La gestione del rischio cardiovascolare e la presa in carico del paziente post acuto

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XV CONGRESSO NAZIONALE CARD ITALIA:

Conferenza Nazionale Cure Domiciliari e Piano delle cronicità

8 -10 giugno 2017
Bologna,

Prevenzione secondaria:
Linea Guida Alfabetica…

- **A** – **A**ntiaggreganti, **A**ce-inibitori
- **B** – **B**etabloccanti
- **C** – **C**olesterolo e **C**igarettes
- **D** – **D**ieta e **D**iabete
- **E** – **E**ducazione ed **E**sercizio

Stratificare il rischio…

1. Classe Killip max ☐
2. Frazione di eiezione <40% ☐
3. Frazione di eiezione ≥40%-<45% con: ☐
   a) pattern di riempimento diastolico restrittivo
   b) insufficienza mitralica >1
   c) WMSI elevato e ventricolo non dilatato
4. Importante variazione del BNP ☐
5. Uso di diuretici dell'ansa ☐

Alto rischio Scompenso Cardiaco

6. Arteriopatia periferica ☐
7. Storia di angina o pregresso infarto miocardico
8. Malattia coronarica multivasale
9. Rivascolarizzazione incompleta
10. Pazienti non rivascolarizzati ☐

Alto rischio Trombotico (Reinfarto)

Greco et al. G Ital Cardiol 2014;15(1 Suppl 1):3S-27S

TERAPIA POST-IMA:
Trattare «meno» = trattare «peggio»

Often the fear of one evil leads us into a worse.

Nicolas Boileau

Keys questions and Gaps in evidence…

- Come prevenire la ricorrenza di eventi cardiovascolari?
- Come ridurre il rischio di «stent-thrombosis»?
- Quali terapie utilizzare?
- Quali target terapeutici?

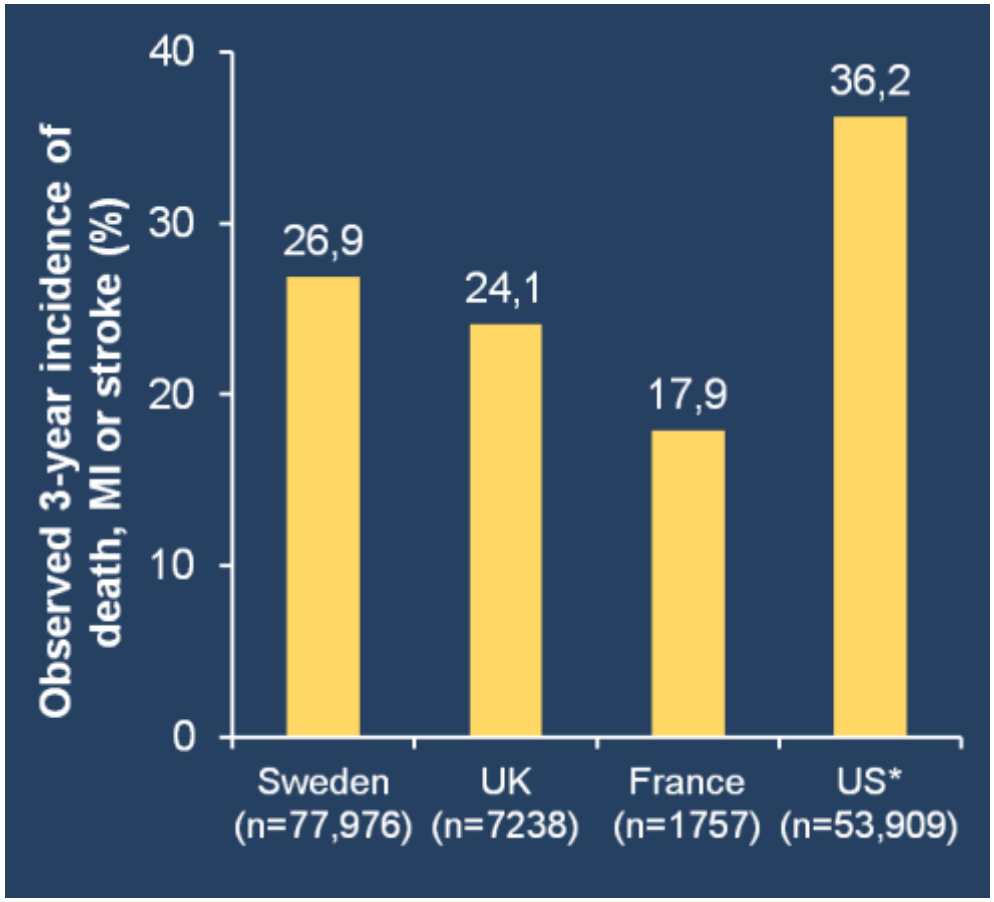
Paziente Post-IMA

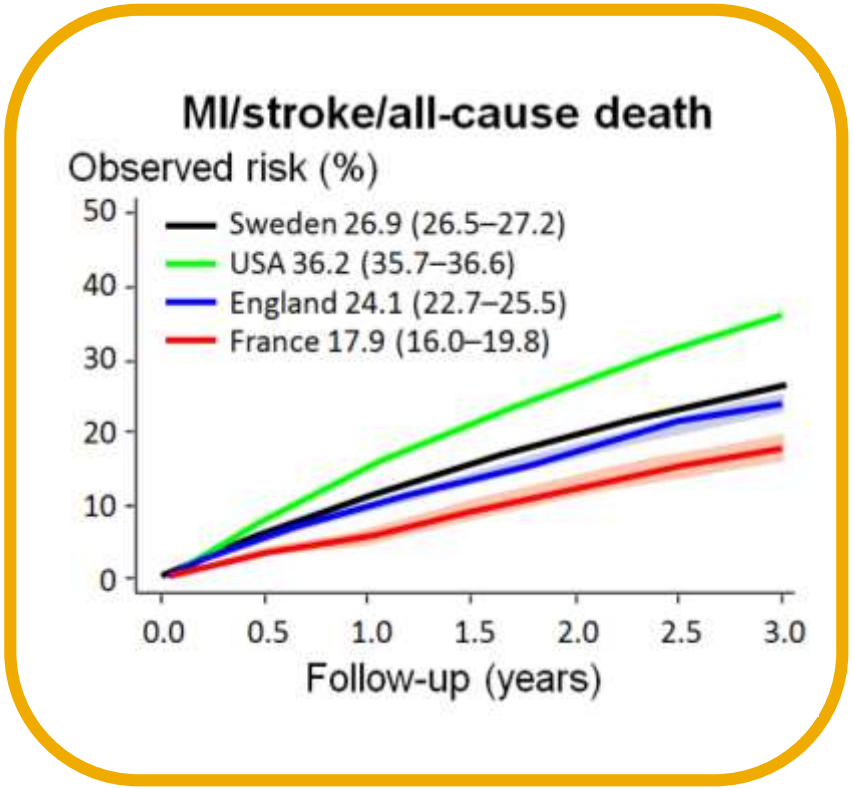
ridurre il rischio...

Ridurre il rischio
ISCHEMICO
TROMBOTICO

Ridurre il rischio di progressione dell'
ATEROSCLEROSI

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 (APOLLO 4-country analysis : Observed Incidence)





Rapsomaniki E, et al. ESC Late Breaking Registry presentation 2014: In press.

ESC NSTEMI (2015)

Long-term $P2Y_{12}$ inhibition			
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	A	184, 186

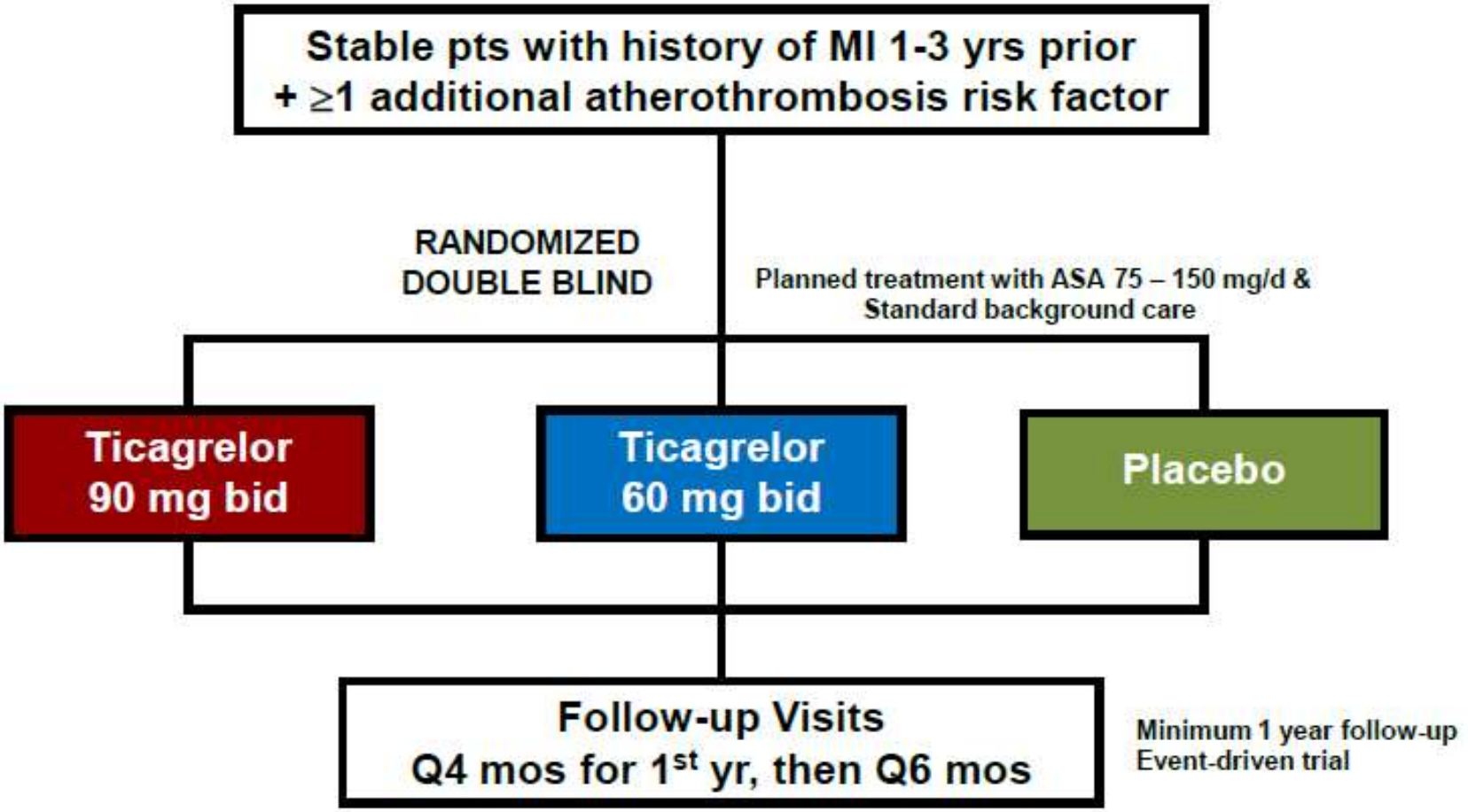
European Heart Journal 2015; doi:10.1093/eurheartj/ehv320

Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin

Marc S. Sabatine, MD, MPH
on behalf of the PEGASUS-TIMI 54
Executive & Steering Committees and Investigators

