Phase IIIb outcome trials with dapagliflozin recently announced[3], and will focus on the efficacy of dapagliflozin in T2DM patients with either CKD or chronic heart failure.

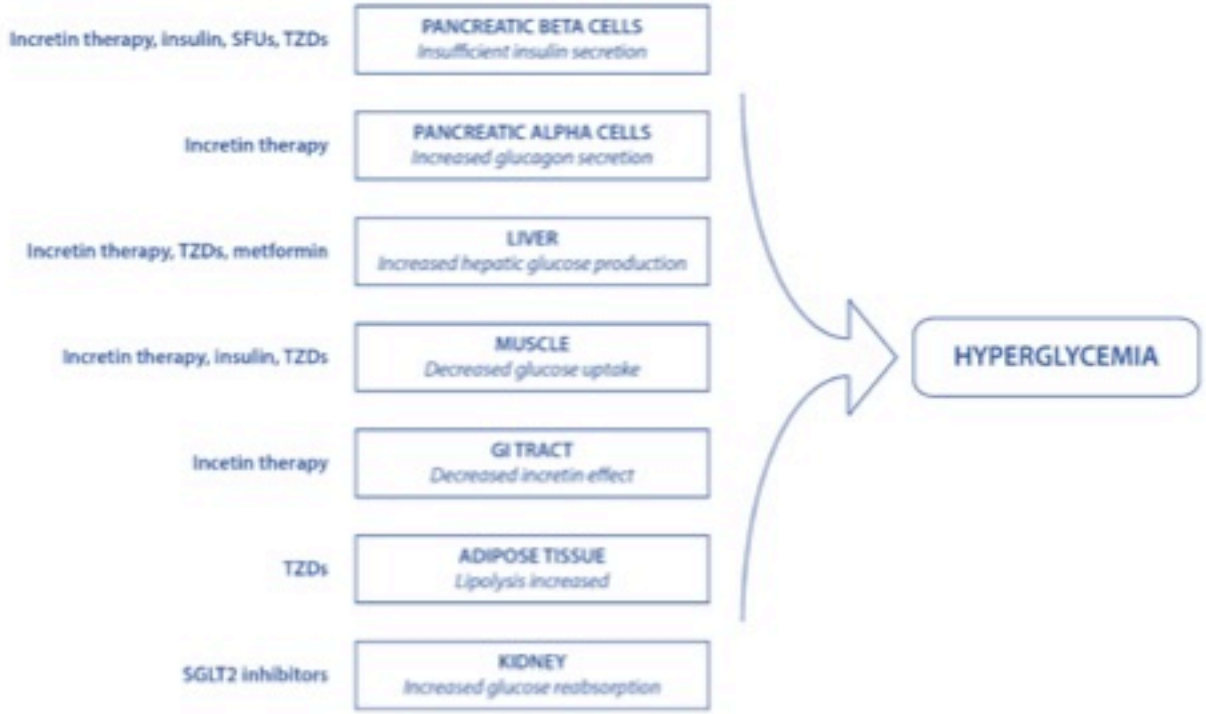
- Renoprotective effects of DPP-4i have not been identified.
- SAVOR-TIMI 53 is the only large scale trial to demonstrate modest benefit with reduced progression of microalbuminuria with saxagliptin[4].

1. A Study to Evaluate the Effect of Dapagliflozin on Blood Glucose Level and Renal Safety in Patients With Type 2 Diabetes (DERIVE). ClinicalTrials.gov; 2016 [cited 2016 14th Aug 2016]; Available from: https://clinicaltrials.gov/ct2/show/NCT02413398; 2. AstraZeneca. A Study to Evaluate the Effect of Dapagliflozin With and Without Saxagliptin on Albuminuria, and to Investigate the Effect of Dapagliflozin and Saxagliptin on HbA1c in Patients With Type 2 Diabestes and CKD3. ClinicalTrials.gov; 2016 [cited 2016 14th Aug 2016]; Available from: https://clinicaltrials.gov/ct2/show/NCT02547935; 3. AstraZeneca Media. Press Release. Accessed: September 12 2016. Available online at: https://www.astrazeneca.com/media-centre/press-releases/2016/astrazeneca-announces-two-new-phase-IIIb-trials-for-Forxiga-in-chronic-kidney-disease-and-chronic-heart-failure-120920161.html; 4. Scirica BM, et al. The New England journal of medicine. 2013 Oct 3;369(14):1317-26.


GIT
↓Gastric emptying
↑Acid secretion
↓GI motility
Brain
↓Apetite
↑Satiety
↑Energy expenditure
Heart
↓Blood pressure
↑Heart rate
↑Myocardial contractility
↑Cardioprotection
GLP-1
or
GLP-1R AGONISTS
Pancreas
↑Insulin secretion
↓Glucagon secretion
↑Insulin biosynthesis
↑ß-cell survival
↑ß-cell proliferation
↑Insulin sensitivity
Kidney
↑Natriuresis
↑ Aquaresis
Liver
↓Hepatic glucose production
Adipose tissue
↑Lyposis
↑FFA synthesis
↑Glucose uptake
Muscle
↑Glycogen synthesis
↑Glucose oxidation


Incretin therapy
TZD
Metformin
Weight loss & Activity
Secretagogue
Incretin → Insulin
Pre Diabetes (IFG, IGT)
Diabetes diagnosis
Post-meal glucose
Fasting glucose
Glucose (mg/dL)
350
300
250
200
150
100
50
Relative amount
250
200
150
100
50
0
Insulin resistance
Incretin effect
Insulin level
Beta cell function
-15
-10
-5
0
5
10
15
20
25
30
Onset Diabetes
Years
Kendall DM, Cuddihy RM, Bergenstal RM. Am J Med. In press. Copyright © 2009 International Diabetes Center. All rights reserved.

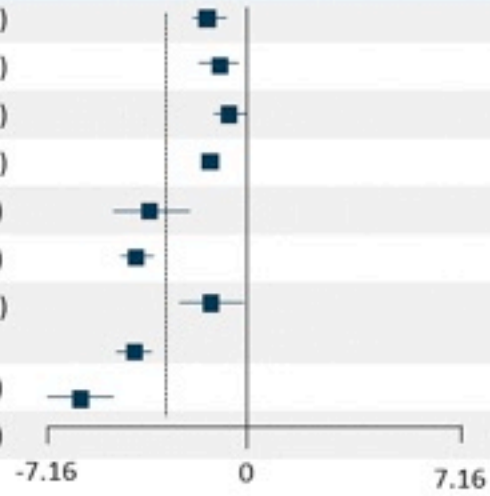
Le incretine hanno assunto un ruolo centrale nella terapia del DM Tipo 2



Grossman S.S Adv Ther 2014 (31) 247-263

Meta-Analysis: Change in Body Weight (kg) in Trials of ≥20 Weeks of Treatment With GLP-1 RAs

Trial	No. of Patients		Mean Change (SD)		Weighted Mean Difference (95% CI)	Weight (%)
	GLP-1 RA	Control	GLP-1 RA	Control		
Bergenstal 2010	160	166	-2.3 (3.0)	-0.8 (0.3)		4.98
Buse 2004	129	123	-1.6 (3.4)	-0.6 (3.3)		4.74
Kendall 2005	241	247	-1.6 (3.1)	-0.9 (3.1)		4.93
Nauck 2009	242	122	-2.8 (0.2)	-1.5 (0.3)		5.09
Garber 2009	246	248	-2.5 (7.8)	1.0 (7.9)		4.71
Diamant 2010	233	223	-2.6 (3.1)	1.4 (3.0)		4.93
Russell-Jones 2009	230	114	-1.8 (5.0)	-0.4 (4.1)		4.59
Heine 2005	282	267	-2.3 (3.9)	1.8 (4.0)		4.86
Bergenstal 2009	124	124	-1.9 (3.8)	4.1 (5.4)		4.44



- Meta-analysis results offer evidence that GLP-1 RAs, when given to obese patients with or without diabetes, results in clinically relevant effects on body weight

Vilsboll T, et al. *BMJ*. 2012;344:d7771.

Digestion

Original Paper

Digestion 2006;73:142–150
DOI: 10.1159/000094334

Received: November 23, 2005
Accepted: April 11, 2006
Published online: June 29, 2006

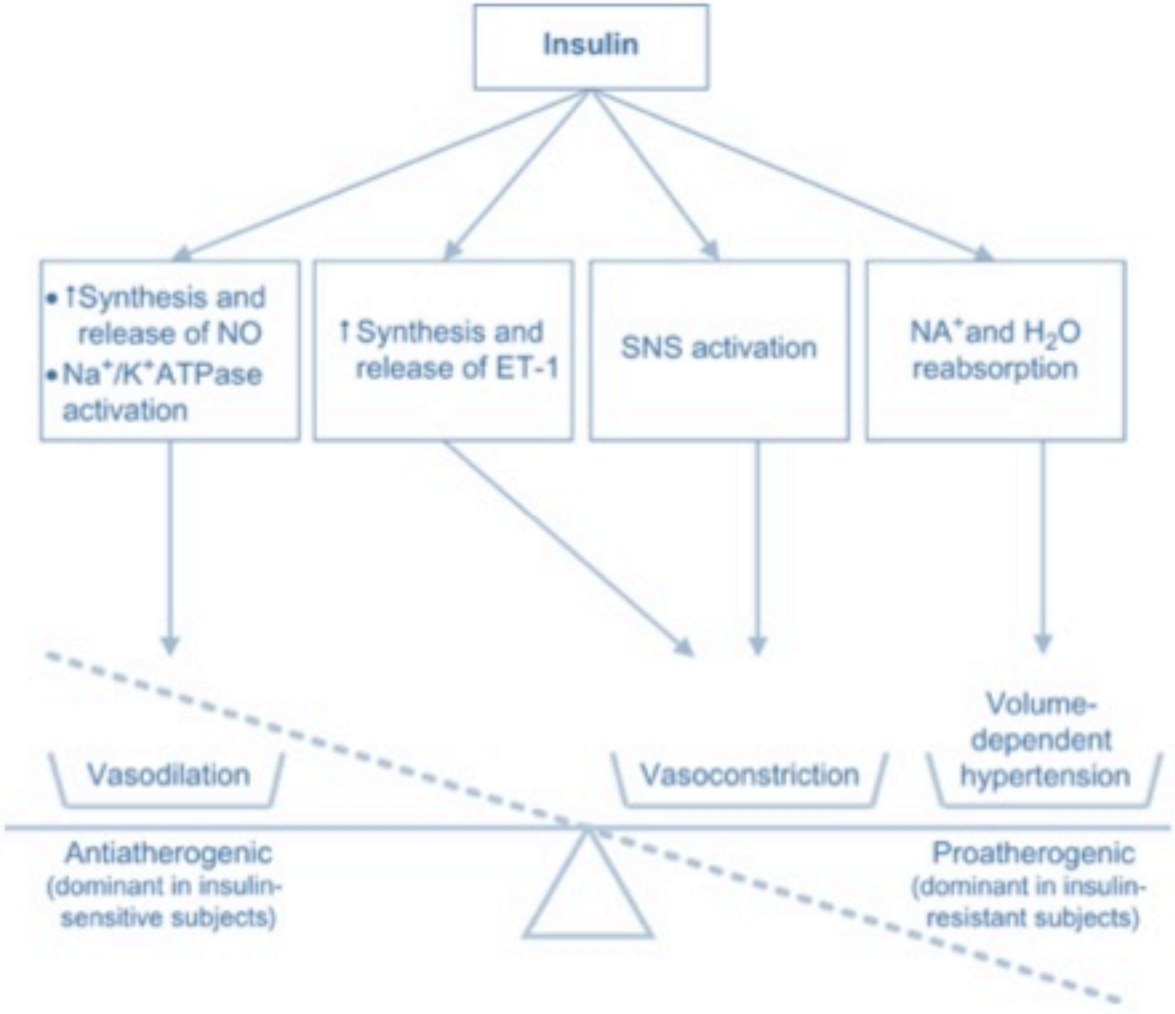
Digestion 2006;73:142–150

Glucagon-Like Peptide-1 Is Involved in Sodium and Water Homeostasis in Humans

Jean-Pierre Gutzwiller[a] Petr Hruz[a] Andreas R. Huber[c] Christian Hamel[c] Carlos Zehnder[d] Juergen Drewe[b] Heike Gutmann[b] Zeno Stanga[c] Daniel Vogel[a] Christoph Beglinger[a]

[a]Division of Gastroenterology and Department of Research, and [b]Department of Clinical Pharmacology, University Hospital, Basel, and [c]Central Laboratory, Kantonsspital Aarau, Aarau, Switzerland; [d]Division of Nephrology, Clinica las Condes, Santiago, Chile; [e]Division of Nutrition, University Hospital, Berne, Switzerland

In conclusion, GLP-1 increases sodium excretion by the kidneys to control extracellular volume expansion, and may reduce sodium absorption by the gastrointestinal tract to prevent volume expansion. In this way, this incretin hormone seems to play a significant role in sodium and water homeostasis.


