Practical everyday use of NOACs

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THE "NEW" ANTICOAGULANTS HISTORY

Oral Inhibitors

Edoxaban

Apixaban

Rivaroxaban

Dabigatran

Ximelagatran

Betrixaban
EXPLORE-Xa Phase II trial

Antistasin (FXa inhibitor)

Hirudin (thrombin -I)

Xabans i.v.

FDA Approves Dabigatran

FDA Approves Rivaroxaban

FDA Approves Apixaban

RELY

ROCKET-AF

ARISTOTLE

ENGAGE AF

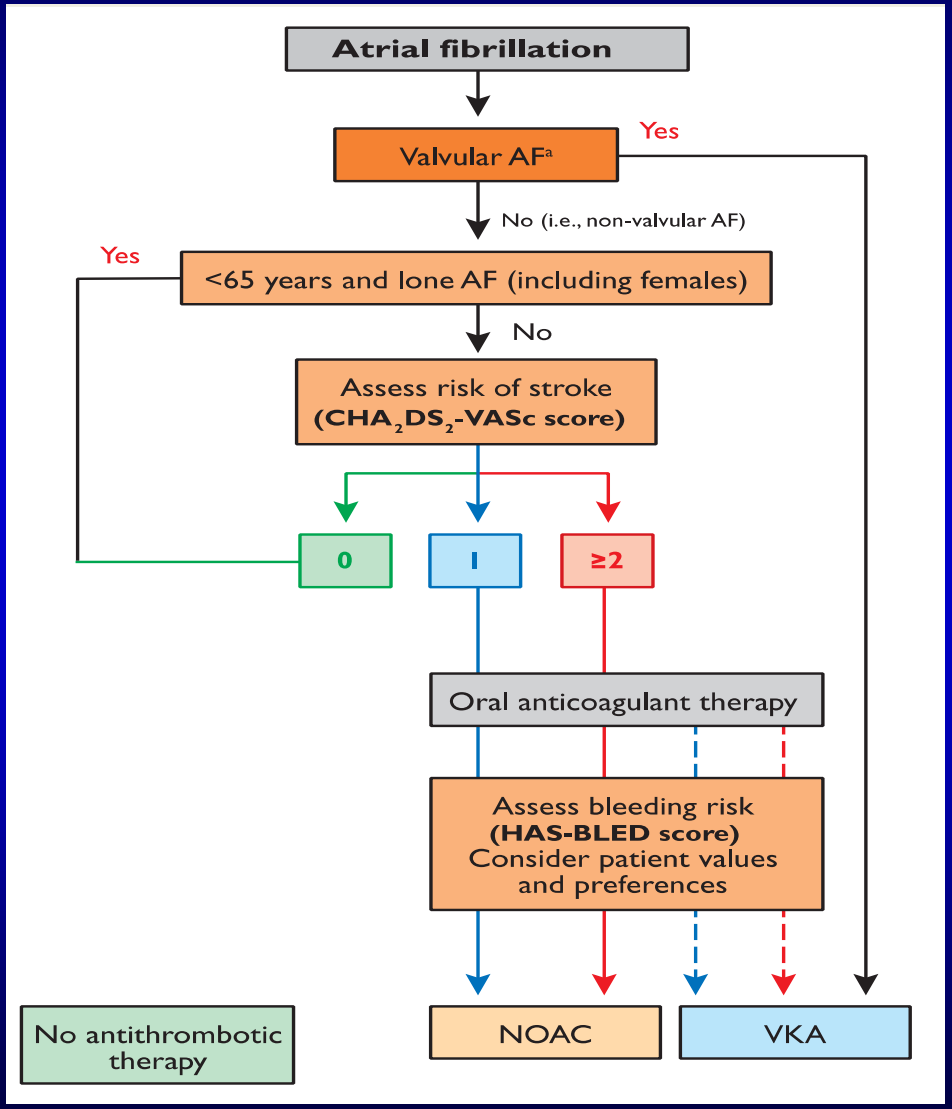
1905-1980 | **1980-1990** | **2000-2008** | **2009** | **2010** | **2011** | **2012** | **2013**

Years

The AF Guideline Changes

† Congestive heart failure, Hypertension. Age ≥ 75 years Diabetes. Stroke/TIA/thrombo-embolism (doubled)

*Other clinically relevant non-major risk factors: age 65–74, female sex, vascular disease



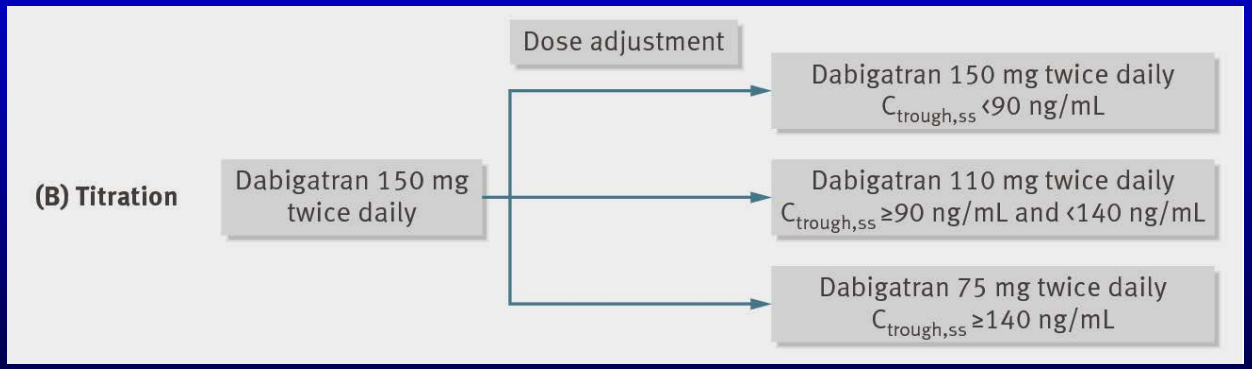
ESC AF Guidelines 2010

2012 Update of the ESC AF Guidelines

Practical everyday use of NOACs

Name	Pradaxa	Eliquis	Xarelto	Lixiana
Target	Dir in		ctor Xa hibitor	Factor Xa inhibitor
Bioavailability			0-80%	40%
Half-life (T ½)	12		7-11 h	8-10
T max h	2		2-4 h	1-5 h
Clearence	80%		% renal % biliary	40% renal
Drug interaction P-gp competition CYP3A4 inhibition	Amiod Quin Verap		onavir(↑) konazole(↑) nidine(↑)	Quinidine(↑) Verapamil(↑)

