My Cancer Patient Has a Clot- Can I prescribe a Direct Oral Anticoagulant (DOAC)?

November 24, 2018

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Disclosures

- I participate in clinical research investigating the use of apixaban in the prevention of cancer-associated thrombosis

- I have received honororia from Leo pharma, Sanofi and Bayer

Mitigating Potential Bias

- All treatment alternatives will be discussed during the presentation

Objectives

- Brief review DOAC data in non-cancer patients and DOAC pharmacology
- Review the evidence for DOACs in cancer-associated VTE (CAT)
- Discuss optimal anticoagulant choice in CAT

Cancer-Associated VTE (CAT)

- ~20% of all VTE are associated with cancer
- VTE is associated with higher mortality
  - 2nd leading cause of death in cancer patients
- Significant burden on the health care community
  - Increased hospitalization
  - Health care costs and resource utilization
- Can cause treatment discontinuation/delays

Heit J.A. et al Arch Intern Med 2000; Wun T. et al Cancer Investigation 2009; Khorana A. et al J Thromb Haemost 2007

Case – Mr. J.S.

- 79 y.o. male with PMHx HTN and diabetes
- Developed bloating and abdominal discomfort in late 2017
  - CT February 2018 → new pancreatic mass consistent with pancreatic adenoCA
- Mass felt to be resectable therefore patient taken to the OR in March 2018
  - Intra-operative frozen sections positive for peritoneal and omental spread

Case – Mr. J.S.

- Started on palliative chemotherapy with gemcitabine and abraxane
- 2 months later develops right calf pain and dyspnea on exertion
  - Hemodynamically stable
  - Hemoglobin 110, platelets 200, eGFR 37 mL/min
  - US → right calf vein DVT
  - CT chest → bilateral segmental PE, no right heart strain

Case –Anticoagulant Options

- Anticoagulant options for Mr. J.S.
  - DOAC
  - LWMH
  - LMWH (or UFH) bridging to warfarin

Case – Anticoagulant options

- You discuss anticoagulation with Mr. J.S.

- He asks you if he can use this new medication he saw on CNN

Case –Anticoagulant Options

- You discuss anticoagulation with Mr. PE.

- He asks you if he can use this new medication he saw on CNN
  - After all his favorite golfer was in the commercial!

Are direct oral anticoagulants a suitable option?

LMWH for Cancer-Associated VTE

- LMWH was previously the standard of care for cancer-associated VTE

- Recommendations for LMWH largely based on results of open-label RCTs
  - **CANTHANOX** study: enoxaparin vs. warfarin
  - **CLOT** study: dalteparin vs. warfarin/acenocoumarol
  - **LITE** study: tinzaparin vs. warfarin
  - **CATCH** study: tinzaparin vs. warfarin

Lee A.Y.Y. et al NEJM 2003; Hull R.D. et al Am J Med 2006; Meyer G. et al Arch Intern Med 2002; Lee A.Y.Y. et al JAMA 2015

LMWH for Cancer-Associated VTE

- LMWH is **more effective then warfarin** for the prevention of recurrent VTE
  - **RR 0.58** (95% CI 0.43 – 0.77)

- LMWH has a safety profile similar to that of warfarin for major bleeding
  - **RR 1.09** (95% CI 0.55 – 2.12)

Kahale L.A. et al Cochrane Database Syst Rev 2018

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LMWH is efficacious, safe, has no chemotherapy/food interactions and does not rely on oral intake

Kahale L.A. et al Cochrane Database Syst Rev 2018

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BUT… LMWH is administered parenterally and is costly

Kahale L.A. et al Cochrane Database Syst Rev 2018

DOACs in Canada

- DOACs are approved in Canada for
  - VTE prophylaxis in total hip/knee replacement
  - Prevention of stroke in non-valvular atrial fibrillation
  - VTE treatment

- DOACs currently available in Canada include
  - Dabiga**t**ran } Anti-**thrombin**
  - Rivaro**xa**ban
  - Api**xa**ban } Anti-**Xa**
  - Edo**xa**ban

DOAC Pharmacology

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa	Vit K dependent factors
Action onset	1 – 3 h	2 – 4 h	1 – 2 h	1-2 h	4-5 days
Half life	14-17 h	7-11 h	8-14 h	9-11 h	40 h
Renal clearance	80%	33%	27%	50%	0%
Dosing	BID	OD (BID)	BID	OD	OD
Lab monitoring	No	No	No	No	YES
Antidote	**YES**	NO	NO	NO	**YES**
Drug interactions	P-gp	P-gp CYP3A4	P-gp CYP3A4	P-gp	**MANY**

Yeh C.H. et al Blood 2014

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Compared to **warfarin** **DOACs** are ← **Fast acting**

Yeh C.H. et al Blood 2014

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Compared to **warfarin** **DOACs** have a

← **Short half life**

Yeh C.H. et al Blood 2014

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Compared to **warfarin** **DOACs** are

Renally cleared

Yeh C.H. et al Blood 2014

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Compared to **warfarin DOACs**

← **Do not require lab monitoring**

Yeh C.H. et al Blood 2014

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Compared to **warfarin DOACs**

Idarucizumab (Dabigatran)

Andexanet (Factor Xa inhibitors)

