Appraisal of the Caravaggio Trial

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer | New Engl J Med 2020;382:1599-607

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Presenter Disclosure

I have no current or past relationships with commercial entities

Speaking Fees for current program:

- I have received a speaker's fee from the Canadian Society of Hospital Pharmacists BC Branch for this learning activity

Commercial Support Disclosure

This learning activity has received no financial or in-kind support from any commercial or other organization

Learning Objectives

By the end of this session, the learner will be able to:

1. List the factors associated with increased risk of venous thromboembolism (VTE) in cancer patients
2. Summarize the results and limitations of the existing literature informing the use of direct oral anticoagulants (DOACs) for VTE in cancer patients
3. Describe the methodology and results of the Caravaggio Trial
4. Determine how to apply the results of this trial to the patients in your practice

Abbreviations

MC: multicenter
R: randomized
NI: noninferiority
ECOG: Eastern Cooperative Oncology Group
Tx: treatment
VTE: venous thromboembolism
HR: hazard ratio
NS: not statistically significant
DVT: deep vein thrombosis
PE: pulmonary embolism
CYP: cytochrome P450 enzyme
PLT: platelet
HGB: hemoglobin
CrCl: creatinine clearance
mITT: modified intention-to-treat
GI: gastrointestinal
GU: genitourinary
CRNMB: clinically relevant nonmajor bleeding
BRAF: B-raf protein

VTE and Cancer

Mechanism

↑ Procoagulant molecules

↓ Natural anticoagulants

↑ Inflammatory cytokines

Cancer Associated

Site

Tumor type

Extent of disease

Chemotherapy choice

Patient Specific

Surgery

Co-morbidities

Central venous catheter

Cancers 2008;10:380

CLOT	HOKUSAI VTE CANCER	SELECT-D	ADAM-VTE
Dalteparin vs warfarin	Edoxaban vs Dalteparin	Rivaroxaban vs Dalteparin	Apixaban vs Dalteparin
MC, R, open-label 6 months	MC, NI, open-label 6 to 12 months	MC, R, open-label 6 months	R, open-label 6 months
N = 676	N = 1046	N = 406	N = 300
62Y, ECOG 1-2, active tx (78%)	64Y, ECOG 0-1, active tx (72%)	67Y, ECOG 0-1, active tx (60%)	64Y, ECOG 0-1, active tx (74%)
Recurrent VTE: 9% vs 17% (HR 0.48, 0.3-0.77)	Recurrent VTE or major bleed: 12.8% vs 13.5% (HR 0.97, 0.7-1.36)*	Recurrent VTE: 4% vs 11% (HR 0.43, 0.19-0.99)	Recurrent VTE: 0.7% vs 6.3% (HR 0.1, 0.01-0.78)
Major Bleed: 6% vs 4% (NS)	* P 0.006 for non-inferiority	Major Bleed: 6% vs 4% (NS)	Major Bleed: 0% vs 1.4%

N Engl J Med 2003;349:146-53 | N Engl J Med 2018;378:615-24 | Clin Oncol 2018;36:2017-23 | J Thromb Haemost 2020;18(2):411-21

Caravaggio Overview

Design	Multicenter, randomized, open-label, noninferiority
Patients N = 1155	**Key Inclusion** ✓ Symptomatic or incidental proximal DVT or PE ✓ Cancer diagnosis * Active: within 6 months of study inclusion History: within 2 years before study inclusion **Key Exclusion** × ECOG 3 or 4, life expectancy less than 6 months × Strong CYP 3A4 inducer/inhibitor, anti-platelet therapy × PLT less than 75, HGB less than 80, CrCl less than 30 ml/min × Hepatitis, cirrhosis

* excluded: basal-cell, primary brain, known intracerebral metastases, acute leukemia

