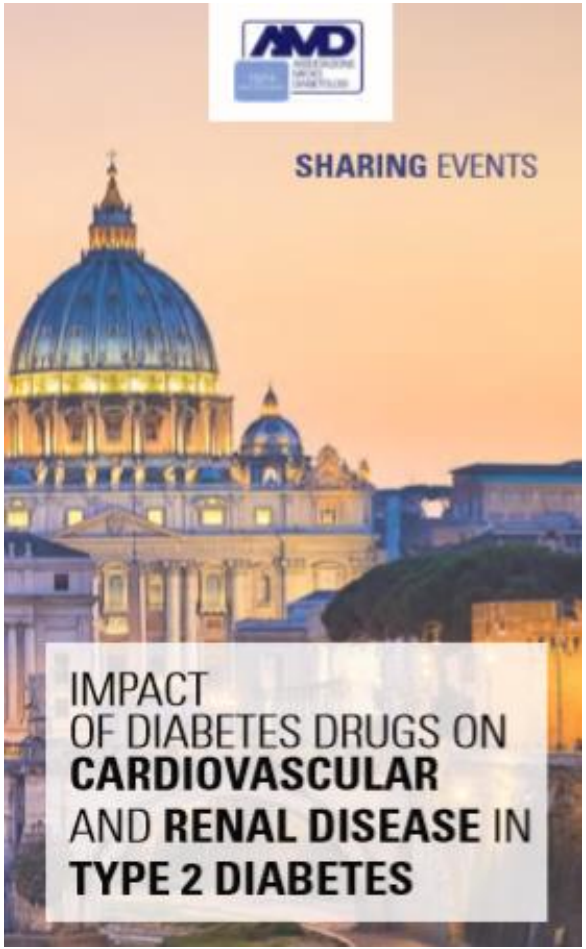


Un nuovo paradigma:
dal treat to target al treat to benefit

Franco Tuccinardi
UOC Diabetologia Ospedale Formia
Azienda USL Latina

Disclosure Statement

Franco Tuccinardi, in the last two years, has received speaking and/or consulting fees from:

Abbott Diabetes Care
AstraZeneca
Boehringer Ingelheim
Eli Lilly
Merck Sharp & Dohme
Novo Nordisk
Roche
Takeda

Is It Time to Change the Type 2 Diabetes Treatment Paradigm?

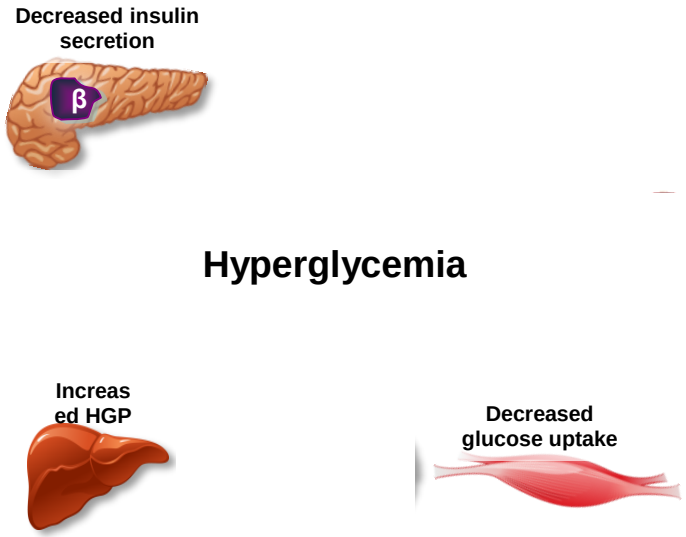
In the last years…

- New physiopathological knowledge
- New therapeutic approaches
- New drugs
- New CV outcome trials

TYPE 2 DIABETES ETIOLOGY IN 1987

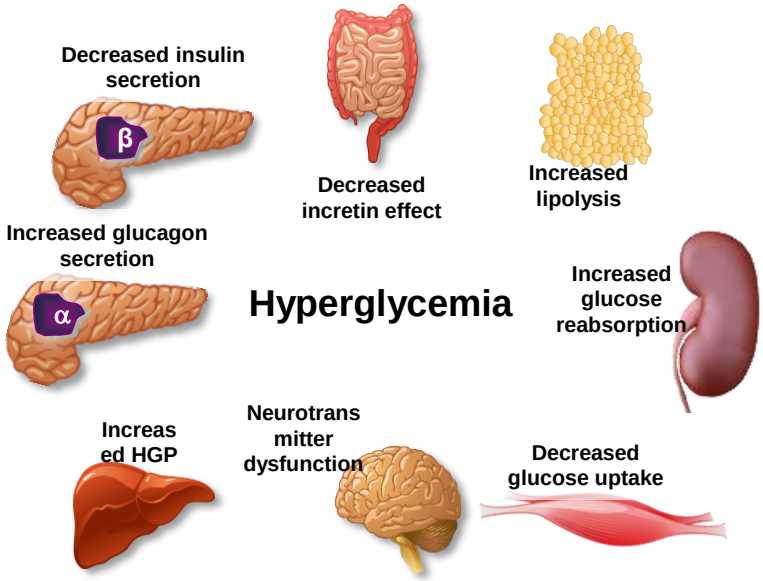
- INSULIN RESISTENCE IN LIVER
- INSULIN RESISTENCE IN MUSCLE
- PROGRESSIVE BETA-CELL FAILURE

TYPE 2 DIABETES ETIOLOGY IN 2008



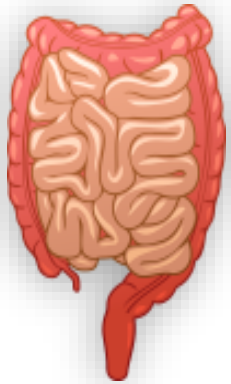
DeFronzo RA. Banting Lecture 2008.

TYPE 2 DIABETES ETIOLOGY IN 2008



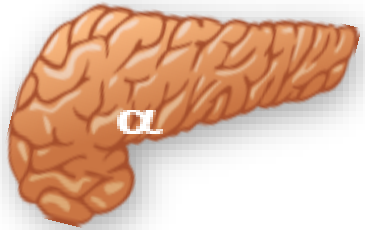
DeFronzo RA. Banting Lecture 2008.

TYPE 2 DIABETES :



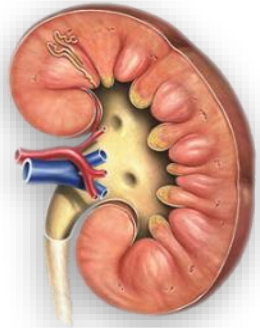
- DECREASE IN AMOUNT OF GLP-1 SECRETED
- BETA-CELL RESISTANCE TO STIMOLATORY EFFECTS OF GLP-1 AND GIP ON INSULIN SECRETION

