Assessment of the safety and efficacy of the DUETT vascular hemostasis device: Final results of the Safe and Effective Vascular Hemostasis (SEAL) trial

The SEAL Trial Study Team

Objective We sought to determine the safety and efficacy of the novel DUETT vascular hemostasis device in comparison with standard manual compression after diagnostic and interventional coronary procedures.

Background Vascular hemostasis devices are increasingly used to improve patient comfort and speed mobilization after coronary and peripheral vascular procedures. Currently available devices have certain limitations, however.

Methods At 16 clinical sites, 630 patients who underwent diagnostic or interventional coronary procedures were randomized 5:3 to the DUETT sealing device or standard manual compression. The primary study end points were time to hemostasis and ambulation and the incidence of major vascular complications at 30 days.

Results Time to hemostasis from the completion of the procedure (catheter removal; median) was 14 minutes (interquartile range [IQR], 10, 17 minutes) in the DUETT group and 195 minutes (IQR, 46, 351 minutes) in the standard compression group (P <.001), and time from sheath removal (median) was 7 minutes (IQR, 6, 8 minutes) and 20 minutes (IQR, 15, 30 minutes) for the 2 groups, respectively (P <.001). Time to ambulation from catheter removal (median) was 338 minutes (IQR, 223, 526 minutes) in the DUETT group and 705 minutes (IQR, 400, 1120 minutes) in the standard compression group (P <.001). Major complications occurred in 3.6% of the DUETT group and 1.7% of the standard compression group (P = .22), with a diminishing risk of complications in the DUETT group as experience was accrued. Similar benefits from DUETT use were seen in patients who underwent both diagnostic and interventional procedures.

Conclusion The DUETT sealing device allows immediate arterial sheath removal after both diagnostic and interventional procedures, dramatically reducing time to hemostasis and patient ambulation without compromising patient safety in comparison with standard compression techniques. (Am Heart J 2002;143:612-9.)

The use of vascular hemostasis devices (VasoSeal, Datascope Corp, Montvale, NJ; Angio-Seal, St Jude Medical, Minneapolis, Minn; Prostar/Techstar, Perclose, Inc, Menlo Park, Calif) has increased in the last several years as physicians attempt to improve patient comfort and minimize the duration of bedrest after diagnostic and interventional coronary procedures. Current devices have several limitations, however, including deployment failure in 2% to 12% of cases,[1] requirement for considerable technical expertise with a prolonged learning curve,[2] an entry port considerably larger than the initial vascular sheath, retained components restricting future groin site access, delayed oozing of blood even with successful device placement, and a possibly increased incidence rate of delayed groin infection.[3]

The DUETT vascular hemostasis device (Vascular Solutions, Minneapolis, Minn) is a novel sealing device that incorporates a unique low profile positioning balloon catheter in combination with a biologic procoagulant mixture containing collagen and thrombin to rapidly facilitate extravascular thrombosis in the perivascular tissue to achieve hemostasis.[4] The purpose of the SEAL study was to evaluate the safety and efficacy of the DUETT sealing device in comparison with manual hemostasis in a group of patients who underwent either diagnostic or interventional coronary procedures.

Methods

Patient population

The SEAL study was performed at 16 hospitals whose institutional review boards had approved the protocol. Patients were eligible for the study if they were to undergo a diagnostic or interventional cardiac procedure with femoral arterial access were 18 years of age or older and could provide written informed consent. Patients who met any of the following criteria were excluded from recruitment: arterial sheath of less

From the SEAL Trial Study.
**A list of the SEAL Trial Study members appears in Appendix A. A list of the SEAL Trial Study sites appears in Appendix B.*
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Figure 1

