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A Randomized Comparison of the *QuikClot® Radial®* Pad versus the Standard of Care TR Band® on Hemostasis after Transradial Artery Access (TRA)

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Funding Sponsor Z-Medica, LLC

Study Product *QuikClot®Radial®*Pad

510 (K) Number K120782 (QuikClot® Interventional Hemostatic Bandage)
K152525 (TR Band Radial Compression Device)

Protocol Number SAIRB-18-0021

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Study Summary

Title	A Randomized Comparison of the *QuikClot® Radial®* Pad versus the Standard of Care TR Band® on Hemostasis after Transradial Artery Access (TRA)
Short Title	*QuikClot® Radial®* pad on hemostasis after TRA
Protocol Number	SAIRB-18-0021
Methodology	Randomized, controlled, prospective study
Study Duration	1 year
Study Center(s)	Single center
Objectives	To evaluate the efficacy and safety of the *QuikClot® Radial®* pad on hemostasis after TRA, compared to the standard of care TR Band®, with the goal to hopefully develop a safe and efficacious technique to achieve more rapid patent hemostasis after TRA, and improve patient care by optimizing radial hemostasis management.
Number of Subjects	Consent up to 600 subjects with possible enrollment of 373
Diagnosis and Main Inclusion Criteria	Patients undergoing TRA for cardiac catheterization (CC) and/or percutaneous coronary intervention (PCI).
Study Product, Dose, Route, Regimen	The QuikClot® Radial® pad will be applied over the radial artery access site covered with either a Coban™ bandage or a TR Band® after TRA. Firm manual compression will then be applied over the QuikClot® Radial® pad after the sheath is removed for 5 minutes in the Coban™ cohort. The Coban™ cohort will then have the Coban™ bandage removed after an additional 25 minutes, then being covered with a Tegaderm™ dressing. In the QuikClot® Radial® pad combined with a TR Band® cohort, the radial sheath is removed and the TR Band® is inflated with 8 – 10 mL of air after a small amount of blood is noted on the QuikClot® Radial® pad. After 30 minutes the TR Band® is removed, leaving the QuikClot® pad covered with the Tegaderm™ dressing over the skin entrance site, to be removed the following morning.
Assigned Interventions	Consented subjects will be randomly assigned in the cardiac cath lab upon completion of their procedure into the following three arms: Arm 1 – Standard of Care with a TR Band® Arm 2 – QuikClot® Radial® pad combined with a Coban™ bandage Arm 3- QuikClot® Radial® pad combined with a TR Band®
Reference therapy	TR Band®

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1. Introduction

This document is a protocol for a prospective, randomized, open-labeled study to evaluate the safety and efficacy of the *QuikClot® Radial®* pad on hemostasis after TRA, compared to the standard of care device, the TR Band®, by assessment of patient tolerance of the device, local vascular complications, and the time taken to achieve hemostasis. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 812 and International Conference on Harmonization guidelines), applicable government regulations and Memorial Healthcare System research policies and procedures. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

1.1 Background

There is growing interest and increased use of the radial artery (RA) as the preferred access site for cardiac catheterization (CC) and/or percutaneous coronary intervention (PCI) due to its proven clinical benefits, including fewer access-site complications,[1-3] lower bleeding risks,[4,5] shorter hospital stays,[2,6] lower costs,[2,7] and mortality benefits in ST-elevation myocardial infarction compared with the femoral artery (FA) approach.[8,9] In addition, patients overwhelmingly prefer RA over FA access because of the increased comfort after the procedure.[2, 3, 7]

Radial artery occlusion (RAO), however, is still an important complication seen in up to 8% of patients undergoing TRA.[10-12] RAO is known to be associated with use of large-size catheters, lack of procedural anticoagulation, and prolonged duration of radial compression after sheath removal.[10-12] Strategies such as higher dose of anticoagulation and shorter duration of hemostatic compression in conjunction with the patent hemostasis technique have been shown to reduce the incidence of RAO.[10-12] Several radial compression hemostatic devices have been introduced into clinical practice, with the aim of aiding radial access site hemostasis and limiting vascular complications.[13] The most common compression device used in the United States is the TR Band® (Terumo, Japan), which is the standard of care device now being used to obtain radial artery hemostasis after TRA. This device wraps around the wrist and applies direct pressure to the radial arteriotomy site, typically for 2 to 3 hours after sheath removal, to achieve hemostasis. It is unclear, however, if using shorter compression times will further reduce the incidence of RAO without compromising hemostasis.

QuikClot® Radial® pad is a new hemostatic dressing that is composed of a kaolin-impregnated gauze. When kaolin contacts blood it immediately initiates the clotting cascade by activating Factor XII, resulting in shortened hemostasis times.[14-16] Application of *QuikClot®* hemostatic pads over femoral artery access sites after PCI has been shown to reduce time to hemostasis with early ambulation.[14] Recently, we applied the *QuikClot® Radial®* pad with an elastic adhesive bandage supplied by Z-Medica, LLC to achieve radial hemostasis after TRA with 5 minutes of manual compression followed by 25 or 55 minutes of elastic adhesive bandage compression in 20 patients. There was 100% successful hemostasis with the use of the *QuikClot® Radial®* pad in both groups with no rebleeding or increased complications noted when compared with the TR band®.[15] Some subjects in this pilot trial complained about the supplied sticky elastic adhesive bandage, though. It was uncomfortable to remove because of the strong adhesive pulling their skin upon bandage removal. The operators also felt the elastic bandage was a bit complicated to apply. Because of this, we conducted another small pilot trial testing the feasibility and efficacy of using either a Coban™ bandage or Tegaderm™ dressing to secure the *QuikClot® Radial®* pad for achieving hemostasis post TRA, in hopes of improving patient comfort and satisfaction. The results showed that 5 minutes of initial manual

compression followed by 25 minutes of light compression with either a Coban™ bandage or Tegaderm™ dressing was successful in the 20 patients who underwent diagnostic cardiac catheterization and/or PCI, with 100% successful initial hemostasis without rebleeding, RAO, and other complications. This preliminary clinical evaluation suggested the *QuikClot® Radial®* pad combined with either a Coban™ bandage or Tegaderm™ dressing was an easy to use and effective hemostatic dressing that allowed for a short duration of compression and a painless hemostasis procedure without vascular or other complications noted.

We were encouraged by the performance of the *QuikClot® Radial®* pad in the above small pilot studies. The small sample sizes did not allow a definitive answer as to whether reduced compression times with the *QuikClot® Radial®* pad would reliably allow significantly shorter hemostasis times allowing for earlier discharge from the hospital, lead to less RAO post procedure, or improve patient comfort. We therefore designed the first version of this larger, adequately powered, prospective randomized trial to investigate the safety and efficacy of the *QuikClot® Radial®* pad combined with either a Coban™ bandage or Tegaderm™ dressing to achieve hemostasis following TRA, compared to the standard of care TR Band®. The *QuikClot® Radial®* pad will be applied over the radial artery access site using either a Coban™ bandage or only a Tegaderm™ dressing after TRA. Then, after sheath removal, firm manual compression will be applied over the *QuikClot® Radial®* pad covered by either the Coban™ bandage or the Tegaderm™ dressing for 5 minutes, followed by 25 minutes of light compression with the Coban™ dressing in the Coban™ cohort or 25 minutes of close observation after release of manual pressure in the Tegaderm™ only cohort.

