Glorenta

a Novel Approch for
Diabetes Management

Objective:

- SGLT2 Inhibitor & DPP-4 inhibitor introduction
- SGLT2 Inhibitor & DPP-4 inhibitor mode of action
- Combination therapy
- Efficacy & Safety studies of Glorenta
- FDA label
- Conclusion

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Making a Choice between Agents?

Sometimes **DPP-4 inhibitor** is a Good Choice

Glycemic control[1]
weight neutral[1]
Lower risk of hypoglycemia[1]
Tolerability priority[1]
CV safety[1]

DPP-4 inhibitor

SGLT2 inhibitor

1. Capuano A, et al. Drug Design Dev Ther 2013;7:989-1001.

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Sometimes **SGLT2 inhibitor** is a Good Choice

Efficient HbA1c reduction[1]

Weight loss priority[1]

Reduction in BP[1]

CV protection effect[1]

Renal protection effect[1]

DPP-4 inhibitor

SGLT2 inhibitor

1. Zinman B et al. N Engl J Med , (2015), 9-1-15

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How a bout Using Both?

Robust lowering of HbA1c[1-3]

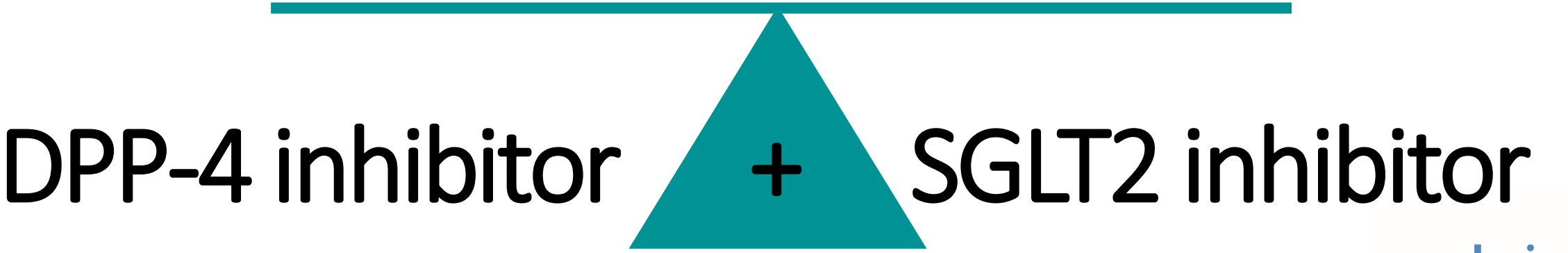
FPG significant reduction[1-3]

Low Hypoglycemia ratio [1-3]

Weight loss [1-3]

Reduction in BP [1-3]

Well tolerated [1-3]



1. DeFronzo et al. (2015). Diabetes Care ;38:384 2. Tan et al. (2016). Annales d'Endocrinologie, 77(5): 557–562
3. Lewin et al. (2015) .Diabetes Care , 38(3):394-402

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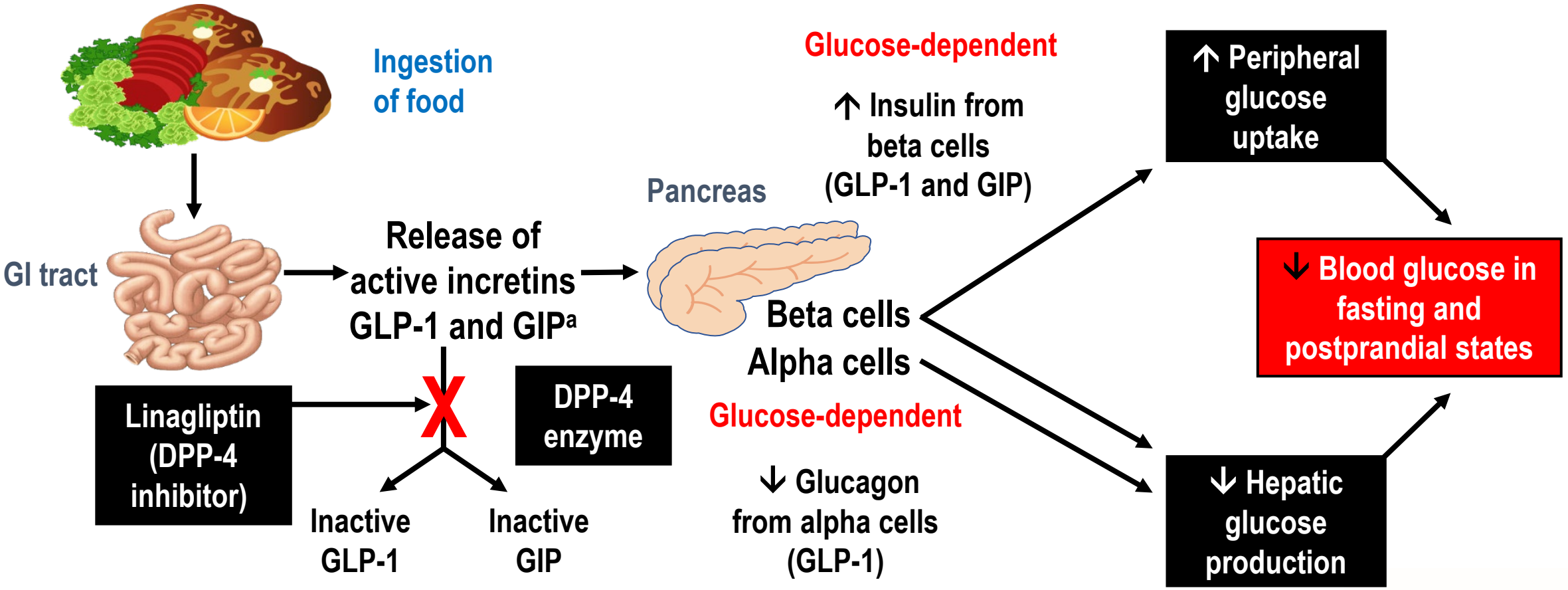
Glorenta
Empagliflozin / Linagliptin

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



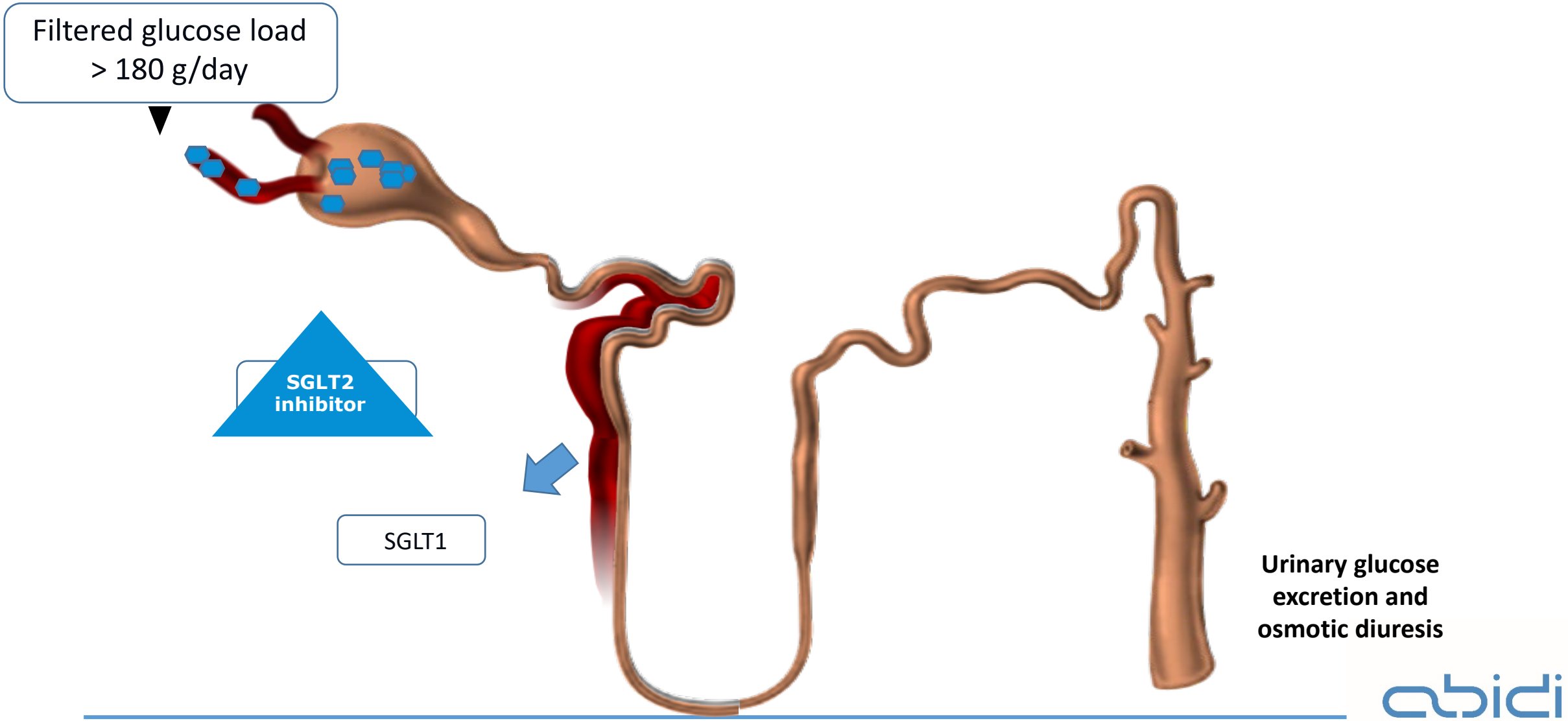
By increasing and prolonging active incretin levels, Linagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

DPP-4=dipeptidyl peptidase 4; GI=gastrointestinal; GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1.
[a]Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal.