Insulin
• ↑Synthesis and release of NO
• Na^+/K^+ATPase activation
↑ Synthesis and release of ET-1
SNS activation
$NA^+$and H_2O reabsorption
Vasodilation
Vasoconstriction
Volume-dependent hypertension
Antiatherogenic
(dominant in insulin-sensitive subjects)
Proatherogenic
(dominant in insulin-resistant subjects)

JCEM

The Journal of Clinical Endocrinology & Metabolism 89(6):3055–3061

doi: 10.1210/jc.2003-031603

Glucagon-Like Peptide 1 Induces Natriuresis in Healthy Subjects and in Insulin-Resistant Obese Men

JEAN-PIERRE GUTZWILLER, STEFAN TSCHOPP, ANDREAS BOCK, CARLOS E. ZEHNDER, ANDREAS R. HUBER, MONIKA KREYENBUEHL, HEIKE GUTMANN, JÜRGEN DREWE, CHRISTOPH HENZEN, BURKHARD GOEKE, AND CHRISTOPH BEGLINGER

Division of Gastroenterology and Department of Research (J.-P.G., S.T., C.B.), and Division of Clinical Pharmacology and Toxicology and Department of Research (H.G., J.D.), University Hospital, CH-4031 Basel, Switzerland; Central Laboratory and Division of Nephrology (A.B., A.R.H., M.K.), Kantonsspital Aarau, CH-5001 Aarau, Switzerland; Division of Nephrology (C.E.Z.), Clinica las Condes, Santiago, Chile; Division of Endocrinology (C.H.), Kantonsspital Luzern, CH-6000 Luzern, Switzerland; and Division of Gastroenterology and Department of Internal Medicine (B.G.), Klinikum Grosshardern, University Hospital, Ludwig Maximilian University, D-81377 Munich, Germany

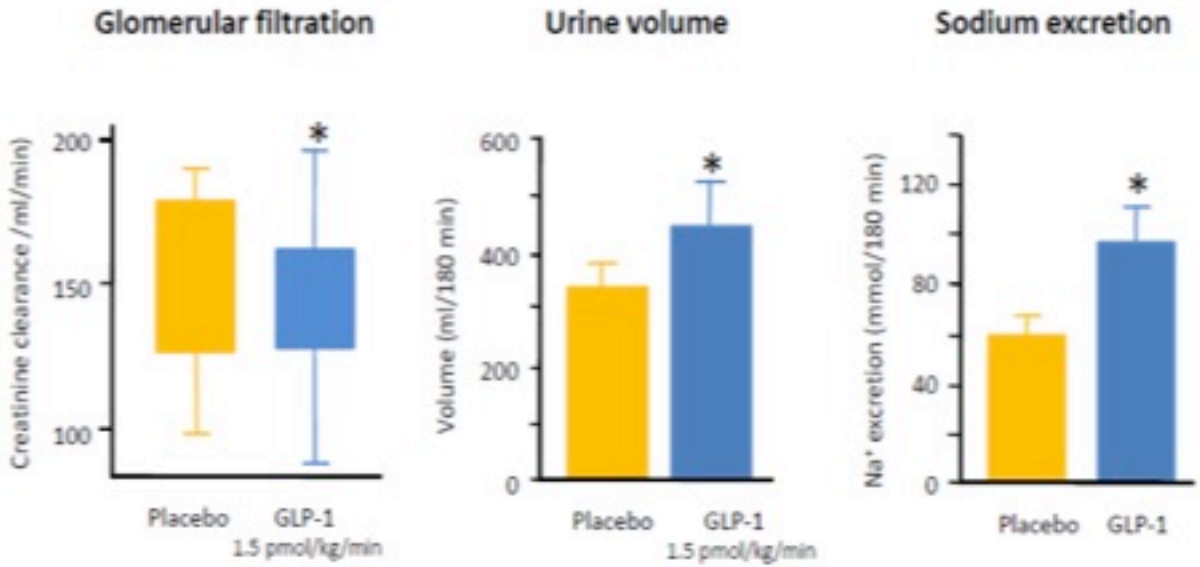
Glucagon-like peptide-1-(7–36)-amide (GLP-1) is involved in satiety control and glucose homeostasis. Animal studies suggest a physiological role for GLP-1 in water and salt homeostasis. This study's aim was to define the effects of GLP-1 on water and sodium excretion in both healthy and obese men.

Fifteen healthy subjects and 16 obese men (mean body mass index, 36 kg/m^2) were examined in a double-blind, placebo-controlled, crossover study to demonstrate the effects of a 3-h infusion of GLP-1 on urinary sodium excretion, urinary output, and the glomerular filtration rate after an iv 9.9-g salt load.

Infusion of GLP-1 evoked a dose-dependent increase in urinary sodium excretion in healthy subjects (from 74 ± 8 to 143 ± 18 mmol/180 min, $P = 0.0013$). In obese men, there was a significant increase in urinary sodium excretion (from 59 to 96 mmol/180 min, $P = 0.015$), a decrease in urinary H^+ secretion (from 1.1 to 0.3 pmol/180 min, $P = 0.013$), and a 6% decrease in the glomerular filtration rate (from 151 ± 8 to 142 ± 8 ml/min, $P = 0.022$).

Intravenous infusions of GLP-1 enhance sodium excretion, reduce H^+ secretion, and reduce glomerular hyperfiltration in obese men. These findings suggest an action at the proximal renal tubule and a potential renoprotective effect. (*J Clin Endocrinol Metab* 89: 3055–3061, 2004)

GLP-1 Reduces Glomerular Hyperfiltration and is Diuretic and Natriuretic in Obese Insulin-Resistant Subjects



Gutzwiller et al, J Clin Endocrinol Metab 2004

Effect of GLP-1 RAs on CVD Risk Factors

Risk Factor	Exenatide 10 mcg BID (3.5 years)[1]	Liraglutide 1.2 mg qd (26 weeks)[2]	Exenatide LAR 2.0 mg qw (1 year)[3]	Albiglutide 30–50 mg qw (32 weeks)[4]	Dulaglutide 1.5 mg qw (26 weeks)[5]
SBP (mm Hg)	–3.5*	–6.7†	–6.2*	N/A	–1.7†
DBP (mm Hg)	–3.3*	–2.3	–2.8*	N/A	–0.4
TC (mg/dL)	–10.8*	–8.1	7.9*	ND	–0.8 to –8.1‡
LDL-C (mg/dL)	–11.8*	–10.8†	–2.2	ND	–1.9 to –7.0‡
HDL-C (mg/dL)	8.5*	–1.2	N/A	ND	N/A
Triglycerides (mg/dL)	–44.4*	–14.7†	–40.0*	ND	–12.4 to –16.8

*P <0.05 vs baseline; †P <0.005 vs placebo; ‡P <0.001 vs placebo.

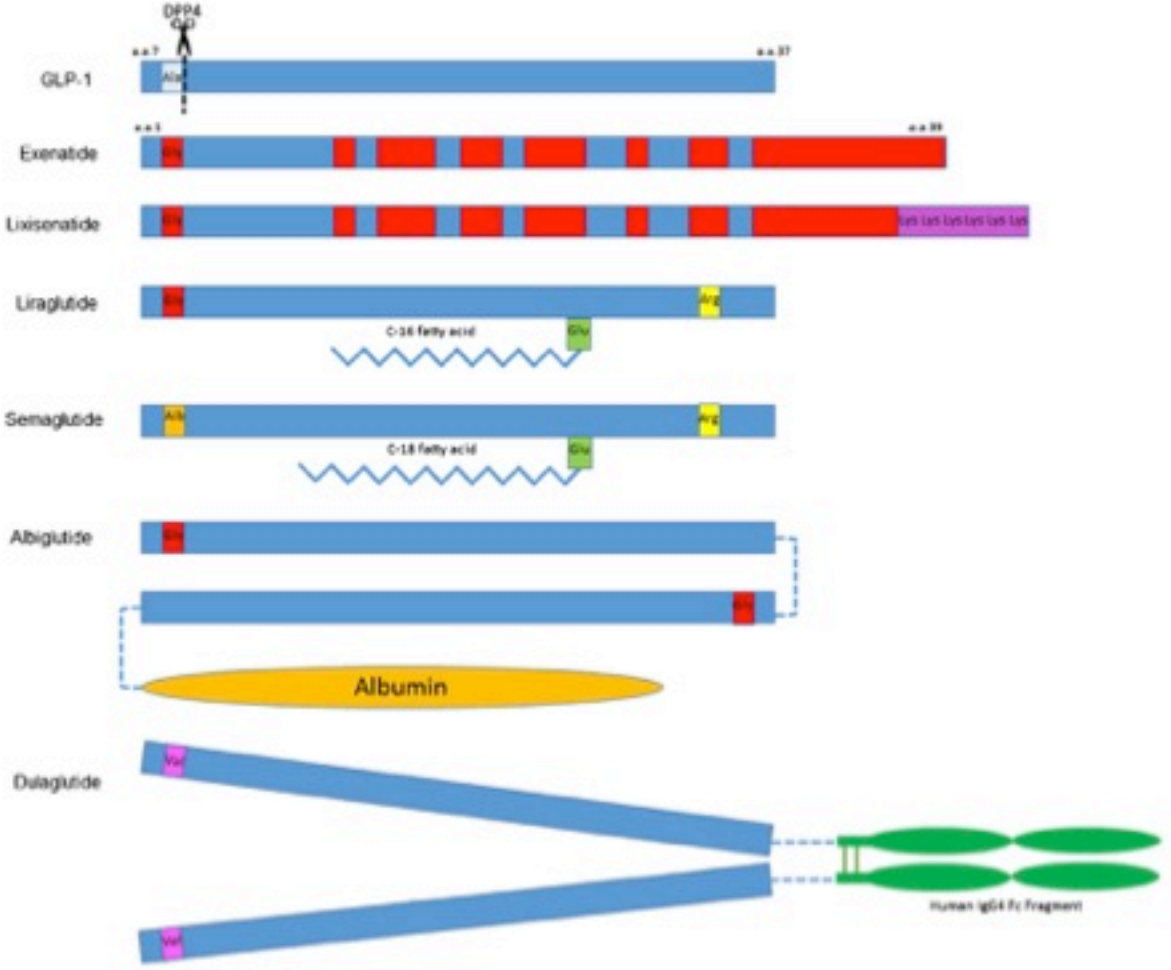
1. Klonoff DC et al. *Curr Med Res Opin*. 2008;24(1):275–286; **2.** Zinman B et al. *Diabetes Care*. 2009;32(7):1224–1230; **3.** Bergenstal R et al. *Diabetes*. 2009;58(suppl 1):165-OR; **4.** Pratley RE et al. *Lancet Diabetes Endocrinol*. 2014;2(4):289–297; **5.** Nauck MA et al. *Diabetes Care*. 2014;37(8):2149–2158.

