Simposio
Questioni sui DOACS in Pronto Soccorso

Perché i DOACS in Pronto Soccorso

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XI congresso nazionale
simeu
ROMA 24-26 MAGGIO 2018

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

ESC European Society of Cardiology

European Heart Journal (2018) **00**, 1–64
doi:10.1093/eurheartj/ehy136

NOACS compared with VKAs

- ✓ *Improved efficacy/safety ratio*
- ✓ *Predictable anticoagulant effect without need for routine coagulation monitoring*
- ✓ *Fewer food and drug interaction*

European guidelines have expressed a preference for NOACs over VKA in stroke prevention for AF patients, especially if newly initiated. This recommendation (Class I, level of evidence A) is based on the overall clinical benefit of NOACs.[3]

American Journal of Emergency Medicine 34 (2016) 9–13

Safety of direct oral anticoagulants: insights from postmarketing studies☆,☆☆,★,★★

Todd C. Villines, MD [a], W. Frank Peacock, MD [b,*]

Table
Bleeding and Myocardial Infarction Risk with DOACs vs Warfarin Given for Stroke Prevention in Atrial Fibrillation in RCTs and Large-Scale Observational Studies (Hazard Ratios and Relative Risks are Adjusted Unless Indicated)

Study	Mean Age	Follow-Up	Adjustment	Major Bleeding Risk (95% CI)	Intracranial Bleeding Risk (95% CI)	GI Bleeding Risk (95% CI)	Myocardial Infarction Risk (95% CI)
Dabigatran etexilate							
RE-LY [5]* (150 mg BID)	71 y	Median 2.0 y	Cox proportional-hazards models	RR 0.93 (0.81-1.07)	RR 0.40 (0.27-0.60)	RR 1.50 (1.19-1.89)	RR 1.38 (1.00-1.91)
U.S. Medicare [1] (75 mg and 150 mg)	>65 y	Total 37,587 patient-years	PSM	HR 0.97 (0.88-1.07)	HR 0.34 (0.26-0.46)	HR 1.28 (1.14-1.44)	HR 0.92 (0.78-1.08)
U.S. Department of Defense [15] (75 mg and 150 mg)	74 y	Mean 297 ± 259 d	PSM	HR 0.87 (0.74-1.03)	Unadjusted HR 0.49† (0.30-0.79)	Unadjusted HR 1.13† (0.94-1.37)	Unadjusted HR 0.65† (0.45-0.95)
MarketScan/Clinformatics [16] (dose not specified)	68 y	Mean 5 mo	PSM	HR 0.75 (0.65-0.87)	HR 0.31 (0.17-0.54)	HR 0.97 (0.79-1.18)	HR 0.89 (0.57-1.38)
Danish Registry of Medicinal Product Statistics [17] (150 mg)	71 y	Median 10.5 mo‡	PSM	HR 0.66 (0.36-1.14)	HR 0.08 (0.01; 0.40)	HR 1.12 (0.67-1.83)	HR 0.40 (0.21-0.70)
Rivaroxaban 20 mg QD							
ROCKET AF [6]*	Median 73 y	Median 707 d	Cox proportional-hazards models	HR 1.04 (0.90-1.20)	HR 0.67 (0.47-0.93)	RR 1.46 P <.001¶	HR 0.81 (0.63-1.06)
U.S. Department of Defense [18]§	78 y	Total 455 d	None	IR 2.86 (2.61-3.13)	IR 0.22 (0.15-0.30)	IR 2.53 (2.30-2.78)	NR
Post-Marketing Safety Surveillance (U.S. Department of Defense) [19]§	78 y	Total 2 y	None	IR 2.89 (2.71-3.08)§	Incidence 0.2% (79 of 39,052)	Incidence 2.2% (846 of 39,052)	NR
Apixaban 5 mg BID							
ARISTOTLE [7]*	Median 70 y	Median 1.8 y	Cox proportional-hazards models	HR 0.69 (0.60-0.80)	HR 0.42 (0.30-0.58)	HR 0.89 (0.70-1.15)	HR 0.88 (0.66-1.17)
Humedica [20]	NR	Total 180 d	Cox proportional-hazards models	HR 0.75 (0.63-0.88)	NR	NR	NR

ARISTOTLE = Apixaban for Reduction In STroke and Other Thromboembolic Events in Atrial Fibrillation; BID = twice daily; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; IR = incidence rate per 100 person-years; MVA = multivariate analysis; NR = not reported; NVAF = nonvalvular atrial fibrillation; PSM = propensity score matched; QD = every day; RCT = randomized controlled trial; RE-LY = Randomized Evaluation of Long-term anticoagulation therapY; ROCKET AF = Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; RR = relative risk; SPAF = stroke prevention in atrial fibrillation.

* These studies are phase 3 RCTs in patients with NVAF.

† Following propensity score matching, the unadjusted and adjusted hazard ratios were almost all identical. For secondary bleeding end points, unadjusted hazard ratios were reported.

‡ Median follow-up includes 110-mg and 150-mg patients.

§ No warfarin group.

¶ RR was calculated from data reported in the primary publication [6].

T.C. Villines, W.F. Peacock / American Journal of Emergency Medicine 34 (2016) 9–13

Data from PMSS evaluations of DOACS provide assurance that risk associated with their use are in line with results seen in RCTs

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

Table 1 Selected indications and contraindications for non-vitamin K antagonist oral anticoagulant therapy in atrial fibrillation patients

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

Hatched—limited data.
PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.

CHEST

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

NOACs in patients with VTE and atrial fibrillation. For the comparison of each of the NOACs with VKA in the initial and long-term treatment of VTE, current evidence for efficacy is moderate or high quality, for safety (risk of bleeding) is moderate or high quality, and overall is moderate or high quality (Tables 2-5, e-Tables 5-8).

