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Metodologia degli studi clinici in diabetologia

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ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D.,

BACKGROUND

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.

RESULTS

At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) ($P<0.001$). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; $P<0.001$) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; $P<0.001$). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).

CONCLUSIONS

In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

From the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W., S.A.M., J.F.K.); Sydney Medical School, National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (A.C.K.); Amgen, Thousand Oaks, CA (N.H., H.W., T.L., S.M.W.); International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London (P.S.S.); and Oslo University Hospital, Ullevål and Medical Faculty, University of Oslo, Oslo (T.R.P.). Address reprint requests to Dr. Sabatine at the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 60 Fenwood Rd., Boston, MA 02115, or at msabatine@partners.org.

*A complete list of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) steering committee and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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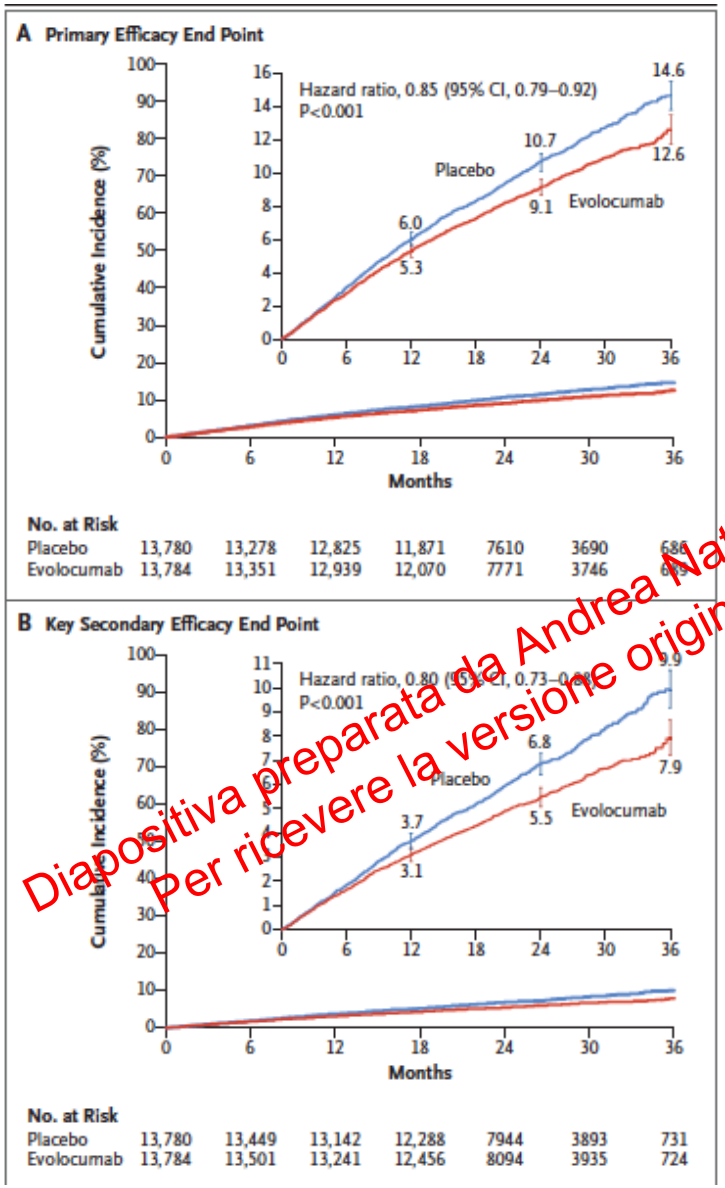


