8th CHALLENGES in CARDIOLOGY

July 2018
6th, 7th

Palace Hotel Monte Real

8th CHALLENGES in CARDIOLOGY

VTE and Atrial Fibrillation in Patients with Cancer

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8th CHALLENGES in CARDIOLOGY

VTE in Patients with Cancer

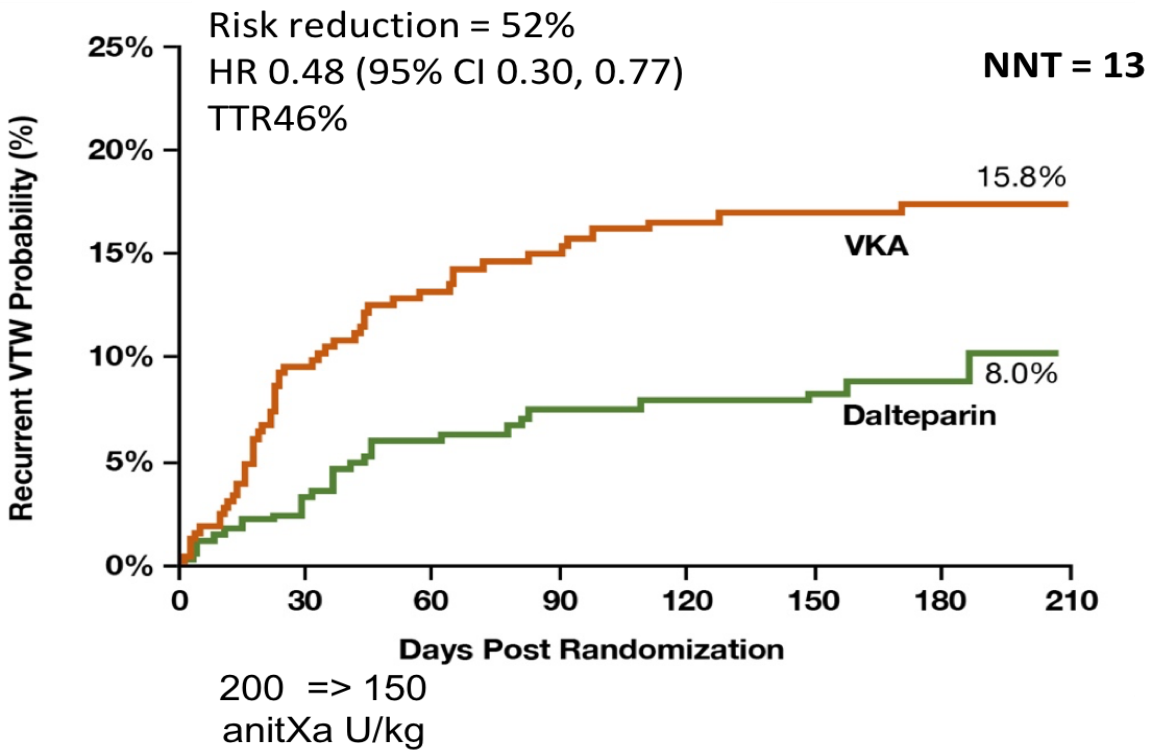
Cancer-Associated VTE

- High burden
- Risk of recurrent VTE and bleeding high

- Guidelines (ACCP, ASCO, ESMO)* recommend LMWH for initial therapy. No studies on long-term management.

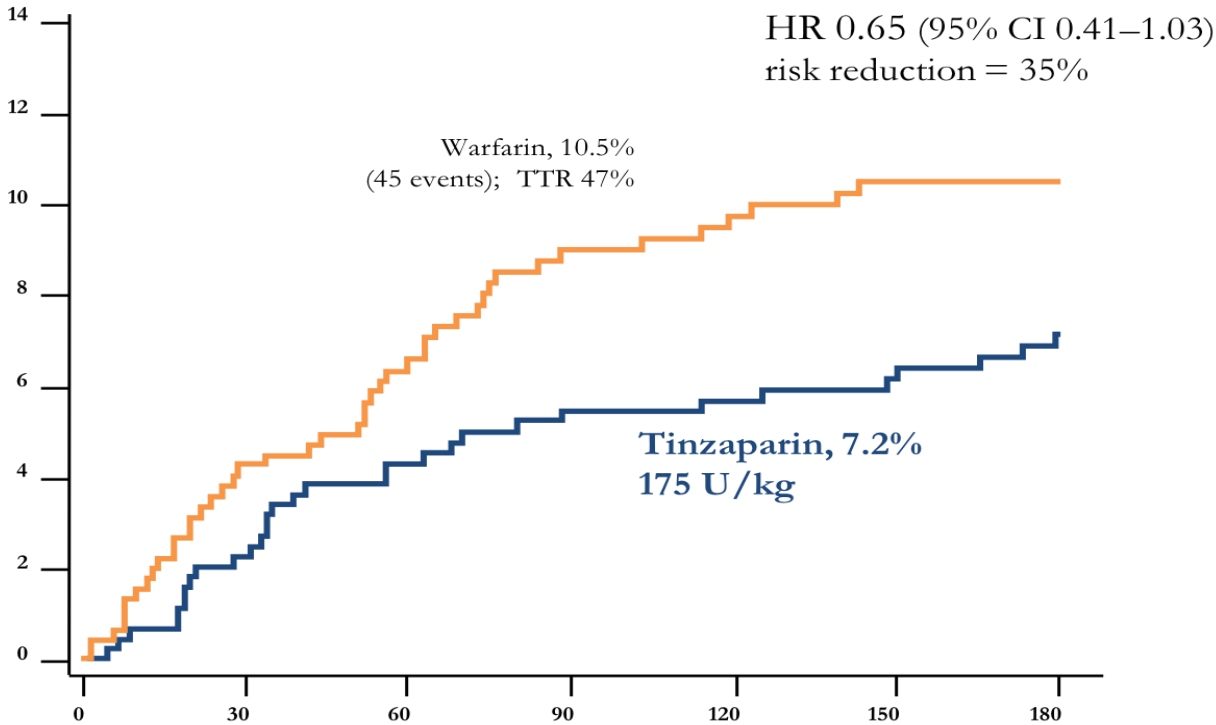
*Kearon et al CHEST 2016; 149: 315 - 352
Lyman et al Journal of Clinical Oncology, 2013, 31:2189 - 2204
Mandala et al Ann Oncol 2011;22 (Suppl 6): 85 – 92
Farge et al JTH 2013; 11: 56 - 70

