FIBRILLAZIONE ATRIALE ED ICTUS CARDIOEMBOLICO

Roma, 13 giugno 2014

GESTIONE INTEGRATA DEL PAZIENTE CON FIBRILLAZIONE ATRIALE

Pasquale Perrone Filardi
Università Federico II, Napoli

Anticoagulation - NOACs

Recommendations for prevention of thromboembolism in non-valvular AF - NOACs		
Recommendations	**Class**	**Level**
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)d … is recommended.	I	B
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)d … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253
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Frequency, Patient Characteristics, Treatment Strategies, and Resource Usage of Atrial Fibrillation (from the Italian Survey of Atrial Fibrillation Management [ISAF] Study).

Zoni-Berisso M, Filippi A, Landolina M, Brignoli O, D'Ambrosio G, Maglia G, Grimaldi M, Ermini G.

Am J Cardiol. 2013 Mar 1;111(5):705-11



- Dei 295.906 pazienti analizzati, rappresentativi della popolazione italiana,
  6.036 (2,04%) presentavano FA:
  - **20,2% parossistica**
  - **24,3% persistente**
  - **55,5% FA permanente**
- La FA si è verificata nello **0,16%** dei pazienti con età compresa tra **16 e 50 anni**, nel **9,0%** dei pazienti con età compresa tra **76 e 85 anni** e nel **10,7%** di quelli con **età ≥85 anni**.
- La FA era sintomatica nonostante la terapia nel 74,6% dei pazienti e risultava associata a cardiopatie nel 75%.

- Tra i pazienti con FA:
  - **24,8%** presentava **insufficienza cardiaca**,
  - **26,8%** presentava **insufficienza renale**,
  - **18%** presentava **ictus/attacco ischemico transitorio,**
  - **29,3%** presentava **≥3 co-morbidità**.
- Il **controllo della frequenza cardiaca** veniva attuato nel 55% dei pazienti.
- Dei 6.036 pazienti con FA, il **46%** era in **terapia con anticoagulanti.**
- La percentuale di successo dell'ablazione del catetere era del 50%.

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Current presentation and management of 7148 patients with atrial fibrillation in cardiology and internal medicine hospital centers: The ATA AF study☆

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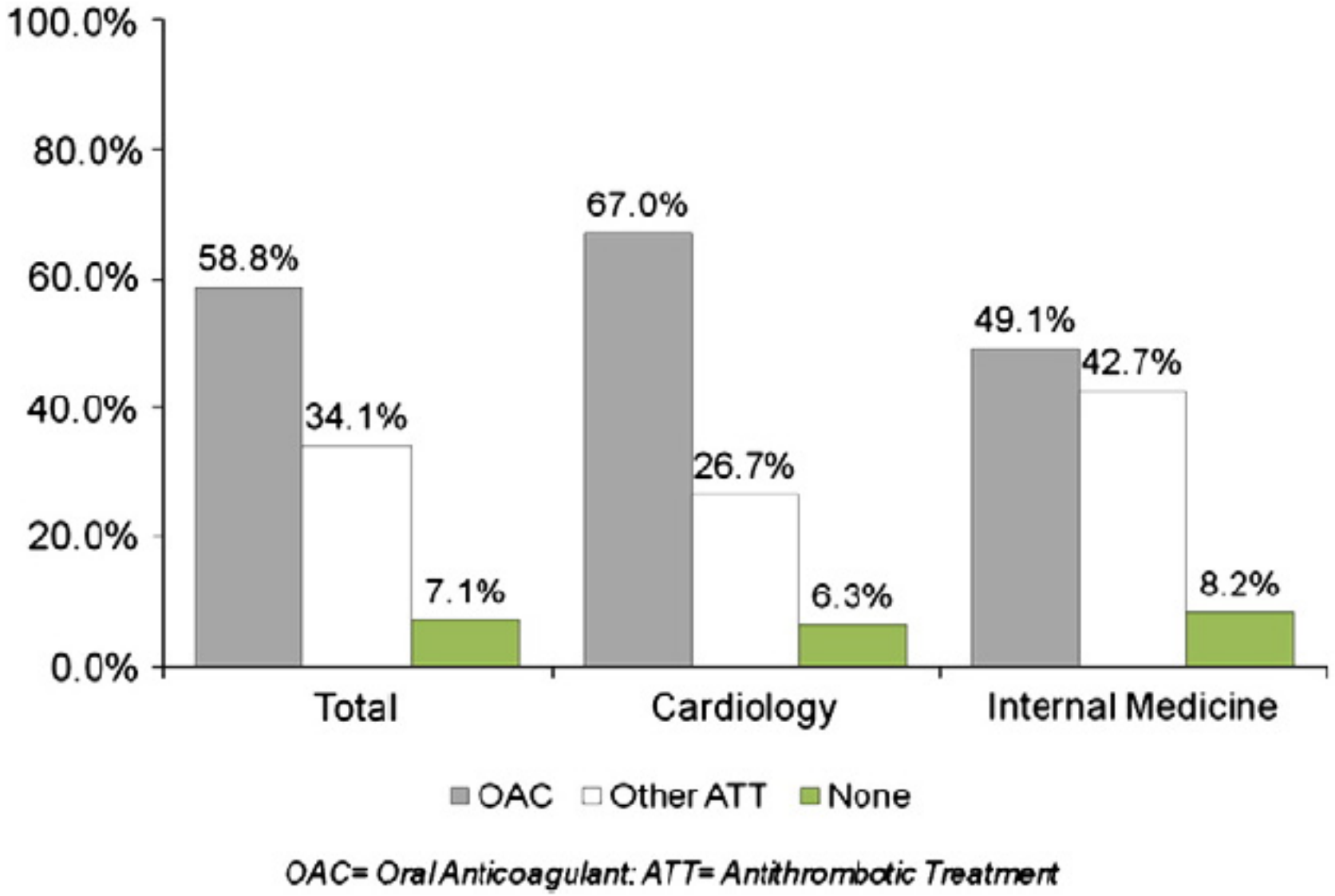


Fig. 2. Antithrombotic treatment in the total population of patients and by setting of enrollment.

Table 2 Risk Differences and Confidence Intervals, in Relation to Differences in the Study Populations at Baseline

Baseline Characteristics	RE-LY (N = 18,113)	ROCKET-AF (N = 14,264)	ARISTOTLE (N = 18,201)	RE-LY vs. ROCKET-AF	RE-LY vs. ARISTOTLE Percent Point (% Study 1; % Study 2)	ROCKET-AF vs. ARISTOTLE Percent Point (% Study 1; % Study 2)
Age, yrs*	71.5 ± 8.7	73 [65–78]	70 [63–76]	—	—	—
Female, %	36.4	39.7	35.2	−3.3 (−4.3; −2.2)	1.1 (0.2; 2.2)	4.5 (3.3; 5.5)
$CHADS_2$, mean	2.2	3.5	2.1	−1.26 (−1.28; −1.23)	0.1 (0.08; 0.12)	1.36 (1.34; 1.38)
$CHADS_2$ 3–6, %	32.5	87.0	30.2	−54.5 (−55.3; −53.6)	2.2 (1.3; 3.2)	56.7 (55.9; 57.6)
Paroxysmal AF, %	32.8	17.6	15.3	15.2 (14.3; 16.1)	17.5 (16.6; 18.4)	2.3 (1.5; 3.1)
Prior stroke, TIA, or systemic embolism, %	20.0	54.8	19.4	−34.8 (−35.8; −33.8)	0.6 (−0.03; 1.4)	35.3 (43.3; 36.3)
Heart failure, %	32.0	62.5	35.4	−30.5 (−31.5; −29.4)	−3.5 (−4.4; −2.5)	27.0 (26.0; 28.1)
Prior myocardial infarction, %	16.6	17.3	14.2	−0.7 (−1.5; 0.1)	2.4 (1.6; 3.1)	3.1 (2.3; 3.9)
Diabetes, %	23.3	40.0	25.0	−16.6 (−17.6; −15.6)	−1.7 (−2.6; −0.8)	14.9 (13.9;16.0)
Hypertension, %	78.9	90.5	87.5	−11.7 (−12.4; −10.9)	−8.6 (−9.4; −7.8)	3.1 (2.9; 3.7)
Medication						
Aspirin, %	39.8	36.5	30.9	3.3 (2.2; 4.3)	8.8 (7.8; 9.8)	5.5 (4.5; 6.6)
Vitamin K antagonist, %	49.6	62.4	57.2	−12.8 (−13.9; −11.7)	−7.5 (−8.5; −6.5)	5.3 (4.2; 6.3)

*Values for RE-LY: mean ± SD; for ROCKET-AF and ARISTOTLE: median [interquartile range].
AF = atrial fibrillation; TIA = transient ischemic attack; other abbreviations as in Table 1.

