

THE
X
FACTOR
Chromogenic

VS

$$\text{INR} = \left(\frac{\text{Patient PT (sec)}}{\text{MN PT (sec)}} \right)^{\text{ISI}}$$

An old trick for a new(ish) problem in transitioning from Argatroban?

Simon Tremblay, B.Pharm., M.Sc, BCPS
March 28 2013

Argatroban

- IV direct thrombin inhibitor
- Uses
 - HIT + warfarin 5-day overlap
- $T_{1/2}$: 40-60 mins
- Hepatically cleared

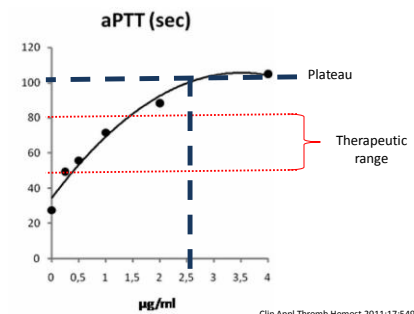
Expert Rev Hematol 2010;3:527-547

Argatroban monitoring

- aPTT generally recommended
 - 1.5-3x normal value
- Variable response vs different **clotting** assays

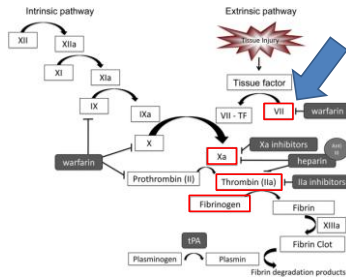
Clin Appl Thromb Hemost 2011;17:549-555

Argatroban and aPTT



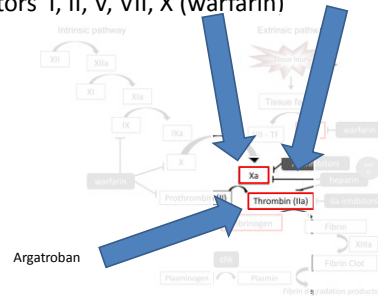
PT/INR

- Factors I, II, V, VII, X (warfarin)

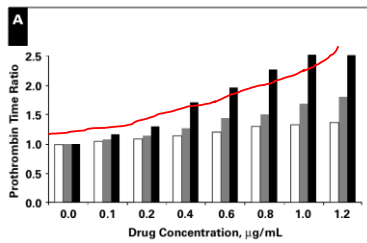


PT/INR

- Factors I, II, V, VII, X (warfarin)



Argatroban and PT/INR



Clin Appl Thromb Hemost 2011;17:549-555
Am J Clin Pathol 2004;121:593-599

Argatroban-INR interaction

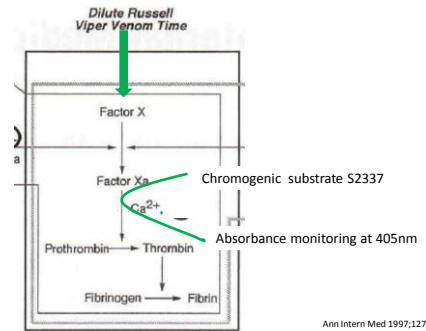
- ↑ INR > other DTIs
- Perceived ↓ in VKA-associated factors
- Measured concentration > clot-based assays
- No ↑ in bleeding with ↑ INRs
- Chomogenic factors not affected

Clin Appl Thromb Hemost 2008;14:325-331

Clinical problem

- Patients are at risk of clotting → argatroban
- Argatroban requires switch to VKA
- Argatroban ↑ INR
 - Does not affect factor VII!
- INR is required to monitor VKA
- Both put patients at higher risk of bleeding

Chromogenic Factor X (CFX)



Chromogenic Factor X (CFX)

$$CFX \text{ result} = \frac{\text{test absorbance}}{\text{control absorbance}} \times 100\%$$

- Used in warfarin + lupus anticoagulant
- ↓ CFX (activity) = ↑ anticoagulation
- CFX 11-42% correlate with INR 2-3.5

Ann Intern Med 1997;127:177-185

Clinical Question

- Can CFX assay help predict a therapeutic INR in patients transitioning from argatroban to warfarin therapy?

Search strategy

Sources	PubMed, Embase, Cochrane, IPA
Search	"Chromogenic Compounds"[Mesh] AND "Factor X"[Mesh]
Terms	AND "argatroban" [Supplementary Concept]
Limits	None
Results	<p>2 trials → effect of argatroban on coagulation factors</p> <p>1 prospective trial</p> <p>1 retrospective trial</p> <p>1 retrospective review of coagulation effects of argatroban</p> <p>1 review of coagulation monitoring</p>

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ORIGINAL RESEARCH ARTICLES

Use of the Chromogenic Factor X Assay to Predict the International Normalized Ratio in Patients Transitioning from Argatroban to Warfarin

Paul A. Arpino, Pharm.D., Zareh Demirjian, M.D., and Elizabeth M. Van Cott, M.D.

