# Combination Therapy for Type 2 Diabetes

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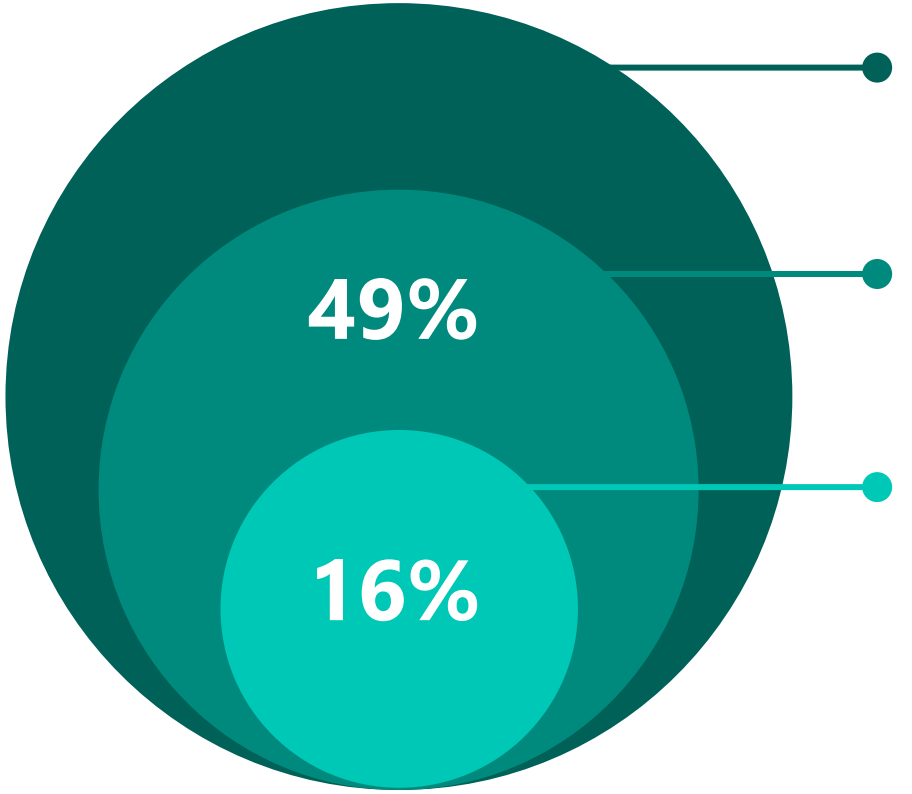
# Educational Objectives

- Discuss the use of combination therapy using agents with complementary mechanisms of action
- Assess patient A1C in determining appropriate combination therapy
- Review the hierarchy of agents in treatment decision-making
- Understand the importance of individualized therapy
- Prescribe appropriate combination therapy for patients at high cardiovascular risk
- Summarize injectable combination therapies

A1C, glycated hemoglobin.

# Approach to Combination Therapy

# A1C Levels in Patients With Diabetes




Total US Population With Diabetes

A1C >7%

A1C >9%

**Many patients with diabetes remain above target levels**

A1C, glycated hemoglobin; ADA, American Diabetes Association.

Carls G, et al. *Diabetes Ther*. 2017;8:863-873.

# Role of A1C

- A1C is an indirect measure of average blood glucose levels over a period of approximately 3 months[1]
- A1C serves as a highly predictive tool for diabetic complications[1]
- Higher A1C targets may be required for individual patients (eg, the elderly) and can change over time[2]
- Some studies have shown higher A1C levels in African Americans than non-Hispanic whites[1]
- It is important to consider individualized SMBG and A1C levels when setting glucose targets[1,2]

A1C, glycated hemoglobin; SMBG, self-monitoring of blood glucose.

1. American Diabetes Association. *Diabetes Care.* 2019;42:S61-S70.
2. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

# A1C Targets: American Association of Clinical Endocrinologists

- When possible and achieved safely and affordably, AACE recommends an A1C target of ≤6.5%
- If adverse outcomes such as severe hypoglycemia result from this lower target, a target of >6.5% may be appropriate

A1C, glycated hemoglobin; AACE, American Association of Clinical Endocrinologists.
Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

# A1C Targets: American Diabetes Association

- A1C <7% is an appropriate goal for many nonpregnant adults
- Select individual patients may target stricter A1C goals (<6.5%) if achievable without adverse effects
  - This includes patients treated only with lifestyle therapy or metformin, or those with more recent-onset diabetes, as well as those with longer projected life span and no CVD
- Other patients may require less rigid A1C goals (<8%), including patients with:
  - Lower life expectancy
  - History of hypoglycemia
  - Advanced vascular complications
  - Considerable comorbid conditions
  - Long-standing treatment-resistant diabetes

A1C, glycated hemoglobin; CVD, cardiovascular disease.
American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.

# A1C Targets, International Diabetes Organizations

| Organization | Recommended A1C Target |
|---|---|
| **American Association of Clinical Endocrinologists**[1] | **≤6.5%**<br>Based on safety and affordability; individualize where appropriate |
| **American Diabetes Association/ European Association for the Study of Diabetes**[2] | **≤7%**<br>Most nonpregnant adults with adequate life expectancy; individualize based on patient characteristics and preferences and risk of adverse events |
| **Diabetes Canada**[3] | **≤6.5%** Adults with low hypoglycemia risk, to reduce CKD and retinopathy risk<br>**≤7%** Most adults<br>**7.1%-8.5%** Elderly (+/- dementia), functionally dependent, at high risk for hypoglycemia, and/or with limited life expectancy |
| **Latin American Diabetes Association**[4] | **≤6.5%** Young, no complications, at low risk for hypoglycemia<br>**<7%** Individualize treatment |
| **National Institute for Health and Care Excellence**[5] | **6.5%** If managed by lifestyle + diet +/- single drug<br>**7.0%** If on a drug associated with hypoglycemia<br>Consider less stringent target if patient has lower life expectancy, high hypoglycemia risk, and/or significant comorbidities |

A1C, glycated hemoglobin; CKD, chronic kidney disease.

1. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90. 2. ADA/EASD. *Diabetes Care*. 2019;42:S61-S70. 3. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes*. 2018;42:S1-S325. 4. Davies MJ, et al. *Diabetologia*. 2018;61:2461-2498. 5. NICE guideline. Updated May 2017. https://www.nice.org.uk/guidance/ng28.

# Individualization of Glycemic Targets

- Evidence supports tailoring glycemic goals to individual patients
- Therapeutic choices should be guided by patient attributes and medication mechanisms of action; consider factors such as disease duration, baseline A1C, and obesity status
- Other factors to consider include patient age, therapeutic goals, potential contraindications, and benefits vs risks of each regimen
  - A1C ≤6.5% for recent onset T2D without clinically significant ASCVD may lead to a reduction in lifetime risk of micro- and macrovascular complications
  - A1C >6.5% is recommended for patients with severe hypoglycemia, shorter life expectancy, advanced renal disease or macrovascular complications, significant comorbidities, or difficult-to-treat long-standing T2D

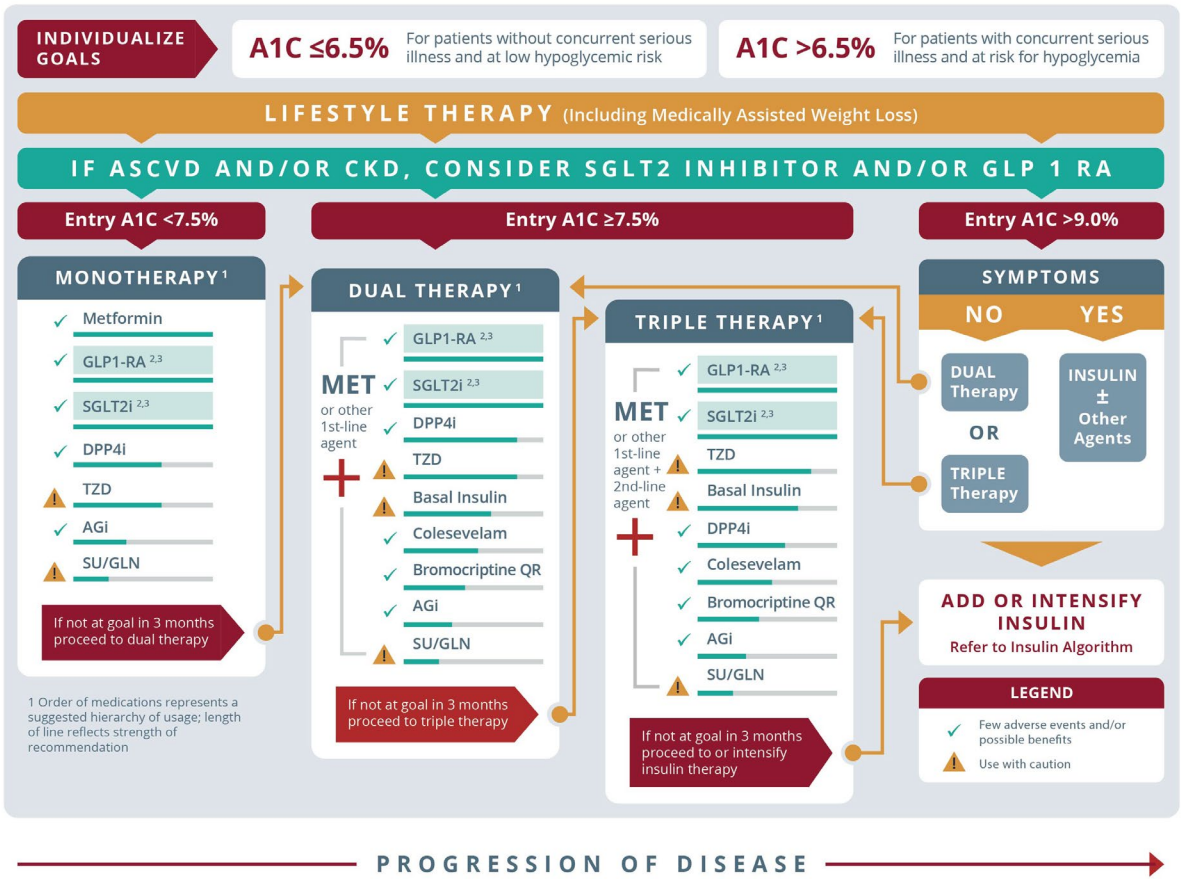
A1C, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; T2D, type 2 diabetes.

Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

# 2019 AACE Glycemic Control Algorithm

Key principles include:

- Individualized goals
- Inclusion of lifestyle therapy
- Prompt initiation of mono-, dual, or triple therapy (including insulin), based on A1C targets

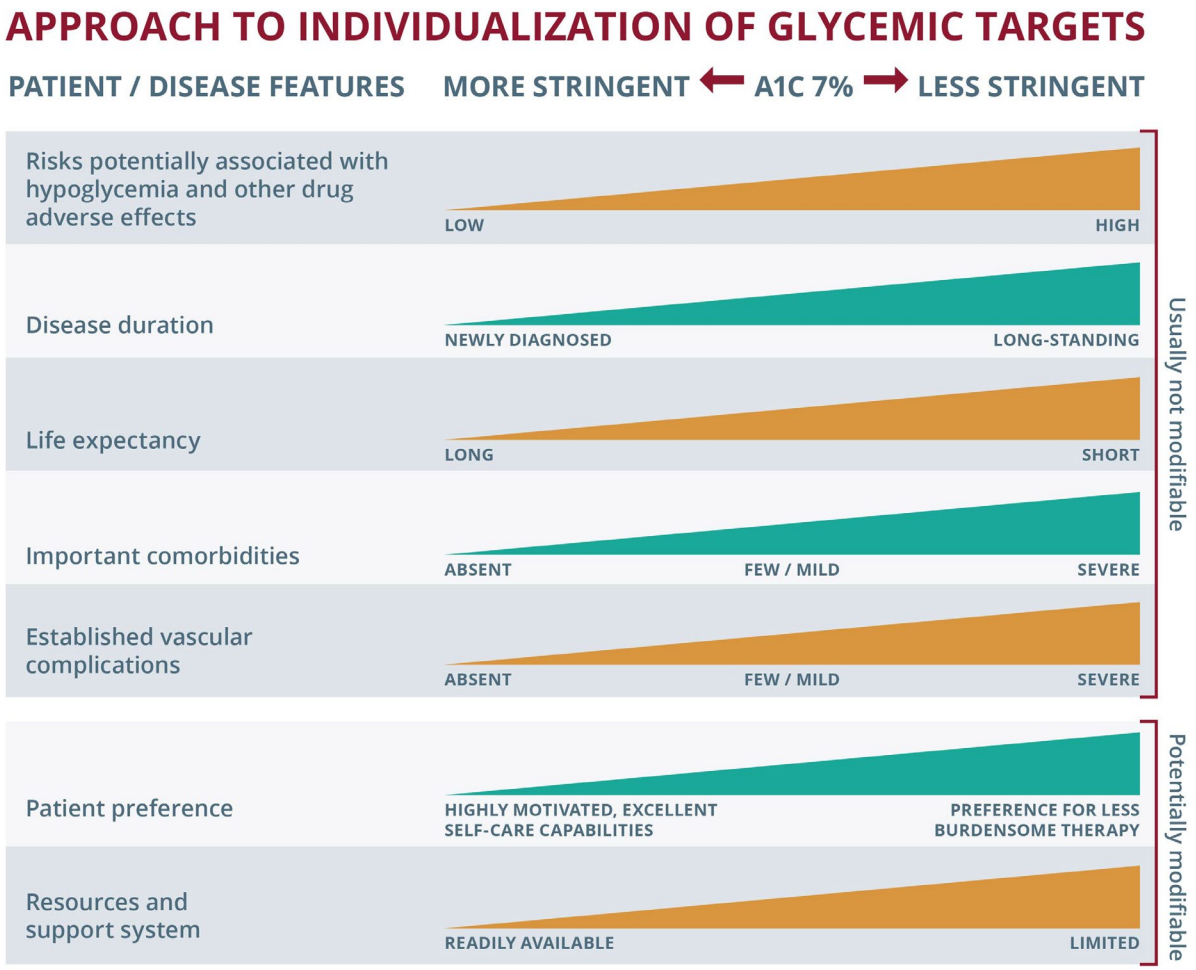



A1C, glycated hemoglobin; AACE, American Association of Clinical Endocrinologists; AGi, alpha-glucosidase inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLN, glinides; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SLGT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; TZD, thiazolidinediones.

Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

# Glycemic Target Individualization: American Diabetes Association

- Patient and disease factors used to determine optimal A1C targets
- Characteristics toward the left justify more stringent efforts to lower A1C
- Characteristics toward the right suggest less stringent efforts
- A1C 7% = 53 mmol/L

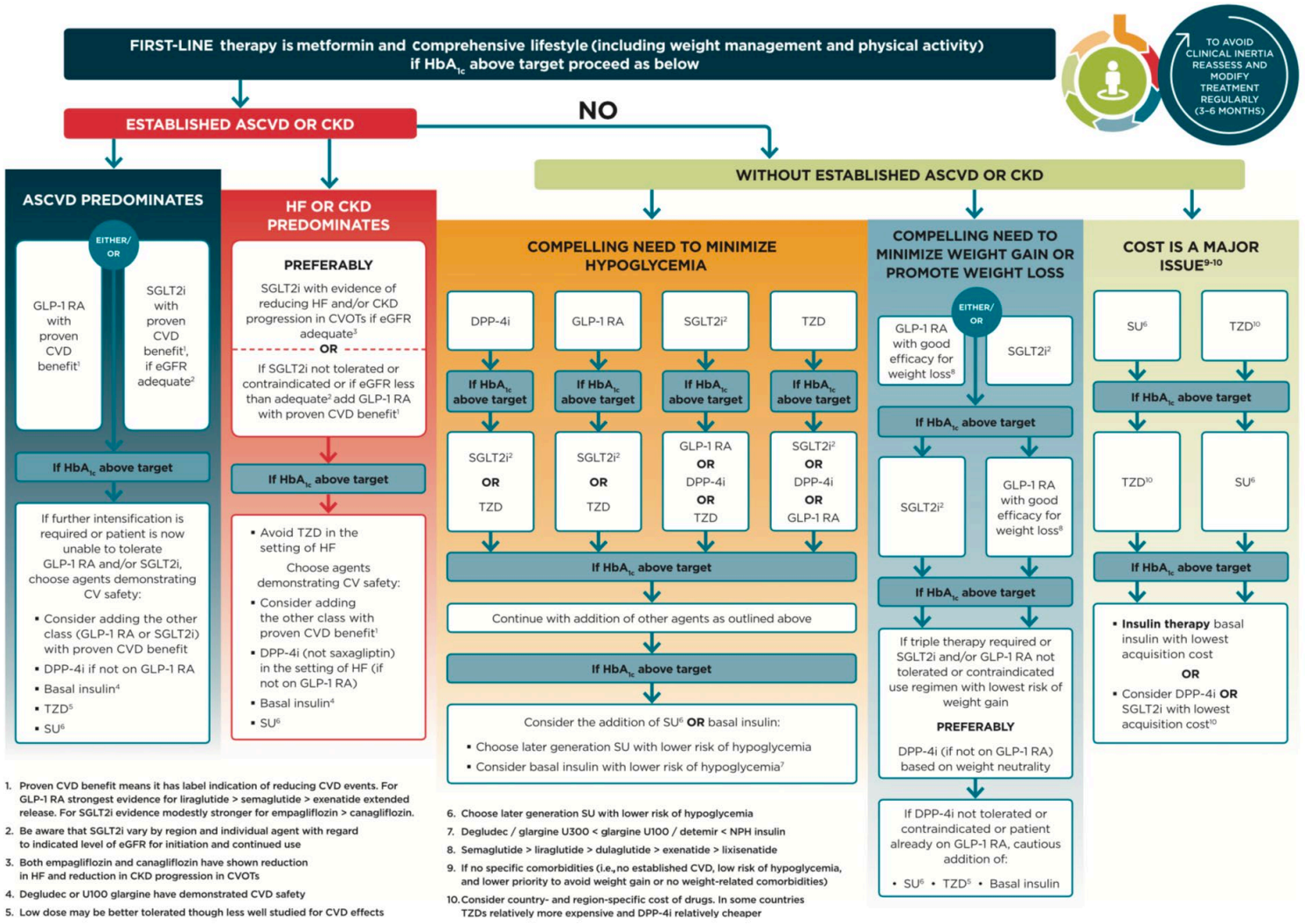



A1C, glycated hemoglobin.