Caratteristiche generali dei pazienti (n=193) in terapia con NAO (al 30 aprile 2014)

Eta' (anni; media±DS);	74 ± 9		**Scompenso cardiaco**	83
>80 anni	58			
Sesso (maschi)	100		**Diabete mellito II**	54
CHA_2DS_2VASc (media±DS)	4 ± 1,6		**Pregresso Ictus cerebrale/TIA/ Episodio trombo-embolico**	54
numero pazienti per classe di rischio	**1**	6	**Ipertensione arteriosa**	179
	2	12	**IM, malattia arteriosa periferica o placca aortica**	68
	3	47	**Insufficienza renale cronica**	34
	4	40	**Insufficienza epatica**	2
	5	41	**Storia di sanguinamento o diatesi emorragica o anemia**	33
	6	27	**Terapia concomitante con antiaggreganti piastrinici**	45
	7	15	**con ASA o clopidogrel**	30
	8	3	**con ASA e clopidogrel**	15
	9	2	**Pazienti Naive**	70
HAS-BLED (media±DS)	2,9 ± 0,9		**Pazienti già in TAO**	123
numero pazienti per classe di rischio	**1**	15	**INR instabile con tempo in range terapeutico < 60%**	112
	2	43	**TTR (%; media±DS)**	48 ± 14,2
	3	78	**Pazienti in terapia con 220 mg/die**	116
	4	50	**Pazienti in terapia con 300 mg/die**	77
	5	6		



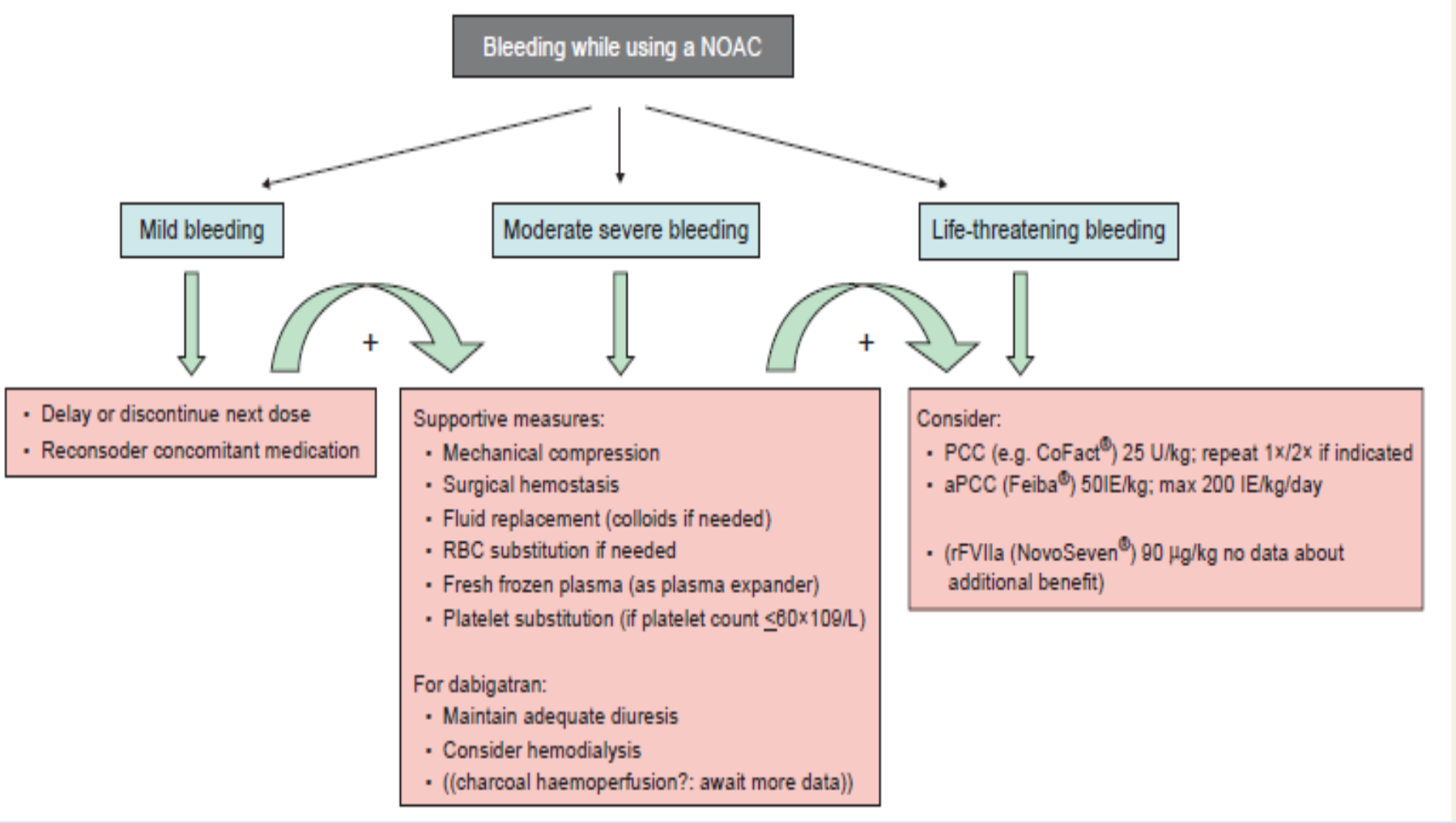
- Practical start-up and follow-up scheme for patients on new oral anticoagulants
- How to measure the anticoagulant effect of new oral anticoagulants?
- Drug–drug interactions and pharmacokinetics of new oral anticoagulants
- Switching between anticoagulant regimens
- Ensuring compliance with new oral anticoagulant intake ?
- How to deal with dosing errors?
- Patients with chronic kidney disease
- Management of bleeding and risk of bleeding
- Patients undergoing a planned surgical intervention or ablation
- Patients undergoing an urgent surgical intervention
- Patient with atrial fibrillation and coronary artery disease

General effects of thrombin and factor Xa inhibition by drugs such as dabigatran and rivaroxaban

Test	Thrombin inhibition	FXa inhibition
Routine anticoagulant assays		
PT	++	+++
INR	Not applicable	Not applicable
APTT	+++	+
ACT	++	+
TT	++++	Not affected
Drug-specific anticoagulant assays		
Chromogenic anti-FXa	Not affected	+++
Dilute plasma TT (e.g. Hemoclot)	+++	Not affected

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants inpatients with non-valvular atrial fibrillation

Management of bleeding in pts taking NOACs



Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

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European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants inpatients with non-valvular atrial fibrillation

Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation	Interventions with low bleeding risk
Dental interventions	Endoscopy with biopsy
Extraction of 1 to 3 teeth	Prostate or bladder biopsy
Paradontal surgery	Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
Incision of abscess	
Implant positioning	
Ophthalmology	Angiography
Cataract or glaucoma intervention	Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Endoscopy without surgery	
Superficial surgery	

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EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants inpatients with non-valvular atrial fibrillation

Classification of elective surgical interventions according to bleeding risk

Interventions with high bleeding risk

Complex left-sided ablation (pulmonary vein isolation; VT ablation)