ALPHA CELL AND GLUCAGON IN TYPE 2 DIABETES



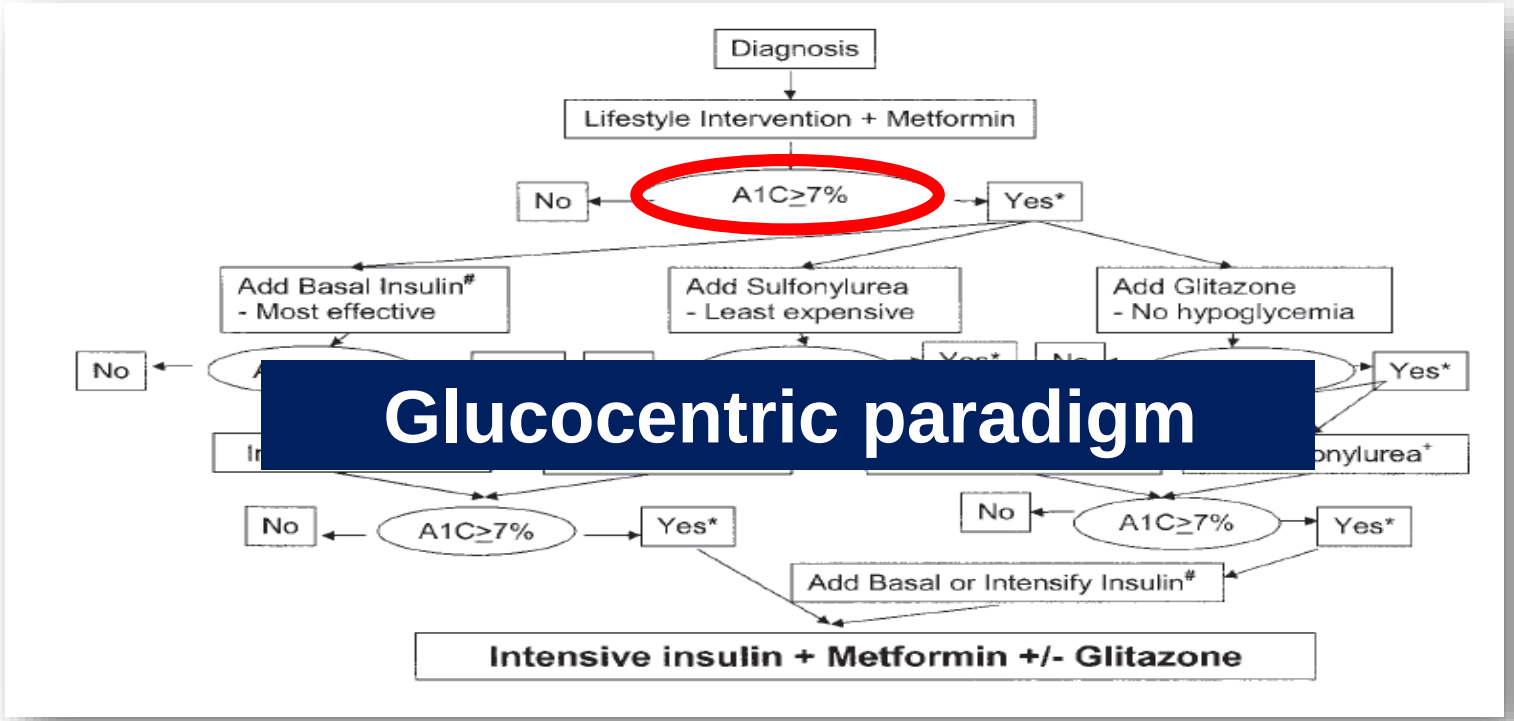
- ALPHA CELL SECRETES TOO MUCH GLUCAGON
- ELEVATED FASTING GLUCAGON LEVELS
- POSTPRANDIAL GLUCAGON LEVELS NOT SUPPRESSED APPROPRIATELY AND PARADOXICALLY INCREASE

- EXCESS FASTING HEPATIC GLUCOSE PRODUCTION
- IMPAIRMENT OF NORMAL POSTPRANDIAL SUPPRESSION OF HEPATIC GLUCOSE PRODUCTION



SGLT2 expression is increased in patients with T2DM, resulting in increased glucose reabsorption and preservation of elevated blood glucose levels

Endocr Pract, 14 (2008), pp. 782-790



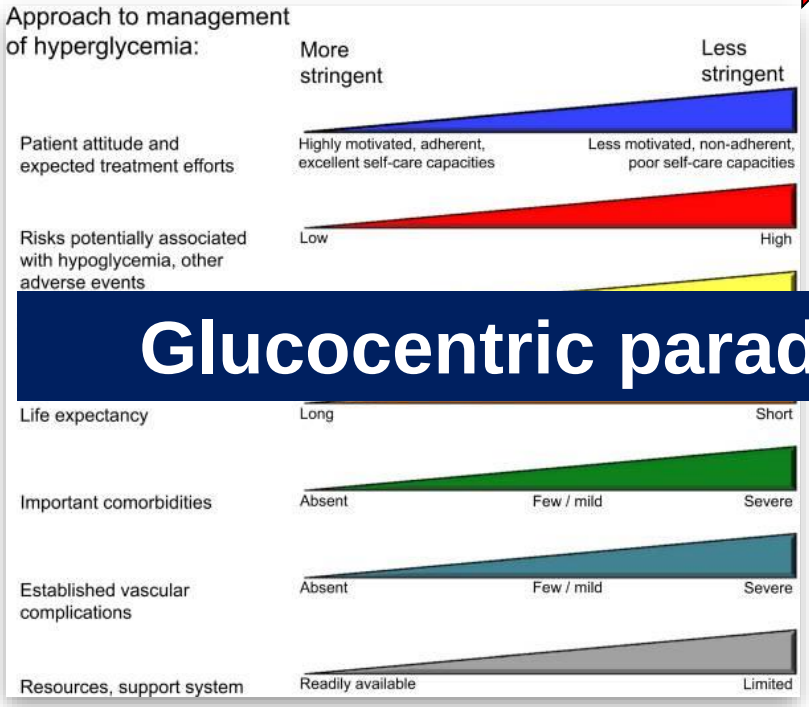
Nathan DM. Diabetes Care 2006;20(8):1963-1972

American Diabetes Association

'… the results of the UKPDS mandate that treatment of type 2 diabetes include aggressive efforts to lower blood glucose levels as close to normal as possible…'

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

6,5% 7,0% 8,5%



Glucocentric paradigm

Diabetes Care. 2012 Jun; 35(6): 1364–1379.

today…

From “Treat to target” to….”Treat to benefit”

Now 4 CVOTs Demonstrate CV Benefit

EMPA-REG OUTCOME[a] Endpoint, n (%)	Empagliflozin (n = 4687)	Placebo (n = 2333)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	490 (10.5)	282 (12.1)	0.86 (0.74, 0.99) *P* = .04
LEADER[b] Endpoint, n (%)	Liraglutide (n = 4668)	Placebo (n = 4672)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	608 (13.0)	694 (14.9)	0.87 (0.78, 0.97) *P* = .001
SUSTAIN-6[c] Endpoint, n (%)	Semaglutide* (n = 1648)	Placebo (n = 1649)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	108 (6.6)	146 (8.9)	0.74 (0.58, 0.95) *P* = .02
CANVAS[d] Endpoint, participants with event per 1000 patient years (%)	Canagliflozin (n = 4795)	Placebo (n = 4347)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	26.9	31.5	0.86 (0.75 0.97) *P* = .02

*The FDA has not yet approved this medication for use.

a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; b. Marso SP, et al. *N Engl J Med*. 2016;375:311-322; c. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844; d. Neal B, et al. *N Engl J Med*. 2017. [Epub ahead of print]

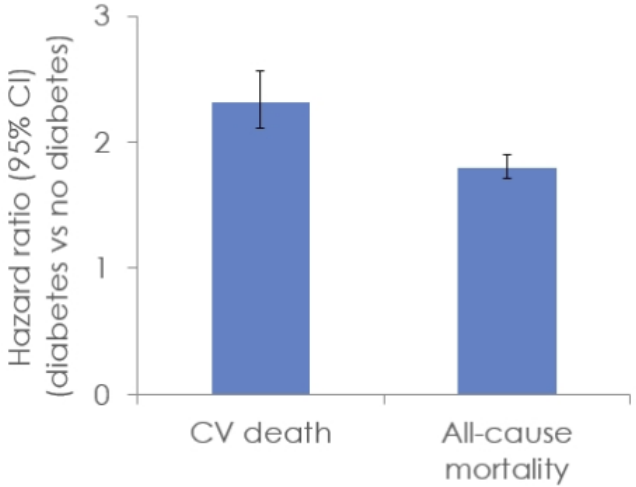
CV safety studies for diabetes drugs

Methodological issues

- Designed for non-inferiority
- Enrolment of very high-risk patients
- Relatively short duration of follow-up
- Attempt at minimizing between-group differences in glucose control

