Trattamento farmacologico delle malattie cardiovascolari: quali le novità più rilevanti negli ultimi 5 anni?

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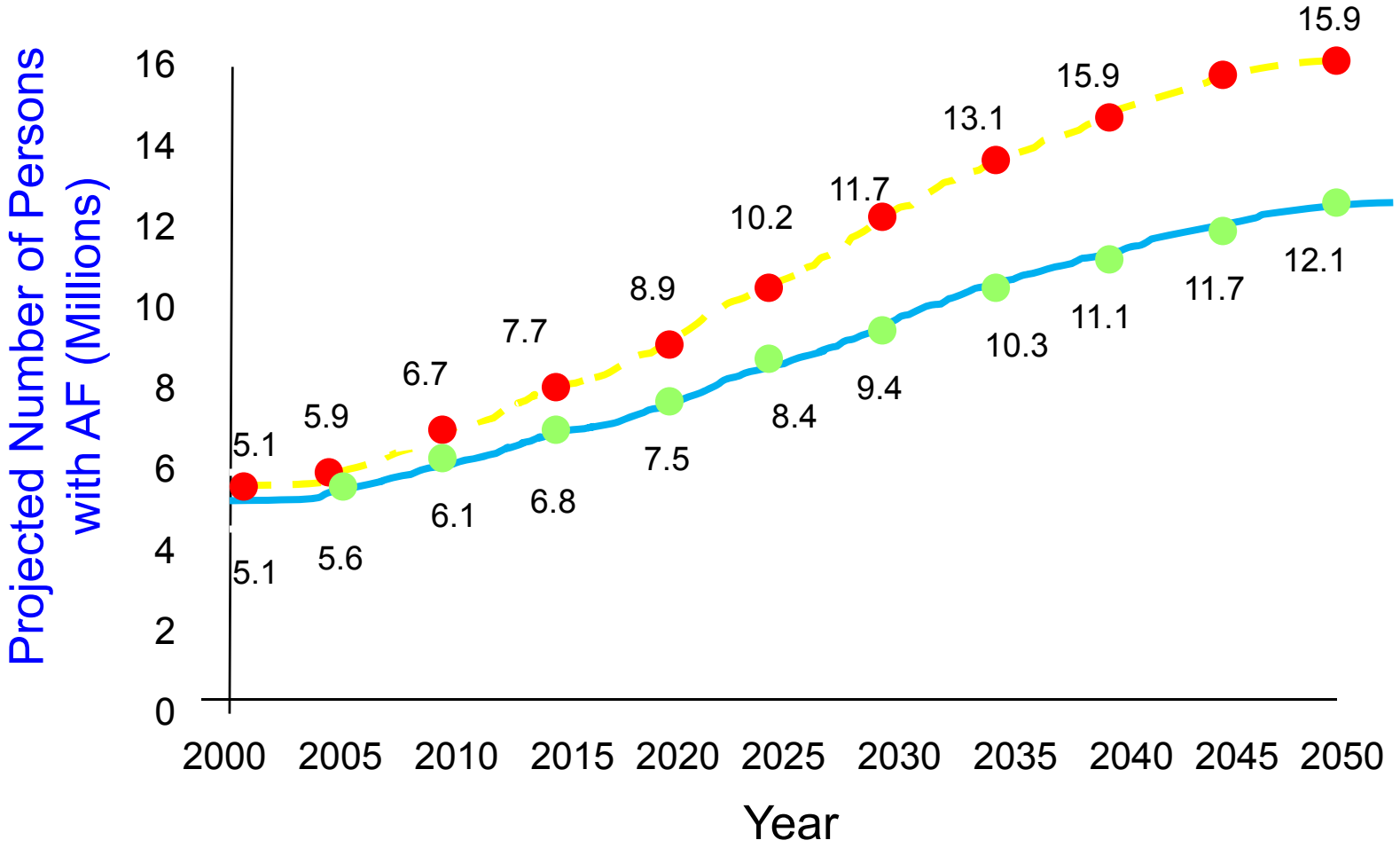
Le novità più rilevanti negli ultimi 5 anni

- **L'introduzione dei NOACs per la profilassi degli eventi tromboembolici nella fibrillazione atriale non valvolare**
- **Netti benefici del prolungamento della durata della doppia terapia antiaggregante dopo SCA**
- **Vantaggi dell'associazione dell'ezetimibe alla terapia con statine**
- **L'introduzione degli inibitori di PCSK9**
- **Il farmaco generico per un trattamento delle malattie cardiovascolai più sostenibile**

NOACs

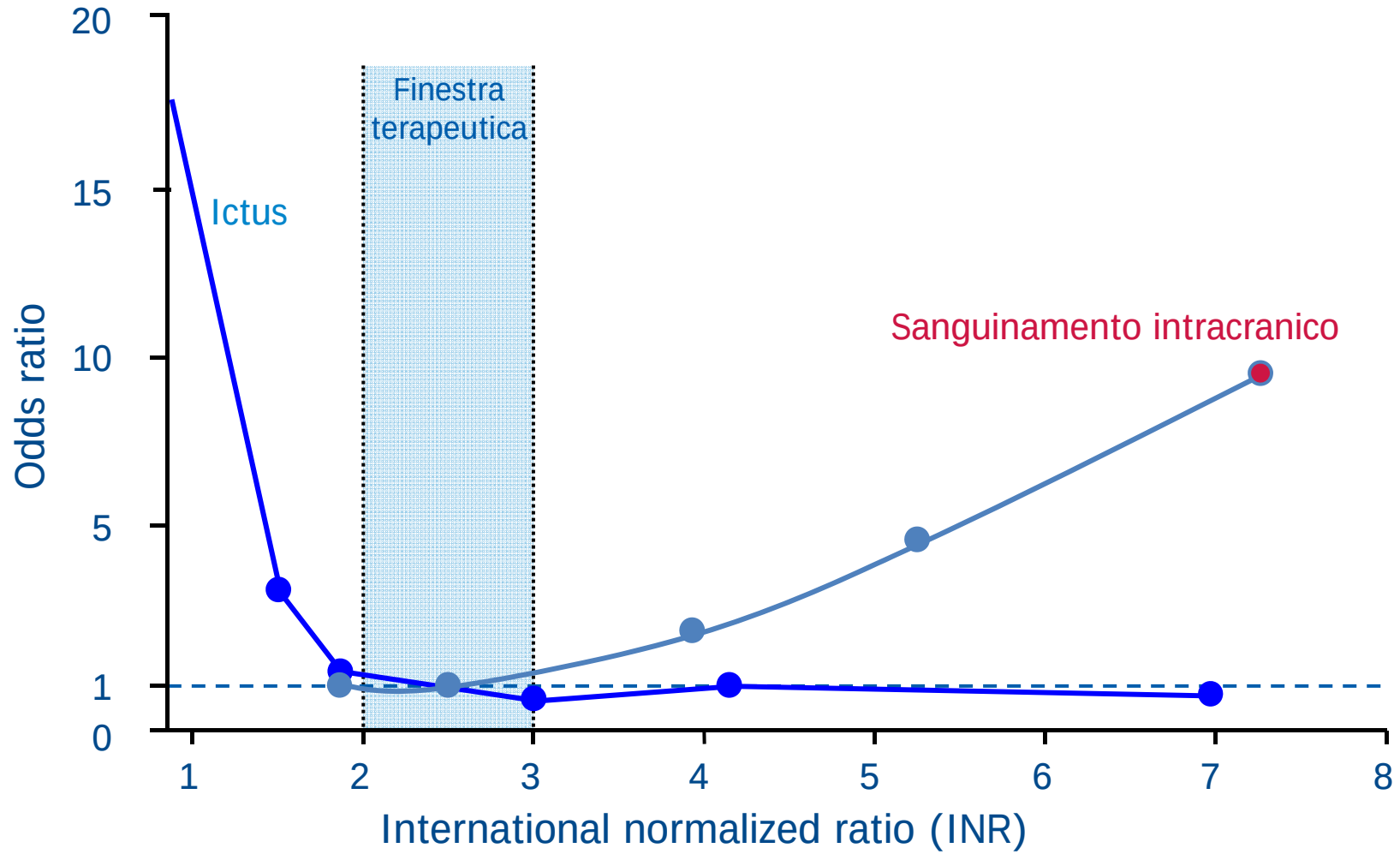
Projected Number of Persons with AF in the U.S. Between 2000-2050



Assumes no further increase in age-adjusted AF incidence (blue curve) and assumes a continued increase in incidence rate as evident in 1980 to 2000 (yellow curve)

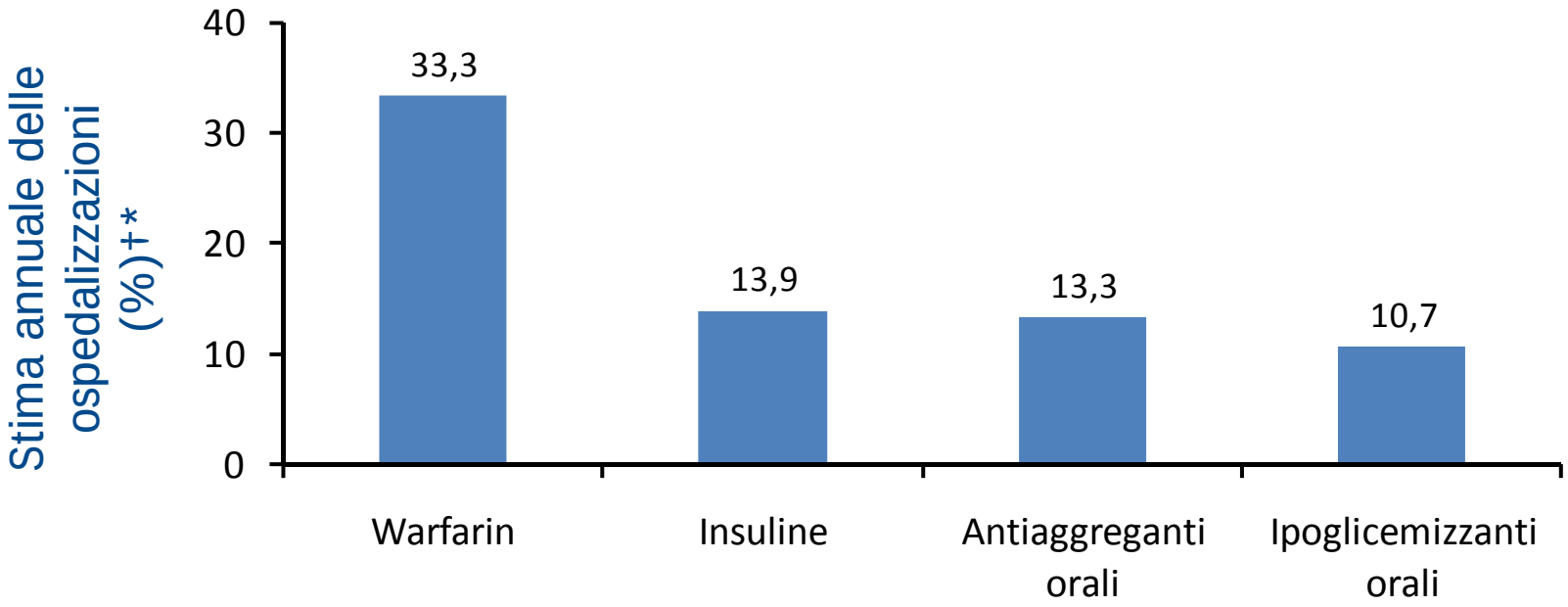
Miyasaka, Y. et al. Circulation 2006;114:119-125[4]

AVK - Ristretta finestra terapeutica



AVK = antagonista della vitamina K; American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society focused update guidelines: Fuster V et al. Circulation 2011;123:e269–367; Wann LS et al. Circulation 2011;123:104–23 & Circulation 2011;123:1144–50

