RISULTATI ATTUALI DEL REGISTRO START-Eventi

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BACKGROUND

- 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 relative recent introduction of these drugs.

- Few data are available from Dresden-Registry and case reports

AIMS

- START-Events, a branch of the START registry (Survey on anTicoagulated pAtients RegisTer), 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) were 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 the end of december 2017, **184 patients** were enrolled:
  - **137** patients with major bleedings
  - **47** patients with thromboembolic complications

BLEEDINGS

MANAGEMENT OF MAJOR BLEEDING AND OUTCOMES IN PATIENTS TREATED WITH DIRECT ORAL ANTICOAGULANTS: RESULTS FROM THE START-Events Registry

Testa S, Ageno W, Antonucci E, Morandini R, Beyer-Westendorf J, Paciaroni M, Righimi M, Sivera P, Verhamme P, Pengo V, Poli D, Palareti G.

Paoletti O, Rojnuckarin P, Wang Tzu –Fei, Guazzaloga G, Migliaccio L, Caramelli B, Provisione M, Wang T, Verhamme P, Rojnuckarin P, Bruno C, Angchaisuksiri P, Paciaroni M, Grifoni E, Guazzaloca G, Sivera P, Grandone E, Turrini A, Rupoli S, Tosetto A, Palareti G.

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RESULTS

- **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.

MAIN CLINICAL CHARACTERISTICS

Major bleeding Cerebral (n°; **%**) Gastrointestinal (n°; **%**) Other (n°;**%**)	**117** 53; **45.3** 42; **35.9** 22; **18.8**
Males (n° %)	73 ;**62**
Median Age (IQR range) years	79 (74-85)
Median Cr Cl mL/min*	59.5 (44-80)
Indication to anticoagulation Non Valvular AF (%) Venous thromboembolism (%)	 99; **84** 18; **16**
Anticoagulant drugs Apixaban (n°; **%**) Dabigatran (n°; **%**) Rivaroxaban (n°; **%**) Edoxaban (n°; **%**)	 32 **(27.4)** 32 **(27.4)** 51 **(43.5)** 2 **(1.7)**
Concomitant Antiplatelet drugs (n°; **%**)	13 (11%)
DOAC low dose (n; **%**)	49 (42%)

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

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

OUTCOMES AT HOSPITAL DISCHARGE AND AFTER 6 MONTHS

Outcome at hospital discharge (n;%)	117
- Complete resolution	87 /117(74)
- Disability (for ICH)	16/53 (30)
- Death	14 /117 (11.9)
- Death for ICH	13/14 (92.8) ; 24.5% ICH
Outcome within 6 months (n;%)	102
- Complete resolution	86/102 (84.3)
- Disability (for ICH)	11/40 (27.5)
- Death	4/102 (3.9)

LAB TESTING

- Time of last 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
- At presentation (median/IQR) DOACs ng/ml:
  - dabigatran =269ng/ml (132-398)
  - apixaban =161 ng/ml (99-571)
  - rivaroxaban =134 (24- 369)

IN SUMMARY

- Our data confirm a high heterogeneity in the management of bleeding complications in patients treated with DOACs.
- PCC are prevalently used in ICH management, while transfusions are the main treatment in GI bleedings
- The use of specific antidotes is emerging
- In this population major bleedings, occurring during DOAC treatment, globally, accounted for 15% of deaths and 24% of disability.
- At present, rarely specific lab testing are requested to guide therapy

CONCLUSION

This experience highlights the following needs:

1. Homogeneous and more structured guidelines
2. Availability of reversal agents
3. DOAC specific measurements, rapidly available in emergency
4. Specific training on anticoagulation reversal for emergency department physicians
5. Availability of specialized consultant on Thrombosis and Haemostasis that could ensure homogeneous and probably more specific management of acute major bleeding complications in anticoagulated patients.

THROMBOEMBOLIC COMPLICATIONS

MAIN CLINICAL CHARACTERISTICS

Number of Patients	41
Males (%)	19 (46%)
Median Age (IQR range) years	74 (63,83)
Indication to anticoagulation Non Valvular AF Venous thromboembolism	 25 (60%) 16 (40%)
Anticoagulant drugs Apixaban Dabigatran Rivaroxaban	 6 (14.6%) 8 (19.5%) 27 (65.9%)
Patients Shifted from Vitamin k antagonist	15 (36.6)%
Antiplatelet drugs	6 (14.6%)
DOAC Low dose	10 (24%)

CHARACTERISTICS OF THROMBOTIC EVENTS

Thrombotic events n, (%)	All (41)	AF (25)	VTE (16)
Deep vein thrombosis	9 (22)	2	7
DVT+PE	4 (9.8)	1	3
Isolated PE	5 (12.2	1	4
TVS	1 (2.4)	-	1
Stroke	13 (31.7)	13	-
TIA (positive imaging)	2 (4.9)	1	1
Peripheral embolism	4 (9.8)	4	-
Acute myocardial infarction	2 (4.9)	2	-
Retinal Vein Occlusion	1 (2.4)	1	-

OUTCOMES

Outcome at discharge	41
Complete resolution	35/41 (85%)
Disability (for patients with stroke)	6/13 (50%)
Death	0
Outcome within six months	40*
Complete resolution	35/40 (87.5%)
Disability (for patients with stroke)	4/12* (36.3%)
Death	1/40 8(2.5%)**

*1 patient lost at follow up; ** 1 patient, with ischemic stroke, died for pulmonary infections one month after the event

LAB TESTING

Test (n° of patients)	Before intervention	Post intervention
	Median (IQR)	-
PT INR (29)	1.12 (0.85-3.1)	-
aPTT ratio (25)	1.47 (0.85-3.19)	-
Hemoglobin (33)	12.3 (6.3-14)	-
Platelet count (34)	228 (85-502)	-
Cr Cl mL/min (27)	59.5 (44-80)	-
Dabigatran DTT (ng/ml) (3/8) (median; range)	23.4(13.9-154)	-
Apixaban aXa (ng/ml) (2/6) (median; range)	64.8 (63.7-66)	-
Rivaroxaban aXa activity (7/27) (median; range)	100 (17.3-167)	-

GENERAL CONSIDERATIONS

- Mortality seems to be significantly lower if compared with bleeding events (1 death after discharge)
- NVAF showed more frequently arterial complications, while VTE occurrs more frequently as recurrence
- Very rarely specific lab testing are requested. Difficult interpretation of aXa levels because all patients were already treated with LMWH at the moment of blood sampling
- Too limited number of patients with thromboembolic complications enrolled to allow possible conclusion
- Necessity to extend the enrollment