# EFFICACY AND SAFETY OF THE NEWER GLUCOSE-LOWERING AGENTS



Steven E. Kahn, M.B., Ch.B.
VA Puget Sound Health Care System
University of Washington
Seattle, WA

# Disclosure of Interests

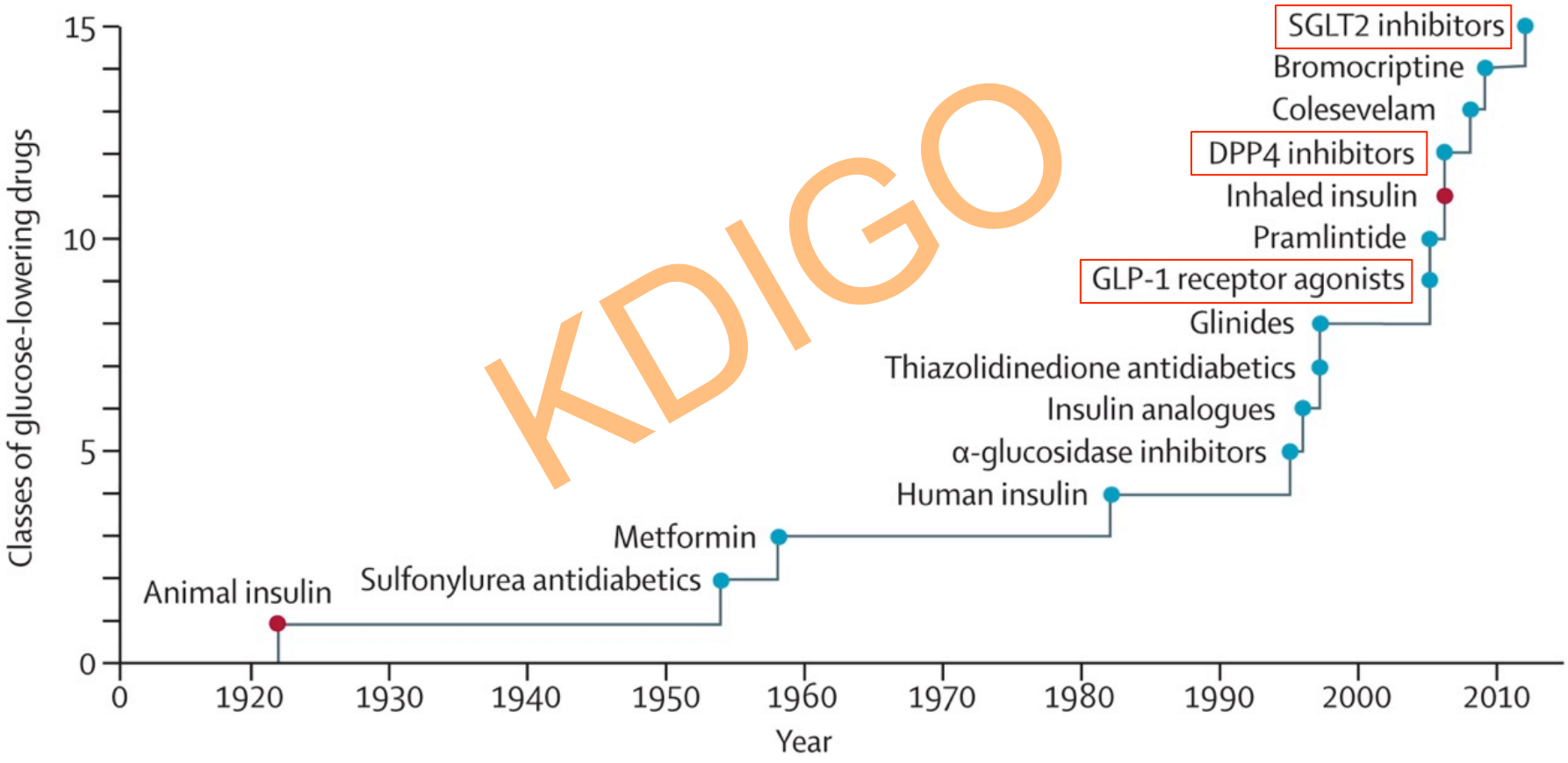
Grant Support / Advisory Board / Consultant

| | |
|---|---|
| Boehringer Ingelheim | Novo Nordisk |
| Janssen | GlaxoSmithKline |
| Elcelyx | Receptos |
| Merck | Intarcia |
| Eli Lilly | Takeda |

Stock

Receptos

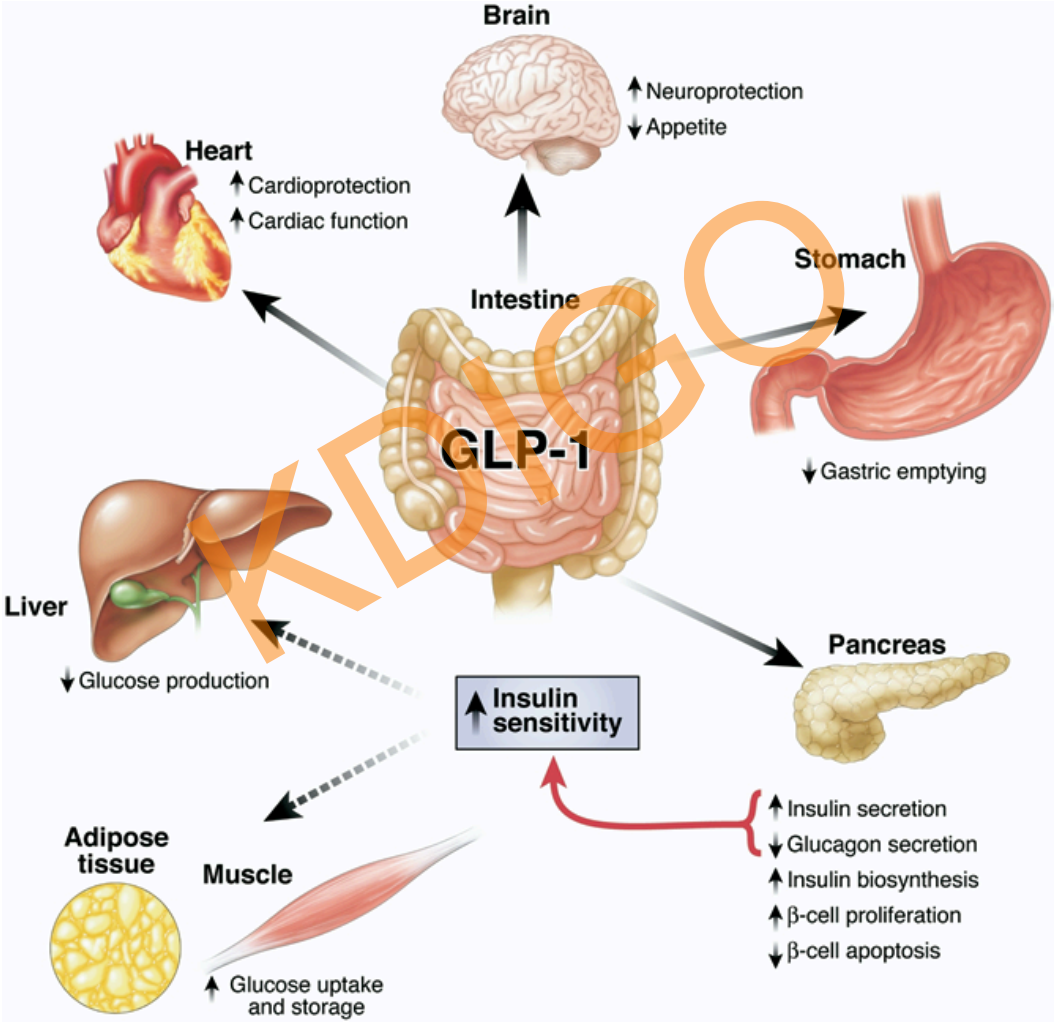
# Classes of Glucose Lowering Agents for Treating Type 2 Diabetes