Curr Diab Rep (2016) 16:120
DOI 10.1007/s11892-016-0823-6

PHARMACOLOGIC TREATMENT OF TYPE 2 DIABETES (HE LEBOVITZ AND G BAHTIYAR, SECTION EDITORS)

A Plethora of GLP-1 Agonists: Decisions About What to Use and When

Susan L. Samson[1] · Alan J. Garber[2]

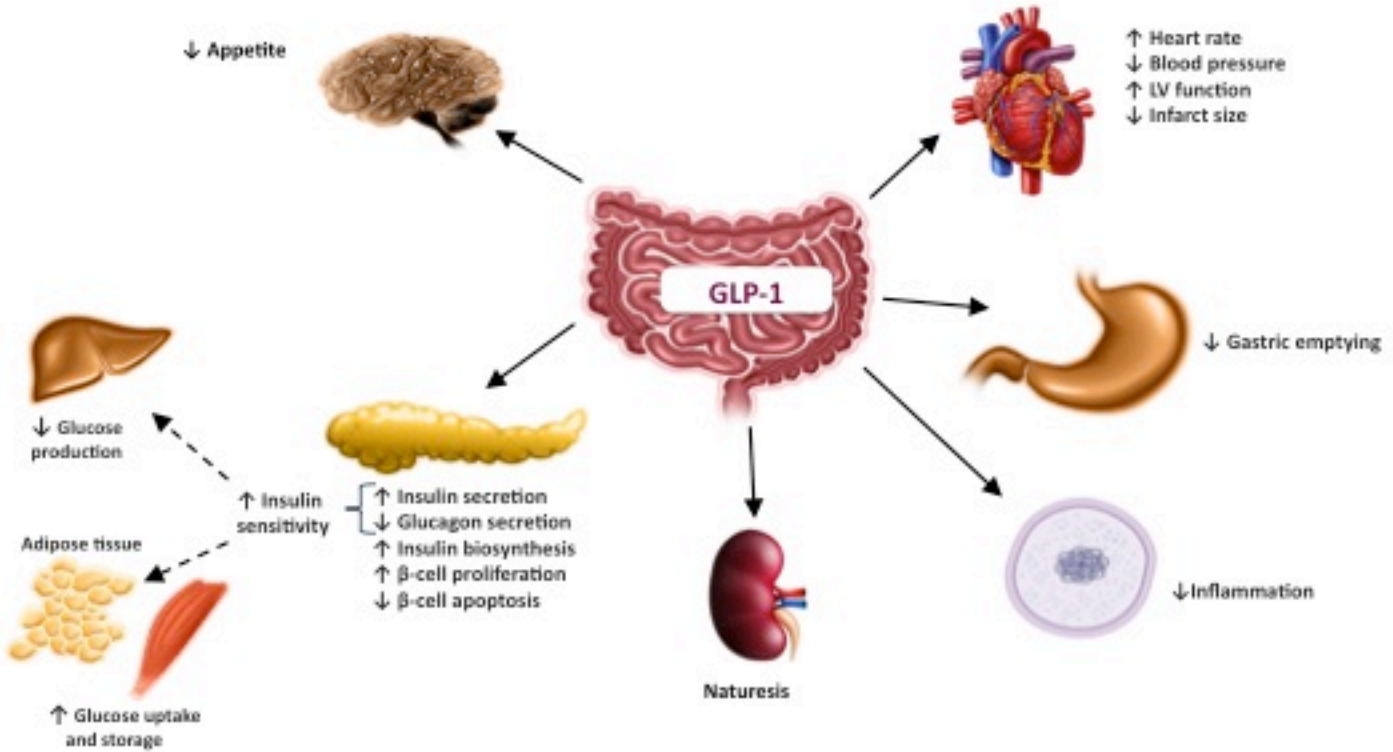

DPP4
GLP-1
Exenatide
Lixisenatide
Liraglutide
C-16 fatty acid
Semaglutide
C-18 fatty acid
Albiglutide
Albumin
Dulaglutide
Human IgG4 Fc Fragment

EMIVITA E FREQUENZA DI SOMMINISTRAZIONE DEGLI AGONISTI DEL RECETTORE DEL GLP-1

	Emivita	Metabolismo
Exenatide BID[4]	2,4 ore	Due volte al dì
Lixisenatide[1,2]	3 ore	Una volta al dì
Liraglutide[3]	13 ore	Una volta al dì
Exenatide QW[5,6]	2 settimane	Una volta alla settimana
Dulaglutide QW[7]	5 giorni	Una volta alla settimana

1. Lyxumia Riassunto delle caratteristiche del prodotto. Accesso: 14 maggio 2013
2. Fineman et al. Diabetes Obes Metab. 2012;14:675-88
3. Victoza Riassunto delle caratteristiche del prodotto. Accesso: 14 maggio 2013
4. BYETTA Riassunto delle caratteristiche del prodotto. Accesso: 14 maggio 2013
5. BYDUREON Riassunto delle caratteristiche del prodotto. Accesso: 14 maggio 2013
6. Murphy CE. Ann Pharmacother. 2012;46:812-21
7. Fineman M et al. Clin Pharmacokinet. 2011;50(1):65-74;

Exenatide Once Weekly: Agonista Recettoriale del GLP-1



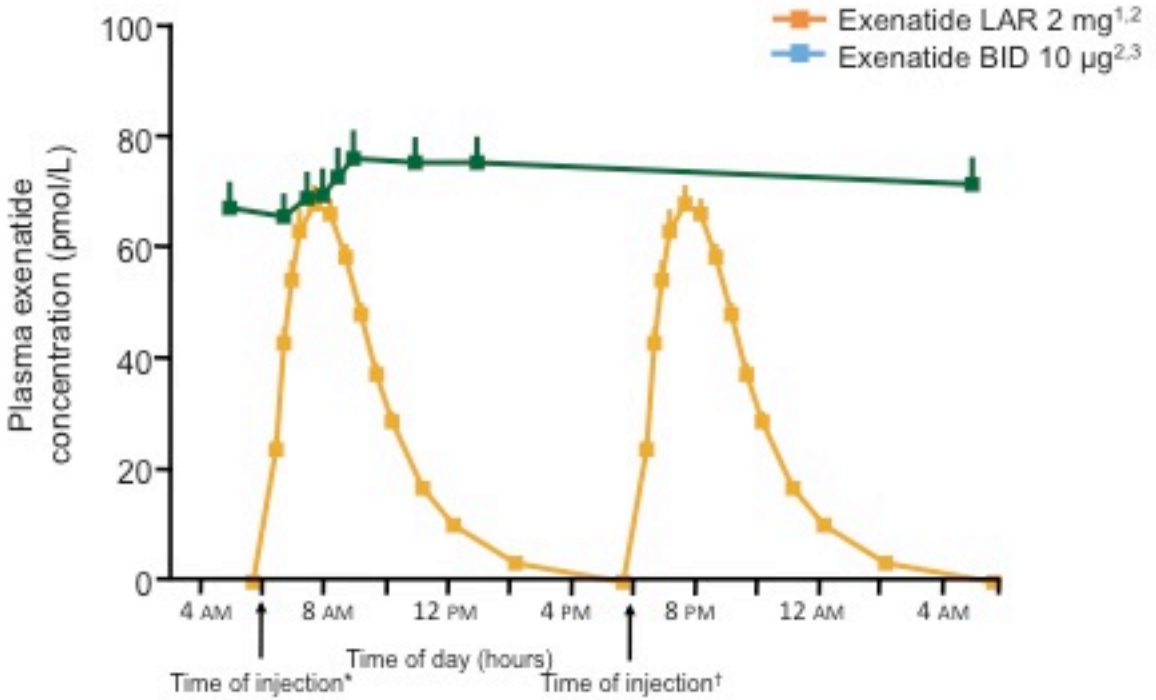
- 1. Drucker DJ, et al. *Diabetes*. 2015;64:3177-326. 2. Campbell JE, et al. *Cell Metab*. 2013;17:819-837. 3. Baggio LL et al. *Gastroenterology*. 2007;132:2131-2157. 4. Ussher JR, et al. *Circ Res*. 2014;114:1788-1803.

CONFRONTO DEGLI EFFETTI TRA DIFFERENTI AGONISTI DEL RECETTORE DEL GLP-1

Agonisti del recettore del GLP-1	Exenatide BID, Lixisenatide QD	Exenatide QW, Liraglutide QD, Albiglutide QW, Dulaglutide QW
Effetti		
Livelli dl glicemia a digiuno	Riduzione modesta[1,2]	Forte riduzione[1,2]
Escursioni glicemiche postprandiali	Forte riduzione[2]	Riduzione modesta[2]
Secrezione di insulina a digiuno	Stimolazione modesta[1,2]	Forte stimolazione[1,2]
Secrezione postprandiale di insulina	Riduzione[1,2]	Stimolazione modesta[1,2]
Secrezione di glucagone	Riduzione[1,2]	Riduzione[1,2]
Tasso di svuotamento gastrico	Decelerazione[1,2]	Modesto[1,2]
Ridotto apporto calorico	Si[1]	Si[1]
Riduzione del peso corporeo	1-5 kg[1]	2-5 kg[1]
Induzione della nausea	Il 20-50% circa, si attenua lentamente (da settimane a mesi)[1]	Il 20-40% circa, si attenua rapidamente (~4-8 settimane)[1]

1. Modificato da Meier JJ. Nat Rev Endocrinol 2012;8:728-42
2. Fineman MS et al. Diabet Obes Metab 2012;14:675-88

Exenatide LAR allo steady state vs BID: Profilo Farmacocinetico

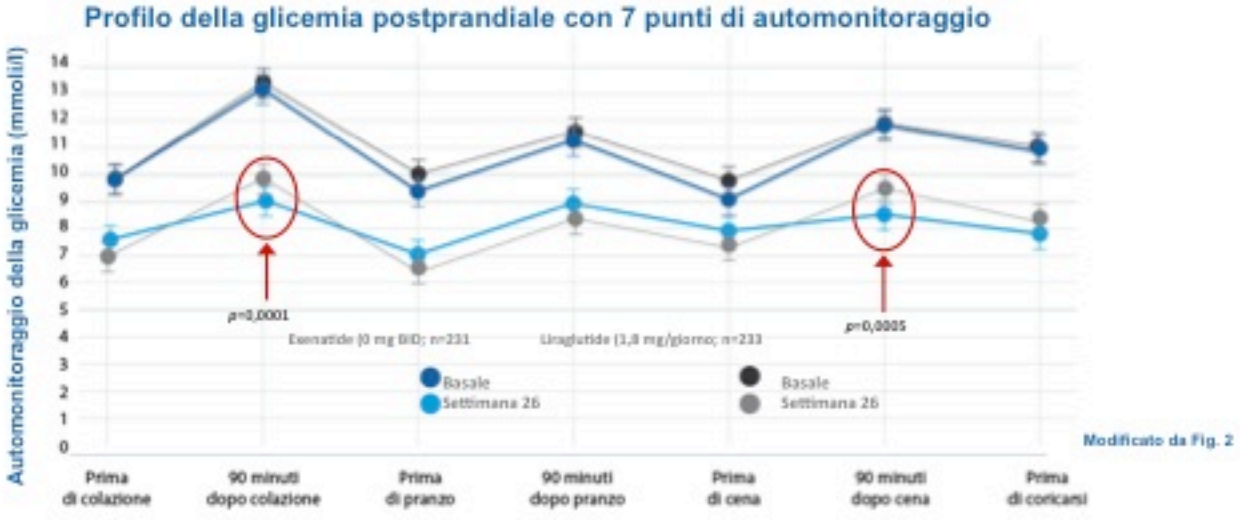


Data are geometric mean + SE; *Bydureon injection, first Byetta injection; †Second Byetta injection.
1. Drucker DJ, *et al. Lancet* 2008;**372**:1240–50; 2. Data on file, Amylin Pharmaceuticals, LLC;
3. Blase E, *et al. J Clin Pharmacol* 2005;**45**:570–7.

Limiti dei GLP-1 short-acting

- Efficacia (riduzione HbA1c)
- Modesto effetto sulla glicemia a digiuno
- Variabilità glicemica
- Frequenti somministrazioni
- Effetti collaterali (nausea, vomito, diarrea)

Exenatide, rispetto a Liraglutide, riduceva significativamente di più la glicemia post-prandiale a colazione e cena [1].



Modificato da Fig. 2

1- Buse JB et al. Lancet 2009; 374: 39-47.