Yeh C.H. et al Blood 2014

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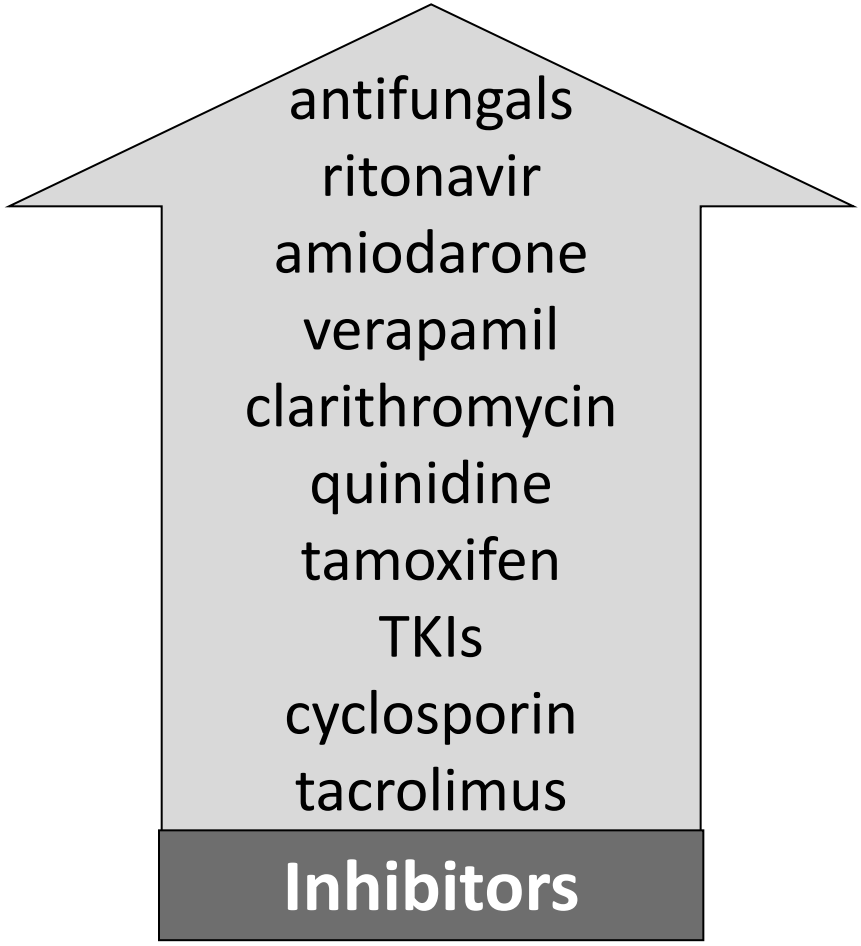
Compared to **warfarin** **DOACs** have