CLOT Trial
VTE recurrence



200 => 150
anitXa U/kg

CATCH Trial
VTE recurrence

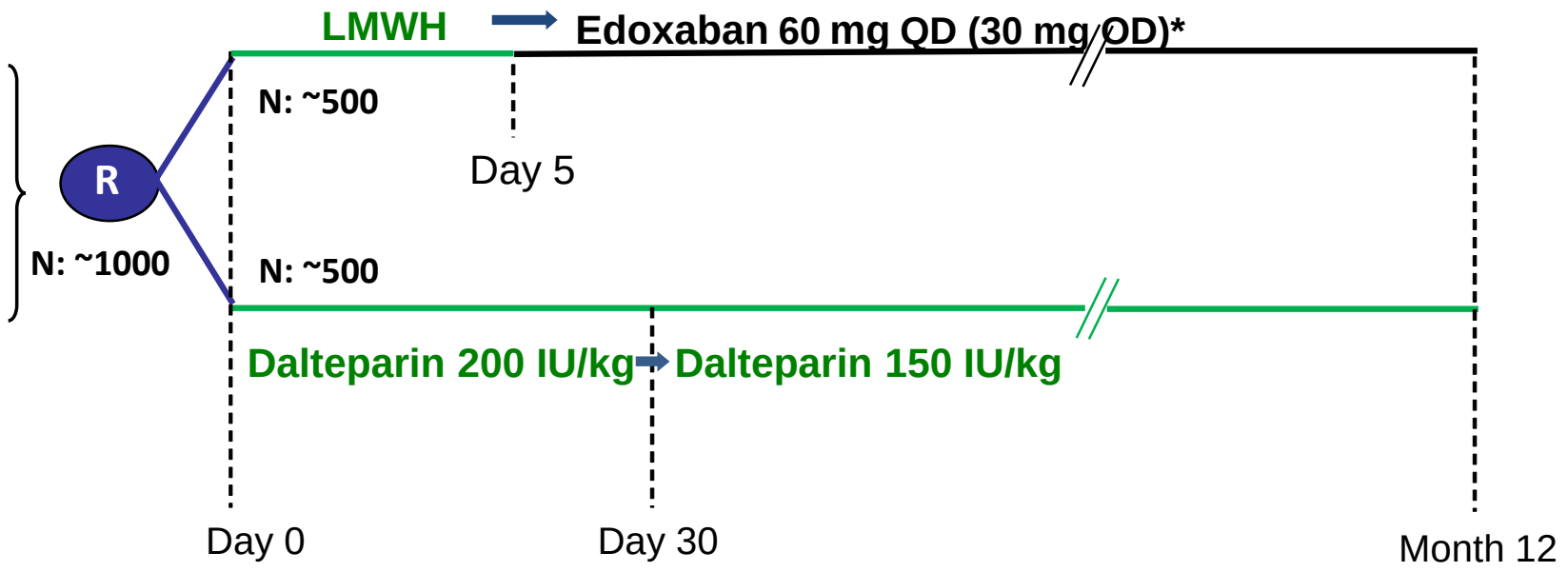


Lee A. NEJM & JAMA

Hokusai VTE - Cancer Study

Objectively Confirmed VTE

- Stratified randomization for
  - Bleeding Risk
  - Dose Adjustment
- PROBE design



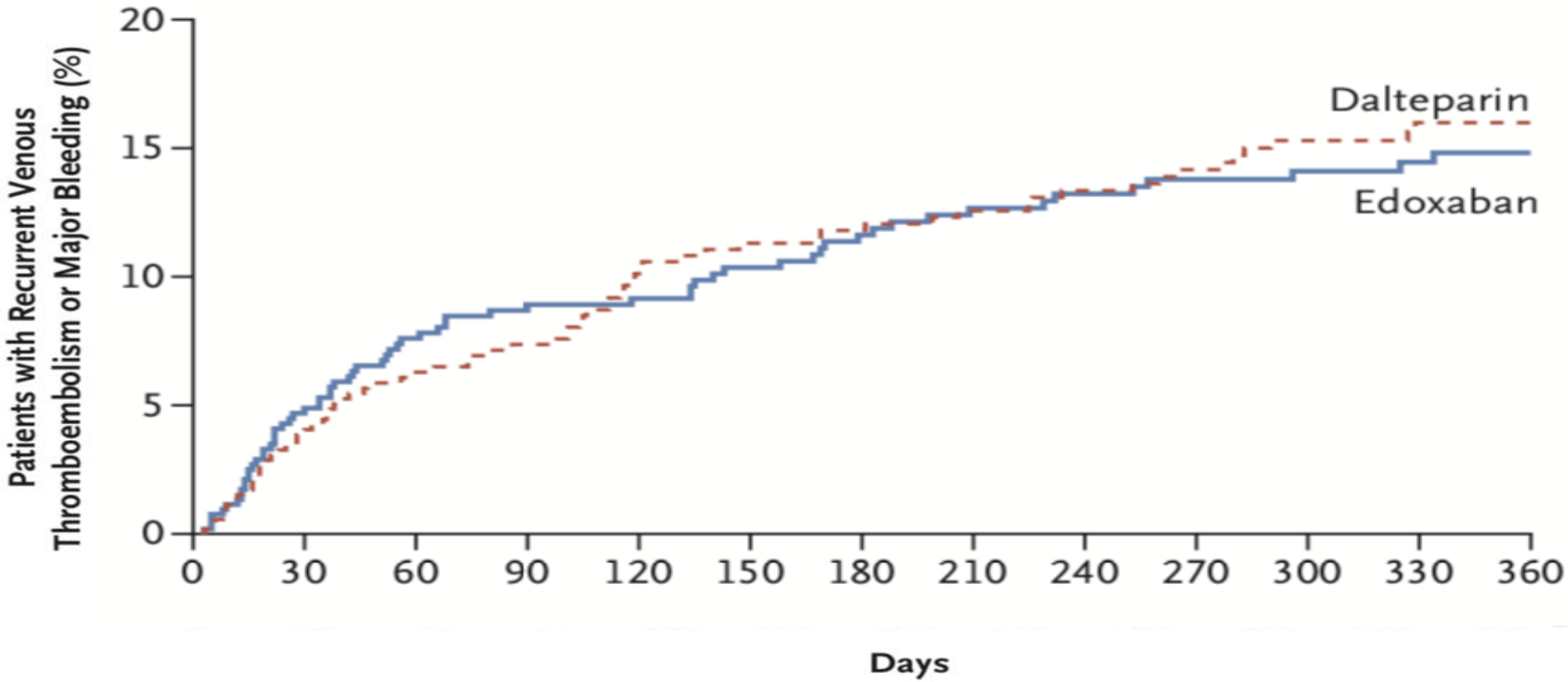
Hokusai VTE CANCER

Raskob, NEJM 2018

Primary Outcome:
Recurrent VTE or Major Bleeding

Hokusai VTE CANCER

Primary Outcome: Recurrent VTE or Major Bleeding

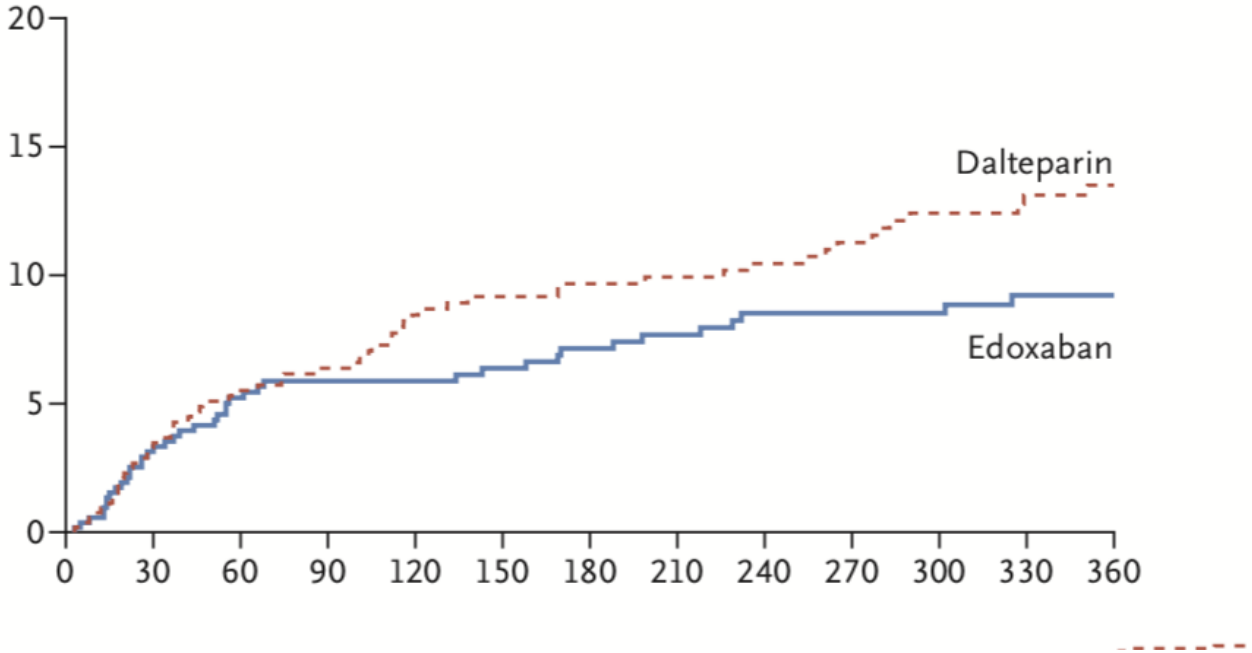


No. at Risk													
Edoxaban	522	472	429	407	388	360	345	328	310	295	270	237	161
Dalteparin	524	485	449	420	385	364	352	340	324	313	276	241	171

