Il razionale delle associazioni terapeutiche sulla protezione cardiovascolare

Alessandra Dei Cas
UOC di Endocrinologia e Malattie del Metabolismo
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Università di Parma

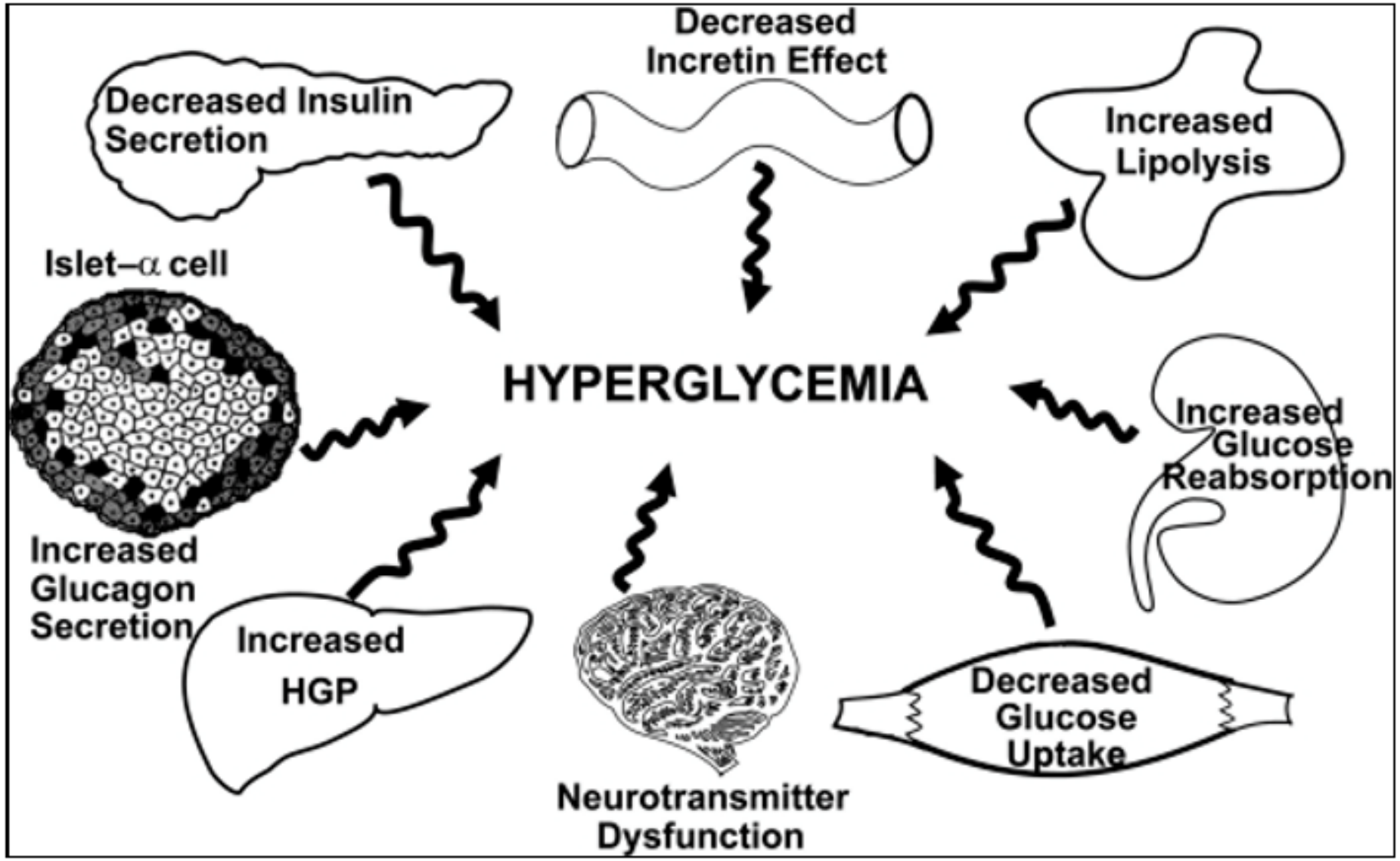
La Dr.ssa Alessandra Dei Cas dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Boehringher
- Elly Lilly Italia
- Sanofi
- Novonordisk
- MSD
- Doc Generici

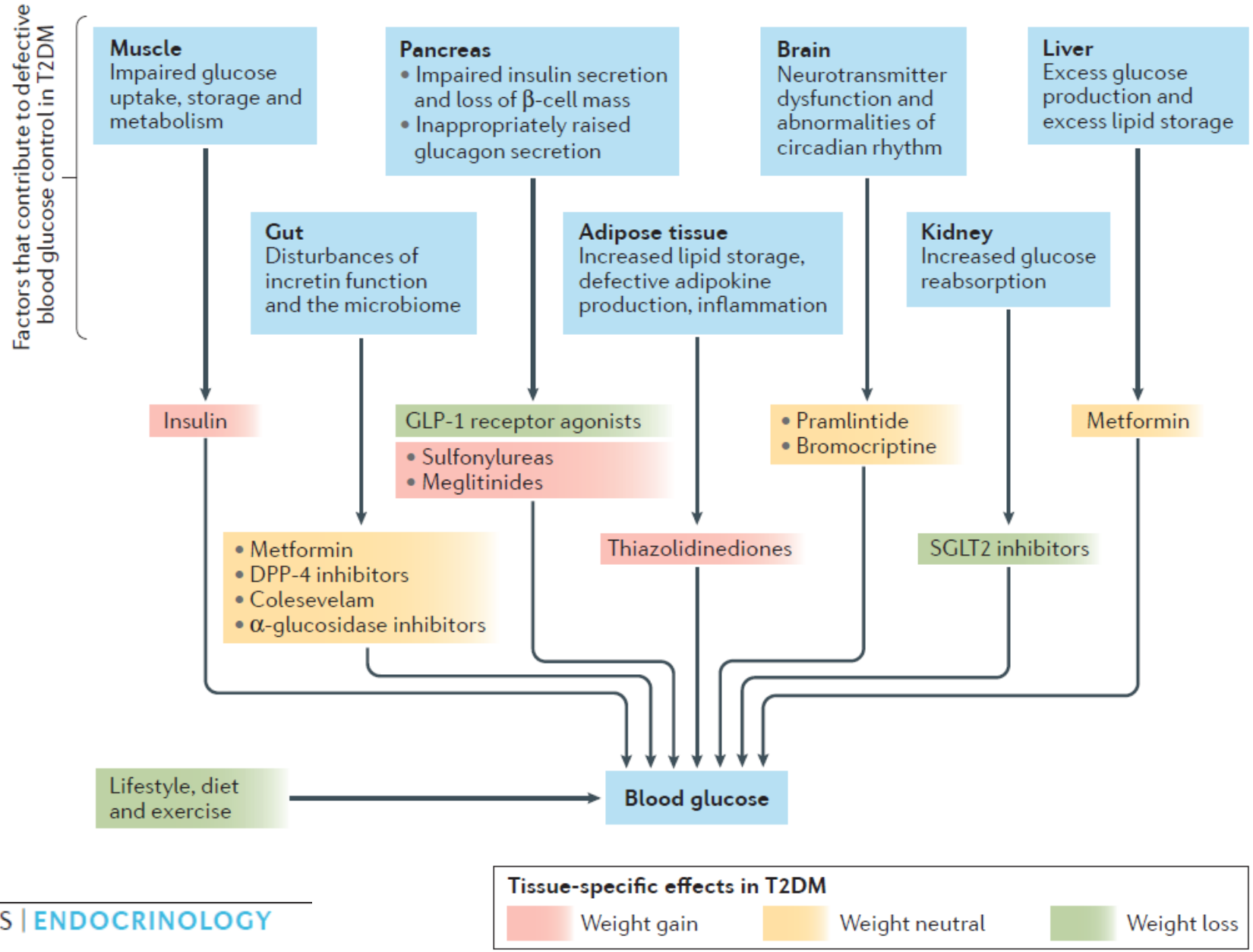
Agenda

- ✓ Razionale fisiopatologico (compatibilità e complementarietà di meccanismo di azione)
- ✓ Razionale *treat to target*
- ✓ Razionale *treat to benefit*

The ominous octet



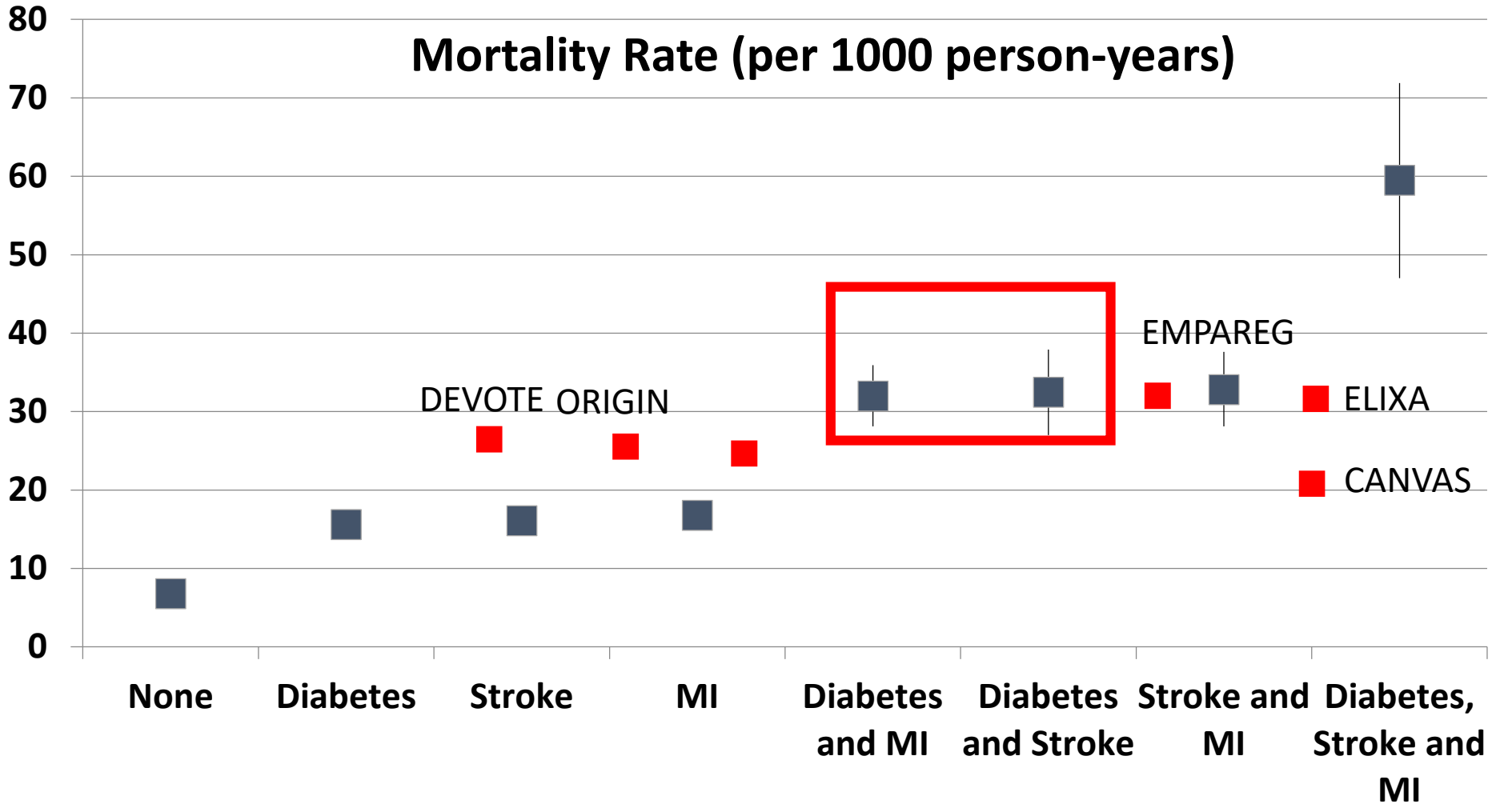
Site of action of glucose lowering agents



