

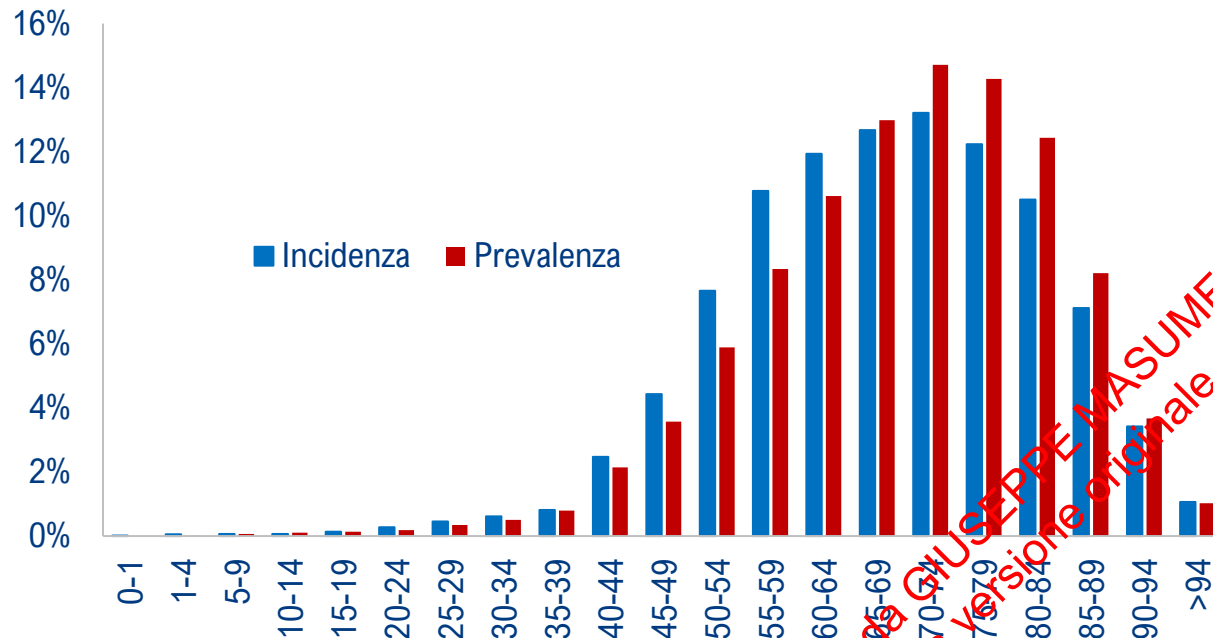


Il rischio cardiorenale ed aterosclerosi: un legame da non dimenticare

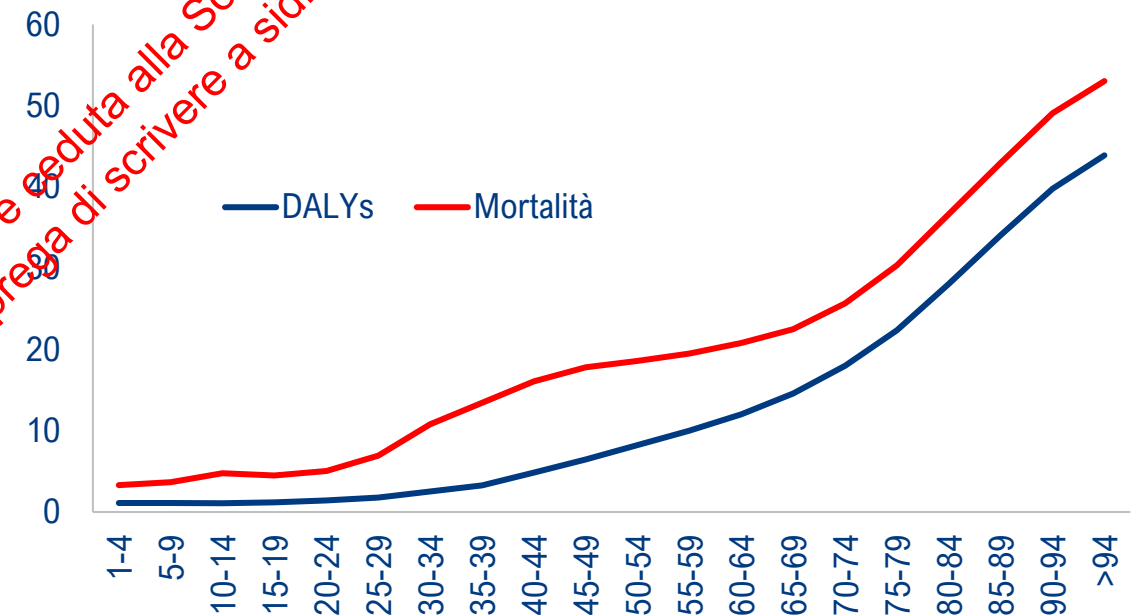
Giuseppe Musumeci
SC Cardiologia
AO Ordine Mauriziano, Torino

La malattie cardiovascolari e cerebrovascolari sono la prima cause di morbosità, invalidità e mortalità

Distribuzione della prevalenza e incidenza delle malattie cardio-cerebrovascolari in Italia per fasce d'età (%), 2019



Mortalità e DALY delle malattie cardio-cerebrovascolari in Italia per fasce d'età (% sul totale di decessi e DALY), 2019



In Italia le **malattie cardiovascolari e cerebrovascolari** rappresentano la **1° causa di mortalità** e la **2° causa di DALY**; rappresentano anche la **1° causa di ricovero ospedaliero**

Fattori di rischio modificabili e rischio residuo CV

Fattori di rischio modificabili^{1,2}

- Diabete
- Ipertensione
- Dislipidemia
- Obesità
- Fumo di sigarette
- Inattività fisica



Fattori di rischio non modificabili^{1,2}

- Età
- Genere
- Fattori genetici
- Etnia



↑ Pressione arteriosa

↑ Glicemia

↑ Insulina resistenza

↑ lipid plasmatici

↑ Infiammazione*



Aterosclerosi

- Disfunzione endoteliale
- Espressione molecole adesione
- Formazione delle cellule schiumose
- Proliferaione cellule muscolari lisce



Trombosi

- Vasi meno elastici
- Rottura della placca



IMA, Ictus e PAD

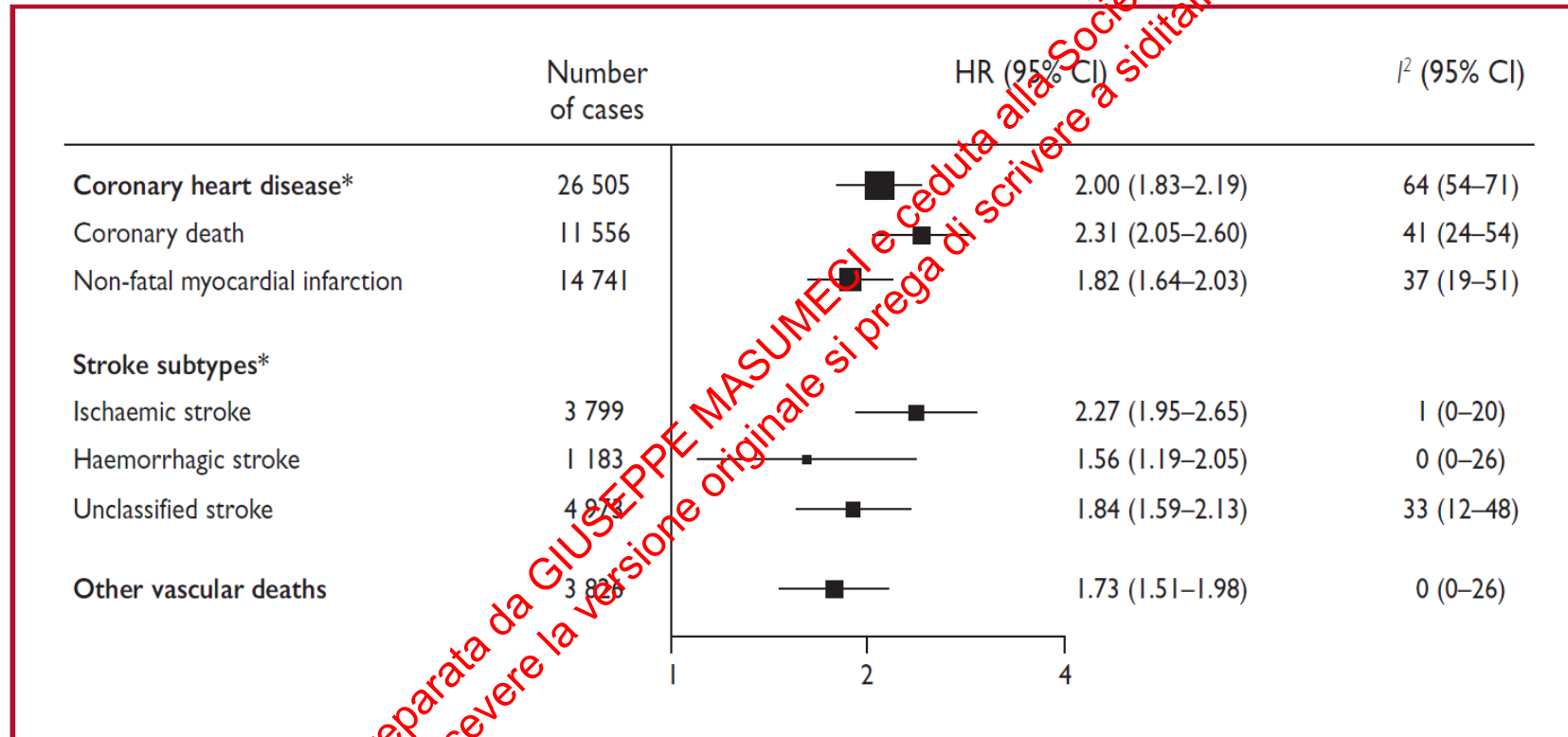


*Increased CRP, IL-6, TNF α , and free fatty acids.

BMI, body mass index; CRP, C-reactive protein; CV, cardiovascular; IL-6, interleukin-6; MI, myocardial infarction; PAD, peripheral arterial disease; TNF α , tumour necrosis factor alpha.

Il diabete mellito aumenta significativamente il rischio di eventi cardiovascolari avversi

Meta-analisi di 102 trials che hanno valutato il rischio CV legato al diabete



Le malattie cardiovascolari rappresentano la principale causa di mortalità e morbidità nelle persone con diabete

Il rischio di morte per cause cardiovascolari aumenta di

2

volte*

Il rischio di infarto e di ictus aumenta di

4

volte*

50-60%

di decessi a causa di malattie cardiovascolari

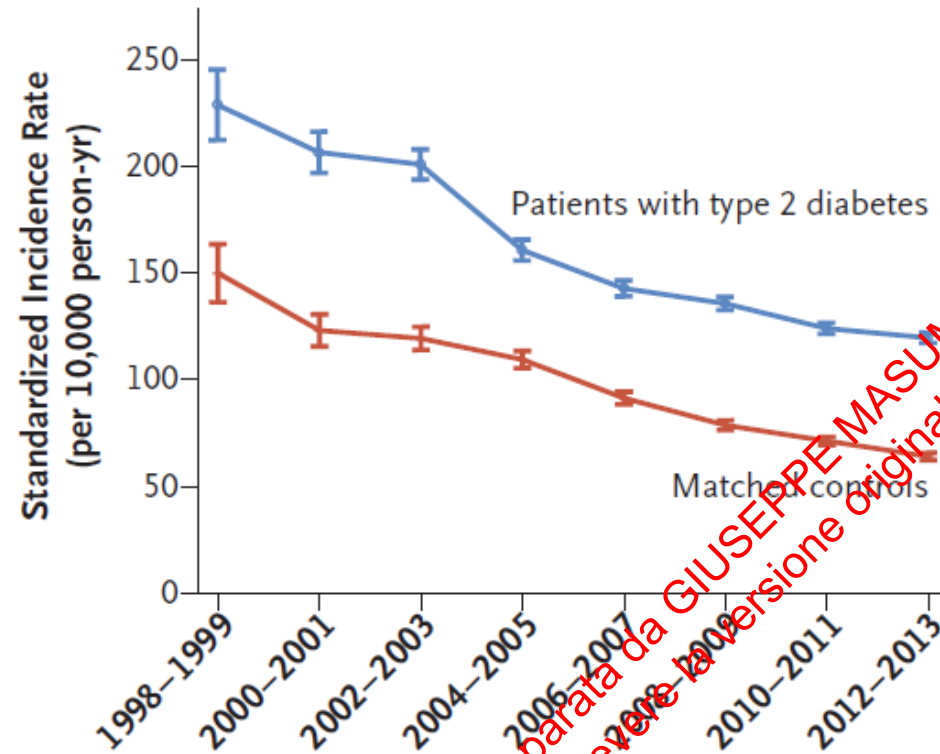
*rispetto alla popolazione non diabetica

1. Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiology, assessment and prevention. *Nat Rev Cardiol*. 2023 Oct;20(10):685-695. <https://doi.org/10.1038/s41569-023-00877-z>
2. Warraich HJ, Rana JS. Diabetic Dyslipidemia: Epidemiology and Prevention of Cardiovascular Disease and Implications of Newer Therapies. *Curr Cardiol Rep*. 2018 Oct 11;20(12):125. <https://doi.org/10.1007/s11886-018-1068-6>
3. Avogaro A. La malattia cardiovascolare nel paziente diabetico: i fattori di rischio, storia clinica e prevenzione [Cardiovascular disease in diabetic patients: risk factors, clinical history and prevention]. *G Ital Cardiol (Rome)*. 2016 Dec;17(12 Suppl 2):3S-12. Italian. <https://doi.org/10.1714/2616.26910>
4. Riccardo Candido, Alberto Agliano, Riccardo, Fornengo, Domenico Mannino. DIABETE E MALATTIA CARDIOVASCOLARE: NUOVE EVIDENZE?. *J AMD*, 21 (4), 2018. [Clicca QUI](#)
5. Diabete, obesità e malattia cardiovascolare. Lo scenario italiano. Benefici cardiovascolari derivanti dei recenti trials. [Clicca QUI](#)

Morte cardiovascolare nei soggetti con diabete mellito

Nonostante un trend in significativa riduzione, le persone con diabete mantengono un rischio di morte cardiovascolare superiore alla popolazione generale senza diabete

B Death from Cardiovascular Disease



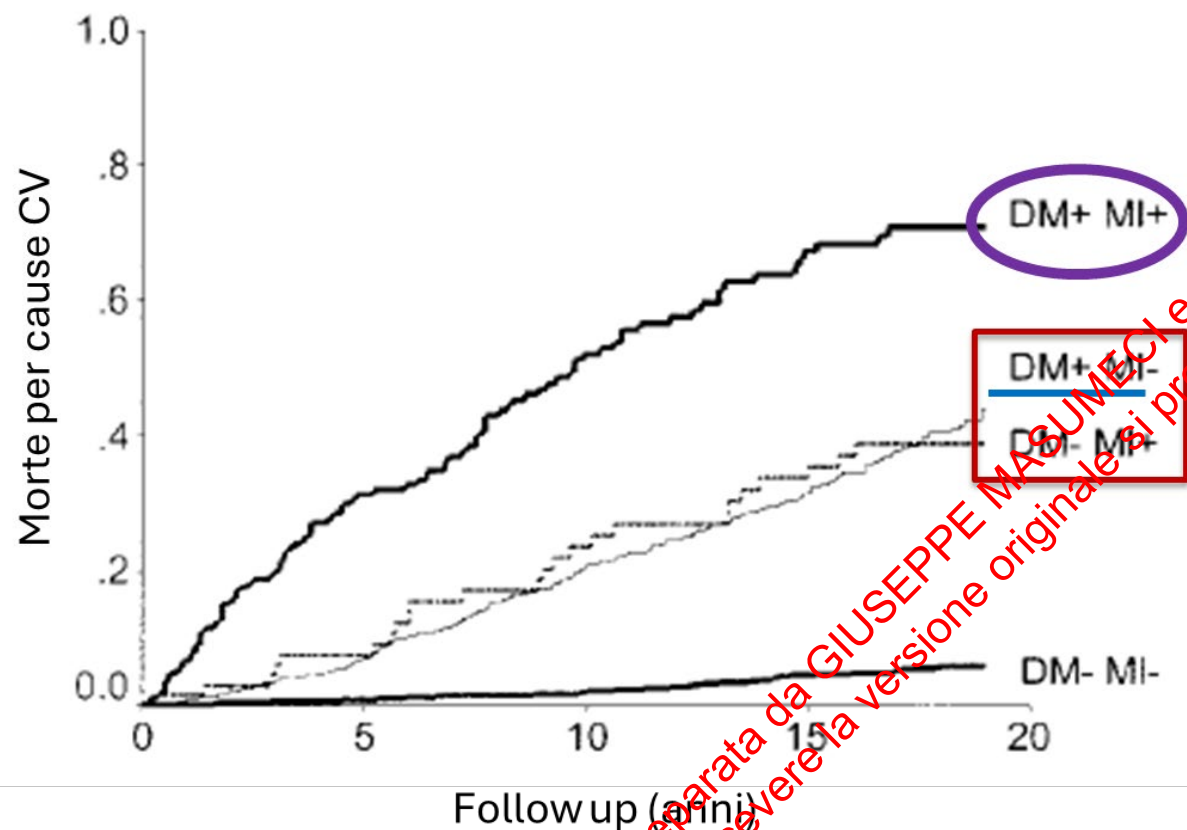
Swedish National Diabetes Registry
1998-2012

↑ 2 x mortalità CV rispetto ai
loro pari senza diabete

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a sliditalia@siditalia.it

Il diabete mellito tipo 2 è un equivalente di malattia coronarica

(Studio prospettico di popolazione in Finlandia, durata 18 anni)



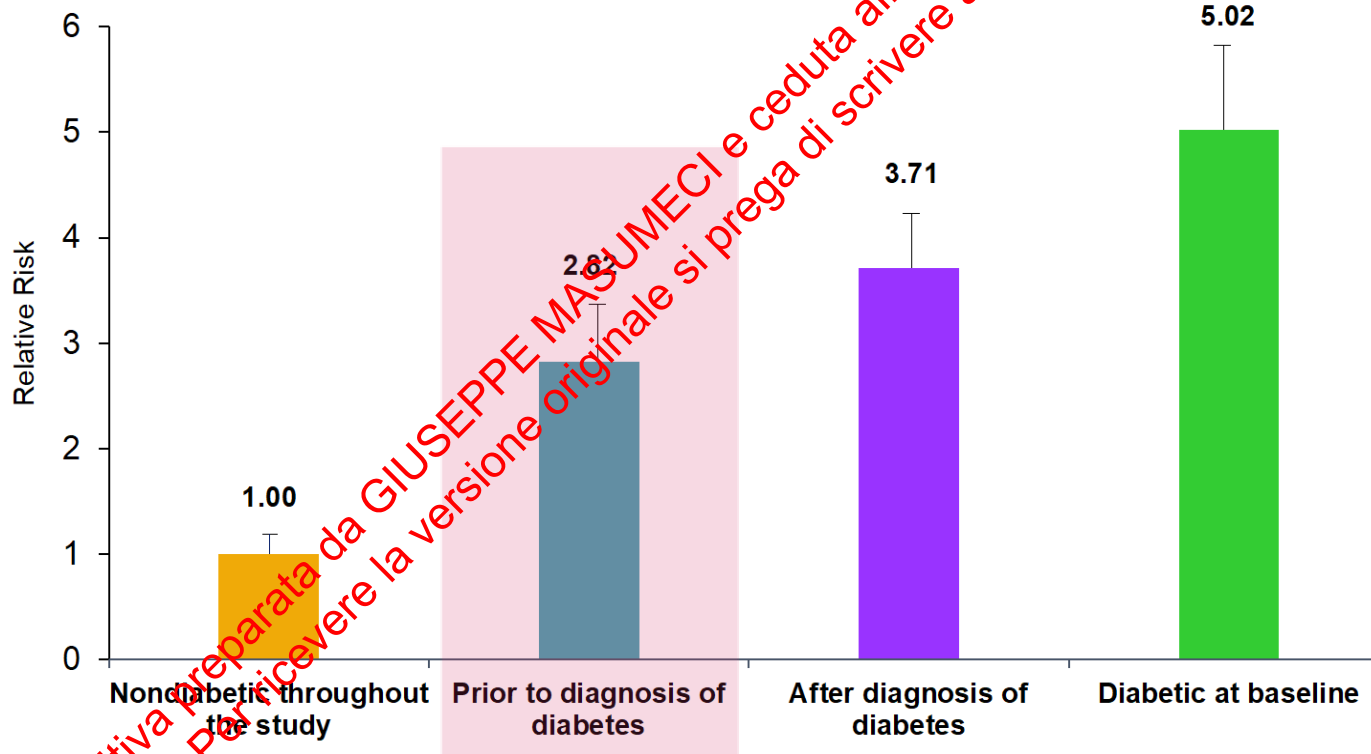
CALL TO ACTION:

- Abbiamo bisogno di più della sola gestione della glicemia
- Dobbiamo agire subito, prima del primo evento CV

Il rischio CV aumenta anche prima della diagnosi clinica di diabete

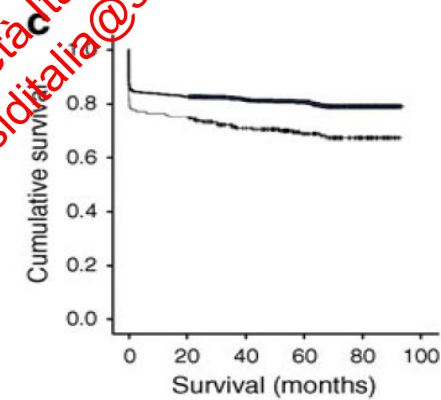
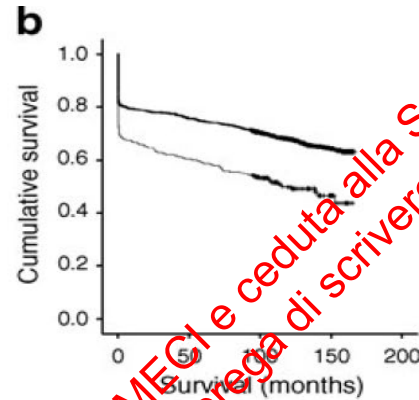
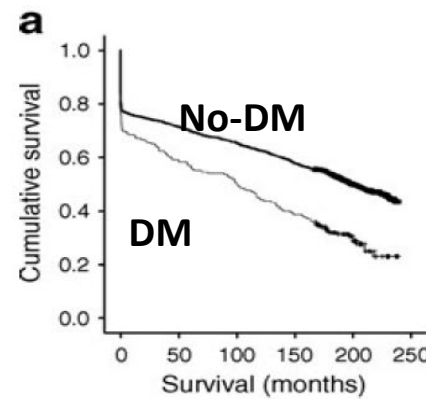
- 117629 infermiere senza malattia CV al basale osservate per 20 anni;
- 1508 avevano diabete al basale

Rischio relativo di end point composito di infarto del miocardio e ictus

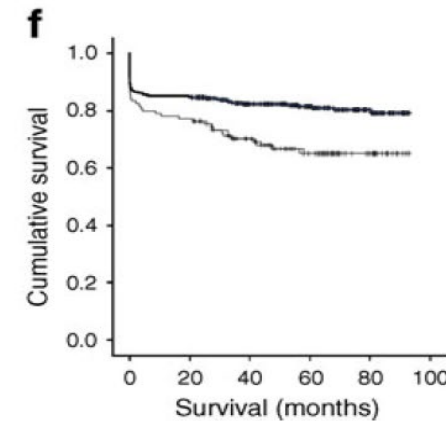
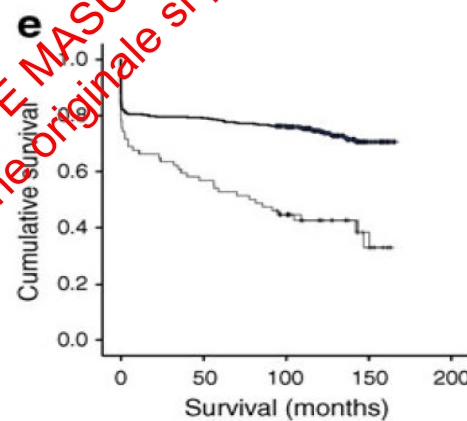
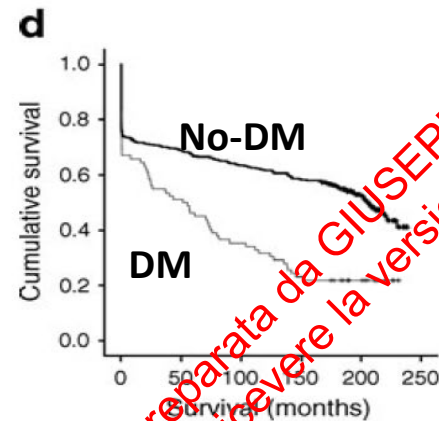


Dopo un primo infarto miocardico il paziente con diabete sopravvive meno rispetto ad un paziente senza diabete

Men



Women



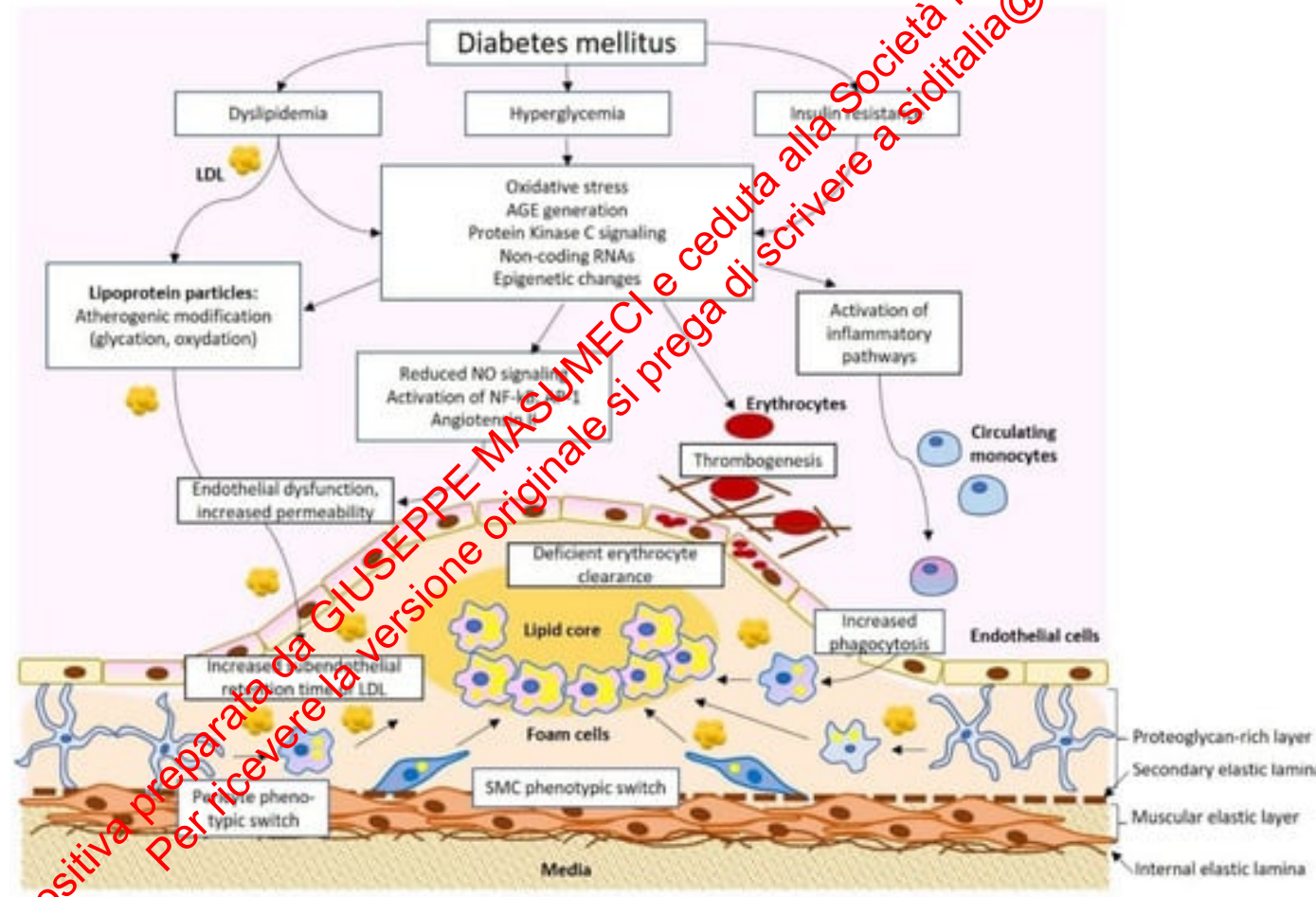
1989–1994

1995–2000

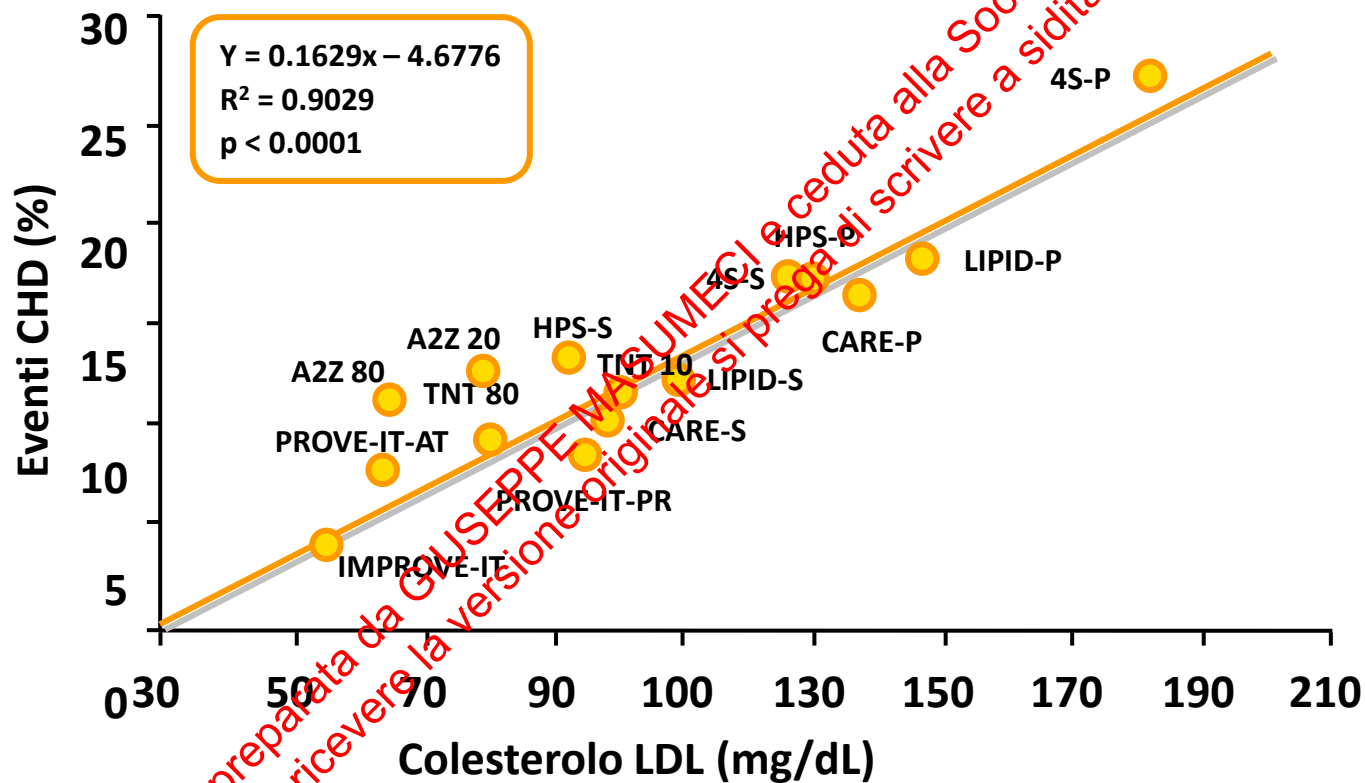
2001–2006

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Iperglicemia e ipercolesterolemia contribuiscono allo sviluppo e alla progressione della malattia cardiovascolare su base ateromastica



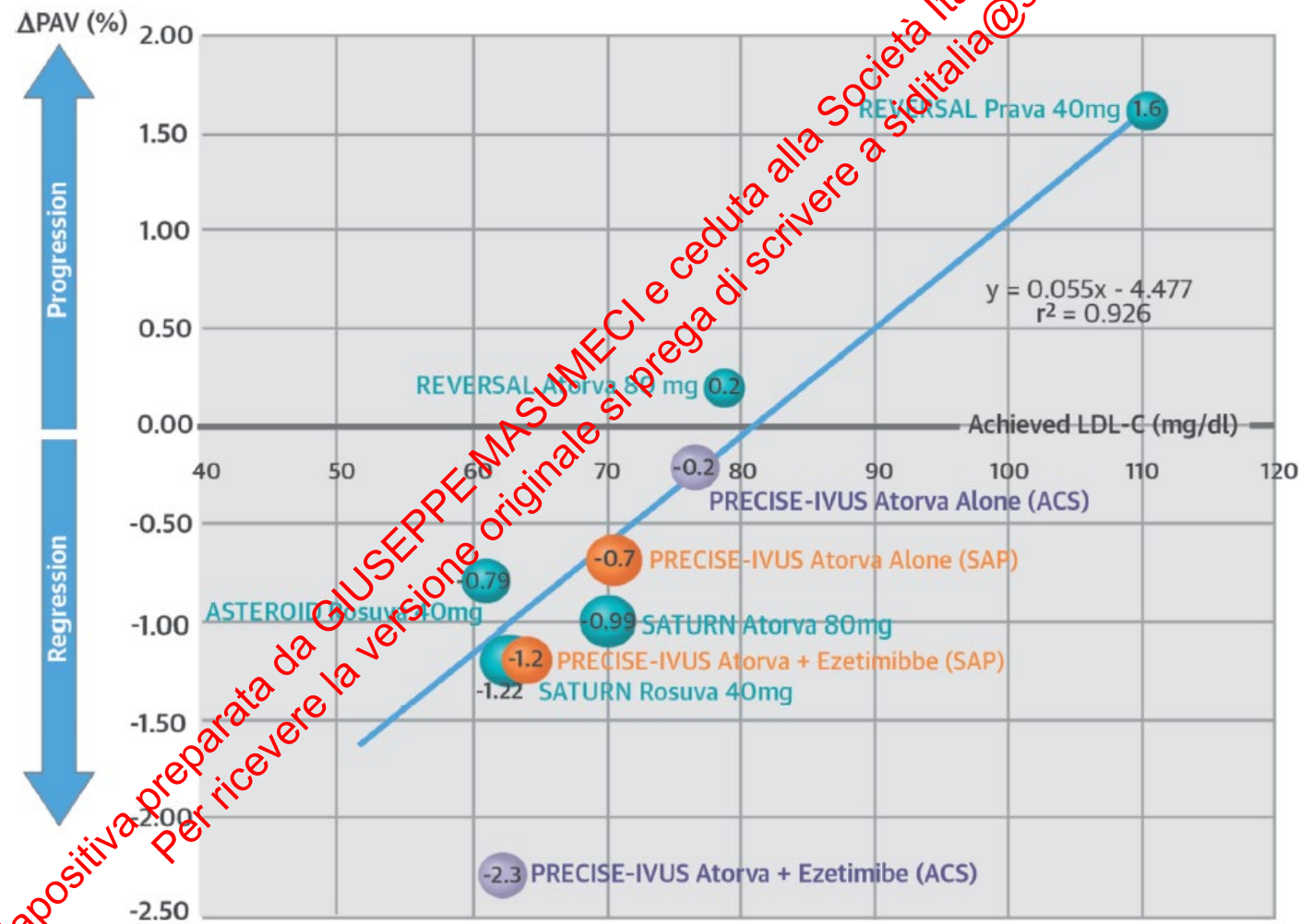
Studi con statine in prevenzione secondaria: riduzione eventi e C-LDL “on trial”



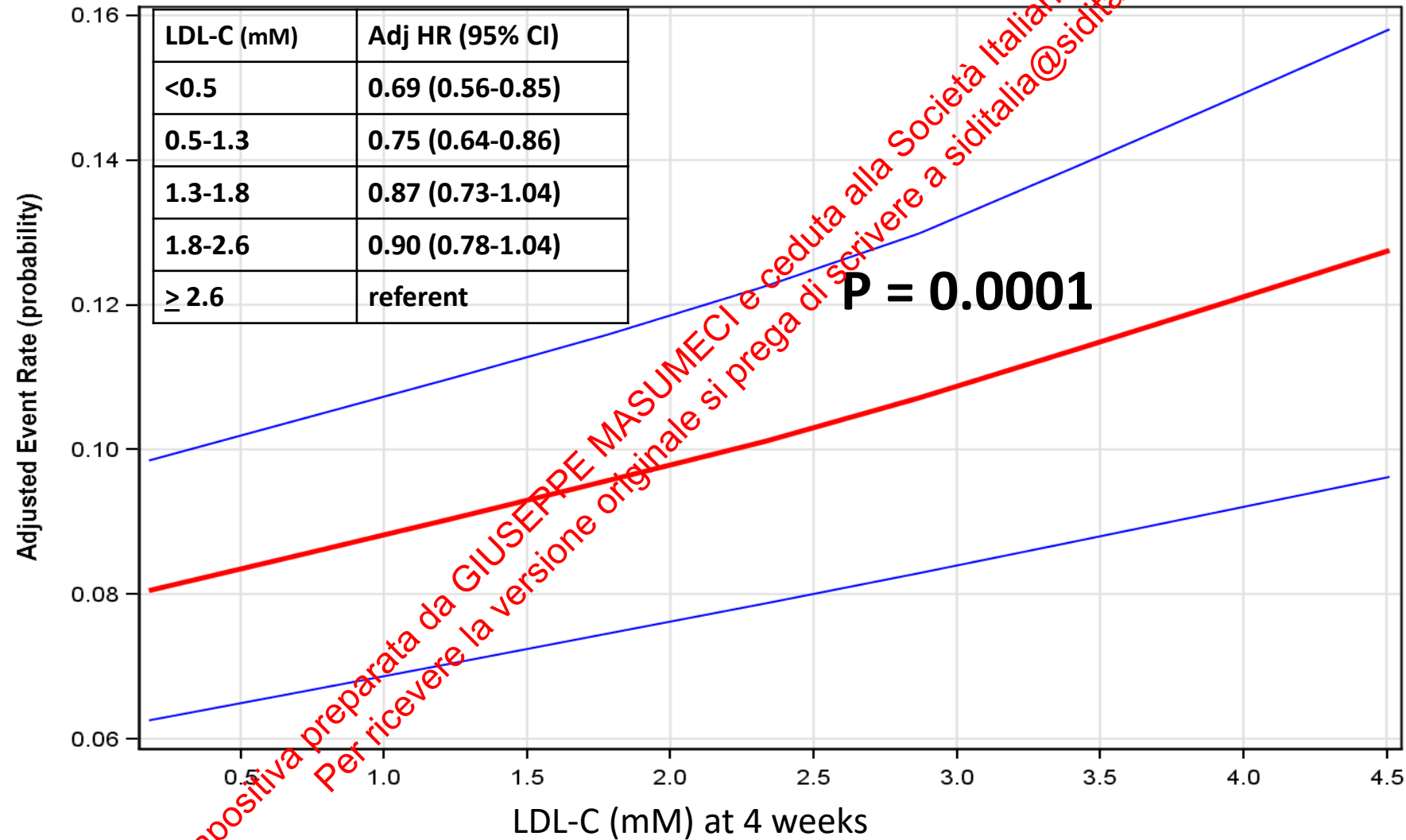
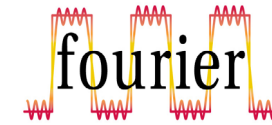
O'Keefe et al, JACC, 2004.

Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention

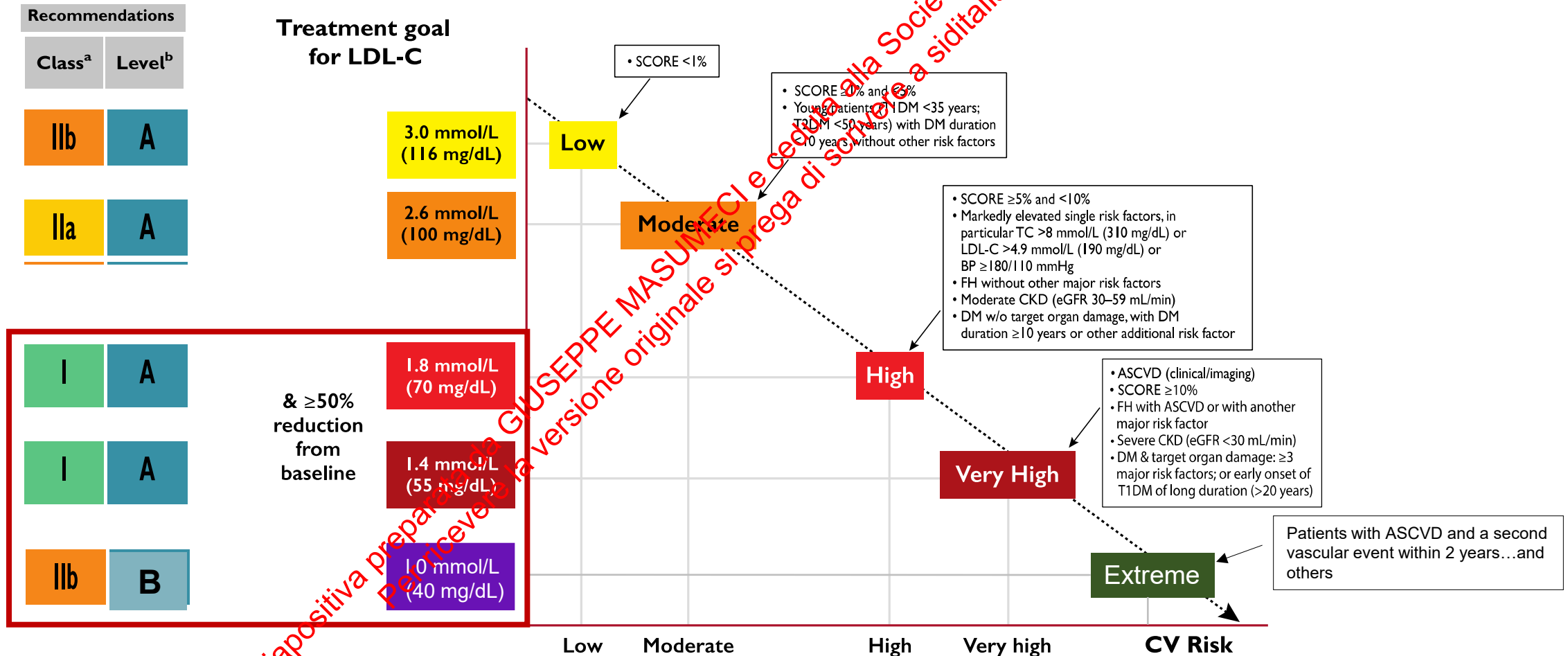
The Multicenter Randomized Controlled PRECISE-IVUS Trial



FOURIER: CV Death, MI, or Stroke



Le Linee Guida ESC/EAS 2019 per la gestione delle dislipidemie hanno stratificato i pazienti in **5 categorie di rischio** definendo target di C-LDL per ciascuna categoria di rischio



L'intensificazione precoce della terapia ipolipemizzante può arrestare la progressione della placca e ridurre l'insorgenza di eventi cardiovascolari

**Rischio
cardiovascolare**

C-LDL

basso

moderato

alto

molto alto

estremo*

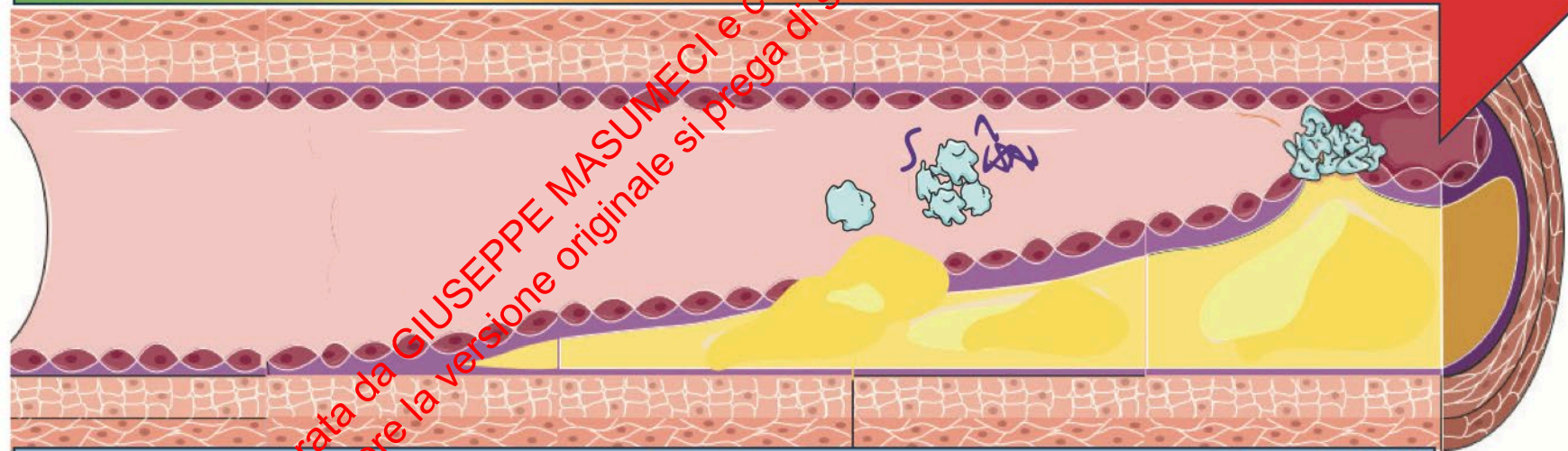
116 mg/dl

100 mg/dl

70 mg/dl

55 mg/dl

40 mg/dl



Statina

Fino a 50%

+ Ezetimibe/Acido bempedoico

Fino a 75%

+ PCSK9 inibitori

Fino a 85%

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

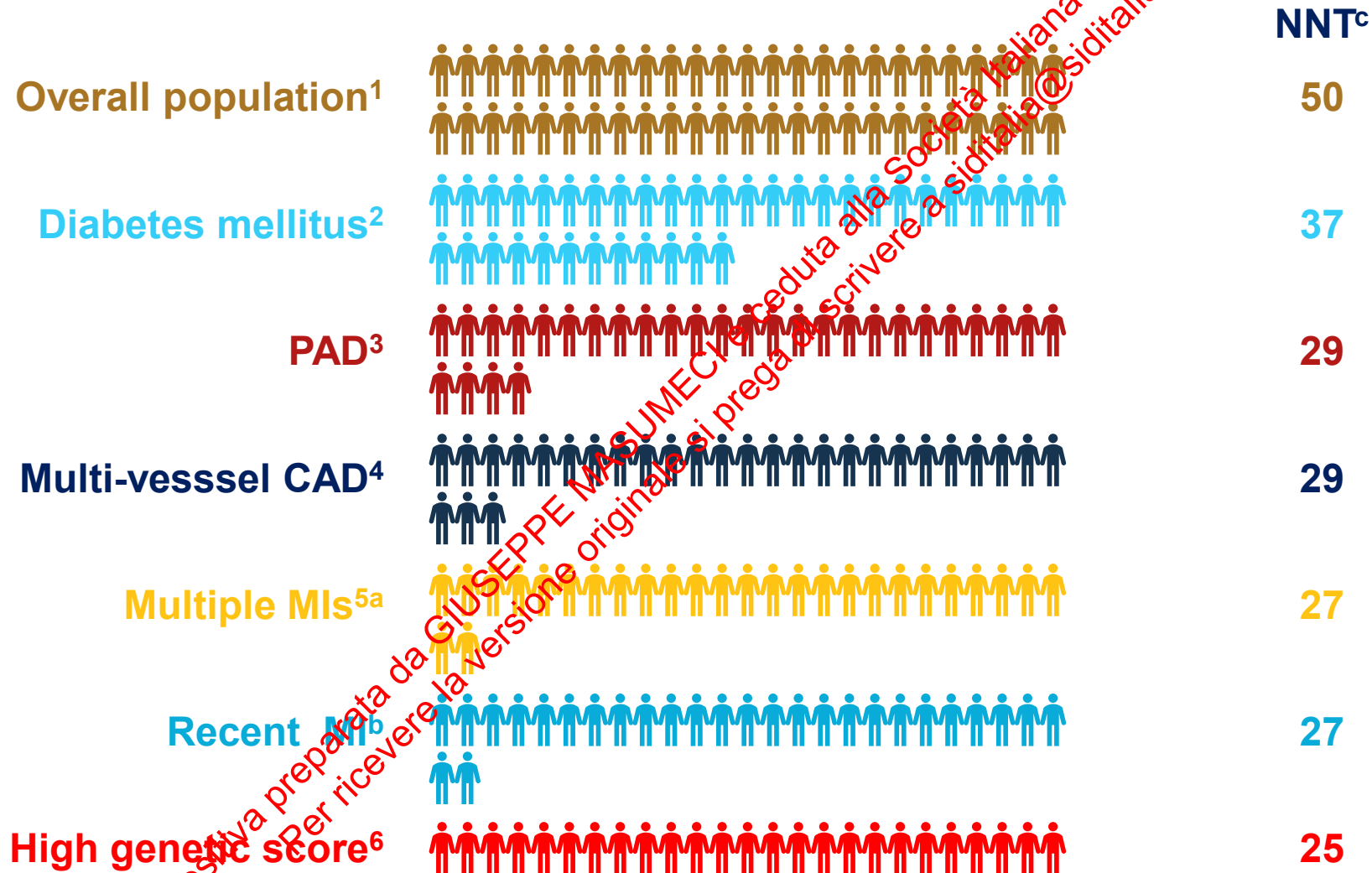


A. O. ORDINE
MAURIZIANO
TORINO



- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL ≥ 70 mg/dl
Aggiunge I-PCSK9 alla dimissione
- Paziente con SCA in terapia con Statine ed LDL ≥ 70 mg/dl
Aggiunge Ezetimibe, Acido Bempedoico ed I-PCSK9 alla dimissione
- Paziente con SCA naive da Statine con LDL ≥ 55 mg/dl ed < 140 mg/dl
Aggiunge combinazione Statine ed Ezetimibe ed Acido Bempedoico alla dimissione e controllo a un mese per valutare I-PCSK9
- Paziente con SCA naive da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV
Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

FOURIER trial: NNT for the primary endpoint with evolocumab vs placebo in high-risk settings at 3 years

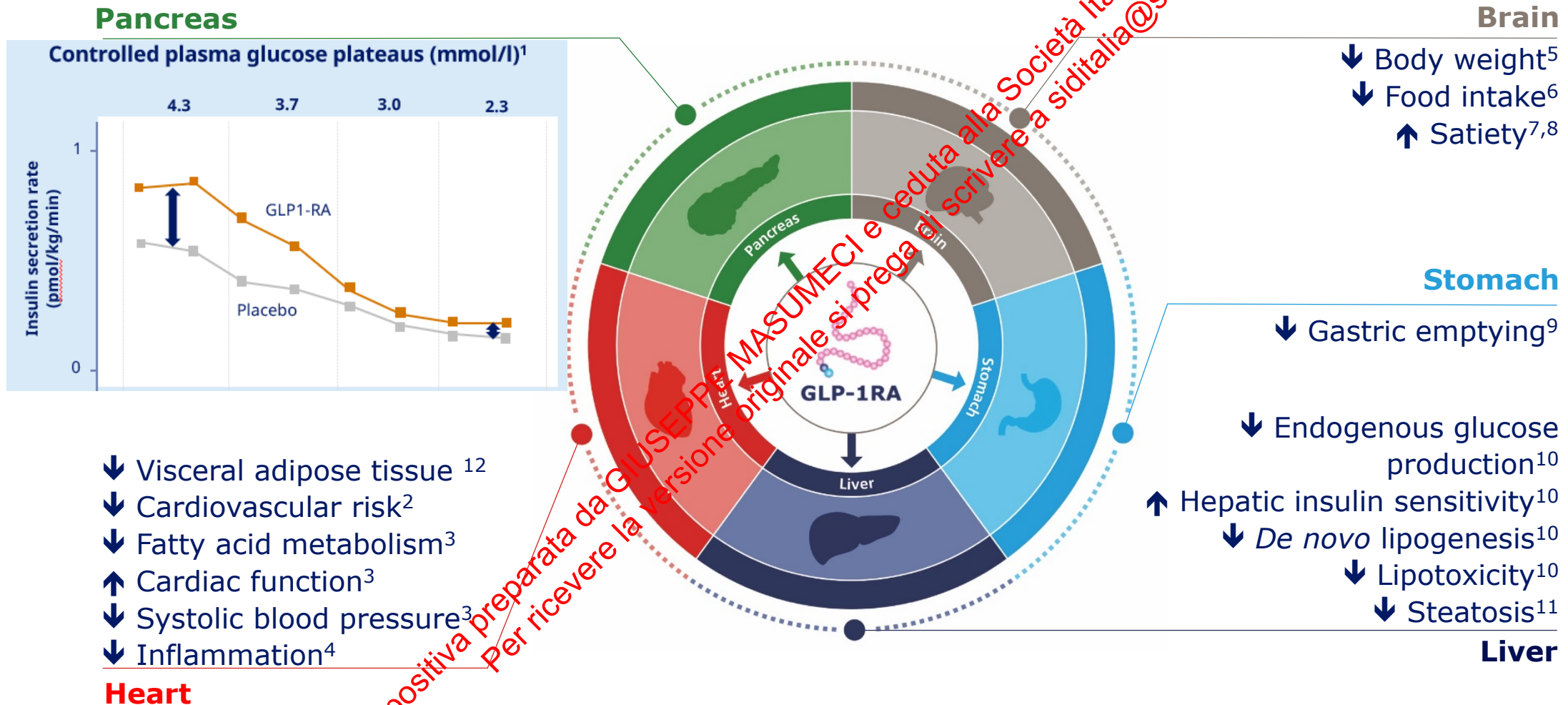


^a ≥2 prior MIs; ^b Within 2 years of most recent MI; ^c NNT = 1/ARR; CAD; coronary artery disease; MI; myocardial infarction; NNT, number needed to treat; PAD, peripheral artery disease

1. Sabatine MS et al. NEJM 2017;376:1713-22; 2. Sabatine MS, et al. *Lancet Diabetes Endocrinol.* 2017;5:941-950; 3. Bonaca MP, et al. *Circulation.* 2018;137:338-350; 4. Sabatine MS, et al. *Circulation.* 2018;138:756-766; 5. Gencer B, et al. *JAMA Cardiol.* 2020;5:952-95; 6. Marston NA, et al. *Circulation.* 2020;141:616-623

GLP-1RAs cardiometabolic drugs with a safe profile

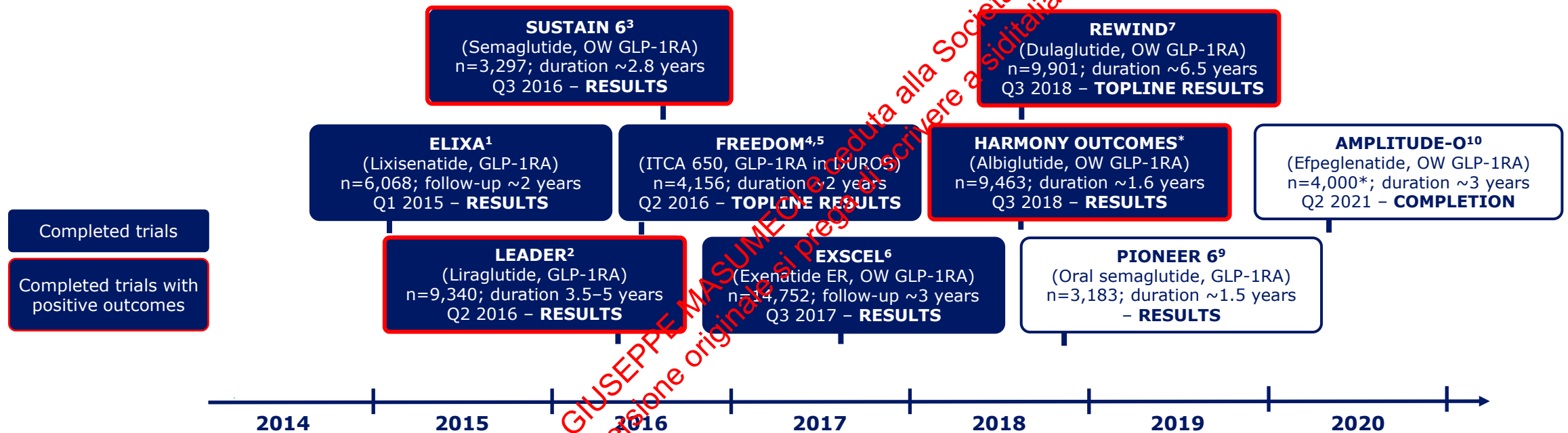
PHARMACOLOGICAL EFFECTS OF GLP-1RA



GLP-1RA, glucagon-like peptide-1 receptor agonist.

Adapted from Campbell JE, Drucker DJ. *Cell Metab* 2013;17:819–37 and Pratley RE, Gilbert M. *Rev Diabet Stud* 2008;5:73–94. A full reference list for this slide can be found in the slide notes.

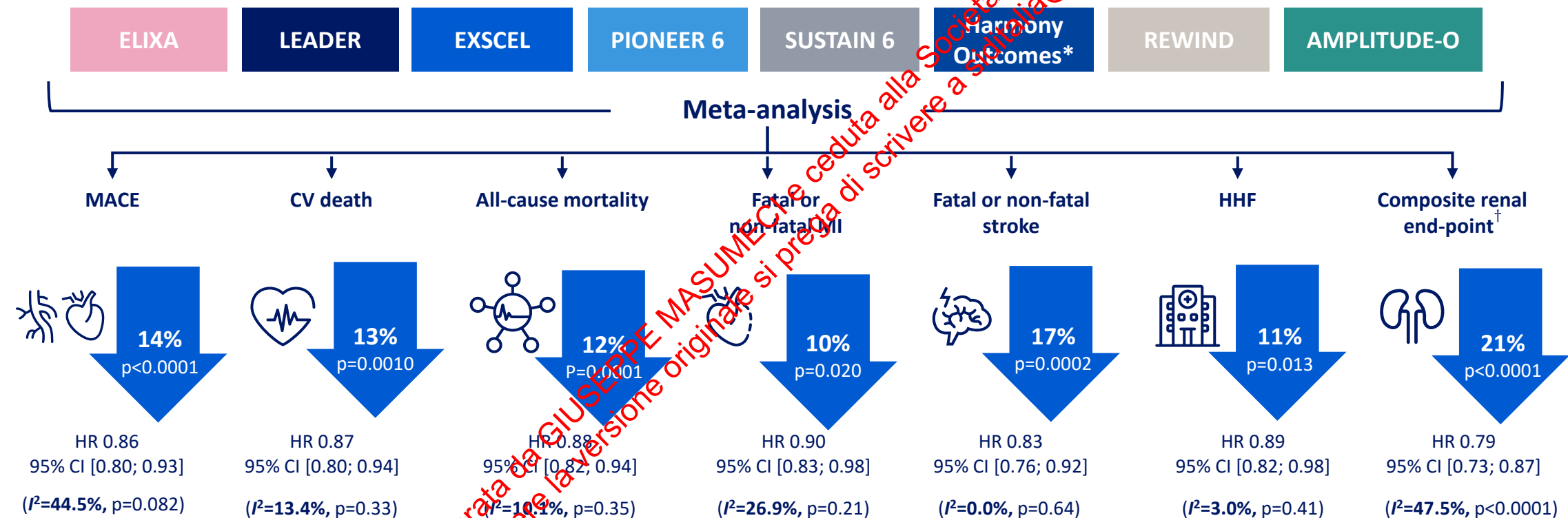
CVOTs investigating GLP-1RA therapies in T2D



Liraglutide, semaglutide e dulaglutide (albiglutide not available) have demonstrated CV risk reduction in high-risk T2D populations

1. Pfeffer MA et al. *N Engl J Med* 2015;373:2247–56. 2. Marso SP et al. *N Engl J Med* 2016;375:311–22; 3. Marso SP et al. *N Engl J Med* 2016;375:1834–44; 4. <https://www.intarcia.com/media/media-archive/press-releases/intarcia-announces-successful-cardiovascular-safety-results-in-p.htm>. Accessed March 2019; 5. <https://clinicaltrials.gov/ct2/show/NCT01455896>. Accessed March 2019; 6. Holman RR et al. *N Engl J Med* 2017;377:1228–39; 7. Gerstein HC et al. *Diabetes* 2018;20:42–9; 8. Hernandez AF et al. *Lancet* 2018;392:1519–29; 9. Bain SC et al. *Diabetes Obes Metab* 2019;21:499–508; 10. ClinicalTrials.gov. AMPLITUDE-O. Available at: <https://clinicaltrials.gov/ct2/show/NCT03496298>. Accessed March 2019.

Meta-analysis of GLP-1 RA CVOTs showed a significant reduction in all cardiovascular events measured



*Albiglutide was withdrawn from worldwide commercial market in July 2018.

[†]Composite renal endpoint including microalbuminuria.

CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1; receptor agonist;

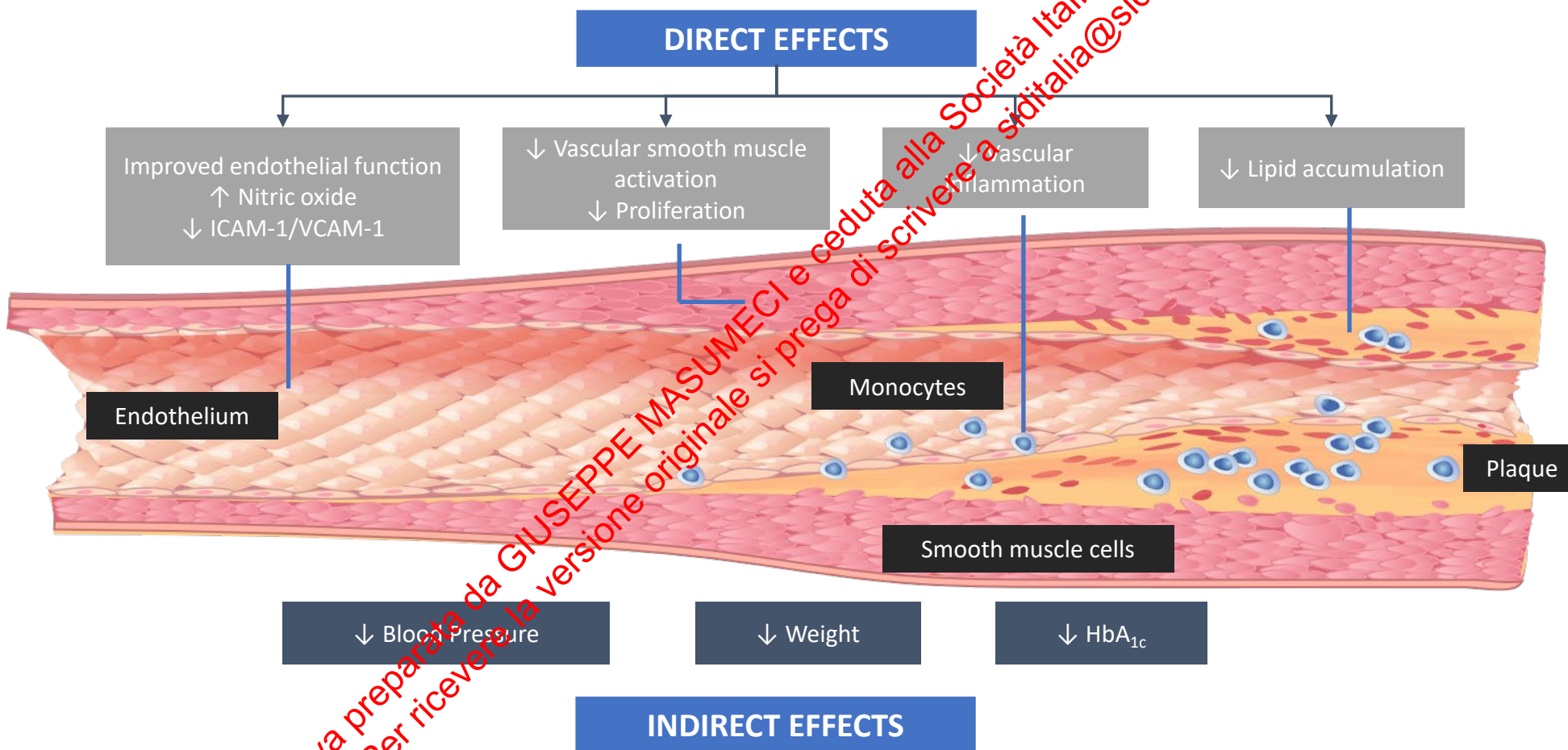
HHF, hospitalisations for heart failure; HR, hazard ratio; I^2 , heterogeneity; MACE, major adverse cardiovascular events; MI, myocardial infarction.

Sattar N et al. Lancet Diabetes Endocrinol 2021;9:653–62.

MORTALITA'

Comparison	Relative effect (odds ratio (95% CI))	Anticipated absolute effects over five years			Anticipated absolute effects (95% CI) over five years
		Baseline risk*	Risk with control	Risk with intervention	
GLP-1 receptor agonist v placebo	0.88 (0.83 to 0.94)	Very low	Placebo: 20 per 1000	GLP-1 receptor agonist: 18 per 1000	2 fewer per 1000 (from 1 fewer to 3 fewer)
			NNT 509		
		Low	Placebo: 70 per 1000	GLP-1 receptor agonist: 62 per 1000	8 fewer per 1000 (from 4 fewer to 11 fewer)
			NNT 133		
		Moderate	Placebo: 120 per 1000	GLP-1 receptor agonist: 107 per 1000	13 fewer per 1000 (from 6 fewer to 18 fewer)
			NNT 86		
		High	Placebo: 170 per 1000	GLP-1 receptor agonist: 153 per 1000	17 fewer per 1000 (from 9 fewer to 25 fewer)
			NNT 69		
		Very high	Placebo: 265 per 1000	GLP-1 receptor agonist: 241 per 1000	24 fewer per 1000 (from 12 fewer to 35 fewer)
			NNT 53		

Anti-atherosclerotic effects of GLP-1RAs





ESC

European Society
of Cardiology

European Heart Journal (2020) 41, 255–323

doi:10.1093/eurheartj/ehz486

ESC GUIDELINES



Table 7 Cardiovascular risk categories in patients with diabetes^a

Very high risk	Patients with DM and established CVD or other target organ damage ^b or three or more major risk factors ^c or early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

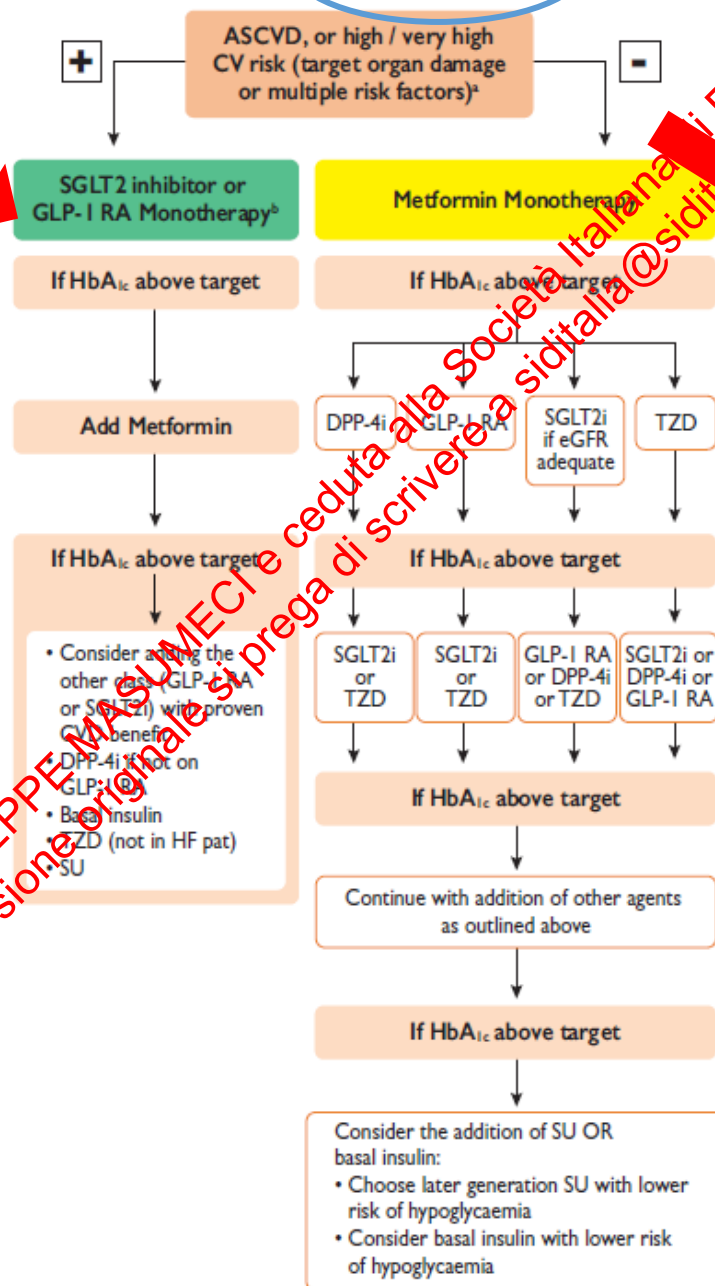
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

^aModified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.²⁷

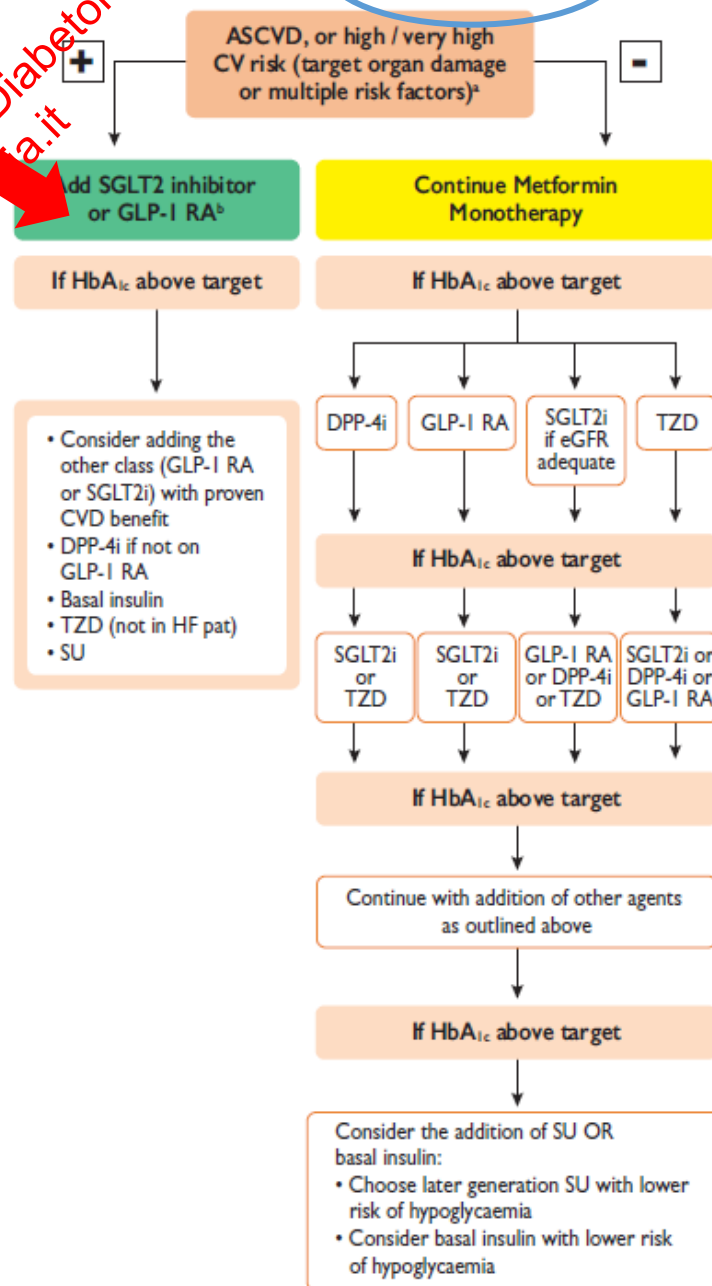
^bProteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.

^cAge, hypertension, dyslipidemia, smoking, obesity.

A Type 2 DM - Drug naïve patients



B Type 2 DM - On metformin



Diapositiva preparata da GIUSEPPE M. SU. MECI e ceduta alla Societa Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

New ESC Guidelines recommend the use of GLP-1RA to reduce CV events in patients with T2DM

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

GLP-1 RAs with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.

In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk $\geq 10\%$, treatment with an SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.

I	A
IIb	C

2024 ESC Guidelines for the management of chronic coronary syndromes

Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

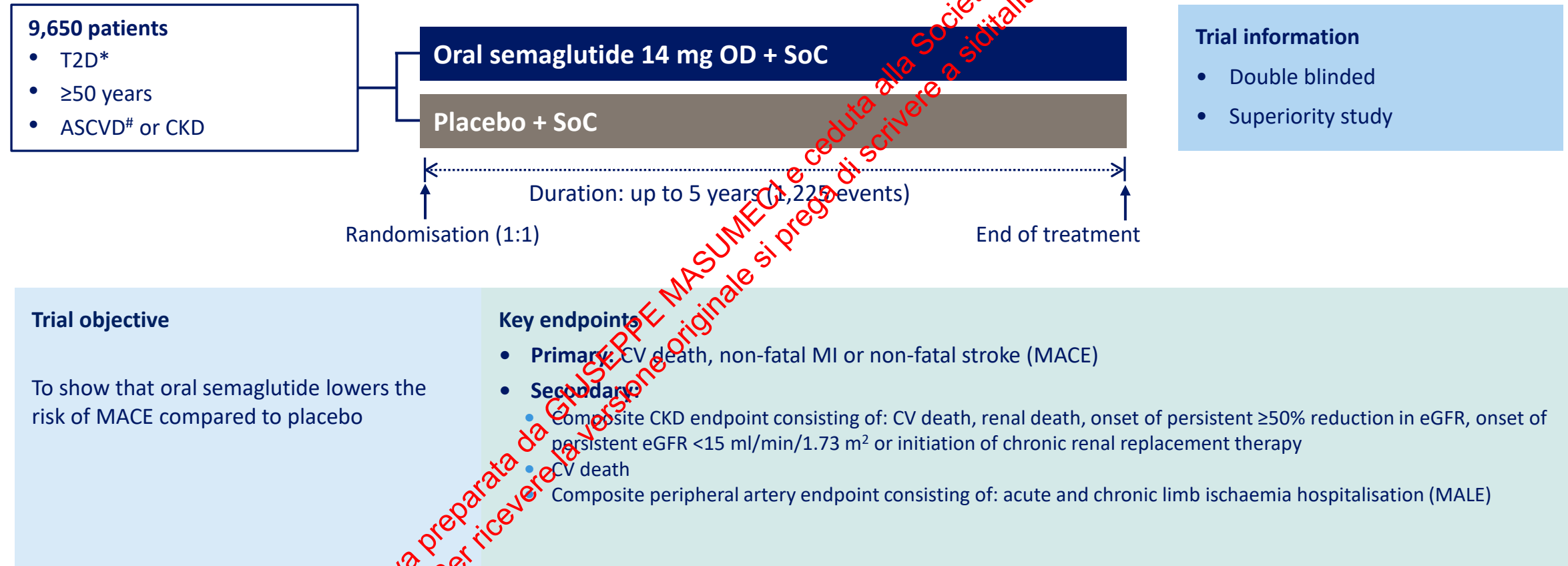
GLP-1 receptor agonists with proven CV benefit^d are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.^{710,711}

I	A
---	---

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
 Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

SOUL: trial design

Oral semaglutide cardiovascular outcomes trial in patients with T2D

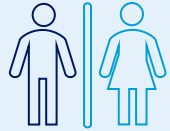


ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PFV, first patient first visit; MACE, major adverse cardiovascular event; SoC, standard of care (will allow all glucose-lowering drugs except GLP-1RAs); MALE, major adverse limb events; SOUL, Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes.

*T2D defined as HbA1c 6.5–10%; #ASCVD defined as at least one of the following conditions: CAD, Cerebrovascular disease or Symptomatic PAD.

1. McGuire, et al. Diabetes Obes Metab. 2023;25(7):1932–1941. 2. SOUL: ClinicalTrials.gov NCT03914326. Accessed October 2024

Demographics and baseline characteristics¹



Male/female (%)

71.1/28.9



Mean age (years)

66.1



Mean HbA_{1c}
(% [mmol/mol])

8.0 (63.5)



Mean BMI (kg/m²)

31.1



Mean T2D duration
(years)

15.4



Coronary heart disease

70.7%

Cerebrovascular disease

21.1%

Chronic heart failure

23.0%

PAD

15.9%



CKD*

42.3%

Mean eGFR^{†2} (mL/min/1.73 m²): **73.8**

- Normal (≥90) **31.1%**
- Mild impairment (60–<90) **38.8%**
- Moderate impairment (30–<60) **26.7%**
- Severe impairment (15–<30) **2.4%**
- End-stage kidney disease (<15) **0.1%**

*Defined as eGFR <60 mL/min/1.73 m². †Calculated with the CKD-EPI method

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; PAD, peripheral artery disease; T2D, type 2 diabetes

1. McGuire DK, et al. Diabetes Obes Metab. 2023;25(7):1932-1941; 2. McGuire DK, et al. N Engl J Med. 2025; DOI: 10.1056/NEJMoa2501006

Oral semaglutide significantly decreased risk of MACE by 14% relative to placebo in ASCVD and/or CKD people with T2D

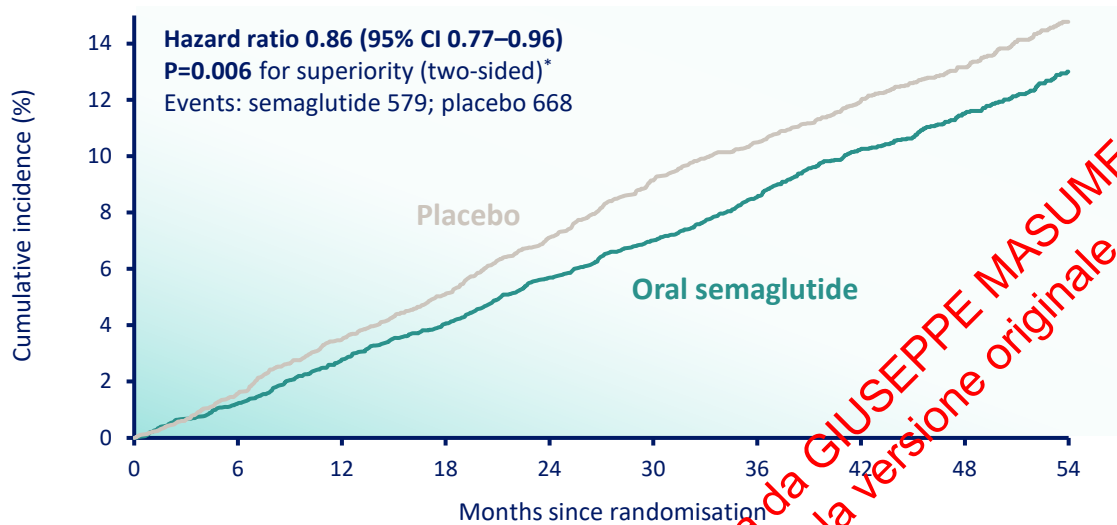
SOUL

NNT=50

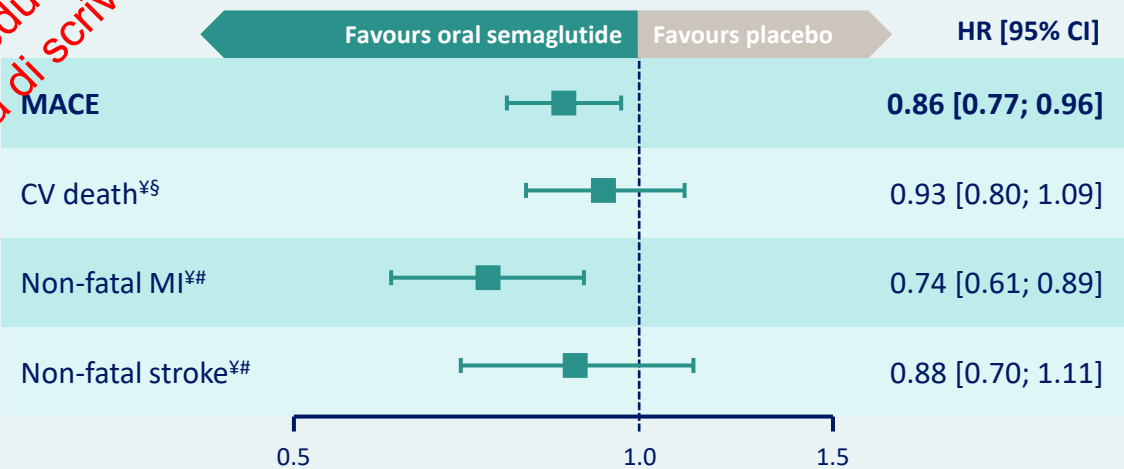
(95% CI, 31-125)



Oral semaglutide reduced the risk of MACE by 14% versus placebo¹



All three MACE components contributed to the reduction¹



Treatment effect on MACE for oral semaglutide was on top of standard of care, with up to 49% of participants being on SGLT2i at some point during the trial²

*The two-sided significance level for the primary endpoint after accounting for the interim analysis was 0.04561. [¥]Superiority of oral semaglutide versus placebo for time from randomisation to first CV death, non-fatal MI or non-fatal stroke was not tested. [§]Confirmatory secondary outcome, because the between-group difference in the 5-point major kidney outcome did not meet the required P value for hierarchical testing, results for the two subsequent confirmatory outcomes in the testing hierarchy are reported as point estimates and 95% CIs

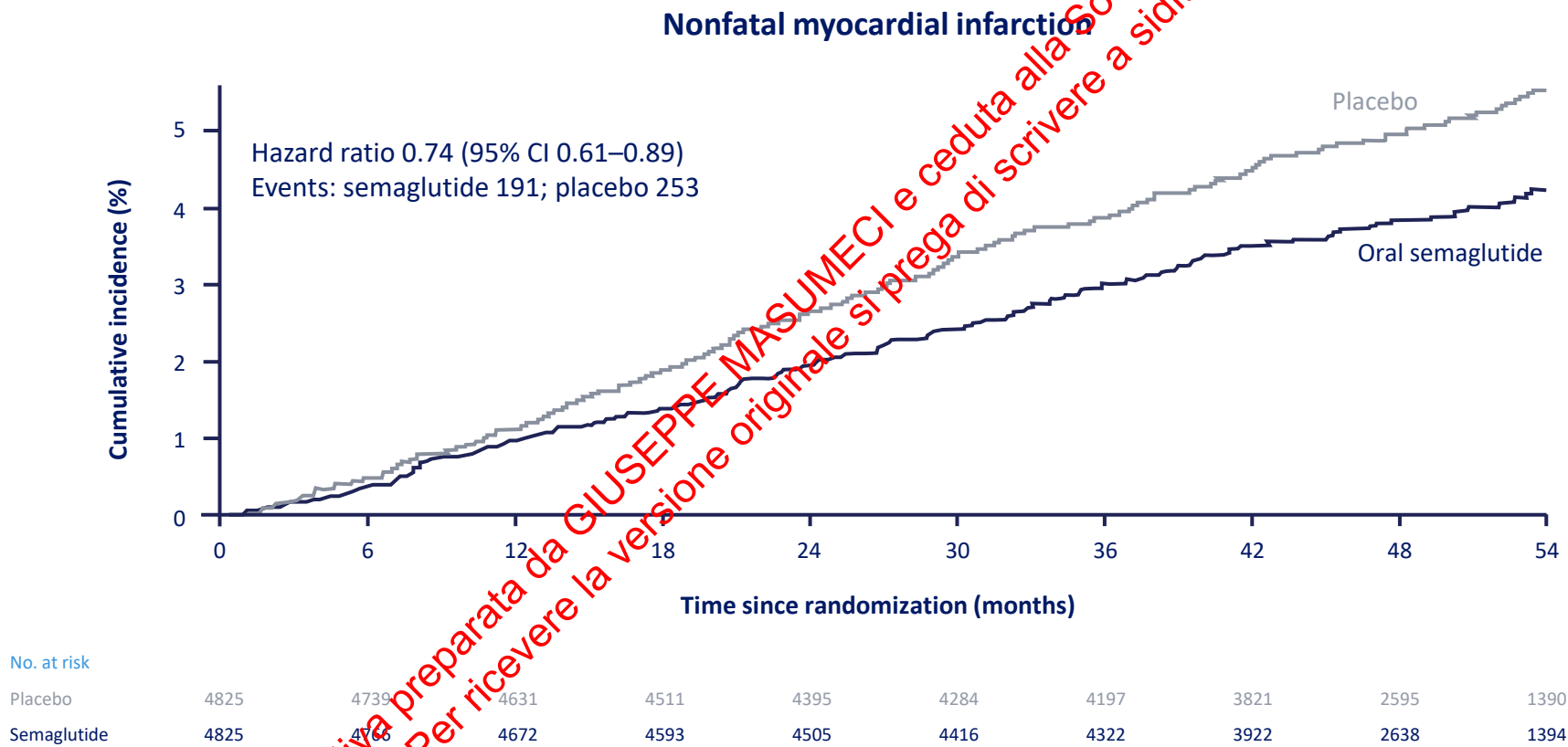
[#]Supportive secondary outcomes, not controlled for multiplicity.

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

1. McGuire DK, et al. N Engl J Med. 2025; DOI: 10.1056/NEJMoa2501006; 2. Marx N, et al. Circulation 2025; DOI: 10.1161/CIRCULATIONAHA.125.074545

Oral semaglutide indicated decreased risk of nonfatal myocardial infarction*

Component of primary outcome



*Not controlled for multiplicity. CI, confidence interval.
McGuire DK., et al. N Engl J Med. 2025; DOI: 10.1056/NEJMoa2501006

Semaglutide shows cardio-reno-metabolic benefits¹⁻⁴

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., Tina Vilsbøll, M.D., D.M.Sc., Mark L. Warren, M.D., and Stephen C. Bain, M.D., for the PIONEER 6 Investigators*

PIONEER 6¹, SUSTAIN 6², SOUL⁵, SELECT³ & FLOW⁴



ESC

European Society
of Cardiology

European Heart Journal (2024) 00, 1–3
<https://doi.org/10.1093/eurheartj/ehae744>

EDITORIAL

Diabetes and metabolic disorders

Pump, pipes, filter, sugar, weight, and more: the pluripotent prowess of semaglutide



NOTA 100 AIFA 25-gennaio 2022

Nota - aggiornamento del 28/05/2022

Nota 100 [0.89 Mb] [PDF] >

Farmaci a carico SSN inclusi nella Nota AIFA INIBITORI SGLT2 • canagliflozin • dapagliflozin • empagliflozin • ertugliflozin AGONISTI RECETTORIALI GLP1 • dulaglutide • exenatide • exenatide LAR • liraglutide • lixisenatide • semaglutide INIBITORI DPP4 • alogliptin • linagliptin • saxagliptin • sitagliptin • vildagliptin ASSOCIAZIONI PRECOSTITUITE • canagliflozin/metformina • dapagliflozin/metformina • empagliflozin/metformina • empagliflozin/linagliptin • ertugliflozin/ metformina • saxagliptin/dapagliflozin • degludec/liraglutide • glargine/lixisenatide • alogliptin/metformina • alogliptin/pioglitazone • linagliptin/metformina • saxagliptin/metformina • sitagliptin/metformina • vildagliptin/metformina	La presente Nota AIFA ha l'obiettivo di definire, sulla base delle principali evidenze disponibili, i criteri di prescrivibilità e di rimborsabilità da parte del SSN degli inibitori del SGLT2, degli agonisti recettoriali del GLP1 e degli inibitori del DPP4 nei pazienti adulti con diabete mellito tipo 2 in controllo glicemico inadeguato (emoglobina glicata -HbA1c- superiore a 65 mmol/mol o 7.0%). La prescrizione a carico del SSN deve avvenire nel rispetto delle indicazioni contenute nella Nota e prevedere la compilazione della Scheda di valutazione e prescrizione (Allegato) da parte dei Medici di Medicina Generale o degli Specialisti secondo quanto riportato nella tabella sottostante. <table border="1"> <thead> <tr> <th>Prescrittori</th><th>Farmaci</th></tr> </thead> <tbody> <tr> <td></td><td> Inibitori SGLT2 (SGLT2i) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con agonisti recettoriali del GLP1 o con inibitori del DPP4) </td></tr> <tr> <td>Tutti i MMG e gli specialisti SSN autorizzati dalle Regioni^A</td><td> Agonisti recettoriali GLP1 (GLP1-RA) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con inibitori del SGLT2) </td></tr> <tr> <td></td><td> Inibitori DPP4 (DPP4i) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con inibitori del SGLT2) </td></tr> <tr> <td>Esclusivamente specialisti del SSN che operano in strutture individuate dalle Regioni per il trattamento del diabete mellito.</td><td> Le associazioni fisse o estemporanee di: - inibitori del SGLT2 + inibitori del DPP4 - inibitori del SGLT2 + agonisti recettoriali del GLP1 (in associazione o in alternativa ad altri farmaci antidiabetici) </td></tr> </tbody> </table> ^A può prescrivere chi è autorizzato dalle Regioni ad accedere al sistema Tessera Sanitaria per la Scheda di valutazione e prescrizione.	Prescrittori	Farmaci		Inibitori SGLT2 (SGLT2i) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con agonisti recettoriali del GLP1 o con inibitori del DPP4)	Tutti i MMG e gli specialisti SSN autorizzati dalle Regioni ^A	Agonisti recettoriali GLP1 (GLP1-RA) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con inibitori del SGLT2)		Inibitori DPP4 (DPP4i) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con inibitori del SGLT2)	Esclusivamente specialisti del SSN che operano in strutture individuate dalle Regioni per il trattamento del diabete mellito.	Le associazioni fisse o estemporanee di: - inibitori del SGLT2 + inibitori del DPP4 - inibitori del SGLT2 + agonisti recettoriali del GLP1 (in associazione o in alternativa ad altri farmaci antidiabetici)
Prescrittori	Farmaci										
	Inibitori SGLT2 (SGLT2i) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con agonisti recettoriali del GLP1 o con inibitori del DPP4)										
Tutti i MMG e gli specialisti SSN autorizzati dalle Regioni ^A	Agonisti recettoriali GLP1 (GLP1-RA) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con inibitori del SGLT2)										
	Inibitori DPP4 (DPP4i) (in monoterapia e in associazione fissa o estemporanea con altri farmaci, ad eccezione dell'associazione con inibitori del SGLT2)										
Esclusivamente specialisti del SSN che operano in strutture individuate dalle Regioni per il trattamento del diabete mellito.	Le associazioni fisse o estemporanee di: - inibitori del SGLT2 + inibitori del DPP4 - inibitori del SGLT2 + agonisti recettoriali del GLP1 (in associazione o in alternativa ad altri farmaci antidiabetici)										

quasi altro specialista del SSN (ad esempio, cardiologi e nefrologi che hanno in carico i pazienti per il trattamento delle principali complicanze)

I MMG e gli altri specialisti (nefrologi, cardiologi, internisti, geriatri, neurologi) che seguono pazienti con DM2 acquisiscono un ruolo primario nella gestione integrata del diabete mellito tipo 2

Prescrivibilità dei farmaci GLP-1 RA indipendentemente dai livelli di HbA1c e dalla concomitante terapia con metformina nei pazienti in prevenzione secondario e anche solo ad elevato CV

GLP1-RA: quando e a chi?

