Topics in Anticoagulation

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This is to acknowledge that Eric Steen, MD has disclosed that he does not have any financial interests or other relationships with commercial concerns reltated directly or in directly to this program. Dr. Steen will not be discussing off-label use of FDA-approved drugs.

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Dr. Steen's major interest is in the clinical education of residents.

Purpose:

To discuss important recommendations from the January 2016 Chest Guidelines for Antithrombotic Therapy for VTE Disease and the evidence comparing warfarin with the novel oral anticoagulants in the treatment of venous thromboembolism and atrial fibrillation.

Educational Objectives:

At the conclusion of this lecture the listener should be able to

a) Make reasoned treatment decisions on length of therapy for unprovoked venous thromboembolism

b) Be familiar with the major trials comparing warfarin and the novel oral anticoagulants(NOAC)

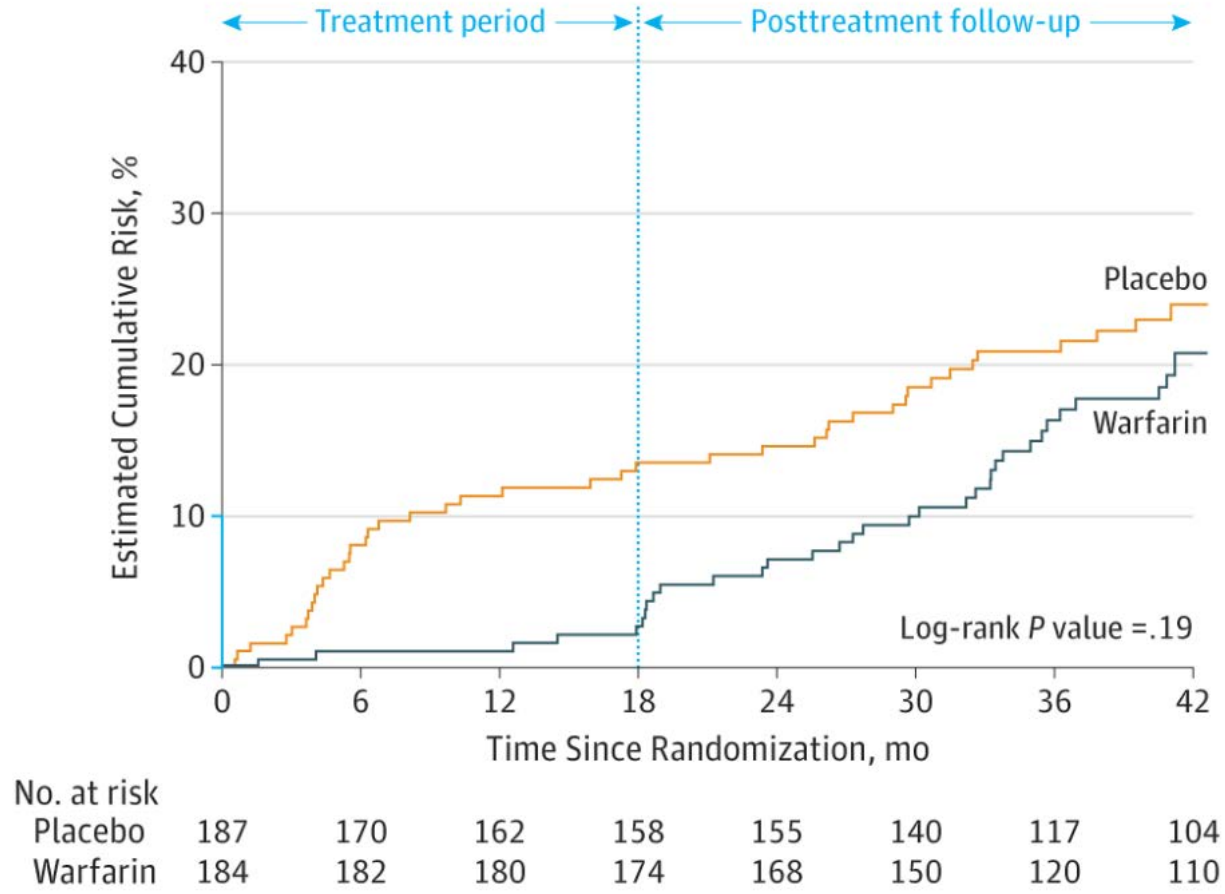
c) State the internet resources for estimating bleeding risk and managing bleeding in a patient on a NOAC

Topics in Anticoagulation

In light of new Chest Guidelines[1] for antithrombotic therapy for venous thromboembolic disease released in Jan 2016 and the availability of multiple novel oral anticoagulant drugs, I chose to discuss several clinical areas of interest in anticoagulation. With approximately three million people on warfarin and 900,000 VTE events per year in the US, coagulation disorders have a significant impact on the health of the United States.

One change in the guidelines concerns the appropriate duration of anticoagulation for venous thromboembolism (VTE) and pulmonary embolism (PE.) Duration for anticoagulation is usually separated into provoked VTE, unprovoked VTE and VTE associated with cancer. This delineation provides prognostic information. VTE provoked by a major transient risk factor such as surgery has a recurrence rate of 3% at five years. A clot provoked by a non-surgical transient risk factor such as estrogen use or air flights over 8 hours has a recurrence rate of 15% at five years. Unprovoked VTE has a recurrence rate of 30% at 5 years while cancer associated VTE has a recurrence rate of 15% annually.

Treatment decisions for VTE weigh recurrence rates and bleeding risk to decide on length of therapy. Provoked events are often treated for 3 months. In the past unprovoked ones often received 6 months of therapy and with some given consideration for longer therapy on a case by case basis. The PADIS-PE[2] trial recently demonstrated that unprovoked VTE recurrence risk continues to increase with time. In this study there were 2 groups, each getting 6 months of Coumadin for an unprovoked VTE. The first group had no further drug therapy while the second group was given 18 more months of Coumadin. At 18 months the treated group had many fewer events. Then both cohorts were followed for another 24 months. At 42 months there were no differences between the groups. The external validity of the study was shown as the recurrence rate at 4 yrs. was close to a generally expected 30% at 5 years.



Since the recurrence rate continues to climb, short term therapy may not protect the patient enough. As the major risk from warfarin is bleeding, patients who have a low bleeding risk may continue therapy indefinitely while those with high bleeding risks would receive a limited course of anticoagulation to cover 3 months, the highest risk period. Bleeding propensity has been divided into three groups by the guidelines. Low risk has no risk factors and 0.8% chance of major bleeding. Moderate risk has one factor and a 1.6% or a 2 fold risk of major bleeding. High risk has 2 or more factors and confers a 6.4% or 8 fold increase.