GLP1 RA Head to Head trials efficacia su HbA1c

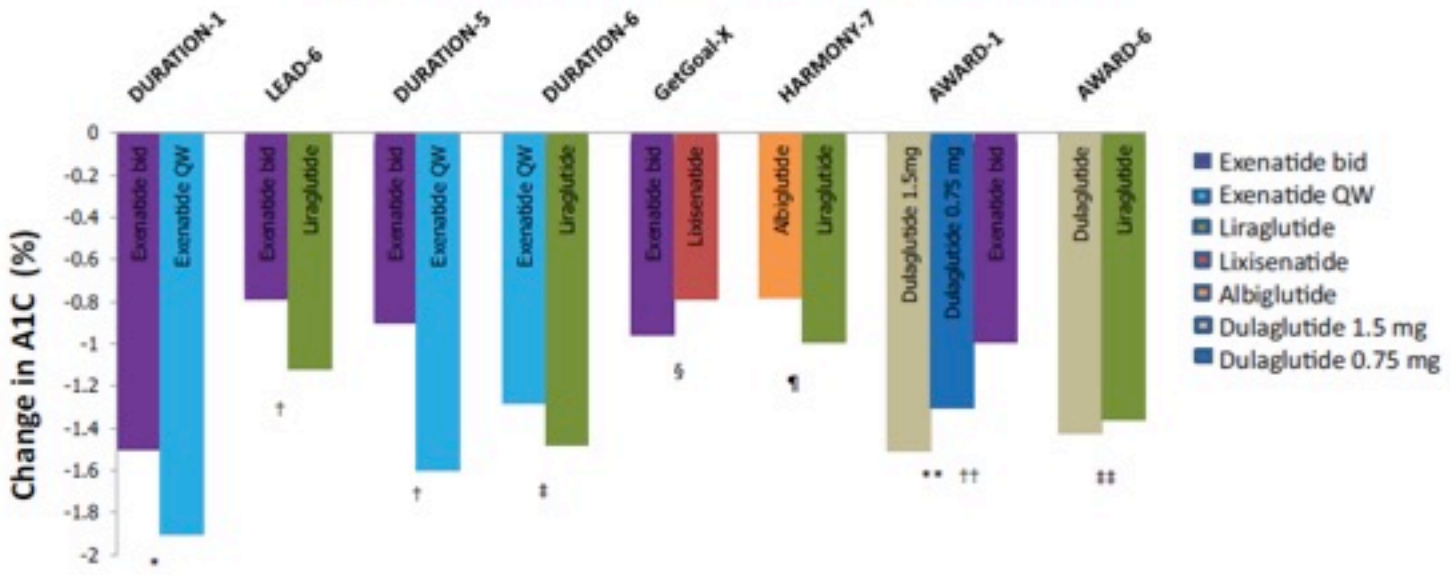


Figure 1. Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority unless otherwise noted as noninferiority; *$p < 0.0025$, †$p < 0.0001$, ‡$p = 0.02$, §p = not significant, noninferiority *p*-value not reported (95% confidence interval 0.033–0.297, meeting predefined noninferiority margin), ¶ noninferiority *p*-value = 0.846 (not meeting predefined noninferiority margin), **$p < 0.001$ for both doses of dulaglutide *versus* exenatide bid, ††p = not significant, noninferiority *p*-value < 0.0001 (meeting predefined noninferiority margin).

JM Trujillo, Ther Adv Endocrinol Metab. 2015 Feb; 6(1): 19–28.

GLP1RA Head to Head trials efficacia su Peso

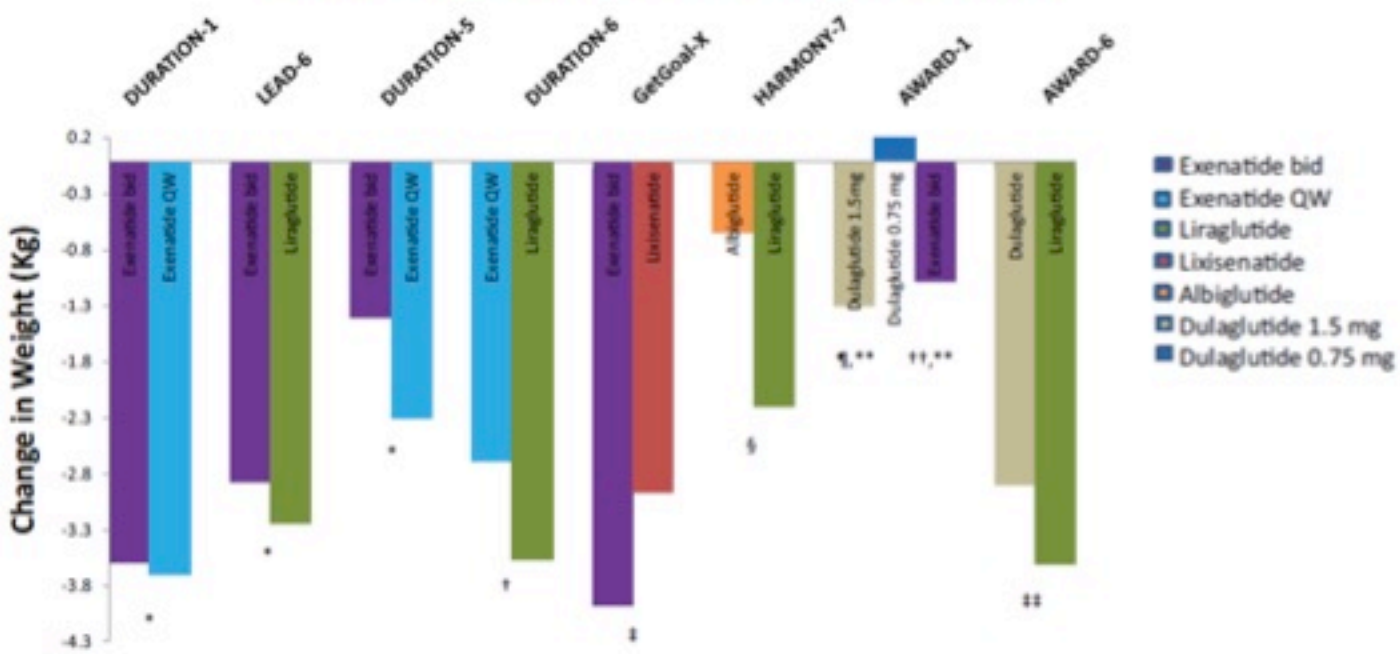
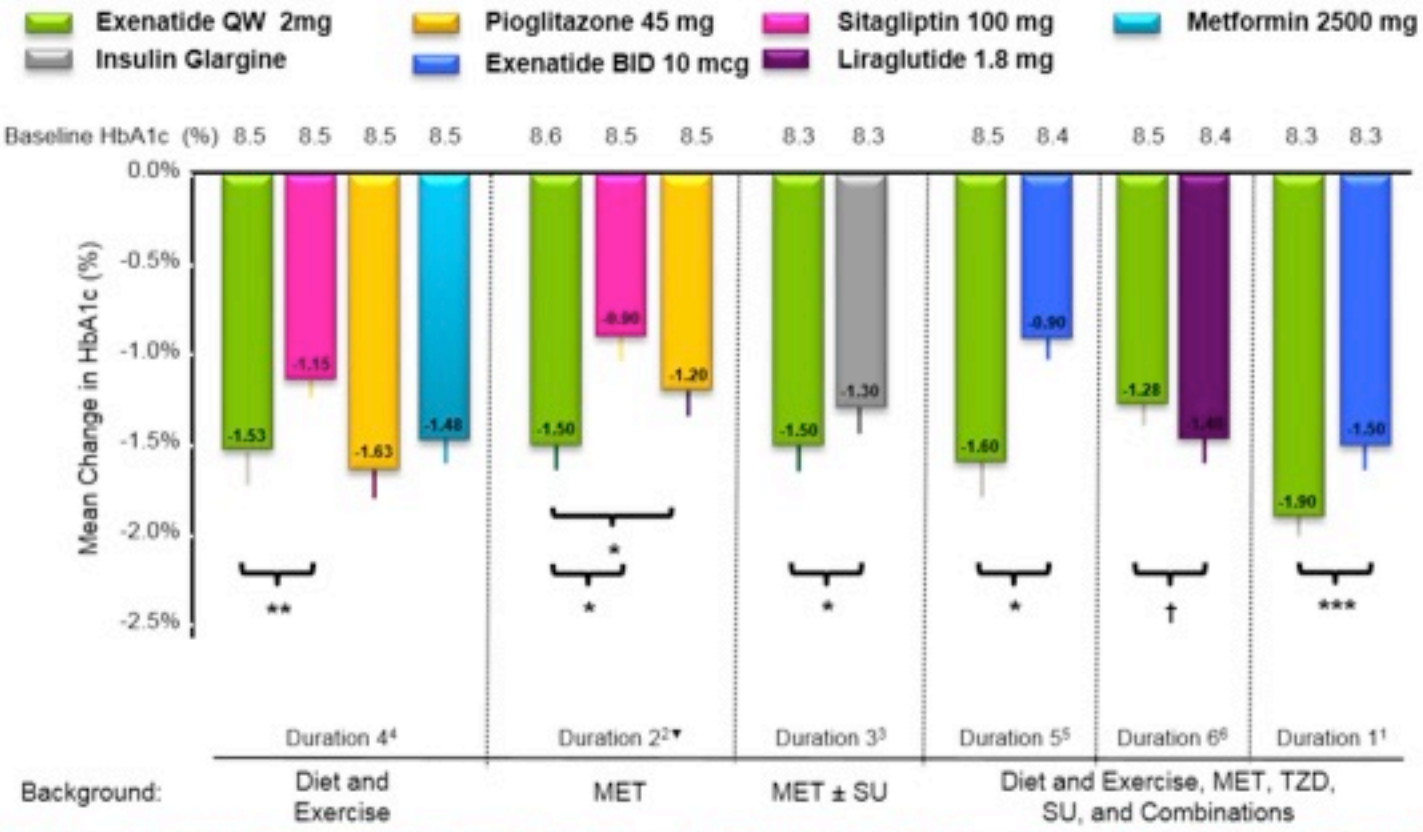


Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority (unless noted for noninferiority); *p = not significant, †$p = 0.0005$, ‡p-value not reported for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), §$p < 0.0001$, ¶ $p < 0.001$ *versus* dulaglutide 0.75 mg, **p = not significant between dulaglutide 1.5 mg *versus* exenatide bid, ‡‡$p = 0.011$.

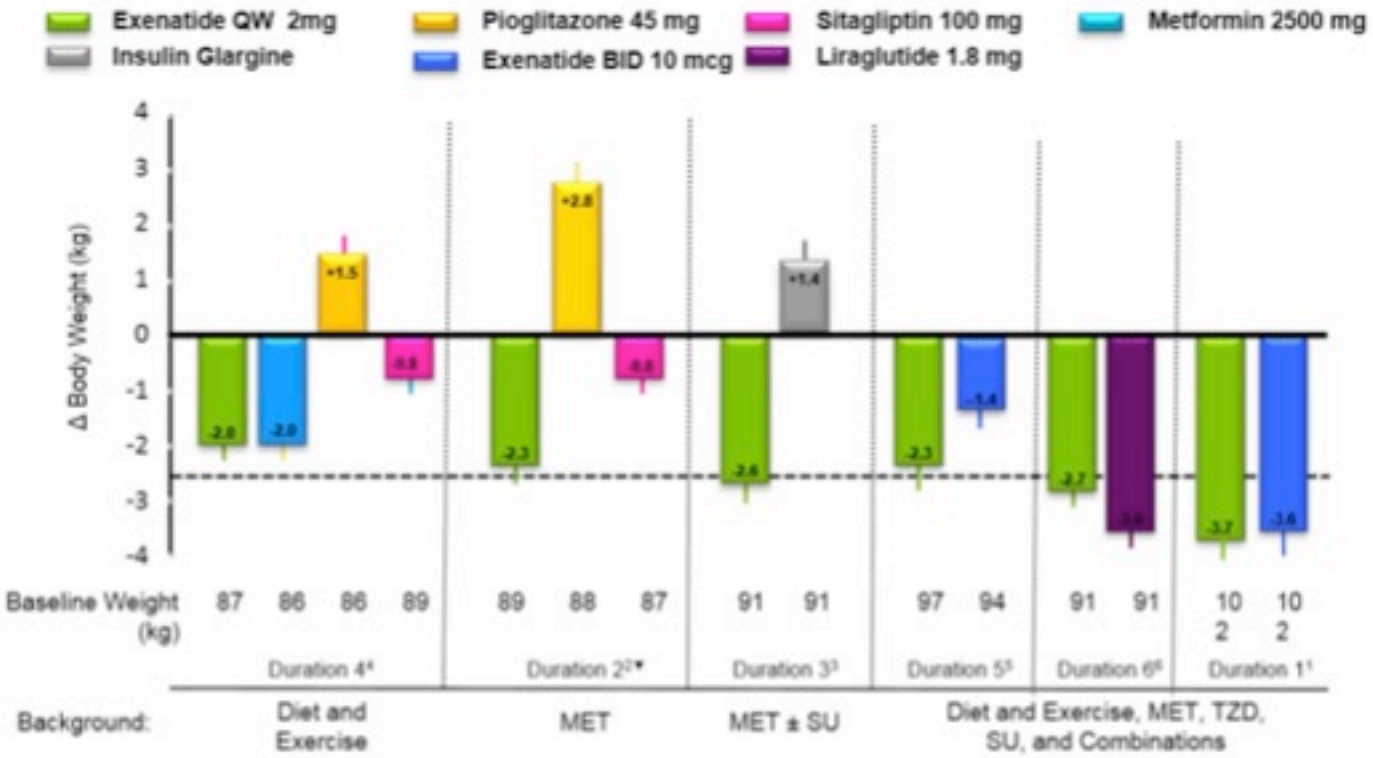
JM Trujillo, Ther Adv Endocrinol Metab. 2015 Feb; 6(1): 19–28.