Unmet Needs in Diabetes Care

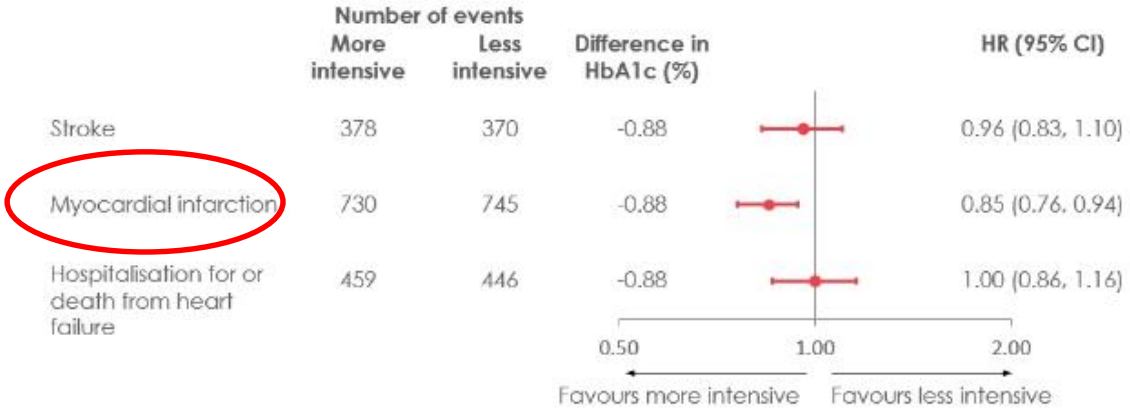
At least 68% of people >65 years with diabetes die of heart disease



Center for disease control and prevention 2011; - Seshasai et al.N Eng J Med 2011;

THE ROLE OF GLUCOSE CONTROL IN MACROVASCULAR DISEASE

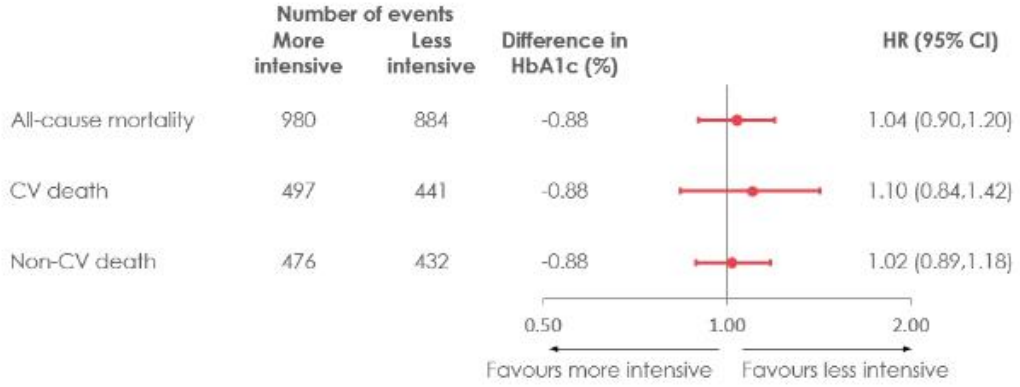
Meta-analysis of intensive glucose control in T2DM:major CV events including heart failure



Meta-analysis of 27,049 partecipants and 2370 major vascular events from:
ADVANCE
UKPDS
ACCORD
VADT

Tumbul FM et al.Diabetologia 2009;52:2268-2297

Meta-analysis of intensive glucose control in T2DM : mortality



Meta-analysis of 27,049 partecipants and 2370 major vascular events from:

ADVANCE
UKPDS
ACCORD
VADT

Tumbul FM et al.Diabetologia 2009;52:2268-2297

- **Cardiovascular mortality is the principal cause of death in individuals with type 2 diabetes**

- **Reduction of plasma glucose concentration has little effect on CV disease risk**

T2DM
More than hyperglycaemia

- Hyperglycemia
- Dyslipidemia
- Hypertension
- Damage to blood vessels
- Clotting abnormalities
- Inflammation

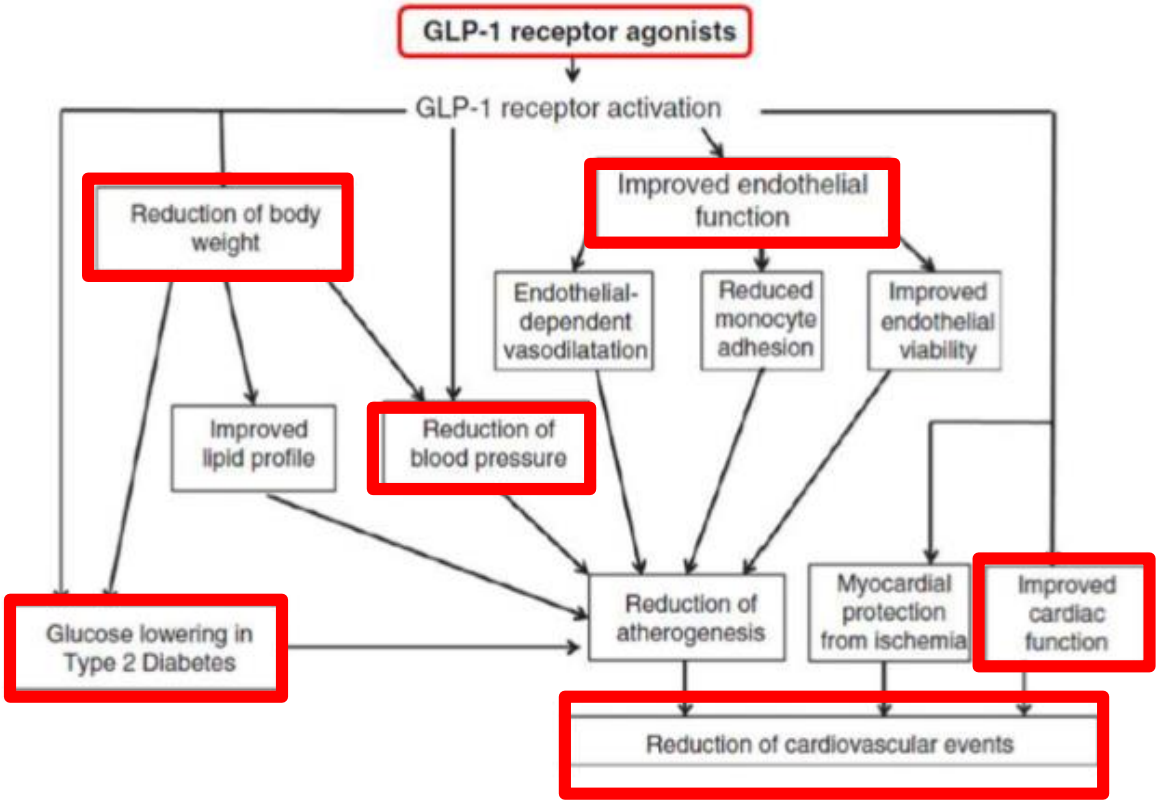
Atherosclerosis

CV Improvements and Novel Glucose-Lowering Agents

The CV and renal benefits observed with long-acting GLP-1 RAs and SGLT2 inhibitors may be the result of an entire milieu of improvements, eg,

