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CHIRURGIA-INTERVENTISTICA
MILANO, 9-11 APRILE 2018
X CONGRESSO NAZIONALE
ECOCARDIOCHIRURGIA 2018

Nuovi dati sui nuovi anticoagulanti orali

Apixaban nella cardioversione della FA. Lo studio EMANATE

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ASST Crema

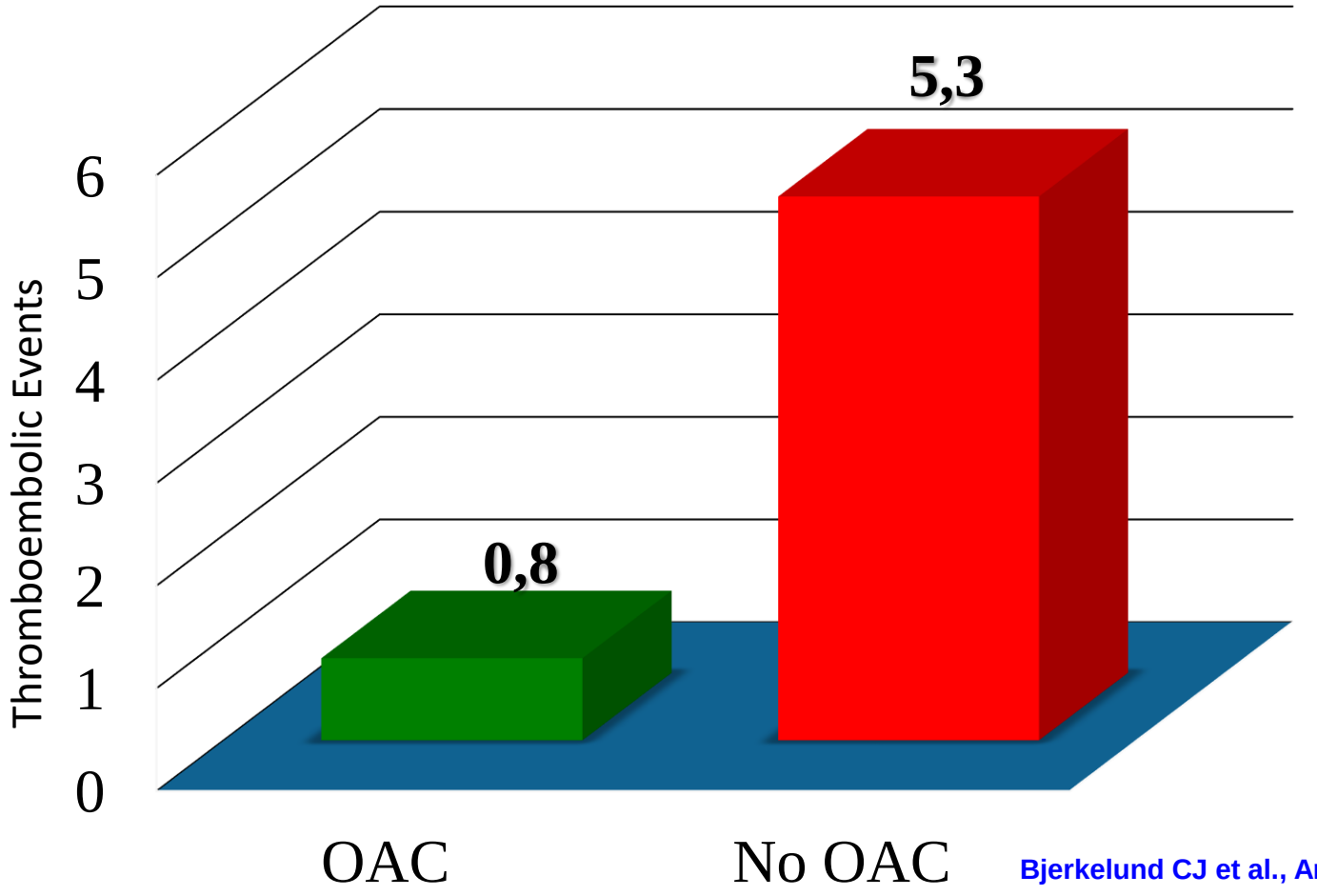
Disclosures

Speakers' bureau appointment with:

- Bayer
- Boehringer Ingelheim
- Boston Scientific
- LivaNova
- Medtronic
- St. Jude Medical (Abbott)

Advisory board relationship with Boston Scientific and Medtronic

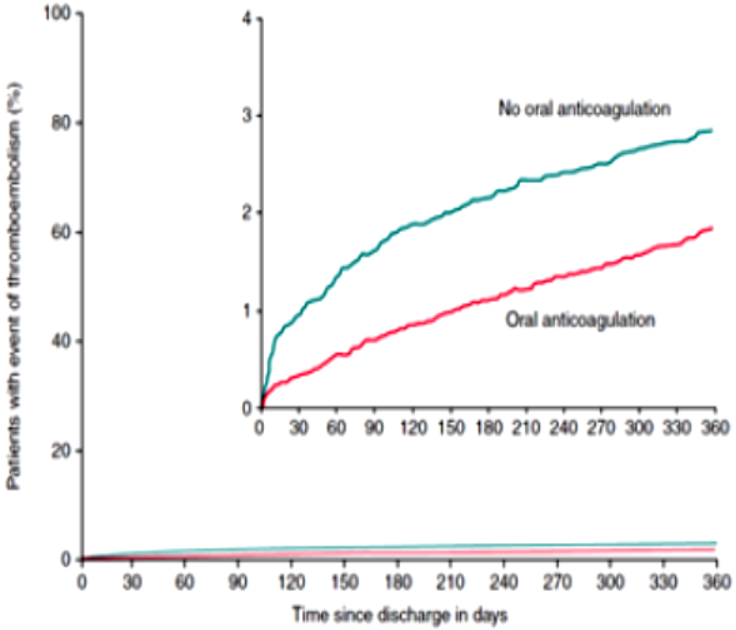
The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation



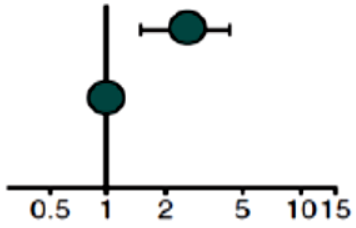
Bjerkelund CJ et al., Am J Cardiol 1969; 23: 208-16

Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy

Oral anticoagulation		N=11,190
	TE events	TE events per 100 patient-years
0–30 days	32	4.00 (2.83–5.66)
	0.29%	



