Listen, Think and Plan

Metodologia degli studi clinici in diabetologia

Le basi teoriche delle sperimentazioni cliniche

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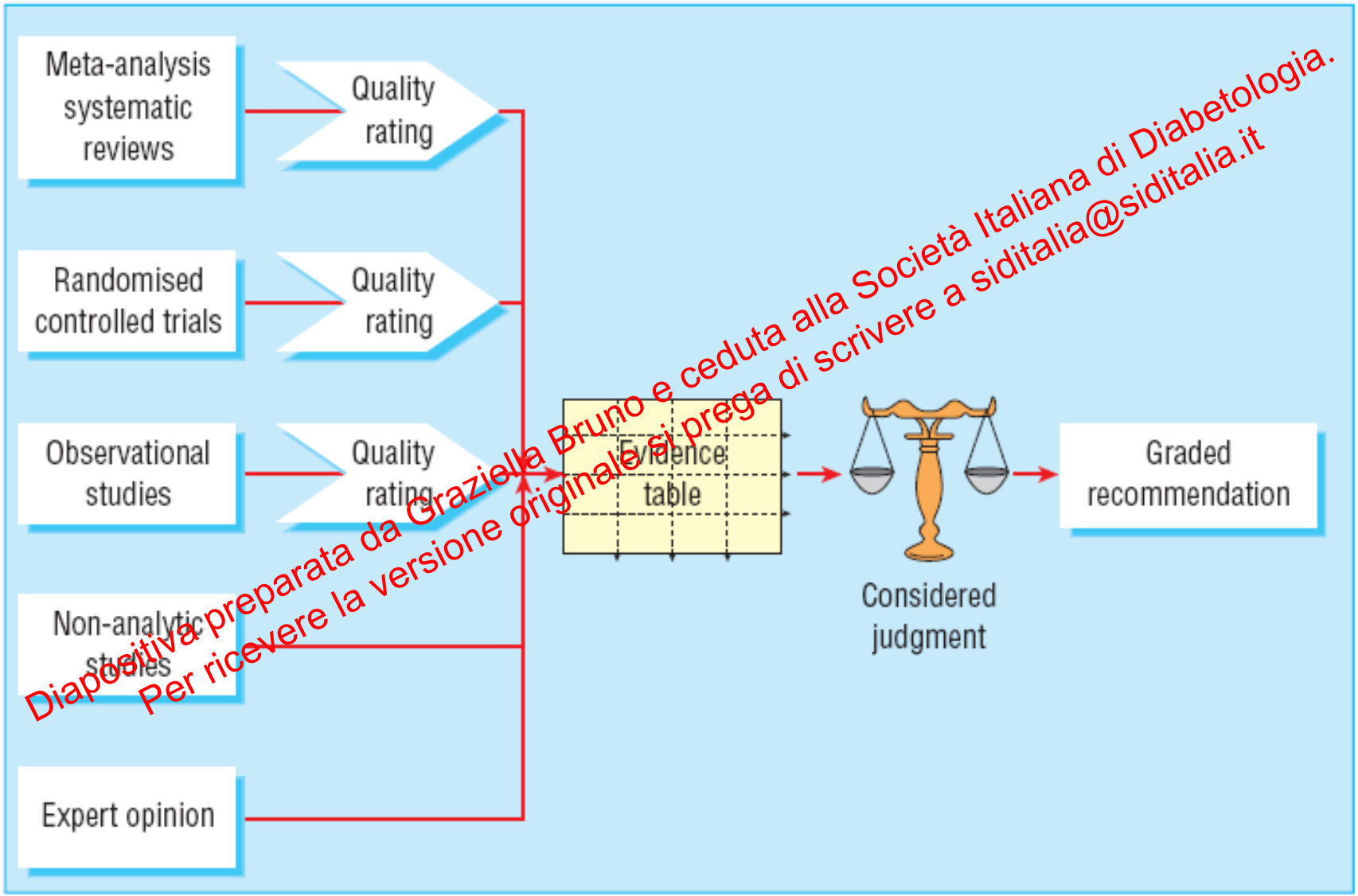
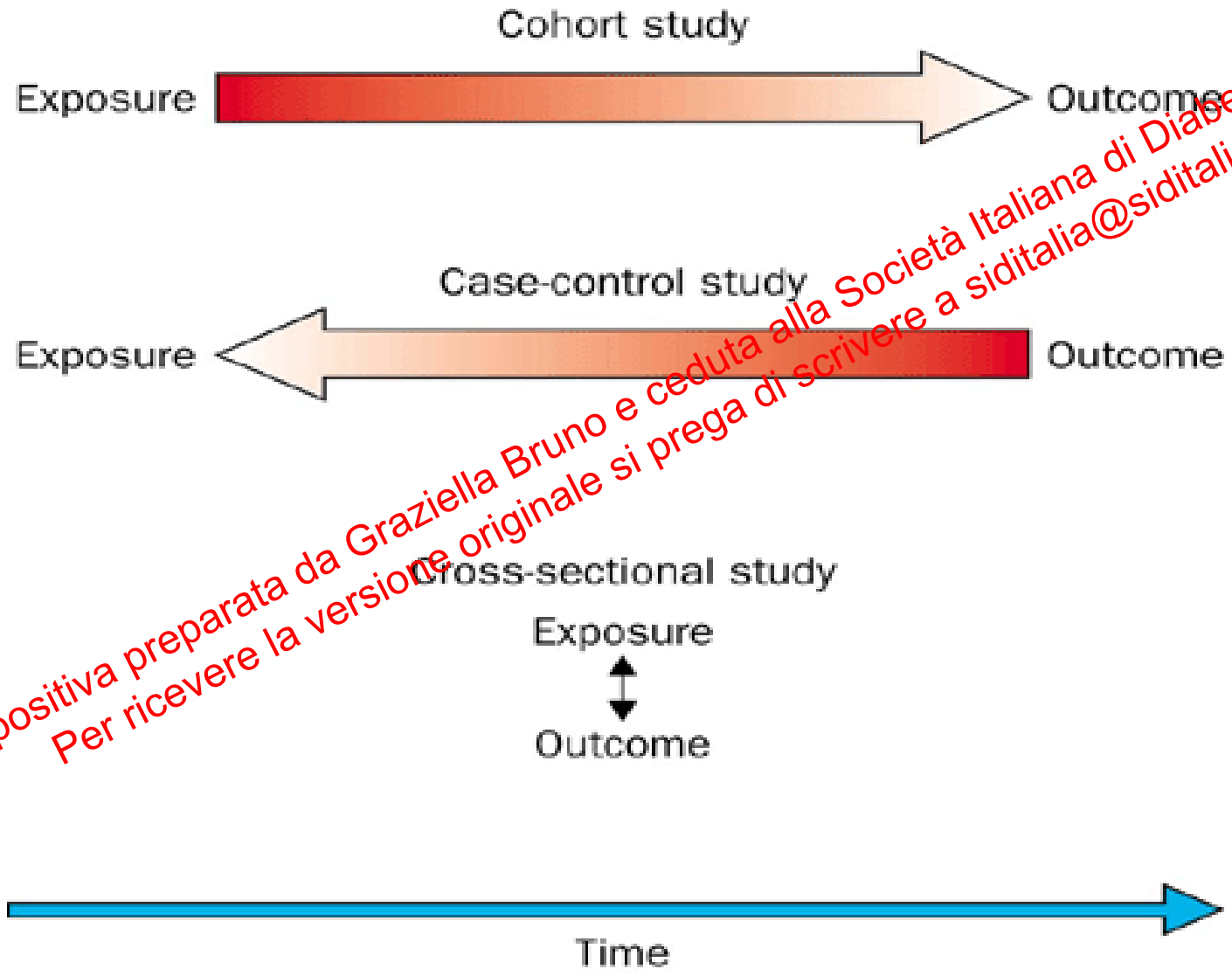




