Combination Therapy

Objectives

- **Fixed Dose Combination (FDC) Therapy**
- **Guidelines: initial combination therapy recommendations**
- **Initial Combination of Empagliflozin and Metformin**
- **Combination of Empagliflozin and Linagliptin**
- **Combination of Linagliptin and Metformin**

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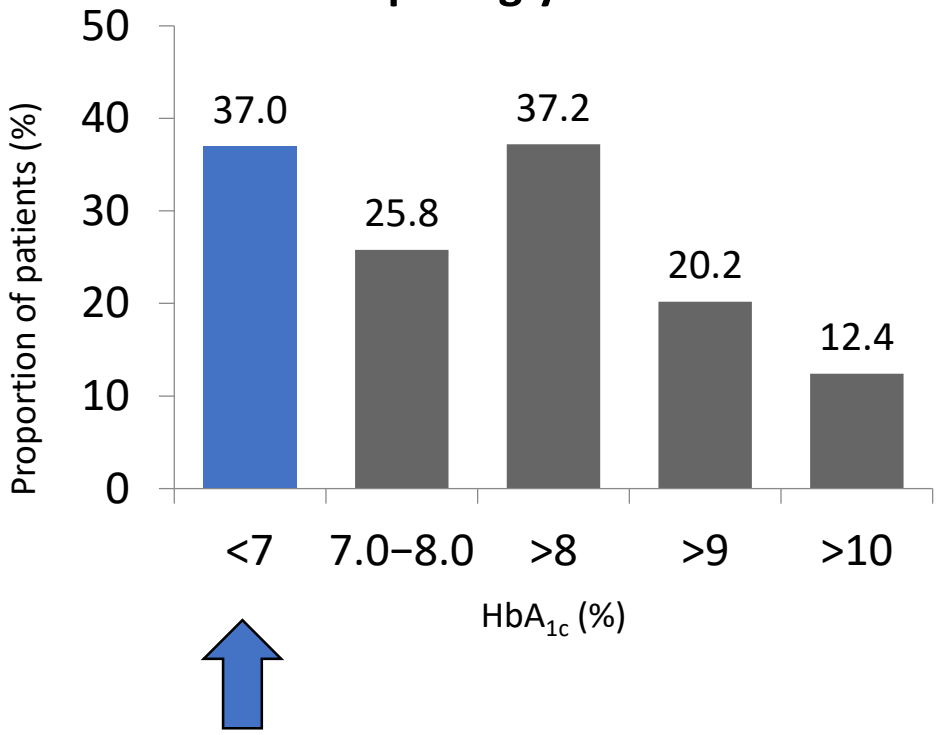
Fixed Dose Combination (FDC) Therapy

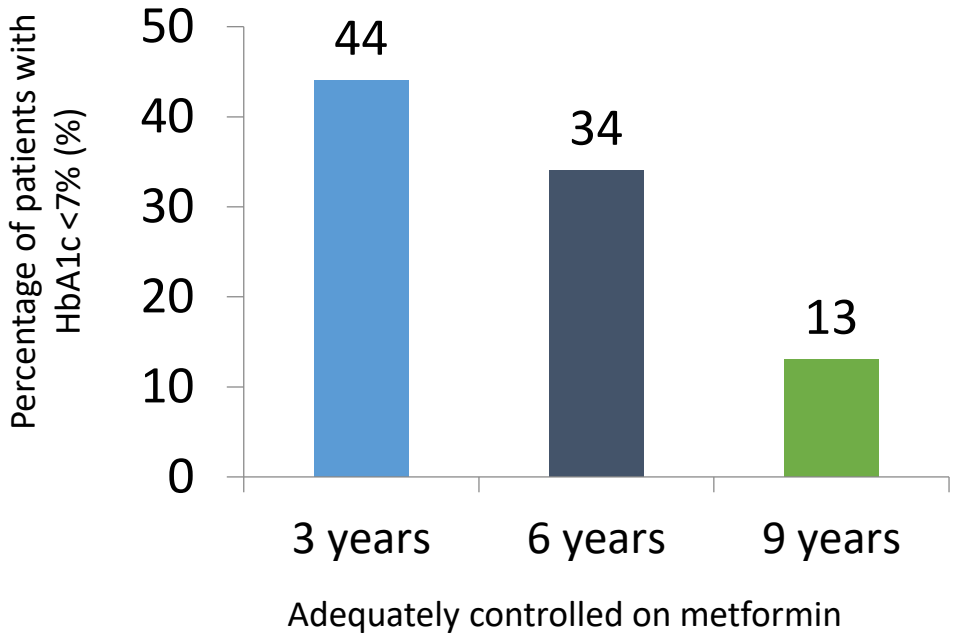
Maintaining glycemic targets can be difficult to achieve

A significant number of patients with T2D have poor glycemic control [1]



Target HbA_{1c} 6.5–7%*

Glycemic control tends to decline over time with monotherapy [2]



**Glycemic targets should be individualised [3,4]*

1. JAMA 2004; 291:335; 2. JAMA 1999; 281:2005; 3. Diab Vasc Dis Res 2009; 6:283; 4. Diabetes Care 2015; 38:140

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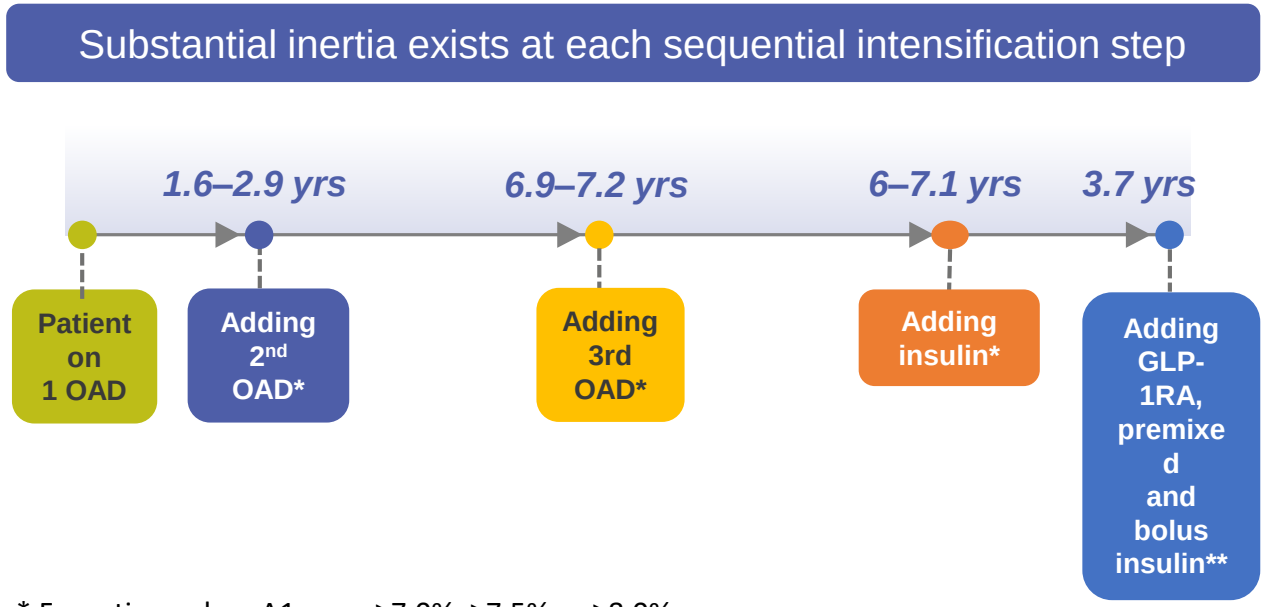
The sequential treatment approach is compounded by substantial inertia to timely intensification of therapy [1,2]



