Outcomes of Urgent Warfarin Reversal Using Fresh Frozen Plasma versus Prothrombin Complex Concentrate in the Emergency Department

Running title: Hickey et al.; Complications from Octaplex versus FFP

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Abstract:

**Background**—Physicians reverse patients’ warfarin anticoagulation with frozen plasma or prothrombin complex concentrate. Our objective was to determine adverse event frequency following urgent reversal using frozen plasma versus the prothrombin complex concentrate Octaplex.

**Methods and Results**—This natural before-after retrospective cohort study in two tertiary care emergency departments (EDs) compared anticoagulation reversal between frozen plasma (utilized from September 2006-August 2008) and Octaplex (from September 2008-August 2010), without other system changes. We included adult patients on warfarin with an INR ≥1.5 and received frozen plasma or Octaplex. Our primary outcome was serious adverse events (death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism or peripheral arterial thromboembolism) within 7 days. Secondary outcomes included time to INR reversal, hospital length of stay and red blood cells transfused within 48 hours. We included 149 patients receiving frozen plasma and 165 receiving Octaplex. Incidence of serious adverse events for the frozen plasma group was 19.5% versus 9.7% for the Octaplex group (p=0.014, Relative Risk (RR) 2.0, 95% CI 1.1 to 3.5). This remained significant after adjusting for baseline history and reason for treatment (p=0.038, adjusted RR 1.85, 95% CI 1.03 to 3.3) using multivariable regression analysis. Median INR reversal was 11.8 hours using frozen plasma and 5.7 hours using Octaplex (p<0.0001). Mean red cell transfusion was 3.2 using frozen plasma and 1.4 using Octaplex (p<0.0001).

**Conclusions**—Octaplex for urgent reversal of warfarin resulted in faster reversal, lower red cell transfusion requirements with fewer adverse events than frozen plasma.

**Key words:** Octaplex, Critical Care, emergency department, anticoagulation, hemorrhage
Introduction

Warfarin administration has been a standard means of preventing thromboembolism in patients with atrial fibrillation, prosthetic heart valves and venous thromboembolism for over 50 years. Because of a narrow therapeutic window, as many as 3 to 7% of patients taking warfarin are at risk of major, life-threatening bleeding and it is generally believed that this requires rapid and complete warfarin reversal. Current guidelines suggest rapid reversal of anticoagulation with a 4-factor prothrombin complex concentrate in addition to 5-10 mg of intravenous Vitamin K. It is believed that the co-administration of Vitamin K in this setting prevents rebound increases in the INR and provides sustained reversal of anticoagulation.

Frozen plasma and prothrombin complex concentrate are two products that are widely used to rapidly achieve replacement of vitamin K dependant clotting factors. Transfusion of frozen plasma for emergency reversal of anticoagulation in the bleeding patient is not ideal. Risks include transmission of infection, allergic reactions, volume overload, incomplete reversal and increased time to administration due to thawing requirements. Therefore, reversal of anticoagulation in the patient with major bleeding with prothrombin complex concentrate may be preferable to frozen plasma. However, numerous previous studies have reported thromboembolic events in patients treated with prothrombin complex concentrate, but these studies are limited by their small sample size and lack of a comparison group.

The clinical importance of this subject lies in the fact that administration of prothrombin complex concentrate for emergency reversal of warfarin induced anticoagulation has become the “standard of care” at our local tertiary care institutions and many others known to the authors, yet we still do not have a complete understanding of the safety profile of these products versus the previous standard of care, frozen plasma.
The objective of this study is to compare the efficacy and safety of frozen plasma to that of Octaplex®, the available 4-factor prothrombin complex concentrate at our emergency departments during the study period. Specifically, we examine adverse effects, time to INR reversal, hospital length of stay and red cell transfusion requirements.

Methods

Design and Setting

This retrospective cohort study was conducted using health records of patients who were treated with frozen plasma or Octaplex for emergency reversal of warfarin anticoagulation therapy in two tertiary emergency departments (ED) at our institution, seeing a total of approximately 120,000 ED visits per year. We compared patients who received frozen plasma over a two-year period prior to the introduction of Octaplex in September 2008, to those who received Octaplex over an equivalent time period after September 2008. The treatments for both groups were given or started within the ED. The dose of Octaplex administered during the study period was governed by transfusion medicine. A standard dose of 1500 IU was administered to patients with intracranial hemorrhage and a dose of 1000 IU was used for all other patients. This study was approved by our institution’s research ethics board.

