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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GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%
- 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%
- 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

Entry A1C > 9.0%
- 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 or intensify insulin therapy

SYMPTOMS
NO
DUAL Therapy
OR
TRIPLE Therapy

YES
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
✓ Few adverse events and/or possible benefits
! Use with caution

PROGRESSION OF DISEASE

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ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

- **A1C < 8%**
  - TDD 0.1–0.2 U/kg
  - Insulin titration every 2–3 days to reach glycemic goal:
    - Fixed regimen: Increase TDD by 2 U
    - Adjustable regimen:
      - FPG > 180 mg/dL: add 20% of TDD
      - FPG 140–180 mg/dL: add 10% of TDD
      - FPG 110–139 mg/dL: add 1 unit
      - If hypoglycemia, reduce TDD by:
        - BG < 70 mg/dL: 10%–20%
        - BG < 40 mg/dL: 20%–40%

- **A1C > 8%**
  - TDD 0.2–0.3 U/kg

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

**Glycemic Control Not at Goal**

**INTEGRITY**

- 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 2 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:

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

*Glycemic Goal:

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

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Una significativa quota di pazienti con DM 2 in Europa non raggiunge i target glicemici.

STUDIO PANORAMA:
su 5817 pazienti arruolati
solo il 62,6% raggiungevano HbA1c <7%

Più alta è la HbA1c di partenza e più è difficile raggiungere il target

Proportion of patients achieving $\text{HbA}_1c < 7\%$ with non-insulin drugs in a systematic review of 218 RCT (n=78,945)

*Metformin, sulfonylureas, $\alpha$-glucosidase inhibitors, thiazolidinediones, glinides, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 analogues

RCT, randomized controlled trial

Clinical Inertia: Patient and Physician Barriers

- Lack of appropriate education
- Excess weight gain
- Complex regimens
- Risks in patients with comorbidities
- Resource issues
- Patient perceptions of insulin treatment and outcomes
- Hypoglycemia
- Impaired quality of life
- Lack of patient adherence to treatment
- Financial restrictions
- Beliefs about patient competence

References:
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.

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

GLP1RA

↓ Glucose-dependent insulin secretion
↑ Appetite
↑ Heart rate
↓ Blood pressure
↑ LV function
↓ Infarct size
Natriuresis
↓ Inflammation
Slows gastric emptying
↓ Blood Glucose
↓ Blood Pressure
↓ Body Weight

SGLT-2i

↑ Urinary glucose excretion
Natriuresis
↓ Systolic Blood Pressure
↓ Vascular stiffness
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

- **Corrects a Novel Pathophysiologic Defect**
- **Reduces HbA1c**
- **Promotes Weight Loss**
- **Reduces Blood Pressure**
- **Implements Glycemic Control and CVRFs**
- **Complements Action of Other Agents with possible multiple tissue effects**
- **Reversal of Glucotoxicity**
- **No Hypoglycemia**
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

Sglt2 inibitori: "grading" per sicurezza

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

![Graphs showing probability of drug ranking for different drug classes](image)

- 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

SGLT-2i: Dapagliflozin

- **Effect of SGLT-2i**
  - ↑ Urinary glucose excretion
  - ↓ FPG and PPG
  - ↓ Body weight
  - ↓ Systolic blood pressure
  - ↓ A1C levels

- Inhibition of SGLT2 (b市场竞争)
- Glucose reabsorption inhibited
- Blood vessel
- Proximal tubule
- SGLT2
- ATPase
- Na⁺ influx
- K⁺ efflux

References:
5. FARXIGA PI.
Il Dapagliflozin è un inibitore dell’SGLT2 altamente selettivo e reversibile\textsuperscript{1}

<table>
<thead>
<tr>
<th>Human transporters</th>
<th>Dapagliflozin mean $EC_{50}$ (nM ± SEM)$^{3,4}$</th>
<th>Dapagliflozin $K_i$ (nM ± SEM)$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2</td>
<td>1.12 ± 0.065</td>
<td>0.2 ± 0.06</td>
</tr>
<tr>
<td>SGLT1</td>
<td>1391 ± 7</td>
<td>610 ± 180</td>
</tr>
<tr>
<td>Selectivity: SGLT2 versus SGLT1</td>
<td>1200</td>
<td>3000</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy¹</th>
<th>Add-on to Met²</th>
<th>Add-on to Glim³</th>
<th>Add-on to Pio⁴</th>
<th>Add-on to Ins⁵</th>
<th>Add-on to Met XR⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HbA₁C</td>
<td>7.92</td>
<td>8.06</td>
<td>8.11</td>
<td>8.37</td>
<td>8.53</td>
<td>9.05</td>
</tr>
</tbody>
</table>