* From time when A1c was ≥7.0%, ≥7.5% or ≥8.0%;
** From time when A1c was ≥7.5%

1. Diabetes Care 2013; 36:3411–7; 2. Diabetes Obes Metab 2016; 18:401–9

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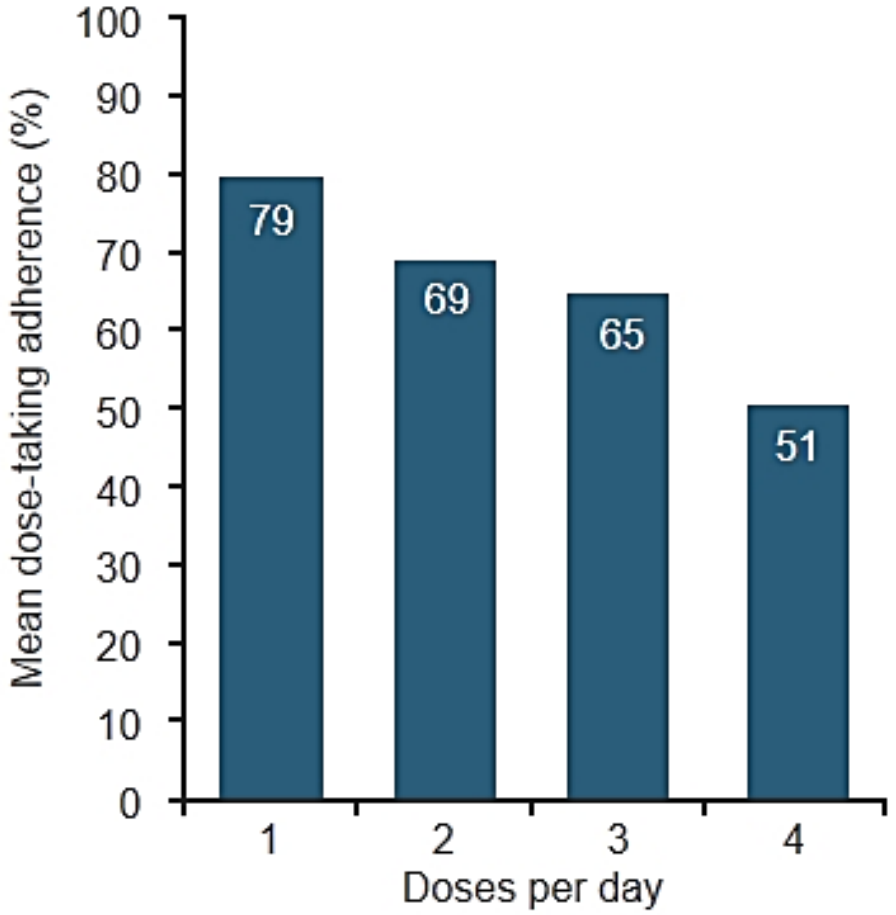
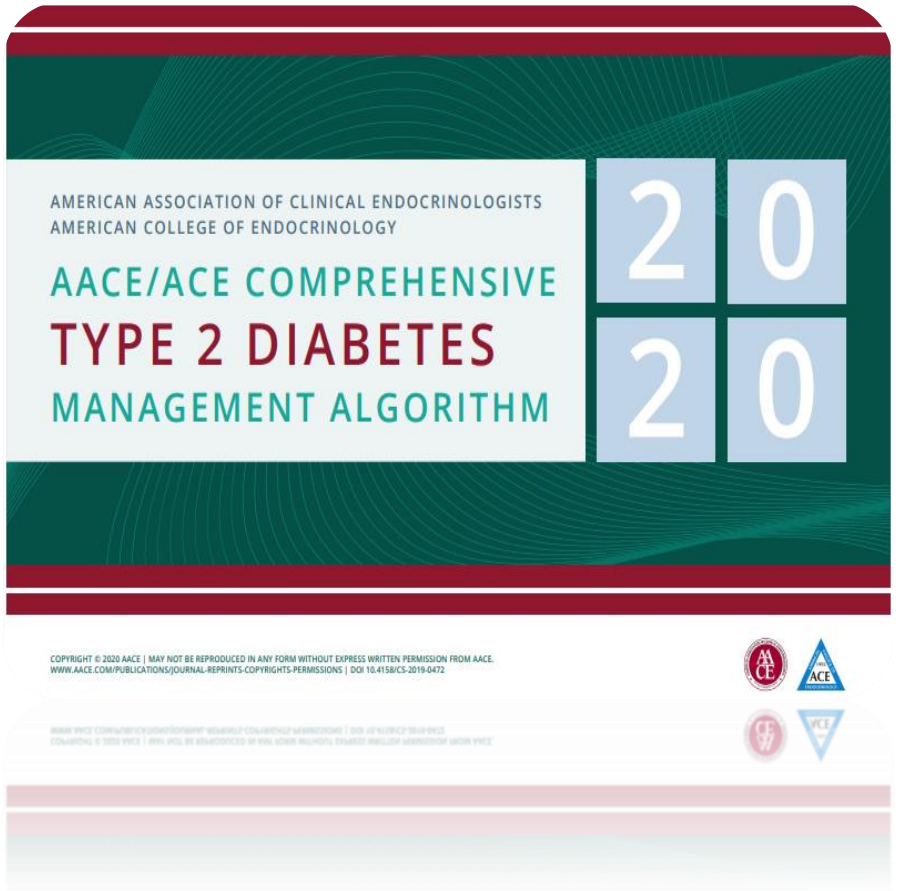
Prescribed Number of Doses/Day Is Inversely Associated With Medication Adherence Across All Conditions[1]

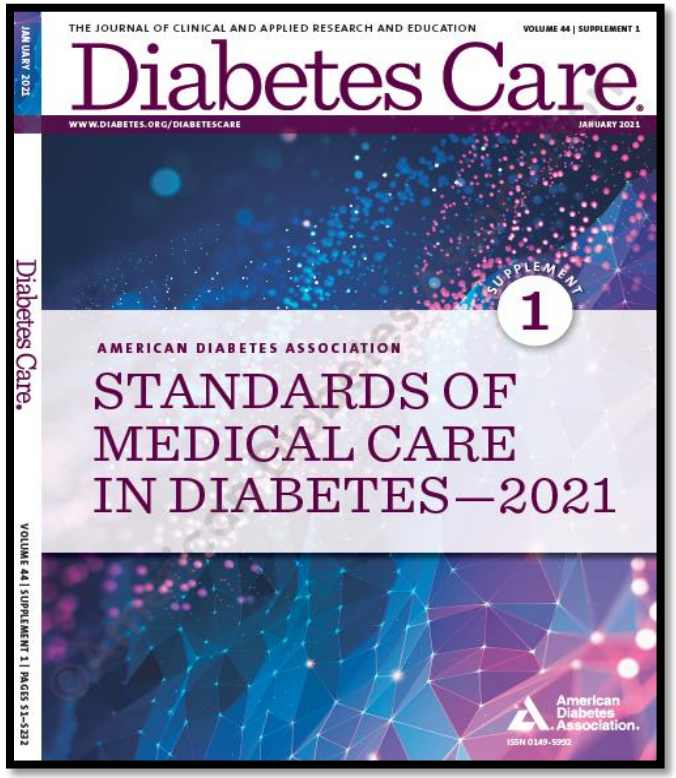


Dose-taking: taking the prescribed number of pills each day.

1- Clin Ther. 2001;23(8):1296-310.

Guidelines: initial combination therapy recommendations





If A1C values are ≥1.5% above target [2]

If A1C values are ≥ 7.5-9 % [1]

If A1C values are ≥1.5-2% above target [3]

1. Endocr Pract 2020;26 (No. 1), 2. Can J Diabetes 2018; 42, S88–S103, 3. Diabetes Care 43, Supplement 1, January 2020

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Advantages of Fixed dose combination

- Improving patient adherence and compliance by reducing polypharmacy. [1,2]
- Improving quality of life and tolerability. [1]
- Improving Lower overall costs. [3]
- Synergistic effect. [4]
- Lower doses of different components. [4]

1. Adv Ther 2012; 29:993-1004; 2. The American Journal of Medicine 2007; 120, 713-719; 3. Diabetes Obes Metab. 2013;15(4): 291–300;
4. Archives of Pharmacal Research 2016; 39(6), 731–746.

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Initial Combination of Empagliflozin and Metformin

Initial Combination of Empagliflozin and Metformin in Patients With Type 2 Diabetes

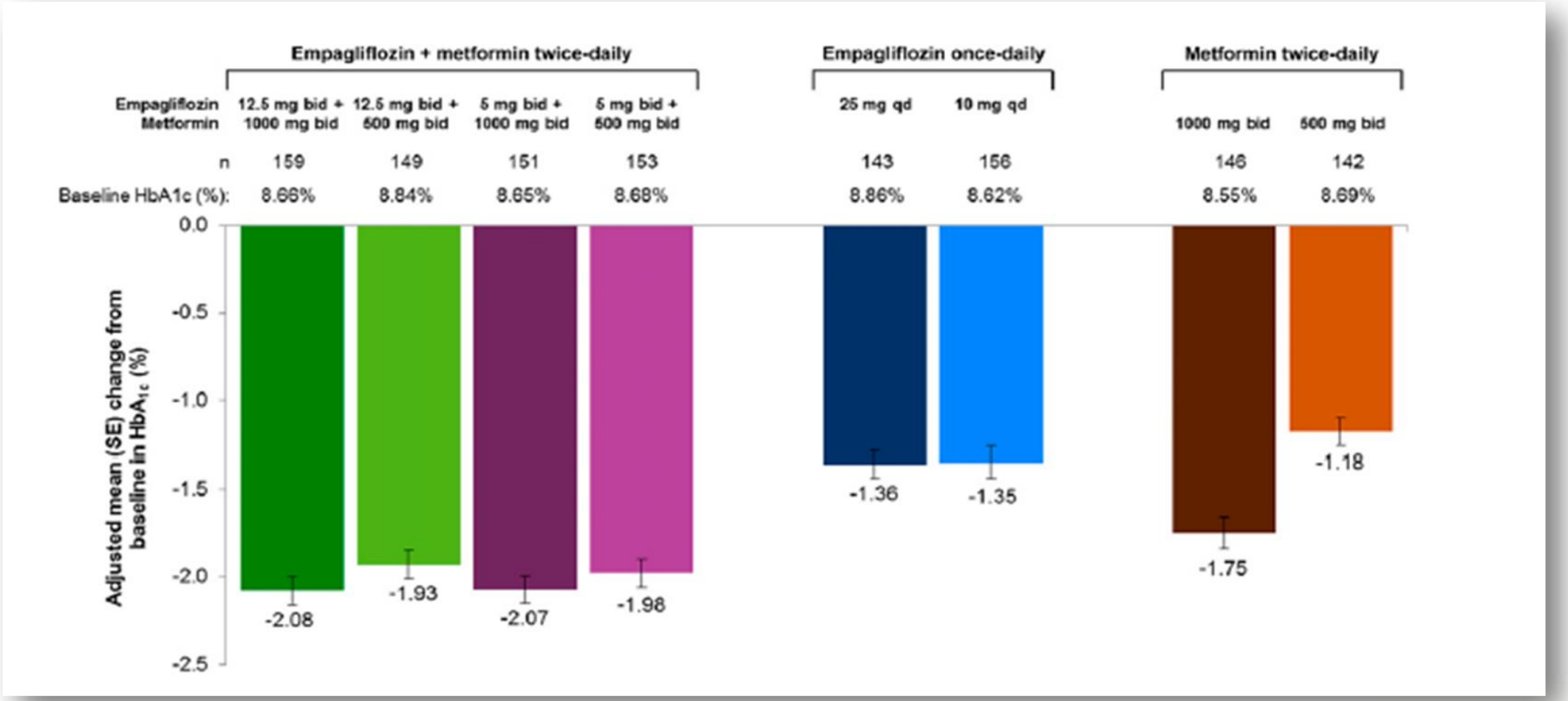
Samy Hadjadj,[1] Julio Rosenstock,[2] Thomas Meinicke,[3] Hans J. Woerle,[4] and Uli C. Broedl[4]

Diabetes Care 2016;39:1718–1728 | DOI: 10.2337/dc16-0522

OBJECTIVE:

This study compared the efficacy and safety of initial combinations of empagliflozin + metformin with empagliflozin and metformin monotherapy in patients with type 2 diabetes

Change from Baseline in HbA1c[1]



