

Type 2 Diabetes Management 2014

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Chief, Division of Endocrinology
Executive Associate Dean, Clinical Research
University of North Carolina School of Medicine**

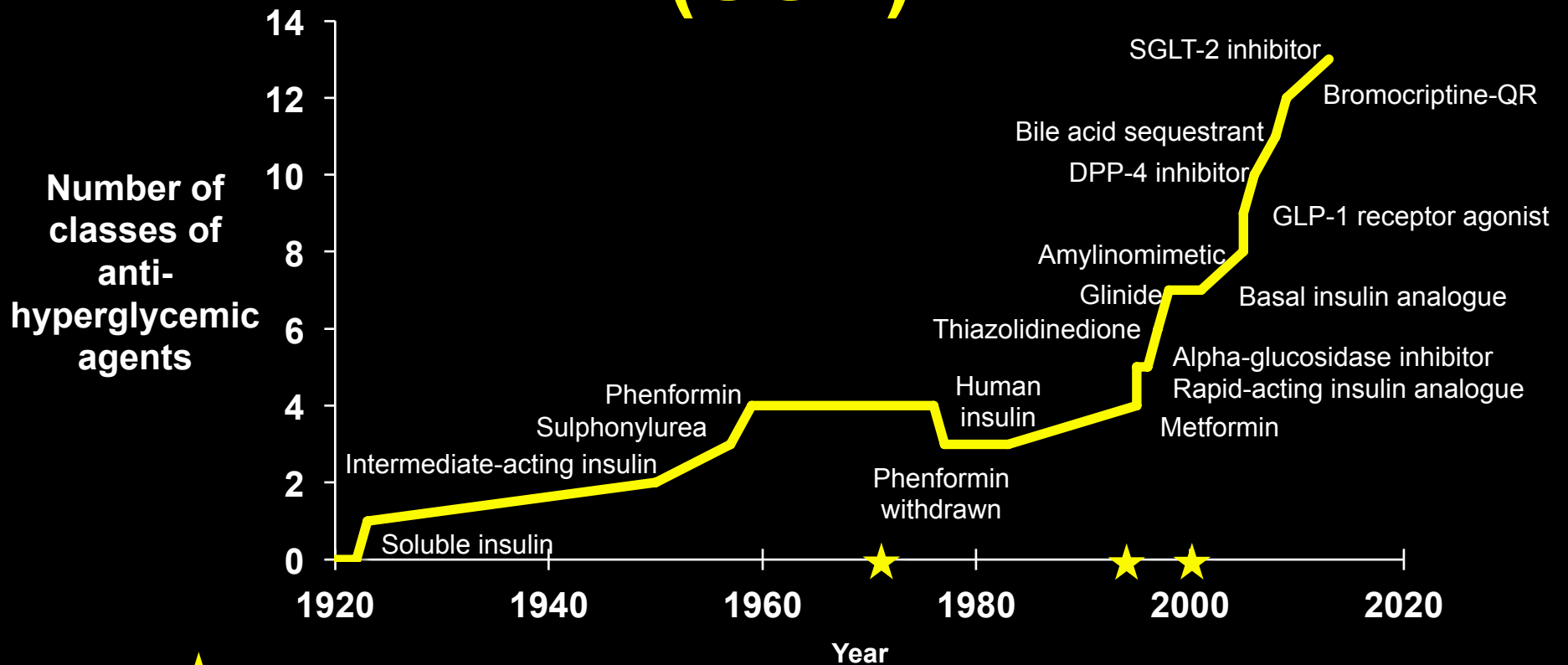
Last Year's Presentation

■ Overview

- Hyperglycemia management matters**
- Adherence**
- Shared decision-making**
- Patient-centered goals**

■ Drug safety/tolerability is a critical issue

100-year History of Antihyperglycaemic Therapeutics (USA)



Antihyperglycemic Agents in Type 2 Diabetes

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R, Lispro, Aspart, Glulisine	Brand	1.5 - 2.5	2-4	Injected	Yes	Gain	Breast Cancer
NPH, Glargine, Detemir	Brand	1.5 - 2.5	1	Injected	Yes	Gain	
Glipizide ER, Glimepiride	Generic	1.5	1	Oral	Yes	Gain	CVD
Repaglinide	Brand	1 - 1.5	3	Oral	Yes	Gain	
Nateglinide	Generic	0.5 - 0.8	3	Oral	Rare	Gain	
Metformin	Generic	1.5	1-2	Oral	No	Neutral	B12 deficiency, lactic acidosis
Acarbose, Miglitol	Generic	0.5 - 0.8	3	Oral	No	Neutral	
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Exenatide OW, albiglutide	Brand	0.9 - 1.6	Every 7d	Injected	No	Loss	ARF, Pancreatitis, MTC, PancCa
Sita-, saxa-, lina-, alo- gliptin	Brand	0.6 - 0.8	1	Oral	No	Neutral	Pancreatitis, PancCa
Colesevelam	Brand	~0.5	1-2	Oral	No	Neutral	Hypertriglyceridemia
Bromocriptine QR	Brand	~0.6	1	Oral	No	Neutral	Various in PI
Cana-, dapa-, empa- gliflozin	Brand	0.6 - 1.2	1	Oral	No	Loss	LDL, ARF, Genital infections, K

ARF=acute renal failure; MTC=medullary thyroid carcinoma

Adapted from: Nathan et al. Diabetes Care. 2009; 32:193-203. ADA. Diabetes Care. 2010;33:S11-S61. Buse et al. In: Williams Textbook of Endocrinology, 12th ed . 2012. Individual agents prescribing information.

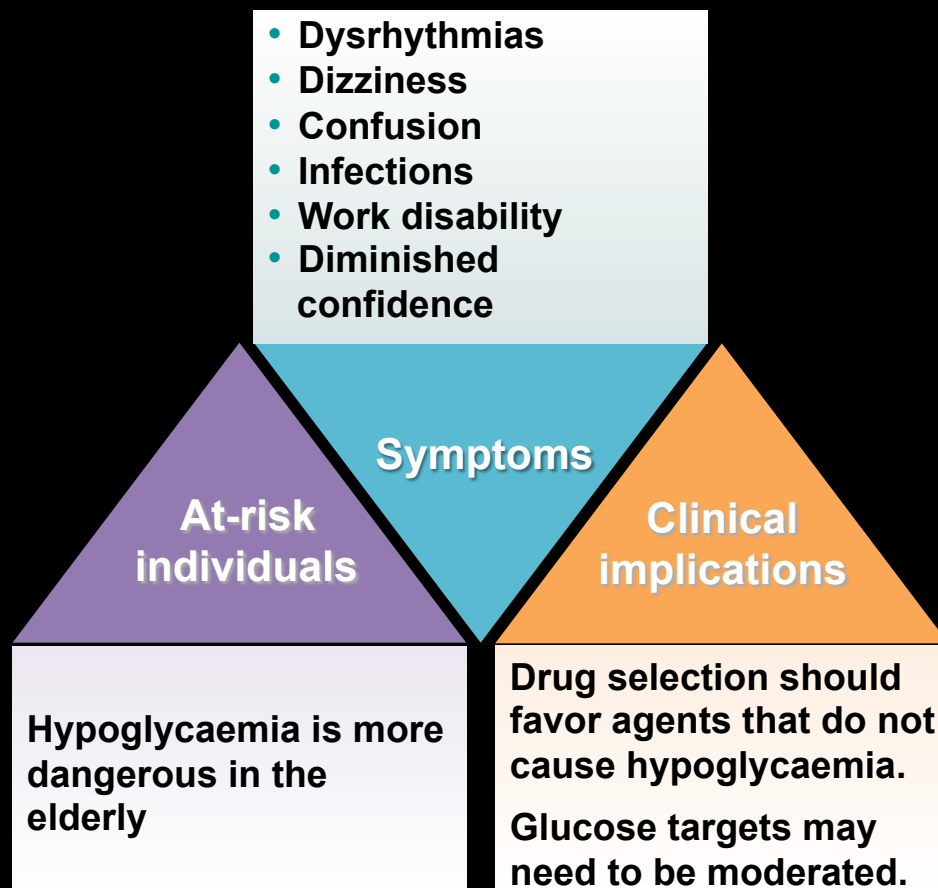
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ADA-EASD Position Statement: Hypoglycaemia



Adapted from Inzucchi et al. Diabetes Care 2012;35:1364–79.

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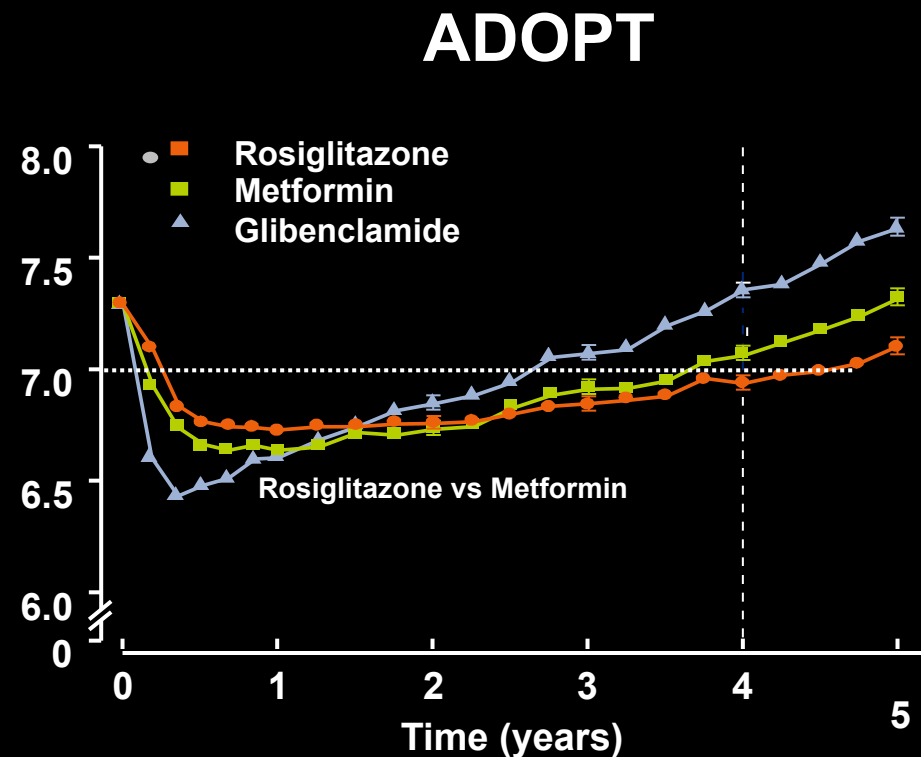
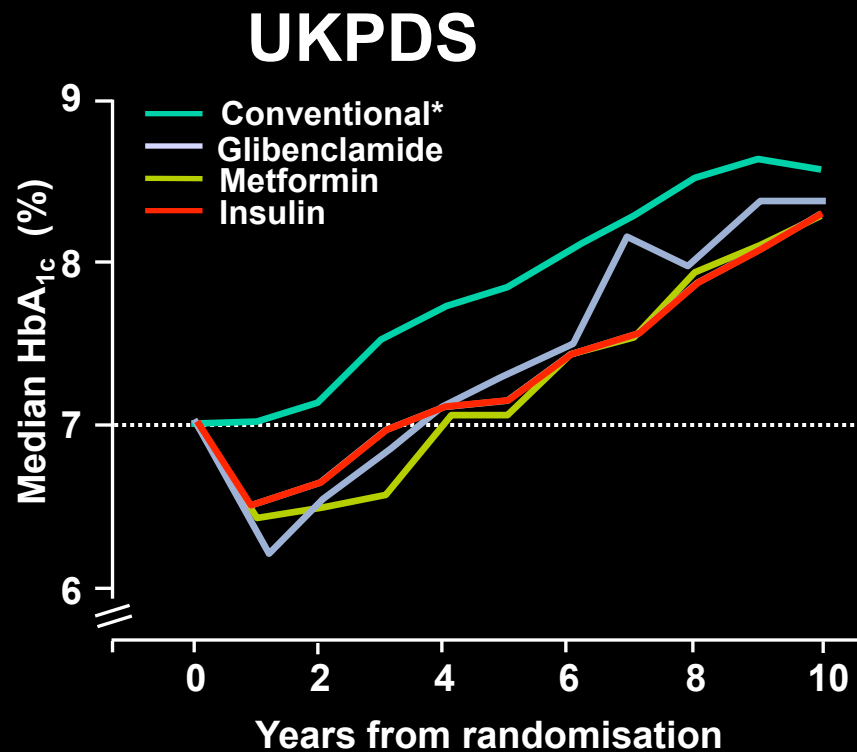
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Secondary Failure: The Problem with Sulfonylureas



