I limiti dei trial randomizzati in diabetologia

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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.

Cardiovascular risk with insulin therapy in T2DM

Observational studies vs RCT

Study [Ref.]	Comparator/Reference	HR [95% CI]	
		Major CV events	All-cause mortality
Observational studies			
Currie et al. 2010[1]	Oral agents	1.31 [1.22-1.42]	1.46 [1.34-1.59]
Vallarino et al. 2013[2]	Pioglitazone	2.27 [2.00-2.56]	NR
Roumie et al. 2014[3]	Sulfonylureas	1.30 [1.07-1.58]	1.44 [1.15-1.79]
Nijjar et al. 2014[4]	No treatment	1.25 [1.13-1.39]	1.31 [1.17-1.42]
Paul et al. 2015[5]	Exenatide BID	2.00 [1.26-3.12]	NR
Randomized controlled trials			
DIGAMI 1997[19]	Conventional therapy	NR	0.72 [0.55-0.92]
UKPDS 1998[17]	Conventional therapy	0.90 [0.76-1.07]	0.87 [0.75-1.01]
	Sulfonylureas	0.96 [0.82-1.14]	1.01 [0.85-1.14]
ORIGIN 2012[20]	Placebo	1.02 [0.94-1.11]	0.98 [0.90-1.08]

Mannucci E, Ferrannini E. *Diabetes Obes Metab*, 2017.

Classification of evidence

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

Centre for Evidence-Based Medicine, http://www.cebm.net.

The limitations of randomized trials

- Selection of population: inclusion and exclusion criteria
- Selection of population: enrolment of hypercompliant, relatively healthy subjects

Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

From trials to real world: the case of DPP4 inhibitors

	Phase II-III	TECOS	AIFA
Age (y)	55	65	62
Duration DM (y)	5	12	9
BMI (kg/m^2)	31.1	30.2	30.8
HbA1c (%)	8.2	7.2	8.3
Insulin treatment (%)	3	23	0
Prior MACE (%)	16	100	--

Monami M, Ahrén B, Dicembrini I, Mannucci E. *Diabetes Obes Metab* 15:112-20, 2013
Green JB et al. *N Engl J Med* 373: 232-242, 2015
Montilla S et al. *Nutr Metab Cardiovasc Dis* 24:1346-53, 2014

