PROGRAMMA SCIENTIFICO

SOCIETÀ MEDICA DI SANTA MARIA NUOVA

L'Ospedale dei Fiorentini

Giornate Mediche di Santa Maria Nuova 2015

VII EDIZIONE

L'ECCELLENZA DELLE CURE IN OSPEDALE:

Santa Maria Nuova si confronta con la sua storia e con l'innovazione

2 - 3 Ottobre 2015

SABATO, 3 OTTOBRE 2015

09,00 Apertura dei lavori

TAVOLA ROTONDA

La terapia con i Nuovi Anticoagulanti orali: la gestione "sul campo" di una classe di farmaci innovativi

Moderatori: R. Abbate; G. Landini

09,10 I "prescrittori":

- Internista
  R. Laureano

- Cardiologo
  M. Milli

Terapia Anticoagulante

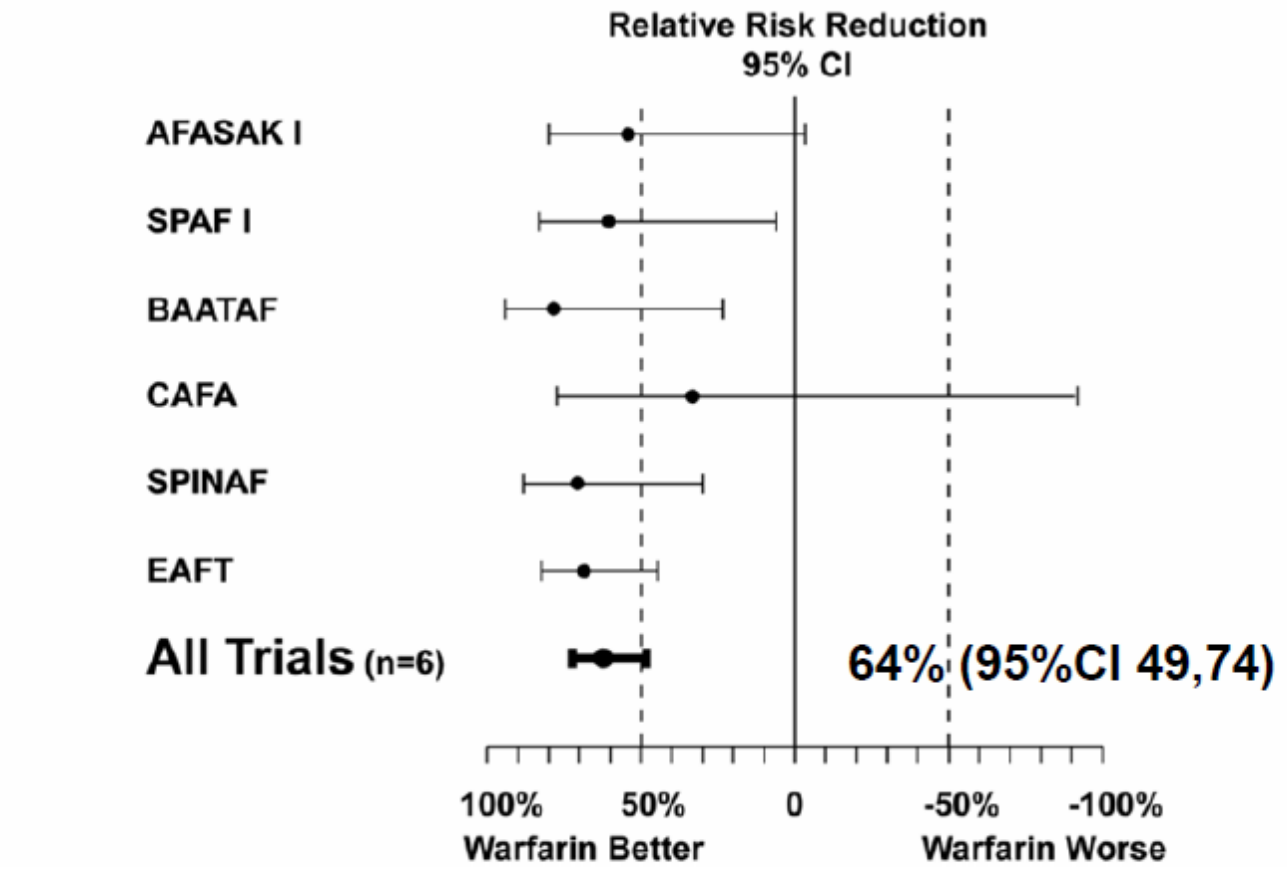
Terapia

- Trombosi arteriose
  - Sindrome coronarica acuta
  - Arteriopatie periferiche
  - Altri distretti
- Embolia polmonare
- Trombosi venose profonde

Profilassi

- Cardioembolismo
  - Protesi valvolari
  - FA non valvolare
  - Altre cardio-vasculopatie emboligene
- Profilassi TEV paziente chirurgico
- Profilassi TEV paziente medico
  - profilassi in Oncologia

Adjusted-dose Warfarin Compared with Placebo/Control



Hart RG, Pearce LA, Aguilar MI. *Ann Intern Med* 2007: 146: 857-67.

Anticoagulanti in prevenzione

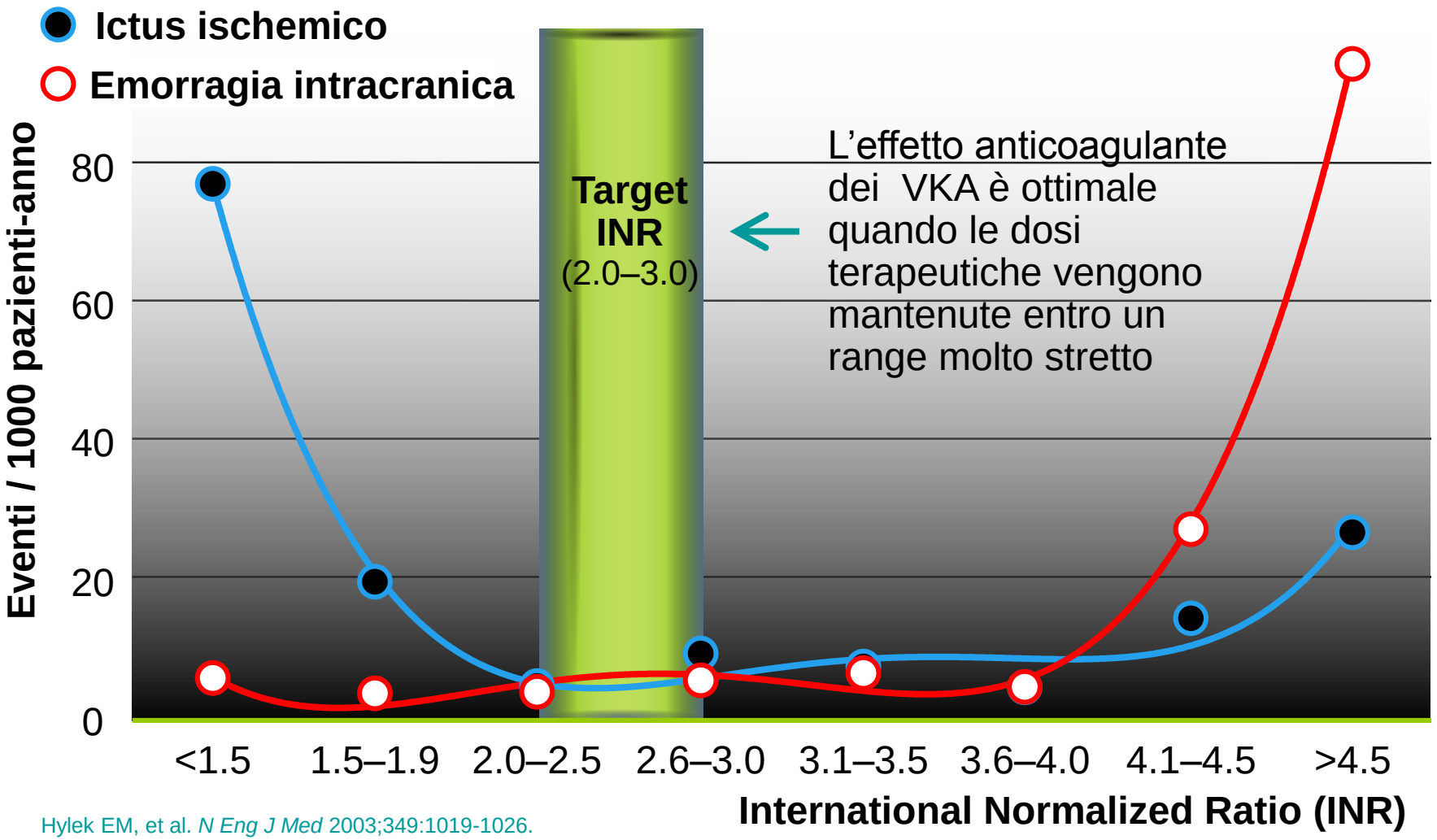
EBPM: Grande efficacia nella prevenzione (- 40-65%) e trattamento del TEV