1. Diabetes Care. 2016 1; 39(10):1718-28

Combination of Empagliflozin and Linagliptin

Diabetes Care

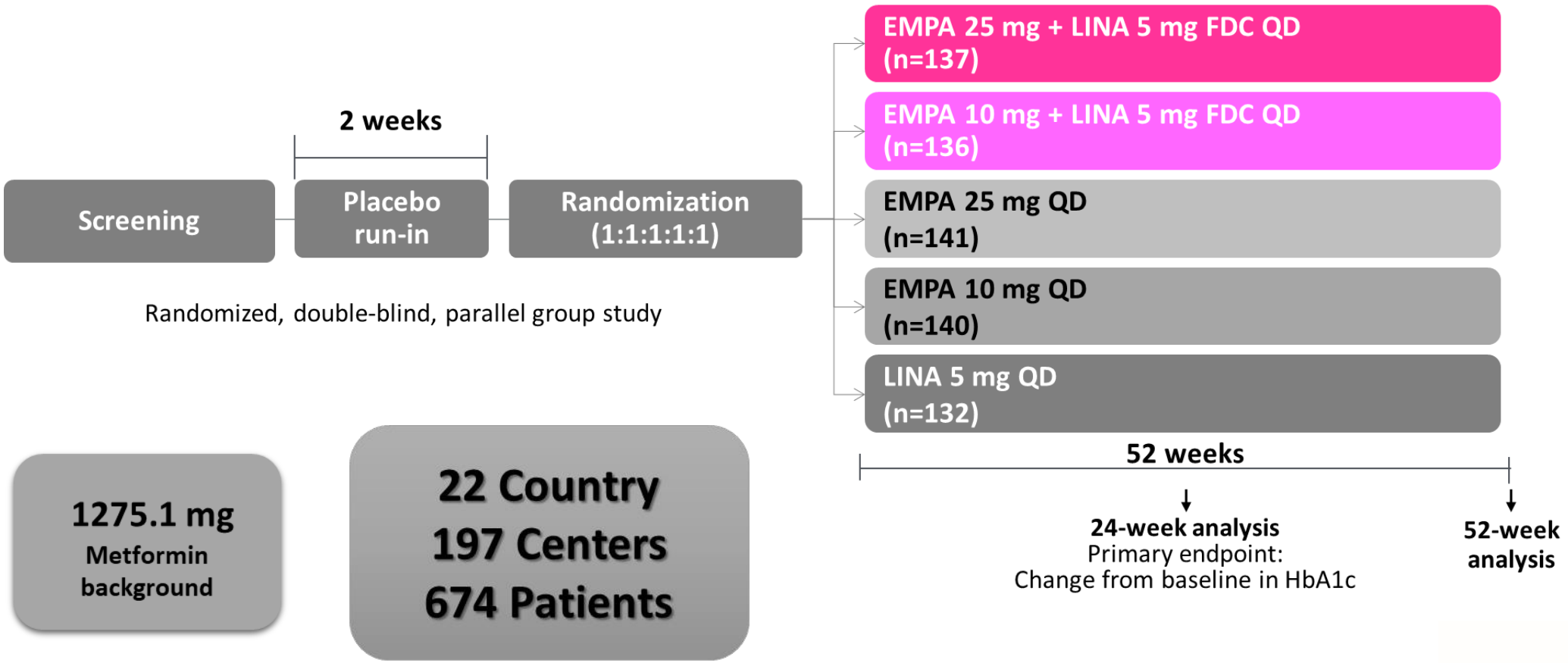
Combination of Empagliflozin and Linagliptin as Second-Line Therapy in Subjects With Type 2 Diabetes Inadequately Controlled on Metformin

Ralph A. DeFronzo,[1] Andrew Lewin,[2] Sanjay Patel,[3] Dacheng Liu,[4] Renee Kaste,[4] Hans J. Woerle,[5] and Uli C. Broedl[5]

DOI: 10.2337/dc14-2364

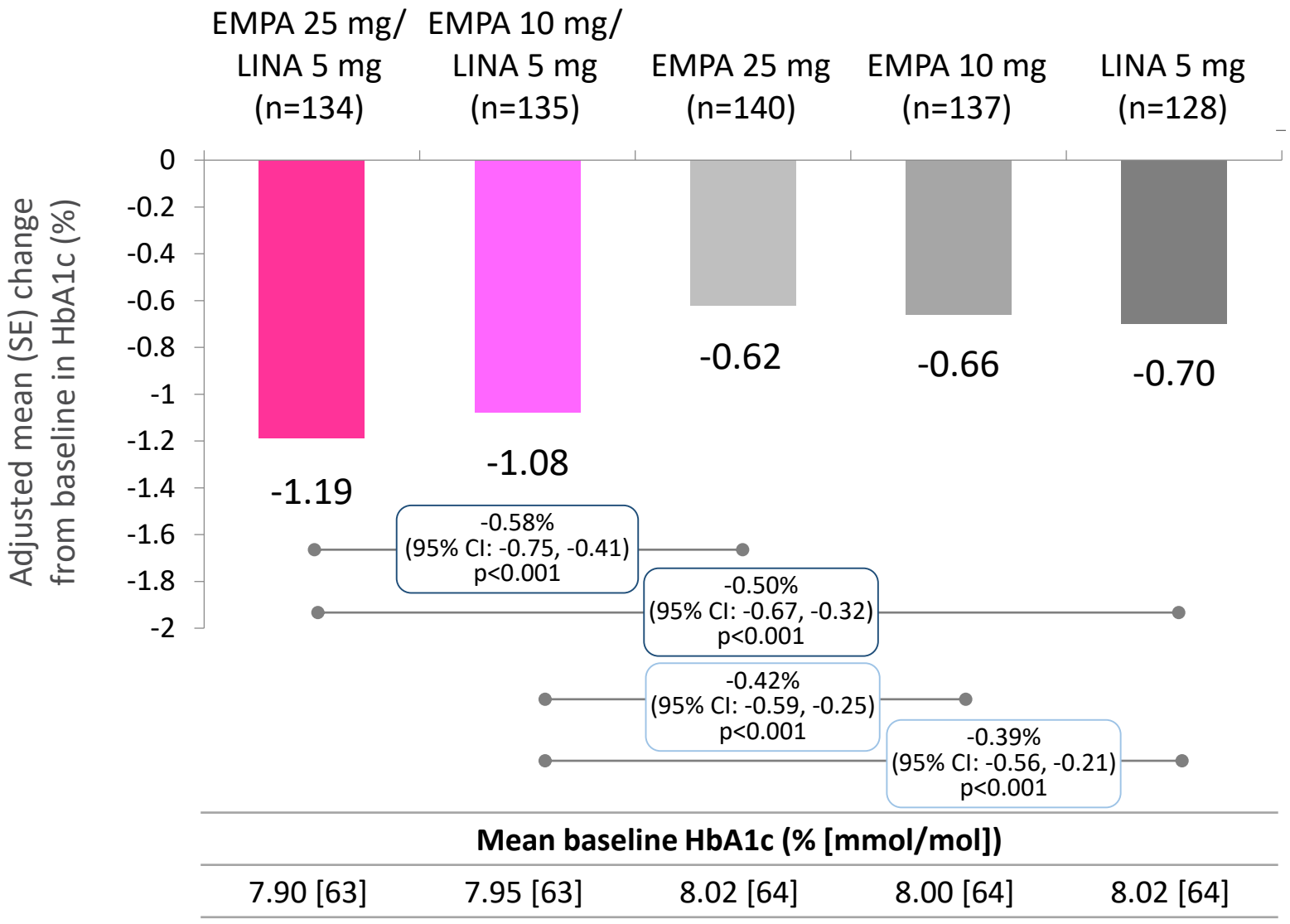
1. DeFronzo et al. (2015). Diabetes Care ;38:384

Study Design



1. DeFronzo et al. (2015). Diabetes Care ;38:384

Change from Baseline in HbA1c at Week 24[1]



1. DeFronzo et al. (2015). Diabetes Care ;38:384

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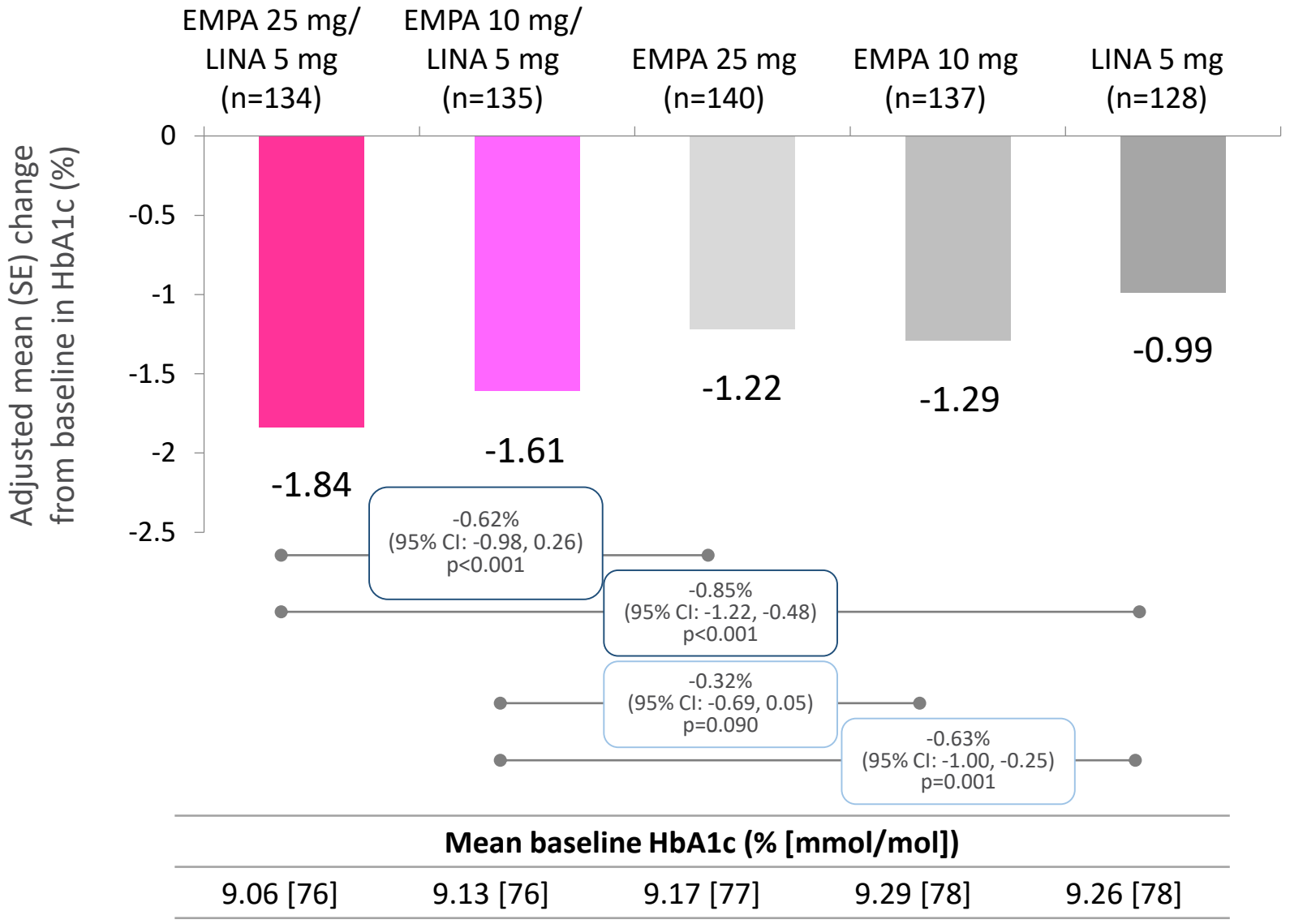
Change in HbA_{1c} at Week 24 in Patients with HbA_{1c} ≥8.5%[1]



