Evidenze e nuove prospettive

nel trattamento delle

Patologie Tromboemboliche

Varese – 16 marzo 2018

Gestione della terapia anticoagulante e antiaggregante nei pazienti sottoposti a PTCA/stent alla luce dei nuovi trials

Alessandro Squizzato

Centro di Ricerca 'Malattie Tromboemboliche e Terapie Antitrombotiche'

Dipartimento di Medicina e Chirurgia

Università dell'Insubria - Varese

Il sottoscritto Alessandro Squizzato

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni ha avuto rapporti anche diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Pfizer, Bristol-Myers Squibb, Bayer Healthcare, Daiichi-Sankyo, Sanofi, Boehringer-Ingelheim

Agenda

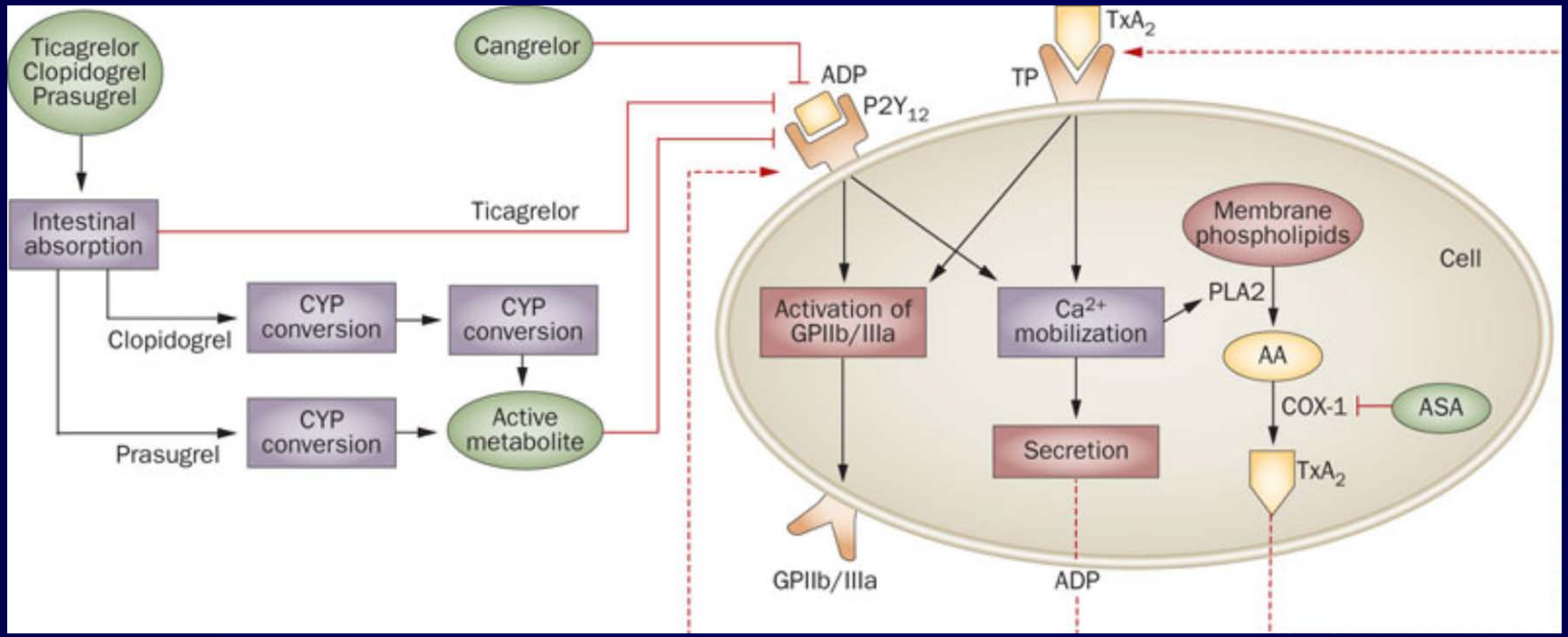
- **Introduzione ‘farmacologica’**

- **Due scenari**
  - **Cardiopatia ischemica senza FA**
  - **Cardiopatia ischemica con FA**

Agenda

- **Introduzione ‘farmacologica’**

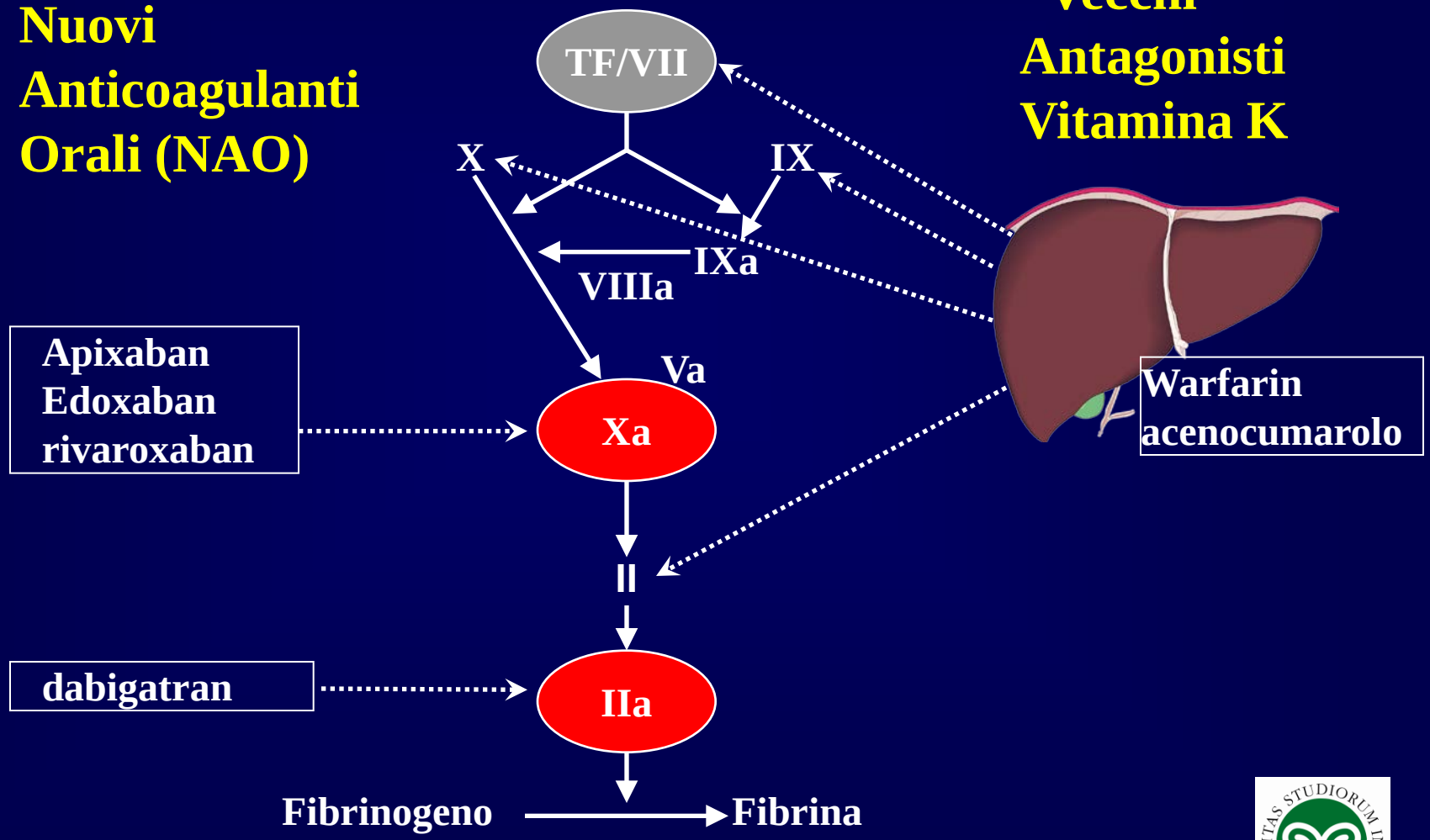
- **Due scenari**
  - **Cardiopatia ischemica senza FA**
  - **Cardiopatia ischemica con FA**


Ticagrelor
Clopidogrel
Prasugrel
Cangrelor
ADP
P2Y12
TxA2
TP
Intestinal absorption
Ticagrelor
Clopidogrel
CYP conversion
CYP conversion
Prasugrel
CYP conversion
Active metabolite
Membrane phospholipids
Cell
Activation of GPIIb/IIIa
Ca2+ mobilization
PLA2
AA
COX-1
ASA
Secretion
TxA2
GPIIb/IIIa
ADP

Nuovi e "Vecchi"

Nuovi Anticoagulanti Orali (NAO)

"Vecchi" Antagonisti Vitamina K



Adapted from Weitz & Bates, *J Thromb Haemost* 2007

Agenda

- **Introduzione ‘farmacologica’**

- **Due scenari**
  - **cardiopatia ischemica senza FA**
  - **cardiopatia ischemica con FA**

1. CaIs senza FA

TRATTAMENTO STANDARD

singola-doppia antiaggregazione (DAPT)

TRATTAMENTO STUDIATO

DAPT + DOACs

ASA + DOACs

DOACs

TRATTAMENTO FUTURO

1. **Singola o doppia ?**
2. **Se singola, quale farmaco ?**
3. **Se doppia per quanto tempo ?**
4. **Se doppia, quali farmaci ?**

TRATTAMENTO STANDARD

singola-doppia antiaggregazione (DAPT)