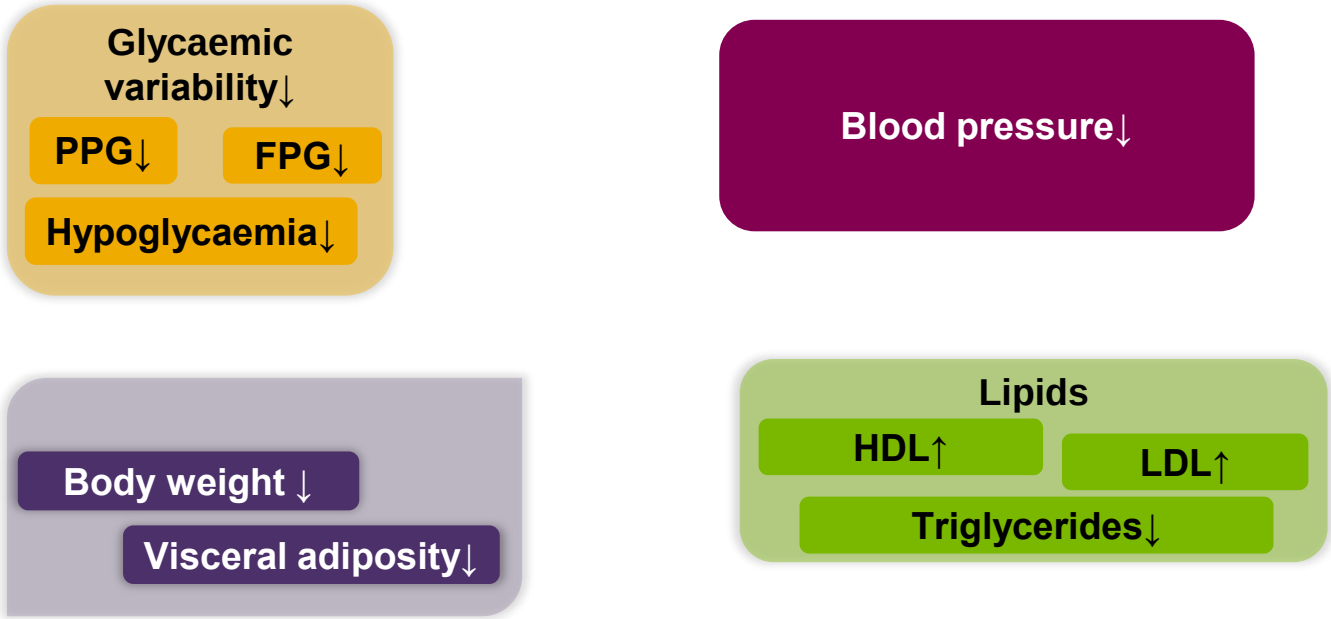
- HbA1c reduction
- Improvements in insulin resistance
- Weight loss
- Blood pressure reduction
- Improvements in lipids
- Improvements in CV function

GLP1 receptor agonists: cardiovascular actions



Mannucci E & Dicembrini I, *Curr Med Res Opin* 28:715-21, 2012

SGLT2i



Modified from: Inzucchi SE, et al. Diab Vasc Dis Res 2015;12:90–100.

CV outcome trials

Treatments	EMPA-REG HR [95% CI]	LEADER HR [95% CI]
MACE	0.86 [0.74 - 0.99]	0.87 [0.78 - 0.97]
CV death	0.62 [0.49 -	0.78 [0.66 - (
All deaths	0.68 [0.57 -	0.85 [0.74 - (
Heart failure	0.65 [0.50 - 0.85]	*0.87 [0.73 - 1.05]*

- 38%

-22%

-32%

-15%

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event

Baseline characteristics: CV risk factors

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Body mass index, kg/m^2	30.7 (5.2)	30.6 (5.2)	30.6 (5.3)
Weight, kg	86.6 (19.1)	85.9 (18.8)	86.5 (19.0)
Waist circumference, cm	105.0 (14.0)	104.7 (13.7)	104.8 (13.7)
Systolic blood pressure, mmHg	135.8 (17.2)	134.9 (16.8)	135.6 (17.0)
Diastolic blood pressure, mmHg	76.8 (10.1)	76.6 (9.8)	76.6 (9.7)
Heart rate, bpm*	70.7 (0.2)	71.0 (0.2)	70.5 (0.2)
LDL cholesterol, mg/dL	84.9 (35.3)	86.3 (36.7)	85.5 (35.2)
HDL cholesterol, mg/dL	44.0 (11.3)	44.7 (12.0)	44.5 (11.8)
eGFR, mL/min/1.73m^2 (MDRD)	73.8 (21.1)	74.3 (21.8)	74.0 (21.4)
≥90 mL/min/1.73m^2	488 (20.9%)	519 (22.1%)	531 (22.7%)
60 to <90 mL/min/1.73m^2	1238 (53.1%)	1221 (52.1%)	1204 (51.4%)
<60 mL/min/1.73m^2	607 (26.0%)	605 (25.8%)	607 (25.9%)

EMPA-REG OUTCOME®

real-world data

CVDREAL

N 309.056 patients with T2D
87% did not have known CVD

Use of SGLT2i vs other glucose-lowering drugs was associated with lover rates of :

- HHF 39 %
- All cause death 51%

SGLT-2i compound use as a function of total exposure time :

- canaglifozin 53%
- dapaglifozin 42%
- empaglifozin 5%

CV risk factors in CV safety trials in diabetes

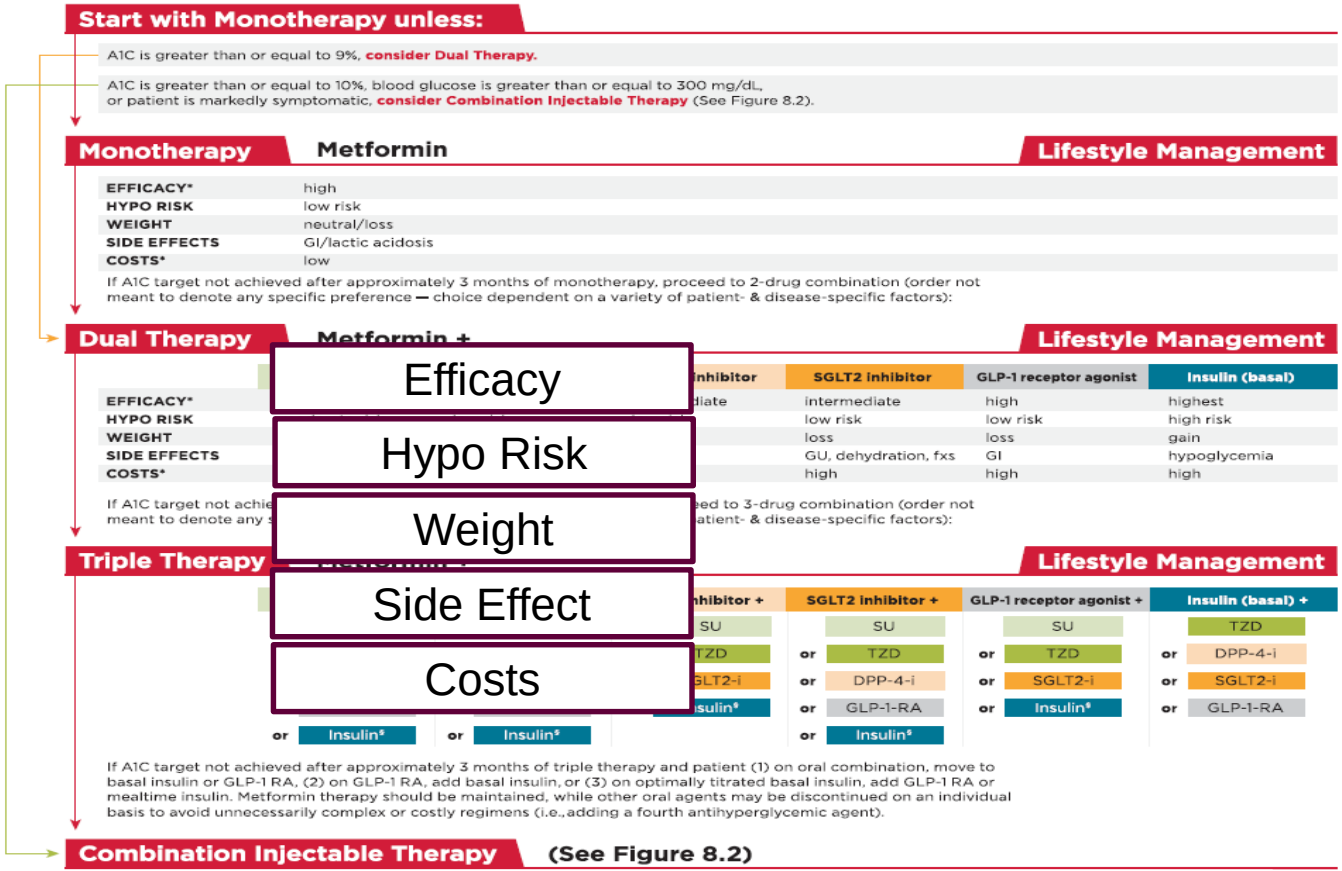
Mean differences between active treatment and placebo

