# COVER PAGE

## STUDY TITLE: RAVE: Radial Artery Vascular complication and rEsource utilization in subjects undergoing an angiogram/PCI (Percutaneous Coronary Intervention)

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# AURORA HEALTH CARE, INC.

**PROTOCOL TITLE:** RAVE: **R**adial **A**rtery **V**ascular complication and r**E**source utilization in subjects undergoing an angiogram/PCI (Percutaneous Coronary Intervention)

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**This protocol was designed and developed by Aurora Healthcare, Inc. It is intended to be used only in conjunction with institution-specific IRB approval for study entry.**

# I. Background and Rationale

Transradial catheterization has been steadily increasing over the years due to reports of lower incidence of bleeding and vascular complications,[1] decreased cost,[2] and improvements in patient satisfaction [2,3] when compared to the transfemoral approach. While the complications associated with the transfemoral approach are reduced by using transradial catheterization, there are unique challenges associated with the use of the transradial approach that require development of evidenced-based practices to allow the cath lab and post procedure staff to manage and prevent these issues.

The most predominate issue associated with transradial catheterization is radial artery occlusion, although it is often asymptomatic due to dual collateral perfusion to the hand.[4] Radial artery occlusion occurs when thrombus forms in the artery that blocks antegrade blood flow, thus precluding future use of the radial artery for procedures. Risk of radial artery occlusion has been associated with use of anticoagulation (i.e., heparin) during the procedure,[5] repeat entry,[6] low radial artery to sheath diameter ratio,[7] and prolonged high-pressure compression to achieve hemostasis.[8]

'Patent' hemostasis, which is the adjustment of pressure using a hemostasis band to stop bleeding without obstructing radial artery flow, has been shown to reduce the occurrence of radial artery occlusion by 75% at 30-days post procedure versus use of hemostasis bands without evaluation of radial artery flow in a randomized clinical trial.[9] Unfortunately, the use of high amounts of anticoagulation during the procedure may render this method ineffective at preventing bleeding at the insertion site. Additionally, the use of these devices requires restriction of wrist movement which may be uncomfortable for the patients. Finally, this approach requires significant monitoring on the part of the cath lab personnel in order for it to be effective.

Hemostatic patches have been suggested as an alternative approach to reduce the time associated with reaching hemostasis, thereby reducing the prolonged application of compression. Current hemostatic patches are coated with a marine toxin, thrombin, or biopolymer to promote rapid hemostasis at the access site.[10] Results of clinical trials using chitosan-based hemostatic pads have shown these products to be effective at reducing time to hemostasis with minimal complications when used following transradial catheterization.[11-12] In a study that randomized 75 participants to either a hemostatic band using the recommended instructions, hemostatic band using a fast-track approach, and chitosan-based pad, Fech et al. (2012) observed a significant reduction in time to hemostasis when a chitosan-based pad was applied versus use of the hemostatic band per manufacturer instructions without an increase in vascular complications.[11] There was no significant differences observed between using the chitosan-based pad and a fast-track approach developed for use of the hemostatic band. In a larger study of subjects (N=600) randomized to either a hemostatic band or chitosan-based pad, the investigators reported that use of the chitosan-based pad significantly reduced the incidence of radial artery occlusion at the time of discharge as well as at 30-day follow-up. Additionally, they observed a significant decline in time of compression, although this was not a primary endpoint of the study design.[12] No studies have been conducted that have looked at patient

satisfaction or cath lab staff involvement related to the use of hemostatic pads in this patient population.

The SoftSeal®-STF hemostatic pad (Chitogen, Inc.) is an FDA-approved, chitosan-based, non-woven pad with a unique, proprietary fiber structure that when hydrated with tissue fluids forms a gel-like synthetic clot. It's mechanism of action is believed to be due to bioadhesion between the chitosan polymer chains, which are positively charged, and the negatively charged blood and tissue components.[13] Several studies have supported the safety of using chitosan-based products for achieving hemostasis and wound healing.[14-16] Additionally, results of a small pilot study (N=30) to determine efficacy of the SoftSeal®-STF hemostatic pad to control bleeding in patients who underwent transradial catheterization showed that average hold time was 13.3 minutes (12-22 minutes) to achieve hemostasis and no complications due to excess bleeding or hematoma were observed.[17]