After an interim analysis of 186 subjects, and a peer data safety and monitoring board (DSMB) committee review of the results, we elected to stop the Tegaderm™ only arm. With a failure to obtain initial hemostasis at 5 minutes in approximately 30% of the subjects in this arm of the protocol, we believed there would be little chance of this Tegaderm™ only protocol being adopted clinically. There were no safety issues with the Tegaderm™ only arm, as with repeated 5 minute manual compression cycles of the QuikClot® pad, hemostasis was obtained in all subjects. Mean hemostasis time in the Tegaderm™ only arm was 8.1 minutes. There was just clinical futility of this arm of the protocol as written, that was not detected in the small pilot trial performed using this protocol.

A new arm 3 will replace the Tegaderm™ only arm. This new arm 3 will use a QuikClot® Radial® Pad under a TR Band® with 30 minutes of compression. We have a large successful anecdotal experience of using a QuikClot® Radial® Pad under a TR Band® with 30 minutes of compression. We and others have demonstrated that use of a hemostatic pad under a TR band® significantly shortenes hemostasis time, as compared to a TR band® alone, with no increased complications noted. [17,18]

We will evaluate patient tolerance of the devices, local vascular complications, and the time taken to achieve hemostasis with the use of the *QuikClot® Radial®* pad and compare with the standard of care TR Band® on hemostasis after TRA. The results to be obtained will refine the *QuikClot® Radial®* pad use in the setting of hemostasis following transradial procedures, to hopefully develop a safe and efficacious strategy to achieve more rapid patent hemostasis following TRA, possibly lower RAO rates with shorter compression times, and improve patient care by optimizing radial hemostasis management.

1.2. Summarized Details of Investigational Products

The below description is taken from the QuikClot 510(k) Summary, dated April 11, 2013.

1.2.1. Device Description

The QuikClot® Radial® pad is made of a soft, white, kaolin-impregnated gauze. The QuikClot® Radial® pad will be provided in a kit form that consists of a hemostatic pad and an adhesive bandage (Figure 1). The adhesive bandage is a Direct Pressure (DP) Bandage. The hemostatic pad is a hemostatic dressing made of soft, white, kaolin impregnated gauze, configured in a 0.8" diameter by 1.5" long roll. The QuikClot® Radial® pad utilizes a layered clay hemostat, kaolin USP, which is bound to medical gauze. The QuikClot® Radial® pad are provided in a sterile, intuitive, simple to use dressing format that conforms readily to the wound. The DP Dressing is a Class 1 exempt device and serves as a fixation/compression bandage which is in contact with the hemostatic dressing, but is not in direct contact with the wound. In the present trial either a Coban™ bandage or a Tegaderm™ dressing will serve as a fixation/compression bandage instead of the supplied DP dressing to secure the QuikClot® Radial® pad over the arteriotomy site.

1.2.2. Intended Use

The *QuikClot® Radial®* pad is applied topically as an adjunct to manual compression and is indicated for the local management and control of surface bleeding from vascular access sites, percutaneous catheters or tubes utilizing introducer sheaths up to 12 Fr and up to 7 Fr and for patients on drug/induced anti-coagulation treatment.

1.2.3. Technological Characteristics and Substantial Equivalence

1.2.3.1. *QuikClot® Radial®* Pad

The *QuikClot®® Radial®* pad is intended for control of surface bleeding from vascular access sites, percutaneous catheters or tubes utilizing introducer sheaths up to 12 Fr. There are several marketed devices with similar indications that utilize alternate technologies to achieve the same indications as the proposed device, such as the Vascular Solutions D-Stat Dry, WoundStat, and the ChitoFlex™ Surgical device. The *QuikClotα Radial®* pad is identical in technology to the *QuikClot®* Interventional™ hemostatic bandage.

The *QuikClot® Radial®* pad and the predicate devices are similar in that they are all indicated as an adjunct to manual compression and are indicated for the control of surface bleeding from vascular access sites and percutaneous catheters or tubes and reducing the time-to-hemostasis in patients undergoing diagnostic endovascular procedures utilizing introducer sheaths.

1.2.3.2. 3M™ Coban™ Self‑Adherent Latex-free Wrap

Figure 2. Coban™ self-adherent latex-free wrap

3M™ Coban™ Self‑Adherent Latex-free Wrap is a sterile, cohesive elastic wrap constructed from a nonwoven material and elastic fibers (Figure 2). The cohesive properties allow the wrap to stick to itself but not to other materials or skin. It is supplied in individually packaged sterile rolls. This product is not regulated under the FDA, and a MSDS is not required for this product by the OSHA Hazard Communication Standard (29 CFR 1910.1200) because, when used as recommended or under ordinary conditions, it should not present a health and safety hazard. Coban™ self‑adherent wrap is intended for use as an elastic wrap to provide compression or support, or to secure dressings or devices. 3M Coban™ Sterile Self‑Adherent Wrap

(Catalog No: 1582S, 2″ X 5 yd) or a generic equivalent (CardinalHealth, Catalog No: CAH25LFS) will be used in this study.

1.2.3.3. 3M™ Tegaderm™ Transparent Film Dressing

Tegaderm™ is a transparent medical dressing manufactured by 3M™. Tegaderm™ Film consists of a thin film backing with a non-latex, hypoallergenic adhesive (Figure 3). The dressing is breathable, allowing good oxygen and moisture vapor exchange. It is waterproof and impermeable to liquids, bacteria, and viruses. An intact dressing protects the site from outside contamination. Tegaderm™ transparent dressings can be used to cover and protect wounds and catheter sites. Tegaderm™ transparent film dressings are routinely used in the Cardiac Cath Labs of MRH.

Figure 3. Tegaderm™ film dressing

1.3. Device Usage

Application of the *QuikClot® Radial®* pad will be performed by properly trained interventional cardiologists. Application of the TR Band® will be performed by properly trained interventional cardiologists or cath lab technicians. Proper training for physicians for either device is defined as performing 2 run in procedures prior to enrolling patients in this study, supervised by a cardiologist or industry representative experienced with the either device. For cath lab technicians, proper training will be meeting the qualifications outlined by the Memorial Cardiac and Vascular Institute cath lab protocol for application of the TR Band®. Dr. Roberts, Dr. Pastor and Dr. Shah are properly trained with the use of the *QuikClot® Radial®* pad hemostatic device and TR Band®.

1.3.1. The method for using the *QuikClot® Radial®* pad with a Coban™ Self-Adherent Wrap is as follows:

After an end-procedure ACT is drawn and the blood pressure is recorded, the arterial access sheath will be partially pulled out of the radial artery, exposing approximately 4 cm of sheath. The level of the access site will be marked on the medial and/or lateral side of the palmar surface of the wrist with a sterile marker pen so that once the pad is applied and covering the access site, the investigator will still be able to know the exact level of the access site, to properly hold pressure in the correct spot. (Fig.4A, *Arrows*). The *QuikClot® Radial®* pad is then applied over the access site, with the sheath still in place, with 1/3 of the pad being distal to the access site and 2/3 of the pad being proximal to the access site (Fig.4B, *Arrows*). The 3M™ Coban™ latex-free self-adherent wrap is then gently applied, wrapping 3-5 layers around the wrist to hold the *QuikClot® Radial®* pad in place (Fig 4. C). When application is complete, the excess self-adherent wrap will be cut off (Fig. 4D). The 3 – 5 layers will then be hand massaged to allow the layers to adhere to each other (Fig. 4E). The sheath is then removed from the radial artery,