Systematic Evaluation of the Quality of Randomized Controlled Trials in Diabetes

VICTOR M. MONTORI, MD, MSC[1,4]
YAQIAN GRACE WANG, BHSC[2]
PABLO ALONSO-COELLO, MD[3]
SUMIT BHAGRA, MBBS[4]

cians. Readers only have access to the methods as reported. When reports leave out critical information about methodological safeguards against bias, readers cannot ascertain whether those safeguards were present or not during trial conduct.

almost exclusively to the rigorousness and reproducibility of the experimental procedures performed on the volunteers

Diabetes Care 29:1833–1838, 2006

OBJECTIVE — We sought to systematically ascertain the quality of randomized controlled trials (RCTs) in diabetes.

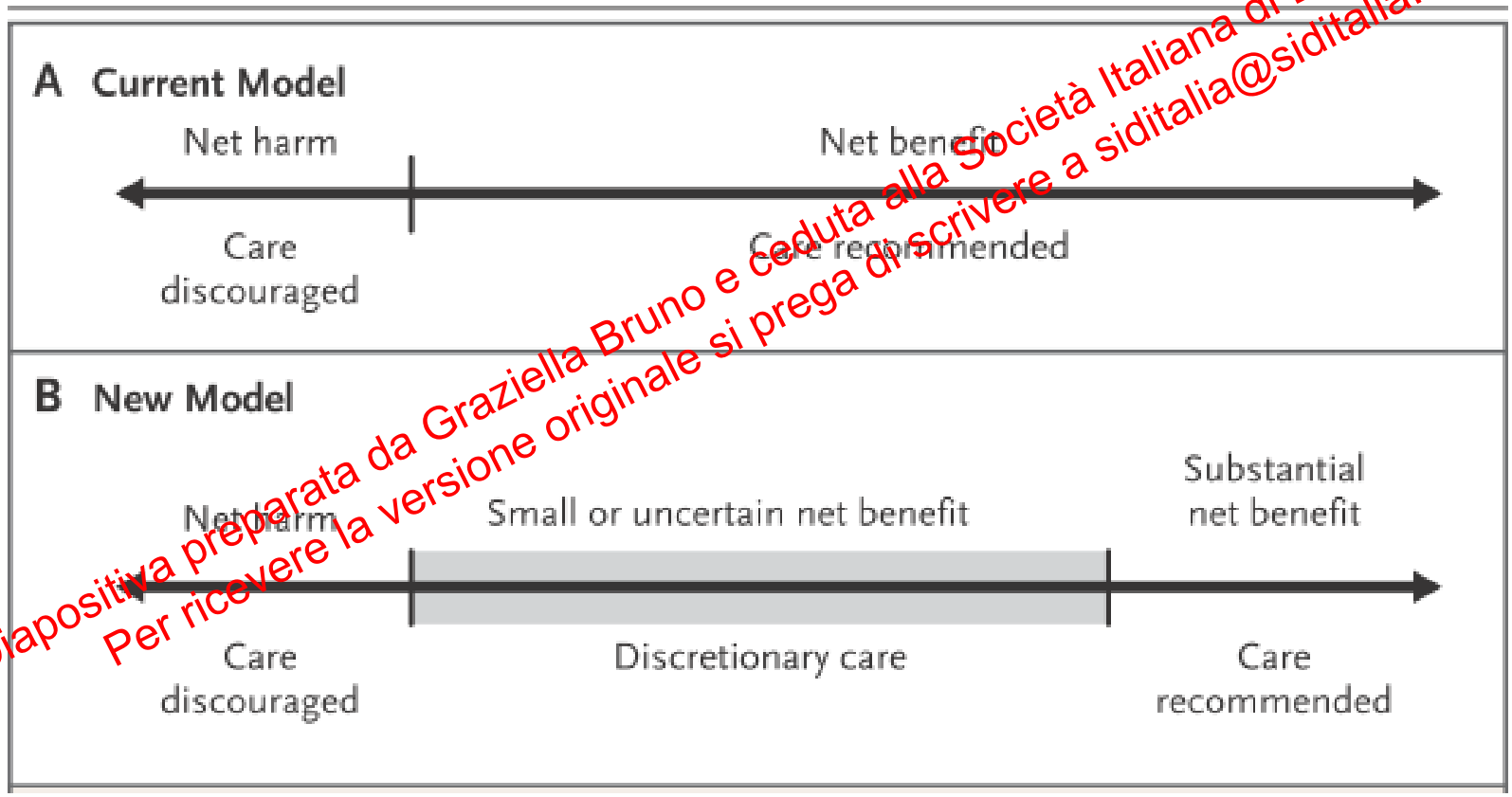
RESEARCH DESIGN AND METHODS — We identified the 10 most recently published trials as of 31 October 2003 in each of six general medical, five diabetes, and five metabolism and nutrition journals and further enriched our sample with 10 additional RCTs from each of five journals that published the most eligible RCTs in a year. We explored the association between trial characteristics and reporting quality using univariate analyses and a preplanned multivariate regression model.

RESULTS — After excluding redundant reports of included trials and one trial that measured outcomes on the health system and not on patients, we included 1990 RCTs: 119 assessed physiological and other labo[illegible] Fifty-three percent were of low methodological morbidity and mortality, qu[illegible] progression or regression, Hb[illegible] quality, as were one-third (36–40%) of trials reporting patient-important or surrogate outcomes and two-thirds (64%) of laboratory investigations. Independent predictors of low quality were nonprofit funding source (odds ratio 3.1 [95% CI 1.5–6.2]), measure of physiological and laboratory outcomes (2.5 [1.2–5.4]), and cross-over design (2.3 [1.1–4.8]), all characteristics of laboratory clinical investigations.