Study	Drug	A1c (%)	BW (kg)	sBP (mmHg)	MACE (%)
TECOS	Sitagliptin	-0.3	0	0	-2
EXAMINE	Alogliptin	-0.3	0	0	-4
SAVOR accord	Saxagliptin	-0.2	0	0	0
ELIXA	Lixisenatide	-0.2	-0.6	-0.8	+2
LEADER	Liraglutide	-0.4	-2.3	-1.2	-13
SUSTAIN-6	Semaglutide	-0.9	-3.9	-1.9	-26
EMPAREG	Empagliflozin	-0.4	-1.0	-2.8	-14

Is Hemoglobin A1C the right outcome for studies of diabetes?

Trials that use outcomes based solely on glycemic parameters are no longer acceptable for clinical decision-making

A new decision making



Efficacy

Hypo Risk

Weight

Side Effect

Costs

1. Metformin

???

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

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2018

Drug-specific and patient factors to consider when selecting anthyperglycemic treatment in adults with type 2 diabetes

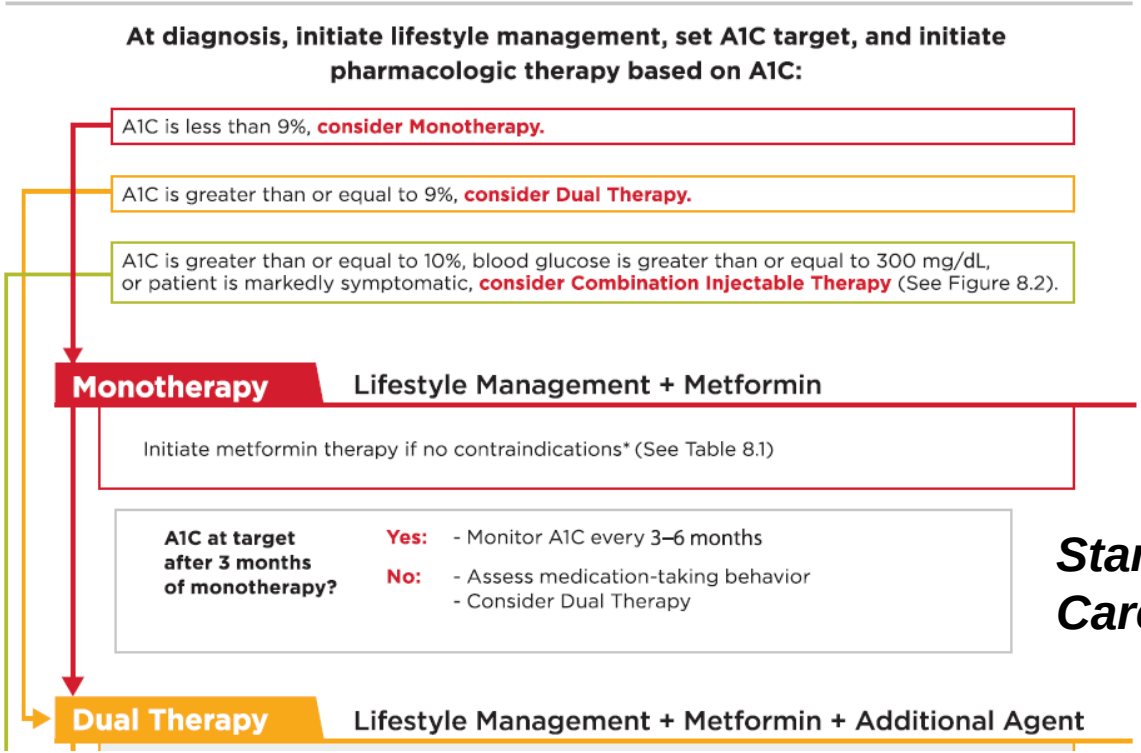
- Efficacy
- Hypo Risk
- Weight
- Side Effect
- Costs
- Cardiovascular effects
- Renal effects

Standards of Medical Care in Diabetes - 2018.

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — **Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — **Analogs**						High	SQ			

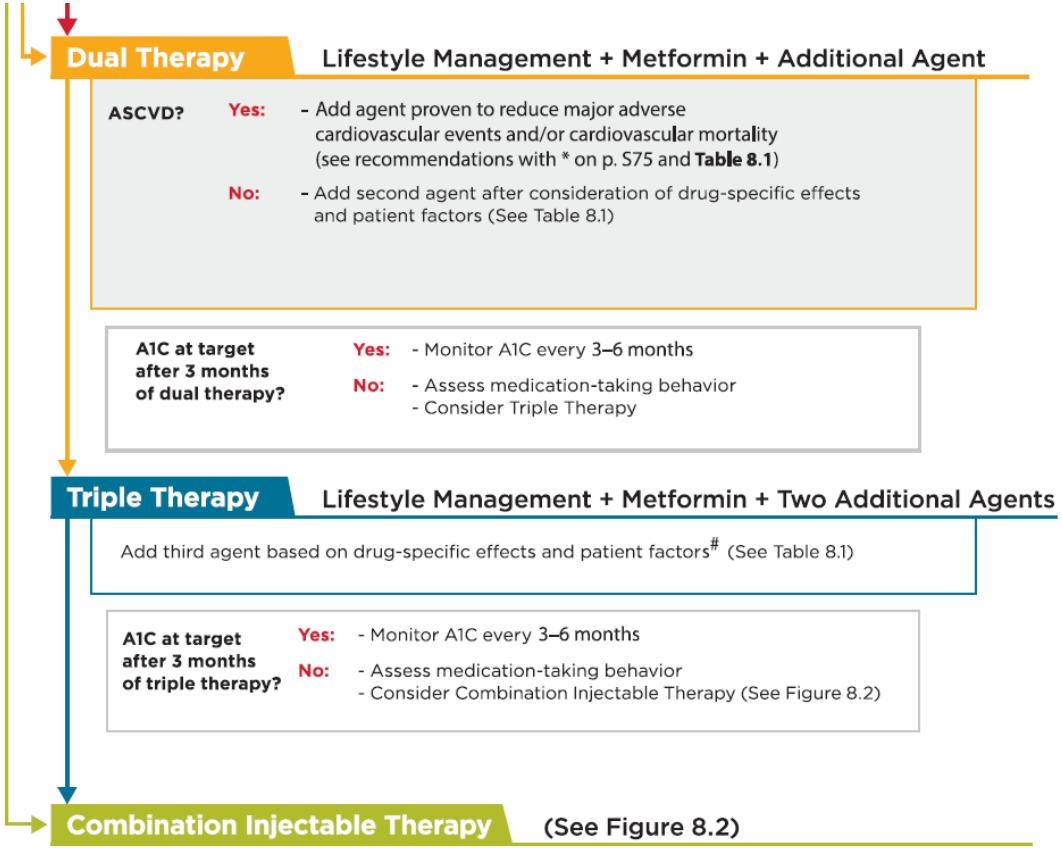
*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