TAO: riduzione del 64% di ictus CardioEmbolico in FA vs Placebo; (ASA – 19%)

MA

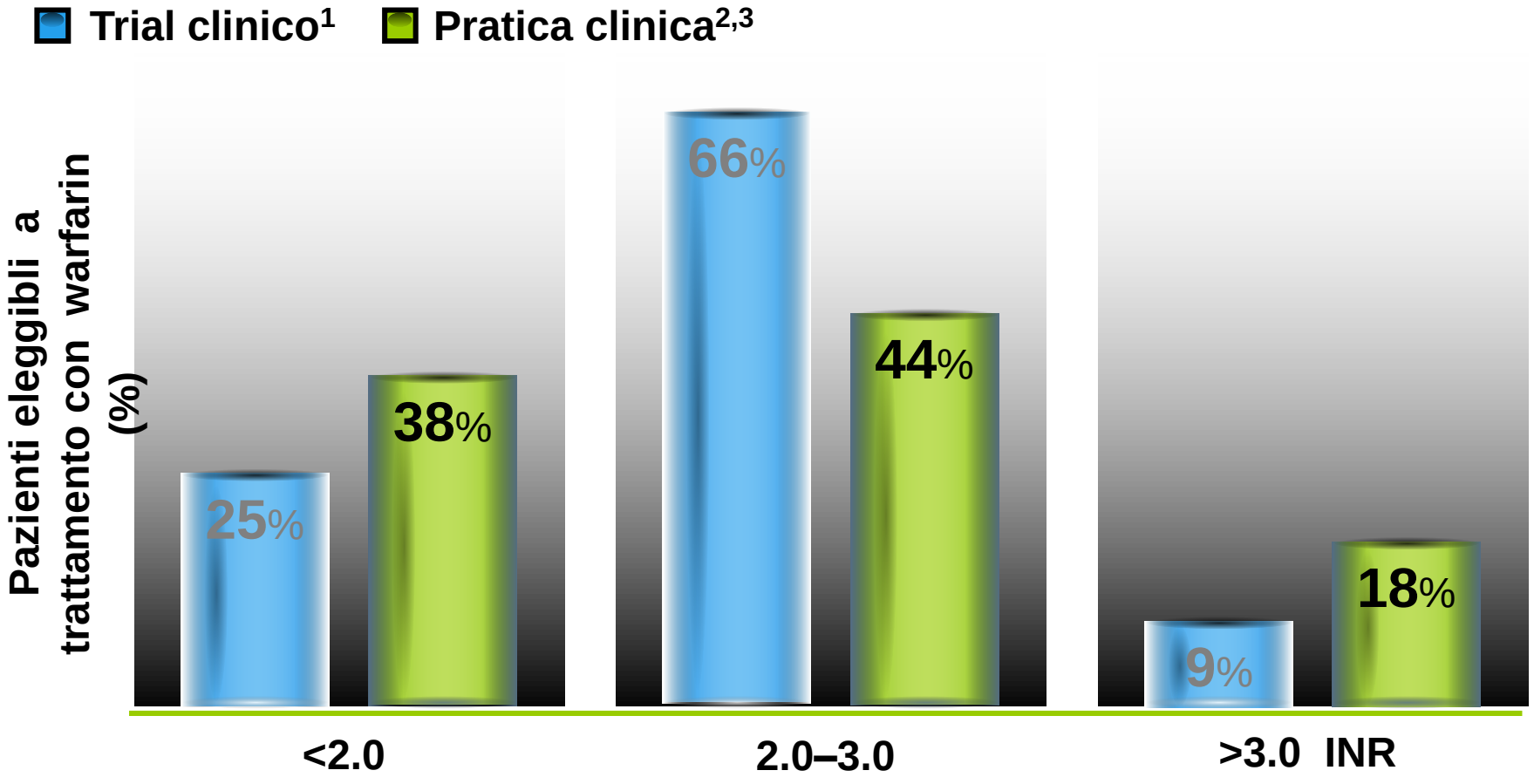
1. **Un significativo numero di pazienti con FA a rischio di stroke non riceve la TAO**
2. **L'intensità della scoagulazione è spesso al di fuori del range terapeutico (INR 2.0 – 3.0)**
3. **E' difficile mantenere nel tempo il range terapeutico**
4. **E' presente un rischio residuo di ictus ischemico (30%)**
5. **E' presente un rischio emorragico**

I VKA hanno un ristretto range terapeutico



Hylek EM, et al. *N Eng J Med* 2003;349:1019-1026.

Controllo dell'INR: Trials clinici vs pratica clinica (TTR)



INR = International Normalized Ratio ; TTR = Tempo in Range Terapeutico (INR 2.0–3.0).

1. Kalra L, et al. *Br Med J* 2000;320:1236-1239; *Pooled data: fino a 83–71% nei singoli trials.
2. Samsa GP, et al. *Arch Int Med* 2000; 160:967-973. 3. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

TTR warfarin nella pratica clinica

European Heart Journal
doi:10.1093/eurheartj/ehq278

ESC GUIDELINES

Guidelines for the management of atrial fibrillation

4.1.5 Optimal international normalized ratio

Currently, the level of anticoagulation is expressed as the INR, which is derived from the ratio between the actual prothrombin time and that of a standardized control serum.

Based on achieving a balance between stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2.0–3.0 is the likely optimal range for prevention of stroke and systemic embolism in patients with non-valvular AF.

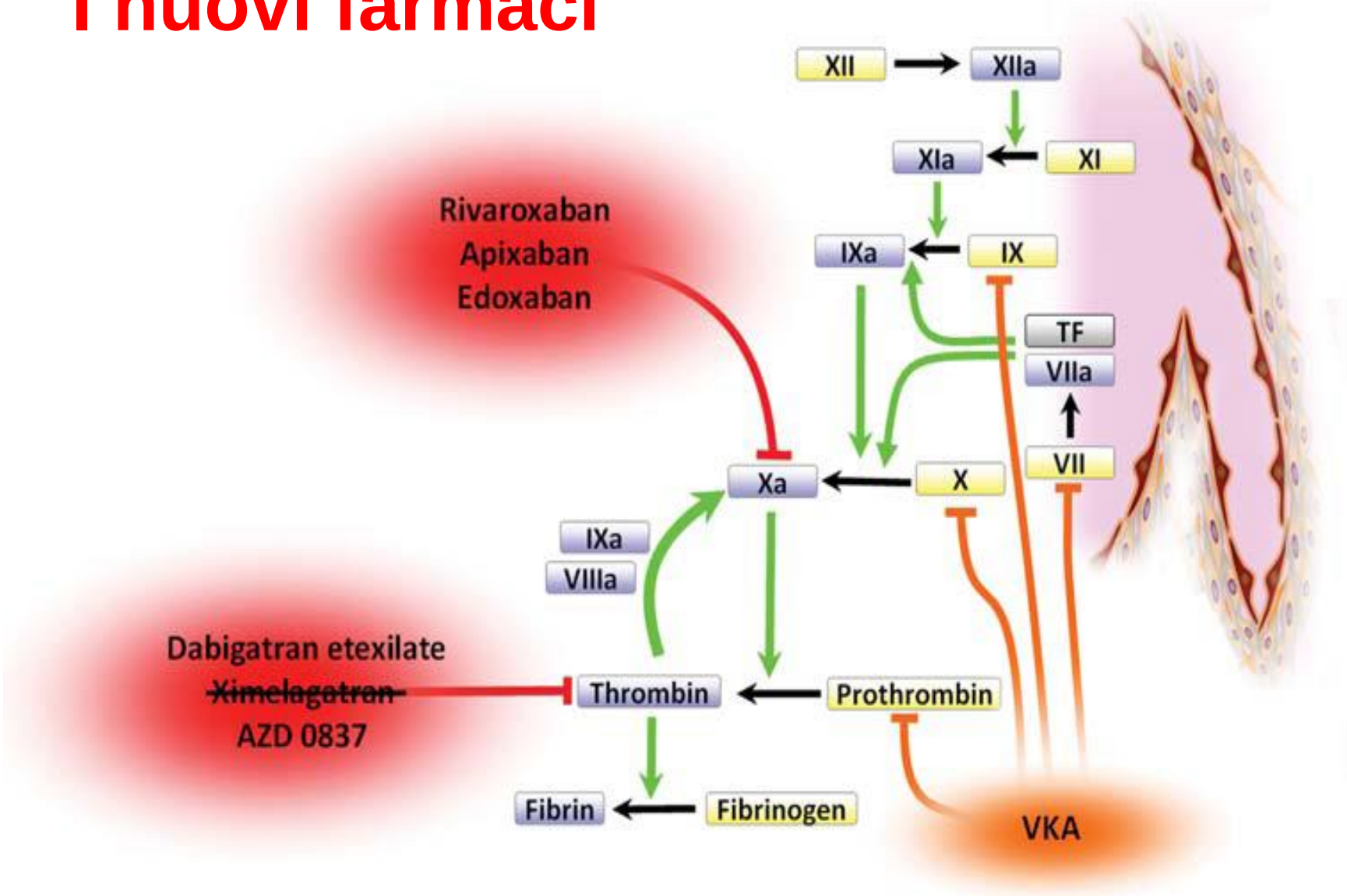
One of the many problems with anticoagulation with VKA is the high interindividual and intraindividual variation in INRs. VKAs also have significant drug, food, and alcohol interactions. On average, patients may stay within the intended INR range of 2.0–3.0 for 60–65% of the time in controlled clinical trials, but many 'real-life' studies suggest that this figure may be <50%. Indeed, having patients below the therapeutic range for <60% of the time may completely offset the benefit of VKA.

