

# Type and Timing of Reversal Agents in Patients Receiving Warfarin Who are Hospitalized for Major Bleeding

Jad Omran, MD<sup>1</sup>, Ben Nordhues MD<sup>2</sup>, Blake Buchert<sup>3</sup>, and Greg C. Flaker, MD, FACC<sup>4\*</sup>

<sup>1</sup>Cardiovascular Medicine Department, University of Missouri Hospital and Clinics

<sup>2</sup>Internal Medicine Department, Mayo Clinic

<sup>3</sup>Vanderbilt University

<sup>4</sup>Cardiovascular Medicine department, University of Missouri Hospital and Clinics

## Abstract

### Background

In patients with warfarin-induced major bleeding, prompt administration of reversal agents increases coagulation factors and may allow early surgical correction of bleeding. However even with reversal agents, mortality is high. In this analysis the type and timing of reversal agents were evaluated

### Methods

Review of warfarin treated non-trauma patients admitted to a University Hospital with ISTH defined major bleeding between October 2009 and January 2013.

### Results

84 patients met entry criteria with a mean age  $67.8 \pm 14.3$  years including 46 % females. The mean INR on admission was  $3.6 \pm 2.4$ . The site of major bleeding was central nervous system in 33 (39%), abdomen in 28 (33%), chest in 6 (7%) and other in 15 (18 %). Reversal agents including vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) were given to 83 patients. Forty patients required either major surgery (25 patients) or a therapeutic procedure (14 patients) to stop bleeding. Death occurred in 15 patients (18%) but the admission INR was not predictive of mortality ( $p=0.52$ , Kruskal-Wallis test). The INR was never completely corrected ( $INR < 1.1$ ) in 31 (37%) patients, 9 of whom died.

### Conclusions

Patients with warfarin-induced major bleeding receive ineffective anticoagulation reversal, have delayed times to therapeutic procedures, and have a high mortality rate. Whether earlier administration of these agents or administration of newer agents would reduce hospital mortality requires further study.

\*Corresponding author: Greg C. Flaker, Cardiovascular Medicine department, University of Missouri Hospital and Clinics, CE 351 University of Missouri, Columbia Mo. 65212, 573-882-2296, Tel: 573-882-2296; Fax: 573-882-8450; E-mail: flakerg@health.missouri.edu

Citation: Omran J, Nordhues B, Buchert B, Flaker GC (2014) Type and Timing of Reversal Agents in Patients Receiving Warfarin Who are Hospitalized for Major Bleeding. Enliven: Clin Cardiol Res 1(1): 001.

Copyright: © 2014 Dr. Greg C. Flaker. This is an Open Access article published and distributed under the terms of the Creative Commons Attribution License, that permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Received Date: 30 June 2014

Accepted Date: 23 July 2014

Published Date: 27 July 2014

## Introduction

Major bleeding associated with warfarin has a high mortality rate [1]. Reversal agents including vitamin K, fresh frozen plasma (FFP) and, more recently, prothrombin complex concentrate (PCC), are recommended to rapidly correct the coagulopathy [2] and to allow early surgical treatment of the bleeding source. However, despite the use of reversal agents, mortality still remains high [3]. The reason for this lack of improvement is uncertain. One hypothesis is that delay in the administration of reversal agents or even administration of less effective reversal agents may contribute to the high mortality in warfarin treated patients who have major bleeding. This manuscript analyzes the type and timing of reversal agents used in these patients.

## Methods

From October 2009 until January 1, 2013, 539 non-trauma patients who were admitted to a University Hospital with an ICD-9 code of hemorrhage, major bleeding, or coagulopathy were identified. Only those patients known to be receiving warfarin at the time of admission and those meeting ISTH criteria for major bleeding [4] were included in this analysis. Summary statistics were calculated and the Wilcoxon Rank Sum test was used to examine associations between mortality and age as well as admission INR, hemoglobin, and estimated glomerular filtration rate.

