DOACs for VTE Treatment and Secondary Prophylaxis in Cancer Patients: A New Direction

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Objectives

- Describe cancer-associated thrombosis (CAT)
- Identify challenges with VTE treatment in cancer patients
- Outline existing guideline recommendations regarding VTE treatment
- Assess use of direct oral anticoagulants (DOACs) in patients with cancer in current literature
- Recommend anticoagulation therapy for patients with CAT

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Abbreviations

BID	Twice daily	**PE**	Pulmonary embolism
CAT	Cancer-associated thrombosis	**QDay**	Once daily
DOAC	Direct oral anticoagulant	**QOL**	Quality of life
DVT	Deep vein thrombosis	**RCT**	Randomized controlled trial
ECOG	Eastern Cooperative Oncology Group	**SubQ**	Subcutaneous
JCO	Journal of Clinical Oncology	**TTR**	Time in therapeutic range
LMWH	Low molecular weight heparin	**VKA**	Vitamin K antagonist
NCCN	National Comprehensive Cancer Network	**VTE**	Venous thromboembolism

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Patient Case: K.T.

51 y/o AA female

CC: Lower left leg pain x 3 days

HPI: Earlier this week, K.T. was discharged after a 2-day hospital stay where she was diagnosed with invasive ductal carcinoma of the breast. She returns to the hospital today and an ultrasound confirms a lower extremity DVT

PMHx: Anxiety (on hydroxyzine PRN), glaucoma (no home medications)

F/SHx: Lives at home with sister and son, denies T/E/D, unfunded

Allergies: SMZ/TMP (reaction unknown)

T	98.5	**WBC**	12.5	**Na**	136	**Ht (in)**	68"
HR	81	**Hgb**	10.1	**K**	3.9	**Wt (kg)**	81.4
BP	108/73	**Plt**	428	**BUN**	8	**BMI**	27.29
INR	1.22	**PTT**	22	**SCr**	0.8	**CrCl**	85

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Cancer-Associated Thrombosis

- Patients with cancer have a significant increased risk of VTE
  - 7-fold increase compared with non-cancer patients
  - Comprises 18% of all incident VTE events
  - Incident VTE increasing due to advances in technology
- 2nd leading cause of death in cancer patients
- Higher rate of complications and VTE recurrence
  - 21% annual risk for recurrent VTE
  - 12% annual risk for bleeding complication

Blom J.W., et al. JAMA 293: 715–722
Elyamany G., et al. Clinical Medicine Insights: Oncology 2014:8 129–137

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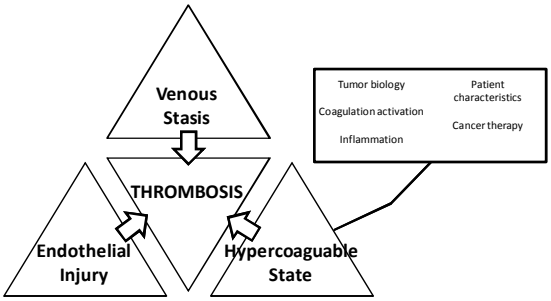
Etiology



Piazza G. Circulation. 2013;128(24):2614-8.

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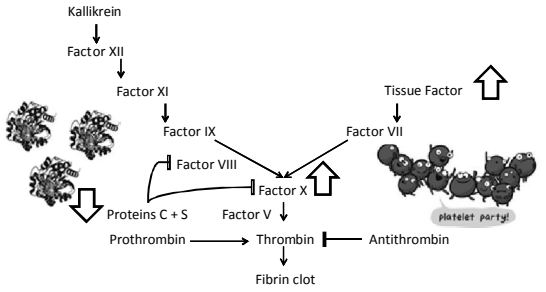
Pathophysiology



Adams RL, et. al., Nephrology (Carlton). 2009;14(5):462-70.

Risk Factors

Table 1: Risk factors for development of VTE in cancer patients

General	Treatment-Related
• Active cancer • Advanced cancer • High risk cancer • Regional lymphadenopathy • Familial/acquired hypercoagulability • Comorbidities • Poor performance status • ECOG score • Older age • Previous VTE	• Major surgery • Central venous catheter • Angiogenesis inhibitor therapy with high-dose dexamethasone • Hormonal therapies
	Modifiable
	• Smoking • Obesity • Activity level/exercise

Elyamany G, et al. Clin Med Insights Oncol. 2014;8:129-37.
National Comprehensive Cancer Network. Cancer-Associated Venous Thromboembolic Disease. Version 1.2016.

