EMORRAGIE NEI PAZIENTI IN DOACs: EPIDEMIOLOGIA E TRATTAMENTO

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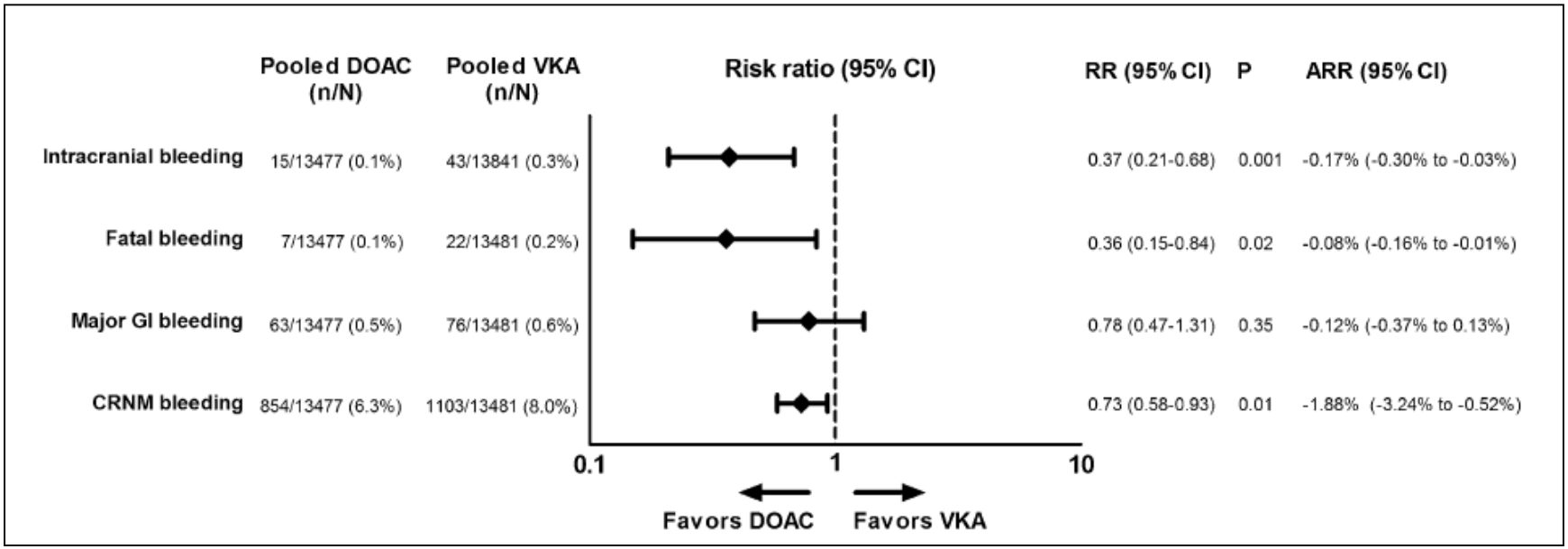
LA SITUAZIONE IN ITALIA

- In Italia si stimano più di 1.000.000 di persone in TAO (AVK /DOAC) pari cioè 1,6% della popolazione generale; circa il 7% delle persone sopra i 65 aa (
- Dati OSMED 2017 : circa 650.000 pazienti in terapia con DOACs
- L'incidenza di complicanze emorragiche maggiori in terapia anticoagulante varia da 1.25 a 3.5 per 100 anni-paziente = circa 17.000-35.000 eventi/anno