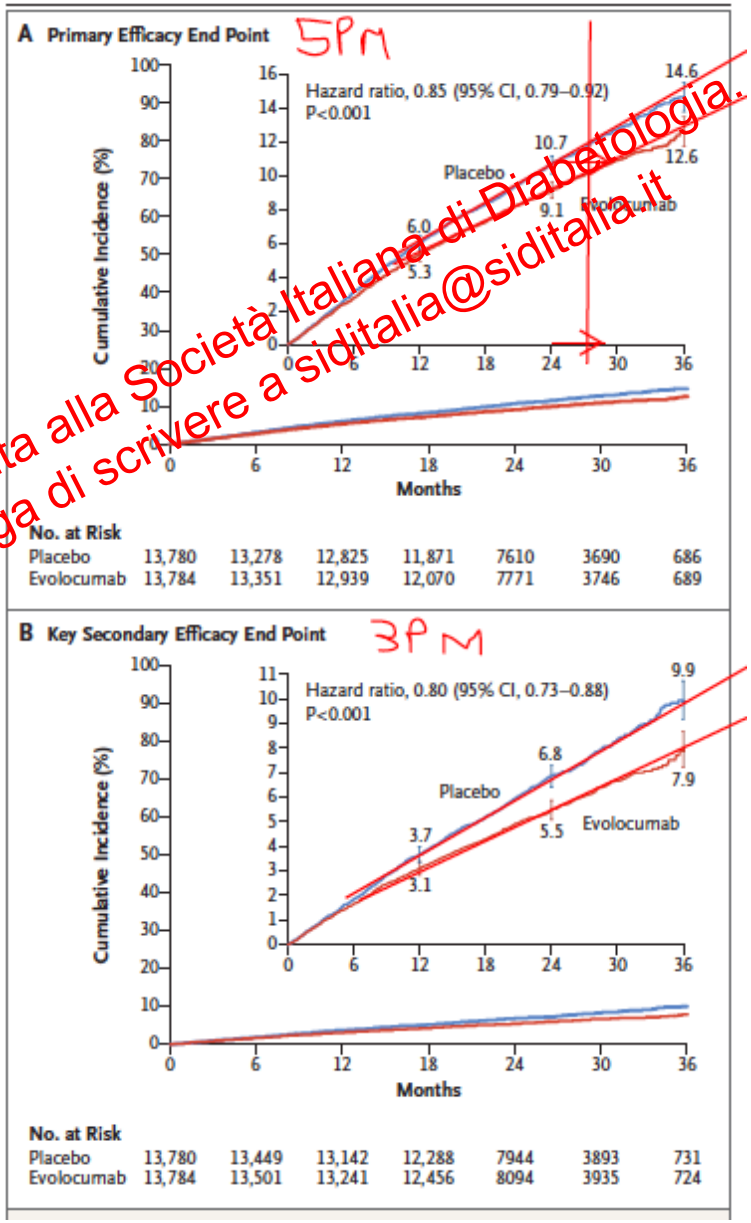


Table 2. Primary and Secondary End Points.

Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	36 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

