Journal of Cardiothoracic and Vascular Anesthesia 31 (2017) 876–882

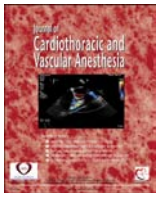
HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

ScienceDirect

journal homepage: www.jcvaonline.com



Bleeding-Related Complications and Readmission Rates Associated With Fibrin Sealant Use in Patients Undergoing Coronary Artery Bypass Graft Surgery in the United States

Yin Wan, MS*, Sangtaeck Lim, MPH†,1, Xin Gao, PhD*, Walter A. Danker III, PhD†, Richard Kocharian, Phd, MD†, Gaurav Gangoli, PharmD†, Ashley P. DeAnglis, PhD†, James Hart, MD, FACS‡

*Pharmerit International, Bethesda, MD
†Ethicon Inc, Somerville, NJ
‡Consultant, Fairfax, VA

Objectives: To compare the clinical and economic outcomes of EVICEL (Ethicon, Inc., Somerville, NJ) and TISSEEL (Baxter Healthcare Corporation, Westlake Village, CA) use in patients undergoing primary coronary artery bypass graft (CABG) surgery.
Design: Retrospective database analysis.
Setting: Premier prospective hospital database (June 2009 through March 2014) covering approximately 20% of hospital discharges in the United States.
Participants: Adults undergoing primary CABG surgery who received either EVICEL or TISSEEL on the day of surgery (index date).
Interventions: Two intervention groups were formed, EVICEL and TISSEEL. Clinical outcomes compared included postoperative bleeding complications (International Classification of Diseases, Ninth Revision, Clinical Modification code: 998.1) and number of blood transfusions received on the index day. Economic outcomes compared included hospital length of stay, hospital costs, and 30-day readmission rates. Propensity-score matching was used to control for patient and hospital characteristics.
Measurements and Main Results: A total of 129,014 primary CABG surgery patients were identified; 986 patients (mean age: 64 years, 73% male) received EVICEL and 6,340 patients (mean age: 65 years, 75% male) received TISSEEL on the index day. After propensity-score matching, patients who received EVICEL compared with TISSEEL had significantly fewer postoperative bleeding complications (3.0% *v* 5.0%, $p = 0.0197$), index-day blood transfusion rates (19% *v* 34%, $p < 0.0001$), readmission rates (18% *v* 32%, $p < 0.0001$), and costs ($40,736 [standard deviation $19,465] *v* $46,005 [standard deviation $24,049], $p < 0.0001$). Results from a sensitivity analysis using a generalized linear model to control for other hemostatic agent use also favored EVICEL over TISSEEL.
Conclusion: Results from this real-world retrospective database analysis showed fewer bleeding complications and lower costs in patients undergoing primary CABG surgery who received EVICEL compared with TISSEEL.

Key Words: bleeding complications; CABG surgery; fibrin sealants; coagulation; transfusions; hospital costs; clotting

The study was funded by Ethicon, Inc. W.A. Danker III and R. Kocharian are employees of Ethicon, Inc., and hold Johnson & Johnson stocks. S. Lim, A.P. DeAnglis, and G. Gangoli are employees of Ethicon, Inc. J. Hart is an independent medical consultant who received research funding from Ethicon, Inc. X. Gao and Y. Wan are consultants for Pharmerit International. Pharmerit International received research funding from Ethicon, Inc. for the study.
[1]*Address reprint requests to* Sangtaeck Lim, MPH, Ethicon Inc., MPH, Rr 22 Box West, Somerville, NJ08876.
E-mail address: SLim19@ITS.JNJ.com (S. Lim).

