Novel (Direct) Oral Anticoagulants in Specific Clinical Situations

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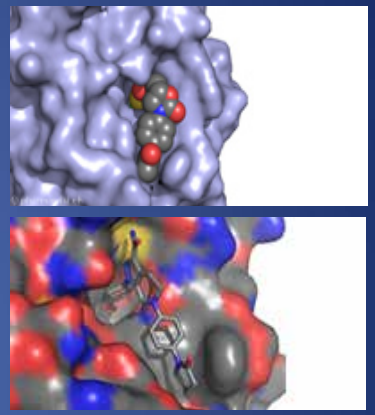
Anticoagulants

- Unfractionated Heparin
- Low Molecular Weight Heparin
- Vitamin K Antagonists

- Direct Oral Anticoagulants
  - Dabigatran 2x/Tag
  - Rivaroxaban 1x/Tag
  - Apixaban 2x/Tag
  - Edoxaban 1x/Tag

Direct oral Anticoagulants (DOAC)



Clotting-cascade

Intrinsic system

Factor XIIa

Factor XIa

Factor IXa

Faktor VIIIa

Extrinsic system

Tissue Factor

Factor VIIa

Vitamin K Antagonists

Factor Xa

Factor Va

Rivaroxaban (Xarelto®)
Apixaban (Eliquis®)
Edoxaban (Lixiana®)

Unfractioned Heparin

Low molecular weight Heparin

Thrombin

Dabigatran (Pradaxa®)

Fibrin Thrombus

Direct Oral Anticoagulants

Prophylaxis after hip or knee-endoprosthesis

Thrombembolism-prophylaxis in non-valvular atrial fibrillation

Treatment of deep vein thrombosis or pulmonary embolism

Novel Anticoagulants

Tabla 1. Tabla comparativa de nuevos anticoagulantes

Fármaco	Mecanismo acción	Dosis profilaxis	Dosis tratamiento	Vida media	Aprobación basada en evidencia
Warfarina	Inh. Epóxido vitamina K reductasa	Según INR	Según INR	35-45 horas	Profilaxis y Tratamiento ETE
Acenocumarol	Inh. Epóxido vitamina K reductasa	Según INR	Según INR	8-24 horas	Profilaxis y tratamiento ETE
Dabigatran	Inh. IIa	150-220 mg QD	110 mg o 150 mg BID	12-17 horas	Profilaxis ETE Tratamiento ETE en FA
Rivaroxaban	Inh. Xa	10 mg QD	20 mg QD (15 mg QD en caso de insuficiencia renal)	5-9 horas	Profilaxis ETE post cirugía rodilla/cadera
Apixaban	Inh. Xa	2,5-5 mg BID		9-14 horas	Estudios fase III en curso
Betrixaban	Inh. Xa	40-80 mgQD			Estudios Fase II en curso
Edoxaban	Inh. Xa	30-60 mg QD			Estudio fase III en curso

Berkovits et al, Rev Med Chile 2011; 139: 1347-1355

Studies DOACS versus Warfarin in non-valvular atrial fibrillation

	Dabigatran 2x150 mg	Dabigatran 2x110 mg	Rivaroxaban 1x20 mg	Apixaban 2x5 mg	Edoxaban 1x60mg
Patient numbers	6075	6011	7131	9020	7032
Age	71.5	71.4	73	70	72
CHADS-score	2.2	2.1	3.48	2.1	2.8

Conolly NEJM 2009, Patel NEJM 2011, Granger NEJM 2011, Gugliano NEJM 2013

Outcomes DOACS versus Warfarin in non-valvular atrial fibrillation (HR, 95% CI)

	Dabigatran 2x150 mg	Dabigatran 2x110 mg	Rivaroxaban 1x20 mg	Apixaban 2x5 mg	Edoxaban 1x60mg
Stroke/ embolism	0.66 (0.53-0.82)	0.91 (0.74-1.11)	0.79 (0.66-0.96)	0.79 (0.66-0-99)	0.79 (0.63-0.99)
Major bleeding	0.93 (0.81-1.07)	0.80 (0.69-0.93)	1.04 (0.90-1.20)	0.69 (0.60-0.80)	0.80 (0.71-0.91)
Intracranial bleeding	0.40 (0.27-0.60)	0.31 (0.20-0.47)	0.67 (0.47-0.93)	0.42 (0.3-0.58)	0.47 (0.34-0.63)

