Le terapie di associazione: vantaggi e limiti

Edoardo Mannucci

23 giugno 2018

Conflitti di interessi

Negli ultimi due anni, E. Mannucci ha ricevuto compensi per relazioni e/o consulenze da:
Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, and Takeda.

La struttura diretta da E. Mannucci ha ricevuto donazioni, finanziamenti per ricerca o compensi per trial clinici da:
AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, and Novo Nordisk.

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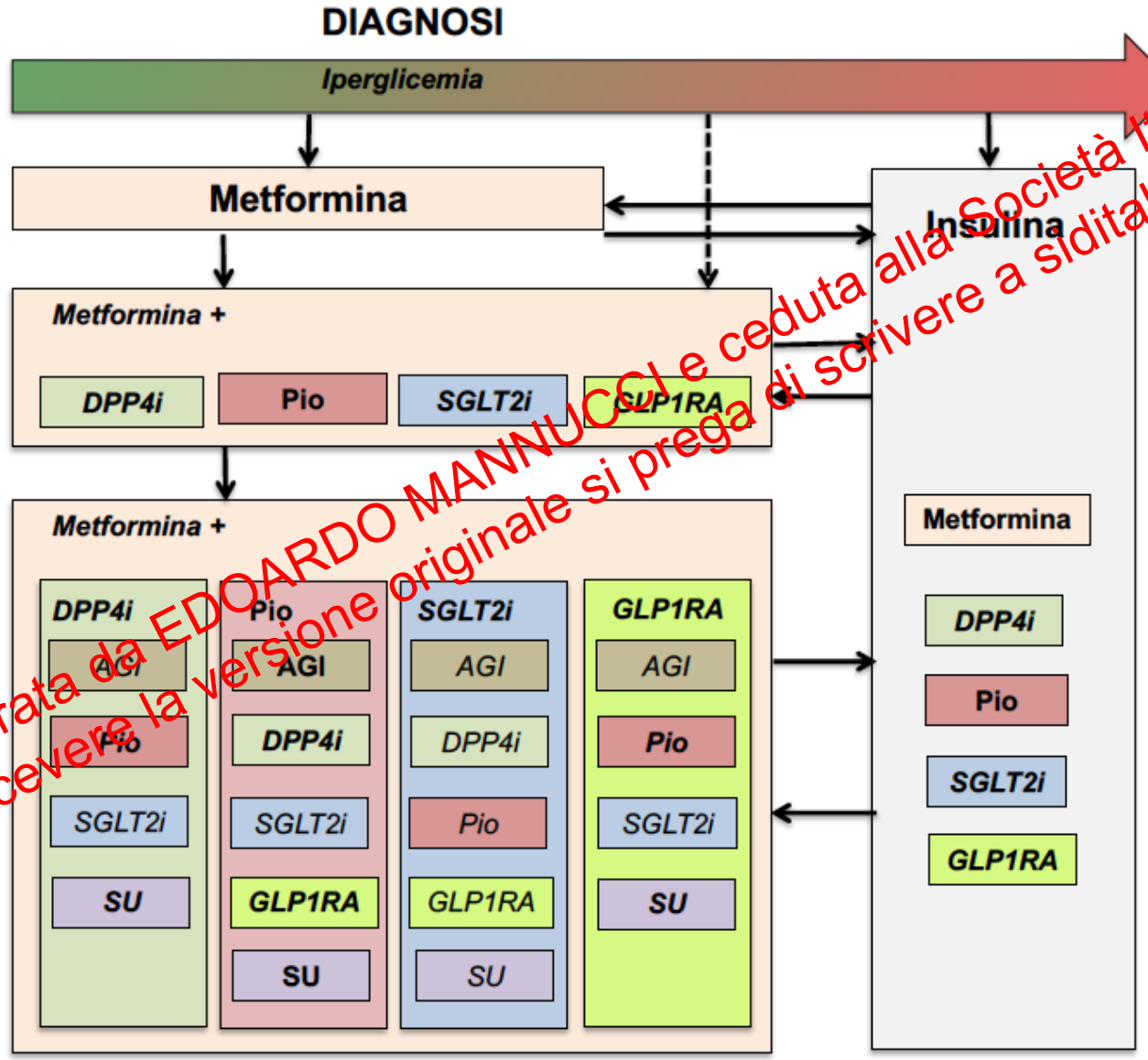