AVK e ospedalizzazioni



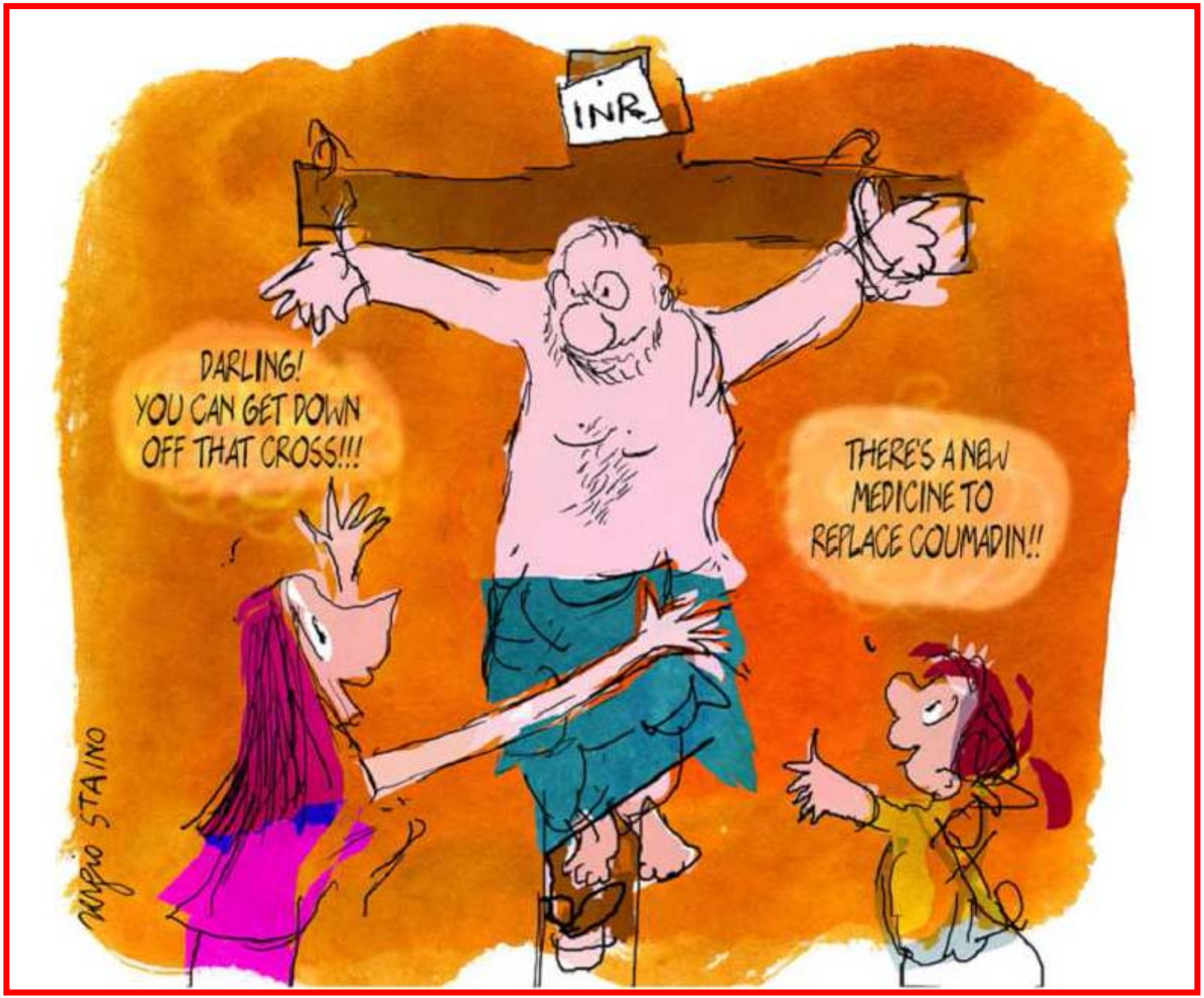
- **Il 63.3% delle ospedalizzazioni correlate al warfarin sono dovute ad emorragie[1]**
- La stima dei costi per le emorragie correlate al warfarin ammonta a centinaia di milioni di dollari ogni anno

†Dati da US National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance project (2007–2009); n=99 628 ospedalizzazioni in emergenza

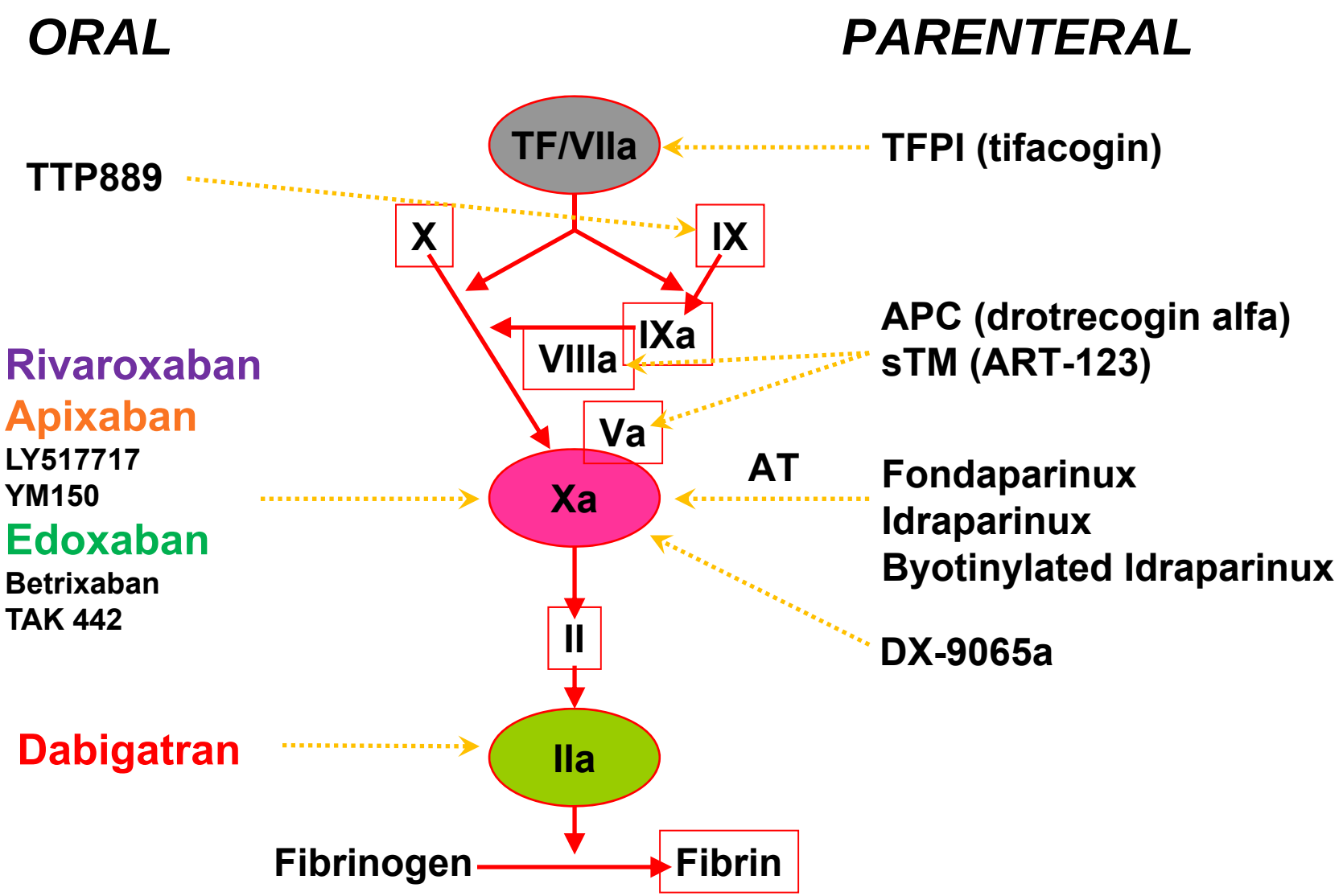
*Sono riportate le classi di farmaci associate ad un tasso di ospedalizzazione ≥10%

VKA = antagonisti della vitamina K

1. Budnitz DS et al. N Engl J Med 2011;365:2002–12

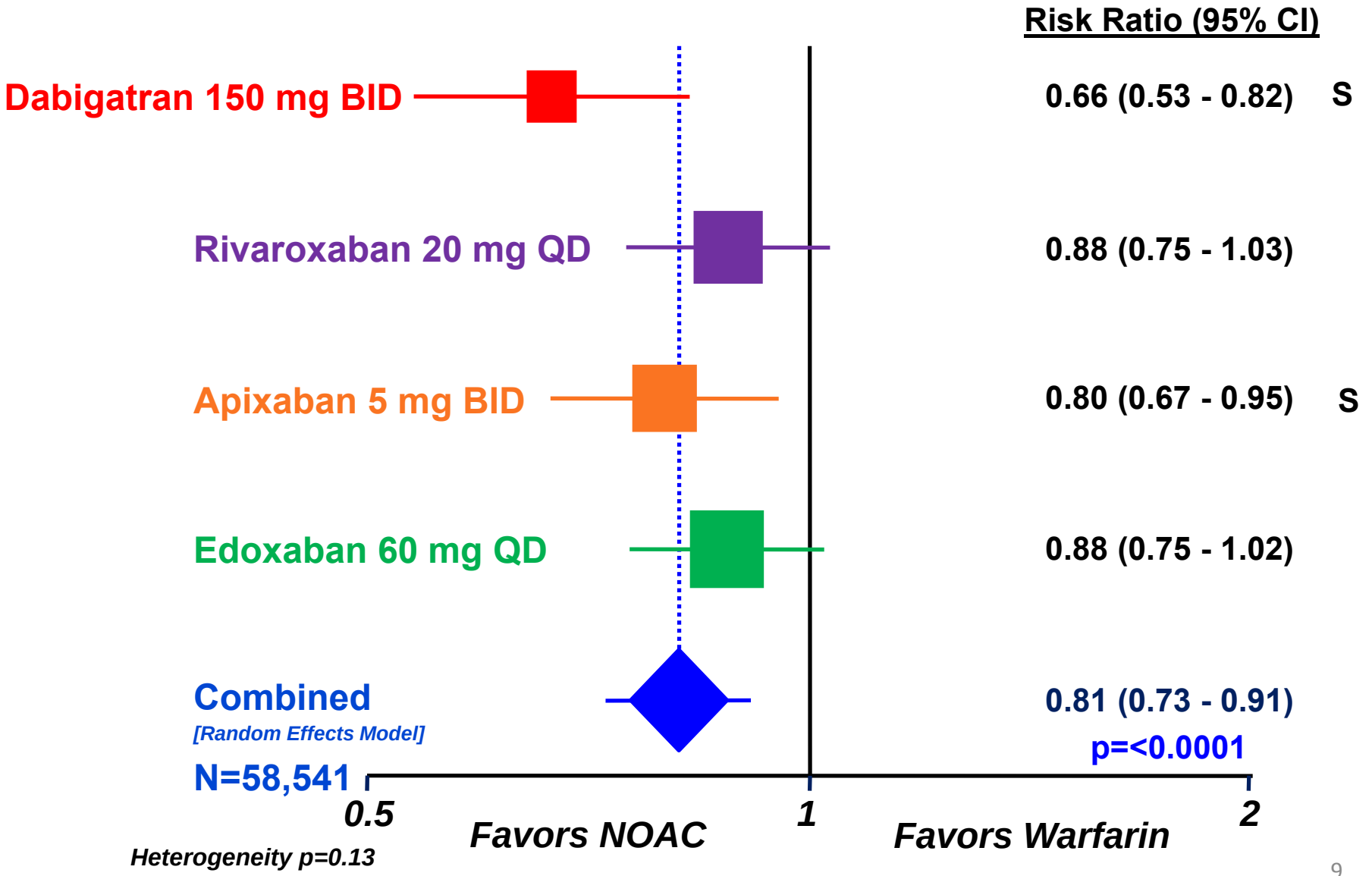

INR
DARLING! YOU CAN GET DOWN OFF THAT CROSS!!!
THERE'S A NEW MEDICINE TO REPLACE COUMADIN!!
Mario STAINO

Novel Anticoagulants



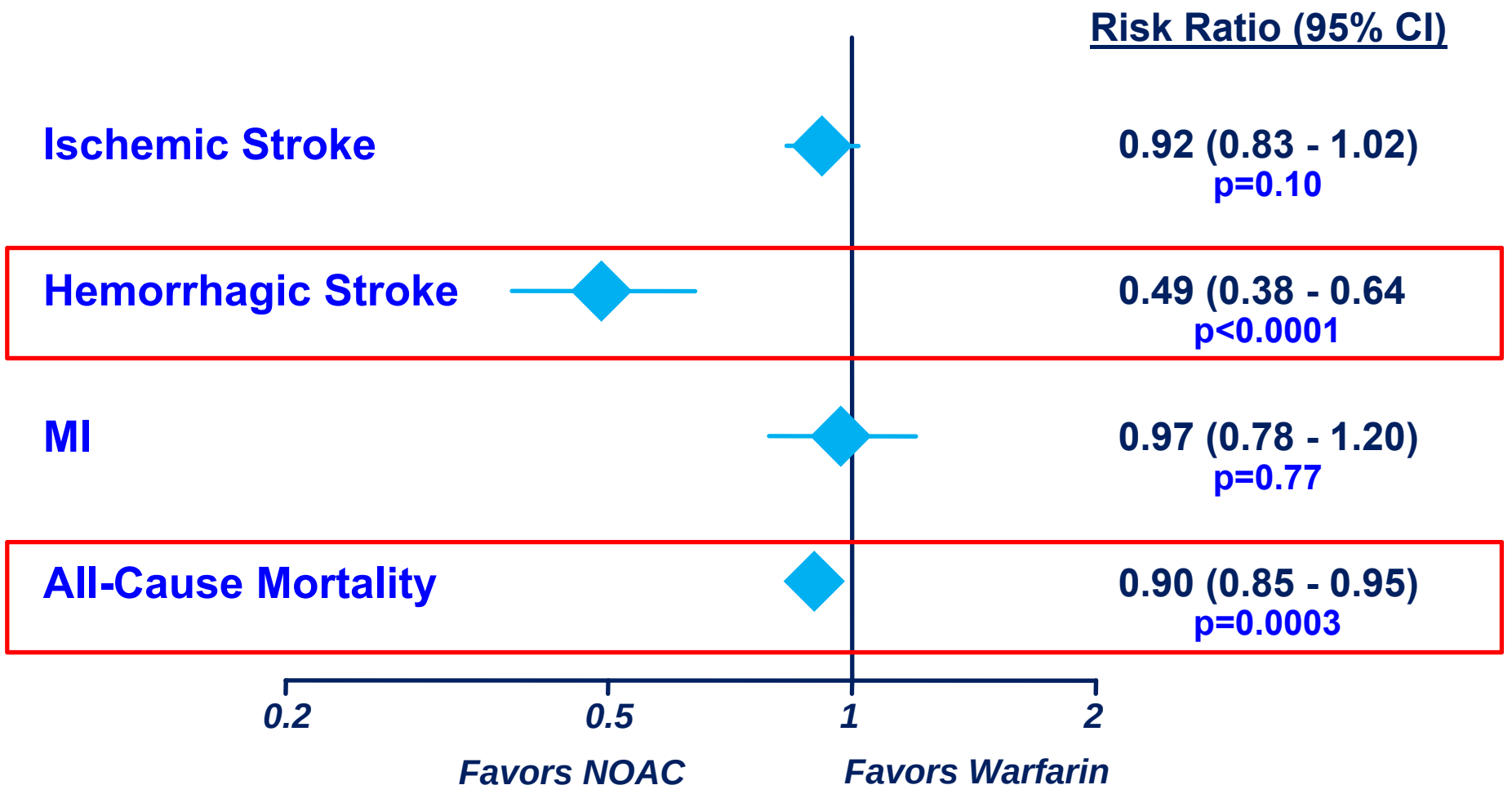
Adapted from Weitz & Bates, J Thromb Haemost 2007

