



ARCADIA



Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

Next Webinar: September 28, 2021 AT 2 PM ET/1 PM CT/12 MT/11 AM PT
Mark your calendar for next month's webinar! October 26, 2021

MILESTONES

Randomized = 729

Consents = 2714

August Randomizations = 21

August Consents = 69

144 Active Sites U.S. = 135 sites & Canada = 9 sites

Open Conference Call

SCs do you have process questions you need help with?

Starting in October, Rebeca and Pam will be hosting an open conference call twice a month. Pop in anytime during this hourly call to listen in or to ask a question.

This will be scheduled the 1st & 3rd Thursday at 12n ET.

This call will focus on process questions only. I/E questions can still be emailed to the arcadia@ucmail.uc.edu.

Check your email for invite

ARCADIA's Hero

Leah Craft RN, BSN, CCRC - PSC



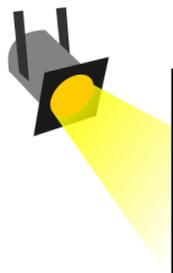
Emory University Hospital & Grady Memorial Hospital

Leah was given a challenge when both her SC coworkers moved on. This left her with multiple studies and many subjects to follow at two busy ARCADIA sites. She has done well catching up the follow up visits, subject CRFs, and clearing the queries.

We thank you for your dedication to both of your sites, your subjects and to ARCADIA during these challenging times.

Well done!

SPOTLIGHT ON SITES



August Top Consenting Site

**OSU Wexner Medical Center
Columbus, OH**

August Top Randomizing Sites

2 Randomizations each site!

**Memorial Hermann Texas Medical Center
Houston, TX**

**OSU Wexner Medical Center
Columbus, OH**

Sites with First Randomizations - August 2021

**London Health Sciences Center
London ,Ontario**

**Sunnybrook Health Sciences Center
Toronto ,Ontario**

Welcome Aboard!

**Brandon Regional Health Center
Brandon, MB**

Science Corner

Prevention of Stroke: News from the European Society of Cardiology Congress 2021



- **The LOOP trial results: Screening for atrial fibrillation using an implanted cardiac monitor in high-risk patients leads to greater detection of AF, but does not necessarily lead to reduction in stroke.**

In a randomized trial among four centers in Denmark, investigators tested the hypothesis that screening high-risk patients for atrial fibrillation using an implanted cardiac monitor would lead to reduced risk of stroke or systemic embolism. They randomized patients aged 70–90 years without atrial fibrillation who had at least one additional stroke risk factor (hypertension, diabetes, previous stroke, or heart failure). Participants were randomly assigned in a 1:3 ratio to implanted loop recorder monitoring or usual care. Anticoagulation was recommended if AF episodes lasted ≥ 6 minutes. The primary outcome was time to first stroke or systemic arterial embolism. Of 6004 patients included (mean age 74.7 ± 4.1 years, 47.3% women; about 18% with a history of prior stroke), 1501 were assigned to the implanted monitor and 4503 to usual care. During a median follow-up of 64.5 months, AF was three times more likely to be diagnosed in those with the monitor (32%) versus those without (12%; HR 3.17, 95% CI 2.81–3.59). Stroke or systemic embolism was uncommon and occurred in 4.5% of those in the implanted monitor group versus 5.6% in the control group (HR 0.80, 95% CI 0.61–1.05). Although these results are consistent with a potential 20–30% reduction in stroke risk with the use of an implanted monitor to detect AF, they do not prove that monitoring reduces stroke risk. A limitation of the study is that it was not blinded. There was also evidence that when analyzed by long-term adherence to the planned monitoring plan, there was a benefit in stroke risk reduction. The results, while relevant to primary prevention of stroke, may be less relevant to ARCADIA, which is of course limited to patients with recent stroke, in whom atrial cardiopathy (or occult AF) may play a role.

Reference: Svendsen JH, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet*. 2021 Aug 27:S0140-6736(21)01698-6. ahead of print. PMID: 34469766.

