The Role of NOACs in AF: What do We Know 4 Years After the RE-LY Study?

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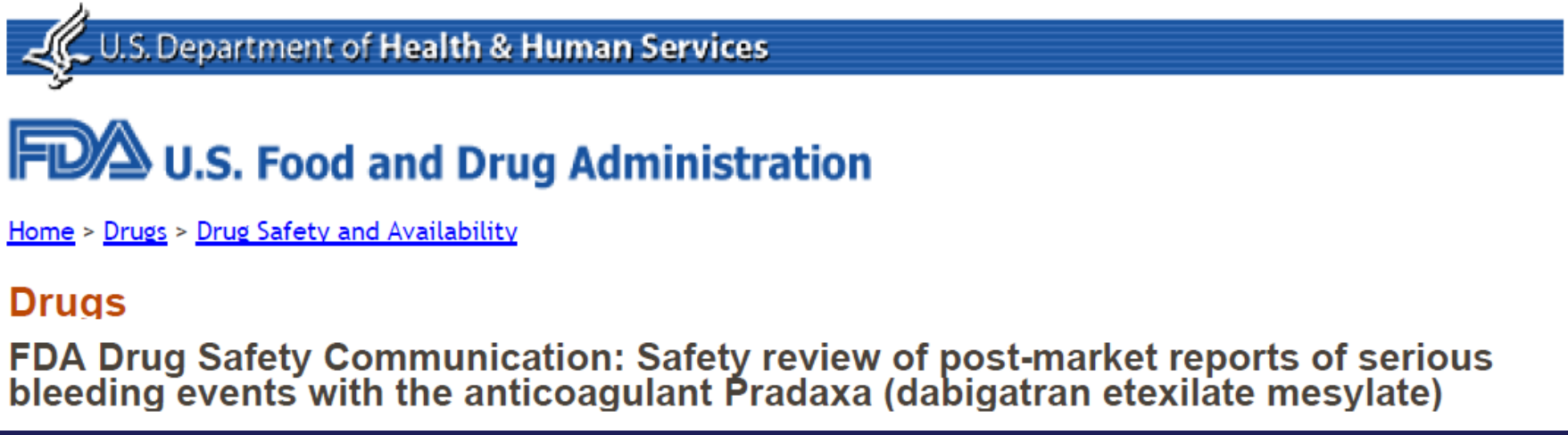
Disclosures

- No relevant Disclosures

Topics

- Reminder of NOACS major trials in AF
- Long term data of major trials (RELY ABLE)
- Real life long term data
- Major and CNS bleeding on NOACS - incidence and sequelae
- Invasive procedures and operations, DCCV, AF ablation
- Use with antiplatelet therapies and in ACS / PCI

RE-LY	ROCKET AF	ARISTOTLE
Dabigatran	**Rivarixoban**	**Apixaban**
Oral Direct thrombin inhibitor	Oral Factor Xa Inh.	Oral Factor Xa Inh.
18,113 patients	14,264 patients	18,201 patients
AF **+ 1** other risk factor for stroke (at least)	AF **+ 2** other risk factor for stroke (at least). Hence HIGH RISK patients	AF **+ 1** other risk factor for stroke (at least)
110mgX2 vs. warfarin 150mgX2 vs. warfarin	20mgX1 vs. warfarin 15mgX1 vs. warfarin (CRF)	5mgX2 vs. Warfarin
Non inferiority +	Non inferiority +	Non inferiority +
Superiority of 150 mg dose	Superiority ??	Superiority +
Reduced risk of bleeding only at the low dose.	Similar risk of major **and** non major bleeding	Reduced risk of major bleeding
Trend toward reducing risk of death from any cause.	Trend toward reducing risk of death from any cause.	Reduced risk of death from any cause by 11%
Reduced risk of hemorrhagic stroke	Reduced risk of hemorrhagic stroke	Reduced risk of hemorrhagic stroke
Not blinded	Double blind	Double blind
Mean% of time in that the INR was at therpautic range: 64%	Mean% of time in that the INR was at therpautic range: 55%	Mean% of time in that the INR was at therpautic range: 62%