http://dx.doi.org/10.1053/j.jvca.2016.11.015

IN 2010, AN ESTIMATED 395,000 coronary artery bypass graft (CABG) surgeries were performed in the United States.[1] Morbidity and mortality rates are increased in cardiac surgery patients who experience bleeding complications.[2] Bleeding events associated with cardiac surgery are frequent, with estimates suggesting that 10% to 15% of the blood supply in the United States is consumed by cardiac surgery patients.[3] Cardiac surgery patients who experience bleeding-related complications have longer intensive care unit and hospital stays and higher hospital costs compared with cardiac surgery patients who do not experience bleeding-related complications.[4] Cardiac surgery patients requiring blood transfusions have been found to have longer times to extubation, longer intensive care unit stays, more postoperative complications, and higher mortality than patients not requiring blood transfusions.[5]

Several strategies can be used to control bleeding in the intraoperative and postoperative periods. Conventional surgical strategies such as manual compression, suture ligation, and cauterization commonly are used to control bleeding during surgery. Prophylactic and therapeutic approaches also are used to decrease the risk of postoperative blood transfusion.[6,7] However, in some situations, these conventional methods are impractical or ineffective, and additional strategies are required.[8] Topical hemostatic agents such as fibrin sealants are another option to control bleeding during surgery.[9]

Fibrin sealants contain both fibrinogen and thrombin[10] and work by mimicking the final stages of the blood coagulation process.[9] Fibrin sealants are used to promote hemostasis in patients undergoing a broad range of surgical procedures, such as cosmetic, cardiovascular, head and neck, neurologic, orthopedic, noncardiac thoracic, and vascular surgery. They are effective across a broad range of bleeding circumstances, such as venous oozing, diffuse raw surface bleeding, and hemorrhage from anastomotic graft sites during vascular surgery.[8,10] At the site of bleeding, fibrin sealants increase the local concentration of fibrinogen and thrombin; the thrombin cleaves the fibrinogen to fibrin, which polymerizes and crosslinks, progressing from a soluble mesh to a stable clot.[11]

Little is known about the real-world clinical and economic outcomes of patients treated with fibrin sealants during cardiac surgery. Such data increasingly are being requested by healthcare decision makers who make policies and payment decisions.[12] To the authors' knowledge, no real-world studies have compared the clinical outcomes and economic burden of patients treated with the fibrin sealants EVICEL (Ethicon, Inc., Somerville, NJ) and TISSEEL (Baxter Healthcare Corporation, Westlake Village, CA). Among the available forms of fibrin sealants in the United States, EVICEL and TISSEEL have the same function (hemostatic) and source (human pooled plasma).[13] A detailed comparison of these 2 products is described in Appendix 1. A few studies have compared the properties of EVICEL versus TISSEEL and clinical implications of the differences. Hickerson et al[16] suggested that the superior clot strength and resilience obtained with EVICEL relative to TISSEEL may be due to the difference in factor XIII concentration. Other differences include the higher thrombin activity in the EVICEL formulation and the presence of plasminogen and aprotinin in the TISSEEL formulation.[16]

The objective of this study was to compare the clinical outcomes (eg, postoperative bleeding events), healthcare resource utilization (eg, hospital length of stay [LOS] and blood transfusion number), and costs between patients who received EVICEL or TISSEEL during CABG surgery.

Methods

Data Source

The Premier Prospective hospital data set contains information from more than 700 hospitals throughout the United States (www.premierinc.com), covering an estimated 20% of hospital discharges. Data elements include hospital and patient identifiers, primary and secondary International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis coding system diagnoses and procedure codes; LOS; admission types and primary payer information. Also available are data elements for patient demographic characteristics, such as age and race, and hospital characteristics, such as provider geographic location, hospital bed size, teaching hospital status, and hospital location.

Patient Selection

Adult patients 18 years or older who underwent primary CABG surgery from January 2009 to March 2014 and received either EVICEL or TISSEEL during the primary CABG surgery were identified in the Premier database. Patients who underwent a CABG procedure were identified using the ICD-9 procedure codes (Appendix 2). Patients were excluded if they received both EVICEL and TISSEEL at any time during the same hospitalization or underwent both CABG and valve surgeries during the same hospitalization. Patients with incomplete hospital stay data (admission and discharge day) during the study time frame also were excluded.