No prior/no subsequent	2.47 (1.49–4.27)
With prior/with subsequent	Reference



Hansen ML, Europace 2015

Anticoagulanti diretti

Studi registrativi

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

N Engl J Med 2009;361:1139-51

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

N Engl J Med 2011;365:883-91

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

N Engl J Med 2011;365:981-92

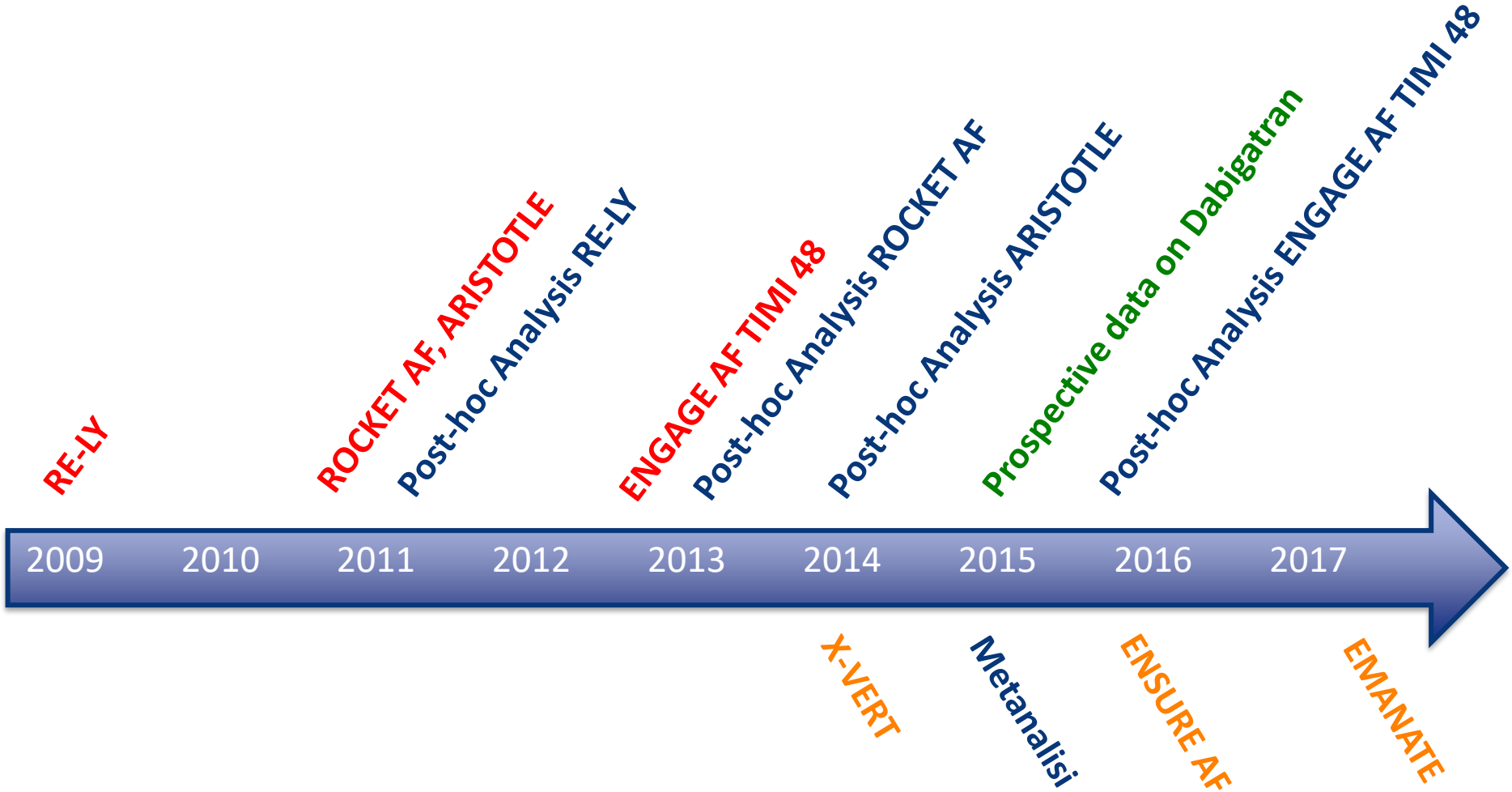
ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

N Engl J Med 2013;369:2093-104

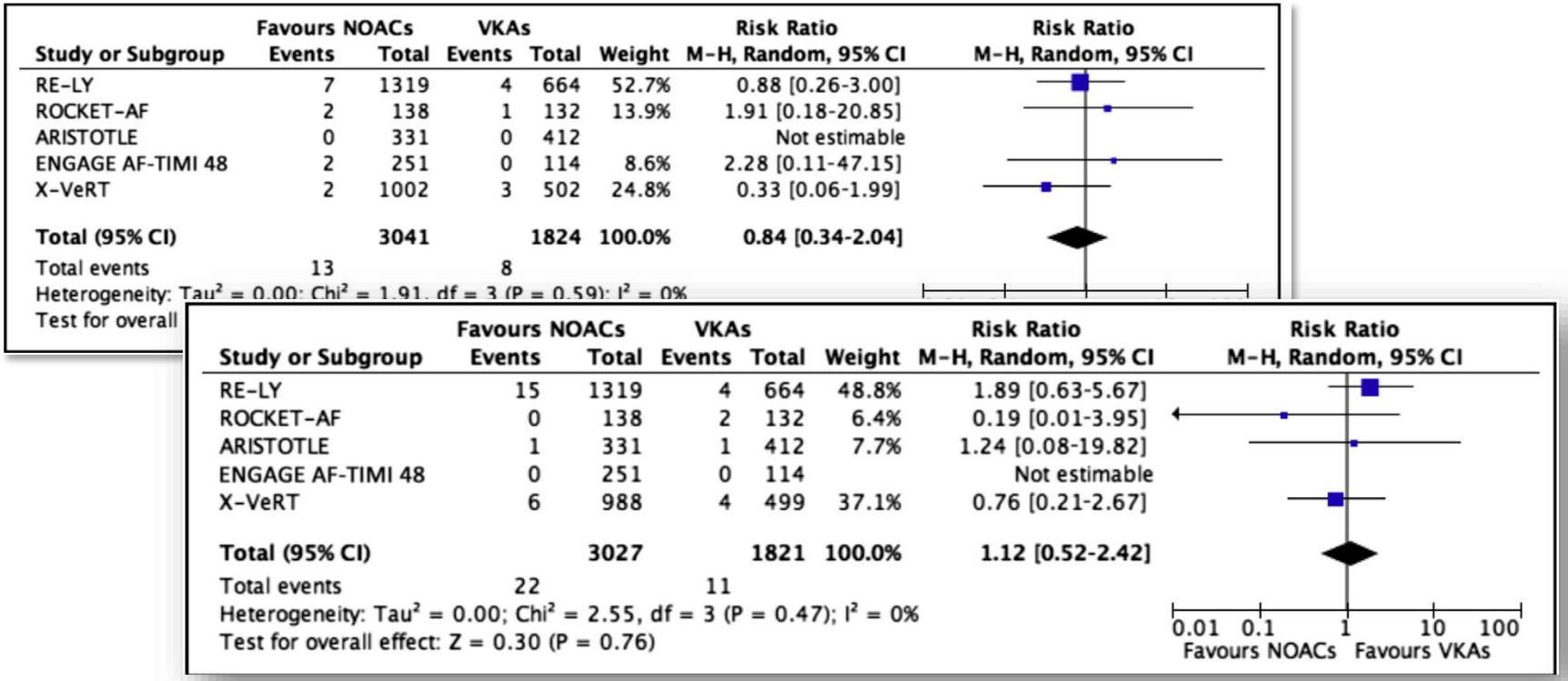
Anticoagulanti diretti e cardioversione elettrica



Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants After Cardioversion for Nonvalvular Atrial Fibrillation

Giulia Renda, MD, PhD,[a] Marco Zimarino, MD, PhD,[a] Fabrizio Ricci, MD,[a] Jonathan P. Piccini, MD,[b] Michael D. Ezekowitz, MD, PhD,[c] Manesh R. Patel, MD, PhD,[b] Riccardo Cappato, MD,[d] Robert P. Giugliano, MD,[e] Raffaele De Caterina, MD, PhD[a]

Stroke/SEE



Bleeding

The American Journal of Medicine (2016) 129, 1117-1123

Post-hoc analysis of DOACs RCTs

Limitations:

- Retrospective analysis of pts undergoing CV
- The RCTs trial were not powered to show a difference in stroke and systemic embolism among treatment arms in the setting of CV
- Low event rates precluded a rigorous statistical analysis between groups
- A definitive superiority study is unlikely to be possible