Kahn SE et al: Lancet 383:1068-83; 2014

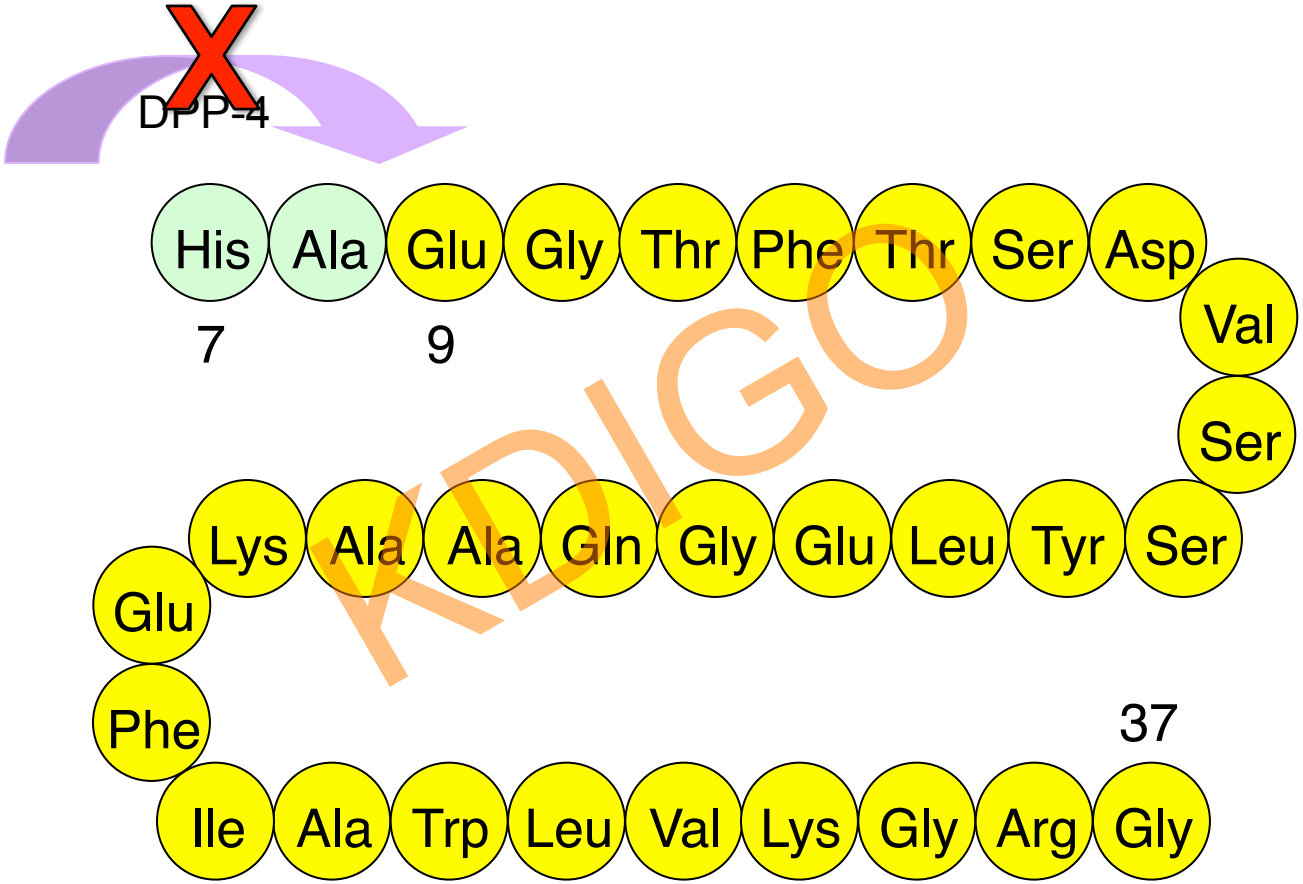
# Effects of Glucagon-Like Peptide-1






Baggio LL, Drucker DJ: Gastroenterology 132:2131-2157; 2007

# Native GLP-1 is Rapidly Degraded by DPP-4





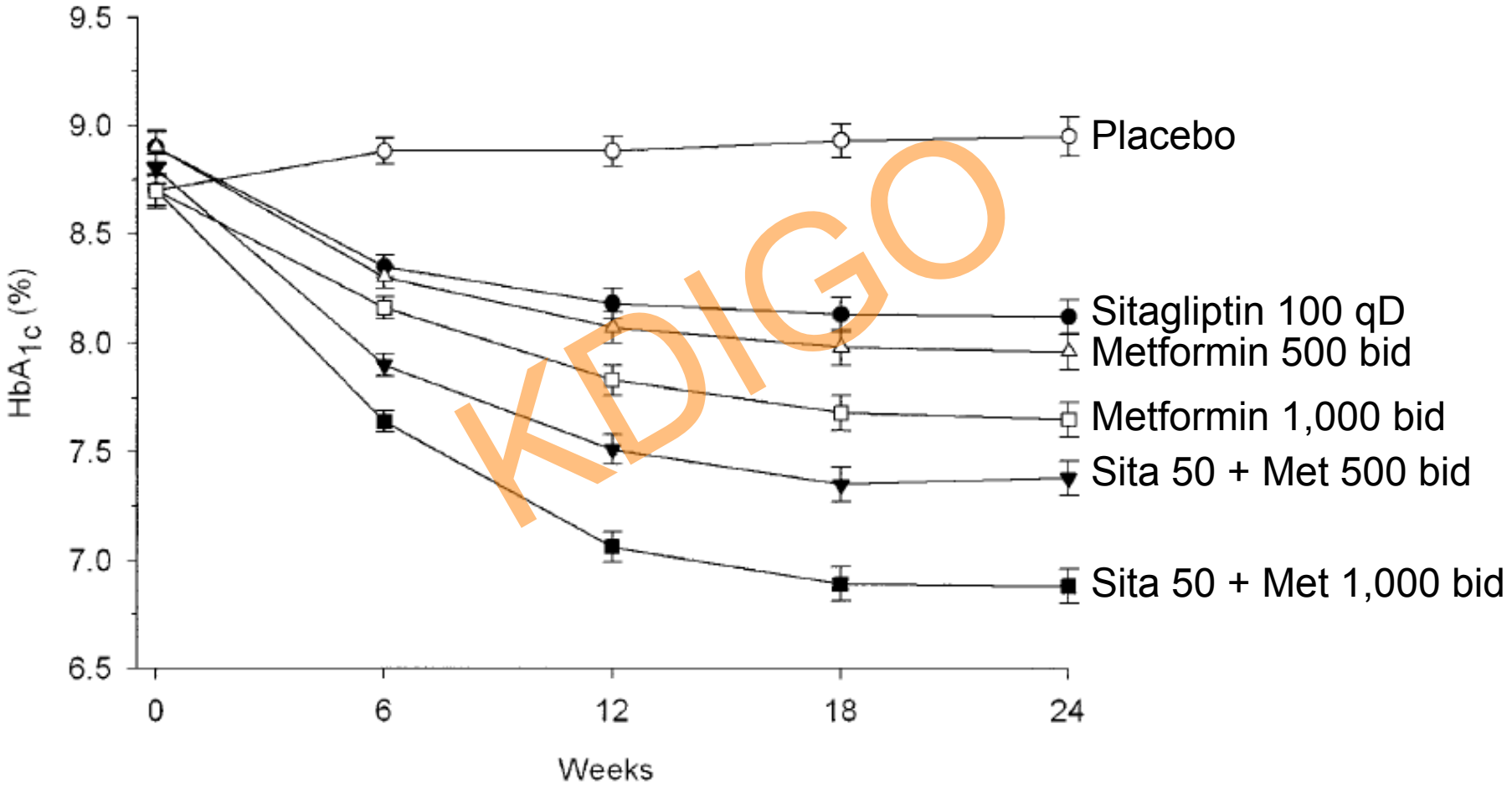

$T_{0.5}$ =1-2 minutes (iv)
MCR = 5-10 l/min

# DPP-4 INHIBITORS

# Approved DPP-4 Inhibitors

- Alogliptin
- Anagliptin
- Linagliptin
- Saxagliptin
- Sitagliptin
- Teneligliptin
- Vildagliptin

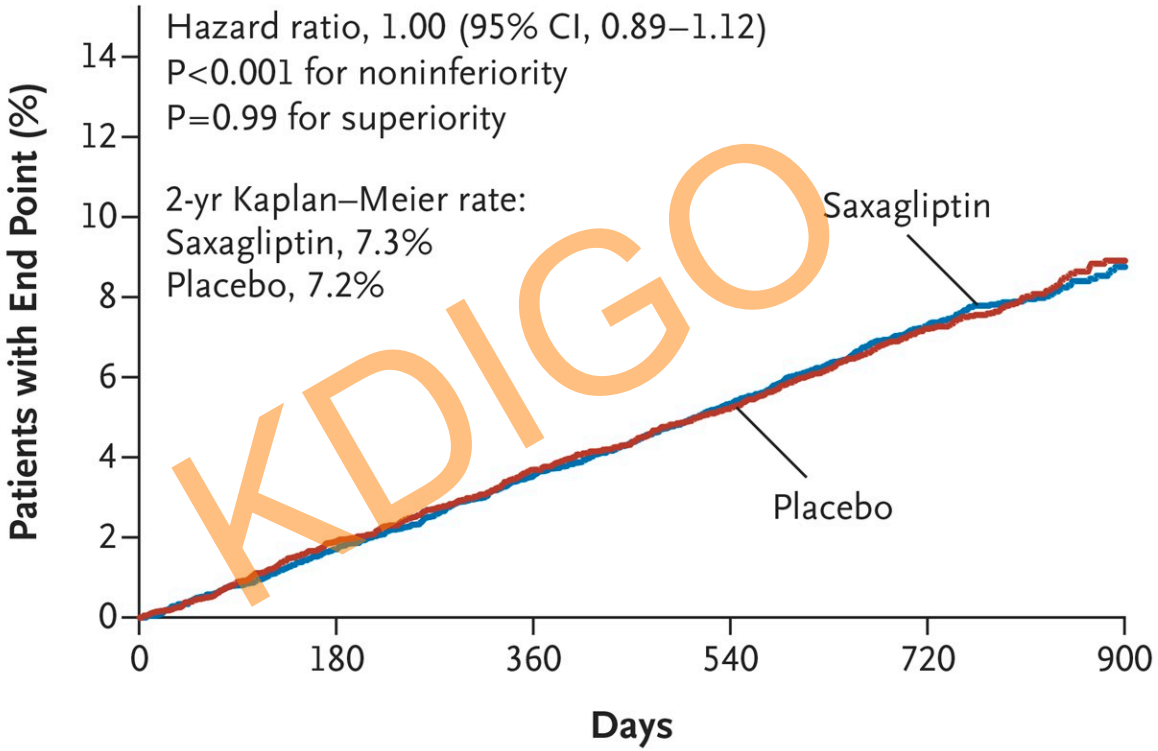
# Effect of Sitagliptin or Metformin on HbA1c in T2DM Patients Off Therapy for 8 Weeks