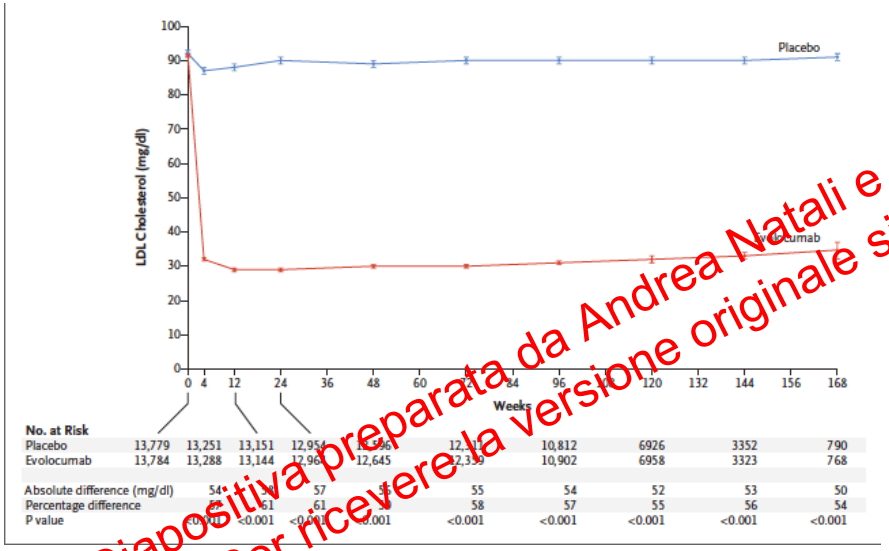
-15%

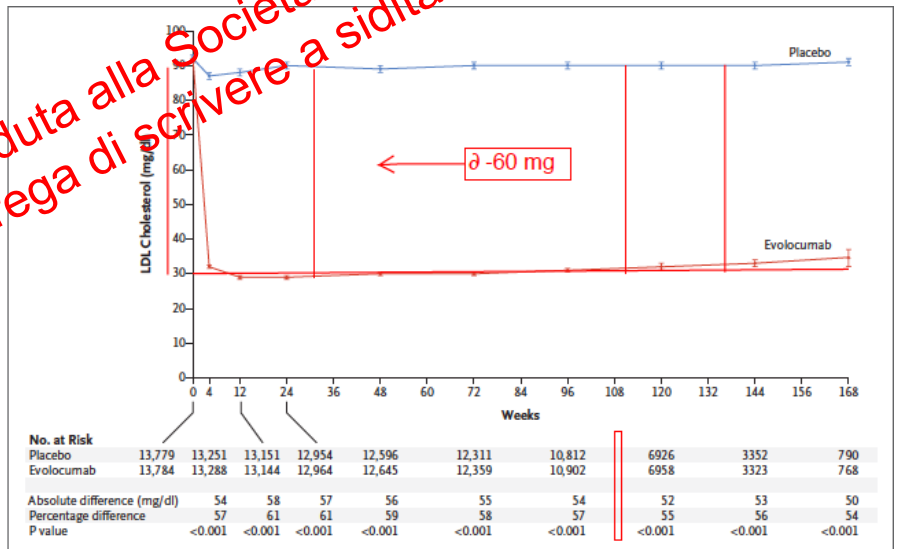
-20%

-27%

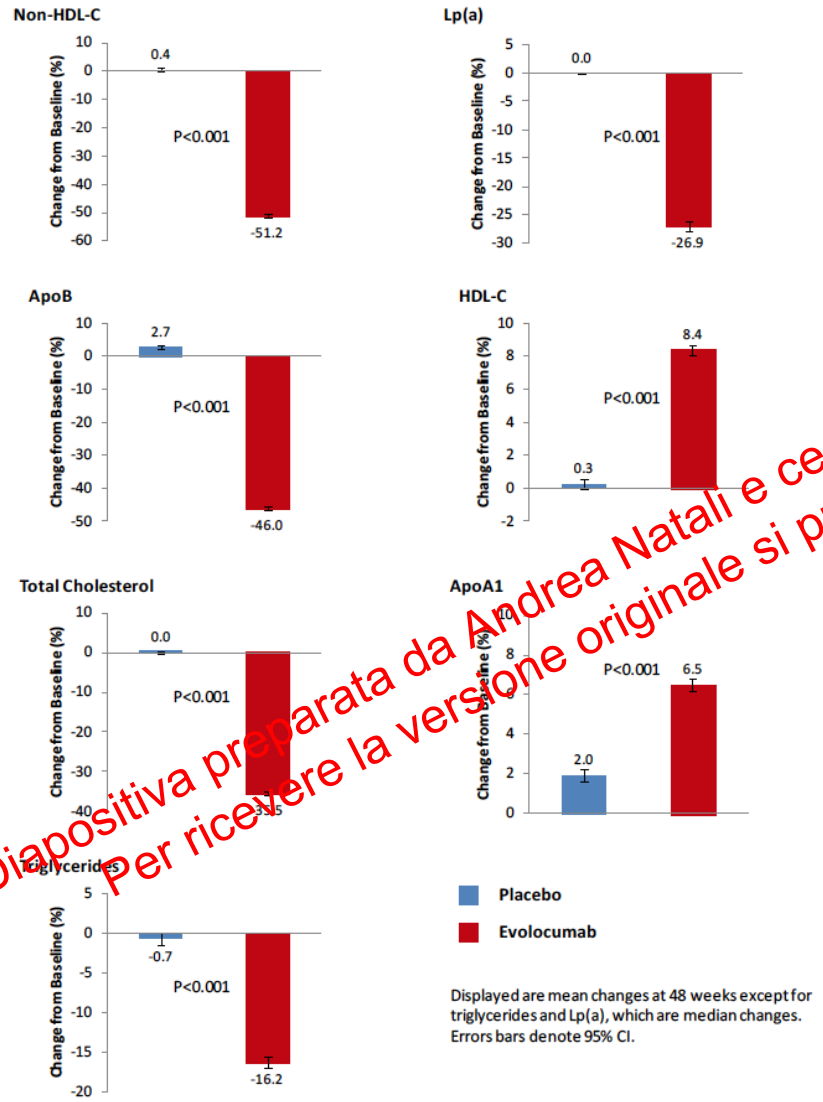
Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N=13,784)	Placebo (N=13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)
White race — no. (%)†	11,748 (85.2)	11,710 (85.0)
Weight — kg	85.0±17.3	85.5±17.4
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)
Type of atherosclerosis‡		
Myocardial infarction — no. (%)	11,145 (80.9)	11,206 (81.3)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)	3.3 (0.9–7.7)
Nonhemorrhagic stroke	2638 (19.5)	2651 (19.2)
Median time from most recent previous stroke (IQR) — yr	3.2 (1.1–7.1)	3.3 (1.1–7.3)
Peripheral artery disease — no. (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications — no./total no. (%)		
Aspirin, $P2Y_{12}$ inhibitor, or both	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB, aldosterone antagonist, or both	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)





Supplementary Figure S3 – Other lipid parameters



Displayed are mean changes at 48 weeks except for triglycerides and Lp(a), which are median changes. Errors bars denote 95% CI.

Effect on all lipid parameter

BP? BMI? HbA1c?

Table 3. Adverse Events and Laboratory Test Results.

Outcome	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events — no. of patients (%)		
Any	10,644 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

DISCUSSION

(2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter). This effect was sustained with-

addition of evolocumab to statin therapy significantly reduced the risk of cardiovascular events, with a 15% reduction in the risk of the primary composite end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization and a 20% reduction in the risk of the more clinically

5 P 1

3 P 1

verse events that were noted to be nominally significantly more common in association with evolocumab were injection-site reactions, but these were rare, and the rate of discontinuation of the study regimen was no higher with evolocumab than with placebo.

The data from our trial provide insight into the benefit of decreasing LDL cholesterol levels to median levels lower than those in previous trials. Previously, significant reductions in major cardiovascular events were found in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) and Treating to New Targets (TNT) trials, in which the more intensive statin regimen lowered LDL cholesterol levels from approximately 100 mg per deciliter (2.6 mmol per liter) to 70 mg per deciliter (1.8 mmol per liter).[13,14] More recently, the addition of ezetimibe to statin therapy in the Improved Reduction of

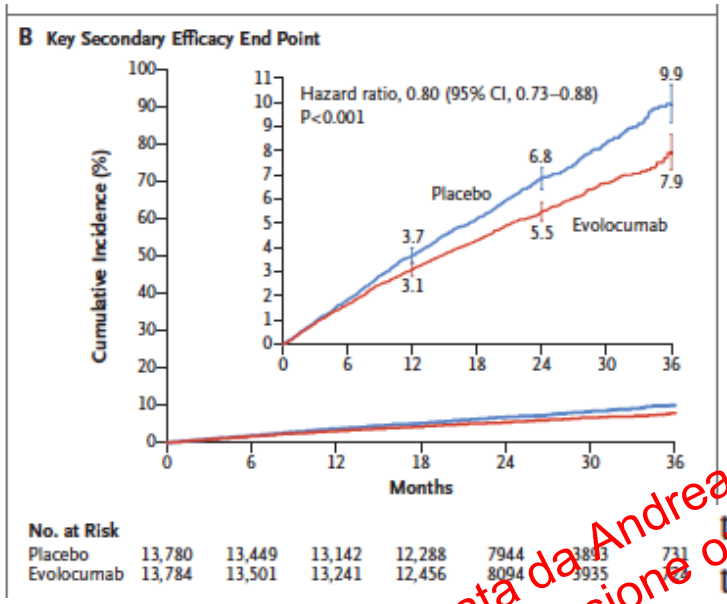
Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) lowered LDL cholesterol levels from 70 mg per deciliter (1.8 mmol per liter) to 54 mg