Study Population

We included patients who were 18 years of age or older, taking warfarin with an INR of 1.5 or higher, and had received either frozen plasma or Octaplex in the ED either for active bleeding or prior to an emergency procedure, whether it was ordered by an emergency physician or consulting service. We excluded patients who were less than 18 years of age, if there was no documentation that the patient was taking warfarin, if frozen plasma or Octaplex was
administered without an initial INR check, or if patients received both frozen plasma and Octaplex within 7 days. There were no predetermined standardized transfusion parameters for either group and patients who received frozen plasma were assumed to receive usual clinical care with regards to resuscitation and transfusion as determined by the most responsible physician. The standard practice at our institution during the study period was to administer 40 ml of Octaplex (approximately 1000 IU of prothrombin complex concentrate), and a repeat INR check approximately 15 minutes after administration. There were no other changes instituted to patient management over this time period. Because of the retrospective nature of this study, there were no risks imposed on any patients.

Data Collection and Management
Consecutive patients who received frozen plasma over a two year period prior to the introduction of Octaplex were identified by a health records analyst at The Ottawa Hospital using WinRecs software (MED2020 Health Care Software Inc, Ottawa, ON). Consecutive patients who received Octaplex over a similar period of time were identified by means of an electronic database maintained by Transfusion Medicine which includes all patients who receive Octaplex at the institution. These charts were identified by personnel not directly involved in the study and unaware of the study design. Once patients were identified, data were collected by means of a review of paper and electronic health records, discharge summaries, diagnostic imaging and laboratory reports. Data were extracted onto standardized data abstraction sheets by two of the investigators (MH and AA). The first 15 patients were independently reviewed by a third investigator (MG).

Outcome Measures
The primary outcome, incidence of serious adverse events within seven days of receiving either
frozen plasma or Octaplex in the ED, was a composite consisting of the following events: death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism and peripheral arterial thromboembolism. Secondary outcomes included time to INR reversal (as defined by an INR < 1.5), hospital length of stay and number of units of packed red blood cells transfused within 48 hours. Adverse outcomes were defined a priori. Myocardial infarction was defined as per the World Health Organization definition with two out of three of: documented typical symptoms of infarction, elevation of plasma cardiac biomarkers and a typical ECG pattern involving the development of Q waves. Ischemic stroke was defined as documented focal neurological deficits consistent with acute ischemic stroke without hemorrhage on neuroimaging. Heart failure was defined as presumed new bilateral pulmonary edema confirmed on a final radiology report of chest radiography combined with documented treatment for volume overload. Pulmonary embolism was defined as confirmed diagnosis on final radiology report of computed tomography or high probability ventilation / perfusion scan and treatment with anticoagulation or insertion of an inferior vena cava filter. Deep venous thrombosis was defined as an acute thrombus either above the elbow, above the knee, or in abdominal / pelvic veins, as confirmed on a final radiology report of a duplex ultrasound. An arterial thromboembolic event was defined as an event confirmed on a final radiology report of conventional or computed tomography angiography or a high suspicion as documented by a vascular surgeon or designate and intervention for the same.

**Analysis and Sample Size Calculation**

Data were entered into SAS (SAS Institute, Cary, NC) by trained data entry personnel. Baseline characteristics and past medical history of study patients were described using mean and standard deviation for continuous variables (or median and first and third quartiles for skewed
distributions) and frequencies and proportions for categorical variables. Differences between the frozen plasma and Octaplex groups were tested using two-sample t-tests (or Wilcoxon tests) for continuous variables, and chi-squared tests for categorical variables. Differences in the reason for anticoagulation and reason for treatment between the groups were tested using Fisher's exact tests. Variables with either statistically or clinically significant differences between the groups were identified as potential confounders.

The incidence of serious adverse events was compared between the groups using Chi-squared tests (or Fisher's exact tests in the case of small expected counts). The relative difference in incidence was described using Relative Risk (RR), together with 95% confidence interval (CI). To account for potential confounders, we conducted a multivariable regression analysis with incidence of serious adverse events as the dichotomous dependent variable, group (Octaplex vs. Frozen Plasma) as the primary predictor variable, and all potential confounders entered as covariates. We used modified Poisson regression analysis with robust error variance\(^\text{14}\) rather than logistic regression because the effect measure of interest is a Relative Risk, rather than an Odds Ratio. The modified Poisson regression analysis as described by Zou\(^\text{14}\) is easily implemented in standard statistical packages alongside logistic regression by specifying the log-link function together with the sandwich variance estimator for the regression coefficients. Variables with multiple categories with small counts (e.g., indications for reversal) were redefined by combining similar categories prior to entry in the multivariable model.