PUNTI DI DISCUSSIONE

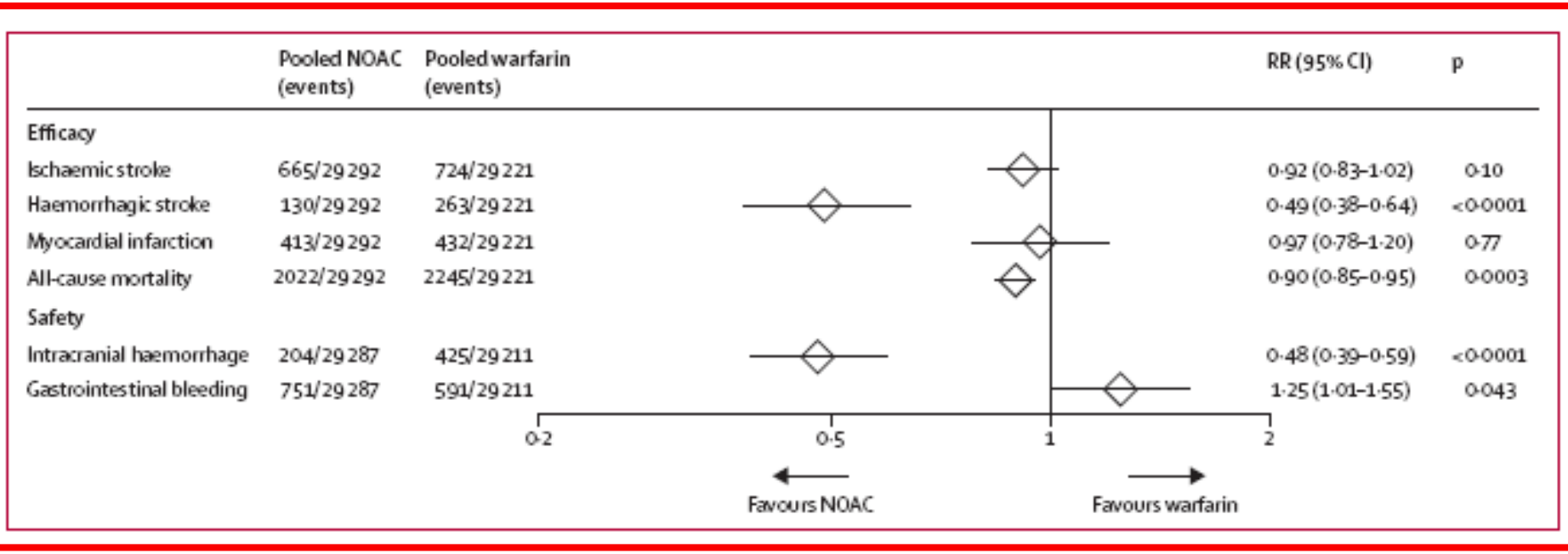
- Emorragie in DOAC
- ”Reverse in AVK e DOAC”
- Linee guida di trattamento delle emorragie maggiori
- Una fotografia della realtà

BLEEDING IN VTE



Van Es, 2014

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials



THROMBOSIS AND HEMOSTASIS

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

BLEEDING RATES PER 100 PATIENT-YEARS

	All patients	SPAF	VTE	*P* value: SPAF vs VTE
n (%)	1775 (100)	1200 (67.6)	575 (32.4)	
Any bleeding, % (95% CI)	59.4 (55.2-63.9)	59.3 (54.4-64.6)	59.6 (51.7-68.4)	.4989
Minor bleeding, % (95% CI)	36.3 (33.2-39.7)	35.8 (32.2-39.7)	37.8 (31.8-44.6)	.4199
NMCR bleeding, % (95% CI)	19.7 (17.6-22.1)	20.7 (18.1-23.5)	17.2 (13.5-21.6)	.1585
Major bleeding, % (95% CI)	3.4 (2.6-4.4)	3.1 (2.2-4.3)	4.1 (2.5-6.4)	.2849

Beyer-Westendorf J, Blood 2014

Real-world effectiveness and safety of oral anticoagulation strategies in atrial fibrillation: a cohort study based on a German claims dataset