Measures

Outcomes

Clinical outcomes evaluated included bleeding complications (ICD-9 diagnosis 998.1: hemorrhage or hematoma or seroma complicating a procedure) after CABG surgery and blood transfusions during 3 time frames. ICD-9 diagnosis codes (99.0x, V58.2), standard charge codes, and current procedural terminology codes were used to identify clinical outcomes during the following 3 time frames: (1) entire index hospitalization, (2) day of index CABG surgery, and (3) after index hospitalization. Economic outcomes evaluated included hospital overall LOS (ie, number of days from hospital admission until discharge), total hospitalization costs, and 30-day readmission rate.

Covariates

Patient demographic and clinical variables evaluated included age, sex, race, marital status, payer type, Charlson Comorbidity Index, admission type, all patient refined diagnostic-related group (APR-DRG) severity of illness and mortality, and bleeding-related comorbidities (eg, anemia [ICD-9 codes 284.0-284.2, 284.8, 284.81, 284.89, 284.9, 285.3, 285.9] and anemia caused by cancer [ICD-9 codes 285.21, 285.22, 285.29]). Hospital characteristics evaluated included hospital size, geographic region, location (ie, urban *v* rural), and teaching status.

Statistical Analysis

Statistical tests were performed to compare demographic, clinical, and hospital characteristics between patients who received EVICEL or TISSEEL. Student *t*-tests were performed to compare continuous variables; chi-square tests were used to compare categorical variables. A propensity-score matching method was used to match patients who received either EVICEL or TISSEEL on the basis of characteristics including age, sex, race, payer, admission method, Charlson Comorbidity Index, APR-DRG severity of illness and mortality, anemia, anemia caused by cancer, hospital size, geographic region, and teaching status. Hospital location (rural *v* urban) was not included because 100% of patients were from urban hospitals within both study groups. A propensity score of the probability of using hemostatic treatment (EVICEL *v* TISSEEL) was created for each patient in the study cohort, and 1 TISSEEL patient was selected for each EVICEL patient (ie, matched at a 1:1 ratio) using the nearest-neighbor method.[20]

Additional sensitivity analyses were performed via regressions to control for differences in the use of hemostatic agents other than EVICEL and TISSEEL during the index CABG surgery within the propensity-score–matched cohorts. The following adjusted outcomes were reported: bleeding complication rate, blood transfusion rate, total hospital costs, and 30-day readmission rate. A 2-sided p value of < 0.05 was considered to be statistically significant.

All data used in this analysis were compliant with the Health Insurance Portability and Accountability Act.

Results

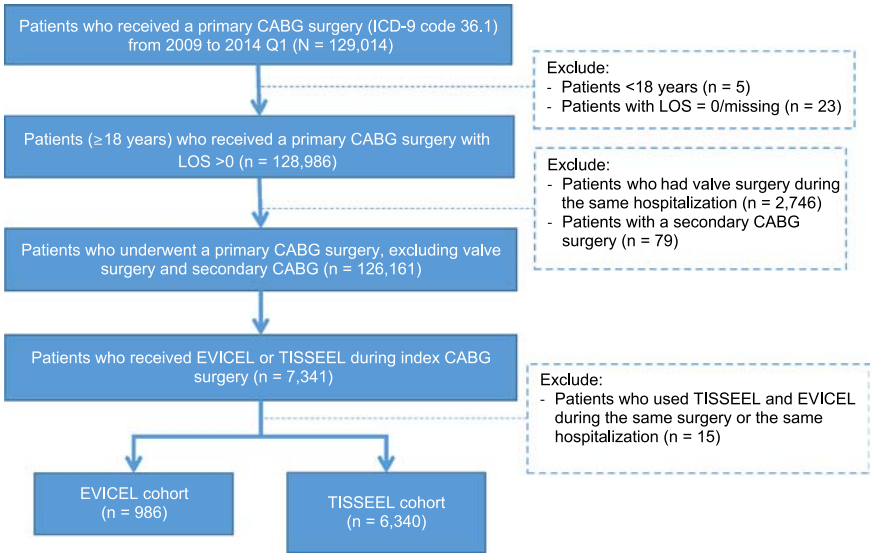
Patient Sample

A total of 986 patients received EVICEL and 6,340 patients received TISSEEL during the study period (Fig 1). Patients who received EVICEL, compared with TISSEEL, experienced more comorbid anemia and a slightly higher APR-DRG severity and were more likely to be admitted to the hospital through the emergency department (Table 1). Compared with patients who received EVICEL, TISSEEL patients were more likely to be admitted to teaching hospitals and hospitals with more than 500 beds (Table 2).