Secondary outcomes were compared using two-sample t-tests (or Wilcoxon tests for variables with a skewed distribution).

The sample size was not calculated based on the number of expected outcomes, but rather based on the maximum time period for which Octaplex data was available at the time the study
was designed.

Results

Figure 1 depicts the number of patients that were identified and met inclusion criteria for the study. Two hundred and twelve (212) patients were identified in the frozen plasma group and 451 patients in the Octaplex group with 63 and 286 patients excluded from each group, respectively, leaving 149 patients who received frozen plasma and 165 patients who received Octaplex in the analysis. Figure 1 presents details regarding excluded patients.

Baseline characteristics for study patients are presented in Table 1. Both groups were similar with the exception of more patients having a history of heart failure and ischemic heart disease in the frozen plasma group and more patients with venous thromboembolism in the Octaplex group.

As depicted in Table 2, both groups had similar indications for anticoagulation therapy, with atrial fibrillation being the most common, followed by prophylaxis for an artificial valve, and treatment or prophylaxis for previous venous thromboembolism.

Table 3 shows the indications for reversal of anticoagulation in both groups. The majority of patients suffered from gastrointestinal bleeding or intracranial hemorrhage. This pattern is consistent with a recent study that also examined the use of prothrombin complex concentrate in reversal of warfarin induced anticoagulation\textsuperscript{15}. However, more patients in the plasma group received treatment for intracranial hemorrhage while more patients in the Octaplex group received treatment prior to a procedure.

Table 4 shows the incidence of each adverse event type observed in the two groups. There was a significantly higher incidence of serious adverse events amongst patients who
received frozen plasma (19.5% versus 9.7%, RR 2.01, 95% CI 1.14 to 3.54, p=0.0164).

Significantly more patients in the frozen plasma group suffered from heart failure after treatment as compared to the Octaplex group (2.7% vs. 0, Fisher’s exact p<0.05). Full reversal of anticoagulation was significantly more rapid in the Octaplex group and transfusion requirements for packed red blood cells significantly lower than in the plasma group (Table 4). Mean hospital length of stay did not differ significantly between groups.

After adjusting for history of heart failure, venous thromboembolism and Ischemic Heart Disease, as well as indication for reversal (defined as a 4-level categorical variable with categories gastrointestinal bleed, intracranial hemorrhage, pre-procedure and other), the incidence of serious adverse events remained significantly higher in the frozen plasma group RR 1.85, 95% CI 1.03 to 3.31, p=0.0384) (Table 4).

**Discussion**

We found that the use of Octaplex for emergency reversal of warfarin anticoagulation in the emergency department achieves reversal faster and is associated with significantly fewer adverse events and lower transfusion requirements. However, hospital lengths of stay were similar between the two groups.

**Comparison with Previous Studies**

This is one of few studies that compared the use of a prothrombin complex concentrate versus conventional therapy for emergency reversal of anticoagulation. It is also the largest study that we are aware of that has focused on anticoagulation reversal within the emergency department setting. A previous small study examined 13 warfarin-anticoagulated patients with intracranial hemorrhage randomized to receive either frozen plasma and Factor IX complex concentrate, or
frozen plasma alone and showed that the use of frozen plasma with Factor IX complex concentrate resulted in significantly faster reversal of anticoagulation than frozen plasma alone. There are conflicting data regarding the safety of administration of prothrombin complex concentrates for reversal of warfarin-induced coagulopathy, and numerous previously published studies have suggested that it may be associated with thromboembolic adverse events. However, most studies on this subject are small retrospective case series that do not have a comparison group of other reversal agents such as frozen plasma, and a recent publication that examined 256 cases of reversal of warfarin induced anticoagulation using prothrombin complex concentrate found no incidence of a thromboembolic event. Additionally, there is some thought that the risk of a patient having a thrombotic adverse event may be based on an underlying inherent risk of thrombogenesis, and may not be entirely caused by the administration of prothrombin complex concentrate.

Clinical and Research Implications
Our study shows that Octaplex can reverse anticoagulation faster than frozen plasma and with fewer adverse events, and should be considered as a first line treatment in such cases as described here. However, clinicians must weigh the risks and benefits of this treatment in relation to the impact of refraining from reversing anticoagulation in a bleeding patient, as thromboembolic events can occur. Further prospective studies should be undertaken to confirm our findings. Furthermore, future research should be done to ascertain the optimal dose of Octaplex to achieve the greatest efficacy while minimizing adverse events.

