January 20, 2021 - Vol 4 Issue 1

ARCADIA

Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

Next Webinar
Tuesday February 23rd at 2p EST/1p CT/12 MT/11p PT

Happy New Year

2020 was a challenging year for all of us! We thank you for your perseverance in overcoming the challenges and hope you have a happy and healthy start to the new year both personally and professionally!

Congratulations!

Thanks to Claudia Moy PhD our Program Director at NINDS on her retirement. We wish you well! Your wisdom and guidance will be missed!

Welcome to Robin Conwit MD who will be Claudia's replacement. We wish you well with many happy years in guiding neurologic research!

December Milestones

Randomized = 573 Consented = 2186

December Randomizations = 14 December Consents = 63

2020 MILESTONES

Top Randomizations for 2020 - Emory with 20
Top Consents for 2020 - Yale with 27
Highest Monthly Randomization Rate - Emory 0.81%
Top Sites with 100% Retention Rate - Emory & UPMC Presbyterian, Pittsburgh

Out of Window Visits

Out of window visits are protocol deviations and must be reported in real time whether they need prompt reporting to the cIRB or non-prompt reporting to the cIRB at the time of the CR.

It has been found that we are accruing more out of window visits that have not been reported. Your site will be contacted and a UAE/PD form will need to be completed if you have unreported out of window visits. A visit scheduler will be provided for each subject that has an out of window visit so that you can make sure you are capturing the subject's data during the appropriate time period.

Please contact your Project Managers, Rebeca or Pam, for assistance with UAE/PD reporting.

SCIENCE CORNER

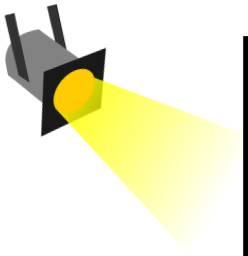
The presence of incidentally-discovered cerebral microbleeds (CMBs) in patients with cardioembolic ischemic stroke has drawn increasing attention recently. CMBs likely represent forms of cerebral vasculopathy (amyloid when cortical, hypertensive when deep) that predispose to an increased risk of clinical intracerebral hemorrhage. A recent cohort study from South Korea[1], however, shows that the presence of CMBs predict not only hemorrhagic complications but ischemic events as well, and that the risks associated with CMBs are apparent for treatment with warfarin but not for direct acting oral anticoagulants like apixaban.

The investigators included 1742 patients with acute ischemic stroke and atrial fibrillation who underwent admission MRI scans. CMBs were defined by presence, burden, and location. Patients were treated according to clinical practice guidelines. The primary outcome was a composite of stroke, acute myocardial infarction, or vascular death (major adverse cardiovascular and cerebrovascular endpoints, or MACCE) over a 2-year period; secondary outcomes included individual outcomes from the composite, including ICH. They found that 23% of patients had at least one CMB. CMB presence was associated with the risk of MACCE (adjusted HR 1.89, 95% CI 1.23 –2.88), though the risk really began with 2 CMBs being present. Both lobar and deep CMB were associated with increased risk of MACCE, and the risk of MACCE was not different according to CMB location. In patients on warfarin, CMB was significantly associated with a risk of MACCE (*P*=0.002), but not in patients treated with direct-acing oral anticoagulants. Notably, the risk of ICH was most elevated for those with CMBs, although each of the individual secondary endpoints, including ischemic stroke and MI was also increased. Absolute event rates of ischemic stroke were more than twice as high as event rates for ICH.

The analysis has implications for the use of anticoagulants in patients with definite or suspected cardioembolic stroke, including in the ARCADIA trial. First, while presence of CMBs, especially multiple CMBs, could be considered a risk factor for adverse effects on anticoagulants, it appears the risks are not limited to hemorrhagic events alone. CMBs may be a general marker of vasculopathy, not only a marker of hemorrhagic risk. Second, the risks of ischemic events are greater than the risks of ICH in these patients, indicating that the benefits of anticoagulants likely outweigh the risks in most patients with CMBs. Finally, the fact that the increased risks associated with CMBs were not present for those on DOACs, like apixaban, is reassuring that our choice of anticoagulant for ARCADIA was correct.

[1]Reference: Choi KH et al. Microbleeds and Outcome in Patients With Acute Ischemic Stroke and Atrial Fibrillation Taking Anticoagulants. *Stroke* 2020;51:3514-3522. PMID: 33028171.