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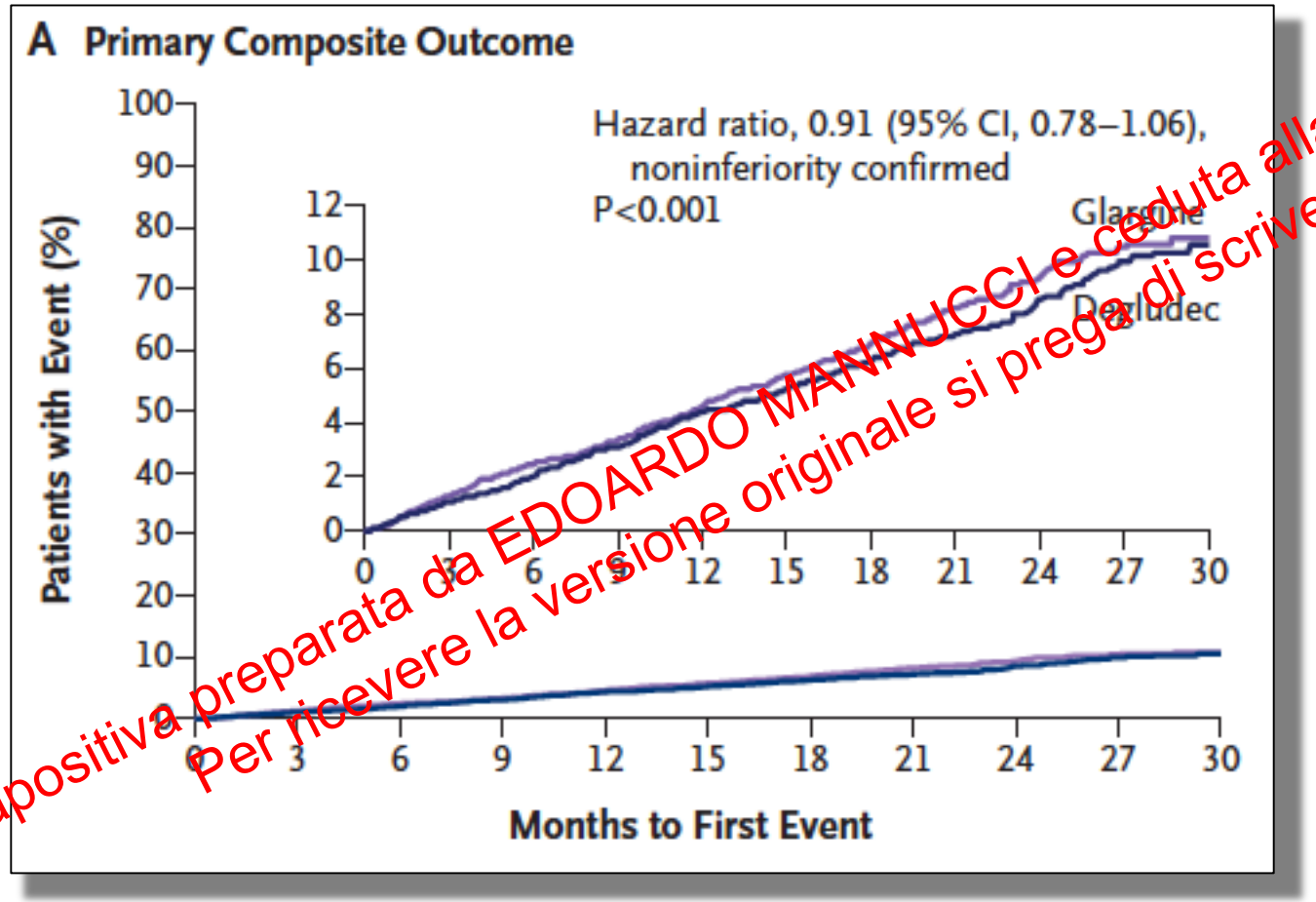
Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

Degludec: effect on major cardiovascular events

Results of the DEVOTE trial



Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

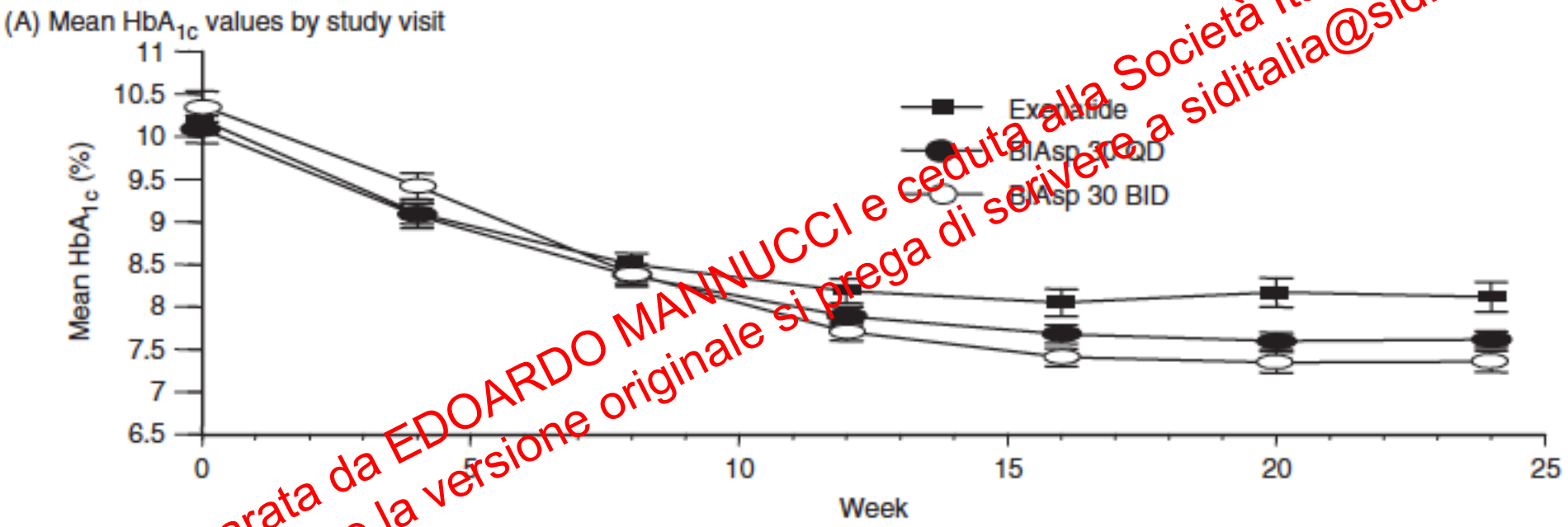
7,637 T2DM patients with prior cardiovascular disease and/or high CV risk, degludec vs glargine U-100 1:1. Follow-up: 2 y