NCT00526474

Trial Design



Bonaca MP et al. *Am Heart J* 2014;167:437-44

Key Inclusion & Exclusion Criteria

PEGASUS TIMI 54

KEY INCLUSION

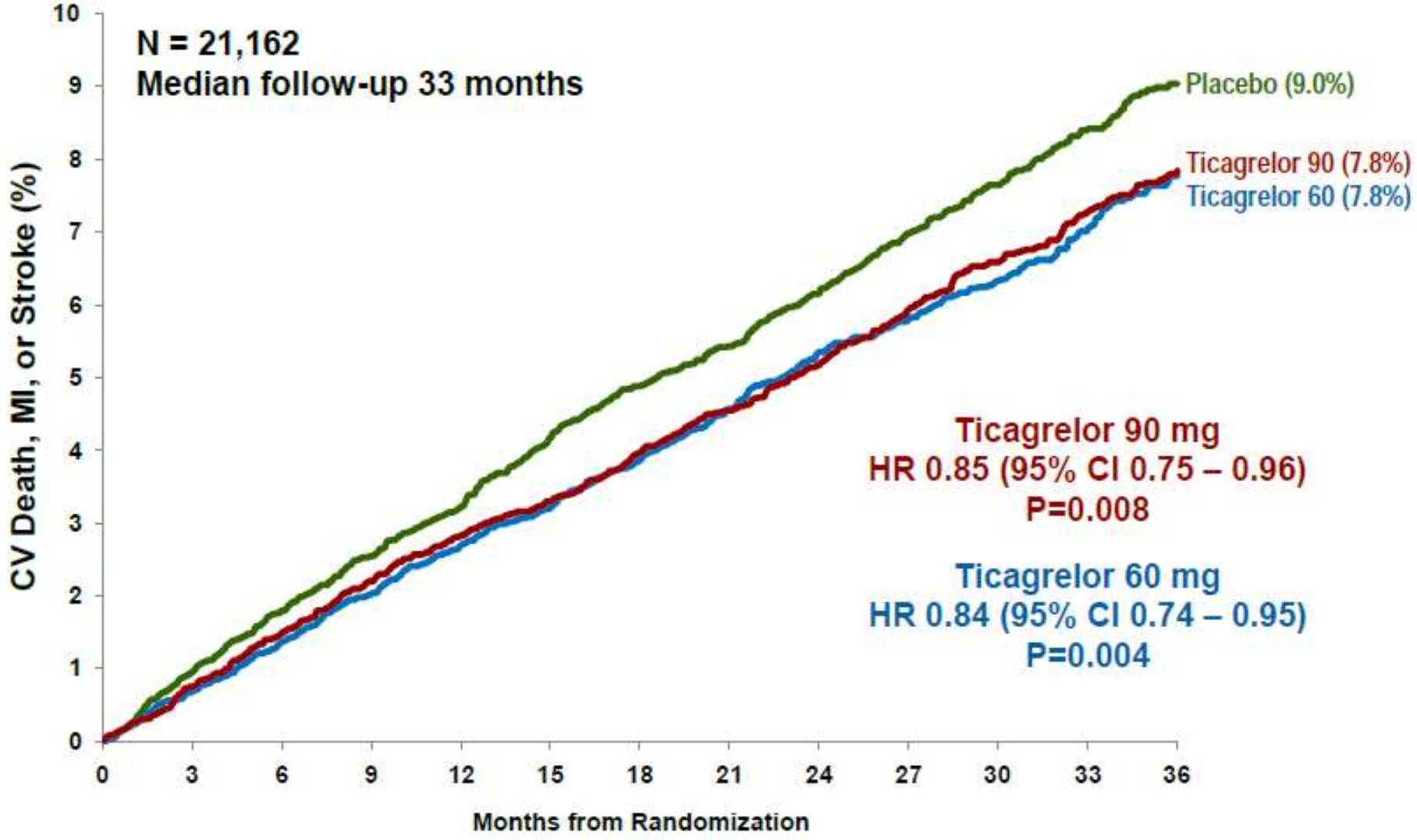
- **Age ≥50 years**
- At least 1 of the following:
  - Age ≥65 years
  - Diabetes requiring medication
  - 2nd prior MI (>1 year ago)
  - Multivessel CAD
  - CrCl <60 mL/min
- Tolerating ASA and able to be dosed at 75-150 mg/d

KEY EXCLUSION

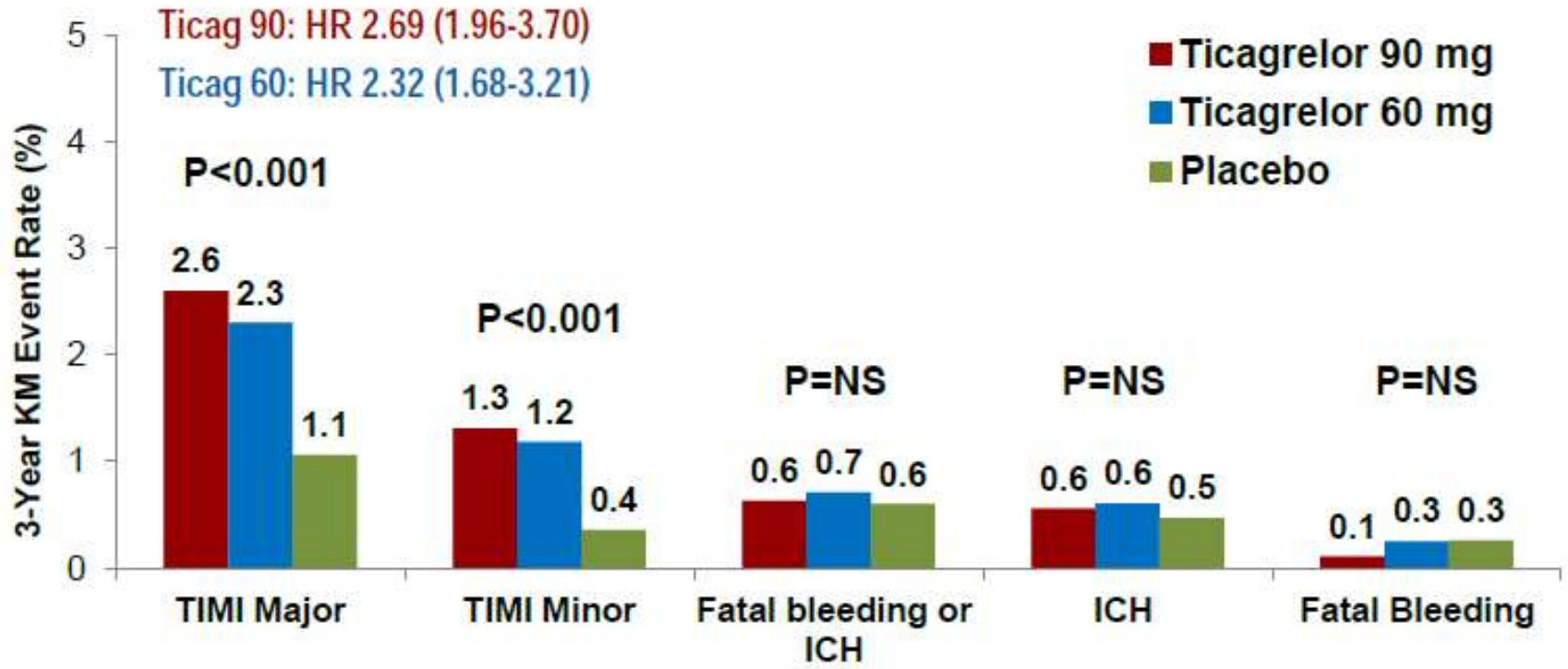
- Planned use of $P2Y_{12}$ antagonist, dipyridamole, cilostazol, or anticoag
- Bleeding disorder
- History of ischemic stroke, ICH, CNS tumor or vascular abnormality
- Recent GI bleed or major surgery
- At risk for bradycardia
- Dialysis or severe liver disease

Bonaca MP et al. *Am Heart J* 2014;167:437-44

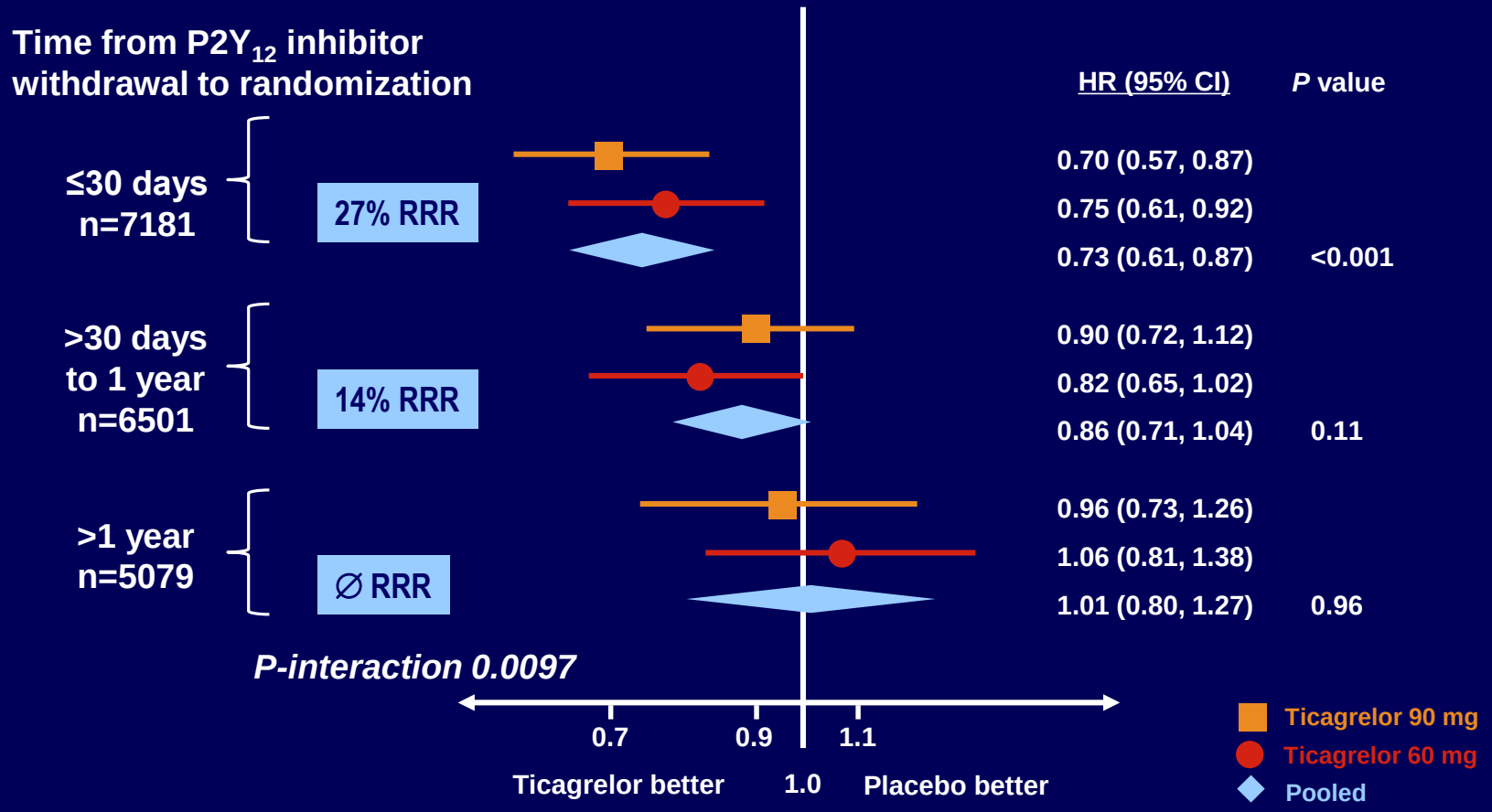
Primary Endpoint



Bleeding


Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)
Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo
3-Year KM Event Rate (%)
0
1
2
3
4
5
P<0.001
2.6
2.3
1.1
P<0.001
1.3
1.2
0.4
P=NS
0.6
0.7
0.6
P=NS
0.6
0.6
0.5
P=NS
0.1
0.3
0.3
TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding

Reduction in CV death, MI or stroke with ticagrelor by time from $P2Y_{12}$ inhibitor withdrawal