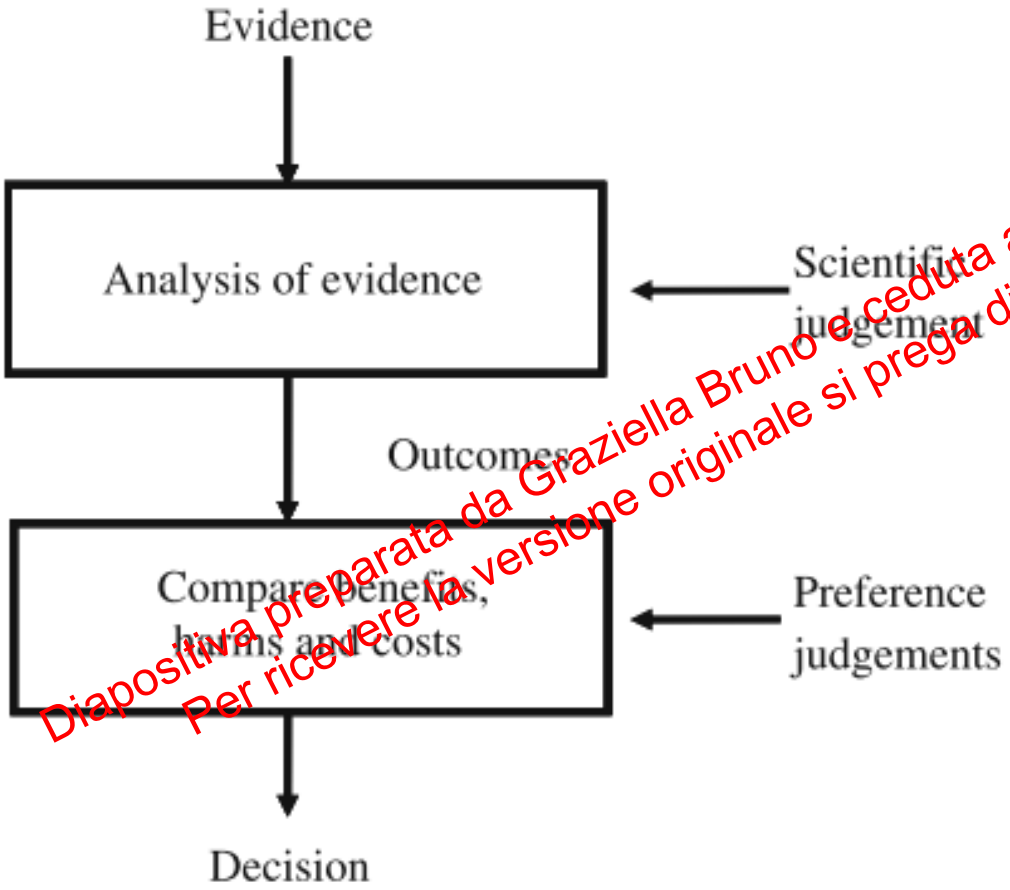
CONCLUSIONS — There is ample room for improving the quality of diabetes trials. To enhance the practice of evidence-based diabetes care, trialists need to pay closer attention to the rigorous implementation and reporting of important methodological safeguards against bias in randomized trials.

Diabetes Care 29:1833–1838, 2006

creating a new risk-benefit model for individualized decision making



Guidelines: we'll always need them, we sometimes dislike them, and we have to make them better



Diabetologia 2010

Tendenza a semplificazione in conclusione binaria: positivo/negativo

L'outcome è positivo o negativo?

-focalizzazione sul valore di significatività (P value<0.05), che non è requisito sufficiente per modificare la pratica clinica

Necessità di valutare la totalità delle evidenze , incluso la definizione degli outcome secondari, la sicurezza (safety), l'ampiezza e la qualità del trial.

Table 1. Key Questions to Ask When the Primary Outcome Is Positive.

Does a P value of <0.05 provide strong enough evidence?
What is the magnitude of the treatment benefit?
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Do concerns about safety counterbalance positive efficacy?
Is the efficacy–safety balance patient-specific?
Are there flaws in trial design and conduct?
Do the findings apply to my patients?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

BACKGROUND

We compared the angiotensin-receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

CONCLUSIONS

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NXY-059 for Acute Ischemic Stroke

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D.,
Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D.,
James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D.,
Hans-Göran Hårdemark, M.D., and Warren W. Wasiewski, M.D.,
for the Stroke–Acute Ischemic NXY Treatment (SAINT I) Trial Investigators*

BACKGROUND

NXY-059 is a free-radical–trapping agent that is neuroprotective in animal models of stroke. We tested whether it would reduce disability in humans after acute ischemic stroke.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 1722 patients with acute ischemic stroke who were randomly assigned to receive a 72-hour infusion of placebo or intravenous NXY-059 within 6 hours after the onset of the stroke. The primary outcome was disability at 90 days, as measured according to scores on the modified Rankin scale for disability (range 0 to 5, with 0 indicating no residual symptoms and 5 indicating bedbound, requiring constant care).

RESULTS

Among the 1699 subjects included in the efficacy analysis, NXY-059 significantly improved the overall distribution of scores on the modified Rankin scale, as compared with placebo (P=0.038 by the Cochran–Mantel–Haenszel test). The common odds ratio for improvement across all categories of the scale was 1.20 (95 percent confidence interval, 1.01 to 1.42). Mortality and rates of serious and nonserious adverse events were each similar in the two groups. NXY-059 did not improve neurologic functioning as measured according to the National Institutes of Health Stroke Scale (NIHSS): the difference between the two groups in the change from baseline scores was 0.1 point (95 percent confidence interval, −1.4 to 1.1; P=0.86). Likewise, no improvement was observed according to the Barthel index (P=0.14). In a post hoc analysis of patients who also received alteplase, NXY-059 was associated with a lower incidence of any hemorrhagic transformation (P=0.001) and symptomatic intracranial hemorrhage (P=0.036).

CONCLUSIONS

The administration of NXY-059 within six hours after the onset of acute ischemic stroke significantly improved the primary outcome (reduced disability at 90 days), but it did not significantly improve other outcome measures, including neurologic functioning as measured by the NIHSS score. Additional research is needed to confirm whether NXY-059 is beneficial in ischemic stroke. (ClinicalTrials.gov number, NCT00119626.)

ORIGINAL ARTICLE

NXY-059 for the Treatment of Acute Ischemic Stroke

Ashfaq Shuaib, M.D., Kennedy R. Lees, M.D., Patrick Lyden, M.D., James Grotta, M.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., Tim Ashwood, Ph.D., Warren W. Wasiewski, M.D., and Ugochi Emeribe, Ph.D., for the SAINT II Trial Investigators*

BACKGROUND

The free-radical–trapping agent NXY-059 showed promise as a neuroprotectant in the Stroke-Acute Ischemic NXY Treatment I (SAINT I) trial, reducing disability when given to patients who had acute ischemic stroke. We sought confirmation of efficacy in a second, larger trial.

METHODS

We enrolled 3306 patients with acute ischemic stroke in a randomized, double-blind trial to receive a 72-hour infusion of intravenous NXY-059 or placebo within 6 hours after the onset of stroke symptoms. Our primary end point was the distribution of disability scores on the modified Rankin scale at 90 days. We examined scores on neurologic and activities-of-daily-living scales as secondary end points. We also tested the hypothesis that NXY-059 would reduce alteplase-related intracranial hemorrhages.

RESULTS

The efficacy analysis was based on 3195 patients. Prognostic factors were well balanced between the treatment groups. Mortality was equal in the two groups, and adverse-event rates were similar. The distribution of scores on the modified Rankin scale did not differ between the group treated with NXY-059 (1588 patients) and the placebo group (1607 patients; P=0.33 by the Cochran–Mantel–Haenszel test; odds ratio for limiting disability, 0.94; 95% confidence interval [CI], 0.83 to 1.06). Analysis of categorized scores on the modified Rankin scale confirmed the lack of benefit: the odds ratio for trichotomization into modified Rankin scale scores of 0 to 1 versus 2 to 3 versus 4 to 6 was 0.92 (95% CI, 0.80 to 1.06). There was no evidence of efficacy for any of the secondary endpoints. Among patients treated with alteplase, there was no difference between the NXY-059 group and the placebo group in the frequency of symptomatic or asymptomatic hemorrhage.