NATURE REVIEWS | ENDOCRINOLOGY

Absolute mortality rates in the Emerging Risk Factors Collaboration Study

(n=689300, FU: 12.8 yrs; confirmed in the UK Biobank n=499808)

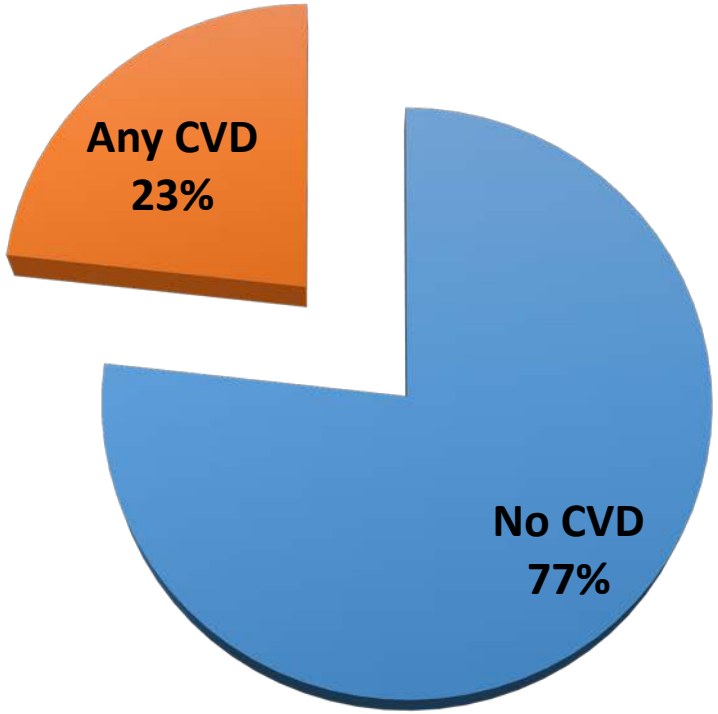


The Emerging Risk Factors Collaboration, JAMA 2015

The RIACE Study: 15993 consecutive patients with diabetes from 19 Outpatient Diabetes Clinics in Italy, years 2007-2008

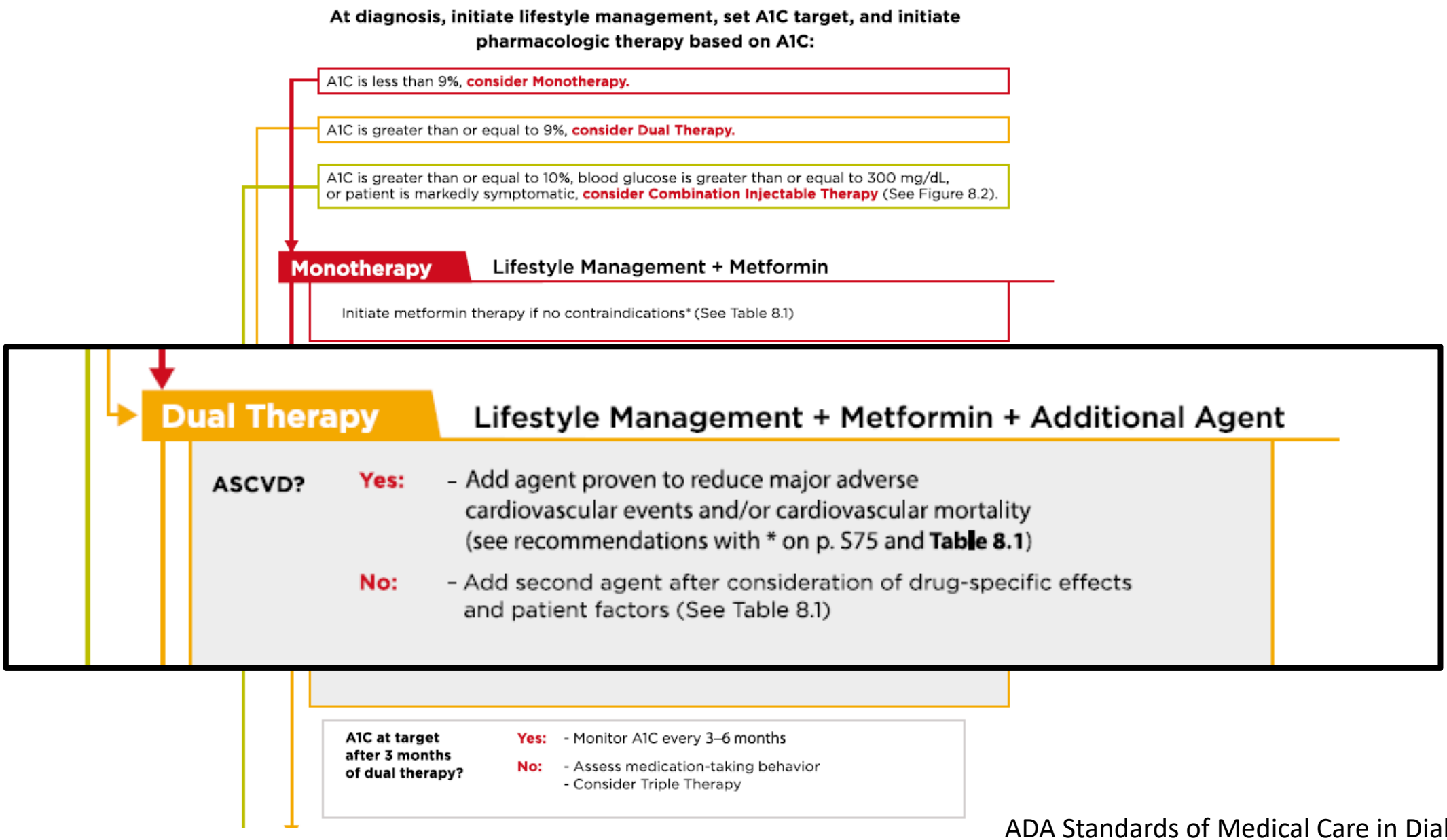
Prevalence of any CVD
in patients attending Outpatient Diabetes Clinics

N= 15,773
In 2007-2008



Pugliese G et al.; Cardiovasc Diabetol 2014

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

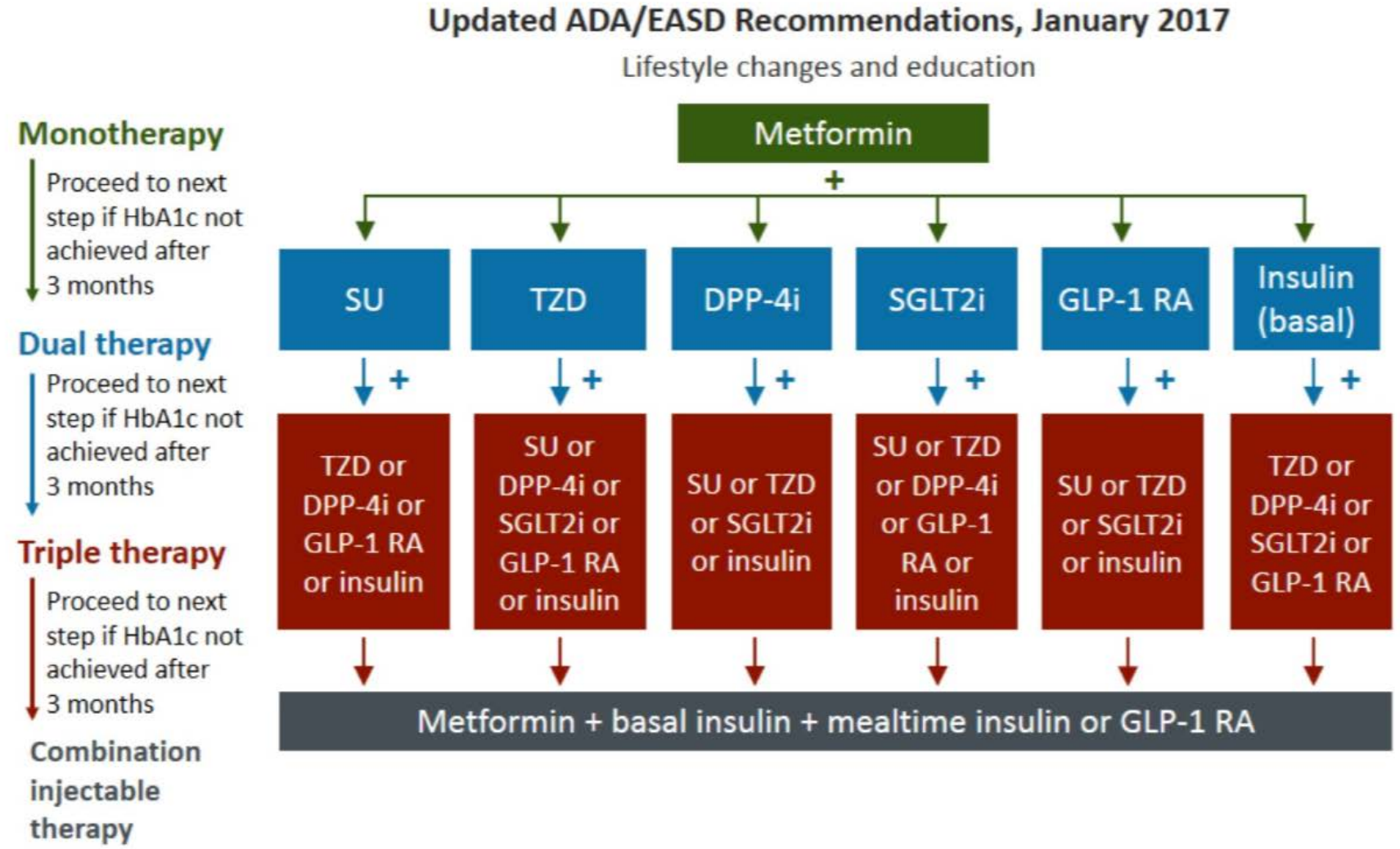


ADA Standards of Medical Care in Diabetes 2018

Agenda

- ✓ Razionale fisiopatologico (compatibilità di meccanismo di azione)
- ✓ Razionale *treat to target*
- ✓ Razionale *treat to benefit*

Glucose-lowering therapy options



ADA. *Diabetes Care*. 2017;40(Suppl 1):S64-S74.