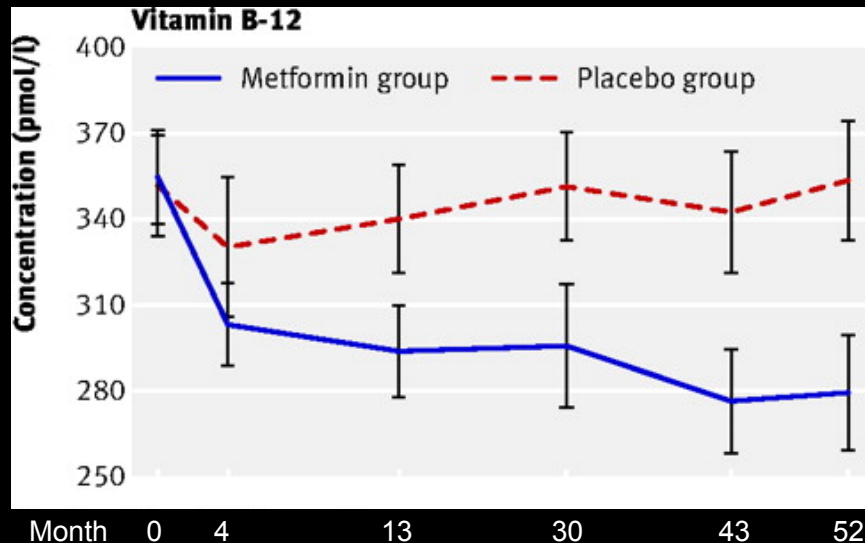
*Diet initially then sulfonylureas, insulin and/or metformin if FPG > 15 mmol/L

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Metformin and B12 Deficiency



- Absolute risk of B12 deficiency (<150 pmol/L) is 7.2% higher with metformin.
- Absolute risk of low B12 (150-220 pmol/L) is 11.2% higher with metformin.
- “Our findings suggest that regular measurement of vitamin B-12 concentrations during long-term metformin treatment should be strongly considered.”
- Other studies suggest that calcium supplements can prevent this effect

Metformin, Lactic Acidosis, and Renal Insufficiency

- Renal insufficiency associated with increased risk of lactic acidosis independent of metformin therapy
- Alternative approach to the prescribing information recommendation to avoid metformin in women with creatinine >1.3 mg/dl and in men >1.4 mg/dl:
 - Avoid use in stage 4, stage 5 CKD
 - Use with caution in stage 3 CKD, perhaps ½ max dose at eGFR 30-45 ml/min/1.73m²
 - No restrictions in stage 1, 2 CKD

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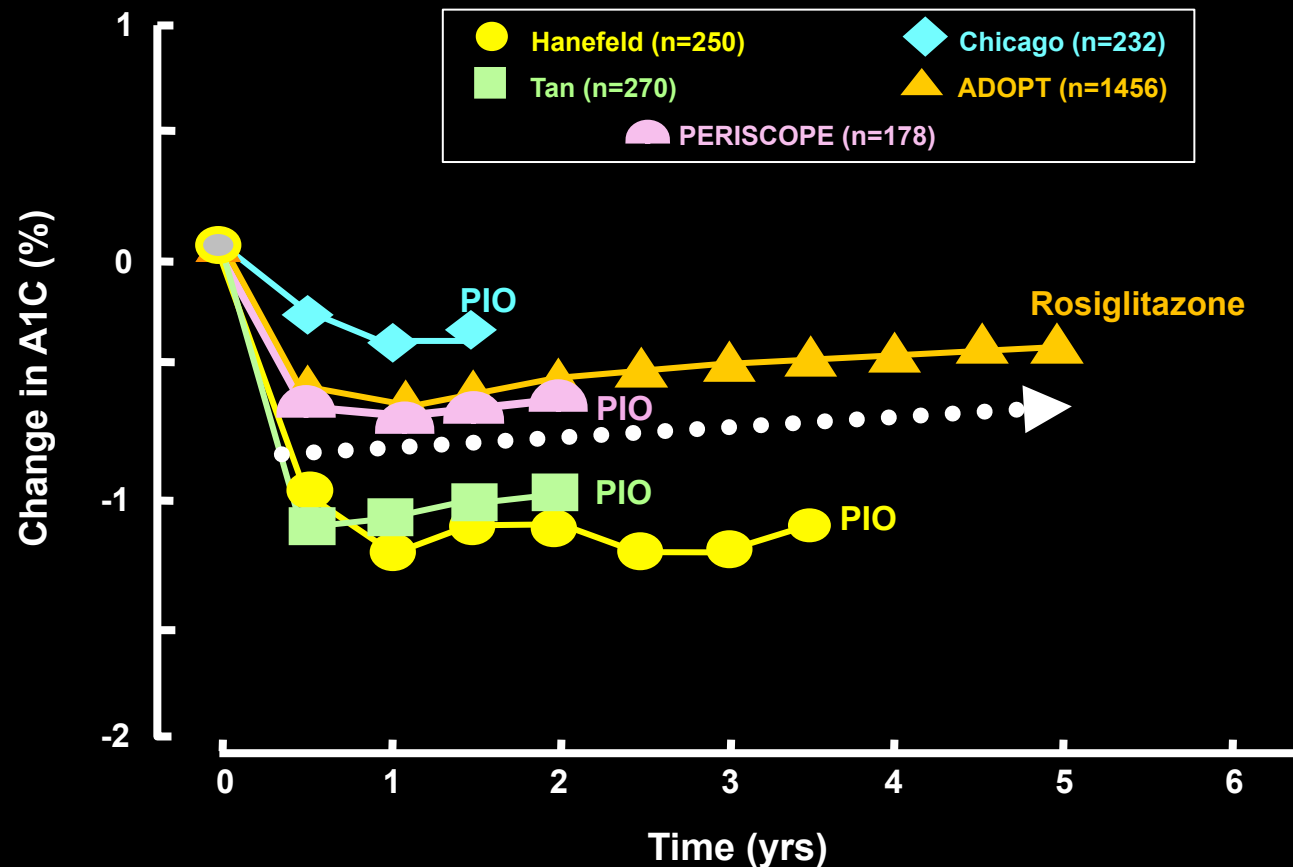
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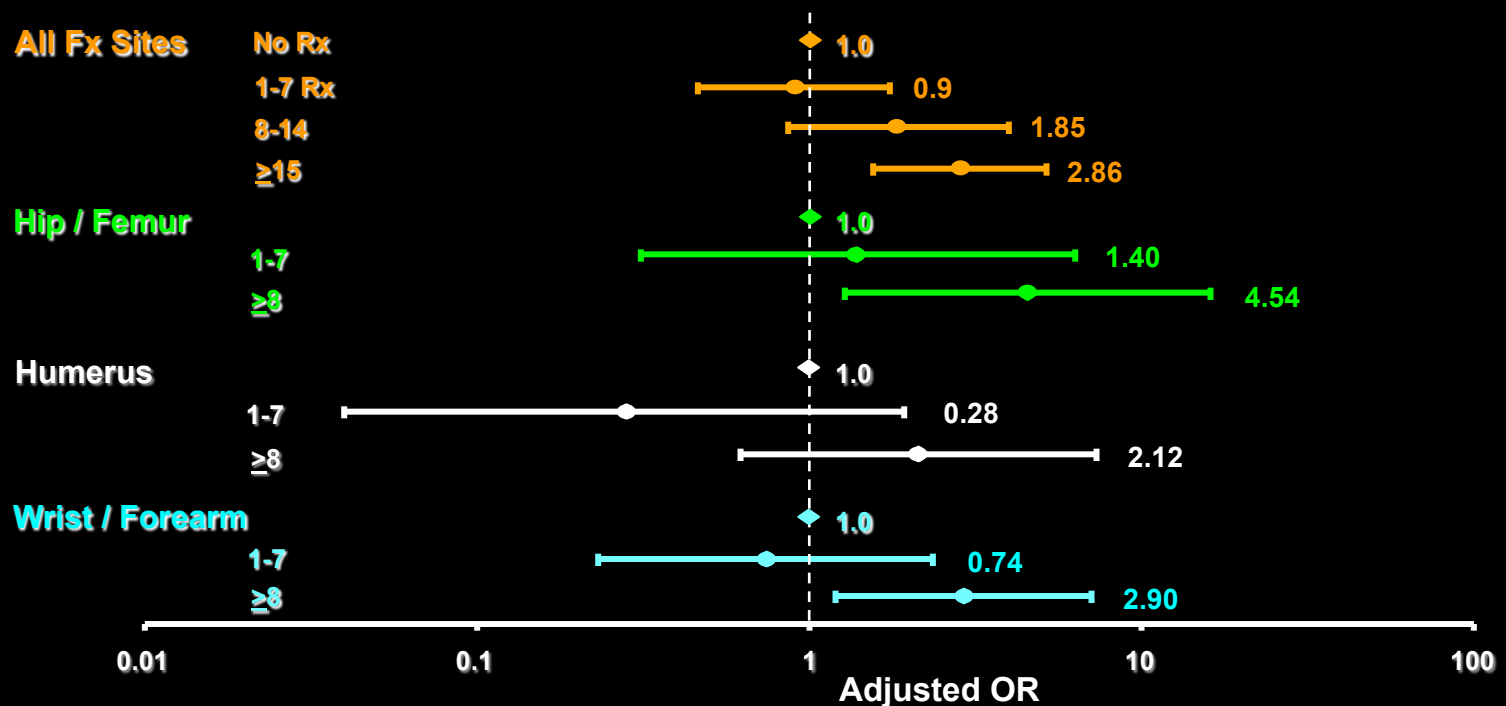
Durability of Glycemic Control with Thiazolidinediones



Kahn. N Engl J Med. 2006;355:2427-43. Mazzone. JAMA. 2006;296:2572-81
 Hanefeld. Cur Med Res Opin. 2006;22:1211-1215. Tan MH. Diabetes Care. 2005;28:544-550
 Nissen et al. JAMA. 2008;299:1567-73.

TZD Use and Fracture Risk: UK General Practice Research Database (1994-2005)

- Observational study (N=66,696)
 - First low trauma fracture (N=1,020)
 - 6% of cases used a TZD (PIO and RSG)



Pioglitazone and Bladder Cancer

- **10-year observational study follow-up**
 - **“The primary analysis found no association between the use of pioglitazone and the risk of bladder cancer. Additionally, no association was found between the risk of bladder cancer and the duration of pioglitazone use, increased cumulative dose of pioglitazone, or the time since initiating pioglitazone.”**

August 29, 2014, press release.

