From the Society for Vascular Surgery

Prospective, randomized, multi-institutional clinical trial of a silver alginate dressing to reduce lower extremity vascular surgery wound complications

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Objective: **Wound complications negatively affect outcomes of lower extremity arterial reconstruction. By way of an investigator initiated clinical trial, we tested the hypothesis that a silver-eluting alginate topical surgical dressing would lower wound complication rates in patients undergoing open arterial procedures in the lower extremity.**

Methods: **The study block-randomized 500 patients at three institutions to standard gauze or silver alginate dressings placed over incisions after leg arterial surgery. This original operating room dressing remained until gross soiling, clinical need to remove, or postoperative day 3, whichever was first. Subsequent care was at the provider's discretion. The primary end point was 30-day wound complication incidence generally based on National Surgical Quality Improvement Program guidelines. Demographic, clinical, quality of life, and economic end points were also collected. Wound closure was at the surgeon's discretion.**

Results: **Participants (72% male) were 84% white, 45% were diabetic, 41% had critical limb ischemia, and 32% had claudication (with aneurysm, bypass revision, other). The overall 30-day wound complication incidence was 30%, with superficial surgical site infection as the most common. In intent-to-treat analysis, silver alginate had no effect on wound complications. Multivariable analysis showed that Coumadin (Bristol-Myers Squibb, Princeton, NJ; odds ratio [OR], 1.72; 95% confidence interval [CI], 1.03-2.87; $P = .03$), higher body mass index (OR, 1.05; 95% CI, 1.01-1.09; $P = .01$), and the use of no conduit/material (OR, 0.12; 95% CI, 0.82-3.59; $P < .001$) were independently associated with wound complications.**

Conclusions: **The incidence of wound complications remains high in contemporary open lower extremity arterial surgery. Under the study conditions, a silver-eluting alginate dressing showed no effect on the incidence of wound complications. (J Vasc Surg 2015;61:419-27.)**

Open vascular surgical procedures in the lower extremity constitute an evidence-based care strategy[1]; however, wound complications substantially negatively affect the effectiveness of these operations.[2,3] The 1999 Centers for Disease Control and Prevention Guideline for Prevention of Surgical Site Infection recommends the use of a sterile dressing to protect closed incisions for 24 to 48 hour postoperatively.[4] However, no evidence-based recommendations are made with regards to dressing types for use in postoperative incision care. Even more recent reviews fail to provide detailed guidance.[5]

A plethora of wound dressings are available in the market, with silver-based dressings among these recent innovations. Topical silver treatment is an effective bactericidal agent that does not induce bacterial resistance when used in therapeutic levels.[6] Acticoat Absorbent (Smith & Nephew PLC, London, United Kingdom) is an antimicrobial barrier dressing coated with nanocrystalline silver that delivers a controlled, sustained (up to 3 days) dose of silver ions, according to the manufacturer. This alginate also dressing absorbs moisture (minimizing wound maceration) and is safe and effective against a broad range of microorganisms. Acticoat is indicated for surgical wounds, chronic wounds, and burn wounds; however, data are lacking regarding in its potential role in postoperative surgical incision wound infection prophylaxis.

We previously reported a nonconcurrent, single-institution study of patients who received a conventional nonsilver-containing dressing vs Acticoat as the

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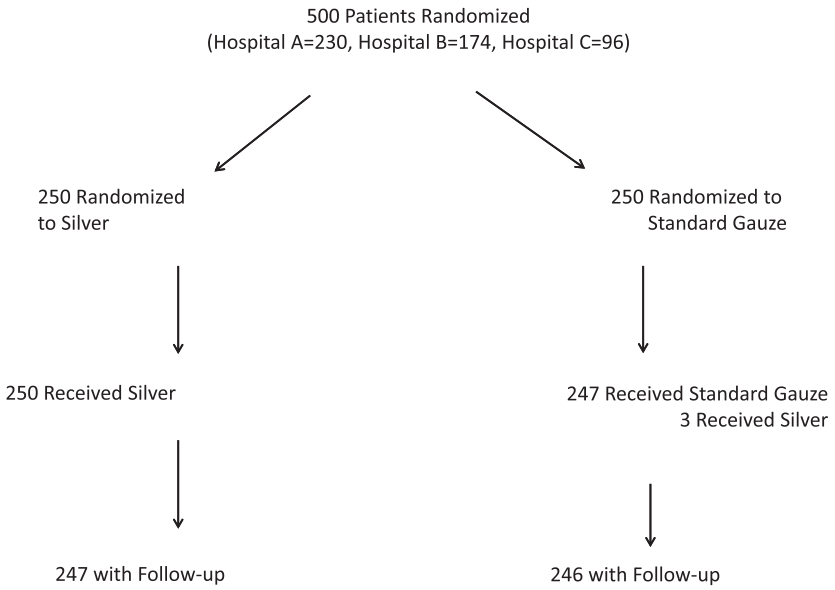