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Conolly NEJM 2009, Patel NEJM 2011, Granger NEJM 2011, Gugliano NEJM 2013

Novel Anticoagulants in the Treatment of Acute Venous Thromboembolism

Substance	Heparin-prephase	Blinded	Duration	Extension Study
Apixaban	no	yes	6 months	yes
Dabigatran	yes	yes	6 months	yes
Edoxaban	yes	yes	Until 12 months, variable	no
Rivaroxaban	no	no	3,6,12 months, predefined	yes

NOACS in VTE Treatment
Comparison of Phase III Studies OR (95%CI)

Substanz	Efficacy outcome	Major bleeding	Major or CRNM Bleeding
Apixaban	0.84 (0.60-1.18)	0.31 (0.17-0.55)	0.44 (0.36-0.55)
Dabigatran	1.05 (0.65-1.84)	0.82 (0.45-1.48)	0.63 (0.47-0.84)
Edoxaban	0.89 (0.70-1.13)	0.84 (0.59-1.21)	0.81 (0.71-0.94)
Rivaroxaban VT	0.68 (0.44-1.04)	0.65 (0.33-1.30)	0.97 (0.76-1.22)
Rivaroxaban PE	1.12 (0.75-1.68)	0.49 (0.31-0.79)	0.90 (0.76-1.07)

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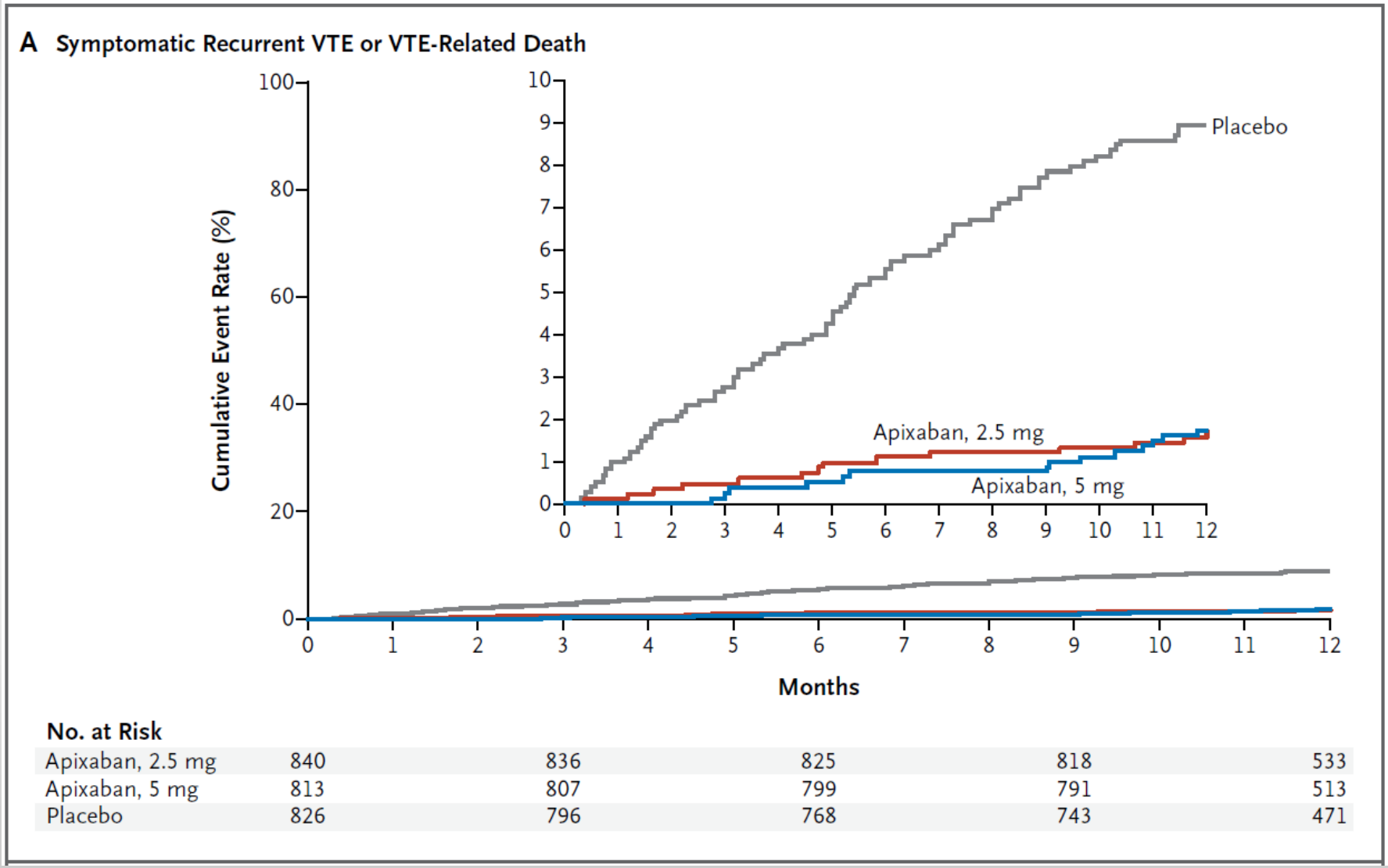
Apixaban for extended treatment of VTE
Recurrent thrombosis