1. Kieffer TJ et al. *Endocr Rev*. 1999;20(6):876–913. 2. Ahrén B. *Curr Diab Rep*. 2003;3(5):365–372. 3. Drucker DJ. *Diabetes Care*. 2003;26(10):2929–2940, 4. Holst JJ. *Diabetes Metab Res Rev*. 2002;18(6):430–441.

Urinary glucose excretion via SGLT2 inhibition

SGLT2 inhibitors work by inhibiting reabsorption of glucose in the kidney[1]

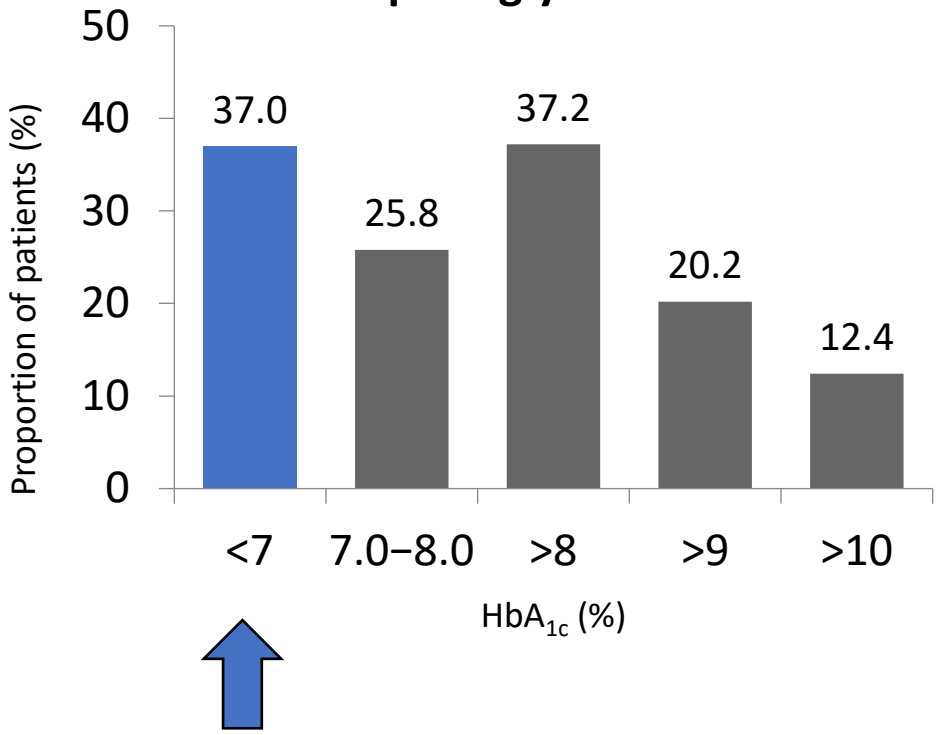


SGLT1, sodium-glucose co-transporter-1, SGLT2, sodium-glucose co-transporter-2

1. Bakris GL et al. Kidney Int 2009;75;1272

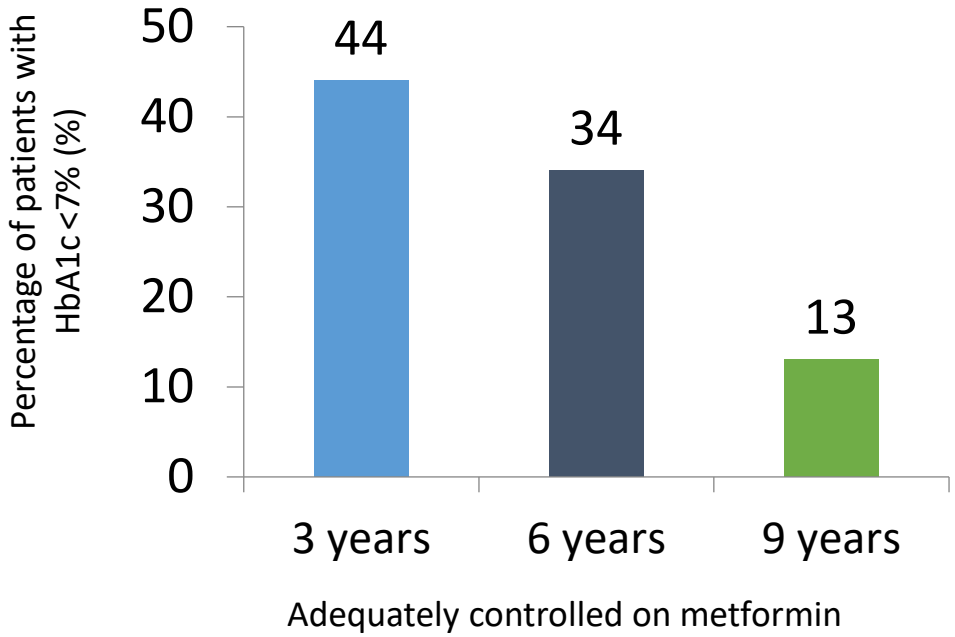
Maintaining glycemic targets can be difficult to achieve

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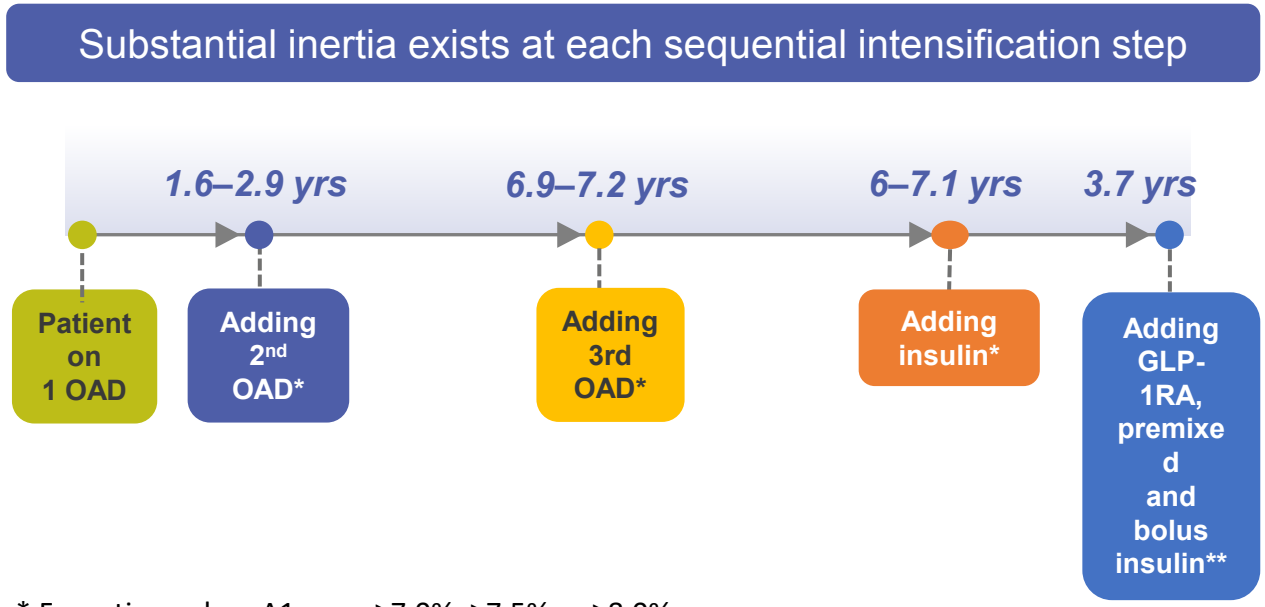
The sequential treatment approach is compounded by substantial inertia to timely intensification of therapy [1,2]



