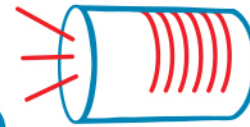


Listen,

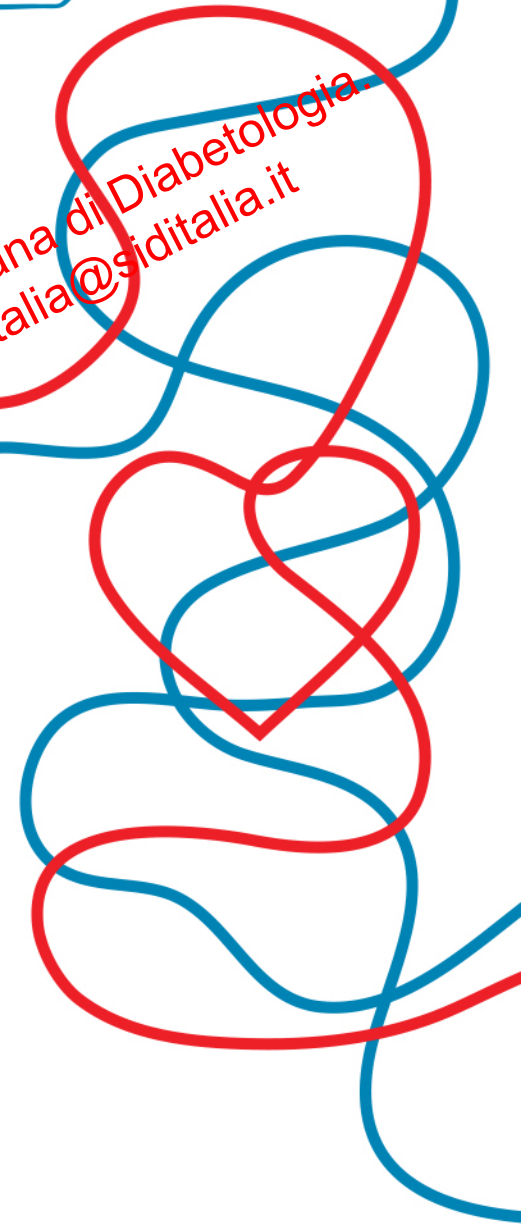
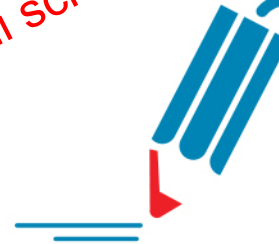


Think
and
Plan



Metodologia
degli studi clinici
in diabetologia

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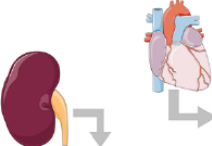


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Cosa hanno detto ?

	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 ^{c-e} , GLP-1RA ^f	SGLT2-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} , SGLT2-I ^g , GLP-1 RA ^f , DPP4-I ^{2,e} , Gliclazide ^{2k} , Insulin ^h	Metformin ² , GLP-1 RA ^f , SGLT2-I ^g , Pioglitazone ³ , DPP4-I ^{2,c-e} , Insulin ^h , Gliclazide ^{2k}	Insulin ^m , DPP4-I ^e , GLP-1RA ^f	SGLT2-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

Fig. 1 A treatment algorithm based on cardiac and renal co-morbidities and CVOTs. ¹To be used with caution because of the risk of hypoglycemia; ²consider dose reduction (except for linagliptin) and monitor eGFR frequently; ³preferred in the presence of marked insulin resistance; ⁴initiation of therapy currently not recommended. ^aUKPDS; ^bPROACTIVE trial; ^cSAVOR; ^dTECOS; ^eEXAMINE; ^fLEADER trial; ^gEMPA-REG Outcome trial; ^hORIGIN trial; ^kADVANCE; ^jELIXA; ^mDIGAMI 1



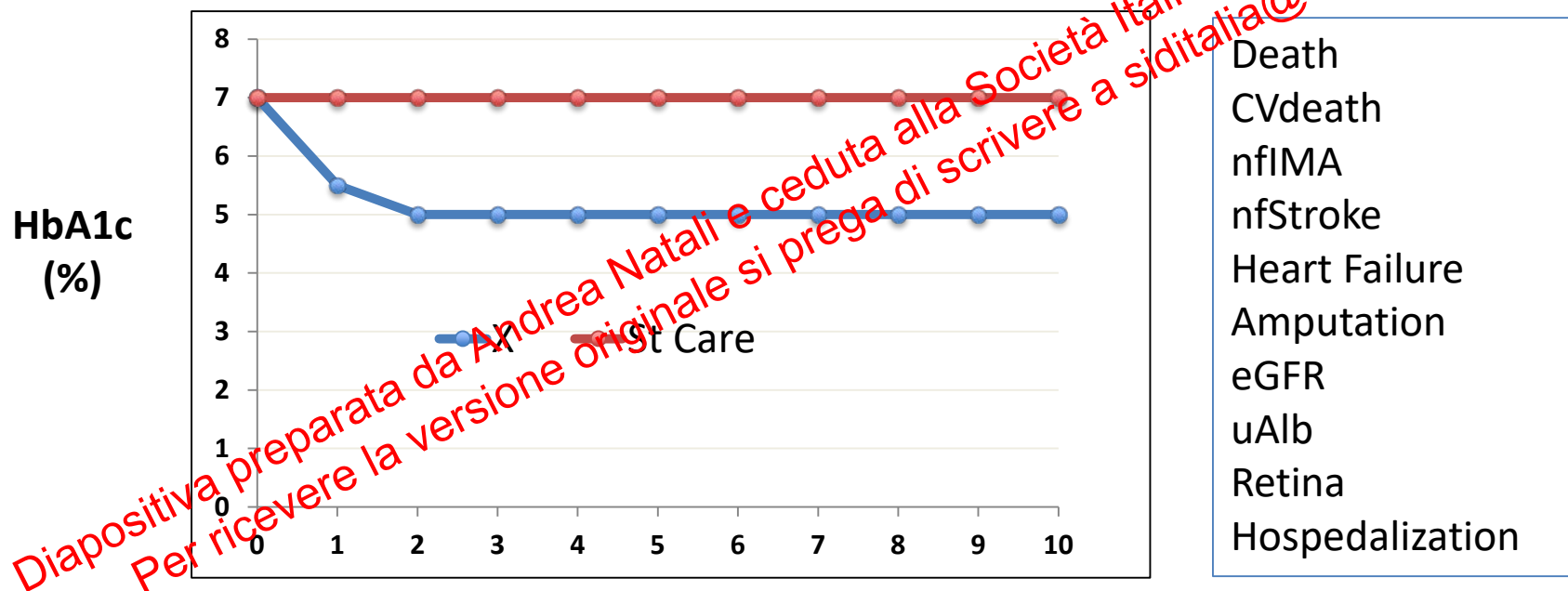
Cosa non hanno detto ?

- 1) Se tengo la HbA1c quasi normale, negoziando con il paziente la modalità, prevengo le complicanze del diabete?
- 2) Esistono combinazioni più sicure ed efficaci di altre ? (e.g. MET+EMPA+SEMA/LIRA vs SU+DDPIV+INS)
- 3) Come scelgo tra farmaci della stessa classe ? (HEART2D: Lispro vs NPH)
- 4) Come scelgo tra 2 farmaci ? (SPREAD-DIMCAD: Metf vs glipizide)
- 5) L'età, il BMI ed il gender sono importanti nella la scelta della terapia ?
- 6) E' cost-effective trattare la glicemia ? (la pressione, il colesterolo?)
- 7) Ma quanti mesi/anni liberi da evento mi aspetto di guadagnare da un trattamento efficace se protratto nel tempo ?

Se quello che facciamo in ambulatorio tutti i giorni ha senso

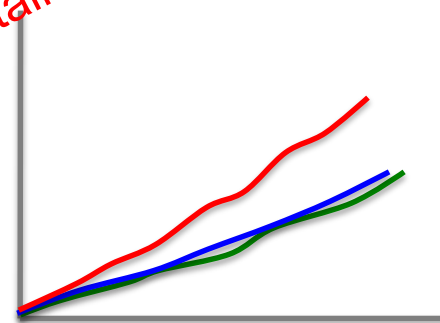
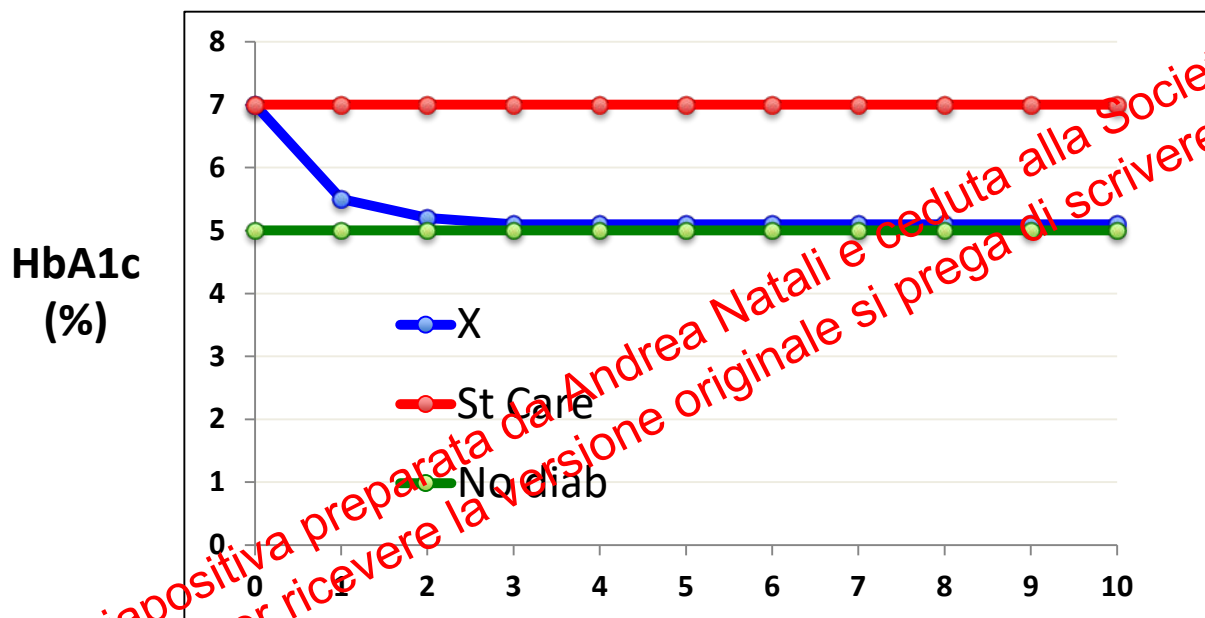


- 1) Cosa accade se si mantiene un buon controllo metabolico (ed un gradiente di glicata) dall'inizio (0-4 aa) della malattia con modalità (farmaco/lifestyle) di vostra scelta in volta negoziate con i pazienti ?