TRATTAMENTO STUDIATO

DAPT + DOACs

ASA + DOACs

DOACs

TRATTAMENTO FUTURO

Sindromi coronariche acute

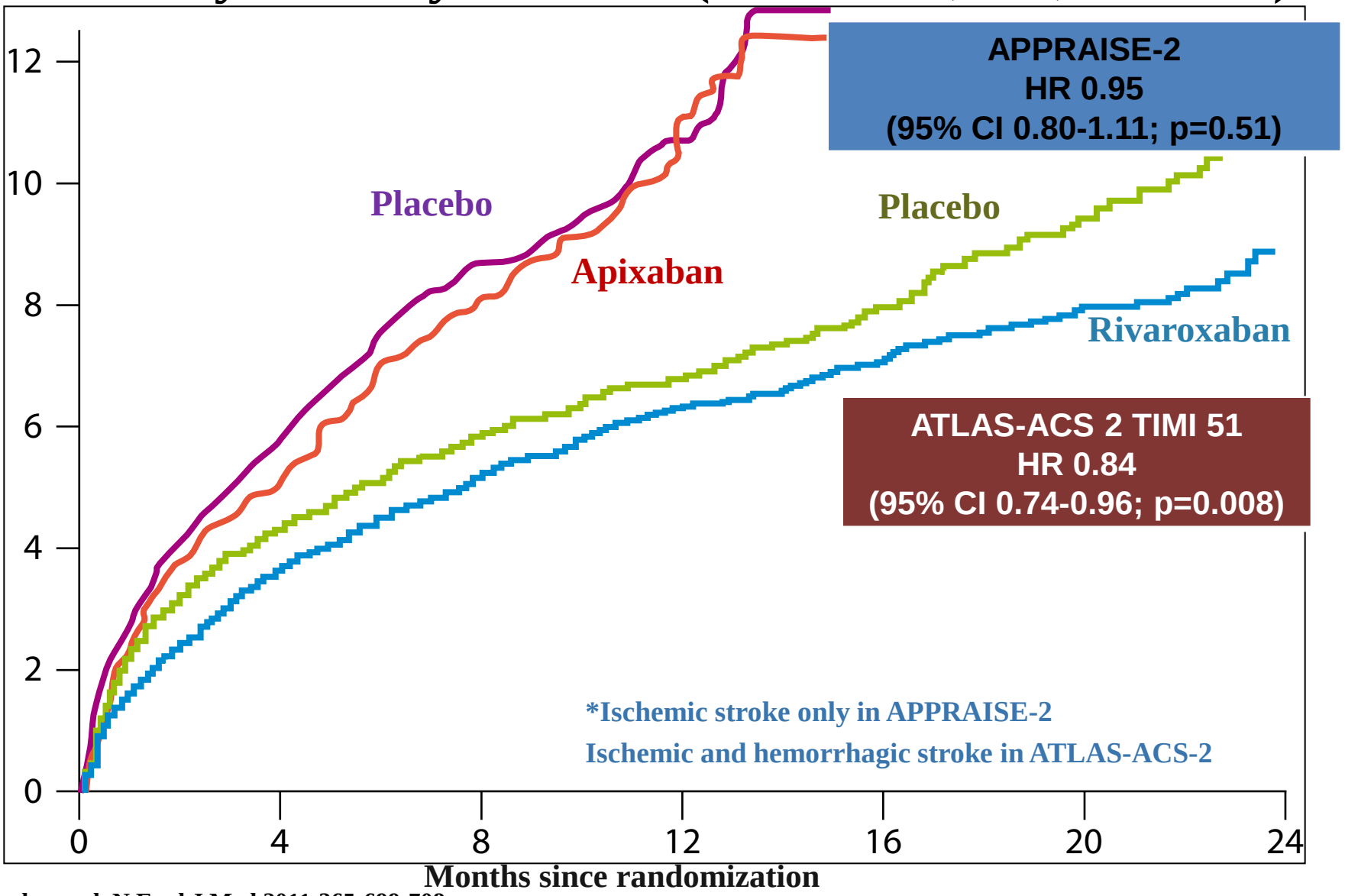
Studi RCT, fase III

apixaban (5 mg x 2) **vs placebo - APPRAISE II**

rivaroxaban (2.5/5 mg x 2) **vs placebo - ATLAS ACS 2-TIMI 51**

APPRAISE-2 and ATLAS-ACS-2:

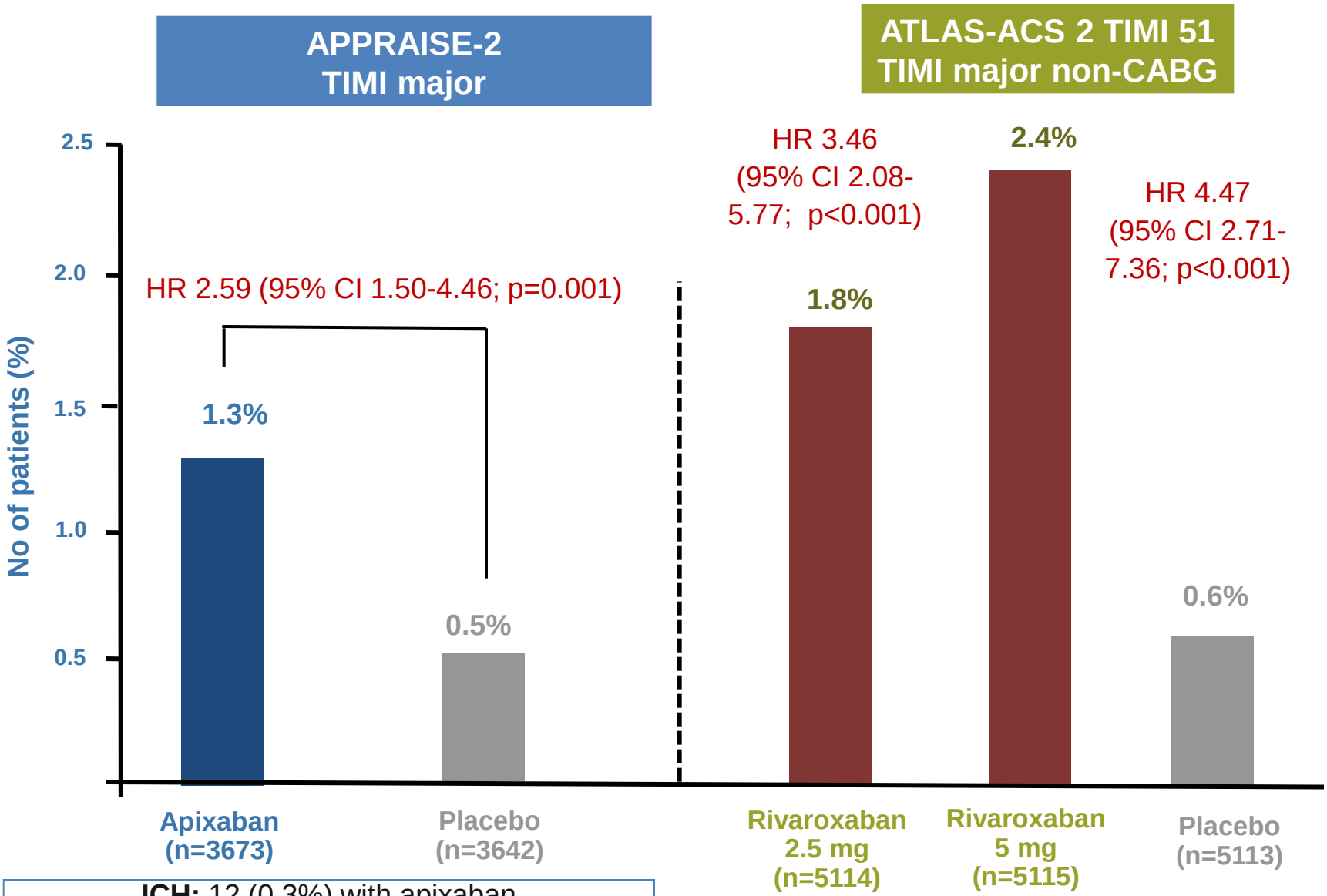
Primary Efficacy outcome (CV Death, MI, Stroke*)



Alexander et al. N Engl J Med 2011;365:699-708.

Mega et al. N Engl J Med 2012;366:9-19.

APPRAISE-2 and ATLAS-ACS-2: Safety



ICH: 12 (0.3%) with apixaban
vs 3 (0.1%) with placebo: p=0.03

ICH: 32 (0.6%) with rivaroxaban
vs 5 (0.2%) with placebo

Alexander et al. N Engl J Med 2011;365:699-708.

Mega et al. N Engl J Med 2012;366:9-19.

Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial

E Magnus Ohman, Matthew T Roe, P Gabriel Steg, Stefan K James, Thomas J Povsic, Jennifer White, Frank Rockhold, Alexei Plotnikov, Hardi Mundl, John Strony, Xiang Sun, Steen Husted, Michal Tendera, Gilles Montalescot, M Cecilia Bahit, Diego Ardissino, Héctor Bueno, Marc J Claeys, Jose C Nicolau, Jan H Cornel, Shinya Goto, Róbert Gábor Kiss, Ümit Güray, Duk-Woo Park, Christoph Bode, Robert C Welsh, C Michael Gibson*

Summary

Background Dual antiplatelet therapy (DAPT), aspirin plus a P2Y12 inhibitor, is the standard antithrombotic treatment following acute coronary syndromes. The factor Xa inhibitor rivaroxaban reduced mortality and ischaemic events when added to DAPT, but caused increased bleeding. The safety of a dual pathway antithrombotic therapy approach

Lancet 2017; 389: 1799–808

P STEMI o non-STEMI (entro 10 giorni)

I riva 2.5 mg x 2 (plus clopidogel o ticagrelor)

C ASA 100 mg (plus clopidogel o ticagrelor)

O Sanguinamenti rilevanti (sec. TIMI)

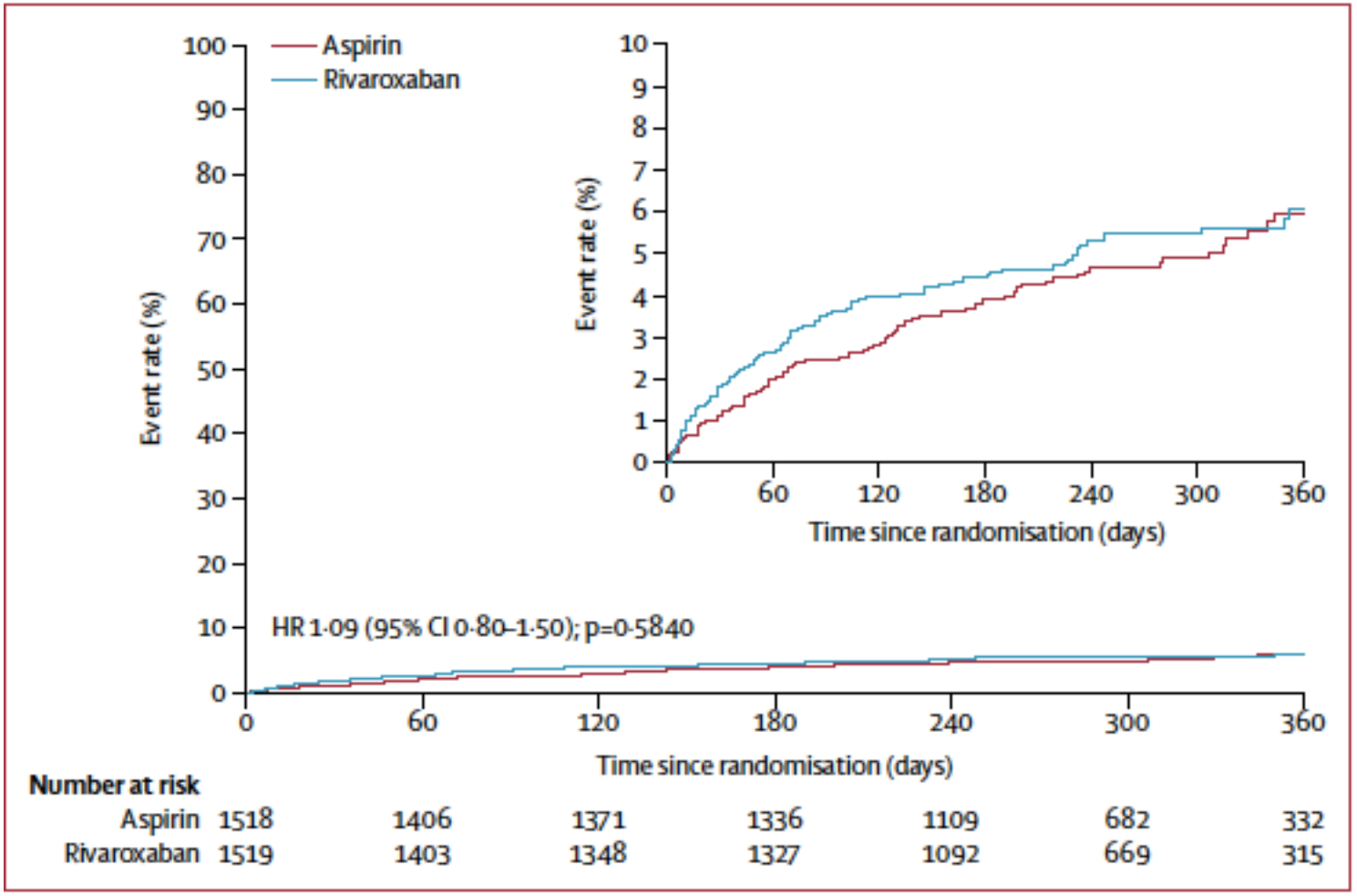


Figure 2: **TIMI non-CABG clinically significant bleeding between treatment groups**
TIMI–thrombolysis in myocardial infarction. CABG–coronary artery bypass graft. HR–hazard ratio.

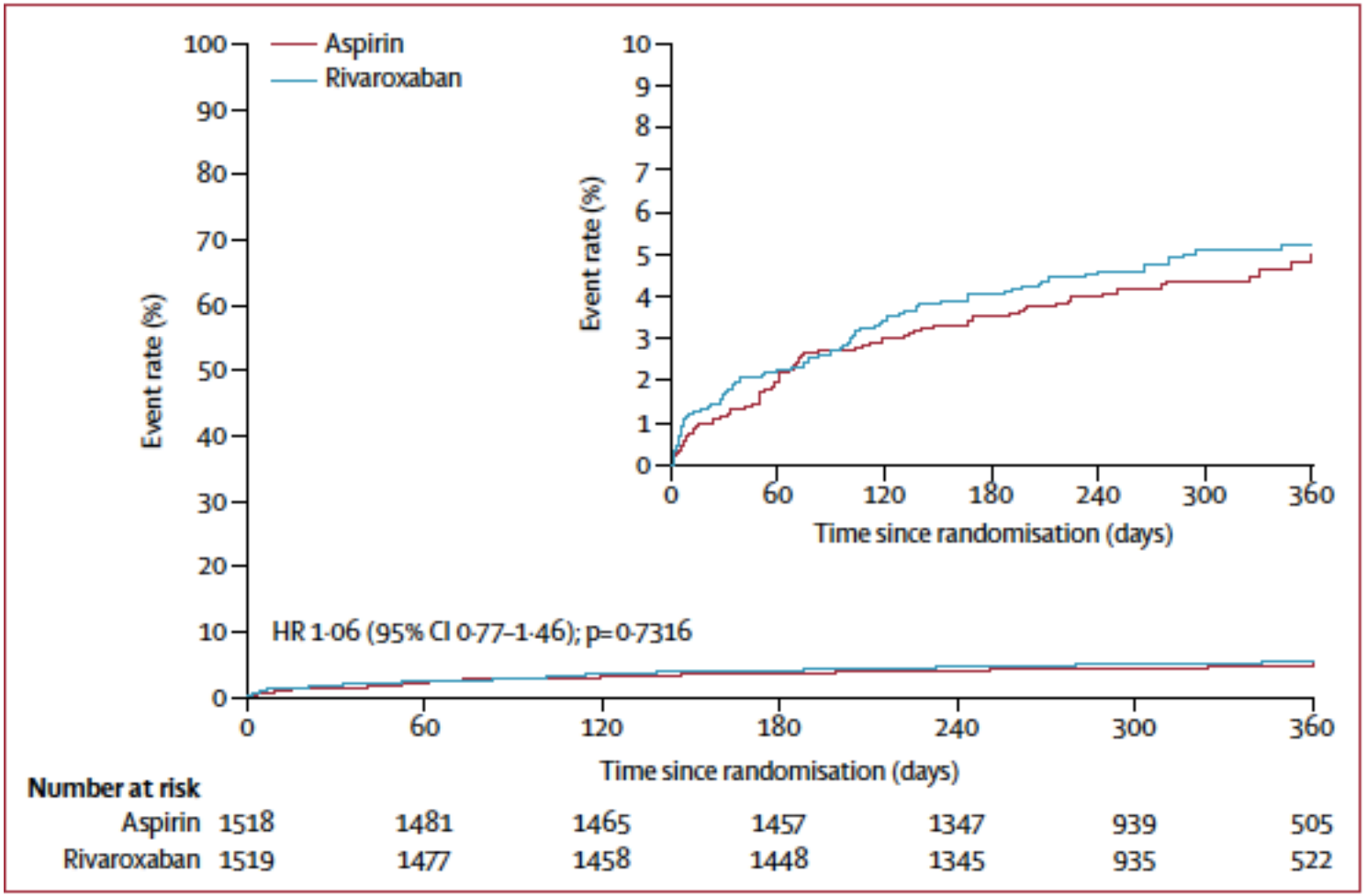


***Figure 4*: Cardiovascular death, myocardian infarction, stroke, or definite stent thrombosis between treatment groups**

HR–hazard ratio.

Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial

*Stuart J Connolly, John W Eikelboom, Jackie Bosch, Gilles Dagenais, Leanne Dyal, Fernando Lanas, Kaj Metsarinne, Martin O'Donnell, Anthony L Dans, Jong-Won Ha, Alexandr N Parkhomenko, Alvaro A Avezum, Eva Lonn, Liu Lisheng, Christian Torp-Pedersen, Petr Widimsky, Aldo P Maggioni, Camilo Felix, Katalin Keltai, Masatsugu Hori, Khalid Yusoff, Tomasz J Guzik, Deepak L Bhatt, Kelley R H Branch, Nancy Cook Bruns, Scott D Berkowitz, Sonia S Anand, John D Varigos, Keith A A Fox, Salim Yusuf, on behalf of the COMPASS investigators**

Summary

Background Coronary artery disease is a major cause of morbidity and mortality worldwide, and is a consequence of acute thrombotic events involving activation of platelets and coagulation proteins. Factor Xa inhibitors and aspirin each reduce thrombotic events but have not yet been tested in combination or against each other in patients with stable coronary artery disease.

