Safety and efficacy of a kaolin-impregnated hemostatic gauze in cardiac surgery: A randomized trial

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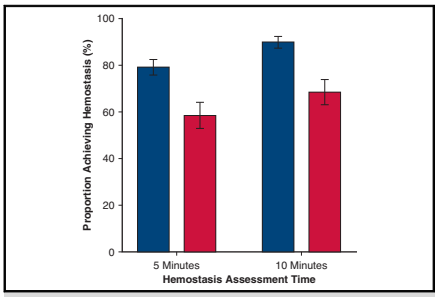
ABSTRACT

Objective: A kaolin-based nonresorbable hemostatic gauze, QuikClot Control+, has demonstrated effective hemostasis and safety when used for severe/life-threatening (grade 3/4) internal organ space bleeding. We evaluated the efficacy and safety of this gauze for mild to moderate (grade 1-2) bleeding in cardiac surgery compared with control gauze.

Methods: This was a randomized, controlled, single-blinded study of patients who underwent cardiac surgery between June 2020 and September 2021 across 7 sites with 231 subjects randomized 2:1 to QuikClot Control+ or control. The primary efficacy end point was hemostasis rate (ie, subjects achieving grade 0 bleed) through up to 10 minutes of bleeding site application, assessed using a semiquantitative validated bleeding severity scale tool. The secondary efficacy end point was the proportion of subjects achieving hemostasis at 5 and 10 minutes. Adverse events, assessed up to 30 days postsurgery, were compared between arms.

Results: The predominant procedure was coronary artery bypass grafting, and 69.7% and 29.4% were sternal edge and surgical site (suture line)/other bleeds, respectively. Of the QuikClot Control+ subjects, 121 of 153 (79.1%) achieved hemostasis within 5 minutes, compared with 45 of 78 (58.4%) controls ($P < .001$). At 10 minutes, 137 of 153 patients (89.8%) achieved hemostasis compared with 52 of 78 controls (68.4%) ($P < .001$). At 5 and 10 minutes, hemostasis was achieved in 20.7% and 21.4% more QuikClot Control+ subjects, respectively, compared with controls ($P < .001$). There were no significant differences in safety or adverse events between treatment arms.

Conclusions: QuikClot Control+ demonstrated superior performance in achieving hemostasis for mild to moderate cardiac surgery bleeding compared with control gauze. The proportion of subjects achieving hemostasis was more than 20% higher in QuikClot Control+ subjects at both timepoints compared with controls, with no significant difference in safety outcomes. (JTCVS Open 2023;14:134-44)



Subject proportions achieving hemostasis at 5 and 10 minutes: QCC+ (*blue*) and control (*red*).

CENTRAL MESSAGE

QCC+ was superior to standard gauze in achieving hemostasis for mild (grade 1)/moderate (grade 2) cardiac surgery bleeding, with QCC+ subjects achieving hemostasis at more than 20% higher proportion at 5 and 10 minutes versus controls.

PERSPECTIVE

Prior clinical and animal studies have demonstrated effective hemostasis using kaolin-impregnated hemostatic gauze in severe to life-threatening internal organ space bleeding. In a first such study, we demonstrate the superior performance of the QCC+ hemostatic gauze, suggesting that it may be preferable to standard gauze for achieving hemostasis in mild to moderate cardiac surgery bleeding.

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The ZM-QCC-01 study and statistical analysis was funded by and QCC+ gauze provided by Teleflex Inc.

Institutional Review Board approval was obtained at all sites (#Pro00042692; May 21, 2020) and patients provided preprocedure written informed consent. The protocol was registered with ClinicalTrials.gov (NCT04415606).

Read at the moderated poster session of the Southern Thoracic Surgical Association 69th Annual Meeting, Fort Lauderdale, Florida, November 9-12, 2022.

Received for publication Dec 28, 2022; accepted for publication March 27, 2023; available ahead of print May 2, 2023.

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2666-2736

https://doi.org/10.1016/j.xjon.2023.03.016

Abbreviations and Acronyms
AE = adverse event
CI = confidence interval
HA = hemostatic agent
QCC+ = QuikClot Control+
QCCG = QuikClot Combat Gauze

Effective surgical hemostasis reduces the need for blood transfusions and improves patient outcomes, as well as improving surgical field visibility and decreasing operating time.[1-5] In one study of 103,829 patients undergoing cardiac surgery, 47.4% experienced a bleeding-related complication during hospitalization.[6] Furthermore, the additional cost and increased length of stay for such complications and blood transfusions were found to be $10,279 and 4.8 days/patient, respectively.[6-9]

During any surgical procedure, a careful balance between bleeding and coagulation must be maintained to allow continuous blood flow to the operative site, while at the same time preventing excessive blood loss.[1] A major factor contributing to cardiac surgical bleeding in complex patients undergoing coronary artery bypass grafting, valve repair or replacement, and aortic aneurysm surgery is the use of multiple systemic anticoagulants and antiplatelet agents while on the cardiopulmonary bypass circuit. Thus, the ability to maintain hemostasis is critical to the success of these procedures, as well as to patient outcomes.[2] Current surgical bleeding management methods include mechanical hemostatic techniques, energy-based surgical devices, and topical hemostatic agents (HAs).[1] Kaolin-based dressings such as QuikClot Control+ (QCC+; Teleflex Inc) are HAs approved by the Food and Drug Administration to be used with patients who are placed on cardiopulmonary bypass and intraoperative cell salvage devices without increasing the risk of systemic complications such as thrombosis. The surgical use of topical HAs can supplement endogenous blood clotting activity and can be broadly categorized into active HAs containing blood clotting agents and nonactive HAs that do not.[10]

Cardiac surgery procedures requiring cardiopulmonary bypass are especially prone to both bleeding and use of blood products.[11,12] Practically, HAs may be used to limit bleeding in the cardiac setting where conventional hemostatic surgical techniques may be of limited efficacy due to diffuse microvascular bleeding.[12] Of the surgical bleeding management methods, the most common are topical hemostats. The first generation QuikClot and QuikClot Combat Gauze (QCCG) products are indicated for control of severely bleeding surgical wounds and traumatic injuries. The second-generation QCC+ is indicated for temporary control of severe to life-threatening (grade 3-4) internal organ space bleeding.

