NOVÉ INDIKACE NOAK

KARDIOVERZE

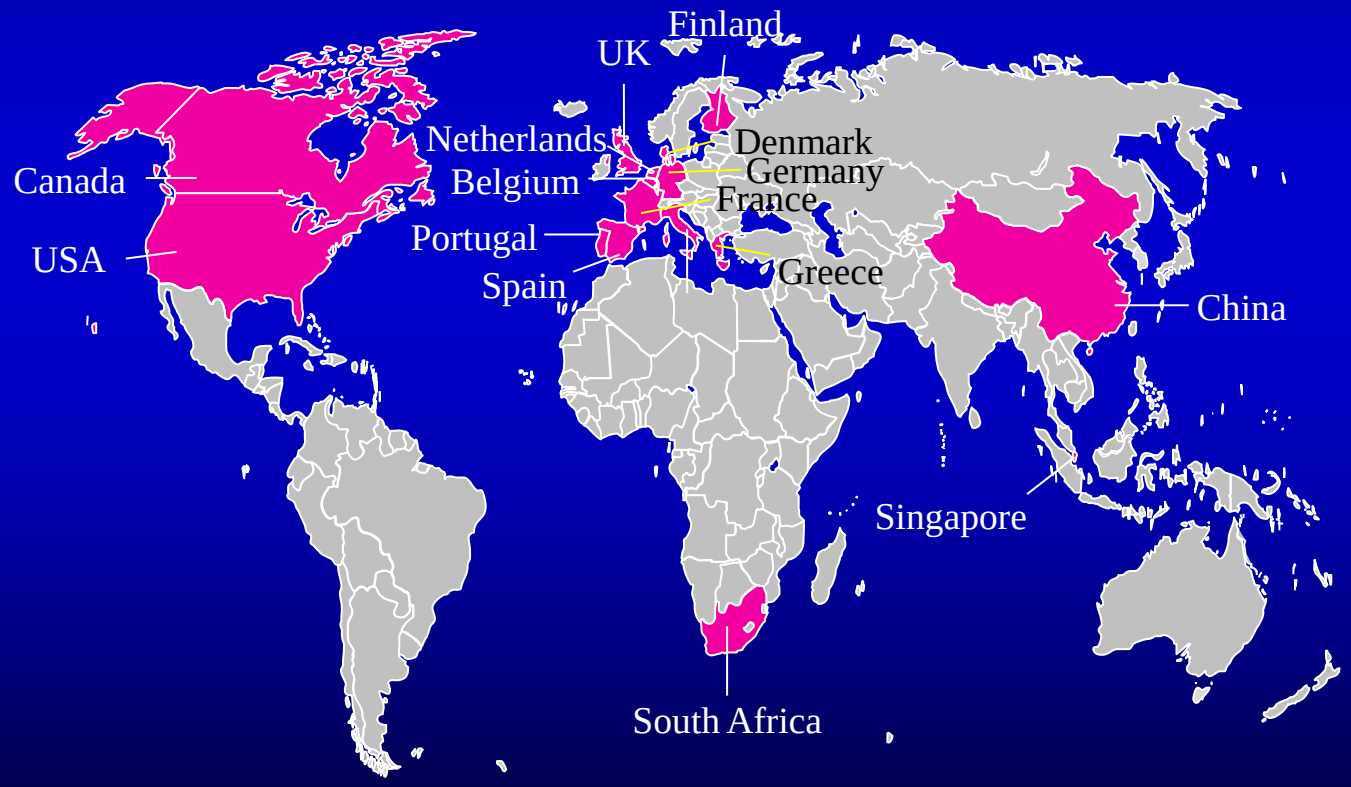
PREVENCE

INFARKT MYOKARDU

Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

1504 patients, 141 Centres across 16 countries

X-VERT Trial

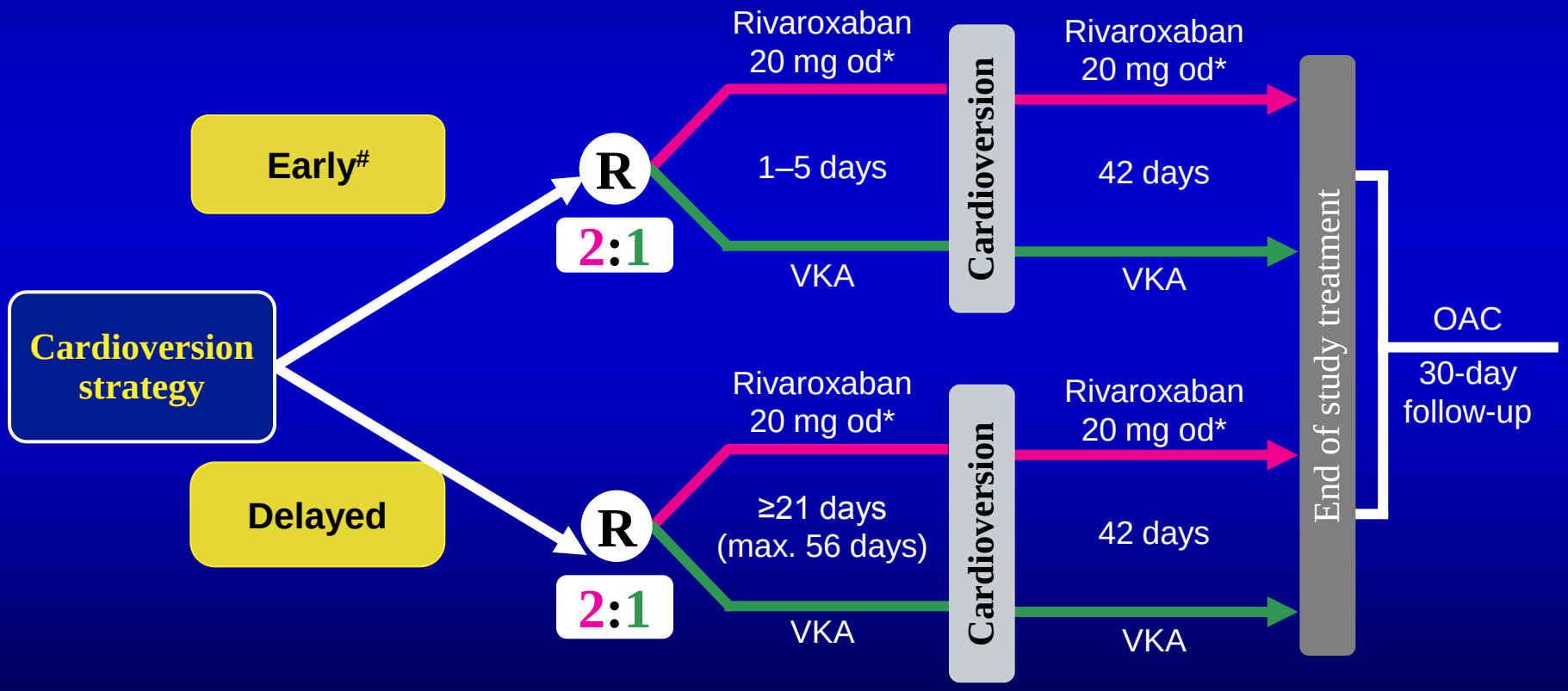


Cappato R. et al. Eur Heart Journal 2014

Randomizovaná, otevřená studie

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

L.CZ.GM.03.2015.0358

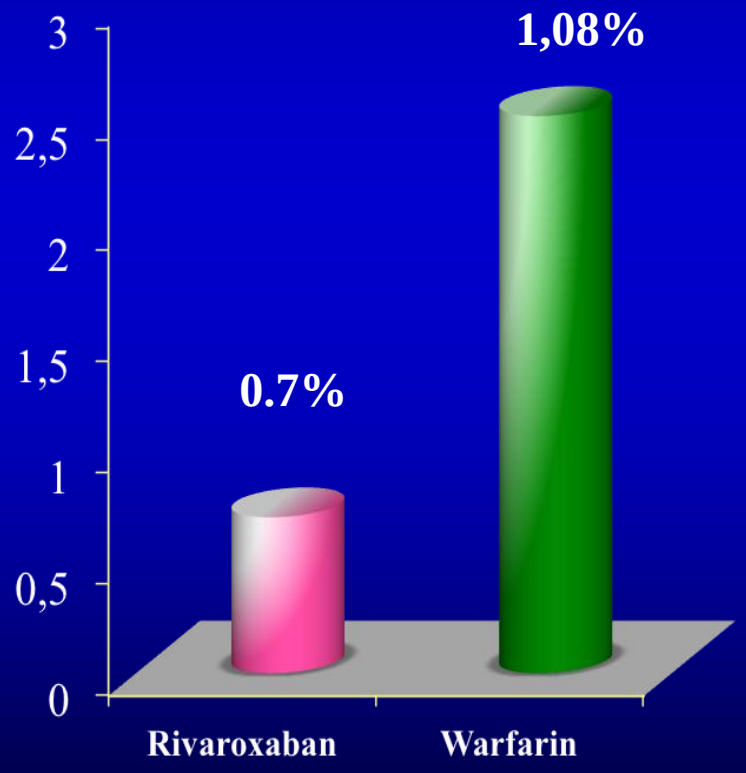
Ezekowitz MD *et al. Am Heart J* 2014;167:646–652;