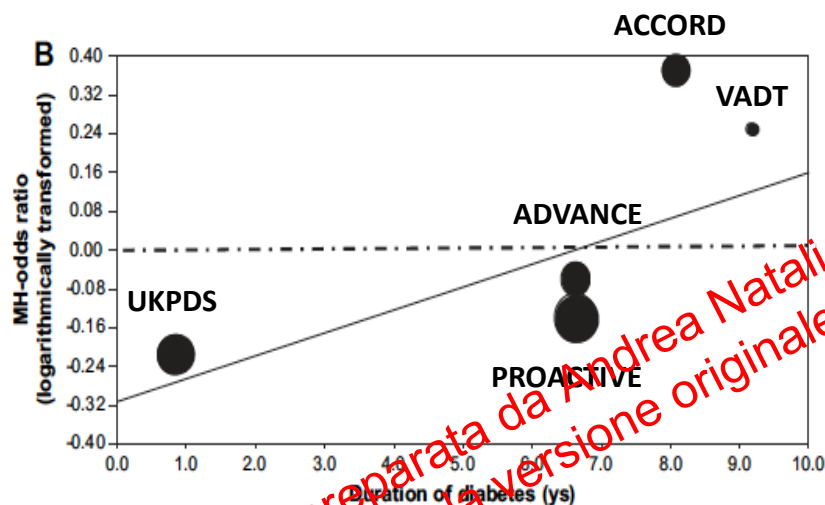
1) Si riesce a trasformarlo in una persona non diabetica ?



Death
CVdeath
nfIMA
nfStroke
Heart Failure
Amputation
eGFR
uAlb
Retina
Hospitalization

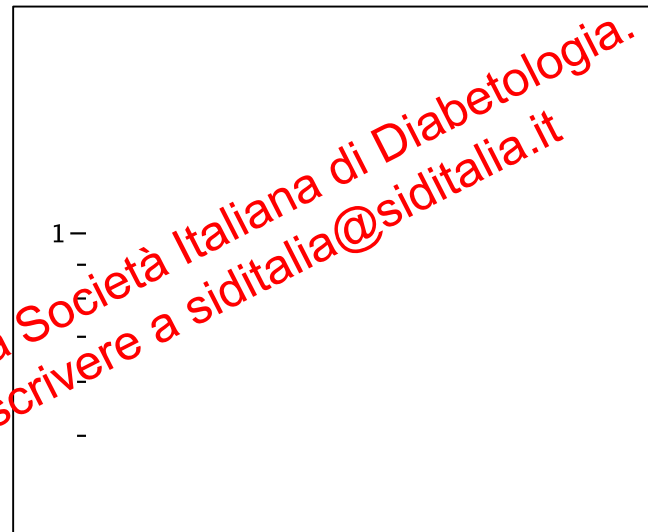


cardiovascular mortality

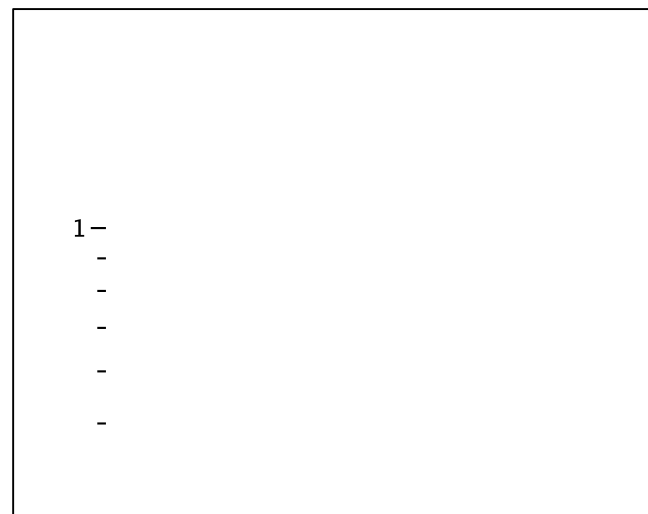


Mannucci, J. M. CD 2009

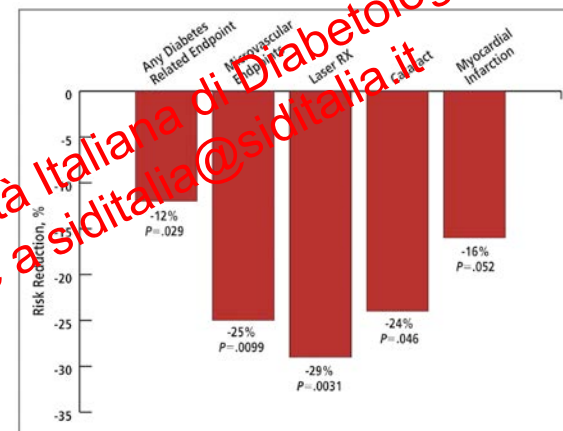
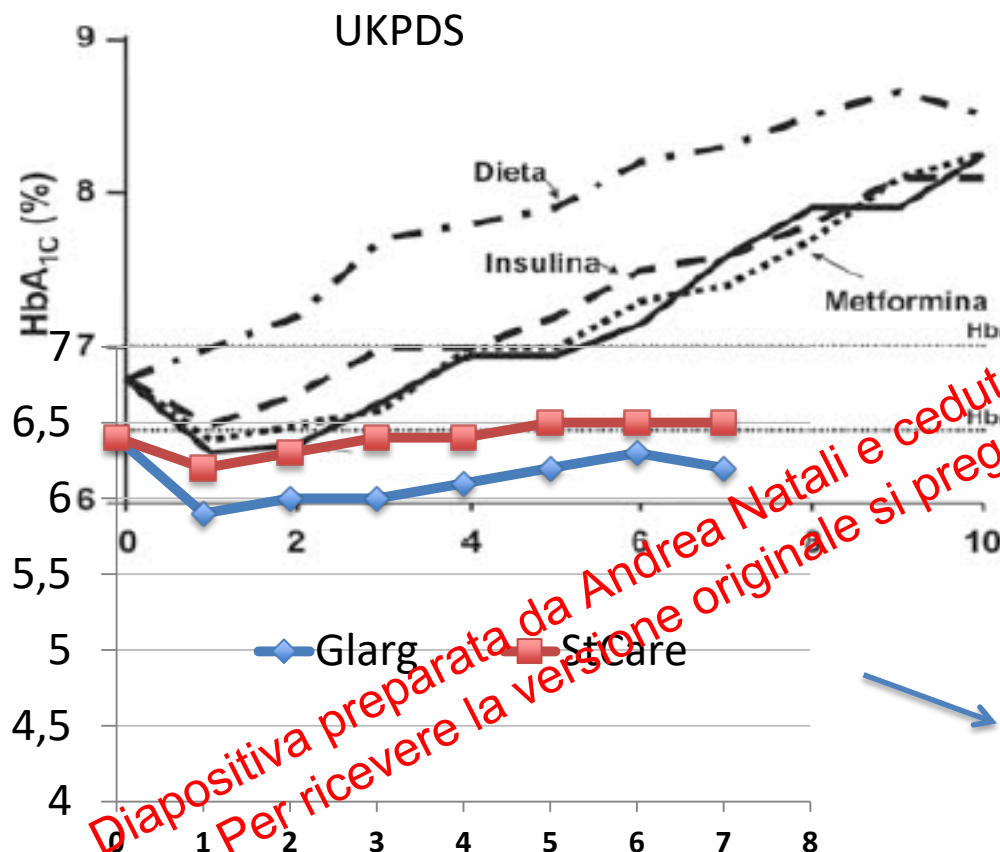
All cause death



CV death



Linear Fit Type=="A vs B"



Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52

0.5 1.0 2.0

Insulin Glargine Better

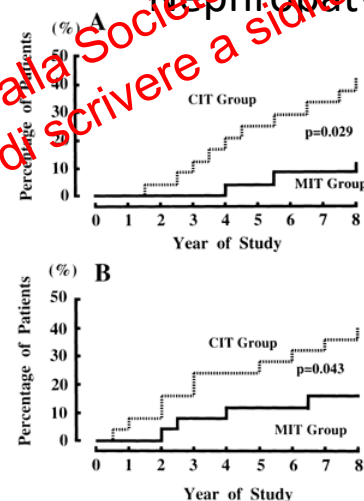
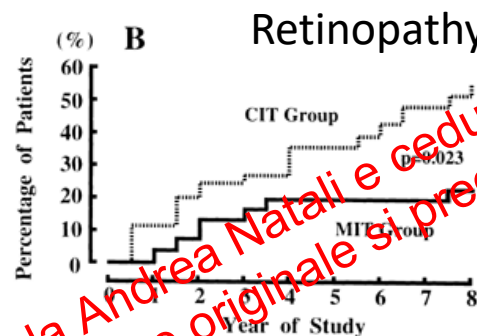
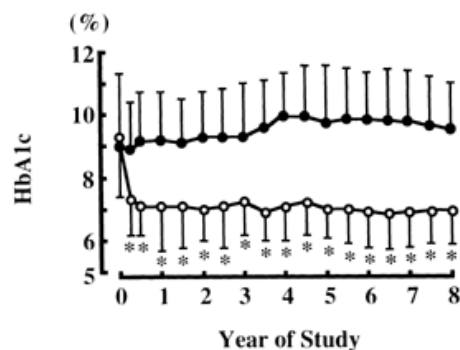
Standard Care Better