* 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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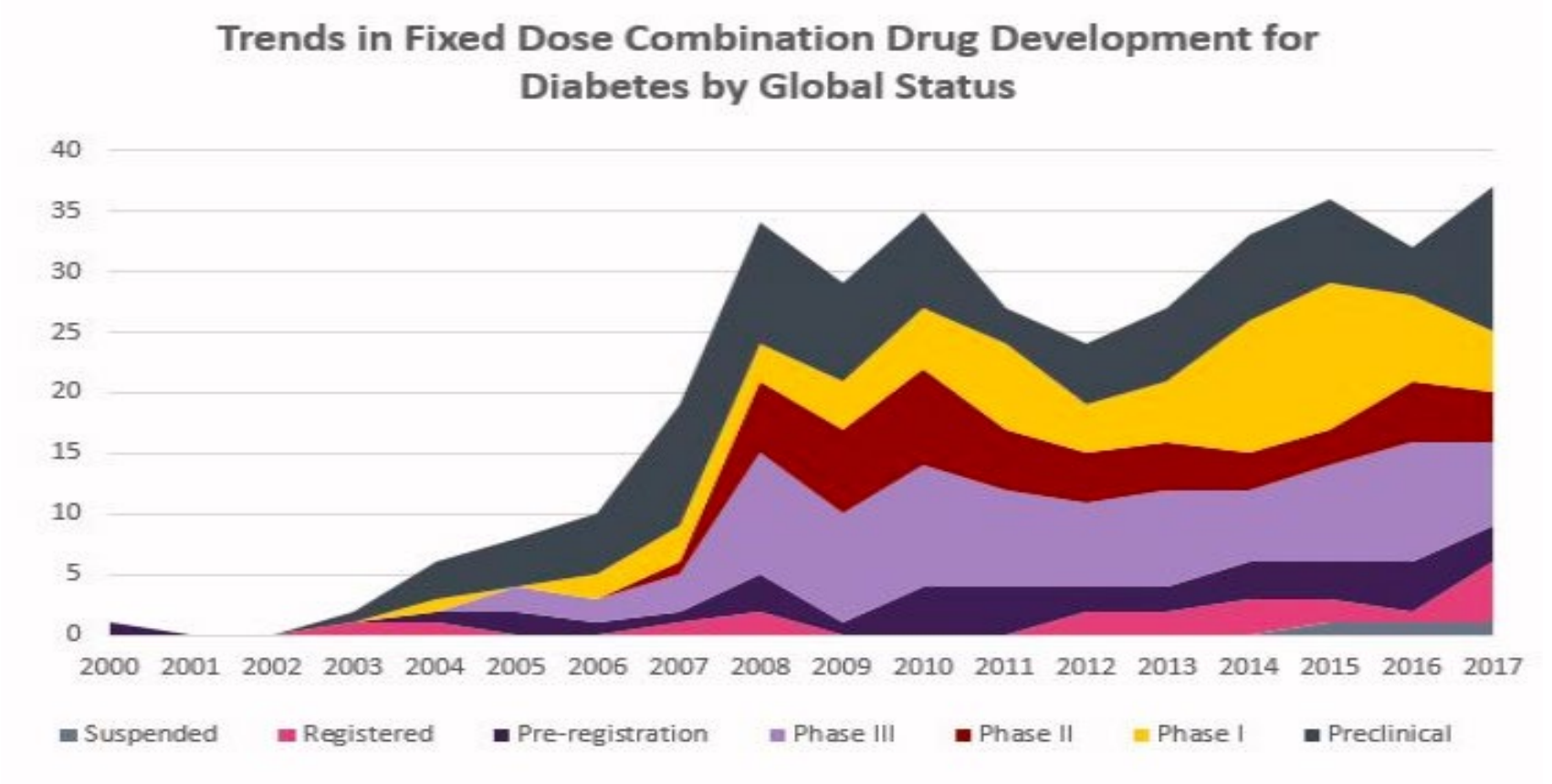
Trends in Fixed Dose Combination Drug Development for Diabetes by Global Status[1]



1. Buse JB (2017). The Future of Combination Therapy in the Treatment of Type 2 Diabetes—Which Classes, Why, and When? Presented at the American Diabetes Association Scientific Sessions, San Diego, CA.

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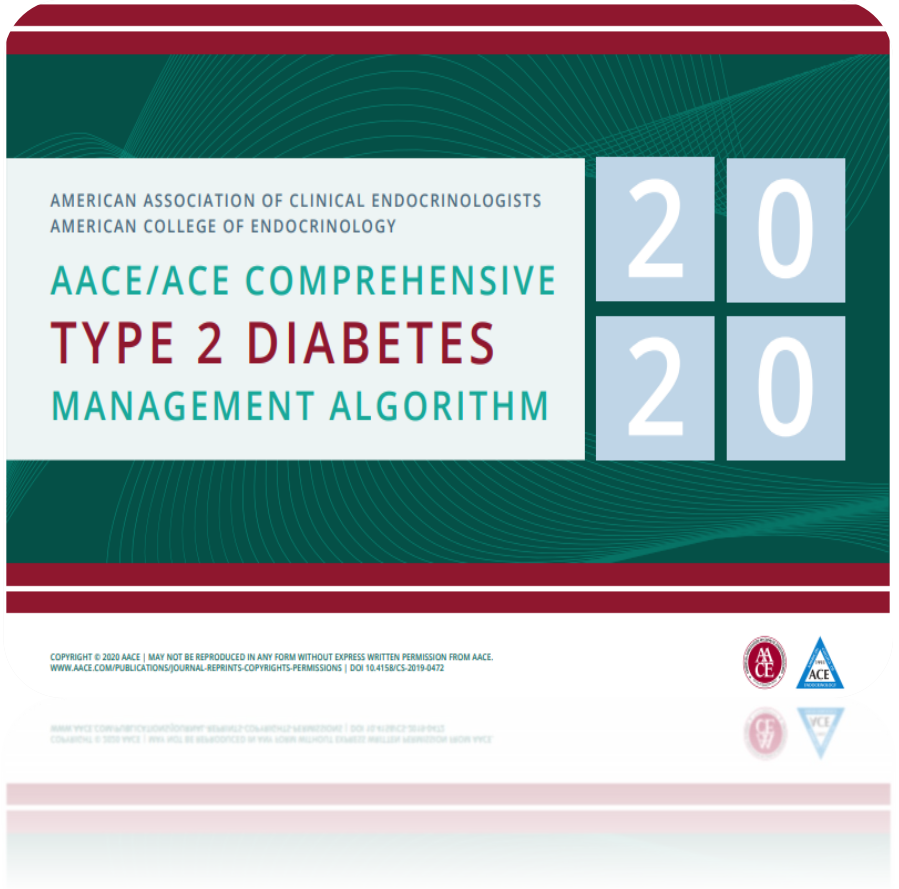
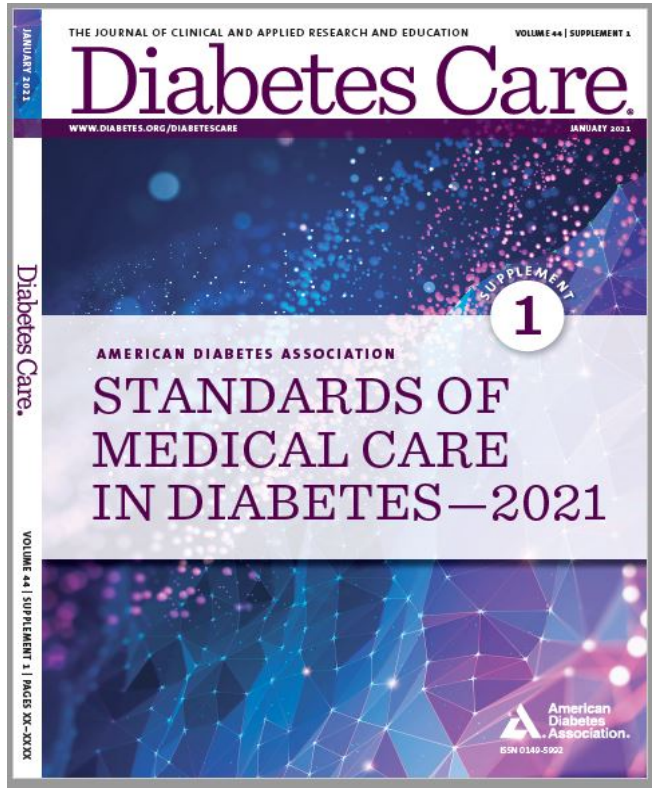
Guidelines: initial combination therapy recommendations