X-VeRT: characteristika nemocných

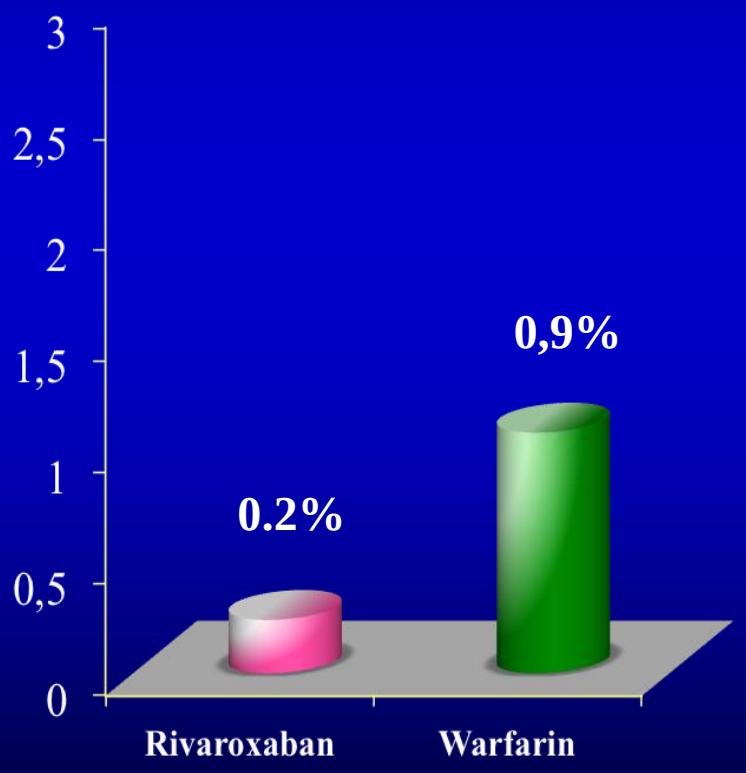
	Total (N=1504)	Rivaroxaban (n=1002)	VKA (n=502)
Age, mean SD, years	**64.9 ±10**	**64.9±10**	**64.7±10**
Male, %	**72.7**	**72.6**	**73.1**
Persistent	**53.9**	**55.9**	**50.0**
Hypertension, %	**66.2**	**65.0**	**68.7**
Renal function/CrCI, % ≥80 ml/min	**60.2**	**61.5**	**57.6**
Prior OAC use for ≥6 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: CMP nebo TIA

768/872 časná KV

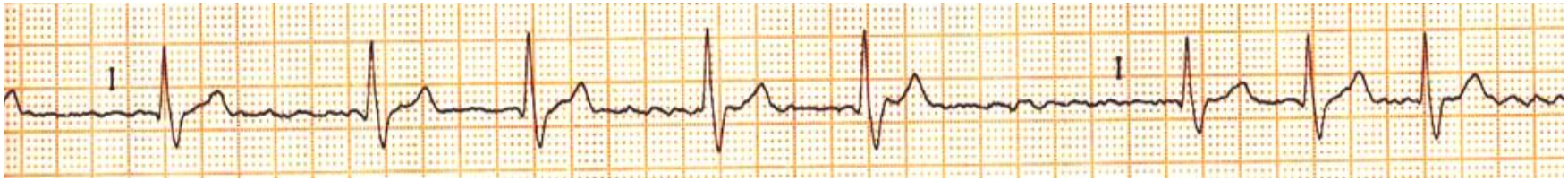


399/632 odložená KV



Cappato R *et al. Eur Heart J* 2014

Studie ENSURE

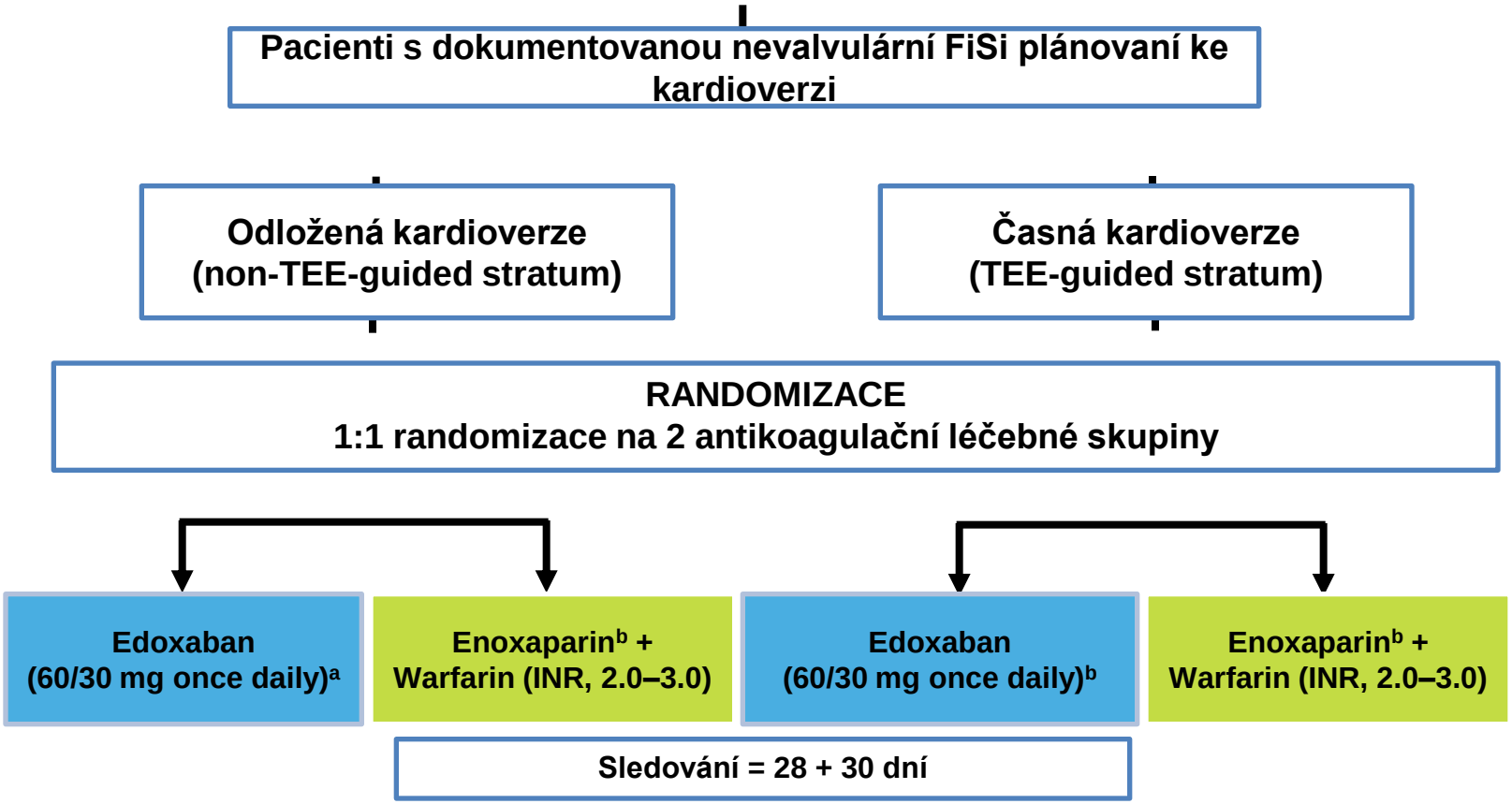


Edoxaban vs Enoxaparin/Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation

The Randomized ENSURE-AF Study

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

Design studie ENSURE



[a] Patients meeting ≥1 of the following criteria: CrCl ≥15 mL/min and ≤50 mL/min; low body weight (≤60 kg); or concomitant use of P-gp inhibitors (with the exception of amiodarone)
[b] Patients with INR at randomization ≥2 did not require enoxaparin
CrCl = creatinine clearance; INR = international normalized ratio; NVAF = nonvalvular atrial fibrillation; TEE = transesophageal echocardiography
Lip GY, et al. *Am Heart J.* 2015;169:597-604

Cíle studie

Primary Efficacy Endpoint

Composite of stroke, SEE, MI, and CV mortality

ITT population (all randomized subjects) during the overall period

Primary Safety Endpoint

Composite of major and CRNM bleeding

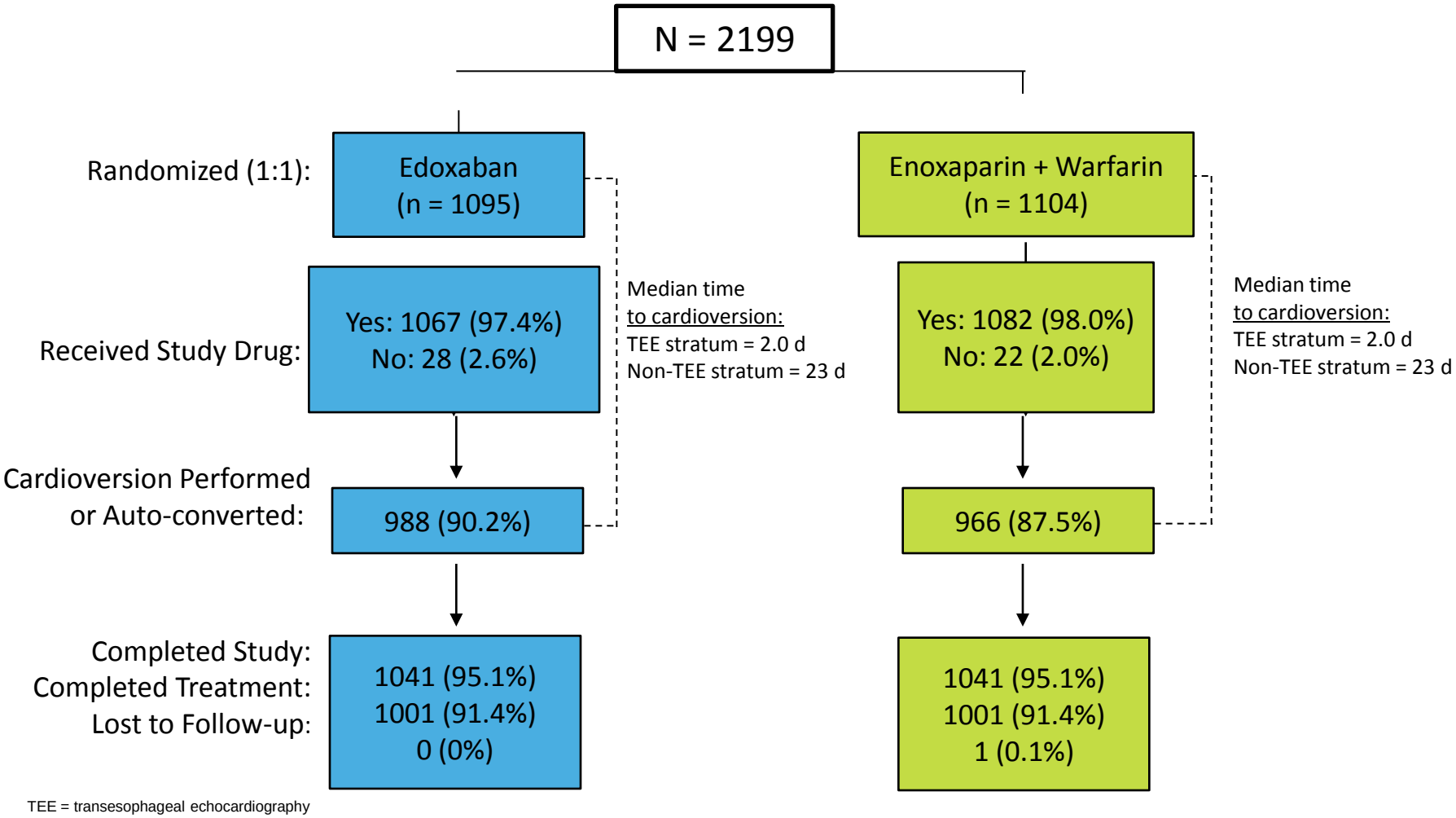
Safety population (all subjects who took ≥1 dose of study drug) during the on-treatment period

Net Clinical Outcome (Secondary Endpoint)

