Cancer and Clots: Approaching the Use of DOACs in the Cancer Population

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Financial Disclosures

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Learning Objectives

- Recognize and discuss the 5 FDA-approved direct oral anticoagulant (DOAC) drugs, their clinical indications, dosing, and special considerations
- Determine patients that would be appropriate candidates for therapy with these DOACs
- Apply currently available data to assess the utility of these medications in patients with cancer

Indications for Anticoagulation

- Atrial fibrillation
- Venous thromboembolic event (VTE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Orthopedic post-operative prophylaxis
- Arterial embolic stroke
- Prosthetic heart valve
- Antiphospholipid syndrome/Lupus anticoagulant

Why are Cancer Patients Unique?

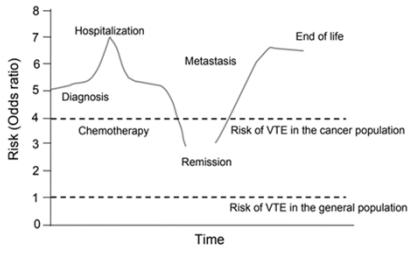
- Greater risk of clots
- Less robust data for management
- Frequent surgical procedures
- Thrombocytopenia due to treatments or disease
- Fluctuating renal/hepatic function
- Inconsistent diet/GI status
- Unique and frequent drug interactions

VTE in Cancer Patients

- Annual incidence of a first episode of DVT or PE in the general population is **1 in 855**.
- Estimates annual incidence of VTE in cancer patients is **1 in 200**
- **Cancer** alone was associated with a **4.2-fold risk** of thrombosis
- **Chemotherapy** increased the risk **6.5-fold**
- In patients receiving outpatient chemo, VTE was identified as COD in 9.2% of deaths
- ** ~10% of patients presenting with idiopathic VTE are diagnosed with cancer within 5-10 years

Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation. 2003;107(23 Suppl 1):I17-21.
Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. J Thromb Haemost. 2007;5(3):632-4.

VTE Risk Over Course of Cancer Treatment



Rao et al., in *Cancer-Associated Thrombosis*. (Khorana and Francis, Eds) 2007

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VTE Treatment in Cancer Patients

- Recommendations from major consensus guidelines:
  - Largely based on extrapolated data
- Subgroup analyses of larger trials with non-cancer patients
- Observational studies and registries
- Underpowered randomized controlled trials

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Questions to Ask

- What are the benefits of DOAC therapy over traditional therapy? (VKA, UFH, LMWH)
- Will DOACs be less efficacious than traditional therapy?
- Will DOAC therapy be safe for my patients?
- Special circumstances
  - Peri-procedure
  - Thrombocytopenia
  - Conversion

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What are the Benefits of DOAC therapy?

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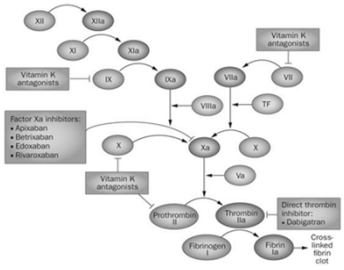
Available DOAC Agents

- Dabigatran Pradaxa ®
- Rivaroxaban Xarelto®
- Apixaban Eliquis®
- Edoxaban Savaysa®
- Betrixaban Bevyxxa®
  - June 2017



John N. Makaryus, Jonathan L. Halperin & Joe F. Lau. Nature Reviews Cardiology 10, 397-409 (July 2013)

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Approved Indications

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban	LMWH
VTE treatment	√	√	√	√	√		√
Secondary VTE prevention	√	√	√	√	√		√
Post-op hip/knee	√	√	√	√			√
Atrial fib	√	√	√	√	√		√
Mechanical valve replacement	√						√
VTE prevention due to medical immobility						√	√

Pradaxa® (dabigatran etexilate mesylate) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc, April 2014
Xarelto® (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc, 2011
Eliquis® (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company, March 2014
Savaysa® (edoxaban) [prescribing information]. Parsippany, NJ: Daiichi Sankyo, Inc, Jan 2015
Bevyxxa ® (betrixaban) [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals, Inc. Jun 2017

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Pharmacology

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban	LMWH
Target	VKORC	Thrombin	Factor Xa	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Dosing Frequency	Daily	BID	BID, then daily	BID	Daily	Load, then daily	BID or daily
Renal dosing?	---	< 30 ml/min	< 30ml/min- DVT- avoid ≥ 15 to < 50 mL/min afib	SCr> 1.5 age > 80, wt < 60 kg	≥ 15 to < 50 mL/min >95ml/min for afib	≥ 15 to < 30 mL/min	< 30 ml/min
Parenteral first?	**YES**	**YES**	No	No	**YES**	No	---
Time-to-peak effect	**5-7 days**	1-3 hr	2-4 hr	3-4 hr	1-2 hr	3-4 hr	3-5 hr
Half-life (hrs)	20 – 60	12 -17 28 (renal)	5 – 9 11 -13 (older)	12	10 – 14	19 – 27	4.5 – 7
Monitoring	**YES**	No	No	No	No	No	*Special situations
Interaction	CYP 2C9, 3A4, 1A2	**P-gp**	CYP 3A4, P-gp	**CYP 3A4, P-gp**	P-gp	**P-gp**	--

Pradaxa® (dabigatran etexilate mesylate) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; April 2014
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Limitations of VKAs

