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Off-Label Use of Recombinant Factor VIIa in United States Hospitals: 2000–2008

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Abstract

Background—Recombinant factor VIIa (rFVIIa) is approved for treatment of bleeding in hemophilia patients with inhibitors but has been applied to a wide range of off-label indications.

Objective—To estimate patterns of off-label rFVIIa use in United States hospitals.

Design—Retrospective database analysis.

Setting—Data were extracted from the Premier Perspectives database (Premier, Inc.; Charlotte, NC), which contains discharge records from a sample of academic and non-academic U.S. hospitals.

Patients—12,644 hospital discharge records for patients who received rFVIIa during a hospitalization.

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Data access

Protocol: Available from the AHRQ website at <http://www.ahrq.gov/>

Statistical Code: Available to interested readers by contacting Dr. Stafford at rstafford@stanford.edu.

Data: Available for purchase from Premier, Inc., 13034 Ballantyne, Corporate Place, Charlotte, NC 28277

Measurements—Hospital diagnoses and patient dispositions from January 1, 2000 to December 31, 2008. Statistical weights for each hospital were used to provide national estimates of rFVIIa use.

Results—Between 2000 and 2008, off-label use of rFVIIa in hospitals increased more than 140-fold, such that in 2008, 97% (95% CI, 96% to 98%) of 18311 in-hospital uses were off-label. In contrast, in-hospital use for hemophilia increased less than 4-fold and accounted for 3% (95% CI, 1.9% to 3.5%) of use in 2008. Cardiovascular surgery (29%; 95% CI, 21% to 33%) and trauma (29%; 95% CI, 19% to 38%) and intracranial hemorrhage (11%; 95% CI, 7.7% to 14%) were the most common indications for rFVIIa use. Across all indications, in-hospital mortality was 27% (95% CI, 19% to 34%), and 43% (95% CI, 35% to 50%) of patients were discharged to home.

Limitations—Accuracy and completeness of the discharge diagnoses and patient medication records in the database sample cannot be verified.

Conclusion—Off-label use of rFVIIa in the hospital setting far exceeds use for approved indications. These patterns raise concern about the application of rFVIIa to conditions that lack strong supporting evidence.

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To be approved for use by the U.S. Food and Drug Administration (FDA), medications must clear significant regulatory hurdles and demonstrate both efficacy and a lack of excessive harms in clinical trials. After a medication has received approval, there are no further limitations on its use, either on- or off-label. In many cases, this leads to medications being approved for narrowly defined indications, followed by substantial use in areas that have not been well-studied (1).

Recombinant factor VIIa (rFVIIa; Novo Nordisk A/S, Bagsvaerd, Denmark) was approved by the FDA in 1999 for treatment of spontaneous or surgical bleeding episodes in patients with hemophilia A or B who have inhibitors to factor VIII or factor IX. When first introduced, rFVIIa was used predominantly for these indications. After it became widely available, however, rFVIIa was rapidly employed in the treatment or prophylaxis of bleeding in other conditions. Although rFVIIa activity is thought to be confined to sites of endothelial injury (2–3), the potential for thromboembolic complications with its use has been demonstrated in several trials and retrospective analyses (4–9), raising concern about potential harms with widespread off-label application. To estimate patterns of off-label, in-hospital rFVIIa use, we performed a retrospective evaluation of data from the Premier Perspectives database of U.S. hospitals. This representative sample was used to project national usage patterns from January 1, 2000 through December 31, 2008.

Methods

Design Overview

We purchased access to data from the Premier Perspectives database from Premier, Inc. (Charlotte, NC). The dataset encompassed all hospitalizations during which rFVIIa was ordered for a patient for the period January 1, 2000 to December 31, 2008. We analyzed this

dataset to categorize the discharge diagnoses and patient outcome for each rFVIIa-associated hospitalization.

Hospital Sample

The Premier Perspectives database contains data from 615 non-federal U.S. hospitals. Institutional participation in the database is voluntary. Data included are patient demographics, primary and secondary diagnoses (coded by International Classification of Diseases, Revision 9; ICD-9), length of stay, medications used, and disposition for each hospitalization. We identified 12,644 hospitalizations in which rFVIIa was administered to patients during 2000–2008. A total of 286,100 diagnosis and procedure ICD-9 codes were reported for this cohort.