- **Salt substitution with potassium chloride reduces stroke risk.**

In the Salt Substitute and Stroke Study (SSaSS), an open-label, cluster-randomized trial among 600 villages in rural China, a potassium-based salt substitute lowered the risk of stroke by 14% and cut the risk of major adverse cardiovascular events by 13% when compared with sodium chloride salt use. In addition, the risk of all-cause mortality was reduced by 12%. Participants had a history of stroke or were ≥ 60 years of age and had high blood pressure. Villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which participants continued to use regular salt (100% sodium chloride). The primary outcome was stroke. A total of 20,995 people were enrolled (mean age 65.4 years, 49.5% female, 73% with history of stroke, and 88% with hypertension). Over a mean follow-up was 4.7 years, the rate of stroke was lower with the salt substitute (29.14 events per 1000 person-years) compared to regular salt (33.65 events per 1000 person-years; rate ratio 0.86, 95% CI 0.77–0.96). Serious adverse events due to hyperkalemia were not significantly higher with the salt substitute than regular salt (rate ratio, 1.04; 95% CI, 0.80 to 1.37). Salt substitution may be a simple, safe, and effective way to reduce stroke risk in high-risk populations, including those with prior stroke. This trial is the first to show that salt substitution not only reduces blood pressure, as did a similar study in Peru last year, but also risk of stroke. (For a different perspective on salt, see this month's Greek Culture Corner!)

References:

Neal B, et al. Effect of Salt Substitution on Cardiovascular Events and Death. *N Engl J Med*. 2021 Sep 16;385(12):1067–1077.

Bernabe-Ortiz A, et al. Effect of salt substitution on community-wide blood pressure and hypertension incidence. *Nat Med*. 2020;26(3):374–378.

Continued on next page.

Science Corner - continued from page 2

• Carotid artery surgery and stenting have comparable results after 5 years of follow up

In the ACST-2 trial among asymptomatic patients with severe carotid artery stenosis, patients were randomly allocated to stenting or surgery and followed up at 1 month and then annually for a mean of 5 years. All patients enrolled were those in whom revascularization was considered indicated. Among 3625 patients from 130 centers randomly allocated to stenting (n=1811) or surgery (n=1814), the Kaplan-Meier estimates of 5-year non-procedural stroke were 2.5% in each group for fatal or disabling stroke (approximately 0.5% annually). Any stroke occurred in 5.3% of those who underwent stenting and 4.5% of those undergoing surgery (rate ratio 1.16, 95% CI 0.86–1.57). The authors concluded that serious complications are uncommon after either stenting or surgery done well, and that the long-term effects of both carotid artery procedures on fatal or disabling stroke are comparable. The results are consistent with other studies that have suggested a slight, though not statistically significant, benefit of surgery compared to stenting. What this trial leaves unanswered, however, in the absence of an untreated group, is whether revascularization is needed for these patients. This hypothesis is being tested in the ongoing CREST-2 trial, another StrokeNet trial.

Reference: Halliday A, et al. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. *Lancet*. 2021 Aug 27;S0140-6736(21)01910-3. Epub ahead of print. PMID: 34469763.

FAQ

Question: Can patients with presumed stroke but negative DWI be enrolled in ARCADIA?

Answer: Yes!!

This topic was nicely addressed in a recent paper and editorial in *Neurology*. In the recently published SMART-MR (Second Manifestations of Arterial Disease– Magnetic Resonance) observational study, 20% of patients with stroke symptoms had negative MRIs. Other evidence suggests that a full 1/3 of mild cortical or lacunar strokes confirmed by neurologists (and 2/3 of patients with TIA) do not have an infarct on highly sensitive diffusion MRI sequences. Patients with imaging-negative strokes are also approximately 3 times more likely than those without stroke to develop new cortical infarcts (RR 2.88, 95% CI 2.17-3.82). Cortical infarcts, in particular, may be more likely to resolve on imaging; cortical location, of course, is a primary imaging characteristic of cryptogenic stroke/ESUS, and thus these patients are definitely eligible for ARCADIA, if the treating clinician believes they have had a stroke.

But remember: symptoms or signs should last more than 24 hours, and be sure that you are not enrolling a “stroke mimic”. Trust your judgment!!

References:

- Rissanen I et al. Association of Ischemic Imaging Phenotype With Progression of Brain Atrophy and Cerebrovascular Lesions on MRI: The SMART-MR Study. *Neurology*. 2021;97:e1063-e1074.
- Wardlaw JM. A Stroke Is a Stroke, With or Without a Visible Infarct. *Neurology*. 2021;97:515-516.
- Makin SDJ et al. Clinically confirmed stroke with negative diffusion-weighted imaging magnetic resonance imaging: longitudinal study of clinical outcomes, stroke recurrence, and systematic review. *Stroke* 2015;46:3142-3148.

