Listen, Think and Plan

Metodologia degli studi clinici in diabetologia

Gli studi di safety cardiovascolare in diabetologia

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The 2008 Food and Drug Administration (FDA) guidance to industry requires experimental evidence that new agents to treat type 2 diabetes do not have an unacceptable increase in cardiovascular risk.

They specify this unacceptable increase to be a risk ratio of 1.3 in non-inferiority trials which may use placebo control.

Clinically, this means that if a new agent achieves this threshold of not being 30% worse than placebo it is declared non-inferior

Guidance for Industry

Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

FDA 2008

1. Cardiovascular end points include a **primary composite of relatively hard** cardiovascular events, including cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, and hospitalization for unstable angina.

2. When other cardiovascular events like **hospitalization for heart failure** or coronary revascularization are occasionally included in the composite end point, discussions with the FDA before trial conduct seek to ensure adequate core major adverse cardiovascular events like death, stroke, and nonfatal myocardial infarction.

3. The **study protocol** and the statistical methods must be standardized and outlined before the initiation of the drug development program with new agents for type 2 diabetes mellitus.
4. Enrollment of high-risk patients in clinical trials including **elderly** patients and patients with advanced diabetes mellitus and **renal impairment**.

5. Independent blinded cardiovascular end points **committee** to ascertain and adjudicate clinical outcomes, including cardiovascular mortality, myocardial infarction, stroke, hospitalization for acute coronary syndrome, urgent revascularization, and heart failure,.

Estimated Event Required in the Design and Conduct of Cardiovascular Outcome Trials Using the FDA Guidance

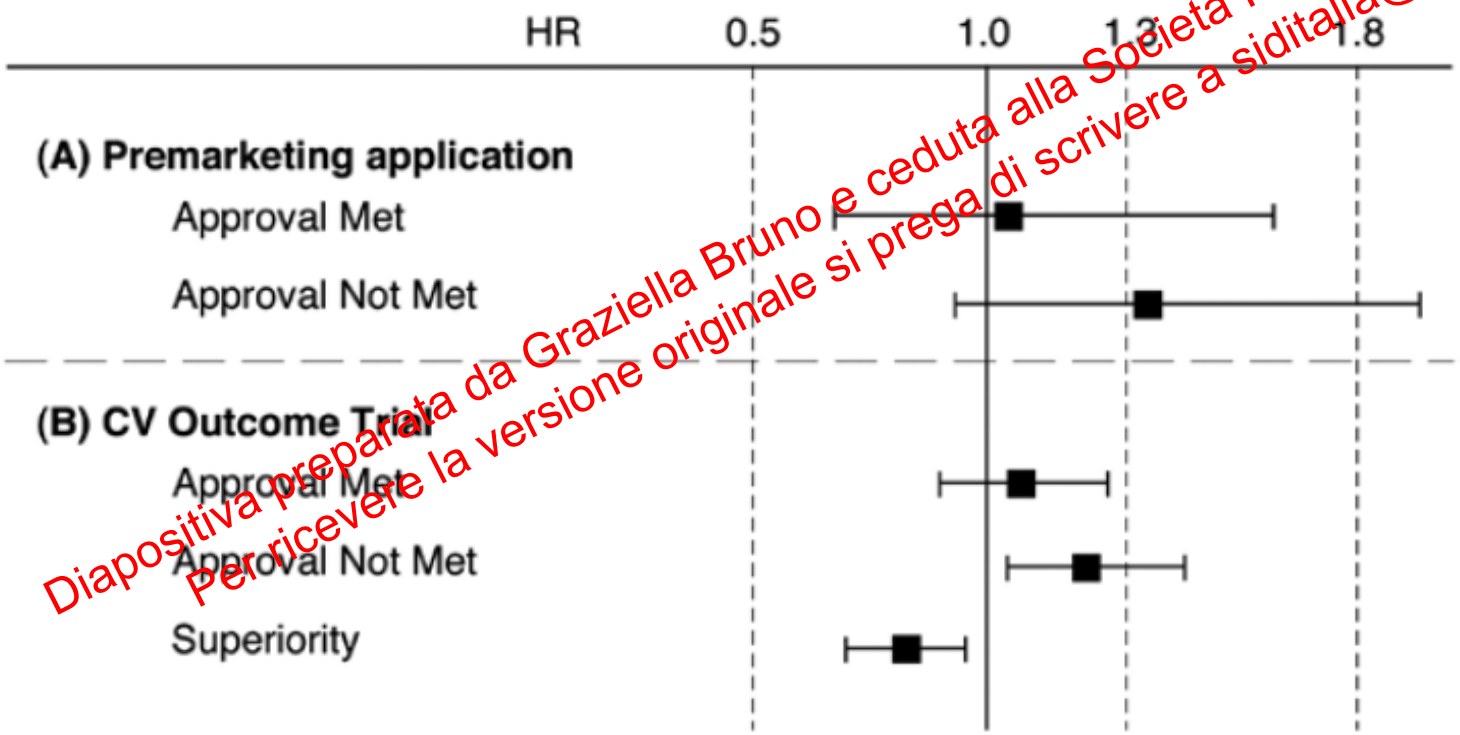
	Power		
Upper HR Boundary	80%	85%	90%
1.8	91	105	122
1.3	456	522	611