American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.

# 2019 ADA/EASD Glycemic Control Algorithm

- Takes into account whether the patient has:
  - Established ASCVD or CKD
  - A compelling need to minimize hypoglycemia and/or weight gain, or promote weight loss
- Cost is also taken into account



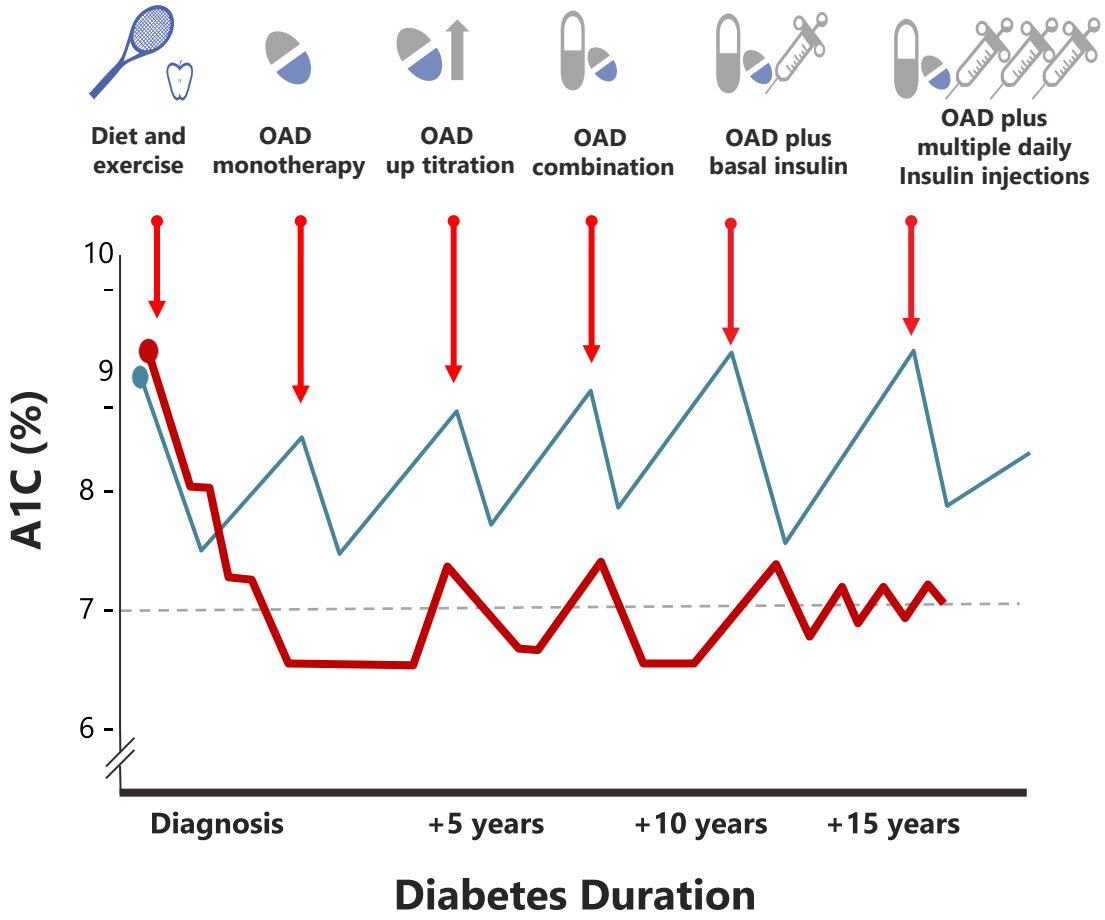

A1C, glycated hemoglobin; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; EASD, European Association for the Study of Diabetes.

ADA/EASD. *Diabetes Care*. 2019;42:S61-S70.

# Agents Used in Combination Therapy

# Sequential Management of Hyperglycemia: "Treatment to Failure"

- A stepwise treatment approach has traditionally been used to manage patients with T2D. New treatments are added only when acute symptoms become apparent.
- Earlier intensification with combination therapy is recommended to achieve and maintain target goals among patients with high A1C levels at baseline.



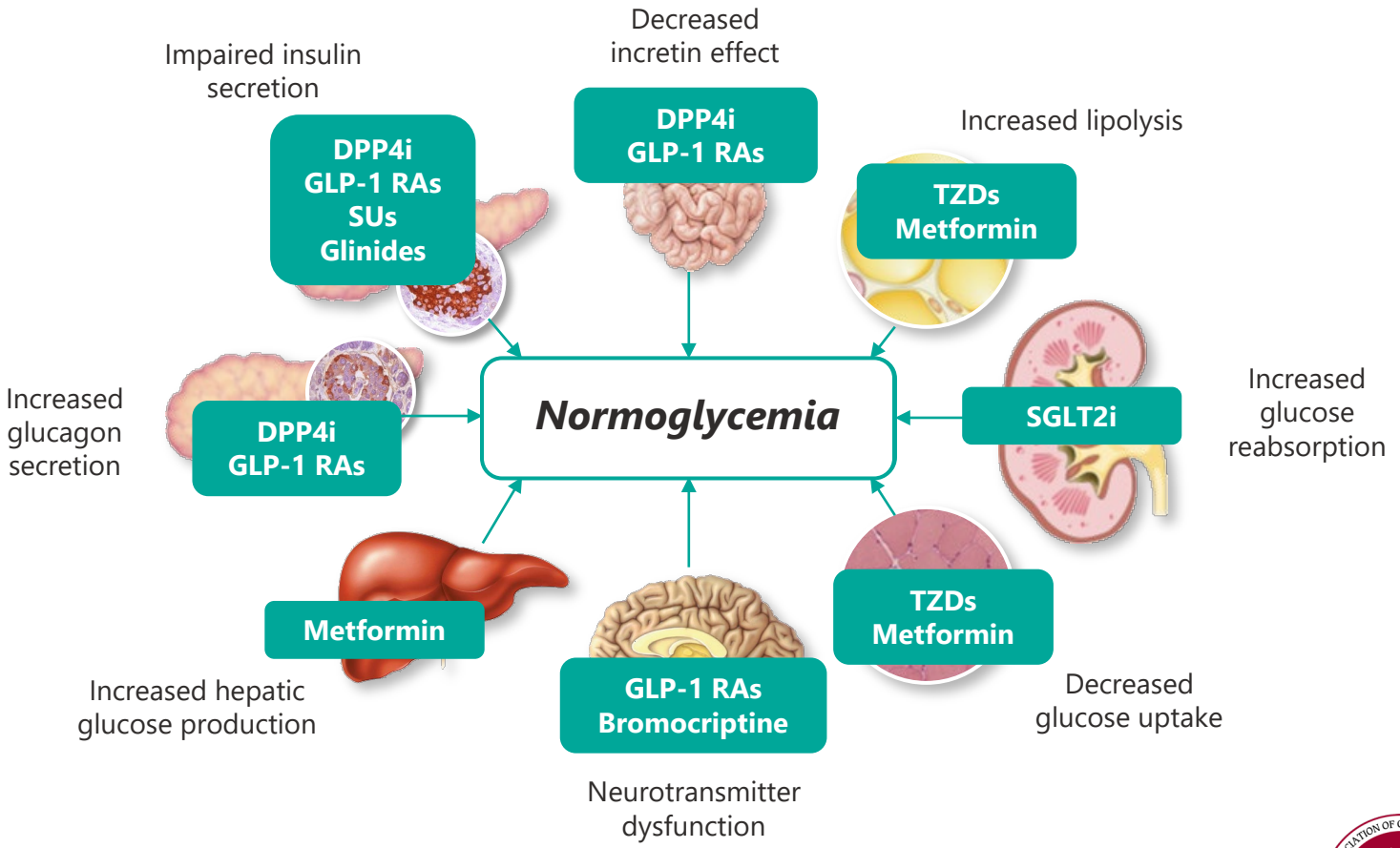

A1C, glycated hemoglobin; OAD, oral antidiabetic drug; T2D, type 2 diabetes.

1. Campbell IW. Br J Cardiol. 2000;7:625-631. 2. Del Prato S, et al. Int J Clin Pract. 2005;59:1345-1355.
3. https://www.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines-treatment-algorithms/comprehensive

# The "Ominous Octet" Multifactorial Pathophysiology of T2D

To optimally manage T2D:

1. Therapy should be individualized based on known pathophysiologic defects
2. Multiple agents are necessary to target different aspects of this disorder




DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SLGT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinediones.
Adapted from DeFronzo RA. *Diabetes* 2009;58:773-795.

# Type 2 Diabetes Pharmacotherapy


DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SLGT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones.

1. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90. 2. Inzucchi et al Diabetes Care. 2015 Jan,38(1):140-9.

# Combination Therapy: Major Second-Line Agents

| Agent | Mechanism of Action | Benefits |
|---|---|---|
| **Glucagon-like peptide-1 receptor agonists** | Mimic GLP-1, resulting in increased insulin secretion and inhibited glucagon secretion[1] | Promote weight loss and strong A1C-lowering with a relatively low risk of hypoglycemia[1,2] |
| **Sodium-glucose cotransporter-2 inhibitors** | Target renal glucose reabsorption by inhibiting SGLT on the luminal membrane of tubular cells of the proximal convoluted tubule, promoting urinary secretion of glucose[3] | Significant reductions in A1C levels, and improved systolic blood pressure and body weight[2] |
| **Dipeptidyl peptidase-4 inhibitors** | Prevent the breakdown of GLP-1 to increase insulin secretion and decrease glucagon secretion[4,5] | Neutral risk of ASCVD and weight gain, low risk for hypoglycemia; modest A1C-lowering effects[5,6]<br><br>Evidence suggests good safety profile in elderly and in patients with T2D and liver dysfunction due to fatty liver[7] |
| **Thiazolidinediones** | Directly decrease insulin resistance in adipose tissue, muscle, and the liver by activating the nuclear receptor, PPAR; this alters the transcription of several genes involved in glucose and lipid metabolism and energy balance[5,8] | Strong A1C lowering, low hypoglycemia risk; low-cost[5,6] |
| **Sulfonylureas** | Stimulate pancreatic beta-cell secretion of insulin by closing ATP-sensitive K+ channels in the cell membrane[9] | Potent A1C reductions and low cost[6,10] |

A1C, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; ATP, adenosine triphosphate; GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferator-activated receptor; SGLT, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

1. Sposito AC, et al. *Cardiovasc Diabetol*. 2018;17:157. 2. Garber AJ, et al. *Endocr Pract*. 2018;24:91-120. 3. Andrianeses V, et al. *Ther Adv Endocrinol Metab*. 2016;7:212-228. 4. Xia C, et al. *Heart Fail Rev*. 2017;22:299-304. 5. Garber AJ, et al. *Endocr Pract*. 2018;24:91-120. 6. American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70. 7. Kanazawa I, et al. *Med Sci Monit*. 2014;20:1662-1667. 8. Hauner H. *Diabetes Metab Res Rev*. 2002;18:S10-S15. 9. Ashcroft FM. *Horm Metab Res*. 1996;28:456-463. 10. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

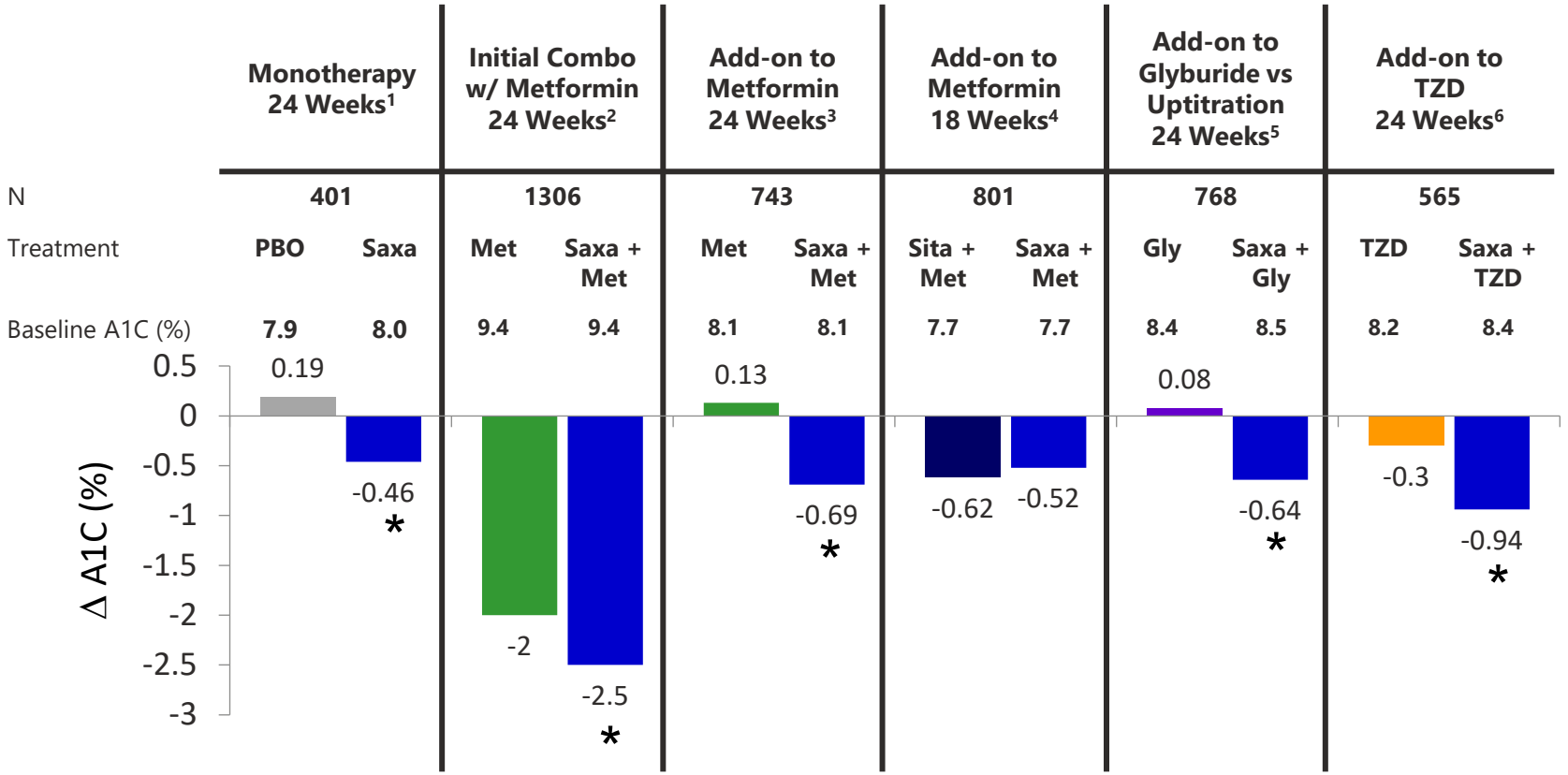
# Initiation of Combination Therapy

- Metformin is the preferred first-line agent for the treatment of T2D[1,2]
- Patients on metformin monotherapy who do not achieve glycemic targets should be started on combination therapy with additional agents, including insulin[2]
- Combination therapy is often required and should include therapeutic agents with complementary mechanisms of action[2]
- For patients with A1C >7.5% who are not on antihyperglycemic agents, metformin plus another agent in addition to lifestyle therapy should be initiated[2]
- Although a medication's efficacy declines somewhat when added as a third agent, the addition may be required to ensure effective treatment[2]
- Symptomatic patients with A1C >9% are likely to achieve great benefit from the addition of insulin, although maximum doses with 2 or 3 other agents may be adequate if the patient has no significant symptoms[2]

A1C, glycated hemoglobin; T2D, type 2 diabetes.