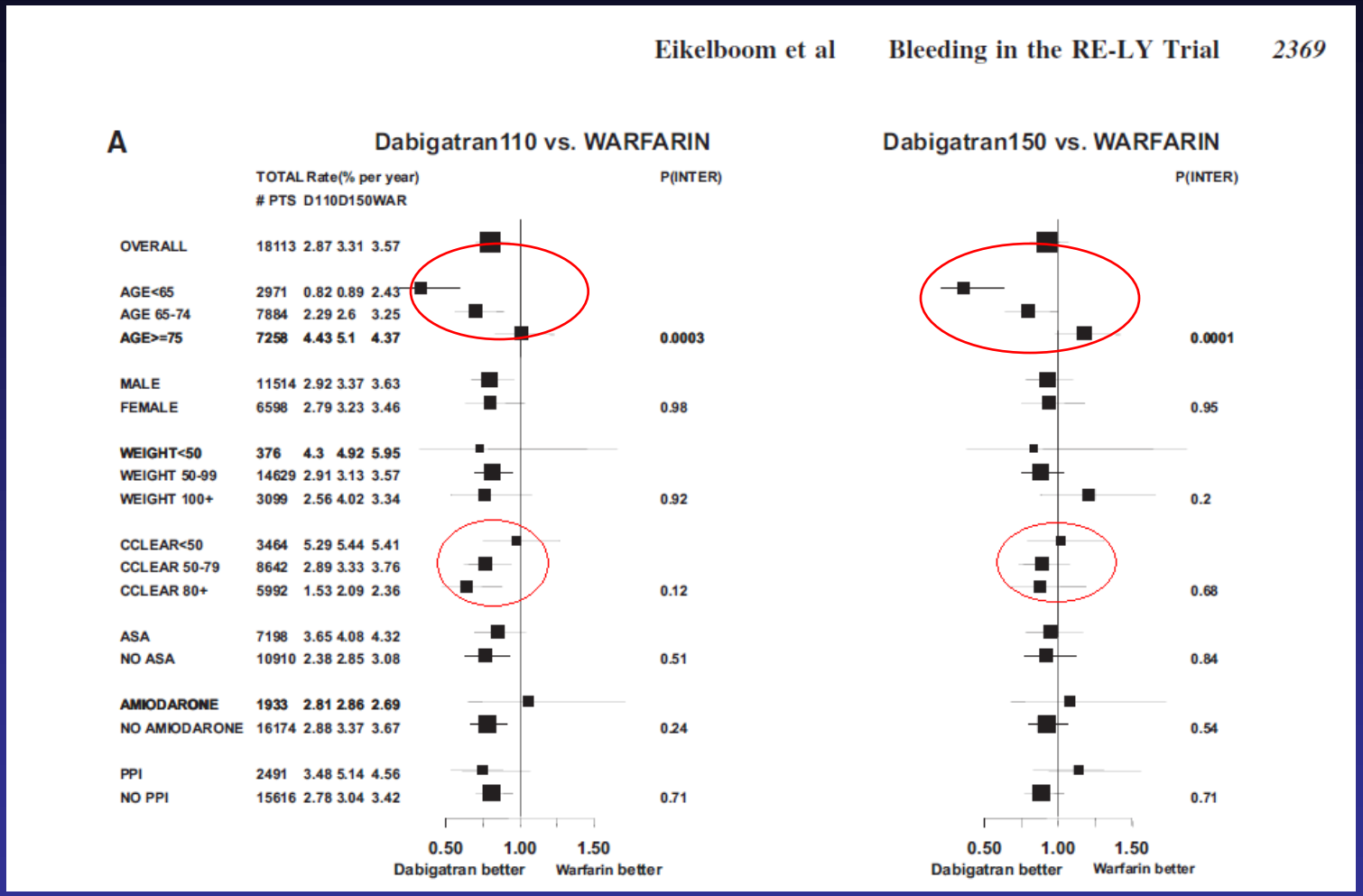
- Following the FDA approval of Dabigatran there wwere many reports of bleeding events via FAERS
- Bleeding events with dabigatran have already prompted safety advisories in Japan and Australia and have led to labeling updates in Europe and the US focusing on the need for monitoring renal function.
- In November, Boehringer Ingelheim confirmed that between March 2008 and October 31, 2011 there were 260 fatal bleeding events worldwide

Bleeding on Dabigatran

- Lack of antidote raises concerns
- Re-ly results demonstrated age-related increased bleeding > 75 yo , mainly due to GI bleeding
- ICH was lower in both Dabigatran doses (and in all NOACs)

Eikelboom Circ 2011

Major Bleeding in the RE-LY



Eikelboom Circ 2011

RELY-ABLE® Study (Connolly et al, AHA 2012)