Table 11.

Risk Factors for Bleeding with Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk categories[a]

Risk Factors[b]
Age >65 y[184, 185, 186, 187, 188, 189, 190, 191, 192 and 193]
Age >75 y[184, 185, 186, 187, 188, 190, 192, 194, 195, 196, 197, 198, 199, 200, 201 and 202]
Previous bleeding[185, 191, 192, 193, 198, 201, 202, 203 and 204]
Cancer[187, 191, 195, 198 and 205]
Metastatic cancer[181 and 204]
Renal failure[185, 191, 192, 193, 196, 199, 201 and 206]
Liver failure[186, 189, 195 and 196]
Thrombocytopenia[195 and 204]
Previous stroke[185, 192, 195 and 207]
Diabetes[185, 186, 196, 200 and 202]
Anaemia[185, 189, 195, 198 and 202]
Antiplatelet therapy[186, 195, 196, 202 and 208]
Poor anticoagulant control[189, 196 and 203]
Comorbidity and reduced functional capacity[191, 196 and 204]
Recent surgery[189 and 209,c]
Frequent falls[195]
Alcohol abuse[191, 192, 195 and 202]
Nonsteroidal anti-inflammatory drug[210]
Categorization of Risk of Bleeding[d]

This is a table from the Chest Guidelines listing risk factors. You will note two different age decision points are listed and that is various papers have used both. Many of the other factors are not specific enough to make decisions e.g. is renal failure Cr 2, GFR < 50 or GFR 25? What is the Hgb level for anemia? References are listed but the criteria do not have to be uniform. Additional caveats are that this risk categorization is not validated, one severe risk could outweigh 2 others, and most references used vitamin K antagonists (VKAs.)

If their system is not validated, is there another way to estimate bleeding risk? Multiple schemes have been proposed and some of the major ones are HEMORRAGES, ATRIA, HAS-BLED, and ORBIT. Apostolakis[3] compared the first three and found HAS-BLED to be slightly better but all C statistics are in the 0.6 range. O'Brien[4] compared the last three and found C statistics of 0.66, 0.64 and 0.67 respectively. She felt ORBIT performed better in other ways. C statistics in this range may not be truly

different from each other and the papers did not use the gold standard of seeing which patients would be reclassified by using the scoring systems. ORBIT is easy to use and remember. It is not trivial to calculate total time in the therapeutic range (TTR) used in HAS-BLED. However Senoo[5] compared the three systems in a different data set and felt HAS-BLED performed better than ATRIA and ORBIT but all had C statistics in the 0.6 range. As bleeding risk is important in the new guidelines, I hope for more clarity regarding the optimum of bleeding scoring system in the near future.

ORBIT Eur Heart J Sept 29, 2015

Association between outcomes registry for better informed treatment risk score components and major bleeding

Variable	Hazard ratio[a]	95% CI HR	Chi-square-value	Points
Older age	1.38	1.17–1.61	15	1
Reduced haemoglobin/Hct/anaemia	2.07	1.74–2.47	66	2
Bleeding history	1.73	1.34–2.23	18	2
Insufficient kidney function	1.44	1.21–1.72	17	1
Treatment with antiplatelets	1.51	1.30–1.75	30	1

- [a]Outcomes registry for better informed treatment bleeding risk score components (point value) = older than 74 (1), reduced haemoglobin/anaemia (2), bleeding history (2), insufficient kidney function (<60 mL/min/1.73 m^2) (1), treatment with antiplatelet (1). Abnormal haemoglobin (<13 mg/dL for males and <12 mg/dL for females) or haematocrit (<40% for males and <36% for females).

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0-2 points low risk 2.4 bleeding events per 100 pt. years

3 points moderate 4.7 events

4 points High 8.1 events

There is no perfect system to predict bleeding risk and thus help decide which patients have a low enough bleeding risk to make long term anticoagulation worthwhile. There are two other factors which may help guide therapy. Women have less risk than men (HR 1.75 higher) and a negative d-dimer at 30d off Coumadin may be useful. Thus women with a negative d-dimer have the same recurrence rate at 5 years as those with a minor transient risk i.e. 15% at 5 years. In summary of the guidelines, provoked VTE get 3 months of therapy. Unprovoked ones with a “high risk “of bleeding get 3 months of therapy. Unprovoked VTE in “low risk” patients get extended therapy with “annual or periodic” review. As

bleeding risk is a judgment call so will be the decision for duration of therapy in unprovoked VTE. Patients and doctors will need to discuss trade-offs with regard to length of treatment. Length of therapy changes suggested by the guidelines may have significant monetary costs also. Three months of a ten cents per day drug is much different than a lifetime of an eleven dollar a day drug (pharmaceutical company dream.)

Since the bleeding risk may outweigh the advantages of anticoagulation in some patients with unprovoked VTE, are there any other options? Aspirin reduces VTE risk by 1/3 and there are two related trials and three papers WARFASA[6], ASPIRE[7], and INSPIRE[8] in support. WARFASA compared 100 mg of asa for two years versus placebo in patients who had completed initial therapy with Coumadin for an unprovoked VTE. Recurrent VTE was the main endpoint and was reached in 28 of 205 (6.6%) on asa and 43 of 197 (11.2%) on placebo. The hazard ratio was 0.58 with confidence intervals (CI) 0.33-0.92 and there was no bleeding difference. ASPIRE used 100 mg of asa for four years versus placebo and had the same primary outcome. It included secondary outcomes of major vascular event defined as VTE plus MACE (major adverse cardiac outcome) and net clinical benefit. On asa there were 57 events in 411 patients (4.8%) and placebo had 73 events in 411 patients (6.5%) HR 0.75 CI 0.52-1.05 P= 0.09. Both secondary outcomes had a HR 0.66 and CI 0.48-0.92. Of note is that both WARFASA and ASPIRE investigators met during recruitment and agreed to combine data for a larger analysis called INSPIRE. INSPIRE had 1224 patients and asa had fewer VTE s 5.1% versus 7.5% on placebo HR 0.68 CL 0.51-0.90. There was no bleeding difference, the relative risk reduction (RRR) was 1/3, the absolute risk reduction (ARR) was 2.4% and the NNT was 42. Though asa does not produce the 80% reduction in recurrent VTE like Coumadin, it may be worth considering in select patients.