1. American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.
2. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

# Combination Therapy: Glucose Control With Saxagliptin

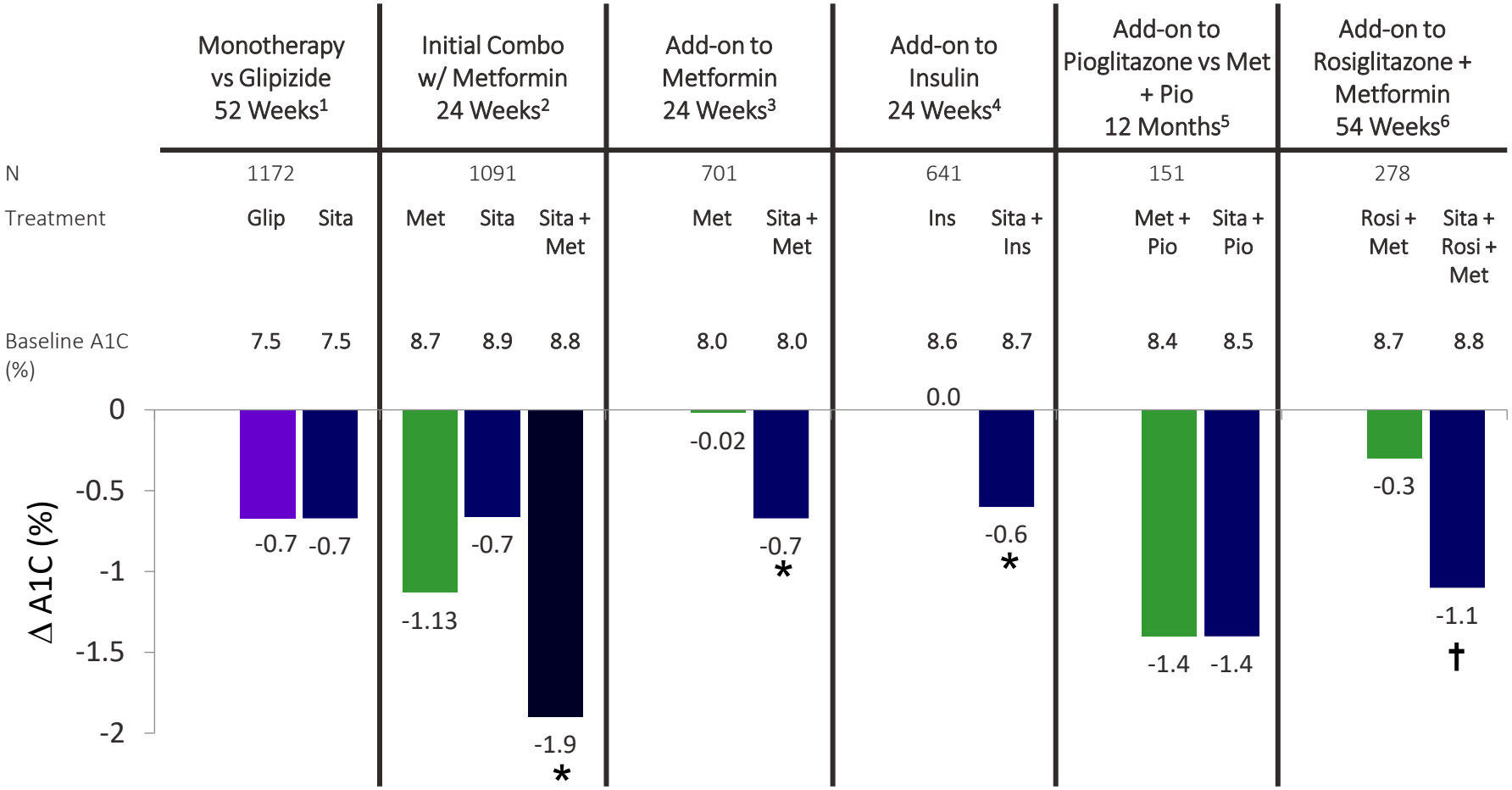



* *P*<0.0001 vs comparator.

A1C, glycated hemoglobin; Gly, glyburide; Met, metformin; PBO, placebo; Saxa, saxagliptin; Sita, sitagliptin; TZD, thiazolidinediones.

1. Rosenstock J, et al. *Curr Med Res Opin*. 2009;25:2401-2411. 2. Jadzinsky M, et al. *Diabetes Obes Metab*. 2009;11:611-622.
3. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 4. Scheen AJ, et al. *Diabetes Metab Res Rev*. 2010;26:540-549. 5. Chacra AR, et al. *Int J Clin Pract*. 2009;63:1395-1406. 6. Hollander P, et al. *J Clin Endocrinol Metab*. 2009;94:4810-4819.

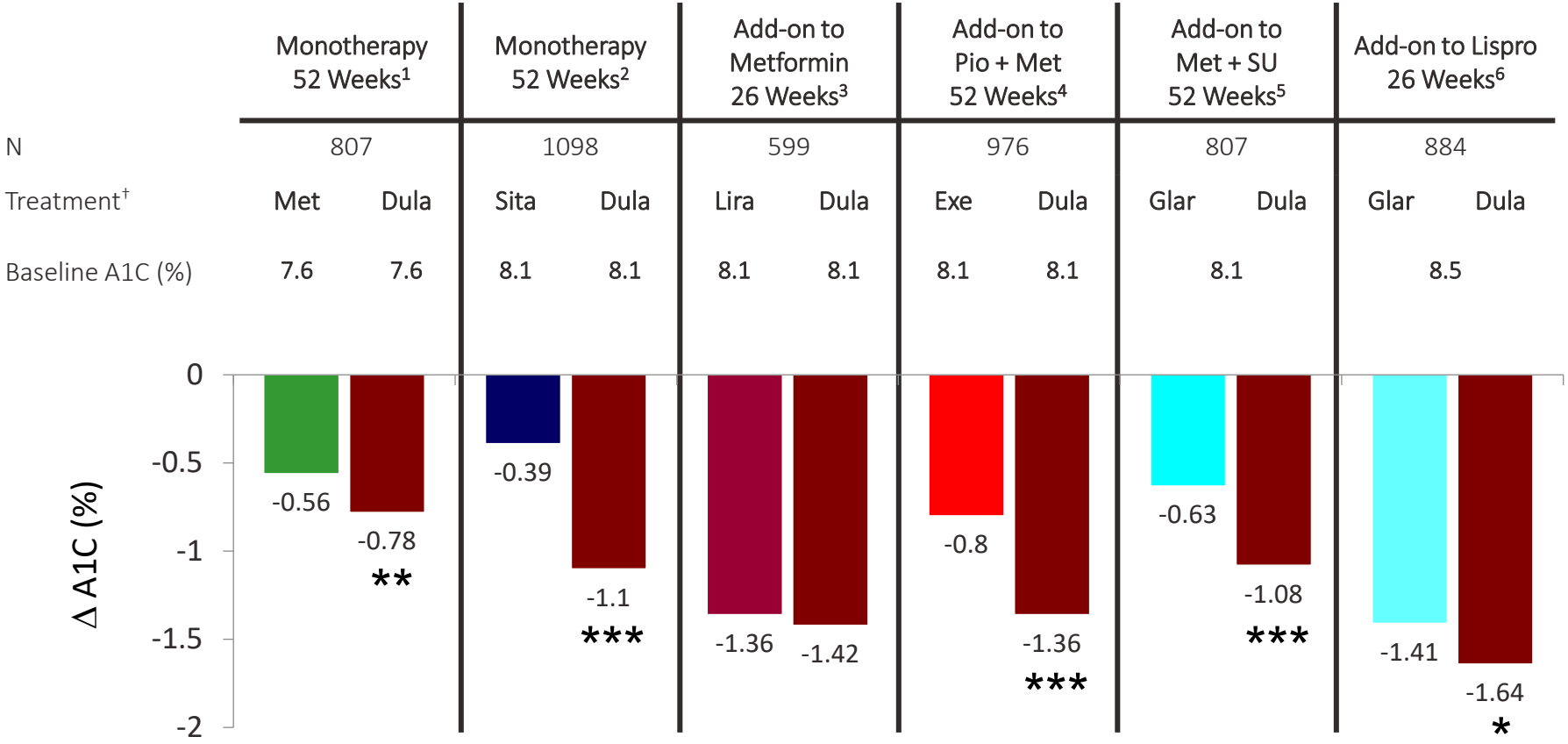
# Combination Therapy: Glucose Control With Sitagliptin




* *P*<0.001 vs active comparator monotherapy. † *P*<0.001 vs active comparator dual therapy.
A1C, glycated hemoglobin; Glip, glipizide; Ins, insulin; Met, metformin; Pio, pioglitazone; Rosi, rosiglitazone; Sita, sitagliptin.


1. Nauck MA, et al. *Diabetes Obes Metab*. 2007;9:194-205. 2. Goldstein BJ, et al. *Diabetes Care*. 2007;30:1979-1987.
3. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 4. Vilsbøll T, et al. *Diabetes Obes Metab*. 2010;12:167-177.
5. Derosa G, et al. *Metab Clin Exp*. 2010;59:887-895. 6. Dobs AS, et al. *J Diabetes*. 2013;5:68-79.

# Combination Therapy: Glucose Control With Dulaglutide



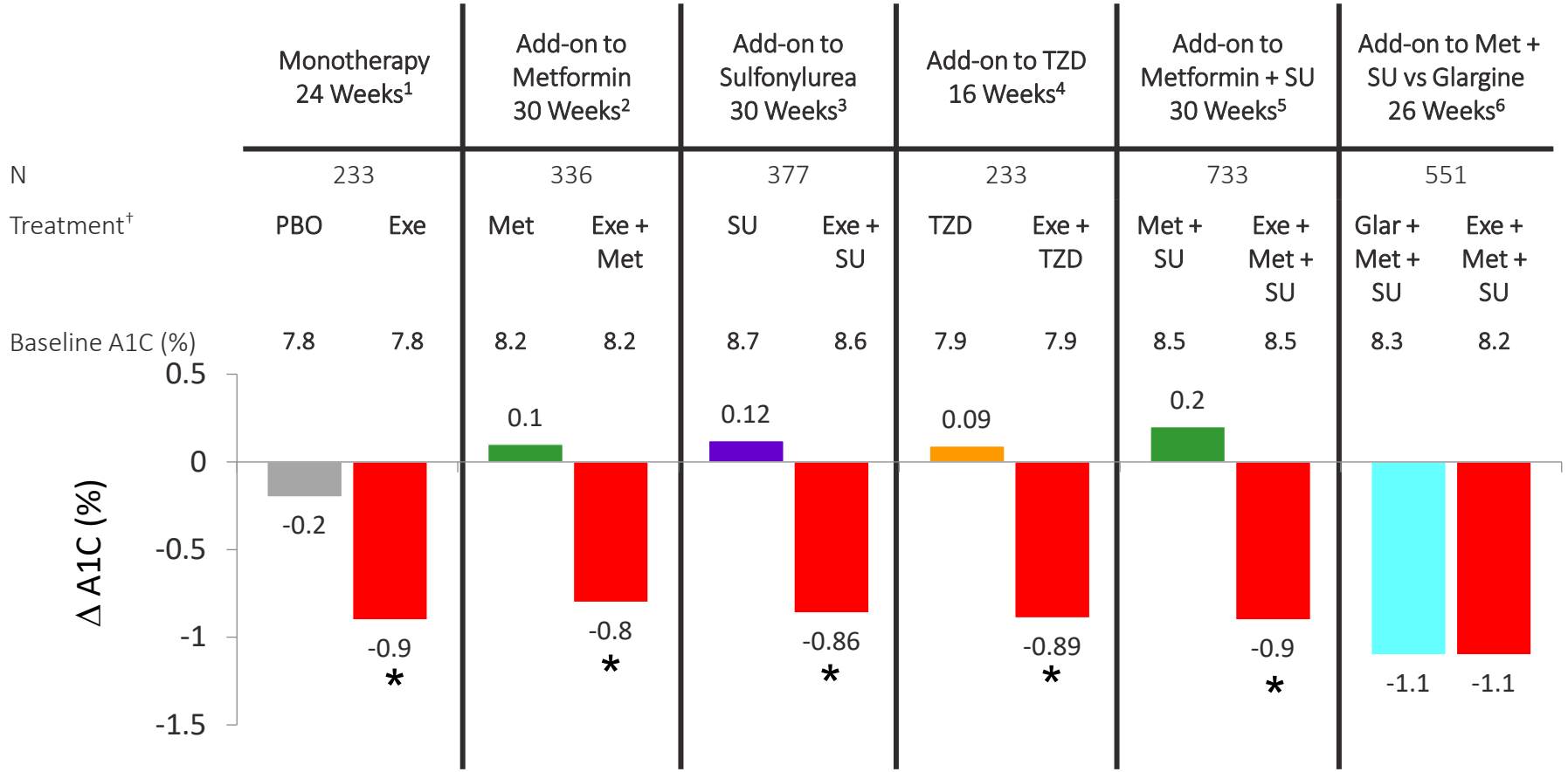

* $P<0.02$ vs glargine. ** $P<0.01$ vs metformin. *** $P<0.001$ vs comparator.

†All dulaglutide dosages shown are 1.5 mg once weekly.

A1C, glycated hemoglobin; Dula, dulaglutide; Exe, exenatide; Glar, glargine; Lira, liraglutide; Met, metformin; Pio, pioglitazone; Sita, sitagliptin; SU, sulfonylureas.

1. Umpierrez G, et al. *Diabetes Care*. 2014;37:2168-2176. 2. Nauck M, et al. *Diabetes Care*. 2014;37:2149-2158. 3. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 4. Wysham C, et al. *Diabetes Care*. 2014;37:2159-2167. 5. Giorgino F, et al. *Diabetes Care*. 2015;38:2241-2249. 6. Blonde L, et al. *Lancet*. 2015:385:2057-2066.