CONCLUSIONS

NXY-059 is ineffective for the treatment of acute ischemic stroke within 6 hours after the onset of symptoms. (ClinicalTrials.gov number, NCT00061022.)

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Do the findings apply to my patients?

Risultato statisticamente significativo ma clinicamente non rilevante

Attenzione a rischi relativi vs rischi assoluti

Attenzione a range di intervallo di confidenza

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. [illegible] NO. [illegible]

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., Kyungah Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

BACKGROUND

Statin therapy reduces low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events, but whether the addition of ezetimibe, a nonstatin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further is not known.

METHODS

We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin–ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

RESULTS

The median time-weighted average LDL cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group (P<0.001). The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; P=0.016). Rates of pre-specified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups.

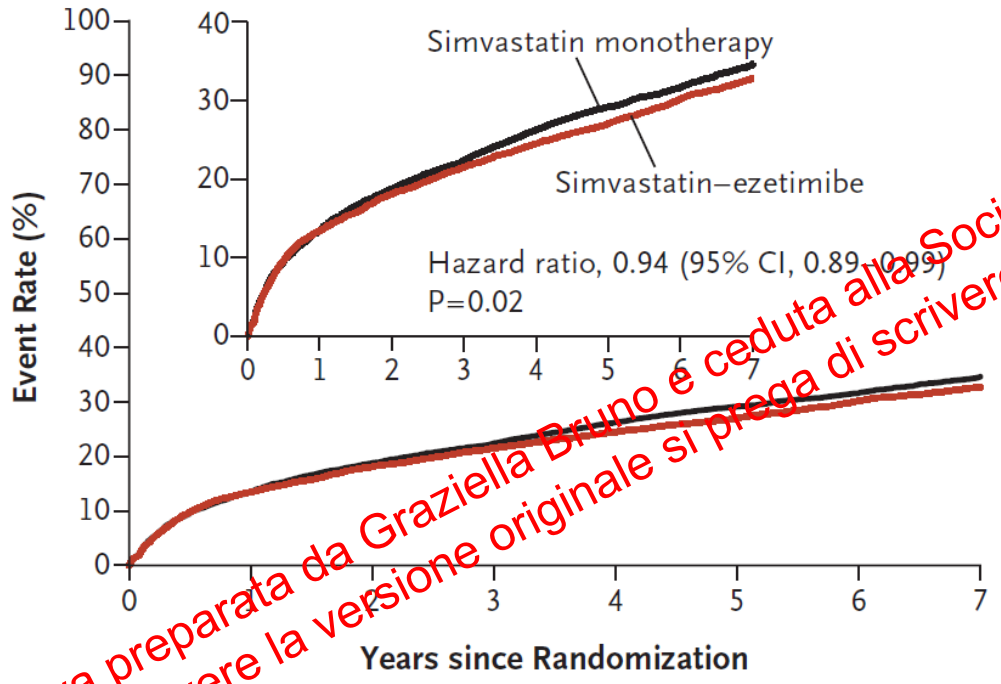
HR= 0.94 95% CI 0.89-0.99

32.7% vs 34.7%

-2%

CONCLUSIONS

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

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Are there flaws in trial design and conduct?
Do the findings apply to my patients?

Surrogate outcomes and composite outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

BACKGROUND

Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

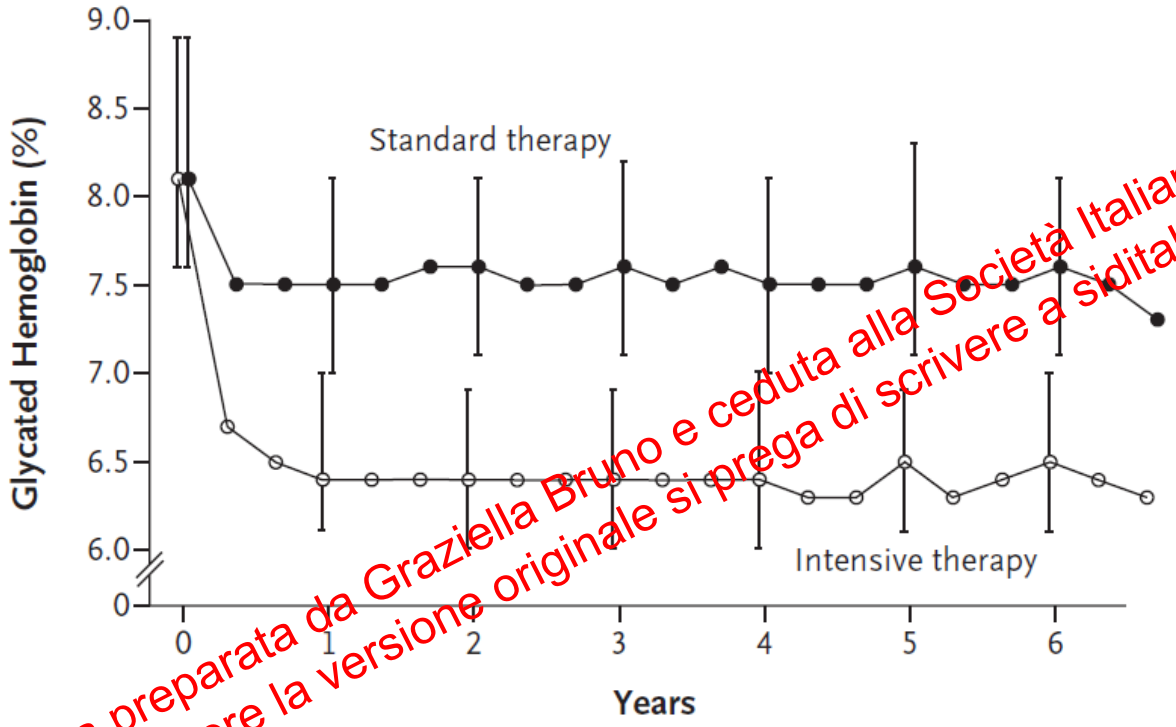
METHODS

In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up.

RESULTS

At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).

glycemic episodes requiring medical assistance



No. at Risk							
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.

I bars denote interquartile ranges.