	DABIGATRAN	APIXABAN	RIVAROXABAN	EDOXABAN
% Stroke/y	D 150mg: 1.11% D 110 mg: 1.56%	1.27%	2.1%	E 60mg: 1.18% E 30mg: 1.61%
% Major Bleeds/ y	D 150mg: 3.31% D 110 mg: 2.71%	2.13%	3.6%	E 60mg: 2.75% E 30mg: 1.61%
Coagulation tests	*aPTT ECT*	*Anti-Fxa chromogenic assays*	*PT Anti-Fxa chromogenic assays*	*PT Anti-Fxa chromogenic assays*



Deborah Cohen BMJ 2014;349

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Coagulation tests	*aPTT* *ECT*	*Anti-Fxa chromogenic assays*	*PT* *Anti-Fxa chromogenic assays*	*PT* *Anti-Fxa chromogenic assays*
Bleedings management	PCC 25 U/Kg aPCC 50 IE/Kg rFVIIa 90 mcg/Kg			
Antidote	IDARUCIZIMAB (Boehringer Ing.) RE-Verse AD study	ANDEXANET ALFA (Portola) ANNEXA- A study		

The pratical everyday use of ORAL ANTICOAGULANT

VALVULAR HEART DISEASE
HYPERTROPHIC CARDIOMYOPATHY

ELECTRICAL CARDIOVERSION

What about NEW oral anticoagulants?

NOACs for VALVULAR HD

3. Stroke and bleeding risk assessment

It is conventional to divide AF into cases which are described as "valvular or "non-valvular". No satisfactory or uniform definition of these terms exists. In this guideline, the term valvular AF is used to imply that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.

ESC AF Guidelines European Heart Journal 2012

Patients with *prosthetic heart valves* should not take dabigatran/rivaroxaban/apixaban nor should pts with *AF that is caused by a heart valve problem*.

www.fda.gov

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

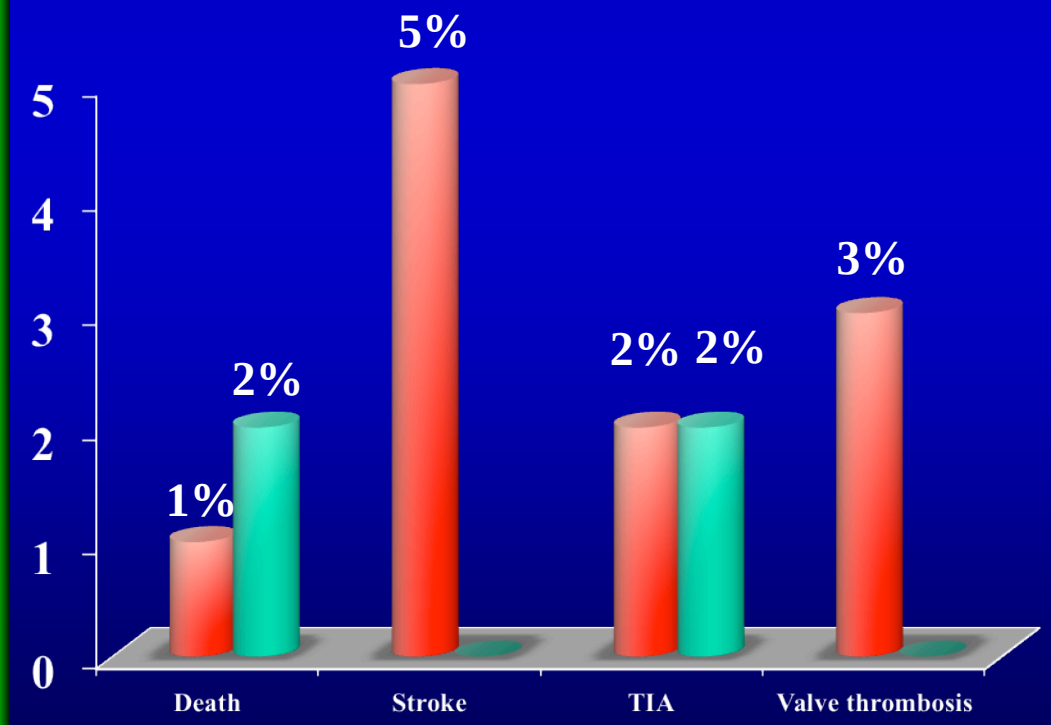
John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D., Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D., for the RE-ALIGN Investigators*

252 pts with bileaflet mechanical prosthetic valves
Mean Euroscore 2.3, mean age 55 y, 70% aortic valve