Stroke or SE in NOACs Phase III Trials



Adapted from Ruff CT et al. Lancet 2014; 383:955-962

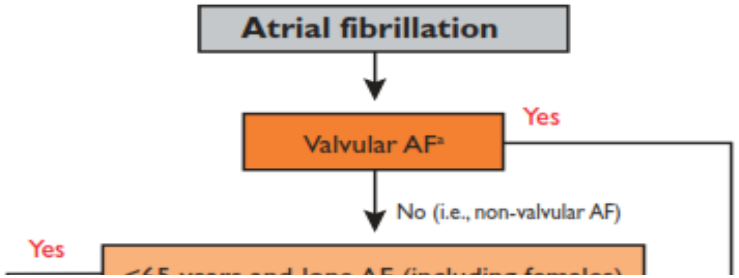
Haemorrhagic Stroke and Mortality in NOACs Phase III Trials



Heterogeneity p=NS for all outcomes

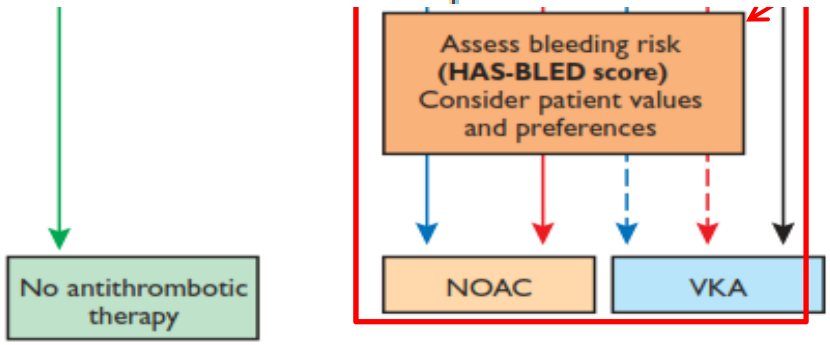
Adapted from Ruff CT et al. Lancet 2014; 383:955-962

ESC 2012 Guidelines



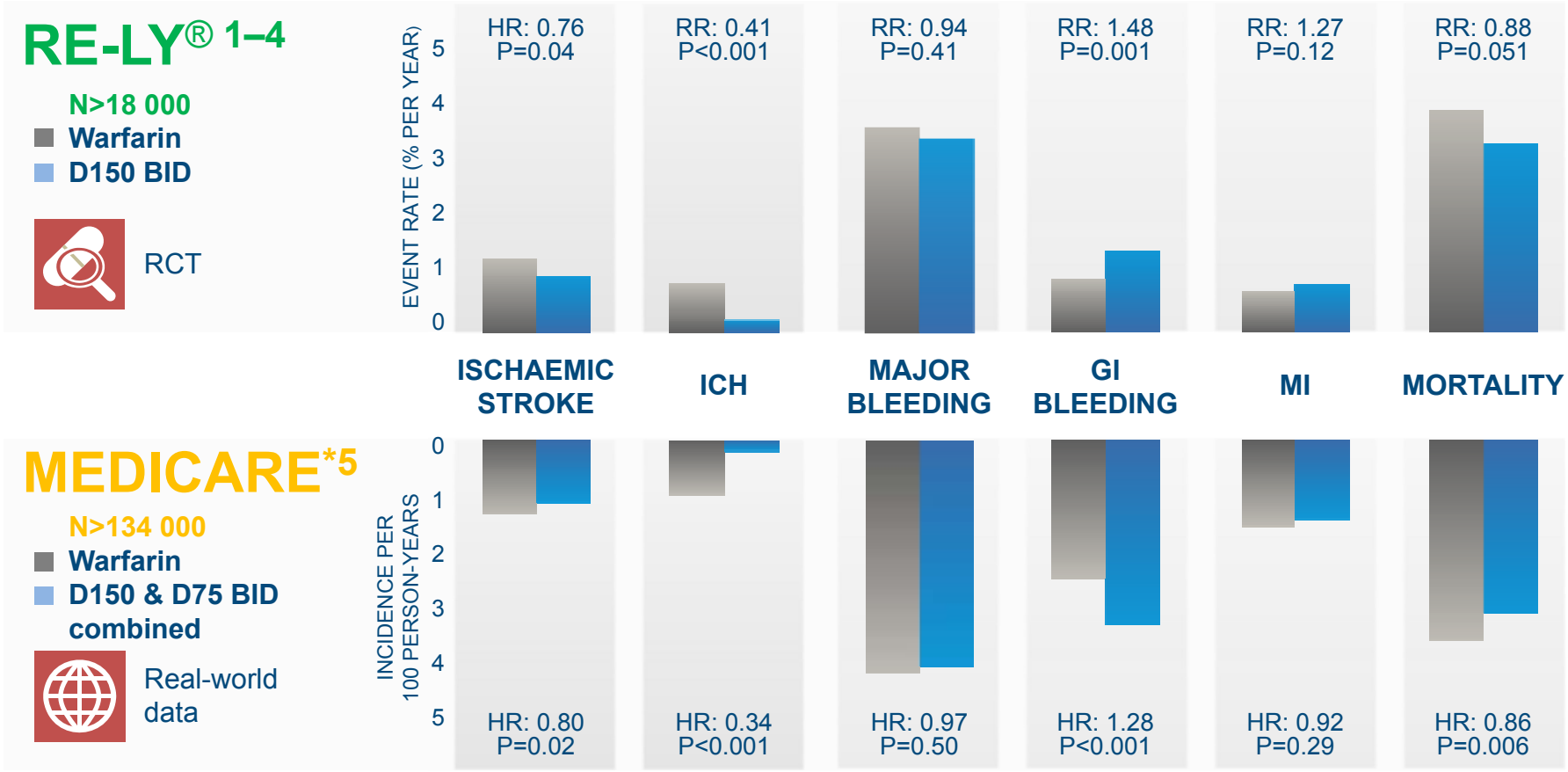
Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to

The NOACs so far tested in clinical trials have all shown non-inferiority compared with VKAs, with better safety, consistently limiting the number of ICH. On this basis, this guideline now recommends them as broadly preferable to VKA in the vast majority of patients with non-valvular AF, when used as studied in the clinical trials performed so far. Since there is still limited



Camm AJ et al. Eur Heart J (2012) 33, 2719–2747

Independent FDA study of Medicare confirmed the positive safety and efficacy of Dabigatran in clinical practice



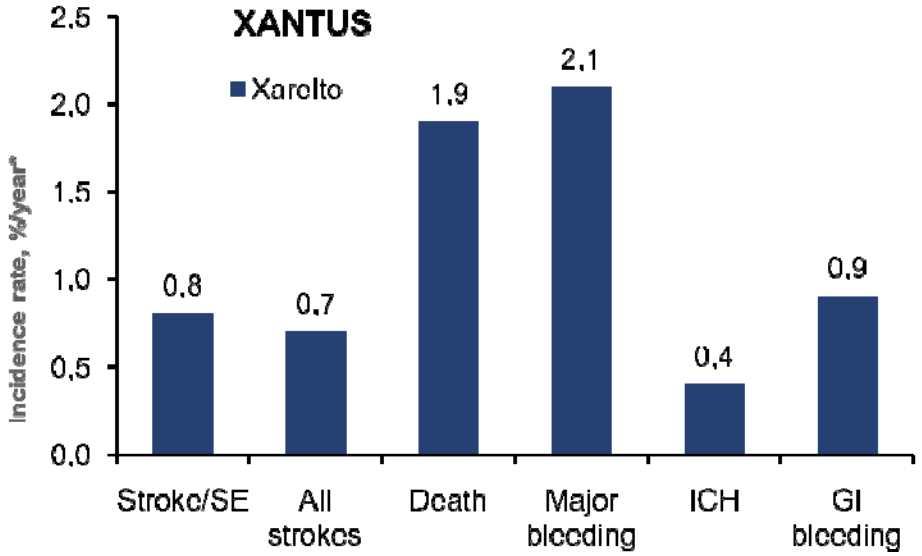
In the USA, the licensed doses for Pradaxa® are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF

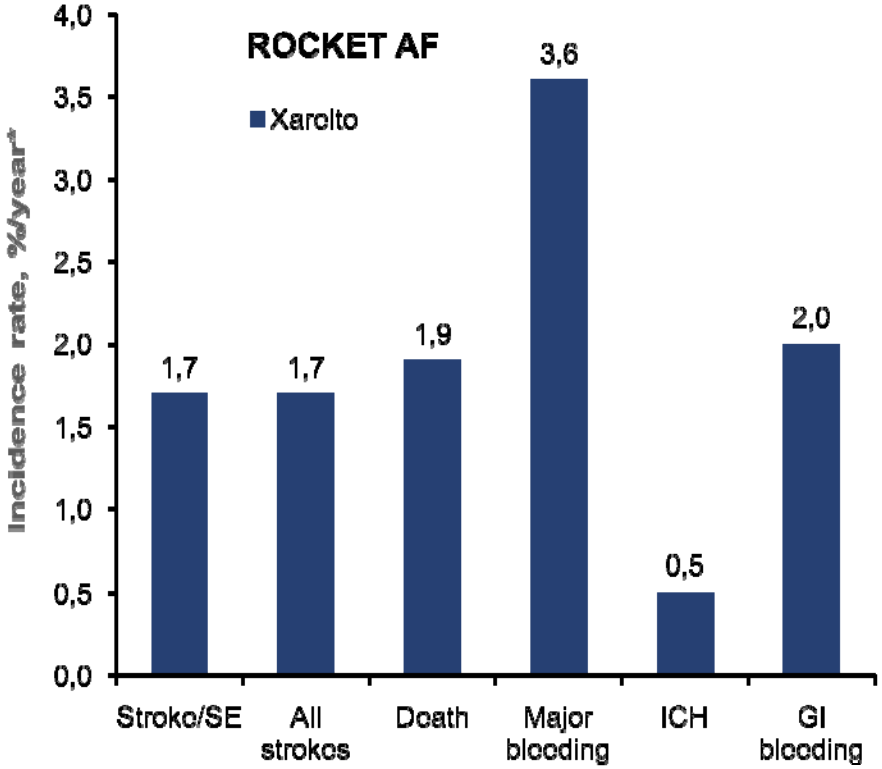
*Primary findings for dabigatran are based on analysis of both 75 mg &150 mg together without stratification by dose

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51
2. Connolly SJ et al. N Engl J Med 2010;363:1875–6
3. Pradaxa®: EU SPC, January 2015
4. Connolly SJ et al. N Engl J Med 2014;371:1464–5
5. Graham DJ et al. Circulation 2015;131:157–64

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	$CHADS_2$	Prior stroke#
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%





Treatment persistence was high: 80% of patients remained on rivaroxaban

#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR et al, N Engl J Med 2011;365:883–891;
2. Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466

Durata della DAPT dopo SCA

European Heart Journal
doi:10.1093/eurheartj/ehu505

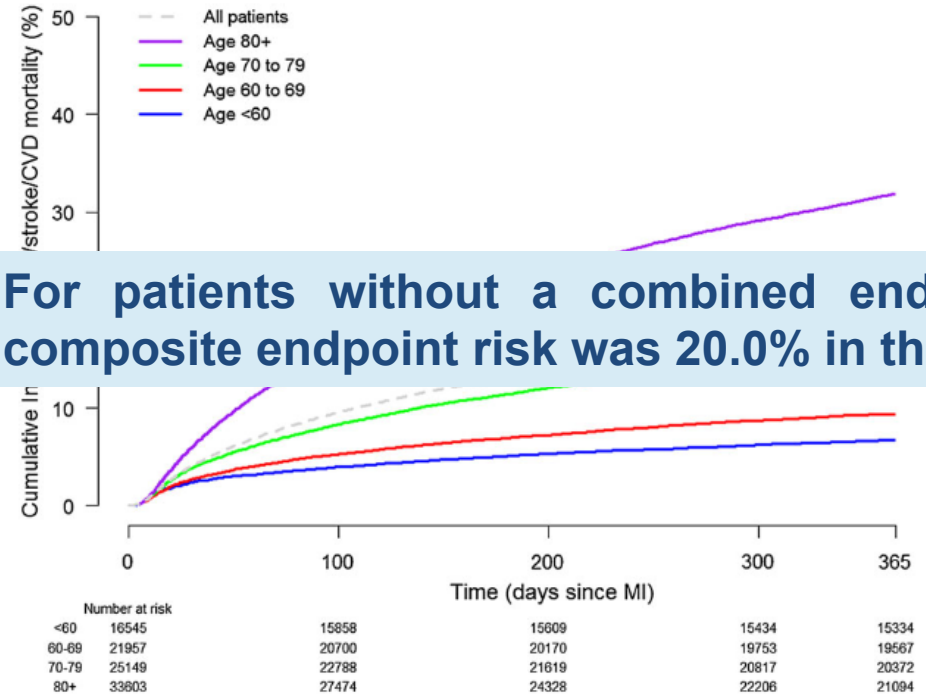
CLINICAL RESEARCH
Acute Coronary Syndrome

Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective

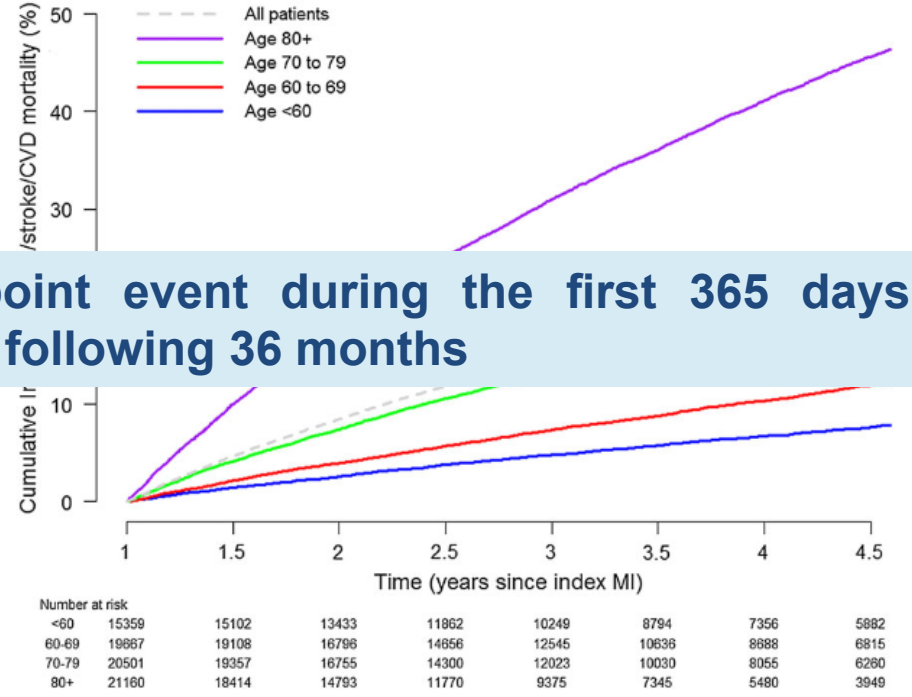
Tomas Jernberg[1]*, Pål Hasvold[2], Martin Henriksson[2], Hans Hjelm[3], Marcus Thuresson[4], and Magnus Janzon[5,6]

K–M Rates of MI, Stroke or CV Death

1 year

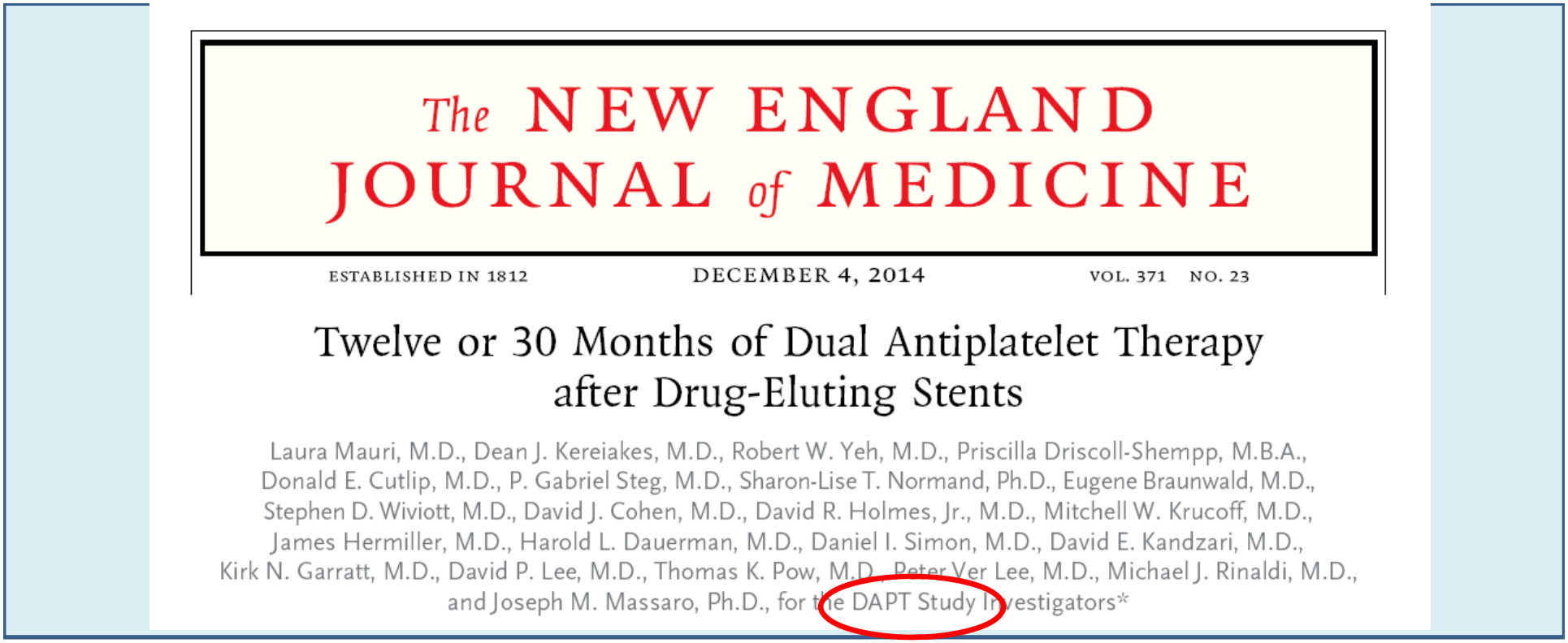


4.5 year



For patients without a combined endpoint event during the first 365 days, composite endpoint risk was 20.0% in the following 36 months

Jernberg T et al. Eur Heart J 2015



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2014 VOL. 371 NO. 23

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

- 9961 patients enrolled after PCI with a DES
- After 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin, patients were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months
- Coprimary efficacy end points: stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months
- Primary safety end point: moderate or severe bleeding

STEMI	534 (10.6)	511 (10.3)
NSTEMI	776 (15.5)	767 (15.5)
Unstable angina¶	838 (16.7)	825 (16.7)
Stable angina	1882 (37.5)	1870 (37.8)

N Engl J Med 2014;371:2155-66

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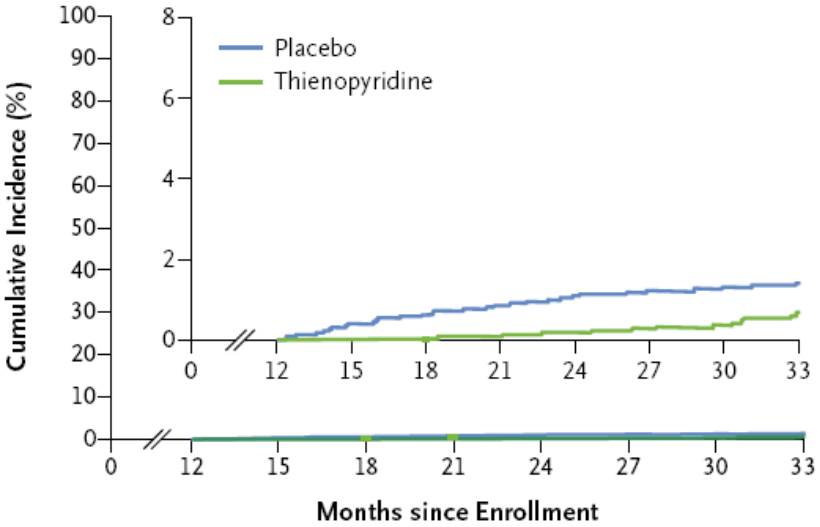
ESTABLISHED IN 1812 DECEMBER 4, 2014 VOL. 371 NO. 23

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Stent Thrombosis

12–30 mo Thienopyridine vs. placebo, 0.4% vs. 1.4%; hazard ratio, 0.29; P<0.001

12–33 mo Thienopyridine vs. placebo, 0.7% vs. 1.4%; hazard ratio, 0.45; P<0.001

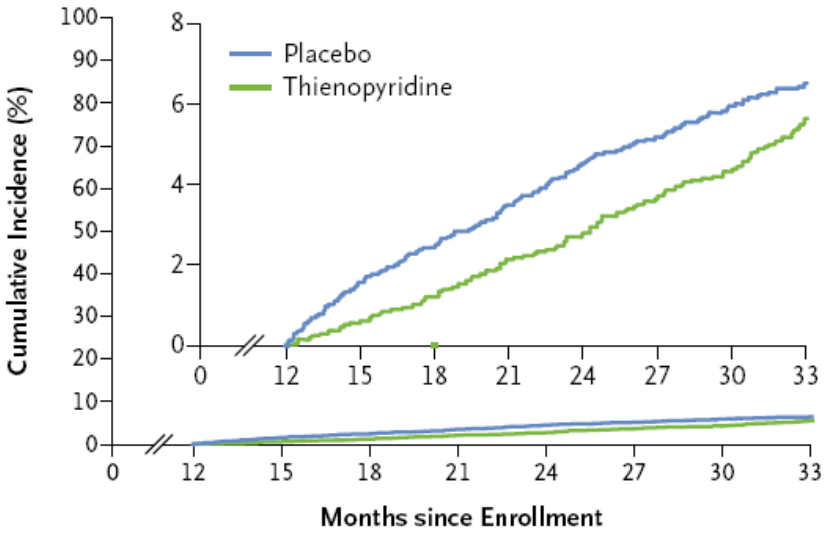


No. at Risk								
Thienopyridine	5020	4934	4870	4828	4765	4686	4642	3110
Placebo	4941	4845	4775	4721	4651	4603	4556	3105

Major Adverse Cardiovascular and Cerebrovascular Events

12–30 mo Thienopyridine vs. placebo, 4.3% vs. 5.9%; hazard ratio, 0.71; P<0.001

12–33 mo Thienopyridine vs. placebo, 5.6% vs. 6.5%; hazard ratio, 0.82; P=0.02



No. at Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

CONCLUSIONS

Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding.

N Engl J Med 2014;371:2155-66

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

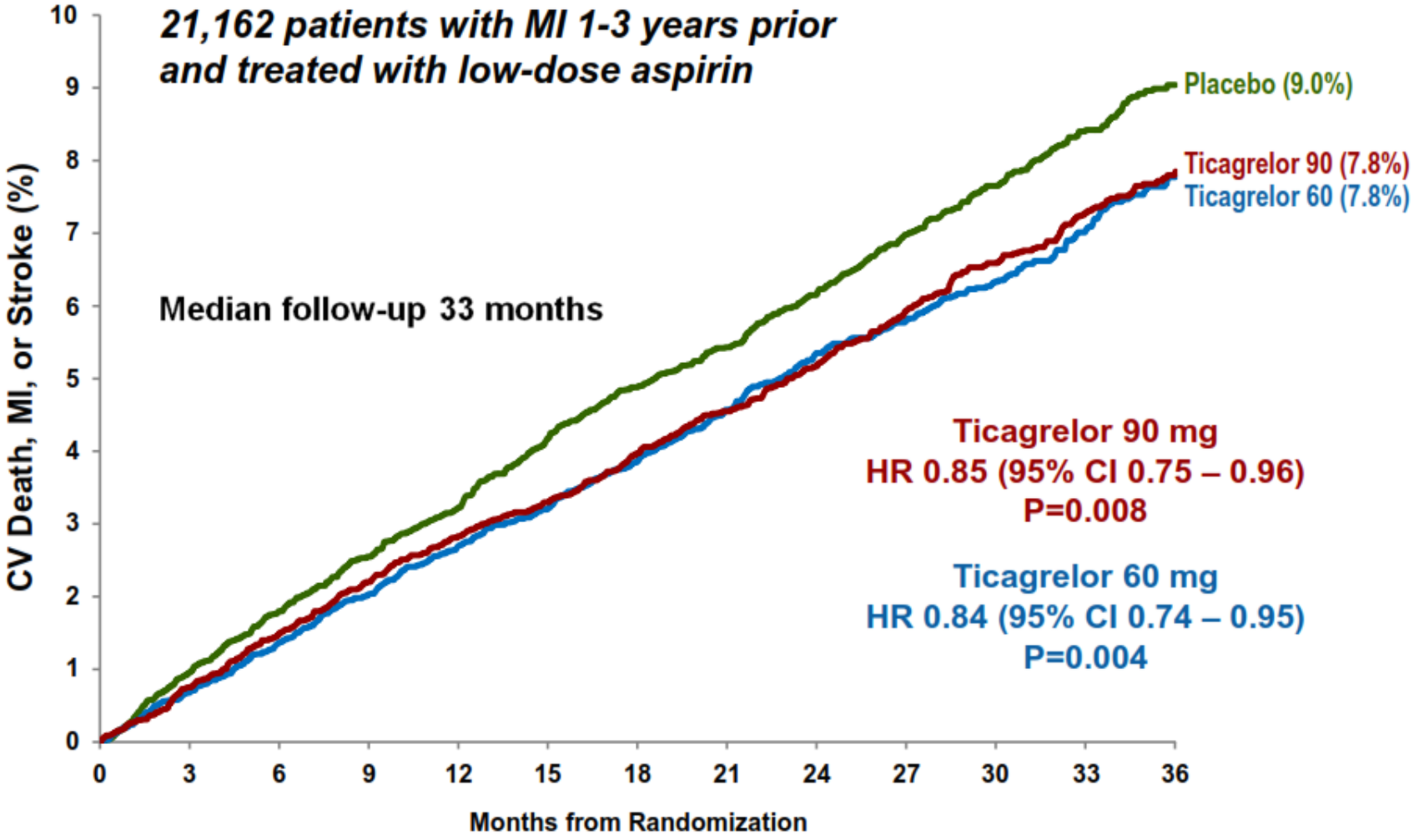
Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer Bansilal, M.D., M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Pierre Theroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D., Shinya Goto, M.D., Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H., for the PEGASUS-TIMI 54 Steering Committee and Investigators*