Goals of Treatment

- Prevent fatal PE and recurrent VTE
- Reduce short-term morbidities associated with VTE
- Minimize side effects and risk of bleeding
- Maximize patient compliance

Coleman R, Maccallum P. Br J Cancer. 2010;102 Suppl 1:S17-23.

DRUG THERAPY

Traditional Anticoagulants

Table 2: Traditional anticoagulant drug classes and FDA approved dosing

Class	Drug(s)	VTE Dosing
Unfractionated heparin (UFH)	Heparin	IV: 80 units/kg bolus then 18 units/kg/hour SubQ: 333 units/kg followed by 250 units/kg Q12hr
Low Molecular Weight Heparin (LMWH)	Enoxaparin (Lovenox®)	SubQ: 1 mg/kg Q12hr
	Dalteparin (Fragmin®)	SubQ: 200 units/kg QDay for 30 days then 150 units/kg QDay
	Tinzaparin (Innohep®)	SubQ: 175 anti-Xa units/kg QDay
Vitamin K Antagonist (VKA)	Warfarin (Coumadin®)	Initial: 2-5 mg QDay PO; adjust dose to INR of 2-3

Heparin sodium in 0.9% sodium chloride [prescribing information]. Lake Forest, IL: Hospira; April 2015.; Coumadin (warfarin) [prescribing information]. Princeton, NJ: Bristol-Meyers Squibb; December 2015.; Lovenox (enoxaparin) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; October 2015.; Fragmin (dalteparin) [prescribing information]. Woodcliff Lake, NJ: Eisai; September 2015.; Innohep (tinzaparin) [package insert]. Parsippany, NJ: LEO Pharma Inc; August 2013.

Direct Oral Anticoagulants (DOACs)

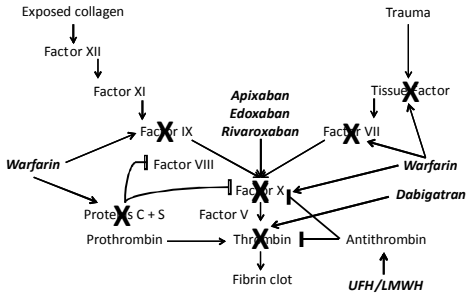
Table 3: Direct oral anticoagulant drug classes and FDA approved dosing

Class	Drug	VTE Dosing
Direct Thrombin Inhibitor	Dabigatran (Pradaxa®)	150 mg BID†
Factor Xa Inhibitor	Apixaban (Eliquis®)	10 mg BID for 7 days then 5 mg BIDΔ
	Edoxaban (Savaysa®)	60 mg QDay†*
	Rivaroxaban (Xarelto®)	15 mg BID with food for 21 days then 20 mg Qday with food‡

†Requires bridging with parenteral heparin or LWMH
Δ Patients with SCr >2.5 or CrCl <25 mL/minute were excluded from clinical trials; exposure may be increased in patients <50kg and decreased in patients >120 kg
*Patient weight ≤60 kg: 30 mg QDay; Concomitant therapy with specific P-gp inhibitors (ie, verapamil, quinidine; the short-term use of azithromycin, clarithromycin, erythromycin, oral itraconazole, oral ketoconazole): 30 mg Qday
‡Avoid use if CrCl <30 mL/min

radaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; November 2015
iquis (apixaban) [prescribing information]. Princeton, NJ: Bristol-Meyers Squibb; July 2016.
avaysa (edoxaban) [prescribing information]. Parsippany, NJ: Daiichi Sankyo; January 2015.

Drug Targets



Adams RL, et. al., Nephrology (Carlton). 2009;14(5):462-70.