Bonaca MP. Presented at ESC Congress 2015 (Abstract 3918)

Paziente Post-IMA

ridurre il rischio…

Ridurre il rischio
ISCHEMICO
TROMBOTICO

Ridurre il rischio di progressione dell'
ATEROSCLEROSI

ESC: Goal-directed Prevention (2016)

European Heart Journal (2016) 37, 2315–2381

Very high Risk:	Subjects with any of the following: ▪ CVD ▪ Type 2 diabetes, or type 1 diabetes & target organ damage ▪ Patients with moderate to severe CKD (GFR <60mL/min/1.73m^2) ▪ SCORE ≥10%
High Risk:	Subjects with: ▪ Markedly elevated single risk factors such as: - Familial dyslipidaemias - Severe hypertension. ▪ SCORE ≥ 5% and <10%
Moderate Risk:	SCORE is ≥1 and <5% at 10 years, further modulated by: ▪ family history of premature CAD ▪ abdominal obesity ▪ physical activity pattern ▪ HDL-C ▪ TG ▪ hsCRP ▪ social class
Low Risk:	SCORE less than 1% and free of qualifiers

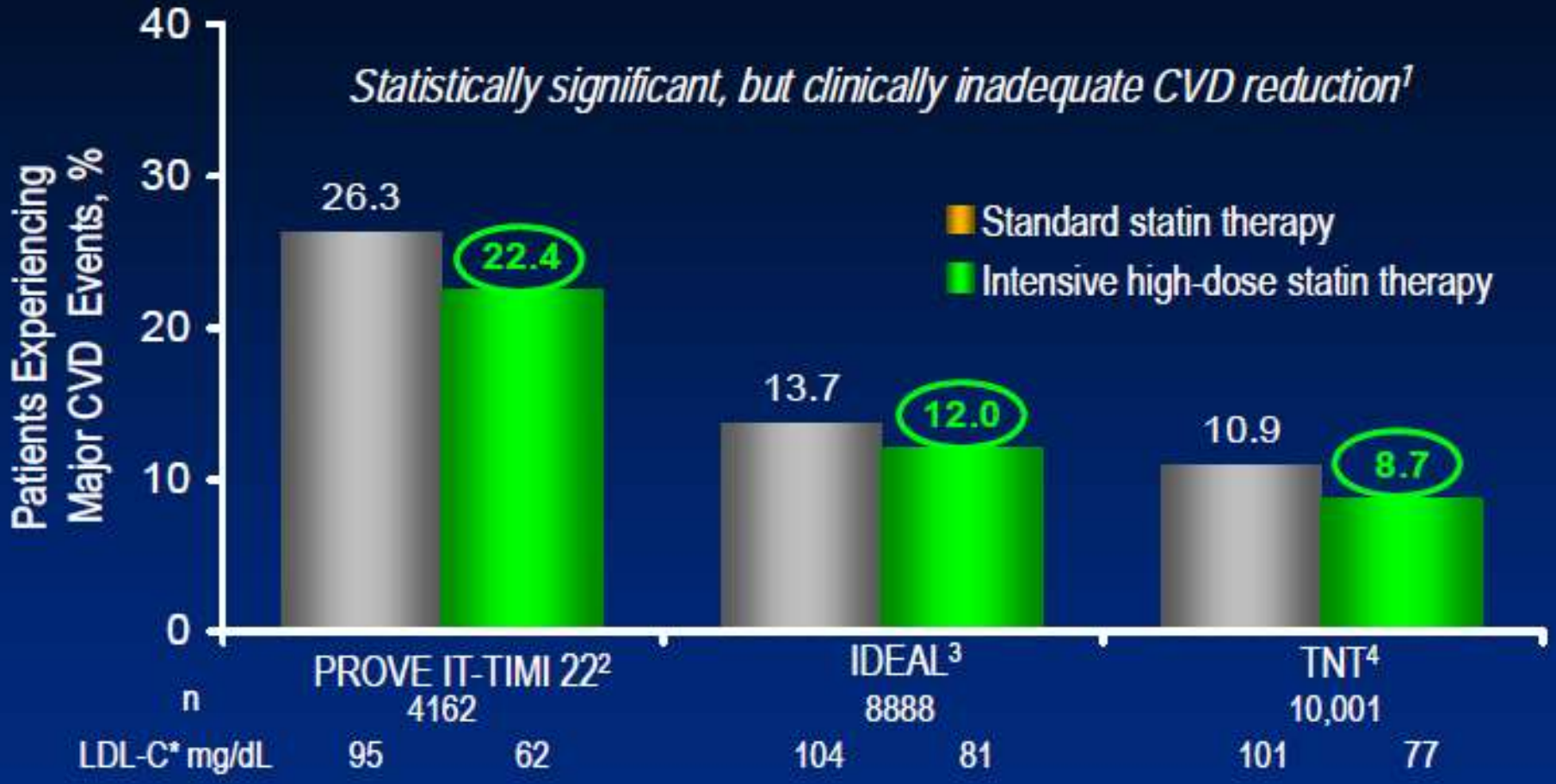
<70 mg/dl

<100 mg/dl

<115 mg/dl

Residual CVD Risk with *Intensive* Statin Therapy

Less, but Still Unacceptably High



[1]Superko HR. *Br J Cardiol.* 2006;13:131-136.
[2]Cannon CP et al. *N Engl J Med.* 2004;350:1495-1504.
[3]Pedersen TR et al. *JAMA.* 2005;294:2437-2445.
[4]LaRosa JC et al. *N Engl J Med.* 2005;352:1425-1435.

*Mean or median LDL-C after treatment

Low-density lipoprotein cholesterol in a global cohort of 57,885 statin-treated patients

Anselm K. Gitt [a, b, *], Dominik Lautsch [c], Jean Ferrieres [d], John Kastelein [e], Heinz Drexel [f, g, h, i], Martin Horack [b], Philippe Brudi [c], Brecht Vanneste [c], Peter Bramlage [j], Francois Chazelle [c], Vasilisa Sazonov [c], Baishali Ambegaonkar [c]

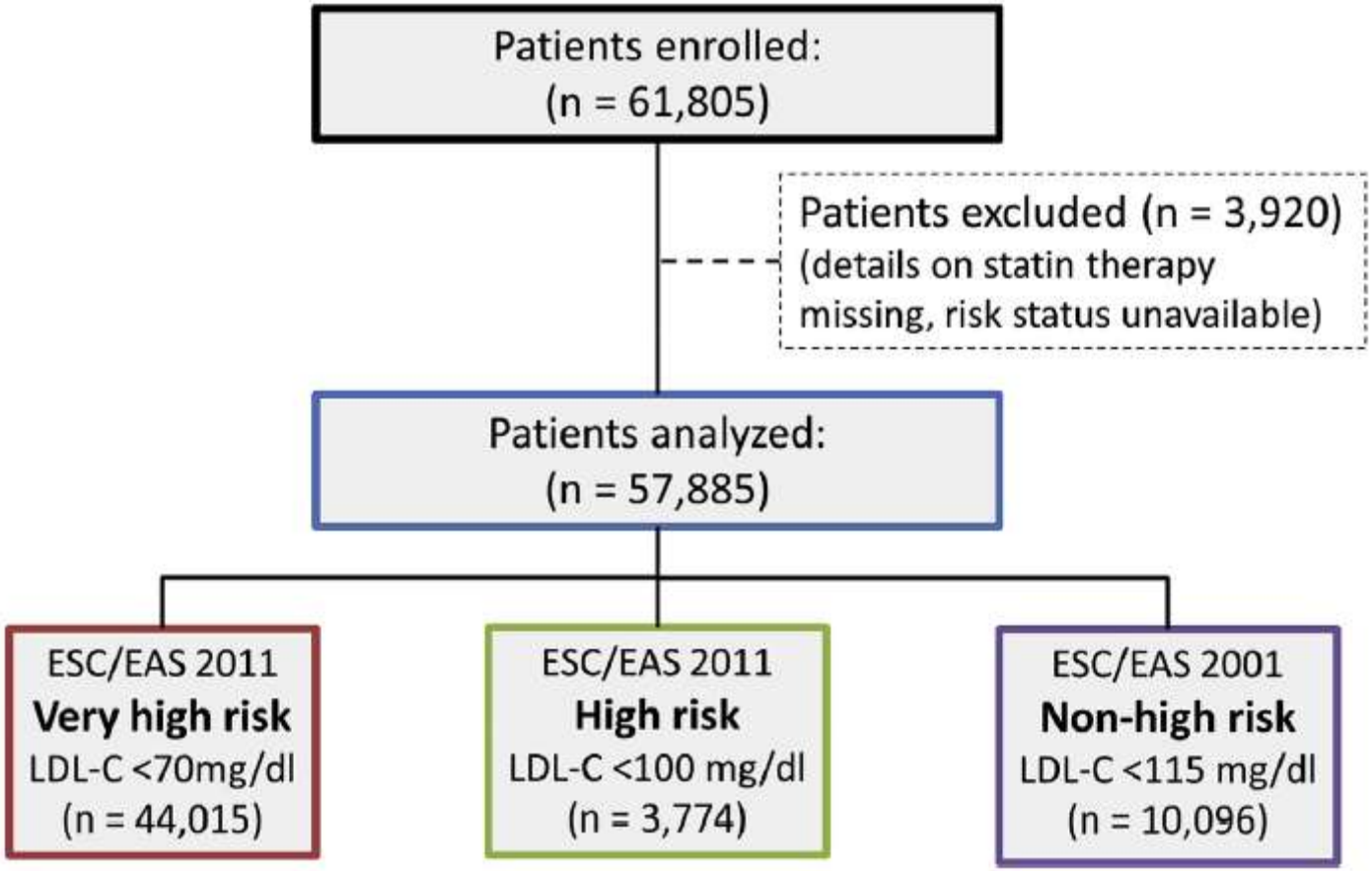


Fig. 1. Patients in DYSIS I.

Atherosclerosis 255 (2016) 200-209

Table 1
Proportions of patients attaining their target LDL-C values.

