Simposio SISET/ATBV/SIAPAV

Esperienza dal mondo reale nella gestione della patologie tromboemboliche e delle terapie anticoagulanti

GESTIONE DEI PAZIENTI CON TROMBOEMBOLISMO VENOSO CON I FARMACI ANTICOAGULANTI ORALI DIRETTI

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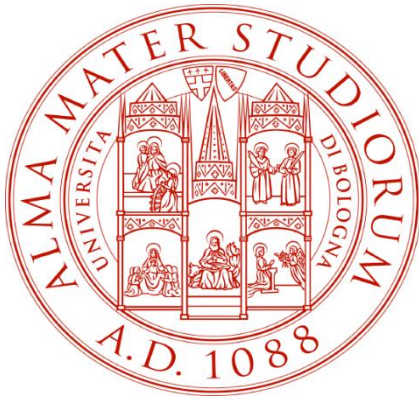

Disclosures of: B. Cosmi

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Other	No conflict of interest to disclose

Treating Acute Venous Thromboembolism — Shift with Care

Mary Cushman, M.D.

Table 1. Key Components of a Protocol for the Use of New Anticoagulant Agents in Patients with Acute Venous Thromboembolism.

Patient preference: Treatment options are presented along with advantages and disadvantages of each.
Patient selection: Selection criteria for treatment are drawn from key trials. (In the current trial,[4] patients with provoked venous thromboembolism due to a transient risk factor [e.g., surgery] were not included unless they had another irreversible risk factor requiring 6 months of treatment. Only 143 patients with cancer were enrolled, and only 18% of the patients were 75 years of age or older.)
Drug interactions: Potentially interacting drugs, such as inducers or inhibitors of P-glycoprotein and the cytochrome P-450 enzyme 3A4, should be taken into consideration. The interactions differ among the three new anticoagulants (apixaban, rivaroxaban, and dabigatran) available in the United States and may relate to characteristics of the patient such as age, body weight, and presence or absence of kidney disease. Readers should refer to the product monograph for each medication.
Compliance: An individualized written "treatment contract," signed by the patient at the start of treatment, is used to ensure that patients understand the treatment instructions. Patients in the real world may be less compliant than those in clinical trials. The new anticoagulants have short half-lives, as compared with warfarin, and some, like apixaban, require twice-daily dosing. If patients miss doses, anticoagulation is rapidly reversed, and they are at risk for recurrent thrombosis. This might be especially true during the first few weeks of treatment.
Follow-up: Follow-up is no less intense than with conventional treatment that requires frequent contact for laboratory monitoring. A few days after treatment initiation or hospital discharge, patients are called by a nurse to ensure compliance. The first clinic visit is 1 to 2 weeks after the start of treatment or hospital discharge, and pill counts are performed in order to document compliance.
Monitoring: Experience with the protocol is recorded for periodic review and revision. Adverse events are reported to the hospital pharmacy and therapeutics committee.

WHICH PATIENTS SHOULD BE TREATED WITH DOACs IN REAL LIFE?

- Characteristics of patients enrolled in RCTs of DOACs for VTE (ideal patients?)
- Real life data: phase IV studies

DIRECT ORAL ANTICOAGULANTS (DOACs) IN REAL LIFE

- Clinical trials provide the strongest evidence for effect of an intervention but
- a controlled situation in very selected patients having:
  - specific inclusion and exclusion criteria
  - regular follow-up of enthusiastic patients by (probably equally enthusiastic) researchers
  - with set and regular protocol-based follow-up appointments.
  - real-world clinical practice can be rather different.

  - DOACs would be prescribed to a broad range of patients, sometimes not restricted to trial inclusion or exclusion criteria, and follow-up arrangements might be less rigid

WHICH PATIENTS HAVE BEEN ENROLLED IN RCTS OF DOACS FOR VTE? INCLUSION CRITERIA

	Age Sex	Weight limits	VTE location	VTE type	Symptomatic	Treatment duration
RECOVER Dabigatran	>18, MF	No	lower limbs proximal DVT /PE	To be treated for 6 months	yes <14 gg	6 mo.
EINSTEIN-DVT Rivaroxaban	>18, MF	No	lower limbs proximal DVT /no PE	Not specified	yes	12 mo. max
EINSTEIN/PE Rivaroxaban	>18, MF	No	PE without DVT	Not specified	yes	12 mesi max
AMPLIFY AMPLIFY-EXT apixaban	>18, MF	No	lower limbs proximal DVT /PE	Idiopathic/ Persistent risk factors	yes	6 mo.
HOKUSAI-VTE Edoxaban	>18, MF	No	lower limbs proximal DVT /PE	Not specified	yes	12 mo.max

