Combination therapy in T2DM

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1401.11.18

Objectives

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

Case presentation:

- اقای 65 ساله بازنشسته بدون سابقه قبلی دیابت باازمایش زیرمراجعه کرده است :
- PMH = neg
- DH= neg

FBS = 189 CBC = Nl

HbA1c = 8.9 %

Cr.= 0.7 LFT = Nl TG= 280 HDL= 45 Cholesterol = 231

FH = DM مادر

معاینه سیستمیک نرمال است.

BP= 140/85 mmHg BMI= 32 Kg/m2

علاوه بررژیم وورزش کدام دارو را توصیه میکنید؟

1 . Metformin.

2 . SGLT2 inh.

3 . Gliclazide.

4 . Met/SGLT2inh.

5 . 0THERS.

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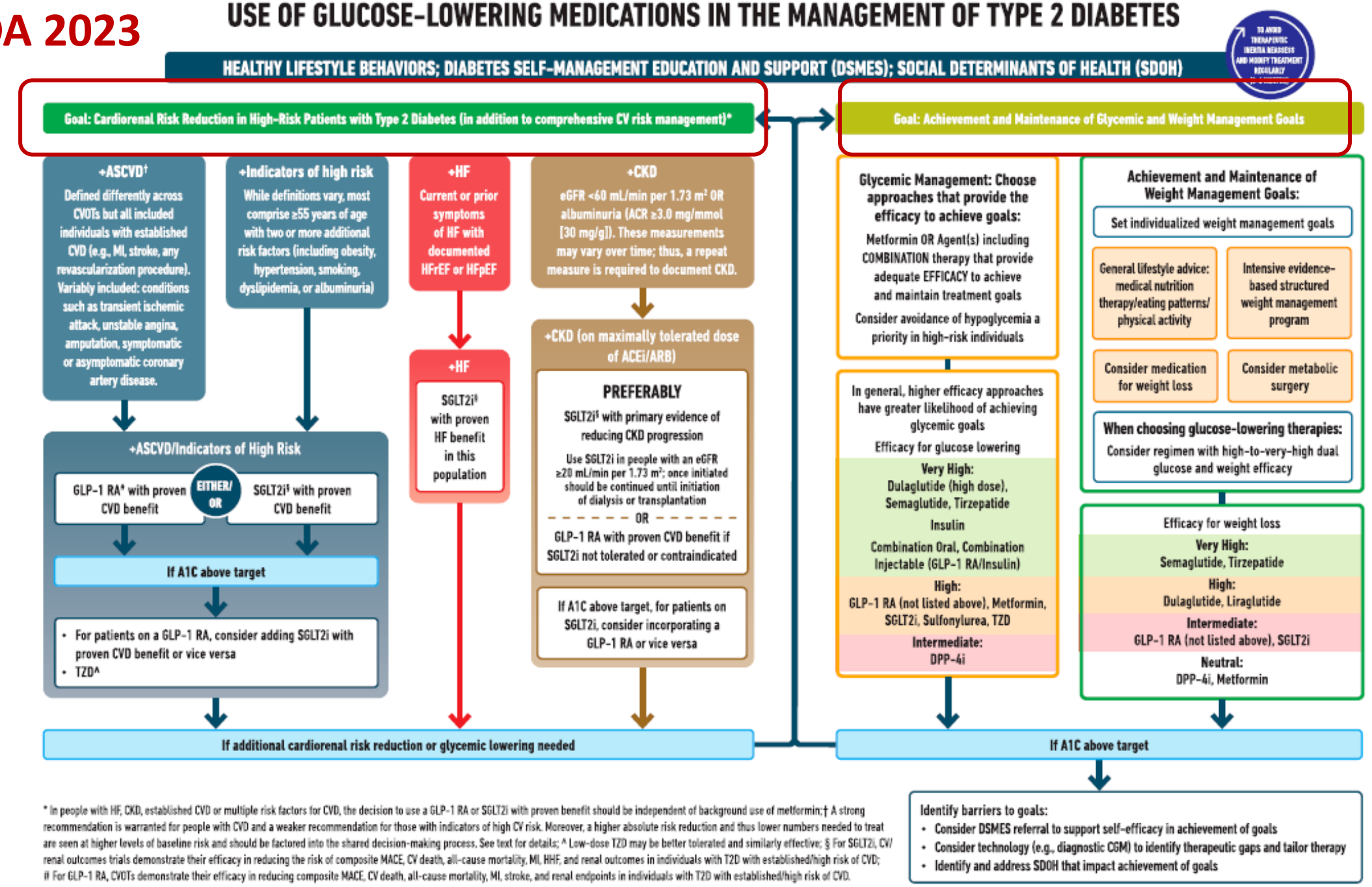
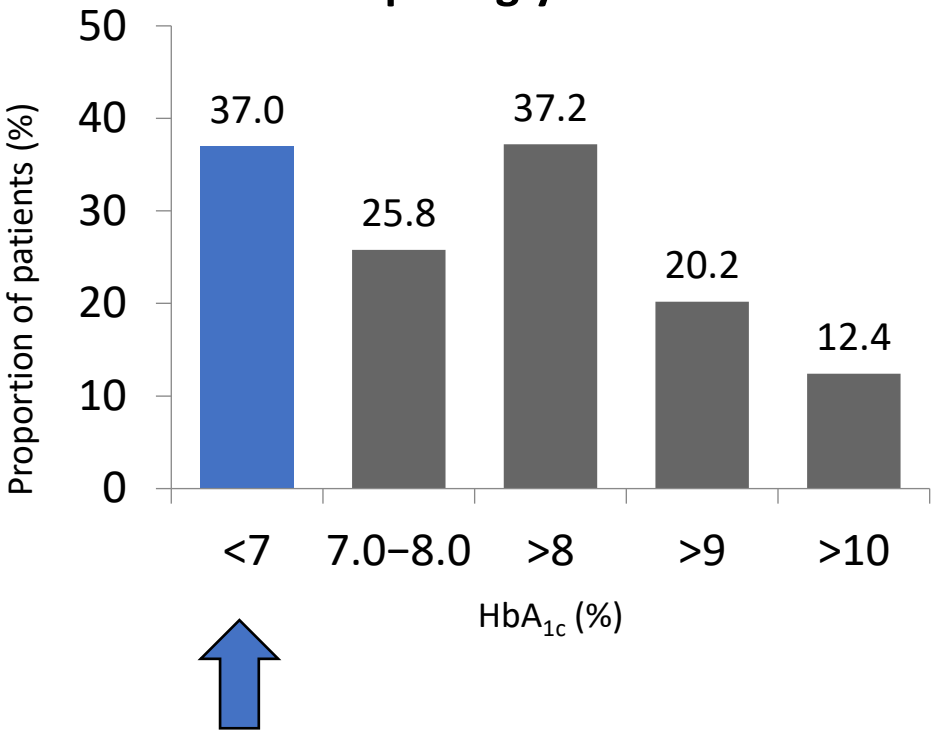