Limitation	Clinical Implications
Slow onset and offset of action	Need for bridging with a rapidly acting anticoagulant
Inter-individual variability in anticoagulant effect	Variability in dosing requirements
Narrow therapeutic index	Need for routine coagulation monitoring
Food and drug interactions	Dietary precautions; need for routine coagulation monitoring
Reduce synthesis of all vitamin K–dependent proteins	Risk of skin necrosis in patients with protein C or S deficiency; potential for osteoporosis

Eikelboom, JW; Weitz JI. Update on Antithrombotic therapy. *Circulation. 2010; 121: 1523-1532.*

Advantages of DOACs

Advantage	Clinical Implications
Rapid onset of action	No need for bridging
Predictable anticoagulant effect	No need for routine coagulation monitoring
Specific coagulation enzyme target	Low risk of off-target adverse effects
Low potential for food interactions	No dietary precautions
Low potential for drug interactions	Few drug restrictions

Eikelboom, JW; Weitz JI. Update on Antithrombotic therapy. *Circulation. 2010; 121: 1523-1532.*

Limitations of DOACs

Limitation	Clinical Implications
Short half-life	Increased risk of embolism with poor drug adherence
No routine coagulation monitoring required	Potential increased risk of embolism with poor drug adherence
No coagulation assay readily available to precisely measure anticoagulation effect	Cannot titrate dose, assess for failure, degree of coagulation in emergency situations
Limited reversal agents	Difficult to manage emergent bleeding situations
Cost	Decreased compliance

Ansell, J. *Circulation. 2012; 125: 165-170.*

Other Concerns for DOACs

- Potential drug interactions with chemotherapeutic agents
  - Fewer interactions than warfarin
  - Interactions with P-gp inhibitors
    - Clinicians not used to identifying
- Gastrointestinal problems
  - Also concerns with warfarin
  - However, short-half life is more concerning if N/V
- Hepatic and renal impairment
  - Also affects warfarin, but adjustments made by INR
  - Adjust based on renal function

Benefits of DOAC therapy?

Over LMWH
- No shots
- Possibly less expensive

Over warfarin
- Faster on/off
- No monitoring required
- Fewer drug interactions
- No food interactions → less variability?

Will DOACs be as effective for cancer patients?

2 situations
- VTE treatment and secondary prevention
- Atrial fibrillation and stroke prevention

2 comparisons
- vs. warfarin
- vs. LMWH

Venous Thromboembolism (VTE)

- 2016 Chest Guidelines
  - VTE without an associated cancer diagnosis
    - All DOACs are recommended over vitamin K antagonist (VKA) therapy (all Grade 2B) and VKA therapy is recommended over low molecular weight heparin (LMWH; Grade 2C)
  - VTE associated with cancer
    - LMWH is recommended over VKA (Grade 2B) or any direct oral anticoagulants (all Grade 2C)
- DOACs vs. VKA in non-cancer
  - VTE recurrence in pooled analysis (2% v. 2.2%)
  - 39% relative risk reduction of major bleed with DOACs

Koopman MM, et al. N Engl J Med. 1996;334:682–7.Kearon C, Akl EA, et al. Chest. 2016;149:315–52.
Levine M, et al. N Engl J Med. 1996;334:677–81.
Segal JB, et al. Am J Med. 2003;115:296–308.

DOACs v. VKA in Non-Cancer Patients

Table 2 Efficacy and safety outcomes for treatment of acute VTE: DOACs versus VKA

Trial Name [Ref]	RE-COVER [15]	RE-COVER II [16]	EINSTEIN-DVT [17]	EINSTEIN-PE [18]	AMPLIFY [19]	Hokusai-VTE [20]
Primary Efficacy Outcome DOAC vs VKA (%)	Recurrent symptomatic VTE or related death: 2.4 vs 2.1[a]	Recurrent symptomatic VTE or related mortality: 2.3 vs 2.2[a]	Recurrent symptomatic VTE: 2.1 vs 3.0[a]	Recurrent symptomatic VTE: 2.1 vs 1.8[a]	Recurrent symptomatic VTE or related mortality: 2.3 vs 2.7[a]	Recurrent symptomatic VTE or related mortality: 3.2 vs 3.5[a]
Primary Safety Outcome(s)	Major bleeding; Major or CRNM bleeding: Any bleeding	Major bleeding Major or CRNM bleeding: Any bleeding	Major or CRNM bleeding	Major or CRNM bleeding	Major bleeding	Major or CRNM bleeding
Major Bleeding DOAC vs VKA (%)	1.6 vs 1.9	1.2 vs 1.7	0.8 vs 1.2	1.1[a] vs 2.2	0.6[a] vs 1.8	1.4 vs 1.6
Major or CRNM Bleeding DOAC vs VKA (%)	5.6 vs 8.8	5.0 vs 7.9	8.1 vs 8.1	10.3 vs 11.4	4.3[a] vs 9.7	8.5[a] vs 10.3

DOAC direct oral anticoagulant, *CRNM* clinically relevant non-major, *DOAC* direct oral anticoagulants, *VKA* vitamin K antagonists, *VTE* venous thromboembolism
[a]Statistically significant difference between the two groups

Piran and Schulman. *Thrombosis Journal* 2016, 14 (Suppl 1): 23

What About Cancer Patients?