Fig. Enrollment, randomization, treatment, and follow up data. More than 99% of patients received their assigned dressing.

postoperative dressing after defined lower extremity revascularizations.[7] The wound complication rate was 14% (17 of 118) for the control group and 5% (7 of 130) for the treatment group. These findings suggested possible effectiveness for an Acticoat-based dressing system. On the basis of these data, we moved forward with a prospective, multi-institutional, randomized clinical trial to test the hypothesis that immediate application of Acticoat as a postoperative dressing would reduce closed incisional wound complications in patients undergoing lower extremity revascularizations involving infrainguinal skin incisions compared with standard nonsilver-eluting dressing material.

METHODS

Appropriate institutional approvals at two academic tertiary care medical centers and one Department of Veterans Affairs medical center were secured. Participation was offered to consecutive eligible patients starting in October 2010 and concluding in September 2013, and patients provided written, informed consent. Inclusion criterion included adults (capable of informed consent) undergoing an open (an incision below the inguinal ligament), nonemergency surgical procedure for peripheral vascular disease involving arteries or bypass grafts, with the anticipation that all incisions would be closed. Open cases combined with endovascular approaches were acceptable. The study excluded patients aged <18 years old, those with a known allergy to silver or alginate, participation in another interventional clinical trial, or prior participation in the current study.

Patients were randomized in the operating room by block design after wound closure was completed but before any dressing was applied. The wound-closure technique was at the discretion of the surgeon. Cyanoacrylate tissue adhesives (eg, Dermabond; Ethicon, Somerville, NJ) were considered as dressings and were not permitted. The final operating room dressing (silver vs standard) was secured on the wound according to surgeon preference. The practice requested of the provider teams at a kick-off presentation and subsequent ongoing education was to leave the original operating room dressing in place until gross soiling impaired standard wound hygiene, there was a clinical need to remove the dressing, or postoperative day 3, whichever came first. Subsequent dressings and wound care was at the discretion of providers.

Incision outcome at 30-days served as the primary end point. Wounds underwent visual wound checks at least at ~2 and 4 weeks by the primary surgical team. Wounds (all infrainguinal incisions, including arterial exposure, vein harvest, etc.) were graded (Appendix I, online only) as having no wound complication, superficial surgical site infection (SSI), deep SSI, dehiscence (wound separation that required local wound care), or other (seroma, lymphocele, hematoma, etc). Although categories were based on the widely accepted National Surgical Quality Improvement Program definitions,[8] more liberal categories were included to capture sometimes murky "dehiscence" and "other" events that affect patient-centric and health care economic outcomes. A host of demographic, clinical, quality of life, and economic data were collected prospectively as patients were enrolled (Appendix II, online only).

The planned study enrollment was based on prior sample size calculations. We estimated an end point event rate of at least 25%[2,3] and set a detection threshold of a 10% absolute (40% relative) wound complication rate reduction.[7] Thus, with a power of 0.8, α of .05, control event rate of

