STUDY TITLE:

DISTAL VS PROXIMAL RADIAL ARTERY STUDY (THE DIPRA STUDY)

"Distal vs. Proximal Radial Artery Access for cardiac catheterization and intervention"

NCT04318990

Protocol IRB #: 019-504

PROTOCOL HISTORY

Date:	October 24, 2022; version 1.3
Principal Investigator:	**Karim Al-Azizi, MD**
Sub-Investigator(s):	**Srini Potluri, MD** **Chadi Dib, MD** **Molly Szerlip, MD** **Sameh Sayfo, MD** **Amr Idris, MD** **Jared Christensen, MD**
Statistician:	**Johanna van Zyl, PhD**
Data Management and Analyst:	**Jasjit Kaur Banwait, Ph.D.**

PROTOCOL SIGNATURE PAGE

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Protocol Number: N/A

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I have read this protocol and agree to adhere to the requirements outlined within. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will review and discuss this material with them and ensure they are fully informed regarding the requirements of this protocol. I will also ensure that this study is conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory agencies and their requirements.

_____

Clinical Investigator (Printed Name)

_____ _____

Clinical Investigator (Signature) Date

STUDY TEAM CONTACT INFORMATION

Name	Contact Information	Role on Study
Karim Al-Azizi, MD	Karim.AlAzizi@BSWHealth.org	Principal Investigator
Johanna van Zyl, PhD	Johanna.VanZyl@BSWHealth.org	Statistician
Jasjit Kaur Banwait, Ph.D.	jasjitkaur.banwait@BSWHealth.org	Data Management/Analyst

Table of Contents

ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
CABG	Coronary artery bypass grafting
CBC	Complete blood count
DASH	Disabilities of the Arm, Shoulder, and Hand Questionnaire
dRA	Distal radial artery
e-CRF	Electronic case report form
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Council for Harmonisation
IRB	Institutional Review Board
PCI	Percutaneous coronary intervention
PHI	Protected health information
PI	Principal Investigator
pRA	Proximal radial artery
SAE	Serious adverse event

SYNOPSIS

Summary/Rationale:	This single-center, prospective, randomized study will evaluate distal radial artery (dRA) vs. proximal radial artery access (pRA) in regards to hand function and radial artery occlusion.
Study Objectives:	Primary objective is to evaluate hand function following distal radial artery access compared to proximal artery access in patients undergoing cardiac catheterization. Hand function will be assessed by: • QuickDASH questionnaire • Hand grip test • Thumb forefinger pinch test utilizing a pinch gauge Secondary objectives: Vascular access success rates, hematoma, bleeding, complications of vascular access and radial artery occlusion.
Study Design:	Single-center, prospective, randomized, study
Study Intervention(s):	Distal and proximal radial artery access
Number of Subjects:	300
Inclusion Criteria:	A patient will be eligible for inclusion in this study if **he or she** meets **all** of the following criteria: 1. Age ≥ 18 years. 2. The distal and proximal radial artery must be palpable and non-occlusive flow must be confirmed by (Doppler) ultrasound. 3. Patient should be able to comply with the protocol. 4. Provide written informed consent before study participation.

Exclusion Criteria:	A patient will be ineligible for inclusion in this study if **he or she** meets **any** of the following criteria: 1. Obligatory femoral or proximal radial access 2. On therapeutic oral anticoagulation. 3. Previous ipsilateral forearm radial artery occlusion. 4. Very large hand/wrist anatomy that will preclude using the available hemostatic radial bands. 5. Enrollment in another study that competes or interferes with this study. 6. Poor clinical condition like cardiogenic shock, which prohibits pre- and post-procedural function tests. 7. Subject with planned complex PCI or procedure necessitating multiple intervention. 8. Any other condition or co-morbidity which, in the opinion of the investigator or operator, may pose a significant hazard to the subject if he or she is enrolled in the study. 9. History of stroke with residual deficit that affects hand function 10. Previous radial artery catheterization within 1 year.
Sponsor:	Baylor Scott and White Research Institute
Principal Investigator:	Karim Al-Azizi, MD
Primary Study Site/Data Center:	The Heart Hospital Baylor Plano 1100 Allied Drive | 5th Floor Research Dept. Plano, Texas 75093
Duration of Study:	2 years

