TERAPIA E PREVENZIONE CARDIOVASCOLARE OGGI
TRA NOVITA', CERTEZZE E DUBBI

SCELTA DELLA MIGLIOR TERAPIA ANTITROMBOTICA NEL PAZIENTE CON FA E SCA

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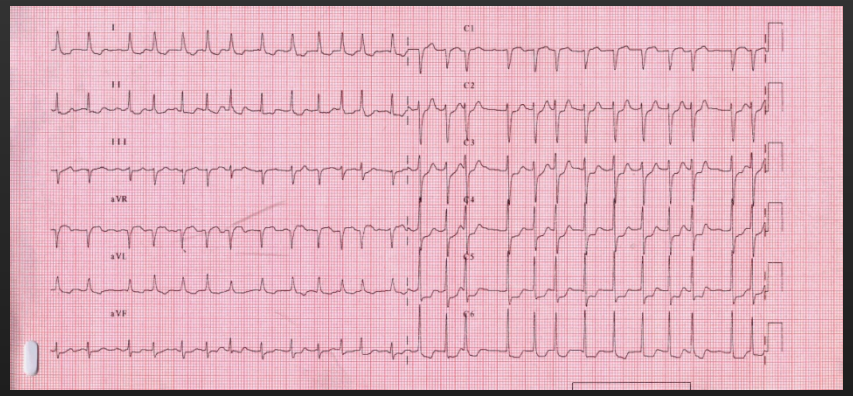
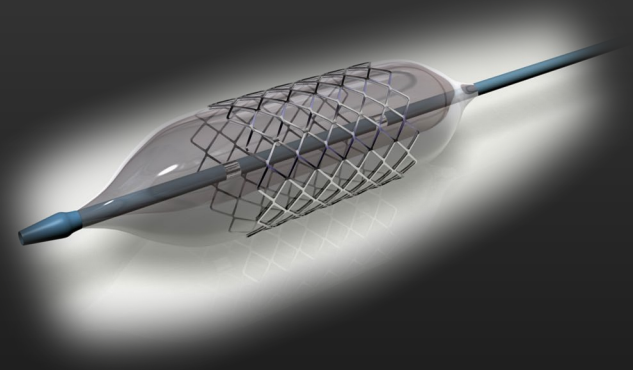
Epidemiologia : FA e CAD

FA and CAD sono spesso sovrapposte a causa della forte associazione tra tali condizioni e l'età oltre che per la sovrapposizione di fattori di rischio

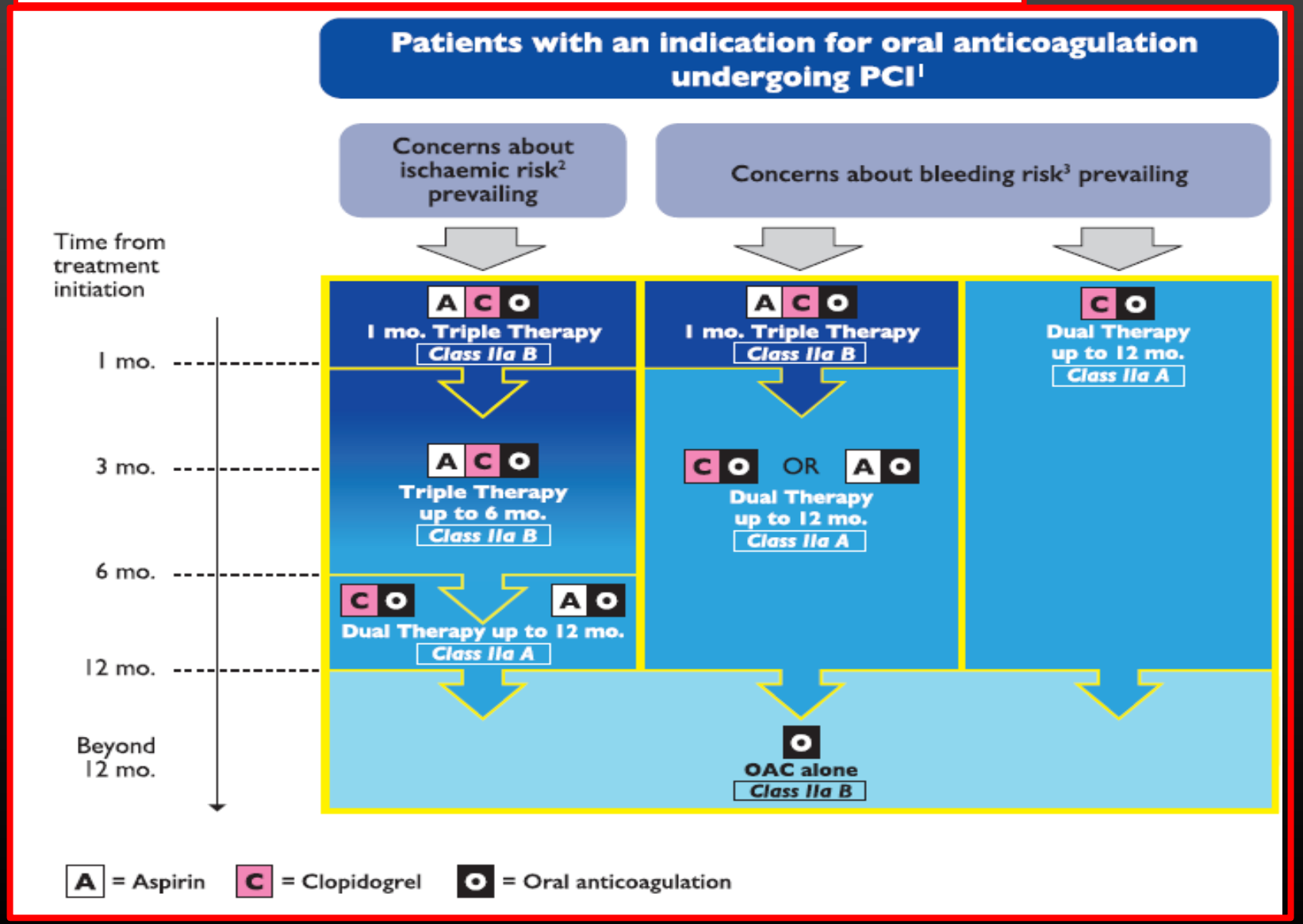




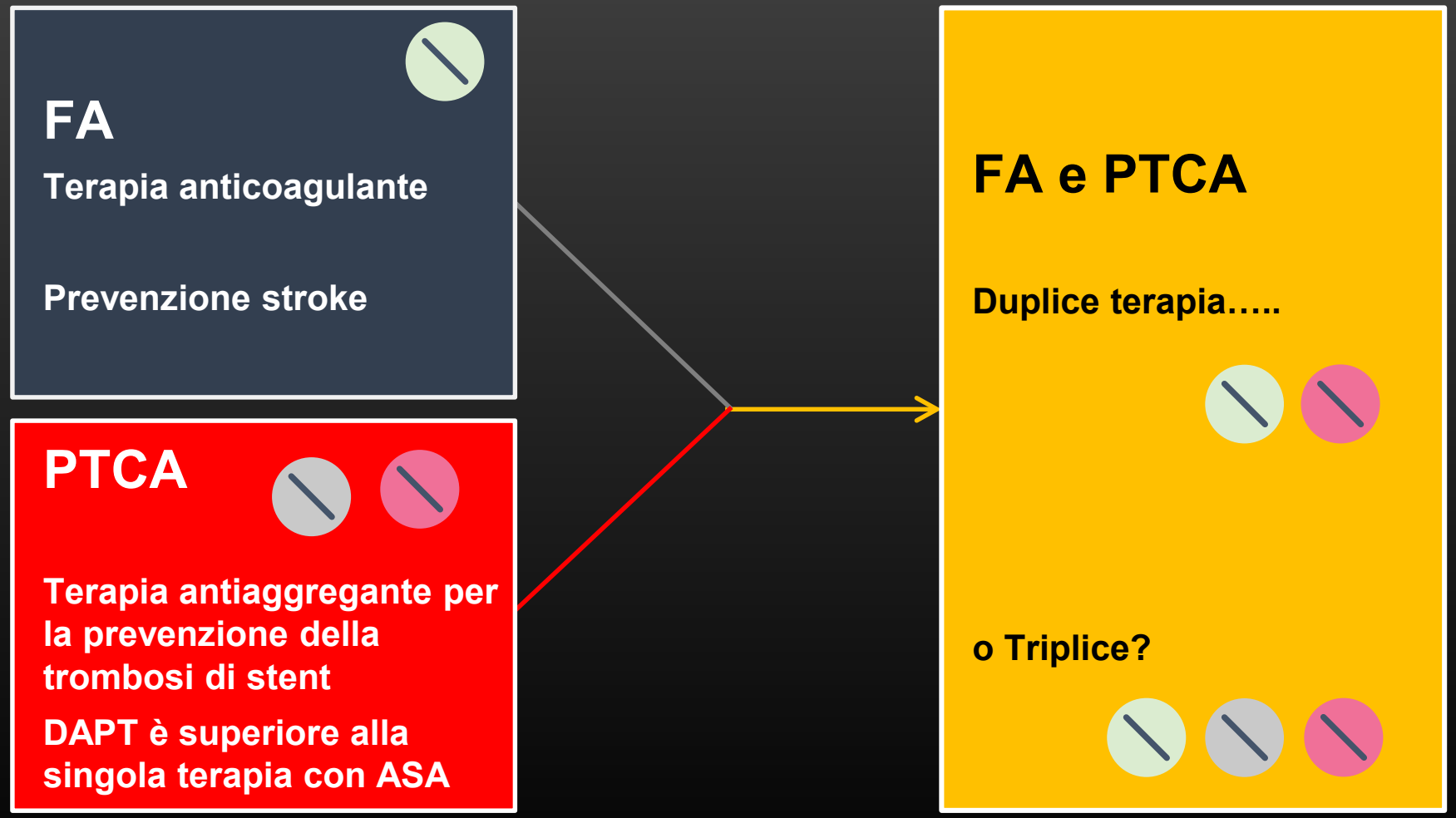
- **US ed Europa:**
- **20 Millioni affetti da AF (1-2% of population)**
- **di cui 16 Millioni con indicazione a TAO (80%)**
- **di cui 4.8 Millioni con CAD (20%-45%) 1,2**
- **e 1- 2 Millioni con potenziale rivascolarizzazione (20%-25%) 3,4**

1. The AFFIRM Investigators. *Am Heart J* 2002;143:991–1001;
2. Carpodanno D *et al*, *Circ Cardiovasc Interv* 2014;7:113–124;
3. Kralev S *et al*, *PLoS One* 2011;6:e24964;
4. Bahit MC *et al*, *Int J Cardiol* 2013;170:215–220

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS



Quale combinazione di terapie nei pazienti affetti da FA a seguito di PTCA?



ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention
Kirchhof et al. Eur Heart J 2016; Lip et al. Eur Heart J 2014

La Gestione ottimale della terapia di fibrillazione atriale e coronaropatia differisce

Fibrillazione atriale (ACTIVE W)[1]:

La combinazione di ASA e clopidogrel non è efficace quanto il *warfarin* nei pazienti con AF[1]

Tuttavia

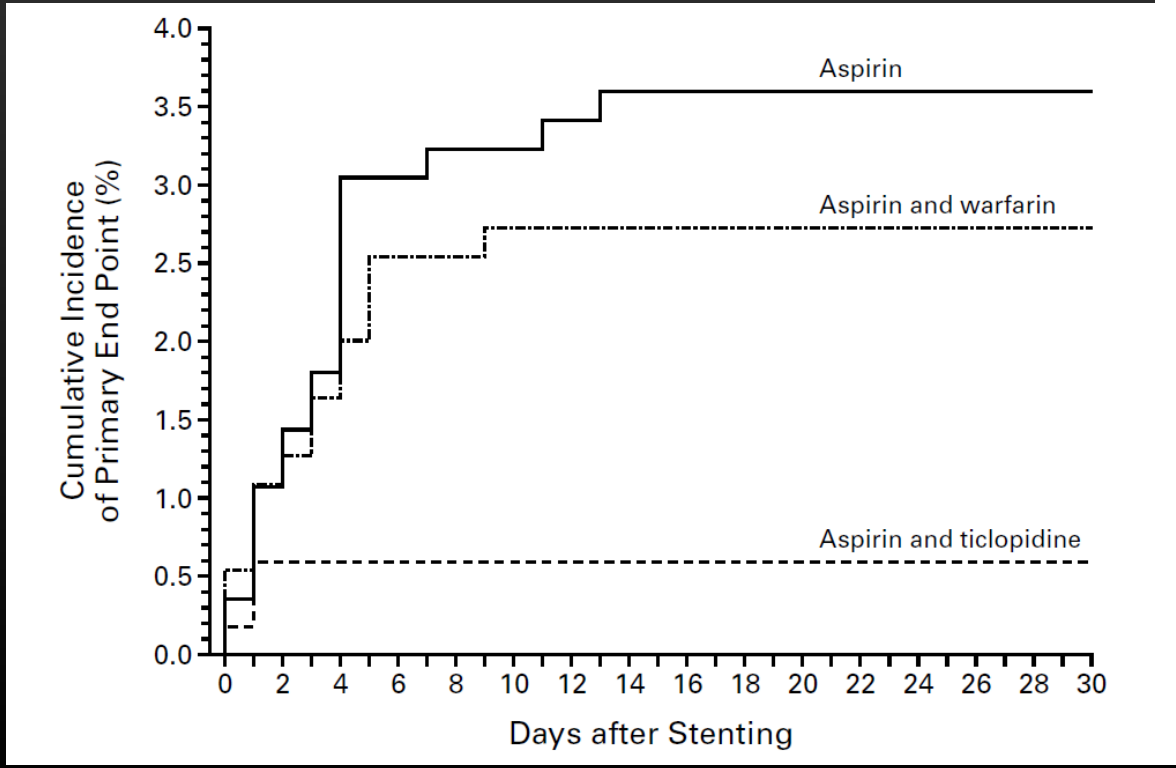
Posizionamento di stent (STARS)[2]:

La combinazione di ASA e tienopiridine è più efficace del warfarin nei pazienti con stent coronarico [2]

1. Lancet 2006 Jun 10;367(9526):1903-12. 2. N Eng J Med 1998 Dec 3;339(23):1665-71.

Il trial STARS

Dato ormai assodato da tempo:



A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

MARTIN B. LEON, M.D., DONALD S. BAIM, M.D., JEFFREY J. POPMA, M.D., PAUL C. GORDON, M.D., DONALD E. CUTLIP, M.D., KALON K.L. HO, M.D., ALEX GIAMBARTOLOMEI, M.D., DANIEL J. DIVER, M.D., DAVID M. LASORDA, D.O., DAVID O. WILLIAMS, M.D., STUART J. POCOCK, PH.D., AND RICHARD E. KUNTZ, M.D., FOR THE STENT ANTICOAGULATION RESTENOSIS STUDY INVESTIGATORS*

Efficacia nettamente superiore della DAPT rispetto a ASA + TAO dopo 1 stent coronarico

The New England Journal of Medicine

Volume 339 Number 23 · 1665

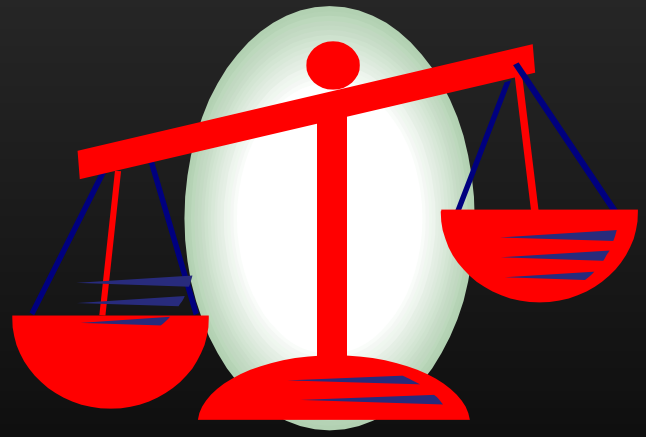
December 3, 1998

La combinazione TAO + antipiastrinici

Potenzialmente riduce il rischio tromboembolico

ma

Incrementa il rischio di sanguinamento di 3-5 volte



Haemorragic risk **Thrombotic risk**

Il bravo Cardiologo tra Scilla e Cariddi

Scilla
Trombosi

Cariddi
Emorragia

L’ASA è necessaria nella triplice terapia?

Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 11, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.05.029

Oral Anticoagulation and Antiplatelets in Atrial Fibrillation Patients After Myocardial Infarction and Coronary Intervention

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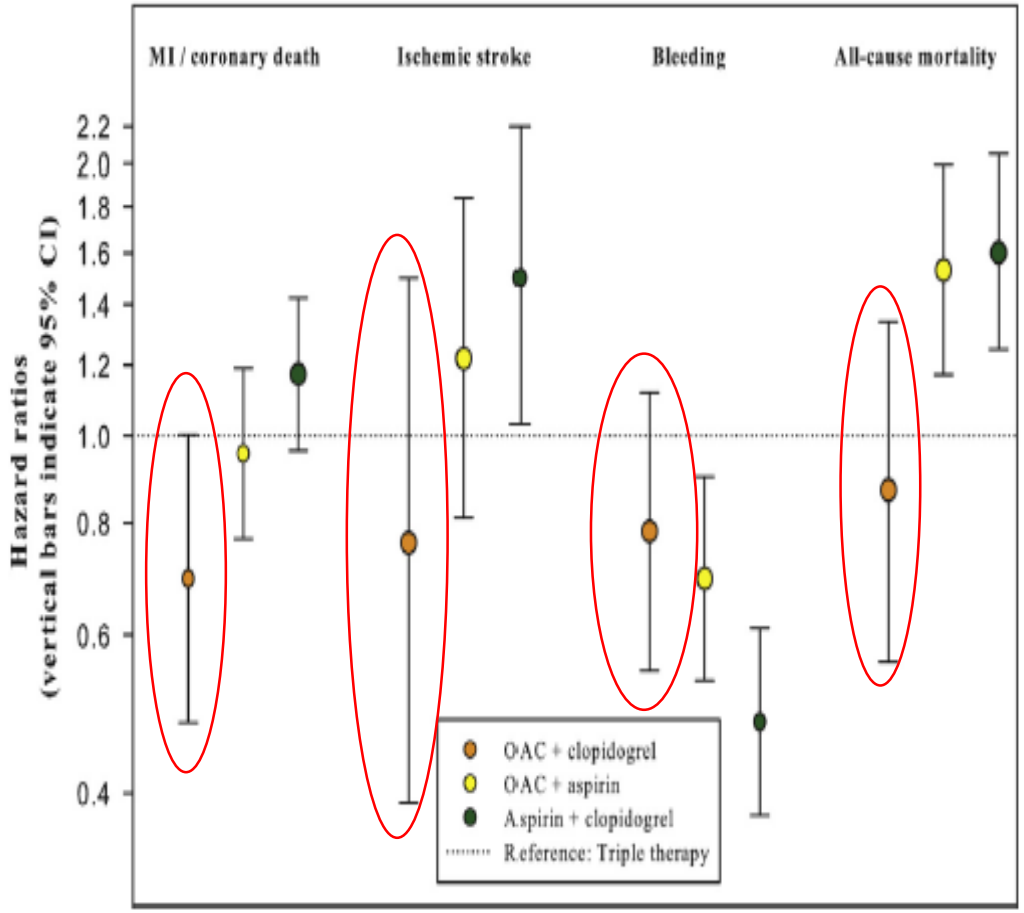
ited Kingdom



In una popolazione reale di pazienti in FA con indicazione a terapia antiaggregante post SCA o PTCA:

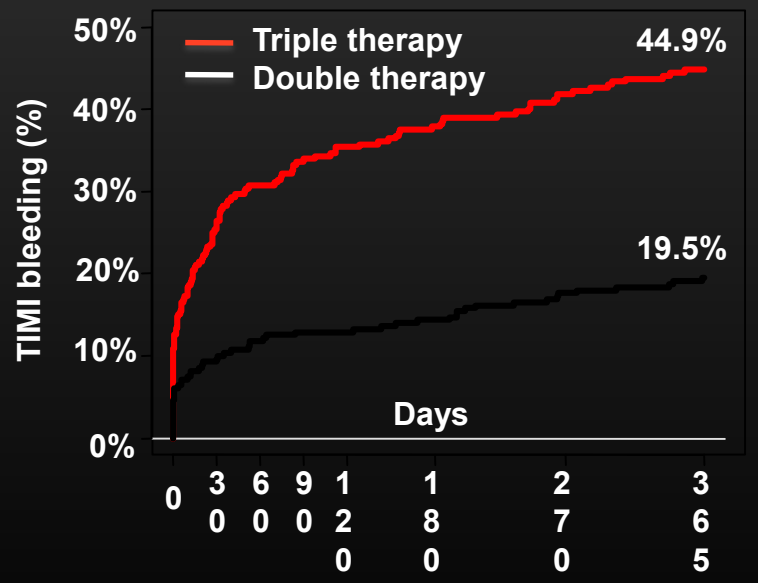
OAC + clopidogrel superiore sia per efficacia che per sicurezza rispetto a OAC + clopidogrel + asa (triplice terapia).

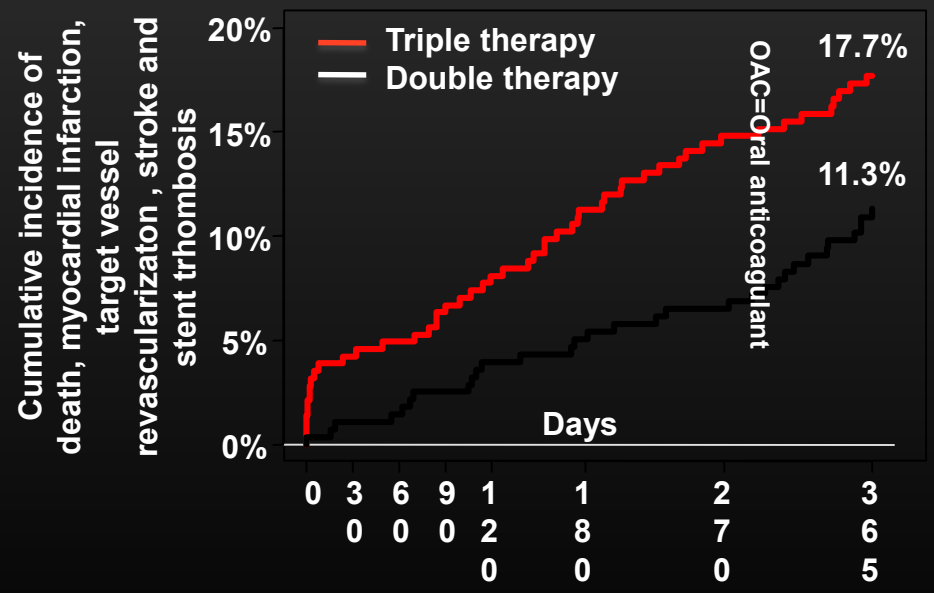
L'ASA NON è INDISPENSABILE !!

L'ASA è necessaria nella triplice terapia? The WOEST

Dual therapy:	*Triple therapy:*
OAC + 75 mg clopidogrel	OAC + 75 mg clopidogrel + 80mg acetylsalicyl acid **OR** 100mg carbasylate calcium
1Month minimum after BMS 1Year minimum after DES	1Month Min. after BMS 1Year Min. after DES

573 pazienti sottoposti a PCI con indicazione ad anticoagulante orale randomizzati a doppia vs triplice regime antitrombotico*





Il doppio regime riduceva significativamente il rischio CV ed I sanguinamenti

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 Tijssen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

Lancet 2013; 381: 1107–15

Inibitori di P2Y12
Quale ruolo nella triplice terapia?

