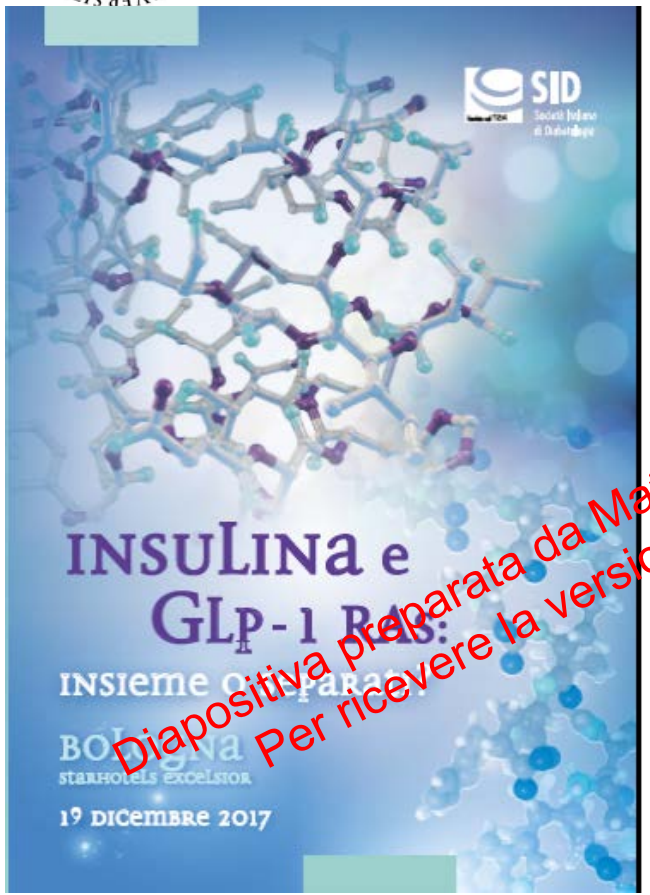
Bologna

19 Dicembre 2017



Vantaggi e limiti della terapia insulinica

Matteo Monami

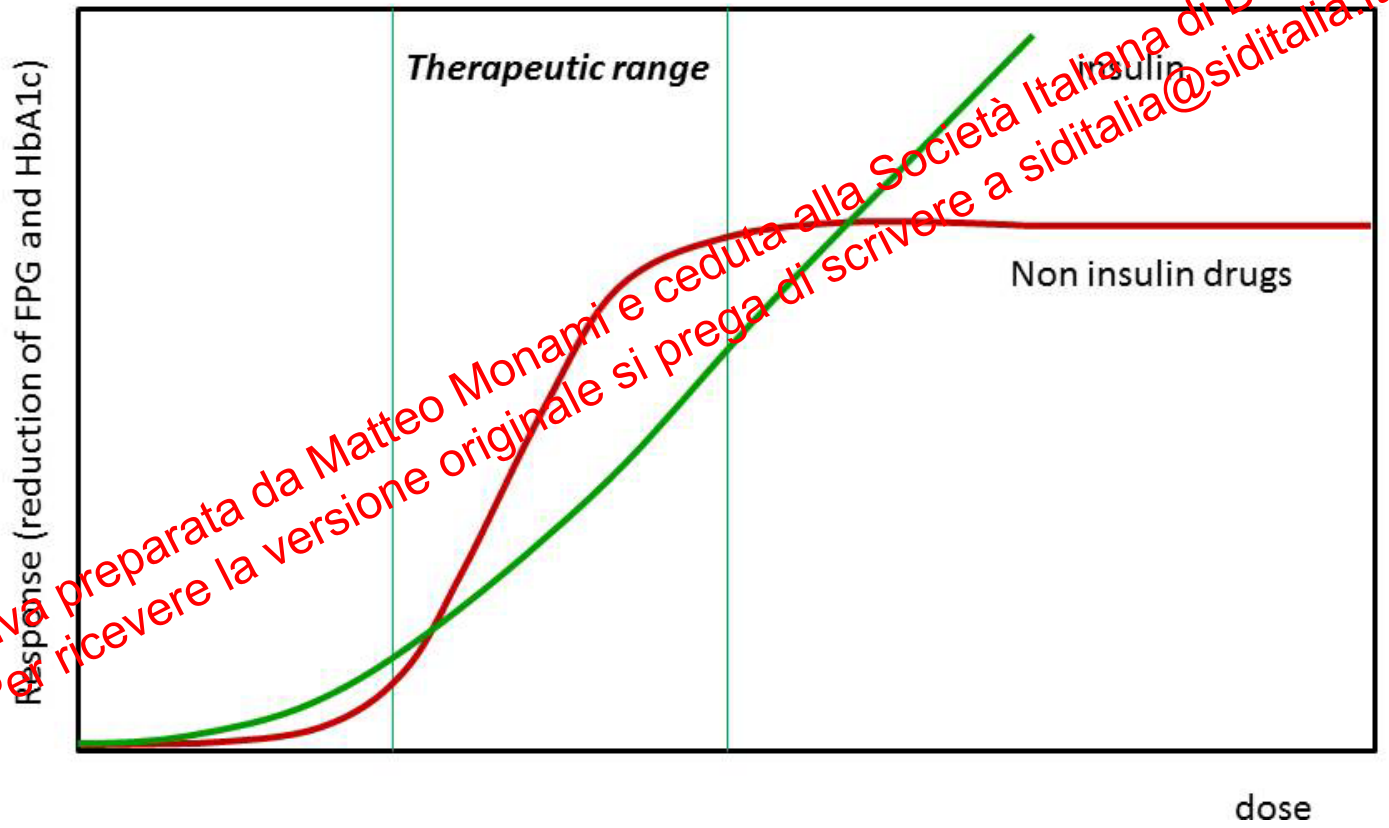
Director Diabetic Foot Unit
Careggi Teaching Hospital
Florence, Italy

Disclosures

- Dr Monami has received consultancy and/or speaking fees from:
  - Merck Sharp & Dohme
  - AstraZeneca
  - Bristol-Myers Squibb
  - Eli Lilly
  - Molteni
  - Novo Nordisk
  - Sanofi
  - Takeda
- In addition, the Diabetic Foot Unit directed by Dr Monami received research grants from AstraZeneca, El.En. Spa, and Molteni.

