71° CONGRESSO NAZIONALE FIMMG METIS

Domus de Maria, 9 ottobre 2015

L'OTTIMIZZAZIONE DELLA TERAPIA IPOLIPEMIZZANTE NEL PAZIENTE POST-SCA ALLA LUCE DELLE REECENTI EVIDENZE

I DATI DELLE REALTA' ITALIANA E LE NUOVE PROSPETTIVE ALLA LUCE DELLE RECENTI EVIDENZE

Pasquale Perrone Filardi
Università Federico II Napoli

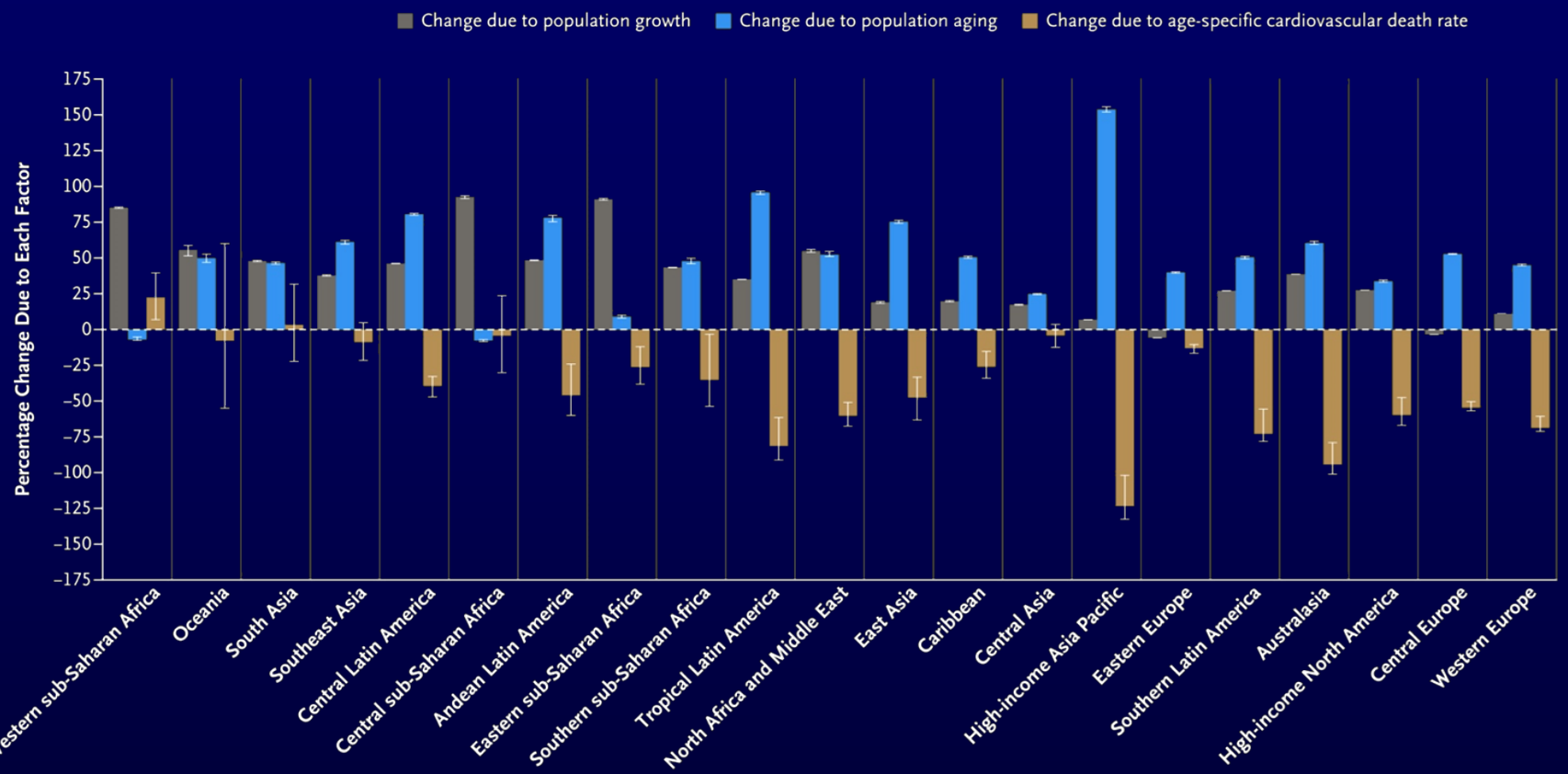
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality

Gregory A. Roth, M.D., M.P.H., Mohammad H. Forouzanfar, Ph.D., Andrew E. Moran, M.D., M.P.H., Ryan Barber, B.A., Grant Nguyen, B.A., Valery L. Feigin, M.D., Ph.D., Mohsen Naghavi, M.D., Ph.D., George A. Mensah, M.D., and Christopher J.L. Murray, M.D., D.Phil.

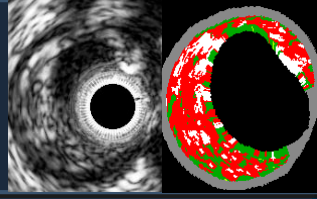
Contribution of Changes in Population Growth, Population Aging, and Rates of Age-Specific Cardiovascular Death to Changes in Cardiovascular Mortality, 1990–2013



	Western sub-Saharan Africa	Oceania	South Asia	Southeast Asia	Central Latin America	Central sub-Saharan Africa	Andean Latin America	Eastern sub-Saharan Africa	Southern sub-Saharan Africa	Tropical Latin America	North Africa and Middle East	East Asia	Caribbean	Central Asia	High-income Asia Pacific	Eastern Europe	Southern Latin America	Australasia	High-income North America	Central Europe	Western Europe
Percentage Change in Cardiovascular Disease Deaths (1990–2013)	100.9	97.5	97.4	90.2	87.2	80.5	80.4	73.9	55.9	49.6	47.2	47.1	44.3	38.1	37.2	21.1	4.7	4.6	1.5	−5.2	−12.8
Additional Cardiovascular Disease Deaths in 2013 vs. 1990	167,685	10,722	1,757,907	630,419	149,646	56,313	27,038	161,463	43,372	140,418	294,430	1,221,994	38,073	85,306	138,018	288,032	9,713	3,769	21,370	(33,423)	(194,351)

N Engl J Med. 2015 Apr 2;372(14):1333-41

The PROSPECT Trial



700 pts with ACS

UA (with ECGΔ) or NSTEMI or STEMI >24º
undergoing PCI of 1 or 2 major coronary arteries
at up to 40 sites in the U.S. and Europe

Metabolic S.
- Waist circum
- Fast lipids
- Fast glu
- HgbA1C
- Fast insulin
- Creatinine

PCI of culprit lesion(s)