Mean basal insulin dose on trial:
0.6 IU/kg*day

Marso SP et al. *N Engl J Med* 377: 723-32, 2017

Exenatide bid vs aspart 30/70 premix: comparison of efficacy

Results of a randomized trial

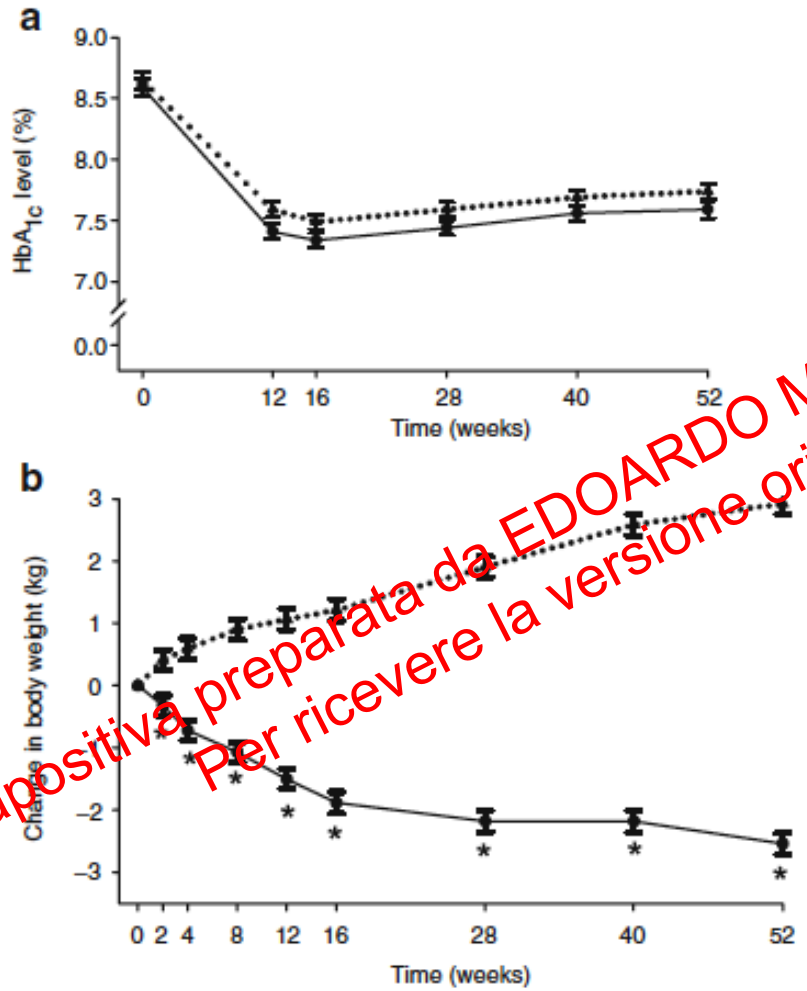


Principal endpoint: HbA1c at 26 wk
Patients: 372 T2DM failing to metformin + SU
Treatments: Exenatide bid, BiAsp 30 OADm BiAsp 30 bid – all add-on to current treatment