Insulin: strenghts and limits

Insulin: dose-response curve



Insulin: indications

- Severe hyperglycemia
- Ketosis/ketonuria
- Lean
- Weight loss
- No other available drugs

Insulin therapy can be prescribed as a transient treatment in some cases

Insulin: indications

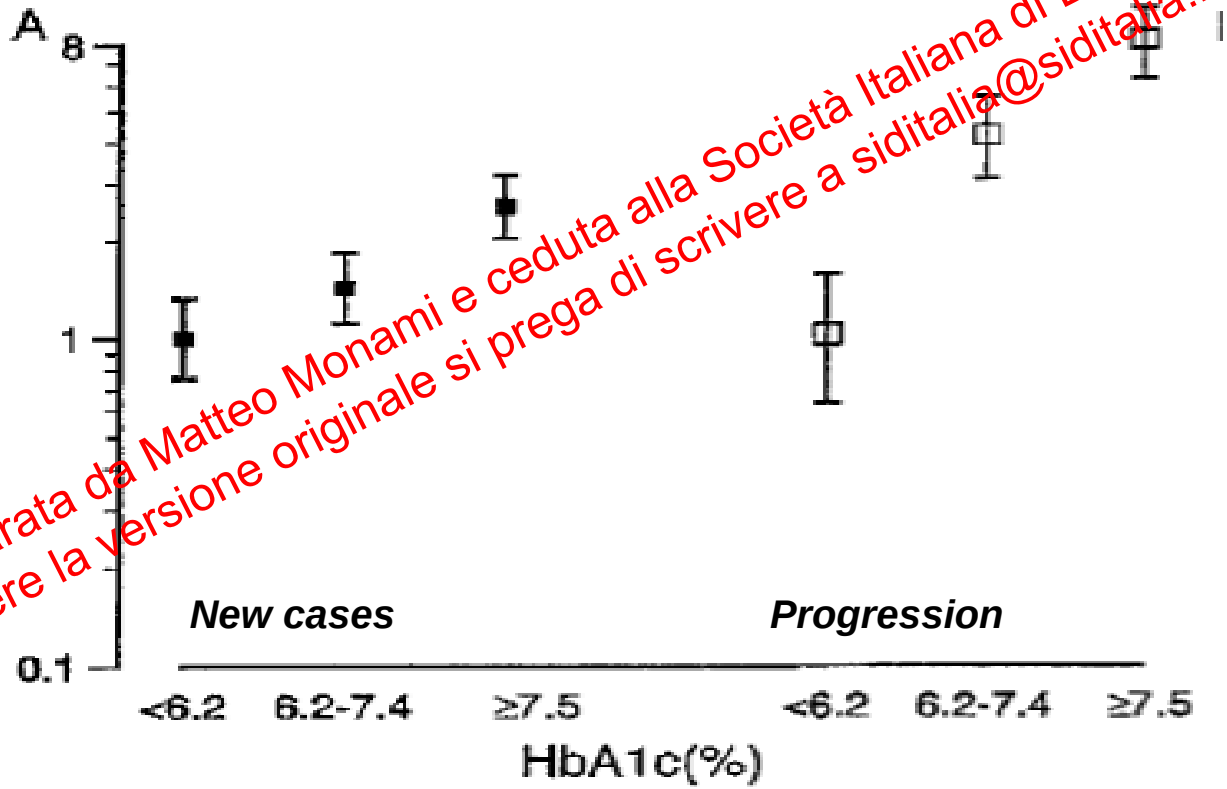
Severe hyperglycemia	Moderate hyperglycemia
Ketosis/ketonuria	No ketosis/ketonuria
Lean	Obese
Weight loss	Weight gain
No other available drugs	Other available drugs

Insulin therapy can be prescribed as a transient treatment in some cases

Epidemiology of retinopathy

United Kindgom Prospective Diabetes Study (UKPDS) 50

Type 2 (N=1,216)



Stratton IM, et al. *Diabetologia* 2001; 44:156-163.

Diabetes and CV risk

A meta-analysis

Type 2 diabetes

Study, Year (Reference)	Events/Persons, *n/n**	RR (95% CI)
Coronary heart disease (fatal and nonfatal)		
Florkowski et al., 1998 (24)	92/422	1.43 (1.02–2.00)
Kuusisto et al., 1994 (36)	33/229	1.29 (0.98–1.70)
Mattock et al., 1998 (53)	20/138	1.25 (1.01–1.55)
Lehto et al., 1997 (32)	256/1059	1.03 (0.96–1.15)
Stratton et al., 2000 (40)	606/3642	1.16 (1.0[illegible]1.27)
Moss et al., 1994 (44)	241/1194	1.[illegible]1.04–1.[illegible])
Pooled	1248/6684	1.13 (1.0[illegible]1.20)

Rischio cardiopatia ischemica: 13%
(Ictus: 14%; IMA: 16%; Morte CV: 15%)

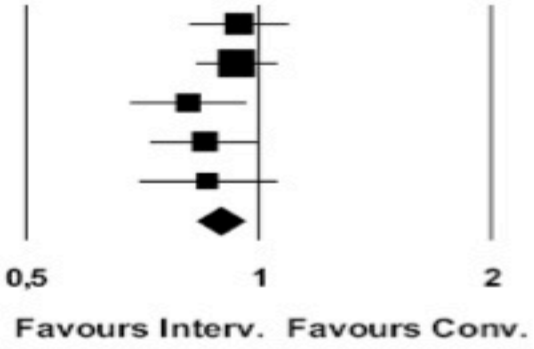
Selvin E, et al. *Ann Intern Med* 2004; 141:421-431

Glycemic control and CVD

Meta-analysis of large-scale RCTs

Cardiovascular events

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	0,944	0,811	1,098	-0,746	0,455
ADVANCE	0,937	0,830	1,059	-1,035	0,301
PROACTIVE	0,811	0,681	0,966	-2,346	0,019
UKPDS 33+34	0,852	0,723	1,003	-1,920	0,055
VADT	0,860	0,700	1,058	-1,425	0,154
OVERALL	0,893	0,832	0,957	-3,182	0,001



Mannucci E, Monami M, Lamanna C, Marchionni N.
Nutr Metab Cardiovasc Dis 2009;19:604-612.