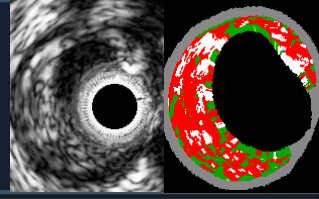
Successful and uncomplicated

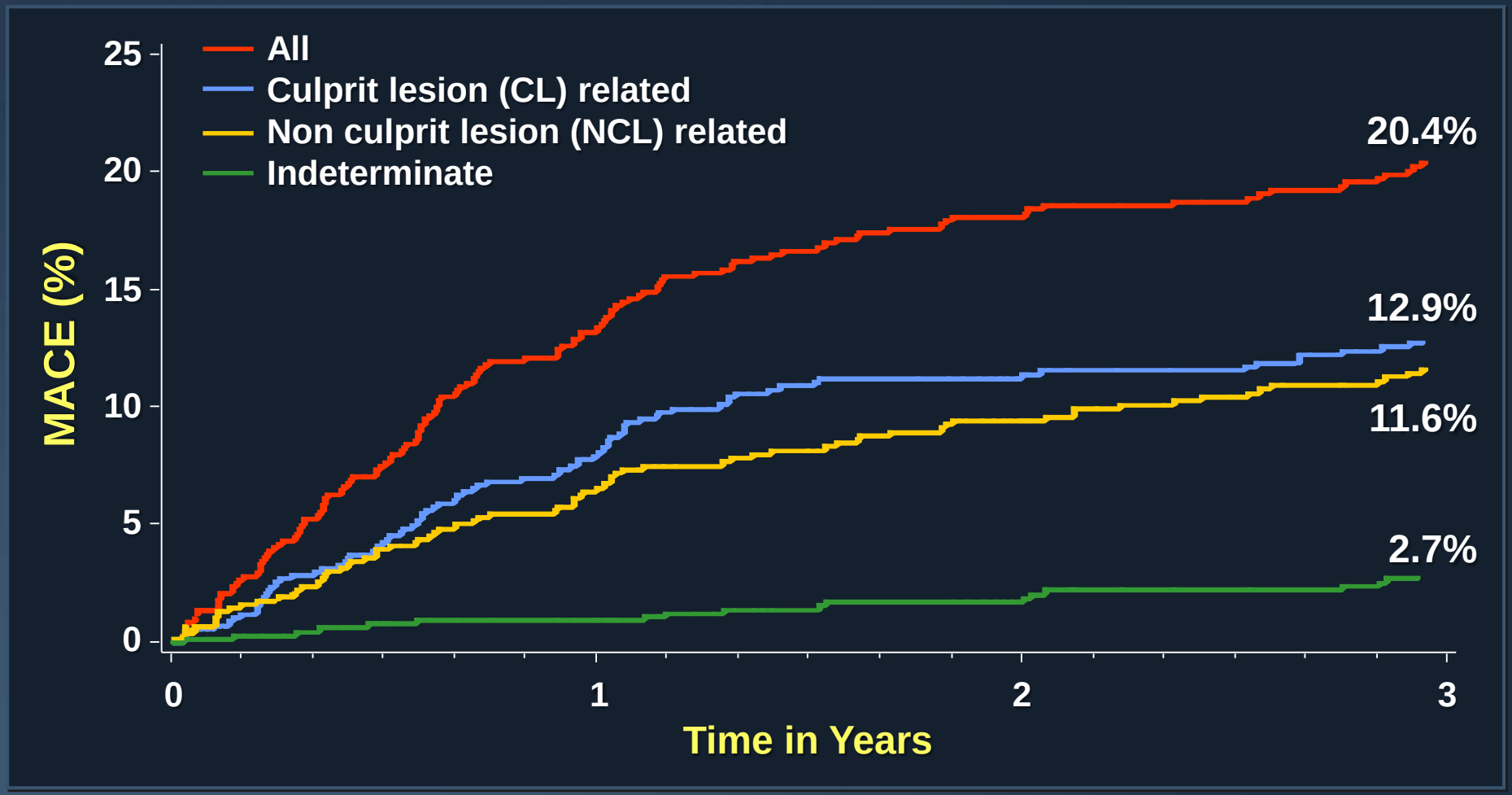
Formally enrolled

Biomarkers
- Hs CRP
- IL-6
- sCD40L
- MPO
- TNFα
- MMP9
- Lp-PLA2
- others

PI: Gregg W. Stone
Sponsor: Abbott Vascular; Partner: Volcano

PROSPECT: MACE

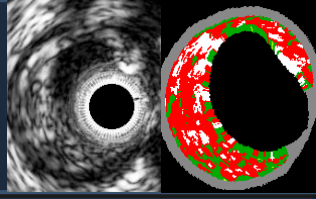


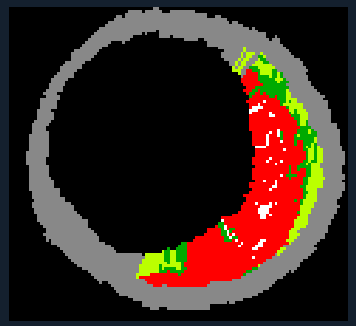


Number at risk

ALL	697	557	506	480
CL related	697	590	543	518
NCL related	697	595	553	521
Indeterminate	697	634	604	583

PROSPECT: VH-TCFA and Non Culprit Lesion Related Events

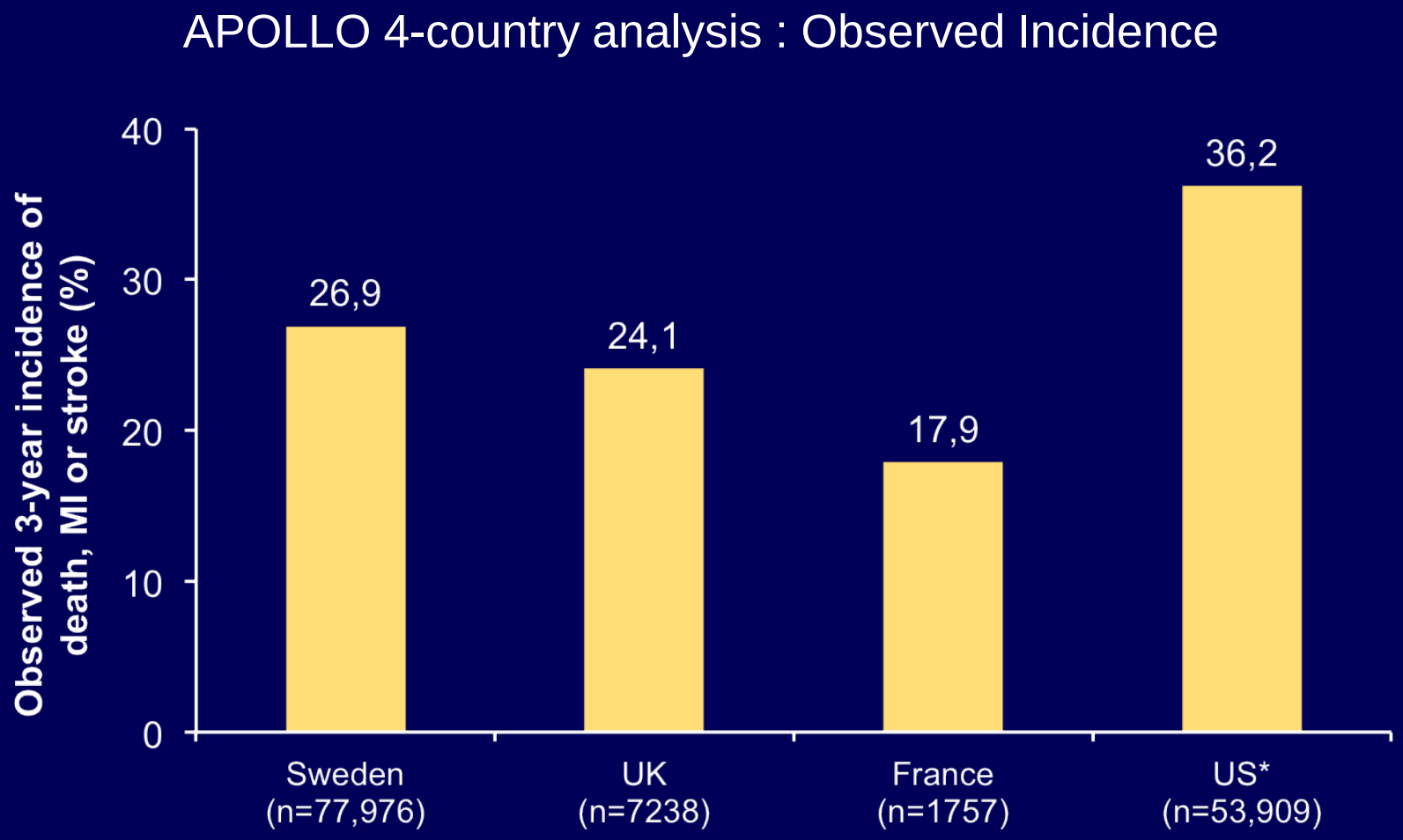




	TCFA	TCFA + MLA ≤4.0mm2	TCFA + PB ≥70%	TCFA + PB ≥70% + MLA ≤4mm2
Lesion HR	3.84 (2.22, 6.65)	6.41 (3.35, 12.24)	10.77 (5.53, 21.00)	10.81 (4.30, 27.22)
P value	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence*	51.2%	17.4%	11.0%	4.6%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

Up to a third of patients who are event free for the first year post-MI, will suffer a MI, stroke or death within 3 years



*US sample restricted to patients aged ≥65 years. MI, myocardial infarction.
Rapsomaniki E, et al. ESC Late Breaking Registry presentation 2014: In press.

PURE Study

Drug use in participants with coronary heart disease or stroke, by country economic status and overall

Yusuf et al. Lancet 2011

	Overall	High-income countries	Upper middle-income countries	Lower middle-income countries	Low-income countries	P_{trend}
Coronary heart disease	5650	669	1396	2857	728	
Antiplatelet drugs	1460 (25·8%)	429 (64·1%)	378 (27·1%)	573 (20·1%)	80 (11·0%)	<0·0001
β blockers	1154 (20·4%)	311 (46·5%)	433 (31·0%)	329 (11·5%)	81 (11·1%)	<0·0001
ACE inhibitors or ARBs	1128 (20·0%)	346 (51·7%)	432 (30·9%)	303 (10·6%)	47 (6·5%)	<0·0001
Diuretics*	768 (13·6%)	102 (15·2%)	262 (18·8%)	375 (13·1%)	29 (4·0%)	<0·0001
Calcium-channel blockers†	753 (13·3%)	150 (22·4%)	163 (11·7%)	387 (13·5%)	53 (7·3%)	<0·0001
Blood-pressure-lowering drugs‡	2427 (43·0%)	524 (78·3%)	712 (51·0%)	1032 (36·1%)	159 (21·8%)	<0·0001
Statins	942 (16·7%)	474 (70·9%)	295 (21·1%)	140 (4·9%)	33 (4·5%)	<0·0001
Stroke	2292	213	691	1042	346	<0·0001
Antiplatelet drugs	557 (24·3%)	113 (53·1%)	137 (19·8%)	294 (28·2%)	13 (3·8%)	<0·0001
β blockers	215 (9·4%)	44 (20·7%)	87 (12·6%)	62 (6·0%)	22 (6·4%)	<0·0001
ACE inhibitors or ARBs	426 (18·6%)	89 (41·8%)	195 (28·2%)	135 (13·0%)	7 (2·0%)	<0·0001
Diuretics*	348 (15·2%)	48 (22·5%)	109 (15·8%)	180 (17·3%)	11 (3·2%)	<0·0001
Calcium-channel blockers†	331 (14·4%)	37 (17·4%)	80 (11·6%)	202 (19·4%)	12 (3·5%)	0·0307
Blood-pressure-lowering drugs‡	916 (40·0%)	129 (60·6%)	293 (42·4%)	449 (43·1%)	45 (13·0%)	<0·0001
Statins	206 (9·0%)	110 (51·6%)	72 (10·4%)	22 (2·1%)	2 (0·6%)	<0·0001
Coronary heart disease or stroke	7519	841	1967	3669	1042	<0·0001
Antiplatelet drugs	1900 (25·3%)	521 (62·0%)	484 (24·6%)	803 (21·9%)	92 (8·8%)	<0·0001
β blockers	1312 (17·4%)	336 (40·0%)	500 (25·4%)	375 (10·2%)	101 (9·7%)	<0·0001
ACE Inhibitors or ARBs	1469 (19·5%)	419 (49·8%)	590 (30·0%)	406 (11·1%)	54 (5·2%)	<0·0001
Diuretics*	1033 (13·7%)	138 (16·4%)	350 (17·8%)	507 (13·8%)	38 (3·6%)	<0·0001
Calcium-channel blockers†	1006 (13·4%)	174 (20·7%)	233 (11·8%)	535 (14·6%)	64 (6·1%)	<0·0001
Blood-pressure-lowering drugs‡	3146 (41·8%)	621 (73·8%)	954 (48·4%)	1371 (37·4%)	200 (19·2%)	<0·0001
Statins	1096 (14·6%)	559 (66·5%)	347 (17·6%)	156 (4·3%)	34 (3·3%)	<0·0001