In the 10th Edition of the Antithrombotic Guideline (AT10), the panel's overall assessment of the relative efficacy and risk of bleeding with different anticoagulant agents is that: (1) the risk reduction for recurrent VTE with all of the NOACs appears to be similar to the risk reduction with VKA,[35] including in patients with cancer[36-39]; (2) in patients with VTE and cancer, the risk

CHEST 2016; 149(2):315-352

Based on less bleeding with NOACS and greater convenience for patients and health care providers, we now suggest that a NOAC is used in preference to VKA for the initial and long term treatment of VTE in patients without cancer

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18.1. Non-vitamin K antagonist oral anticoagulants in the frail and older patients

The ≥75-year-old patient

The incidence of AF rises steadily with each decade.[392,393] Stroke prevention in older AF patients is important as stroke risk rises dramatically with age.[394] However, OAC remains underutilized in older age groups.[395] Older people with AF do better on OAC than not and on NOACs rather than VKA.[396–398]

All trials of NOAC treatment in AF included significant populations of older people (defined as ≥75 years) ranging from 31% to 43% in the individual trials, comprising over 27 000 older patients in whom

In summary, frailty per se should not be an exclusion criterion to anticoagulate since frail and older patients are at an increased risk of stroke and have been shown to benefit from OAC. The benefit of

stroke and have been shown to benefit from OAC. The benefit of

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Data have shown that administration in crushed form, e.g. via a nasogastric tube, does not alter the bioavailability for apixaban, rivaroxaban, and edoxaban.[162–164] Also an oral solution of apixaban 5 mg

Antidotes

IDARUCIZUMAB Target: dabigatran	Phase I	Phase II	**Phase III** Patients requiring urgent surgery/major bleeding; May 2014[2,3]	**Approved** **FDA/EMA** Dec 2015
ANDEXANET Alfa (PRT064445) Target: FXa inhibitors	Phase I	Phase II	**Phase III** Patients with bleeding; Jan 2015[4]	
CIRAPARANTAG (PER977) Target: universal	Phase I	**Phase II** Ongoing[5]		

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FDA Approves First Factor Xa Inhibitor Antidote, *Andexxa*

May 04, 2018

The US Food and Drug Administration (FDA) has approved *Andexxa* (coagulation factor Xa [recombinant] inactivated-zhzo) to reverse the anticoagulation effects of factor Xa inhibitors when needed due to life-threatening or uncontrolled bleeding, Portola Pharmaceuticals has announced.

An estimated 4 million people are taking factor Xa inhibitors, such as rivaroxaban (*Xarelto*, Bayer/Janssen Pharmaceuticals) and apixaban (*Eliquis*, Bristol-Myers Squibb), but until now, there has been no approved reversal agent.

Last month, the FDA gave full approval to idarucizumab (*Praxbind,* Boehringer Ingelheim) to reverse the anticoagulant effect of dabigatran (*Pradaxa*, Boehringer Ingelheim), a direct thrombin inhibitor, in the event of urgent surgery or life-threatening or uncontrolled bleeding.

In the United States alone, there were approximately 117,000 hospital admissions attributable to factor Xa inhibitor-related bleeding and nearly 2000 bleeding related deaths per month, according to the company's news release, posted May 3.

Portola expects to launch Andexxa in early June under an early-supply program with a generation 1 product, with a broader commercial rollout expected in early 2019 upon FDA approval of its generation 2 manufacturing process, the news release states.

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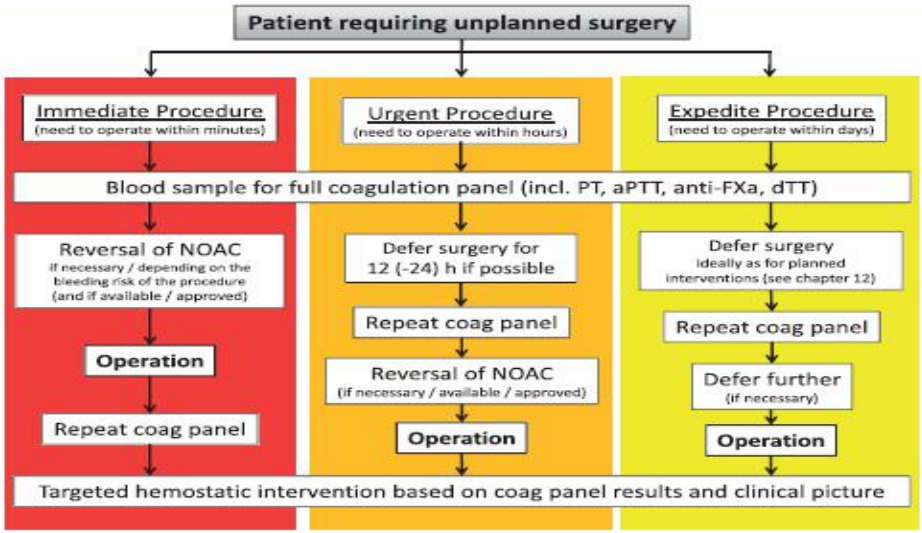

Figure 9 Non-vitamin K antagonist oral anticoagulant management in the setting of unplanned surgery.

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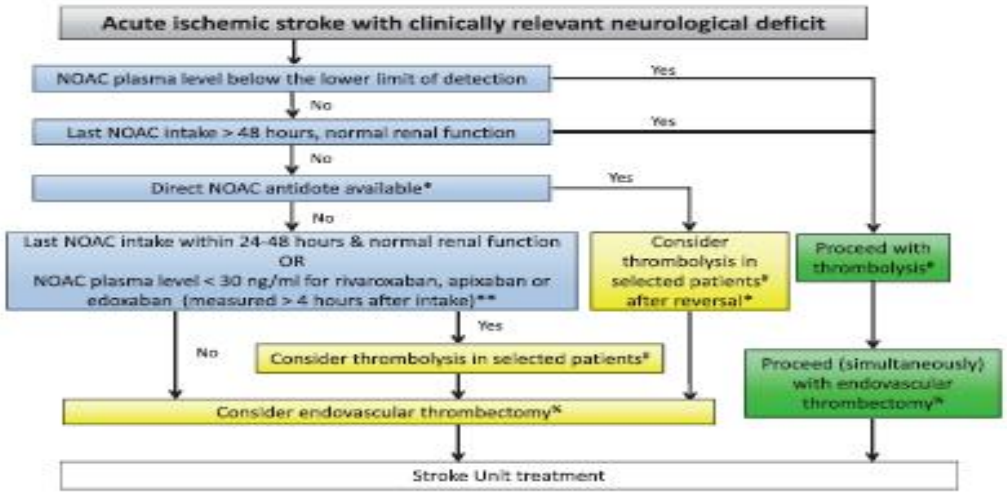

Figure 13 Acute management of acute ischaemic stroke in a patient on non-vitamin K antagonist oral anticoagulant. *Currently only available for dabigatran (idarucizumab). #Perform systemic thrombolysis only if there are no (other) contraindications for intravenous application of recombinant tissue plasminogen activator according to its label. *Perform endovascular thrombectomy only if there is a target vessel occlusion and procedure is indicated and feasible according to present evidence. **According to expert consensus.[370]