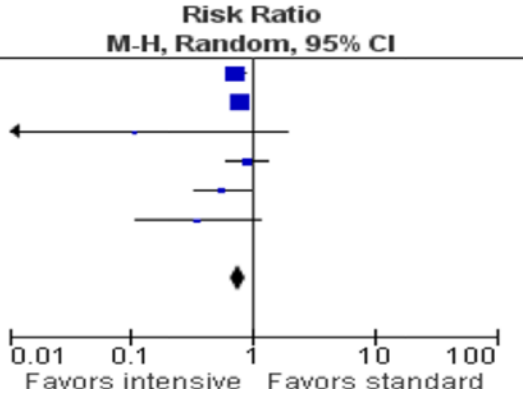
HbA1c and retinopathy

A Meta-analysis

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	195	4397	272	4424	38.4%	0.72 [0.60, 0.86]
ADVANCE	230	5571	292	5569	42.5%	0.79 [0.67, 0.93]
Kumamoto	0	52	4	10	0.6%	0.11 [0.01, 1.94]
UKPDS 33	72	2277	33	938	10.4%	0.90 [0.60, 1.35]
VADT	20	693	36	703	6.2%	0.56 [0.33, 0.96]
VADT Feasibility Trial	3	24	10	28	1.4%	0.35 [0.11, 1.13]
Total (95% CI)		**13011**		**11712**	**100.0%**	**0.74 [0.65, 0.85]**
Total events	520		647			

Heterogeneity: Tau² = 0.00; Chi² = 3.73, df = 5 (P = 0.33); I² = 13%

Test for overall effect: Z = 4.24 (P < 0.0001)



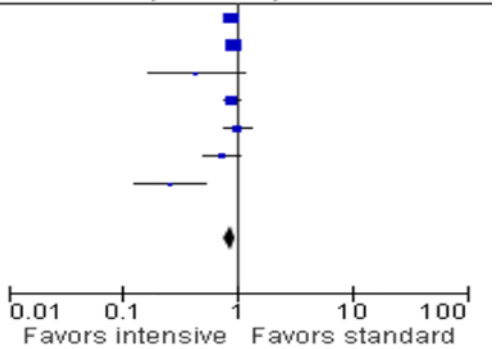
HbA1c and nephropathy

A Meta-analysis

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	720	3250	828	3273	27.3%	0.88 [0.80, 0.96]
ADVANCE	1318	5571	1434	5569	49.8%	0.92 [0.86, 0.98]
Kumamoto	5	52	11	50	1.3%	0.44 [0.16, 1.17]
UKPDS 33	368	2277	172	938	14.8%	0.88 [0.75, 1.04]
UKPDS 34	79	342	95	411	2.2%	1.00 [0.77, 1.30]
VADT	43	442	91	463	7.6%	0.74 [0.51, 1.07]
VADT Feasibility Trial	7	42	30	46	2.5%	0.26 [0.13, 0.52]
Total (95% CI)		11976		10750	100.0%	**0.86 [0.76, 0.96]**
Total events	2540		2631			

Heterogeneity: Tau² = 0.01; Chi² = 16.71, df = 6 (P = 0.01); I² = 64%

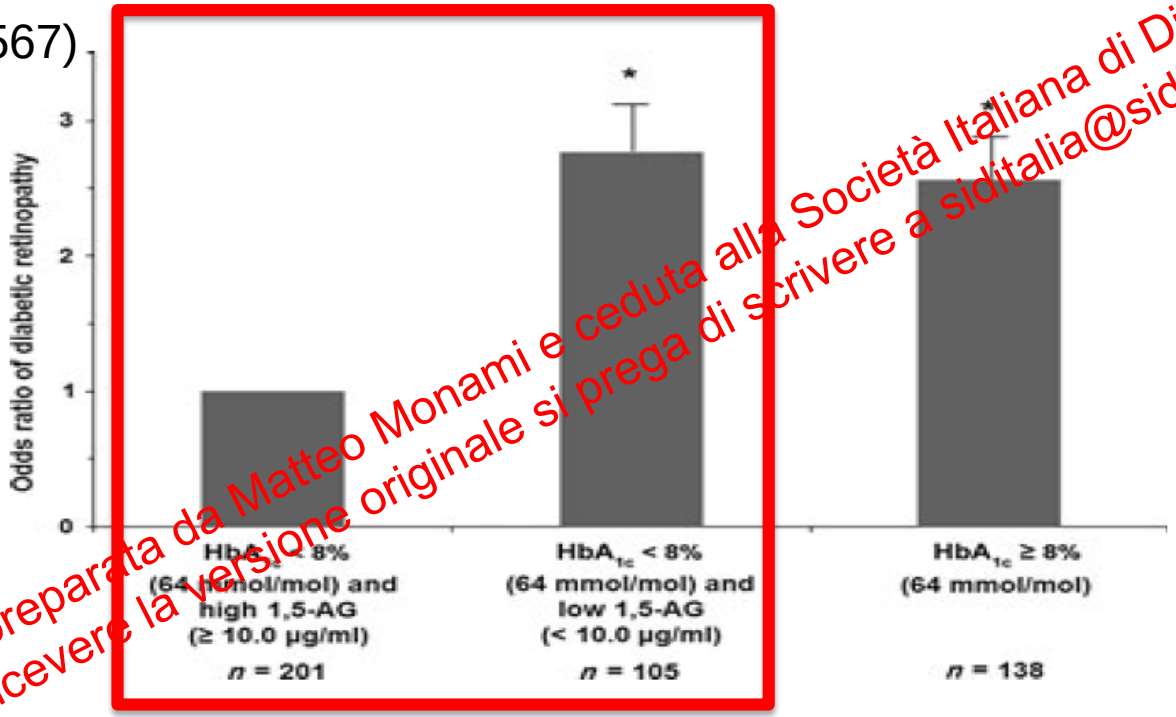
Test for overall effect: Z = 2.60 (P = 0.009)



Glucose variability and retinopathy

1,5 AG and incidence of DR in T2DM

Type 2 DM (N=567)



Subjects with low 1,5-anhydroglucitol were more likely to experience diabetic retinopathy than those with high AG

Kim WJ et al., *Diabet Med* 2012; 29:1184-1197.