SECONDARY PREVENTION IN ITALY

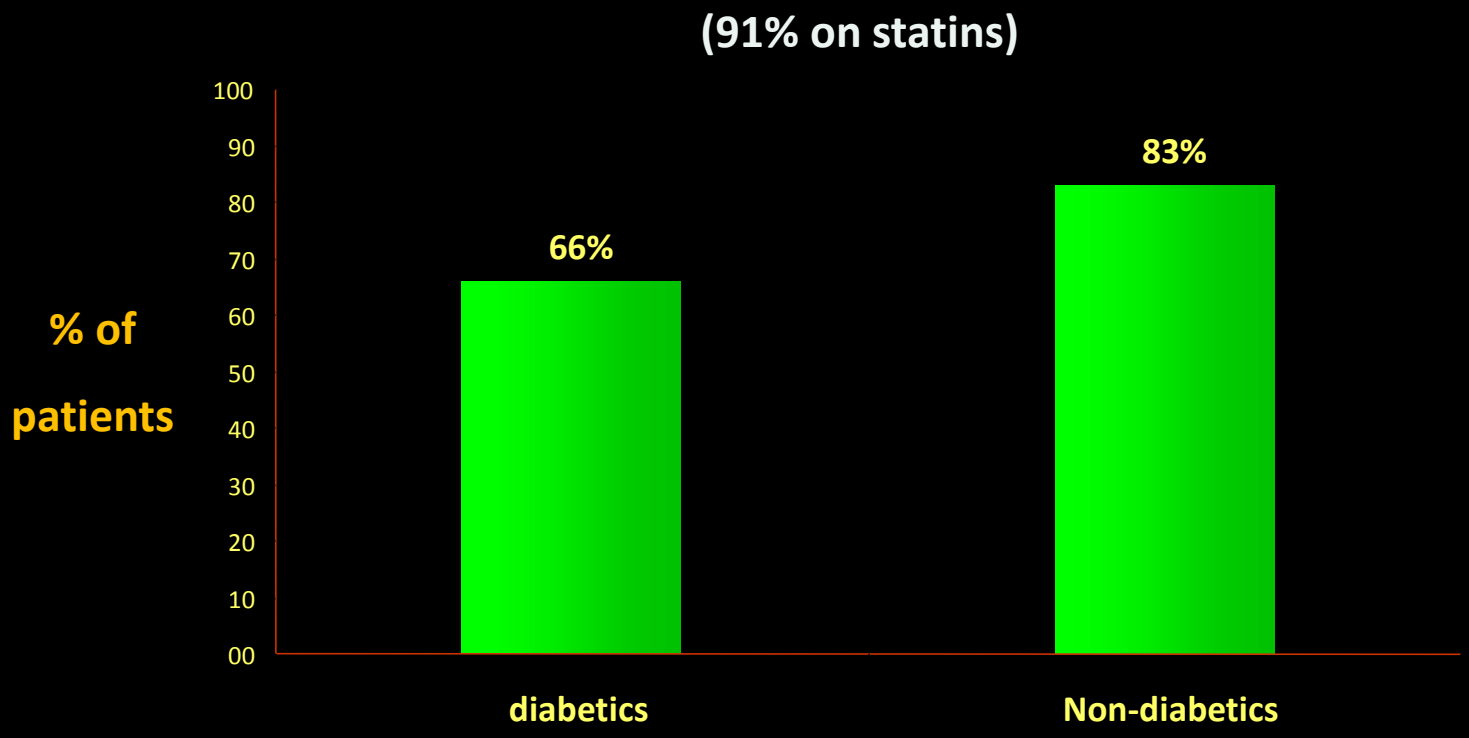
Perrone Filardi et al. Nutr, Met and Cardiovasc Dis 2012

NORD	*20 centri*	*288 paz.*
CENTRO	*7 centri*	*192 paz.*
SUD	*15 centri*	*286 paz.*
SICILIA	*5 centri*	*58 paz.*
SARDEGNA	*2 centri*	*89 paz.*
TOTALE	*49 centri*	*913 paz.*

Periodo di osservazione:
30 Nov 2006 – 19 Feb 2008

SECONDARY PREVENTION IN ITALY
% OF PATIENTS WITH PREVIOUS CARDIOVASCULAR EVENTS AND LDL-C > 70 mg/dl

Perrone Filardi et al. Nutr, Met and Cardiovasc Dis 2012



European Journal of Preventive Cardiology

EUROPEAN SOCIETY OF CARDIOLOGY®

Original scientific paper

Secondary prevention after acute myocardial infarction: Drug adherence, treatment goals, and predictors of health lifestyle habits. The BLITZ-4 Registry

Stefano Urbinati[1], Zoran Olivari[2], Lucio Gonzini[3], Stefano Savonitto[4], Rosario Farina[5], Maurizio Del Pinto[6], Alberto Valbusa[7], Giuseppe Fantini[8], Alessandra Mazzoni[9] and Aldo P Maggioni[3], for the BLITZ-4 Investigators*

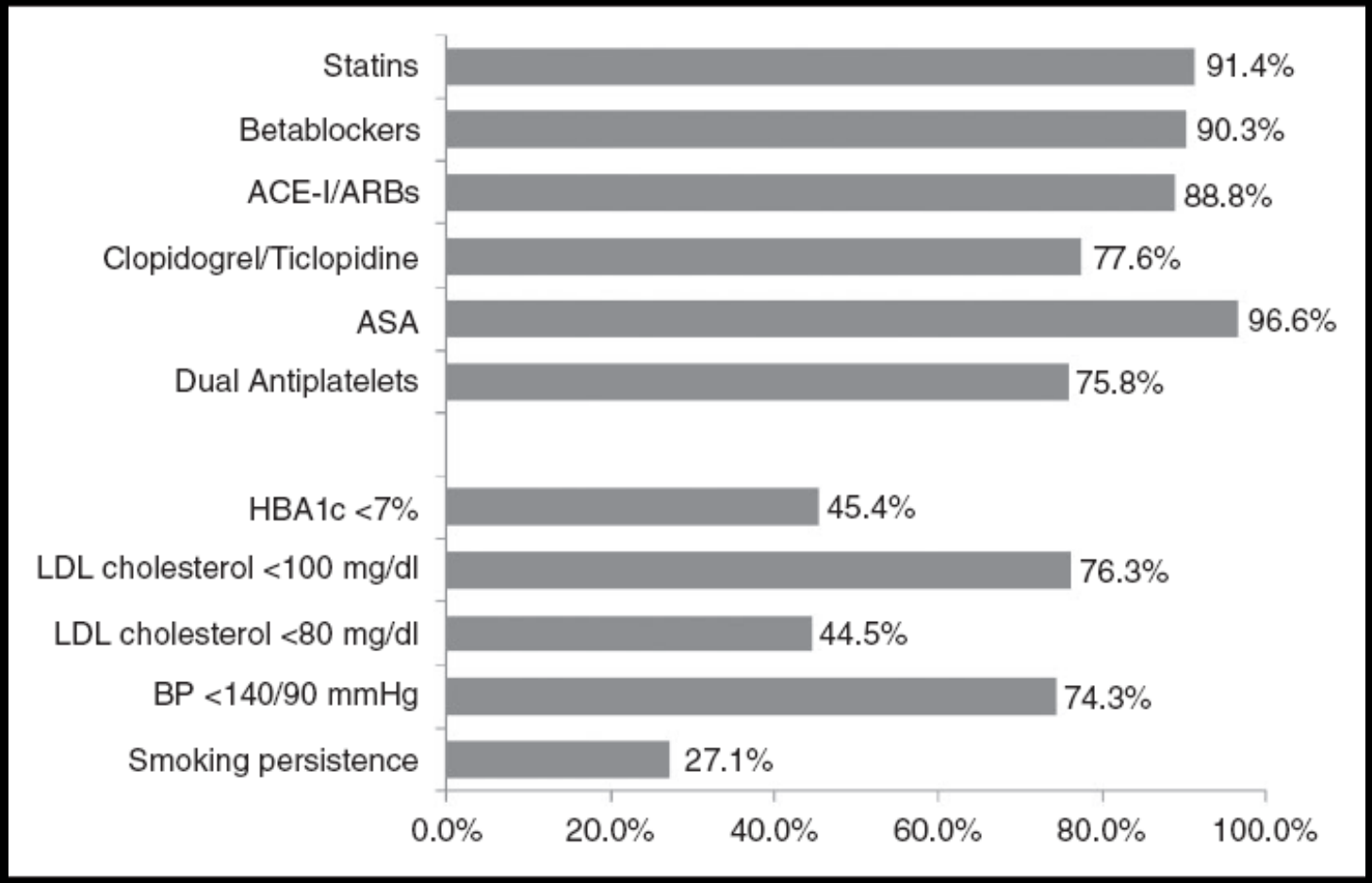
European Journal of Preventive Cardiology
0(00) 1–9

