Jan 18, 2022 - Vol 5, Issue 1

ARCADIA

ARCADIA

Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

Please join us January 25, 2022 for our virtual Investigator Meeting
(1-4p ET/12-3p CT/11-2p MT/10-1p PT)

MILESTONES

Randomized = 790 Consents = 2969

December Randomizations = 18 December Consents = 62

143 Active Sites U.S. = 132 sites & Canada = 11 sites

We have reached 71.8% of our recruitment goal.

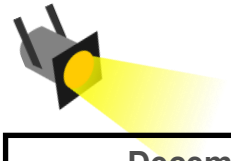
Calendar of Events

- January 20 - SC Open Call
- January 25 - Virtual Investigator Meeting (1-4p ET / 12-3p CT / 11-2p MT / 10-1p PT)
- January 26 - NIH StrokeNet January Coordinator Webinar
- February 3 - SC Open Call
- February 17 - SC Open Call

ARCADIA Heroes

We thank all of the Coordinator Heroes who continued to screen, enroll, randomize and follow participants despite being sent home once again to work virtually as the Omicron variant started surging this winter!

Happy New Year ARCADIA!



SPOTLIGHT ON SITES

December Top Consenting Sites

UPMC Presbyterian - 4 Consents

Methodist, London Health and Medical University of South Carolina - 3 Consents

December Firsts

1st Consent - UCLA Ronald Reagan

1st Randomization - Salinas Valley

Congratulations!

December Top Randomizing Site

University of New Mexico, Albuquerque

2 randomizations!

Welcome Aboard!

No new sites were released to enroll in December 2021.

Many new sites in start up and should be released to enroll soon.

Science Corner

Off-label underdosing of direct-acting oral anticoagulants increased risk of thromboembolic events without decreasing the risk of bleeding.

Practitioners often prescribe direct-acting oral anticoagulants (DOACs), like apixaban, at doses that are higher or lower than the recommended doses due to perceived concerns about patient bleeding or elevated risk of thrombotic events. The efficacy and safety of this type of "off label" prescribing is unknown. In a meta-analysis of randomized trials and observational studies, investigators compared off-label versus on-label dosing of DOACs. The primary outcome was ischemic stroke or systemic embolism, and the safety outcome was major bleeding. Among 16 studies (N=130,609 patients), off-label underdosing of DOACs was associated with a higher risk of thromboembolic events compared with on-label dosing (HR 1.22, 95% CI 1.05-1.42). Major bleeding, however, was similar between the two groups (i.e., not reduced): HR 0.95, 95% CI 0.82-1.11). Off-label underdosing was also associated with a higher risk of the composite outcome of thromboembolic events, major bleeding, and total mortality (HR 1.19, 95% CI 1.04-1.40). Off-label overdosing showed higher risks of both thromboembolic and bleeding events. These results indicate that changing the dose of DOACs due to a perceived increased risk of bleeding is unlikely to benefit patients, and it may increase their risk of ischemic events without a reduction in risk of bleeding. As clinicians, we should therefore stick to the prescribing guidelines on the label.

Reference: Zhang XL et al. Off-Label Under- and Overdosing of Direct Oral Anticoagulants in Patients With Atrial Fibrillation: A Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2021 Dec;14(12):e007971. doi: 10.1161/CIRCOUTCOMES.121.007971.

Check out the accompanying editorial as well: Shurrab M et al. Off-Label Direct Oral Anticoagulant Dos-ing: Caution Advised. Circ Cardiovasc Qual Outcomes. 2021 Dec;14(12):e008608. doi: 10.1161/CIRCOUTCOMES.121.008608.

Among patients 65 years or older with atrial fibrillation, apixaban significantly reduced risk of major ischemic or hemorrhagic events compared to rivaroxaban.

In an NIH-funded comparative effectiveness study using claims data for US Medicare beneficiaries ≥65 years, from January 1, 2013--November 30, 2018, patients with atrial fibrillation (N=581,451) who began rivaroxaban or apixaban treatment were followed up for 4 years. There were 227,572 patients on rivaroxaban and 353,879 on apixaban. The primary outcome was a composite of stroke/systemic embolism and major hemorrhagic events. Results were adjusted for baseline comorbidities with inverse probability of treatment weighting. The adjusted outcome rate for rivaroxaban was 16.1 per 1000 person-years vs 13.4 per 1000 person-years for apixaban (HR for rivaroxaban 1.18, 95% CI 1.12-1.24). The rivaroxaban group had increased risk for both major ischemic and hemorrhagic events, as well as total mortality (HR, 1.06, 95% CI 1.02 -1.09). The risk of the primary outcome was increased for rivaroxaban in both those receiving the reduced dose and the standard dose groups. These data may be used to reassure patients that apixaban is highly effective medication when compared with another commonly prescribed DOAC.