**Primary endpoint for 24-week adjusted A from baseline HbA₁C (%)**

-0.23
-0.3
-0.13
-0.37
-0.53
-0.98

*P<0.001 vs placebo

- Dapagliflozin reduces HbA₁C vs. placebo over 24 weeks (as monotherapy or add-on therapy)¹-⁶

Dapa=dapagliflozin; MET=metformin; Glim=glimipiride; Pio=pioglitazone; Ins=insulin; HbA1C=glycated haemoglobin

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

BOLLINGER J. - J Clin Endocrinol Metab. 2012 Mar;97(3):1020-31
Dapagliflozin in associazione a Metformina verso SU, risultati a 4 anni: “efficacia e durabilità” su HbA1c con basso rischio ipoglicemicico.
Dapagliflozin in associazione a Metformina verso SU risultati a 4 anni: efficacia su peso corporeo e pressione arteriosa

- +0.73 kg (95% CI: 0.36 to 1.09)
- 4.38 kg difference
- -3.65 kg (95% CI: -4.3 to -3.0)

Sample size (including data after rescue)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>12W</th>
<th>24W</th>
<th>36W</th>
<th>48W</th>
<th>60W</th>
<th>72W</th>
<th>96W</th>
<th>108W</th>
<th>120W</th>
<th>144W</th>
<th>168W</th>
<th>180W</th>
<th>192W</th>
<th>208W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin + metformin</td>
<td>400</td>
<td>312</td>
<td>224</td>
<td>129</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + metformin</td>
<td>412</td>
<td>315</td>
<td>221</td>
<td>129</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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

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

A Phase II, multicentre, randomised, double-blind, parallel-group, 52-week, glycemic controlled, non-intervention study with a double-blind extension to evaluate the efficacy and safety profile of dapagliflozin 10 mg + metformin (2500-5000 mg/d) versus glipizide + metformin (2500-5000 mg/d) in patients with inadequately glycemic control (HbA1c >7.5% and <10.0%) on metformin alone.

C. confidence interval, SBP, systolic blood pressure, SU, sufglucose
Dapagliflozin in associazione a Insulina, risultati a 2 anni: efficacia su HbA1c e peso corporeo (con risparmio di dosi insuliniche)

↓ 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 diabeticci ad alto rischio CV l'efficacia di Dapagliflozin si associa a un buon 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.

Dapagliflozin: dal “Trial Clinico” alla “Real Life”

**Clinical trial data††1,2**

As add-on to metformin and insulin at 24 weeks, dapagliflozin delivers:

- **HbA\(_1c\)**: Add-on to MET: -0.84%\(^1\)  
  Add-on to insulin: -0.96%\(^2\)

- **Weight**:
  - Add-on to MET: -2.9 kg\(^1\)  
  - Add-on to insulin: -1.6 kg\(^2\)

- **SBP**:
  - Add-on to MET: -5.1 mmHg\(^1\)  
  - Add-on to insulin: -6.7 mmHg\(^2\)

**Real-world data§§**

As add-on to various agents including metformin and insulin over 6–12 months, dapagliflozin delivers:

- **HbA\(_1c\)**: -0.80 to -1.16%\(^3–5\)

- **Weight**:
  - -2.5 to -4.6 kg\(^3,5\)

- **SBP**:
  - -2.3 mmHg\(^3\)

---

*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.