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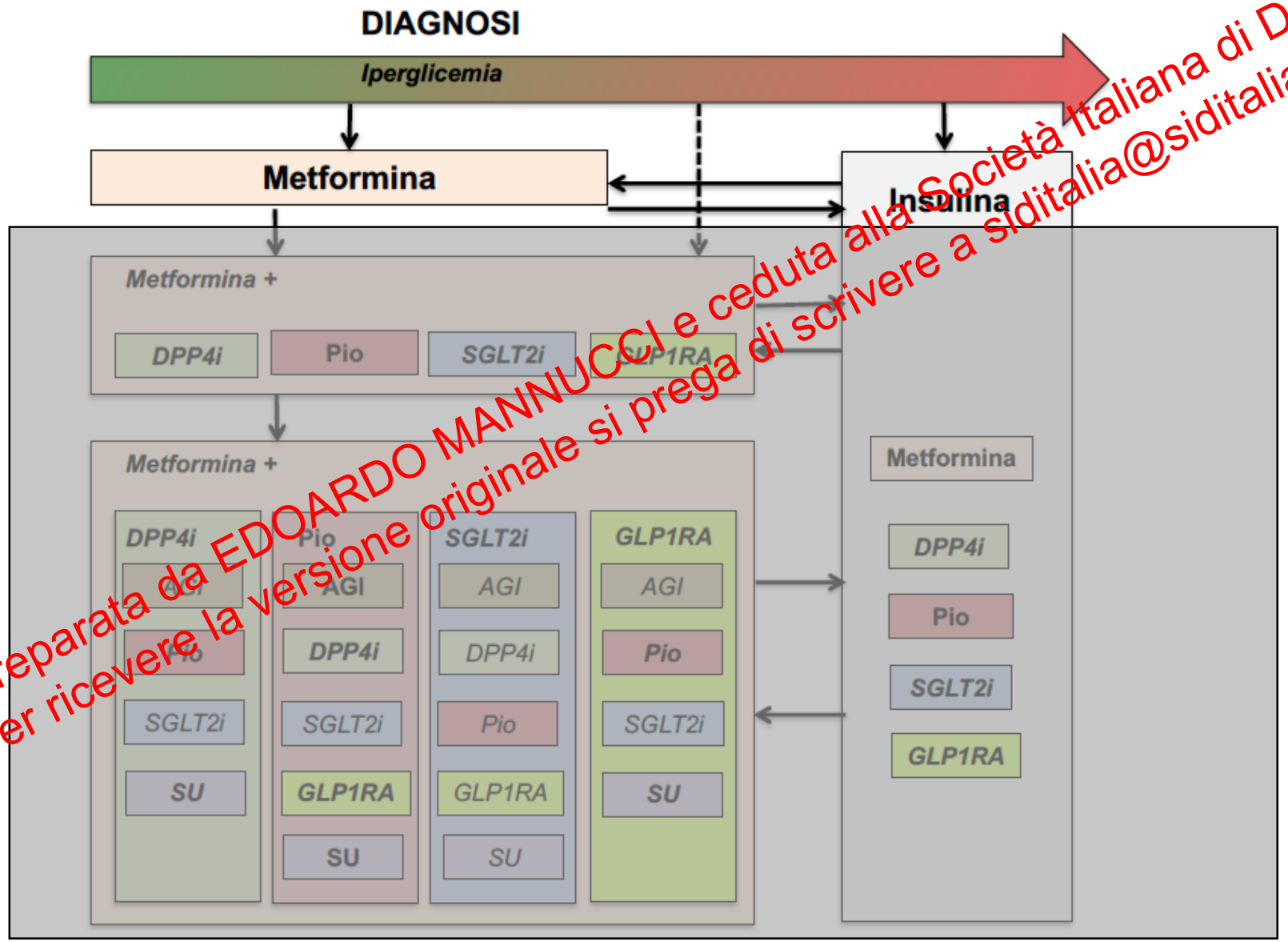

Pre-requisites for combination therapy

- Different mechanisms of action

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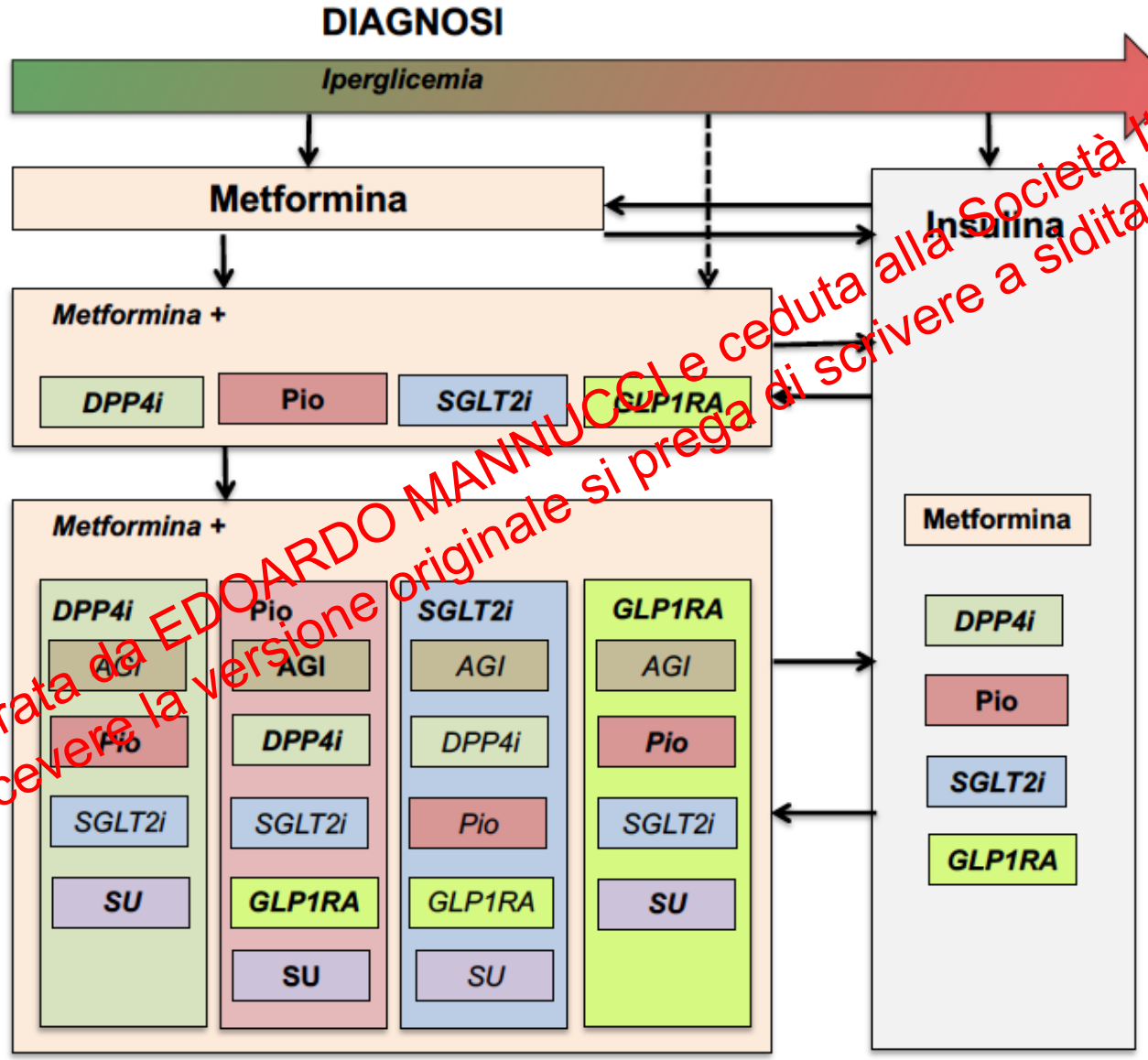


