Le Pubblicazioni Scientifiche

Emilia Antonucci

Bologna 7-8 febbraio 2019

ANTICOAGULANT: VKA/DOAC

- Palareti G et al.The American College of Chest Physician score to assess the risk of bleeding during anticoagulation in patients with venous thromboembolism: reply. **J Thromb Haemost 2018**
- Palareti G et al. ACCP score to assess the risk of bleeding during anticoagulation: application to real-life data from the START2-REGISTRY **J Thromb Haemost 2018**
- Poli D et al . High risk for reoperation among patients with bioprosthetic heart valves and indication for long-term anticoagulation. **Open Heart 2018**
- Testa S, et al. Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Events Registry. **Intern Emerg Med 2018**
- Poli D et al. Mechanical Prosthetic Heart Valves: quality of anticoagulation and thromboembolic risk. The observational multicentre PLECTRUM Study. **Intern Journ of Cardiol 2018**
- Gentian D, et al.Warfarin prescription in patients with non-valvular atrial fibrillation and one non-gender relted risk factor (CHA2DS2VASc 1 or 2): a treatment dilemma. **Cardiovascular Therapeutics 2017**
- Tosetto A, et al. External validation of the DASH prediction rule: a retrospective cohort study. **J Thromb Haemost 2017**
- Palareti G et al on behalf of FCSA-START-Register (The ISCOAT 2016 study). Vitamin K Antagonist Therapy: Changes in the Treated Populations and in Management Results in Italian Anticoagulation Clinics Compared with those recorded 20 years ago. **Intern and Emerg Med 2017**
- Poli D, et al. Comparison of HAS-BLED and HAS-BED Versus CHADS2 and CHA2DS2VASC Stroke and Bleeding Scores in patients with atrial fibrillation. **Am J Cardiol 2017**
- Palareti G et al . The SAME-TT2R2 score predicts the quality of anticoagulation control in patients with acute VTE. A real-life inception cohort study**.** **Thromb Haemost 2016**
- Antonucci E, et al. The Italian START-Register on Anticoagulation with Focus on Atrial Fibrillation. **PLosOne 2015**

LABORATORY

- S. Testa et al, Edoxaban plasma levels in patients with non-valvular atrial fibrillation: inter and intra-individual variability, correlation with coagulation screening test and renal function. **Thromb Res (Accepted)**
- Testa S, et al. Drug Levels And Bleeding Complications In Atrial Fibrillation Patients Treated With Direct Oral Anticoagulants. **J Thromb Haemost (major revision)**
- Cini M et al, An in-vitro study to investigate the interference of enoxaparin on plasma levels of direct oral factor Xa inhibitors measured by chromogenic assays. **Intern Journ Lab Hemat 2019**
- Testa S et al. Low Drug Levels And Thrombotic Complications In High Risk Atrial Fibrillation Patients Treated With Direct Oral Anticoagulants. **J Thromb Haemost 2018**
- Cini M et al. Comparison of five specific assays for determination of dabigatran plasma concentrations in patients enrolled in the START-Laboratory Register. **Intern Journal of Lab Hemat 2018**
- Testa S. et al. START-Laboratory Register. Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics. **Thromb Res 2016**
- Testa S et al. Poor comparability of coagulation screening test with specific measurement in patients on direct oral anticoagulants: results from a multicenter/multiplatform study. **J Thromb Haemost 2016**

ANTIPLATELET

- Patti G, et al . Impact of Chronic Renal Failure on Ischemic and Bleeding Events at 1 Year in Patients With Acute Coronary Syndrome (from the Multicenter START ANTIPLATELET Registry). **American Journal of Cardiology 2018**
- Cirillo P, et al. Gender-related differences on the choice of antiplatelet therapy and its impact on one-year clinical outcome in patients presenting with Acute Coronary Syndrome: Insights from the START Antiplatelet Registry. **Angiology 2018**
- Calabrò P et al. Epidemiology and management of patients with acute coronary syndromes in real-world practice: evolving trends from the EYESHOT study to the START-ANTIPLATELET registry. **Angiology 2018**
- Patti G et al. Prevalence and predictors of dual antiplatelet therapy prolongation beyond one year in patients with acute coronary syndrome. **PLosOne 2017**