Dapagliflozin: “Potenziale di protezione cardiovascolare”

<table>
<thead>
<tr>
<th>Table 1: DAPA</th>
<th>Patients with Events</th>
<th>Favors</th>
<th>Hazard Ratio vs Control (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVENT rate/100 p-y</td>
<td>DAPA → Control</td>
<td></td>
</tr>
<tr>
<td>MACE in patients with CVD history</td>
<td>50/1799 2.21</td>
<td>45/1325 2.76</td>
<td>0.80 (0.53, 1.22)</td>
</tr>
<tr>
<td>CV death</td>
<td>16/1632 0.74</td>
<td>13/1213 0.85</td>
<td>0.79 (0.37, 1.69)</td>
</tr>
<tr>
<td>MI</td>
<td>18/1677 0.82</td>
<td>22/1246 1.39</td>
<td>0.58 (0.30, 1.11)</td>
</tr>
<tr>
<td>Stroke</td>
<td>18/1388 0.95</td>
<td>14/1130 0.96</td>
<td>1.01 (0.49, 2.07)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>10/1486 0.51</td>
<td>14/1132 0.94</td>
<td>0.37 (0.16, 0.89)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: EMPA</th>
<th>Patients with Events</th>
<th>Favors</th>
<th>Hazard Ratio vs Control (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVENT rate/100 p-y</td>
<td>EMPA → Control</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>490 EMPA=4687</td>
<td>282 Placebo=2333</td>
<td>0.86 (0.74, 0.99)</td>
</tr>
<tr>
<td>CV death</td>
<td>172 EMPA=137</td>
<td>137 Placebo=137</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
<tr>
<td>MI</td>
<td>213 EMPA=121</td>
<td>121 Placebo=121</td>
<td>0.87 (0.70, 1.09)</td>
</tr>
<tr>
<td>Stroke</td>
<td>150 EMPA=60</td>
<td>60 Placebo=60</td>
<td>1.24 (0.92, 1.67)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>126 EMPA=95</td>
<td>95 Placebo=95</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
</tbody>
</table>

2. Zinman, B et al. NEJM 2015;373:2117-28
Dapagliflozin: sicurezza CV

Dapagliflozin: Ospedalizzazione per Scompenso Cardiaco

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

DECLARE – Dapagliflozin Effects on Cardiovascular Events

**Inclusion Criteria**
- T2DM, ≥40 yrs
- Established CVD or Multiple Risk Factors

**Screening**
- N ~17,150

**Duration is event-driven:**
- 1,390 events
- ~6 years median follow-up ~4.5 yrs

**Primary Endpoint**
- MACE: CV Death, MI, Ischemic Stroke

CVD, cardiovascular disease

Available at: [https://clinicaltrials.gov/ct2/show/NCT01730534](https://clinicaltrials.gov/ct2/show/NCT01730534)
La funzionalità renale (eGFR) rimane stabile a 2 anni

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>50</th>
<th>63</th>
<th>76</th>
<th>89</th>
<th>102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, n:</td>
<td>1955</td>
<td>873</td>
<td>1671</td>
<td>1558</td>
<td>605</td>
<td>585</td>
<td>551</td>
<td>521</td>
</tr>
<tr>
<td>DAPA 10 mg, n:</td>
<td>2026</td>
<td>961</td>
<td>1777</td>
<td>1663</td>
<td>712</td>
<td>692</td>
<td>656</td>
<td>627</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; DAPA=dapagliflozin.
Dapagliflozin should not be used in patients with moderate to severe renal impairment (eGFR persistently <60 mL/min/1.73 m² by MDRD or CrCl persistently <60 mL/min by Cockcroft-Gault.
Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers

H. J. L. Heerspink1, E. Johnsson2, I. Gause-Nilsson3, V. A. Cain3 & C. D. Sjöström2

1University of Bergen, Bergen, Norway, 2Karolinska Institutet, Stockholm, Sweden, 3Proteos AB, Malmö, Sweden

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) −43.4% to −13.2%]. The reduction in albuminuria was also present after adjusting for age, sex and changes in HbA1c, SBP, body weight and eGFR: −33.5% (90% CI −37.8% to −30.3%). 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 on 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 glycemic 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
Dapagliflozin: efficacia su UACR in diabetici ipertesi in trattamento con ACEi/ARB

- Dapagliflozin unspecified effect (-17%)
- HbA1c mediated (-9%)
- SBP mediated (-6%)
- BW mediated (-3%)
- eGFR mediated (-1%)

**Change in UACR (%) at week 12**

**Change from baseline in UACR, % (95% CI)**

- PBO + ACEi/ARB
- DAPA 10 mg + ACEi/ARB

<table>
<thead>
<tr>
<th>Sample size per time point, n</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12 Follow-up (Week 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + ACEi/ARB</td>
<td>185</td>
<td>182</td>
<td>172</td>
<td>163</td>
</tr>
<tr>
<td>DAPA 10 mg + ACEi/ARB</td>
<td>166</td>
<td>160</td>
<td>154</td>
<td>153</td>
</tr>
</tbody>
</table>