Goldstein BJ et al: Diabetes Care 30:1979-1987; 2007

# SAVOR-TIMI 53: No Impact of Saxagliptin on Primary Outcome (MACE)






| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 8212 | 7983 | 7761 | 7267 | 4855 | 851 |
| Saxagliptin | 8280 | 8071 | 7836 | 7313 | 4920 | 847 |

Scirica BM et al: N Engl J Med 369:1317-1326; 2013

# SAVOR-TIMI 53: Prespecified Clinical End Points

**Table 2. Prespecified Clinical End Points.***

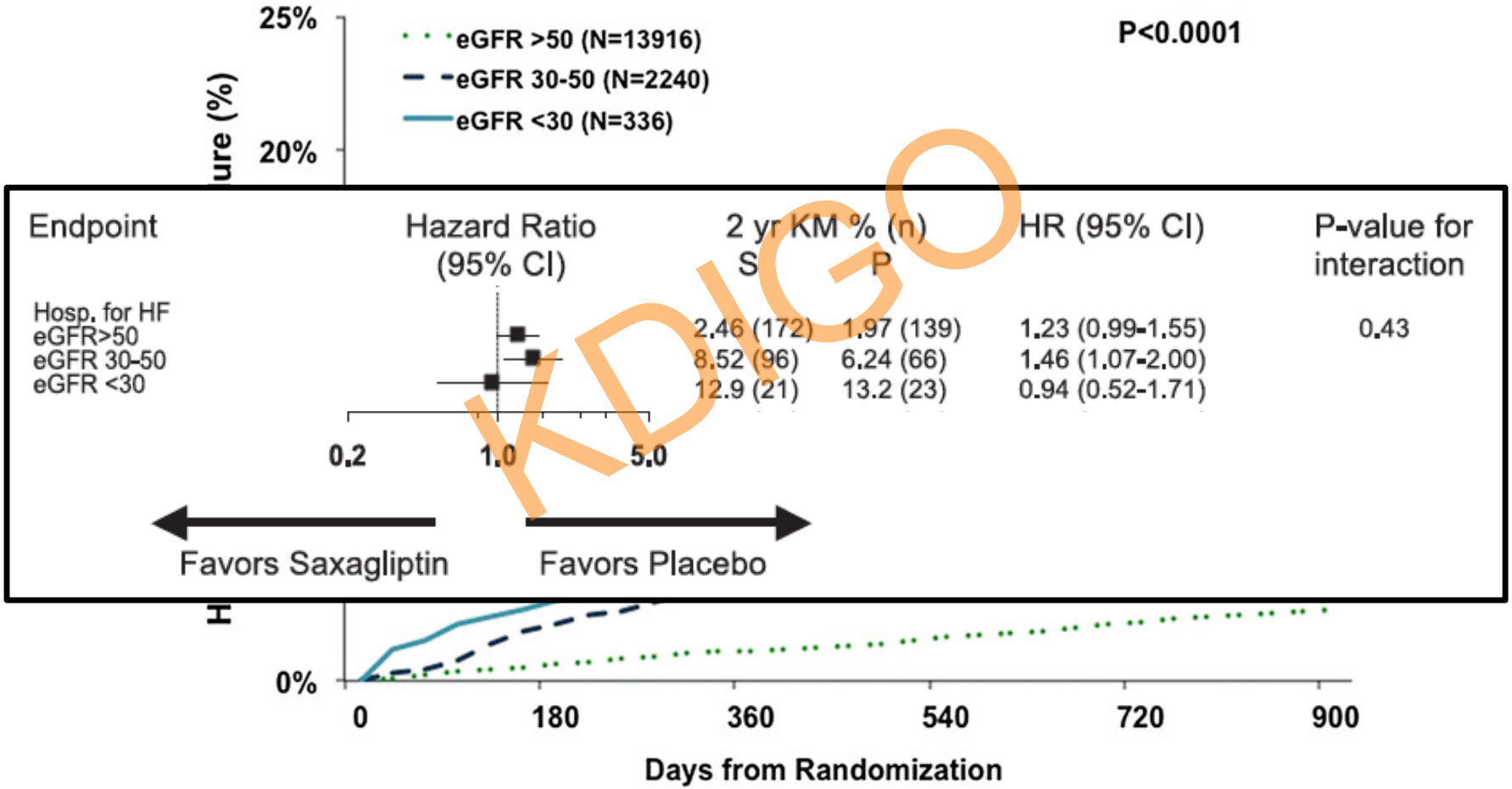
| End Point | Saxagliptin (N=8280) | Placebo (N=8212) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. (%)* | | | |
| Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point | 613 (7.3) | 609 (7.2) | 1.00 (0.89–1.12) | 0.99 |
| Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point | 1059 (12.8) | 1034 (12.4) | 1.02 (0.94–1.11) | 0.66 |
| Death from any cause | 420 (4.9) | 378 (4.2) | 1.11 (0.96–1.27) | 0.15 |
| Death from cardiovascular causes | 269 (3.2) | 260 (2.9) | 1.03 (0.87–1.22) | 0.72 |
| Myocardial infarction | 265 (3.2) | 278 (3.4) | 0.95 (0.80–1.12) | 0.52 |
| Ischemic stroke | 157 (1.9) | 141 (1.7) | 1.11 (0.88–1.39) | 0.38 |
| Hospitalization for unstable angina | 97 (1.2) | 81 (1.0) | 1.19 (0.89–1.60) | 0.24 |
| Hospitalization for heart failure | 289 (3.5) | 228 (2.8) | 1.27 (1.07–1.51) | 0.007 |
| Hospitalization for coronary revascularization | 423 (5.2) | 459 (5.6) | 0.91 (0.80–1.04) | 0.18 |
| Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter) | 194 (2.2) | 178 (2.0) | 1.08 (0.88–1.32) | 0.46 |
| Hospitalization for hypoglycemia | 53 (0.6) | 43 (0.5) | 1.22 (0.82–1.83) | 0.33 |

* Event rates and percentages are 2-year Kaplan–Meier estimates.



Scirica BM et al: N Engl J Med 369:1317-1326; 2013

# SAVOR-TIMI 53: Effect of Renal Function on Hospitalization for Heart Failure






Udell JA et al: Diabetes Care 2015, in press

# SAVOR-TIMI 53: Effect of Renal Function on Progressive Microalbuminuria

**Table 3—Frequency of progressive microalbuminuria by completion of follow-up according to renal function**

| | Total | Worsened | No change | Improved | *P* value* |
|---|---|---|---|---|---|
| eGFR >50 mL/min/1.73 $m^2$ (*n* = 10,621) | | | | | <0.0001 |
| Saxagliptin | 5,380 (50.7) | 682 (12.7) | 4,139 (76.9) | 559 (10.4) | |
| Placebo | 5,241 (49.3) | 790 (15.1) | 4,003 (76.4) | 448 (8.5) | |
| eGFR 30–50 mL/min/1.73 $m^2$ (*n* = 1,533) | | | | | 0.037 |
| Saxagliptin | 775 (50.6) | 134 (17.3) | 547 (70.6) | 94 (12.1) | |
| Placebo | 758 (49.4) | 166 (21.9) | 519 (68.5) | 73 (9.6) | |
| eGFR <30 mL/min/1.73 $m^2$ (*n* = 206) | | | | | 0.61 |
| Saxagliptin | 110 (53.4) | 17 (15.5) | 76 (69.1) | 17 (15.5) | |
| Placebo | 96 (46.6) | 13 (13.5) | 72 (75.0) | 11 (11.5) | |

Data are reported as *N* (%), unless otherwise indicated. The risk of progressive microalbuminuria was defined as a treatment difference in the number and proportion of patients with worsening, no change, or improvement in urinary ACR, defined as a shift from baseline category (<3.4, ≥ 3.4 to ≤ 33.9, or >33.9 mg/mmol) over the duration of follow-up among patients with complete data. *Based on $\chi^2$ or Fisher exact test.