Estimated Events Required in the Design and Conduct of Cardiovascular Outcome Trials Using the FDA Guidance as a Function of the Expected True HR of the Intervention

	Upper HR Boundary	
True HR	<1.8	<1.3
0.80	64	179
0.85	75	233
0.90	88	311
0.95	103	427
1.0	122	611
1.05	145	921
1.1	174	1505

The values shown are the number of cardiovascular outcome events. HR indicates hazard ratio.

FDA 2008: Two-step approach to obtain a new drug approval



ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

METHODS

We randomly assigned patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy. The study design was a double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Table 3. Major Safety End Points.

End Point	Placebo (N = 2679)	Alogliptin (N = 2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

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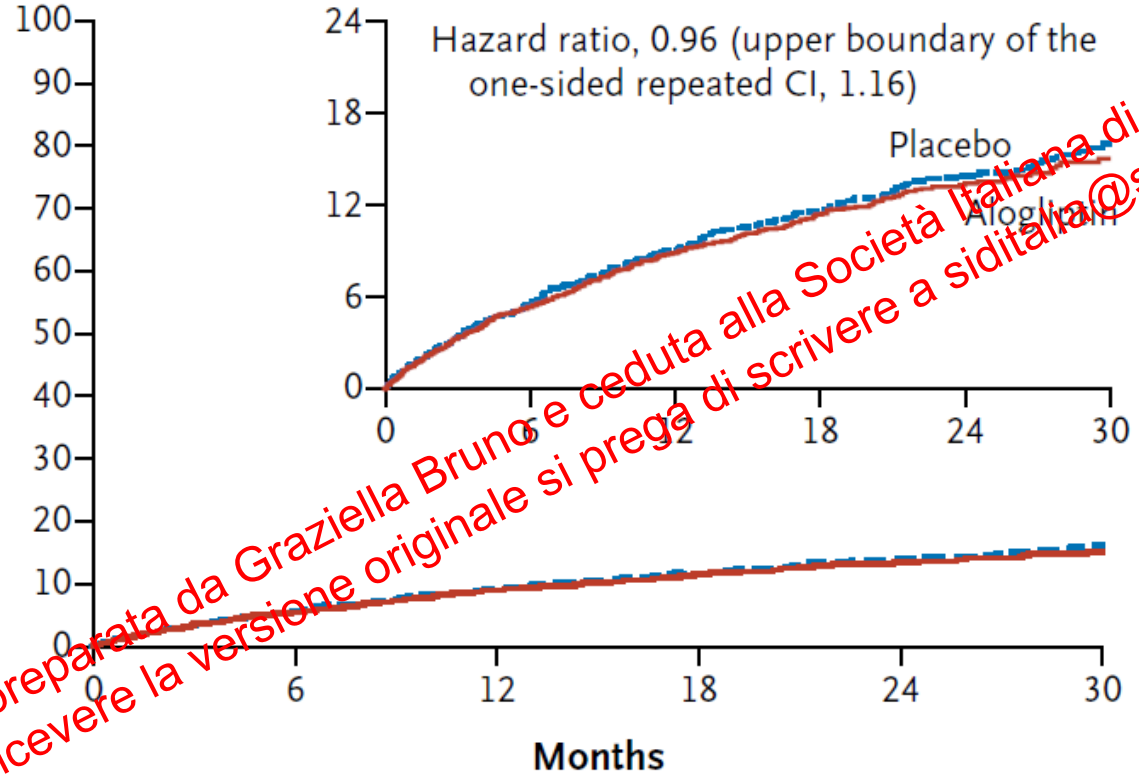