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

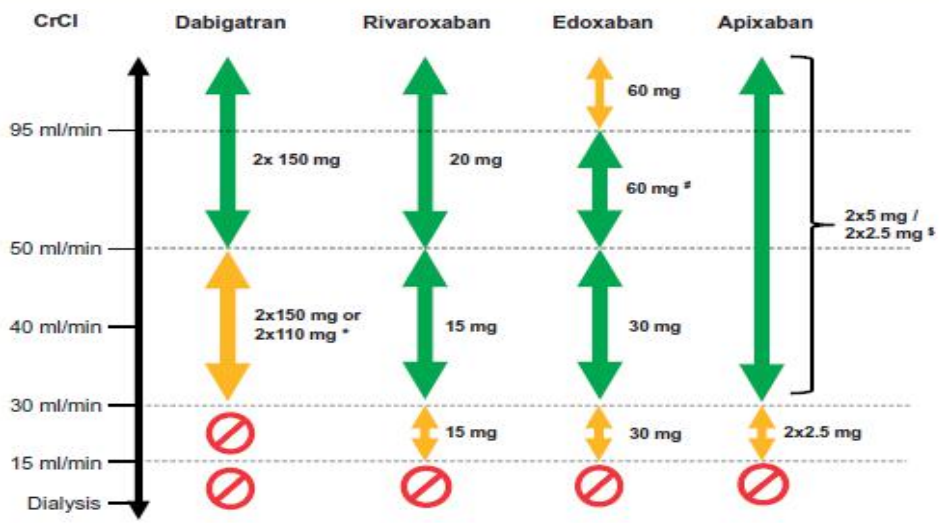

Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

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Table 13 NOACs and approved/studied doses across indications

Stroke prevention in atrial fibrillation (SPAF)		
	Standard dose	**Comments/dose reduction**
Apixaban[30]	2 × 5 mg	2 × 2.5 mg if two out of three weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/l (1.5 mg/dL) [*or* if CrCl 15–29 mL/min]
Dabigatran[28]	2 × 150 mg / 2 × 110 mg	No pre-specified dose-reduction criteria[a]
Edoxaban[31]	1 × 60 mg	1 × 30 mg if: weight ≤60 kg, CrCl ≤50 mL/min, concomitant therapy with strong P-Gp inhibitor (see **chapter 5**)
Rivaroxaban[29]	1 × 20 mg	1 × 15 mg if CrCl ≤50 mL/min
Treatment of DVT/PE		
	Initial therapy	**Remainder of treatment phase**
Apixaban[330]	2 × 10 mg, 7 days	2 × 5 mg, no dose reduction
Dabigatran[331]	Heparin/LMWH	No pre-specified dose-reduction criteria[b]
Edoxaban[332]	Heparin/LMWH	1 × 60 mg, same dose reduction as for SPAF (see above)
Rivaroxaban[333,334]	2 × 15 mg, 21 days	1 × 20 mg, no dose reduction[c]
Long-term prevention of recurrent DVT/PE (i.e. after 6 months)		
	Standard dose	**Comments/dose reduction**
Apixaban[335]	2 × 2.5 mg	
Dabigatran[336]	2 × 150 mg	No pre-specified dose-reduction criteria[d]
Edoxaban	not specifically studied	
Rivaroxaban[337]	1 × 10 mg	e
VTE prevention post-major orthopaedic surgery		
	Standard dose	**Comments/dose reduction**
Apixaban[338]	2 × 2.5 mg	
Dabigatran[339,340]	1 × 220 mg	f
Edoxaban[341,342]	1 × 30 mg	Not approved in Europe (only studied in Asia)
Rivaroxaban[343–346]	1 × 10 mg	

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Stroke prevention post-PCI (with concomitant atrial fibrillation)[g]		
	Standard dose	**Comments/dose reduction**
Apixaban	To be determined (pending results of AUGUSTUS trial)	
Dabigatran[141]	150 mg BID or 110 mg BID	+Clopidogrel or Ticagrelor; no dose reduction
Edoxaban	To be determined (pending results of ENTRUST-AF PCI trial)[310]	
Rivaroxaban[308]	15 mg OD (+Clopidogrel)	Dose reduction to 10 mg OD if CrCl 30–49 mL/min

Secondary prevention of atherothrombotic events post-ACS (without AF)		
	Standard dose	**Comments/dose reduction**
Rivaroxaban[171]	2.5 mg BID	In addition to Aspirin ± $P2Y_{12}$ inhibitor
Secondary prevention of atherothrombotic events in stable CAD (without AF)[h]		
	Standard dose	**Comments/dose reduction**
Rivaroxaban[347]	2.5 mg BID	In addition to Aspirin[h]

ACS, acute coronary syndrome; CAD, coronary artery disease.
[f]SmPC: 2 × 110 mg if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.
[g]SmPC: 2 × 110 mg if age ≥80 years, concomitant verapamil, increased risk of GI bleeding (based on PK/PD analyses; not studied in this setting).
[h]SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analysis; not studied in this setting).
[i]SmPC: 2 × 110 mg if age ≥80 years, concomitant verapamil (both based on PK/PD analysis; not studied in this setting).
[j]SmPc: 1 × 20 mg in patients. At high risk of recurrence.
[k]SmPc: 1 × 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.
[l]As outlined in detail in **chapter 14**, both PIONEER AF-PCI as well as RE-DUAL PCI were powered for safety and were underpowered to determine non-inferiority for individual efficacy endpoints.
[m]As studied in COMPASS; approval of this indication and regimen is pending.

Cve e rischio tromboembolico

European Heart Journal (2016) **37**, 2893–2962
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Immediate initiation of anticoagulation is important in all patients scheduled for cardioversion

?

« Tutti i pazienti »:

- ✓ significa anche quelli con insorgenza di FA databile entro le 48 h ?
- ✓ è indifferente la modalità di cardioversione ? (farmacologica *vs* elettrica)

LINEE GUIDA AIAC PER LA GESTIONE E IL TRATTAMENTO DELLA FA - AGGIORNAMENTO 2013

Tabella 23. Raccomandazioni per la terapia antitrombotica in corso di cardioversione elettrica.

	Terapia antitrombotica raccomandata	Classe[a]	Livello[b]
FA insorta <48h	Cardioversione senza anticoagulazione	IIa	C
FA insorta ≥48h o non databile per insorgenza	– Warfarin (INR 2.0-3.0) – Dabigatran per 3 settimane pre-cardioversione e per 4 settimane post-cardioversione (indefinitamente in caso di CHA_2DS_2-VASc score ≥2)	I IIa	B B
FA insorta ≥48h o non databile per insorgenza	Strategia eco-guidata – Warfarin (INR 2.0-3.0) per 4 settimane post-cardioversione	I	B

1) Ha senso considerare le 48 ore uno spartiacque sicuro per procedere alla CV senza rischio tromboembolico ?