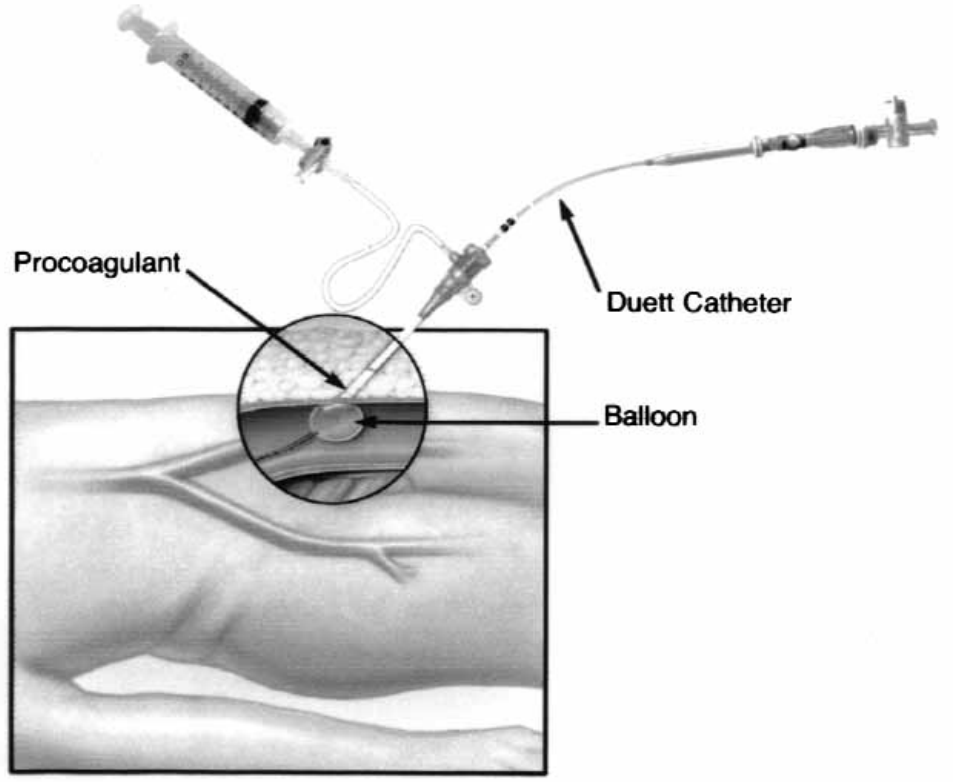


Diagram of components of DUETT device.

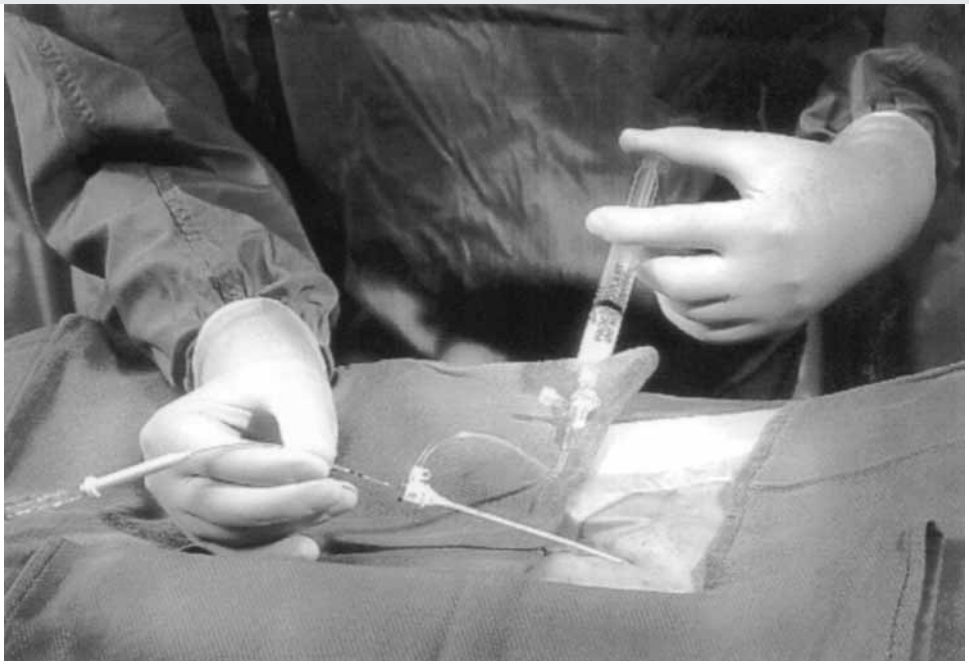
than 5F, more than 9F, or longer than 10 cm; presence of a 6 cm–diameter or more hematoma before initial sheath removal; presence of clinically severe peripheral vascular disease manifested by claudication at <100 feet, weak or absent pulses in the affected limb, ankle brachial index of <0.5 at rest, or known stenosis ≥50% in the iliac or femoral artery on the affected side; prior vascular bypass surgery or stent placement involving the affected femoral artery; suspected posterior femoral artery puncture or puncture distal to the common femoral artery bifurcation (iliofemoral angiography was required in all patients before randomization); known bleeding disorder, including platelet count of <100,000 or receipt of thrombolytic therapy within the previous 24 hours; hemoglobin of <10 gm/dL; international normalized ratio of >1.5; activated clotting time of >400 seconds at the conclusion of the catheterization procedure; suspected pregnancy; life expectancy of less than 1 year; Q wave myocardial infarction within 72 hours; uncontrolled severe hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg); medical indication for continued intravenous heparin therapy after the procedure; known allergy to bovine-derived products; and estimated femoral artery diameter of <6 mm on the basis of femoral angiography results.