Limitations
There are several limitations to our study. There may have been some unobserved differences between the groups. While we endeavored to have two very similar groups with our design by...
enrolling consecutive patients in each arm, we may not have been completely successful. While the groups seem generally well-balanced in terms of baseline characteristics, there were more patients in the frozen plasma group with a previous history of heart failure and more patients in the frozen plasma group requiring reversal for an intracranial hemorrhage. We adjusted for these imbalances using multivariable regression analyses and found similar results after adjustment.

Another limitation is that the data were obtained retrospectively. While retrospective data collection has risks of missing data, the data points collected for our primary outcome and baseline characteristics are ones reliably available within the medical records. In this retrospective study, we were not able to standardize the timing of the interventions, and as such there may have been some differences between groups. However such differences are more likely related to the ease of administration of the frozen plasma or the Octaplex as there were no other systematic changes that we are aware of during the study period. Additionally, the timing of INR measurements following administration of frozen plasma and Octaplex was highly variable, despite recommendations in the Octaplex protocol for measurements at 15 minutes, leading to missing time points in our data. We estimate that documentation of effective reversal would have been even sooner in the Octaplex group, given its high success rate as measured on first INR.

We limited our follow-up to 7 days, as we thought that it would be difficult to attribute a causal link to reversal agents for events occurring outside this time window. Also, we felt that the majority of patients receiving emergent warfarin reversal would likely still be in hospital or receiving close follow-up during this time period. This would limit the chances of patients having a serious adverse event which was not documented within the health records at our own institution. There is a small risk that some of our patients may have had a serious adverse event.
for which they died out of hospital or they sought care at another local institution, however given that our institution is the only tertiary care center in the region and that most patients were still admitted at 7 days, the likelihood is small. In addition, due to our before-after quasi-experimental design, the likelihood of this is equal in both the frozen plasma and Octaplex groups.

Patient outcomes were adjudicated in an unblinded fashion. This may have resulted in some ascertainment bias. We minimized this risk by having a-priori definitions of serious adverse events, including clear and strict definitions of each component of this composite outcome. Finally, we excluded patients treated with both frozen plasma and Octaplex. It is possible that more aggressively treated patients may have had different underlying risks for adverse events. Patients excluded for these reasons were similar, about 11%, in both groups. Given that this difference is small, we believe that the magnitude of selection bias will be small, and unlikely to account for all the differences found.

Conclusion

Our study found that Octaplex administration for emergency reversal of warfarin induced anticoagulation was faster, led to lower red cell transfusion requirements and was associated with fewer adverse events than that of frozen plasma. Our before-after observational study therefore suggests that Octaplex may be superior to frozen plasma when used in this context.

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Conflict of Interest Disclosures: None.

References:


12. Song MM, Warne CP, Crowther MA. Prothrombin complex concentrate (PCC, Octaplex®)


Table 1. Baseline Characteristics and Past Medical History of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frozen Plasma (N=149)</th>
<th>Octaplex (N=165)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD), yr</td>
<td>76 (11.2)</td>
<td>77 (10.8)</td>
<td>0.664</td>
</tr>
<tr>
<td>Male (%)</td>
<td>81 (54.4)</td>
<td>99 (60)</td>
<td>0.313</td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>50 (33.6)</td>
<td>32 (19.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Venous Thromboembolism (%)</td>
<td>10 (6.7)</td>
<td>22 (13.3)</td>
<td>0.053</td>
</tr>
<tr>
<td>Ischemic Heart Disease (%)</td>
<td>62 (41.6)</td>
<td>52 (31.5)</td>
<td>0.063</td>
</tr>
<tr>
<td>Gastrointestinal Bleed (%)</td>
<td>15 (10.1)</td>
<td>12 (7.3)</td>
<td>0.379</td>
</tr>
<tr>
<td>Hemodialysis (%)</td>
<td>4 (2.7)</td>
<td>6 (3.6)</td>
<td>0.753</td>
</tr>
<tr>
<td>Ischemic Stroke (%)</td>
<td>31 (20.8)</td>
<td>33 (20.0)</td>
<td>0.860</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (%)</td>
<td>13 (8.7)</td>
<td>8 (4.8)</td>
<td>0.170</td>
</tr>
<tr>
<td>Anti-platelet (%)</td>
<td>33 (22.1)</td>
<td>40 (24.2)</td>
<td>0.661</td>
</tr>
<tr>
<td>Initial INR (Median, Q1-Q3)</td>
<td>2.9 (2.2-5.2)</td>
<td>3.0 (2.3-4.5)</td>
<td>0.432</td>
</tr>
</tbody>
</table>