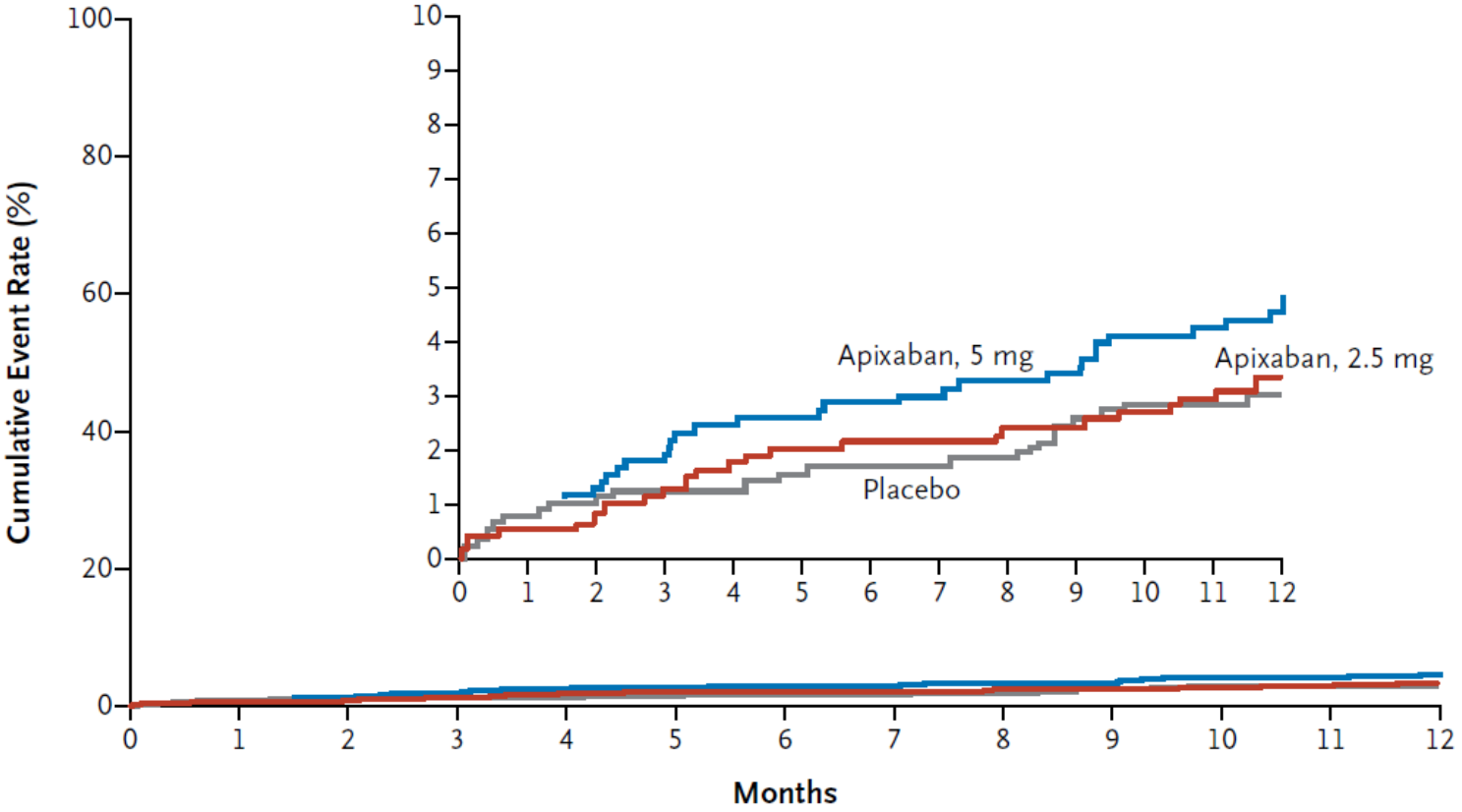


No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

Agnelli et al, NEJM 2012

Apixaban for extended treatment of VTE Bleedings

B Major or Clinically Relevant Nonmajor Bleeding



No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

Agnelli et al, NEJM 2012

NOACS
Specific Clinical Situations

- Elderly patients
- Renal insufficiency
- Compliance
- NOACS in cancer patients
- Bleeding management

Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: RIETE registry

Age > 75 years	**2.16**	**1.49–3.16**	**< 0.001**
Recent major bleeding	2.64	1.44–4.83	0.002
Immobility ≥ 4 days	1.99	1.40–2.83	< 0.001
Metastatic cancer	**3.80**	**2.56–5.64**	**< 0.001**
Anemia	1.54	1.07–2.22	0.021
Platelet count < 100 × 10^9 L^{-1}	2.23	1.16–4.29	0.016
Abnormal prothrombin time	2.09	1.34–3.26	0.001
CrCl levels < 30 mL min^{-1}	**2.27**	**1.49–3.44**	**< 0.001**
Distal DVT	0.39	0.16–0.95	0.038

Nieto et, JTH 2010, 8:1216

Anticoagulation in elderly patients with AF (>75 years)

Rate of patients > 75 years

Re-ly (Dabigatran):	40%
Rocket (Rivaroxaban):	38%
Aristotle (Apixaban):	31%

Similar efficacy and safety compared to vitamin K antagonists in elderly patients in relation to younger patients

Renal insufficiency and NOACs

Efficacy and safety

Atrial fibrillation (AF) in Chronic kidney disease (CKD)

- AF prevalence in patients with end-stage renal disease 13 – 27%