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European Heart Journal, 2010*
Guidelines for the management of atrial fibrillation

Obiettivi nello sviluppo di nuovi anticoagulanti

- effetto dose risposta prevedibile
- assenza interazioni con cibo e farmaci
- possibilità di somministrazione a dosi fisse senza monitoraggio di laboratorio
- semplificare terapia anticoagulante a lungo termine (via orale)

I nuovi farmaci



Jan Steffel and Eugene Braunwald, European Heart Journal (2011) 32, 1968–1976

	Atrial Fibrillation	DVT prevention	DVT treatment	ACS
Apixaban (Pfizer / BMS)	AVERROES ARISTOTLE	*Orthopaedic* ADVANCE 1 (49) ADVANCE-2 (50) ADVANCE-3 *Medical* ADOPT (NCT00457002) *Long-term secondary prevention* AMPLIFY-Ext (NCT00633893)	AMPLIFY (NCT00643201)	APPRAISE (54) APPRAISE-2 (NCT00831441)
Edoxaban (Daiichi Sankyo)	ENGAGE AF TIMI 48 (NCT00781391)		NCT00986154	
Dabigatran Etexilate (Boehringer Ingelheim)	Re-LY (13) RELY-ABLE (NCT00808067)	*Orthopaedic* RE-NOVATE (21) RE-MODEL (22) RE-MOBILIZE (69) *Long-term secondary prevention* RE-MEDY (NCT00329238) NCT00558259	RE-COVER (25) RE-COVER II (NCT00680186) RE-SONATE	RE-DEEM
Rivaroxaban (Bayer)	ROCKET-AF	*Orthopaedic* RECORD I (37) RECORD II (40) RECORD III (38) RECORD IV (39) *Medical* MAGELLAN (NCT00571649) *Long-term secondary prevention* EINSTEIN-Ext (42)	EINSTEIN-DVT (42) EINSTEIN-PE (NCT00439777)	ATLAS-TIMI 46 (43) ATLAS-TIMI 51 (NCT00809965)

Green, met pre-defined endpoint; red, did not meet pre-defined endpoint or was terminated early due to safety concerns (APPRAISE-2); black, ongoing.

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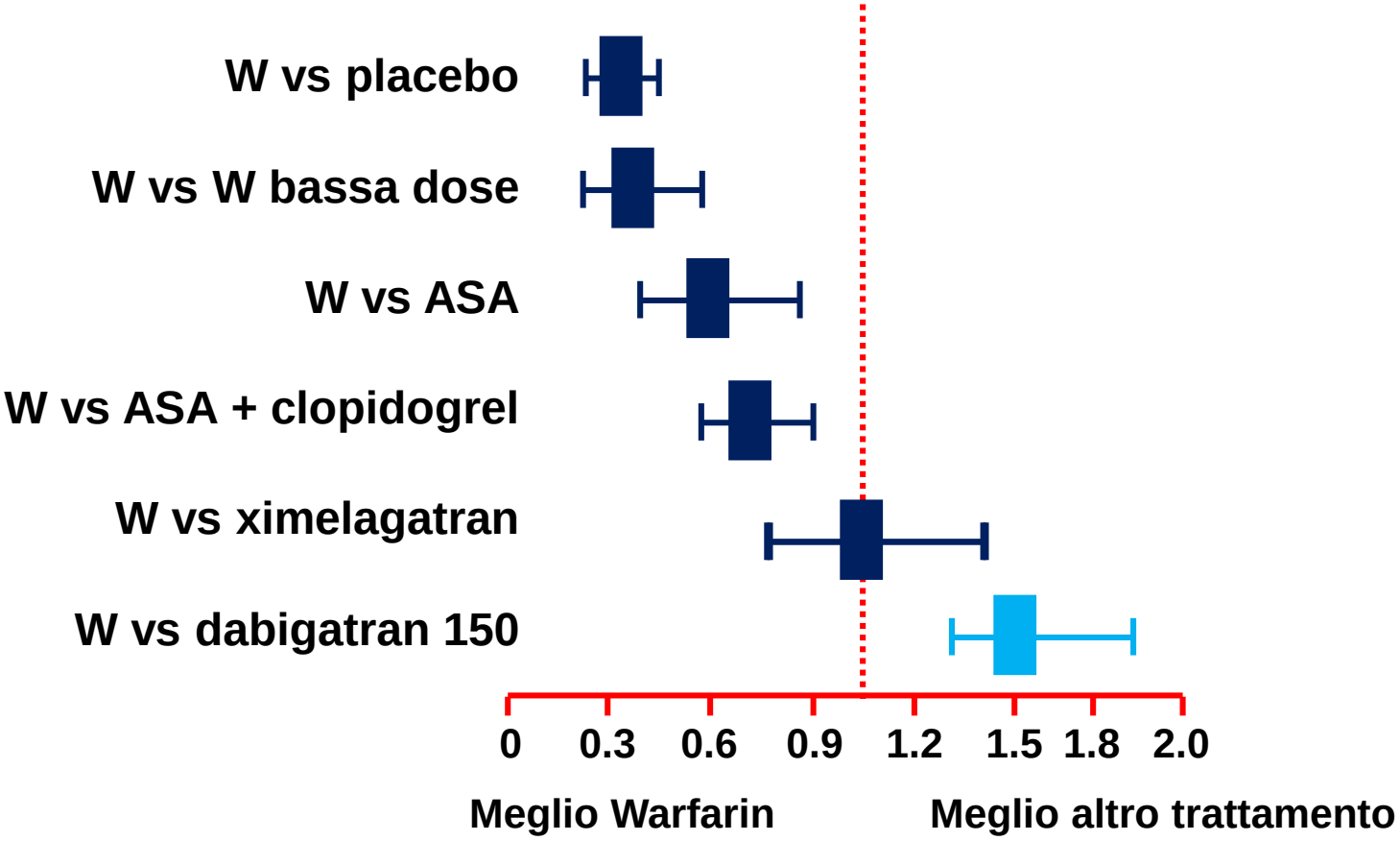
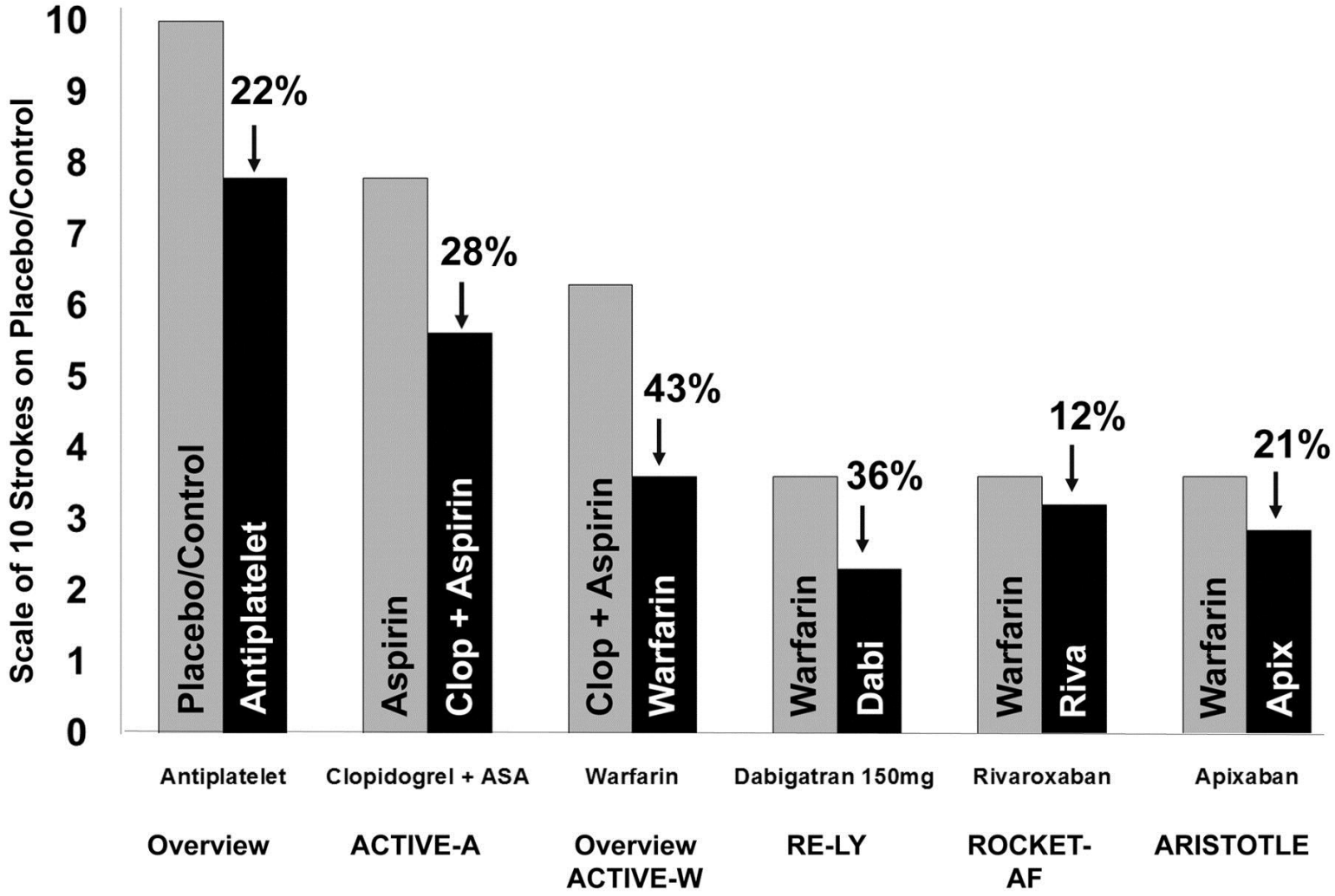
Indicazioni x NAO

RE-LY®: il primo studio clinico in cui il gigante (warfarin) esce “ridimensionato dopo 50 anni”



Camm J.: Oral presentation at ESC on Aug 30th 2009.