Previous studies have demonstrated positive results for control of visceral hemorrhage after using QCC+/QCCG.[13,14] Koko and colleagues[13] demonstrated that use of QCC+ in a penetrating retrohepatic inferior vena cava injury porcine model improved hemorrhage control and significantly decreased blood loss over laparotomy sponges. A preclinical safety study of QCC+ versus standard gauze in a porcine model evaluated treatment of bleeding from suture lines on incisional surgical wounds in the carotid and femoral arteries, as well as epicardial lacerations (performed while the animal was on bypass). Criteria were met for hemostatic success, vessel patency, and overall tissue response to the test article with QCC+ performing comparably to standard gauze (Gould and colleagues, 2020, unpublished data). However, to date no study has examined the efficacy of a hemostatic dressing in cardiac surgery bleeding or mild to moderate internal organ space bleeding. In contrast to severe and life-threatening bleeding, mild (grade 1) bleeding is defined as an ooze with the appearance of a capillary-like mild bleed and blood loss between 1 and 5 mL/min and moderate (grade 2) bleeding as a continuous flow having the appearance of a venule- or arteriolar-like moderate bleed with blood loss between 5 and 10 mL/min[15] The objective of the current study focused on cardiac surgery to evaluate the safety and efficacy of QCC+ for mild to moderate bleeding compared to compression with standard gauze (ie, control treatment). Figure 1 shows a Graphical Abstract of the study.

PATIENTS AND METHODS

Study Design and Patient Population

A randomized, controlled, single-blinded, pivotal study of QCC+ was conducted in cardiac surgery patients experiencing mild to moderate sternal edge (ie, bone marrow or sternal periosteum, excluding internal thoracic artery bed), surgical site (suture line), or overall (ie, tears, lacerations or abrasions) bleeding. Study participants were enrolled by the study nurse at 7 academic and community hospitals in the United States. Institutional Review Board approval was obtained at all sites (#Pro00042692; May 21, 2020), and patients provided preprocedure written informed consent for publication of study data. The protocol was registered with ClinicalTrials.gov (NCT04415606).

The primary and secondary efficacy end points were the rate at which subjects achieved hemostasis through 10 minutes of hemostat application and compression at the bleeding site, and proportion achieving hemostasis at 5 and 10 minutes, respectively. The bleeding assessment time intervals were selected on the basis of those reported by Trabattoni and colleagues[16] in a clinical trial with a similar efficacy end point. The safety of QCC+ was characterized by the incidence of device-related adverse events (AEs). Last, patient demographics, medical history, and procedure details were compared between treatment arms.

After meeting preoperative and intraoperative eligibility criteria, study participants were randomized 2:1 to QCC+ or control. Randomization sequences were created by an independent biostatistician using a random

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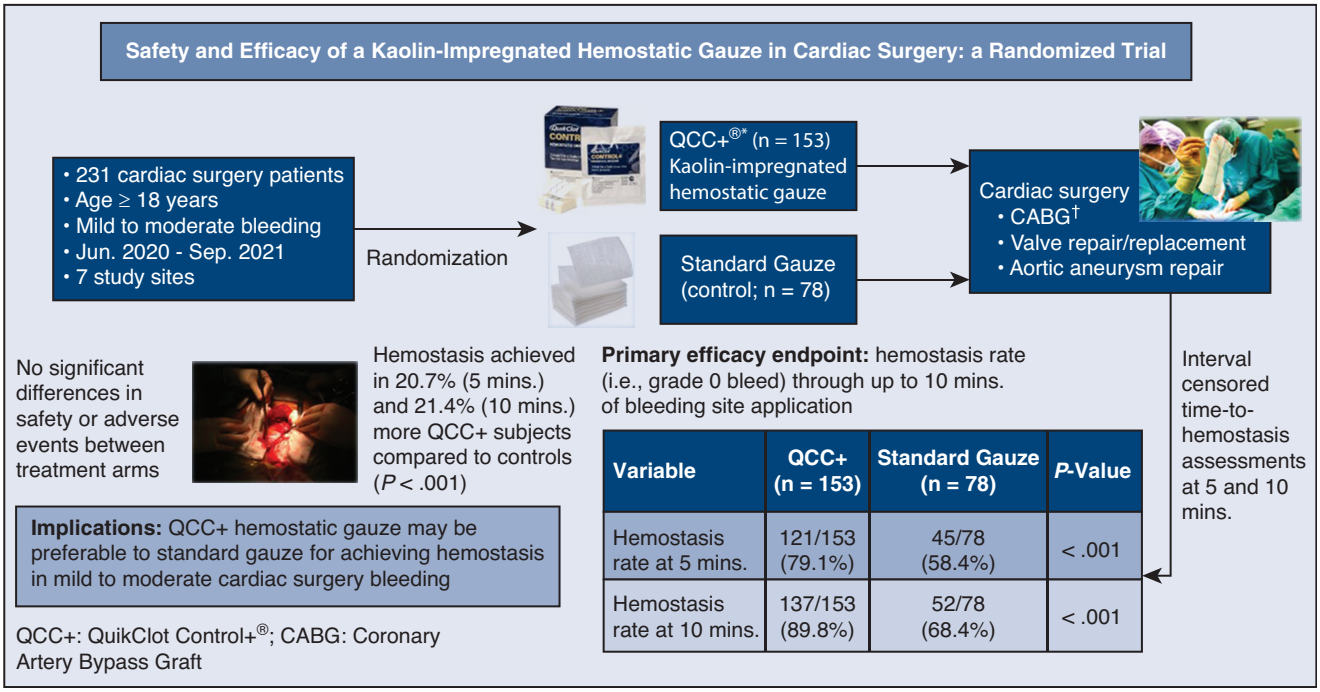