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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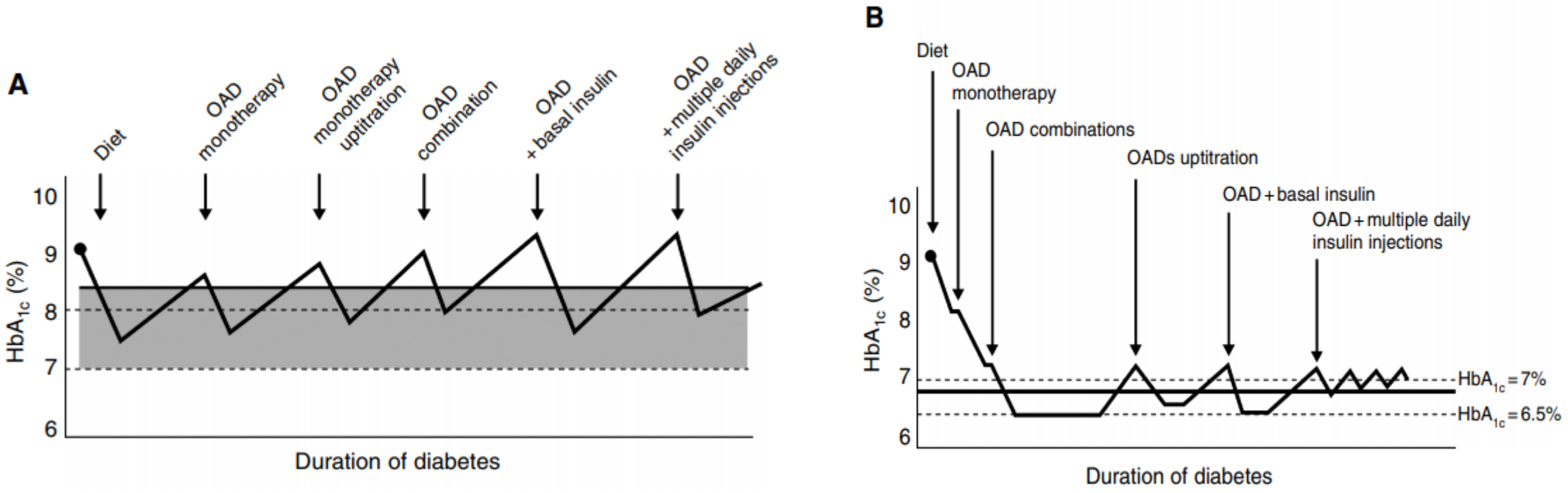
Improving Glycemic Control in T2DM Achieving Glycemic Goals Sooner May Reduce the Risk of Complications [1,2]



Conservative vs. proactive management: (A) **traditional stepwise approach** and (B) **early combination** approach. OAD, oral antidiabetic drug

1. Int J Clin Pract 2005; 59:1345–1355. 2. BMJ 2000; 321:405–412.

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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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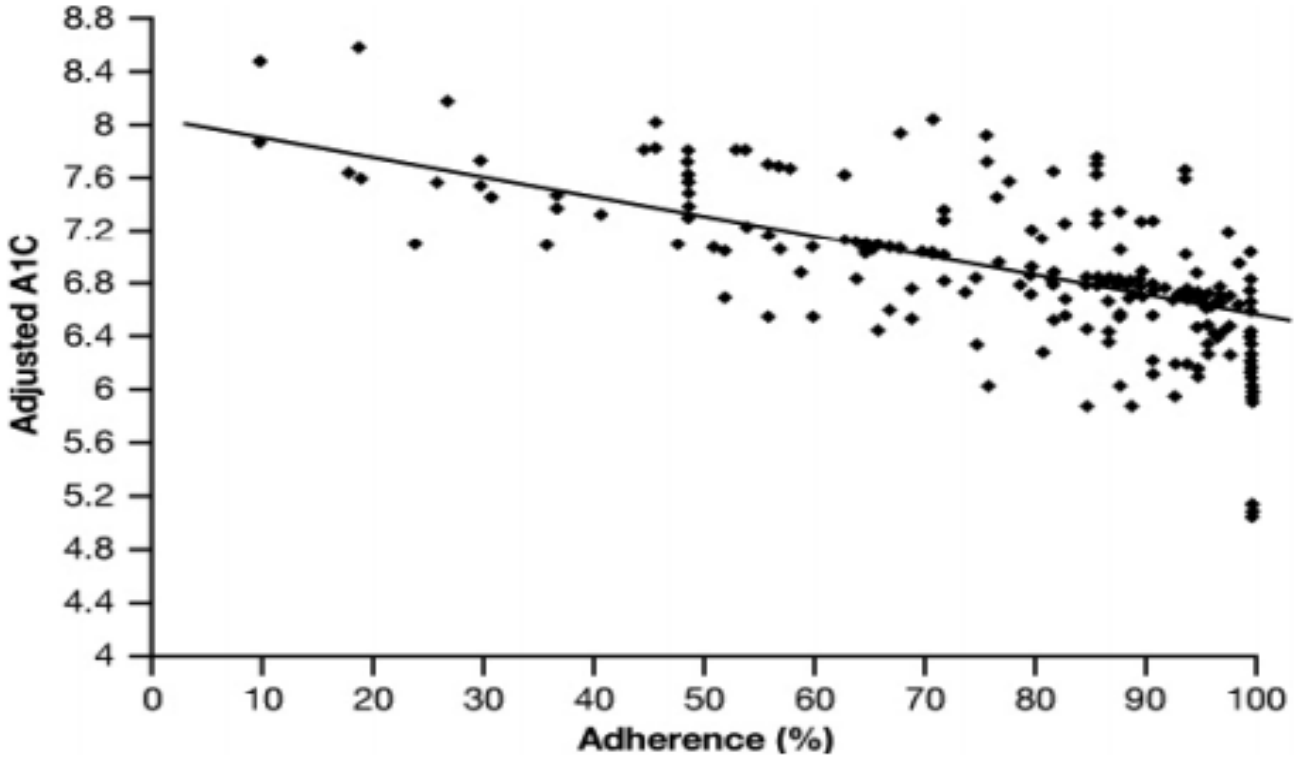
Better adherence to oral glucose-lowering therapy is associated with better glycaemic control[1]



1. Diabetes UK. Diabetic Medicine 2010; 27, 739–743

Diabetes Care

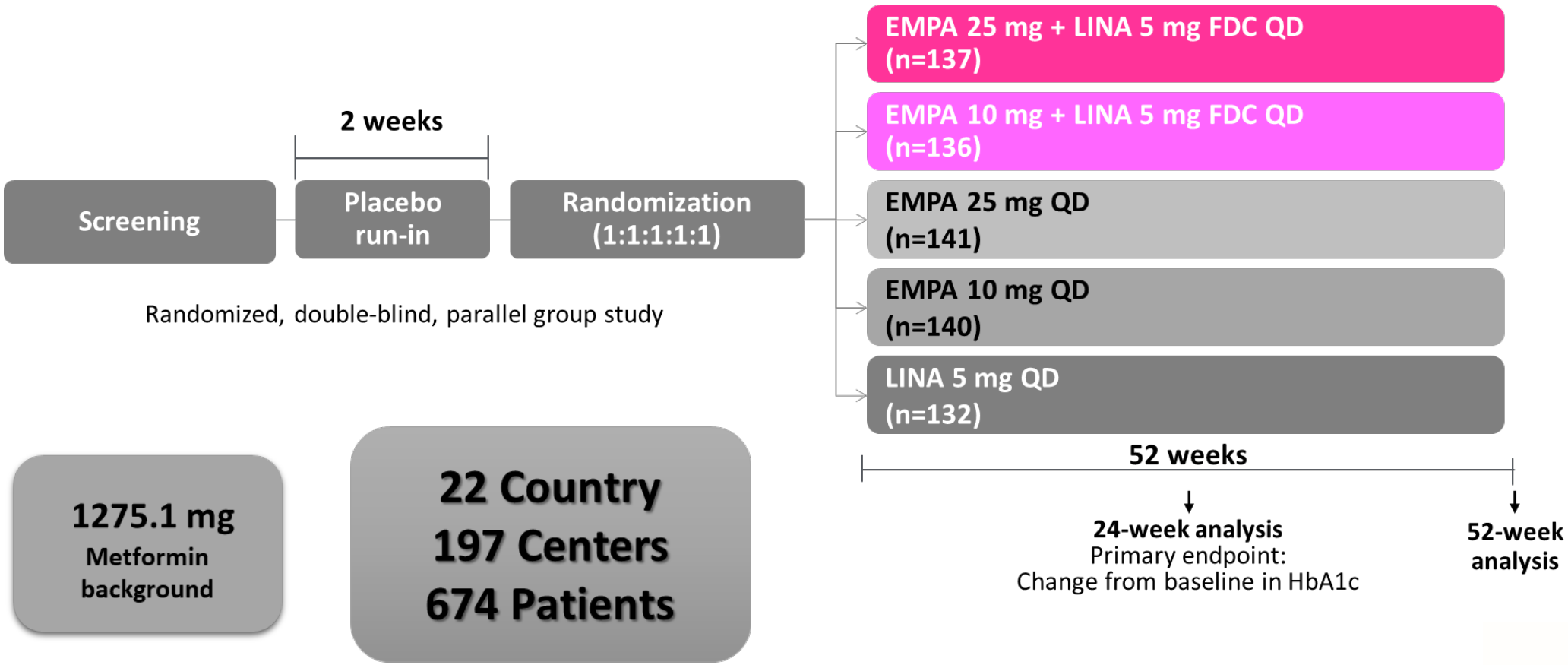
Combination of Empagliflozin and Linagliptin as Second-Line Therapy in Subjects With Type 2 Diabetes Inadequately Controlled on Metformin

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

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

Study Design



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

Objective & End point

OBJECTIVE:

- To evaluate the efficacy and safety of empagliflozin/linagliptin in subjects with type 2 diabetes.

