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Abstract

Background

Recombinant activated factor VII (rFVIIa) is being increasingly used as a treatment option in settings of uncontrolled bleeding. Despite this, national practice guidelines are lacking, resulting in widespread practice variation between providers.

Aim

This investigation aimed to describe the differences in use of rFVIIa across Australian and New Zealand hospitals.

Methods

Data were extracted from the Haemostasis Registry that collects both contemporaneous and retrospective cases of off-licence (i.e. in non-haemophilia patients) rFVIIa use in participating institutions. Hospitals were classified according to geographical location and service provision.

Results

2075 cases from 87 hospitals were recorded on the Haemostasis Registry. Across all hospital categories, over 41% of cases received rFVIIa in relation to cardiac surgery. Case complexity varied between providers, with large urban centres treating more severely ill patients. This was reflected in significant differences in the use of blood components and products before rFVIIa administration. Despite differences in patient complexity and use of blood products between hospital categories, response to treatment and patient outcomes remained similar across providers, with survival rates ranging from 68.29% to 70.41%.

Conclusion

This is the largest study of off-licence use of rFVIIa. There is significant regional variation in the administration of rFVIIa in Australian and New Zealand hospitals, with little documentation of adherence to guidelines. National consensus guidelines based on available evidence should be developed and promulgated to ensure optimal outcomes.

Key Words

Haemostasis

Haemorrhage

Factor VIIa

NovoSeven

Dosage

Introduction

The effective management of bleeding episodes in patients with haemophilia as well as Glanzmann's thrombasthenia and congenital factor VII deficiency has led to extended use of rFVIIa in off-label indications for patients suffering uncontrolled haemorrhage and coagulopathy primarily due to trauma and surgical interventions. Reports of increased mortality associated with the transfusion of blood components have increased the appeal of prohaemostatic agents such as rFVIIa in off-label settings.^{1,2} This interest has been accompanied by an increase in publication of randomised control trials investigating the off-label use of rFVIIa in a variety of clinical settings. While such trials have demonstrated some positive effects for patients with intracerebral haemorrhage, gastrointestinal bleeding, liver disease or hematopoietic stem cell transplantation, little improvement in patient outcomes or in the rate of adverse thromboembolic events with different rFVIIa dosage regimes have been reported.^{3,4,5,6}

Reduced blood product replacement has been widely documented as a marker of rFVIIa's clinical effectiveness,⁷ however of greater interest is the association between rFVIIa administration and thromboembolic adverse events (TAE) and mortality. TAE's remain rare events with many studies unable to demonstrate statistically significant associations between rFVIIa administration and the development of DVT, CVA or arterial thrombosis.⁸⁻¹¹ Suggestions of a possible dose dependent link between rFVIIa and the development of TAEs has reinforced the need for further examination of the current administration practices in Australian and New Zealand hospitals.

Therefore, in this paper we examine the current off-label use of rFVIIa across different hospital levels from Australia and New Zealand facilities participating in the Haemostasis Registry. This investigation aimed to describe possible clinical and non-clinical factors that may be associated with differing rFVIIa administrations across hospital categories using data from the Haemostasis Registry. The Registry was

established to gain information on the safety, efficacy, appropriateness of use, dosage details and cost effectiveness of off licence rFVIIa and to provide observational data of value for the development of prospective trials through which clinical guidelines may be developed. Results from this investigation represent an important first step in determining current practice variation based on hospital location and the consequent availability of blood products and serve to inform future studies examining use of rFVIIa by clinical indication. Data from April 2000 to September 2008 is presented.

Methods

The Haemostasis Registry captures all cases of off-label use of rFVIIa in non-haemophiliac patients treated at participating hospitals in Australia and New Zealand. The Haemostasis Registry has been established in the Department of Epidemiology and Preventive Medicine, Monash University since 2005. Ethics approval has been obtained from the Standing Committee on Ethical Research involving Humans of Monash University as well as all participating hospitals. The Registry collects de-identified information and does not require informed patient consent. Data is extracted from the medical record by trained data collectors at each site using a standardised electronic case report form for direct web based entry. All data entries are then verified and validated by central registry staff prior to inclusion on the registry. Any additional information required is then ascertained from local investigators. Outcomes are collected up to 28 days following rFVIIa administration.

Patients

Since its beginnings in 2005, the Haemostasis Registry has expanded to now include patients treated within 87 hospitals across Australia and New Zealand. All non-haemophiliac patients treated with rFVIIa in all participating hospitals are recorded on the registry. Patients are identified by local investigators through haematology and/or pharmacy records following administration of rFVIIa. In this study all patients receiving rFVIIa until September 2008 were included.