In summary, radial artery occlusion is a complication associated with transradial catheterization that can be prevented by reducing time of compression required to reach hemostasis. Mechanical compression devices that apply pressure at the insertion site do not lead to radial artery occlusion when used to achieve 'patent' hemostasis, but may not be effective for preventing bleeding when high levels of anticoagulation are used. Additionally, use of these devices may result in discomfort to the patients due to restrictions of wrist movement. Currently marketed chitosan-based hemostatic pads have been shown to be at least as efficacious in achieving hemostasis following transradial catheterization as the use of a hemostatic band, but questions still remain as to whether improvements in time of compression and vascular complications can be reliably realized. Additionally, no studies have compared patient satisfaction and quality of life between the different types of devices used.

The results of this study will be used to develop evidenced-based practices and guidelines to reduce complications unique to transradial catheterizations. The researchers anticipate that use of the SoftSeal®-STF hemostatic pad with a vascular compression device will result in improved time to hemostasis as well as reductions in vascular complications. These results may lead to increased overall satisfaction among patients as well as cath lab staff responsible for managing these patients. Finally, use of the SoftSeal®-STF hemostatic pad may benefit the healthcare community by further reducing the time to discharge and cost associated with providing care to patients undergoing transradial catheterization.

## II. Study Objectives

III. The primary objective of this study is to determine if there is a reduction in time to hemostasis in subjects treated with SoftSeal®-STF hemostatic pad when used in conjunction with a vascular compression device after radial transcatheter procedure.

Secondary objectives of this study include:

- Assessment of procedure-related measures of patient satisfaction following use of the SoftSeal®-STF hemostatic pad with vascular compression devices.

- Assessment of vascular complications due to bleeding associated with transradial catheterization.

We hypothesize that:

- The use of SoftSeal®-STF hemostatic pad when used with vascular compression devices will be associated with a significant reduction in time to hemostasis and a decrease in vascular complications of radial artery occlusion.

- Decrease in time to hemostasis will allow for an earlier patient discharge and increase in staff productivity. This in combination with the low incidence of vascular complications will lead to overall patient satisfaction.

## IV. Study Design

This is an open-label, prospective clinical study to evaluate the SoftSeal®-STF hemostatic pad when used with a vascular compression device. The first 100 patients enrolled into the study will receive the SoftSeal®-STF hemostatic pad and the RadAR EasyCLik. After successful completion of the first 100 then the next 100 patients enrolled will receive the SoftSeal®-STF hemostatic pad and the TR BAND® Radial Compression Device.

Data from the SoftSeal®-STF hemostatic pad with compression devices (RadAR EasyCLik and TR BAND®) will be compared to data previously collected for study purposes to the SoftSeal®-STF hemostatic pad alone using manual compression and those who received VascBand™ Hemostat.

## V. Selection and Withdrawal of Subjects

Subjects will be recruited from Aurora Health Care sites

Subjects will be required to provide informed consent and meet all inclusion/exclusion criteria prior to being enrolled in the study listed below.

### a. Inclusion Criteria

- ≥ 18 years
- Scheduled for an angiogram/PCI
- Planned transradial approach

### b. Exclusion Criteria

- Evidence of impaired dual perfusion to the hand when tested using Allen's test
- Inaccessible radial arteries due to anatomic variations
- Infection or other skin disorder at the puncture site

- Undergoing an emergent or unplanned angiogram using the transradial approach
- Evidence of severe cognitive impairment or inability to understand the study procedures and answer follow-up questions
- Known sensitivity or allergic reaction to materials in the study devices
- Unwilling to participate in the study and follow all study-related procedures
- Participating physician deems the subject to not be a good candidate
- Inability to achieve radial access

Subjects may be withdrawn from the study at the request of the participating physician or the Principal Investigator due to non-compliance with the study protocol. Subjects may also request withdrawal from the study at any time by notifying the Principal Investigator or designee without reason or prejudice to treatment. If a subject is withdrawn from the study, any data collected up to the point of the withdrawal will be retained in the study file. No new data will be collected.