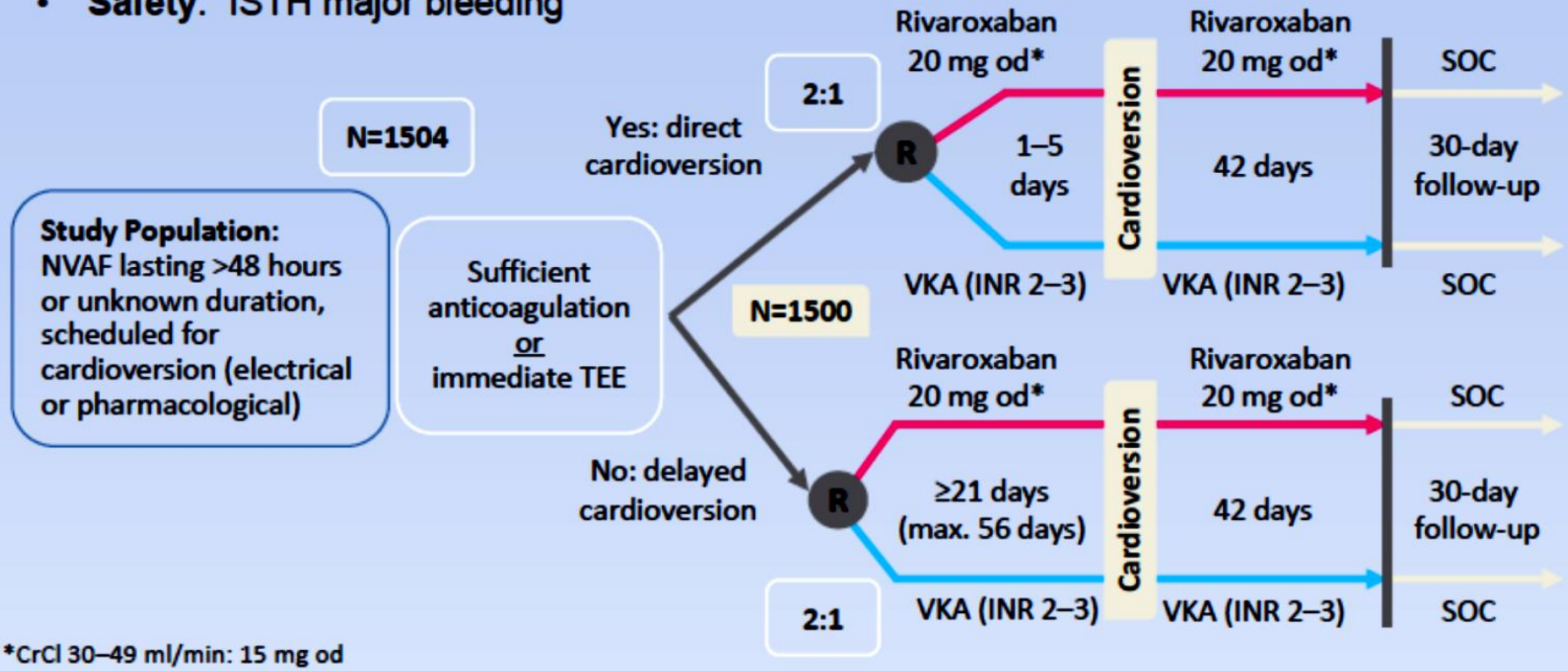

Studi randomizzati su DOACs e cardioversione

X-VERT

Objective: efficacy and safety of rivaroxaban 20 mg OD compared with dose adjusted VKA for the prevention of CV events in patients with NVAF scheduled for cardioversion

Primary Endpoints

- **Efficacy**: composite of stroke, TIA, non-CNS systemic embolism, MI or CV death
- **Safety**: ISTH major bleeding



*CrCl 30–49 ml/min: 15 mg od

Cappato R et al. Eur Heart J 2014: doi: 10.1093/eurheartj/ehu367;

Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

	Total by treatment		
	Rivaroxaban	**VKA**	**RR (95% CI)**
Efficacy, *n* (%)[a]	*n* = 978	*n* = 492	
Primary end-point	5 (0.51)	5 (1.02)	0.50 (0.15–1.73)

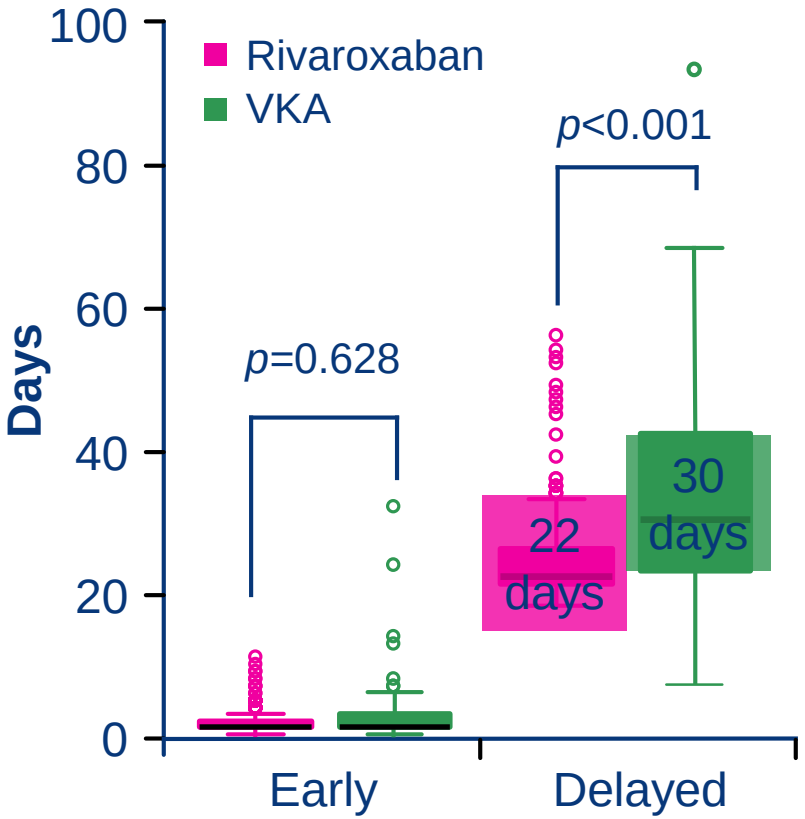
	Total by treatment		**Early**		**Delayed**	
	Rivaroxaban (*n* = 1002)	**VKA (*n* = 502)**	**Rivaroxaban (*n* = 585)**	**VKA (*n* = 287)**	**Rivaroxaban (*n* = 417)**	**VKA (*n* = 215)**
CHA_2DS_2-VASc score, *n* (%)						
0 (or 1, if female only)	147 (14.7)	65 (12.9)	67 (11.5)	31 (10.8)	80 (19.2)	34 (15.8)
1 (except for female alone)	215 (21.5)	118 (23.5)	128 (21.9)	66 (23.0)	87 (20.9)	52 (24.2)
≥2	640 (63.9)	319 (63.5)	390 (66.7)	190 (66.2)	250 (60.0)	129 (60.0)

All-cause death	5 (0.51)	3 (0.61)
Safety, *n* (%)[b]	*n* = 988	*n* = 499
Major bleeding	6 (0.61)	4 (0.80) 0.76 (0.21–2.67)
Fatal	1 (0.10)	2 (0.40)
Critical site	2 (0.20)	3 (0.60)
ICH	2 (0.20)	1 (0.20)
Hb decrease ≥2 g/dL	4 (0.40)	1 (0.20)
Transfusion ≥2 units RBCs or whole blood	3 (0.30)	1 (0.20)