Current Guideline Recommendations

CLOT: Lee A.Y., et al. 2008

Design	• Open-label, RCT • N = 676
Population	• Patients with active cancer • Acute, symptomatic proximal DVT, PE, or both
Interventions	• Dalteparin alone vs. dalteparin followed by a VKA (e.g., warfarin) • Patients treated for 6 months in both groups
Results	• Recurrent VTE: 9% in the dalteparin group vs.17% in the VKA group (p=0.002) • Major bleeding: 6% in the dalteparin group vs. 4% in the VKA group (p=0.27) • Any bleeding: 14% in the dalteparin group vs. 19% in the VKA group (p=0.09)
Conclusions	• Dalteparin more effective than VKA in reducing the risk of recurrent VTE without increased risk of bleeding

Lee, A.Y., et al. N Engl J Med 2003;349:146-53.

CATCH: Lee A.Y., et al. 2015

Design	• Open-label, superiority, RCT • N = 900
Population	• Patients with active cancer • Acute, symptomatic proximal DVT, PE, or both
Interventions	• Tinzaparin alone vs. tinzaparin followed by a VKA (i.e., warfarin) • Patients treated for 6 months in both groups
Results	• Recurrent VTE: 6.9% in the tinzaparin group vs.10% in the VKA group (p=0.07) • Major bleeding: 2.7% in the tinzaparin group vs. 2.4% in the VKA group (p=0.77) • CRNM: 10.9% in the tinzaparin group vs. 15.3% in the VKA group (p=0.004)
Conclusions	• Tinzaparin was not superior to VKA in reducing recurrent VTE, overall mortality or major bleeding but was associated with a lower rate of CRNM bleeding

Lee A.Y., et al. JAMA. 2015;314(7):677-86.

Guideline Consensus

JCO (2014)	• LMWH is recommended for the initial treatment for VTE • Treatment with LMWH for at least 6 months • **DOACs are not recommended**
NCCN (2016)	• LMWH preferred • Minimum 3 months of therapy is recommended • **DOACs are not recommended**
CHEST (2016)	• **LMWH over VKA and DOACs** • No preference for DOAC or VKA when LMWH is not used • Extended therapy (>3 months) with periodic reassessment

Lyman GH, et al. J Clin Oncol. 2015;33(6):654-6.
National Comprehensive Cancer Network. Cancer-Associated Venous Thromboembolic Disease. Version 1.2016.
Kearon, C., et al. CHEST 2016; 149(2):315-352

Patient Case: K.T.

Clinical course: With confirmation of her DVT, K.T. is started on enoxaparin 80 mg (1mg/kg) subQ q12hr and warfarin 5 mg PO daily by her IM team. Her baseline INR is 1.22.

It is likely K.T. would need to undergo surgery to place a port for chemotherapy administration. No procedure date is scheduled at this time. Since admission her INR values are as follows:

	Day 1	Day 2	Day 3	Day 4	Day 5
Warfarin dose:	5 mg	5 mg	5 mg	7.5 mg	Not given yet
INR:	1.22	1.25	1.23	1.22	1.34

Patient Case: K.T.

Today is day 5. Based on current guideline recommendations, what would you suggest to the primary team to manage K.T.'s DVT treatment?

	Day 1	Day 2	Day 3	Day 4	Day 5
Warfarin dose:	5 mg	5 mg	5 mg	7.5 mg	Not given yet
INR:	1.22	1.25	1.23	1.22	1.34

A) Continue as is until her INR is 2-3, then discontinue enoxaparin

B) Discontinue warfarin and continue therapeutic enoxaparin

C) Discontinue warfarin and enoxaparin, then start a heparin drip

D) Her INR is therapeutic, enoxaparin can be discontinued

DOAC Major Clinical Trials

Subgroup Analysis

EINSTEIN: Prins, M.H., et al. 2013

Design
- Pooled subgroup analysis of the EINSTEIN-DVT and EINSTEIN-PE trials
- Open-label, non-inferiority, phase III RCT
- Separated for DVT or PE and randomized 1:1 to treatment or control

Population
- History of cancer; active cancer at baseline; or cancer diagnosed during the trial
- Acute, symptomatic proximal DVT, PE, or both

Interventions
- Study drug: Rivaroxaban 15 mg twice daily for 21 days then 20 mg daily
- Comparator: Enoxaparin 1mg/kg twice daily followed by VKA; INR goal 2-3
- Intended treatment periods of 3, 6, or 12 months

Prins, M.H., et al. Thromb. J. 2013;11:21.
Bauersachs R, et al. N Engl J Med. 2010;363(26):2499-510.