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES
HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)
Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*
Goal: Achievement and Maintenance of Glycemic and Weight Management Goals
+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.
+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.
+ASCVD/Indicators of High Risk
GLP-1 RA* with proven CVD benefit
EITHER/ OR
SGLT2i§ with proven CVD benefit
If A1C above target
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
TZD^
+HF
SGLT2i§ with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiorenal risk reduction or glycemic lowering needed
Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycemia a priority in high-risk individuals
In general, higher efficacy approaches have greater likelihood of achieving glycemic goals
Efficacy for glucose lowering
Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate:
DPP-4i
Achievement and Maintenance of Weight Management Goals:
Set individualized weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management program
Consider medication for weight loss
Consider metabolic surgery
When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy
Efficacy for weight loss
Very High:
Semaglutide, Tirzepatide
High:
Dulaglutide, Liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
DPP-4i, Metformin
If A1C above target
Identify barriers to goals:
Consider DSMES referral to support self-efficacy in achievement of goals
Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of goals
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; ‖ For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

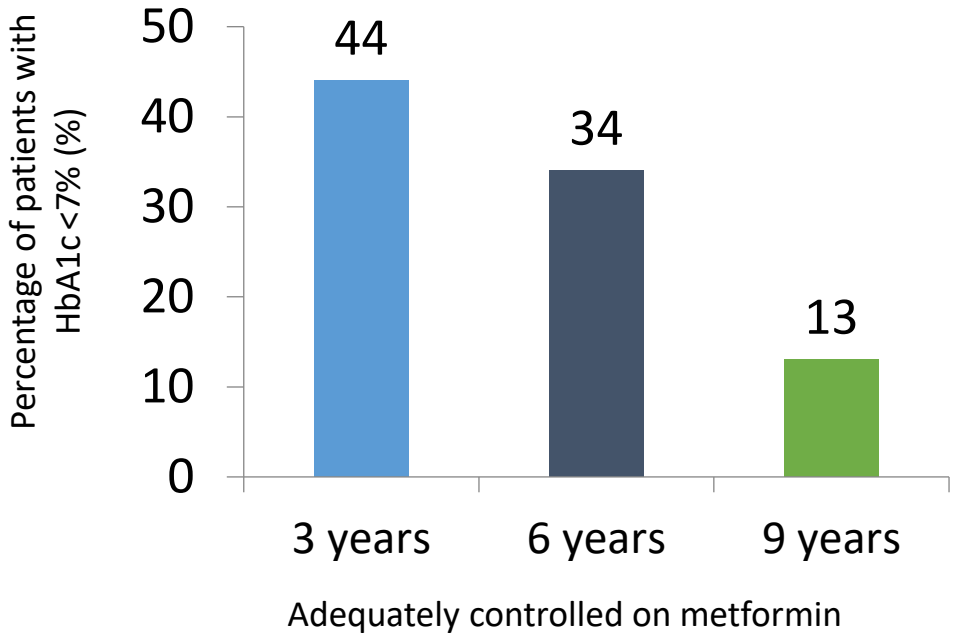
Maintaining glycemic targets can be difficult to achieve

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



Target HbA_{1c} 6.5–7%*

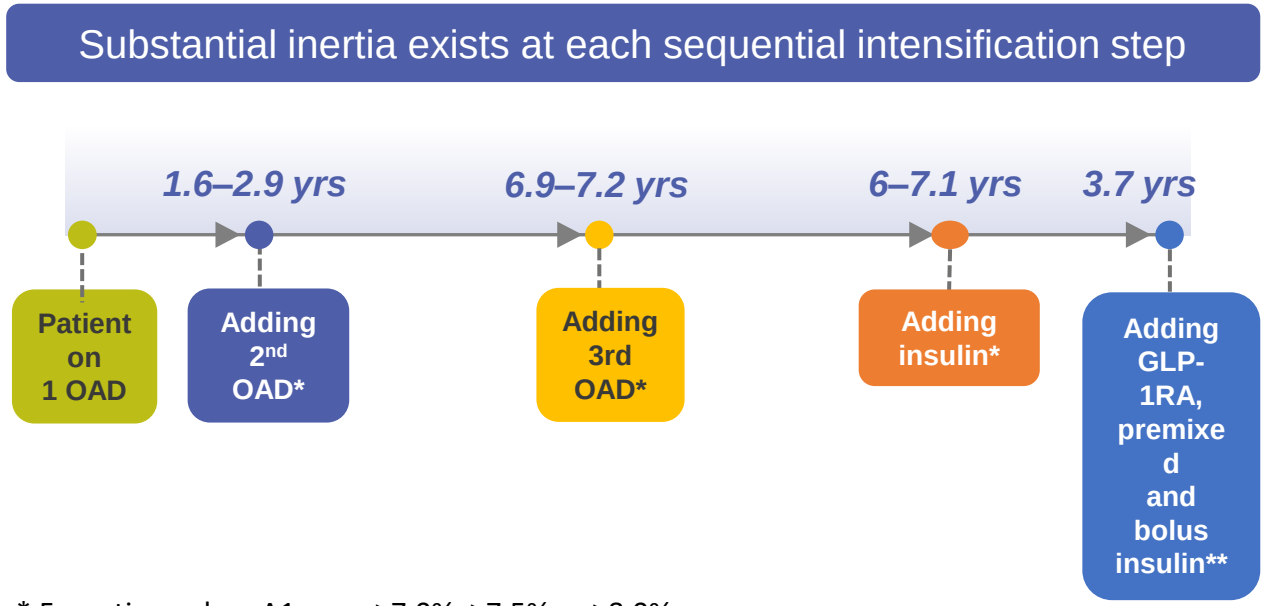
Glycemic control tends to decline over time with monotherapy [2]



**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

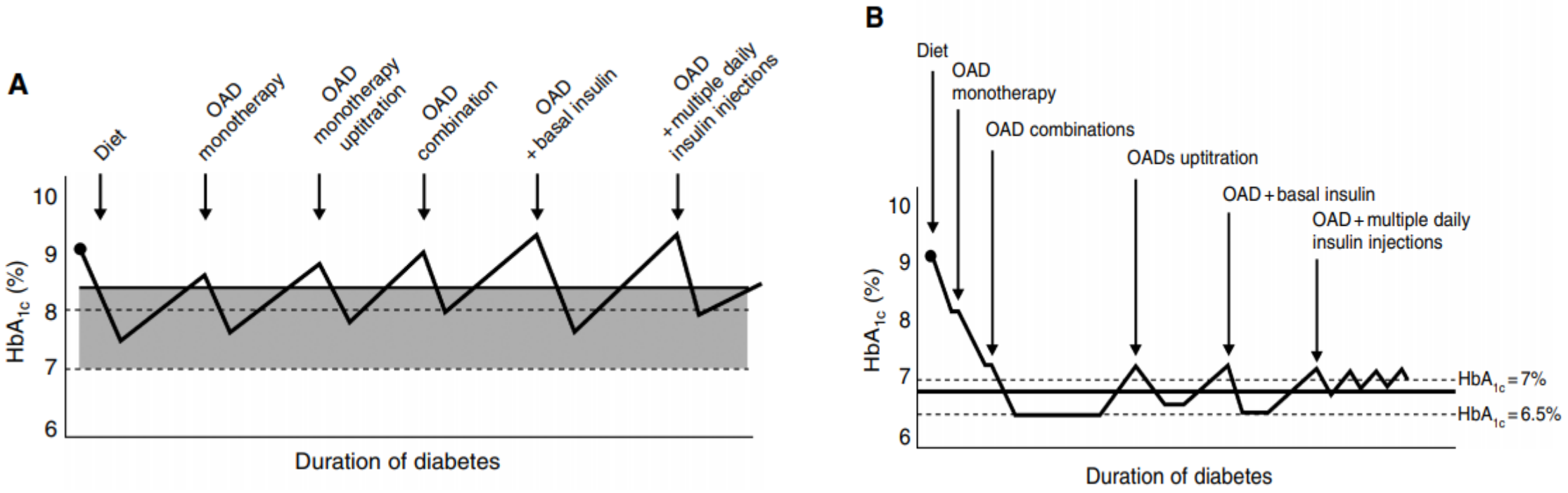
The sequential treatment approach is compounded by substantial inertia to timely intensification of therapy