Primary end point:

- Change from baseline in HbA1c at week 24

Key Secondary end point:

- Change from baseline in FPG at week 24
- Change from baseline in body weight at week 24
- proportion of subjects with baseline HbA1c ≥7% (≥ 53 mmol/mol) who had HbA1c <7% (< 53 mmol/mol) at week 24.

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

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Objective & End point Cont.

Exploratory end points:

- Change from baseline in HbA1c at week 24 in subgroups of subjects with HbA1c ≥ 8.5 and < 8.5% at baseline.
- Change from baseline in HbA1c, FPG, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at week 52.
- Proportion of subjects with baseline HbA1c ≥ 7% (≥ 53 mmol/mol) who had HbA1c < 7% (< 53 mmol/mol) at week 52.

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

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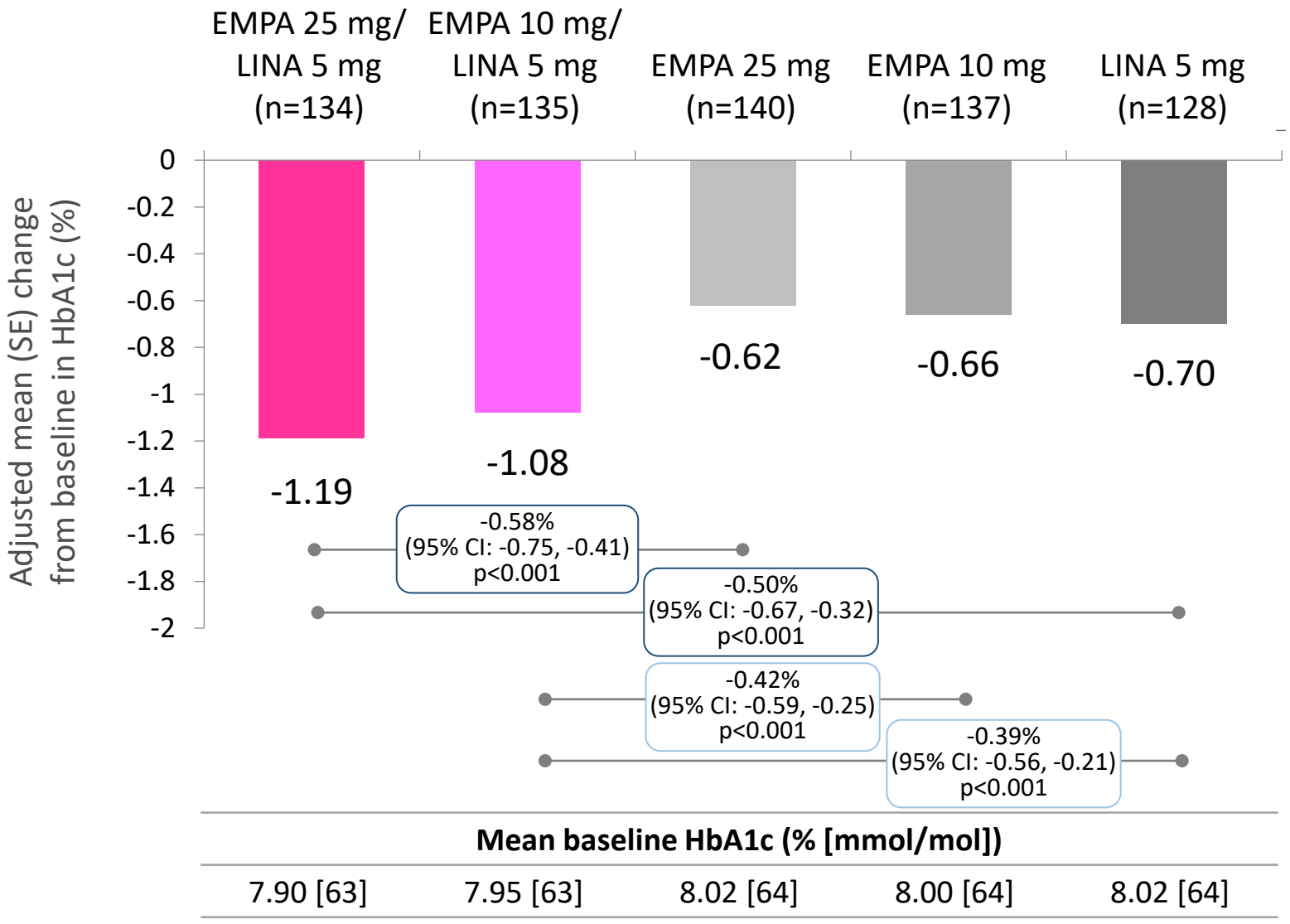
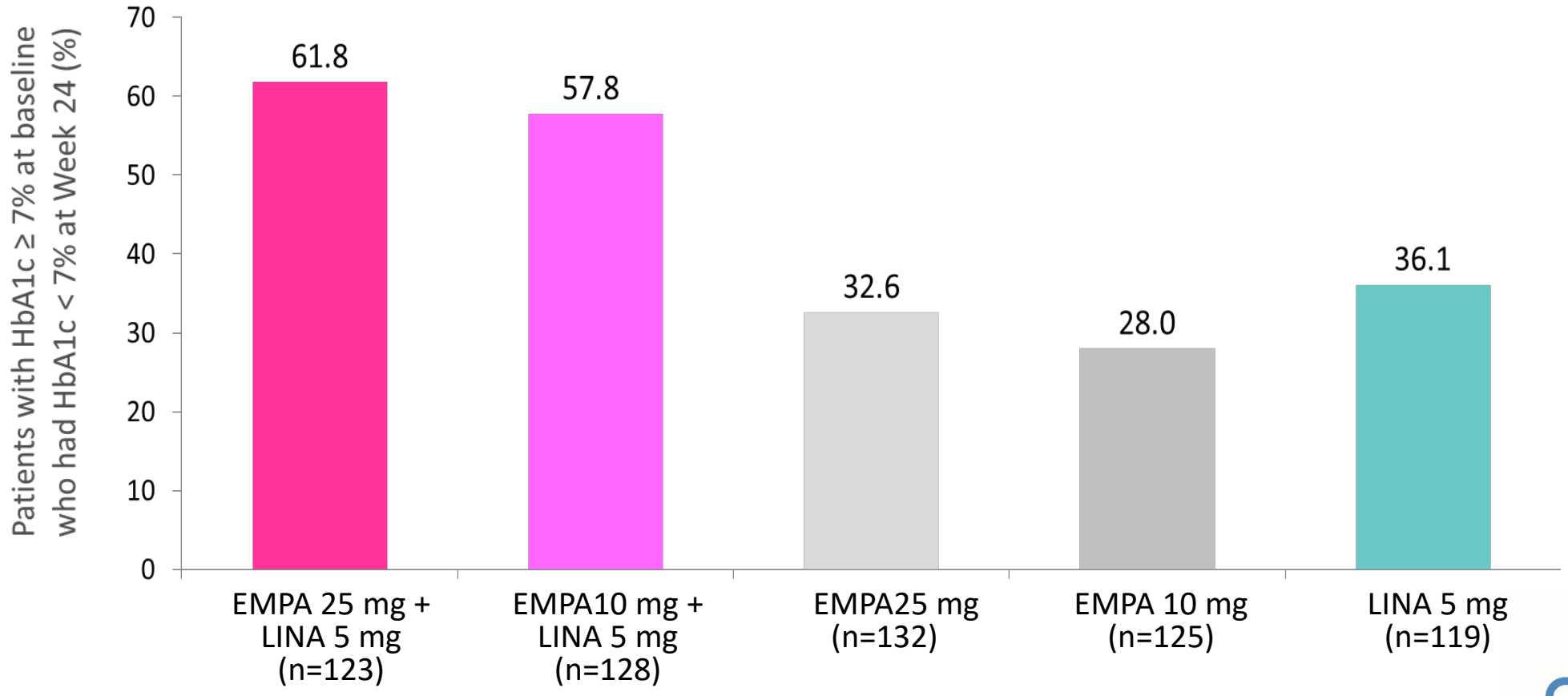
Change from Baseline in HbA1c at Week 24[1]



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

Patients with HbA1c ≥7% at baseline who had HbA1c <7% at week 24[1]