Antihyperglycemic Therapy in Adults with T2DM



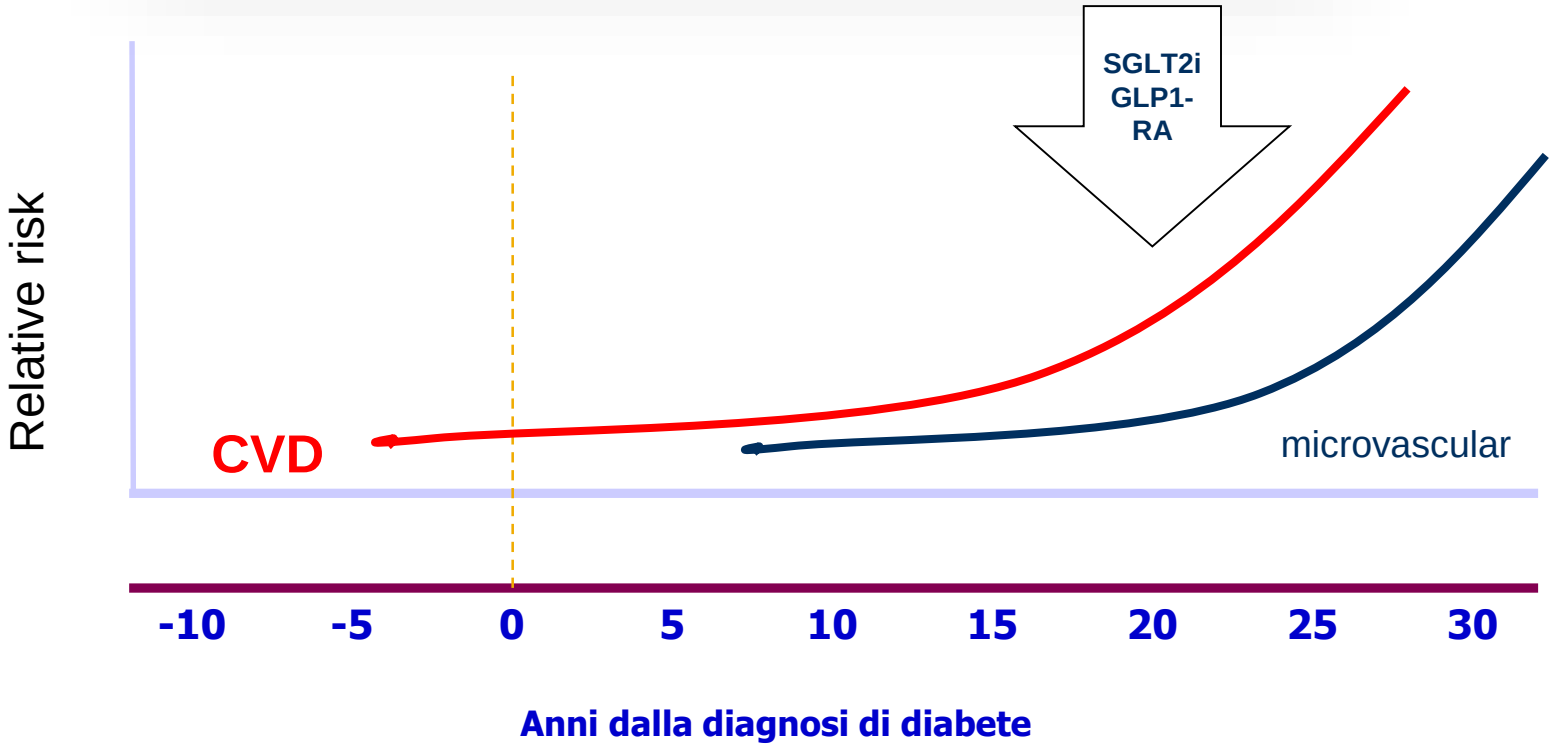
Standards of Medical Care in Diabetes - 2018.

Antihyperglycemic Therapy in Adults with T2DM

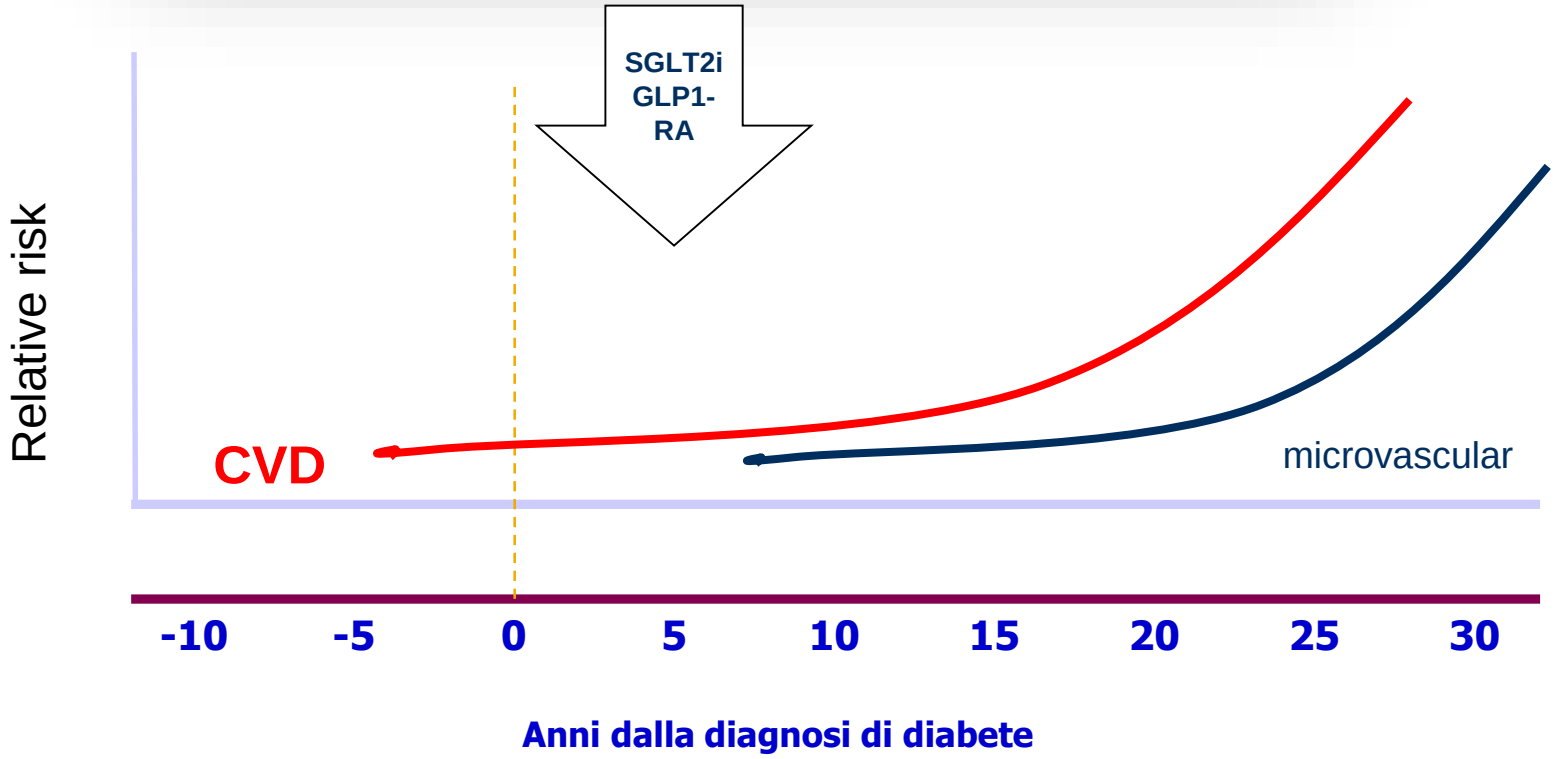


Standards of Medical Care in Diabetes - 2018.