Spinal or epidural anaesthesia; lumbar diagnostic puncture

Thoracic surgery

Abdominal surgery

Major orthopedic surgery

Liver biopsy

Transurethral prostate resection

Kidney biopsy

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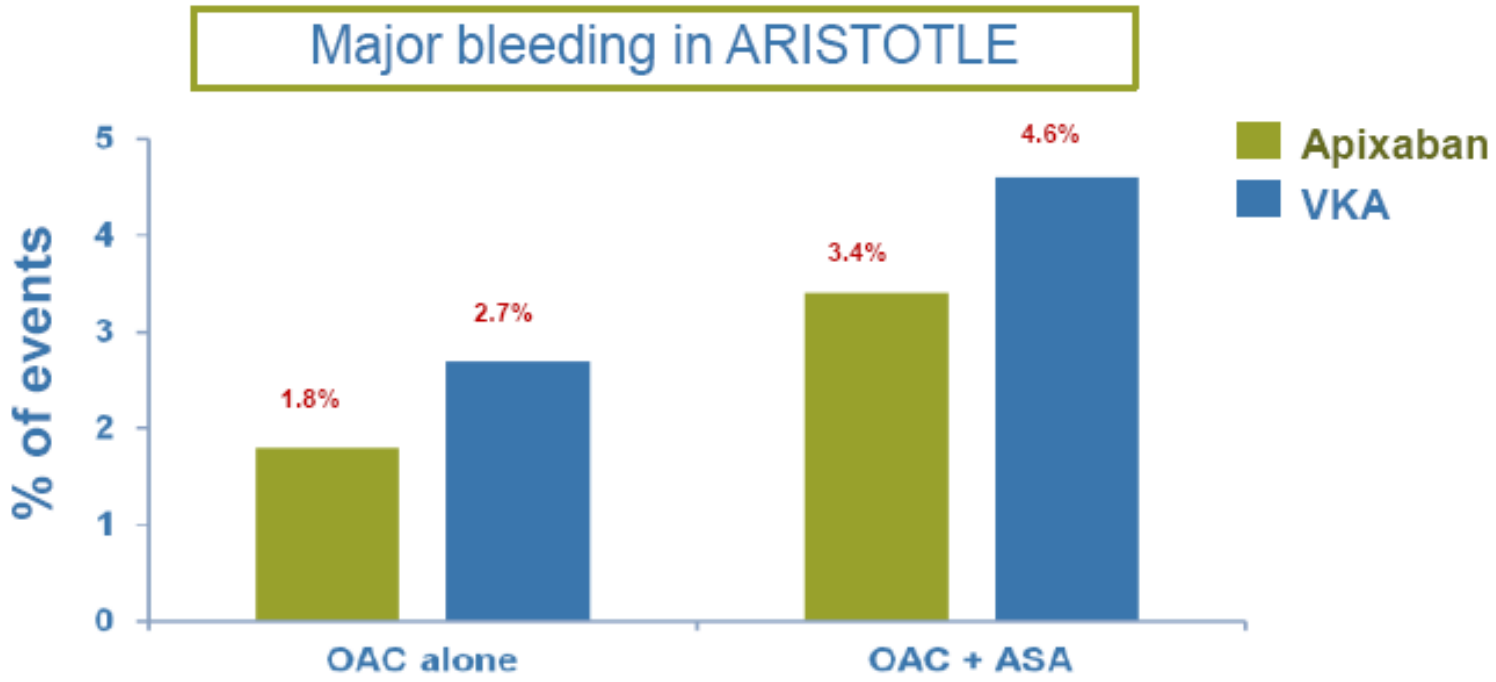
Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

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Apixaban and antiplatelet therapy in AF patients

In a clinical trial of patients with AF, concomitant use of ASA increased the major bleeding risk:

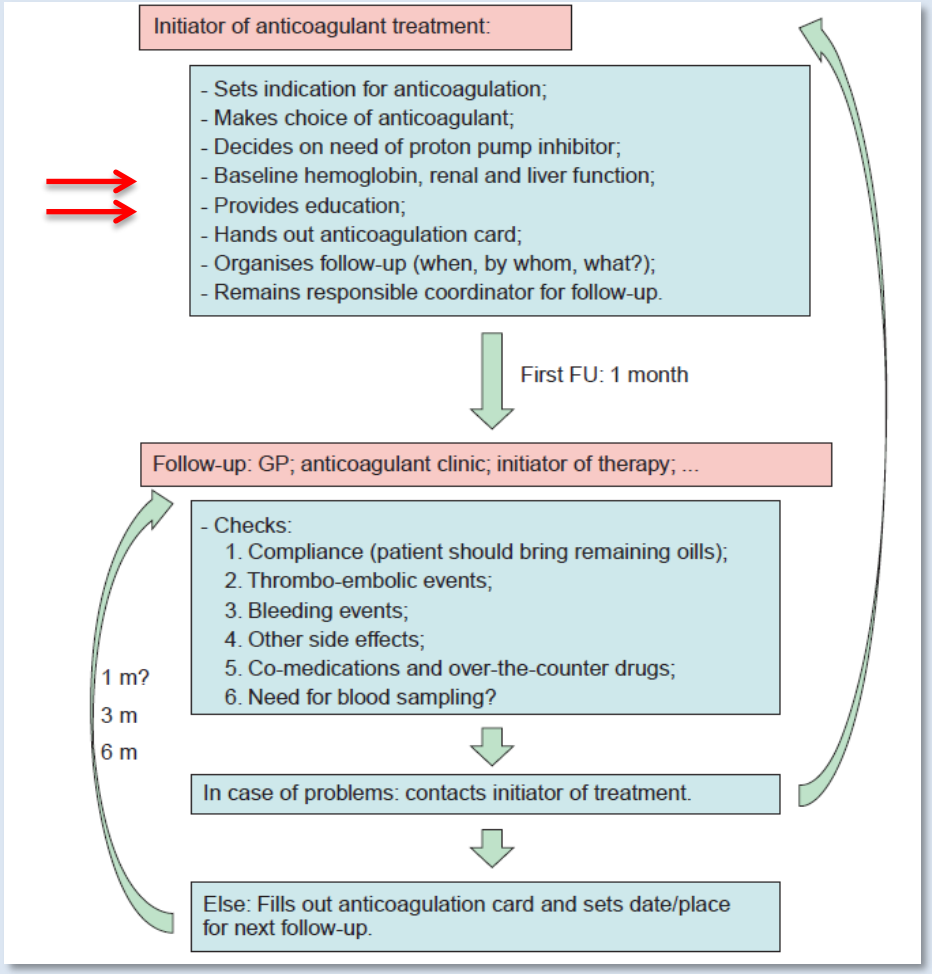


*There was limited (**2.1%**) use of concomitant dual antiplatelet therapy*

Apixaban. SmPC 2012.