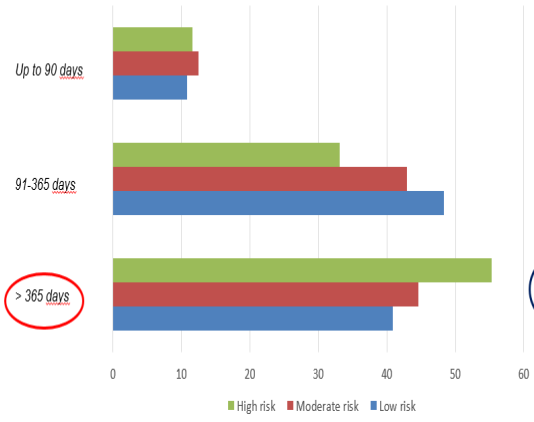
Journal of Thrombosis and Haemostasis, **16**: 1994–2002 DOI: 10.1111/jth.14253

ORIGINAL ARTICLE

The American College of Chest Physician score to assess the risk of bleeding during anticoagulation in patients with venous thromboembolism

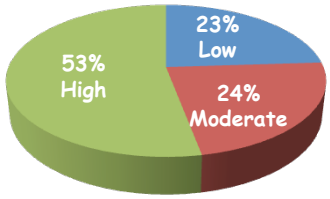
G. PALARETI,* E. ANTONUCCI,* D. MASTROIACOVO,† W. AGENO,‡ V. PENGO,§ D. POLI,¶ S. TESTA,** A. TOSETTO†† and P. PRANDONI‡‡

Duration of treatment in relation to ACCP class risk



p=0.0001 High vs Low

Distribution of patients according to ACCP Score Risk Categories



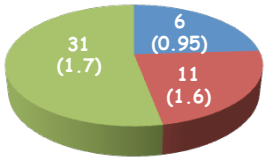
- ✓ The distribution among the three categories was similar in patient with provoked and unprovoked index event.
- ✓ More patient in high risk category were treated with VKA

2263 VTE patients
1522 VKA (Fup 2216)
741 DOACS (Fup 914)
Median age 67 yrs
Males 51%

Bleeding events

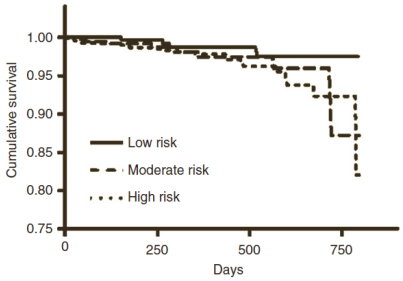
Patients	2263
Total follow-up, pt-yrs	3130
Bleeding events, n (rate x 100 pt-yrs)	48 (1.5)
Major Bleeds, n (rate x 100 pt-yrs) ICH GI Other	28 (0.9) 8 7 13
CRNMB	20 (0.6)

Distribution of bleeding events (number, rate x 100pt-yrs)



RR High vs low/moderate risk = 1.2 (0.7-2.5)

Probability of bleeding-free survival for the three risk class in the first 24 months from anticoagulation inception



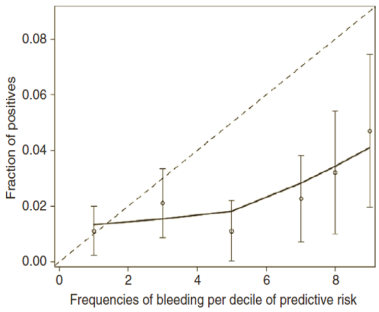
Patients with bleeding were significantly older median age 74 years [IQR 63, 81] vs. 64 [51, 77]; p = 0.02

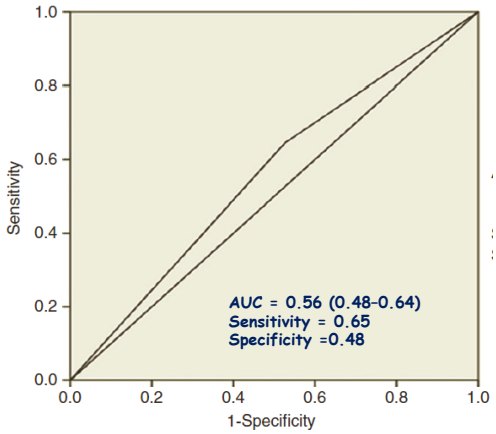
Bleeding was significantly more frequent in women than in men :2.2%/year vs. 0.9%/year, RR 2.5 [95% CI 1.2-5.1].