Variable	QCC+ (n = 153)	Standard Gauze (n = 78)	P-Value
Hemostasis rate at 5 mins.	121/153 (79.1%)	45/78 (58.4%)	< .001
Hemostasis rate at 10 mins.	137/153 (89.8%)	52/78 (68.4%)	< .001

FIGURE 1. Graphical Abstract providing an overview of the methods, results, and implication of the study. The QCC+ product demonstrated superior performance in achieving hemostasis in mild to moderate cardiac surgery bleeding compared to control. The difference between groups in the proportion of subjects achieving hemostasis was greater than 20% at both 5- and 10-minute assessment times, with no significant difference in safety outcomes. *QCC+*, QuikClot Control+; *CABG*, coronary artery bypass grafting.

permuted block design stratified by study site. These were implemented using sequentially numbered sealed envelopes, with the subject blinded to the assignment. The investigators were not blinded to the treatment assignment because of the unique physical characteristic appearance of the study device when compared with standard gauze. Preoperative eligibility criteria included age 18 years or more and need for cardiac surgery. Intraoperative inclusion criteria included a mild to moderate severity bleeding site. Exclusion criteria included emergency surgery, surgical site infection/endocarditis, kidney/liver dysfunction, hematological abnormalities, pregnancy, concurrent investigational therapy, and predicted subject noncompliance. After randomization by the study nurse, the designated device was applied, covering the bleeding site.

A total of 231 subjects were randomized, 153 to QCC+ and 78 to standard gauze (Figure 2), with the option of enrolling up to 3 roll-in subjects per site treated with QCC+ before subject randomization. Twenty-one roll-in subjects were enrolled and excluded from the intention-to-treat (randomized) analysis. Each site was limited to enrolling 70 randomized subjects to prevent sizable imbalances in enrollment between sites. Each subject underwent preprocedure and surgical procedure visits and was followed through hospital discharge and up to 30 days postsurgery.

Hemostatic Dressing

The QCC+, kaolin-based, sterile, x-ray detectable, nonwoven hemostatic dressing, is the first nonresorbable device indicated for temporary control of severe to life-threatening internal organ space bleeding and has demonstrated effective hemostasis.[13] The procoagulant kaolin, an aluminum silicate impregnated into the gauze, activates Factor XII on the intrinsic coagulation pathway, which in turn accelerates the clotting cascade.[17-24] The novel kaolin binding on QCC+ minimizes eluting from the product, particularly important for internal bleeding. One of 6 available QCC+ sizes was chosen and the removal time after hemostasis selected, both at the investigator's discretion. Standard gauze (surgical/laparotomy sponges) was used on control subjects.

Intraoperative Management

Cardiac surgery procedures, including coagulation and blood pressure management, as well as blood product administration, followed standard operating procedures and practices at each site. The randomized study device could be used at any time during the procedure as the initial bleeding management method for 1 bleeding assessment location. The study device could be used before heparinization, during cardiopulmonary bypass, or after anticoagulation reversal, because restricting the timing of device application would impact the generalizability of the study results. The study protocol incorporated a validated intraoperative bleeding scale for appropriate selection of the bleeding assessment site by the investigator or sub-investigator immediately before randomization, either mild or moderate, and subsequent assessment of hemostasis (grade 0 or no bleeding with blood loss < 1.0 mL/min) at 5 minutes and 10 minutes (if applicable). The semiquantitative, validated, clinician-reported bleeding scale used in the study has an average intraobserver concordance of 0.98 and an interobserver concordance of 0.91 (with a concordance of 1.0 being perfect). In the validation of the bleeding scale there was unanimous agreement by 102 surgeons (24% of whom were cardiac surgeons) that the scale can be implemented into clinical studies. The scale also fulfills all Food and Drug Administration criteria for a clinician-reported scale.[15] Investigators performing the bleeding assessments received in-person training on the

scoring method using validated videos representing the five bleeding severities on the bleeding severity scale before enrolling any subjects (Table E1). During the study, these videos were readily accessible in the operating room for real-time comparison and evaluation of the injury site, if needed.

The QCC+ or control gauze was applied with compression in direct contact and covering the entire bleeding site. The study device was then removed and hemostasis assessed at 5 and 10 minutes of application and compression at the bleeding site by the same investigator or subinvestigator. If hemostasis was not observed at 5 minutes, the same or new product was reapplied and assessed at 10 minutes. Sterile saline could be used to aid in removal if the product was adhered to the wound. If hemostasis was still not achieved at 10 minutes, additional eligible standard of care hemostatic measures could be used, or if hemostasis was achieved at either timepoint, the product could remain in place for the duration of the procedure, both judgments at the investigator's discretion.

Additional bleeding sites were controlled with QCC+, standard gauze, or other nonthrombin- or fibrin-containing HAs. Use of other HAs on additional injury sites was recorded and whether successful hemostasis was achieved. For sternotomies where bone wax would typically be used to control bleeding, the study device was applied bilaterally; however, only the left received study effectiveness end point assessment because of direct line view of the surgeon. The assessment was performed with the sternum separated, eliminating any bleeding contribution from the right sternal edge.

