Oct. 24, 2021 - Vol 4, Issue 8

ARCADIA

Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

Next Webinar: October 26, 2021 AT 2 PM ET/1 PM CT/12 MT/11 AM PT

MILESTONES

Randomized = 743 **Consents = 2790**

September Randomizations = 9 **September Consents = 66**

143 Active Sites **U.S. = 134 sites & Canada = 9 sites**

79 Sites with 100% Retention Rate

Calendar of Events

October 26 - Monthly Webinar

November 4 - SC Open Conference Call

November 18 - SC Open Conference Call

November 23 - Monthly Webinar

November 11 - Veterans Day

November 25 - Thanksgiving

WebDCU STUDY REMINDERS

Once a subject is deemed ineligible for randomization, the EOS visit needs to be completed.

AE Reporting & CRF Completion
The Adverse Event CRF (F104) should only be completed if the subject experiences 1) a serious adverse event, 2) a clinical outcome, or 3) an adverse event of special interest. If the subject dies as the result of a previously reported event, the CRF capturing the previously reported event should be updated to reflect the correct grade, outcome, and any additional details that are available. A separate F104 is not needed to report the death.

SPOTLIGHT ON SITES

September Top Consenting Site

Methodist University Hospital
Memphis, TN

6 Consents!

Welcome Aboard!

No new sites were released to enroll in September but 14 new sites are in start-up!

Sites with First Consents - September 2021

Kelowna General Hospital - Kelowna, BC

No First Randomizations in September

September Top Randomizing Sites

All sites randomizing had 1 each!

OSU Wexner Medical Center - Columbus, OH

St. Joseph's Hospital & Med. Ctr. - Phoenix, AZ

Methodist University Hospital– Memphis, TN

University of New Mexico Hospital—Albuquerque, NM

University of Alabama Hospital - Birmingham, AL

University of Michigan University Hospital - Ann Arbor, MI

London Health Sciences Center - London, ON

Sunnybrook Health Sciences Center - Toronto, ON

University of Nebraska Medical Center - Omaha, NE

Science Corner

Strokes in patients with PAF tend to occur within a short time window after individual episodes of AF

Paroxysmal atrial fibrillation (PAF) is an important risk factor for stroke, but the mechanism by which PAF leads to stroke remains uncertain. The ARCADIA trial has as its central hypothesis that patients with unexplained stroke with underlying atrial disease are at increased risk of recurrent stroke, even if they do not have episodes of PAF. Atrial cardiopathy, in other words, is a precursor of stroke even without AF. Some of the ARCADIA patients, however, are likely to develop PAF during the course of the trial, and their stroke risk may be even further increased if they develop PAF. There is ongoing uncertainty regarding the temporal relationship between the occurrence of an episode of PAF and the occurrence of stroke: some studies among people with long-term implanted devices that allow continuous recording of rhythm have suggested that strokes can occur 30 or more days apart from when the patient experiences an episode of PAF. Other studies suggest that the risk of stroke occurs in greater proximity to when a patient is in PAF. In a recent analysis of a large database including data from implanted cardiac devices and clinical outcomes, investigators conducted a case-crossover analysis to explore the relationship of timing of PAF events (defined as duration of $\geq$5.5 hours) and stroke. Among 466,635 patients included, there were 891 patients (median age 76 years) with stroke and at least 120 days of cardiac monitoring prior to their stroke. Most (93%) had either no AF in both the case (1-30 day) and control (91-120 day) periods or AF in both periods, and therefore could not contribute to the analysis of timing in relation to stroke. There were 66 patients who provided information because of discordant arrhythmic states, with 52 having AF of 5.5 hours or more in the 30-day case period vs 14 in the control period (OR 3.7, 95%CI 2.1-6.7). The highest stroke risk occurred during the 1 to 5 days after an episode of PAF (OR 5.0, 95%CI 2.6-9.6). These results provide evidence that an episode of PAF likely carries some heightened risk of stroke. It does not, however, demonstrate that all of the risk of atrial cardiopathy is related to the eventual occurrence of PAF. The majority of patients in the database were excluded from the case-crossover analysis since they could not provide informative data. Most had no AF at all prior to stroke: it is plausible (and we think likely) that some of these stroke patients had atrial cardiopathy that never manifested as PAF but did contribute to their risk of stroke. These data contribute to an emerging way of thinking about the relationship between atrial disease and stroke risk: patients with atrial cardiopathy carry an increased stroke risk, and some of these patients may develop AF which, acting like a stroke trigger, further increases stroke risk for a short period of time. Whether treating patients with anticoagulation only during these periods of heightened risk, or addressing the underlying atrial cardiopathy by continuing anticoagulation for a longer period of time, remains the subject of ongoing clinical trials, including ARCADIA.