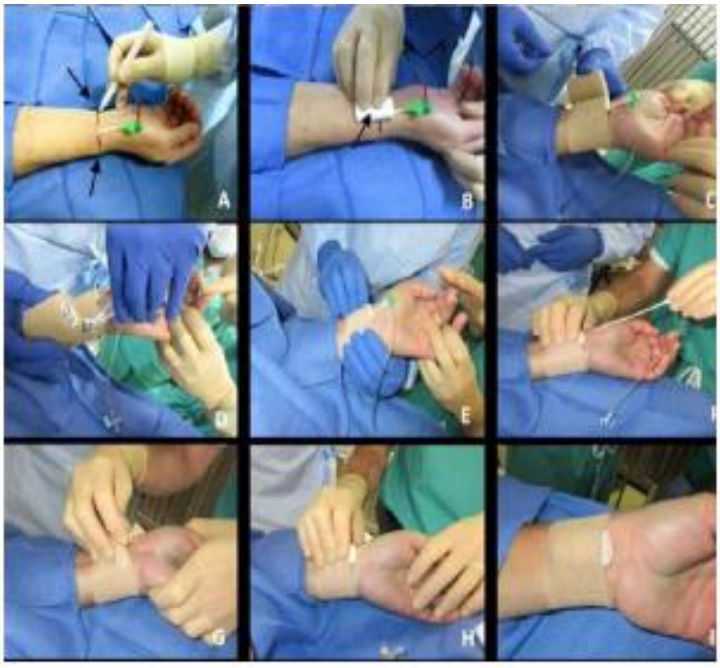


Fig 1. Application of the QuikClot®Radial® pad with the Coban™.

being pulled out from underneath the *QuikClot® Radial®* pad, with the investigator slightly pulling up on the distal portion of the pad, allowing for a small amount of bleeding to partially saturate the under surface of the *QuikClot® Radial®* pad to initiate the kaolin-blood reaction (Figs. 4, F and G). 5 minutes of firm manual compression is then held with several fingers on top of the *QuikClot® Radial®* pad, directly over the access site and just proximal to the access site, with the thumb wrapped under the wrist (Fig. 4H). After release of manual pressure, the investigator will observe for bleeding under the *QuikClot® Radial®* pad/Coban™ wrap for one minute (Fig. 4I). If there is not hemostasis, manual pressure will again be applied over the *QuikClot® Radial®* pad for another 5 minutes, and this cycle will be repeated until there is hemostasis. Once there is hemostasis, the previously applied Coban™ will be removed 25 minutes (± 5 minutes) after manual pressure is released, keeping the *QuikClot® Radial®* pad in place over the access site. A clear adhesive film dressing (Tegaderm™) is then applied over the *QuikClot® Radial®* pad, to be removed the following morning. If there is oozing/bleeding after the Tegaderm™ dressing is applied, the investigator may use his/her discretion to reapply manual pressure to the *QuikClot® Radial®* pad, or use mechanical compression with a TR Band®.

1.3.2. The method for application of the TR Band®

After an end-procedure ACT is drawn and the blood pressure is recorded, application of the TR Band® for transradial hemostasis will be performed as described previously[15] with the modifications described below. Briefly, the arterial access sheath is partially pulled out of the artery, exposing approximately 4 cm of sheath. A dry 4 inch by 4 inch gauze will be placed under the exposed sheath, cinched up to the skin entrance site of the sheath. The TR Band® will be applied snuggly around the wrist, with the sheath still in place, with the green dot of the TR Band® 2 – 3 mm proximal to the skin entrance site of the sheath. 10 mL of air will then be used to inflate the TR Band®. The sheath is then pulled out of the radial artery and out from under the TR Band®. The 4 x 4 gauze is then pulled out from under the TR Band®. If there is not hemostasis when the sheath is removed, additional air will be added in 1 – 2 mL increments until hemostasis occurs. When there is hemostasis, radial artery patency will be assessed by the reverse Barbeau test and recorded. Then, the TR Band® will remain in place for 60 minutes. At the end of 60 minutes (± 5 minutes) of compression, 2 mL of air will be removed, and then additional 2 mL at 80 minutes (± 5 minutes), and then 3 mL at 100 minutes (± 5 minutes), and then the remaining air slowly deflated over 30 seconds at 120 minutes (± 5 minutes). If oozing/bleeding occurs at any point during the weaning of air, the previously removed amount of air will be re-inflated into the TR Band®, and weaning will again commence in 20 minutes. Once all the air has been removed and hemostasis confirmed, the TR Band® will be removed, and a Band Aid or a dry gauze pad under a Tegaderm™ dressing will be placed over the skin entrance site, to be removed the following morning.

1.3.3 The method for application of the QuikClot® Radial® pad under a TR Band®

After an end-procedure ACT is drawn and the blood pressure is recorded, the arterial access sheath will be partially pulled out of the radial artery, exposing approximately 4 cm of sheath. The level of the skin access site will be marked on the medial side of the palmar surface of the wrist with a sterile marker pen, so that once the pad is applied and covering the access site, the investigator will still be able to know the exact position of the skin access site, to properly apply pressure with the TR Band® in the correct spot. (Fig 5. A). The QuikClot® Radial® pad is then applied over the access site, with the sheath still in place, with approximately 1/2 of the pad being distal to the skin access site and 1/2 of the pad being proximal to the access site (Fig 5. C). This is best accomplished by placing the seam side of a QuikClot® Radial® pad face down on the sticky side of a Tegaderm™ (Fig 5. B), centering it in the middle of the Tegaderm™. The Tegaderm with a QuikClot® Radial® pad stuck to it is then positioned slightly

above the wrist (Fig 5. C), with the QuikClot® Radial® pad centered to the sheath, with one half of the pad above the skin access site and one half of the pad distal to the skin insertion site. The QuikClot® Radial® pad is then lowered onto the wrist, being held in the correct position with the Tegaderm dressing (Fig 5 D) A TR Band® will then be loosely applied over the QuikClot® pad covered with Tegaderm™, centering the TR Band® green dot 2 – 3 mm proximal to the marked skin entrance level (Fig 5, E). The sheath is then rapidly pulled, and the operator will observe for a small amount of blood on the undersurface of the QuikClot Radial Pad, then quickly fill the TR Band® with 8 – 10 mL of air (Fig 5. F, G, H). It is very important for blood to be in contact with the kaolin, to initial the hemostasis reaction. If no bleeding is seen on the under surface of the QuikClot® pad with the TR Band® still being uninflated, the operator may lift up the uninflated TR Band® and QuikClot® pad under it, to initiate a small amount of bleeding, and then fill the TR Band® with 8 – 10 mL of air. If there is continued bleeding after inflating the TR Band® with 8 – 10 mL of air, additional 1 – 2 mL increments of air should be added to obtain hemostasis. When there is hemostasis, radial artery patency will be assessed by the reverse Barbeau test and recorded. After 30 minutes of compression with the TR Band®, it will be deflated slowly over 1 minute. The deflated TR Band® will be left in place for 5 minutes, to allow for rapid reinflation if bleeding occurs. If there is hemostasis after 5 minutes of observation with the deflated TR Band®, the TR Band® will be removed, leaving the QuikClot® pad covered with the Tegaderm™ dressing. If bleeding occurs upon weaning of air, the TR Band® will be reinflated to obtain a total of 8 – 10 mL of air in the TR Band® bladder for an additional 20 minutes. The TR Band® will then again be slowly deflated over 1 minute, leaving the deflated TR Band® in place for an

