Original Work

Pharmacist Managed Warfarin Dosing Using Chromogenic Factor X Assay During Direct Thrombin Inhibitor Overlap Therapy

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Abstract

Objective: To compare patients transitioned from direct thrombin inhibitor (DTI) to warfarin using INR versus chromogenic factor X (CFX) assay after the creation and implementation of a pharmacist managed CFX protocol.

Methods: Encounters of patients who received argatroban or bivalirudin at our institution between June 1, 2017 and June 30, 2018 were screened for inclusion through retrospective chart review. Individual patient encounters were included if they had overlapping therapy with a DTI and transitioned to anticoagulation with warfarin alone.

Post intervention patients were identified from October 1, 2018 through June 13, 2019 using the same inclusion criteria. They were monitored by the established pharmacist protocol using a CFX levels during the transition from DTI to warfarin.

Results: Ahe pre-intervention group included 18 encounters (17 argatroban, 1 bivalirudin) and the post intervention group included 17 encounters (16 argatroban, 1 bivalirudin). The percent therapeutic confirmatory INR was similar in the two groups (44% in the pre-intervention group and 71% in the post intervention group, P = 0.12). However, median days of warfarin and DTI overlap was significantly higher in the pre-intervention group than in the post intervention group (6.5 days vs. 5 days P = 0.04). No adverse events were observed in either group.

Conclusions: CFX offers a potentially effective alternative method to assess anticoagulation status in patients transitioning from DTI to warfarin. Using CFX may result in a higher percentage of therapeutic INRs compared to monitoring INRs alone and decreased length of overlap therapy.

The vast majority of patients requiring anticoagulation with direct thrombin inhibitors (DTIs) and warfarin overlap therapy will be patients with a history of heparin-induced thrombocytopenia (HIT) or an acute HIT diagnosis. HIT is a life-threatening, immunologically mediated adverse drug reaction to heparin containing products with a prevalence ranging from 0.1-5% of patients receiving heparin. Additionally, HIT causes a hypercoagulable state and approximately 35-50% of patients with HIT will develop thrombosis.[1] Due to the high risk for thrombosis, immediately upon clinical suspicion for HIT, all heparin containing products should be discontinued and initiation of non-heparin parenteral anticoagulants is recommended.[2] Further laboratory evaluation for a HIT diagnosis includes a positive platelet factor 4 (PF4) and a positive serotonin release assay (SRA), along with a clinical assessment and diagnosis from a physician, ideally a specialist in hematology.

The most commonly used and FDA approved parenteral anticoagulant for the treatment HIT is the DTI argatroban. While not FDA approved specifically for HIT, bivalirudin is a DTI that has been shown to effectively treat HIT.[2] Both of these medications, especially argatroban, prolong the prothrombin time in a dose-related manner which results in an elevated international normalized ratio (INR).[2] This false elevation in INR makes it challenging to determine the appropriate time to discontinue the DTI infusion and transition to warfarin alone at goal INR. Direct thrombin inhibitor infusions are started and continued alone in patients with acute HIT until platelets have substantially recovered to at least 100-150x109/L.[2] After platelet recovery, per current guidelines, warfarin is recommended to be started and overlapped with a non-heparin parenteral anticoagulant for a minimum of 5 days. The INR should then be rechecked after the anticoagulant effect of the non-heparin anticoagulant has dissipated and a confirmatory INR should be drawn.[2]

The negative consequences associated with the narrow therapeutic index of warfarin and hypercoagulable state of HIT add to the complexity of deciding when to discontinue parenteral anticoagulation and continue with warfarin anticoagulation alone. On one hand, clinicians may risk underdosing and an increased risk of thrombosis, and on the other hand, they may risk overdosing and an increased risk of bleeding making this clinical scenario particularly difficult to

manage. Although some efficacy and safety data is available for use of the direct oral anticoagulants (DOACs) in acute HIT, the limited evidence makes warfarin the preferred oral anticoagulant choice for most patients.[3]