Table I. Demographics and medical history

Variables	*Total (N = 500)*	*Intent to treat*		P *value*
		Silver (n = 250)	*Conventional (n = 250)*	
Age, mean (SD), years	67.6 (10.5)	68.4 (10.2)	66.9 (10.6)	.12
Race, No. (%)				
White	418 (83.6)	213 (85.2)	205 (82.0)	.18
Black	62 (12.4)	29 (11.6)	33 (13.2)	
Hispanic	17 (3.4)	5 (2.0)	12 (4.8)	
Asian/Pacific Islander	2 (0.4)	2 (0.8)	0 (0)	
Native American	1 (0.2)	1 (0.4)	0 (0)	
Sex, No. (%)				
Female	139 (27.8)	69 (27.6)	70 (28.0)	.92
Male	361 (72.2)	181 (72.4)	180 (72.0)	
Height, mean (SD) inches	67.7 (3.8)	67.7 (3.9)	67.7 (3.7)	.95
Weight, mean (SD) pounds	180.5 (43.7)	180.5 (44.1)	180.6 (43.4)	.98
BMI, mean (SD) kg/m^2	27.6 (5.7)	27.6 (5.6)	27.6 (5.9)	.90
Prior CAD intervention (PTCA/CABG), No. (%)	165 (33.0)	83 (33.2)	82 (32.8)	.92
DM, No. (%)				
None	276 (55.2)	143 (57.2)	133 (53.2)	.67
IDDM	113 (22.6)	54 (21.6)	59 (23.6)	
NIDMM	111 (22.2)	53 (21.2)	58 (23.2)	
Renal function, No. (%)				
Normal	464 (92.8)	229 (91.6)	235 (94.0)	.32
Renal insufficiency (creatinine >2 mg/dL)	23 (4.6)	15 (6.0)	8 (3.2)	
Dialysis	13 (2.6)	6 (2.4)	7 (2.8)	
History of				
Hypertension, No. (%)	446 (89.2)	224 (89.6)	222 (88.8)	.77
Myocardial infarction, No. (%)	115 (23.0)	58 (23.2)	57 (22.8)	.92
Stroke, No. (%)	54 (10.8)	25 (10.0)	29 (11.6)	.56
Laboratory values, mean (SD)				
WBC, $\times 10^9$/L	8 (2.6)	8 (2.6)	8 (2.6)	.93
Hematocrit, %	42.8 (106.2)	37.6 (6.0)	47.9 (150.0)	.28
Platelets $\times 10^9$/L	246.2 (101.8)	252.6 (117.8)	239.9 (82.6)	.16
Glucose, mg/dL	122.4 (46.2)	122.9 (45.4)	121.8 (47.0)	.78
Creatinine, mg/dL	1.2 (1.0)	1.2 (1.2)	1.2 (0.8)	.44
Albumin, g/dL	4.3 (4.9)	4.5 (7.0)	4.0 (0.5)	.42
Hemoglobin A_{1c}, %	8.7 (21.7)	10.5 (31.3)	7.1 (1.6)	.32
C-reactive protein, mg/L	32.5 (44.5)	27.2 (41.2)	44.6 (52.5)	.40
Medications, No. (%)				
Aspirin	423 (84.9)	211 (84.4)	212 (85.5)	.74
ACE inhibitor	256 (51.4)	128 (51.2)	128 (51.6)	.93
Antibiotics	84 (16.9)	37 (14.8)	47 (19.0)	.22
β-Blocker	330 (66.3)	173 (69.2)	157 (63.3)	.16
Coumadin[a]	88 (17.7)	43 (17.2)	45 (18.2)	.78
Low-molecular-weight heparin	19 (3.8)	10 (4.0)	9 (3.6)	.83
Clopidogrel	120 (24.1)	60 (24.0)	60 (24.2)	.96
Statin	408 (81.9)	201 (80.4)	207 (83.5)	.37
Steroids	30 (6.0)	12 (4.8)	18 (7.3)	.25

ACE, Angiotensin converting enzyme; *BMI,* body mass index; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *DM,* diabetes mellitus; *IDDM,* insulin-dependent diabetes mellitus; *NIDMM,* noninsulin-dependent diabetes mellitus; *PTCA,* percutaneous coronary angioplasty; *SD,* standard deviation; *WBC,* white blood cells.
[a]Bristol-Myers Squibb, Princeton, NJ.

0.25, treatment event rate of 0.15, and 1:1 randomization, a total study sample size of 250 per group (500 total) was planned.

Clinical data were collected using the Research Electronic Data Capture (REDCap)[9] system, a secure, Web-based application for research. All data were analyzed as intention-to-treat. Continuous variables were analyzed using the Student *t*-test or analysis of variance, as appropriate, and categoric data were analyzed using χ^2 tests. Multivariable analysis was performed using logistic regression models with backwards elimination using inclusion threshold of $P = .20$. An $\alpha = .05$, corresponding to $P = .05$, and 95% confidence intervals (CIs) were used as the criteria for statistical significance. Statistical analysis was performed using SAS 9.3 software (SAS Institute Inc, Cary, NC).

RESULTS

The 500 study participants were enrolled on timetable. The Veterans Administration site was added in May 2012