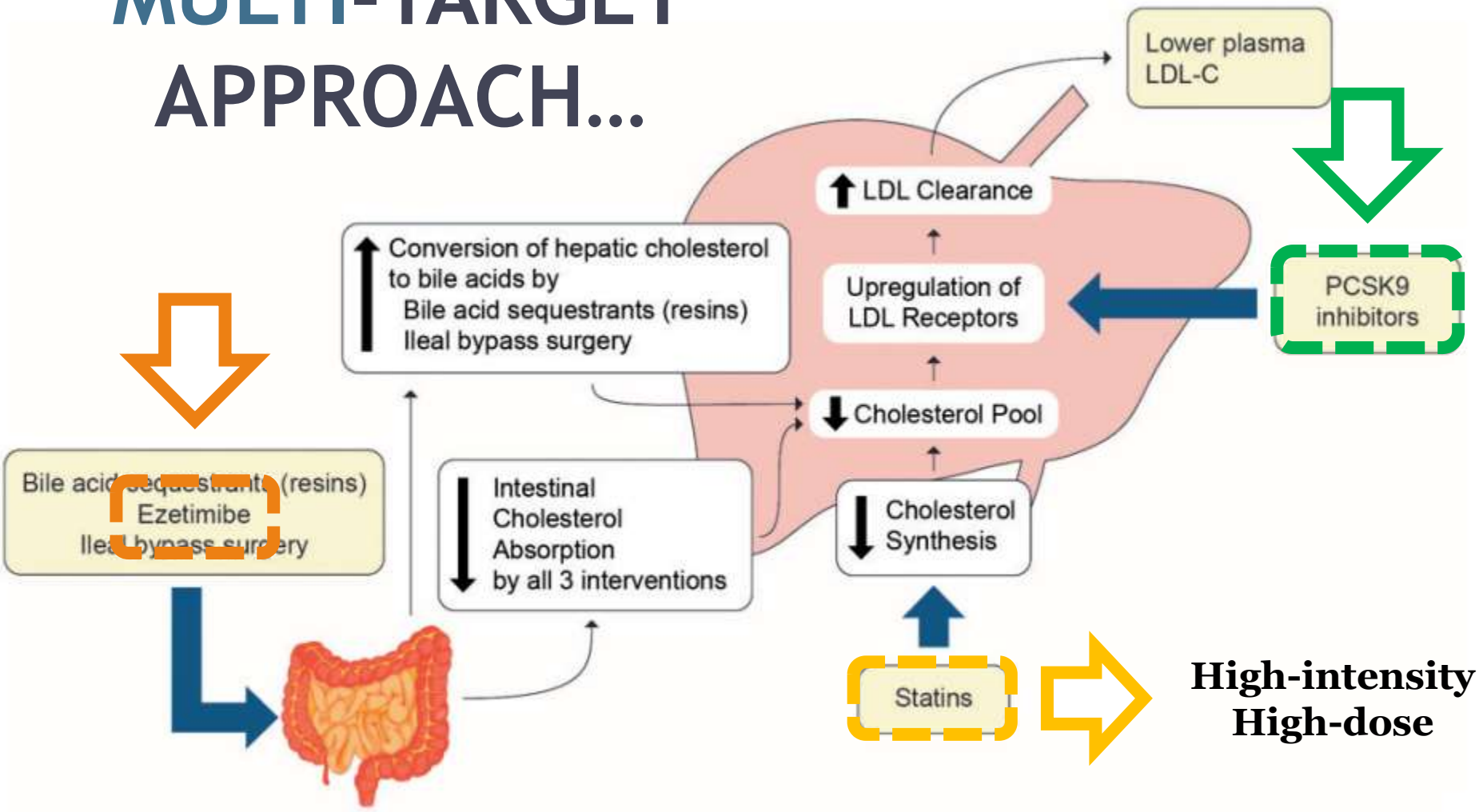
Country (*n*)	Total % (*n*/*N*)	Very high-risk[a] % (*n*/*N*)	High-risk[a] % (*n*/*N*)	Non-high-risk[a] % (*n*/*N*)	*P*-value
Europe/Canada/Israel					
Austria (*n*=881)	15.9 (123/772)	12.9 (85/657)	20.7 (6/29)	37.2 (32/86)	<0.0001
Baltics (*n*=1797)	15.9 (282/1779)	10.9 (151/1386)	20.5 (24/117)	38.8 (107/276)	<0.0001
Belgium (*n*=909)	35.7 (310/868)	21.6 (116/536)	40.5 (34/84)	64.5 (160/248)	<0.0001
Canada (*n*=2436)	45.6 (1098/2410)	40.7 (787/1933)	50.3 (79/157)	72.5 (232/320)	<0.0001
Denmark (*n*=933)	37.7 (338/897)	30.2 (196/650)	45.4 (49/108)	66.9 (93/139)	<0.0001
France (*n*=4192)	20.6 (835/4061)	14.4 (385/2677)	16.6 (50/302)	37.0 (400/1082)	<0.0001
Germany (*n*=4216)	14.3 (555/3879)	11.2 (371/3300)	18.9 (44/233)	40.5 (140/346)	<0.0001
Greece (*n*=755)	17.8 (132/741)	9.2 (42/456)	19.1 (9/47)	34.0 (81/238)	<0.0001
Ireland (*n*=900)	43.5 (376/865)	35.9 (222/618)	58.6 (51/87)	64.4 (103/160)	<0.0001
Israel (*n*=100)	29.1 (223/766)	20.3 (121/597)	49.0 (24/49)	65.0 (78/120)	<0.0001
Italy (*n*=766)	30.7 (206/671)	22.7 (95/419)	29.4 (15/51)	47.8 (96/201)	<0.0001
The Netherlands (*n*=1199)	30.8 (354/1151)	27.4 (279/1019)	34.1 (15/44)	68.2 (60/88)	<0.0001

Table 2
Median distance to treatment targets.

Data inBrief (2016)616–620

Country (*n*)	Total[a] mg/dl (IQR)	Very high-risk[b] mg/dl (IQR)	High-risk[b] mg/dl (IQR)	Non-high-risk[b] mg/dl (IQR)
Europe/Canada/Israel				
Austria (*n*=881)	33.0 (18.0, 58.0)	33.0 (19.0, 58.0)	31.0 (9.0, 67.0)	25.5 (9.0, 56.0)
Baltics (*n*=1797)	42.1 (20.5, 71.9)	42.5 (21.6, 73.9)	33.0 (12.9, 69.4)	38.1 (15.3, 60.9)
Belgium (*n*=909)	24.3 (11.0, 44.0)	27.5 (14.0, 47.0)	14.5 (7.0, 30.0)	14.0 (5.0, 33.5)
Canada (*n*=2436)	18.8 (8.5, 34.4)	18.9 (8.5, 34.4)	17.7 (6.3, 33.4)	17.1 (8.4, 31.9)
Denmark (*n*=933)	24.2 (11.2, 42.1)	26.7 (13.9, 42.1)	22.6 (8.3, 46.9)	16.5 (4.9, 28.9)
France (*n*=4192)	35.0 (18.0, 58.0)	38.0 (19.0, 61.0)	36.5 (17.0, 61.0)	28.0 (15.0, 48.0)
Germany (*n*=4216)	38.0 (20.0, 61.0)	39.0 (22.0, 62.0)	31.0 (14.8, 54.0)	28.1 (15.0, 45.9)
Greece (*n*=755)	37.0 (20.0, 60.0)	40.0 (22.0, 65.0)	35.0 (21.0, 50.0)	28.0 (15.0, 50.0)
Ireland (*n*=900)	25.5 (11.2, 46.0)	26.7 (12.6, 46.0)	26.8 (14.7, 44.4)	19.6 (8.7, 38.1)
Israel (*n*=100)	21.0 (9.0, 38.0)	21.3 (9.0, 39.0)	23.0 (12.0, 29.0)	13.0 (7.0, 29.0)
Italy (*n*=766)	29.0 (13.0, 53.0)	32.0 (17.0, 55.5)	22.5 (7.0, 61.5)	22.0 (9.0, 37.0)
The Netherlands (*n*=1199)	26.7 (11.6, 42.5)	26.7 (11.2, 42.1)	27.6 (13.7, 46.9)	31.8 (10.1, 39.7)

POST-MI "MULTI-TARGET" APPROACH…



Ference BA et al. European Heart Journal (2017) 0, 1–14

IMPROVE-IT

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Study Design

IMPROVE-IT

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

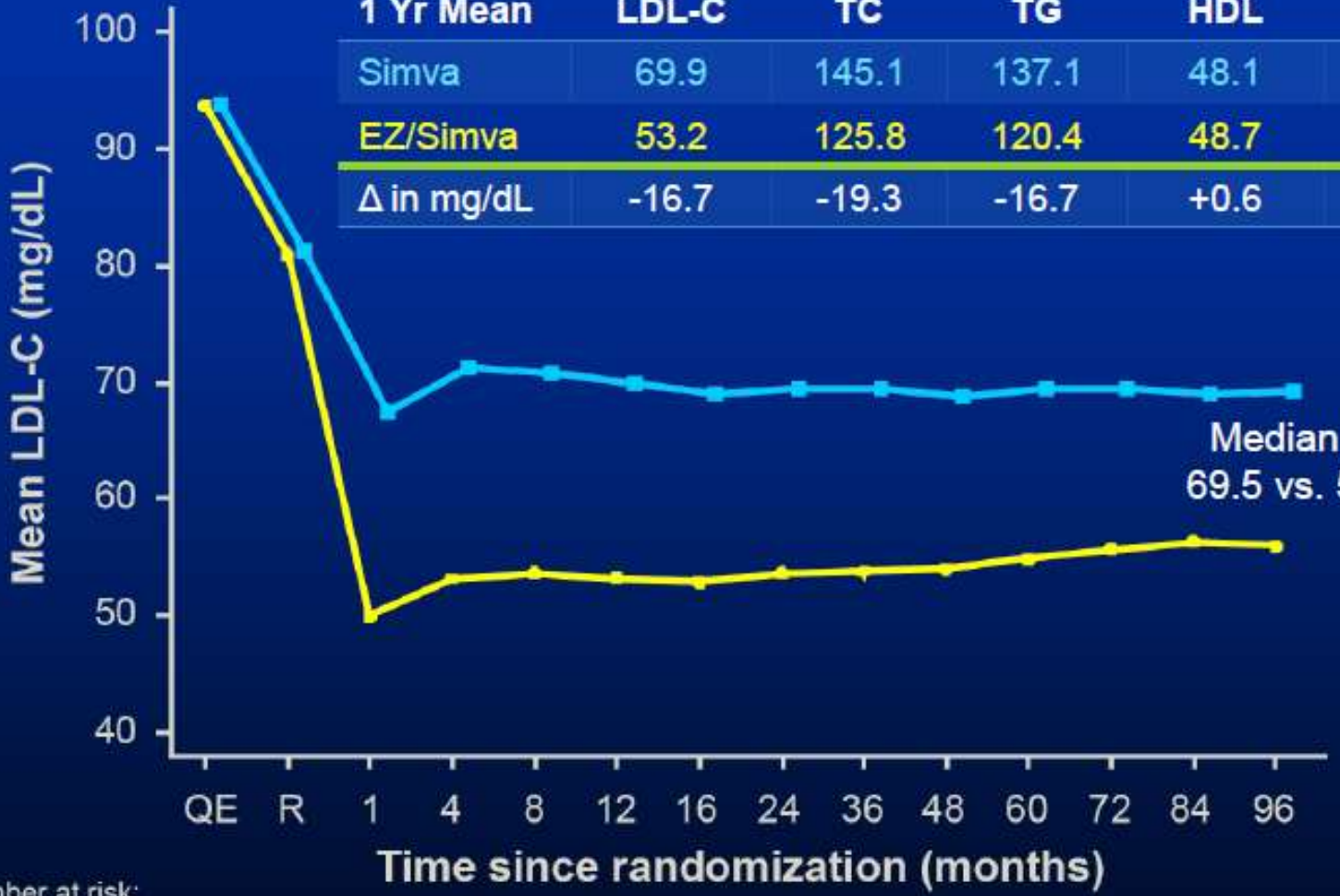
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