Exenatide QW : efficacia su HbA1c



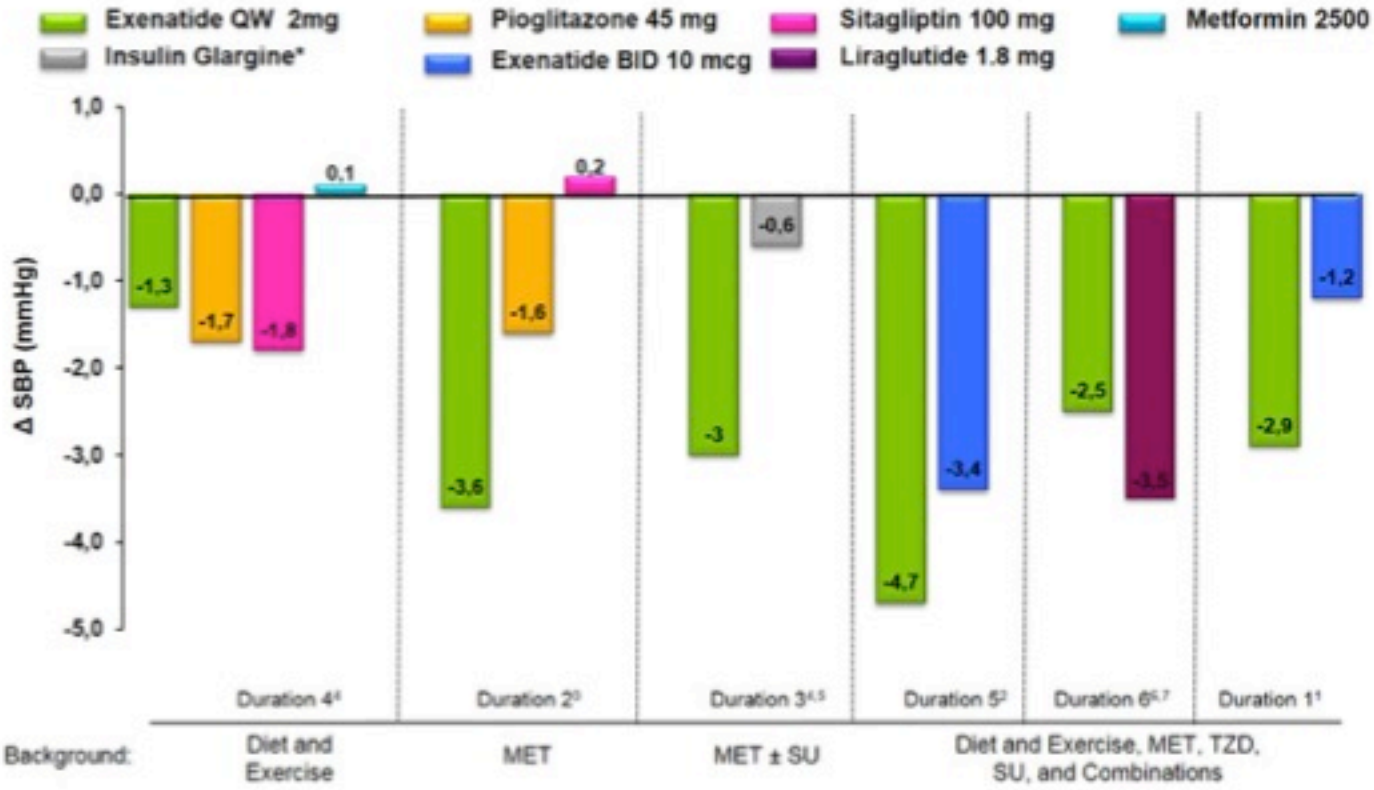
1-Drucker DJ, et al. *Lancet*. 2008;372(9645):1240-1250. 2-Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-439. 3-Diamant M, et al. *Lancet*. 2010;375(9733):2234-2243. 4-Russell-Jones D, et al. Diabetes Care. 2012;35(2):252–258. doi:10.2337/dc11-1107. 5-Blevins T, et al. *J Clin Endocrinol Metab*. 2011;96(5):1301-1310. 6-Buse JB, et al. *Lancet*. 2013;381(9861):117-124.

Exenatide QW : efficacia su Peso Corporeo



1-Drucker DJ, et al. *Lancet*. 2008;372(9645):1240-1250. 2-Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-439. 3-Diamant M, et al. *Lancet*. 2010;375(9733):2234-2243. 4-Russell-Jones D, et al. Diabetes Care. 2012;35(2):252–258. doi:10.2337/dc11-1107. 5-Blevins T, et al. *J Clin Endocrinol Metab*. 2011;96(5):1301-1310. 6-Buse JB, et al. *Lancet*. 2013;381(9861):117-124.

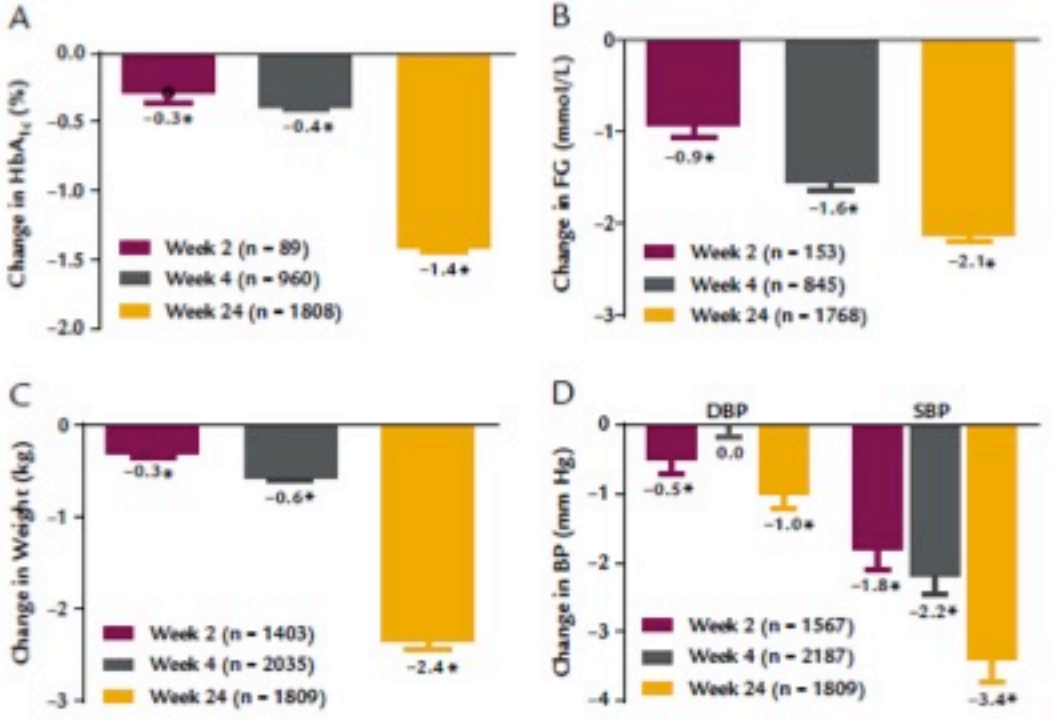
Exenatide QW : efficacia su Pressione Arteriosa Sistolica



1-Drucker DJ, et al. *Lancet*. 2008;372(9645):1240-1250. 2-Blevins T, et al. *J Clin Endocrinol Metab*. 2011;96(5):1301-1310. 3-Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-439. 4-Diamant M, et al. [abstract 277-OR]. Paper presented at: American Diabetes Association 71rst Scientific Sessions; June 24 - 28, 2011; San Diego, CA. Available at: http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=86858# Accessed: 11.18.13 5-Diamant M, et al. *Lancet*. 2010;375(9733):2234-2243. 6-Buse JB, et al. [abstract 75-OR]. Paper presented at: European Association for the Study of Diabetes; September 12 - 16, 2011; Lisbon, Portugal. 7-Buse JB, et al. *Lancet*. 2013;381(9861):117-124.

Exenatide OW: Timeline della efficacia su HbA1c, FBG, Peso e PAS

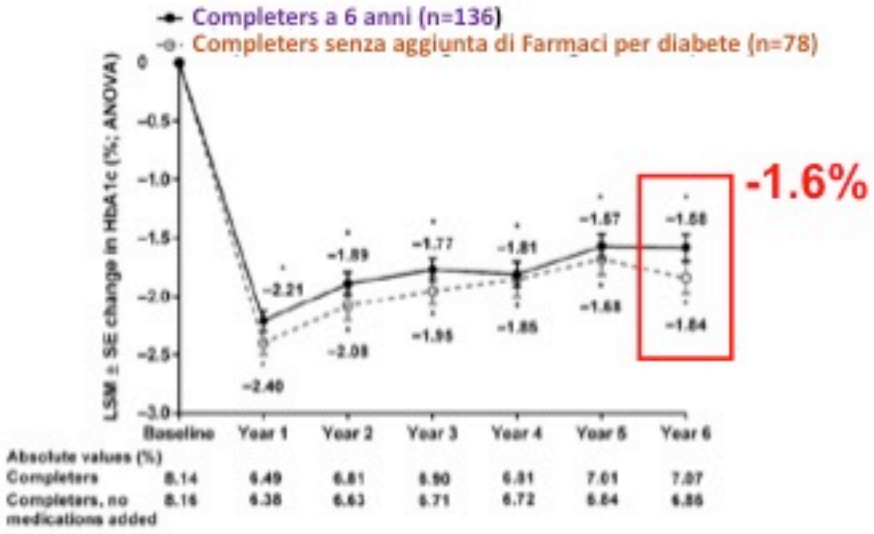
Pooled data da 12 trials in cui 2190 pazienti furono trattati con exenatide once weekly
(i pazienti avevano al baseline una media di HbA1c di 8.4% e una media di peso di 87 kg)

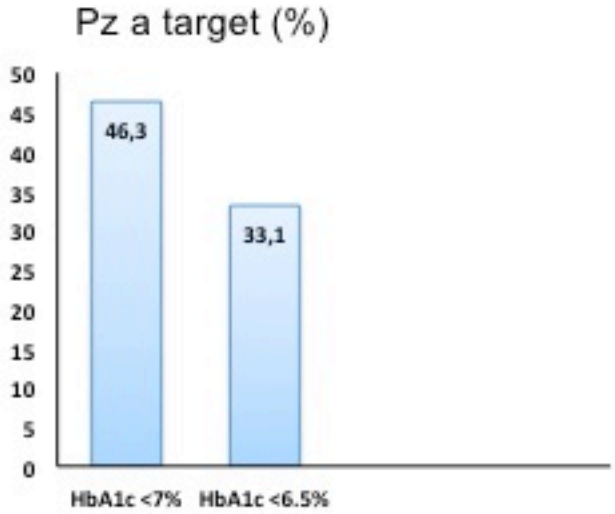


Effetto di Exe OW già a partire dalla seconda settimana e praticamente su tutti i parametri presi in considerazione