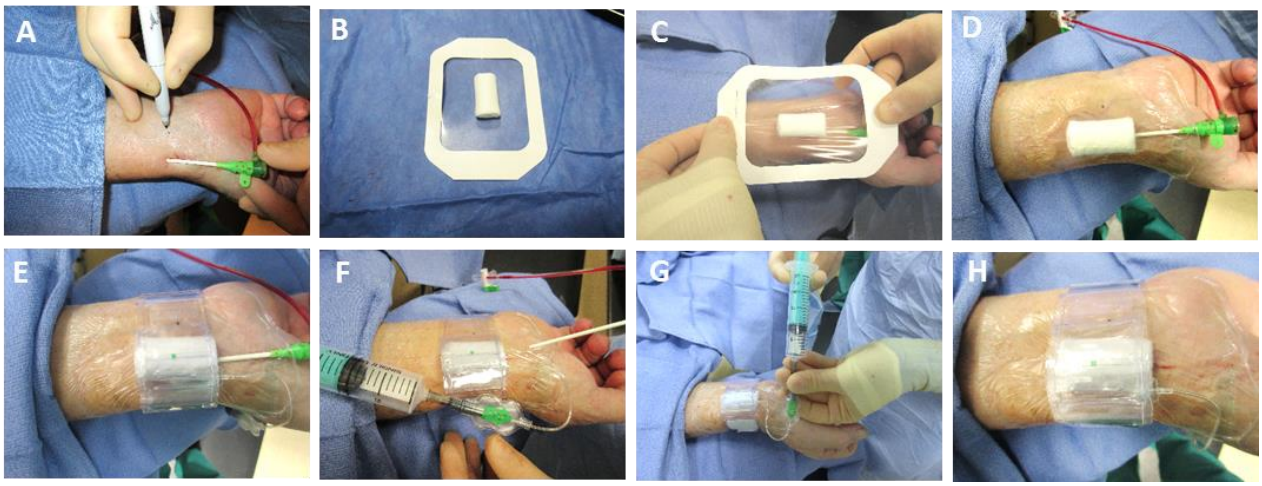


Fig 5. Application of the QuikClot®Radial® pad under the TR Band®.

additional 5 minutes. This cycle will be repeated until there is hemostasis. The operator will have the option to remove the QuikClot® pad, and use just a TR Band®, if the subject has failed at least one subsequent re-inflation cycle.

1.4. Clinical Data to date

The *QuikClot® Radial®* pad has received FDA clearance for use in local management of bleeding wounds such as vascular access sites. It provides an alternative to other hemostatic devices and could potentially reduce

hemostatic time, reduce vascular complications and shorten time in hospital stay. By PubMed search with key words including *QuikClot® Radial®* pad, vascular access, hemostatic devices, and hemostasis showing the available clinical data to date regarding use of the *QuikClot® Radial®* pad as following:

Additional Clinical Data/References:

Several peer reviewed clinical publications support the use of QuikClot Interventional Hemostatic Bandage in human patients on drug/induced anticoagulant therapy.

TABLE 2

Study Name/Description	**Trabattoni D, et al.** ***A New Kaolin-based Hemostatic Bandage Use after Percutaneous Coronary Diagnostic and Interventional Procedures*****; Internat J Cardiol; 2010 Nov 172.**
Number of sites/investigators (OUS/US)	One site (OUS). Three investigators
Number of subjects	40 subjects
Inclusion/ **Exclusion**	Patients undergoing diagnostic angiography or percutaneous coronary intervention via a femoral artery approach Not described in publication
Procedure	Prospective single arm pilot trial of QuikClot Interventional Hemostatic Bandage in cardiac catheterization. Introducer sheath size 6 Fr (90%) or 7 Fr (10%) Femoral artery sheath removed once the ACT < 180 seconds All patients were treated with QuikClot Interventional Hemostatic bandage after arterial sheath removal
Study endpoints and assessment protocol	Complete 100% bleeding cessation at 5 minutes and safe ambulation at 4 hours
Duration of follow-up	30 days
Patient Demographics	75% male Mean Age = 68+/- 11 years
Patient condition (means of achieving anticoagulation, level of anticoagulation)	Patient undergoing diagnostic angiogram (62%) vs. Percutaneous Coronary Intervention PCI (38%) via femoral artery approach 6F (90%) 7F (10%). QuikClot n=40 LMW Heparin 2.5% Aspirin + Clopidogrel 27.5% Aspirin 60% Aspirin + Warfarin 5% IV Heparin 38% No anticoagulation 5%
Study results	Mean ACT value at hemostasis 138 + 24 seconds (range 95-186 seconds) Mean cumulative hemostasis time 4.9±1.05 min • Diagnostic procedures 4.2±0.9 min • Interventional procedures 5.3±0.95 min Ambulation time 4 h for all patients
Adverse events	One PCI patient required extra compression time to achieve hemostasis and developed a small (< 5cm) hematoma

Medica, LLC

TABLE 3

Study Name/Description	**Trabattoni D, et al.** ***A New Kaolin-based Haemostatic Bandage Compared with Manual Compression for Bleeding Control after Percutaneous Coronary Procedures*****; Eur Radiol, 2011 Aug 21(8): 1687-91.**
Number of sites/investigators (OUS/US)	One site (OUS), six investigators
Number of subjects	200 subjects Prospective randomized trial of QuikClot(n=100) vs. manual compression (n=100)
Inclusion/ **Exclusion**	Undergoing angiography or percutaneous coronary intervention via a femoral approach Patients with baseline INR > 1.4 excluded Patients who had previous arterial access at the same femoral site within 30 days excluded
Procedure	Femoral arterial sheath removed once the ACT ≤ 180 seconds Patients randomized to receive QCI gauze or manual compression after femoral sheath removal Patient ambulation at 4 hours.
Study endpoints and assessment protocol	Complete 100% bleeding cessation at 5 minutes and safe ambulation at 4 hours
Duration of follow-up	30 days
Patient demographics	Male 70% QuikClot vs. 60% Control Mean age (years) 65.7±13 vs. 73.6±6.2 Weight (Kg) 73.9±12 vs. 71.2±15 Diagnostic procedure (n=98) vs. Percutaneous coronary intervention (n=102) Introducer sheath size 6 Fr (90%) or 7 Fr (10%)
Patient condition (means of achieving anticoagulation, level of anticoagulation)	

	QuikClot	Control
LMW Heparin	4%	2%
Aspirin + Clopidogrel	29%	26%
Aspirin	60%	60%
Aspirin + Warfarin	7%	3%
IV Heparin	51%	49%
No anticoagulation	0%	9%

Study results	Mean ACT value at hemostasis 146 + 24 seconds (range 98 – 198 seconds) Hemostasis with QCI bandage = 5.4 ± 1.5 min Hemostasis with manual compression = 25 ± 15 min p<0.001 No hemostasis failure in either group
Adverse events	Major Bleeding: 1 patient in each group Haematoma, > 5 cm 1* pt (QuikClot) vs. 2 pts (control) Pseudoaneurysm 1* pt (QuikClot) vs. 1 pt (control) *Same patient

