Terapia con analoghi del GLP-1: quando e perché - II FASE
Roma, 29 ottobre 2019

Possiamo stringere di nuovo il target glicemico?

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Conflitti di Interesse

- Il sottoscritto dichiara di avere avuto rapporti professionali con le seguenti aziende:
  - Sanofi
  - MSD
  - Lilly
  - Boheringer Ingelheim
  - Ogilvy
  - Jansenn

Agenda

- E’ stato affrettato abbandonare il controllo intensivo?
- E’ necessario ridiscutere l’obiettivo glicemico?
- Abbiamo sufficienti elementi per rivalutare l’obiettivo glicemico?
- A quali obiettivi possiamo ambire?

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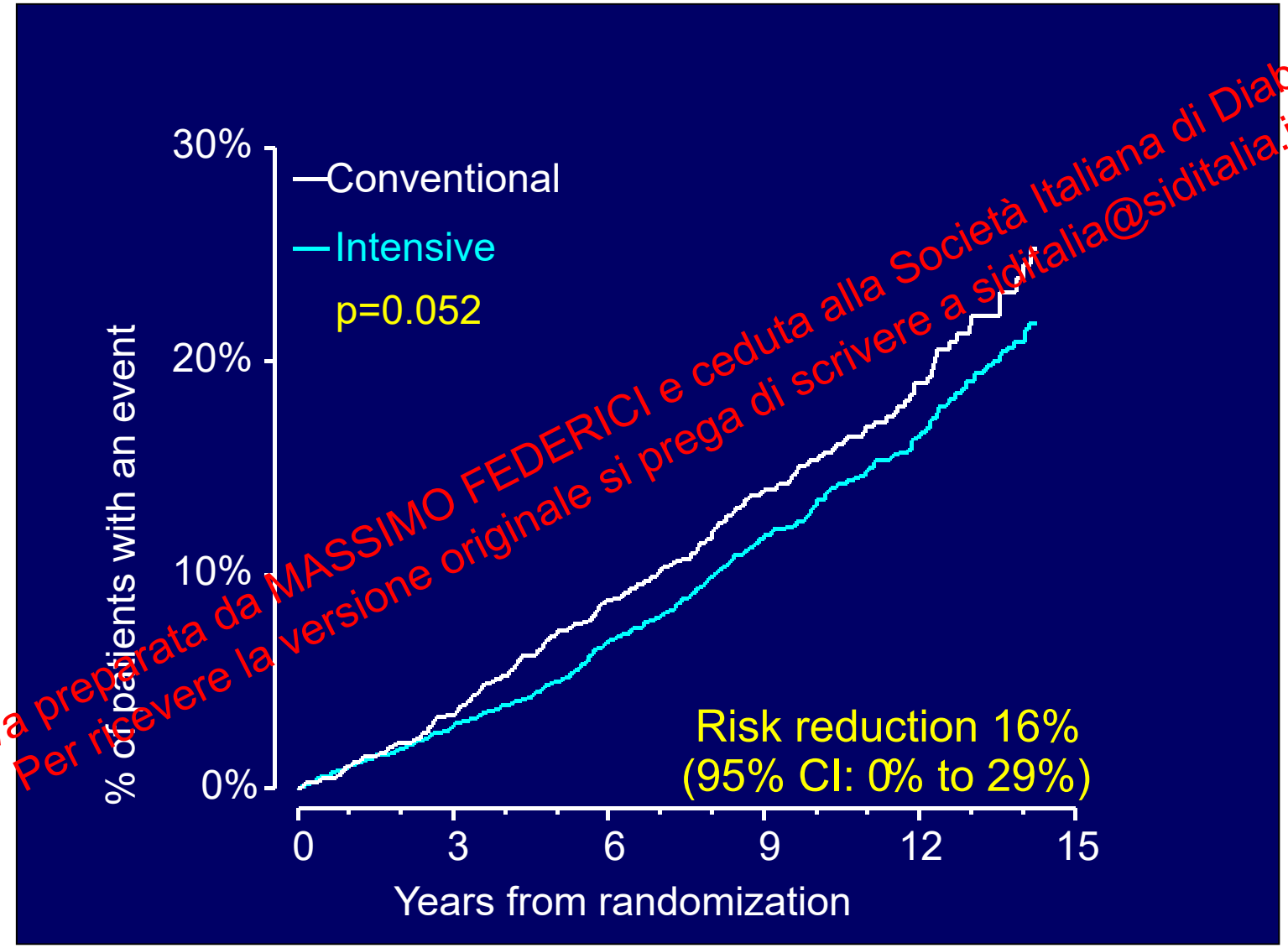
- A quali obiettivi possiamo ambire?

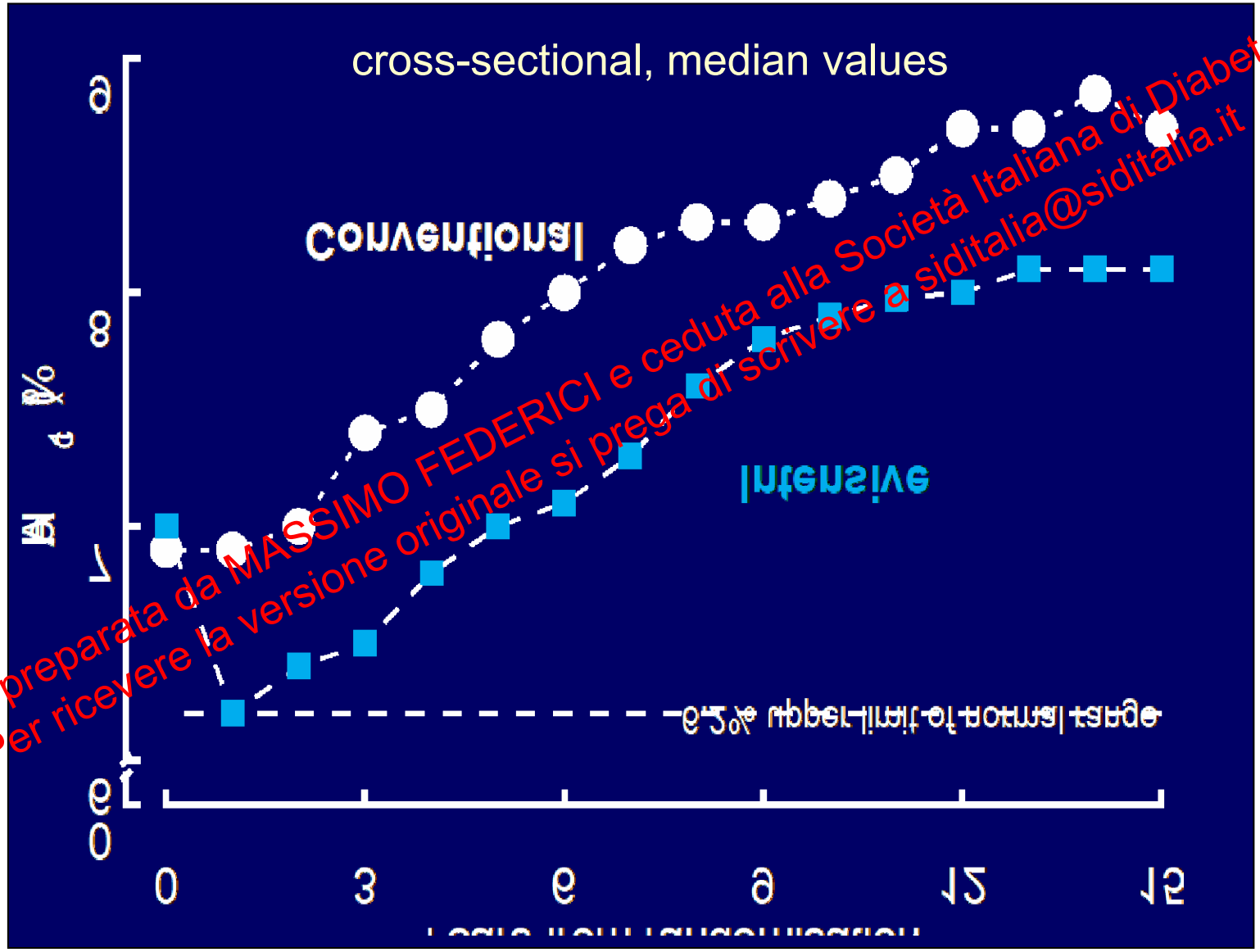
UKPDS Myocardial Infarction (cumulative)

fatal or non fatal myocardial infarction, sudden death573 of 3867 patients (15%)



UKPDS 35*: Lancet*. 1998, 352:837-53.

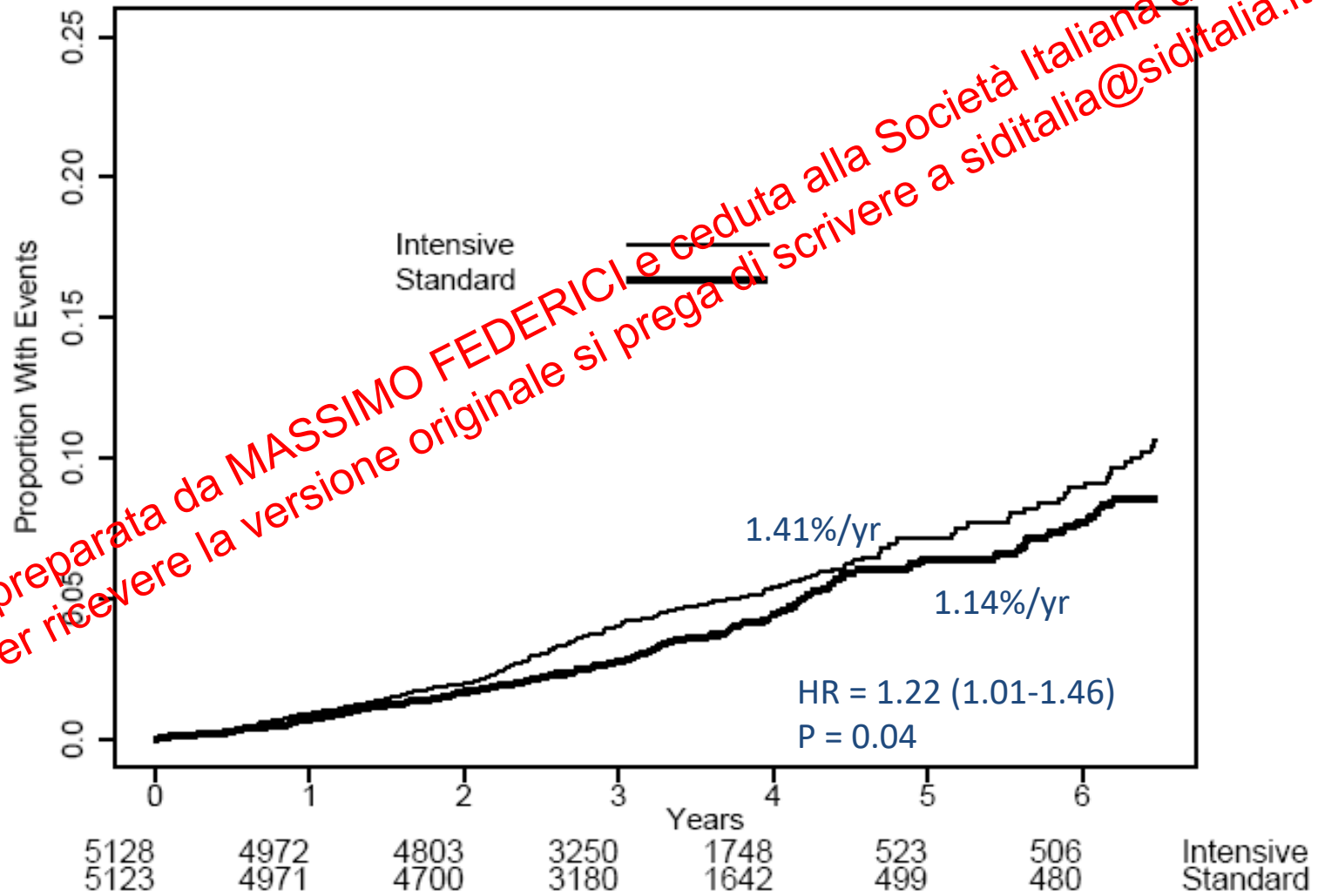
UKPDS HbA_{1c} trend



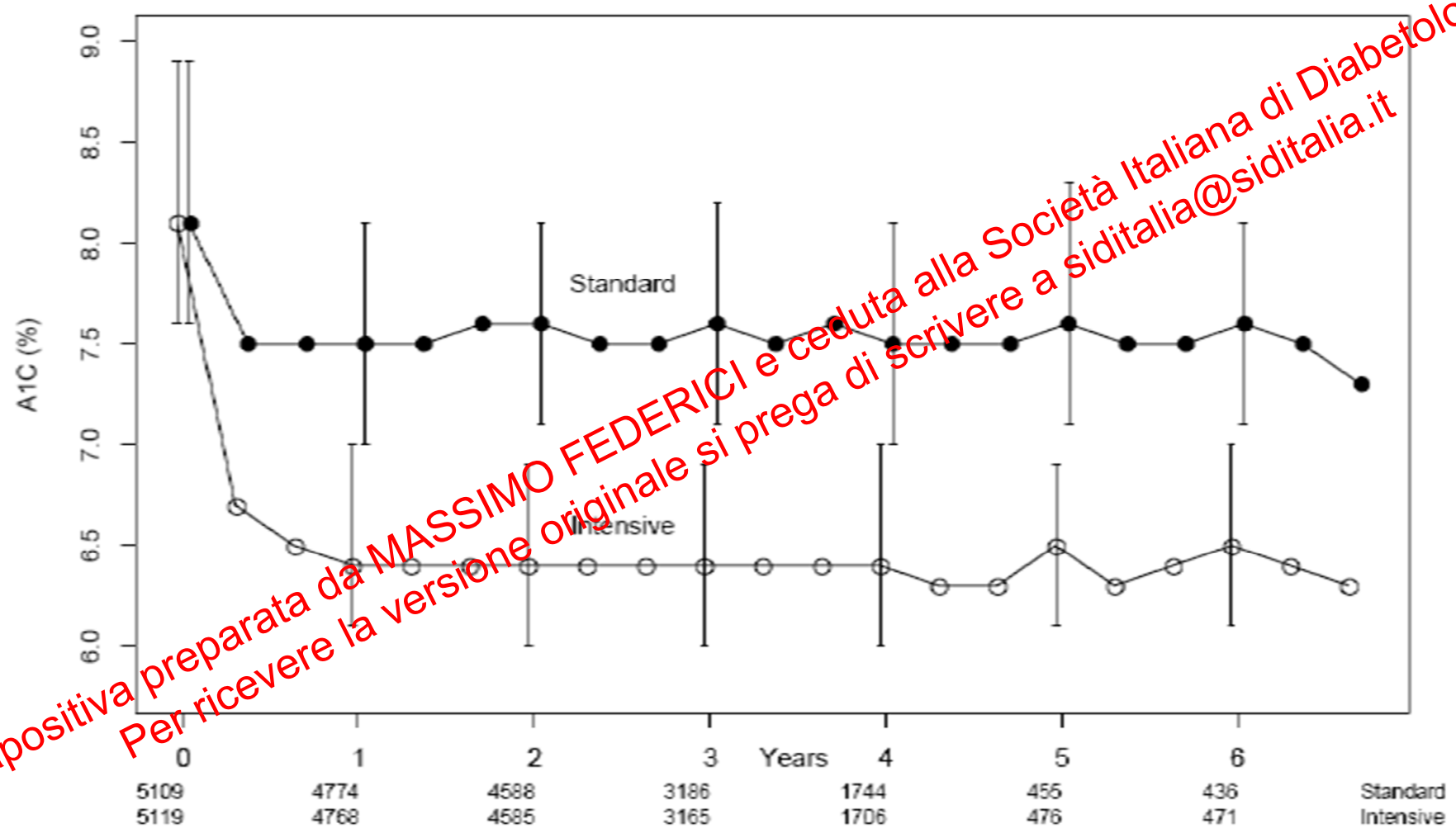
UKPDS 35*: Lancet*. 1998, 352:837-53.