- ✓ Non esiste nessun lavoro che in maniera esplicita abbia dimostrato che le 48 h costituiscano il cut off per la genesi del trombo
- ✓ Esistono evidenze che dimostrano come FA di più lunga durata (>1 settimana) e dimensioni atriali di maggiore entità siano correlate ad un maggior potenziale trombogeno. Sulla base di questi dati per molto tempo si è ritenuto che la CV entro 48 h senza terapia antitrombotica fosse sicura.
- ✓ Tuttavia studi con ETE, RM cardiaca e autoptici hanno evidenziato presenza di trombi auricolari anche in soggetti con episodi di fibrillazione atriale parossistica di pochi minuti (< 48 h)

Acute cardioversion. In AF known to be of <2 days duration, cardioversion has been reported to be safe even without anticoagulation

JASE JOURNAL OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY

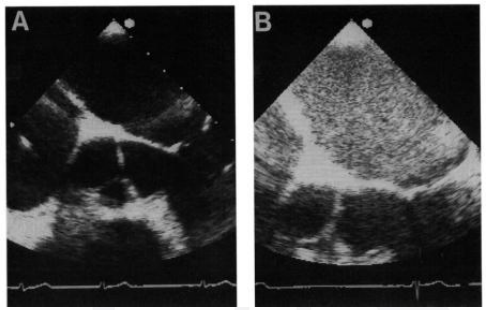
Prevalence of Left Atrial Thrombus and Dense Spontaneous Echo Contrast in Patients With Short-Term Atrial Fibrillation < 48 Hours Undergoing Cardioversion: Value of Transesophageal Echocardiography to Guide Cardioversion

J Am Coll Cardiol 1995;25:452–9

J Am Coll Cardiol 2013;62:1187–92

J Am Soc Echocardiogr 2009;22:1403–8

2) Ha senso la somministrazione di un agente antitrombotico post procedura di CV anche se essa è condotta entro le 48 ore ?



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

Stunning of the left atria seems responsible for an increased risk of thromboembolic events after successful cardioversion, regardless of whether the method is electrical, pharmacological, or spontaneous

Atrial stunning: Determinants and cellular mechanisms

AHJ American Heart Journal

Esistono molte evidenze che documentano come il momento della cardioversione sia associato ad un maggior rischio tromboembolico a prescindere dalla preesistenza di un trombo in atrio, per il rischio che esso possa formarsi dalle 24 h alle 4 settimane successive alla CV a causa del fenomeno dello «stunning atriale»

…thods of cardioversion of atrial fibrilla-
…gical, and spontaneous. It is a function of
…hm, regardless of the method used for
…tion of the preceding atrial fibrillation,
…unning. A shorter duration of atrial fibril-
lation and … atrial diameters are associated with a relatively less severe stunning, lasting for a shorter duration.

Atrial stunning after cardioversion of atrial fibrillation of <1 week usually resolves within 24 hours, and atrial stunning after cardioversion of chronic atrial fibrillation usually resolves within 4 weeks. Tachycardia-induced atrial cardiomyopathy, atrial cytosolic calcium alterations with down-regulation of the L-type Ca2+ channels and up-regulation of the Na+/Ca2+ exchanger, atrial hibernation with myocyte dedifferentiation and myolysis, and atrial fibrosis are the suggested mechanisms underlying atrial stunning. Atrial stunning determines the risk of postcardioversion thrombus formation in atria and atrial appendages, the duration of postcardioversion anticoagulation therapy, the recovery of the atrial contribution to the ventricular function, and the functional recovery of the patients after successful cardioversion of atrial fibrillation.

(Am Heart J 2003;145:787-94.)

Fibrillazione atriale Entro le 48 h

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.
Learn and Live.

2006

ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart

European Heart Journal (2010) **31**, 2369–2429
doi:10.1093/eurheartj/ehq278

ESC GUIDELINES

Guidelines for the management of atrial fibrillation

2010

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

In patients with a definite AF onset, 48 h, cardioversion can be performed expediently under the cover of UFH administered i.v. followed by infusion or subcutaneous LMWH

CHEST Supplement

2012

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for Atrial Fibrillation

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

For patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (Grade 2C)

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Cve e terapia anticoagulante

European Heart Journal (2016) 37, 2893–2962
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

11.1.4 Anticoagulation in patients undergoing cardioversion

Cardioversion carries an inherent risk of stroke in non-anticoagulated patients,[642] which is reduced substantially by the administration of anticoagulation.[643] Immediate initiation of anticoagulation is important in all patients scheduled for cardioversion.[644–646] Patients who have been in AF for longer than 48 h should start OAC at least 3 weeks before cardioversion and continue it for 4 weeks afterwards (in patients without a need for long-term anticoagulation). OAC should be continued indefinitely in patients at risk of stroke. This practice has never been evaluated in controlled trials, but seemed safe in a large observational data set from Finland.[647] When early cardioversion is desired, TOE can exclude the majority of left atrial thrombi, allowing immediate cardioversion.[648,649] Ongoing studies will inform about the safety and efficacy of newly initiated anticoagulation using NOACs in patients scheduled for cardioversion.

Stroke prevention in patients designated for cardioversion of AF		
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.	IIa	B
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.	I	B
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.	I	B
Early cardioversion can be performed without TOE in patients with a definite duration of AF <48 hours.	IIa	B
In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.	I	B
In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks.	I	C
A repeat TOE to ensure thrombus resolution should be considered before cardioversion.	IIa	C

Meta-analisi ed RCTs confermano che I noac sono simili ai vka in termini di sicurezza ed efficacia per la cardioversione

3512 patients with AF undergoing cardioversion

- Meta-analysis of data from four RCTs evaluating NOACs (dabigatran, apixaban, or rivaroxaban; n=2200) vs VKA (n=1312)
  - RE-LY®, ARISTOTLE, ROCKET-AF (all post hoc analyses) + X-VeRT
- Outcomes assessed up to 30 or 42 (X-VeRT only) days post cardioversion
  - Primary outcome: ischaemic stroke/SE
  - Secondary outcomes: major bleeding, MI, mortality

NOAC outcomes:

- Similar to VKA in preventing ischaemic stroke/SE (RR 0.60, 95% CI 0.20–1.80)
- No differences vs VKA in risks of major bleeding (1.27, 0.58–2.81), MI (0.71, 0.10–5.04) or mortality (0.87, 0.24–3.08)