DOI: 10.1177/2047487314561876
ejpc.sagepub.com

SAGE

Table 1. Baseline characteristics

	$n = 11{,}706$
Females, *n* (%)	3557 (30.4)
Age, years, mean ± SD	68 ± 13
Age, years (females), mean ± SD	73 ± 12
Age, years (males), mean ± SD	66 ± 13
Active smokers, *n* (%)	3716 (31.7)
Arterial hypertension, *n* (%)	7051 (60.2)
Dyslipidaemia, *n* (%)	4234 (36.2)
Diabetes mellitus, *n* (%)	2977 (25.4)
Known renal failure, *n* (%)	970 (8.3)
COPD, *n* (%)	823 (7.0)
Prior MI, *n* (%)	1493 (12.8)
Prior PCI, *n* (%)	1612 (13.8)
Prior CABG, *n* (%)	662 (5.7)
Killip class II, *n* (%)	1744 (14.9)
Killip class III–IV, *n* (%)	784 (6.7)


Statins
91.4%
Betablockers
90.3%
ACE-I/ARBs
88.8%
Clopidogrel/Ticlopidine
77.6%
ASA
96.6%
Dual Antiplatelets
75.8%
HBA1c <7%
45.4%
LDL cholesterol <100 mg/dl
76.3%
LDL cholesterol <80 mg/dl
44.5%
BP <140/90 mmHg
74.3%
Smoking persistence
27.1%
0.0%
20.0%
40.0%
60.0%
80.0%
100.0%

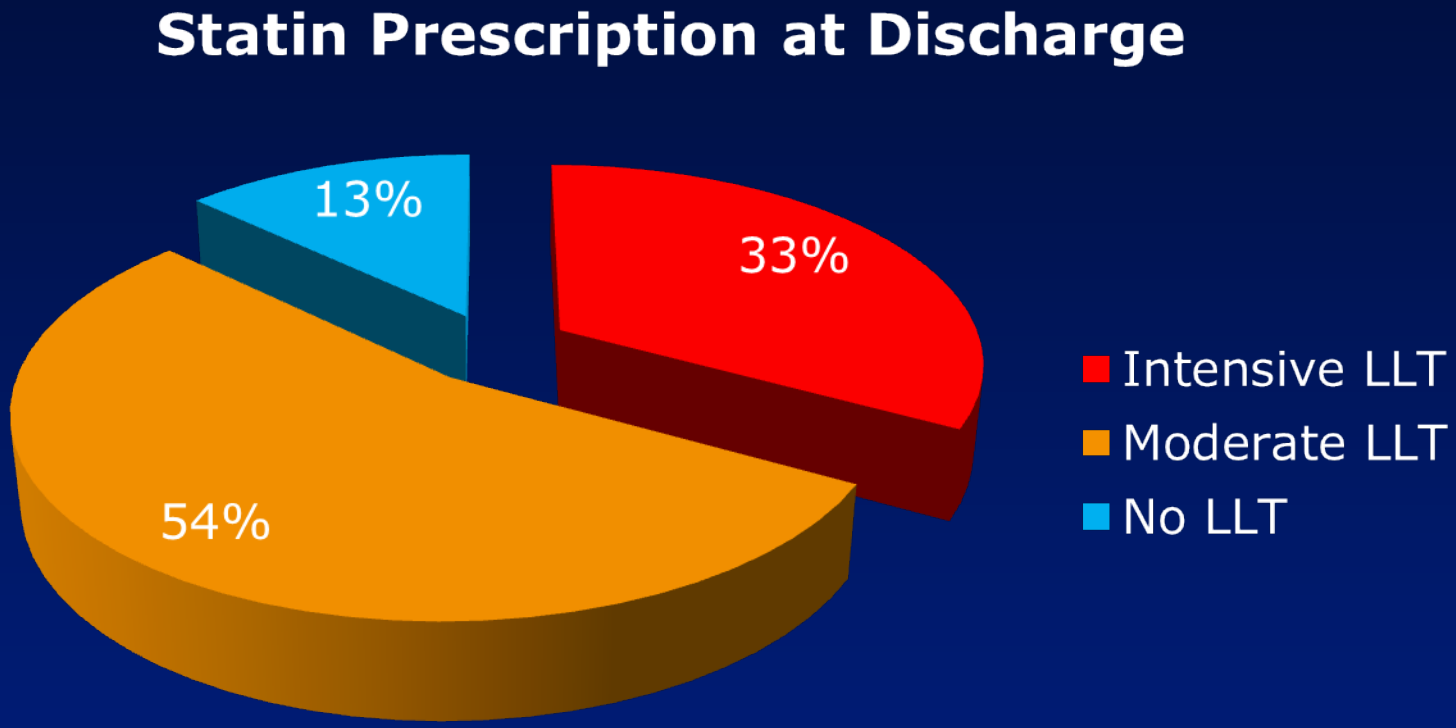
High- Moderate- and Low-Intensity Statin Therapy

(Used in RCTs reviewed by the Expert Panel)

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Circulation. 2013 Nov;12

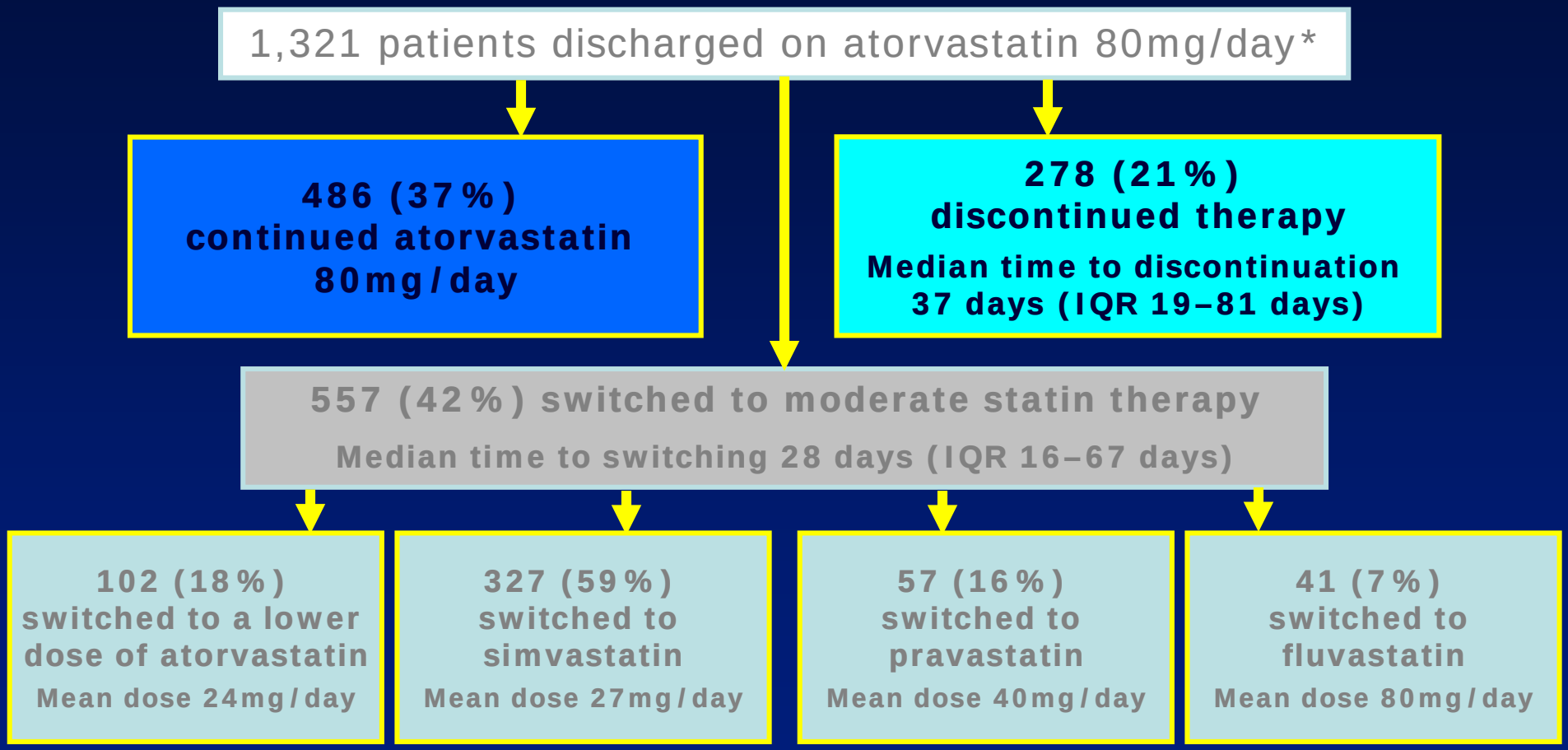
Use of intensive lipid-lowering therapy in patients with ACS in the "Get With The Guidelines" Program



- 138,216 patients discharged, 119,387 (86.4%) receiving LLT and 14,279 (10.3%) without LLT; LLT contraindicated in 4,550 (3.3%).
- Intensive LLT defined as therapy likely to achieve a 50% reduction in LDL-C - *atorvastatin 40-80 mg, rosuvastatin 20-40 mg, simvastatin 80 mg, any statin + ezetimibe*

Am Heart J 2011;161:418-424

Switching from intensive to moderate statin therapy after an acute coronary event