Table II. Operative indications and characteristics

Variables	*Total (N = 500)*	*Intent to treat*		P *value*
		Silver (n = 250)	*Conventional (n = 250)*	
Indication, No. (%)				
Claudication	158 (31.6)	76 (30.4)	82 (32.8)	.71
Critical limb ischemia	207 (41.4)	100 (40.0)	107 (42.8)	
Rest pain	71 (14.2)	37 (14.8)	34 (13.6)	
Tissue loss	136 (27.2)	63 (25.2)	73 (29.2)	
Abdominal aneurysm	56 (11.2)	32 (12.8)	24 (9.6)	
Peripheral aneurysm	22 (4.4)	10 (4.0)	12 (4.8)	
Bypass revision	32 (6.4)	17 (6.8)	15 (6.0)	
Other	25 (5.0)	15 (6.0)	10 (4.0)	
Procedure side, No. (%)				
Left	179 (35.8)	96 (38.4)	83 (33.2)	.38
Right	196 (39.2)	97 (38.8)	99 (39.6)	
Bilateral	125 (25.0)	57 (22.8)	68 (27.2)	
Surgical site, No. (%)				
Suprainguinal inflow to femoral	47 (9.5)	21 (8.5)	26 (10.5)	.96
Femorofemoral	17 (3.4)	7 (2.8)	10 (4.0)	
Groin only	159 (32.1)	79 (31.9)	80 (32.3)	
Femoral above-knee popliteal	55 (11.1)	31 (12.5)	24 (9.7)	
Femoral below-knee popliteal	56 (11.3)	26 (10.5)	30 (12.1)	
Femoral tibial/pedal	102 (20.6)	54 (21.8)	48 (19.4)	
Popliteal tibial/pedal	26 (5.2)	13 (5.2)	13 (5.2)	
Tibial/pedal	2 (0.4)	1 (0.4)	1 (0.4)	
Other	32 (6.5)	16 (6.5)	16 (6.5)	
Conduit, No. (%)				
Autogenous	213 (42.6)	104 (41.6)	109 (43.6)	.23
Nonautogenous	231 (46.2)	112 (44.8)	119 (47.6)	
No conduit	56 (11.2)	34 (13.6)	22 (8.8)	
Clean classification, No. (%)	463 (92.8)	228 (91.6)	235 (94.0)	.29
Sterile preparation solution, No. (%)				
Betadine based	45 (9.0)	21 (8.4)	24 (9.6)	.66
Chlorhexidine based	437 (87.6)	222 (88.8)	215 (86.4)	
Other	17 (3.4)	7 (2.8)	10 (4.0)	
Estimated blood loss, mean (SD), mL	375.5 (429.5)	354.5 (383.2)	396.6 (471.1)	.27
Operative time, mean (SD), minutes	263 (104)	253 (97)	273 (110)	.03
Incision length, mean (SD), cm	32.2 (23.2)	31.6 (22.3)	32.8 (24.2)	.53

SD, Standard deviation.

to facilitate timely study completion. The Fig depicts enrollment data. There were no dressing-specific complications, and >99% of patients received their assigned dressing. Two patients crossed over from standard gauze to the silver-eluting alginate when the operating room team misunderstood the assigned randomization, and one crossed over when a participating investigator felt that the assigned dressing disadvantaged the patient's recovery from the operation.

The cohort represented both sexes (male-to-female ratio: 2.6:1), displayed some racial diversity (~84% white), and held medical comorbidities typical of contemporary vascular surgery practices (Table I). Indications for operation were primarily related to arterial occlusive disease, with critical limb ischemia the most common (Table II). Groin exposures were required in 56 patients for suprainguinal endovascular aneurysm repair. Reconstruction material was used in 440 patients (88.8%), including autogenous in 211 (42.2%), prosthetic, including heterograft, in 220 (44.0%), composite in 6 (1.2%), and homografts in 7 (1.4%). Most of the cases were clean cases, and chlorhexidine-based preparation solutions were used in almost nine of ten patients. The incision length at risk for the primary outcome averaged 32.2 ± 23.2 (standard deviation) cm. Of the factors examined, only operative time differed significantly between randomization groups, at 273 minutes with conventional gauze vs 253 minutes with silver alginate ($P = .028$).

On the basis of an intention-to-treat analysis, the primary end point event rate was statistically identical between groups ($P = .87$; Table III). Analysis by actual dressing type did not change this finding. Restriction of the complications to those that were infections also failed to demonstrate any effect of dressing type ($P = .639$).

Because groin exposure for endovascular aneurysm repair (EVAR) stands as a distinct entity from the other procedures for infrainguinal vascular disease, we analyzed these patients separately (Table IV). Wound problems developed in 33% of non-EVAR cases, whereas the complication rate was 6.6% for the EVAR patients. Again, analyses of the dressing type in the non-EVAR and EVAR cohorts showed no effect.

Table III. Wound complications

Variables	*Overall (N = 500), No. (%)*	*Intent to treat*		P *value*
		Silver (n = 250), No. (%)	*Conventional (n = 250), No. (%)*	
Patients with follow-up	493	247	246	
Worst complication				
No wound complication	352 (70.4)	175 (70.0)	177 (70.8)	.84
Other	25 (5.0)	10 (4.0)	15 (6.0)	
Wound dehiscence	43 (8.6)	23 (9.2)	20 (8.0)	
Superficial SSI	61 (12.2)	32 (12.8)	29 (11.6)	
Deep SSI	19 (3.8)	10 (4.0)	9 (3.6)	
Any SSI (superficial or deep)	80 (16.2)	42 (17.0)	38 (15.5)	.64
Any wound complication	148 (30.0)	75 (30.4)	73 (29.7)	.87

SSI, Surgical site infection.