Hokusai VTE CANCER

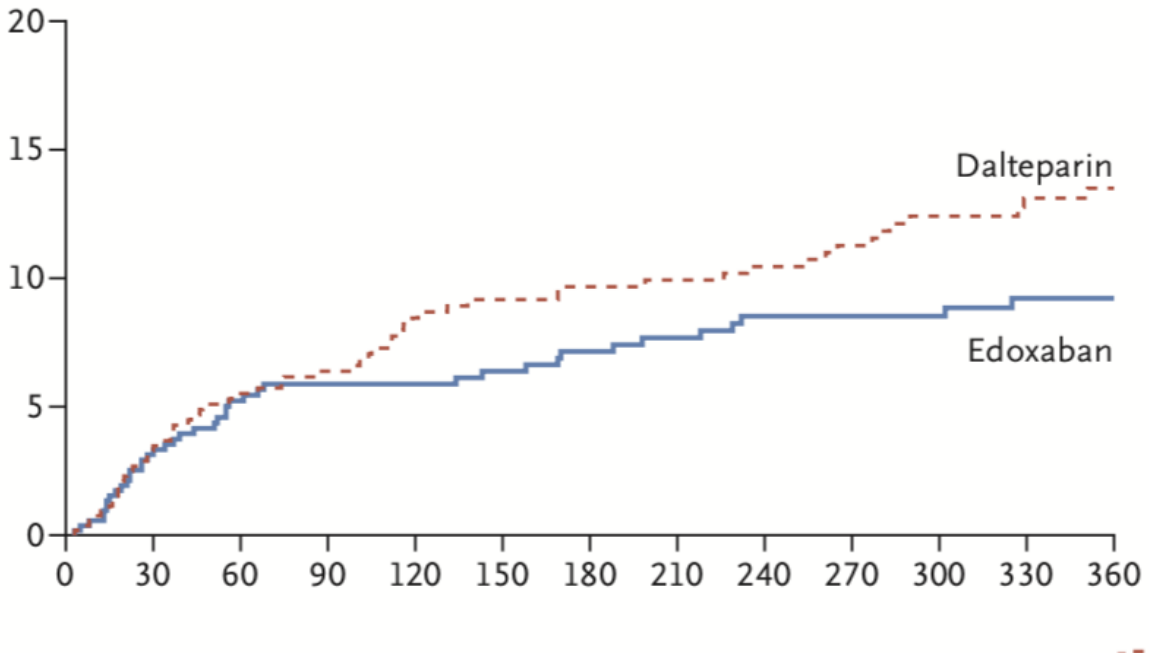
Raskob, NEJM 2018

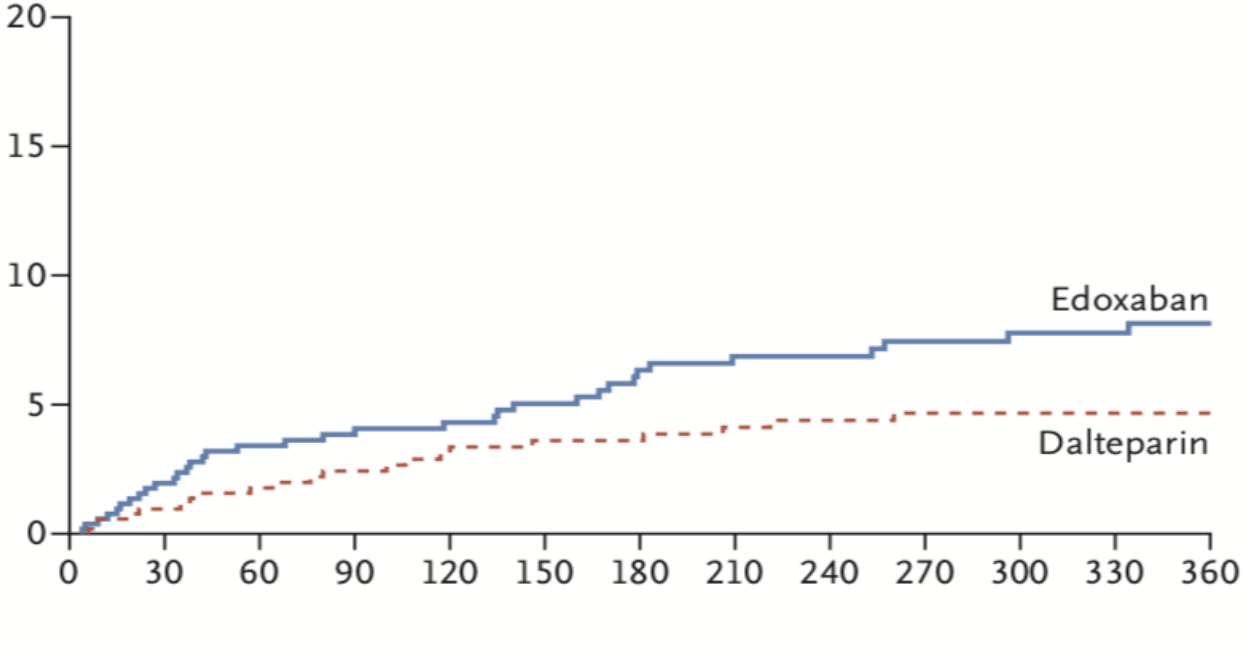
Recurrent VTE



Hokusai VTE CANCER

Recurrent VTE and Major Bleeding





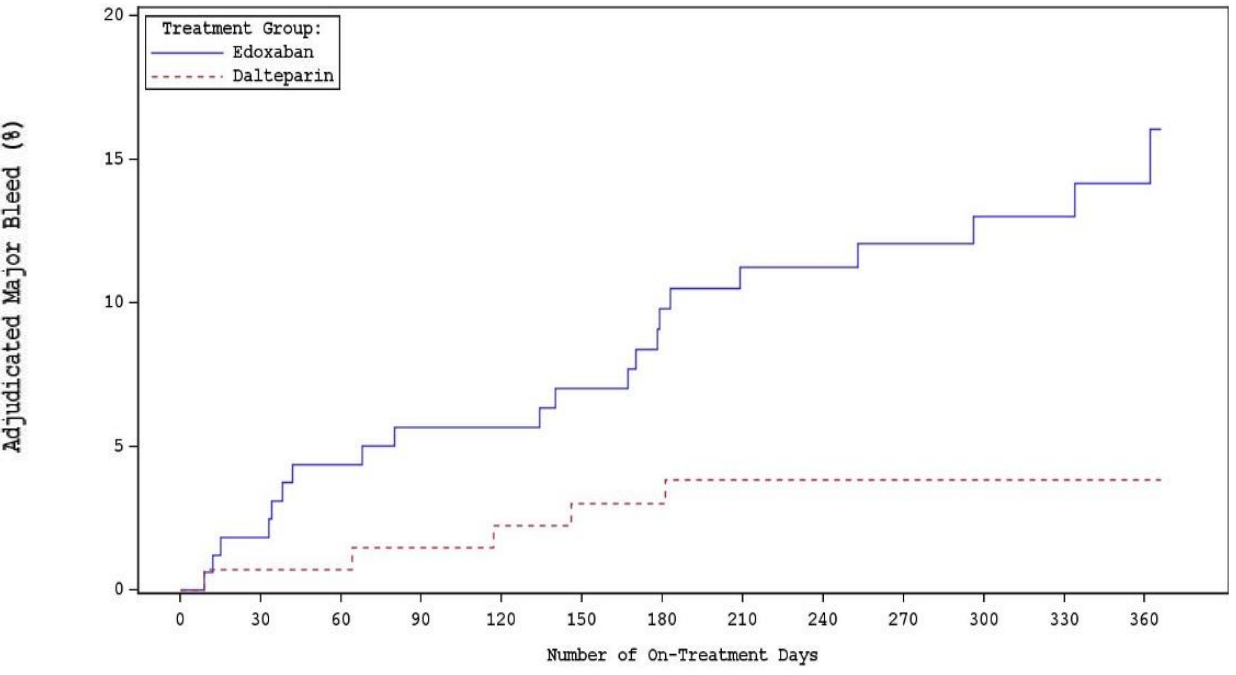
Hokusai VTE CANCER

First recurrent VTE or Major bleeding event

	Edoxaban (N = 522)	Dalteparin (N = 524)	Risk Difference (95% CI)
Recurrent VTE	34 (6.5%)	54 (10.3%)	- 3.8 (- 7.1, - 0.4)
Fatal	0	0	
DVT only	13	30	
Symptomatic	22	40	
Major bleeding	33 (6.3%)	17 (3.2%)	3.1 (0.5, 5.7)
Fatal	0	2	
Intracranial	2	4	
GI upper	17	3	
GI lower	3	3	