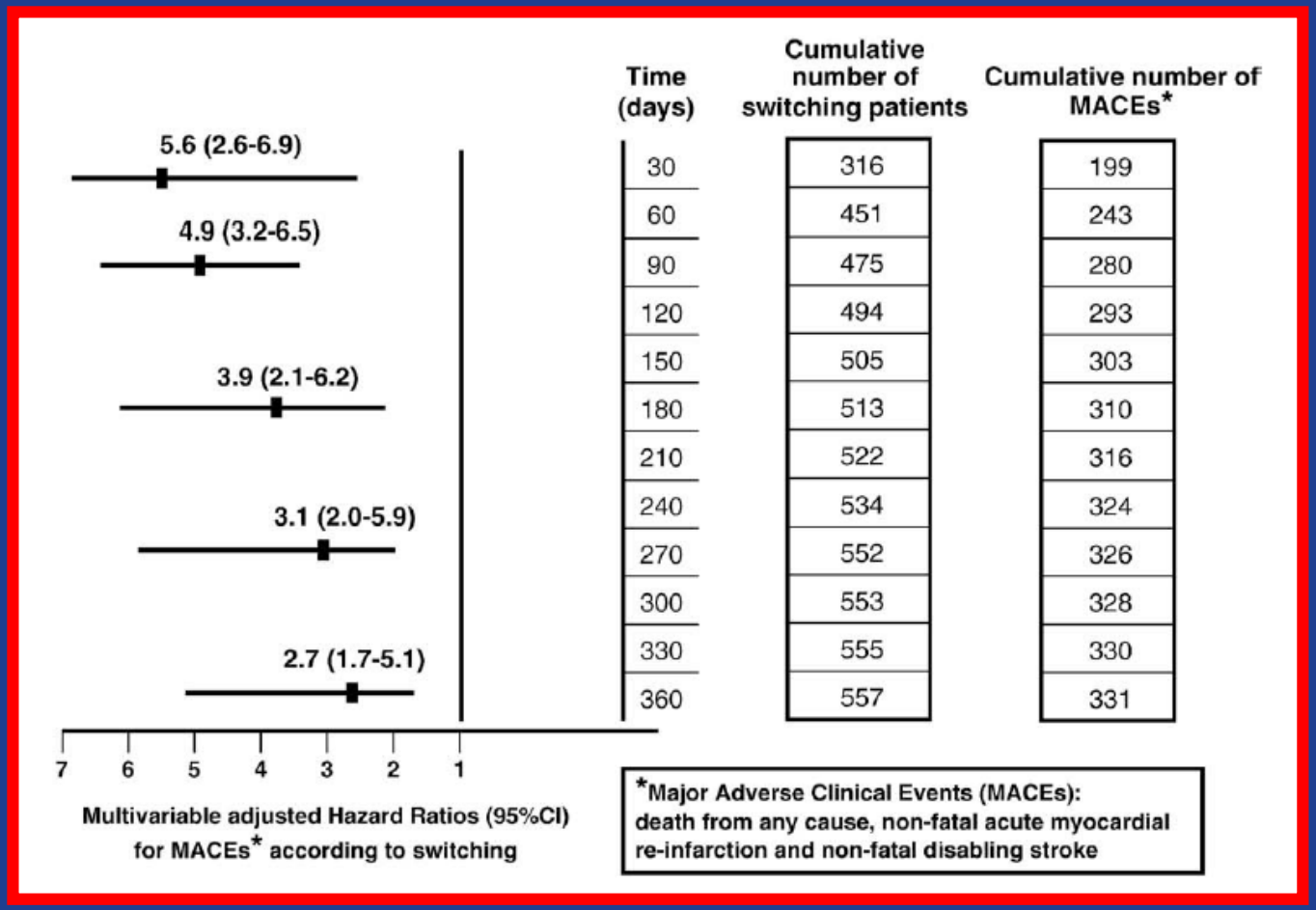


***1321 consecutive patients (886 men, mean age 71.1 ± 8.7 years) discharged on atorvastatin 80mg/day after an ACS in a 6.5-year period**

Colivicchi F, et al. Int J Cardiol (2011), 152: 56-60

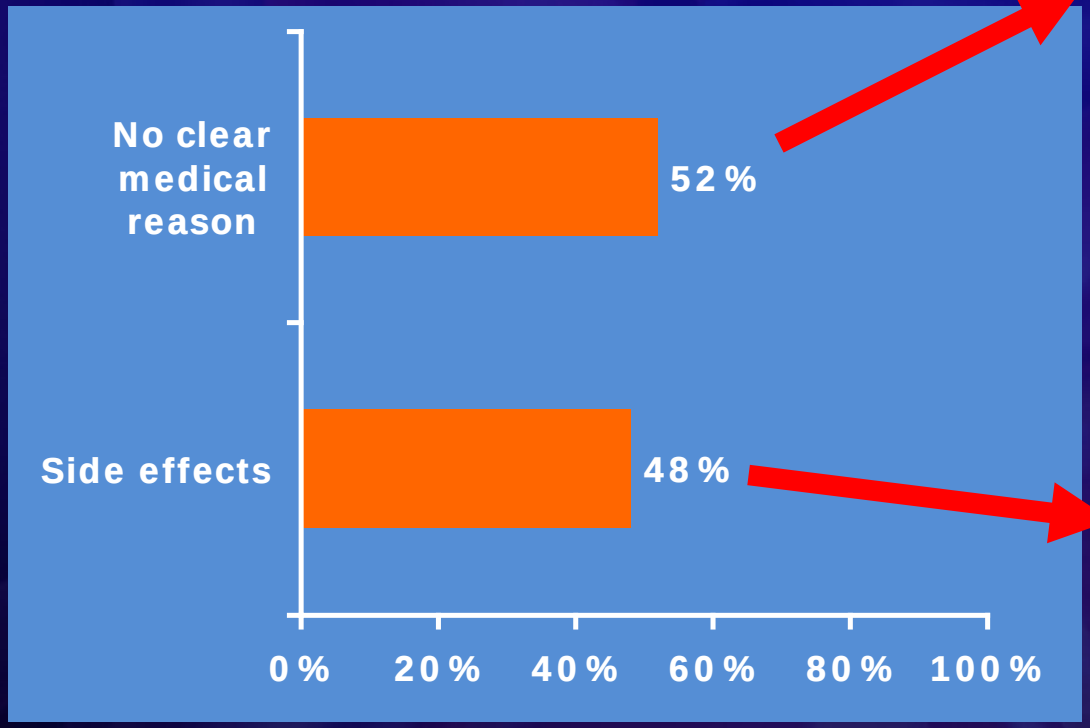
La sostituzione dell'atorvastatina 80 mg con una terapia ipolipemizzante meno efficace si associa ad un significativo peggioramento della prognosi clinica

Incremento di circa 3 volte della probabilità di eventi cardiovascolari sfavorevoli. In caso di interruzione precoce (entro 30 giorni dalla dimissione) la probabilità di eventi sfavorevoli aumenta fino ad oltre 5 volte.



Colivicchi F, et al. Int J Cardiol (2011); 152: 56-60

Cause riferite di interruzione della terapia con statine dopo un evento coronarico acuto



"Troppe pillole"

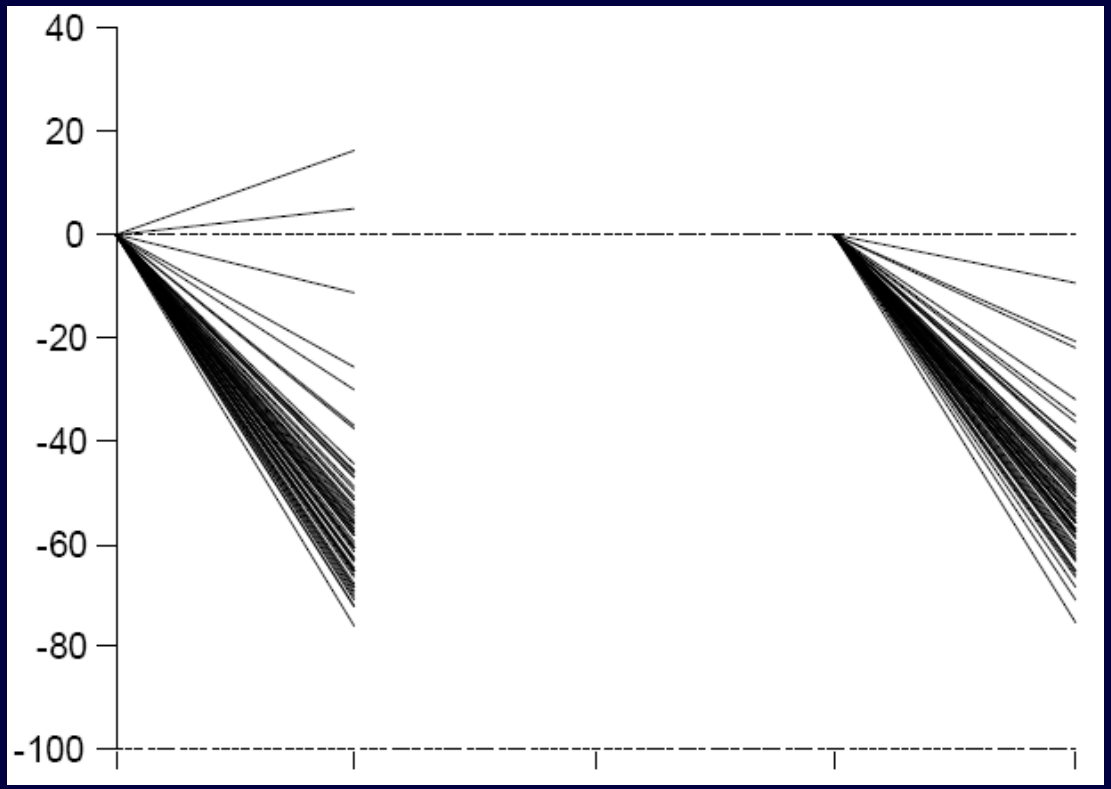
Effetti collaterali riferiti

- Dispepsia
- Astenia
- Cefalea
- Mialgie
- Aumento asintomatico delle transaminasi
- Aumento asintomatico del CK totale