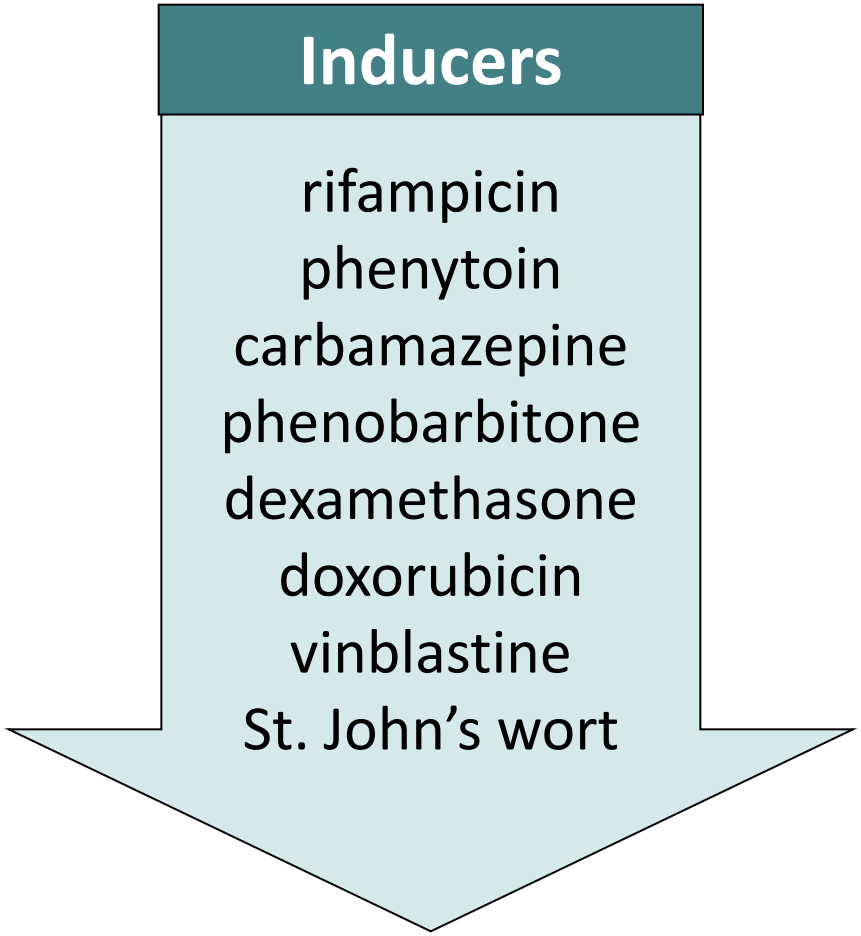
← **Few drug interactions**

Yeh C.H. et al Blood 2014

DOAC Drug Interactions



Increase DOAC Levels



Decrease DOAC Levels

Lee A.Y.Y. et al Thromb Res 2014

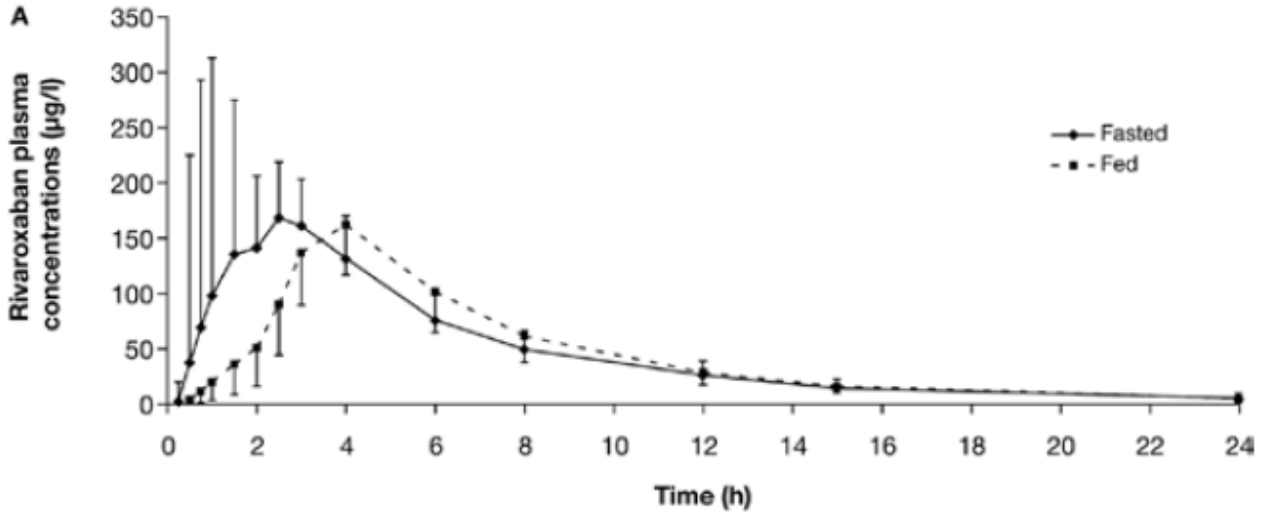
DOAC Absorption - Location

- Apixaban
  - Throughout the GI tract (55% in distal SB/proximal colon)
- Edoxaban
  - Proximal small intestine
- Rivaroxaban
  - Stomach (Cmax ↓ by 56% if delivered directly in SB)
- Dabigatran
  - Stomach and proximal small intestine
  - Capsules cannot be crushed/broken/chewed

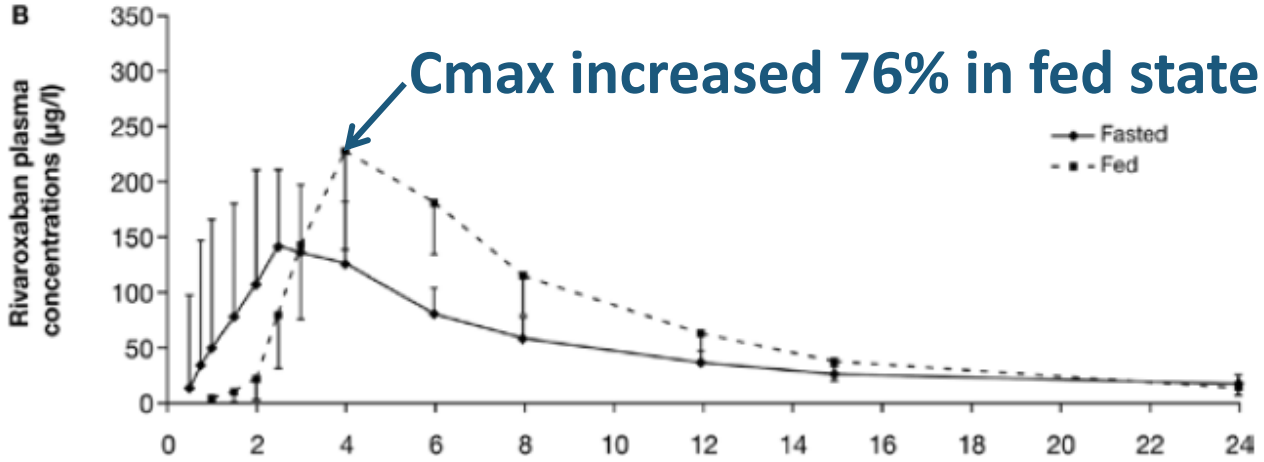
Hakeam H. et al J Thomb Thrombolysis 2017

Rivaroxaban Absorption - Food Effect

10 mg Dose



20 mg Dose



Cmax increased 76% in fed state

Stampfuss J. et al. Int J Clin Pharm 2013

DOAC Absorption - GI Surgery

- Limited data (Case reports/case series)

DOAC	Surgical intervention				
	Total gastrectomy	Partial gastrectomy	RYGB	Distal resection and SBS	Colectomy
Rivaroxaban	Reduced up to 56% Janssen Pharmaceuticals Inc [34]	Possibly reduced	Possibly reduced	Unlikely affected four cases Christensen et al. [37], Douros et al. [45]	Unlikely affected
Dabigatran	Possibly reduced	Possibly reduced	Possibly reduced one case Daniel Lee et al. [44]	Possibly reduced one case Douros et al. [45]	Unlikely affected
Apixaban	Unlikely affected	Unlikely affected	Unlikely affected	Possibly reduced	Possibly reduced
Edoxaban	Possibly reduced	Possibly reduced	Possibly reduced	Unlikely affected	Unlikely affected

DOACs direct acting oral anticoagulants, *SBS* short bowel syndrome, *RYGB* Roux-en-Y gastric bypass

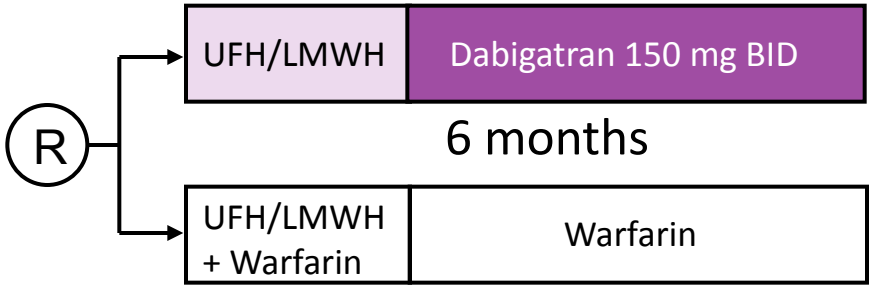
Hakeam H. et al J Thomb Thrombolysis 2017