Bergenstal R et al. *Curr Med Res Opin* 25:65-75, 2009

Exenatide bid vs aspart 30/70 premix: comparison of efficacy

Results of a randomized trial



Principal endpoint: HbA1c at 52 wk

Patients: 501 T2DM failing to combined metformin + SU

Treatments: Exenatide bid vs BiAsp 30 bid – both add-on to current treatment

Nauck MA et al. *Diabetologia* 50:259-67, 2007

Exenatide bid vs aspart 30/70 premix: comparison of efficacy

Methods of two randomized trials

FBG and/or pre-supper SMBG (mg/dL) PG value	Adjustment
< 90	−2 U
90–110	No adjustment
111–140	+2 U
141–180	+4 U
> 180	+6 U

Bergenstal R et al. *Curr Med Res Opin* 25:65-75, 2009

A forced titration schedule was not used in this trial. Investigators were instructed to adjust insulin doses to achieve an optimal balance between glycaemic control and risk of hypoglycaemia as dictated by best clinical practice. The decision to adjust insulin therapy, and the mode of patient empowerment to self-adjust insulin doses, was ultimately left up to each investigator's clinical judgement.

Nauck MA et al. *Diabetologia* 50:259-67, 2007

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- Specific setting: frequency of visits, recalls, etc.
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Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

Exenatide LAR: effect on pancreatitis

Results of the EXSCEL trial

Event	Exenatide (N=7344)	Placebo (N=7332)
Events of clinical interest		
Adjudicated pancreatitis‡		
Patients with event — no. (%)	26 (0.4)	22 (0.3)
Severity of event — no. of patients (%)		
Mild	24 (0.3)	20 (0.3)
Severe	2 (<0.1)	2 (<0.1)
Unknown	1 (<0.1)	0
First-event rate per 100 patient-years	0.11	0.09
No. of events	28	23
No. of events per patient		
1	24	21
2	2	1
≥3	0	0
Event rate per 100 patient-years	0.12	0.10

Power calculation:

Baseline incidence:
0.09 events/100 pty

Relevant increase
defined as HR 1.50

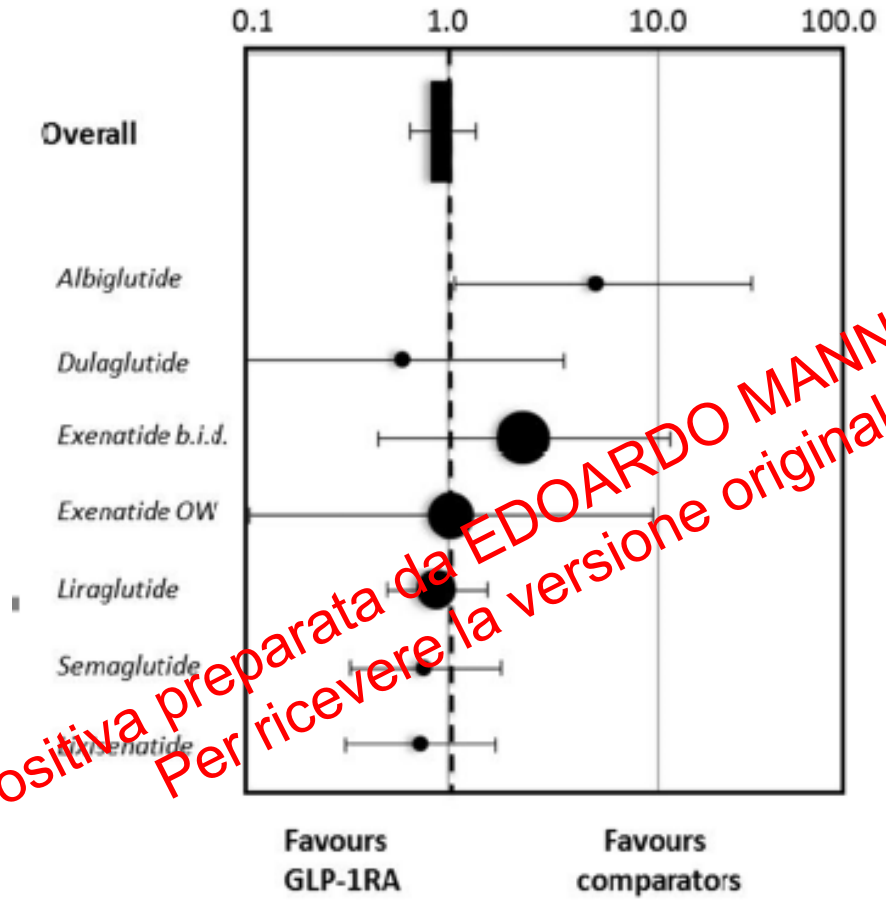
Power 80%, p<0.05

Sample size:
211,752

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

GLP1RA and pancreatitis

Meta-analysis of randomized trials



	N trials	MH-OR, 95% CI	p
Overall	*25*	*0.93*	*[0.79; 0.98]* *0.017*
Albiglutide	4	5.01	[1.06; 28.61] 0.040
Dulaglutide	4	0.60	[0.10; 3.57] 0.57
Exenatide b.i.d.	4	2.30	[0.46; 11.52] 0.31
Exenatide OW	2	1.03	[0.11; 9.39] 0.98
Liraglutide	8	0.87	[0.51; 1,51] 0.63
Semaglutide	1	0.75	[0.31; 1.78] 0.51
Lixisenatide	5	0.72	[0.32; 1.66] 0.45

Power calculation, post-hoc:

Relevant increase defined as HR 1.50

Power 80%, p<0.05

Power: **12%**

Monami M, Sesti G, Mannucci E, et al. *Diabetes Obes Metab* 19: 1223-41, 2017

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- Duration of trial (inadequate for effects with a long latency)

Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

Glargine insulin: effect on major cardiovascular events

Results of the ORIGIN trial

Table S4: Effect of Insulin Glargine vs. Standard Care on Cancer by Site

	HR (95%CI)	P	Insulin Glargine		Standard Care	
			N (%)	/100 p-y	N (%)	/100 p-y
Breast	1.01 (0.60, 1.71)	0.95	28 (0.4)	0.08	28 (0.4)	0.08
Lung	1.21 (0.87, 1.67)	0.27	80 (1.3)	0.22	66 (1.1)	0.18
Colon	1.09 (0.79, 1.51)	0.61	76 (1.2)	0.21	70 (1.1)	0.19
Prostate	0.94 (0.70, 1.26)	0.70	88 (2.1)	0.36	89 (2.2)	0.38
Melanoma	0.88 (0.44, 1.75)	0.71	15 (0.2)	0.04	17 (0.3)	0.05
Other	0.93 (0.80, 1.14)	0.59	233 (3.7)	0.64	245 (3.9)	0.67