Composite of stroke, SEE, MI, CV mortality, and major bleeding

ITT population (all randomized subjects) during the overall period

Počty pacientů



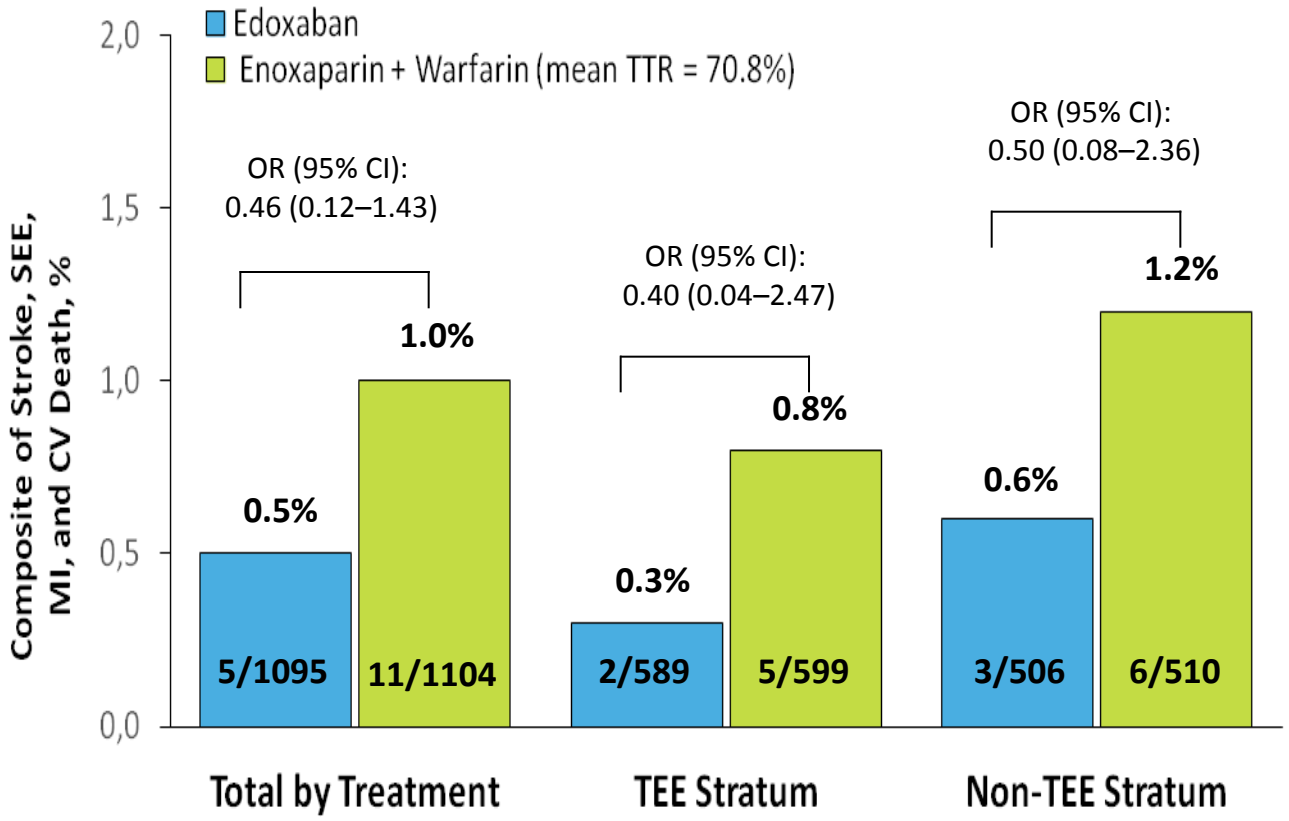
TEE = transesophageal echocardiography

Baseline demografie

	Total by Treatment		TEE Stratum		Non-TEE Stratum	
	Edoxaban (n = 1095)	Enoxaparin + Warfarin (n = 1104)	Edoxaban (n = 589)	Enoxaparin + Warfarin (n = 594)	Edoxaban (n = 506)	Enoxaparin + Warfarin (n = 510)
Age (y), mean	64.3	64.2	64.9	64.5	63.6	63.8
Male, n (%)	721 (65.8)	722 (65.4)	385 (65.4)	389 (65.5)	336 (66.4)	333 (65.3)
BMI (kg/m^2), mean	30.6	30.7	30.4	30.4	31.0	31.0
CHA_2DS_2-VASc, mean	2.6	2.6	2.7	2.7	2.5	2.5
Paroxysmal AF (≤7 days), n (%)	208 (19.0)	207 (18.8)	138 (23.4)	132 (22.2)	70 (13.8)	75 (14.7)
Persistent AF (>7 days, <1 y), n (%)	887 (81.0)	890 (80.6)	451 (76.6)	458 (77.1)	436 (86.2)	432 (84.7)
Anticoagulant experienced, n (%)	791 (72.2)	808 (73.2)	426 (72.3)	440 (74.1)	365 (72.1)	368 (72.2)
Medical history, n (%)						
Congestive heart failure	476 (43.5)	484 (43.8)	258 (43.8)	259 (43.6)	218 (43.1)	225 (44.1)
Coronary artery disease	181 (16.5)	197 (17.8)	89 (15.1)	111 (18.7)	92 (18.2)	86 (16.9)
Diabetes	218 (19.9)	197 (17.8)	115 (19.5)	105 (17.7)	103 (20.4)	92 (18.0)

AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or TIA or thromboembolism, Vascular disease, Age 65–74 years, Sex category; TEE = transesophageal echocardiography; TIA = transient ischemic attack

Primární cíl



[a] Composite of stroke, SEE, MI, and CV mortality assessed in the ITT population during overall period

CI = confidence interval; CV = cardiovascular; ITT = intent-to-treat; MI = myocardial infarction; OR = odds ratio; SEE = systemic embolic event; TEE = transesophageal echocardiography; TTR = time in therapeutic range

Závěry

- Studie nebyla dostatečně velká, aby prokázala statisticky významný rozdíl.
  - Na základě počtu příhod ve studii ENSURE by bylo potřeba provést studii alespoň na 10 000 nemocných.
- Studie byla open-label design, ale měla zaslepené výsledky primárního účinnostního i bezpečnostního cíle.
- Na základě studie ENSURE můžeme doporučit provádět kardioverzi pod novými antikoagulancii.
- Edoxaban je minimálně stejně účinný a bezpečný jako enoxaparin/warfarin strategie

Publication in *The Lancet*

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**

Summary

Background Edoxaban, an oral factor Xa inhibitor, is non-inferior for prevention of stroke and systemic embolism in patients with atrial fibrillation and is associated with less bleeding than well controlled enoxaparin–warfarin therapy. Few safety data about edoxaban in patients undergoing electrical cardioversion are available.

Methods We did a multicentre, prospective, randomised, open-label, blinded-endpoint evaluation trial in 19 countries with 239 sites comparing edoxaban 60 mg per day with enoxaparin–warfarin in patients undergoing electrical cardioversion of non-valvular atrial fibrillation. The dose of edoxaban was reduced to 30 mg per day if one or more factors (creatinine clearance 15–50 mL/min, low bodyweight [≤60 kg], or concomitant use of P-glycoprotein inhibitors)

Published Online August 30, 2016 http://dx.doi.org/10.1016/PII

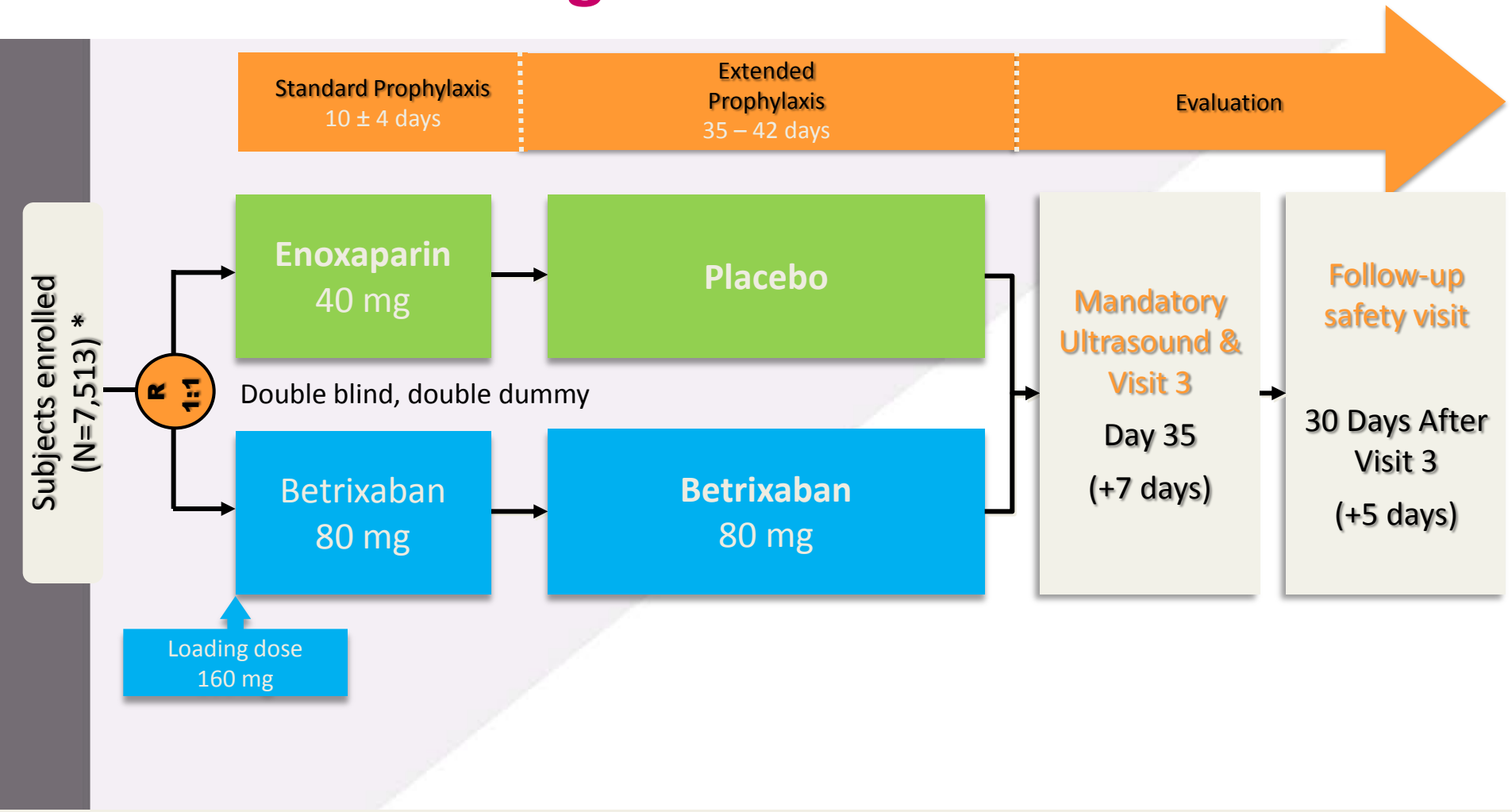
See Online/Comment http://dx.doi.org/10.1016/S0140-6736(16)31410-6

*Co-principal investigators and joint senior authors

Studie APEX

- Acute Medically ill VTE Prevention with EXtended Duration Betrixaban (APEX) study
  - Multicentrická
  - Randomizovaná
  - Cíle: bezpečnost a účinnost
  - Srovnávající prodloužené podávání Betrixabanu (Factor Xa inhibitor) se standardní léčbou Enoxaparinem jako prevence tromembolické nemoci u akutně hospitalizovaných nemocných
  - 35 Zemí & 460 Center