Categorizations of Use

We constructed a descending hierarchy of ICD-9 codes to categorize each case into mutually exclusive indication categories (Appendix Table 1). This hierarchy started with the most relevant, most reliable, and most specific clinical diagnoses, followed successively by less relevant, less reliable, or less specific diagnoses. A case was assigned to a diagnostic category based on the ICD-9 code that placed it in the highest category within the hierarchy.

The higher order diagnoses in this hierarchy were the FDA-approved indications of hemophilia A and B, followed by unapproved indications similar to hemophilia or approved in other nations (e.g., Glanzmann's thrombasthenia). If these diagnoses were noted, the hospitalization was classified into that category regardless of whether other potential indications were also noted. All remaining hospitalizations were then categorized successively for an array of off-label indications (Appendix Table 1). Sensitivity analyses of this coding hierarchy had little effect on the main findings. The greatest change in the distribution between indications was seen when trauma was moved lower in the hierarchy, which suggests that trauma frequently occurs in the setting of other disease processes. We chose to prioritize trauma as the indication for treatment in these instances, as it was likely trauma and not the associated diagnoses that instigated the use of rFVIIa.

The non-hemophilia hematologic conditions were divided into two groups. We gave high priority to primary clotting disorders that represent distinct and usually isolated defects in the clotting process. We gave lower priority to secondary clotting disorders that are more likely the end product of other pathological conditions, as with traumatic bleeding causing consumptive coagulopathy or the disruption of clotting produced by liver disease.

Projections

Statistical weights associated with each hospital by quarter were applied for projection of estimated rFVIIa use at the national level. Hospitals providing data for the Premier database represent a convenience sample and may differ from hospitals nationwide; however, the Premier database is the largest hospital-based, service-level comparative database in the country. Statistical weighting allows national projections to be made under the assumption that Premier hospitals of specific types resemble hospitals nationwide with these same characteristics. For each type of hospital (defined by size, region, teaching status, and

ownership) weights are calculated as the inverse of the fraction of national admissions for this subgroup represented in Premier database. These aggregate national estimates are made using data from the American Hospital Association. This statistical weight assigned to each type of hospital by quarter allows derivation of national projections (for additional details, see ref. 26). While this is a relatively rudimentary adjusted projection strategy, it enables national projections that account for some, but not all, selection biases in the Premier sample. The statistical weights vary from around 10 per Premier-documented case in 2000 to around 5.5 in 2008 as a function of the increasing number of hospitals included in the database over time. For our sample of 12,644 hospitalizations, we projected 73,747 (95% CI, 51,247 to 96,245) cases of rFVIIa use nationwide during the study period.

Statistical methods

Our analyses identified annual trends in national in-hospital rFVIIa use. To characterize patterns of use by indication, we produced a cross-tabulation of indication category by year. We performed similar analyses for patient age, discharge disposition, and hospital characteristics. The unit of analysis was any “case” of rFVIIa use—defined as any hospitalization during which rFVIIa was administered one or more times. We chose this case-based unit of analysis because it captures the medical decision-making component of care about whether to use or not use rFVIIa for a given patient. Alternative methods of analysis by dosing were considered (e.g., volume of rFVIIa dispensed by the pharmacy) but were determined to have significant disadvantages: possible discrepancies between dispensed rFVIIa and the amount actually administered, lack of consistent hospital coding of rFVIIa dispensing, and outlier cases. Analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC). We calculated 95% confidence intervals for counts of hospital cases and proportions using the SAS SURVEYMEANS procedure, which accounted for selection of a national sample of hospitals.