http://www.takeda.com/news/2014/20140829_6714.html

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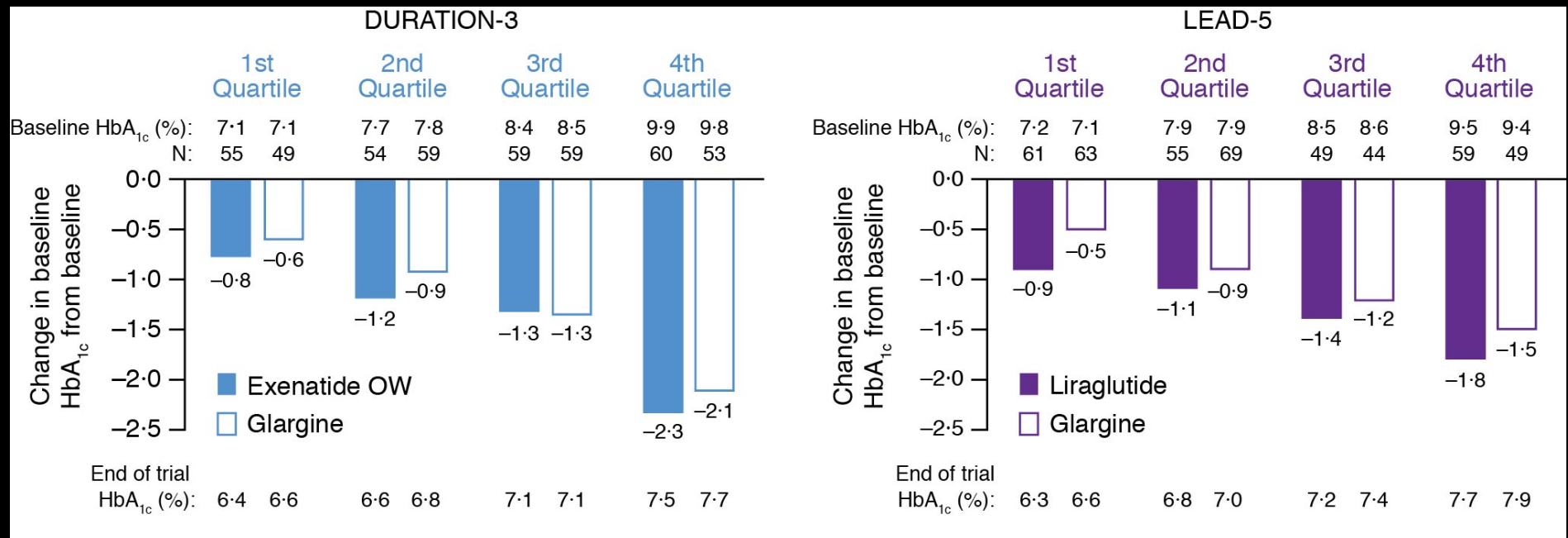
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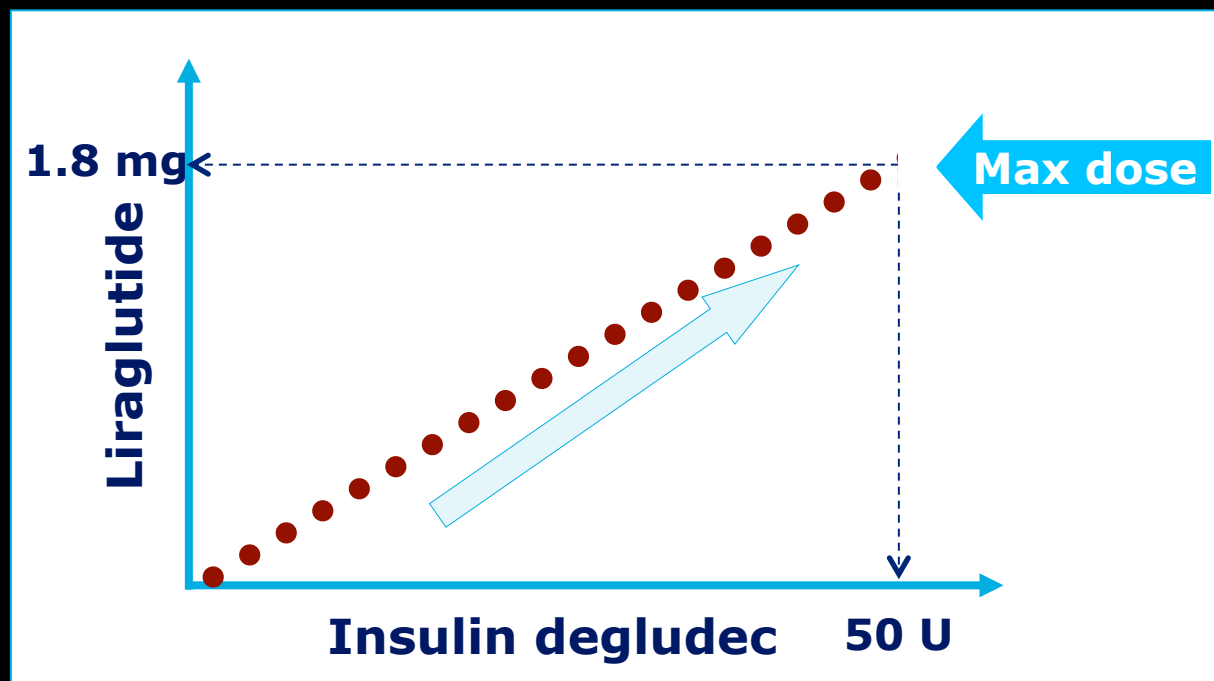
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Is Insulin the Most Effective Injectable Antihyperglycemic Therapy?



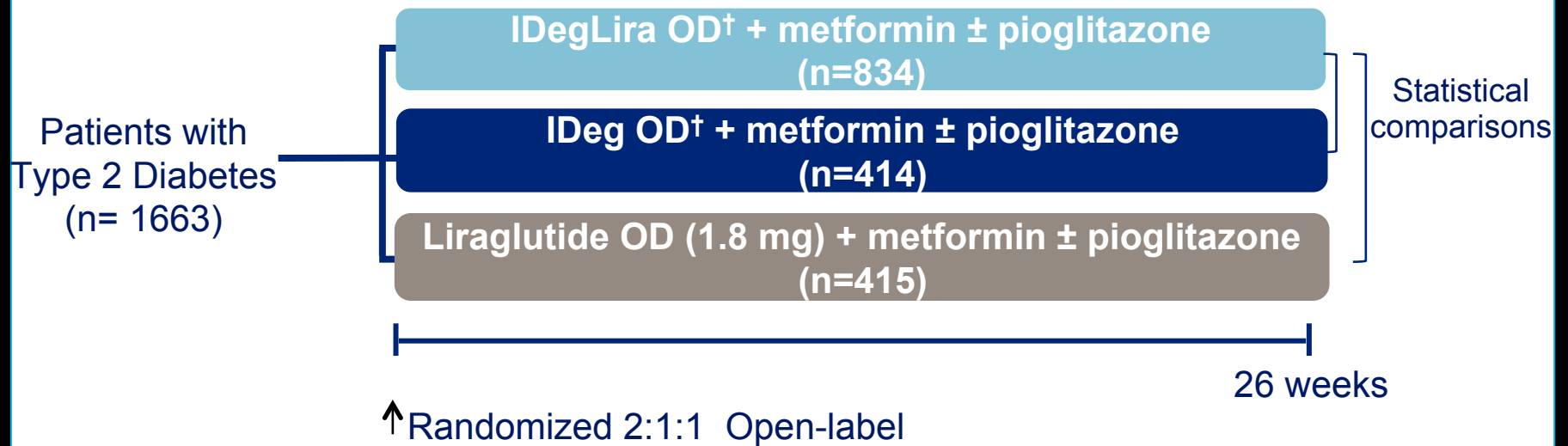
IDegLira*

Fixed-ratio Combination of Insulin Degludec* and Liraglutide



One dose step = 1 U insulin degludec and 0.036 mg liraglutide

DUAL-1 Study Design



Inclusion criteria

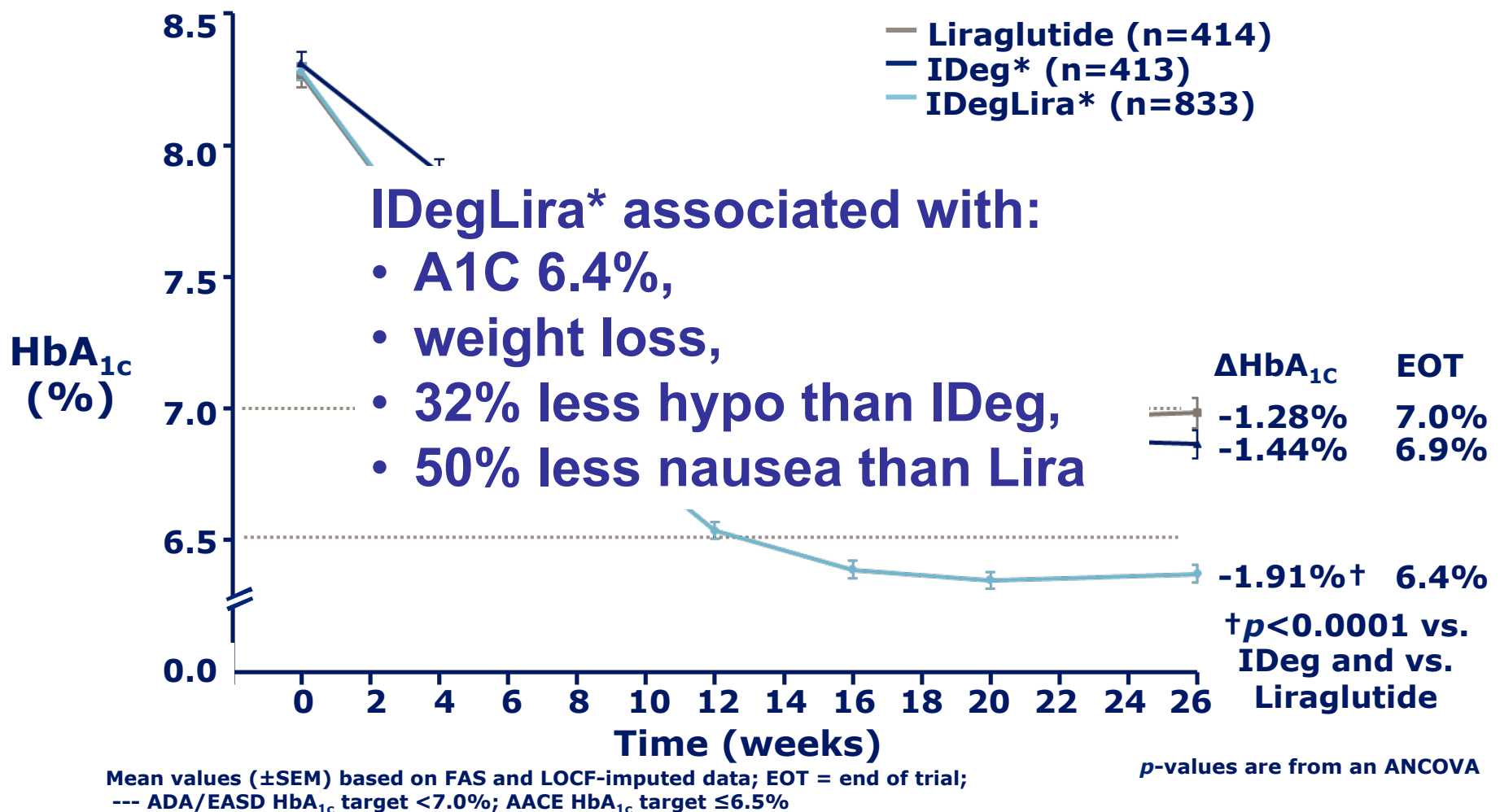
- Type 2 diabetes
 - Insulin-naïve, treated with metformin ± pioglitazone
 - HbA_{1c} 7.0–10.0%
 - BMI ≤40 kg/m²
 - Age ≥18 years*
- * Singapore, age ≥21 years

Titration algorithm: IDegLira and IDeg

Mean fasting PG		Dose change
mg/dL	mmol/L	dose steps or U
<72	<4.0	-2
72–90	4.0–5.0	0
>90	>5.0	+2

[†]Not FDA approved

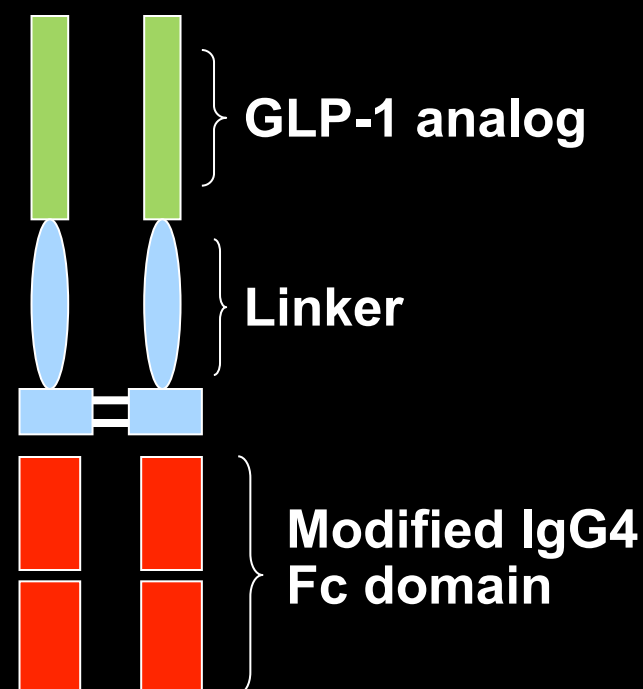
DUAL-1 Study: HbA_{1c} Over Time



Dulaglutide

A recombinant GLP-1 Fc fusion protein linking a human GLP-1 peptide analog and a variant of a human IgG4 Fc fragment^{1,2}