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants inpatients with non-valvular atrial fibrillation

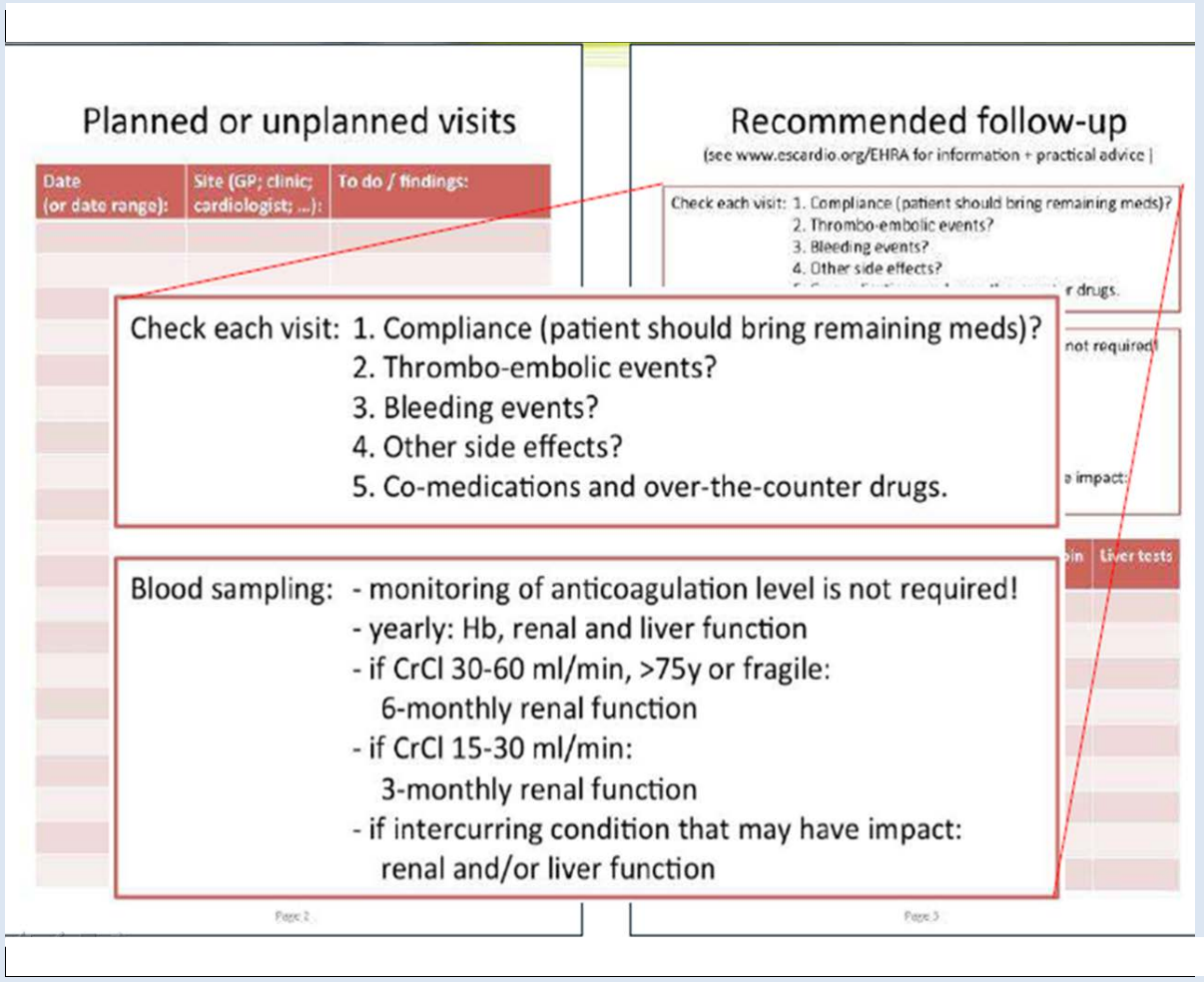
How to organize follow-up



Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants inpatients with non-valvular atrial fibrillation

EHRA practical guide on NOAC in AF
Proposal of a universal patient card



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Il TTR nei diversi studi

	RE-LY	ROCKET AF	ARISTOTLE
Time in Therapeutic Range (TTR)	64% **67% warfarin-experienced** 61% warfarin-naïve	Mean 55% Median 58%	62%

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011



- **Practical start-up and follow-up scheme for patients on new oral anticoagulants**
- **How to measure the anticoagulant effect of new oral anticoagulants?**
- **Drug–drug interactions and pharmacokinetics of new oral anticoagulants**
- **Switching between anticoagulant regimens**
- **Ensuring compliance with new oral anticoagulant intake**
- **How to deal with dosing errors?**
- **Patients with chronic kidney disease**
- **Management of bleeding and risk of bleeding**
- **Patients undergoing a planned surgical intervention or ablation**
- **Patients undergoing an urgent surgical intervention**
- **Patient with atrial fibrillation and coronary artery disease**

Table 1 Summary of the Main Clinical Trials Involving Novel Anticoagulants for Stroke Prevention in Nonvalvular AF

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)
Drug characteristics			
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	60–80	50
Time to peak levels, h	3	3	3
Half-life, h	12–17	5–9	9–14
Excretion	80% renal	2/3 liver, 1/3 renal	25% renal, 75% fecal
Dose	150 mg BID	20 mg OD	5 mg BID
Dose in renal impairment	110 mg BID	15 mg OD (if creatinine clearance 30–49 ml/min)	2.5 mg BID
Special considerations	Intestinal absorption is pH dependent and is reduced in patients taking proton pump inhibitors.	Higher levels expected in patients with renal or hepatic failure. Activity lower in fasted patients, so should be taken after food.	
Study characteristics			
Study design	Randomized open label	Multicenter, randomized, double-blind, double-dummy	Randomized control, double-blind, parallel arm
Number of patients	18,113	14,264	18,201
Follow-up period, months	24	40	40
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg BID, 110 mg BID)	Dose-adjusted warfarin vs. rivaroxaban 20 mg OD	Dose-adjusted warfarin vs. apixaban 5 mg BID

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BID = twice daily; OD = once daily; RE-LY = Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

I nuovi anticoagulanti: risultati degli studi di fase III nella FA

	RE-LY Dabigatran 110	RE-LY Dabigatran 150	ROCKET-AF Rivaroxaban	ARISTOTLE Apixaban
Stroke ed embolia sistemica	Non inferiorità	Superiorità	Non inferiorità	Superiorità
Stroke ischemico	Non inferiorità	Superiorità	Non inferiorità	Non inferiorità
Mortalità	Non inferiorità	Non inferiorità	Non inferiorità	Superiorità
Emorragia intracranica	Superiorità	Superiorità	Superiorità	Superiorità
Emorragie maggiori	Superiorità	Non inferiorità	Non inferiorità	Superiorità

Linee Guida 2012 - European Society of Cardiology

Raccomandazioni	Classe	Livello
In pazienti con CHA_2DS_2-VASc score ≥2, una terapia anticoagulante orale con: • AVK ben controllato (INR 2–3); o • Un inibitore diretto della trombina (dabigatran); o • Un inibitore orale del Fattore Xa (es. rivaroxaban, apixaban) … è raccomandata salvo controindicazione	I	A
In pazienti con CHA_2DS_2-VASc score 1, una terapia anticoagulante orale con: • AVK ben controllato (INR 2–3); o • Un inibitore diretto della trombina (dabigatran); o • Un inibitore orale del Fattore Xa (es. rivaroxaban, apixaban) … dovrebbe essere considerata, sulla base di una valutazione del rischio di complicanze emorragiche e delle preferenze del paziente	IIa	A

INR = international normalized ratio; AVK = antagonista della vitamina K

Camm AJ *et al. European Heart Journal* (2012) 33, 2719–2747

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doi:10.1093/europace/eut083

EHRA PRACTICAL GUIDE

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

- All 4 NOAC covered
- Experts from all NOAC companies as “medical consultants”
- Publication on April 26, 2013: Full paper (EP Eropace) Executive summary (EHJ)

Measuring (≠ monitoring) the intensity of anticoagulation caused by a new oral anticoagulant

- Before surgery or an invasive procedure, such as spinal anesthesia, when a patient has taken a drug in the previous 24 h (or longer if the patient has renal impairment);

- When a patient is bleeding;
- When a patient has taken an overdose;
- When a patient has deteriorating renal function.

Switching between anticoagulants

- VKA to NOAC
  - INR < 2: start NOAC
  - INR 2 – 2.5: start NOAC (immediately or) next day
  - INR > 2.5: estimate new INR check depending on VKA half-life
- Unfractionated heparin to NOAC
  - administer NOAC at time of discontinuation IV heparin (cf. $t_{1/2}$ ±2h)
- LMWH to NOAC
  - start NOAC at the time of next planned LMWH administration
- NOAC to VKA
  - administer concomitantly until INR >2 (checked before NOAC intake!),
  - retest INR 24h after last NOAC intake,
  - monitor INR closely within first month (goal = 3 consecutive INRs between 2 and 3)!