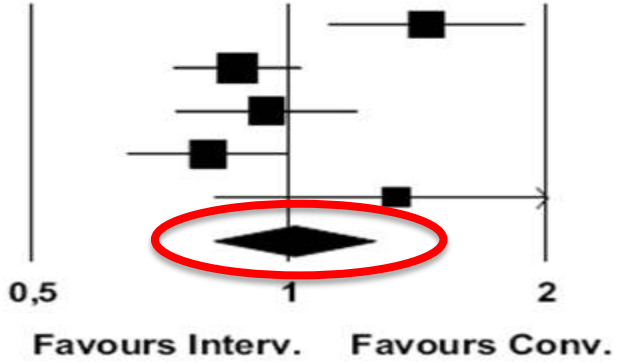
Glycemic control and CVD

Meta-analysis of large-scale RCTs

Cardiovascular mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	1,447	1,108	1,888	2,718	0,007
ADVANCE	0,869	0,731	1,033	-1,569	0,112
PROACTIVE	0,941	0,734	1,206	-0,480	0,631
UKPDS 33+34	0,805	0,643	1,007	-1,950	0,051
VADT	1,335	0,816	2,184	1,150	0,250
OVERALL	1,018	0,815	1,257	0,110	0,912

Odds ratio and 95% CI



Mannucci E, Monami M, Lamanna C, Marchionni N.
Nutr Metab Cardiovasc Dis 2009;19:604-612.

Glycemic control and CVD

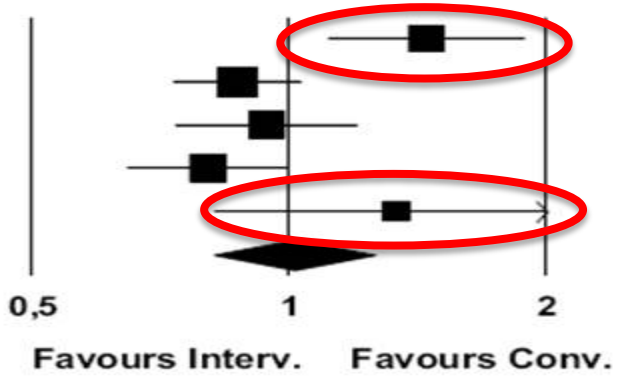
Meta-analysis of large-scale RCTs

Cardiovascular mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	1,447	1,108	1,888	2,718	0,007
ADVANCE	0,869	0,731	1,033	-1,569	0,112
PROACTIVE	0,941	0,734	1,206	-0,480	0,631
UKPDS 33+34	0,805	0,643	1,007	-1,950	0,051
VADT	1,335	0,816	2,184	1,150	0,250
OVERALL	1,012	0,895	1,257	0,110	0,912

Statistics for each study

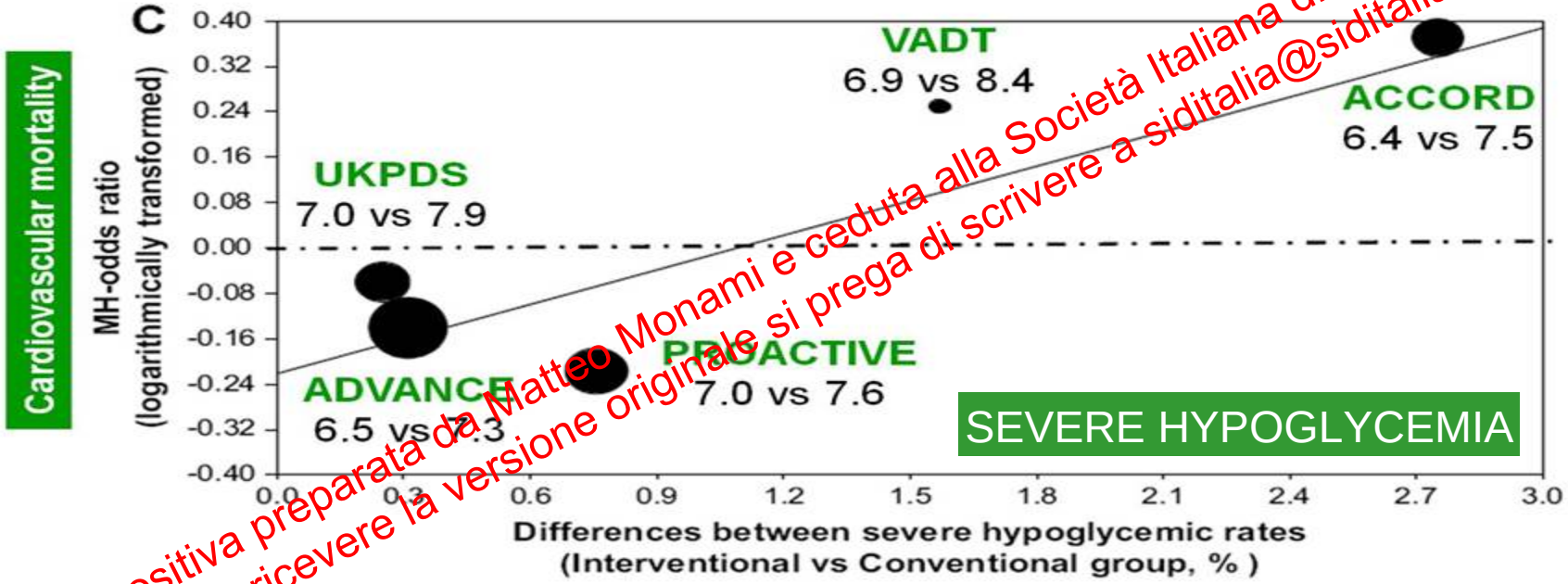
Odds ratio and 95% CI



Mannucci E, Monami M, Lamanna C, Marchionni N.
Nutr Metab Cardiovasc Dis 2009;19:604-612.