WHICH PATIENTS HAVE BEEN EXCLUDED IN RCTS OF DOACS FOR VTE? EXCLUSION CRITERIA

	Hemodynamically unstable PE / vena cava filter/ thrombectomy/thrombolysis	Liver disease	creatinine Clearance	ASA	Non controlled arterial hypertension	Use of inducers/ inhibitorsCYP-450 3A4
RECOVER Dabigatran	Yes	AST x 2	< 30 ml/m'	>100 mg DAPT	Not spec	Not spec
EINSTEIN-DVT/PE Rivaroxaban	Yes	ALTX3 hepatitis/cirrhosis	< 30 ml/m'	Non specificato	Yes Syst >180 Diast>110	Yes
AMPLIFY AMPLIFY-EXT apixaban	Yes	AST/ALTx3 Bilirubin x 1.5	< 25ml/m'	>165 mg DAPT	YES Syst >180 Diast>110	Not spec
HOKUSAI-VTE Edoxaban	Yes	AST/ALTx3 Bilirubin x 1.5	< 30 ml/m'	>100 mg DAPT	Yes Syst >170 Diast>110	Yes

WHICH PATIENTS HAVE BEEN EXCLUDED IN RCTS OF DOACS FOR VTE? EXCLUSION CRITERIA

	high bleeding risk	Thrombocyto-penia	Cancer	Pregnancy	Breast feeding
RECOVER Dabigatran	Yes	Not specified	Yes	Yes	Yes
EINSTEIN-DVT/PE Rivaroxaban	Yes	Not specified	Yes	Yes	Yes
AMPLIFY AMPLIFY-EXT apixaban	Yes	< 100.000	Yes	Yes	Yes
HOKUSAI-VTE Edoxaban	Yes	Not specified	Yes	Yes	Yes

WHICH PATIENTS HAVE BEEN ENROLLED?

	Age:mean range Sex	Weight mean,range	VTE location	Cancer	Previous VTE	TTR
RECOVER Dabigatran Non inf margin:57%	55,18-97 F:42%	85; 38-175	DVT:69% DVT+EP:9.8% EP:21%	5%	25%	59%
EINSTEIN-DVT Rivaroxaban Non inf margin:50%	56; F :43%	<50 kg: 2% 50-100:83% >100 kg:14%	--	7%	19%	58%
EINSTEIN/PE Rivaroxaban	57 F: 46%	<50 kg: 2% 50-100:83% >100 kg:14%	Multiple lobes > 25%entire vascul: 25%	5%	18%	63%
AMPLIFY Apixaban Non inf margin:70%	57 F:42%	84;<60: 8.6% 60-100: 71% >100:19%	DVT:65% DVT+EP:9.4% EP:25%	2.5%	17%	61%
HOKUSAI-VTE Edoxaban Non inf margin:70%	55 > 75y:13% F:42%	<60:13% >100:15%	DVT: 59% PE:41% Ext PE/DVT: 45%	10%	NA	63%

QUALI PAZIENTI CON TEV DA TRATTARE CON NAO: TRASFERIBILITA' DEI RISULTATI NELLA PRATICA CLINICA

- TVP prossimali arti inferiori /EP sintomatiche senza neoplasia senza IRC severa

- Problemi aperti:

- età > 75 aa
- pesi estremi
- compliance
- sedi diverse di TEV (distali, TVS, arto sup, viscerali, seni cerebrali?)
- uso pediatrico
- trattamento a lungo termine

Real life data: phase IV studies

- Popular notion: drugs are thoroughly studied before they are marketed: WRONG
- It is not possible to study more than a few thousand patients in clinical trials for economic reasons.
- Additional knowledge about drugs comes from
  - scientific, rather than commercial, interest through research done by investigators with academic interest
  - Generally, such studies are possible only after the drug receives regulatory approval and becomes commercially available.
  - Drug tested in a wide spectrum of patients, with varied ethnicity, various underlying diseases, and a range of concomitant medication.