Guardiamo all'efficacia…

	Metfor-mina	Acarbosio	GLP-1	Gliflo-zina	Glip-tina	Pioglita-zone	SU/ glinide	Insulina basale	Insulina basal-bolus
Riduzione della HbA_{1c} a breve termine (3-6 mesi)*	+++	+	+++	++	++	+	+++	+++	++++
Riduzione della HbA_{1c} a medio termine (1-2 anni)*	++	+	+++	++	++	++	++	+++	++++
Riduzione della HbA_{1c} a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+	+++	++++
Riduzione del peso corporeo	+/-	+/-	+++	++	-	-	-	-	-
Riduzione della pressione arteriosa	+/-	-	+	++	-	+	-	-	-

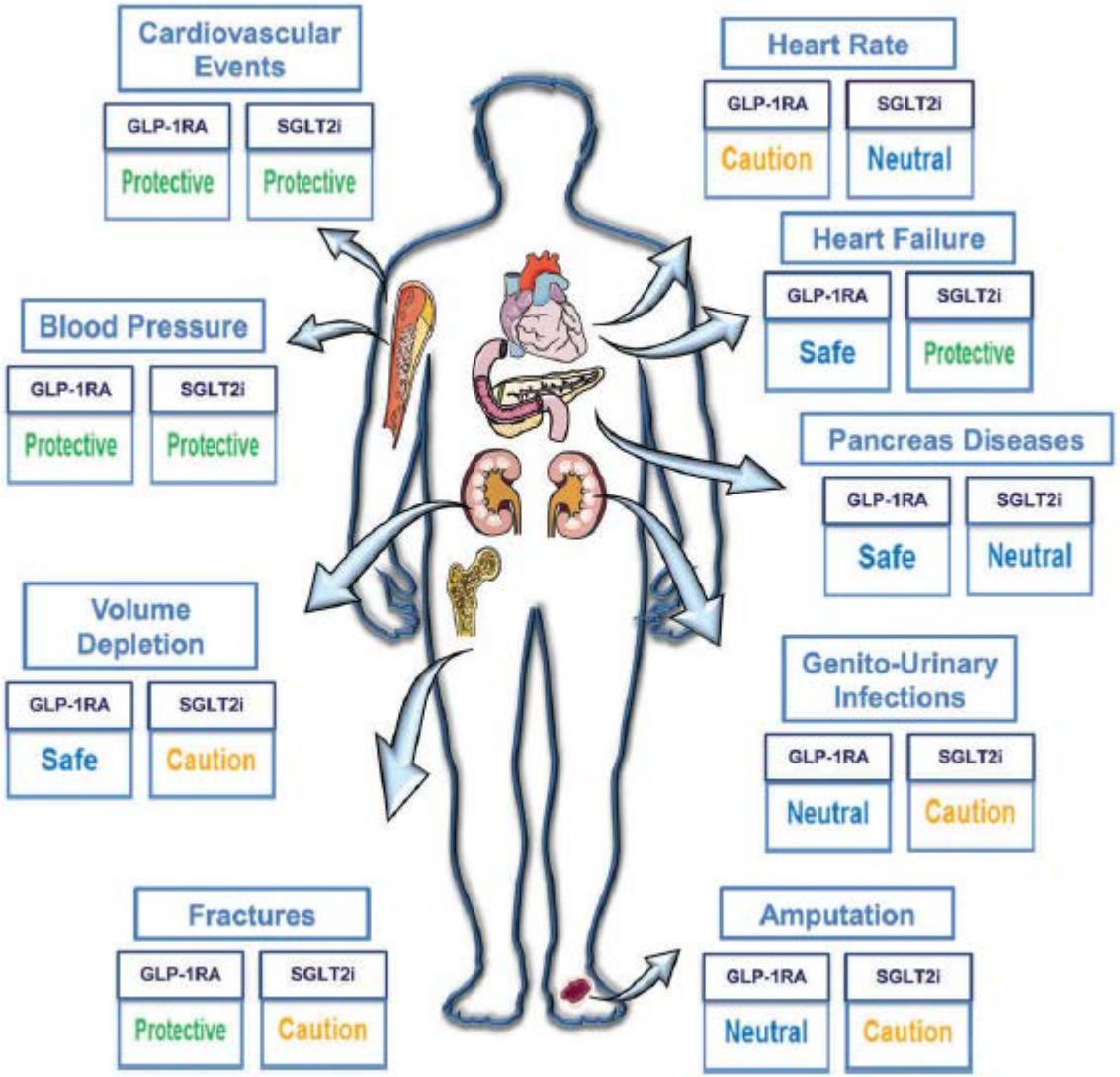
Standard di cura SID-AMD 2016

Effetti collaterali dei farmaci anti-diabetici

	Metfor-mina	Acarbosio	Agon-sta GLP-1	Gliflo-zina	Glip-tina	Pioglita-zone	SU/ glinide	Insulina basale	Insulina basal-bolus
Interazioni con altri farmaci	-	-	-	-	-	+	+++	+++	++++
Ipoglicemie	-	-	-	-	-	-	++	+++	++++
Aumento di peso	-	-	-	-	-	++	+	+++	++++
Pancreatiti	-	-	+/-	-	+/-	-	-	-	-
Fratture	-	-	-	-/+[a]	-	+++	-	-	-
Scompenso cardiaco	-	-	-	-	-/+[b]	++	+	-	-
Disturbi gastrointe-stinali	++	+++	++	-/+	-	-	-	-	-
Infezioni genitali	-	-	-	+	-	-	-	-	-

Standard di cura SID-AMD 2016

Actions and potential side effects of GLP-1RA and SGLT2i

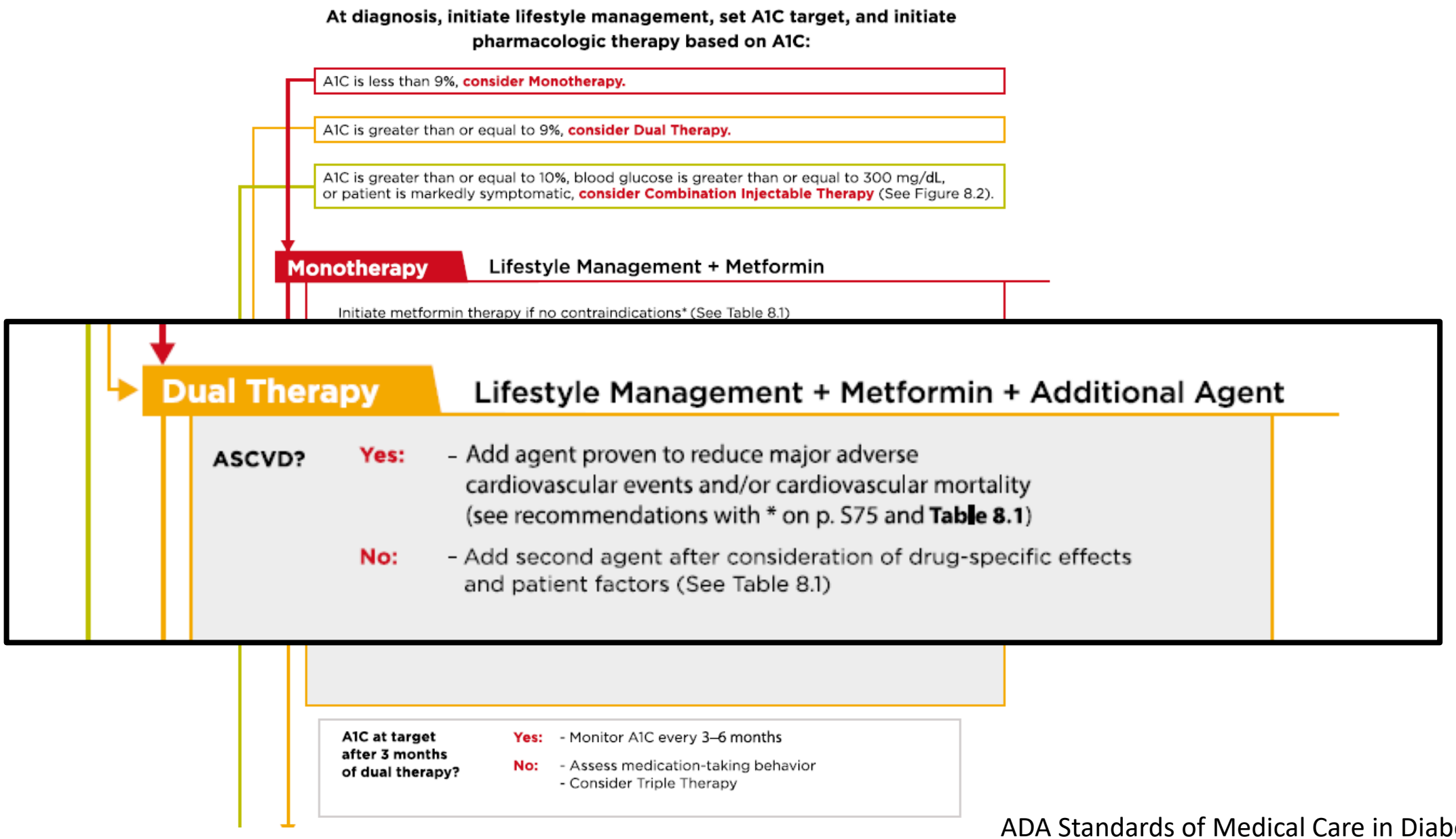


EXPERT OPINION ON DRUG SAFETY, 2018
VOL. 17, NO. 3, 293–302

Agenda

- ✓ Razionale fisiopatologico (compatibilità di meccanismo di azione)
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Antihyperglycemic Therapy in Adults with Type 2 Diabetes