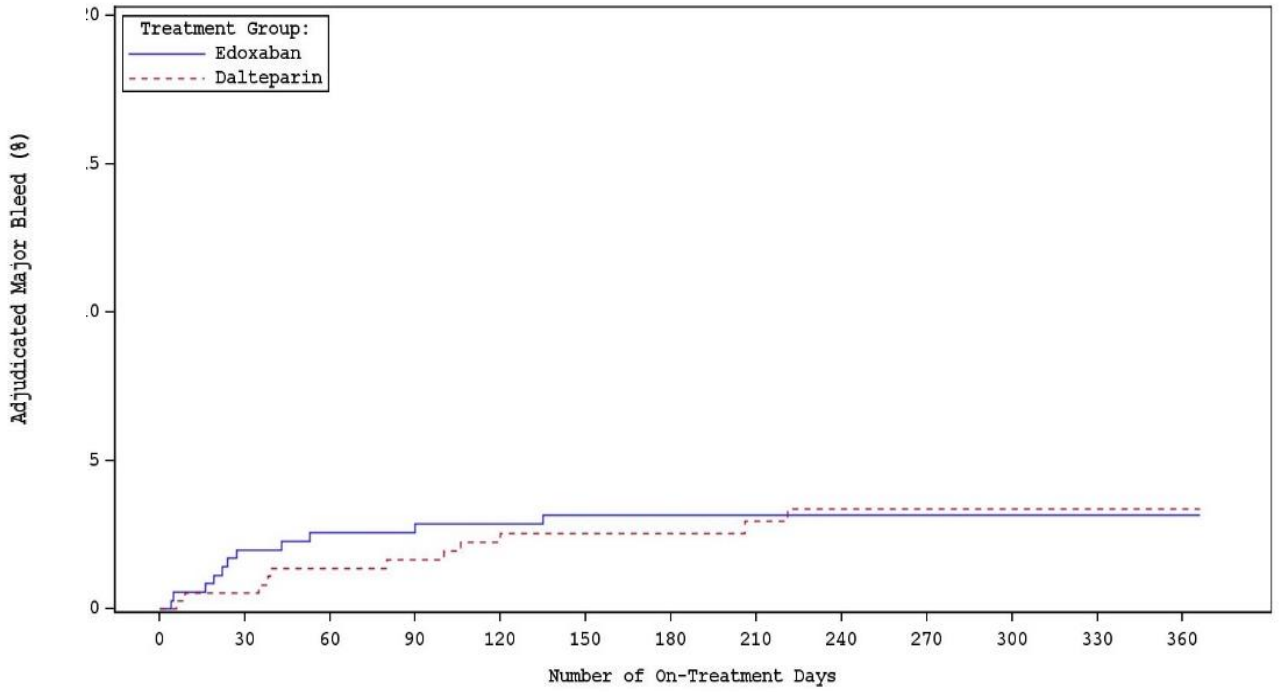
Major Bleeding: Gastro-Intestinal Cancer

GI Cancer



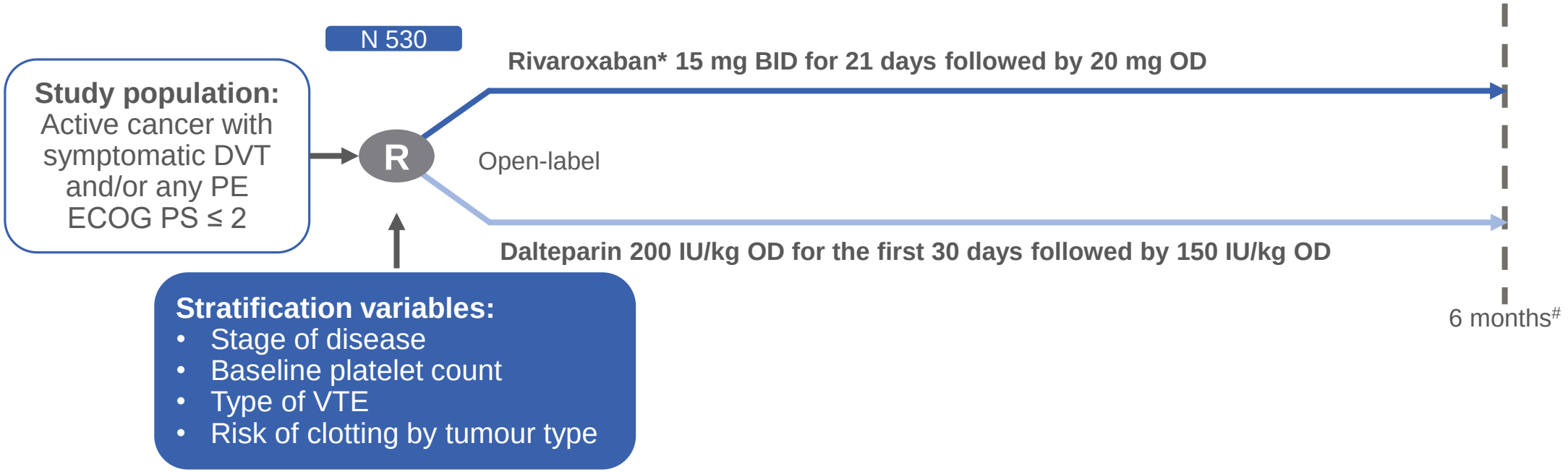
mber at Risk:													
Edoxaban	165	134	121	108	97	89	79	70	64	59	48	38	28
Dalteparin	140	123	116	108	94	89	79	67	60	54	48	40	25

Other cancers



umber at Risk:													
Edoxaban	357	315	284	271	255	234	220	190	179	171	144	123	88
Dalteparin	384	347	305	278	254	236	216	151	138	131	108	95	63

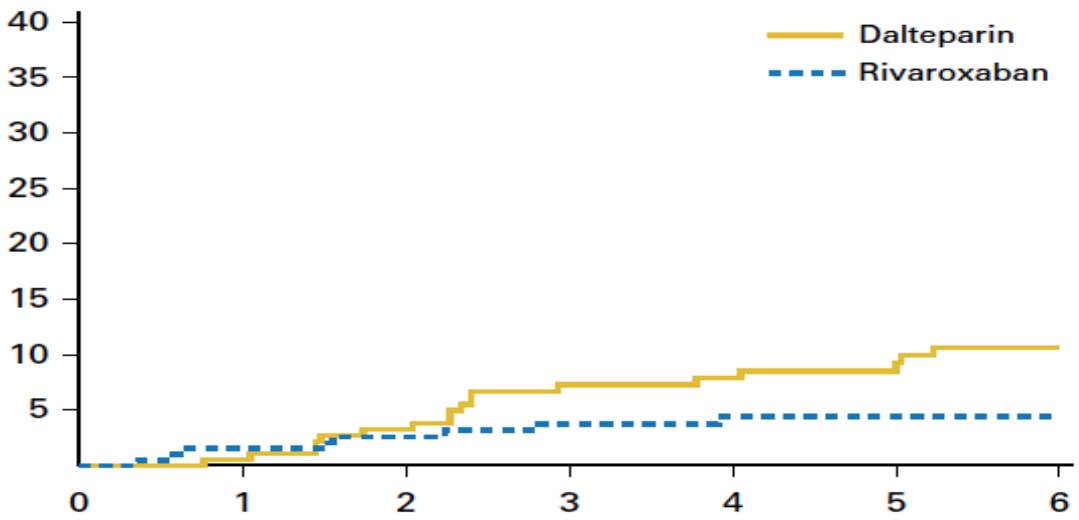
Select-d: Rivaroxaban versus Dalteparin for the Treatment of Cancer Associated Thrombosis