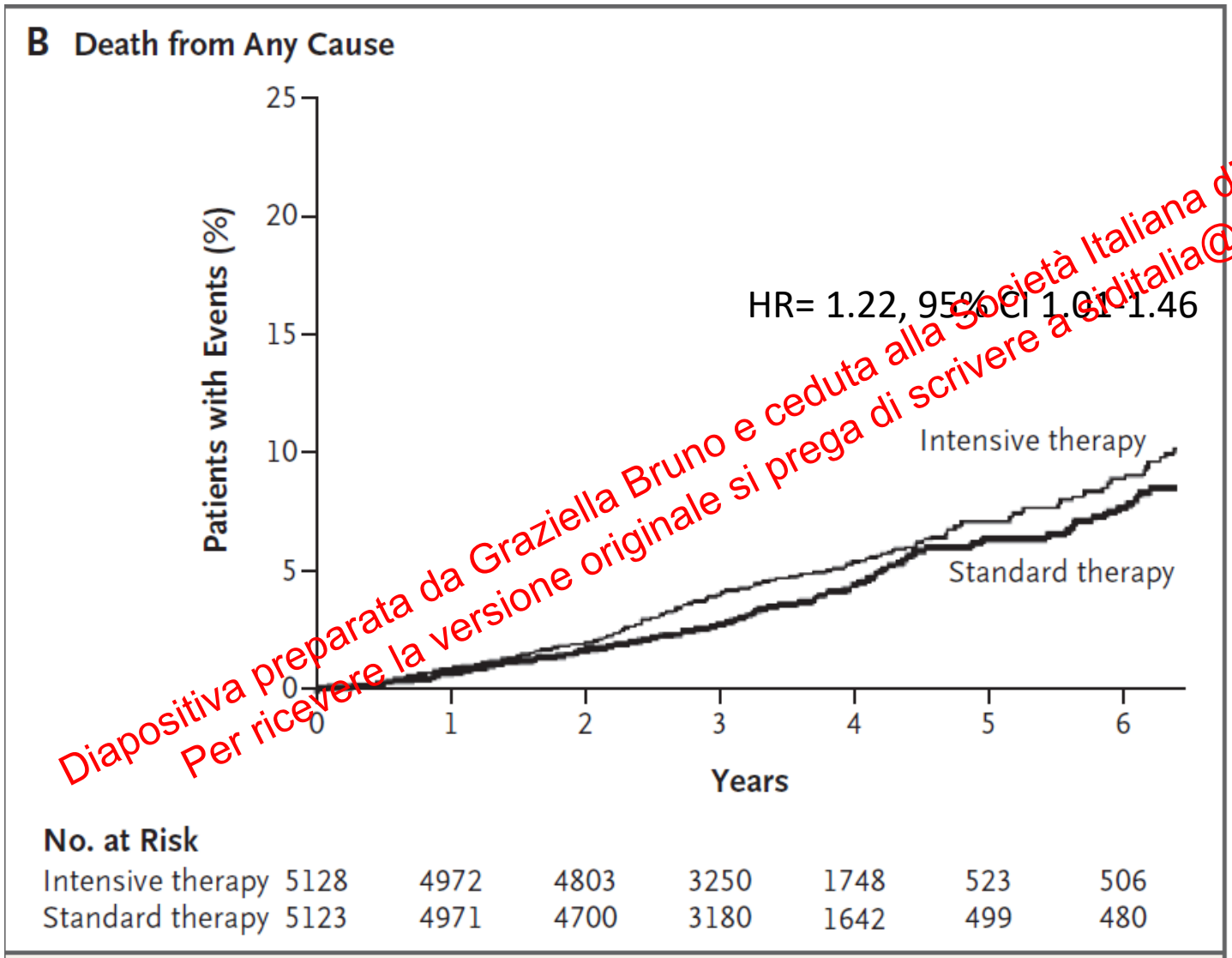


Figure 2. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.

Articles

Composite outcomes…

Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial

K A A Fox, P A Poole-Wilson, R A Henderson, T C Clayton, D A Chamberlain, T A D Shaw, D J Wheatley, S J Pocock, for the Randomized Intervention Trial of unstable Angina (RITA) investigators†*

Background Current guidelines suggest that, for patients at moderate risk of death from unstable coronary-artery disease, either an interventional strategy (angiography followed by revascularisation) or a conservative strategy (ischaemia-driven or symptom-driven angiography) is appropriate. We aimed to test the hypothesis that an interventional strategy is better than a conservative strategy in such patients.

Methods We did a randomised multicentre trial of 1810 patients with non-ST-elevation acute coronary syndromes (mean age 62 years, 38% women). Patients were assigned an early intervention or conservative strategy. The antithrombin agent in both groups was enoxaparin. The co-primary endpoints were a combined rate of death, non-fatal myocardial infarction, or refractory angina at 4 months, and a combined rate of death or non-fatal myocardial infarction at 1 year. Analysis was by intention to treat.

Findings At 4 months, 86 (9·6%) of 895 patients in the intervention group had died or had a myocardial infarction or refractory angina, compared with 133 (14·5%) of 915 patients in the conservative group (risk ratio 0·66, 95% CI 0·51–0·85, p=0·0001). This difference was mainly due to a halving of refractory angina in the intervention group. Death or myocardial infarction was similar in both treatment groups at 1 year (68 [7·6%] *vs* 76 [8·3%], respectively; risk ratio 0·91, 95% CI 0·67–1·25, p=0·58). Symptoms of angina were improved and use of antianginal medications significantly reduced with the interventional strategy (p<0·0001).

RR= 0.66 , 95% CI 0.51-0.85

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Is the efficacy–safety balance patient-specific?
Are there flaws in trial design and conduct?
Do the findings apply to my patients?

Effetto di outcome primario ha maggior forza se è supportato anche da analoghi effetti su outcome secondari

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

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

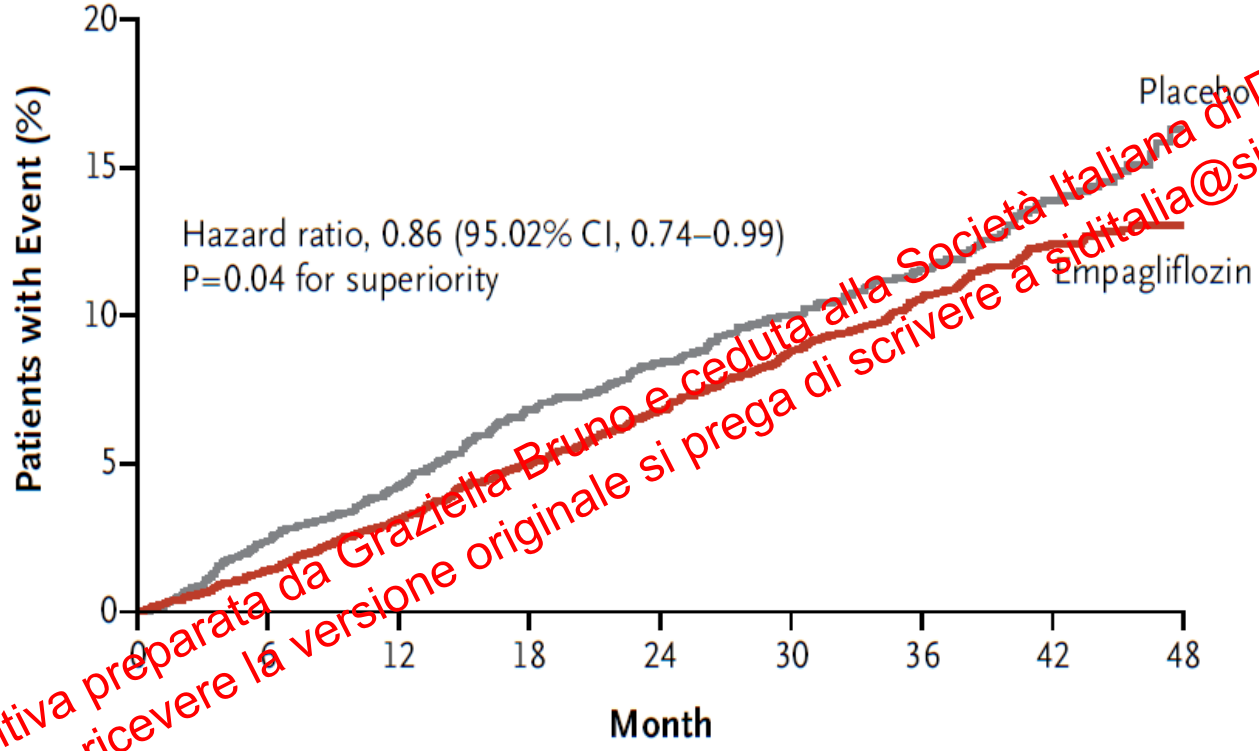
METHODS

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.