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

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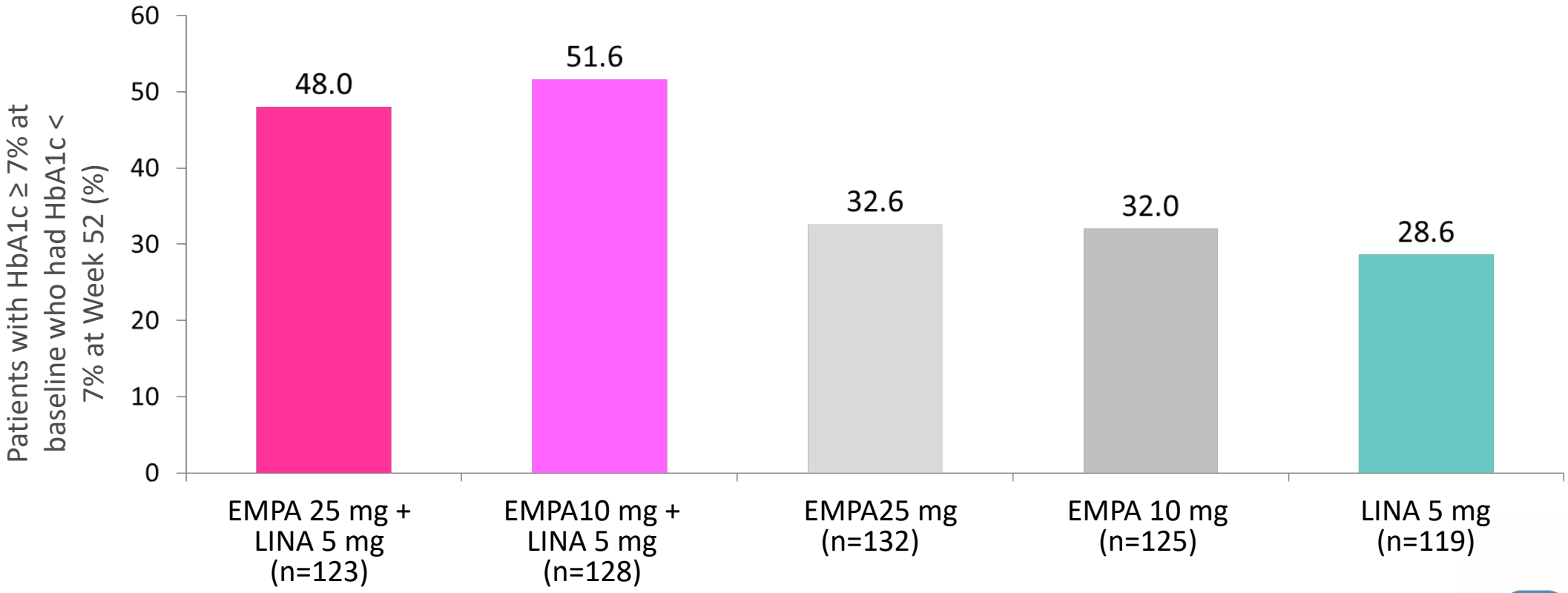
Patients with HbA1c ≥7% at baseline who had HbA1c <7% at week 52[1]



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

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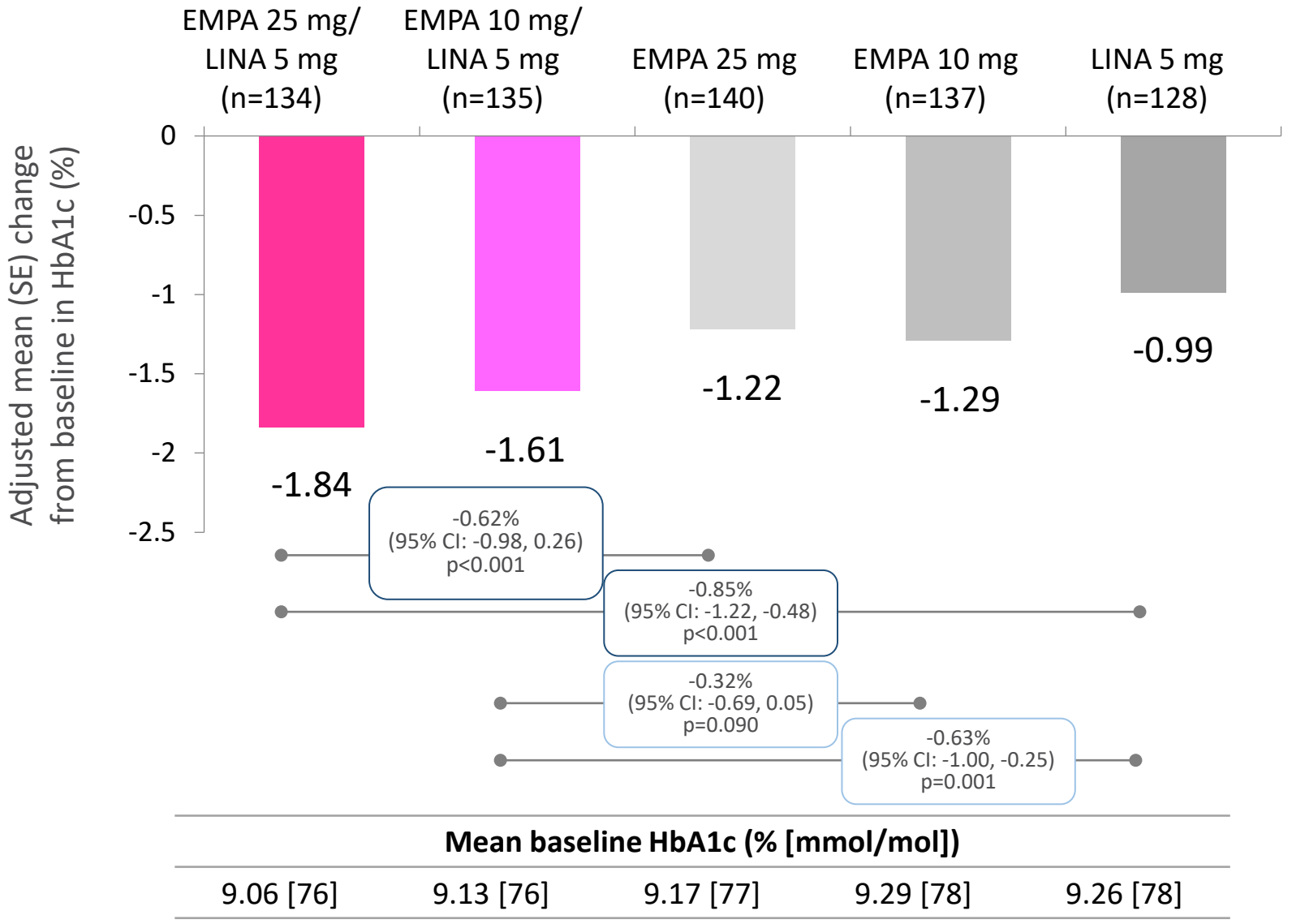
Change in HbA_{1c} at Week 24 in Patients with HbA_{1c} ≥8.5%[1]



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

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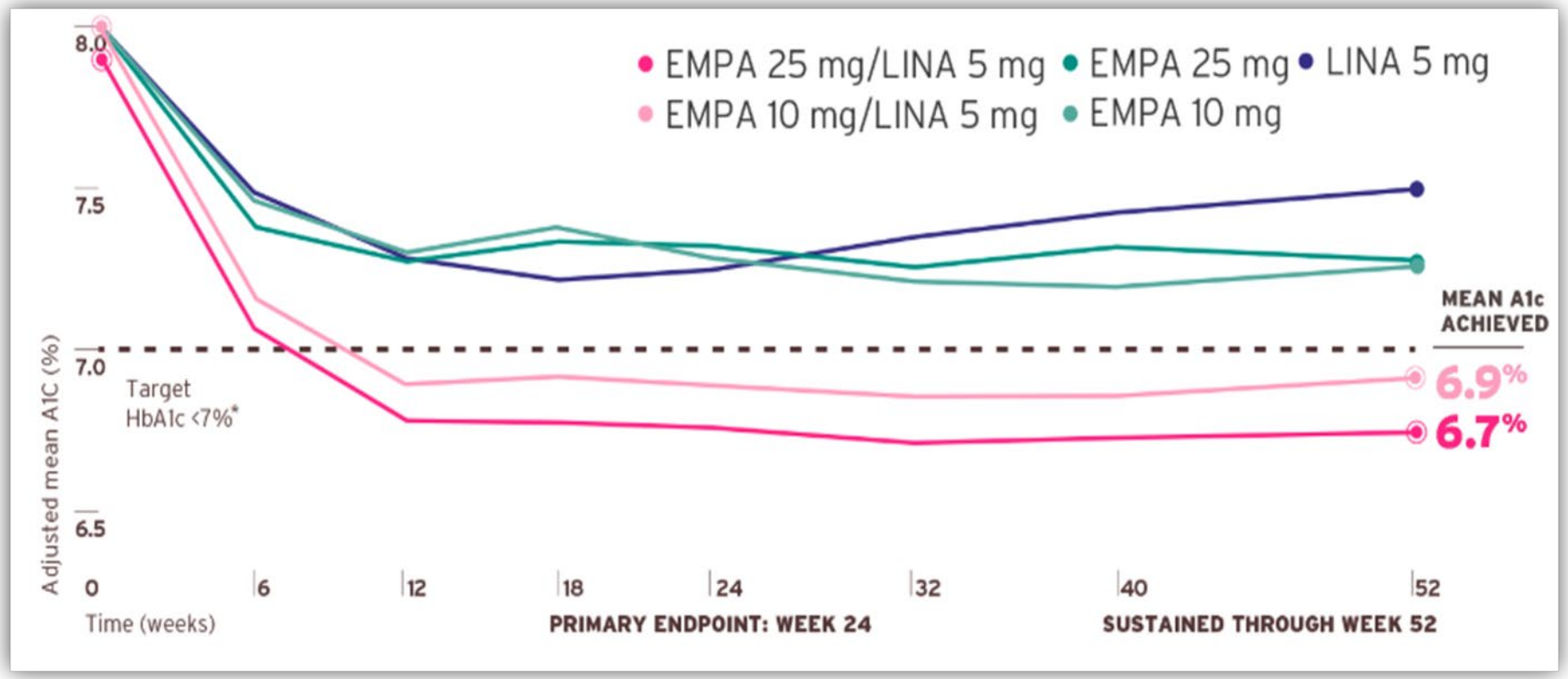
Combination of Empagliflozin+Linagliptin Demonstrates Early and Durable Achievement of Goal[1]