Results

From 2000 through 2008, there were an estimated 73,747 (95% CI, 51,247 to 96,245) hospital cases in the U.S. where rFVIIa use was reported. Over this period, off-label rFVIIa cases increased 140-fold (Figure 1) from 125 (95% CI, 0 to 543) in 2000 to 17813 (95% CI, 14,381 to 22,240) in 2008. Use increased most rapidly for cardiovascular surgery and trauma. There have been more modest increases for non-traumatic intracranial hemorrhage (ICH), liver disease, gastrointestinal bleeding, and other off-label indications (Table 1).

Hemophilia and related conditions

Initial use of rFVIIa was predominantly for the FDA-approved indications, including hemophilia A and B, as well as related (though not FDA-approved) conditions, such as other clotting factor deficiencies, von Willebrand disease and Glanzmann’s thrombasthenia (“primary clotting disorders” in Table 1). Use for the hemophilias has increased 3.8-fold since 2000 but appears to have plateaued, while there has been a 7.4-fold increase in use for the other primary clotting disorders. These two groups remained the most common cluster of indications from 2000 through 2003, but their proportion of use fell from 93% (95% CI, 71% to 100%) of use in 2000 to 7.1% (95% CI, 5.3% to 8.8%) in 2008. Hemophilia A and B

alone account for 4.2% (95% CI, 2.6% to 5.9%) of use overall and 2.7% (95% CI, 1.9% to 3.5%) of use in 2008.

Cardiovascular surgery

rFVIIa use in cardiovascular surgery was initially observed in 2002, and by 2008 was one of the most frequent and rapidly increasing indications. While use in pediatric cardiovascular surgery, largely for repair of congenital anomalies, has been modest (2.3% of uses overall and 2.1% in 2008), use in adult cardiovascular surgery, largely for aortic valve, mitral valve and CABG procedures, has rapidly increased, accounting for 16% (95% CI, 12% to 21%) of cases overall and 27% (95% CI, 21% to 33%) in 2008 (Table 1 and Appendix Figure 1).

Trauma

Sizable use of rFVIIa for traumatic bleeding began in 2002, and it remained the dominant indication for off-label use until it was equaled in prevalence by cardiac surgery (adult and pediatric) in 2008. While use for body and brain trauma leveled off in 2008 (Table 1 and Appendix Figure 1), trauma other than brain trauma ("Body trauma" in Table 1) remains the second most common indication for rFVIIa use and accounts for 16% (95% CI, 8.3% to 23%) of overall 2000–08 use and 18% (95% CI, 12% to 23%) of use in 2008. Use in brain trauma, particularly traumatic subdural hematoma constitutes 9.7% (95% CI, 5.2% to 14%) of overall 2000–08 use and 11% (95% CI, 7.0% to 15%) of use in 2008.

Intracranial hemorrhage

rFVIIa use in non-traumatic ICH, particularly intracerebral hemorrhage, reached sizable scale in 2004. Use for this indication also has grown, with use in 2008 nearly 8-fold higher than was reported in 2004, although use fell slightly from 2007 to 2008 (Table 1 and Appendix Figure 1). ICH accounts for 11% (95% CI, 6.9% to 14%) of rFVIIa cases overall and 11% (95% CI, 7.7% to 14%) in 2008.

Liver disease

A range of indications related to liver disease account for 6% (95% CI, 2.5% to 9.3%) of all uses, including liver biopsy (1.2%), variceal bleeding (1.2%), liver transplant (0.2%), and other liver indications (3.3%).

Other conditions

Gastrointestinal bleeding other than that associated with esophageal varices or liver disease accounted for 5.3% (95% CI, 3.2% to 7.4%) of cases overall. Management of aortic aneurysm, in the presence and absence of surgical intervention, represented 1.7% of use overall and in 2008. Other conditions contributed minimally to rFVIIa use, including pulmonary indications, particularly biopsy and lung transplant (1.5% overall); cancer-related conditions, particularly leukemia (1.5%); neonatal indications (1%); obstetrical conditions, particularly post-partum hemorrhage (0.9%); and a number of surgical procedures, none of which were individually prominent (5.3% overall, 2.2% in 2008). A variety of secondary clotting disorders were associated with rFVIIa use (5.1% overall, 4.2% in 2008), including secondary thrombocytopenias and complications of warfarin anticoagulation.