T2DM – Changing Treatment Paradigm



T2DM – Changing Treatment Paradigm



Grazie per la vostra attenzione

conclusioni

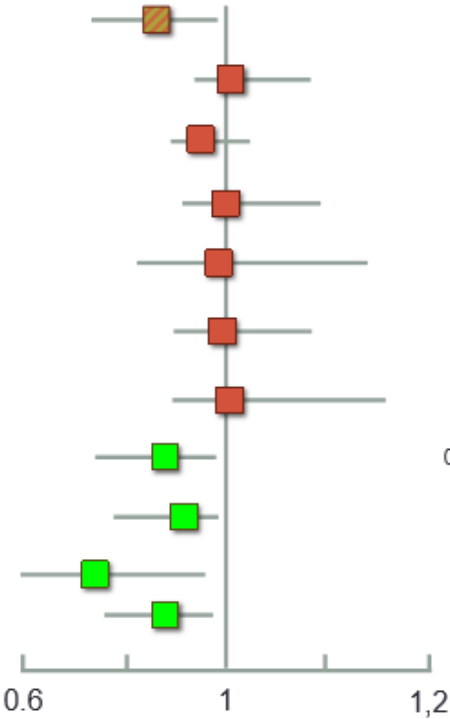
Sulla base dei risultati di studi recenti, l'uso di farmaci che hanno dimostrato di ridurre le complicanze cardiovascolari dovrebbe essere prioritario nei pazienti con CVD accertata

Algoritmi attuali basati principalmente sui valori di HbA1c dovrebbero spostarsi verso **un nuovo paradigma** che valuta il rischio CV dei pazienti e l’uso di farmaci ipoglicemizzanti capaci di ridurre il rischio CVD.

Pharmacologic Approaches to Glycemic Treatment
Newrecommendationsforantihyperglycemictherapyforadultswitht ype2diabetes have been added to reflect recent cardiovascular outcomes trial (CVOT) data, indicating that people with atherosclerotic cardiovascular disease (ASCVD) should beginwithlifestylemanagementandmetformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and/or cardiovascularmortalityafterconsideringdrug-specific and patient factors.

Effect of Glucose-Lowering Drugs on 3-Point MACE* in T2DM Patients

Study	Year	Glucose-lowering drug	HR	95% CI	*P*-value
PROACTIVE	2005	Pioglitazone	0.84	0.72 - 0.98	0.02
ORIGIN	2012	Insulin glargine	1.02	0.94 - 1.11	NS
DEVOTE	2017	Insulin degludec	0.91	0.78 - 1.06	NS
SAVOR	2013	Saxagliptin	1.00	0.89 - 1.12	NS
EXAMINE	2013	Alogliptin	0.96	0.80 - 1.15	NS
TECOS	2015	Sitagliptin	0.98	0.89 - 1.08	NS
ELIXA	2015	Lixisenatide	1.02	0.89 - 1.17	NS
EMPA-REG	2015	Empagliflozin	0.86	0.74 - 0.99	0.038
LEADER	2016	Liraglutide	0.87	0.78 - 0.97	0.01
SUSTAIN-6	2016	Semaglutide	0.74	0.58 - 0.95	0.02
CANVAS	2017	Canagliflozin	0.86	0.75 - 0.97	