Table 1 Characteristics of observed AF patient samples

Characteristics	All observed AF-patients	Unmatched			PS-matched		
		Cohort 1 (NOAC)	Cohort 2 (VKA)	Cohort 1 versus 2 (*p*-value)	Cohort 1 (NOAC)	Cohort 2 (VKA)	Cohort 1 versus 2 (*p*-value)
N	483,149	51,155	128,274	–	37,439	37,439	–
Mean follow-up time since index date (SD); median	–	341.2 days (245.29); 290	393.1 days (311.30); 239	$p<0.001$	348.5 days (247.57); 299	365.5 days (290.74); 197	$p>0.100$
Mean age in years (SD)	76.24 (13.33)	78.21 (8.56)	76.61 (8.34)	$p<0.001$	78.21 (7.40)	78.16 (7.37)	$p>0.100$
Gender; Female N (%)	253,750 (52.52)	26,519 (51.84)	66,112 (51.54)	$p>0.100$	19,659 (52.51)	19,622 (52.41)	$p>0.100$
Mean CCI without age factor (SD)	3.56 (2.79)	5.09 (2.74)	4.45 (2.46)	$p<0.001$	4.78 (2.60)	4.80 (2.55)	$P<0.500$
Mean CHA_2DS_2 VASc score (SD)	2.47 (1.54)	3.09 (1.09)	2.88 (1.00)	$p<0.001$	2.96 (1.04)	2.95 (1.03)	$p>0.100$
Prescribed DDDs of study medication[a]	NA	1.21 (1.97)	0.81 (1.67)	–	1.19 (1.87)	0.82 (1.80)	–
Prescribed DDDs of Heparins or Clopidogrel[b]	NA	3.27 (21.20)	3.32 (13.12)	$p<0.001$	3.16 (22.22)	3.67 (16.66)	$p<0.001$

Mueller S et al, 2018

Real-world effectiveness and safety of oral anticoagulation strategies in atrial fibrillation: a cohort study based on a German claims dataset

Events	Own analysis				Known major clinical trials		
	PSM-IRRs (95% CI; *p*-value)	PSM-HRs (95% CI; *p*-value)	aHRs (95% CI; *p*-value)	PSM-HRs (95% CI; *p*-value) for therapy-naive patients	HRs (95% CI; *p*-value) – RE-LY[8]	HRs (95% CI; *p*-value) – ROCKET AF[9]	HRs (95% CI; *p*-value) – ARISTOTLE[15]
Death	1.22**** (1.17–1.28; *p*<0.001)	1.22**** (1.17–1.28; *p*<0.001)	1.10**** (1.06–1.15; *p*<0.001)	1.11** (1.03–1.20; *p*<0.010)	0.88 (0.77–0.00; NSR)	0.85 (0.70–1.02; NSR)	0.89* (0.80–1.00; *p*<0.050)
IS	1.90**** (1.69–2.15; *p*<0.001)	1.92**** (1.69–2.19; *p*<0.001)	1.52**** (1.37–1.69; *p*<0.001)	1.175**** (1.42–2.17; *p*<0.001)	0.76* (0.60–0.98; *p*<0.050)	0.94 (0.75–1.17; NSR)	0.92 (0.74–1.13; NSR)
Hemorrhagic stroke	0.94 (0.76–1.17; NSR)	0.95 (0.76–1.21; NSR)	0.68**** (0.56-0.82; *p*<0.001)	0.76 (0.52–1.11; NSR)	0.26**** (0.14–0.49; *p*<0.001)	0.59* (0.37–0.93; *p*<0.050)	0.51**** (0.35–0.75; *p*<0.001)
Severe bleedings	1.92**** (1.71–2.15; *p*<0.001)	1.95**** (1.74–2.20; *p*<0.001)	1.57**** (1.43–1.73; *p*<0.001)	1.58 (1.30–1.92; NSR)	0.93 (0.81–1.07; NSR)	1.03 (0.90–1.18; NSR)	0.71**** (0.61–0.81; *p*<0.001)

Mueller S et al, 2018

Fatal oral anticoagulant-related intracranial hemorrhage: a systematic review and meta-analysis