## VI. Study Devices

The medical device to be assessed in this protocol is the Softseal®-STF hemostatic pad (Chitogen, Inc.). The SoftSeal®-STF hemostatic pad (Chitogen, Inc.) is an FDA-approved, chitosan-based, non-woven pad with a unique, proprietary fiber structure that when hydrated with tissue fluids forms a gel-like synthetic clot.

In this study the RadAR EasyCLik and TR BAND® Compression devices will be used with the SoftSeal®-STF hemostatic pad to promote hemostasis at the puncture site. Data previously collected for study purposes utilizing the VascBand™ Hemostat will also be included in the final analysis. All vascular compression devices are FDA approved.

## VII. Experimental Design and Methods (or Study Procedures)

Patients will be identified for potential enrollment in this study from the cath lab schedules at Aurora Health Care. The potential subject medical record will be screened to determine eligibility. Patients found to be eligible will be considered for enrollment and may be contacted prior to the procedure to assess interest in participation. See Table 1 for a schedule of study events.

### a. Screening

Potential subjects identified from the cath lab schedule may be contacted by a research coordinator who will explain the study, answer questions, ascertain interest in participating in the study, and screen for inclusion/exclusion criteria.

### b. Day of Cath Lab Procedure

On the day of the scheduled procedure, a research coordinator will approach potential subjects and obtain informed consent. The signed informed consent form

will be placed in the subject's electronic medical record. A Barbeau test will be performed prior to the procedure.
The subject will undergo their scheduled transradial catheterization in accordance with cath lab protocol. Point of care activated clotting time (ACT) will be assessed prior to applying the hemostatic device. Demographic and medical history data will be collected by the research coordinator and included on the data collection form. Intra and post procedure data will be collected by the cath lab/post procedure staff. The research team will review the electronic medical record (EMR) and reference the procedure log along with the post procedure charting on the flowsheets to collect all of the data and information listed on the data collection forms.

Hemostasis will be obtained with the SoftSeal®-STF hemostatic pad and a vascular compression device.

The SoftSeal®-STF hemostatic pad will be applied over the puncture site and the vascular compression device placed to hold the pad gently in place over the puncture site.

The physician will remove the sheath and follow manufactures recommendation for vascular compression device. A small amount of blood (< 0.2 mL) should contact the surface of the hemostatic pad.

The compression device will remain in place for 30 minutes. After 30 minutes the vascular compression device will have pressure gradually reduced over 5 minutes being careful not to dislodge the SoftSeal®-STF hemostatic pad. Once all the air is removed, the site with the vascular compression device in place will be observed for an additional 5 minutes. If no bleeding is observed, the vascular compression device will be removed.

In the event of bleeding, do not remove vascular compression device or SoftSeal®-STF hemostatic pad. Tighten Easyclik ™ or reinflate TR Band ®. Continue to monitor patient with device in place for an additional 30 minutes, then reattempt removal process. If after the additional 30 minutes, SoftSeal®-STF hemostatic pad is saturated from excessive bleeding, initiate standard of care treatment.

In the event of hematoma, notify physician for additional guidance.

Post procedure, staff will perform a reverse Barbeau to assess the subjects for vascular complications (e.g., bleeding, hematoma), hemostatic device-related complications (e.g., rash, ischemia), and subject report of access site pain utilizing the Pain Assessment Visual Analog Scale (VAS) rating on a scale of 1 to 10 prior to discharge. Data associated with post procedure activities will be recorded as indicated on the data collection tool.

### c. Telephone Assessment (day 3 +/- 1 day)

Subjects will be contacted via telephone (or in person if in-patient). The staff will assess for subject-reported complications, discomfort, and pain utilizing the Pain Assessment Visual Analog Scale (VAS) rating on a scale of 1 to 10. Results of this assessment will be recorded on the data collection tool.

### d. Post Procedure Follow-Up Visit (within 45 days)

Subjects will be scheduled for an in-person follow-up visit. During this follow-up visit, staff will assess for subject-reported complications, discomfort, and pain utilizing the Pain Assessment Visual Analog Scale (VAS) rating on a scale of 1 to 10. In addition, an Allen's test will be performed to determine radial artery patency and overall patient satisfaction will be evaluated.