Table IV. Wound complications by procedure

Variables	*Overall, No. (%)*	*Intent to treat*		P *value*
		Silver, No. (%)	*Conventional, No. (%)*	
Revascularizations (non-EVAR)				
No.	438	215	223	
No. used (have follow-up data)	432	212	220	
Worst complication:				
No wound complication	294 (67.1)	143 (66.5)	151 (67.7)	.84
Other	23 (5.3)	9 (4.2)	14 (6.3)	
Wound dehiscence	42 (9.6)	22 (10.2)	20 (9.0)	
Superficial SSI	61 (13.9)	32 (14.9)	29 (13.0)	
Deep SSI	18 (4.1)	9 (4.2)	9 (4.0)	
Any SSI (superficial or deep)	79 (18.3)	41 (19.3)	38 (17.3)	.58
Any wound complication	144 (33.3)	72 (34.0)	72 (32.7)	.79
EVAR				
No.	62	35	27	
No. used (have follow-up data)	61	35	26	
No wound complication	58 (93.6)	32 (91.4)	26 (96.3)	.66
Other	2 (3.2)	1 (2.9)	1 (3.7)	
Wound dehiscence	1 (1.6)	1 (2.9)	0 (0)	
Superficial SSI	0 (0)	0 (0)	0 (0)	
Deep SSI	1 (1.6)	1 (2.9)	0 (0)	
Any SSI (superficial or deep)	1 (1.6)	1 (2.9)	0 (0)	.38
Any wound complication	4 (6.6)	3 (8.6)	1 (3.9)	.46

EVAR, Endovascular aneurysm repair; *SSI,* surgical site infection.

A subset of 223 patients had groin incisions. The wound complication rate for this subset was 21.9% in the setting of standard gauze and 20.2% for patients who received the silver alginate dressing ($P = .75$ by χ^2).

In secondary analyses, we noted a trend based on initial case wound classification. Complications occurred in seven of 21 nonclean silver dressing patients (clean/contaminated, contaminated, or dirty/infected; 33.3%) and in 10 of 15 (66.6%) in the setting of a standard gauze dressing ($P = .048$ by χ^2). Note that there is some uncertainty in the quality of these data because 25 patients were classified as "clean/contaminated," which typically indicates entry of a hollow viscus or clear break in sterile technique.

Multivariable analysis (Table V) showed that preoperative Coumadin (Bristol-Myers Squibb, Princeton, NJ) use (odds ratio [OR], 1.72, 95% CI, 1.03-2.87; $P = .03$), higher body mass index (BMI; OR, 1.05; 95% CI, 1.01-1.09; $P = .01$), and the use of no conduit/material (OR, 0.12; 95% CI, 0.82-3.59; $P < .001$) were independently associated with wound complications.

DISCUSSION

The current study finds continued high wound complication rates for open vascular surgery in the lower extremity. A silver-eluting alginate dressing displayed no apparent effect on these complication rates.

One of the most common postoperative complications of surgical procedures remains SSI, which causes significant morbidity and health care costs among hospitalized patients.[10,11] Surgical wounds for lower extremity revascularization are particularly prone to infection and dehiscence, with rates in some series as high as 44%.[2] One attempt at mitigating this problem is the use of less invasive approaches, including endoscopic vein harvest.[12] Because

Table V. Wound complications by patient characteristics

	Bivariate		*Multivariable*	
Variables	*OR (95% CI)*	P *value*[a]	*OR (95% CI)*	P *value*[a]
Silver dressing	1.03 (0.70-1.52)	.87	0.91 (0.61-1.37)	.65
Age	0.99 (0.97-1.01)	.14		
Race				
White	Reference			
Black	0.93 (0.51-1.66)	.80		
Other	0.57 (0.19-1.73)	.32		
Sex				
Female	Reference			
Male	0.71 (0.47-1.09)	.12		
BMI	1.04 (1.01-1.08)	.02	1.05 (1.01-1.09)	.01
Prior CAD intervention (PTCA/CABG)	1.22 (0.82-1.84)	.33		
Abnormal renal function	0.76 (0.35-1.66)	.50		
History of				
Diabetes (IDDM or NIDMM)	1.03 (0.70-1.51)	.90		
Hypertension	0.99 (0.53-1.84)	.98		
Myocardial infarction	1.18 (0.75-1.85)	.47		
Stroke	0.84 (0.44-1.61)	.61		
Indication				
Claudication	Reference			
Critical limb ischemia	0.75 (0.49-1.17)	.20		
Abdominal aortic aneurysm	0.13 (0.04-0.36)	<.001		
Peripheral aneurysm	0.60 (0.22-1.61)	.31		
Bypass revision	0.31 (0.11-0.84)	.02		
Other	0.62 (0.24-1.57)	.31		
Revascularization	Reference			
EVAR	0.14 (0.05-0.39)	<.001		
Surgical site				
Groin only	Reference			
Groin and leg mixed	2.42 (1.59-3.67)	<.0001		
All wounds lower than groin	1.45 (0.69-3.04)	.33		
Conduit				
Autogenous	Reference		Reference	
Nonautogenous	0.58 (0.39-0.87)	.01	0.82 (0.49-1.39)	.47
No conduit	0.09 (0.03-0.29)	<.0001	0.12 (0.03-0.41)	<.001
Nonclean classification	2.22 (1.12-4.40)	.02	1.72 (0.82-3.59)	.15
Sterile preparation solution				
Betadine based	Reference			
Chlorhexidine based	1.37 (0.67-2.79)	.39		
Other	1.29 (0.37-4.47)	.69		
Estimated blood loss	1.00 (1.00-1.00)	.17		
Operative time	1.00 (1.00-1.00)	.01		
Total incision length	1.02 (1.01-1.03)	<.0001	1.01 (1.00-1.02)	.16
Laboratory values				
WBC	1.02 (0.94-1.10)	.65		
Hematocrit	1.00 (1.0-1.01)	.42		
Platelets	1.00 (1.00-1.00)	.09		
Glucose	1.0 (0.99-1.00)	.43		
Creatinine	0.87 (0.68-1.10)	.25		
Albumin	0.81 (0.51-1.30)	.39		
Hemoglobin A_{1c}	0.99 (0.95-1.04)	.66		
C-reactive protein	1.00 (0.98-1.02)	1.00		
Medication use				
Aspirin	1.30 (0.74-2.27)	.36		
ACE inhibitors	1.10 (0.75-1.62)	.63		
Antibiotics	1.22 (0.73-2.03)	.44		
β-Blockers	0.97 (0.65-1.46)	.89		
Coumadin[b]	1.71 (1.05-2.77)	.03	1.72 (1.03-2.88)	.04
Low-molecular-weight heparin	1.37 (0.53-3.55)	.52		
Clopidogrel	1.32 (0.85-2.06)	.21		
Statins	1.21 (0.72-2.02)	.47		
Steroids	0.99 (0.44-2.22)	.99		