LDL-C and Lipid Changes

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



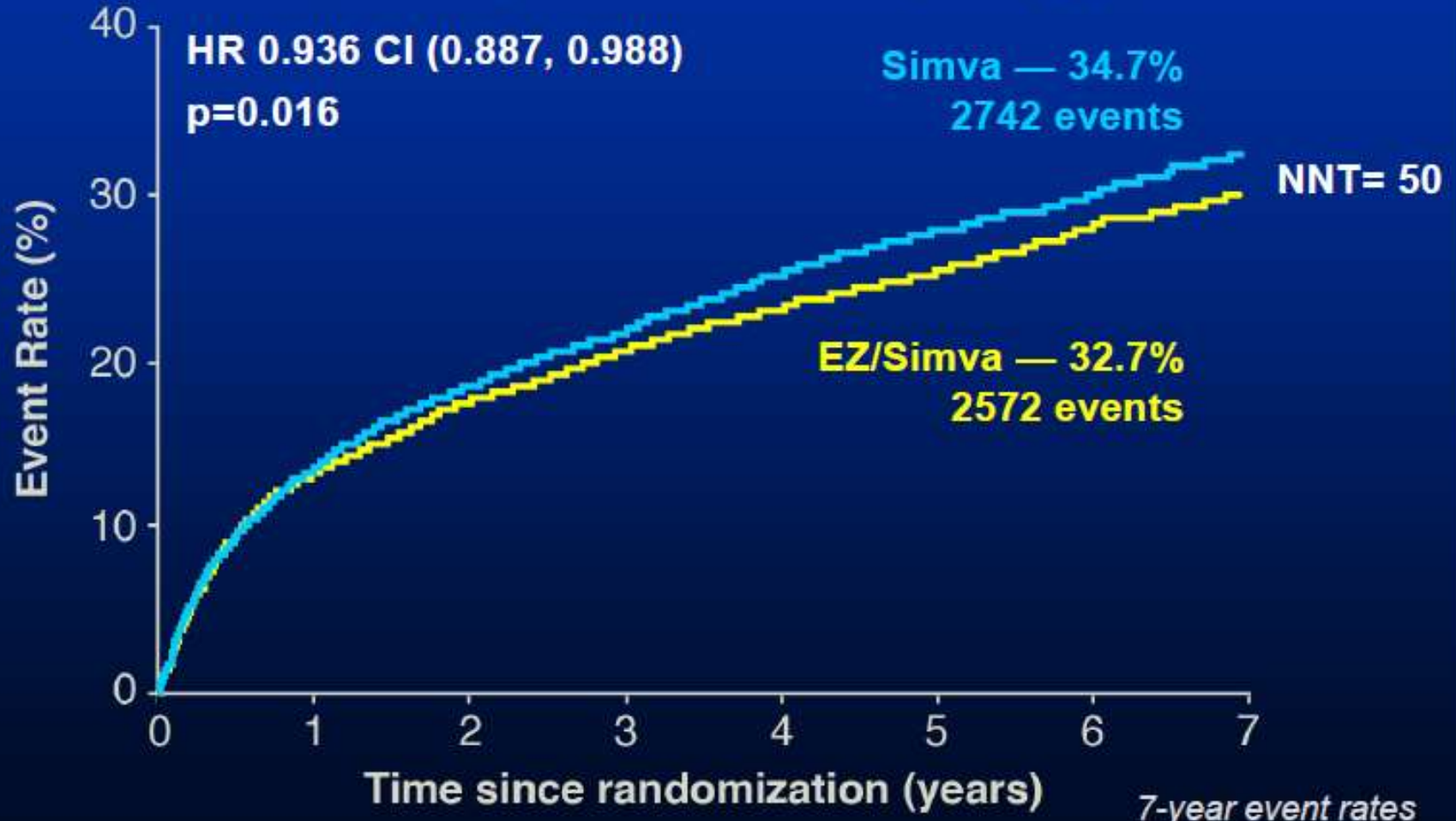
Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Primary Endpoint — ITT

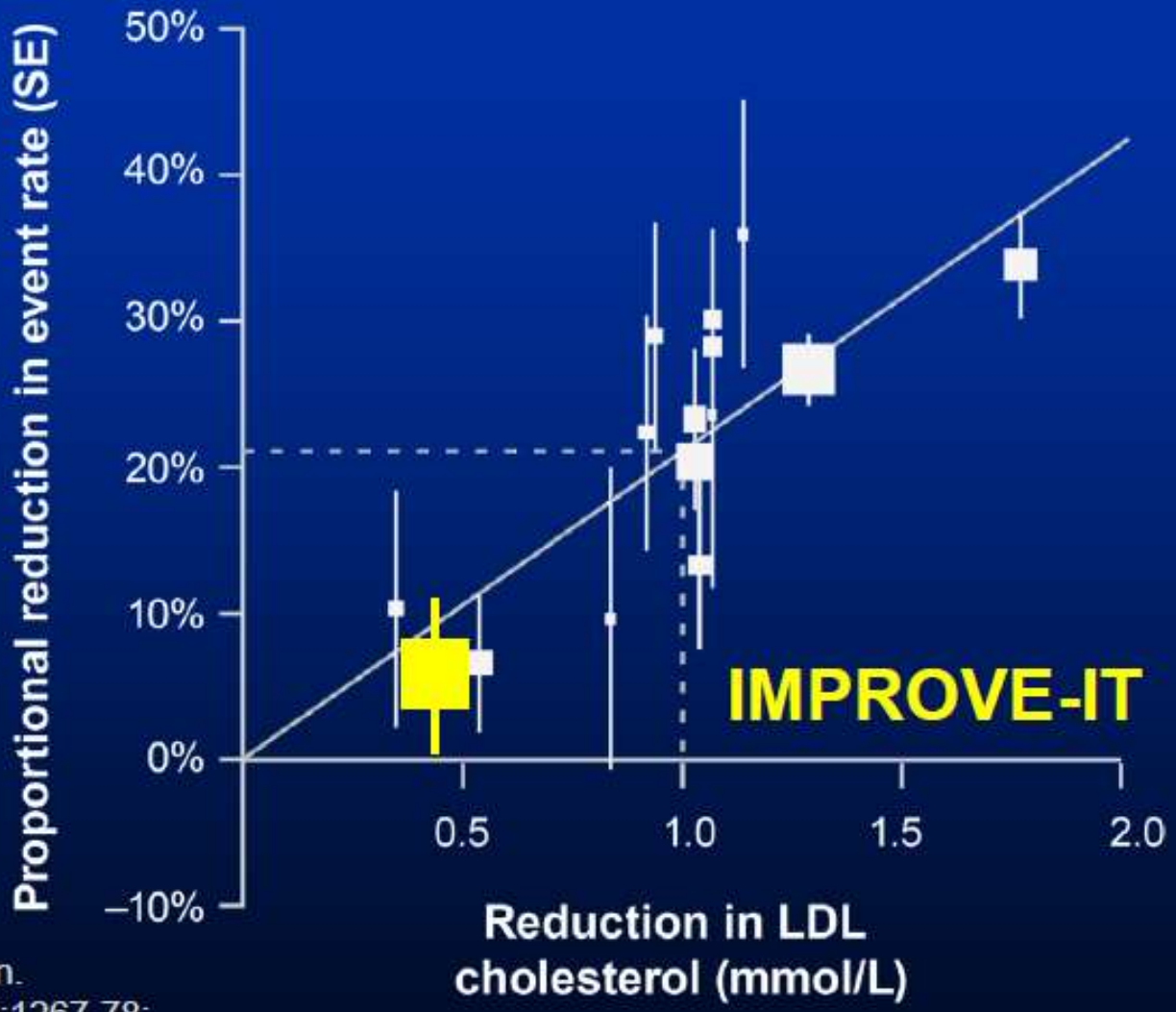
IMPROVE-IT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Conclusions

IMPROVE-IT

IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

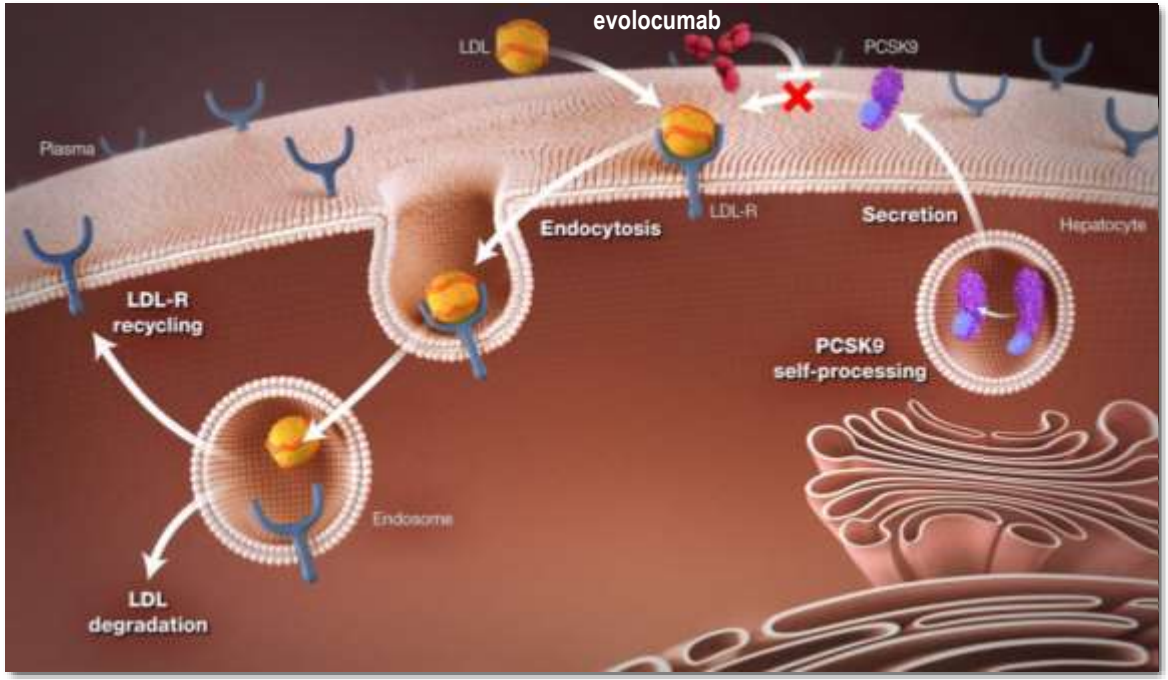
➡ **Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events**

➡ **Results could be considered for future guidelines**

Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

- Chaperones LDL-R to destruction → ↑ circulating LDL-C
- Loss-of-fxn genetic variants → ↑ LDL-R → ↓ LDL-C & ↓ risk of MI



Evolocumab

- Fully human anti-PCSK9 mAb
- ~60% ↓ LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Exploratory data suggested ↓ CV events

Sever P & Mackay J. *Br J Cardiol* 2014;21:91-3
Giugliano RP, et al. *Lancet* 2012;380:2007-17
Sabatine MS, et al. *NEJM* 2015;372:1500-9

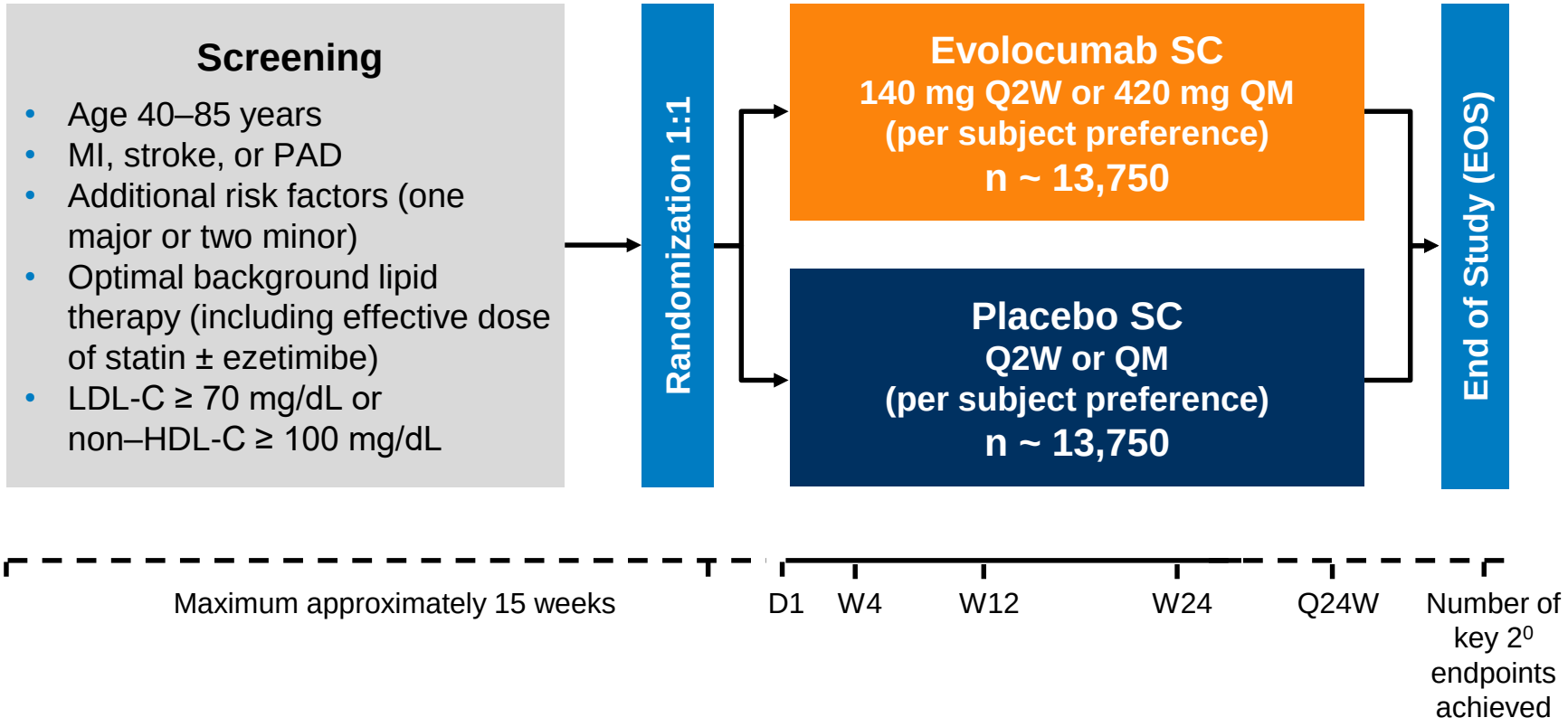
Repatha Outcomes Trial: Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, MD, MPH,[a] Robert P. Giugliano, MD,[a] Anthony C. Keech, MD,[b] Narimon Honarpour, MD, PhD,[c] Stephen D. Wiviott, MD,[a] Sabina A. Murphy, MPH,[a] Julia F. Kuder, MA,[a] Huei Wang, PhD,[c] Thomas Liu, PhD,[c] Scott M. Wasserman, MD,[c] Peter S. Sever, PhD, FRCP,[d] and Terje R. Pedersen, MD[e] for the FOURIER Steering Committee and Investigators