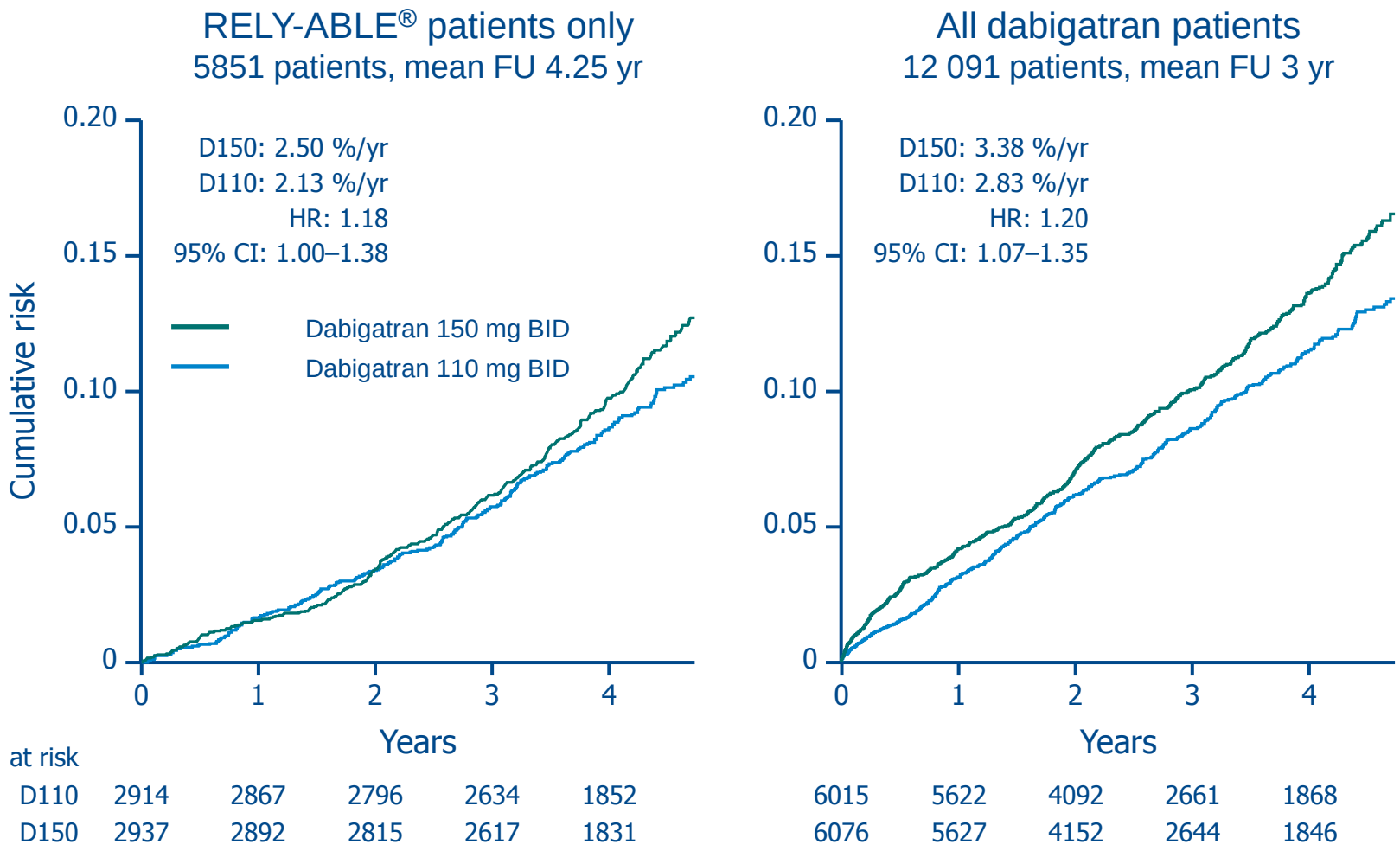
- Goals
  - To describe the long-term efficacy and safety of ongoing dabigatran therapy following RE-LY®
- Methods
  - Patients eligible at completion of RE-LY® study if:
    - Alive and still receiving study dabigatran
    - Being followed at centre participating in RELY-ABLE®
  - Dabigatran blinded dose continued in RELY-ABLE® for 2.3 years
- Analysis
  - Two follow-up periods described
    - RELY-ABLE® (post-RE-LY®)
    - RE-LY® + RELY-ABLE® (beginning of RE-LY® to end of RELY-ABLE®)

Together with RE-LY® , this allows for over 4 years of follow-up in total

Patient flow: dabigatran patients in RE-LY® and RELY-ABLE®

Event	Dabigatran 110 mg	Dabigatran 150 mg
Randomized to dabigatran in RE-LY®	6015	6076
Completed RE-LY® alive, still receiving dabigatran	4492 (75%)	4519 (74%)
Followed at site participating in RELY-ABLE®	3395 (76%)	3397 (75%)
Patient enrolled in RELY-ABLE®	2914 (86%)	2937 (87%)
Completed RELY-ABLE®, still receiving dabigatran	2511 (86%)	2508 (85%)
Continued in RELY-ABLE® beyond month 28 visit	1082 (44%)	1104 (44%)