No. at Risk

Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

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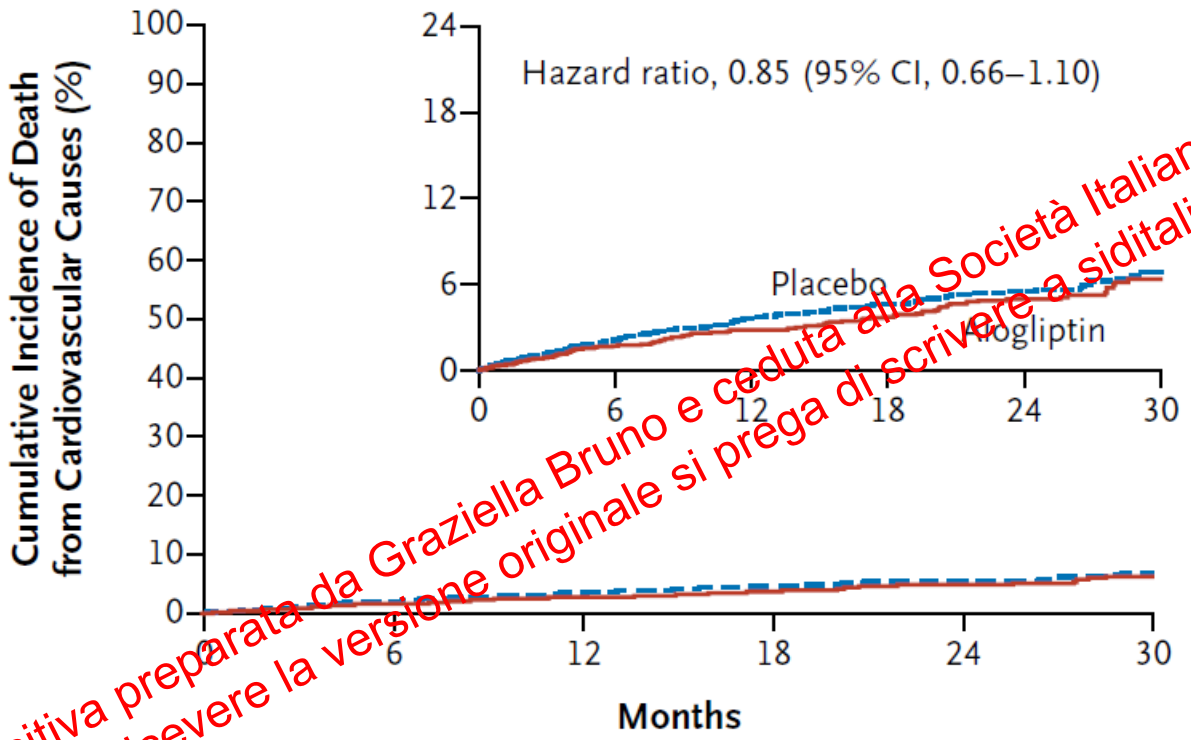

No. at Risk						
Placebo	2679	2384	1996	1477	889	324
Alogliptin	2701	2402	2023	1504	894	320