Reason for Anticoagulation

<table>
<thead>
<tr>
<th>Reason for Anticoagulation</th>
<th>Frozen Plasma (N=149)</th>
<th>Octaplex (N=165)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation (%)</td>
<td>122 (81.9)</td>
<td>126 (76.4)</td>
<td>0.7312</td>
</tr>
<tr>
<td>Artificial Valve (%)</td>
<td>13 (8.7)</td>
<td>15 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Venous Thromboembolism* (%)</td>
<td>9 (6)</td>
<td>13 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Low Ejection Fraction (%)</td>
<td>2 (1.3)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Previous Stroke (%)</td>
<td>2 (1.3)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Hypercoagulable (%)</td>
<td>1 (0.7)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>0 (0)</td>
<td>3 (1.8)</td>
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</tr>
</tbody>
</table>

*for treatment or secondary prophylaxis of DVT and PE

Table 2. Reason for Anticoagulation Reversal Treatment

<table>
<thead>
<tr>
<th>Reason for Reversal Treatment (%)</th>
<th>Frozen Plasma (N=149)</th>
<th>Octaplex (N=165)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Bleed</td>
<td>63 (42.3)</td>
<td>61 (37.0)</td>
<td></td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>44 (29.5)</td>
<td>35 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Pre-procedure</td>
<td>21 (14.1)</td>
<td>37 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Major Trauma</td>
<td>1 (0.7)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Other Bleeding</td>
<td>5 (3.4)</td>
<td>10 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15 (10.1)</td>
<td>18 (10.9)</td>
<td></td>
</tr>
</tbody>
</table>

p-value for difference between groups using Fisher's exact test is 0.1398
Table 3. Adverse Events and Secondary Outcomes

<table>
<thead>
<tr>
<th>Adverse Event (%)</th>
<th>Frozen Plasma (N=149)</th>
<th>Octaplex (N=165)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>29 (19.5)</td>
<td>16 (9.7)</td>
<td>0.014</td>
</tr>
<tr>
<td>Death</td>
<td>22 (14.8)</td>
<td>15 (9.1)</td>
<td>0.120</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2 (1.3)</td>
<td>1 (0.6)</td>
<td>0.606</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>4 (2.7)</td>
<td>0 (0)</td>
<td>0.0496</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Deep Venous Thrombosis</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0.475</td>
</tr>
<tr>
<td>Arterial Thromboembolism</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Any Adverse Event Excluding Death</td>
<td>7 (4.7)</td>
<td>1 (0.6)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Secondary Outcomes

| Time to INR reversal (hours) (Median, Q1-Q3) | 11.8 (8.3-17.5) | 5.7 (3.4-11.0) | <0.0001 |
| Hospital length of stay (days) (Median, Q1-Q3) | 5 (2-12) | 4 (2-11) | 0.245 |
| Mean units of packed red blood cells (Mean, SD) | 3.2 (1.8) | 1.4 (1.7) | <0.0001 |

Table 4. Multivariable Regression Analysis to Obtain Adjusted Relative Risk of Serious Adverse Events

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen Plasma vs. Octaplex</td>
<td>1.85</td>
<td>1.03 to 3.3</td>
</tr>
<tr>
<td>Reason for treatment</td>
<td></td>
<td>0.0043</td>
</tr>
<tr>
<td>Gastrointestinal Bleed vs. other</td>
<td>3.21</td>
<td>0.77 to 13.4</td>
</tr>
<tr>
<td>Intracranial Hemorrhage vs. other</td>
<td>5.87</td>
<td>1.41 to 24.4</td>
</tr>
<tr>
<td>Pre-procedure vs. other</td>
<td>5.03</td>
<td>1.18 to 21.5</td>
</tr>
<tr>
<td>Pre-existing conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.04</td>
<td>0.58 to 1.87</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>0.51</td>
<td>0.22 to 1.15</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>0.40</td>
<td>0.09 to 1.69</td>
</tr>
</tbody>
</table>

Figure Legend:

Figure 1. Study Enrollment.
Eligible Frozen Plasma Patients
N=212

- Excluded
  N=63
    - 24 received both
    - 19 received outside of ED
    - 15 not on warfarin
    - 3 incorrect chart number
    - 2 duplicates

Patients Enrolled
N=149

Eligible Octaplex Patients
N=451

- Excluded
  N=286
    - 213 not on warfarin
    - 48 received both
    - 18 outside of ED
    - 7 incorrect chart number

Patients Enrolled
N=165
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