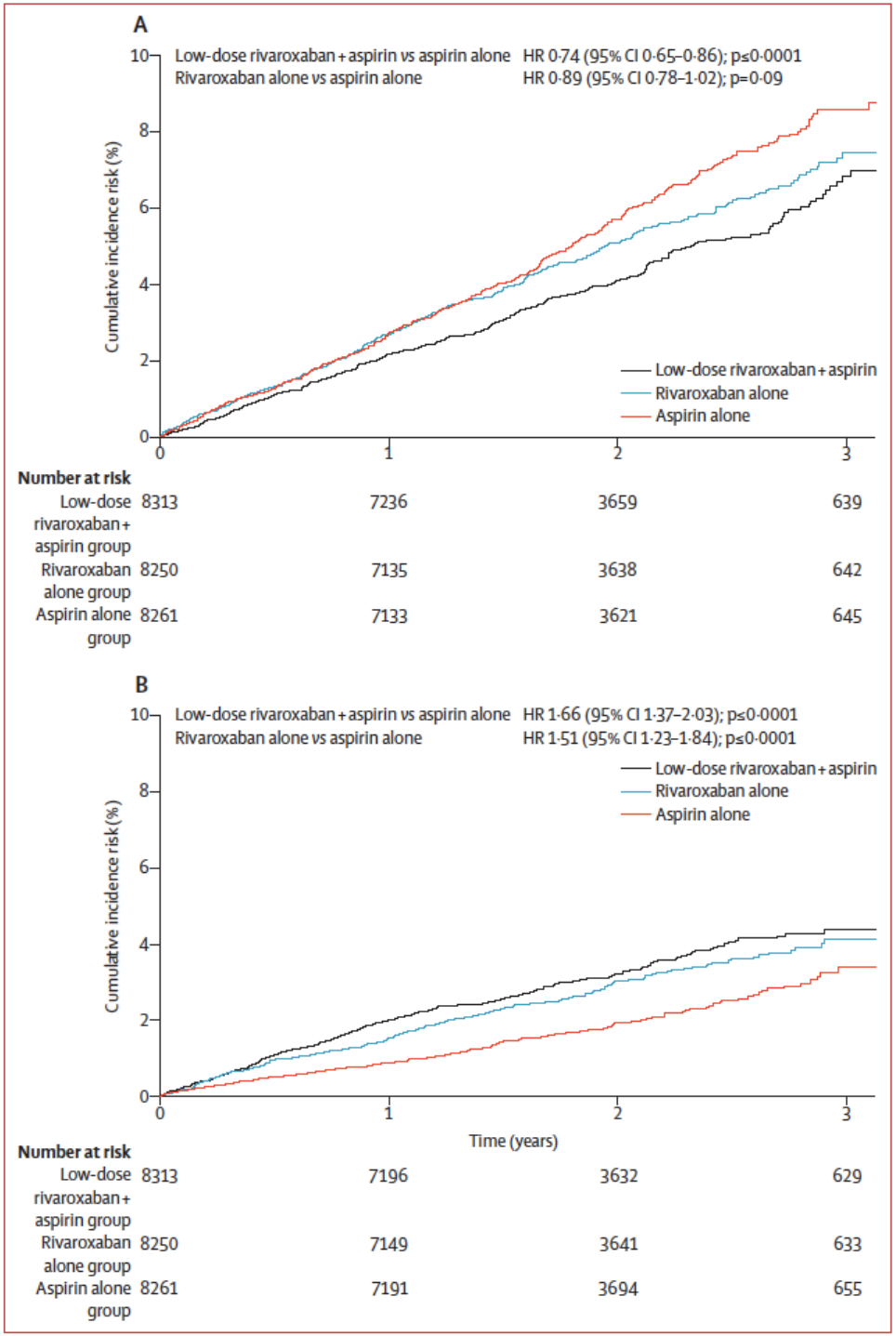
www.thelancet.com **Published online November 10, 2017**

P cardiopatia ischemica stabile

I riva 2.5 mg x 2 + ASA 100 mg /
riva 5 mg x 2

C ASA 100 mg

O IMA+stroke+morte cardiovascolare


A
Low-dose rivaroxaban + aspirin vs aspirin alone HR 0·74 (95% CI 0·65–0·86); p≤0·0001
Rivaroxaban alone vs aspirin alone HR 0·89 (95% CI 0·78–1·02); p=0·09
Cumulative incidence risk (%)
10
8
6
4
2
0
0
1
2
3
Low-dose rivaroxaban + aspirin
Rivaroxaban alone
Aspirin alone
Number at risk
Low-dose rivaroxaban + aspirin group 8313 7236 3659 639
Rivaroxaban alone group 8250 7135 3638 642
Aspirin alone group 8261 7133 3621 645
B
Low-dose rivaroxaban + aspirin vs aspirin alone HR 1·66 (95% CI 1·37–2·03); p≤0·0001
Rivaroxaban alone vs aspirin alone HR 1·51 (95% CI 1·23–1·84); p≤0·0001
Cumulative incidence risk (%)
Time (years)
Number at risk
Low-dose rivaroxaban + aspirin group 8313 7196 3632 629
Rivaroxaban alone group 8250 7149 3641 633
Aspirin alone group 8261 7191 3694 655

TRATTAMENTO STANDARD

singola-doppia antiaggregazione (DAPT)

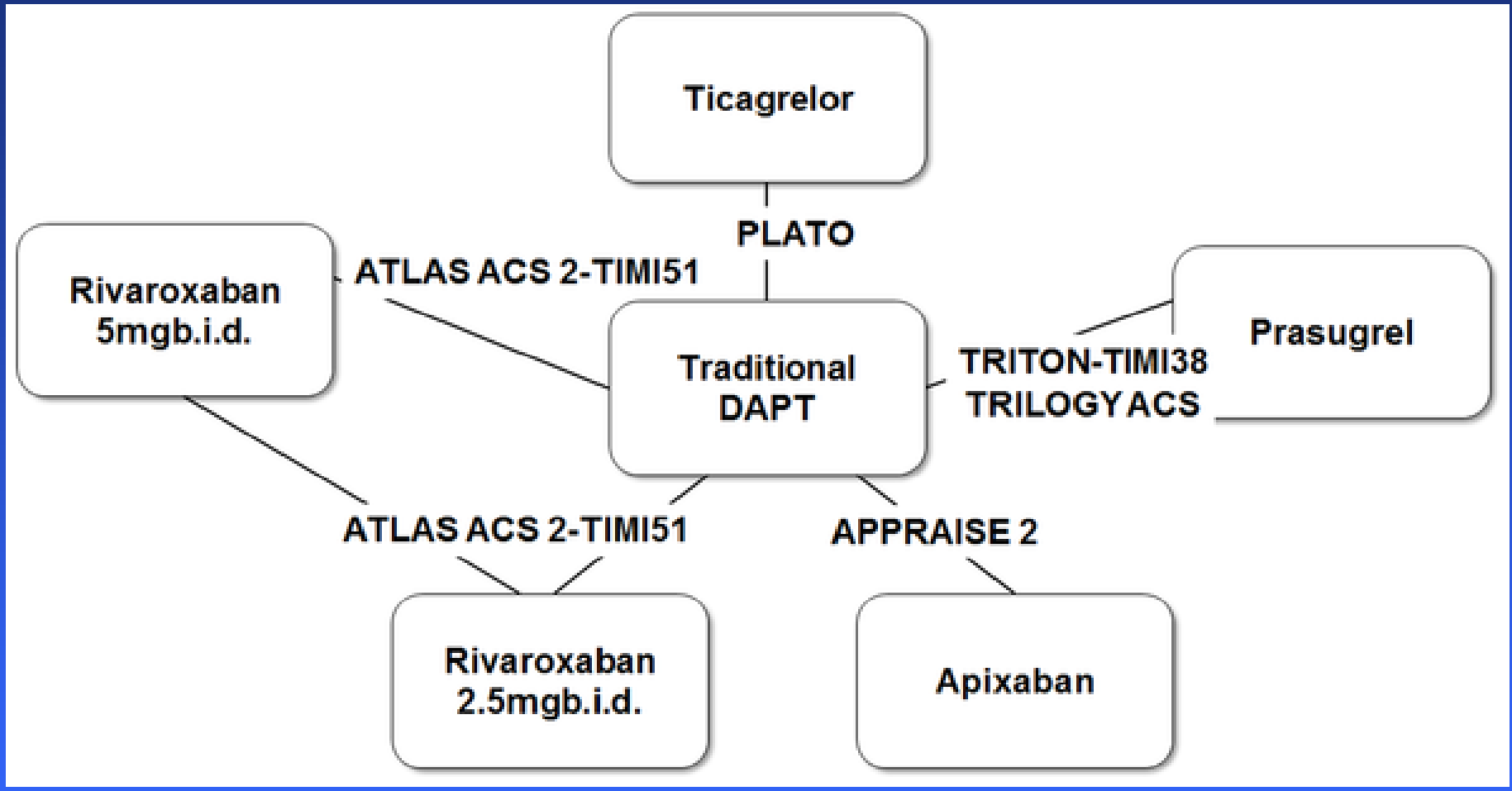
TRATTAMENTO STUDIATO

DAPT + DOACs

ASA + DOACs

DOACs

TRATTAMENTO FUTURO



Ye Y, Xie H, Zeng Y, Zhao X, et al. (2014) Optimal Oral Antithrombotic Regimes for Patients with Acute Coronary Syndrome: A Network Meta-Analysis. PLoS ONE 9(3): e90986. doi:10.1371/journal.pone.0090986
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0090986

Table 2. Patient Factors Related to Risk of Thrombotic and Bleeding Events

Factor	Thrombotic Risk	Bleeding Risk
Age	+++	++
Female sex	...	++
Renal dysfunction (creatinine clearance or serum creatinine)	+++	+++
Anemia	++	+++
ST-deviation or ST-elevation status	+++	+
Anterior myocardial infarction location	++	...
Left bundle-branch block	+	...
Cardiac marker elevation	+++	+
Heart rate elevation	++	++
Systolic blood pressure	++	++
Heart failure or Killip class	+++	++
Peripheral vascular disease or stroke	++	++
Diabetes mellitus	++	+
Low body weight	+	++
Prior history of bleeding	...	++

Thrombotic risk includes death or death/myocardial infarction. Bleeding risk by various definitions: GRACE model,[65] CRUSADE score,[42] ACUITY bleeding model,[44] and Nikolsky score.[66] Plus signs are related to the frequency with which these factors are identified as risk factors for thrombotic and bleeding outcomes.

