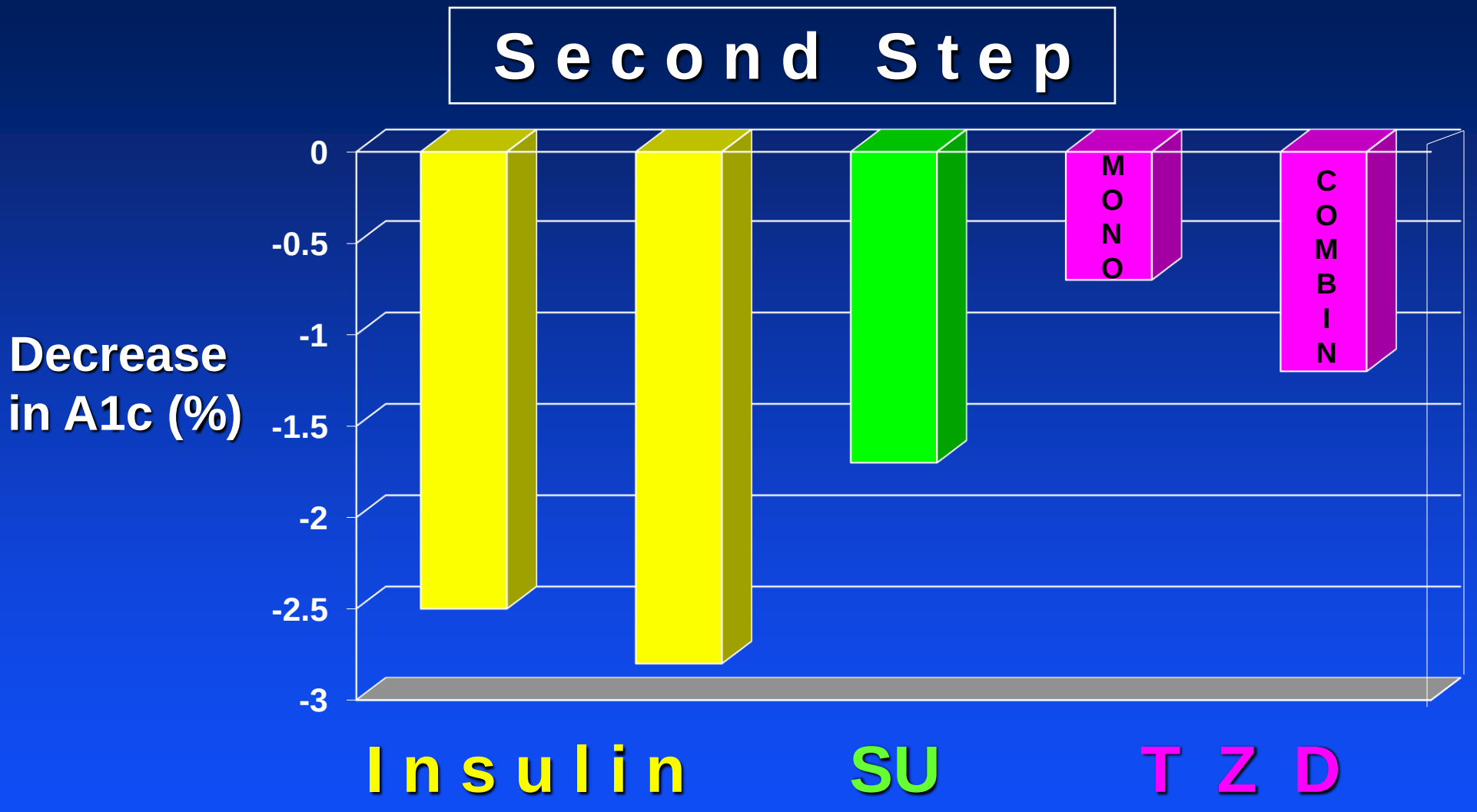
Intensive Therapy of Type 2 diabetes

Thiazolidinediones: PPAR γ agonists

- Relatively weak as monotherapy (HbA1c ↓ by ~ 0.7%)
- More potent in combination with insulin, metformin, or sulfonylurea/glitinide (HbA1c ↓ by ~ 1.2 or more)
- Rosiglitazone (barely) and pioglitazone available
- Generally well tolerated- but edema, CHF, bone loss
- Liver function monitoring no longer obligatory
- Pioglitazone has better lipid effects, ?bladder cancer
- Pioglitazone shown to improve liver in NAFLD
- Pioglitazone may reduce CVD (PROACTIVE study)