Il ruolo del cardiologo con Nota 100



DM2 con ASCVD o rischio CV alto/molto alto
Indipendentemente dal valore di HbA1c

non ancora trattato o di nuova
diagnosi
(es. in corso di ricovero)



Iniziare semaglutide Orale
(+Metf se non controindicata o
non tollerata)

già trattato con
METFORMINA



Aggiungere
semaglutide orale

già trattato con
METFORMINA +
SULFANILUREA



Aggiungere semaglutide
orale sostituendo la SU

Già trattato con
METFORMINA
+ DPP-IV



Aggiungere semaglutide
orale sostituendo il Dpp4-i



In collaborazione con diabetologi

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a masumeci@siditalia.it



CARDIOPATIA ISCHEMICA E DIABETE MELLITO TIPO II

GLIFLOZINE/INIBITORI DPP-4



SEMAGLUTIDE



CONSULENZA
DIABETOLOGICA

METFORMINA



SEMAGLUTIDE



NOTA 100
(Cardiologo)

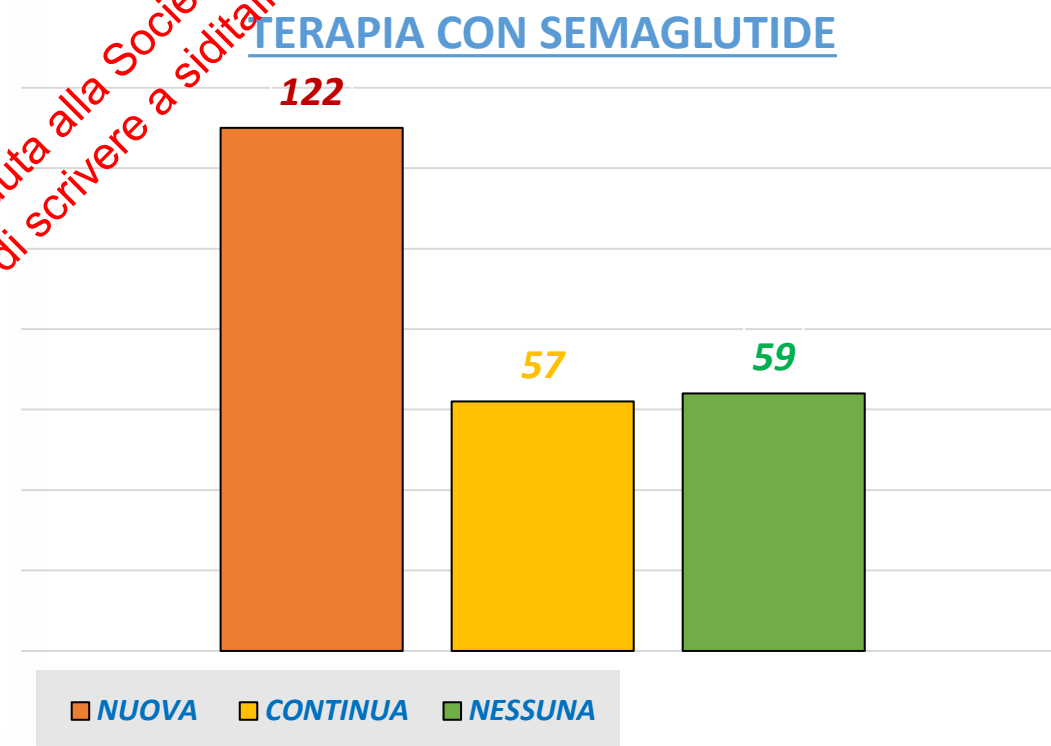
CAD 2023 Ospedale Mauriziano Torino

Overall, 720 consecutive CAD patients (282 ACS and 428 CCS) hospitalized between January and December 2023 were enrolled; **179 of whom were discharged with oral Semaglutide (75%)**



Pz diabetici → 238
Pz non diabetici → 482

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



Semaglutide: 51% nuovi pazienti
24% già in terapia,
25% dimessi senza

Conclusioni

- ✓ Il diabete aumenta il rischio di eventi avversi cardiovascolari
- ✓ Gli eventi cardiovascolari sono la prima causa di morte nel paziente diabetico
- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ I GLP-1 RA sono oggi raccomandati dalle LG come farmaci di prima linea nei pazienti con malattia cardiovascolare e DM di tipo 2 o alto rischio CV e DM tipo 2
- ✓ La Semaglutide è l'unico farmaco di questa classe disponibile per via orale e rappresenta una nuova e efficace opzione terapeutica per trattare il rischio aterotrombotico del paziente con DM tipo 2

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Conclusioni

- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ L'aggiunta degli I-PCSK9 in fast-track (in-H/dimissione) è raccomandata nei pazienti ACS o eventi CV multipli già in statine e LDL ≥ 70 mg/dl e nei pazienti ACS naive da statine ed LDL ≥ 140 mg/dl e garantisce raggiungimento del target e prognosi migliore
- ✓ L'acido bempedoico si è dimostrato in grado di ridurre in maniera significativa i livelli di C-LDL, sia in aggiunta alla massima dose di statina tollerata sia in pazienti con intolleranza alle statine, con un effetto ancora maggiore quando utilizzato in combinazione con l'ezetimibe.
- ✓ Inclisiran con le sue caratteristiche di somministrazione, efficacia e sicurezza potrebbe essere ideale nel paziente elettivo garantendo il raggiungimento del target e l'aderenza terapeutica

PIONEER 6: trial design

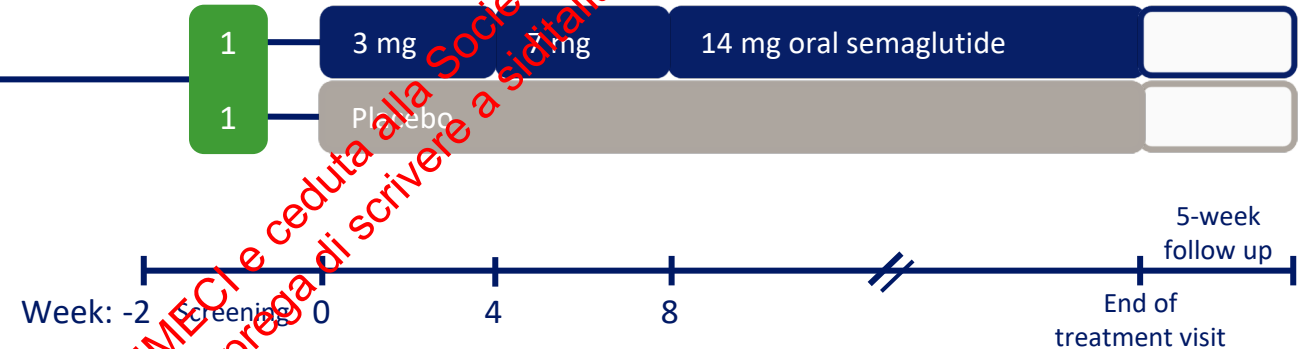
Key inclusion criteria

- Age ≥ 50 years and clinical evidence of CVD or CKD
- Age ≥ 60 years and CV risk factors only
- Diagnosed with T2D

Trial information

- Randomised, double-blind, placebo- controlled trial designed to rule out an excess CV risk of 80% for oral semaglutide vs placebo when added to standard of care in subjects with T2D at high risk of CV events (pre-approval CVOT)

3183 subjects were enrolled



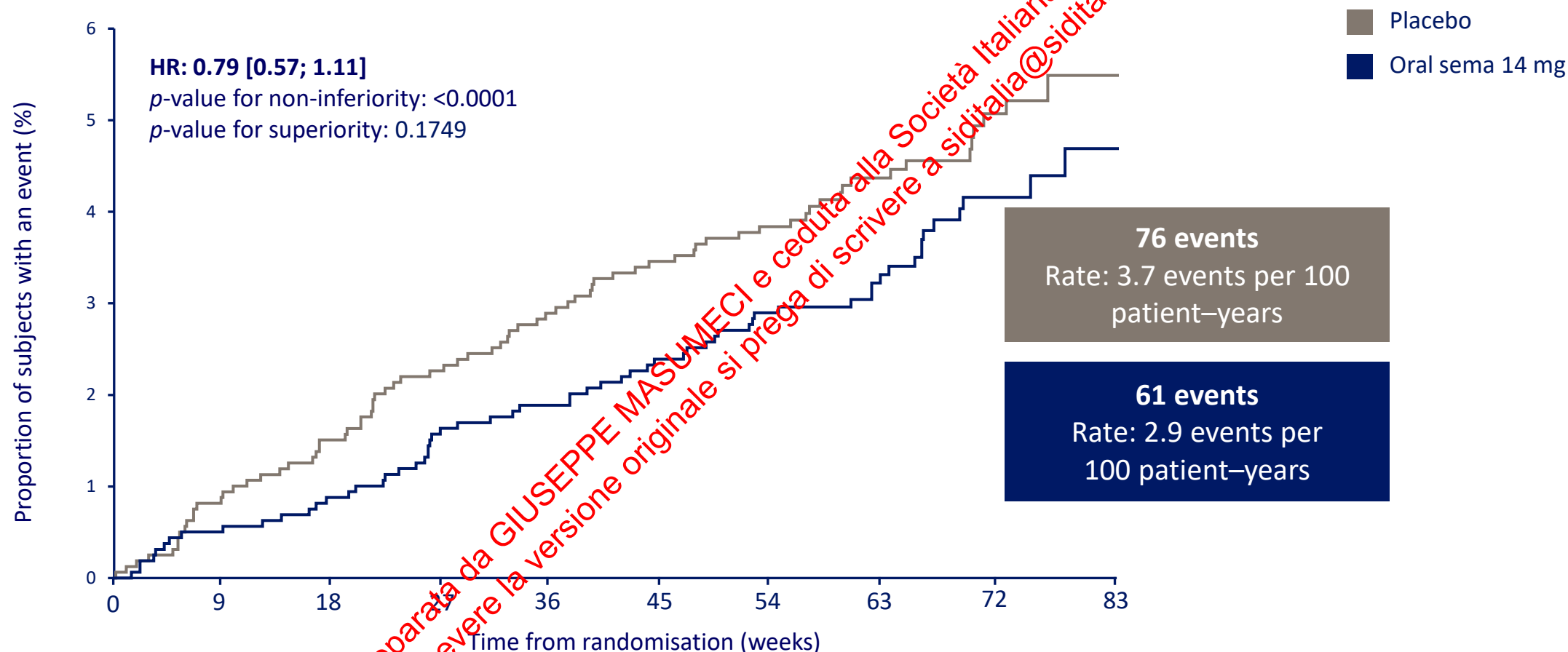
Primary endpoint

- Time to first MACE (CV death, non-fatal stroke, or non-fatal MI)

Supportive secondary endpoints included

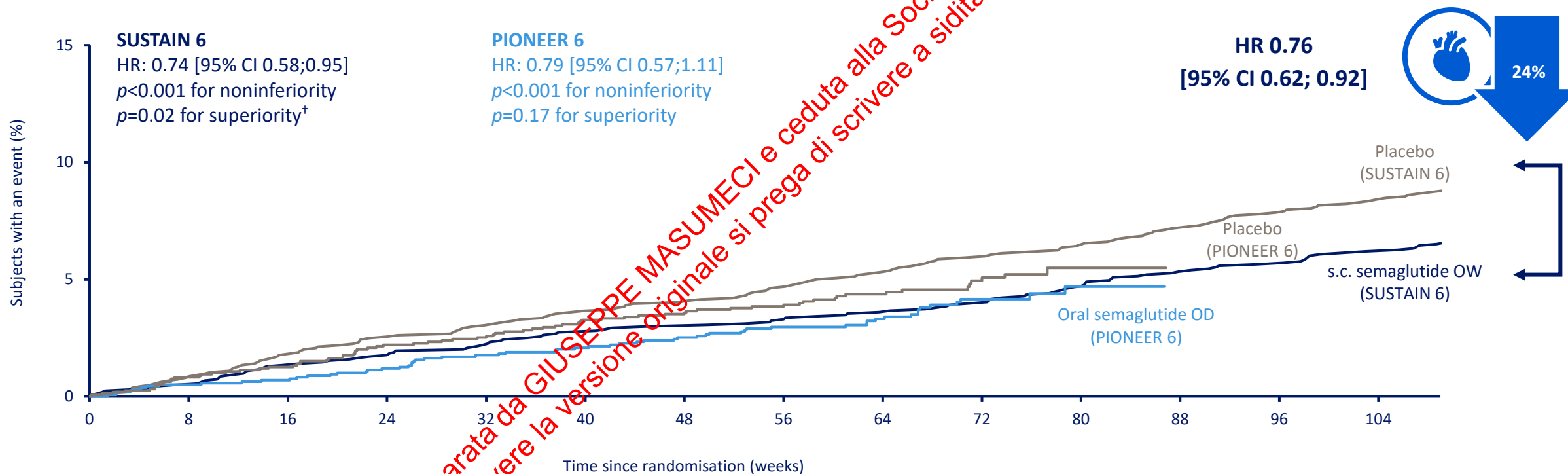
- Time to all cause death
- Time to expanded MACE endpoint

PIONEER 6: First MACE – primary endpoint



All events confirmed by EAC. Cumulative incidence estimate plot for first EAC-confirmed CV death, non-fatal MI and non-fatal stroke using 'in-trial' data from subjects in the full analysis set. Time from randomisation to first EAC-confirmed CV death, non-fatal MI and non-fatal stroke was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of CV disease at screening. Subjects were censored at the end of their in-trial observation period. CV, cardiovascular; EAC, event adjudication committee; HR, hazard ratio; MI, myocardial infarction; MACE, major adverse cardiovascular event; sema, semaglutide.
Husain M et al. N Engl J Med 2019;381:841–51.

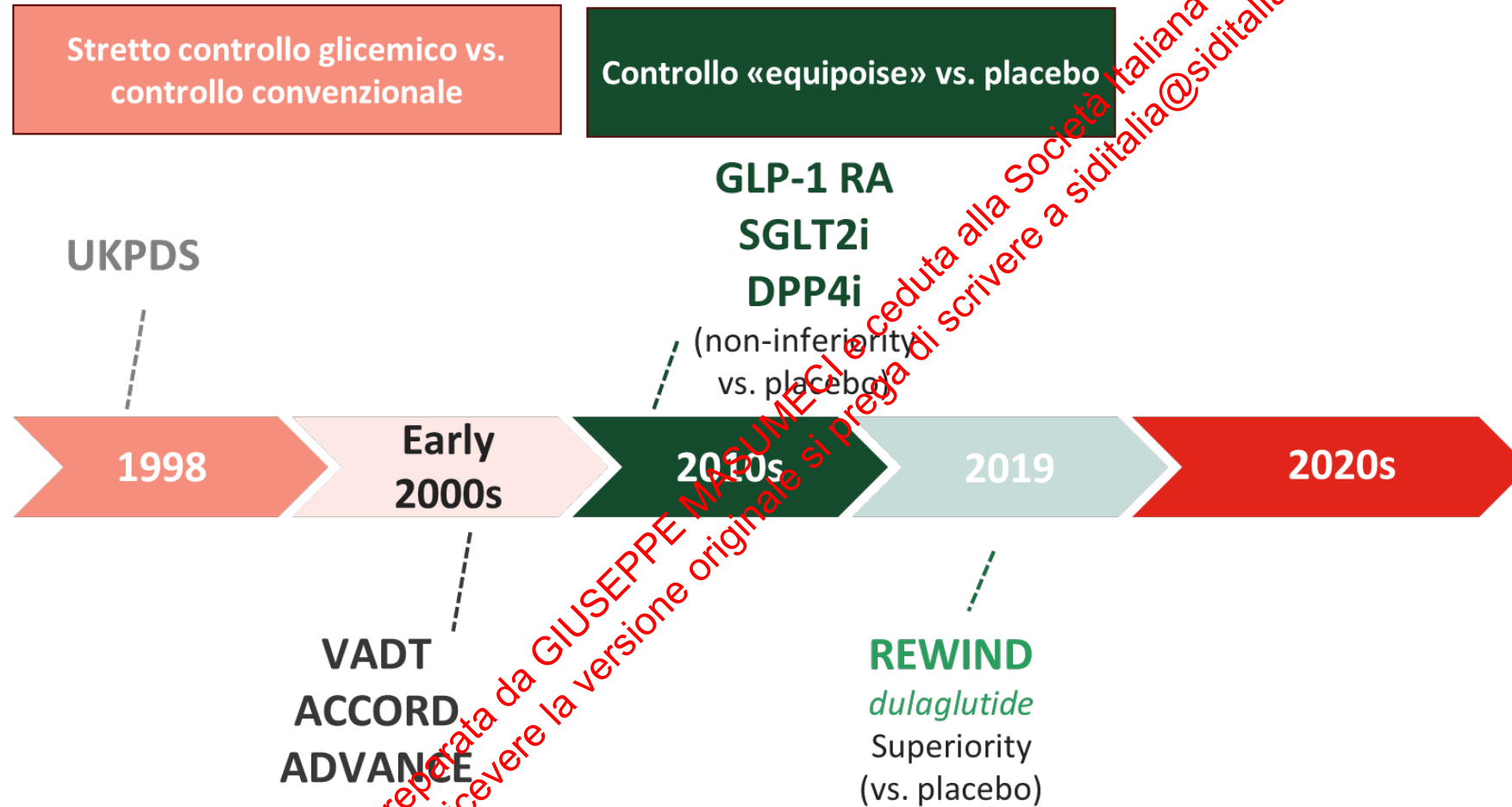
Time to first occurrence of MACE* with semaglutide vs placebo



*Three-component MACE included CV death, nonfatal MI, and nonfatal stroke. Combined population omitted owing to different trial durations; SUSTAIN 6 and PIONEER 6 have already been individually reported. [†]Not pre-specified. CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; OD, once daily; OW, once weekly; PIONEER, peptide innovation for early diabetes treatment; s.c., subcutaneous; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes.

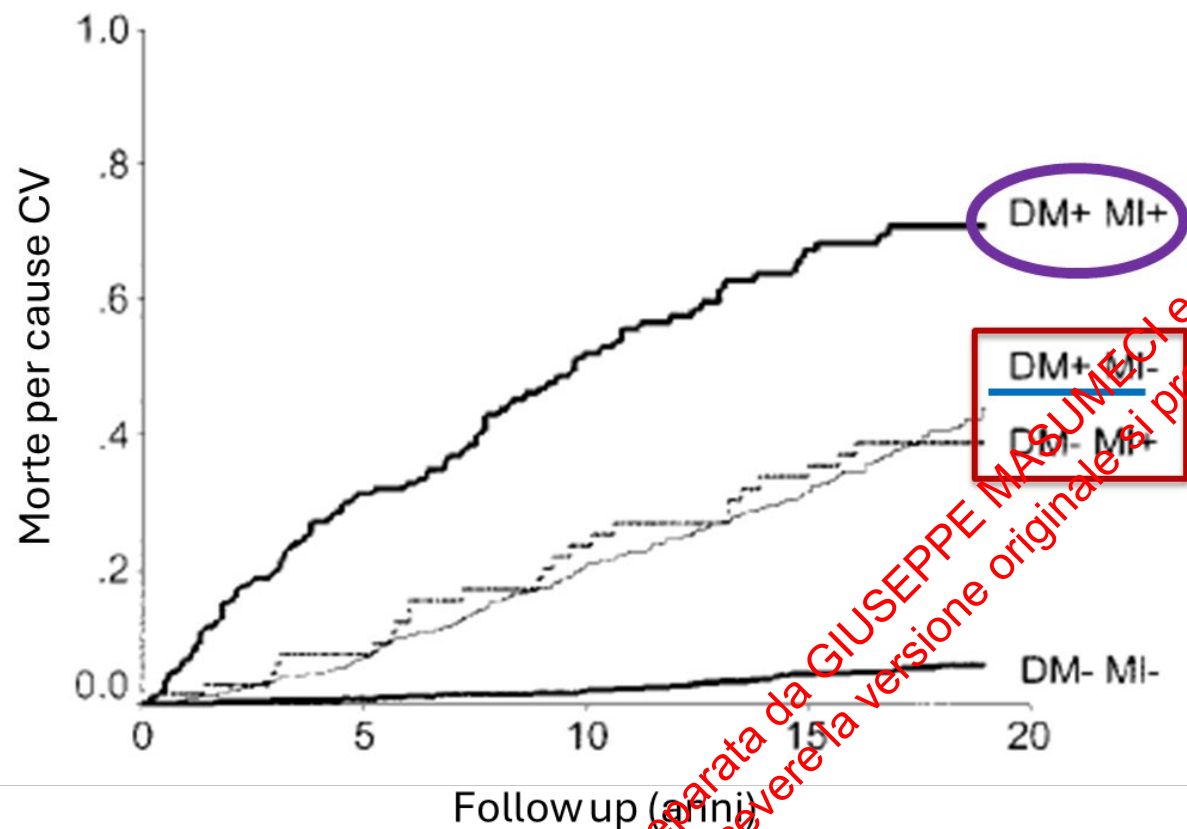
Marso SP et al. *N Engl J Med* 2016;375:1834–44; Husain M et al. *N Engl J Med* 2019;381:841–51; Husain M et al. *Diabetes Obes Metab* 2020;22(3):442–51.

L'evoluzione degli studi protezione cardiovascolare nel T2DM



Il diabete mellito tipo 2 è un equivalente di malattia coronarica

(Studio prospettico di popolazione in Finlandia, durata 18 anni)



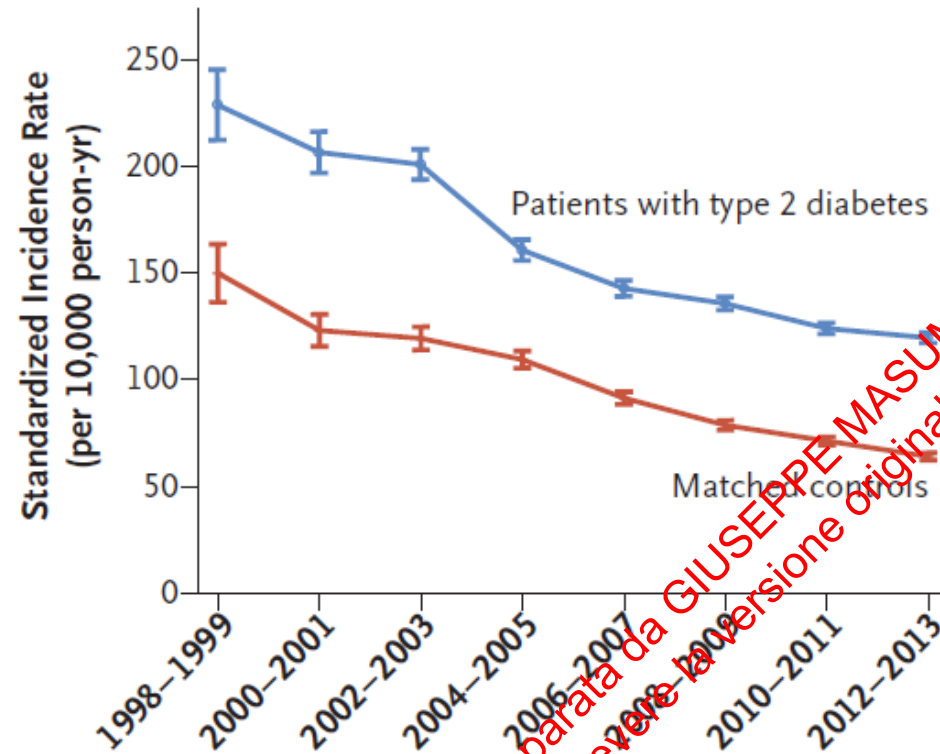
CALL TO ACTION:

- Abbiamo bisogno di più della sola gestione della glicemia
- Dobbiamo agire subito, prima del primo evento CV

Morte cardiovascolare nei soggetti con diabete mellito

Nonostante un trend in significativa riduzione, le persone con diabete mantengono un rischio di morte cardiovascolare superiore alla popolazione generale senza diabete

B Death from Cardiovascular Disease



Swedish National Diabetes Registry
1998-2012

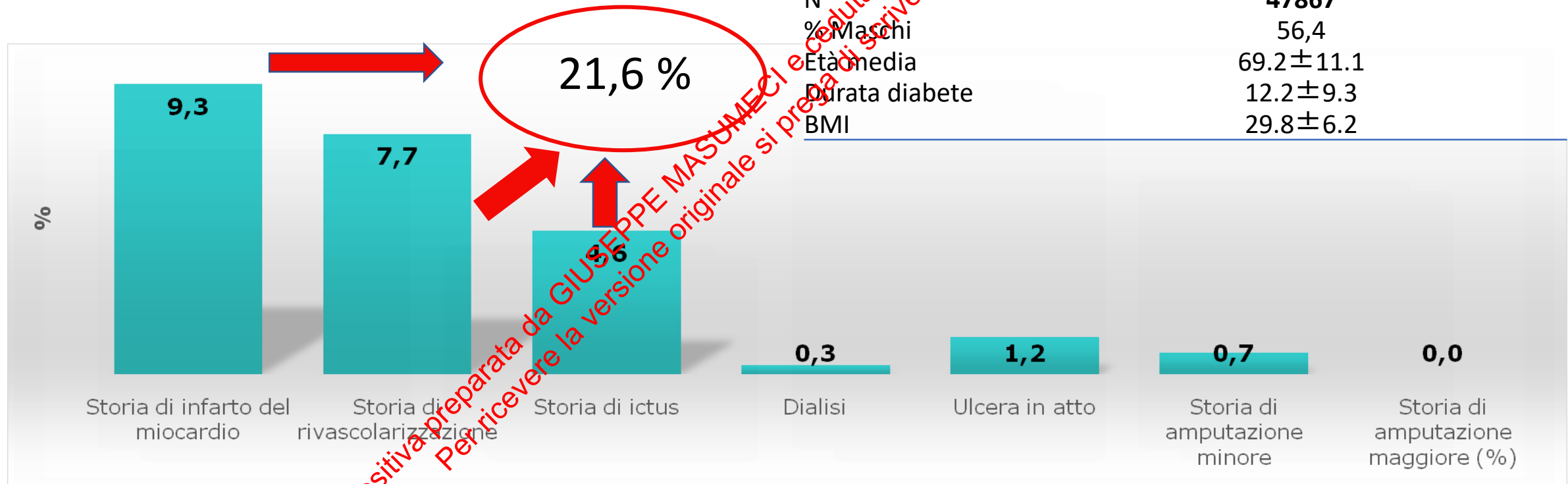
↑ 2 x mortalità CV rispetto ai
loro pari senza diabete

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a sliditalia@sidiitalia.it



AMD Full Data Circle 2015: Le complicanze cardiovascolari nei soggetti con T2DM in Italia

Indicatori di esito finale
% soggetti con:



FDC 2015,
17 UO Diabetologia

N

N	47867
% Maschi	56,4
Età media	69.2 ± 11.1
Durata diabete	12.2 ± 9.3
BMI	29.8 ± 6.2

Outcome cardiovascolari e renali con GLP-1 RA nel DMT2

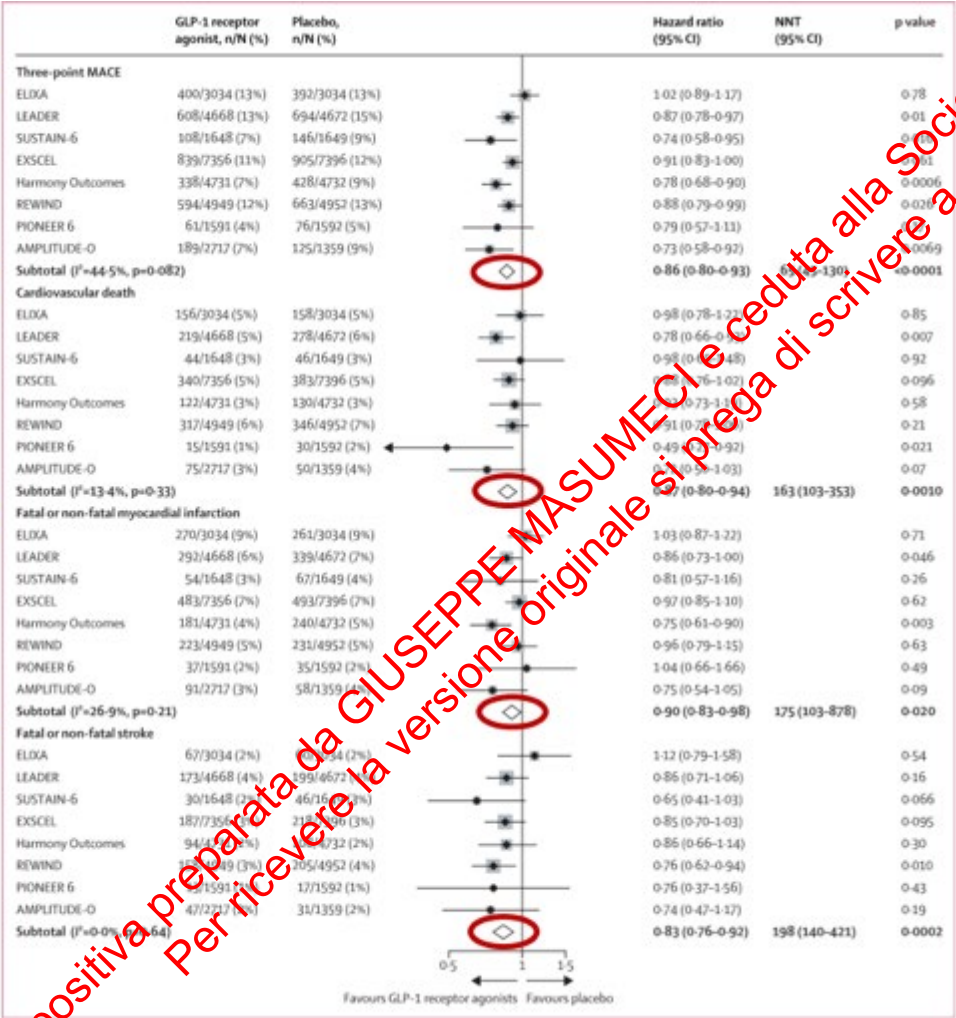
I GLP-1 RA hanno ridotto il MACE a tre punti e le sue componenti in pazienti con DMT2 e aumentato rischio CV o con malattia cardiovascolare conclamata

3-P MACE

CV death

Fatal or non-fatal MI

Fatal or non-fatal stroke



3-P MACE



RR 14%

DECESSI PER EVENTI CV



RR 13%

FATAL or NON-FATAL MI



RR 10%

FATAL or NON-FATAL STROKE



RR 17%

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

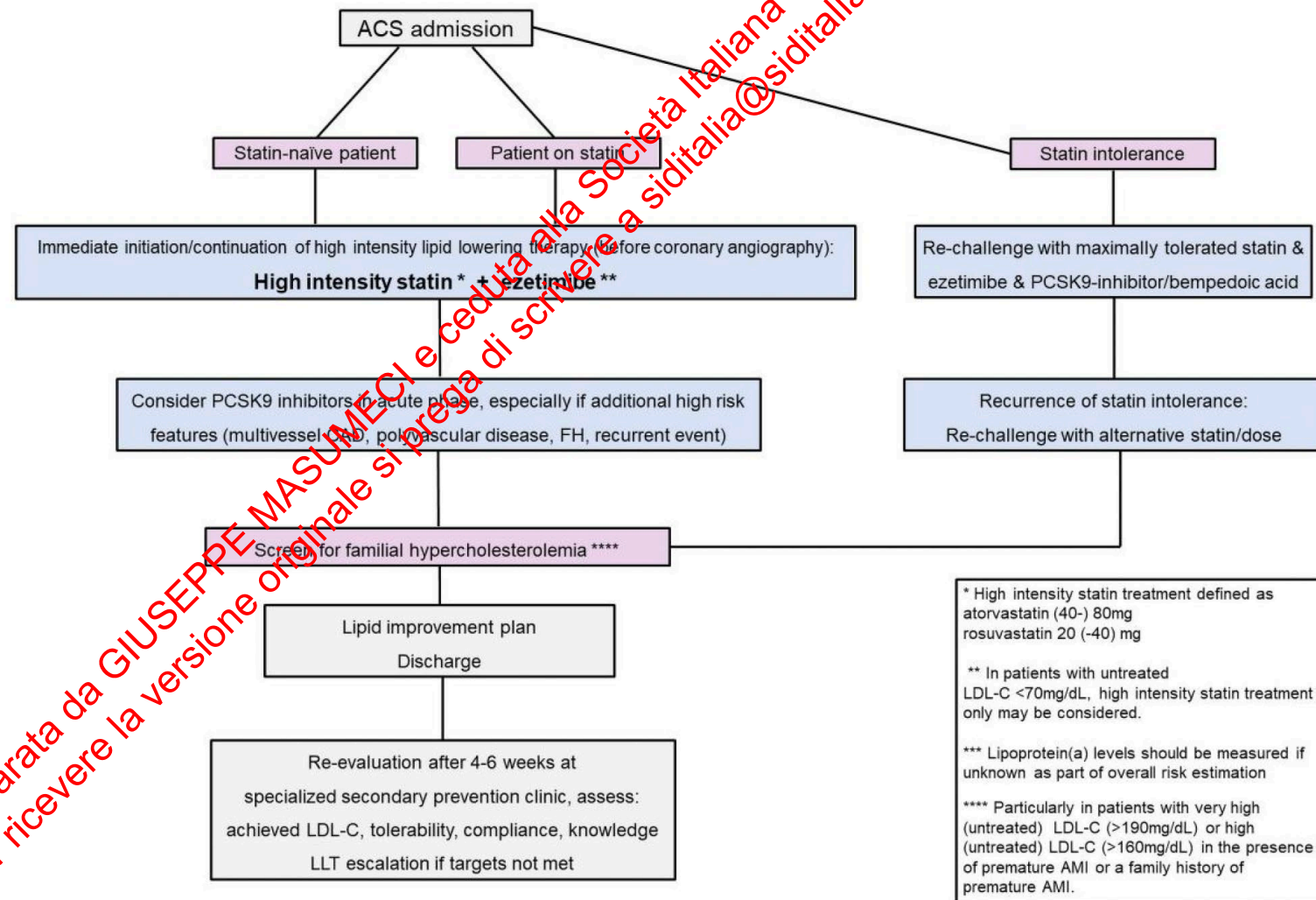
MORTALITA'

Comparison	Relative effect (odds ratio (95% CI))	Anticipated absolute effects over five years			Anticipated absolute effects (95% CI) over five years
		Baseline risk*	Risk with control	Risk with intervention	
GLP-1 receptor agonist v placebo	0.88 (0.83 to 0.94)	Very low	Placebo: 20 per 1000	GLP-1 receptor agonist: 18 per 1000	2 fewer per 1000 (from 1 fewer to 3 fewer)
			NNT 509		
		Low	Placebo: 70 per 1000	GLP-1 receptor agonist: 62 per 1000	8 fewer per 1000 (from 4 fewer to 11 fewer)
			NNT 133		
		Moderate	Placebo: 120 per 1000	GLP-1 receptor agonist: 107 per 1000	13 fewer per 1000 (from 6 fewer to 18 fewer)
			NNT 86		
		High	Placebo: 170 per 1000	GLP-1 receptor agonist: 153 per 1000	17 fewer per 1000 (from 9 fewer to 25 fewer)
			NNT 69		
		Very high	Placebo: 265 per 1000	GLP-1 receptor agonist: 241 per 1000	24 fewer per 1000 (from 12 fewer to 35 fewer)
			NNT 53		

Acute LDL-C reduction post ACS: strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

Konstantin A. Krychtiuk^{1,2,†}, Ingo Ahrens^{3†}, Heinz Drexel^{4,5,6‡}, Sigrun Halvorsen^{7,8†}, Christian Hassager^{9†}, Kurt Huber^{10,11,12†}, Donata Kurpas¹, Alexander Niessner¹³, Francois Schiele^{14†}, Anne Grete Semb^{15§}, Alessandro Sionis^{16,17†}, and Marc J. Claeys^{18†}

Document reviewers: José Barrabes^{19,20} (review coordinator), Santiago Montero², Peter Sinnaeve²², Roberto Pedretti²³, and Alberico Catapano²⁴



Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

FAST TRACK PER IMA <12 MESI E EVENTI CV MULTIPLI

Profilo lipidico

Si riferisce a controlli effettuati precedentemente all'inizio del trattamento con Repatha.

Il trattamento di almeno sei mesi con statina ad alta potenza al massimo della dose tollerata è una delle condizioni obbligatorie ai fini dell'eleggibilità con questo medicinale.

E' necessario inserire 3 determinazioni, eseguite in momenti diversi, del profilo lipidico.

Ai fini dell'eleggibilità, il sistema considera che tutti e tre i valori di colesterolo LDL siano al di sopra del target specifico.

Solo nel caso di paziente con IMA recente o eventi CV multipli è richiesta una sola determinazione del profilo lipidico (da inserire nel 3° campo a seguire).