- 20% annual risk of VTE recurrence
- 5 randomized trials have compared LMWHs to VKAs in cancer patients
  - 3 showed benefit of LMWH preventing VTE recurrence
  - 2 showed no difference
- Relative risk reduction with LMWH is ~50%
- Meta-analyses have validated the superiority of LMWHs over VKAs

Lyman GH, Khorana AA, Kuderer NM, et al. *J Clin Oncol.* 2013;31(17):2189-2204.
Mandalà M, Falanga A, Roila F. *Ann Oncol.* 2011;22(suppl 6):vi85–vi92.
Kearon C, Akl EA, Comerota AJ, et al. *Chest.* 2012;141(2 suppl):e419S–e494S.

What About Cancer Patients?

Table 3 Comparison of trials on LMWH versus VKA for treatment of VTE in cancer patients

Trial Name	CANTHANOX	CLOT	MAVHLITE	ONCENOX	CATCH
Year of Publication [Ref]	2002 [43]	2003 [44]	2006 [45]	2006 [46]	2015 [47]
Design	Open-label	Open-label	Open-label	Open-label	Open-label
Number of Patients	146	676	200	122	900
Treatment Protocol	Enoxaparin 1.5 mg/kg daily	Dalteparin 200 IU/kg once daily for the first month then 150 IU/kg for 5 months	Tinzaparin 175 IU/kg once daily	Enoxaparin 1 mg/kg every 12 h for 5 days then enoxaparin 1 mg/kg or 1.5 mg/kg daily	Tinzaparin 175 IU/kg once daily
Duration of Therapy (months)	3	6	3	6	6
Primary Efficacy Outcome LMWH vs VKA (%)	Combination of major bleeding or recurrent VTE: 10.5 vs 21.1	Recurrent symptomatic VTE: 9[a] vs 17	Recurrent symptomatic VTE: 7 vs 10	Recurrent symptomatic VTE: enoxaparin 1 mg vs. 1.5 mg vs VKA 6.8 vs 6.3 vs 10.0	Composite of recurrent symptomatic VTE, fatal PE, or incidental VTE: 7.2 vs 10.5
Safety Bleeding Outcomes LMWH vs VKA (%)	Major bleeding: 7 vs 16; Fatal bleeding: 0 vs 8[a]	Major bleeding: 6 vs 4; Any bleeding 14 vs 19	Major bleeding: 7 vs 2; Any bleeding: 27 vs 24	Major bleeding: enoxaparin 1 mg vs. 1.5 mg vs VKA : 6.5 vs 11.1 vs 2.9	Major bleeding: 2.7 vs 2.4 CRNM bleeding: 10.9[a] vs 15.3

CRNM clinically relevant non-major, *DOAC* direct oral anticoagulants, *LMWH* low-molecular weight heparin, *PE* pulmonary embolism, *VKA* vitamin K antagonists, *VTE* venous thromboembolism
[a]Statistically significant difference between the two groups

Piran and Schulman. *Thrombosis Journal* 2016, 14 (Suppl 1): 23

2013 ASCO VTE Guidelines

- LMWH > UFH for the initial 5-10 days
- LMWH for at least 6 months is preferred
  - Guidelines list VKA as acceptable if unable to use LMWH long-term
- Treatment beyond 6 months is acceptable
- Presence of CNS malignancy does not preclude treatment
- Incidental VTE finding should be treated the same as symptomatic VTE
- DOACs are not recommended- insufficient evidence
- 2015 Guideline update- no changes

Lyman GH, Khorana AA, Kuderer NM, et al. *J Clin Oncol.* 2013;31(17):2189-2204.

Subgroups of Cancer Patients

Table 1. Recurrent VTE and major bleeding event rates in cancer patients enrolled in the RECOVER, EINSTEIN-DVT, EINSTEIN-PE, AMPLIFY, and Hokusai trials[33-36]

	VTE or VTE death, patients, n/N (%)		Major bleed, patients, n/N (%)	
RECOVER				
Cancer status*	Dabigatran	Control	Dabigatran	Control
No cancer	58/2380 (2.4)	50/2392 (2.1)	18/2297 (0.8)	33/2310 (1.4)
Active cancer	10/173 (5.8)	12/162 (7.4)	6/159 (3.8)	7/152 (4.6)
EINSTEIN				
Cancer status†	Rivaroxaban	Control	Rivaroxaban	Control
No cancer	70/3834 (1.8)	75/3850 (1.9)	31/3820 (0.8)	58/3832 (1.5)
Cancer at entry	6/232 (2.6)	8/198 (4.0)	6/232 (2.6)	8/196 (4.1)
Cancer diagnosis during study	10/84 (11.9)	12/83 (14.5)	3/84 (3.6)	6/82 (7.3)
AMPLIFY				
Cancer status‡	Apixaban	Control	Apixaban	Control
No cancer	56/2528 (2.2)	66/2557 (2.6)	13/2589 (0.5)	45/2609 (1.7)
Active cancer	3/81 (3.7)	5/78 (6.4)	2/87 (2.3)	4/80 (5.0)
Hokusai				
Cancer status§	Edoxaban	Control	Edoxaban	Control
No cancer	103/3658 (2.8)	99/3629 (2.7)	39/3658 (1.1)	48/3629 (1.3)
History of cancer	10/269 (3.7)	21/294 (7.1)	5/269 (1.9)	10/294 (3.4)
Active cancer	4/109 (3.7)	7/99 (7.1)	5/109 (4.6)	3/99 (3.0)

*Active cancer defined as having metastatic disease, recurrent cancer, or having been diagnosed or received treatment for cancer within 5 years prior to study enrollment.
†Active cancer was not defined.
‡Active cancer defined as having metastatic disease, recurrent cancer, or having been diagnosed or received treatment for cancer within 6 months prior to study enrollment.
§Active Cancer was defined according to the discretion of the local investigator.