## Results

A total of 84 patients met entry criteria. The mean age was  $67.8 \pm 14.3$  years and 46% were female. The mean INR on admission was  $3.6 \pm 2.4$ . The site of bleeding was central nervous system (33 patients), abdominal (28 patients), chest (6 patients) and other site (15 cases). The mean hemoglobin on admission was  $10.6 \pm 2.8$  gm/dl. The most common reversal agent used was a combination of vitamin K and fresh frozen plasma (Table 1).

The average time from admission to administration of a reversal agent was  $5.6 \pm 8.1$  hours. The admission service was a medical specialty in 39 patients and a surgical specialty in 45 patients. A total of 40 patients (30%) underwent either major surgery (25 patients) or other therapeutic procedure (14 patients) to stop bleeding. The average time from admission to corrective procedure was  $17.8 \pm 34.9$  hours including one patient with a time to procedure of 168 hours. Overall, only 61.9% of patients had their INR corrected during hospitalization. The mean number of days in the ICU was  $6.3 \pm 8$  days; the mean hospital stay was  $10.9 \pm 9.2$  days. A total of 15 patients died during the hospitalization. No significant ( $p < 0.05$ ) association between mortality and age, admission INR, hemoglobin, or estimated glomerular filtration rate was noted (Table 1).

## Discussion

A disadvantage of novel oral anticoagulant agents is the lack of a reversal agent. However, this study demonstrates a high mortality rate in patients with a modestly elevated INR, the majority of whom received a reversal agent for major bleeding. We report substantial delays in the administration of these agents and substantial delays in the time to surgical procedures required to stop bleeding. In addition, the use of PCC, which provides factors II, IX, and X (three factor) or II, VII, IX, X (four factor) and which now is the preferred reversal agent, was used infrequently in this study. The infrequent use of PCC for major bleeding in patients receiving anticoagulation has also been reported in a recent clinical trial [5]. Whether or not more timely administration of reversal agents or the use of more effective reversal agents will reduce mortality in warfarin treated patients with major bleeding should be the subject of future studies.

Reversal agent(s)	Admission INR	Time to Reversal Therapy (hours)	Time to Procedure to Correct Bleed (hours)	Mortality Rate
Vitamin K n=49	$4.4 \pm 2.8$	$4.9 \pm 6.7$	$11.7 \pm 8.3$	18.4 %
Fresh Frozen Plasma(FFP) n=78	$3.6 \pm 2.4$	$5.3 \pm 7.6$	$11.1 \pm 10.0$	17.9 %
Prothrombin Complex n=2	$5.9 \pm 4.5$	$0.6 \pm 0.5$	5.5	0 %
Vitamin K and FFP n=45	$4.4 \pm 2.8$	$4.2 \pm 4.7$	$11.7 \pm 8.3$	17.8 %

Table:1

## References

1. De Caterina R, Connolly SJ, Pogue J, Chrolavicius S, Budaj A, et al. (2010) Mortality predictors and effects of antithrombotic therapies in atrial fibrillation: insights from ACTIVE-W. *Euro Heart J* 17: 2133-2137.
2. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, et al. (2012) Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141: e44S-88S.
3. Dowlatshahi D, Butcher K, Asdaghi N, Nahirniak S, Bernbaum M, et al. (2012) Poor Prognosis in Warfarin-Associated Intracranial Hemorrhage Despite Anticoagulation Reversal. *Stroke* 43:1812-1817.
4. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 3: 692-694.
5. Majeed A, Hwang H, Connolly SJ, Eikelboom JW, Ezekowitz MD, et al. (2013) Management and Outcomes of Major Bleeding During Treatment with Dabigatran or Warfarin. *Circulation* 128: 2325-2332.

**Submit your manuscript at**  
**<http://enlivenarchive.org/submit-manuscript.php>**  
**New initiative of Enliven Archive**

Apart from providing HTML, PDF versions; we also provide **video version** and deposit the videos in about 15 freely accessible social network sites that promote videos which in turn will aid in rapid circulation of articles published with us.