Hospitals are designated to one of four categories based upon their geographical location and services offered. Hospitals operating a Major Trauma, Cardiac or Transplant service are categorised as Category 1 hospitals, while other services without such facilities but within metropolitan regions are designated Metropolitan services (Category 2). Similarly, hospitals serving regional communities are classified as Regional services (Category 3), while those providers delivering specialist care to women, children or cancer patients are classified as Specialist services (Category 4).

Data

The following data items were extracted from the Haemostasis Registry for each patient: age, gender, hospital service category, context of bleed, blood components administered prior to rFVIIa (cryoprecipitate, red blood cells, platelets, fresh frozen plasma and total blood products), initial dose volume of rFVIIa, mortality, thromboembolic adverse events (CVA, TIA, DVT, PE, Arterial thrombosis), blood tests performed (International Normalised Ratio, haemoglobin, fibrinogen and platelet count) and the clinician's judgement of the patient's response to initial rFVIIa dose (responded or did not respond).

Statistical Analysis

Descriptive data are presented as percentage values, mean and standard deviation values (for dose amount) as well as median units of blood products accompanied by inter-quartile range values. Where indicated, testing for significant differences between hospital categories was undertaken using χ^2 and the non-parametric Mann-Whitney U test for skewed data (employed for analysis of blood products administered). Dose data (in mcg/kg) was log transformed and then analysed using a one way ANOVA for assessing differences in mean dose between hospital categories. All analyses were conducted using Stata v. 9.2 (Stata Corp, Texas USA).

Results

The Haemostasis Registry includes 2075 cases of off-label rFVIIa use in 87 hospitals distributed across Australia and New Zealand.

Demographics

The median age of included patients was 57 years (IQR 37, 70 years). Females accounted for a smaller proportion of total cases (34.17%). Cases were unevenly distributed across the hospital services (Figure 1), with the majority of cases seen within a Category 1 centre (1540, 74.22%). Category 2 hospitals accounted for 338 (16.29%) cases, while 82 (3.95%) and 115 (5.54%) cases were recorded in Category 3 and Category 4 hospitals respectively. The mean initial dose of rFVIIa was 92.3 mcg/kg (SD 79.94 mcg/kg). Category 1 and 2 hospitals administered similar doses of 87.17 mcg/kg and 87.72 mcg/kg respectively, while Category 3 services administered a mean dose of 78.47.5 mcg/kg. In contrast, Category 4 hospitals administered the highest mean dose of 113.33 mcg/kg (Figure 6).

Context of Bleeding

Across the Registry, a significant proportion of patients were administered rFVIIa for reasons relating to cardiac surgery (854, 41.64%). Both trauma and other surgery accounted for moderate levels of rFVIIa administration (14.07% and 18.80% respectively). Stratification by service type demonstrated similar distributional characteristics for Category 1 and 2 services, with cardiac surgery, trauma and other surgery accounting for the majority of rFVIIa administrations in both service divisions (Figure 3). In contrast, regional hospitals administered most rFVIIa in trauma and obstetric settings (35.37% and 12.20% respectively). Case complexity differed across services, with many cardiac surgery patients in regional centres undergoing isolated or CABG or valve surgery (88.90%), compared to Category 1 and Category 2 services that largely delivered complex procedures including heart transplants, classified as 'other surgery' (66.29% and 63.20% in Category 1 and Category 2 services respectively, Figure 2).

Furthermore, trauma patients treated within Category 1 or 2 centres appeared to present with more severe injuries, with approximately 60% in each Category recording an Injury Severity Score (ISS) greater than 26, while in Regional services, 34.62% of trauma patients had an ISS of greater than 26 (Figure 2). Unsurprisingly, specialist centres that comprised Women's and Children's hospitals as well as a major cancer treatment centre, administered rFVIIa to significant proportions of obstetric and haematology/oncology patients.

Blood Components

Figure 4 describes the median units of blood components administered to patients prior to the initial dose of rFVIIa by hospital service. Regional Services administered the lowest median doses of blood replacement components, with 0 units of cryoprecipitate, 2 units of platelets, 5 units of FFP and 8 units of red blood cells. In total, Category 1 centres administered the highest number of median blood component units.