events across the range of baseline LDL cholesterol levels. Specifically, there was a 17% reduction in the risk of the key secondary end point among patients in the top quartile for baseline LDL cholesterol level, in whom evolocumab lowered the median LDL cholesterol level from 126 mg per deciliter (3.3 mmol per liter) to 43 mg per deciliter (1.1 mmol per liter) (with the achieved level similar to that achieved with ezetimibe in patients in the lowest quartile for admission LDL cholesterol levels in IMPROVE-IT[16]), and there was a 22% reduction in the risk of the key secondary end point among the patients in the lowest quartile for baseline LDL cholesterol level, in whom evolocumab lowered the median LDL cholesterol level from 73 mg per deciliter (1.9 mmol per liter) to 22 mg per deciliter (0.57 mmol per liter).

∂ -83 mg/dl = 17%

∂-51 mg/dl = -22%

A delay between th



the magnitude of the risk reduction with regard to the key secondary end point appeared to grow over time, from 16% during the first year to 25% beyond 12 months, which suggests that the translation of reductions in LDL cholesterol levels into cardiovascular clinical benefit requires time. Overall, 74 patients would need to be treated over a period of 2 years to prevent a cardiovascular death, myocardial infarction, or stroke.

NNT

Arrampicarsi
sulgli specchi

therapy,[15,25] we found no effect of additional lowering of LDL cholesterol levels on cardiovascular mortality. The rate of use of evidence-based cardiovascular pharmacotherapies that lower cardiovascular mortality was very high in FOURIER, in which the rates of cardiovascular mortality were one third of the rates in the Scandinavian Simvastatin Survival Study (4S).[26] Similar to the findings in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) and IMPROVE-IT, in our trial we found no effect on hospitalization for unstable angina. The advent of increasingly sensitive cardiac troponin assays probably makes cardiac ischemia increasingly questionable as the true cause of a hospitalization for chest-pain symptoms without biochemical evidence of myocyte injury.[27] Finally,

Verificare ?

Given these caveats, the magnitude of benefit of evolocumab in reducing the risk of major coronary events, stroke, and urgent coronary revascularization is largely consistent with the benefit seen with statins on a per–millimole-per-liter basis of LDL cholesterol lowering (Fig. S6 in the Supplementary Appendix). These observations are in accord with meta-analyses of data from clinical trials of different lipid-lowering interventions, which show consistent clinical benefits per unit reduction in LDL cholesterol.[28] Likewise, these observations are supported by data from a recent mendelian randomization study in which variants in *PCSK9* and variants in *HMGCR* were associated with nearly identical lower risks of cardiovascular events per unit reduction in LDL cholesterol.[29]

in the overall rates of adverse events or in rates of study-regimen discontinuation. The rate of discontinuation of evolocumab injections because of adverse events that were ascribed to the drug was similar to the rate with placebo (0.28% vs. 0.67% per year) and compares favorably to the rates that were not borne out in this trial. In contrast to recent data for bococizumab (a humanized but not fully human monoclonal antibody against PCSK9),[32] evolocumab-binding antibodies were rarely detected in our trial, no neutralizing antibodies developed, and the overall LDL choles-

The major limitation of this trial was a relatively short duration of follow-up as compared with that in other lipid-lowering trials, in which follow-up periods have averaged approximately 5 years.[28] Although the median follow-up period in FOURIER was originally planned to be approximately 4 years, an event rate that was approximately 50% higher than had been postulated led to a shorter required duration of follow-up to accrue the prespecified number of events. Most

In conclusion, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from the lowering of LDL cholesterol levels below current targets.

Appendix E – Supplemental Results

A total of 1,209 (8.8%) patients allocated to evolocumab and 1,120 (8.1%) patients allocated to placebo either switched to a less intensive statin regimen or discontinued a statin during FOURIER. Conversely, 95 (0.7%) patients allocated to evolocumab and 141 (1.0%) patients allocated to placebo switched to a more intensive statin regimen. Ezetimibe was started in 67 (0.5%) and 145 (1.1%) patients in the evolocumab and placebo arms, respectively, during the trial, and 2 patients in the evolocumab arm stopped it.

switch

The placebo-controlled mean LDL cholesterol reduction at 12 weeks with evolocumab was 61.1% (95% CI 60.5-61.7) for patients who chose every two week dosing and 56.9% (95% CI 55.3-58.6) for those who chose monthly dosing.