Design studie APEX

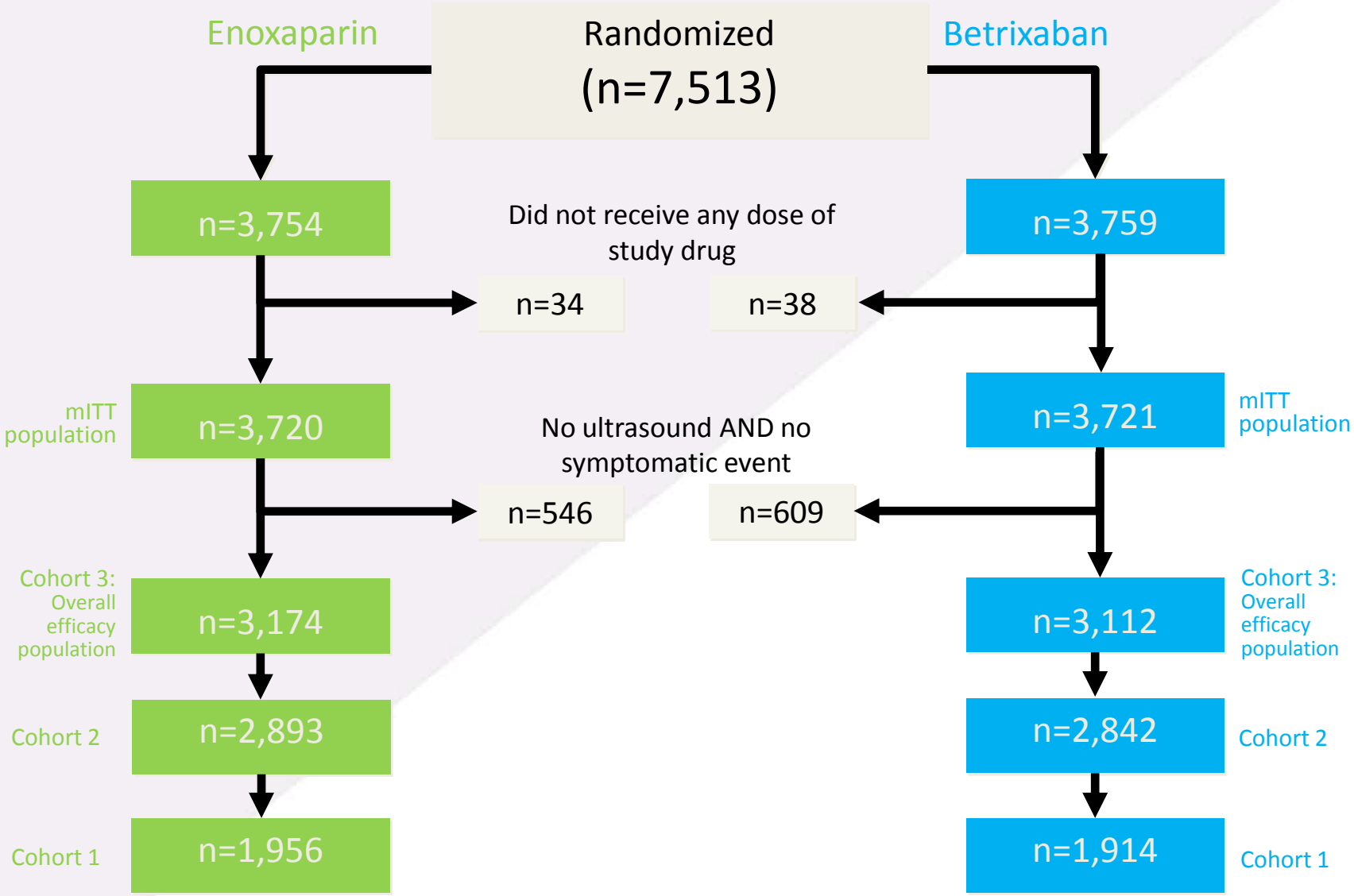


Primary Efficacy Endpoint: Composite of asymptomatic proximal DVT (detected on ultrasound), symptomatic DVT (proximal or distal), non-fatal PE, and VTE-related death through Visit 3

Primary Safety Endpoint: ISTH Major bleeding through 7 days after drug discontinuation

**Patients were eligible if they were 40 years of age or older, had been hospitalized for less than 96 hours for a specified acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke), and had reduced mobility and specific risk factors for venous thromboembolism.*

APEX Study Results - Population



MARINER

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Reference Gibson et. al. ISTH SSC 2016 – May 27, 2016

APEX Study Results – Baseline Characteristics
Primary Reasons for Hospital Admission

	Enoxaparin (n=3,754)	Betrixaban (n=3,759)
Acute CHF NYHA III-IV, % (n)	44.5% (1,672)	44.6% (1,677)
Acute infection, % (n)	28.2% (1,058)	29.6% (1,112)
Acute respiratory failure, % (n)	12.6% (474)	11.9% (448)
Acute ischemic stroke w/ immobilization, % (n)	11.5% (432)	10.9% (411)
Acute rheumatic disorder, % (n)	3.1% (117)	2.9% (109)

MARINER

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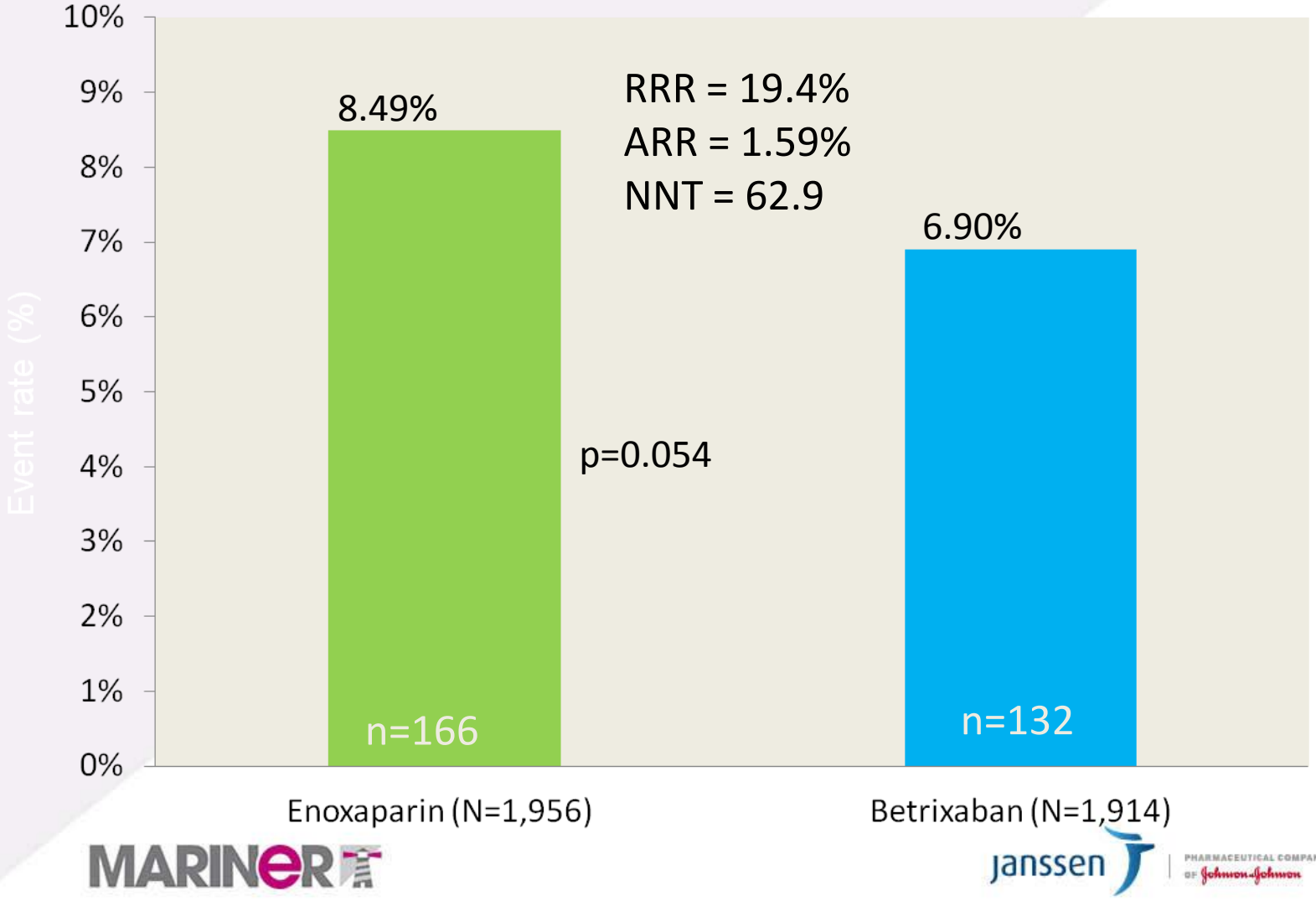
Values provided for all patients randomized, no significant differences between treatment arms.
Data not available for 2 patients in the betrixaban arm and 1 patient in the enoxaparin arm.