Lee AYY. *ASH Education Handbook:* Hematology 2014. 312-317

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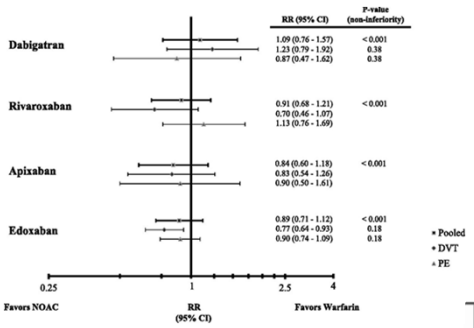
Recurrent VTE and VTE-related Death in Phase 3 Trials for Acute VTE Treatment

blood



Calvin H. Yeh et al. Blood 2014;124:1020-1028

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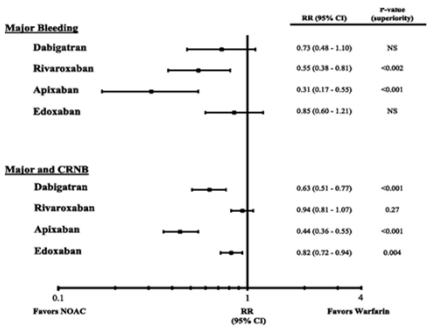
Major Bleeding in Phase 3 Trials for Acute VTE Treatment

blood



Calvin H. Yeh et al. Blood 2014;124:1020-1028

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Meta-Analysis

- Six studies were included
  - Two with dabigatran, two with rivaroxaban, one with edoxaban, and one with apixaban → 1132 cancer patients
- VTE recurrence: 3.9% vs. 6% in DOAC vs conventional tx
- Major bleeding: 3.2% vs. 4.2%
- Authors' Conclusion: DOACs are at least as effective and as safe as conventional treatment

Vedovati MC, etal. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest.2015;147:475–83.

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Issues with this Data

- Definition of "cancer"
  - 6 months- 5 years prior to study entry
  - At investigator discretion
  - Not defined at all
- Subsets
  - Tend to be healthier by selection criteria
  - Not appropriately powered
- "Conventional treatment"
- Hokusai VTE-cancer randomized open label trial is currently underway (ClinicalTrials.gov identifier: NCT02073682)
  - Edoxaban v. LMWH

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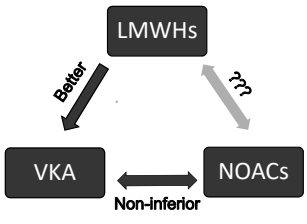
What do we know?

- No prospective, randomized comparative data of LMWH to DOACs yet



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ASH 2016 Abstract 5016

- Single institution data from University of Arizona
- Retrospective data from 2013-2016
- 137 cancer patients with active VTE treated with DOAC (112 on rivaroxaban)
- 4 patients experienced clot on therapy
  - 2 recurrent VTE, 1 recurrent PE, 1 PVT
- 34/137 (25%) patients experienced a total of 37 bleeding episodes
  - Of which 33/37 were classified as clinically relevant non-major bleeding and 4/37 as minor bleeding

McBride A, et al. Blood 2016 128:5016

ASH 2016 Abstract 5013

- Single institution data from Ohio State University
- Retrospective review 2010-2016
- 290 cancer patients on LMWH and 190 on DOAC (167 were rivaroxaban)
- They found no difference in VTE recurrence, while LMWH was associated with increased bleeding

Table 1: Primary and secondary outcomes at 6 months

	LMWH (n=290); n (%)	DOAC (n=190); n (%)	p
Recurrent VTE	21 (7.2%)	12 (6.3%)	0.70
Major bleeding	22 (7.8%)	5 (2.6%)	0.03
CRNMB	76 (26.2%)	34 (17.9%)	0.04
Death	66 (22.8%)	26 (13.7%)	0.01

Phelps MK, et al. Blood 2016 128:5013

Risk of Major Bleeding

- ASH 2016 Poster- Department of Defense Health System Cohort
  - Khorana et al. Blood 2016 128:1447
- Queried over 10 million electronic medical records (EMRs)- "real world" data
- 9,638 VTE patients on rivaroxaban
  - 1,728 (17.9%) with active cancer, 1,548 (16.1%) with history of cancer, 6,362 (66.0%) with no cancer
- 130 (1.3%) experienced MB
  - 28 (1.6%), 26 (1.7%), and 76(1.2%) respectively
- No significant difference in MB between those with cancer (active or history) and those without cancer (HR 1.01; 95% CI 0.70-1.47, p-value 0.94) after adjusting for age, sex, and baseline comorbidities.

What about Atrial Fibrillation?

- Patient 1: has established AF currently on a DOAC and newly diagnosed cancer
  - Most often encountered
  - Most often continued
- Patient 2: has active cancer and new-onset AF
  - Should prompt drug review (ex, ibrutinib)
- Patient 3: has history of cancer and new-onset AF
  - Likely least concerning scenario

What about AF?