TABLE 4

Study Name/Description	**Politi L, et al.** ***Randomized Clinical Trial on Short-Time Compression with Kaolin Filled Pad: A New Strategy to Avoid Early Bleeding and Subacute Radial Artery Occlusion after Percutaneous Coronary Intervention*****; J Internat Card; 2011; Vol 24; 65-72**
Objective	To evaluate the occurrence of 24 hour radial artery occlusion and the rate of bleeding of a novel hemostatic device for radial closure after percutaneous interventions, in adjunct to short-time compression.
Number of sites/investigators (OUS/US)	One site (OUS). Ten investigators
Number of subjects	120 subjects divided in 3 groups: Group 1 (QuikClot n=50) Group 2 (control short time – 15 minute compression n=20) Group 3 (control 2 hours compression time n=50)
Inclusion/ **Exclusion**	All patients undergoing transradial elective diagnostic or interventional coronary procedures between November 1, 2009 and January 31, 2010 Abnormal Allen's test before puncture Failure to provide written informed consent
Procedure	QuikClot was applied to the radial artery over the sheath which was then removed. Pressure was maintained for 15 minutes and then completely relaxed.
Study endpoints and assessment protocol	The main end-point was subacute Radial Artery Occlusion (RAO) The secondary end-point was failure of the closure technique (death, MI or major bleeding occurring in hospital) Groups 1 and 2: 15 minute assessment for bleeding Group 3: 2 hour assessment for bleeding All groups: Radial artery patency assessed at 24 hours using Barbeau's Test
Duration of follow-up	Until patient discharge and follow-up visit. Follow-up at 6 months was done for patients who developed RAO
Patient demographics	Age (years) Group 1 = 64.16 ± 11.53, Group 2 = 61.30 ± 14.22, Group 3 = 59.72 ± 14.23 (p=N/S) Male 37 (74%), 14 (70%), 36 (72%) (p=N/S) Weight (kg) 76.42 ± 11.13, 80.00 ± 14.96, 82.02 ± 13.26 (p=N/S)
Patient condition (means of achieving anticoagulation, level of anticoagulation)	
Randomization Assignment	Based on computer generated randomization list patient received one of the three treatment groups below: Group 1: Compression of radial artery using QuikClot Interventional hemostatic pad with folded gauze over the pad and taped for 15 minutes; Compression dressing then removed

	QuikClot	Control Group 1	Control Group 2
Aspirin	46 (92%)	19 (95%)	50 (100%)
Clopidogrel	10 (20%)	2 (10%)	11 (22%)
LMW Heparin	8 (16%)	5 (25%)	5 (10%)
Warfarin	6 (12%)	5 (25%)	5 (10%)
IV heparin	100%	100%	100%
No anticoagulation	0%	0%	0%
Several patients received multiple therapies			

A previous study showed that after removal of 15 minutes of compression with the *QuikClot®*Interventional™ pad, active bleeding occurred in 20% of patients, compared to 90% with 15 minutes of manual compression only after percutaneously accessed femoral arteries.[16]

Our pilot study in 30 patients undergoing TRA demonstrated that application of the *QuikClot® Radial®* pad with 5 minutes of manual compression followed by a light compressive elastic bandage supplied by Z-Medica LLC for 25 minutes or 55 minutes achieved 100% hemostasis following TRA, with no increased complications noted (see Table below).[15]

Post-procedure outcomes with the use of QuikClot® Radial® pad

	TR Band® (n = 10)	QuikClot® 30 min. (n = 10)	QuikClot® 60 min. (n = 10)	*P* Value
Compression time (min)	149.4 ± 36.5	30.7 ± 2.2	60.9 ± 2.9	< 0.001
Initial hemostasis	5 (50%)	10 (100%)	10 (100%)	< 0.001
Pain scale	0	0	0	NS
Recovery unit time (min)	263.3 ± 56.3	238.9 ± 114.8	237.6 ± 71.6	NS
Access-site complications				
Radial artery occlusion	0 (%)	0 (0%)	0 (0%)	NS
Hematoma	0 (0%)	1 (10%)	0 (0%)	NS
Ecchymosis	0 (%)	0 (0%)	1 (10%)	NS
Edema	0 (%)	0 (0%)	0 (0%)	NS
Rebleeding	0 (%)	0 (0%)	0 (0%)	NS
Other	0 (0%)	0 (0%)	0 (0%)	NS

Results are mean ± standard deviation or n (%); NS, Not significant

Our recent other preliminary study (data not yet published) further demonstrated that application of the *QuikClot® Radial®* pad with 5 minutes of initial manual compression following by 25 minutes of light compression with either a Coban™ bandage or Tegaderm™ dressing was successful in all 20 patients who underwent diagnostic cardiac catheterization and/or PCI, with 100% hemostasis without rebleeding, RAO, and other complications. This preliminary clinical evaluation suggests that the *QuikClot® Radial®* pad combined with either a Coban™ bandage or Tegaderm™ dressing is an easy to use and an effective hemostatic dressing that allowed for a short duration of compression and a painless hemostasis procedure. Thus, there is a need to assess the true efficacy and safety of the *QuikClot® Radial®* pad combined with either a Coban™ bandage or Tegaderm™ dressing in the management of radial hemostasis following TRA in a larger number of patients.

1.5. Dose Rationale and Risk/Benefits

The use of *QuikClot® Radial®* pad has been reported in patients undergoing percutaneous radial procedures, and the results demonstrated that application of the *QuikClot® Radial®* pad with short-term (15 minutes) radial compression had 20% rebleeding at the radial access site.[16] Our recent preliminary results demonstrated that application of the *QuikClot® Radial®* pad with 5 minutes of initial manual compression following by 25 minutes of light compression with either a Coban™ bandage or Tegaderm™ dressing was successful in all 20 patients who underwent diagnostic

cardiac catheterization and/or PCI, with 100% hemostasis without rebleeding, RAO, and other complications (unpublished data). We therefore chose these same compression times for this proposed larger study.

After an interim analysis of 186 subjects, with a failure to obtain initial hemostasis at 5 minutes in approximately 30% of the subjects in the Tegaderm™ only arm of the protocol, we believed there would be little chance of this Tegaderm™ only protocol being adopted clinically. Our DSMB committee reviewed the results and recommended to stop the Tegaderm™ only arm in the prior protocol. There were no safety issues with the Tegaderm™ only arm, as with repeated manual compression cycles of the QuikClot® pad, hemostasis was obtained in all subjects. There was just clinical futility of this arm of the protocol as written that was not detected in the small pilot trial performed using this protocol. A new arm 3 will replace the old Tegaderm™ only arm in this present revised protocol. This new arm 3 will use a QuikClot® pad under a TR Band® with 30 minutes of compression. We have a large successful anecdotal experience of using a QuikClot® pad under a TR Band® with 30 minutes of compression. Other hemostatic pads have been successfully used under a TR Band® [17, 18]. As we have a large anecdotal successful experience of 30 minutes of compression with QuikClot® Radial and QuikClot Interventional Pads under a TR Band®, we choose a compression time of 30 minutes for the QuikClot®/TR Band® arm.

Although the TR Band® radial compression device has been used for years as the standard of care for hemostasis after TRA, there is no "standardized" compression/weaning technique. In a previous study, we used 40 minutes of compression with the TR Band® and then began weaning. 50% of subjects had to have air re-inflated upon the initial weaning of the TR Band®.[15] Carrington reported that a 1-hour commencement of TR Band® weaning following TRA appears to be safe, with an 84% success rate.[19] Because of this, the TR Band® in this study will be inflated for 60 minutes of compression without weaning, and then weaned over the next 60 minutes to hopefully achieve a high rate of hemostasis with a low rate RAO.

Potential risks may include: bleeding, pseudoaneurysm formation, hematoma, radial artery occlusion, local skin reaction (redness, swelling, and rash), pain, and numbness. Subjects may or may not have some or all of these risks from treatment with either one of the devices used in this study. The risks for the use of the *QuikClot® Radial®* pad are the same as for standard of care with TR Band®.