STUDY REMINDERS

- ◆ You cannot dispense study medication without first speaking to the subject to assess if they can still be on study drug and/or need a change of dosage.
- ◆ If you have subjects, not on study drug, that have requested less follow up contact, you still need to complete the interval visit by EMR check.
- ◆ Study drug adherence must be completed during the follow up visit. If you are shipping study drug to the subject then conduct a study drug count when you are confirming the arrival of the study drug shipment.
- ◆ All out of window and missing visits are protocol deviations and must be reported using the UAE/PD form in WebDCU.
- ◆ Check your lab kit inventory with the number in WebDCU and let us know if there is a difference. We want to make sure you have lab kits onsite.

Just For Fun!

ARCADIA Cryptogram

This puzzle is called a Cryptogram. At the top there is a KEY that lists all the letters from A thru Z with a box below. Each of the letters has a number that goes with it.

The bottom part contains a secret quote. Each of the blanks has a number underneath it. Fill in the letters that correspond to the numbers below the blanks to solve the phrase.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z

8 20 2 5 8 22 17 8 2 15 5 21 16 8 20 24 23 8 26 15

8 26 20 5 20 24 2 21 12 25 21 20 5 17 15 2 10 18 14 5 26

16 2 13 19 13 26 20 5 21 26 8 11 20 13 2 17 2 23 16 20 21 18 13 26 5 17

14 20 2 21 4 13

August Word Search Answer Key

A E W B W Y A Z Z F S E **E N I N I T A E R C D E T A V E L E**
M J B G **A N T I P L A T E L E T N E E D E D** S I M W F S G I
A P T Y H V P U E **E Z I M O D N A R O T E L B A** V W N C G Y L
V P **N E E D F O R A N T I C O A G U L A N T** L Z T Z I X Y R
I O E Q I D J P D E W S A O T Q J U E **E C G** X W C W N M O K X
B Z Y I L Y **Y T I L I B A L U G A O C R E P Y H** G E L G X Z
X S I X A **Y D U T S R E H T O N A N I T N A P I C I T R A P**
N K W U T N K G G Z U M J J A B D I M A P O W W C O F A E C
F N J Q Q U L **Y R O T S I H G N I D E E L B** J A J J E E F A
L E F T V E N T R I C U L A R E F W L S R V R R K K J C X F F
I L **E V L A V L A C I N A H C E M** K L K W D U N X H G Z J I
H J D O J X F V N D Q O V Y Z S T V H P I R M O **O H K R B**
G O Q G Q Z V W F S E Q S F S Y G T M A L S O W N H W M J T
M L O B Z I I D U M Y A U C L I P W C Q K S X N P T G V K R
S E **A T R I A L M Y X O M A B Q B R S** N X G Z A B P N O J N
S I T I D R A C O D N B E L T K H S X L U T G P D H H Z M B
W T L I F F I W X P X E E V K Y H Q T N T J T I N **H R T O S**
X C K J T G U Z D H M E Z P T I Z K B P C U I X D I T U D V
M Z F S Y B W A A Q **O L I H N I N F I G W E L A N S V S I R**
Q G X U X A S M Y A J P M Z Y S I O Q R O R T B U T Y N F W
X O **P R E G N A N T** U M Q S R V K D X H H V F A Q O J L I X
P **A I N E P O T Y C O B M O R H T** B N R R V V N N R X G E J
G O **T N E S N O C N I A T B O O T E L B A N U** A Z Y F P D E
K R X O Y Q A U I T T V C Q R A I V S C A I K L W O E I R C
T X O F I I Z I N G H M N K O H X N J K M Z I L L F E S A E
H **S** S B Z N O Y X Z U A **A N E M I A** C S B A H E H I Z V N M
U U T A U R R G I S N N N X **N T P R O B N P** W R P C R E K S
D S T F I D P F R W K Y P O H B R M T R H E Y G R H G O I T
L E I N I G **E K O R T S R A N U C A L** A E E H Y U C K N I
R G G Y X S Q O W V Q O W R W B P M M N Q E M G E P Q A T G

Mark Your Calendars

**Your are invited to the
NIH StrokeNet Steering Committee
FALL Virtual Meeting**

Wednesday October 13th

11a - 2p ET

Invitation to be sent later.