1. DeFronzo et al. (2015). Diabetes Care ;38:384

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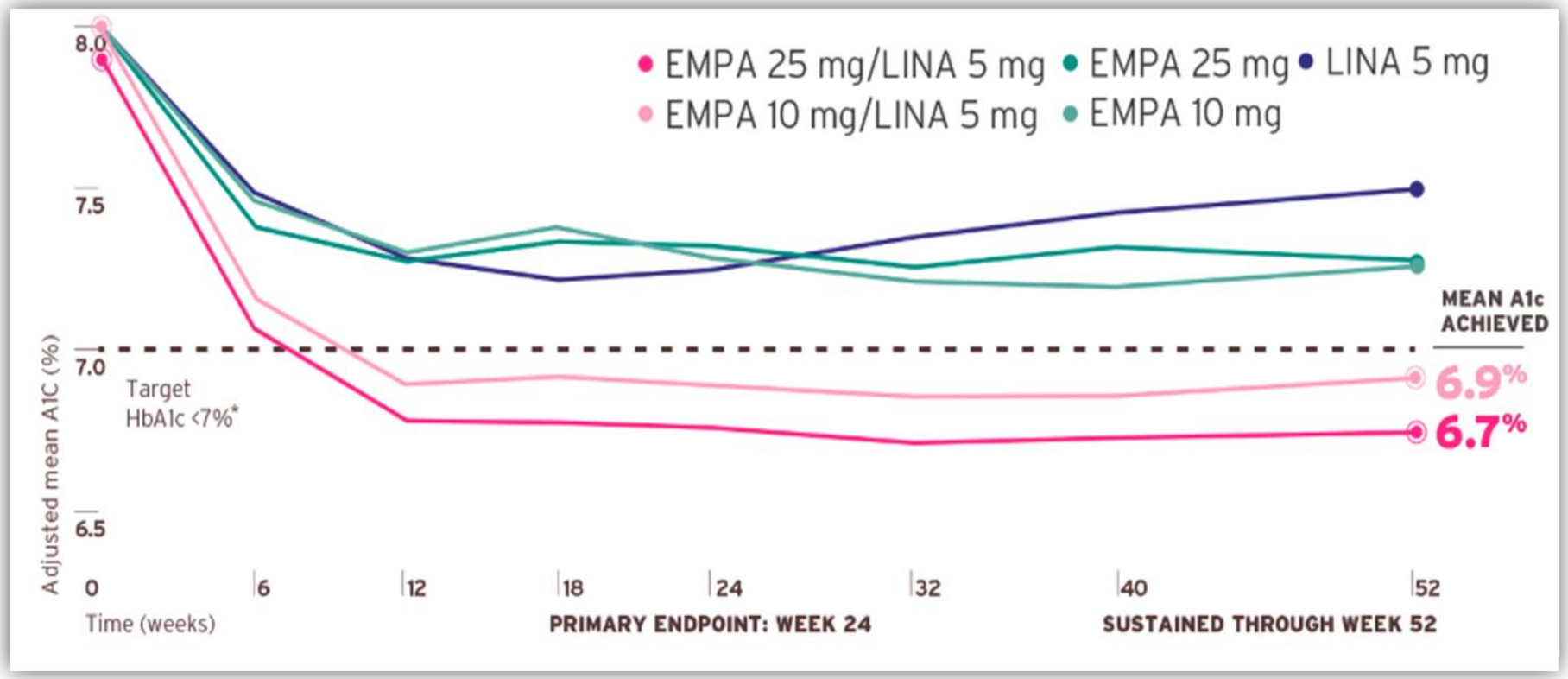
Combination of Empagliflozin+Linagliptin Demonstrates Early and Durable Achievement of Goal[1]



* ADA recommends an A1C target of <7%. Individual goal of patient should be determined by their physician[2].
Change from baseline vs individual components, p<0.0001.[1]

1. DeFronzo et al. (2015). Diabetes Care ;38:384 2. ADA Standards of Medical Care 2018

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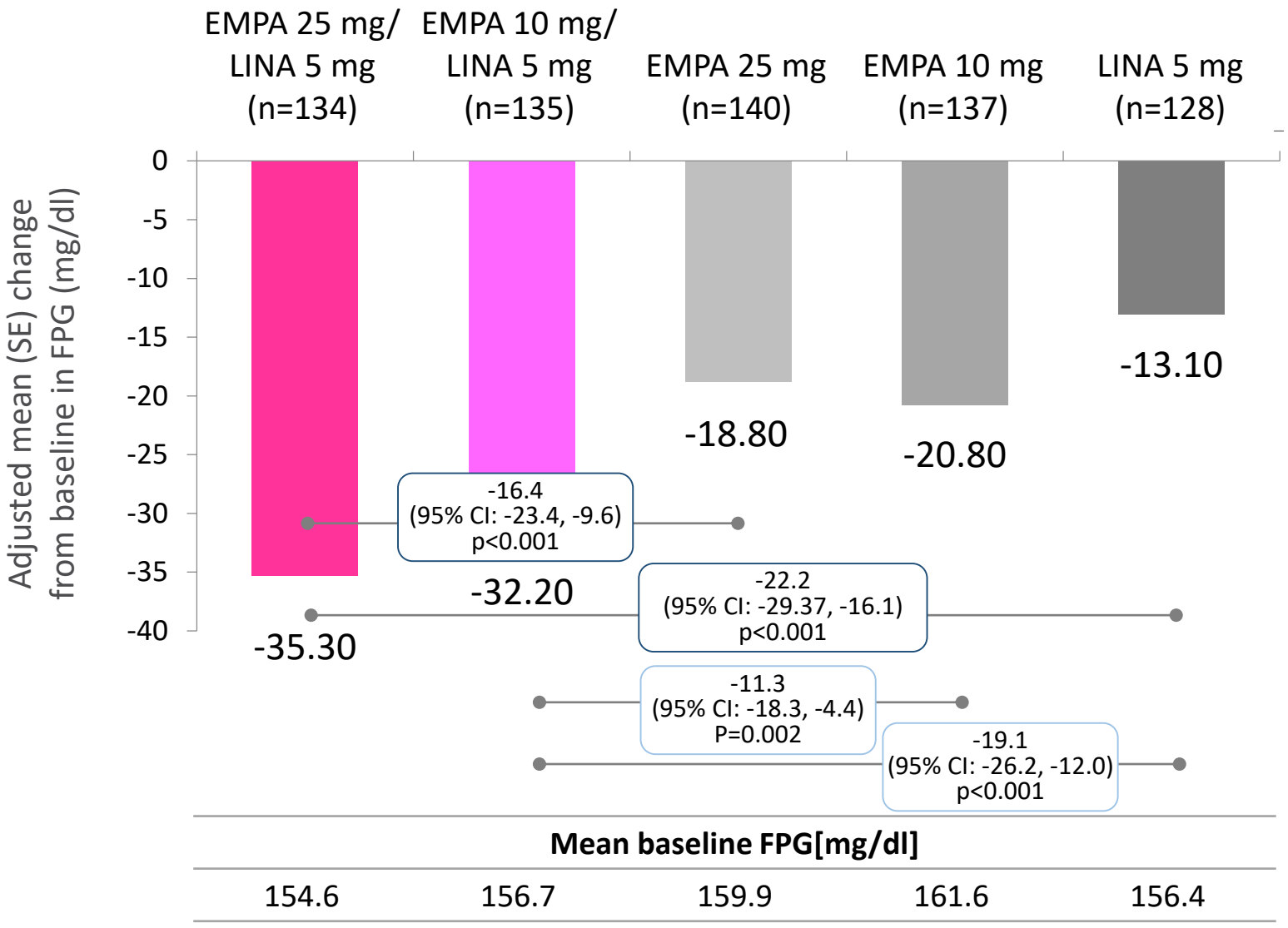
Change from Baseline in FPG at Week 24[1]