- Extended plasma half-life (~5 days)
- Minimal renal clearance
- Low immunogenic potential
- Once weekly dosing
- Solution injection: no reconstitution needed

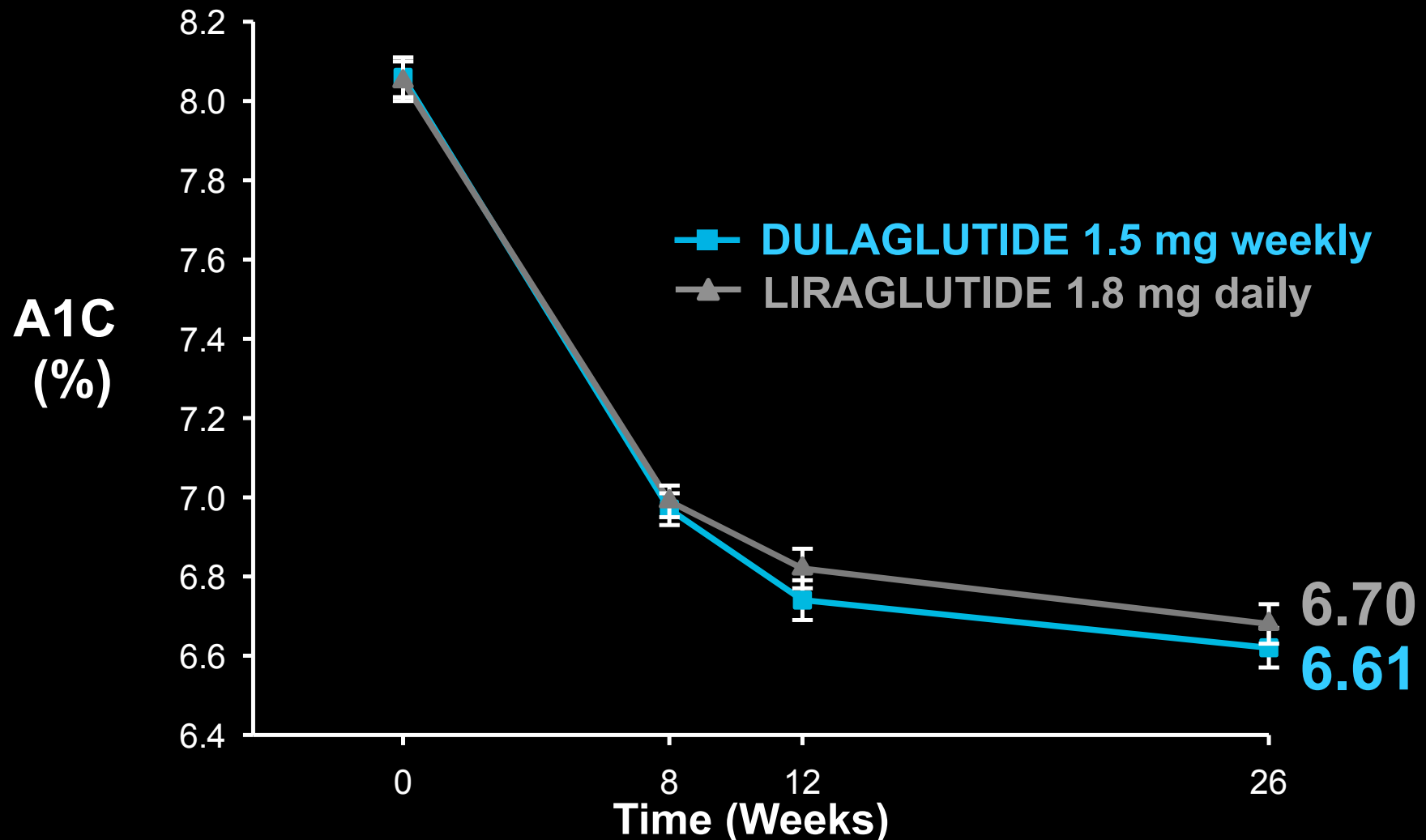


1. Glaesner et al. Diabetes Metab Res Rev 2010;26:287-96

2. Nauck et al. Diabetes Care 2014;(Ahead of print)

Dulaglutide vs. Liraglutide: A1C

Baseline A1C = 8.1%



Data presented are LS means $\pm$ SE. ITT, MMRM analysis

Dungan et al. Lancet. 2014 Jul 10. pii: S0140-6736(14)60976-4. doi: 10.1016/S0140-6736(14)60976-4. [Epub ahead of print]

AWARD-4: Dulaglutide vs Glargine

(on background of premeal lispro $\pm$ metformin)

- T2 diabetes. Age >18y. A1C 7-11%. BMI 23-45. On 1-2 shots of any kind of insulin at baseline.
 - Mean: age 59; duration 13; total insulin 56 units; A1C 8.5%.
- 9 week run-in to stop OADs except metformin and adjust insulin. Randomized to glargine at bedtime or one of two doses of dulaglutide once weekly (0.75 mg or 1.5 mg)
- At randomization, lispro insulin at total dose of 50% of end of run-in total (and in glargine arm, 50% as glargine)

	@	DULA 1.5	DULA 0.75	Glargine
A1C change (%)	26 wk	-1.6*	-1.6*	-1.4*
Lispro dose (units)	26 wk	93	97	68
Glargine dose (units)	26 wk	0	0	65
Weight change (kg)	52 wk	-0.35	0.9	2.9
Symptomatic hypo (events/p-y)	52 wk	31	35	40
Severe hypo (N)	52 wk	11	15	22
Nausea (%)	52 wk	26	18	3

Jendle et al. EASD abstract #42. Available on-line at <http://www.easdvirtualmeeting.org/resources/15089>.

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Pramlintide	Brand	0.5 - 0.9	3	Injected	No	Loss	
Exenatide	Brand	0.7 - 1.0	2	Injected	No	Loss	ARF, Pancreatitis, PancCa
Liraglutide	Brand	0.9 - 1.4	1	Injected	No	Loss	ARF, Pancreatitis, MTC, PancCa
Exenatide OW, albiglutide	Brand	0.9 - 1.6	Every 7d	Injected	No	Loss	ARF, Pancreatitis, MTC, PancCa
Sita-, saxa-, lina-, alo- gliptin	Brand	0.6 - 0.8	1	Oral	No	Neutral	Pancreatitis, PancCa
Colesevelam	Brand	~0.5	1-2	Oral	No	Neutral	Hypertriglyceridemia

ARF=acute renal failure; MTC=medullary thyroid carcinoma

Adapted from: Nathan et al. Diabetes Care. 2009; 32:193-203. ADA. Diabetes Care. 2010;33:S11-S61. Buse et al. In: Williams Textbook of Endocrinology, 12th ed . 2012. Individual agents prescribing information.

Antihyperglycemic Agents in Type 2 Diabetes

Class	Generic or Brand	A1C Reduction	Usual Dosing (times/day)	Injected or Oral	Severe Hypoglycemia	Weight Change	Other Safety Concerns (beyond hypoglycemia and weight gain)
R, Lispro, Aspart, Glulisine	Brand	1.5 - 2.5	2-4	Injected	Yes	Gain	Breast Cancer
NPH, Glargine, Detemir	Brand	1.5 - 2.5	1	Injected	Yes	Gain	
Glipizide ER, Glimepiride	Generic	1.5	1	Oral	Yes	Gain	CVD
Repaglinide	Brand	1 - 1.5	3	Oral	Yes	Gain	
Nateglinide	Generic	0.5 - 0.8	3	Oral	Rare	Gain	
Metformin	Generic	1.5	1-2	Oral	No	Neutral	B12 deficiency, lactic acidosis
Acarbose, Miglitol	Generic	0.5 - 0.8	3	Oral	No	Neutral	
Pioglitazone	Brand	0.5 - 1.4	1	Oral	No	Gain	CHF, Bone fx, Bladder Ca
Pramlintide	Brand	0.5 - 0.9	3	Injected	No	Loss	
Exenatide	Brand	0.7 - 1.0	2	Injected	No	Loss	ARF, Pancreatitis, PancCa
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Sita-, saxa-, lina-, alo- gliptin	Brand	0.6 - 0.8	1	Oral	No	Neutral	Pancreatitis, PancCa
Colesevelam	Brand	~0.5	1-2	Oral	No	Neutral	Hypertriglyceridemia
Bromocriptine QR	Brand	~0.6	1	Oral	No	Neutral	Various in PI

ARF=acute renal failure; MTC=medullary thyroid carcinoma

Adapted from: Nathan et al. Diabetes Care. 2009; 32:193-203. ADA. Diabetes Care. 2010;33:S11-S61. Buse et al. In: Williams Textbook of Endocrinology, 12th ed . 2012. Individual agents prescribing information.

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Repaglinide	Brand	1 - 1.5	3	Oral	Yes	Gain	
Nateglinide	Generic	0.5 - 0.8	3	Oral	Rare	Gain	
Metformin	Generic	1.5	1-2	Oral	No	Neutral	B12 deficiency, lactic acidosis
Acarbose, Miglitol	Generic	0.5 - 0.8	3	Oral	No	Neutral	
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Colesevelam	Brand	~0.5	1-2	Oral	No	Neutral	Hypertriglyceridemia
Bromocriptine QR	Brand	~0.6	1	Oral	No	Neutral	Various in PI
Cana-, dapa-, empa- gliflozin	Brand	0.6 - 1.2	1	Oral	No	Loss	LDL, ARF, Genital infections, K

ARF=acute renal failure; MTC=medullary thyroid carcinoma

Adapted from: Nathan et al. Diabetes Care. 2009; 32:193-203. ADA. Diabetes Care. 2010;33:S11-S61. Buse et al. In: Williams Textbook of Endocrinology, 12th ed . 2012. Individual agents prescribing information.

Summary of Observed Efficacy of SGLT2 Inhibitors

- **Similar to other oral antihyperglycemic agents in A1C reduction**
 - Reduces both FPG and PPG
- **Modest weight loss**
 - ~3 kg at 26 weeks vs placebo
 - Slightly greater weight loss at 52 weeks
 - Weight loss vs placebo sustained at 102 weeks
- **Modest blood pressure reduction**
 - 2-7 mm Hg vs placebo
- **Minimal improvements in TG and HDL**

***Abnormally frequent urination**

Hasan et al. Diabetes Res Clin Pract. 2014;104:297-322.

Tahrani et al. Lancet Diabetes Endocrinol. 2013;1:140-51.