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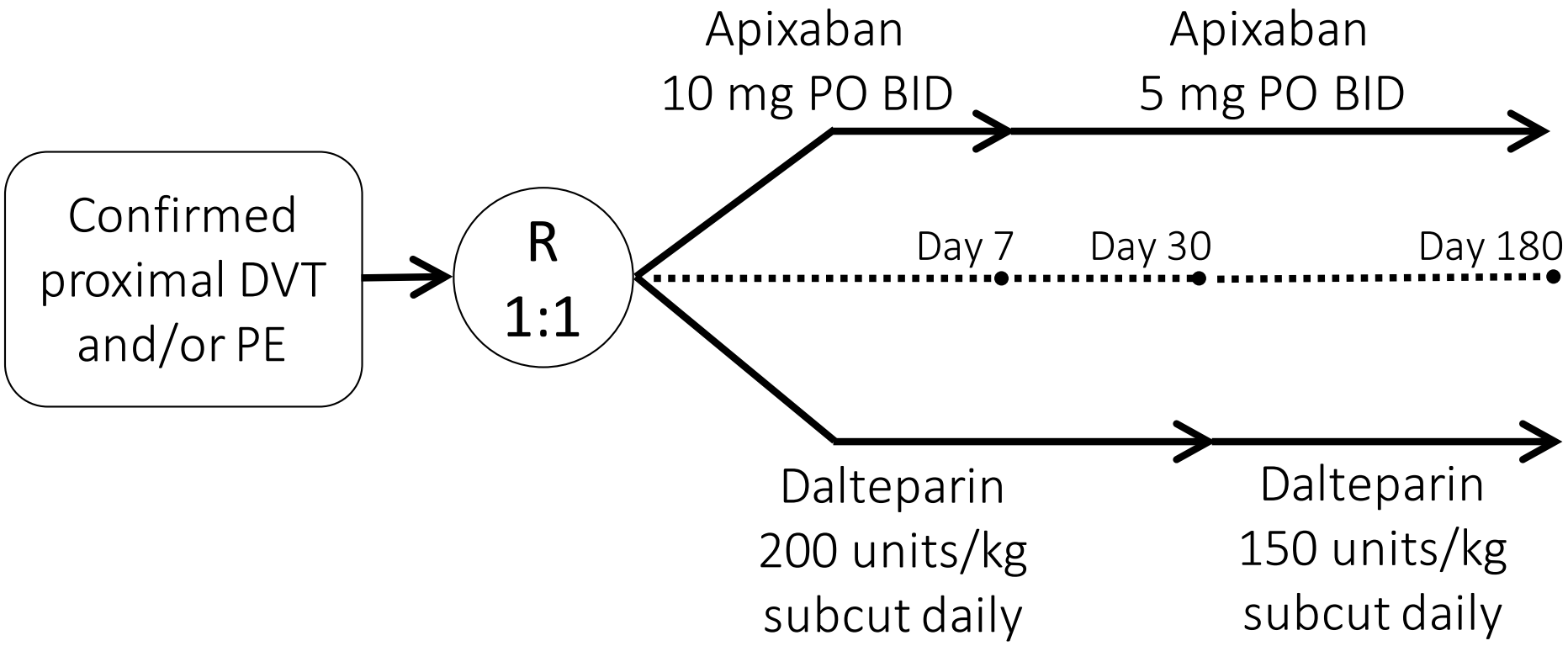
Caravaggio Overview



Primary Outcome:
Recurrent VTE

Principal Safety Outcome:
Major Bleeding

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Patient Characteristics

67 years old
Average 76 kg

32% ECOG 0
49% ECOG 1
19% ECOG 2

47% DVT only
53% PE ± DVT
80% Symptomatic VTE
20% Incidental VTE

97% Active cancer

7% Pancreatic
4% Gastric
18% Lung
12% GU
10% GYNE

14% Breast
20% Colorectal
2% Head and neck

61% Active treatment
25% Treatment within 6 months

19% Antimetabolite
10% Hormonal therapy
3% Alkylating agent
2-3% Anthracycline
1-2% Vinca alkaloids
2-3% Bevacizumab
4-5% Kinase Inhibitors

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Primary Outcome

	Apixaban N = 576	Dalteparin N = 579	Hazard Ratio	P value
Recurrent VTE				
mITT	32 (5.6%)	46 (7.9%)	0.63 (0.37-1.07)	< 0.001 for non-inferiority ‡
Per-protocol	27 (5.2%) *	41 (8%) *	0.62 (0.34-1.14)	

* Per-protocol: apixaban N = 524, dalteparin N = 512

‡ Non-inferiority Margin = 2

Recurrent DVT	13 (2.3%)	15 (2.6%)	0.87 (0.34-2.21)
Recurrent PE	19 (3.3%)	32 (5.5%)	0.54 (0.29-1.03)
Fatal PE	4 (0.7%)	3 (0.5%)	1.93 (0.4-9.41)