2. CaIs con FA

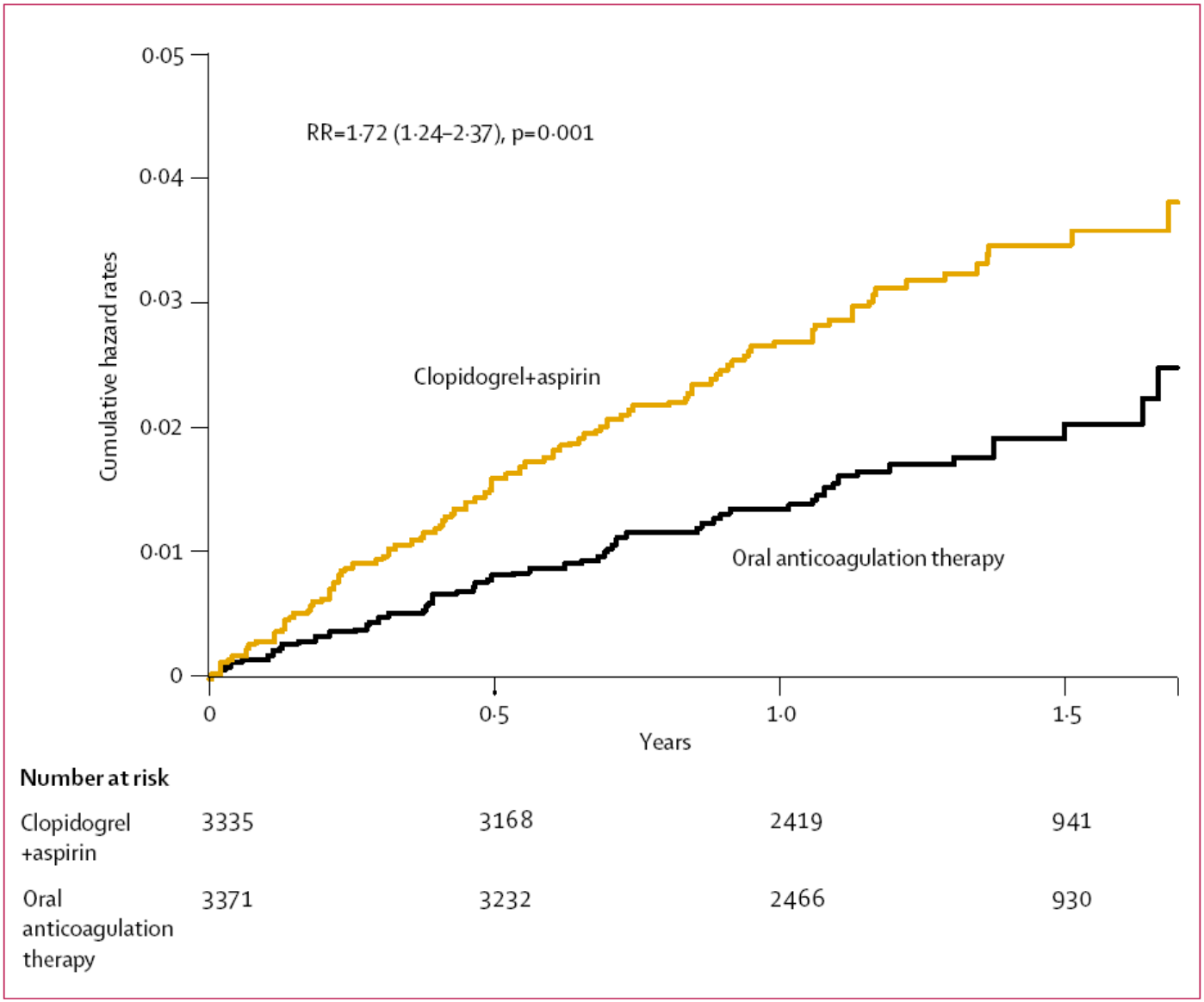
TRATTAMENTO STANDARD

Tripla terapia (DAPT + AVK)

TRATTAMENTO STUDIATO

Doppia terapia (SAPT + AVK/DOACs)

TRATTAMENTO FUTURO



Number at risk

Clopidogrel +aspirin	3335	3168	2419	941
Oral anticoagulation therapy	3371	3232	2466	930

Figure 3: Cumulative risk of stroke

Lancet 2006; 367: 1903–12

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

TRATTAMENTO STANDARD

Tripla terapia (DAPT + AVK)

TRATTAMENTO STUDIATO

Doppia terapia (SAPT + AVK/DOACs)

TRATTAMENTO FUTURO

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

Lancet 2013; 381: 1107–15
Published Online

Summary

Background If percutaneous coronary intervention (PCI) is required in patients taking oral anticoagulants, antiplatelet therapy with aspirin and clopidogrel is indicated, but such triple therapy increases the risk of serious bleeding. We

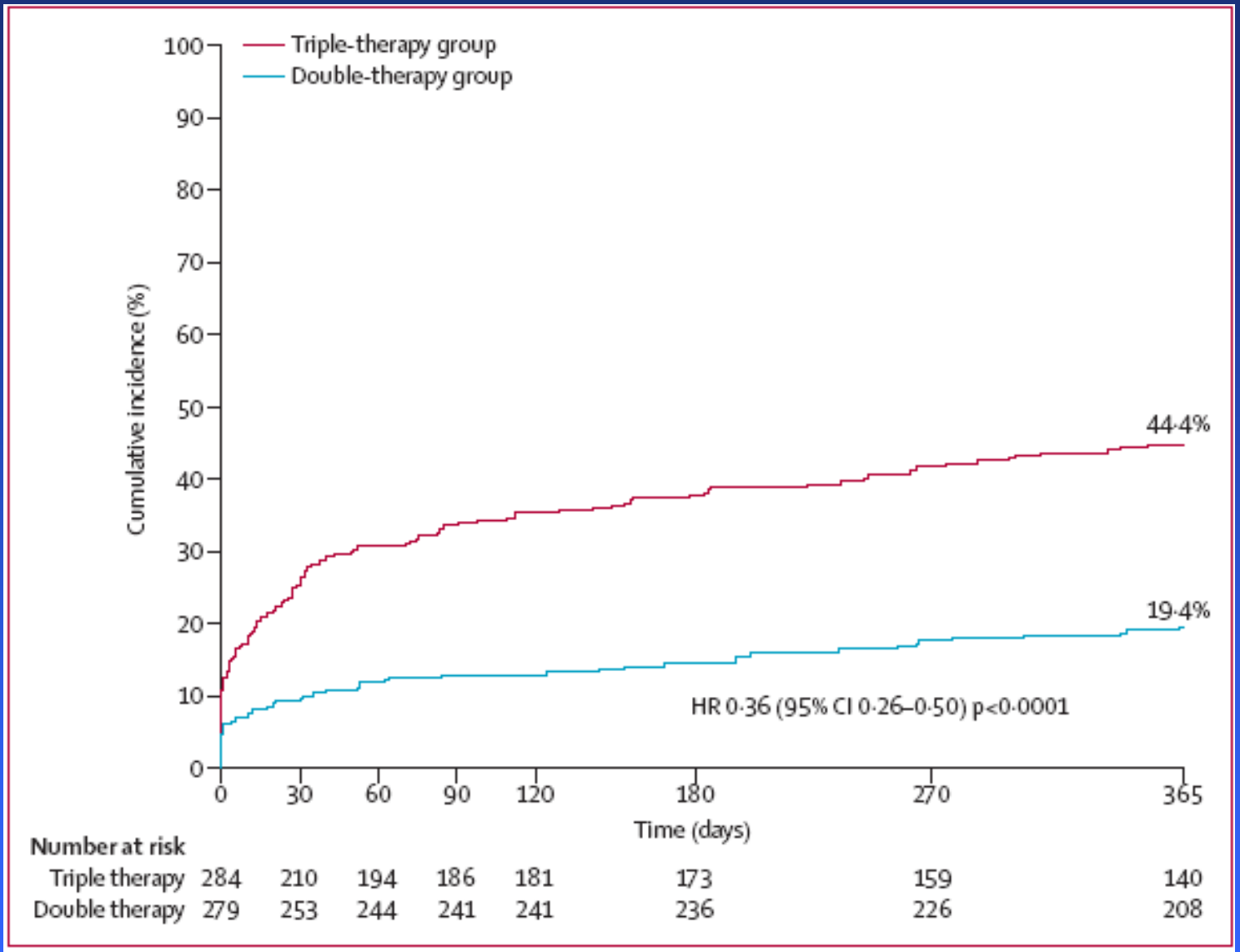


Figure 2: **Incidence of the primary endpoint (any bleeding)**
HR=hazard ratio.