From the [a]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [b]Sydney Medical School, NHMRC Clinical Trials Centre, University of Sydney, Sydney, [c]Amgen, Thousand Oaks, CA, [d]International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, and [e]Oslo University Hospital, Ullevål and Medical Faculty, University of Oslo, Oslo.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Evolocumab Outcomes Trial: Study Design Overview



D = day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; Q2W = every 2 weeks; Q24W = every 24 weeks; QM = every month; SC = subcutaneous; W = week.

Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

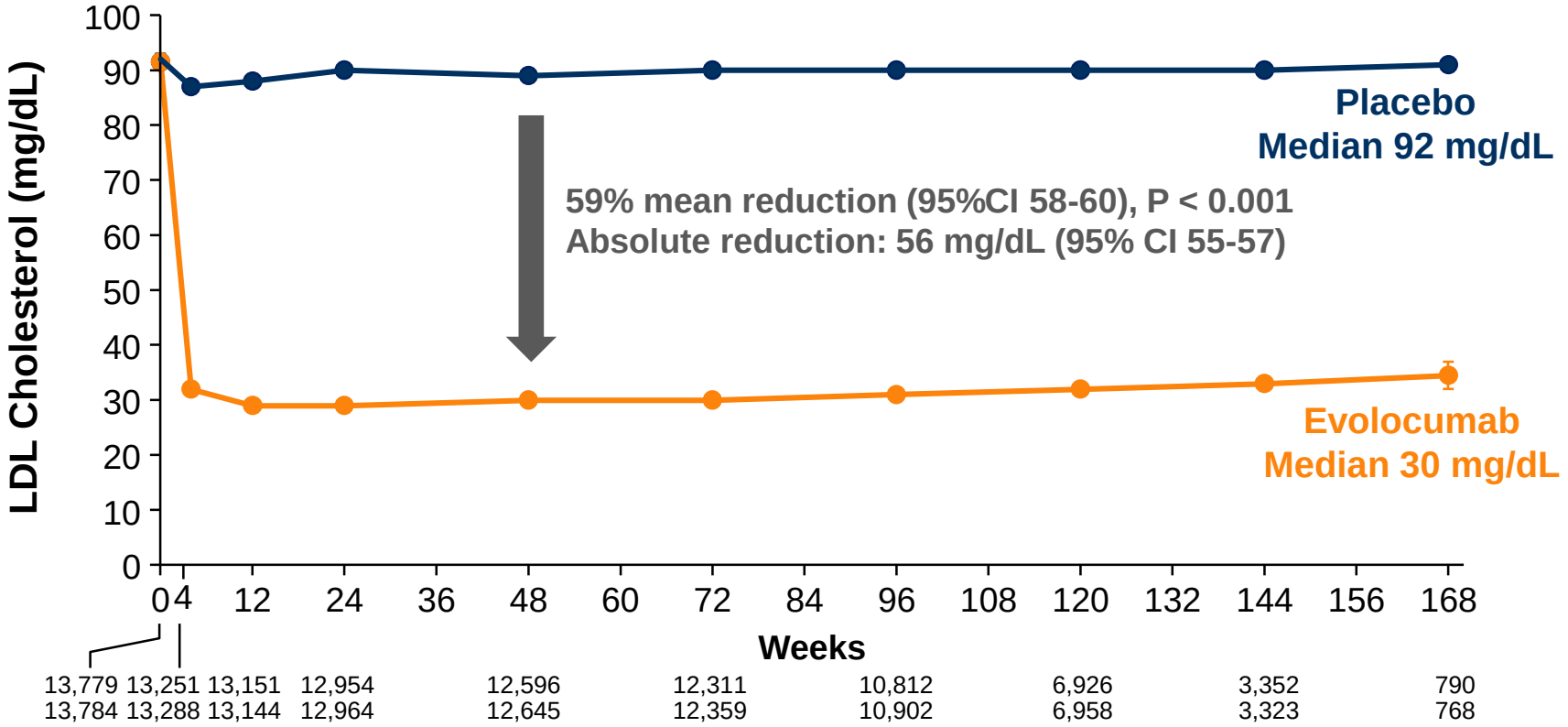
Evolocumab Outcomes Trial: Key Eligibility Criteria

- Men or women aged 40–85 years
- **Clinically evident CVD (prior MI, prior non-hemorrhagic stroke, or symptomatic PAD)**
- At least 1 major additional risk factor (e.g., diabetes, current smoker, MI or non-hemorrhagic stroke at ≤ 6 months of screening) or 2 minor additional risk factors (e.g., history of non-MI–related coronary revascularization, metabolic syndrome, LDL-C ≥ 130 mg/dL or non–HDL-C ≥ 160 mg/dL)
- Fasting LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL on an optimized stable lipid-lowering therapy
  - At least atorvastatin 20 mg daily or equivalent +/- ezetimibe

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease.

Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664 (Supplementary Appendix C)

Median LDL-C Levels Over Time: All Patients



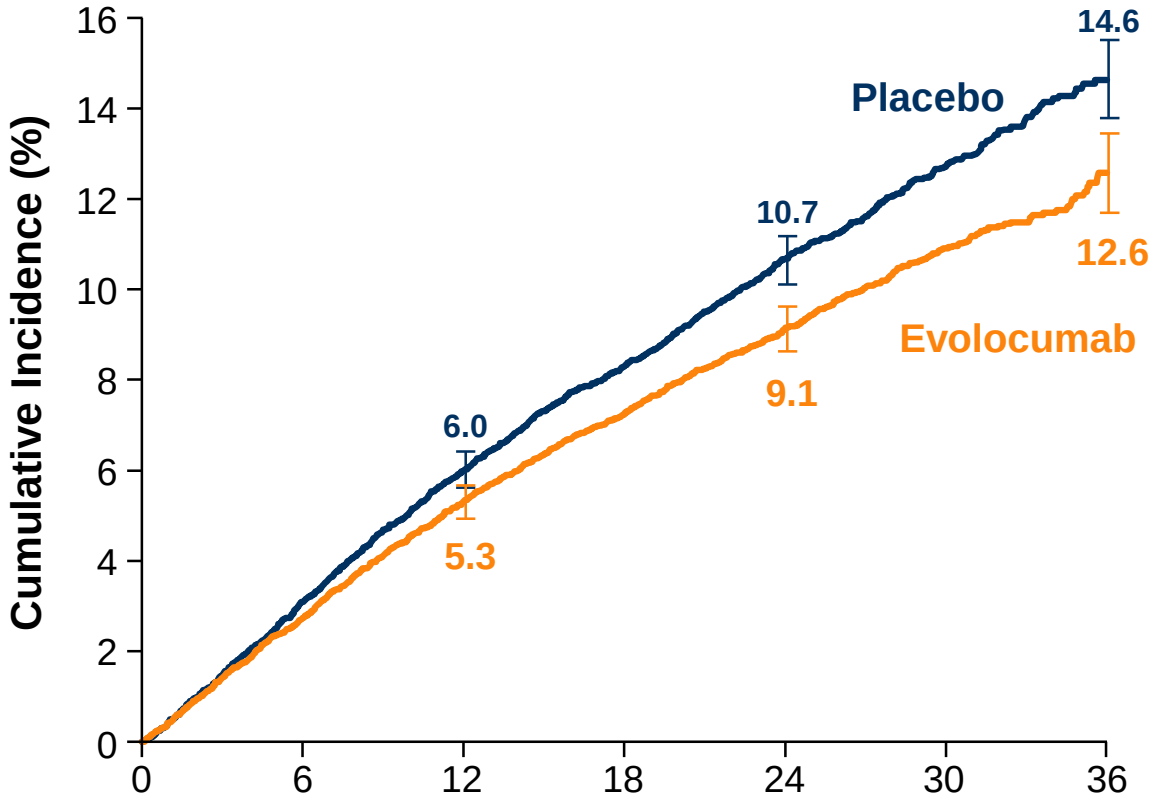
No. at risk											
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6,926	3,352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6,958	3,323	768

LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group

Data shown are median values with 95% confidence intervals in the two arms; ITT.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization



No. at Risk

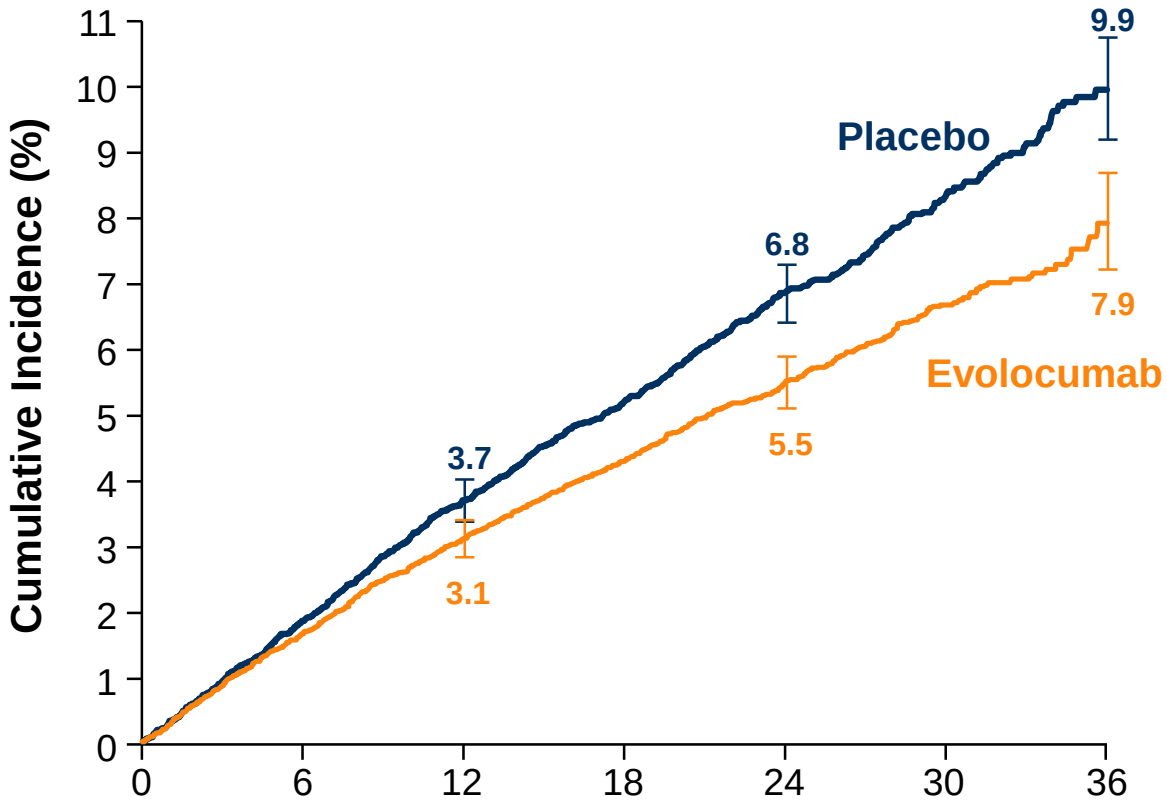
Placebo	13,780	13,278	12,825	11,871	7,610	3,690	686
Evolocumab	13,784	13,351	12,939	12,070	7,771	3,746	689

HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Key Secondary Endpoint:
Composite of CV Death, MI, or Stroke



No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7,944	3,893	731
Evolocumab	13,784	13,501	13,241	12,456	8,094	3,935	724

HR 0.80 (95% CI 0.73 to 0.88); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; HR = Hazard ratio

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Adverse Events in the Safety Population*

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Any	10,664 (77.4)	10,644 (77.4)
Serious	3,410 (24.8)	3,404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)

No notable differences in the rate of AEs, SAEs, or AEs leading to discontinuation

*Safety evaluations included all randomized patients who received at least one dose of study treatment and for whom post-dose data are available.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Gaps in Clinical Practice…

Adherence in Lipid Lowering Therapy:

People do not take their pills…


Patients spend more than 99.9% of their lives far away from this room

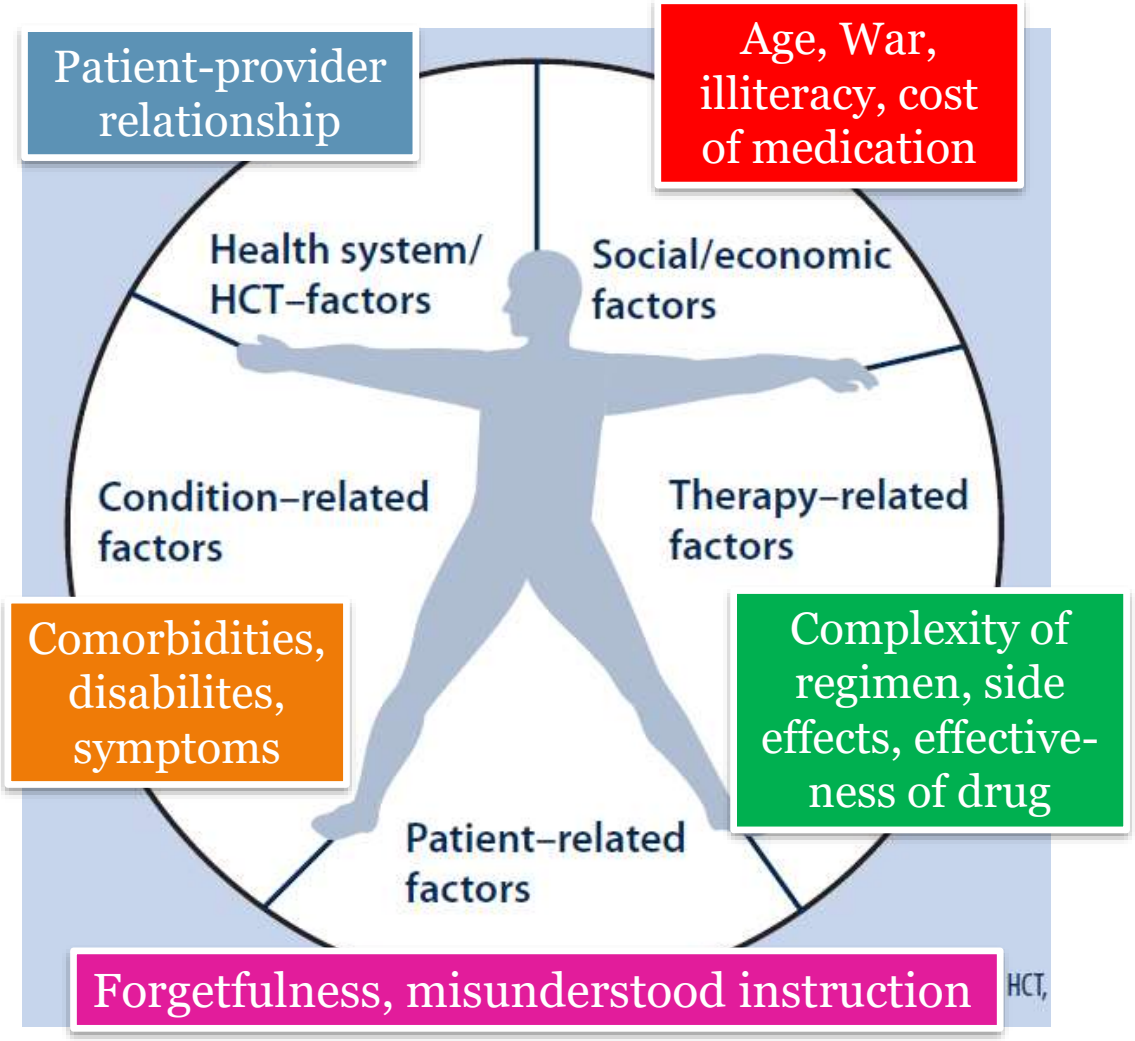
Patients' adherence

	Class	Level	GRADE
Physicians must assess adherence to medication, and identify reasons for non-adherence in order to tailor further interventions to the individual needs of the patient or person at risk.	I	A	Strong
In clinical practice, reducing dosage demands to the lowest acceptable level is recommended. In addition, repetitive monitoring and feedback should be implemented. If feasible, multisession or combined behavioural interventions should be offered in case of persistent non-adherence.	IIa	A	Strong

www.escardio.org/guidelines

European Heart Journal 2012:33;1635–1701
European Journal of Preventive Cardiology 2012;19: 4:585-667

FIVE DIMENSIONS OF ADHERENCE

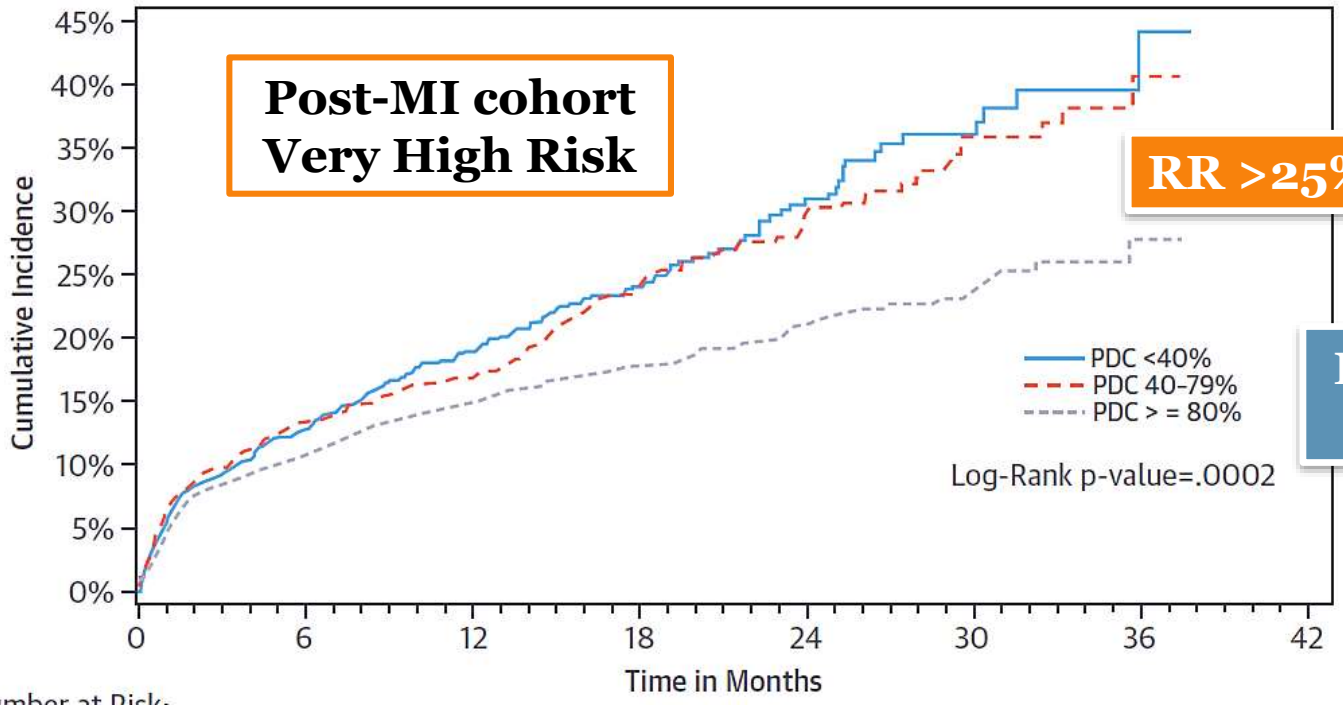


Adherence is a multidimensional phenomenon.

The common belief that patients are solely responsible for taking their treatment is misleading and most often reflects a misunderstanding of how other factors affect people's behaviour and capacity to adhere to their treatment.

Adherence to long term therapies
WHO 2003

Assessing the Impact of Medication Adherence on Long-Term Cardiovascular Outcomes



JACC 2016;68(8):789–801.

In the post-MI cohort, to accrue benefit required a very high level of adherence (>80%). No statistical difference was observed between the nonadherent and partially adherent groups

Aderenza terapeutica: come migliorarla?

MODIFICAZIONI DELLA PRESCRIZIONE TERAPEUTICA

- Riduzione del numero delle dosi
- Somministrazione transdermica
- Adattare il regime terapeutico allo stile di vita
- Facilitare la scorta di farmaci

INTERVENTI SUL COMPORTAMENTO

- Counseling motivazionale
- Controlli a breve termine dopo l'inizio della terapia
- Uso di promemoria (calendari, diari, porta-pillole)
- Conteggi programmati delle pillole residue
- Visite domiciliari

MONADHERENCE-PCSK9i
Monaldi Hospital single-center experience on Adherence to PCSK9i

MONADHERENCE-PCSK9i: Obiettivi

- Valutare i livelli di aderenza alla terapia con PCSK9i nei pazienti ad alto rischio CV e confrontare i risultati con i dati sulla terapia statinica.

- Valutare i livelli di aderenza alla terapia statinica nei pz in terapia con PCSK9i.