EINSTEIN: Results

Outcome	History of Cancer		Active Cancer		Cancer Diagnosis During Study	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
Primary Efficacy Outcome†	N=233	N=236	N=258	N=204	N=96	N=97
Recurrent VTE	2%	2%	2%	4%	10%	12%
Secondary Efficacy Outcome†						
Mortality	2%	2%	15%	18%	21%	18%
Net clinical benefit	4%	4%	5%	9%	14%	20%
Primary Safety Outcome‡	N=231	N=236	N=257	N=202	N=96	N=96
Major bleeding	<1%	2%	2%	4%	3%	7%
Clinically relevant bleeding	11%	9%	12%	13%	19%	23%

All p-values >0.05%
† *intention to treat population*
‡ *modified intention to treat population*

Prins, M.H., et al. Thromb. J. 2013;11:21.
Bauersachs R, et al. N Engl J Med. 2010;363(26):2499-510.

EINSTEIN: Results

Outcome	Active Cancer		(95% CI)	P-value
	Rivaroxaban	Enoxaparin/VKA		
Primary Efficacy Outcome†	N=354	N=301		
Recurrent VTE	16%	20%	0.67 (0.35-1.30)	0.24
Mortality	16%	18%	0.93 (0.64-1.35)	0.70
Net clinical benefit	7%	13%	0.54 (0.33-0.90)	0.018
Primary Safety Outcome‡	N=353	N=298		
Major bleeding	2%	5%	0.42 (0.18-0.99)	0.047
Clinically relevant bleeding	14%	16%	0.08 (0.54-1.20)	0.28

Data are % and HR (95% CI)
† *intention to treat population*
‡ *modified intention to treat population*

Prins, M.H., et al. Thromb. J. 2013;11:21.
Bauersachs R, et al. N Engl J Med. 2010;363(26):2499-510.

AMPLIFY: Agnelli G, et al. 2015

Design
- Subgroup analysis of the AMPLIFY trial
- Randomized, double-blind trial

Population
- History of cancer; active cancer at baseline; or no active cancer/cancer history
- Acute, symptomatic proximal DVT, PE, or both

Interventions
- Study drug: Apixaban 10 mg twice daily for 7 days then 5 mg twice daily
- Comparator: Enoxaparin 1mg/kg twice daily followed by warfarin; INR goal 2-3
- Intended treatment period of 6 months

Agnelli G, et al. J Thromb Haemost. 2015;13(12):2187-91.
Agnelli G, et al. N Engl J Med. 2013;369(9):799-808.

AMPLIFY: Results

Outcome	History of Cancer		Active Cancer		No Active Cancer/ Cancer History	
	Apixaban	Enoxaparin/VKA	Apixaban	Enoxaparin/VKA	Apixaban	Enoxaparin/VKA
Primary Efficacy Outcome†	N=179	N=175	N=81	N=78	N=2349	N=2382
VTE/VTE related death	1.1%	6.3%	3.7%	6.4%	2.3%	2.3%
	0.17 (0.04-0.78)		*0.56 (0.13-2.37)*		*0.99 (0.69-1.44)*	
P value = 0.07						
Primary Safety Outcome‡	N=184	N=179	N=87	N=80	N=2405	N=2430
Major bleeding up to 2 days after stopping drug	0.5%	2.8%	2.3%	5.0%	0.5%	1.7%
	0.45 (0.08-2.46)		*0.20 (0.02-1.65)*		*0.30 (0.16-0.58)*	
P value = 0.83						

Data are % and RR (95% CI)
† *intention to treat population*
‡ *modified intention to treat population*

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Agnelli G, et al. J Thromb Haemost. 2015;13(12):2187-91.
Agnelli G, et al. N Engl J Med. 2013;369(9):799-808.