ORIGIN

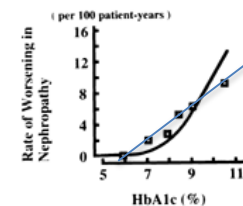
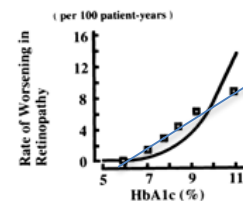
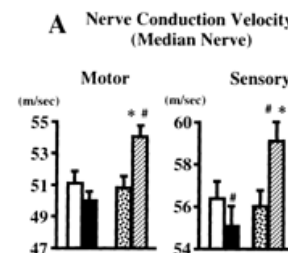
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Kumamoto Study, 110 T2D, MIT vs CIT, 50 yrs, BMI=21, DD=6 yrs



Neuropathy

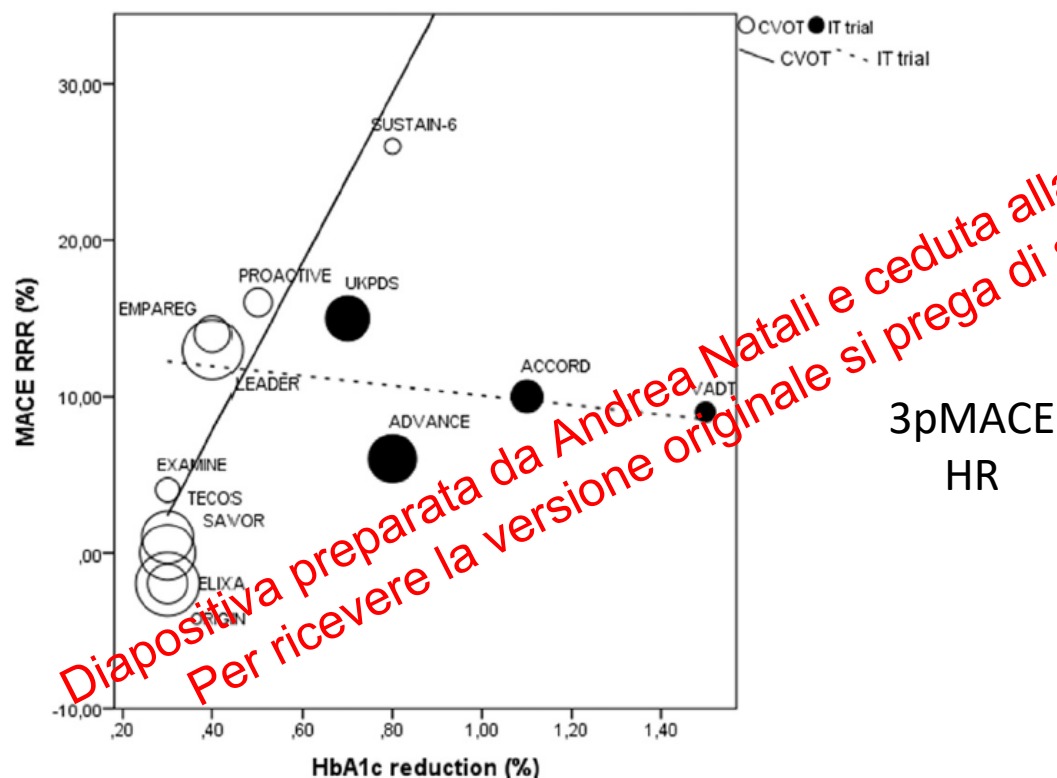


Cardiovascular events
0.6 vs 1.3 %/yr RR=0.5!!

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2) Cosa accade se si migliora il controllo metabolico con i farmaci più sicuri (e.g. MET+EMPA+GLP-1/DDP4 vs SU+INS)

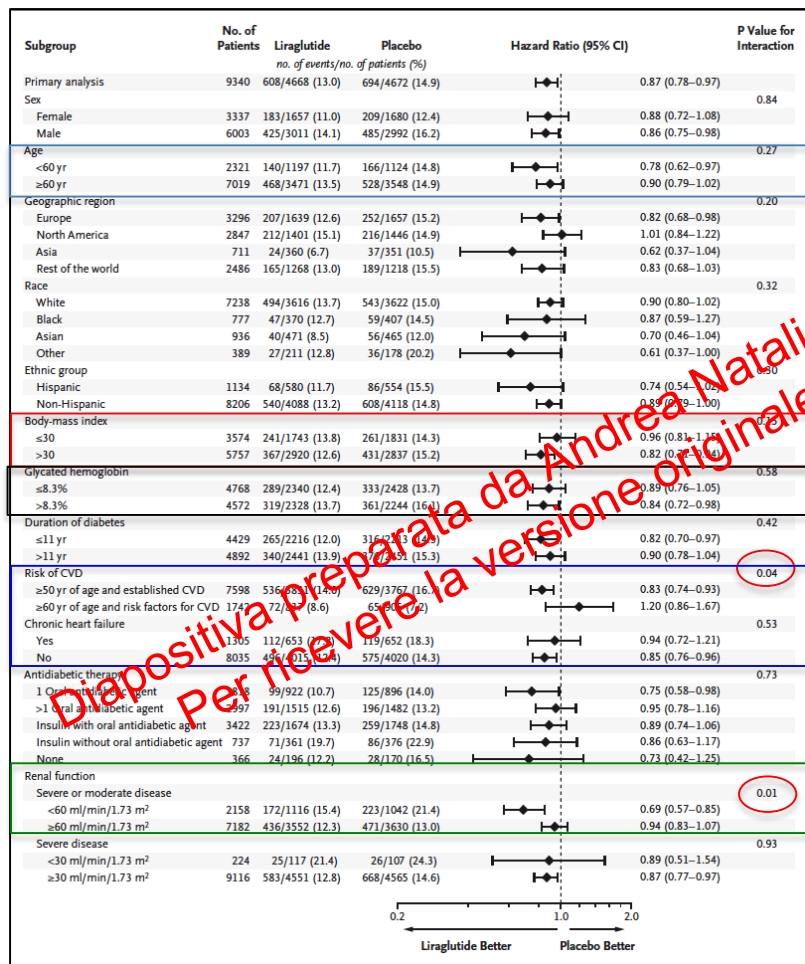


T	1	UKPDS-33
	2	UKPDS-34
	3	Kumamoto
M	4	PROACTIVE
A	5	ACCORD
	6	ADVANCE
P	7	STENO-2
B	8	ADDITION- Europe
V	9	VADT
L	10	ORIGIN
N	11	SAVOR-TIMI 53
H	12	EXAMINE
S	13	TECOS
F	14	ELIXA
R	15	SUSTAIN-6
K	16	LEADER
G	17	EMPA-REG
D	18	BARI-2D
I	19	HEART2D
O	20	SPREAD-DIMCAD
Q	21	STOP-NIDDM
E	22	DREAM-ROSI

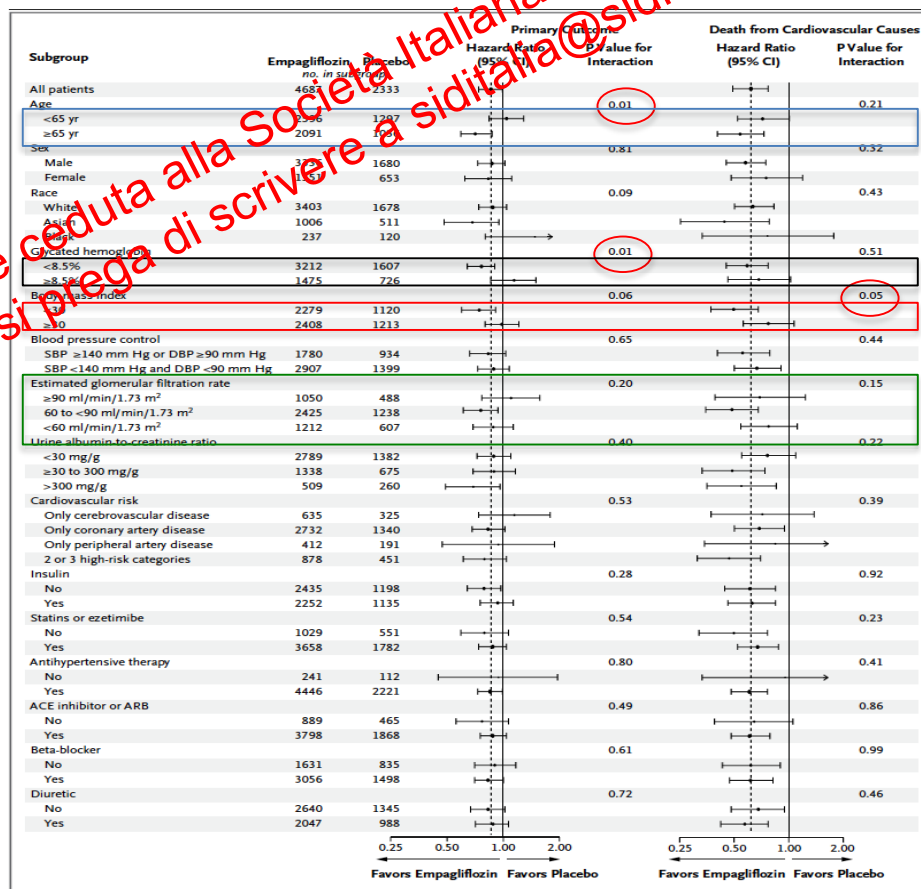


2) POSSIBILI SINERGIE

LEADER



EMPA-REG





3) Confronti tra strategie o farmaci

(A) Treatment goals with any drugs

ACCORD (neg), VADT (neg), UKPDS (+/-pos), DCCT (pos)