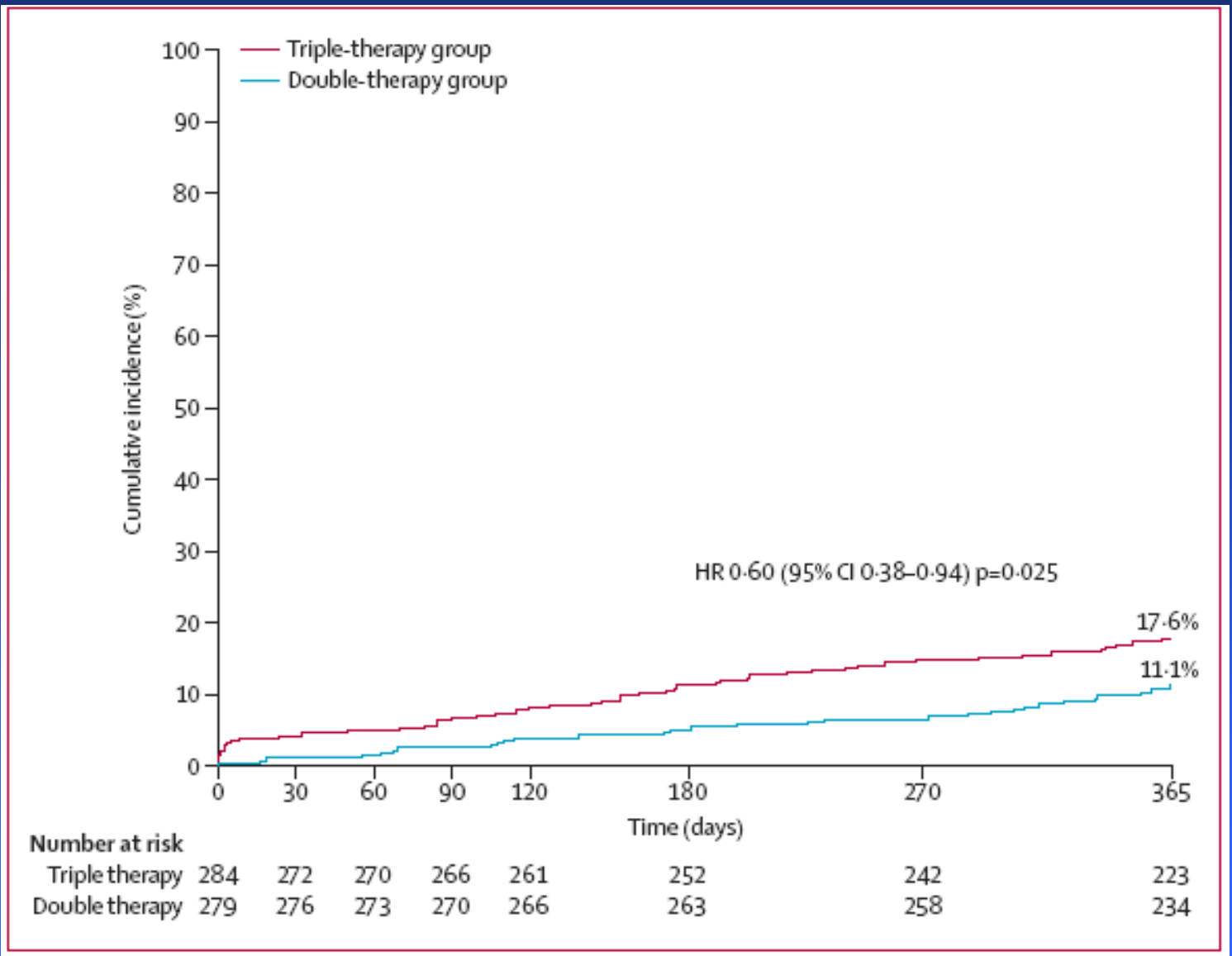


Figure 3: Cumulative incidence of the secondary endpoint (death, myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

ABSTRACT

BACKGROUND

In patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) with placement of stents, standard anticoagulation with a vitamin K antagonist plus dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin reduces the risk of thrombosis and stroke but increases the risk of bleeding. The effectiveness and safety of antico-

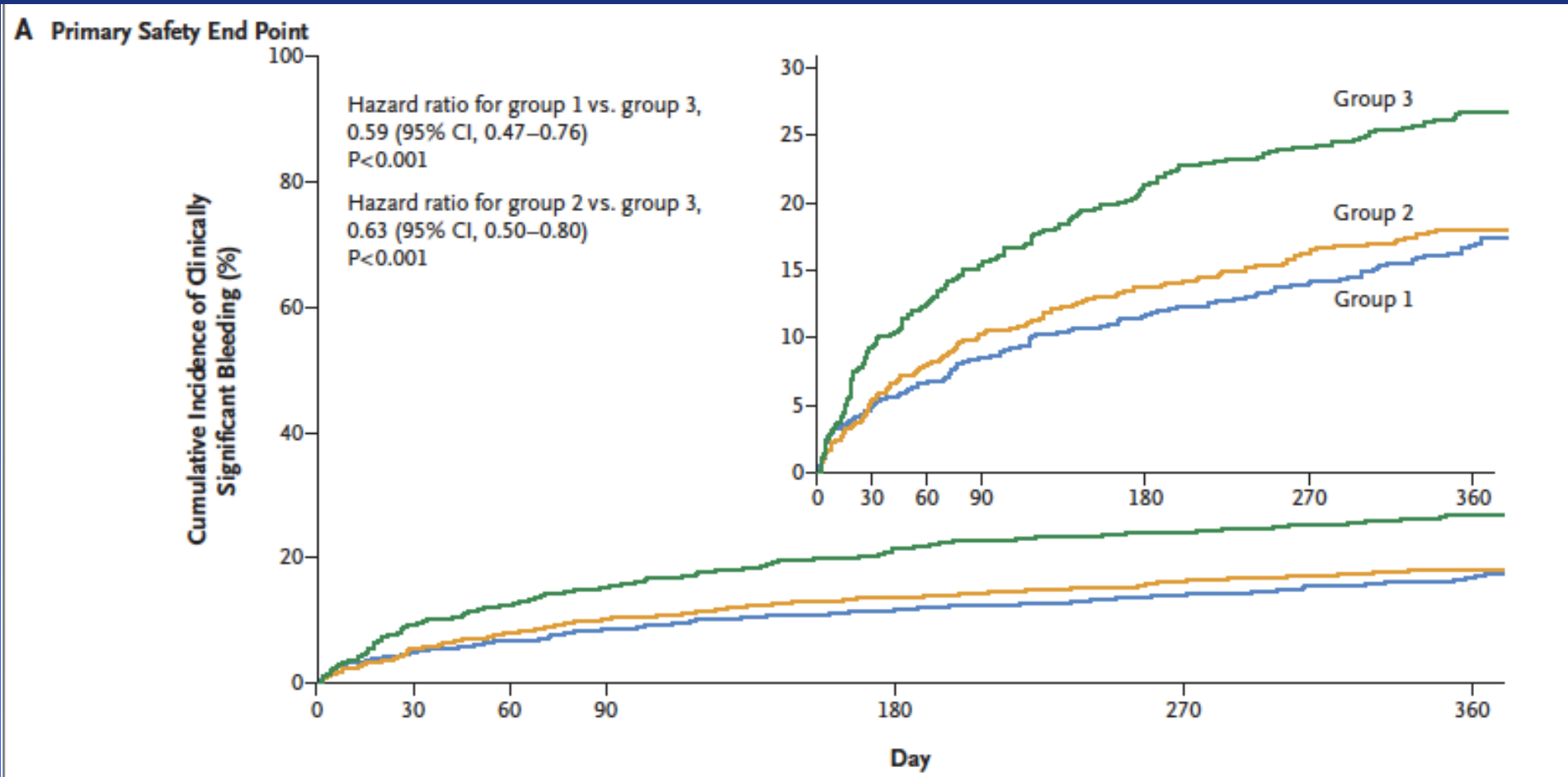
From the Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston (C.M.G., S.K., Y.D.); the Cardiovascular Institute, Mount Sinai Medical

P PCI con stent + FAnv

I riva 15 mg + P2Y12 inibitore (gruppo 1)
riva 2.5 x 2 mg + DAPT (gruppo 2)

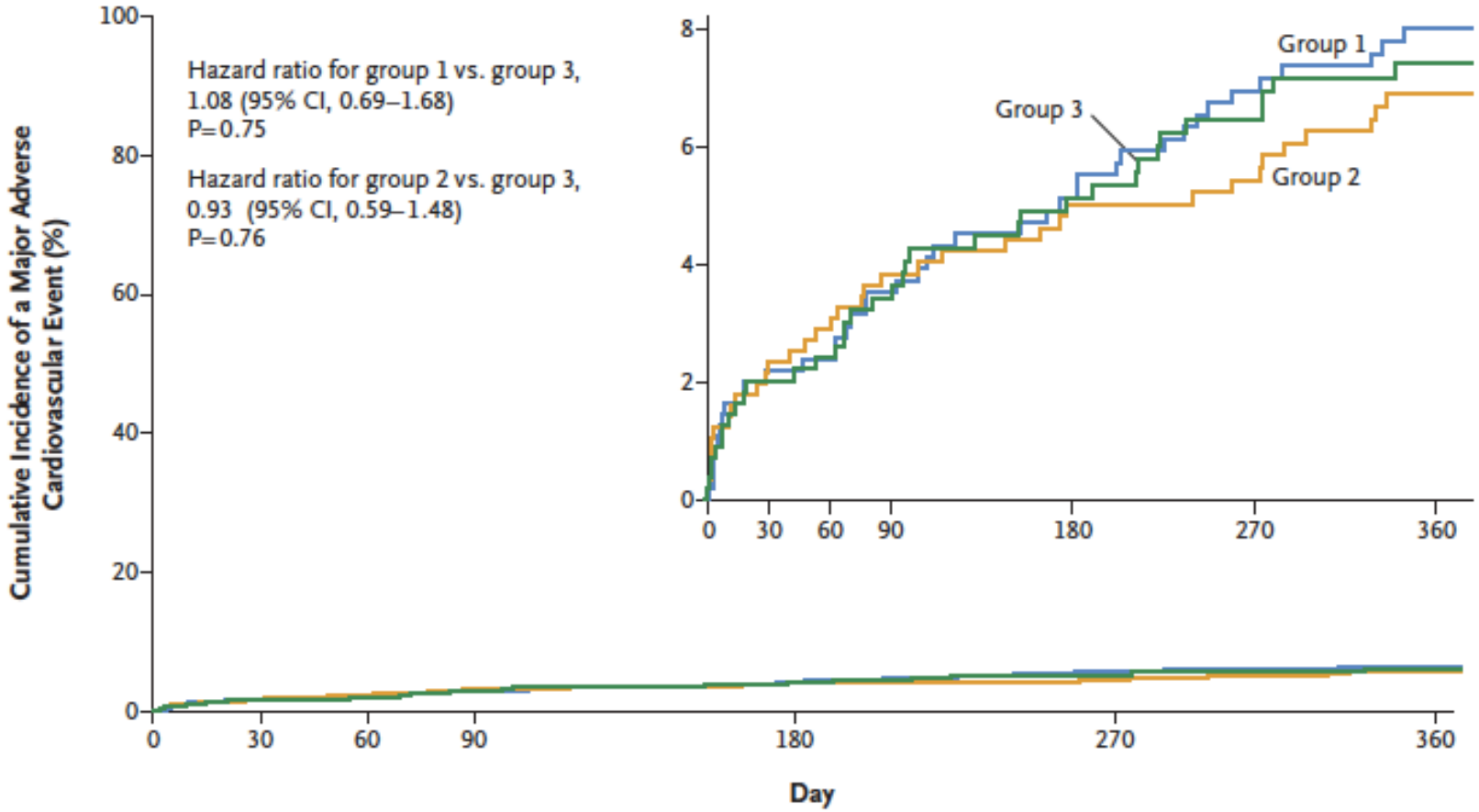
C AVK + DAPT (gruppo 3)