Palareti G et al , JTH 2018

ROC curve ACCP bleeding risk score for the prediction of bleeding complications during long-term anticoagulant treatment

Calibration plot model: frequencies of bleeding per decile of predictive risk





C Statistic:
Low = 0.55 (0.48-0.63)
Moderate = 0.50 (0.42-0.58)
High= 0.56 (0.48-0.64)

Palareti G et al , JTH 2018

Conclusion

- ✓ According to the bleeding prediction rule and score proposed by the ACCP guideline, more than 50% of all patients managed by some Italian anticoagulation clinics for an acute VTE were categorized as at high risk of bleeding
- ✓ The majority of patients at high bleeding risk (according to the ACCP score) received extended anticoagulation and their bleeding rate was very low during long-term AC
- ✓ The ACCP score has very limited predictive value for bleeding occurrence and can hardly be used to guide decisions about suggesting or excluding an extended treatment for the prevention of recurrences in patients with unprovoked VTE
- ✓ New prediction tools for risk of bleeding, updated in relation to the contemporary available therapeutic instruments are required

Palareti G et al , JTH 2018

ORAL ANTICOAGULATION WITH VKAs OR DOACs in VERY ELDERLY PATIENTS WITH ATRIAL FIBRILLATION. RESULTS FROM THE PROSPECTIVE MULTICENTER START2-REGISTER STUDY

Daniela Poli[1] MD, Emilia Antonucci MSc[2], Walter Ageno[3] MD, Lorenza Bertù[3] PhD, Ludovica Migliaccio[2] BSc, Lucia Martinese[4] MD, Giuseppe Pilato[4] MD, Sophie Testa MD[5], Gualtiero Palareti[2] MD coordinator of START2 Register

January 2012-April 2018
1124 AF patients
who started VKA/DOACS at ≥85 yrs

Descriptive statistics of baseline features by treatment group

	All VKAs (N=660)	DOACs naive (N=322)		All DOACs (N=464)	
	N%	N (%)	p-value*	N (%)	p-value**
Sex- Female	374(56.7)	196 (60.9)	0.21	265 (57.5)	0.77
Age (Years) - Mean (SD)	87.4 (2.2)	88.4 (2.8)	**<0.0001§**	88.2 (2.7)	**<0.0001§**
Co-morbidity					
Renal failure (creatinine clearance<30)	163 (24.7)	33 (10.3)	**<0.0001**	40 (8.6)	**<0.0001**
Previous cancer	103 (15.6)	50 (15.5)	0.97	72 (15.5)	0.97
Active cancer	18 (2.7)	4 (1.2)	0.14	8 (1.7)	0.27
Diabetes mellitus	113 (17.1)	56 (17.4)	0.92	80 (17.2)	0.96
Hypertension	562 (85.2)	262 (81.4)	0.13	386 (83.2)	0.37
Previous stroke	106 (16.1)	80 (24.8)	**0.001**	109 (23.5)	**0.001**
Previous bleeding	17(2.6)	18 (5.6)	**0.02**	32 (6.9)	**0.001**
Coronary artery disease	147 (22.3)	44 (13.7)	**0.001**	63 (13.6)	**0.0002**
Heart Failure	202 (30.6)	89 (27.6)	0.34	130 (28.0)	0.35
POAD	64 (9.7)	27 (8.4)	0.51	36 (7.8)	0.26
COPD	97 (14.7)	36 (11.2)	0.13	60 (12.9)	0.40
Frail subjects[£]	61 (9.2)	36 (11.2)	0.34	57 (12.3)	0.10

Median CHA2DS2VASc and HAS-BLED scores were similar between the two groups

Poli D et al, submitted

Survival analysis - Cox proportional hazard model, Weighted propensity score for major bleeding, stroke/TIA and death

Adverse event	rate	type of OA	N	Univariate HR	Univariate 95% CI	Propensity Score Weighted HR	Propensity Score Weighted 95% CI
Major bleeding	2.24	*VKAs*	31/660	1.00	Ref.	1.00	Ref.
	2.46	*DOACs*	11/322	0.99	0.50;1.97	0.88	0.42;1.80
Stroke/TIA	0.58	*VKAs*	8/660	1.00	Ref.	1.00	Ref.
	1.84	*DOACs*	8/322	3.24	1.25;8.40	4.04	1.60; 10.20
Death	16.2	*VKAs*	224/660	1.00	Ref.	1.00	Ref.
	9.2						
		DOACs	42/322	0.67	0.48;0.94	0.64	0.46;0.91