E' NECESSARIO 1 SOLO PROFILO LIPIDICO CON LDL-C>100

Entro 30 gg dalla data di valutazione

1 SOLO CAMPO DA COMPILARE PER IL PROFILO LIPIDICO

Diapositiva preparata da GIUSEPPE MAUMI e ceduta alla Società Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Data prelievo 1a determinazione:		
Colesterolo totale 1a determinazione:		
Colesterolo HDL 1a determinazione:		
Trigliceridi 1a determinazione:		
☒	Colesterolo LDL 1a determinazione:	
Data prelievo 2a determinazione:		
Colesterolo totale 2a determinazione:		
Colesterolo HDL 2a determinazione:		
Trigliceridi 2a determinazione:		
☒	Colesterolo LDL 2a determinazione:	
Data prelievo 3a determinazione *:		20/03/2019
Colesterolo totale 3a determinazione *:		300 mg/dl
Colesterolo HDL 3a determinazione *:		50 mg/dl
Trigliceridi 3a determinazione *:		100 mg/dl
☒	Colesterolo LDL 3a determinazione *:	150 mg/dl
Altri parametri lipidici disponibili *:		☒ Nessuno ☐ Lp(a) ☐ ApoB ☐ ApoA1 ☐ Altro

PER COMPLETARE CORRETTAMENTE L'ELEGGIBILITA' DEL PAZIENTE POST-MI <12 M O DEL PAZIENTE CON EVENTI CV MULTIPLI OCCORRE:

- **COMPILARE ESCLUSIVAMENTE IL TERZO CAMPO («COLESTEROLO LDL 3° DETERMINAZIONE»)** del PROFILO LIPIDICO



A. O. ORDINE
MAURIZIANO
TORINO



- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL ≥ 70 mg/dl
Aggiunge I-PCSK9 alla dimissione
- Paziente con SCA in terapia con Statine ed LDL ≥ 70 mg/dl
Aggiunge Ezetimibe ed I-PCSK9 alla dimissione
- Paziente con SCA naive da Statine con LDL ≥ 55 mg/dl ed < 140 mg/dl
Aggiunge combinazione Statine ed Ezetimibe alla dimissione e controllo a un mese per valutare I-PCSK9
- Paziente con SCA naive da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV
Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

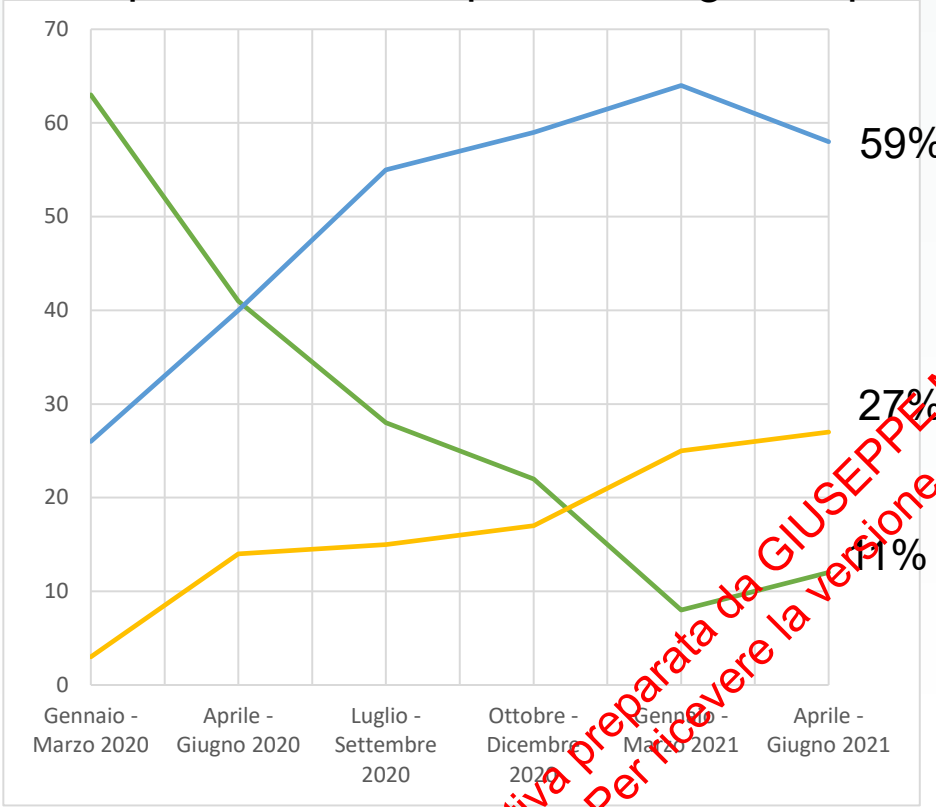


- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL > 100 mg/dl
Aggiunge I-PCSK9 alla dimissione
- Paziente con SCA in terapia con Statine ed LDL > 100 mg/dl
Aggiunge Ezetimibe ed I-PCSK9 alla dimissione
- Paziente con SCA naive da Statine con LDL > 55 mg/dl ed < 140 mg/dl
Aggiunge combinazione Statine ed Ezetimibe alla dimissione e controllo a un mese per valutare I-PCSK9
- Paziente con SCA naive da Statine con LDL > 140 mg/dl
Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

Early, Effective and Established strategies for LDL-C management Translating clinical evidence into real world effectiveness: Ospedale Mauriziano Torino experience

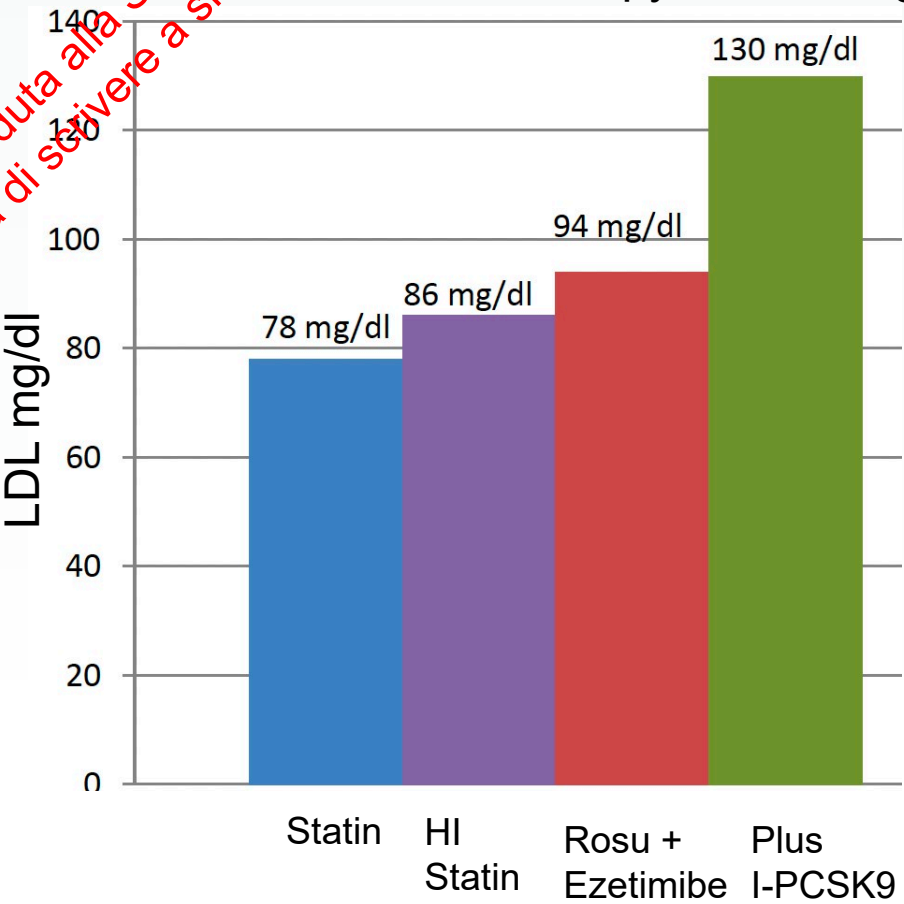
Overall, 496 consecutive ACS patients hospitalized between April 2020 and June 2021 were enrolled; 104 of whom were discharged with I-PCSK9 (21%)

Prescription trends of lipid-lowering therapies



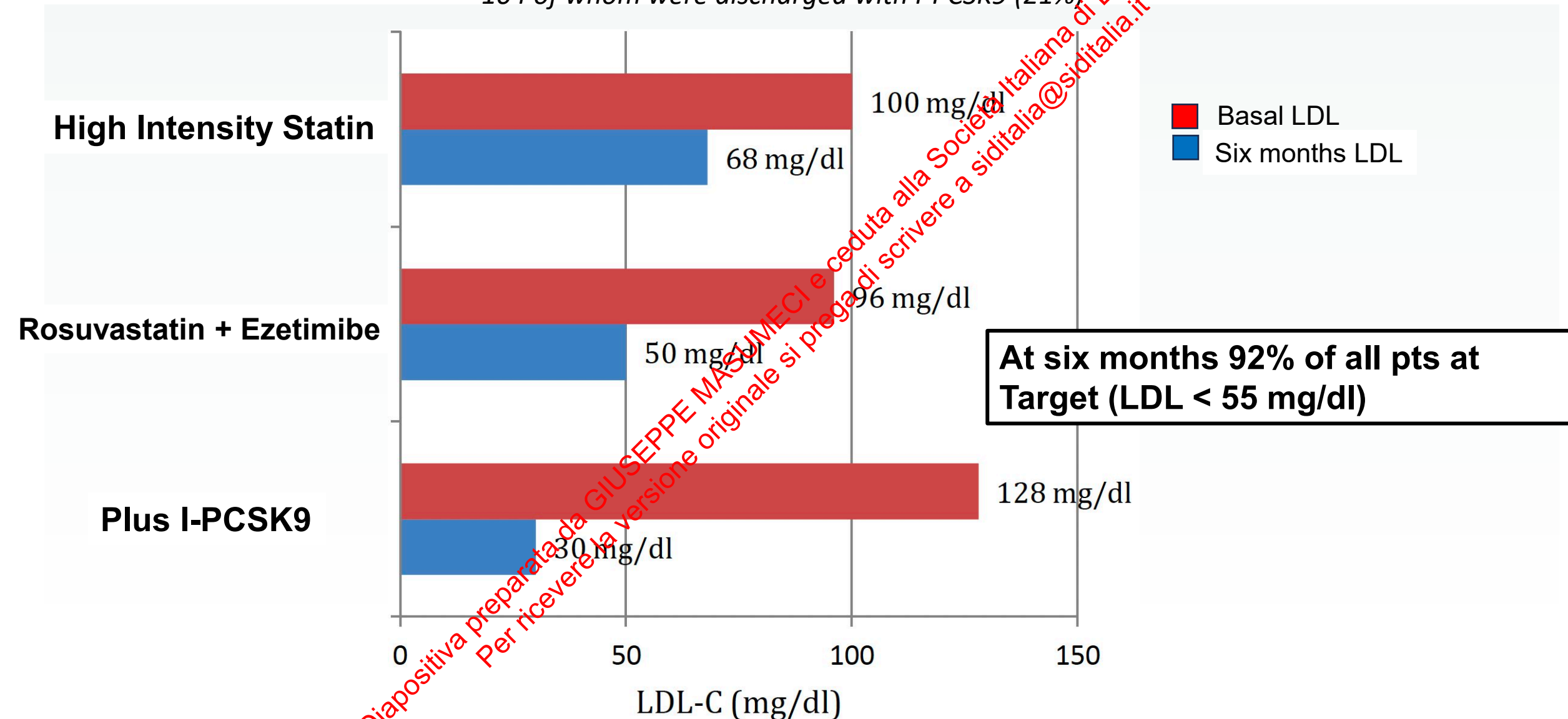
- High Intensity Statin
- Rosuvastatin + Ezetimibe
- Plus I-PCSK9

Baseline LDL and therapy at discharge



Ospedale Mauriziano Torino experience

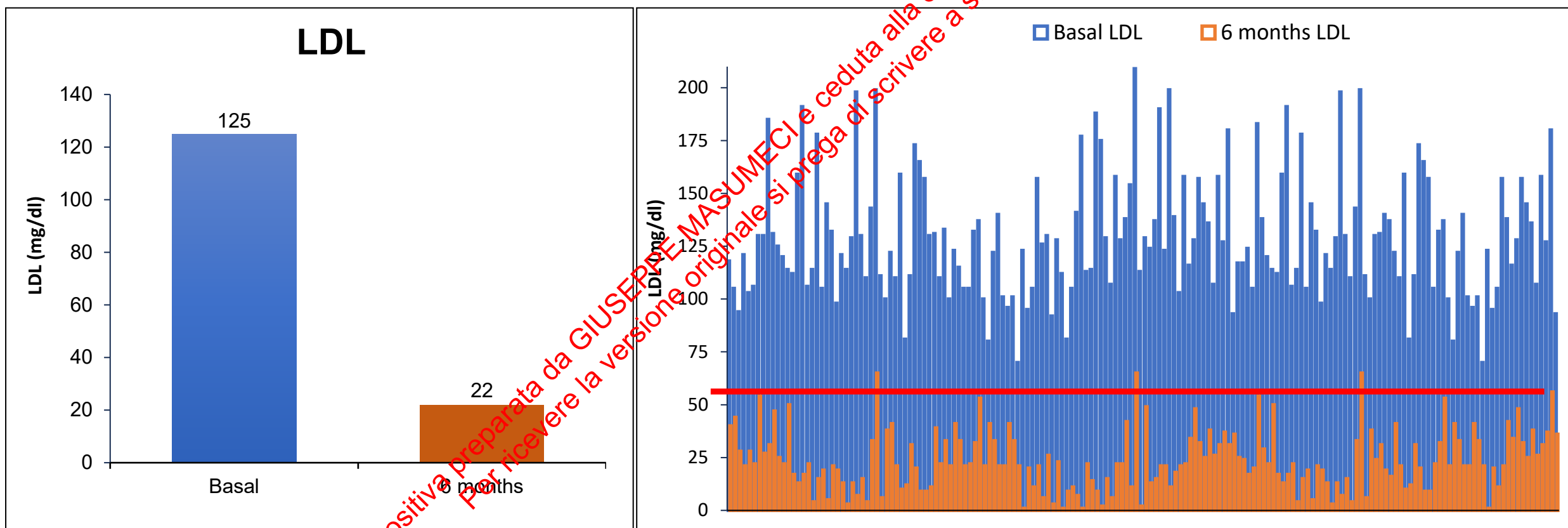
Overall, 496 consecutive ACS patients hospitalized between April 2020 and June 2021 were enrolled;
104 of whom were discharged with I-PCSK9 (21%)



LDL levels in ACS patients on PCSK9-I at discharge

1067 consecutive ACS patients hospitalized between April 2020 and March 2023 256 patients (24%) were discharged with PCSK9-I
6-month follow-up in 248 patients (97%)

PCSK9-I 6 months post-discharge: 244 reached <55 mg/dl (98%)



Dal 16 Giugno 2022 nuova soglia di rimborsabilità per Evolocumab ed Alirocumab a **LDL > 70 mg/dl**

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 163° - Numero 138


GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

PARTE PRIMA Roma - Mercoledì, 15 giugno 2022 SI PUBBLICA TUTTI I GIORNI NON FESTIVI

DIREZIONE E REDAZIONE PRESSO IL MINISTERO DELLA GIUSTIZIA - UFFICIO PUBBLICAZIONE LEGGI E DECRETI - VIA ARENULA, 70 - 00186 ROMA
AMMINISTRAZIONE PRESSO L'ISTITUTO POLIGRAFICO E ZECCA DELLO STATO - VIA SALARIA, 691 - 00138 ROMA - CENTRALINO 06-85081 - LIBRERIA DELLO STATO
PIAZZA G. VERDI, 1 - 00198 ROMA

La **Gazzetta Ufficiale, Parte Prima**, oltre alla **Serie Generale**, pubblica cinque **Serie speciali**, ciascuna contraddistinta da autonoma numerazione:

- 1^a **Serie speciale**: Corte costituzionale (pubblicata il mercoledì)
- 2^a **Serie speciale**: Unione europea (pubblicata il lunedì e il giovedì)
- 3^a **Serie speciale**: Regioni (pubblicata il sabato)
- 4^a **Serie speciale**: Concorsi ed esami (pubblicata il martedì e il venerdì)
- 5^a **Serie speciale**: Contratti pubblici (pubblicata il lunedì, il mercoledì e il venerdì)

La **Gazzetta Ufficiale, Parte Seconda**, "Foglio delle inserzioni", è pubblicata il martedì, il giovedì e il sabato

...zienti di età' ≤ 80 aa con
...go... o ipercolesterolemia non
...livelli di LDL-C ≥ 70 mg/dL

Experience at Ospedale Mauriziano and Maria Vittoria Hospital, Turin, Italy



Overall, 264 consecutive ACS patients hospitalised between July 2023 and November 2023 were enrolled; 77 of whom were discharged with PCSK9i (29%)

Therapy at discharge

ACS in patient on statin + ezetimibe therapy and LDL >100 mg/dL^a



Added PCSK9i

ACS in patient on statin therapy and LDL >100 mg/dL^b



Addition of ezetimibe and PCSK9i

ACS in naïve patient with LDL >100 mg/dL^a but <140 mg/dL^b



Introduction of statin + ezetimibe

ACS in naïve patient with LDL >140 mg/dL^b



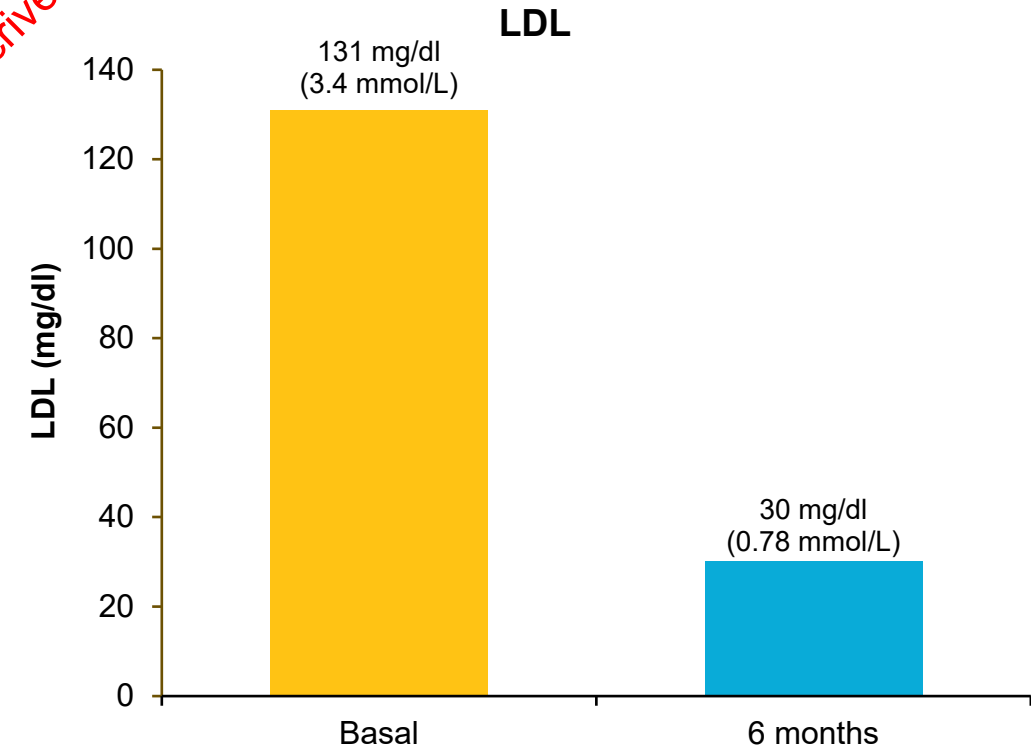
Introduction of statin + ezetimibe + PCSK9i

ACS in naïve patient with LDL >70 mg/dL^c and Diabetes/MVD/PAD



Introduction of statin + ezetimibe + PCSK9i

Patients on triple therapy



^a>2.6 mmol/L; ^b>3.6 mmol/L; ^c>1.8 mmol/L

ACS, acute coronary syndrome; LDL, low density lipoprotein; MVD, multivessel disease; PAD, peripheral arterial disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor
Delnevo F, et al. Atherosclerosis. 2024 (in press). Presented at the European Atherosclerosis Society (EAS) congress 2024. Abstract 1263

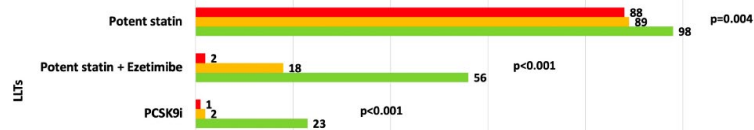
Impact of personalized, SES LL approach vs conventional strategies on LDL-c levels and CV outcomes



Period A (N=198; January-June 2019): LDL-C goal <70 mg/dL

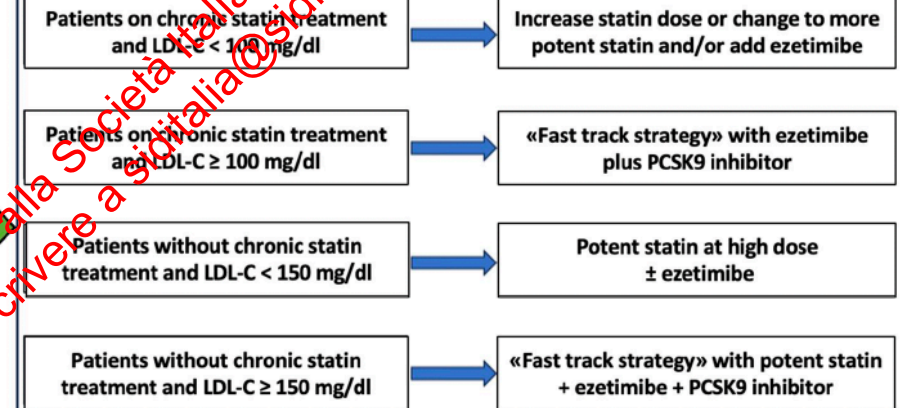
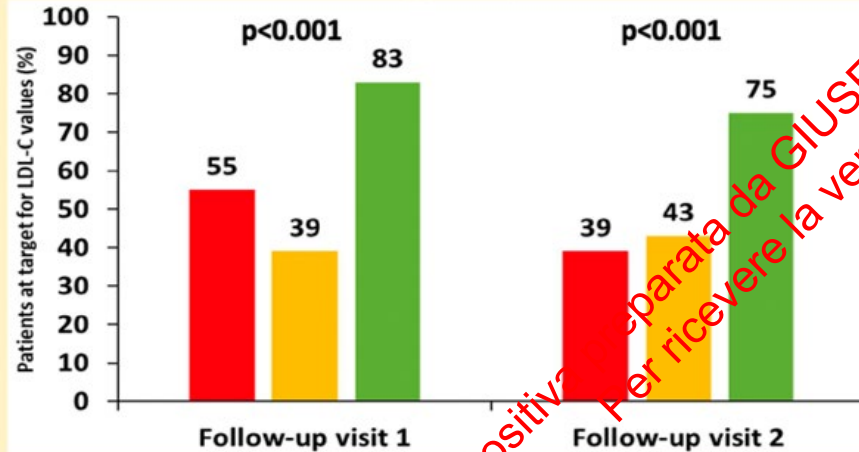
Period B (N=180; January-June 2021): LDL-C goal <55 mg/dL and stepwise approach

Period C (N=122; January-June 2023): LDL-C goal <55 mg/dL and personalized, SES lipid-lowering strategy



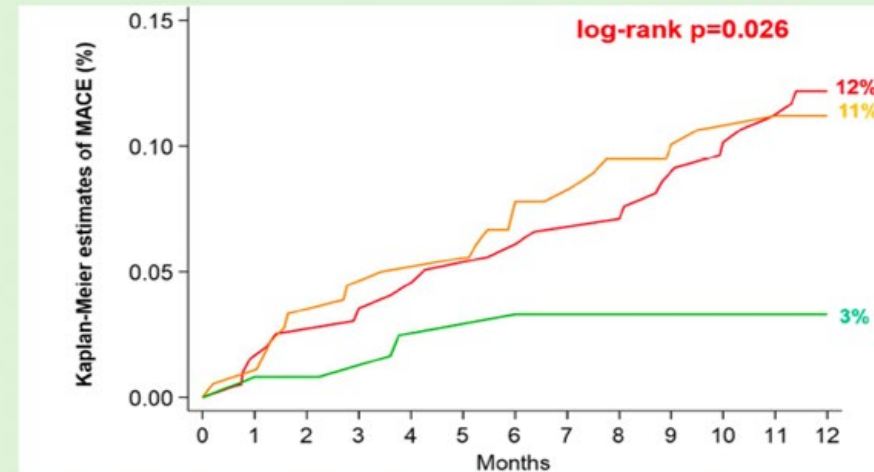
Primary Laboratory Endpoint

Prevalence of patients who achieved LDL-C goal in at least one visit during follow-up



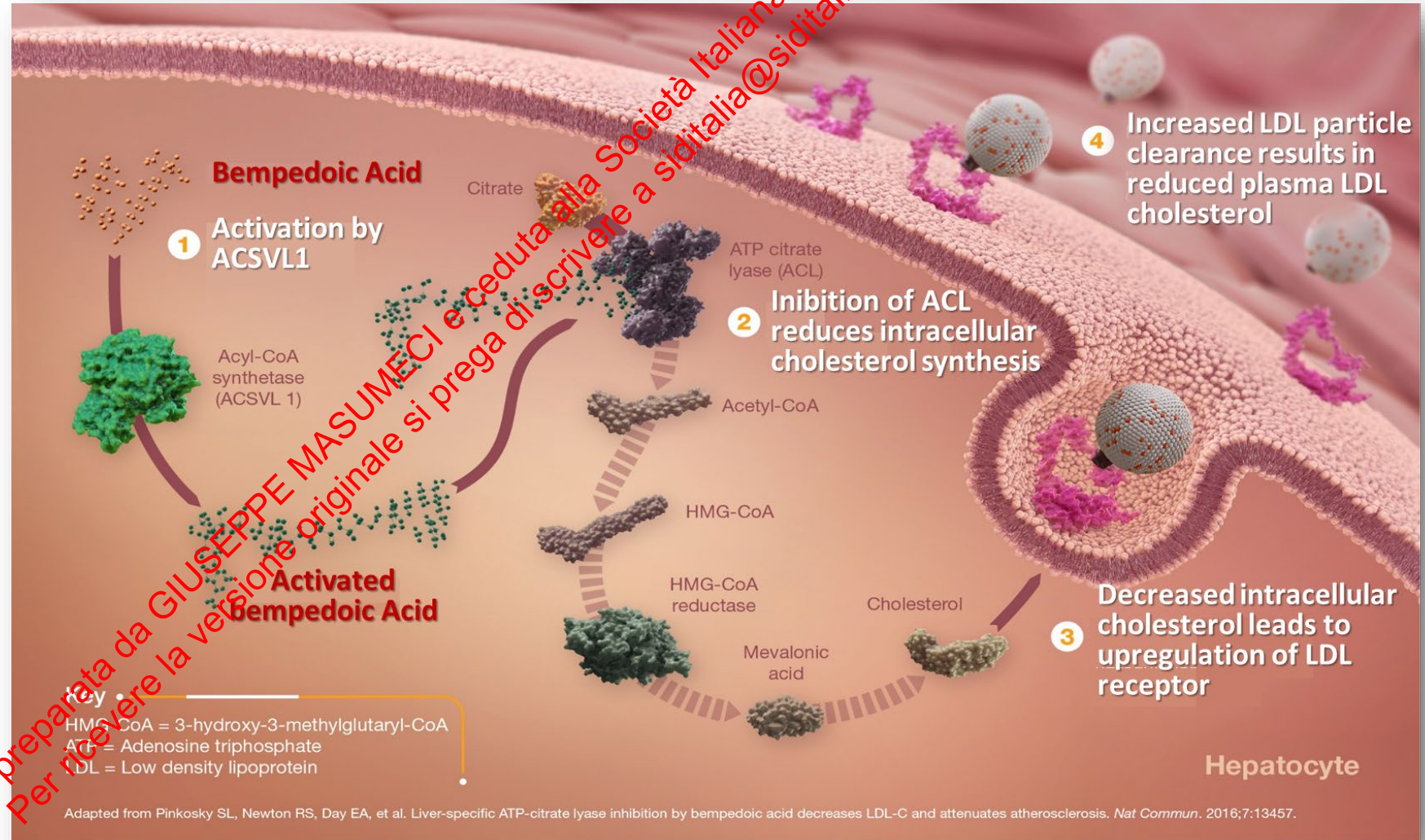
Primary Clinical Endpoint

Kaplan-Meier curves for the incidence of MACE at one year in the three periods

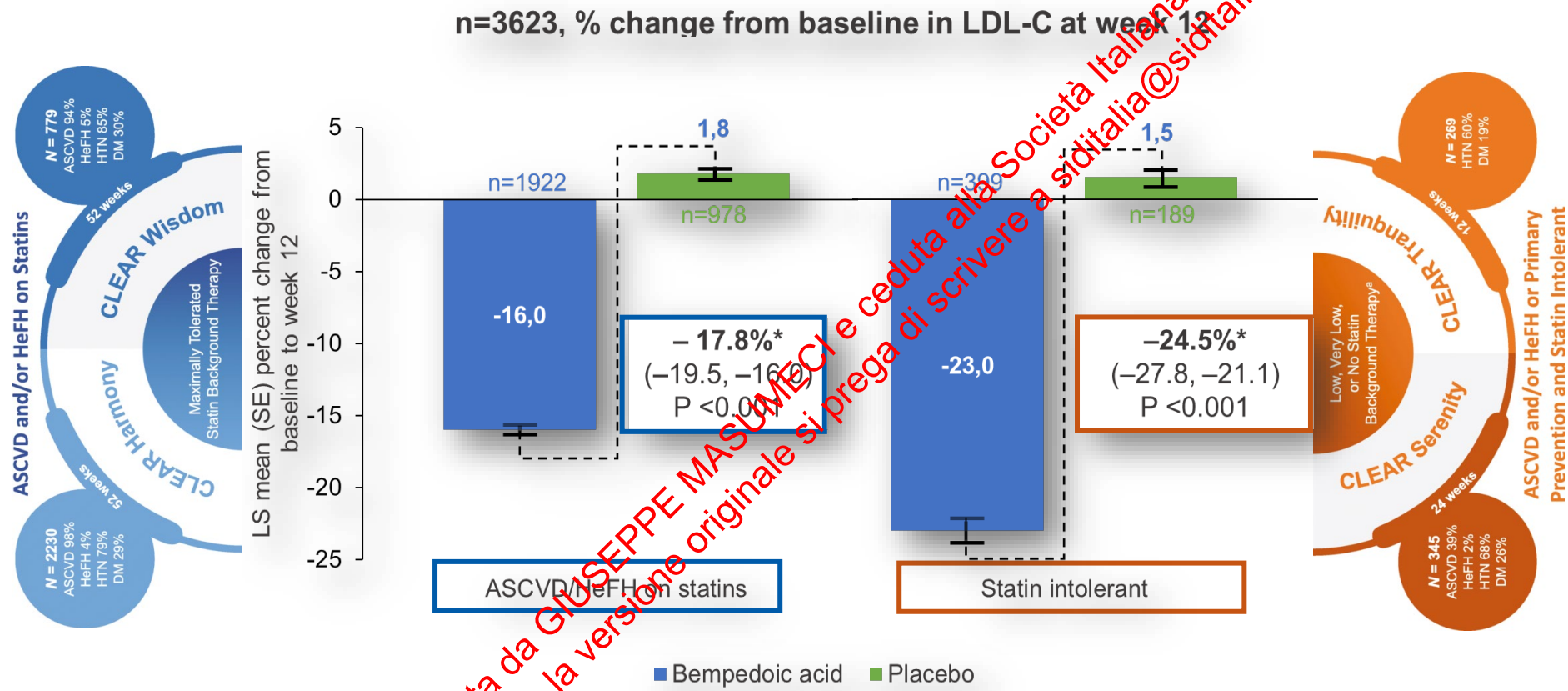


Il meccanismo d'azione unico dell'acido bempedoico è complementare ma distinto da quello delle statine e delle altre LLT

- Attivato principalmente a livello epatico, l'acido bempedoico inibisce l'enzima ATP citrato liasi (ACL) nella ben nota via di sintesi del colesterolo, a monte rispetto al target delle statine
- La conseguente sovra-regolazione dei recettori per le LDL determina un'aumentata captazione di LDL da parte delle cellule epatiche con relativa riduzione dei livelli plasmatici di C-LDL



L'Acido Bempedoico ha dimostrato di ridurre LDL in un ampio spettro di pazienti





Paziente intollerante alla terapia con statine



In CLEAR Outcomes, 13,970 patients at high or very high risk, primary and secondary prevention, unwilling or unable to take a statin were randomised to bempedoic acid or placebo



At 6 months, bempedoic acid reduced LDL-C from a baseline of 139.0 mg/dL by a mean of 29.2 mg/dL (21.1%), compared with placebo



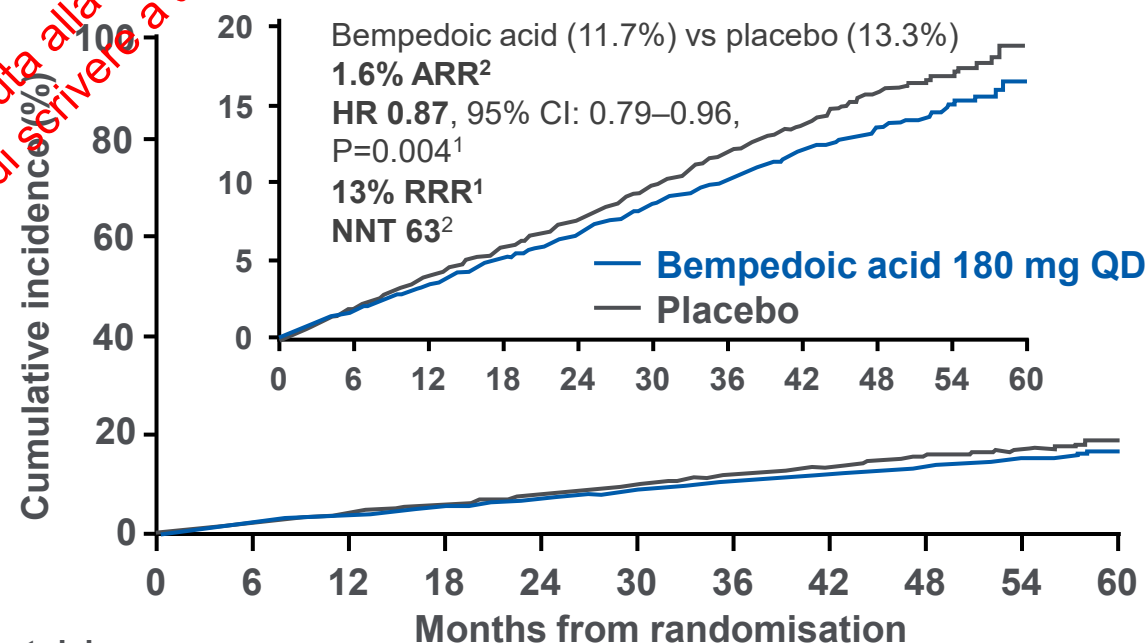
Treatment with bempedoic acid reduced 4-component MACE, 3-component MACE (non)-fatal MI, and coronary revascularisation compared with placebo



Bempedoic acid was well tolerated, with similar overall rates of adverse events, serious adverse events, or adverse events leading to drug discontinuation, compared with placebo

CLEAR Outcomes

4-component MACE*



No. at risk

Placebo	6978	6779	6579	6401	6206	5995	5105	2524	1207	513	55
Bempedoic acid	6992	6816	6654	6472	6293	6106	5257	2601	1240	556	74

4-component MACE, CV death, nonfatal MI, nonfatal

*The primary efficacy endpoint is the time to first occurrence of an adjudicated event of 4-component MACE.

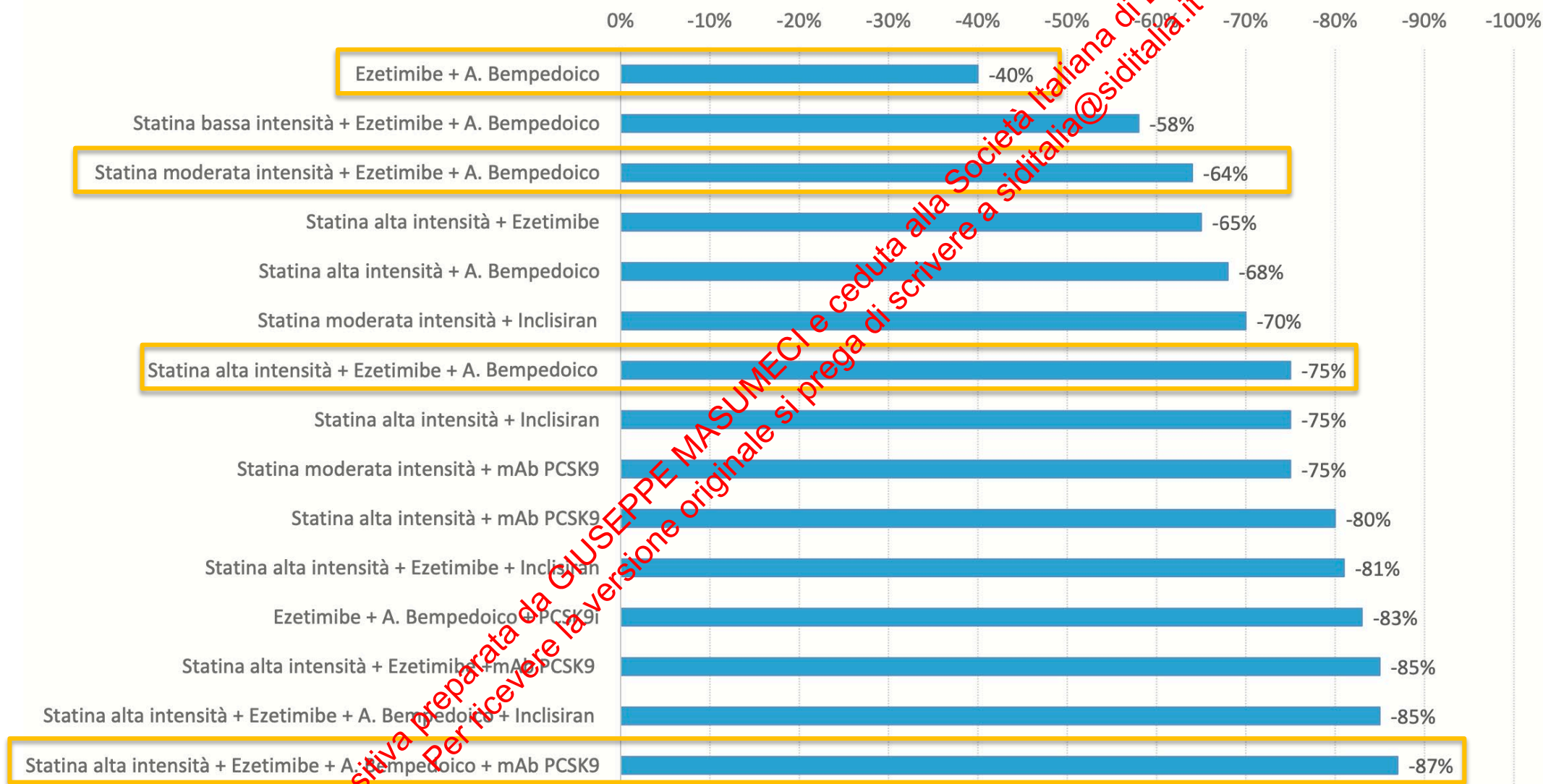
stroke, or coronary revascularisation;

3-component MACE, CV death, nonfatal MI, or nonfatal stroke. ARR, absolute risk reduction; CI, confidence interval; HR, hazards ratio;

LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction; QD, once daily

1. Nissen SE, et al. N Engl J Med. 2023;388:1353–1364; 2. Banach M, et al. Prog Cardiovasc Dis. 2023;S0033-0620(23)00026-9

Riduzioni di C-LDL attese con le diverse combinazioni delle terapie ipolipemizzanti



Raccomandazioni per l'uso di Acido Bempedoico nella Pratica Clinica in Piemonte: il progetto Clear Path



Paziente intollerante alla terapia con statine



Paziente a rischio cardiovascolare
Moderato, Alto e Molto Alto



Paziente Diabetico



Paziente Anziano



Paziente con SCA e c-LDL < 140 mg/sl,
senza fattori di rischio aggiuntivo



Paziente sottoposto a PCI elettiva,
senza storia di eventi CV acuti recenti



Paziente con Sindrome Coronarica Cronica



Paziente con storia di Ictus Ischemico
non cardioembolico
e/o Arteriopatia Carotidea



Paziente con Arteriopatia Periferica

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@sidiitalia.it

Raccomandazioni dei Panelist per l'uso di Acido Bempedoico nella Pratica Clinica



Paziente intollerante alla terapia con statine



Paziente a rischio cardiovascolare
Moderato, Alto e Molto Alto,
senza storia di eventi CV



Paziente Diabetico



Paziente Anziano



Paziente con SCA e c-LDL < 140 mg/dl,
senza fattori di rischio aggiuntivo



Paziente sottoposto a PCI elettiva,
senza storia di eventi avversi CV



Paziente con Sindrome Coronarica Cronica



Paziente con storia di Ictus Ischemico
non cardioembolico
e/o Arteriopatia Carotidea



Paziente con Arteriopatia Periferica

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

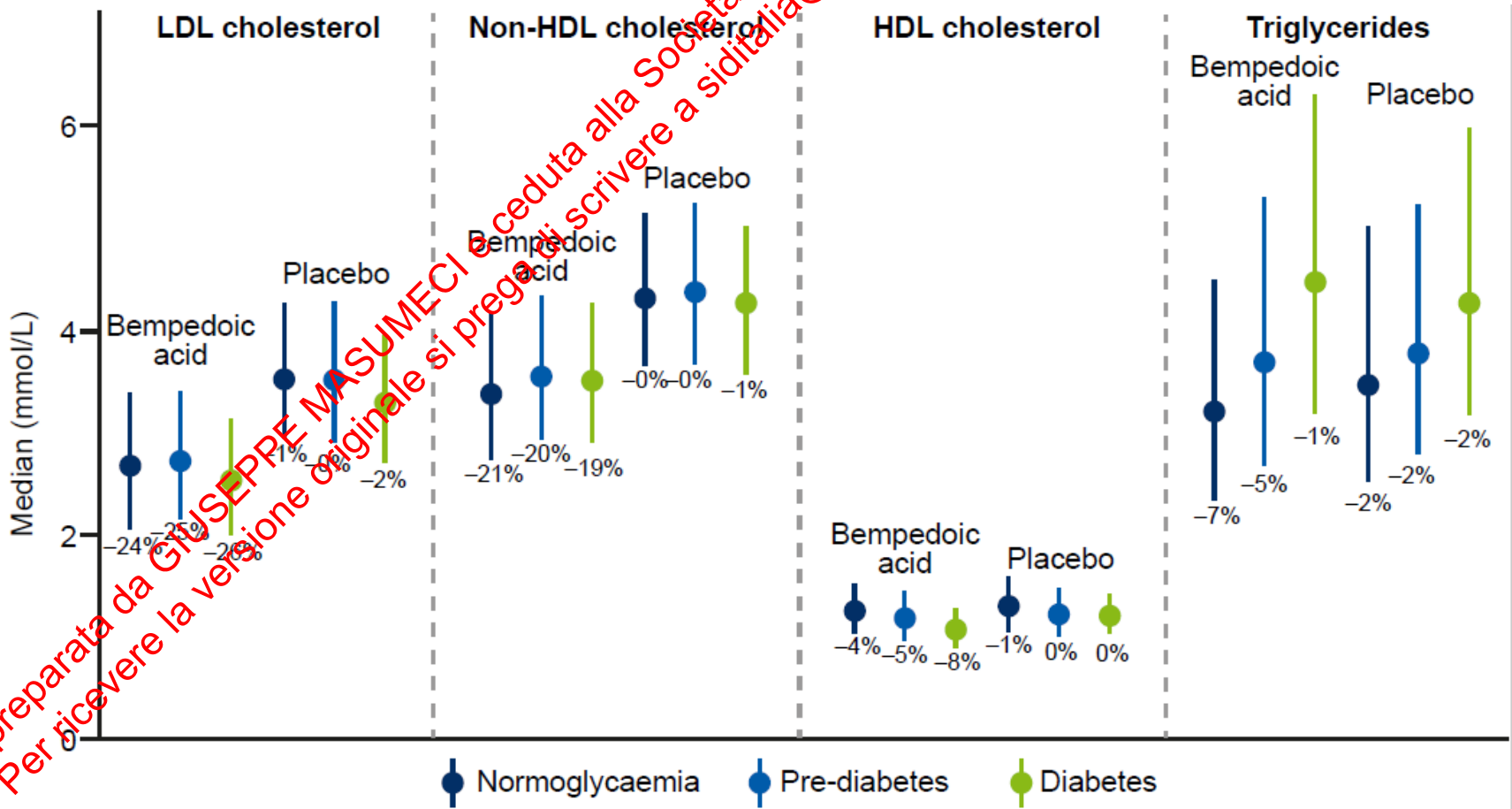


Paziente Diabetico

Clear Outcomes At Six Months
LDL-C and Non-HDL-C
Reductions with BA Were Similar
Across Glycaemia Strata

Reduction in LDL-C

- Diabetes -24%
- Pre-diabetes -25%
- Normoglycaemia -26%

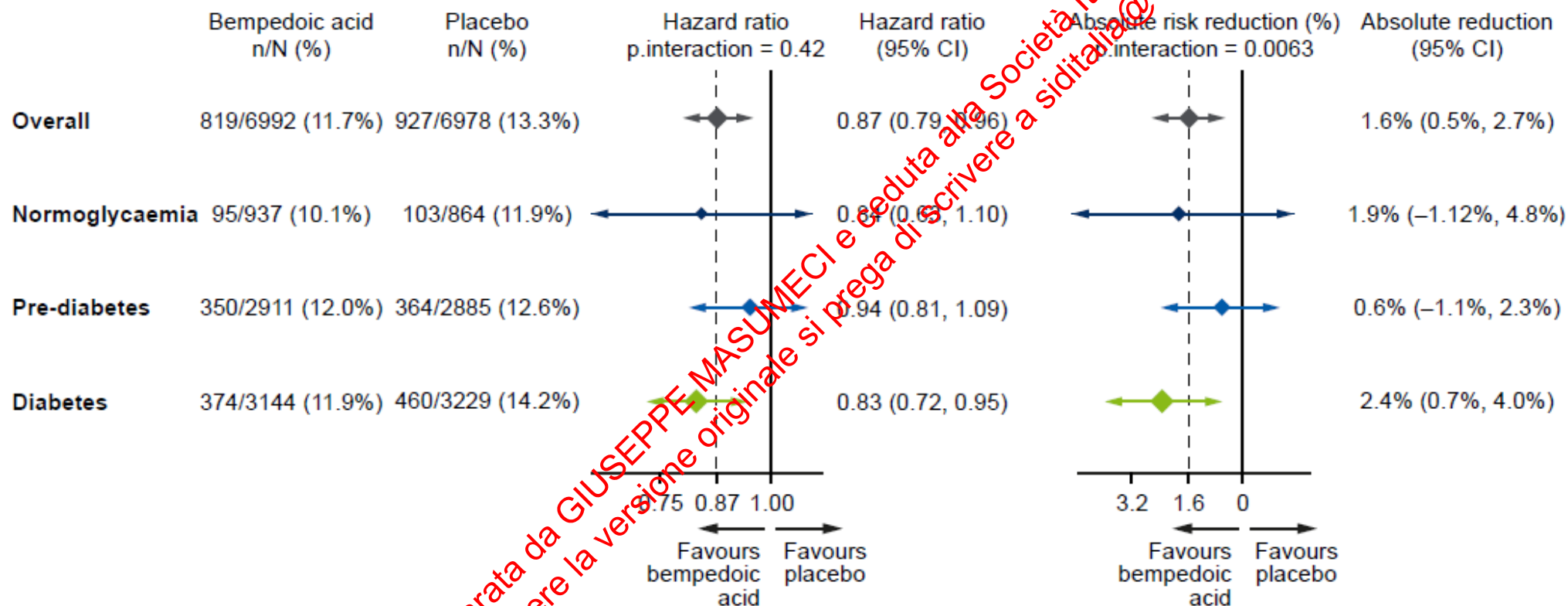


Error bars are IQRs. Median within-patient percentage changes from baseline. BA, bempedoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Presented on 26 August as a late-breaker oral presentation at ESC 2023, Amsterdam, Netherlands



Paziente Diabetico

BA Provided Similar Relative but Greater Absolute Benefits on 4-Component MACE in Those With DM



ARR with BA was higher in patients with **diabetes** (ARR: 2.4%) compared to patients with **pre-diabetes** (ARR: 0.6%) and **normoglycaemia** (ARR: 1.9%)



Paziente Diabetico

Acido Bempedoico – dati di sicurezza nel paziente diabetico
Nessun aumento di AE nell'acido bempedoico rispetto al placebo sia negli studi di fase III che nel Clear Outcomes



Il diabete mellito di nuova insorgenza è risultato numericamente inferiore nel gruppo dell'acido bempedoico rispetto al placebo in tutti i pazienti senza diabete e si è mantenuto più basso in quelli ulteriormente classificati con prediabete o normoglicemia al basale.