Patients were randomly allocated to 1 of the 2 treatment groups with a closed envelope system and permuted block design supplied by the coordinating center. Patients were stratified on the basis of interventional or diagnostic procedure and by treatment site. Randomization favored the DUETT sealing device numerically in a 5:3 ratio and interventional procedures in a 2:1 ratio over diagnostic procedures.

DUETT deployment/standard compression

If the patient was randomized to the DUETT sealing device, the 3F DUETT catheter (Figure 1) was placed through the indwelling arterial introducer sheath, the distal occlusion balloon was inflated, and the device was retracted until firm resistance signifying pressure of the balloon against the inner aspect of the arterial wall was noted by the investigator (Figure 2). While this pressure was maintained, the introducer sheath was withdrawn 5 to 10 mm and negative aspiration from the sheath side arm was attempted to assure balloon occlusion of the arterial puncture site. The procoagulant suspension comprised of 250 mg of bovine microfibrillar collagen (Avitene, Davol Inc, Woburn, Mass) and 10,000 units of bovine thrombin (Jones Medical Inc, St Louis, Mo) was slowly injected via the sheath side arm as the sheath was slightly withdrawn. The occlusion balloon then was deflated and extended with the movable core wire, and the entire device was withdrawn as an assistant held firm manual pressure at and above the site of arterial entry. A light pressure dressing then was applied to the femoral access site for 1 hour after hemostasis was observed.

Figure 2



Injection of procoagulant with DUETT device in proper position.

Patients randomized to the control arm underwent treatment with manual compression with the standard of care at that clinical site. The Femostop device (Radi Medical Systems, Uppsala, Sweden) and C-clamp were allowed as adjuncts to manual compression, but no other vascular hemostasis devices were permitted.

Ambulation and monitoring

The chronology of clinical and laboratory assessment is provided in Table I. For the determination of time to hemostasis and time to ambulation, the clock was considered to start at the time of the completion of the antecedent procedure, as evidenced by removal of all diagnostic or interventional catheters and the physician's verbal indication of the end of the procedure. Time to hemostasis also was assessed with the time of sheath removal as "time zero." For patients randomized to the DUETT device who had undergone diagnostic evaluation only, assessment of hemostasis was made at 2-minute intervals until hemostasis was achieved. For patients randomized to the DUETT device who had undergone interventional procedures, the first assessment was at 5 minutes and was followed by subsequent assessment at 2-minute intervals as necessary. Achievement of hemostasis was defined as that time when there was no significant bleeding at the puncture site after release of any manual pressure. Whether randomized to the DUETT device or to manual compression, the puncture site was observed continually for 5 minutes to confirm hemostasis.

Patients randomized to the DUETT device were to be ambulated according to guidelines noted in Table II. Patients randomized to standard compression were ambulated according to the institution's practice standards. In both instances, patients were not to be ambulated until no active bleeding was shown at the puncture site and the systolic blood pressure in the supine and sitting position was 100 mm Hg or more. The time of ambulation was recorded as that time when the patient had gotten out of bed and walked 110 feet without loss of hemostasis.