Advantages of DOACs

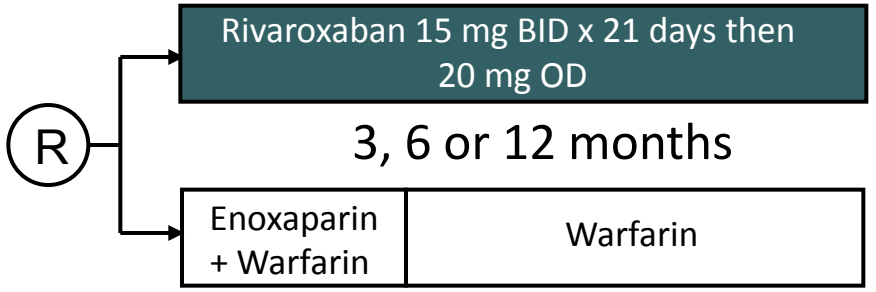
Feature	Warfarin	DOACs
Onset	Slow	Rapid
Offset	Long	Short
Dosing	Variable	Fixed
Food effect	Yes	No
Lab monitoring	Yes	Not required
Drug interactions	Many	Few

Phase III Studies: DOAC vs. warfarin

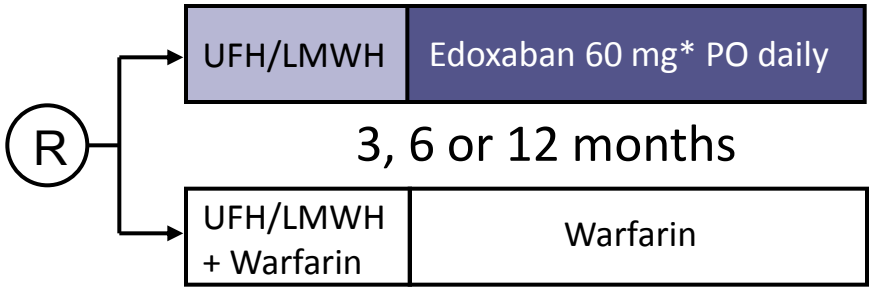
Dabigatran: RE-COVER and RE-COVER II



Rivaroxaban: EINSTEIN DVT AND EINSTEIN PE

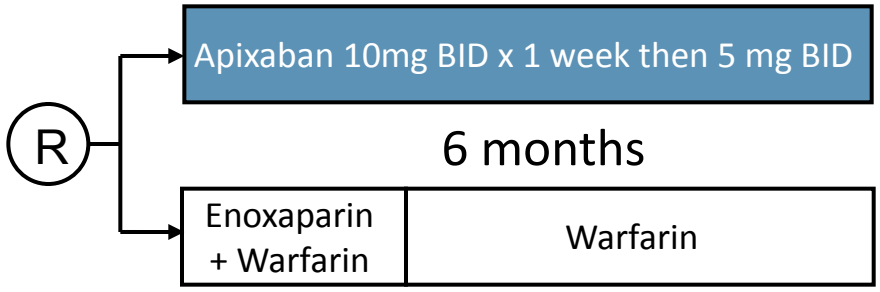


Edoxaban: HOKUSAI



30 mg* PO daily if CrCl 30-50 or weight<60kg or use of P-gp inhibitor