Postoperative Management and Follow-up

Postprocedure follow-up followed study site standard operating procedures and practices. Study assessments were performed 24-hours postoperatively and at discharge, with a final visit at 30 ± 16 days postsurgery. Adverse events were documented at every study visit, and adverse device effects and device deficiencies were documented intraoperatively or at any postprocedure study visit.

Data Collection

Collected data included demographics, medical history, concomitant medications, vital signs, central venous pressure, electrocardiogram, urine output, laboratory assessments, intraoperative bleeding grade, time to hemostasis, drainage/chest tube assessments, AEs, and reinterventions due to bleeding. Preoperative and postoperative data and procedural details were collected from patient chart operative reports or through study participant interviews.

Statistical Analysis

Hemostasis rates for the study arms were compared over time using a 2-sided log-rank test. The primary effectiveness end point was analyzed as an interval censored time-to-hemostasis with assessments at 5 and 10 minutes after application. The primary cohort analysis was conducted on an intention-to-treat basis. A sample size of 231 was calculated on the basis of a power of 80%, a difference of 20% success rate cumulatively through 10 minutes between study arms, a 2-tailed significance level of P less than .05, and a sample size inflation of 2.5%. Continuous data are presented as mean ± standard deviation when normally distributed or median and interquartile range for skewed data, and categorical data are presented as counts and percentages. For primary and secondary efficacy outcomes, if the QCC+ or control gauze was applied and a subsequent bleeding assessment was not performed, multiple imputation was used for analysis. Imputations were performed separately for patients in whom QCC+ versus standard gauze were applied. Fully conditional logistic regression imputation

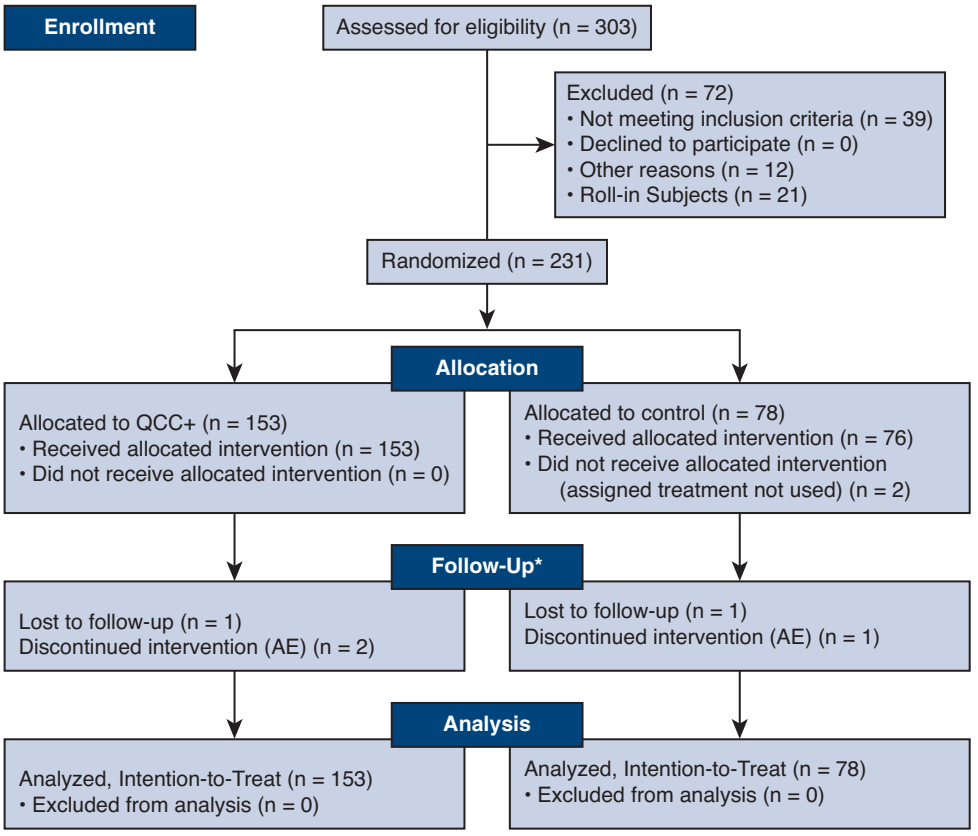

FIGURE 2. CONSORT diagram. *QCC+*, QuikClot Control+; *AE*, adverse event. *Follow-up: 30 ± 16 days postsurgery.

TABLE 1. Subject baseline demographics, medications, laboratory studies, and vital signs