4. INTRODUCTION

4.1 Background

Radial artery catheterization has established itself as a superior arterial access over femoral arterial access for cardiac and interventional vascular procedures given its safety and faster recovery for patients, Distal radial artery access has been of growing interest for cardiac catheterization as an alternative to conventional proximal radial artery access and femoral access especially in patients with prior CABG. Multiple reports, case series as well as small sized studies reported feasibility of the distal radial artery access in the anatomical snuff box of the hand. Distal radial artery access has theoretical advantages including utilizing the left arm to better assess CABG patients while maintaining good patient and operator ergonomics as well as eliminating the increased risk with femoral access. However, the distal radial artery is a smaller artery and runs in the hand close to the radial nerve, which raises the concern of hand function. Radial artery access has been known to have a very small risk of radial artery occlusion. The rate of radial artery occlusion in the distal radial artery is unknown. There are no studies comparing distal radial artery access to proximal radial artery access.

5. STUDY OBJECTIVES

The primary objective of this study is to evaluate hand function following distal radial artery access compared to proximal artery access in patients undergoing cardiac catheterization.

Hand function will be assessed by:

- QuickDASH questionnaire
- Hand grip test
- Thumb forefinger pinch test utilizing a pinch gauge

Secondary endpoints include success rates, hematoma, bleeding, rates of radial artery occlusion and complications of vascular access.

6. STUDY DESIGN

This is a prospective, randomized, single-center clinical trial.

This study will assess the outcomes of hand function utilizing the QuickDASH questionnaire, hand strength using the hand grip test, and the thumb and forefinger pinch using an electronic pinch gauge. Rates of radial artery occlusion in patients undergoing cardiac catheterization using dRA compared to pRA will be analyzed using ultrasound doppler at 1 month and 1 year.

Approximately 300 patients undergoing coronary angiography or angioplasty at The Heart Hospital Baylor Plano will be randomized 1:1 to distal or proximal radial access for cardiac catheterization.

7. ASSESSMENT OF HAND FUNCTION

Hand function will be assessed by the following:

1. *QuickDASH questionnaire*

The DASH outcome measurement is used around the world by clinicians and researchers as a tool for self-reported outcome concerning upper-limb musculoskeletal disorders (Hudak P). It consists of two components: symptom questions of 30 items with scores from 1 to 5, and optional high performance (sport/music or work) section of 4 items also with scores of 1 to 5.

The optional modules which concern sport, music or work are not used as those are mainly utilized to identify the specific limitations by professional athletes and performing artists or other group of workers.

This study will be using the abbreviated, QuickDASH questionnaire. The purpose of the QuickDASH is to use 11 items to measure physical function and symptoms. It decreases responder and data entry burden while maintaining a high degree of correlation to the original length DASH.

2. *Pinch grip by use of a pinch grip dynamometer*. Baseline® Mechanical Pinch Gauge (Baseline Medical, Quakertown, PA, USA) will be used to measure pinch force between thumb and forefinger. This device is CE certified and is commonly used by physiotherapists. It is utilized to evaluate tendon or nerve injury and neuromuscular disorders. Pinch strength will be recorded in kilograms.

3. *Hand Grip Test (using a Jamar Hand Hydraulic dynamometer)*

l8. STUDY POPULATION

The study population will consist of adult male and female patients undergoing cardiac catheterization at The Heart Hospital Baylor Plano.

8.1 Eligibility Criteria

8.1.1 Inclusion Criteria

A patient will be eligible for inclusion in this study if **he or she** meets **all** of the following criteria:

1. Age ≥ 18 years.

2) The distal and proximal radial artery must be palpable and non-occlusive flow must be confirmed by (Doppler) ultrasound.

3) Patient should be able to comply with the protocol.

4) Provide written informed consent before study participation.

8.1.2 Exclusion Criteria

A patient will be ineligible for inclusion in this study if **he or she** meets **any** of the following criteria:

1) Obligatory femoral or forearm radial access
2) Previous ipsilateral forearm radial artery occlusion.
3) Patient on therapeutic oral anticoagulation.
4) Very large hand/wrist anatomy that will preclude using the available hemostatic radial bands.
5) Enrolment in another study that competes or interferes with this study.