- All major DOAC trials in AF excluded cancer patients
- 24,000 patients with newly diagnosed malignancy reported that 2.4% of patients had pre-existing AF at the time of their cancer diagnosis
  - $CHADS_2$ score only accurate with baseline AF
  - Not predictive in new-onset AF after cancer diagnosis
- Stroke risk and bleed risk difficult to determine
  - CHA_2DS_2-VASc score and HAS-BLED score have not been validated in patients with active malignancy
- Warfarin may not be effective for cancer patients
  - Retrospective study: no difference between warfarin and no tx
  - Only 12% of VKA patients achieved INR 2.0-3.0

Lee AY, et al. N Engl J Med. 2003;349:146–53
Asnani, A, et al. Cardio-Oncology. 2017

What about AF?

- Poster at ASH 2016- MSKCC
- Rivaroxaban for non-valvular AF and active cancer
- 163 patients, med age 72, 56% men
- 85% solid tumor, 50% of these having metastases
- Data seems comparable to what was observed for the general population in the ROCKET-AF study

Table: Cumulative Incidence of Competing risks for Patients in the Acute, Chronic and Combined Phases of Anticoagulation*

	Acute Phase N=59	Chronic Phase N=138	Combined Period N=163
Ischemic stroke, % (95% CI)	0 (0-0)	1.8 (0-4.3)	1.4 (0-3.4)
Major bleeding, % (95% CI)	0 (0-0)	1.5 (0-3.6)	1.2 (0-2.9)
Death, % (95% CI)	11.4 (1.4-20.3)	14.2 (7.3-20.5)	22.6 (12.2-31.7)
CRNMB, % (95% CI)	9.8 (0.2-18.4)	5.4 (1.1-9.5)	14 (4.2-22.7)

Laube ES, et al. Blood 2016 128:2621

What about AF?

- Oral abstract at ASH 2016
- All DOACs for non-valvular AF and active cancer identified in MarketScan databases
- 6,075 cancer patients with AF who were on DOACs (rivaroxaban 2808, dabigatran 2189, and apixaban 1078) compared to 10,021 on warfarin
- Each of the DOACs was superior to warfarin in lowering the risk of incident VTE, with p values < 0.0001
- Ischemic stroke did not differ significantly
- Bleeding incidence was either no different, or less in the DOAC group

Shah S, et al. Blood 2016 128:87

Direct Oral Anticoagulants in Patients with Cancer

Table 2. Adjusted hazard ratios (95% confidence intervals) comparing NOAC users to matched control users for the treatment of non-valvular atrial fibrillation in cancer patients, MarketScan, 2010-2014

Rivaroxaban vs. Warfarin	Rivaroxaban User (n=2,808)		Matched Warfarin User (n=5,673)		Hazard Ratio	
	# Events	Person-years	# Events	Person-years	(95% Confidence Interval)	p-value
Ischemic stroke	16	2277	59	5279	0.74 (0.40, 1.39)	0.35
Severe bleeding	68	2245	181	5207	1.09 (0.79, 1.50)	0.59
Other bleeding	50	2213	177	5031	0.79 (0.55, 1.13)	0.20
VTE	124	2046	472	3903	0.51 (0.41, 0.63)	<0.0001
Asthma (control outcome)	41	2259	91	5253	0.99 (0.64, 1.51)	0.94

Dabigatran vs. Warfarin	Dabigatran User (n=2,189)		Matched Warfarin User (n=8,339)		Hazard Ratio	
	# Events	Person-years	# Events	Person-years	(95% Confidence Interval)	p-value
Ischemic stroke	26	3310	127	10878	0.89 (0.56, 1.42)	0.63
Severe bleeding	70	3273	329	10706	0.96 (0.72, 1.27)	0.75
Other bleeding	40	3236	306	10376	0.58 (0.41, 0.84)	0.003
VTE	49	3199	743	8206	0.28 (0.21, 0.38)	<0.0001
Asthma (control outcome)	38	3302	183	10825	0.75 (0.51, 1.10)	0.14

Apixaban vs. Warfarin	Apixaban User (n=1,078)		Matched Warfarin User (n=2,775)		Hazard Ratio	
	# Events	Person-years	# Events	Person-years	(95% Confidence Interval)	p-value
Ischemic stroke	4	550	18	1773	0.71 (0.19, 2.60)	0.60
Severe bleeding	10	551	84	1744	0.37 (0.17, 0.79)	0.01
Other bleeding	9	538	72	1699	0.58 (0.25, 1.31)	0.19
VTE	7	540	218	1325	0.14 (0.07, 0.32)	<0.0001
Asthma (control outcome)	13	549	40	1760	0.99 (0.53, 2.22)	0.98

Shah S, et al. Blood 2016 128:87

Will DOACs be as effective and safe?