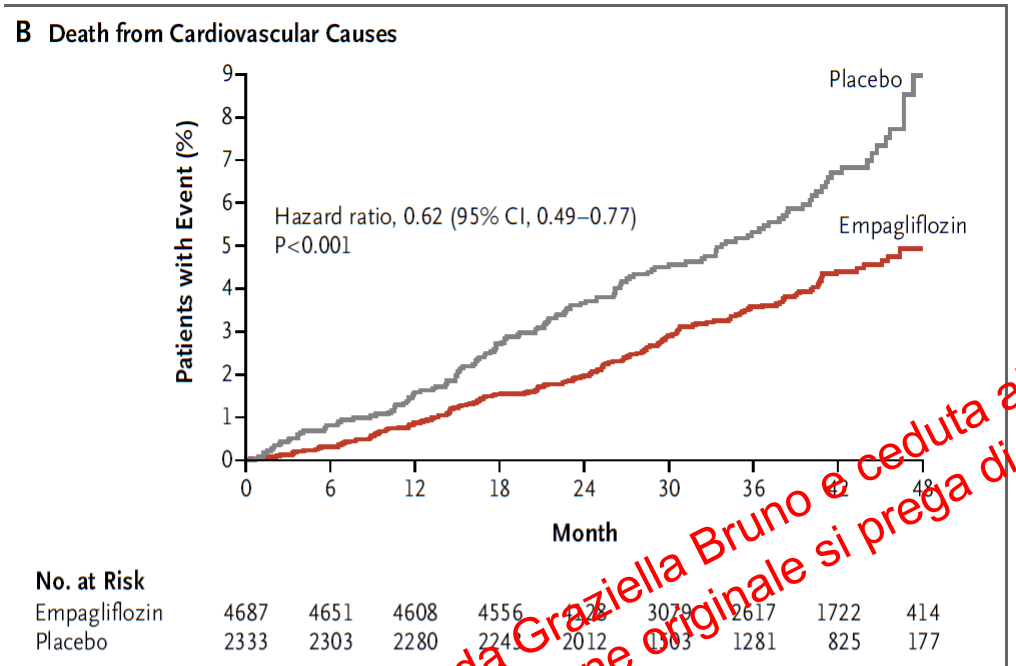
RESULTS

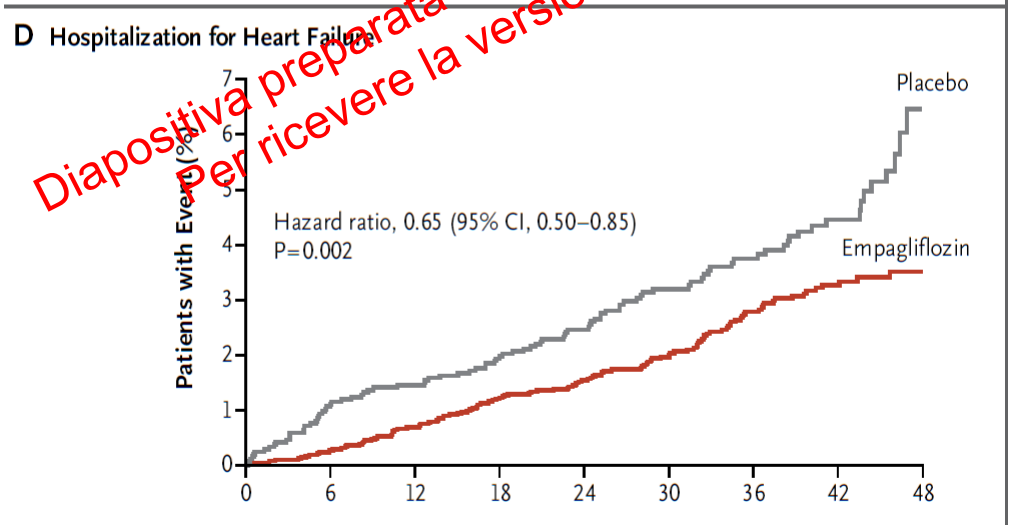
A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 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.

A Primary Outcome



No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166





Il risultato di end-point composito è dato in larga misura da end-point «forte»

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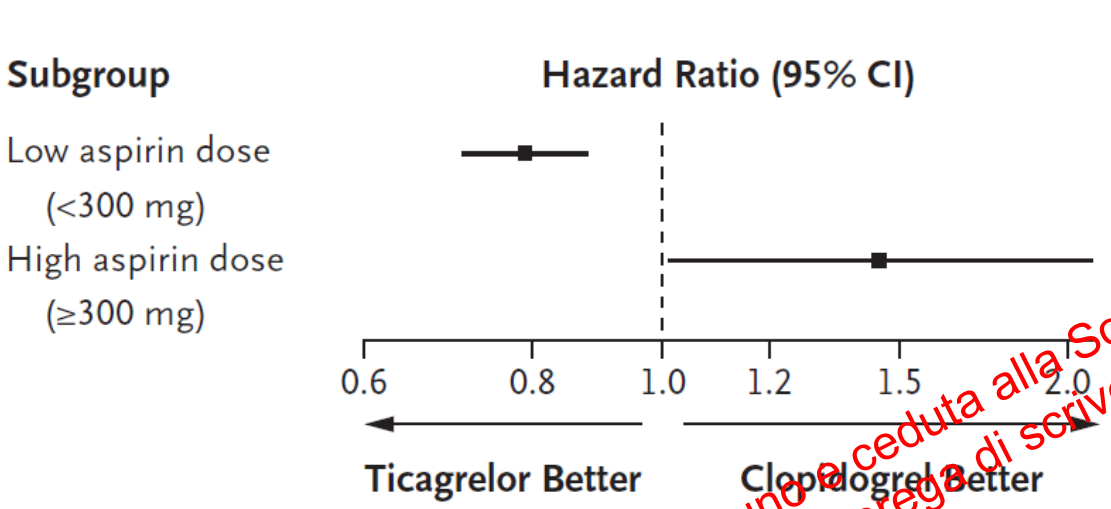

Warning FDA: evitare ASA> 100 mg in associazione a Ticagrelor

Figure 2. Apparent Interaction between a Maintenance Dose of Aspirin and Randomization to Ticagrelor or Clopidogrel and the Primary Efficacy End Point from the PLATO Trial.