RECOVER I/II: Schulman S., et al. 2015

Design
- Post hoc subgroup analysis of the RECOVER I and RECOVER II trials
- Randomized, double-blind, double-dummy sister studies

Population
- Diagnosis/treatment for cancer within 5 years; or recurrent/metastatic cancer
- Acute, symptomatic proximal DVT, PE, or both

Interventions
- Study drug: UFH, LMWH, or fondaparinux followed by dabigatran 150 mg BID
- Comparator: UFH, LMWH, or fondaparinux followed by warfarin; INR goal 2-3
- Intended treatment period of 6 months

Schulman S., et al. N Engl J Med. 2009;361(24):2342-52.
Schulman S., et al. Circulation. 2014;129(7):764-72.
Schulman S., et al. Thromb Haemost. 2015;114(1):150-7.

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RECOVER I/II: Results

Outcome	History of Cancer		Active Cancer		No Cancer Diagnosis	
	Dabigatran	Enoxaparin/VKA	Dabigatran	Enoxaparin/VKA	Dabigatran	Enoxaparin/VKA
Primary Efficacy Outcome†	N=114	N=107	N=59	N=55	N=2390	N=2392
VTE/VTE related death	3.5%	4.7%	8.5%	13%	2.1%	1.8%
	0.74 (0.20-2.7)		*0.63 (0.20-2.0)*		*1.19 (0.79-1.79)*	
Safety Analysis‡	N=105	N=100	N=54	N=52	N=2297	N=2310
Major bleeding	3.8%	3.0%	3.7%	7.7%	0.8%	1.4%
	1.23 (0.28-5.5)		*0.43 (0.08-2.3)*		*0.55 (0.31-0.97)*	
Major/CRNM bleeding	13%	9%	17%	21%	3.7%	7.3%
	1.48 (0.64-3.4)		*0.65 (0.27-1.6)*		*0.50 (0.39-0.65)*	
Any bleeding	25%	16%	24%	37%	13.7%	20.3%
	1.57 (0.84-2.9)		*0.53 (0.29-1.1)*		*0.65 (0.56-0.75)*	

Data are % and HR (95% CI), † *intention to treat population;* ‡ *modified intention to treat population*

Schulman S., et al. N Engl J Med. 2009;361(24):2342-52.
Schulman S., et al. Circulation. 2014;129(7):764-72.
Schulman S., et al. Thromb Haemost. 2015;114(1):150-7.

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HOKUSAI: Raskob, G.E., et al. 2016

Design
- Post hoc, subgroup, non-inferiority analysis of the HOKUSAI-VTE study
- Randomized, double-blind, double-dummy study

Population
- History of cancer or active cancer
- Acute, symptomatic proximal DVT, PE, or both

Interventions
- Study drug: UFH or enoxaparin followed by edoxaban 60 mg once daily
- Comparator: UFH or enoxaparin followed by warfarin; INR goal 2-3
- Intended treatment period of 3 months up to 12 months

Buller H.R., et al. N Engl J Med. 2013;369(15):1406-15.
Raskob, G.E., et al. The Lancet Haematology , Volume 3 , Issue 8 , e379 - e387.

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HOKUSAI: Results

Outcome	History of Cancer		Active Cancer		No Cancer	
	Edoxaban	Enoxaparin/VKA	Edoxaban	Enoxaparin/VKA	Edoxaban	Enoxaparin/VKA
Primary Efficacy Outcome†	N=378	N=393	N=109	N=99	N=3658	N=3629
Recurrent VTE	4%	7%	4%	7%	3%	3%
	0.53 (0.28-1.00)		*0.55 (0.16-1.85)*		*1.03 (0.78-1.36)*	
P = 0.0007						
Primary Safety Outcome‡	N=378	N=393	N=109	N=99	N=3658	N=3629
Major or CRNM bleeding	12%	19%	18%	25%	8%	9%
	0.64 (0.45-0.92)		*0.72 (0.40-1.30)*		*0.83 (0.71-0.97)*	
P = 0.017						

Data are % and HR (95% CI)
† *intention to treat population*
‡ *modified intention to treat population*

Buller H.R., et al. N Engl J Med. 2013;369(15):1406-15.
Raskob, G.E., et al. The Lancet Haematology , Volume 3 , Issue 8 , e379 - e387.