Sia nel PLATO (ticagrelor)

che nel

TRITON-TIMI 38 (prasugrel)

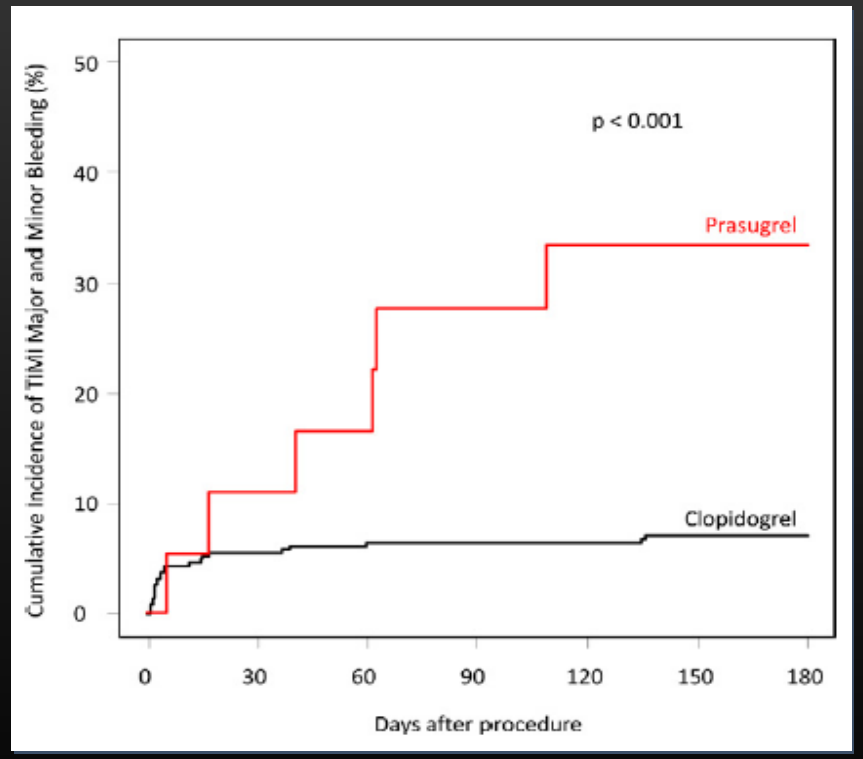
Erano esclusi dall'arruolamento i pazienti in terapia con VKA

Triple Therapy With Aspirin, Prasugrel, and Vitamin K Antagonists in Patients With Drug-Eluting Stent Implantation and an Indication for Oral Anticoagulation

Nikolaus Sarafoff, MD,* Amadea Martischnig, MD,† Jill Wealer, MS,† Katharina Mayer, MD,† Julinda Mehilli, MD,* Dirk Sibbing, MD,* Adnan Kastrati, MD†

Munich, Germany

(J Am Coll Cardiol 2013;61:2060–6)

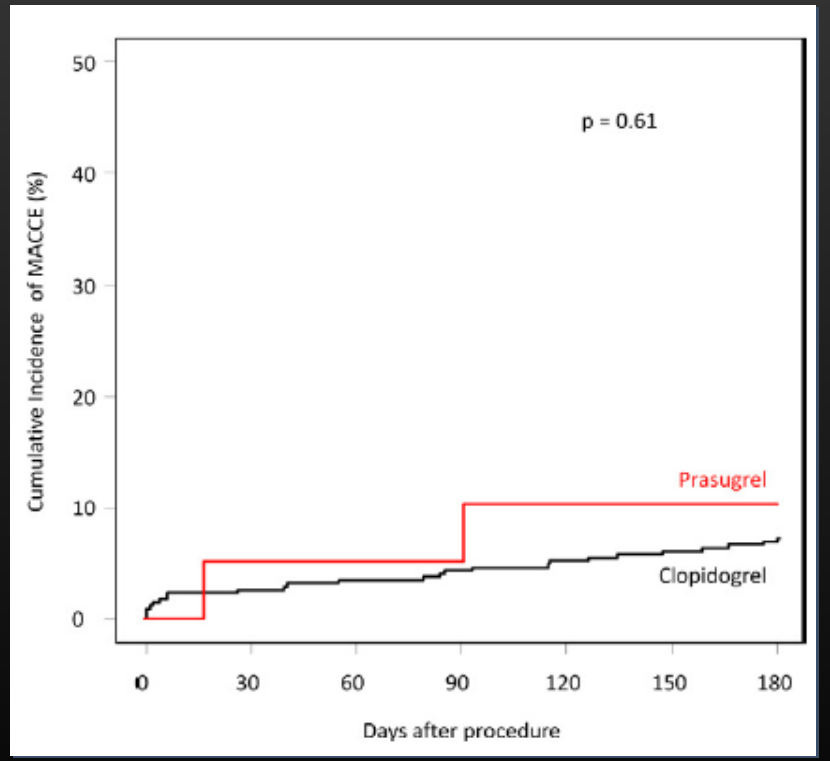


377 pazienti

Prasugrel + ASA + VKA
Clopidogrel + ASA+ VKA

incremento sanguinamenti

Non migliora l'efficacia



La terapia anticoagulante è sempre necessaria nella triplice terapia?

La terapia anticoagulante è necessaria nella triplice terapia?

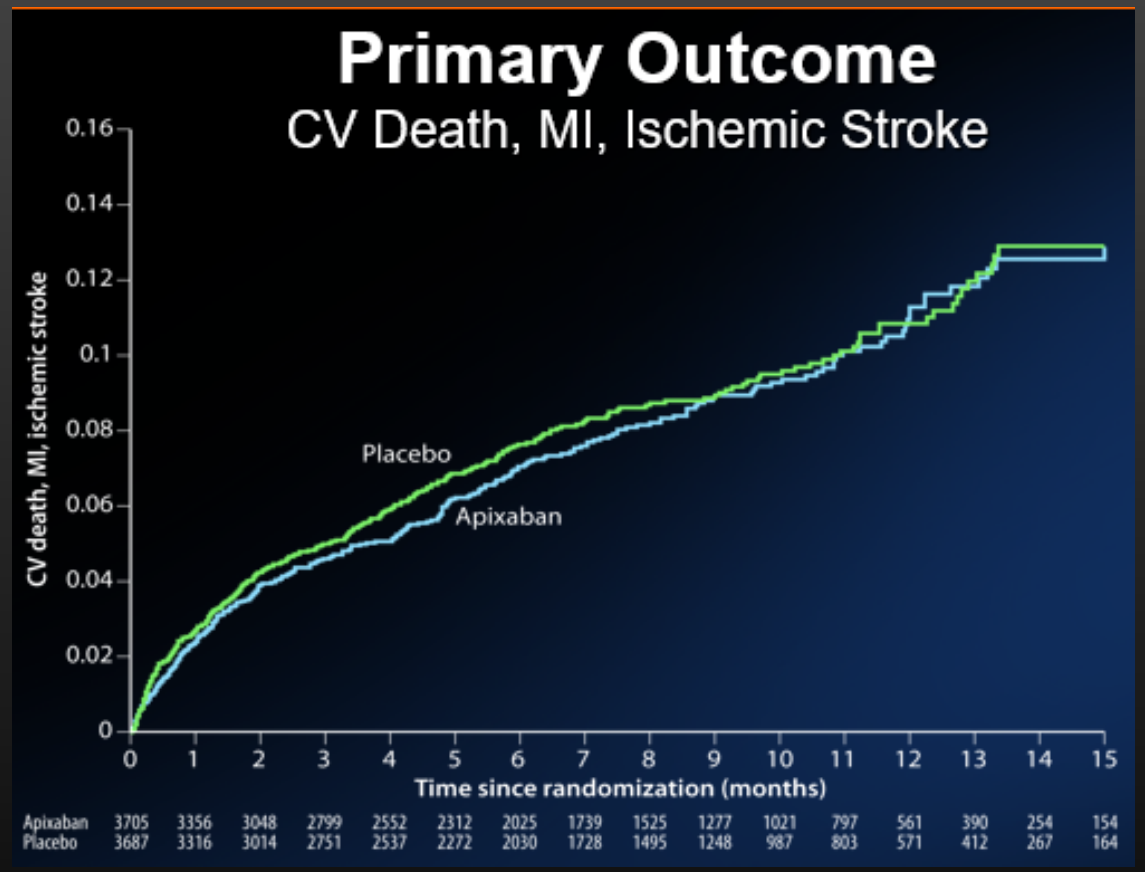
APPRAISE 2 trial

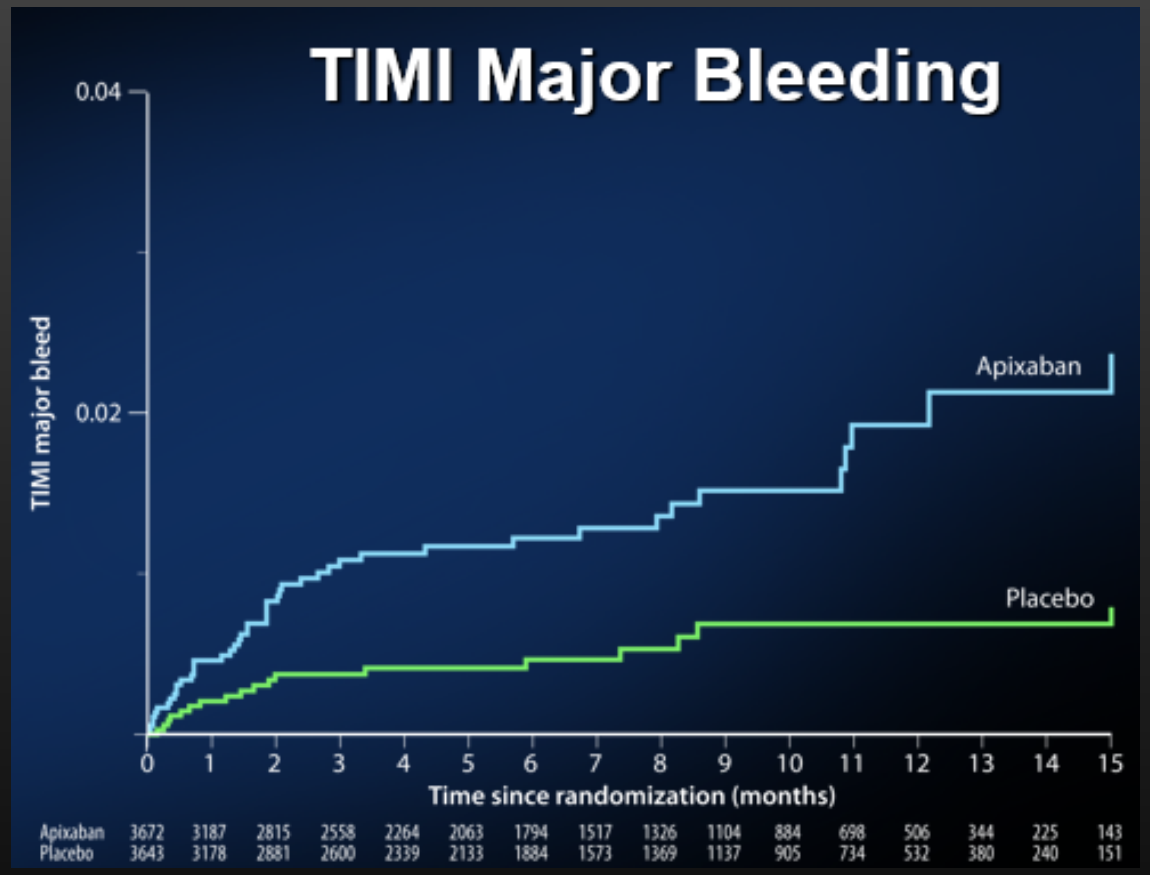
- **I pazienti affetti da SCA presentano eventi ricorrenti ischemici nonostante la rivascolarizzazione e la terapia antiaggregante.**
- **Gli antagonisti della vitamina K si sono dimostrati efficaci nel ridurre ULTERIORMENTE tali eventi se associati ad aspirina.**

- **Per determinare se apixaban 5 mg bid riduce il rischio composito di morte cardiovascolare, IMA o ictus con un rischio emorragico accettabile in pazienti ad alto rischio per eventi ischemici ricorrenti che ricevono terapia antiaggregante a seguito di una sindrome coronarica acuta**

La terapia anticoagulante è necessaria nella triplice terapia?