### e. Chart Review- 30 Day Follow up

A medical chart review will be conducted by a member of the study team in order to determine if the subject returned to the hospital within 30-days of the procedure for a vascular-related complication associated with the radial access site.

Table 1: Schedule of Study Events

| **Study Procedure** | Screening | Day of Procedure | Prior to Discharge | Telephone/ In person contact 3d, +/-1d | Office visit within 45d | Chart review |
|---|---|---|---|---|---|---|
| Inclusion/exclusion | **X** | **X** | | | | |
| Informed consent | | **X** | | | | |
| Medical history/ demographics | | **X** | | | | |
| Medication History | | **X** | | | | |
| Allen's Test | | | | | **X** | |
| Barbeau/ Reverse Barbeau Test | | **X** | **X** | | | |
| Perform transradial angiogram | | **X** | | | | |
| ACT assessment | | **X** | | | | |
| Application Hemostasis product | | **X** | | | | |
| Adverse event(s), | | **X** | **X** | **X** | **X** | **X** |
| Access site assessment | | | **X** | **X** | **X** | |
| Patient Satisfaction Assessment | | | | | **X** | |

## Statistical Considerations

## a. Endpoints

- The primary endpoint for this study is Time to hemostasis. This is defined as the time interval in minutes beginning with sheath removal and ending with removal of hemostatic device and/or observed hemostasis

The secondary endpoints for this study are:

- Rate of acute radial artery occlusion post procedure
- Major access site bleeding defined as a ≥ 3 mg/dL drop in hemoglobin, or required blood transfusion or vascular repair to control bleeding prior to discharge
- Minor access site bleeding defined as light bleeding without hematoma formation prior to discharge
- Minor access site bleeding defined as light bleeding without hematoma formation at 30day f/u
- Hematoma formation that is ≥ 3 cm in diameter prior to discharge
- Pain at access site as measured on a numeric scale of 1-10 prior to discharge
- Pain at access site as measured on a numeric scale of 1-10 reported at follow up visits
- Evidence of hand/digit ischemia defined as pain, tingling, or numbness in the hand and/or fingers reported Pre-discharge
- Evidence of hand/digit ischemia defined as pain, tingling, or numbness in the hand and/or fingers reported on follow-up
- Readmission for vascular complication within 30-days
- Bruising, swelling, or redness at or near access site reported on follow-up

## b. Statistical Hypotheses – Primary Endpoint

The statistical hypothesis for the primary endpoint is that time to hemostasis with both the RadAR EasyCLik and TR BAND® Compression devices will be significantly reduced with the use of SoftSeal®-STF hemostatic pad. In other words, the use of SoftSeal®-STF hemostatic pad will allow time to hemostasis to be reduced from a standard 2 hours with a vascular compression device (VascBand™ Hemostat) to 30 minutes. The null and alternative hypotheses for the primary endpoint are:

$H_0$: Time to hemostasis with vascular compression device + SoftSeal®-STF hemostatic pad $>30$ minutes

$H_1$: Time to hemostasis with vascular compression device + SoftSeal®-STF hemostatic pad $\leq 30$ minutes

## c. Sample Size – Primary Endpoint

We will analyze a convenient sample of two hundred patients with the SoftSeal®-STF hemostatic pad and vascular compression devices (RadAR EasyCLik and TR BAND®) to allow for parametric statistical methods. The first one hundred consecutive patients will be allocated to RadAR EasyCLik plus SoftSeal®-STF hemostatic pad while the following 100 consecutive patients will be allocated to TR BAND® Radial Compression Device plus SoftSeal®-STF hemostatic pad. Additional data on 100 subjects previously involved and collected for study purposes who received SoftSeal®-STF hemostatic pad alone and those who received VascBand™ Hemostat will be included in the final analysis.

## d. Statistical Methods

Baseline data will be summarized between the two treatment groups; including demographics, clinical history, bleeding risk factors, pre-procedure and procedure characteristics using descriptive statistics of n, mean, standard deviation, median, range, and interquartile range for continuous variables and frequency and proportions for discrete variables. Between groups comparisons for randomized subjects will be conducted using Chi-square or Fisher's Exact test (accordingly) for discrete variables and ANOVA or Kruskal-Wallis test for continuous variables.