* 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

Improving Glycemic Control in T2DM Achieving Glycemic Goals Sooner May Reduce the Risk of Complications

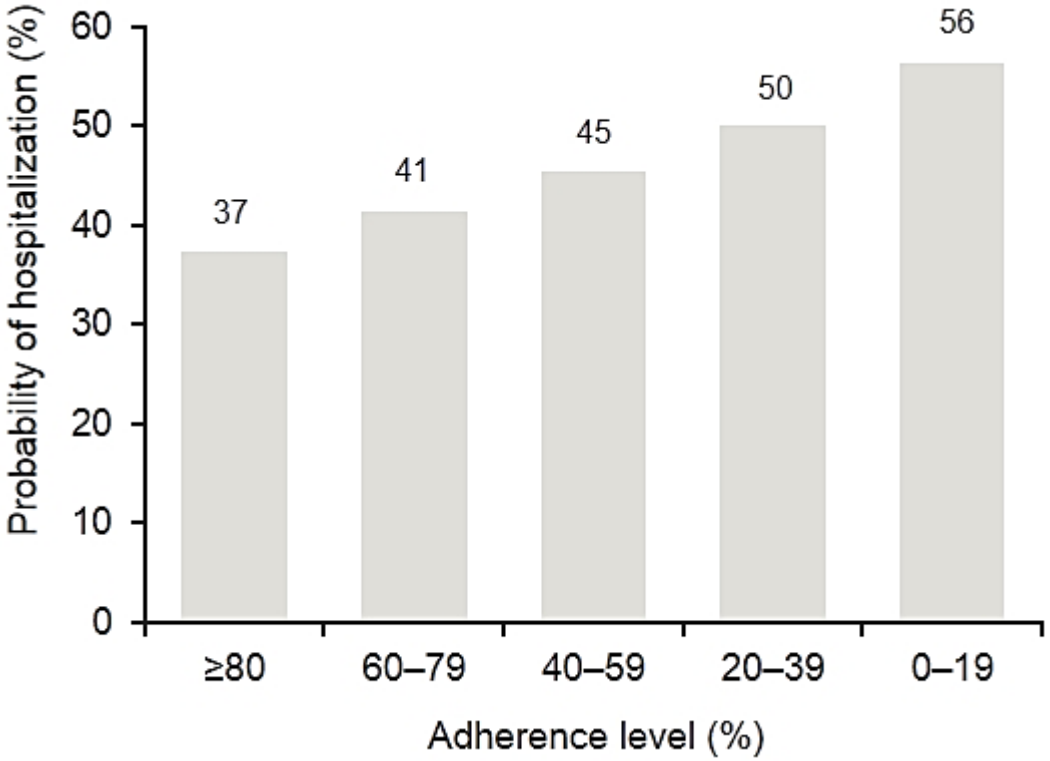


Conservative vs. proactive management: (A) traditional stepwise approach and (B) early combination approach. OAD, oral antidiabetic drug

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

Poor Adherence Translates to an Increased Risk of Hospitalization and All-Cause Mortality

Association between hospitalization risk and adherence[1]

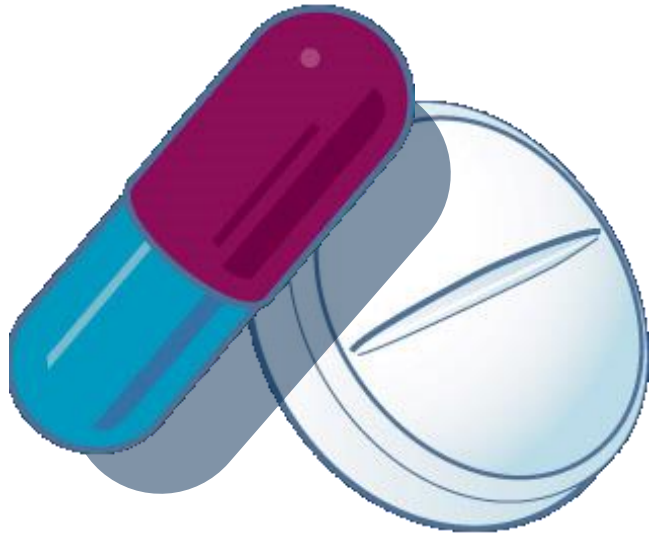


A 39% increased risk of All-cause mortality due to poor adherence to oral anti-hyperglycemic drugs.[2]

1- Patient Prefer Adherence. 2016; 10: 1573–1581. 2-Arch Intern Med. 2006 Sep 25;166(17):1836-41.

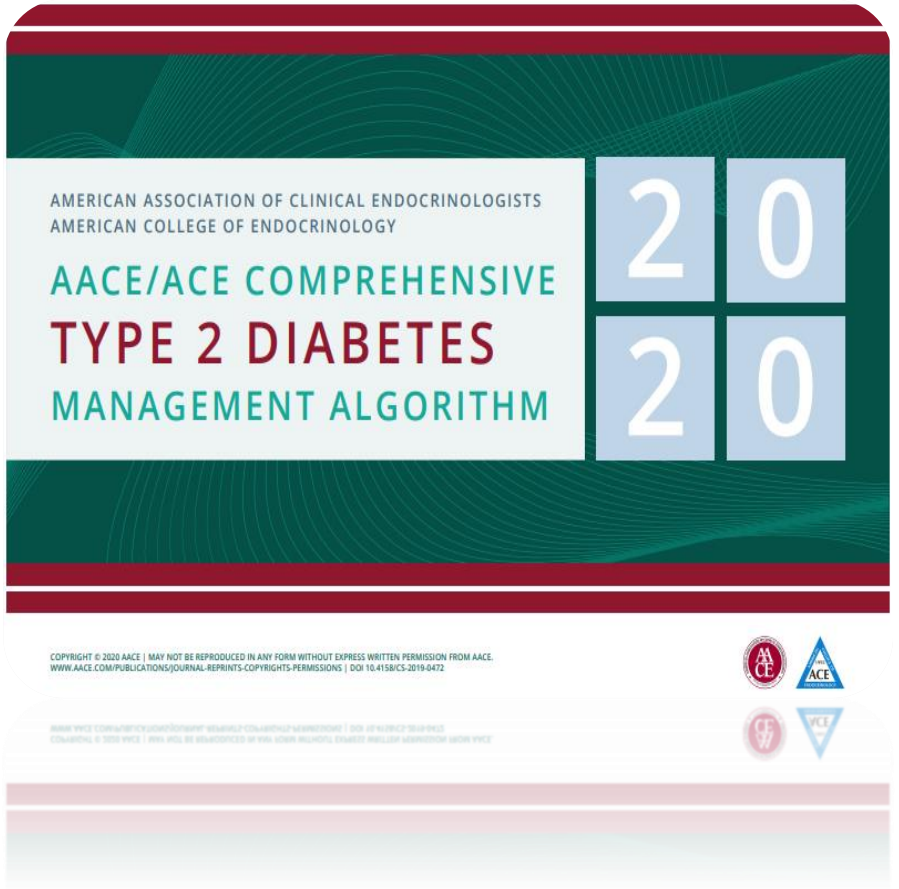
Early Combination Therapy for T2DM Management