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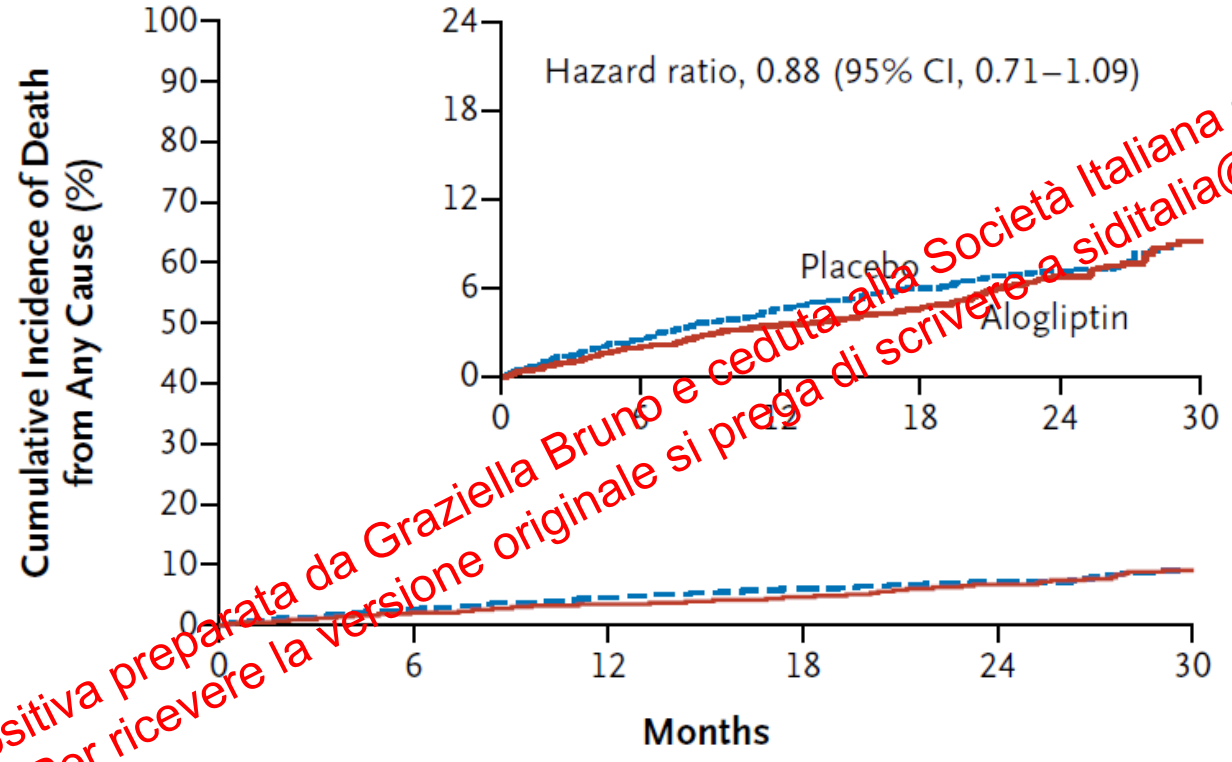

No. at Risk						
Placebo	2679	2384	1996	1477	889	324
Alogliptin	2701	2401	2023	1504	894	320

RESULTS

A total of 5380 patients underwent randomization and were followed for up to 40 months (median, 18 months). A primary end-point event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; P<0.001 for noninferiority). Glycated hemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, −0.36 percentage points; P<0.001). Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

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METHODS

We randomly assigned 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke.