Exenatide LAR: effect on major cardiovascular events

Results of the EXSCEL trial

Subgroup	Exenatide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Antihyperglycemic oral agent therapy				0.37
Yes	660/6213 (10.6)	703/6278 (11.2)	0.93 (0.84–1.04)	
No	179/1143 (15.7)	202/1118 (18.1)	0.84 (0.69–1.03)	
Insulin therapy				0.45
Yes	467/3397 (13.7)	519/3439 (15.1)	0.89 (0.78–1.00)	
No	372/3959 (9.4)	386/3957 (9.8)	0.95 (0.83–1.10)	
DPP-4 inhibitor therapy				0.17
Yes	126/1118 (11.3)	113/1085 (10.4)	1.08 (0.84–1.39)	
No	713/6238 (11.4)	792/6311 (12.5)	0.89 (0.80–0.99)	

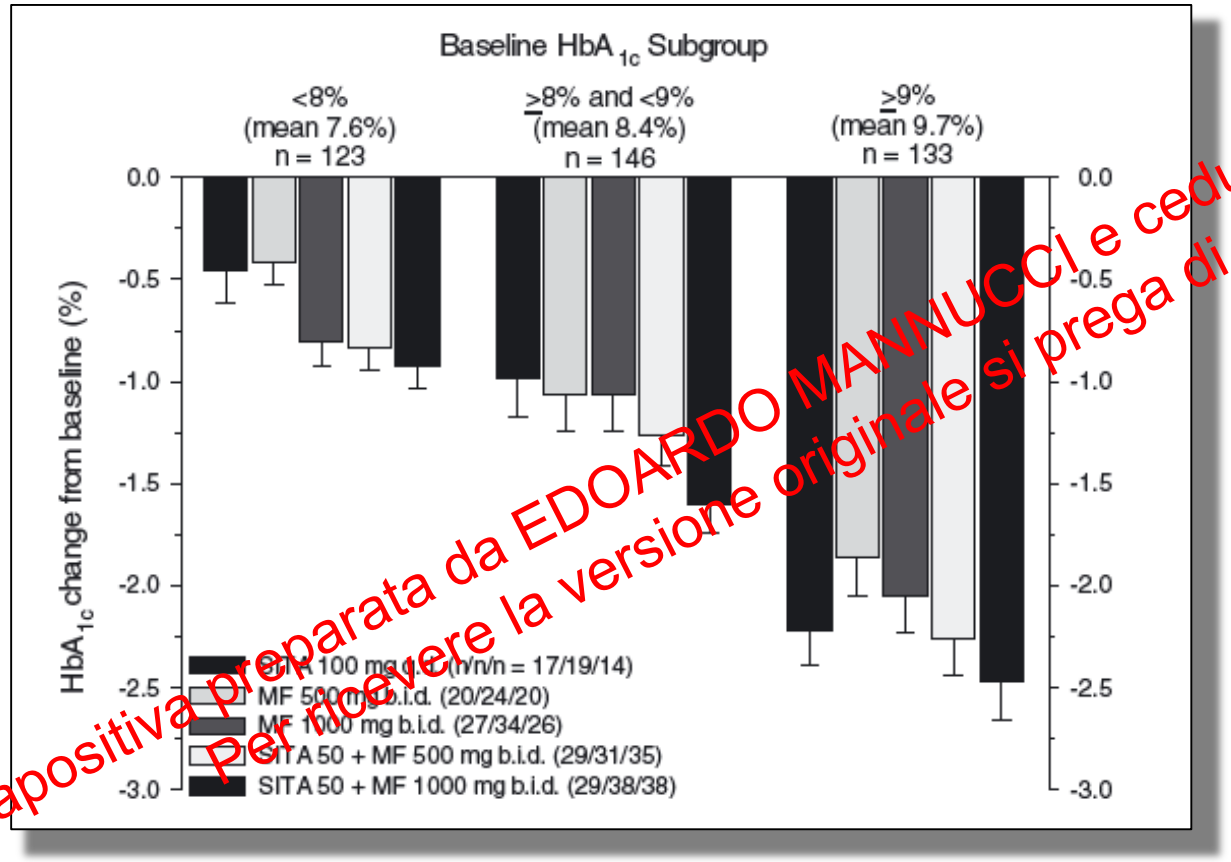
Holman RR et al. *N Engl J Med* 377: 1228-39, 2016