Outcomes

In unadjusted analyses, patients who received EVICEL were less likely to develop bleeding complications (4% *v* 6%, $p < 0.001$) and require blood transfusions (41% *v* 64%, $p < 0.001$, during the entire hospitalization) compared with patients who received TISSEEL (Table 3). Overall, patients who received EVICEL had lower hospital costs compared with patients who received TISSEEL; there was no difference in LOS between study groups.

After propensity-score matching, there were no statistically significant differences in patient demographics, clinical



LOS = Length of Stay, CABG = Coronary artery bypass grafting

Fig 1. Flowchart for cohort selection.

Table 1
Patient Demographic and Clinical Characteristics

	TISSEEL (n = 6,340)	EVICEL (n = 986)	p Value
Age, mean (standard deviation)	65.2 (10.4)	64.3 (10.2)	0.014
Male (n, %)	4,742 (75)	716 (73)	0.14
Race (n, %)			< 0.001
White	5,082 (80)	727 (74)	
Black	382 (6.0)	36 (3.7)	
Hispanic	105 (1.7)	18 (1.8)	
Other	770 (12)	205 (21)	
Marital status (n, %)			< 0.001
Married	4,102 (65)	592 (60)	
Single	2,046 (32)	374 (38)	
Other	187 (3.0)	16 (1.6)	
Discharge year (n, %)			< 0.0001
2009	1,322 (21)	175 (18)	
2010	1,309 (21)	232 (24)	
2011	1,247 (20)	210 (21)	
2012	1,272 (20)	141 (14)	
2013	978 (15)	182 (18)	
2014 (Q1)	212 (3)	46 (5)	
Payer (n, %)			< 0.001
Medicare	3,465 (55)	489 (50)	
Medicaid	301 (4.7)	98 (9.9)	
Managed care	2,077 (33)	332 (34)	
Other	496 (7.8)	67 (6.8)	
APR-DRG mortality (disease severity indicator) (n, %)			0.30
Minor	1,240 (20)	179 (18)	
Moderate	2,181 (34)	352 (36)	
Major	1,947 (31)	287 (29)	
Extreme	971 (15)	168 (17)	
APR-DRG severity (disease severity indicator) (n, %)			0.51
Minor	270 (4.3)	39 (4.0)	
Moderate	2,237 (35)	329 (33)	
Major	2,513 (40)	396 (40)	
Extreme	1,319 (21)	222 (23)	
Admission type (n, %)			< 0.001
Emergency	1,582 (25)	436 (44)	
Urgent	2,091 (33)	176 (18)	
Elective	2,657 (42)	366 (37)	
Other	9 (< 1)	8 (< 1)	
CCI category (n, %)			0.0054
0	1,371 (22)	238 (24)	
1	1,798 (28)	314 (32)	
2	1,351 (21)	192 (19)	
≥ 3	1,820 (29)	242 (25)	
Anemia (n, %)	781 (12)	201 (20)	< 0.001
Anemia caused by cancer (n, %)	167 (2.6)	37 (3.8)	0.06

Abbreviations: APR-DRG, patient refined diagnostic-related group; CCI, Charlson Comorbidity Index.

covariates, or hospital characteristics between the cohorts. The study results remained in favor of EVICEL over TISSEEL after adjusting for the covariates using a propensity score approach. Patients who received EVICEL compared with TISSEEL experienced fewer bleeding complications (3% *v* 5%, p = 0.0197); lower blood transfusion rates (41% *v* 53%, p < 0.0001, during the entire hospitalization); 30-day readmission rates (18% *v* 32%, p < 0.0001); and hospital costs ($40,736 ± $19,465 *v* $46,005 ± $24,049, p < 0.0001) (Table 4).