ADA Standards of Medical Care in Diabetes 2018

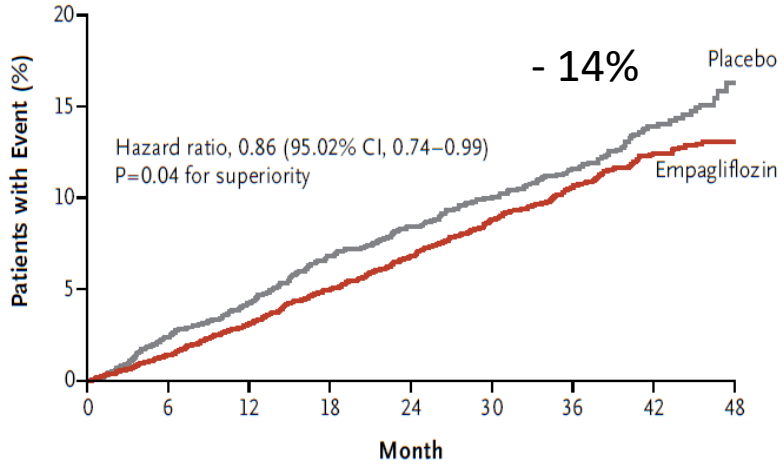
CVOT trials and CV outcomes

	MACE	CV mortality	Non-fatal MI	Non-fatal stroke	Retino-pathy	Nephro-pathy	Neuro-pathy	Heart failure	HbA1c Δ (%)
Intensive glycemic control, 1998–2009 [3, 8]	↓	↔	↓	↔	↓	↓	↔	↔	0.90
Glargine, 2012 [10, 11]	↔	↔	↔	↔	↔/↓	↔/↓	?	↔	0.30
Saxagliptin, 2013 [12, 15]	↔	↔	↔	↔	?	↓	?	↑	0.20
Alogliptin, 2013 [13]	↔	↔	↔	↔	?	↔	?	↔	0.36
Sitagliptin, 2015 [14]	↔	↔	↔	↔	?	↔	?	↔	0.29
Lixisenatide, 2015 [17]	↔	↔	↔	↔	?	↔	?	↔	0.27
Empagliflozin, 2015 [18, 23]	↓	↓	↔	↔	?	↓	?	↓	0.35
Liraglutide, 2016 [19]	↓	↓	↔	↔	↔	↓	?	↔	0.40
Semaglutide, 2016 [21]	↓	↔	↔	↓	↑	↓	?	↔	0.80
Canagliflozin, 2017 [22]	↓	↔	↔	↔	?	↓	?	↓	0.58

MACE major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stoke), *CV* cardiovascular, *MI* myocardial infarction, *CVOT* cardiovascular outcomes; arrow down: significant decrease; arrow up: significant increase; bidirectional arrow: neutral effect; question mark: not evaluated or not published yet

Primary outcome reduction in the EMPAREG-outcome and CANVAS program

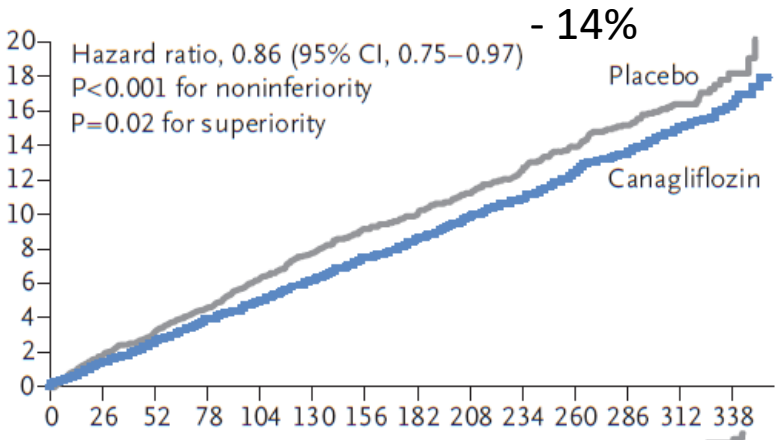
Median FU= 3.1 yrs



No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

NNT= 154/year

Median FU= 2.4 yrs



No. at Risk														
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

NNT= 217/year

N Engl J Med 2015;373:2117-28.

N Engl J Med 2017;377:644-57.

Weighted means of HRs in Denmark, Norway and Sweden for new users of dapagliflozin vs new DDP-4i (PS 1:3 matched for age, gender, frailty, comorbidity and treatment)

	Dapagliflozin N=10,227		DPP-4i N=30,681		Weighted average estimates N=40,908		
	No. events	Events/100 PYR	No. events	Events/100 PYR	Hazard ratio	95% CI	p-value
MACE	177	1.86	695	2.34	0.79	(0.67-0.94)	0.006
Nonfatal myocardial infarction	87	0.91	304	1.02	0.91	(0.72-1.16)	0.445
Nonfatal stroke	69	0.72	270	0.90	0.79	(0.61-1.03)	0.086
Cardiovascular mortality	38	0.40	160	0.53	0.76	(0.53-1.08)	0.122
HHF	95	0.99	467	1.57	0.62	(0.50-0.77)	<0.001
MACE +	202	2.12	779	2.63	0.81	(0.69-0.94)	0.007
Unstable angina	37	0.39	107	0.36	1.09	(0.75-1.59)	0.655
MACE ++	285	3.01	1164	3.96	0.75	(0.66-0.86)	<0.001
All-cause mortality	120	1.03	644	1.75	0.44	(0.33-0.60)	<0.001
Atrial fibrillation	140	1.47	469	1.58	0.92	(0.76-1.12)	0.414
Severe hypoglycemia	91	0.95	300	1.01	0.94	(0.74-1.19)	0.618

Lancet Diabetes Endocrinol. 2017;5(9):709-717

Table 1 Reported number of total outcomes from PROactive (entire population)

Endpoint	Pioglitazone ($n = 2605$), n (%)	Placebo ($n = 2633$), n (%)	HR (95% CI)
Primary outcome			
All-cause mortality, MI (including silent MI), stroke, ACS, coronary revascularization, major leg amputation, leg revascularization	514 (19.7)	572 (21.7)	0.90 (0.80–1.02), $P = 0.095$
Main secondary outcome			
All-cause mortality, MI (excluding silent MI), stroke	301 (11.6)	358 (13.6)	0.84 (0.72–0.98), $P = 0.027$
Other secondary outcomes			
CV mortality	127 (4.9)	136 (5.2)	0.94 (0.74–1.20), $P = 0.62$
All-cause mortality	177 (6.8)	186 (7.1)	0.96 (0.78–1.18), $P = 0.68$
Non-fatal MI (including silent MI)	119 (4.6)	144 (5.5)	0.83 (0.65–1.06), $P = 0.13$
Stroke	86 (3.3)	107 (4.1)	0.81 (0.61–1.07), $P = 0.14$
ACS	56 (2.1)	72 (2.7)	0.78 (0.55–1.11), $P = 0.17$
Coronary revascularization	169 (6.5)	193 (7.3)	0.88 (0.72–1.08), $P = 0.23$
Major leg amputation	26 (1.0)	26 (1.0)	1.01 (0.58–1.73), $P = 0.98$
Leg revascularization	80 (3.1)	65 (2.5)	1.25 (0.90–1.73), $P = 0.19$
Other pre-specified outcomes			
Fatal/non-fatal MI (excluding silent MI)	108 (4.1)	140 (5.3)	0.77 (0.60–1.00), $P = 0.046$
CV mortality, MI (excluding silent MI), stroke	257 (9.9)	313 (11.9)	0.82 (0.70–0.97), $P = 0.020$

Summary of design and outcomes of ELIXA, LEADER, SUSTAIN-6 and EXSCEL trials

Study	Agents	*N*	Duration (years)	Exposure period (years)	Discontinuation rate (%)	Primary outcome	All-cause mortality	CV mortality	Non-fatal MI	Non-fatal stroke
ELIXA	Lixisenatide vs placebo	6068	2.1	1.9	27.5	No difference	No difference	No difference	No difference	No difference
LEADER	Liraglutide vs placebo	9340	3.8	3.5	9.5*	Liraglutide superior	Liraglutide superior	Liraglutide superior	No difference	No difference
SUSTAIN-6	Semaglutide vs placebo	3297	2.1	2	19.9 for 0.5 mg, 22.6 for 1.0 mg	Semaglutide superior	No difference	No difference	No difference	Semaglutide superior
EXSCEL	Exenatide LAR vs placebo	14,752	3.2	2.4	43.0	No difference	No difference	No difference	No difference	No difference

Primary outcome = composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina in ELIXA d composite of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in the other trials

*Discontinuation due to adverse events. Overall discontinuation rate not reported