Real life data: phase IV studies

- The entire post-marketing research can be distinguished in Phase IV trials and post-marketing surveillance studies (PMS).
- Phase IV trials are interventional and a comparator can be employed.
- PMS are non- interventional or observational and conducted primarily to monitor safety in every day clinical practice.
- PMS are designed to detect any rare or long-term adverse effect over a larger patient population and longer time period than was possible during the pre-approval trials.
- They can include measures of efficacy

REAL LIFE DATA OF DOACs in VTE

- (i) Dresden Noac Registry

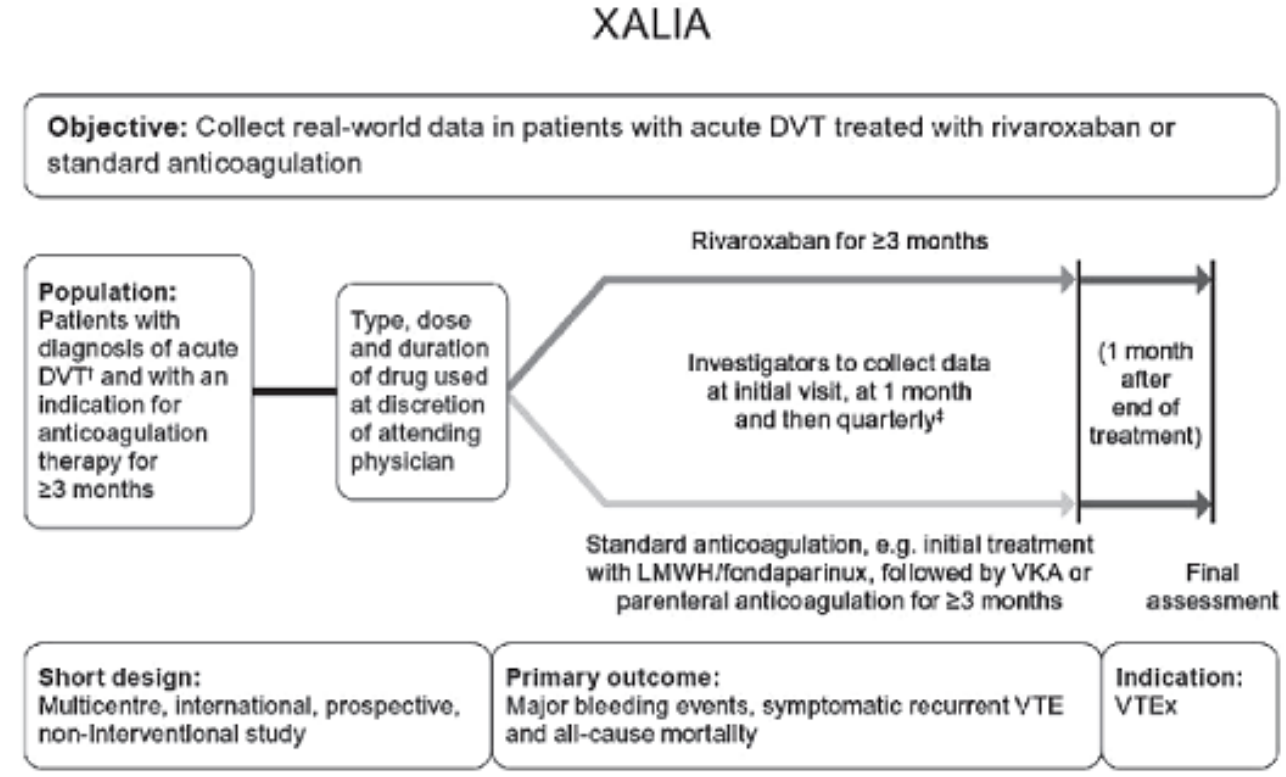
- (ii) **XALIA study**: non-interventional observational cohort study investigating rivaroxaban in VTE treatment in routine clinical practice

- (iii) PREFER in VTE, a multicentre, prospective observational disease registry for quality of life and treatment satisfaction for 4000 patients with VTE across Europe

- (iv) The GARFIELD-VTE registry, an observational study for about 10,000 patients to look at the acute and long term management of VTE, its complications and healthcare resource utilization.