Adverse Event	BA n (%)	Placebo n (%)
At least 1 serious AE	1767 (25.2)	1733 (24.9)
At least 1 AE leading to IMP discontinuation	759 (10.8)	722 (10.4)
Myalgia	393 (5.6)	471 (6.8)
New onset diabetes	621 (16.1)	640 (17.1)
Gout/gouty arthritis	na (3.2)	na (2.2)
Discontinuation of study due to gout	8 (0.1)	2 (<0.1)
Elevated hepatic enzymes	317 (4.5)	209 (3.0)
Renal impairment	802 (11.5)	599 (8.6)
Cholelithiasis	152 (2.2)	81 (1.2)

AE, adverse events; BA, bempedoic acid; IMP, investigational medicinal product; SMQ, standardised medical query

Nissen S E et al N Engl J Med 2023; DOI: 10.1056/NEJMoa2215024
Bays HE, et al. J Clin Lipidol. 2023; S1933–2874(23)00313–6

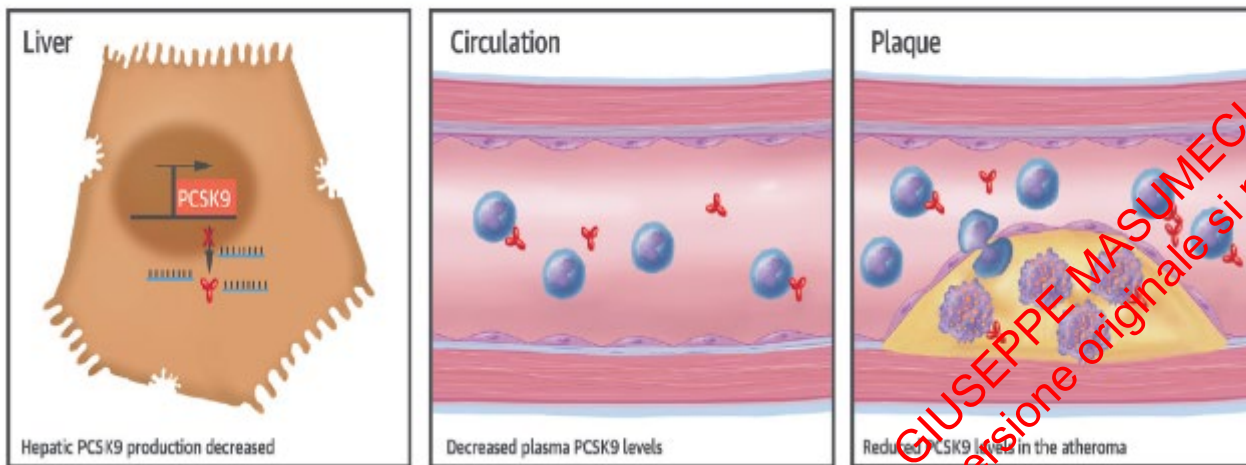
The Evolving Future of PCSK9 Inhibitors

Robert S. Rosenson, MD,^a Robert A. Hegele, MD,^b Sergio Fazio, MD, PhD,^c
Christopher P. Cannon, MD^d



Inclisiran previene la sintesi dei PCSK9 a livello epatico

siRNA Blocking PCSK9 Transcription

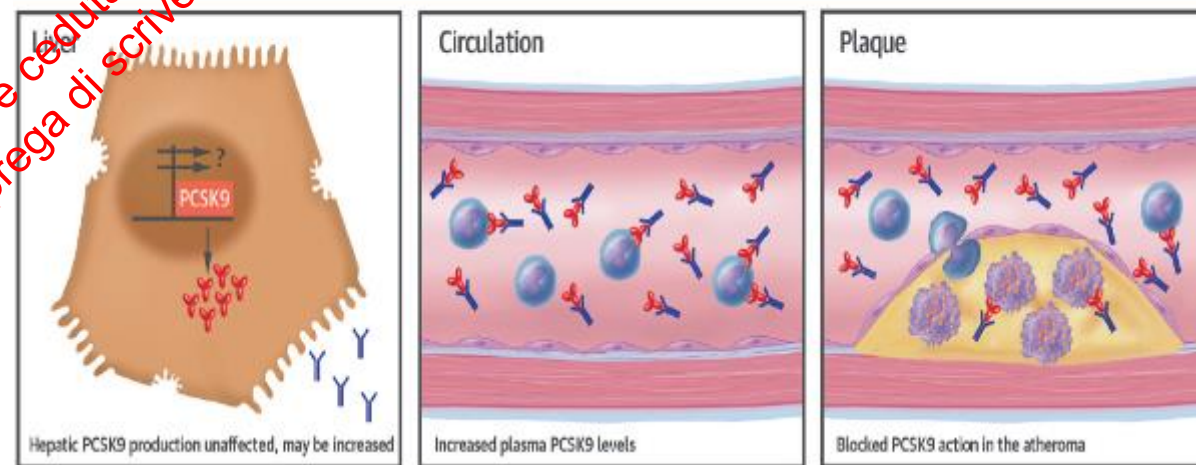


Inclisiran cliva l'mRNA del PCSK9 nel fegato, prevenendone la produzione

I livelli di PCSK9 in circolo e a livello dell'ateroma vengono ridotti

I mAbs bloccano la PCSK9 a livello plasmatico

Monoclonal Antibody Blocking Plasma PCSK9



I mAbs anti PCSK9 non alterano la produzione epatica della proteina ma agiscono inibendone la funzione

I mAbs anti PCSK9 legano la proteina a livello circolatorio e dell'ateroma. I livelli di PCSK9 in circolo aumentano

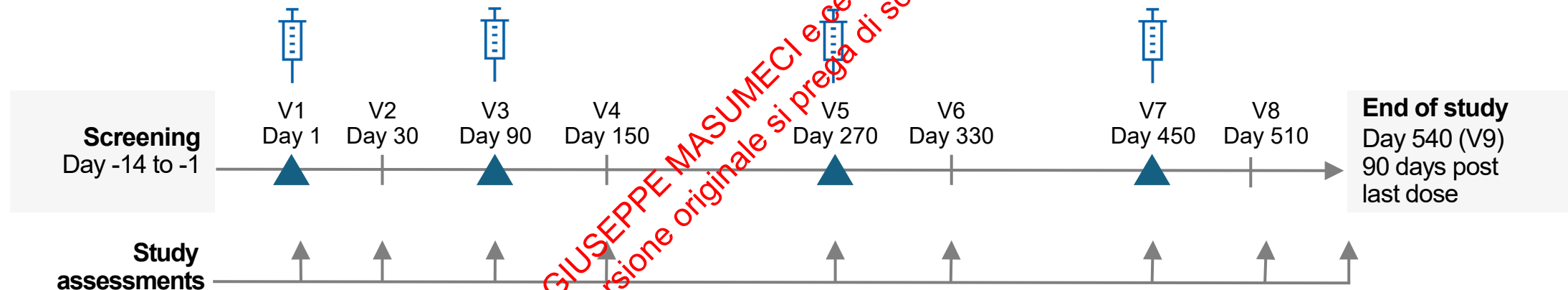
PCSK9i= proprotein convertase subtilisin/kexin type 9 inhibition.

1. Rosenson RS et al. *J Am Coll Cardiol*. 2018;72(3):314-329.
2. Khvorova A. *N Engl J Med*. 2017;376(1):4-7.

ORION 9, 10, 11: Study design and endpoints ¹⁻⁴

18-month, double-blind, randomized, placebo-controlled

Randomized 1:1 inclisiran 300 mg* vs placebo—on top of maximally tolerated statin dose



*300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.

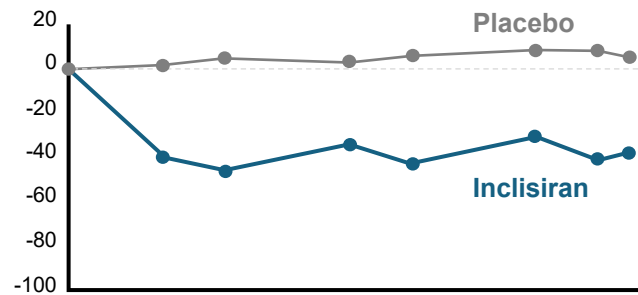
1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530. 2. Raal FJ, et al. [supplementary appendix] *N Engl J Med.* 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805. 3. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519. 4. Ray KK, et al. [supplementary appendix] *N Engl J Med.* doi: 10.1056/NEJMoa1912387.

ORION 9-10-11: extended reduction of LDL-C for 18 months.

LDL-C Percent change from baseline

ORION^{1,3}

9



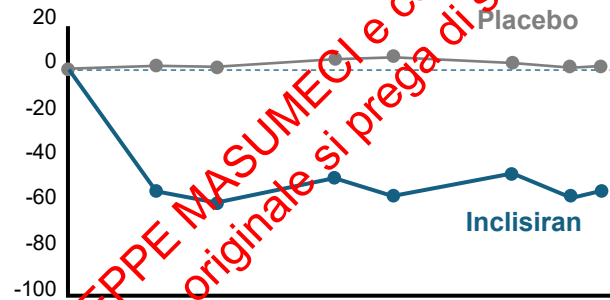
Between group difference

-47,9%

(P<0,001)

ORION^{2,4}

10



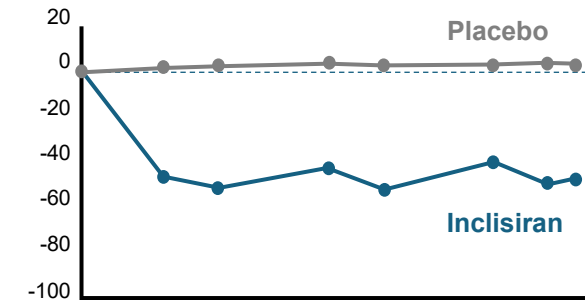
Between group difference

-52,3%

(P<0,001)

ORION^{2,4}

11



Between group difference

-49,9%

(P<0,001)

1. Raal FJ, et al. N Engl J Med. 2020;382(16):1520-1530. 2. Ray KK, et al. N Engl J Med. 2020;382(16):1507-1519.
3. Raal FJ, et al. [supplementary appendix]. N Engl J Med. 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805.
4. Ray KK, et al. [supplementary appendix]. N Engl J Med. doi: 10.1056/NEJMoa1912387

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Linee Guida ESC/EAS 2019: Pazienti con SCA, PAD, CAD, ICTUS sono classificati come pazienti a **rischio cardiovascolare molto alto**

ASCVD DOCUMENTATA CLINICAMENTE O TRAMITE IMAGING

SCA

RIVASCULARIZZAZIONE CORONARICA

ICTUS O TIA

PAD

ASCVD DOCUMENTATA TRAMITE IMAGING

PLACCA RILEVANTE ALL'ANGIOGRAFIA CORONARICA, O ALLA TAC (MALATTIA CORONARICA MULTIVASALE, CON DUE ARTERIE EPICARDICHE PRINCIPALI CON STENOSI >50%) O ALL'ULTRASONOGRAFIA CAROTIDEA.

DIABETE MELLITO (DM) CON DANNO D'ORGANO (MICROALBUMINURIA, RETINOPATIA, NEUROPATIA) O ALMENO 3 FATTORI DI RISCHIO CV, O DM DI TIPO 1 COMPARSO PRECOCEMENTE E PRESENTE

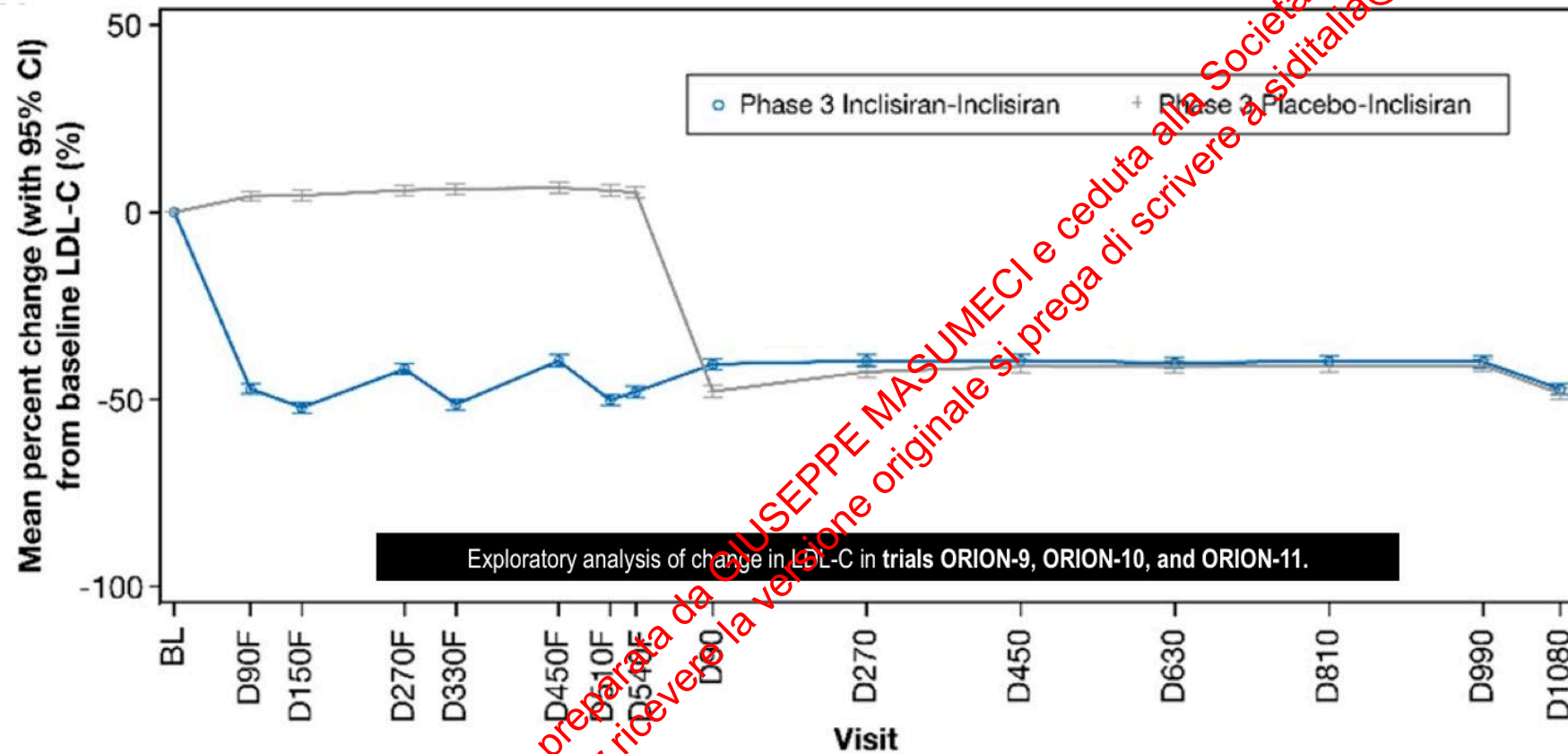
SCORE $\geq 10\%$ PER IL RISCHIO A 10 ANNI DI CVD FATALE

IPERCOLESTEROLEMIA FAMILIARE CON ASCVD O UN ALTRO FATTORE DI RISCHIO CV

RISCHIO CV MOLTO ALTO

ORION 8: long term efficacy

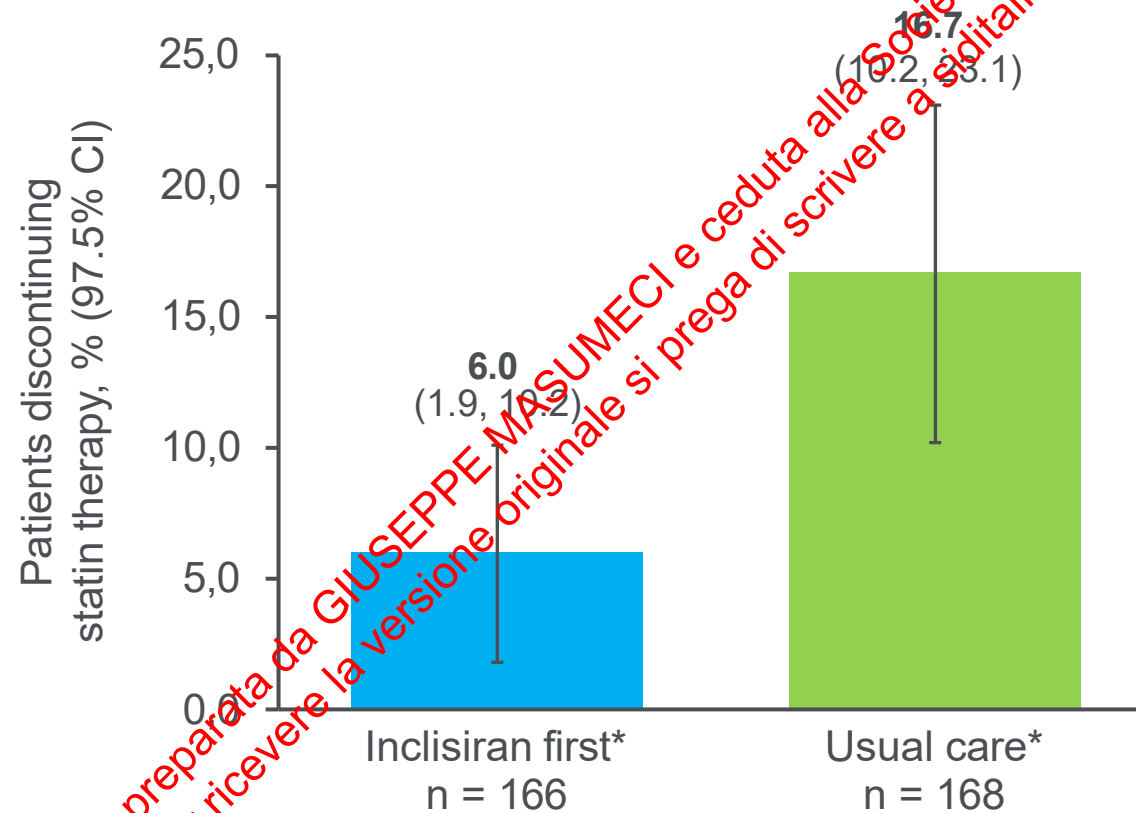
Cardiovascular Research (2024) **120**, 1400–1410



VICTORION-INITIATE Randomized Trial

Co-primary endpoint: statin discontinuation

The non-inferiority margin (15%) met comparing “inclisiran first” and usual care (-10.6% [97.5% CI: -18.3% , -3.0%])



*Only patients without a history of statin intolerance.
CI, confidence interval.



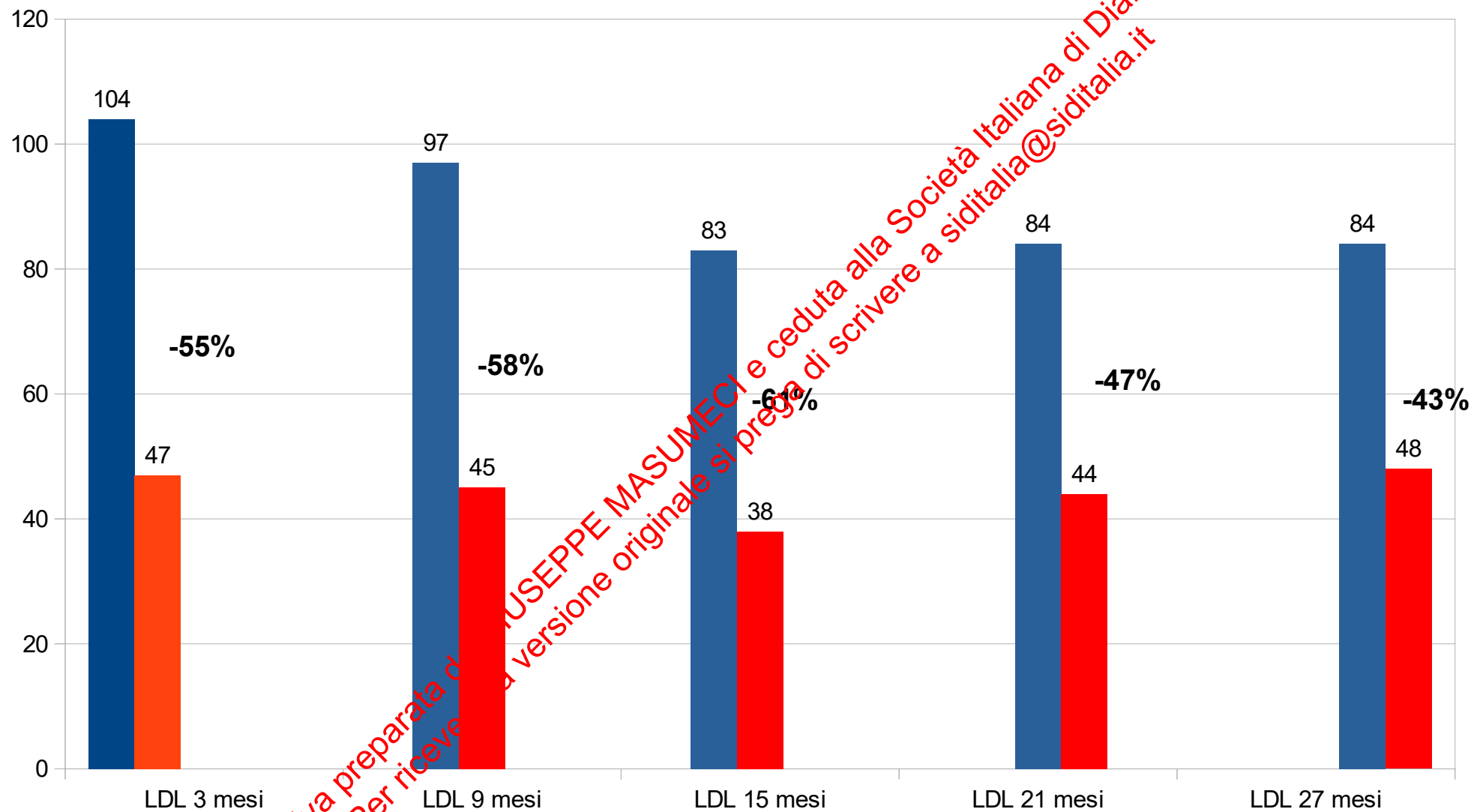
A. O. ORDINE
MAURIZIANO
TORINO



- Paziente con SCA o PCI elettiva in terapia con Statine ed Ezetimibe ed LDL ≥ 70 mg/dl
Aggiunge I-PCSK9 alla dimissione
- Paziente con SCA o PCI elettiva in terapia con Statine ed LDL ≥ 70 mg/dl
Aggiunge Ezetimibe, Acido Bempedoico ed I-PCSK9 alla dimissione
- Paziente con SCA o PCI elettiva naïve da Statine con LDL ≥ 55 mg/dl ed < 140 mg/dl
Aggiunge combinazione Statine ed Ezetimibe ed Acido Bempedoico alla dimissione e controllo a un mese per valutare I-PCSK9
- Paziente con SCA o PCI elettiva naïve da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV
Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione



Pazienti Totali	71
Maschi	65%
Morte per cause non CV	2 (2,8%)
Fallimento Terapeutico (LDL non a target)	4 (5,6%)
Drop Out	4 (5,6%)
Terapia ipolipemizzante di associazione	
Statina + ezetimibe + acido bempedoico	7 (9%)
Statina + ezetimibe	38 (54%)
Statina + acido bempedoico	1 (1%)
Acido bempedoico + ezetimibe	8 (12%)
Solo ezetimibe	5 (7%)
Nessuna terapia ipolipemizzante	12 (17%)



Conclusioni

- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ L'aggiunta degli I-PCSK9 determina un'ulteriore riduzione dei livelli di LDL e un conseguente miglioramento della prognosi ed è raccomandata in Classe I
- ✓ L'aggiunta degli I-PCSK9 in fast-track (in-H dimissione) è raccomandata nei pazienti ACS o eventi CV multipli già in terapia con statine e LDL ≥ 70 mg/dl e nei pazienti ACS naive da statine ed LDL ≥ 140 mg/dl in particolare se a rischio proibitivo (DM, MV, PAD, recidivanti)
- ✓ Applicando linee guida e fast track circa il 25% dei pazienti con ACS dovrebbero ricevere I-PCSK9 alla dimissione ma purtroppo attualmente i pazienti sono sottotrattati

Conclusioni

- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ Il paziente trattato con angioplastica elettiva è un paziente very high risk
- ✓ Ridurre il colesterolo LDL nel paziente very high risk ci permette di arrestare la progressione della placca e prevenire gli eventi avversi cardiovascolari acuti
- ✓ L'aggiunta degli inibitori del PCSK9 determina un'ulteriore riduzione dei livelli di LDL e un conseguente miglioramento della prognosi ed è raccomandata in Classe I
- ✓ Inclisiran con le sue caratteristiche di somministrazione, efficacia e sicurezza potrebbe essere ideale nel paziente elettivo garantendo il raggiungimento del target e l'aderenza terapeutica

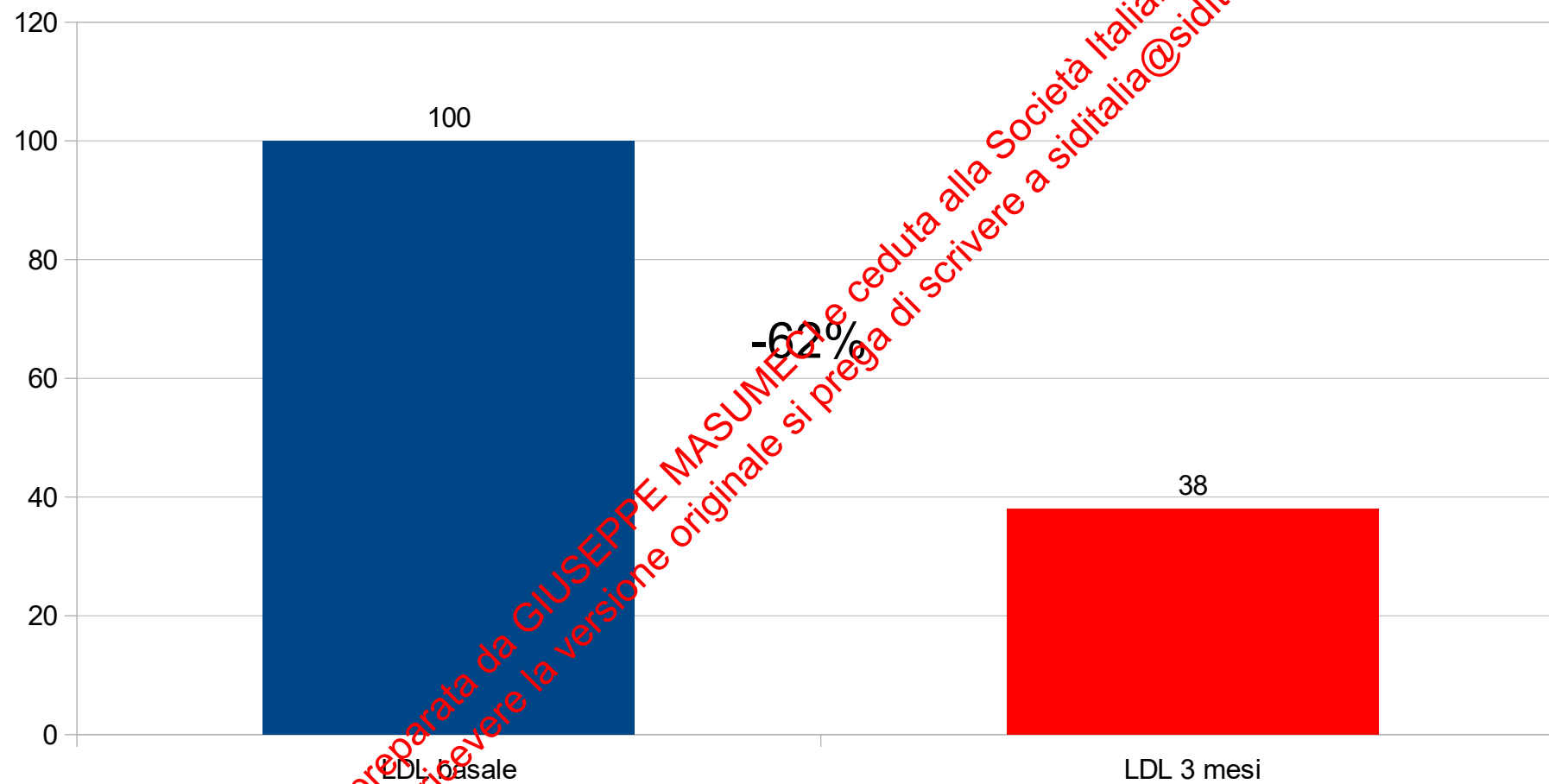
Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Conclusioni

- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ L'acido bempedoico si è dimostrato in grado di ridurre in maniera significativa i livelli di C-LDL, sia in aggiunta alla massima dose di statina tollerata sia in pazienti con intolleranza alle statine, con un effetto ancora maggiore quando utilizzato in combinazione con l'ezetimibe.
- ✓ **L'acido bempedoico ha un meccanismo d'azione complementare rispetto all'ezetimibe.**
L'associazione di acido bempedoico ed ezetimibe ha il vantaggio di ridurre significativamente i livelli di C-LDL senza aumentare il rischio di eventi avversi.
- ✓ L'acido bempedoico in triplice terapia con ezetimibe e atorvastatina 20mg ha permesso di ottenere i valori di C-LDL raccomandati dalle linee guida in più del 90% dei pazienti arruolati, con oltre il 95% dei pazienti che ottiene una riduzione dei livelli di C-LDL >50%

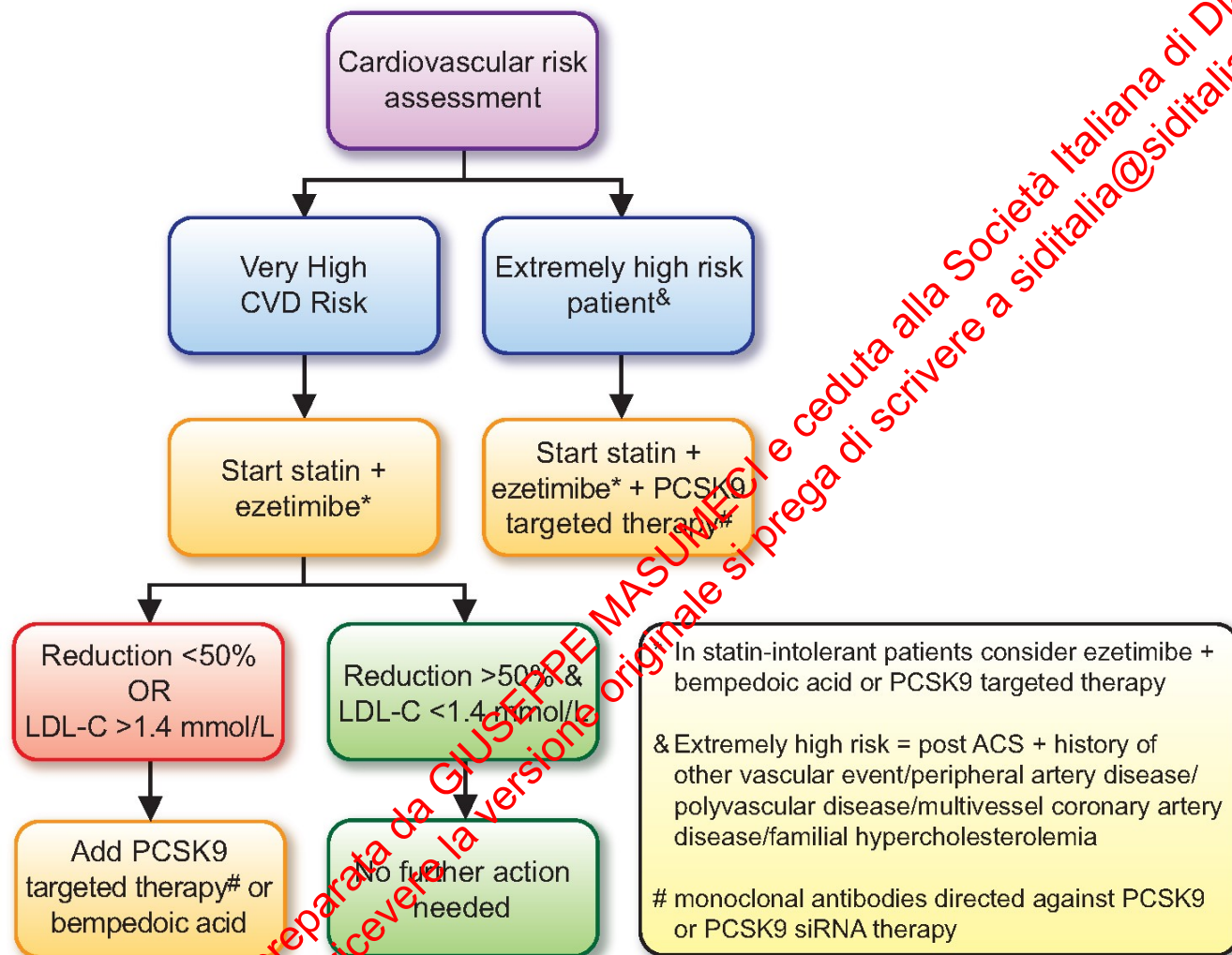
Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

34 pazienti con statina



Diapositiva preparata da GIUSEPPE MASUMEDIO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Combination lipid-lowering therapy as first line strategy in very high-risk patients



Cardiovascular risk categories: clinical assessment

Very-high-risk

People with any of the following:

Documented ASCVD, either clinical or unequivocal on imaging.

Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CTA scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound.

DM with target organ damage, ≥3 major risk factors or early onset of

T1DM of long duration (>20 years).

Severe CKD (eGFR <30 mL/min/1.73 m²).

FH with ASCVD or with another major risk factor.

A calculated SCORE ≥10% for a 5-year risk of fatal CVD.

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8–3.5 mmol/L (70–135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓

Changes in recommendations (3)



ESC
European Society
of Cardiology

2016	2019
Pharmacological LDL-C lowering	Pharmacological LDL-C lowering
In patients at very-high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
	For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.



A. O. ORDINE
MAURIZIANO
TORINO



- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL ≥ 70 mg/dl
Aggiunge I-PCSK9 alla dimissione
- Paziente con SCA in terapia con Statine ed LDL ≥ 70 mg/dl
Aggiunge Ezetimibe ed I-PCSK9 alla dimissione
- Paziente con SCA naive da Statine con LDL ≥ 70 mg/dl ed < 140 mg/dl
Aggiunge combinazione Statine ed Ezetimibe alla dimissione e controllo a un mese per valutare I-PCSK9
- Paziente con SCA naive da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV
Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

VICTORION-INITIATE Randomized Trial

VICTORION-INITIATE (NCT04929249): prospective, randomized, open-label, Phase 3b trial that evaluated an “inclisiran first” (i.e. adding inclisiran immediately if patients fail to reach LDL-C <70 mg/dL on maximally tolerated doses of statins) implementation strategy compared with usual care in patients with ASCVD in representative US clinical settings



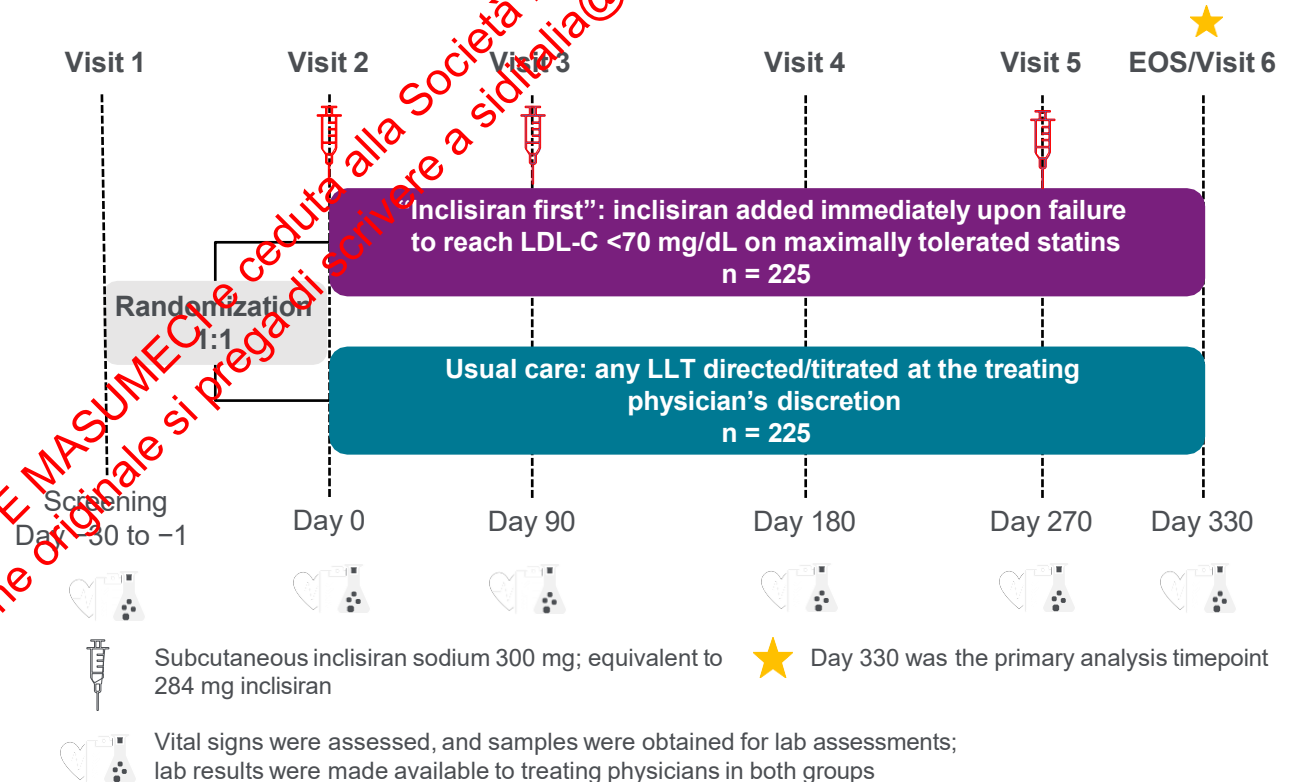
Population

- Adults ≥ 18 years of age with a history of ASCVD*
- LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL and fasting triglycerides <500 mg/dL
- Receiving maximally tolerated statin therapy† or had documented statin intolerance‡



Setting and procedures

- 45 sites selected from diverse settings
- Stratification by baseline health insurance status
- Study physician oversight without interference in lipid management beyond “inclisiran first” administration
- Managing physicians were provided lipid results and encouraged to follow AHA/ACC/Multisociety guidelines¹ and add therapies at their discretion



*Coronary heart disease, cerebrovascular disease, or peripheral artery disease. †Maximally tolerated statin therapy was determined by the investigator; no immediate plans to modify LLT were permitted.

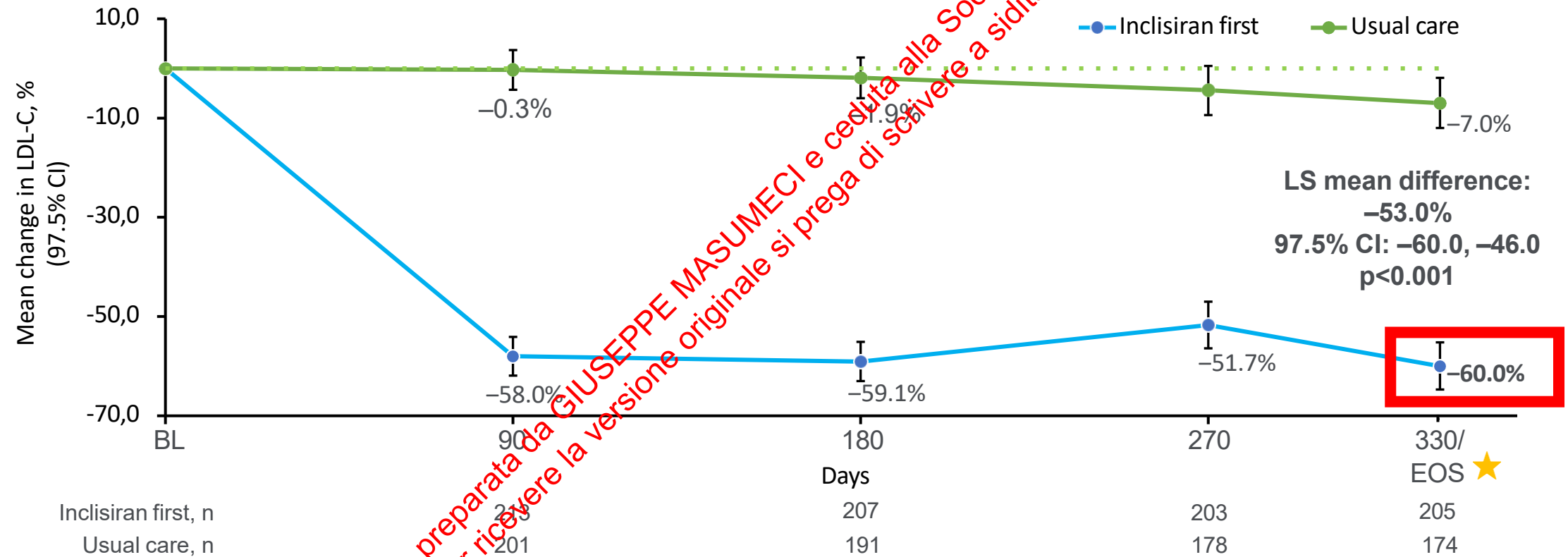
‡Documented side effects on ≥ 2 different statins, including one at the lowest standard dose.

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; EOS, end of study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; US, United States.

1. Grundy SM, et al. Circulation. 2018;139(10):1082–1143.

Co-primary endpoint: percent change in LDL-C

At Day 330/EOS the mean percent change in LDL-C from baseline was -60.0% (97.5% CI: -64.7, -55.2) with "inclisiran first" and -7.0% (97.5% CI: -12.0, -1.9) with usual care

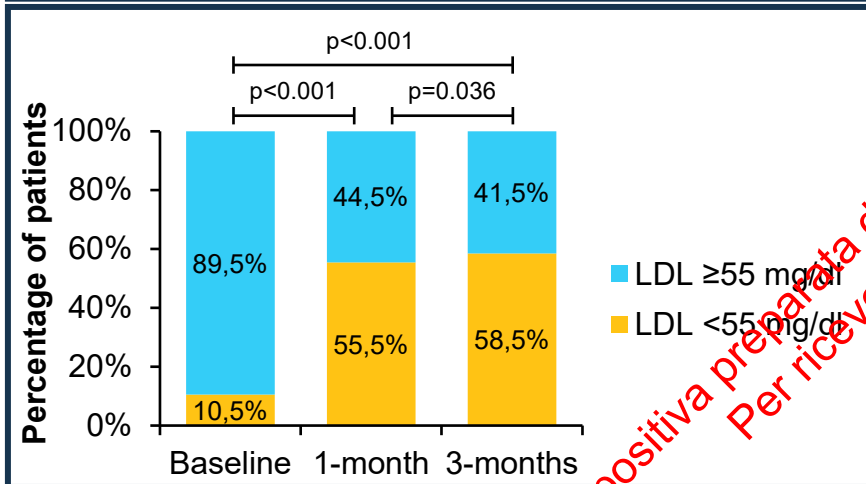
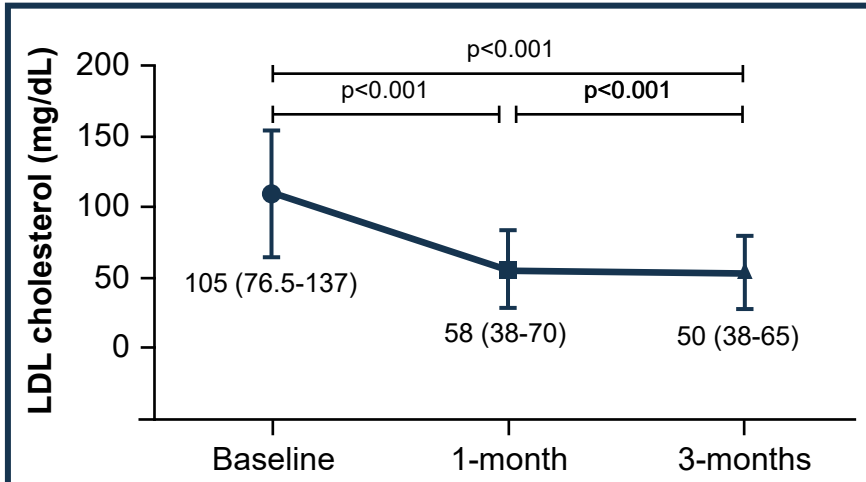


★ Day 330 is the primary analysis timepoint. The dotted line represents baseline LDL-C.
BL, baseline; CI, confidence interval; EOS, end-of-study; LDL-C, low-density lipoprotein cholesterol; LS, least squares.