Pre-requisites for combination therapy

- Different mechanisms of action
- Additive/synergistic effects

Effects of sitaglitpin and metformin on HbA1c

Results of a RCT, initial therapy



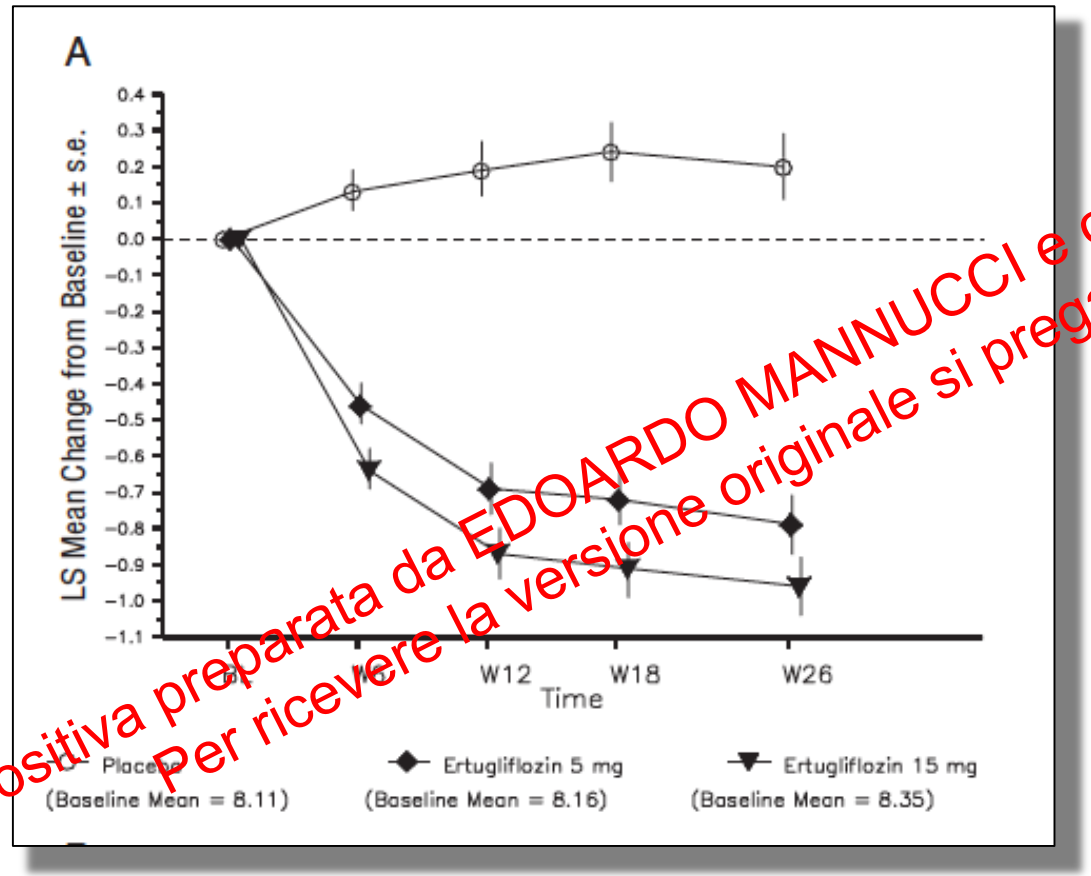
Principal endpoint:
HbA1c

T2DM patients
Ertugliflozin vs placebo, 104 wk

Williams-Herman D, et al. *Diabetes Obes Metab* 12:442-51, 2010.

Effects of ertugliflozin on HbA1c

Results of a RCT, monotherapy



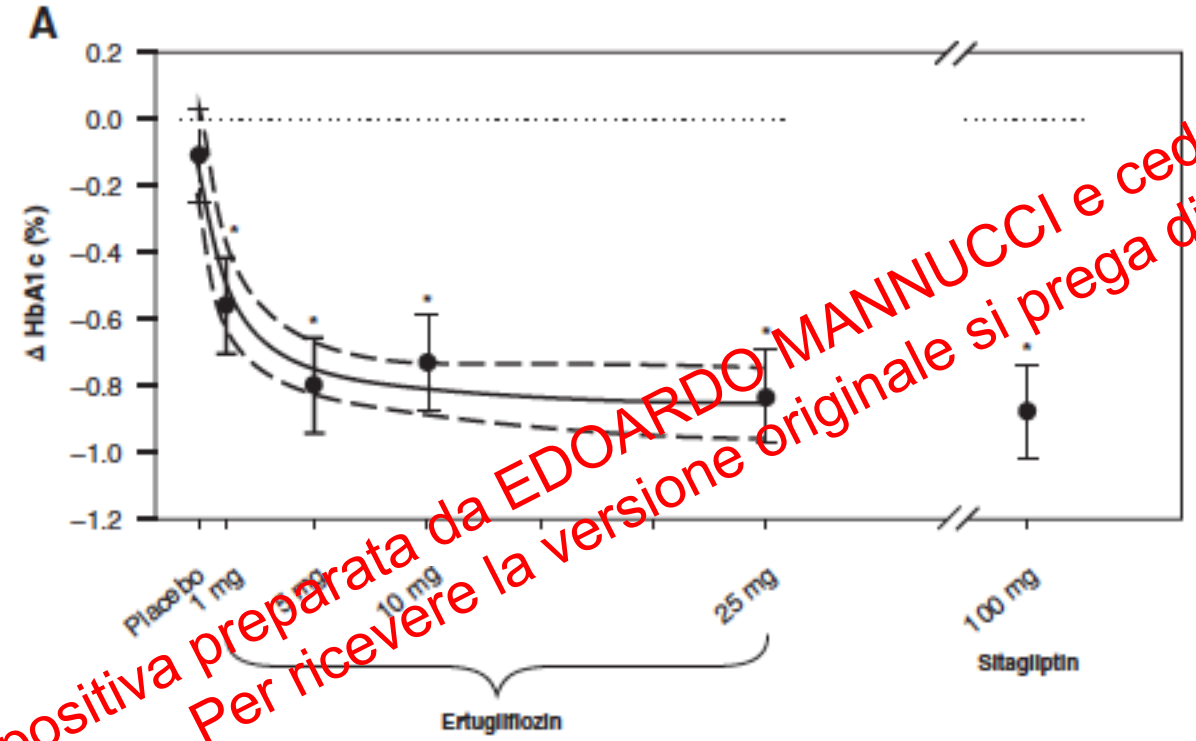
Principal endpoint:
HbA1c

461 T2DM patients
Ertugliflozin vs placebo, 26 wk
Baseline HbA1c: 8.2%

Terra SG, et al. *Diabetes Obes Metab* 19:721-8, 2017.