Trautman M.E et al Clin Ther. 2016;38:1464–1473

Exenatide OW: Duration-1 dato a 6 anni: efficacia sulla HbA1c

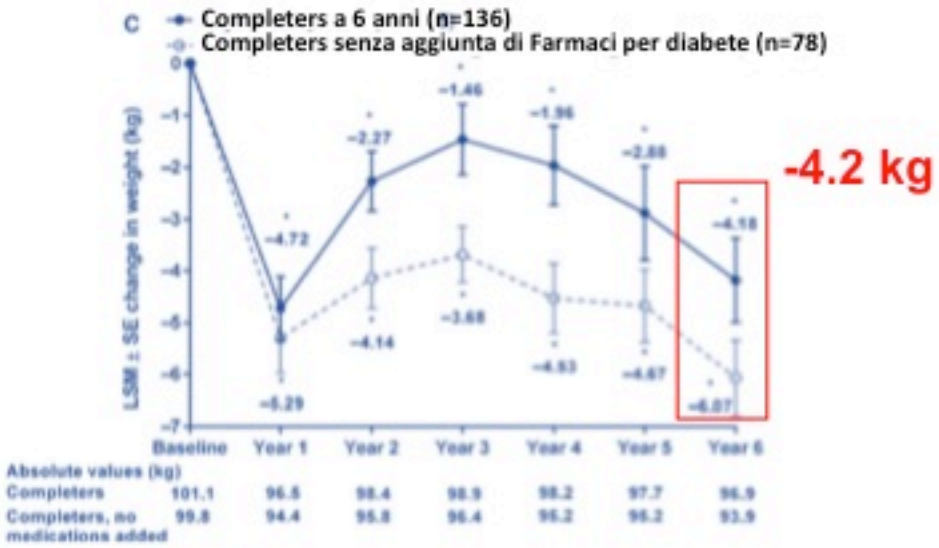




- Riduzione di HbA1c a 6 anni -1.6%
- 57% dei completers a 6 anni non ha aggiunto altri farmaci per il diabete DMT2, con riduzione HbA1c -1.84%
- Pz a target <7%= 46.3%

Henry RR et al., Diabetes Technology & Therapeutics Volume 18 (10), 2016

Exenatide OW: Duration-1 dato a 6 anni: efficacia sul peso corporeo



- Riduzione del peso a 6 anni è - 4.2 kg
- Nei completers a 6 anni che non hanno aggiunto altri farmaci per il diabete DMT2, riduzione – 6 kg

Henry RR et al., Diabetes Technology & Therapeutics Volume 18 (10), 2016

Duration-1 dato a 6 anni: Dislipidemia

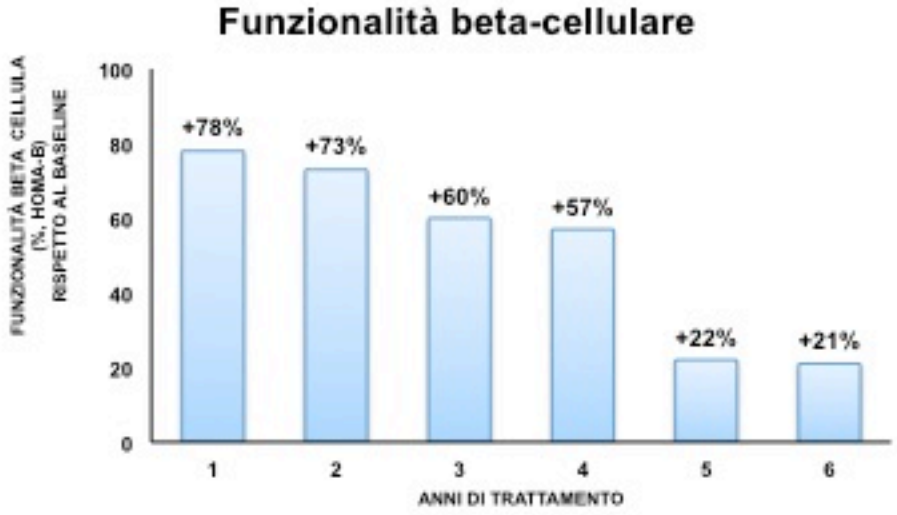
Completers a 6 anni (n=136)

Parameter	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total cholesterol, mg/dL, LSM (95% CI)*	170.0 ± 3.7	−8.3	−6.3	−7.9	−9.3	−9.9	−10.1
		(−14.9, −3.7)	(−13.3, +0.8)	(−14.8, −1.0)	(−15.9, −2.8)	(−16.4, −3.4)	(−17.0, −3.1)
LDL cholesterol, mg/dL, LSM (95% CI)*	90.7 ± 3.2	−3.7	−2.7	−5.9	−7.7	−8.5	−9.8
		(−8.2, +0.7)	(−8.4, +3.0)	(−12.0, +0.2)	(−13.2, −2.3)	(−13.9, −3.1)	(−15.6, −4.0)
HDL cholesterol, mg/dL, LSM (95% CI)*	45.3 ± 0.9	−0.8	+1.5	+2.2	+2.0	+3.0	+2.6
		(−2.2, +0.7)	(−0.4, +3.4)	(+0.6, +3.8)	(+0.3, +3.7)	(+1.1, +4.8)	(+0.7, +4.5)
LDL/HDL cholesterol ratio, median (range)	1.95	−0.07	−0.05	−0.19	−0.26	−0.20	−0.22
	(0.58, 6.16)	(−3.00, +2.30)	(−3.33, +1.79)	(−2.62, +3.50)	(−3.78, +2.32)	(−2.16, +2.49)	(−2.10, +3.35)
Triglycerides, mg/dL, median (range)	151.0	−15.0	−22.0	−14.0	−9.0	−11.0	−8.0

- **Miglioramento di multipli parametri della dislipidemia**

Henry RR et al., Diabetes Technology & Therapeutics Volume 18 (10), 2016

Duration-1 dato a 6 anni: Beta-cellula



- **Miglioramento della funzionalità beta-cellulare fino a 6 anni**

Henry RR et al., Diabetes Technology & Therapeutics Volume 18 (10), 2016

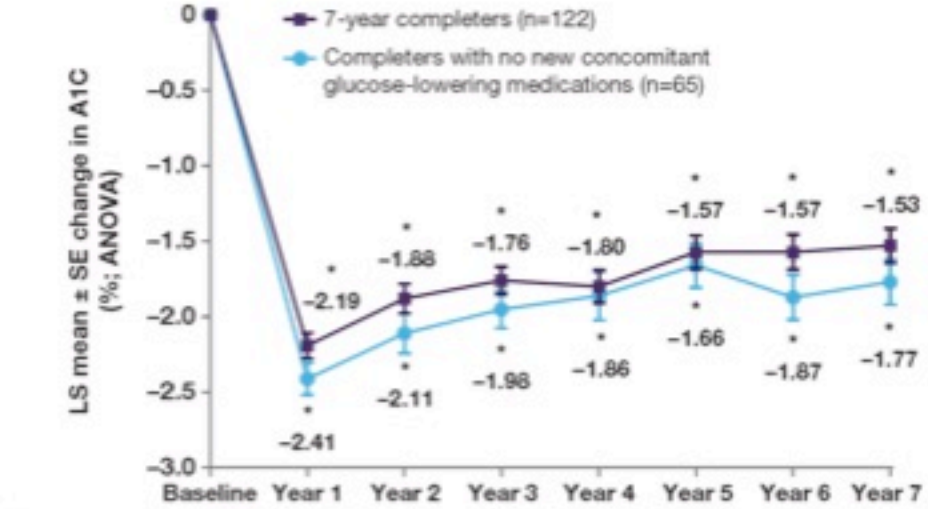
Duration-1 dato a 6 anni: Sicurezza & tollerabilità

	30-Week assessment (n = 148)		*Open-ended assessment (n = 278)*	
Adverse event	*Incidence, %*	*Annual event rate, events/year*	*Incidence, %*	*Annual event rate, events/year*
Upper respiratory tract infection	8.1	0.162	41.9	0.172
Nasopharyngitis	6.8	0.187	28.3	0.160
Diarrhea	16.2	0.373	26.0	0.102
Sinusitis	4.7	0.087	21.7	0.104
Arthralgia	4.7	0.124	19.0	0.067
Back pain	4.7	0.087	18.6	0.057
Urinary tract infection	10.1	0.224	18.2	0.076
Nausea	27.0	0.846	17.1	0.076
Pain in extremity	0.7	0.025	15.9	0.050
Vomiting	10.8	0.361	15.5	0.069
Hypertension	3.4	0.062	15.1	0.043
Bronchitis	2.7	0.050	14.3	0.047
Musculoskeletal pain	1.4	0.025	13.6	0.042
Cough	3.4	0.062	10.5	0.032
Gastroenteritis, viral	8.1	0.149	10.1	0.033
Constipation	10.1	0.199	9.7	0.028
Injection-site pruritus	18.2	0.510	5.4	0.016

- Il tasso di eventi avversi GI decresce nel tempo
- Gli unici eventi avversi riportati al sito di iniezione sono prurito ed eritema che decrescono a 6 anni
- La % di AE che han portato all'interruzione della terapia è del 6.2 %

Henry RR et al., Diabetes Technology & Therapeutics Volume 18 (10), 2016

Duration 1, dato a 7 anni: efficacia su HbA1c



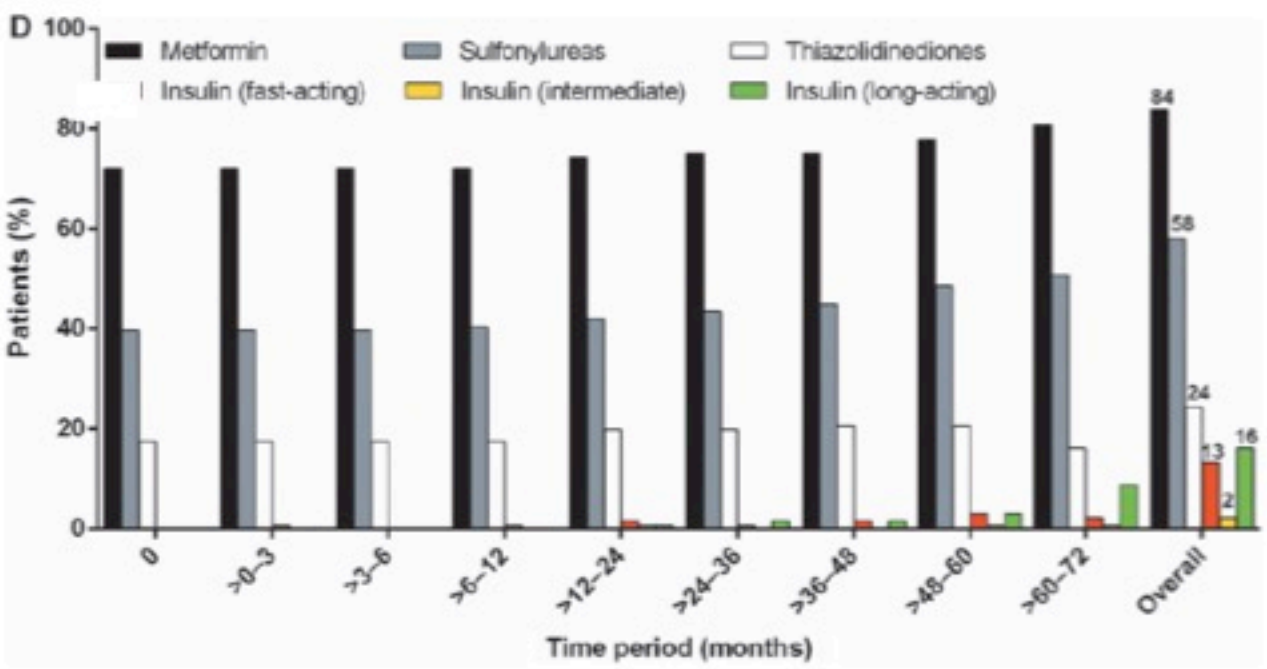
Mean A1C values (%)								
Completers	8.2	6.5	6.8	6.9	6.8	7.0	7.1	7.1
Completers, no medications added	8.2	6.3	6.6	6.7	6.7	6.8	6.8	6.9

*p<0.05.

- **Riduzione di HbA1c a 7 anni -1.53%**
- **53% dei completers a 7 anni non ha aggiunto altri farmaci per il diabete DMT2, con riduzione HbA1c -1.77%**

Wysham CH et al. Presented at 76th Scientific Sessions of the American Diabetes Association, June 10-14, 2016; New Orleans, LA.