ACCORD

All Cause Mortality



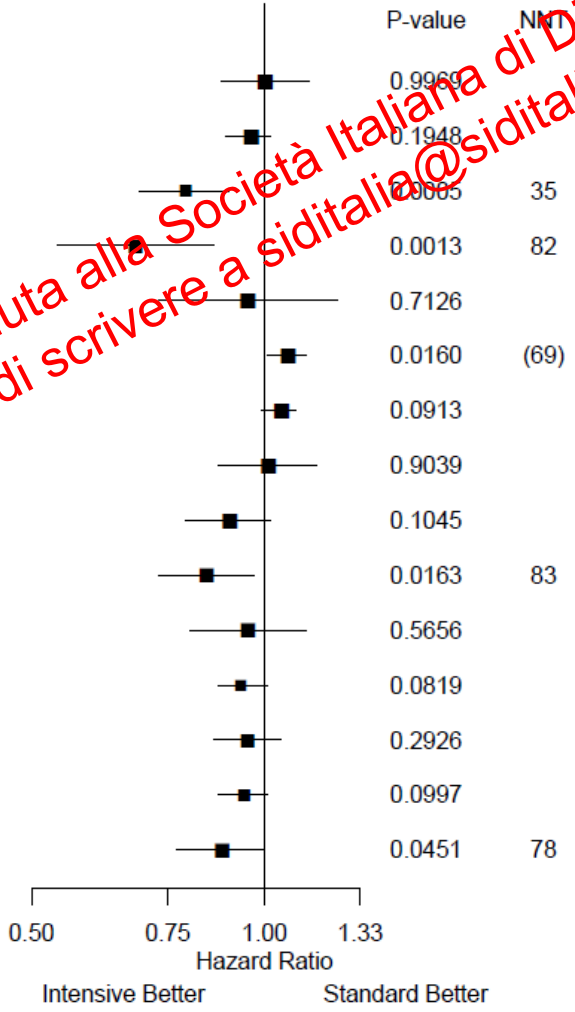
Median A1C and Interquartile Ranges



Summary of Microvascular Results

Up to Transition

Outcome	Intensive %	Intensive N	Standard %	Standard N	HR (95% CI)	P-value	NNT
Primary	8.7	5107	8.7	5108	1.00 (0.88,1.14)	0.9969	
Secondary	31.2	5107	32.5	5108	0.96 (0.89,1.02)	0.1948	
Neph-1	12.5	3204	15.3	3232	0.79 (0.69,0.90)	0.0005	35
Neph-2	2.7	4334	3.9	4361	0.68 (0.54,0.86)	0.0013	82
Neph-3	2.1	5107	2.2	5108	0.95 (0.73,1.24)	0.7126	
Neph-4	53.6	5035	52.2	5034	1.07 (1.01,1.13)	0.0160	(69)
Neph-5	54.4	5107	53.8	5108	1.05 (0.99,1.10)	0.0913	
Eye-1	7.2	4886	7.1	4910	1.01 (0.87,1.17)	0.9039	
Eye-2	9.1	4886	10.1	4912	0.90 (0.79,1.02)	0.1045	
Eye-3	8.1	4450	9.8	4483	0.84 (0.73,0.97)	0.0163	83
Eye-4	5.5	4651	5.8	4689	0.95 (0.80,1.13)	0.5656	
Neuro-1	45.4	2815	47.9	2791	0.93 (0.87,1.01)	0.0819	
Neuro-2	18.2	4209	19.1	4209	0.95 (0.86,1.05)	0.2926	
Neuro-3	37.1	3298	38.9	3265	0.94 (0.87,1.01)	0.0997	
Neuro-4	9.3	4577	10.5	4564	0.88 (0.77,1.00)	0.0451	78

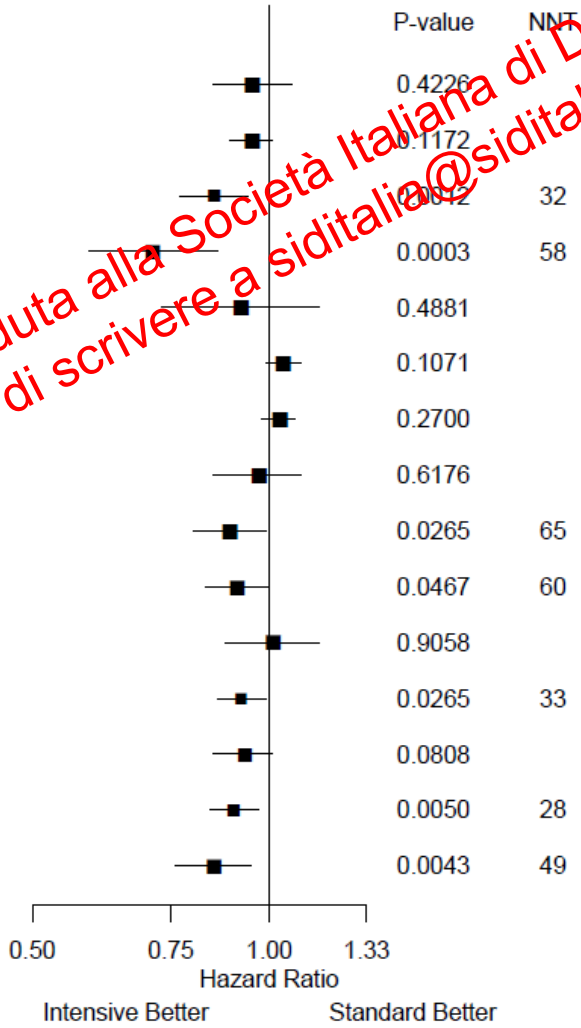


Pr(≥ 1 significant test) = 0.54

Summary of Microvascular Results

Through End of Study

Outcome	Intensive %	Intensive N	Standard %	Standard N	HR (95% CI)	P-value	NNT
Primary	10.9	5119	11.5	5115	0.95 (0.85,1.07)	0.4226	
Secondary	38.2	5119	40	5115	0.95 (0.89,1.01)	0.1172	
Neph-1	22.2	3250	25.3	3273	0.85 (0.77,0.94)	0.0012	32
Neph-2	4.4	4397	6.1	4424	0.71 (0.59,0.86)	0.0003	58
Neph-3	2.7	5119	3	5115	0.92 (0.73,1.16)	0.4881	
Neph-4	58.6	5041	58.5	5035	1.04 (0.99,1.10)	0.1071	
Neph-5	59.7	5119	60.2	5115	0.93 (0.98,1.08)	0.2700	
Eye-1	9	4915	9.2	4983	0.97 (0.85,1.10)	0.6176	
Eye-2	14.2	4915	15.7	4983	0.89 (0.80,0.99)	0.0265	65
Eye-3	19.1	4716	20.7	4725	0.91 (0.83,1.00)	0.0467	60
Eye-4	8.1	4748	8.1	4774	1.01 (0.88,1.16)	0.9058	
Neuro-1	56	2829	58.6	2797	0.92 (0.86,0.99)	0.0265	33
Neuro-2	23.2	4227	24.9	4217	0.93 (0.85,1.01)	0.0808	
Neuro-3	45.7	3312	49.3	3271	0.90 (0.84,0.97)	0.0050	28
Neuro-4	12.1	4596	14.1	4573	0.85 (0.76,0.95)	0.0043	49



P (≥ 1 significant test) = 0.54

Conclusions

- Intensive treatment of glycemia in the ACCORD cohort did not reduce the risk of composite measures of advanced microvascular outcomes
- Intensive therapy delayed the onset of albuminuria and some measures of eye complications and neuropathy
- Microvascular benefits of intensive therapy should be weighed against increase in total and CVD-related mortality, increased weight gain, and high risk for severe hypoglycemia

Tightening our understanding of intensive glycaemic control

Lancet Diabetes Endocrinol 2017

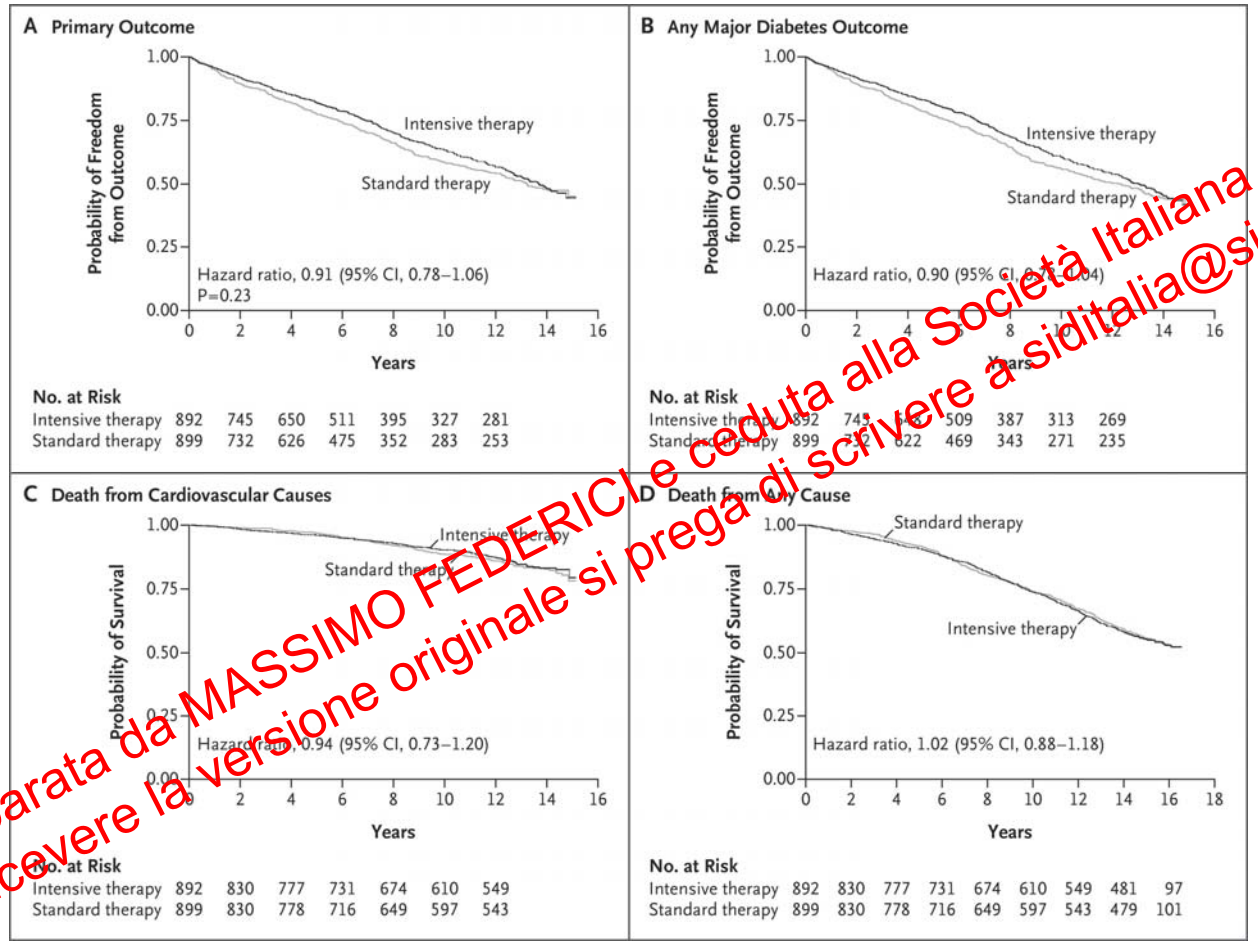
ACCORD, ADVANCE, UKPDS, and VADT

	More intensive glycaemic control (n=14 320)	Less intensive glycaemic control (n=12 729)	Hazard ratio (95% CI)
Known benefit			
Major cardiovascular disease	1194 (8%)	1176 (9%)	0·91 (0·84–0·99)
Kidney disease	761 (5%)	865 (7%)	0·80 (0·72–0·88)
Eye disease	428 (3%)	367 (3%)	0·87 (0·76–1·00)
Harm			
Severe hypoglycaemia	1071 (7%)	372 (3%)	2·48 (1·91–3·21)
Any death	980 (7%)	884 (7%)	1·04 (0·90–1·20)

Data are n (%) participants from within the first 5 years of follow-up, adapted from CONTROL Group meta-analyses.[1,2]

***Table*: More versus less intensive glycaemic control in the four trials contributing to the CONTROL Group meta-analyses**

Kaplan–Meier Curves for the Primary and Secondary Outcomes during the Trial and Follow-up Period.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up

Peter D. Reaven, M.D., Nicholas V. Emanuele, M.D., Wyndy L. Wiitala, Ph.D., Gideon D. Bahn, Ph.D., Domenic J. Reda, Ph.D., Madeline McCarren, Ph.D., William C. Duckworth, M.D., and Rodney A. Hayward, M.D., for the VADT Investigators*

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VADT

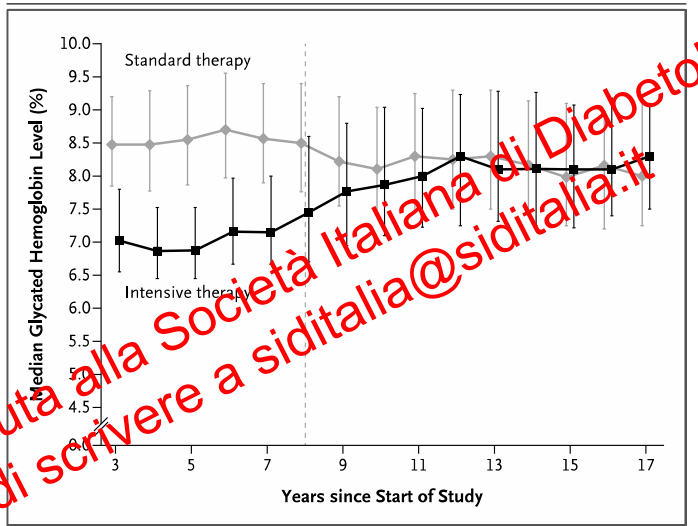

Figure 1. Median Glycated Hemoglobin Levels According to Year since Start of the Trial, Starting at Year 3.

Year 3 was a point at which all the participants had been enrolled and had been receiving treatment per protocol for at least 3 months. The I bars (slightly offset for better visibility) represent interquartile ranges. The dotted line represents the end of the interventional component of the trial and the beginning of the follow-up period. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50.

- Participants with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had a lower risk of cardiovascular events than those who received standard therapy only during the prolonged period in which the glycated hemoglobin curves were separated.
- There was no evidence of a legacy effect or a mortality benefit with intensive glucose control.

Effect of Intensive Glucose Therapy on Major Cardiovascular Events during Periods of Separation of Glycated Hemoglobin Curves (Years 0–10) and No Separation (Years 11–15).

Table 3. Effect of Intensive Glucose Therapy on Major Cardiovascular Events during Periods of Separation of Glycated Hemoglobin Curves (Years 0–10) and No Separation (Years 11–15).*

Variable	Years 0–10	Years 11–15
No. of participants	1791	633
No. of events	502	145
Model and predictors — hazard ratio (95% CI)		
Model 1		
Intensive therapy or standard therapy	0.83 (0.70–0.99)	1.26 (0.90–1.76)
Model 2		
Intensive therapy or standard therapy	0.83 (0.70–0.99)	1.27 (0.91–1.76)
Baseline glycated hemoglobin level	1.06 (1.00–1.12)	1.08 (0.96–1.21)
Model 3		
Intensive therapy or standard therapy	0.86 (0.71–1.04)	1.24 (0.89–1.74)
Most recent glycated hemoglobin level, as a time-varying covariate	1.03 (0.97–1.09)	0.93 (0.84–1.04)
Model 4		
Intensive therapy or standard therapy	0.94 (0.77–1.15)	1.37 (0.95–1.96)
Cumulative mean glycated hemoglobin level, as a time-varying covariate	1.11 (1.02–1.20)	1.09 (0.92–1.28)

* Shown are results from Cox proportional-hazards models for primary cardiovascular outcomes according to time intervals during the Veterans Affairs Diabetes Trial and the follow-up study. Years 0 through 10 reflect the interval of time for which there was evident separation of the glucose curves between the treatment groups. Years 11 through 15 reflect the initial interval when the glycated hemoglobin levels had merged between the two treatment groups and during which all data (from the Veterans Affairs, Centers for Medicare and Medicaid Services, and National Death Index databases) were available. Model 1 examined the effect of treatment group only on primary cardiovascular events during two time periods (years 0 through 10 and years 11 through 15). Models 2, 3, and 4 were applied to the same two time periods and included two predictors: the treatment group (intensive therapy or standard therapy) and the glycated hemoglobin level (baseline value, most recent value as a time-varying covariate, or cumulative mean as a time-varying covariate, respectively). In a sensitivity analysis, we found that only glycated hemoglobin levels from the most recent 3 years were needed to explain the treatment effect and that levels that were observed more than 3 years earlier had no evidence of either predictive value for cardiovascular events or evidence of mediation of the observed reduction in the risk of cardiovascular events in the clinical trial (see the Results Section in the Supplementary Appendix). The numbers of participants in each group reflect the number of participants enrolled in the trial who had not yet had a primary outcome at the beginning of the indicated intervals. The confidence intervals were not adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.