Reference: Gibson et. al. ISTH SSC 2016 – May 27, 2016

APEX Study Results: Primary Efficacy Endpoint

Cohort 1: D-Dimer ≥ 2 x ULN

Composite of Adjudicated Asymptomatic Proximal DVT, Symptomatic Proximal or Distal DVT, non-fatal PE, or VTE-related Death



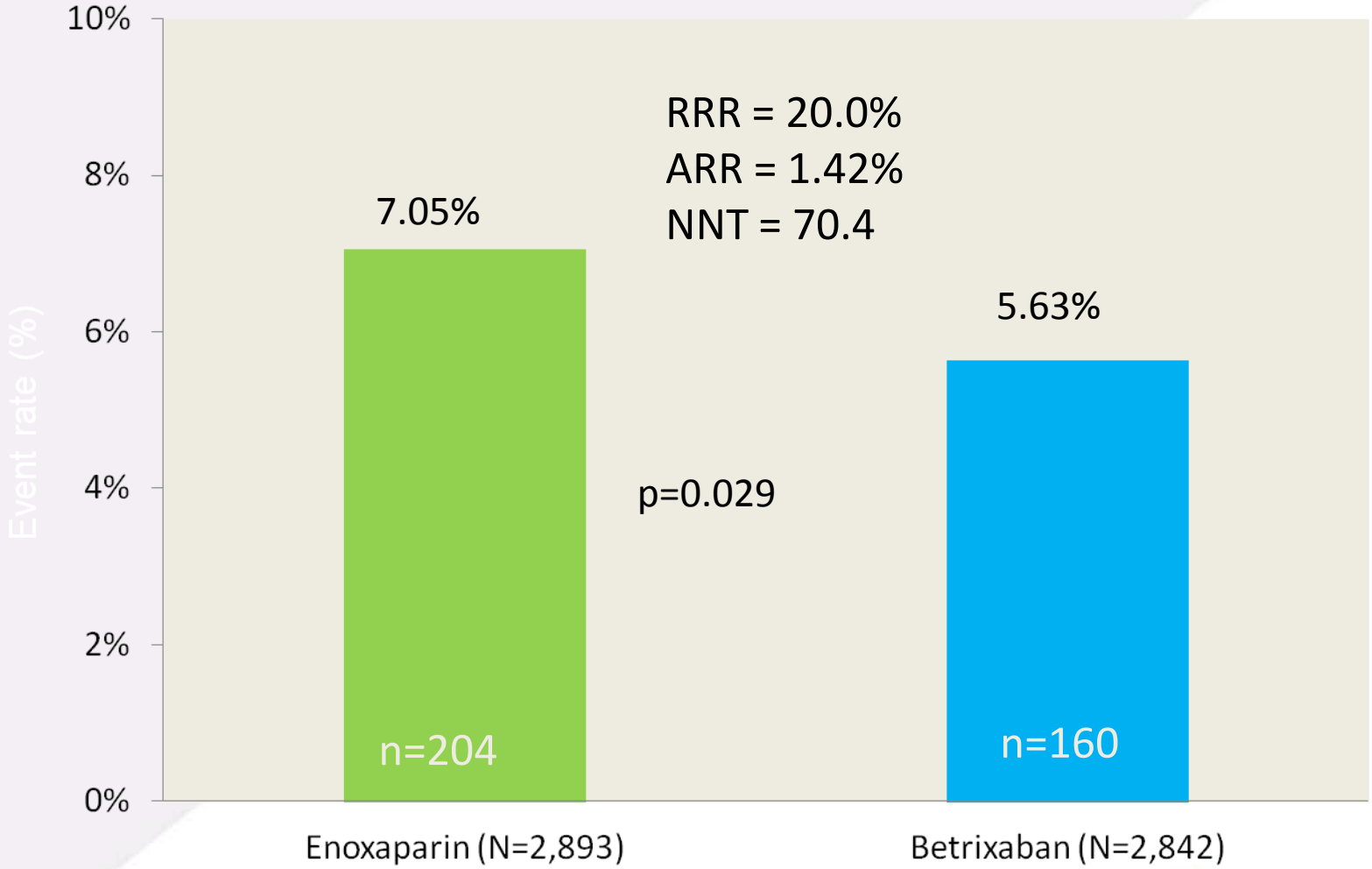
P-values reported using the Mantel-Haenszel test stratified for dosing criteria (ie. No adjustment, renal insufficiency, P-gp inhibitor).
Symptomatic events from Day 1 till Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42; Asymptomatic DVT between Day 32 and 47.

Reference: Gibson et. al. ISTH SSC 2016 – May 27, 2016

APEX Study Results: Primary Efficacy Endpoint

(Exploratory Analysis) Cohort 2: : D-Dimer ≥ 2 x ULN OR Age ≥75

Composite of Adjudicated Asymptomatic Proximal DVT, Symptomatic Proximal or Distal DVT, non-fatal PE, or VTE-related Death