6) Poor clinical condition like cardiogenic shock, which prohibits pre- and post-procedural function tests.
7) Subject with planned complex PCI or procedure necessitating multiple intervention.
8) Any other condition or co-morbidity which, in the opinion of the investigator or operator, may pose a significant hazard to the subject if he or she is enrolled in the study.
9) History of stroke with residual deficit that affects hand function.
10) Previous radial artery catheterization within 1 year.

9. STUDY VISITS AND ACTIVITIES

9.1 Screening and Baseline

Subjects must meet the inclusion criteria and have none of the exclusion criteria in order to be eligible for participation in this study.

Screening assessments will be collected through review of medical records and by interview after informed consent is signed. These screening evaluations may include:

- Complete Medical History (including history of myocardial infarction, diabetes mellitus, hypertension, hypercholesterolemia, previous CABG and PCI)
- Demographics
- Vital Signs (Including height and weight)
- Physical Exam
- Labs
    - Complete Blood Count (CBC) including platelet count
    - Basic metabolic panel
    - INR, PTT if available, not mandated

Women of child-bearing potential will also receive a pregnancy test.

If measurement of any of the above assessments does not occur in the normal course of patient care, clinical practice should not be changed to accommodate collection of additional data.

A mandatory screening assessment for research purposes will include, assessing the patency of the proximal and distal radial artery with Doppler ultrasound.

Pre-Procedure Baseline evaluations will include:

1. Assessment of hand function (bilaterally)
    - Completion of the QuickDASH questionnaire
    - Assessment of the hand grip strength using the hand dynamometer.
    - Assessment of pinch grip by use of a pinch grip dynamometer. Baseline® Mechanical Pinch Gauge

9.2 Enrollment

The lead statistician will use a random number generator to produce a randomization scheme that will be used by the study coordinator(s) to allocate study participants to distal or proximal access study arms after informed consent is obtained, all inclusion/exclusion is assessed, and the participant is found to be eligible for the study.

Participants randomized to proximal access will receive conventional access procedure according to standard of care.

9.3 Distal Radial Access Procedure

Participants randomized to distal radial access will have the procedure as follows (Kiemeneij). Patients will receive appropriate peri-procedural antiplatelet and anticoagulation medications according to standard hospital practice.

The left or the right upper arm is placed comfortably on a cushion on the ipsilateral side of the patient. The hand is placed in a mid-supination position. For right distal radial access, the right wrist rests on a comfortable underground which brings the wrist in passive ulnar flexion. The patient is asked to bring the thumb under the other four fingers. This brings the artery more to the surface which allows easier puncture. After disinfection, the patient is covered with a sterile drape. A brachial drape is applied to the hand exposing the anatomical snuff box and the proximal radial.

Under ultrasound guidance, local anesthesia is applied by subcutaneous injection of 5cc of lidocaine filling the radial fossa. The puncture will be performed at the point of maximal pulsation proximal in the anatomical snuffbox. If this fails, a puncture more distal, just outside the snuffbox can be attempted. The puncture is preferably done with the traditional radial needle. After successful anterior wall puncture a radial sheath wire is advanced. Proper position is verified by fluoroscopy or by ultrasound to ensure the wire didn't traverse the palmar arch. This is followed by introduction of a hydrophilic sheath. The size of the sheath used will be documented (5 or 6 french radial sheaths). In order to prevent damage to the tip of the introducer and sheath, which might damage the artery, a small skin incision can be made followed by introducing the sheath. After administration of a spasmolytic cocktail containing 200-400 mcg of nitroglycerin and 5 mg of verapamil, the operator can take up a position at the level of the patient's knees. The choice of wire is at discretion of the operator. In case of left sided access, usually the wire encounters some resistance at the flexed left elbow. Careful manipulation of the wire direction with the tip of the catheter will usually solve the problem. If necessary a hydrophilic wire under fluoroscopy, can be used with special attention not entering small side branches in order to prevent perforation.

Hemostasis is performed using a radial hemostatic band, but with the least possible pressure and the shortest possible time (patent hemostasis). Technique, device used, and time will be recorded in the electronic case report form (e-CRF). Following the procedure, the patient is free to use both arms. No special supportive slings or other mobility limitation measures are required.

9.4 Follow-up

Subject management post-procedure will proceed via standard institutional protocol. Subjects will have a follow-up visit one month and 12 months post-procedure (± 10 days).