- Among very elderly AF patients we confirm the overall safety and effectiveness of anticoagulant treatment.
- Similar bleeding risk between patients treated with DOACs and VKAs.
- Higher risk for cerebral thrombotic events in DOACs patients.
- Lower mortality rates in DOACs patients, independently of the baseline clinical characteristics

Poli D et al, submitted

Anticoagulant treatment of very old patients with venous thromboembolism (VTE): Results from the prospective multicenter START2-Register study

Adverse events	n. (rate x 100 pt-yrs)
Major Bleeds	5 (1.22)
On VKAs	3 (0.91)
On DOACs	2 (2.53)
VTE recurrence	2 (0.5)
On VKAs	1/175 (0.30)
On DOACs	1/85 (1.26)
Death	
On VKAs	54 (16.5)
On DOACs	6 (7.6)

Type of anticoagulant	n. (%)
AVK	174 (67.5)
DOACs	85 (32.5)
DOACs (low dose regimen)	38 (45.2)

259 VTE
Females 65%
DVT 58%
Fup 406 pt-yrs
Median time of treatment 13 mths
Median time of treatment 12 mths (first event)

- Elderly VTE patients showed lower rate of co-morbidity than elderly AF patients
- Elderly VTE patients are maintained frequently on long-term treatment
- When a DOAC was used, in 45% of cases a low-dose regimen was adopted.
- Both major bleeding and VTE recurrence were higher among DOACs treated patients.
- Higher mortality among AVK treated patients

Poli D et al, Draft

ISOLATED PULMONARY EMBOLISM. IS IT THE SAME DISEASE THAN DEEP VENOUS THROMBOSIS WITH OR WITHOUT PULMONARY EMBOLISM? CHARACTERISTICS OF PATIENTS AND CLINICAL EVOLUTION. DATA FROM THE START2-REGISTRY

Gualtiero Palareti*, Emilia Antonucci*, Francesco Dentali&, Daniela Mastroiacovo†, Nicola Mumoli††, Vittorio Pengo§, Daniela Poli¶, Sophie Testa** Pietro Luigi Pujatti§§, Vincenzo Giannicola Menditto&&, Davide Imberti¶¶, Andrea Fontanella#

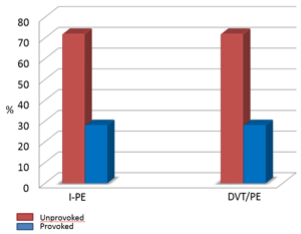
Main clinical characteristic

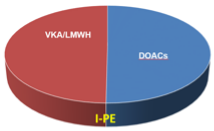
	I-PE	DVT/PE	P	OR (95%CI)
Total n. 3573	693 (19.4)	2880 (80.6)		
Males	298 (43.0)	1487 (51.6)	0.001	1.4(1.19-1.67)
Females	395 (57.0)	1393 (48.4)		
Median age (IQR) years	66 (55,8)	64 (52,8)	0.001	
Age ≤50 y	141(20.3)	675 (23.4)		
Age >75 y	257 (37.1)	843 (29.3)	0.001	1.4 (1.13-1.69)

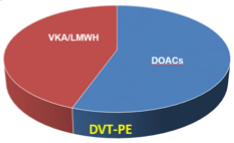
Complication during follow-up

	I-PE n. 693	DVT/PE n. 2880	p
Follow-up years n.	993	3511	
Anticoagulant treatment stopped during follow-up	219 (31.6)	1171 (40.6)	0.001
Previous bleeding (MB in the history)	22 (3.2)	84 (2.9)	0.7
Major bleeding events (rate % pt-yrs)	11 (1.1)	37 (1.0) 5 Fatal	
Type of bleeds			
ICH	4/171 (2.3)	11/710 (1.5)	
GIB	7/882 (0.8)	26/3341 (0.77)	
Thrombotic events (rate % pt-yrs)	13 (1.3) 1 Fatal	64 (1.8) 1 Fatal	
Death	44 (6.3)	140 (4.9)	0.1