Age distribution

Consistent with the growth of off-label indications, the mean age of patients has increased from 3 years (95% CI, 1.0 to 4.7 years) in 2000 to 59 years (95% CI, 56 to 61 years) in 2008. The age distribution of rFVIIa use varies by indication. Use for hemophilia A and B occurs predominantly in patients 25 years of age and younger (63%; 95% CI 48% to 77%). For ICH, 58% (95% CI, 55% to 61%) of use is in patients 65 years of age and older, with 36% (95% CI, 33% to 39%) in those 75 years and older. Other conditions where use in patients 65 years and older is prominent include aortic aneurysm (82%; 95% CI, 77% to 87%), prostatectomy (66%; 95% CI, 33% to 98%), brain trauma (58%; 95% CI 54% to 63%), cardiovascular surgery (57%; 95% CI 54% to 61%), and non-variceal gastrointestinal bleeding (57%; 95% CI, 51% to 64%).

Discharge disposition

Overall in-hospital mortality among patients receiving rFVIIa was 27% (95% CI, 19% to 34%). Only 43% (95% CI, 26% to 59%) of patients were discharged directly home (Table 2). Most of the remaining patients were transferred to other facilities (e.g., nursing homes and rehabilitation hospitals). Mortality increased from 5% (95% CI, 0% to 35%) in 2000 to a peak of 31% (95% CI, 24% to 37%) in 2004 but declined slightly to 27% (95% CI, 25% to 30%) in 2008. Mortality among patients with hemophilia A and B was 4% (95% CI, 1.8% to 5.8%). The highest mortality rates were associated with aortic aneurysm (54%; 95% CI, 43% to 65%), neonatal indications (47%; 95% CI, 35% to 59%), and non-variceal complications of liver disease (40%; 95% CI, 32% to 48%). Regarding the most common indications, mortality was 34% (95% CI, 31% to 38%) for spontaneous ICH, 33% (95% CI, 20% to 47%) for brain and body trauma, and 23% (95% CI, 21% to 26%) for adult cardiovascular surgery.

Hospital characteristics

rFVIIa use was reported in 235 of the 615 hospitals (38%) represented in the Premier database. Most rFVIIa use occurred in non-academic hospitals (68% of use; 95% CI, 39% to 97%), a pattern that was consistent for the majority of the indications we studied (Figure 2). Over time, the proportion of rFVIIa use in non-academic hospitals grew from 11% (95% CI, 0% to 43%) in 2000 to a peak of 73% (95% CI, 31% to 71%) in 2005 followed by 67% (95% CI, 57% to 77%) in 2008. Off-label use of rFVIIa was lower at academic hospitals (92%; 95% CI, 88% to 96%) compared with non-academic hospitals (97%; 95% CI, 96% to 98%).

Comment

The potential for rFVIIa to be used as an emergency hemostatic agent outside the setting of hemophilia was recognized soon after its clinical introduction (10–11). Although this agent is currently approved by the FDA for certain uncommon conditions, its in-hospital use for these is now far exceeded by its use for off-label indications. Using a representative database of individual hospitalizations across the U.S., we found that 96% of all in-hospital cases of rFVIIa use between 2000 and 2008 and 97% of cases in the year 2008 were off-label. These findings are consistent with past reports (Appendix Table 2) (12–20).

Adult cardiovascular surgery is the most rapidly emerging indication for rFVIIa use. In 2008, over one in four cases receiving rFVIIa were treated in the context of cardiovascular surgery. There is limited evidence to support this use. Diprose and colleagues reported a randomized controlled trial (RCT) with 20 patients (9 received rFVIIa) in which a single dose of rFVIIa was used prophylactically at the termination of cardio-pulmonary bypass in non-coronary cardiovascular surgery (21). Although the need for allogeneic blood transfusion was significantly reduced after the administration of rFVIIa, there was no impact on patient survival. More recently, Gill and colleagues reported a placebo controlled RCT in which patients with bleeding after cardiovascular surgery were randomly assigned to a single dose of rFVIIa at 40 (n=35) or 80 (n=69) micrograms per kilogram versus placebo (n=68) (22). Significant decreases in the need for re-operation and allogeneic blood transfusions were seen in the groups receiving rFVIIa, but there were no differences in mortality. Furthermore, there were increases in thromboembolic adverse events, particularly stroke, in the rFVIIa groups, although they did not reach statistical significance.