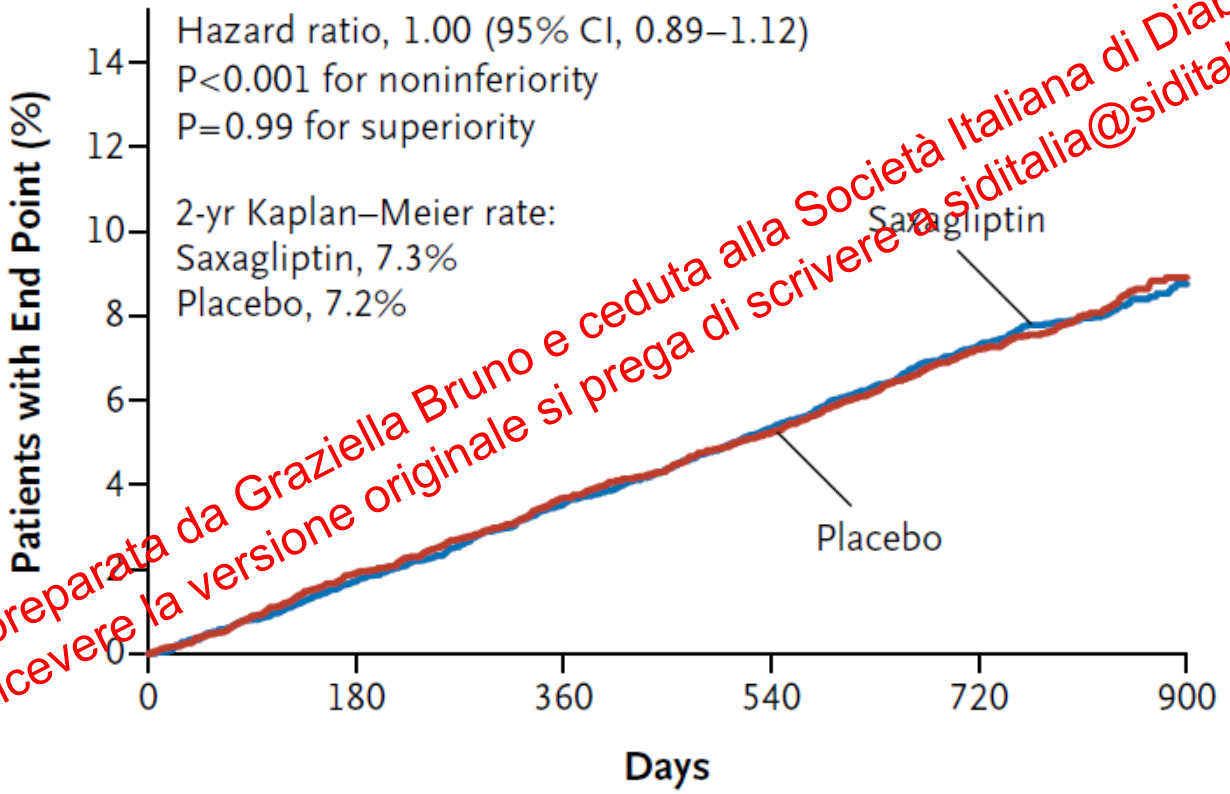
STATISTICAL ANALYSIS

The primary safety and efficacy analyses were performed according to the intention-to-treat principle on data from all patients who underwent randomization, with the use of a Cox proportional-hazards model, with stratification according to baseline renal-impairment category and baseline cardiovascular risk group and with treatment as a model term. One planned interim

significance for the primary analysis. The trial was designed as a superiority trial, with a closed testing hierarchy to preserve the alpha level that prespecified that a test for noninferiority with respect to the primary composite end point should be performed first and a test for superiority performed thereafter. An on-treatment (modified intention-to-treat) analysis, which included events that occurred within 30 days after the last dose of study medication was administered, was

Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33



No. at Risk

Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

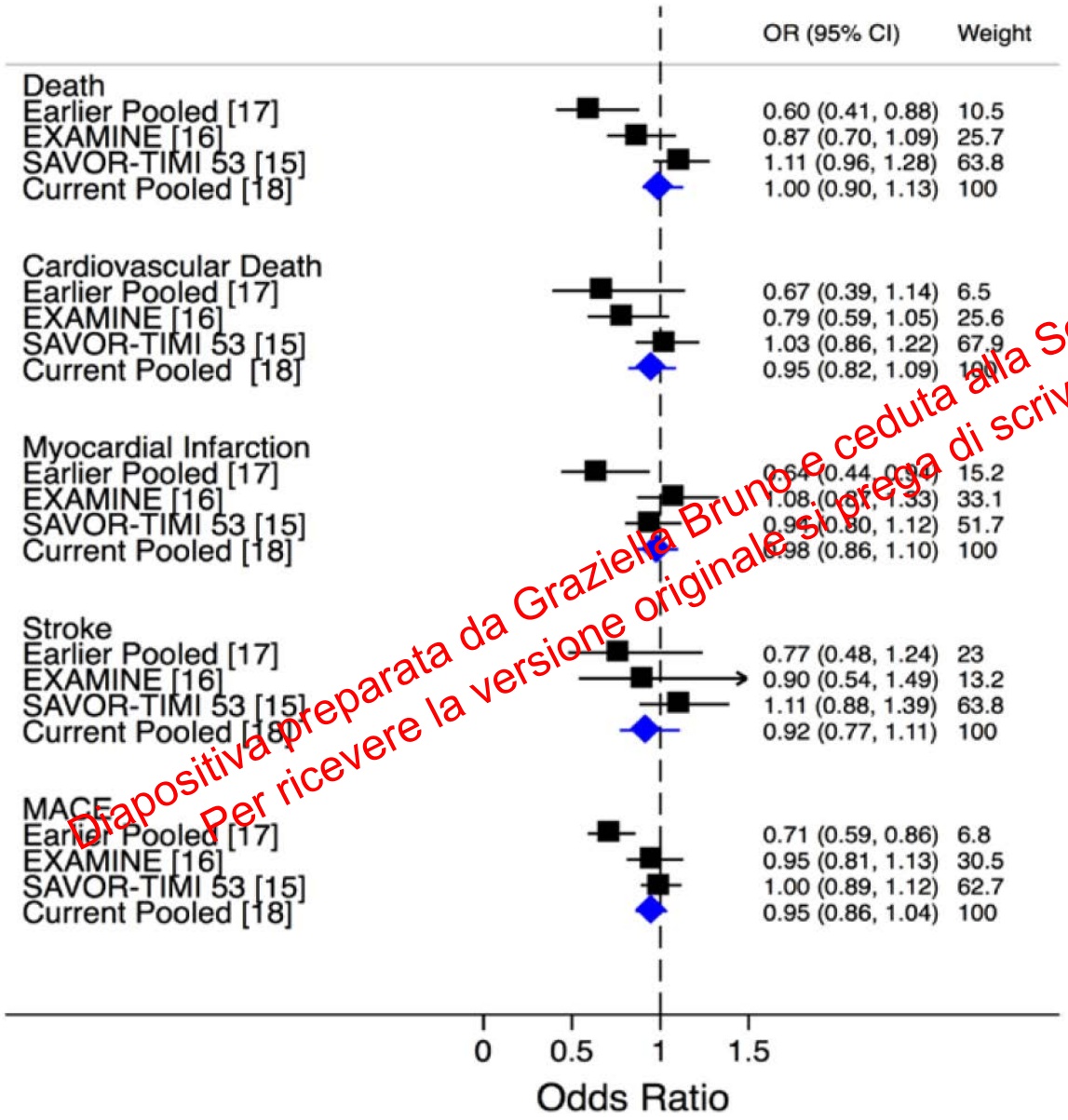
RESULTS

A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95% confidence interval [CI], 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the "on-treatment" analysis (hazard ratio, 1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1% in the two groups, respectively).

CONCLUSIONS

A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95% confidence interval [CI], 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the "on-treatment" analysis (hazard ratio, 1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1% in the two groups, respectively).

	EXAMINE	SAVOR
Agent evaluated	Alogliptin	Saxagliptin
Comparator	Standard of care	Standard of care
Design	Double-blind noninferiority	Double-blind superiority
Number of subjects	5380	16492
Events to be accrued	550/650	1040
Inclusion clinical criteria	Recent acute coronary syndrome 15–90 days before randomization	Age >40 y with 1. Previous clinical CAD, PVD, or cerebrovascular disease or 2. Multiple cardiovascular risk factors
Inclusion glycemic criteria	Type 2 DM with HbA1c between 6.5%–11% and 7%–11% if on insulin	Type 2 DM with HbA1c between 6% and 12%
Primary end point	CV death, nonfatal MI, and nonfatal stroke	CV death, nonfatal MI, and nonfatal stroke
Median follow-up in years	18 months	25 months



Menon V, Circulation 2014

1. The glucocentric approach led to trials with **inclusion criteria** that focused on subjects most likely to show glucose reductions, while excluding those at high risk for cardiovascular and other complications.
2. Although the **durations** of most trials of diabetic agents were long enough to prove efficacy with regard to glucose homeostasis, they were too short to ascertain the impact of the intervention on clinical safety and efficacy end points that might be relevant from the patient and regulatory perspective
3. multiple studies challenged the validity of using biochemical **surrogate end points**, such as the reduction in fasting blood sugar or hemoglobin A1c or improvement in lipids, to predict effects on cardiovascular events
4. **end point definitions varied** from one study to another, and independent ascertainment of events across a drug development program were usually inconsistent.

The desire to hasten approval of these agents commercially may dissuade manufacturers from performing **large trials in low-risk patients** with impaired glucose tolerance and early diabetes mellitus, in whom there may actually be the greater potential to reverse and mitigate the deleterious macrovascular consequences of diabetes mellitus.

High-risk characteristics of enrolled subjects

Parameter	SAVOR	EXAMINE
Mean age, y	65.1±8.5	61
Age >65 y, %	N/A	36
Age >75 y, %	14	N/A
Nonwhite, %	25	27
GFR <60 mL, %	N/A	29
eGFR <50 mL	15	NA
Median duration of diabetes mellitus in years	10.3	7.3

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

STATISTICAL ANALYSIS

The primary hypothesis was noninferiority for the primary outcome with empagliflozin (pooled doses of 10 mg and 25 mg) versus placebo with a margin of 1.3 for the hazard ratio. We used a four-step hierarchical-testing strategy for the pooled empagliflozin group versus the placebo group in the following order: noninferiority for the primary outcome, noninferiority for the key secondary outcome, superiority for the primary outcome, and superiority for the key secondary outcome.