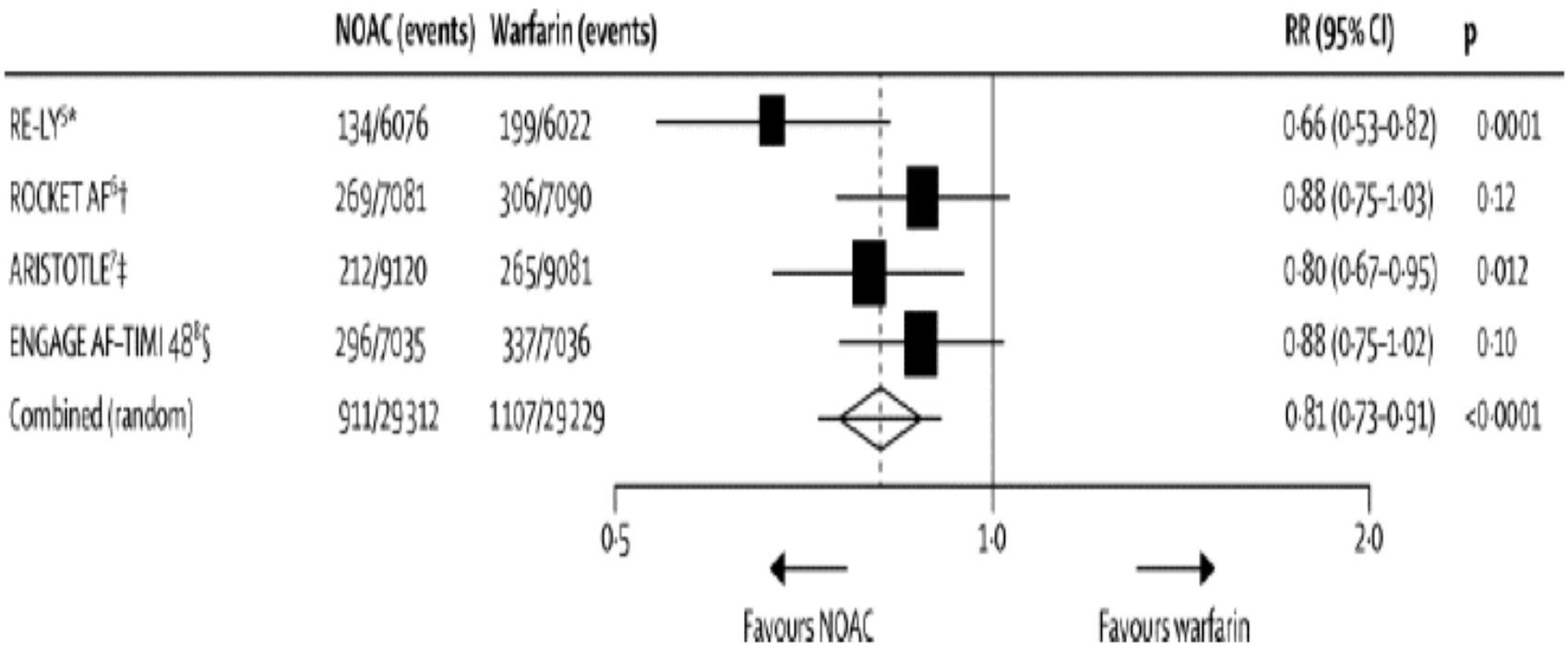
Stroke risk reductions from randomized trials of antithrombotic agents in atrial fibrillation.



Granger C B , and Armaganijan L V Circulation 2012;125:159-164

American Heart Association
Learn and Live

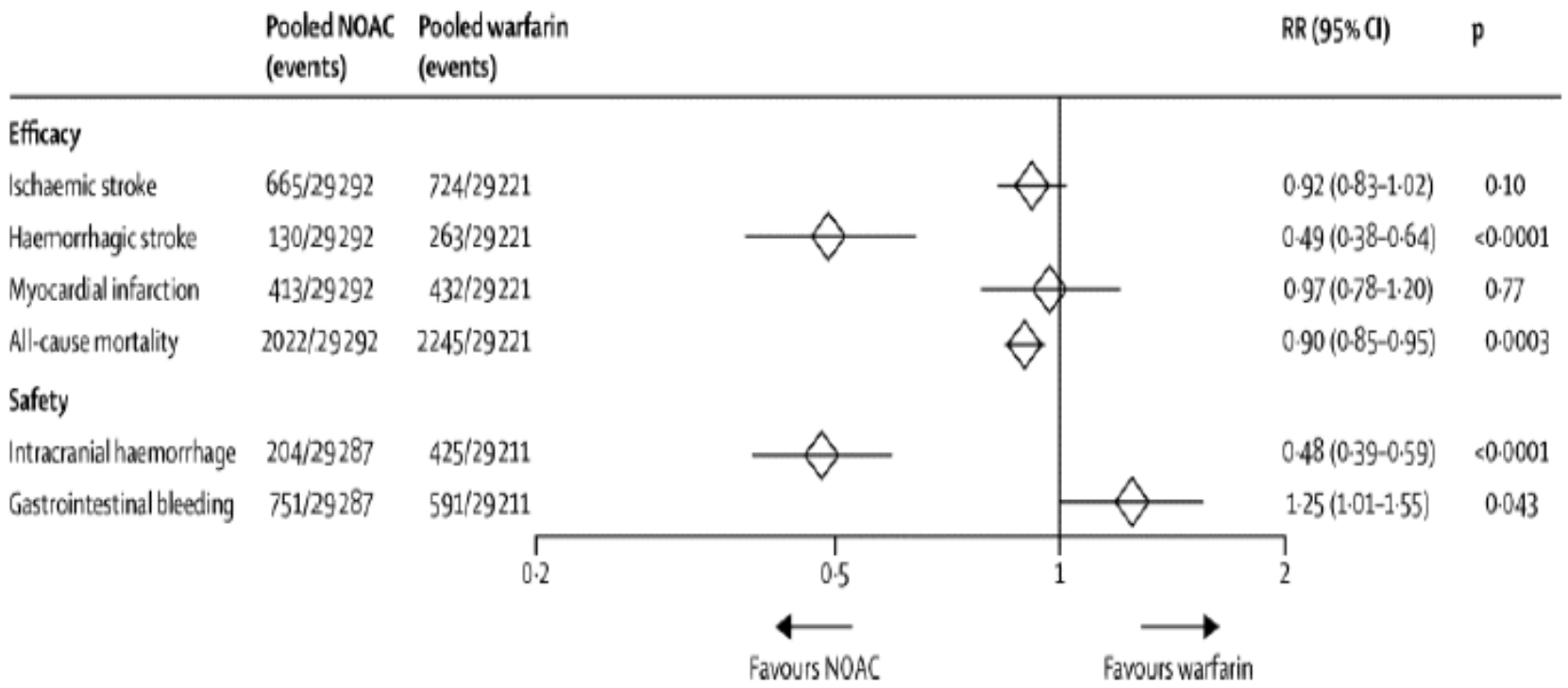
Stroke or systemic emboli (primary outcome events) in 4 large randomized trials comparing DOACs with high-quality warfarin anticoagulation



Data shown are for higher dosages of dabigatran (150mg twice daily) and edoxaban (60mg daily).