Heidbuchel et al, EHRA Practical Guide for use of NOAC in AF, Eur Heart Journal & EP Europace 2013

Dosing intake errors

- Missed dose
  - no double dose to make up
  - if <50% of dosing interval has passed (i.e. 6 to 12h): still take
  - if >50% of dosing interval has passed (i.e. 6 to 12h): wait for next
- Double dose
  - for QD NOAC: continue normal dosing scheme
  - for BID NOAC: skip next dose (or take, depending on risk profile)
- Uncertainty about intake
  - for QD NOAC: take another pill; then continue planned scheme
  - for BID NOAC: do not take another pill; wait until next dose

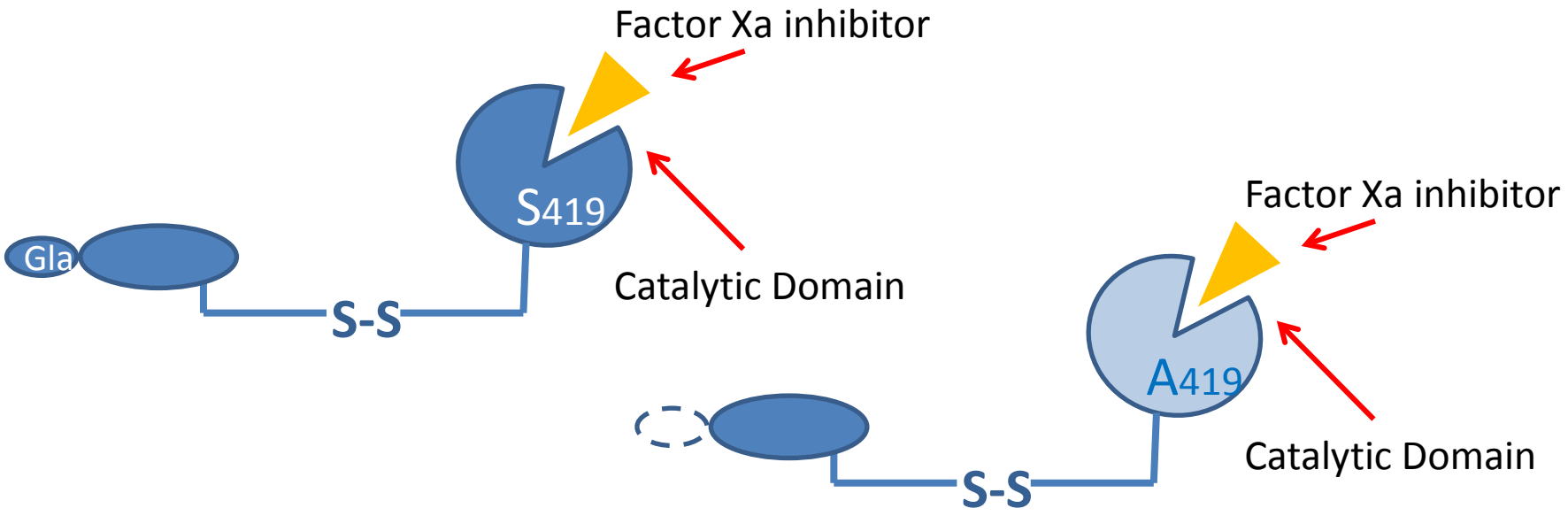
Heidbuchel et al, EHRA Practical Guide for use of NOAC in AF, Eur Heart Journal & EP Europace 2013

Andexanet: designed to reverse activity of Factor Xa

Acts as FXa decoy and retains high affinity for all FXa inhibitors

Change of Serine to Alanine to eliminate catalytic activity and prevent thrombin cleavage

Dabigatran binding to the neutralizing monoclonal antibody, aDabi-Fab.



Lu G et al Nature Medicine 2013

NOAC and coagulation assays

	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
plasma peak level	2h after ingestion	1-4h after ingestion	1-2h after ingestion	2-4h after ingestion
plasma trough level	12-24h after ingestion	12-24h after ingestion	12-24h after ingestion	16-24h after ingestion
PT	cannot be used	cannot be used	prolonged but no known relation with bleeding risk	prolonged: may indicate excess bleeding risk but local calibration required.
INR	cannot be used	cannot be used	cannot be used	cannot be used
aPTT	at trough: >2x ULN suggests excess bleeding risk	cannot be used	prolonged but no known relation with bleeding risk	cannot be used
dTT	at trough: >200 ng/ml = >65 sec: excess bleeding risk	cannot be used	cannot be used	cannot be used
anti-FXa chromogenic assays	not applicable	no data yet	quantitative; no data yet on threshold values for bleeding or thrombosis	quantitative; no data yet on threshold values for bleeding or thrombosis
Ecarin clotting time (ECT)	at trough: >3 to 4x ULN: excess bleeding risk	not affected	not affected	not affected

*: no EMA approval yet. Needs update after finalisation of SmPC

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How to measure the anticoagulant effect of new oral anticoagulants

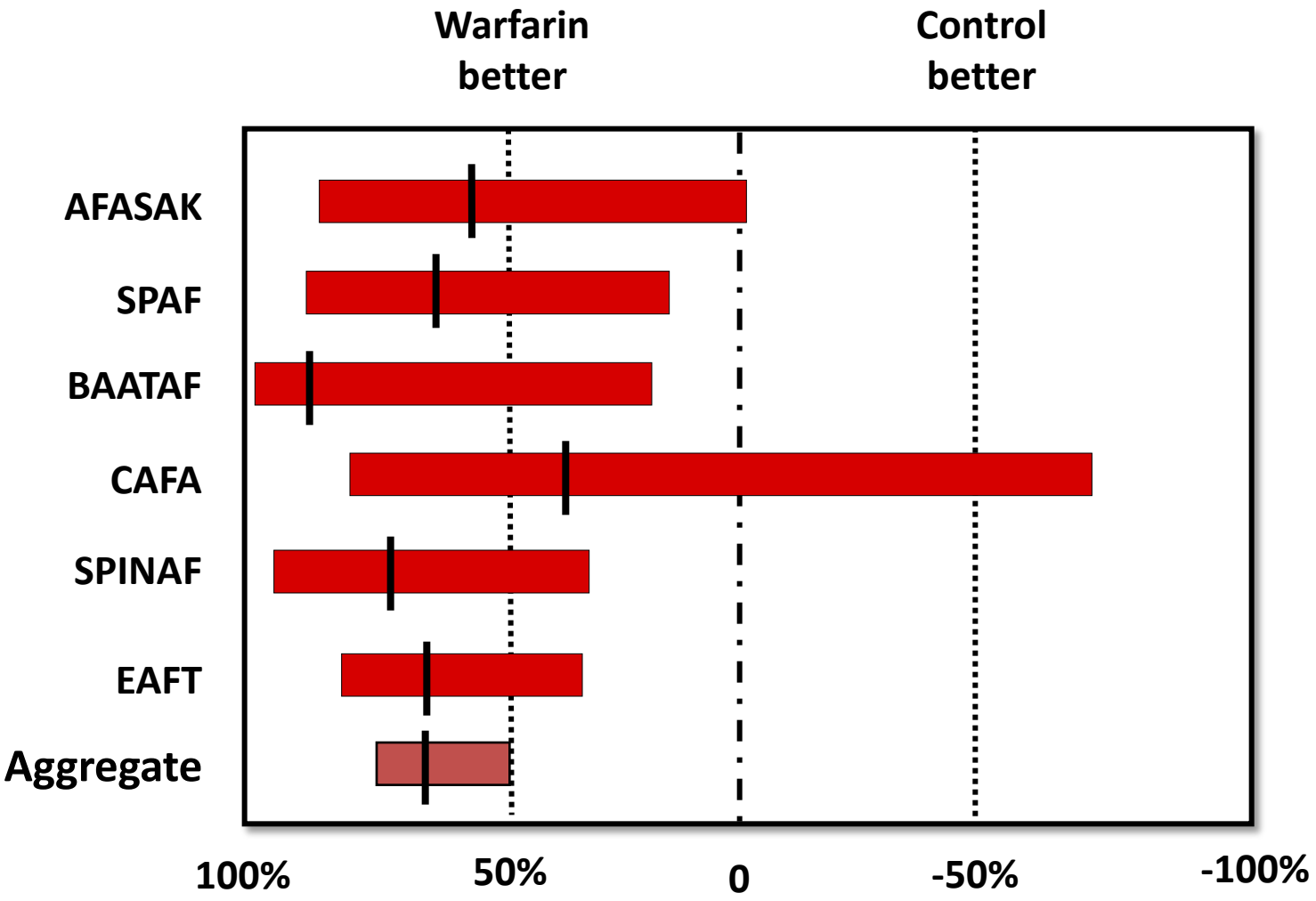
	Dabigatran	Apixaban	Rivaroxaban
Plasma Peak level	2h after ingestion	1-4h after ingestion	2-4h after ingestion
Plasma trough level	12- 24h after ingestion	12-24h after ingestion	12-24h after ingestion