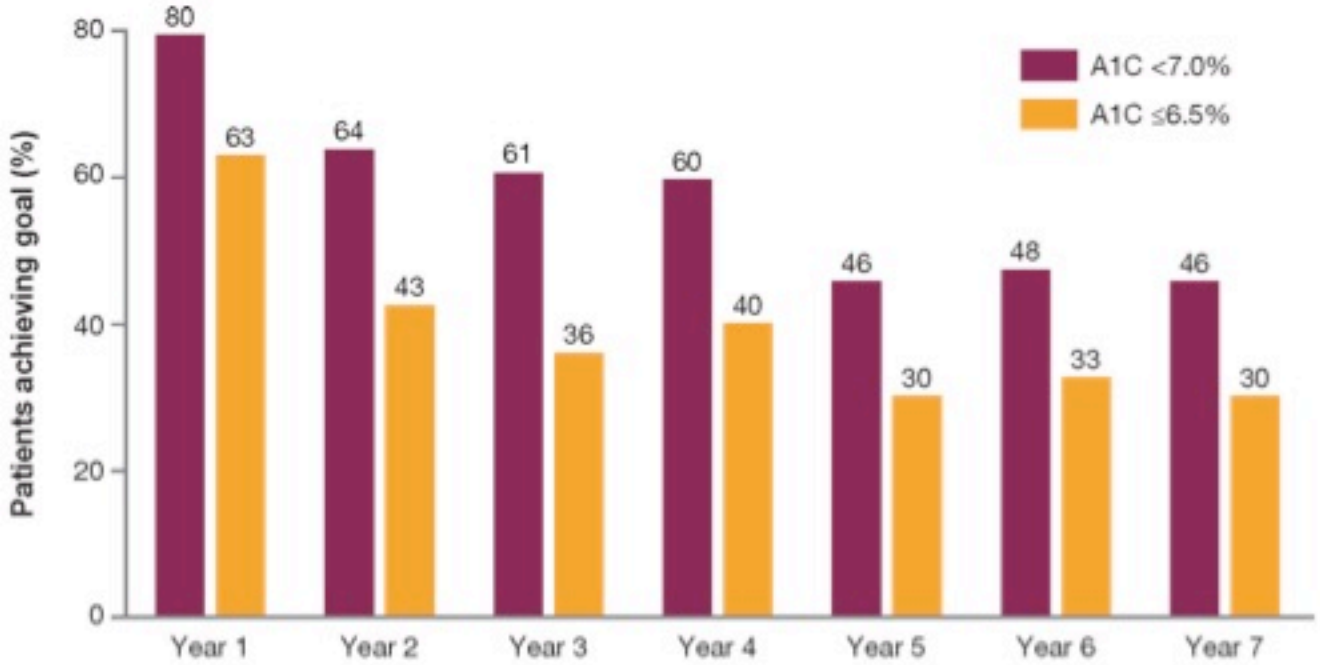
Duration 1 a 7 anni: Utilizo di farmaci ipoglicemizzanti nel tempo



- **Uso delle insuline meno frequente rispetto quello dei farmaci orali (fast-acting fino a 2.9%; intermediate-acting, 0.7%; long-acting, 8.8%)**

Wysham CH et al. Presented at 76th Scientific Sessions of the American Diabetes Association, June 10-14, 2016; New Orleans, LA.

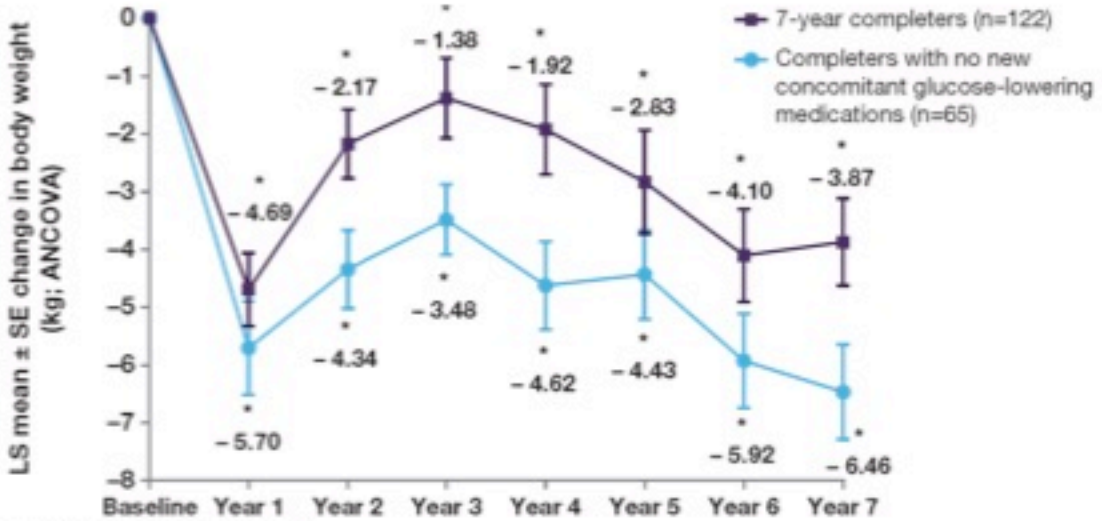
Duration 1 a 7 anni: Percentuale di pz a target di HbA1c



- **Il 46% dei pz raggiunge il target glicemico < 7%**

Wysham CH et al. Presented at 76th Scientific Sessions of the American Diabetes Association, June 10-14, 2016; New Orleans, LA.

Duration 1, dato a 7 anni: efficacia su Peso Corporeo



Mean body weight values (kg)								
Completers	101.2	96.7	98.7	99.2	98.4	97.9	97.1	97.1
Completers, no medications added	99.3	93.6	95.1	96.1	94.7	95.0	93.7	93.4

*p<0.05.

- **Riduzione del peso a 7 anni è – 3.87 kg**
- **Nei completers a 7 anni che non hanno aggiunto altri farmaci per il diabete DMT2, riduzione – 6.46 kg**

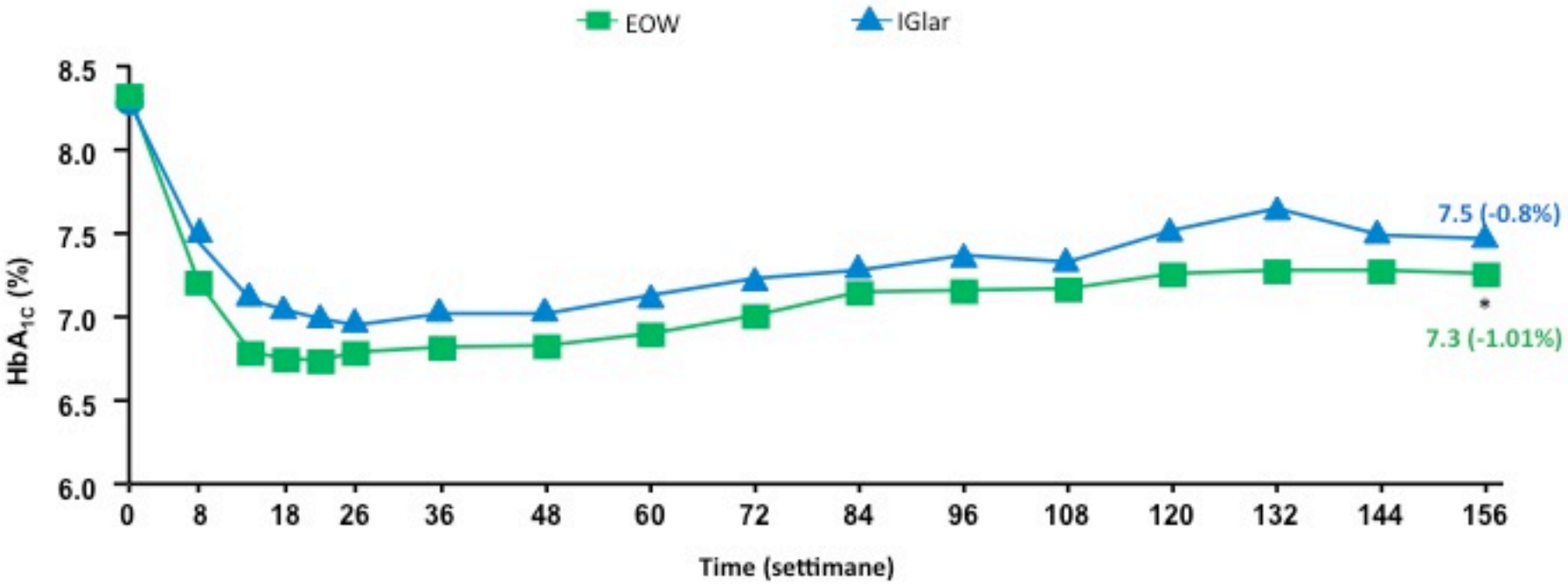
Wysham CH et al. Presented at 76th Scientific Sessions of the American Diabetes Association, June 10-14, 2016; New Orleans, LA.

Eventi Avversi

- Riduzione dell'incidenza di eventi avversi durante il follow up a 7 anni
- Nausea riscontrata nel 35.8% dei pz nelle prime 30 settimane e nel 28.7% a 7 anni
- Nessun caso di ipoglicemie maggiori

Wysham CH et al. Presented at 76th Scientific Sessions of the American Diabetes Association, June 10-14, 2016; New Orleans, LA.

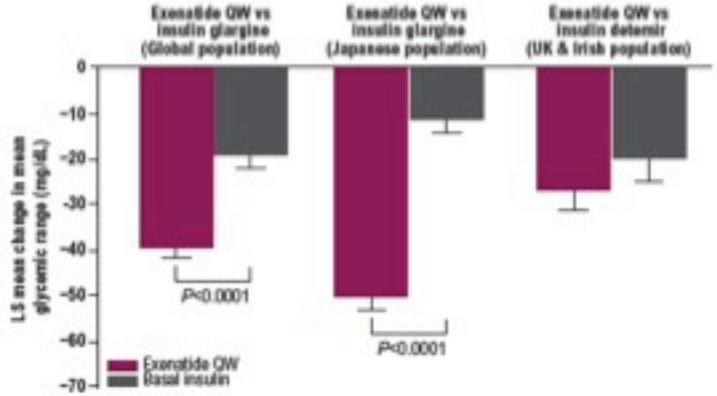
Riduzione della HbA_{1c} a 3 anni nel confronto tra Exe OW e Ins Glargine



Diamant M, et al. Lancet Diabetes Endocrinol 2014;2:464–473

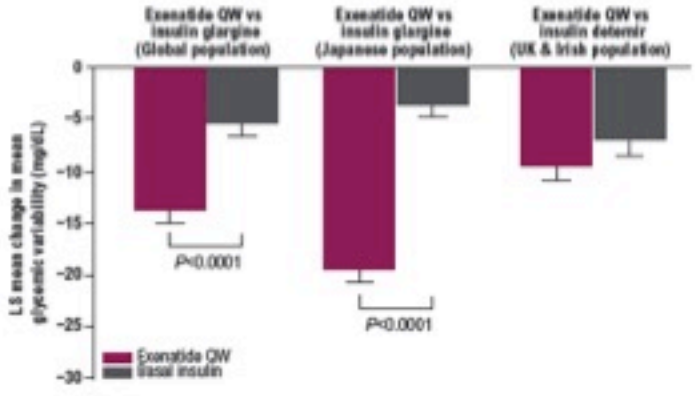
Exe OW nel confronto con Insulina Glargine: minori fluttuazioni glicemiche

Figure 3. Greater reductions in glycemic range with exenatide QW vs insulin glargine



LS, least squares; QW, once weekly.