Limitations

- Results are based on study-level data, not on individual patients' data
- Outcomes pooled for all NOACs (some outcomes data not available)
- Pooled data underpowered to confirm non-inferiority of NOACs

Caldeira D et al. Clin Res Cardiol 2015; [Epub ahead of print]

ENSURE AF

Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial

Andreas Goette*, Jose L Merino, Michael D Ezekowitz, Dmitry Zamoryakhin, Michael Melino, James Jin, Michele F Mercuri, Michael A Grosso, Victor Fernandez, Naab Al-Saady, Natalya Pelekh, Bela Merkely, Sergey Zenin, Mykola Kushnir, Jindrich Spinar, Valeriy Batushkin, Joris R de Groot, Gregory Y H Lip*

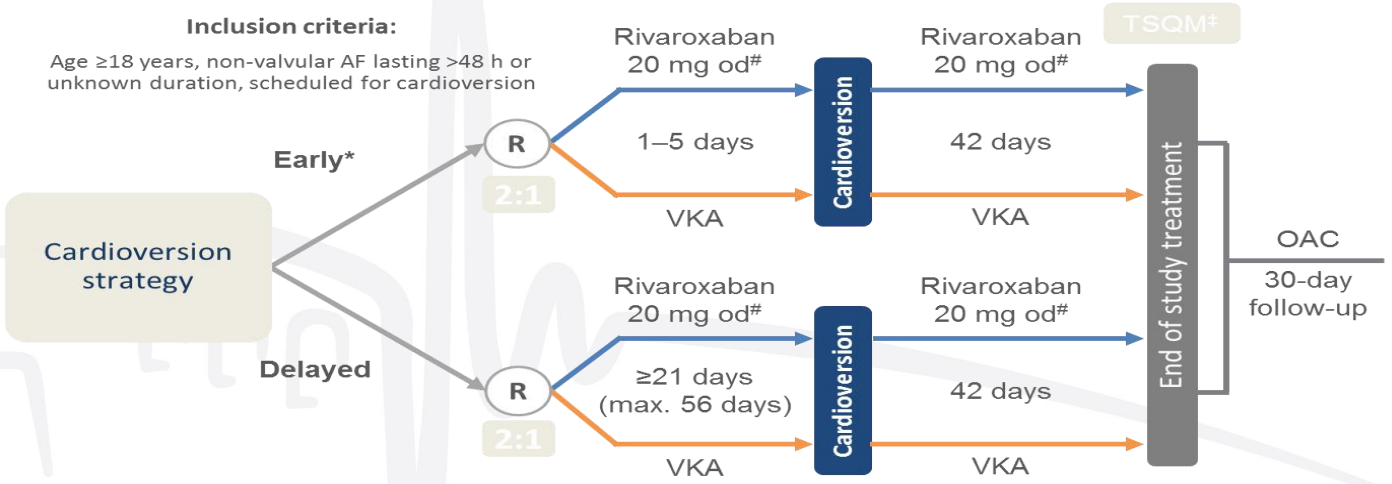
www.thelancet.com Published online August 30, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31474-X

European Heart Journal (2014) 35, 3346–3355
doi:10.1093/eurheartj/ehu367

Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

X-VeRT (eXplore the efficacy and safety of once-daily oral rivaroxaban for the prevention of caRdiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion) was a multinational, randomized, open-label, parallel-group phase IIIb study of patients with haemodynamically stable non-valvular AF of >48 h or of unknown duration

Design: Randomized, Open-Label, Parallel-Group, Active-Controlled Multicentre Study



In X-VeRT:
- Rivaroxaban appears to be an effective and safe alternative to VKA
- Rivaroxaban provided important practical advantages over VKAs, with significantly more patients able to undergo cardioversion as planned and after a significantly shorter duration of pre-cardioversion anticoagulation

*Protocol recommended only if adequate anticoagulation or immediate TEE; #15 mg if CrCl 30–49 ml/min; VKA with INR 2.0–3.0;
‡TSQM questionnaire was completed at the end of study treatment

Cappato R *et al*, *Eur Heart J* 2014;35:3346–3355

Europace (2015) 17, 1467–1507
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

RISULTATI

Cardioverting atrial fibrillation of >48 h in a patient not on non-vitamin K antagonist oral anticoagulant

In the delayed cardioversion group, Rivaroxaban allowed cardioversion after a shorter treatment period (mean 25 days) compared with VKAs (mean 34 days) because of the inability to achieve adequate anticoagulation prior to cardioversion, rivaroxaban allowed cardioversion after a shorter in the VKA group at 3 weeks (95 patients compared with 1 patient in the rivaroxaban group).

In the early cardioversion group, rivaroxaban administered at least 4 h before cardioversion provided effective and safe anticoagulation.

In X-VeRT, 1504 AF patients with AF of > 48 h or of unknown duration, scheduled for cardioversion, were prospectively randomized to receive rivaroxaban or VKA in a 2:1 fashion.

The cardioversion strategy was either early (with TOE, or without TOE in case the patient was known to be anticoagulated with VKA or NOAC for ⩾3 weeks) or delayed (with 3–8 weeks anticoagulation before cardioversion). In the early group, the target was to cardiovert within 1–5 days after randomization. There was no difference in ischaemic or bleeding events between anticoagulant or timing groups.

Therefore, a strategy with at least a single NOAC dose ⩾4 h before cardioversion is safe and effective in patients with AF of > 48 h duration, provided that a TOE is performed prior to cardioversion