Laboratory Testing Practices

The adherence to pre-dose coagulation parameter testing and laboratory testing by hospital service is outlined in Figure 5. Overall, haemoglobin was the most widely investigated parameter, while fibrinogen the least documented laboratory result. While most centres demonstrated similar documentation practices across each of the parameters, Category 2 services recorded the lowest fibrinogen documentation of any service, with 55.92% of patients receiving documented fibrinogen investigations prior to rFVIIa administration ($p < 0.05$).

Response and Outcome

No statistically significant difference could be detected in the documentation of rFVIIa effectiveness, response to treatment or outcomes across hospital Categories. Table 2 demonstrates similar response rates across each of the services, with 66.6% of patients classified as responders in Category 1 centres,

65.47% in Category 2 services and 63.77% in Category 3 centres. Similarly, survival rates did not differ significantly between hospital Categories, with 69.87% of patients treated with rFVIIa in Category 1 surviving to discharge, 70.41% surviving in Category 2 services and 68.29% surviving in Category 3 services.

Table 3 reports the thromboembolic adverse events by hospital service. In total, 109 (5.25%) patients experienced a thromboembolic adverse event. Cerebrovascular accidents (CVAs) accounted for the largest proportion of all adverse events, and were highest in Category 1 and 4 centres. Other adverse events occurred at very low rates. Of note, across hospital services, Category 3 services recorded the highest proportion of patients developing DVTs (3.66%) as well as the second highest proportion of patients developing CVAs (2.44%).

Discussion

In the absence of national guidelines for the off-label use of rFVIIa, this investigation reports on the largest series of off-label rFVIIa administrations, and suggests the presence of practice variation across Australian and New Zealand providers. Internationally, efforts have been made to establish prescribing guidelines for the use of rFVIIa,¹³ while in Australia, subgroups of patients, including obstetric patients have been the focus of guideline development.¹⁴ While these efforts continue, it is timely to review the current off-label use of rFVIIa across different providers.

Those appropriate for off-licence treatment with rFVIIa represent a critical patient group at risk of elevated mortality and morbidity. Bleeding in such patients is routinely associated with severe injury or complex surgery, and requires timely and intensive medical intervention. While Category 1 hospitals accounted for less than 25% of all participating facilities on the registry, they treated in excess of 70% of registry patients. The contextual profile of rFVIIa administrations in both Category 1

and Category 2 centres appeared similar with cardiac and 'other' surgeries accounting for just over 60% of all rFVIIa administrations in both hospital divisions. Results suggest that patients within these better resourced centres received a greater number of total blood products than patients treated at other facilities. The relationship between use of blood components/ products and rFVIIa is widely discussed in the literature. Following rFVIIa administration in cardiac surgery patients, many have reported decreased transfusion of red blood cells, cryoprecipitate, platelets and fresh frozen plasma.⁹ ¹⁵ Potential savings in both cost and blood replacement resources are therefore attractive features of rFVIIa usage.¹² However, it is unlikely that protocols adopted in Category 1 centres are driving the increased transfusion of blood products prior to rFVIIa, rather patients treated within Category 1 centres may present with greater transfusion demands as a result of illness acuity. The greater number of trauma patients with ISS>26 and the increased complexity of cardiac surgery patients treated at Category 1 and 2 centres compared to Category 3 centres, highlights the increased acuity of patients treated within metropolitan services. Alternatively, potentially limited access to blood components as well as other surgical or radiological options in Regional centres may lead to more constrained resource use and earlier administration of rFVIIa.

This investigation also found variance in rFVIIa dosing regimen between hospital categories. With the development of institution specific dosing practices for cardiac surgery patients, the dose variation across hospitals in the present investigation would be expected.¹⁶ Protocols across hospitals therefore vary considerably, with recommended initial dose volumes ranging from 50 to 100 mcg/kg.¹⁷ In the current study, dosing practices of rFVIIa appear to be similar across Category 1 and 2 facilities, with both administering a mean dose of approximately 87 mcg/kg. In contrast, results suggest that Category 3 services administer significantly lower doses, with the mean dose reported as 78.47 mcg/kg ($p<0.05$). Determining if this variation is due to reduced product access, education programs, adoption of regional specific practice regimes or a reflection of the reduced underlying acuity of the regional patient group requires further determination.