ACE, Angiotensin-converting enzyme; *BMI,* body mass index; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *CI,* confidence interval; *EVAR,* endovascular aneurysm repair; *IDDM,* insulin-dependent diabetes mellitus; *NIDMM,* noninsulin-dependent diabetes mellitus; *OR,* odds ratio; *PTCA,* percutaneous coronary angioplasty; *WBC,* white blood cell.

[a] $P < .05$ indicates statistical significance.

[b] Bristol-Myers Squibb, Princeton, NJ.

fresh vascular surgical leg incisions and their overlying dressings are a potential avenue for subsequent underlying devitalized tissue contamination and infection in these frequently immunologically incompetent patients, we theorized that lowering bacterial counts overlying the incisions early postoperatively might have a durable beneficial effect on postoperative wound problems.

Silver pharmacologic compounds and silver-eluting biomaterials have shown efficacy in a variety of clinical applications for infection prophylaxis and therapy,[6] largely in the chronic wound and burn settings. For closed postoperative surgical incisions, a trial in 110 elective colorectal surgery patients showed safety and efficacy in preventing SSI (13% with silver nylon dressing vs 33% with standard gauze).[13] However, another trial in colorectal patients showed only a statistically insignificant trend in SSI.[14] In the lower extremity, silver hydrogel sheet dressings (petroleum-based control dressing) on foot and ankle surgical incisions displayed fewer infections and incisional complications, although the power of the report was low.[15]

In a study reported in 2007, we observed fewer lower extremity revascularization wound infections associated with the use of a silver-eluting dressing.[7] In that report and in the current trial, the surgeons and other providers found the dressing regimen was easy to apply and care for postoperatively. Revascularization pulses could be palpated through the dressing, and the low profile permitted identification of postoperative soft tissue changes such as hematomas. Compressive Ace bandages (3M, St. Paul, Minn) could be applied without disturbing the original dressing.

However, the beneficial wound healing effects of the dressing were not noted in the current trial. There are confounding factors that occurred during the original 2007 report. The 39-month study period may explain the discrepancy between the current prospective, multiinstitutional randomized trial findings and the original nonconcurrent cohort report.[7] For instance, it is possible that in the second half (months 16-39) of the earlier nonconcurrent study when the practice switched to the silver alginate dressing, there was increased attention to practices such as perioperative antibiotics, normothermia, and use of skip incisions that might have led to the better results compared with the period (months 1-15) when conventional sterile cotton gauze was.

The current trial generated almost 64,000 individual data points that give some insights into risk factors for lower extremity vascular wound complications. Like others, we found that a high BMI is associated with increased risk.[10,16,17] However, contrary to two of these prior reports[16,17] and others,[3] gender was not associated with wound complication rates. Similar to the Project of Ex-Vivo Vein Graft Engineering Via Transfection (PREVENT) III data set,[18] Coumadin was linked with increased wound complications.[3] Coumadin use may be a marker for a medically complex patient prone to wound problems, anticoagulation may generate hematomas and collections prone to infection, or there may of course be undefined biologic mechanisms underlying the association of this drug to wound complications. Operative time, incision length, autogenous conduit, and groin combined with leg incisions were all positively associated with postoperative wound problems, and these may in part be markers for more extensive vascular surgical procedures. Conversely, the protective effect in multivariate analyses for no conduit/material probably relates to this being a marker for a more straightforward vascular reconstruction.