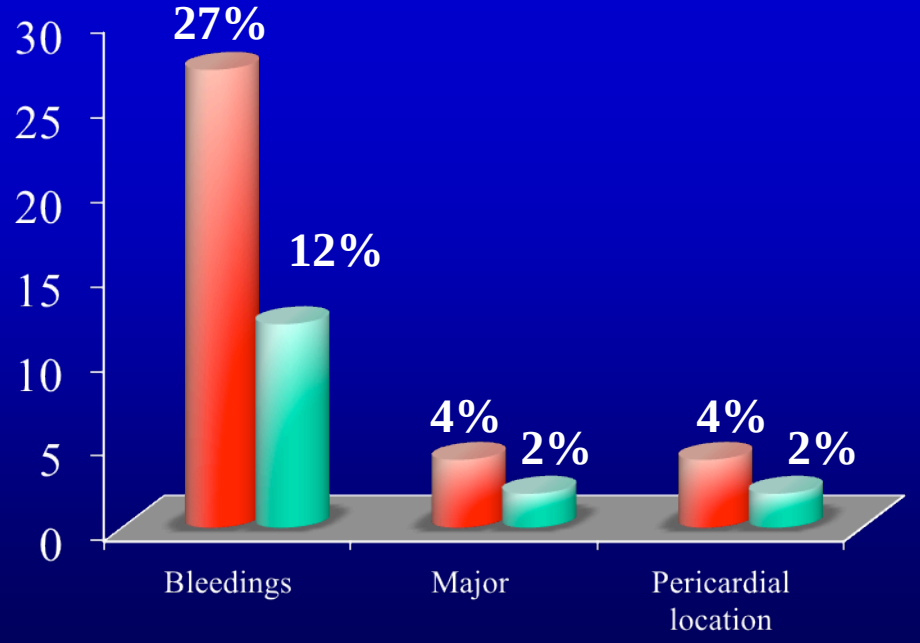
recently implanted (population A) or implanted more than 3 months prior to enrollment (population B)

Dabigatran (150 mg, 220 mg, 300 mg BD) vs Warfarin

Death & TE complications



Bleedings



N Engl J Med 2013

Exclusion criteria regarding valvular disease in NOACs trials

Trial	Exclusion criteria
ROCKET AF[5,6]	Haemodynamically significant mitral valve stenosis. Prosthetic heart valve. Annuloplasty with or without prosthetic ring, commissurotomy, and/or valvuloplasty are permitted. Planned invasive procedure with potential for uncontrolled bleeding, including major surgery
RE-LY[1,2]	3950/18113 pts (22%) Ezekowitz et al. Poster contributions JACC 2014
ARISTOTLE[7,8]	4808/18201 (26%) pts Oral presentation ESC Congress 2013
ENGAGE[9,10]	Moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves and/or valve repair could be included)

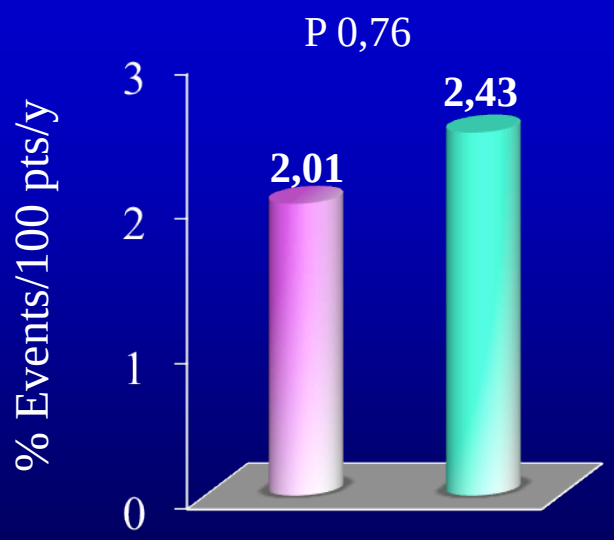
Breithardt G. et al Eur Heart Journal 2014

Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial

Valvular Heart Disease 1992 pts (14%)

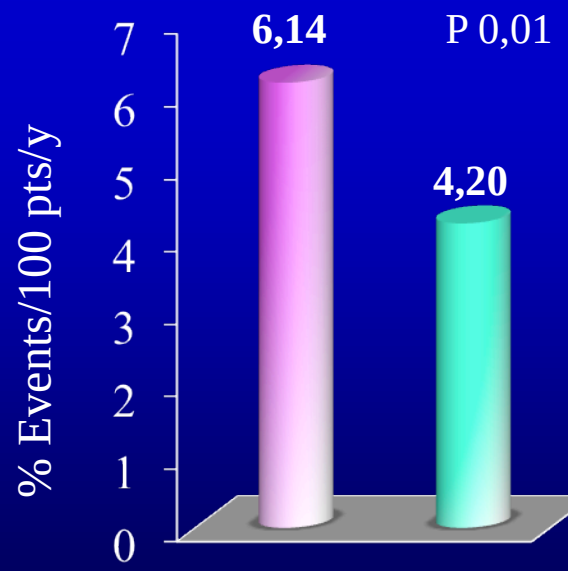
90% mitral regurgitation (only 3% post-rheumatic)

Stroke or SE



- Rivaroxaban
- Warfarin

Major Bleedings



Breithardt G. et al Eur Heart Journal 2014

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy

- **In HCM pts *CHA_2DS_2VASC score* to calculate stroke risk is *not recommended***