Characteristic	All patients (n = 231)	QCC+ Group (n = 153)	Control Group (n = 78)	*P* value
Age, y	64.5 ± 12.2 22.0-88.0	64.5 ± 12.0 28.0-88.0	64.7 ± 12.6 22.0-87.0	.90
Female	72/231 (31.2%)	48/153 (31.4%)	24/78 (30.8%)	.93
Race				
White	219/231 (94.8%)	144/153 (94.1%)	75/78 (96.2%)	.76
Black/African American	7/231 (3.0%)	6/153 (3.9%)	1/78 (1.3%)	.43
Other	2/231 (0.9%)	2/153 (1.3%)	0/78 (0.0%)	>.99
Not reported	3/231 (1.3%)	1/153 (0.7%)	2/78 (2.6%)	.26
Ethnicity				
Hispanic/Latino	1/231 (0.4%)	0/153 (0.0%)	1/78 (1.3%)	
Not Hispanic/Latino	230/231 (99.6%)	153/153 (100.0%)	77/78 (98.7%)	
Medication use				
Antiplatelets/anticoagulants	165/231 (71.4%)	111/153 (72.5%)	54/78 (69.2%)	.51
Antiplatelets	151/231 (65.3%)	102/153 (66.7%)	49/78 (62.8%)	.41
Anticoagulants	59/231 (25.5%)	42/153 (27.5%)	17/78 (21.8%)	.22
Warfarin	6/231 (2.6%)	4/153 (2.6%)	2/78 (2.6%)	1.00
INR	1.09 ± 0.18 0.88-2.26 (n = 138)	1.11 ± 0.21 0.90-2.26 (n = 91)	1.06 ± 0.09 0.88-1.30 (n = 47)	.03
Nonsteroidal anti-inflammatory/aspirin	7/231 (3.0%)	6/153 (3.9%)	1/78 (1.3%)	.16
Diabetes medication	66/231 (28.6%)	43/153 (28.1%)	23/78 (29.5%)	.83
Blood pressure medication	153/231 (66.2%)	100/153 (65.4%)	53/78 (67.9%)	.60
Laboratory studies				
Platelet count	234.2 ± 70.2 116.0-712.0 (n = 231)	234.4 ± 74.1 120.0-712.0 (n = 153)	233.8 ± 62.3 116.0-419.0 (n = 78)	.95
Hemoglobin	14.0 ± 1.5 10.0-17.7 (n = 231)	14.0 ± 1.6 10.0-17.7 (n = 153)	14.0 ± 1.4 10.2-16.7 (n = 78)	.98
Vital signs				
Heart rate (beats/min)	71.9 ± 14.0 44.0-144.0	72.4 ± 13.4 44.0-110.0	70.9 ± 15.2 45.0-144.0	.46
Systolic blood pressure (mm Hg)	137.5 ± 20.2 99.0-195.0	135.5 ± 19.5 99.0-187.0	141.4 ± 21.1 102.0-195.0	.04
Diastolic blood pressure (mm Hg)	76.4 ± 12.7 40.0-113.0	77.3 ± 12.3 51.0-113.0	74.7 ± 13.5 40.0-108.0	.14
Mean arterial pressure (mm Hg)	96.8 ± 12.8 66.0-138.0	96.7 ± 12.5 75.0-138.0	96.9 ± 13.4 66.0-126.0	.91

Data expressed as n (%), mean ± standard deviation, min-max. *QCC+*, QuikClot Control+; *INR*, International Normalized Ratio.

models were used at the 5- and 10-minute assessment timepoints for the binary outcome of whether the bleeding assessment was grade 0 following application at the bleeding site. Sensitivity analyses for the primary efficacy end point were performed, including analysis using the per protocol data set, which by definition includes only patients with no missing data. Statistical analysis was performed with SAS Version 9.4 (SAS Institute, Inc).

RESULTS

Study Population

Of the subjects who were screened for participation and met inclusion criteria, 231 were randomized and 21 were roll-in subjects, all undergoing surgical procedures. The average number of subjects enrolled and randomized per study site was 33 (range, 11-69), and the results were found to be poolable across study sites. Subjects completed study visits from June 2020 to September 2021.

Baseline Characteristics

Subject demographics were similar between groups (Table 1). Mean age was 64.5 ± 12.2 years, and subjects were predominantly male (68.8%) and White (94.8%). Baseline medication categories were balanced between randomized arms. Of note, 42 of 153 (27.5%) QCC+ subjects and 17 of 78 (21.8%) control subjects were on anticoagulant medication ($P = .215$). Accordingly, a higher proportion of QCC+ subjects had baseline international normalized ratio greater than 1.1 (19/91 = 21%) compared with the standard gauze arm (7/47 = 15%). All baseline

TABLE 2. Intraoperative characteristics

Characteristic	All patients (n = 231)	QCC+ group (n = 153)	Control group (n = 78)	*P* value
Procedure type				
CABG	122/231 (52.8%)	82/153 (53.6%)	40/78 (51.3%)	.78
Valve repair/replacement	72/231 (31.2%)	44/153 (28.8%)	28/78 (35.9%)	.30
CABG or valve repair/ replacement	212/231 (91.8%)	141/153 (92.2%)	71/78 (91.0%)	.80
Aortic aneurysm surgery	19/231 (8.2%)	12/153 (7.8%)	7/78 (9.0%)	.80
Total operating room time (min)	252.9 ± 98.2 113.0-677.0	249.4 ± 98.3 114.0-677.0	260.2 ± 98.4 113.0-582.0	.44
Bleeding assessment site				
Sternal edge	161/231 (69.7%)	108/153 (70.6%)	53/78 (67.9%)	.76
Surgical site	68/231 (29.4%)	43/153 (28.1%)	25/78 (32.1%)	.55
Overall bleed	2/231 (0.9%)	2/153 (1.3%)	0/78 (0.0%)	.55
Initial bleeding assessment				
Mild/Grade 1	93/231 (40.3%)	62/153 (40.5%)	31/78 (39.7%)	>.99
Moderate/Grade 2	138/231 (59.7%)	91/153 (59.5%)	47/78 (60.3%)	>.99
Blood product				
Red blood cell	45/231 (19.5%)	30/153 (19.6%)	15/78 (19.2%)	>.99
Fresh-frozen plasma	17/231 (7.4%)	11/153 (7.2%)	6/78 (7.7%)	>.99
Cryoprecipitate	26/231 (11.3%)	12/153 (7.8%)	14/78 (17.9%)	.03
Platelets	51/231 (22.1%)	29/153 (19.0%)	22/78 (28.2%)	.13
Any blood product	76/231 (32.9%)	47/153 (30.7%)	29/78 (37.2%)	.38

Data expressed as n (%), mean ± standard deviation, min-max. *QCC+*, QuikClot Control+; *CABG*, coronary artery bypass grafting.

complete blood count measurements and vital signs were balanced between arms, except for systolic blood pressure (QCC+: 135.5 ± 19.5; control: 141.4 ± 21.1; $P = .037$; Table 1).