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

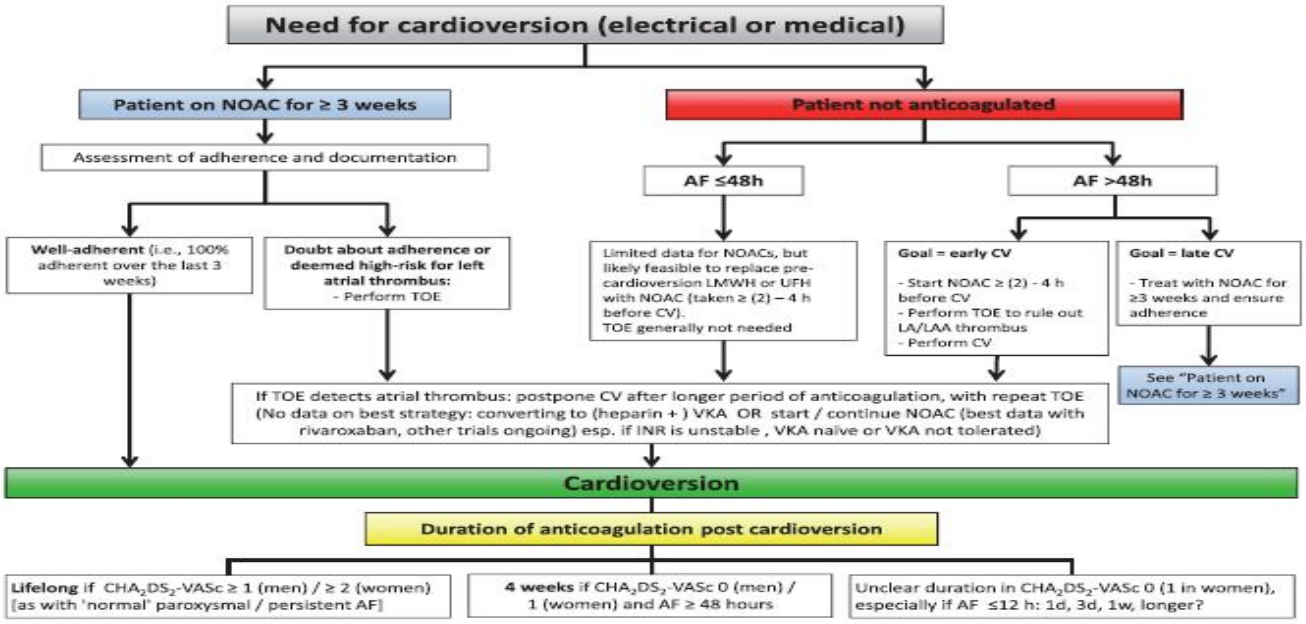


Figure 12 Cardioversion work-flow in atrial fibrillation patients treated with NOACs, depending on the duration of the arrhythmia and prior anti-coagulation. TOE, transoesophageal echocardiography.

REGIONE LAZIO

Direzione Regionale Salute e Politiche Sociali
Area Risorse Farmaceutiche
GR/11/46

Prot. GR/11/46 Roma,

Direzioni Generali
Direzioni Sanitarie

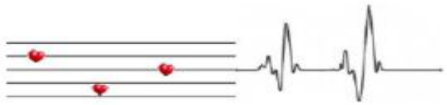
Policlinici Universitari
I.R.C.C.S
Aziende Ospedaliere
Aziende Sanitarie Locali

OGGETTO: Avvio della terapia dei Nuovi Anticoagulanti Orali (NAO) in Medicina di Urgenza/Pronto Soccorso

Al fine di consentire, come previsto dalle linee guida internazionali, l'utilizzo dei nuovi anticoagulanti orali anche nelle patologie tromboemboliche che per la loro peculiarità (Trombosi Venosa Profonda, Cardioversione) necessitano di una dispensazione del farmaco anticoagulante immediata sin dalla dimissione dalla Medicina di Urgenza / Pronto Soccorso, si dispone che debba essere reso disponibile alle dimissioni dal reparto medicina d'urgenza/pronto soccorso, l'anticoagulante orale prescritto dal medico a copertura di un mese di terapia.

Al fine di garantire la continuità terapeutica, il medico, all'atto della dimissione, dovrà, indirizzare il paziente verso un centro prescrittore al fine della successiva valutazione e prescrizione della terapia tramite attivazione del Registro AIFA e piano terapeutico regionale on line.

Via Rosa Raimondi Garibaldi, 7 – 00147 ROMA
tel. 06/5168.4473-5323 fax 06/5168.5450
e-mail: atiberio@regione.lazio.it
posta certificata: politicadelfarmaco@regione.lazio.legalmail.it



- ReFASi
- Registro Fibrillazione Atriale SIMEU Lazio

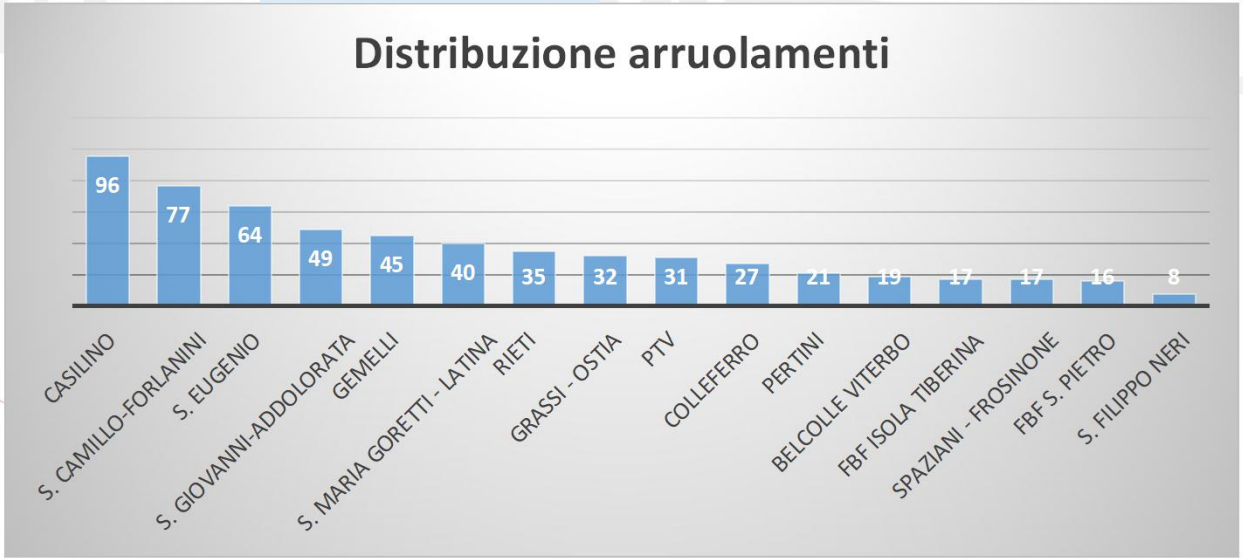
REFASI

Ospedale	Paz Arruolati
Casilino	96
S. Camillo-Forlanini	77
S. Eugenio	64
S. Giovanni-Addolorata	49
Gemelli	45
S. Maria Goretti - Latina	40
Rieti	35
Grassi - Ostia	32
PTV	31
Colleferro	27
Pertini	21
Belcolle Viterbo	19
FBF Isola Tiberina	17
Spaziani - Frosinone	17
FBF S. Pietro	16
S. Filippo Neri	8
TOT	**594**