The next leading indication for rFVIIa use, body trauma, accounted for 18% of use in 2008 and was addressed by two simultaneously reported RCTs. While these trials demonstrated a significant decrease in transfusion requirements and possible decrease in acute respiratory distress syndrome, they also censored patients who died within the first 48 hours of rFVIIa administration and yet demonstrated no mortality benefit (23). The recently published CONTROL trial, which was terminated early due to failure to demonstrate a mortality benefit with use of rFVIIa in blunt and penetrating trauma at a pre-planned interim analysis, suggest that other aspects of trauma management have improved sufficiently that mortality is not significantly affected by pro-coagulant administration, even with severe hemorrhage (24). Brain trauma and non-traumatic intracranial hemorrhage (ICH) each constituted 11% of use in 2008. Non-traumatic ICH is the subject of perhaps the best quality RCT in this field to date. Mayer and colleagues demonstrated no mortality or functional outcome benefit after early treatment of ICH with rFVIIa, in spite of evidence that this treatment reduced hematoma expansion (25). The results of this study may have contributed to the decline in rFVIIa use for ICH in 2008.

Together, the three major indications of cardiac surgery (adult and pediatric), trauma (body and brain), and non-traumatic ICH account for 55% cases of in-hospital rFVIIa use from 2000–2008 and 69% of cases in 2008. Remaining use is dispersed amongst a multitude of medical and surgical indications. Most of these have not been well-studied. Thus, use of rFVIIa is growing in the absence of clear evidence of therapeutic efficacy and without close surveillance for associated harms. In addition, we identified its use in 38% of hospitals, with a shift from academic (89% in 2000) to non-academic hospitals (67% in 2008), such that the bulk of overall rFVIIa use has occurred in non-academic settings (Figure 2). This suggests wide adoption of rFVIIa as a therapy in spite of concerns regarding its efficacy and safety.

We also have conducted a comparative effectiveness review of in-hospital, off-label use of rFVIIa for five indications which demonstrated no evidence of mortality reduction but an increased risk of arterial thromboembolic events in cardiovascular surgery and non-traumatic intracranial hemorrhage (26, and Yank, et al. in this issue of *Annals*). Levi and colleagues similarly confirmed an increase in arterial thrombotic adverse events amongst all

published randomized controlled trials investigating off-label use of rFVIIa (27). Prior analyses of voluntary reports to the FDA Adverse Event Reporting System identified deep vein thromboses, ischemic cerebrovascular accidents, and myocardial infarctions as the most common adverse events associated with rFVIIa use (17, 18). As noted by Aledort, rare adverse events may not be clearly associated with an intervention based on an individual trial; however, meta-analysis of multiple trials may provide insight into the risk of rare events such as the thromboembolic adverse events that appear to be associated with off-label rFVIIa use (28). In the present study, we were unable to estimate the incidence of patient harm associated with rFVIIa use due to insufficient information in the Premier database on the temporal relationship between thromboembolic events and the use of rFVIIa.

An indirect measure of the efficacy of rFVIIa in the care of patients who receive it is survival to discharge. In the nationwide sample of hospitals we analyzed, in-hospital mortality for patients receiving rFVIIa was high—27% overall, and as high as 40–50% for several indications (Table 2). In-hospital mortality has been noted to be higher in retrospective studies of rFVIIa use outside of clinical trials as compared to that seen in carefully selected clinical trial populations (7, 12, 26, 29–30).