There may be an immediate potential benefit to patients. Application of the *QuikClot® Radial®* pad may shorten the time of compression compared with the standard of care TR Band®. Shorter radial artery compression times have been associated with less radial artery occlusion, thus potentially reducing the incidence of post-procedural radial artery occlusion. The light compression with either a Coban™ may help maintain patent hemostasis. Patient discomfort may also be reduced by shorter compression times and lower compression pressure.

1.6. Anticoagulation

For diagnostic cardiac catheterization using TRA in this study, a heparin dose of 70 units/kg will be used, with a minimum of 4000 units and a maximum of 7000 units. For PCI, additional heparin to attain an ACT of > 250 – 300 seconds will be used, or bivalirudin at standard FDA approved doses described in the package insert may be used at the operator's discretion. The option of continuing a heparin or bivalirudin infusion after the PCI will be at the operator's discretion.

2. Study Objectives

The objective of this study is to evaluate the safety and efficacy of a kaolin–based *QuikClot® Radial®* pad combined

with either a Coban™ bandage or TR Band® to achieve hemostasis after TRA, compared with 'standard of care' mechanical compression with the TR Band®, with the aim to hopefully develop a safe and possibly superior hemostatic method after transradial access, thus improving patient care by optimizing radial hemostasis management.

3. Study Design

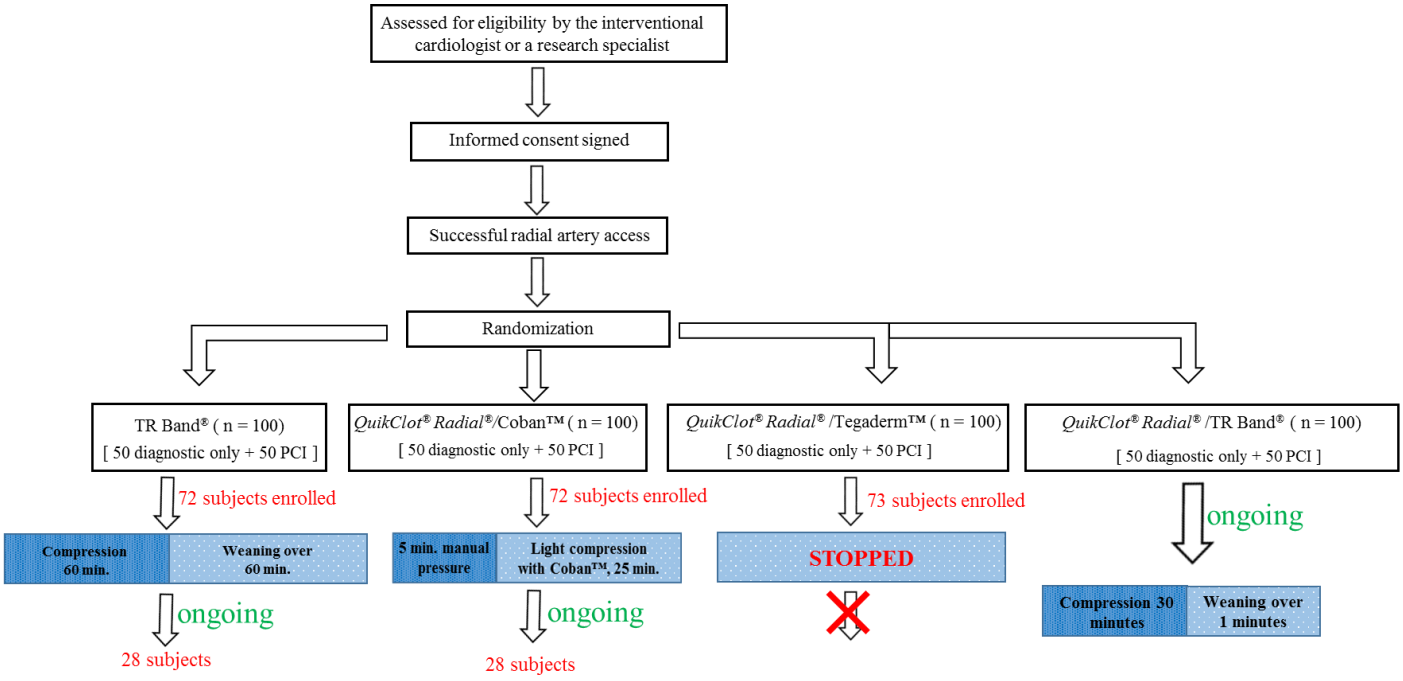
3.1. General Design

The SPIRIT (Standard Protocol Items for randomized Trials) recommendations were followed in preparing the protocol.[20, 21] The study is a single center, prospective, randomized, controlled trial with three arms (below) to compare hemostasis times and potential complications after TRA in patients undergoing diagnostic cardiac catheterizations and/or PCI.

Arms	Assigned Interventions
TR Band®: Hemostasis will be achieved by TR Band® after the transradial procedure. TR Band® will be applied over the arteriotomy site for 60 minutes and weaned over the next 60 minutes.	Device: TR Band®, Terumo
***QuikClot® Radial®* pad + Coban™:** Hemostasis will be achieved by the *QuikClot® Radial®* pad secured with a Coban™ after the transradial procedure. 5 minutes of initial manual compression will be applied on the *QuikClot® Radial®* pad/Coban™ bandage, followed by 25 minutes of light compression with the Coban® bandage only. The Coban™ bandage is then removed, and a Tegaderm™ dressing is applied over the *QuikClot® Radial®* pad, to be removed the following morning.	Device: QuikClot® Radial® pad, Z-Medica, LLC. Coban™, 3M
***QuikClot® Radial®* pad + TR Band®:** Hemostasis will be achieved by the *QuikClot® Radial®* pad with a TR Band® inflated with 8-10 cc of air after the transradial procedure. The QuikClot® Radial® pad is placed over the access site and covered by a Tegaderm™ dressing, then a TR Band® will be applied over the *QuikClot® Radial®* pad/Tegaderm™ for 30 minutes, then deflated within 1 minutes, followed by the Tegaderm™ dressing covering the *QuikClot®* pad until the following morning.	Device: QuikClot® Radial® pad, Z-Medica, LLC. Tegaderm™, 3M

Up to now, 217 subjects have been enrolled in this trial per the previous version of this protocol, including 73 in the QuikClot®/Tegaderm™ arm, 72 in the TR Band® only arm, and 72 in the QuikClot®/Coban™ arm. This amended protocol will continue enrolling a total of 100 subjects for both the TR Band® only and the QuikClot®/Coban™ arms, respectively. The new arm 3, QuikClot®/TR Band®, will also enroll a total of 100 subjects. In this amended protocol, a total of 373 subjects will be enrolled, including the 217 that have been enrolled in the prior version of the protocol, and an additional 156 subjects enrolled in this amended protocol. Randomization of the 156 subjects in the amended protocol will continue into the 3 cohorts. As 100 subjects will be needed to fill the new Arm 3, QuikClot®/TR Band®, and only 28 subjects will be needed to fill each of Arms 1 and 2, i.e. the TR Band® and QuikClot®/Coban™ Arms,arms 1 and 2 will fill well before the new Arm 3. After Arms 1 and 2 are filled, participants assigned to Arms 1 and 2 will be considered screen failures. All screen failures in this revised protocol will be assigned into the new Arm 3, the QuikClot®/TR Band® arm. As the old arm 3 is terminated, future participants randomized into arm 3 will be considered screen failures, as our REDCap data base will consider them in the old Arm 3. All screen failures that occur during randomization in the additional 156 subjects in this revised protocol will be assigned to the new Arm 3. An example of this would be a subject randomized to Arm 1 (TR Band®) who is a diagnostic cath only, and the 50 diagnostic only cases in Arm 1 are already filled. This subject would then be assigned to new Arm 3, the QuikClot®/TR Band® arm. Another example would be a participant randomized to Arm 3. As the old Arm 3 from the prior protocol is now closed, any

subsequent participants randomized to Arm 3 will be considered screen failures, and will be assigned to the new Arm 3 of this revised protocol. Each arm of 100 patients will include 50 diagnostic-only cardiac catheterizations and 50 PCIs. Simultaneous accrual of diagnostic-only cardiac caths and PCIs will occur.