The time delay between intake and blood sampling should be carefully recorded

Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

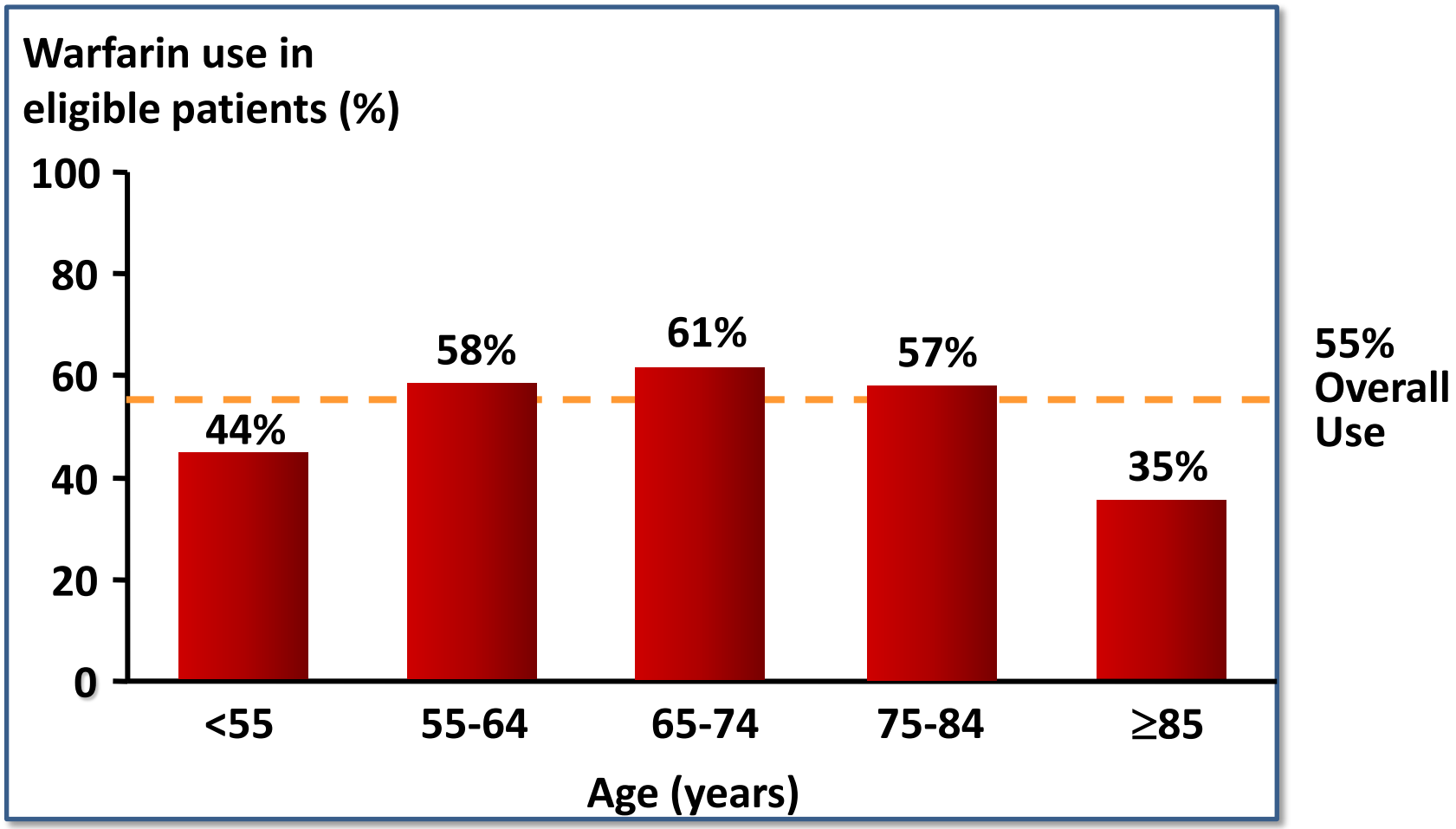
Impatto di warfarin sulla riduzione dello stroke nella FA



Hart RG et al, Ann Intern Med 1999;131:492

Warfarin per la Fibrillazione Atriale

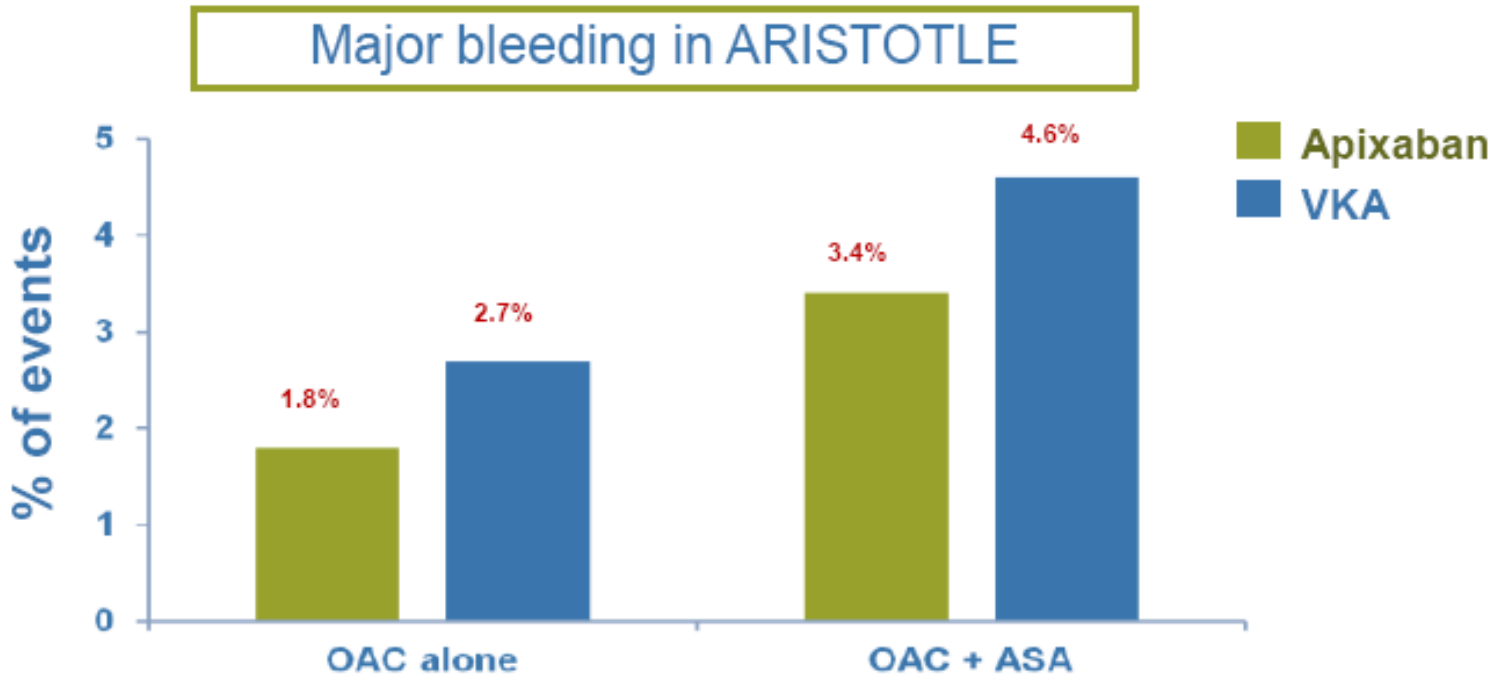
I limiti portano ad un uso ridotto



Go A et al, Ann Intern Med 1999;131:927

Apixaban and antiplatelet therapy in AF patients

In a clinical trial of patients with AF, concomitant use of ASA increased the major bleeding risk:

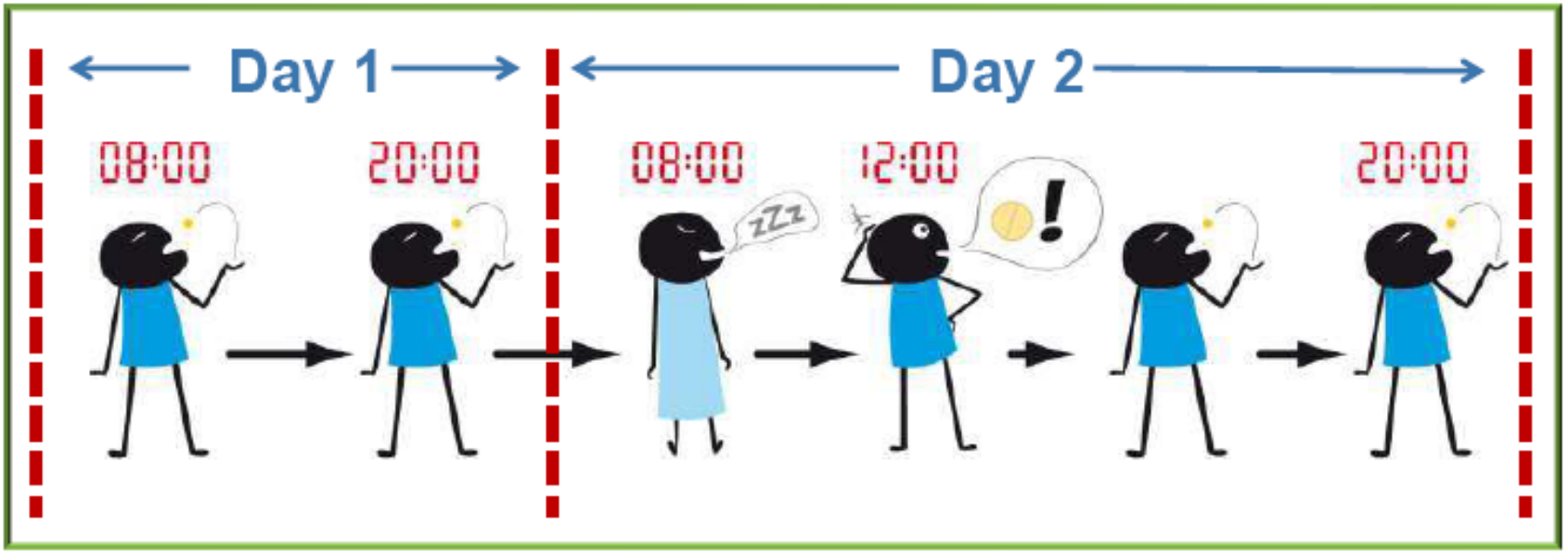


*There was limited (**2.1%**) use of concomitant dual antiplatelet therapy*

Apixaban. SmPC 2012.

Apixaban SmPC recommendations in the event of missed dose

- Lapses in therapy should be avoided
- If a dose is missed, the patient should take apixaban immediately and then continue with twice daily intake as before



Apixaban SmPC 2012.

Apixaban SmPC recommendations in AF patients requiring switch from VKA to apixaban or apixaban to VKA

Converting patients from VKA therapy to apixaban

Discontinue warfarin or other VKA therapy → Monitor INR at regular intervals until INR is < 2.0 → Start apixaban BD

Converting patients from apixaban to VKA therapy

Continue apixaban for at least 2 days after beginning VKA → After 2 days, get an INR reading before next dose of apixaban → Continue both apixaban and VKA until INR is ≥ 2.0

Switching treatment from parenteral anticoagulants (and *vice versa*) can be done at the next scheduled dose

Apixaban SmPC 2012.

Bleeding complications
Possible measures to take

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
None life-threatening bleeding	Inquire last intake + dosing regimen.	Inquire last intake + dosing regimen.
	Estimate normalisation of haemostasis: Normal renal function: 12-24h CrCl 50-80 ml/min: 24-36h CrCl 30-50 ml/min: 36-48h CrCl <30 ml/min: ≥48h	Normalisation of haemostasis: 12-24h
	Maintain diuresis.	
	Local haemostatic measures.	Local haemostatic measures.
	Fluid replacement (colloids if needed).	Fluid replacement (colloids if needed).
	RBC substitution if necessary.	RBC substitution if necessary.
	Platelet substitution (in case of thrombocytopenia ≤ 60 x 10^9/L or thrombopathy).	Platelet substitution (in case of thrombocytopenia ≤ 60 x 10^9/L or thrombopathy).
	FFP as plasma expander (not as reversal agent)	FFP as plasma expander (not as reversal agent)
	Tranexamic acid can be considered as adjuvans.	Tranexamic acid can be considered as adjuvans.
	Desmopressin can be considered in special cases (coagulopathy or thrombopathy)	Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
	Consider dialysis (preliminary evidence: -65% after 4h).	
	Charcoal haemoperfusion not recommended (no data).	
Life-threatening bleeding	All of the above.	All of the above.
	Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence).	Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence).
	Activated PCC ~~50 IE/kg; max 200 IE/kg/day~~): no strong data about additional benefit over PCC. Can be considered before PCC if available.	Activated ~~PCC 50 IE/kg; max 200 IE/kg/day~~): no strong data about additional benefit over PCC. Can be considered before PCC if available.
	Activated factor ~~VII (rFVIIa; 90 ug/kg)~~ no data about additional benefit and expensive (only animal evidence)	Activated factor ~~VII (rFVIIa; 90 ug/kg)~~ no data about additional benefit and expensive (only animal evidence)

Limiti del warfarin

- Stretta finestra terapeutica (INR 2.0-3.0).
- *Numerose interazioni con cibi e farmaci*
- Necessità di monitoraggio terapeutico.
- *L'INR è nel range terapeutico per tempo subottimale (TTR <70%)*
- Rischio di emorragia intracranica soprattutto negli anziani
- *Il trattamento con warfarin è la principale causa di reazione avversa da farmaco nei dipartimenti di emergenza*

Linee Guida 2012 - European Society of Cardiology

..Infatti, per i pazienti con fibrillazione atriale che abbiano ≥1 fattore di rischio, è raccomandata una terapia efficace per la prevenzione dell'ictus che è rappresentata essenzialmente da anticoagulanti orali: AVK ben controllato con INR 2.0-3.0 mantenuto ad un elevato TTR (per esempio, almeno 70%) oppure uno dei nuovi anticoagulanti orali