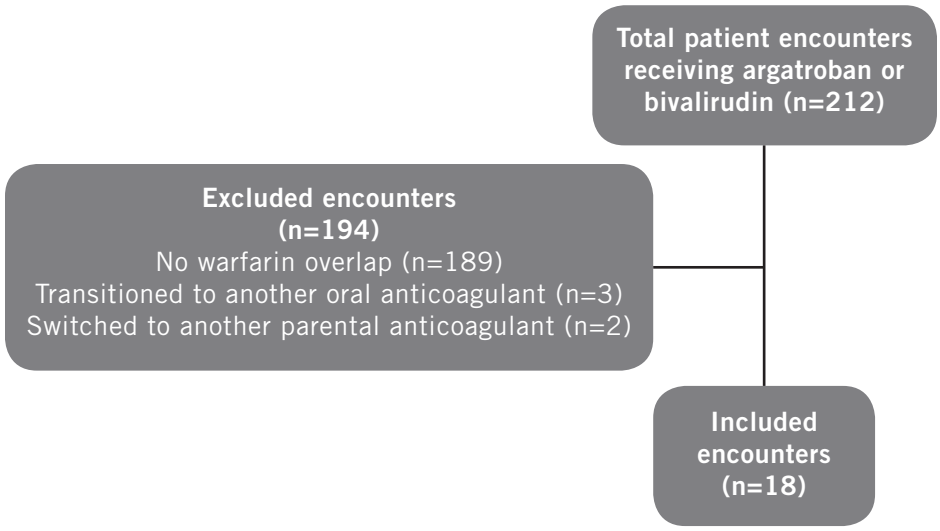
Currently, there is no true standard of practice amongst institutions or clinical practice guideline on the recommended method for transitioning patients from DTI infusions to warfarin. Therefore, health systems around the United States typically manage this transition in one of two ways:

1. Target an INR greater than 4 on overlap therapy with argatroban and warfarin; then argatroban can be discontinued when the INR is greater than 4 with combined therapy. After argatroban is discontinued, repeat the INR measurement in 4-6 hours to ensure INR remains therapeutic. If INR is subtherapeutic, argatroban should be restarted and the process is repeated until a therapeutic confirmatory INR is obtained. This is the present practice at our institution which is consistent with the argatroban package labeling.[4]
2. Based on an institution specific protocol, use chromogenic factor X assay and target the therapeutic range for CFX of approximately 20-45% while on combined DTI and warfarin therapy.[5-7] Once CFX is in therapeutic range, argatroban can be discontinued. Then a confirmatory INR should be measured 4-6 hours after argatroban discontinuation, to ensure that INR is therapeutic. If that INR is less than 2 the argatroban should be restarted and warfarin dose should be increased.

The CFX assay measures the amount of factor X activity and is not influenced by the DTI. In the lab, russell viper venom is added to the plasma, which converts only the carboxylated factor X to activated factor Xa. Since warfarin works by inhibiting carboxylation of the vitamin K dependent coagulation factors (II, VII, IX, X) the percentage carboxylated will be lower in a patient taking warfarin. This reaction is then quantified via chromatography and reported as a percentage of factor X activity with a higher percentage correlating with greater factor X activity.[8] Therefore, the CFX will decrease when patients take warfarin. Published literature supports CFX as an effective alternative to INR, but currently none of the most updated guidelines reviewed suggest using CFX levels. However, the 2008 CHEST guidelines on HIT recommend, "patients receiving argatroban who are being transitioned to a vitamin K antagonist, we suggest that factor X levels measured using a chromogenic assay be used to adjust the dose of the vitamin K antagonist" (Grade 2C).[9] Along with that, the 2012 CHEST guidelines on parenteral anticoagulants state that "Because holding argatroban may expose patients to a risk of thrombosis, another option is to monitor the vitamin K antagonist with a chromogenic factor X assay".[10] The primary literature supporting its use is from transitioning patients to warfarin from DTI and also in warfarin monitoring for patients with coagulation abnormalities affecting INR.[11,12]

This article will describe a quality improvement project that compared patients transitioned from DTIs to warfarin using INRs (pre-intervention) and patients transitioned using CFX levels after the creation and implementation of a pharmacist managed warfarin dosing protocol (post intervention). The primary objective was to compare the difference in therapeutic confirmatory INRs between the pre-intervention group transitioned from DTI to warfarin using INR and the post intervention group transitioned from DTI to warfarin using CFX. It was hypothesized that a higher percentage of therapeutic confirmatory INRs and a lower number of DTI and warfarin overlap days would be seen in the post intervention group.