- (v) START Register a multicentre registry to assess the efficacy and safety of DOAC

Safety and eff ectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study



12 mo

Inclusion	Exclusion
• Female or male patients ≥18 years of age • Diagnosis of acute DVT, objectively confirmed • Indication for anticoagulation therapy for at least 12 weeks • Patients willing to participate in the study and available for follow-up	• Patients with acute symptomatic PE† • Other exclusion criteria are dependent on local product information

Ageno W et al, Lancet Hematol 2016

Safety and eff ectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study

	Rivaroxaban (n=2619)	Standard anticoagulation therapy* (n=2149)	p value	Early switchers (n=368)
Age, years	59·0 (45·0–71·0)	66·0 (47·0–73·0)	<0·0001	61·0 (47·5–73·0)
Age group, years	..	..	<0·0001	..
<60	1366 (52%)	824 (38%)	..	172 (47%)
≥60	1253 (48%)	1325 (62%)	..	196 (53%)
Sex			0·074	
Men	1428 (55%)	1116 (52%)	..	211 (57%)
Women	1191 (45%)	1033 (48%)	..	157 (43%)
Bodyweight	..	..	0·0092	..
<50 kg	22 (1%)	34 (2%)	..	2 (1%)
≥50 to <70 kg	525 (20%)	505 (23%)	..	75 (20%)
≥70 kg to <90 kg	881 (34%)	713 (33%)	..	131 (36%)
≥90 kg	636 (24%)	500 (23%)	..	93 (25%)
Missing	555 (21%)	397 (19%)	..	67 (18%)
First available CrCl	..	..	<0·0001	..
<30 mL/min	13 (1%)	61 (3%)	..	4 (1%)
≥30 to <50 mL/min	88 (3%)	157 (7%)	..	20 (5%)
≥50 to <80 mL/min	419 (16%)	398 (19%)	..	71 (19%)
≥80 mL/min	1125 (43%)	797 (37%)	..	169 (46%)
Missing	974 (37%)	736 (34%)	..	104 (28%)

TTR:56.2%

Ageno W et al, Lancet Hematol 2016

Safety and eff ectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study

	Rivaroxaban	Standard		
Index diagnosis	--	--	<0·0001	--
Deep-vein thrombosis only	2399 (92%)	1894 (88%)	--	291 (79%)
Deep-vein thrombosis with pulmonary embolism	220 (8%)	255 (12%)	--	77 (21%)
Type of deep-vein thrombosis†	--	--	0·0033	--
Provoked	896 (34%)	823 (38%)	--	126 (34%)
Unprovoked	1692 (65%)	1300 (61%)	--	232 (63%)
Missing	31 (1%)	26 (1%)	--	10 (3%)
Previous venous thromboembolism	630 (24%)	481 (22%)	--	79 (22%)
Active cancer at baseline	146 (6%)	411 (19%)	<0·0001	30 (8%)
Known thrombophilic condition	157 (6%)	112 (5%)	0·24	25 (7%)
Previous major bleeding episode	37 (1%)	64 (3%)	0·0002	17 (5%)

Ageno W et al, Lancet Hematol 2016

Safety and eff ectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study

	Safety population†			Propensity score adjustment†		
	Rivaroxaban (n=2619)	Standard anticoagulation (n=2149)	Hazard ratio (95 % CI)	Rivaroxaban (n=2505)	Standard anticoagulation (n=2010)	Hazard ratio (95 % CI)
Major bleeding (adjudicated)	19 (0.7 %)	48 (2.3 %)	0.41 (0.24–0.70)	19 (0.8 %)	43 (2.1 %)	0.77 (0.40–1.50)
Recurrent VTE	37 (1.4 %)	55 (2.6 %)	0.67 (0.44–1.03)	36 (1.4 %)	47 (2.3 %)	0.91 (0.54–1.54)
All-cause mortality	12 (0.5 %)	88 (4.1 %)	0.26 (0.14–0.49)	11 (0.4 %)	69 (3.4 %)	0.51 (0.24–1.07)

Ageno W et al, Lancet Hematol 2016

Safety and eff ectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study

- rivaroxaban-treated patients
- younger and having fewer cancers
- lower risk profile than those treated with standard anticoagulation, although the propensity score adjusted results show no significant difference in efficacy and safety with rivaroxaban compared with standard of care.