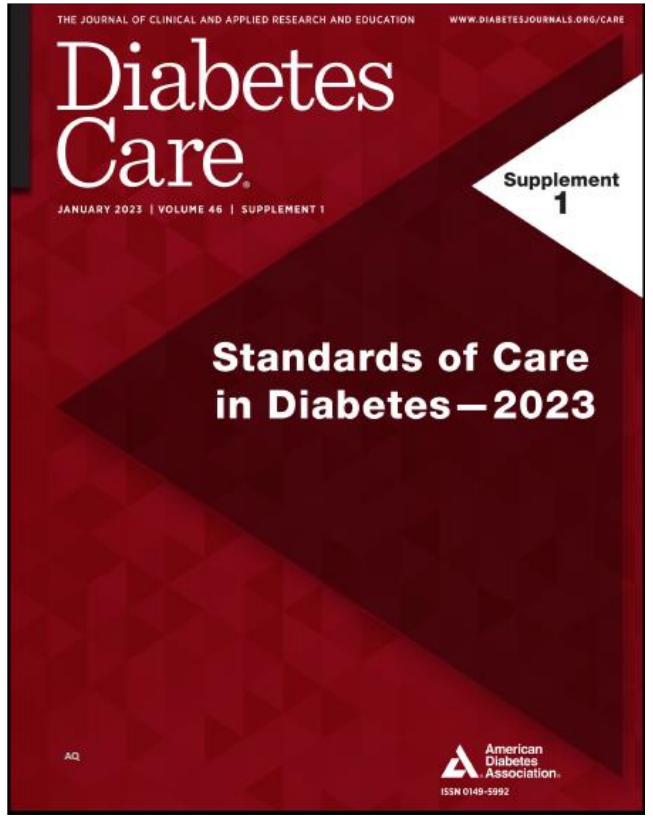
- Ensure Prompter and Better Glycemic Control
- Improving patient's Adherence to Treatment
- Possibly Reducing Clinical Inertia
- More Opportunity to Address Individual Needs
- Reducing Risk of Diabetes Complications



1-Lancet. 2019;394(10208):1519-1529.

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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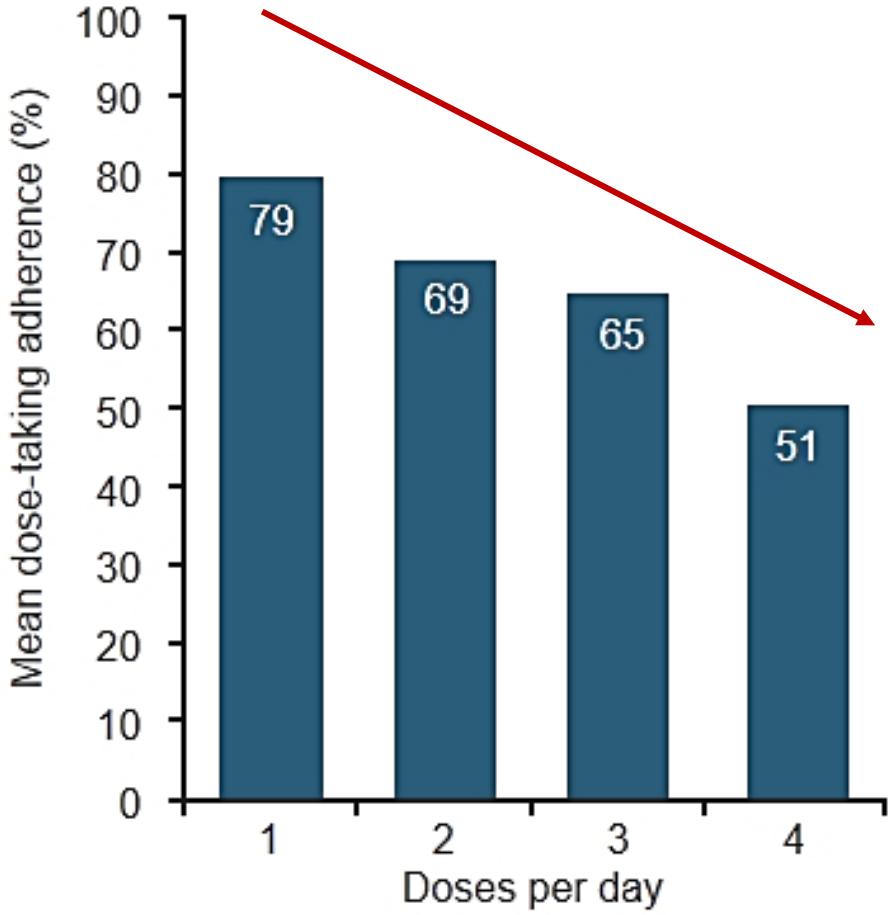
Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. A

WhenA1C is ≥ 1.5% above the glycemic for appropriate targets ,many individuals will require dual- combination therapy.