Table 1 Overview of included studies

Study name	Agent	RCT	Total no. of patients (*n*)	Patients with ICH (*n*)	Fatal ICH (%)	Time of evaluation (days)
ARISTOTLE [6]	Apixaban (2.5 mg/5 mg)	Yes	9088	53	45.3	30
	Warfarin		9052	123	42.3	
ENGAGE AF-TIMI 48 [7]	Edoxaban (30 mg)	Yes	7002	41	29.3	30
	Edoxaban (60 mg)		7012	61	39.3	
	Warfarin		7012	132	31.8	
RE-LY [8]	Dabigatran (110 mg)	Yes	6015	27	40.7	30
	Dabigatran (150 mg)		6076	37	35.1	
	Warfarin		6022	90	35.5	
ROCKET AF [9]	Rivaroxaban (15 mg/20 mg)	Yes	7111	55	56.3	90
	Warfarin		7125	84	64.3	
ANNEXA-4 [4]	Factor Xa inhibitors antidote	No	67	28	21.4	30
RE-VERSE AD [10]	Idarucizumab	No	503	98	16.3	30

ICH, intracranial hemorrhage; RCT, randomized controlled trial.

Katsanos AH et al, EJN 2018

EMORRAGIE IN TAO

- Trattamento dipende dalla SEVERITA' e dalla SEDE dell'emorragia

- In caso di EMORRAGIA SEVERA o in ORGANI CRITICI:
  - Sospendere la TAO
  - RIPRISTINARE IN TEMPI RAPIDI IL NORMALE ASSETTO COAGULATIVO (REVERSE)
  - Trattare la causa del sanguinamento

“REVERSE”: DEFINIZIONE

Sostantivo: *contrario, opposto, inverso*

Verbo: *invertire, rovesciare, ribaltare, capovolgere*

Normalizzazione della bilancia emostatica nel paziente in cui si presuppone un’ alterazione del meccanismo fisiologico della coagulazione indotto dai farmaci anticoagulanti

COME POSSIAMO EFFETTUARE UN “REVERSE” SE NON MISURIAMO?

TAO (AVK/DOAC)

1. Quali agenti emostatici utilizzare (come effettuare il reverse)

2. Per trattare la complicanza e' utile conoscere il livello di anticoagulazione (= comprendere patogenesi per orientare il trattamento)?

NEUTRALIZZAZIONE DELLA TAO CON AVK

- Vitamina K1 ev: 10 mg in 100 mL fisiologica in 30 min
- Complesso protrombinico:
  - INR <2.0 → 20 U/kg
  - INR 2.0-4.0 → 30 U/kg
  - INR 4.0-6.0 → 40 U/kg
  - INR > 6 → 50 U/kg
- Verificare l'avvenuta correzione (ripetere PT-INR dopo 5 min dopo l'infusione e a distanza di 12 ore)
- Se INR < 1.5 il reverse e' giudicato concluso
- Se INR > 1.5 infondere CCP al dosaggio corrispondente INR residuo

(2018)

AVK

- Gestione clinica del paziente condotta in base al controllo dei livelli di anticoagulazione
- Il controllo e' espressione dell'entita' dell'anticoagulazione e guida le necessita' posologiche relative alla correzione emostatica
- Reverse efficace e sicuro con CCP+vit K
- Possibilita' di intervenire con livelli di anticoagulazione PT INR < 1.5 (cut off di intervento)

Chest 2012, LG FCSA 2018

E I PAZIENTI IN DOAC?

INFORMAZIONI INDISPENSABILI PER LA GESTIONE DELLE EMERGENZE

1. E’ in terapia con anticoagulanti?
2. Se si, QUALE FARMACO?

- Orario di assunzione del farmaco
- Indicazione al trattamento

EXPECTED C-PEAK AND C-TROUGH DOAC LEVELS IN NVAF AND VTE PATIENTS ENROLLED IN PHASE II-III CLINICAL STUDIES

	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Indication	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE
Dose	150 mg bid	150 mg bid	20 mg qd	20 mg qd	5 mg bid	5 mg bid	60 mg qd	60 mg qd
Peak concentration, ng/mL	175[a] (117–275)	175[a] (117–275)	249[b] (184–343)	270[b] (189–419)	171[c] (91–321)	132[c] (59–302)	170[d] (125–245)	234[e] (149–317)
Trough concentration, ng/mL	91[a] (61–143)	60[a] (39–95)	44[b] (12–137)	26[b] (6–87)	103[c] (41–230)	63[c] (22–177)	36[e] (19–62)	19[e] (10–39)