APPRAISE 2 trial





Il 15 novembre 2010 il Comitato di monitoraggio dei dati ha raccomandato di arrestare il trial a causa di un eccesso di emorragie clinicamente importanti nel braccio apixaban senza una riduzione controbilanciata negli eventi ischemici.

LA RIDUZIONE DEL DOSAGGIO DELL'ANTICOAGULANTE?

LA RIDUZIONE DEL DOSAGGIO DELL'ANTICOAGULANTE?
The ATLAS trial

Recente ACS: STEMI, NSTEMI, UA
No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine
Stabilized 1-7 Days Post-Index Event

Stratified by Thienopyridine use at MD Discretion

+ ASA 75 to 100 mg/day

Placebo
N=5,176
ASA + Thieno, n=4,821
ASA, n=355

RIVAROXABAN
2.5 mg BID
n=5,174
ASA + Thieno, n=4,825
ASA, n=349

RIVAROXABAN
5.0 mg BID
N=5,176
ASA + Thieno, n=4,827
ASA, n=349

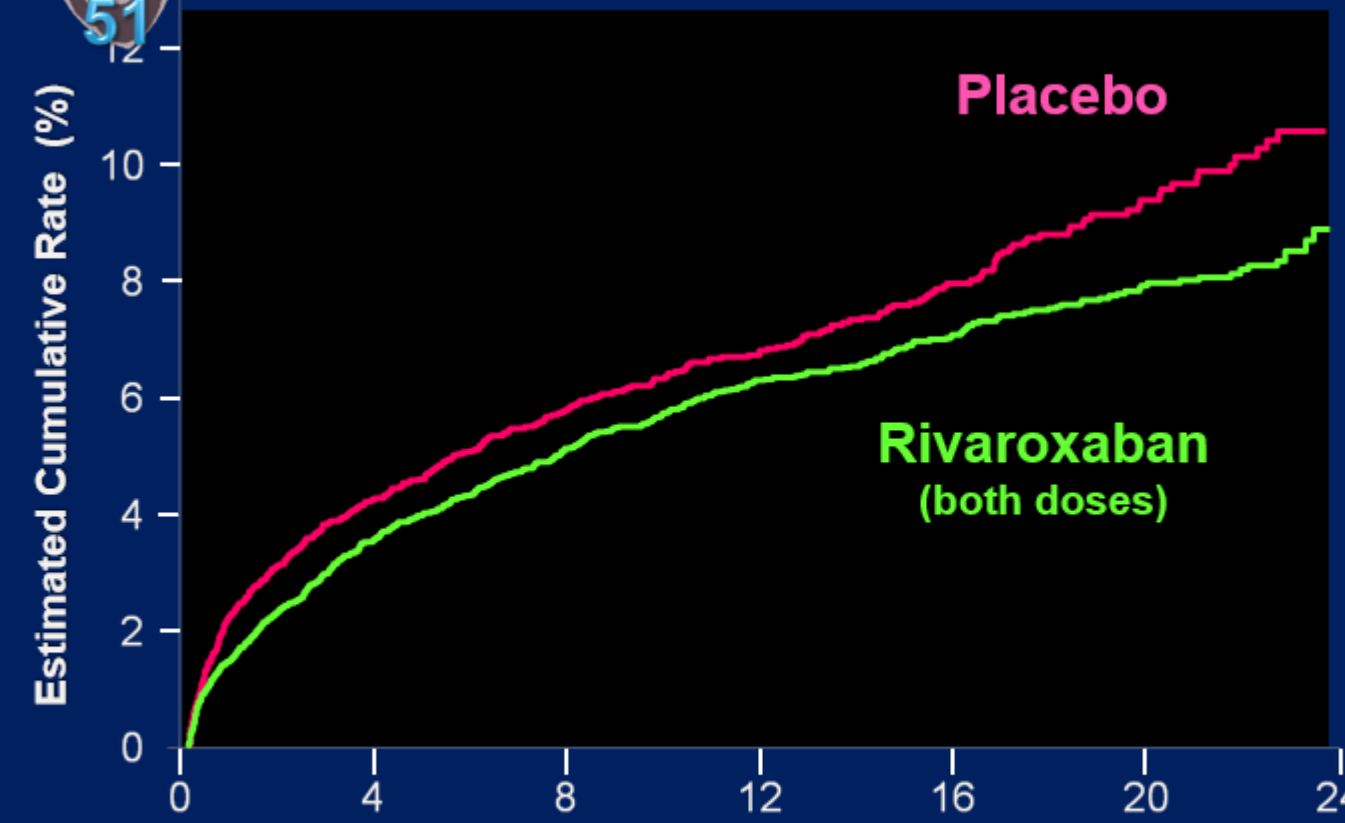
PRIMARY ENDPOINT:
EFFICACY: CV Death, MI, Stroke* (Ischemic + Hemg.)
SAFETY: TIMI major bleeding not associated with CABG
Event driven trial of 1,002 events in 15,342 patients**

* Stroke includes ischemic stroke, hemorrhagic stroke, and uncertain stroke
** 184 subjects were excluded from the efficacy analyses prior to unblinding

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke* (Ischemic + Hemg.)



2 Yr KM Estimate

10.7%

8.9%

HR 0.84
(0.74-0.96)
ARR 1.7%

mITT p = 0.008
ITT p = 0.002

NNT = 59

No. at Risk							
Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; ARR=Absolute Relative Reduction; NNT=Number needed to treat; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.

SAFETY ENDPOINTS

Treatment-Emergent Non CABG TIMI Major Bleeding*

Analysis	Placebo	2.5 mg Rivaroxaban	5.0 mg Rivaroxaban
2 Yr KM Estimate	0.6%	1.8% HR 3.46	2.4% HR 4.47

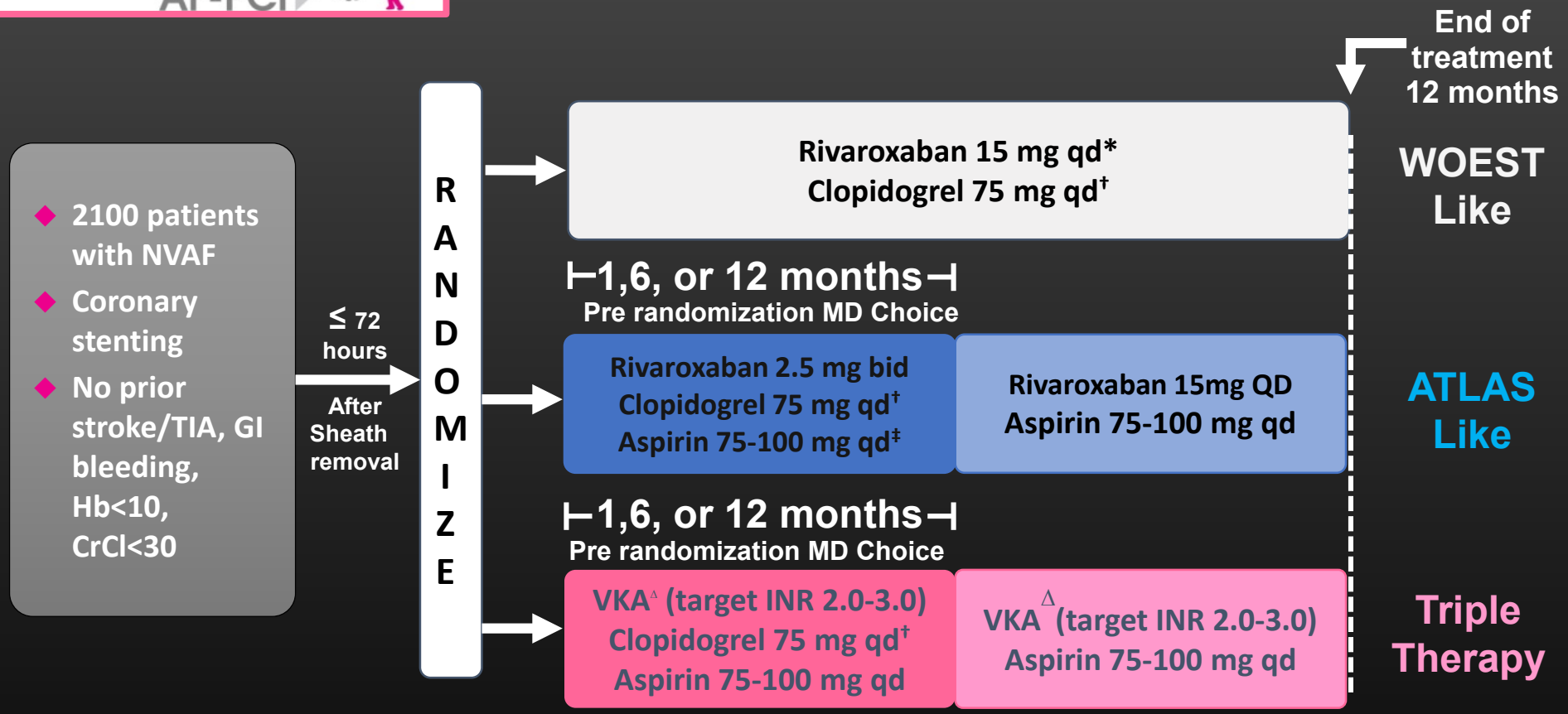
p<0.001

p<0.001

There was no excess of either combined ALT > 3x ULN and Total Bilirubin > 2x ULN cases among patients treated with Rivaroxaban, or SAEs.

*: First occurrence of Non-CABG TIMI major bleeding events occurred between first dose to 2 days post last dose as adjudicated by the CEC across thienopyridine use strata; Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine are provided; Stratified log-rank p-values are provided; #: Raw percentage for CV death/MI/stroke (ischemic, hemorrhagic, uncertain) ; ##: Raw percentage of subjects with abnormal value measured between first dose to 2 days post last dose among subjects with normal baseline measurement.

PIONEER AF-PCI



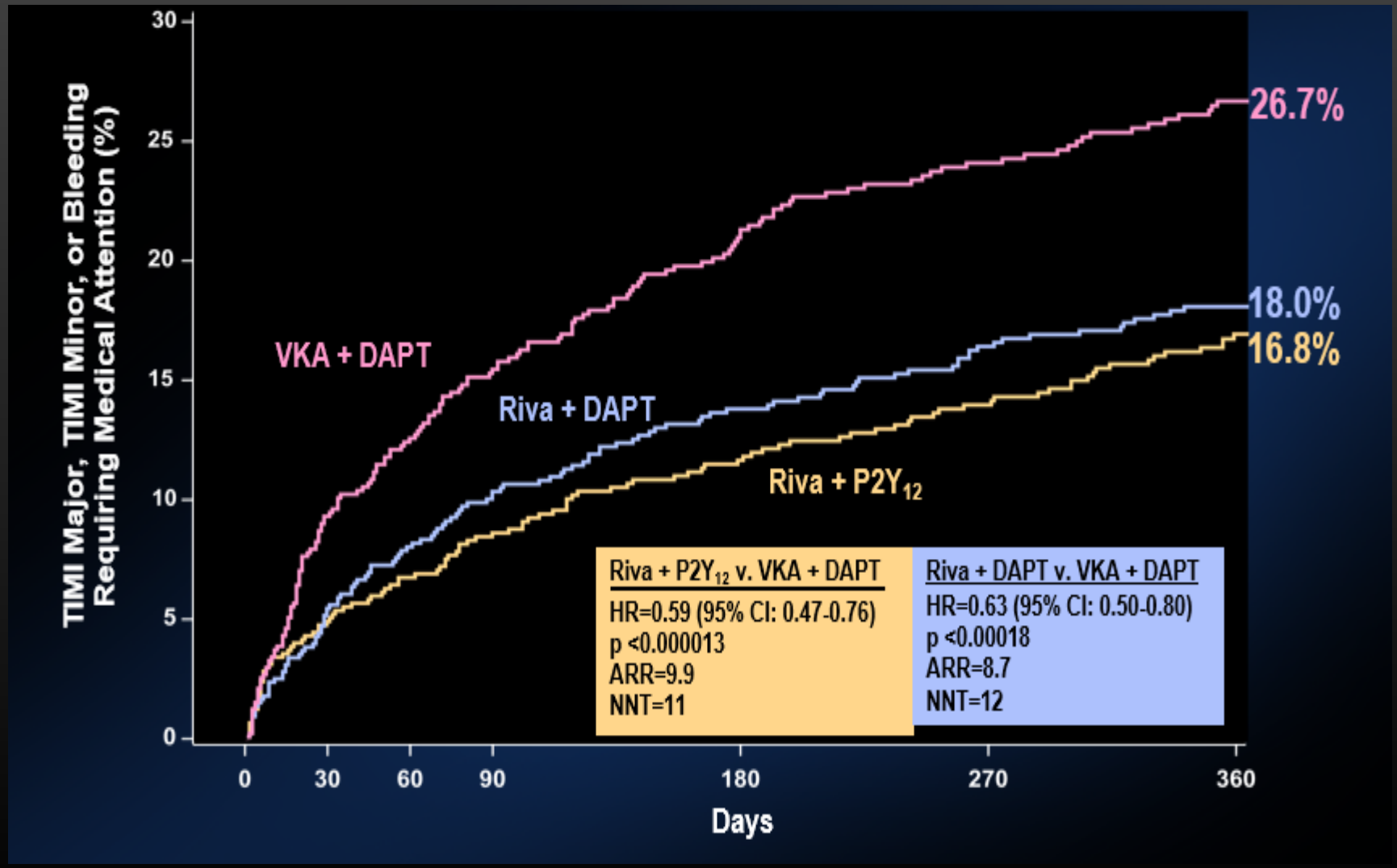
- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.