Results from sensitivity analysis performed using the propensity-score–matched cohort found that the majority of EVICEL- and TISSEEL-treated patients received other hemostatic agents (91% *v* 77%, p < 0.001); the most commonly used additional agent was thrombin. Additional regression analyses were performed to adjust for differences in other hemostatic agent use. Results from these additional regression analyses conducted within the matched cohorts found that the study results remained in favor of EVICEL compared with TISSEEL. Patients who received EVICEL compared with the TISSEEL cohort had significantly fewer postoperative bleeding complications (2.7% *v* 5.0%, p < 0.001), blood transfusion rates on the index day (17.1% *v* 35.3%, p < 0.001), readmission rates (17.6% *v* 31.9%, p < 0.001), and costs ($40,512 [95% confidence interval $39,387-$41,669] *v* $46,048 [95% confidence interval $44,769-$47,363]).

Discussion

Surgical hemostasis is needed in cardiac surgery to control intraoperative bleeding and thereby reduce morbidity and the related costs from bleeding-related complications.[21] An estimated 30% of cardiac surgery patients will experience a bleeding-related complication.[4] Cardiac surgery patients who experienced bleeding-related complications were found to have longer intensive care unit (4.9 *v* 2.1 days) and hospital (11.0 *v* 6.2 days) stays and higher mean total adjusted hospital costs ($39,050 *v* $28,771 [year 2007 US]) compared with cardiac surgery patients who did not experience bleeding-related complications.[4] Cardiac surgery patients requiring red blood cell transfusions were found to have significantly longer times to extubation after surgery (8.0 *v* 4.3 hours, p ≤ 0.001), intensive care unit stays (1.6 *v* 1.2 days, p ≤ 0.001), and hospital stays (7.2 *v* 4.3 days, p ≤ 0.001); more postoperative complications (p ≤ 0.001); and higher 30-day hospital mortality (3.1% *v* 0 %, p ≤ 0.001) compared with cardiac surgery patients not requiring red blood cell transfusions.[5] In addition,

Table 2
Hospital Characteristics

	Patients, n (%)		p Value
	TISSEEL (n = 6,340)	EVICEL (n = 986)	
Teaching hospital	3,876 (61)	259 (26)	< 0.0001
Hospital location			0.0852
Rural	19 (0)	0 (0)	
Urban	6,321 (100)	986 (100)	
Bed number			< 0.0001
≤ 500 beds	2,566 (40)	839 (85)	
> 500 beds	3,774 (60)	147 (15)	
US region			< 0.0001
Midwest	121 (2)	62 (6)	
Northeast	1,913 (30)	15 (2)	
South	3,313 (52)	302 (31)	
West	993 (16)	607 (62)	

Table 3
Unadjusted Clinical and Economic Outcomes Between Study Groups

	TISSEEL (n = 6,340)	EVICEL (n = 986)	p Value
Blood transfusion on index date, n (%)	3,113 (49)	182 (18)	< 0.001
Blood transfusion after index date, n (%)	877 (14)	86 (9)	< 0.001
Any blood transfusion during the hospitalization, n (%)	4,057 (64)	404 (41)	< 0.001
Postoperative bleeding complication, n (%)	389 (6)	37 (4)	0.002
30-day readmission, n (%)	1,644 (26)	177 (18)	< 0.0001
LOS, mean (standard deviation)	9.74 (6.40)	9.40 (5.95)	0.12
Total cost ($), index hospitalization, mean (standard deviation)	42,968 (26,103)	41,291 (19,402)	0.048

Abbreviation: LOS, length of stay.

a positive correlation was noted for red blood cell transfusion and increased time to extubation, intensive care unit LOS, postoperative LOS, and mortality.