Summary of Adverse Effects of SGLT2 Inhibitors

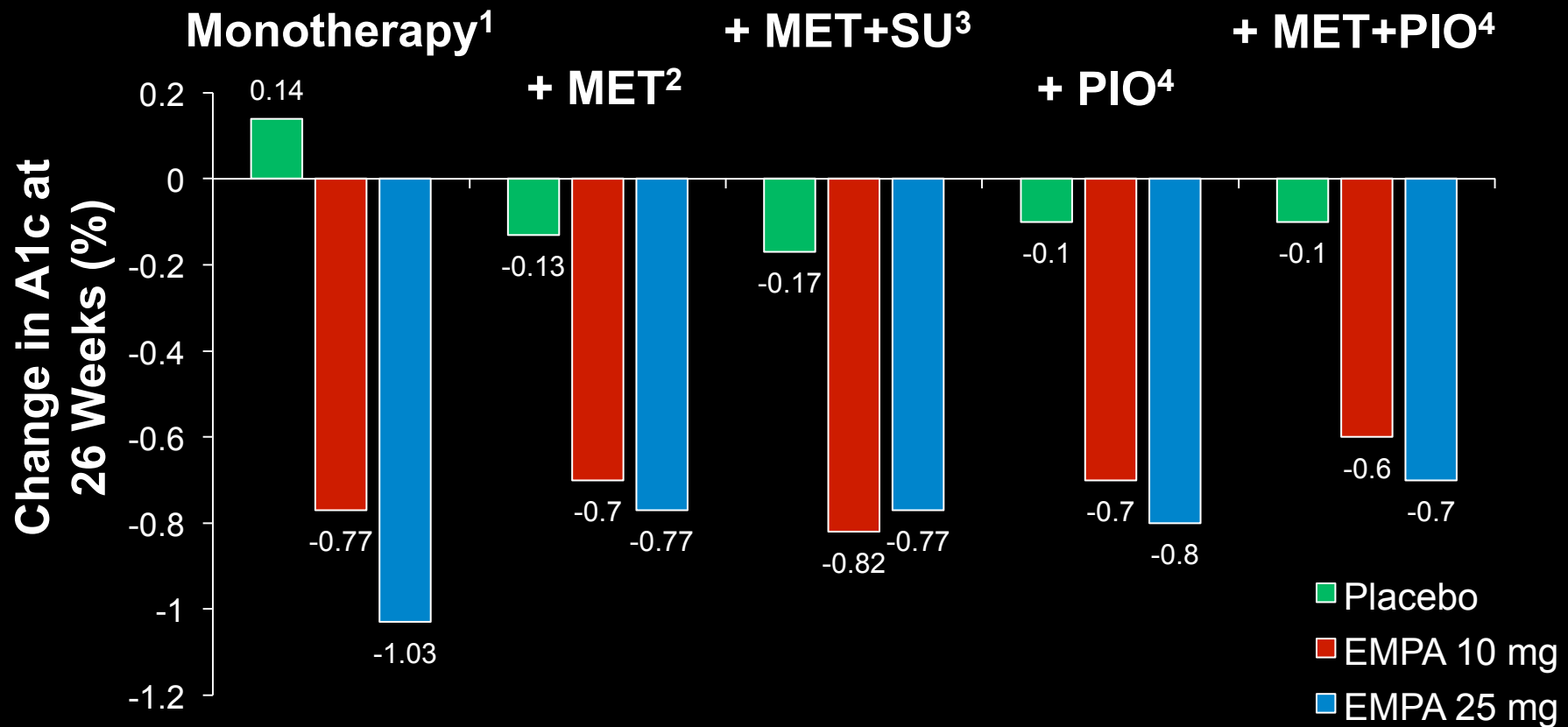
- Genital mycotic infections
- Pollakiuria*
- Genital infections
- Warnings:
 - *Hypotension*: Before initiating SGLT-2i assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.
 - *Impairment in renal function*: Monitor renal function during therapy.
 - *Increased LDL-c*

*Abnormally frequent urination

Hasan et al. Diabetes Res Clin Pract. 2014;104:297-322.

Tahrani et al. Lancet Diabetes Endocrinol. 2013;1:140-51.

Empagliflozin as an Exemplar of Broad Efficacy

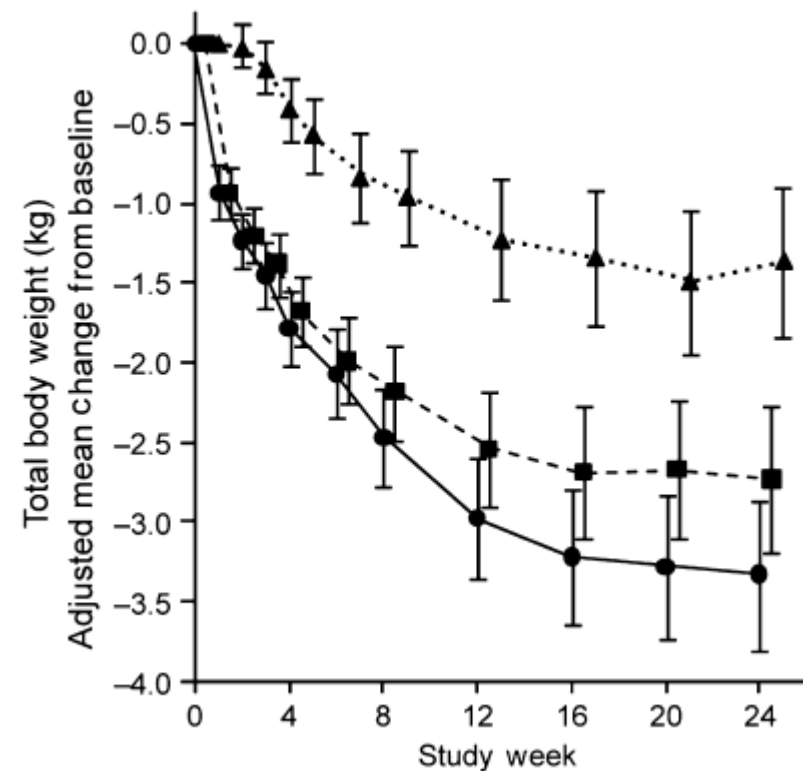
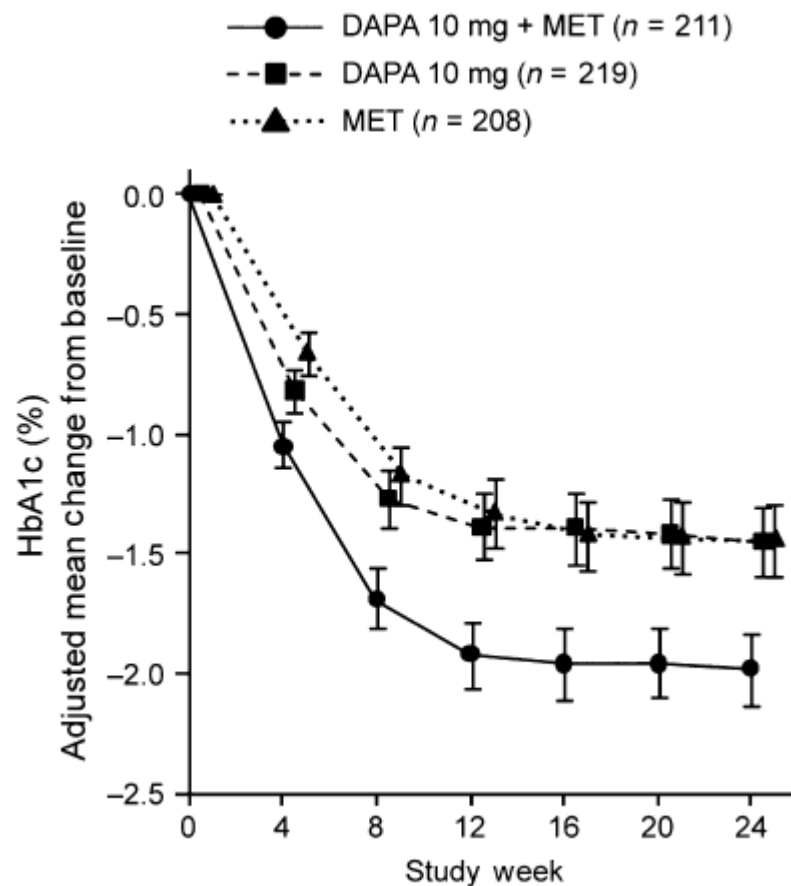


MET, metformin; SU, sulfonylurea; PIO, pioglitazone

1. Roden et al. Lancet Diabetes Endocrinol. 2013;1:208-19.
2. Haring et al. Diabetes Care. 2014;37:1650-9.
3. Haring et al. Diabetes Care. 2013;36:3396-3404.
4. Kovacs et al. Diabetes Obes Metab. 2013. Epub ahead of print.

Dapagliflozin vs. Metformin vs. Both

- Double-blind 24 week study in treatment naïve participants with A1C 7.5-12%
- Dapagliflozin 10 mg vs Metformin XR 2000 mg vs both



Canagliflozin vs. Glimepiride

■ Patient population:

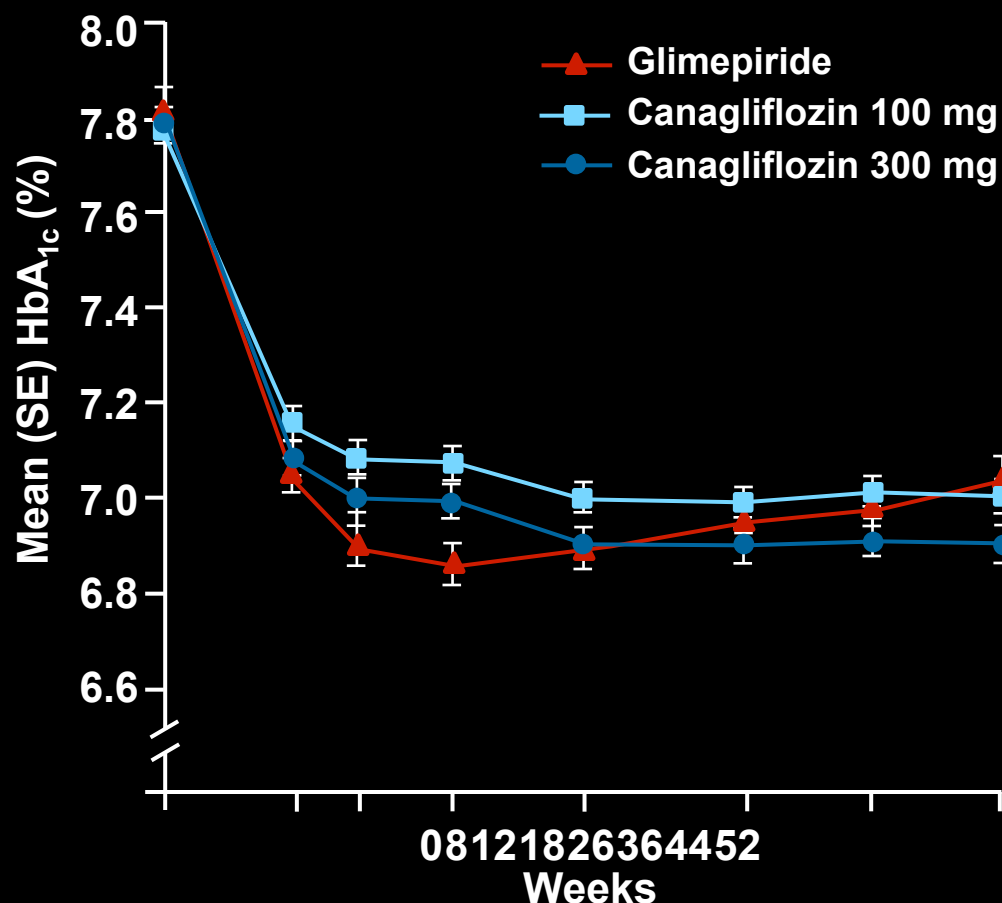
- Receiving metformin
- 18-80 years
- A1c = 7.0%-9.5%
- N=1450

■ Treatment groups:

- CANA – 100 or 300 mg qd
- Glimepiride titrated to 6 or 8 mg qd

■ Duration of study:

- 52 weeks



Drug	Change in weight (SE)
Canagliflozin 100 mg	-4.4 kg (0.6)
Canagliflozin 300 mg	-4.2 kg (0.7)
Glimepiride	0.8 kg (0.7)

Canagliflozin vs. Sitagliptin

■ Patient population:

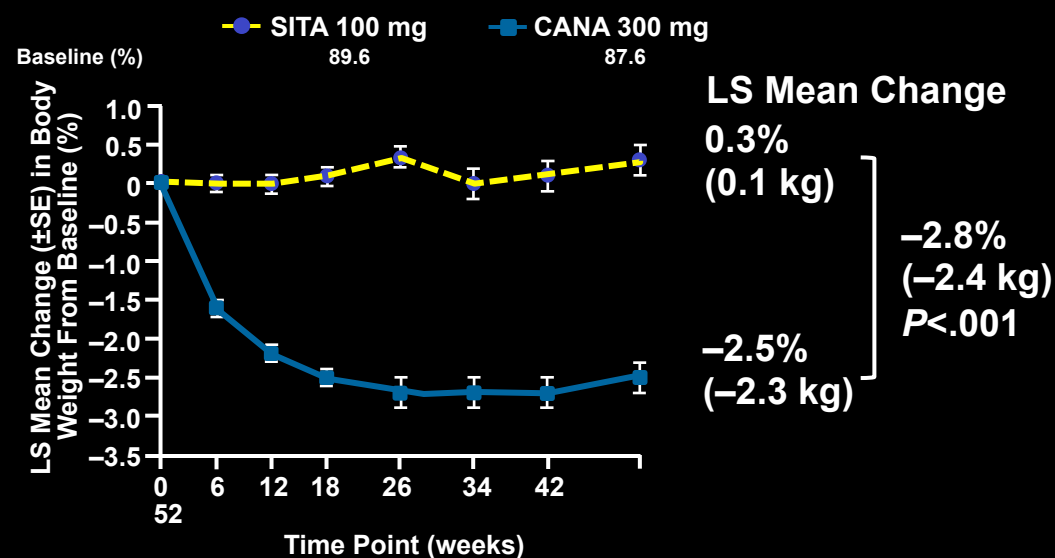
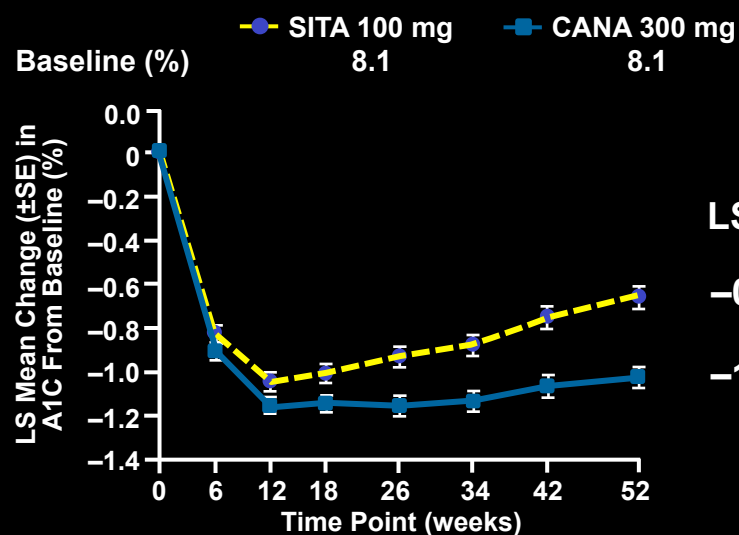
- Receiving metformin + SU
- N=755

■ Treatment groups:

- CANA – 300 mg qd
- SITA – 100 mg qd

■ Duration of study:

- 52 weeks



Dapagliflozin in Patients on High Doses of Insulin

■ Patient population:

- N=808 T2DM patients 18-80 years of age
- Receiving insulin ≥ 30 IU/day (mean baseline=74 IU/day) $\pm 1-2$ oral antidiabetic drugs
- A1c: 7.5%-10.5% (mean baseline=8.5%)

■ Treatment groups:

- DAPA 2.5, 5, or 10 mg qd
- Placebo

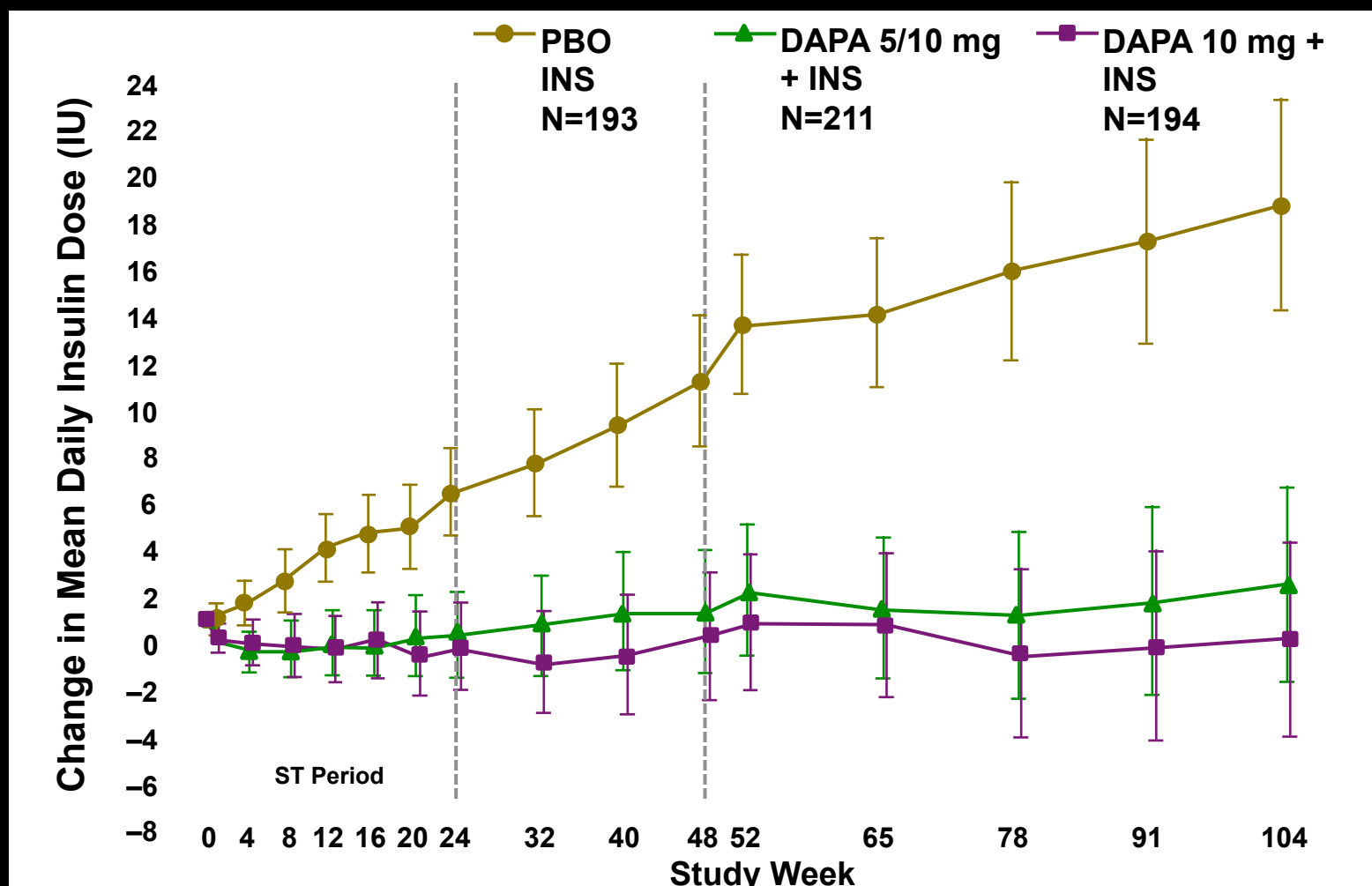
■ Duration of study:

- 24 weeks¹/104-week extension²

1. Wilding et al. Ann Intern Med. 2012;156:405-15.

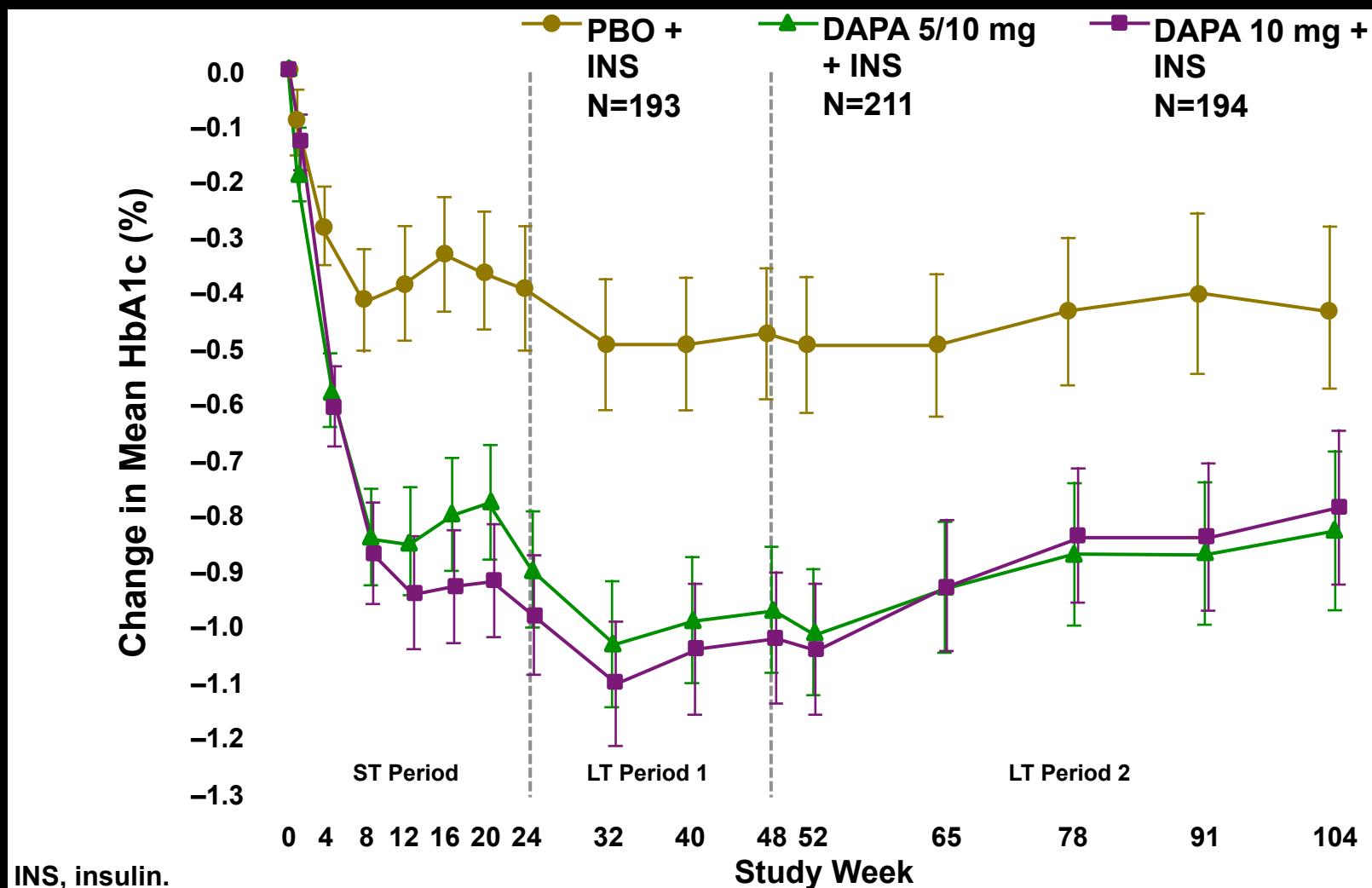
2. Wilding et al. Diabetes Obes Metab. 2014;16:124-36.

Dapagliflozin in Patients on High Doses of Insulin - Dose



Data for the 2.5 mg dose of DAPA is available in the original publication
Wilding et al. Diabetes Obes Metab. 2014;16:124-36.