Gosselin RC, et al. Thromb Haemost 2018;118:437-50

DIMENSIONI EMORRAGIA E INR

- Nei pazienti in AVK occorre ottenere una rapida e completa normalizzazione della coagulazione per evitare un ulteriore peggioramento del focolaio emorragico (effetto "rubinetto aperto")
- Un INR>2.0 è un importante fattore di rischio indipendente per l'aumento delle dimensioni del focolaio emorragico

Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage

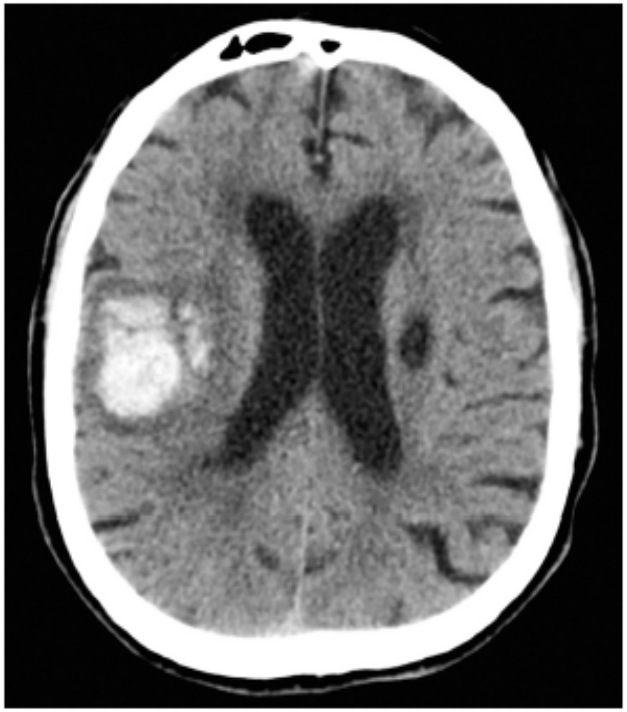
S.M. Davis, MD; J. Broderick, MD; M. Hennerici, MD; N.C. Brun, MD; M.N. Diringer, MD; S.A. Mayer, MD; K. Begtrup, MSc; and T. Steiner, MD, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators

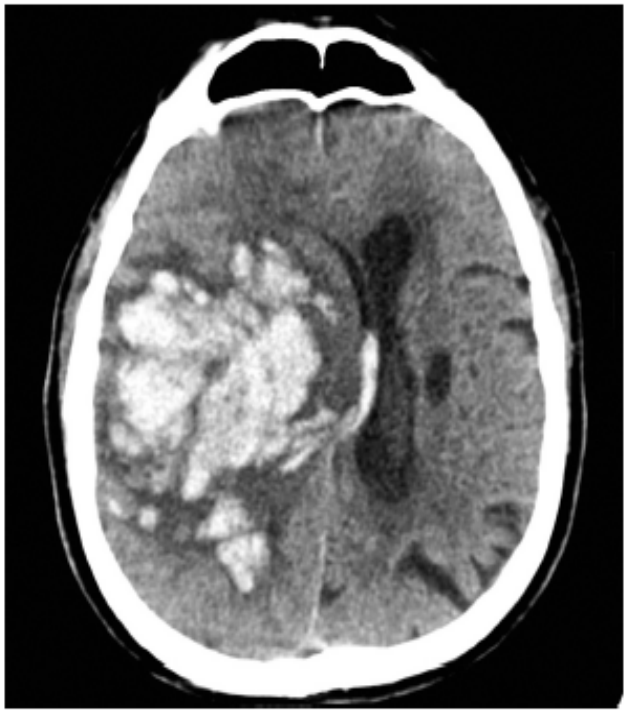
Metanalysis of 281 patients prospectively enrolled as controls in three treatment trials

Hematoma growth is an independent determinant of both mortality and functional outcome after intracerebral hemorrhage. Attenuation of growth is an important therapeutic strategy

NEUROLOGY 2006;66:1175–1181

Dabigatran-Related Intracerebral Hemorrhage Resulting in Hematoma Expansion





Ore 16.30: PTT = 59sec, PT =1.3

Ore 22.00 :Volume 15ml dopo 6 ore ore 4.00:volume 185 mL

Simonsen CZ, 2013

COME EFFETTUARE LA NORMALIZZAZIONE DEI LIVELLI DI ANTICOAGULAZIONE (REVERSE) NEL PAZIENTE IN TERAPIA CON DOACs?