  - Stroke incidence per US Renal Data System:
    - 15.1 % in hemodialysis (HD) patients
    - 9.6% patients at other CKD stages
    - 2.6% in the control group
- CHADS2 may underestimate stroke risk with AF in stage 3 CKD (eGFR 30 – 59 mL/min)
- Proteinuria increased thromboembolism risk by 54%

Reinecke H. J Am Soc Nephrol 2009;20(4):705-711.Hart RG. J Am Soc Nephrol.2011;6(11):2599-2604. Marinigh R. JACC. 2011; 57 (12): 1339-48. Go AS. Circulation 2009. 119; 1363-69.

Anticoagulantion
Renal Clearance

Anticoagulant	Renal elimination
LMW-Heparin	90%
Vitamin K-Antagonists	0%
Apixaban	25%
Dabigatran	90%
Edoxaban	35%
Rivaroxaban	35%

Anticoagulation with NOACs
Influence of renal function on drug half lives

Table 6 Estimated drug half-lives and effect on area under the curve NOAC plasma concentrations in different stages of chronic kidney disease compared to healthy controls

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I and II	~14 h[48]	No data	~8.6 h[49]	~8.5 h[50] (+44%)
CrCl 30–60 ml/min CKD Stage III	~18 h[48]	No data	~9.4 h[49]	~9 h (+52%)
CrCl 15–30 ml/min CKD Stage IV	~28 h[48]	No data	~16.9 h[49]	~9.5 h (+64%)
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data

[a]No EMA approval yet. Needs update after finalisation of SmPC.
CKD, chronic kidney disease; CrCl, creatinine clearance.
Hatching, no available data yet.