Pharmacotherapy 2005;25:157-164

Arpino *et al.*

Design	Prospective cohort December 2003 – May 2004 Massachusetts General Hospital
P	<ul style="list-style-type: none"> All patients with CFX assay on argatroban Common practice PT/PTT > 18h after CFX Argatroban may still be present aPTT > 4h post D/C > 1.5 normal
I	CFX < 40% = INR > 2 If CFX satisfactory, d/c argatroban 4h post: PT/INR ± CFX
C	None
O	Assess the utility of CFX in the transition from argatroban to warfarin

Pharmacotherapy 2005;25:157-164

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Arpino *et al.*

- Outcomes
 - ROC
 - Predict the INR free of argatroban
- Assay
 - DiaPharma factor X kit
 - STA-R coagulation analyzer

Pharmacotherapy 2005;25:157-164

Arpino *et al.*

- Statistical analyses
 - No sample size calculation
- Results
 - Population: 62/146 patients
 - No PT/PTT: 50
 - PT/PTT > 18h: 18
 - PTT > 40 sec: 16

Pharmacotherapy 2005;25:157-164

Arpino *et al.*

Characteristic	Value
	Mean ± SD
Age (yrs)	66 ± 13
Weight (kg)	74 ± 17
Liver function tests	
Aspartate aminotransferase (U/L)	54 ± 97
Alanine aminotransferase (U/L)	34 ± 35
Total bilirubin (mg/dl)	0.7 ± 0.5
Direct bilirubin (mg/dl)	0.3 ± 0.2
Sex	
Female	26 (42)
Indication for anticoagulation	
Heparin-induced thrombocytopenia ^a	29 (47)
Atrial fibrillation	9 (15)
DVT, PE	9 (15)
Mechanical heart valve	6 (10)

Pharmacotherapy 2005;25:157-164

Arpino *et al.*

Variable	At Time of Chromogenic Factor X Measurement	At Time of Confirmatory Coagulation Studies ^a
Dosage		
Argatroban (µg/kg/min)	1.8 ± 1.7	
Warfarin (mg/day)	5.2 ± 2.3	
Laboratory tests		
aPTT (sec)	58 ± 10	34 ± 5
PT (sec)	28 ± 8	20 ± 5
INR	5.5 ± 3.4	2.7 ± 1.4
CX (%)	45 ± 16	
CX (n=10) (%) ^b	41 ± 7	43 ± 10

Pharmacotherapy 2005;25:157-164

Let's review first

- Likelihood ratios (LR)

$$LR+ = \frac{\text{sensitivity}}{1 - \text{specificity}} = \frac{\text{probability of an individual with the condition having a positive test result}}{\text{probability of an individual without the condition having a positive test result}}$$

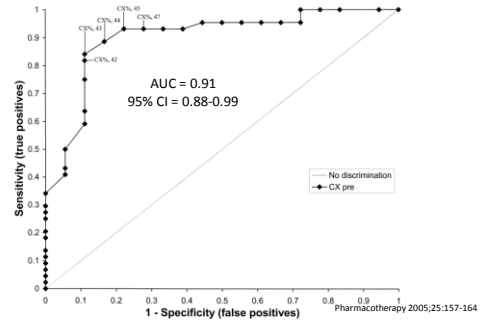
$$LR- = \frac{1 - \text{sensitivity}}{\text{specificity}} = \frac{\text{probability of an individual with the condition having a negative test result}}{\text{probability of an individual without the condition having a negative test result}}$$

Let's review first

- Likelihood ratios (LR)

LR	Interpretation
> 10	Large increase in likelihood of INR > 2
5-10	Moderate increase in likelihood of INR > 2
1-5	Small increase in likelihood of INR > 2
1	No change in likelihood of INR > 2
0.5-1	Minimal decrease in likelihood of INR > 2
0.1-0.5	Moderate decrease in likelihood of INR > 2
< 0.1	Large decrease in likelihood of INR > 2

Arpino et al.



Arpino et al.

- Data from ROC

Chromogenic Factor X Level (%)	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Positive Predictive Value (%)	Negative Predictive Value (%)
42	82 (67-92)	89 (65-99)	95	68
43	84 (70-93)	89 (65-99)	95	70
44	87 (75-96)	84 (59-96)	93	75
45	93 (81-99)	78 (52-94)	91	82
47	93 (81-99)	72 (47-90)	89	81

Pharmacotherapy 2005;25:157-164

Arpino et al.