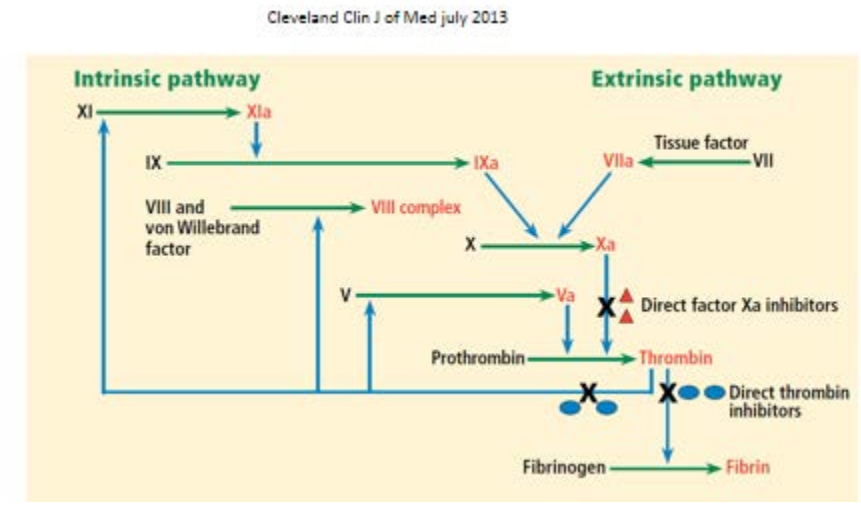
For prevention of recurrent VTE in cancer, the Chest Guidelines recommend low molecular weight heparin (LMWH) over Coumadin. The efficacy data are not overwhelming and it is worthwhile to review the recent CATCH[9] trial and the older CLOT[10] trial data. Prevention of recurrence of VTE in cancer is especially important as the recurrence rate is 15% per year and not per five years. The recent Guidelines favored low molecular weight heparin (LMWH) over vitamin K antagonists (VKA) because it is harder to keep VKAs in the therapeutic range during chemotherapy, vomiting can prevent patients from taking oral VKAs, LMWH are easier to stop for procedures, and there is “moderate quality” evidence that LMWH were more effective than VKAs in recurrence prevention. The CLOT trial (published 2003) was a RCT comparing Coumadin verses LMWH for the primary outcome of recurrent VTE. 27 of 336 subjects on LMWH had an event while 53 of 336 on Coumadin did for a HR 0.48, CI 0.3-0.77, RRR 52%, and an ARR of 8% at 6 months. Of note is that 20 of the VKA events occurred when the INR was <2. Also all of the benefit was in DVT and none in PE, fatal or otherwise (PE total 30.) The CLOT study started the major shift towards LMWH in cancer even though there was no benefit in PE. The CATCH trial (published 2015) was somewhat larger, had more centers, and used the same primary outcome. 31 of 449 on LMWH had recurrent VTE while 45 of 451 on VKA did. The HR was 0.65 CI 0.41-1.03. There was a 3.2% absolute difference but the CI crossed 1 so there was no statistical difference. Again there was no difference in PEs. The CLOT patients were somewhat sicker in that they had more metastasis, more chemotherapy, and a worse ECOG score. The total time in range (TTR) for warfarin was the same at 46% and 47% respectively. LMWH can be a good choice in cancer considering GI toxicity associated with

chemotherapy, frequent malnutrition, drug interactions, and possibly some increased efficacy. I will note that LMWH cost $26 per day (80 mg bid) at Walmart and Coumadin is $10 for 3 months. If a patient refuses shots or cost is a big issue, then VKAs can be used.

The next logical question is whether the novel oral anticoagulants (NOACs) work in cancer associated VTE. The National Comprehensive Cancer Network Clinical practice Guidelines on VTE (Version 2.2014) favor VKAs over NOACs due to insufficient data when LMWH is not an option. Sardar[11] analyzed six trials that reported separate outcome data for cancer patients in order to compare VKAs and NOACs, mainly rivaroxaban and dabigatran. The numbers were small but the NOAC and VKA results were similar. Bott[12] reviewed data on rivaroxaban from their MAYO NOAC VTE registry. They found that the 118 patients with active cancer had the same outcome as the 178 patients who did not have cancer. NOACs may work in cancer but there are no RCTs demonstrating efficacy.

The Chest Guidelines for VTE favor the use of the novel oral anticoagulants (NOAC) over VKA in many instances. They note there is less bleeding, especially CNS bleeding and that the drugs are more convenient for the patient and doctor. I will add that there is a long list of financial disclosures for the authors. However, Coumadin is not an ideal drug. Dosing varies greatly between individuals and effective levels vary day to day in the same individual. Drugs and diet are very important and the INR is in the therapeutic range only 50-60% of the time even in studies and with warfarin clinics. The fact that Coumadin clinics exist is testament to the difficulty in maintaining an effective dose. The novel agents have fewer drug/diet interactions and reportedly do not require monitoring of blood levels.

The clotting cascade is not as simplistic as depicted in this old "waterfall model" but it is helpful in demonstrating relationships between clotting factors.



The NOACs include 3 factor Xa inhibitors and one DTI shown below with the monthly drug cost.

Dabigatran DTI $340 for 60 pills

Rivaroxaban anti-FXa $340 for 30 pills (PMH much less?)

Apixaban anti-FXa $340 for 60 pills

Edoxaban anti FXa $291 for 30 pills

Coumadin VKA $4 for 30 pills

A summary of the trials comparing NOACs and VKAs in VTE is in the tables below. The major points are the NOACs are non-inferior to warfarin for recurrent VTE and there is less bleeding.

www.ncbi.nlm.nih.gov/pmc/articles/PMC4133479/table/T2/

Blood

Design and patient characteristics of the trials comparing NOACs with conventional therapy for acute VTE treatment

	Dabigatran	Rivaroxaban		Apixaban	Edoxaban
Trial	RE-COVER I & II	EINSTEIN		AMPLIFY	Hokusai-VTE
Indication	VTE	DVT	PE	VTE	VTE
Design	Double-blind	PROBE		Double-blind	Double-blind
Number of patients	2539 2568	3449	4832	5365	8240
Mean age ± SD (y)	54.9 ± 16.0	56.1 ± 16.4	57.7 ± 7.3	57.0 ± 16.0	55.8 ± 16.3
CrCl <30 mL/min, n (%)	22 (0.4)	15 (0.4)	6 (0.1)	29 (0.5)	n/a
Age ≥75 y, n (%)	529 (10)	440 (13)	843 (17)	768 (14)	1104 (13)
Prior VTE (%)	22	19	20	16	18
Unprovoked VTE (%)	35	62.0	64.5	89.8	65.7
Index event PE ± DVT (%)	31	0.7	100	34	40
Noninferiority margin	2.75	2.0		1.8	1.5
Bridge with heparin/LMWH	Yes	No		No	Yes
Treatment protocol	150 mg BID	15 mg BID for 3 wk; then 20 mg OD		10 mg BID for 7 d; then 5 mg BID	60 mg OD; 30 mg OD for those with a creatinine clearance of 30-50 mL/min, weight <60 kg, or taking potent P-gp inhibitors
Duration (mo)	6	3, 6, 12		6	3-12
TTR (%)	60	58	63	61	64