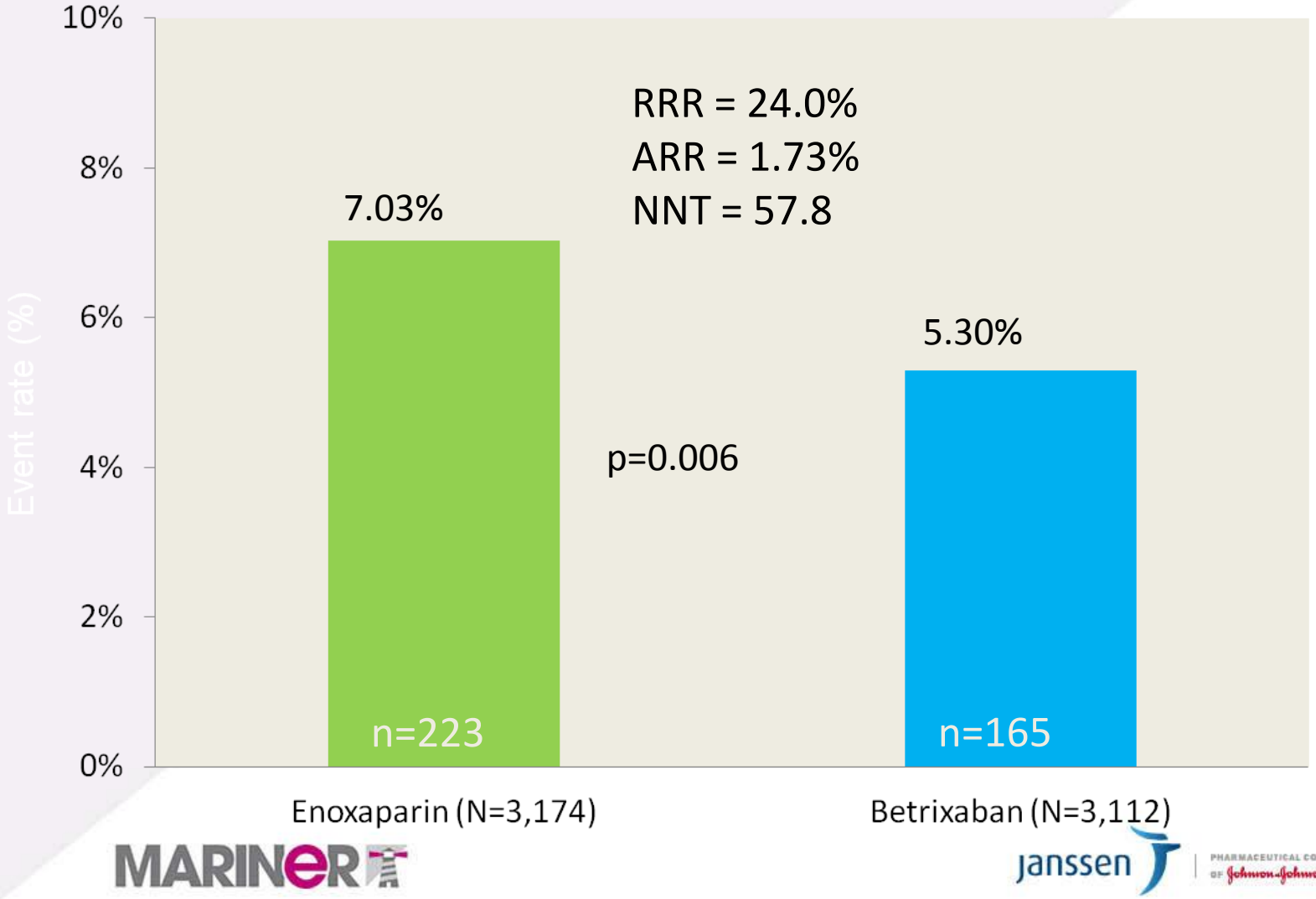


P-values reported using the Mantel-Haenszel test stratified for dosing and entry criteria (ie. No adjustment, renal insufficiency, or P-gp inhibitor / DD > 2x ULN or DD < 2x ULN).Symptomatic events from Day 1 till Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42; Asymptomatic DVT between Day 32 and 47.

Reference: Gibson et. al. ISTH SSC 2016 – May 27, 2016

APEX Study Results: Primary Efficacy Endpoint (Exploratory Analysis) Cohort 3: Overall Efficacy Population

Composite of Adjudicated Asymptomatic Proximal DVT, Symptomatic Proximal or Distal DVT, non-fatal PE, or VTE-related Death



MARINER

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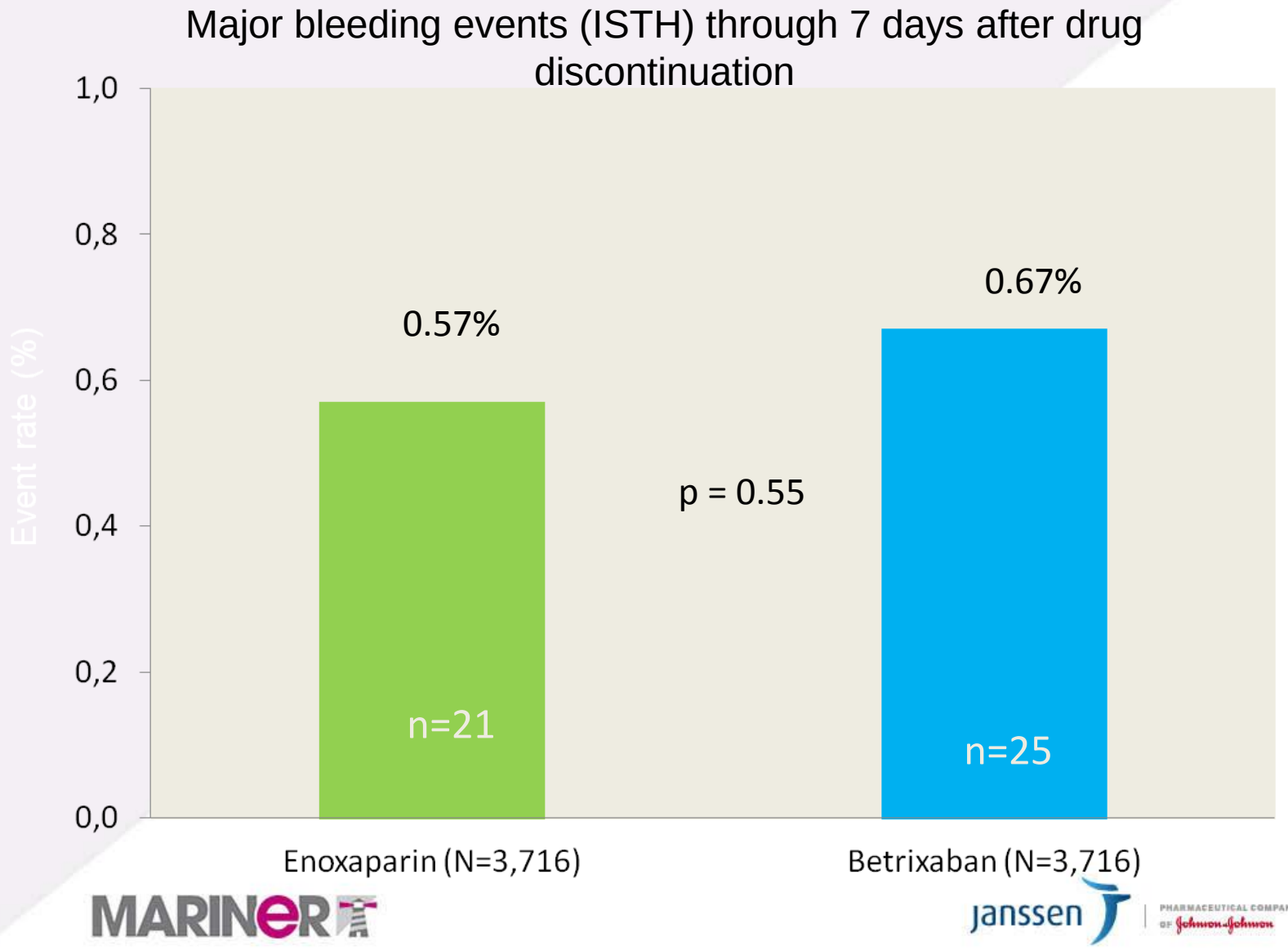
P-values reported using the Mantel-Haenszel test stratified for dosing and entry criteria (ie. No adjustment, renal insufficiency, or P-gp inhibitor / DD > 2x ULN or DD < 2x ULN).
Symptomatic events from Day 1 till Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42; Asymptomatic DVT between Day 32 and 47.

Reference: Gibson et. al. ISTH SSC 2016 – May 27, 2016

APEX Study Results: Primary Safety Endpoint ISTH Major Bleeding – Safety Population



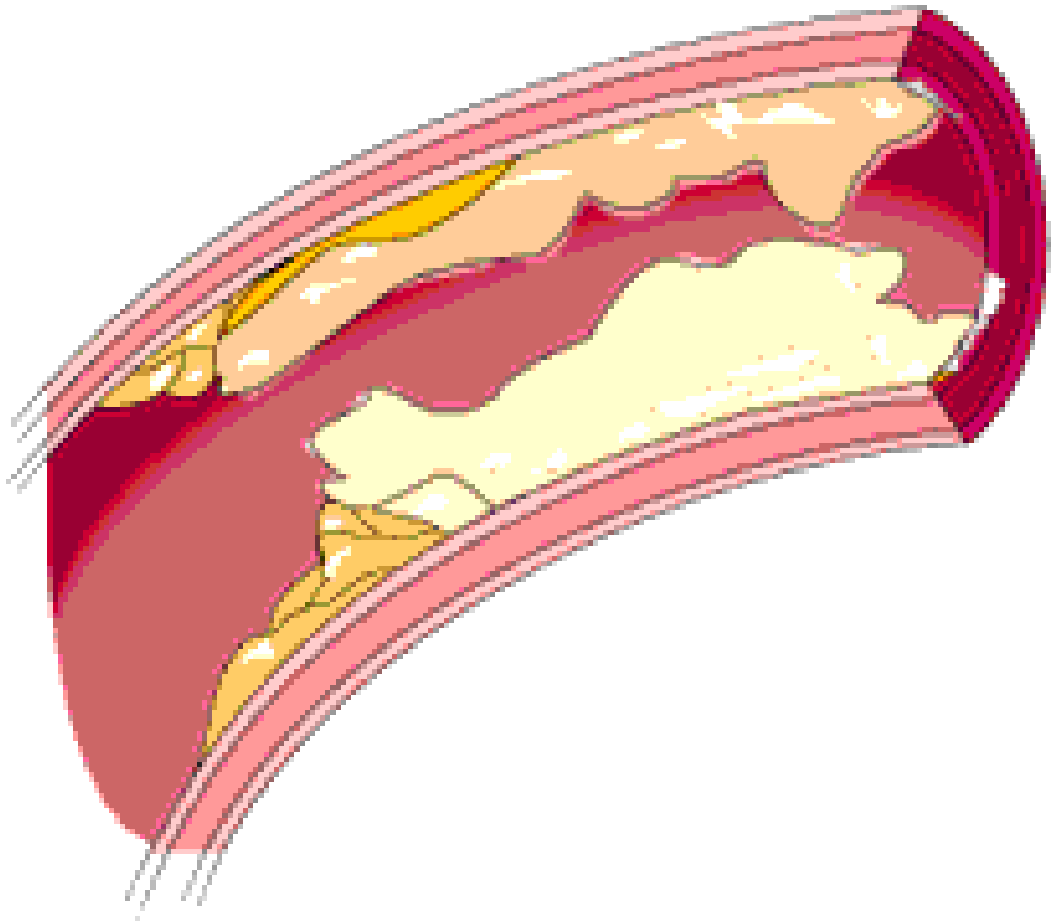
Safety population defined as patients who received at least one dose of active study drug. Analysis by actual treatment. NNH not reported given p=NS.