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Principal Safety Outcome

	Apixaban N = 576	Dalteparin N = 579	Hazard Ratio	P value
Major Bleeding	22 (3.8%)	23 (4%)	0.82 (0.4-1.69)	0.6
Major GI Bleed	11 (1.9%)	10 (1.7%)		
Upper	5	6	1.05 (0.44-2.5)	
Lower	6	4		
Major Non-GI Bleed	11 (1.9%)	13 (2.2%)		
Intracranial	0	2		
GU	4	1	0.68 (0.21-2.2)	
Muscle	0	2		
Lungs	1	1		

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Secondary Outcomes

	Apixaban N = 576	Dalteparin N = 579	Hazard Ratio
Recurrent VTE or major bleeding	51 (8.9%)	66 (11.4%)	0.7 (0.45-1.07)
CRNMB	52 (9%)	35 (6%)	1.42 (0.88-2.3)
Cutaneous	6	4	
GU, hematuria	15	7	
GU, vaginal bleeding	4	3	
Upper airways	12	3	
GI	11	15	
Major or CRNMB	70 (12.2%)	56 (9.7%)	1.16 (0.77-1.75)
Death from any cause	135 (23.4%)	153 (26.4%)	0.82 (0.62-1.09)

CRNB, Clinical relevant non-major bleeding

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Author's Conclusion

"Apixaban is noninferior to dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleeding"

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Limitations

Trial Design	Generalizability
Industry sponsored trial Open-label design	Clinically relevant tumor groups excluded Small proportion of GI cancers American population accounted for 11%

Dose capping of dalteparin
Dalteparin dose adjustment and platelet count
Inclusion of upper extremity DVT
Duration/follow-up

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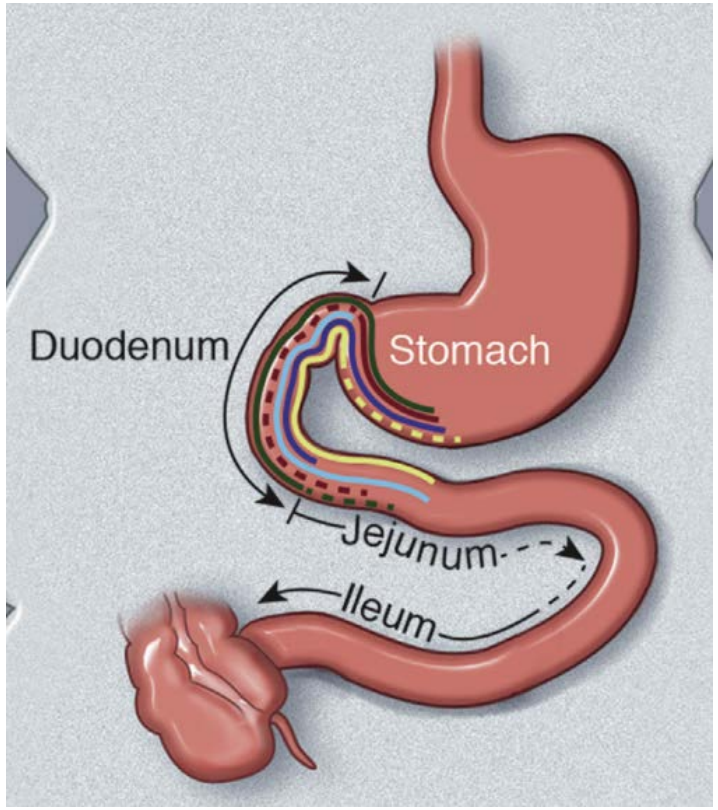
DOAC Absorption and Surgical Patients



	Site of Absorption	Distal Resection	Colectomy
Apixaban	Throughout, 55% in distal and ascending colon	Possibly reduced	Possibly reduced
Rivaroxaban	Stomach	Unlikely affected	Unlikely affected
Edoxaban	Proximal small intestine	Unlikely affected	Unlikely affected

J Thromb Thrombolysis 2017;43:343-351

Am J Med 2017;130:517-524

Application Considerations

Apixaban-oncology therapy interactions

- ↑ apixaban levels: tyrosine kinase inhibitors, retinoic acid derivatives
- ↓ apixaban levels: BRAF kinase inhibitors

Renal and liver dysfunction
Mucositis risk and variability in absorption

Optimal duration: EVE trial, API-CAT trial
Cost

J Oncol Pract 2014;10:e255-68

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