1. DeFronzo et al. (2015). Diabetes Care ;38:384

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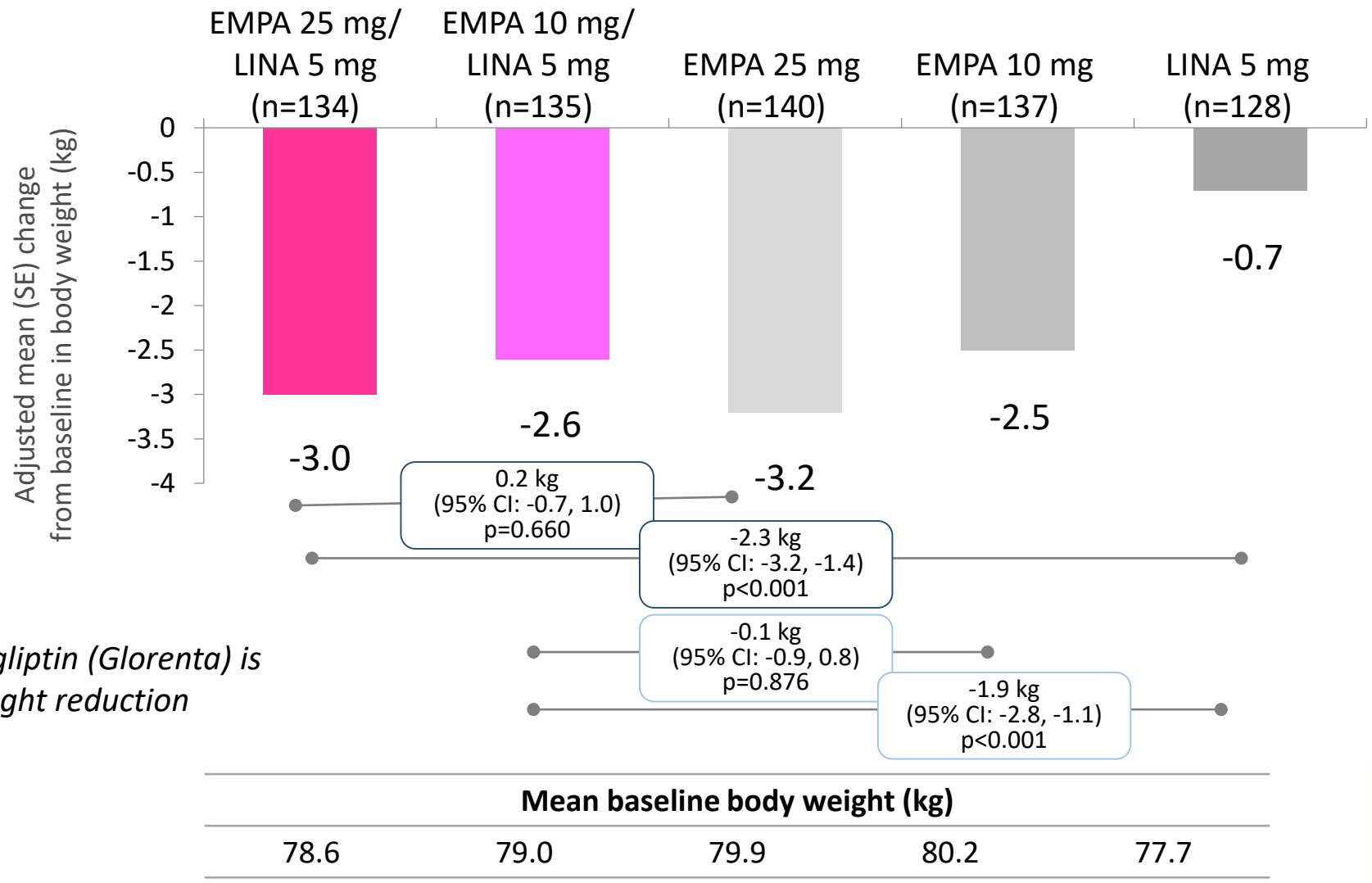
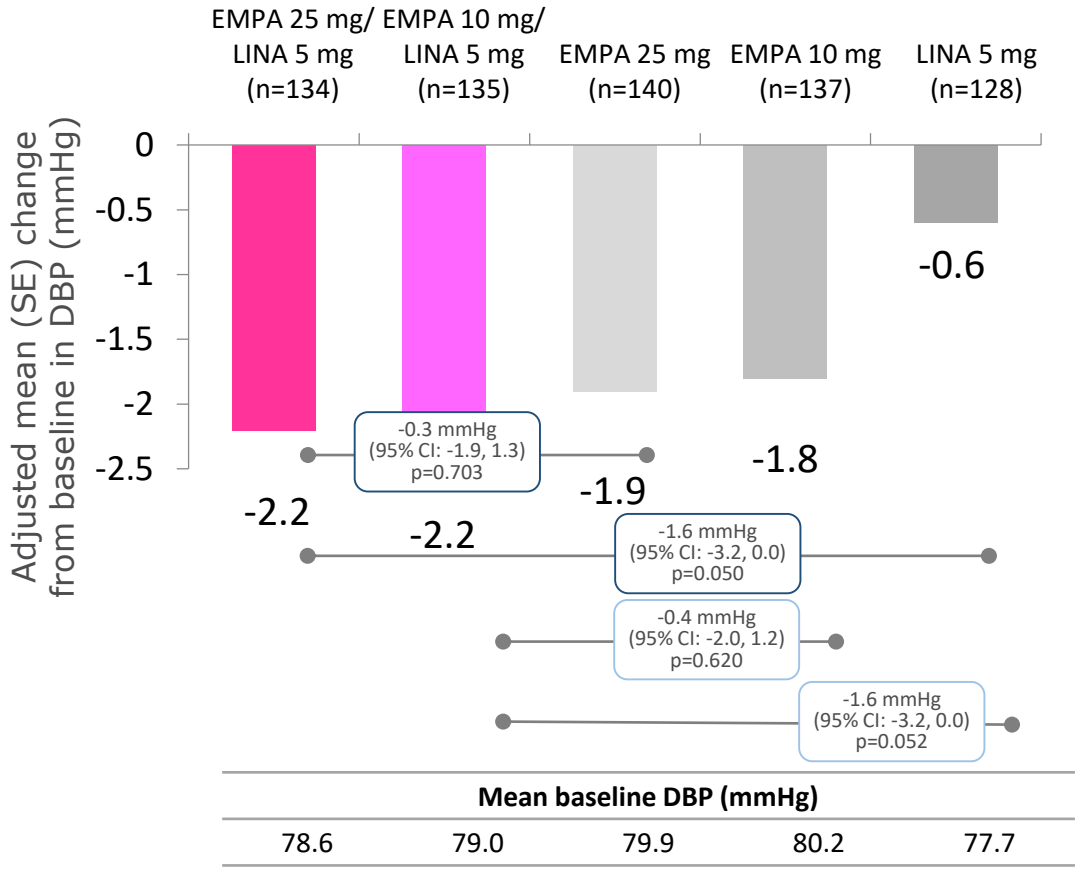
Change from baseline in body weight at Week 24[1]

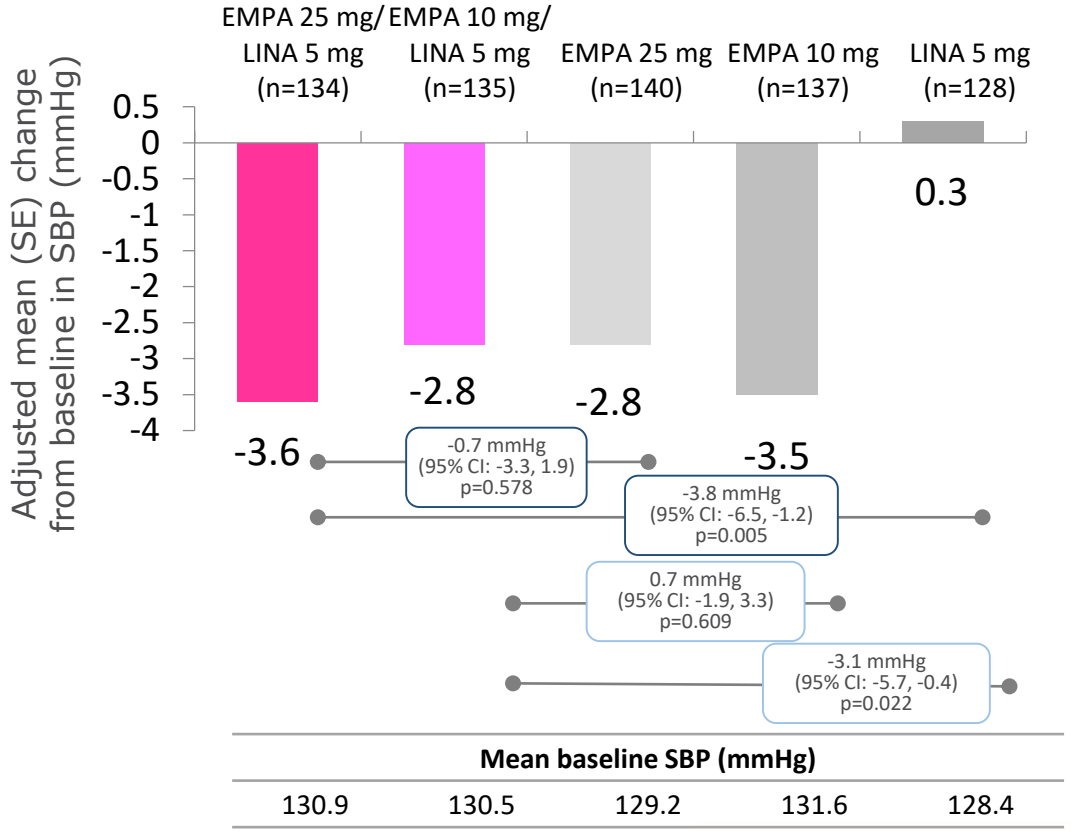


❖ *Empagliflozin + Linagliptin (Glorenta) is not indicated for weight reduction*

1. DeFronzo et al. (2015). Diabetes Care ;38:384

Change from baseline in BP (mmHg) at Week 52[1]





1. DeFronzo et al. (2015). Diabetes Care ;38:384

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Conclusion

Glorenta as the combination of Empagliflozin & Linagliptin with their complementary mechanisms of action:

- Empagliflozin, the only OAD indicated to reduce cardiovasular death in T2D among ASCVD patients.
- Linagliptin, which is proven CV safe among patients with CV risks and renal disease

- Provides a powerful HbA1c reduction, effective glycemic control and weight loss compared to the individual components, with a low risk of hypoglycemia

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Dosage and Administration (Once Daily Tablet)[1]

- Recommended starting dose: 10/5mg (10mg Empagliflozin/ 5mg Linagliptin).
- Do not initiate GLORENTA if eGFR is below 45 mL/min/1.73 m².
- Discontinue GLORENTA if eGFR falls persistently below 45 mL/min/1.73 m²