Lip GYH et al, Lancet Hematol 2016

Safety and eff ectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study

- Standard care: poor quality of anticoagulation:57%

- Median duration of treatment was 181 days (IQR 94–310) with rivaroxaban and 190 days (97–368) with standard anticoagulation

- Longer term follow-up would provide additional supportive information, especially on the (very) long-term chronic use of rivaroxaban, which is highly relevant for treatment adherence and persistence, as well as long term outcomes

Ageno W et al, Lancet Hematol 2016

The management of patients with venous thromboembolism in Italy: insights from the PREFER in VTE registry

Table 1 Number of patients in the participating European countries/areas enrolled between January and December 2013

Country/area	France	DACH	Italy	Spain	UK	Total
Patients per country	248	565	816	199	15	1843

DACH Germany/Switzerland/Austria

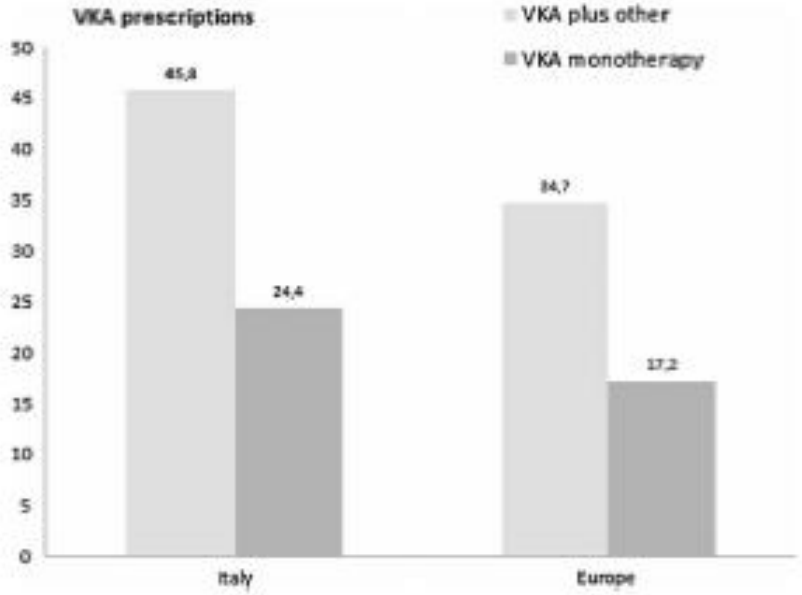


Fig. 1 VKA prescriptions in Italy and in Europe. *VKA* vitamin K antagonist

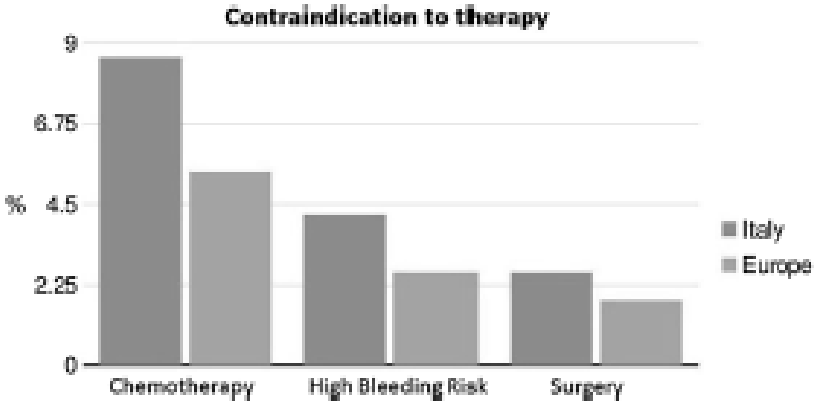


Fig. 2 Contraindication to therapy in Italy and in Europe

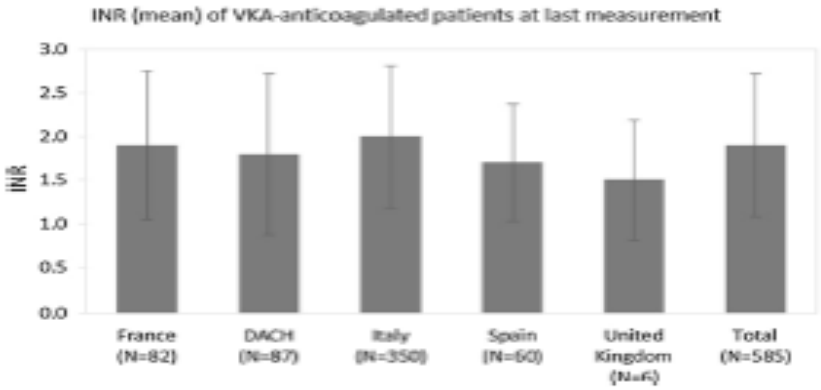


Fig. 3 INR in VKA-anticoagulated patients at last measurement. *INR* international normalized ratio, *DACH* Germany/Swizerland/Austria, *VKA* vitamin K antagonist

Guercini F Intern Emerg Med
DOI 10.1007/s11739-

START–Register