Results of Metformin Plus Other Therapy



Exendin-4

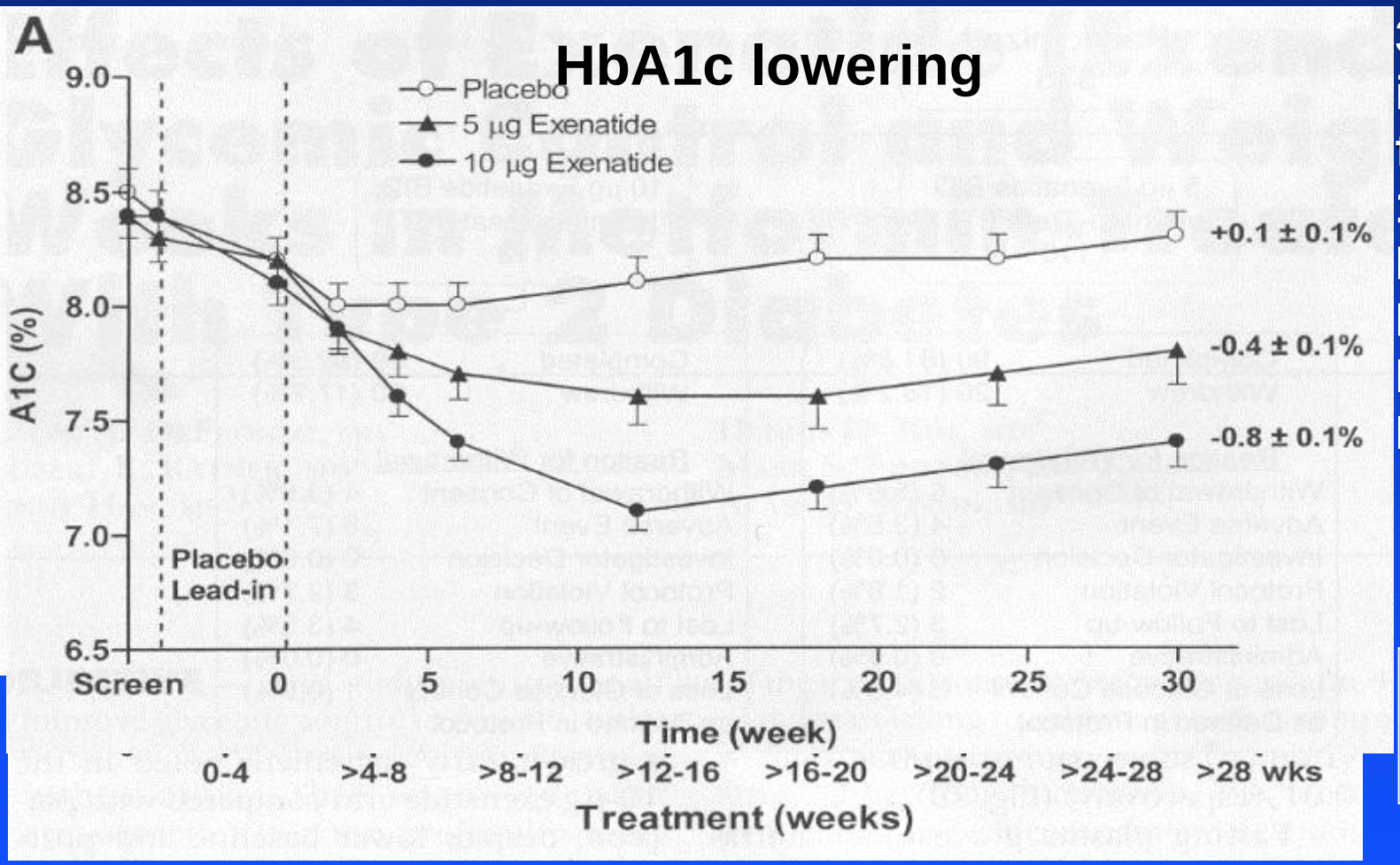
Exenatide- 39 amino acid

Similar to naturally occurring GLP 1, 7-37

- **Stimulates insulin secretion**
- **Suppresses glucagon**
- **Delays gastric emptying**
- **May decrease appetite**
- **GI side-effects**

"New" Drugs

Exenatide



30 week CCT
in metformin failures (n=336)
19% loss to f/u.
BMI- 34 kg/m^2
HbA1c- 8.2%
Inactive placebo
Injected BID