Effect of ertugliflozin on HbA1c

Dose-ranging study, add-on to metformin



Principal endpoint:
HbA1c

Dose-randing study,
ertugliflozin vs placebo,
add-on to metformin, 12 wk.
Baseline HbA1c: 8.2%

Amin NB, et al. *Diabetes Obes Metab* 17:591-98, 2015.

Myths about combination therapy

- Two drugs with different mechanisms of action have synergistic effects

Myths about combination therapy

- Two drugs with different mechanisms of action have synergistic effects
- Treatment with two drugs at low dose has the same efficacy and a greater tolerability of a full-dose monotherapy

Pre-requisites for combination therapy

- Different mechanisms of action
- Additive/synergistic effects
- Absence of negative pharmacocynetic/pharmacodynamic interactions

Pre-requisites for combination therapy

- Different mechanisms of action
- Additive/synergistic effects
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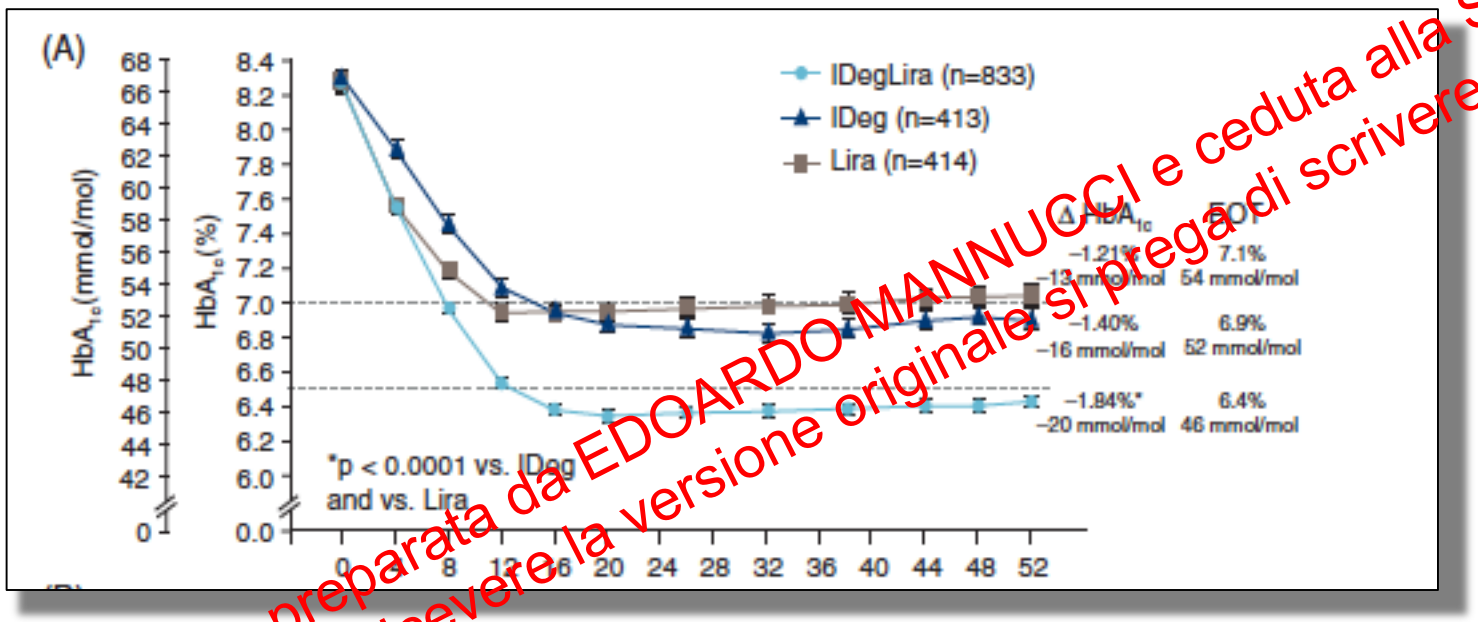
In addition, for fixed-dose combinations:

- Same route of administration
- No need for dose titration

IDegLira vs liraglutide and degludec: effects on HbA1c

Results of a RCT, add-on to metformin



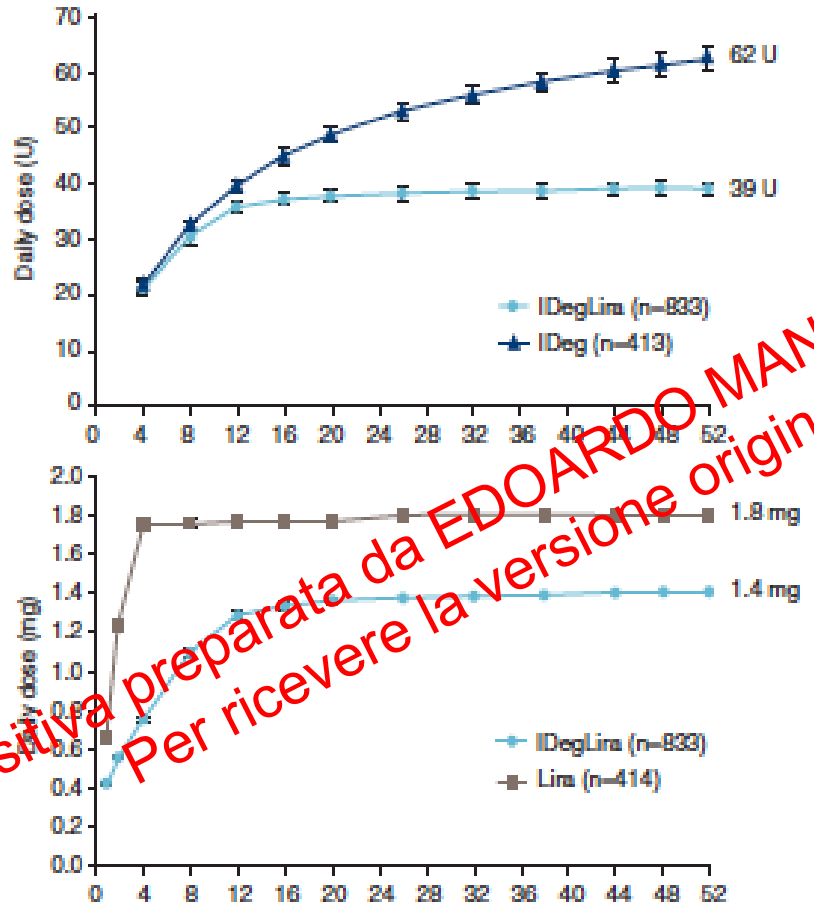
Principal endpoint:
HbA1c

1661 T2DM patients

Gough SCL, et al. *Diabetes Obes Metab* 17:965-73, 2015.

IDegLira vs liraglutide and degludec: insulin and liraglutide doses

Results of a RCT, add-on to metformin



Principal endpoint:
HbA1c

1661 T2DM patients

Gough SCL, et al. *Diabetes Obes Metab* 17:965-73, 2015.

Advantages of fixed-dose combinations

- Simpler dosing schedule
- Compliance/adherence
- Lower price

Available oral fixed-dose combinations

- Metformin + low-dose SU
- Metformin + DPP4i
- Metformin + SGLT2i
- Metformin + piogitazone
- DPP4i + piogitazone
- DPP4i + SU
- DPP4i + SGLT2i

