RISULTATI ATTUALI DEL REGISTRO START-Eventi

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Participants

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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 2018, **256 patients** were enrolled:
  - 165 patients with major bleedings
  - 13 patients with non major clinically relevant bleedings
  - 16 patients with minor bleedings
  - 62 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, Tosetto, 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*	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

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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

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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**

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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)
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)

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**

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UPDATES

- 7 pts (4 ICH, 1 GI, 1 retrop, 1 emovitreo) had been treated with idarucizumab and all survived.
- 13 NMCRB
- 16 MINOR BLEEDINGS

- SPECIFIC DOAC measurements very rarely requested

THROMBOEMBOLIC COMPLICATIONS

MAIN CLINICAL CHARACTERISTICS

Number of Patients	62
Males (%)	33 (53%)
Median Age (IQR range) years	74 (63,83)
Indication to anticoagulation	
Non Valvular AF	35 (56%)
Venous thromboembolism	27 (44%)
Anticoagulant drugs	
Apixaban	13(21%)
Dabigatran	10 (16%)
Rivaroxaban	38 (61.4%)
Edoxaban	1 (1.6)
Antiplatelet drugs	6 (9.7%)
Outcome at discharge	62
Complete resolution	49 (79%)
Disability	13 (21%)
Death	0
Outcome within six months	60*
Complete resolution	46 (77%)
Disability (for patients with stroke)	13 (21.6%)
Death	1/60 8(2.5%)**

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

CHARACTERISTICS OF THROMBOTIC EVENTS

Thrombotic events n, (%)	All (62)	AF (35)	VTE (27)
Deep vein thrombosis	15 (24)	2	13
DVT+PE	5 (8.1)	1	4
Isolated PE	8(13)	2	6
TVS	1 (2.4)	-	1
Stroke	20 (32.3)	19	1
TIA (positive imaging)	4 (6.4)	3	1
Peripheral embolism	5 (9.7)	5	-
Acute myocardial infarction	3 (4.8)	2	1
Retinal Vein Occlusion	1 (1.6)	1	-

LAB TESTING

Test (n° of patients)	Before intervention	Post intervention
	Median (IQR)	-
PT INR (44)	1.12 (0.85-3.1)	-
aPTT ratio (42)	1.47 (0.85-3.19)	-
Hemoglobin (53)	12.3 (6.3-14)	-
Platelet count (53)	228 (85-502)	-
Cr Cl mL/min (50)	64 (44-87)	-
Dabigatran DTT (ng/ml) (4/10) (median; range)	24(16-121)	-
Apixaban aXa (ng/ml) (5/13) (median; range)	127 (64-154)	-
Rivaroxaban aXa activity (9/38) (median; range)	120 (39-146)	-

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 occurr more frequently as recurrence
- Very rarerely specific lab testing are requested. Difficult interpretation of aXa levels because nearly the majority of patients were already treated also with LMWH
- Too Limited number of patients with thromboembolic complications enrolled to allow possible conclusion
- Necessity to extend the enrollment

DISTRIBUTION OF EVENTS IN RELATION TO TREATMENT

Events	Apixaban (6)	Dabigatran (8)	Rivaroxaban (27)
DVT	1	1	7
DVT+EP	-	-	4
EP	-	1	4
SVT	-	-	1
Stroke	2	4	7
TIA (positive imaging)	0	0	2
Peripheral embolism	1	1	2
Acute myocardial infarction	2	-	-
Retinal Vein Occlusion	-	1	-

FATAL BLEEDINGS

	apixaban (30)	dabigatran (29)	rivaroxaban (49)	Total (108)
Intracerebral ICH (n°)	2	1	-	3
Deep ICH (n°)	2	1	5	8
Subdural ICH (n°)	-	-	1^	1
G.I. Bleeding (n°)	2	-	-	2
Retroperitoneal B. (n°)	-	1*	-	1
Total (n°;%)	**6**; (20)	**3**; (10)	**6**; (12.2)	**15**;(13.8)

n°of fatal bleedings and percentage calculated on total complications for each drug
* post-traumatic; ^post-traumatic riv +ticagrelor

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.