DeFronzo et al. Diabetes Care 2005;28:1092

New(er) GLP-1 Agonists

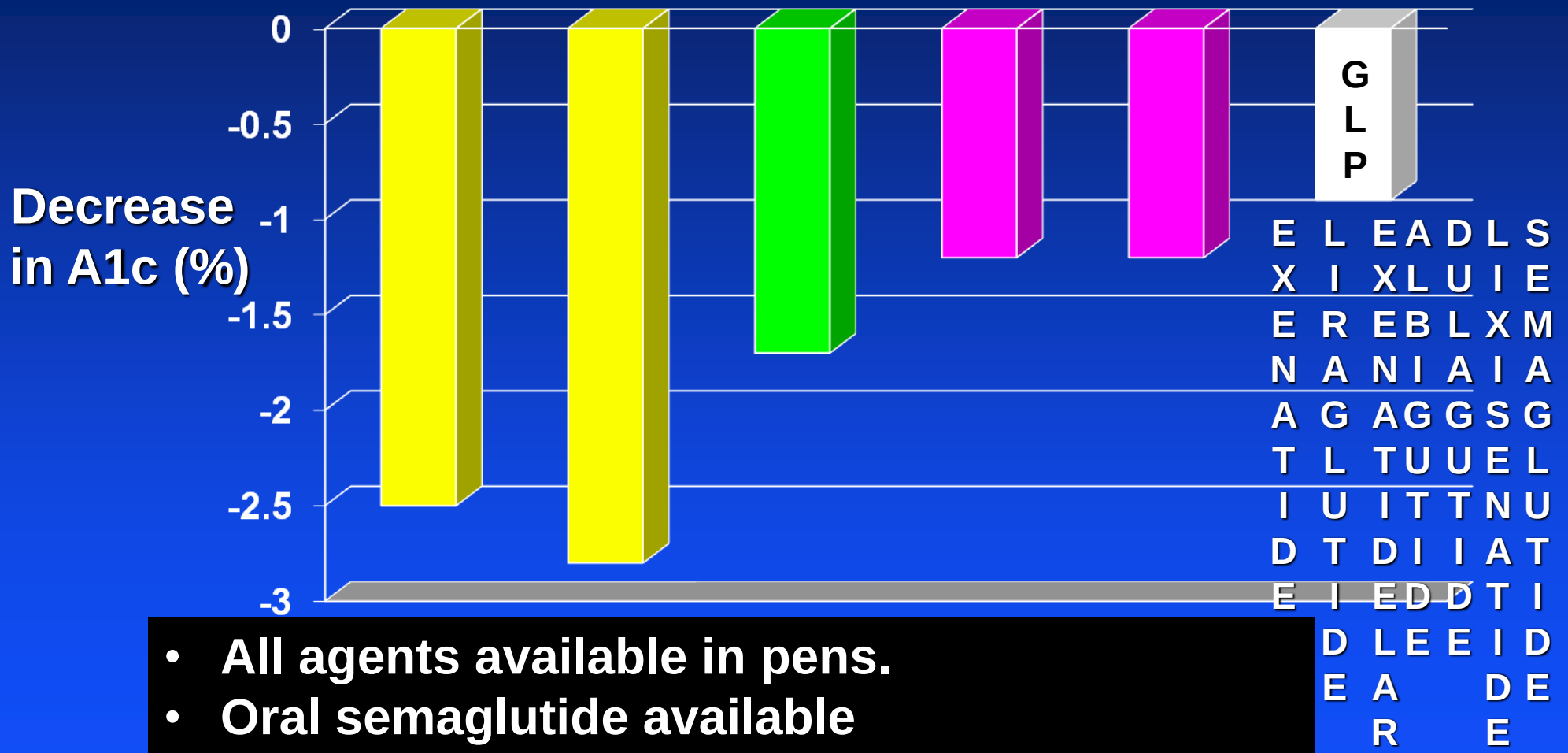
Liraglutide, Exenatide LAR, Albiglutide, Dulaglutide, Lisixenatide, Semaglutide, Efpeglenatide*

- All agents share same effects as exenatide, frequency of administration is major difference
- Modified GLPs have extended duration of action since less vulnerable to catabolism by DPP-4
- Other agents once per day or once per week injections
- Oral semaglutide the first oral formulation
- ? Increased risk for pancreatitis, pancreatic cancer, medullary thyroid carcinoma