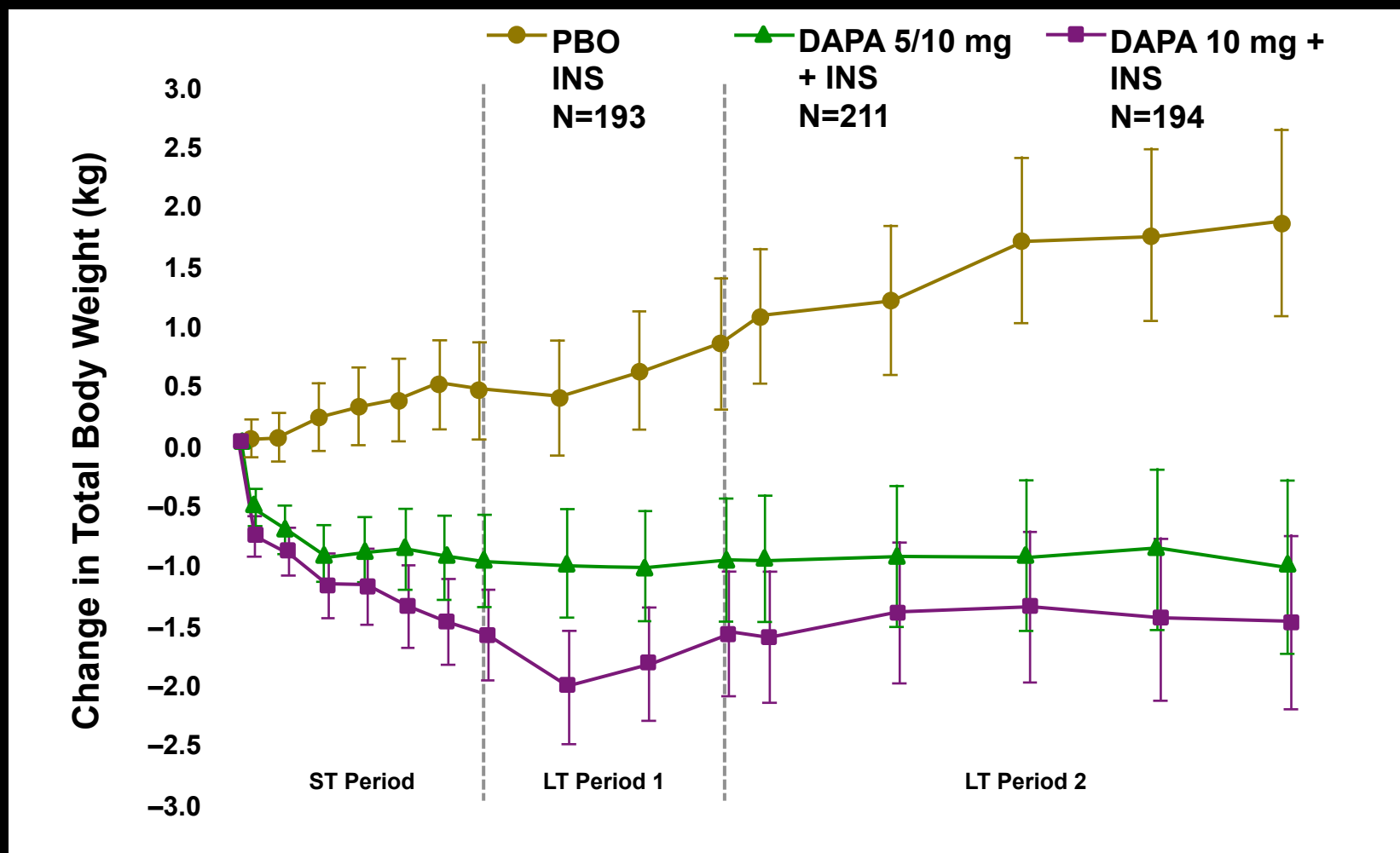
Dapagliflozin in Patients on High Doses of Insulin – A1C



Data for the 2.5 mg dose of DAPA is available in the original publication

Wilding et al. Diabetes Obes Metab. 2014;16:124-36.

Dapagliflozin in Patients on High Doses of Insulin - Weight



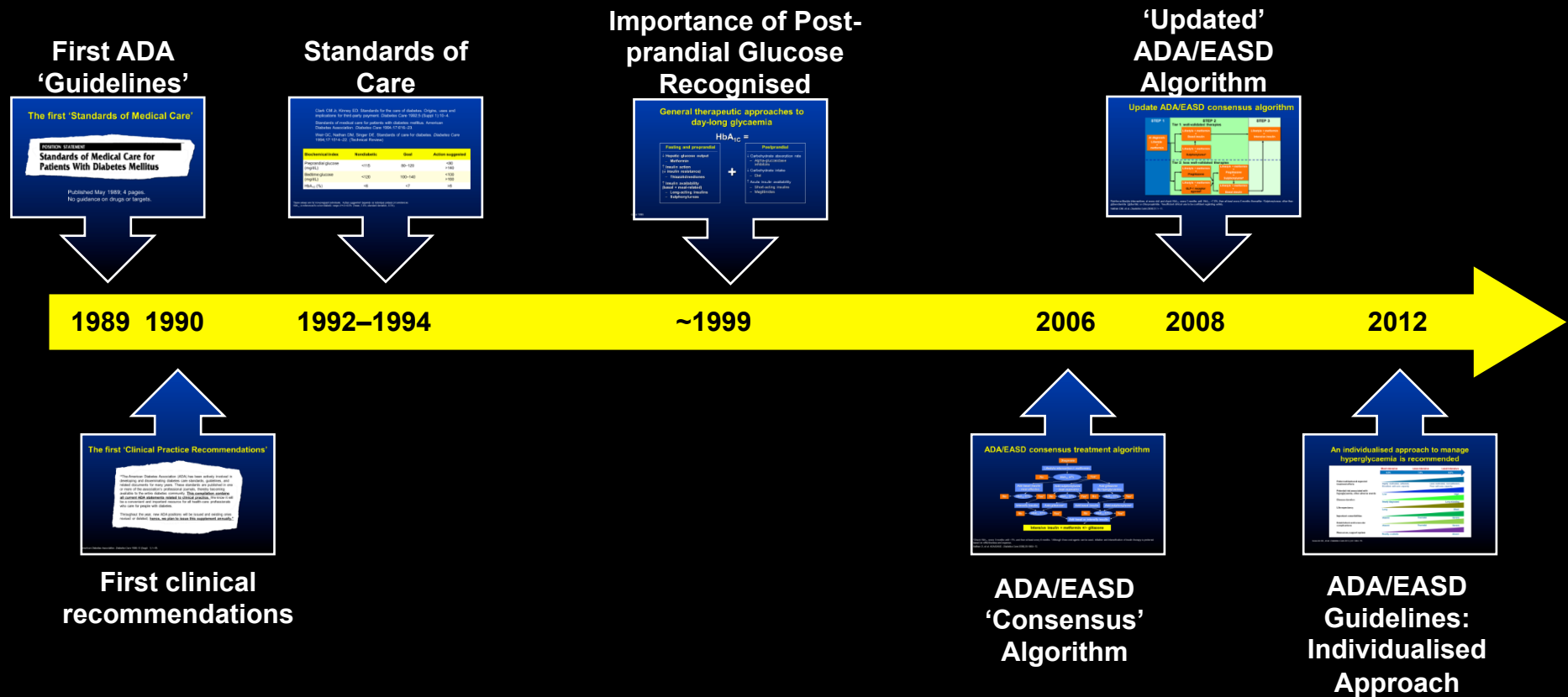
Data for the 2.5 mg dose of DAPA is available in the original publication
Wilding et al. Diabetes Obes Metab. 2014;16:124-36.

SGLT-2 Inhibitor Dosing Recommendations

Canagliflozin (100 or 300 mg qd)	- Therapy should not be initiated if eGFR <45 mL/min/1.73m² - Patients should be initiated at 100 mg qd - Dose may be increased to 300 mg qd for patients requiring better glycemic control if well tolerated <u>and</u> eGFR >60 mL/min/1.73m² - Patients should be discontinued if eGFR falls below 45 mL/min/1.73m²
Dapagliflozin (5 or 10 mg qd)	- Therapy should not be initiated if eGFR <60 mL/min/1.73m² - Patients should be initiated at 5 mg qd and may be increased to 10 mg qd for patients requiring better glycemic control if well tolerated - Patients should be discontinued if eGFR falls persistently below 60 mL/min/1.73m²
Empagliflozin (10 or 25 mg qd)	- Therapy should not be initiated if eGFR <45 mL/min/1.73m² - Patients should be initiated at 10 mg qd. The dose may be increased to 25 mg qd if well tolerated - Patients should be discontinued if eGFR falls persistently below 45 mL/min/1.73m²

Prescribing information; Yang et al. Eur J Clin Pharmacol. 2014 Aug 16. [Epub ahead of print]; Aylsworth et al. Ann Pharmacother. 2014;48:1202-08; Neumiller. Drugs Context. 2014;3:212262. doi: 10.7573/dic.212262. eCollection 2014.

Key Milestones in Development of Guidelines



**Initial drug
monotherapy**

Efficacy (↓ HbA1c)

Hypoglycemia

Weight

Side effects

Costs

Healthy eating, weight control, increased physical activity

Metformin

high

low risk

neutral/loss

GI / lactic acidosis

low

Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations

Inzucchi et al. Diabetes Care 2012;35:1364–79.

Initial drug monotherapy

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs



Two drug combinations

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs

Healthy eating, weight control, increased physical activity					
Metformin					
	high	low risk	neutral/loss	GI / lactic acidosis	low
If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):					
Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	GLP-1 receptor agonist	Insulin (usually basal)	
high	high	intermediate	high	highest	
moderate risk	low risk	low risk	low risk	high risk	
gain	gain	neutral	loss	gain	
hypoglycemia	edema, HF, fx's	rare	GI	hypoglycemia	
low	high	high	high	variable	

Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations

Inzucchi et al. Diabetes Care 2012;35:1364–79.

Initial drug monotherapy

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs

Two drug combinations

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs

Three drug combinations

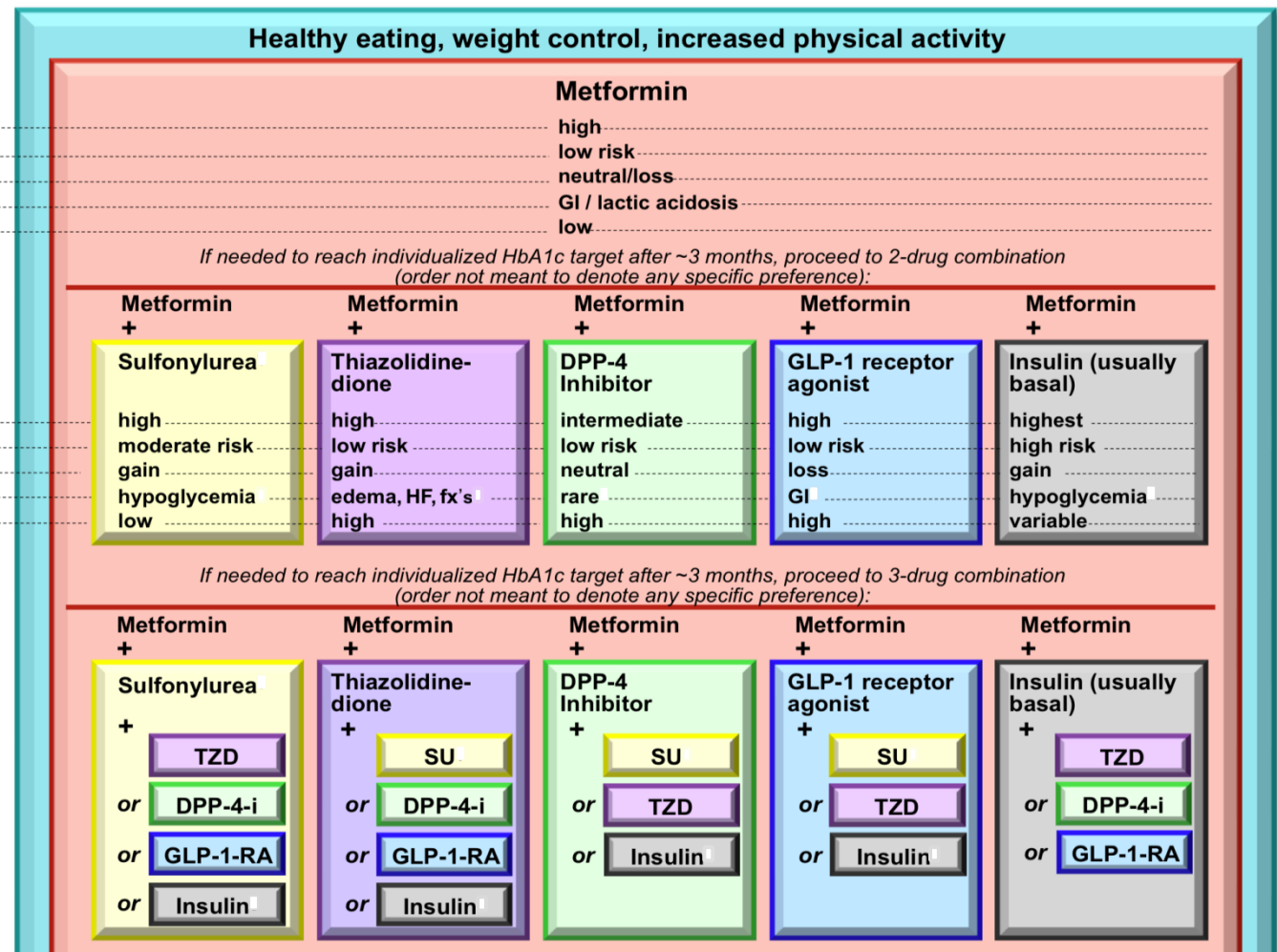


Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations

Inzucchi et al. Diabetes Care 2012;35:1364–79.