Patients from 5 centers (n = 214) were requested to return for 30-day follow-up femoral artery duplex ultrasound scan examination. The tapes of these examinations were forwarded to the core ultrasound scan laboratory at Beth Israel Deaconess Medical Center in Boston for treatment-masked analysis.

Data collection and statistical analysis

Locally collected data were transmitted for data entry, quality control, and analysis at Cardiovascular Data Analysis Center, Boston, Mass. A Clinical Events Committee, completely independent of the sponsor, reviewed and adjudicated all major complications without knowledge of treatment assignment. A formal Data and Safety Monitoring Committee assessed the progress of the clinical investigation.

The primary efficacy endpoints were to show a reduced time to hemostasis and ambulation with the DUETT sealing device compared with standard compression. The primary safety endpoint was the incidence of major complications (vascular surgery, ultrasound scan–guided compression to treat a pseudoaneurysm, bleeding requiring transfusion, infection of the puncture site requiring extended hospitalization, and antibiotic administration within 30 days) with the DUETT

Table I. Assessment schedule

Assessment	Evaluation point				
	Before catheterization procedure	After procedure, before deployment	After deployment	Discharge	30 days
Assessment of femoral artery puncture site	X	X	X	X	X
Assessment of distal pedal pulses	X		X	X	X
Laboratory tests: Hgb, Hct, platelets	X			X	
Vital signs (heart rate, blood pressure)	X	X	X	X	X
INR (only for patients with warfarin therapy)	X				
Activated clotting time		X			
Limited femoral angiogram		X			
Time to hemostasis			X		
Time to ambulation			X		
Ultrasound scan assessment of treated femoral artery (214 consecutive randomized patients)					X

Hgb, Hemoglobin; *Hct,* hematocrit; *INR,* international normalized ratio.

Table II. DUETT patient ambulation guidelines

Patient condition	Sheath size	Recommended ambulation guidelines
No anticoagulation	5F–6F	1–2 hours after procedure
	7F–8F	2–4 hours after procedure
Anticoagulation*	5F–6F	3–4 hours after procedure
	7F	4–5 hours after procedure
	8F	5–6 hours after procedure
	9F	6–7 hours after procedure
Any approved GP IIb/IIIa platelet receptor blocker	5F–9F	Left to investigator's discretion, but no earlier than recommendations used for patients with anticoagulation

*Anticoagulation: 50 u/kg or more of heparin during procedure or predeployment ACT 200 seconds or more. Also, with full dose of enoxaparin (1 mg/kg twice per day) within 8 hours of DUETT deployment, ambulation should follow anticoagulation guidelines. *GP,* Glycoprotein.

device and standard compression. All patients were to undergo clinical examination at 30 days. The timing and incidence of these endpoints were to be compared for the 2 methods of hemostasis used in the combined group of patients for diagnosis and intervention. Secondary objectives included the device success rate, time to discharge, and an analysis of the components of the primary endpoint dividing patients into those with diagnostic and interventional procedures. The sample size was determined as the largest patient number necessary to provide adequate statistical power ($\alpha = 0.05$; $\beta = 0.80$) for the time-dependent endpoints (with independent Student *t* test) and for the major complication rate (with the Blackwelder method of assessing equivalence with estimated complication incidence rate of 6% in the 2 study groups and a prespecified significant difference of 5%).[5] The final sample size was determined with the sample size estimate for major complications as 630 patients (400 patients for intervention, 200 patients for evaluable diagnosis, and 30 patients assumed likely to be lost to follow-up examination). Two hundred fourteen patients were prospectively assigned to 30-day ultrasound scan follow-up examination at 1 of 5 sites. Formal economic and quality of life substudy analysis was performed at 8 of the clinical sites, the details of which will be reported separately.

Data are presented as mean ± standard deviation, median with interquartile range, or proportion, as appropriate. Although the primary analysis called for a comparison combining the patients for diagnostic and interventional procedures, for the purposes of clarity and comparison, these data are also presented separately. All formal statistical analyses were performed with the intention-to-treat principle. Between group tests for differences in outcome used Fisher exact test and Mann-Whitney *U* test (for skewed data), as appropriate. Multivariate logistic regression analysis was used to assess independent correlates of major complications. A 2-sided *P* value of <.05 was considered significant.