FIGURE 1. Pre-intervention Patient Encounter Inclusion and Exclusion Diagram



Methods

This quality improvement project was reviewed and approved by the Institutional Review Board at Aurora Health Care. All patients who received argatroban or bivalirudin at our institution between June 1, 2017 and June 30, 2018 were identified and screened for inclusion into the pre-intervention group through data available in the electronic health record. Patients were eligible for inclusion if they were at least 18 years of age and had overlapping therapy with a DTI (argatroban or bivalirudin) and warfarin transitioning to warfarin therapy alone. Patients were excluded if argatroban or bivalirudin therapy did not overlap with warfarin, patients were switched to another parenteral agent (e.g heparin or fondaparinux), patients were transitioned from DTI therapy to other non-warfarin oral anticoagulants (e.g. apixaban or rivaroxaban) or if death occurred during the DTI and warfarin overlap time period.

The primary outcomes of this project were percentage of therapeutic INRs and days of DTI and warfarin overlap between the two groups. The secondary outcomes

TABLE 1. Pre and Post Intervention Demographics (n= Number of Patient Encounters)

	Pre-Intervention (n = 18)	*Post Intervention (n = 17)*
Age, in years, Median (Range)	58.5 (30 - 89)	68 (37 - 85)
Sex Male, N (%)*	13 (72%)	6 (35%)
Race, N (%) White African American Asian	 16 (89%) 2 (11%) 0 (0%)	 14 (82%) 2 (12%) 1 (5%)
**Statistically significant difference (p= 0.03)*		

were INR on DTI therapy alone, INR day of DTI discontinuation, confirmatory INR, percent of subtherapeutic confirmatory INR (<2.0), percent of supratherapeutic confirmatory INR (>3.5), dose of DTI (mcg/kg/min), days of DTI therapy, length of hospital stay from day 1 of overlap (days), number of thrombosis events, number of major bleeding events.

The pre-intervention patient group was transitioned from DTI to warfarin using INRs alone with no specific established protocol. The argatroban labeling recommendations for transitioning to warfarin were followed along with health care team's clinical judgement.[4] The process outlined in our institution was to initially target an INR greater than 4 on overlapping therapy with argatroban and warfarin. Argatroban can then be discontinued when the INR is greater than 4 with combined therapy. After argatroban is discontinued, repeat the INR measurement in 4-6 hours to ensure therapeutic INR values.

For post intervention patients, an institution specific "Pharmacist Managed Warfarin Dosing Using Chromogenic Factor X Assay During Direct Thrombin Inhibitor Overlap Therapy" protocol was developed. The protocol developed utilizes goal therapeutic CFX levels of approximately 20-40% correlating to an INR of 2.0-3.0 based on the approximate results of previously published literature and incorporates an institution specific warfarin dosing table based on the correlation between CFX and INR.[5-7] This protocol was created by pharmacists in collaboration with physicians on the hematology and oncology physician committee for feedback and approval. Education was presented to multiple other physician groups including cardiovascular surgery, critical care, cardiology, as well as clinical pharmacists. Hospitalists and nurse practitioners were educated on the process on a case by case basis. This protocol served as a guideline to manage post intervention patients in this project.

Post intervention patients were identified from October 1, 2018 through June 13, 2019. The same inclusion and exclusion criteria described above was used. The post intervention patients were monitored using the established pharmacist managed protocol using CFX levels in combination with the clinical judgement of the healthcare team. For the purposes of this project, a 'confirmatory INR' was defined as an INR 4-24 hour after DTI infusion was discontinued and therapeutic INR was defined as 2.0-3.5.

The Wilcoxon two-sample test was used for continuous variables and the chi-square or Fisher's exact test was used for categorical variables. Chromogenic factor X assays were performed using a Biophen Factor X Kit on a BCS-BCSXP analyzer by trained laboratory personnel.