ORIGIN trial investigators. *N Engl J Med* 367:319-28, 2012

Glargine and risk of breast cancer

Results of a retrospective cohort study on the UK CPRD Database

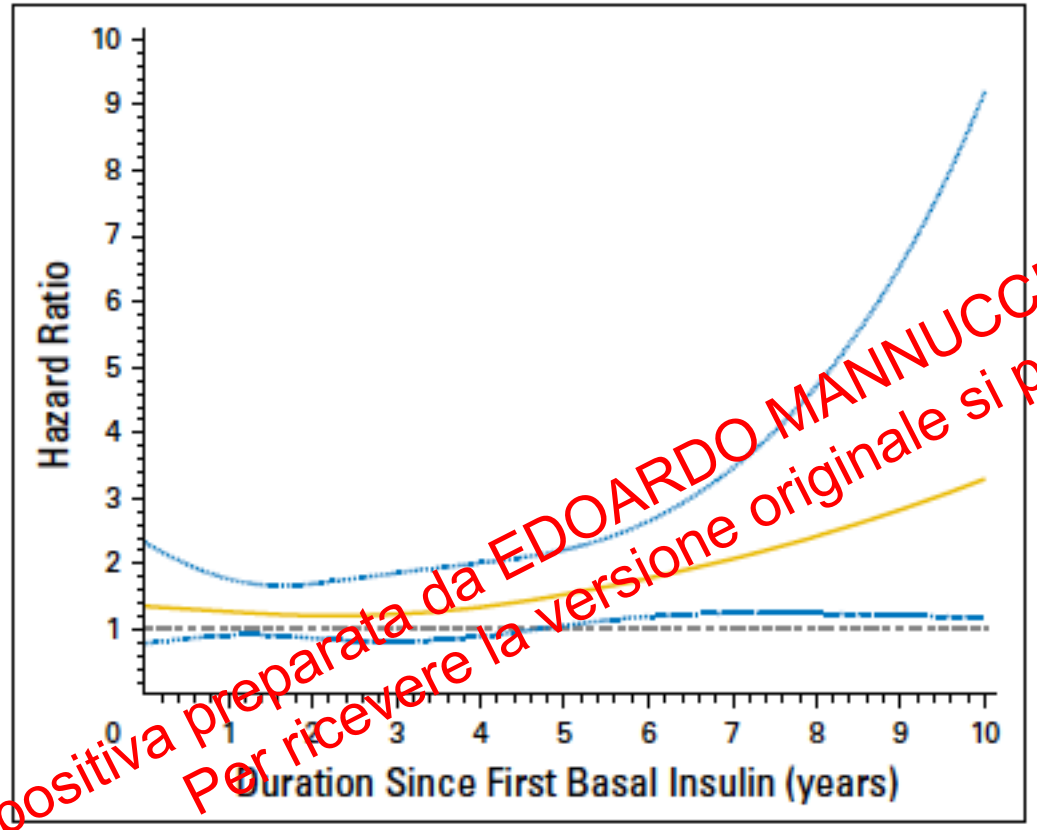


Fig 2. Restricted cubic splines of the adjusted hazard ratio (solid line) and 95% CIs (dotted lines) for breast cancer incidence as a function of duration since first insulin glargine prescription compared with neutral protamine Hagedorn in the entire cohort (gray dashed line represents the reference hazard ratio = value 1).

Risk of breast cancer, glargine vs NPH

Women aged>40 y using any basal insulin, in any combination.

HR adjusted for confounders (including prior and concurrent treatments, comorbidities, age, etc.)