Dapagliflozin rispetto al PBO reduce l'Albuminuría a 2 anni in pazienti diabetic ci con CKD3 e questa riduzione della Albuminuría appare indipendente da modifiche di HbA1c, Pressione arteriosa e eGFR.
Meccanismi di cardio e nefroprotezione con gli SGLT2i

SGLT2 inhibition

Glycosuria
- Negative caloric balance
  - Total body fat mass
    - Epicardial fat
    - Inflammation
    - Fibrosis
  - Cardiac contractility

- HbA1c
  - Inflammation
  - Glucose toxicity

- Uricosuria
  - Plasma uric acid
  - Arterial stiffness
  - Myocardial stretch
  - Ventricular arrhythmias
  - Activation of ACE2 – Ang1/7
  - Intraglomerular hypertension
  - Hyperfiltration

Natriuresis
- Blood pressure
- Plasma volume
- Tubuloglomerular feedback

Cardiac & Renal Protection

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. placebo².

3) Plans for 2 further Phase IIIb outcome trials with dapagliflozin recently announced³, 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 saxagliptin⁴.

GLP-1 or GLP-1R agonists increase insulin sensitivity. This leads to increased insulin secretion, decreased glucagon secretion, increased insulin biosynthesis, increased β-cell survival, and increased β-cell proliferation. In the liver, this results in decreased hepatic glucose production. In adipose tissue, there is increased lipolysis, increased FFA synthesis, and increased glucose uptake. In muscle, there is increased glycogen synthesis and increased glucose oxidation. In the brain, there is decreased appetite and increased satiety, leading to increased energy expenditure. In the heart, there is increased blood pressure, increased heart rate, increased myocardial contractility, and cardioprotection. In the kidney, there is increased natriuresis and aquareasis.
Le incretine hanno assunto un ruolo centrale nella terapia del DM Tipo 2.

- **Incretin therapy, insulin, SFUs, TZDs**
  - **Pancreatic Beta Cells**
    - Insufficient insulin secretion

- **Incretin therapy**
  - **Pancreatic Alpha Cells**
    - Increased glucagon secretion

- **Incretin therapy, TZDs, metformin**
  - **Liver**
    - Increased hepatic glucose production

- **Incretin therapy, insulin, TZDs**
  - **Muscle**
    - Decreased glucose uptake

- **Incretin therapy**
  - **GI Tract**
    - Decreased incretin effect

- **TZDs**
  - **Adipose Tissue**
    - Lipolysis increased

- **SGLT2 inhibitors**
  - **Kidney**
    - Increased glucose reabsorption

---

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

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

- 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.

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


A Department of Gastroenterology and Department of Research, and B Department of Clinical Pharmacology, University Hospital, Basel, and C Central Laboratory, Kantonshospital 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.
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, JURGEN 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 Grosshadern, 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/m²) 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

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

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

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

Susan L. Samson¹ · Alan J. Garber²
<table>
<thead>
<tr>
<th></th>
<th>Emivita</th>
<th>Metabolismo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>2,4 ore</td>
<td>Due volte al dì</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>3 ore</td>
<td>Una volta al dì</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>13 ore</td>
<td>Una volta al dì</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>2 settimane</td>
<td>Una volta alla settimana</td>
</tr>
<tr>
<td>Dulaglutide QW</td>
<td>5 giorni</td>
<td>Una volta alla settimana</td>
</tr>
</tbody>
</table>

1. Lyxumia Riassunto delle caratteristiche del prodotto. Accesso: 14 maggio 2013
2. Fineman et al. Diabetes Obes Metab. 2012;14:675-88
4. BYETTA Riassunto delle caratteristiche del prodotto. Accesso: 14 maggio 2013
5. BYDUREON Riassunto delle caratteristiche del prodotto. Accesso: 14 maggio 2013
Exenatide Once Weekly: Agonista Recettoriale del GLP-1

