Should Direct Oral Anticoagulants Be Utilized in Cancer Patients to Prevent Thrombosis? Position – Yes

Chiara Melloni, MD, MHS, FACC
Associate Professor of Medicine
Duke Clinical Research Institute

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

DEBATE: Things to consider

- RCTs comparison
  - CLOT and CATH
  - HOKUSAI and SELECT-D
- Mortality
- Adherence: RCT vs real world data
- Cost
- Pt preference and values should be considered in treatment decision
- Drug Interactions

Baseline Characteristics	CLOT	CATCH	HOKUSAI-VTE	SELECT-D
N pf patients	676	900	1046	406
Study design	Open-label, multicenter, assessor blinded	Open-label, multicenter, assessor blinded	Open-label, multicenter, assessor blinded	Open-label, multicenter, assessor blinded
LMWH	Dalteparin	Tinzaparin	Dalteparin	Dalteparin
Mean age (years)	62	60	64	67
Tumor type				
Breast	16	9	12	10
Colorectal	16	13	16	25
Lung	13	12	15	12
GI	13	10	6	10
GU	10	23	13	4
Hematologic	10	10	10	7
Active cancer treatment	78	53	72	70
Metastatic disease	67	55	53	58
TTR	46	47		

Outcomes (%)	CLOT		CATCH		HOKUSAI-VTE		SELECT-D	
	LMWH	Warf	LMWH	Warf	LMWH	Edox	LMWH	Rivarox
Symptomatic VTE	7.9	15.7	6.9	10	11.3	7.9	8.8	3.9
Symptomatic DVT	4.1	10.9	2.7	5.3	6.7	3.6	7.0	3.0
Non-fatal PE	2.4	2.7	0.7	0.4	5.3	5.2	4.0	1.5
Fatal PE	1.5	2.1	3.8	3.8			0.5	0.5
Major bleeding	6.0	4.0	2.7	2.4	4.0	6.0	4.0	6.0
NMCRB								
Death	39	41	33	30	37	39	28	24

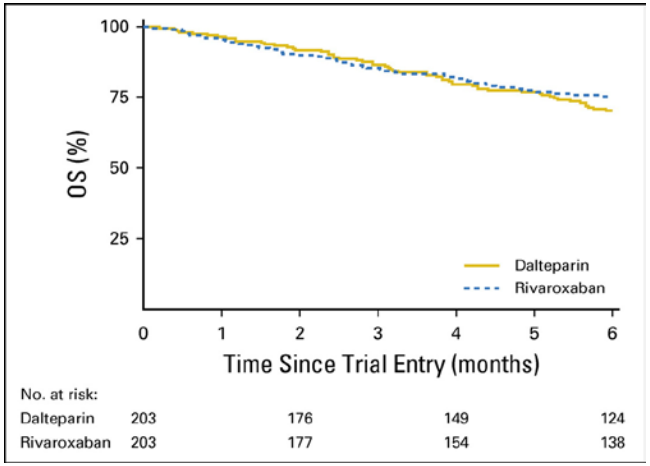
Overall Mortality

- **HOKUSAI-VTE cancer**
  - Deaths from all causes: Edoxaban vs Dalteparin 140 (26.8%) 127 (24.2%) HR, 95% CI 1.14 (0.90-1.45)

- No fatal bleed reported

- **SELECT-D**
  - Overall survival at 6 months: Dalteparin vs rivaroxaban 70% vs 75%

- No critical site bleed



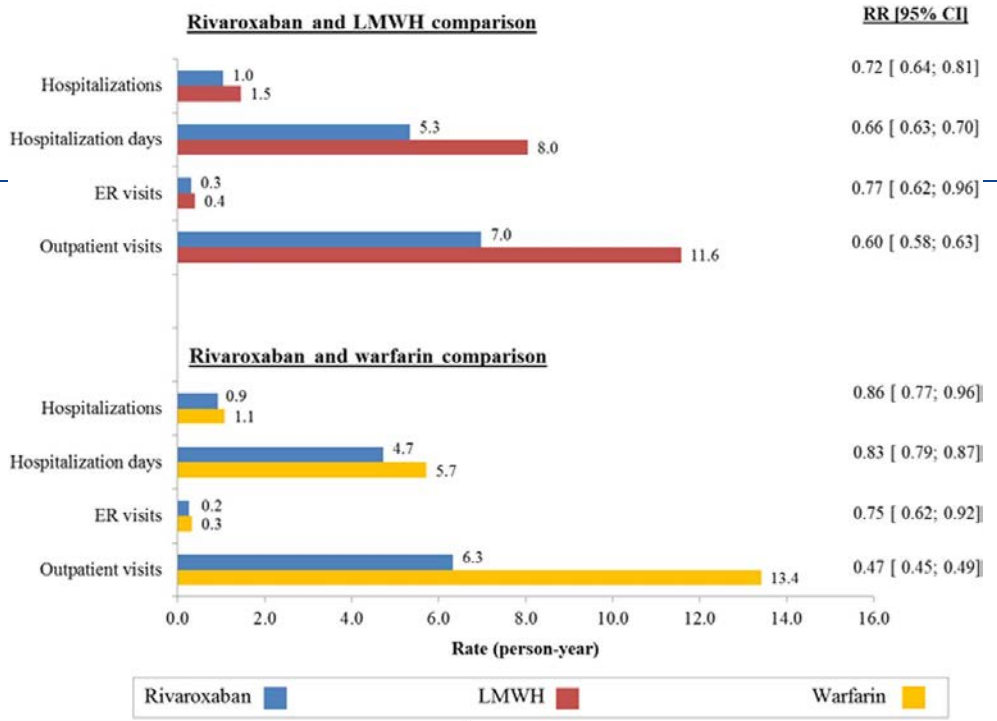
Adherence

Percentage of patients with cancer who remained on anticoagulant therapy.