ESC
European Society of Cardiology
European Heart Journal (2018) **39**, 1330–1393
doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Table 10 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening major bleeding	• Inquire about last intake + dosing regimen • Local haemostatic measures • Fluid replacement • RBC substitution, if necessary • Platelet substitution (in case of thrombocytopenia ≤60 × 109/L or thrombopathy) • Fresh frozen plasma not as reversal agent (may be considered as plasma expander) • Tranexamic acid can be considered as adjuvant (1 g i.v., repeat every 6 h, if necessary) • Desmopressin can be considered in special cases such as coagulopathy or thrombopathy; 0.3 µg/kg i.v. infusion (max dose 20 µg)	

	• Estimate normalization of plasma levels:
	  • Normal renal function: 12–24 h
	  • CrCl 50–80 mL/min: 24–36 h
	  • CrCl 30–50 mL/min: 36–48 h
	  • CrCl <30 mL/min: ≥48 h
	• Maintain diuresis
	• Consider idarucizumab (see below)
		• Normalization of plasma levels: 12–24 h

Life-threatening bleeding	• All of the above
	• Direct reversal: Idarucizumab 5 g i.v. in two doses a 2.5 g i.v. no more than 15 min apart
		• All of the above
		• Direct reversal: Andexanet alpha (if available and approved)[a]
		  • Bolus over 15–30 min, followed by 2-h infusion
		  • Rivaroxaban (last intake >7 h before) or apixaban: 400 mg bolus, 480 mg infusion @ 4 mg/min
		  • Rivaroxaban (last intake <7 h before or unknown) or enoxaparin or edoxaban: 800 mg bolus, 960 mg infusion @ 8 mg/min

	• Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) • Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC, if available	

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.
[a]Andexanet alpha is currently neither approved nor available and final results of the ANNEXA-4 study are pending.

1. Pazienti possono presentarsi con livelli di farmaco estremamente elevati (anche 10 volte superiori rispetto ai valori estremi della variabilità biologica misurata a valle e 2-3 volte superiori ai valori estremi di picco)
2. La quantità di antidoto infusa a dosi fisse non inibisce l'effetto dei DOAC in tutti i pazienti (e forse è eccessiva nei pazienti con dosi più basse di farmaco)
3. Misurare è clinicamente utile

Targeted Anti-Anticoagulants

Kenneth A. Bauer, M.D.

- Dati convincenti rispetto alla normalizzazione dell'effetto anticoagulante di idarucizumab
- Non possibili conclusioni rispetto ai benefici clinici per mancanza di un gruppo di controllo
- La misura dell'attività di dabigatran è stata centralizzata e non utilizzata per gestire il reverse
- In circa ¼ dei pazienti trattati con antidoto il dTT era normale (assenza di farmaco)
- Pertanto è utile avere la disponibilità IN TEMPO REALE DI TEST SPECIFICI PER LA MISURA DELL'EFFETTO ANTICOAGULANTE che possa guidare l'utilizzo degli antidoti per evitare un loro sovrautilizzo e consumo inutile di risorse

BAUER , N Engl J Med 2015

COME MISURARE I DOAC?