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Review of Major Trials

Table 4: Comparison of major anticoagulation trial results in cancer patients

Study	N	Study Drug	Comparator	TTR, %	Recurrent VTE (study drug vs. comparator)	Bleeding (study drug vs. comparator)
CATCH†	900	Tinzaparin	Tinzaparin/VKA	A: 47%	A: 7.2% vs. 10.5%	A: 25.4% vs. 24.4%
CLOT†	676	Dalteparin	Dalteparin/VKA	A: 47%	A: 8% vs. 15.8%	A: 14% vs. 19%
EINSTEIN	1124	Rivaroxaban	Enoxaparin/VKA	A: 57% H: 63% D: 59%	A: 2% vs. 4% H: 2% vs. 2% D: 10% vs. 12%	A: 12% vs. 13% H: 11% vs. 9% D: 19% vs. 23%
AMPLIFY	534	Apixaban	Enoxaparin/VKA	A: 57.5% H: 64.5%	A: 3.7% vs. 6.4%; H: 1.1% vs. 6.3%	A: 12.6% vs. 22.5%; H: 6% vs. 15%
RECOVER	335	Dabigatran	Enoxaparin/VKA	48%‡	B: 3.5% vs. 4.7% D: 8.5% vs. 13%	B: 25% vs. 16% D: 24% vs. 37%
HOKUSAI	771	Edoxaban	Enoxaparin/VKA	63.6%	A: 4% vs. 7% H: 4% vs. 7%	A: 18% vs. 25% H: 12% vs. 19%

Data represented are: A = active cancer; B = cancer at baseline; D = cancer diagnosed during the study; H = history of cancer
†*The CATCH and CLOT studies only included patients with active cancer*
‡*The RECOVER subanalysis only reported TTR for those with recurrent VTE*
N: number of patients in subgroup analysis
TTR: time in therapeutic range

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Clinical Considerations

- Efficacy
- Cancer type
- Compliance
- Future surgical plans
- Drug-drug interactions
- Nutritional status
- Reversal agent
- Cost

Patient Case: K.T.

Clinical course: Despite your recommendation, K.T. was continued on warfarin 7.5 mg until a port placement and punch biopsy were scheduled for today (day 8).

	Day 5	Day 6	Day 7	Day 8
Warfarin dose:	7.5 mg	Held	Held	Held
INR:	1.34	1.97	2.79	2.54

Yesterday, fresh frozen plasma (FFP) was ordered to reverse K.T.'s anticoagulation in preparation of the pending procedures. However, last night K.T. refused medical treatment and surgery. She is scheduled for a follow-up appointment in one week.

K.T. cannot afford enoxaparin. She qualifies for a medical assistance program which provides 14 days outpatient enoxaparin at no charge.

Patient Case: K.T.

What anticoagulant would you suggest K.T. be discharged with today?

A) Switch her back to warfarin 7.5 mg PO daily

B) Prescribe enoxaparin 80 mg subQ q12hr

C) Prescribe apixaban 5 mg BID

D) Start her on dabigatran 150 mg PO qDay

Conclusion

- Inpatient treatment should begin with UFH or LMWH
- Outpatient treatment should consider:
  - Cancer status/type
  - Patient risk factors
  - Medical coverage
- DOACs are likely as effective compared to warfarin and LMWH
- DOAC choice should be based on patient characteristics

Looking Forward

Table 6: Future trials evaluating DOAC use in cancer patients

Study	Design	Interventions	Endpoints	Population
HOKUSAI-VTE 3b	Randomized, blinded, non-inferiority	Edoxaban vs. LMWH	1° - Recurrent VTE or major bleeding 2° - Event free survival	Active cancer or diagnosis in past 2 years
NCT02585713	Randomized, open-label, phase III, safety	Apixaban vs. dalteparin	1° - Major Bleeding 2° - Any bleeding event, recurrent VTE	Active cancer, ECOG 0,1, and 2
NCT02583191 (CONKO-011)	Randomized, open-label, phase III	Rivaroxaban vs. LMWH	1° - Pt reported treatment satisfaction with Rivaroxaban 2° - Rate of recurrent VTE within 3 mos after tx start; bleeding; overall mortality; QOL; rate of MI/stroke	Active malignancy
NCT02744092 (CANVAS)	Randomized, open-label, interventional	DOACs vs. LMWH +/- warfarin	1° - Cumulative VET recurrence 2° - Cumulative rate of major bleeding, HRQOL, treatment burden, mortality	Diagnosis of advanced cancer OR diagnosis of early stage cancer