Reference:
Singer DE et al. Temporal Association Between Episodes of Atrial Fibrillation and Risk of Ischemic Stroke. JAMA Cardiol. 2021 Sep 29:e213702. doi: 10.1001/jamacardio.2021.3702. Epub ahead of print. PMID: 34586356; PMCID: PMC8482300.

Age and NT-proBNP identify ESUS patients with increased risk of developing AF

Detection of AF among patients with unexplained strokes, with or without atrial cardiopathy, has become a mainstay of stroke evaluation and secondary prevention. Many ARCADIA patients undergo prolonged rhythm monitoring for detection of AF. It would be helpful, however, to be able to identify those patients most likely to develop AF to target evaluation and monitoring more precisely, and prior studies have found clinical and physiologic variables, including age, history of hypertension and heart failure, and electrocardiographic abnormalities, to be predictors of which patients with unexplained stroke will develop AF. In a recent secondary analysis of the RE-SPECT ESUS trial, investigators explored predictors for developing AF. RE-SPECT ESUS was an international, randomized, controlled trial that tested dabigatran versus aspirin for the prevention of recurrent stroke in patients with ESUS. Of 5390 patients enrolled, 7.5% had AF detected during 19 months of follow-up. In a multivariable model, age, hypertension, diabetes (inversely associated), and body mass index independently predicted AF detection. In an analysis restricted to the 1117 patients with baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations available (about 20% of the total study population), only age (odds ratio per 10 years 1.34, 95%CI 1.08-1.66) and higher NT-proBNP (OR per 1 unit increase on logarithmic scale 1.74, 95%CI 1.40-2.16) were significant independent predictors of AF. These results support the notion that NT-proBNP is a marker of atrial disease, including but not necessarily limited to AF, in patients with stroke, and more generally supports our use of NT-proBNP as a marker of atrial cardiopathy. Whether NT-proBNP predicts response to anticoagulation is as yet undetermined and being addressed by ARCADIA. Be cause the RESPECT-ESUS data are hypothesis-generating, we do not endorse the use of NT-proBNP measures to deter mine whether to search for AF or pre-screen patients for ARCADIA.

Reference
Bahit MC et al. Predictors of Development of Atrial Fibrillation in Patients With Embolic Stroke Of Undetermined Source: An Analysis of the RE-SPECT ESUS Trial. Circulation 2021. doi: 10.1161/CIRCULATIONAHA.121.055176. Epub ahead of print. PMID: 34649459.

PROJECT MANAGER STUDY REMINDERS

- If your consent version changes due to changes in language, phone numbers &/or addresses of the study team, your subject needs to know this new information. Your subjects will need to be reconsented using the new version of your site's consent.
- Once a document is approved by the cIRB and your site makes a change to that document, the document is no longer valid and will need to be submitted back to the cIRB for approval.
- All out of window and missing visits are protocol deviations and must be reported using the UAE/PD form in Web-DCU.
- ECHOs
  - To determine ESUS the echo can be either TTE or TEE. However, to determine if the subject meets the atrial cardiopathy criteria for randomization, (Lt atrial diameter index > 3cm/m²) this measurement can only be measured on a TTE.
  - The shipping date needs to be entered in F505.
- Please email all of the orders to CALM lab & send them separately from other items so they don't get missed if they are part of a multiple page document.
- SSRI and SNRIs are discouraged medications, not prohibited. An updated ARCADIA prohibited/ discouraged medications list will be disseminated in the near future.

FAQ

Question: A patient with ESUS has been participating in an ongoing drug trial with an experimental JAK inhibitor for alopecia areata. Questions:

1) Are they eligible for ARCADIA if the JAK inhibitor might be the cause of the patient's stroke?
2) Can they be enrolled in ARCADIA if they are in another drug trial?
3) If they agree to stop their participation in the other drug trial, what is the wash out period before they can start in ARCADIA?

Answer: JAK inhibitors—such as tofacitinb (Xeljanz), baricitinib (Olumiant), and upadactinib (Rinvoq)—may be associated with an increased risk of thromboembolic event including stroke. These drugs are used for the treatment of rheumatological disorders, including rheumatoid arthritis, ulcerative colitis, psoriasis, and others. The data on whether they are associated with major cardiovascular events has been gradually accumulating from post-marketing and other studies, and interpretation is made difficult by the fact that conditions like rheumatoid arthritis themselves appear to be associated with an increased risk of thromboembolic events. While there may be differences among the individual drugs in terms of cardiovascular risk, the FDA is treating these as a drug class effect. In September 2021, the FDA mandated that the manufacturers of JAK inhibitors include black box warnings on the package inserts stating that there is an increased risk of serious cardiac events such as heart attack or stroke, cancer, blood clots, and death.