Topical hemostatic agents are used by surgeons to help control bleeding, potentially decreasing bleeding-related complications and the need for red blood cell transfusions. The topical fibrin sealants EVICEL and TISSEEL can be used as an adjunct to hemostasis in patients undergoing surgery. These sealants work by replicating the final steps in the coagulation pathway, ultimately resulting in the formation of a stable clot.[11] The stable clots formed after fibrin sealant administration provide sustained hemostasis because they remain at the site of application for up to 2 weeks, a period that well exceeds the critical risk period for postoperative rebleeding.

Although data from randomized controlled clinical trials demonstrated the efficacy of EVICEL and TISSEEL in cardiac surgery,[22,23] few studies have compared their performance in the real world. Therefore, the authors of this study performed a hospital database analysis to compare clinical and economic outcomes in patients who received either EVICEL or TISSEEL during their primary cardiac surgery. Results from the analyses, after adjusting for covariate differences between the study cohorts, showed that in primary CABG surgery patients, the use of EVICEL versus TISSEEL was associated with fewer postoperative bleeding events, fewer blood transfusions, less utilization of additional resources, and lower hospital costs, even after controlling for the concomitant use of other hemostatic products such as thrombin.

Table 4
Adjusted Clinical and Economic Outcomes Between Study Groups After Propensity-Score Matching

	TISSEEL (n = 900)	EVICEL (n = 900)	p Value
Clinical outcomes			
Postoperative bleeding complications, n (%)	44 (5)	25 (3)	0.0197
Blood transfusions, n (%)			
Index date	306 (34)	167 (19)	< 0.0001
Post-index date	135 (15)	80 (9)	< 0.0001
During entire hospitalization	476 (53)	366 (41)	< 0.0001
Economic outcomes			
30-day readmission, n (%)	288 (32)	158 (18)	< 0.0001
LOS, days (standard deviation)	9.3 (6.2)	9.3 (6.0)	0.8144
Total cost, US ($) (standard deviation)*	46,005 (24,049)	40,736 (19,465)	< 0.0001

NOTE. Data presented as number of patients (%) unless otherwise noted.
Abbreviation: LOS, length of stay.
*Total cost of index hospitalization.

The results of increased hospital costs with increased bleeding-related complications were similar to the results from the real-world study performed by Stokes et al.[4] In the study by Stokes et al, increased hospital LOS and costs were demonstrated in surgery patients with bleeding-related complications and/or need for blood transfusions. These increased costs were not evident only in cardiac surgery patients but also in patients undergoing spinal, vascular, solid organ, noncardiac thoracic, general, knee/hip replacement, and reproductive organ surgeries. Although Stokes et al documented increased costs in surgical patients with bleeding-related complications and/or need for transfusions, the effect of hemostatic agent use was not evaluated.

The results of this study need to be considered in the context of several limitations. First, detailed clinical information, such as the location of hemostatic agent application and patient laboratory data, were not available, given that the study was a retrospective database analysis. In addition, because the patients were not assigned randomly to a treatment group, the authors cannot be sure that unrecognized differences did not exist between patients who received EVICEL or TISSEEL. For example, preoperative antiplatelet therapy between the EVICEL and TISSEEL groups was not captured. However, because similar percentages of patients in both groups underwent elective, urgent, and emergency procedures, it may be reasonable to assume that antiplatelet therapy use was similar between the study groups. Future studies, such as prospective randomized trials, are warranted to measure/control for the use of antiplatelet drug or therapy and timing. Second, bleeding complications were identified using ICD-9 diagnosis codes, which may underestimate the actual bleeding complication rate because less-severe complications may not be documented in a patient's medical record and therefore not coded in the database. In addition, some of the bleeding complications identified using diagnosis codes could be misclassified, given that the administrative database originally was for billing instead of research purposes. Third, the causal relationship

between fibrin sealant use and the bleeding-related complication rate cannot be established because of the nature of retrospective databases analyses. The observed differences in economic and clinical outcomes identified between EVICEL and TISSEEL administration could not be explained based on the data obtained for this analysis. Additional studies are warranted to further evaluate the differences identified in this analysis. Finally, because this was a retrospective analysis, the authors were unable to evaluate factors that influenced the product administered. Product choice potentially was influenced more by product availability than product characteristics. Future studies should examine factors that affect selection of particular fibrin sealants.