Major bleeding: RE-LY® + RELY-ABLE® periods

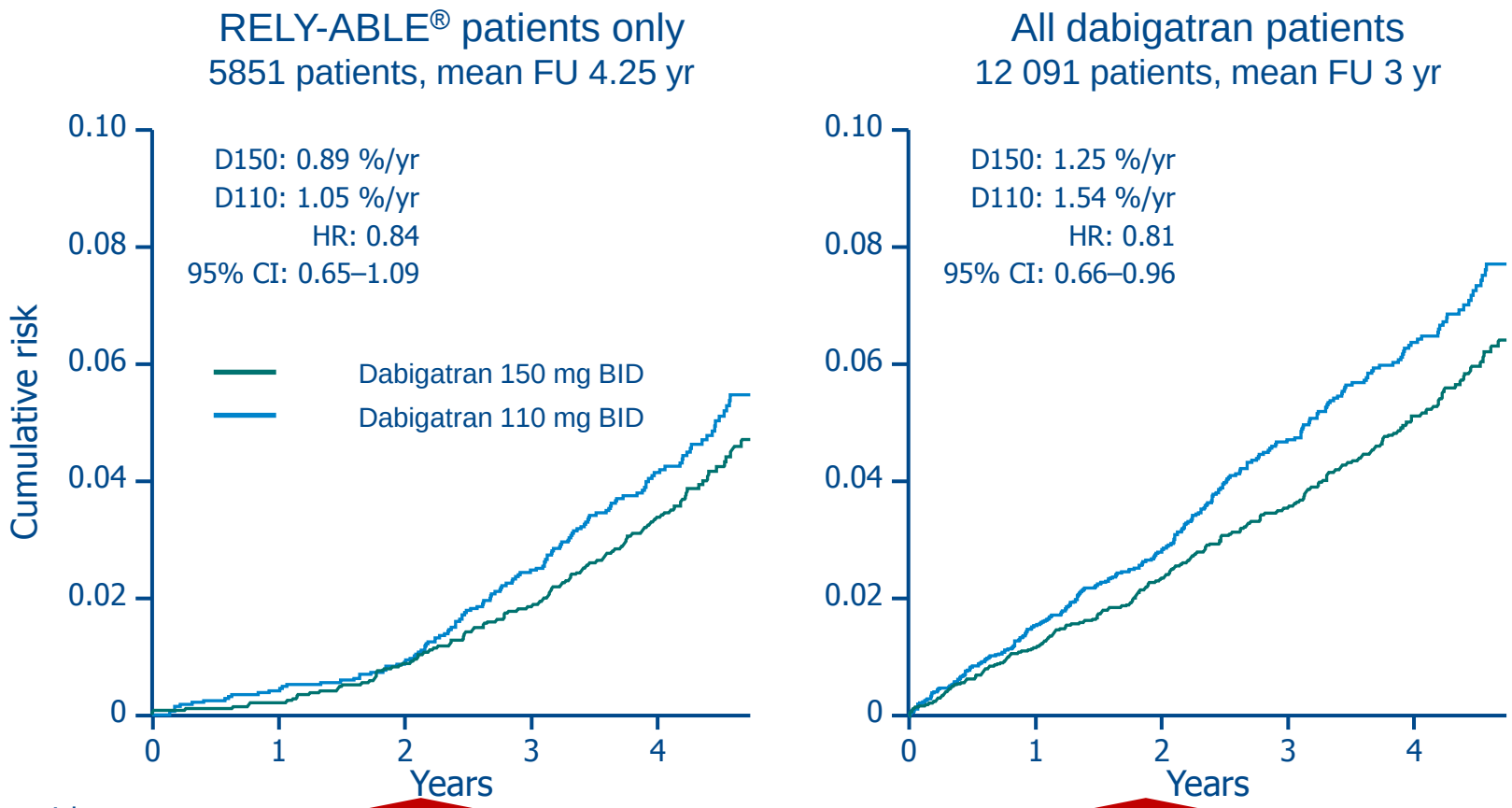


No. at risk

D110	2914	2867	2796	2634	1852	6015	5622	4092	2661	1868
D150	2937	2892	2815	2617	1831	6076	5627	4152	2644	1846

BID = twice daily; D150 and D110 = dabigatran 150 and 110 mg BID, respectively; FU = follow -up; HR = hazard ratio

Stroke/systemic embolism: RE-LY® + RELY-ABLE®



No. at risk

D110 291 ... 921

D150 293 ... 943

BID = twice da

HR = hazard ra

In the secondary analysis of RE-LY® and RELYABLE®, dabigatran 150 mg BID was associated with a lower rate of stroke and systemic embolism than the 110 mg BID dose

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were on

Conclusions:

- Bleeding rates on DAB were not higher than with Warfarin
- The large numbers of early reports was related to novelty of the drug and to reporting stimulated by media coverage

NEJM 2013

Accepted Manuscript

Efficacy and safety of dabigatran etexilate and warfarin in 'real world' patients with atrial fibrillation: A prospective nationwide cohort study

Torben Bjerregaard Larsen, Lars Hvilsted Rasmussen, Flemming Skjøth, Karen Margrete Due, Torbjörn Callréus, Mary Rosenzweig, Gregory Y.H. Lip

- **Objectives:** to assess the efficacy and safety in an 'everyday clinical practice' population of anticoagulant-naïve patients with AF treated with dabigatran following its post-approval availability in Denmark, compared to warfarin.
- **Danish Registry** of Medicinal Product Statistics
  - Dabigatran-treated group , **n=4978**
  - Warfarin-treated group , **n=8936** (1:2 propensity matched)

JACC 2013

Results – Danish Study

- **Similar stroke/systemic embolism, and major bleeding rates with dabigatran (both doses) compared to warfarin.**
- **Mortality, ICH, PE, and MI were lower with dabigatran, compared to warfarin.**
- **No evidence of an excess of bleeding events or MI amongst dabigatran treated patients in comparison with warfarin.**

Management and outcomes of major bleeding on dabigatran or warfarin

Ammar Majeed,[1] Hun-Gyu Hwang,[2] Martina Brueckmann,[3] Stuart Connolly,[4] John Eikelboom,[4] Michael Ezekowitz,[5] Lars Wallentin,[6] Salim Yusuf[4], and Sam Schulman[4]

[1]Hematology Center, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden; [2]Soon Chun Hyang University Hospital, Gumi, South Korea; [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; [4]Department of Medicine, McMaster University, Hamilton, ON, Canada; [5]Jefferson Medical College, Wynnewood, PA; [6]Uppsala Clinical Research Center, Uppsala, Sweden

Dec 2012

Patient population: Phase III dabigatran trials – methods

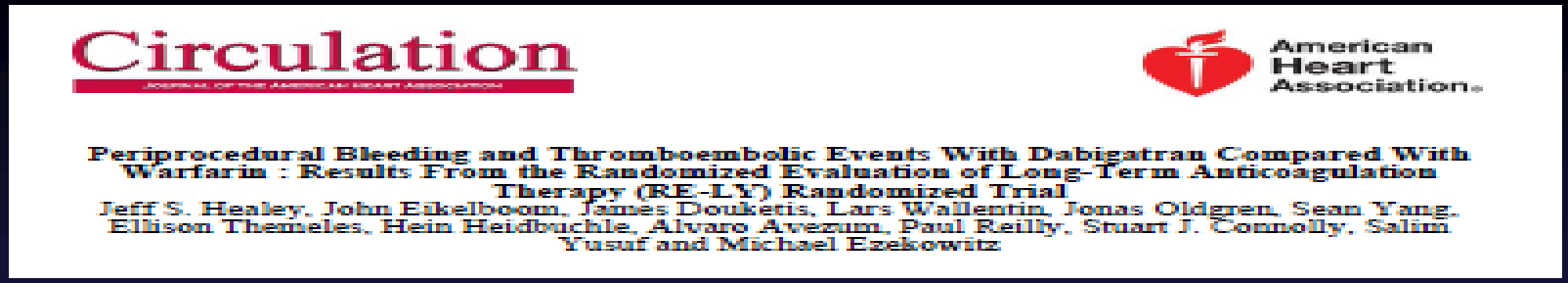
Phase III trial	Patients	Treatments	Duration of treatment
RE-LY®[1]	18 113 patients with AF (stroke prevention)	• Dabigatran 110 mg • Dabigatran 150 mg BID • Warfarin	Median 2 years
RE-COVER[2]	2539 patients with VTE (treatment)	• Dabigatran 150 mg BID • Warfarin	6 months
RE-COVER II[3]	2568 patients with VTE (treatment)	• Dabigatran 150 mg BID • Warfarin	6 months
RE-MEDY[4]	2856 patients with VTE (secondary prevention)	• Dabigatran 150 mg BID • Warfarin	Mean, 15.5 months
RE-SONATE[5]	1343 patients with VTE (secondary prevention)	• Dabigatran 150 mg BID • Placebo	6 months
Patients randomized and treated in these five trials: N=27 419 (dabigatran n=16 755; warfarin n=10 002; placebo n=662)			