For rFVIIa to work effectively, adequate substrate, including platelets and fibrinogen must be present. The precise levels required are not known but a previous report has suggested a fibrinogen level ≥ 50 mgdl⁻¹ and a platelet level $\geq 50,000 \times 10^9$ L⁻¹.¹⁸ In the absence of these parameters, rFVIIa use may occur on the basis of empirical replacement therapy. Our study suggests that fibrinogen levels are poorly documented across all hospitals. It is interesting to note that, despite low case numbers, rural and regional hospital perform as well as Category 1 hospitals in terms of the proportion of laboratory tests recorded. Category 2 hospitals recorded significantly lower proportions of tests in fibrinogen levels and INR. It is not clear whether this represents an insufficiency in protocols in these hospitals or poor adherence to guidelines. The significantly different results for testing obtained by the Category 4 hospitals is likely to be a reflection of the obstetric haemorrhage context.

Despite the apparent practice variation existing in Australian and New Zealand hospitals in the off-label use of rFVIIa, patient outcomes appear to be similar. Approximately 65% of all patients were judged to have responded to the initial dose of rFVIIa. Such subjective assessments have been reported by others, however the broad groupings of responders and non-responders may mask subgroups more or less amenable to rFVIIa.¹⁵ Despite metropolitan and regional differences in the use of blood components and products prior to rFVIIa, the mortality rate across hospital categories appears to be similar. While the higher acuity of patients treated within Category 1 facilities may be seen to carry a greater mortality risk than those treated within Metropolitan or Regional centres, the heterogeneity of patients across hospital categories is likely to make comparison of mortality misleading.

A recent meta analysis of randomised control trials investigating the off-label use of rFVIIa was unable to find sufficient evidence of a beneficial effect from off-label rFVIIa administration.¹⁹ Thromboembolic adverse events occurred in patients in both treatment and placebo arms of the included studies. The authors concluded that if an increased risk of TAE was indeed associated with

rFVIIa administration, it was in the magnitude of approximately 1%.¹⁹ The current study is limited by the small regional sample, however results suggest that rates of DVT and CVA in regional centres may be elevated compared to their metropolitan counterparts. The increased risk of thromboembolism in trauma patients may assist in explaining this finding, as regional services in this study recorded greater proportions of trauma admissions than any other patient group.²⁰ While specialist centres recorded the highest rate of CVAs, it is likely that this reflects underlying patient factors rather than issues relating to rFVIIa administration.

This study had several limitations. Firstly, while all major treatment centres are currently included on the registry, not every metropolitan or regional facility in Australia and New Zealand participates. In addition, analyses are restricted to variables routinely collected on the registry. Therefore, alternative factors influencing patient response and outcomes are beyond the scope of collection. Moreover, this study is limited by the quality and consistency of data recording in the medical record. The Registry is therefore investigating ways of improving the documentation of blood product and component use across providers in Australia and New Zealand. Category divisions based on geographic location and medical services allow comparison of inter-hospital administration practices, however may incompletely describe a facility's functions. Further, the hospital Categories employed in the current investigation are likely to divide patients based on acuity, making inter-institution comparisons difficult. Further efforts at hospital classifications are ongoing.

Determining the current patterns of rFVIIa administration by hospital categories may inform future decisions on the optimal practice regimen for the off-label use of rFVIIa through large scale, randomised control trials. Some have suggested that such trials would need in excess of 4000 patients to detect a 10-15% relative reduction in mortality.¹⁹ In the absence of such evidence, this study presents the largest series of off-label rFVIIa use to date, and suggests that practice variation exists between hospitals. For effective administration of rFVIIa, standardised critical bleeding protocols

based on the best available evidence, developed by clinical expert groups, must be adopted nationally.
This will also facilitate better monitoring of adverse events and outcomes.

Acknowledgements

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References

1. Charles A, Shaikh AA, Walters M, Huehl S and Pomerantz R. Blood transfusion is an independent predictor of mortality after blunt trauma. *The American Surgeon* 2007; 73: 1-5
2. Scott BH, Seifert FC and Grimson R. Blood transfusion is associated with increased resource utilisation, morbidity and mortality in cardiac surgery. *Annals of cardiac anaesthesia* 2008; 11: 15-9
3. Jeffers L, Chalasani N, Balart L, Pysopoulos N and Erhardtsen E. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology* 2002; 123: 118-26
4. Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, González Abraldes J, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology* 2004; 127: 1123-30
5. Pihusch M, Bacigalupo A, Szer J, von Depka Prondzinski M, Gaspar-Blaudschun B, Hyveled L, et al. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. *Journal of thrombosis and haemostasis* 2005; 3: 1935-44
6. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringner MN, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *New England Journal of Medicine*, The 2008; 358: 2127-37