Limitations are acknowledged. Wound complications were essentially self-reported by the primary surgical team, and the study lacked the resources for an independent follow-up observer. To bolster the overall data set quality, local National Surgical Quality Improvement Program data were used (after appropriate approvals) at the two academic medical centers to verify the primary trial data. The observed wound complication rates also support a high rate of event capture. Owing to a protocol design oversight, we did not collect smoking status on enrollees. In addition, although the patients and providers were not formally blinded to the type of original postoperative dressing, the study physicians generally reported an inability to recall which dressing the patient had received at the late follow-up visits.

We do not have culture data for patients who developed a SSI. Finally, we also did not tightly regulate the manner in which the dressing was secured against the incision or track the subsequent early incisional care.

Despite these limitations the findings provide insights into wound complication rates in the endovascular era (leaving the most complicated cases for open approaches) and in an increasingly aging population with a rising BMI and incidence of diabetes. The negative results under the condition of this trial raise questions into our concepts of wound complications in these patients. It is possible that bacterial invasion of these wounds initiates well before the dressings are applied. Also, the etiology of these wound complications may fundamentally relate to local ischemia rather than to a purely infectious primary origin.

CONCLUSIONS

The incidence of wound complications remains high in contemporary open arterial surgery in the lower extremity. Under the study conditions, a silver-eluting alginate dressing showed no effect on wound complication incidence. Recognition of perioperative risk factors may allow for closer surveillance and possible mitigation of wound problems.

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AUTHOR CONTRIBUTIONS

Concetion and design: CO, MB, LN
Analysis and interpretation: CO, NH, LN
Data collection: CO, AH, NB, MW, NH, MB, LN
Writing the article: CO

Critical revision of the article: CO, AH, NB, MW, NH, MB, LN
Final approval of the article: CO, LN
Statistical analysis: NH
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DISCUSSION

Dr Jon Matsumura (*Madison, Wisc*). What other process measures were in place to address wound complications during the study? Methicillin-resistant *Staphylococcus aureus* screening, normothermia, antibiotic selection and timing?

Dr C. Keith Ozaki. Over the last decade, we have had many changes and redesign of our care processes to address these issues. More attention to normothermia, more attention to timely perioperative antibiotics, increased considerations of approaches, such as skip incisions, all of those continued to be implemented over time and may account for some of the differences between the current report and the prior nonconcurrent study that had the original control group first and then at a later date had the silver alginate dressing cohort.

There were a variety of wound practices at these three different institutions, so I cannot summarize those in just a few statements. But we did try to design this trial to be applicable to several different settings, both the civilian and the Veterans Administration population.

Dr Peter Lawrence (*Los Angeles, Calif*). Did you classify wounds by degree of contamination? Clean contaminated wounds in patients with foot infections might benefit from this dressing, while the average clean wound would not. Did you calculate the cost/benefit for each group?

Dr Ozaki. That is an excellent point. The cost data related to this, especially the cost of having a wound complication, will be presented at Eastern Vascular and New England meetings this fall. These dressings are actually quite inexpensive. For a 4-by-5 inch piece, the actual General Services Administration price, and that translates pretty well to the civilian price, is less than $10.00. We tested an approach that we thought might be cost-effective even if there was a very small clinical benefit. Whenever we broke the cases down into those that were nonclean, we actually by χ^2 analysis did see a statistically significant benefit for the silver dressing. I did not present those data though because I do not trust the data. Half of those cases were labeled as clean-contaminated. And by the technical definition, that means you either enter a hollow viscus or you have a

clear break in sterile technique. So I am concerned about the primary quality of that information.

But you are correct, from our data set we should be able to select patients most at risk, and maybe for that select population there could be a role for this type of dressing.

Dr David Yu (*Seattle, Wash*). I was wondering if the immunocompetence status of these patients were taken into consideration for the study?

Dr Ozaki. I do not have any specific assays of immune status. We did have a subset of the patients that were on immunosuppressive prednisone, and there was no differential in the wound complication rates for these patients.

Dr Jens Eldrup-Jorgensen (*Portland, Me*). Surgical site infections in our institution have received a lot of scrutiny of late. I think a lot of the value of this study is to give us a contemporary assessment of what realistic surgical site infection rates are. We find that in our institution they are very similar to what you are reporting here, and yet the expectation is that they should be much lower, at least from some parties.

We have also tried using a silver-based dressing on a more empiric approach. And now with the failure of this to show any efficacy, are you trialing the negative-pressure dressings in some of these more complex wounds?

Dr Ozaki. Based on some of the earlier reports, I am intrigued by the negative-pressure dressings even for the closed incisions. That technique warrants further investigation. Actual infection rates are in the midteens for our lower extremity revascularizations and 6.6% when you have to cut down to do an endovascular aneurysm repair. I think that is useful data, and I think it is real. All our study institutions had these rates.