Key criteria for inclusion in bleeding case narrative analysis:
only centrally adjudicated major bleeding within 3 days of the last dose

BID = twice daily; VTE = venous thromboembolism; **1**. Connolly SJ et al. N Engl J Med 2009;361:1139–51; **2**. Schulman S et al. N Engl J Med 2009;361:2342–52; **3**. Schulman S et al. ASH 2011; abstr 205; **4**. Schulman S et al. J Thromb Haemost 2011;9:22 (abstr O-Thu-033); **5**. Schulman S et al. J Thromb Haemost 2011;9;22 (abstr O-Mo-037)

RESULTS

- Use of special blood products was similar
- Similar hospitalization rate
- More blood transfusions in DAB
- Shorter ICU stay for DAB
- Similar Rankin score following ICH
- Strong trend (0.052) toward reduced mortality following hemorrhages related to DAB



- 4591 pts underwent interventions during the Rely study
- DAB stopped 24-120 hours prior to procedure (avg =49h)
- Restarted when hemostasis achieved
- Bridging heparin given to 15-17% of DAB pts and 28% of Warfarin

Results

- Similar rates of bleeding in both groups in all types of surgery
- Similar low rates of TE events
- DAB better when urgent surgery performed < 24 hours from cessation

Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

Table 9 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
[a]No EMA approval yet. Needs update after finalisation of SmPC.
[b]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (15 mg QD).
Low risk = surgery with low risk of bleeding; high risk = surgery with high risk of bleeding. See also Table 10.
CrCl, creatinine clearance.

Rely Cardioversion subgroup analysis: baseline characteristics

- >80% of cardioversions were electric
- TEE performed before conversion in more dabigatran patients (P<0.0001 for each dose vs warfarin)
- For patients undergoing TEE, no difference between treatment groups in incidences of left atrial spontaneous echo contrast or LAA thrombus

	Dabigatran 110 mg BID		Dabigatran 150 mg BID		Warfarin	
	n	%	n	%	n	%
Total randomized	6015		6076		6022	
Cardioversions performed						
Electrical	554	85.6	550	81.9	553	83.3
Pharmacological	91	14.1	122	18.2	111	16.7
TEE	165	25.5	162	24.1	88	13.3
Normal sinus rhythm at discharge	566	87.5	596	88.7	595	89.6