Results

During the pre-intervention project period, 212 patient encounters received argatroban (80) or bivalirudin (132) and were screened for inclusion into this group. 192 of those encounters were excluded for the following reasons: no overlap with warfarin or death before DTI discontinuation. The majority of patients were not continued on argatroban or overlapped with warfarin for reasons including: negative PF4 or SRA and switch back to heparin products, short-term procedural use of DTI, transition to DOAC, transition to fondaparinux or death (Figure 1). The pre-intervention group included 18 encounters (17 argatroban, 1 bivalirudin) and the post intervention group included 17 encounters (16 argatroban, 1 bivalirudin). There were no deaths in either group during warfarin and DTI overlap therapy. The baseline demographic characteristics of patient population are presented in Table 1. Sex between groups was the only identified difference (p= 0.03).

The primary outcome of percent therapeutic confirmatory INR was similar between the two groups. (44% in the pre-intervention group and 71% in the post intervention group, p = 0.12). However, median days of warfarin and DTI overlap was significantly higher in the pre-intervention group than in the post intervention group (6.5 days vs. 5 days p = 0.04). No adverse bleeding or thrombotic events were observed in either group.

The secondary outcomes of INR day of DTI discontinuation, confirmatory INR, percent of subtherapeutic confirmatory INR, percent of supratherapeutic confirmatory INR, dose of DTI, total days of DTI therapy, length of hospital stay from day 1 of overlap, number of thrombosis events, number of major bleeding events are listed in Table 2. There were no differences between the two groups.

Discussion

To our knowledge, there are no other projects describing the implementation of a pharmacist managed protocol for transitioning patients from DTI to warfarin using CFX.

The pre-intervention results of this project were similar to findings in other published literature about using INR to transition patients from argatroban to warfarin. Hursting et al. retrospectively reviewed the outcome of therapeutic confirmatory INR in 108 patients who were transitioned, without specific guidelines or institutional protocols, from argatroban to warfarin therapy using INRs. This study found that 40% (43/108) patients achieved a therapeutic INR after argatroban therapy was discontinued.[13] We found similar results to this (44%, 8/18).

The results demonstrated by the post intervention group in this project show that CFX may be a useful assay for the healthcare team in determining when to discontinue the DTI infusion and have a confirmatory therapeutic INR on warfarin alone. McGlasson et. al, found that CFX was inversely related to and correlated well with INR (R= 0.964).[5] The CFX range was 18-48% (mean 28%) for patients with an INR 2.0-3.0 and that CFX yielded a sensitivity of 91.7% and a specificity of 91.9% for discriminating INR of at least 2.0. Their data suggests that the CFX can be a highly discriminative tool for differentiating therapeutic and subtherapeutic INRs in situations where confounders to INR may be present (e.g. DTI and warfarin overlap therapy).[5] From this project's pre-intervention findings as well as the other published literature it is evident that there is an opportunity for process improvement during this clinical scenario.

Furthermore, a few previously published articles have described a successful transition from DTI to warfarin using CFX and a relatively high percentage of therapeutic confirmatory INRs.[6-7] Arpino et al., conducted a prospective observational analysis in patients transitioning from argatroban to warfarin at their institution where use of CFX is the predominant method for measuring anticoagulation with patients on DTIs.[6] The authors found that a CFX level equal to or less than 45%, predicted a confirmatory INR of greater than or equal to 2 with an accuracy of 89%. They also found an average of 6 ± 3 doses of warfarin were administered during the overlap period, similar to the results found in this study. Similarly, Austin et al. found a sensitivity of 78.2%, specificity of 77.8% for CFX to accurately predict an INR greater than 2.0 in patients who received the recommended 5 or more days overlap with argatroban and warfarin.[7] These prior publications along with the results of this project, suggest that CFX is an accurate alternative method of measuring anticoagulation when converting hospitalized patients from argatroban to warfarin.

The clinical significance of increasing the percentage of obtaining therapeutic confirmatory INRs in terms of reducing adverse events is difficult to ascertain from a small population size. However, it can be hypothesized that the risk of bleeding events from supratherapeutic INRs as well as risk of thrombotic events from subtherapeutic INRs can be decreased by obtaining a therapeutic confirmatory INR, like any other disease state that requires anticoagulation with warfarin. Beyond patient safety and efficacy benefits, a therapeutic confirmatory INR will likely also decrease the medication cost of argatroban due to less days of overlap therapy and decrease hospital length of stay. Patients with subtherapeutic confirmatory INRs likely need to remain hospitalized and restart the argatroban resulting in an increased length of stay and increased drug costs. While patients with supratherapeutic INRs after argatroban discontinuation will not need to restart the infusion, they will have received longer than necessary DTI therapy and may require increased monitoring for signs of bleeding which can result in increased hospitalization.