Results

Baseline patient characteristics and preprocedural medications are enumerated in Table III. There were no significant differences between the DUETT and standard compression groups in any of the parameters measured. Arterial sheath size and activated clotting time are shown in Table IV. Primary efficacy and safety data are described in Table IV. All patients were followed through hospital discharge. Thirty days after enroll-

Table III. Patient characteristics

Patient characteristic	DUETT sealing device: all patients (n = 392)	Standard compression: all patients (n = 238)	DUETT sealing device: patients for intervention (n = 266)	Standard compression: patients for intervention (n = 155)	DUETT sealing device: patients for diagnosis (n = 126)	Standard compression: patients for diagnosis (n = 83)
Age (y)	62 ± 11	63 ± 12	62 ± 11	63 ± 11	62 ± 11	64 ± 13
Male sex	78.8%	69.3%	77.8%	72.9%	71.4%	62.6%
Cigarette/cigar smoking	59.6%	53.4%	58.6%	57.8%	59.3%	45.1%
Diabetes mellitus	27.3%	22.7%	27.4%	23.2%	27%	21.7%
Hypertension requiring treatment	66.8%	66%	65.8%	69%	68.3%	60.2%
Hyperlipidemia requiring treatment	48.5%	44.5%	52.6%	49.7%	39.7%	34.9%
Prior MI	33.1%	28.7%	37.2%	29.7%	24.2%	26.8%
MI within 2 months	6.9%	6.8%	7.9%	7.1%	4.8%	6.1%
History of PVD/claudication	3.8%	3%	4.5%	2.6%	2.4%	3.6%
History of CVA/TIA	3.3%	6.3%	3.4%	4.5%	3.2%	9.6%
Catheterization within past 30 days	28.9%	24.8%	40.8%	35.5%	4%	4.8%
Height (inches)	68.0 ± 3.8	67.5 ± 3.9	68.0 ± 3.8	67.5 ± 4.0	68.1 ± 3.7	67.5 ± 3.8
Weight (lbs)	188 ± 38	184 ± 35	187 ± 39	182 ± 34	188 ± 35	187 ± 37
Systolic blood pressure (mm Hg)	137 ± 20	139 ± 20	137 ± 20	138 ± 21	138 ± 19	140 ± 19
Diastolic blood pressure (mm Hg)	76 ± 13	75 ± 11	75 ± 13	75 ± 11	77 ± 13	75 ± 12
Preprocedure medications						
ASA	91.6%	88.6%	94.7%	93.5%	84.9%	79.5%
Persantine	0.3%	0.8%	0	0.6%	0.8%	1.2%
Ticlopidine hydrochloride	16.8%	17.3%	21.8%	22.7%	6.3%	7.2%
Clopidogrel bisulfate	14.3%	12.2%	18%	15.5%	6.3%	6%
Heparin	21.5%	17.2%	24.5%	18.7%	15.2%	14.5%
Low–molecular weight heparin	1.8%	1.7%	2.3%	1.9%	0.8%	1.2%
Coumadin	1.5%	1.7%	1.9%	1.3%	0.8%	2.4%
GP IIb/IIIa receptor blockers	5.1%	5.5%	7.5%	7.7%	0	1.2%

No between-group differences existed ($P < .05$). *MI,* Myocardial infarction; *PVD,* peripheral vascular disease; *CVA,* cerebrovascular accident; *TIA,* transient ischemic attack; *ASA,* aspirin only; *GP,* glycoprotein.

ment, follow-up examination was 95.3% complete. Twenty-one patients for DUETT (5.4%) and 8 patients for standard compression (3.4%) could not be contacted. In addition, 4 patients for DUETT (1.0%) died. None of the deaths were related access site complications. Times to hemostasis and ambulation were significantly reduced in the DUETT group for diagnostic procedures, interventional procedures, and the com-