Agenda to follow.



**This meeting is not required but you are
welcome to attend**

ARCADIA Contacts

ARCADIA@ucmail.uc.edu

24/7 Hotline: (833) 427-2234 if unable to reach please call (206) 535-1229

For an emergency that requires knowing whether patient is taking apixaban (Eliquis) or aspirin

Principal Investigators

Mitchell Elkind, MD, MS, Columbia University; mse13@columbia.edu
Hooman Kamel, MD, Weill Cornell Medicine; hok9010@med.cornell.edu
Will Longstreth, MD, MPH, University of Washington; wl@uw.edu
David L. Tirschwell, MD, MSc, University of Washington; tirsch@uw.edu

Project Manager	Pam Plummer	plummepa@ucmail.uc.edu	513-558-3941
Project Manager	Rebeca Aragon	ra2356@cumc.columbia.edu	212-342-0102
Canadian Project Manager	Angie Djuric	Angie.Djuric@phri.ca	905-521-2100 x40545
StrokeNet Pharmacy Core	Brittany Dornheggen	strokenetcpharm@ucmail.uc.edu	513-584-3166
StrokeNet Pharmacy Core	Hirut (Ruth) Akalu	strokenetcpharm@ucmail.uc.edu	513-584-3166
StrokeNet Pharmacist	Noor Sabagha	Noor.sabagha@uchealth.com	513-584-3166
WebDCU	Faria Khattak	khattak@musc.edu	984-221-0266
Monitoring Manager	Aaron Perlmutter	perlmutt@musc.edu	843-792-2784
Lab Core	Erin Popavich	ep2681@cumc.columbia.edu	212-305-4837
ECG Core	Sayed Soliman	esoliman@wakehealth.edu	
ECHO Core	Marco Di Tullio, MD	md42@cumc.columbia.edu	212-305-9875
ECHO Core	Rui Lui	rl483@cumc.columbia.edu	212-305-2820

Greek Culture Corner Salt in Ancient Greece

The results of recent trials demonstrating the benefits of salt substitution to blood pressure and health—including stroke prevention—provide an opportunity to reflect on the history of salt consumption in world history. For ancient cultures, including the Greeks, salt (sodium chloride) was essential for preserving foods such as meat, fish, and vegetables. According to an ancient Greek saying, “no one should trust a man without first eating a peck of salt with him.” In ancient Rome, roads, such as the Via Salaria, were built to make transportation of salt to the capital easier. The word “salary” comes from the Latin word for salt, and a *salarium* may have been an allowance paid to Roman soldiers for the purchase of salt. In Africa, Timbuktu was a noted salt and slave market. The expression “not worth his salt” likely originated in the ancient slave trade.

One of the earliest towns in Europe, Solnitsata (in modern day Bulgaria), was built around salt production more than 6000 years ago, even before ancient Greek civilization. Salzburg (literally “salt city”), in Austria, was named for its salt mines. The *gabelle*—a French salt tax—was enacted in 1286 and maintained until 1790. Because of the gabelles, common salt was of such a high value that it caused mass population shifts and exodus, attracted invaders and caused wars. During the Indian movement for independence, Gandhi organized the Salt Satyagraha protest to demonstrate against the British salt tax.



The health benefits of salt were also appreciated by the ancient Greeks. Hippocrates, traditionally recognized as the Father of Medicine, encouraged his followers to use salt water to cure illnesses by immersing patients in sea water. Millenia later, in 1753, Richard Russell, an English physician, published *The Uses of Sea Water* in which he stated that salt was a “common defence against the corruption of...bodies” and “contribut[es] greatly to all cures”. The benefits of salt have their limits, however, as we have learned from recent studies (see the update from the European Society of Cardiology Congress 2021 above, for examples). Too much sodium chloride can contribute to hypertension and stroke risk!

Brine being boiled down to produce salt at the Xinhai Well in Zigong, China. (photo credit Art Yang, 2006). (references: Guest Contribution, “The History of Salt in Ancient Civilizations”, *History Cooperative*, May 15, 2019, . Accessed September 16, 2021. Also Wikipedia.)