It is important to remember laboratory interaction and false elevation in INR is directly related to the argatroban dose. Patients on lower doses of argatroban (typically <1 mcg/kg/min) will likely have less INR elevation than patients on higher doses. So waiting for co-therapy INR is 4.0 or greater may result in prolonged argatroban use and a supratherapeutic INR once the argatroban is discontinued. Furthermore, the FDA package labeling for argatroban dosing was derived from healthy patients in an outpatient setting and may not necessarily be representative of the effect of argatroban in hospitalized patients with other significant comorbidities.

Much published literature has described the value of pharmacists in the inpatient setting through integration and collaboration of pharmacists within the healthcare team and has demonstrated optimization of patient care. Specifically, for anticoagulation with direct thrombin inhibitors, Lobo et al. demonstrated significantly improved patient care. Results included fewer dosing errors, fewer bleeding events, and improved

TABLE 2. Primary and Secondary Outcomes

	Pre-Intervention (n = 18)	*Post Intervention (n = 17)*	*P-value*
Primary			
Therapeutic Confirmatory INR, N (%)	8 (44%)	12 (71%)	0.12
Days of Warfarin and DTI Overlap, Median (Range)	6.5 (3 - 17)	5 (3 - 16)	0.04
Secondary			
INR Day of DTI Discontinuation, Median (Range)	4.2 (2.4 - 10.4)	3.5 (2.1 - 12.0)	0.22
Confirmatory INR, Median (Range)	2.7 (1.6 - 7.1)	2.2 (1.7 - 4.0)	0.30
Confirmatory INR Group, N (%) Subtherapeutic (<2.0) Therapeutic (2.0 - 3.5) Supratherapeutic (>3.5)	 3 (17) 8 (44) 7 (39)	 3 (18) 12 (71) 2 (12)	0.36
Dose of DTI (mcg/kg/min), Median (Range)	0.60 (0.05 - 5.30)	0.50 (0.10 - 5.00)	0.25
Total days of DTI Therapy, Median (Range)	10 (5 - 31)	7 (3 - 23)	0.06
Length of Hospital Stay from Day 1 of Overlap, Median (Range)	15 (6 - 52)	8 (4 - 56)	0.07
Thrombosis Events, N (%)	0 (0)	0 (0)	N/A
Major Bleeding Events, N (%)	0 (0)	0 (0)	N/A

documentation when pharmacists were more involved and managed DTIs for patients with HIT through a pharmacist-managed protocol.[14] Their findings suggest that the combination of a pharmacist's skillset and set protocols can benefit patient care. The intent of this project was to improve patient care by implementing a pharmacist managed warfarin dosing protocol for patients transitioning from DTI to warfarin using CFX. Overall, physicians at our institution agreed that transitioning patients from argatroban to warfarin presents a challenging clinical situation and were in full support of a pharmacist managed warfarin dosing protocol utilizing CFX to monitor these patients. In addition, there was overwhelming support from the hematology/oncology physician committee to include pharmacists in the role of managing the transition in collaboration with the consulting physician.

This quality improvement project was not without limitations in project design, patient population and implementation challenges. First, it is important to recognize that there are many confounding variables that happen over the course of a hospitalization that could have impacted results which were outside the scope of this project. Second, there was a small patient population and relatively short length of data collection period in both the pre and post intervention groups. Third, CFX assay was a send-out lab with a turnaround time was approximately 18 hours, potentially leading to continuing the DTI infusion for longer than necessary until the CFX level resulted.

Conclusion

Using only INRs during the DTI and warfarin overlap period does not result in achieving a confirmatory therapeutic INR in most patients and room for improvement in this process exists. It appears CFX offers an effective alternative to clinicians transitioning patients from argatroban to warfarin that may result in a greater percentage of therapeutic confirmatory INRs and decreases days of overlap therapy. Future studies are necessary to further evaluate the clinical usefulness, cost effectiveness and patient safety benefits of using CFX as an alternative to INR to measure the anticoagulation effects of warfarin when transitioning patients from argatroban to warfarin.

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