1. GLYXAMBI® (empagliflozin and linagliptin) tablets label FDA 2018

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Limitation of Use [1]

Not recommended for:

- Patients with type 1 diabetes
- Patients with history of pancreatitis
- The treatment of diabetic ketoacidosis

1. GLYXAMBI® (empagliflozin and linagliptin) tablets label FDA 2018

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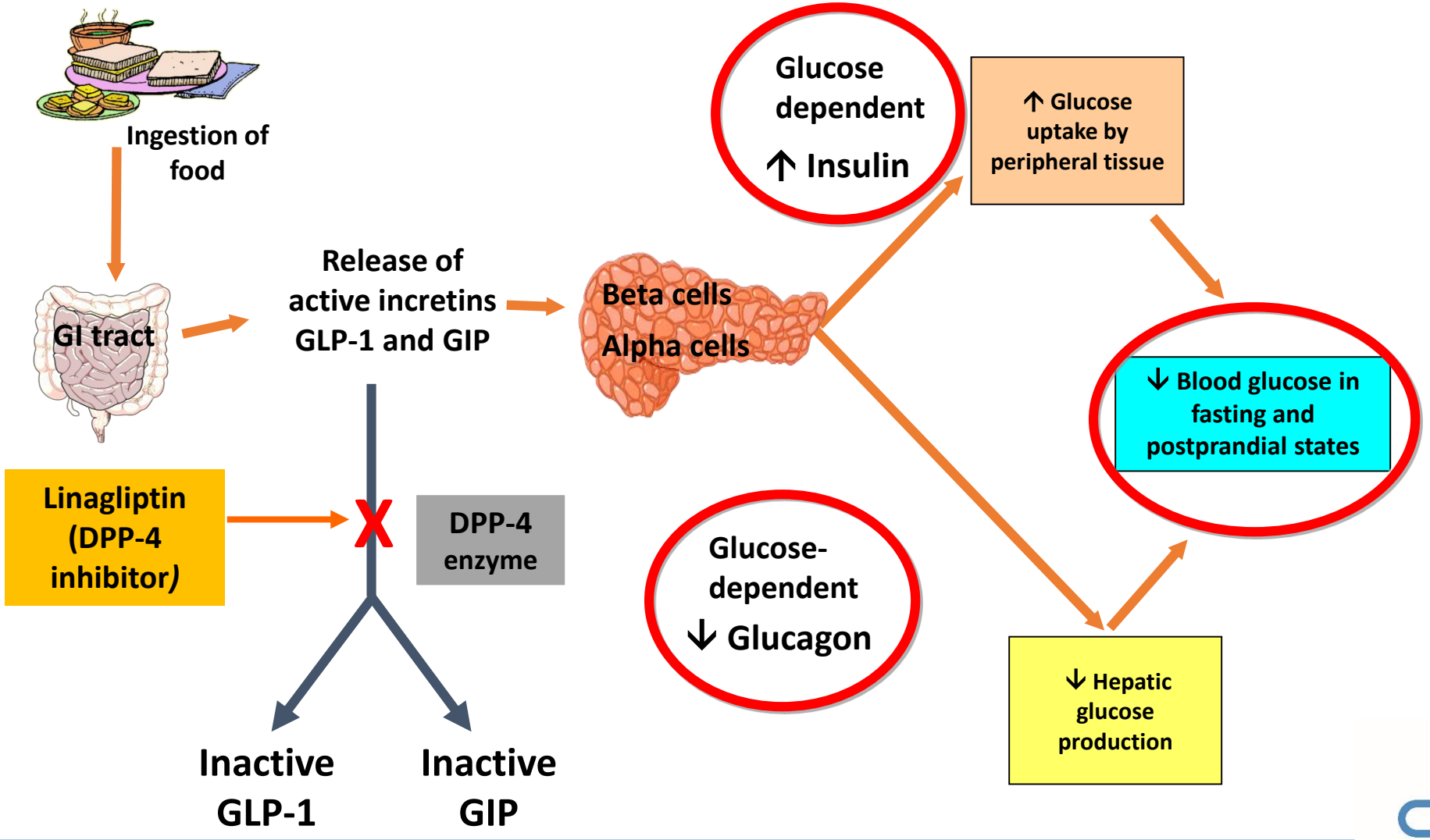
Combination of Linagliptin and Metformin

DPP4-inhibitors Provide an Effective Pharmacological Approach in T2DM[1-4]



GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

1-Endocrinology. 2004 ;145(6):2653-9. 2- Lancet. 2002 ;359(9309):824-30. 3-Curr Diab Rep. 2003;3(5):365-72. 4-Buse JB et al. In Williams Textbook of Endocrinology. 10th ed., 2003:1427–1483.

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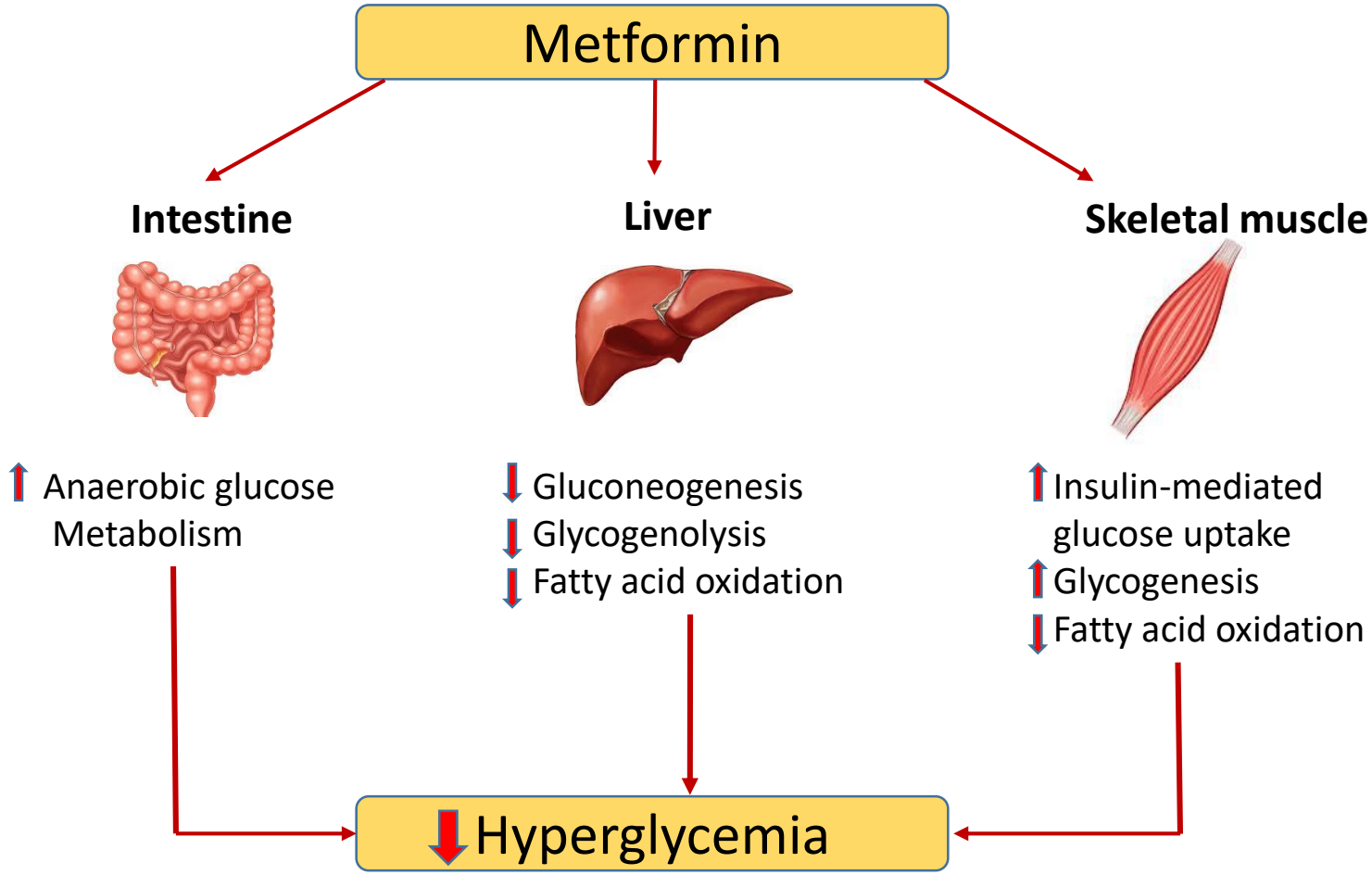
Metformin Targets the Pathophysiology of T2DM[1]



1-Diabetologia. 2017; 60(9): 1577–1585.