(C) Treatment goals with specific drug and/or strategies

ADVANCE: Glicazide vs any other (neg, only microV)

HEART2D: Prandial vs Basal insulin (neg)

(B) Specific drug/class vs any other

DDP-4: Saxa/SAVOR-TIMI 53, Saxa/TECOS, Alo/EXAMINE, Lina/CARMELINA

GLP-1 a: Lixi/ELIXA, Lira/LEADER, Semaglutide/SUSTAIN

SGLT-2: EMPA REG OUTCOME, Dapa/DECLARE TIMI 58, Cana/CANVAS

(D) Comparison of 2 different drugs/class/strategy

HEART2D: Glarg vs lispro (=)

BARI 2D: Ins sens vs Ins provision (=)

SPREAD-DIMCAD: Metf vs Glipizide (Metf better)

CAROLINA: Lina vs Glimepiride (ongoing)

DEVOTE: Degludec vs Glargine (ongoing)

TOSCA: PIO vs SU (ongoing)

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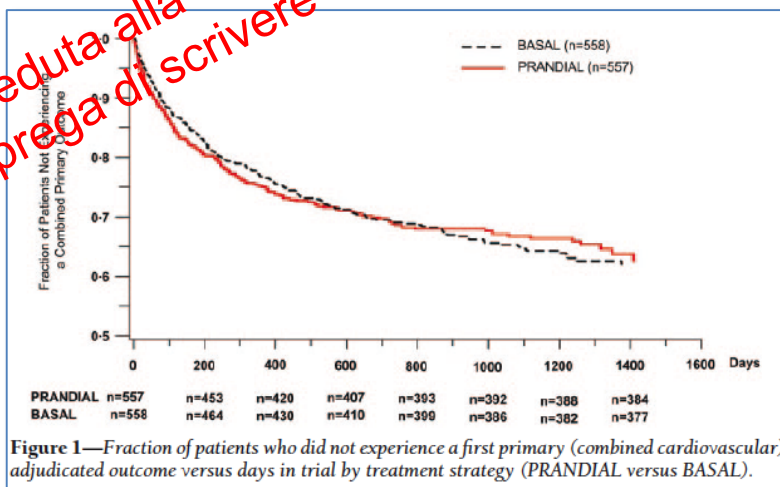
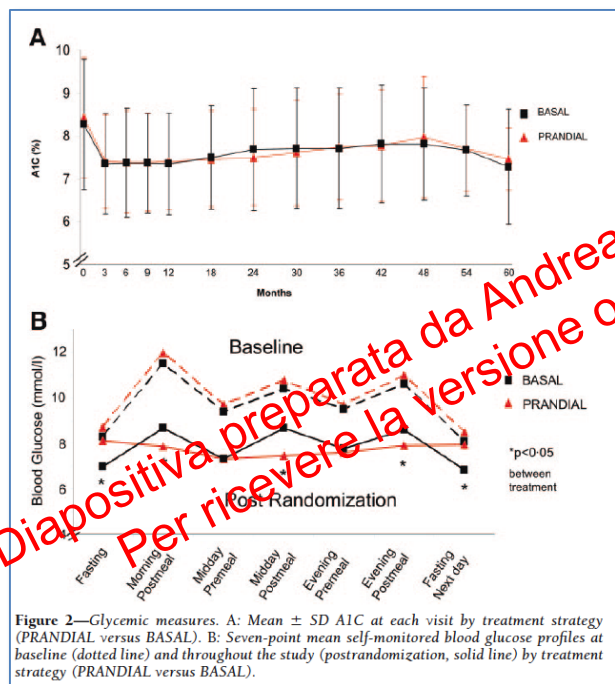


3) Confronto strategia (HEART2D): Lispro vs NPH

1,115 T2D+AMI, 61 yrs, 36% female, BMI 29

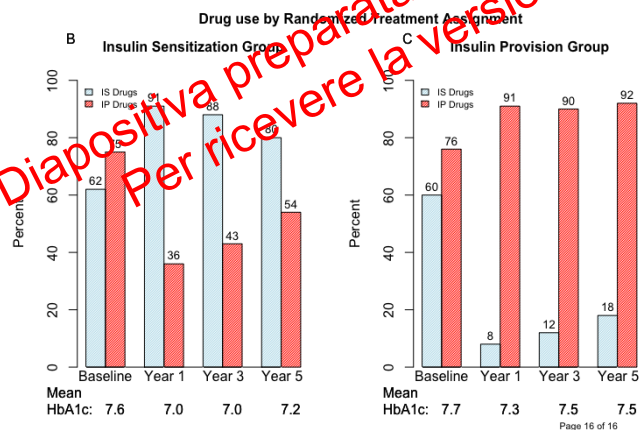
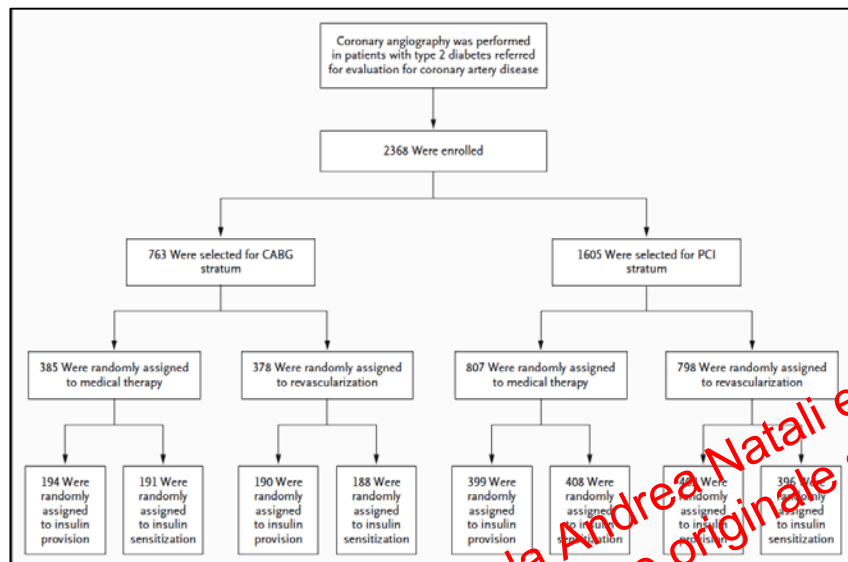
5pMACE:

CV death, nf MI, nf stroke, coronary revasc., or hosp. ACS

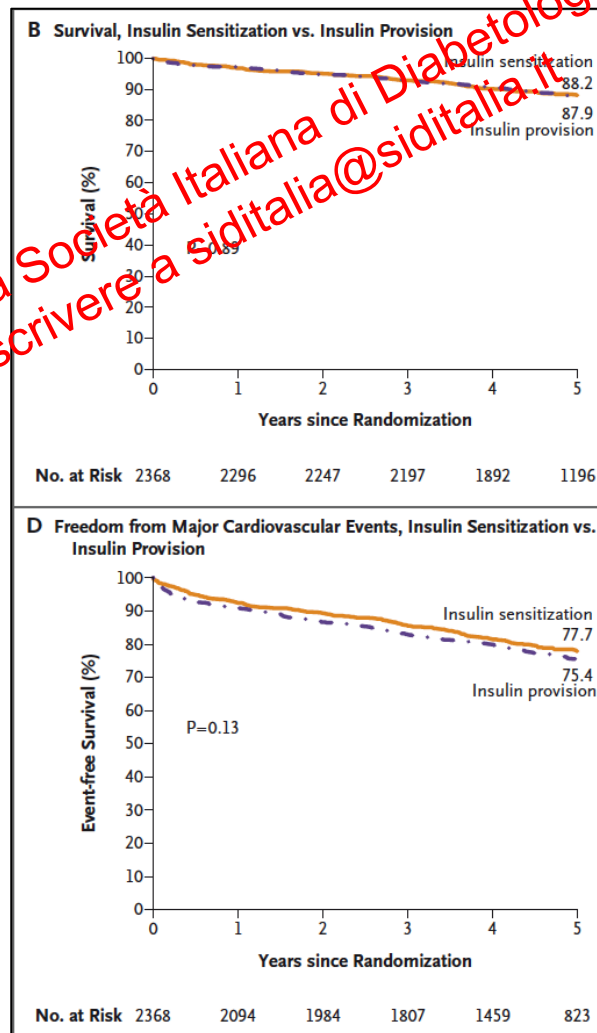




3) Confronto strategia (BARI-2D): Insulin prov. (SU/ins) vs Insulin sens (TZD/MET)



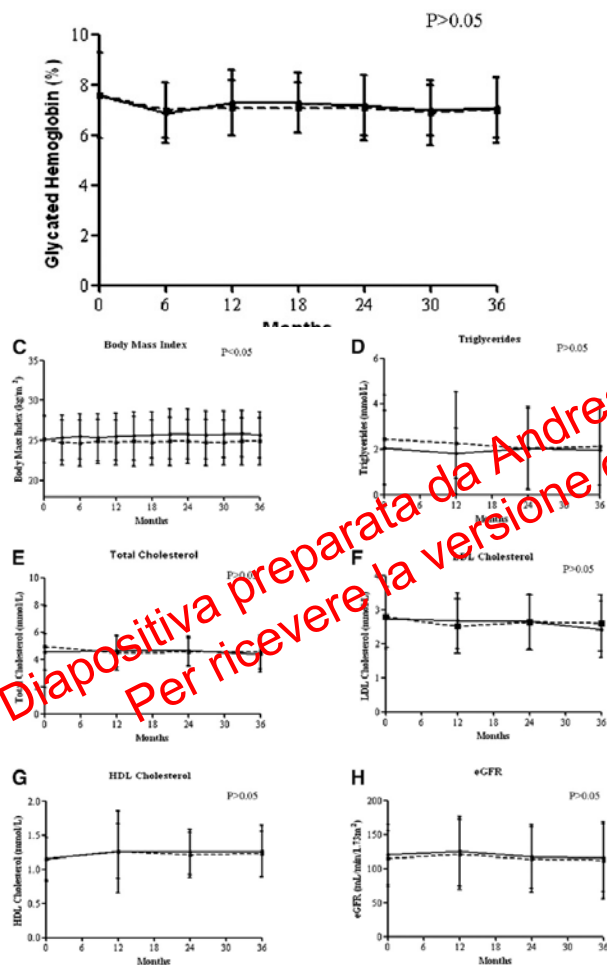
HbA1c
IS: 7.0
IP: 7.5





3) Confronti “Head to Head” (SPREAD-DIMCAD): **Metf vs glipizide**

304 T2D+CAD, 63+/-9 yrs, DD 5 yrs, BMI=25, 23% female



Composite 1st endpoint (5p)

CV death, AC death, nfMI, nf stroke, arterial revasc.