Table IV. Treatment and major outcomes

	DUETT sealing device: all patients (n = 392)	Standard compression: all patients (n = 238)
8F sheath and larger	48%	59%
Periprocedural GP IIb/IIIa blockers	24%	24.5%
ACT at removal (seconds)	227 (148, 276)	144 (126, 161)*
Time to hemostasis† (minutes)	7 (6, 8)	20 (15, 30)*
Time to hemostasis‡ (minutes)	14 (10, 17)	195 (46, 351)*
Time to ambulation‡ (minutes)	338 (223, 526)	705 (400, 1120)*
Major complications	3.6%	1.7%
Surgery for vascular complications	1.8%	0.8%
Ultrasound scan–guided compression	1.3%	0.4%
PTA or other percutaneous procedures	0.5%	0
Bleeding requiring transfusion	1.5%	1.3%
Infection requiring extended hospitalization	0	0

Data are presented as median (interquartile range). *ACT,* Activated clotting time; *PTA,* percutaneous transluminal angioplasty.
*$P < .001$.
†From time of sheath removal.
‡From time of catheter (diagnostic or interventional) removal.

bined patient cohorts (P <.001 for all). The incidence rate of major vascular complications was low and statistically not different between the treatment groups (P = .22). Failure of the DUETT sealing device deployment occurred in 6.9% of cases, in 6 instances (1.5%) because of device component failure (eg, balloon leakage). Inadvertent intravascular injection of the procoagulant mixture resulting in distal limb ischemia occurred in 2 patients (0.5%), both relatively early (patients #6 and #13) in the experience of 1 investigator. Both patients were seen with acute extremity pain. One underwent successful treatment with intraarterial urokinase. The other underwent a successful femoral popliteal thrombectomy. One hundred ninety-three patients had evaluatable 30-day ultrasound scans for core laboratory analysis. Of these, 2 of the 142 patients for DUETT (1.4%) had a pseudoaneurysm (0.2 and 1.9 cm in diameter). None of the 51 patients for standard compression had a pseudoaneurysm. No patient had an AV fistula. Importantly, there did appear to be a modest learning curve effect associated with the use of the DUETT device. Complications occurred in 5.6% of the earliest tercile of experience (9 patients per site), compared with 2.4% and 2.9% in the second and third terciles. Low body surface area (odds ratio [OR] per meter squared, 0.01 [.008 to .12]; P <.001) and, to a lesser extent, catheterization within the previous 30 days (OR, 2.8 [1.0-7.8]; P = .05), and hypertension requiring treatment (OR, 6.9 [.9-53.2]; P = .06) were independently correlated with the likelihood of major complications.

Ninety-four patients for DUETT and 58 patients for standard compression received intravenous glycoprotein IIb/IIIa inhibitors. Time to hemostasis (median, 14 vs 214 minutes; P <.001) and time to ambulation (median, 453 vs 889 minutes; P <.001) were significantly shorter with randomization to the DUETT device, and there was no significant difference in the incidence rate of major complications (DUETT 4.3% vs standard compression 0.0%; P = .30).

At both 7-day and 30-day follow-up examinations in the quality of life substudy patient group in whom detailed information was obtained, there was no difference in response to the question "do you have discomfort at the catheter placement site." The DUETT group (n = 227) had discomfort at 7 days of 24% and at 30 days of 22%. The standard compression group (n = 137) had discomfort at 7 days of 25% and at 30 days of 24% (both P = not significant).

Discussion

The results of this study show a significant and considerable reduction in times to hemostasis and ambulation with the use of the DUETT device compared with traditional compression techniques for patients undergoing both diagnostic and interventional procedures. At the same time, there were no significant differences in the 1% to 5% incidence rate of major complications observed between treatment strategies, a finding similar to that of other randomized trials in this field.[3,5,6]

Overall use of vascular hemostasis devices appears to be increasing. It is estimated that nearly 1.2 million devices have been used worldwide as of early 1999.[1] The driving force behind this increased utilization appears to be patient comfort and rapidity of mobilization. No well-controlled study has showed a reduction in major vascular complications after diagnostic and interventional procedures with any of these devices.[1,3,6-10] Direct device-device comparisons