Yeh et al Blood Aug 14, 2014

Table 4

Efficacy and safety outcomes of the trials comparing NOACs with conventional therapy for acute VTE treatment

	Efficacy outcome			Safety outcomes					
	Recurrent VTE and VTE-related death			Major bleeding			Major and CRNB		
	NOAC, n/N(%)	Warfarin, n/N (%)	ARR, % (95% CI)	NOAC, n/N (%)	Warfarin, n/N (%)	ARR % (95% CI)	NOAC n/N (%)	Warfarin, n/N (%)	ARR % (95% CI)
Dabigatran[15]	60/2553 (2.4)	55/2554 (2.2)	0.2 (−0.6, 1.0)	37/2553 (1.4)	51/2554 (2.0)	−0.5 (−1.3, 0.2)	136/2553 (5.3)	217/2554 (8.5)	−3.2 (−4.6, −1.8)
Rivaroxaban[27]	86/4130 (2.1)	95/4131 (2.3)	−0.2 (−0.8, 0.4)	40/4130 (1.0)	72/4116 (1.7)	−0.8 (−1.3, −0.3)	388/4130 (9.4)	412/4116 (10.0)	−0.6 (−1.9, 0.7)
Apixaban[18]	59/2609 (2.3)	71/2635 (2.7)	−0.4 (−1.3, 0.4)	15/2676 (0.6)	49/2689 (1.8)	−1.3 (−1.8, −0.6)	115/2676 (4.3)	261/2689 (9.7)	−5.4 (−6.8, −4.1)
Edoxaban[19]	130/4118 (3.2)	146/4122 (3.5)	−0.4 (−1.2, 0.4)	56/4118 (1.4)	66/4122 (1.6)	−0.2 (−0.8, 0.3)	349/4118 (8.5)	423/4112 (10.3)	−1.8 (−3.1, −0.6)

ARR, absolute risk reduction; CRNB, clinically relevant nonmajor bleeding; n/N (%), number of events/number of patients in group (percentage).

As the NOACs are more convenient, should we use them for heart valves? The short answer is no. Eikelboom[13] published a phase ll trial in 2013 of dabigatran, a direct thrombin inhibitor (DTI,) against warfarin. There were 252 patients assigned to DTI and VKA in a ratio of 2:1. 199 were fresh valve replacements and 53 had their valve replaced more than 3 months ago. Nine people (5%) on the DTI had a stroke and none on VKAs. Five DTI subjects (3%) had asymptomatic valve thrombosis and none on VKA. Any bleeding was reported in 45 patients (27%) on DTI and 10 (12%) on VKA. A composite endpoint of CVA, embolism, MI, and death was calculated to be 9% for dabigatran and 5 % on Coumadin HR 1.94 CI 0.6-5.86. In light of these results the study was stopped early. It may be that other NOACs could work but there is little enthusiasm for another study in this area now.

There are four major drug trials of NOAC vs. VK in AF. These trials are the best source of data for comparisons between VKAs and NOACs and NOACs themselves.

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%
Creatinine clearance‡												
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%	19%	19%
50–80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%	45%	45%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%	36%	36%
Previous VKA use§	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%	57%	57%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%	34%	34%
Median follow-up (years)¶	2·0	2·0	2·0	1·9	1·9	1·8	1·8	2·8	2·8	2·8	2·2	2·2
Individual median TTR	NA	NA	67 (54–78)	NA	58 (43–71)	NA	66 (52–77)	NA	NA	68 (57–77)	NA	65 (51–76)

Data are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. $CHADS_2$=stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age ≥75 years, and diabetes, and two points are given for history of stroke or transient ischaemic attack. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range. NA=not available. *ROCKET-AF and ARISTOTLE included patients with systemic embolism. †ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left ventricular ejection fraction<40%. ‡RE-LY <50 mL/min, 50–79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50–80 mL/min, >80 mL/min. §RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 patients who used VKAs for ≥61 days; ROCKET AF patients who used VKAs for ≥6 weeks at time of screening. ¶IQRs not available.

Table: **Baseline characteristics of the intention-to-treat populations of the included trials**

The RE –LY[14] trial included 18,113 patients with a mean age of 71 and CHADSVASC of 2.1. It compared 2 doses of the DTI dabigatran with warfarin who had a "risk of stroke." There were 515 primary outcomes of CVA or embolism and >1000 secondary events such as major vascular events, major bleeding, and death. Dabigatran at the lower dose had the same stroke risk as Coumadin but less bleeding. At the higher dose dabigatran had a lower stroke risk and equal bleeding leading to a higher net benefit. The absolute net benefit was in the 0.5% range so the NNT was 200. A controversy arose when Deborah Cohen published in BMJ[15] that Boehringer Ingleheim internal documents noted that monitoring drug levels could reduce GI bleeds by 30-40%. One of the passages read "optimally titrated dabigatran has potential to provide patients even better efficacy and safety profile than fixed dose." BI did not want this known as "this may not be a onetime test and could result in a more complex message and a weaker value proposition." Fixed dose prescribing was felt to be a better selling point. The internal documents noted that trough levels between 50-200 ng/ml may be ideal but this was not made official in any way. This drug may benefit from drug level monitoring though not as much as warfarin.

ROCKET-AF[16] had 14,264 patients with a mean age of 73 and CHADSV of 3.4. There were approximately 500 primary outcomes and no significant difference in stroke or systemic embolism between rivaroxaban and Coumadin. The event rate was the same as in RE-LY giving support to external validity. Rivaroxaban had less bleeding overall but a small increase in GI bleeds. However four years after the test

was completed the point of care INR testing device was found to read falsely low and recalled. Warfarin might have been overdosed and lead to excess bleeding. In this case rivaroxaban would compare more favorably to warfarin. The NEJM[17] reported in March 2016 that the data had been redone and no substantial changes needed to be made in the original papers conclusions. A letter to the Editor and reply published on the web July 6, 2016(DOI:10.1056/NEJMc1604020) had more information. Only 6% of all samples obtained were paired POC versus in the laboratory. POC was in the same range with respect to treatment category (<2, 2-3,>3) 60% of the time and lower 36% of the time. Thus 36% may have been overdosed for a period of time. The authors excluded patients with discordant INR values for their March report but there still may be a degree of uncertainty over the trial conclusions. This NOAC may not have less bleeding than warfarin.