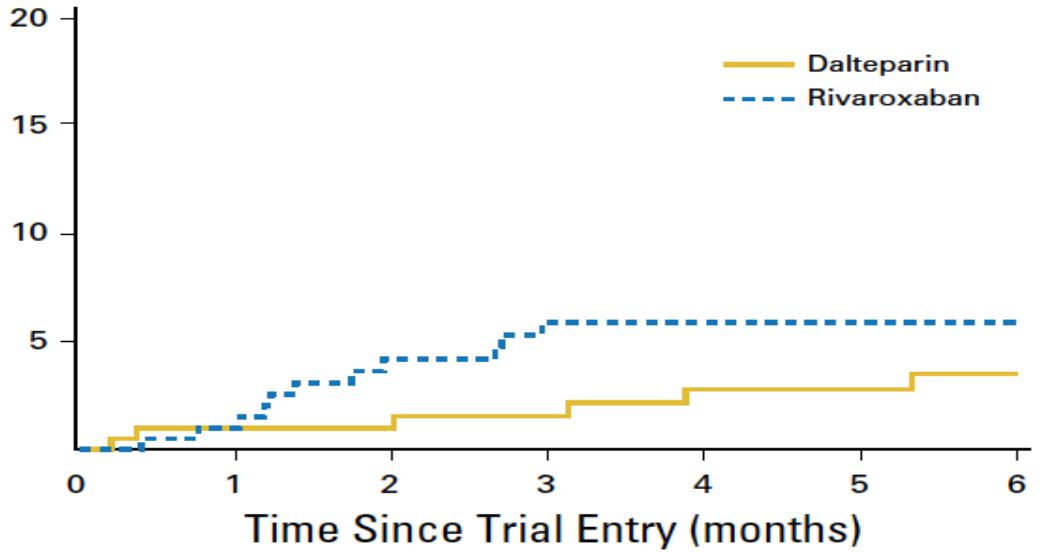


Study design: Prospective, randomized, open-label, multicentre pilot phase III study

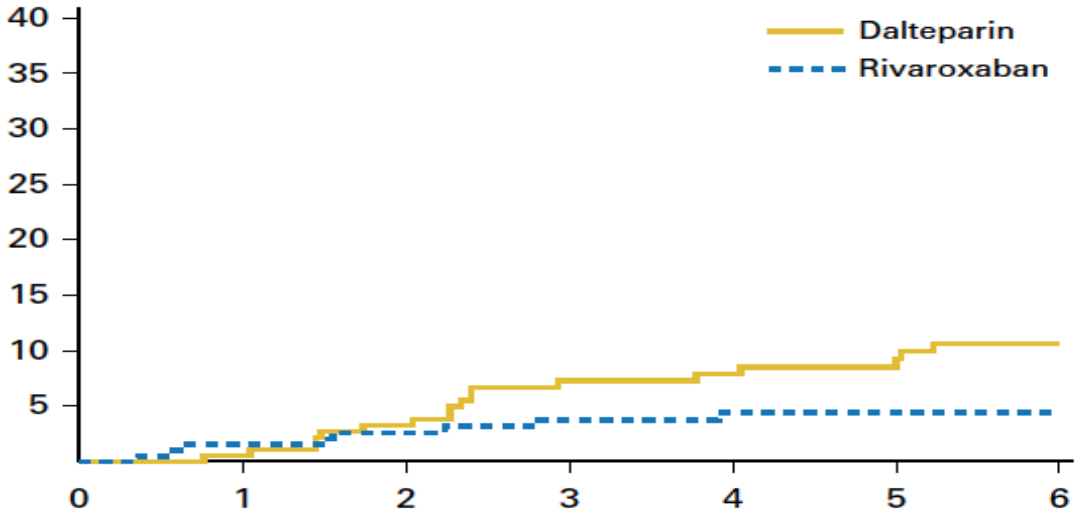
Young A *et al*, *Thromb Res* 2016;140:S172–S173; EudraCT number: 2012-005589-37; Bach M *et al*, *Thromb Haemost* 2016;116:S24–S32; Data on File

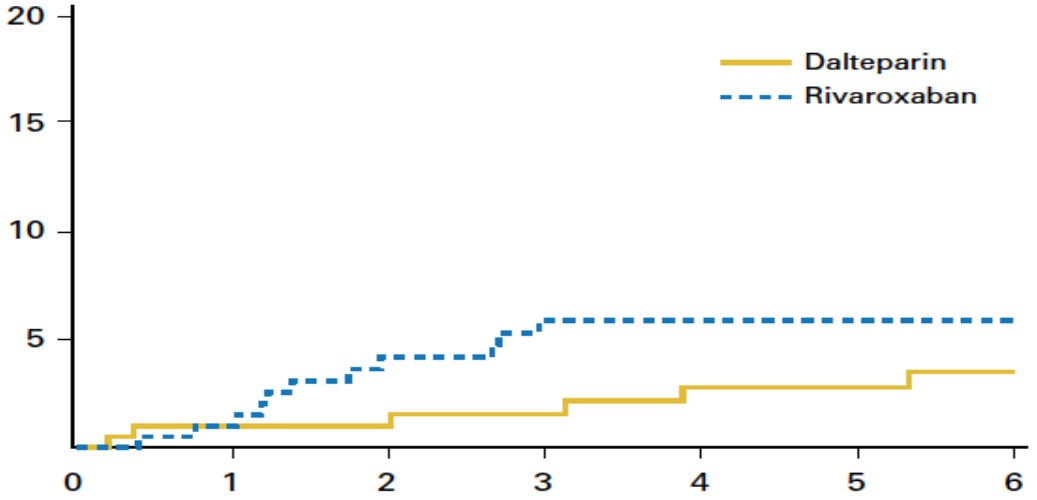
Recurrent VTE and Major Bleeding

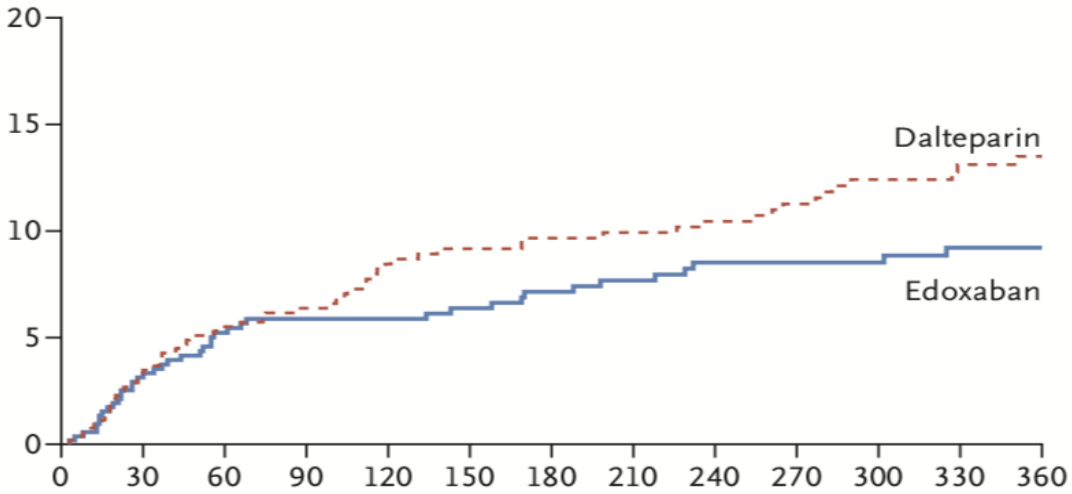


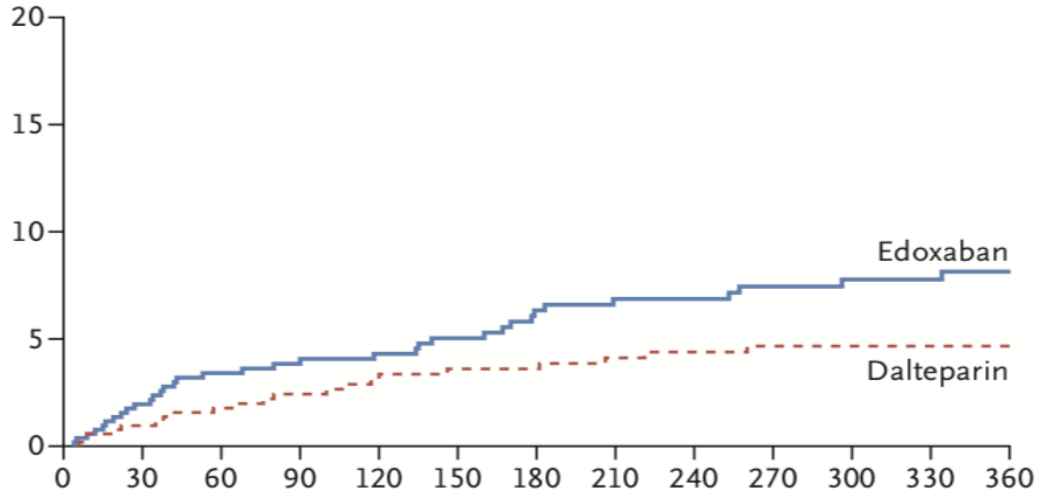


Recurrent VTE and Major Bleeding









A new era for CAT?