*Not FDA approved

Results of Metformin Plus Other Therapy

Second Step



- All agents available in pens.
- Oral semaglutide available
- Generally titrate dose based on GI tolerance

GLP and DPP4 Inhibitors

GLP and its Analogues **DPP 4 Inhibitors**

CVD Safety Studies

DPP 4 inhibitors

- SAVOR (saxagliptin): increased CHF hospitalizations
- EXAMINE (alogliptin): no risk
- TECOS (sitagliptin): no risk

NO CVD BENEFIT with any of the DPP4 inhibitors to date

GLP-1 Receptor agonists

- CVD benefit with liraglutide, semaglutide, efpeglenatide
- No benefit with lixisenatide or exenatide LAR

- CKD benefit-2º intervention
- Expensive

What's New: Tirzepatide

- Combination of a GLP-1RA and GIP (glucose-dependent insulinotropic peptide)-RA.
- GIPs also stimulate beta-cell (with effects self-limited in setting of hypoglycemia), and suppress glucagon, appetite.
- SURPASS studies have examined inferiority and superiority compared with glargine and GLP-1RA (semaglutide).
- CVOT safety studies ongoing.

FDA approves Lilly diabetes drug that analysts expect to be a big seller

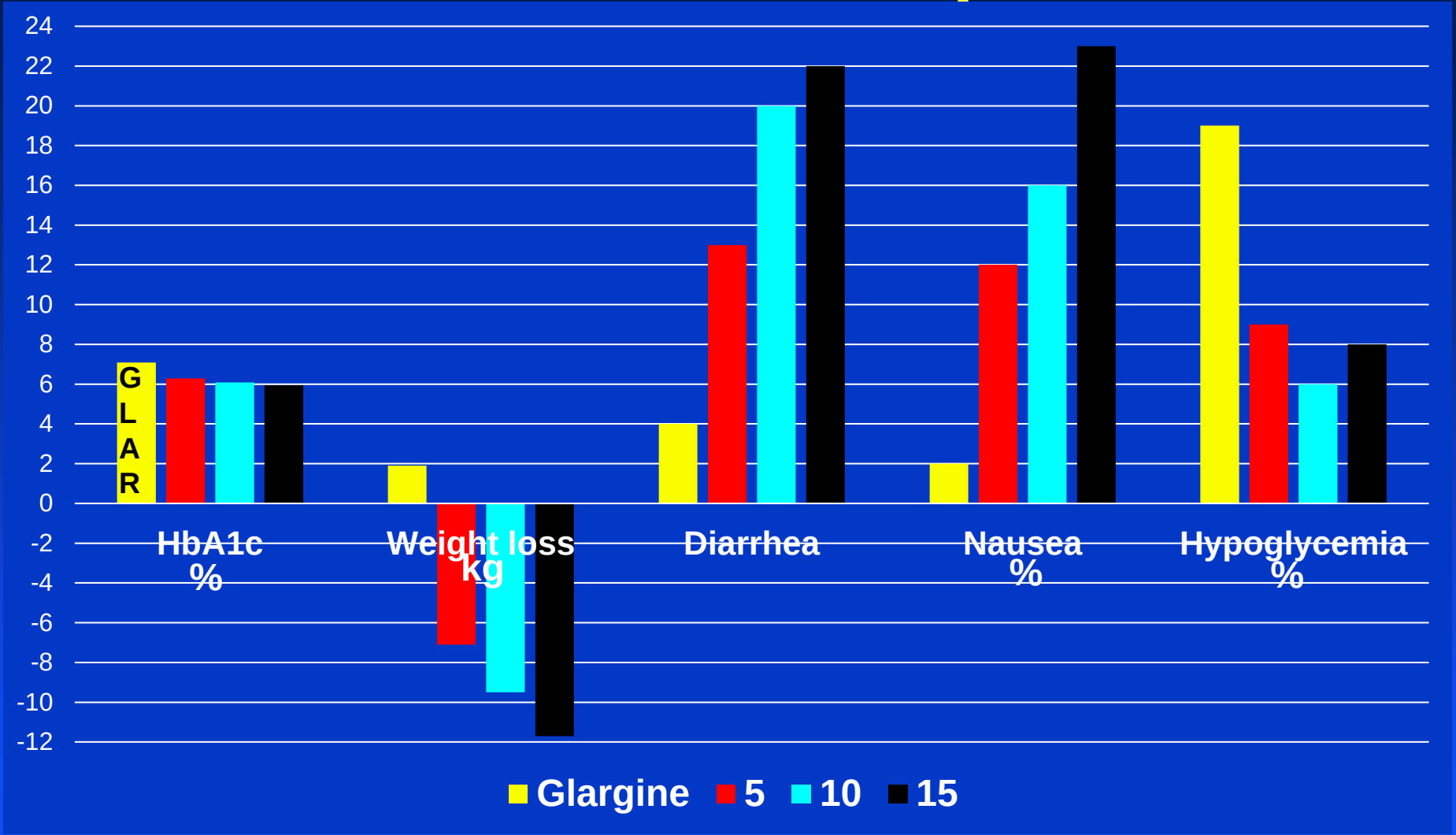
By Matthew Herper May 13, 2022 Reprints

KRISTOFFER TRIPPLAAR/AP

The Food and Drug Administration said Friday it had approved Mounjaro, a new injection for type 2 diabetes made by Eli Lilly that lowers blood sugar and can help patients lose weight.