SURVEY ON ANTICOAGULATED PATIENTS – REGISTER

Registro computerizzato per la raccolta dei dati di pazienti trattati cronicamente con anticoagulanti

FCSA-START Study: bleeding and thrombotic events in an italian prospective cohort of patients treated with DOAC

Antonucci E, Migliaccio L, Marongiu F, Pengo V, Poli D, Testa S, Tripodi A, Guazzaloca G , Moia M, Palareti G on behalf of the FCSA-START-Register participating centers

XXIV Congresso Nazionale
Abano 9-12- Novembre 2016

Organizzazione follow-up

- Prescrizione del farmaco
- Controllo ad un mese dalla prescrizione
- Controllo a 6 mesi dalla prescrizione
- Controllo a 12 mesi dalla prescrizione

- Controllo a 24 mesi dalla prescrizione

Lost at follow-up
1.0%

Characteristic of patients in relation to indication

	AF	VTE
Number	1196	691
Median Age, y (IQR)	76.5 (71,82)	60 (46,73)
Males (%)	54.9	58.0
Type of DOACs Apixaban Dabigatran Rivaroxaban	 35.5% 36.4% 28.1%	 4.7% 6.3% 89.0%
CrCl 30-60 ml/min^2 CrCl ≤30 ml/min^2	36% 1.4%	16% 0.5%
Patients Shifted from VKA	47.7%	31%
Low Dose DOACS	42.4%	36.5 %

DOAC patients Follow-up

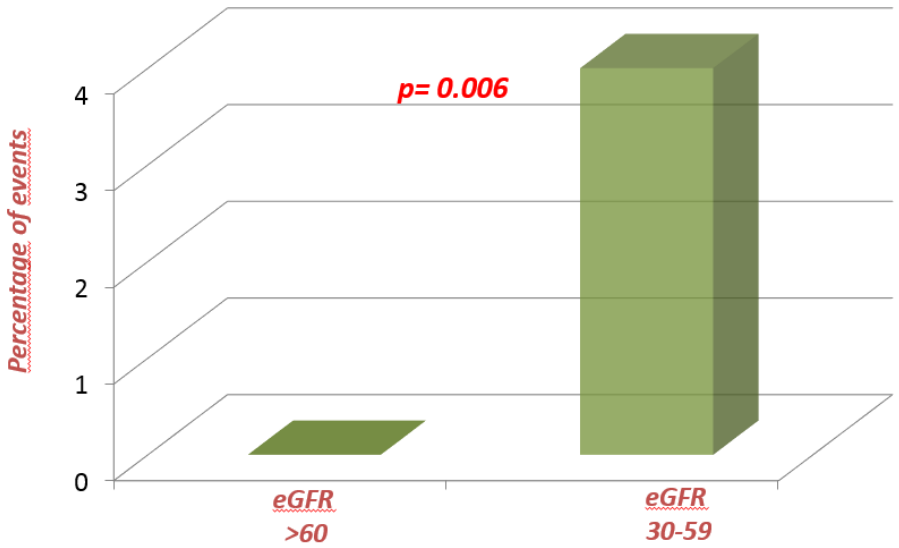
Bleeding and thrombotic events

	AF	VTE
Fup (pt-yrs)	1350	523
Major bleeding rate: x100 pt yrs	30* (2.2)	3 (0.57)
Cerebral Gastrointestinal Other	6* 14 10*	- 2 1
Fatal	3 (0.22)	
NMCRB Rate: x100 pty rs	21 (1.5)	5 (0.95)
Thromboembolic events Rate: x100 pt yrs	11 (0.8)	10 (1.9)