Wu JW et al. *J Clin Oncol* 35:3647-53, 2017

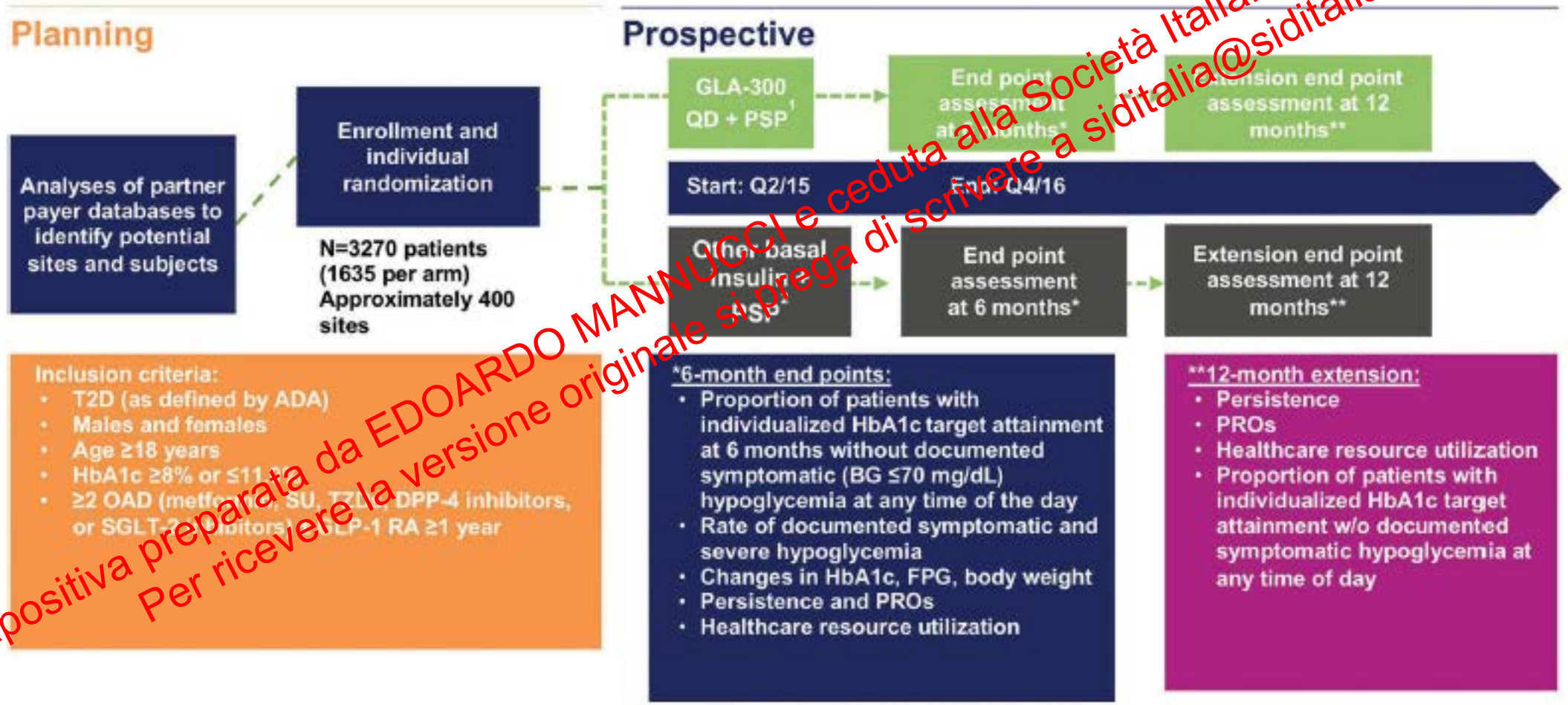
From trials to the real world: pragmatic trials

Randomized trials comparing two treatments, with:

- Inclusion criteria: indications
- Exclusion criteria: contraindications
- Procedures: the same as standard clinical practice

Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

Design of a pragmatic trial on glargine U-300



Oster G, et al. *Postgrad Med* 128:731-739, 2016

The limitations of randomized trials: pragmatic trials

- ✓ Selection of population: inclusion and exclusion criteria
- ✓ Selection of population: enrolment of hypercompliant, relatively healthy subjects
- ✓ Specific setting: frequency of visits, recalls, etc.
- ✓ Treatment schedules and dose titration different from routine practice
- ❑ Sample size (inadequate for rare adverse events)
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Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

What observational studies on drug treatments can say

- Verify the characteristics of patients receiving treatment
- Explore predictors of therapeutic response
- Extend results of available clinical trials to other populations
- Explore rare adverse events
- Explore adverse events with a very long latency (e.g., malignancies)
- Explore potential drug interactions
- Compare drugs within the same class (with similar profiles)

What observational studies on drug treatments cannot say

- Demonstrate efficacy on HbA1c
- Demonstrate efficacy in preventing cardiovascular disease
- Substitute randomised trials as a demonstration of cardiovascular safety