Figure 4. Greater reductions in glycemic variability with exenatide QW vs insulin glargine



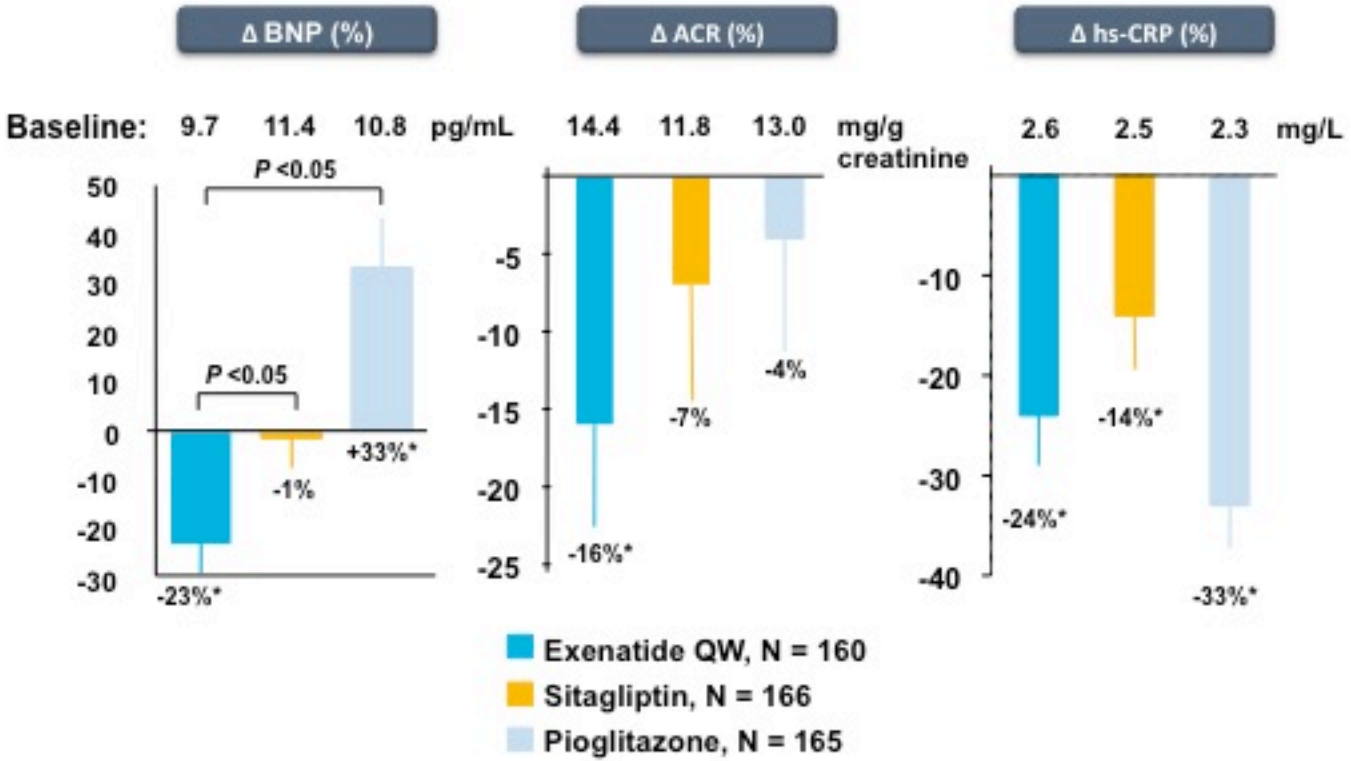
LS, least squares; QW, once weekly.

- Nei 3 studi analizzati, exenatide QW riduce la glicemia a digiuno meno dell'insulina basale, ma riduce la glicemia dopo cena più dell'insulina basale
- Exenatide QW riduce la fluttuazione glicemica più dell'insulina glargine, indicando che questo maggiore effetto sulla glicemia post-prandiale migliora il controllo glicemico per tutto il giorno
- Diversi indici di variabilità glicemica indicano differenze statisticamente significative a favore exenatide QW rispetto al trattamento con insulina basale glargine

Vora J, et al. ADA Scientific Sessions 2014; Sat., June 14 11:30 - 1:30PM, Poster 997-P

Exenatide QW: efficacia su marcatori di rischio cardiovascolare

ITT population, N = 491; *P <0.05 vs baseline; BNP, B-type natriuretic peptide; ACR, albumin-to-creatinine ratio; hs-CRP, High-sensitivity C-reactive protein;



Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-9

Kidney & Blood Pressure Research

Original Paper

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Exenatide Reduces Urinary Transforming Growth Factor-β_1 and Type IV Collagen Excretion in Patients with Type 2 Diabetes and Microalbuminuria

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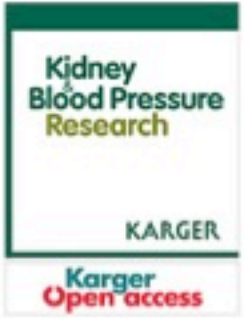
Kidney Blood Press Res 2012;35:483–488



Abstract

Aims: It was reported that exenatide ameliorated renal injury in diabetic rats. The present study was carried out to evaluate the effect of exenatide on 24-hour urinary albumin, urinary transforming growth factor-β_1 (TGF-β_1) and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. ***Methods:*** 31 type 2 diabetic patients with microalbuminuria were randomly allocated to receive exenatide (group Exe, n = 13) or glimepiride treatment (group Glm, n = 18) for 16 weeks. Body mass index (BMI), fasting plasma glucose, 2-hour postprandial plasma glucose, glycated hemoglobin A_{1c}, systolic blood pressure, diastolic blood pressure, 24-hour urinary albumin, urinary TGF-β_1 and type IV collagen concentration were analyzed between the two treatment groups. 20 age- and BMI-matched healthy subjects were chosen as the normal control group (group NC, n = 20). ***Results:*** After 16 weeks of treatment, 24-hour urinary albumin, urinary TGF-β_1 and type IV collagen in group Exe were significantly lower than those of group Glm ($p < 0.01$), while glycemic control had no statistical difference between the two groups. ***Conclusions:*** Our results indicate that exenatide reduces urinary TGF-β_1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria, which may be partly contributory to its directly renoprotective role.

Original Paper

Kidney Blood Pressure Research

Exenatide Reduces Urinary Transforming Growth Factor-β_1 and Type IV Collagen Excretion in Patients with Type 2 Diabetes and Microalbuminuria

[illegible]

Kidney Blood Pressure Research

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Kidney Blood Press Res 2012;35:483–488

EXSCEL

The EXenatide Study of Cardiovascular Event Lowering (EXSCEL) clinical trial will find out if giving people with type 2 diabetes a drug called Exenatide alongside their usual diabetes care regime can reduce their risk of heart disease.

EXSCEL is a phase IIIb/IV multinational trial, being conducted in around 30 countries across Australasia, Asia, Europe, North America and Latin America.
Coordinated by DTU and Duke Clinical Research Institute (DCRI), and sponsored by Amylin Pharmaceuticals LLC, (a wholly owned subsidiary of AstraZeneca) the trial began in June 2010.

18,000 people with type 2 diabetes aged 18 years or older whose HbA1c is ≥6.5% and ≤10% will be recruited to the trial. Each participant will receive an injection of study medication (Exenatide/ Placebo) once a week.

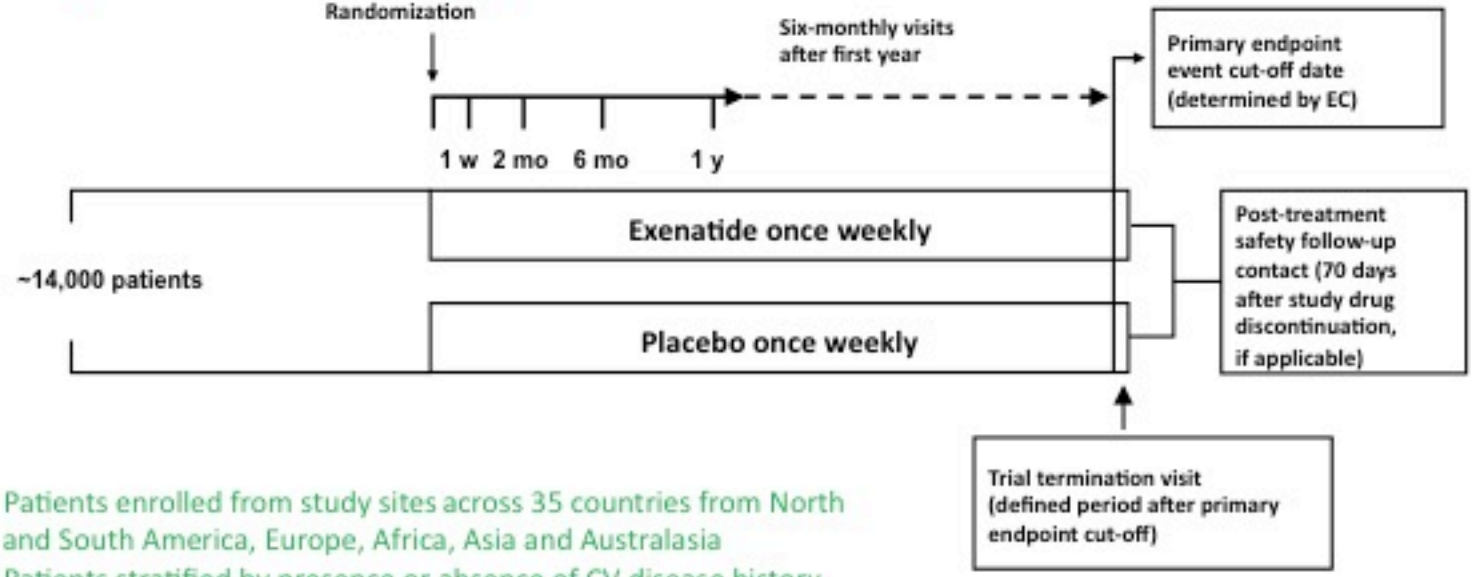
The recruitment period is expected to be around 5 years and an additional 2 - 3 years follow up may be required (total duration of up to approximately 7.5 years)

We expect that results of this pragmatic trial (which aims to measure how beneficial a treatment would be in real clinical practice) will be available in 2018.

Primary Objective :

To evaluate the effect of Exenatide Once Weekly used in conjunction with the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes

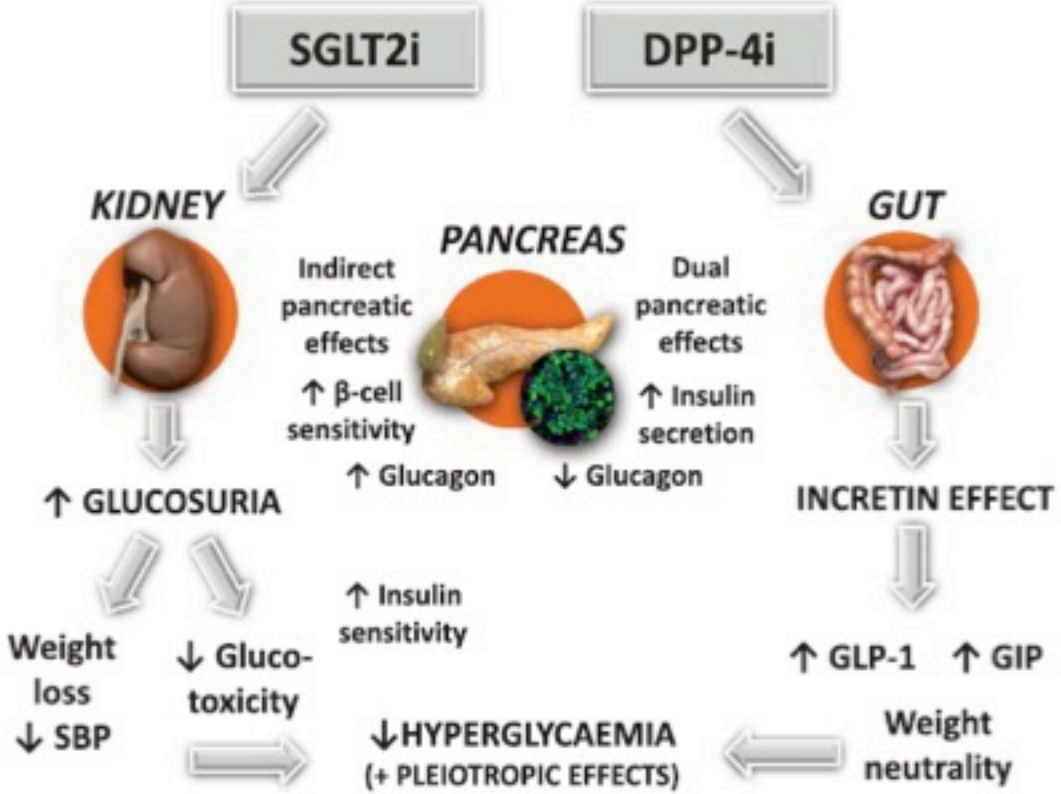
Studio EXSCEL (CVOT con Exe OW)



- Patients enrolled from study sites across 35 countries from North and South America, Europe, Africa, Asia and Australasia
- Patients stratified by presence or absence of CV disease history

- Patients managed by usual care provider according to local standard of diabetes care and CV risk management
- Study will continue until:
  - N=1360 with a confirmed primary composite CV endpoint have been accrued OR
  - Independent DSMB recommends otherwise

Razionale della combinazione SGLT2i plus DPP4i



Sheen A.J . EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY , Jul 2016

Grazie per l’attenzione !