This study has several limitations. The Premier Perspectives database we queried gathers data from a voluntary alliance of non-federal hospitals and thus is not a random selection of healthcare facilities nation-wide. Our analysis of indications associated with use of rFVIIa was confined to the primary and secondary diagnoses (as listed by ICD-9 code) reported for each hospitalization. We cannot validate these diagnoses, nor can we identify diagnostic codes that may have been omitted. In addition, the indication hierarchy we used to categorize rFVIIa use may not have captured the nuances of each individual case. For instance, we are unable to determine at what point in a disease process rFVIIa was used (e.g., as prophylaxis, treatment, or for end-stage catastrophic bleeding). We also did not have access to data on patients with similar clinical scenarios where rFVIIa was not used.

Although it is to be expected that utilization of medications will change over time as additional hypotheses regarding patient therapeutics are examined, the key question is at what point a new indication has attained sufficient evidence-base to justify greatly expanded use. Given the absence of supporting data and the suggestion of patient harm, our analysis has identified probable nationwide overuse of rFVIIa outside the conditions approved by the FDA. We hope that this and other similar analyses of “real-world” medication use will provide guidance for the design of clinical trials and evidence reviews that adequately address the efficacy and associated harms of individual agents in the contexts in which they are most commonly employed. If concerning patterns of off-label use exist for other medications, these analyses may also help highlight areas for improvement in systems responsible for drug-approval and subsequent surveillance.

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Figure 1.

Estimated Annual In-Hospital Cases* of rFVIIa Use for Hemophilia and Off-Label Indications.

* Cases signify the number of hospitalizations during which rFVIIa was used. The graph depicts all cases for each year. The width of each segment represents the number of cases for each category as indicated by differential shading. Hemophilia = Hemophilia A and B; ICH = Non-Traumatic Intracranial Hemorrhage; Trauma = Body and Brain Trauma; CV = Cardiovascular.

Figure 2.
Use of rFVIIa at Academic and Non-Academic Institutions During 2000–2008.

Appendix Figure 1.

A, Estimated Annual In-Hospital Cases Using rFVIIa for Cardiovascular Surgery in the Adult and Pediatric Populations. B, Annual Use for Trauma and Intracranial Hemorrhage.

Table 1

Indications for In-Hospital Use of Recombinant Factor VIIa.

Clinical Indication	Hospitalizations 2000–2008		Hospitalizations 2008 only	
	Estimated Cases	Percentage of Total	Estimated Cases	Percentage of Total
FDA approved indications				
Hemophilia A and B	3121	4.2	498	2.7
Off-label indications				
Adult cardiovascular surgery	12086	16.4	4862	26.6
Body trauma	11689	15.9	3214	17.6
Intracranial hemorrhage	7755	10.5	2005	11.0
Brain trauma	7158	9.7	2033	11.0
Primary clotting disorders	4104	5.6	792	4.3
Non-variceal GI bleeding	3881	5.3	713	3.9
Secondary clotting disorders	3744	5.1	766	4.2
Other liver disease	2451	3.3	539	2.9
Pediatric cardiovascular surgery	1684	2.3	387	2.1
Other vascular procedures	1515	2.0	381	2.1
Aortic aneurysm	1216	1.6	306	1.7
Pulmonary hemorrhage	1119	1.5	275	1.5
Cancer/stem cell transplant	1094	1.5	138	0.8
Variceal bleeding	897	1.2	235	1.3
Liver biopsy/resection	867	1.2	122	0.7
Neonatal indications	729	1.0	135	0.7
Obstetrical hemorrhage	672	0.9	220	1.2
Neurosurgery	500	0.7	108	0.6
Liver transplantation	132	0.2	58	0.3
Prostatectomy	120	0.2	0	0.0
Other procedures	3867	5.2	407	2.2
Other diagnoses	3345	4.5	117	0.6
Total treated with rFVIIa	73747	100	18311	100

Table 2

Disposition of Hospitalizations Involving Use of rFVIIa During 2000–2008.