Prevention of cardiovascular disease through glycemic control in type 2 diabetes

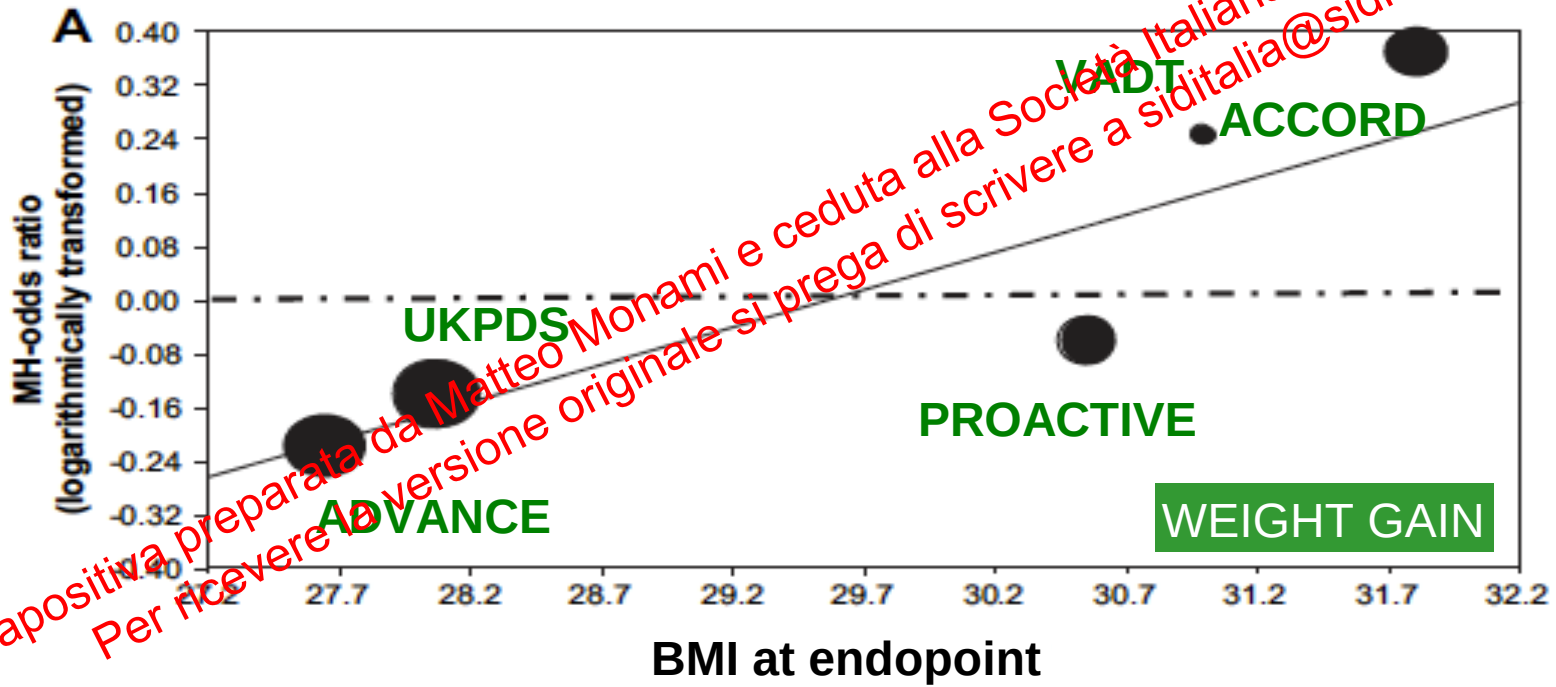
A meta-analysis of randomized clinical trials



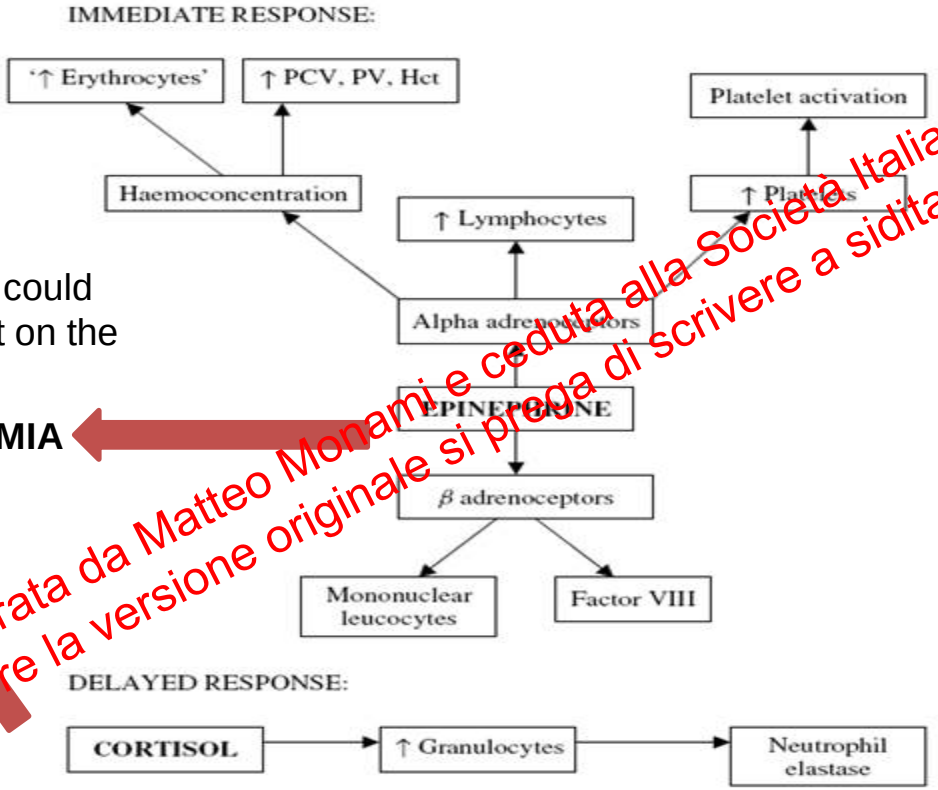
Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N.
NMCD 2009; 19: 604-612