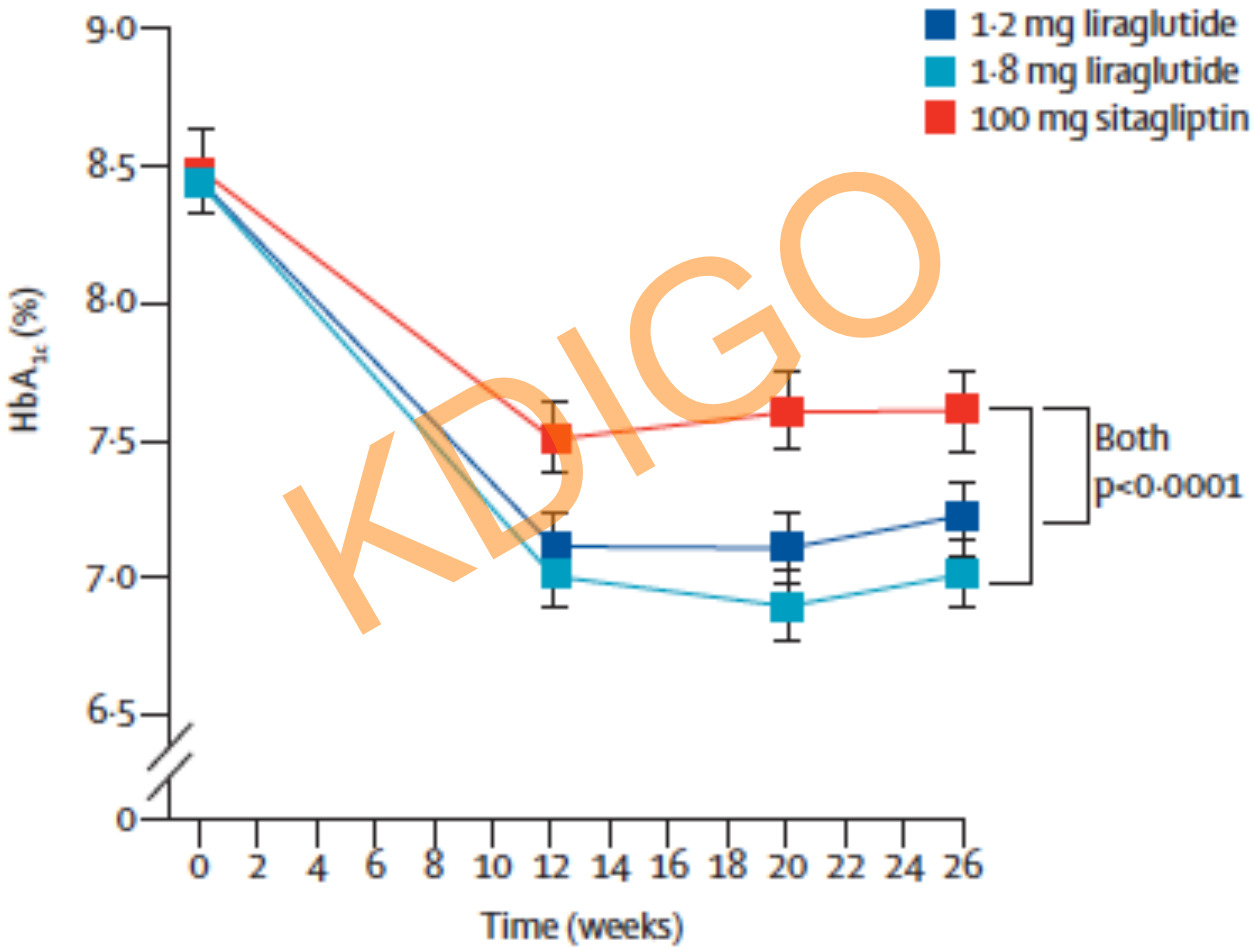
Udell JA et al: Diabetes Care 2015, in press

# GLP-1 RECEPTOR ANALOGS

# Approved GLP-1 Receptor Agonists

- Albiglutide
- Dulaglutide
- Exenatide
- Liraglutide
- Lixisenatide

# Effect of Liraglutide and Sitagliptin in Metformin Treated Patients with T2DM






Pratley RE et al: Lancet 375:1447-1456; 2010

# Increased Risk of Pancreatitis with Liraglutide in with Type 2 Diabetes

RESULTS

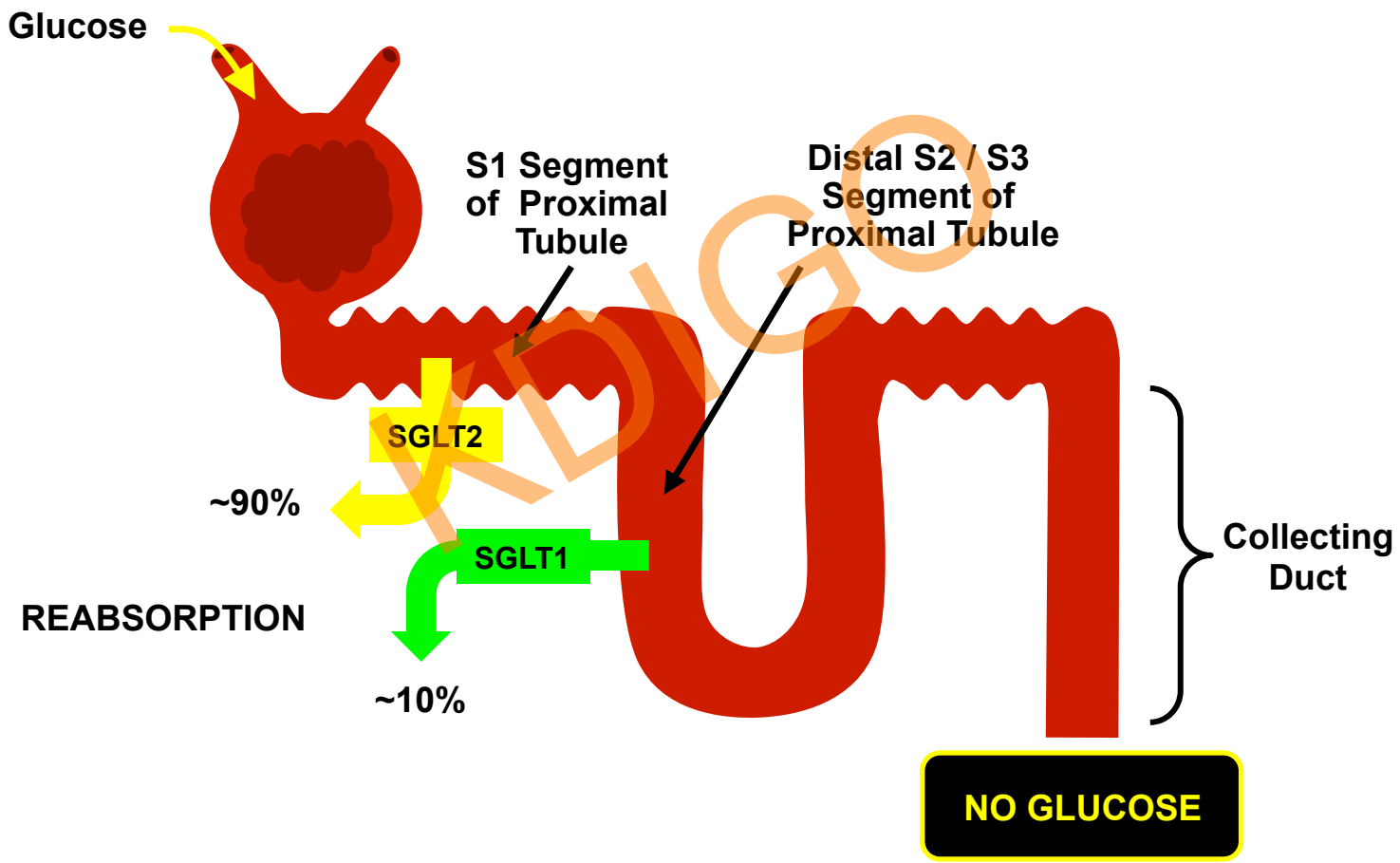
Total exposure to liraglutide and active comparators was 5,021 and 1,354 patient-years, respectively (*n* = 6,345 and 1,846, respectively). Eight cases of acute pancreatitis (AP) with liraglutide and one with any comparator (glimepiride) were found. The incidence of AP was 1.6 cases/1,000 patient-years exposure (PYE) for liraglutide vs. 0.7 cases/1,000 PYE for active comparators. One of the eight AP cases reported with liraglutide did not meet diagnostic criteria for AP. In six of these eight cases, recognized risk factors for AP were present and/or the onset of AP occurred >6 months after liraglutide initiation. All patients were receiving multiple medications. Four cases of chronic pancreatitis (CP) with liraglutide and none with comparators were found. One of these four cases fulfilled diagnostic criteria for CP; these criteria were not met or information was missing in the remaining three.