Indication	Total	Died* (%)	Other [‡] (%)	Home (%)
Aortic aneurysm	1216	54.4	26.6	19.0
Neonatal indications	729	46.7	15.0	38.3
Other liver disease	2451	40.4	27.7	31.9
Variceal bleeding	897	39.0	28.8	32.2
Other vascular procedures	1515	38.5	30.3	31.2
Liver transplant	132	38.1	14.3	47.6
Liver biopsy	867	35.9	18.9	45.2
Non-traumatic ICH	7755	34.4	49.7	15.9
Body trauma	11689	33.1	36.7	30.2
Brain trauma	7158	33.1	44.2	22.7
Secondary clotting disorders	3744	30.1	28.6	41.3
Non-variceal GI bleed	3887	29.7	30.8	39.5
Pulmonary hemorrhage	1119	24.5	29.7	45.8
Adult CV surgery	12086	23.3	28.5	48.2
Pediatric CV surgery	1684	21.7	5.0	73.3
Primary clotting disorders	4104	16.8	26.0	57.2
Obstetrical hemorrhage	672	14.6	7.8	77.6
Cancer/Stem cell transplant	1094	13.8	18.8	67.4
Other procedures	3867	9.4	26.0	64.6
Other diagnoses	3345	5.8	17.5	76.7
Hemophilia A and B	3121	3.8	11.4	84.8
Prostatectomy	120	0.0	19.1	80.9

* In-hospital deaths.

[‡] Inter-hospital transfers and transfers to skilled nursing facilities or hospice.

CV=Cardiovascular; GI=Gastrointestinal; ICH=Intracranial Hemorrhage

Appendix Table 1

Diagnostic Hierarchy for Analysis of the Premier Perspectives Database.

Rank in Hierarchy	Description	Most Frequent Conditions or Procedures
1	Hemophilia A and B	Hemophilia A, Hemophilia B
2	Primary clotting disorders	Other clotting factor deficiencies, Glanzmann's
3	Brain trauma	Subdural hemorrhage, subarachnoid hemorrhage
4	Body trauma	Motor vehicle accident, fall, assault
5	Intracranial hemorrhage	Intracerebral hemorrhage, subdural hemorrhage
6	Neurosurgery	Excision of lesion, craniotomy
7	Pediatric cardiac surgery	Transposition of the great vessels, ASD
8	Adult cardiac surgery	Aortic valve replacement, CABG, mitral valve
9	Obstetrical hemorrhage	Immediate post-partum hemorrhage, pre-eclampsia
10	Neonatal indications	Respiratory distress syndrome
11	Aortic aneurysm	Abdominal aortic aneurysm, thoracic aortic aneurysm
12	Prostatectomy	Retropubic prostatectomy
13	Other vascular procedures	Vascular bypass, intrabdominal venous shunt
14	Liver transplantation	Liver transplantation
15	Liver biopsy	Closed biopsy of liver, open biopsy of liver
16	Variceal bleeding	Esophageal varices
17	Other liver disease	Non-alcoholic cirrhosis, alcoholic cirrhosis
18	Non-variceal gastrointestinal bleed	Unspecified GI bleed, ischemic bowel
19	Secondary clotting disorders	Unspecified coagulation defect, defibrination syndrome
20	Pulmonary hemorrhage	Closed bronchial biopsy, hemoptysis
21	Cancer/stem cell transplant	Acute lymphoid leukemia, acute myeloid leukemia
22	Other surgical procedures	Various
23	Other diagnoses	Various

Appendix Table 2

Prevalence of Off-Label rFVIIa Use at Academic (Single or Multiple Institution) and Non-Academic Medical Centers.

Study	Latest year included	Setting	Cases	Off-label (%)
This report	2008	Academic/Non-academic	12644 [*]	97.0
Hsia, et al. (12)	2007	Academic (single)	94	88.3
Magnetti, et al. (13)	2005	Academic (multiple)	2660	89.0
Carcao, et al. (14)	2005	Academic (multiple)	196	80.0
Heller, et al. (15)	2005	Academic (single)	111	79.0
Webert, et al. (16)	2005	Academic/Non-academic	85	83.6
O'Connell, et al. (18)	2004	Academic/Non-academic [†]	168	89.9
MacLaren, et al. (19)	2004	Academic/Non-academic	701	92.0
Goodnough, et al. (20)	2004	Academic (single)	130	93.8

* Number of unweighted observations.

[†] Subset of sample used for this report.