ARISTOTLE: Outcomes by Renal Function

Cockcroft-Gault

Outcome	eGFR mL/min Cockcroft-Gault	Apixaban %/year	Warfarin %/year	Hazard Ratio (95% CI)	P-value
Stroke/ Systemic Embolism	> 80	0.99	1.12	0.88 (0.64-1.22)	0.705
	> 50 – 80	1.24	1.69	0.74 (0.56-0.97)	
	≤ 50	2.11	2.67	0.79 (0.55-1.14)	
Primary endpoint of stroke/systemic embolism occurred less frequently in patients on apixaban vs. warfarin, regardless of renal function.					
All Cause Mortality	> 80	2.33	2.71	0.86 (0.70-1.06)	0.627
	> 50 – 80	3.41	3.56	0.96 (0.81-1.14)	
	≤ 50	7.12	8.30	0.86 (0.70-1.05)	
Annual all-cause mortality rate was three-fold higher in patients with moderate/severe renal dysfunction					
Major Bleeding	> 80	1.46	1.84	0.80 (0.61-1.04)	0.030
	> 50 – 80	2.45	3.21	0.77 (0.62-0.94)	
	≤ 50	3.21	6.44	0.50 (0.38-0.66)	

Hohnloser S H et al. Eur Heart J 2012;33:2821-2830

Stroke prophylaxis with dabigatran in patients with AF - efficacy in patients with renal insufficiency

Subgroup	Patients *total no.*	Dabigatran 110 mg *% per yr*	Dabigatran 150 mg *% per yr*	Warfarin *% per yr*	Hazard Ratio with Dabigatran, 110 mg (95% CI)	P Value for Interaction	Hazard Ratio with Dabigatran, 150 mg (95% CI)	P Value for Interaction
Creatinine clearance						0.60		0.54
<50 ml/min	3,505	2.15	1.52	2.78				
50–79 ml/min	8,766	1.70	1.20	1.76				
≥80 ml/min	5,826	0.94	0.75	0.98				

Conolly et al, NEJM 2009, 361: 1139

Adherence - data from antihypertensive treatment

- 76 patients with resistant hypertension, evaluated through toxicologic urine analysis
  - 53% “non-adherent”, 30% complete, 70% incomplete adherence (85% took less than 50% of medication)

Jung, J Hypertens 2013, 31:766

Adherence of dabigatran medication in patients with AF

- National cohort of 5,376 patients with NVAF, initiated on dabigatran between 10/2010 and 9/2012 at all Veterans Affairs hospitals
- Adherence measured in proportion of days covered by drug-intake

Shore et a, Am Heart J 2014, 167:810

Adherence of dabigatran medication in patients with AF

- 28% had a proportion of days covered (PDC) of < 80%
- Lower adherence was associated with increased risk for combined all-cause mortality and stroke

Shore et a, Am Heart J 2014, 167:810

NOACS in cancer patients

- The treatment of choice in cancer patients with venous thrombosis or pulmonary embolism is low molecular weight heparin

Are NOACS equally effective?

Presently no studies comparing NOACS with LMWH in cancer patients

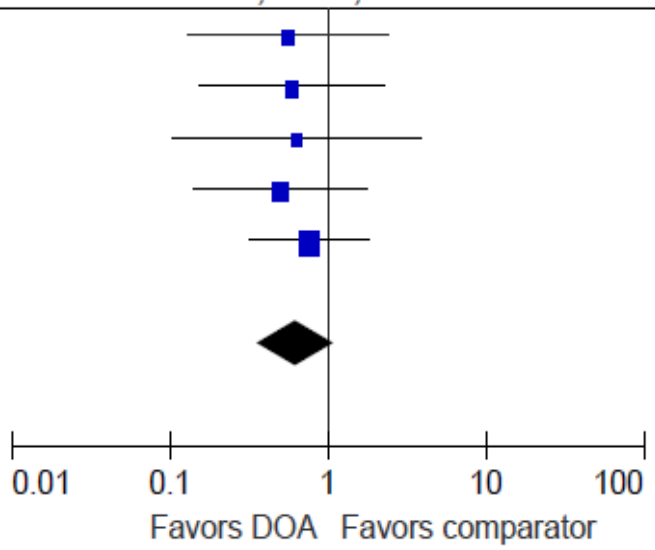
Meta-analysis of 6 randomized studies NOAC versus VKA in cancer patients