Colivicchi F, et al. Eur Heart J 2008;29 (Suppl. 1):68

Comparison of the Effects of Maximal Dose Atorvastatin and Rosuvastatin Therapy on Cholesterol Synthesis and Absorption Markers : a post-analysis of STELLAR Trial

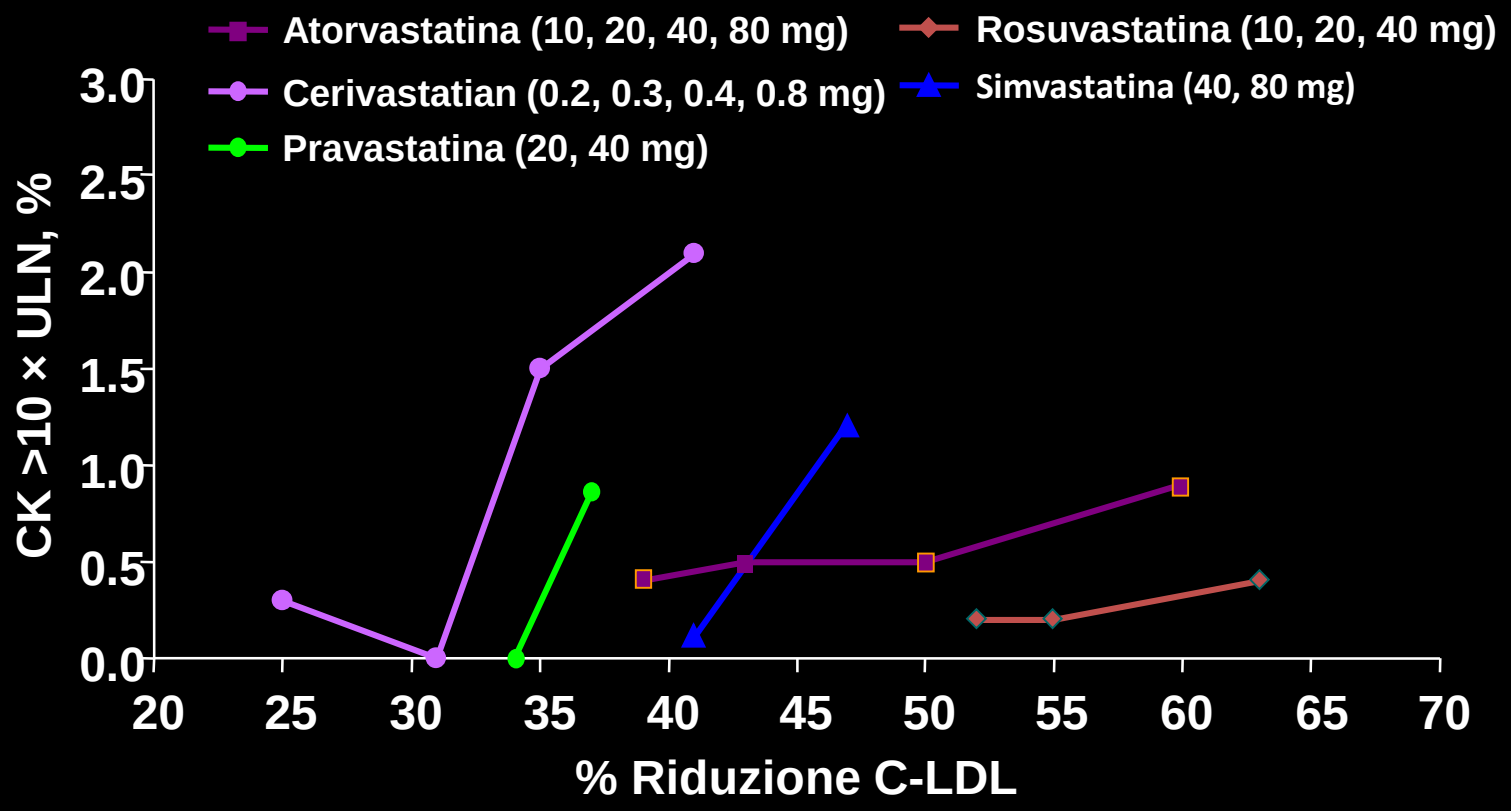
Wide individual response to therapy for LDL-C



Mean % ↓ LDL-C - 55% - 53%

van Himbergen et al J Lipid Res 2009

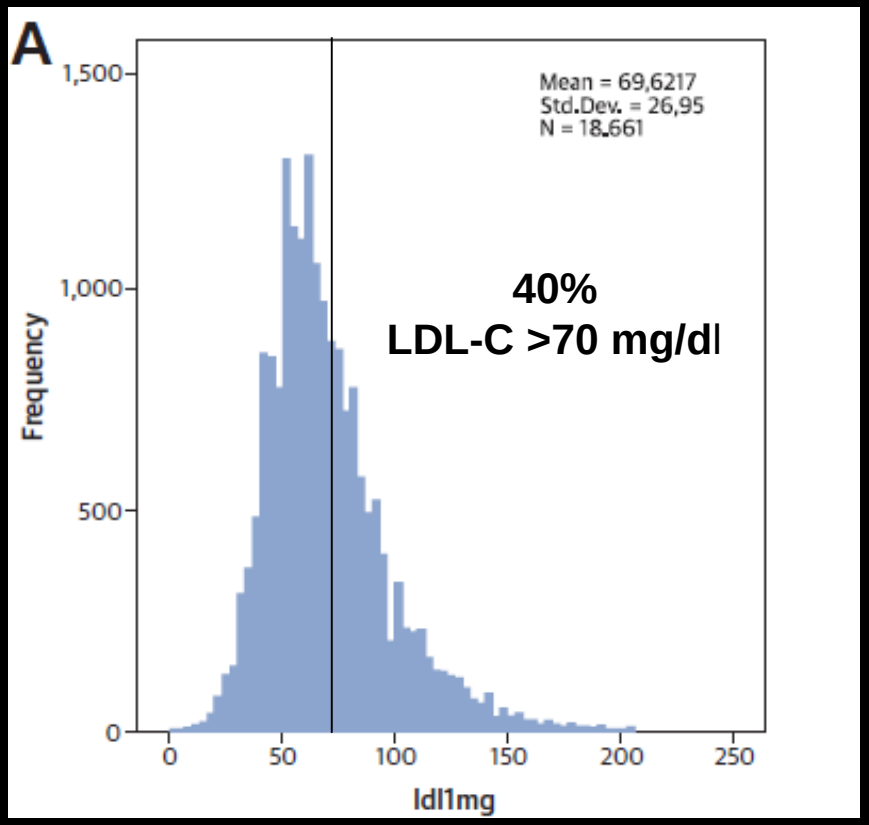
LDL-c ed incremento delle CK



Brewer HB Jr. Am J Cardiol 2003; 92:23K-29K

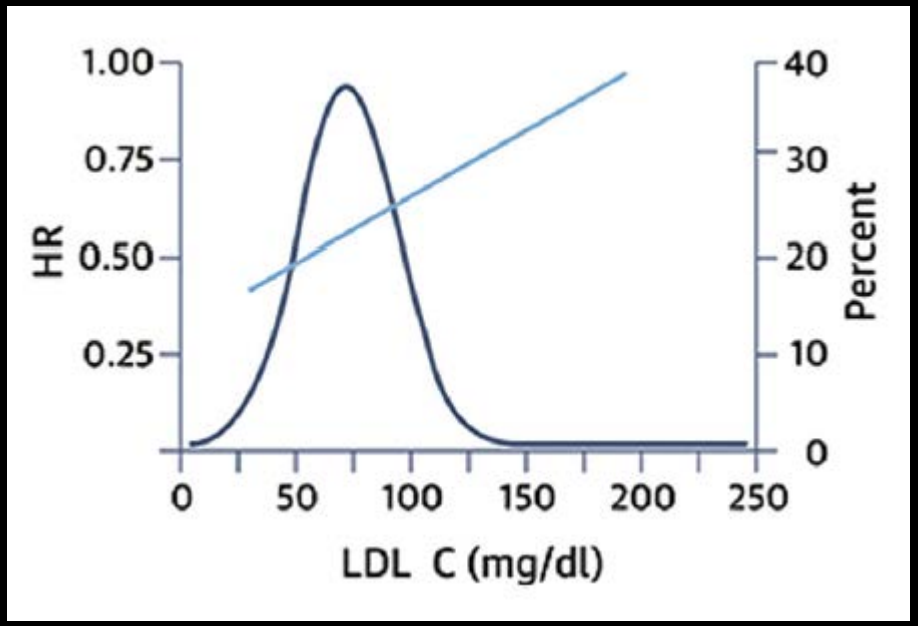
Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events : A Meta-Analysis of Statin Trials

A total of 38,153 study participants



Histograms displaying the distribution of achieved LDL-C in patients treated with high-dose statins

Distribution of achieved on-statin LDL-C levels and the risk of major CV events



JACC 2014 Aug 5;64:485-94.