Camm et al., - European Heart Journal (2012) 33, 2719–2747

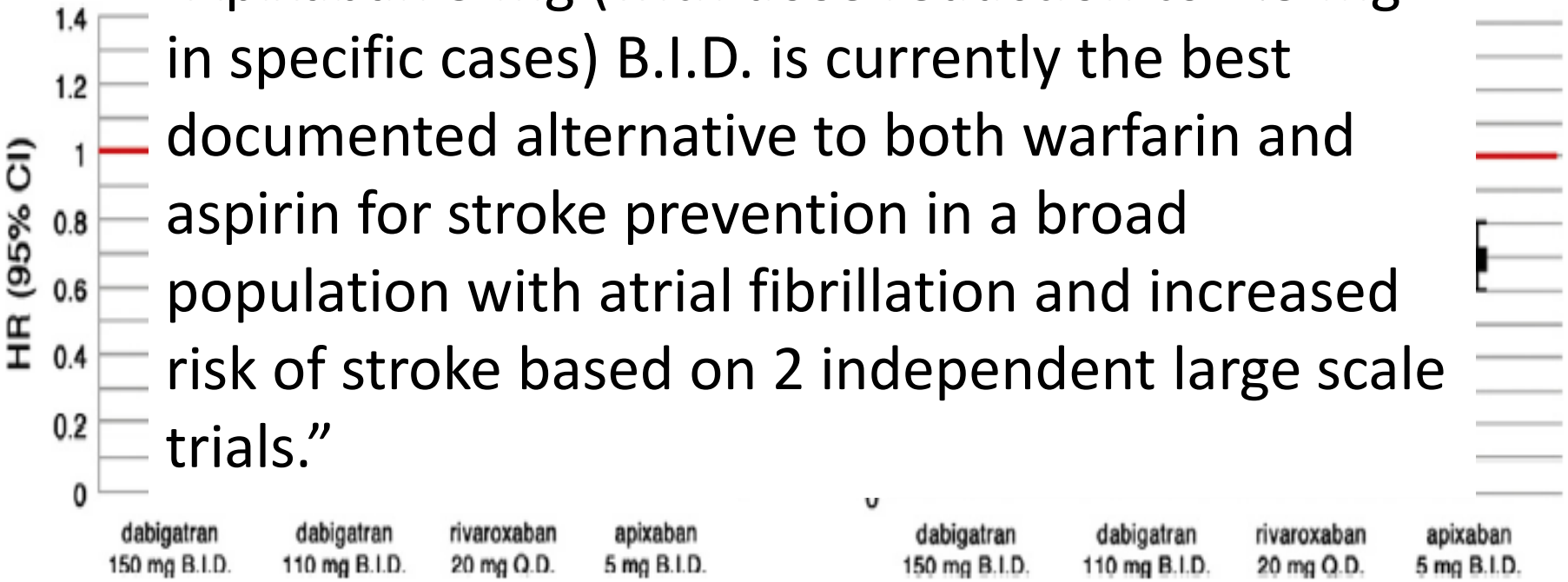
New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes

ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper

JACC

Comparable Primary Efficacy **Comparable Primary Safety**

"Apixaban 5 mg (with dose reduction to 2.5 mg in specific cases) B.I.D. is currently the best documented alternative to both warfarin and aspirin for stroke prevention in a broad population with atrial fibrillation and increased risk of stroke based on 2 independent large scale trials."



De Caterina R et al JACC 2012

Agenzia Italiana del Farmaco
AIFA

AIFA Concept Paper

I nuovi anticoagulanti orali nella prevenzione di ictus e tromboembolismo sistemico in pazienti con fibrillazione atriale non valvolare

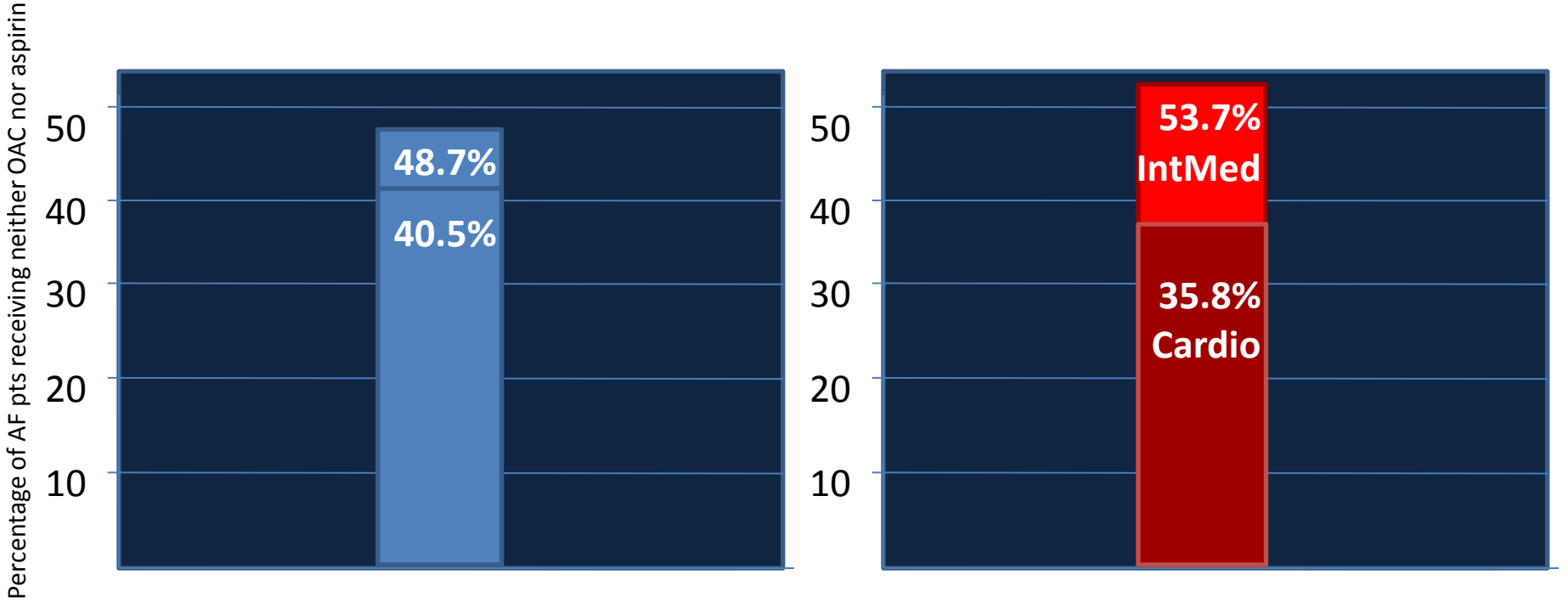
Le NOACs finora testati in studi clinici hanno dimostrato la non inferiorità rispetto al AVK, con un superiore profilo di sicurezza. limitando il numero di ICH. Su questa base, ora è ampiamente preferibile la terapia a base di VKA nella stragrande maggioranza dei pazienti con AF non valvolare. Poiché vi è ancora una limitata esperienza con questi agenti, il rispetto rigoroso delle indicazioni approvate dalle agenzie regolatorie e un'attenta sorveglianza post-marketing sono fortemente raccomandate.

Oral anticoagulation use by patients with atrial fibrillation in Germany[1] and Italy[2]

183,448 AF patients from two large mandatory German medical insurance databases in 2008

Average $CHADS_2$ score : 2.8

7148 AF patients in cardiology and internal medicine hospital centers in 2010



1_Wilke T et al Thromb Haemost 2012

2_Di Pasquale G et al Int JCcardiol 2012

I nuovi anticoagulanti: disegno degli studi di fase III nella FA

	RE LY		ROCKET-AF	ARISTOTLE
Farmaco	Dabigatran	Dabigatran	Rivaroxaban	Apixaban
Dose (mg) Freq	110 BID	150 BID	20 (15*) QD	5 (2.5*) BID
N	6015	6076	14,266	18,206
Disegno	PROBE	PROBE	2x blind	2x blind
% VKA naive	49.9%	49.8%	38%	43%

I nuovi anticoagulanti: disegno degli studi di fase III nella FA - 2

	RE LY		ROCKET-AF	ARISTOTLE
	Dabigatran 110	Dabigatran 150	Rivaroxaban	Apixaban
$CHADS_2$ medio	2.1	2.2	3.47	2.1
Età media	71.4	71.5	73	70
CHF %	32	32	63	35
Pregresso ictus %	19.9	20.3	55	19