Reference: Ray WA et al. Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation. JAMA. 2021 Dec 21;326(23):2395-2404.

Study Reminders

- **If your subject is on study drug, a pill count must be completed before starting a new kit.**
- **Do not dispense study drug without first assessing your subject to see if they can safely continue.**
- **Your subjects' ECHO discs must be in DICOM format and sent to the ECHO lab, per the protocol.**
- **Do not wait until the last minute to find that you are out of lab kits or the vacutainer tubes have expired. Keep QA checks and order supplies in a timely manner.**
- **If your site needs to change the Principal Investigator, the proposed new PI must be approved by the National PIs.**
- **WebDCU is the study repository for the research regulatory documents. If your site has documents that are missing or expired, you must attend to those immediately.**
- **F101 must be completed in full. If it's not completed then WebDCU will never clear a subject for randomization even if they meet criteria through NTproBNP, ECG or ECHO.**

ARCADIA INVESTIGATOR MEETING

Date: Tuesday, January 25, 2022 1-4 ET/10-1 PT
Total time: 3 hrs./180 minutes

Invitations have been sent by email:

By Zoom: Meeting ID: 946 4038 6307 Passcode: 544828

Agenda

	Presenter(s)	Time
Welcome and Introductions		*[12 min]*
Welcome NIH/NINDS NCC	Mitch Elkind Scott Janis Joe Broderick	2 min 5 min 5 min
Session 1: Status Update		*[48 min]*
Recruitment update, future projections, and protocol update	Hooman Kamel	12 min
Administrative and DSMB Update	Mitch Elkind	6 min
Brief overview of demographics of cohort and study metrics	David Tirschwell/ Will Longstreth	12 min
ARCADIA-CSI	Ron Lazar	6 min
Canadian Site Update	Jeff Healey/David Gladstone/ Angie Djuric	6 min
Q and A/Discussion	PIs	6 min
ARCADIA GENERATION SLIDESHOW	Rebeca Aragon/ Pam Plummer	5 min
Session 2: How can we do better?		*[55 min]*
Strategies to enhance recruitment	Rebeca Aragon	12 min
Improving retention and follow up Out of window visits Prohibited medications Subject visits and pill counts EMR checks	Pam Plummer	12 min
Site strategies to enhance recruitment, retention, and adherence Methodist, Memphis, Tennessee Rhode Island Hospital, Rhode Island	 Balaji Krishnaiah/ Quentin Thacker Tina Burton/ Deepica Chaudhary/ Catrina Elizardo	 6 min 6 min
Causative Classification Stroke (CCS)	Hakan Ay	12 min
Q and A/Discussion	PIs and speakers	7 min
Break		5 min
Session 3: State of the Science	PIs	*[55 min]*
Preliminary analyses/results from ARCADIA	Chinwe Ibeh Rachael Schutz	8 min 8 min
Proposed Ancillary studies		
Proteomics	James Floyd	8 min
Infection and stroke	Kieron South	8 min
Ongoing studies of subclinical AF/atrial cardiopathy NOAH-AFNET 6 ARTESiA MOSES	 Jeff Healey Mira Katan	 8 min 8 min
Q and A/Discussion	All	7 min

FAQ

Question: We have a patient that we are screening for ARCADIA but she has Moyamoya Disease. Does she qualify?

Answer: Moyamoya disease is a rather rare entity that is characterized by occlusions of bilateral distal carotid arteries (not in the neck where atherosclerosis commonly causes problems, but up higher at the skull base). Patients then develop so-called "moyamoya" vessels as collateral channels around the occlusions. These tiny, fragile vessels have the appearance of a puff of smoke billowing up on angiography and are named "moyamoya" after the Japanese word for "like a puff of smoke" (more or less). The occlusions can cause ischemic stroke, and the fragile small vessels can bleed, leading to intracerebral hemorrhage. The disease often occurs in children, especially of Asian heritage, but can occur in older people as well. Sometimes it is secondary to other causes, like sickle cell disease, diabetes, oral contraceptives, smoking, and other disorders (moyamoya syndrome); and sometimes it is idiopathic (moyamoya disease).

Patients with moyamoya disease or syndrome are typically considered to have that as the etiology of their stroke, so she would be unlikely to be eligible for ARCADIA, particularly if the stroke is in the anterior circulation territory. In the unlikely event that the patient had a stroke in the posterior circulation territory, without relevant stenosis (moyamoya can eventually progress to involve posterior circulation vessels as well), and no other cause, then she could potentially have ESUS and be considered eligible. Even so, it would be essential to check with her treating providers as to whether or not they would accept her being on an anticoagulant, especially because of the potential hemorrhagic risk. In addition, many patients with moyamoya undergo surgical intervention, so she might not be an ideal candidate for that reason.