O Sanguinamenti maggiori e minori (TIMI)



No. at Risk							
Group 1	696	628	606	585	543	510	383
Group 2	706	636	600	579	543	509	409
Group 3	697	593	555	521	461	426	329

B **Secondary Efficacy End Point**



No. at Risk

Group 1	694	648	633	621	590	562	430
Group 2	704	662	640	628	596	570	457
Group 3	695	635	607	579	543	514	408

ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Triple antithrombotic therapy with warfarin plus two antiplatelet agents is the standard of care after percutaneous coronary intervention (PCI) for patients with

This article was published on August 27, 2017, at NEJM.org.

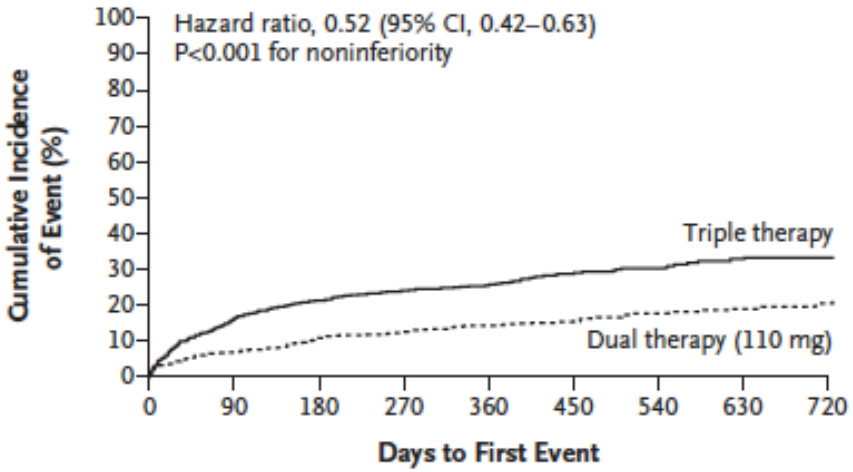
P PCI con stent + FAnv

I dabi 150 x 2 mg + P2Y12 inibitore
dabi 110 x 2 mg + P2Y12 inibitore

C AVK + DAPT

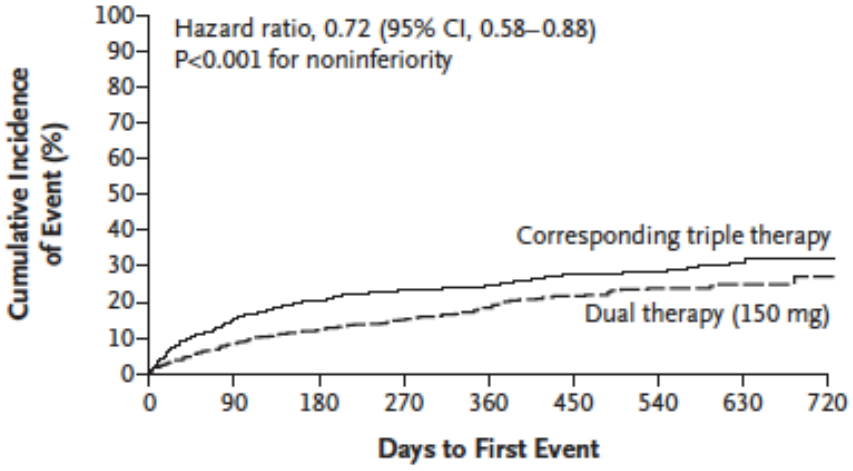
O Sanguinamenti maggiori e minori (TIMI)

A **Primary End Point in Dual-Therapy Group (110 mg) vs. Triple-Therapy Group**



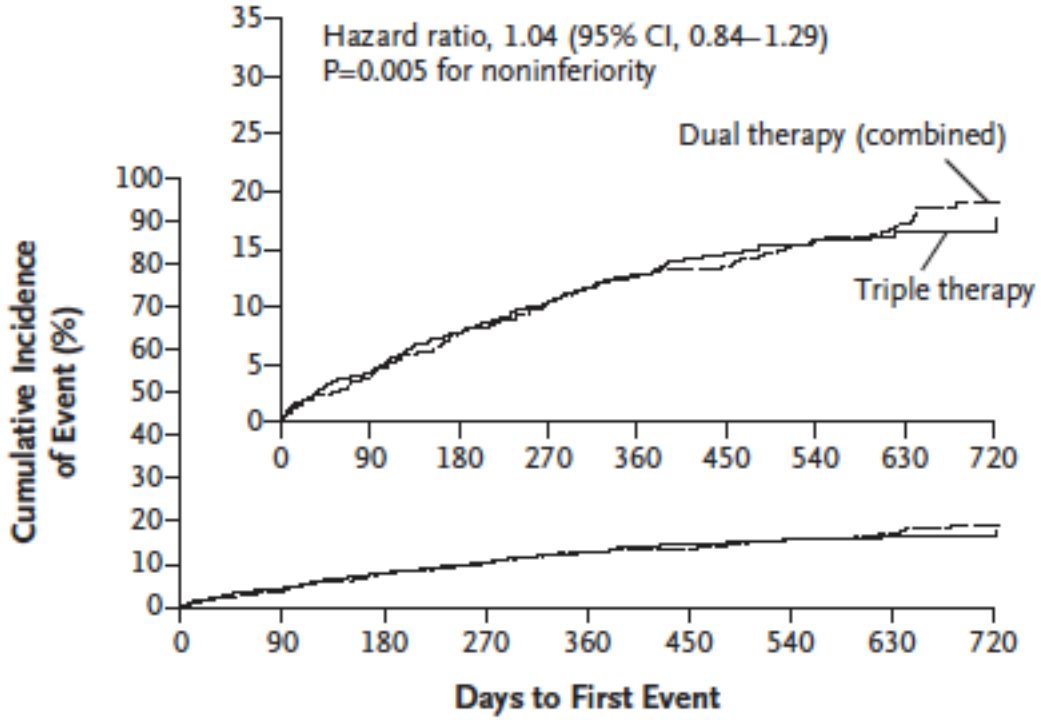
No. at Risk									
Dual therapy (110 mg)	981	898	834	671	538	384	258	162	86
Triple therapy	981	800	719	580	453	302	205	124	63

B **Primary End Point in Dual-Therapy Group (150 mg) vs. Triple-Therapy Group**



No. at Risk									
Dual therapy (150 mg)	763	694	640	514	404	278	182	113	65
Corresponding triple therapy	764	630	562	446	349	222	152	88	47

C Secondary Efficacy End Point in Dual-Therapy Groups (Combined) vs. Triple-Therapy Group



No. at Risk

Dual therapy (combined)	1744	1660	1561	1257	1003	720	481	295	161
Triple therapy	981	921	854	700	548	383	259	161	81

TRATTAMENTO STANDARD

Tripla terapia (DAPT + AVK)

TRATTAMENTO STUDIATO

Doppia terapia (SAPT + AVK)

TRATTAMENTO FUTURO

ENTRUST PCI AF

P PCI con stent + FAnv

I Edo 60 mg (o 30) + P2Y12 inibitore

C warfarin + DAPT

O Sanguinamenti maggiori e clinicamente rilevanti (ISTH)

Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

Inclusion
- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS and/or PCI with planned P2Y12 inhibitor for 6 months

Randomize
n =4,600
Patients

Exclusion
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

Apixaban | **Warfarin**

P2Y12 inhibitor for all patients x 6 months
Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

ASA | **placebo** | **ASA** | **placebo**

Primary outcome: major/clinically relevant bleeding (through 6 months)