Fixed Dose Combination (FDC) Therapy

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

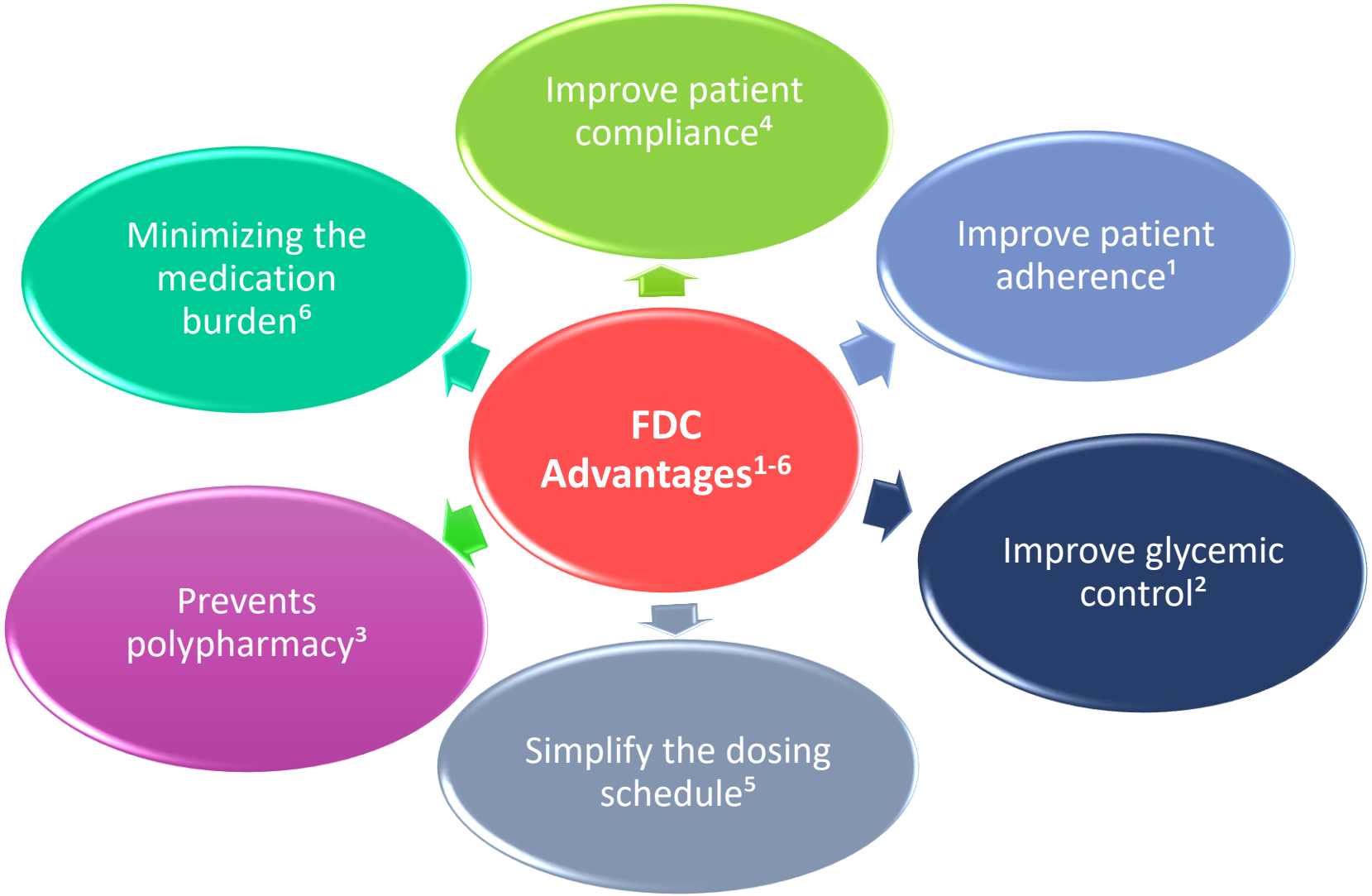


Dose-taking: taking the prescribed number of pills each day.

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

Ration for Choosing Fixed-Dose Combinations:

Fixed-Dose Combination Therapy Delivers Optimal Therapeutic Advantages for the patients



1- Curr Ther Res Clin Exp. 2017; 84: 4–9. 2- Diabetes Res ClinPract. 2013;102:16–24.3- Int J Endocrinol. 2015;2015:1–15. 4- J Assoc Physicians India. 2019 Dec;67(12):58-64. 5- Diabetes Obes Metab. 2013;15(4):291-300 6- Diabetes Ther. 2020 Jul;11(7):1513-1525.

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]

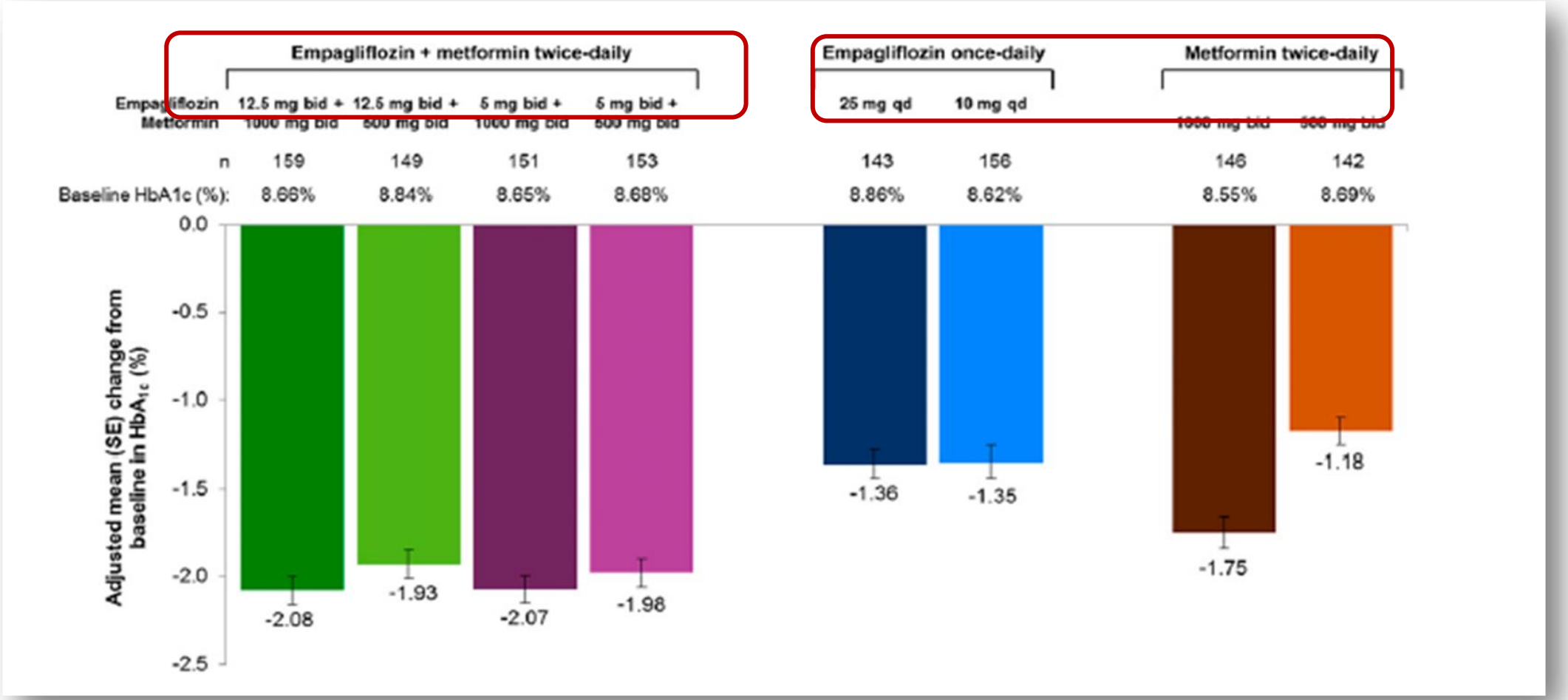
Diabetes Care 2016;39:1718–1728 | DOI: 10.2337/dc16-0522