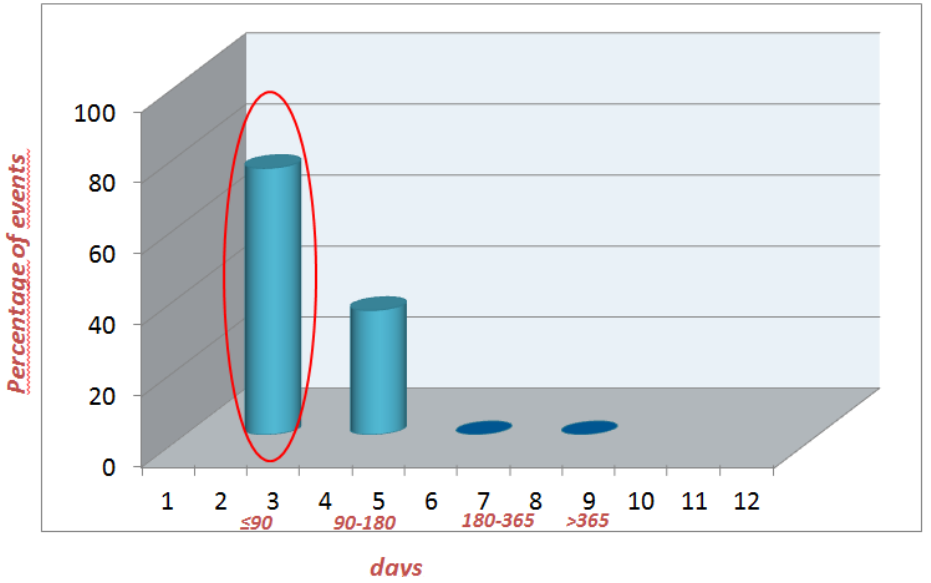
Fatal bleeding

*2 cerebral; 1 other

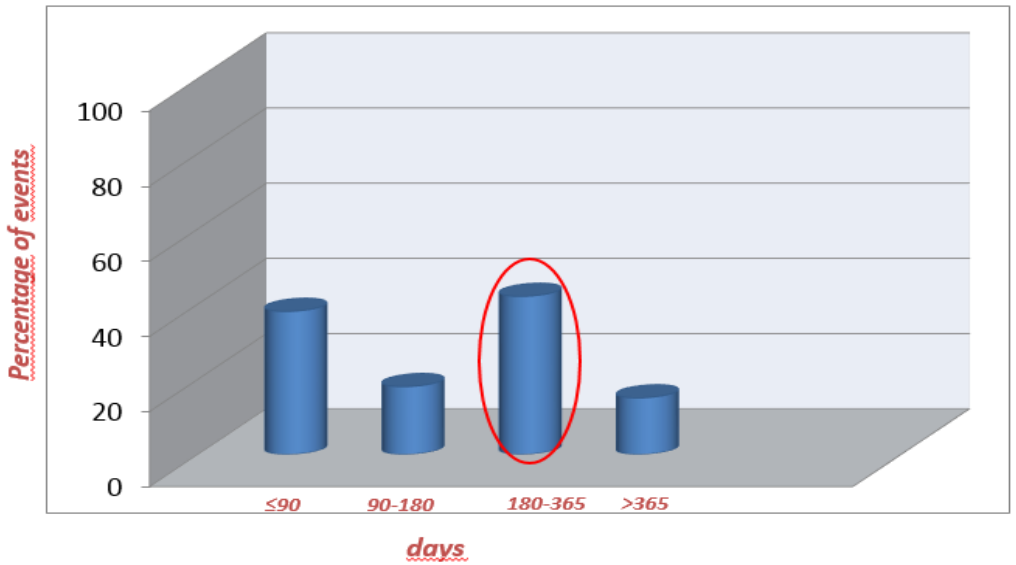
Bleeding events and renal impairment



Time of major bleeding events



Time of thrombotic events



Real-life treatment of venous thromboembolism with direct oral anticoagulants: The influence of recommended dosing and regimens Trujillo-Santos J, et al RIETE Investigators.

- to compare the outcomes in patients with VTE receiving DOACs
- according to the recommendations of the product label versus in those receiving non-recommended doses and/or regimens.