VTE:
- At least as effective as warfarin
- Safer than warfarin
- Little evidence compared to LMWH

AF:
- Even less data available
- Individualized approach to each patient
- Post-market data seems highly favorable

Drug Interactions

- Warfarin
  - CYP 3A4
  - CYP 2C9
  - CYP 1A2
- Rivaroxaban, apixaban
  - CYP 3A4
  - P-glycoprotein inhibitors
- Dabigatran, edoxaban, betrixaban
  - P-glycoprotein inhibitors

Drug Interactions

CYP 3A4 inducers- clot risk	CYP 3A4 inhibitors- bleed risk	P-gp inhibitors	Warfarin interactions
• **Dexamethasone** • Phenytoin • **Progesterone** • Rifampin • Phenobarbital • Nafcillin • St. John's Wort	• Amiodarone • Diltiazem • Verapamil • Macrolide antibiotics • Valproic acid • Grapefruit juice • **Azole antifungals** • **Metronidzaole** • **H2RAs** • **PPIs** • **SSRIs** • **Dexamethasone** • **Cyclosporine** • **Vinka Alkaloids** • **Docetaxel**	• Amiodarone • Verapamil • Macrolide antibiotics • **Cyclosporine** • **PPIs** • **Doxorubicin** • **Vinblastine** • **Tamoxifen** • **TKIs**	• **Acute alcohol ingestion** • **Vit K rich food** • Many herbal supplements • **Most antibiotics** • Allopurinol • Androgens • Barbiturates • Statins • **Aprepitant** • **Capecitabine** • **Etoposide** • **5 FU** • **Gemcitabine** • **Ifosfamide** • **TKIs** • **HDACs**

Lexi-Comp, Inc. (Lexi-Drugs). Lexi-Comp, Inc.; March 17, 2017.

		Oral Anticoagulants				
		Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Tyrosine Kinase Inhibitors	Afatinib					
	Axitinib					
	Bosutinib					
	Cabozantinib					
	Ceritinib	*↑OAC levels*		*↑OAC levels*	*↑OAC levels*	
	Crizotinib	↑OAC levels	*↑OAC levels**	*↑OAC levels**	↑OAC levels*	*↑OAC levels**
	Dasatinib	↑OAC levels & effect	↑OAC effect	↑OAC levels & effect	↑OAC levels & effect	↑OAC effect
	Erlotinib	↑OAC levels				
	Gefitinib	↑OAC effect				
	Ibrutinib	↑OAC effect	*↑OAC levels & effect**	↑OAC levels & effect*	↑OAC levels & effect*	*↑OAC levels & effect**
	Imatinib	*↑OAC levels & effect*		↑OAC levels	↑OAC levels	
	Lapatinib		*↑OAC levels**	↑OAC levels*	↑OAC levels*	*↑OAC levels**
	Lenvatinib					
	Nilotinib	↑OAC levels	*↑OAC levels**	*↑OAC levels**	*↑OAC levels**	*↑OAC levels**
	Osimertinib	↑OAC levels		↑OAC levels	↑OAC levels	
	Pazopanib					
	Ponatinib					
	Regorafenib	↑OAC effect				
	Ruxolitinib					
	Sorafenib	*↑OAC levels & effect*			↑OAC levels	
	Sunitinib		*↑OAC levels**	↑OAC levels*	*↑OAC levels**	↑OAC levels*
	Vandetanib		*↑OAC levels**	↑OAC levels*	*↑OAC levels**	↑OAC levels*

Asnani, A, et al. Cardio-Oncology. 2017

ASH Poster 2015

- Cambareri et al at Yale Cancer Center
- 75 patients from 2012-2014 all on rivaroxaban
- Incidence of recurrent VTE and CRB was 7.0% (n = 5) and 25.3% (n = 19), respectively
  - Two fatal events, one due to recurrent VTE and one due to major gastrointestinal bleed
- ½ of patients had known DDI- most common such agents were ciprofloxacin, fluconazole, azithromycin and voriconazole
- Advanced stage solid tumor emerged as a statistically significant (p = 0.0151) risk factor for bleeding while on rivaroxaban

Renal Impairment

	VTE	AF
Dabigatran	CrCL< 30: Avoid use 30-50 + P-gp: Avoid use	CrCl 15-30: 50% reduction (CHEST says avoid use) <15: Avoid Use
Rivaroxaban	CrCL< 30: Avoid use	CrCl 15-50: 15mg daily <15: Avoid use
Apixaban	CrCl<25: Avoid Use	SCr>1.5 + [age>80 or wt <60kg]: 2.5mg daily
Edoxaban	CrCl 15-50: 30mg daily* <15: Avoid use	CrCl 15-50: 30mg daily* <15: Avoid use

Betrixaban-Medical Immobility: CrCl 15-30: decrease dose by 50%

Liver Cirrhosis

- Oregon Health Sciences University
- 27 cirrhotic patients on DOAC and 18 on a traditional anticoagulant (either LMWH or warfarin)
  - Similar total bleeding events (8 DOAC vs. 10 traditional anticoagulation, $p = 0.12$)
  - Significantly less major bleeding episodes in the DOAC group, (1 (4%) vs. 5 (28%), $p = 0.03$) and less intracranial bleeding (3 (17%) vs. 0 (0%) p=0.06)
  - Recurrent thrombosis or stroke occurred in 1 (4%) patient in the DOAC group and 1 (6%) patient in the traditional group ($p = 1.0$)

Hum J, et al. Blood 2016 128:5015

Case 1

- Chris is a patient with pre-existing AF who has been stable on apixaban and now presents to your clinic with newly diagnosed mantle cell lymphoma
- He will need placement of a tunneled central catheter for treatment
- The physician decides that continuing apixaban for his AF is appropriate at this time

- How should you recommend managing his therapy for line placement?