Dosing diff

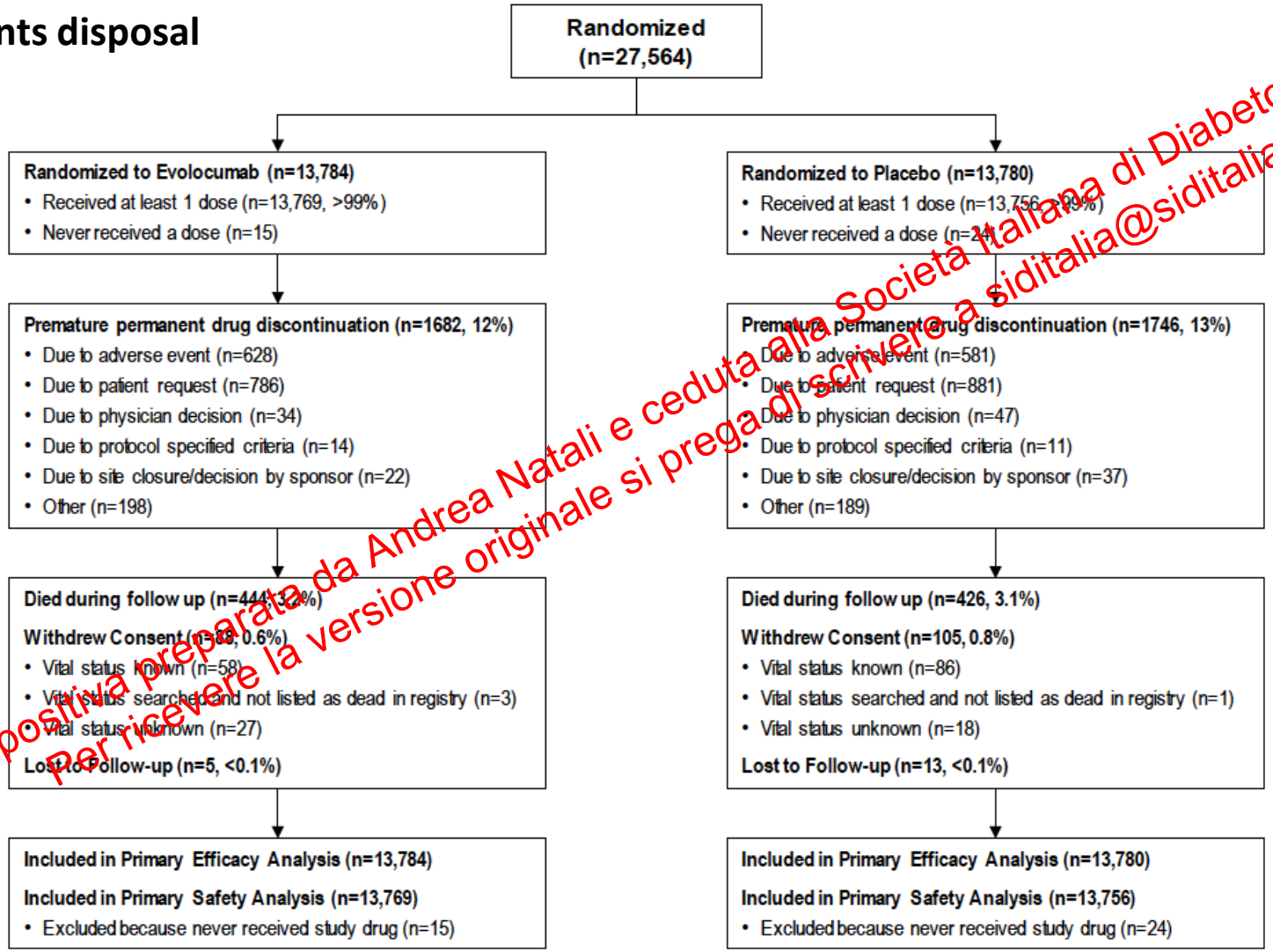
The between-group difference in LDL cholesterol at 48 weeks with imputation for missing values as per the Cholesterol Treatment Trialists Collaboration approach was 53.4 mg/dL (1.38 mmol/L).

?

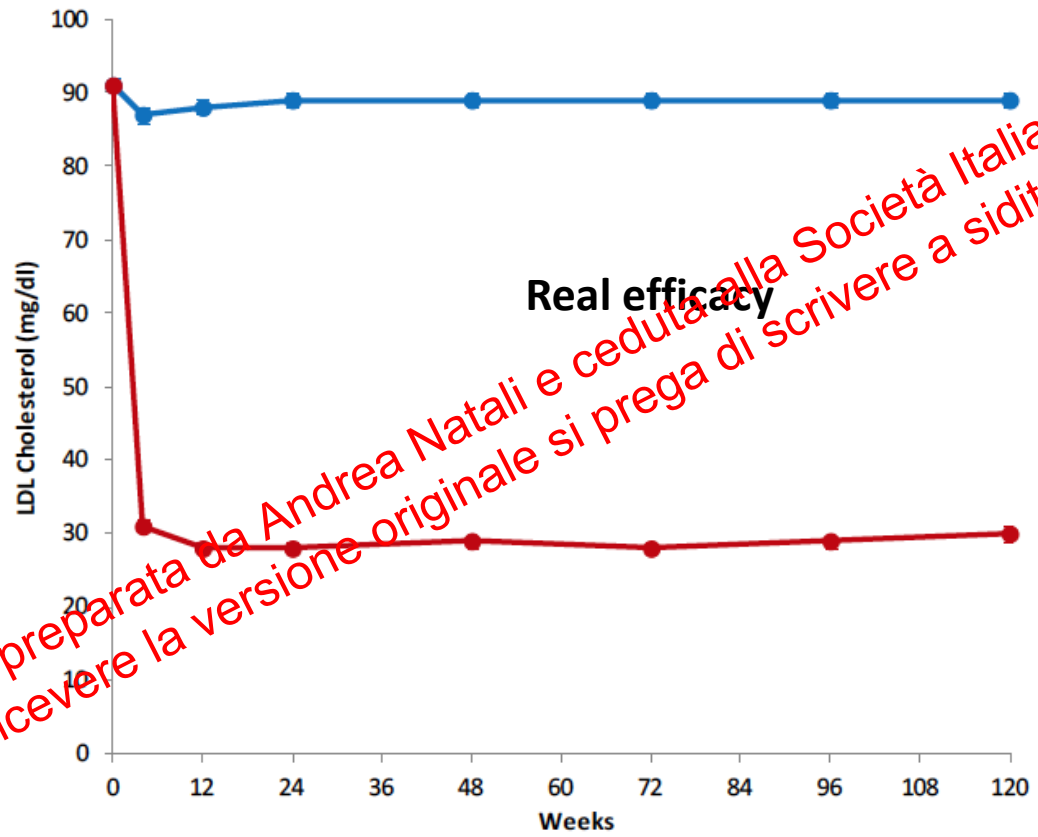
The level of C-reactive protein was 1.7 mg/L (IQR 0.9-3.6) at baseline and by 48 weeks was 1.4 mg/L (IQR 0.7-3.1) in both arms.