SPOTLIGHT ON SITES



December Top Randomizing Sites

14 Sites randomized during December

University of Nebraska	UVA
University of Kentucky	OU Medical
Methodist	Wake Forest
University of Mississippi	Emory
Mercy St. Vincent	Rhode Island
UPMC Presbyterian	UT Health
Houston Methodist	
Medical University of South Carolina	

December Top Consenting Site

Tampa General

4 Consents

Welcome Aboard

Saint Luke's Hospital of Kansas City

Release to enroll mid December

135 Sites Released & Active Post COVID Pause

FAQs

Q: A subject had been permanently discontinued from study drug due to A-fib but remained in study follow-up. The subject now presents to the hospital with a new stroke, which is a primary outcome and will be removed from the study. Can this subject's participation be ended immediately so that they can be enrolled into the ASPIRE research study?

A: No. The subject must remain in the ARCADIA study for 30 days post primary outcome for adjudication of the stroke by the medical monitor and to be monitored for further SAEs. After the 30 days, the subject's participation will be ended and they can be enrolled into another trial, if the other trial allows the participation.

Updates/Reminders/Tips

1) Protocol changes are coming.
   - Options of collecting subject data instead of withdrawing from study; a) decreased follow-up visits, b) collection of data from family of physician with subject permission, c) collection of data via EMR.
   - Subjects who permanently stop study drug will no longer have their SAEs or AEs of special interest followed after 30 days
2) As discussed during the virtual IM, please do not prescreen for the cardiopathy criteria.
3) Common Misconceptions Preventing Enrollment
   a) Thinking you cannot enroll patients with hemorrhagic conversion
   b) Thinking you cannot enroll patients with PFO if they are not having the PFO closed
   c) Thinking all chronic kidney disease patients are ineligible.
   d) Thinking cancer patients are ineligible.
   e) Not approaching patients just because they were discharged on DAPT, which may be temporary.
4) At least 24 hours of continuous heart-rhythm monitoring is required before consenting.
5) Focus on retention of your randomized subjects. Relationship with your subject is key!
6) Complete the biobank section of the consent even if the patient does not want to participate.
7) If using a witness, please have the witness sign on the main & biobank section of the consent and complete the section as to why a witness is being used.
8) Resolve any DCRs (queries) as soon as possible in WebDCU.
9) QI Reports coming to your site in 2021.
10) You must reassess your subjects medication at each study visit and enter the date on the CRF.
11) If your subject has a positive COVID PCR test, please complete an AE. You do not need to complete a UAE for COVID.
12) Please obtain your ECHO discs in DICOM format and ship with your NTproBNP specimen to the lab.
13) If your subject is returning to the office for randomization, do not randomize the subject until they are in the office. If you are randomizing remotely, contact the subject to ensure they still want to participate and complete the assessment prior to obtaining a study drug kit. Obtain the kit and ship overnight. Discuss study drug administration, prohibited meds and the next follow up visit when you call the subject the next day when study drug has arrived.

Virtual Investigator Meeting

Thanks to all for attending our 1st Virtual Investigator Meeting. We appreciate all of the nice comments we have received. The slides are available on the ARCADIA webpage found on the StrokeNet website. The sessions were recorded and uploaded to YouTube. The links can be found below and on the ARCADIA webpage.

Full meeting, including the PI Breakout Session: https://youtu.be/LanlWUZMius

Coordinator Breakout Room: https://youtu.be/gyAzizY-hBk

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

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Greek Culture corner

As we enter the new year, it is worth remembering one of our most valuable and cherished assets as North Americans: democracy. The culture that first introduced democracy to the world was, of course, ancient Greece. In 507 B.C., the Athenian leader Cleisthenes introduced *demokratia*, or "rule by the people." Like our own democracy, *demokratia* was composed of three separate institutions: the *ekklesia*, which drafted legislation and determined foreign policy; the *boule*, a council of representatives from the ten Athenian tribes; and the *dikasteria*, the court system. Ancient Greek democracy entailed a direct participatory vote, distinct from our representative government. Only about 40,000 male citizens over age 18 were allowed to participate in the *ekklesia,* out of a population of about 260,000, including 150,000 slaves. The *ekklesia* met 40 times per year; about 5000 men would attend each meeting, and decisions were determined by a simple majority vote of the attendees. The boule handled most day to day matters, and included 500 members (50 from each of ten tribes), each chosen by lot and serving for one year, who met daily. Jurors in the *dikasteria* were also chosen by lot, much like we do today. Athenian democracy survived only two centuries, done in by the end in part by the plaque of Athens (discussed in a previous ARCADIA newsletter last year). But democracy remains one of ancient Greece's most enduring legacies. Let's hope ours continues to survive much longer.

(Source: https://www.history.com/topics/ancient-greece/ancient-greece-democracy)

Figure legend: *A marble relief showing the People of Athens being crowned by Democracy, inscribed with a law against tyranny passed by the people of Athens in 336 B.C. (*Leemage/Universal Images Group/Getty Images)