Target LDL cholesterol level in patients with ACS undergoing PCI: The JET-LDL REGISTRY



A multicenter, prospective, real-world data collection carried out during a 3-month (2022) period including consecutive ACS pts undergoing PCI at 95 Italian hospitals

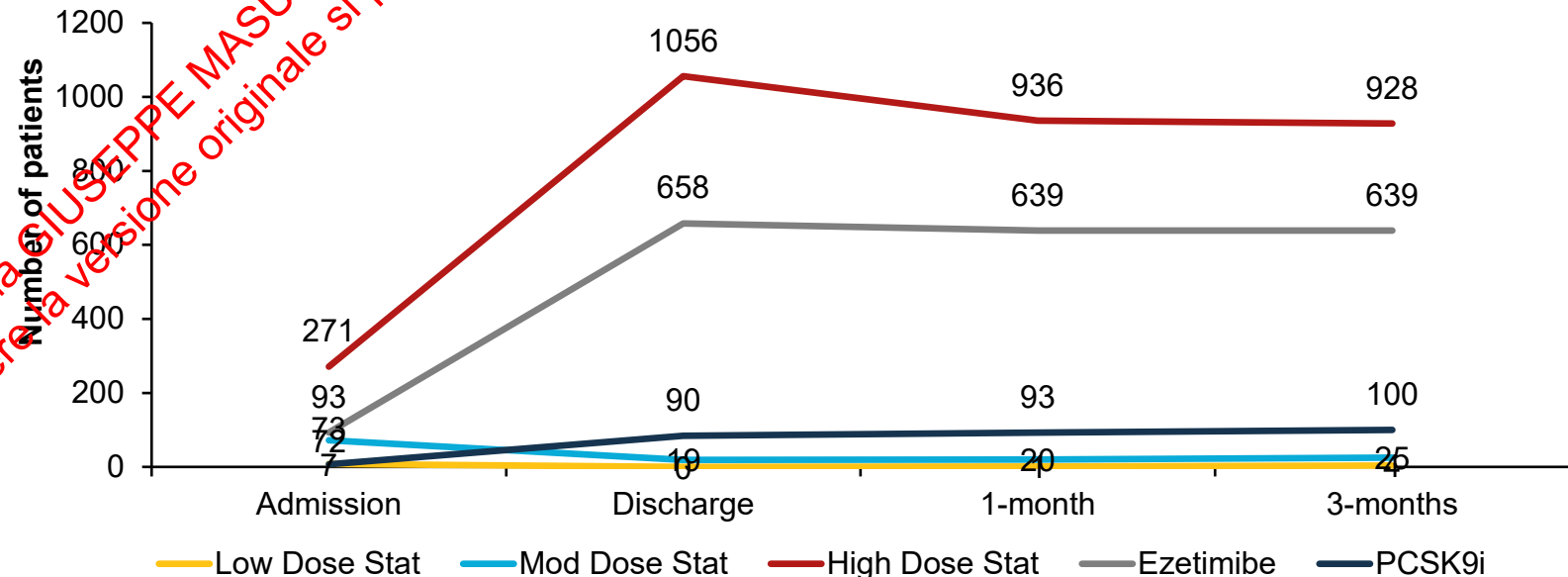


LDL 55 mg/dL = 1.4 mmol/L

ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); PCI, percutaneous coronary intervention; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

Ferlini M, et al. and G. Musumeci Int J Cardiol. 2024;397:131659

- A total of 1095 patients were included
- At hospital discharge, 442 patients (40%) received statin monotherapy, 547 (50%) statin plus ezetimibe and 90 a PCSK9i (8.5%)
- At 1 month, LDL-C was at recommended target levels in 55.5% of patients, but PCSK9i prescription was not significantly increased



Editorial

Optimizing LDL-cholesterol management in ACS patients: Breaking inertia and implementing intensified therapies

Luis Ortega-Paz^a, Marc Bonaccio,

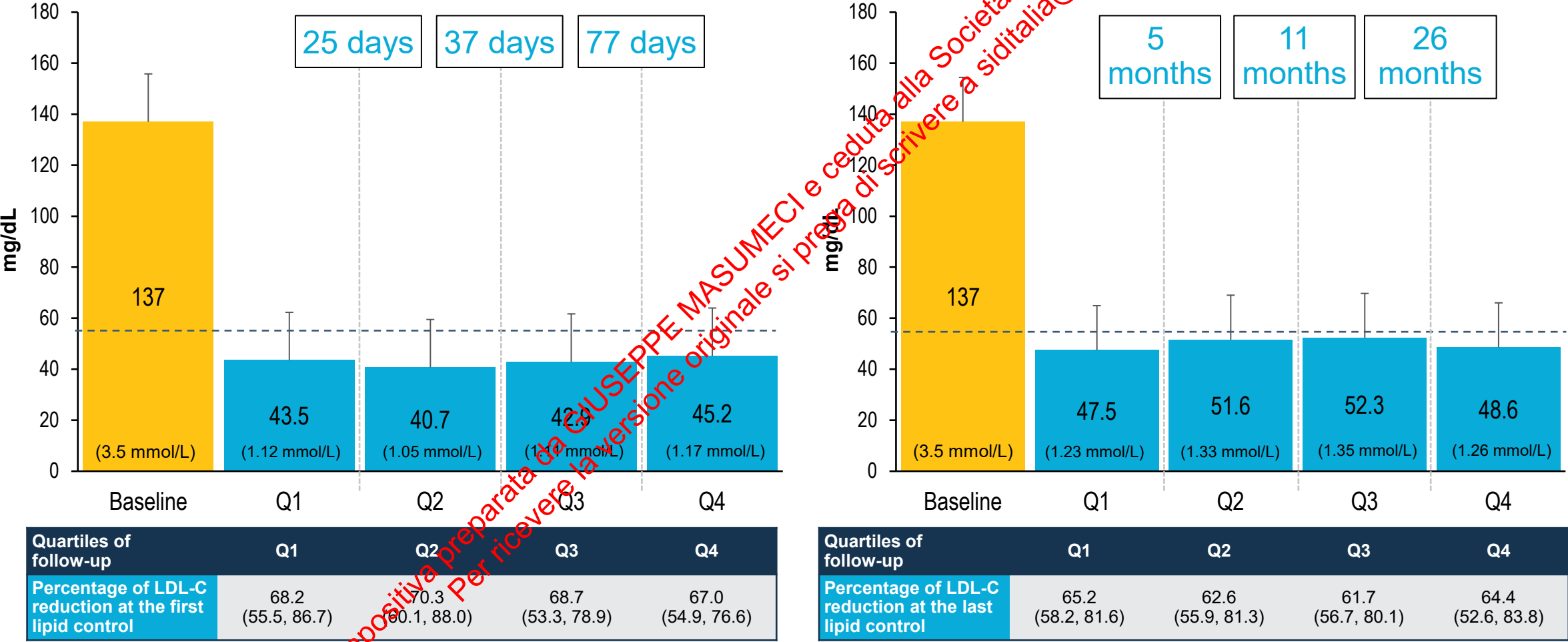
Dominick J. Angiolillo^a  

The extensive body of evidence revealing the low compliance with current recommendations for LDL-C optimization in patients with ACS should serve as a call to action. The cardiovascular community, healthcare administrators, and policymakers must rise to the occasion and promptly offer specific solutions to known barriers. A key takeaway for practitioners is to break the therapeutic inertia and implement early intensified lipid-lowering therapy early (i.e., during the inpatient recovery phase). Given the consistent data showing that lower LDL levels correlate with better outcomes, it is reasonable to consider the immediate initiation of PCSK9 inhibition following a myocardial infarction (MI). This approach is being investigated in the EVOLVE MI trial (NCT05284747). As coined by several ESC associations:

Strike early and strike strong!

Effects of the strike early-strike strong lipid lowering strategy with PCSK9i in patients with ACS. A real-world evidence from the AT-TARGETIT registry

771 ACS patients treated with PCSK9i prescription during hospitalization or at discharge in 22 Italian centres



ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q, quartile
P. Gargiulo, G. Musumeci, P. Fillardi et al. Eur J Prev Cardiol. 2024 May 24:zwae170

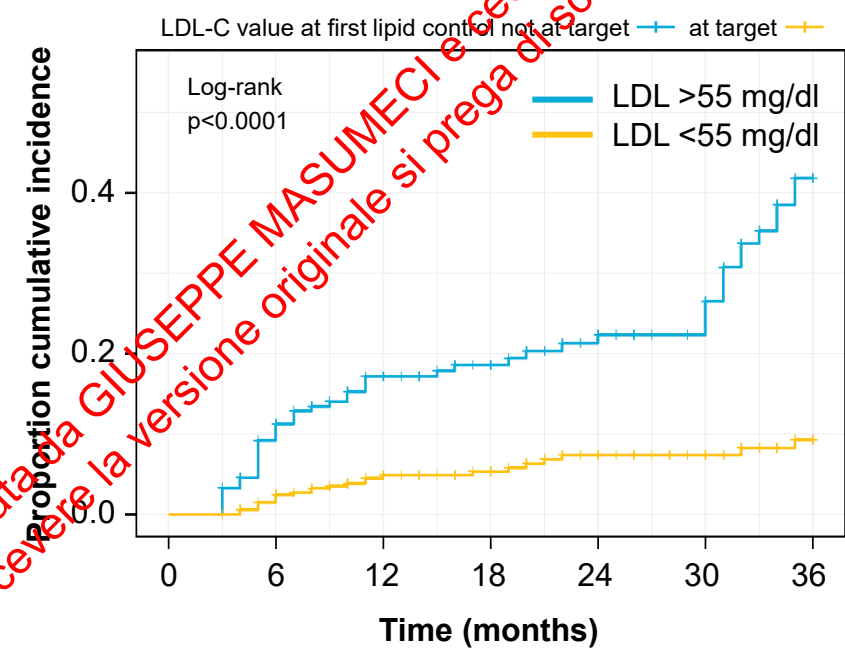
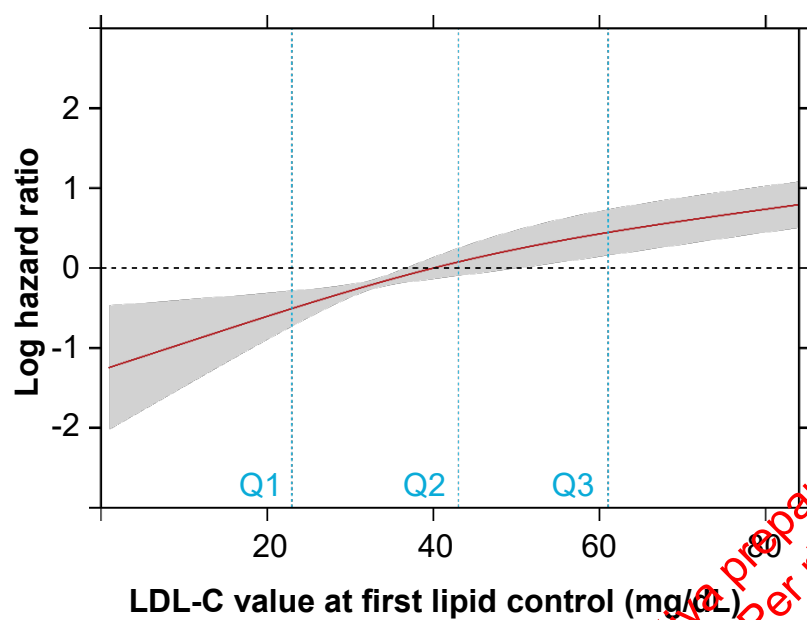
Effects of the strike early-stroke strong lipid lowering strategy with PCSK9i in patients with ACS. A real-world evidence from the AT-TARGETIT registry



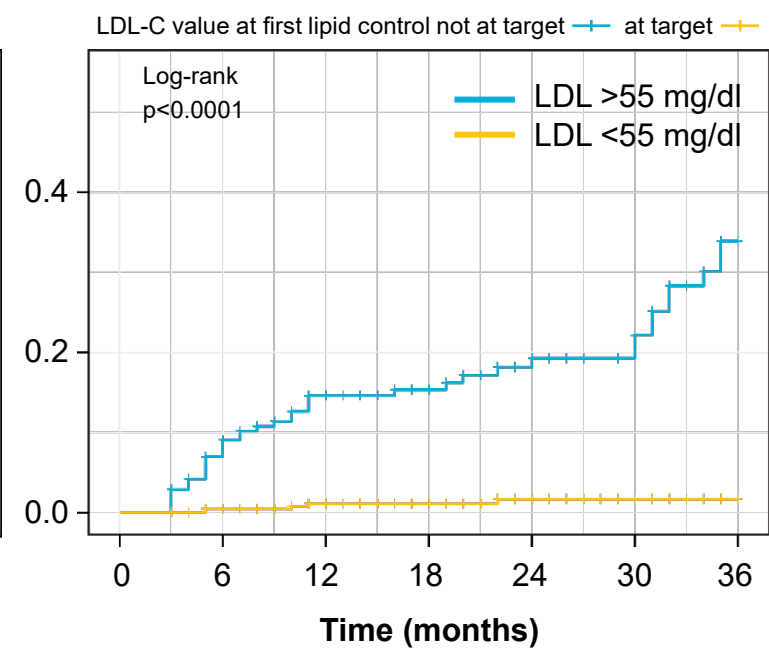
771 ACS patients treated with PCSK9i prescription during hospitalization or at discharge in 22 Italian centres

Better prognosis in patients at target

3P-MACE: Death, non-fatal MI and Stroke



All-cause mortality

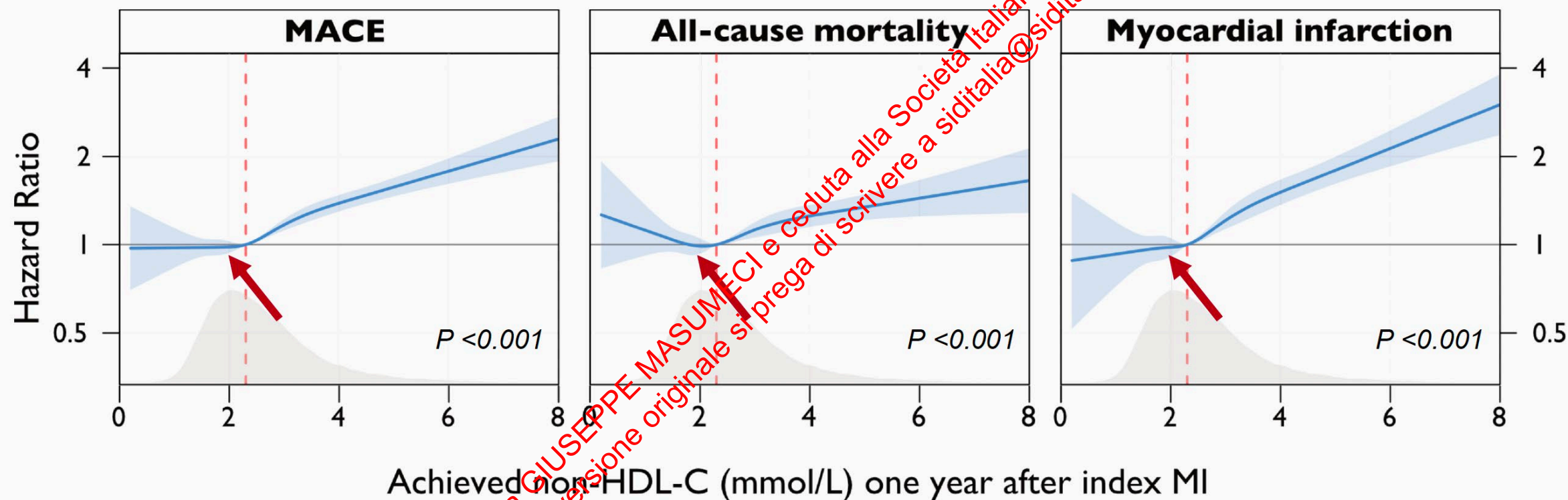


LDL 55 mg/dl = 1.4 mmol/L

3-P, 3-parameter; ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); MACE, major adverse cardiovascular event; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q, quartile

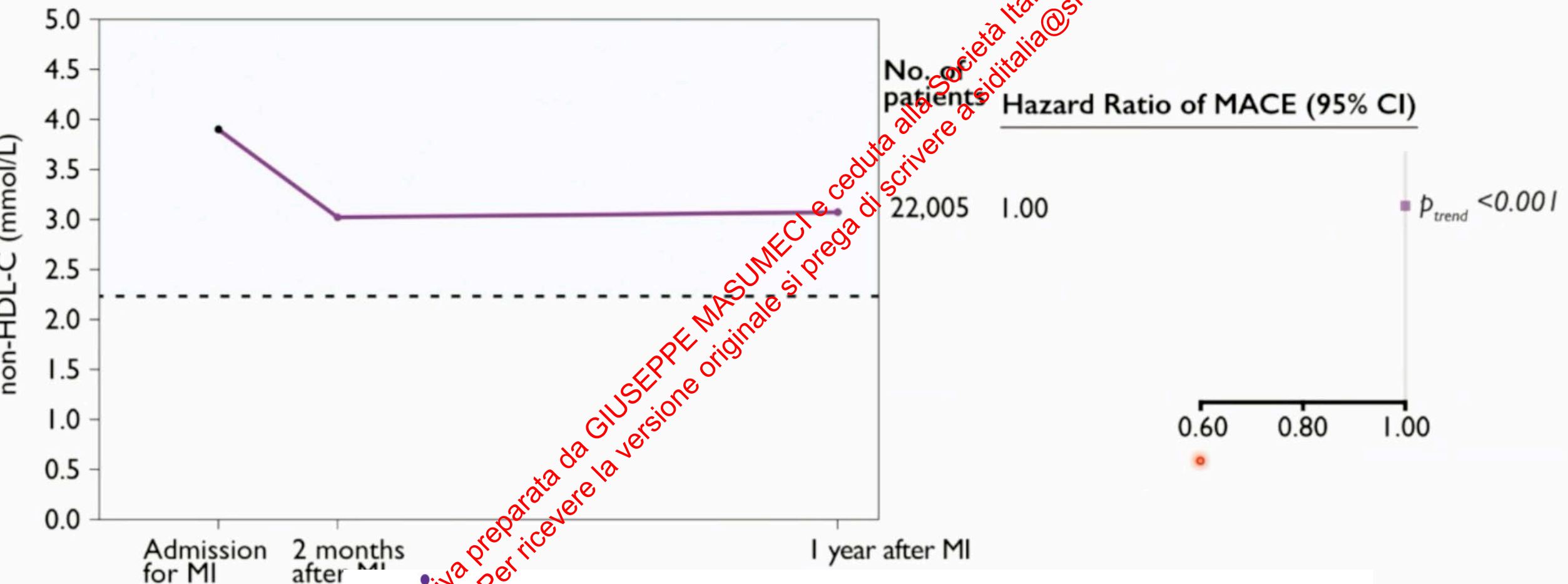
P. Gargiulo, G. Musumeci, P. Fillardi et al. Eur J Prev Cardiol. 2024 May 24;zwae170. doi: 10.1093/eurjpc/zwae170. Online ahead of print

Risk of outcomes by achieved non-HDL-C



Cox regression modelled in restricted cubic spline, adjusting for age at follow-up, statin intensity at admission, systolic blood pressure at 1-year follow-up, smoking at 1-year follow-up, sex, statin intensity at 1-year follow-up, body mass index at 1-year follow-up, history of diabetes, creatinine at admission, non-HDL-C at admission, and left ventricular ejection fraction at admission.

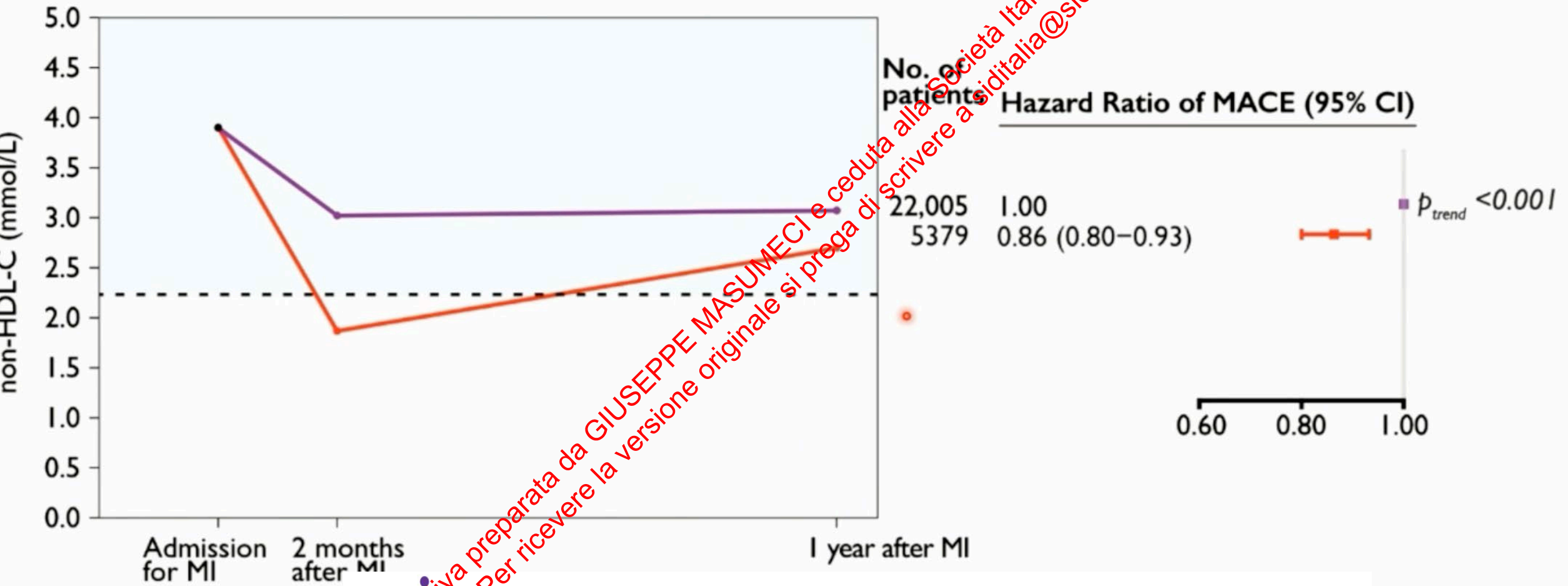
Sometimes speed really matters- Post MI- Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained lowering vs all other approaches the SWEDEHEART registry



Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

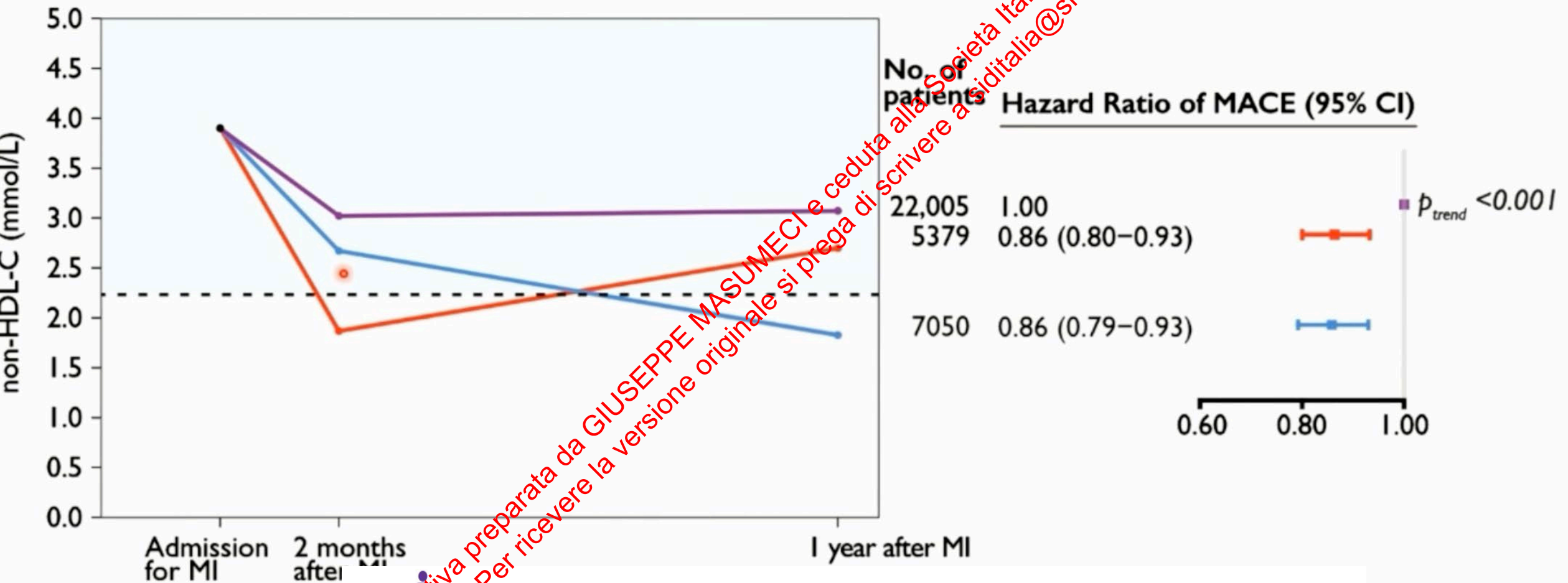
46 518 patients with MI and 7407 MACE (all-cause mortality, MI, or stroke)

Sometimes speed really matters- Post MI- Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained lowering vs all other approaches the SWEDEHEART registry



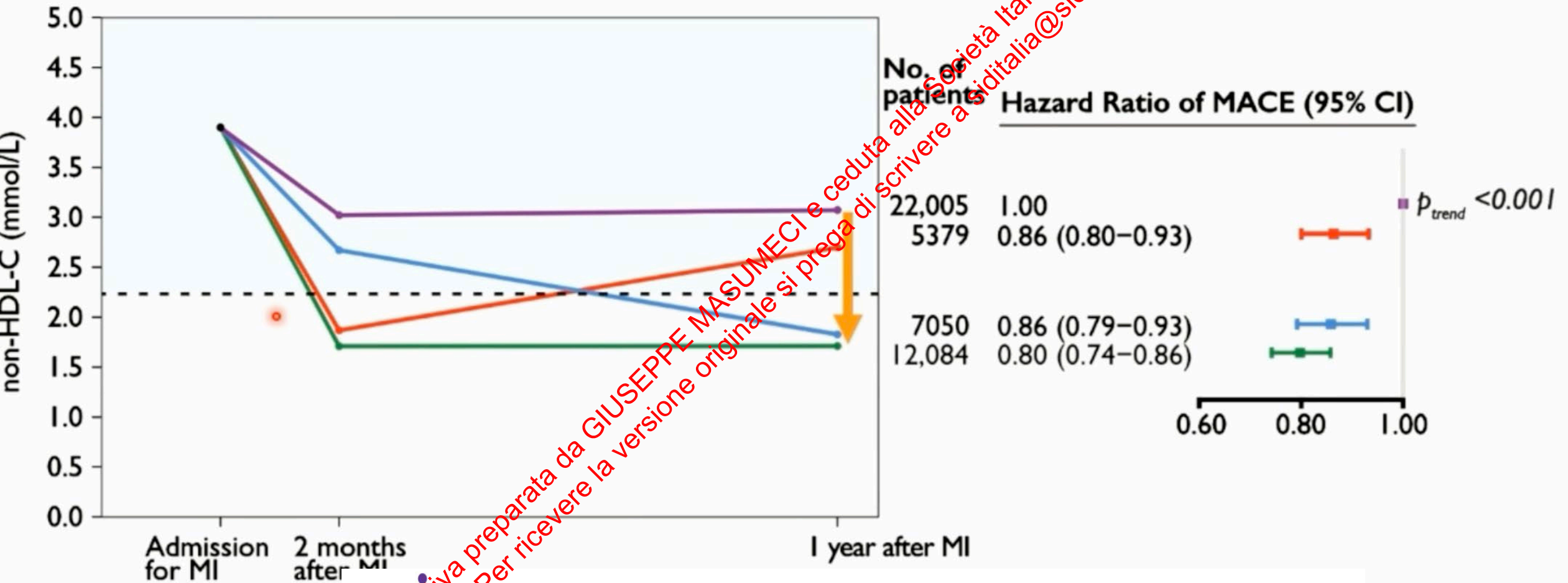
Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Sometimes speed really matters- Post MI- Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained lowering vs all other approaches the SWEDEHEART registry



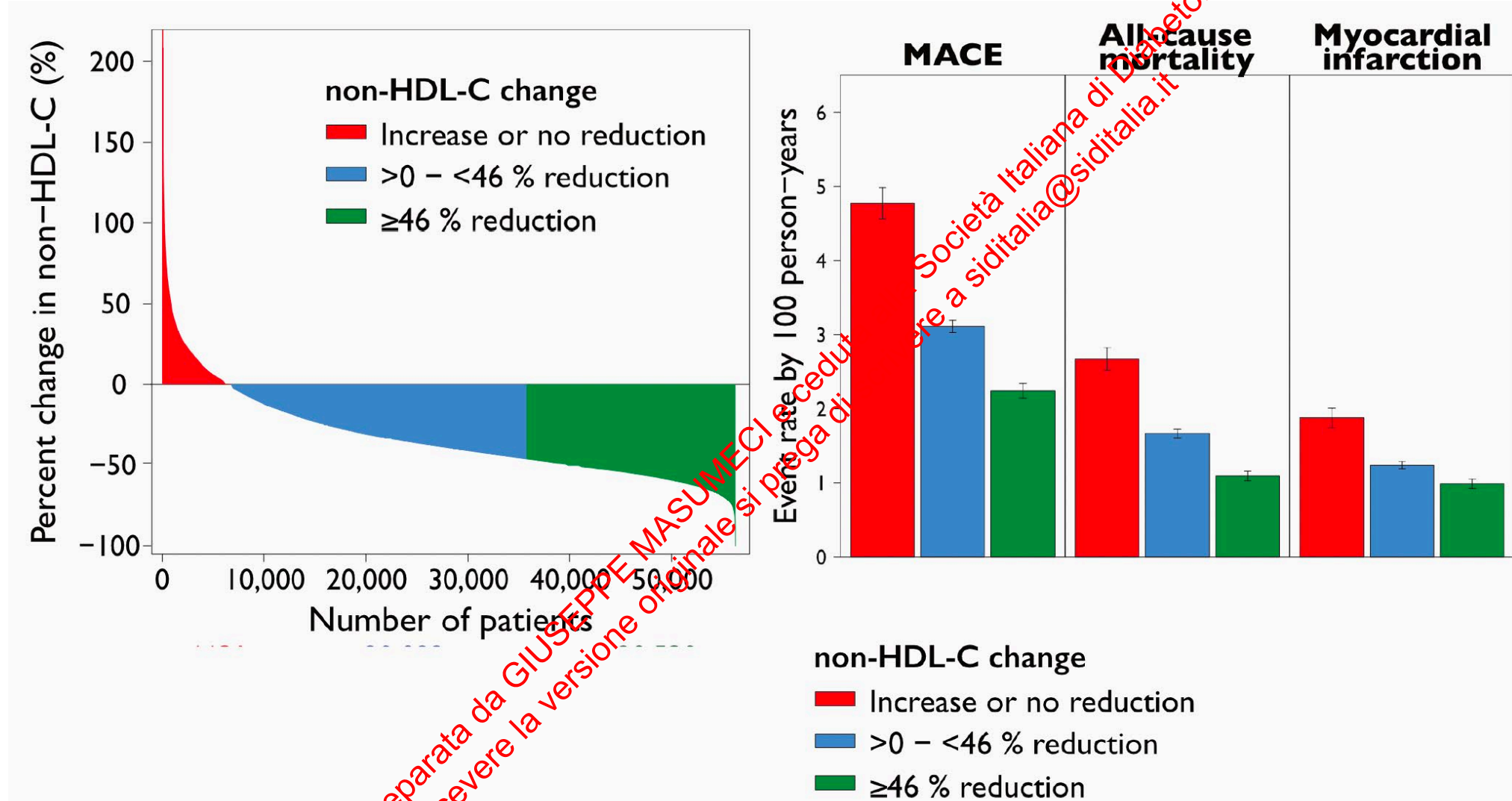
46 518 patients with MI and 7407 MACE (all-cause mortality, MI, or stroke)

Sometimes speed really matters- Post MI- Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained lowering vs all other approaches the SWEDEHEART registry



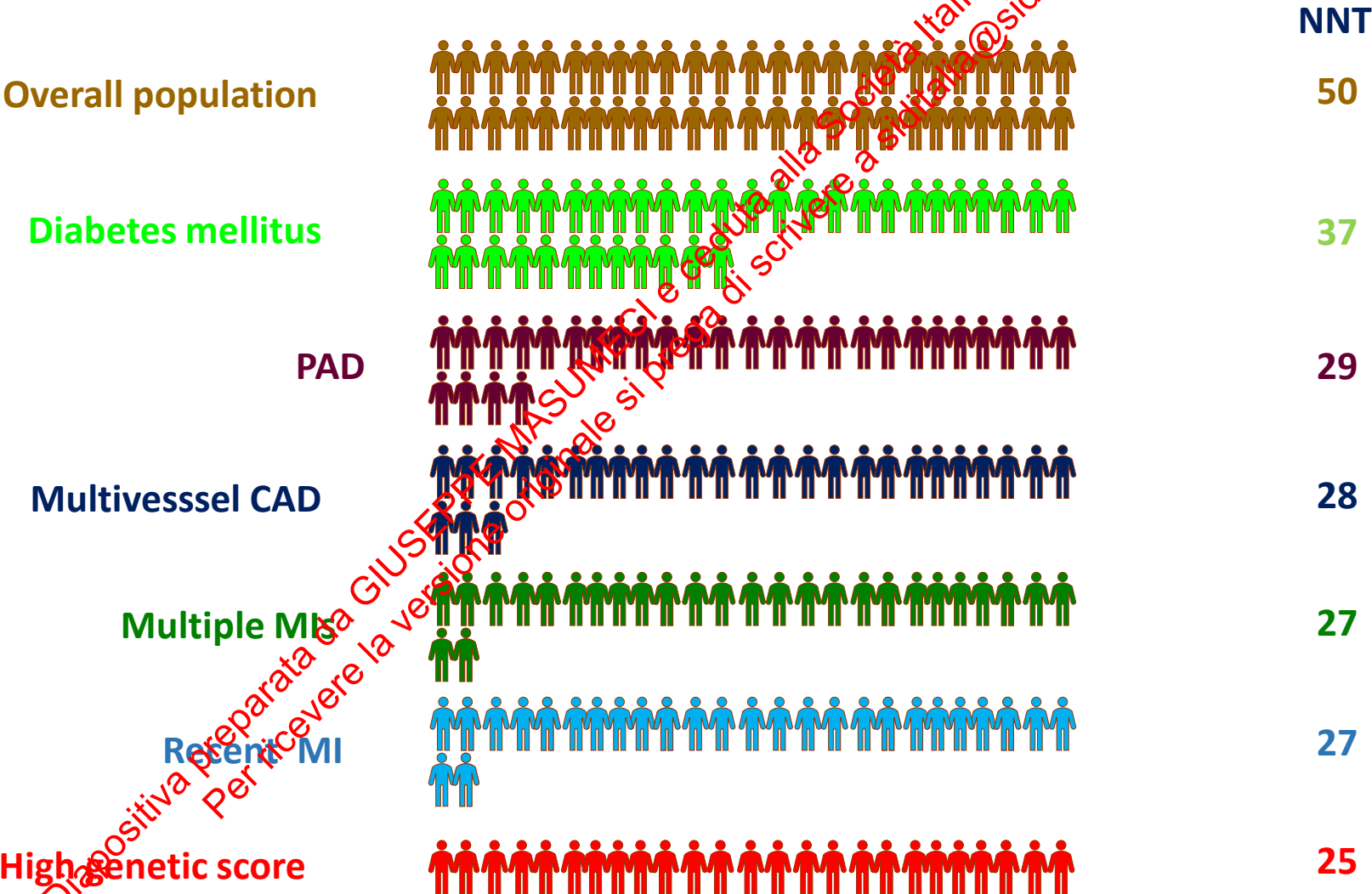
46 518 patients with MI and 7407 MACE (all-cause mortality, MI, or stroke)

Reduction, how to achieve it and association with outcomes



The current step-wise lipid lowering strategy might lead to delayed target achievement and risk of harm

FOURIER trial: NNT for the primary endpoint with evolocumab vs placebo in high-risk settings

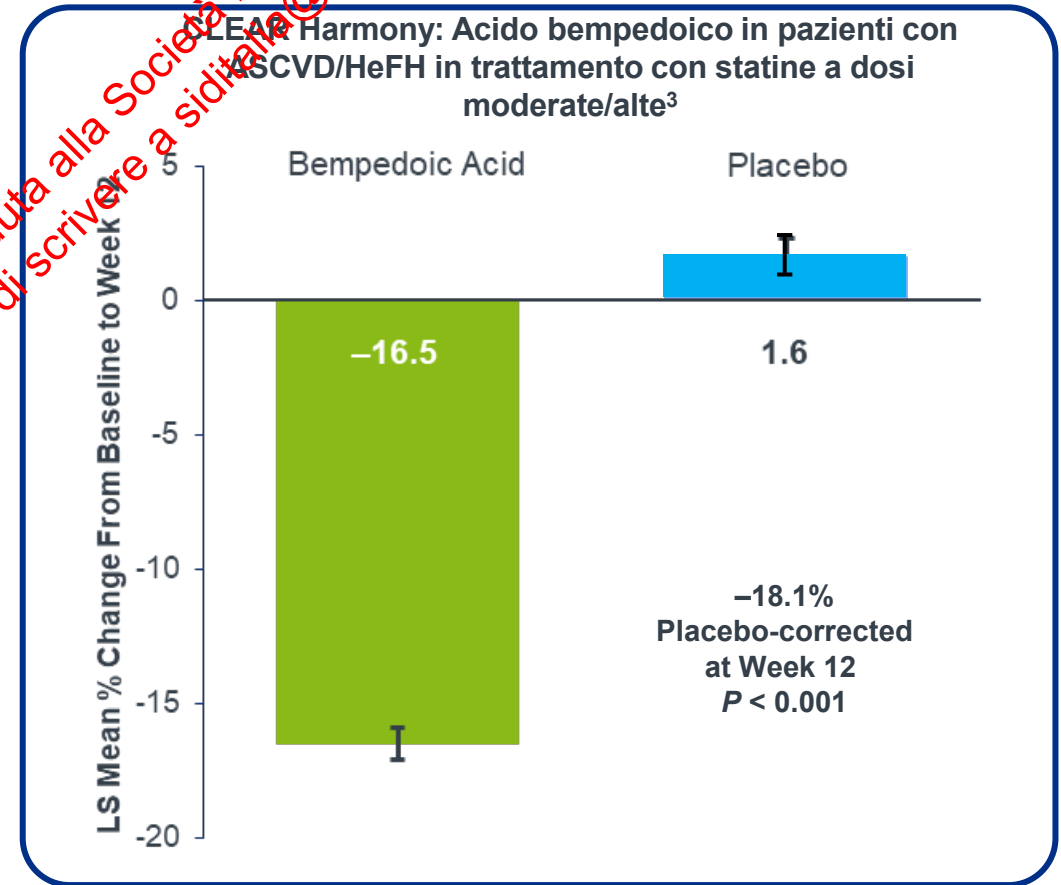


Pazienti in trattamento con statine ad intensità alta/moderata

CLEAR Harmony: acido bempedoico riduce i livelli di LDL-C in maniera significativa

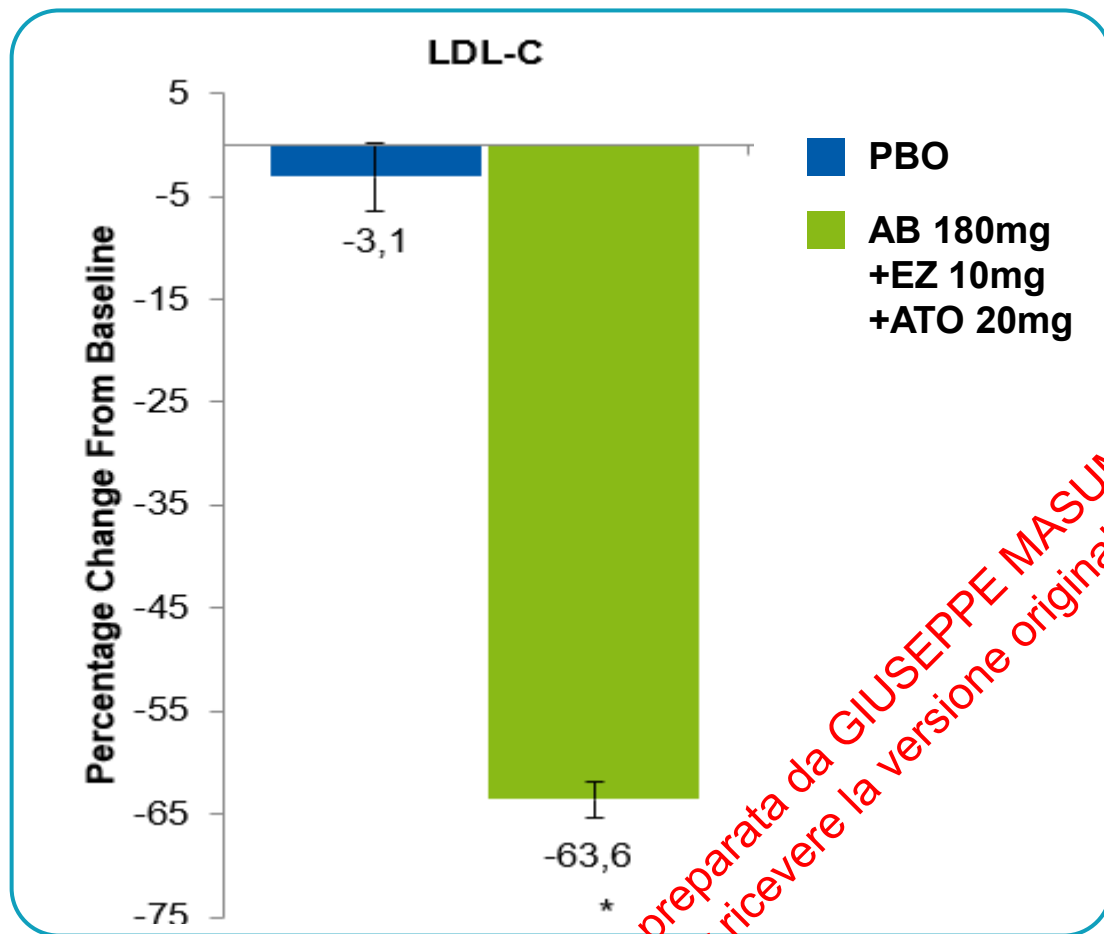
- Una percentuale di pazienti significativamente maggiore nel gruppo acido bempedoico ha raggiunto valori di LDL-C < 70 mg/dL alla settimana 12 rispetto al gruppo placebo (32.4% vs 9.0%; $p < 0.001$)
- L'efficacia dell'acido bempedoico non è risultata influenzata dal tipo né dall'intensità delle LLT sottostanti (-20% nei pazienti in trattamento con statine a bassa-moderata intensità vs -17.5% nei pazienti in trattamento con statine ad elevata intensità; p di interazione 0.18) ed era simile nei principali sottogruppi.

Riduzione di LDL-C del 18.1%



Triple Add-on: Acido Bempedoico, Ezetimibe e Atorvastatina 20 mg

In questo studio di fase 2 la terapia di *add-on* riduce i valori di LDL-C di oltre il 60%



Alla settimana 6:

- Nel 95% dei pazienti è stata raggiunta una riduzione di LDL-C $\geq 50\%$ rispetto al basale
- Il 90% dei pazienti ha raggiunto LDL-C < 70 mg/dL
- Il 58.5% dei pazienti ha raggiunto LDL-C < 55 mg/dL

Tripla terapia

Una potenziale strategia di combinazione per un'efficace riduzione dei livelli di colesterolo in pazienti ad alto rischio CV che non riescono a raggiungere gli obiettivi di trattamento con le terapie convenzionali.

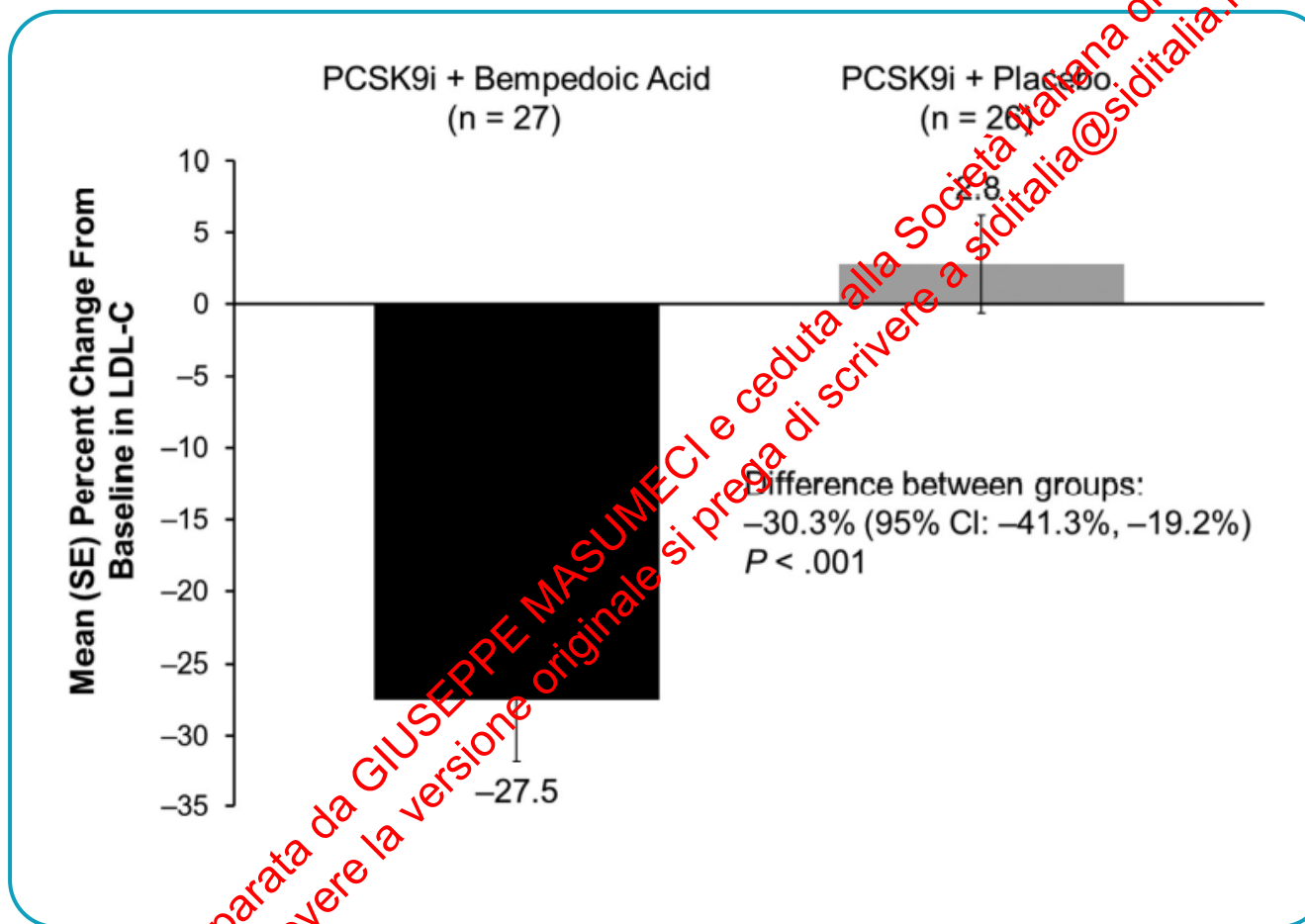
Least squares mean percentage changes from baseline to Week 6. Values are least-squares mean $\pm$ SE

*p < .001 for the comparison of triple therapy vs placebo

Acido bempedoico in pazienti trattati con PCSK9i

Riduzione LDL-C

Dati di Fase II
a 8 settimane

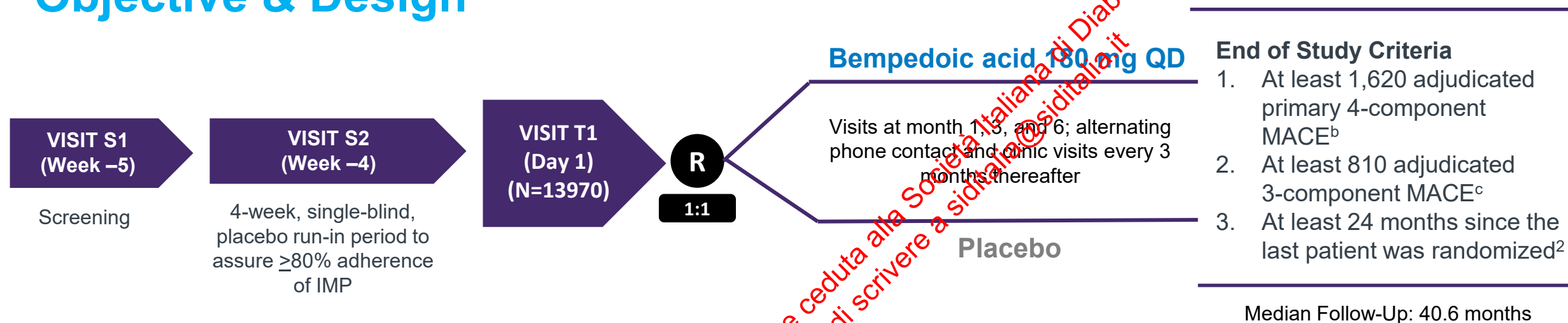


Least squares mean percentage changes from baseline to Month 2. Values are least-squares mean $\pm$ SE. Data for high-sensitivity C-reactive protein (hsCRP) are medians

* $p < 0.001$; † $p=0.029$

LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TC: total cholesterol; apoB: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein.