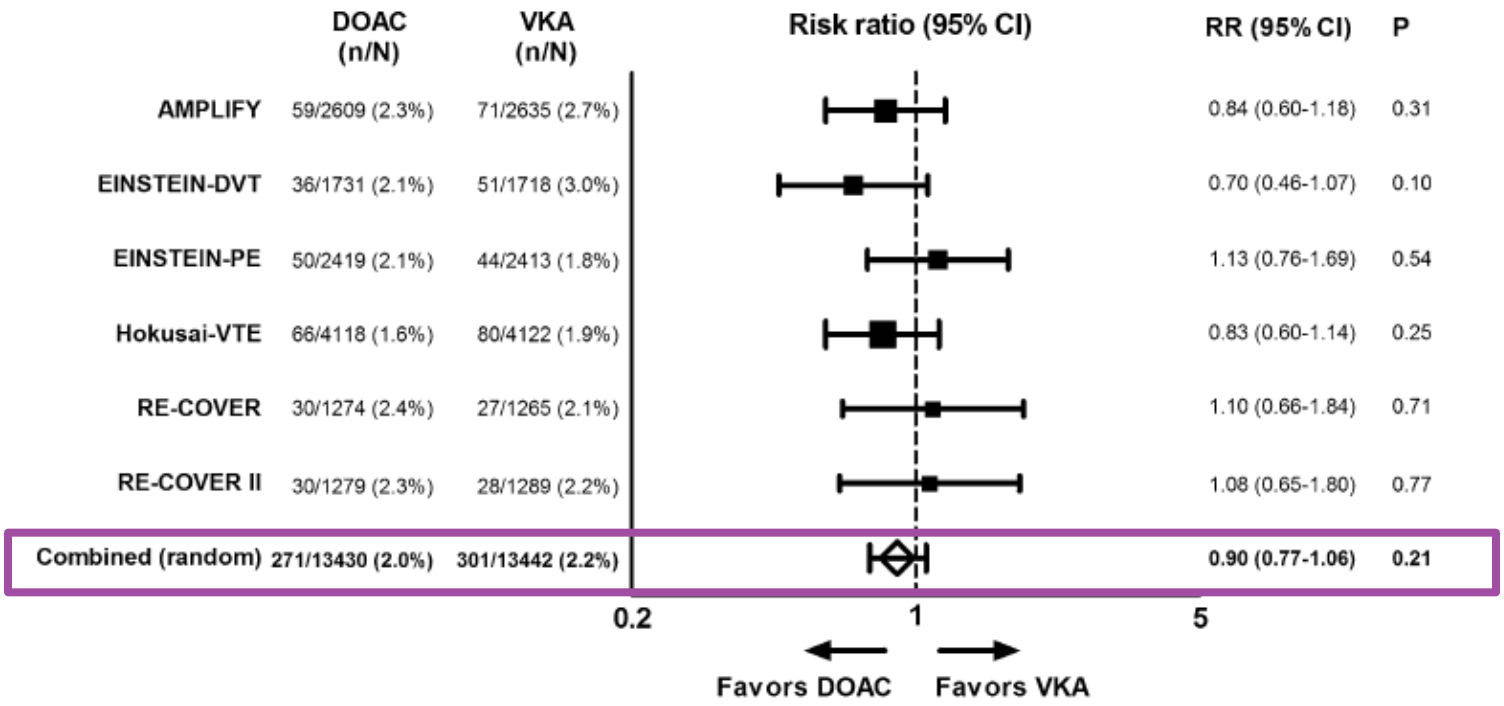
Apixaban: AMPLIFY



Schulman S NEJM 2009; Schulman S Circulation 2013; EINSTEIN Investigators NEJM 2012; EINSTEIN PE Investigators NEJM 2012; Prins MH Thrombosis Journal 2013; Agnelli G NEJM 2013; HOKUSAI-VTE Investigators NEJM 2013

DOACs vs. Warfarin – pooled data

Recurrent VTE

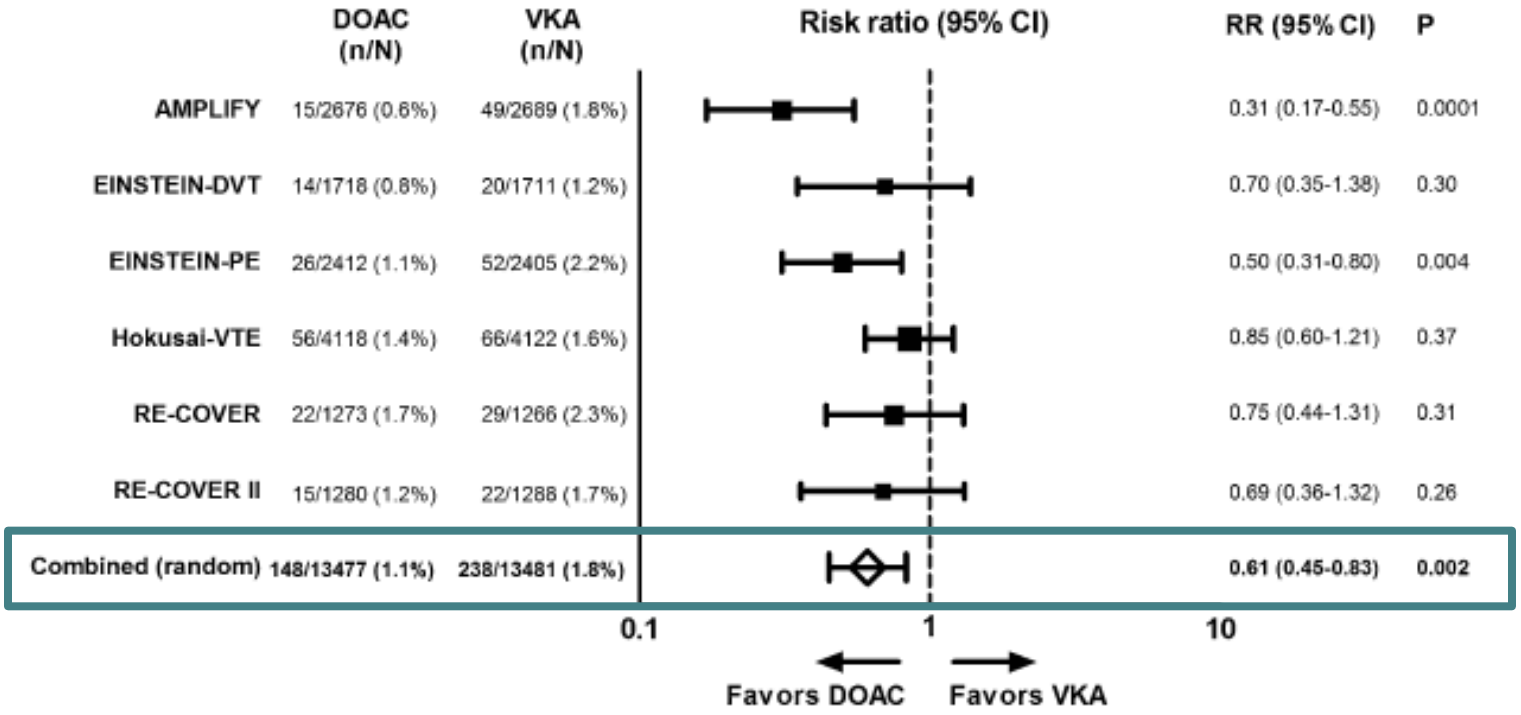


All DOACs non-inferior to warfarin for prevention of recurrent VTE
RR 0.90 (95% CI 0.77-1.06)