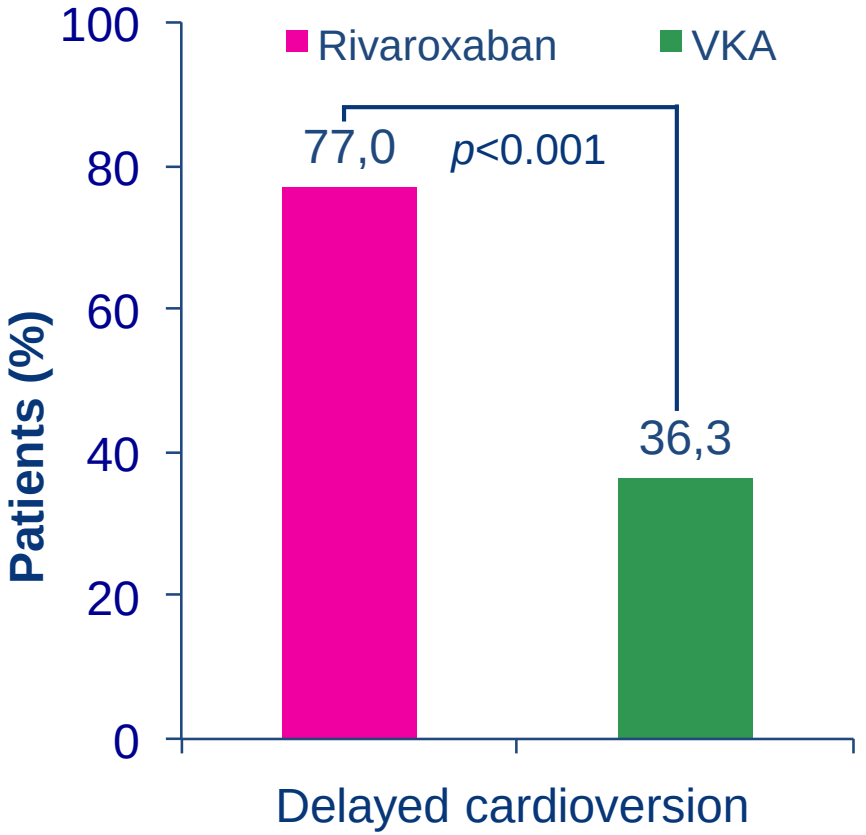
Cappato et al. Eur Heart J. 2014;35:3346-55

Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

Median time to cardioversion



Patients cardioverted as scheduled*



*Reason for not performing cardioversion as first scheduled from 21–25 days primarily due to inadequate anticoagulation (indicated by drug compliance <80% for rivaroxaban or weekly INRs outside the range of 2.0–3.0 for 3 consecutive weeks before cardioversion for VKA)

Cappato et al. Eur Heart J. 2014;35:3346-55

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

Non valvular AF for at least 48 hours but ≤12 months planned for electrical cardioversion and anticoagulation therapy

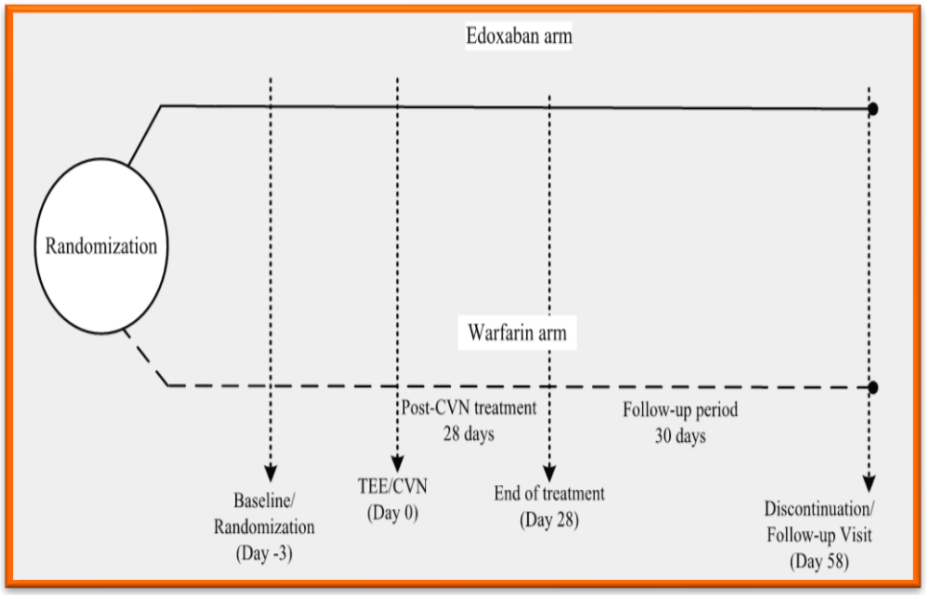
- **Primary efficacy objective:**
  - **Compare the incidences of the composite endpoints of stroke, SEE, MI and CV mortality between the edoxaban group and the enoxaparin/warfarin group from randomization to end of follow up (FU).**
- **Primary safety objective:**
  - **Compare the incidence of the composite endpoints of major and CRNM bleeding between the edoxaban group and the enoxaparin/warfarin group from the first administration of study drug to end of treatment + 3 days.**
- **Secondary objective:**
  - **Compare the incidences of the composite endpoints of stroke, SEE, MI, CV mortality and major bleedings between the edoxaban group and the enoxaparin/warfarin group from randomization to end of follow up (FU).**

Goette A. et al. Lancet 2016; 388: 1995–2003

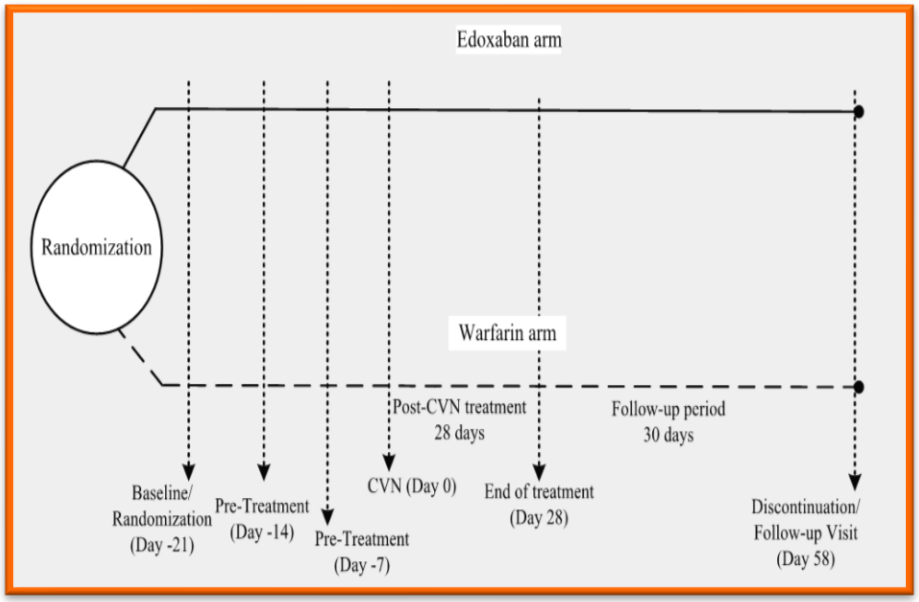
Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial

Study Flow Diagram:

2200 subjects planned to be randomized (1100 per treatment arm)