- **Study design: Randomized, double-blind 1:1:1**
- **Population: 21,162 pts who had had a MI 1 to 3 years earlier to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo**
- **F-up: 33 months**
- **Primary efficacy end point: composite of cardiovascular death, myocardial infarction, or stroke**
- **Primary safety end point: TIMI major bleeding**

Bonaca M. P. et al. NEJM.org. March 14, 2015

PEGASUS TIMI 54: Primary endpoint

K–M Rates of CV Death, MI, and Stroke through 3 Years



Bonaca M. P. et al. NEJM.org. March 14, 2015

Vantaggi dell’associazione dell’ezetimibe alla terapia con statine

IMPROVE-IT: Study design

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

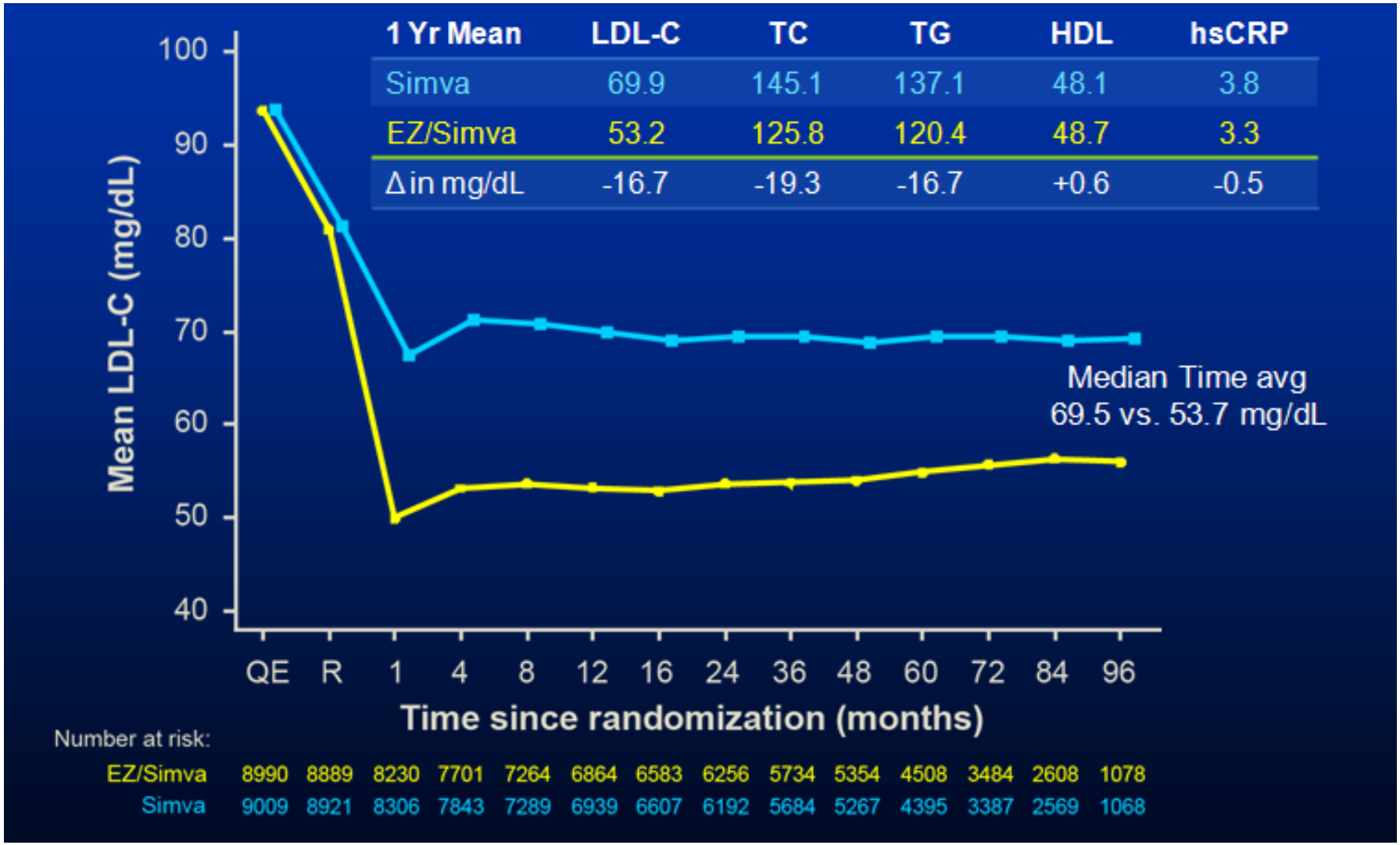
90% power to detect ~9% difference

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

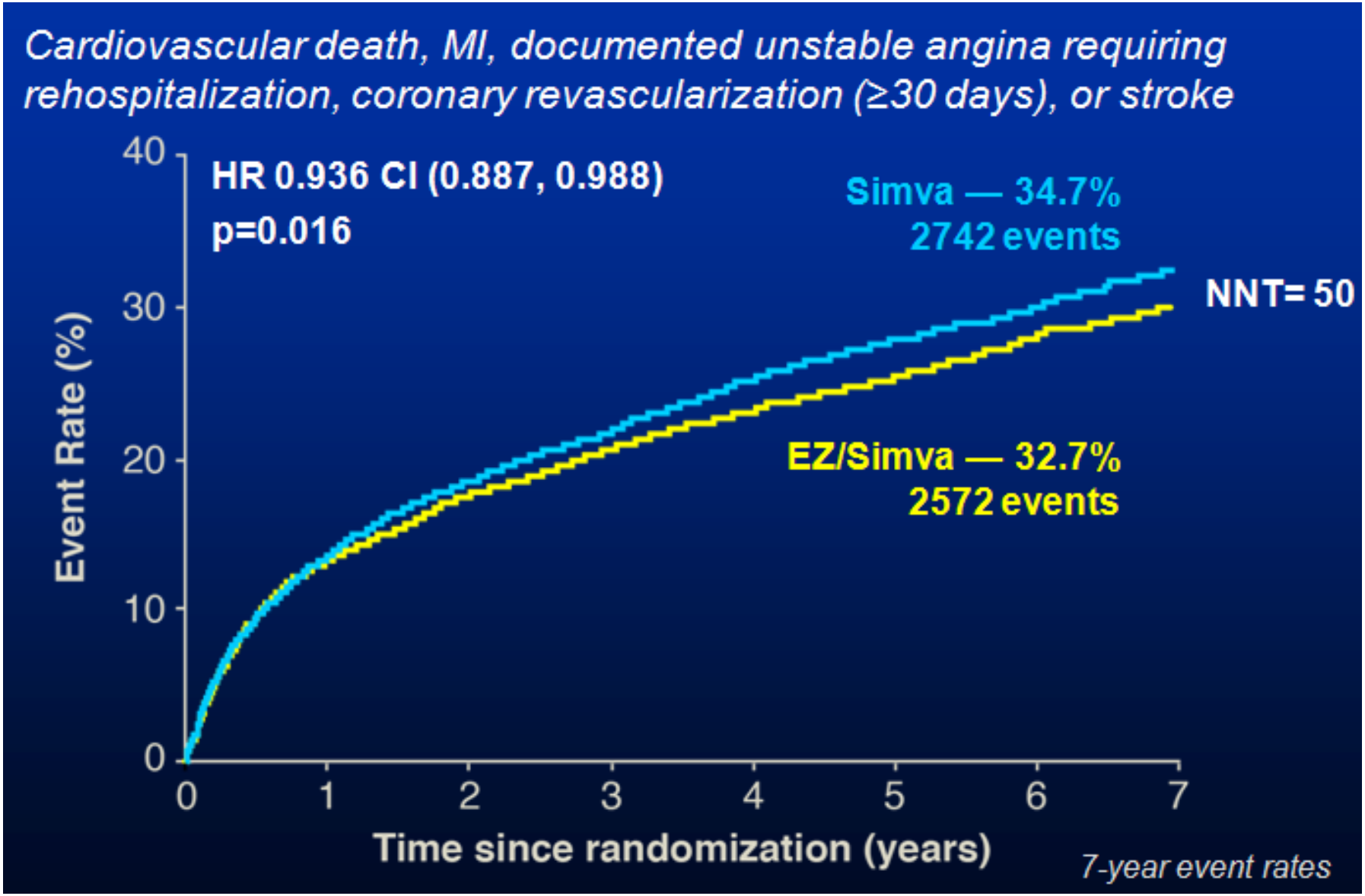
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

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

IMPROVE-IT: LDL-C and Lipid Changes

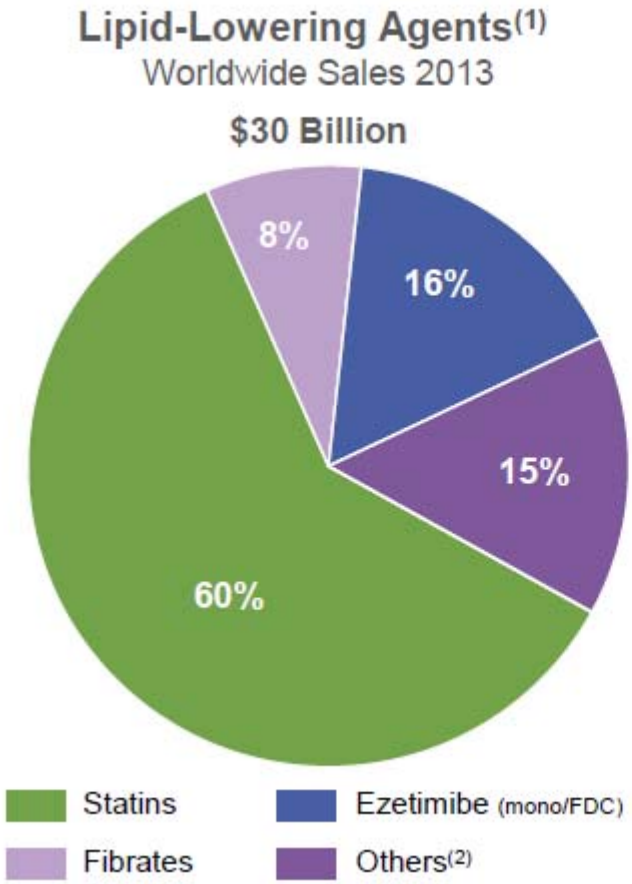


IMPROVE-IT: Primary Endpoint — ITT



Inibitori di PCSK9

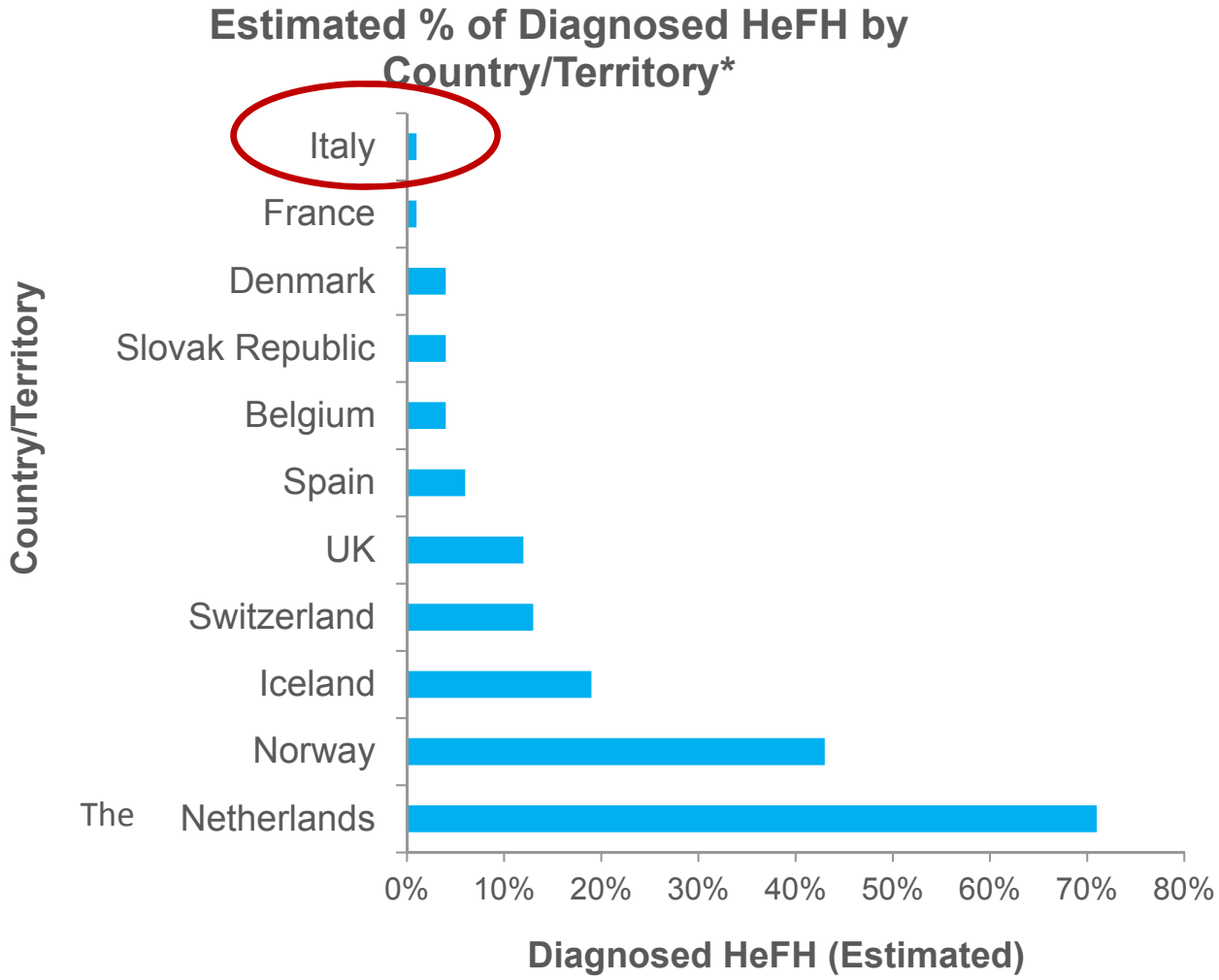
Despite Current Therapies, There Exists a Significant Population of Patients at High Cardiovascular Risk