Parenteral agent preferred

- GI tumor
- Mucosal lesions (GI, GU), mucositis,
- Thrombocytopenia
- DDI
- Sepsis / acute illness
- Nausea / vomiting,…

Oral agent preferred

- Avoidance of SC
- Patient's and Physician's Preference
- Cost
- Long-term treatment

8th CHALLENGES in CARDIOLOGY

VTE and Atrial Fibrillation in Patients with Cancer

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Atrial Fibrillation in Patients with Cancer

Malignancy and Atrial Fibrillation

- Increasingly frequent
- Increasingly complex

- Undertreatment of atrial fibrillation in cancer patients?

- NOACs - ‘the unknown’

Vitamin K Antagonists

Pro

- Experience
- Monitoring

Con

- Inconvenient
- Monitoring
- Drug-drug Interactions
- Bleeding

LMWH

Pro

- Experience
- Efficacy/safety in VTE
- Subcutaneous
- Short half-life
- Flexible dosing
- No drug-drug interactions

Con

- Subcutaneous
- Optimal dose unknown

NOAC

Pro

- Safer than VKA
- Effective for stroke prevention
- Oral
- Convenient

Con: Barriers in Cancer patients?

- No dedicated studies
- (Fear of) Bleeding & Emergencies
- Unmonitored anticoagulation
- Drug-drug Interactions
- Confusion with VTE recommendations
- Renal insufficieny
- Platelet
- Liver function

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

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15. Non-vitamin K antagonist anticoagulants vs. vitamin K antagonists in atrial fibrillation patients with a malignancy

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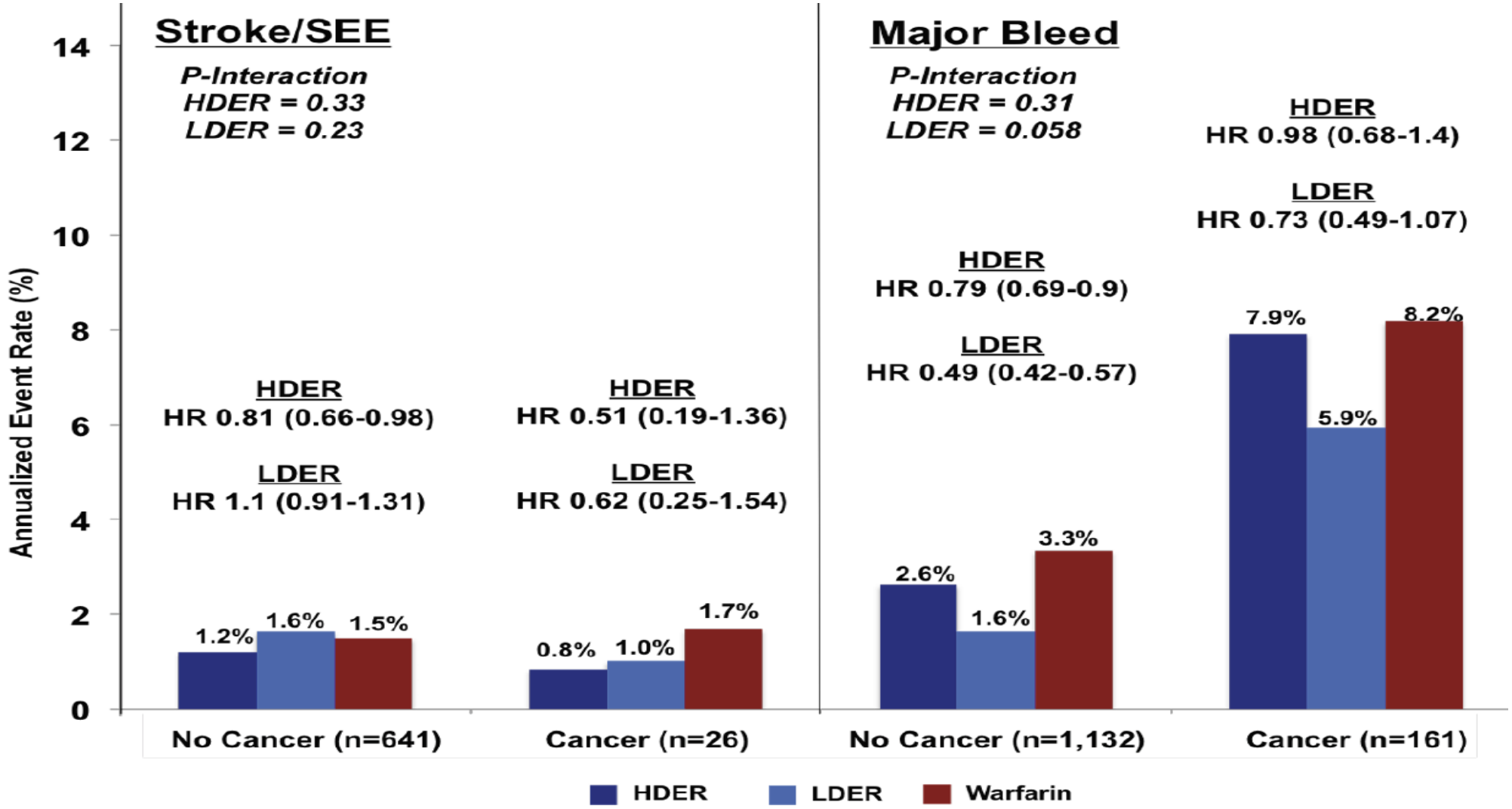
15. Non-vitamin K antagonist anticoagulants vs. vitamin K antagonists in atrial fibrillation patients with a malignancy

When anticoagulant therapy needs to be newly initiated in a patient with malignancy developing AF, therapy with **VKAs or heparins** should be considered over NOACs…

EFFICACY AND SAFETY OF EDOXABAN IN PATIENTS WITH ATRIAL FIBRILLATION AND ACTIVE MALIGNANCY



Efficacy and Safety of Apixaban Versus Warfarin in Patients with Atrial Fibrillation and a History of Cancer: Insights from the ARISTOTLE Trial

Chiara Melloni, MD, MHS,[a,b] Allison Dunning, MS,[a] Christopher B. Granger, MD,[a,b] Laine Thomas, PhD,[a] Michel G. Khouri, MD,[b] David A. Garcia, MD,[c] Elaine M. Hylek, MD, MPH,[d] Michael Hanna, MD,[e] Lars Wallentin, MD, PhD,[f] Bernard J. Gersh, MB, ChB, DPhil,[g] Pamela S. Douglas, MD,[a,b] John H. Alexander, MD, MHS,[a,b] Renato D. Lopes, MD, MHS, PhD[a,b]

	Cancer (n = 1236)			No Cancer (n = 16,947)			
	Event (Rate*)			Event (Rate*)			
	Apixaban (n = 615)	Warfarin (n = 621)	HR (95% CI)	Apixaban (n = 8493)	Warfarin (n = 8454)	HR (95% CI)	*P* Value†
Ischemic outcomes							
Stroke or SE	15 (1.4)	14 (1.2)	1.09 (0.53-2.26)	196 (1.3)	251 (1.6)	0.77 (0.64-0.93)	.3671
Death from any cause	54 (4.7)	42 (3.6)	1.32 (0.88-1.97)	548 (3.4)	626 (4.0)	0.87 (0.77-0.97)	.0504
Ischemic stroke	14 (1.3)	9 (0.8)	1.59 (0.69-3.66)	147 (0.9)	166 (1.1)	0.88 (0.70-1.10)	.1807
Bleeding outcomes							
ISTH major bleeding	24 (2.4)	32 (3.2)	0.76 (0.45-1.29)	303 (2.1)	430 (3.1)	0.69 (0.59-0.80)	.7227
Major or CRNM bleeding	53 (5.5)	67 (6.9)	0.80 (0.56-1.14)	560 (4.0)	810 (5.9)	0.67 (0.60-0.75)	.3682

Rivaroxaban for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation and Active Cancer

The American Journal of Cardiology

The estimated 1-year cumulative incidence of

ischemic stroke	1.4% (95% CI 0% to 3.4%)
major bleeding	1.2% (95% CI 0% to 2.9%)
clinically relevant nonmajor **bleeding leading to discontinuation**	14.0% (95% CI 4.2% to 22.7%).
mortality	22.6% (95% CI 12.2% to 31.7%)

Am J Cardiol 2017;120:213–217

Table 16 Atrial fibrillation and malignancy

Interdisciplinary teamwork
(1) Estimate individual patient risk profile • AF-related risk factors (CHA_2DS_2-VASc, bleeding risk) • Cancer-related risk factors (type, liver metastases, coagulopathy, renal/hepatic function etc. • Treatment-related risk factors (thrombocytopenia, surgery, radiation, central lines etc.) (2) Choose anticoagulant • Current standard of care: VKA/(LMWH)[a] • NOACs: Available data scarce, but encouraging • Consider patient preference (VKA vs. NOAC) (3) Protect the patient • Gastric protection (PPI/H2 blockers) • Beware of drug–drug interactions (*Table 4*) • Dose reduction/treatment interruption (if platelets <50k, renal dysfunction, bleeding, . . .)
Beware • Risk of thromboembolism ↑ • Risk of bleeding ↑

[a]If oral therapy is not possible reversion to LMWH is reasonable.