METFORMIN: **0.54** (95%CI 0.30–0.90; $p = 0.026$)



5) ETA' - ≥ 75 ? Mah.

meanAge-2SD & 4 more vs. ACRONIMO

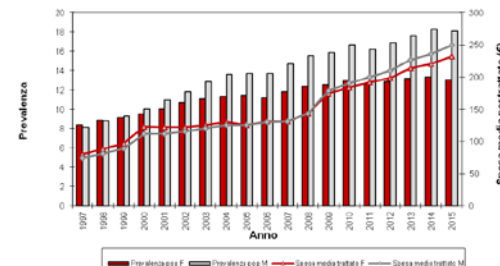
12% di tutti i
diab

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L'USO DEI FARMACI ANTIDIABETICI NEGLI ANZIANI NEL TEMPO

Grafico 10

Andamento temporale (1997-2015) della prevalenza del diabete farmaco-trattato e della spesa media per trattato in funzione del sesso - POPOLAZIONE OVER 65 ANNI





5) ETA' – > 0 < 65 ?

ACCORD

Primary EP



AC Death

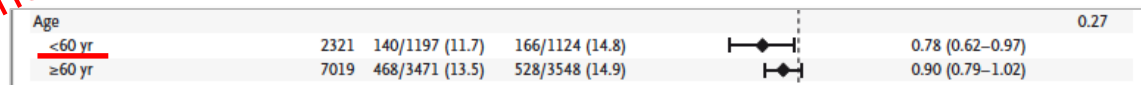


EMPAREG Primary EP&CVD



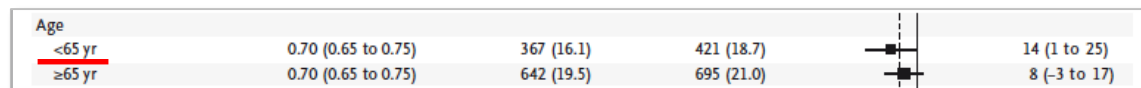
LEADER

Primary EP



ADVANCE

Primary EP

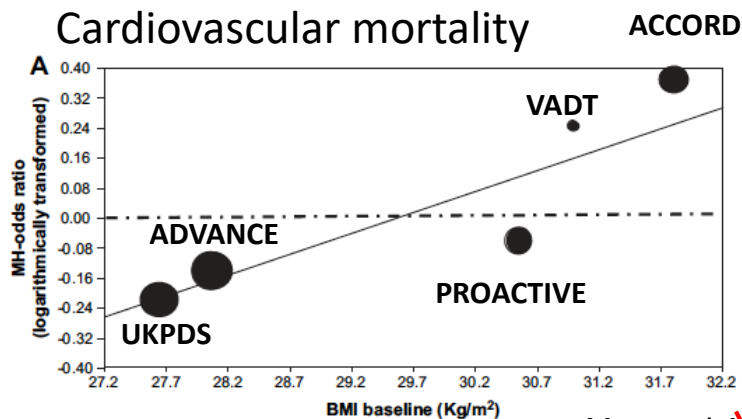


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5) BMI – > 30 kg/m²

All cause death



Mannucci, WCD 2009

ADVANCE

Body-mass index					
<28	0.68 (0.64 to 0.72)	558 (18.9)	663 (22.1)		15 (5 to 24)
≥28	0.65 (0.60 to 0.69)	451 (17.3)	452 (17.6)		2 (-11 to 14)

EMPA REG

Body-mass index					
<30	2279	1120		0.06	0.05
≥30	2408	1213			

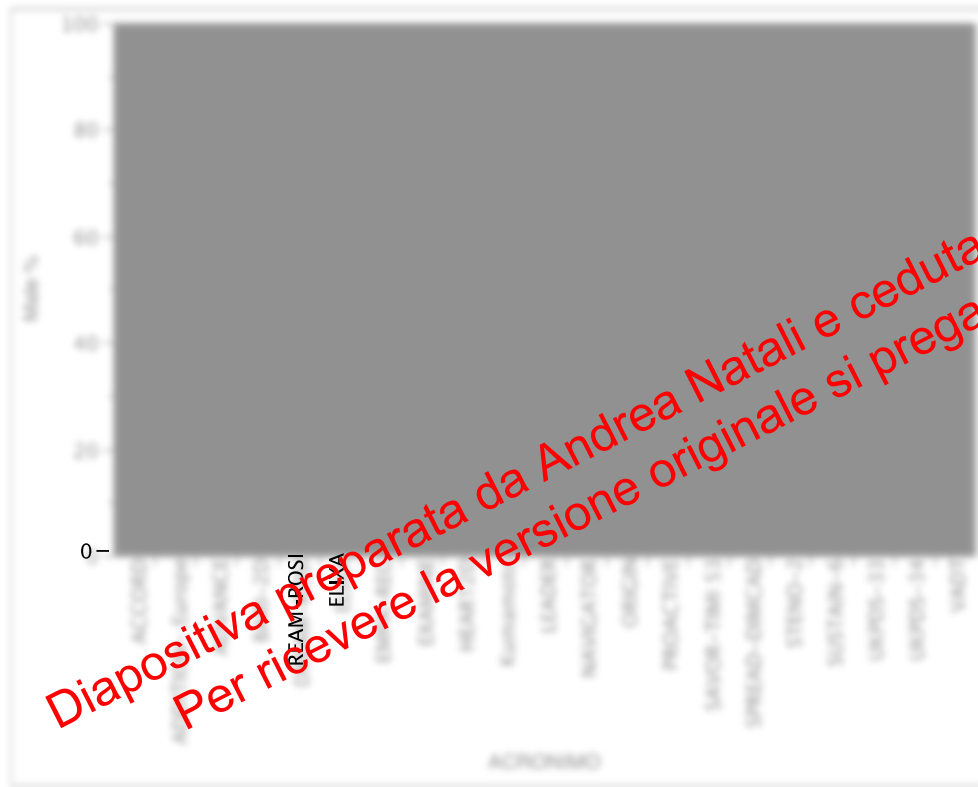
LEADER

Body-mass index					
≤30	3574	241/1743 (13.8)	261/1831 (14.3)		0.96 (0.81–1.15)
>30	5757	367/2920 (12.6)	431/2837 (15.2)		0.82 (0.71–0.94)

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5) Genere – Donne ? Poche.



1° Outc

3p MACE

All C Death

CV Death

Nf IMA

Stroke

$p=0.07$

% male

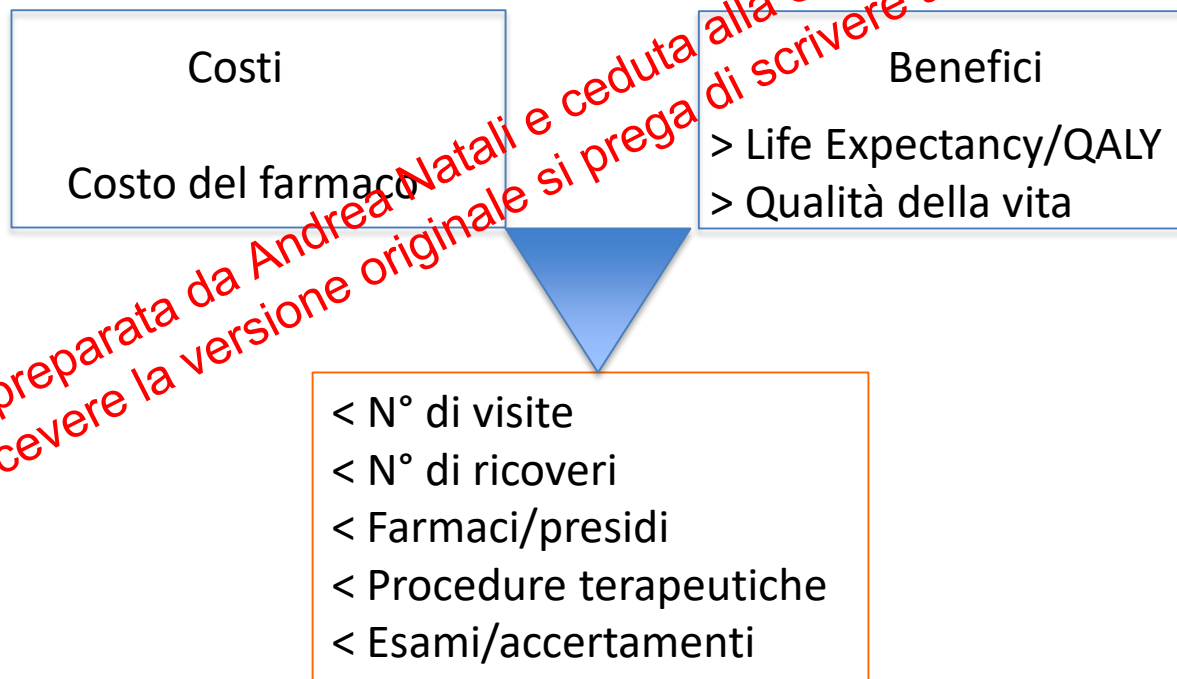


6) E' cost-effective

il farmaco nuovo (più costoso) rispetto al vecchio (meno costoso) ?

trattare la glicemia ? (la pressione, il colesterolo?)

cosa offro al paziente ? (ore, giorni, mesi o anni liberi da evento)



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Evaluation of the long-term cost-effectiveness of liraglutide vs lixisenatide for treatment of type 2 diabetes mellitus in the UK setting

Diabetes Obes Metab 2017; 1–8

TABLE 1 Treatment effects applied in the first year of the analysis

	Liraglutide 1.8 mg Mean	Lixisenatide 20 µg Mean
HbA1c (%)	-1.83 ¹	-1.21
Systolic blood pressure (mm Hg)	-4.70	-3.49
Total cholesterol (mg/dL)	-2.99	-0.75
HDL cholesterol (mg/dL)	+0.36	+0.72
LDL cholesterol (mg/dL)	-1.64	+0.41
Triglycerides (mg/dL)	-0.39	-0.23
Body mass index (kg/m ²)	-1.48	-1.28
Severe hypoglycaemic event rate (events per 100 patient-years)	0.00	0.00
Non-severe hypoglycaemic event rate (events per 100 patient-years)	4.20	8.70

¹ Statistically significant difference at 95% confidence level.