- Statins remain the primary treatment option for high LDL-C
- Many hypercholesterolemic patients not at LDL-C goal with statins
  - Patients with LDL-C too high at maximally tolerated statin dose
  - Patients unable to tolerate a recommended statin dose
  - Patients completely statin intolerant
- Approximately 8 million patients worldwide receive ezetimibe(1) (mono/FDC)

(1) Worldwide MAT sales in €bn of dyslipidemia market, IMS MIDAS
(2) Niacin, omega-3 therapies
FDC = fixed dose combination

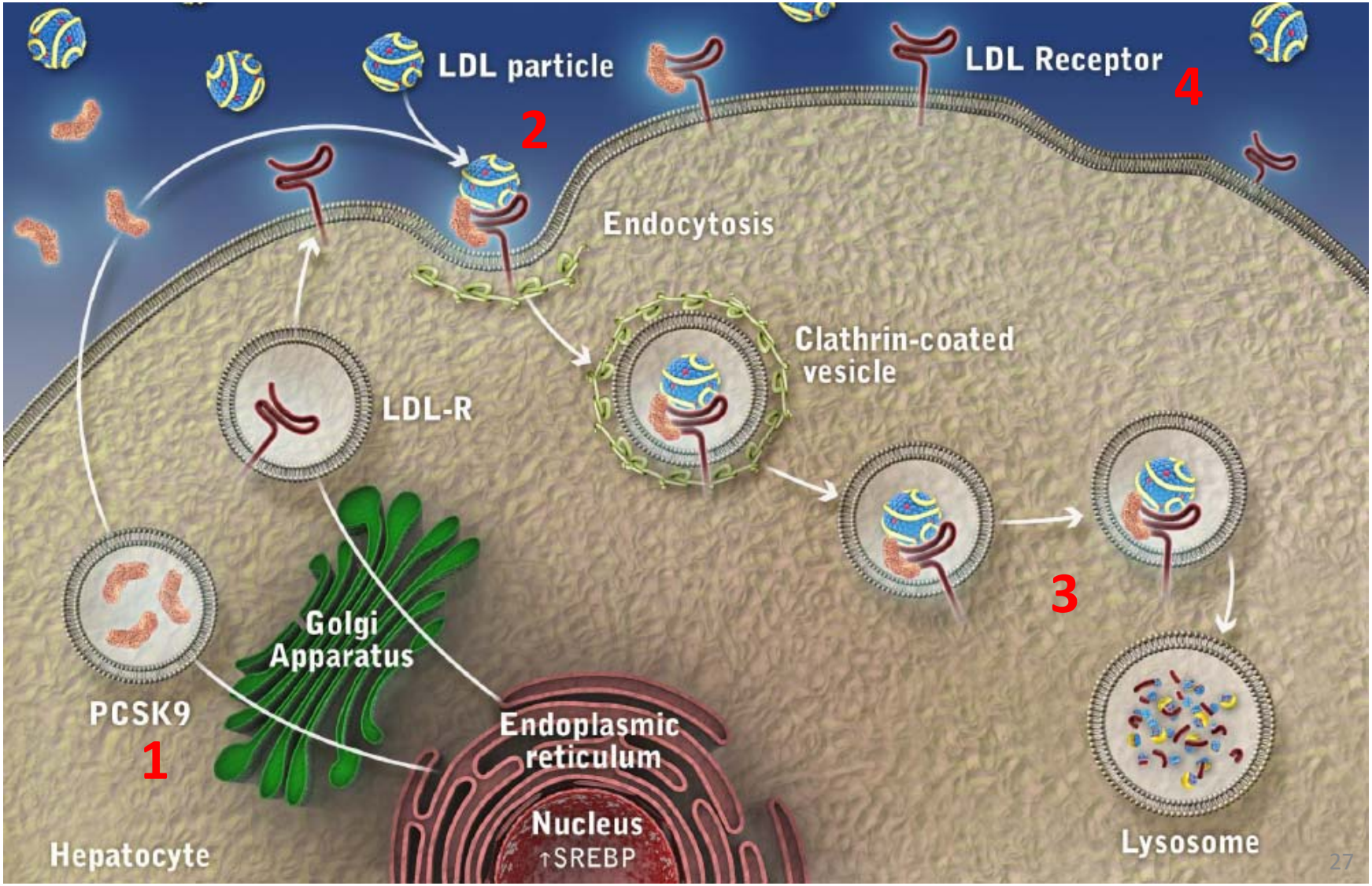
L’ipercolesterolemia familiare è uno dei più comuni disordini genetici e che rimane sotto-diagnosticata



*Percentage derived from diagnoses values from expert clinician/scientists in local areas, as well as prevalence of 1 in 500 in the general population are FH heterozygotes

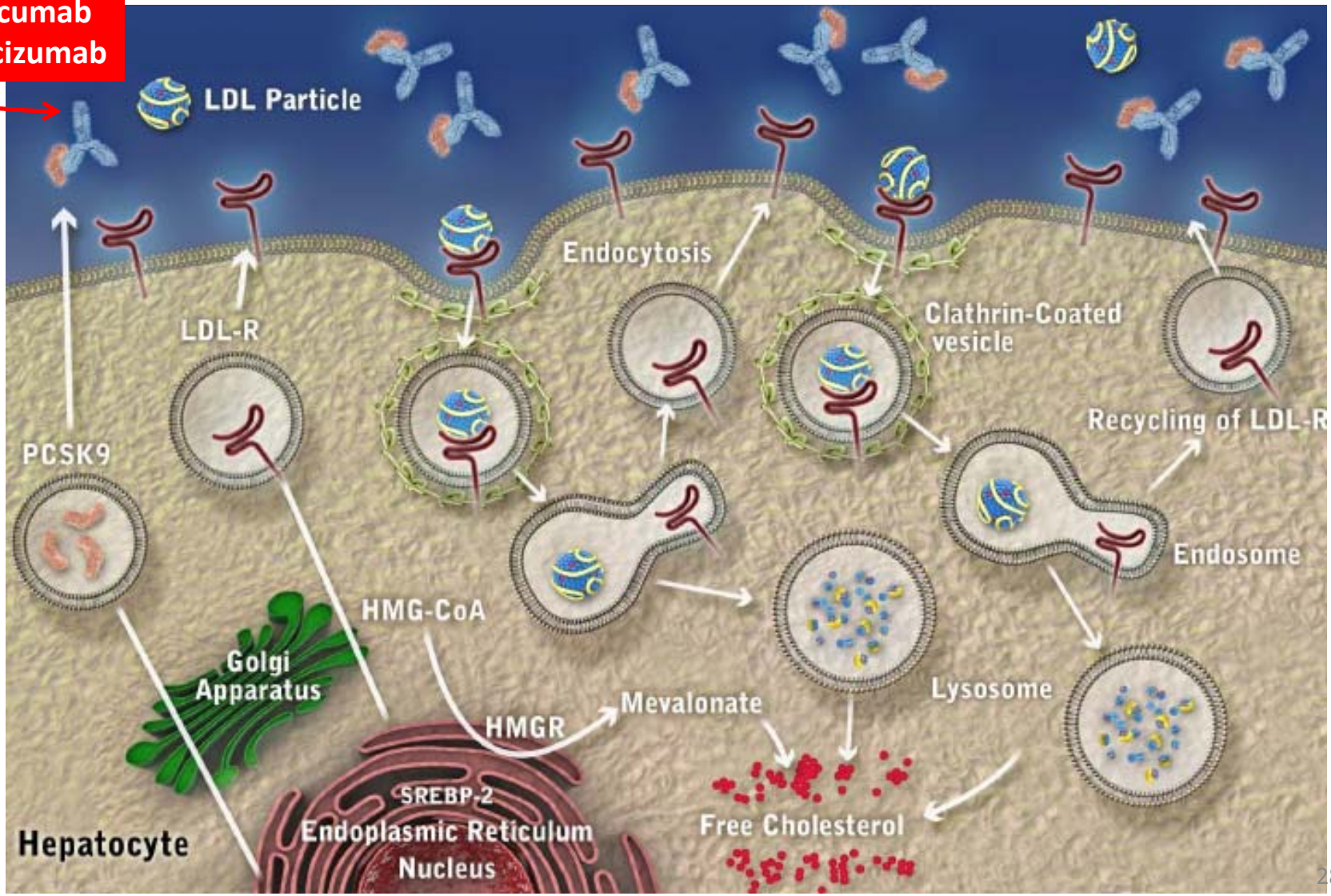
1. Goldberg AC et al. *J Clin Lipid.* 2011;5:S1–S8. 2. Nordestgaard BG et al. *Eur Heart J.* 2013;34:3478–3490;
3. Sjouke B et al. *Eur Heart J.* 2014;doi:10.1093/eurheartj/ehu058 [Epub ahead of print]

Role of PCSK9 in regulation of LDL receptor

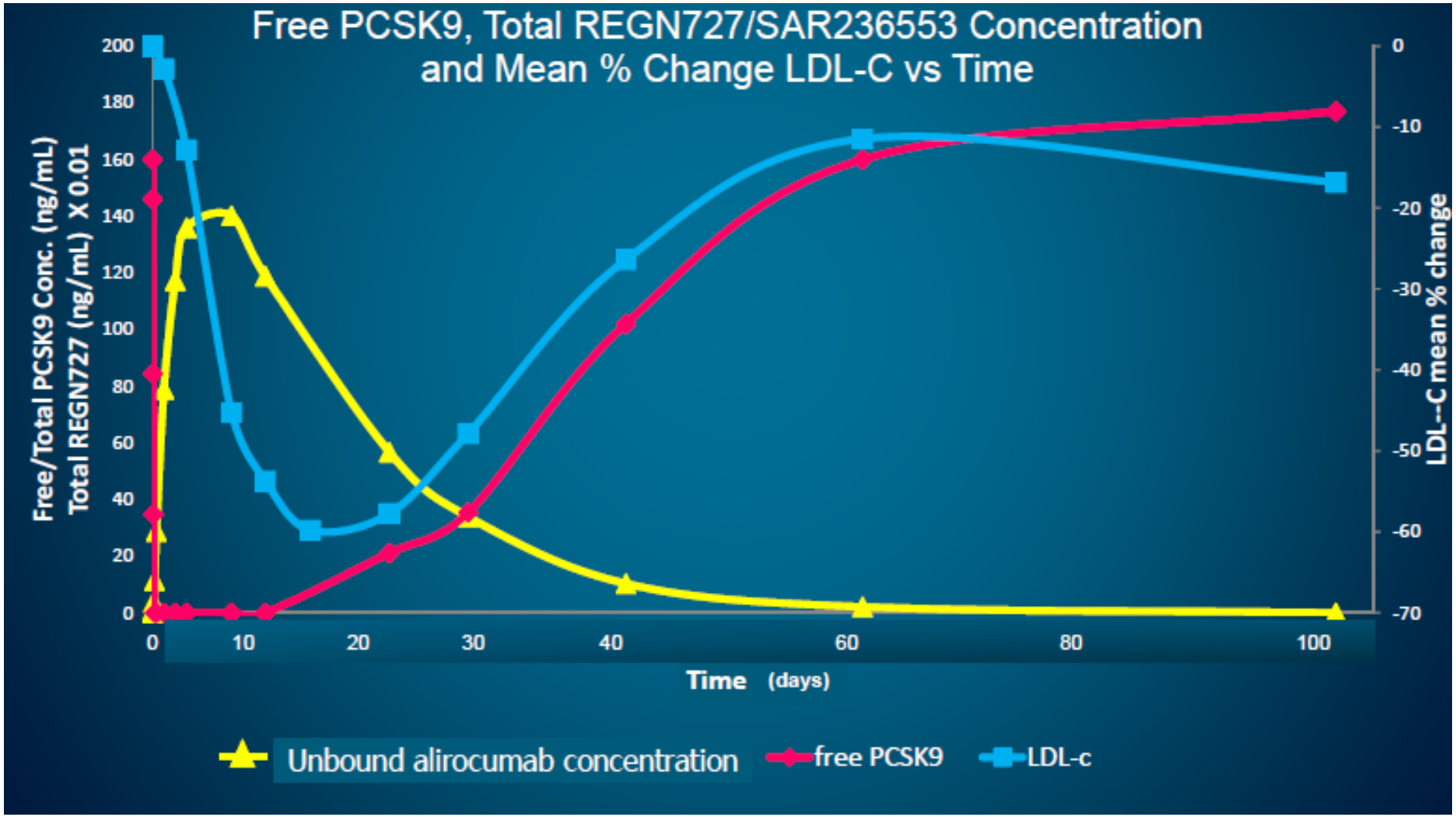


Impact of mAb on LDL-Omeostasis

Alirocumab
Evolocumab
Bococizumab



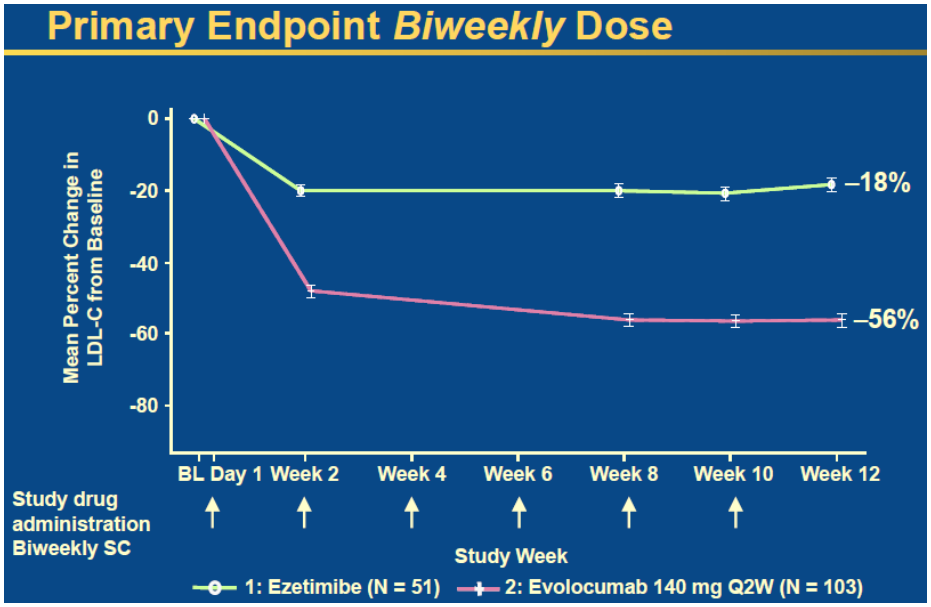
Alirocumab 150 mg SC: Dynamic relationship between mAb Levels, PCSK9 and LDL-C