TEE-Guided Stratum



Non-TEE-Guided Stratum

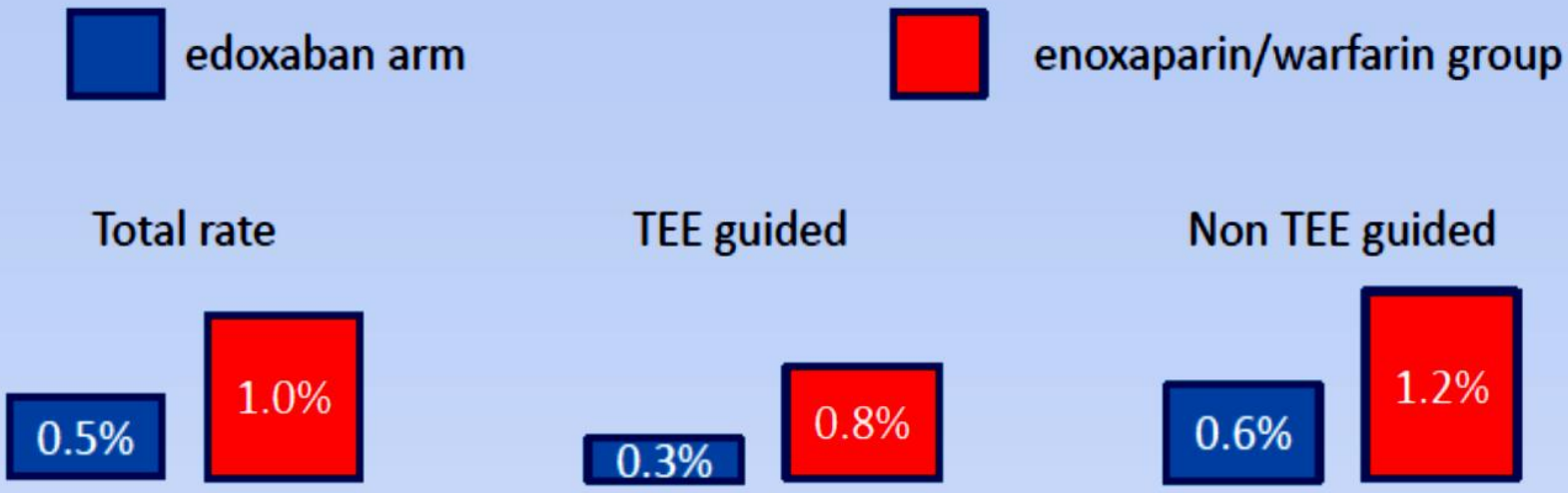
Goette A. et al. Lancet 2016; 388: 1995–2003

ENSURE-AF

2199 patients enrolled

edoxaban (n=1095) enoxaparin–warfarin (n=1104)

The primary efficacy outcome was the 28-day composite of stroke or other systemic embolic events, MI, or cardiovascular mortality.



The combined rate of **major or clinically relevant non major bleeding** through 30 days was 1.5% with edoxaban and 1.0% with enoxaparin plus warfarin.

Goette A. et al. Lancet 2016; 388: 1995–2003

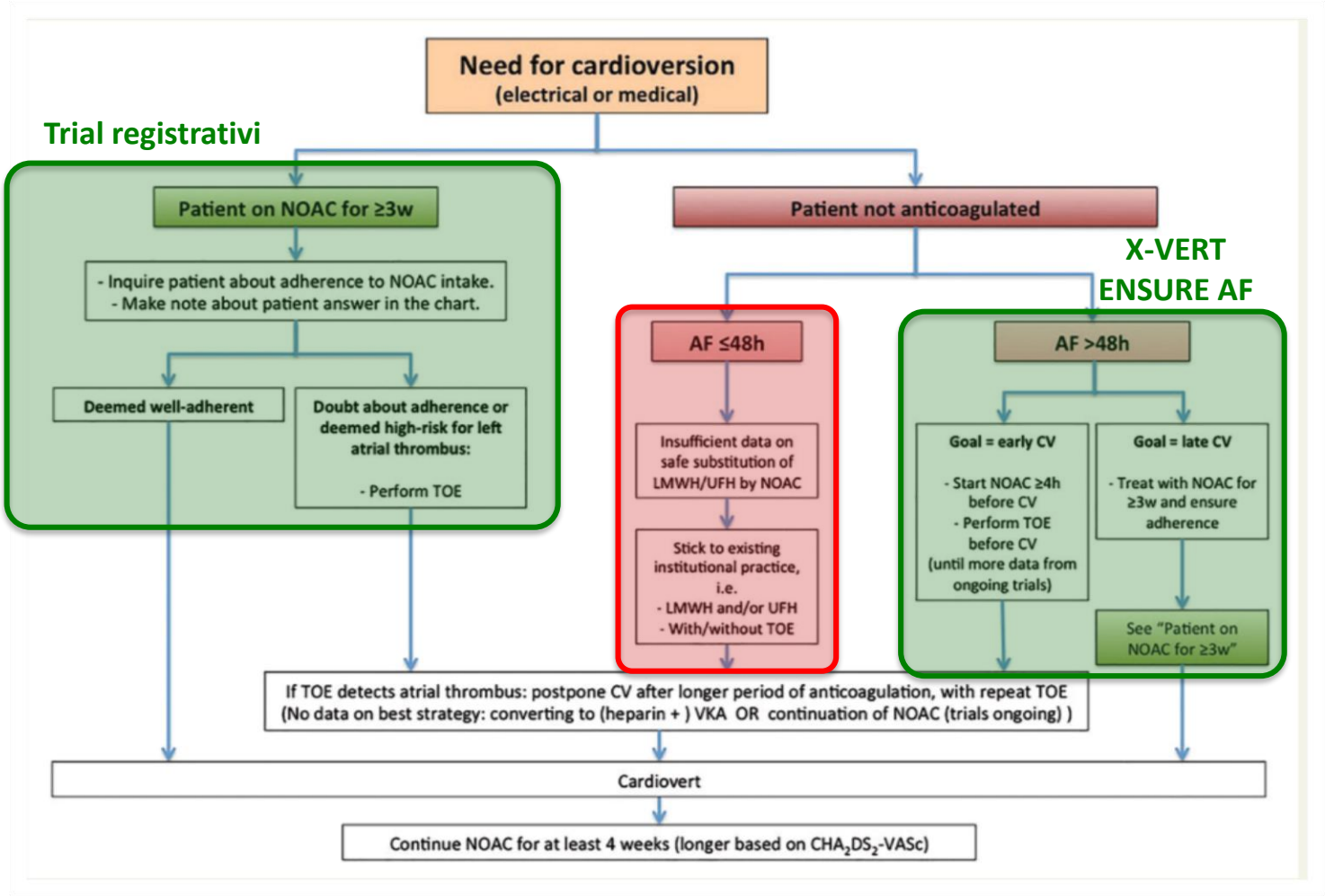
Il punto della situazione…

- Post hoc analyses of cardioversions in the RE-LY, ARISTOTLE, ROCKET-AF and ENGAGE-AF trials found low rates of both events.[1-4] A limitation was a prolonged period of pre-cardioversion anticoagulation.

- For more immediate cardioversion prospective trials comparing rivaroxaban (X-VeRT)[5] and edoxaban (ENSURE-AF)[6] against heparin/VKA in patients undergoing cardioversion found comparable efficacy and safety with low event rates.