Intraoperative Characteristics

The predominant procedure was coronary artery bypass grafting (with or without valve repair/replacement; 60.6%). Of the bleeding assessment sites, 69.7% were sternal edge and 29.4% were surgical site, with moderate bleeds (59.7%) outnumbering mild bleeds (40.3%). The most common of the 6 different QCC+ sizes used were 4 × 8 (8-ply; 62.1%), Z-Fold (28.8%), and 4 × 8 (6-ply; 11.1%), and for the control group the most often used gauze sizes were 18 × 18 (50.0%) and 4 × 4 (44.9%). Most procedure characteristics were comparable between the randomized arms, including total operating room time (Table 2).

Primary end point data analysis found that 121 of 153 QCC+ subjects (79.1%) achieved hemostasis within 5 minutes, compared with 45 of 78 controls (58.4%) ($P < .001$). At 10 minutes, 137 of 153 QCC+ subjects (89.8%) achieved hemostasis compared with 52 of 78 controls (68.4%) ($P < .001$); missing data handled using multiple imputation, if needed (Table 3). At the 5- and 10-minute secondary end points, hemostasis was achieved in 20.7% (95% confidence interval [CI], 8.0-33.4) and 21.4% (95% CI, 9.9-33.0) more QCC+ subjects, respectively, compared with controls ($P < .001$). A sensitivity analysis conducted to address the potential impact of missing data in this intention-to-treat analysis population found that QCC+ was consistently superior to standard gauze in achieving hemostasis also in the as-treated and per-protocol analysis populations. Even with 1 QCC+ subject and 3 control subjects missing hemostasis assessment at 10 minutes analyzed as not achieving and achieving hemostasis, respectively, the primary end point was still met ($P < .001$). In addition, the hazard ratio for the intention-to-treat analysis was 1.89 (95% CI, 1.35-2.66; $P < .001$), indicating that the instantaneous hemostasis rate increase in QCC+ subjects was nearly twice that of control subjects.

The difference in hemostasis at both timepoints in QCC+ and control subjects with grade 2 bleeds was 2- to 4-fold higher than that achieved by those with grade 1 bleeds

TABLE 3. Hemostasis rate by time

Variable	QCC+ Group* (n = 153)	Control Group* (n = 78)	*P* value
Hemostasis rate at 5 min	121/153 (79.1%)	45/78 (58.4%)	<.001
Hemostasis rate at 10 min	137/153 (89.8%)	52/78 (68.4%)	<.001

QCC+, QuikClot Control+. *Missing data handled using multiple imputation, if needed.

TABLE 4. Difference in achieving hemostasis between QCC+ and control subjects by bleeding grade, bleeding site, and age

Sub-group	Time	QCC+ Group (n = 153)	Control Group (n = 78)	Difference (95% CI)	*P* value
Bleeding grade					
Mild/grade 1	5 min	91.9% (85.2%, 98.7%)	80.6% (66.7%, 94.6%)	11.3% (−2.5%, 29.1%)	.081
	10 min	98.4% (95.3%, 100.0%)	91.3% (80.9%, 100.0%)	7.1% (−5.2%, 19.4%)	.126
Moderate/grade 2	5 min	70.3% (60.9%, 79.7%)	43.7% (29.3%, 58.1%)	26.6% (9.8%, 43.5%)	<.001
	10 min	83.9% (76.3%, 91.6%)	53.3% (38.6%, 67.9%)	30.7% (14.5%, 46.9%)	<.001
Bleeding site					
Sternal edge	5 min	81.5% (74.2%, 88.8%)	54.7% (41.3%, 68.1%)	26.8% (11.7%, 41.7%)	<.001
	10 min	89.2% (83.3%, 95.2%)	63.4% (50.2%, 76.6%)	25.8% (11.6%, 40.1%)	<.001
Surgical site or overall bleed	5 min	73.3% (60.4%, 86.3%)	66.1% (47.1%, 85.2%)	7.2% (−15.4%, 29.8%)	.265
	10 min	91.1% (82.8%, 99.4%)	78.9% (62.5%, 95.4%)	12.3% (−6.6%, 31.2%)	.100
Age (y)					
≥65	5 min	77.5% (68.9%, 86.2%)	61.7% (47.8%, 75.6%)	15.8% (0.0%, 32.2%)	.027
	10 min	86.9% (79.8%, 94.1%)	71.5% (58.3%, 84.7%)	15.4% (0.5%, 30.4%)	.021
<65	5 min	81.3% (71.7%, 90.8%)	53.3% (35.4%, 71.3%)	27.9% (8.2%, 47.7%)	.003
	10 min	93.8% (87.8%, 99.7%)	63.6% (46.4%, 80.9%)	30.2% (12.5%, 47.9%)	<.001

Rate estimate (95% CI); difference (95% CI). *QCC+*, QuikClot Control+; *CI*, confidence interval.

(Table 4). For subjects not yet achieving hemostasis at either timepoint, a marked difference in bleeding grade was also observed between study arms. A difference in the rate of hemostasis between study arms was found with sternal edge bleeds at both timepoints when compared with subjects with surgical site or overall bleeds (Table 4). Stratification by age revealed that the difference in hemostasis at both timepoints in QCC+ and control subjects aged 65 years or more was approximately half that of those aged less than 65 years (Table 4).