- ↓ Appetite
- ↓ Glucose production
- ↓ Adipose tissue
- ↑ Glucose uptake and storage
- ↑ Insulin sensitivity
- ↑ Insulin secretion
- ↓ Glucagon secretion
- ↑ Insulin biosynthesis
- ↑ β-cell proliferation
- ↓ β-cell apoptosis

GLP-1

↑ Heart rate
↓ Blood pressure
↑ LV function
↓ Infarct size

Naturesis

↓ Gastric emptying

↓ Inflammation

---

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

<table>
<thead>
<tr>
<th>Agonisti del recettore del GLP-1</th>
<th>Exenatide BID, Lixisenatide QD</th>
<th>Exenatide QW, Liraglutide QD, Albiglutide QW, Dulaglutide QW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effetti</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Livelli di glicemia a digiuno</td>
<td>Riduzione modesta(^{1,2})</td>
<td>Forte riduzione(^{1,2})</td>
</tr>
<tr>
<td>Escursioni glicemiche postprandiali</td>
<td>Forte riduzione(^{2})</td>
<td>Riduzione modesta(^{2})</td>
</tr>
<tr>
<td>Secrezione di insulinina a digiuno</td>
<td>Stimolazione modesta(^{1,2})</td>
<td>Forte stimolazione(^{1,2})</td>
</tr>
<tr>
<td>Secrezione postprandiale di insulinina</td>
<td>Riduzione(^{1,2})</td>
<td>Stimolazione modesta(^{1,2})</td>
</tr>
<tr>
<td>Secrezione di glucagone</td>
<td>Riduzione(^{1,2})</td>
<td>Riduzione(^{1,2})</td>
</tr>
<tr>
<td>Tasso di svuotamento gastrico</td>
<td>Decelerazione(^{1,2})</td>
<td>Modesto(^{1,2})</td>
</tr>
<tr>
<td>Ridotto apporto calorico</td>
<td>Si(^{1})</td>
<td>Si(^{1})</td>
</tr>
<tr>
<td>Riduzione del peso corporeo</td>
<td>1-5 kg(^{1})</td>
<td>2-5 kg(^{1})</td>
</tr>
<tr>
<td>Induzione della nausea</td>
<td>Il 20-50% circa, si attenua lentamente (da settimane a mesi)(^{1})</td>
<td>Il 20-40% circa, si attenua rapidamente (~4-8 settimane)(^{1})</td>
</tr>
</tbody>
</table>

2. Fineman MS et al. Diabet Obes Metab 2012;14:675-88
Exenatide LAR allo steady state vs BID: Profilo Farmacocinetico

Graph showing plasma exenatide concentration (pmol/L) over time of day (hours) and time of injection.

Data are geometric mean + SE; *Bydureon injection, first Byetta injection; †Second Byetta injection.
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 \(^1\).
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].

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.
Exenatide QW: efficacia su HbA1c

Mean Change in HbA1c (%)

Baseline HbA1c (%)
8.5 8.5 8.5 8.5 8.5 8.6 8.5 8.5 8.5 8.3 8.4 8.5 8.3 8.3

Exenatide QW 2mg
Insulin Glargine
Pioglitazone 45 mg
Sitagliptin 100 mg
Metformin 2500 mg
Exenatide BID 10 mcg
Liraglutide 1.8 mg

Background:
Diet and Exercise
MET
MET ± SU
Diet and Exercise, MET, TZD, SU, and Combinations

Duration 4
Duration 5
Duration 6
Duration 1

Exenatide QW: eficacia su Peso Corporeo

Exenatide QW : efficacia su Pressione Arteriosa Sistolica

![Graph showing the effect of different treatments on systolic blood pressure (SBP).](image)

- **Exenatide QW 2mg**
- **Insulin Glargine**
- **Pioglitazone 45 mg**
- **Sitagliptin 100 mg**
- **Metformin 2500 mg**
- **Exenatide BID 10 mcg**
- **Liraglutide 1.8 mg**

**Background:**
- **Diet and Exercise**
- **MET**
- **MET ± SU**
- **Diet and Exercise, MET, TZD, SU, and Combinations**

**Δ SBP (mmHg):**
- Duration 4: -1.3, -1.7, -1.8
- Duration 2: -3.6, -1.6
- Duration 3: 0.2
- Duration 5: -0.6, -2.3, -2.5
- Duration 6: -3.4, -3.5, -2.9
- Duration 1: -1.2