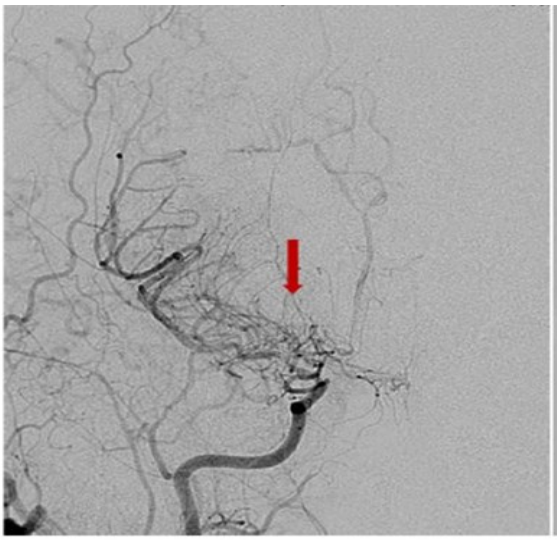


Figure 1a

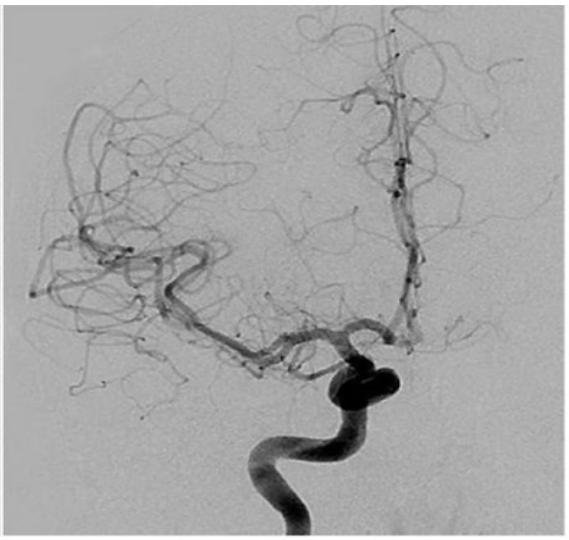


Figure 1b

Figure 1a: AP view of a brain angiogram showing the right internal carotid artery narrowing into the small tangles of moyamoya "puff of smoke" vessels (red arrow). Figure 1b: A normal angiogram for comparison. (From Baylor Medicine online: https://www.bcm.edu/healthcare/specialties/neurosurgery/cerebrovascular-and-stroke-surgery/moyamoya-disease

December Trivia Answers

1. Mistletoe	10. Latkes	19. December 26
2. Turkey	11. Italy	20. Krampus
3. Clay	12. Boxing Day	21. Teddy Roosevelt
4. 1966	13. Chocolate	22. White, the purity of Jesus; red, the blood that Jesus shed
5. 1843	14. Kinara	23. 2 or more
6. Jingle Bells	15. The crown of thorn that Jesus wore	24. Germany
7. Lights	16. A Christmas gift from France in 1886	25. Antiochus IV
8. Eight	17. 8 days	26. A Swahili word that means first & signifies the 1st fruits of the harvest. It also celebrates the 7 values the African culture.
9. 364	18. Alabama	

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

NCC Project Manager	Pam Plummer	plummepa@ucmail.uc.edu	513-558-3941
PRIME 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- The Greek Alphabet

The Greek Alphabet has gotten a lot of attention recently since it serves as the basis for the naming of variants of the coronavirus that are causing the COVID-19 (now COVID-22!) pandemic. As most people know by now, the latest variant that has caused so much concern around the globe is the Omicron variant. Note that the WHO skipped naming a variant after Nu (because Nu variant could be confused with “new” variant) and Xi (since the WHO did not want to name a variant after the Chinese Premier Xi Jinping!). So here we are at Omicron.

So what is the history of the Greek alphabet?

In brief, the Greek alphabet first appears in the archaeological record during the 8th century BCE. Previous alphabets had been used to write Greek, but the current one had certain advantages. The Greeks adapted the Phoenician writing system to represent their own language. During the early first millennium BCE, the Phoenicians, originally from the region of modern-day Lebanon, became successful mariners and merchants, gradually establishing outposts throughout the Mediterranean. The Phoenician language was closely related to Canaanite and Hebrew.

The Greeks made some important changes to the Phoenician alphabet. The major one is that they dropped the signs for which there was no consonant equivalent in Greek and used them instead for individual vowel sounds. As a result, the Greek vowel letters A (alpha), E (epsilon), I (iota), O (omicron), Y (upsilon) and H (eta), were adaptations of Phoenician letters for consonant sounds that were absent in the Greek language. By using individual symbols to represent consonants *and* vowels, the Greeks created a writing system that could, perhaps for the first time, represent speech in an unambiguous manner. Our own modern Latin alphabet is derived from the Greek alphabet, and in fact the Greek alphabet is the root of most of the scripts used today in the western world.