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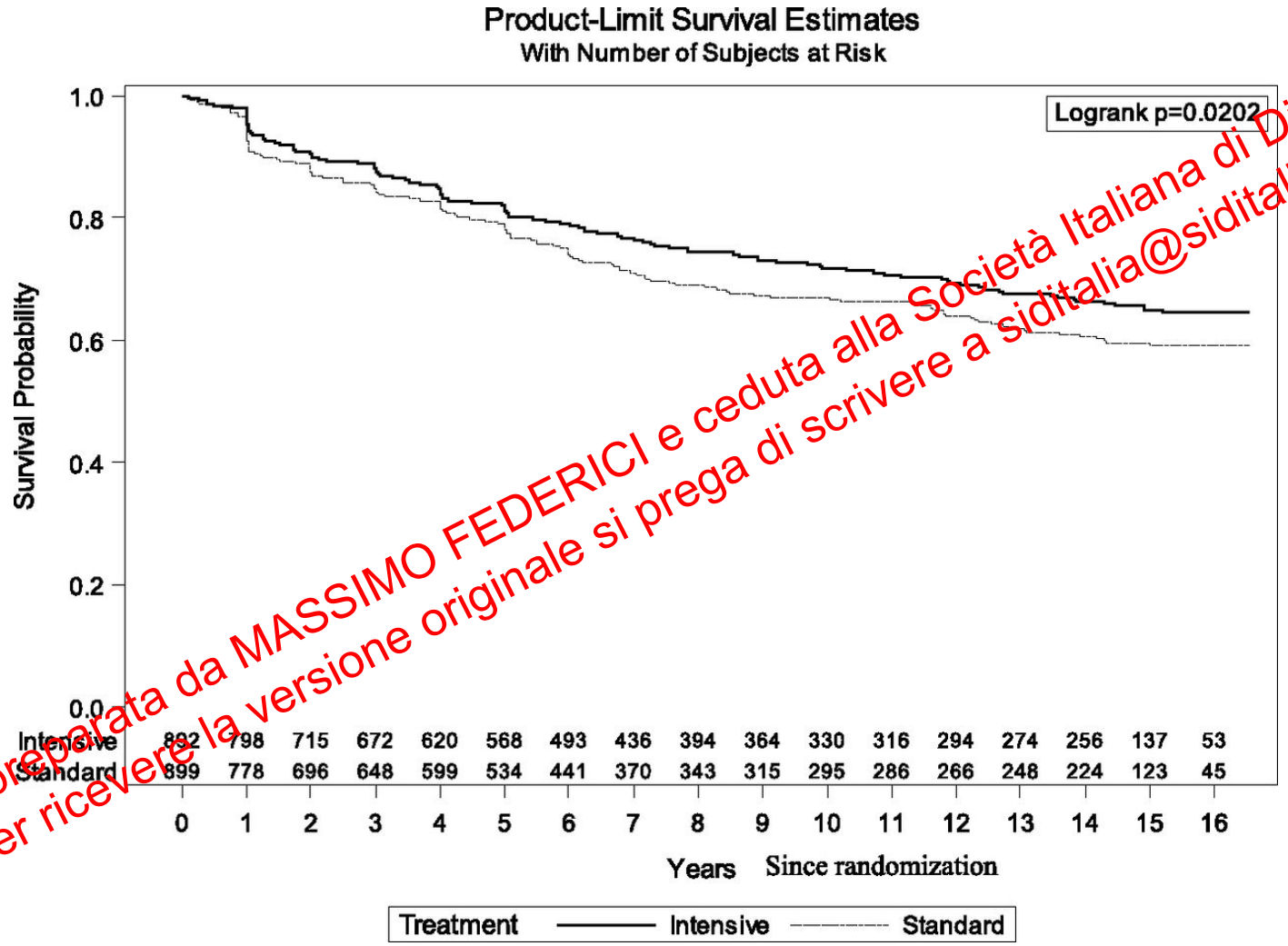
Kaplan-Meier analysis of time to renal composite from randomization in the VADT to end of 15 years (15 November 2000–30 June 2017).



Lily Agrawal et al. Dia Care 2019;42:e181-e182

American Diabetes Association.

Agenda

- E’ stato affrettato abbandonare il controllo intensivo?
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Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

Craig J Currie, John R Peters, Aodán Tynan, Marc Evans, Robert J Heine, Oswaldo L Bracco, Tony Zagar, Chris D Poole

Lancet 2010; 375: 481–89

	HbA_{1c} deciles										All (n=27 965)
	1 (n=3513)	2 (n=3501)	3 (n=3374)	4 (n=3136)	5 (n=2884)	6 (n=2684)	7 (n=2437)	8 (n=2334)	9 (n=2133)	10 (n=1969)	
HbA_{1c} post index* (% total haemoglobin)	6·42% (3·30–6·72)	6·94% (6·73–7·11)	7·27% (7·12–7·40)	7·54% (7·41–7·68)	7·82% (7·69–7·96)	8·11% (7·97–8·26)	8·44% (8·27–8·63)	8·85% (8·64–9·11)	9·41% (9·12–9·84)	10·47% (9·85–16·20)	7·73% (3·30–16·20)
Men	1973 (56%)	1939 (55%)	1928 (57%)	1824 (58%)	1699 (59%)	1596 (60%)	1410 (58%)	1370 (59%)	1254 (59%)	1055 (54%)	16 048 (57%)
Age† (years)	67·4	66·3	65·5	64·7	64·0	63·7	62·7	62·1	61·0	59·7	64·1
Previous SBP‡ (mm Hg)	145 (17)	144 (16)	144 (16)	144 (16)	144 (17)	143 (17)	144 (17)	144 (17)	144 (17)	145 (18)	144 (17)
Smoked ever (%)	2178 (62%)	2240 (64%)	2159 (64%)	1976 (63%)	1846 (64%)	1745 (65%)	1487 (61%)	1447 (62%)	1322 (62%)	1201 (61%)	17618 (63%)
Previous total cholesterol‡ (mmol/L)	5·2 (1·0)	5·3 (1·0)	5·3 (1·0)	5·4 (1·1)	5·4 (1·0)	5·5 (1·1)	5·6 (1·1)	5·6 (1·1)	5·7 (1·2)	5·8 (1·3)	5·4 (1·1)
Male weight (kg)	90 (16)	89 (16)	88 (15)	89 (16)	90 (16)	90 (16)	91 (17)	91 (17)	92 (18)	93 (19)	90 (16)
Female weight (kg)	79 (17)	79 (16)	78 (16)	78 (16)	78 (16)	79 (17)	79 (17)	81 (17)	81 (18)	84 (19)	79 (17)
Previous LVD§	892 (25%)	846 (24%)	760 (23%)	702 (22%)	629 (22%)	620 (23%)	552 (23%)	466 (20%)	403 (19%)	360 (18%)	6230 (22%)
Diabetes duration¶ (years)											
Mean (SD)	5·3 (4·2)	5·3 (4·1)	5·5 (4·1)	5·4 (3·9)	5·4 (3·9)	5·6 (4·1)	5·6 (4·0)	5·5 (4·0)	5·2 (3·7)	5·4 (3·9)	5·4 (4·0)
Median (IQR)	4·2 (2·2–7·3)	4·2 (2·3–7·1)	4·5 (2·4–7·4)	4·5 (2·4–7·4)	4·4 (2·4–7·4)	4·6 (2·4–7·4)	4·8 (2·5–7·8)	4·6 (2·5–7·5)	4·3 (2·4–7·0)	4·4 (2·3–7·6)	4·4 (2·4–7·4)
Previous vision problem	502 (14%)	486 (14%)	509 (15%)	424 (14%)	351 (12%)	343 (13%)	278 (11%)	246 (11%)	253 (12%)	212 (11%)	3604 (13%)
Creatinine >130 μmol/L‖	248 (7%)	204 (6%)	184 (6%)	167 (5%)	133 (5%)	111 (4%)	110 (5%)	86 (4%)	71 (3%)	57 (3%)	1366 (5%)
Deaths	301 (9%)	238 (7%)	231 (7%)	207 (7%)	190 (7%)	179 (7%)	175 (7·%)	168 (7%)	161 (8%)	185 (9%)	2035 (7%)

Achieved HbA_{1c} was the mean of any values recorded between the index date and death or censor. Data are median (range), n (%), mean (SD), or median (IQR) unless otherwise stated. HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. LVD=large-vessel disease. *Mean HbA_{1c} recorded between study index date and event or censor date. †At index date. ‡Mean of all observations in year before index date. §Clinically emergent large-vessel disease before index date (defined by ACCORD[6] trial criteria). ¶Duration of diabetes before index date from first relevant clinical event. ‖Any record of serum creatinine test result >130 μmol/L before index date.

Table 1: **Baseline characteristics of cohort 1 (oral hypoglycaemic agents) by baseline, stratified by mean HbA_{1c} decile group**

Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

Craig J Currie, John R Peters, Aodán Tynan, Marc Evans, Robert J Heine, Oswaldo L Bracco, Tony Zagar, Chris D Poole

Lancet 2010; 375: 481–89

	HbA_{1c} deciles										All (n=20 005)
	1 (n=1289)	2 (n=1291)	3 (n=1424)	4 (n=1661)	5 (n=1878)	6 (n=2148)	7 (n=2354)	8 (n=2463)	9 (n=2660)	10 (n=2837)	
HbA_{1c} post index* (% total haemoglobin)	6·38% (3·97–6·72)	6·95% (6·73–7·11)	7·28% (7·12–7·40)	7·55% (7·41–7·68)	7·83% (7·69–7·96)	8·11% (7·97–8·26)	8·45% (8·27–8·63)	8·87% (8·64–9·11)	9·42% (9·12–9·84)	10·56% (9·85–18·80)	8·31% (3·97–18·80)
Men	680 (53%)	726 (56%)	780 (55%)	911 (55%)	1035 (55%)	1128 (53%)	1263 (54%)	1315 (53%)	1320 (50%)	1409 (50%)	10 566 (53%)
Age† (years)	65·9 (11·2)	66·3 (10·3)	65·5 (10·0)	64·9 (10·5)	64·4 (10·5)	64·7 (10·5)	63·4 (10·6)	63·1 (10·9)	62·3 (11·3)	60·3 (11·5)	63·6 (11·0)
Previoius SBP‡ (mmHg)	145 (19)	145 (18)	145 (18)	144 (18)	144 (18)	144 (18)	143 (17)	143 (18)	143 (18)	142 (18)	143 (18)
Smoked ever (%)	786 (61%)	852 (66%)	897 (63%)	1030 (62%)	1202 (64%)	1332 (62%)	1483 (63%)	1527 (62%)	1649 (62%)	1731 (61%)	12603 (63%)
Total cholesterol‡ (mmol/L)	5·3 (1·2)	5·3 (1·1)	5·3 (1·1)	5·3 (1·0)	5·4 (1·1)	5·4 (1·1)	5·4 (1·1)	5·5 (1·2)	5·6 (1·2)	5·6 (1·2)	5·5 (1·2)
Male weight‡ (kg)	88 (17)	87 (16)	86 (16)	88 (16)	86 (16)	86 (16)	87 (16)	87 (17)	88 (17)	90 (19)	88 (17)
Female weight‡ (kg)	77 (18)	79 (17)	79 (18)	77 (17)	79 (17)	77 (16)	78 (17)	79 (17)	79 (19)	81 (19)	79 (18)
Previous LVD§	459 (36%)	435 (34%)	411 (29%)	505 (30%)	569 (30%)	625 (29%)	733 (31%)	711 (29%)	766 (29%)	723 (26%)	5937 (30%)
Diabetes duration¶ (years)											
Mean (SD)	6·8 (5·2)	7·5 (5·1)	8·1 (6·4)	7·8 (5·3)	8·0 (5·1)	8·2 (5·1)	8·0 (5·0)	7·9 (5·1)	7·9 (5·0)	7·3 (4·9)	7·8 (5·1)
Median (IQR)	5·9 (2·6–9·3)	6·9 (3·4–10·8)	7·4 (3·8–11·5)	7·1 (3·5–11·1)	7·2 (4·0–11·3)	7·4 (4·3–11·4)	7·4 (4·0–11·2)	7·2 (3·8–11·2)	7·2 (4·0–11·2)	6·5 (3·4–10·4)	7·1 (3·7–11·0)
Previous vision problems	351 (20%)	272 (21%)	320 (23%)	341 (21%)	380 (20%)	501 (23%)	524 (22%)	523 (21%)	557 (21%)	556 (20%)	4225 (21%)
Creatinine >130 µmol/L‖	205 (16%)	185 (14%)	182 (13%)	215 (13%)	203 (11%)	248 (12%)	213 (9%)	251 (10%)	257 (10%)	250 (9%)	2209 (11%)
Deaths	232 (18%)	204 (16%)	209 (15%)	192 (12%)	211 (11%)	271 (13%)	305 (13%)	334 (14%)	404 (15%)	472 (17%)	2834 (14%)

Achieved HbA_{1c} was the mean of any values recorded between the index date and death or censor. Data are median (range), n (%), mean (SD), or median (IQR). HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. LVD=large-vessel disease. *Mean HbA_{1c} recorded between study index date and event date or censor date. †At index date. ‡Mean of all observations in year before index date. §Clinically emergent large-vessel disease before index date (defined by ACCORD[6] trial criteria). ¶Duration of diabetes before index date from first relevant clinical event. ‖Any record of serum creatinine test result >130 µmol/L before index date.

Table 2: **Baseline characteristics of cohort 2 (insulin treated) at baseline, stratified by mean HbA_{1c} decile group**

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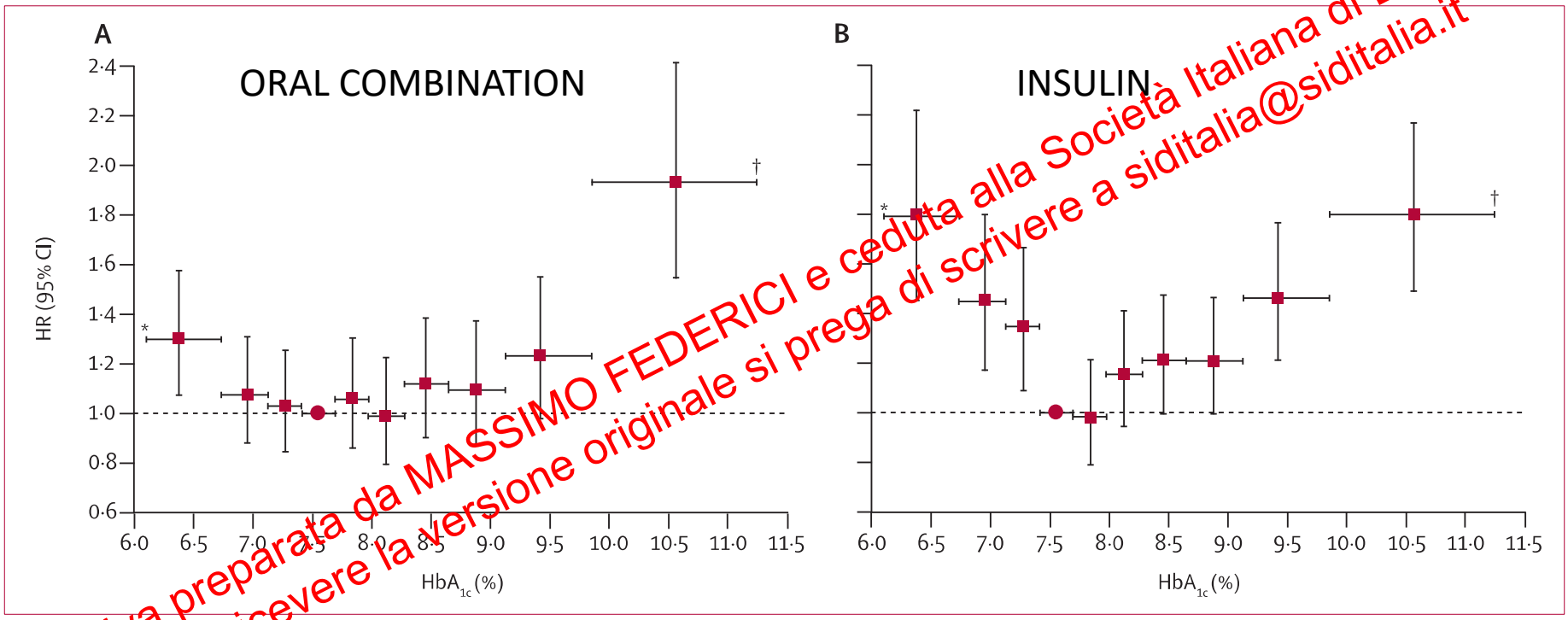