FDA approved May 13, 2022

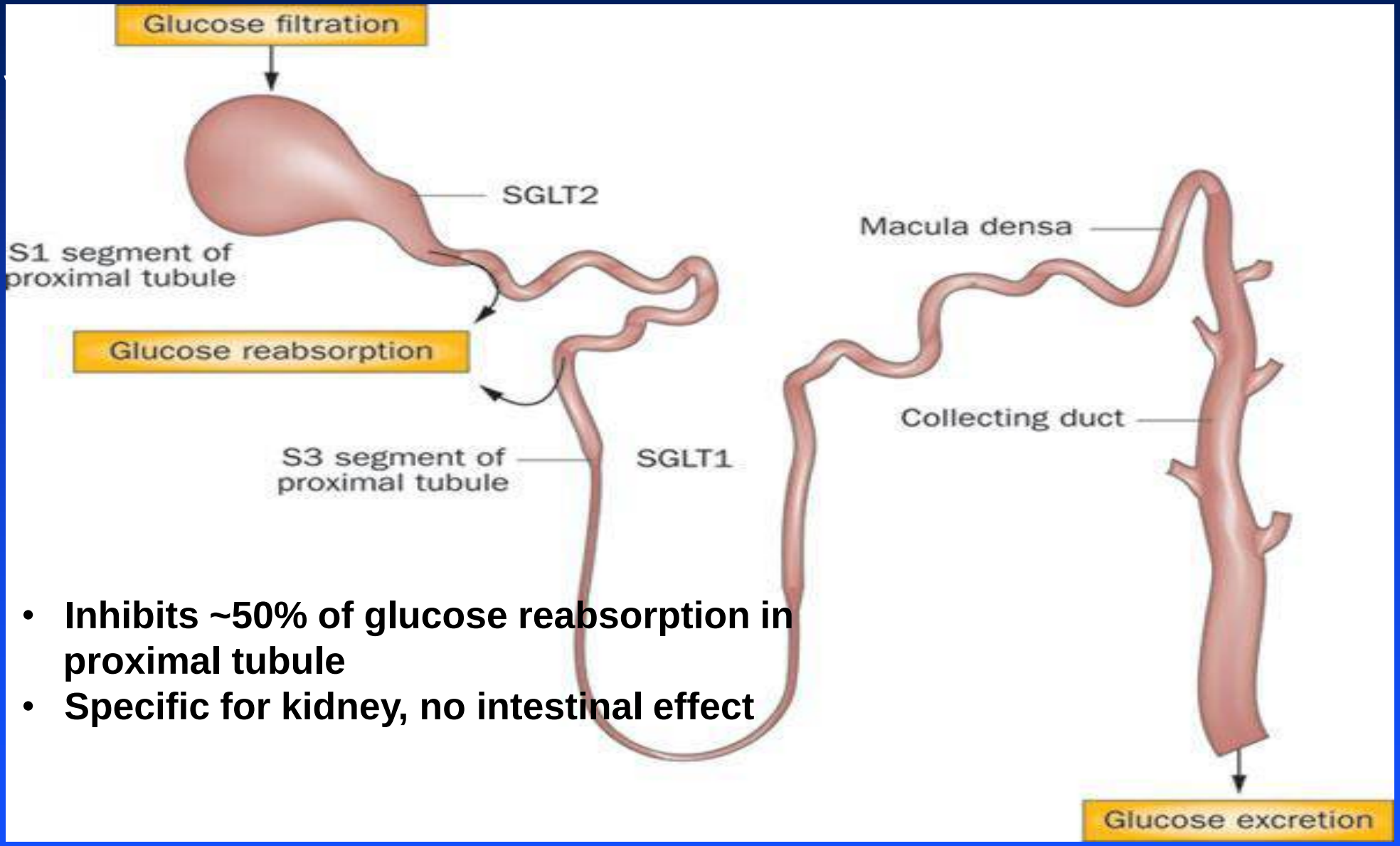
What's New: Tirzepatide