# Combination Therapy: Glucose Control With Exenatide



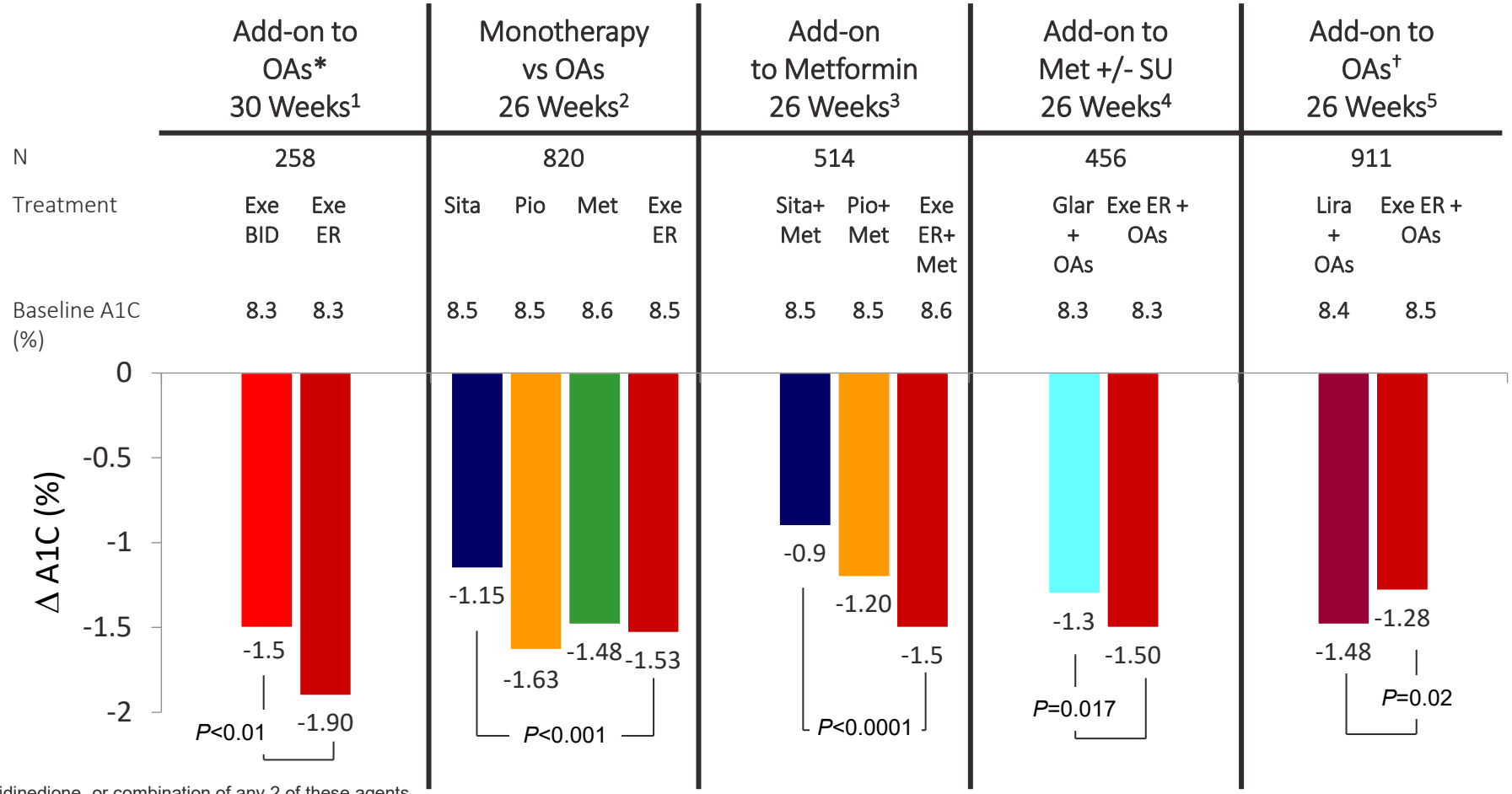

* *P*<0.001 vs comparator.

† All exenatide dosages shown are 10 µg BID.

A1C, glycated hemoglobin; Exe, exenatide; Glar, glargine; Met, metformin; PBO, placebo; SU, sulfonylureas; TZD, thiazolidinediones.

1. Moretto TJ, et al. *Clin Ther*. 2008;30:1448-1460. 2. DeFronzo RA, et al. *Diabetes Care*. 2005;28:1092-1100. 3. Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635. 4. Zinman B, et al. *Ann Intern Med*. 2007;146:477-485. 5. Kendall DM et al. *Diabetes Care*. 2005;28:1083-1091. 6. Heine RJ, et al. *Ann Intern Med*. 2005;143:559-569.

# Combination Therapy: Glucose Control With Exenatide ER



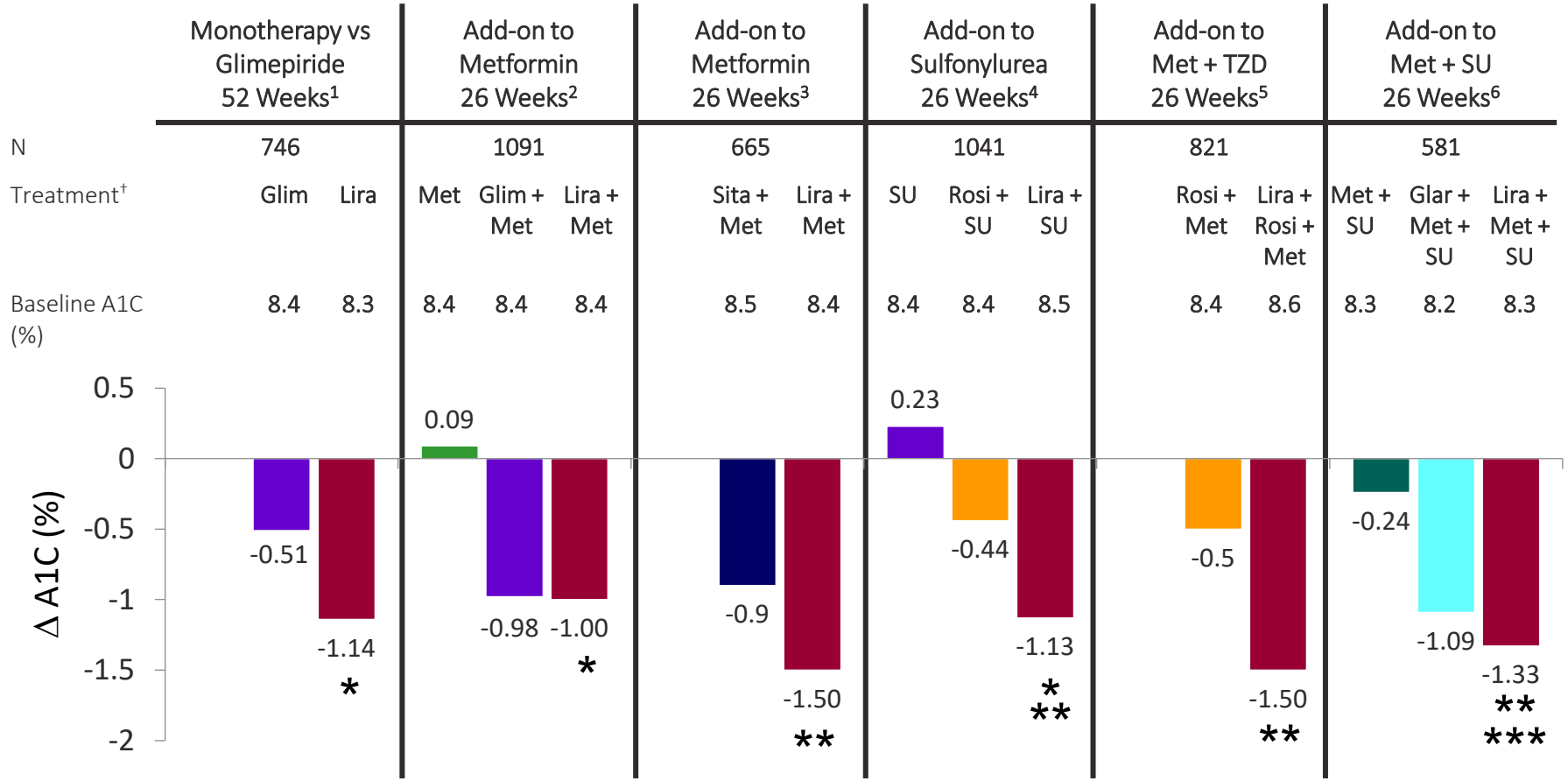

* Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.

† Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

A1C, glycated hemoglobin; Exe, exenatide; ER, extended release; Glar, glargine; Lira, liraglutide; Met, metformin; OAs, oral agents; Pio, pioglitazone; Sita, sitagliptin; SU, sulfonylureas.

1. Drucker DJ, et al. *Lancet*. 2008;372:1240-1250. 2. Russell-Jones D, et al. *Diabetes Care*. 2012;35:252-258. 3. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 4. Diamant M, et al. *Lancet*. 2010;375:2234-2243. 5. Buse JB, et al. *Lancet*. 2013;381:117-124.

# Combination Therapy: Glucose Control With Liraglutide



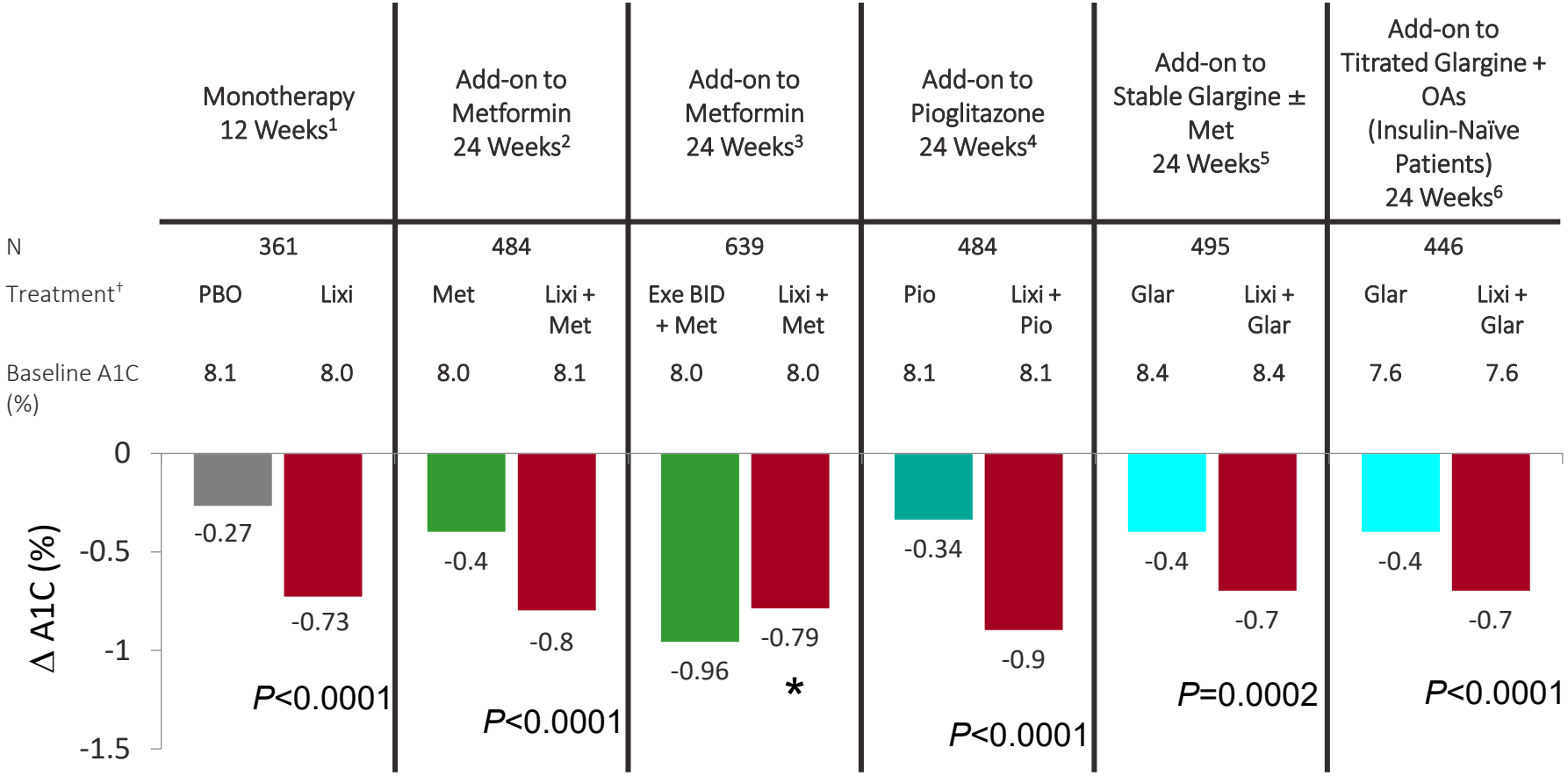

* *P*<0.0001 vs monotherapy. ** *P*<0.0001 vs dual therapy. *** *P*=0.0015 vs glargine.

† All liraglutide dosages shown are 1.8 mg QD.

A1C, glycated hemoglobin; Glar, glargine; Glim, glimepiride; Lira, liraglutide; Met, metformin; QD, once daily; Rosi, rosiglitazone; Sita, sitagliptin; SU, sulfonylureas; TZD, thiazolidinediones.


1. Garber A, et al. *Lancet*. 2009;373:473-481. 2. Nauck M, et al. *Diabetes Care*. 2009;32:84-90. 3. Pratley RE, et al. *Lancet*. 2010;375:1447-1456.
4. Marre M, et al. *Diabet Med*. 2009;26:268-278. 5. Zinman B, et al. *Diabetes Care*. 2009;32:1224-1230. 6. Russell-Jones D, et al. *Diabetologia*. 2009;52:2046-2055.

# Combination Therapy: Glucose Control With Lixisenatide




* Noninferiority criteria met.

† All lixisenatide dosages shown are 20 μg QD, administered in a 2-step dose increase regimen.

A1C, glycated hemoglobin; Exe, exenatide; Glar, glargine; Lixi, lixisenatide; Met, metformin; OAs, oral agents; PBO, placebo; Pio, pioglitazone; QD, once daily.

1. Fonseca VA, et al. *Diabetes Care*. 2012;35:1225-1231. 2. Bolli GB, et al. *Diabet Med*. 2014;31:176-184. 3. Rosenstock J, et al. *Diabetes Care*. 2013;36:2945-2951. 4. Pinget M, et al. *Diabetes Obes Metab*. 2013;15:1000-1007. 5. Riddle MC, et al. *Diabetes Care*. 2013;36:2489-2496. 6. Riddle MC, et al. *Diabetes Care*. 2013;36:2497-2503.

# Combination Therapy
# Glucose Control With Canagliflozin


* All canagliflozin dosages shown are 300 mg.

† Estimated glomerular filtration rate 30-50 mL/min/1.73 $m^2$.

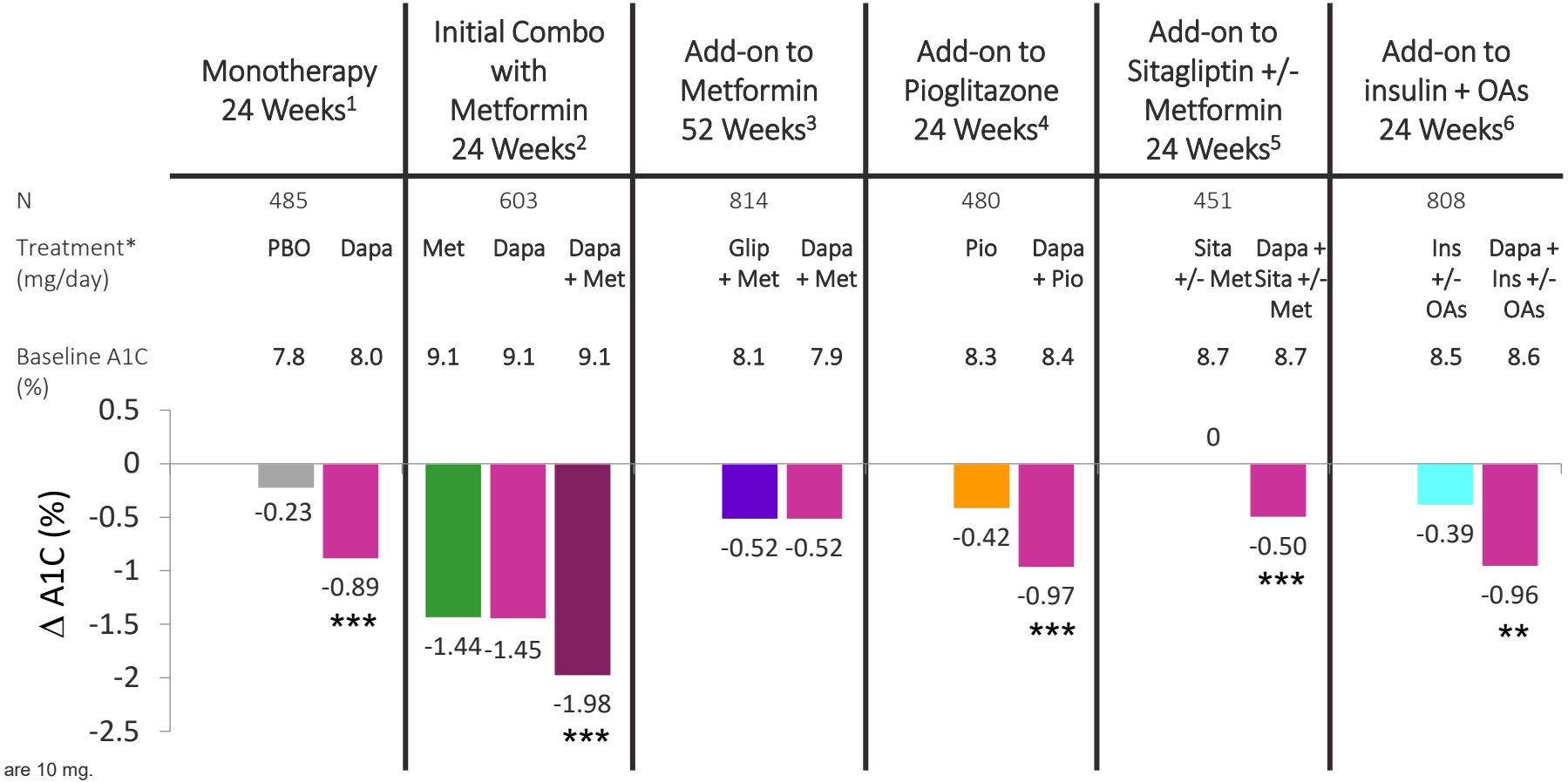
** *P*<0.001 vs placebo.