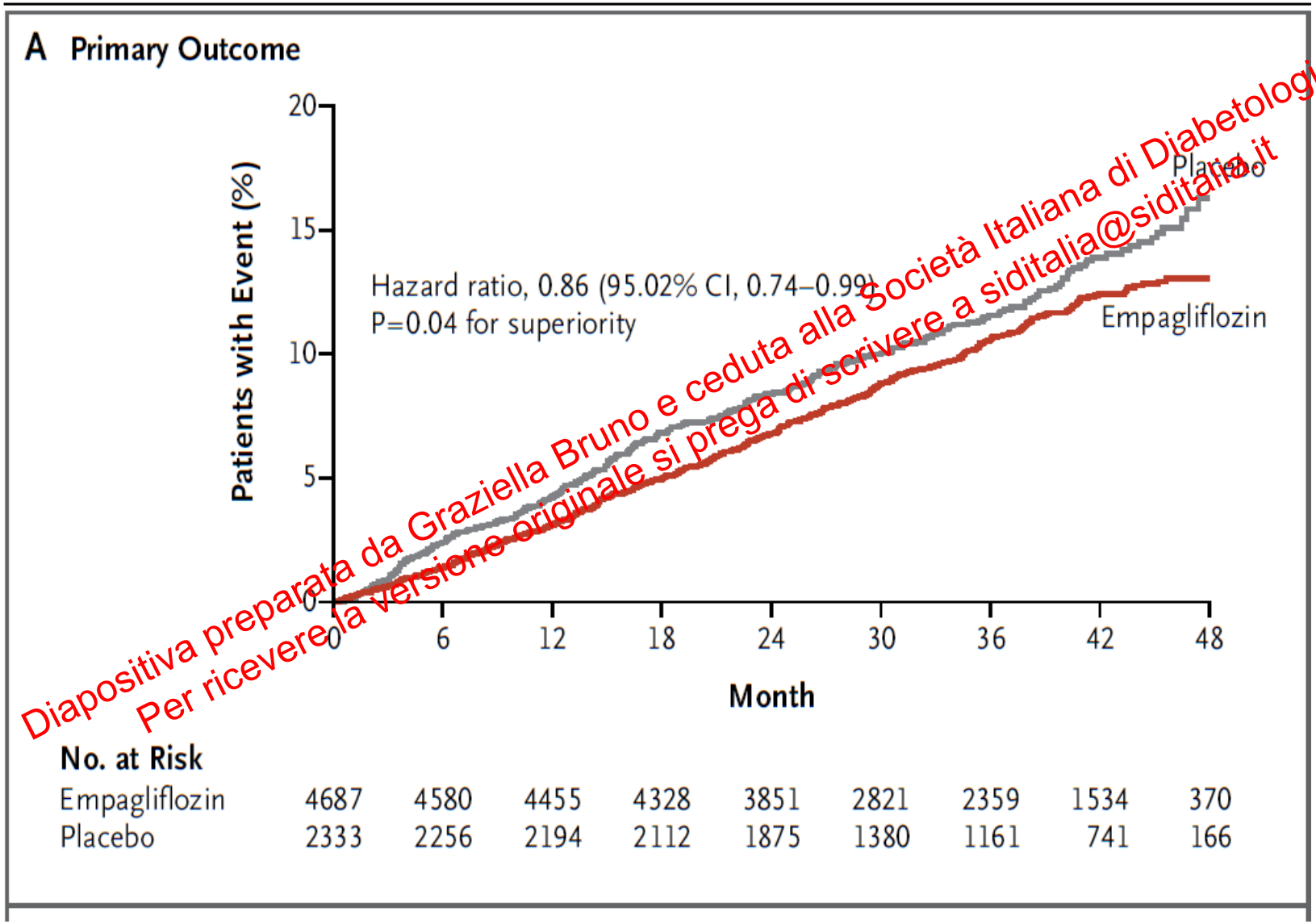

Table 2 Outcomes of the two CV safety NI studies that claim superiority

	Placebo (N=2333) Number (%)	Incident rate Number of events/1000 patient-years	Epaglifozin (N=4687) Number (%)	Incident rate Number of events/1000 patient-years	HR (95% CI)	p Value
Primary composite outcome	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74 to 0.99)	p<0.001 NI p=0.04 superiority
Non-fatal MI	121 (5.2)	18.5	213 (4.5)	16	0.87 (0.70 to 1.09)	0.22
Non-fatal CVA	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92 to 1.67)	0.16
CV death	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49 to 0.77)	<0.001

	Placebo (N=4672) Number (%)	Incident rate Number of events/ 100 patient-years	Liraglutide (N=4668) Number (%)	Incident rate Number of events/ 100 patient-years	HR (95% CI)	p Value (superiority)
Primary composite outcome	694 (14.9)	3.9	608 (13)	3.4	0.87 (0.78 to 0.97)	0.01
Non-fatal MI	317 (6.8)	1.8	281 (6)	1.6	0.88 (0.75 to 1.03)	0.11
Non-fatal CVA	177 (3.8)	1.0	159 (3.4)	0.9	0.89 (0.72 to 1.11)	0.30
CV death	278 (6)	1.6	219 (4.7)	1.2	0.78 (0.66 to 0.93)	0.007