- LRs

CFX (%)	LR+	LR-	60% pretest		80% pretest	
			+	-	+	-
42	7.5	0.2	92	23	96	44
43	7.6	0.18	92	21	97	42
44	5.4	0.15	89	20	96	37
45	4.2	0.09	86	11	94	26
47	3.3	0.09	83	11	93	26

Pharmacotherapy 2005;25:157-164

Arpino *et al.*

- Authors' conclusion
 - “a chromogenic factor X level of 45% or less is a reliable predictor that the INR will be therapeutic when argatroban therapy is discontinued. Further study is necessary”

Pharmacotherapy 2005;25:157-164

Arpino *et al.*

Question	Clear and pragmatic
Design	Non-randomized, uncontrolled
Internal validity	15% with CFX \leq 45%: INR $>$ 3.5 Design Confounding by indication? Assay calibration, validation
External validity	Select population vs liver dysfx Availability in centres Clinical outcomes
Conclusion	CFX \leq 45% may help in predicting INR $>$ 2 CFX \leq 47% can help in predicting INR $<$ 2

Use of the Chromogenic Factor X Assay in Patients Transitioning from Argatroban to Warfarin Therapy

Jennifer H. Austin, Pharm.D., Candace R. Stearns, Pharm.D., Anne M. Winkler, M.D., and Christopher A. Paciullo, Pharm.D.

Pharmacotherapy 2012;32:493-501

Austin *et al.*

Design	Retrospective cohort January 2003 – July 2010 2 Emory University Hospitals
P	<ul style="list-style-type: none"> • All patients with CFX assay on argatroban + warfarin Common practice • No CFX 24h before D/C argatroban • No INR 4-24h after D/C argatroban • Argatroban not D/C before discharge
I	CFX $<$ 20-45% = INR $>$ 2
C	None
O	Assess the utility of CFX in the transition from argatroban to warfarin

Pharmacotherapy 2012;32:493-501

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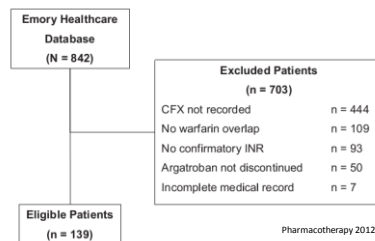
Austin *et al.*

- Outcomes
 - Correlation between INR and CFX
 - Sens, Spec, NPV, PPV
 - Predict the INR free of argatroban
 - Clinical outcomes
- Assay
 - DiaPharma factor X kit
 - BCS coagulation analyzer

Pharmacotherapy 2012;32:493–501

Austin *et al.*

- Statistical analyses
 - No sample size calculation
- Results



Pharmacotherapy 2012;32:493–501

Austin *et al.*

Characteristic	Value
Age, yrs (mean ± SD)	59 ± 15
Weight, kg (mean ± SD)	80.6 ± 25.3
Sex, no. (%)	
Male	65 (46.8)
Female	74 (53.2)
Admission diagnosis, no. (%)	
Cardiovascular	72 (51.8)
Respiratory	15 (10.8)
Infection or fever	11 (7.9)
Venous thromboembolism	8 (5.6)
Gastrointestinal	5 (3.6)
Renal dysfunction	7 (5.0)
Other	21 (15.1)
Hepatic impairment, no. (%)	26 (18.7)

Pharmacotherapy 2012;32:493–501

Austin *et al.*

- Results

Variable	Value
Days of warfarin therapy	4.4 ± 2.7
INR	3.72 ± 1.64
CFX (%)	49.5 ± 19.4
aPTT (sec)	89.9 ± 24.2
Platelet count (x 10 ³ /mm ³)	260 ± 151

Pharmacotherapy 2012;32:493–501

Austin *et al.*

• Outcomes

	CFX20-45%	CFX 20-45% + 5d warf	INR \geq 4 (n=116)
Sensitivity	63.2%	78.2%	30.2%
Specificity	80%	77.8%	100%
PPV	93.5	95.6	100
NPV	32.3	36.8	22.1

- Thrombosis: 9/139 (CFX 26-70%)
- Major bleeds: 8/139 (CFX 19-54%)

Pharmacotherapy 2012;32:493-501

Austin *et al.*

• LR

	LR+	LR-	60% pretest		80% pretest	
			+	-	+	-
CFX 20-45%	3.2	0.46	82	40	92	64
CFX 20-45% + 5d warf	3.5	0.28	84	30	93	53
INR \geq 4	∞ ?	0.7	∞ ?	51	80	74

Pharmacotherapy 2012;32:493-501

Austin *et al.*

• Authors' conclusion

- “ We recommend the use of CFX levels as an alternative method for patients transitioning from argatroban to warfarin therapy”

Pharmacotherapy 2012;32:493-501

Austin *et al.*

Question	Clear and pragmatic
Design	Non-randomized, uncontrolled, retrospective
Internal validity	18% liver disease Confounding by indication Information bias Assay calibration, validation No indication for argatroban use
External validity	Availability in centres Clinical outcomes
Conclusion	CFX \leq 45% may be inferior in predicting INR better than waiting for INR $>$ 4 INR $>$ 4 has poor LR-

CFX

- Helps determining when F X is depleted vs INR (FVII)
- Less interruptions in argatroban
- Turnaround time?
- Availability?
- Cost?
- Clinical outcomes?

Questions?



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