Time from VTE diagnosis, months	LMWH	Warfarin	Rivaroxaban	Fondaparinux
0 to <1	100%	100%	100%	100%
1 to <3	30%	63%	54%	32%
3 to <6	13%	32%	30%	14%

Khorana AA, Thrombosis Research 2016

VTE Related Health Care Cost



Health care costs, PPPY (US$ 2015)	Rivaroxaban Cohort (N= 685)	LMWH Cohort (N= 682)	Cost difference	95% CI	P-value
Hospitalizations	$7,468	$14,461	-$6,993	[-11,179 ; -3,486]	<0.001
ER visits	$266	$599	-$333	[-708 ; -101]	<0.001
Outpatient visits	$3,364	$5,842	-$2,479	[-3,728 ; -1,147]	<0.001
Pharmacy	$2,495	$4,695	-$2,200	[-2,697 ; -1,683]	<0.001
Total	**$13,592**	**$25,597**	**-$12,004**	**[-16,834 ; -7,942]**	**<0.001**

	Rivaroxaban Cohort (N= 892)	Warfarin Cohort (N= 876)	Cost difference	95% CI	P-value
Hospitalizations	$6,434	$6,957	-$522	[-2,168 ; 1,175]	0.5440
ER visits	$203	$257	-$55	[-118 ; 21]	0.1440
Outpatient visits	$2,707	$3,746	-$1,039	[-1,874 ; -213]	0.0240
Pharmacy	$2,378	$859	$1,519	[1,293 ; 1,740]	<0.0001
Total	**$11,722**	**$11,819**	**-$97**	**[-2,065 ; 2,225]**	**0.9000**

Streiff M et al Blood 2016 128:3524

Patient Preference and Value

- Patients involvement is critical
- Variations exist in the perceptions of burden by patients

Thromb Haemost 2018;118:553–561.

Table 1: The Effect of Drug–Drug Interactions on Direct Oral Anticoagulant Plasma Levels

	Mechanism	Warfarin*	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs						
Amiodarone (and its metabolite desethylamiodarone)	Inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6 and P-gp	↑	↑	Not known	↑	↑ (minor)
Diltiazem	Inhibitor of CYP3A4	↑	No effect	↑	Not known	↑ (minor)
Dronedarone	Moderate inhibitor of CYP3A4; inhibitor of P-gp	↑	↑	Not known	↑	↑
Propafenone	Inhibitor of CYP3A4	↑	Not known	Not known	Not known	Not known
Propranolol	Inhibitor of CYP1A2	↑	Not known	Not known	Not known	Not known
Quinidine	Inhibitor of CYP3A4 and P-gp	↑	↑	Not known	↑	↑ (minor)
Telmisartan	Inhibitor of CYP3A4	↑				
Verapamil	Weak inhibitor of CYP3A4; P-gp competition	↑	↑	Not known	↑	↑ (minor)
Other cardiovascular drugs						
Statins (atorvastatin, lovastatin, rosuvastatin and simvastatin)	Inhibitor of CYP3A4	↑	↑	Not known	No effect	No effect
Antibiotics						
Clarithromycin and erythromycin	Moderate inhibitor of CYP3A4; P-gp competition	↑	↑	Not known	↑	↑
Isoniazid	Inhibitor of CYP2C9	↑	Not known	Not known	Not known	Not known
Metronidazole	Inhibitor of CYP1A2 and CYP2C9	↑	Not known	Not known	Not known	Not known
Quinolones (e.g. ciprofloxacin)	Strong inhibitor of CYP1A2	↑	Not known	Not known	Not known	Not known
Rifampicin	Inducer of CYP3A4 and CYP2C9	↓	↓	↓	↓	↓
Trimethoprim/sulfametaoxasole	Inhibitor of CYP3A4	↑	Not known	Not known	Not known	Not known
Antiviral drugs						
HIV protease inhibitors (e.g. ritonavir)	Inhibitor of CYP3A4; P-gp/Bcrp competition	↑	Not known	↑	Not known	↑
Fungostatics						
Fluconazole	Moderate inhibitor of CYP3A4, CYP1A2 and CYP2C9	↑	Not known	Not known	Not known	↑
Itraconazole, ketoconazole, posaconazole and voriconazole	Strong inhibitor of CYP3A4, CYP1A2 and CYP2C9; P-gp competition	↑	↑	↑	↑	↑
Immunosuppressants						
Cyclosporin and tacrolimus	P-gp competition	↑	Not recommended	Not known	↑	↑
Antiphlogistics						
Non-steroidal anti-inflammatory drugs	Inhibitor of CYP2C9; competition for protein-binding sites	↑	Not known	↑	No effect	Not known
Antacids						
Cimetidine and proton-pump inhibitors	Gastrointestinal absorption	↓	↓	No effect	No effect	No effect
Others						
Barbiturates (e.g. phenobarbital)*	Inducer of CYP3A4, CYP2J and P-gp/BCRP	↓	↓	↓	↓	↓
Carbamazepine*	Inducer of CYP3A4, CYP2J and P-gp/BCRP	↓	↓	↓	↓	↓
Phenytoin*	Inducer of CYP3A4, CYP2J and P-gp/BCRP	↓	↓	↓	↓	↓

Based on theoretical assumptions. Adapted from Heidbuchel, et al., 2015.