Abbreviations: HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

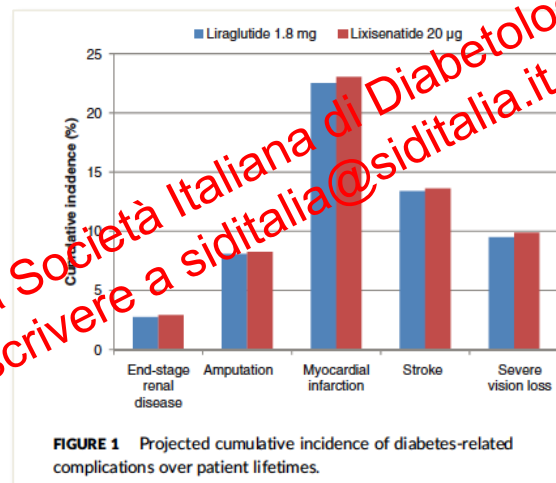
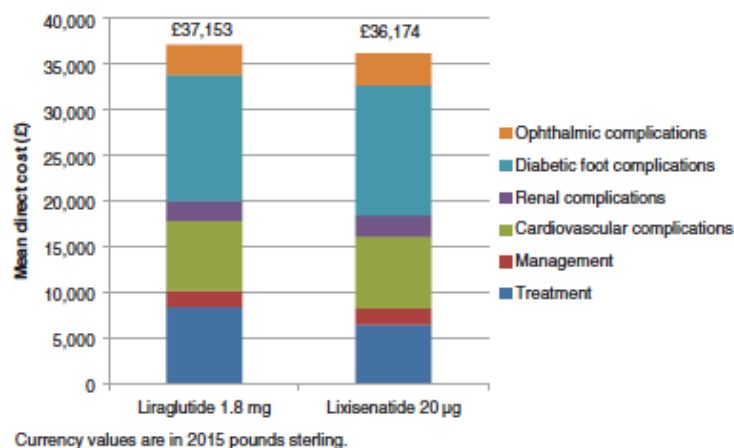


FIGURE 1 Projected cumulative incidence of diabetes-related complications over patient lifetimes.



Currency values are in 2015 pounds sterling.

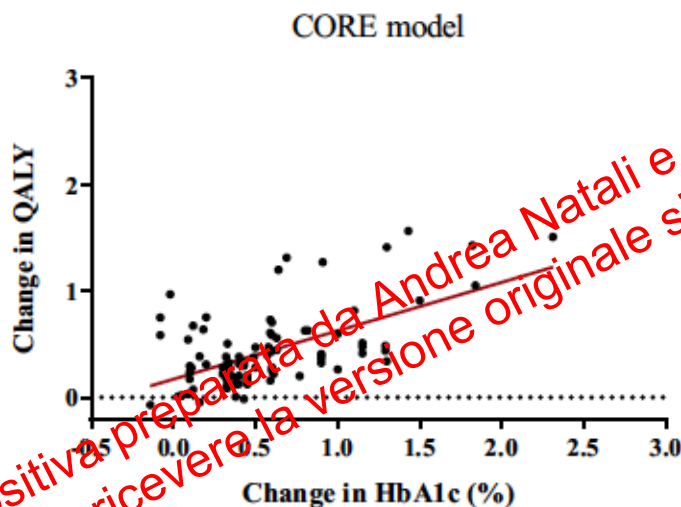
Diapositiva preparata da Andrea Natali e ceduta alla Società Italiana di Diabetologia.
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How Consistent is the Relationship between Improved Glucose Control and Modelled Health Outcomes for People with Type 2 Diabetes Mellitus? a Systematic Review

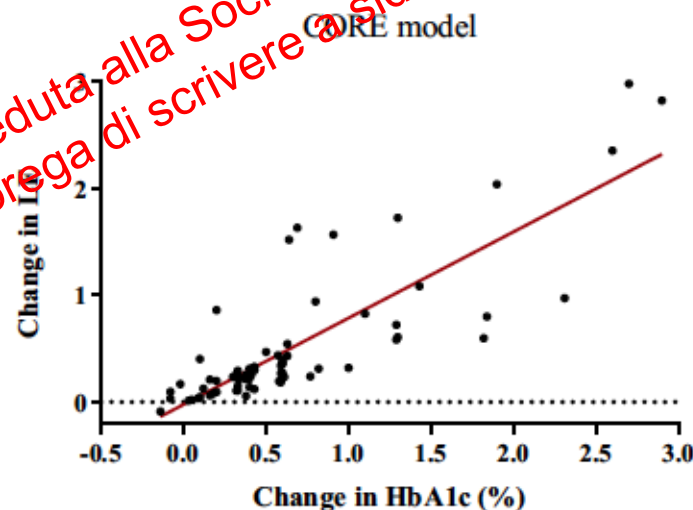
PharmacoEconomics (2017) 35:319–329

life-time quality-adjusted life years



$\partial 1\% = 0.37 \text{ yr}$

life expectancy

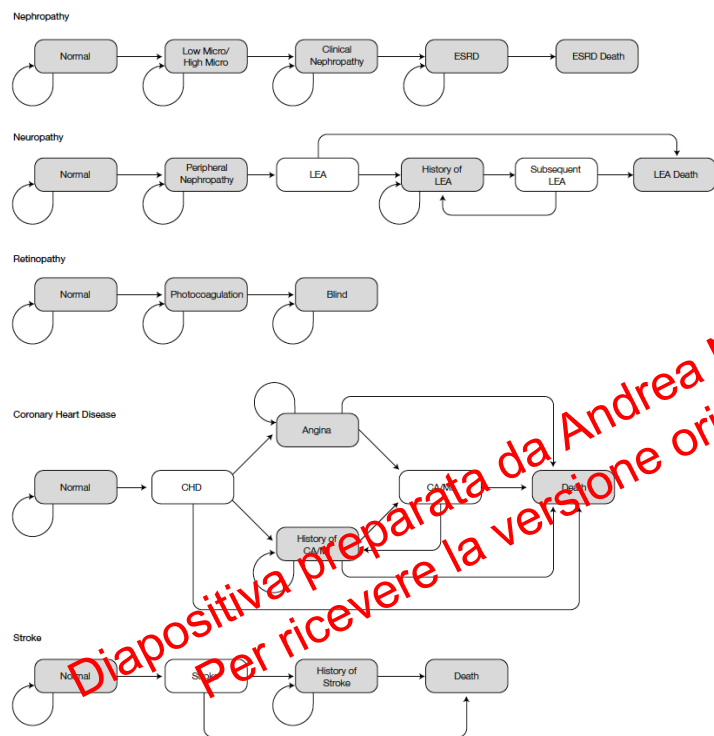


$\partial 1\% = 0.64 \text{ yr}$

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E' meglio trattare la glicemia, la pressione o il colesterolo ? Group CDCDC, JAMA 2002

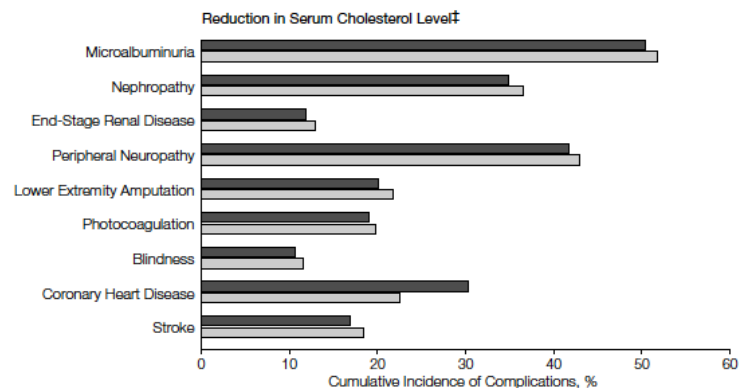
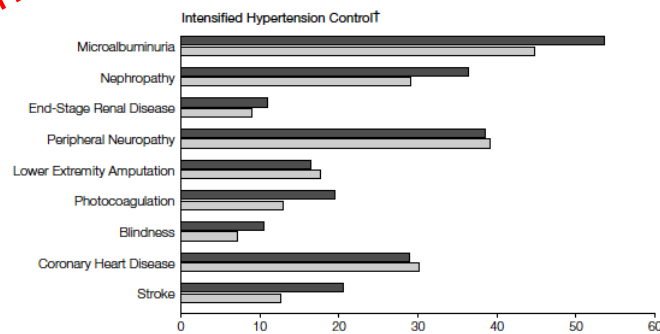
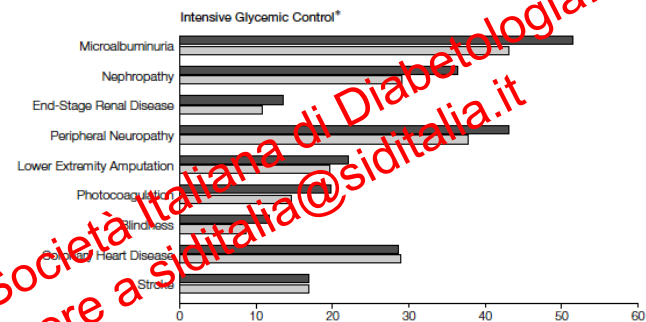


Arrows represent transitions between states; there is a transition probability associated with each transition. Micro indicates microalbuminuria; ESRD, end-stage renal disease; LEA, lower extremity amputation; CHD, coronary heart disease; and CA/MI, cardiac arrest/myocardial infarction.