*Insulin Glargine Treat to Target A1c <7.0%*

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

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

-1.6%

- 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

-4.2 kg

- 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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL, LSM (95% CI)</td>
<td>170.0 ± 3.7</td>
<td>-0.3</td>
<td>-0.3</td>
<td>-0.9</td>
<td>-0.3</td>
<td>-0.9</td>
<td>-10.1</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL, LSM (95% CI)</td>
<td>90.7 ± 3.2</td>
<td>-3.7</td>
<td>-2.7</td>
<td>-3.9</td>
<td>-3.7</td>
<td>-3.9</td>
<td>-9.8</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL, LSM (95% CI)</td>
<td>45.3 ± 0.9</td>
<td>-0.8</td>
<td>+1.5</td>
<td>+2.2</td>
<td>+2.0</td>
<td>+3.0</td>
<td>+2.6</td>
</tr>
<tr>
<td>LDL/HDL cholesterol ratio, median (range)</td>
<td>1.95</td>
<td>-0.07</td>
<td>-0.05</td>
<td>-0.19</td>
<td>-0.26</td>
<td>-0.20</td>
<td>-0.22</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (range)</td>
<td>151.0</td>
<td>-15.0</td>
<td>-22.0</td>
<td>-14.0</td>
<td>-9.0</td>
<td>-11.0</td>
<td>-8.0</td>
</tr>
</tbody>
</table>

- 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

Funzionalità beta-cellulare

- 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

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>30-Week assessment (n = 148)</th>
<th>Open-ended assessment (n = 278)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence, %</td>
<td>Annual event rate, events/year</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8.1</td>
<td>0.162</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6.8</td>
<td>0.187</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.2</td>
<td>0.373</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4.7</td>
<td>0.087</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.7</td>
<td>0.124</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.7</td>
<td>0.087</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10.1</td>
<td>0.224</td>
</tr>
<tr>
<td>Nausea</td>
<td>27.0</td>
<td>0.846</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>9.7</td>
<td>0.025</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.8</td>
<td>0.361</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.4</td>
<td>0.062</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2.7</td>
<td>0.050</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1.4</td>
<td>0.025</td>
</tr>
<tr>
<td>Cough</td>
<td>3.4</td>
<td>0.062</td>
</tr>
<tr>
<td>Gastroenteritis, viral</td>
<td>8.1</td>
<td>0.149</td>
</tr>
<tr>
<td>Constipation</td>
<td>10.1</td>
<td>0.199</td>
</tr>
<tr>
<td>Injection-site pruritus</td>
<td>18.2</td>
<td>0.510</td>
</tr>
</tbody>
</table>

- 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

- 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: Utilizzo 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

- 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

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;

Δ BNP (%)
Baseline: 9.7 11.4 10.8 pg/mL
-23%* 33%* P < 0.05

Δ ACR (%)
Baseline: 14.4 11.8 13.0 mg/g creatinine
-16%* 7% -4% P < 0.05

Δ hs-CRP (%)
Baseline: 2.6 2.5 2.3 mg/L
-24%* -14%* -33%* P < 0.05

Exenatide QW, N = 160
Sitagliptin, N = 166
Pioglitazone, N = 165

Exenatide Reduces Urinary Transforming Growth Factor-β₁ and Type IV Collagen Excretion in Patients with Type 2 Diabetes and Microalbuminuria

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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-β1 (TGF-β1) 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 A1c, systolic blood pressure, diastolic blood pressure, 24-hour urinary albumin, urinary TGF-β1 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-β1 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-β1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria, which may be partly contributory to its directly renoprotective role.
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
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

**SGLT2i**
- Kidney
  - Indirect pancreatic effects
  - $\uparrow$ $\beta$-cell sensitivity
- Glucosuria
- Weight loss
- $\downarrow$ Glucotoxicity
- $\downarrow$ Hyperglycaemia (+ pleiotropic effects)

**DPP-4i**
- Pancreas
  - Dual pancreatic effects
  - $\uparrow$ Insulin secretion
  - $\downarrow$ Glucagon
- Incretin effect
  - $\uparrow$ GLP-1
  - $\uparrow$ GIP
- Weight neutrality

Sheen A.J. EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, Jul 2016
Grazie per l’attenzione!