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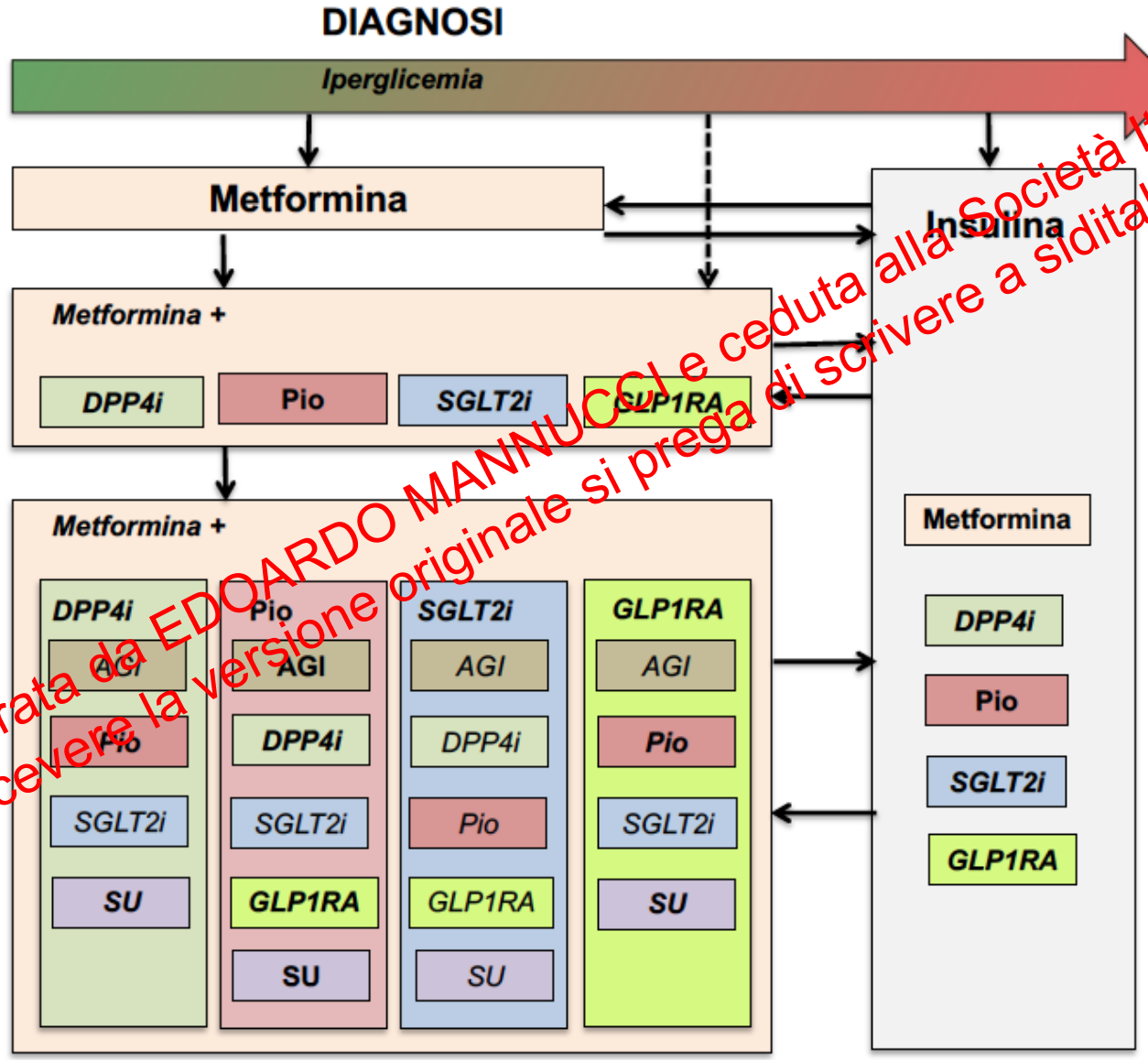
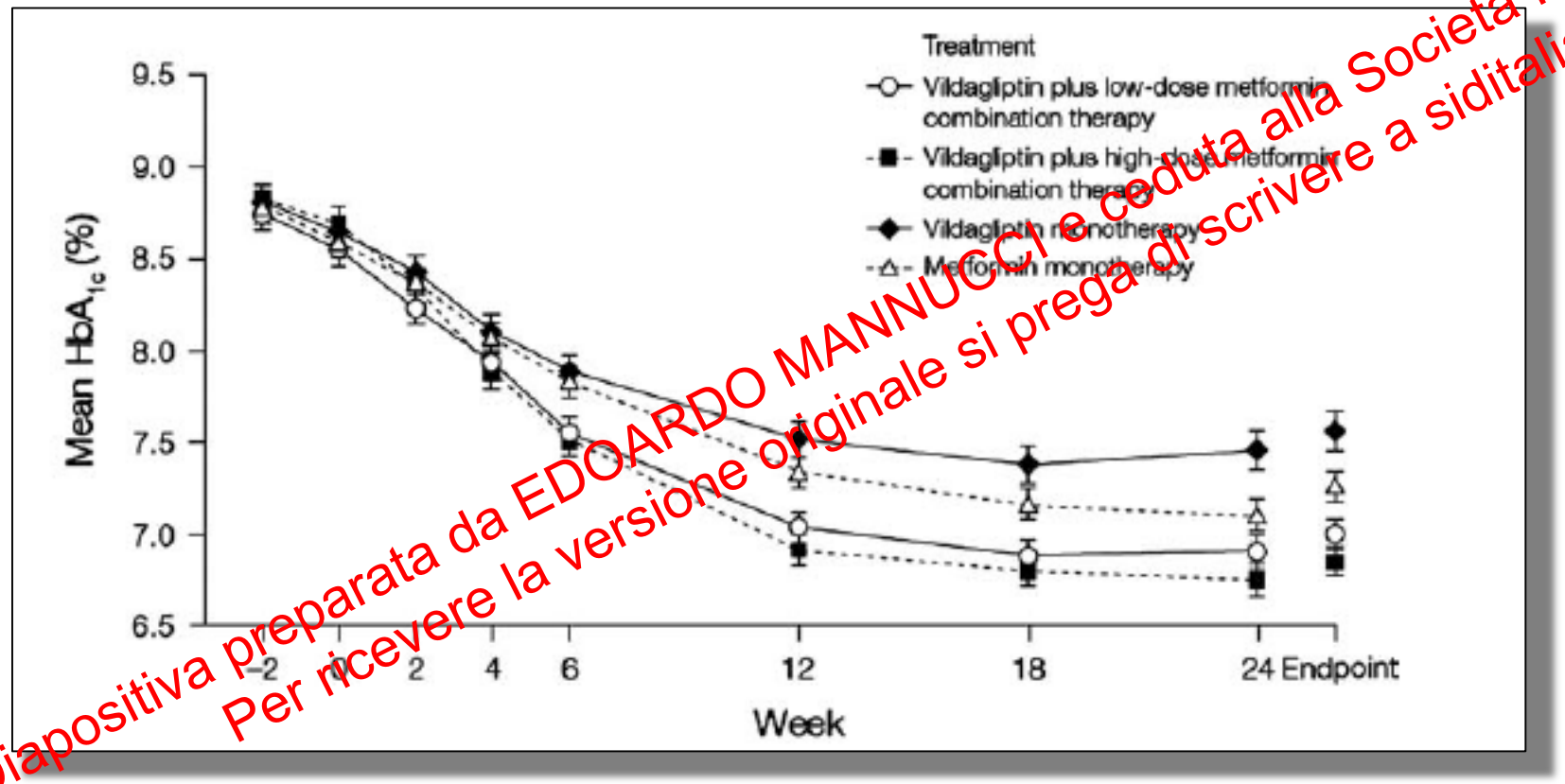