DUETT sealing device: patients for intervention (n = 266)	Standard compression: patients for intervention (n = 155)	DUETT sealing device: patients for diagnosis (n = 126)	Standard compression: patients for diagnosis (n = 83)
67%	71%	9%	8%
35.1%	36.8%	0.8%	1.2%
256 (224, 294)	151 (132, 164)*	132 (117, 151)	130 (116, 152)
7 (6, 9)	23 (15, 30)*	5 (4, 7)	18 (15, 27)*
14 (11, 19)	297 (195, 384)*	12 (9, 16)	38 (29, 52)*
385 (325, 732)	960 (692, 1204)*	155 (121, 262)	359 (286, 422)*
4.1%	1.9%	2.4%	1.2%
1.9%	0.6%	1.6%	1.2%
1.1%	0	1.6%	1.2%
0.4%	0	0.8%	0
1.5%	1.3%	1.6%	1.2%
0	0	0	0

should be made with considerable caution, however, owing to differences in patient populations and treatment algorithms, such as sheath size and use of glycoprotein IIb/IIIa inhibitors.

The results of this study should be viewed in context of several limitations: 1, the exclusion of patients at high risk, such as those with advanced peripheral vascular disease or activated clotting time of more than 400 seconds; 2, limited power to detect differences in major complications, owing primarily to the low incidence rate of major complications noted in both groups; 3, inability to ascertain whether or not earlier ambulation might have been safe in patients randomized in either group; and 4, the apparent "learning curve," which in retrospect might have been less apparent with a longer run-in pilot phase.

The results of this study, and several attractive design and effectiveness issues relative to other vascular hemostasis devices, including that both the arteriotomy and tissue tract size are not enlarged with use of the device, that no intraarterial foreign body remains, and that rapid and complete hemostasis is achieved without tissue tract oozing, strongly support the initial clinical utilization of this device. At the same time, it is recognized that further enhancements are desirable and will need to be tested.

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Appendix A

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SEAL trial study sites: Alton Ochsner Medical Foundation, Beth Israel Deaconess Medical Center, Beth Israel Medical Center, The Cleveland Clinic Foundation, Cardiology Research Foundation, Columbia Medical Center Phoenix, Dr Müller Hospital, Florida Hospital, Minneapolis Heart Institute, New York Hospital–Cornell Medical Center, Scripps Clinic and Research, Spokane Cardiology, University of Arkansas for Medical Sciences, University of Chicago Hospitals, and University of Texas Health Science Center.

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Appendix B

Clinical sites and investigators and coordinators (number of patients enrolled in randomized trial)

University of Arkansas: David Talley, MD, Jorge Saucedo, MD, Chris Valentine, MT (n = 69); Dr Mueller Hospital: Sigmund Silber, MD, Birgit Mau, RN (n = 61); Scripps Clinic: Paul Teirstein, MD, Karen Patel, RN, MSN (n = 60); Florida Hospital: Ralph Rodriguez, MD, Penny Porteous, RN (n = 57); Cornell Medical Center: Timothy Sanborn, MD, Tracey Shannon, RN (n = 53); University of Chicago: Ted Feldman, MD, Cindy Kienlen, RN (n = 48); Washington Hospital Center:

Martin Leon, MD, Augusto Pichard, MD, Joseph Brennan, RN (n = 47); The Cleveland Clinic Foundation: Stephen G. Ellis, MD, Marsha Lowrie, RN, MSN (n = 43); Minneapolis Heart Institute: Michael Mooney, MD, Barb Kummer, RT (n = 40); Ochsner Clinic: Tyrone Collins, MD, Steven Ramee, MD, Nancy McCarthy, RN (n = 39); Beth Israel Medical Center: James Wilentz, MD, Denise McDermott, RN (n = 34); Northwest Cardiovascular Research Institute: Pierre Leimgruber, MD, DeeAnne McGhee, RN, Carlos Sanchez, RN (n = 30); Beth Israel–Deaconess Medical Center: David Cohen, MD, Ann Slater, RN (n = 23); Columbia Medical Center: Richard Heuser, MD, Wendy Schroeder, RN (n = 16); University of Texas Medical Center: Richard Smalling, MD, Carol Underwood, RN (n = 10).

Principal Study Investigator: Stephen G. Ellis, MD.

Economic Substudy Medical Director: William S. Weintraub, MD.

Ultrasound Core Laboratory Substudy Medical Director: Deborah Levine, MD.

Data Safety and Monitoring Board Chairman: Neal A. Scott, MD.

Clinic Events Committee Chairman: Donald Cutlip, MD.