Interruption for Procedures

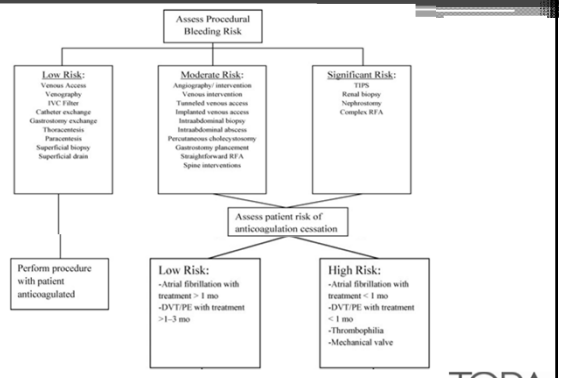
- Low risk procedures
  - Ex: PICC placement, PIV, skin punch biopsy, thoracentesis
  - No need to interrupt
- Moderate risk procedures
  - Tunneled/implanted venous access, tooth extraction, intrathecal chemotherapy
  - May take DOAC until day prior to procedure (~24 hours)
  - Hold day of procedure
  - Resume 24 hours after procedure

Douketis JD, Spyropoulos AC, et al. American College of Chest Physicians. Chest. 2012;141(2 Suppl):e326S
Cook, BW. Semin Intervent Radiol. 2010 Dec; 27(4): 360–367.

Interruption for Procedures

- Major procedures
  - Abdominal surgeries, tumor resections, etc.
  - Hold DOAC for 5 half-lives (~2.5-3 days) prior to procedure
  - Resume once bleeding is no longer imminent
    - Typically 48-72 hours
- Must take renal dysfunction into account for clearance of drug
- No data to suggest need for parenteral "bridging"

Douketis JD, Spyropoulos AC, et al. American College of Chest Physicians. Chest. 2012;141(2 Suppl):e326S



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Do not take apixaban dose the day of the line placement, resume the following day

Case 2

- Jessica is a MM patient > 1 year out from autoSCT on maintenance bortezomib. She went to her local ED with painful RUE swelling and redness. US showed brachial and subclavian venous occlusions
- Her copay for LWMH was $550 per month. She was started on apixaban 10mg BID x 7 days, then 5mg BID for $30
- She presents to your clinic the following week for her scheduled bortezomib injection

Oncology Flowsheet	Target/Unit	5/23/2017
Oncology Labs		
General Labs		
WBC	10^3/uL	2.3 10^3/uL
MCV	fL	110 fL
Neutrophils	%	38 %
Absolute Neut	10^3/uL	0.9 10^3/uL
HGB	g/dL	10.9 g/dL
HCT	%	32 %
Platelet	10^3/uL	80 10^3/uL
Sodium Level	mmol/L	139 mmol/L
Potassium Level	mmol/L	3.5 mmol/L
Chloride Level	mmol/L	105 mmol/L
CO2	mmol/L	28 mmol/L
Albumin Level	g/dL	3.6 g/dL
BUN	mg/dL	18 mg/dL
CREATININE	mg/dL	1.1 mg/dL
Est. GFR Non-African ...	mL/min/1....	48 mL/min/1.73_m2
Est. GFR African Amer...	mL/min/1....	58 mL/min/1.73_m2
Calcium Level	mg/dL	8.6 mg/dL
Total Bilirubin	mg/dL	0.6 mg/dL
ALT	[IU]/L	17 [IU]/L
AST	[IU]/L	18 [IU]/L
Alkaline Phosphatase	[IU]/L	42 [IU]/L
Glucose Level	mg/dL	93 mg/dL

- The provider asks you what to do with this apixaban

Thrombocytopenia

- Recommendations for LMWH:
- Acute VTE (< 1 month)
  - Transfuse to keep platelets > 50, continue full dose AC
- Platelet counts between 20 and 50 × 10^9/L
  - Half-dose LMWH or prophylactic dose LMWH can be considered with close follow-up
  - Weigh risks of clotting versus risk of bleeding on individual patient case
- Platelet count <20 × 10^9/L
  - Therapeutic doses of anticoagulation should be held

Lee and Peterson. Blood. 2013;122(14):2310- 2317)
Carrier, M, et al. Journal of Thrombosis and Haemostasis, 11: 1760–1765

ASH 2015

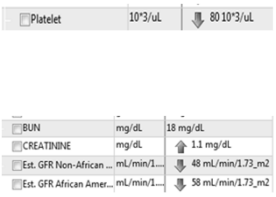
- MSKCC quality assessment project of LMWH dosing
- 95% level of compliance with the guidelines
- 101 patients with 144 episodes of thrombocytopenia
- No recurrent VTE events or major bleeding episodes when the LMWH was reduced or held

Miao, et al. Blood 2015

DOAC with Thrombocytopenia

- No clear guidance
- No evidence to support reduced dose of DOAC
- Reasonable approach based on risk:
  - AF indications: hold for platelets < 50k
  - VTE indications based on risk of re-clotting
    - < 1 month since most recent clot: transfuse platelets to > 50k and continue full dose DOAC
    - > 1 month since more recent clot: hold while platelets < 50k
    - Line-associated DVT with line removed?

Back to Case 2



- Continue full-dose apixaban
- Don't forget renal function!