LAA = left atrial appendage; TEE = transoesophageal echocardiography

Nagarakanti R et al. Circulation 2011;123:131–6

Cardioversion subgroup analysis: antithrombotic therapy

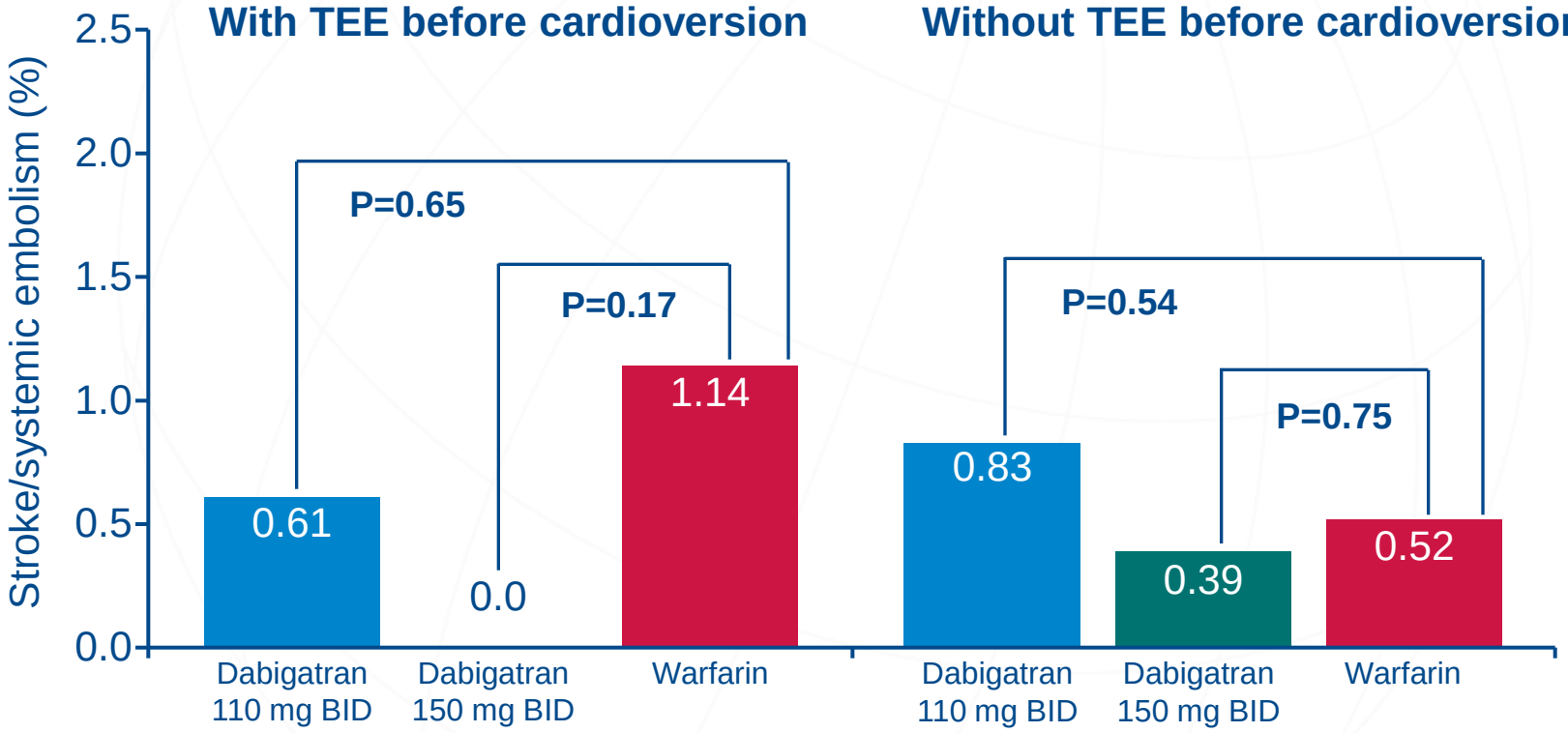
- Most patients received study drug for ≥3 weeks before conversion
  - D110 76.4%; D150 79.2%; warfarin 85.5%
  - D110 vs warfarin P<0.0001; D150 vs warfarin P=0.002
- Some patients were switched to a non-study oral anticoagulant
  - Proportion was higher for both dabigatran doses vs warfarin
  - D110 9.7%; D150 8.6%; warfarin 5.4%
  - D110 vs warfarin P=0.003; D150 vs warfarin P=0.02
- Most patients continued on randomized treatment within 30 days after cardioversion
  - D110 85.8%; D150 88.7%; warfarin 94.3%
  - D110 vs warfarin P<0.0001; D150 vs warfarin P=0.0003

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily

Nagarakanti R et al. Circulation 2011;123:131–6

Similar rates of stroke/SE with and without TEE before cardioversion

Similar rates of stroke or systemic embolism with/without TEE before cardioversion



BID = twice daily; SE = systemic embolism; TEE = transoesophageal echocardiography

Nagarakanti R et al. Circulation 2011;123:131–6

Cardioversion on NOACs

- Cardioversion is safe also with Rivaroxaban based on rocket AF (Piccini JACC 2013)
- Similar data on Apixaban from Aristotle available in an abstract form **(Flaker EHJ 2012)**
- 3 week compliance with medication must be verified and documented or TEE used **(EHRA practical guide 2013)**

Dabigatran etexilate vs warfarin periablation for AF: meta-analysis

- Current practice involves Warfarin with bridging or continuous Warfarin (better)
- Several studies looked at periablation dabigatran vs warfarin (± heparin bridging)
- Meta-analysis of nine studies in AF:
  - 874 patients on dabigatran
  - 1331 patients on warfarin
    - 73% on continuous warfarin
  - Dabigatran stopped 2.5–48 hours preprocedure, restarted 0–24 hours afterwards

Musat D. Presented at the American Heart Association Congress, Los Angeles, USA, November 2012.

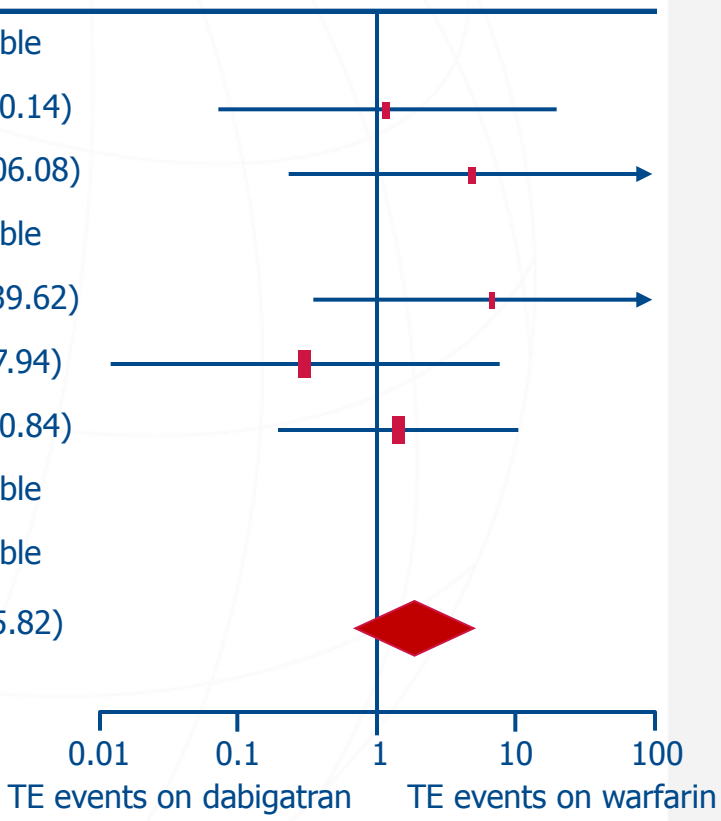
Dabigatran etexilate vs warfarin periablation for AF: thromboembolic (TE) events