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

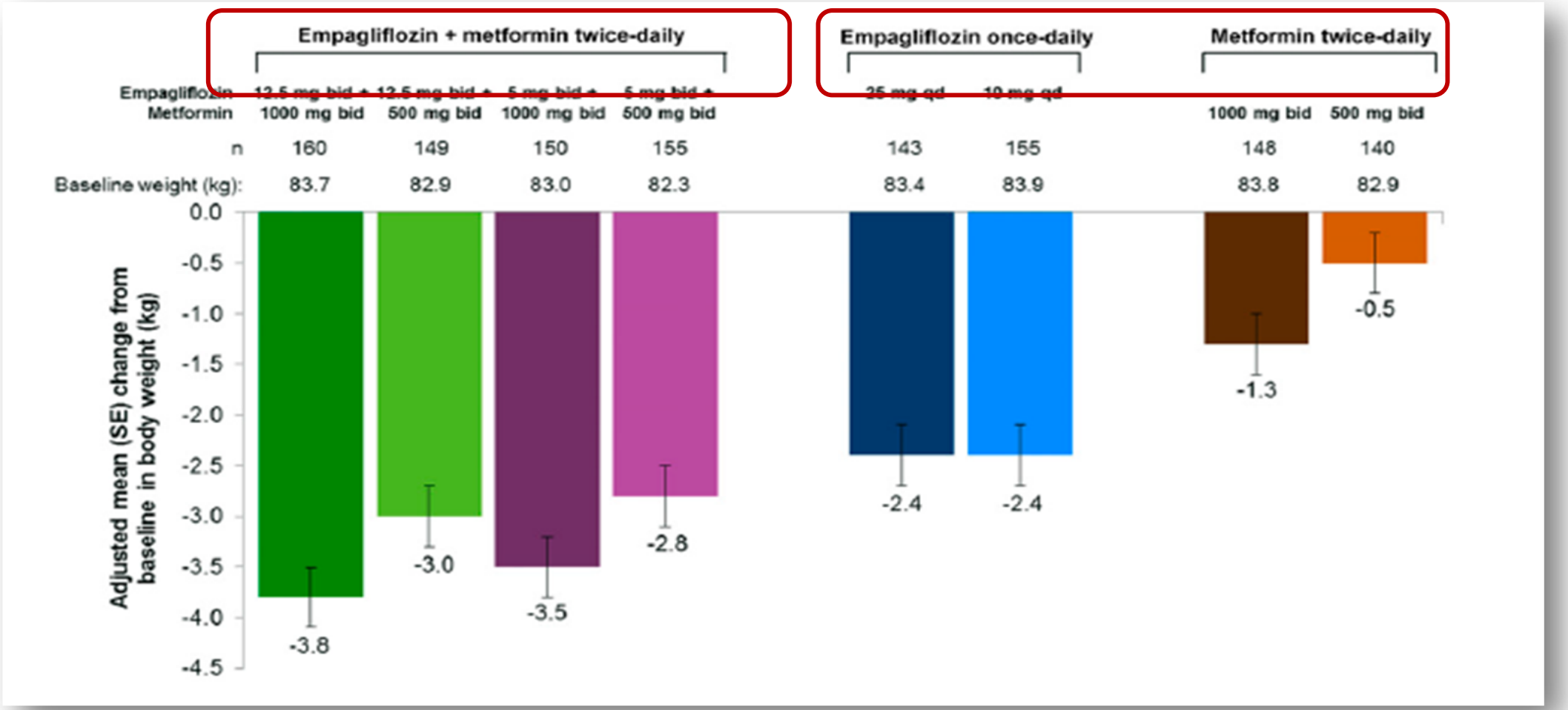
Diabetes Care. 2016 1; 39(10):1718-28

Change from Baseline in HbA1c



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

Change from Baseline in Weight



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

Combination of Linagliptin and Metformin

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*

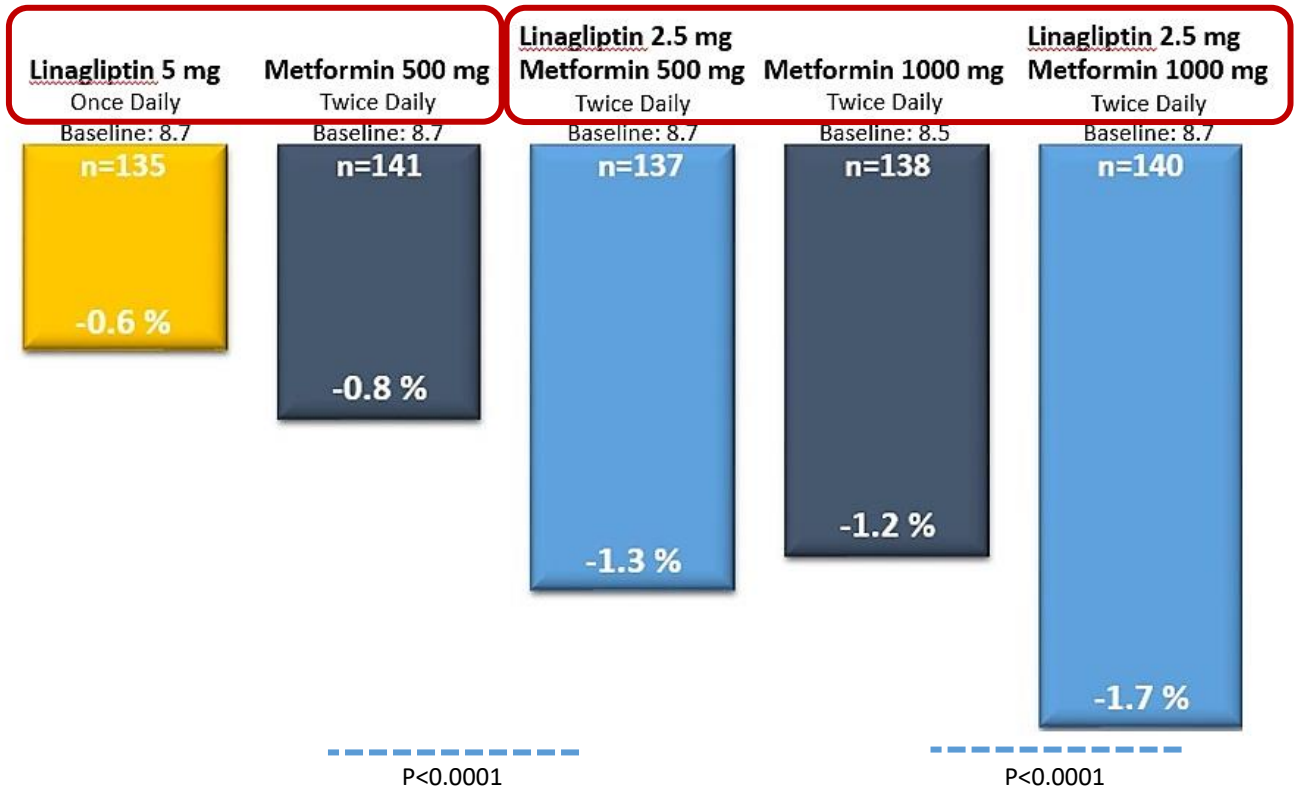
ORIGINAL ARTICLE

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.

Lina/Met 2.5/1000 mg:
1.7 % HbA1c Reduction With Initial Combination Therapy



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.