Reference: Gibson et. al. ISTH SSC 2016 – May 27, 2016

Studie APEX - závěry

- U nemocných akutně hospitalizovaných a se zvýšenými D dimery nebyl statisticky signifikantní rozdíl mezi léčnou betrixabanem ve srovnání se standardní léčbou enoxaprinem.
- Byl však jasný trend ve prospěch betrixabanu.
- Na studii navazuje podobná klinická studie s rivaroxabanem pod názem MARINER, která k 1.5.2017 randomizovala již > 7 000 nemocných.
- Podobné studie: ADOPT, ECLAIM, MAGELLAN

Infarkt myokardu



February 8, 2017

Dear Investigators,

On Tuesday February 7, 2017, the COMPASS Data and Safety Monitoring Committee recommended that the rivaroxaban, rivaroxaban plus aspirin, and the aspirin arms of the study stop. The reason for stopping is that one of the rivaroxaban arms of the study met the pre-specified criteria for premature termination of the trial for efficacy. In other words, one of the rivaroxaban treatment arms showed greater than expected benefit in the study primary outcome. The pantoprazole and pantoprazole-placebo arm will continue as planned.

Bayer has issued the following press release: http://www.press.bayer.com/baynews/baynews.nsf/id/Phase-III-COMPASS-study-Bayers-Rivaroxaban-Patients-Coronary-Peripheral-Artery-Disease-Shows?OpenDocument&sessionID=1486577351

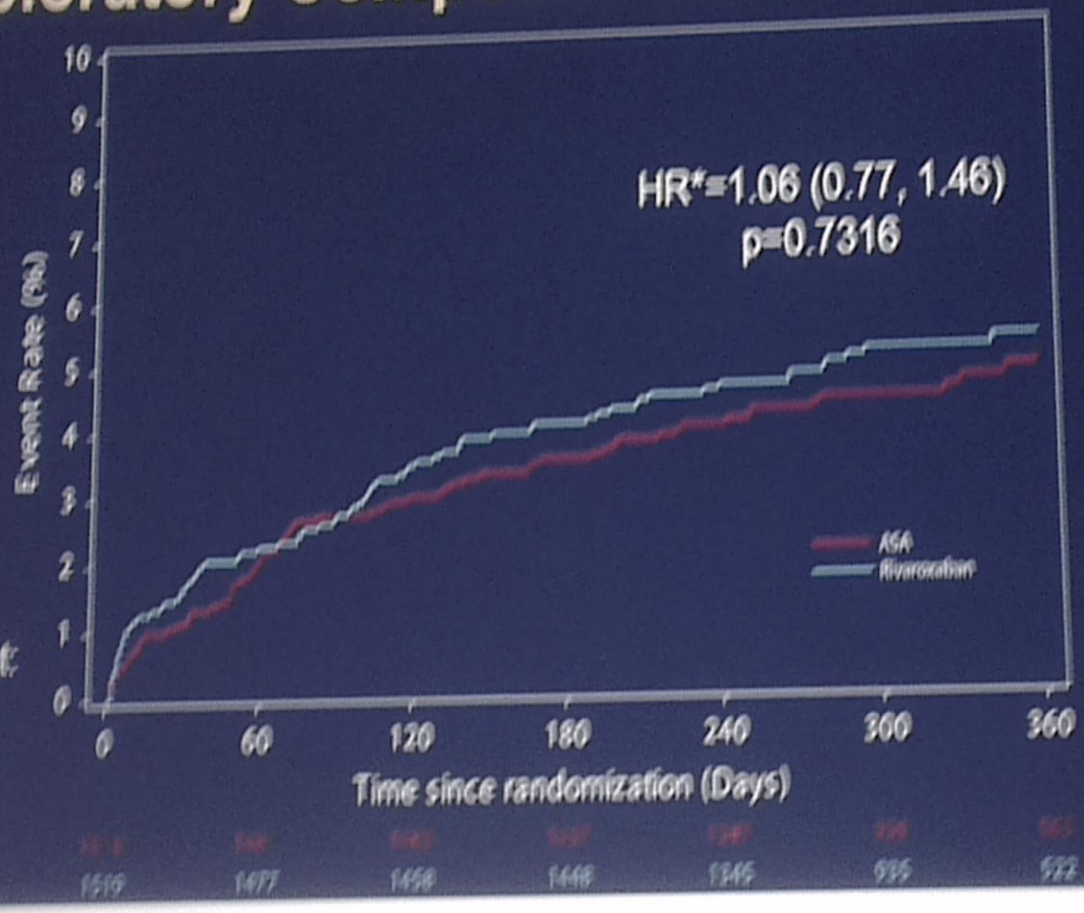
We are currently preparing a detailed patient close-out plan and hope to begin close-out visits in the very near future. We are aiming to complete study close-out visits by June.

A plan to provide patients with rivaroxaban after discontinuation of study medications is under discussion.

Baseline Characteristics: Aspirin vs Rivaroxaban

	Aspirin (N=1518)	Rivaroxaban (N=1519)	Total (N=3037)
Cardiac procedures for index event			
Catheterization performed	1430 (94%)	1425 (94%)	2855 (94%)
PCI performed	1320 (87%)	1325 (87%)	2645 (87%)
Stent placed	1286 (84.7%)	1295 (85.3%)	2581 (85.0%)
DES	870 (68.0%)	859 (66.5%)	1729 (67.3%)
BMS	423 (33.1%)	438 (33.9%)	861 (33.5%)
Bioabsorbable stent	8 (0.6%)	16 (1.2%)	24 (0.9%)
CABG performed	4 (<0.5%)	5 (<0.5%)	9 (<0.5%)
Concomitant medication at randomization, no. (%)			
Beta-blocker	984 (65%)	970 (64%)	1954 (64%)
ACE inhibitors/ARB	960 (63%)	947 (62%)	1907 (63%)
Statins	1065 (70%)	1038 (68%)	2103 (69%)
Ticagrelor	852 (56%)	852 (56%)	1704 (56%)
Clopidogrel	666 (44%)	667 (44%)	1333 (44%)

Exploratory Composite Ischemic Endpoint



Exploratory composite ischemic endpoint: cardiovascular death, MI, stroke, or definite stent thrombosis.

*Hazard Ratio (95%CI)

Beth Israel Deaconess Medical Center

Duke Clinical Research Institute

GEMINI ACS1

Conclusion

- In this phase 2 trial we observed similar risk of TIMI non-CABG clinically significant bleeding with the combination of rivaroxaban 2.5 mg twice daily and a P2Y12 inhibitor compared with DAPT
- The exploratory composite ischemic outcomes were also similar, but the trial was not powered for assessing this endpoint
- There was no treatment interaction between the choice of P2Y12 inhibitor and randomized treatment of rivaroxaban 2.5 mg twice daily or aspirin on either the primary bleeding or the exploratory ischemic endpoint
- Defining the best intensity of antithrombotic therapy while patients transition from the acute thrombotic setting to chronic prevention deserves more research

Děkuji Vám za pozornost