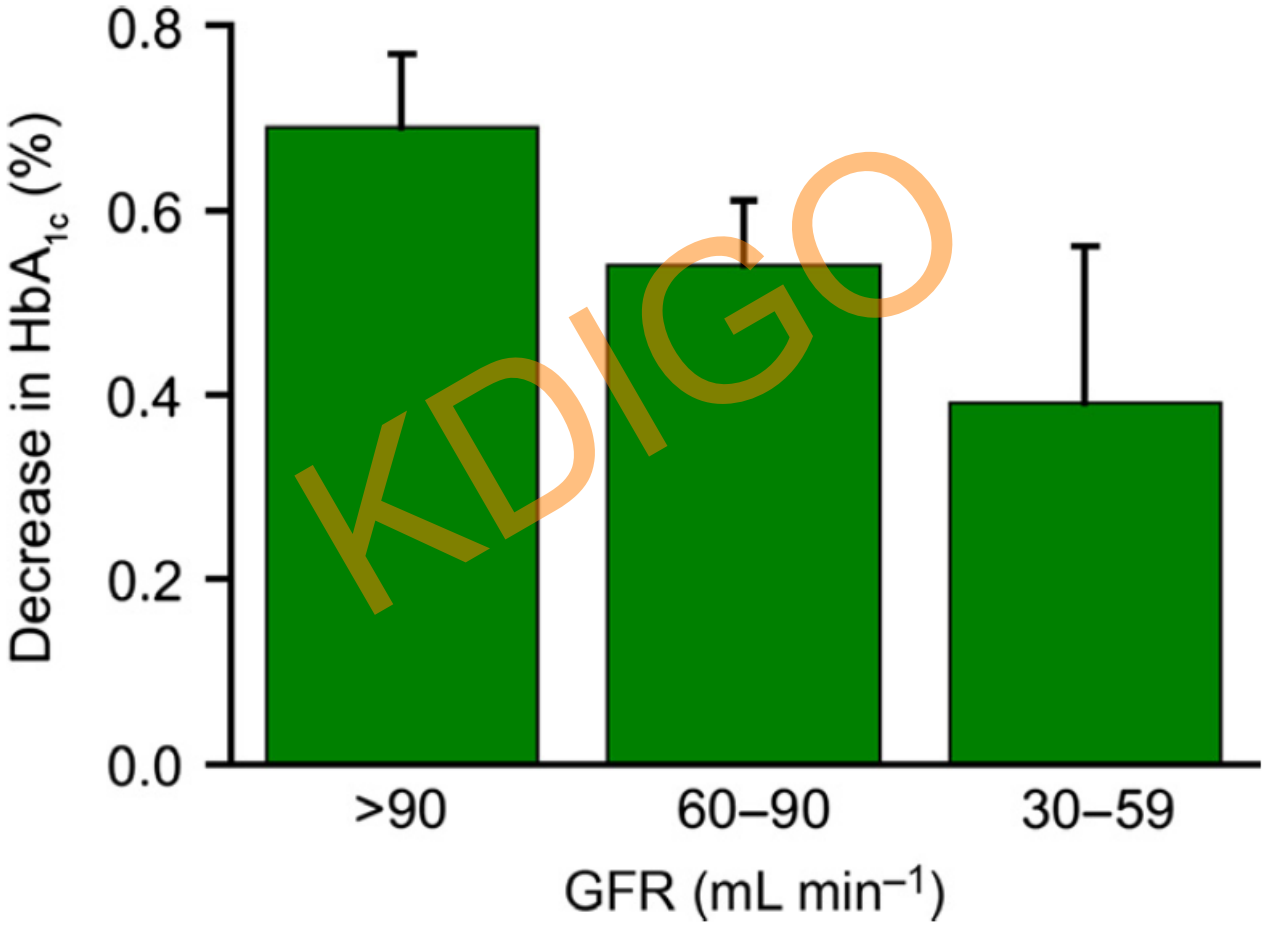
Jensen TM et al: Diabetes Care 2015, in press

# SGLT2 INHIBITORS

# Renal Glucose Handling in Healthy Subjects



# SGLT2 Inhibition: Decreased GFR Results in Decreased Glucose-Lowering Efficacy



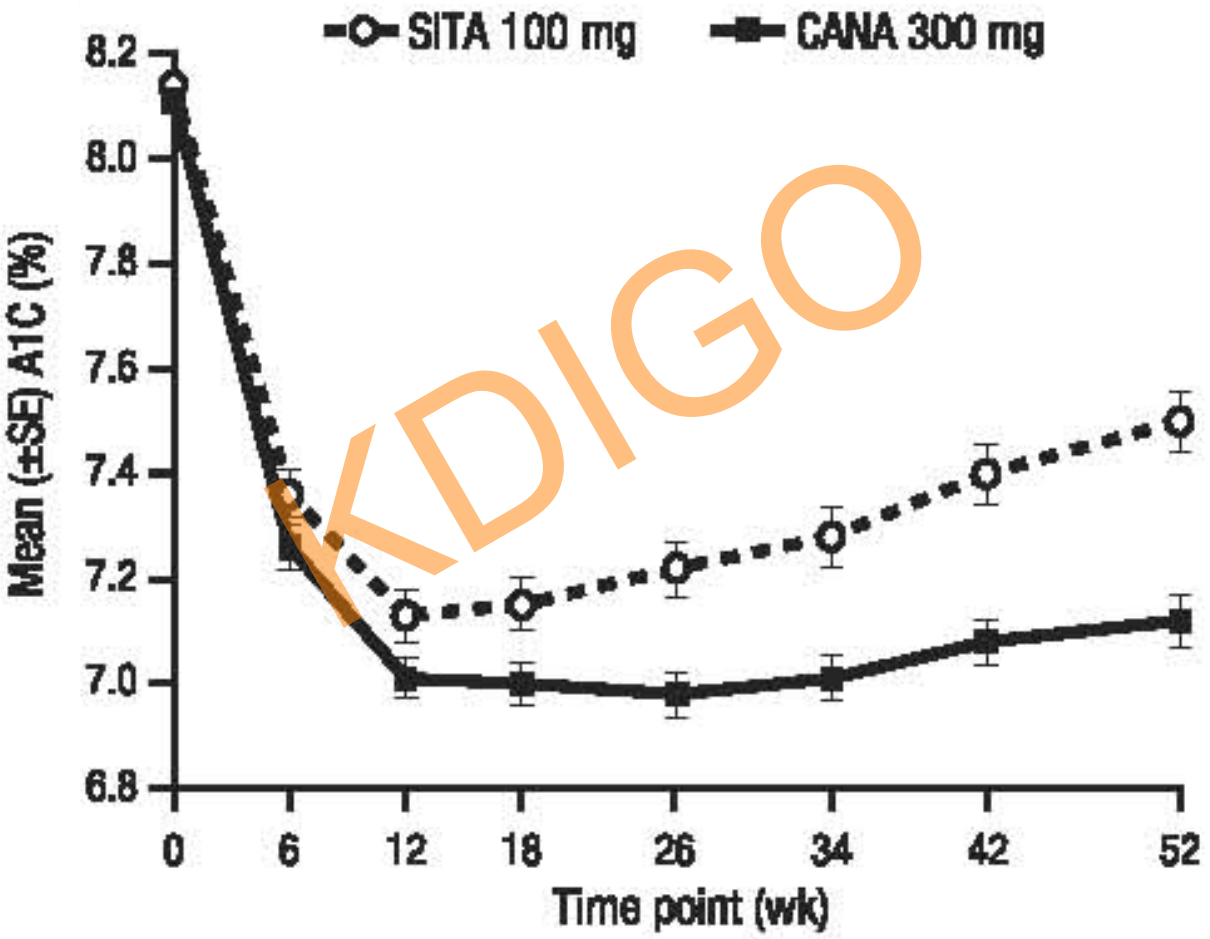



Abdul-Ghani MA, DeFronzo RA: J Intern Med 276:352-363; 2014
(Adapted from Bristol Myers Squibb NDA)