Conclusion

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

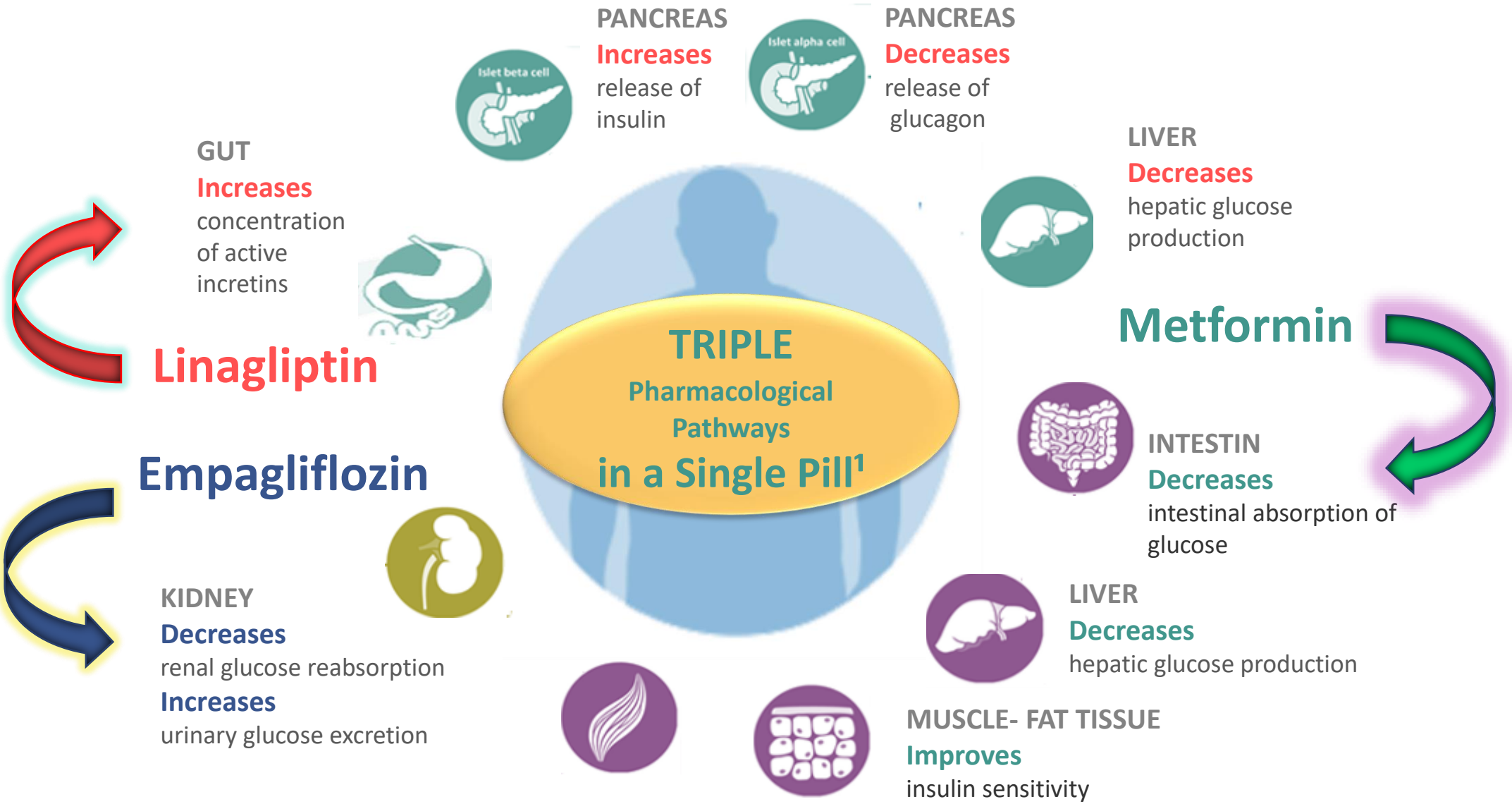
- Reducing HbA1c
- Reducing FPG levels

with the additional benefits of:

- No weight gain
- Low risk of hypoglycemia

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

Combination of Empagliflozin and Linagliptin and Metformin



1. Diabetes Care. 2015;38(3):384-393. DPP-4:Dipeptidyl Peptidase-4; SGLT2:Sodium Glucose co-transporter-2.

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

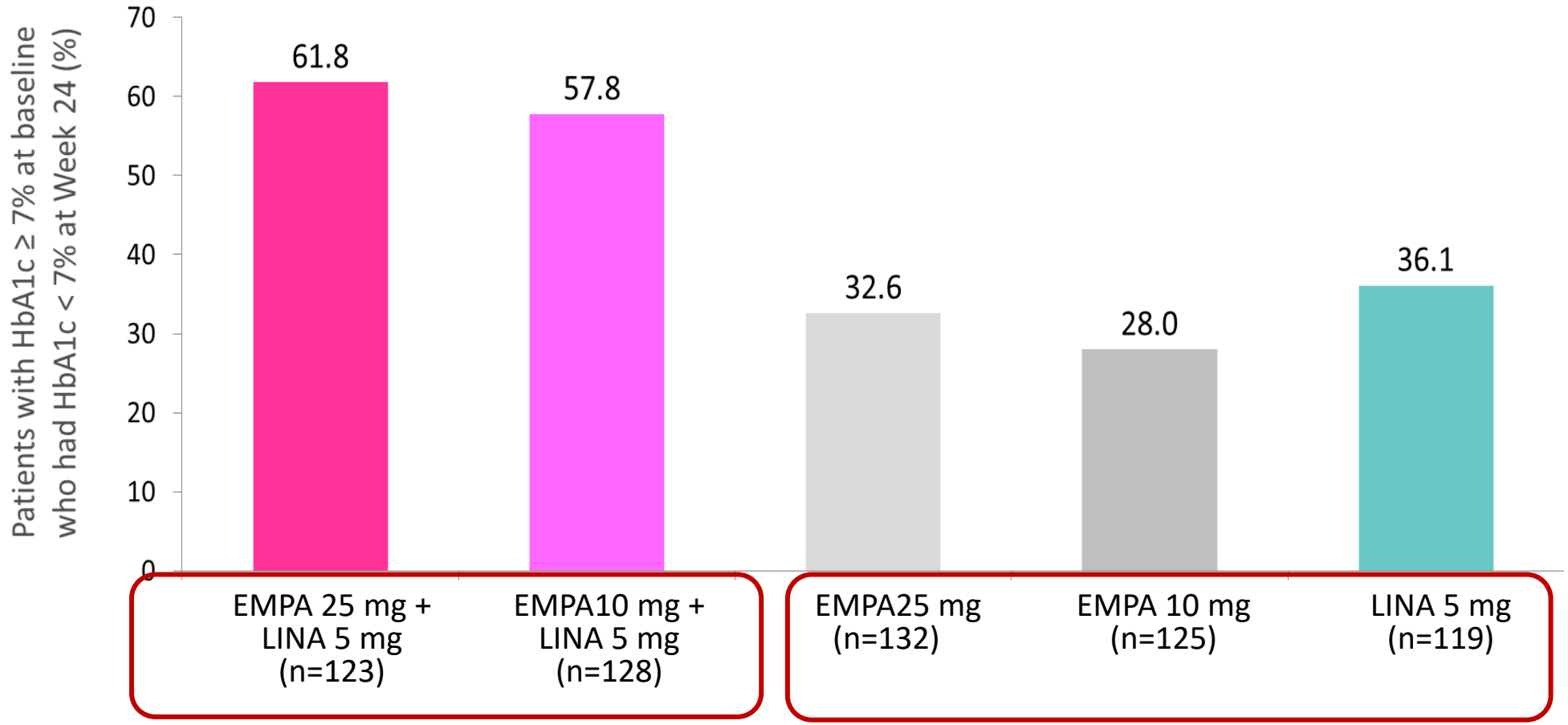
Phase III randomized, double blind, parallel-group study[1]