- No significant difference for dabigatran vs warfarin

Study or subgroup	Dabigatran Events	Dabigatran Total	Warfarin Events	Warfarin Total	Weight	Odds ratio (95% CI)
Bassiouny et al	0	47	0	54		Not estimable
Ellis et al	1	84	1	104	17.8%	1.24 (0.08–20.14)
Haines et al	2	178	0	178	10.0%	5.06 (0.24–106.08)
Kaseno et al	0	110	0	101		Not estimable
Lakkireddy et al	3	145	0	145	9.9%	7.15 (0.37–139.62)
Mendoza et al	0	60	1	58	30.5%	0.32 (0.01–7.94)
Rowley et al	2	113	2	169	31.8%	1.50 (0.21–10.84)
Snipelisky et al	0	31	0	125		Not estimable
Yamaji et al	0	106	0	397		Not estimable
Total (95% CI)		874		1331	100.0%	2.00 (0.69–5.82)
Total events	8		4			

Heterogeneity: χ^2=2.51, df=4 (P=0.64); I^2=0%

Test for overall effect: Z=1.28 (P=0.20)



Musat D. Presented at the American Heart Association Congress, Los Angeles, USA, November 2012.

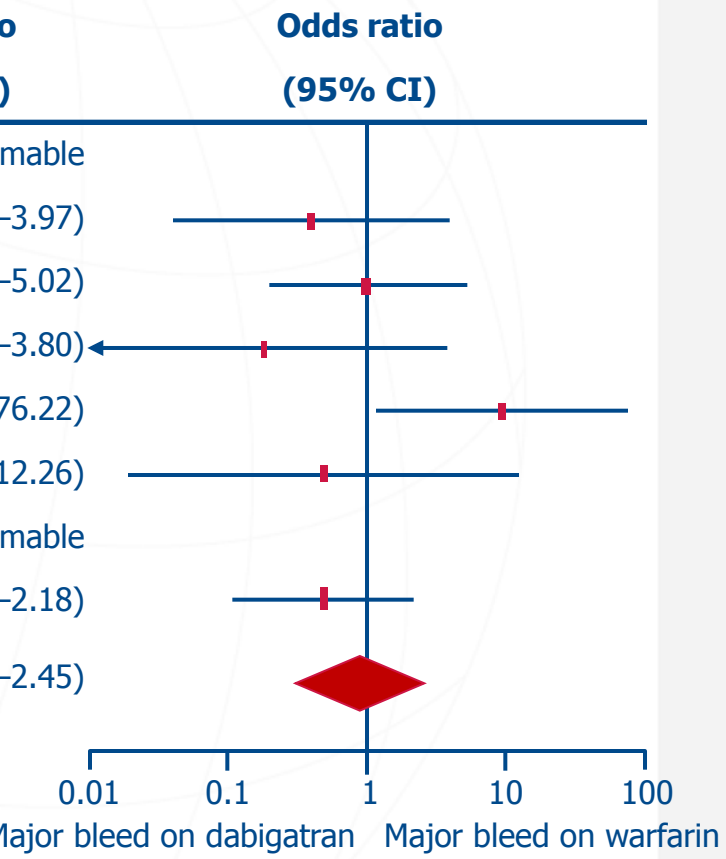
Dabigatran etexilate vs warfarin periablation for AF: major bleeding

- No significant difference for dabigatran vs warfarin

Study or subgroup	Dabigatran Events	Dabigatran Total	Warfarin Events	Warfarin Total	Weight	Odds ratio (95% CI)
Bassiouny et al	0	47	0	54		Not estimable
Ellis et al	1	84	3	104	15.1%	0.41 (0.04–3.97)
Haines et al	3	178	3	178	23.5%	1.00 (0.20–5.02)
Kaseno et al	0	110	2	101	9.7%	0.18 (0.01–3.80)
Lakkireddy et al	9	145	1	145	17.2%	9.53 (1.19–76.22)
Rowley et al	0	113	1	169	8.9%	0.49 (0.02–12.26)
Snipelisky et al	0	31	0	125		Not estimable
Yamaji et al	2	106	15	397	25.5%	0.49 (0.11–2.18)
Total (95% CI)		814		1273	100.0%	0.85 (0.30–2.45)
Total events	15		25			

Heterogeneity: τ^2=0.56, χ^2=7.46, df=5 (P=0.19); I^2=33%

Test for overall effect: Z=0.30 (P=0.77)



Musat D. Presented at the American Heart Association Congress, Los Angeles, USA, November 2012