Conclusion

This real-world retrospective study found that patients who received EVICEL had fewer bleeding-related complications and lower costs than patients who received TISSEEL during CABG surgery. The results remained robust after adjusting for the observed differences between study groups. Specifically, within the matched cohorts the authors found that patients who received EVICEL compared with TISSEEL experienced significantly fewer postoperative bleeding complications, lower blood transfusion rates on the day of surgery, lower hospital readmission rates, and lower hospital costs. Future analyses should further evaluate factors that could explain these differences and determine whether these differences are unique to CABG surgery patients.

Acknowledgment

The authors wish to thank Beth A. Lesher, PharmD, BCPS, for her assistance in writing this manuscript.

APPENDIX 1. DETAILED COMPARISON OF EVICEL AND TISSEEL

Comparison of Fibrin Sealants

	EVICEL	TISSEEL
Fibrinogen (mg/mL)	55-85[14]	67-106[15]
Thrombin (IU/mL)	800-1,200[14]	400-625[15]
FXIII (IU/mL)	9[16]	Not detected[16]/1-3[17]
Bovine aprotinin (KIU/mL)	None	2,250-3,750[15]
Plasminogen (μg/mL)	7[17]	40-120[17]
Plasminogen removed	Yes	No
No restrictions between (°C)	2-37	33-37

The detailed differences between these 2 fibrin sealants are described in the following:

- Plasminogen is the inactive precursor protein to the enzyme plasmin, which is responsible for degrading fibrin clots. The EVICEL manufacturing process includes a specific affinity chromatography step designed to remove plasminogen, making the EVICEL clot inherently more stable, whereas other fibrin sealants, including TISSEEL, use aprotinin, an inhibitor of plasmin to stabilize the formulation. However, aprotinin can diffuse rapidly from the clot in vivo, thus limiting its ability to prevent plasmin-mediated fibrin degradation.[18] Comparing the 2 fibrin sealants, the concentration of plasminogen in EVICEL was reported to be 7 μg/mL, whereas the level of plasminogen in TISSEEL was 40-120 μg/mL.[17] The clinical impact of this difference in plasminogen concentration is unknown.
- The primary active components in fibrin sealant formulations are fibrinogen and thrombin. When the 2 components are mixed, thrombin acts on fibrinogen to enzymatically convert soluble fibrinogen to an insoluble fibrin clot, which then is stabilized by the action of factor XIIIa. EVICEL was reported to contain higher levels of FXIII compared with that of Tisseel.[16,17] This difference in FXIII between the products translated to EVICEL clots having greater mechanical strength and stability in in vitro studies.[16]
- In heparinized animal models, it was reported that the thrombin concentration of the fibrin sealant inversely correlated with bleeding time and blood loss.[19] The activity of the thrombin component in EVICEL is 800-to-1,200 IU/mL, which is higher than other fibrin sealants that typically have approximately 500 IU/mL. Even though there are quantitative differences in the level of thrombin activity between EVICEL and TISSEEL, the clinical implications of this difference are not understood completely.
- EVICEL and TISSEEL have different temperature requirements during clinical use. EVICEL does not have restrictions within a range of 2-to-37°C,[14] whereas TISSEEL must be used within a range of 33-to-37°C[15] to avoid challenges with fibrin sealant spraying or dripping due to high viscosity at low temperatures. No studies have investigated whether the use of the fibrin sealants at different temperatures could have clinical implications.

APPENDIX 2. CABG PROCEDURES ICD-9 CODES

ICD-9 Diagnosis Codes	Description
36.10	Aortocoronary bypass NOS
36.11	Aortocoronary bypass, 1 artery
36.12	Aortocoronary bypass, 2 arteries
36.13	Aortocoronary bypass, 3 arteries
36.14	Aortocoronary bypass, 4 arteries
36.15	Single mammary
36.16	Double mammary
36.17	Abdominal coronary artery bypass
36.19	Bypass anastomosis heart revascularization

NOS, not otherwise specified.