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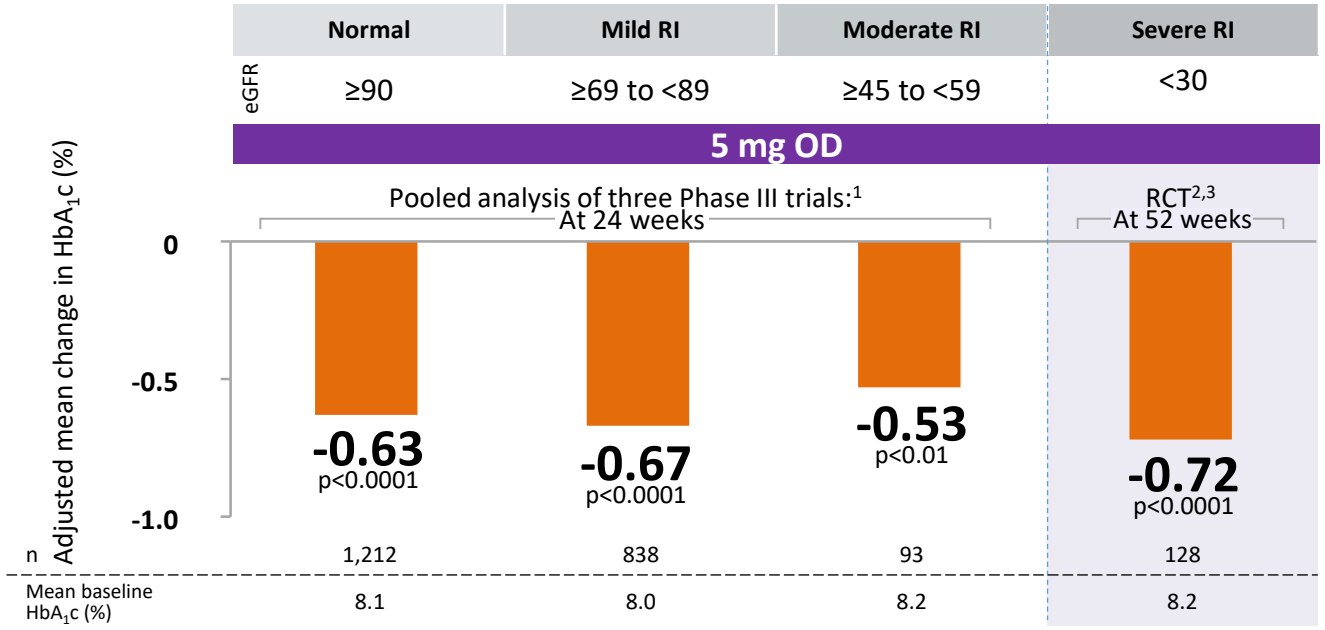
Linagliptin Reduces HbA1c Significantly Regardless of Level of Renal Impairment [1-3]



1- Diabetes Obes Metab 2014;16(6):560-568. 2-Diabetes Care 2013;36:237-244. 3-TRAJENTA® Summary of Product Characteristics. February 2016.

original article

Diabetes, Obesity and Metabolism 14: 565–574, 2012.

Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study

T. Haak[1], T. Meinicke[2], R. Jones[3], S. Weber[4], M. von Eynatten[4] & H.-J. Woerle[4]

[1] Diabetes Center Mergentheim, Bad Mergentheim, Germany
[2] Boehringer Ingelheim, Biberach, Germany
[3] Boehringer Ingelheim, Bracknell, UK
[4] Boehringer Ingelheim, Ingelheim, Germany

ORIGINAL ARTICLE

Aims:

To evaluate the efficacy and safety of initial combination therapy with linagliptin plus metformin versus linagliptin or metformin monotherapy in patients with type 2 diabetes.

1-Diabetes Obes Metab. 2012;14(6):565-74.

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Study Endpoints[1]:

- The primary efficacy endpoint was the mean **change in HbA1c** from baseline to week 24.

- Secondary endpoints assessed at week 24 included mean **change in FPG** from baseline.

1-Diabetes Obes Metab. 2012;14(6):565-74.

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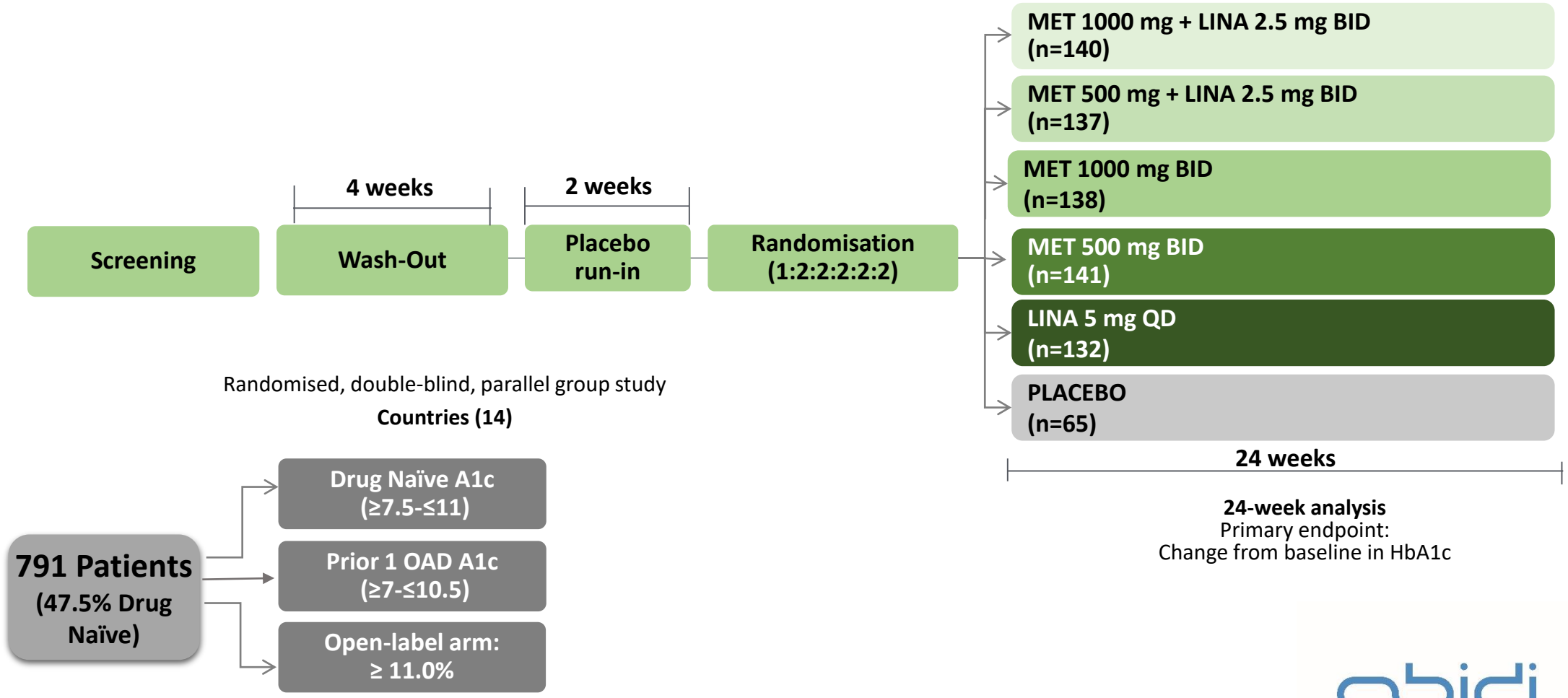
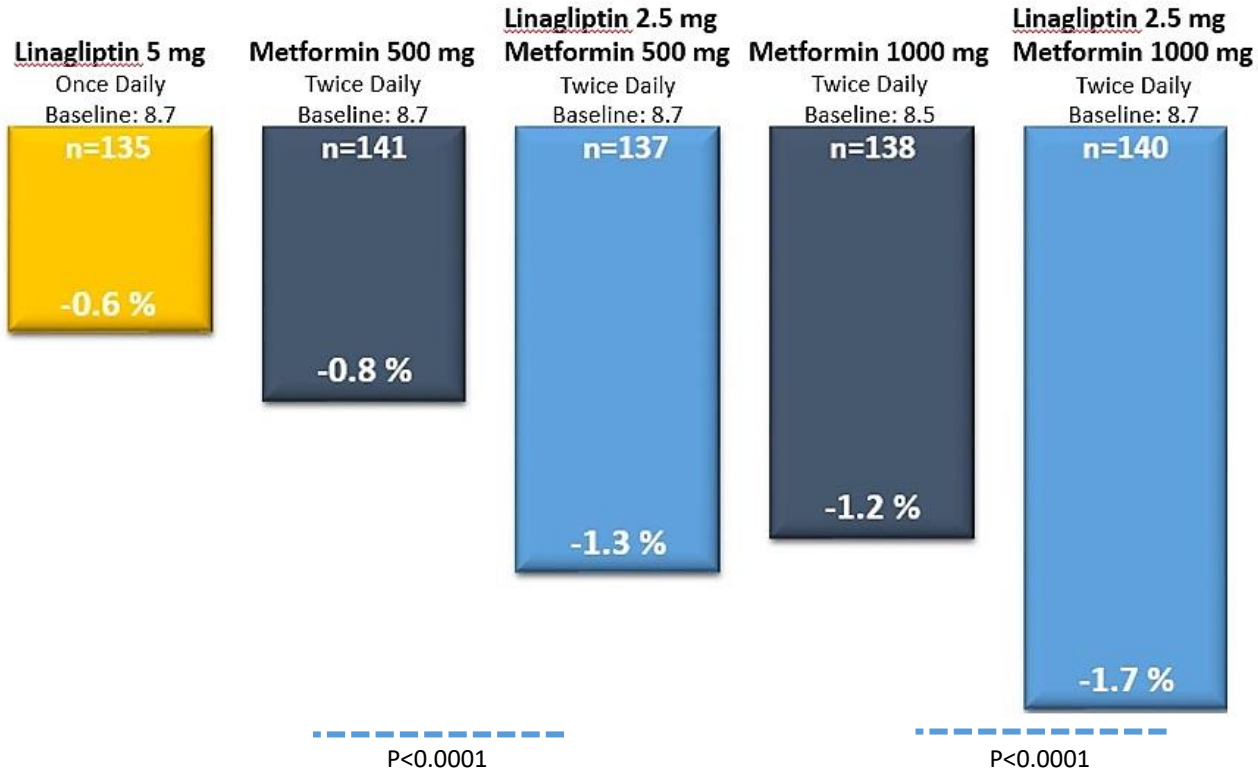
Study Design[1]



1-Diabetes Obes Metab. 2012;14(6):565-74.