# Approved SGLT2 Inhibtors

- Canagliflozin
- Dapagliflozin
- Empagliflozin

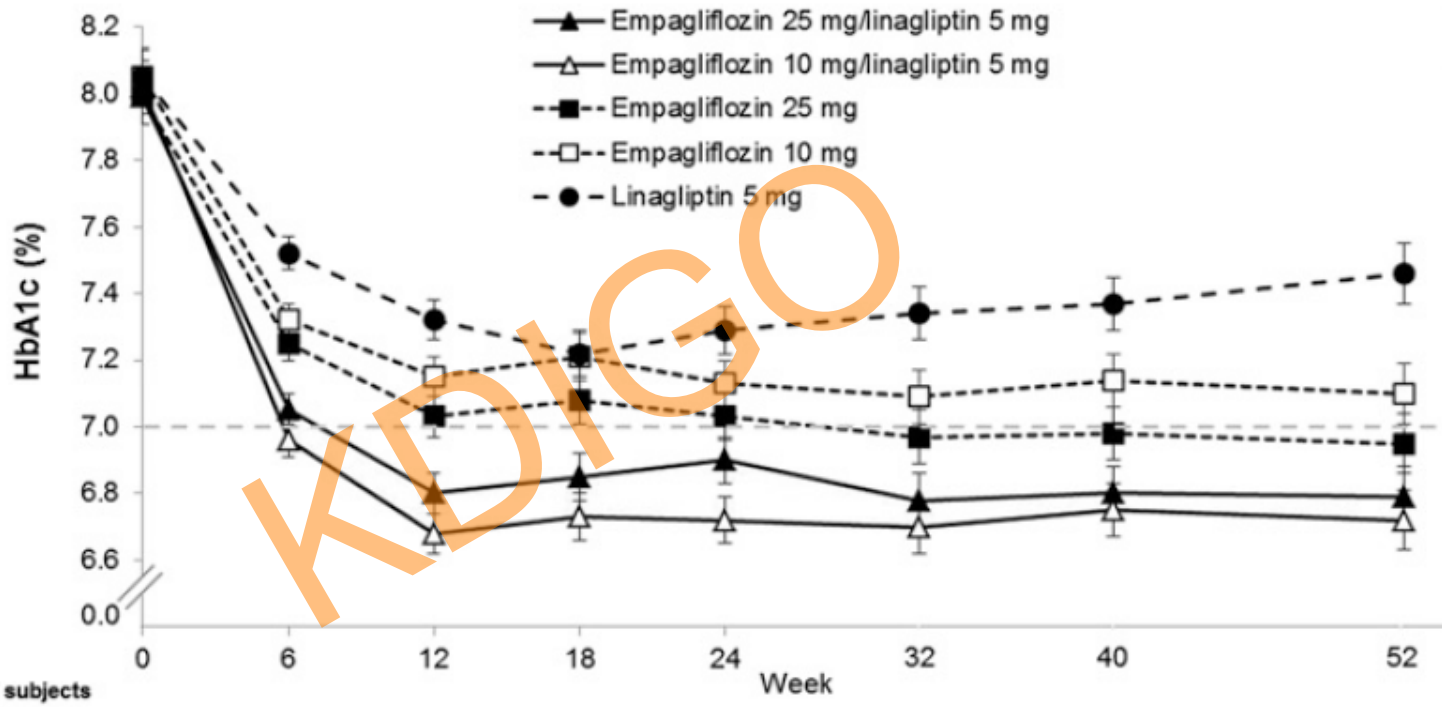
# Effect of Sitagliptin or Canagliflozin Add-on to Metformin Plus Sulfonylurea on HbA1c






Schernthaner G et al: Diabetes Care 36:2508-2515; 2013

# Effect of Combination Linagliptin and Empagliflozin on HbA1c



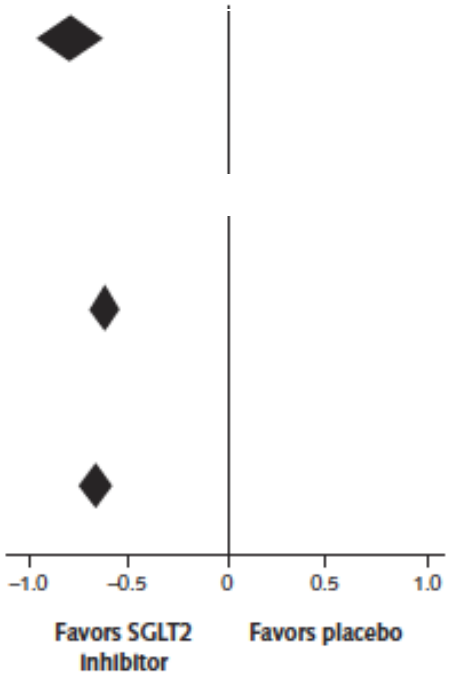



| Number of subjects | | | | | | | |
|---|---|---|---|---|---|---|---|
| Empagliflozin 25 mg/linagliptin 5 mg | 134 | 134 | 130 | 126 | 123 | 121 | 115 | 109 |
| Empagliflozin 10 mg/linagliptin 5 mg | 134 | 134 | 130 | 127 | 124 | 119 | 114 | 108 |
| Empagliflozin 25 mg | 133 | 132 | 129 | 128 | 121 | 116 | 114 | 106 |
| Empagliflozin 10 mg | 131 | 131 | 127 | 126 | 120 | 112 | 109 | 95 |
| Linagliptin 5 mg | 133 | 132 | 123 | 122 | 114 | 107 | 98 | 90 |

Lewin A et al: Diabetes Care 2015, in press

# SGLT2 Inhibition: Placebo Subtracted Difference from Baseline in HbA1c

| Study, Year (Reference) | SGLT2 Inhibitor Mean Change (SD), % | SGLT2 Inhibitor Total, *n* | Placebo Mean Change (SD), % | Placebo Total, *n* | Weight, % | Mean Difference IV, Random (95% CI) |
|---|---|---|---|---|---|---|
| **Monotherapy** | | | | | | |
| Subtotal | | 652 | | 591 | 24.9 | –0.79 (–0.96 to –0.62) |
| Heterogeneity: tau-square = 0.04; chi-square = 20.42; $P = 0.002$; $I^2 = 71\%$ | | | | | | |
| Test for overall effect: $Z = 9.18$ ($P < 0.001$) | | | | | | |
| **Add-on Treatment** | | | | | | |
| Subtotal | | 3802 | | 3603 | 75.1 | –0.61 (–0.69 to –0.53) |
| Heterogeneity: tau-square = 0.02; chi-square = 67.36; $P < 0.001$; $I^2 = 73\%$ | | | | | | |
| Test for overall effect: $Z = 14.79$ ($P < 0.001$) | | | | | | |
| Total | | 4454 | | 4194 | 100.0 | –0.66 (–0.73 to –0.58) |
| Heterogeneity: tau-square = 0.03; chi-square = 106.92; $P < 0.001$; $I^2 = 77\%$ | | | | | | |
| Test for overall effect: $Z = 16.40$ ($P < 0.001$) | | | | | | |
| Test for subgroup differences: chi-square = 3.64; $P = 0.056$; $I^2 = 72.5\%$ | | | | | | |

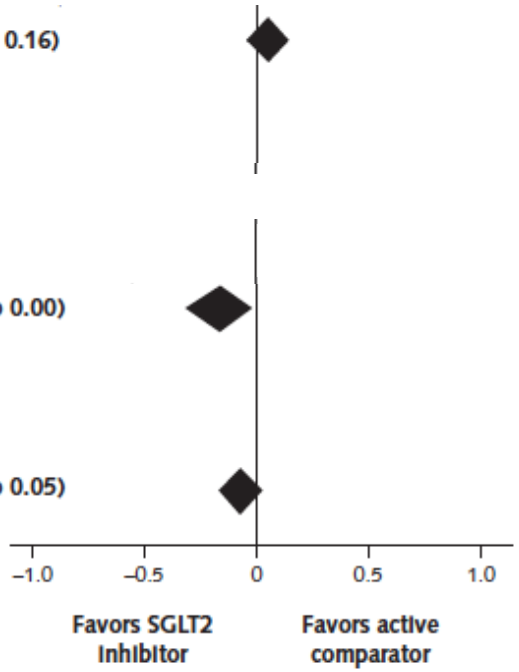





Vasilakou D et al: Ann Intern Med 59:262-274; 2013

# SGLT2 Inhibition: Change in HbA1c Versus Active Comparator

| Study, Year (Reference) | SGLT2 Inhibitor Mean Change (SD), % | SGLT2 Inhibitor Total, *n* | Active Comparator Mean Change (SD), % | Active Comparator Total, *n* | Weight, % | Mean Difference IV, Random (95% CI) |
|---|---|---|---|---|---|---|
| **Monotherapy** | | | | | | |
| Subtotal | | 608 | | 603 | 47.2 | 0.05 (–0.06 to 0.16) |
| Heterogeneity: tau-square = 0.00; chi-square = 2.76; $P = 0.60$; $I^2 = 0\%$ | | | | | | |
| Test for overall effect: $Z = 0.88$ ($P = 0.38$) | | | | | | |
| **Add-on Treatment** | | | | | | |
| Subtotal | | 1303 | | 1313 | 52.8 | –0.16 (–0.32 to 0.00) |
| Heterogeneity: tau-square = 0.02; chi-square = 16.72; $P < 0.001$; $I^2 = 82\%$ | | | | | | |
| Test for overall effect: $Z = 1.92$ ($P = 0.05$) | | | | | | |
| Total | | 1911 | | 1916 | 100.0 | –0.06 (–0.18 to 0.05) |
| Heterogeneity: tau-square = 0.02; chi-square = 27.70; $P < 0.001$; $I^2 = 71\%$ | | | | | | |
| Test for overall effect: $Z = 1.07$ ($P = 0.28$) | | | | | | |
| Test for subgroup differences: chi-square = 4.35; $P = 0.037$; $I^2 = 77.0\%$ | | | | | | |