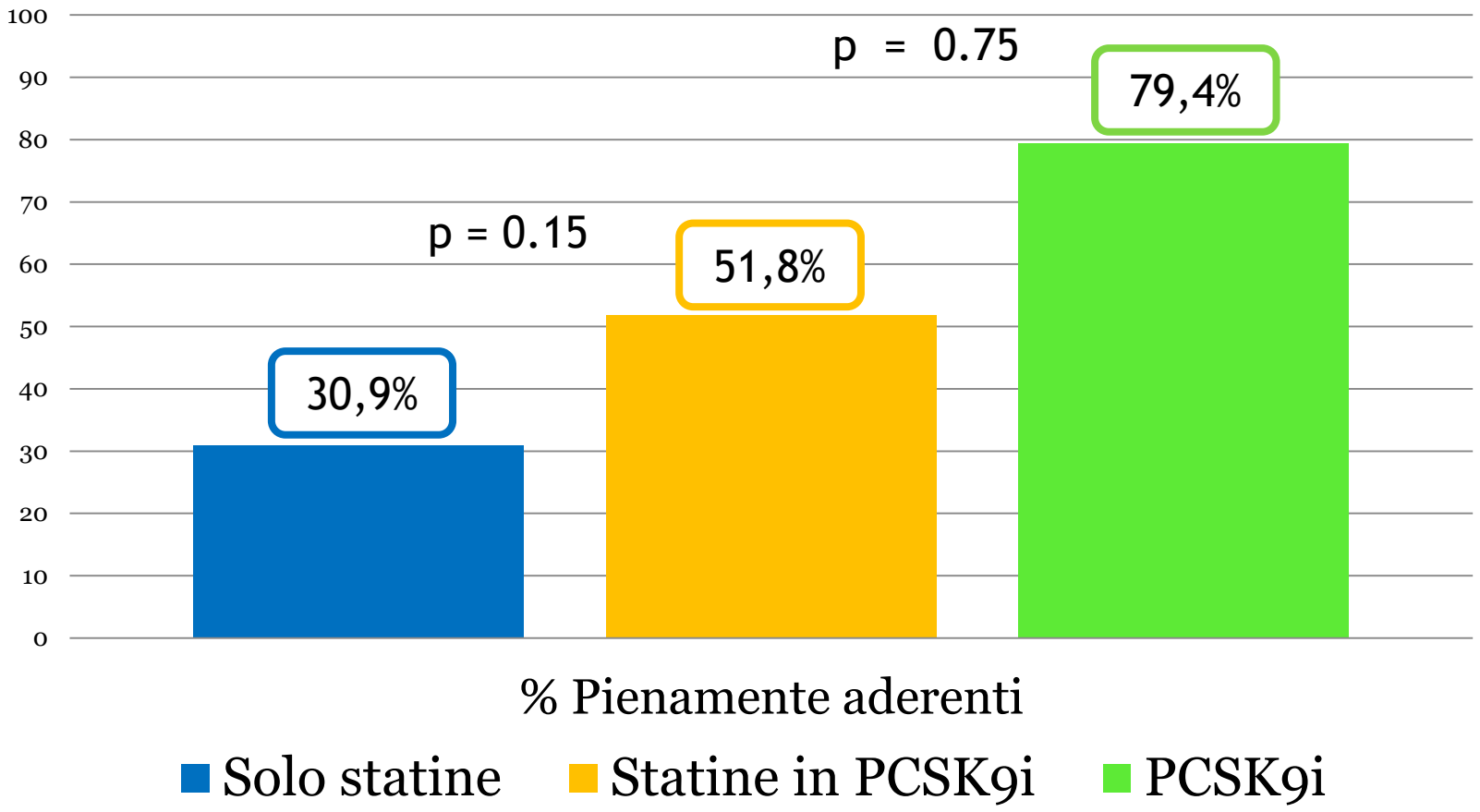
Valutazione dell'aderenza

Conteggio delle pillole/siringhe

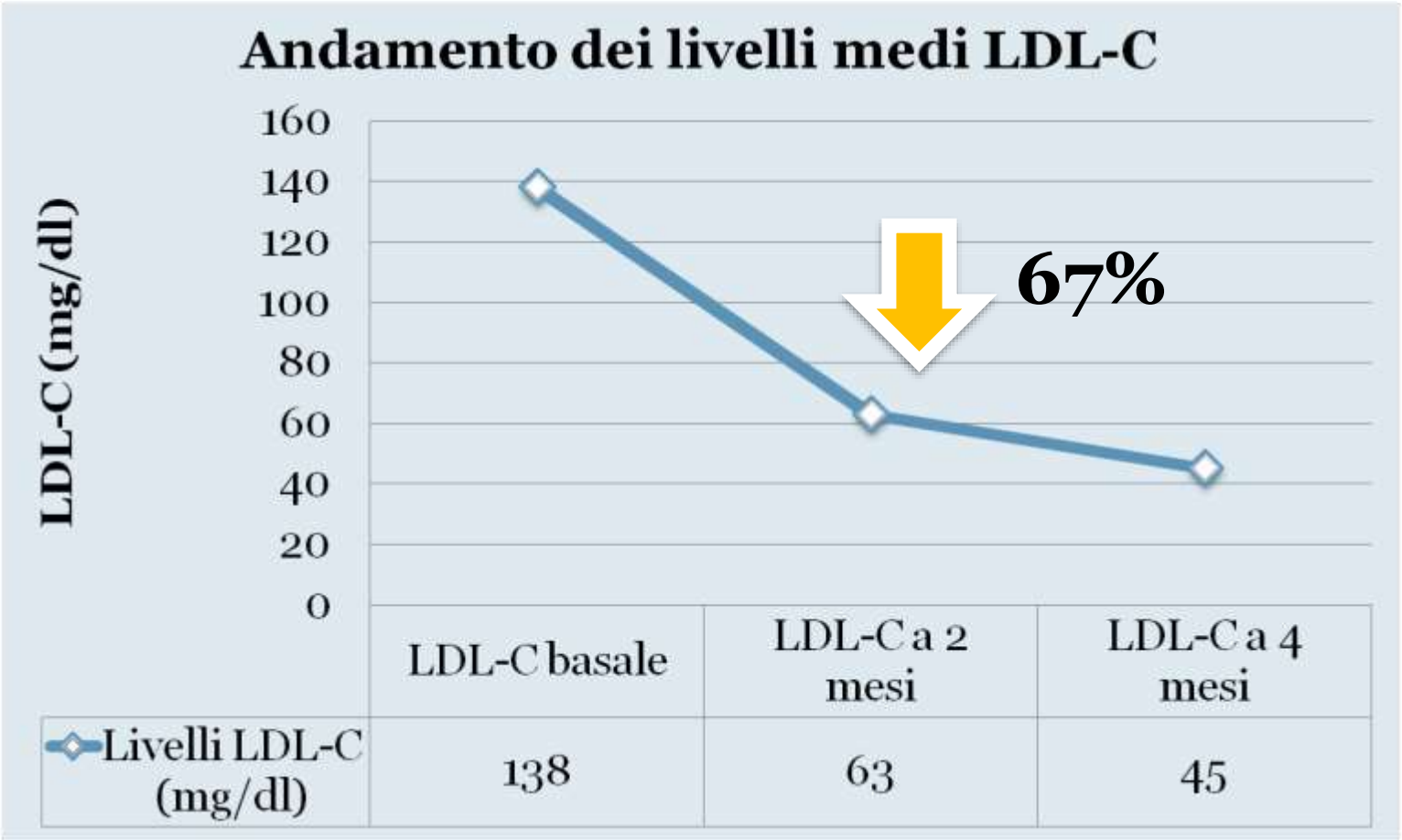
Scala di Morisky

1. Ha mai dimenticato di assumere la statina?
2. È occasionalmente poco attento nell'assunzione delle statine?
3. Quando si sente meglio, a volte interrompe la terapia statinica?
4. Quando si sente peggio, a volte interrompe la terapia statinica?
Ogni risposta positiva ha un punteggio di 0 ed ogni negativa di 1.

Risultati: % pz pienamente aderenti alla terapia con statine e PCSK9i



Livelli di LDL-C nel gruppo PCSK9i



Next future: outpatients monitoring?

Time for Cardiac tele-rehabilitation?

European Journal of Preventive Cardiology 2013; 20(S2): 1–24

It can control:

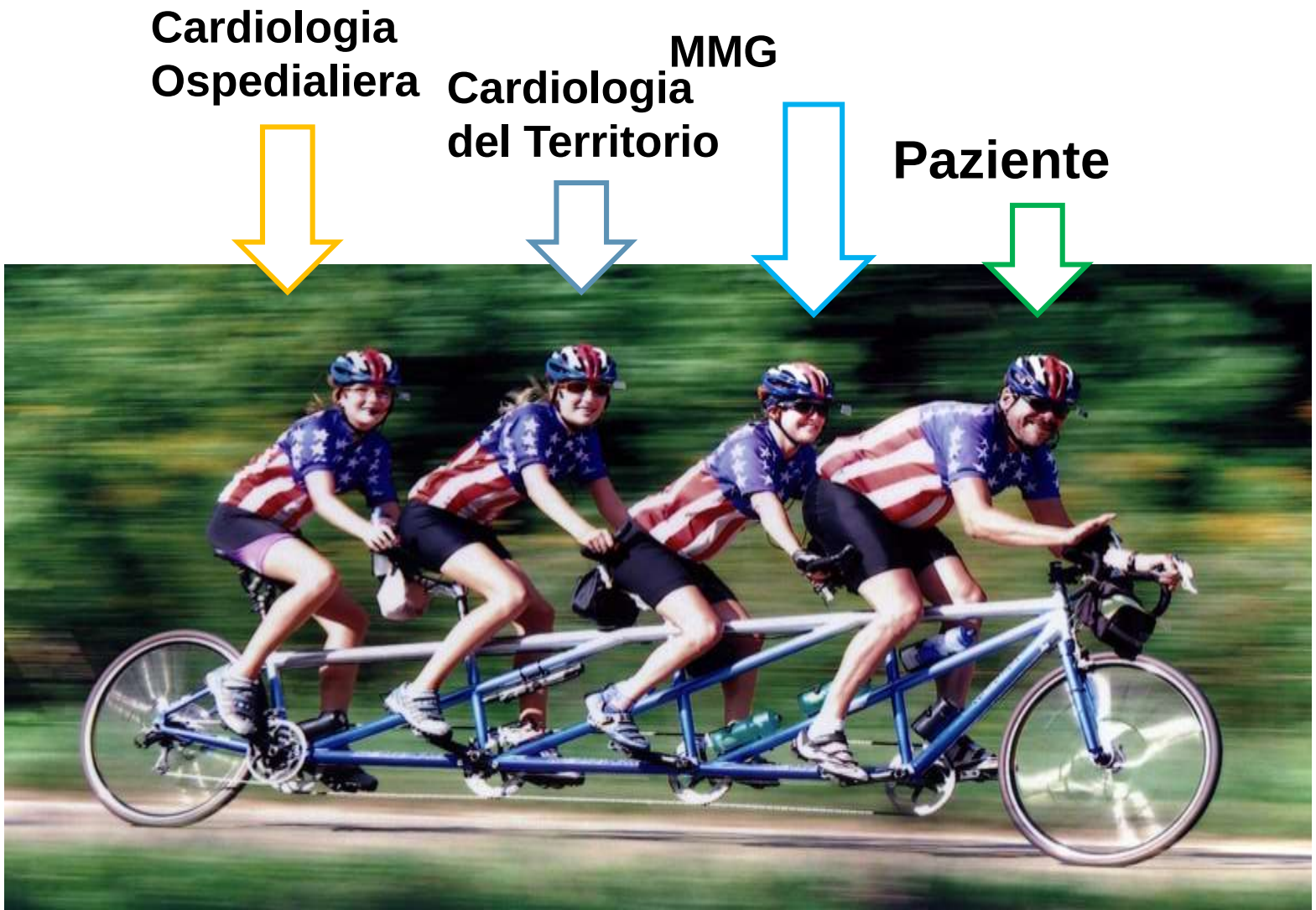
- clinical status
- **compliance to treatment**
- physical activity
- healthy nutrition, weight control
- smoking cessation.

VESTI LA SALUTE…

Alla dimissione e …

…alle visite di follow-up

La rete sanitaria:
condividere gli stessi obiettivi…



GRAZIE DELL'ATTENZIONE

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