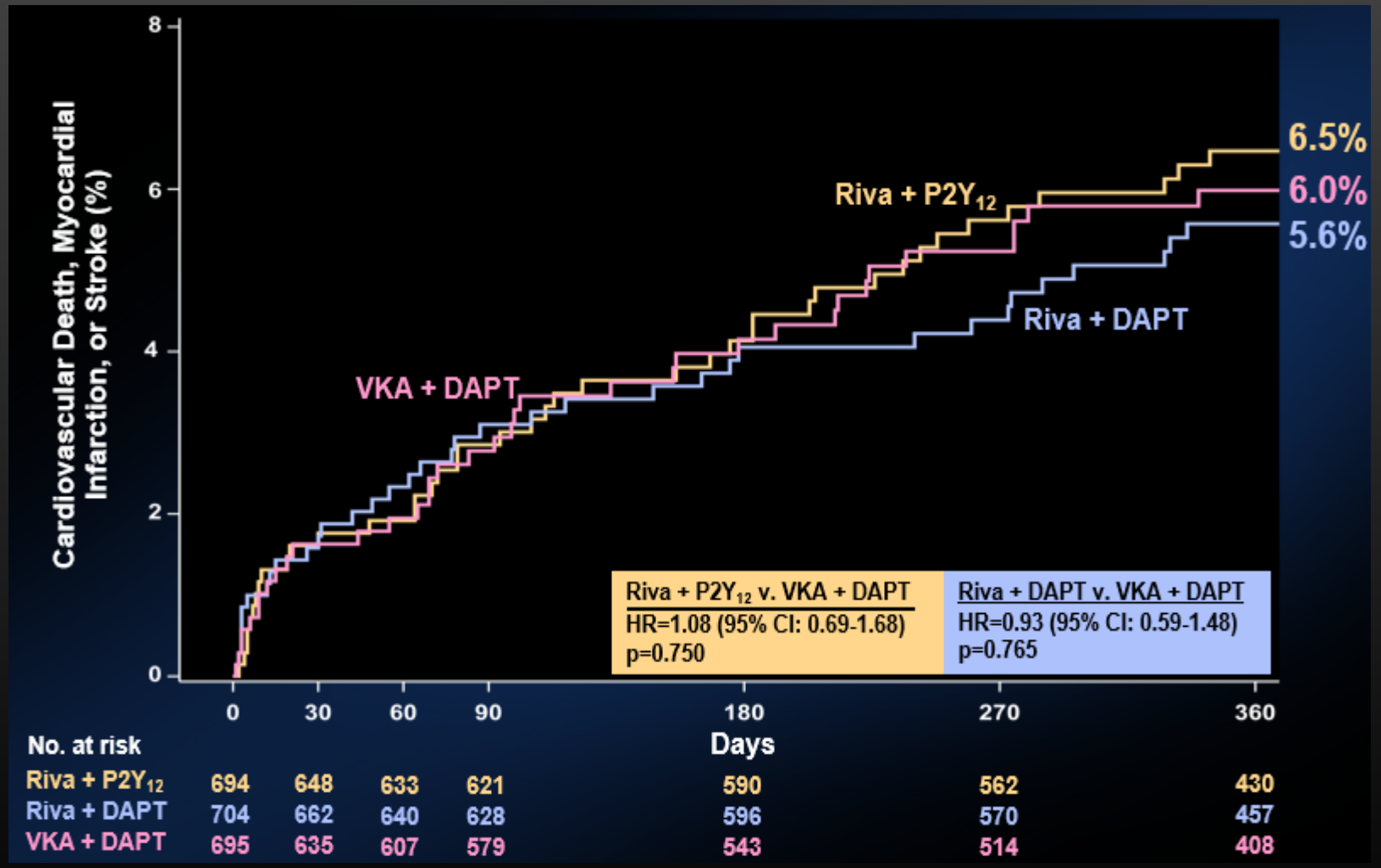
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

Primo sanguinamento clinicamente significativo



CV Death, MI or Stroke



*** La numerosità dello studio lo rendeva UNDERPOWERED per questo end-point**

Ospedalizzazioni ricorrenti per eventi avversi

ORIGINAL RESEARCH ARTICLE

Recurrent Hospitalization Among Patients With Atrial Fibrillation Undergoing Intracoronary Stenting Treated With 2 Treatment Strategies of Rivaroxaban or a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy

BACKGROUND: Patients with atrial fibrillation who undergo intracoronary stenting traditionally are treated with a vitamin K antagonist (VKA) plus dual antiplatelet therapy (DAPT), yet this treatment leads to high risks of bleeding. We hypothesized that a regimen of rivaroxaban plus a $P2Y_{12}$ inhibitor monotherapy or rivaroxaban plus DAPT could reduce bleeding and thereby have a favorable impact on all-cause mortality and the need for rehospitalization.

METHODS: Stented subjects with nonvalvular atrial fibrillation (n=2124) were randomized 1:1:1 to administration of reduced-dose rivaroxaban 15 mg daily plus a $P2Y_{12}$ inhibitor for 12 months (group 1); rivaroxaban 2.5 mg twice daily with stratification to a prespecified duration of DAPT of 1, 6, or 12 months (group 2); or the reference arm of dose-adjusted VKA daily with a similar DAPT stratification (group 3). The present post hoc analysis assessed the end point of all-cause mortality or recurrent hospitalization for an adverse event, which was further classified as the result of bleeding, a cardiovascular, or another cause blinded to treatment assignment.

RESULTS: The risk of all-cause mortality or recurrent hospitalization was 34.9% in group 1 (hazard ratio=0.79; 95% confidence interval, 0.66–0.94; *P*=0.008 versus group 3; number needed to treat=15), 31.9% in group 2 (hazard ratio=0.75; 95% confidence interval, 0.62–0.90; *P*=0.002 versus group 3; number needed to treat=10), and 41.9% in group 3 (VKA+DAPT). Both all-cause death plus hospitalization potentially resulting from bleeding (group 1=8.6% [*P*=0.032 versus group 3], group 2=8.0% [*P*=0.012 versus group 3], and group 3=12.4%) and all-cause death plus rehospitalization potentially resulting from a cardiovascular cause (group 1=21.4% [*P*=0.001 versus group 3], group 2=21.7% [*P*=0.011 versus group 3], and group 3=29.3%) were reduced in the rivaroxaban arms compared with the VKA arm, but other forms of rehospitalization were not.

CONCLUSIONS: Among patients with atrial fibrillation undergoing intracoronary stenting, administration of either rivaroxaban 15 mg daily plus $P2Y_{12}$ inhibitor monotherapy or 2.5 mg rivaroxaban twice daily plus DAPT was associated with a reduced risk of all-cause mortality or recurrent hospitalization for adverse events compared with standard-of-care VKA plus DAPT.

CLINICAL TRIAL REGISTRATION: URL: https://clinicaltrials.gov. Unique identifier: NCT01830543.

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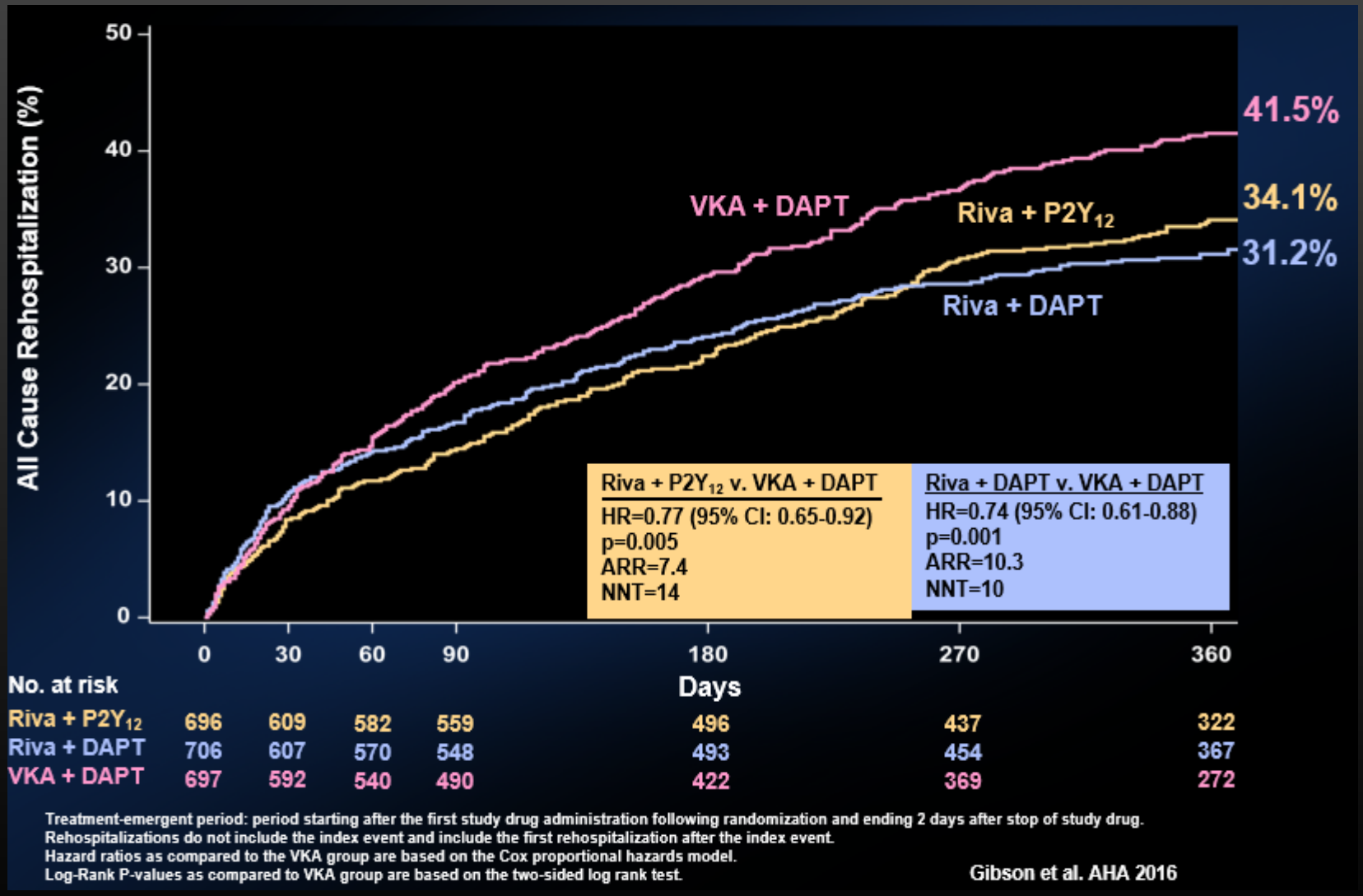
Sources of Funding, see page XXX

Key Words: atrial fibrillation ■ percutaneous coronary intervention ■ rivaroxaban ■ vitamin K



…et voilà, il problema è risolto!