Van Es N. et al Blood 2014

DOACs vs. Warfarin – pooled data

Major Bleeding

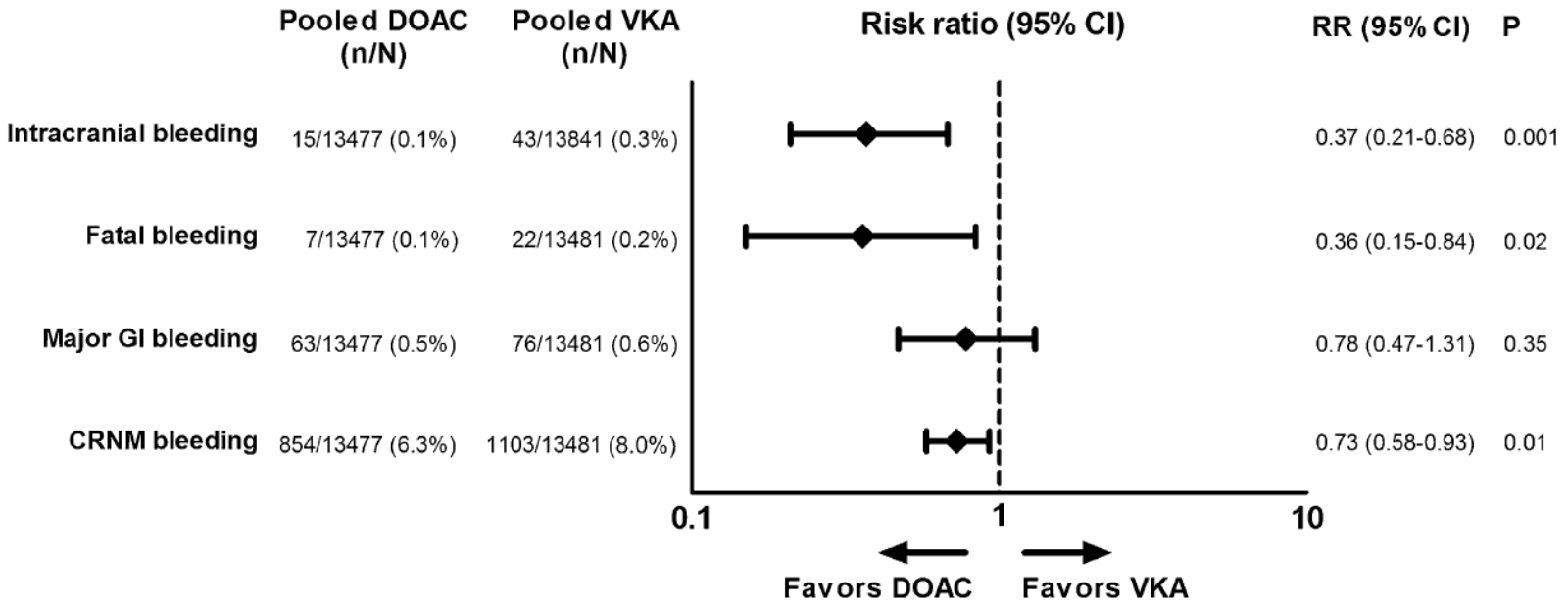


Similar or reduced risk of major bleeding
RR 0.61 (95% CI 0.45-0.83)

Van Es N. et al Blood 2014

DOACs vs. Warfarin – pooled data

Bleeding Subgroups



Reduced risk of intracranial bleeding
RR 0.63 (95% CI 0.21-0.68)

Van Es N. et al Blood 2014

DOACs in Cancer Patients

- What data exits for the use of DOACs in cancer patients?

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  - Randomized studies of DOAC vs. LMWH in cancer population
  - Observational data

DOACs in Cancer Patients

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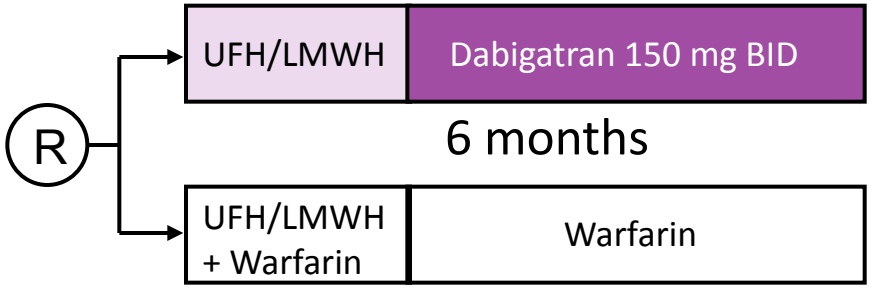
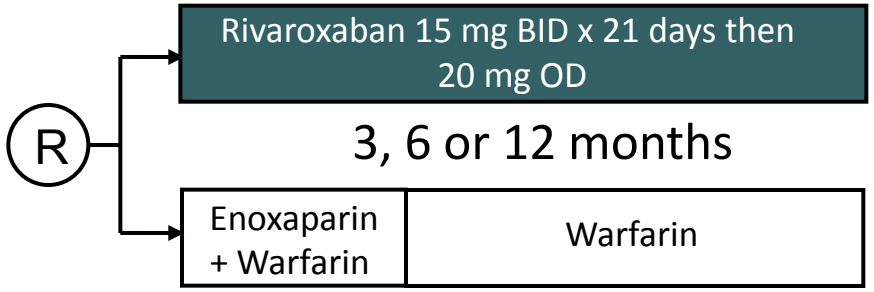
Cancer Patients in Phase III Studies

Dabigatran: RE-COVER and RE-COVER II



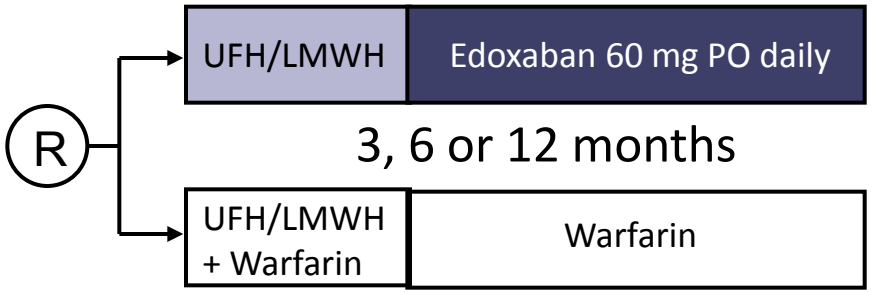
9.5% active cancer

Rivaroxaban: EINSTEIN DVT AND EINSTEIN PE



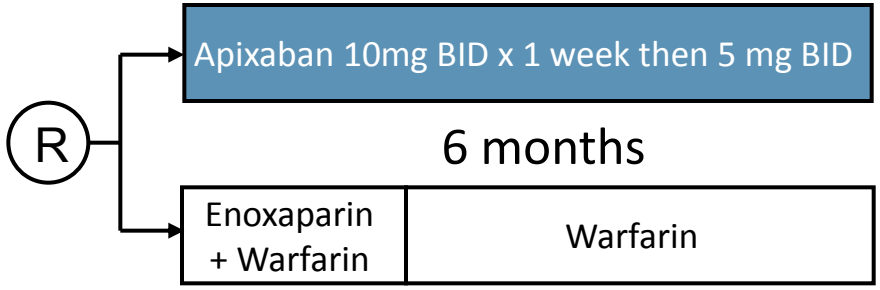
9.2% active cancer

Edoxaban: HOKUSAI



9.4% active cancer

Apixaban: AMPLIFY



5.3% active cancer

Schulman S NEJM 2009; Schulman S Circulation 2013; EINSTEIN Investigators NEJM 2012; EINSTEIN PE Investigators NEJM 2012; Agnelli G NEJM 2013; HOKUSAI-VTE Investigators NEJM 2013