CLEAR Outcomes Objective & Design



Objective²

To evaluate whether long-term treatment with bempedoic acid versus placebo reduces the risk of MACE-4 in patients with, or at high risk for, CVD who are statin intolerant.

Composite Primary Efficacy Endpoint:

Time to first occurrence of MACE (composite of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization)

Key Secondary Endpoints:

Time to first occurrence of:

- The composite of CV death, nonfatal MI, nonfatal stroke (MACE-3)
- Fatal + nonfatal MI
- Coronary revascularization
- Fatal + nonfatal stroke

Time to:

- CV death
- All-cause mortality

^aEnrollment of high-risk patients without a history of atherosclerotic CVD was capped at 30%.

^bIncluding CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.

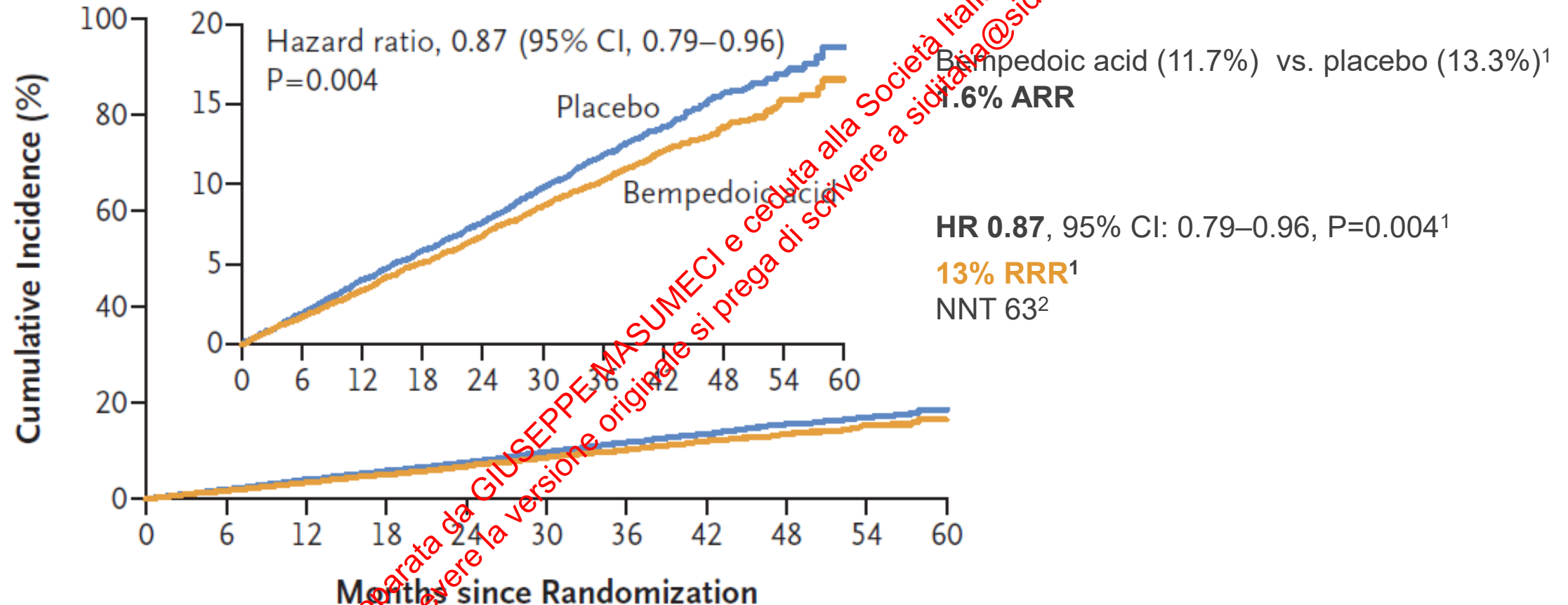
^cIncluding CV death, nonfatal MI, or nonfatal stroke.

CVD=cardiovascular disease; LDL-C=low-density lipoprotein cholesterol; QD=once daily; MACE=major adverse cardiovascular event; MI=myocardial infarction; HbA1c=hemoglobin A1c; IMP=investigational medicinal product

CLEAR Outcomes

Primary CV Endpoint: MACE-4

A Four-Component MACE (Primary End Point)



- The primary efficacy endpoint (MACE-4) is the time to first occurrence of an adjudicated event for a composite that includes **death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularisation**.
- **All RRR % and hazard ratios (HR) in publicly available sources have been rounded;**
- **ARR**, absolute risk reduction; **CI**, confidence interval; **HR**, hazard ratio; **MACE**, major adverse cardiovascular events; **NNT**, number needed to treat; **RRR**, relative risk reduction.

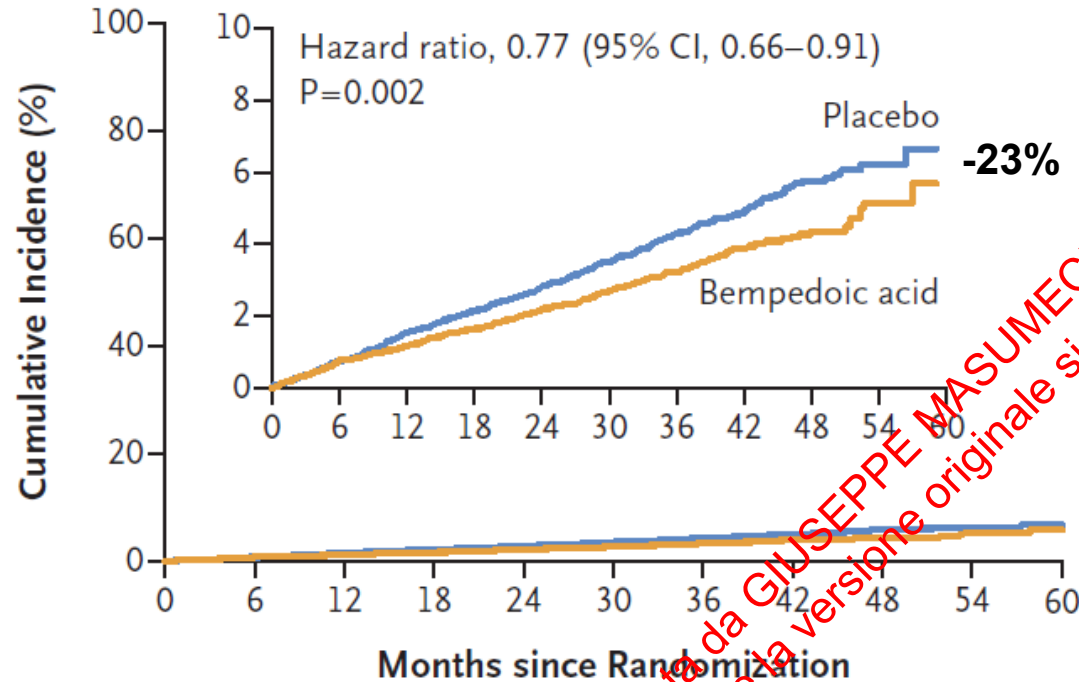
1. Nissen SE, et al. N Engl J Med. 2023; 388:1353–1364 DOI: 10.1056/NEJMoa2215024.

2. Banach M, et al. Prog Cardiovasc Dis. 2023;S0033-0620(23)00026-9. doi: 10.1016/j.pcad.2023.03.001

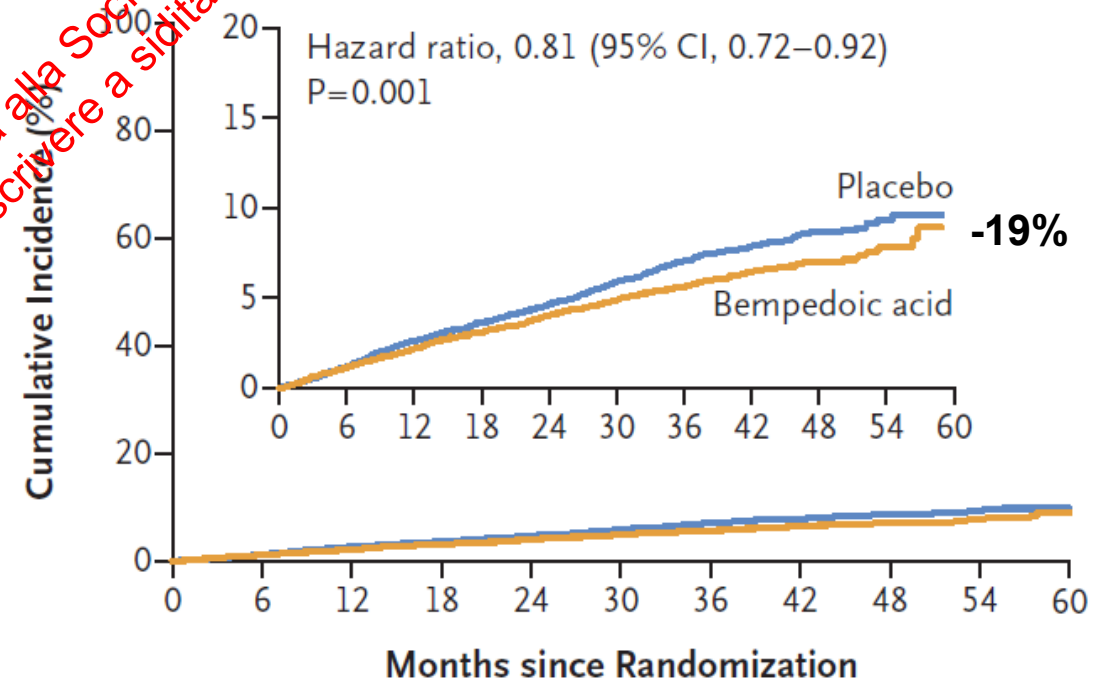
CLEAR Outcomes

Key Secondary CV Endpoints

C Fatal or Nonfatal Myocardial Infarction

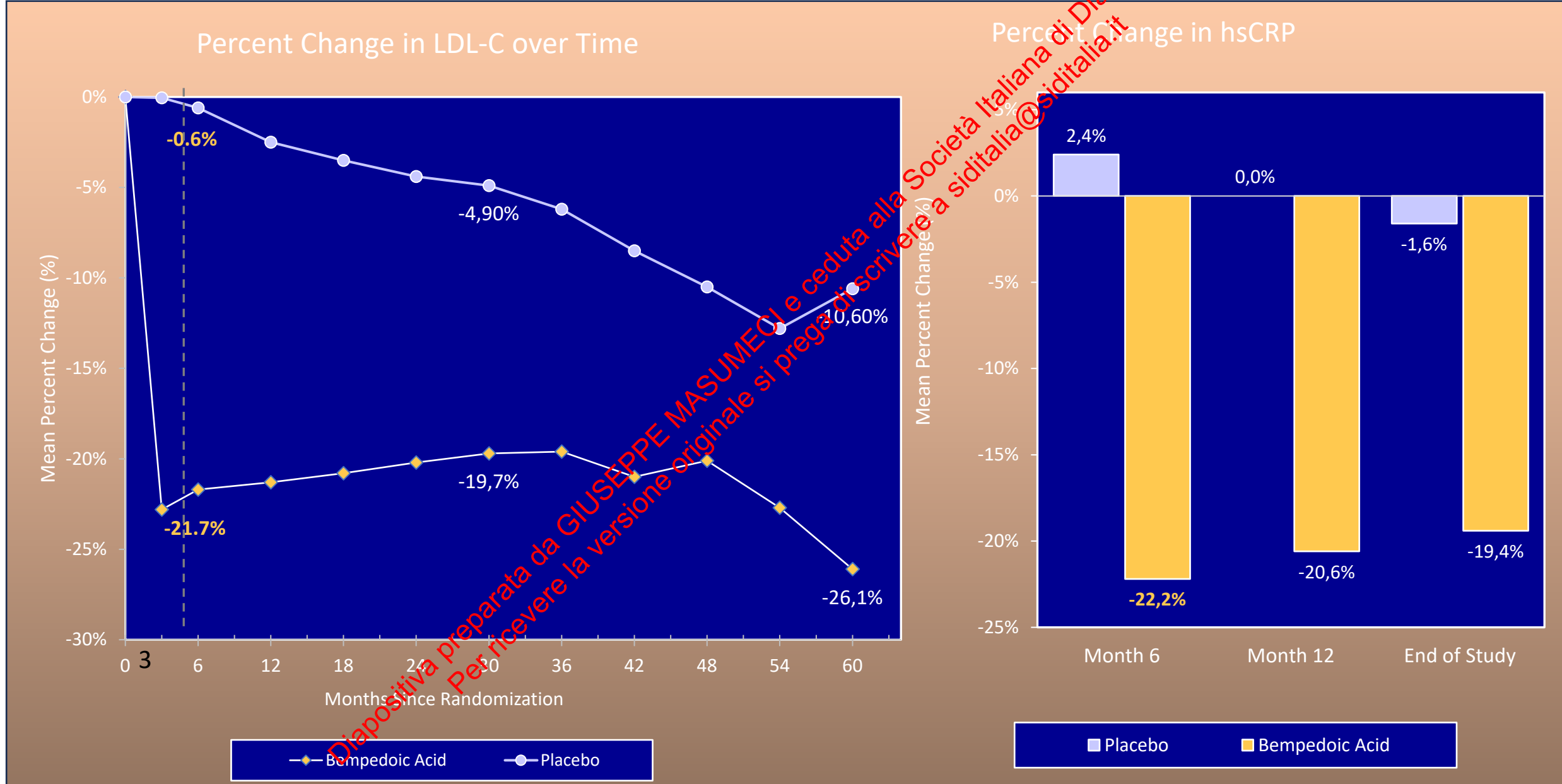


D Coronary Revascularization



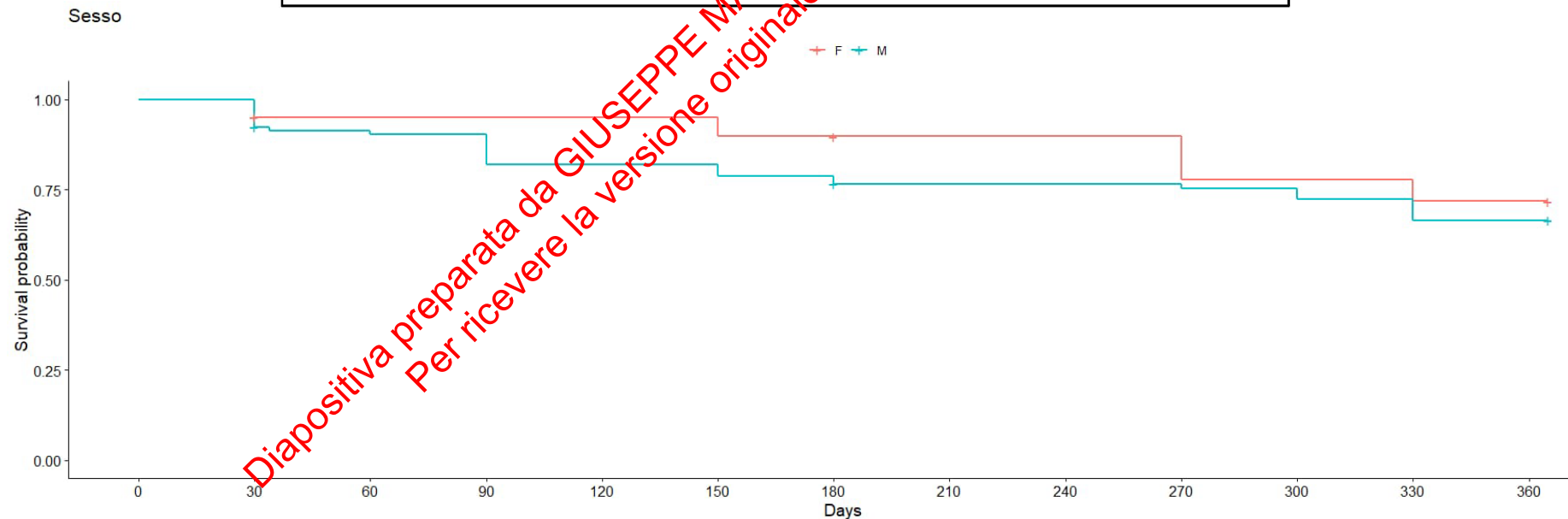
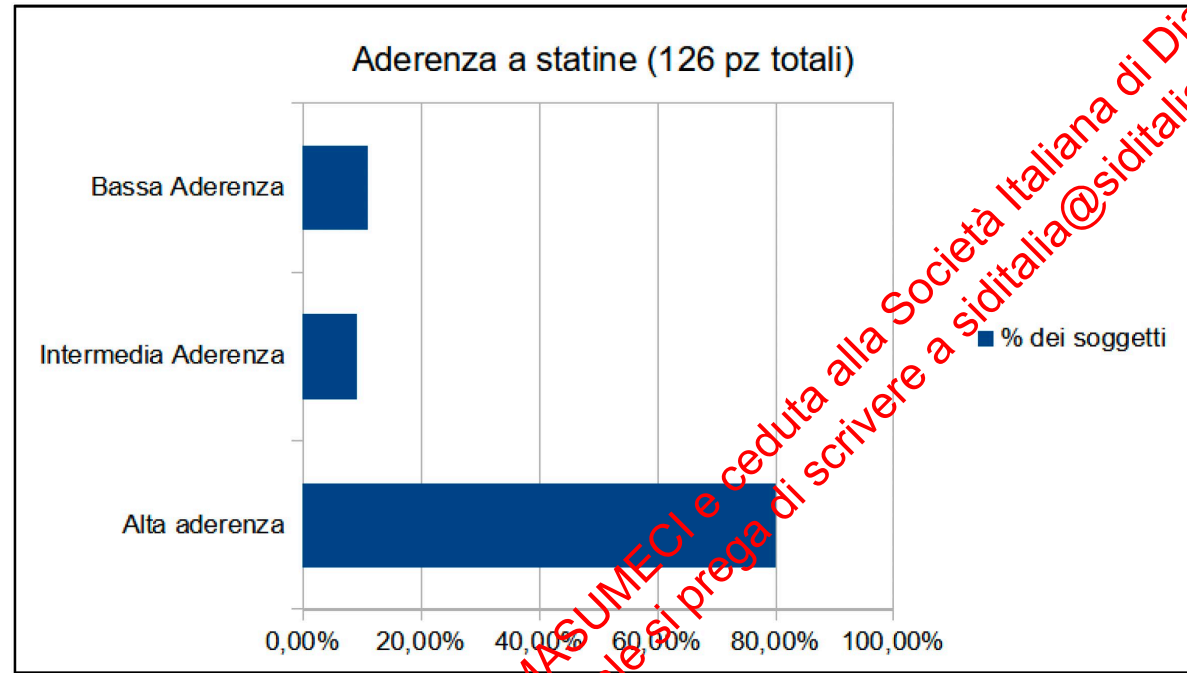
- All RRR % and hazard ratios (HR) in publicly available sources have been rounded;
- CI, confidence interval; MACE, major adverse cardiovascular events; RRR, relative risk reduction;

Effect of Trial Regimens on LDL-C and hsCRP



High Statin Adherence in patients treated with PCSK9-I

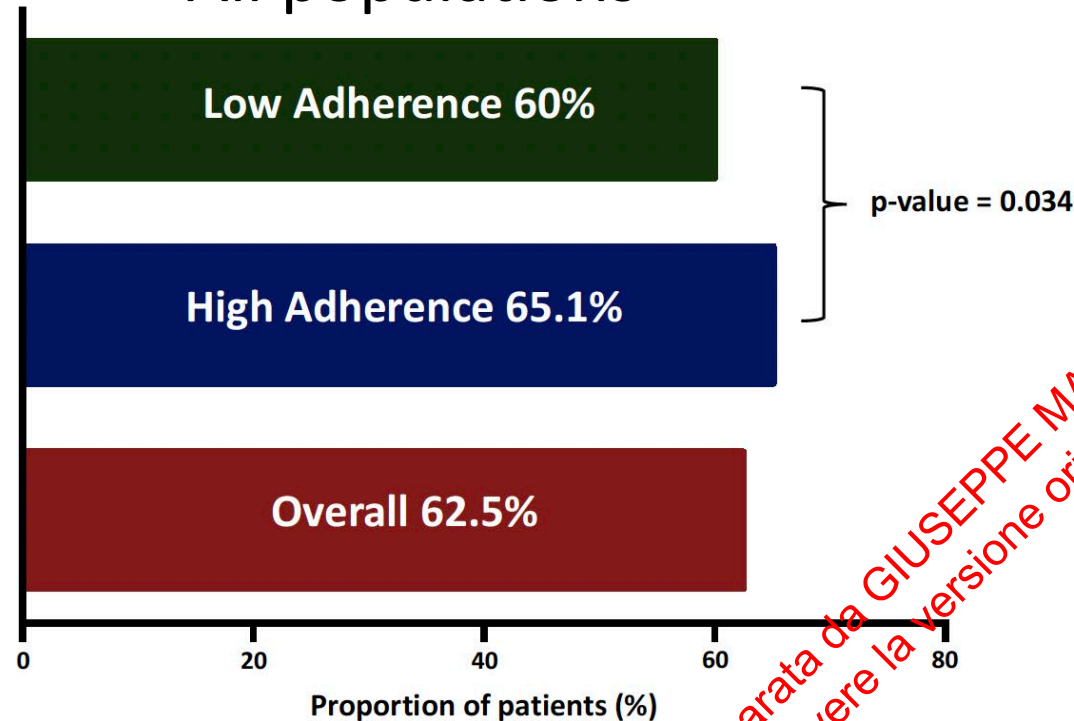
Ospedale Mauriziano and ASL Città di Torino



The high and sustained effect of PCSK9-I on LDL-C goal achievement was not influenced by adherence

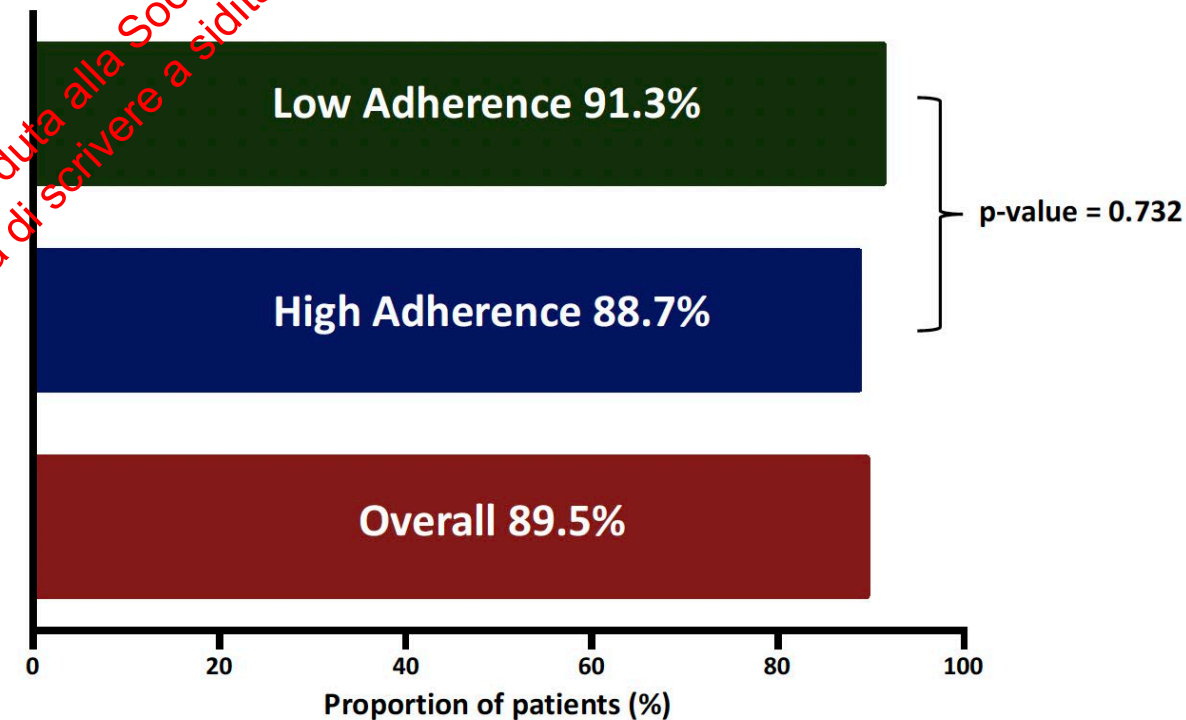
Primary analysis

All populations



Sensitivity analysis

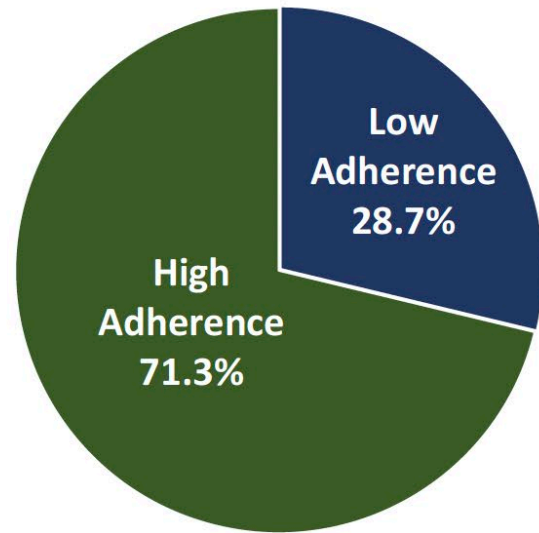
I-PCSK9



At hospital discharge, the rate of patients treated with statin and/or ezetimibe (mainly as triple therapy in combination with PCSK9-i) was lower in the LA than in the HA group. The same trend in LLT use was observed at 1- and 3-months FU

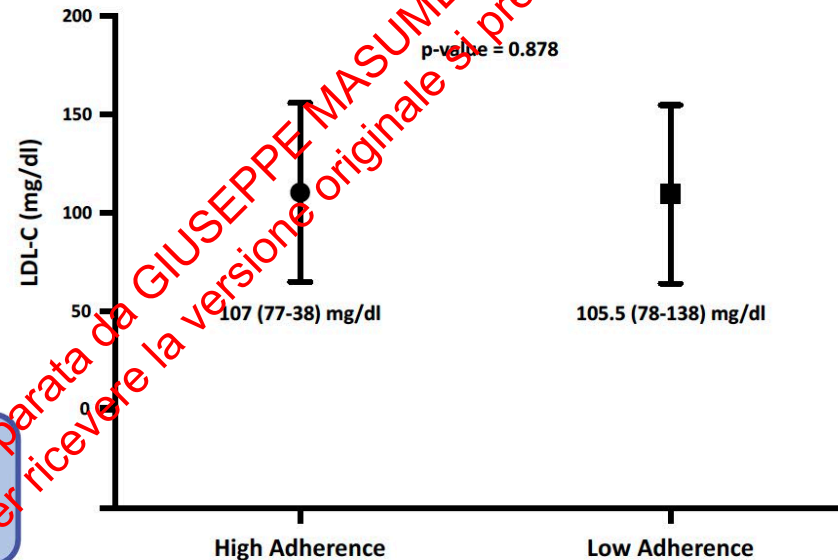
Jet-LDL registry: 1095 patients with ACS treated with LLT according to current European guidelines

For **963 patients**: availability of 3-months self-reported adherence. LLT assessed using **the MMAS**



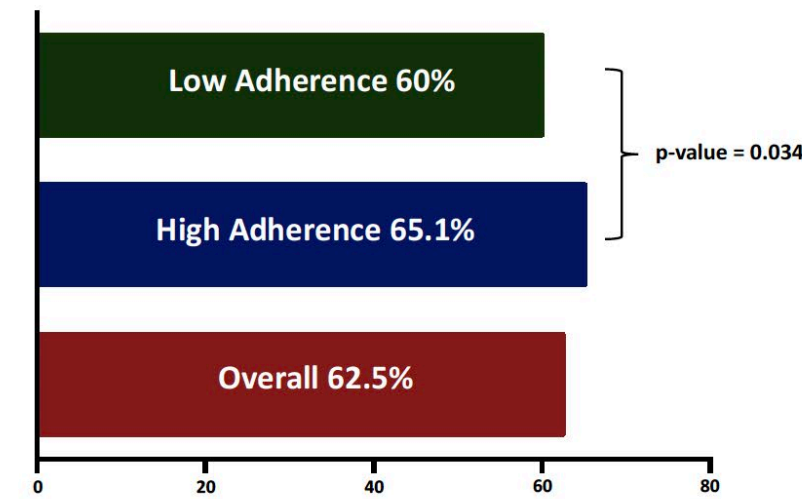
- MMAS score ≥ 6 : high adherence
- MMAS score < 6 : low adherence

Baseline LDL-C levels



Primary endpoint

(LDL-C reduction $> 50\%$ from baseline or level < 55 mg/dl at 1-month)



Very short-term effects of a single dose of a PCSK9 inhibitor before PCI

Short-Term Effects of PCSK9 Inhibitor (PCSK9i) on Coronary Plaques

Prospective, single-arm, single-center interventional study



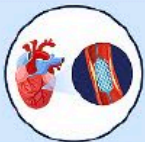
Patients with coronary artery disease (N = 27)



Near-infrared spectroscopy intravascular ultrasound (NIRS-IVUS) during coronary angiography



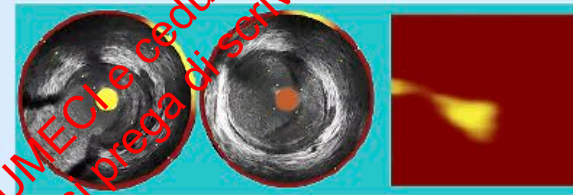
Single dose of 420 mg evolocumab (PCSK9i)



Repeat NIRS-IVUS during percutaneous coronary intervention (PCI) after 2–6 weeks

Changes in LAD lesion

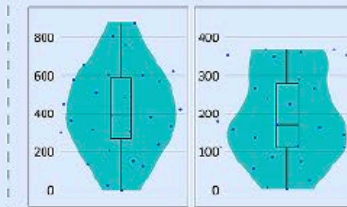
Before evolocumab administration



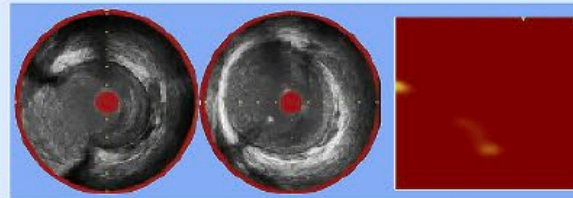
Lesion LCBI: 74, Max-LCBI_{4mm}: 215

Max
LCBI_{4mm}

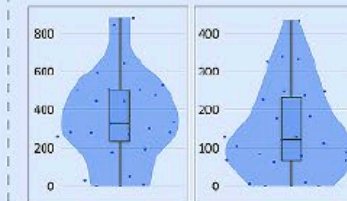
Lesion
LCBI



After evolocumab administration



Lesion LCBI: 9, Max-LCBI_{4mm}: 31



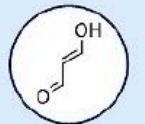
Lipid profile changes after PCSK9i dose



↓ LDL cholesterol



↓ Lipoprotein (a)



↓ Malondialdehyde-modified LDL

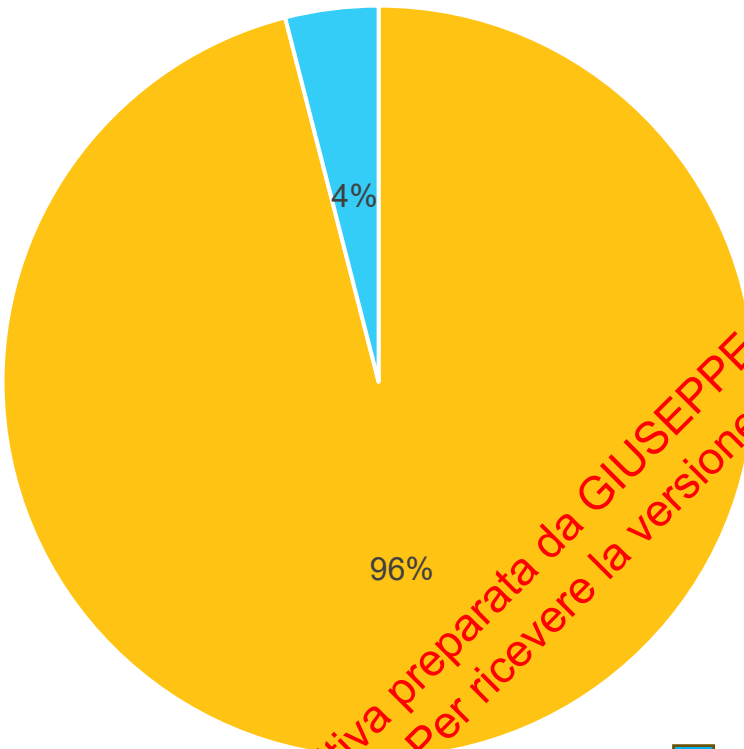
A single dose of evolocumab before PCI significantly reduces lipid-core plaques within 2–6 weeks

Ospedale Mauriziano Torino experience in 2023

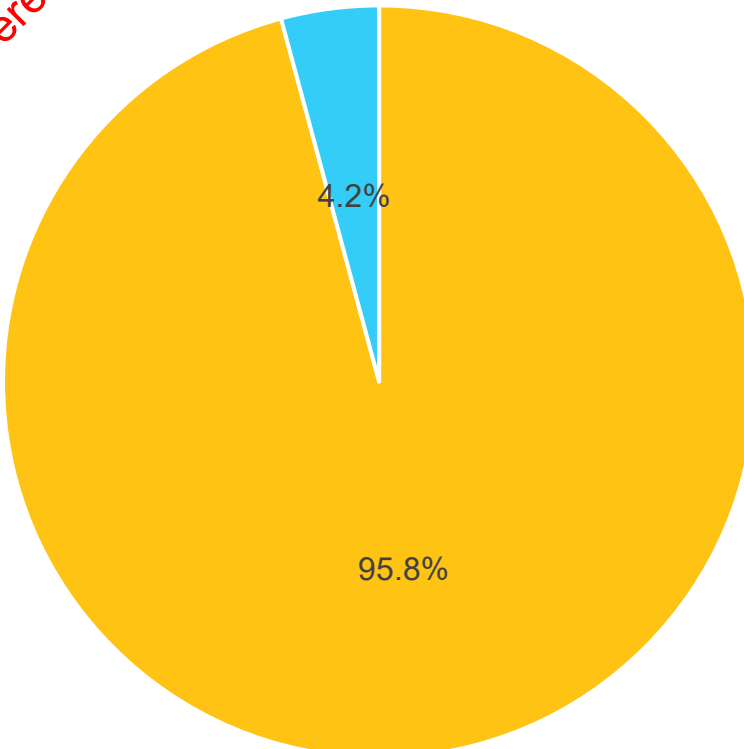


Overall, 720 consecutive CAD patients hospitalized between January and Dicembre 2023 were enrolled;
691 of whom were discharged with combination Rosuvastatin/Ezetimibe (96%)

281 ACS Patients



439 CCS Patients



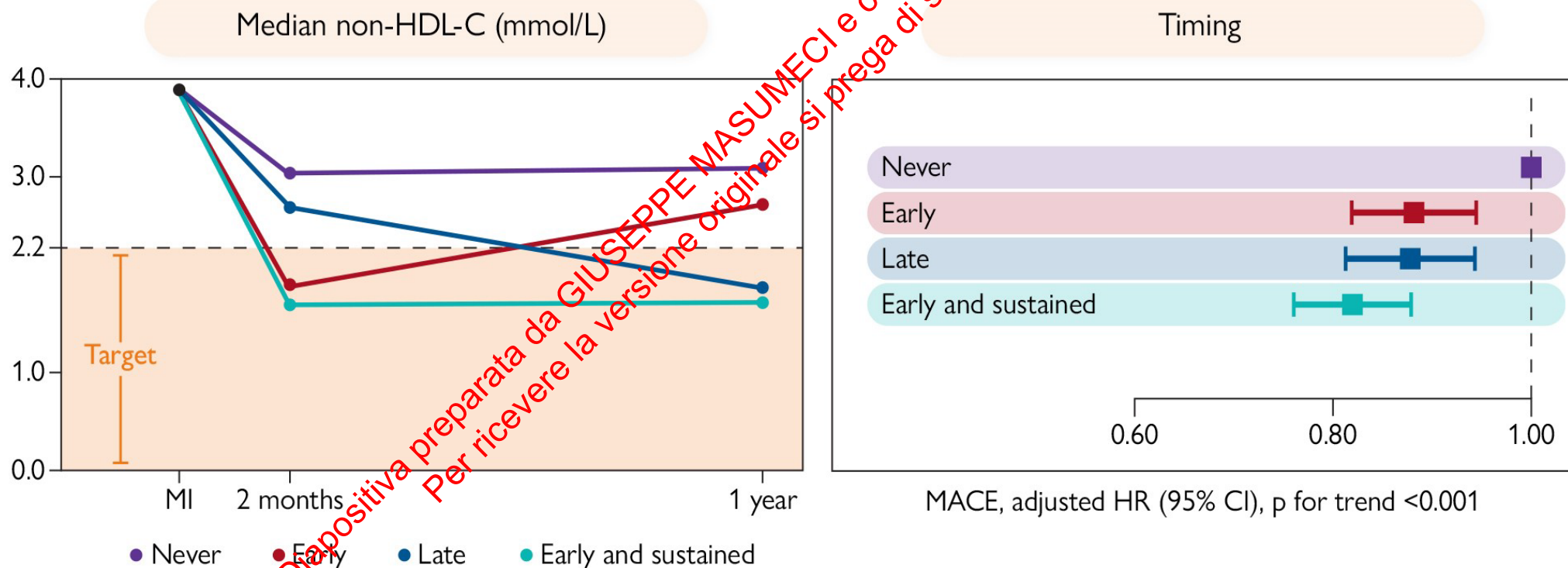
- Statin monotherapy
- Rosuvastatin + Ezetimibe

Diapositiva preparata da GIUSEPPE MASUMECI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@sidi.it

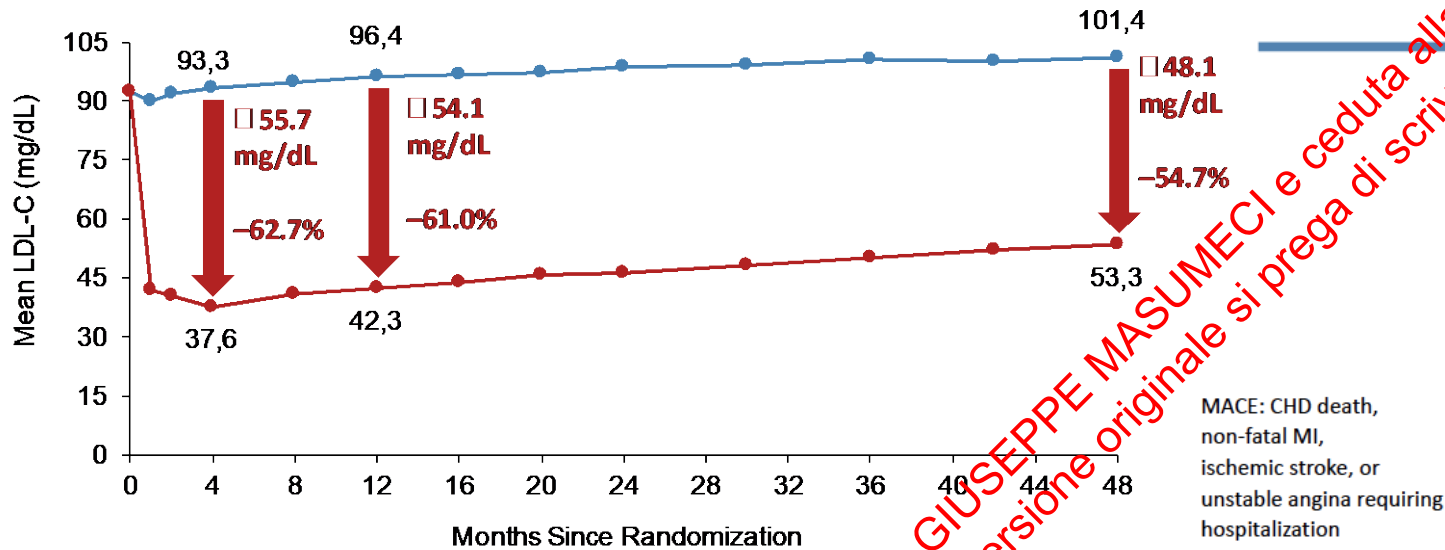
Intensive early and sustained lowering of non-high-density lipoprotein cholesterol after 1 myocardial infarction and prognosis: the SWEDEHEART registry

Timing of reaching and duration of staying at non-HDL-C target

46 518 patients with MI and 7407 MACE (all-cause mortality, MI, or stroke)