- Tutti i test coagulativi di screening possono essere variamente influenzati dai DOAC a seconda del tipo di reagente
- PT, aPTT e TT, per la scarsa o eccessiva sensibilità, NON SONO TEST UTILI per esprimere l'attività anticoagulante dei DOAC
- PT/PTT nella norma non escludono presenza di concentrazioni significative di DOAC così come PT/PTT allungati si osservano in assenza di farmaco.
- Sono disponibili test specifici per ogni molecola, semplici, di facile esecuzione e a basso costo

Kitchen S et al, BJH 2015; Testa S et al, JTH 2016; Tripodi A et al, 2018; Gosselin et al 2018

QUANDO L'EFFETTO FARMACODINAMICO PUO' ESSERE DIVERSO DALL'ATTESO E QUANDO E' UTILE IL DOSAGGIO DELL'ATTIVITA' ANTICOAGULANTE

- Patients presenting in emergency with adverse events (Thrombosis, Bleeding)
- Recurrent thrombosis on DOAC
- Immediate reverse of anticoagulation
- Perioperative management
- Renal Disease / Liver Disease
- Suspicion or known interaction with other drugs
- Fragile elderly patients
- Under/over weight

UNA FOTOGRAFIA DELLA REALTÀ

START Events Registry

Coordination: Walter Ageno & Sophie Testa

Partecipants	Country
Walter Ageno	Italy
Pantep Angchaisuksiri	Thailand
Bruno Caramelli	Brazil
Elvira Grandone	Italy
Giuliana Guazzaloca	Italy
Maurizio Paciaroni	Italy
Vittorio Pengo	Italy
Daniela Poli	Italy
Michela Provisione	Italy
Marc Righini	Swisse
Ponlapat Rojnuckarin	Thailand
Piera Sivera	Italy
Sophie Testa	Italy
Alberto Tosetto	Italy
Anna Turrini	Italy
Serena Rupoli	Italy
Peter Verhamme	Belgium
Jan Beyer-Westendorf	Germany

THE CLINICAL CONTEXT

- Management of major bleedings and thromboembolic complications in patients treated with direct oral anticoagulants (DOAC) is still not well established because of the limited clinical experience due to the relatively recent introduction of these drugs.
- Some data are currently available from the Dresden-Registry and from small case series

AIMS

- *S*TART-Events aims to describe the actual management of bleeding or thromboembolic complications, occurring in patients treated with DOACs, in routine clinical practice.

METHODS

- The START-Events registry is a prospective, observational, multicenter, international study. Approval was obtained from local ethics committees.
- Patients aged =>18years presenting with bleeding complications or thromboembolic events during DOACs treatment for atrial fibrillation (AF) or venous thromboembolism (VTE) are enrolled.
- Baseline characteristics (demographic, clinical, risk factors), laboratory data at admission and during the follow up, site of bleeding, type of thromboembolic complication, therapeutic strategies and outcomes at the time of hospital discharge and after 6 months were recorded on a web–based case report forms (CRF).

PATIENTS ENROLLED IN THE START-EVENT REGISTER

- From January 1st 2015 until July 11th 2018, **192 patients** were enrolled:

  - **143** patients with major bleedings (**117** of them described in a recent publication on Intern Emerg Med)

  - **49** patients with thromboembolic complications

BLEEDINGS

START-EVENT

Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry

Sophie Testa[1] · Walter Ageno[2] · Emilia Antonucci[3] · Rossella Morandini[1] · Jan Beyer-Westendorf[4] · Maurizio Paciaroni[5] · Marc Righini[6] · Piera Sivera[7] · Peter Verhamme[8] · Vittorio Pengo[9] · Daniela Poli[10] · Gualtiero Palareti[3]

- **117 patients** with major bleeding complications on DOACs were enrolled.
- **NVAF** was the indication in 84%; 62% were males
- Bleeding events occurred **within the first 90 days** of DOAC treatment in **45 % of patients.**
- **94 bleedings (80.4%) were spontaneous,** while 23 (19.6%) were post-traumatic, prevalently subdural ICH.