Vasilakou D et al: Ann Intern Med 59:262-274; 2013

# SGLT2 Inhibition: Beyond Glucose Lowering – Added "Benefits"

| Outcome | Comparison† | Studies Contributing Data, *n* | Participants Analyzed, *n* | | Participants With Outcome, *n* | | Effect Estimate‡ (95% CI) | $I^2$, % |
|---|---|---|---|---|---|---|---|---|
| | | | SGLT2 Inhibitor | Comparator | SGLT2 Inhibitor | Comparator | | |
| Mean percentage of change in body weight from baseline | SGLT2 inhibitor vs. placebo | 8 | 2222 | 2209 | NA | NA | −2.37 (−2.73 to −2.02) | 65 |
| | Dapagliflozin vs. placebo | 3 | 982 | 994 | NA | NA | −2.06 (−2.38 to −1.74) | 0 |
| | Canagliflozin vs. placebo | 5 | 1240 | 1215 | NA | NA | −2.61 (−3.09 to −2.13) | 66 |
| | SGLT2 inhibitor vs. active agent | 3 | 488 | 499 | NA | NA | −2.14 (−3.02 to −1.25) | 67 |
| Mean change in systolic blood pressure (mm Hg) from baseline | SGLT2 inhibitor vs. placebo | 21 | 3666 | 3548 | NA | NA | −3.77 (−4.65 to −2.90) | 44 |
| | Dapagliflozin vs. placebo | 14 | 2273 | 2180 | NA | NA | −3.20 (−4.20 to −2.21) | 29 |
| | Canagliflozin vs. placebo | 6 | 1327 | 1303 | NA | NA | −4.79 (−6.39 to −3.18) | 53 |
| | SGLT2 inhibitor vs. active agent | 6 | 1240 | 1247 | NA | NA | −4.45 (−5.73 to −3.18) | 34 |
| | Dapagliflozin vs. active agent | 4 | 799 | 804 | NA | NA | −3.95 (−5.57 to −2.33) | 38 |
| Mean change in diastolic blood pressure (mm Hg) from baseline | SGLT2 inhibitor vs. placebo | 16 | 1762 | 1652 | NA | NA | −1.75 (−2.27 to −1.23) | 0 |
| | Dapagliflozin vs. placebo | 12 | 1348 | 1242 | NA | NA | −1.74 (−2.35 to −1.13) | 0 |
| | Canagliflozin vs. placebo | 3 | 348 | 345 | NA | NA | −1.84 (−2.96 to −0.72) | 0 |
| | SGLT2 inhibitor vs. active agent | 6 | 1240 | 1247 | NA | NA | −2.01 (−2.62 to −1.39) | 0 |
| | Dapagliflozin vs. active agent | 4 | 799 | 804 | NA | NA | −1.72 (−2.48 to −0.96) | 0 |



Vasilakou D et al: Ann Intern Med 59:262-274; 2013

# SGLT2 Inhibition: Beyond Glucose Lowering - Selected Adverse Effects

| Outcome | Comparison† | Studies Contributing Data, *n* | Participants Analyzed, *n* | | Participants With Outcome, *n* | | Effect Estimate‡ (95% CI) | $I^2$, % |
|---|---|---|---|---|---|---|---|---|
| | | | SGLT2 Inhibitor | Comparator | SGLT2 Inhibitor | Comparator | | |
| **Hypoglycemia** | SGLT2 inhibitor vs. placebo | 21 | 1920 | 1857 | 204 | 174 | 1.28 (0.99 to 1.65) | 0 |
| | Dapagliflozin vs. placebo | 12 | 1315 | 1255 | 144 | 128 | 1.20 (0.88 to 1.64) | 0 |
| | Canagliflozin vs. placebo | 4 | 360 | 356 | 55 | 42 | 1.53 (0.93 to 2.54) | 0 |
| | Ipragliflozin vs. placebo | 3 | 147 | 148 | 5 | 2 | 2.02 (0.49 to 8.24) | 0 |
| | SGLT2 inhibitor vs. active agent§ | 7 | 1059 | 1058 | 169 | 169 | 1.01 (0.77 to 1.32) | 0 |
| | Dapagliflozin vs. active agent§ | 3 | 469 | 465 | 5 | 11 | 0.49 (0.18 to 1.39) | 0 |
| **Urinary tract infection** | SGLT2 inhibitor vs. placebo | 21 | 2059 | 1944 | 139 | 103 | 1.34 (1.03 to 1.74) | 0 |
| | Dapagliflozin vs. placebo | 12 | 1455 | 1393 | 108 | 75 | 1.43 (1.05 to 1.94) | 0 |
| | Canagliflozin vs. placebo | 3 | 350 | 347 | 19 | 17 | 1.12 (0.57 to 2.19) | 0 |
| | Ipragliflozin vs. placebo | 3 | 147 | 148 | 11 | 10 | 1.12 (0.47 to 2.68) | 0 |
| | SGLT2 inhibitor vs. active agent | 8 | 1465 | 1465 | 116 | 84 | 1.42 (1.06 to 1.90) | 25 |
| | Dapagliflozin vs. active agent | 4 | 875 | 873 | 89 | 55 | 1.69 (1.19 to 2.40) | 7 |
| **Genital tract infection** | SGLT2 inhibitor vs. placebo | 20 | 2049 | 1981 | 137 | 37 | 3.50 (2.46 to 4.99) | 0 |
| | Dapagliflozin vs. placebo | 13 | 1466 | 1401 | 108 | 30 | 3.48 (2.33 to 5.20) | 0 |
| | Canagliflozin vs. placebo | 3 | 350 | 347 | 17 | 5 | 3.26 (1.23 to 8.61) | 0 |
| | SGLT2 inhibitor vs. active agent | 8 | 1465 | 1465 | 150 | 32 | 5.06 (3.44 to 7.45) | 0 |
| | Dapagliflozin vs. active agent | 4 | 875 | 873 | 93 | 21 | 4.81 (2.97 to 7.81) | 0 |



Vasilakou D et al: Ann Intern Med 59:262-274; 2013

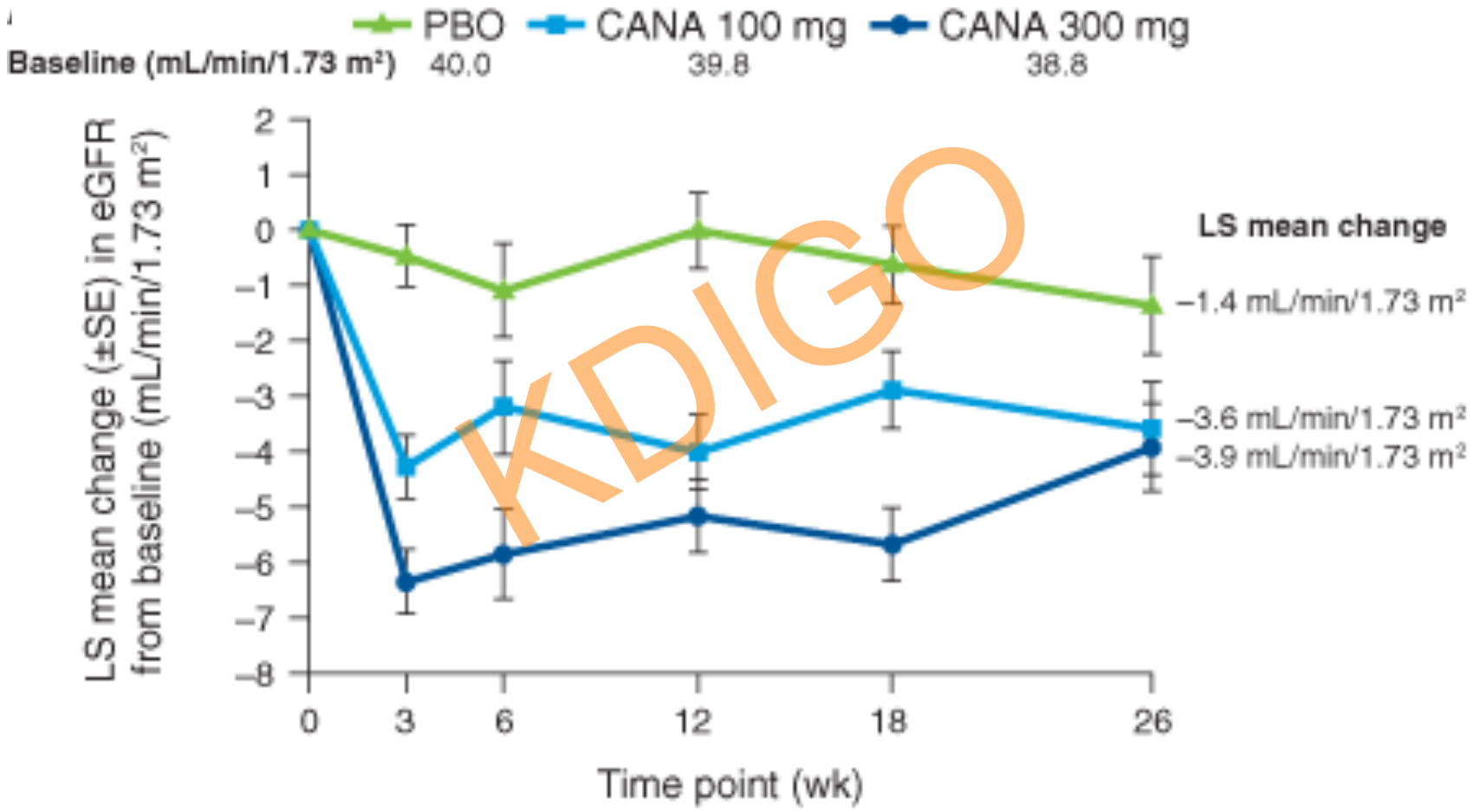
# SGLT2 Inhibition: Beyond Glucose Lowering - Selected Adverse Effects

| Outcome | Comparison† | Studies Contributing Data, *n* | Participants Analyzed, *n* | | Participants With Outcome, *n* | | Effect Estimate‡ (95% CI) | $I^2$, % |
|---|---|---|---|---|---|---|---|---|
| | | | SGLT2 Inhibitor | Comparator | SGLT2 Inhibitor | Comparator | | |
| **Hypotension** | SGLT2 inhibitor vs. placebo | 12 | 1535 | 1468 | 14 | 7 | 1.57 (0.74 to 3.35) | 0 |
| | Dapagliflozin vs. placebo | 9 | 1239 | 1177 | 10 | 6 | 1.38 (0.59 to 3.24) | 0 |
| | Canagliflozin vs. placebo | 3 | 296 | 291 | 4 | 1 | 2.49 (0.47 to 13.27) | 0 |
| | SGLT2 inhibitor vs. active agent | 5 | 1252 | 1251 | 18 | 6 | 2.68 (1.14 to 6.29) | 2 |
| | Dapagliflozin vs. active agent | 4 | 875 | 873 | 12 | 5 | 2.14 (0.83 to 5.53) | 10 |