Figure 1: **Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies**
Cox proportional hazards models were used, with the HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

Craig J Currie, John R Peters, Aodán Tynan, Marc Evans, Robert J Heine, Oswaldo L Bracco, Tony Zagar, Chris D Poole

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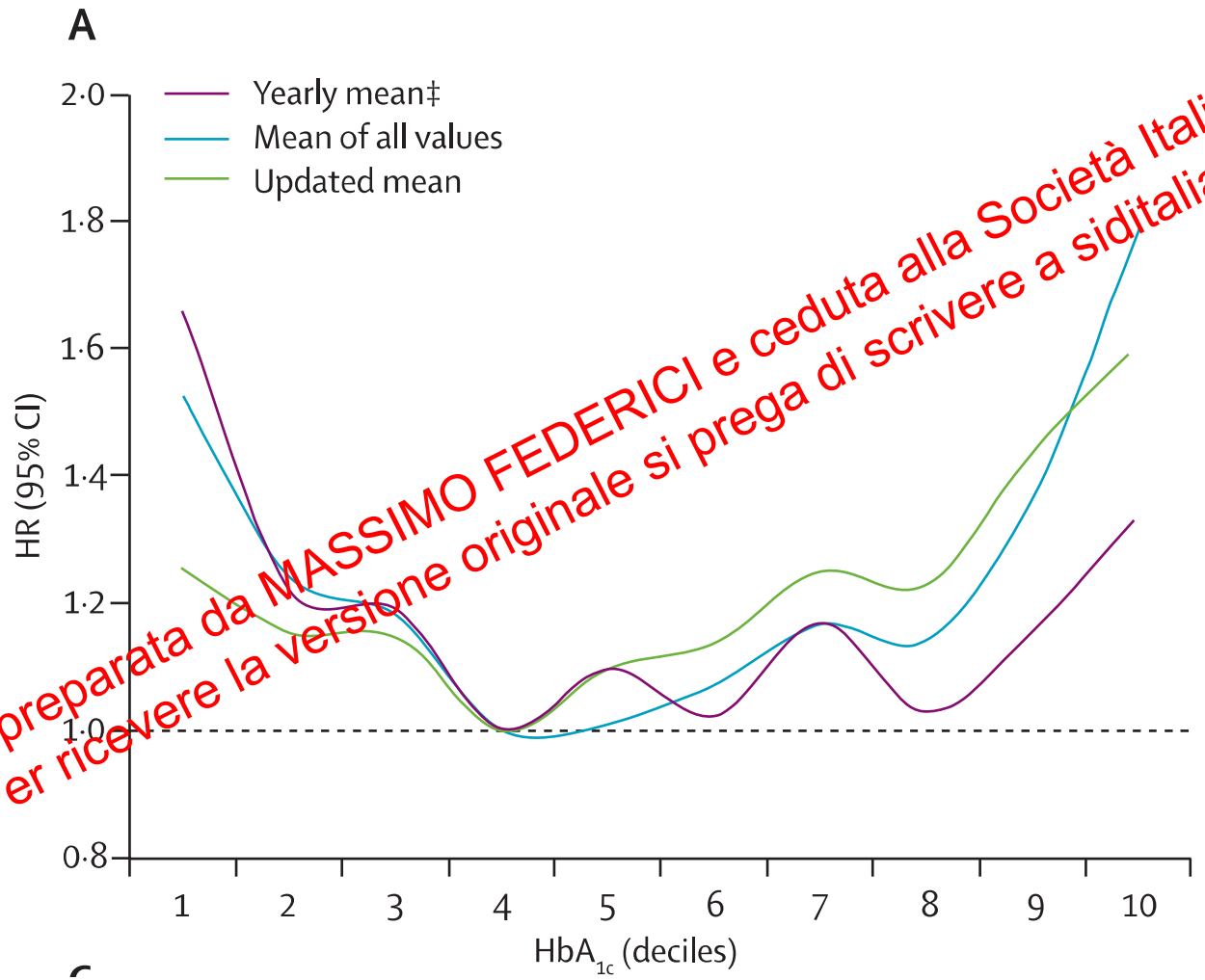

Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

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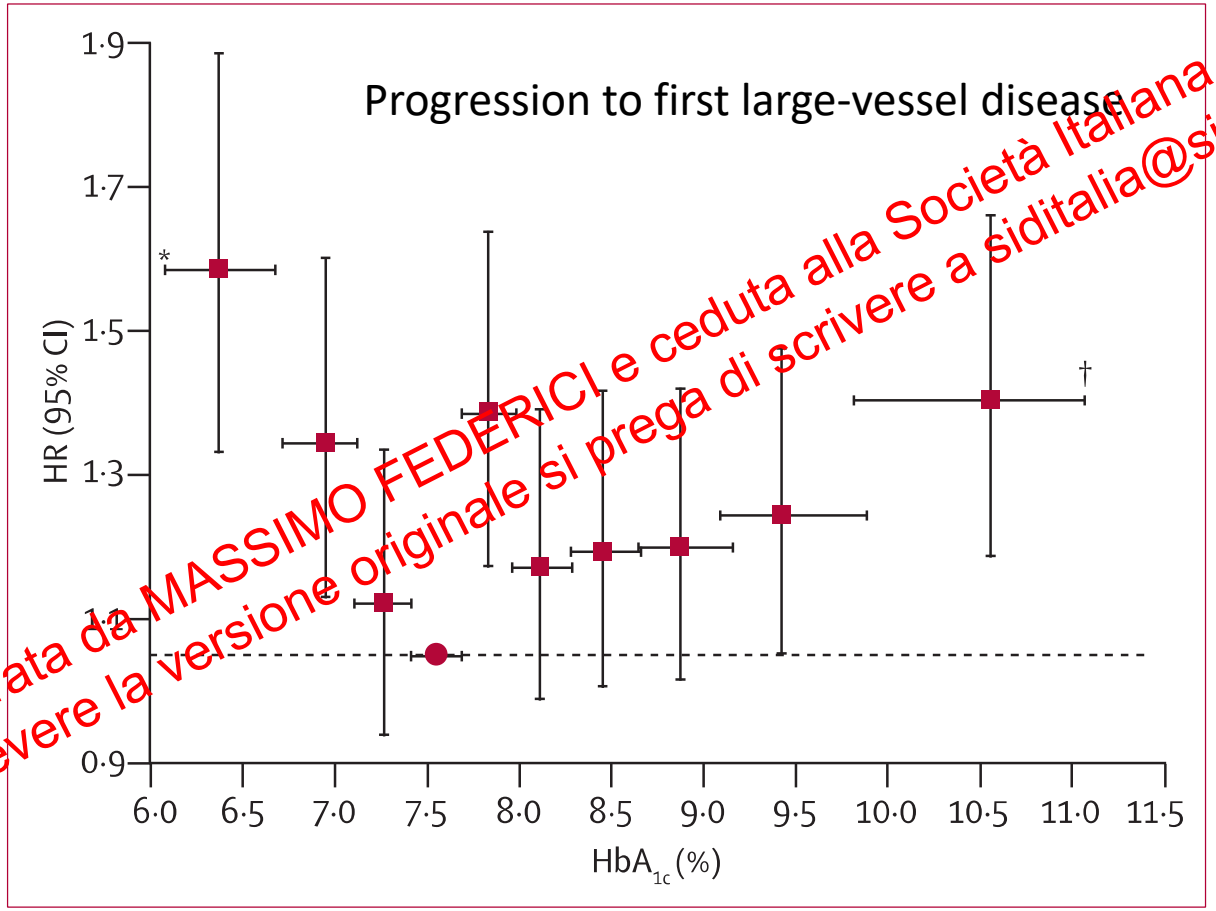

Figure 3: Hazard ratios for progression to first large-vessel disease event by HbA_{1c} decile, with Cox proportional hazards model

Agenda

- E’ stato affrettato abbandonare il controllo intensivo?
- E’ necessario ridiscutere l’obiettivo glicemico?
- Abbiamo sufficienti elementi per rivalutare l’obiettivo glicemico?
- A quali obiettivi possiamo ambire?

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John J V McMurray

Lancet Diabetes Endocrinol 2019

	ELIXA (n=6068)[7]	LEADER (n=9340)[8,14]	SUSTAIN-6 (n=3297)[9]	EXSCEL (n=14 752)[11]	Harmony Outcomes (n=9463)[10]	REWIND (n=9901)[12,13]	PIONEER 6 (n=3183)[14]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide (oral)
Structural basis	Exendin-4	Human GLP-1	Human GLP-1	Exendin-4	Human GLP-1	Human GLP-1	Human GLP-1
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral
Dose	20 µg per day	1·8 mg per day	0·5 or 1 mg per week	2 mg per week	30 or 50 mg per week	1·5 mg per week	14 mg per day
Age (years)	60 (10)	64 (7)	65 (7)	62 (9)	64 (7)	66 (7)	66 (7)
Sex							
Men	4207 (69%)	6003 (64%)	2002 (61%)	9149 (62%)	6569 (69%)	5312 (54%)	2176 (68%)
Women	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)	2894 (31%)	4589 (46%)	1007 (32%)
Ethnic origin							
White	4576 (75%)	7238 (77%)	2736 (83%)	11 175 (76%)	6583 (70%)	7498 (76%)	2300 (72%)
Other	1492 (25%)	2102 (23%)	561 (17%)	3577 (24%)	2880 (30%)	2403 (24%)	883 (28%)
BMI (kg/m²)	30·1 (6·6)	32·5 (6·1)	32·8 (6·2)	32·7 (6·4)	32·3 (5·9)	32·3 (5·7)	32·3 (6·5)
Diabetes duration (years)	9·2 (8·2)	12·8 (8·0)	13·9 (8·1)	13·1 (8·3)	14·2 (8·8)	10·6 (7·2)	14·9 (8·5)
HbA_{1c} (%)	7·7 (1·3)	8·7 (1·6)	8·7 (1·5)	8·1 (1·0)	8·7 (1·5)	7·3 (1·1)	8·2 (1·6)
Established cardiovascular disease	6068 (100%)	7598 (81%)	2735 (83%)	10 782 (73%)	9463 (100%)	3114 (31%)	2695 (85%)
History of heart failure	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	853 (9%)	388 (12%)
Systolic blood pressure (mm Hg)	129 (17)	136 (18)	136 (17)	135 (17)	135 (17)	137 (17)	136 (18)
eGFR (mL/min per 1·73 m²)*	78 (21)	80 (NR)	80 (61–92)	77 (61–92)	79 (25)	75 (24)	74 (21)
Glucose-lowering drugs used							
Insulin	2374 (39%)	4169 (45%)	1913 (58%)	6838 (46%)	5597 (59%)	2363 (24%)	1930 (61%)
Biguanides	4021 (66%)	7144 (76%)	2414 (73%)	11 295 (77%)	6969 (74%)	8037 (81%)	2463 (77%)
Sulfonylurea	2004 (33%)	4733 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	4552 (46%)	1027 (32%)
Thiazolidinedione	95 (2%)	575 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	118 (4%)
DPP-4 inhibitor	NA	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	88 (1%)	2 (<1%)
SGLT2 inhibitor	NA	NA	5 (<1%)	77 (1%)	575 (6%)	12 (<1%)	305 (10%)

Numerical data are mean (SD) or n (%), unless otherwise specified. GLP-1=glucagon-like peptide-1. eGFR=estimated glomerular filtration rate. NR=not reported. DPP-4=dipeptidyl peptidase-4. SGLT2=sodium-glucose co-transporter-2. *eGFR data are median (IQR) for SUSTAIN-6 and EXSCEL.

Table: **Baseline characteristics and use of glucose-lowering drugs across included trials**

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Lancet Diabetes Endocrinol 2019