References

1 National Hospital Discharge Summary: 2010 table. CDC/National Center for Health Statistics. Available at: https://www.cdc.gov/nchs/data/nhds/4procedures/2010pro4_numberrate.pdf. Accessed May 19, 2016.

2 Tackett SM, Calcaterra D, Magee G, et al. Real-world outcomes of hemostatic matrices in cardiac surgery. J Cardiothorac Vasc Anesth 2014;28:1558–65.

3 Ferraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944–82.

4 Stokes ME, Ye X, Shah M, et al. Impact of bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients. BMC Health Serv Res 2011;11:135.

5 Scott BH, Seifert FC, Grimson R. Blood transfusion is associated with increased resource utilisation, morbidity and mortality in cardiac surgery. Ann Card Anaesth 2008;11:15–9.

6 Shore-Lesserson L, Manspeizer HE, DePerio M, et al. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999;88:312–9.

7 Fremes SE, Bill IW, Lee E, et al. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. Ann Thorac Surg 1994;58:1580–8.

8 Boucher BA, Traub O. Achieving hemostasis in the surgical field. Pharmacotherapy 2009;29:2S–7S.

9 Samudrala S. Topical hemostatic agents in surgery: A surgeon's perspective. AORN J 2008;88:S2–11.

10 Spotnitz WD, Burks S. State-of-the-art review: Hemostats, sealants, and adhesives II: Update as well as how and when to use the components of the surgical toolbox. Clin Appl Thromb Hemost 2010;16:497–514.

11 Dhillon S. Fibrin sealant (evicel® [auxil®/crosseal™]): A review of its use as supportive treatment for haemostasis in surgery. Drugs 2011;71:1893–915.

12 Garrison Jr LP, Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: The ISPOR Real-World Data Task Force report. Value Health 2007;10:326–35.

13 Spotnitz WD. Fibrin sealant: The only approved hemostat, sealant, and adhesive—a laboratory and clinical perspective. ISRN Surg 2014;2014:1–28.

14 Ethicon: Product monograph. EVICEL fibrin sealant (human). Available at: http://www.ethiconinstitute.com/sites/default/files/EVICEL_Product-Monograph_2.pdf. Accessed November 16, 2016.

15 Baxter: TISSEEL: Prescribing information. Available at: http://www.tisseel.com/us/pdf/TISSEEL_PI.pdf. Accessed November 16, 2016.

16 Hickerson WL, Israel N, Meidler R. A comparison of the mechanical, kinetic, and biochemical properties of fibrin clots formed with two different fibrin sealants. Blood Coagul Fibrinolysis 2011;22:19–23.

17 Hedrich HC, Simunek M, Reisinger S, et al. Fibrin chain cross-linking, fibrinolysis, and in vivo sealing efficacy of differently structured fibrin sealants. J Biomed Mater Res B Appl Biomater 2012;100B:1507–12.

18 Lorentz KM, Kontos S, Frey P, et al. Engineered aprotinin for improved stability of fibrin biomaterials. Biomaterials 2011;32:430–8.

19 Nur I, Lyahovetsky Y, Bar L, et al. Commercial fibrin sealants are not equivalent in a rabbit liver-resection model which quantitatively evaluates hemostasis and formation of adhesions. Eur Surg Res 2005;37:159–65.

20 Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33–8.

21 Krishnan S, Conner TM, Leslie R, et al. Choice of hemostatic agent and hospital length of stay in cardiovascular surgery. Semin Cardiothorac Vasc Anesth 2009;13:225–30.

22 Chalmers RT, Darling Iii RC, Wingard JT, et al. Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures. Br J Surg 2010;97:1784–9.

23 Rousou JA. Use of fibrin sealants in cardiovascular surgery: A systematic review. J Card Surg, 28; 238–47.