Scheme 1. Proposed workflow for two compression devices: *QuikClot® Radial®* pad and TR Band®

3.2. Primary Study Endpoints

3.2.1. Initial successful hemostasis: Initial successful hemostasis is defined as no evidence of external bleeding from the TRA puncture site or expanding hematoma of the forearm after completion of the above described TR Band® and *QuikClot® Radia®* pad protocols, without the need for reinflation of air in the TR Band® or reapplication of manual pressure over the *QuikClot® Radial®*pad secured with a Coban™ bandage, or use of manual compression over the arteriotomy site. If an EASY grade class 1 forearm hematoma (see below section 3.3.3) develops while either hemostatic device is in place and is successfully treated without altering the weaning protocol of either device (i.e. the need for reinflation of air upon weaning the TR Band® or manual recompression of the *QuikClot® Radial®* pad after the initial 5 minute hold), this will be considered successful hemostasis.

3.2.2. Total time to hemostasis: Total time to hemostasis will be calculated as the time needed from sheath removal to achieving complete hemostasis, as described below:

For the *QuikClot® Radial®* pad + Coban™ bandage arm, total time to hemostasis includes the initial 5

minutes of manual compression and 25 minutes of light compression with the Coban™ bandage, and plus any additional protocol directed recompression time needed to obtain complete hemostasis.

For the *QuikClot® Radial®* pad + TR band® arm, total time to hemostasis includes the initial 30 minutes of compression plus 1 minute of weaning, and any additional protocol directed recompression and/or weaning times needed to obtain complete hemostasis.

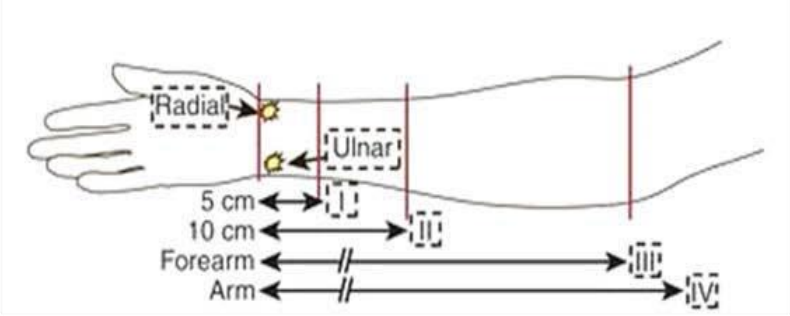
For the standard of care TR Band® arm, total time to hemostasis includes the initial 60 minutes of compression plus 60 minutes of weaning, plus any additional protocol directed recompression and/or weaning time needed to obtain complete hemostasis.

3.3. Secondary Study Endpoint

3.3.1. Radial artery occlusion (RAO): RAO will be assessed one to two hours after completed hemostasis, using the reverse Barbeau's test.[20] Completed hemostasis in the TR Band® cohort will be after the device is removed and the puncture site is covered with a Band-Aid or a dry gauze pad under a Tegaderm™ dressing without further bleeding/oozing from the access site or development of a forearm hematoma. Completed hemostasis in the *QuikClot® Radial®* pad/Coban™ cohort is defined as no further bleeding/oozing or development of a forearm hematoma after the Coban™ bandage is removed and the *QuikClot® Radial®* pad is secured with a Tegaderm™ dressing. Completed hemostasis in the QuikClot®/TR Band® cohort will be after the TR Band® is removed without further bleeding/oozing at the access site or development of a forearm hematoma. RAO is evaluated one to two hours after completed hemostasis based on previous findings which demonstrated the highest incidence of RAO immediately after band removal.[11]

3.3.2. Patient comfort/pain: Patients will be asked to rate their comfort level associated with the hemostatic device they have been assigned. A verbal numeric rating scale (VNRS) will be utilized to evaluate patient comfort with each device. This scale will use a 0 to 10 numeric rating to assess overall discomfort or pain related to the access site compression with each device, where 0 indicates no discomfort or pain at all and 10 indicates the worst pain the patient can imagine. The research coordinator will review the VNRS with each patient just prior to assessment of radial artery patency with the reverse Barbeau's test.[20] The research coordinator will record the patient's response.

3.3.3. Access site complications: Complications related to the device will be followed up to resolution or discharge, whichever comes first. Research staff will observe and record bleeding and hematomas that occur related to the access site. The severity of bleeding and forearm hematoma will be recorded using the criteria of the Early Discharge after Transradial Stenting of Coronary Arteries (EASY) classification.[21] See Figure below for radial artery hematoma classification. Cases of device failure, procedural difficulties, and evidence of vascular complications associated with the closure procedure will be recorded, and appropriate therapy will be given.



Radial Artery Hematoma Classification				
Grade I	**Grade II**	**Grade III**	**Grade IV**	**Grade V**
• < 5 cm • Access site related (distal to elbow)	• 5–10 cm • Access site related (distal to elbow)	• > 10 cm • Access site related (distal to elbow)	• Proximal to elbow (nonaccess site related)	• Compartment syndrome

4. Subject Selection and Withdrawal

4.1. Inclusion Criteria

1. Patients undergoing CC and/or PCI via the radial artery as part of their standard of care treatment
2. Patients able and willing to give written informed consent
3. Patient $\geq$ 18 years of age

4.2. Exclusion Criteria

1. Patients presenting with acute ST segment elevation myocardial infarction (STEMI)
2. Oral anticoagulation therapy as described below:
    a. If on a DOAC (direct acting oral anticoagulants – ie dabigatran, rivaroxaban, apixaban, endoxaban), patients will be excluded if DOAC taken within 48 hours and eGFR > 30 ml/min or DOAC taken within 72 hours and eGFR $\leq$ 30 ml/min.
    b. If patient is on warfarin, excluded if INR > 1.5
3. Liver Failure
4. Life threatening illness that patient would not be expected to live more than 6 months post procedure
5. Major unanticipated event in the cardiac cath lab (i.e. cardiac arrest) of an already consented patient, but before randomization, where the operator believes participation in this trial is now inappropriate.

6. Thrombocytopenia, with a platelet count of < 75,000.

4.3. Subject Recruitment and Screening

All eligible subjects undergoing transradial coronary procedures from our hospital will be recruited directly by the investigators and research staff. The subjects will be asked in the pre-procedural unit if they wish to participate in this study comparing the two FDA approved hemostatic devices at the completion of their radial artery access procedure. The investigator or his qualified designee will then obtain written informed consent according to ICH GCP (International Conference on Harmonization Good Clinical Practice). The completed consent forms will be retained by the Investigator and a copy of the consent form will be provided to the study participant.