- **There are *no data* on the use of *NOACs* in HCM pts**

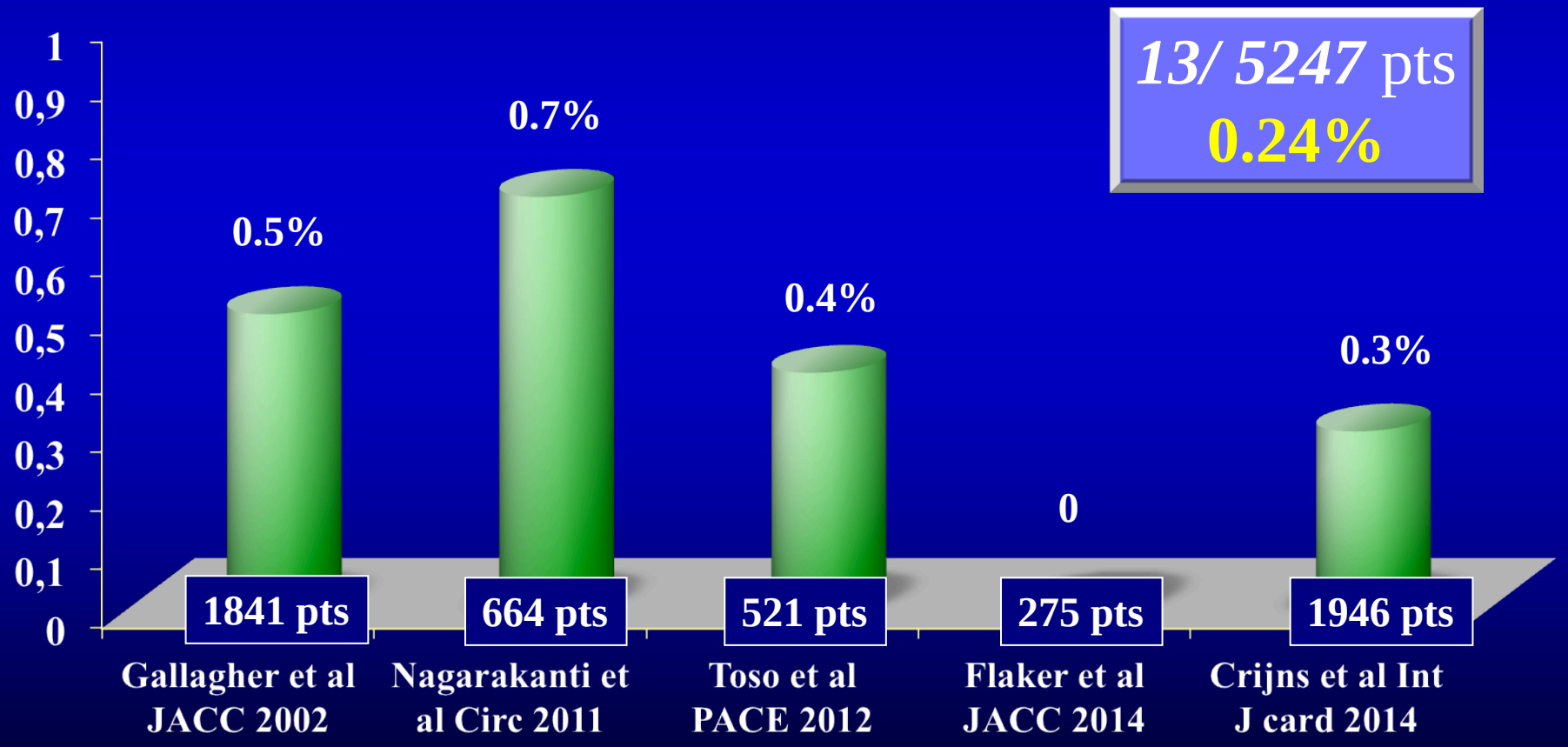
The pratical everyday use of ORAL ANTICOAGULANT

VALVULAR HEART DISEASE
HYPERTROPHIC CARDIOMYOPATHY

ELECTRICAL CARDIOVERSION

Electrical Cardioversion on *warfarin*

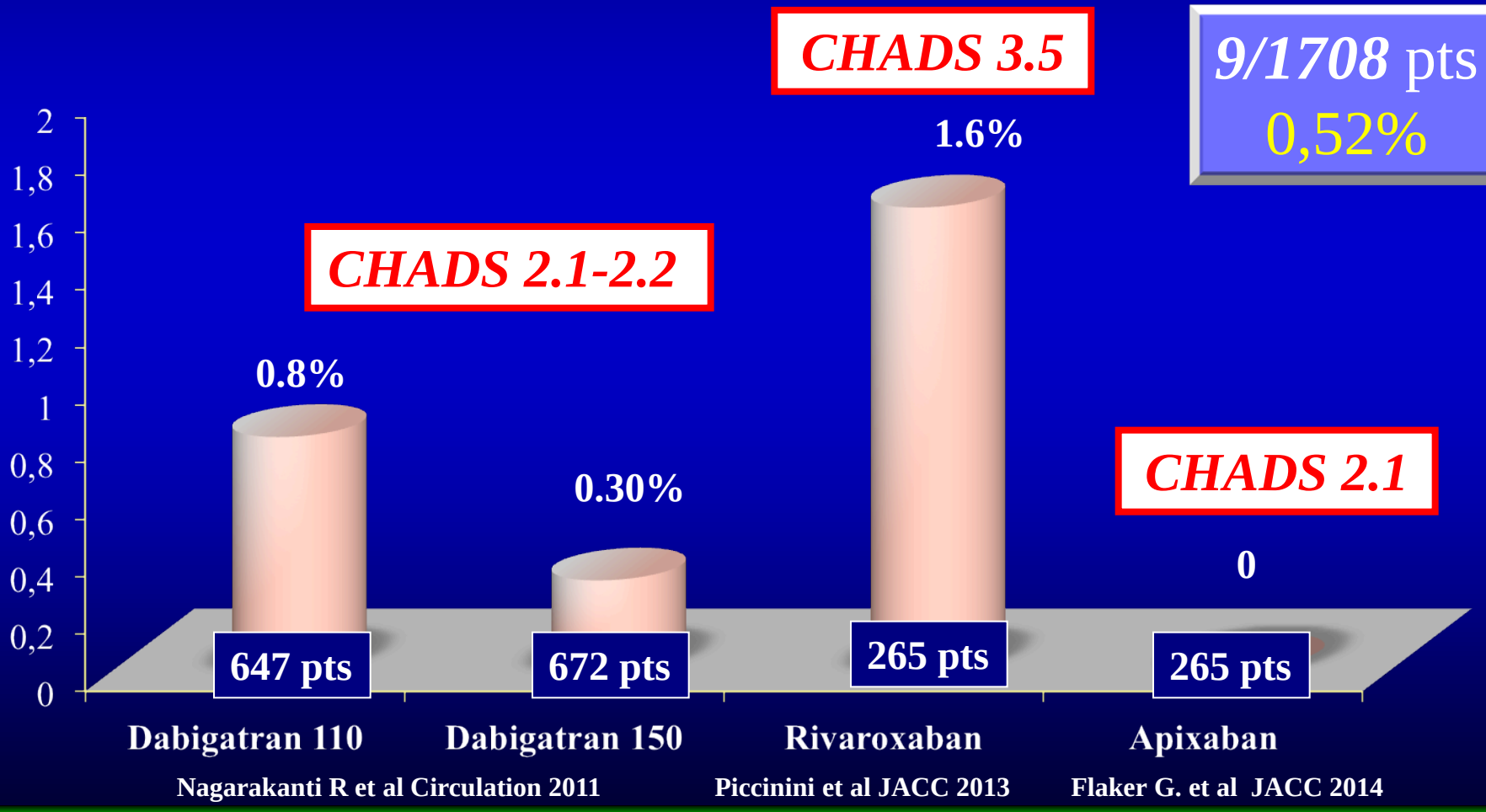
Sintomatic cerebrovascular complications