JAK inhibitors inhibit members of the family of proteins known as Janus kinase (JAK), which is a part of the JAK-stat cytokine pathway. Janus kinase is named for Janus, the Roman god of beginnings, endings, and duality (figure from Wikipedia, statue representing Janus, from the Vatican Museum). The protein has two near-identical phosphate-transferring domains, one of which exhibits kinase activity, while the other negatively regulates the kinase activity of the first.

With regard to ARCADIA, we recommend use of best clinical judgment in deciding whether to include such patients. We would consider patients with underlying rheumatological conditions that could be a cause of stroke, or those taking medications that could be a cause of stroke, the way we have recommended handling of those with cancer or other potential hypercoagulable states, such as use of post-menopausal hormone therapy. These possible contributors to stroke risk are not definite proximal causes of stroke, in the way that carotid stenosis or atrial fibrillation, are. They are closer to risk factors, like hypertension or hyperlipidemia. Determining the cause of a single stroke in an individual patient is a challenge, even in the best of circumstances. In short, the use of a medication that may increase stroke risk should *not* be considered a contraindication to participation in ARCADIA.

In this particular case, the patient cannot be enrolled in ARCADIA if they remain in the investigational drug trial. They could be enrolled if they were to be on open label therapy with a JAK inhibitor, however. If the patient agrees to exit the trial, there should probably be a brief wash out period between trials. ARCADIA does not have mandated duration of time for this wash out period, and it would depend on the recommendations from the sponsor of that drug. However, all else being equal, we believe thirty days is a reasonable amount of time between the investigational drug and enrolment in ARCADIA.

Just For Fun!

Our ARCADIA States, Districts, & Provinces

We have 42 States/Districts & 4 Provinces in the ARCADIA study. Can you guess them? No clues!

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

September Cryptogram Answer Key. Who got this one!

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	25	17	15	13	11	18	24	5	7	4	22	12	26	21	16	3	2	14	20	10	19	1	9	23	6

A	T	R	I	A	L
8	20	2	5	8	22

C	A	R	D	I	O	P	A	T	H	Y
17	8	2	15	5	21	16	8	20	24	23

A	N	D
8	26	15

A	N	T	I	T	H	R	O	M	B	O	T	I	C
8	26	20	5	20	24	2	21	12	25	21	20	5	17

D	R	U	G	S
15	2	10	18	14

I	N
5	26

P	R	E	V	E	N	T	I	O	N
16	2	13	19	13	26	20	5	21	16

A	F	T	E	R
8	11	20	13	2

C	R	Y	P	T	O	G	E	N	I	C
17	2	23	16	20	21	18	13	26	5	17

S	T	R	O	K	E
14	20	2	21	4	13

ARCADIA Contacts

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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

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Happy Halloween!
Ancient Greece Edition

Ghosts were a thing in ancient Greece too! Death was a mystical process, with many steps, according to Greek mythology. First, upon death, a coin was placed in the corpse's mouth to pay Charon, the Ferryman, to take the soul across the river Styx. Once across the river, the dead would pass by the three-headed dog Cerberus (remember from Harry Potter!?) and then stand before three judges to give an account of their lives. Then the dead person would drink a cup of water from the River Lethe, the waters of forgetfulness, and begin to forget life on earth.

The judges would then assign the soul a destimation: Warriors who died in battle went to the Elysian Fields, considered a paradise. Those who had been good in life went to the Plain of Asphodel, another nice place. The evil, however, were dispatched to Tartarus, a dark place where the soul stayed until it had atoned for its sins during life, after which it could rise to the Plain of Asphodel.

Though lost souls were not expected to return to the mortal world, some did, and may be considered ghosts. The Greeks recognized three kinds of ghosts: *ataphoi*, *aōroi* and *biaiothanatoi*. The *ataphoi* were the deceased who were not buried with proper rituals. The *aōroi* were those who died untimely or premature deaths, such as women who died before having children; they could return to avenge their death. The *biaiothanatoi* were the souls of those who died by violence, including the victims of war. In many instances, the war dead also could not be given a proper burial, and so they continued to wander the earth until their human remains could be buried properly.

According to Pliny the Younger, late one night the stoic philosopher Athenodorus (see figure, by Henry Justice Ford, circa 1900) was visited by a ghost in a house he had rented. The ghost, bound with chains, beckoned Athenodorus to follow him to a nearby courtyard, and then vanished. The following day, Athenodorus dug up the courtyard and found the skeleton of an old man, bound with chains. After the skeleton was given a proper burial, the ghost was never seen again. Enjoy your candy!