1. Nagarakanti R et al. Circulation. 2011;123:131-136
2. Flaker G et al. J Am Coll Cardiol. 2014;63:1082-1087
3. Piccini JP et al. J Am Coll Cardiol. 2013;61:1998-2006
4. Plitt A et al. Clin Cardiol. 2016;39:345-346
5. Cappato R et al. Eur Heart J. 2014;35:3346-3355
6. Goette A et al. Lancet. 2016;388:1995-2003

Cardioversione elettrica: TAO



H. Heidbuchel et al Europace 2015

Apixaban versus Heparin/Vitamin K Antagonist in Anticoagulation-naïve Patients with Atrial Fibrillation Scheduled for Cardioversion: EMANATE TRIAL

Objectives

- To prospectively compare the outcomes of stroke, systemic embolism, major bleeding, and clinically relevant non-major (CRNM) bleeding in patients with < 48 hours anticoagulation randomized to apixaban or heparin/VKA in an open-label trial with blinded endpoint adjudication.
- To gain insight into the role of image guidance.
- To assess the value of a loading dose of apixaban in patients rapidly transitioned to cardioversion.

Ezekowitz MD et al., Am Heart J 2016;179:59-68

EMANATE: study design

If an immediate cardioversion was planned, a single 10-mg dose (or 5 mg if the dose was titrated down) was administered at least 2 hours prior to cardioversion to more rapidly bring exposure up to steady state

Early image-guided cardioversion is encouraged

1500 patients

- **Newly diagnosed NVAF patients**
- **Indicated for cardioversion**
- **Pts receiving an anticoagulant for <48 hours during the index episode of AF**

R 1:1

Cardioversion

Treatment period

30 Days (± 7 days)

Usual care (parenteral heparin/VKA*)

- **Cardioversion may be attempted up to 90 days after randomization.**
- **Patients are followed for 30 days following CV or 90 days post-randomization if cardioversion is not performed within that timeframe.**

Apixaban 5 mg twice daily (2.5 mg BID in selected patients**)

Five doses of apixaban will be administered prior to CV to achieve steady state blood levels.

* Excluding other novel oral anticoagulants
** 2.5 mg twice daily if creatinine clearance 15–29 mL/min or if two of the following criteria: age ≥80 years, weight ≤ 60kg or creatinine ≥1.5 mg/dL (133 µmol)

Clinical endpoints

- **Stroke**
- **Systemic embolism**
- **Major bleeding**
- **Clinically relevant non-major bleeding**
- **All-cause death**

Ezekowitz MD et al., Am Heart J 2016;179:59-68

Apixaban versus Heparin/Vitamin K Antagonist in Anticoagulation-naïve Patients with Atrial Fibrillation Scheduled for Cardioversion: EMANATE TRIAL

Key baseline patient demographics

	Apixaban			Heparin/VKA
	All (n=753)	5-mg loading dose (n=11)	10-mg loading dose (n=331)	(n=747)
Age, years, mean (SD)	64.7 (12.2)	80.5 (7.4)	63.2 (12.2)	64.5 (12.8)
Sex, female, n (%)	248 (32.9)	4 (36.4)	123 (37.2)	250 (33.5)
Race, white, n (%)	654 (86.9)	10 (90.9)	322 (97.3)	648 (86.7)
Weight, kg, mean (SD)	87.9 (20.6)	69.1 (15.5)	90.2 (21.0)	86.3 (19.8)
Hypertension, n (%)	496 (65.9)	9 (81.8)	221 (66.8)	481 (64.4)
LVEF <40, n (%)	45 (6.0)	0	21 (6.3)	54 (7.2)
Diabetes, n (%)	154 (20.5)	1 (9.1)	75 (22.7)	140 (18.7)
CHA_2DS_2-VASc score, mean (SD)	2.4 (1.7)	4.4 (1.8)	2.3 (1.7)	2.4 (1.7)
Creatinine clearance, mL/min, mean (SD)	79.2 (50.6)	41.0 (13.4)	91.7 (52.1)	78.5 (49.0)

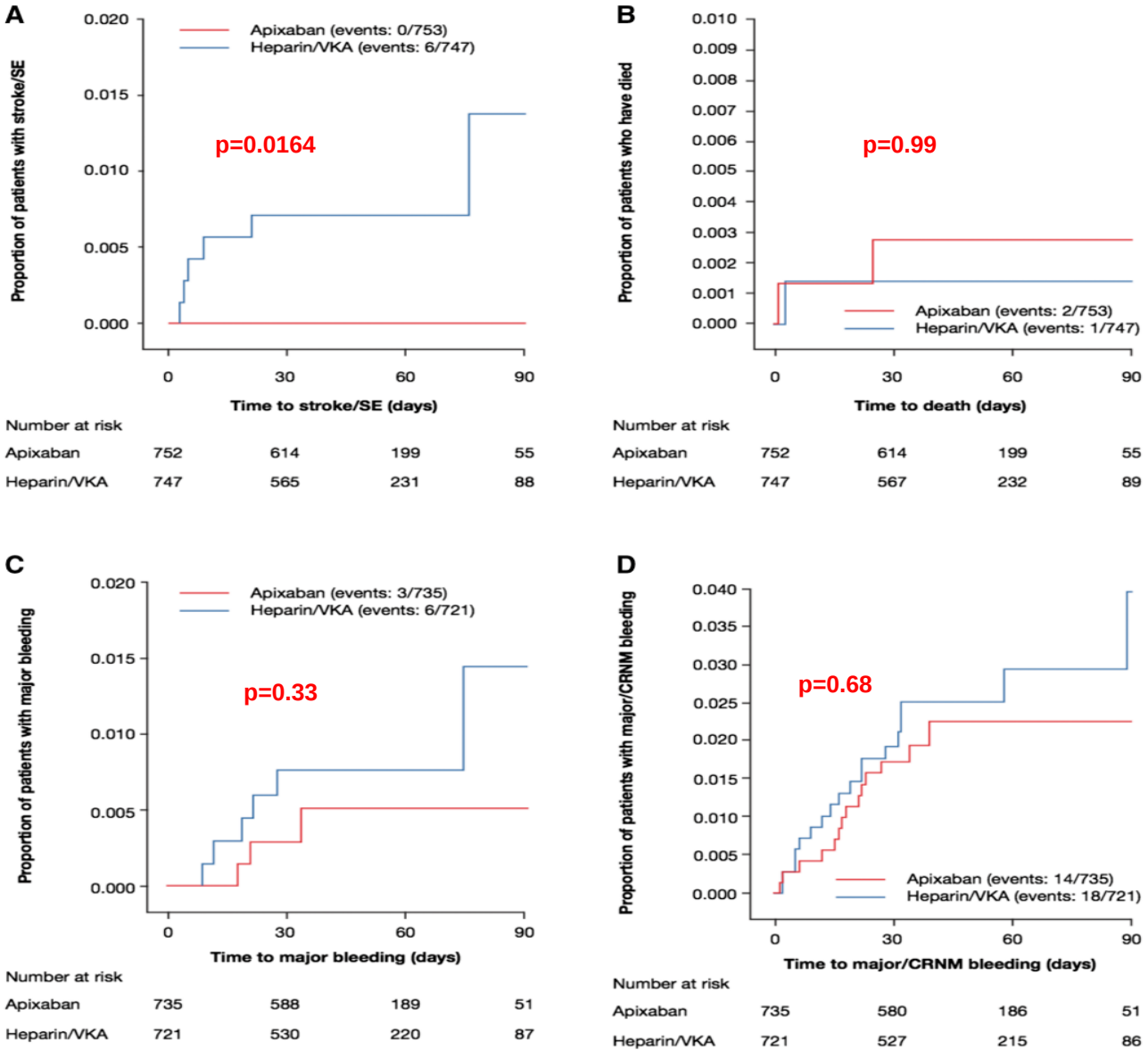
Ezekowitz MD et al., Am Heart J 2016;179:59-68