Ruff CT et al. *Lancet* 2013 (on-line Dec 4th)

Individual outcomes in 4 large randomized trials comparing DOACs with high-quality warfarin anticoagulation*



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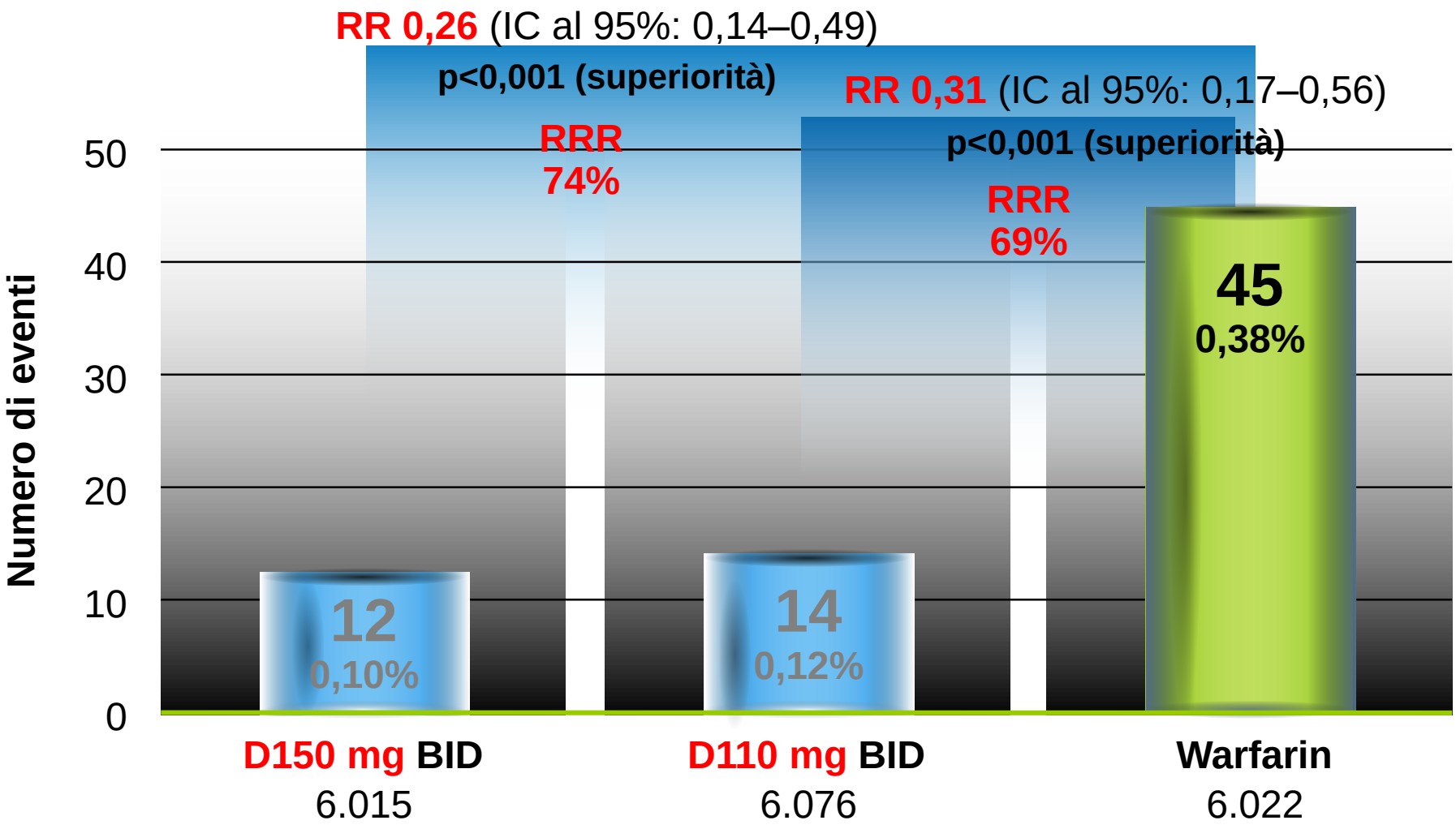
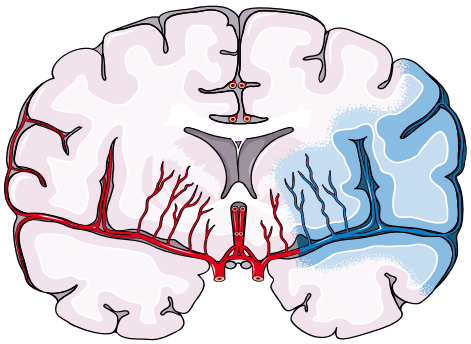
Ruff CT et al. *Lancet* 2013 (on-line Dec 4th)

Ictus emorragico



Connolly SJ, et al. N *Engl J Med* 2009;361:1139-1151.