* 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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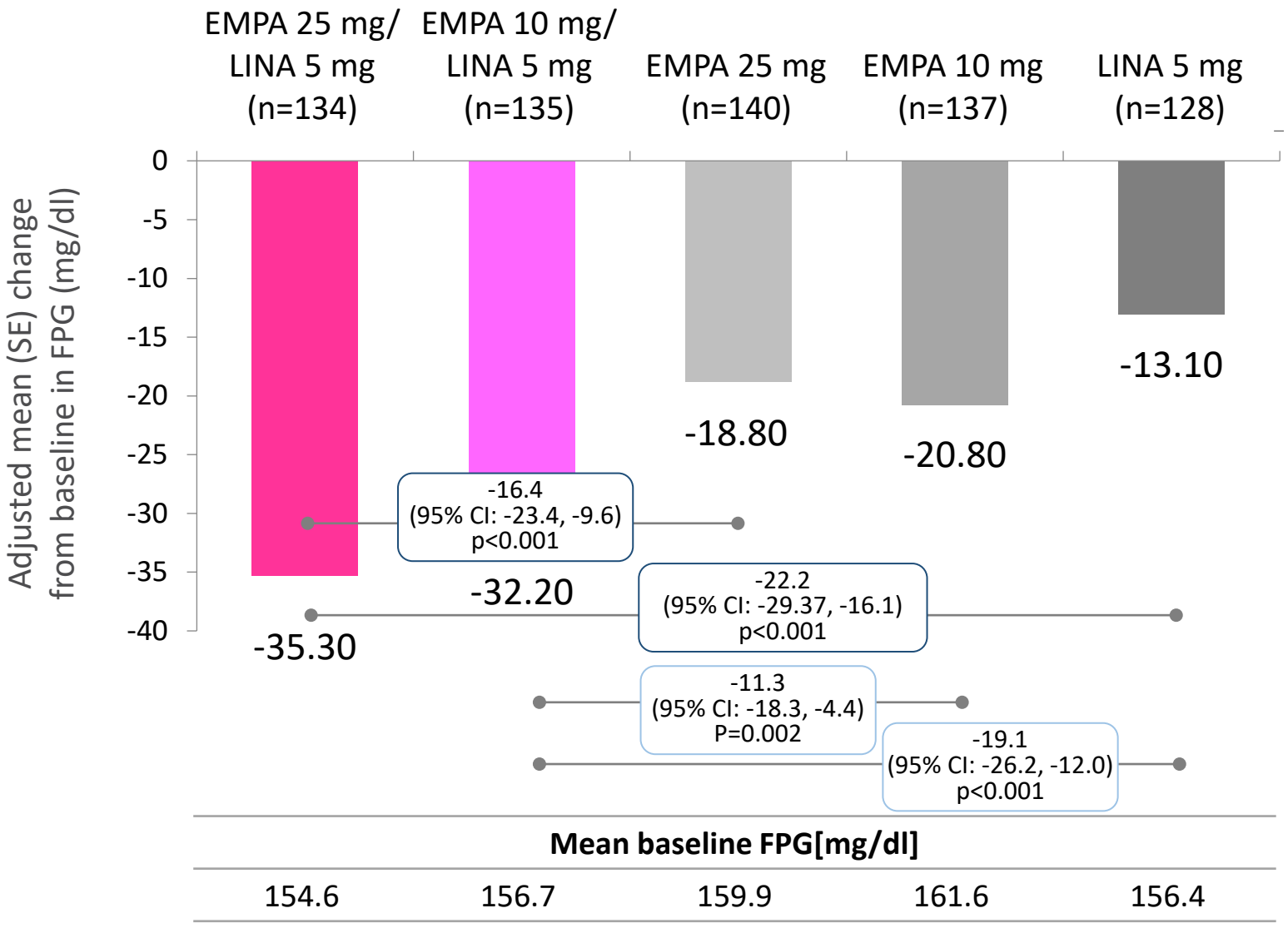
Change from Baseline in FPG at Week 24[1]



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

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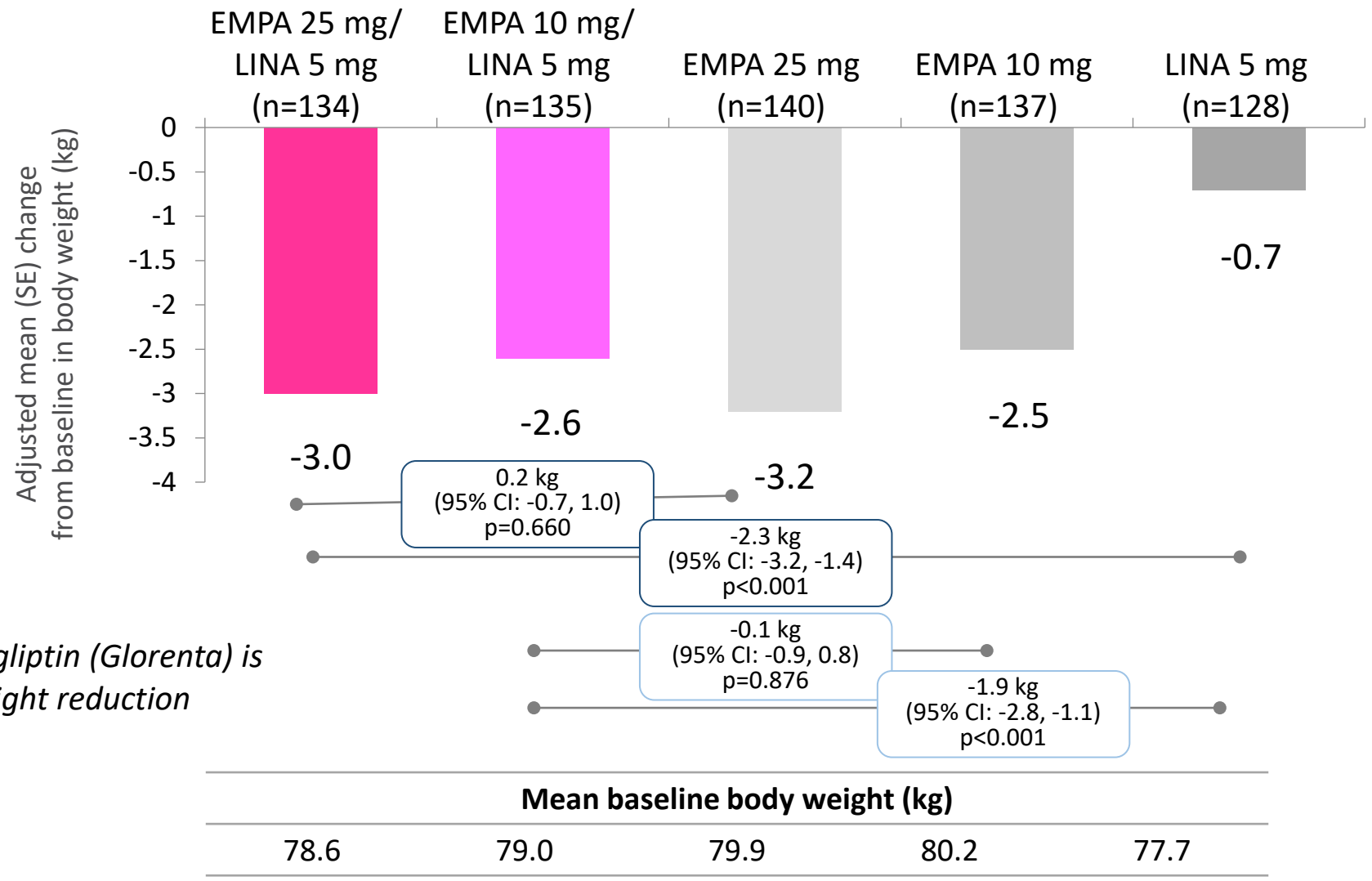
Change from baseline in body weight at Week 24[1]