ARISTOTLE[18] compared apixaban and Coumadin in 18,201 subjects with a mean age of 70 and CHADSVASC of 2.1. There were 477 primary events of stroke or embolism and apixaban was noted to have a 0.3% ARR (1.27 v 1.6) primary event rate. In secondary outcomes Apixaban had less major bleeding with an ARR 0.9% (2.13-3.09). Death was reduced by an ARR 0.4% (3.5-3.9) and hemorrhagic stroke ARR 0.2% (0.24-0.47)

ENGAGE AF TIMI 48[19] used edoxaban in 2 dose versus Coumadin in 21,105 patients with a mean age of 72 and CHADSV of 2.8. There were 667 primary outcomes of stroke or embolism. Edoxaban was non-inferior at both doses with regard to the primary outcome but had less major bleeding ARR 0.68% high dose and 1.82% low dose edoxaban respectively. Daiichi-Sankyo knew of the controversy in dabigatran levels in the RE-LY trial and published their blood level data. They note it was possible that drug levels may improve safety especially in patients with renal insufficiency. At the other end of the renal function spectrum, edoxaban has a black box warning for patients with a GFR over 95 as levels may be too low for protection.

As these four large trials were similar in design and size and had over 2000 primary outcomes and 4000 secondary outcomes, they have been used by multiple authors to try to compare all of the NOACs and VKA. Renda[20] used the data to create a net clinical benefit. For the combination of ischemic and hemorrhagic stroke dabigatran at the 150 mg (higher dose/US approved) bid and apixaban were better. Disabling stroke and life threatening bleeding (as defined in RE-LY and ENGAGE) were reduced by all of the NOACs. A comprehensive outcome of ischemic stroke, embolism, MI, hemorrhagic stroke and major bleeding was compiled and weights were given to each outcome e.g. and averted CNS bleed was more important than an averted ischemic stroke. Apixaban and both doses of edoxaban were significantly better as shown in the table below.

Renda et al

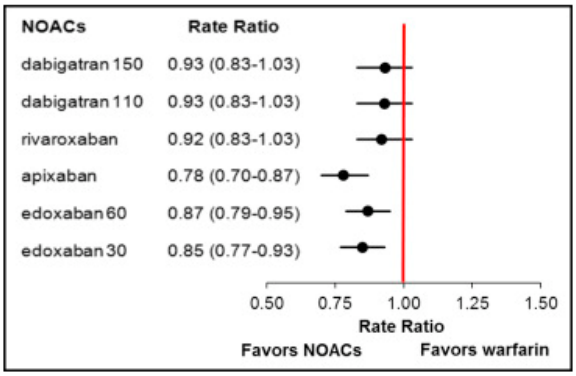


Figure 1

RR and 95% CI of all treatment arms in the phase III trials comparing a non-vitamin K antagonist oral anticoagulants with warfarin for the overall composite outcome including unweighed ischemic stroke + systemic embolism + myocardial infarction + hemorrhagic stroke + adjusted major bleeding (major bleeding minus hemorrhagic stroke). NOAC = non-vitamin K antagonist oral anticoagulant.

Treatment	Ischemic Stroke + Hemorrhagic Stroke	Disabling Stroke + Life-threatening Bleeding	Ischemic Stroke + Hemorrhagic Stroke + Myocardial Infarction + Systemic Embolism + Adjusted Major Bleeding
Dabigatran 150 mg	0.65 (0.51-0.81)	0.8 (0.67-0.95)	0.93 (0.83-1.03)
	<.001	**.009**	.201
Dabigatran 110 mg	0.91 (0.74-1.12)	0.78 (0.66-0.93)	0.93 (0.83-1.03)
	.382	**.005**	.205
Rivaroxaban	0.83 (0.68-1.00)	0.70 (0.56-0.87)	0.92 (0.83-1.03)
	.058	**<.001**	.151
Apixaban	0.79 (0.66-0.96)	0.55 (0.44-0.68)	0.78 (0.70-0.87)
	.015	**<.001**	**<.001**
Edoxaban 60 mg	0.88 (0.75-1.02)	0.67 (0.53-0.84)	0.87 (0.79-0.95)
	.106	**<.001**	**.004**
Edoxaban 30 mg	1.12 (0.96-1.30)	0.69 (0.55-0.88)	0.85 (0.77-0.93)
	.146	**.002**	**<.001**

RR and 95% CI of each treatment arm versus warfarin are reported in each case, with *P* value immediately below, for the various composite outcomes; statistically significant *P* values are in bold. Adjusted major bleeding = major bleeding – hemorrhagic stroke.

Treatment	Ischemic Stroke + Hemorrhagic Stroke		Disabling Stroke + Life-threatening Bleeding		Ischemic Stroke + Hemorrhagic Stroke + Myocardial Infarction + Systemic Embolism + Adjusted Major Bleeding	
	+ Cardiovascular Mortality	+ All-cause Mortality	+ Cardiovascular Mortality	+ All-cause Mortality	+ Cardiovascular Mortality	+ All-cause Mortality
Dabigatran 150 mg	0.78 (0.68-0.89)	0.82 (0.74-0.92)	0.83 (0.74-0.93)	0.86 (0.77-0.95)	0.90 (0.83-0.98)	0.91 (0.84-0.98)
	<.001	**<.001**	**.002**	**.003**	**.034**	**.035**
Dabigatran 110 mg	0.91 (0.80-1.02)	0.91 (0.81-1.01)	0.85 (0.76-0.95)	0.87 (0.78-0.96)	0.92 (0.84-1.01)	0.92 (0.85-1.00)
	.128	.086	**.006**	**.006**	.092	.068
Rivaroxaban	0.85 (0.74-0.98)	0.83 (0.72-0.95)	0.79 (0.68-0.92)	0.77 (0.67-0.89)	0.91 (0.83-1.00)	0.90 (0.82-0.98)
	.025	**.006**	**.002**	**<.001**	.064	**.024**
Apixaban	0.85 (0.75-0.96)	0.87 (0.79-0.95)	0.75 (0.66-0.85)	0.81 (0.73-0.89)	0.81 (0.75-0.89)	0.83 (0.77-0.90)
	.007	**.004**	**<.001**	**<.001**	**<.001**	**<.001**
Edoxaban 60 mg	0.87 (0.79-0.95)	0.91 (0.83-0.98)	0.82 (0.74-0.91)	0.88 (0.80-0.96)	0.87 (0.81-0.93)	0.89 (0.83-0.96)
	.004	**.025**	**<.001**	**.005**	**<.001**	**.001**
Edoxaban 30 mg	0.95 (0.87-1.04)	0.94 (0.87-1.02)	0.83 (0.74-0.92)	0.85 (0.77-0.93)	0.85 (0.79-0.92)	0.86 (0.81-0.92)
	.284	.181	**<.001**	**<.001**	**<.001**	**<.001**

These analyses are exploratory but are generally in line with the individual RCTs. Ruff[21] pooled NOACs to compare with warfarin and found the major advantage was in hemorrhagic strokes and intracerebral hemorrhage. The advantage in stroke or embolism is expected and a small mortality benefit was noted.