LEADER MACE NNT= 200/year

SUSTAIN-6 MACE NNT=83/year

Cardiovasc Drugs Ther (2018) 32:65–72

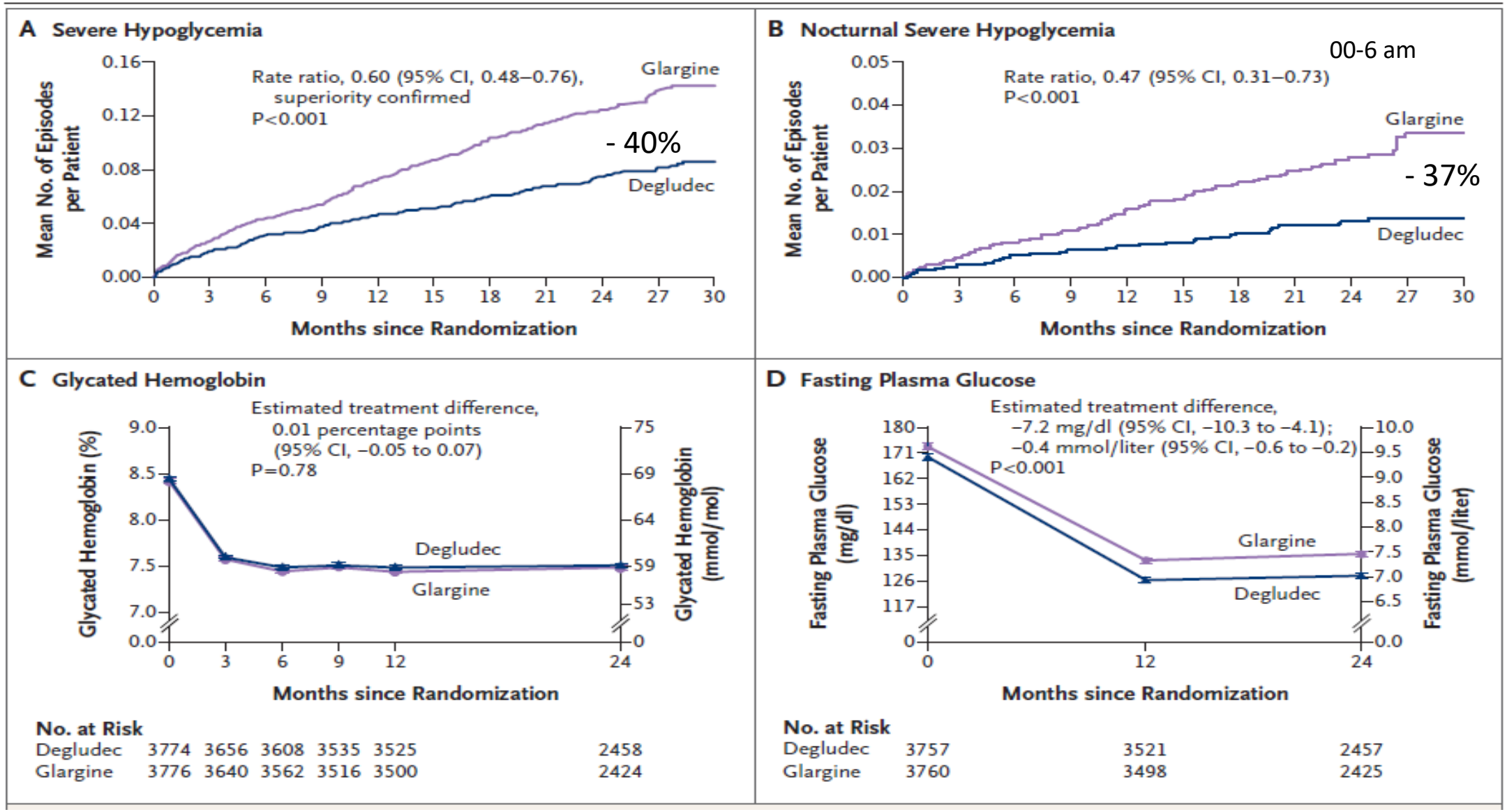
A classification of GLP-1 RAs

Comparison of prandial vs. non-prandial GLP-1 receptor agonists

Parameters	Prandial GLP-1 Ras (short-acting, exendin-4 derived)	Non-prandial GLP-1 Ras (long-acting, mostly GLP-1 derived*)
Compounds	Exenatide, Lixisenatide	Exenatide-LAR, Liraglutide*, Albi*-, Dula-*, Taspo*-, Sema*-glutide
Half-life	2-5h	12h-several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Post-prandial glucose levels	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Post-prandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0-2 bpm)	Moderate increase (2-5 bpm)
Body weight reduction	1-5kg	2-5kg
Induction of nausea	20-50%, attenuates slowly (weeks-many months)	20-40%, attenuates quickly (~4-8 weeks)

Meier J et al.; Nat Rev Endocrinol 2012 (modified)

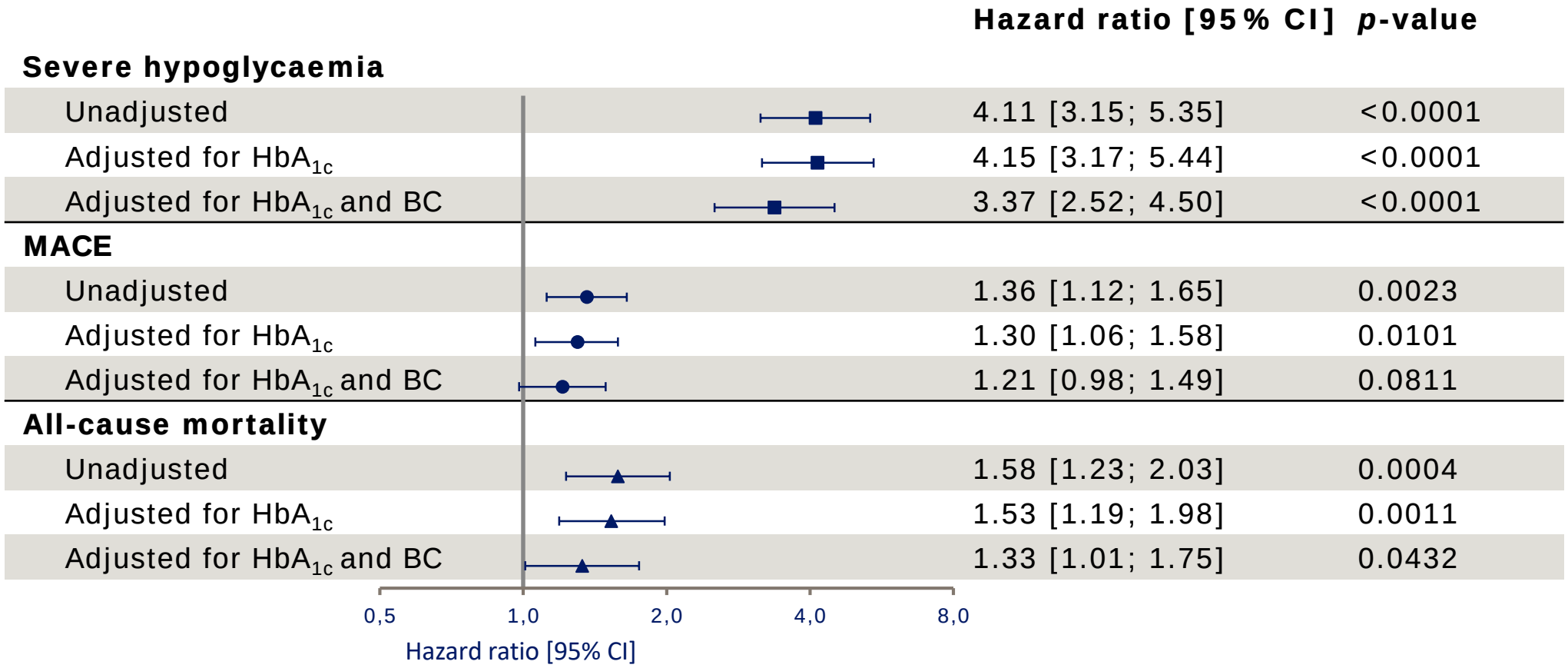
Severe Hypoglycemia and Glucose Control in the DEVOTE trial



(NNT 40)

N Engl J Med. 2017 Aug 24;377(8):723-732.

Association between day-to-day fasting glycaemic variability and outcomes (DEVOTE-2)



Variability is reported on a continuous scale
Adjusted for HbA_{1c}: most recent HbA_{1c} on a continuous scale. Adjusted for HbA_{1c} and BC: most recent HbA_{1c} on a continuous scale and BC (investigational product, sex, region, age at baseline, smoking status at baseline, diabetes duration at baseline, cardiovascular risk-group inclusion criteria, insulin-naïve at baseline and renal function [eGFR] at baseline).
BC, baseline characteristics

Zinman *et al. Diabetologia* 2017

Prossime associazioni precostituite….

SGLT2i+DPP4i

- ✓ saxagliptin and dapagliflozin 2.5/5 or 5/10 mg
- ✓ linagliptin 5 mg and empagliflozin 10 or 25 mg

GLP-1 RA+insulin basale

- ✓ IDegLira (degludec 300U+Lira 10.8)
- ✓ iGlarLixi (glargine 100 e lixisenatide rapporto 2:1 o 3:1)

DPP4i+Pioglitazone

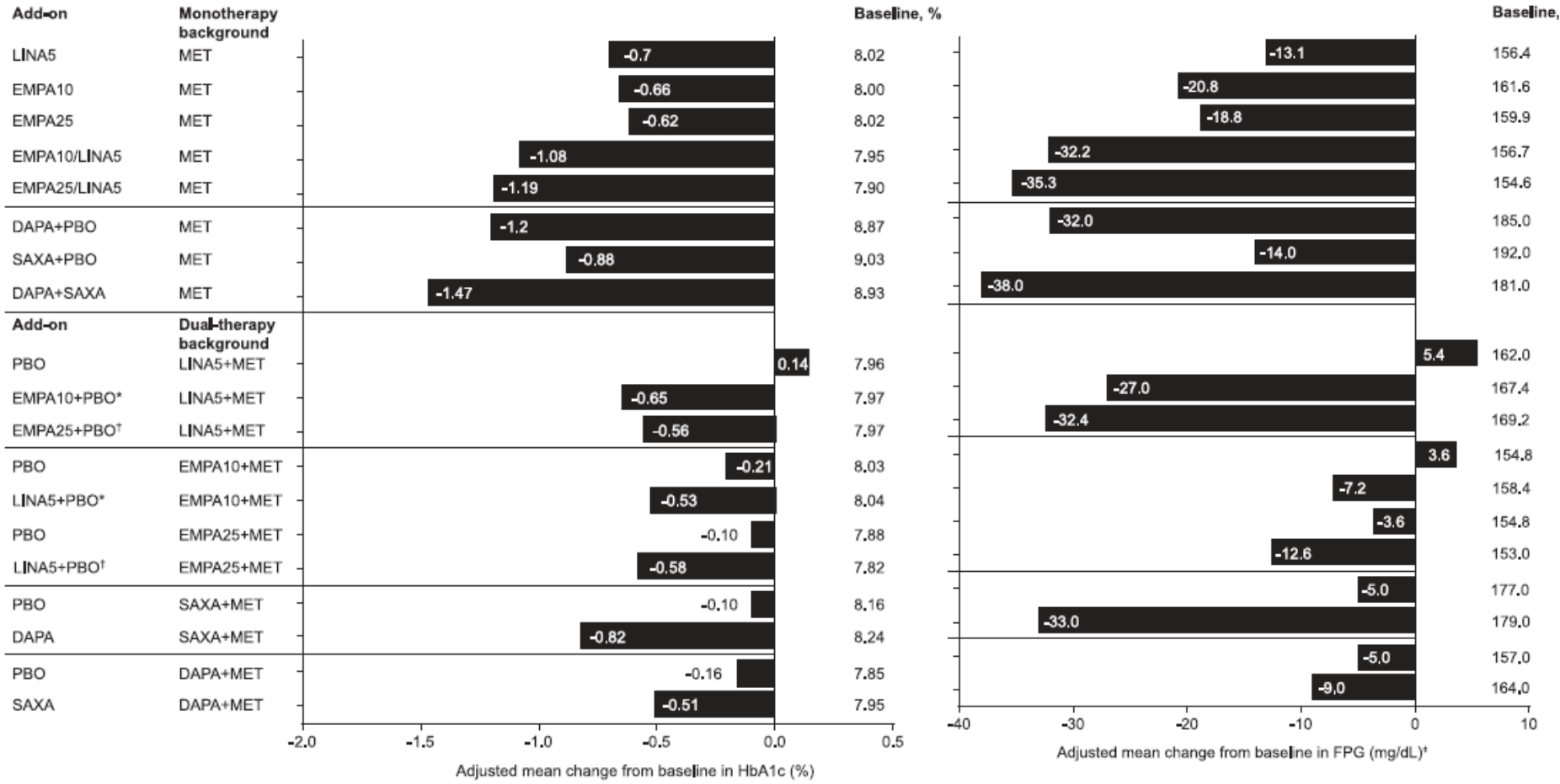
- ✓ pioglitazone and DPP-4 inhibitors

Conclusions

- ✓ The use of drug combinations is mandatory to target DM pathophysiological mechanisms
- ✓ Combining therapies offers opportunities to enhance efficacy (HbA1C, weight, blood pressure) and diminish side effects
- ✓ Cardiovascular safety of drug combination should refert to that of the single monocomponent