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John J V McMurray

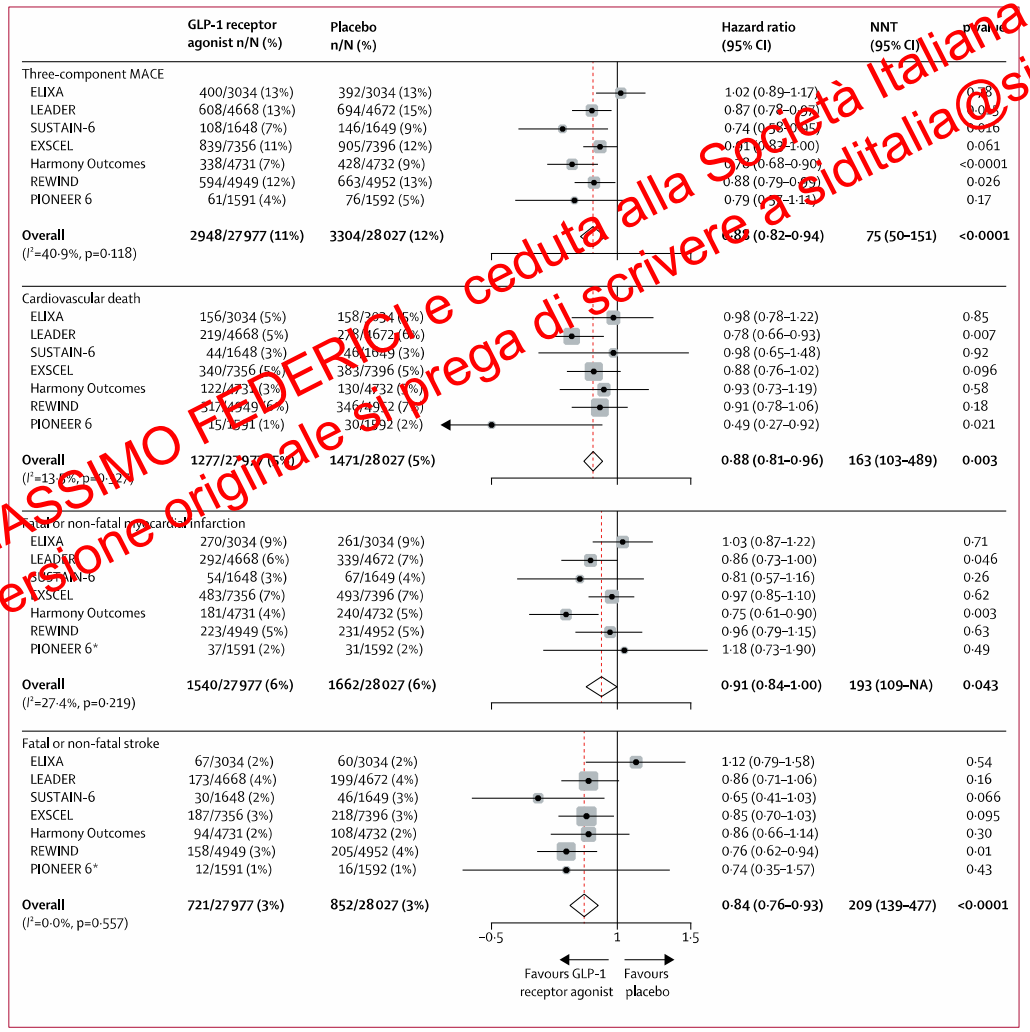

Figure 2: Risk of MACE and each of its components

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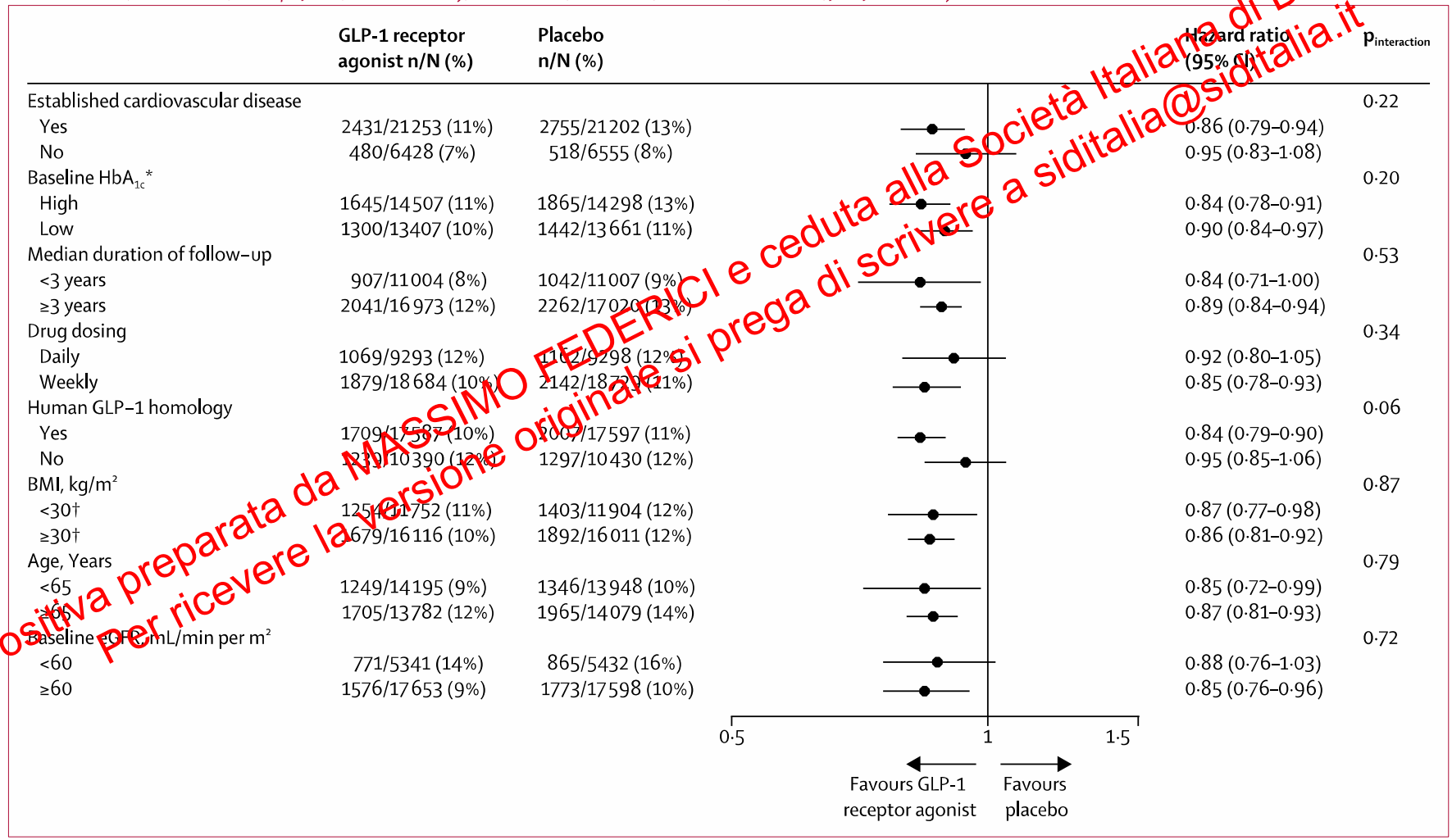

Figure 3: **Subgroup analyses for risk of three-component MACE**

SGLT2i

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

Lancet Diabetes Endocrinol 2019

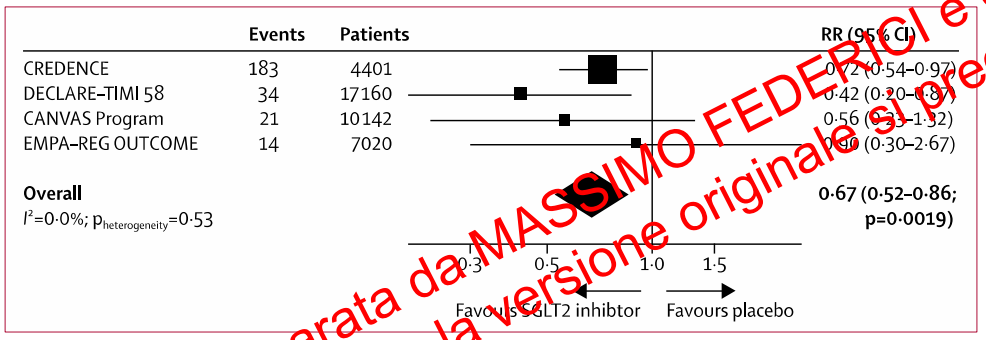

Figure 1: **Effect of SGLT2 inhibitors on dialysis, transplantation, or death due to kidney disease**

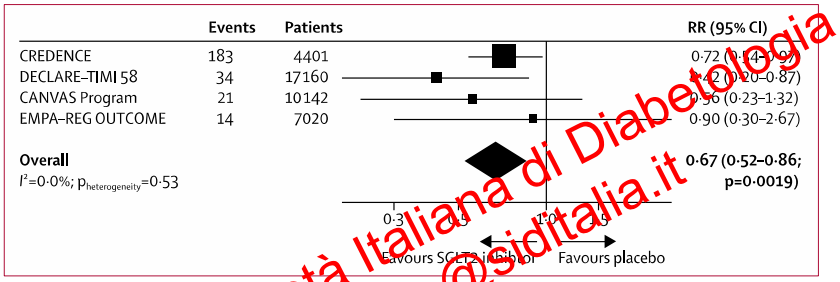

Figure 1: **Effect of SGLT2 inhibitors on dialysis, transplantation, or death due to kidney disease**
Weights were from random-effects meta-analysis. Data from DECLARE-TIMI 58 have not been previously reported. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

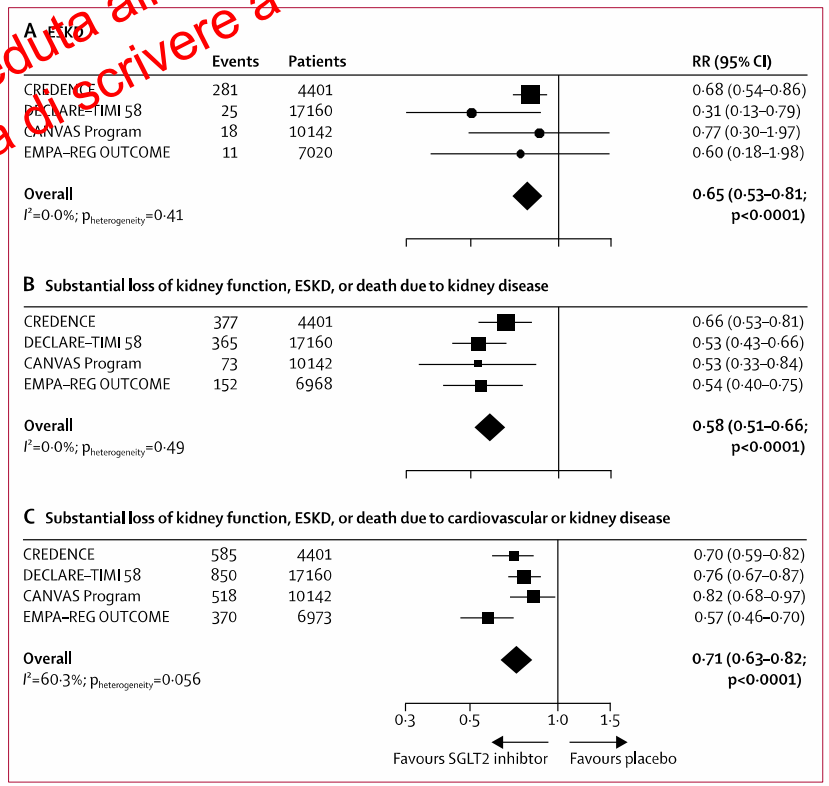

Figure 2: **Effect of SGLT2 inhibitors on ESKD (A), substantial loss of kidney function, ESKD, or death due to kidney disease (B), and substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease (C)**

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Lancet Diabetes Endocrinol 2019

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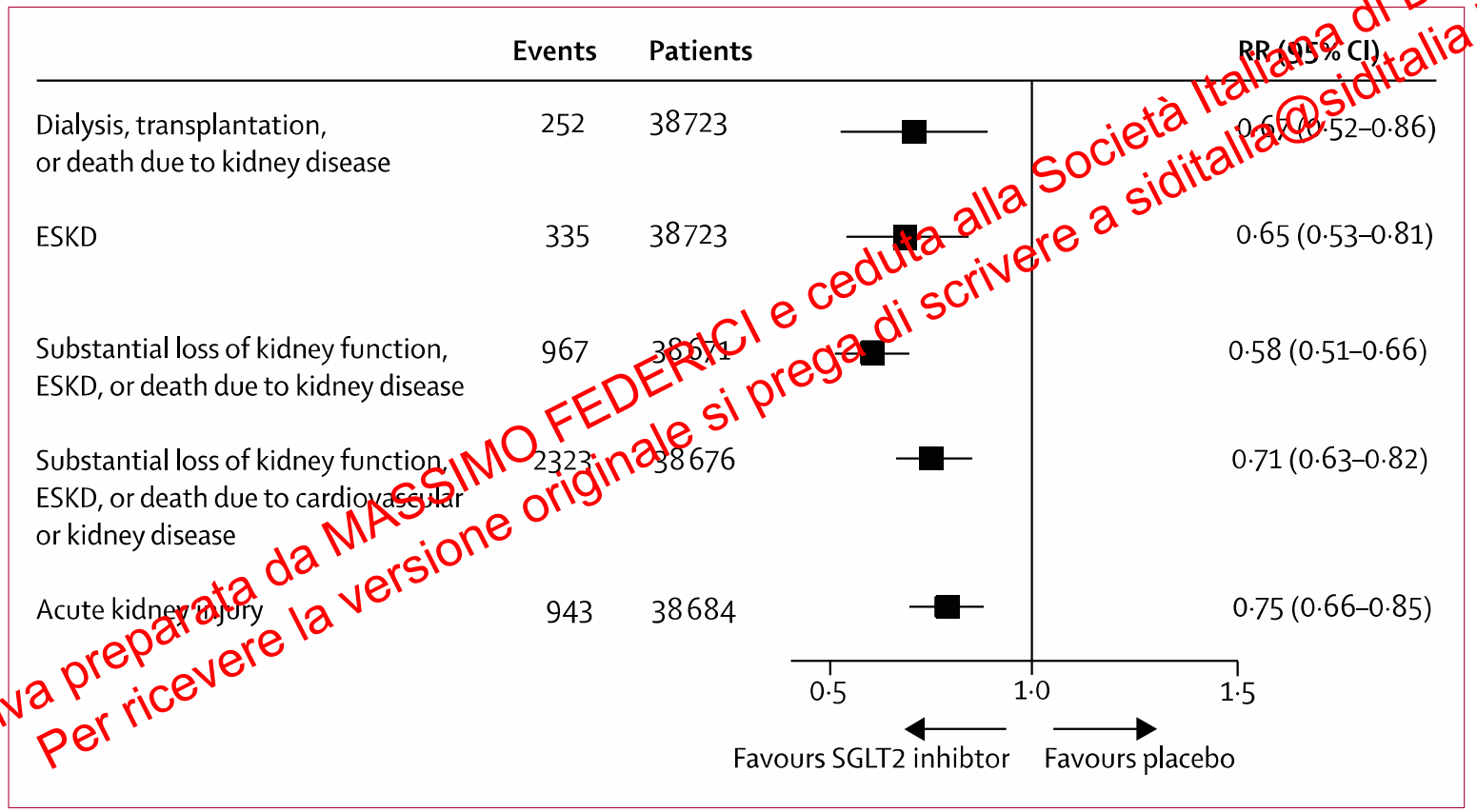

Figure 4: **Summary of the effects of SGLT2 inhibition on major kidney outcomes**
ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

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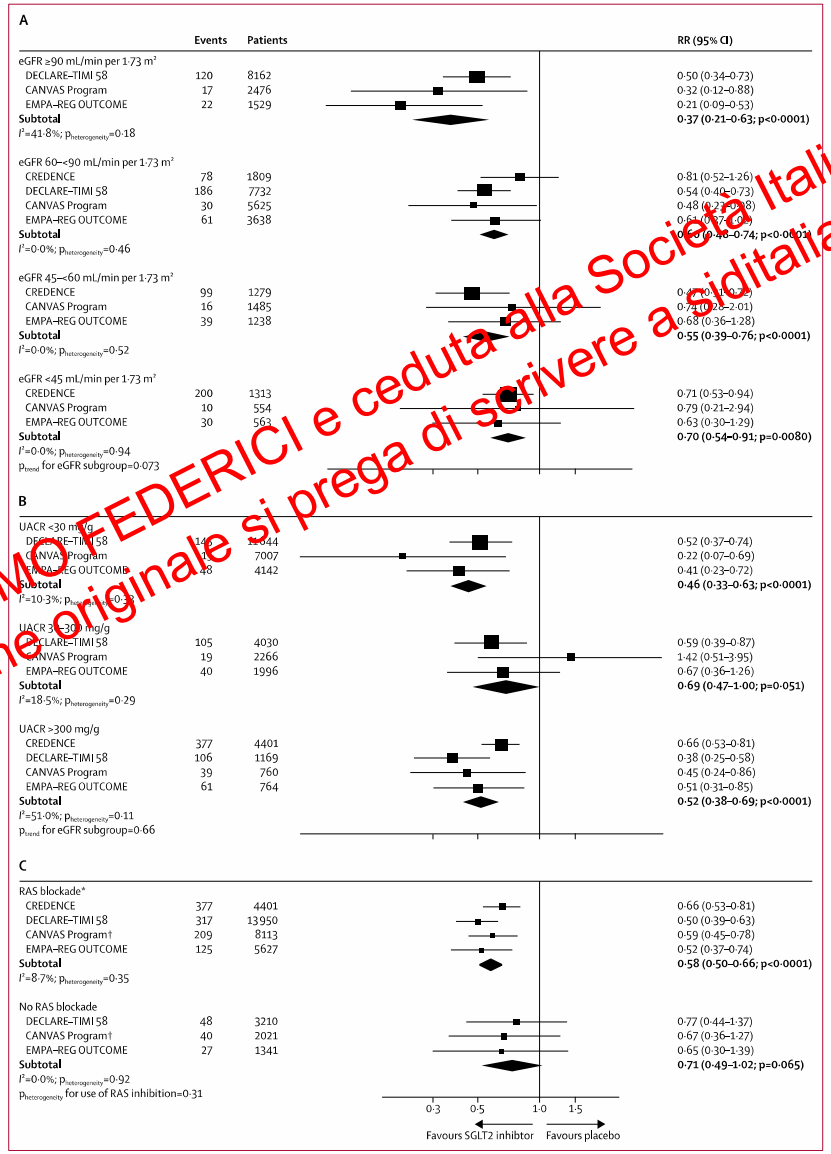

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

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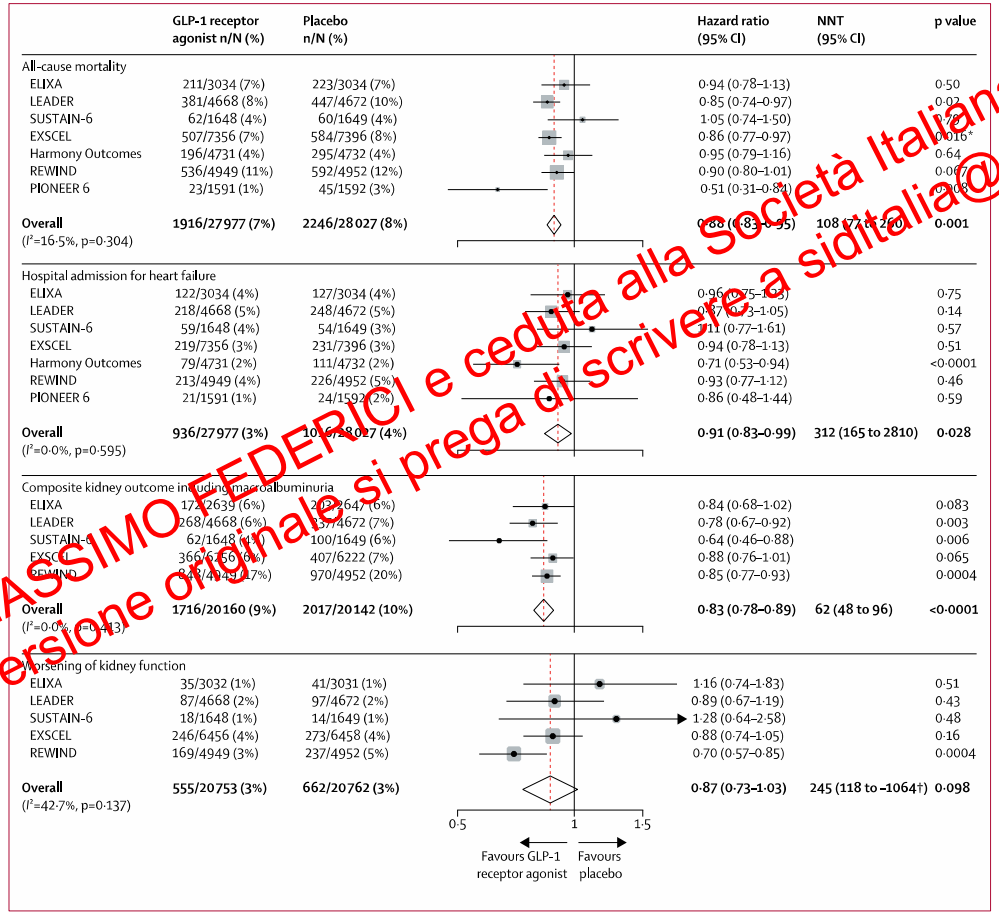

Figure 4: **All-cause mortality, hospital admission for heart failure, and kidney outcomes**
Data for kidney outcomes were not available for Harmony Outcomes or PIONEER 6. The broader composite kidney outcome including macroalbuminuria consisted of development of macroalbuminuria, doubling of serum creatinine or 40% or greater decline in estimated glomerular filtration rate (eGFR), development of end-stage kidney disease, or death due to kidney disease (details in appendix [pp 3–4]); for EXSCEL, data are for new-onset macroalbuminuria alone. The narrower worsening of kidney function outcome was defined as either doubling of serum creatinine or 40% or greater decline in eGFR (details in appendix [pp 3–4]); for EXSCEL, the narrower worsening of kidney function outcome included development of end-stage kidney disease or death due to kidney disease. NNTs are calculated over an estimated median follow-up of 3·2 years. GLP-1=glucagon-like peptide-1. NNT=number needed to treat. *Not regarded as significant because of hierarchical statistical testing plan. †Negative value indicates a number needed to harm.