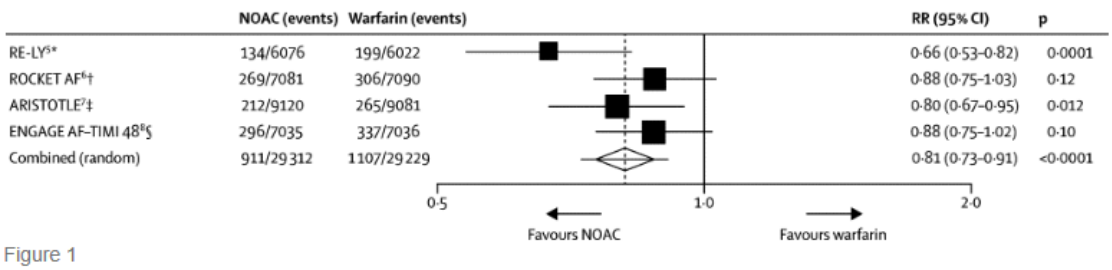
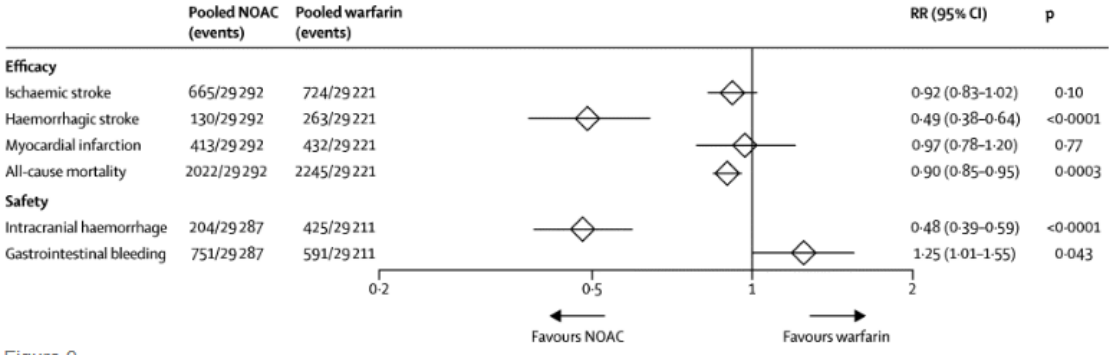


Figure 1

Stroke or systemic embolic events

Data are n/N, unless otherwise indicated. Heterogeneity: I^2 =47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio.

*Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.



Hicks[22] did a systematic review and meta-analysis of a total of 12 studies comparing the NOACs as a group to warfarin. He had concordant results showing a benefit to NOACS in stroke or embolism, ICH, and mortality which was driven by the reduction in ICH. Major bleeding was less.

The question of how these drugs will perform in a usual care or non-study environment is important. Patients on Coumadin will still be seen regularly to encourage adherence and their compliance will be confirmed by INR levels. Will NOAC patients be seen yearly or monthly with drug monitoring which would increase costs and negate some of the advantages? The Danish National Cohort Study[23] evaluated 61,678 patients on Coumadin (57%), dabigatran (21%), rivaroxaban (12%) and apixaban (10%) using three national databases. Larsen found no differences in ischemic strokes. The risk of death and major bleeding was less with apixaban or dabigatran while rivaroxaban had a lower risk of the combined endpoint of ischemic stroke or embolism. Though Denmark likely has a well- organized and standardized medical system, many of the NOAC characteristics were preserved in a usual care scenario.

One other real world problem is what to do with bleeding patients who may be taking NOACs. The lack of a reversal agent for all NOACs has caused especial concern in CNS bleeding. The mortality for ICH is 40% but counter-intuitively reversal agents do not help. The FAST[24] trial had 841 ICH bleeds on Coumadin randomized to placebo or two different doses of recombinant factor 7. The drug reduced the

hematoma size but the mortality in all groups was 20%. The mortality was not 40% (external validity was preserved) as patients with Glasgow coma scale <5 were excluded. Poor outcomes (Rankin 5 or 6) were 26%, 30% and 24% for low dose, high dose, and placebo respectively. No benefit was noted. For those who do think recombinant factor 7 does not work because it does not include factor ll, Dowlatshahi[25] published Canadian prothrombin complex registry results and again found no outcome difference.

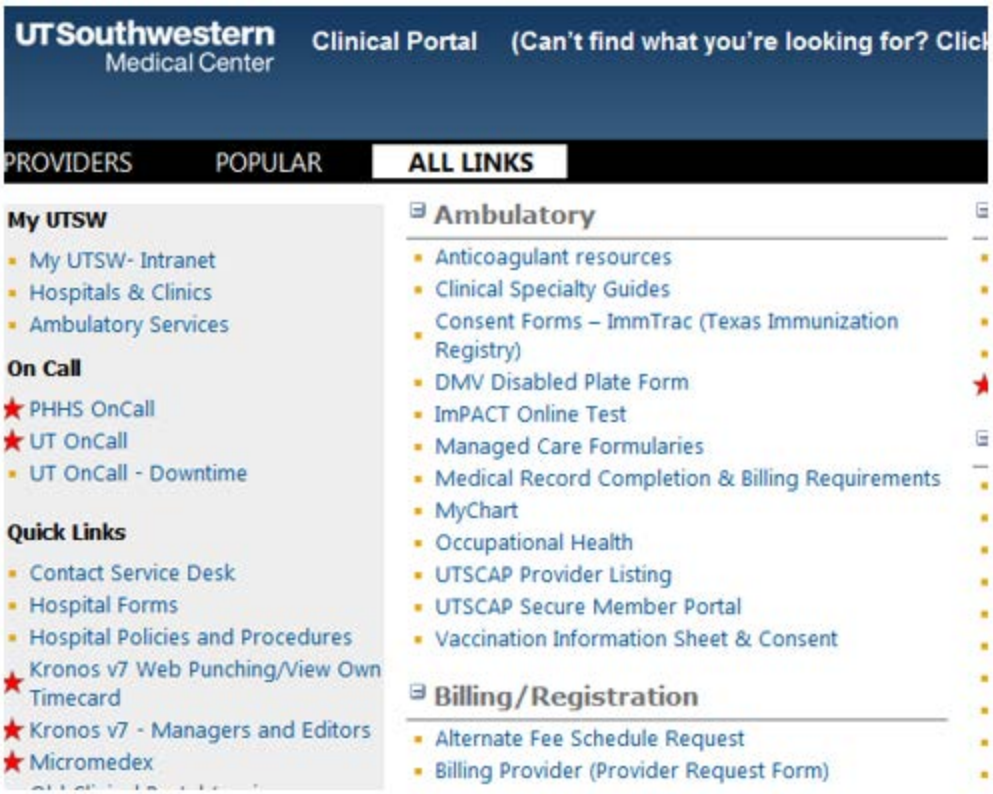
Other sites of bleeding and peri-operative management are important with NOACs and VKAs. The first is that just because a patient is prescribed a drug does not mean it is in his system. Yao[26] found that real world compliance was less than 50%. 64,661 patients with AF on NOAC or VKA from Optum Labs Data warehouse (private insurance and Medicare Advantage) were evaluated. The major study endpoint was stroke or major bleeding but what is most important is that they gathered pharmacy data. The total days covered by anticoagulation was determined by pharmacy fill dates and days of supply on claims. Only 47.5% of subjects on NOACs had 80% of their days covered and 40% on VKAs were covered. The actual amount in the patients system is lower as just having the pills does not mean the pills were ingested. Medication adherence was further refined by drug and adjusted by CHADSVASC score.