Van es N, et al. Thromb Haemost. 2015;114(6):1268-76.
Academic and Community Cancer Research United. In: ClinicalTrials.gov [Internet]. NLM Identifier: NCT02585713
AIO-Studien-gGmbH, In: ClinicalTrials.gov [Internet]. NLM Identifier: NCT02583191

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DOACs for VTE Treatment and Secondary Prophylaxis in Cancer Patients: A New Direction
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Appendix

Table 1. Khorana Risk Model with expanded criteria included

Patient Characteristic	**Score**
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy WBC count >11x10^9	1
Prechemotherapy platelet count >350 x10^9/L	1
Hemoglobin <10 g/dL	1
Erythropoietin stimulating agents	1
BMI ≥35 kg/m2	1
Expanded:	
High risk cancer: Added brain tumors, myeloma, and kidney carcinoma	
sP-selectin > 53.1 ng/mL	1
D-Dimer > 1.44 µg/mL	1

Score	**VTE Risk**
0	1.0%
1	4.4%
2	3.5%
3	10.3%
4	20.3%
>5	35.0%

References: [1] Cihan, A., et al. Blood. 2010;116(24):5377-5382 [2] Khorana, A.A., et al. Blood. 2008;111:4902-4907

Table 2. Comparison of anticoagulant properties

Drug	Steady State	Bioavailability	Renally cleared?	Drug/Food interactions	Discontinuation time before surgery	Reversal agent?
LMWH	1-2 days	100%	40%	• Minimal	>24 hours	Yes
VKA	5-7 days	80-100%	92%	• CYP3A4 • Vitamin K containing foods	>5 days	Yes
Apixaban	1-2 days	57%	25%	• CYP3A4 • P-gp	>48 hours	None approved
Edoxaban	1-2 days	52%	50%	• CYP3A4	>24 hours	None approved
Rivaroxaban	1-2 days	60-80%	66%	• CYP3A4 • P-gp • Take with food	>24 hours (may need longer if CrCl <50)	None approved
Dabigatran	1-2 days	3-7% (prodrug)	80%	• P-gp	3-5 days	Yes

References: [1] Mohrien, K., et al. Consultant. 2013;53(12):918-919 [2] Weitz JI, Gross PL, et al. Hematology Am Soc Hematol Educ Program. 2012;2012:536-40 [3] Castellucci LA., et al. JAMA. 2014;312(11):1122-1135

Table 3. Cost comparison of anticoagulants

	Enoxaparin (60 mg BID)	**Warfarin** (5 mg daily)	**Apixaban** (5 mg BID)	**Edoxaban** (60 mg daily)	**Rivaroxaban** (20 mg daily)	**Dabigatran** (150 mg BID)
AWP (30 day supply)	$859.20	$66.80 (100 tablets)	$431.90	$582.60 (50 tablets)	$1,294.60 (90 tablets)	$419.89
Walmart (GoodRX app)	$592.25	$4.00	$371.26	$307.09	$378.55	$368.53
Walgreens (GoodRX app)	$1,009.00	$10.00	$378.87	$302.06	$370.95	$361.17

References: [1] GoodRX, Inc. (2016). GoodRX (Version 4.5.5) [Mobile application software]. Retrieved from http://itunes.apple.com [2] Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed October 2, 2016.

Table 4. Abbreviations

BID	Twice daily	**PE**	Pulmonary embolism
CAT	Cancer-associated thrombosis	**QDay**	Once daily
DOAC	Direct oral anticoagulant	**QOL**	Quality of life
DVT	Deep vein thrombosis	**RCT**	Randomized controlled trial
ECOG	Eastern Cooperative Oncology Group	**SubQ**	Subcutaneous
JCO	Journal of Clinical Oncology	**TTR**	Time in therapeutic range
LMWH	Low molecular weight heparin	**VKA**	Vitamin K antagonist
NCCN	National Comprehensive Cancer Network	**VTE**	Venous thromboembolism