Post-procedure information will be collected and summarized between groups using the same descriptive statistical methods as for baseline data.

Baseline and post-procedure univariate comparisons will be performed by a either a paired t-test or a Wilcoxon signed rank test if the variable of interest is continuous or by comparing proportions with either a Chi-squared or a Fisher's exact test. Differences between treatment arms will be compared with appropriate inferential statistical methods, depending on the outcome of interest. When comparing categorical outcomes, a logistic regression will be performed, when comparing continuous outcomes, a repeated measures ANOVA or repeated measures analysis will be utilized.

Adverse event and serious adverse event rates reported after randomization will be recorded. Adverse events and serious adverse events will be recorded for a period of 30 days from the time of randomization.

All statistical analyses will be performed using Stata version 15 (StatCorp, College Station, TX).

### e. Interim Analyses

An interim analysis will be performed on the first 25 enrolled subjects. Any alterations to the study design or sample size will be made based on the results of the interim analysis

## VIII. Data Management

### a. Data Collection and Processing

This research study plans to store and manage their entire dataset in Academic REDCap, a secure electronic data capture application that is based on Vanderbilt University's REDCap application. Flexible for a variety of types of research, Academic REDCap provides an intuitive data-entry interface for end users into study-specific data collection forms associated with study events. The application includes real time validation rules and query management, audit trails, and the automated export of study data into statistical programs. The Academic REDCap platform is compliant with GCP predicate rule requirements and US FDA 21 CFR Part 11 pertaining to the use of electronic records and signatures. Aurora Health Care, Inc. has executed an agreement for use of the application with nearly all research studies conducted at Aurora.

Access to data housed in Academic REDCap and associated with this research study will be limited to those individuals listed on the IRB approved research study, as well as caregivers from Research Analytics for administrative reasons. Study team members access to the system and the data itself will be limited in accordance with need (i.e., biostatisticians may be limited to simply export the dataset to statistical tools, research coordinators may be limited to entering data, etc.). Overall, limiting access to study team members by need should reduce the risk of accidental disclosure and breach of confidentiality. However, using a cloud-based application may incidentally raise the risk of a breach in confidentiality, and, therefore, Aurora Health Care, Inc. has negotiated strong protections with the vendor in the event of a breach of confidentiality.

### b. Data Review

An interim monitoring plan to perform periodic checks of the data will be reviewed by the Biostatisticians to determine measurement aspects, data integrity and accuracy, consistency with study objectives and hypotheses as well as preliminary analysis.

### c. Data Retention

Data will be retained by the Principal Investigator in a secure location by at Aurora Health Care for a period of 3 years following completion of all study-related activities and data collection. Data may be moved to an off-site storage location approved by Aurora Health Care during that time. The Principal Investigator is responsible for making sure that all essential documents related to the study are not damaged or destroyed. If for any reason the Principal Investigator withdraws his responsibility, the responsibility will be transferred to another individual within Aurora Health Care.

## IX. Potential Risks and Benefits

### a. Risks

Risks associated with the study are no more than those that may be encountered during standard of care for patients undergoing an angiogram using the transradial approach.

Risks associated with the use of the SoftSeal®-STF hemostatic pad include the following:

| | |
|---|---|
| Bleeding | Hematoma |
| Pseudoaneurysm | Rash |
| Swelling | |

The FDA approved labeling for the SoftSeal®-STF hemostatic pad does not include an allergic warning. Results of testing on chitosan-derived hemostatic products have shown them to be non-allergenic.[13] Although, some manufacturers of chitosan-based products recommend that patients with known allergies to shell-fish be cautious when using these products.

Risks associated with the use of the TR BAND® Radial Compression Device include the following:

| | |
|---|---|
| Allergic reaction | Hematoma |
| Vessel occlusion | Bleeding |
| Local venous thrombosis | Peripheral nerve damage |
| Regional pain syndrome | |

Use of the Vascular compression devices is contraindicated in patients who are hypersensitive to the materials in the device; have an infection or other skin disorder at the puncture site; and/or have an abnormal Allen Test, radial supply, or insufficient dual arterial supply.[18]

Use of vascular compression devices for unusually long periods of time may result in tissue damage. It is recommended that the arterial pulse distal to the compression site be monitored to ensure that total occlusion has not occurred.