Dr Cassius Iyad Ochoa Chaar (*New Haven, Conn*). I congratulate you on doing a study that is sponsored by industry but still have data independently analyzed with the investigators. What were the lengths of those incisions, and were the anatomical locations comparable in both groups? And for the groin specifically, were you able to compare vertical and transverse incisions?

Dr Ozaki. The average incision length was just over 32 cm. There was not a difference between the groups in incision length. Regarding the orientation of the groin incision, there were many confounding factors, such as whether this was a redo surgery that had a prior vertical incision, whether this was an obese patient, etc. Most of the endovascular aneurysm repair participants had a transverse groin incision vs those with extensive occlusive disease that needed a long profundoplasty might have had vertical. So I am nervous about analyzing that data under these study conditions because of those confounding factors. However we do have a lot of granularity in the data set with regards to location of incisions, types of incisions, and there will be future analyses of those issues.

Dr Palma Shaw (*Syracuse, NY*). Given the number of different silver dressings, with different amounts of silver in each dressing, do you think that there is a role for looking at different amounts of silver and seeing if this has an effect?

Dr Ozaki. Yes, that is a great point. There are a variety of silver dressing products. If you talk to another silver dressing manufacturer, they will suggest that the reason your study was negative is because you used the wrong dressing. If there are any industry partners out there thirsty to really look at this, we are anxious to have something that will help these patients.

APPENDIX I (online only). Wound grades (at least at postoperative weeks 2 and 4)

→**No wound complication**
→**Superficial incisional SSI:** Infection that occurs ≤30 days after the operation and infection involves only skin/subcutaneous tissue of the incision and at least one of the following:
- Purulent drainage, with or without laboratory confirmation
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least one of the following signs/symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by the surgeon, unless incision is culture-negative
- Diagnosis of superficial incisional SSI by surgeon/attending

Do not report stitch abscess (minimal inflammation and discharge confined to the points of suture penetration) as SSI.
→**Deep incisional SSI:** Infection that occurs ≤30 days after operation and infection appears to be related to the operation and infection involved deep tissues (fascial/muscle layers) of the incision and at least one of the following:
- Purulent drainage from the deep incision
- A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
- Diagnosis of deep incision SSI by surgeon/attending

→**Dehiscence:** Skin separation requiring local wound care without SSI criteria
→**Other:** Seroma, lymphocele, hematoma, etc

SSI, Surgical site infection.

APPENDIX II (online only). Data collected (record reviews, phone calls, clinic visit as needed):

- Patient age, gender
- Selected medical history (IDDM, NIDDM; no medications or surgical history)
- Clinical indication for revascularization (claudication, rest pain, tissue loss)
- Most recent selected laboratory results (WBC, hematocrit, platelets, creatinine, blood glucose, albumin)
- Operation date
- Primary attending surgeon
- Revascularization procedure: record all, including laterality (nonfemoral inflow to femoral, fem-fem, groin reconstruction only, fem-AK popliteal, fem-BK popliteal, fem tibial/pedal, popliteal-tibial, tibial-tibial) and conduit (autogenous, prosthetic, composite prosthetic/composite, homograft)
- Sterile preparation solution
- Case length (incision to dressing in minutes)
- Perioperative antibiotics and time from incision, intraoperative doses
- PACU/ICU first postoperative temperature
- EBL
- Postoperative therapeutic anticoagulation
- Anesthetic approach (regional vs general)
- Intraoperative transfusions (units of PRBC, FFP, platelets)
- Surgical wound classification (clean, clean-contaminated, contaminated, dirty/infected)
- Wound complications, classified generally according to NSQIP8 ≤30 days, either leg
- EQ-5D at consent/baseline, 2 weeks, and 4 weeks
- Primary, primary assisted, and secondary patency rates at 30 days and 1 year via life table
- Limb loss with 1 year by life-table analysis
- Readmission for wound complications, LOS
- Death ≤30 days
- Measured post operative incision length, as a proxy for quantity of dressing utilized
- Index LOS
- Days of antibiotic administration
- Days of active incisional wound care during and after discharge (including at home and at rehabilitation facilities)
  - Type and frequency of wound care
- Readmission LOS for wound care and cumulative LOS for the duration of the study period
- Additional operative procedures required for incisional wound care during index LOS and readmission LOS

AK, Above knee; *BK,* below knee; *EBL,* estimated blood loss; *FFP,* fresh frozen plasma; *ICU,* intensive care unit; *IDDM,* Insulin-dependent diabetes mellitus; *LOS,* length of stay; *NIDDM,* non-insulin-dependent diabetes mellitus; *NSQIP,* National Surgical Quality Improvement Program; *PACU,* postanesthesia care unit; *PRBC,* packed red blood cells; *WBC,* white blood cell.