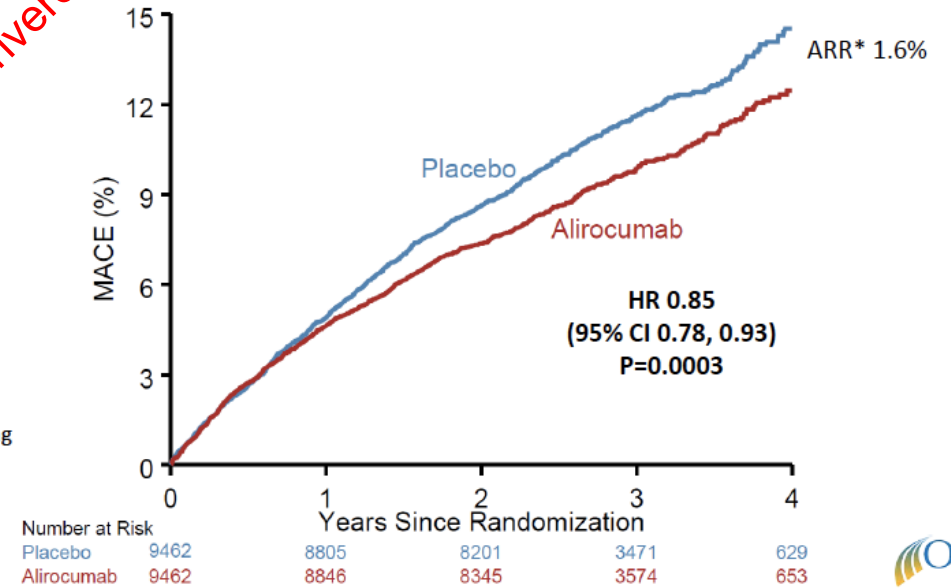
ODYSSEY OUTCOMES Alirocumab



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

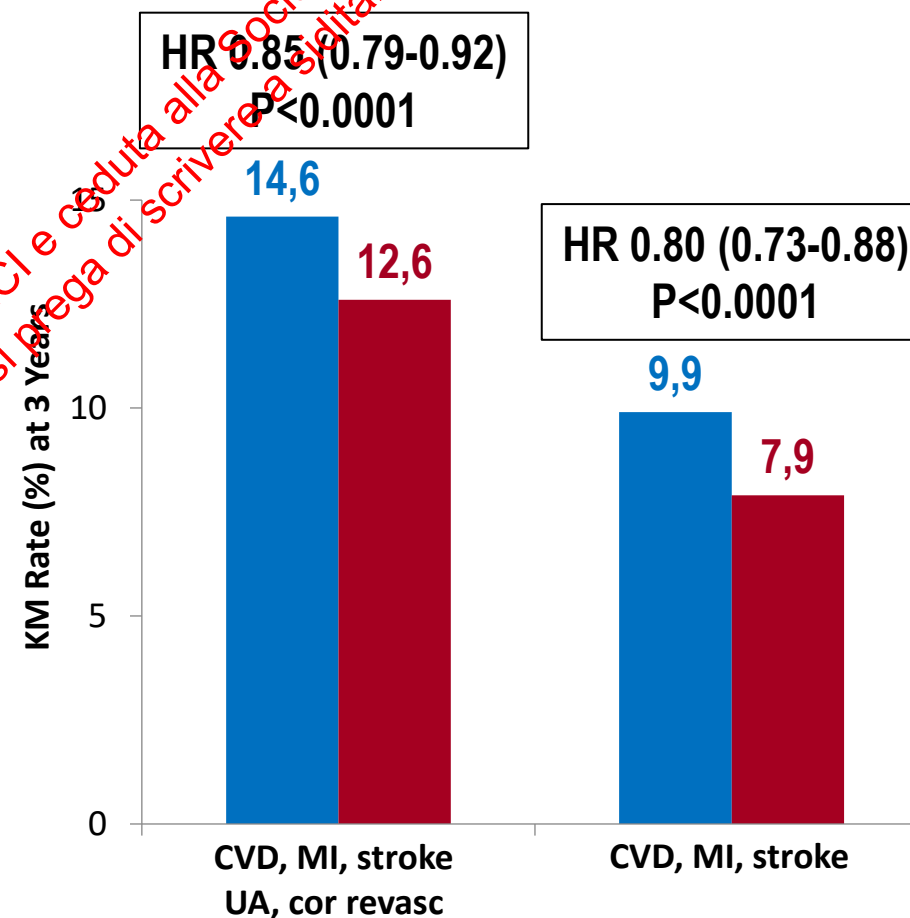
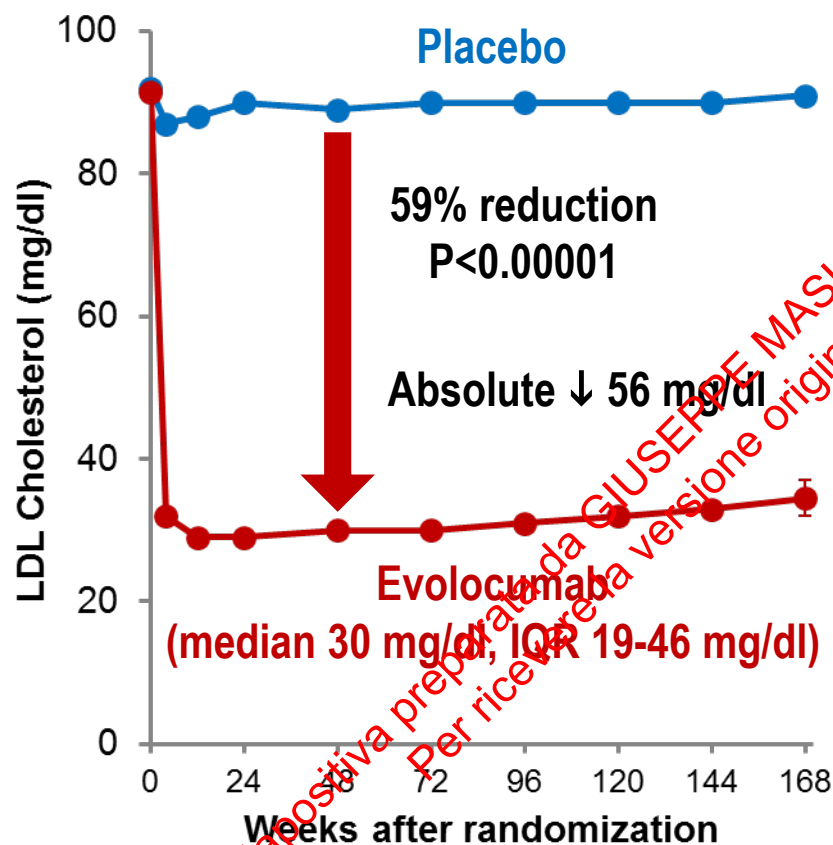
*Based on cumulative incidence

Primary Efficacy Endpoint: MACE



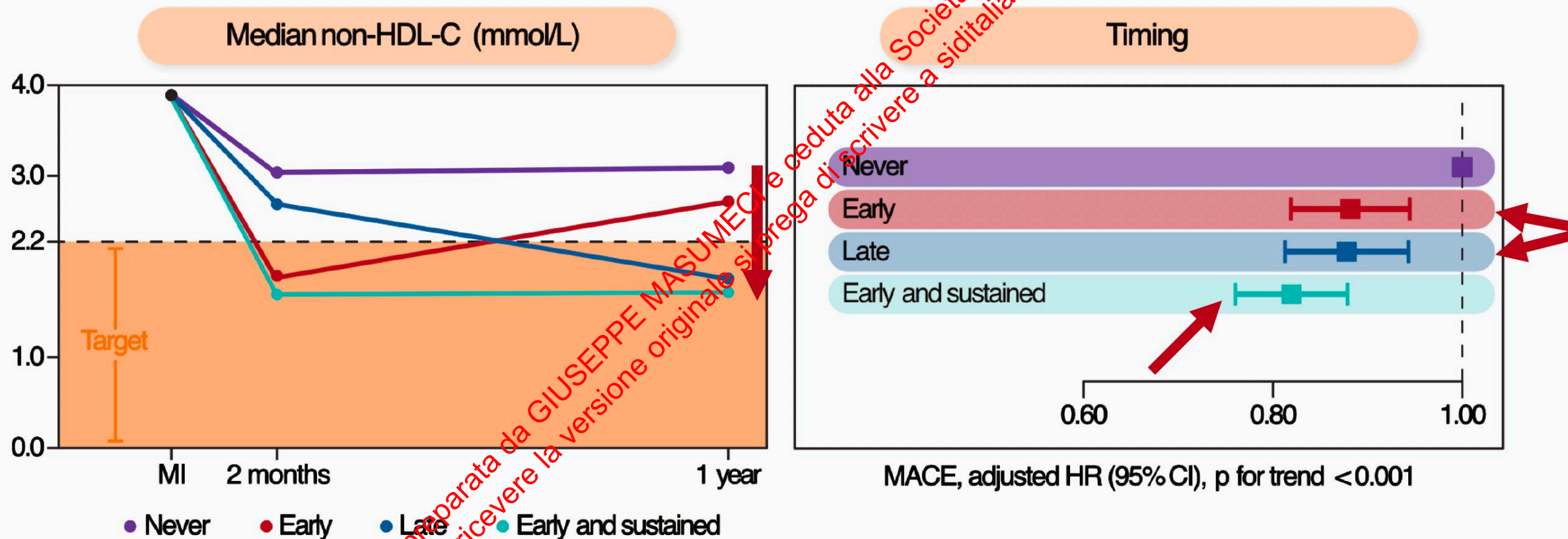
FOURIER Trial *Evolocumab*

- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated

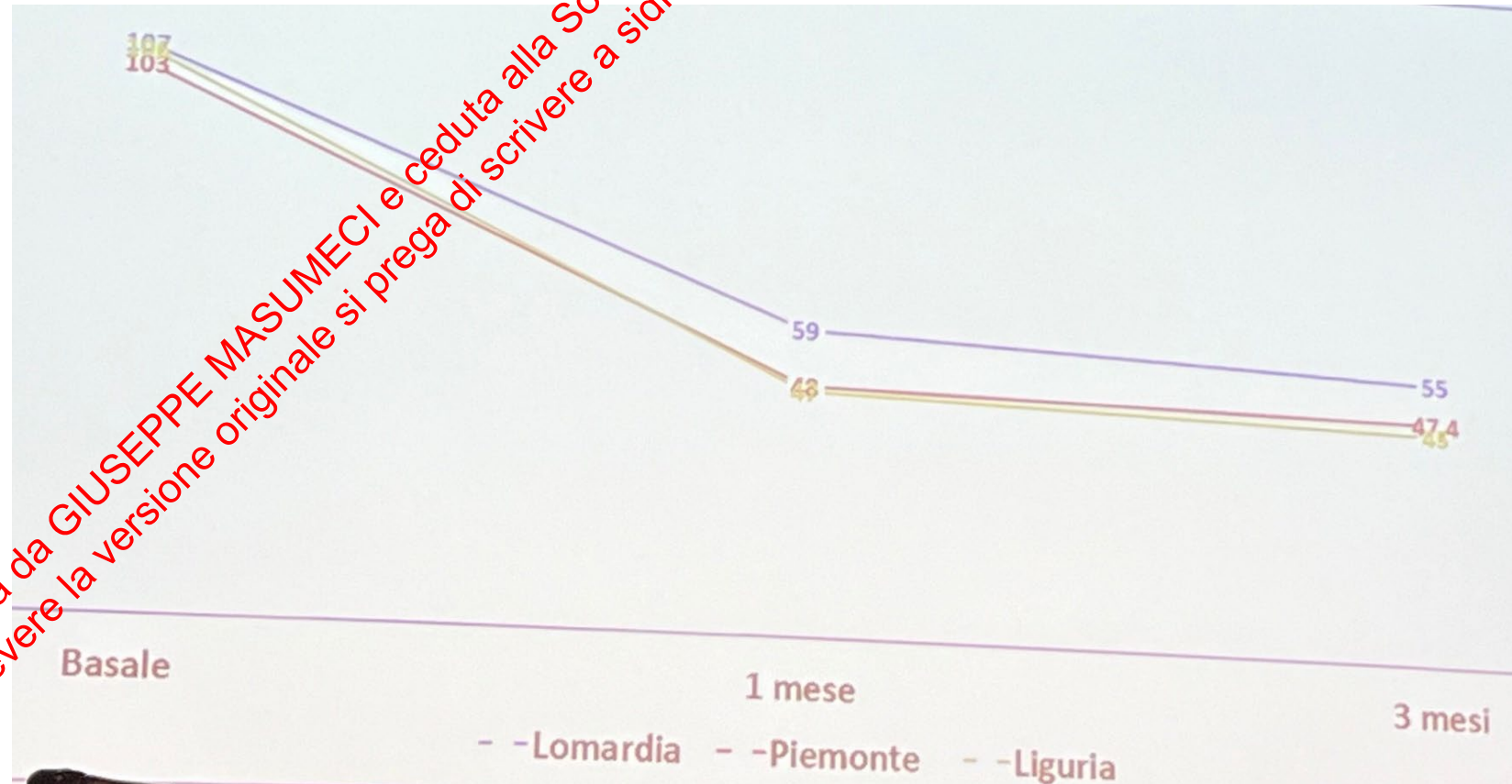
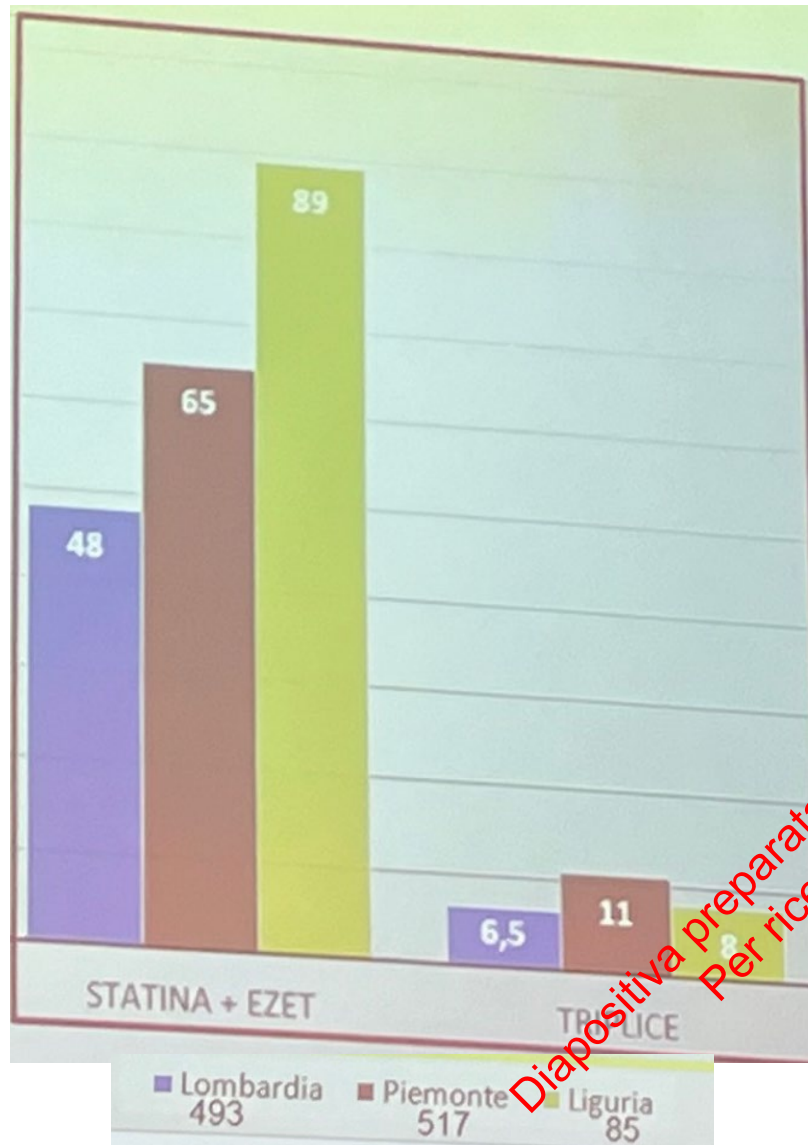


Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained

46 518 patients with MI and 7407 MACE events (all-cause mortality, MI, or stroke)



JET-LDL Registry: Lombardia vs Piemonte vs Liguria

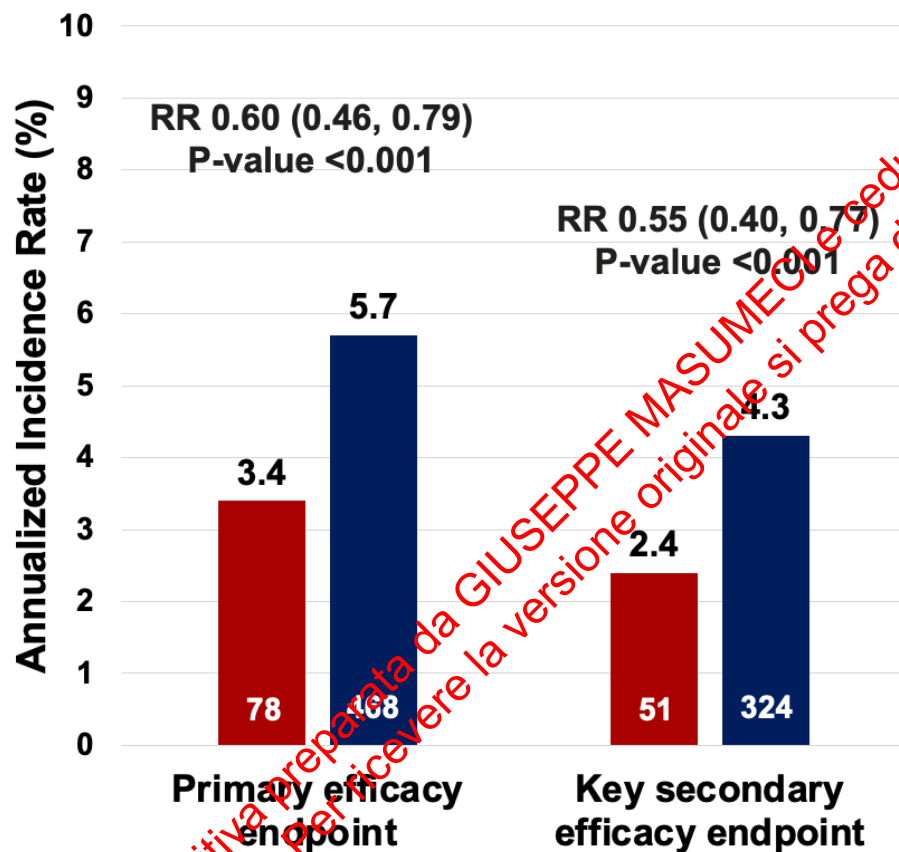




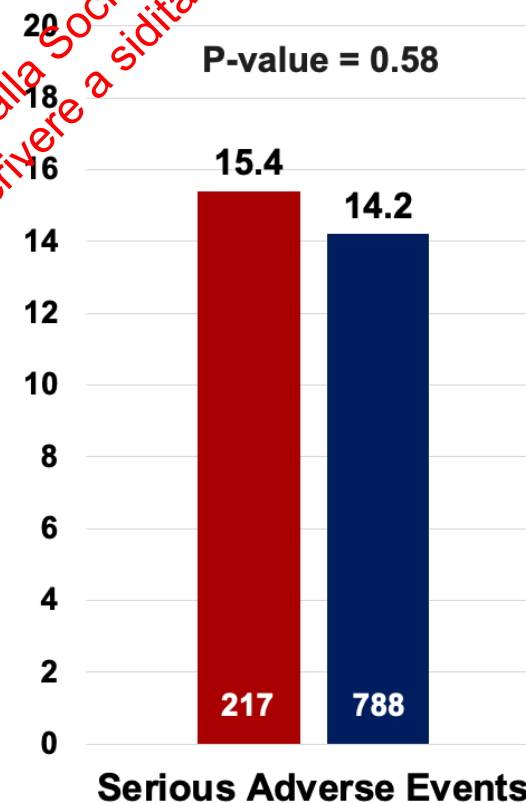
MACE & Safety w/ LDL-C <10 vs ≥100 mg/dL



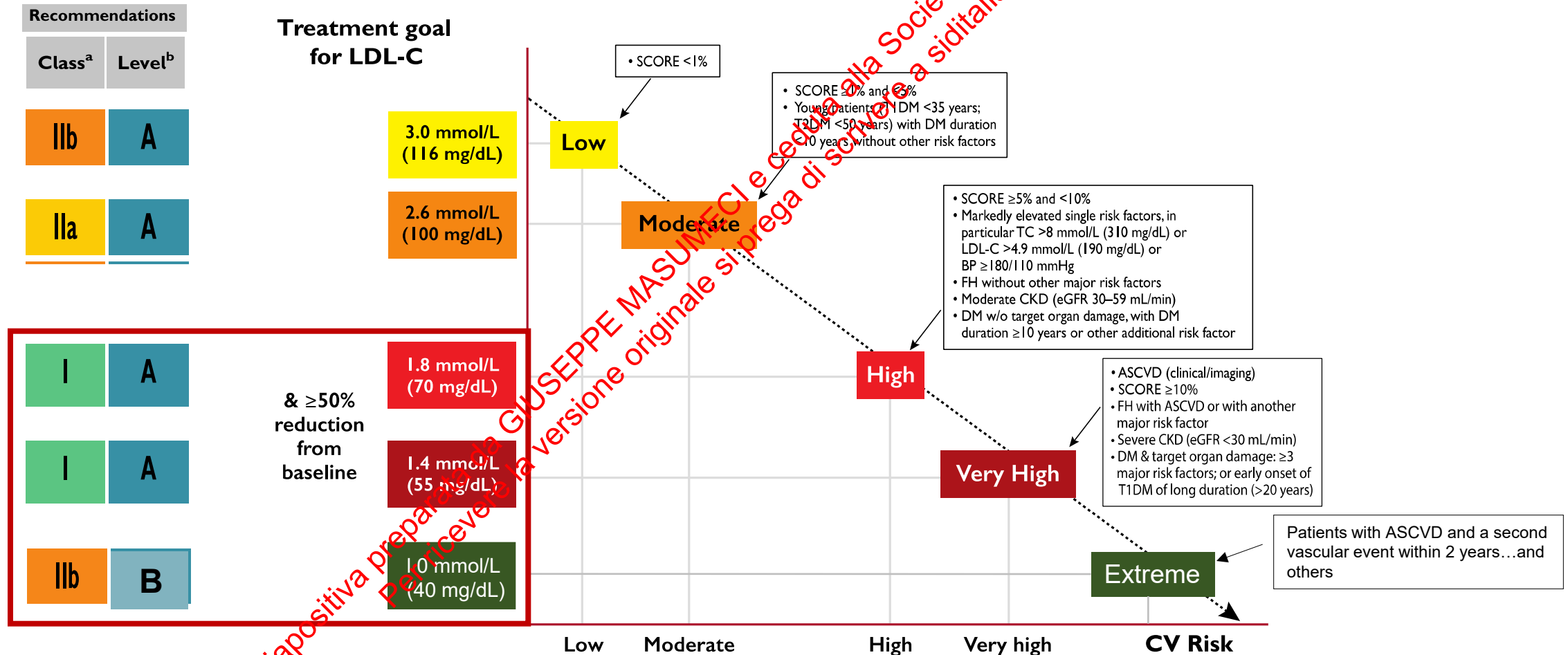
A. Cardiovascular Outcomes



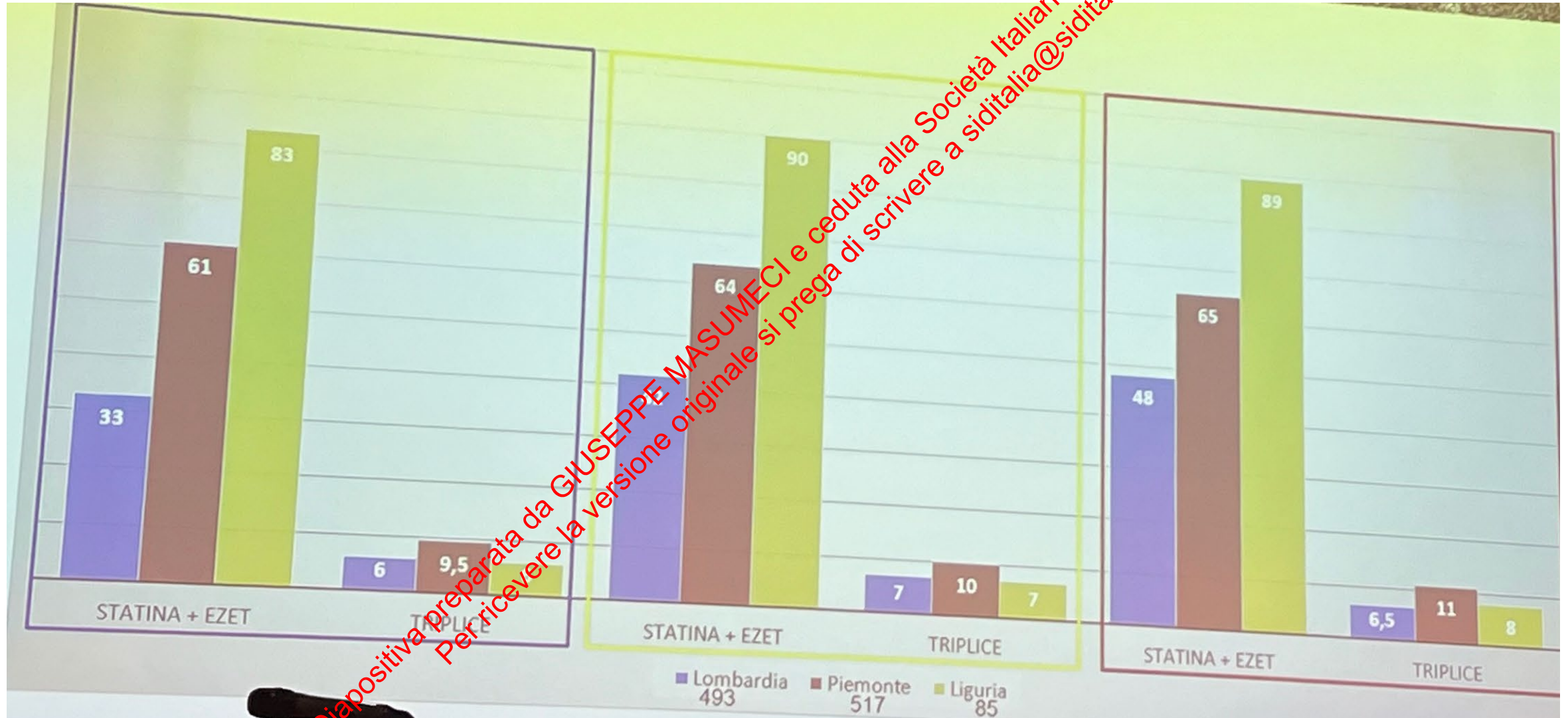
B. Safety



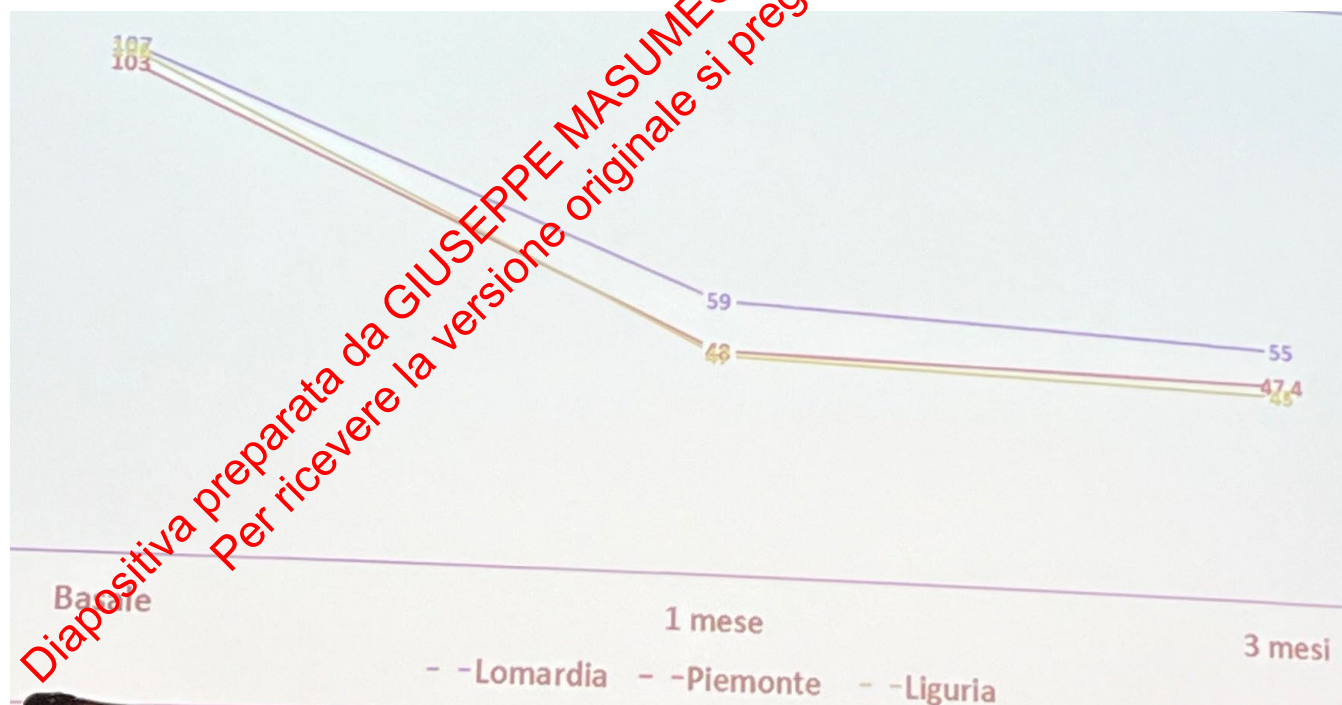
Le Linee Guida ESC/EAS 2019 per la gestione delle dislipidemie hanno stratificato i pazienti in 5 categorie di rischio definendo target di C-LDL per ciascuna categoria di rischio



JET-LDL Registry: Lombardia vs Piemonte vs Liguria



JET-LDL Registry: Lombardia vs Piemonte vs Liguria

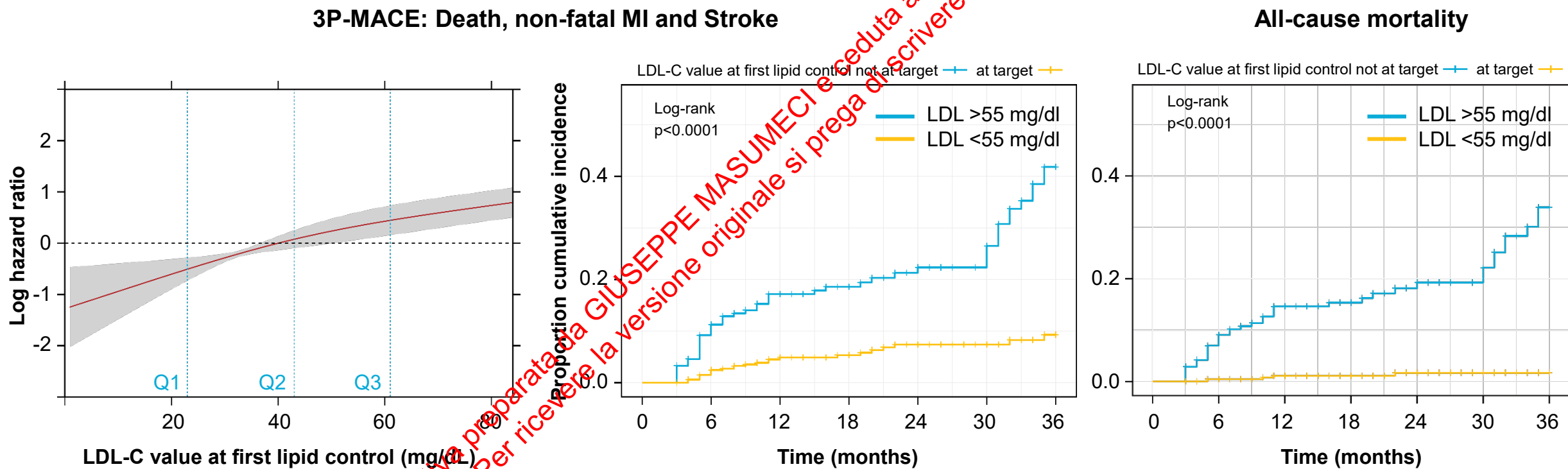


Effects of the strike early-stroke strong lipid lowering strategy with PCSK9i in patients with ACS. A real-world evidence from the AT-TARGETIT registry



771 ACS patients treated with PCSK9i prescription during hospitalization or at discharge in 22 Italian centres

Better prognosis in patients at target

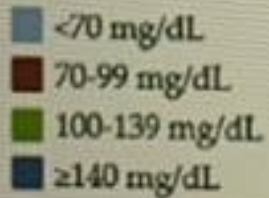
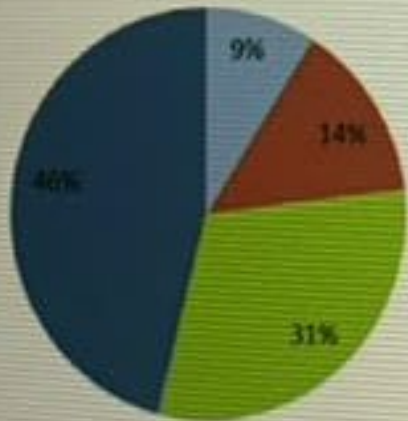


LDL 55 mg/dl = 1.4 mmol/L
3-P, 3-parameter; ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); MACE, major adverse cardiovascular event; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q, quartile
P. Gargiulo, G. Musumeci, P. Fillardi et al. Eur J Prev Cardiol. 2024 May 24;zwae170. doi: 10.1093/eurjpc/zwae170. Online ahead of print

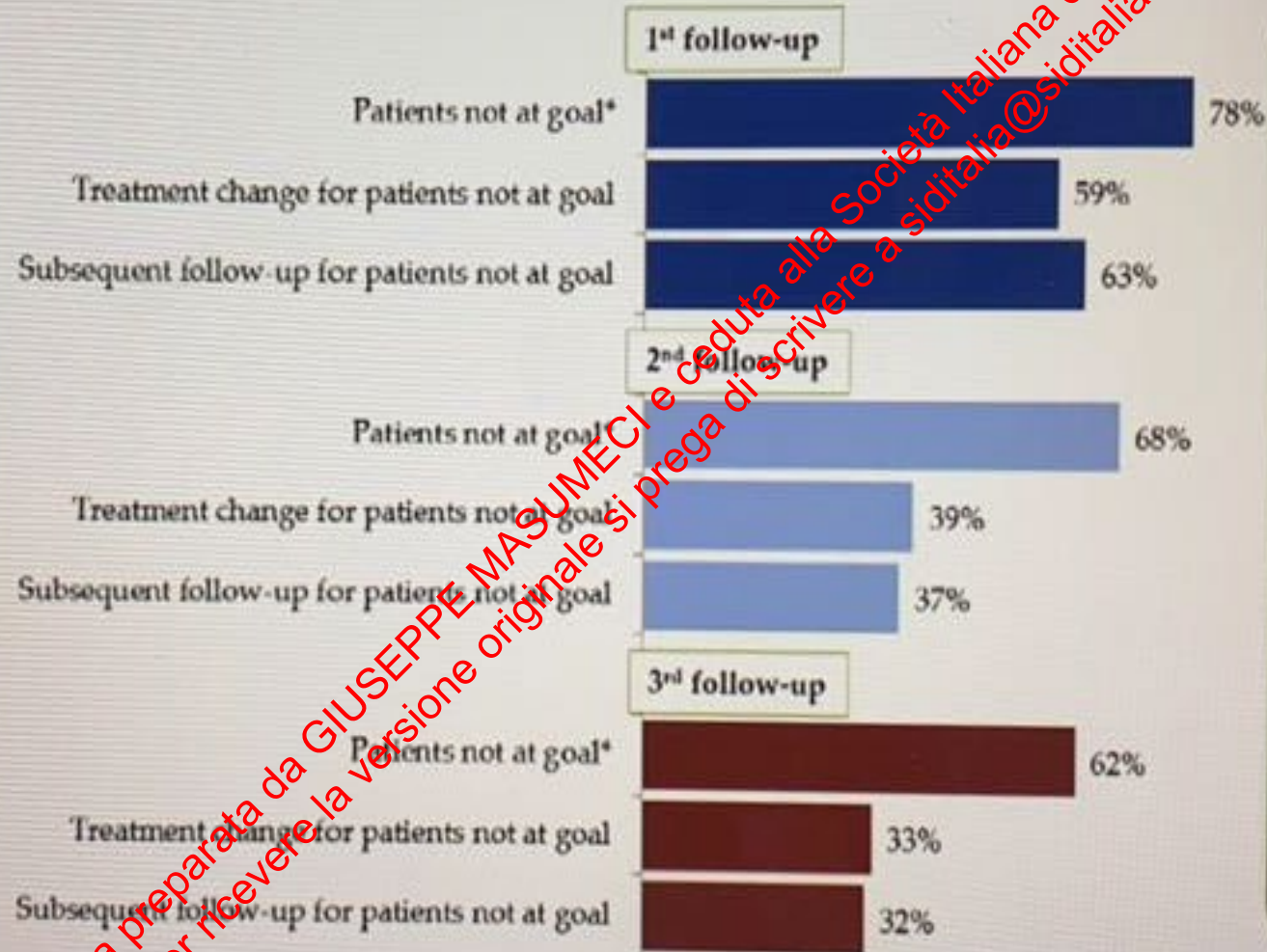
Patients not at goal, treatment changes and follow-up planning during three follow-up visits

The ACS patient pathway project

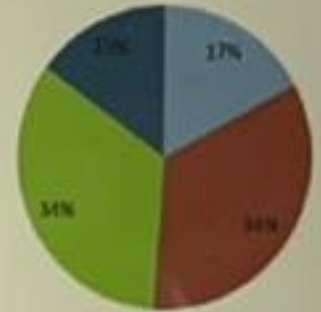
Acute phase



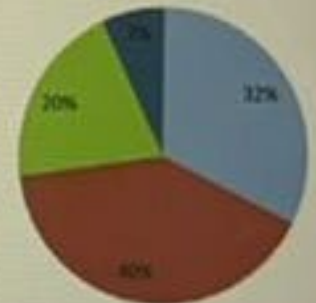
93% received LLT
66% Hi Statin



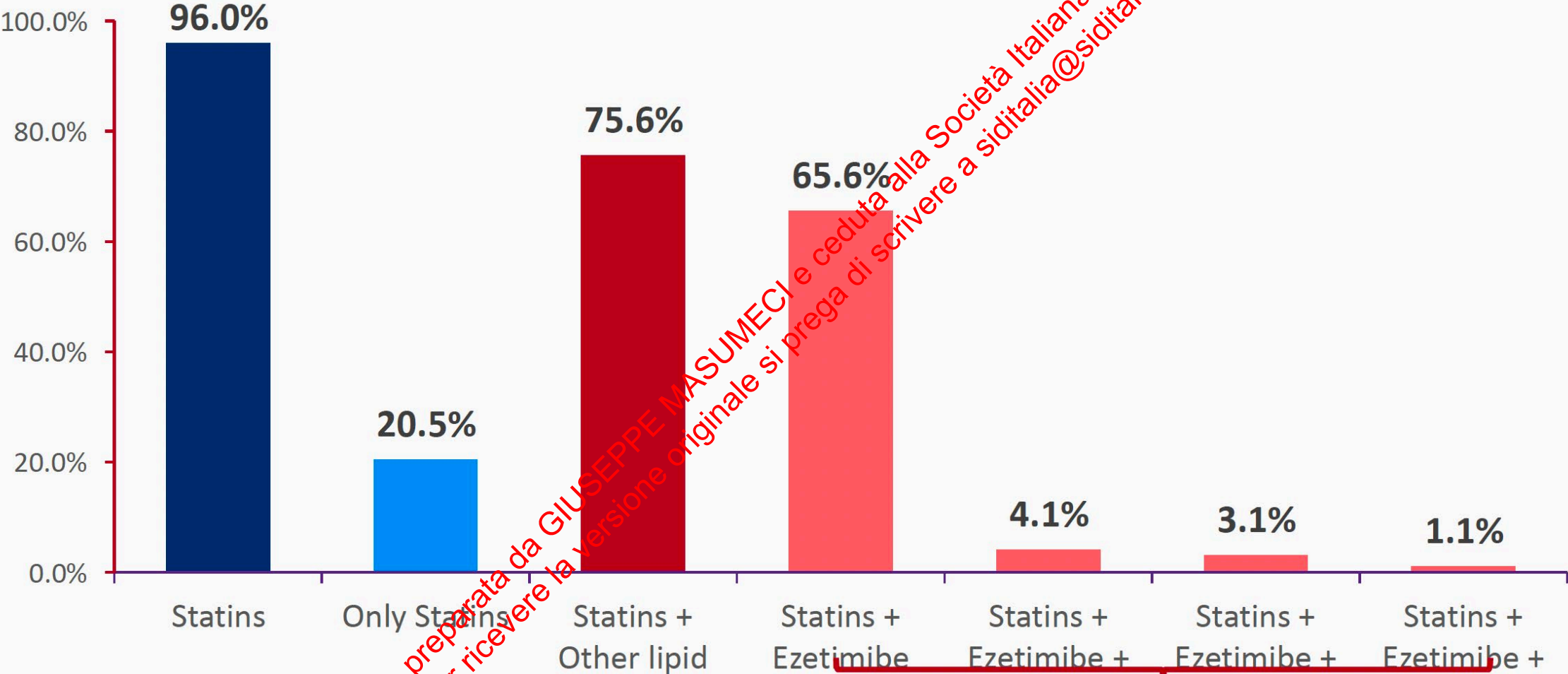
1st follow-up



2nd follow-up



Lipid Lowering Therapy prescribed (4790 pts)



Associations prescribed in >1% of cases

A nationwide longitudinal registry of MI patients in Sweden

Data sourced from

SWEDHEART
registry

Patient
Register



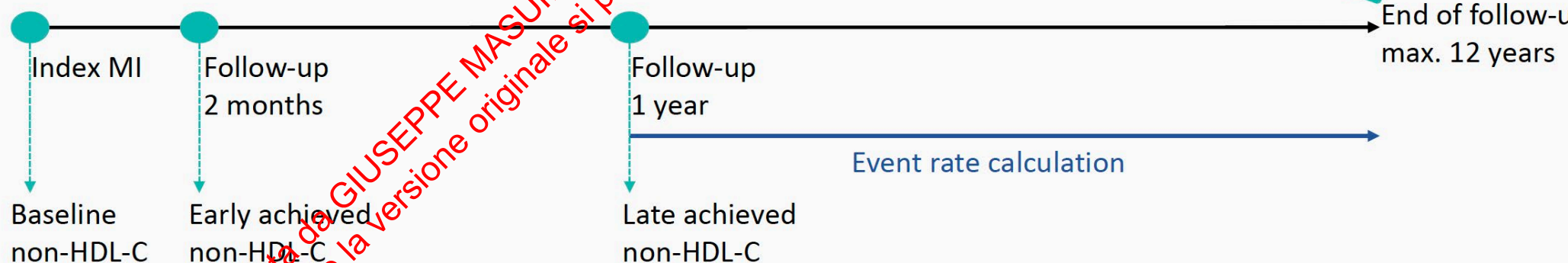
Prescribed
Drug Register



Cause of Death
Register



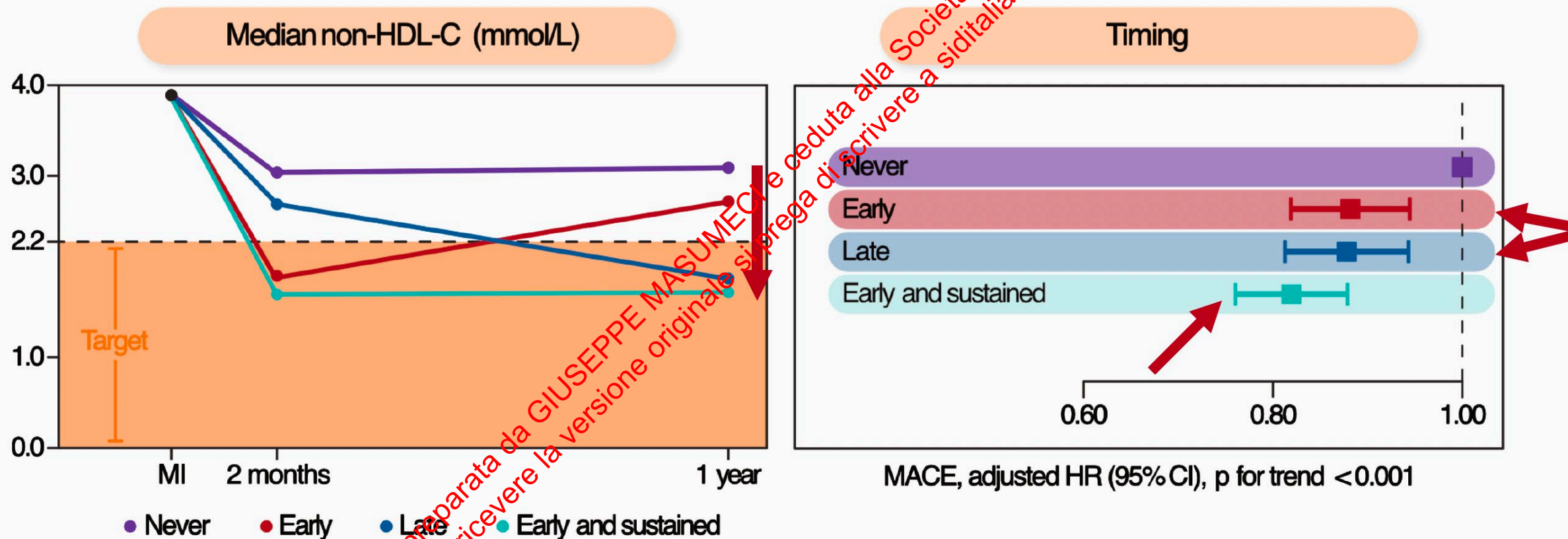
56 262 patients, 26% women
Median age 64 years
Median follow-up 5.4 years



**Target LDL-C 1.4 mmol/L
corresponds to
non-HDL-C < 2.2 mmol/L**

Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained

46 518 patients with MI and 7407 MACE events (all-cause mortality, MI, or stroke)



Reduction, how to achieve it and association with outcomes

Figure S8. 46% reduction in non-HDL-C at 1 year