- VKA 39% covered(59% of pts)
- Apixaban 52%(6%)
- Rivaroxaban 48%(19%)
- Dabigatran 46%(16%)

VKA looks somewhat inferior but anticoagulant protection may be better than what is apparent as warfarin's half-life is much longer than the NOACs. This evidence of poor compliance is important for anyone who thinks NOAC patients do not need regular monitoring. If a patient is bleeding or needs a procedure and may be taking a NOAC, testing to detect coagulation derangements should be done. PT and PTT are not reliable. For dabigatran, a DTI, a thrombin time should be performed. For FXa antagonists an anti-Xa LMWH assay (not UFH assay) is performed. Normal clotting studies exclude significant drug activity. A rivaroxaban level may be available at CUH.

If coagulation is impaired and reversal is indicated, dabigatran has a reversal agent in idarucizumab. Since the AWP is $4200 and possibly PMH cost of $1622 it should be used wisely. Four hours of hemodialysis can reduce levels by 50% though levels can rebound 7-15% 4-8 hours later. For FXA inhibitors no reversal agent exists so 4 factor PCC is given in a dose of 50u/kg with a max dose of 3500u. The cost is between $4700 and $8855 at PMH. This increases factors ll and X and has shown some benefit in animal models. Reversal agents for FXa inhibitors are under development and one is being subsidized by two NOAC producers. Andexanet alpha reverses coagulation parameters in minutes in FXa antagonists and recruiting for a phase lll trial has begun. Aripazine reverses UFH, LMWH, DTI and anti-factor Xa drugs in healthy volunteers but is not as far along in development as andexanet.