Prevention of cardiovascular disease through glycemic control in type 2 diabetes

A meta-analysis of randomized clinical trials



Hypoglycemia and CV death



Adrenercic activation could have a negative impact on the prognosis of

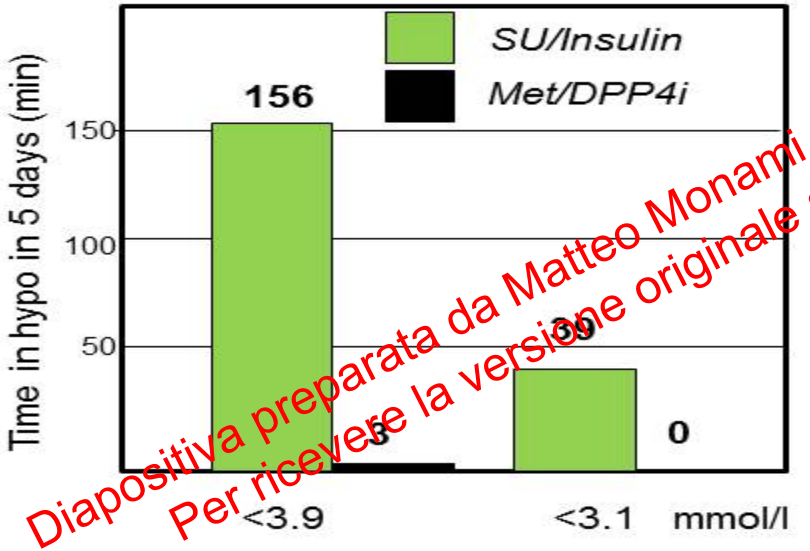
MYOCARDIAL ISCHEMIA

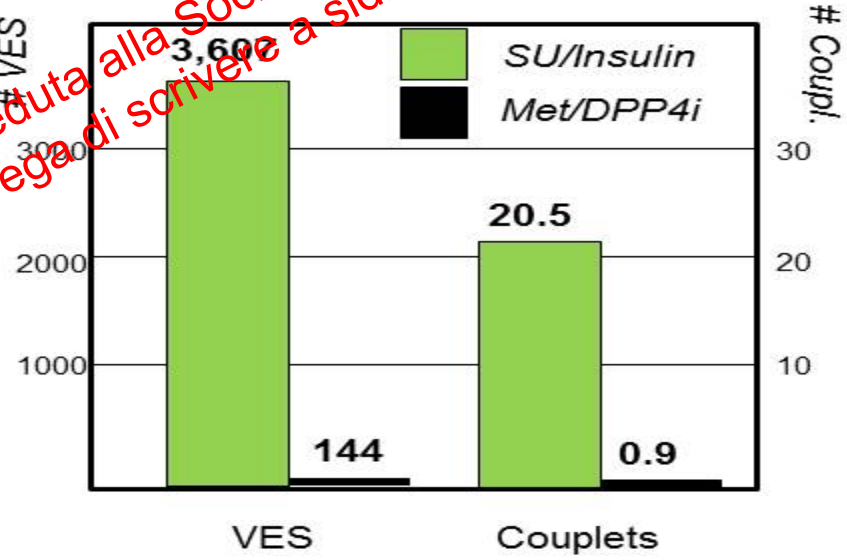
Wright RJ, Frier BM. *Diabetes Metab Res Rev* 2008; 24: 353-365.

Hypoglycemia and arrhythmia

A matched cohort study

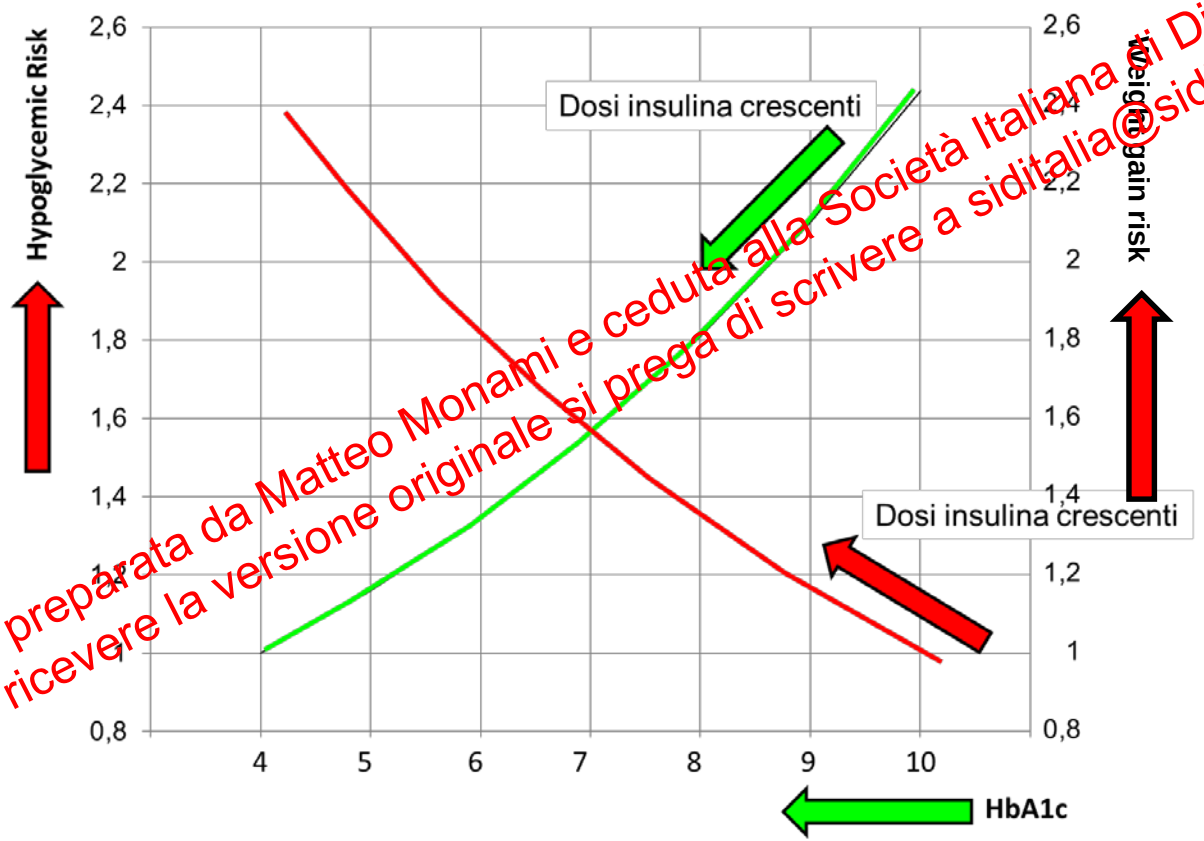
30 patients with T2DM and established CVD on insulin and/or SU
12 matched patients on metformin and/or DPP4 inhibitors.
5-day CGM and Holter-ECG recording