7. Raivio P, Suojaranta-Ylinen R and Kuitunen AH. Recombinant factor VIIa in the treatment of postoperative hemorrhage after cardiac surgery. *The Annals of thoracic surgery* 2005; 80: 66-71

8. Karkouti. Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. *Canadian journal of anesthesia* 2006; 53: 802-9

9. Bishop CV, Renwick WEP, Hogan C, Haeusler M, Tuckfield A and Tatoulis J. Recombinant activated factor VII: treating postoperative hemorrhage in cardiac surgery. *The Annals of thoracic surgery* 2006; 81: 875-9

10. Diprose P, Herbertson MJ, O'Shaughnessy D and Gill RS. Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study. *British journal of anaesthesia* 2005; 95: 596-602

11. Tritapepe L, De Santis V, Vitale D, Nencini C, Pellegrini F, Landoni G, et al. Recombinant activated factor VII for refractory bleeding after acute aortic dissection surgery: a propensity score analysis. *Critical care medicine* 2007; 35: 1685-90

12. Isbister J, Phillips L, Dunkley S, Jankelowitz G, McNeil J and Cameron P. Recombinant activated factor VII in critical bleeding: experience from the Australian and New Zealand Haemostasis Register. *Internal medicine journal* 2008; 38: 156-65

13. Vincent J-L, Rossaint R, Riou B, Ozier Y, Zideman D and Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding--a European perspective. *Critical care* 2006; 10: R120
14. Welsh A, McLintock C, Gatt S, Somerset D, Popham P and Ogle R. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. *The Australian & New Zealand journal of obstetrics & gynaecology* 2008; 48: 12-6
15. McCall P, Story DA and Karapillai D. Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery. *Canadian journal of anesthesia* 2006; 53: 926-33
16. Johnson SJ, Ross MB and Moores KG. Dosing factor VIIa (recombinant) in nonhemophiliac patients with bleeding after cardiac surgery. *American journal of health-system pharmacy* 2007; 64: 1808-12
17. Goodnough LT, Lublin DM, Zhang L, Despotis G and Eby C. Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004; 44: 1325-31
18. Labattaglia MP and Ihle B. Recombinant activated factor VII: current perspectives and Epworth experience. *Heart, lung & circulation* 2007; 16 Suppl 3: S96-101

19. Hsia CC, Chin-Yee IH and McAlister VC. Use of Recombinant Activated Factor VII in Patients Without Hemophilia: A Meta-Analysis of Randomized Control Trials. *Annals of Surgery* 2008; 248: 61 - 68

20. Sharma OP, Oswanski MF, Joseph RJ, Tonui P, Westrick L, Raj SS, et al. Venous thromboembolism in trauma patients. *The American Surgeon* 2007; 73: 1173-80

Table 1: Primary Context of Bleeding for all Registry

Primary Context of bleeding	No. Patients (%)
	N= 2075
Trauma	292 (14.07)
Obstetric	113 (5.45)
Intra-Cranial Haemorrhage	53 (2.55)
Cardiac Surgery	864 (41.64)
Medical/Other	118 (5.69)
Known Coagulopathic State	22 (1.06)
Other Surgery	390 (18.80)
Haematology/ Oncology	112 (5.40)
Liver	111 (5.35)

Table 2: Effect on Bleeding and 28 day outcome following initial dose

		No. Patients (%)			P
		Major Centre	Metropolitan Service	Regional Service	
Effect on	<i>Effect Recorded</i>	1322 (85.84)	278 (82.25)	69 (84.15)	0.234
Bleeding	<i>Responded</i>	876 (66.26)	182 (65.47)	44 (63.77)	0.892
	<i>Did not Respond</i>	446 (33.74)	96 (34.53)	25 (36.23)	
28 Day	<i>Living</i>	1076 (69.87)	238 (70.41)	56 (68.29)	0.931
Outcome	<i>Deceased</i>	464 (30.13)	100 (29.59)	26 (31.71)	

Table 3: Thrombo-embolic Adverse Events by Hospital Service

No. Patients (%)				
Event	Major Centre	Metropolitan Service	Regional Service	Specialist Centre
CVA	54 (3.51)	7 (2.07)	2 (2.44)	6 (5.22)
TIA	2 (0.13)	2 (0.59)	0 (0.00)	0 (0.00)
DVT	20 (1.30)	1 (0.30)	3 (3.66)	3 (2.61)
PE	12 (0.78)	2 (0.59)	1 (1.22)	0 (0.00)
Arterial Thrombosis	21 (1.36)	2 (0.59)	1 (1.22)	3 (2.61)