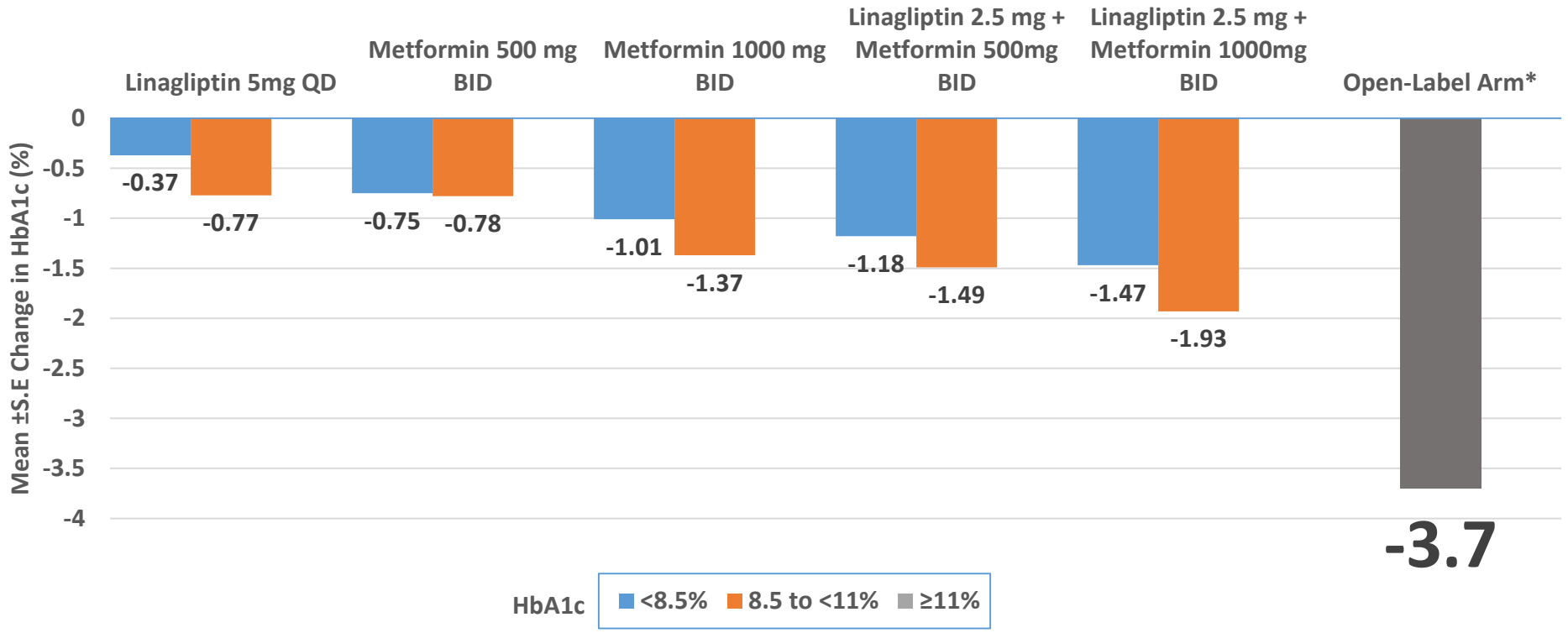
Liroprim 2.5/1000 mg:
1.7 % HbA1c Reduction With Initial Combination Therapy [1]



Placebo-adjusted Mean Difference In A1c at 24 Weeks in Patients Receiving Linagliptin and Metformin, Alone or in Combination (%) [1]

1-Diabetes Obes Metab. 2012;14(6):565-74.

3.7 % HbA1c Reduction With Liroprim 2.5/1000 in Patients With Severe Hyperglycemia[1]

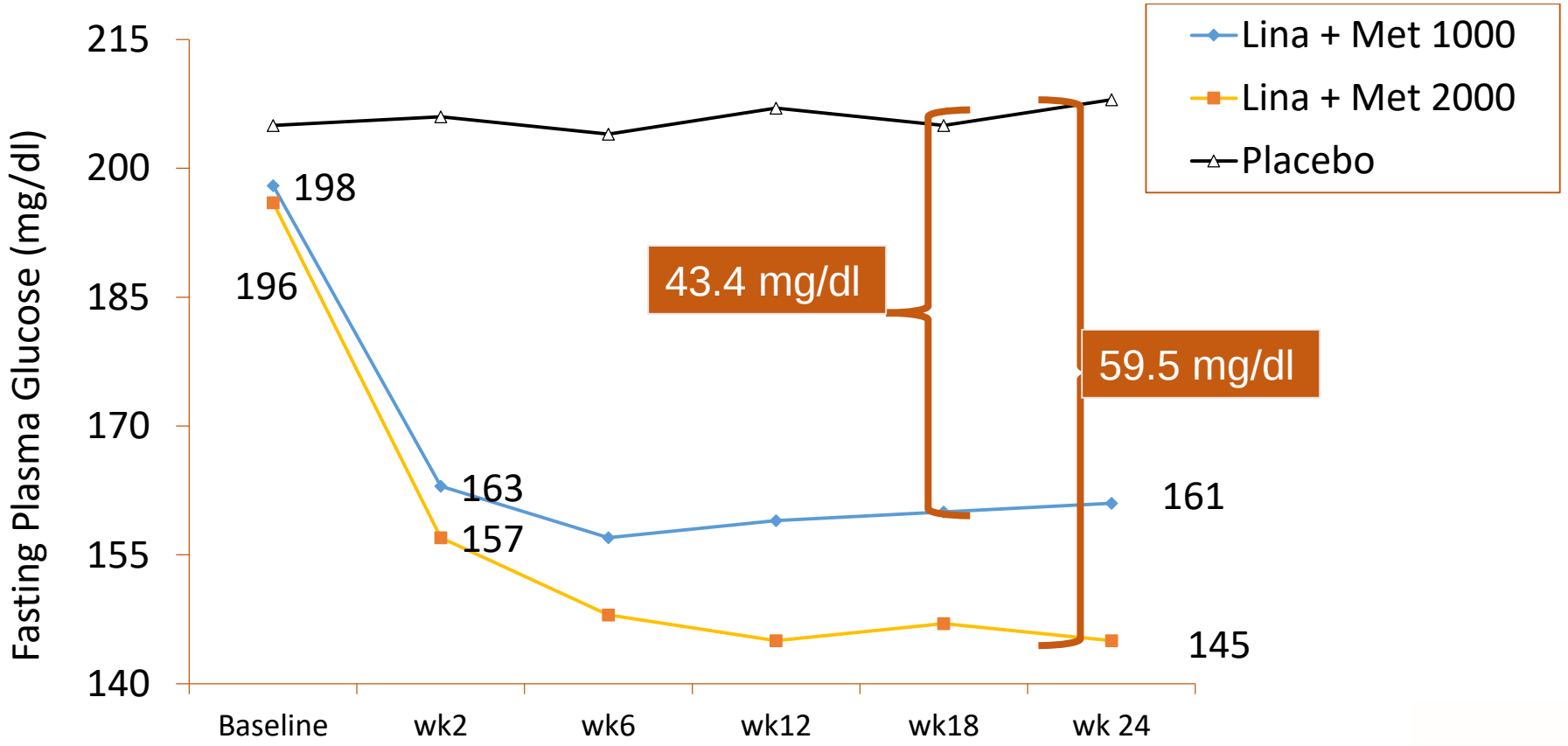


Adjusted Mean Change in Hemoglobin A1c (HbA1c) at Week 24 by HbA1c Category at Baseline in Randomized Patients (Adjusted Placebo Corrected) and Open-label Arm Patients [1]

*Patients in the open-label arm were treated with linagliptin 2.5 mg + metformin 1000 mg bid; 53% were drug naïve and 47% on prior one Oral Anti Diabetic Drugs.

1-Diabetes Obes Metab. 2012;14(6):565-74.

Fasting Plasma Glucose Reduction Starts Early and Is Sustained [1]



1-Diabetes Obes Metab. 2012;14(6):565-74.

Conclusion[1]

Initial combination therapy with **linagliptin** and **metformin** was superior to metformin monotherapy in:

- **Reducing HbA1c**
- **Reducing FPG levels**

with the additional benefits of:

- **No weight gain**
- **Low risk of hypoglycemia**

1-Diabetes Obes Metab. 2012;14(6):565-74.

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Indications and Usages[1]:

LIROPRIM contains **linagliptin**, a dipeptidyl peptidase-4 (DPP-4) inhibitor and **metformin hydrochloride (HCl)**, a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in **adults with type 2 diabetes mellitus**.

1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

Dosage Forms and Strengths[1]:

- 2.5 mg linagliptin/500 mg metformin HCl

- 2.5 mg linagliptin/1000 mg metformin HCl

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1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

Dosage and Administration[1]:

Individualize the starting dose of **LIROPRIM** based on the patient's current regimen.

Give **twice** daily **with meals**, with gradual dose escalation to reduce the gastrointestinal effects due to metformin.

The maximum recommended dose is **2.5 mg linagliptin/1000 mg metformin HCl** twice daily.

1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

Limitations of Use[1]:

- **Type 1 diabetes**
- **Diabetic ketoacidosis**
- In patients with a history of **pancreatitis**

1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

Recommended Dosing in Renal Impairment [1]:

- Prior to initiation, assess renal function with estimated glomerular filtration rate **(eGFR):**

  - Do not use in patients with eGFR **below 30 mL/min/1.73 m^2**
  - Initiation is not recommended in patients with eGFR **between 30-45 mL/min/1.73 m^2**
  - Assess risk/benefit of continuing if eGFR **falls below 45 mL/min/1.73 m^2**
  - Discontinue if eGFR **falls below 30 mL/min/1.73 m^2**

1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

Contraindications[1]:

- Severe renal impairment (**eGFR below 30 mL/min/1.73 m^2**)
- Metabolic acidosis, including **diabetic ketoacidosis**
- **Hypersensitivity** to linagliptin, metformin or any excipients in LIROPRIM

1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

Drug Interactions[1]:

With Metformin	With Linagliptin
• Carbonic Anhydrase Inhibitors • Drugs that Reduce Metformin Clearance • Alcohol	• Inducers of P-glycoprotein and CYP3A4 Enzymes

1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

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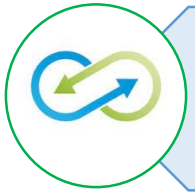
Conclusion[1]:

Linagliptin + Meftormin significantly has superior glycemic control compared to linagliptin and metformin monotherapy, in terms of improving glycosylated hemoglobin, fasting and postprandial glucose levels.

An excellent tolerability profile, without promoting weight gain and hypoglycemic episodes.



Exert synergistic (complementary) pharmacodynamic effects, including an enhanced incretin effect, suppressed hepatic glucose production, and improved peripheral insulin sensitivity.

Address multiple defects of type 2 diabetes pathophysiology (pancreatic islet dysfunction, insulin resistance, increased hepatic glucose output), and most importantly, in the context of a safe, efficacious, flexible, and convenient therapeutic regimen.

1- Adv Ther. 2012;29(12):993-1004.

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Thank you