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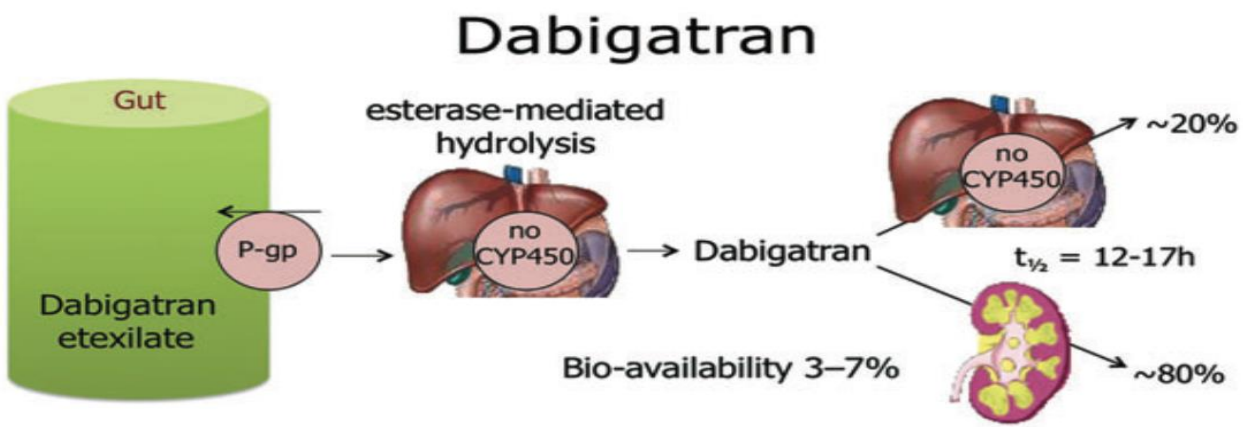
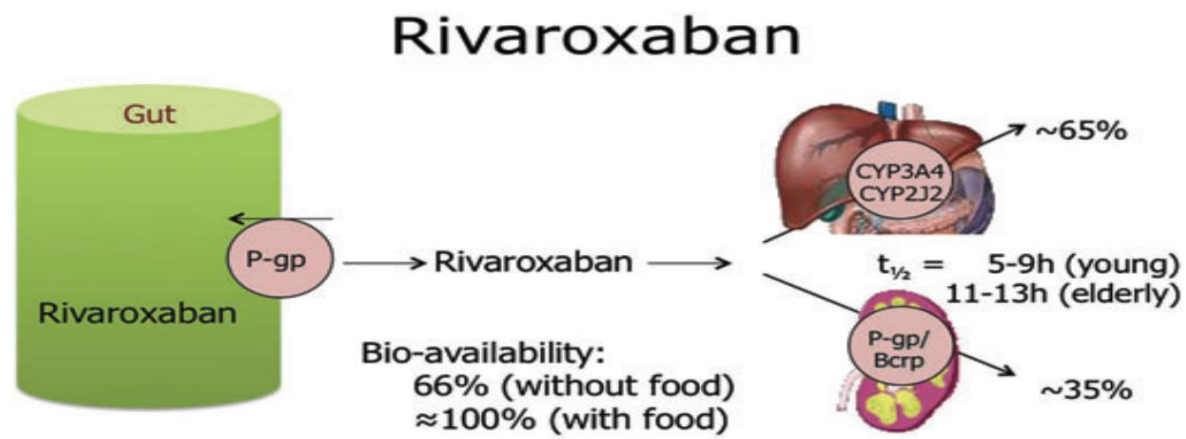
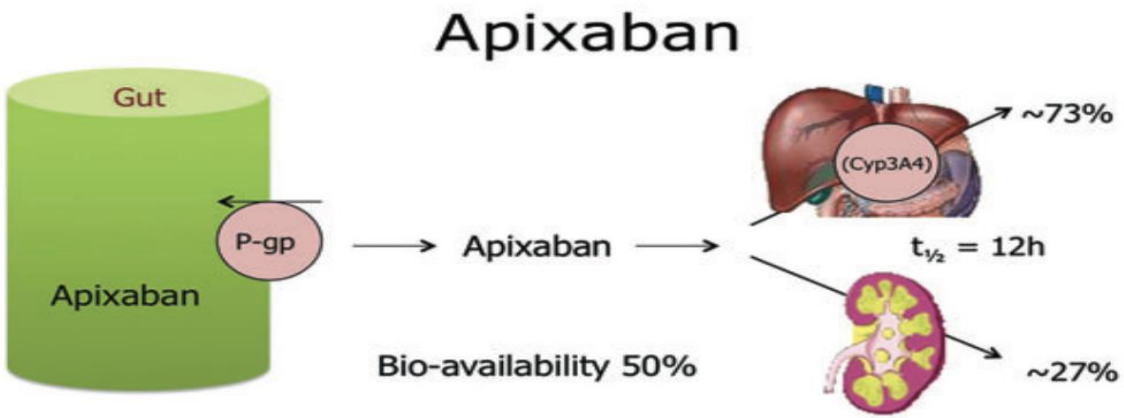
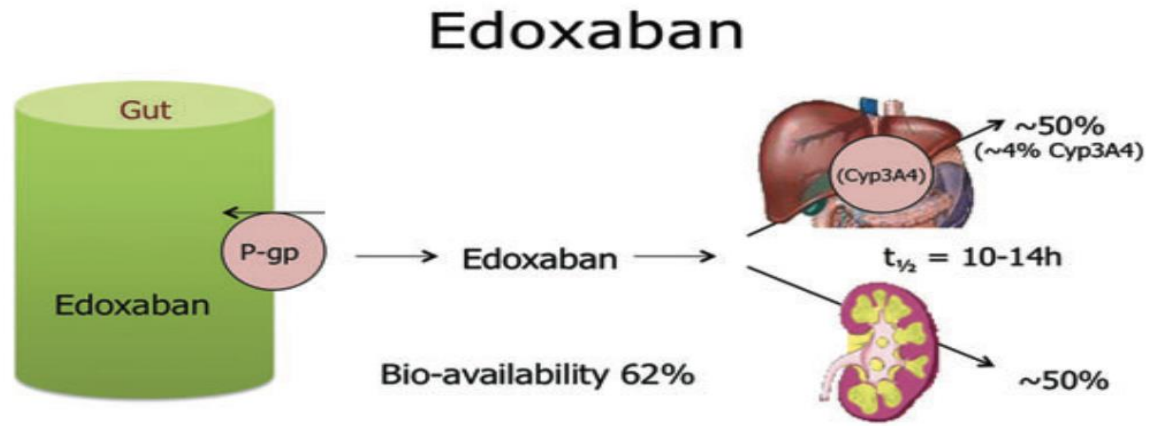

Dabigatran
Gut
Dabigatran etexilate
P-gp
esterase-mediated hydrolysis
no CYP450
Dabigatran
no CYP450
~20%
t½ = 12-17h
~80%
Bio-availability 3–7%


Rivaroxaban
Gut
Rivaroxaban
P-gp
Rivaroxaban
CYP3A4 CYP2J2
~65%
t½ = 5-9h (young)
11-13h (elderly)
P-gp/ Bcrp
~35%
Bio-availability:
66% (without food)
≈100% (with food)


Apixaban
Gut
Apixaban
P-gp
Apixaban
(Cyp3A4)
~73%
t½ = 12h
~27%
Bio-availability 50%