Table 4: Hospital Divisions

Category	Service Type	Hospitals in Category
Category 1	Major Trauma, Cardiac or Transplant Centre	21
Category 2	Metropolitan Service	41
Category 3	Regional Service	15
Category 4	Specialist Centre	10

Fig 1

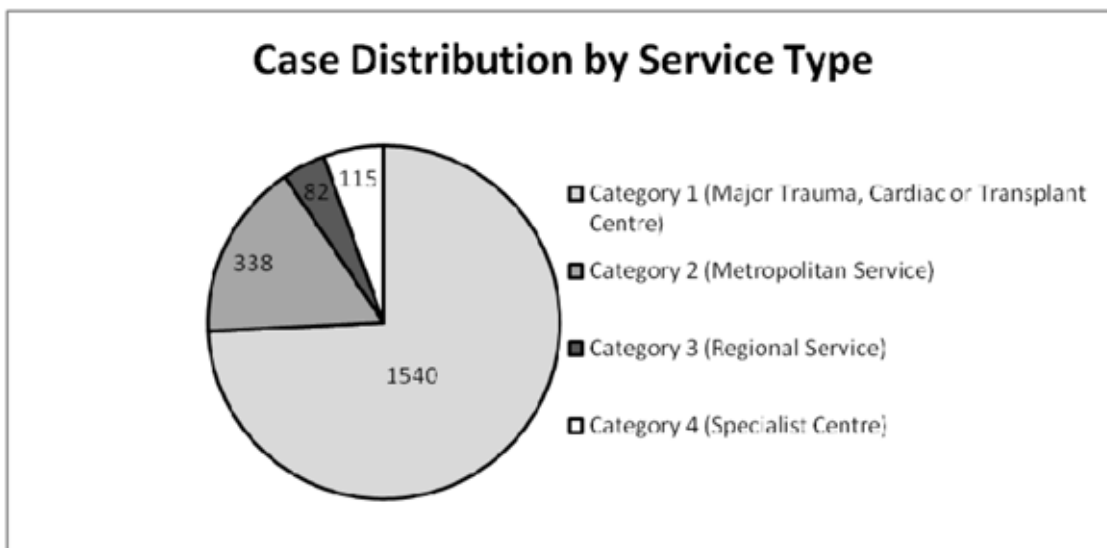


Figure 2

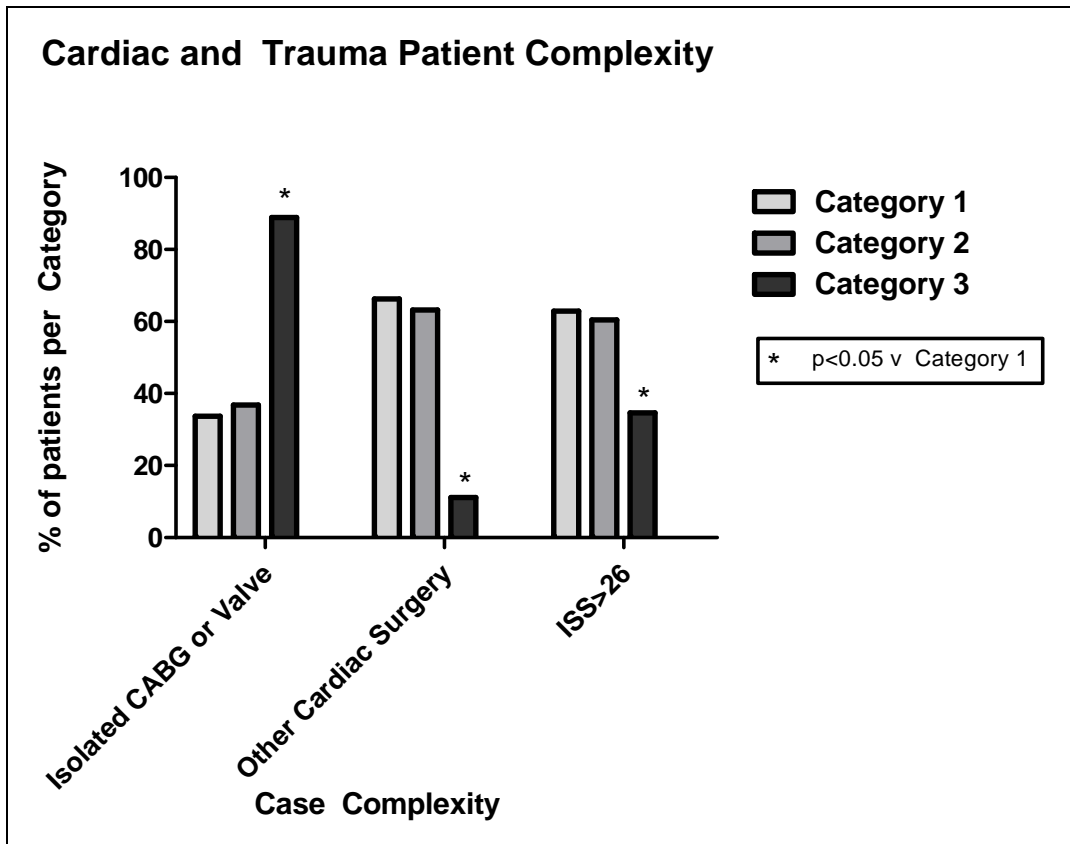