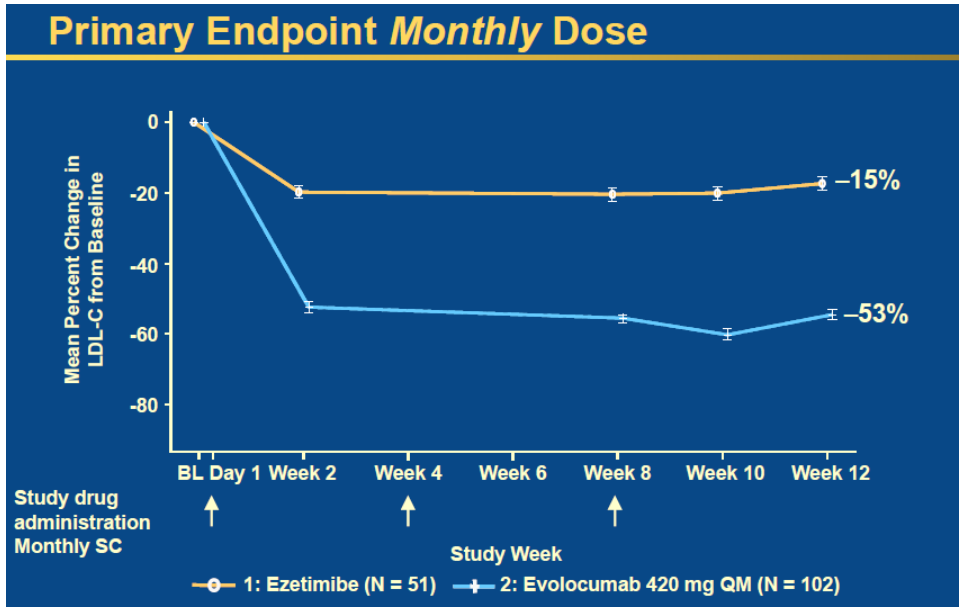


Stein EA et al. NEJM 2012; 366: 1008-1118

GAUSS 2 Study: Evolocumab in statin-intolerant hypercholesterolemic patients

Primary Endpoint

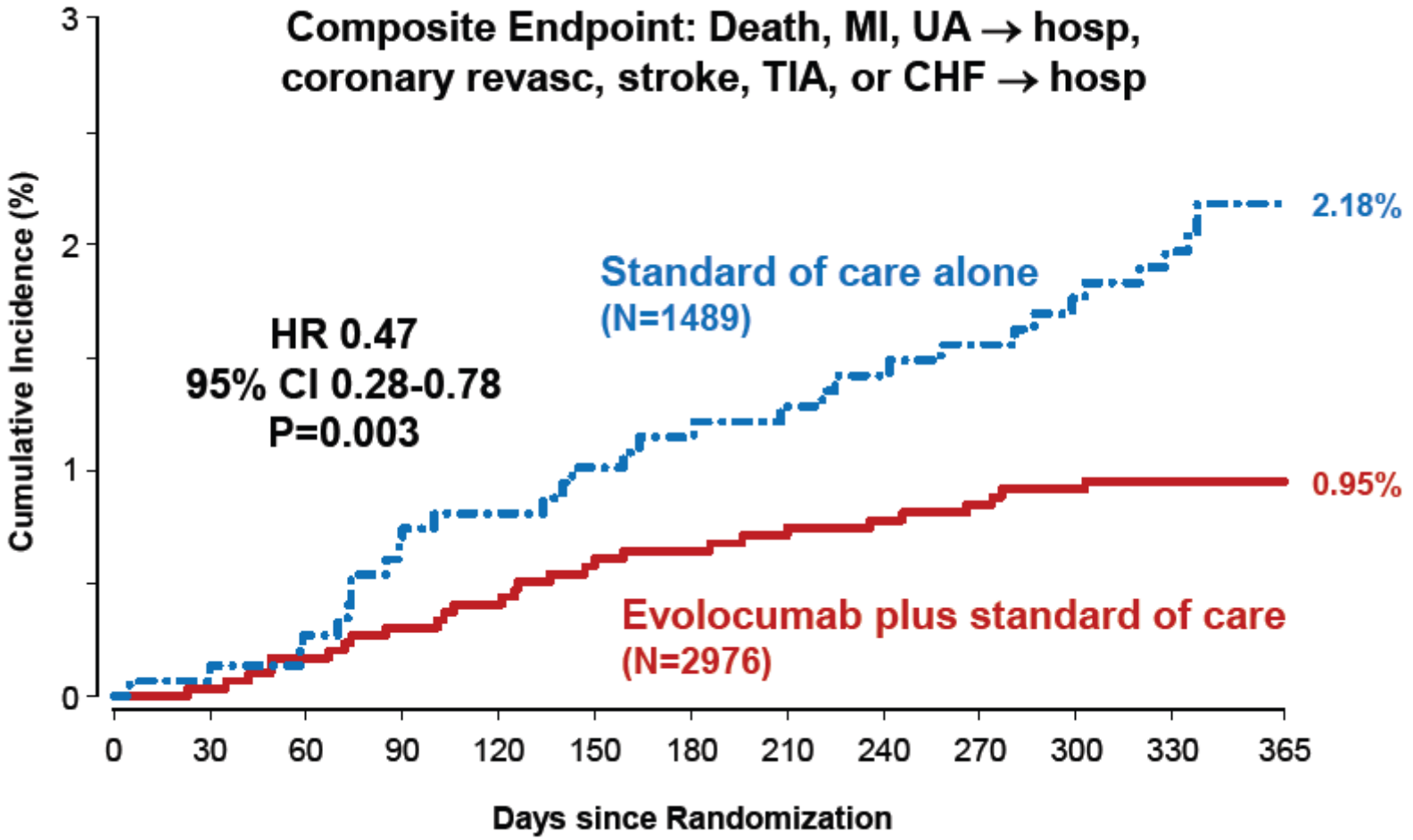




Stroes E. et al., J Am Coll Cardiol. 2014 Jun 17;63(23):2541-8.

OSLER: Results

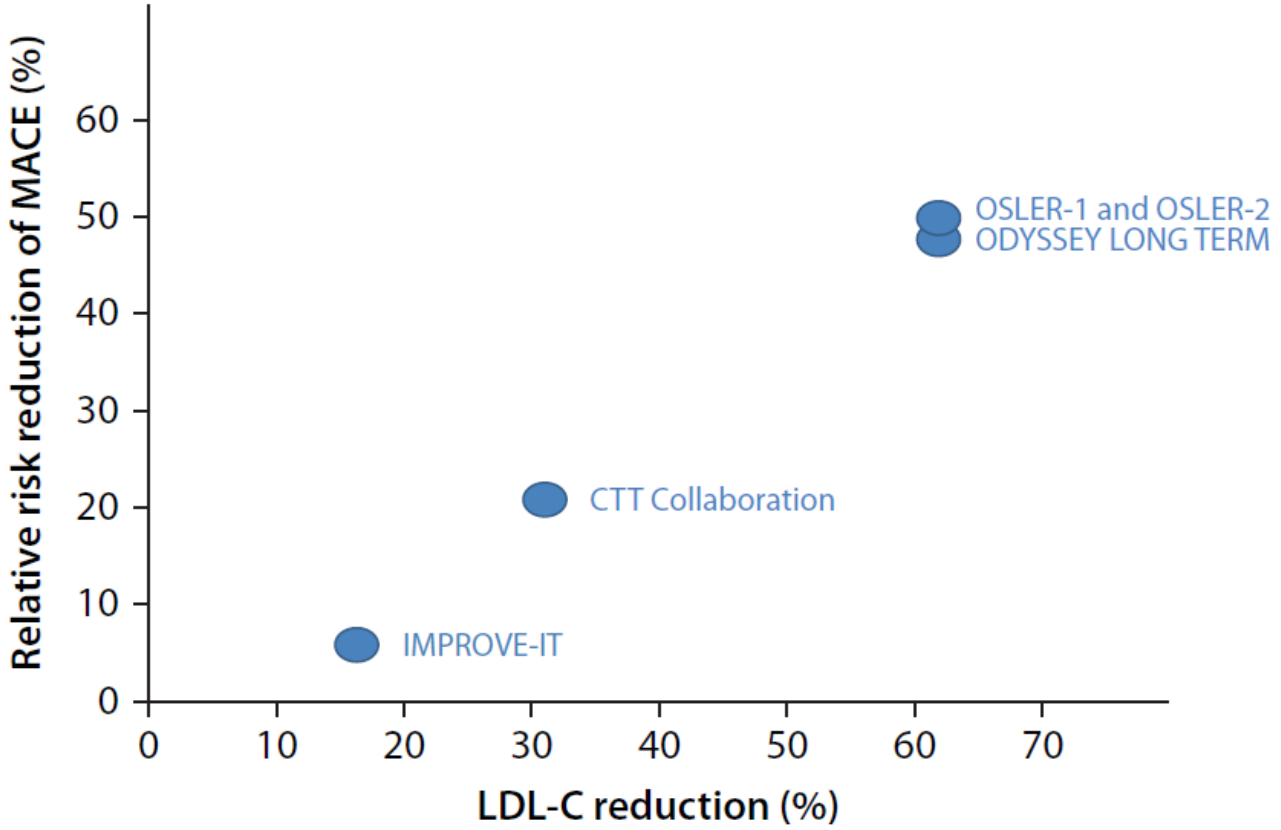
Cardiovascular Outcomes



Sabatine M.C. et. al. N Engl J Med 2015;372:1500-9

OSLER and ODYSSEY LONG TERM: PCSK9 inhibitors on the right track of reducing cardiovascular events

Mohamed Hassan*



Gencer B et al. Eur. Heart J. 2015

Farmaci Generici

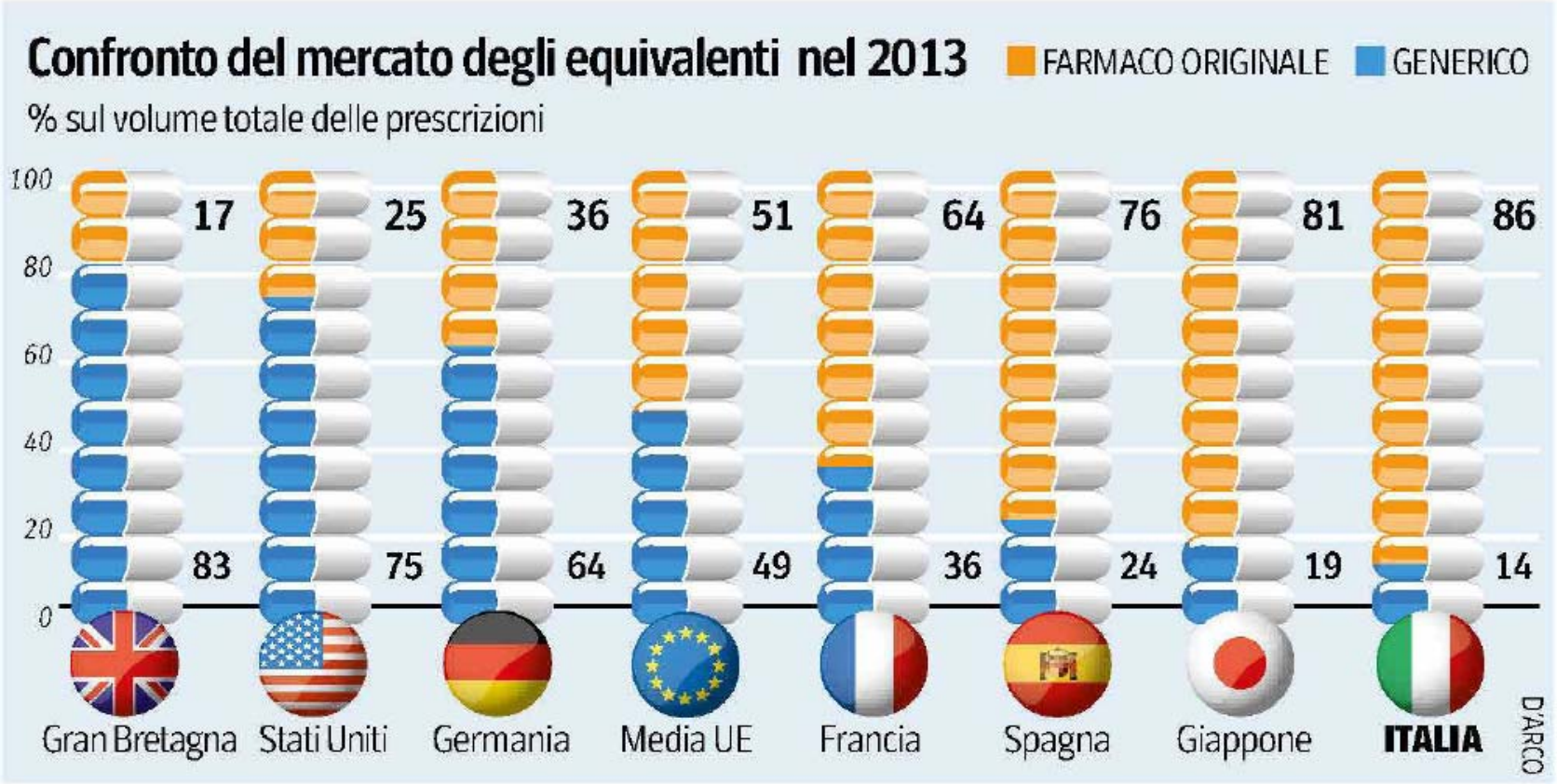
Data:
venerdì 06.06.2014

SETTE

Estratto da Pagina:
46

Misteri italiani Nell'impiego di prodotti farmaceutici fuori brevetto siamo il fanalino di coda della Ue