VTE recurrence

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
Total (95% CI)		**595**		**537**	**100.0%**	**0.63 [0.37, 1.10]**
Total events	23		32			

Heterogeneity: $Chi^2 = 0.36$, $df = 4$ ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 1.62$ ($P = 0.10$)



Vedovati et al, Chest 2014, in press

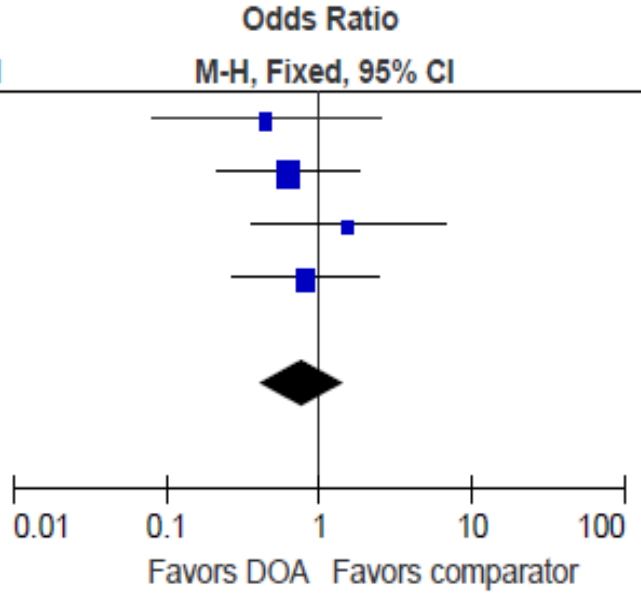
Meta-analysis of 6 randomized studies NOAC versus VKA in cancer patients

Major bleeding

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	2	87	4	80	18.2%	0.45 [0.08, 2.51]
EINSTEIN DVT & PE 2013	6	232	8	196	37.7%	0.62 [0.21, 1.83]
HOKUSAI 2013	5	109	3	99	13.4%	1.54 [0.36, 6.61]
RECOVER I & II 2013	6	159	7	152	30.7%	0.81 [0.27, 2.47]
Total (95% CI)		**587**		**527**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	19		22			

Heterogeneity: $Chi^2 = 1.40$, $df = 3$ ($P = 0.70$); $I^2 = 0\%$

Test for overall effect: $Z = 0.81$ ($P = 0.42$)