Apixaban is ok with SCr < 1.5

Measuring Anticoagulant Effect

- *No regular monitoring needed*
- PT/INR and aPTT are incomplete and possibly misleading
  - Correlation with intensity of effect is poor
  - May be normal with therapeutic anticoagulation
- Anti-Xa activity
  - Calibrated kits for rivaroxaban and apixaban
  - Not readily available
- Dilute thrombin time
  - Poor quantification, but normal value excludes clinically relevant drug levels
- No "therapeutic" level, more "expected" values
- No guidance for adjustment

Garcia DA. *ASH Education Handbook*: Hematology 2014. 510-513.
J Am Coll Cardiol 2014;64:1128–39

When to Consider a Level

- Compliance questions
- Prior to urgent procedure
- Unavoidable drug interactions
- Recurrent clots on DOAC
- Major bleed on DOAC
- Extremes in weight

- Retrospective case series from UNC (Martin and Moll)
- DOAC prescriptions written over 3 years: Rivaroxaban 12,164; apixaban 7,700; dabigatran 3,128.
- 28 patients; 48 levels sent

Martin K, Moll S. [in preparation] from FDA: Workshop: "DOAC Diagnostic Testing" Oct 26th, 2015

Case 3

- Justin is your patient with NHL in CR being followed by observation. He is on rivaroxaban for treatment-induced AF
- Justin had a very traumatic softball accident and after examination has a displaced tib/fib fracture requiring surgical fixation
- He is stable now and not actively bleeding. Orthopedics is the primary service
- They call you for help with his DOAC since you follow this patient in clinic
- He last took his rivaroxaban with dinner two nights ago, was admitted through the ED yesterday afternoon, and they would like to plan surgical fixation later today or tomorrow. They want to know how they can reverse this new drug!?

The Antidote Question

- Anticoagulant effect dissipates ~12 hrs after last dose
- Fewer major bleeds, fatal bleeds, and ICHs that comparator in RCTs
- If antidote were available, most often wouldn't be used
  - RE-LY trial of dabigatran listed PCC or rFVIIa in protocol for DOAC-associated bleeding. Only used in 2.2% of over 400 patients with a major bleed
- Warfarin reversal remains imperfect
  - INR normalizes rapidly with Vit K
  - Lacks mortality benefit
  - >10% patients will still die, despite normalized INR

Garcia DA. *ASH Education Handbook*: Hematology 2014. 510-513.

Antidotes

- "Bypassing" agents that overcome the effect of drug
  - Fresh frozen plasma (FFP)- likely insufficient alone, volume issue
  - Prothrombin complex concentrate (PCC)
  - Activated coagulation factor VII (FVIIa)
  - Activated PCCs (aPCCs)
- Direct "antidote" that inactivates the drug
  - Idarucizumab- humanized antibody fragment against dabigatran
    - Only licensed reversal agent, based on phase 1 study
    - Phase III RE-VERSE AD- currently ongoing
  - Andexanet alpha- "decoy" factor Xa
    - >90 % reduction of mean anti-Factor Xa activity within five minutes
    - Phase 3 ANNEXA™-R/A currently ongoing
  - Ciraparantag (also called Aripazine)- Xa and IIa inhibitor
    - 90% reduction in bleeding, no evidence of prothrombotic effects

Lessire S, et al. Biomed Res Int. 2014; 2014: 616405.
Presentation in Oral Session at American College of Cardiology's (ACC) 4th Annual Scientific Session on Monday, March 16, 2015.

Idarucizumab

- Updated results from the REVERSE-AD study were presented in 2016
  - 123 patients given idarucizumab for dabigatran reversal: 66 patients with a MB and 57 patients undergoing an emergent procedure
  - In 48 assessable patients with a MB, the median time to bleeding cessation was 9.8 hours
  - Thrombotic events occurred in five patients between 2 and 24 days after
  - Twenty-six (21%) of the 123 patients died due to worsening of the emergency situation or comorbidities

Am J Med. 2016 Nov;129(11S):S89-S96.

Challenges to Antidotes

- Limited experience with new agents
- Variability in patient scenarios
- Duration of antidote v. DOAC
  - Andexanet alfa → fast on, fast off. Bleeding may recur
  - Ciraparantag→ long activity. Resumption of anticoagulation difficult
- Concentrated clotting factors +/- antidote??
- How to assess response to antidote?
- When can you stop therapy?

Case 3

- Justin has been off rivaroxaban ~36 hrs at this point
- Anticoagulant effect has largely decreased
- 5 half-lives will give complete drug clearance (~80 hours)
- If ortho is comfortable scheduling the procedure for tomorrow morning (> 60 hrs) then NO reversal agent needed
- Concentrated clotting factors should not be used: increase risk of post-surgical thrombosis
- Rivaroxaban-calibrated anti-Xa activity level could be considered

Summary

- Initial VTE treatment with LMWH for 6 months is still preferred for cancer patients
- Early data suggest DOAC use > warfarin for secondary VTE prevention in cancer patients
  - Potential for DOAC as initial treatment- although more robust data needed
- Less data for AF in cancer patients, despite this, use remains high
  - Early evidence seems to favor DOACs
  - Continuation is likely safe through cancer therapy
  - Further evidence needed to routinely recommend
- When selecting an agent, consider:
  - Renal dose adjustments, BID vs QDay dosing, drug interactions

Summary

- Some coordination required around procedures
- Thrombocytopenia still presents a challenge, but no more than with LMWH or warfarin
- Reassure providers that levels are typically not needed and routine coagulation studies are not reliable
- Reversal of DOACs is rarely needed, but agents are emerging that could provide better options

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Charlotte, NC

Thank You

TOPA