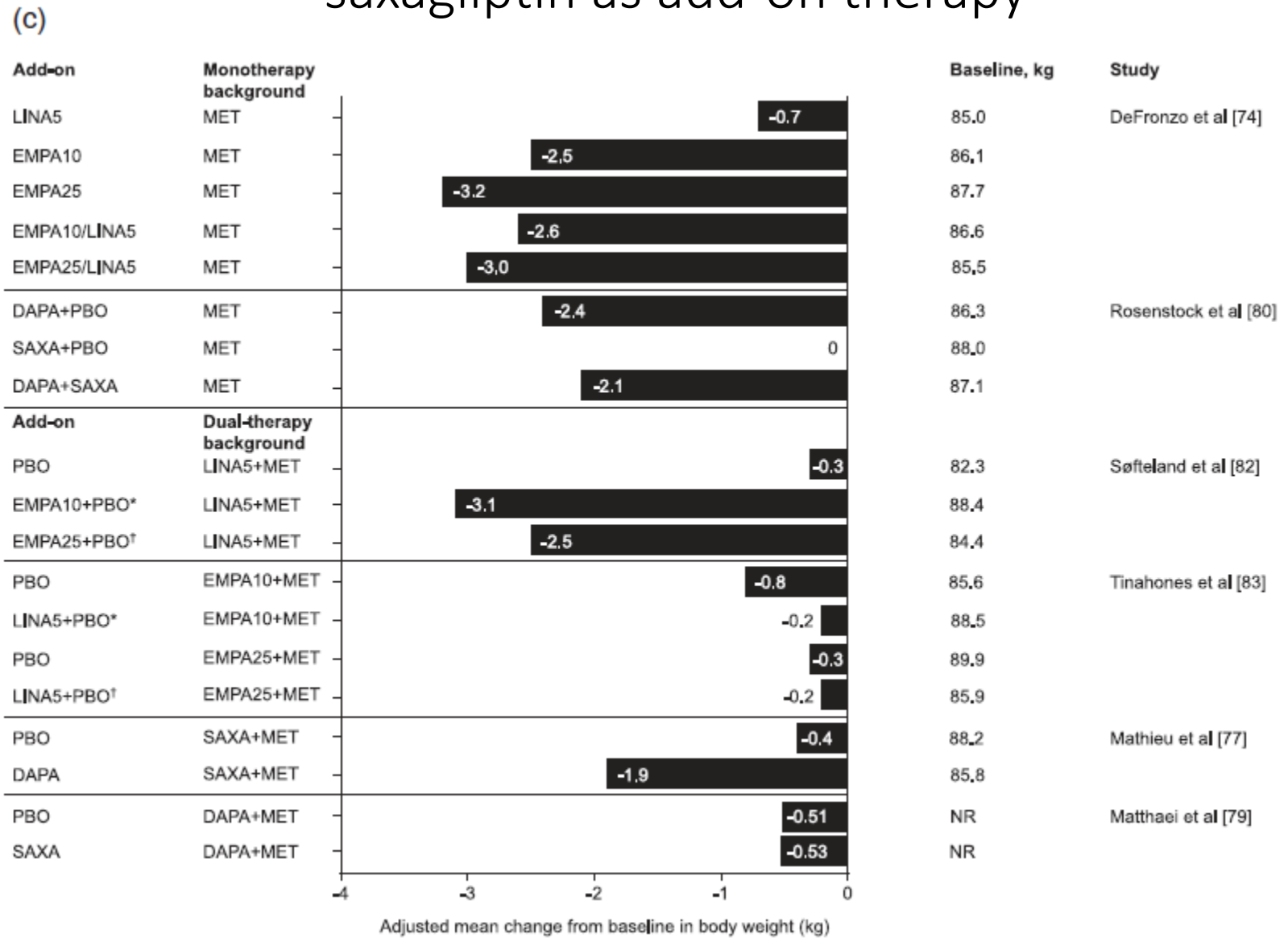
Efficacy in HbA1C reduction in patients receiving empagliflozin and linagliptin or dapagliflozin and saxagliptin as add-on therapy

* At 52 weeks



Postgraduate Medicine 2017;129:409-420

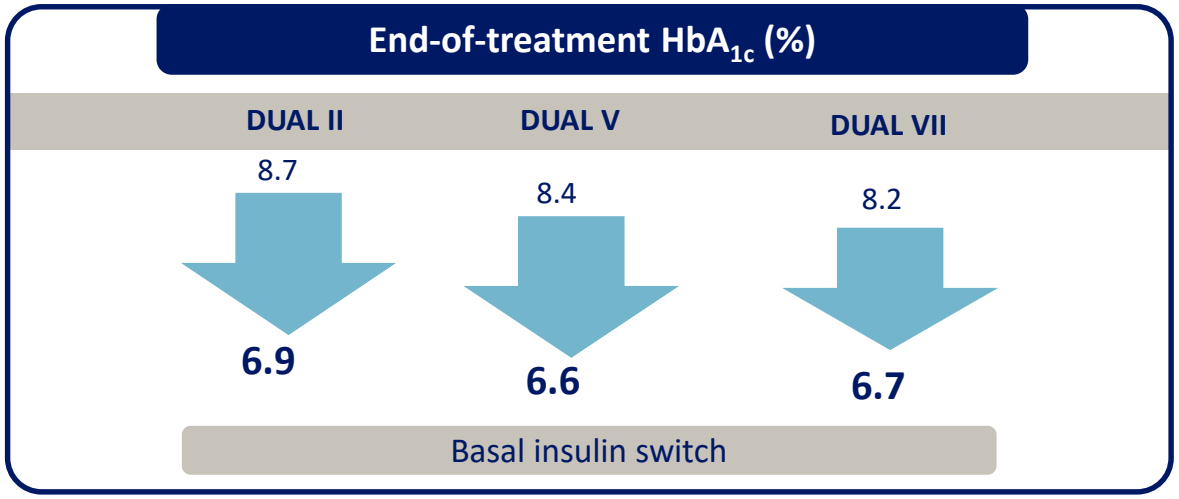
Body changs in patients receiving empagliflozinand linagliptin or dapagliflozin and saxagliptin as add-on therapy

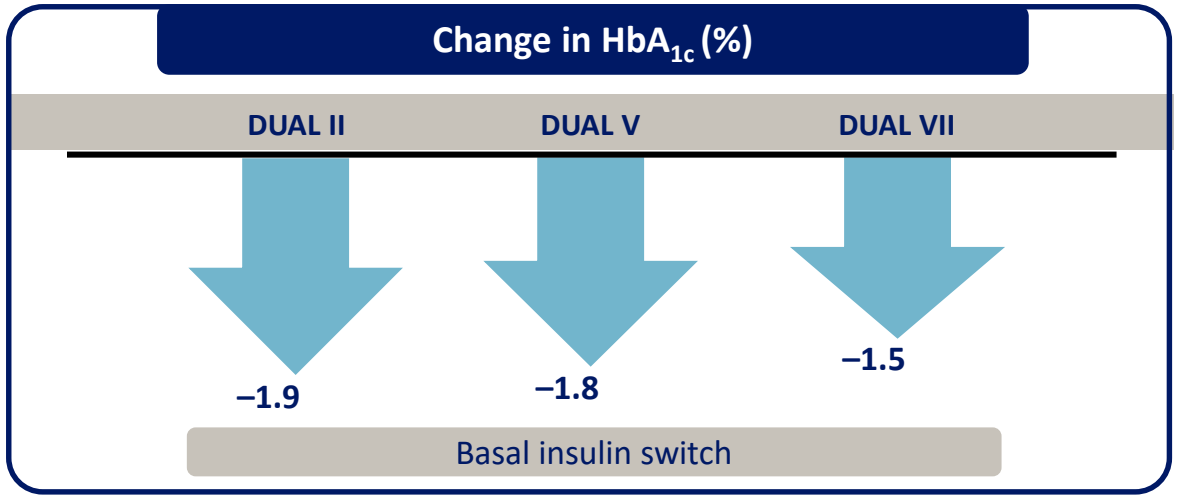


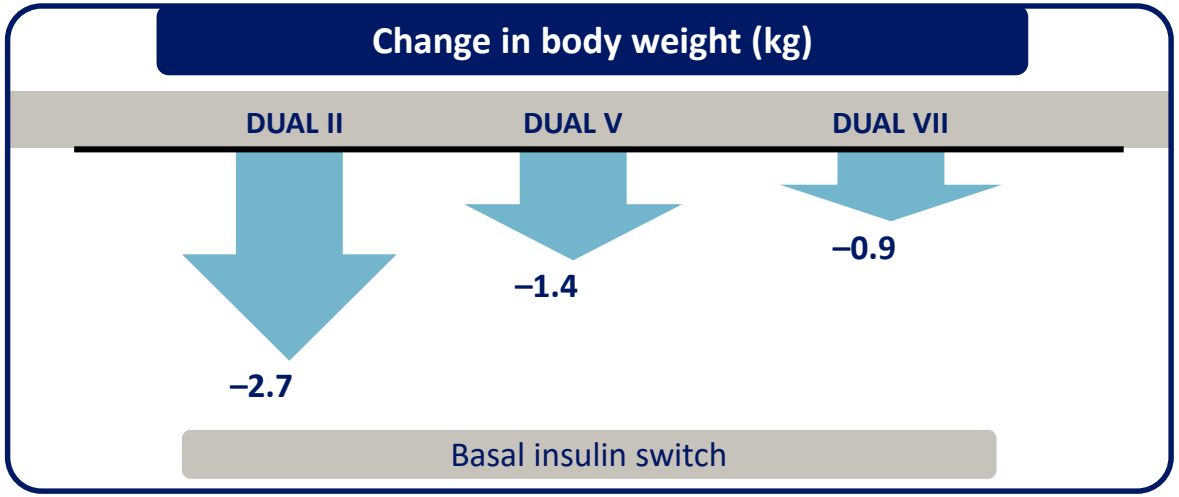
Postgraduate Medicine 2017;129:409-420

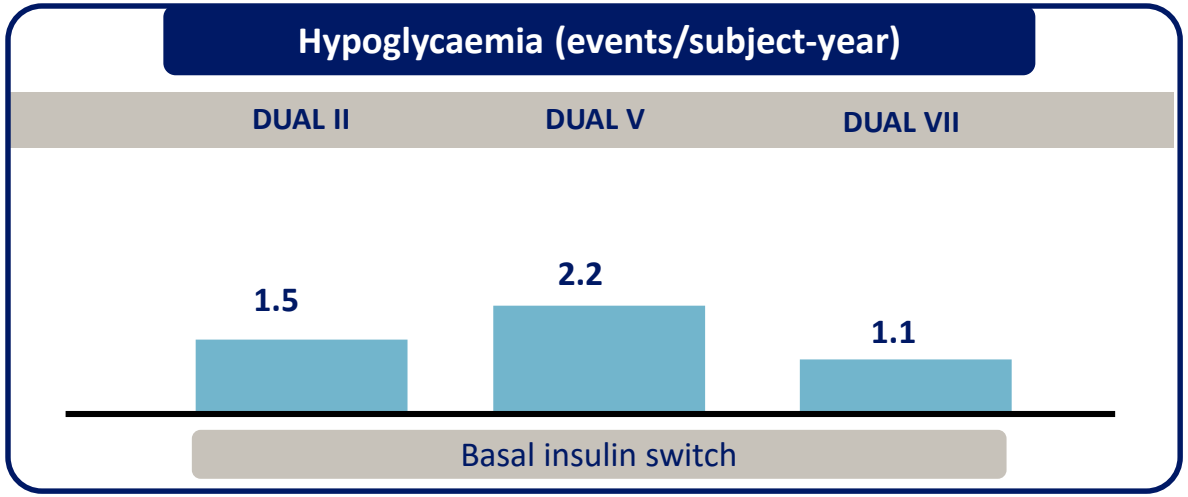
IDegLira in subjects uncontrolled on basal insulin