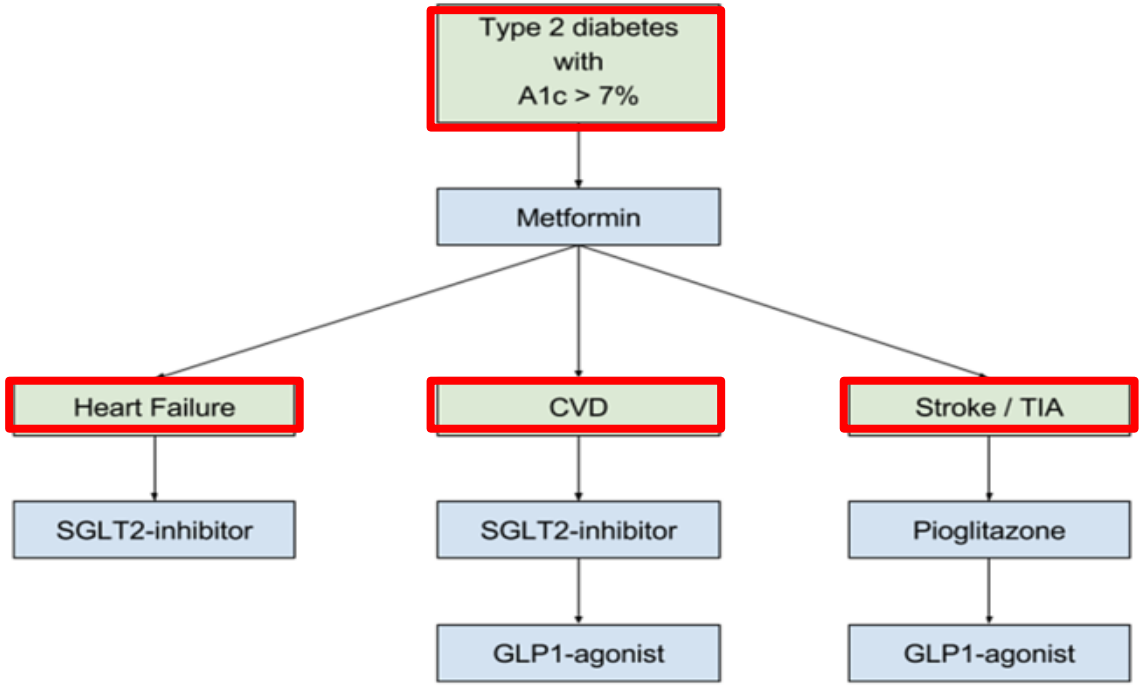


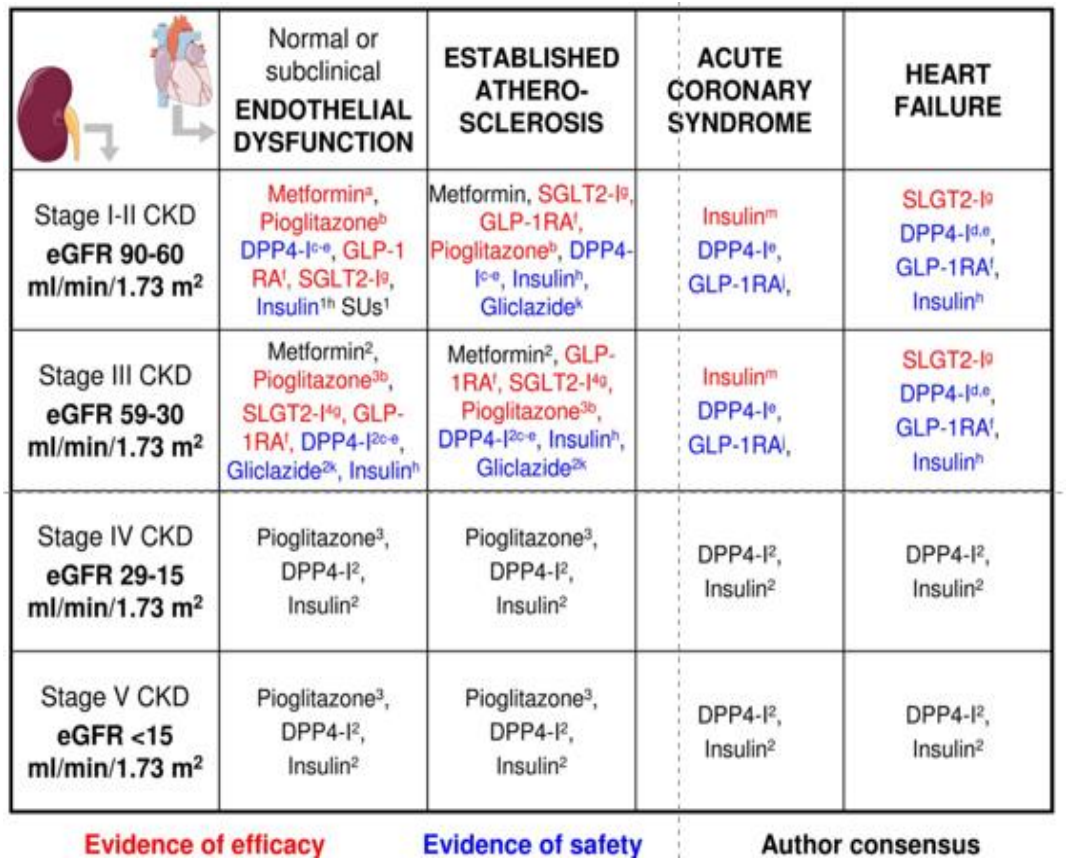
conclucions

- Based on the results of recent trials, the use of medications now proven to reduce CV complications should be prioritized in patients with established CVD

- Current algorithms for the management of type 2 diabetes based primarily on HbA1c values ought to shift towards a new paradigm that incorporates patients' CV risk and their likelihood of realizing a CVD benefit into the glucose-lowering drug selection process.

Algoritmo «treat to benefit»





	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[f],	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[f],	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**

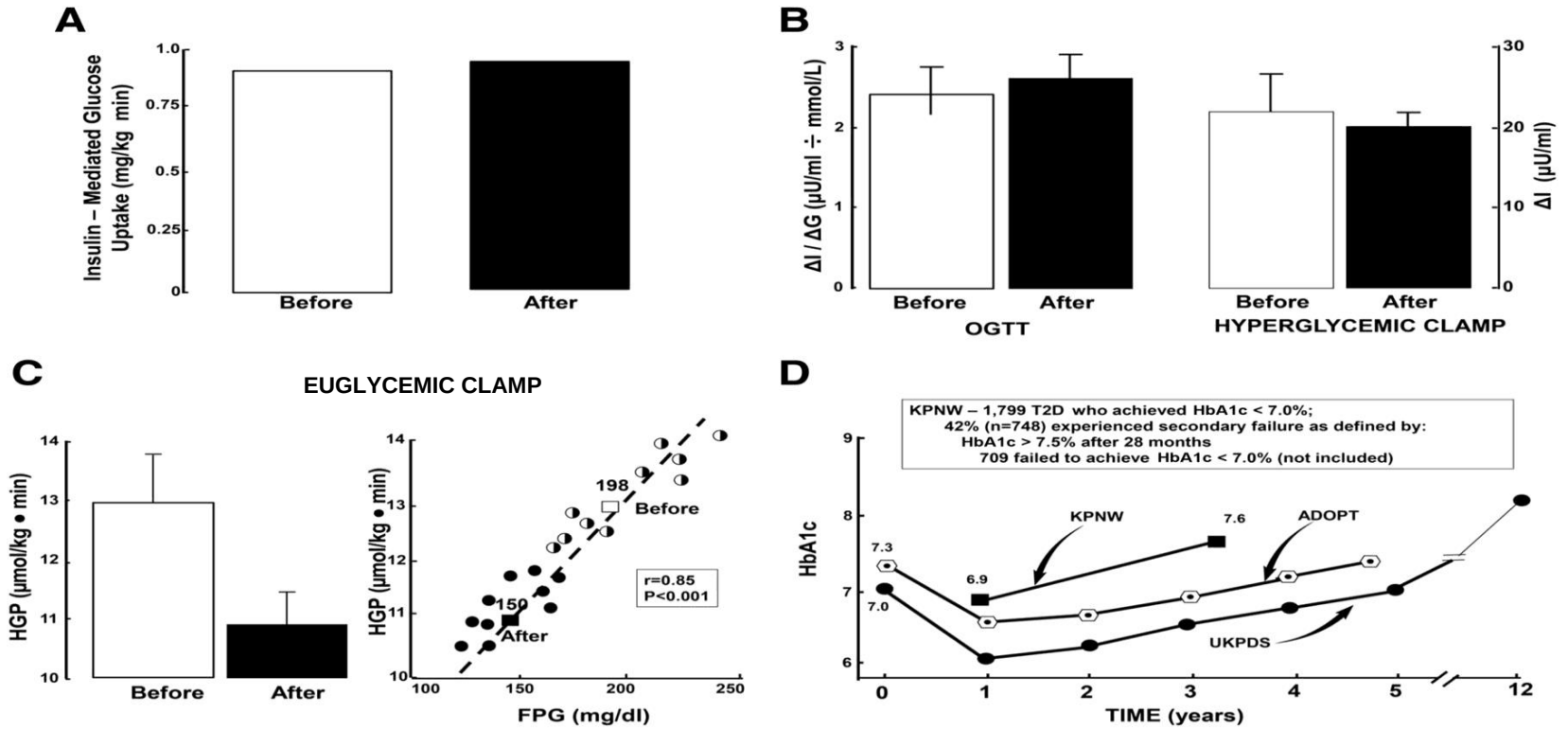
«Patient's phenotype, degree of renal function, presence of heart failure, allows for a further patient's population breakdown for more appropriate pharmacologic treatment selection"

Avogaro et al *Cardiovasc Diabetol (2016)*

Personalizzazione del trattamento nel diabete di tipo 2

- Con rare eccezioni, trattiamo tutti i pazienti con diabete di tipo 2 allo stesso modo
- Enorme mancanza di comprensione per quanto riguarda le differenze interindividuali nella risposta alle terapie
  - Pochi studi di confronto diretto (testa a testa)
  - Inadeguato fenotipo / genotipo
  - Anche quando eseguita la fenotipizzazione / genotipizzazione, non ci sono outcomes analizzati in base alle differenze di popolazione
- Probabile eterogeneità nelle risposte alle terapie
- Potenziali conseguenze cliniche ed economiche in individualizzazione della terapia

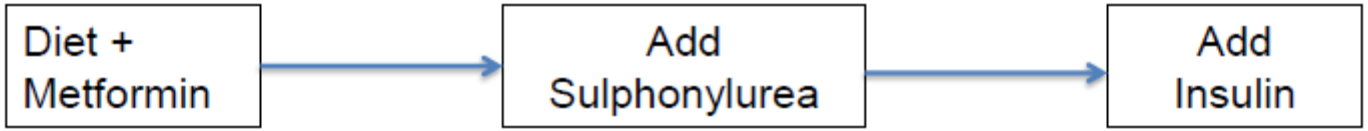
Effect of metformin on glycemic control, insulin secretion, and insulin sensitivity in T2D.



Muhammad Abdul-Ghani, and Ralph A. DeFronzo Dia Care 2017;40:1121-1127

American Diabetes Association.

Glycaemia treatment paradigm for Type 2 diabetes ca. 1997



NB Driven by glycaemic severity, not by subtype