hsCRP

Patients disposal



Supplementary Figure S2 – LDL cholesterol values over time

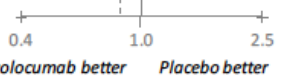


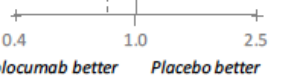
Data are in a fixed cohort of 11,077 patients who had all measurements through 120 weeks, did not discontinue study drug, and did not change concomitant background lipid lowering therapy. Shown are median values with 95% confidence intervals in the two arms. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Sottogruppi

Supplementary Figure S5 – Efficacy in Key Subgroups

Subgroup	Patients	3-yr KM rate (%) Primary Endpoint EvoMab	Pbo	Hazard Ratio (95% CI)	HR (95% CI)	$P_{interaction}$	3-yr KM rate (%) Key Secondary Endpoint EvoMab	Pbo	Hazard Ratio (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6		0.85 (0.79-0.92)		7.9	9.9		0.80 (0.73-0.88)	
Age						0.90					0.79
<65	15310	12.6	14.6		0.86 (0.78-0.94)		7.3	9.1		0.79 (0.69-0.90)	
≥65	12254	12.6	14.6		0.85 (0.76-0.95)		8.7	10.9		0.81 (0.71-0.92)	
Sex						0.48					0.44
Female	6769	9.9	12.5		0.81 (0.69-0.95)		6.5	9.2		0.74 (0.61-0.90)	
Male	20795	13.5	15.3		0.86 (0.80-0.94)		8.4	10.2		0.81 (0.73-0.90)	
Race						0.04					0.048
Caucasian	23458	12.7	14.4		0.88 (0.81-0.95)		7.8	9.6		0.83 (0.75-0.92)	
Non-Caucasian	4106	12.5	16.2		0.70 (0.57-0.86)		9.0	12.4		0.64 (0.50-0.81)	
Region						0.1					0.012
North America	4571	15.7	20.8		0.77 (0.66-0.90)		8.6	13.5		0.62 (0.51-0.76)	
Europe	17335	11.9	13.1		0.91 (0.83-1.00)		7.6	8.9		0.90 (0.80-1.01)	
Latin America	1823	14.9	14.3		0.86 (0.63-1.15)		11.3	10.8		0.85 (0.58-1.24)	
Asia/Pacific	3835	14.1	13.5		0.73 (0.58-0.91)		9.2	10.1		0.67 (0.51-0.88)	
Type of disease						0.19					0.38
MI alone	19113	11.7	13.5		0.88 (0.80-0.96)		6.5	8.7		0.80 (0.71-0.90)	
Stroke alone	3366	9.2	11.7		0.70 (0.54-0.90)		8.0	9.6		0.77 (0.58-1.02)	
PAD alone	1501	9.4	12.6		0.67 (0.47-0.96)		5.5	10.3		0.57 (0.38-0.88)	
Polyvascular disease	3563	21.5	21.5		0.88 (0.75-1.03)		16.0	16.7		0.86 (0.71-1.04)	
Baseline LDL-C						0.69					0.96
Q1 (<80 mg/dL)	6961	11.0	13.6		0.80 (0.69-0.93)		7.4	8.8		0.78 (0.64-0.95)	
Q2 (80-92 mg/dL)	6886	11.4	14.4		0.82 (0.71-0.96)		6.8	9.3		0.79 (0.65-0.96)	
Q3 (93-109 mg/dL)	6887	13.6	14.3		0.89 (0.77-1.03)		8.7	10.3		0.79 (0.66-0.94)	
Q4 (>109 mg/dL)	6829	14.2	16.2		0.89 (0.77-1.02)		8.7	11.3		0.83 (0.70-0.99)	
Baseline statin intensity						0.37					0.33
High	19103	12.7	14.7		0.87 (0.80-0.95)		8.0	9.8		0.82 (0.74-0.92)	
Not High	8461	12.9	14.8		0.80 (0.70-0.92)		8.0	10.6		0.74 (0.63-0.88)	
Ezetimibe						0.26					0.76
Yes	1440	16.1	17.0		0.98 (0.74-1.31)		9.4	13.0		0.74 (0.52-1.06)	
No	26124	12.4	14.5		0.84 (0.78-0.91)		7.8	9.7		0.80 (0.73-0.88)	
Initial Dosing Regimen						0.83					0.89
Every 2 weeks	24774	12.7	14.6		0.85 (0.79-0.92)		8.0	10.0		0.80 (0.72-0.88)	
Monthly	2790	10.3	15.6		0.82 (0.64-1.04)		5.8	10.9		0.80 (0.59-1.09)	