13/ 5247 pts
0.24%

Electrical Cardioversion on *NOACs*

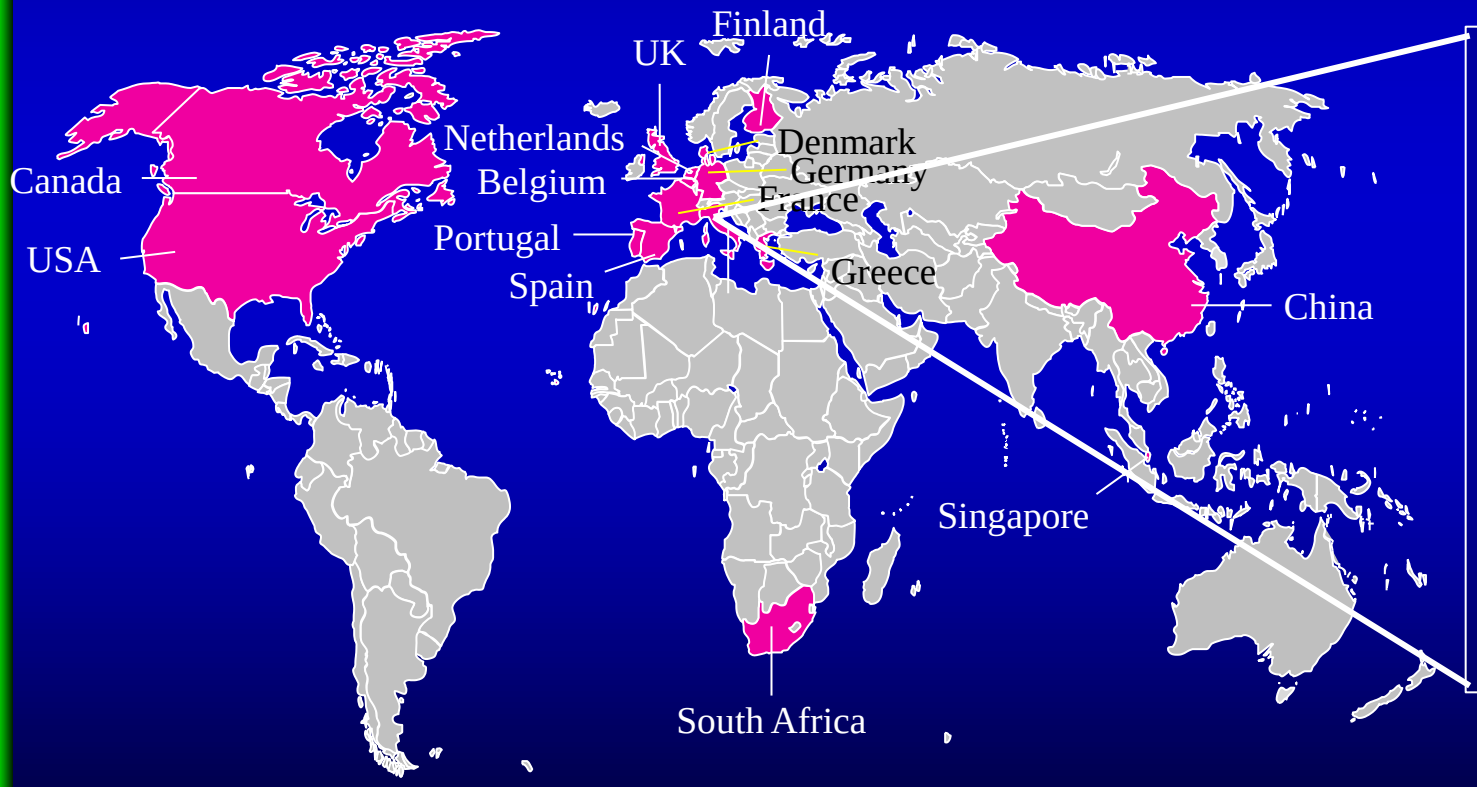
Sintomatic cerebrovascular complications



Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

X-VERT Trial

1504 patients, 141 Centres across 16 countries



Italy:

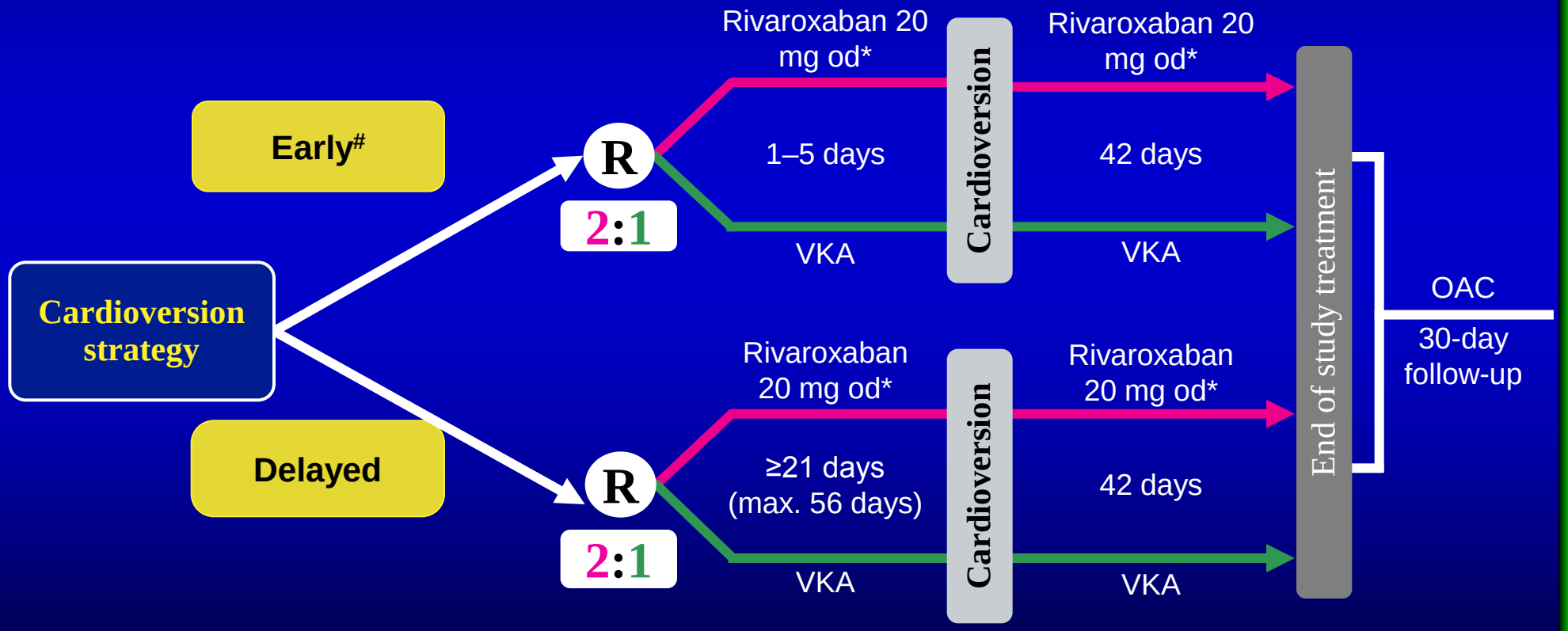
- Botto GL
- Calò L
- Cappato R
- Capucci A
- Gaita F
- Grimaldi M
- Gulizia MM
- Themistoclakis S

Cappato R. et al. Eur Heart Journal 2014

Randomized, open-label, parallel-group, active-controlled multicentre study

Inclusion criteria:

Age ≥18 years, non-valvular AF lasting >48 h or unknown duration, scheduled for cardioversion



*15 mg if CrCl 30–49 ml/min; VKA with INR 2.0–3.0;
#protocol recommended only if adequate anticoagulation or immediate TEE

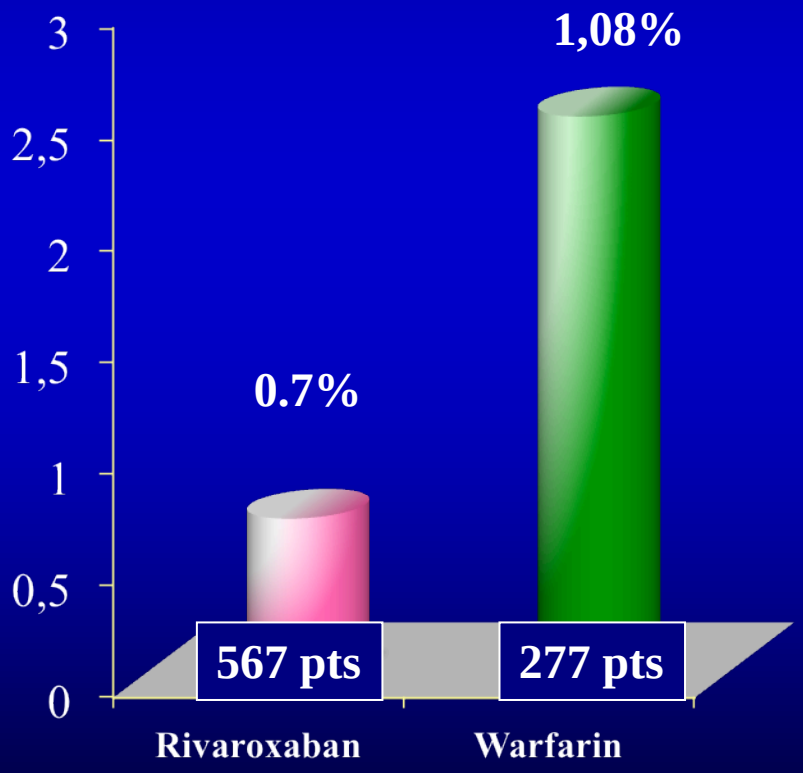
Ezekowitz MD *et al. Am Heart J* 2014;167:646–652;