Nature of index event





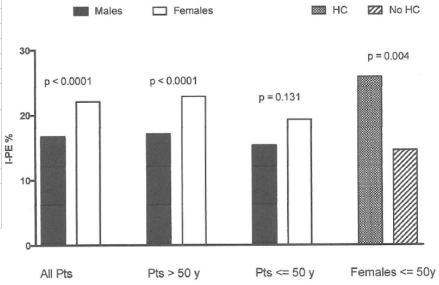


Anticoagulant treatment

Risk Factors for I-PE univariate and multivariate analysis

Risk Factors	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Females	1.3 (1.1-1.5)	0.001	1.2 (1.1-1.5)	0.006
Age >75 years	1.1 (1.0-1.3)	0.06	1.3 (1.0-1.5)	0.01
Previous stroke/TIA	1.1 (0.9-1.2)	0.2		
Hypertension	1.0 (0.8-1.1)	0.7		
Heart failure	1.6 (1.1-2.4)	0.006	1.6 (1.0-2.3)	0.03
CAD	1.3 (1.0-1.8)	0.02	0.9 (0.5-1.8)	0.6
PAD	1.0 (0.7-1.5)	0.7		
All cardiovascular diseases &	1.0 (0.9-1.1)	0.9		
Cardiovascular diseases, except hypertension	1.3 (1.0-1.6)	0.01	1.6 (0.8-3.1)	0.2
Moderate-severe renal insufficiency (CrCl 30-60 ml/min)	0.9 (0.8-1.1)	0.7		
Atrial fibrillation	1.4 (1.0-2.0)	0.04	1.3 (0.9-1.9)	0.08
Cancer (active)	1.5(1.2-1.6)	0.001	1.5 (1.2-1.9)	0.001
Hormonal contraception users in females aged < 50 years	2.1(1.6-2.9)	0.001	2.0 (1.4-2.9)	0.001

Prevalence of I-PE in all patients analyzed



About 20% of all VTE patients included in a large, inception registry had a I-PE

Baseline clinical characteristics of I-PE patients differed significantly from DVT/PE patients

I-PE patients had less venous complications but more cardiovascular events than DVT/PE patients

Older age, female sex, and the presence of heart failure or cancer, are risk factors for the presentation as I-PE

I-PE was more frequent among young females who used HC

Palareti G et al, submitted

Work in progress…….

Draft

START ANTICOAGULANT

- ✓ Bleeding risk ed eventi cardiovascolari in pazienti con piastrine > o < a 150.000 dopo aggiustamento per fattori di rischio e TTR (Pignatelli P, Pastori D, Violi F))
- ✓ Efficacia e sicurezza dei farmaci AVK e DOAC nei primi 90 giorni di trattamento vs trattamento più prolungato. Identificazione e caratteristiche che possono predire il rischio emorragico (Riva N)
- ✓ Qualità della terapia con avk in paz che ricevono nutrizione artificiale a lungo termine vs pz anticoagulati non in nutrizione artificiale (Barco S)
- ✓ Effetto dei farmaci anticoagulanti (AVK e DOAC) sulla funzionalità renale (Palareti G, Zanazzi M)

START ANTIPLATELET

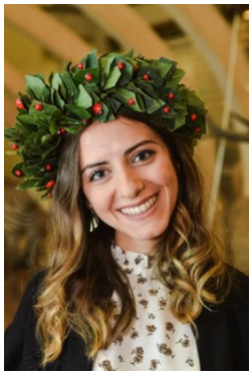
- ✓ Sotto-analisi su terapia antiaggregante ed outcome nei pazienti a differente BMI; (P. Calabrò)
- ✓ Sotto-analisi su terapia antiaggregante ed outcome nei pazienti ad alto rischio emorragico (P. Calabrò)
- ✓ Analisi dell'impatto della "optimal medical therapy" nei pazienti arruolati nello START (P. Cirillo)
- ✓ Impatto dell'ACEF score sui pazienti arruolati nello START Antiplatelet(P. Cirillo)
- ✓ Valutazione a sei mesi dei pazienti trattati con ticagrelor per un periodo di 12 mesi dopo il trattamento standard (G. Patti)

Nuovi progetti

- Onco START VTE (A. Falanga)
- Onco AF START (P. Pignatelli)
- START Antifosfolipidi (V. Pengo)
- Iside START (B. Cosmi)
- SVT START (M. Di Nisio)

Scuola di Farmacia, Biotecnologie e Scienza Motorie
Alma-Mater Studorium-Università di Bologna

Anticoagulanti orali di recente introduzione nella pratica clinica: Risultati ottenuti dallo START2 Registry in pazienti trattati per tromboembolismo venoso"



http://www.start-register.org

Start$_2$-Register

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www.fondazionearianna.org www.ariannafoundation.org
www.anticoagulazione.it