680 Patients randomized

22 Countries, **197** Sites

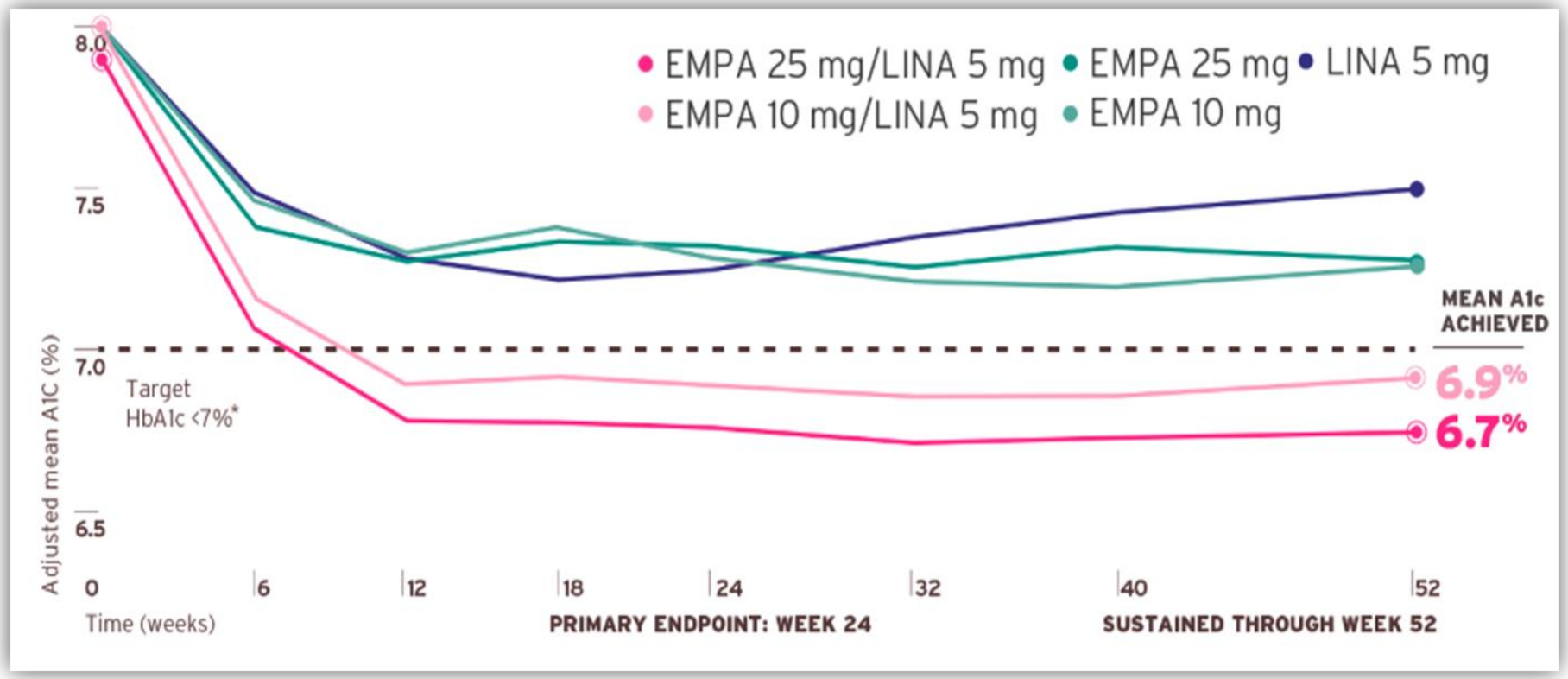
1- Diabetes Care. 2015;38(3):384-393.

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



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

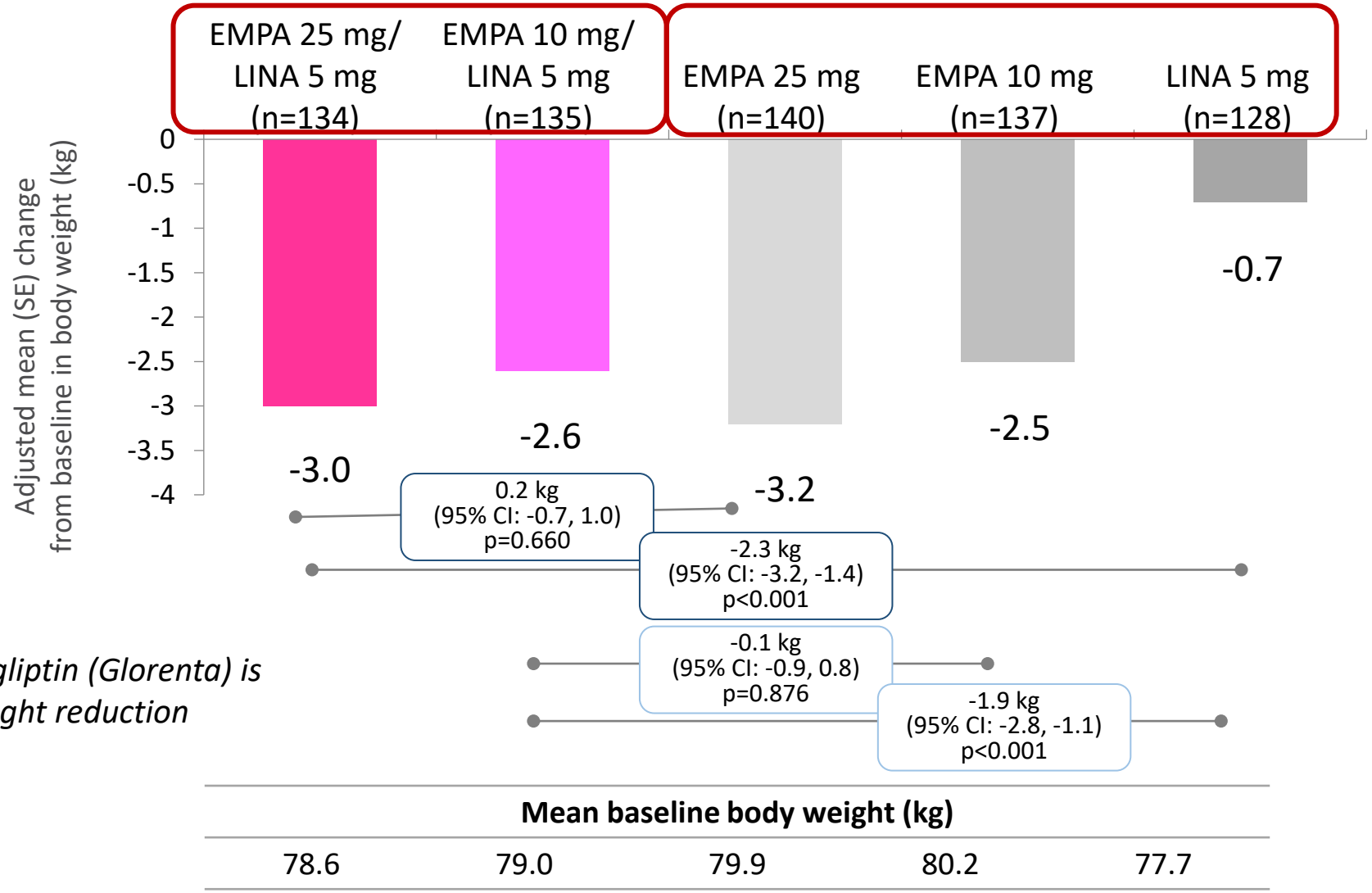
Combination of Empagliflozin+Linagliptin Demonstrates Early and Durable Achievement of Goal



* 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

Change from baseline in body weight at Week 24



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

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

Conclusion

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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