Intern Emerg Med, 201

SITE OF MAJOR BLEEDINGS

	apixaban (32)	dabigatran (32)	rivaroxaban (51)	edoxaban (2)	Total (117)	
Lobar ICH (n; **%**) Fatal n°	4 (12.5) 2	4 (12.5)2 1	6 (11.8) 0	0 0	14 3	
Deep ICH (n; **%**) Fatal n°	5 (15.6) 2	2 (6.2) 1	13 (25.4) 6	1 0	21 9	45.3%
Subdural ICH (n; **%**) Fatal n°	8 (25.0) 0	4 (12.5) 0	6 (11.8) 1	0 0	18 1	
G.I. bleeding (n; **%**) Fatal n°	8 (25.0) 1	12 (37.5) 0	21 (41.1) 0	1 0	42 1	35.9%
Retinal bleeding (n; **%**) Fatal n°	1 (3.1) 0	0 0	1 (1.9) 0	0 0	2 0	
Musc. Haematoma (n; **%**) Fatal n°	3 (9.4) 0	3 (9.4) 0	1 (1.9) 0	0 0	7 0	18.8%
Others (n; **%**) Fatal n°	3 (9.4) 0	6 (18.7) 0	4 (7.8) 0	0 0	13 0	

Others: retropertitoneal b. , pericardial b., haematuria, metrorrhagia

Intern Emerg Med, 2018

BLEEDING MANAGEMENT

	ICH (53)	GI BLEEDING (42)	OTHER (22)	Total (117)	Death (1-3d) (14)	Death (6 m.) (4)
No therapy n (%)	19 (36)	12 (28.6)	3 (13.6)	34 (29.1)	5 (35.7)	1
Symptomatic treatment *	0	17 (40.5)	9 (41.2)	26 (22.2)	0	2
Antifibr.	4 (7.5)	0	0	4 (3.4)	3 (21.5)	0
Antidote (idarucizumab)	2 (3.8)	0	1(4.5)	3 (2.6)	0	0
PCC (**)	21 (39.6)	4 (9.5)	2 (9.0)	27 (23.0)	5 (35.7)	0
Surgery + PCC	4 (7.5)	0	1 (4.5)	5 (4.3)	1 (7.1)	0
Surgery /invasive procedures	3 (5.6)	9 (21.4)	6 (27.2)	14 (11.9)	0	0

* Fluid replacement +/- red blood transfusion
**PCC at 3-4 F +/- antifibrinolytics, Vitamin K, oral charcoal

Intern Emerg Med, 2018

LAB TESTING

- Time of last DOAC dose intake was available in 49% of patients and varied from 4 to 12 hours
- Haemoglobin, PT and aPTT results were available in nearly 80% of cases at admission
- CrCl mL/min median level was = 59.5 (44-80)
- **Specific DOACs measurements were available in only 23% of cases pre-treatment and 10% post-treatment**

Intern Emerg Med, 2018

MAJOR BLEEDINGS: SUMMARY

- Our data confirm a high heterogeneity in the management of bleeding complications in patients treated with DOACs.
- In this population major bleedings, occurring during DOAC treatment, globally, accounted for 15% of deaths and 24% of disability.
- We observed that **nearly 50% of the total population received no treatment or symptomatic support only.**
- **The high mortality (24.5%) and disability (27.5%) rates associated to ICH bleeding strongly indicate a need for a rapid normalization of haemostasis**. An approach only based on, clinical observation, the evaluation of renal function and drug half-life, may not guarantee a rapid normalization of haemostasis.
- PCC are prevalently used in ICH management, while transfusions are the main treatment in GI bleedings
- The use of specific antidotes is emerging
- At present, **rarely specific lab testing are requested to guide therapy**

Intern Emerg Med, 2018

TO EXTEND ENROLLMENT: WHY?

Because we need to:

1. Learn and understand how to approach DOAC patients with complications and which are the current limitations in treatments and health care organizations
2. Increase competence and knowledge, above all, in Emergency Departments, also through specific training on anticoagulation reversal
3. Use better strategies (i.e. the lab) to guide patient management and implement DOAC specific measurements, rapidly available in emergency
4. Guarantee the promptly availability of antidotes and reversal agents
5. “Organize/Create” the availability of specialized consultant on Thrombosis and Haemostasis, that could ensure homogeneous and, probably, more specific management of complications in anticoagulated patients.

For any information and to partecipate

mail: info@start-register.org