Follow-up visit assessments at 1 month and 12 months will include:

1. Any clinical change, reinterventions using the radial artery between the index procedure and follow up, is to be recorded.
2. Assess patency of the proximal and distal radial artery with Doppler ultrasound.
3. Assessment of hand function
    - Completion of the QuickDASH questionnaire
    - Assessment of the hand grip, using the hand dynamometer.
    - Assessment of pinch grip by use of a pinch grip dynamometer. Baseline® Mechanical Pinch Gauge

9.5 Withdrawal from Study

Subjects may voluntarily discontinue participation in the study at any time, for any reason. The Investigator also has the right to discontinue subjects from the study if he/she feels it is in the best interest of the subject.

10. COMPENSATION

Participants will not receive any compensation for participating in this study.

11. COSTS

Participants will not incur any additional research-related costs due to study participation. Subject or their insurance company will be required to pay for all expenses related to regular care including procedure and other hospital care.

12. RISK AND BENEFITS TO PARTICIPANTS

12.1. Potential Benefits

There is no guarantee of direct benefit to the subjects who participate in this study. There is a possibility that dRA will reduce the risk of bleeding and radial artery occlusion as well as improve patient comfort. Future patients may benefit from the knowledge gained.

12.2. Potential Risks

12.2.1 Physical Risks

Possible risks include loss of sensory function in part of the hand if the cutaneous nerve running in the anatomical snuffbox becomes damaged, distal embolization can result in digital ischemia and occlusion of the branch supplying the scaphoid bone can result in bone necrosis.

A study with 656 patients reported an incidence of distal radial artery occlusion of 1.5%, haematoma of wrist and forearm (0,8%), edema (0.2%), numbness (0.6%), dissection (0.3%), arteriovenous fistula (0.2%), transient ischemic attack (0.2%), stroke (0.2%), aneurysm (0.2%), death (0.5%) (Kaledin AL, 2014;27).

A skilled and experienced operator minimizes such complications. Operators with adequate experience in distal radial access at the discretion of the Principal Investigator are eligible to participate.

12.2.2 Psychosocial & Privacy Risks

Any time information is collected there is a potential for loss of confidentiality. Every effort will be made to keep participant's information confidential, however this cannot be guaranteed. Participation in research study may make participants feel uncomfortable. Participants will be informed that they may refuse to participate or stop their participation at any time without effect on future medical treatment or relationship with the treating physician.

12.2.3 Adverse Event Reporting

An Adverse Event (AE) is any untoward sign, symptom or medical condition occurring at any time after the subject receives his/her procedure, even if the event is not considered to be related to the study. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The adverse events that will be monitored and reported from the start of the study procedure until 1 year after the index procedure are complications related to the procedure which include:

- Bleeding
- Hematoma
- Radial Occlusion

A Serious Adverse Event (SAE) is an undesirable sign, symptom or medical condition which:

- is fatal
- is life threatening
- requires or prolongs hospitalization
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly or a birth defect
- is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above
- Hospitalizations not necessarily considered to be SAEs are hospitalizations for:
- treatment, which was elective or preplanned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

All SAEs will be followed up until resolution or permanent outcome of the event.

13. RISK/BENFIT ASSESSMENT

Local hematoma formation or prolonged compression may cause sensory damage or ischemia after radial access interventions. Distal radial access allows the arm to stay in a more natural and comfortable position for the patient and may reduce the risk of bleeding and artery occlusion. Advancing the understanding of distal radial access procedures will contribute to potentially easier and safer peri-procedural management of patients undergoing cardiac catheterization.

14. STATISTICAL METHODS

14. Statistical Methods

Patient demographics and characteristics will be reported and compared between the radial distal access (rDA) and proximal distal access (pDA) cohorts. Continuous variables will be reported as means ± standard deviations or medians [quartile 1, quartile 3], if skewed. Categorical variables will be reported as frequencies and percentages. Differences between demographic and clinical variables, as well as safety and compliance, will be assessed via two sample t-tests and Chi-square tests (or Wilcoxon's Rank Sum test and Fisher's Exact test), as appropriate.