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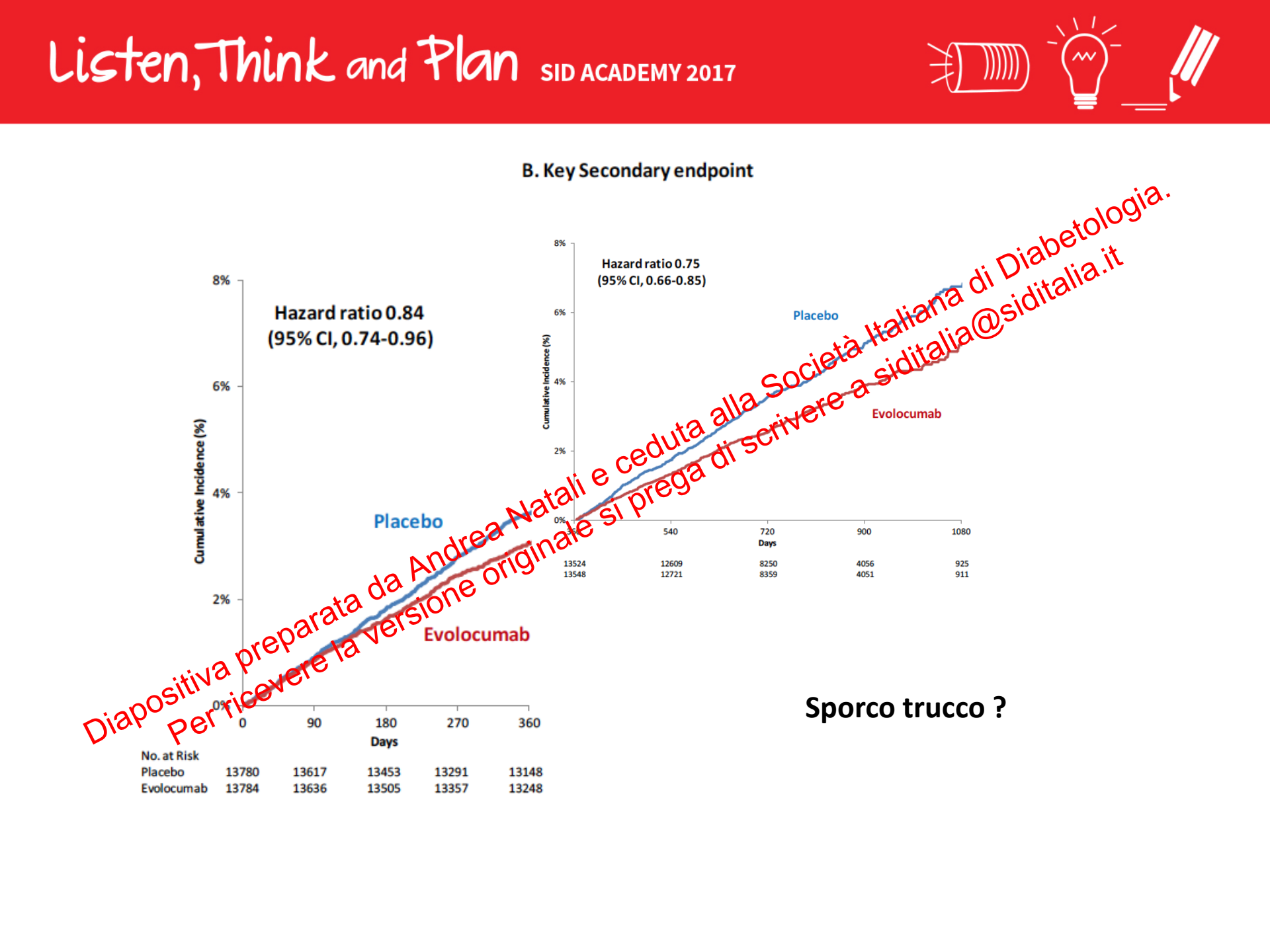

Diapositiva preparata da Andrea Natali e ceduta alla Società Italiana di Diabetologia.
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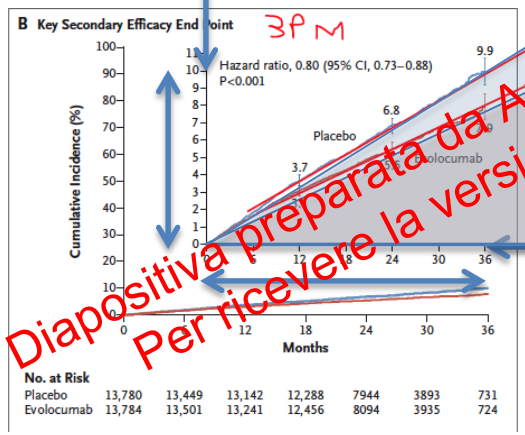
Sporco trucco ?