Glicemia
Insulina e SU
(UKPDS)

Pressione
ACEi e β -B
(UKPDS)

Colesterolo
Pravast.
(WOSCOP/CARE)





E' meglio trattare la glicemia, la pressione o il colesterolo ? Group CDCDC, JAMA 2002

Table 4. Incremental Cost-effectiveness by Intervention

	Cost, \$*				Remaining Life-Years (Not Discounted)	Quality-Adjusted Life-Year (QALYs)*	Incremental Cost-effectiveness Ratio (Total Cost/QALY), \$
	Standard Treatment	Complications	Intervention	Total			
Intensive glycemic control†							
Conventional glycemic control (standard treatment)	10 741	37 602	0	48 343	17.2067	11.8791	
Intervention	10 785	33 271	12 213	56 270	17.5240	12.0707	
Incremental	44	-4330	12 213	7927	0.3173	0.1915	41 384
Intensive hypertension control‡							
Moderate hypertension control (standard treatment)	10 679	33 738	0	44 417	14.4380	10.3990	
Intervention	11 030	28 902	3708	43 641	14.9124	10.7952	
Incremental	351	-4836	3708	-776	0.4744	0.3962	-1959
Reduction in serum cholesterol levels§							
Standard treatment	10 353	34 819	0	45 171	16.3187	11.4690	
Intervention	10 756	36 505	15 942	63 204	16.9909	11.8165	
Incremental	404	1687	15 942	18 033	0.6722	0.3475	51 889

*Discounted at 3% annual rate. Costs are for patient's lifetime and are reported in 1997 dollars.

†All patients who were newly diagnosed as having type 2 diabetes.

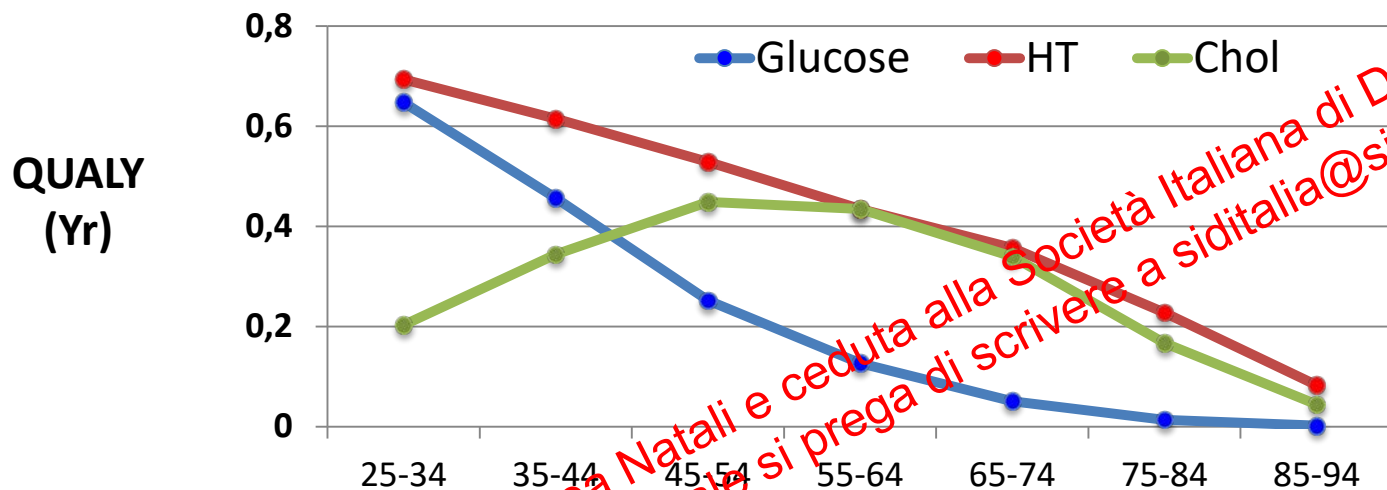
‡All patients who were newly diagnosed as having type 2 diabetes and hypertension.

§All patients who were newly diagnosed as having type 2 diabetes and above normal serum cholesterol level.

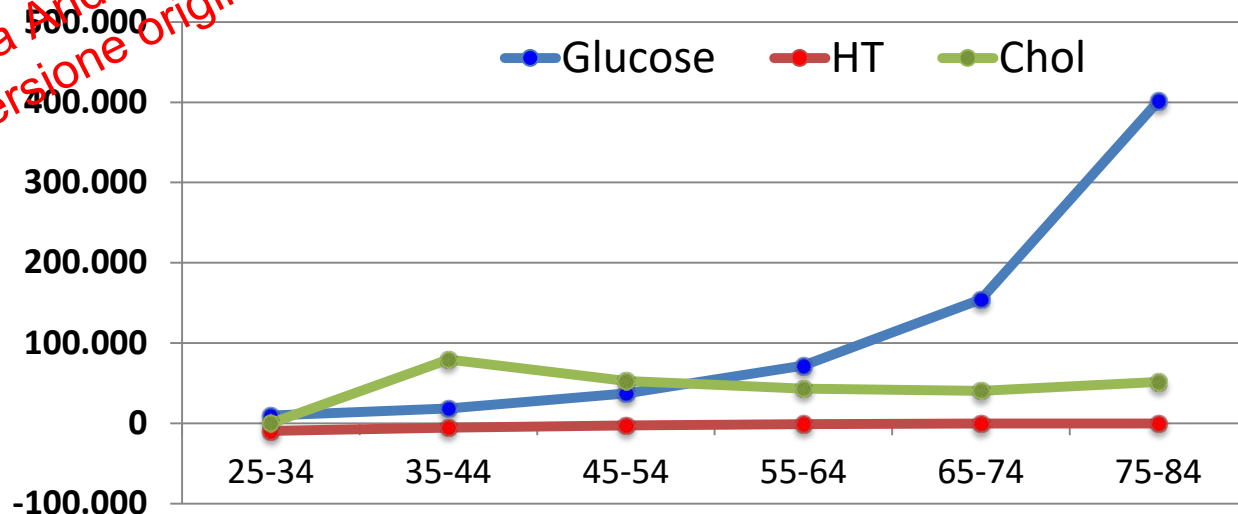
Diapositiva preparata da Andrea Natali e ceduta alla Società Italiana di Diabetologia.
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E' meglio trattare la glicemia, la pressione o il colesterolo ? Group CDCDC, JAMA 2002

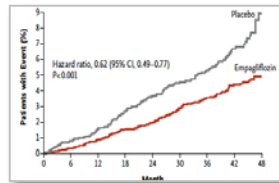


Cost Effectiveness (\$/QALY)

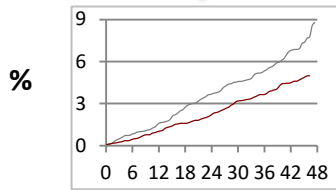




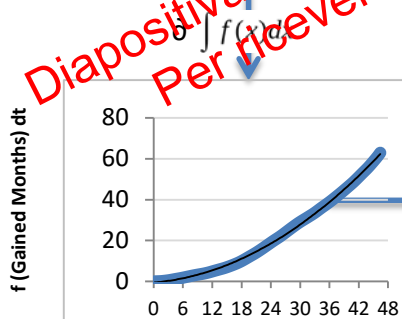
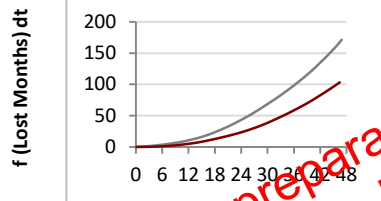
CV death