594 pazienti

16 Ospedali della Regione

45 giorni giugno – luglio 2017



XI congresso nazionale simeu ROMA 24-26 MAGGIO 2018

- ✓ *Pazienti con primo episodio di Fibrillazione Atriale o recidiva*
- ✓ *In pazienti con Fibrillazione atriale nota se è la stessa a determinare il motivo dell'accesso*

FA	
Primo episodio	261
Recidiva	333

Esordio	
<48h	424
>48h	170
tot	594

REFASI

594 pazienti

16 Ospedali della Regione

REFASI

ETA'

media	*69,6*
mediana	*71*

SESSO

M	*303*
F	*291*

594 pazienti

16 Ospedali della Regione

CHA2DS2VASc

0	54
1	107
2	127
3	132
4	114
5	45
6	14
7	1
8	0
9	0

CHA2DS2VASC
MEDIA 2,6

XI congresso nazionale simeu
ROMA 24-26 MAGGIO 2018

Terapia Anticoagulante

Paz arruolati 594	*Anticoagulanti al basale*		Anticoagulanti in dimissione			
			nuove terapie	%	%	conferme terapie
Nessuno	387(65%)		7	2,9		120 (20%)
AVK	60 (10%)		4	1,7		49 (8%)
EBPM	29	478	125	51,9		21
EBPM+AVK	0		6	2,5		0
Eparina Sodica	0		1	0,4		0
Fondaparinux	2		2	0,8		2
Dabigatran 150	13		17	16,5	21,4	12
Dabigatran 110	8		5	4,9		8
Rivaroxaban 20	35		30	29,1	38,8	31
Rivaroxaban 15	11		10	9,7		9
Apixaban 5	31		26	25,2	33,0	29
Apixaban 2.5	10		8	7,8		9
Edoxaban 60	8		4	3,9	6,8	8
Edoxaban 30	0		3	2,9		0
NAO	116 (19,5%)		103	42,7		
TOT ac			241 (40%)			178

TOT NAO 37%

Terapia Anticoagulante

			AC in dimissione (solo nuove)							
	ESITO		Nessuno	NAO	EBPM	EBPM+AVK	Eparina Sod.	AVK	Fondaparinux	Ricovero
	Domicilio	331	93	52 (21%)	60 (25%)	2	1	3	1	
	Ricovero	132	18	6 (5%)	51 (43%)	2	0	1	1	47
	Rifiuto del ricovero	22								
	Str. Ambulatoriale	97	16	37	13	1	0	0	0	
	Trasferimento	11	0	2	1	1	0	0	0	4

CHEST

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

NOACs in patients with VTE and atrial fibrillation. For the comparison of each of the NOACs with VKA in the initial and long-term treatment of VTE, current evidence for efficacy is moderate or high quality, for safety (risk of bleeding) is moderate or high quality, and overall is moderate or high quality (Tables 2-5, e-Tables 5-8).

In the 10th Edition of the Antithrombotic Guideline (AT10), the panel's overall assessment of the relative efficacy and risk of bleeding with different anticoagulant agents is that: (1) the risk reduction for recurrent VTE with all of the NOACs appears to be similar to the risk reduction with VKA,[35] including in patients with cancer[36-39]; (2) in patients with VTE and cancer, the risk

CHEST 2016; 149(2):315-352

Based on less bleeding with NOACS and greater convenience for patients and health care providers, we now suggest that a NOAC is used in preference to VKA for the initial and long term treatment of VTE in patients without cancer

PERCORSO PAZIENTE TEV: GESTIONE

- **TVS con estensione fino a 3 cm dalla “crosse”: trattamento domiciliare**
- **TVP distale: trattamento domiciliare**
- **TVP prossimale: breve ricovero con early discharge, raramente domiciliare**

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PODCAST

CHEST 2016; 149(2):315-352

Treatment of Acute PE Out of the Hospital

Treatment of PE with a NOAC that does not require initial heparin therapy (eg. rivaroxaban, apixaban) facilitates treatment without hospital admission

Criteria for treatment of acute PE out of hospital (all to be satisfied):

- ✓Clinically stable with good cardiopulmonary reserve;
- ✓No contraindications such as recent bleeding, severe renal or liver disease or severe thrombocytipenia (i.e. < 70.000/mm^3)
- ✓Expected to be compliant with treatment;
- ✓The patient feels well enough to be treated at home:
- ✓(sPESI : 0)

acute PE, we agree that the presence of right ventricular dysfunction or increased cardiac biomarker levels should discourage treatment out of the hospital.[130,132-138] The quality of the evidence for treatment of acute PE at home remains moderate because of marked imprecision.

CHEST

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CrossMark

PODCAST

CHEST 2016; 149(2):315-352

Treatment of Acute PE Out of the Hospital

***20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2B).**

Efficacy and safety of outpatient treatment with direct oral anticoagulation in pulmonary embolism

R. Ghazvinian[1] · A. Gottsäter[1] · J. L. Elf[1]

Journal of Thrombosis and Thrombolysis (2018) 45:319–324

The Swedish Quality Registry for Anticoagulants AuricolA

- ✓ *245 consecutively registered patients with Acute PE selected for outpatient treatment with DOAC*
- ✓ *risk for VTE recurrence, death and bleeding during 6 months*

Efficacy and safety of outpatient treatment with direct oral anticoagulation in pulmonary embolism