‡ Met criteria for noninferiority and superiority (upper limit of confidence interval <0.0%).

A1C, glycated hemoglobin; Cana, canagliflozin; CKD, chronic kidney disease; Glim, glimepiride; Ins, insulin; Met, metformin; OAs, oral agents; PBO, placebo; Sita, sitagliptin; SU, sulfonylureas.

1. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382. 2. Rosenstock J, et al. *Diabetes Care*. 2012;35:1232-1238. 3. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 4. Schernthaner G, et al. *Diabetes Care*. 2013;36:2508-2515. 5. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473.

# Combination Therapy: Glucose Control With Dapagliflozin



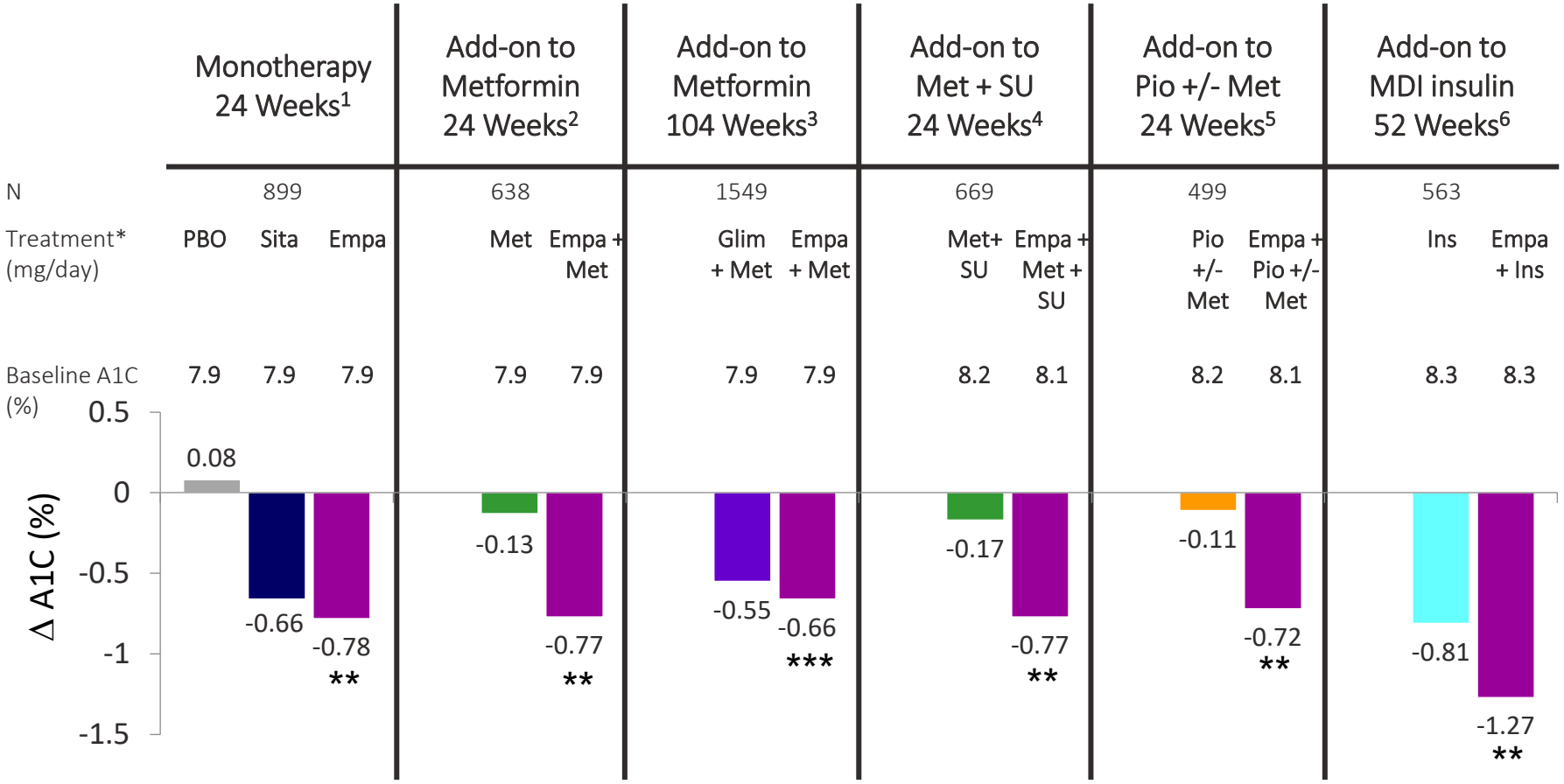

* All dapagliflozin dosages shown are 10 mg.

** *P*<0.001 vs placebo. *** *P*<0.0001 vs comparator.

A1C, glycated hemoglobin; Dapa, dapagliflozin; Ins, insulin; Glip, glipizide; Met, metformin; OAs, oral agents; PBO, placebo; Pio, pioglitazone; Sita, sitagliptin.


1. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224. 2. Henry RR, et al. *Int J Clin Pract*. 2012;66:446-456.
3. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 4. Rosenstock J, et al. *Diabetes Care*. 2012;35:1473-1478.
5. Jabbour SA, et al. *Diabetes Care*. 2014;37:740-750. 6. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415.

# Combination Therapy: Glucose Control With Empagliflozin




* All empagliflozin dosages shown are 25 mg. ** *P*<0.001 vs placebo. *** *P*<0.05 vs active comparator.

A1C, glycated hemoglobin; Empa, empagliflozin; Ins, insulin; Glim, glimepiride; MDI, multiple dose injection; Met, metformin; PBO, placebo; Pio, pioglitazone; Sita, sitagliptin; SU, sulfonylureas.

1. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219. 2. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659. 3. Ridderstrale M, et al. *Lancet Diabetes Endocrinol*. 2014;2:691-700. 4. Haring HU, et al. *Diabetes Care*. 2013;36:3396-3404. 5. Kovacs CS, et al. *Diabetes Obes Metab*. 2014;16:147-158. 6. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.

# Fixed-Dose Combination Agents for T2D

| Single-pill oral | Injectable |
|---|---|
| DPP4i + biguanide[1-3] | GLP-1 RA + basal insulin |
| Meglitinide + biguanide[1] | FDCs available for patients with T2D |
| SGLT2i + biguanide[1,4-7] | |
| SU + biguanide[1] | |
| TZD + biguanide[1] | |
| SGLT2i + DPP4i[1] | |
| DPP4i + TZD | |
| SU + TZD | |

- Evidence from retrospective pharmacy claims analyses suggests that adherence is improved with FDC compared with 2-pill combinations[8-10]
- Improved adherence has also been shown when switching from monotherapy to FDC, rather than separate pill combinations[10]

DPP4i, dipeptidyl peptidase-4 inhibitors; FDC, fixed-dose combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinediones.

1. Vijayakumar TM, et al. *Curr Ther Res Clin Exp*. 2017;84:4-9. 2. Jentadueto® (linagliptin and metformin hydrochloride) tablets [prescribing information]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2019. 3. Kazano (alogliptin and metformin HCl) tablets [prescribing information]. Takeda Pharmaceuticals America, Inc.; 2017. 4. Invokamet® (canagliflozin and metformin hydrochloride) tablets [prescribing information]. Janssen Pharmaceuticals, Inc.; 2016. 5. Xigduo® XR (dapagliflozin and metformin HCl extended-release) tablets [prescribing information]. AstraZeneca Pharmaceuticals LP; 2018. 6. Synjardy® (empagliflozin and metformin hydrochloride) tablets [prescribing information]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2018. 7. Segluromet™ (ertugliflozin and metformin hydrochloride) tablets [prescribing information]. Merck & Co., Inc.; 2018. 8. Melikian C, et al. *Clin Ther*. 2002;24:460-467. 9. Blonde L, et al. *Diabetes Obes Metab*. 2003;5:424-431. 10. Blonde L, et al. *Adv Ther*. 2012;29:1-13.

# Approved Oral Fixed-Dose Combination Therapies

| Drug Class | Formulation | Mechanism of Action |
|---|---|---|
| **DPP4i + Biguanide**[1-3] | Alogliptin, linagliptin, saxagliptin, or sitagliptin + metformin | Stimulates postprandial insulin, suppresses glucagon secretion + reduces hepatic gluconeogenesis |
| **Meglitinide + biguanide**[1] | Repaglinide + metformin | Increases insulin secretion + reduces hepatic gluconeogenesis |
| **SGLT2i + biguanide**[1,4-7] | Canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin + metformin | Reduces renal glucose absorption + reduces hepatic gluconeogenesis |
| **SU + biguanide**[1] | Glipizide or glyburide + metformin | Increases insulin secretion from pancreatic beta cells + reduces hepatic gluconeogenesis |
| **TZD + biguanide**[1] | Pioglitazone or rosiglitazone + metformin | Increases insulin sensitivity + reduces hepatic gluconeogenesis |
| **SGLT2i + DPP4i**[1] | Dapagliflozin + saxagliptin<br>Empagliflozin + linagliptin<br>Ertugliflozin + sitagliptin | Reduces renal glucose absorption + stimulates postprandial insulin, suppresses glucagon secretion |
| **DPP4i + TZD** | Alogliptin + pioglitazone | Stimulates postprandial insulin, suppresses glucagon secretion + increases insulin sensitivity |
| **SU + TZD** | Glimepiride + pioglitazone | Increases insulin secretion from pancreatic beta cells + increases insulin sensitivity |

DPP4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones.

1. Vijayakumar TM. *Curr Ther Res Clin Exp*. 2017;84:4-9. 2. Jentadueto® (linagliptin and metformin hydrochloride) tablets [prescribing information]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2019. 3. Kazano (alogliptin and metformin HCl) tablets [prescribing information]. Takeda Pharmaceuticals America, Inc.; 2017. 4. Invokamet® (canagliflozin and metformin hydrochloride) tablets [prescribing information]. Janssen Pharmaceuticals, Inc.; 2016. 5. Xigduo® XR (dapagliflozin and metformin HCl extended-release) tablets [prescribing information]. AstraZeneca Pharmaceuticals LP; 2018. 6. Synjardy® (empagliflozin and metformin hydrochloride) tablets [prescribing information]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2018. 7. Segluromet™ (ertugliflozin and metformin hydrochloride) tablets [prescribing information]. Merck & Co., Inc.; 2018.

# Efficacy of Second Therapy Added To Metformin

| Combination | Reduction in A1C vs metformin monotherapy* | Weight change | Hypoglycemia risk RR (95% CI) |
|---|---|---|---|
| **SU/glinide + metformin** | -0.68% | +2.6 kg | 8.91 (1.46, 54.34) |
| **SGLT2i + metformin** | -0.47% | -2.0 kg | 1.37 (0.64, 2.92) |
| **TZD + metformin** | -0.44% | +1.93 kg | 1.60 (1.05, 2.46) |
| **DPP4i + metformin** | -0.44% | +0.38 kg | 1.15 (0.84, 1.55) |

*Weighted mean difference

CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; RR, relative risk; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones.
Cai X, et al. *Diabetes Ther*. 2018;9:1995-2014.

# Injectable Combination Therapies

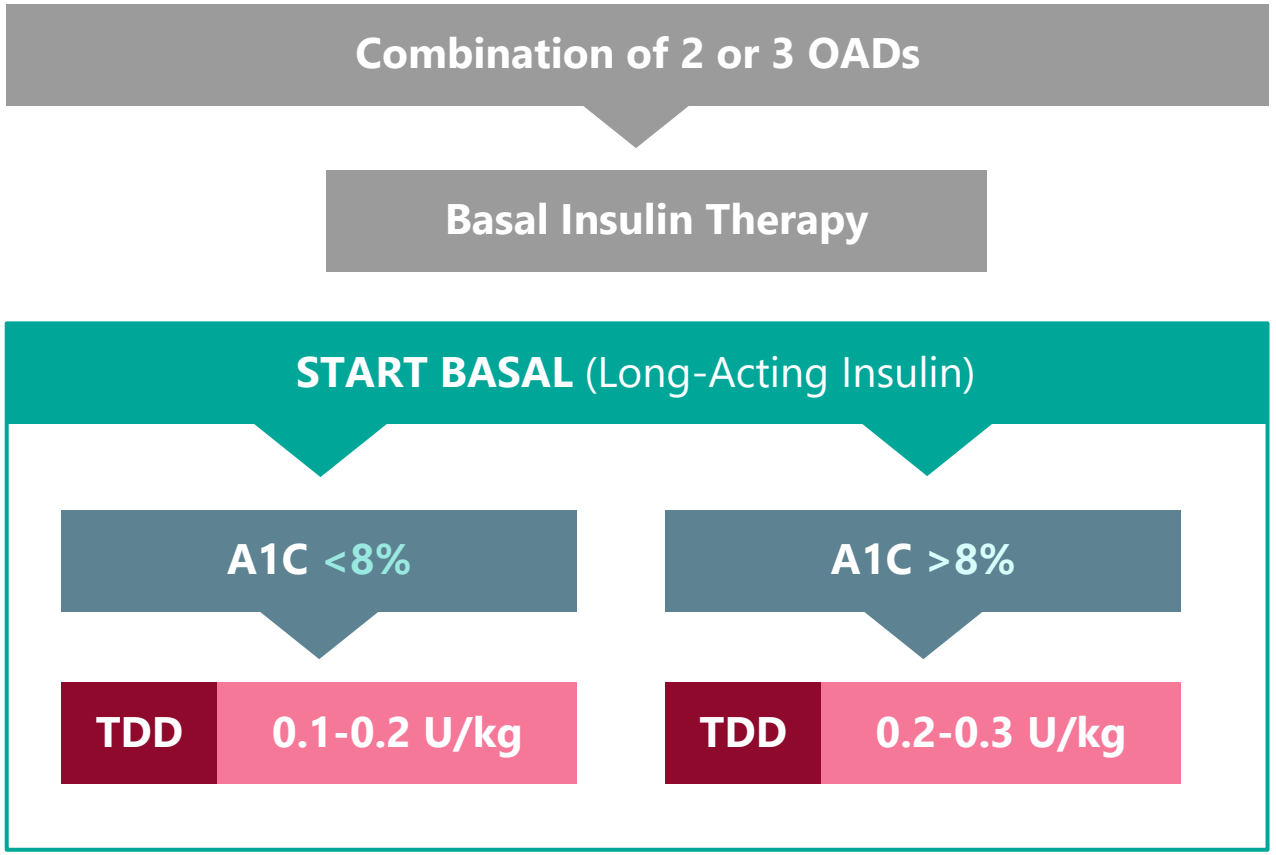
# Considerations for Adding Insulin Therapy

- Basal insulin, the most convenient first-line insulin regimen, can be used in combination with metformin and other anti-hyperglycemic agents[1,2]
- Basal insulin's primary action is to prevent the liver from producing glucose, thus ensuring normal glucose levels overnight and between meals[1]
- Patients on basal insulin who do not achieve A1C target levels should be considered for combination injectable therapy[1,2]

A1C, glycated hemoglobin.