Additional intraoperative data analysis found a numerical difference in hemostasis rate at 5 minutes between QCC+ and control subjects with an activated clotting time at or above the median value (26.3% [95% CI, 9.2-43.3]) vs those below the median (15.0% [95% CI, −2.9% to 33.7%]; $P = .48$). Intraoperative blood product use showed similarity between arms except for cryoprecipitate, where 7.8% of QCC+ subjects received cryoprecipitate and 17.9% of subjects received standard gauze ($P = .028$; Table 2).

Last, there were a limited number of study protocol deviations related to intraoperative use of the assigned product or assessment of the outcome (QCC+: 1 subject; control: 5 subjects). For QCC+ subjects, all were treated with the device and included in the intention-to-treat and as-treated population analyses. However, 1 QCC+ subject and 3 control subjects were excluded from the Per Protocol population because the product was not reapplied after the 5-minute bleeding assessment. Two control subjects were treated with hemostatic control measures rather than gauze and were considered technical failures not achieving hemostasis at either timepoint. However, no subjects crossed over to receive the opposite treatment than the one to which they were randomized.

Early Postoperative Outcomes and Follow-up

No significant differences in postoperative characteristics were observed, including chest tube drainage volume, although minor numerical differences in use of blood products between study arms were noted, including use of cryoprecipitate (QCC+: 16/153 [10.5%] vs control: 16/78 [20.5%]; $P = .04$). All 3 instances of reoperation for bleeding occurred within 24 hours to subjects in the QCC+ arm and were adjudicated as definitely procedure related. The first of 2 instances of operative mortality occurred on postoperative day 2 and the AE Adjudication Committee classified the event as definitely related to the operative procedure and not study device related. The second, occurring on postoperative day 10, was adjudicated as probably procedure related and not study device related. Mean length of stay was 6.4 days for QCC+ subjects and 6.9 days for control subjects ($P = .54$). Completing the end of study follow-up visit were 226 of 231 subjects (97.8%), with 5 exiting the study due to AEs or loss to follow-up.

Adverse Events

Equivalent safety profiles were demonstrated, with 1.3% of subjects in each arm having a device-related serious adverse event (possibly device related), consisting of 3 infections (QCC+: 2/153; control: 1/78). The first QCC+ arm surgical site infection occurred 4 days postprocedure but before discharge, with resolution 11 days after discharge. The second infection occurred 24 days postprocedure, resolving with sequelae 17 days later. The control arm surgical site infection occurred 10 days postprocedure and resolved 18 days later. No product failures or unanticipated device effects occurred during the study.

DISCUSSION

This multicenter, randomized, controlled, single-blinded study demonstrated that QCC+ hemostatic gauze was superior to standard gauze in achieving hemostasis for mild to moderate bleeding in this cardiac surgery patient population. This conclusion was consistent across the intention-to-treat, as-treated, and per-protocol analysis populations. Of note, the proportion of subjects achieving hemostasis at both 5 and 10 minutes was more than 20% higher in the QCC+ group compared with controls ($P < .001$).

Of the bleeding sites observed, sternal edge not only was the predominant site but also had the highest difference in proportion of QCC+ subjects achieving hemostasis versus control subjects when compared with surgical site or overall bleeds. The greater effect of the QCC+ device found at the sternal edge was most likely because bleeding is particularly difficult to control at this site due to the highly vascular bones of the sternum. As a result, the efficacy of the QCC+ was particularly pronounced with sternal edge bleeding versus surgical site or overall bleeds. It should be noted that the surgical site and particularly the overall bleed sample sizes were smaller than for the sternal edge bleed and may have contributed to the positive treatment effect observed. In addition, both the QCC+ and the control subjects benefited from the ease of device application with sternal edge bleeding, and thus this is unlikely to have been the cause of the improved hemostasis at this specific bleeding site. Last, all but 2 subjects were followed through completion of the study.

The statistical differences in the performance of QCC+ versus standard gauze were evident for the sternal edge bleeding assessment site, moderate initial bleeding grade, and age less than 65 years subgroups, and safety outcomes were similar between study arms. All 3 device-related AEs occurring during the study were infections adjudicated as serious adverse events possibly related to QCC+ or the control device. Remarkably, the likelihood of QCC+ subjects achieving hemostasis over the 10-minute assessment period was almost twice as high compared with control subjects (hazard ratio = 1.89; $P < .001$), with a nonlinear change in the proportion of QCC+ subjects achieving hemostasis over the assessment period (5 minutes: 79.1%; 10 minutes: total of 89.8%). At 15 minutes, the difference in the proportion of QCC+ and control subjects achieving hemostasis is expected to be maintained, because by this time interval all QCC+ subjects should have achieved grade 0 bleeding.

Recommendations on QCC+ use as a result of this study include application of the product in direct contact and with compression, covering the entire bleeding site, with the preferred QCC+ product size being 4 × 8, 8-ply. The largest differences in achieving hemostasis between QCC+ and control subjects were found in those aged less than 65 years, with moderate bleeding, and at the sternal edge. It should also be noted that the QCC+ product should not be a stand-alone solution to surgical bleeding, but should be used in concert with meticulous surgical technique at sternotomy incision and careful hemostasis with conventional means of hemorrhage control.

This is the first clinical study to date examining the efficacy of a hemostatic dressing in cardiac surgery with mild to moderate bleeding. Animal model and clinical studies have examined the effectiveness of QCCG/QCC+ in a variety of situations, including comparisons with chitosan-based products. A study by Sena and colleagues[14] using a hypothermic coagulopathic swine model showed that compared with laparotomy pads kaolin-impregnated gauze for intracorporeal packing in cases of severe hepatic injury reduced postoperative hemorrhage and resuscitation requirements. Kheirabadi and colleagues[22] examined the efficacy of the chitosan-based dressings HemCon RTS, Celox-D, and TraumaStat, as well as QCCG and standard gauze, concluding that QCCG was most effective in a groin arterial hemorrhage porcine model. Last, a study of QCCG and Celox Rapid by Johnson and Johnson[25] found QCCG more effective than Celox Rapid in initial hemostasis and clot maintenance after femoral artery arteriotomy in a porcine model.