Initial combination therapy with vildagliptin and metformin

Results of a RCT



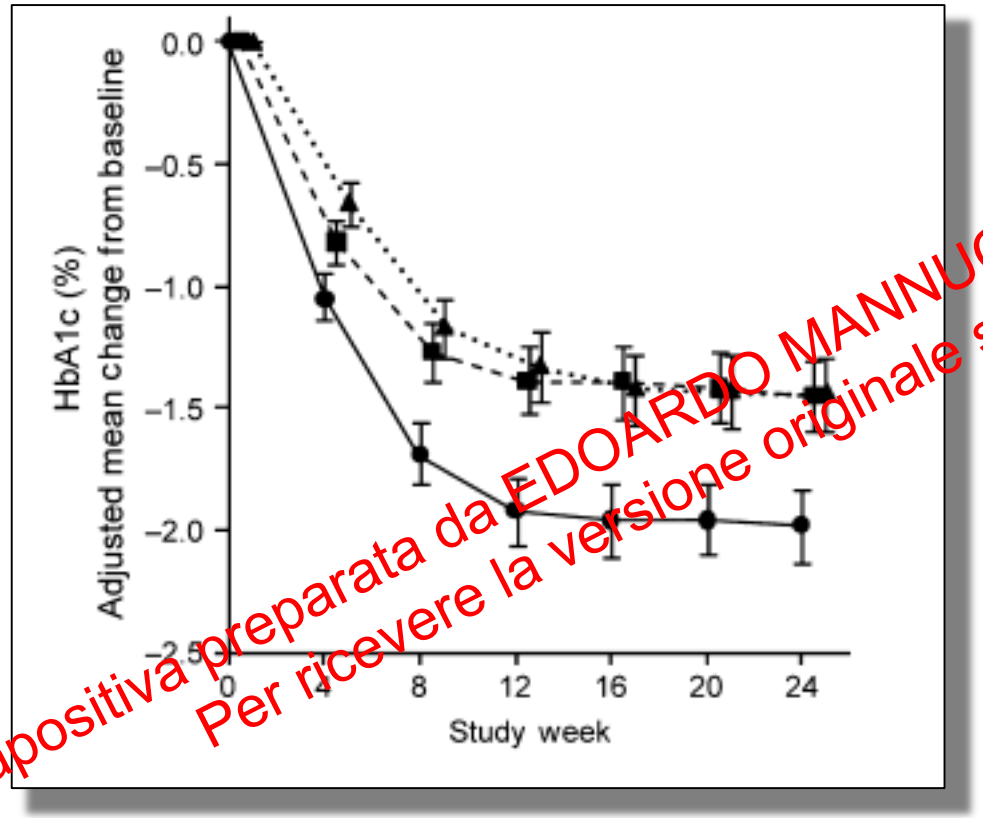
Principal endpoint:
HbA1c

1179 patients with T2DM

Bosi E, et al. *Diabetes Obes Metab* 11:506-15, 2019.

Initial combination therapy with dapagliflozin and metformin

Results of a RCT



Principal endpoint:
HbA1c

638 patients with T2DM;
Baseline HbA1c 9.1%

Henry RR, et al. *Int J Clin Pract* 66:446-56, 2012.

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Il farmaco di prima scelta per il trattamento dei soggetti con diabete tipo 2 è la metformina. **I A**

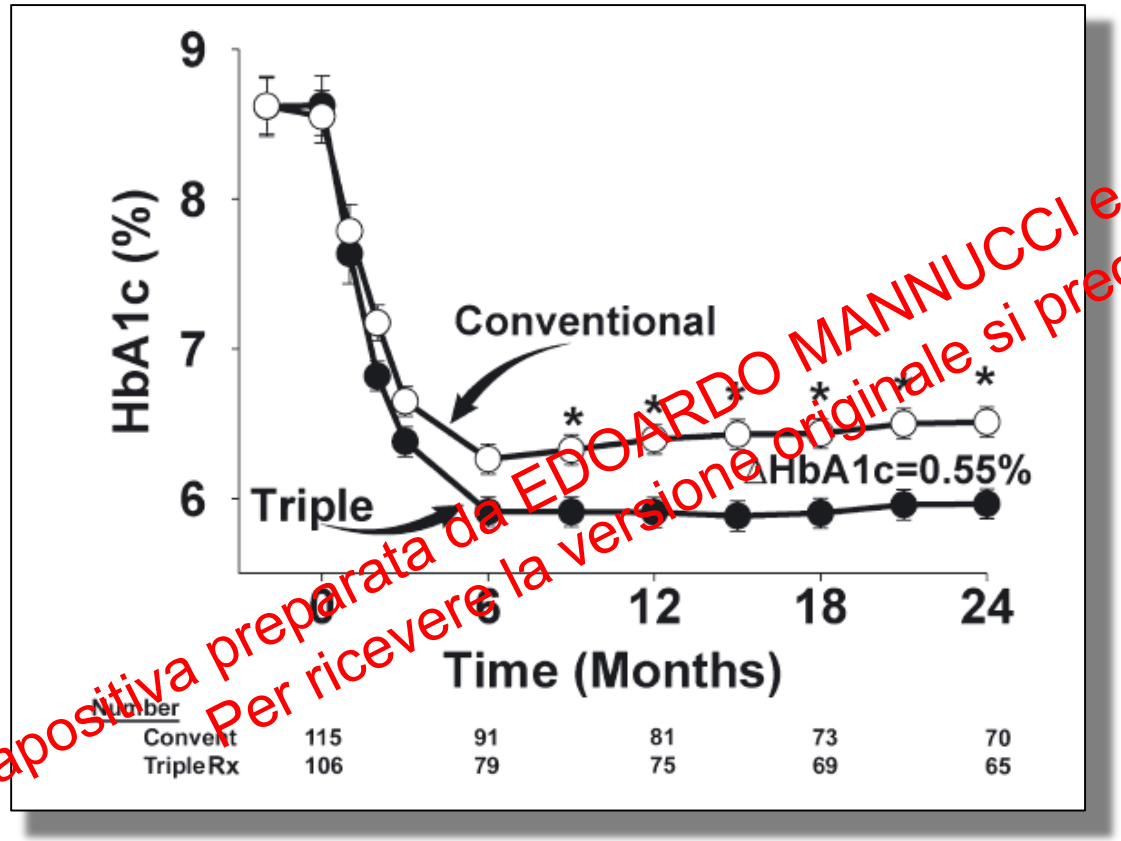
In caso di marcato scompenso glicometabolico o presenza di sintomi specifici del diabete, anche nel paziente non precedentemente trattato con farmaci si può prendere in considerazione sin dall'inizio la terapia con metformina da subito associata a un'altra molecola. **I B**

Which patients should start with double therapy?

- Higher HbA1c
- Lower BMI?
- More regular eating and exercise habits?

Initial triple combination with metformin, pioglitazone and exenatide

Results of a RCT



Principal endpoint:
HbA1c

249 patients with T2DM;
Baseline HbA1c 8.6%

Triple: Metformin+pioglitazone+exenatide
Conventional:
- Metformin
- If failure, add SU
- If failure, add insulin

Abdul-Ghani RR, et al. *Diabetes Obes Metab* 17:268-75, 2015.