In the PLATO trial, which involved 18,624 patients who presented with an acute coronary syndrome, ticagrelor was more effective than clopidogrel with respect to the primary composite outcome of cardiovascular death, myocardial infarction, or stroke among patients who were on a low maintenance dose of aspirin (<300 mg) but not among those who were on a high maintenance dose of aspirin (≥300 mg), a qualitative interaction that was statistically significant. Data are from Carroll et al.[22]

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The New England Journal of Medicine

PREVENTION OF RADIOGRAPHIC-CONTRAST-AGENT–INDUCED REDUCTIONS IN RENAL FUNCTION BY ACETYLCYSTEINE

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Methods We prospectively studied 83 patients with chronic renal insufficiency (mean [±SD] serum creatinine concentration, 2.4±1.9 mg per deciliter [216±116 μmol per liter]) who were undergoing computed tomography with iopromide, a nonionic, low-osmolality contrast agent. Patients were randomly assigned either to receive the antioxidant acetylcysteine (600 mg orally twice daily) and 0.45 percent saline intravenously, before and after administration of the contrast agent, or to receive placebo and saline.

Results Ten of the 83 patients (12 percent) had an increase of at least 0.5 mg per deciliter (44 μmol per liter) in the serum creatinine concentration 48 hours after administration of the contrast agent: 1 of the 41 patients in the acetylcysteine group (2 percent) and 9 of the 42 patients in the control group (21 percent; P=0.01; relative risk, 0.1; 95 percent confidence interval, 0.02 to 0.9). In the acetylcysteine group, the mean serum creatinine concentration decreased significantly (P<0.001), from 2.5±1.3 to 2.1±1.3 mg per deciliter (220±118 to 186±112 μmol per liter) 48 hours after the administration of the contrast medium, whereas in the control group, the mean serum creatinine concentration increased nonsignificantly (P=0.18), from 2.4±1.3 to 2.6±1.5 mg per deciliter (212±114 to 226±133 μmol per liter) (P<0.001 for the comparison between groups).

1/41 vs 9/42 RR=0.10, 95% CI 0.02-0.90, p=0.01

Conclusions Prophylactic oral administration of the antioxidant acetylcysteine, along with hydration, prevents the reduction in renal function induced by iopromide, a nonionic, low-osmolality contrast agent, in patients with chronic renal insufficiency. (N Engl J Med 2000;343:180-4.)

Conclusione troppo forte rispetto all'entità numerica, infatti smentita da metanalisi successive….

Table 1. Key Questions to Ask When the Primary Outcome Is Positive.

Does a P value of <0.05 provide strong enough evidence?
What is the magnitude of the treatment benefit?
Is the primary outcome clinically important (and internally consistent)?
Are secondary outcomes supportive?
Are the principal findings consistent across important subgroups?
Is the trial large enough to be convincing?
Was the trial stopped early?
Do concerns about safety counterbalance positive efficacy?
Is the efficacy–safety balance patient-specific?
Are there flaws in trial design and conduct?
Do the findings apply to my patients?

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A Randomized Trial of Intensive versus Standard Blood-Pressure Control

BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

RESULTS

At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.

HR= 0.75, 95% CI 0.64-0.89)

The exceptional speed to publication was surprising; only 4 weeks lapsed between the time that the trial was stopped and the time at which the manuscript was submitted for publication.

The quality and completeness of any interim database are inevitably imperfect — there will be outstanding primary (and other) events yet to be ascertained and adjudicated.

In addition, the moment at which a trial is stopped is the time at which an exaggerated estimate of efficacy is more likely to be present.

Orderly trial closure after early stoppage takes several months and is necessary to achieve robust interpretation of all the evidence. Earlier reporting of preliminary, incomplete results is usually unwise.

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Subgroup	Intensive Treatment (N=4678)	Standard Treatment (N=4683)
	no. of events (percent)	
Primary outcome	243 (5.2)	319 (6.8)
Death from any cause	155 (3.3)	210 (4.5)
Heart failure	62 (1.3)	100 (2.1)
Serious hypotensive episode	158 (3.4)	93 (2.0)
Serious syncope episode	163 (3.5)	113 (2.4)
Serious acute renal event	204 (4.4)	120 (2.6)

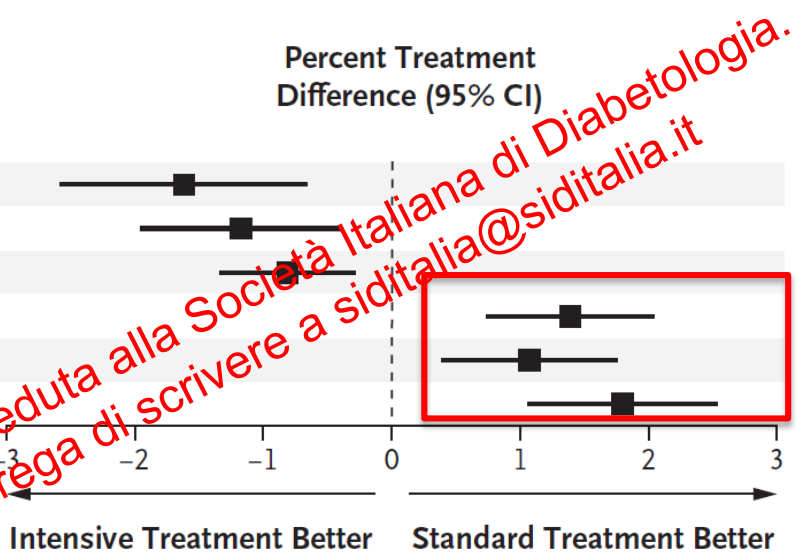


Figure 3. Balancing Efficacy and Safety Outcomes in SPRINT.

In the SPRINT trial, among 9361 selected patients with a systolic blood pressure of 130 mm Hg or more who were randomly assigned to intensive treatment (a systolic blood-pressure target of <120 mm Hg) or standard treatment (a target of <140 mm Hg), intensive treatment resulted in a substantially lower rate of the composite primary outcome of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or cardiovascular death than standard treatment and in lower rates of all-cause death and heart failure. However, intensive treatment was associated with significantly higher rates of serious adverse events related to hypotension, syncope, and acute kidney injury. Data are from the SPRINT Research Group.[31]

COME CALCOLARE L' NNT
Number Needed to Treat

EER: experimental event rate

incidenza di eventi nel gruppo sperimentale

CER: control event rate

incidenza di eventi nel gruppo di controllo

ARR: absolute risk reduction

(CER-EER)

$$NNT = \frac{1}{ARR}$$

numero di pazienti che è necessario trattare per prevenire un evento

1° esempio:

gruppo sperimentale : incidenza eventi: 10%

controllo : 20%

riduzione relativa del rischio: 20% / 10% = 50%

riduzione assoluta 20% - 10% = 10%

NNT 1/0.10 =10

2° esempio:

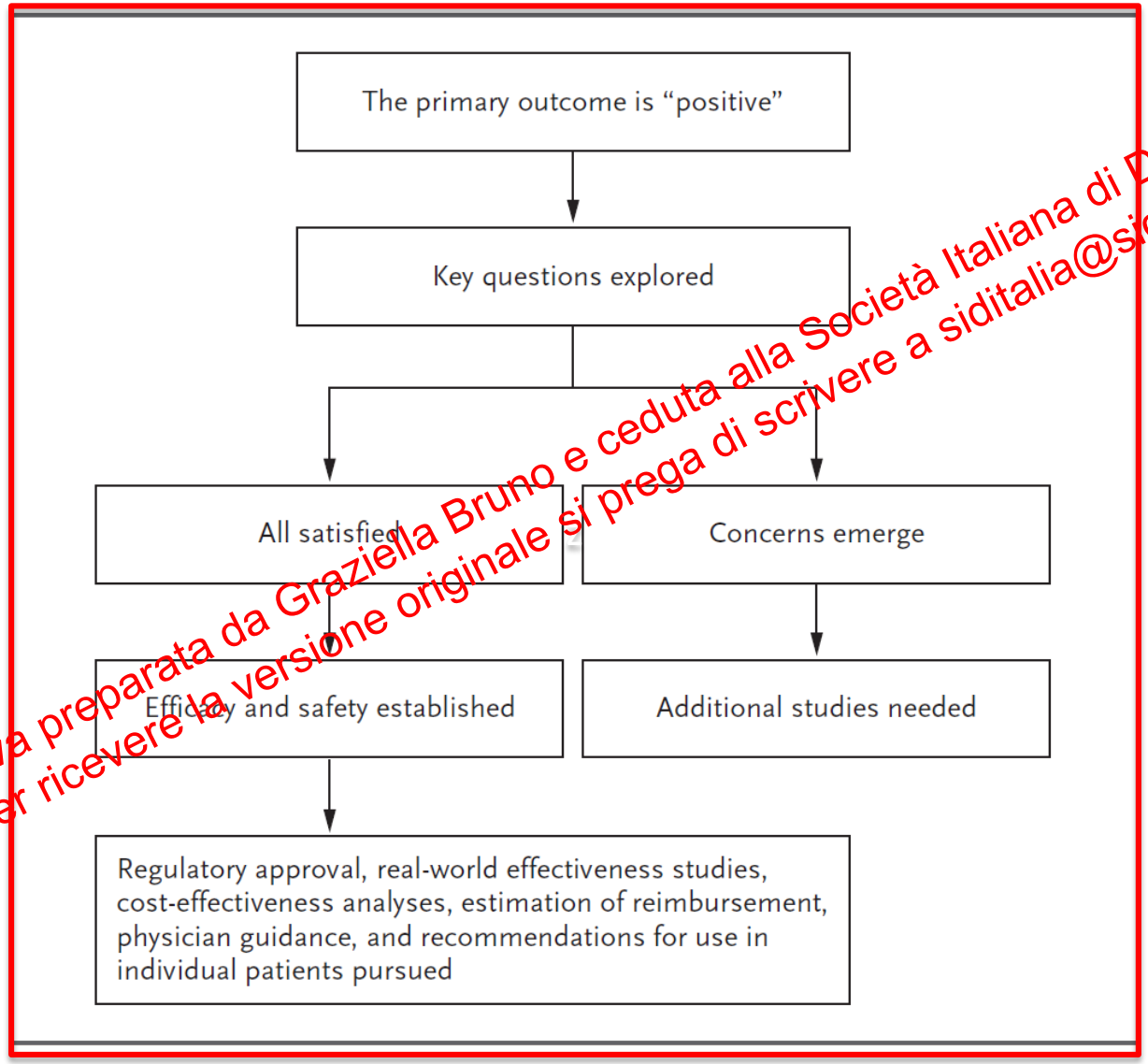
gruppo sperimentale: incidenza eventi: 1%

controllo : 2%

riduzione relativa del rischio: 2% / 1% = 50%

riduzione assoluta 2% - 1% = 1%

NNT 1/0.01=100



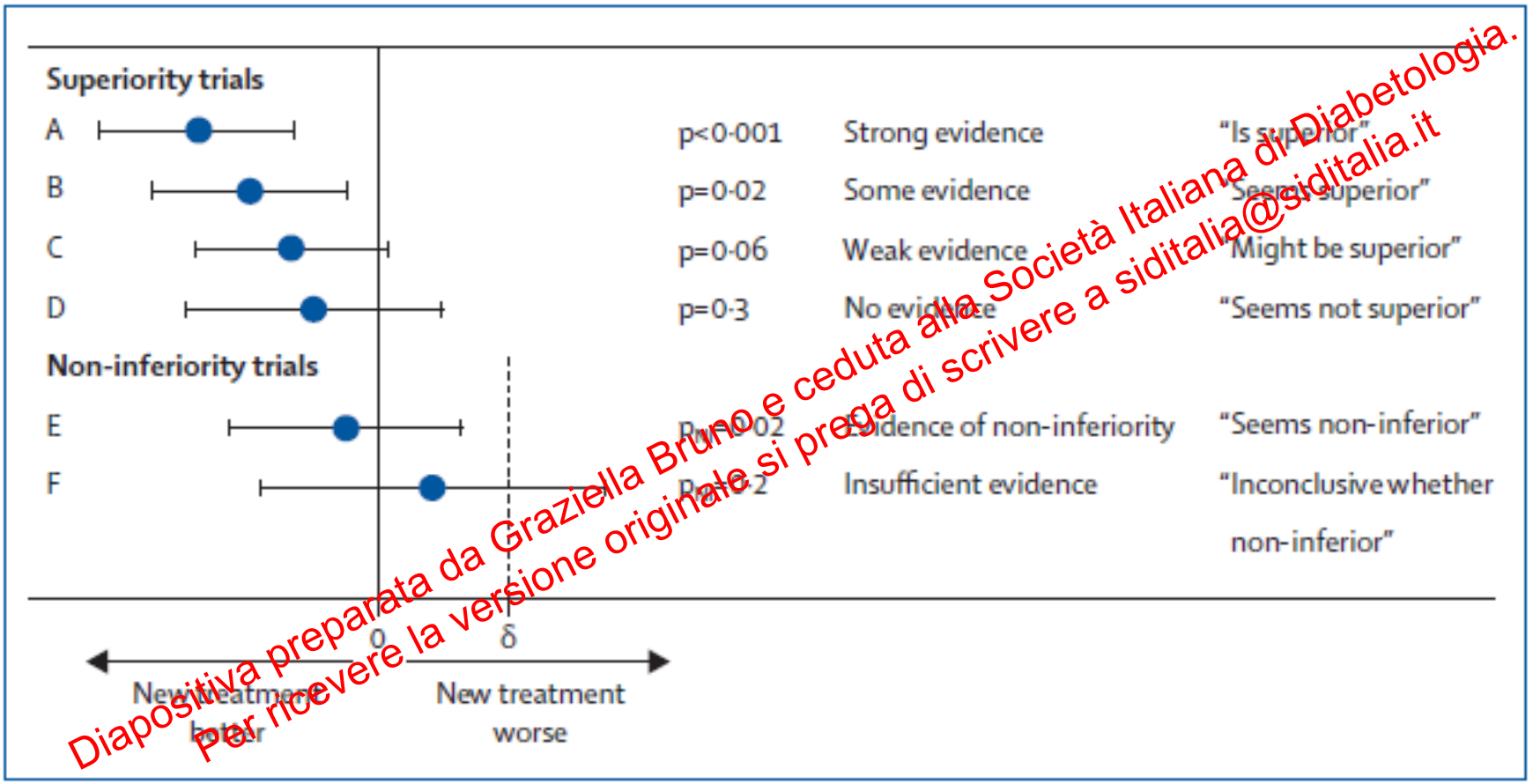


Figure: **Six scenarios for primary endpoint of randomised trial comparing new and standard treatment groups**
Each displays estimated treatment difference and its 95% CI, p value, strength of evidence, and appropriate comment for use in conclusions. For non-inferiority scenarios, non-inferiority margin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