Cancer Patients in Phase III Studies

- All cancer patients were highly selected
  - Clinically well
  - No bleeding
  - No significant renal/hepatic dysfunction
  - Heterogeneous definition of active cancer

Cancer Patients in Phase III Studies

- Meta-analysis of RECOVER, EINSTEIN, HOKUSAI and AMPLIFY studies
  - 1132 cancer patients included
  - DOACs did not show a significant reduction in the risk of recurrent cancer-associated VTE compared to Vitamin K antagonists
    - **RR 0.66 (95% CI 0.39 – 1.11)**

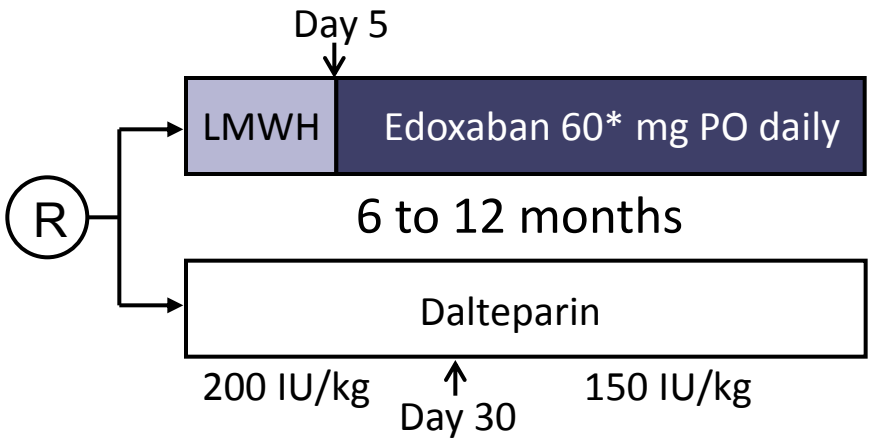
Khorana A. et al J Thromb Thrombolysis 2016

DOACs in Cancer Patients

- What data exits for the use of DOACs in cancer patients?
  - Subgroup analysis of DOAC vs. warfarin RCTs
  - **Randomized studies of DOAC vs. LMWH in a cancer population**
  - Observational data

Hokusai VTE and SELECT-D Studies

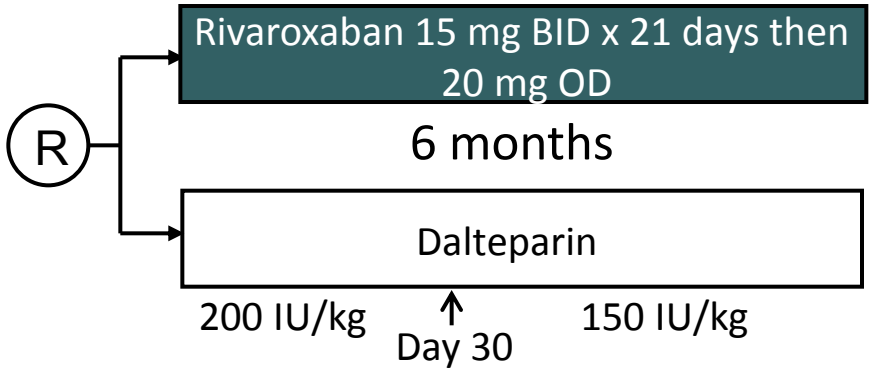
Edoxaban: HOKUSAI VTE Cancer



30* mg PO daily if CrCl 30-50 or weight<60kg or use of P-gp inhibitor

- Open-label, non-inferiority study
- **Primary outcome**: composite of recurrent VTE or major bleeding
- **Published 2017**

Rivaroxaban: SELECT-D



- Open-label, pilot study
- **Primary outcome**: recurrent VTE
- **Published 2018**

Raskob G.E. et al NEJM 2017; Young A. JCO 2018

Hokusai VTE and SELECT-D Studies

Edoxaban: HOKUSAI VTE Cancer

Inclusion Criteria

- Active cancer or diagnosed within 2 years of randomization
- Objectively confirmed symptomatic or incidental proximal DVT/PE
- Age≥ 18 years
- Plan for 6 months of LMWH

Rivaroxaban: SELECT-D

Inclusion Criteria

- Active cancer
- Objectively confirmed symptomatic or incidental PE or symptomatic proximal DVT
- ECOG 1-2
- Age≥ 18 years
- Adequate hematologic function (hemoglobin and platelets >100)
- Adequate renal and hepatic function (LE < 3xULN and CrCl ≥30)

Active cancer: diagnosed or treated within 6 months, metastatic or recurrent cancer, hematologic cancer not in remission

Hokusai VTE and SELECT-D Studies

Edoxaban: HOKUSAI VTE Cancer

Exclusion criteria

- Active bleeding
- ECOG 3/4 (life expectancy <3 mo)
- CrCl < 30 mL/min
- AST/ALT> 3x ULN or t bili>2x ULN
- Platelets <50
- Uncontrolled HTN
- Thrombolysis or IVC filter

Rivaroxaban: SELECT-D

Exclusion criteria

- Active bleeding
- Esophageal/GE junction cancer**
- Weight <40 kg
- AST/ALT> 3x ULN or significant hepatic disease
- Platelets <50
- Uncontrolled HTN