Hypoglycemia= BG<54 mg/dl or severe

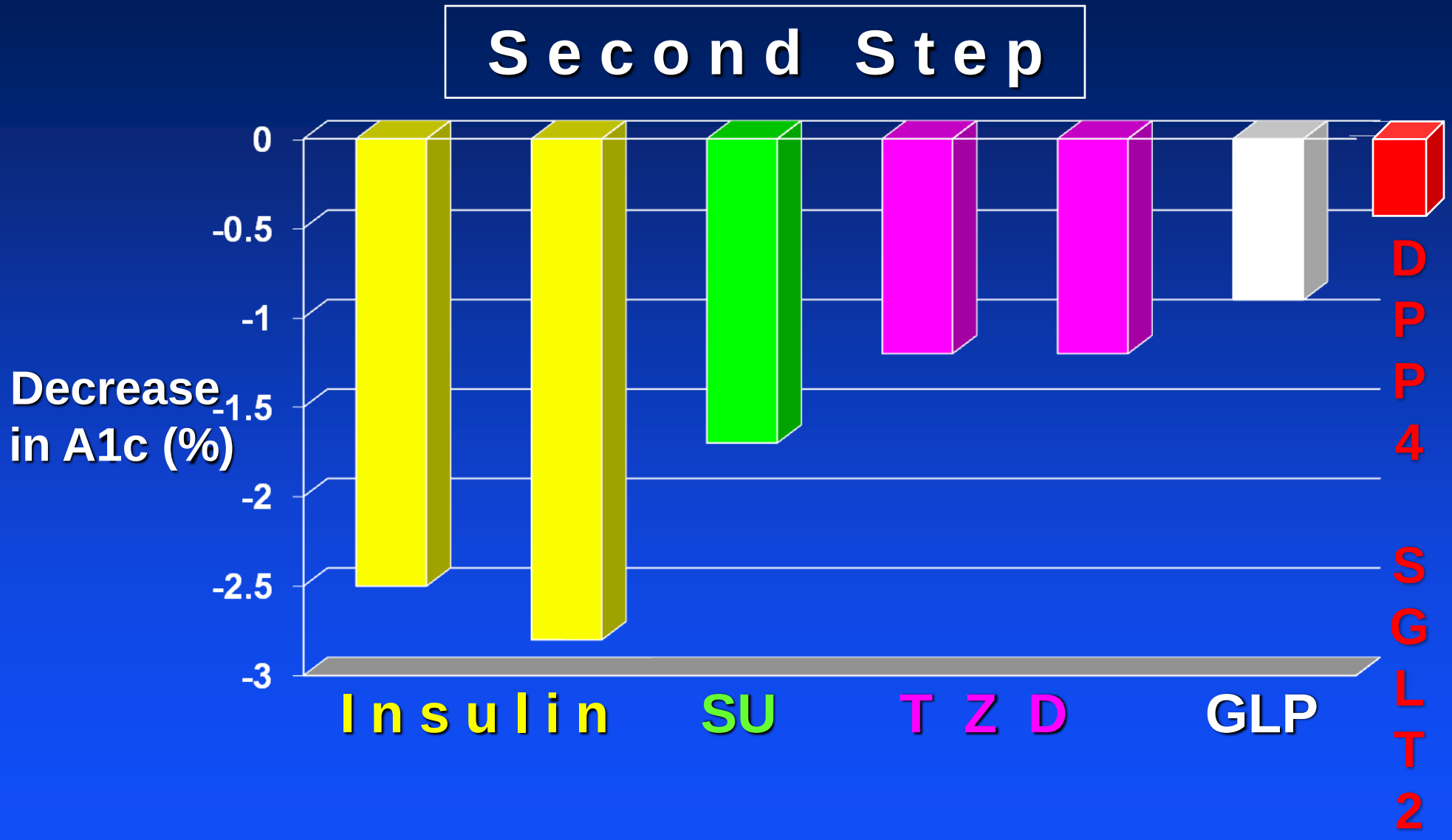
DelPrato S, SURPASS Investigators
Lancet, 2021