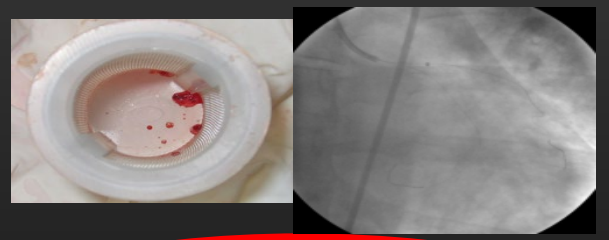
RAPPORTO RISCHIO-BENEFICIO DEL SINGOLO PAZIENTE

Caratteristiche cliniche

età avanzata, IRA,sesso femminile, basso peso, diabete mellito, arteriopatia periferica, scompenso cardiaco, ipertensione arteriosa, anemia preesistente, precedenti cerebrovascolari

Esecuzione di procedure invasive

(vie di accesso arteriose)



Utilizzo di farmaci anticoagulanti

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

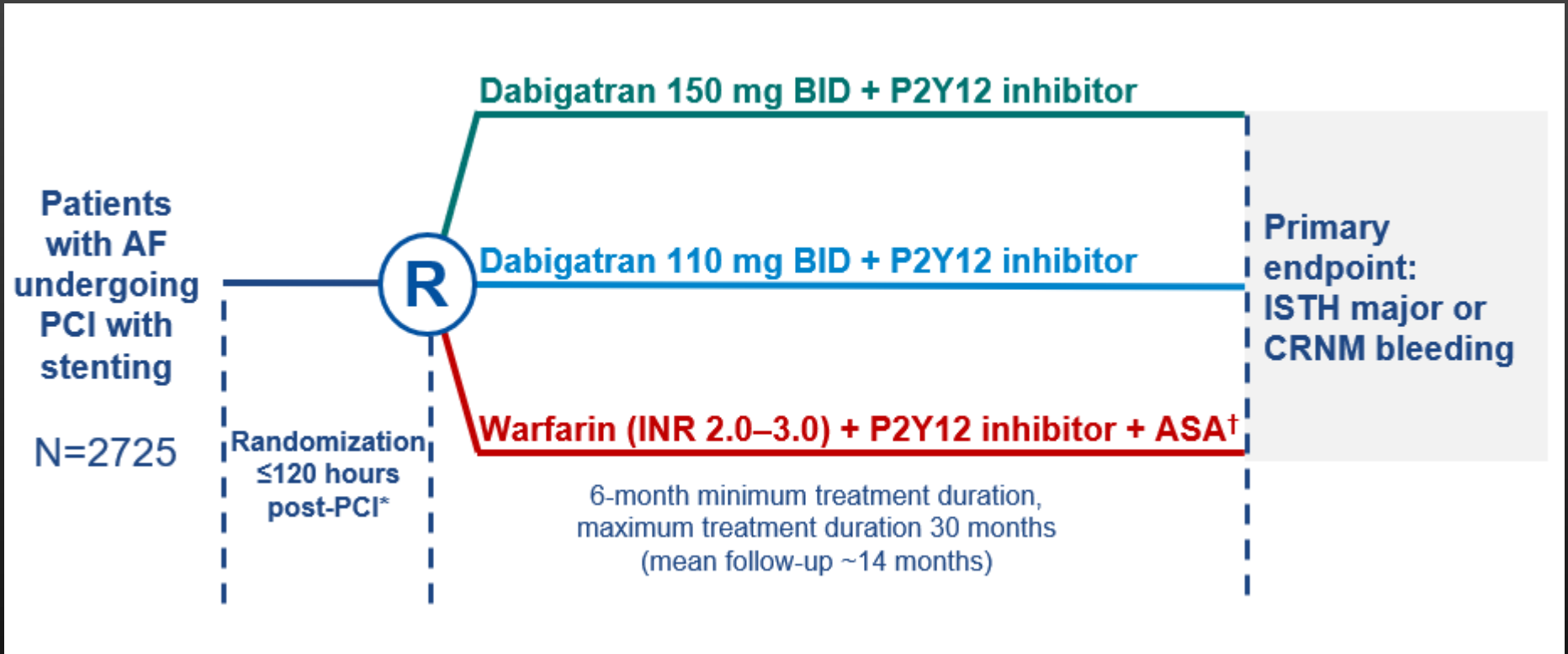
Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

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*

The RE-DUAL PCI trial

- Studio randomizzato
- Duplice terapia (P2Y12 inib. + Dabigatran) vs triplice terapia con Warfarin nei pazienti con NVAF che hanno subito PTCA + stent
- Dabigatran (150 mg o110 mg bid) + singolo antiaggregante vs Warfarin + DAPT
- Emorragie clinicamente rilevanti ed eventi trombotici (tasso combinato di morte, infarto miocardico e ictus)

RE-DUAL PCI tested the safety and efficacy of two regimens of dual therapy with dabigatran without ASA vs triple therapy with warfarin



- The primary endpoint was time to first ISTH major or clinically relevant non-major bleeding event
- Formally tested endpoints included:
  - non-inferiority and superiority of 110 mg and 150 mg dual therapy in time to first ISTH major bleeding event or clinically relevant non-major bleeding event
  - time to first event of death, thromboembolic event (MI, stroke, systemic embolism) with and without unplanned revascularization
- 100% of outcome events were independently adjudicated by blinded external committee

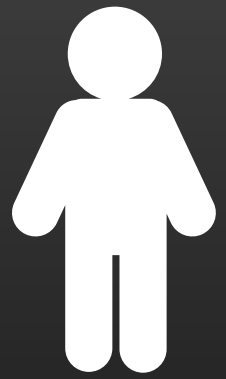
Baseline characteristics

	Dabigatran 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabigatran 150 mg dual therapy (n=763)	Warfarin triple therapy (n=764)
Age, years, mean	71.5	71.7	68.6	68.8
≥80 (USA, ROW), ≥70 (Japan), %	22.9	22.9	1.0	1.0
<80 (USA, ROW), <70 (Japan), %	77.1	77.1	99.0	99.0
Male, %	74.2	76.5	77.6	77.7
Baseline CrCl, mL/min, mean	76.3	75.4	83.7	81.3
Diabetes mellitus, %	36.9	37.9	34.1	39.7
CHA_2DS_2–VASc score (mean)	3.7	3.8	3.3	3.6
Modified HAS-BLED score at baseline (mean)	2.7	2.8	2.6	2.7
ACS indication for PCI, %	51.9	48.4	51.2	48.3
DES placed only, %	82.0	84.2	81.4	83.5

ROW, rest of world; ACS, acute coronary syndrome; DES, drug-eluting stent; PCI, percutaneous coronary intervention;

Cannon et al. N Engl J Med 2017; Cannon et al. ESC 2017

RE-DUAL PCI key inclusion and exclusion criteria



Patients aged ≥18 years with paroxysmal, persistent or permanent NVAF

ACS successfully treated by PCI and stenting (BMS or DES)

Stable CAD with ≥1 lesion eligible for PCI that was successfully treated by elective PCI and stenting (BMS or DES)

Exclusion

- **Cardiogenic shock during current hospitalization**
- **Use of fibrinolytics within 24 hours of randomization that, in the investigator's opinion, will put patient at high risk of bleeding**
- **Stroke or major bleeding event within 1 month prior to screening visit**
- **Severe renal impairment (CrCl <30mL/min)**

ACS, acute coronary syndrome; BMS, bare-metal stent; CAD, coronary artery disease; DES, drug-eluting stent; PCI, percutaneous coronary intervention; Cannon et al. Clin Cardiol 2016

RE-DUAL PCI primary endpoint

RE-DUAL PCI primary safety endpoint: time to first…

…ISTH major bleeding event

- Symptomatic bleeding in a critical area or organ*, and/or
- Bleeding associated with reduced haemoglobin ≥2 g/dL (1.24 mmol/L) or transfusion of ≥2 units of blood or packed cells† and/or
- Fatal bleed

OR

…ISTH CRNM bleeding event

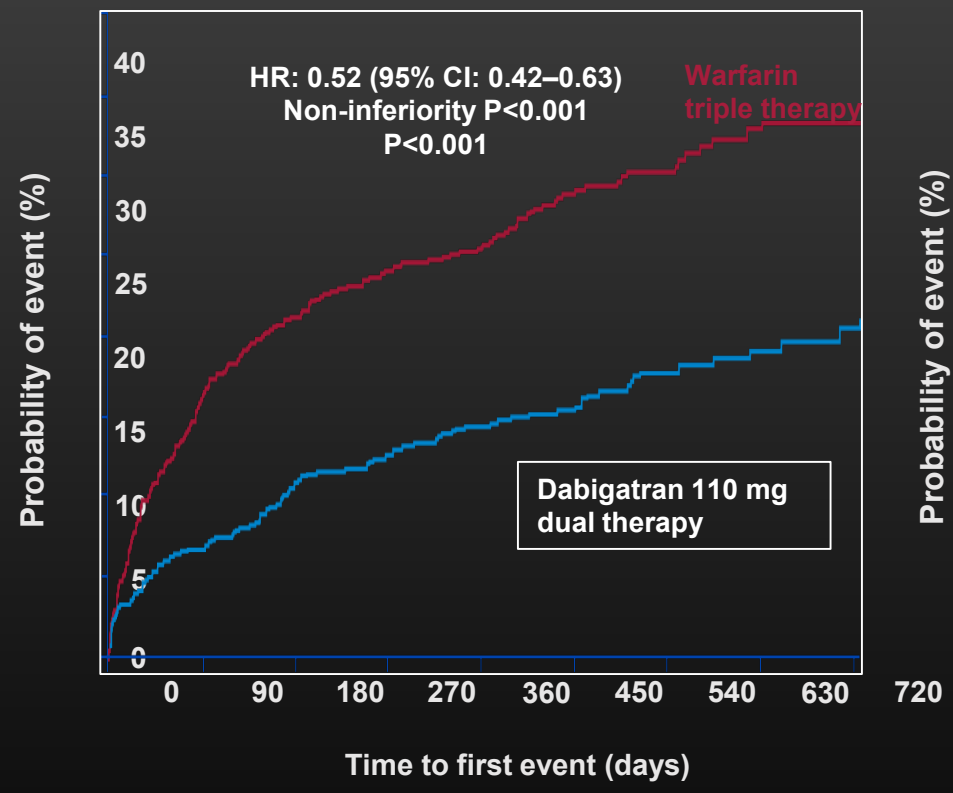
Not meeting criteria for a major bleed but prompts ≥1 of:

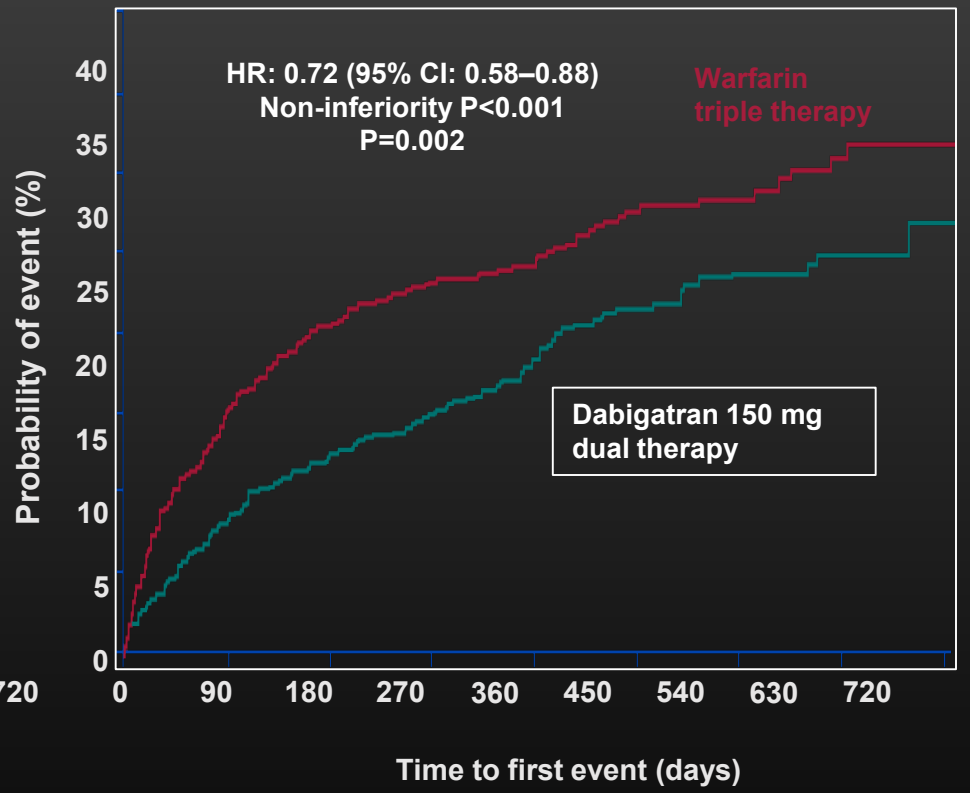
- Hospital admission
- Physician-guided medical or surgical treatment
- Physician-guided change, interruption (≥1 dose) or discontinuation of study drug

All primary and secondary endpoints were adjudicated by a treatment-blinded independent central committee

*E.g. intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; †Bleeding should be overt and haemoglobin drop should be considered due to and temporally related to bleeding event.
CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis;
Cannon et al. Clin Cardiol 2016; Kaatz et al. J Thromb Haemost 2015; Schulman et al. J Thromb Haemost 2005

La duplice terapia con Dabigratran + Clopidogrel (o altra tienopidirina) riduce significativamente l'incidenza di sanguinamenti (maggiori e clinicamente rilevanti)

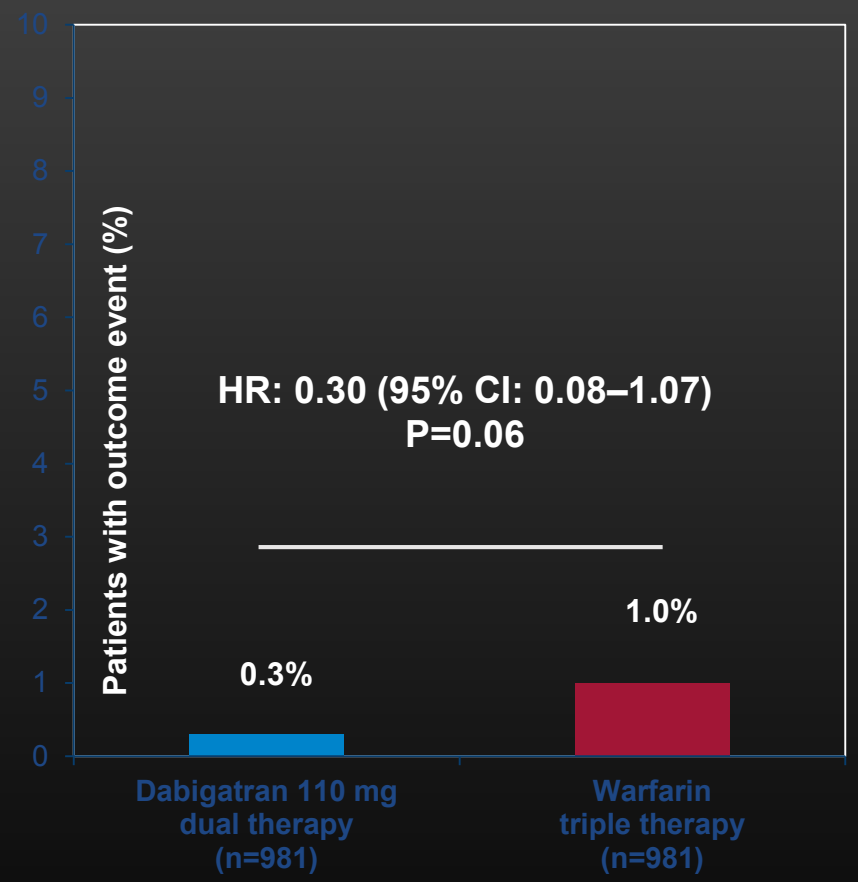


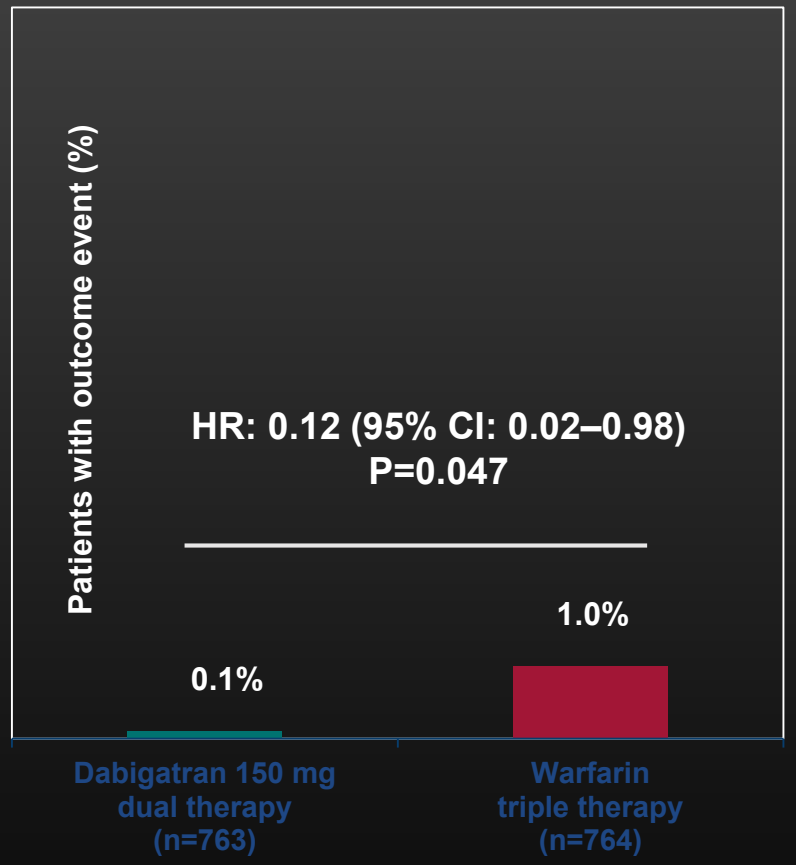


For the dabigatran 150 mg vs warfarin comparison, elderly patients outside the USA (≥80 years) and Japan (≥70 years) are excluded. Full analysis set presented

CRNMBE, clinically relevant non-major bleeding event; ISTH, International Society on Thrombosis and Haemostasis;
Cannon et al. ESC 2017; Cannon et al. N Engl J Med 2017

Emorragie intracraniche

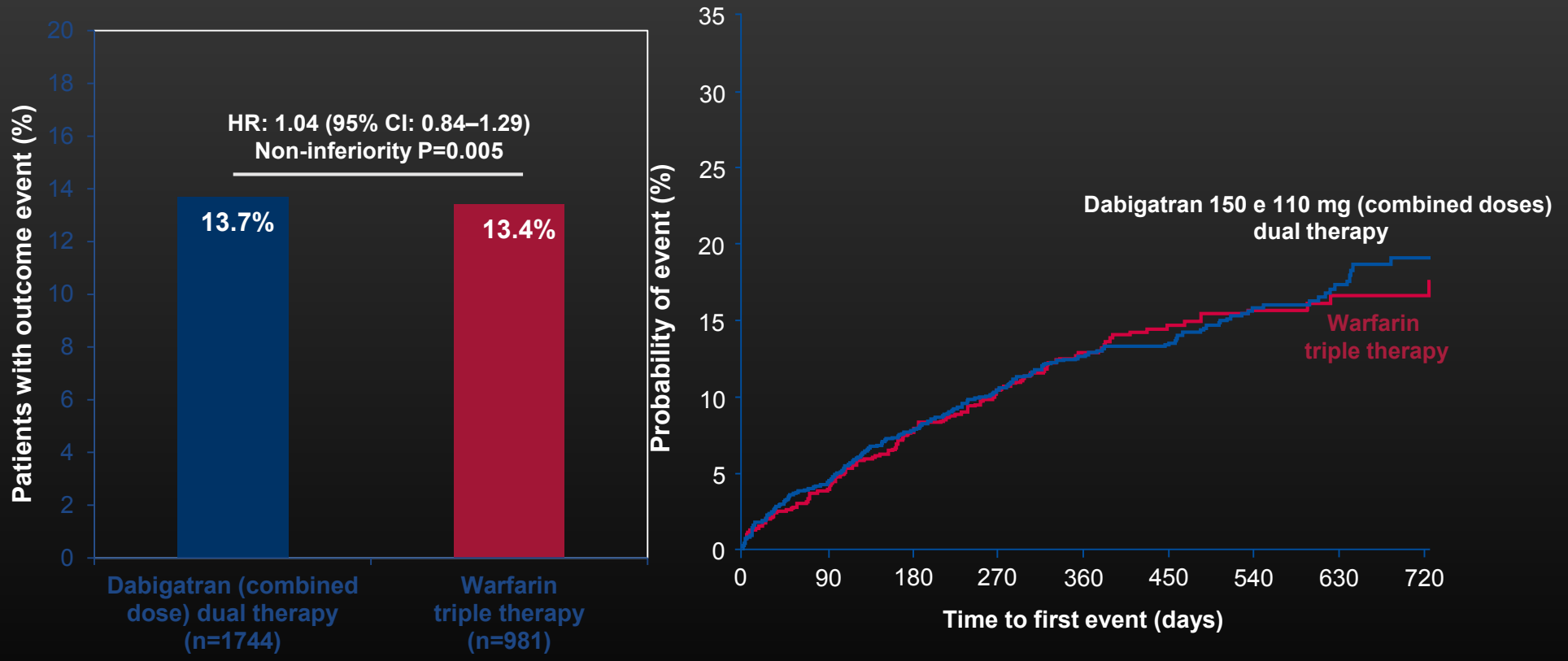




Cannon et al. N Engl J Med 2017

Non inferiorità della duplice con Dabigatran + tienopiridine rispetto a triplice con VKA nel ridurre gli eventi ischemici coronarici e stroke embolico

Composite endpoint of death or thromboembolic event (MI, stroke or systemic embolism) or unplanned revascularization (PCI/CABG)



CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; Cannon et al. N Engl J Med 2017; Cannon et al ESC 2017