EMANATE trial: results

- EMANATE evaluated 1500 patients scheduled for cardioversion. All received < 48 hrs anticoagulation and 61% were not anticoagulated prior to randomization.
- There were 1038 active and 300 spontaneous cardioversions; 162 patients were not cardioverted.
- TOE was performed in 855 patients. Imaging identified left atrial appendage thrombi in 61 patients; all continued anticoagulation.
- Among 342 patients receiving the loading dose of apixaban, there were 0 strokes, 1 major bleed, and 1 death (3 w. after CV due to perforated colonic diverticulitis)

Ezekowitz Md et al., EHJ 2018, doi:10.1093/eurheartj/ehy148

EMANATE trial: efficacy and safety outcomes



Ezekowitz Md et al., EHJ 2018, doi:10.1093/eurheartj/ehy148

Apixaban versus Heparin/Vitamin K Antagonist in Anticoagulation-naïve Patients with Atrial Fibrillation Scheduled for Cardioversion: EMANATE TRIAL

Safety Outcomes (Safety Population*, N= 1456)

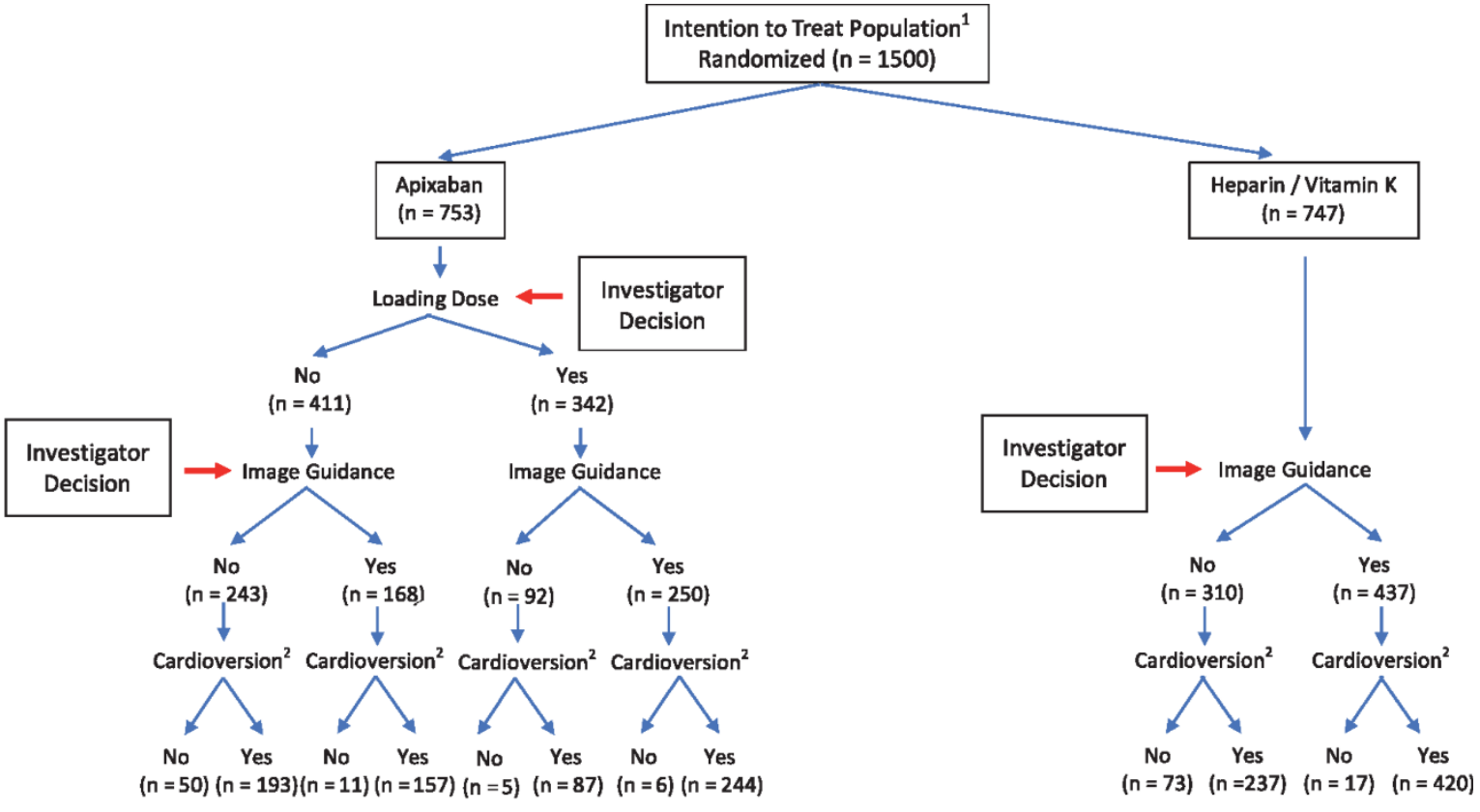
	Apixaban Total (n=735)	Apixaban Loading Dose Subset (n=342)	Heparin/VKA Total (n=721)
Major bleeds	3	(1)	6
Clinically relevant non-major bleeds	11	(4)	13

*Randomized and received ≥ 1 dose of study medication (by treatment received).

Ezekowitz Md et al., EHJ 2018, doi:10.1093/eurheartj/ehy148

Apixaban versus Heparin/Vitamin K Antagonist in Anticoagulation-naïve Patients with Atrial Fibrillation Scheduled for Cardioversion: EMANATE TRIAL

Patient disposition (ITT population)