Clinical studies include an investigation by Kim and colleagues[26] that showed a reduction in packed red blood cell transfusions during preperitoneal pelvic packing in patients with hemodynamic instability due to severe pelvic fractures when comparing QCCG with surgical pads. QCCG was also used in a study by Lamb and colleagues[23] to control cannulation site bleeding in 5 patients with percutaneous extracorporeal membrane oxygenation support with 17 applications of QCCG, demonstrating a significant reduction in bleeding complications and need for blood transfusion.

In addition to improved hemorrhage control and reduction in blood transfusion confirmed by the aforementioned studies, effective surgical hemostasis has demonstrated improved surgical field visibility, decreased operating time, improved patient outcomes, shorter length of hospitalization, and lower healthcare costs, particularly important as the Department of Health and Human Services continues to move toward bundled payment models for cardiovascular care and surgery.[1-4,6-9]

Over the past 25 years, many studies have been conducted in the cardiac setting evaluating the efficacy of mechanical, active, and flowable HAs, as well as fibrin or synthetic sealants. Although many of these studies have produced favorable results, further randomized controlled trials are needed to compare the various topical HAs used in cardiac surgery to address the issue of bleeding-related complications.[10] Costs for the 4 categories of topical HA, mechanical, active, flowable, and fibrin sealant, can range from $50 per milliliter of liquid product to more than $800 for a single fibrin sealant patch.[27] Examples of HAs costing

less than $50 are bone wax and chitosan. Agents costing between $50 and $100 include absorbable gelatin, oxidized regenerated cellulose, microporous polysaccharide spheres, and hemafiber. The microfibrillar collagen and topical thrombin agents cost between $101 and $300, with the cost of kaolin impregnated gauze for internal use (eg, QCC+) falling in these second or third groups. Last, the thrombin/gelatin, thrombin/collagen, and fibrin sealant (human fibrinogen and human thrombin) can range from $301 to $500, and dry fibrin sealant dressing and bovine albumin-glutaraldehyde tissue adhesive can command costs as much as $501 to $800[28] or more.

Study Limitations

This study was powered to detect a primary end point difference of 20% or more between arms, somewhat limiting the ability to observe significant differences in subgroup analyses examining the effectiveness of QCC+ versus standard gauze by bleeding site or grade, even if trends emerged. Additionally, bleeding was assessed using a semiquantitative, validated intraoperative bleeding severity scale designed for use in clinical studies investigating HAs. However, surgical sponge weight and suction canister volume data were not collected as part of this clinical trial. It should also be noted that the investigators were not blinded to the randomization assignment, potentially introducing detection bias into the bleeding assessments. In terms of AEs, as in many clinical trials, this study may be limited in part by the difficulty faced by AE Adjudication Committees to correctly determine if an AE was device-related, procedure-related, neither, or both. Cardiac surgeries are complex, and AE assessment and determination of relatedness for gauze, particularly involving infection, may be challenging. Last, the study protocol deviations related to use of the assigned product or assessment of the hemostasis outcome included 1 QCC+ subject and 3 control subjects in whom the product was not reapplied after the 5-minute bleeding assessment, as well as 2 control subjects in whom hemostatic control measures were used rather than gauze. However, after sensitivity analyses the study conclusions were found to be robust to these limited protocol deviations.

CONCLUSIONS

The QCC+ product demonstrated superior performance in achieving hemostasis in cardiac surgery for mild to moderate bleeding compared with control. The ability of QCC+ to achieve effective hemostasis was also demonstrated separately at the 5- and 10-minute assessment times. The difference between groups in the proportion of subjects achieving hemostasis was more than 20% at both timepoints. Of note, the safety of QCC+ was comparable to that of the control.

Conflict of Interest Statement

Dr Mumtaz discloses a financial relationship with Abbott, Edwards Lifesciences, Medtronic, and Teleflex. Dr Moon discloses a financial relationship with Edwards Lifesciences and Medtronic. Dr Sultan discloses a financial relationship Abbott, Artivion, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr Reece discloses a financial relationship with Teleflex and Terumo Aortic, and is on the editorial board for *The Journal of Thoracic and Cardiovascular Surgery* and *The Annals of Thoracic Surgery*. Dr Keeling discloses a financial relationship with AngioDynamics and Penumbra. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The authors thank Teleflex for study funding, Ajesh Raju, BASc, for study operations oversight, Colin Edwards, PhD, for manuscript editing, and Tyson Rogers, MS, for statistical support.

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Key Words: bleeding control, clinical trial, hemostatic device, kaolin, time to hemostasis

TABLE E1. Validated bleeding severity scale

Grade	Visual presentation	Anatomic appearance	Qualitative description	Visually estimated rate of blood loss (mL/min)
0	No bleeding	No bleeding	No bleeding	≤1.0
1	Ooze or intermittent flow	Capillary-like bleeding	Mild	>1.0-5.0
2	Continuous flow	Venule and arteriolar-like bleeding	Moderate	>5.0-10.0
3	Controllable spurting or overwhelming flow	Noncentral venous- and arterial-like bleeding	Severe	>10.0-50.0
4	Unidentified or inaccessible spurting or gush	Central arterial- or venous-like bleeding	Life threatening*	>50.0

Scale designed and validated for use in clinical studies to generate labeling claims. Likert-type scale, in which user assigns grade based on overall agreement of items listed.
*Systemic resuscitation required (eg, volume expanders, vasopressors, or blood products).