Edoxaban
Gut
Edoxaban
P-gp
Edoxaban
(Cyp3A4)
~50%
(~4% Cyp3A4)
t½ = 10-14h
~50%
Bio-availability 62%

	Via[440]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Antimitotic agents					
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competition				
Docetaxel, Vincristine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Antimetabolites					
Metotrexate	P-gp competition; no relevant interaction anticipated				
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated				
Topoisomerase inhibitors					
Topotecan	No relevant interaction anticipated				
Irinotecan	CYP3A4/P-gp competition; No relevant interaction anticipated				
Etoposide	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Anthracyclines / Anthracenediones					
Doxorubicin	Strong P-gp induction, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Idarubicin	Mild CYP3A4 inhibition; P-gp competition				
Daunorubicin	P-gp competition; No relevant interaction anticipated				
Mitoxantrone	No relevant interaction anticipated				
Alkylating agents					
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				
Busulfan	CYP3A4 competition; No relevant interaction anticipated				
Bendamustine	P-gp competition; No relevant interaction anticipated				
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	No relevant interaction anticipated				
Platinum-based agents					
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated				
Intercalating agents					
Bleomycin, Dactinomycin	No relevant interaction anticipated				
Mitomycin C	No relevant interaction anticipated				
Tyrosine kinase inhibitors					
Imatinib, Crizotinib	Strong P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition				
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vandetanib, Sunitinib	Strong P-gp induction; CYP3A4 competition				

Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				
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Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vandetanib, Sunitinib	Strong P-gp induction; CYP3A4 competition				
Erlotinib, Gefitinib	CYP3A4 competition; No relevant interaction anticipated				
Monoclonal antibodies					
Brentuximab	CYP3A4 competition; No relevant interaction anticipated				
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevant interaction assumed				
Hormonal agents					
Abiraterone	Moderate CYP3A4 inhibition, strong P-gp inhibition; CYP3A4/P-gp competition				
Enzalutamide	Strong CYP3A4 induction, strong P-gp inhibition; CYP3A4/P-gp competition				
Bicalutamide	Moderate CYP3A4 inhibition				
Tamoxifen	Strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4 competition				
Anastrozole	Mild CYP3A4 inhibition				
Flutamide	CYP3A4 competition; No relevant interaction anticipated				
Letrozole, Fulvestrant	CYP3A4 competition; No relevant interaction anticipated				
Raloxifene, Leuprolide, Mitotane	No relevant interaction anticipated				
Immune-modulating agents					
Cyclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73%[441]	
Dexamethasone	Strong CYP3A4/P-gp induction; CYP3A4/P-gp competition				
Tacrolimus	Strong-to-moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC			

Which dose?

- Patient on fluconazole?
  ibrutinib?
  tamoxifen?
  sunitinib?
  tacrolimus?

Which dose?

- Platelet count
  - > 100K
  - 50-100K
  - 30-50K
  - 20-30K
  - <20K

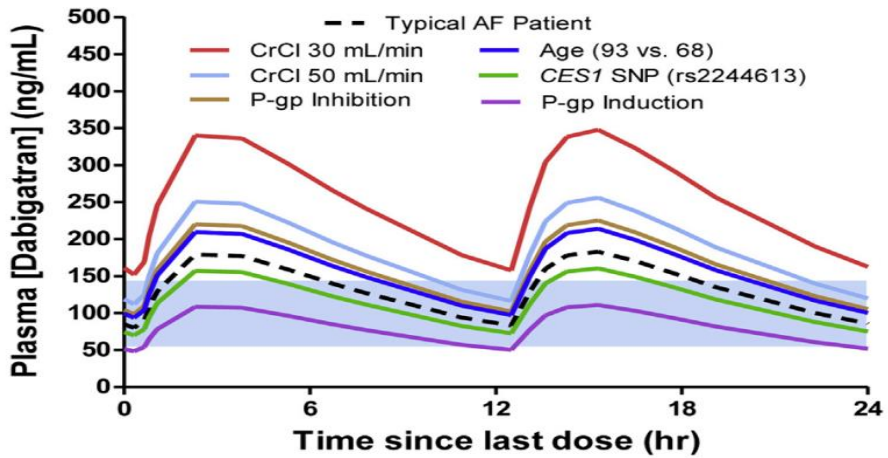
Which dose?

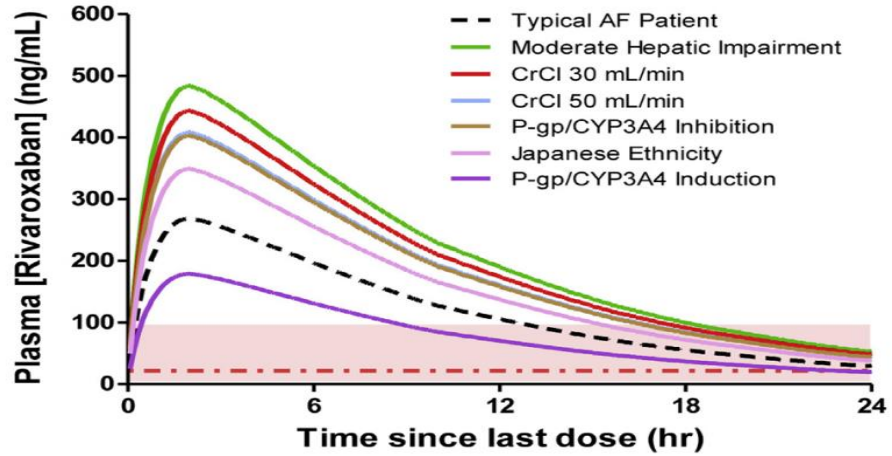
- Renal function
  - > 60 ml/min
  - 50 – 60 ml/min
  - 30 – 50 ml/min
  - 15 – 30 ml/min
  - < 15 ml /min

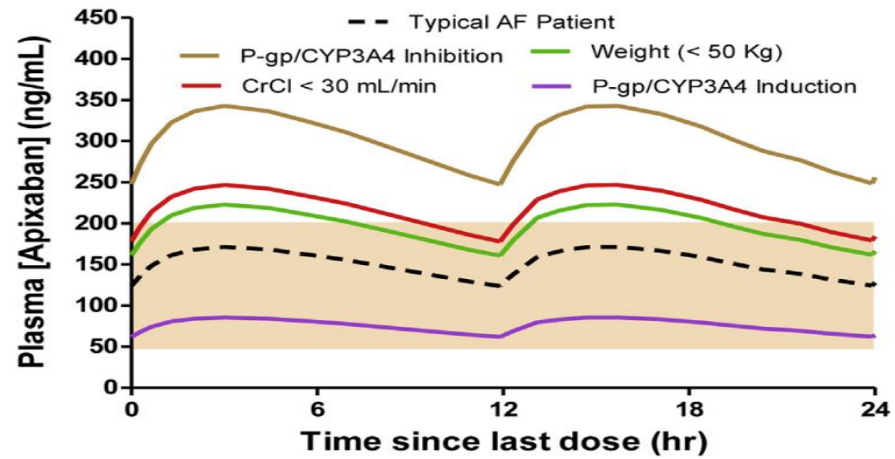
Which dose?

- Low body weight
- Nausea and vomiting after chemotherapy?
  Diarrhea and mucositis?
- Unable for oral medication?

Monitoring of drug levels?


Typical AF Patient
CrCl 30 mL/min
CrCl 50 mL/min
P-gp Inhibition
Age (93 vs. 68)
CES1 SNP (rs2244613)
P-gp Induction
Plasma [Dabigatran] (ng/mL)
Time since last dose (hr)


Typical AF Patient
Moderate Hepatic Impairment
CrCl 30 mL/min
CrCl 50 mL/min
P-gp/CYP3A4 Inhibition
Japanese Ethnicity
P-gp/CYP3A4 Induction
Plasma [Rivaroxaban] (ng/mL)
Time since last dose (hr)


Typical AF Patient
P-gp/CYP3A4 Inhibition
CrCl < 30 mL/min
Weight (< 50 Kg)
P-gp/CYP3A4 Induction
Plasma [Apixaban] (ng/mL)
Time since last dose (hr)

Cancer-associated VTE and Afib

- Expanding role of DOACs
- Different bleeding pattern with NOACs
- Periodical evaluation of the need for anticoagulation and the optimal modality, based on patient’s characteristics and patient’s/physicians preferences

8th CHALLENGES in CARDIOLOGY

VTE and Atrial Fibrillation in Patients with Cancer

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