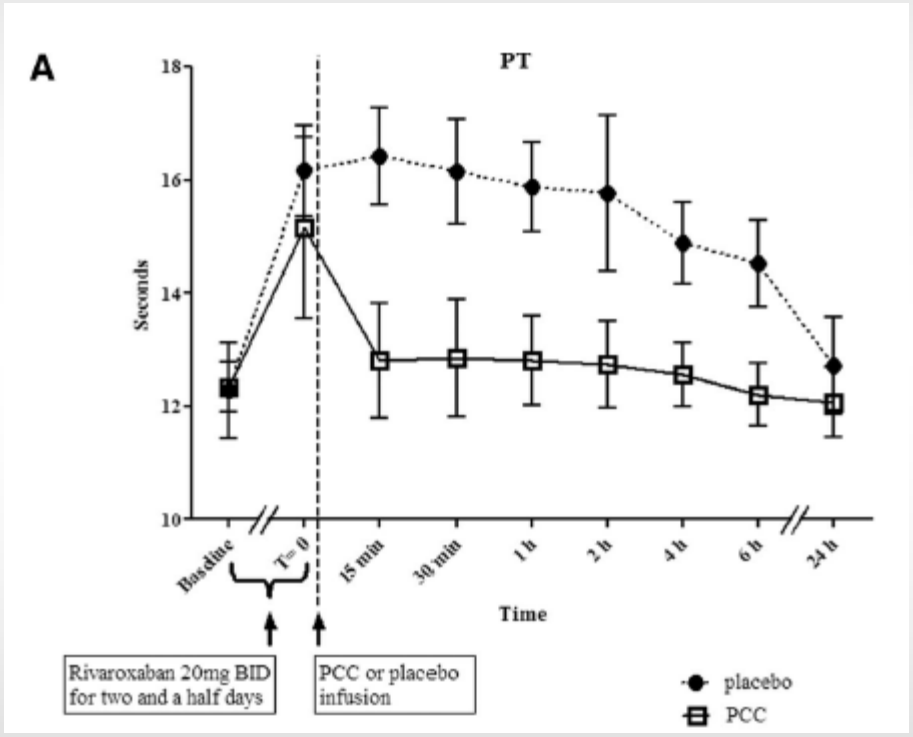
Vedovati et al, Chest 2014, in press

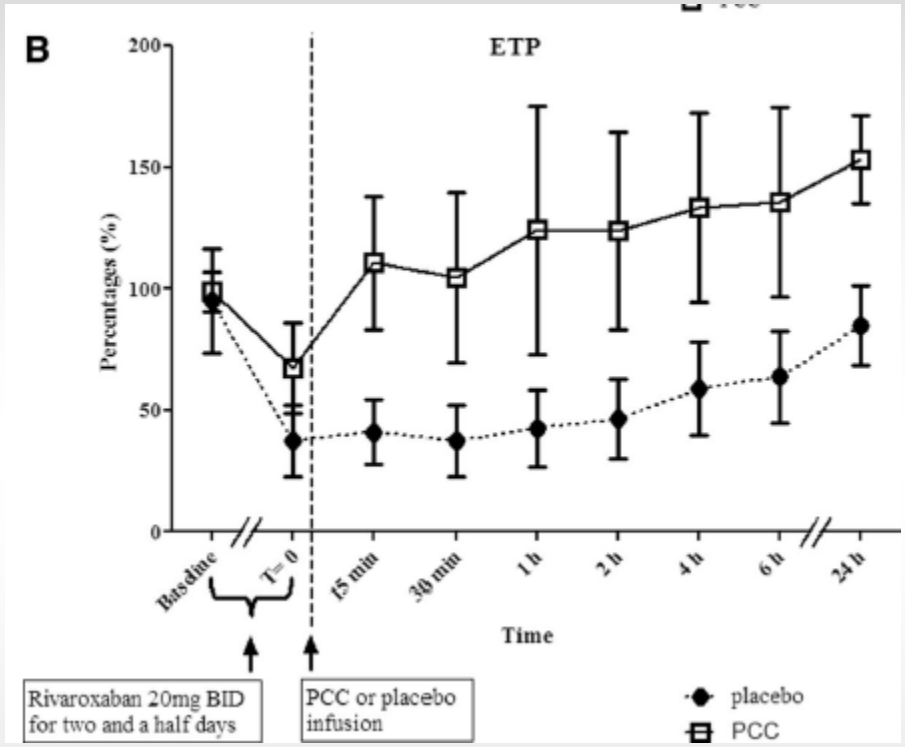
Reversal of anticoagulation with NOACS

- Presently no direct antidote available
  - Fully humanized antibody fragment (Fab) rapidly reversed the anticoagulation effect of dabigatran in healthy male volunteers in a phase I study, phase III study ongoing
- Partial reversal of factor Xa antagonists possible by prothrombin complex concentrates, activated prothrombin complex concentrates (FEIBA) and factor VII a