Hokusai VTE and SELECT-D Studies

	Rivaroxaban (SELECT-D)	Edoxaban (HOKUSAI VTE Cancer)
Total Number of Patients	406	1046
Male Sex	52.7%	51.6%
Active Cancer	100%	97.9%
Metastatic disease	58.1%	52.9%
Incidental PE	52.4%	32.5%
Active Cancer Treatment	69.5%	72.4%

Raskob G.E. et al NEJM 2017; Young A. et al JCO 2018

Hokusai VTE and SELECT-D Studies

	Rivaroxaban (SELECT-D)		Edoxaban (HOKUSAI VTE Cancer)	
Treatment	**Riva**	LWMH	**Edox**	LWMH
Number of Patients	**203**	203	**522**	524
Recurrent VTE or major bleeding	**--**	--	**12.8%**	13.5%
Recurrent VTE	**4.0%**	11.0%	**7.9%**	11.3%
Major bleeding	**4.0%**	3.0%	**6.9%**	4.0%
Major bleeding + CRNMB	**17.0%**	5.0%	**18.6%**	13.9%
Death	**30.0%**	26.0%	**39.5%**	36.6%

Raskob G.E. et al NEJM 2017; Young A. et al JCO 2018

CRNMB: clinically relevant non-major bleeding

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Edoxaban non-inferior to LMWH for recurrent VTE or major bleeding
HR 0.97 (95% CI 0.70-1.36)

Raskob G.E. et al NEJM 2017; Young A. et al JCO 2018

CRNMB: clinically relevant non-major bleeding

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Death	**30.0%**	26.0%	**39.5%**	36.6%

Edoxaban HR 0.71 (95% CI 0.48-1.06)
Rivaroxaban HR 0.43 (95% CI 0.19 to 0.99)

Raskob G.E. et al NEJM 2017; Young A. et al JCO 2018

CRNMB: clinically relevant non-major bleeding

Hokusai VTE and SELECT-D Studies

*Most major and CRNMB bleeding events were GI bleeds

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Treatment	**Riva**	LWMH	**Edox**	LWMH
Number of Patients	**203**	203	**522**	524
Recurrent VTE or major bleeding	**--**	--	**12.8%**	13.5%
Recurrent VTE	**4.0%**	11.0%	**7.9%**	11.3%
Major bleeding*	**4.0%**	3.0%	**6.9%**	4.0%
Major bleeding + CRNMB*	**17.0%**	5.0%	**18.6%**	13.9%
Death	**30.0%**	26.0%	**39.5%**	36.6%

Edoxaban significantly more major bleeding then LMWH
Rivaroxaban significantly more CRNMB and CRNMB/MB then LMWH

Raskob G.E. et al NEJM 2017; Young A. et al JCO 2018

CRNMB: clinically relevant non-major bleeding

Study Limitations

- **Hokusai study**
  - Used non-validated score (in addition to ISTH criteria of major bleeding) to grade bleeding events

- **Select D study**
  - Pilot study
  - Closed early
  - **Primary end-point adjudicated post-hoc**
  - Included “other” VTE in primary endpoint

DOAC Limitations in Cancer Patients

- Unreliable administration and absorption in patients with n/v, diarrhea and mucosal erosion
- **Higher risk of bleeding**
- **Liver and renal dysfunction is common** in cancer patients
- **Drug interactions may be clinically important**
- Lack of readily available measurement in BC

DOAC Limitations in Cancer Patients

- No antidote in Canada (except dabigatran)
- Paucity of clinical data
  - RCT data compared to LMWH only available for edoxaban and rivaroxaban

Upcoming RCTs

- Apixaban
  - CARAVAGGIO (1168 patients, completion June 2019)
- Rivaroxaban
  - CONKO_011 (450 patents, completion Dec 2018)
  - CASTA-DIVA (159 patients, completion April 2018)

clinicaltrials.gov

Guidelines for CAT

- ACCP Guidelines (2016)
  - In patients with DVT of the leg or PE and cancer as long-term (first 3 months) anticoagulant therapy, we **suggest LMWH** over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).

- ASCO Guidelines (2015)
  - **LMWH** is recommended for the **initial 5 to 10 days** of treatment of established deep vein thrombosis and pulmonary embolism **as well as for long-term secondary prophylaxis for at least 6 months**

Kearon C. et al CHEST 2016, Lyman G. et al JCO 2015

Guidelines for CAT

- NCCN Guidelines (2018)
  - Category 1: dalteparin, edoxaban
  - Category 2A: enoxaparin, rivaroxaban, fondaparinux, apixban, dabigatran
  - Category 2B: UFH

Summary

- DOACs (rivaroxaban and edoxaban) are an option for CAT

- Patients must be carefully selected
  - Low bleeding risk (should avoid in upper GI tumours)
  - No significant renal/hepatic dysfunction
  - No drug interactions
  - No significant nausea/vomiting

Case –Anticoagulant Options

- Anticoagulant options for Mr. J.S.
  - DOAC
  - LWMH
  - LMWH (or UFH) bridging to warfarin

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- Anticoagulant options for Mr. J.S.
  - DOAC
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BUT… how is he going to pay for his anticoagulant?

Drug Coverage in BC

- **Edoxaban**
  - No yet covered by pharmacare
  - Cost 100-150$ per month
- **Rivaroxaban**
  - **Covered by pharmacare for first 6 months** for acute VTE treatment (cost 100-150$ per month)
  - Patient must pay deductible
  - No coverage beyond first 6 months (unless there is a patient specific contraindication to warfarin)

Drug Coverage in BC

- **LMWH** (dalteparin, tinzaparin)
  - **Covered for 6 months at a time** (cost up to 1500$ per month depending on dose)
  - Patient must pay deductible
  - Covered by pharmacare ONLY if warfarin cannot be used due to **contraindication or drug interaction**

Questions?