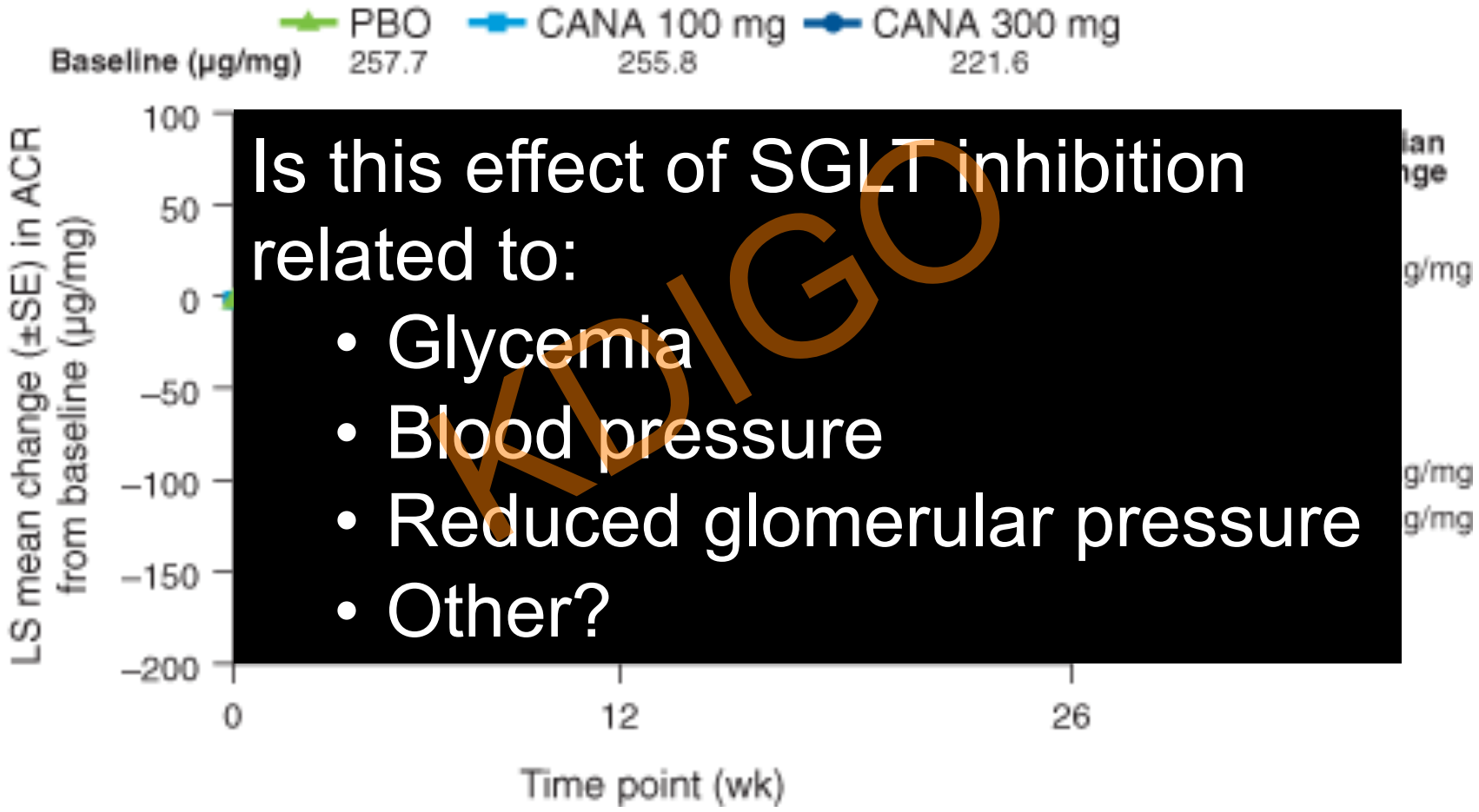
Vasilakou D et al: Ann Intern Med 59:262-274; 2013

# SGLT2 Inhibition: Effect on eGFR




Yale J-F et al: Diabetes Obes Metab 15:463-473; 2014

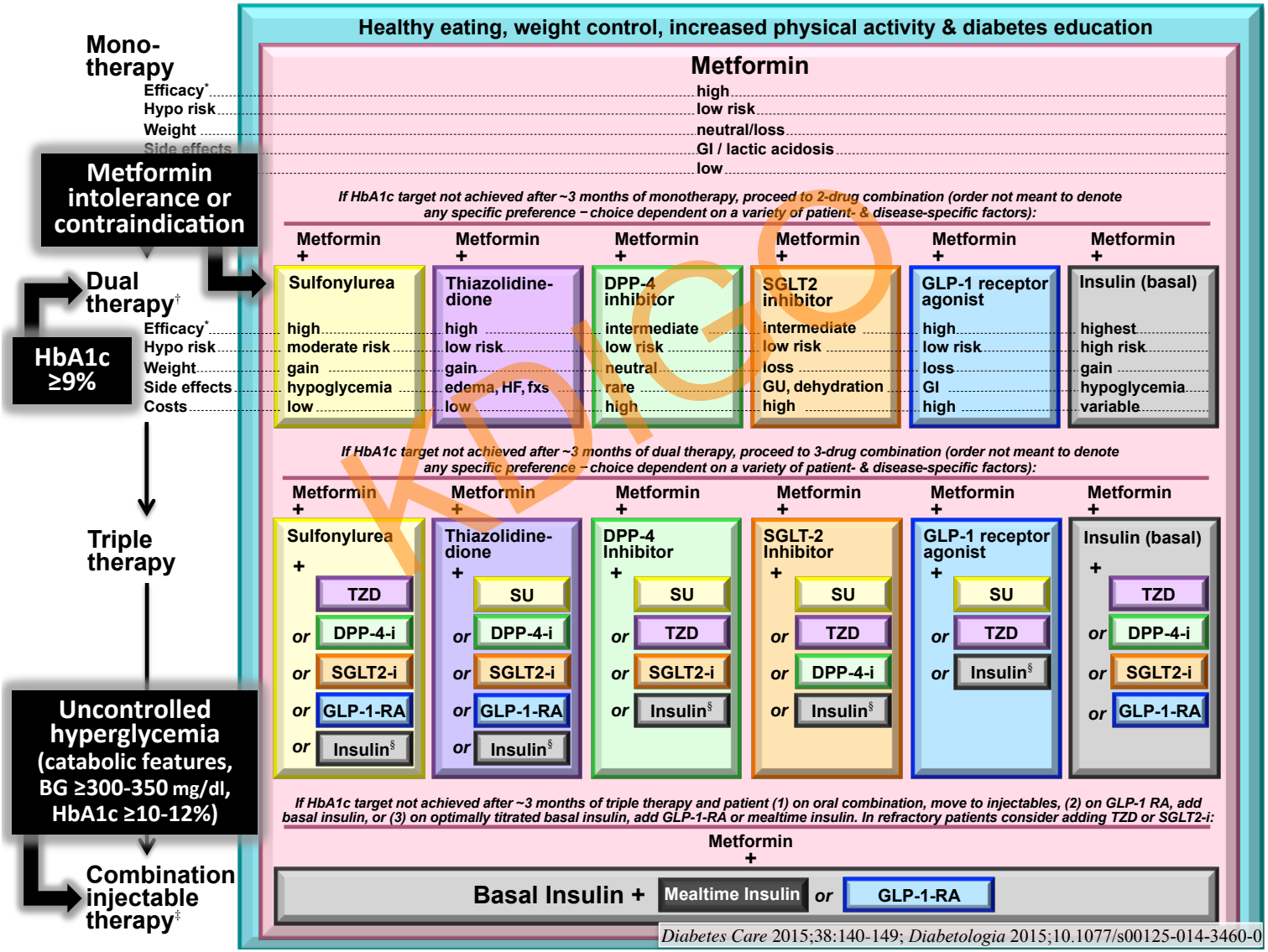
# SGLT2 Inhibition: Effect on Albuminuria






Yale J-F et al: Diabetes Obes Metab 15:463-473; 2014

# ADA-EASD Patient-Centered Algorithm for Managing Hyperglycemia




*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

# Acknowledgements

The thousands of research volunteers who have allowed us to learn about the efficacy and safety of glucose-lowering agents.