Coagulation advice is available on the UTSW clinical portal

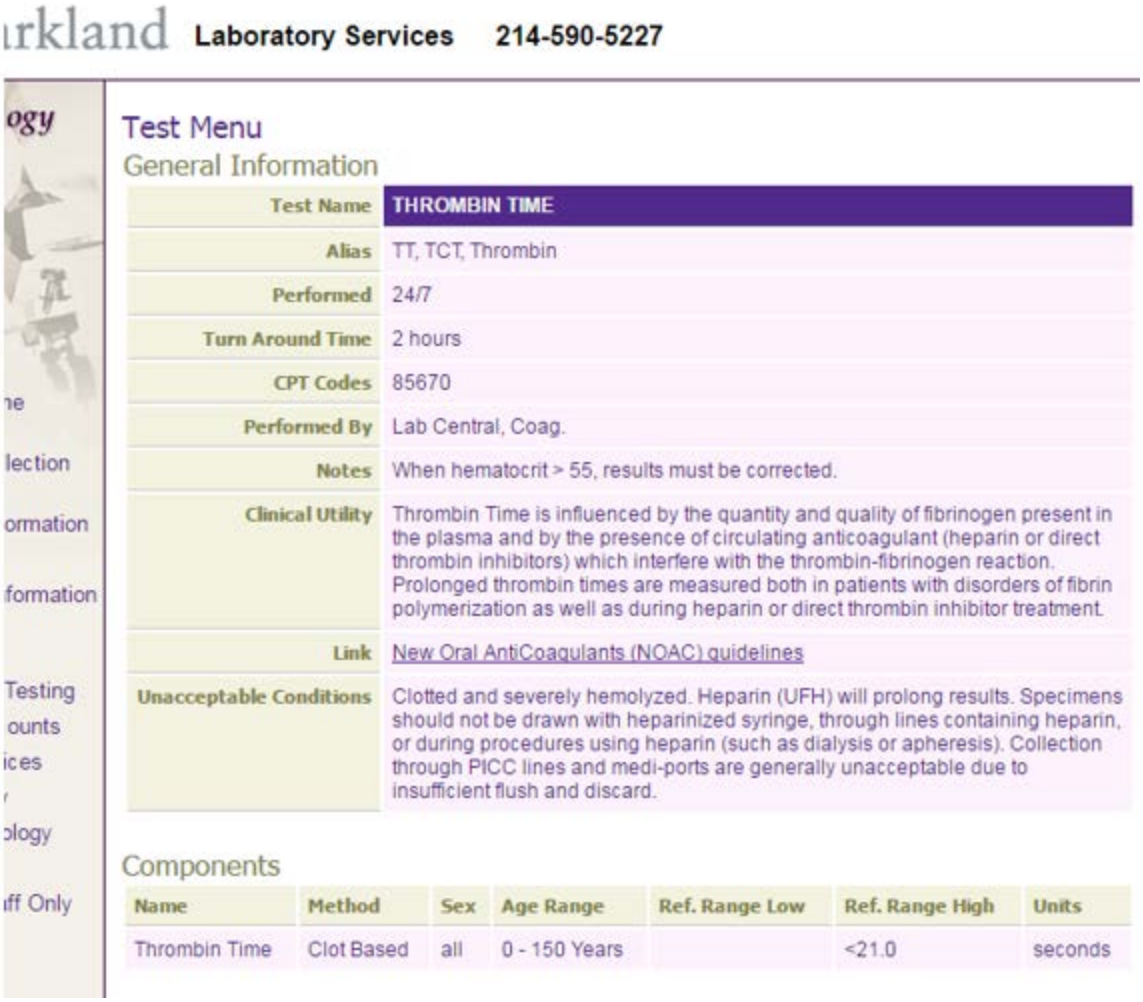


One section of drug management

		hold	Half life	Confirm absence	
Direct Oral AntiCoagulants (DOACs)					
Apixaban (Eliquis)	Direct factor Xa inhibitor	>/=24hrs (consider >/=48hrs if procedure is moderate or high risk of bleeding)	12hrs (longer if elderly or hepatic impairment)	**Anti-Xa** level (enter as **"low molecular weight heparin"** in epic) - "< 0.1" suggests lack of activity	NO specific antidote
Dabigatran (Pradaxa)	Direct factor IIa inhibitor	Based on type of procedure and renal fucntion, see comments	12-17hrs (longer if elderly or renal impairment)	**Thrombin Time** - within normal range suggests lack of activity	(1) There is no specific antidote for this drug (2) Per package insert hold dabigatran as follows based on renal function: (a) 1-2days if eCLcr >/=50ml/min; (b) 3-5days if eCLcr <50ml/min; (c) longer for procedures that require complete hemostasis
Edoxaban (Savaysa)	Direct factor Xa inhibitor	>/=24hrs	10-14hrs (longer if elderly or renal or hepatic impairment)	**Anti-Xa** level (enter as **"low molecular weight heparin"** in epic) - "< 0.1" suggests lack of activity	(1) NO specific antidote; (2) Per package insert, hold for at least 24hrs before invasive or surgical procedures. (3) Hold longer if renal or hepatic impairment.
Rivaroxaban (Xarelto)	Direct factor Xa inhibitor	>/=18hrs (longer if procedure is moderate or high risk of bleeding) - see comments	5-9hrs (longer if elderly or renal or hepatic impairment)	**Anti-Xa** level (enter as **"low molecular weight heparin"** in epic) - "< 0.1" suggests lack of activity	(1) NO specific antidote; (2) **STANDARD** risk of bleeding: (a) 18-24hrs for eCLcr >/=50ml/min, (b) 24-48hrs for eCLcr <50ml/min, (c) 24hrs for Child-Pugh A, (d) >/=48hrs for Child-Pugh B, (e) 72-120hrs for Child-Pugh C; (3) **HIGH** risk of bleeding: (a) 24-48hrs for eCLcr >/=50ml/min, (b) >48hrs for eCLcr <50ml/min, (c) 24-48hrs for Child-Pugh A, (d) >/=4 days for Child-Pugh B, (e) >/= 1week for Child-Pugh C

N.B. This was written before idarucizumab for dabigatran

Texas Health Resources plans to update this advice in 30d. Information at PMH can be found under Thrombin time under lab services. There is also an inpatient NOAC bleeding order set.



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Test Menu

General Information

Test Name	**THROMBIN TIME**
Alias	TT, TCT, Thrombin
Performed	24/7
Turn Around Time	2 hours
CPT Codes	85670
Performed By	Lab Central, Coag.
Notes	When hematocrit > 55, results must be corrected.
Clinical Utility	Thrombin Time is influenced by the quantity and quality of fibrinogen present in the plasma and by the presence of circulating anticoagulant (heparin or direct thrombin inhibitors) which interfere with the thrombin-fibrinogen reaction. Prolonged thrombin times are measured both in patients with disorders of fibrin polymerization as well as during heparin or direct thrombin inhibitor treatment.
Link	New Oral AntiCoagulants (NOAC) guidelines
Unacceptable Conditions	Clotted and severely hemolyzed. Heparin (UFH) will prolong results. Specimens should not be drawn with heparinized syringe, through lines containing heparin, or during procedures using heparin (such as dialysis or apheresis). Collection through PICC lines and medi-ports are generally unacceptable due to insufficient flush and discard.

Components

Name	Method	Sex	Age Range	Ref. Range Low	Ref. Range High	Units
Thrombin Time	Clot Based	all	0 - 150 Years		<21.0	seconds

The North American Thrombosis Forum AF Action Initiative Consensus Document[27] was published in May 2016. They felt NOACs provide consistent benefit over VKA with regard to hemorrhagic stroke, mortality, and ICH. N.B. the panel members financial disclosures took up ¾ of an entire page. The forum felt the best candidates for VKA would be those with a GFR<15 ml/min. The big trials usually excluded those <30 ml. Also possibly people with poor compliance (warfarin has a longer ½ life) may benefit. Those who cannot afford NOACs would also do better with VKAs. The forum noted there were no direct comparisons of NOACs to help choose among them but FXas are favored over DTIs in moderate CKD as FXas are less dependent on renal excretion. Dabigatran is only one with superiority in ischemic stroke. Apixiban and edoxaban had less bleeding and apixaban was the only one with less GI bleeding than VKAs. Rivaroxaban and edoxaban are once daily.

Costs are dramatically different between anticoagulants. Coumadin is $40 per year and the cheapest NOAC is $3500 per year. A Coumadin clinic charge at PMH is $80 and $55 at POB ll if a dosing adjustment is made and free if not. A POC INR is $10. A thrombin time has a fast turnaround and is “only a few dollars” in cost but perhaps not charge. FXa levels have to be sent to Children’s at night and are

much more expensive- $100? The Chief of Pathology did not know the cost or charge. Coumadin expenses would be $1660 per year based on drug cost and 18 visits with INR per year. If we assume an NNH for ICH of 200 (probably higher) and a CMS charge of $50,000 (high range) we add $250 to get $1910 as a high estimate. This number is much less than even the acquisition cost for any NOAC and visits and lab tests would clearly be more. If PMH has 2,000 warfarin clinic patients the cost would be several million dollars if everyone switched. If we assume six NOAC visits per year at $480, PMH would need to obtain a NOAC for $1300-1400 per year to be price competitive with warfarin. This estimate is very sensitive to the number of visits and visit costs which may be much less than the charges. As Yao showed <50% of all patients had >80% of days covered by medicine (though not necessarily ingested) clinic visits may be of great importance in maintaining compliance. Poor compliance is shown not to protect and may be harmful. It is clearly cheaper to be non-compliant with a cheap drug than an expensive one too.

We are fortunate to have more options for anti-coagulation. The NOACs easier to use and are non-inferior for VTE recurrence and ischemic stroke with AF. They likely have less bleeding. The NOAC RRR for ICH is 50% but the ARR is 0.2-0.3%. Coumadin may be safer in significant renal impairment and heart valves and likely has cost advantages. Drug levels may be perfected for the NOACs to make them even safer and reversal agents are in development. We will all see how the drugs perform in open use and hopefully drug acquisition costs will decline.

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