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Lancet 2019; 393: 31–39

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

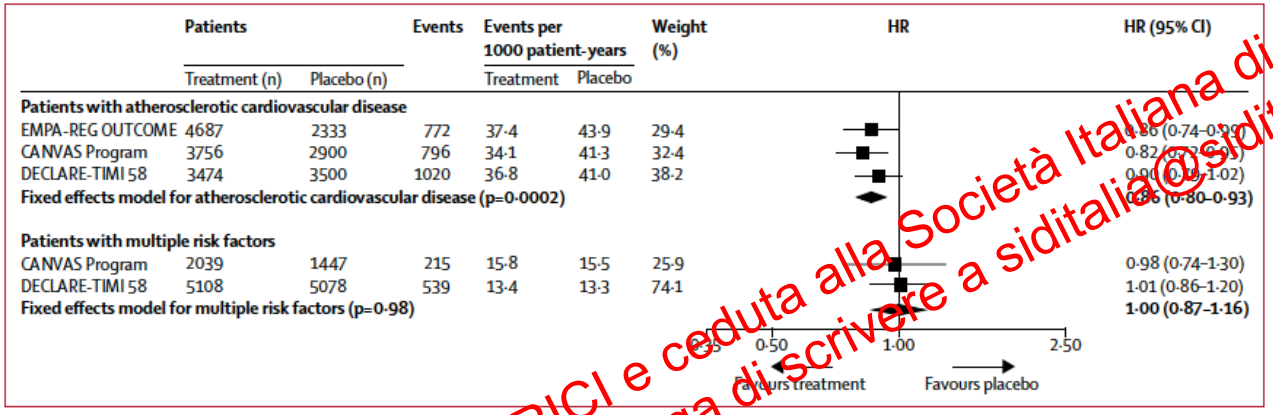

Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

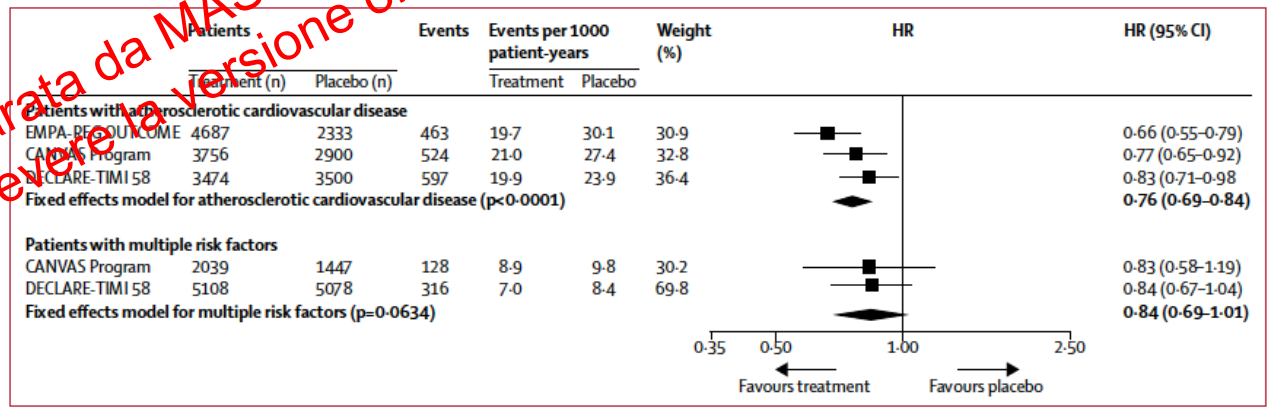

Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**

Atherosclerotic cardiovascular disease: Q statistic=3·49, p=0·17, I^2=42·7%; multiple risk factors: Q statistic=0·00, p=0·96, I^2=0%. The p value for subgroup differences was 0·41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

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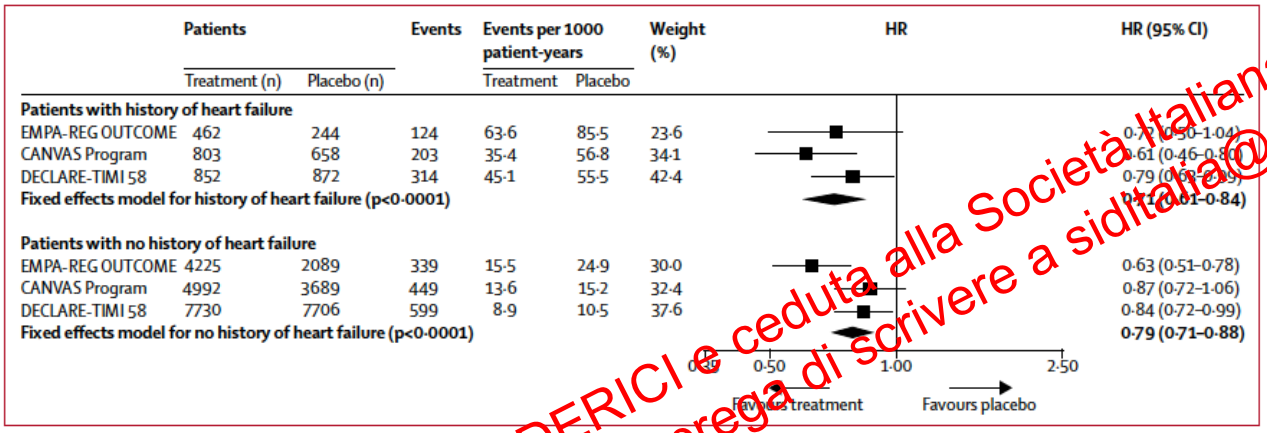

Figure 3: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure**
History of heart failure: Q statistic=2·02, p=0·37, I^2=0·8%; no history of heart failure: Q statistic=5·89, p=0·0527, I^2=66%. The p value for subgroup differences was 0·51. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

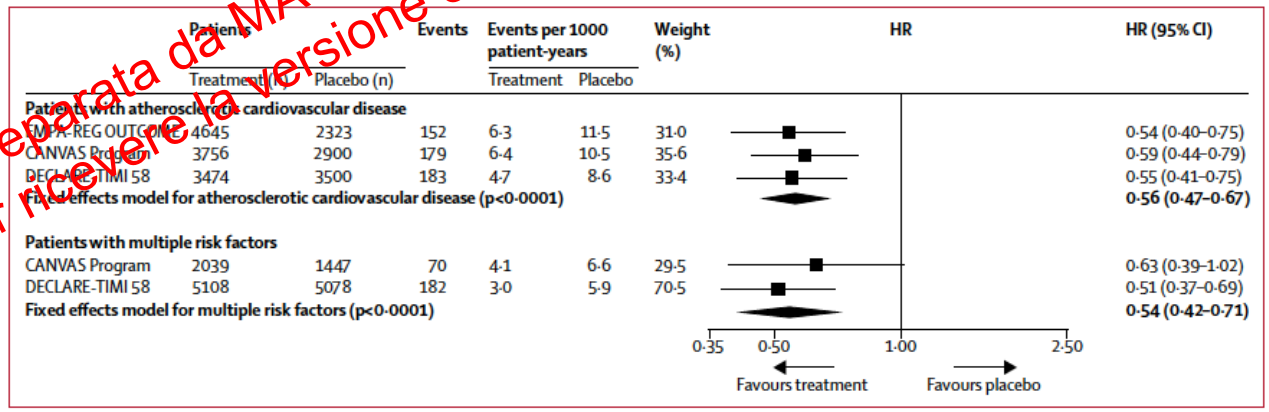

Figure 4: **Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease**
Atherosclerotic cardiovascular disease: Q statistic=0·19, p=0·91, I^2=0%; multiple risk factors: Q statistic=0·52, p=0·47, I^2=0%. The p value for subgroup differences was 0·71. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Agenda

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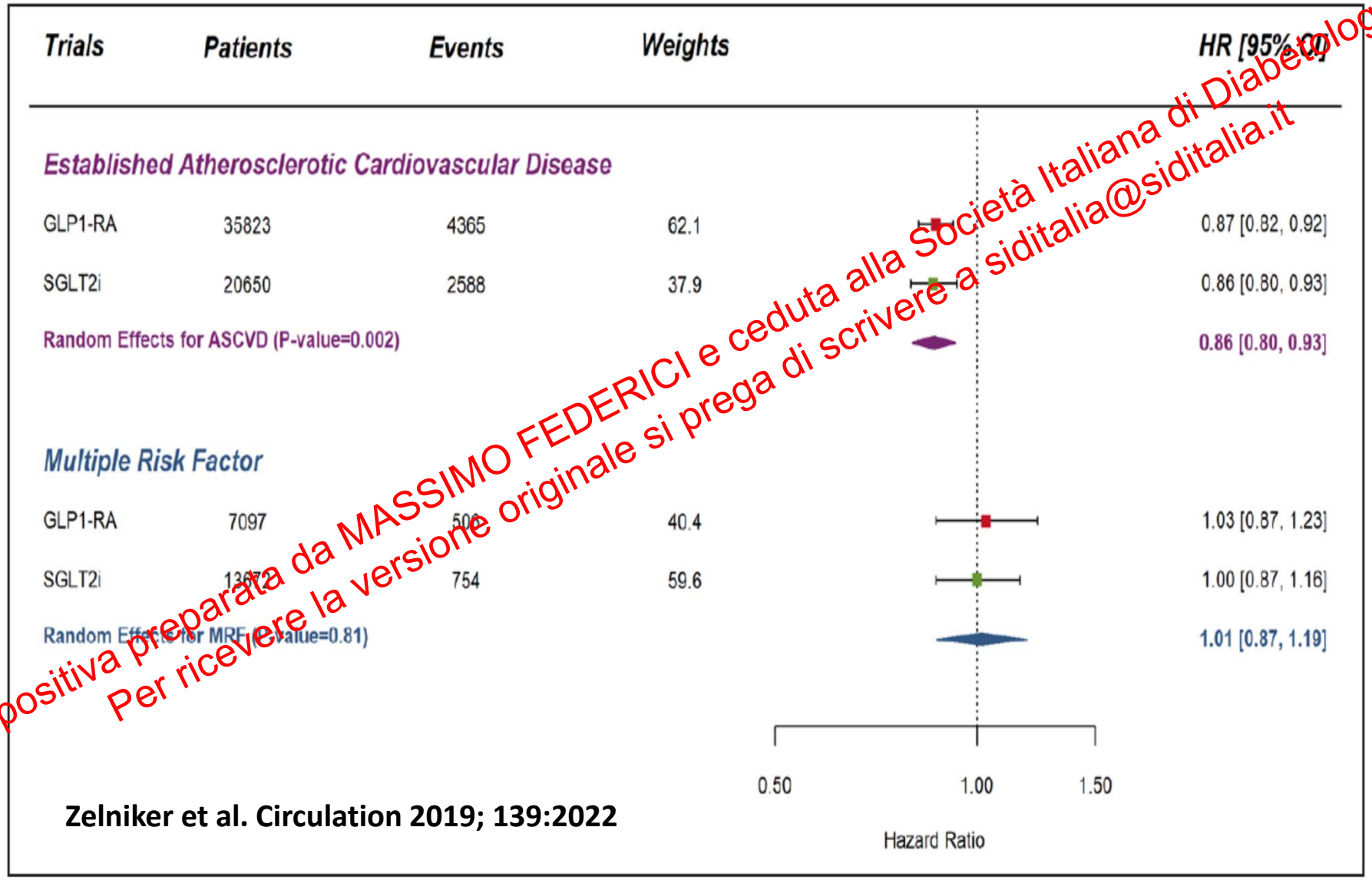
CVOTs, outcomes and metabolic control (data extracted from original publications)

	A1c (finale)	MACE	MICRO
EMPA-REG	7.6	+	+
CANVAS	8	-/+	+
DECLARE	7.9	-/+	+
CREDENCE	7.8	+	+
ELIXA	7.3	-	+
LEADER	7.5	+	+
SUSTAIN 6	7/7.5	+	+
EXSCEL	7.6	-	+
HARMONY	8	+	+
REWIND	6.7	+	+
PIONEER 6	7.1	-	-

Meta-Analysis of GLP1-RA and SGLT2i trials

MACE



Zelniker et al. Circulation 2019; 139:2022

Hypoglycemia, Cardiovascular Outcomes, and Death: The LEADER Experience

https://doi.org/10.2337/dc17-2677

*Bernard Zinman,[1] Steven P. Marso,[2] Erik Christiansen,[3] Salvatore Calanna,[3] Søren Rasmussen,[3] John B. Buse,[4] for the LEADER Publication Committee on behalf of the LEADER Trial Investigators**

Table 1—Baseline characteristics of patients with and without hypoglycemia during the trial