Ictus emorragico

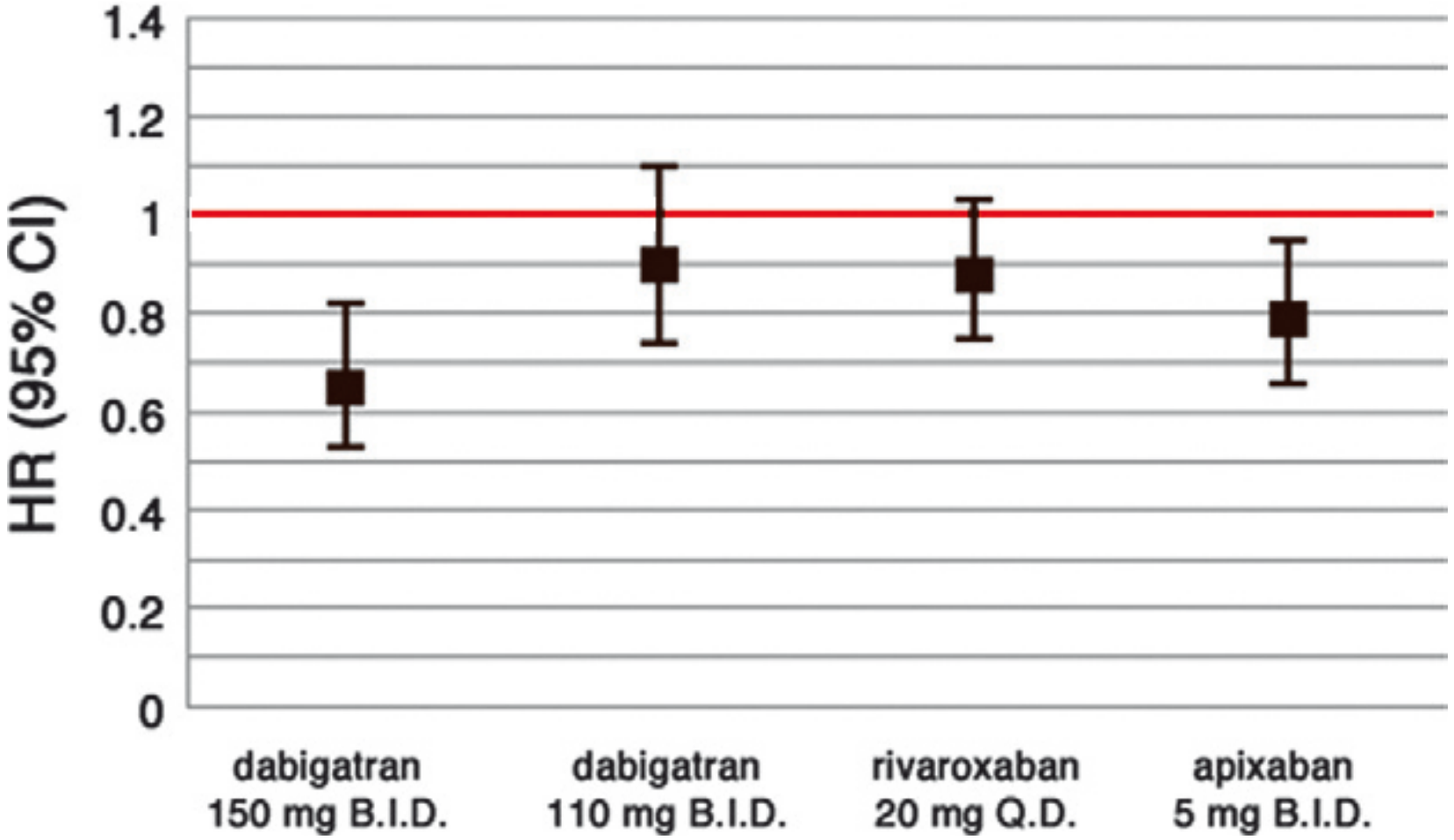


Proteine vitamina K dipendenti

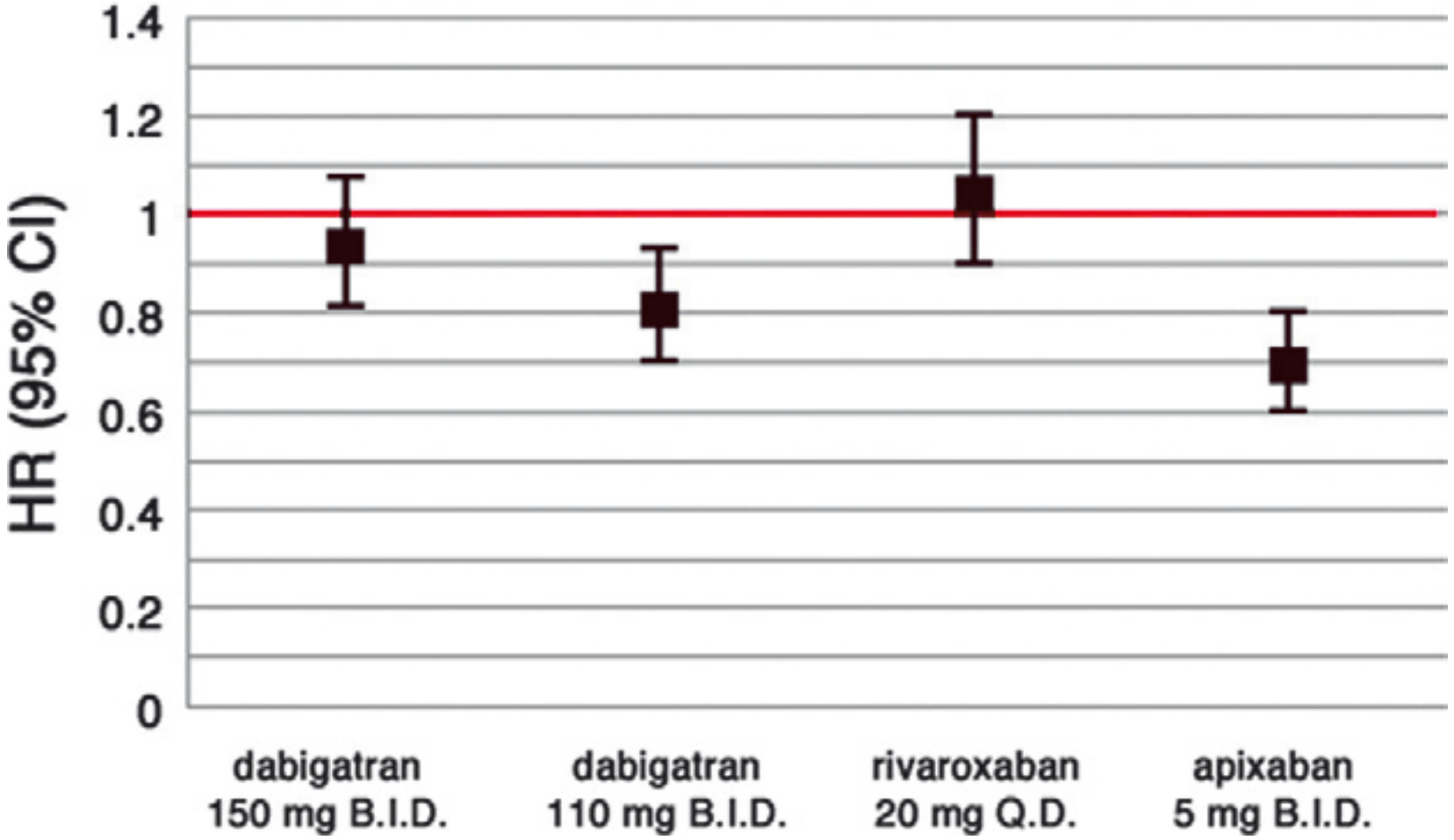
proteina Matrix GLA (o MGP)

Emorragie cerebrali

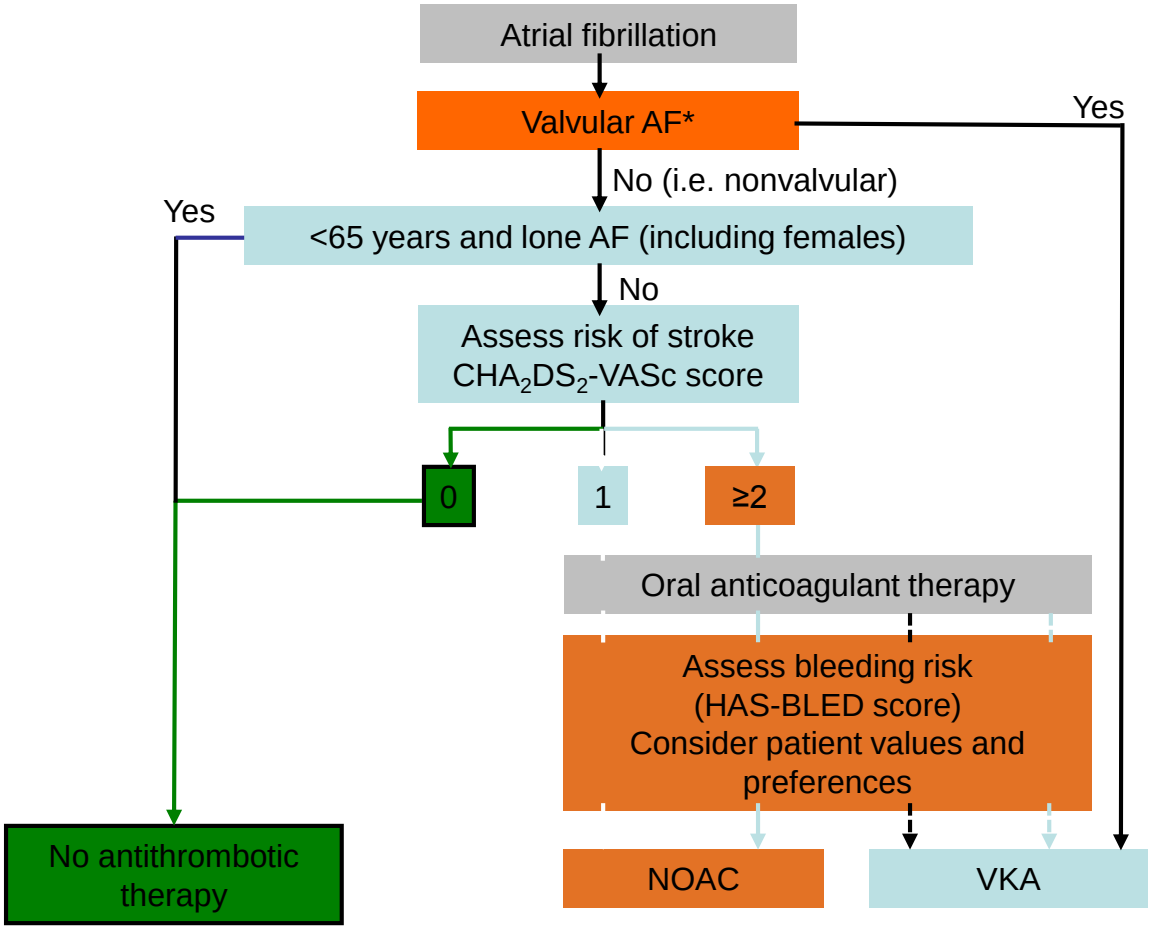
Confronto tra gli endpoint primari di efficacia di dabigatran, rivaroxaban e apixaban rispetto al warfarin



Confronto tra gli endpoint primari di sicurezza (sanguinamenti maggiori) di dabigatran, rivaroxaban e apixaban rispetto al warfarin



2012 focused update of the ESC Guidelines for the management of atrial fibrillation



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Opzione preferibile

alternativa

Camm AJ et al. Eur Heart J

Nuovi Anticoagulanti Orali (NAO): a quali pazienti?

1. **Pz con difficoltà di accesso o adesione controlli**
2. **Pazienti con elevato rischio ischemico**
3. **Politrattati per rischio interferenze**
4. **Nuovi pazienti che non vogliono intraprendere TAO**
5. **Pz con PT INR non adeguatamente controllato**
6. **Pz in FA con pregressa emorragia cerebrale**