R. Ghazvinian[1] · A. Gottsäter[1] · J. L. Elf[1]

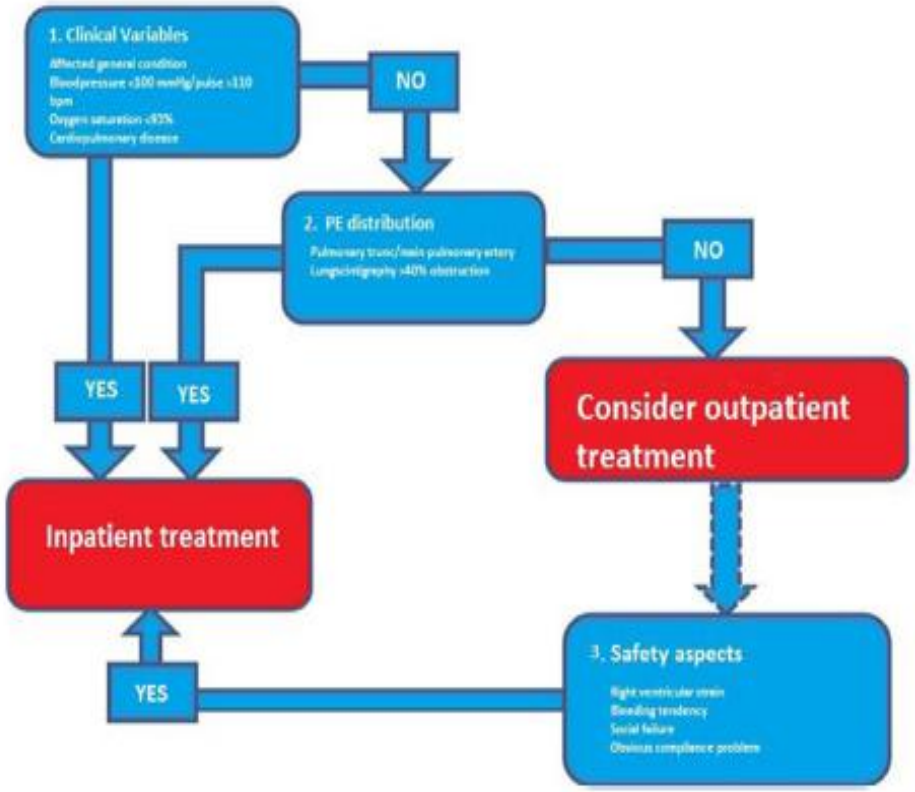
Variabili cliniche:

- *Condizioni generali compromesse*
- *P.A. < 100 mmHg/F.C. > 100 bpm*
- *SaO2 < 93%*
- *Patologia cardiopolmonare*

Localizzazione dell'embolia:

- *Tronco polmonare/arteria polmonare principale*
- *Ostruzione > 40% alla Scintigrafia Polmonare*

Fig. 1 Flow chart used at our institution for selection of patients with PE suitable for outpatient treatment



XI congresso nazionale simeu
ROMA 24-26 MAGGIO 2018

Sicurezza: dilatazione ventricolo destro – rischio emorragico - disagio sociale – scarsa compliance

Efficacy and safety of outpatient treatment with direct oral anticoagulation in pulmonary embolism

R. Ghazvinian[1] · A. Gottsäter[1] · J. L. Elf[1]

Table 2 Treatment data in 245 patients in the Skåne region treated with direct DOAC because of PE during 2013–2015, *n* (%)

	Total
Treatment for 6 months	238 (97)
< 6 months	7 (3)
Dabigatran[a]	2 (1)
Rivaroxaban[a]	225 (92)
Apixaban[a]	23 (9)

[a] Three patients changed from rivaroxaban to apixaban and one patient from rivaroxaban to dabigatran

Table 3 6 months follow-up of 245 patients in the Skåne region treated with direct DOAC because of PE during 2013–2015, *n* (%)

At 6 months	Total, *n* = 245
Death	1 (0,4)
Major bleeding	1 (0.4)
Minor bleeding	5 (2)
Objective imaging for recurrent PE	9 (4)
Recurrent VTE	0 (0)
Newly detected malignancy	3 (1)

DVT Deep venous thromboembolism, *ED* emergency department

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

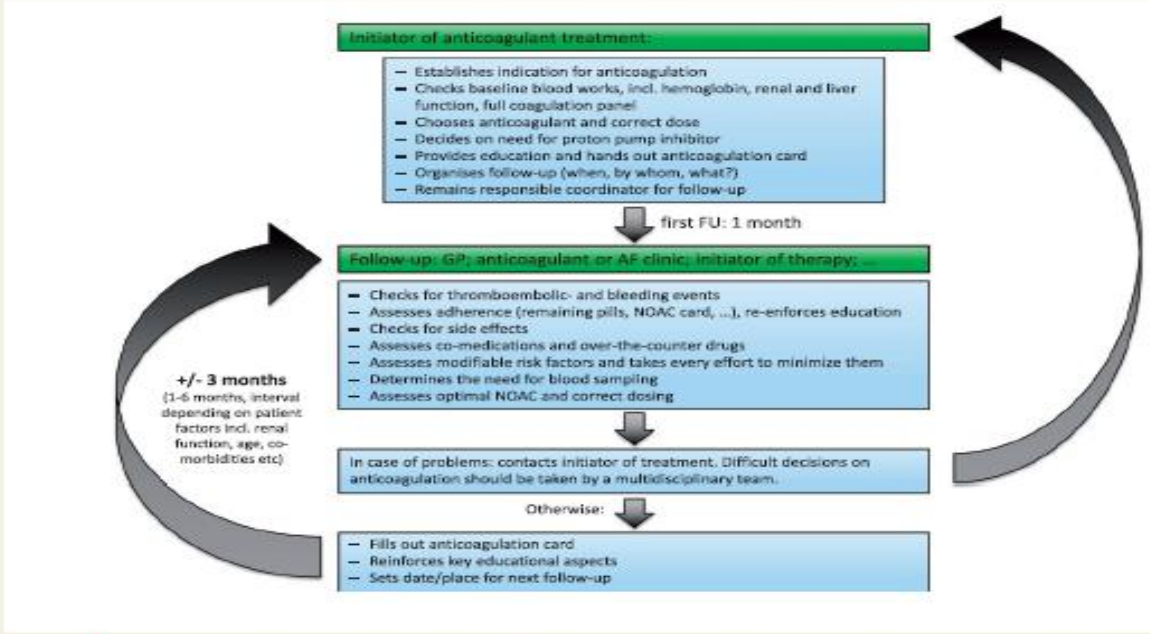


Figure 1 Structured follow-up. Initiation and structured follow-up of patients on non-vitamin K antagonist oral anticoagulants. It is mandatory to ensure safe and effective drug intake. The anticoagulation card is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every person following up the patient is well-informed. Moreover, written communication between different healthcare providers is required to inform them about the follow-up plan and execution. FU, follow-up.

Grazie per l'attenzione

Conclusions

- ENSURE-AF study is the largest prospective randomized clinical trial to date of anticoagulation with a NOAC for electrical cardioversion in nonvalvular AF
- Overall, the rates of the composite primary efficacy endpoint and of major or CRNM bleeding were similarly low in both treatment arms, irrespective of a TEE-guided strategy
- The net clinical outcome was numerically lower but not statistically different in the edoxaban arm vs enoxaparin/warfarin arm
- The results suggest that edoxaban may be an effective and safe alternative to enoxaparin/VKA strategy, and may allow prompt cardioversion to be performed when following a TEE-guided approach

AF = atrial fibrillation; CRNM = clinically relevant nonmajor; NOAC = nonvitamin K antagonist oral anticoagulant; TEE = transesophageal echocardiography; VKA = vitamin K antagonist

Goette A, et al. *Lancet*. 2016