	Severe hypoglycemia		Confirmed hypoglycemia	
Characteristic	Yes (n = 267)	No (n = 9,073)	Yes (n = 4,169)	No (n = 5,171)
Male	166 (62.2)	5,837 (64.3)	2,631 (63.1)	3,372 (65.2)
Age, years	66.4 ± 7.7	64.2 ± 7.2	64.6 ± 7.7	64.0 ± 7.3
Diabetes duration, years	16.0 ± 8.3	12.7 ± 8.0	14.1 ± 8.4	11.7 ± 7.7
Insulin use	180 (67.4)	3,989 (44.0)	2,311 (55.7)	1,858 (35.7)
Geographic region				
Europe	83 (31.1)	3,213 (35.4)	1,300 (31.2)	1,996 (38.6)
North America	96 (36.0)	2,741 (30.3)	1,329 (31.9)	1,518 (29.4)
Asia	17 (6.4)	694 (7.6)	319 (7.7)	392 (7.6)
Rest of the world	71 (26.6)	2,415 (26.6)	1,221 (29.3)	1,265 (24.5)
HbA_{1c}, %	8.8 ± 1.7	8.7 ± 1.5	8.7 ± 1.5	8.7 ± 1.6
HbA_{1c}, mmol/mol	73.0 ± 18.9	71.5 ± 16.6	71.4 ± 16.3	71.6 ± 17.0
BMI, kg/m^2	32.3 ± 6.4	32.5 ± 6.3	32.0 ± 6.2	32.9 ± 6.3
Body weight, kg	90.4 ± 21.5	91.8 ± 20.9	89.7 ± 20.6	93.4 ± 21.2
Systolic blood pressure, mmHg	137.6 ± 20.7	135.8 ± 17.6	135.3 ± 18.2	136.4 ± 17.4
Diastolic blood pressure, mmHg	78.5 ± 10.1	77.1 ± 10.2	76.1 ± 10.3	77.9 ± 10.1
Heart rate, bpm	73.4 ± 12.0	72.6 ± 11.4	72.3 ± 11.5	72.9 ± 11.2
CV medication				
Antihypertensive therapy	255 (95.5)	8,376 (92.3)	3,914 (93.9)	4,717 (91.2)
β-blockers	146 (54.7)	5,035 (55.5)	2,389 (57.3)	2,792 (54.0)
Diuretics	151 (56.6)	3,755 (41.4)	1,857 (44.5)	2,049 (39.6)
Statins	196 (73.4)	6,545 (72.1)	3,177 (76.2)	3,564 (68.9)
Platelet aggregation inhibitors	174 (65.2)	6,152 (67.8)	2,976 (71.4)	3,350 (64.8)
Established CVD (age ≥50 years)	229 (85.8)	7,369 (81.2)	3,456 (82.9)	4,142 (80.1)
Prior myocardial infarction	89 (33.3)	2,775 (30.6)	1,347 (32.3)	1,517 (29.3)
Prior stroke or transient ischemic attack	51 (19.1)	1,456 (16.0)	686 (16.5)	821 (15.9)
Prior revascularization	108 (40.4)	3,530 (38.9)	1,730 (41.5)	1,908 (36.9)
>50% stenosis of coronary, carotid, or lower-extremity arteries	60 (22.5)	2,319 (25.6)	1,115 (26.7)	1,264 (24.4)
Documented symptomatic CHD*	16 (6.0)	802 (8.8)	349 (8.4)	469 (9.1)
Documented asymptomatic cardiac ischemia†	60 (22.5)	2,412 (26.6)	1,093 (26.2)	1,379 (26.7)
Heart failure NYHA II–III	56 (21.0)	1,249 (13.8)	559 (13.4)	746 (14.4)
Chronic kidney disease‡	119 (44.6)	2,188 (24.1)	1,245 (29.9)	1,062 (20.5)
CVD risk factors (age ≥60 years)	38 (14.2)	1,704 (18.8)	713 (17.1)	1,029 (19.9)
Microalbuminuria or proteinuria	26 (9.7)	1,033 (11.4)	459 (11.0)	600 (11.6)
Hypertension and left ventricular hypertrophy	8 (3.0)	491 (5.4)	193 (4.6)	306 (5.9)
Left ventricular systolic or diastolic dysfunction	6 (2.2)	388 (4.3)	160 (3.8)	234 (4.5)
Ankle-brachial index <0.9	10 (3.7)	216 (2.4)	88 (2.1)	138 (2.7)
Renal function, eGFR mL/min/1.73 m^2				
Normal (≥90)	67 (25.1)	3,208 (35.4)	1,228 (29.5)	2,047 (39.6)
Mild impairment (60–89)	82 (30.7)	3,825 (42.2)	1,767 (42.4)	2,140 (41.4)
Moderate impairment (30–59)	96 (36.0)	1,838 (20.3)	1,036 (24.9)	898 (17.4)
Severe impairment (<30)	22 (8.2)	202 (2.2)	138 (3.3)	86 (1.7)
Creatinine, μmol/L	108.4 ± 63.2	86.8 ± 38.3	92.3 ± 42.4	83.5 ± 36.4
Albumin/creatinine ratio, mg/g	536.9 ± 1,482.8	180.1 ± 874.3	217.6 ± 730.8	168.2 ± 1,014.3
Alanine aminotransferase, units/L	23.8 ± 14.1	26.8 ± 16.2	25.8 ± 15.7	27.6 ± 16.4
Bilirubin, μmol/L	7.3 ± 4.2	7.8 ± 4.2	7.5 ± 3.9	8.1 ± 4.4
Sodium, mmol/L	140.1 ± 2.8	140.0 ± 2.7	140.1 ± 2.7	139.9 ± 2.7
Potassium, mmol/L	4.6 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5

Values are mean ± SD or number of patients (proportion of patients with or without severe or confirmed hypoglycemia [%]). CHD, coronary heart disease; CVD, cardiovascular disease; NYHA, New York Heart Association. *Positive exercise stress test or any cardiac imaging or unstable angina with electrocardiogram changes. †Positive nuclear imaging test, exercise test, or dobutamine stress echo. ‡eGFR <60 mL/min/1.73 m^2 per MDRD formula or Cockcroft-Gault formula.

Hypoglycemia, Cardiovascular Outcomes, and Death: The LEADER Experience

https://doi.org/10.2337/dc17-2677

*Bernard Zinman,[1] Steven P. Marso,[2] Erik Christiansen,[3] Salvatore Calanna,[3] Søren Rasmussen,[3] John B. Buse,[4] for the LEADER Publication Committee on behalf of the LEADER Trial Investigators**

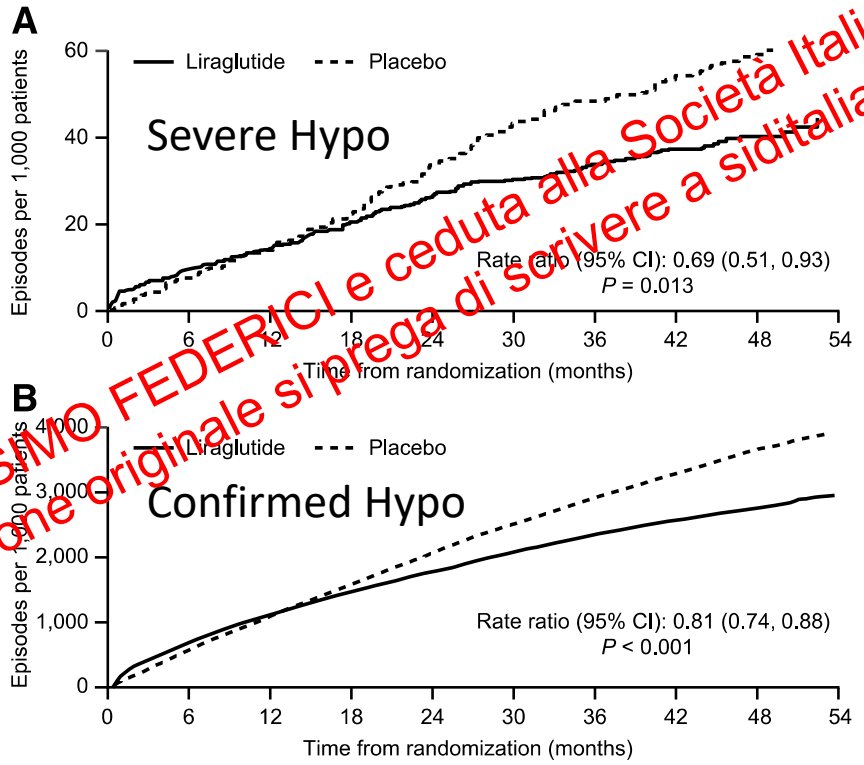


Figure 1—Severe (*A*) and confirmed (*B*) hypoglycemia over time among patients treated with liraglutide or placebo. Severe hypoglycemia was defined according to American Diabetes Association criteria as hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (16). Confirmed hypoglycemia was defined as severe hypoglycemia or minor hypoglycemia (defined as plasma glucose <3.1 mmol/L [<56 mg/dL] with or without symptoms). The number of episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the observation time (100 years) as offset.

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Patients who experienced severe hypoglycemia during the trial were more likely than those without severe hypoglycemia to experience MACE, CV death, non-CV death, or all-cause death ($P < 0.005$ for all four outcomes)

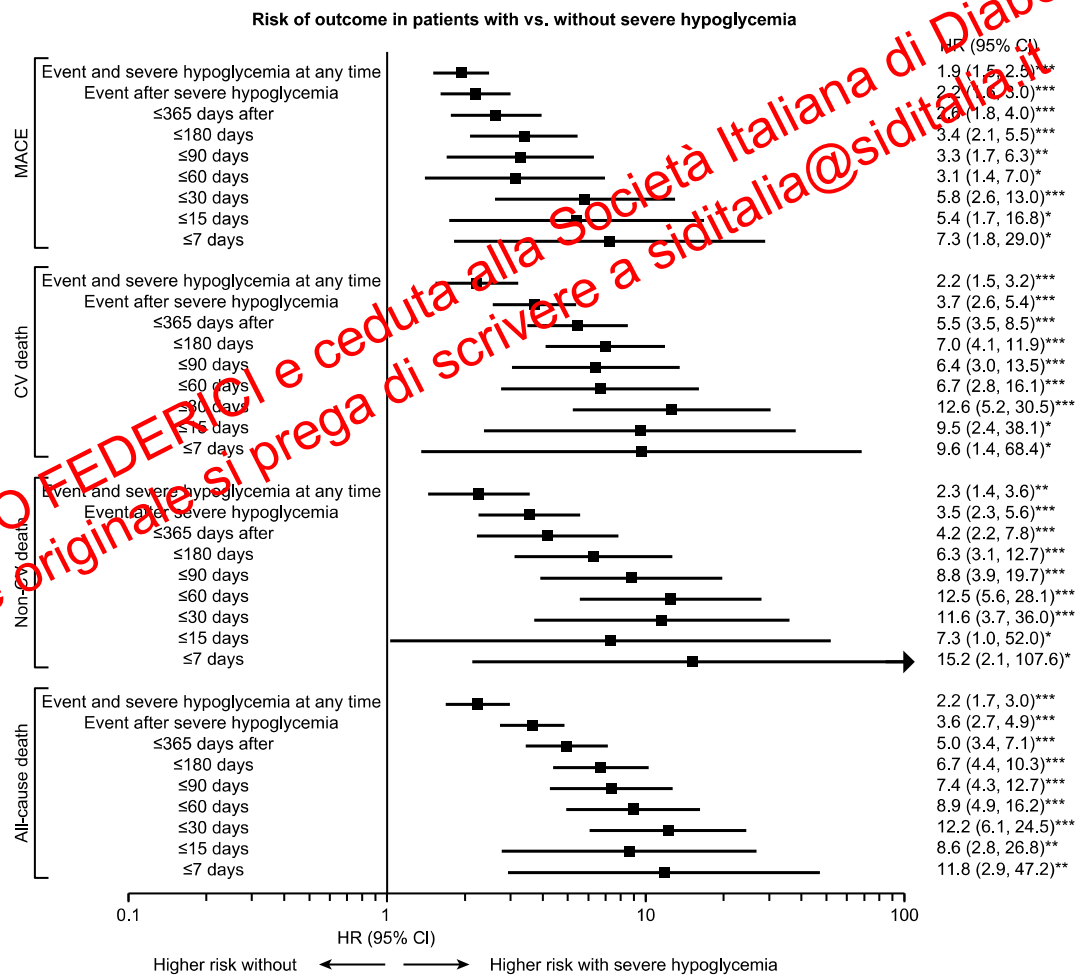

Figure 2—Association between severe hypoglycemia and CV events and death. Risk of outcome with event and severe hypoglycemia at any time is based on analysis of time to first MACE, CV death, non-CV death, or all-cause death, using Cox regression with severe hypoglycemia (yes/no) at any time as a factor. Risk of outcome with events after severe hypoglycemia is based on severe hypoglycemic episodes prior to MACE, CV death, non-CV death, or all-cause death, using a time-dependent covariate Cox regression: all events (follow-up until last contact date), follow-up within 7, 15, 30, 60, 90, 180, and 365 days. *$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$.

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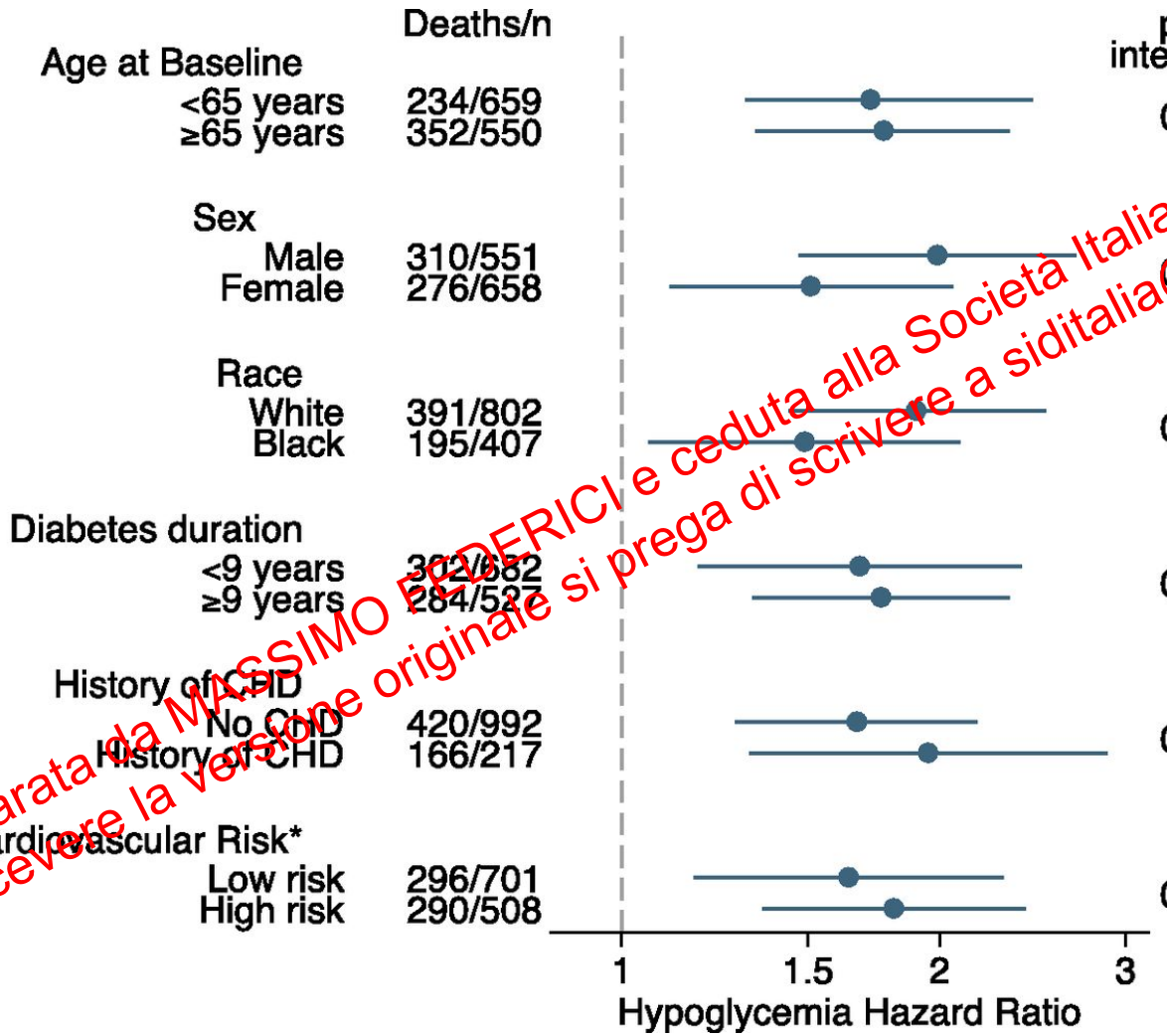
Table 2—MACE according to severe hypoglycemia and treatment group

	Liraglutide		Placebo			
Patient population	*n*	MACE*	*n*	MACE*	HR (95% CI)	*P*-interaction
All	4,668	608	4,672	694	0.87 (0.78, 0.97)	
With severe hypoglycemia	114	26	153	40	0.85 (0.52, 1.39)	0.90
Without severe hypoglycemia	4,554	582	4,519	654	0.88 (0.78, 0.98)	

HRs were estimated with the use of a Cox proportional hazards model with treatment as a covariate. *First MACE (CV death, nonfatal myocardial infarction, or nonfatal stroke).