14.1 Analysis of Primary Composite Outcome

The primary composite outcome of hand function will be defined utilizing the average Z-score approach (O'Brien, 1984; Sun, 2012). The average z-score for each subject is calculated as the average of the z-scores of the differences between pre- and 1-month post-operation measurements for three individual tests. The three tests that measure everyday functionality and strength of a subject's hand included in the composite outcome are: (a) the QuickDASH questionnaire score (0-100) calculated as [(sum of n responses / n) – 1] * 25, (b) Thumb and forefinger pinch strength test (kg), and (c) hand grip strength test (kg). The average of the three z-scores are then compared between rDA and pDA using the Wilcoxon rank-sum test.

14.2 Analysis of Secondary Outcomes

The composite outcome of hand function will be compared at 12-months post-operation using the average z-score approach outlined in the primary outcome analysis. The success rate, hematoma, bleeding, and radial artery occlusion will be compared between rDA and pDA cohorts using a Chi-square test (or Fisher's exact test). The rate of complications (including occurrence of hematoma, bleeding, radial artery occlusion, and complications of vascular access) per subject will be compared between the study cohorts using a Poisson Exact test.

14.3 Exploratory Objectives

Associations with radial artery occlusion will be explored using a logistic regression model and adjusted for significant confounders and study cohort if the event rate for occlusion allows for a multivariable model.

14.4 Sample Size

A Monte Carlo simulation study was utilized to study the sample size necessary to achieve at least 80% power to detect a small clinical difference between dRA and pRA in the primary composite outcome of hand function. A small clinical effect is defined as a 10% ± 10% change in pre- to post-operation scores in at least one of the three tests for one of the study cohorts. Results from the Monte Carlo study indicate that a sample size of n=125 per group is sufficient to achieve at least 80% power under a correlation of 0.3 between the three tests. Allowing for a loss-to-follow-up rate of 15%, the total number of patients that should be enrolled for the entire study is at least 296 (148 per arm).

14.5 Loss to Follow-up

Subjects lost to follow-up will be excluded from the analyses. Demographics and baseline characteristics will be compared between included and lost-to-follow-up subjects.

15. PROCEDURES AND INSTRUCTIONS

15.1 Protocol Amendments

Any substantive changes will be made as formal amendments to the protocol and will be submitted for appropriate review by the institutional review board (IRB).

Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB. Examples of amendments requiring such approval are:

1. A significant change in the study design (e.g., addition or deletion of a control group)
2. An increase in the number of invasive procedures to which subjects are exposed
3. Addition or deletion of a test procedure for safety monitoring

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator to ensure the safety of all subjects included in the study.

15.2 Recording of Data, Documentation, and Retention of Documents

Data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. All study records must be available for inspection by the Sponsor (BSWRI), its authorized representatives, the FDA and other regulatory authorities.

Data on subjects collected on CRFs during the study will be documented in an anonymous fashion and the subject will only be identified by the study number and by initials if also required.

The Investigator must maintain source documents for each subject in the study including a copy of the signed ICF.

15.3 Publication of Results

An integrated clinical and statistical report will be prepared at the completion of the treatment period. However, it is intended that the results of the study will be included on http://clinicaltrials.gov and published and/or presented at scientific meetings.

15.4 Disclosure and Confidentiality

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. The Investigator will keep a subject enrollment log relating codes to the names of subjects. The Investigator should maintain documents not for submission to the Sponsor (Baylor Scott & White Research Institute), e.g., subjects' signed consent forms, in strict confidence.

16. ETHICS AND GOOD CLINICAL PRACTICE

16.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects will be reviewed by the BSWRI IRB. The Investigators will not begin any study subject activities until approval from the IRB has been documented and provided as a letter to the Investigator. Before implementation, the Investigators will submit to and receive documented approval from the IRB of any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB approval, with the exception of those necessary to reduce immediate risk to study subjects.

16.2 Informed Consent

Each subject will be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. No subject can enter the study before his/her informed consent has been obtained.

17. REFERENCES

Hudak P, A. P. (n.d.). Development of an Upper Extremity Outcome Measure: The DASH (Disabilities of the Arm, Shoulder, and Hand). *American Journal of Industrial Medicine 1996; 29:602-608.*

Kaledin AL, K. I. (2014;27). Pecularities of arterial access in endovascular surgery in elderly patients. *Adv Gerontol*, 115-9.

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O'Brien, P. (1984). Procedures for comparing samples with multiple endpoints. *Biometrics, 40*, 1079–1087.

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