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

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

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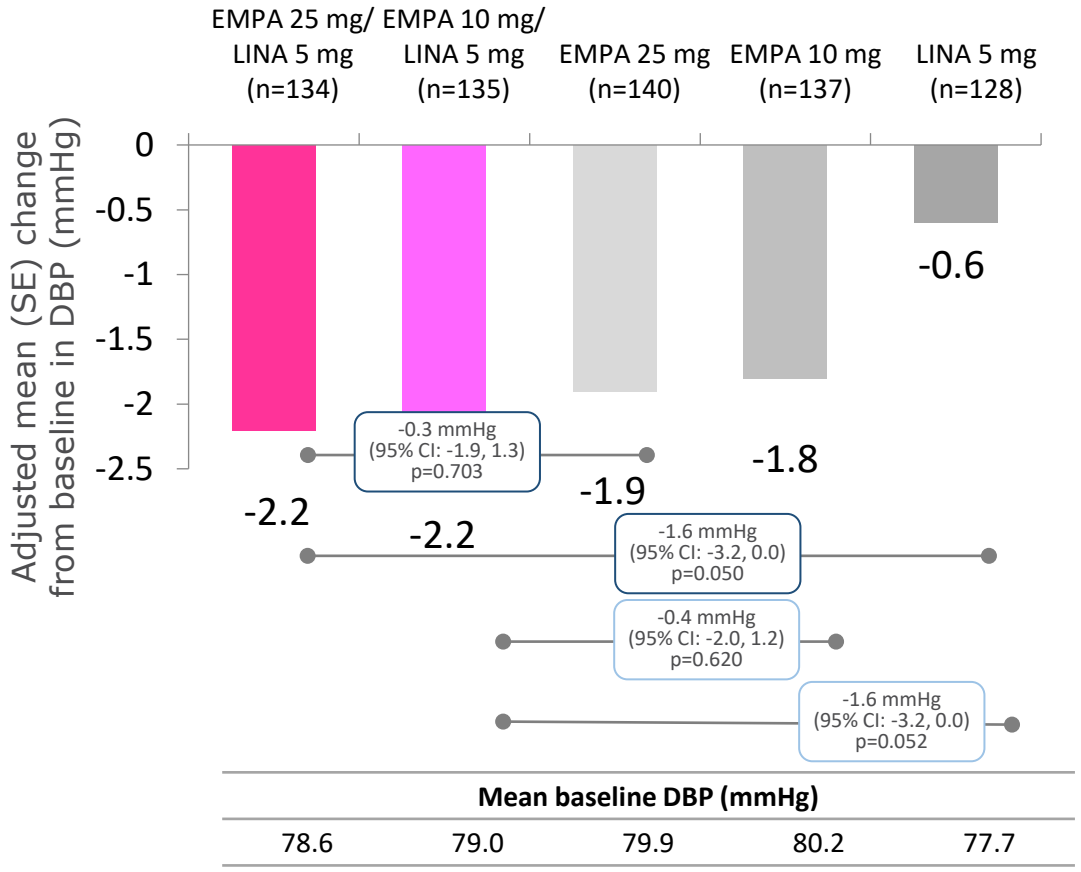
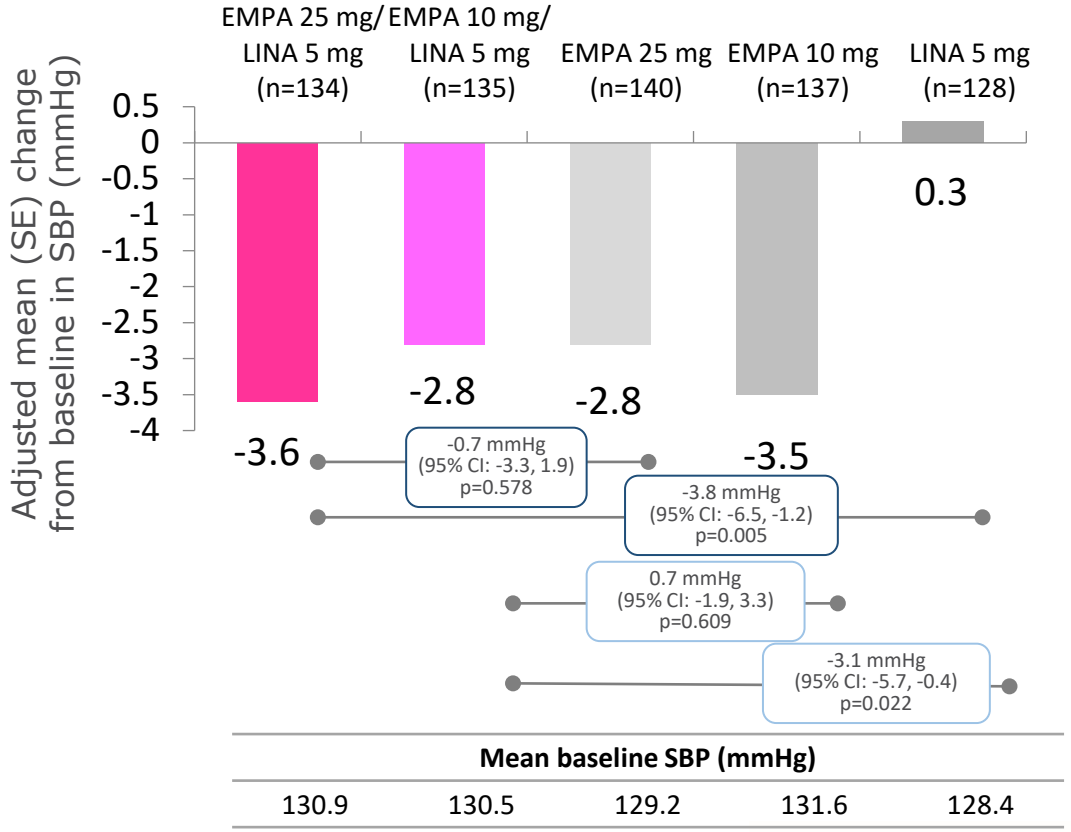
Change from baseline in BP (mmHg) at Week 52[1]





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

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Conclusion[1]

- The combination of empagliflozin +linagliptin led to significantly greater reductions in glycated hemoglobin (HbA1c) and fasting plasma glucose compared with either drug alone over 24 weeks [1].
- T2DM patients treated with the drug combination were >3 times more likely to achieve HbA1c <7% than those on either monotherapy [1].
- Weight reduction was significantly greater in the combination group only when compared with linagliptin monotherapy [1].
- Safety profile was similar between combination treatment and monotherapies [1].
- This combination, administered once daily, can reduce regimen complexity, enhance adherence and improve outcomes in clinical practice [1].
- With the use of FDCs, polypharmacy, fear for side effects, cost, and clinical (therapeutic) inertia both from patients and physicians can be minimized and patient adherence to treatment can be improved, thereby increasing the likelihood of achieving treatment goals [1].

1. Diabetes, Obes Metab, 2020; 22(6):1001-1005

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Conclusions

Combination of empagliflozin/linagliptin:

- Significantly Reduced HbA1c compared with the individual components and were well tolerated.
- FPG was significantly reduced with empagliflozin 25 mg/linagliptin 5mg compared with individual components
- The combination of empagliflozin and linagliptin added on to metformin offered a sustained reduction in HbA1c, FPG, weight, and blood pressure, which persisted up to week 52.

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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 m^2.
- Discontinue GLORENTA if eGFR falls persistently below 45 mL/min/1.73 m^2

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

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DEPARTMENT OF HEALTH & HUMAN SERVICES • USA
U.S. PUBLIC HEALTH SERVICE
1798
FDA
U.S. Department of Health and Human Services
Food and Drug Administration

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

Contraindications [1]

1. Severe renal impairment, end-stage renal disease or dialysis

2. History of serious hypersensitivity reaction to empagliflozin, linagliptin:

- Anaphylaxis
- Angioedema
- Exfoliative skin conditions
- Urticaria

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

Adverse Reactions[1]

- Urinary tract infections
- Upper respiratory tract infections
- Nasopharyngitis

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

Use in Specific Communication [1]

- Pregnancy
- Lactation
- Pediatric Patients
- Geriatric Patients

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

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Conclusions[1]

Glorenta as the combination of Gloripa & Lirenta with their complementary mechanisms of action:

- Is the only OAD that has compelling and relevant CVOT data among its individual components:
  - Gloripa, the only OAD indicated to reduce cardiovasular death in T2D among ASCVD patients.
  - Lirenta, 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

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

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Thank you