Patients experiencing severe hypoglycemia were at greater risk of CV events and death, particularly shortly after the hypoglycemic episode. While causality remains unclear, reducing hypoglycemia remains an important goal in diabetes management

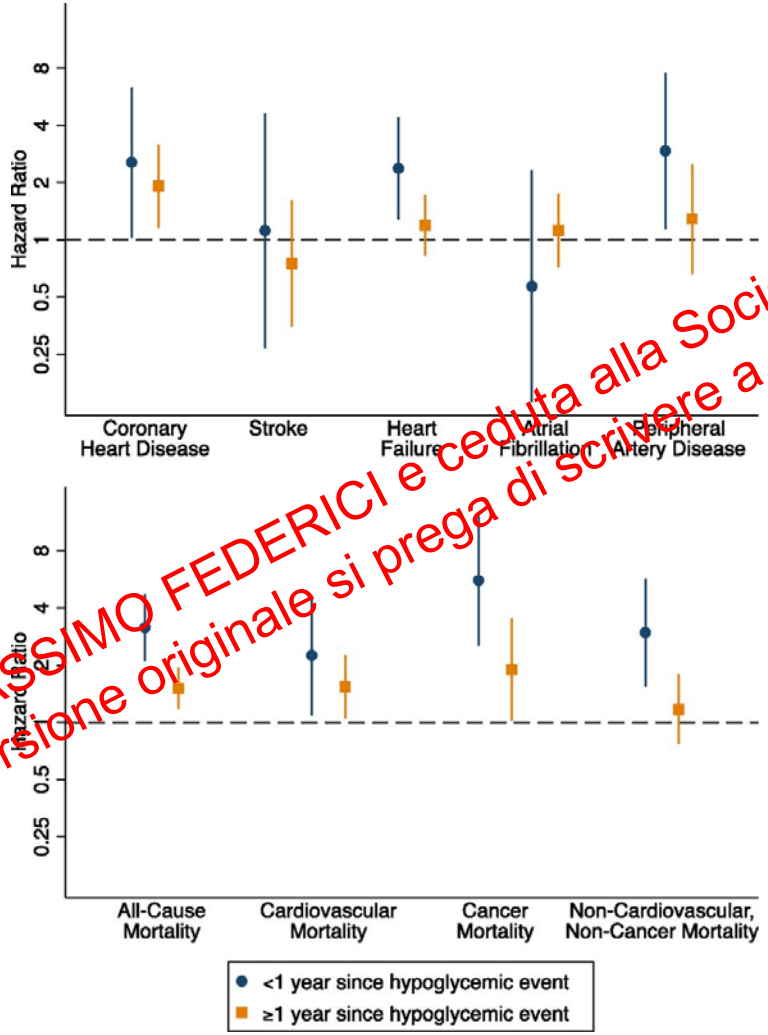
Severe hypoglycemia HRs and 95% CIs for all-cause mortality by subgroups of the study population.



Alexandra K. Lee et al. Dia Care 2018;41:104-111

American Diabetes Association.

Hypoglycemia HRs and 95% CIs for cardiovascular disease and mortality outcomes by time since severe hypoglycemic event.



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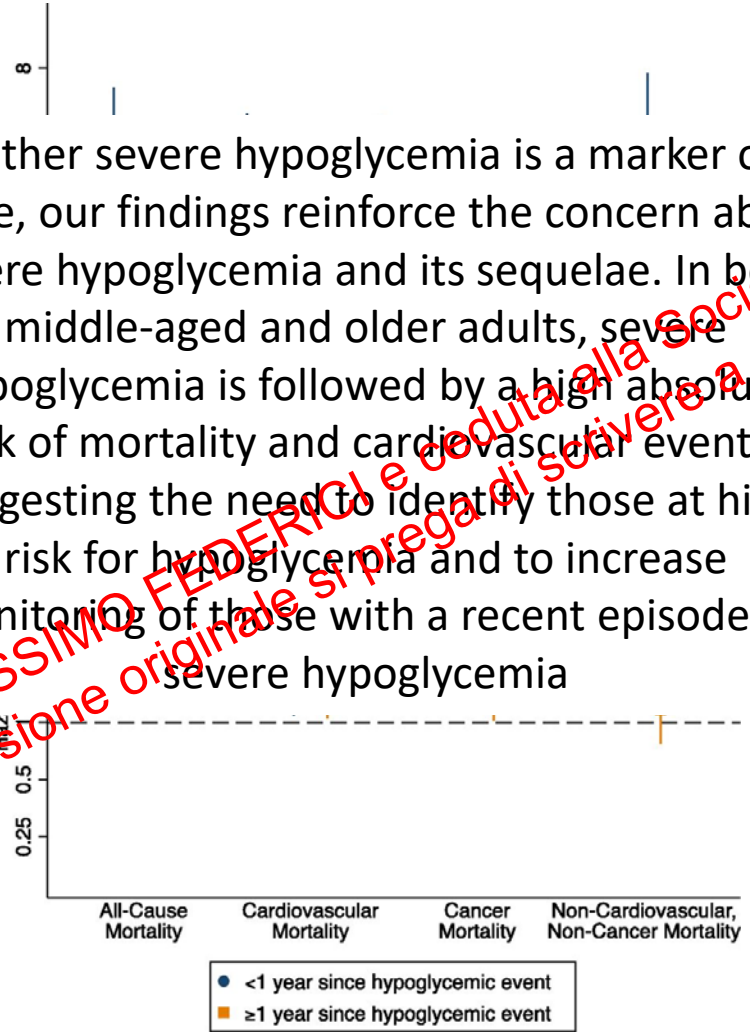


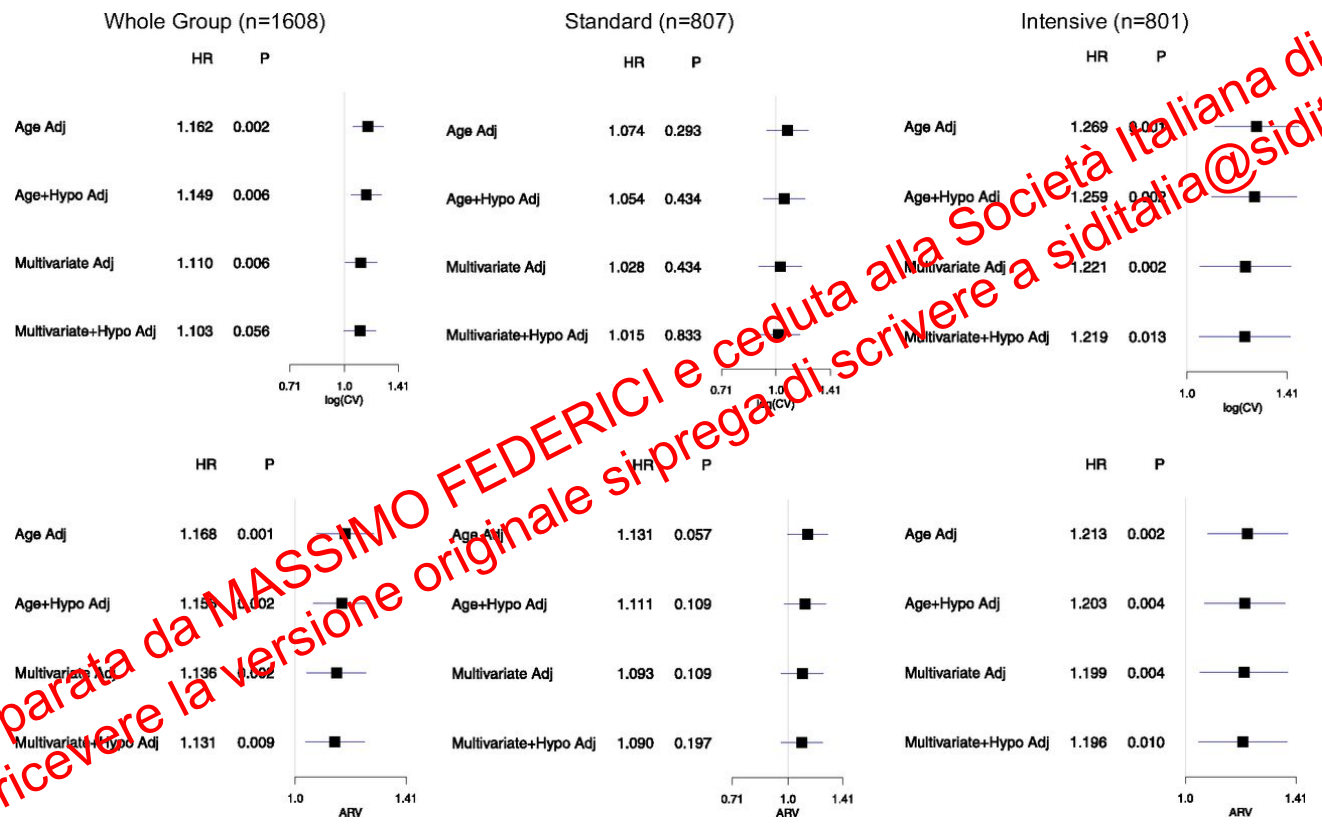
whether severe hypoglycemia is a marker or a cause, our findings reinforce the concern about severe hypoglycemia and its sequelae. In both middle-aged and older adults, severe hypoglycemia is followed by a high absolute risk of mortality and cardiovascular events, suggesting the need to identify those at high risk for hypoglycemia and to increase monitoring of those with a recent episode of severe hypoglycemia

Alexandra K. Lee et al. Dia Care 2018;41:104-111

American Diabetes Association.

HRs of log(CV) and ARV and their 95% CI for the primary CVD outcome with and without adjustment for severe hypoglycemia (Hypo) events.

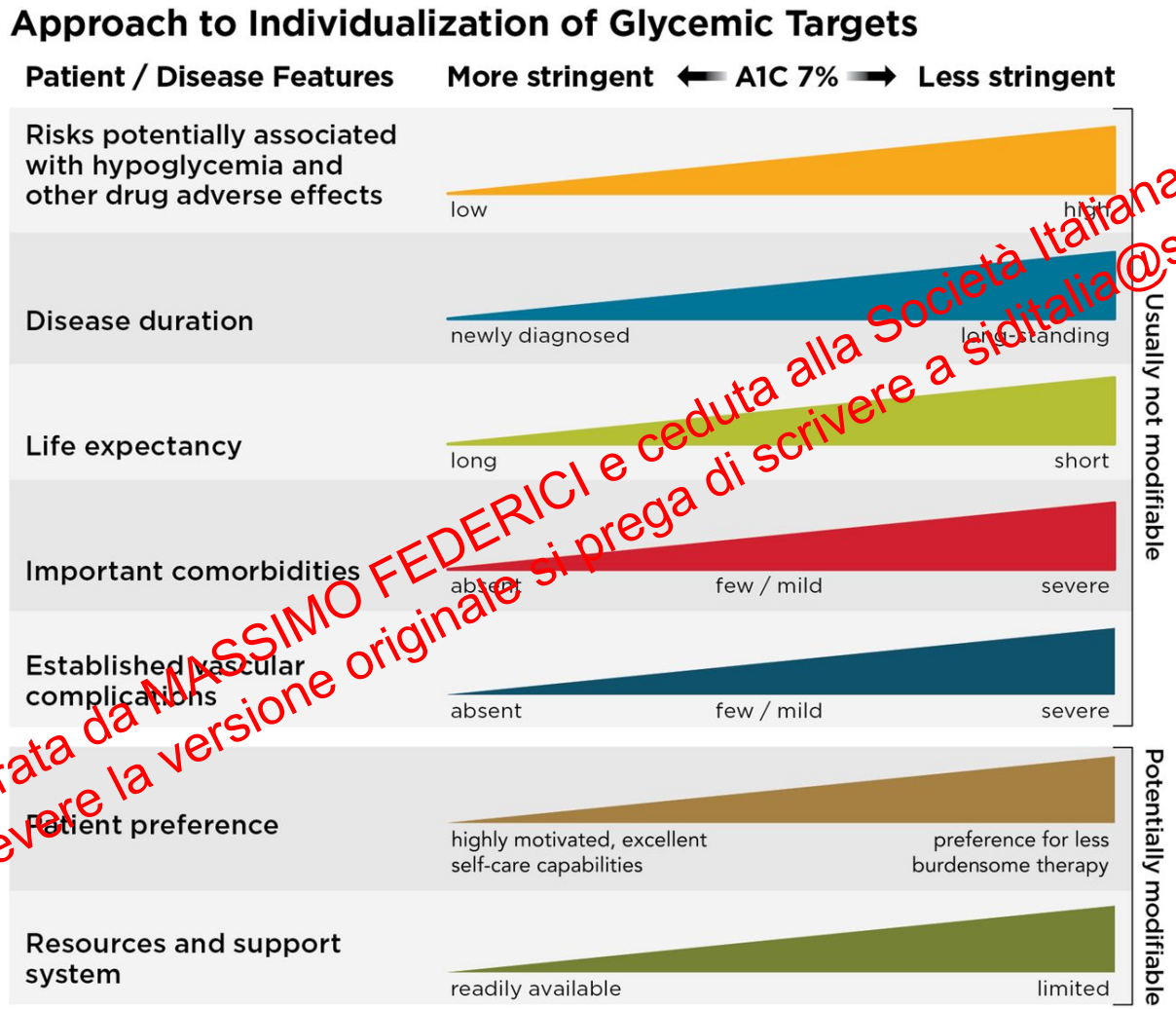
Jin J. Zhou et al. Dia Care 2018;41:2187-2194



In the VADT, variability of fasting glucose plays a role in the development of CVD complications beyond the influence of standard fasting glucose measures. The adverse consequences of fasting glucose variability on CVD appear greatest in those receiving intensive glucose contro

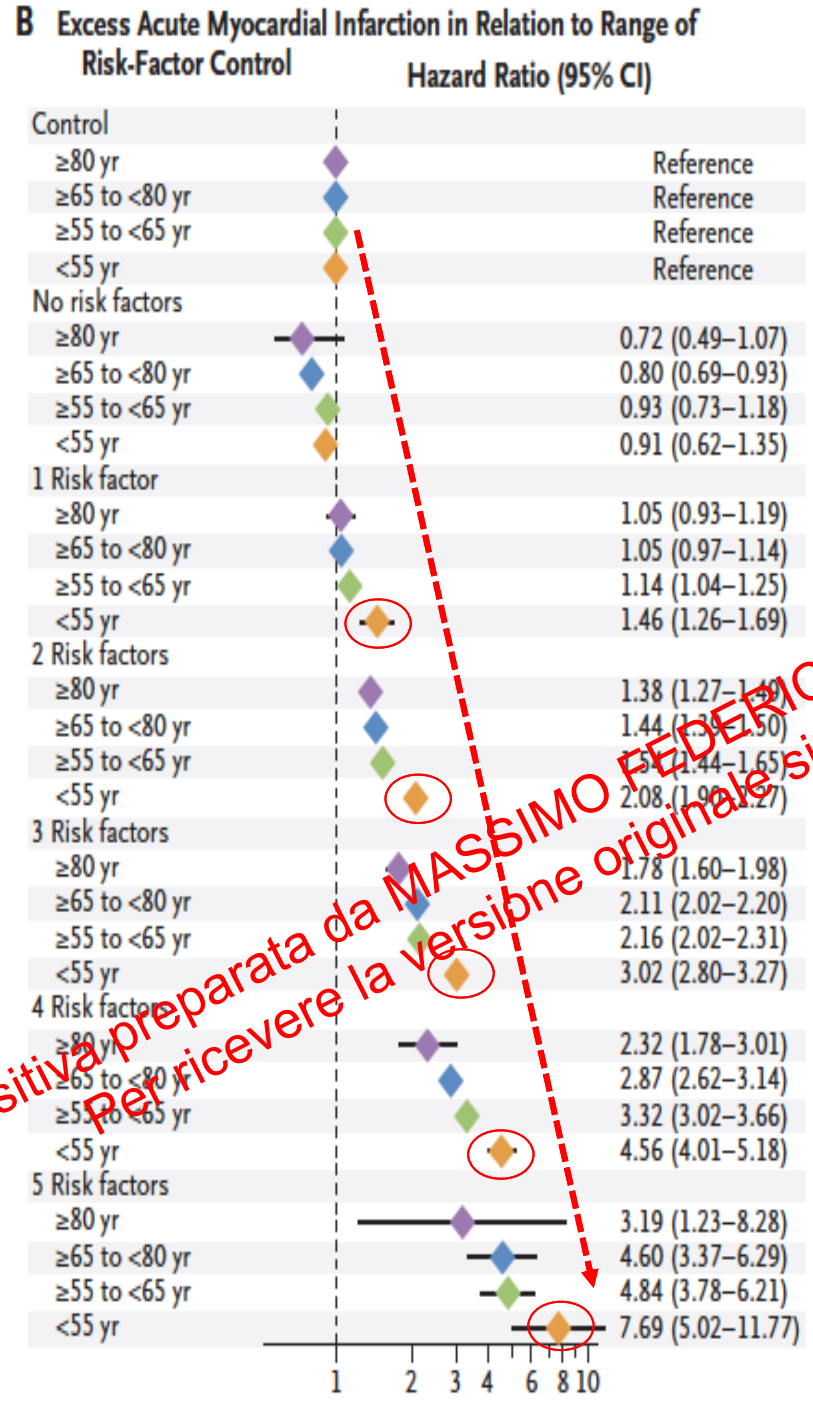
American Diabetes Association.

Depicted are patient and disease factors used to determine optimal A1C targets.



American Diabetes Association Dia Care 2019;42:S61-S70

American Diabetes Association.



CONCLUSIONI

- I CVOTs non hanno stretto il target glicemico quanto ACCORD
- Anche nei CVOTs l'ipoglicemia resta un fattore di rischio CV
- L'ipoglicemia sembra però più legata all'innesco di complicanze legate all'aterotrombosi