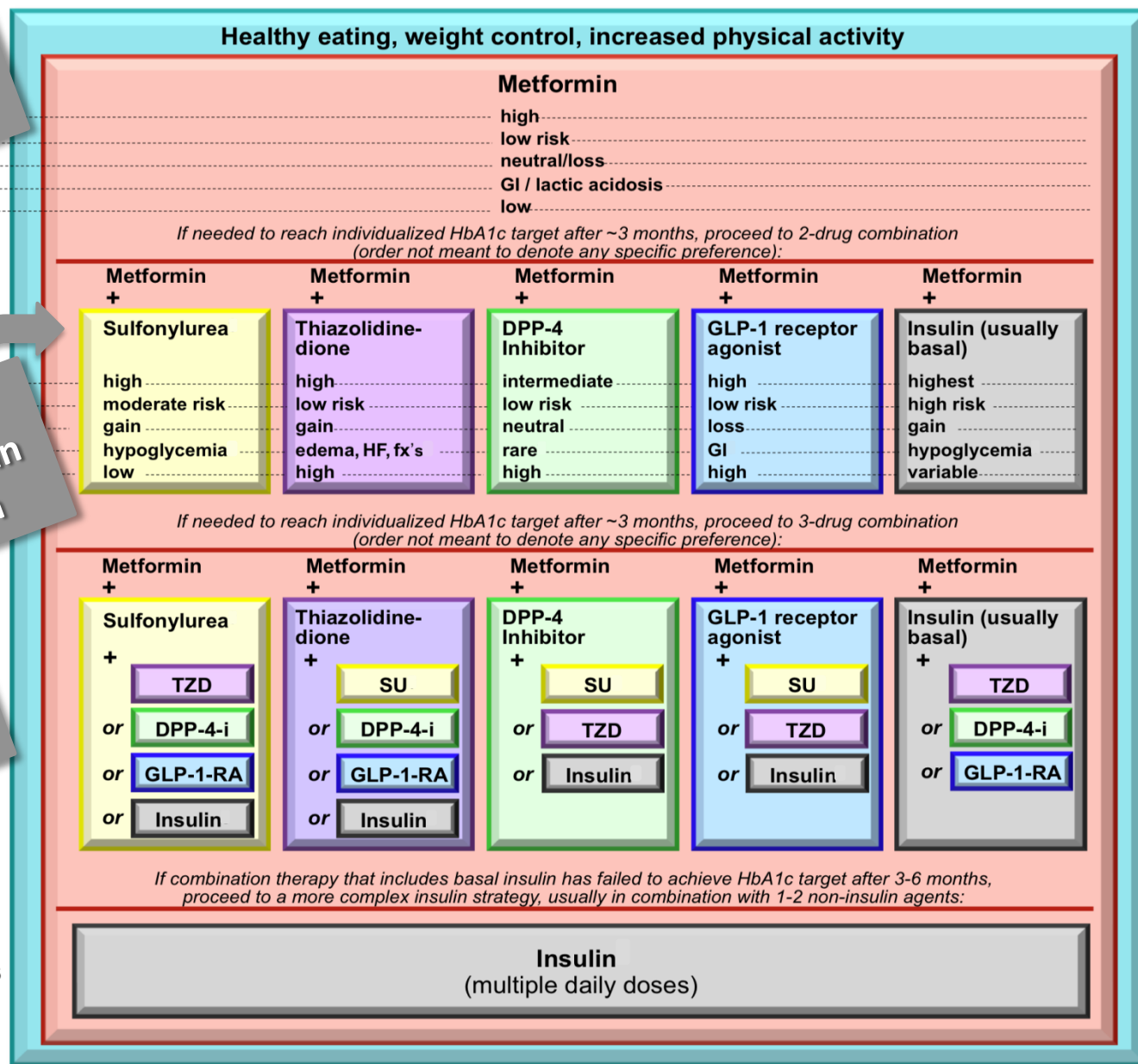
Consider initial dual combination therapy if A1c >9%

Two drug combinations

Begin with these options if metformin contraindication

Consider initial insulin therapy when A1c >10-12%

More complex insulin strategies





GLYCEMIC CONTROL ALGORITHM

LIFESTYLE MODIFICATION

(Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ DPP4-i
- ✓ AG-i
- ⚠ SGLT-2**
- ⚠ TZD
- ⚠ SU/GLN

If A1c > 6.5%
in 3 months add
second drug
(Dual Therapy)



ENTRY A1c ≥ 7.5%

DUAL THERAPY*

- GLP-1 RA ✓
- DPP4-i ✓
- TZD ⚠
- ** SGLT-2 ⚠
- Basal insulin ⚠
- Coarsevelam ✓
- Bromocriptine QR ✓
- AG-i ✓
- SU/GLN ⚠

MET
or other
first-line
agent

If not at goal in 3
months proceed
to triple therapy



TRIPLE THERAPY*

- GLP-1 RA ✓
- TZD ⚠
- ** SGLT-2 ⚠
- Basal insulin ⚠
- DPP4-i ✓
- Coarsevelam ✓
- Bromocriptine QR ✓
- AG-i ✓
- SU/GLN ⚠

MET
or other
first-line
agent

If not at goal in 3
months proceed
to or intensify
insulin therapy



ENTRY A1c > 9.0%

NO SYMPTOMS

SYMPTOMS

DUAL
THERAPY

OR

TRIPLE
THERAPY

INSULIN
± OTHER
AGENTS

ADD OR INTENSIFY INSULIN

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

LEGEND



= Few adverse events
or possible benefits



= Use with caution

PROGRESSION OF DISEASE

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What's Next?

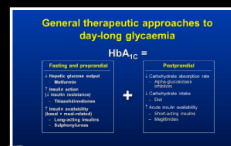
First ADA 'guidelines'



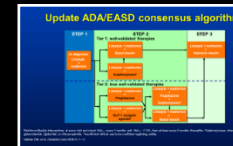
Standards of care

[illegible]

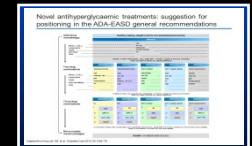
Importance of post-prandial glucose recognised



Updated ADA/EASD
algorithm



New ADA/EASD algorithm?



1989 1990

1992–1994

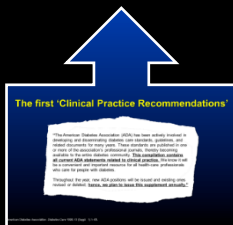
~1999

2006

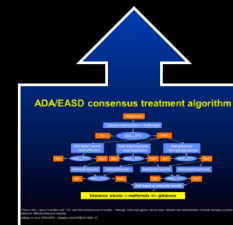
2008

2012

2014



First clinical recommendations



ADA/EASD algorithm



ADA/EASD guidelines:
individualised approach

Initial drug monotherapy

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs

Two drug combinations*

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs

Three drug combinations

More complex insulin strategies

Healthy eating, weight control, increased physical activity

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high
low risk
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GI / lactic acidosis
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Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea†	Thiazolidinedione	DPP-4 Inhibitor	GLP-1 receptor agonist	Insulin (usually basal)
high efficacy	high efficacy	intermediate efficacy	Higher efficacy	Higher efficacy
moderate risk	low risk	low risk	low risk	high risk
weight gain	weight gain	neutral	loss	gain
hypoglycemia†	edema, HF, +	rare†	GI†	hypoglycemia†
low costs	high costs	high costs	high costs	variable costs

SGLT-2 inhibitor

high
low risk
loss
GU, renal
high

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

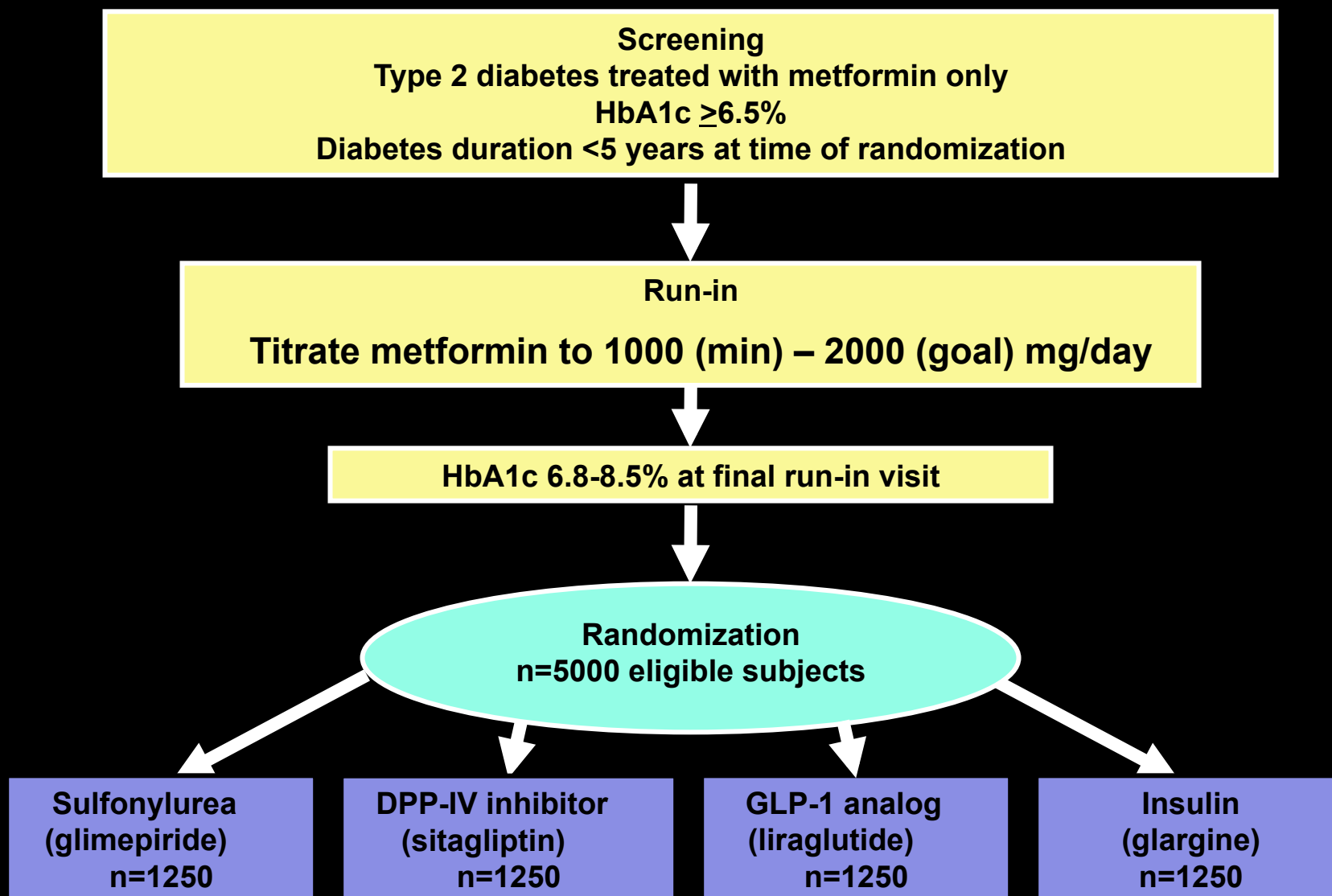
Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea†	Thiazolidinedione	DPP-4 Inhibitor	GLP-1 receptor agonist	Insulin (usually basal)
+ TZD	+ SGLT-2i	+ SU†	+ SU†	+ TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or DPP-4-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§	or SGLT-2i	or SGLT-2i	or SGLT-2i

SGLT-2 inhibitor +

SU
or TZD
or DPP-4i
or GLP-1RA
or Insulin

on the basis of basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

Insulin (Multiple Daily Injections) OR GLP-1 receptor agonist + Insulin
OR SGLT-2 Inhibitor + Insulin



First patient, first visit June 2013.

Last patient last visit 2020.

Nathan et al. Diabetes Care. 2013; 36:2254-61.

GRADE