Data extraction



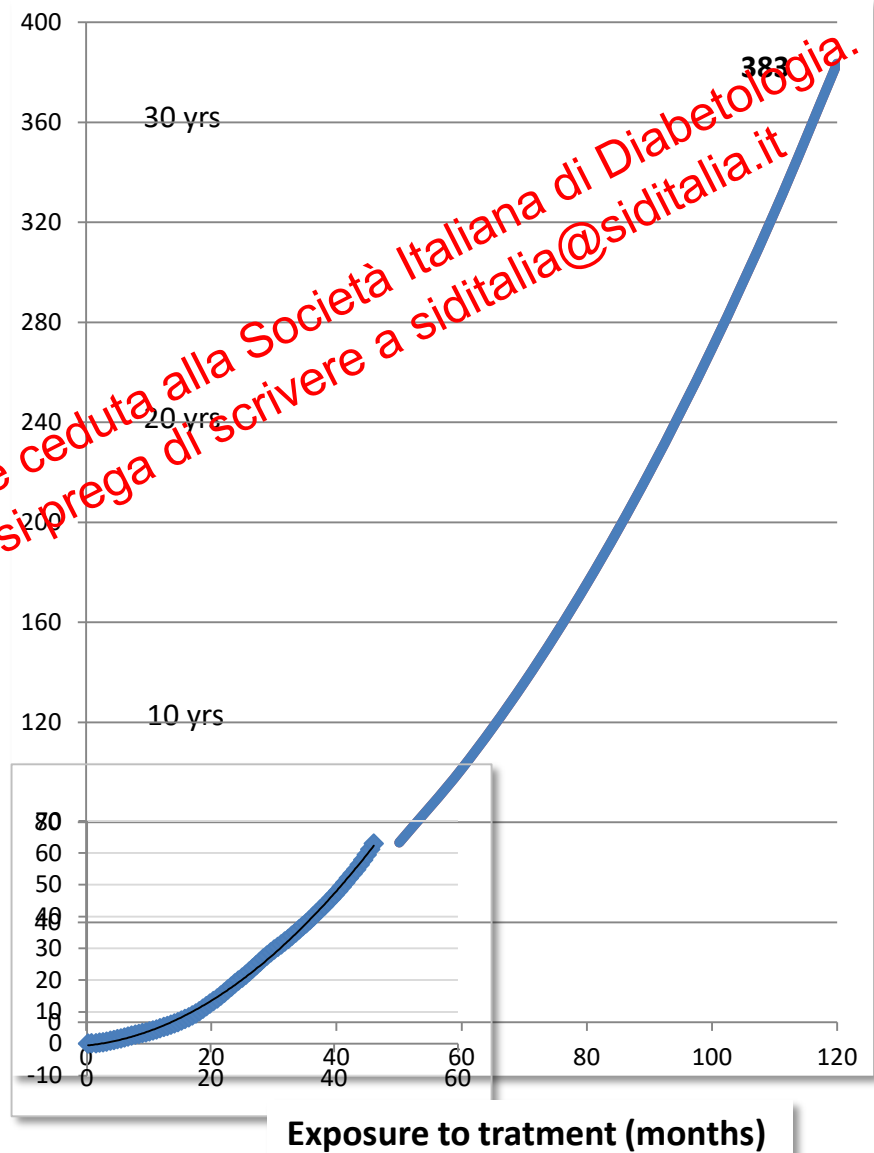
$\int f(x)dx$



Data fit

$$y = 0.025x^2 + 0.2x - 0.55$$

Predicted time free of CV death with Empagliflozin
(months/100 pts)



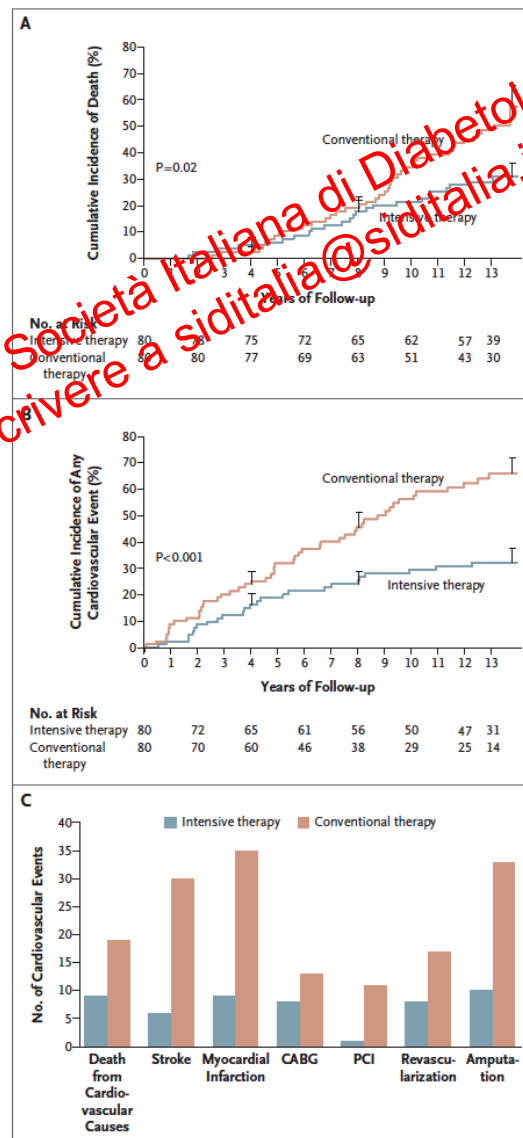
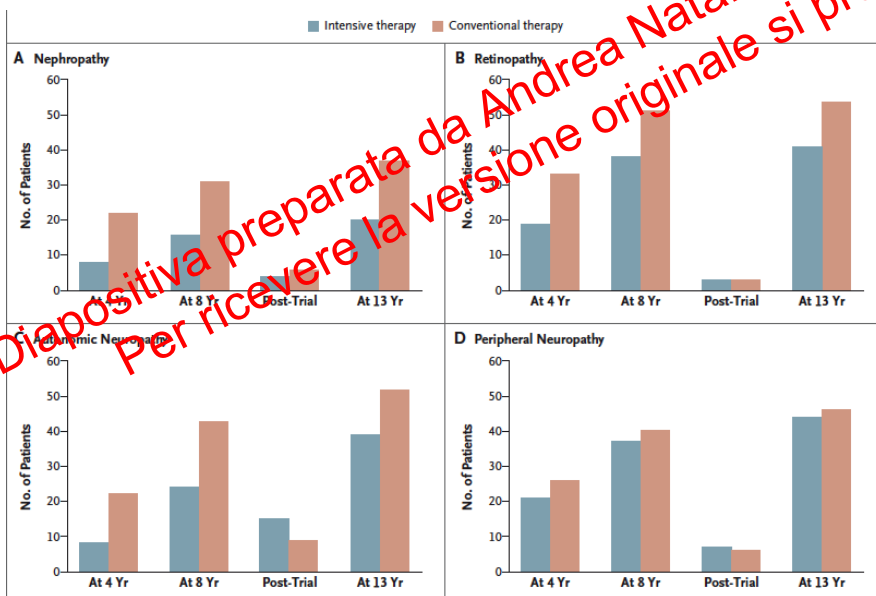
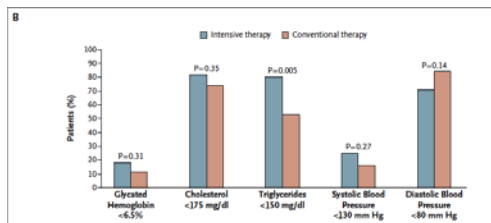
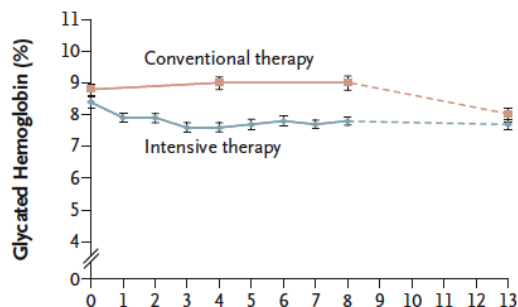
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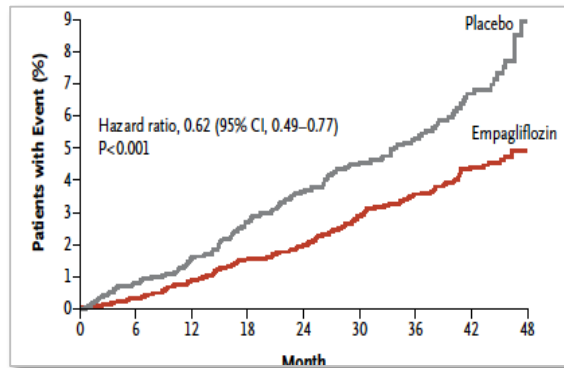
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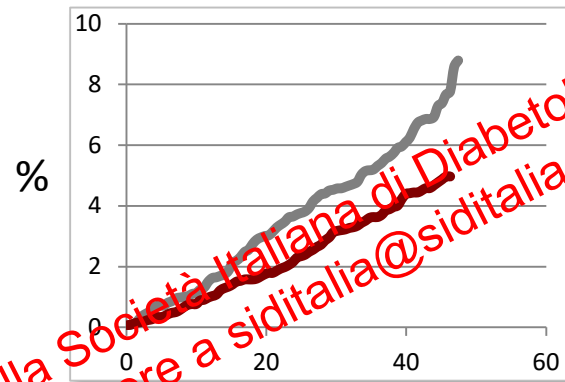
STENO-2, 160 patients uAlb, 55 aa, BMI 30



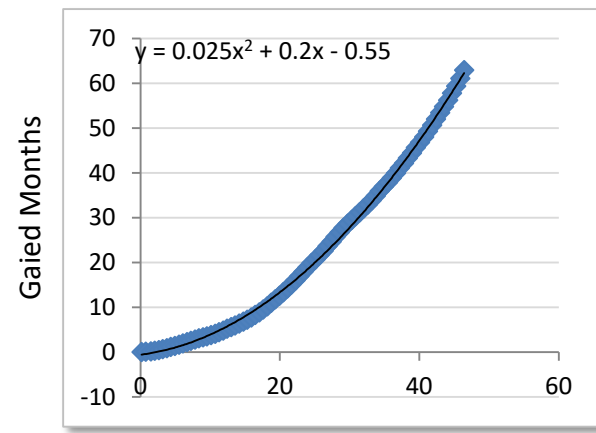
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Data extraction



$\partial \int f(x) dx$



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Tipo di studio

(A) Treatment goals with any drugs

ACCORD (neg), VADT (neg), UKPDS (+/-pos), DCCT (pos)

(C) Treatment goals with specific drug and/or strategies

ADVANCE: Glicazide vs any other (neg, only microV)

HEART2D: Prandial vs Basal insulin (neg)

(B) Specific drug/class vs any other

DDPIV: Saxa/SAVOR-TIMI 53, Sitagliptin/TECOS, Alo/EXAMINE, Lina/CARMELINA

GLP-1 a: Lixi/ELIXA, Lira/LEADER, Sema/SUSTAIN

SGLT-2: EMPA REG OUTCOME, Dapa/DECLARE TIMI 58, Cana/CANVAS

(D) Comparison of 2 different drugs/class

BARI 2D: Ins sens vs Ins provision (neg)

CAROLINA: Lina vs Glimepiride (ongoing)

DEVOTE: Degludec vs Glargine (ongoing)

TOSCA: PIO vs SU (ongoing)

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