X-VeRT: clinical characteristics

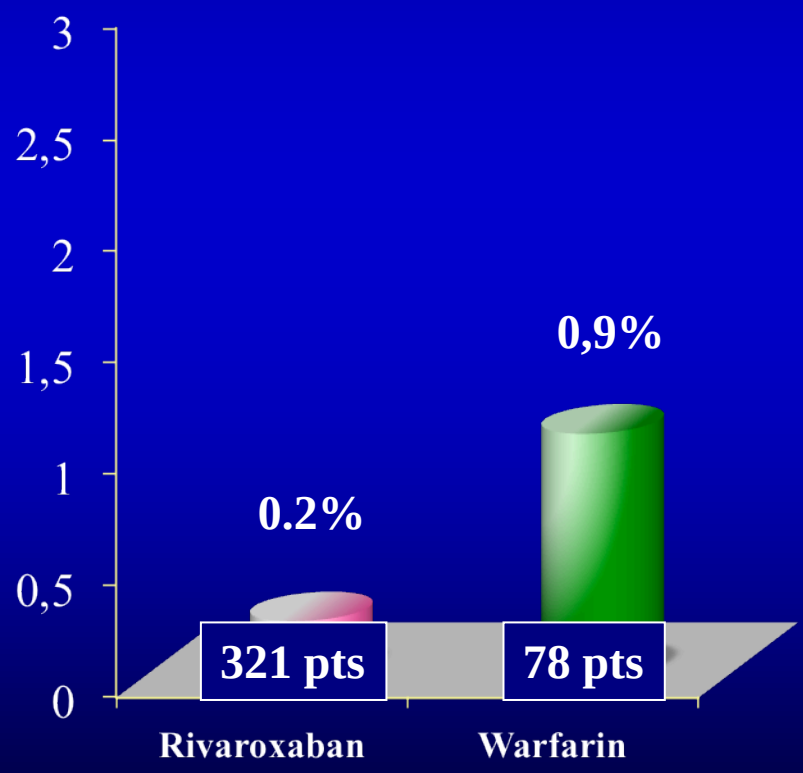
	Total (N=1504)	Rivaroxaban (n=1002)	VKA (n=502)
Age, mean SD, years	**64.9 ±10**	**64.9±10**	**64.7±10**
Male, %	**72.7**	**72.6**	**73.1**
Persistent	**53.9**	**55.9**	**50.0**
Hypertension, %	**66.2**	**65.0**	**68.7**
Renal function/CrCI, % ≥80 ml/min	**60.2**	**61.5**	**57.6**
Prior OAC use for ≥6 weeks, %	**42.8**	**42.3**	**43.8**
Previous stroke/TIA or SE, %	**7.7**	**6.7**	**9.8**
$CHADS_2$ score, mean SD	***1.4±1.1***	***1.3±1.1***	***1.4±1.1***
CHA_2DS_2-VASc score, mean SD	***2.3±1.6***	***2.3±1.6***	***2.3±1.6***