1. American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.
2. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

# Basal Insulin as Add-on to Oral Antidiabetic Drugs in Patients With T2D



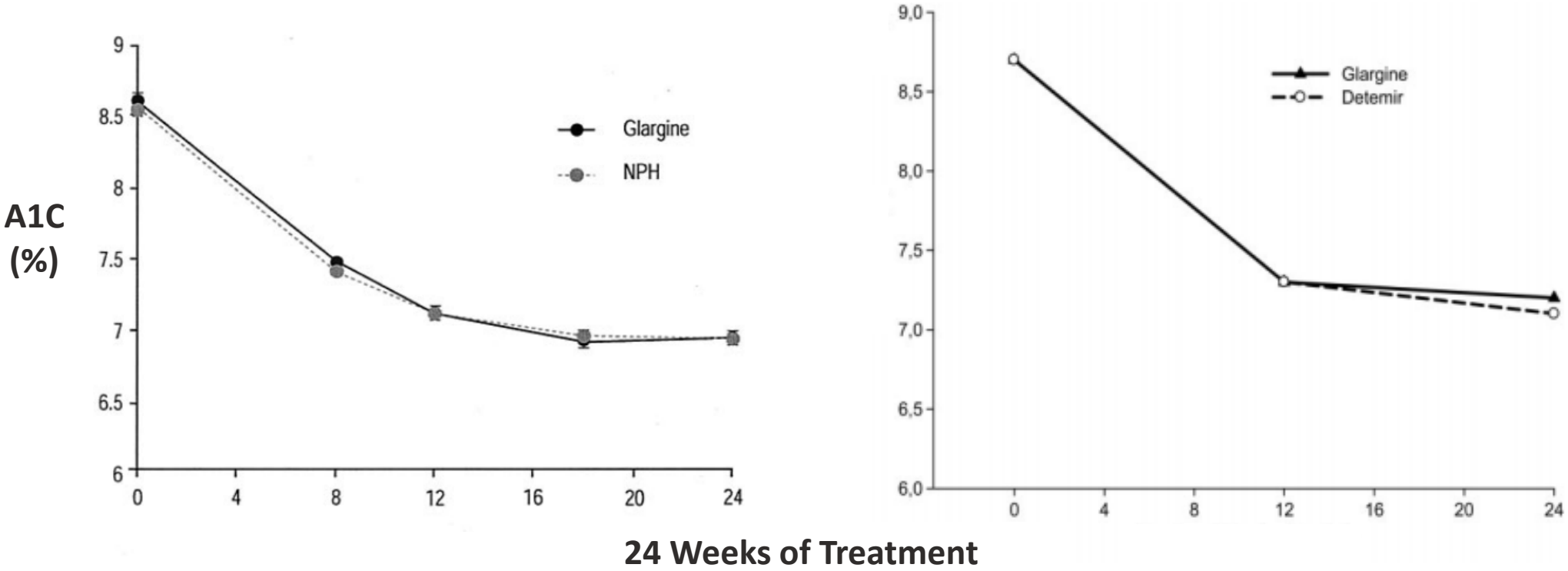

A1C, glycated hemoglobin; OAD, oral antidiabetic agent; T2D, type 2 diabetes; TDD, total daily dose.

Garber EJ, et al. *Endocr Pract*. 2018;24:91-120.

# Basal Insulin Added to OADs Improves Glycemic Control: "Treat to Target" Trials

N=756
Baseline A1C 7.5% to 10.0%
Treated with 1 or 2 OADs (MET, SU, or TZD)

N=973
Baseline A1C 7.0% to 10.5%
Treated with OADs, including MET

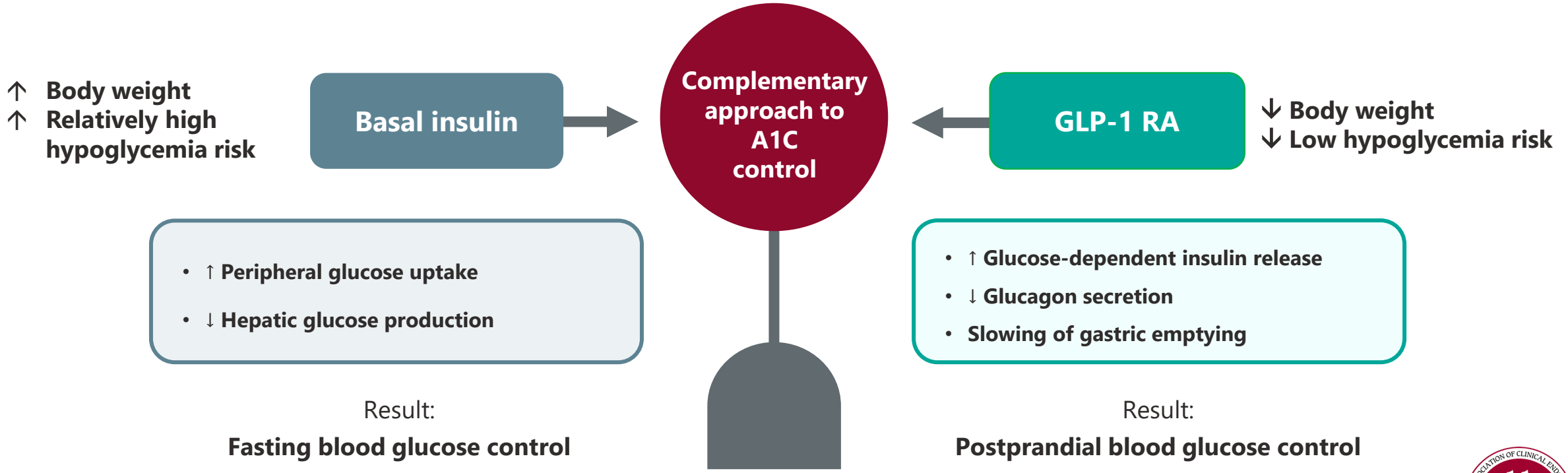



A1C, glycated hemoglobin; MET, metformin; NPH, neutral protamine Hagedorn insulin; OAD, oral antidiabetic agent; SU, sulfonylureas; TZD, thiazolidinediones.

1. Riddle MC, et al. *Diabetes Care*. 2003;26:3080-3086. 2. Swinnen SG, et al. *Diabetes Care*. 2010;33:1176-1178.

# Basal Insulin + GLP-1 RA: Complimentary Clinical Effects

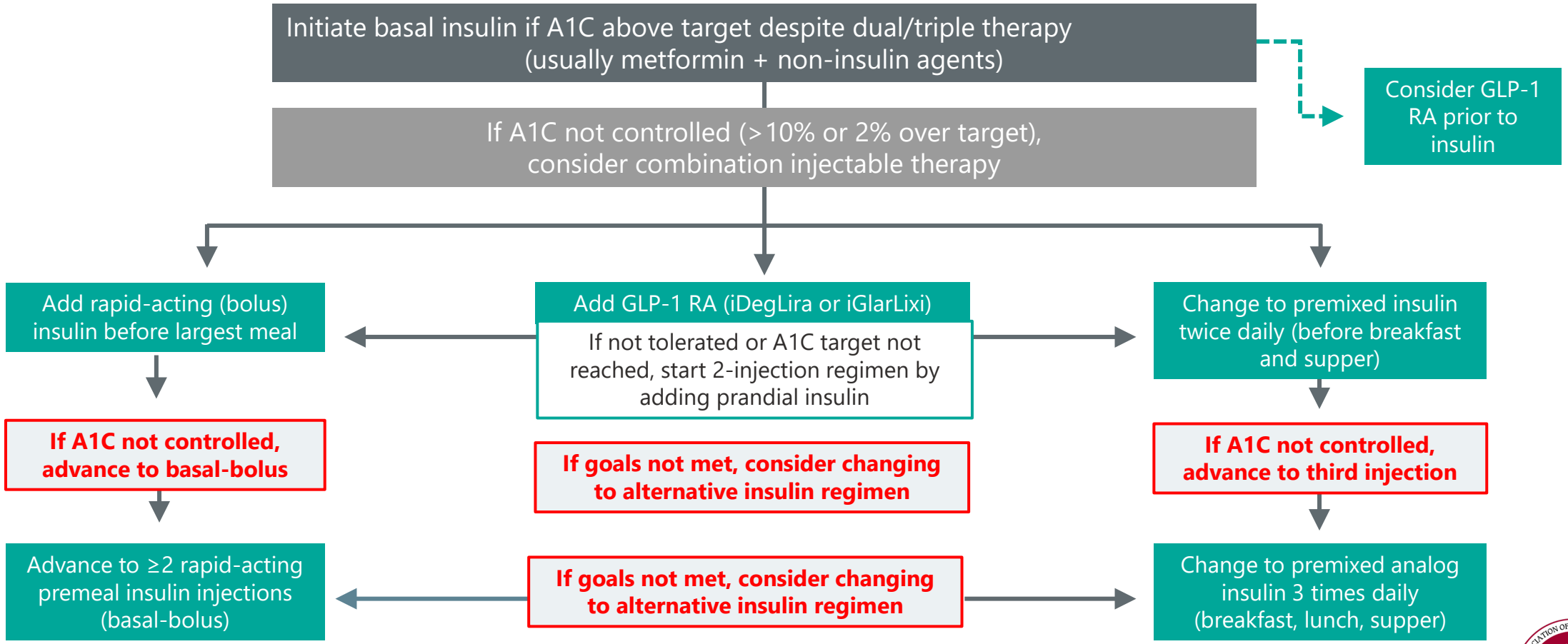
***Combined effect is to decrease both fasting blood glucose and postprandial glucose excursions***




A1C, glycated hemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

1. Balena R, et al. *Diabetes Obes Metab*. 2013;15:485-502. 2. Baggio LL, et al. *Gastroenterol*. 2007;132:2131-2157. 3. Wang Z, et al. *Diabetes Care*. 2010;33:1555-1560. 4. Holst JJ, et al. *Physiol Rev*. 2007;87:1409-1439.

# Considerations for Combination Injectable Therapy




A1C, glycated hemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iDegLira, insulin degludec and liraglutide; iGlarLixi, insulin glargine and lixisenatide.

1. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.
2. Davies MJ, et al. *Diabetologia*. 2018;61:2461-2498.

# Benefits of Basal Insulin/GLP-1 RA Fixed Ratio Combinations

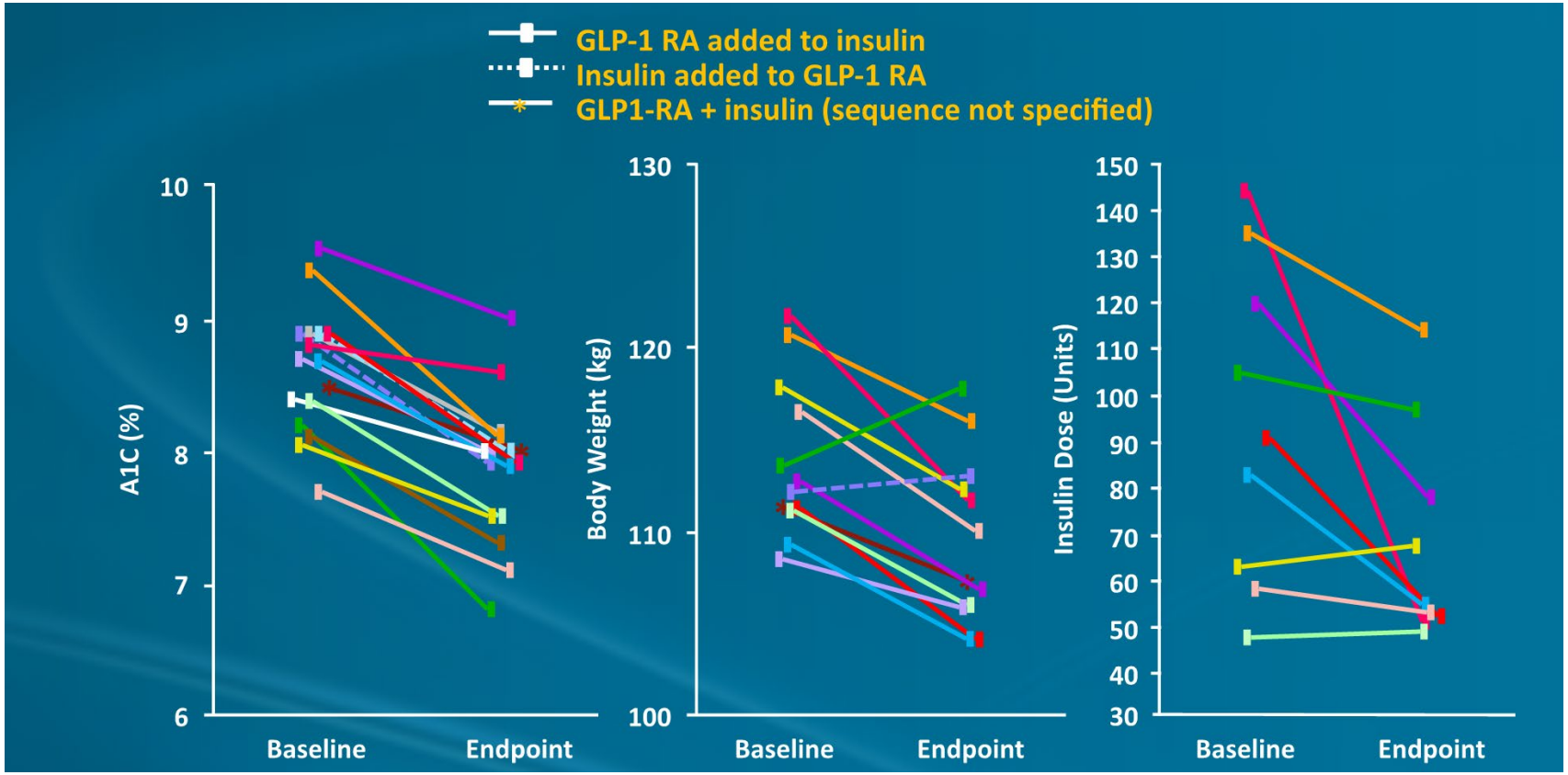
- Target both FPG and PPG to improve glycemic control (vs individual components)
- No individual risks of hypoglycemia vs basal insulin alone (despite improved glycemic control)
- Weight neutrality or loss
- Slow up-titration reduces gastrointestinal effects vs GLP-1 RA alone
- A simplified regimen—reduced complexity vs premixed and basal bolus regimens may increase patient adherence

FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPG, postprandial plasma glucose.

1. Rosenstock J, et al. *Diabetes Care.* 2016;39:2026-2035.
2. Aroda VR, et al. *Diabetes Care.* 2016;39:1972-1980.
3. Gough S, et al. Lancet Diabetes Endocrinol. 2014;2:885-889.
4. Buse JB, et al. Diabetes Care. 2014;37:2926-2933.

# GLP-1 RA Plus Insulin: Systematic Review

**Results from 7 RCTs and 15 clinical practice or observational studies including at least 30 patients with T2D**




GLP-1 RA, glucagon-like peptide-1 receptor agonist; RCT, randomized clinical trial; T2D, type 2 diabetes.

Balena R, et al. *Diabetes Obes Metab*. 2013;15:485-502.

# Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA


- iGlarLixi 100/33
- Insulin glargine and lixisenatide injection
- Approved by FDA November 2016
- Indication: Adults with T2D inadequately controlled on basal insulin (<60 units daily) or lixisenatide
- 1 unit contains:
  - 1 U insulin glargine and
  - 0.33 mcg lixisenatide (a GLP-1 RA)
- Administered SC once daily
- Starting dose: 15 or 30 units (15 or 30 U insulin glargine and 5 or 10 mcg lixisenatide)
- SoloStar pen

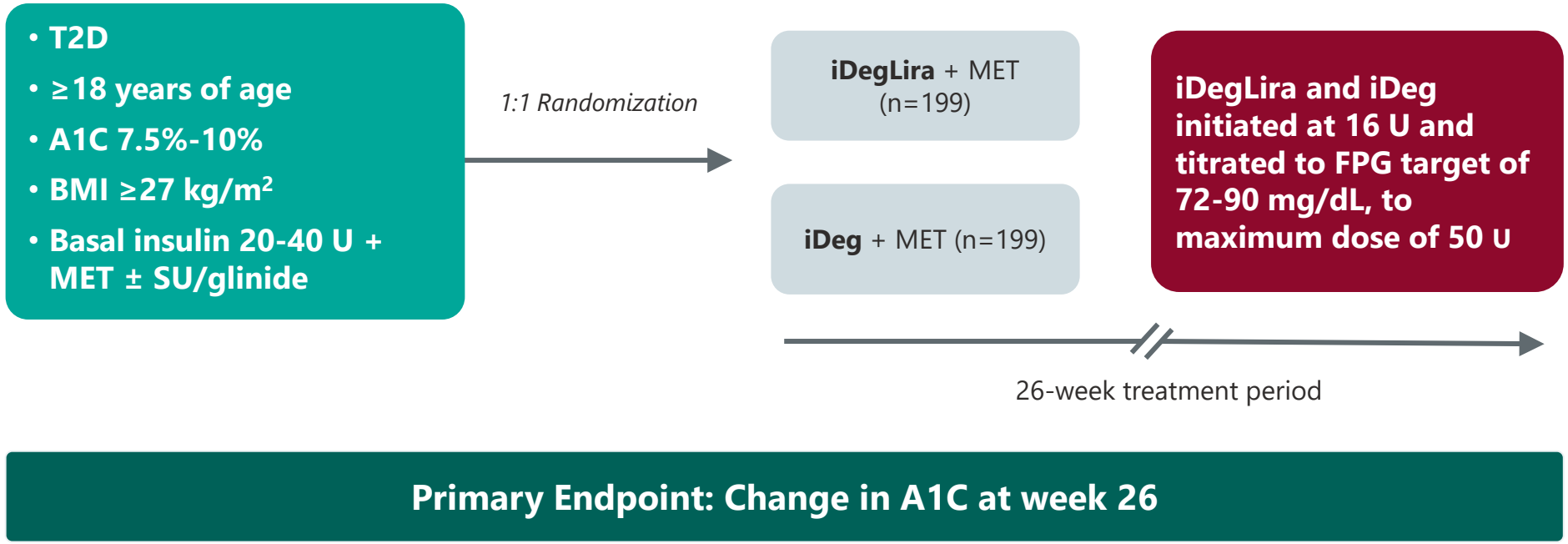

- iDegLira 100/3.6
- Insulin degludec and liraglutide injection
- Approved by FDA November 2016
- Indication: Adults with T2D inadequately controlled on basal insulin (<50 units daily) or liraglutide
- 1 unit contains:
  - 1 U insulin degludec and
  - 0.036 mg liraglutide (a GLP-1 RA)
- Administered SC once daily
- Starting dose: 16 units (16 U insulin degludec and 0.58 mg liraglutide)
- FlexTouch pen

FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SC, subcutaneous; iDegLira, insulin degludec and liraglutide; iGlarLixi, insulin glargine and lixisenatide; T2D, type 2 diabetes.

1. Soliqua™ 100/33 (insulin glargine and lixisenatide injection). Prescribing Information, Sanofi-Aventis US. November 2016.
2. Xultophy® 100/3.6 (insulin degludec and liraglutide injection). Prescribing Information, Novo Nordisk. November 2016.

# iDegLira (100/3.6) in Patients With T2D Inadequately Controlled on Basal Insulin Alone

**26-week, randomized, double-blind study in patients with T2D inadequately controlled on basal insulin + MET (± SU/glinide)**



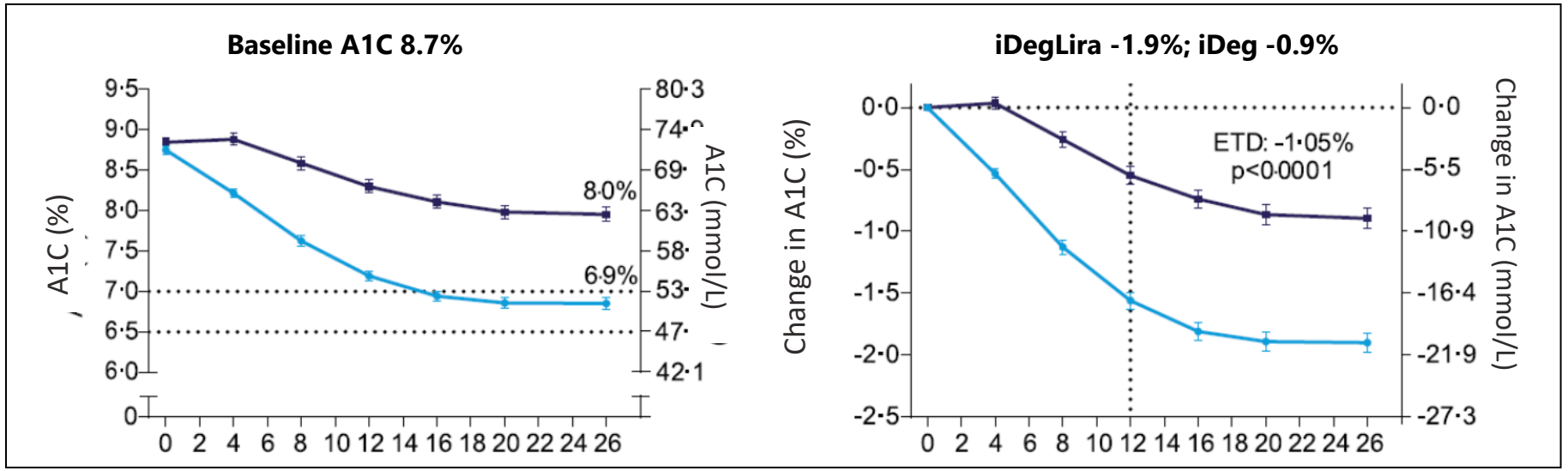

**Primary Endpoint: Change in A1C at week 26**

A1C, glycated hemoglobin; FPG, fasting plasma glucose; iDeg, insulin degludec; iDegLira, insulin degludec and liraglutide; MET, metformin; SU, sulfonylureas; T2D, type 2 diabetes.

Buse JB, et al. *Diabetes Care.* 2014;37:2926-2933.

# iDegLira (100/3.6) in Patients With T2D Inadequately Controlled on Basal Insulin Alone

**Change in A1C after 26 weeks of therapy:**

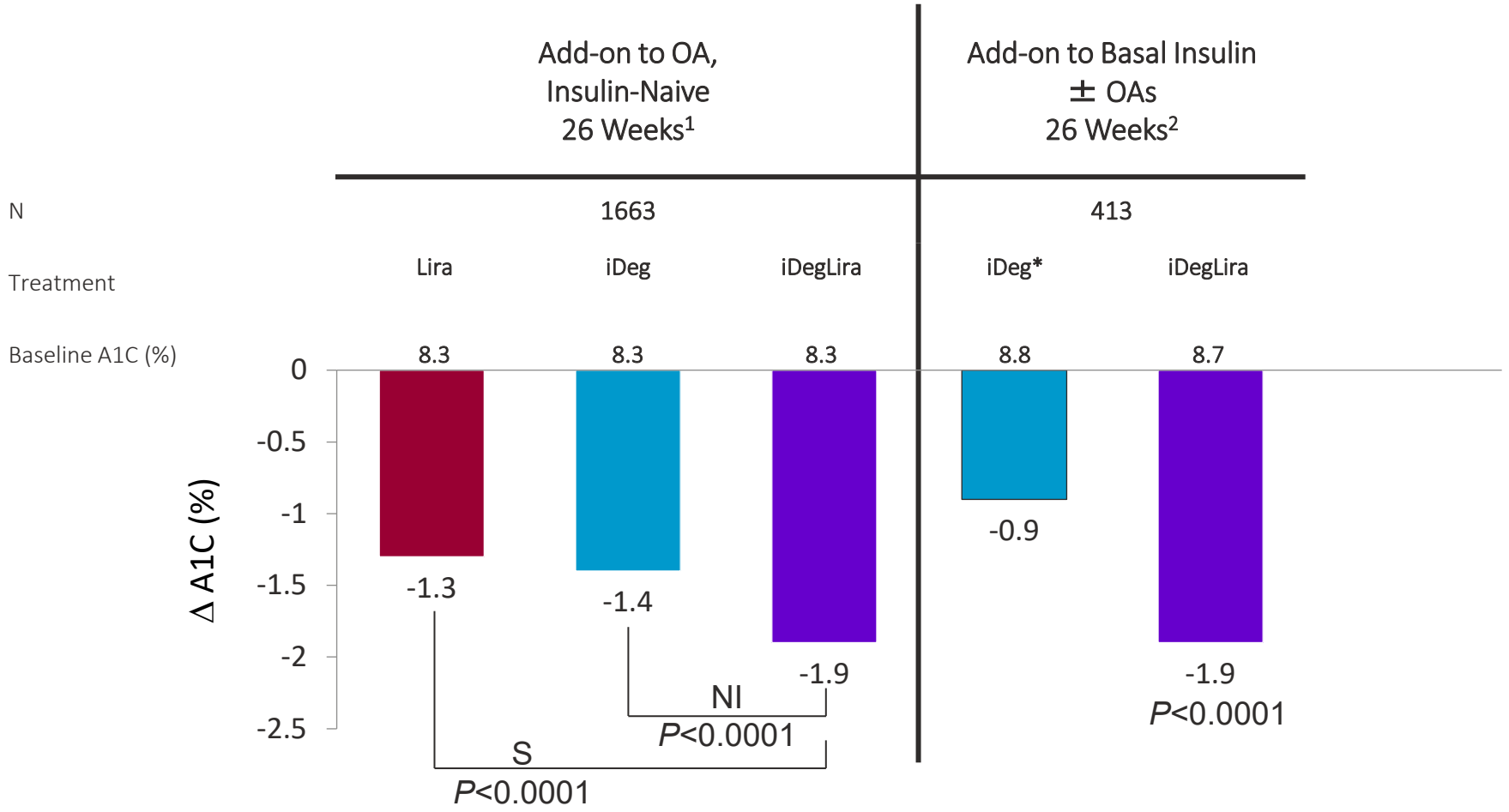



**A1C targets and composite endpoints:**

- **60%** of patients in the iDegLira arm achieved A1C <7.0% (vs 23% with iDeg)
- **40%** of patients in the iDegLira arm achieved A1C <7.0% with no confirmed hypoglycemia during final 12 weeks of treatment and with no weight gain (vs 8.5% with iDeg)

A1C, glycated hemoglobin; iDeg, insulin degludec; iDegLira, insulin degludec and liraglutide.
Buse JB, et al. *Diabetes Care.* 2014;37:2926-2933.

# Glucose Control With iDegLira



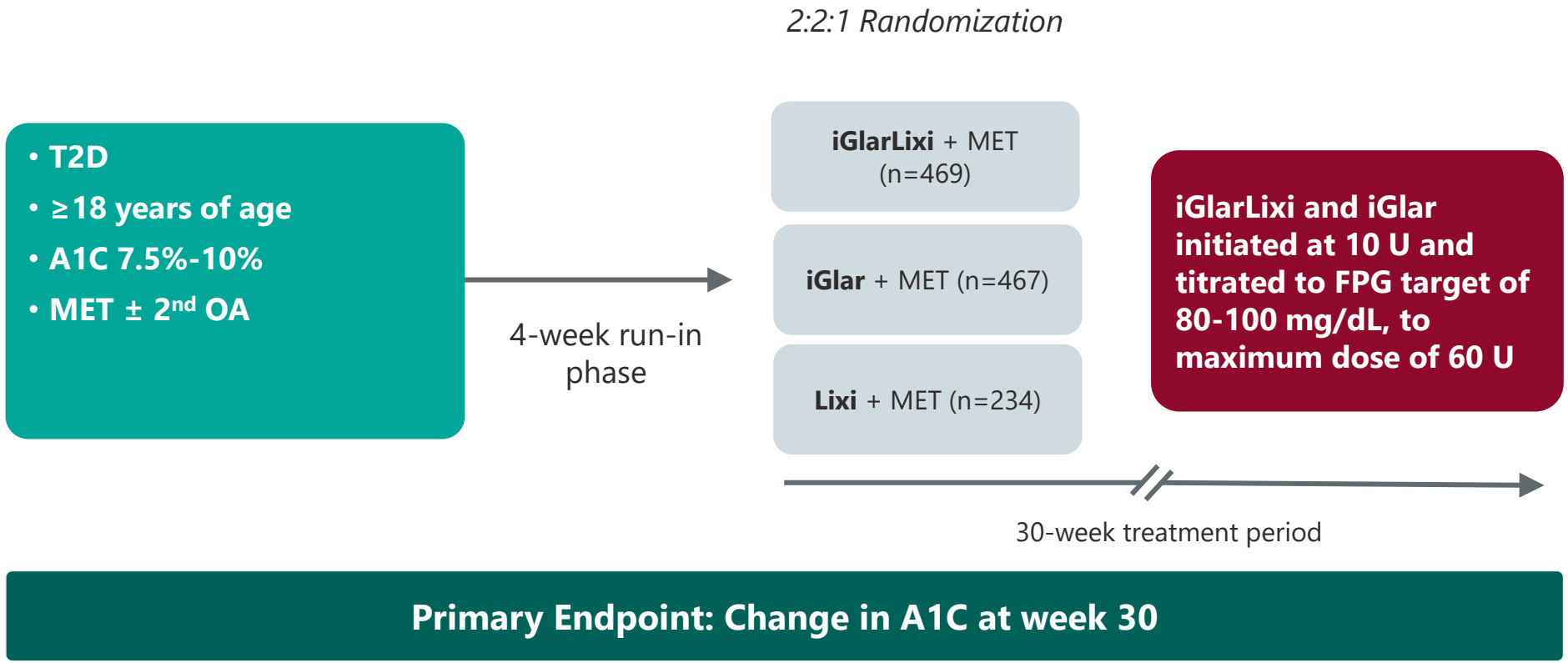

*Per protocol maximum dose: 50 units/day (no maximum dose of degludec alone was specified in the insulin naïve trial).

A1C, glycated hemoglobin; iDeg, insulin degludec; iDegLira, insulin degludec and liraglutide; Lira, liraglutide; NI, noninferior; OAs, oral agents; S, superior.

1. Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-893. 2. Buse JB, et al. *Diabetes Care*. 2014;37:2926-2933 .

# iGlarLixi (100/33) in Patients With T2D Inadequately Controlled With Oral Agents

**30-week, randomized, open-label study in patients on metformin ± 2nd oral agent**

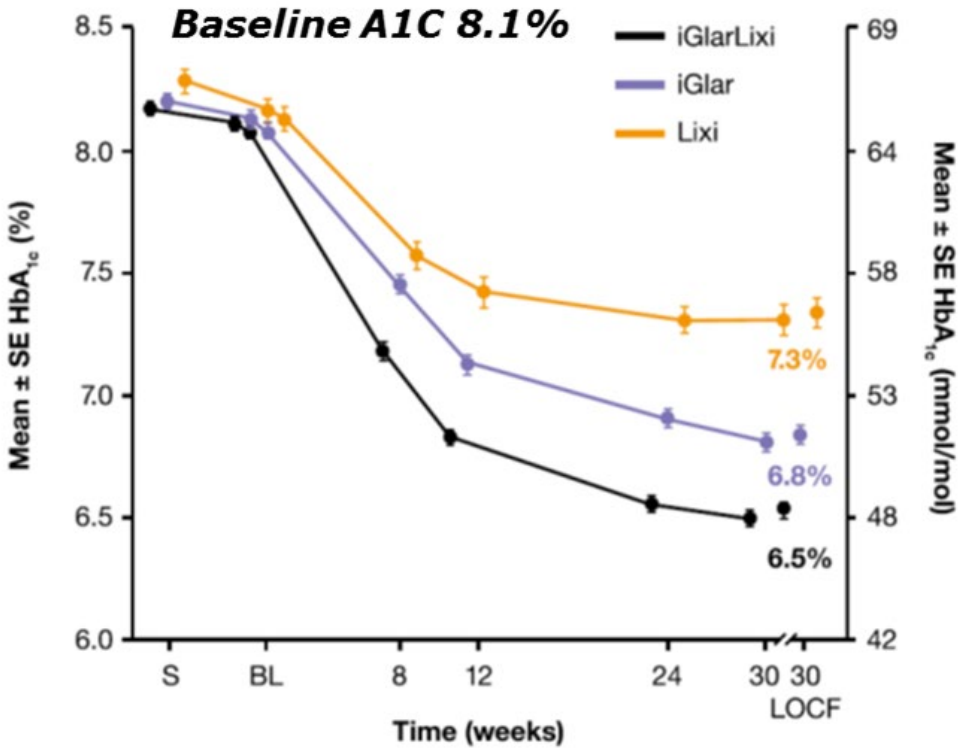



A1C, glycated hemoglobin; FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, insulin glargine and lixisenatide; Lixi, lixisenatide; MET, metformin; T2D, type 2 diabetes.

Rosenstock J, et al. *Diabetes Care.* 2016;39:2026-2035.