Summary of key clinical findings from DUAL II, V and VII





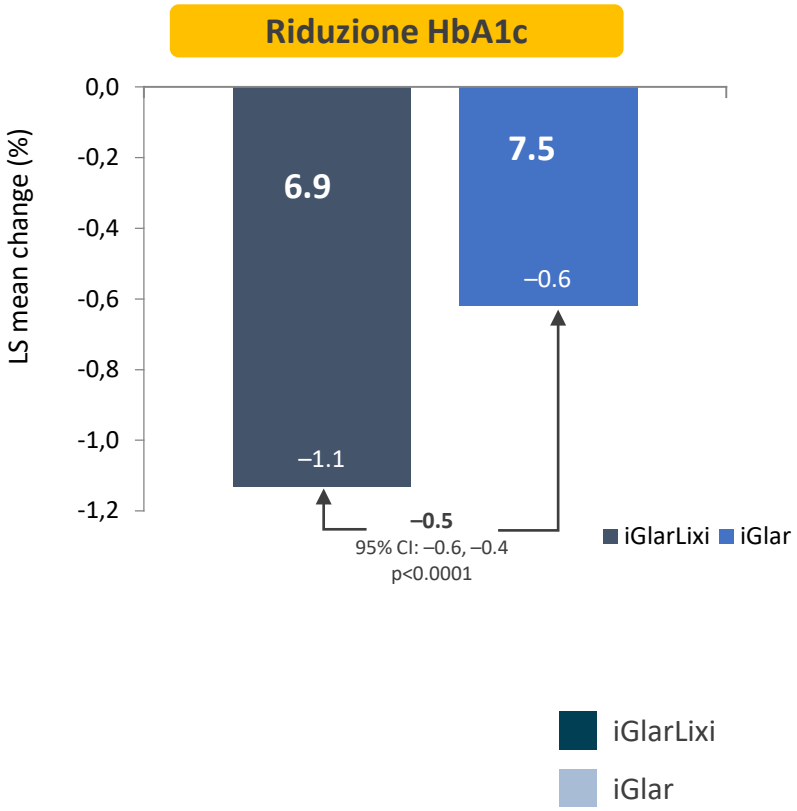


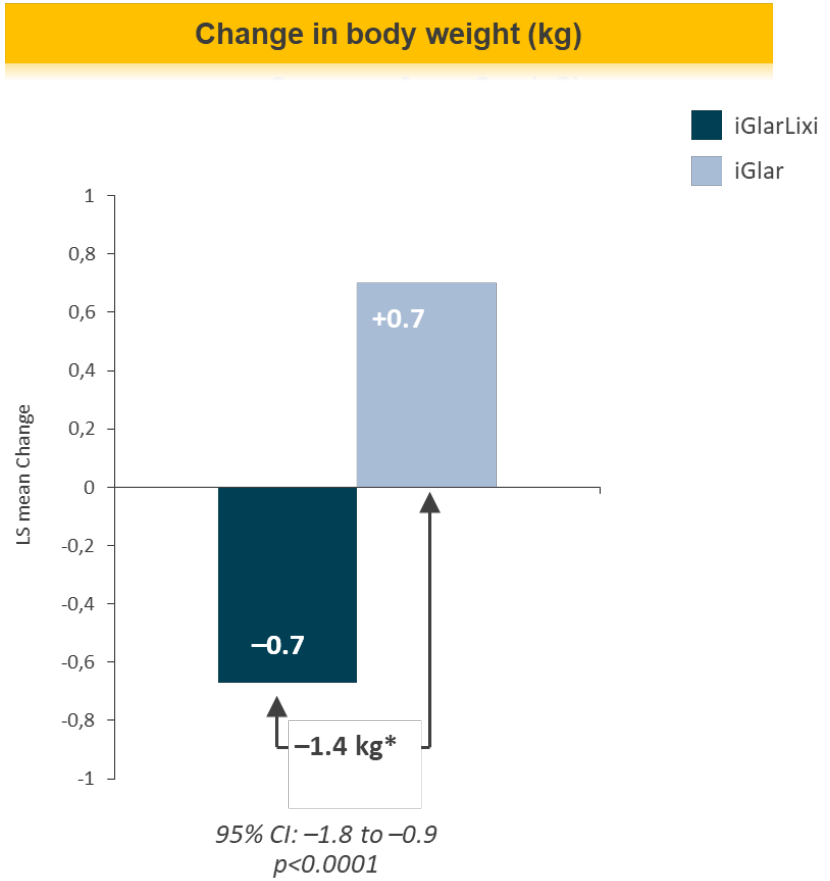


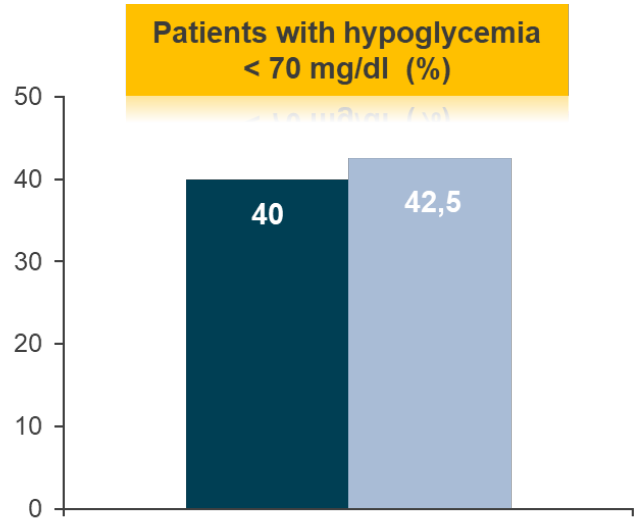
IDegLira, insulin degludec/liraglutide

Buse *et al. Diabetes Care* 2014;37:2926–33; Lingvay *et al. JAMA* 2016;315:898-907; Billings et al. *ADA 2017;136-OR*

Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial



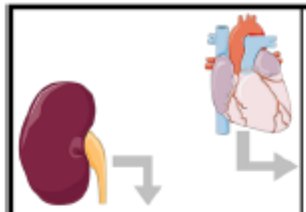




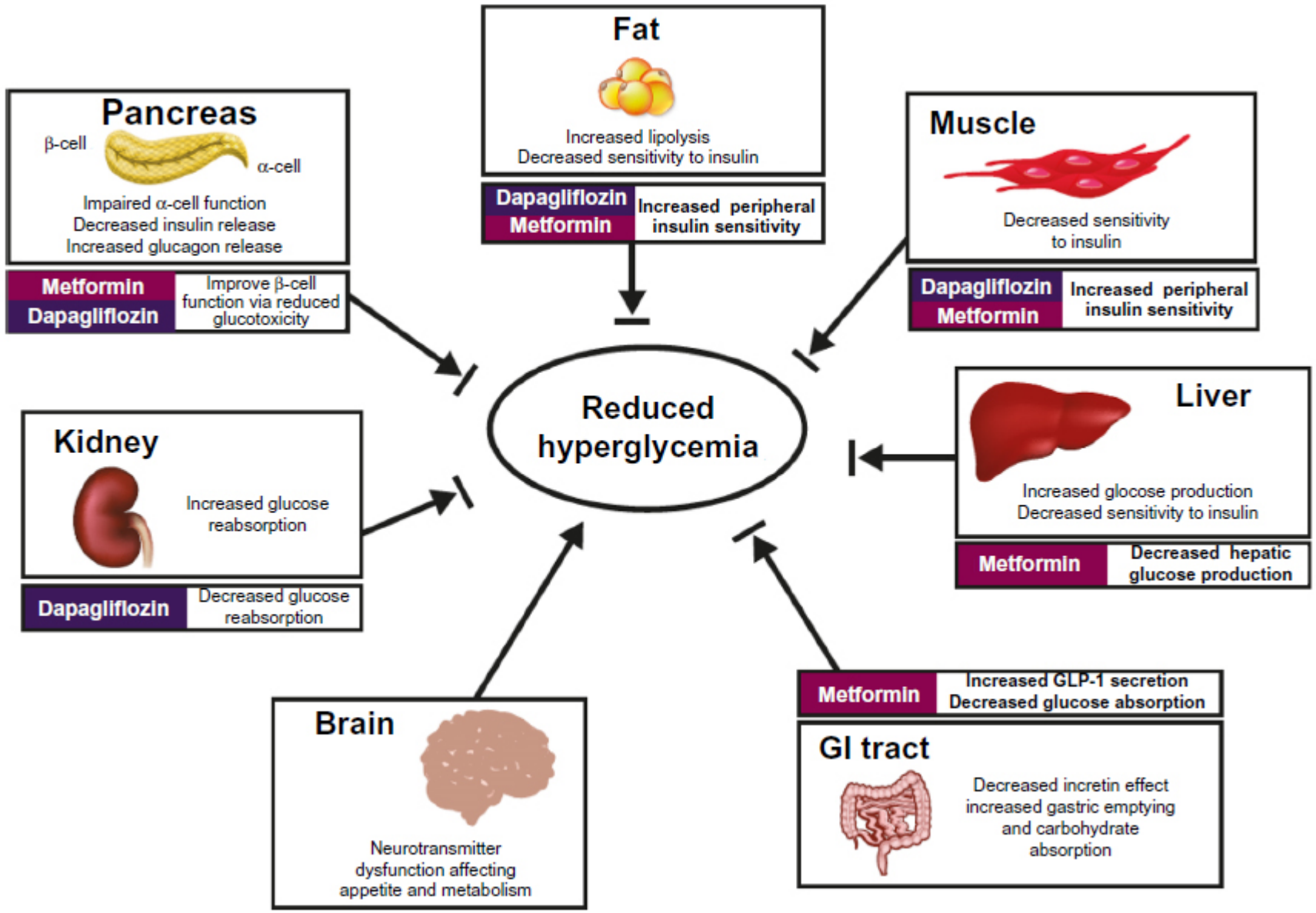
At week 30

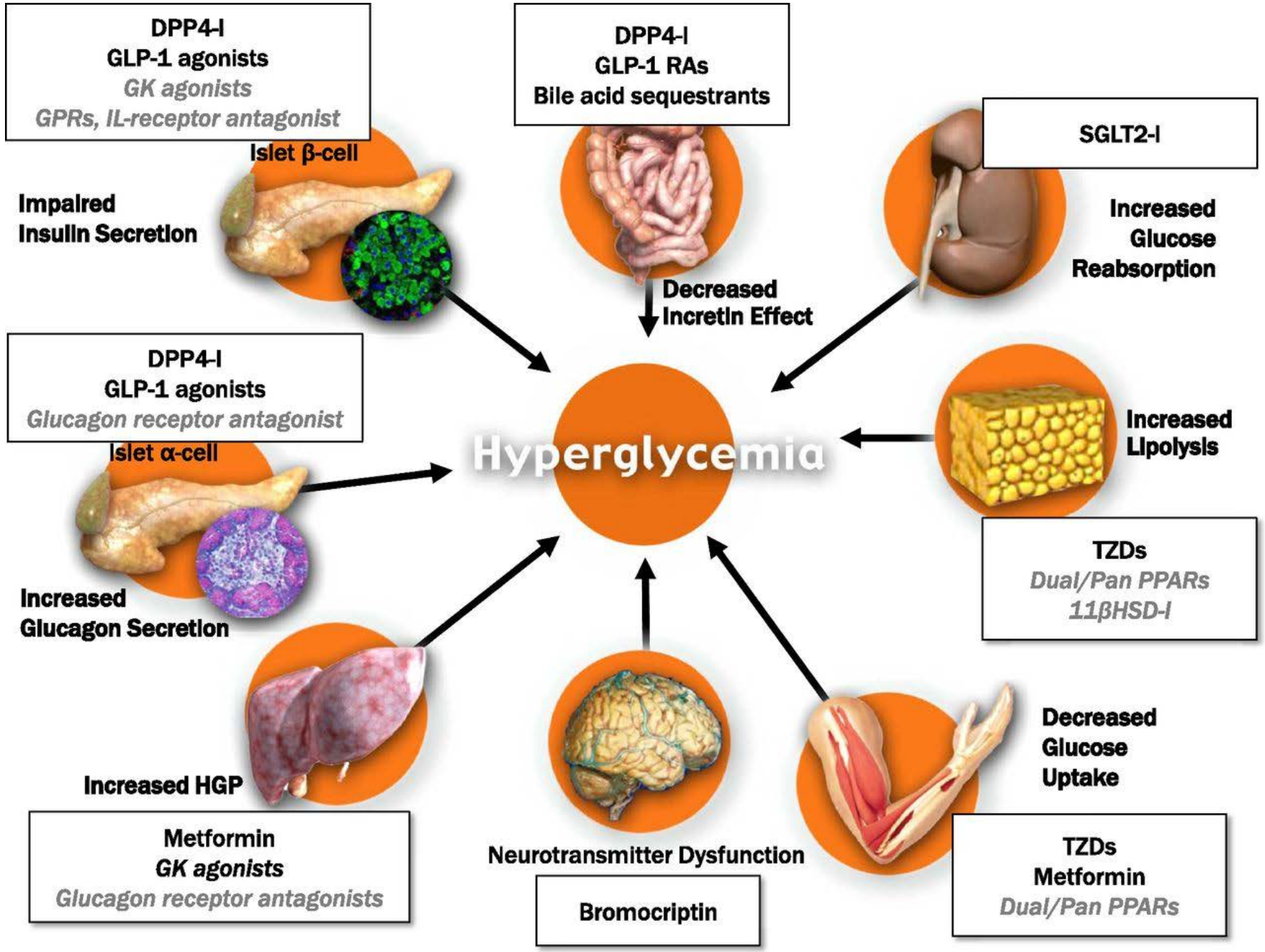
Aroda VR, et al. Diabetes Care 2016

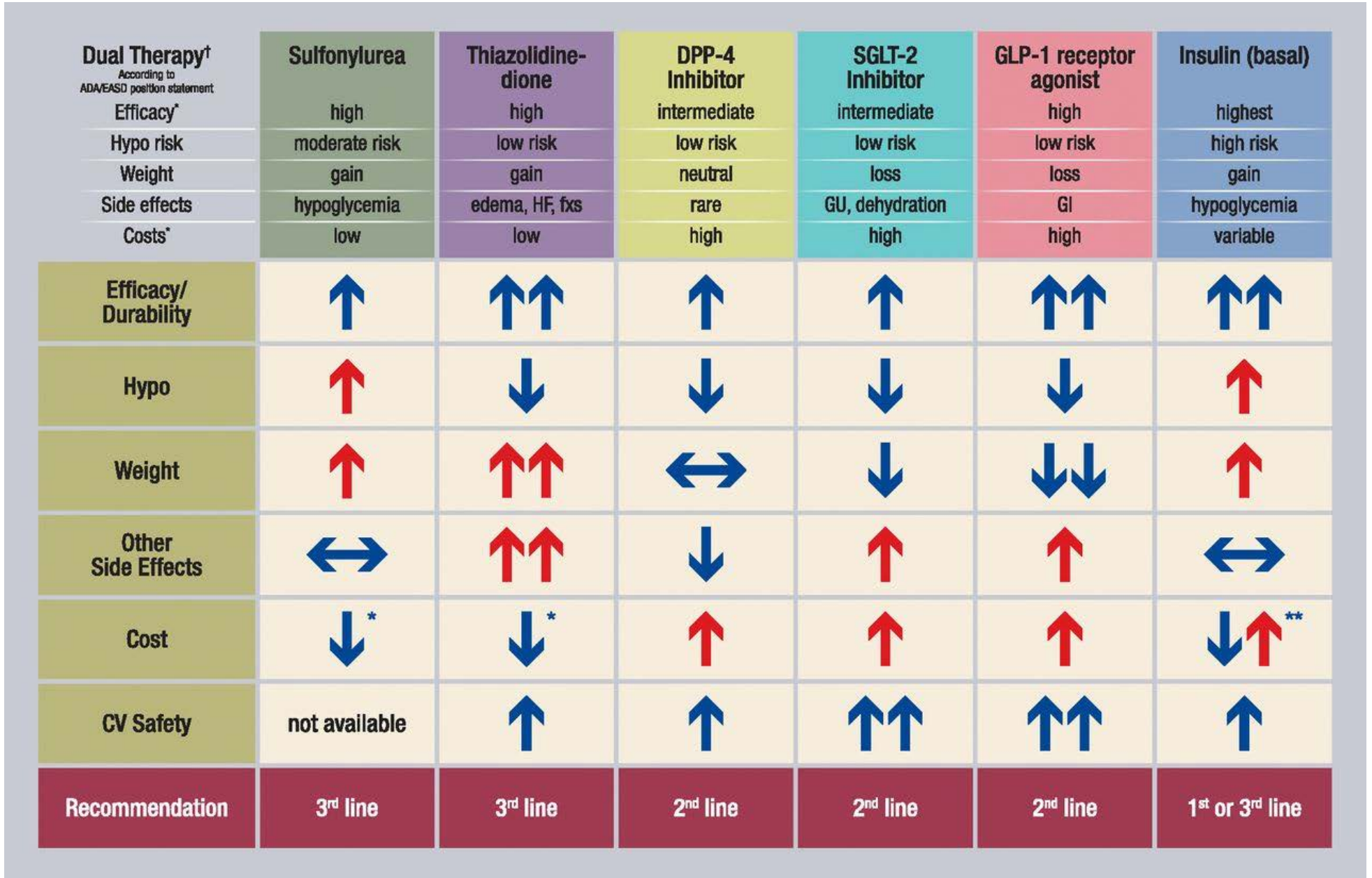
A treatment algorithm based on cardiac and renal co-morbidities and CVOTs.

	Normal or subclinical **ENDOTHELIAL DYSFUNCTION**	**ESTABLISHED ATHERO-SCLEROSIS**	**ACUTE CORONARY SYNDROME**	**HEART FAILURE**
Stage I-II CKD **eGFR 90-60 ml/min/1.73 m²**	Metformin[a], Pioglitazone[b] DPP4-I[c-e], GLP-1 RA[f], SGLT2-I[g], Insulin[1h] SUs[1]	Metformin, SGLT2-I[g], GLP-1RA[f], Pioglitazone[b], DPP4-I[c-e], Insulin[h], Gliclazide[k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage III CKD **eGFR 59-30 ml/min/1.73 m²**	Metformin[2], Pioglitazone[3b], SLGT2-I[4g], GLP-1RA[f], DPP4-I[2c-e], Gliclazide[2k], Insulin[h]	Metformin[2], GLP-1RA[f], SGLT2-I[4g], Pioglitazone[3b], DPP4-I[2c-e], Insulin[h], Gliclazide[2k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage IV CKD **eGFR 29-15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]
Stage V CKD **eGFR <15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]

Evidence of efficacy **Evidence of safety** **Author consensus**


Fat
Increased lipolysis
Decreased sensitivity to insulin
Dapagliflozin
Metformin
Increased peripheral insulin sensitivity
Pancreas
β-cell
α-cell
Impaired α-cell function
Decreased insulin release
Increased glucagon release
Metformin
Dapagliflozin
Improve β-cell function via reduced glucotoxicity
Muscle
Decreased sensitivity to insulin
Dapagliflozin
Metformin
Increased peripheral insulin sensitivity
Reduced hyperglycemia
Kidney
Increased glucose reabsorption
Dapagliflozin
Decreased glucose reabsorption
Liver
Increased glocose production
Decreased sensitivity to insulin
Metformin
Decreased hepatic glucose production
Brain
Neurotransmitter dysfunction affecting appetite and metabolism
Metformin
Increased GLP-1 secretion
Decreased glucose absorption
GI tract
Decreased incretin effect
increased gastric emptying
and carbohydrate absorption


DPP4-I
GLP-1 agonists
GK agonists
GPRs, IL-receptor antagonist
Islet β-cell
Impaired
Insulin Secretion
DPP4-I
GLP-1 RAs
Bile acid sequestrants
Decreased
Incretin Effect
SGLT2-I
Increased
Glucose
Reabsorption
DPP4-I
GLP-1 agonists
Glucagon receptor antagonist
Islet α-cell
Increased
Glucagon Secretion
Hyperglycemia
Increased
Lipolysis
TZDs
Dual/Pan PPARs
11βHSD-I
Increased HGP
Metformin
GK agonists
Glucagon receptor antagonists
Neurotransmitter Dysfunction
Bromocriptin
Decreased
Glucose
Uptake
TZDs
Metformin
Dual/Pan PPARs


Dual Therapy†
According to ADA/EASD position statement
Sulfonylurea
Thiazolidine-dione
DPP-4 Inhibitor
SGLT-2 Inhibitor
GLP-1 receptor agonist
Insulin (basal)
Efficacy*
high
high
intermediate
intermediate
high
highest
Hypo risk
moderate risk
low risk
low risk
low risk
low risk
high risk
Weight
gain
gain
neutral
loss
loss
gain
Side effects
hypoglycemia
edema, HF, fxs
rare
GU, dehydration
GI
hypoglycemia
Costs*
low
low
high
high
high
variable
Efficacy/ Durability
Hypo
Weight
Other Side Effects
Cost
*
*
**
CV Safety
not available
Recommendation
3rd line
3rd line
2nd line
2nd line
2nd line
1st or 3rd line