X-VeRT: Stroke or TIA

768/872 early CV performed



399/632 delayed CV performed

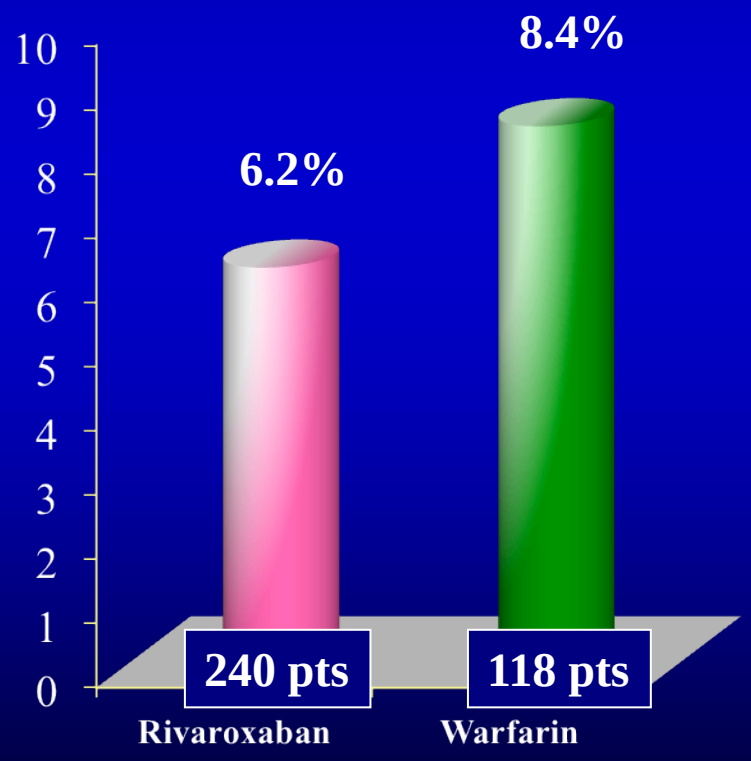


Cappato R *et al. Eur Heart J* 2014

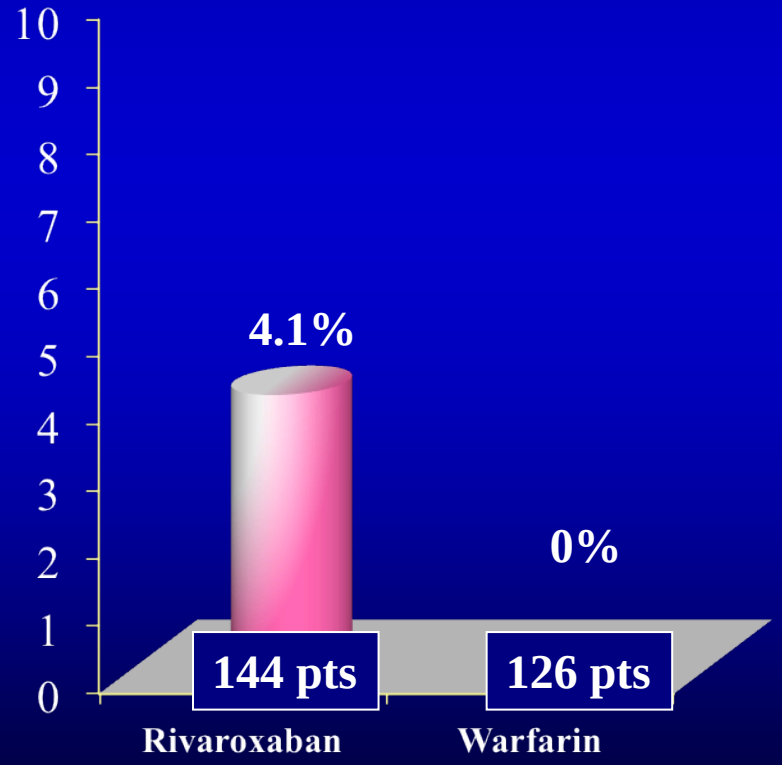
X-VeRT: LAA Thrombi

628 TEE performed

358 TEE in early CV



270 TEE in delayed CV



Cappato R *et al. Eur Heart J* 2014

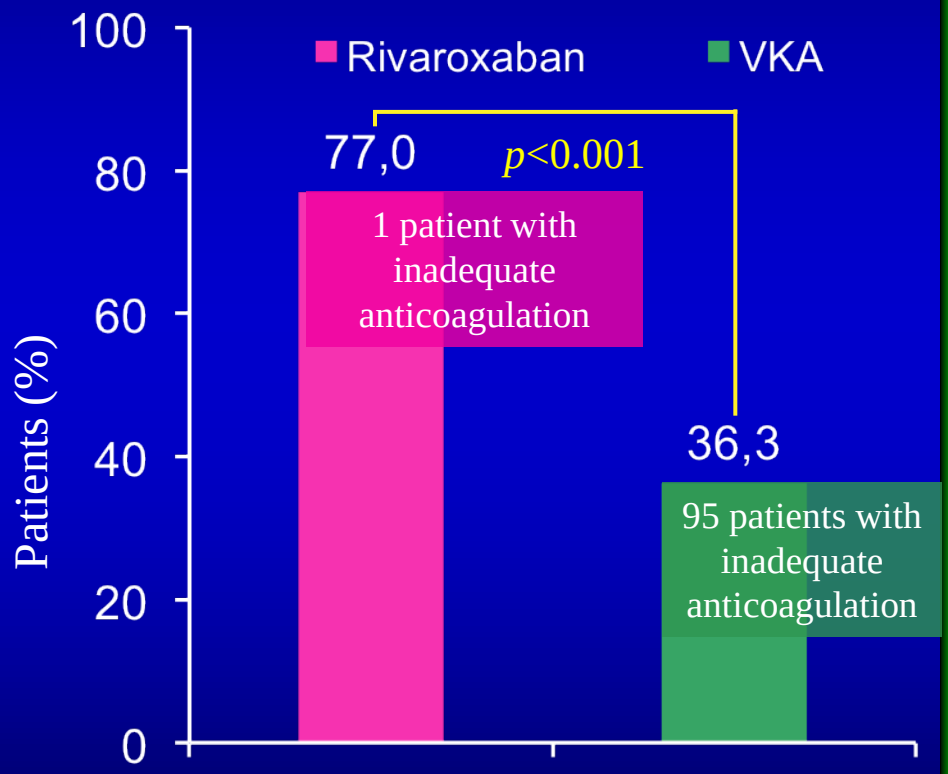
X-VeRT: time to cardioversion

Patients cardioverted as scheduled

Rivaroxaban: 841/1002 pts (84%)
Warfarin: 385/502 pts (77%)

Delayed cardioversion

Rivaroxaban: 321/417 pts (77%)
Warfarin: 78/215 pts (36.3%)

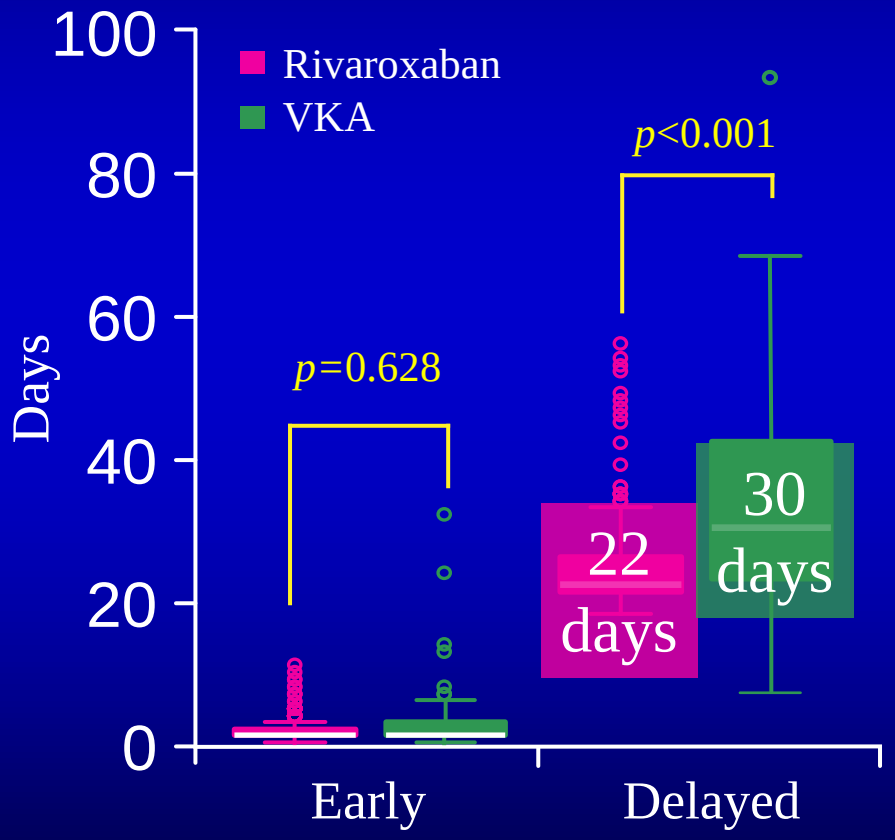


Cappato R *et al. Eur Heart J* 2014

X-VeRT: time to cardioversion

The time between randomization and CV was similar or shorter in **Rivaroxaban** vs **Warfarin**
Early median 1 (1-2) vs 1 (1-3)
Delayed 22 (21-26) vs 30 (23-42)

Median time to cardioversion



Cappato R *et al. Eur Heart J* 2014

For a proper everyday use of NOACs in the clinical practice:

Make the right choice (the 5 RIGHT)

Avoid the grey zone:
Valvular HD, Hypertrophic CM

Electrical cardioversion on NOACs is safe, particularly Rivaroxaban may be considered an alternative to VKA

ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY

XXVI Giornate Cardiologiche Torinesi

AZIENDA OSPEDALIERO-UNIVERSITARIA
Città della Salute e della Scienza di Torino

UNIVERSITÀ DEGLI STUDI DI TORINO

From Caliper to Catheter

JMC
JOINT MEETING OF CARDIOLOGY

Thanks for the attention!

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Sebastiano Marra

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