Secondary objective: Death, MI, stroke, stent thrombosis

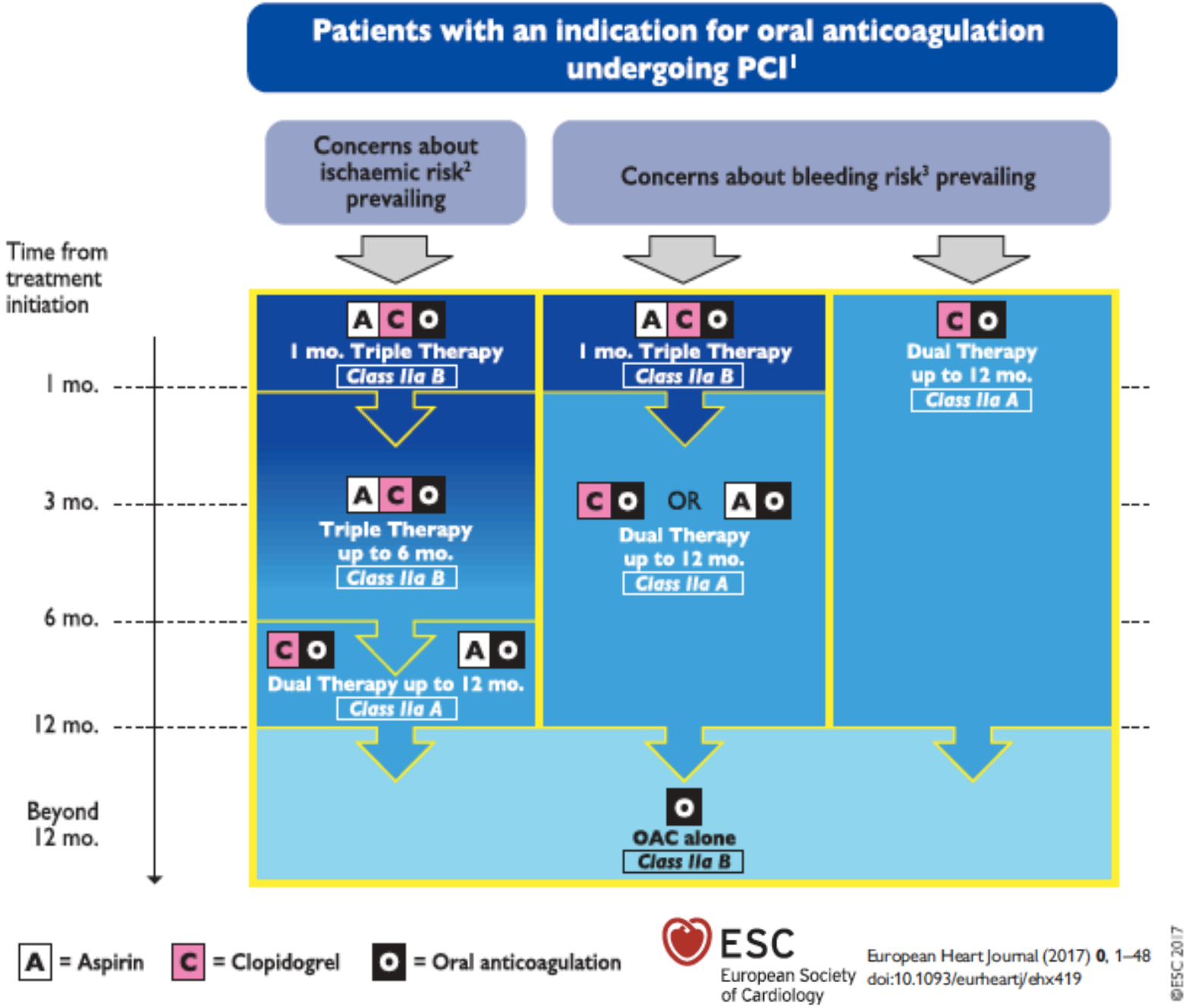
E dopo 1 anno dalla SCA ?

... con o senza stent medicato ...

Table 2 Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Lifelong: warfarin (INR 2.0–3.0) alone
	Elective	Drug eluting	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[a]
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal/drug eluting	6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[a]
			Lifelong: warfarin (INR 2.0–3.0) alone
High	Elective	Bare metal[b]	2–4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal[b]	4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day); mg/day);[a]
			Lifelong: warfarin (INR 2.0–3.0) alone

European Heart Journal (2010) 31, 1311–1318
doi:10.1093/eurheartj/ehq117


Patients with an indication for oral anticoagulation undergoing PCI[1]
Concerns about ischaemic risk[2] prevailing
Concerns about bleeding risk[3] prevailing
Time from treatment initiation
1 mo.
3 mo.
6 mo.
12 mo.
Beyond 12 mo.
A C O
1 mo. Triple Therapy
Class IIa B
A C O
1 mo. Triple Therapy
Class IIa B
C O
Dual Therapy up to 12 mo.
Class IIa A
A C O
Triple Therapy up to 6 mo.
Class IIa B
C O OR A O
Dual Therapy up to 12 mo.
Class IIa A
C O
A O
Dual Therapy up to 12 mo.
Class IIa A
O
OAC alone
Class IIa B
A = Aspirin
C = Clopidogrel
O = Oral anticoagulation
ESC
European Society of Cardiology
European Heart Journal (2017) 0, 1–48
doi:10.1093/eurheartj/ehx419
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The New England
Journal of Medicine

VOLUME 347 SEPTEMBER 26, 2002 NUMBER 13

WARFARIN, ASPIRIN, OR BOTH AFTER MYOCARDIAL INFARCTION

METTE HURLEN, M.D., MICHAEL ABDELNOOR, M.P.H., PH.D., PÅL SMITH, M.D., PH.D., JAN ERIKSSEN, M.D., PH.D., AND HARALD ARNESEN, M.D., PH.D.*

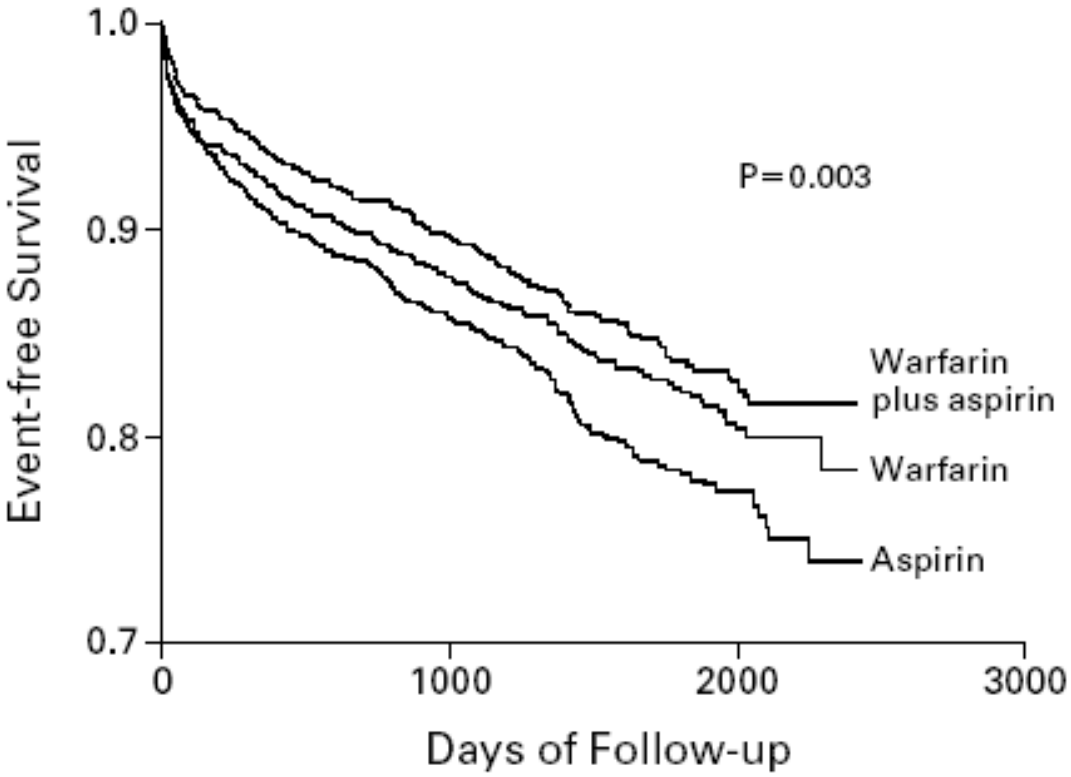
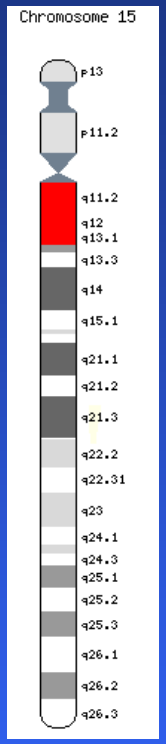
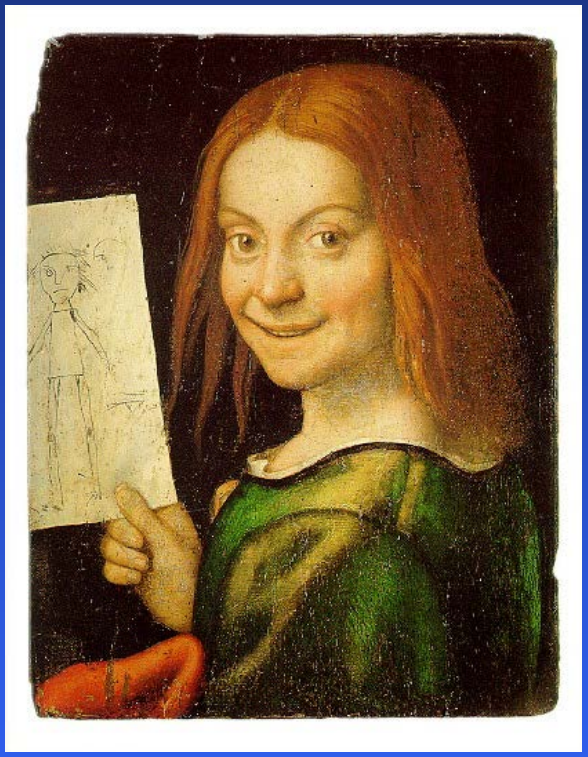


Figure 1. Event-free Survival Curves for the Composite End Point of Death, Nonfatal Reinfarction, and Thromboembolic Stroke.

CONCLUSIONI

1. Necessari studi di stratificazione del rischio trombotico/emorragico del paziente con CaIs
2. Possibile utilizzo dei DOACs nei pazienti con stents
3. Non più vera la raccomandazione di non associare i DOACs con i P2Y12 moderni
4. Invece che scegliere fra 3 o 2 farmaci, spesso potrò scegliere 2.5





”I may not speak, but I have much to say”

The ‘Angel’ Pietro