- rate of VTE recurrences, major bleeding and death during the course of therapy.
- As of March 2016, 1635 VTE patients had received
- DOACs for initial therapy and 1725 for long-term therapy.
- Pts not receiving the recommended therapy
- For initial therapy,

18 % on rivaroxaban and 50 % on apixaban

- For long-term therapy,

14 % on rivaroxaban,36 % on apixaban, 46 % on dabigatran

Thromb Haemost. 2016 Oct 27.
[Epub ahead of print]

Real-life treatment of venous thromboembolism with direct oral anticoagulants: The influence of recommended dosing and regimens

Trujillo-Santos J, et al RIETE Investigators.

During the course of therapy with DOACs,
8 patients developed VTE recurrences,
14 had major bleeding and
13 died.

Patients receiving DOACs at non-recommended doses and/or regimens experienced a

- higher rate of VTE recurrences (adjusted HR: 10.5; 95 %CI: 1.28-85.9)
- similar rate of major bleeding (adjusted HR: 1.04; 95 %CI: 0.36-3.03) or death (adjusted HR: 1.41; 95 %CI: 0.46-4.29) than
- those receiving the recommended doses and regimens.

Thromb Haemost. 2016 Oct 27. [Epub ahead of print]

Clinical trials with direct oral anticoagulants for stroke prevention in atrial fibrillation: how representative are they for real life patients?

468 patient with AF from the UZ Brussel Stroke Registry,
less than half of real life patients are eligible for therapy with one of the DOACs

Table 3 Number and percentage of patients eligible for DOAC treatment according to the clinical trials' inclusion and exclusion criteria and SmPC indications and contraindications

	Based on the clinical trials ($n = 468$)	Based on the SmPC ($n = 468$)
Dabigatran etexilate	223 (47.6 %)	341 (72.9 %)
Rivaroxaban	184 (39.3 %)	354 (75.6 %)
Apixaban	213 (45.5 %)	290 (62.0 %)

- Reasons for non-eligibility
- concomitant use of antiplatelet agents with apixaban,
- impaired renal function in dabigatran,
- concomitant use of rifampicin and anti-fungal drugs and
- presence of valvular heart diseases.

Pharmacol (2016) 72:1125–1134

REAL LIFE DATA

- Real-life studies have their inherent weaknesses
- such as non-controlled and heterogeneous patient groups
- uncontrolled influence of non-compliance
- other concomitant medications and co-morbidities.
- However, they provide a wealth of data and insight into how DOACs are used in the real world.

Despite the reassuring real world data on use of DOACs in routine care, the benefits of DOACs are not applicable to all patients

Table 16: Study Characteristics —EXTENDED treatment

Study	Population	Initial acute therapy		Extended therapy		End of study	Length of follow-up; comparator /intervention	No. randomized		
		Treatment	Duration	Treatment	Treatment duration			Comparator	Intervention 1	Intervention 2
Direct thrombin inhibitors										
Schulman 2013: RE-SONATE	Symptomatic DVT or PE	Approved anticoagulant or DOAC (DBG; from RECOVER or RECOVER II trials)	6-18	Placebo/DBG, 150 mg, BID	6 mo	12 mo after completion of treatment	Intended: 18 mo	668	685	NA
Schulman 2013: RE-MEDY	Symptomatic DVT or PE	Approved anticoagulant or DOAC (DBG; from RECOVER or RECOVER II trials)	3-12	VKA/ DBG, 150 mg, BID	36 mo	1 additional follow-up visit 30 days after end of treatment	Intended: 36 mo	1431	1435	NA
Factor Xa inhibitors										
Bauersachs 2010: EINSTEIN-EXT	Symptomatic DVT	Acenocoumarol or warfarin (EINSTEIN trial or routine care) or RVX (EINSTEIN trials)	6–12 mo	Placebo/RVX, 20 mg, QD	6 or 12 mo	1 additional follow-up visit 30 days after end of treatment	Intended: 7 or 13 mo	595	602	NA
Agnelli 2013: AMPLIFY-EXT	Symptomatic DVT or PE	Standard anticoagulant	6–12 mo	Placebo/APX, 2.5 mg, BID/APX, 5	12 mo	1 additional follow-up visit 30	Intended: 13 mo	829	842	813

Wells Ga et al, 2016