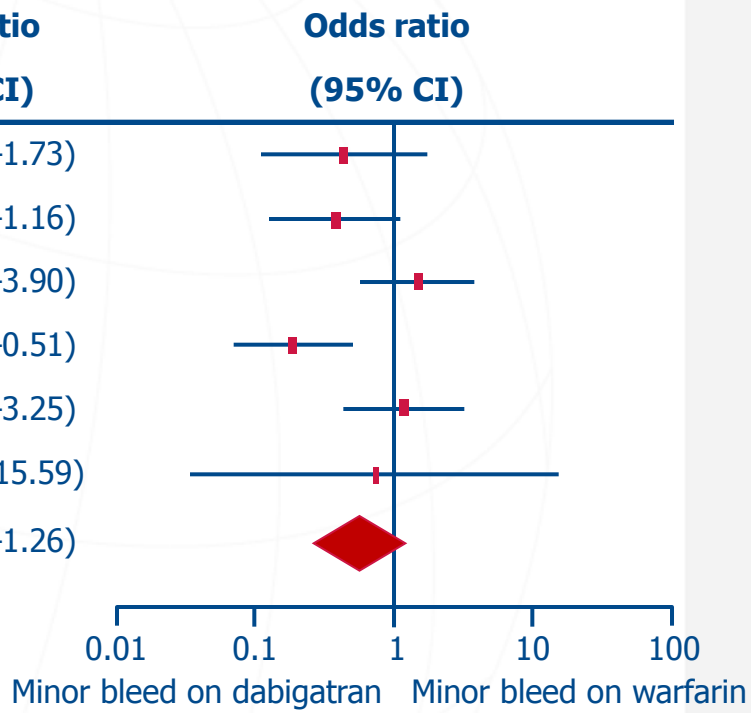
Dabigatran etexilate vs warfarin periablation for AF: minor bleeding

- No significant difference for dabigatran vs warfarin

Study or subgroup	Dabigatran Events	Dabigatran Total	Warfarin Events	Warfarin Total	Weight	Odds ratio (95% CI)
Ellis et al	3	84	8	104	15.4%	0.44 (0.11–1.73)
Kaseno et al	5	110	11	101	18.6%	0.39 (0.13–1.16)
Lakkireddy et al	12	145	8	145	20.95	1.55 (0.61–3.90)
Rowley et al	5	113	33	169	20.2%	0.19 (0.07–0.51)
Snipelisky et al	6	31	21	125	19.8%	1.19 (0.43–3.25)
Yamaji et al	0	106	2	397	5.1%	0.74 (0.04–15.59)
Total (95% CI)		589		1041	100.0%	0.59 (0.28–1.26)
Total events	31		83			

Heterogeneity: τ^2=0.49, χ^2=12.06, df=5 (P=0.03); I^2=59%

Test for overall effect: Z=1.36 (P=0.17)



Musat D. Presented at the American Heart Association Congress, Los Angeles, USA, November 2012

AF ablation with NOACS

- Not enough evidence to support continuous Dabigatran during the procedure
- Dabigatran is a safe alternative to Warfarin if stopped for 12 - 24 hours before the procedure and resumed 1-4 hours after it
- There are preliminary undetailed data on Rivaroxaban as well (Piccini JACC 2013)

Mixed data on APT+NOACS

- ACS pts have different bleeding profiles than otherwise stable pts
- Information from observational studies on ACS + AF patients is heterogeneous and influenced by comorbidities
- ACS studies with NOACS (no AF) included mostly lower doses of NOACS other than Dabigatran
- No information on new antiplatelet agents

Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial

Antonio L. Dans, MD, MSc; Stuart J. Connolly, MD; Lars Wallentin, MD, PhD; Sean Yang, MSc; Juliet Nakamya, PhD; Martina Brueckmann, MD; Michael Ezekowitz, MBChB, DPhil; Jonas Oldgren, MD, PhD; John W. Eikelboom, MD; Paul A. Reilly, PhD; Salim Yusuf, DPhil, FRCPC, FRSC

- 38% of Rely pts received anti platelet therapy at some stage (4.5% DAPT)
- APT increased bleeding risk in ALL treatment groups (X1.6 and X2.3 in SAPT and DAPT)
- Advantages of Dabigatran (efficacy in higher dose safety in lower dose) were maintained despite concomitant APT
- 110 bid should be considered and is expected to be safer than Warfarin in combination with APT

Circulation 2013

AF pt on NOACS Presents with ACS

- D/C NOAC
- Give DAPT unless high bleeding risk then ASA only and delay Plavix until NOAC effect wanes
- IV anticoagulation when NOACs effect wanes
- In NSTEMI delay PCI if possible
- In PCI consider BMS, balloon angioplasty
- Try to avoid chronic Prasugrel and Ticagrelor with NOACS
- When restarting consider lower dose NOAC

EHRA Practical Guide 2013

New Onset AF in a pt with Recent (< 1y) ACS

- When Grace risk is low to moderate and HAS BLED high consider VKA only (1-3 m post BMS, 6 m post DES)
- High GRACE risk use VKA+SAPT (clopidogrel)
- High GRACE low CHADVASC (≤1) – DAPT without OAC
- If NOAC indicated - Dabigatran 110 bid

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New Onset AF in pt with Remote (>1y) ACS

- OAC only for stable CAD pts
- NOACS are a safe and effective alternative to VKAs
- No preference to any specific NOAC
- If felt to have high atherothrombotic risk consider Dabigatran 110 bid + ASA

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Conclusions

- Long term data with Dabigatran are as favorable as the early Rely data
- Despite lack of antidote bleeding events on Dabigatran carry a better prognosis
- Surgery can be safely performed in NOAC pts when the NOAC is stopped for relatively short periods
- Cardioversions are safe on NOACS

Conclusions – cont.

- AF ablations can be performed in pts on Dabigatran with short intermission of the treatment
- Combination of APT and NOACS is studied mainly with Dabigatran , where it increases bleeding risk to the same extent as with VKA . 110 bid maintains its safety advantage over Warfarin
- Minimize high risk and unknown situations: DES, new antiplatelet agents , triple therapy , high dose NOAC

Thank You !