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9
12

Years "lost" per 100 pts in 12 years

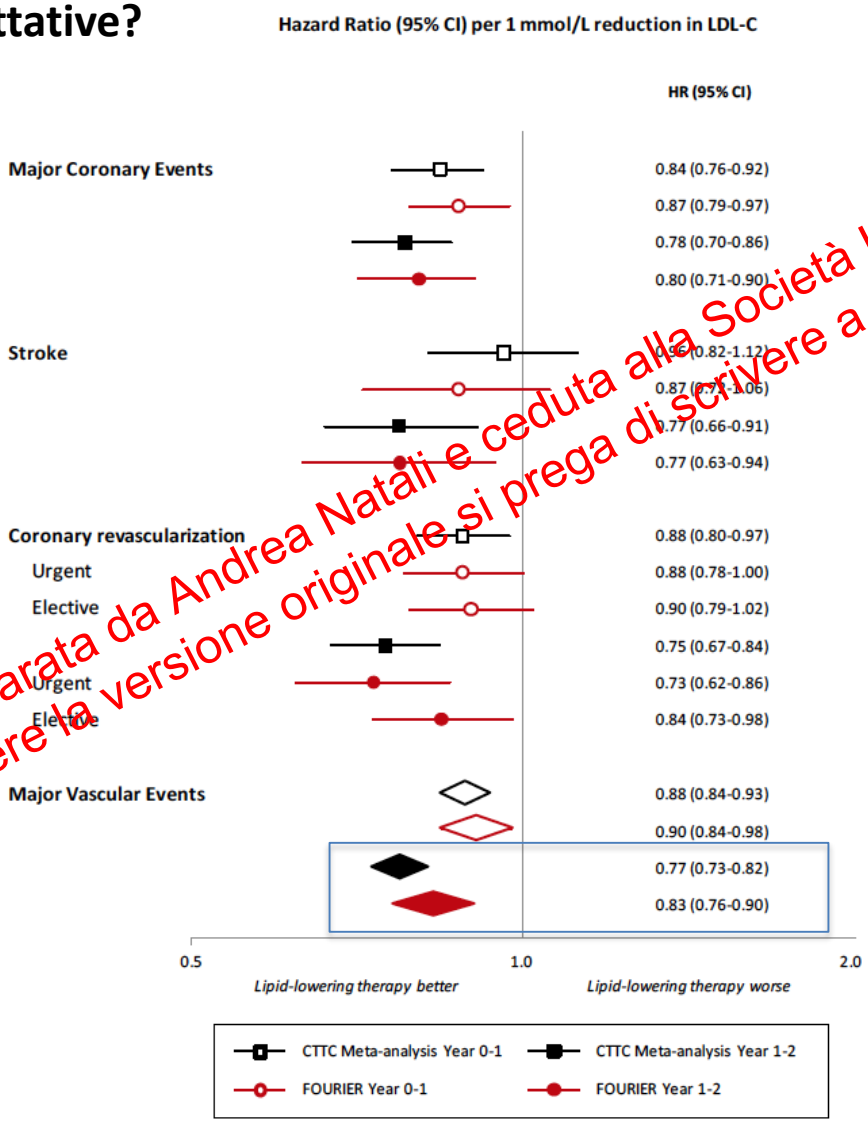
30*12/2= 180
40*12/2= 240

240-180= 60
60/30= 2.0

400E*100pts*12m*12y = 5.760M

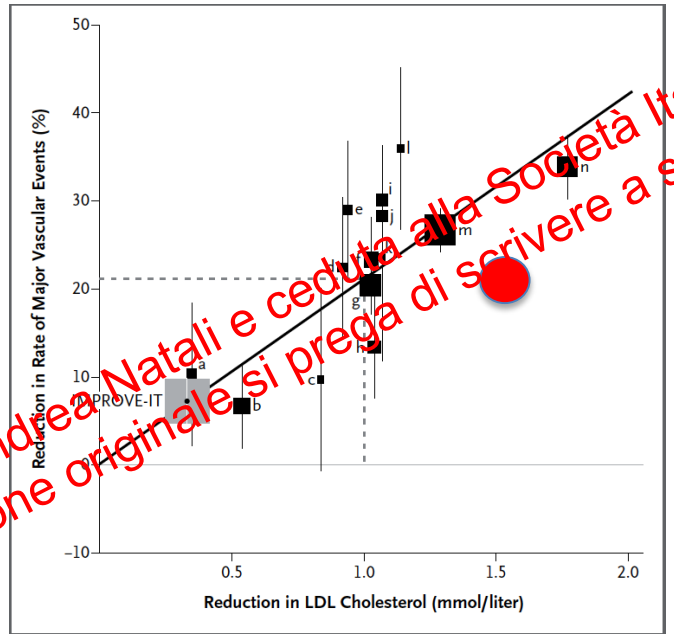
5.760M/60= 96.000 E/y

Ha atteso le aspettative?



?

38/22 = 0.57 %/mg



60/20 = 0.33 %/mg

0.33/0.57 = 0.57

a: (GISSI Prevenzione)
b: (ALLHAT-LLT);
c: (ALERT)
d: (LIPS)
e: (AFCAPS/TexCAPS)
f: (CARE)
g: (LIPID)
H: (PROSPER)
i: (ASCOT-LLA)
J: (WOSCOPS)
k: (Post CABG)
L: (CARDS)38
m: (HPS)
n:(4S)

Lettura critica di un articolo scientifico

1) Chi lo ha scritto?
2) Abstract Razionale
   Conclusioni
   Metodi
   Risultati

3) Caratteristiche della Popolazione
4) Effetto dell'intervento sui parametri rilevanti
4) Effetto dell'intervento sugli outcomes
5) Discussione
6) Appendice