IMPLICATIONS FROM IMPROVE IT TRIAL

- PATHOPHYSIOLOGICAL
  - IMPROVE IT RESULTS POINT TO EVEN MORE INTENSIVE LDL REDUCTION FOR TREATMENT OF RESIDUAL RISK IN SECONDARY PREVENTION

- GUIDELINES
  - MORE STRINGENT IMPLEMENTATION OF ESC GUIDELINES LDL TARGET IN SECONDARY PREVENTION

  - EZITIMIBE IS FIRST NON STATIN DRUG DEMONSTRATING CLINICAL BENEFIT IN RCT

  - UPGRADE CLASS OF RECOMMENDATION IN GUIDELINES

  - EVIDENCE FOR NEW LDL TARGET?

- CLINICAL PRACTICE
  - COMBINATION THERAPY AS FIRST CHOICE OPTION IN PATIENTS REQUIRING >50% REDUCTION OF LDL (EVEN IF AND ABLE TO ASSUME HIGH POTENCY STATINS)
  - FIRST CHOICE OPTION IN STATIN INTOLERANT PATIENTS

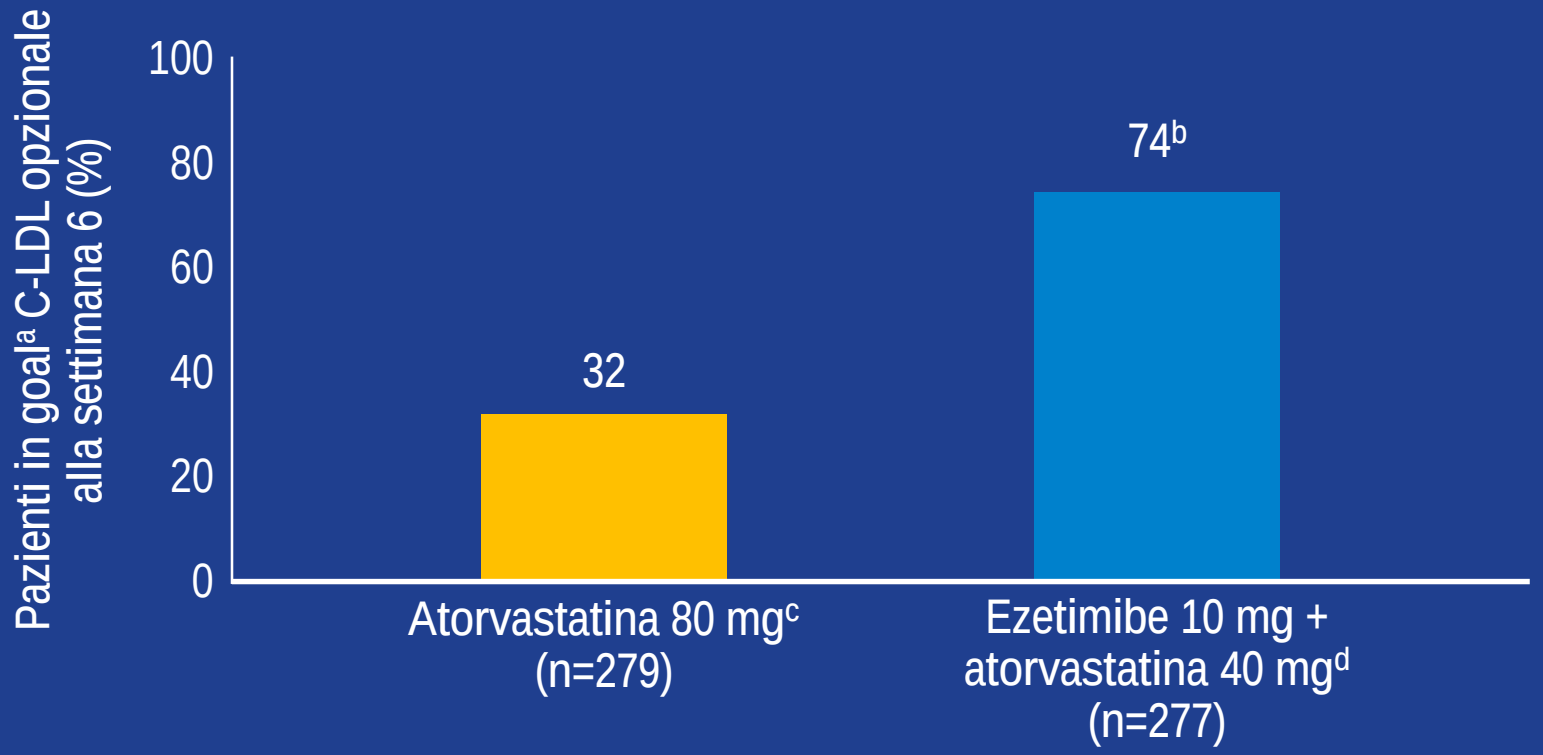
Recommendations for long-term management after non-ST-elevation acute coronary syndromes

Recommendations (for the recommendations on antithrombotic treatment, see sections 5.2.9 and 5.3.3)	**Class**[a]	**Level**[b]	**Ref.**[c]
It is recommended to advise all patients on lifestyle changes (including smoking cessation, regular physical activity and a healthy diet).	I	A	536, 537
It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long term.	I	A	522, 527, 528
An ACE inhibitor is recommended in patients with LVEF ≤40% or heart failure, hypertension or diabetes, unless contraindicated. An ARB provides an alternative, particularly if ACE inhibitors are not tolerated.	I	A	478–481, 530, 531, 538
Beta-blocker therapy is recommended in patients with LVEF ≤40%, unless contraindicated.	I	A	482–486
Mineralocorticoid receptor antagonists, preferably eplerenone, are recommended in patients with LVEF ≤35% and either heart failure or diabetes after NSTE-ACS but no significant renal dysfunction or hyperkalaemia.[d]	I	A	487, 488, 525
A diastolic blood pressure goal of <90 mmHg is recommended (<85 mmHg in diabetic patients).	I	A	539, 540
Participation in a well-structured cardiac rehabilitation programme to modify lifestyle habits and increase adherence to treatment should be considered.	IIa	A	535, 541–546
In patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) despite a maximally tolerated statin dose, further reduction in LDL cholesterol with a non-statin agent[e] should be considered.	IIa	B	529
A systolic blood pressure goal of <140 mmHg should be considered.	IIa	B	547–549

Eur Heart J. 2015 Aug 29. pii: ehv320

Studio EZ-PATH

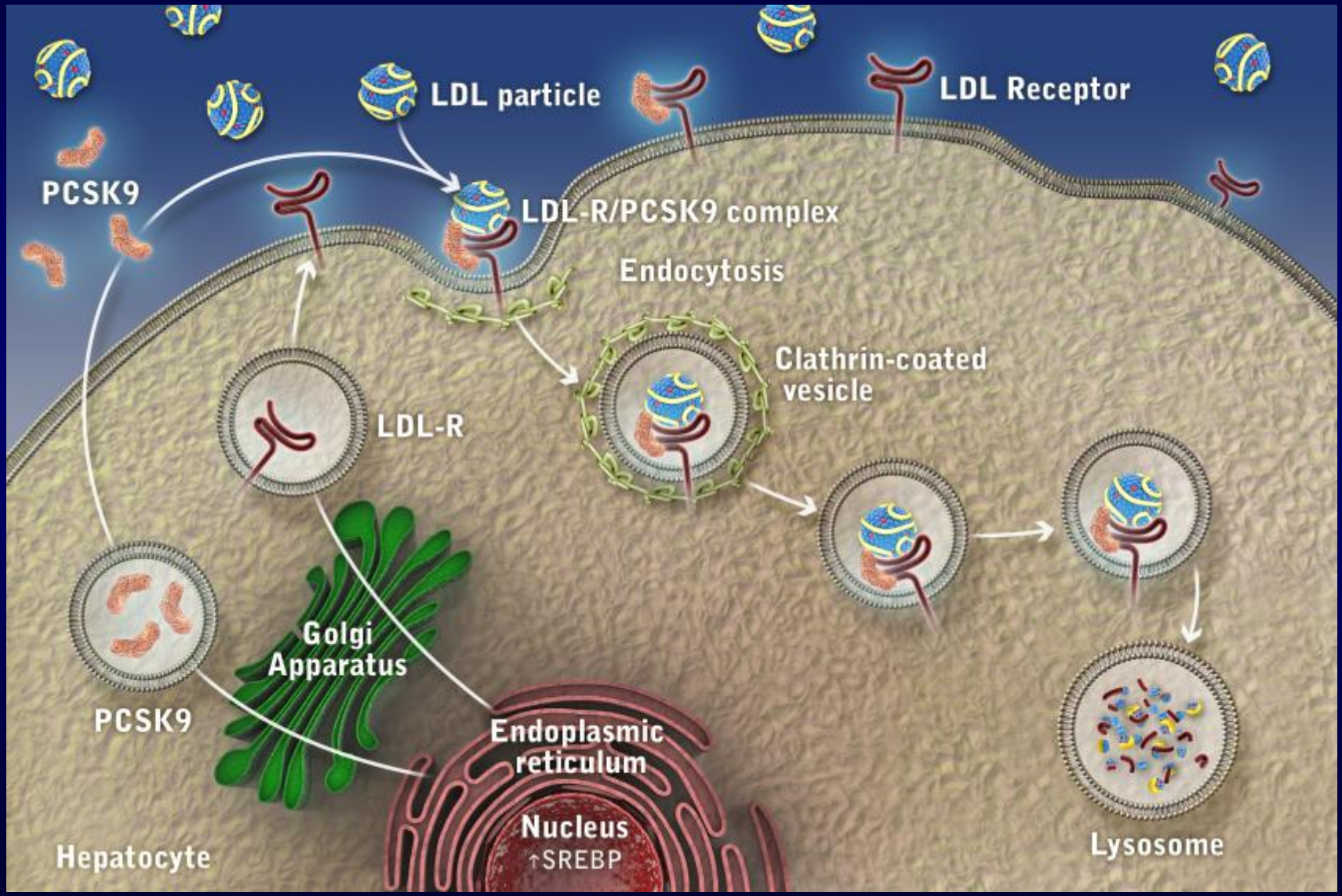
Confronto tra raddoppio di atorvastatina e aggiunta di ezetimibe nel raggiungere l'obiettivo di C-LDL<70 mg/dl