4.4. Method for Assigning Subjects to Treatment Groups

Subjects undergoing CC and/or PCI via the radial artery as part of their standard of care treatment, and who have signed informed consent, will be randomized in the cardiac cath lab upon completion of their procedures. The REDCap randomization tools will be used to facilitate randomization. A statistician will create a random allocation table (randomization list) that will be uploaded into the REDCap project. The statistician will generate the random allocation table according to study design specifications as determined by the statistician and principal investigator. Participants will be randomized when the research coordinator enters a participant's REDCap record and clicks the "Randomize" button before sheath removal by the physician. Clicking this button triggers REDCap to check the allocation table and display the group to which the participant should be randomly assigned. This assignment is permanent and not editable within the participant's record and, like all other activity within REDCap, is tracked and not modifiable in the audit log. All subjects randomized into the old arm 3 (QuikClot®/Tegaderm™) by REDCap will be considered screen failures, and all screen failed subjects per this amended protocol will be assigned into the new arm 3 (QuikClot®/TR Band®), and a data collection instrument for the new arm 3 will be developed and added to the REDCap for this trial.

4.5. Compliance Monitoring

The protocol will be monitored for compliance by the Principal Investigator with oversight by the Office of Human Research (OHR)'s Monitoring and Compliance Officer. The task of the study monitor is to guarantee the best conduct of the study through frequent contacts by phone and in person with the responsible Investigator and research nurse/specialist, in accordance with the Monitor's Operating Procedures, with the purpose of facilitating the work and fulfilling the objectives of the study.

The *QuikClot® Radial®* pad compression device and Coban™ bandages will be stored in a locked area and access will be limited to the research team. The *QuikClot® Radial®* pad compression device and Coban™ bandages will be only used as described in this trial. Subjects will receive the *QuikClot® Radial®* pad compression device and Coban™ bandages without charge.

5. Study Procedures

Participation in the study will involve two clinical visits as follows:

5.1. Visit 1 –At time of Standard of Care Cardiac Catheterization and/or PCI

All subjects will be closely monitored for bleeding from the radial artery access site. Monitoring will be continued until complete hemostasis from the radial artery has been achieved. Use of reapplication of the *QuikClot® Radial®* pad or a TR band® will be at the discretion of the investigator if hemostasis is not achieved at the end of compression period. One hour after complete hemostasis, the numeric analog pain scale will be administered and recorded by

the research coordinator, and then radial artery patency will be assessed by the research coordinator using the reverse Barbeau's test.[20]

The research coordinator will then:

- Schedule a phone call (or bedside visit, if applicable, for those subjects still in the hospital) for Visit 2.
- Instruct the subject to call the research coordinator the day after enrollment to notify the research team of any occurrence of adverse events related to the application of either device. The subject may leave a message on the research coordinator's voicemail, if the research coordinator is not able to answer the telephone, with their condition and any adverse events. The voicemail will be checked daily. For any perceived serious adverse event by the subject, they should call the interventional cardiologist who performed the procedure or seek emergency care.

5.2. Visit 2-One day after enrollment

For subjects who are still in the hospital, the research coordinator will visit the subjects in their hospital room the day after the procedure, to assess the subject's condition and adverse events related to application of either hemostatic device. For patients who are already at home the day after their procedure, the research coordinator will contact the subjects by telephone one day after TRA to assess the subject's condition and adverse events related to application of either hemostatic device. If it is on weekend, the research coordinator will contact the subjects by telephone the next business day. For those subjects who cannot be reached by telephone on the first attempt, the research coordinator will make three attempts, once daily, to reach the subjects.

6. Safety and Adverse Events

6.1. Definitions

Adverse Event: An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event: Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient

hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

6.2. Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. Only SERIOUS ADVERSE EVENTS will be reported on for this study.

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

6.3. Recording of Adverse Events

All serious adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome.

6.4. Reporting of Serious Adverse Events

Reports of all serious adverse events (including follow-up information) will be submitted to the IRB within 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the Principal Investigator's binder. The funding sponsor of *QuikClot*® *Radial*® pad will be notified of serious adverse events related to the device (FDA Medwatch report).

7. Data Handling and Record Keeping

7.1. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

7.2. Data Management

Data management will be managed by OHR of Memorial Healthcare System. Study data will be collected and managed using REDCap electronic data capture tools hosted at OHR of Memorial Healthcare System. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. .

7.3. Sample Size and Statistics

Based on the previous study[17] on the use of TR Band® and our pilot study on the *QuikClot® Radial®* pad with either a Coban™ bandage or Tegaderm™ dressing for radial hemostasis, we anticipate an average initial successful hemostasis rate of 95% or higher in patients using the *QuikClot® Radial®* pad compression device, compared to an initial successful hemostasis rate of 84% in patients using the TR Band®, and no significant differences between the two *QuikClot® Radial®* pad arms. Using a type 1 error of 0.05 for each of the two comparisons of the *QuikClot® Radial®* pad with the TR Band® and power of 80% to detect an 11% difference in the rate of initial successful hemostasis between the TR Band® arm and either *QuikClot® Radial®* pad arm, a sample size of 100 will be needed for each of the three arms of the trial. Assuming that there may be a 50% screen failure rate (patients withdraw, ulnar access is used, radial access failure, events occur during the procedure that the investigator does not wish to enter the subject or the diagnostic only cases of the study are already filled), a total of up to 600 consecutive subjects undergoing transradial diagnostic cardiac catheterization and/or PCI, who sign informed consent to participate, will be recruited into the three arms of the trial.

An interim analysis was not originally planned for the study, but was conducted after enrolling 186 participants. The results obtained from the interim analysis showed that there was a failure to obtain initial hemostasis at 5 minutes in approximately 30% of the subjects in the QuikClot®/Tegaderm™ arm of the protocol, compared to a failure to obtain initial hemostasis of 11% in the TR Band® cohort (odds ratio = 3.2, 95% CI, 1.2 – 8.1, $p = 0.013$) and a failure to obtain initial hemostasis of 8% in the QuikClot®/Coban™ cohort (odds ratio = 4.7, 95% CI, 1.7 – 12.1, $p = 0.003$). Our DSMB committee reviewed the results and recommended to stop the Tegaderm™ only arm. We here institute a new arm 3 using a QuikClot® Radial® Pad under a TR Band® with 30 minutes of compression to replace the old arm 3 in this trial. The sample size of the new arm 3 is the same as the old arm 3, with 100 participants including 50 diagnostic-only cardiac catheterizations and 50 PCIs.

Statistical summaries and analyses of data will be performed at Memorial Healthcare System. Descriptive analysis will be performed for all data including means and standard derivation or medians for continuous variables and proportions for categorical variables. The t-test will be used to describe the differences of clinical outcomes between the two compression devices after TRA, and a two-sided p-value of 0.05 will be considered to be statistically significant.

7.4. Dissemination Plan

The principal investigator and co-investigators of this study will be responsible for ensuring the results obtained from this study, irregardless of the outcomes, to be reported to Schulman Institutional Review Board (IRB) within a reasonable timeframe after conclusion of the study.

8. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject, and the investigator-designated research professional obtains the consent.

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10. Lists of abbreviations

TRA, Transradial Access
CC, Cardiac Catheterization
PCI, Percutaneous Coronary Intervention
FDA, Food and Drug Administration
RA, Radial Artery
FA, Femoral Artery
RAO, Radial Artery Occlusion
VNRS, Verbal Numerical Rating Scale
STEMI, ST segment elevation myocardial infraction DOAC, Direct acting Oral Anticoagulants
eGFR, Estimated Glomerular Filtration Rate
AE, Adverse Event
IRB, Institutional Review Board
HIPAA, Health Insurance Portability and Accountability Act
PHI, Protected Health Information
CRF, Case Report form
INR, International Normalized Ratio
ACT, Activated clotting time
US, United States
REDCap: Research Electronic Data Capture