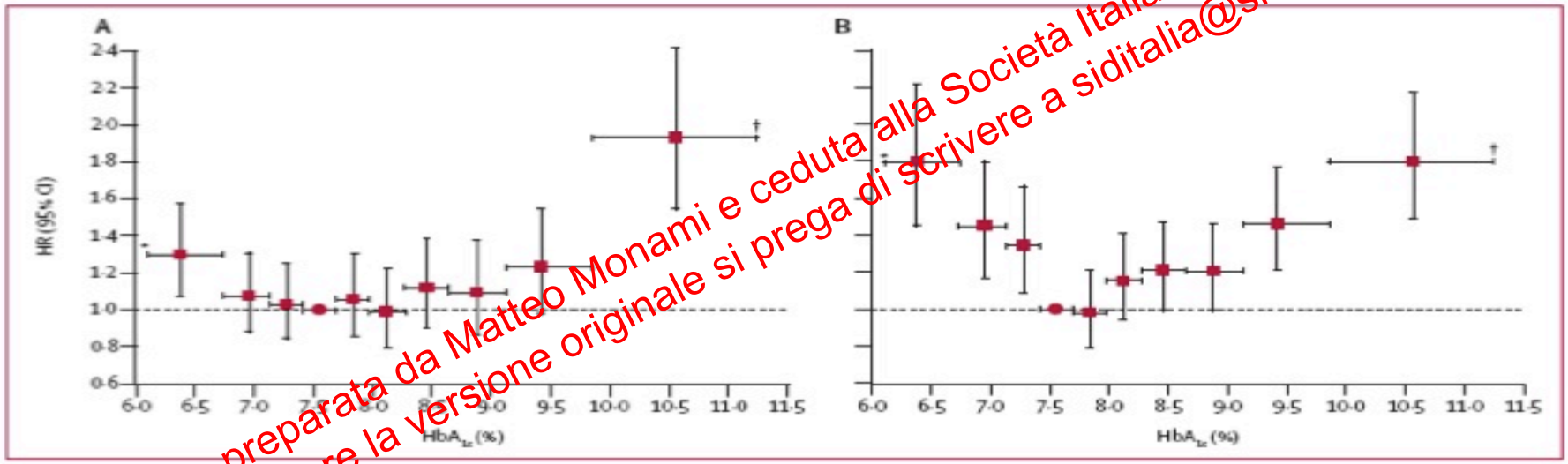
Stahn A et al., *Diabetes Care* 2014

Vantaggi e limiti della terapia insulinica



All-cause mortality in T2DM

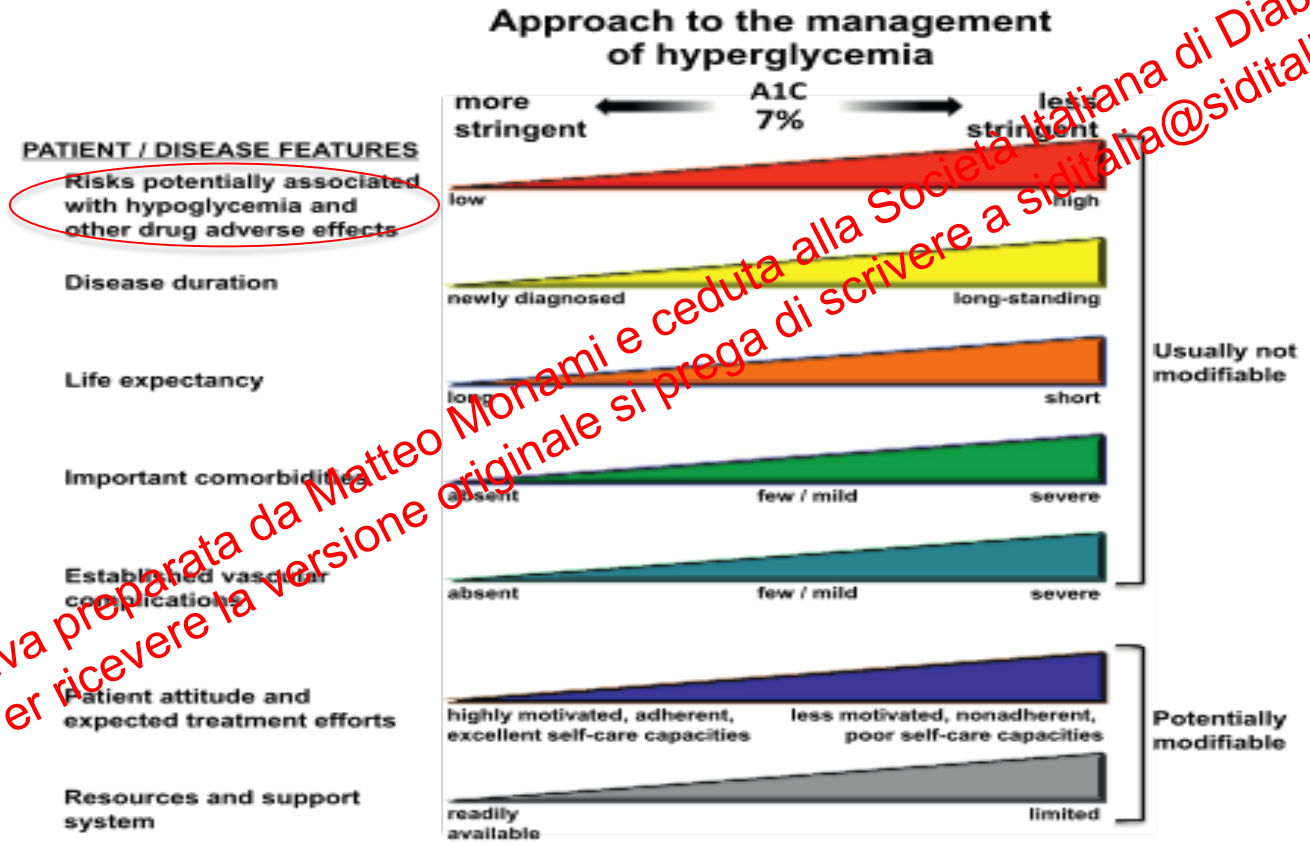
Relationship with HbA1c



Sulfonylureas **Insulin**

Currie CJ et al. *Lancet* 315:481-9, 2010

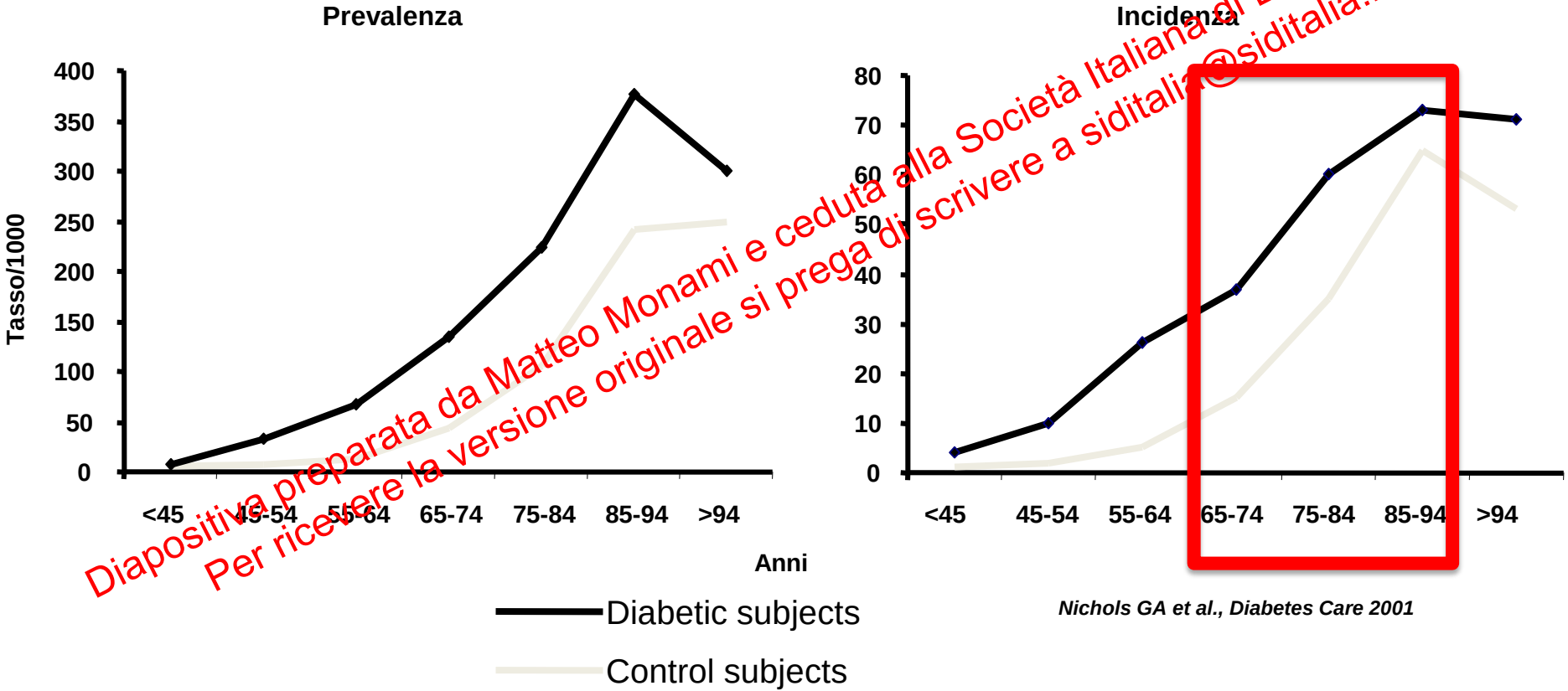
A1c target: personalization



Higher risk of hypos (beyond therapy)

- Comorbidity
- Renal function
- Cognitive function
- Duration of diabetes
- Autonomy and social support

Epidemiology of IHD in diabetes



Nichols GA et al., Diabetes Care 2001

Insulin: indications

Severe hyperglycemia	Moderate hyperglycemia
Ketosis/ketonuria	No ketosis/ketonuria
Lean	Obese
Weight loss	Weight gain
No other available drugs	Other available drugs

Insulin therapy can be prescribed as a transient treatment in some cases

Drugs for T2DM