Things to know about the DOACs

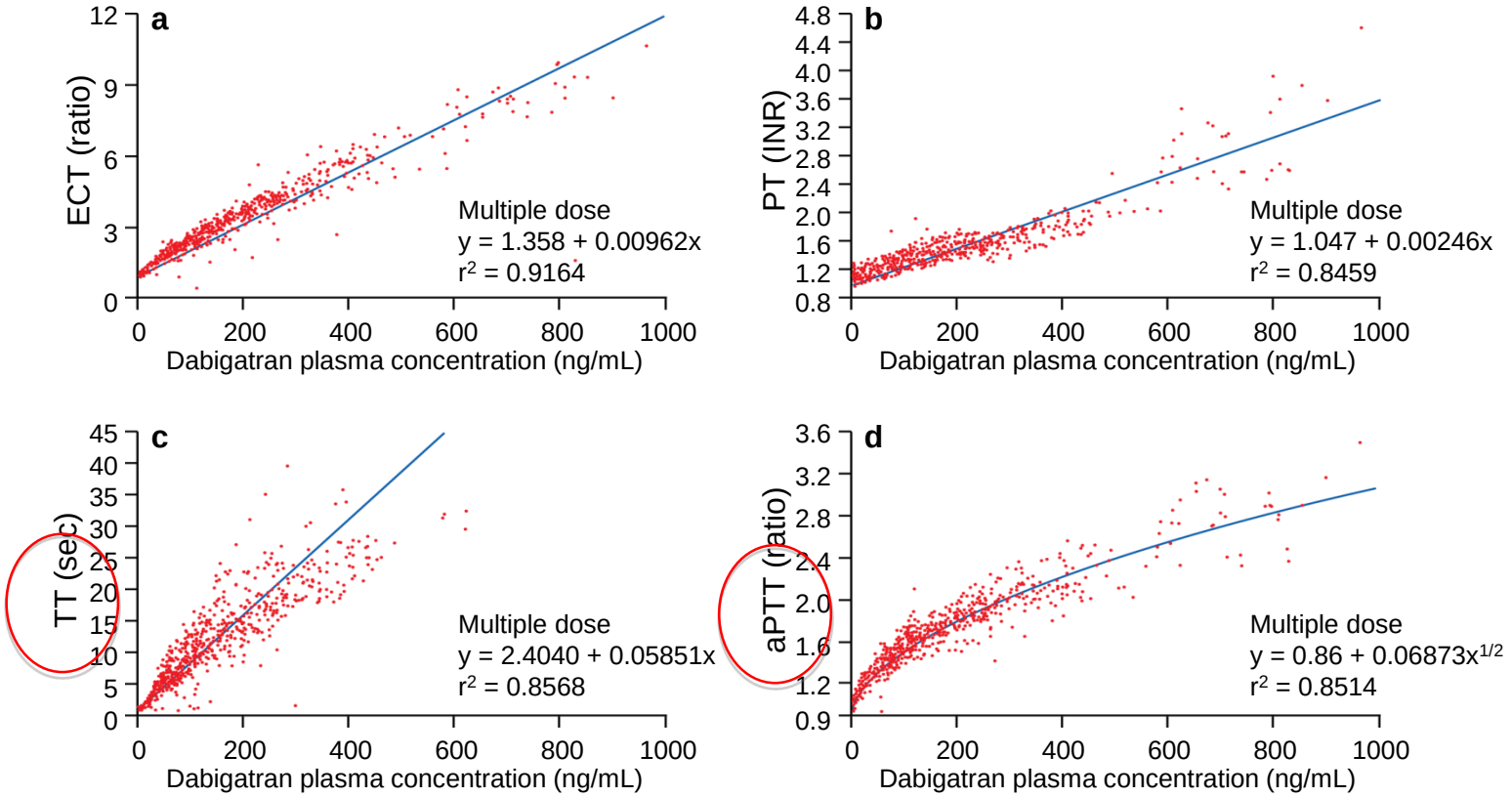
1. More favorable benefit/risk profile vs. warfarin in atrial fibrillation, with sharply reduced intracranial bleeding
2. Lack of antidote an over-emphasized.
3. Not just "easy-to-use warfarin"; don't work for all anticoagulation indications.
4. Each DOAC has different dosing and specific issues; how to choose?
5. Regular follow-up is required.

Table I Effect on new oral anticoagulant plasma levels ('area under the curve, AUC') from drug–drug interactions and recommendations towards new oral anticoagulant dosing

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[39]	no data yet	no effect[40]	no effect[41, 42]
Digoxin	P-gp competition	no effect [43]	no data yet	no effect[40]	no effect[42, 44]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[45] (reduce dose and take simultaneously)	no data yet	+53% (SR)[40] (Reduce dose by 50%)*	minor effect (use with caution if CrCl 15-50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	no effect[45]	+40%[SmPC]	no data yet	minor effect (use with caution if CrCl 15-50 ml/min)
Quinidine	P-gp competition	+50%	no data yet	+80%[40] (Reduce dose by 50%)§	+50%
Amiodarone	P-gp competition	+12-60%[45]	no data yet	no effect[40]	minor effect (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	[illegible]	no data yet	+85% (Reduce dose by 50%)*	[illegible]
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	[illegible]	[illegible]	no data yet	[illegible]

fluconazole	moderate CYP3A4 inhibition	no data yet	no data yet	no data yet	+42% (if systemically administered)[42]
Cyclosporin; tacrolimus	P-gp competition	no data yet	no data yet	no data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15-20%	no data yet	no data yet	+30-54%[42, 46]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	no data yet	Strong [illegible]	no data yet	up to x [illegible]
Rifampicin; St. John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	[illegible]	[illegible]	-35%	up to -50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	-12-30%[45, 48, 49]	no data yet	no effect	no effect[50, 51]
Other factors:					
Age ≥ 80 years	Increased plasma level			no data yet	
Age ≥75 years	Increased plasma level			no data yet	
Weight ≤ 60 kg	Increased plasma level			[52]	
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

NO monitoraggio, SI misurazione
(in alcuni setting particolari)



INR non è sufficientemente sensibile e non può essere raccomandato

van Ryn J et al. Thromb Haemost 2010;103:1116–27

Monitoring

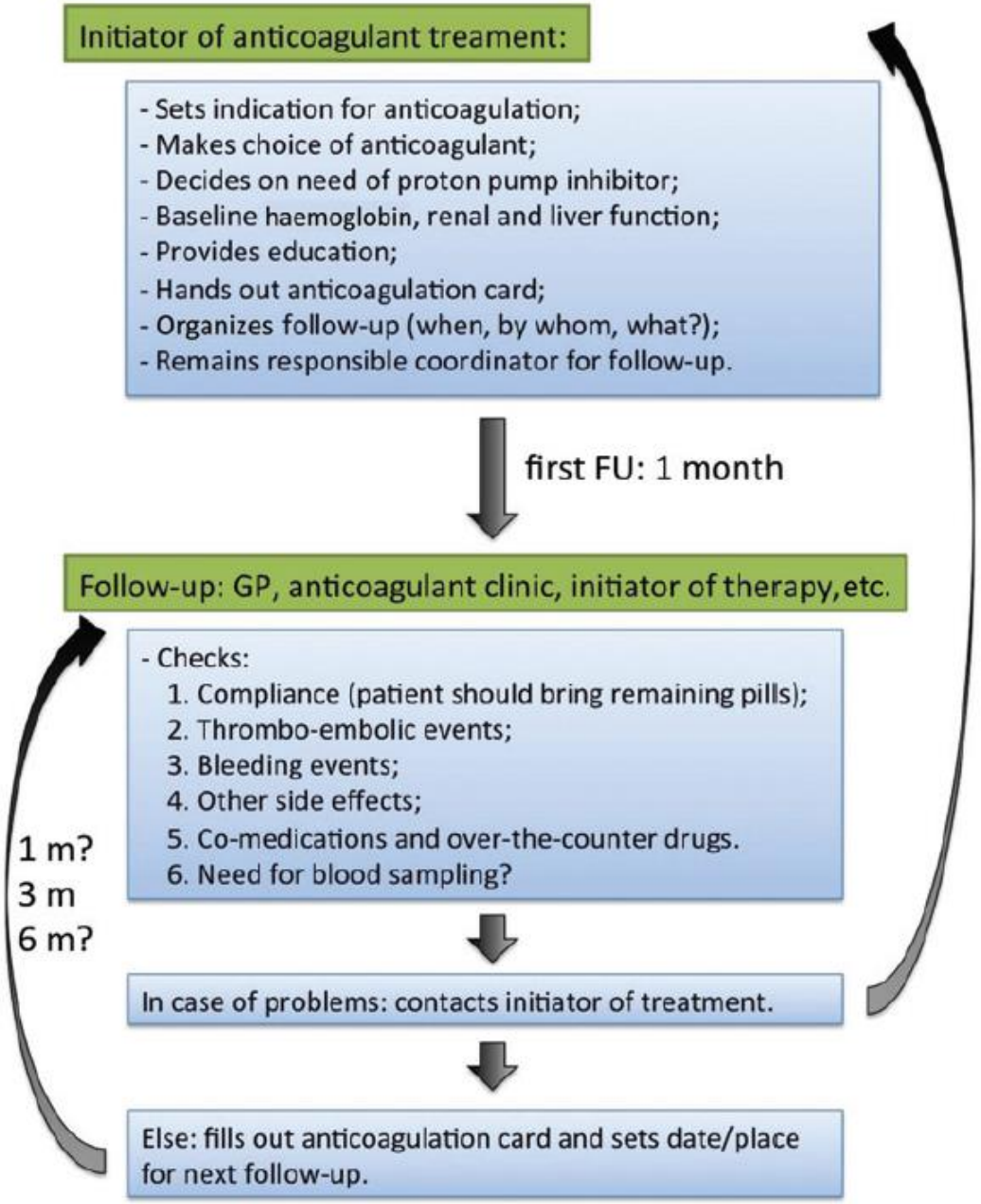
- Dabigatran
  - aPTT
  - Anti-IIa activity
- Xa inhibitors
  - INR
  - Prothrombin time
  - Anti-Xa levels