There is also a risk of breach of confidentiality associated with being in this study. In order to mediate this risk, all subject data will be stored in a secure location that is only accessible to the principal investigator or approved designee(s). Subjects will be assigned a non-identifiable subject identification number at the time of enrollment and randomization. Information collected using the data collection form will be entered into an Excel spreadsheet stored on an Aurora-owned, password protected computer. Data within the spreadsheet will only be identified through the subject identification number. A code list linking the spreadsheet data to patient information will be created and stored on a separate Aurora owned computer that is only available to the principal investigator or approved designee(s).

### b. Benefits

Subjects may experience less discomfort due to an expected decrease in time to hemostasis.

Results of this study may also be generalizable to the larger healthcare community by informing standard of care guidelines for obtaining hemostasis following transradial catheterization. Improvements in standard of care as well as cost savings may be realized through reductions in vascular complications associated with the transradial approach as well as decreased time of direct nursing care and length of stay.

## X. Adverse Event Reporting

### a. Definitions

Adverse event: Any untoward medical occurrence, unintended disease or injury or untoward clinical signs in subjects, users, or other persons, whether or not related to the medical device.

Serious adverse event: Any adverse event that led to

- Death
- Life-threatening illness or injury
- Permanent impairment
- Prolonged hospitalization or change to inpatient status
- Requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment
- Fetal distress, fetal death, or congenital abnormality or birth defect

### b. Reporting Requirements

All observed or volunteered adverse events occurring from the time of randomization to 30-days post randomization will be recorded in the subjects'

case histories, regardless of the study group or suspected causal relationship. For all adverse events, sufficient information will be obtained in order to permit: 1) adequate determination of the seriousness, and 2) causal relationship of the adverse event. Adverse events or serious adverse events found to be a result of the treatment regimen will be followed until resolution of the adverse event.

Reportable adverse events include:

- Excessive Bleeding
- Hematoma
- Ischemia
- Infection
- Rash at access site

All adverse events and serious adverse events are to be reported to the Aurora Health Care Internal Review Board as outlined in the applicable policies.

### c. Assessment of Relationship

The Principal Investigator is responsible for assessing the relationship of the adverse event or serious adverse event to the treatment.

## XI. Informed Consent and Privacy Plan

In order to protect patient privacy, potential subjects will be identified by a research coordinator from the cath lab schedule at Aurora St. Luke's medical center. The research coordinators may also receive recommendations for potential candidates from participating physicians. Initial contact with potential subjects will be through direct phone contact with the patient. Informed consent will be obtained on the day of the procedure. The research coordinator will approach the potential subject in a private location (e.g., outpatient room, office). All standard of care and study-related procedures will be performed by cath lab staff or research coordinators using the same protocols and processes applied to patients who are not enrolled in a research study.

All study-related subject data and informed consent forms will be stored for a period of 3 years following the completion of all study-related activities and data collection. It will be stored in a secure location that is only accessible to the principal investigator or approved designee(s).

## XII. Quality Control and Assurance

Independent monitoring of the clinical study will be performed for protocol compliance at least once during the study conduct period. Continuing review will be submitted to the Aurora Health Care IRB on at least an annual basis.

## XIII. Regulatory Requirements

Approval from the Aurora Health Care IRB will be obtained to perform this study, which includes approval of all associated informed consent forms. All protocol modifications and

corresponding informed consent forms will be submitted for review and approval prior to implementing.

The Principal Investigator is responsible for ensuring that all study personnel have appropriate training and experience to perform the assigned duties.

The Principal Investigator will ensure that the study is performed in accordance with the approved protocol, and will document and report protocol deviations as required by the Aurora Health Care IRB policies.

This study will be listed on ClinicalTrials.gov prior to enrollment of subjects.

## XIV. Publication Policy

It is expected that the results of this study will be presented at professional meetings and published in peer-reviewed medical journals. The Principal Investigator will follow the authorship criteria established by the International Committee of Medical Journal Editors (https://www.icmje.org). The study authors will disclose financial any potential conflicts of interest in presentations and publications.

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