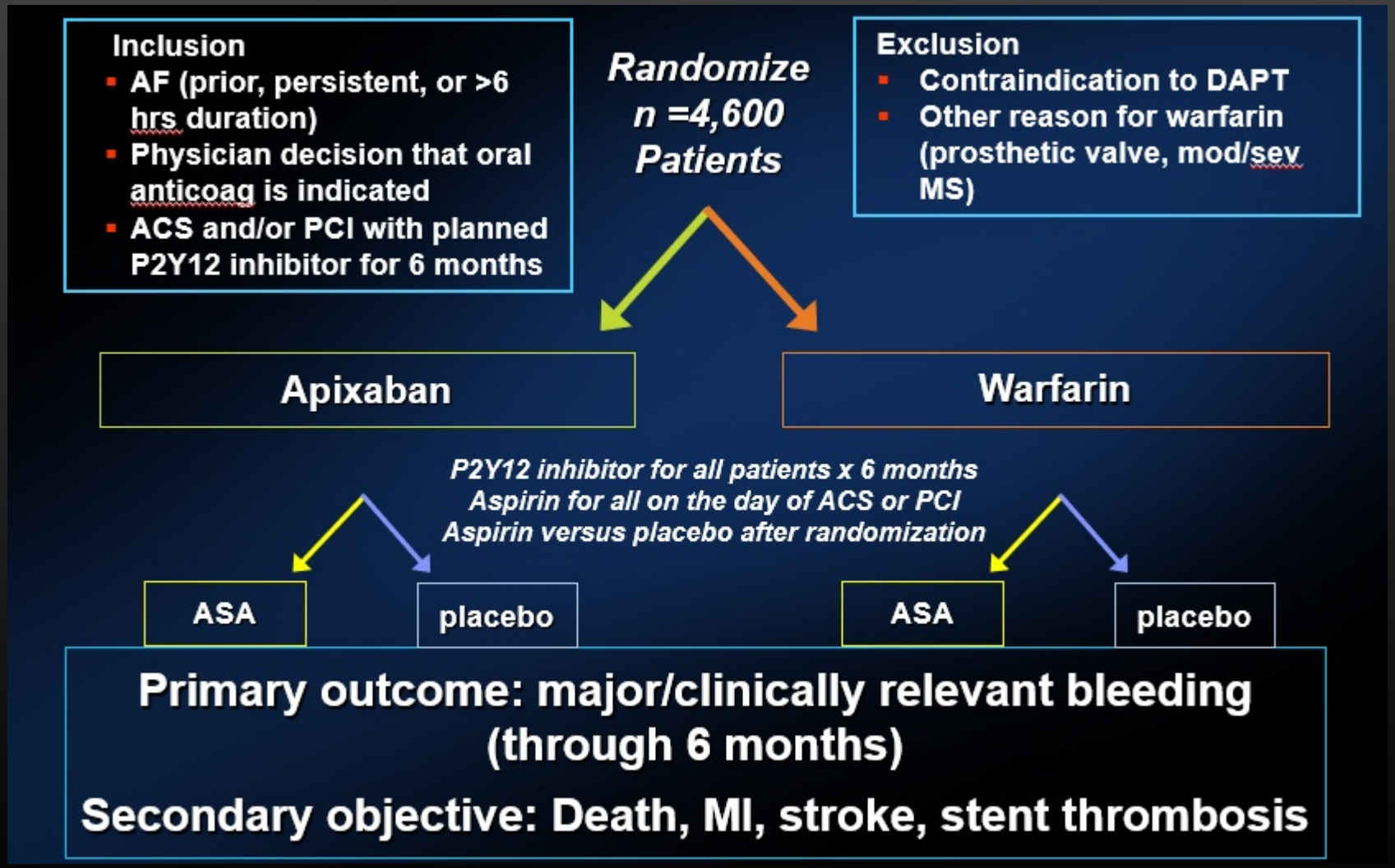
RE-DUAL PCI key points

1. Duplice terapia con Dabigatran + tienopidirina riduce il rischio di sanguinamenti rispetto alla triplice con Warfarin risultando non inferiore per tutti gli eventi tromboembolici

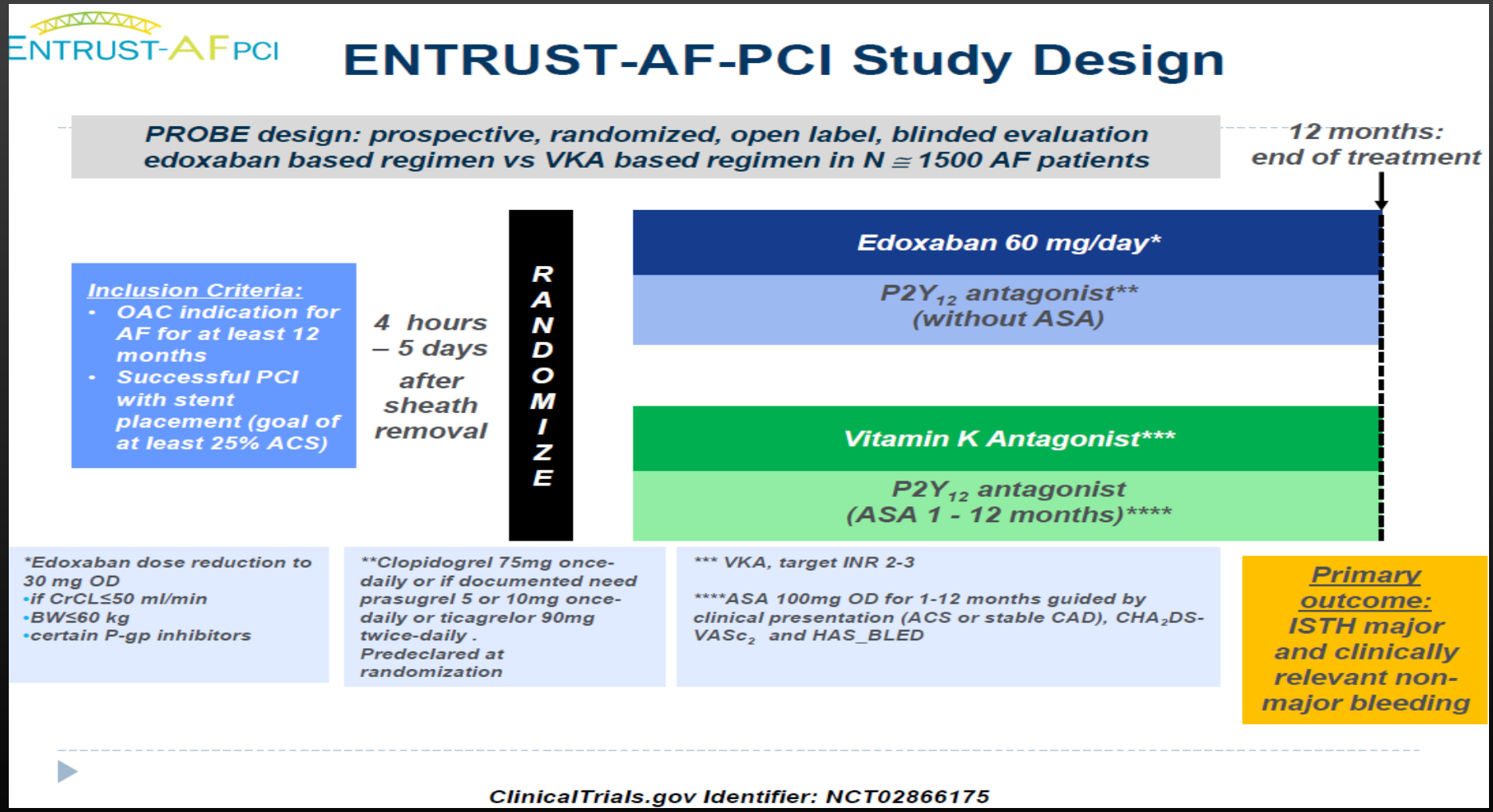
2. Il rischio di sanguinamento è ridotto sia nel braccio 110 mg, sia nel braccio 150 mg

3. La duplice terapia con dabigatran + tienopiridina è un'alternativa da considerare nei pazienti con FA non valvolare sottoposti ad impianto di stent coronarico

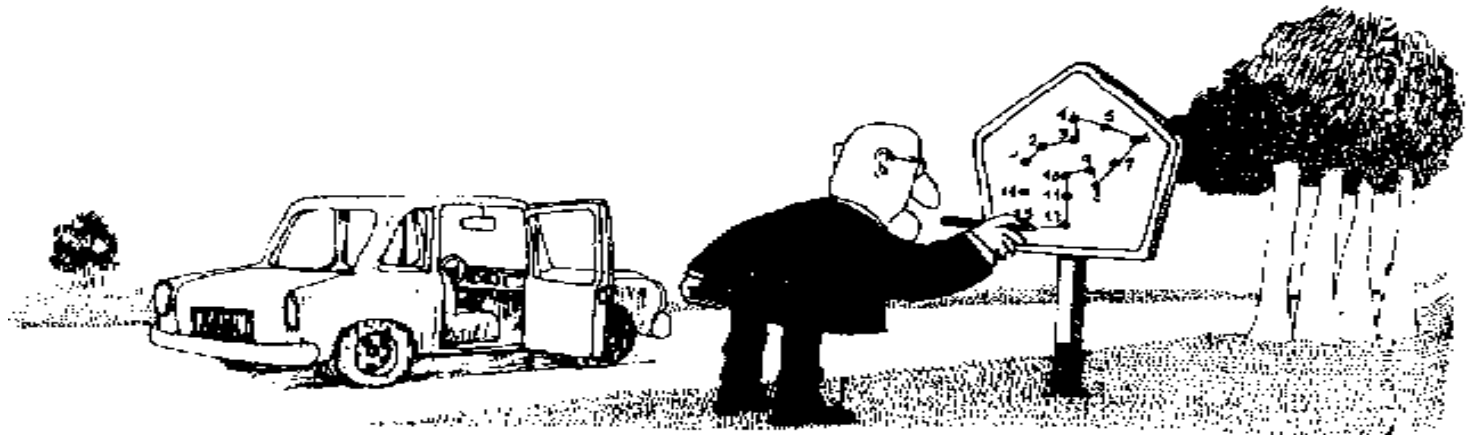
The AUGUSTUS Trial: la prova dell'Apixaban



Il Trial ENTRUST: la prova dell'Edoxaban



Qual è la direzione giusta?



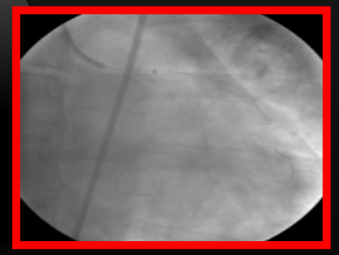
dare il giusto peso alle cose…

Cosa rappresentano i sanguinamenti ?

Associazione diretta tra morte e sanguinamenti fatali o intracranici.

Associazione con interruzione parziale o completa del regime antitrombotico.
Statine e Beta-bloccanti possono anche essere sospesi e poi non più ripresi.

A causa dei sanguinamenti maggiori possono essere necessari ricoveri
che portano ad una serie di test e procedure, con aumento del rischio di infezioni nosocomiali,
o altre sequele avverse.



Strategie per ridurre i sanguinamenti :

1. Ridurre il rischio di sanguinamenti periprocedurali con approccio radiale
2. Ridurre intensità anticoagulazione (warfarin) INR 2-2.5
3. Evitare i più nuovi inibitori $P2Y_{12}$ (i.e., prasugrel, ticagrelor) nella triplice terapia
4. Limitare la durata della triplice terapia
5. Eliminare asa dalla triplice terapia

Ma oggi, in un mondo in cui si dà troppo credito all'apparenza, forse vale ricordare che…l'apparenza inganna !

IL PAZIENTE REALE

- **Alto rischio trombotico ($CHADS_2VASC_2$ > 3)**
- **Alto rischio emorragico (HAS-BLED > 3)**
- **Insufficienza renale ed epatica**
- **Età avanzata (>80 anni)**
- **Cardiopatia ischemica**
- **Fibrillazione atriale persistente**
- **Scarsa compliance alla terapia**

IL PAZIENTE REALE

CHA2DS2-VASc

Stroke Risk Factor	Score
Congestive Heart Failure / LV Dysfunction	1
Hypertension	1
Age (≥ 75 years)	**2**
Diabetes	1
Prior **S**troke / TIA / thrombo-embolism	2
Vascular Disease1	**1**
Age 65-74	**1**
Sex **C**ategory (female)	**1**
Max Score	**9**

HAS-BLED risk criteria	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. age >65 yrs)	1
Drugs or alcohol (1 point each)	1 or 2

Necessità di valutazione del profilo di rischio trombotico ed emorragico

Take Home Messages

Nel paziente con fibrillazione atriale sottoposto a PCI:

- Il regime antitrombotico attualmente raccomandato è la triplice terapia → **warfarin/NAO + aspirina + clopidogrel (ESC 2017)**
- Durante la triplice terapia, vanno attuate misure per contenere rischio emorragico
- Si attendono i risultati dei trial non completati e degli studi in corso circa possibili ulteriori regimi antitrombotici
- Va presa ora in considerazione la duplice terapia con **DOACs + clopidogrel**

E’ importante la durata della vita,
ma anche la sua qualitá…