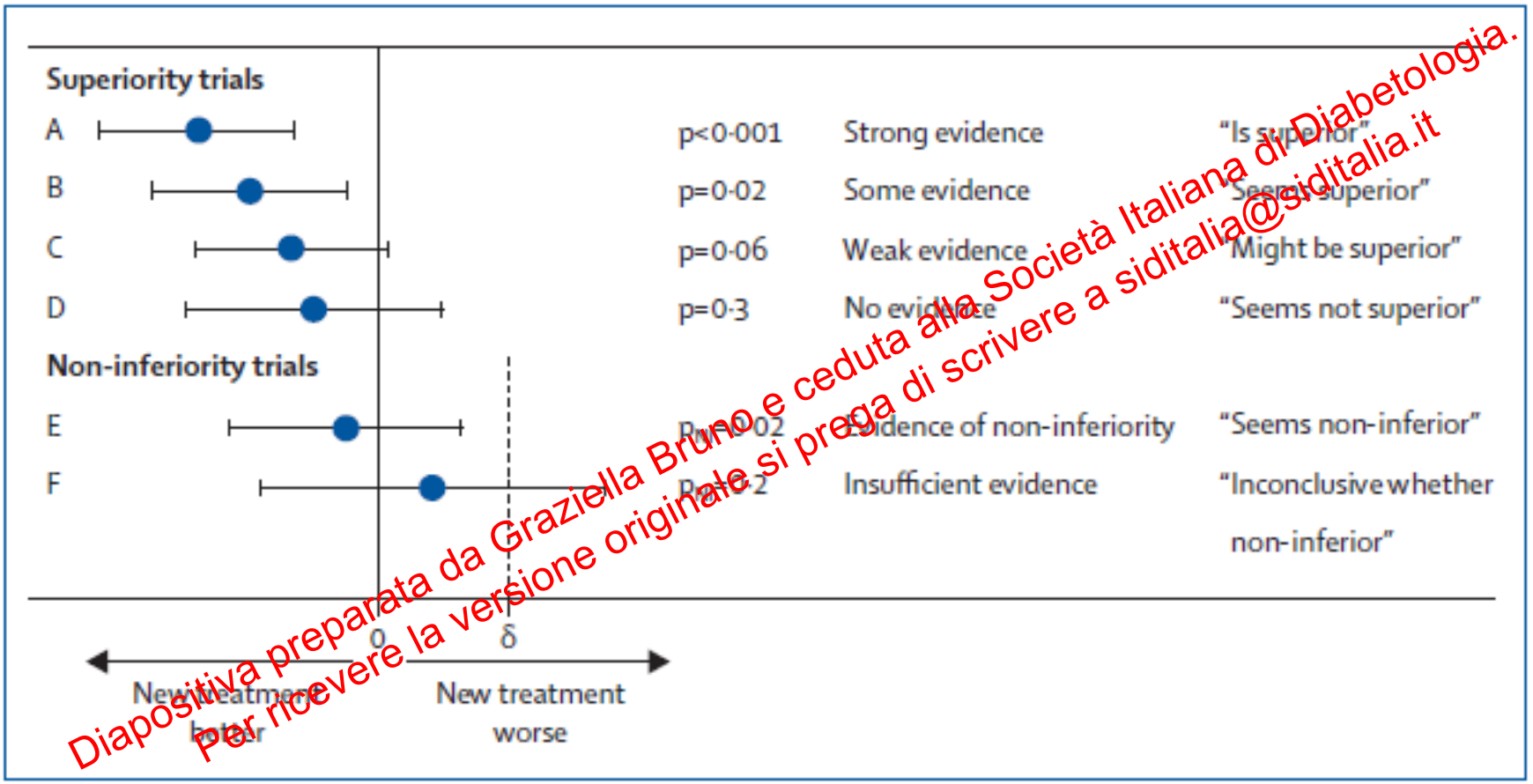

Figure: **Six scenarios for primary endpoint of randomised trial comparing new and standard treatment groups**
Each displays estimated treatment difference and its 95% CI, p value, strength of evidence, and appropriate comment for use in conclusions. For non-inferiority scenarios, non-inferiority margin δ is shown, and p_{NI} is for consequent test of non-inferiority.