Antagonisation of rivaroxaban by PCC

Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects





PT= Prothrombinzeit, ETP=Endogenous Thrombin Potential

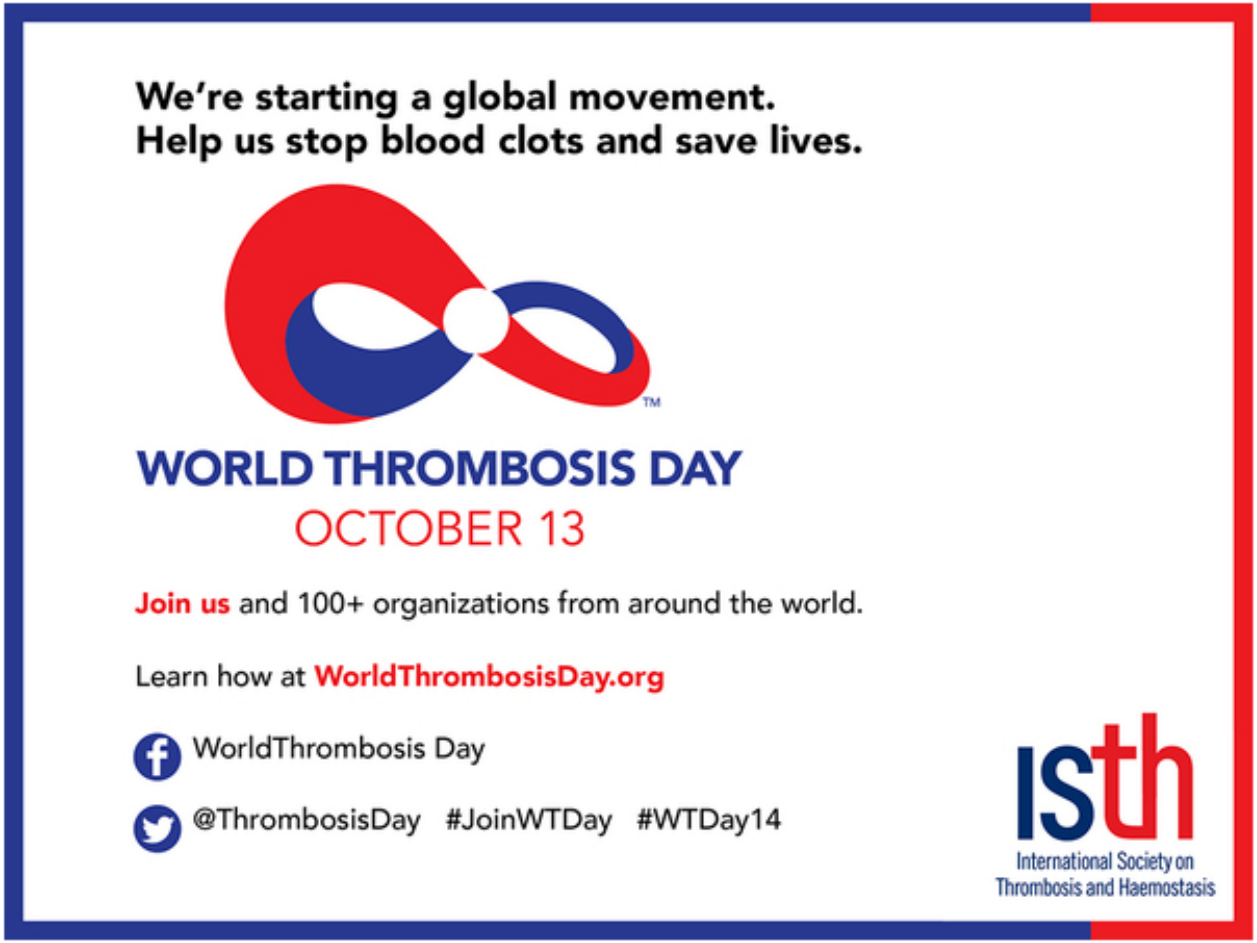
PT und ETP reversed by **PCC 50 IE/kg BW**

Erenberg et al, Circulation 2011

Summary – Take home messages

- NOACS have an improved profile with regard to efficacy and safety
- Kidney function has to be tested prior to treatment before each NOAC
  - Crucial for Dabigatran (mostly eliminated renally)
  - Test regularly kidney function, when a patient‘s condition deteriorates
- Adherence may be less than with vitamin K antagonists
  - Patient education is important
- NOACs in cancer patients: May be an alternative, when patients do not tolerate daily injections and after 3-6 months of LMWH

World Thrombosis Day





Muchas gracias !

Thank you !

Vielen Dank !