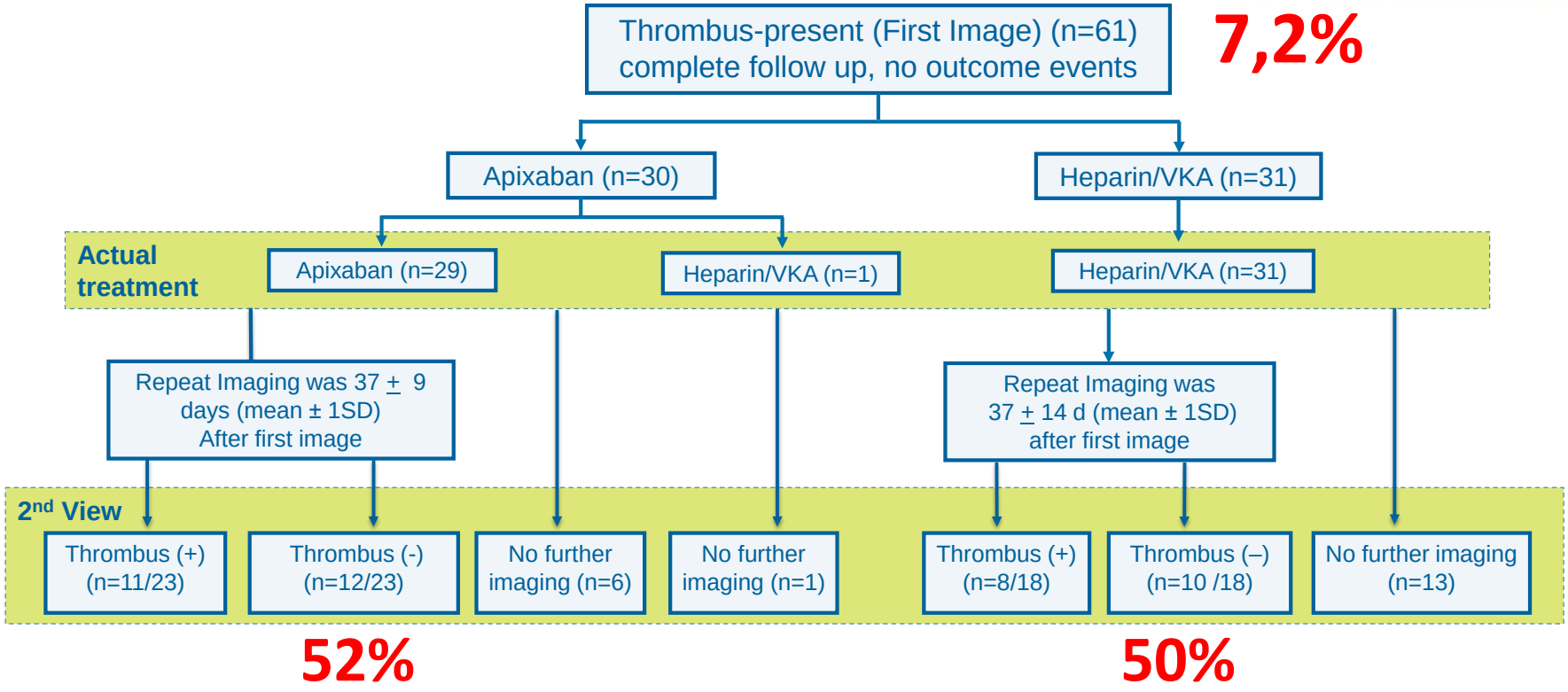
Reason for no cardioversion

Adverse events	4	4	2	1	4	5
Withdrew consent	1	1	0	0	3	0
Investigator Decision	10	1	1	1	5	3
Other	10	5	1	4	17	9
Not recorded	25	0	1	0	44	0

Ezekowitz Md et al., EHJ 2018, doi:10.1093/eurheartj/ehy148

Apixaban versus Heparin/Vitamin K Antagonist in Anticoagulation-naïve Patients with Atrial Fibrillation Scheduled for Cardioversion: EMANATE TRIAL

Image-Guided Strategy (n=855)



Ezekowitz Md et al., EHJ 2018, doi:10.1093/eurheartj/ehy148

Summary and conclusion

- There were 0 vs 6 strokes in the apixaban vs heparin/VKA group (*p*=0.0164*), 3 vs 6 major bleeds, 2 vs 1 deaths, and no systemic embolic events in either group.
- Among 342 patients receiving the loading dose of apixaban, there were 0 strokes, 1 major bleed, and 1 death.
- Imaging identified left atrial appendage thrombi in 61 patients; all continued anticoagulation. There were no outcome events. Among those with repeat imaging (37 ± 11 days after the initial imaging) thrombi resolved in 52% vs 56% in the apixaban and heparin/VKA groups.
- Limitation: Like the other prospective cardioversion studies, EMANATE was underpowered.
- The findings observed in EMANATE support the use of apixaban in patients with AF undergoing cardioversion.

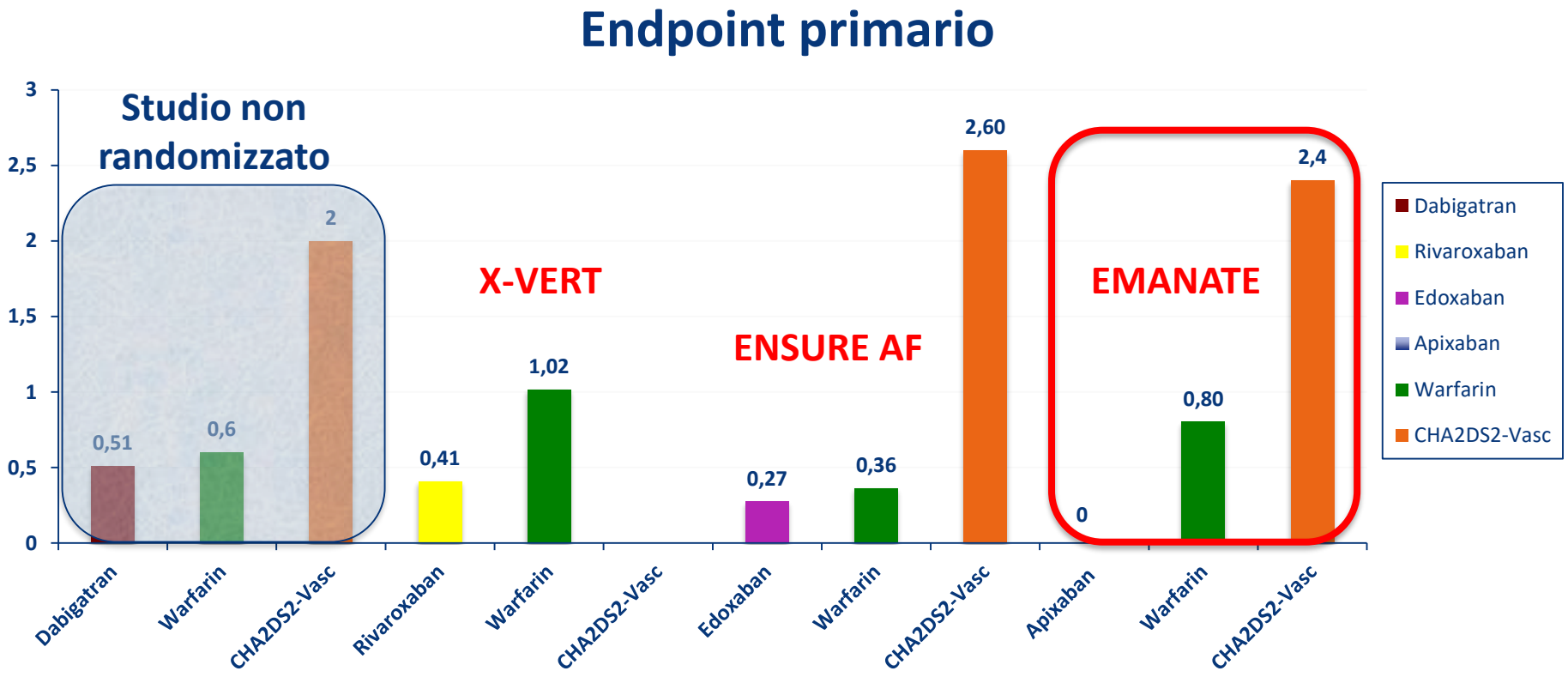
Apixaban compared with parenteral heparin and/or vitamin K antagonist in patients with nonvalvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE trial

clinical outcomes are the occurrence of acute stroke, systemic embolism, all-cause death, major bleeding, and clinically relevant nonmajor bleeding.

To adequately power for noninferiority, 480 end points would be needed (similar to ARISTOTLE[15]). In this study, follow-up is limited to 30 days after cardioversion or 90 days postrandomization. An estimated event rate of approximately 1% would require 48,000 participants, a number far in excess of practicality. The figure of 1,500 patients was considered clinically meaningful and achievable.

(Am Heart J 2016;179:59-68.)

DOACs e cardioversione



CONCLUSIONI

- **Il rischio tromboembolico secondario alla CVE in profilassi tromboembolica è basso.**
- **La cardioversione elettrica eseguita in profilassi con gli anticoagulanti diretti è fattibile e sicura**
- **Il trattamento con apixaban è risultato più efficace del warfarin nel prevenire eventi tromboembolici secondari alla cardioversione elettrica**
- **Il trattamento con apixaban è fattibile anche nella cardioversione per aritmia di durata inferiore alle 48 ore**

ESC 2016
AF management guidelines

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

Kirchhof P et al. Eur Heart J. 2016 Aug 27