Dottore, mi dà un generico? Così risparmio un miliardo



Una media europea di tutto rispetto

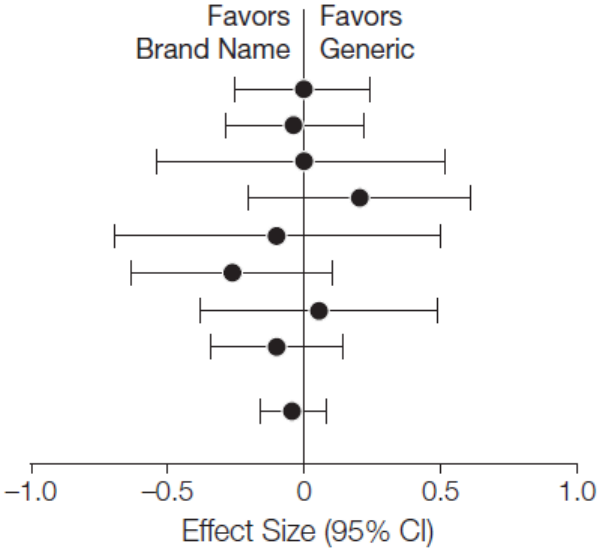
Dal grafico, elaborato da Ims, società internazionale di informazione sul mercato farmaceutico, Gran Bretagna, Usa e Germania sono i Paesi dove si impiegano di più i farmaci fuori brevetto.

Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

A Systematic Review and Meta-analysis

Drug Class and Aggregate Meta-analyses of Trials Comparing Generic and Brand-Name Drugs Used in CV Disease

Drug Class	No. Studies	No. Subjects	Effect Size (95% CI)
β-Blockers	6	135	0.00 (–0.24 to 0.25)
Diuretics	10	135	–0.03 (–0.28 to 0.22)
Calcium channel blockers	4	242	0.00 (–0.53 to 0.53)
Antiplatelet agents	2	50	0.21 (–0.19 to 0.61)
ACE inhibitors	1	23	–0.09 (–0.68 to 0.50)
Statins	2	71	–0.25 (–0.62 to 0.12)
α-Blockers	1	43	0.06 (–0.37 to 0.50)
Warfarin	4	138	–0.09 (–0.33 to 0.15)
Overall	30	837	–0.03 (–0.15 to 0.08)



ACE indicates angiotensin-converting enzyme; CI, confidence interval.

Kesselheim AS, JAMA 2008

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PLOS ONE

Off-Patent Generic Medicines vs. Off-Patent Brand Medicines for Six Reference Drugs: A Retrospective Claims Data Study from Five Local Healthcare Units in the Lombardy Region of Italy

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Abstract

The scientific documentation supporting the potential clinical and economic benefits of a growing use of off-patent generic drugs in clinical practice seems to be limited in Italy as yet.

Methods: We compared differences in outcomes between off-patent generic drugs and off-patent brand drugs in real clinical practice. The outcomes were: persistence and compliance with therapy, mortality, and other health resources consumption (hospitalizations, specialist examinations, other drugs) and total costs. Retrospective analysis was carried out by using the administrative databases of five Local Healthcare Units (ASLs - Aziende Sanitarie Locali) in the Lombardy Region of Italy. Data from the five ASLs were aggregated through a meta-analysis, which produced an estimate indicator of the mean or percentage difference between the two groups (branded vs. generic) and their respective significance tests. The therapeutic areas and studied drugs were: diabetes: metformin - A10BA02; hypertension: amlodipine - C08CA01; dyslipidemia: simvastatin - C10AA01; psychiatry: sertraline - N06AB06; cardiology: propafenone - C01BC03; osteoporosis: alendronate - M05BA04.

Results: The 5 Local Healthcare Units (ASL) represent a population of 3,847,004 inhabitants. The selected sample included 347,073 patients, or 9.02% of the total ASL population; 67% of the patients were treated with off-patent brand drugs. The average age was 68 years, with no difference between the two groups. After 34 months of observation, compliance and persistence were in favor to generic drugs in all therapeutic areas and statistically significant in the metformin, amlodipine, simvastatin, and sertraline groups. The clinical outcomes (hospitalizations, mortality, and other health costs) show no statistically significant differences between off-patent generic vs. off-patent brand medicines.

Conclusions: Off-patent generic drugs appear to be a therapy option of choice in Italy as well, based on clinical outcomes and economic consequences, both for the National Health Service and patients, considering that the price difference between brand and generic drugs is completely charged on patients.

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Impact of substitution among generic drugs on persistence and adherence: A retrospective claims data study from 2 Local Healthcare Units in the Lombardy Region of Italy

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Abstract

Background: The use of generics, equivalent but less expensive drugs, is an important opportunity to reduce healthcare expenditure.
Methods: The purpose of this study was to investigate the effect of substitution between unbranded generics on persistence and adherence to therapy in two Italian Local Health Units (ASL) in real-world clinical practice in 5 therapeutic areas using tracing drugs. Substitution of generic drugs is any change in the name of the manufacturer of the generic drug. The therapeutic areas were: diabetes (metformin); hypertension (amlodipine); dyslipidemia (simvastatin); psychiatry (sertraline); cardiology (propafenone); osteoporosis (alendronate). The retrospective analysis was carried out on the administrative databases of two Local Healthcare Units (ASL – Azienda sanitaria locale Bergamo (BG) and Pavia (PV)) in the Lombardy Region of Italy. The correlation between persistence and adherence with the different cohorts of generic substitution frequency within each therapeutic area was then calculated.
Results: According to the inclusion criteria, 123,773 patients were evaluated. Patients were observed for a period of 36 months starting from the first drug delivery (index date). The median age of the overall population was above 61 years in all therapeutic areas. The generic drug substitution occurred in 61.5% of patients (BG: 57.6% and PV: 65.4% respectively); Hypertension was the therapeutic area with the highest percentage of patients with substitutions. Patients' adherence, evaluated by the Medical Possession Rate (MPR) and persistence to the treatment decreases with the increase in the frequency of generic substitutions. This observation was confirmed by a statistically significant negative correlation (p-value of <0.001) between the adherence and persistence and the number of generic substitutions in each therapeutic area and Local Healthcare Units (ASL).
Discussion: Adherence is one of the pillars of the patient's health management in the control and prevention of progression of the disease. Several factors, such as ageing, comorbidities, and polypharmacy, may affect adherence and influence the outcome of treatments. These results are in line with studies supporting the possibility that the change of package appearance each time a new prescription is dispensed may create confusion and ultimately reduce patients' adherence. Clinicians and decision makers should consider the impact of frequent generic substitutions on persistence and adherence, which may influence efficacy and/or safety.

Impact of substitution among generic drugs on persistence and adherence: A retrospective claims data study from 2 Local Healthcare Units in the Lombardy Region of Italy

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Number and percentage of pts with no substitution or with at least 1 substitution of generic drugs during the observation period by therapeutic area and by ASL

	ASL BERGAMO				ASL PAVIA			
	No substitution		At least one substitution		No substitution		At least one substitution	
THERAPEUTIC AREA	N	%	N	%	N	%	N	%
Diabetes	1754	45.68	2086	54.32	903	39.66	1374	60.34
Dyslipidemia	1907	41.99	2635	58.01	1154	33.12	2330	66.88
Hypertension	1063	35.77	1909	64.23	996	30.68	2250	69.32
Osteoporosis	273	48.66	288	51.34	187	42.12	257	57.88
Psychiatry	572	44.44	715	55.56	405	36.16	715	63.84
Total	5569	42.18	7633	57.82	3645	34.48	6926	65.52

Paper In press : Atherosclerosis Supplements 2016

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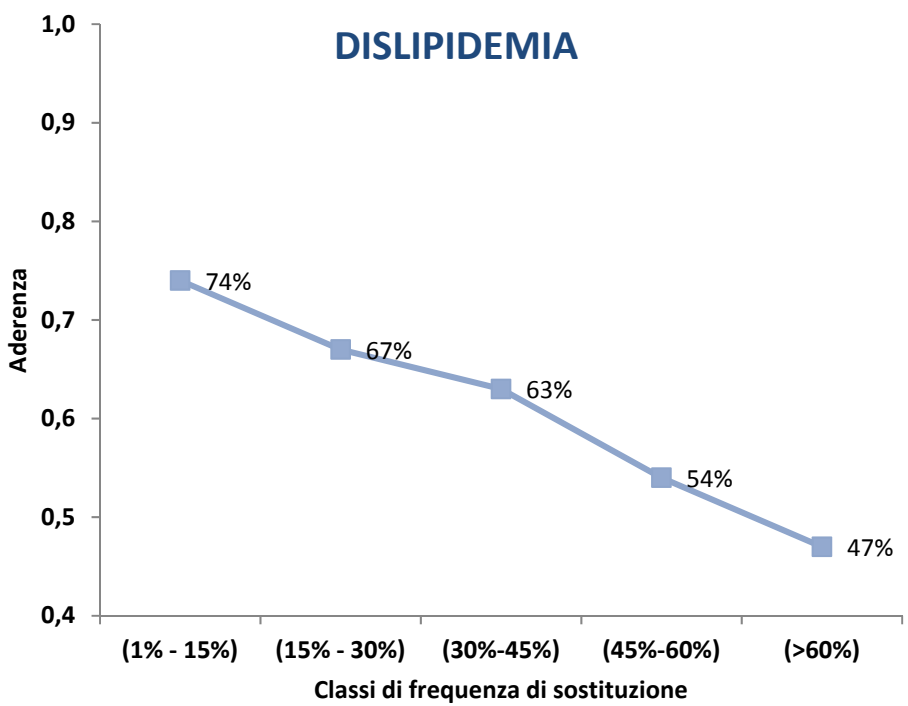
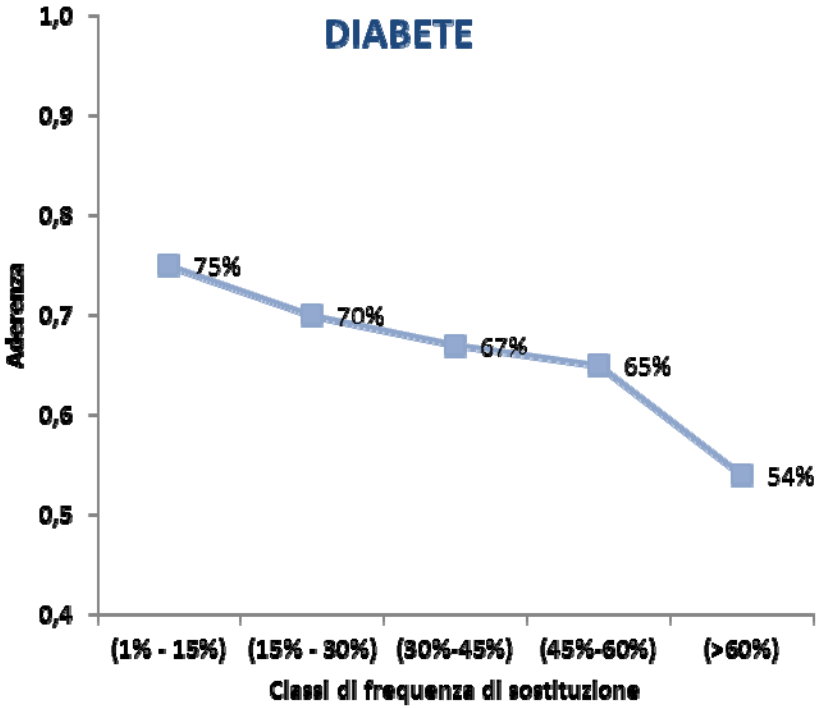
Sostituzione orizzontale e aderenza

Risultati della metanalisi (Asl Bergamo e Asl Pavia)





Sostituzione orizzontale e aderenza

Risultati della metanalisi (Asl Bergamo e Asl Pavia)