AZIENDA SANITARIA FIRENZE

TERAPIA ANTICOAGULANTE: GUIDA ALL'USO DEI NUOVI FARMACI ANTICOAGULANTI

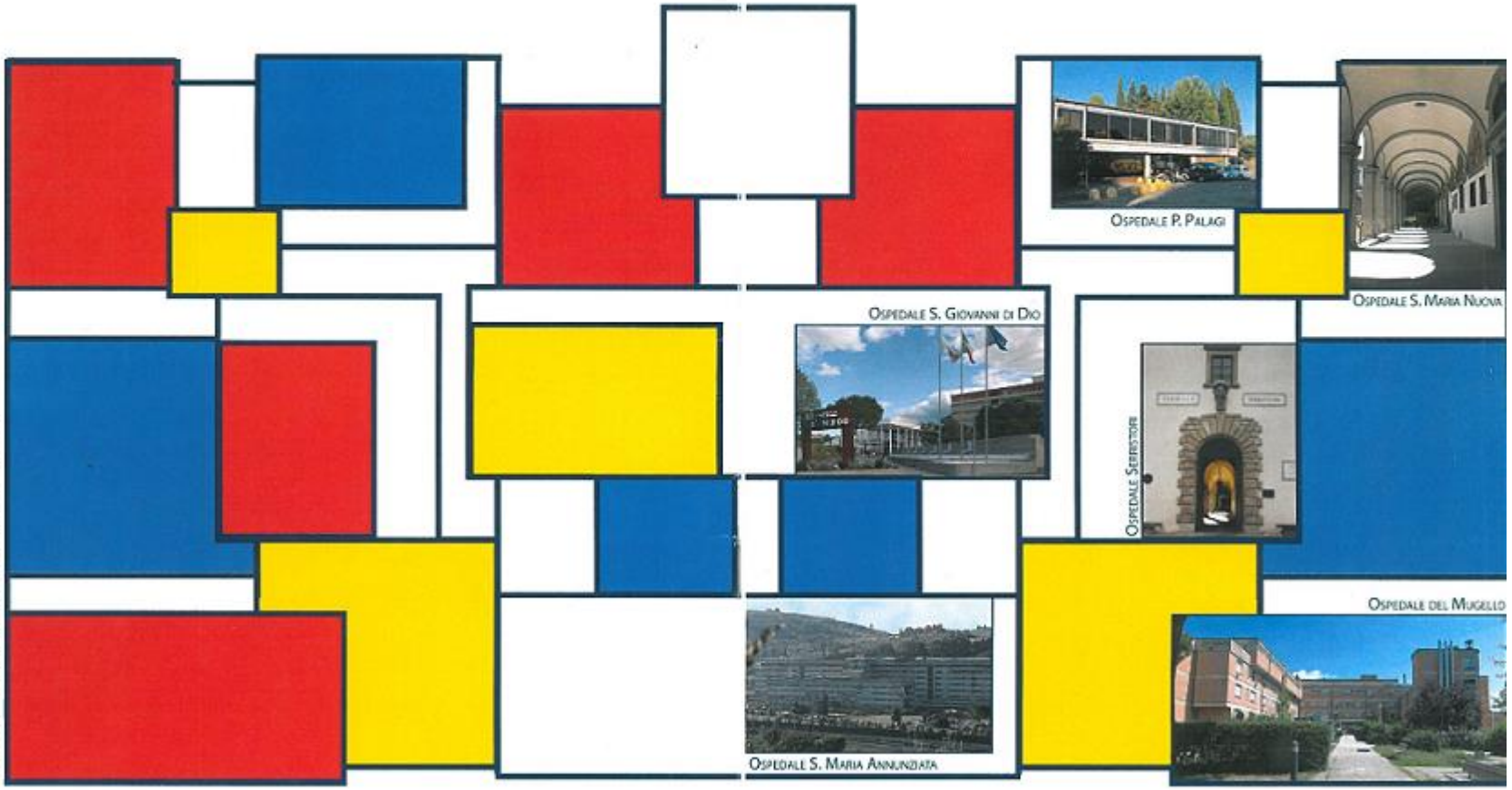
FOLLOW UP

- Compliance
- Eventi tromboembolici
- Eventi emorragici
- Altri effetti indesiderati
- Terapia associata
- Creatinina, Cr. Clearance, Hb, funzione epatica


Initiator of anticoagulant treament:
- Sets indication for anticoagulation;
- Makes choice of anticoagulant;
- Decides on need of proton pump inhibitor;
- Baseline haemoglobin, renal and liver function;
- Provides education;
- Hands out anticoagulation card;
- Organizes follow-up (when, by whom, what?);
- Remains responsible coordinator for follow-up.
first FU: 1 month
Follow-up: GP, anticoagulant clinic, initiator of therapy, etc.
- Checks:
1. Compliance (patient should bring remaining pills);
2. Thrombo-embolic events;
3. Bleeding events;
4. Other side effects;
5. Co-medications and over-the-counter drugs.
6. Need for blood sampling?
1 m?
3 m
6 m?
In case of problems: contacts initiator of treatment.
Else: fills out anticoagulation card and sets date/place for next follow-up.

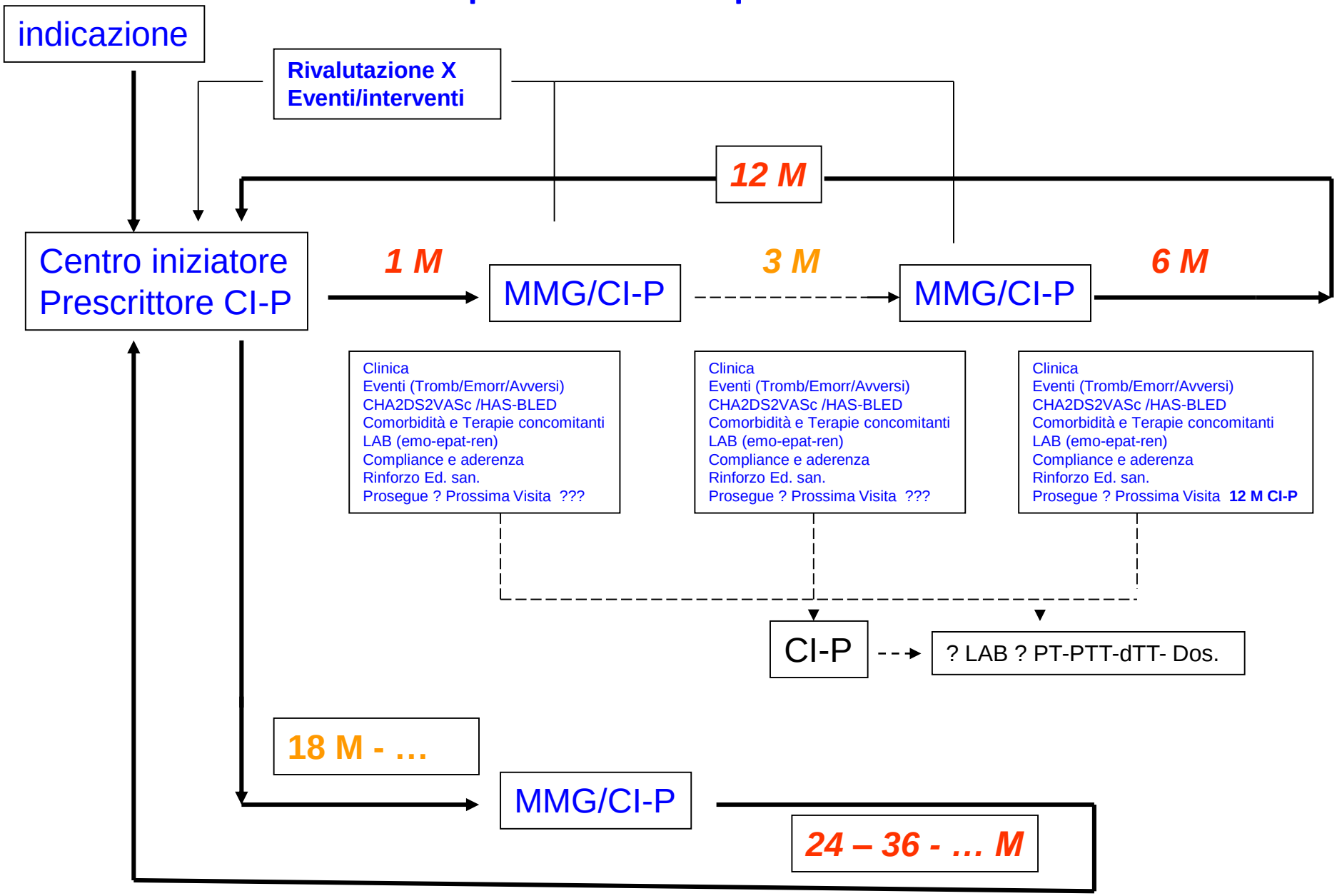
TERAPIA ANTICOAGULANTE

GUIDA ALL'USO DEI NUOVI FARMACI ANTICOAGULANTI ORALI



TPX 4098 Impaginazione a cura di Tipografia ASF - R.F.

Proposta di follow-up strutturato



Prescrizioni di NAO
Dispensazione da Farmacie Ospedaliere + DPC (ritiro cfn)
Firenze gennaio – giugno 2015

N conf x terapia mensile (30/60 cp)

	DABI 110	DABI 150	APIX 2,5	APIX 5	RIVA 15	RIVA 20
OSP	*1156*	*538*	*453*	*485*	*566*	*833*
DPC	*3340*	*1392*	*1090*	*1280*	*1648*	*3280*
Tot	4496	1930	1543	1765	2214	4113
= N. Pz x 6 m	750	321	257	294	369	685

Tot. NAO Area FI: 2676 Paz. (bassa dose 1376, Alta dose 1300)

Ettore Saffi Giustini. La prescrizione e il farmaco. Vademecum sull'attività prescrittiva in medicina generale. Maggio 2015