# iGlarLixi (100/33) in Patients With T2D Inadequately Controlled With Oral Agents

**Change in A1C after 30 weeks of therapy:**

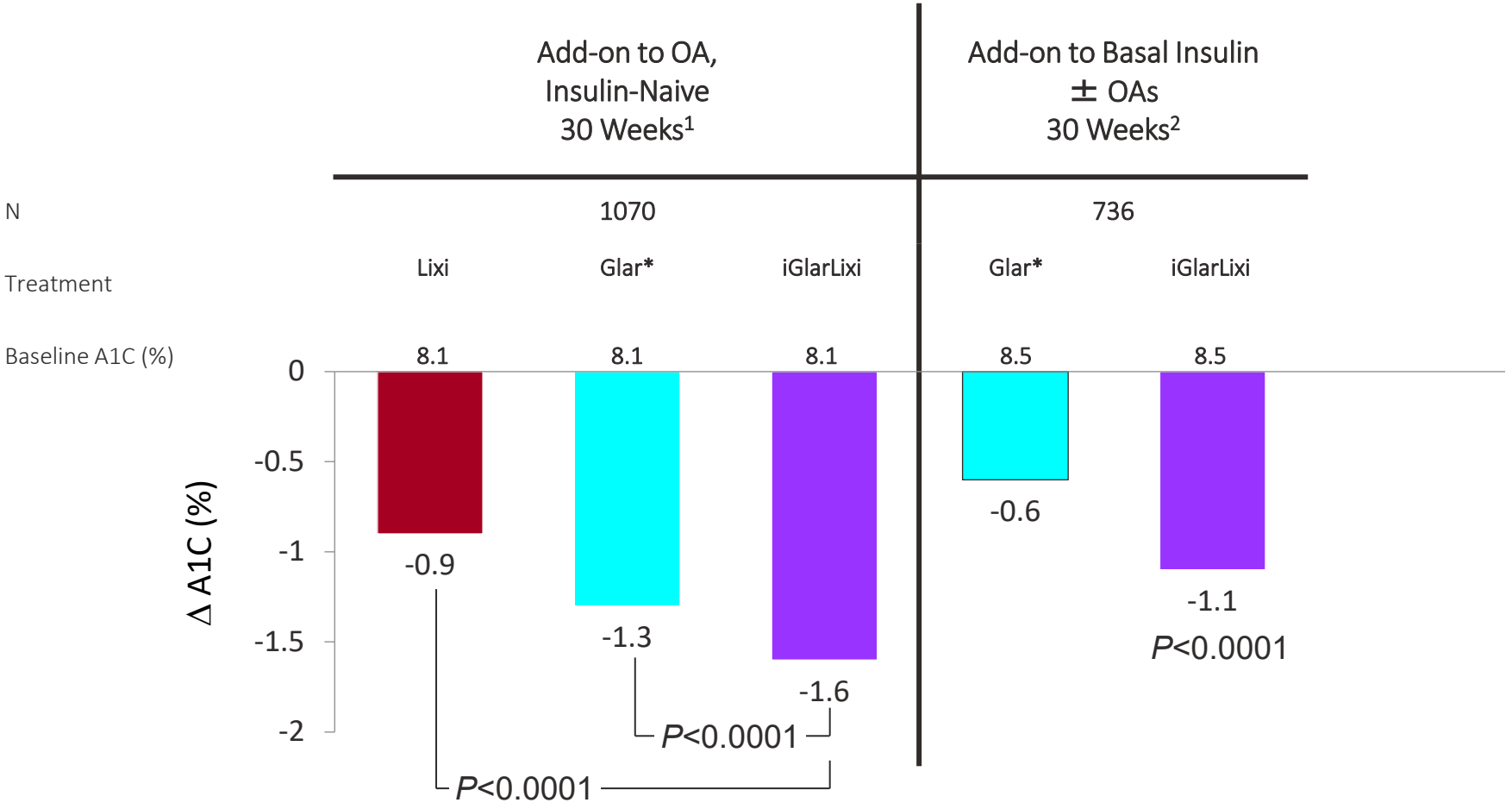



- **74%** of patients in the iGlarLixi arm achieved an A1C <7.0% (vs 59% with glargine and 33% with lixisenatide)
- **54%** of iGlarLixi patients achieved an A1C <7.0% with no documented symptomatic hypoglycemia (vs 44% with glargine and 31% with lixisenatide)
- **32%** of iGlarLixi patients achieved an A1C <7.0% with no weight gain and no documented symptomatic hypoglycemia (vs 19% with glargine and 26% with lixisenatide)

A1C, glycated hemoglobin; iGlarLixi, insulin glargine and lixisenatide.

Rosenstock J, et al. *Diabetes Care.* 2016;39:2026-2035.

# Glucose Control With iGlarLixi




Per protocol maximum dose: 60 units/day.

A1C, glycated hemoglobin; iGlarLixi, insulin glargine and lixisenatide; OAs, oral agents.

1. Rosenstock J, et al. *Diabetes Care*. 2016;39:2026-2035. 2. Aroda VR, et al. *Diabetes Care*. 2016;39:1972-1980.

# Combination Therapy for Patients With High Cardiovascular Risk

# Combination Therapy: Patients With High CV Risk

- Substantial historical evidence indicates that intensive, ongoing glucose control in newly diagnosed T2D patients may decrease long-term CVD rates[1]
- In 2008, FDA guidance mandated CV safety assessment of all new antihyperglycemic agents[2]
  - RCT studies required to demonstrate that study drug was not associated with more major adverse CV events than placebo (noninferiority)
    - Some studies tested for superiority if noninferiority criteria were met
  - **Primary outcome:** Composite of CV death, nonfatal MI, and nonfatal stroke
    - Some studies included additional endpoints
- Several studies of SGLT-2 inhibitors and GLP-1 RA have shown superiority compared with placebo.

CV, cardiovascular; CVD, cardiovascular disease; FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MI, myocardial infarction; RCT, randomized controlled trial; SGLT-2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

1. American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.

2. FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. https://www.fda.gov/media/71297/download.

# Summary of Published DPP4i Cardiovascular Outcomes Trials

| | EXAMINE* | SAVOR-TIMI 53 | TECOS | CARMELINA |
|---|---|---|---|---|
| **Primary outcome, HR (95% CI)** | 0.96 (≤1.16)‡ | 1.00 (0.89-1.12) | 0.98 (0.88-1.09) | 1.02 (0.89-1.17) |
| **CV death, HR (95% CI)** | 0.79 (0.60-1.04) | 1.03 (0.87-1.22) | 1.03 (0.89-1.19) | 0.96 (0.81-1.14) |
| **Fatal or nonfatal MI, HR (95% CI)** | 1.08 (0.88-1.33) | 0.95 (0.80-1.12) | 0.95 (0.81-1.11) | 1.12 (0.90-1.40) |
| **Fatal or nonfatal stroke, HR (95% CI)** | 0.91 (0.55-1.50) | 1.11 (0.88-1.39) | 0.97 (0.79-1.19) | 0.91 (0.67-1.23) |
| **All-cause mortality, HR (95% CI)** | 0.88 (0.71-1.09) | 1.11 (0.96-1.27) | 1.01 (0.90-1.14) | 0.98 (0.84-1.13) |
| **HF hospitalization, HR (95% CI)** | | 1.27 (1.07-1.51) | 1.00 (0.83-1.20) | 0.90 (0.74-1.08) |

‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01. * Numerical imbalance (not statistically significant) with increased hospitalizations for heart failure with alogliptin.

CI, confidence interval; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CV, cardiovascular; DPP4i, dipeptidyl peptidase-4 inhibitors; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin


1. White WB, et al. *N Engl J Med*. 2013 Oct 3;369(14):1327-35.

2. Scirica BM, et al. *N Engl J Med*. 2013 Oct 3;369(14):1317-26.

3. Green JB, et al. *N Engl J Med*. 2015 Jul 16;373(3):232-42.

4. Rosenstock J, et al. *JAMA*. 2019 Jan 1;321(1):69-79.

# Summary of Published SGLT-2i Cardiovascular Outcomes Trials

| | EMPA-REG OUTCOME | CANVAS/CANVAS-R | DECLARE - TIMI 58 | CREDENCE‡ |
|---|---|---|---|---|
| MACE outcome (HR [95% CI])* | 0.86 (0.74-0.99) | 0.86 (0.75-0.97) | 0.93 (0.84-1.03)** | 0.80 (0.67-0.95) |
| CV death | 0.62 (0.49-0.77) | 0.87 (0.72-1.06) | 0.98 (0.82-1.17) | 0.78 (0.61-1.00) |
| Fatal or nonfatal MI | 0.87 (0.70-1.09) | 0.89 (0.73-1.09) | 0.89 (0.77-1.01) | |
| Fatal or nonfatal stroke | 1.18 (0.89-1.56) | 0.87 (0.69-1.09) | 1.01 (0.84-1.21) | |
| All-cause mortality | 0.68 (0.57-0.82) | 0.87 (0.74-1.01) | 0.93 (0.82-1.04) | 0.83 (0.68–1.02) |
| Heart failure hospitalization | 0.65 (0.50-0.85) | 0.67 (0.52-0.87) | 0.73 (0.61-0.88) | 0.61 (0.47–0.80) |

*MACE outcome: cardiovascular death, non-fatal MI, non-fatal stroke (primary outcome in EMPA-REG, CANVAS/CANVAS-R, and DECLARE-TIMI 58, secondary outcome in CREDENCE). **Additional primary outcome in DECLARE-TIMI 58: CV death and hospitalization for heart failure, HR= 0.83 (0.73–0.95). ‡ CREDENCE enrolled patients with diabetic kidney disease. Primary outcome included composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 $m^2$ sustained for at least 30 days), doubling of the serum creatinine level, or death from renal or cardiovascular disease. The primary outcome was lower in those receiving canagliflozin HR= 0.7 (0.59-0.82).

CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus; CV, cardiovascular; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MI, myocardial infarction; SLGT2, sodium-glucose cotransporter 2. CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation.

Adapted from Das SR, et al. *J Am Coll Cardiol.* 2018;72:3200-3223.

# Summary of Published GLP-1 RA Cardiovascular Outcomes Trials

| | LEADER | SUSTAIN-6 | EXSCEL | ELIXA | HARMONY | REWIND |
|---|---|---|---|---|---|---|
| Primary outcome, HR (95% CI) | 0.87 (0.78-0.97) | 0.74 (0.58-0.95) | 0.91 (0.83-1.00) | 1.02 (0.89-1.17) | 0.78 (0.68-0.90) | 0·88 (0.79-0.99) |
| CV death, HR (95% CI) | 0.78 (0.66-0.93) | 0.98 (0.65-1.48) | 0.88 (0.76-1.02) | 0.98 (0.78-1.22) | 0.93 (0.73-1.19) | 0·91 (0.78-1.06) |
| Fatal or nonfatal MI, HR (95% CI) | 0.86 (0.73-1.00) | 0.74 (0.51-1.08) | 0.97 (0.85-1.10) | 1.03 (0.87-1.22) | 0.75 (0.61-0.90) | 0·96 (0.79-1.15) |
| Fatal or nonfatal stroke, HR (95% CI) | 0.86 (0.71-1.06) | 0.61 (0.38-0.99) | 0.85 (0.70-1.03) | 1.12 (0.79-1.58) | 0.86 (0.66-1.14) | 0·76 (0.62-0.94) |
| All-cause mortality, HR (95% CI) | 0.85 (0.74-0.97) | 1.05 (0.74-1.50) | 0.86 (0.77-0.97) | 0.94 (0.78-1.13) | 0.95 (0.79-1.16) | 0.90 (0.80-1.01) |
| HF hospitalization, HR (95% CI) | 0.87 (0.73-1.05) | 1.11 (0.77-1.61) | 0.94 (0.78-1.13) | 0.96 (0.75-1.23) | | 0·93 (0.77-1.12) |

CV, cardiovascular; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HARMONY, Harmony Outcomes (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus); HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

1. Adapted from Das SR, et al. J Am Coll Cardiol. 2018;72:3200-3223.
2. Gerstein HC, et al. Lancet. 2019;http://dx.doi.org/10.1016/S0140-6736(19)31149-3; e-pub ahead of print.

# CVOT for GLP-1 agonists

## Cardiovascular outcomes of trials[a] of antidiabetic agents [6,7,9,11,14-17,19-24]

| Medication | Trial | Median duration | Participants (% with CV disease) | Noninferior outcomes | Superior outcomes | Other outcomes |
|---|---|---|---|---|---|---|
| **GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS** | | | | | | |
| Albiglutide | HARMONY[19] | 1.6 y | 9463 (100%) | | Albiglutide reduced MACE-3 by 22% | No significant difference in the rate of death from any cause occurred with albiglutide compared to placebo |
| Dulaglutide | REWIND[20,21] | 5.4 y | 9901 (31%) | | Dulaglutide reduced MACE-3 in patients with and without CV disease | Dulaglutide reduced the incidence of new-onset macroalbuminuria |
| Exenatide | EXSCEL[17] | 3.2 y | 14,752 (73%) | Exenatide had no adverse effect on CV health in patients with type 2 diabetes | | Exenatide showed a numerical, but nonsignificant, reduction in MACE-3 |
| Liraglutide | LEADER[15] | 3.8 y | 9340 (81%) | | Liraglutide reduced primary CV-related deaths; reduced CV causes, nonfatal MI, and nonfatal stroke, as well as reduced death by any cause | Liraglutide was associated with a reduced incidence of nephropathy compared to placebo |
| Lixisenatide | ELIXA[14] | 2.1 y | 6068 (100%) | Lixisenatide was noninferior to placebo for reducing MACE-3 | | |
| Semaglutide | SUSTAIN-6[16] | 2.1 y | 3297 (83%) | | Semaglutide reduced the composite MACE-3 and expanded composite outcomes (death from CV causes, nonfatal MI, nonfatal stroke, coronary revascularization and hospitalization for angina pectoris or HF) | Semaglutide was associated with a 1.2% absolute increase in retinopathy complications |



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# Summary of SGLT-2 Inhibitor CV & RENAL Benefits

| SODIUM–GLUCOSE COTRANSPORTER-2 INHIBITORS | | | | | | |
|---|---|---|---|---|---|---|
| Cana-gliflozin | CANVAS[23] | 2.4 y | 10,142 (71%) | | Canagliflozin reduced MACE-3 by 14% | Canagliflozin did not alter the occurrence of CV death or overall mortality<br>Canagliflozin was associated with a reduction in the progression of albuminuria<br>Canagliflozin was associated with an increased incidence of fractures and amputations |
| Dapa-gliflozin | DECLARE-TIMI 58[24] | 4.2 y | 17,160 (40.5%) | Dapagliflozin failed to reduce MACE-3 outcomes | Dapagliflozin reduced the risk of CV death or HHF by 17% | |
| Empa-gliflozin | EMPA-REG OUTCOME[22] | 3.1 y | 7020 (99%) | | Empagliflozin reduced MACE-3 by 14% compared to placebo<br>A 32% decrease in all-cause mortality, 38% reduction in CV death, and 35% reduction in HHF were documented | Empagliflozin did not alter the occurrence of nonfatal MI or stroke<br>Empagliflozin use was associated with a reduction in incident or worsening nephropathy |

**Dapagliflozin**

For CKD patients w/ or w/o DM risk of sustained ↓ of eGFR of at least 50%, ESRD, or death from renal or CV causes is significantly lower than with placebo

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# Summary

- Historically, therapeutic recommendations have focused on stepwise escalation—the addition of agents over time in response to treatment failure
- Current evidence supports earlier initiation of combination therapy, based on A1C targets
  - A1C is highly predictive of diabetes complications
- A1C targets should be individualized to specific patient characteristics
  - Internationally, A1C targets range from ≤6.5% to 8.5%, depending on patient attributes
- Metformin is the preferred first-line agent
  - Start combination therapy when patient A1C is above target
  - Incorporate agents with complementary mechanisms of action
  - Add agents with cardiorenal protection (ie, SGLT-2 inhibitor or GLP-1 RA) in high-risk patients

A1C, glycated hemoglobin.; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT, sodium-glucose cotransporter 2.

# Conclusions

- Health care professionals should consider patient-specific risk factors when determining antihyperglycemic treatment regimens for patients with T2D
- Such patient-specific risk factors include, but are not limited to, disease duration, baseline A1C level, life expectancy, obesity, comorbidities, cardiovascular risk, and age
- Affordability of treatment is also a concern
- Treatment has been shown to be more effective when tailored to patient comorbidities and specific adverse event profiles
- Recent clinical evidence supports the safety and efficacy of the earlier initiation of combination therapy in patients with T2D

A1C, glycated hemoglobin; T2D, type 2 diabetes.