Newest Medication Class



- **Inhibits ~50% of glucose reabsorption in proximal tubule**
- **Specific for kidney, no intestinal effect**

Results of Metformin Plus Other Therapy



Characteristics of CVD Safety Studies

	SGLT-2 inhibitors		GLP-1 Receptor Agonists				
	EMPA-REG	CANVAS	LEADER	SUSTAIN-6	EXCSEL	AMPLITUDE-O	REWIND
Duration	58% >10 y	13.5 y	13 y	14 y	12 y	16 y	9.5y
Therapy	empaglif.	canaglif.	liraglut.	semaglut.	exen.LAR	efpeglen.	dulaglut.
Prior CVD	100%	66%	81%	73%	73%	90%	32%
Follow-up (yr)	3.1	3.6	3.8	2.1	2.4	1.8	5.4
HbA1c (%) Med(Cont)	7.6(8.0)	7.7(8.3)	7.7(8.1)	7.6(8.3)	7.5(8.0)	~7.5(8.5)	6.8(7.4)
HbA1c diff. (%)	0.45	0.58	0.40	0.7-1.0	0.53	~1.0	0.61
	Zinman *NEJM* 2015 373:2117	Neal *NEJM* 2017; 377:644	Marso *NEJM* 2016; 375:311	Marso *NEJM* 2016; 375:1834	Holman *NEJM 2017* 377:1228	Gerstein *NEJM 2021* 385:896	Gerstein *Lancet 2020* 394:121

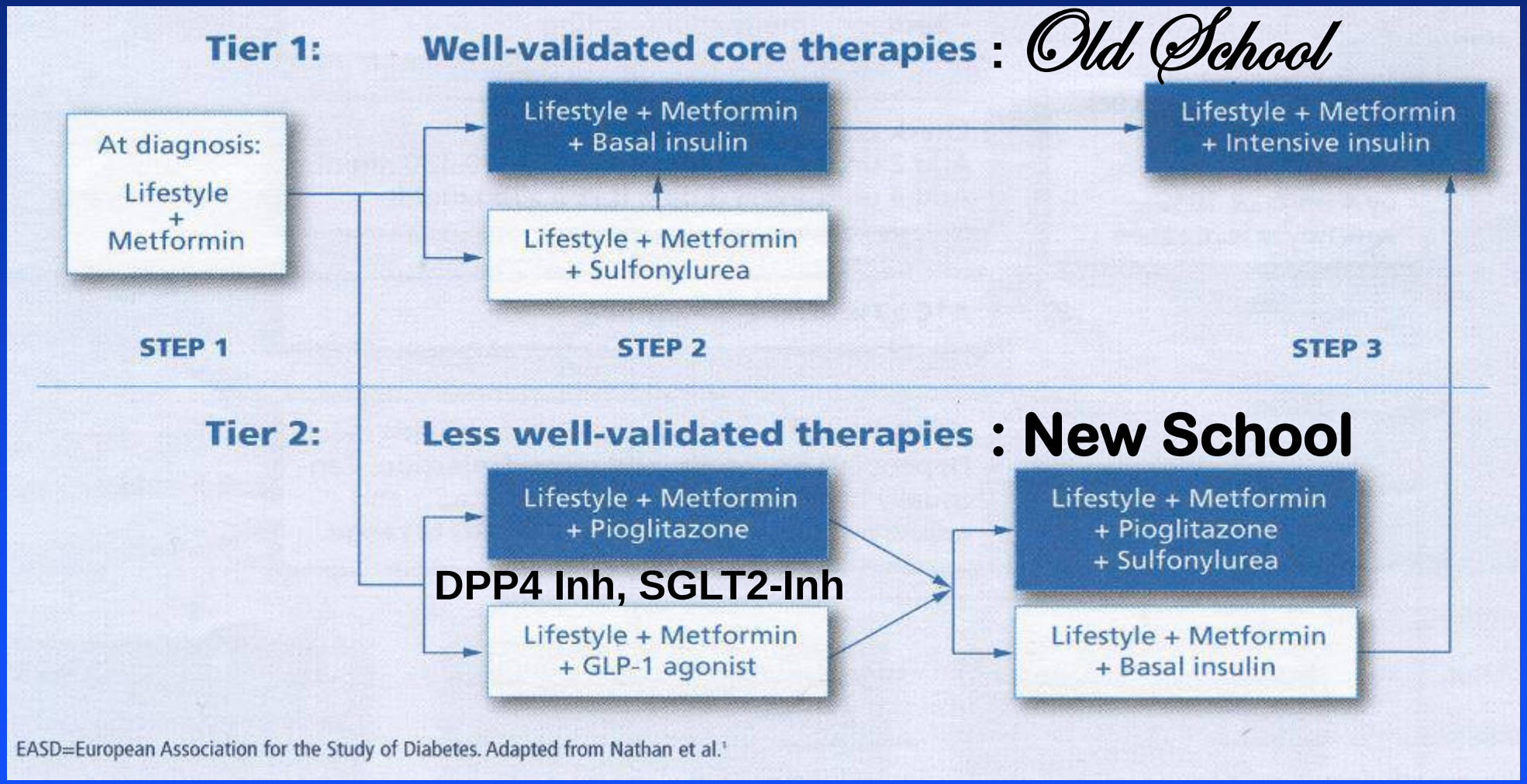
Based on the REWIND study, dulaglutide approved (2020) for reduction in CVD in patients with T2DM, independent of whether they have pre-existing CVD.

Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

D. M. Nathan · J. B. Buse · M. B. Davidson · E. Ferrannini · R. R. Holman · R. Sherwin · B. Zinman

Diabetologia 2009; 52:17-30
Diabetes Care 2009;32:193-203



EASD=European Association for the Study of Diabetes. Adapted from Nathan et al.[1]

If you Use a New(er) Drug

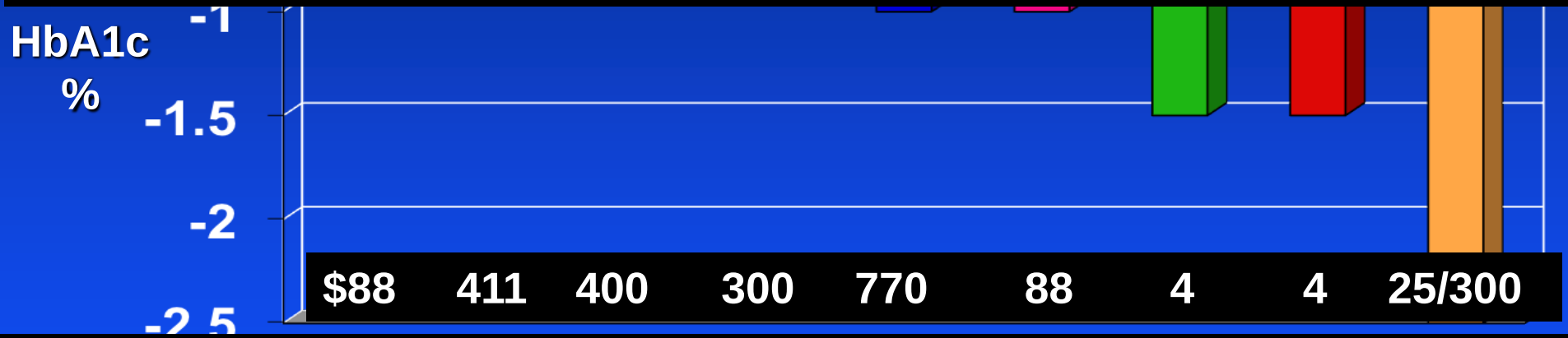
Class	Advantage	Disadvantage	When to Use
DPP-4	Well-tolerated Probably safe One dose	Weak Expensive	Mild DM
GLP-1	Weight loss No hypos CVD, CKD	GI side effects Limited efficacy Injections Expensive	Moderate DM If weight gain or risk of hypos is dominant. CVD/CKD
TZDs	No hypos	Edema, CHF, bone loss, ?bladder cancer	Never? NASH, very insulin resistant
SGLT-Inhib.	No hypos. Dec. BP, CVD, CKD, HF	Weak, UTIs, yeast/Fourniers Expensive	Mild DM, advanced CVD, HF advanced CKD.

Glycemic Potency vs Costs

Decrease in HbA1c: Potency of Monotherapy vs Cost

21st Century | 20th Century

Outside of CVD/CKD, are the benefits of the new medications worth a 10-100 fold higher cost than the "old school" approach??



Medication costs have risen faster than for any other disease

6 → 13 → 30 → 60 billion

2001 2007 2013 2020