Figure 3

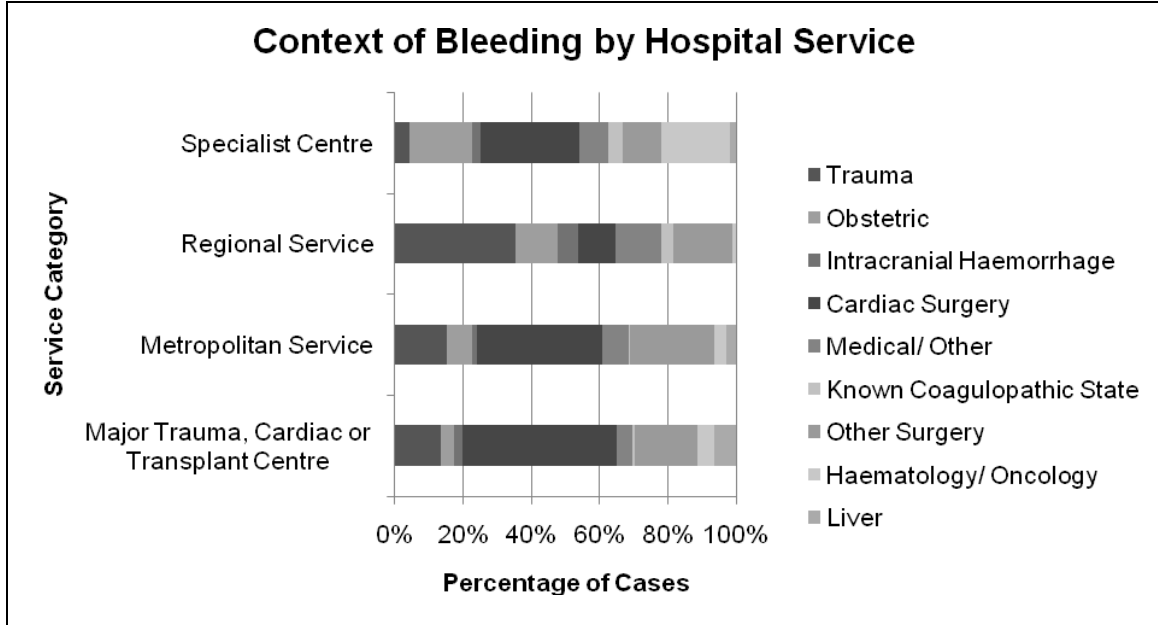


Figure 4

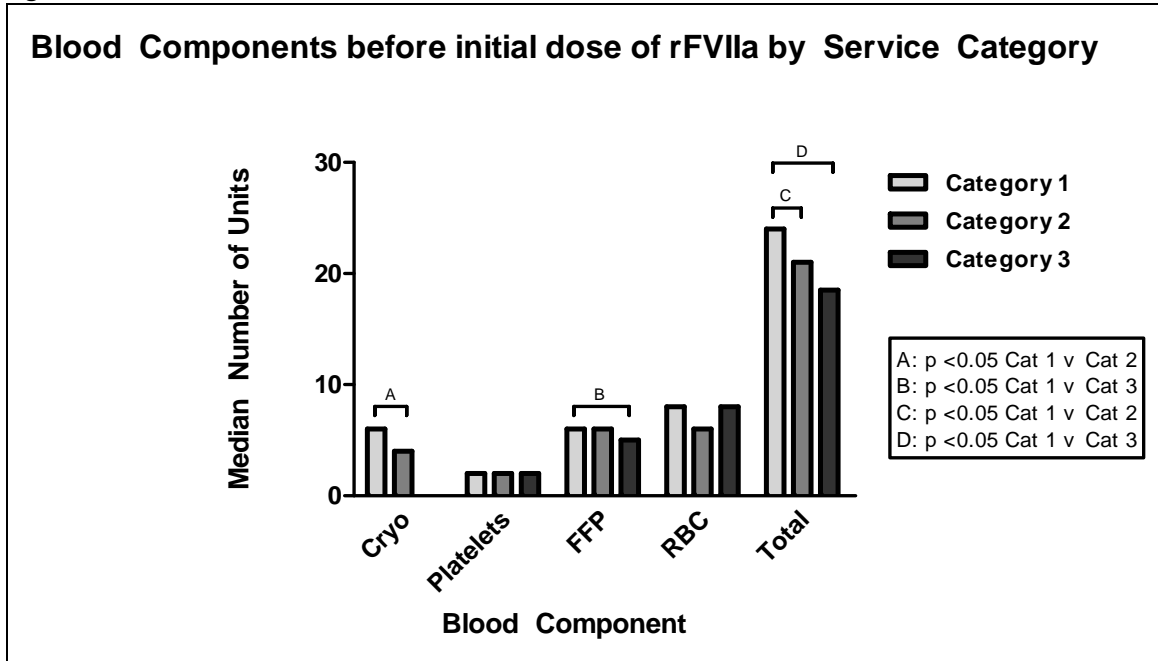


Figure 5

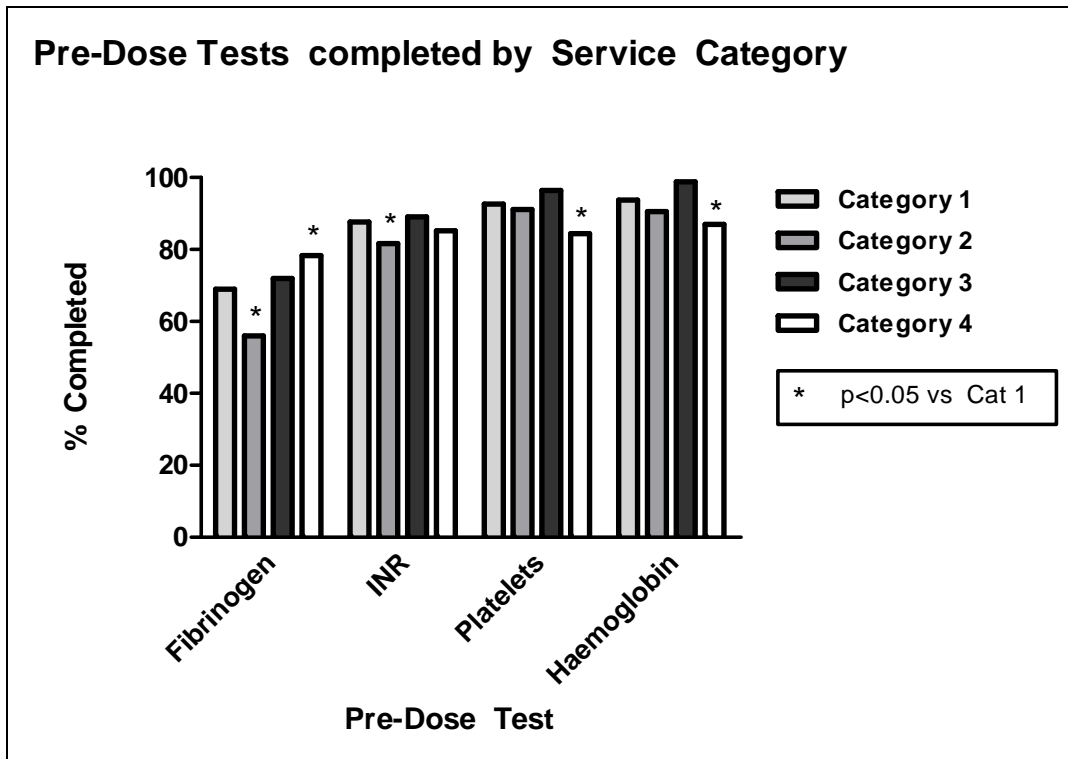


Figure 6