[a]<70 mg/dl (<1,8 mmol/l); [b]p <0,001 vs atorvastatina 80 mg; [c]C-LDL basale = 90 mg/dl; [e]C-LDL basale = 89 mg/dl

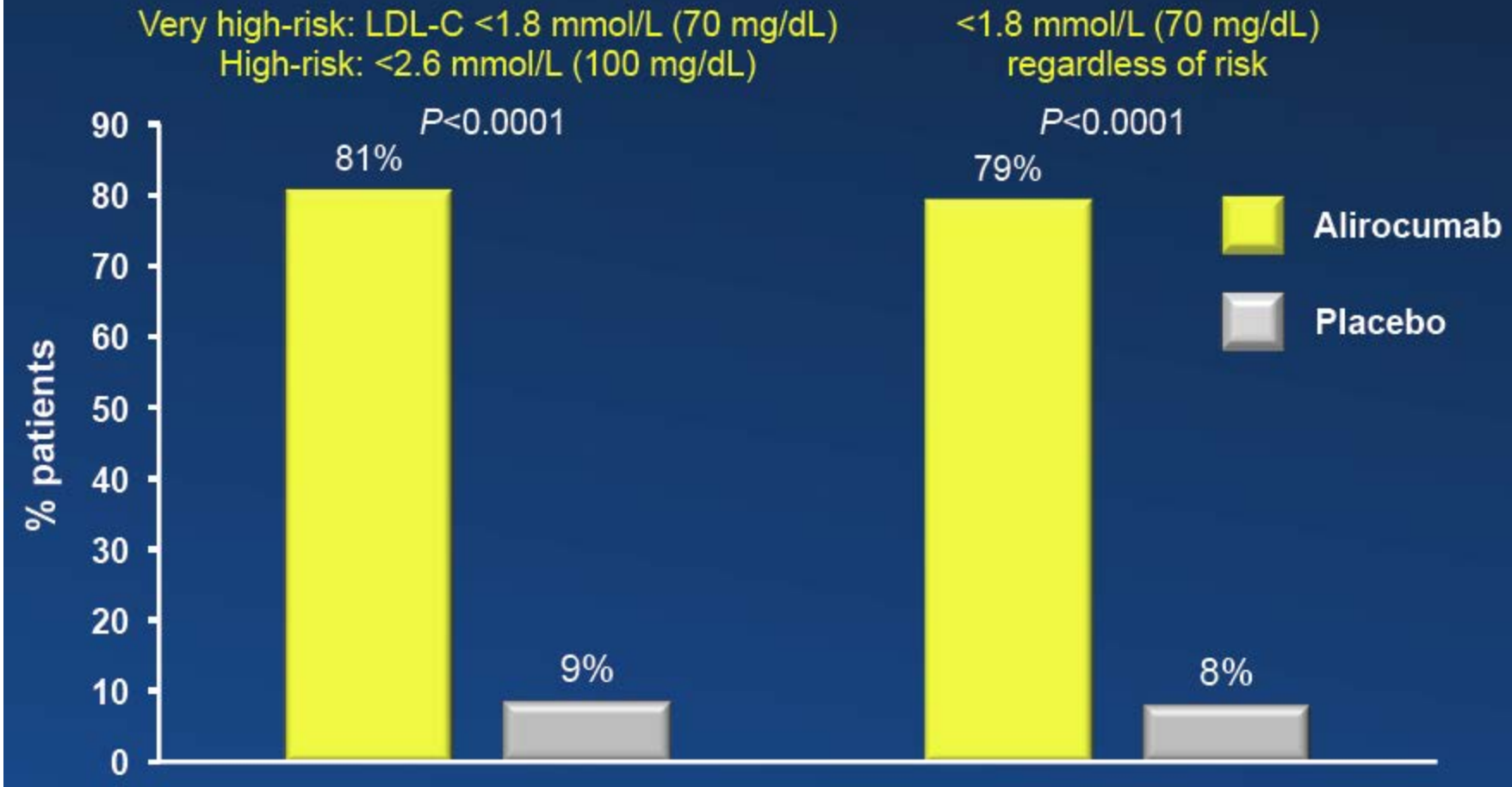
Leiter et al. Am J Cardiol 2008;102:1495-1501

The Role of PCSK9 in the Regulation of LDL Receptor Expression



Most Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals

Proportion of patients reaching LDL-C goal at Week 24



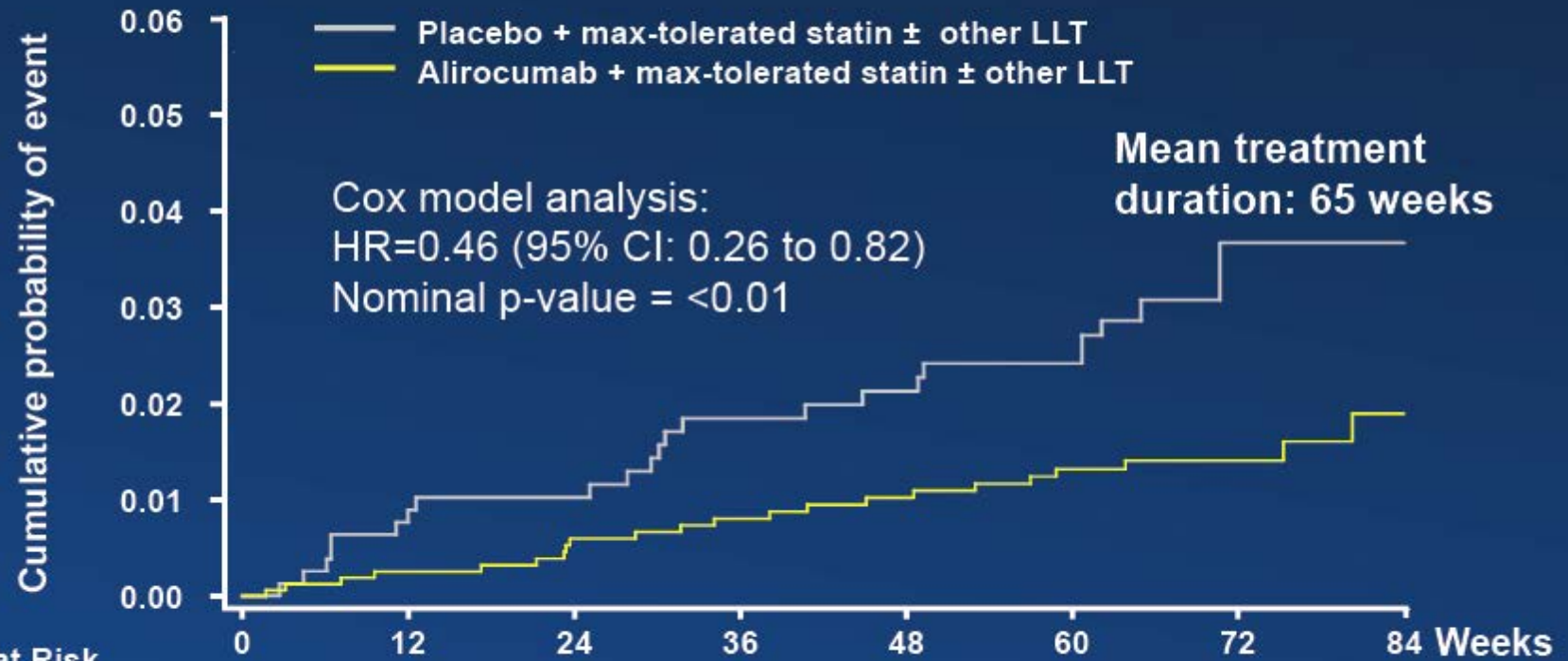
Intent-to-treat (ITT) analysis; LLT = lipid-lowering therapy

Post-hoc Adjudicated Cardiovascular TEAEs†

Safety Analysis (at least 52 weeks for all patients in ongoing study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)



No. at Risk								
Placebo	788	776	731	703	682	667	321	127
Alirocumab	1550	1534	1446	1393	1352	1335	642	252

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. LLT, lipid-lowering therapy

ODYSSEY

PERSPECTIVES

- EFFICACY AND SAFETY OF VERY LOW LDL VALUES
- CLINICAL VALUE OF NON LDL TREATMENTS
  - HDL (NO MENDELIAN RANDOMIZATION CONFIRMATION)
  - TG (MENDELIAN RANDOMIZATION CONFIRMATION)
  - MIXED DYSLIPIDEMIA
  - LIP_a
  - APOC3
- CLINICAL VALUE OF NON LDL TARGETS
  - NON HDL CHOLESTEROL
  - TG, HDL, LIP_a